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(54) **Title:** A METHOD FOR ACHIEVING IMPROVED POLYPEPTIDE EXPRESSION

(57) **Abstract:** The present invention relates to methods of optimization of a protein coding sequences for expression in a given host cell. The methods apply genetic algorithms to optimise single codon fitness and/or codon pair fitness sequences coding for a predetermined amino acid sequence. In the algorithm generation of new sequence variants and subsequent selection of fitter variants is reiterated until the variant coding sequences reach a minimum value for single codon fitness and/or codon pair fitness. The invention also relates to a computer comprising a processor and memory, the processor being arranged to read from and write into the memory, the memory comprising data and instructions arranged to provide the processor with the capacity to perform the genetic algorithms for optimisation of single codon fitness and/or codon pair fitness. The invention further relates to nucleic acids comprising a coding sequence for a predetermined amino acid sequence, the coding sequence being optimised with respect to single codon fitness and/or codon pair fitness for a given host in the methods of the invention, to host cells comprising such nucleic acids and to methods for producing polypeptides and other fermentation products in which these host cells are used.

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A method for achieving improved polypeptide expression

Field of the invention

The present invention relates to a method for producing a polypeptide in a host cell, wherein the nucleotide sequences encoding the polypeptide have been modified with respect to their codon-usage, in particular the codon-pairs that are used, to obtain improved expression of the nucleotide sequence encoding the polypeptide and/or improved production of the polypeptide.

Background of the art

The present invention relates to improved methods for producing polypeptides. Numerous approaches have been applied in generating strains for protein over-expression and/or production. This includes, but is not limited to, making strains with multi-copies of the gene encoding the protein of interest (POI) and applying strong promoter sequences.

Each specific amino acid is encoded by a minimum of one codon and a maximum of six codons. Prior research has shown that codon usage in genes encoding the cell's polypeptides is biased among species (Kanaya, S, Y. Yamada, Y. Kudo and T. Ikemura (1999) Studies of codon usage and tRNA genes at 18 unicellular organisms and quantification of *Bacillus subtilis* tRNAs: gene expression level and species-specific diversity of codon usage based on multivariate analysis. *Gene* 238:143-155). Prior publications disclose optimization of codon use in a given host cell to improve polypeptide production (as example see WO 97/11086). More specifically, WO 03/70957 describes optimized codon use in filamentous fungi for producing plant polypeptides. In all these cases of 'classic' codon optimization, a native codon has been substituted by the most frequent codon from a reference set of genes, whereas the rate of codon translation for each amino acid is designed to be high (optimized).

More recently, in WO 03/85114 a harmonization of codon use was described which takes into effect the distribution of all codons in genes of the host organism, assuming that these effect protein folding.

The availability of fully sequenced genomes of many organisms in recent years, *e.g.* *Bacillus subtilis* (Kunst et al. 1997), *Bacillus amiloliquefaciens, Aspergillus niger* (Pel et al., 2007, Nat Biotech. 25: 221-231), *Kluyveromyces lactis, Saccharomyces cerevisiae* (http://www.yeastgenome.org/), various plant genomes, mouse, rat and human, has offered the possibility of analyzing different aspects of the gene sequences themselves in relation to their

natural expression level (mRNA or protein level). A good example is codon usage (bias) analysis, and subsequent single-codon optimization. Note that single-codon optimization is herein understood to refer to codon optimization or codon harmonization techniques that focus on the optimization of codons as single independent entities, in contrast to codon-pair optimization, which is the topic of the current invention.

Whereas single-codon usage (bias) has been studied extensively before (for an overview, see Gustafsson et al., 2004, Trends Biotechnol. 22:346-353), there are only a few reports on codon pair usage and for optimization of codon-pairs.

The effect of a few specific codon-pairs on ribosomal frameshifts in *E. coli* has e.g. been investigated for the AGG-AGG codon-pair (Spanjaard and van Duin, 1988, Proc. Natl. Acad. Sci. USA 85:7967-7971; Gurvich et al., 2005, J. Bacteriol. 187:4023-432), and for UUU-YNN sites (Schwarz and Curran, 1997, Nucleic Acids Res. 25:2005-2011).

Gutman and Hatfield (1989, Proc. Natl. Acad. Sci USA 86:3699-3703) analyzed a larger set of sequences for all possible codon pairs for *E. coli* and found that codon pairs are directionally biased. In addition, they observed that highly underrepresented pairs are used almost used twice as frequently as overrepresented ones in highly expressed genes, whereas in poorly expressed genes overrepresented pairs are used more frequently. US 5,082,767 (Hatfield and Gutman, 1992) discloses a method for determining relative native codon pairing preferences in an organism and altering codon pairing of a gene of interest in accordance with said codon pairing preferences to change the translational kinetics of said gene in a predetermined manner, with examples for *E. coli* and *S. cerevisiae*. However, in their method, Hatfield and Gutman only optimize individual pairs of adjacent codons. Moreover, in their patent (US 5,082,767), it is claimed to increase translational kinetics of at least a portion of a gene by a modified sequence in which codon pairing is altered to increase the number of codon pairs that, in comparison to random codon pair usage, are the more abundant and yet more under-represented codon pairs in a organism. The present invention discloses a method to increase translation by a modified sequence in which codon pairing is altered to increase the number of codon pairs that, in comparison to random codon pair usage, are the more over-represented codon pairs in an organism.

Moura et al. (2005, Genome Biology, 6:R28) analyzed the entire *S. cerevisae* ORFeome but did not find a statistically significant bias for about 47% of the codon pairs. The respective values differed from one species to another, resulting in "codon context maps" that can be regarded as "species-specific fingerprints" of the codon pair usage.

Boycheva et al. (2003, Bioinformatics 19(8):987-998) identified two sets of codon pairs in *E. coli* referred to as hypothetically attenuating and hypothetically non-attenuating by looking for over- and under-represented codon pairs among genes with high and poor expression. However, they do not propose a method to apply this finding, nor gave any experimental prove for their hypothesis. Note that these groups are defined completely opposite to the ones defined by Gutman and Hatfield (1989, 1992, *supra*), who proposed a non-attenuating effect for highly underrepresented pairs in highly expressed genes.

Buchan, Aucott and Stanfield (2006, *Nucleic Acids Research* 34(3):1015-1027) analyzed tRNA properties with respect to codon pair bias.

As for the implications of biases in codon pair utilization, Irwin et al. (1995, J. Biol. Chem. 270:22801-22806) demonstrated in *E. coli* that the rate of synthesis actually decreased substantially when replacing a highly underrepresented codon pair by a highly overrepresented one and increased when exchanging a slightly underrepresented codon pair for a more highly underrepresented. This is quite remarkable as it is rather the opposite of what one would expect given the influence of single codon bias on protein levels.

However, none of the above-cited art discloses how to optimize the codon-pair usage of a full-length codon sequence taking account of the fact that by definition codon pairs overlap and that therefore optimization of each individual codon pair affects the bias of the overlapping up- and downstream codon pairs. Moreover, none of the cited art discloses a method that combines optimization of both single codons as well as codon pairs. Codon pair optimization taking into account said codon pair overlapping and optional combination of said codon-pair optimization with single-codon optimization would greatly improve expression of the nucleotide sequence encoding the polypeptide of interest and/or improve production of said polypeptide.

There is thus still a need in the art for novel methods for optimization of coding sequences for improving the production a polypeptide in a host cell.

Summary of the invention

An object of the present invention is to provide a method for optimizing the coding sequence for efficient gene transcription and protein translation. To that effect, the invention provides a method of optimization of a nucleotide sequence encoding a predetermined amino acid sequence, whereby the coding sequence is optimized for expression in a predetermined host cell, the method comprising: (a) generating at least one original coding sequence that codes for the predetermined amino acid sequence; (b) generating at least one newly generated coding sequence from this at least one original coding sequence by replacing in this at least one original

coding sequence one or more codons by a synonymous codon; (c) determining a fitness value of said at least one original coding sequence and a fitness value of said at least one newly generated coding sequence while using a fitness function that determines at least one of single codon fitness and codon pair fitness for the predetermined host cell; (d) choosing one or more selected coding sequence amongst said at least one original coding sequence and said at least one newly generated coding sequence in accordance with a predetermined selection criterion such that the higher is said fitness value, the higher is a chance of being chosen; and (e) repeating actions b) through d) while treating said one or more selected coding sequence as one or more original coding sequence in actions b) through d) until a predetermined iteration stop criterion is fulfilled.

In embodiments, the invention addresses aspects like single codon usage, codon harmonization, dinucleotide usage, and related to that codon-pair bias. The method can be performed by a computer program running on a computer that uses a mathematical algorithm for sequence analysis and sequence optimization that may be implemented in MATLAB (http://www.mathworks.com/).

In addition to positive codon optimization (e.g. for modulation of gene expression and protein production in a positive way), the invention also provides a method for adapting codons towards "bad" codon pairs (i.e. negative codon-pair optimization). The latter method is useful for control purposes as well as for modulating gene expression in a negative way.

Brief description of the drawings

It is observed that the present invention will be illustrated with reference to several figures which are only intended to illustrate the invention and not to limit its scope which is defined by the annexed claims and its equivalents.

Figure 1 shows a computer arrangement on which the method of the invention can be performed.

Figure 2 shows a flow chart of an embodiment of the invention.

Figure 3 shows a distribution of codon pair bias values for 3,721 sense:sense codon pairs in different organisms. The numbers in the top right corner of each histogram are the standard deviations for the observed distribution; the mean values (not shown) are between -0.06 and -0.01 for all organisms.

Figure 4 shows the correlation in codon pair bias of various organisms. The correlation coefficient is shown in the top right corner of each subplot.

Figure 5 shows a codon bias map for *A. niger*. The bias values range from –0.67 to 0.54, where in other organisms they might even get slightly above +-0.9 (see also Figure 3). The highest intensities of black in these diagrams represent values of 0.9 (Figures 5A and 5C for the positive values, green in the original) and –0.9 (Figures 5B and 5D for the negative values, red in the original). In Figures 5A and B the rows and columns are sorted according to the codons their alphabetical order. In Figures 5C and 5D the rows are sorted according to the alphabetical order of the third position nucleotide as first sorting criterion and the middle position nucleotide as second sorting criterion, and first position nucleotide as third sorting criterion.

Figure 6 shows a codon bias map for *B. subtilus*. The bias values range from –0.97 to 0.87, where in other organisms they might even get slightly above +-0.9 (see also Figure 3). The highest intensities of black in these diagrams represent values of 0.9 (Figure 6A for the positive values, green in the original) and –0.9 (Figure 6B for the negative values, red in the original).

Figure 7 shows a codon bias map for *E. coli*. The bias values range from –0.97 to 0.85, where in other organisms they might even get slightly above +-0.9 (see also Figure 3). The highest intensities of black in these diagrams represent values of 0.9 (Figure 7A for the positive values, green in the original) and –0.9 (Figure 7B for the negative values, red in the original).

Figure 8 shows a codon bias map for 479 highly transcribed genes of *A. niger*, analogous to the previous Figures 5-7. The highest intensities of black in these diagrams represent values of 0.9 (Figure 8A for the positive values, green in the original) and –0.9 (Figure 8B for the negative values, red in the original). The maximum bias value in this group is 0.9l the minimum is –1, i.e. some possible codon pairs do not occur at all, although their individual codons and the encoded amino acid pair do. This might be a result of the smaller size of 188,067 codon pairs, compared to 5,885,942 in the full genome. However, the main reason will be the real under representation of such pairs due to selection in highly expressed genes.

Figure 9 shows a Scatter plot of bias in a group of 479 highly expressed genes (vertical axis) versus the bias in all genes (horizontal) of *A. niger*. All 3,721 codon pairs not involving stop codons are shown. Colours from light grey to black were assigned according to the absolute values of the z-scores in the overall genome, i.e. light dots in the plot do not have a significant bias in all genes), as were sizes according to the absolute z-scores in the highly expressed group, i.e. very small dots do not have a significant bias there (here |z-score|<1.9). The solid black line indicates where both bias values are equal; the dashed line shows the best linear approximation of the actual correlation (identified by principal component analysis); its slope is around 2.1.

Figure 10 Fitness values of the 4,584 *A. niger* genes compared to the logarithm of their transcription levels. The correlation coefficient is -0.62.

Figure 11 shows single codon *vs.* codon pair optimization. The wild type ($fit_{sc}(g_{FUA})$=0.165, $fit_{cp}(g_{FUA})$=0.033) does not fit on this plot (it would be far to the right and above). It is clear that the *cpi* parameter determines a trade-off between single codon and codon pair fitness. The optimal gene is always the one with the lowest values for fit_{sc} and fit_{cp}. Given the position of the dots, it is therefore not clear for which value of *cpi* the best gene could be obtained, since we do not know yet whether single codon usage or codon pair usage is more important. Although, the examples provides strong evidence that codon pair fitness is very important in addition to single-codon fitness, which means that *cpi* should be chosen at least >0.

Figure 12 shows two diagrams that show the sequence quality of the first 20 (out of 499) codons of the aforementioned FUA (see also Example 2). The black dots indicate the desired codon ratios, whereas the x-marks show the actual ones (in the whole gene), connected via a dashed line. Single codon fitness can then be interpreted as the average of the lengths of these dashed lines (note that for codons where desired and actual ratio are equal, as for example TGG (which has no synonymous codons) on position 4 and 5, this "length" is zero; note also that "length" can never be negative). The black bars, in turn, show the weights of the pair formed by the two adjacent codons. The black dots (in the middle, below the bars) indicate the minimum weight of any codon pair that encodes the same dipeptide. The codon pair fitness is then the average height of these bars (note that height as used here can well be negative).

Figure 13 depicts the convergence of fit_{combi} using the described genetic algorithm approach of the invention for optimization of the amyB gene that results in SEQ ID NO. 6.

Figure 14 depicts, for reasons of explanation, a part of a single-codon distribution diagram, like one is shown for example in Figure 15. The two graphs indicate the single-codon usage for the two synonymous codons that code for phenylalanine: UUU (top) and UUC (bottom). The X- axis and Y- axis of both graphs goes from 0% to 100%. The grey histogram is a codon-usage histogram, normalized for each amino acid (group of synonymous codons), for a group of 250 highly expressed *A. niger* genes, where the genes are binned in groups having 0%, >0 - <10%, 10 – <20%, … , 90 - <100%, 100%. For example, 50% of the highly-expressed genes fall in the group with 0% usage of the UUU codon, and consequently 100% usage of the UUC codon for coding phenylalanine. The white bar gives the codon-usage of gene A (WT amyB in this case) in similar bins as for the histogram; thus 100% in bin 20-30% (20% with 3/15 codons being UUU) for gene A, and consequently 100% in bin 80-<90% (80% with 12/15 being UUC). The black bar gives the statistics for gene B (the single-codon optimized variant for amyB in this case). In a similar way, one can create a matrix of 16 times 4 graphs, showing statistics for all 64 codons, see for example Figure 15.

Figure 15 (parts 1 and 2) depicts the single-codon frequency for the single-codon optimized amyB gene (black) versus the wild-type amyB gene (white). The grey histogram depicts the statistics for 250 highly-expressed genes in *A. niger*. It is clear that certain codons, like the one for cysteine (UGU/UGC), histidine (CAU/CAC), tyrosine (UAU/UAC) and others were subject to real improvements.

Figure 16 (parts 1 and 2) depicts the single-codon frequency for an amyB gene that has been optimized with respect to both single-codon and codon-pairs (black) versus the wild-type amyB gene (white). The grey histogram depicts the statistics for 250 highly-expressed genes in *A. niger*. It is clear that these graphs highly resemble the situation for the single-codon optimized gene depicted in Figure 15.

Figure 17 depicts a part of the full diagram (Figure 18) with single-codon and codon pair statistics for the WT amyB gene of *A. niger*. On the X-axis, one finds the subsequent codons in a gene starting at position 1 with the start-codon ATG. The black dot '.' indicates the target single-codon ratio for the codon at this position with respect to its synonymous codons. For ATG this is 1.0 (100%). The cross 'x' is the actual codon ratio it the shown gene; a dotted line shows the difference between the target ratio and the actual ratio. The codon-pair weight is a value between –1 and 1. The bar indicates the actual codon-pair weight of the adjacent codons, while the pentagram indicates the weight of the optimal achievable synonymous codon-pair (not taking into account the neighboring pairs). For example the first bar is –0.23 which is the weight for 'ATG-GTC', second is 0.66 being the weight for 'GTC –GCG'.

Figure 18 depicts the single codon and codon pair statistics for SEQ ID NO. 2 (WT AmyB).

Figure 19 depict the single codon and codon pair statistics for SEQ ID NO. 5 (single codon-optimized AmyB).

Figure 20 depict the single codon and codon pair statistics for SEQ ID NO. 6 (single codon and codon pair optimized WT AmyB).

Figure 21 depicts a plasmid map of expression vector pGBFINFUA-1. Figure 21 also provides a representative map for plasmid pGBFINFUA-2 and pGBFINFUA-3. All clones originate from the pGBFIN-12 (described in WO99/32617) expression vector. Indicated are the *gla*A flanking regions relative to the variant sequences of the *amy*B promoter and the *A. niger* amyB cDNA sequence encoding alpha-amylase. The *E. coli* DNA can be removed by digestion with restriction enzyme *Not*I, prior to transformation of the *A. niger* strains.

Figure 22 depicts a schematic representation of integration through single homologous recombination. The expression vector comprises the selectable amdS marker, and the *gla*A

promoter connected to the *amyB* gene. These features are flanked by homologous regions of the *gla*A locus (3' *gla*A and 3" *gla*A, respectively) to direct integration at the genomic *glaA* locus.

Figure 23 depicts alpha-amylase activity in culture broth for *A. niger* strains expressing three different constructs. Depicted is the alpha-amylase activity in culture broth of *A. niger* strains expressing a native *amyB* construct, wherein (1) the translation initiation sequence and the translation termination sequence were modified (pGBFINFUA-1), and (2) the translation initiation sequence, the translation termination sequence and the single-codon usage were modified (pGBFINFUA-2), and (3) the translation initiation sequence, the translation termination sequence and the single-codon usage and codon-pair usage were modified (pGBFINFUA-3) according a method of the invention. Alpha-amylase activities are depicted in relative units [AU], with the average of the 6 one-copy strains of the FUA1 group of 10 strains at day 4 set at 100%. The ten transformants per group indicated are independently isolated and cultivated transformants.

Figure 24 (A and B) depicts the single-codon frequency for the single-codon optimization for *Bacillus species.* An explanation of the sub-graphs is given by Figure 14. The grey histogram presents the codon distribution for the 50 highest expressed genes in *B. subtilis*, see text. The black bars indicate the target single-codon frequency.

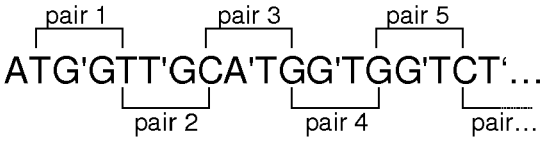
Figure 25 depicts the single codon and codon pair statistics for SEQ ID NO. 14 (1/3), SEQ ID NO. 17 (2/3) and SEQ ID NO. 14 (3/3), the sequenced optimized using codon pair + single codon (1/3), single-codon (2/3), and negative codon-pair + single codon optimization (3/3), respectively. See Figure17 for an explanation of the graph.

Figure 26. *E.coli/Bacillus* shuttle vector pBHA-12. The multiple cloning sites (MCS) 1 and 2 are depicted.

Figure 27. An example of cloning of a gene in the *E.coli/Bacillus* shuttle vector pBHA-12. The Figure shows the cloned part A and B (grey arrows) of the SEQ ID NO. 9. The cloning sites of the part 1A are depicted: *Nde*I and *Bam*HI, for the part 1B *Sma*I and *Kpn*I. The *E.coli* part was excised using *Pvu*II.

Detailed description of the invention

In addition to single codon bias, other structures in the nucleotide sequence are likely to influence protein expression as well, e.g. dinucleotides or repeats of certain short nucleotide sequences (codon usage after all can be interpreted as a pattern in tri-nucleotide sequences in line with the reading frame). This work presents a method for identifying a preference for certain codon pairs, i.e. whether codons appear in the gene as if they were selected according to the identified codon usage ratios, but then distributed randomly in the gene (with respect to the amino acid sequence), or whether some codons appear more often next to certain codons and less often next to others.



An analysis of codon pairs also covers other aspects, namely dinucleotide usage around the reading frame borders and a possible preference for certain single nucleotides next to a codon. The present invention discloses methods for generating a codon-pair bias table for a given host organism whereby either all identified ORFs of sequenced full genomes are used as input or selected groups of genes, e.g. highly expressed genes. The present invention discloses a method wherein a codon-pair bias table thus identified is subsequently applied for optimization of codon-pair distribution in a gene of interest (GOI) for improving the expression of the corresponding protein of interest (POI).

Single codon optimization offers a good starting point for improving expression levels of proteins of interest. Whereas others tried to overcome drawbacks resulting from the presence of rejected codons in the gene of interest by adaptation of the host organism, inserting additional copies of tRNA genes for tRNAs with low abundance (*e.g.* Stratagene BL-21 CodonPlus™ competent cells, Novagen Rosetta™ host strains, both *E. coli*), the present inventors have focused on the adaptation of the genes of interest themselves. Unwanted codons in a genetic sequence have been replaced by synonymous ones so that the single codon distribution of the resulting sequence was as close as possible to previously identified desired codon ratios.

This codon harmonization, however, still has a very large number of possible genes that are equally "optimal" since the overall codon distribution in an optimized gene is the selection criterion, so further desired properties of the codon sequence can easily be taken into account, for example the absence of certain enzyme's restriction sites or codon pairs known to cause

frameshifts. One step further, one could optimize codon pair usage to a limited extent. But when optimizing codon pairs of a gene, *e.g.* towards the usage of the most abundant ones, the single codon usage of the resulting sequence might not be close to the optimum, since there might be preferred codon pairs consisting of underrepresented single codons, so a balance between single codon and codon pair optimization must be found. The present invention discloses methods that allow balancing both single codon and codon pair optimization. Codon pair optimization taking into account codon pair overlapping and optional combination of said codon-pair optimization with single-codon optimization greatly improve expression of the nucleotide sequence encoding the polypeptide of interest and/or improve production of said polypeptide.

In the context of this invention, a nucleotide coding sequence or coding sequence is defined as a nucleotide sequence encoding a polypeptide. The boundaries of the coding sequence are generally determined by the start codon (usually ATG in eukaryotes, while it can be one of ATG, CTG, GTG, TTG in prokaryotes) located at the beginning of the open reading frame at the 5' end of the mRNA and a stop codon (generally one of TAA, TGA, TAG, although exceptions to this 'universal' coding exists) located just downstream of the open reading frame at the 3' end of the mRNA. A coding sequence can include, but is not limited to, DNA, cDNA, RNA, and recombinant nucleic acid (DNA, cDNA, RNA) sequences (note that it is well known in the art that Uracil, U, replaces the deoxynucleotide Thymine, T, in RNA). If the coding sequence is intended for expression in a eukaryotic cell, a polyadenylation signal and transcription termination sequence will usually be located 3' to the coding sequence. A coding sequence comprises a translational initiator coding sequence, and optionally a signal sequence, and optionally one or more intron sequences. Even though the terms "coding sequence" and "gene" strictly do not refer to the same entity, both term are frequently used interchangeably herein and the skilled person will understand from the context whether the term refers to a full gene or only its coding sequence.

Method and computer arrangement for single codon and/or codon pair adaptation

As for the single codon usage properties of highly expressed genes, a "manual" comparison of single codon ratios in all genes and a group of highly expressed ones has lead to some "desired codon ratios" for the improvement of genes with respect to their expression level.

Single codon adaptation of a gene can then be performed by: (1) calculating the actual ratios in the gene, repeatedly picking a codon (e.g. randomly) whose desired ratio is lower than the actual one and replacing it by a synonymous one with a too low ratio; or (2) calculating the desired number of each codon using the "desired codon ratios", making groups of synonymous

codons, and repeatedly picking a codon (e.g. randomly) from a synonymous group coding for the pre-specified amino acid, for each position in the gene.; making multiple variants using method (1) and/or (2) and based on additional selection criteria picking the most relevant gene (e.g. wanted and unwanted restriction sites and/or folding energy).

Yet this approach is not suitable for codon pair adaptation, firstly because visual inspection of bias data for all codon pairs is out of the question in view of the complexity and secondly because altering of one codon pair, which means replacing at least one of the two participating codons, will also affect at least one of the adjacent codon pairs, so "desired codon pair ratios" would be unachievable. Because of the constraints implied by this, a deterministic approach was considered too complex and not promising enough and a "genetic algorithm" approach was then chosen.

It is observed that the term "genetic algorithm" may be confusing in the sense that it seems to relate to genetic engineering. However, a "genetic algorithm" is an approach from computer science that is used to approximate solutions to multidimensional optimization problems (Michalewicz, Z., Genetic Algorithms + Data Structure = Evolution Programs, Springer Verlag 1994; David E. Goldberg. Genetic Algorithms in Search, Optimization and Machine Learning. Addison-Wesley, Reading MA, 1989; http://en.wikipedia.org/wiki/Genetic_algorithm). In the present invention, this approach is used in solving the optimization problem of selecting the "best" possible gene, i.e. coding sequence for a particular protein of interest. In this approach, each position in the gene, i.e. each codon can be considered one dimension, with the set of values being discrete and determined by the available synonymous codons.

Generally, in a genetic algorithm, at first a set of possible "solutions" to the problem is often generated randomly, or by variations on initial provided solutions (although many other methods approaches exist). This set is called "population"; its elements are "individuals" or "chromosomes", mostly represented by vectors (in the mathematical sense) containing coordinates for each dimension. Since genetic algorithms were modeled after processes involved in natural selection, much of the terminology is borrowed from genetics. However, since they are (unlike in this case) mostly applied in the field of computer science and to, but also some example to application of genetic algorithms in biological science problems have been presented, e.g. for protein secondary structure prediction (Armano et al. 2005 BMC Bioinformatics 1(6) Suppl. 4:S3); *in silico* metabolic network optimization (Patil et al. 2005 BMC Bioinformatics. 23(6):308); clustering gene expression data (Di Gesu et al. 2005 BMC Bioinformatics.7(6):289).

In the present case, a vector contains codons. From that population, new individuals are created by altering certain positions of an existing individual ("mutation") or by combining a part (i.e. certain coordinates) of an individual with another part (i.e. the coordinates for the other dimensions) from another individual ("crossover"). It is then examined how good these individuals are (since the new ones are also possible solutions to the initial optimization problem) and the better ("fittest") of the individuals are taken again as initial population for generating new individuals ("next generation"; e.g. , the best 10, 20, 30, 40, 50, 60% are kept, but many other possibilities exist to selecting a subset for offspring for obtaining a convergence toward fitter individuals, e.g. roulette wheel selecting, see Michalewicz, Z, 1994). When allowing the best individual from the initial population to be taken over to the next generation, it is ensured that with every population the quality of the possible solutions gets better or at least stays the same. It is then assumed that with a run of this algorithm for many generations (= iterations; some hundred to several thousand, depending on the complexity of the problem) one will get a solution close to the optimum. Genetic algorithms have been investigated closely in computer science, including properties such as optimal proportion of population size and number of generations, how to prevent the algorithm from getting stuck in local optima etc., but this should not matter much here now. For information on how to set these parameters for the actual optimization procedure, see the description implemented genetic algorithm in MATLAB in Example 2.

This will be explained in detail with reference to Figure 2. Figure 2 shows a flow chart of a genetic algorithm for gene optimization. Such a genetic algorithm can be performed on a suitably programmed computer, an example of which will be shown in and explained first with reference to Figure 1. Figure 1 shows an overview of a computer arrangement that can be used to carry out the method according to the invention. The arrangement comprises a processor 1 for carrying out arithmetic operations.

Note that genetic algorithms are generally non-deterministic as they involve randomized steps (e.g. randomized selection criteria and/or randomized operator choice and/or randomized generation of potential solutions), however, exceptions exist that perform in a deterministic way. "Genetic algorithms" is a generic tool for those algorithms that deal with a group (called population) of potential solutions, which is by screening and/or selection and/or removal, and/or (re)introduction of (newly) generated solutions driven toward and optimal solution by using one or multiple objectives. Considering this definition, also methods described as evolutionary programming, evolutionary algorithms, classic genetic algorithms, real-coded genetic algorithms, simulated annealing, ant algorithms, and also Monte-Carlo and chemotaxis methods,

belong to a similar class of algorithms, opposite to methods that are based on the convergence of a single potential solutions toward an optimal solution using a deterministic algorithm, like linear programming and gradient algorithms. Furthermore, a skilled person will understand from the context whether another original term refers to the same class of algorithms. Moreover, although a genetic algorithm is the preferred method, we do not exclude any other method than genetic algorithms for solving the single-codon and/or codon-pair optimization problem as described within this invention.

The processor 1 is connected to a plurality of memory components, including a hard disk 5, Read Only Memory (ROM) 7, Electrically Erasable Programmable Read Only Memory (EEPROM) 9, and Random Access Memory (RAM) 11. Not all of these memory types need necessarily be provided. Moreover, these memory components need not be located physically close to the processor 1 but may be located remote from the processor 1.

The processor 1 is also connected to means for inputting instructions, data etc. by a user, like a keyboard 13, and a mouse 15. Other input means, such as a touch screen, a track ball and/or a voice converter, known to persons skilled in the art may be provided too.

A reading unit 17 connected to the processor 1 is provided. The reading unit 17 is arranged to read data from and possibly write data on a data carrier like a floppy disk 19 or a CDROM 21. Other data carriers may be tapes, DVD, memory sticks etc. as is known to persons skilled in the art.

The processor 1 is also connected to a printer 23 for printing output data on paper, as well as to a display 3, for instance, a monitor or LCD (Liquid Crystal Display) screen, or any other type of display known to persons skilled in the art.

The processor 1 may be connected to a communication network 27, for instance, the Public Switched Telephone Network (PSTN), a Local Area Network (LAN), a Wide Area Network (WAN), etc. by means of I/O means 25. The processor 1 may be arranged to communicate with other communication arrangements through the network 27.

The data carrier 19, 21 may comprise a computer program product in the form of data and instructions arranged to provide the processor with the capacity to perform a method in accordance with the invention. However, such computer program product may, alternatively, be downloaded via the telecommunication network 27.

The processor 1 may be implemented as stand alone system, or as a plurality of parallel operating processors each arranged to carry out subtasks of a larger computer program, or as one or more main processors with several sub-processors. Parts of the functionality of the invention may even be carried out by remote processors communicating with processor 1 through the network 27.

Now the genetic algorithm of Figure 2 will be explained, as may be performed on processor 1 when it runs a computer program stored in its memory.

In action 32 the computer generates one or more genes that code for a predetermined protein. This can be done by taking data to that effect from a table stored in the memory of the computer. Such genes may e.g. be:

- ATG'GTT'GCA'TGG'TGG'TCT'…
- ATG'GTA'GCA'TGG'TGG'TCA'…
- …

For the purpose of the algorithm, these generated genes are termed "original genes".

After action 32, the computer program performs one or more iteration loops by performing actions 34-40 one or more times.

In action 34, the computer program generates new genes by replacing one or more of the codons in the original gene(s) by synonymous codons such that the newly generated gene(s) still code for the predetermined protein (crossover & mutation process). To be able to do so, the memory of the computer stores a codon usage table which shows which codons code for which amino acids. (Note that deviations from the "universal code" exist and are taken into account if this is the case for the specified host organisms, see for example Laplaza et al., 2006, Enzyme and Microbial Technology, 38:741-747). Knowing the sequence of amino acids in the protein, the computer program can select alternative codons from the table as are well known in the art.

Using the example of action 32, the newly generated genes may be (indicated in bold):

- ATG'GTT'GCA'TGG'TGG'TCT'…
- ATG'GTA'GCA'TGG'TGG'TCA'…
- **ATG'GTT'GCA'TGG'TGG'TCA'…**
- ATG'GTA'GCA'TGG'TGG'TCA'…
- **ATG'GTA'GCC'TGG'TGG'TCA'…**

In action 36, a quality value of all genes including the original and the newly generated genes is determined by the computer program using a fitness function which determines at least one of codon fitness and codon pair fitness. Examples of such fitness functions will be explained in detail below in the section "Performing codon pair optimization".

In action 38, a number of genes showing a best fitness based on the fitness function are selected for taking part in the "breeding process" (crossover and mutation), and a number of genes showing worst fitness based on the fitness function are selected for removal from the population. These numbers may be predetermined numbers or depend on a predetermined amount of improvement of fitness. The selection of those genes might be deterministic, but

generally a stochastic process is followed where the "fittest genes" having a higher change for being selected for breeding, and the opposite for deletion from the population. This method is called roulette-wheel selection.

The resulting selected genes for breeding may e.g. be (non-selected genes are shown with a deletion line):

- ATG'GTT'GCA'TGG'TGG'TCT'...
- ~~ATG'GTA'GCA'TGG'TGG'TCA'...~~
- ATG'GTT'GCA'TGG'TGG'TCA'...
- ~~ATG'GTA'GCA'TGG'TGG'TCA'...~~
- ~~ATG'GTA'GCC'TGG'TGG'TCA'...~~

In action 40, the computer program tests whether one or multiple termination criteria are fulfilled. Often one of the termination criteria is a predetermined maximum number of iterations. Alternative criteria are checking if the fitness obtained by the selected genes is improved with at least a minimum threshold value relative to the fitness of the original genes, or checking if the fitness obtained by the selected genes is improved with at least a minimum threshold value relative to the fitness of the gene with had best fitness n iterations ago (preferably n is a value in <10,100> is chosen). If the overall termination coterie is not fulfilled the computer program jumps back to action 34 while treating the selected genes as "original genes".

If, in action 40, the computer program establishes that the improvement is below the minimum threshold value further iteration of the actions 34-38 does not make much sense and the computer program continues with action 42.

It is to be understood that any other suitable iteration stop criterion, like the number of iterations performed, can be used in action 40 to leave the iteration actions 34-40 and continue with action 42.

In action 42, the gene with the best fitness amongst all selected genes is selected and presented to the user, e.g. via the monitor or via a printout by means of printer.

In the case of gene adaptation using a genetic algorithm, it has to be assured that the crossover is always performed at a reading frame position, because otherwise the resulting amino acid sequence might be changed when combining one nucleotide of one and two nucleotides of another codon. For better convergence, a modified mutation operator is proposed that for this mutation operator only those synonymous codon replacements have been allowed that result in at least one of better single codon or better codon pair usage.

So an important question for codon pair optimization now is how to measure the quality of the individuals. This so-called fitness function can be regarded the central part of the genetic algorithm, since it is the actual function to be optimized. In the present invention, a preferred approach is to assign a real number (called weight) to each codon pair and take the average of the weights in a gene as its "fitness", thus resulting in a function to be minimized.

It the current description, the inventors describe the process of gene optimization as a minimization problem. This is a rather arbitrarily approach. Note that, if a function f were to be maximized, one could as well look for the minimum of $-f$, so this is no restriction to generality.

Hence, a method for determining codon pair weights has to be identified, where codon pairs considered good for expression level have a low weight and pairs considered bad a high one.

Identification of codon pair weights for gene adaptation

For identification of codon pair weights that relate to a higher transcription/expression level, and which may serve as input for adaptation of codon pair usage, the following methods may be applied, which are herein exemplified by *A. niger*, for which a transcription levels for most of the expressed genes are known, and for *B. subtilis*, for which data on transcription levels was available and also a set of 300 highly expressed genes.

In *A. niger*, where a complete ranking extracted from GeneChip data was available for the aforementioned set of 4,584 actually expressed genes (see Example 1), the mean codon pair weights of each gene (i.e. the equivalent of the $fit_{cp}(g)$ values) were calculated. Then the genes were sorted according to fitness values (ascending order) and expression level (descending order). Since highly expressed genes are supposed to have low codon pair fitness values, these two rankings would be equal when using ideal codon pair weights, so a comparison of these two rankings can give information about the quality of the weights used in the fitness function (where slightly more attention was given to the "correct" ranking of the highly expressed genes than to the ranking of the mediocre ones). Additionally, the correlation coefficient (covariance divided by the standard deviation of each variable) between ranking and average codon pair weights of the 4,584 genes was calculated.

Several possible sets of weights may be used in the methods of the invention, including on or more selected from the group consisting of: (i) bias values from the whole genome; (ii) bias values from a group of highly expressed genes; (iii) bias with all the values that do not have a certain minimum z-score set to zero (whereby the z-score is determined as described in Example 1.1.4); (iv) bias values raised to the power of 2 or 3, 4, 5 or higher (to give highly preferred or

rejected codons a lower/higher influence); (v) z-scores themselves; (vi) difference of bias values/z-scores from the highly expressed group and the full genome; and, (vii) combinations of one or more of (i) - (vi).

For the genetic algorithm, their negations have been used, since preferred codon pairs had been arbitrarily identified with positive values, whereas the genetic algorithm performs minimization. This applies to all the above-mentioned weights.

A more preferred weight matrix may be obtained – as described above – by calculating the codon pair "bias" in a highly expressed group using expected values calculated based on the codon ratios of the whole genome. Let $r_{sc}^{all}(c_k)$ still denote the single codon ratio of c_k in the whole genome data set and $n_{obs}^{high}((c_i,c_j))$ the occurrences of a pair (c_i,c_j) in the highly expressed group, then the calculation of the "combined expected values" $n_{exp}^{combi}((c_i,c_j))$ corresponds to

$$n_{exp}^{combi}((c_i,c_j)) = r_{sc}^{all}(c_i)\cdot r_{sc}^{all}(c_j)\cdot \sum_{\substack{c_k \in syn(c_i)\\ c_l \in syn(c_j)}} n_{obs}^{high}((c_k,c_l))$$

and thus

$$w((c_i,c_j)) = \frac{n_{exp}^{combi}((c_i,c_j)) - n_{obs}^{high}((c_i,c_j))}{\max(n_{obs}^{high}((c_i,c_j)), n_{exp}^{combi}((c_i,c_j)))}.$$

Where $w((c_i,c_j))$ is defined as a weight of a codon pair (c_i,c_j) in a sequence g of codons. Note that since the optimization function will look for a minimum average weight, the two terms of the numerator have been reversed compared to the equation for the bias values, but this does not affect the correlation with the expression levels other than that it changes the sign.

Unlike all other weight sets tested, codon pairs involving codons that are more underrepresented in the highly expressed group get a slight disadvantage here. Thus, these weights are the only ones that also reflect the different single codon bias of the highly expressed group and all genes. Using these weights carries the risk of rejecting some codon pairs that actually have a positive bias in the highly expressed group, but consist of (in the highly expressed group) rarely used codons. However, since our desired single codon ratios are usually not identical to those in the group of genes with high expression, but more "extreme" than these, single codon optimization would replace these underrepresented anyway, so we can consider the weights described above very convenient for codon pair optimization. Thus, although the codon pair weights also reflect single codon bias to a limited extend, for the optimization, single codon usage is regarded as a separate, additional issue.

Optimization of single codons and codon pairs using a genetic algorithm

In the method of the invention preferably a computer arrangement programmed to perform a genetic algorithm as described herein above is used to perform codon pair adaptation or combined single codon and codon pair adaptation have been performed. Applying a genetic algorithm for single codon adaptation is also possible and not excluded from the invention, but here undesired codons can be replaced by synonymous codons without constraints with respect to neighboring codons and therefore using a genetic algorithm is not really necessary.

As for codon pairs, changing a single codon will usually alter the weight of two codon pairs, and therefore codon pair optimization is heavily constrained because a single codon change replacing an unwanted codon pair will always change another codon pair, and this is not necessarily a change for the better, and correcting a change for the worse in an adjacent codon pair will then again alter another pair, and so on.

For the mutation operator, only those alterations of the codon sequence have been allowed that did not change the encoded peptide sequence and that improved at least one of single codon fitness and codon pair fitness, i.e. before changing a codon the mutation operator looks for synonymous codons that are either underrepresented (according to the desired single codon ratios) or one where the two codon pairs it is involved in have better weights. It is selected randomly which one of the two types of mutation is performed. Performing the former "mutation" operator on every single codon is sufficient for creating a single-codon-optimized gene without any use of the genetic algorithm.

The quality of a gene is determined considering two aspects, namely single codon "fitness" and codon pair "fitness". The latter is simply the average of the weights $w((c(k), c(k+1))$ of all codon pairs in a sequence g of codons (or gene). I.e., when g again symbolizes the sequence of codons, $|g|$ its length (in codons) and $c(k)$ its k-th codon:

$$fit_{cp}(g) = \frac{1}{|g|-1} \cdot \sum_{k=1}^{|g|-1} w((c(k), c(k+1)))$$

Single codon fitness is defined to be the difference of the actual codon ratios in the gene and the target codon ratios, normalized for the number of occurrences of every codon. Single codon ratios are defined and may be determined as described in Example 1.1.2 herein. Let $r_{sc}^{target}(c(k))$ be the desired ratio (or frequency) of codon c_k and $r_{sc}^{g}(c(k))$ as before the actual ratio in the gene g, then the single codon fitness is defined as

$$fit_{sc}(g) = \frac{1}{|g|} \cdot \sum_{k=1}^{|g|} \left| r_{sc}^{target}(c(k)) - r_{sc}^{g}(c(k)) \right|.$$

Thus, fit_{sc} can reach values in [0,1] with the optimal sequence being close to 0, whereas fit_{cp} is limited by the weights, which here are also in [-1,1].

To optimize for both aspects, in an embodiment, a combined fitness function has been introduced:

$$fit_{combi}(g) = \frac{fit_{cp}(g)}{cpi + fit_{sc}(g)}.$$

Here, *cpi*, which stands for "codon pair importance", is a real value greater than zero and determines which of the two fitness functions has more influence on the combined fitness. With *cpi* close to zero, the denominator approaches zero when $fit_{sc}(g)$ gets better (i.e. also close to zero) and thus small changes in $fit_{sc}(g)$ influence $fit_{combi}(g)$ more than small changes in $fit_{cp}(g)$, whereas with a high *cpi* slight improvements in $fit_{cp}(g)$ may have a larger effect on $fit_{combi}(g)$ than medium improvements in $fit_{sc}(g)$. Note that fit_{combi} values that are obtained using different values of *cpi* are not comparable (*cpi* close to 0 might result in fit_{combi} values close to -100, whereas is fit_{combi} usually between 0 and -1 for $cpi > 0.2$).

In an embodiment, a "penalty" is added if *g* contains certain unwanted sequences, e.g. restriction sites or sequences resulting in undesired secondary structures in mRNA. This may be useful when constructing synthetic genes, but in itself is unrelated to optimization of single codon and codon pair usage. A modified fitness function becomes:

$$fit^{*}_{combi}(g) = \frac{fit_{cp}(g)}{cpi + fit_{sc}(g)} + P(g)$$

where $P(g)$ denotes a penalty function that creates a positive weight in case an unwanted sequence structure is part of gene *g*.

It is to be understood that in the embodiments of the invention herein the nucleotide and amino acid sequences may be theoretical sequences that exist only on e.g. paper or another preferably computer readable data carrier, or they may exist as a tangibly, physically created embodiment.

In a first aspect the invention therefore relates to a method of optimization of a nucleotide coding sequence that codes for a predetermined amino acid sequence, whereby the coding sequence is optimized for expression in a predetermined host cell. The method preferably comprises the steps of: (a) generating at least one original coding sequence that codes for the predetermined amino acid sequence; (b) generating at least one newly generated coding sequence from this at least one original coding sequence by replacing in this at least one original coding sequence one or more codons by a synonymous codon; (c) determining a fitness value of

said at least one original coding sequence and a fitness value of said at least one newly generated coding sequence while using a fitness function that determines at least one of single codon fitness and codon pair fitness for the predetermined host cell; (d) choosing one or more selected coding sequence amongst said at least one original gene and said at least one newly generated coding sequence in accordance with a predetermined selection criterion such that the higher is said fitness value, the higher is a chance of being chosen; and, (e) repeating actions b) through d) while treating said one or more selected coding sequence as one or more original coding sequence in actions b) through d) until a predetermined iteration stop criterion is fulfilled.

According to an embodiment of the invention, the method preferably comprises the steps of: (a) generating at least one original coding sequence that codes for the predetermined amino acid sequence; (b) generating at least one newly generated coding sequence from this at least one original coding sequence by replacing in this at least one original coding sequence one or more codons by a synonymous codon; (c) determining a fitness value of said at least one original coding sequence and a fitness value of said at least one newly generated coding sequence while using a fitness function that determines codon pair fitness for the predetermined host cell; (d) choosing one or more selected coding sequence amongst said at least one original gene and said at least one newly generated coding sequence in accordance with a predetermined selection criterion such that the higher is said fitness value, the higher is a chance of being chosen; and, (e) repeating actions b) through d) while treating said one or more selected coding sequence as one or more original coding sequence in actions b) through d) until a predetermined iteration stop criterion is fulfilled.

According to another embodiment of the invention, the method preferably comprises the steps of: (a) generating at least one original coding sequence that codes for the predetermined amino acid sequence; (b) generating at least one newly generated coding sequence from this at least one original coding sequence by replacing in this at least one original coding sequence one or more codons by a synonymous codon; (c) determining a fitness value of said at least one original coding sequence and a fitness value of said at least one newly generated coding sequence while using a fitness function that comprises determining single codon fitness and codon pair fitness for the predetermined host cell; (d) choosing one or more selected coding sequence amongst said at least one original gene and said at least one newly generated coding sequence in accordance with a predetermined selection criterion such that the higher is said fitness value, the higher is a chance of being chosen; and, (e) repeating actions b) through d)

while treating said one or more selected coding sequence as one or more original coding sequence in actions b) through d) until a predetermined iteration stop criterion is fulfilled.

In the methods preferably the predetermined selection criterion is such that said one or more selected coding sequence have a best fitness value according to a predetermined criterion. The methods according to the invention, may further comprises, after action e): selecting a best individual coding sequence amongst said one or more selected coding sequences where said best individual coding sequence has a better fitness value than other selected coding sequences.

In the methods of the invention, the said predetermined iteration stop criterion preferably is at least one of: (a) testing whether at least one of said selected coding sequences have a best fitness value above a predetermined threshold value; (b) testing whether none of said selected coding sequences has a best fitness value below said predetermined threshold value; (c) testing whether at least one of said selected coding sequences has at least 30% of the codon pairs with associated positive codon pair weights for the predetermined host cell in said original coding sequence being transformed into codon pairs with associated negative weights; and, (d) testing whether at least one of said selected coding sequences has at least 10, 20, 30, 40, 50, 60, 70, 80 or 90% of the codon pairs with associated positive weights above 0 for the predetermined host cell in said original coding sequence being transformed into codon pairs with associated weights below 0.

In the methods of the invention the fitness function preferably defines single codon fitness by means of:

$$fit_c(g) = 100 - \frac{1}{|g|} \cdot \sum_{k=1}^{|g|} \left| r_c^{t\arg et}(c(k)) - r_c^{g}(c(k)) \right| \cdot 100$$

where g symbolizes a coding sequence, $|g|$ its length, $g(k)$ its k-th codon, $r_c^{t\arg et}(c(k))$ is a desired ratio of codon c(k) (APPENDIX 2; CR vectors) and $r_c^{g}(c(k))$ an actual ratio in the nucleotide coding sequence g.

In the methods of the invention the fitness function preferably defines codon pair fitness by means of:

$$fit_{cp}(g) = \frac{1}{|g|-1} \cdot \sum_{k=1}^{|g|-1} w((c(k), c(k+1))$$

where $w((c(k), c(k+1))$ is a weight of a codon pair in a coding sequence g, $|g|$ is length of said nucleotide coding sequence and $c(k)$ is k-th codon in said coding sequence.

More preferably, in the methods of the invention the fitness function is defined by means of:

$$fit_{combi}(g) = \frac{fit_{cp}(g)}{cpi + fit_{sc}(g)}$$

where

$$fit_{cp}(g) = \frac{1}{|g|-1} \cdot \sum_{k=1}^{|g|-1} w((c(k), c(k+1))$$

$$fit_{sc}(g) = \frac{1}{|g|} \cdot \sum_{k=1}^{|g|} \left| r_{sc}^{target}(c(k)) - r_{sc}^{g}(c(k)) \right|$$

cpi is a real value greater or equal zero, $fit_{cp}(g)$ is codon pair fitness function, $fit_{sc}(g)$ is a single codon fitness function, $w((c(k), c(k+1))$ is a weight of a codon pair in a coding sequence *g* (APPENDIX 3; CPW matrix), $|g|$ is length of said coding sequence, c(*k*) is *k*-th codon in said sequence of codons, $r_{sc}^{target}(c(k))$ is a desired ratio of codon c(*k*) and $r_{sc}^{g}(c(k))$ an actual ratio in the coding sequence *g*. Preferably *cpi* is between 0 and 10, more preferably between 0 and 0.5 and most preferably about 0.2.

In the methods of the invention, the codon pair weights *w* (APPENDIX 3) may be taken from a 64×64 codon pair matrix including stop codons. Note that the weights for stop:sense pairs and stop:stop pairs are always zero. The codon pair weights *w* are preferably calculated on the basis of a computer-based method, using as input at least one of: (a) a genome sequence of the predetermined host cell for which at least 5, 10, 20 or 80% of the protein encoding nucleotide sequences are sequenced; (b) a genome sequence of a related species to the predetermined host cell for which at least 5, 10, 20 or 80% of the protein encoding nucleotide sequences are sequenced; (c) a group of nucleotide sequences consisting of at least 200 coding sequences of the predetermined host cell; and, (d) a group of nucleotide sequences consisting of at least 200 coding sequences of a species related to the predetermined host cell. A related species is herein understood to refer to a species of which the nucleotide sequence of the small subunit ribosomal RNA has at least 60, 70, 80, or 90% identity with the nucleotide sequence of the small subunit ribosomal RNA of the predetermined host cell (Wuyts et al., 2004, Nucleic Acids Res. 32: D101-D103).

The codon pair weights *w* need not be determined for all of the possible 61×64 codon pairs including the termination signal as stop codon but may be determined for only a fraction thereof,

e.g. for at least 5%, 10%, 20%, 50%, and preferably 100% of the possible 61×64 codon pairs including the termination signal as stop codon.

Selection highly expressed genes

For calculation of the codon pair weight matrices and the single codon target ratio vectors one can apply a set of nucleotide sequences from the specified host cell itself, a set of nucleotide sequences from a related species, or a combination of both. The set A of nucleotide sequences is called the 'reference set all'. Most preferably this set contains the full set of open reading frames (ORFs) for an organism that is completely sequenced (>95%).

In a preferred embodiment of the invention, a subset B is selected that contains a subset that is overrepresented with highly expressed genes or genes coding for highly expressed proteins. This set can be determined using measurements, and subsequent ranking, like a mRNA hybridization using array technology, e.g. arrays from Affymetrix, Nimblegen, Agilent or any other source for the reference set A. Other measurements can be RT-PCR, protein gels, MS-MS analysis, or any other measurement technique known by the person skilled in the art. Besides making a ranking on the basis of measurements, one can also apply bioinformatics tools to either predict directly a group of highly expressed genes, for example by selecting the most biased genes (Carbone et al, 2003), or by selecting genes known to be highly expressed in a wide range of organisms. Among these are, ribosomal proteins, glycolytic and TCA cycle genes involved in primary metabolism, genes involved in transcription and translation.

Preferably, the codon pair weights w are calculated on the basis of a computer-based method, using as input the group of highly expressed genes in the predetermined host cell. Highly expressed genes are herein understood to mean genes whose mRNA's can be detected at a level of at least 10, preferably 20, more preferably 50, more preferably 100, more preferably 500 and most preferably at least 1,000 copies per cell. For example, Gygi *et al.* measured ~15,000 mRNA molecules per yeast cell. The abundance of specific mRNAs was determined to be in the range of 0.1-470 per cell (Gygi, S.P., Y. Rochon, B.R. Franza and R. Aebersold (1999). Correlation between protein and mRNA abundance in yeast. *Mol. Cel. Biol.* 19(3):1720-30) or a factor 10 lower: 0.01-50 per cell (by Akashi, H. (2003). Translational selection and yeast proteome evolution. *Genetics* 164(4): 1291-1303.).

Alternatively, the group of highly expressed genes in the predetermined host cell may be the group comprising the 1000, 500, 400, 300, or 200 or 100 most abundant mRNA's or proteins. The skilled person will recognize that for calculation of single-codon ratio's the group-size of highly expressed genes might be small, since at maximum only 64 target values are being

specified. Here a reference set with high-expressed genes might be as low as 1 gene, but generally one considers 1% of the genome size a representive set of the highly expressed genes, see for example Carbone, A. *et al.* (2003) (Codon adaptation index as a measure of dominating codon bias. *Bioinformatics.* 19(16):2005-15). For the calculation of a codon-pair weight matrix, usually a set of 200-500 reference genes fulfils, which corresponds with 2-7% of a bacterial genome (3000-15000 genes).

Another possibility is to derive a subset of presumably highly expressed genes from literature. For example, for *Bacillus subtilis*, being a model organism, quite some literature on single-codon bias exists. A good overview on the state-of-the-art for *B. subtilis* is given by the work of Kanaya *et al.* (1999). In our approach, see example 4, we group the data in a subset of highly-expressed groups on the basis of mRNA levels measured by Affymetrix technology, and compare these sequences with the whole set of genome ORFs. Other options that have been used in literature are protein expression data, and functional categorical groups of (expected) genes like ribosomal proteins, proteins involved in translation and transcription, sporulation, energy metabolism, and the flagellar system (Kanaya *et al.*, 1999; Karlin and Mrazek, 2000).

Indeed one often finds, for example, high codon bias in the ribosomal proteins, as well as in the other named groups. However, generally not all genes in the latter groups show such behavior. Also, we do not know how ribosomal proteins react in low-growth production conditions. Therefore, a straightforward measurement technique to deriving a subset of highly expressed genes seems to be logic. Then we can choose transcriptomics (TX) and/or proteomics (PX) data. For both there are pros and cons. TX gives a rather complete picture for mRNA levels of genes in the full genome, while PX data might be biased by overrepresentation of water-soluble proteins. TX data is a direct measure for the available mRNA that is subject to translation, while protein is part of an accumulation process in which turnover also plays an important role. Anyway, TX and PX data are shown to correlate for the highly-expressed genes (Gygi et al, 1999). Another interesting work is the prediction of highly-expressed (PHX) genes by deviation from the average codon usage and similarity to ribosomal proteins, and those involved in translation and transcription processing factors, and to chaperone degradation proteins (Karlin and Mrazek, 2000). In particular for fast growing organisms, like *Bacillus*, *E. coli*, etc., major glycolytic genes and tricarboxylic acid cycle genes are found to belong to the above group. The method prediction compares well with known highly-expressed genes at mRNA data and protein expression.

The skilled person will appreciate that both the single codon weights and codon-pair weights w may be determined for modified host cells that have been modified with respect to the

content and nature of their tRNA encoding genes, i.e. host cells comprising additional copies of existing tRNA genes, new (exogenous) tRNA genes, including non-natural tRNA genes, including genes encoding tuna's that have been modified to include non-natural amino-acids or other chemical compounds, as well as host cells in which one or more tRNA genes have been inactivated or deleted.

In the method of the invention, the original coding nucleotide sequence that codes for predetermined amino acid sequence may be selected from: (a) a wild-type nucleotide sequence that codes for the predetermined amino acid sequence; (b) a reverse translation of the predetermined amino acid sequence whereby a codon for an amino acid position in the predetermined amino acid sequence is randomly chosen from the synonymous codons coding for the amino acid; and, (c) a reverse translation of the predetermined amino acid sequence whereby a codon for an amino acid position in the predetermined amino acid sequence is chosen in accordance with a single-codon bias for the predetermined host cell or a species related to the host cell.

Host cells

In the methods of the invention the predetermined host may be any host cell or organism that is suitable for the production of a polypeptide of interest by means of expression of an optimized nucleotide coding sequence. The host cell may thus be a prokaryotic or a eukaryotic host cell. The host cell may be a host cell that is suitable for culture in liquid or on solid media. Alternatively, the host cell may be a cell that is part of a multicellular tissue or and multicellular organism such as a (transgenic) plant, animal or human.

The host cells may be microbial or non-microbial. Suitable non-microbial host cells include e.g. mammalian host cells such as Hamster cells: CHO (Chinese hamster ovary), BHK (Baby Hamster Kidney) cells, mouse cells (e.g. NS0), monkey cells such as COS or Vero; human cells such as PER.C6^{TM} or HEK-293 cells; or insect cells such as Drosophila S2 and Spodoptera Sf9 or Sf21 cells; or plant cells such as tobacco, tomato, potato, oilseed rape, cabbage, pea, wheat, corn, rice, *Taxus* species such as *Taxus brevifolia*, *Arabidopsis* species such as *Arabidopsis thaliana*, and *Nicotiana* species such as *Nicotiana tabacum*. Such non-microbial cells are particularly suitable for the production of mammalian or human proteins for use in mammalian or human therapy.

The host cell may also be microbial host cells such as bacterial or fungal cells. Suitable bacterial host cells include both Gram-positive and Gram-negative bacteria. Examples of suitable bacterial host cells include bacteria from the genera *Bacillus*, *Actinomycetis*,

Escherichia, Streptomyces as well as lactic acid bacteria such as *Lactobacillus*, *Streptococcus, Lactococcus, Oenococcus, Leuconostoc, Pediococcus, Carnobacterium, Propionibacterium, Enterococcus* and *Bifidobacterium.* Particularly preferred are *Bacillus subtilis*, *Bacillus amyloliquefaciens*, *Bacillus licheniformis*, *Escherichia coli*, *Streptomyces coelicolor*, *Streptomyces clavuligerus*, and *Lactobacillus plantarum, Lactococcus lactis.*

Alternatively, the host cell may be a eukaryotic microorganism such as a yeast or a filamentous fungus. Preferred yeasts as host cells belong to the genera *Saccharomyces*, *Kluyveromyces*, *Candida*, *Pichia*, *Schizosaccharomyces*, *Hansenula*, *Kloeckera*, *Schwanniomyces*, and *Yarrowia.* Particularly preferred *Debaromyces* host cells include *Saccharomyces cerevisiae*, and *Kluyveromyces lactis.*

According to a more preferred embodiment, the host cell of the present invention is a cell of a filamentous fungus. "Filamentous fungi" include all filamentous forms of the subdivision Eumycota and Oomycota (as defined by Hawksworth et al., 1995, supra). The filamentous fungi are characterized by a mycelia wall composed of chitin, cellulose, glucan, chitosan, mannan, and other complex polysaccharides. Vegetative growth is by hyphal elongation and carbon catabolism is obligatory aerobic. Filamentous fungal genera of which strains may be used as host cells in the present invention include, but are not limited to, strains of the genera *Acremonium, Aspergillus, Aureobasidium, Cryptococcus, Filibasidium, Fusarium, Humicola, Magnaporthe, Mucor, Myceliophthora, Neocallimastix, Neurospora, Paecilomyces, Penicillium, Piromyces, Schizophyllum, Chrysosporium, Talaromyces, Thermoascus, Thielavia, Tolypocladium*, and *Trichoderma.* Preferably a filamentous fungus belonging to a species selected from the group consisting of *Aspergillus niger, Aspergillus oryzae, Aspergillus sojae, Trichoderma reesei* or *Penicillium chrysogenum.* Example of suitable host strains include: *Aspergillus niger* CBS 513.88 (Pel et al., 2007, Nat Biotech. 25: 221-231), *Aspergillus oryzae* ATCC 20423, IFO 4177, ATCC 1011, ATCC 9576, ATCC14488-14491, ATCC 11601, ATCC12892, *P. chrysogenum* CBS 455.95, *Penicillium citrinum* ATCC 38065, *Penicillium chrysogenum* P2, *Acremonium chrysogenum* ATCC 36225 or ATCC 48272, *Trichoderma reesei* ATCC 26921 or ATCC 56765 or ATCC 26921, *Aspergillus sojae* ATCC11906, *Chrysosporium lucknowense* ATCC44006 and derivatives thereof.

The host cell may be a wild type filamentous fungus host cell or a variant, a mutant or a genetically modified filamentous fungus host cell. Such modified filamentous fungal host cells include e.g. host cells with reduced protease levels, such as the protease deficient strains as *Aspergillus oryzae* JaL 125 (described in WO 97/35956 or EP 429 490); the tripeptidyl-aminopeptidases-deficient *A. niger* strain as disclosed in WO 96/14404, or host cells with

reduced production of the protease transcriptional activator (prtT; as described in WO 01/68864, US2004/0191864A1 and WO 2006/040312); host strains like the *Aspergillus oryzae* BECh2, wherein three TAKA amylase genes, two protease genes, as well as the ability to form the metabolites cyclopiazonic acid and kojic acid have been inactivated (BECh2 is described in WO 00/39322); filamentous fungal host cells comprising an elevated unfolded protein response (UPR) compared to the wild type cell to enhance production abilities of a polypeptide of interest (described in US2004/0186070A1, US2001/0034045A1, WO01/72783A2 and WO2005/123763); host cells with an oxalate deficient phenotype (described in WO2004/070022A2 and WO2000/50576); host cells with a reduced expression of an abundant endogenous polypeptide such as a glucoamylase, neutral alpha-amylase A, neutral alpha-amylase B, alpha-1, 6-transglucosidase, proteases, cellobiohydrolase and/or oxalic acid hydrolase (as may be obtained by genetic modification according to the techniques described in US2004/0191864A1); host cells with an increased efficiency of homologous recombination (having deficient *hdfA* or *hdfB* gene as described in WO2005/095624); and host cells having any possible combination of these modifications.

In a method of the invention, the predetermined amino acid sequence may be an amino acid sequence (of a polypeptide of interest) that is heterologous to said predetermined host cell, or it may be an amino acid sequence (of a polypeptide of interest) that is homologous to said predetermined host cell.

The term "heterologous" when used with respect to a nucleic acid (DNA or RNA) or protein refers to a nucleic acid or protein that does not occur naturally as part of the organism, cell, genome or DNA or RNA sequence in which it is present, or that is found in a cell or location or locations in the genome or DNA or RNA sequence that differ from that in which it is found in nature. Heterologous nucleic acids or proteins are not endogenous to the cell into which it is introduced, but has been obtained from another cell or synthetically or recombinantly produced. Generally, though not necessarily, such nucleic acids encode proteins that are not normally produced by the cell in which the nucleic acid is expressed. Any nucleic acid or protein that one of skill in the art would recognize as heterologous or foreign to the cell in which it is expressed is herein encompassed by the term heterologous nucleic acid or protein. The term heterologous also applies to non-natural combinations of nucleic acid or amino acid sequences, i.e. combinations where at least two of the combined sequences are foreign with respect to each other.

The term "homologous" when used to indicate the relation between a given (recombinant) nucleic acid or polypeptide molecule and a given host organism or host cell, is understood to mean that in nature the nucleic acid or polypeptide molecule is produced by a host cell or organisms of the same species, preferably of the same variety or strain.

The predetermined amino acid sequence may be the sequence of any polypeptide of interest having a commercial or industrial applicability or utility. Thus, the polypeptide of interest may be an antibody or a portion thereof, an antigen, a clotting factor, an enzyme, a hormone or a hormone variant, a receptor or portions thereof, a regulatory protein, a structural protein, a reporter, or a transport protein, intracellular protein, protein involved in secretion process, protein involved in folding process, chaperone, peptide amino acid transporter, glycosylation factor, transcription factor. Preferably, the polypeptide of interest is secreted into the extracellular environment of the host cell by the classical secretion pathway, by a non-classical secretion pathway or by an alternative secretion pathway (described in WO 2006/040340). In case the polypeptide of interest is an enzyme it may e.g. be an oxidoreductase, transferase, hydrolase, lyase, isomerase, ligase, catalase, cellulase, chitinase, cutinase, deoxyribonuclease, dextranase, esterase. More preferred enzymes include e.g. carbohydrases, e.g. cellulases such as endoglucanases, β-glucanases, cellobiohydrolases or β-glucosidases, hemicellulases or pectinolytic enzymes such as xylanases, xylosidases, mannanases, galactanases, galactosidases, pectin methyl esterases, pectin lyases, pectate lyases, endopolygalacturonases, exopolygalacturonases rhamnogalacturonases, arabanases, arabinofuranosidases, arabinoxylan hydrolases, galacturonases, lyases, or amylolytic enzymes; hydrolase, isomerase, or ligase, phosphatases such as phytases, esterases such as lipases, proteolytic enzymes, oxidoreductases such as oxidases, transferases, or isomerases, phytases, aminopeptidases, carboxypeptidases, endo-proteases, metallo-proteases, serine-proteases, catalases, chitinases, cutinases, cyclodextrin glycosyltransferases, deoxyribonucleases, alpha-galactosidases, beta-galactosidases, glucoamylases, alpha-glucosidases, beta-glucosidases, haloperoxidases, invertases, laccases, mannosidase, mutanases, peroxidases, phospholipases, polyphenoloxidases, ribonucleases, transglutaminases, glucose oxidases, hexose oxidases, and monooxygenases. Several therapeutic proteins of interest include e.g. antibodies and fragment thereof, human insulin and analogs thereof, human lactoferrin and analogs thereof, human growth hormone, erythropoietin, tissue plasminogen activator (tPA) or insulinotropin. The polypeptide may be involved in the synthesis of a metabolite, preferably citric acid. Such polypeptides e.g. include: aconitate hydratase, aconitase hydroxylase, 6-phosphofructokinase, citrate synthase, carboxyphosphonoenolpyruvate phosphonomutase, glycolate reductase, glucose

oxidase precursor goxC, nucleoside-diphosphate-sugar epimerase, glucose oxidase, Manganese-superoxide-dismutase, citrate lyase, ubiquinone reductase, carrier proteins, citrate transporter proteins, mitochondrial respiratory proteins and metal transporter proteins.

Computer, program and data carrier

In a further aspect the invention relates to a computer comprising a processor and memory, the processor being arranged to read from said memory and write into said memory, the memory comprising data and instructions arranged to provide said processor with the capacity to perform the method of the invention.

In another aspect the invention relates to a computer program product comprising data and instructions and arranged to be loaded in a memory of a computer that also comprises a processor, the processor being arranged to read from said memory and write into said memory, the data and instructions being arranged to provide said processor with the capacity to perform the method of the invention.

In yet another aspect the invention relates to a data carrier provided with a computer program product as defined above.

Nucleic acid molecules

In a further aspect the invention relates to a nucleic acid molecule comprising a coding sequence coding for a predetermined amino acid sequence. The coding sequence preferably is a nucleotide sequence that does not resemble a naturally occurring coding sequence. Rather the coding sequence in the nucleic acid molecule is a nucleotide sequence that is not found in nature but is an artificial, i.e. an engineered, man-made nucleotide sequence that was generated on the basis of the method for optimization of single codon and/or codon pair bias for a predetermined host cell in accordance with the methods defined herein and that was subsequently synthesized as a tangible nucleic acid molecule. Preferably, the coding sequence has a $fit_{sc}(g)$ of at least below 0.2, or more preferably below 0.1 and most preferably below 0.02 for a predetermined host cell. More preferably, the coding sequence has a $fit_{cp}(g)$ of at least below 0 for a predetermined host cell. Most preferably, the coding sequence has a $fit_{cp}(g)$ of at least below –0.1 for a predetermined host cell, or more preferably at least below -0.2. Preferably the number of codon-pair in an optimized gene g contains at least 60, 70, 75, 80, 85% codon pairs and most preferably at least 90% codon pairs with associated negative codon-pairs for the specified host organisms

The predetermined amino acid sequence encoded by the coding sequence may be any polypeptide of interest as herein defined above and also the predetermined host cell may be any host cell as defined above herein.

In the nucleic acid molecule, the coding sequence preferably is operably linked to an expression control sequence that are capable of directing expression of the coding sequence in the predetermined host cell. In the context of the invention, a control sequence is defined as a nucleotide sequence operatively associated to a coding sequence when present together and which include all components necessary or advantageous for expression of the nucleotide sequence encoding the polypeptide to be produced. Each control sequence may be native or foreign to the nucleotide sequence encoding the polypeptide to be produced. Such control sequences may include, but are not limited to, a leader sequence, a polyadenylation sequence, a propeptide sequence, a promoter, a translational initiator sequence, a translational initiator coding sequence, a translational transcription terminator and a transcription terminator sequence. The control sequences may be provided with linkers, e.g., for the purpose of introducing specific restriction sites facilitating ligation of the control sequences with the coding region of the nucleotide sequence encoding a polypeptide.

Expression control sequences will usually minimally comprise a promoter. As used herein, the term "promoter" refers to a nucleic acid fragment that functions to control the transcription of one or more genes, located upstream with respect to the direction of transcription of the transcription initiation site of the gene, and is structurally identified by the presence of a binding site for DNA-dependent RNA polymerase, transcription initiation sites and any other DNA sequences, including, but not limited to transcription factor binding sites, repressor and activator protein binding sites, and any other sequences of nucleotides known to one of skill in the art to act directly or indirectly to regulate the amount of transcription from the promoter. A "constitutive" promoter is a promoter that is active under most environmental and developmental conditions. An "inducible" promoter is a promoter that is active under environmental or developmental regulation.

A DNA segment such as an expression control sequence is “operably linked” when it is placed into a functional relationship with another DNA segment. For example, a promoter or enhancer is operably linked to a coding sequence if it stimulates the transcription of the sequence. DNA for a signal sequence is operably linked to DNA encoding a polypeptide if it is expressed as a pre-protein that participates in the secretion of the polypeptide. Generally, DNA sequences that are operably linked are contiguous, and, in the case of a signal sequence, both contiguous and in reading phase. However, enhancers need not be contiguous with the coding

sequences whose transcription they control. Linking is accomplished by ligation at convenient restriction sites or at adapters, linkers, or PCR fragments by means know in the art.

The selection of an appropriate promoter sequence generally depends upon the host cell selected for the expression of the DNA segment. Examples of suitable promoter sequences include prokaryotic, and eukaryotic promoters well known in the art (see, e.g. Sambrook and Russell, 2001, "Molecular Cloning: A Laboratory Manual (3rd edition), Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, New York). The transcriptional regulatory sequences typically include a heterologous enhancer or promoter that is recognized by the host. The selection of an appropriate promoter depends upon the host, but promoters such as the trp, lac and phage promoters, tRNA promoters and glycolytic enzyme promoters are known and available (see, e.g. Sambrook and Russell, 2001, *supra*). Examples of preferred inducible promoters that can be used are a starch-, copper-, oleic acid-inducible promoters. Preferred promoters for filamentous fungal host cells e.g. include the glucoamylase promoter of *A. niger* or the TAKA amylase promoter of *A. oryzae* and the promoters described in WO2005/100573.

The nucleotide sequence of the invention may further comprise a signal sequence, or rather a signal peptide-coding region. A signal sequence codes for an amino acid sequence linked to the amino terminus of the polypeptide, which can direct the expressed polypeptide into the cell's secretory pathway. Signal sequences usually contain a hydrophobic core of about 4-15 amino acids, which is often immediately preceded by a basic amino acid. At the carboxyl-terminal end of the signal peptide there are a pair of small, uncharged amino acids separated by a single intervening amino acid that defines the signal peptide cleavage site. von Heijne, G. (1990) J. Membrane Biol. 115: 195-201. Despite their overall structural and functional similarities, native signal peptides do not have a consensus sequence. Suitable signal peptide-coding regions may be obtained from a glucoamylase or an amylase gene from an *Aspergillus* species, a lipase or proteinase gene from a *Rhizomucor* species, the gene for the alpha-factor from *Saccharomyces cerevisiae*, an amylase or a protease gene from a *Bacillus* species, or the calf pre-pro-chymosin gene. However, any signal peptide-coding region capable of directing the expressed protein into the secretory pathway of a host cell of choice may be used in the present invention. Preferred signal peptide coding regions for filamentous fungus host cells are the signal peptide coding region obtained from *Aspergillus oryzae* TAKA amylase gene (EP 238 023), *Aspergillus niger* neutral amylase gene, *Aspergillus niger* glucoamylase, the *Rhizomucor miehei* aspartic proteinase gene, the *Humicola lanuginosa* cellulase gene, *Humicola insolens* cellulase, *Humicola insolens* cutinase the *Candida antarctica* lipase B gene or the *Rhizomucor miehei* lipase gene and mutant, truncated, and hybrid signal sequence thereof. In a preferred

embodiment of the invention the nucleotide sequence encoding the signal sequence is an integral part of the coding sequence that is optimized with respect to single codon and/or codon pair bias for the predetermined host.

In the nucleic acid molecule of the invention, the coding sequence is further preferably operably linked to a translational initiator sequence. In eukaryotes, the nucleotide consensus sequence (6-12 nucleotides) before the initiator ATG-codon is often called Kozak consensus sequence due to the initial work on this topic (Kozak, M. (1987): an analysis of 5'-noncoding sequences from 699 vertebrate messenger RNAs. *Nucl. Acid Res.* 15(20): 8125-47). The original Kozak consensus sequence CCCGCCGCCrCC(ATG)G, including a +4 nucleotide derived by Kozak is associated with the initiation of translation in higher eukaryotes. For prokaryote host cells the corresponding Shine-Delgarno sequence (AGGAGG) is preferably present in the 5'-untranslated region of prokaryotic mRNAs to serve as a translational start site for ribosomes.

In the context of this invention, the term "translational initiator sequence" is defined as the ten nucleotides immediately upstream of the initiator or start codon of the open reading frame of a DNA sequence coding for a polypeptide. The initiator or start codon encodes for the amino acid methionine. The initiator codon is typically ATG, but may also be any functional start codon such as GTG, TTG or CTG.

In a particularly preferred embodiment of the invention, the nucleic acid molecule comprises a coding sequence coding for a predetermined amino acid sequence that is to be expressed in a fungal host cell, i.e. the predetermined host cell is preferably a fungus of which filamentous fungi are most preferred. Nucleic acid molecules comprising coding sequences that are optimized for expression in fungi in accordance with the invention may further comprise the one or more of the following elements: 1) a fungal consensus translational initiator sequence; 2) a fungal translational initiator coding sequence; and 3) a fungal translational termination sequence.

A consensus fungal translational initiator sequence preferably is defined by the following sequences: 5'-mwChkyCAmv-3', using ambiguity codes for nucleotides: m (A/C); r (A/G); w (A/T); s (C/G); y (C/T); k (G/T); v (A/C/G); h (A/C/T); d (A/G/T); b (C/G/T); n (A/C/G/T). According to a more preferred embodiment, the sequences are: 5'-mwChkyCAAA-3'; 5'-mwChkyCACA-3' or 5'-mwChkyCAAG-3'. Most preferably the translational initiation consensus sequence is 5'-CACCGTCAAA-3' or 5'-CGCAGTCAAG-3'.

In the context of this invention, the term "consensus translational initiator coding sequence" is defined herein as the nine nucleotides immediately downstream of the initiator codon of the open reading frame of a coding sequence (the initiator codon is typically ATG, but

may also be any functional start codon such as GTG). A preferred fungal consensus translational initiator coding sequence has the following nucleotide sequence: 5'-GCTnCCyyC-3', using ambiguity codes for nucleotides y (C/T) and n (A/C/G/T). This leads to 16 variants for the translational initiator coding sequence of which 5'- GCT TCC TTC -3' is most preferred. Using a consensus translational initiator coding sequence, the following amino acids are allowed at the amino acid positions mentioned: alanine at +2, alanine, serine, proline, or threonine at +3, and phenylalanine, serine, leucine or proline at +4 position in the polypeptide that is encoded. Preferably in the present invention, the consensus translational initiator coding sequence is foreign to the nucleic acid sequence encoding the polypeptide to be produced, but the consensus translational initiator may be native to the fungal host cell.

In the context of this invention, the term "translational termination sequence" is defined as the four nucleotides starting from the translational stop codon at the 3' end of the open reading frame or coding sequence. Preferred fungal translational termination sequence include: 5'-TAAG-3', 5'- TAGA-3' and 5'-TAAA-3', of which 5'-TAAA-3' is most preferred.

A coding sequence coding for a predetermined amino acid sequence that is to be expressed in a fungal host cell is further preferably optimized with respect to single codon frequency such that at least one, two, three, four or five original codons, more preferably at least 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 50%, 75%, 80%, 85%, 90%, or 95% of the original codons have been exchanged with a synonymous codon, the synonymous codon encoding the same amino acid as the native codon and having a higher frequency in the codon usage as defined in the Table A than the original codon.

Table A: Optimal filamentous fungal codon frequency for synonymous codons in %.

	.T.	.C.	.A.	.G.	
T . .	Phe 0	Ser 21	Tyr 0	Cys 0	. . T
T . .	Phe 100	Ser 44	Tyr 100	Cys 100	. . C
T . .	Leu 0	Ser 0	Stop 100	Stop 0	. . A
T . .	Leu 13	Ser 14	Stop 0	Trp 100	. . G
C . .	Leu 17	Pro 36	His 0	Arg 49	. . T
C . .	Leu 38	Pro 64	His 100	Arg 51	. . C
C . .	Leu 0	Pro 0	Gln 0	Arg 0	. . A

C . .	Leu 32	Pro 0	Gln 100	Arg 0	. . G
A . .	Ile 27	Thr 30	Asn 0	Ser 0	. . T
A . .	Ile 73	Thr 70	Asn 100	Ser 21	. . C
A . .	Ile 0	Thr 0	Lys 0	Arg 0	. . A
A . .	Met 100	Thr 0	Lys 100	Arg 0	. . G
G . .	Val 27	Ala 38	Asp 36	Gly 49	. . T
G . .	Val 54	Ala 51	Asp 64	Gly 35	. . C
G . .	Val 0	Ala 0	Glu 26	Gly 16	. . A
G . .	Val 19	Ala 11	Glu 74	Gly 0	. . G

A even more preferred coding sequence coding for a predetermined amino acid sequence that is to be expressed in a fungal host cell is further preferably optimized with respect to single codon frequency such that at least one, two, three, four or five original codons, more preferably at least 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 50%, 75%, 80%, 85%, 90%, or 95% of the original codons have been exchanged with a synonymous codon, the synonymous codon changing the codon frequency such that the value of the absolute difference between the percentage for said codon in said frequency and listed optimal percentage becomes smaller after modification, applying the following list of optimal percentages: cysteine encoded by TGC (100%); phenylalanine by TTC (100%); histidine by CAC (100%); lysine by AAG (100%); asparagine by AAC (100%); glutamine by CAG (100%); tyrosine by TAC (100%); alanine by GCT (38.0%) , GCC (50.7%), or GCG (11.3%); aspartate by GAC (63.2%); glutamate by GAG (74.2%); glycine by GGT (49.0%), GGC (35.9%), GGA (15.1%); isoleucine by ATT (26.7%), ATC (73.3%); leucine by TTG (12.7%), CTT (17.4%), CTC (38.7%), CTG (31.2%); proline by CCT (35.6%), CCC (64.4%); arginine by CGT (49.1%), CGC (50.9%); serine by TCT (20.8%), TCC (44.0%), TCG (14.4%), AGC (20.8%); threonine by ACT (29.7%), ACC (70.3%) and/or valine by GTT (27.4%), GTC (54.5%), GTG (18.1%); all other possible amino acid encoding codons (0%).

The above defined nucleic acid molecules comprising the coding sequences of the invention (for expression in a predetermined host cell) may further comprise the elements that are usually found in expression vectors such as a selectable marker, an origin of replication and/or sequences that facilitate integration, preferably through homologous recombination at a

predetermined site in the genome. Such further elements are well known in the art and need no further specification herein.

In a further aspect the invention pertains to a host cell comprising a nucleic acid molecule as defined herein above. The host cell preferably is a host cell as herein defined above.

In yet a further aspect the invention relates to a method for producing a polypeptide having the predetermined amino acid sequence. The method preferably comprises culturing a host cell comprising a nucleic acid molecule as defined herein above, under conditions conducive to the expression of the polypeptide and, optionally, recovery of the polypeptide.

In again a further aspect the invention relates to method for producing at least one of an intracellular and an extracellular metabolite. The method comprising culturing a host cell as defined in herein above under conditions conducive to the production of the metabolite. Preferably, in the host the polypeptide having the predetermined amino acid sequence (that is encoded by the nucleic acid molecule as defined above) is involved in the production of the metabolite. The metabolite (be it a primary or secondary metabolite, or both; be it intra-, extracellular or both) may be any fermentation product that may be produced in a fermentation process. Such fermentation products e.g. include amino acids such as lysine, glutamic acid, leucin, threonin, tryptophan; antibiotics, including e.g. ampicilline, bacitracin, cephalosporins, erythromycin, monensin, penicillins, streptomycin, tetracyclines, tylosin, macrolides, and quinolones; preferred antibiotics are cephalosporins and beta-lactams; lipids and fatty acids including e.g. poly unsaturated fatty acids (PUFAs); alkanol such as ethanol, propanol and butanol; polyols such as 1,3-propane-diol, butandiol, glycerol and xylitol; ketons such as aceton; amines, diamines, ethylene; isoprenoids such as carotenoids, carotene, astaxanthin, lycopene, lutein; acrylic acid, sterols such as cholesterol and ergosterol; vitamins including e.g. the vitamins A, B2 B12, C, D, E and K, and organic acids including e.g. glucaric acid, gluconic acid, glutaric acid, adipic acid, succinic acid, tartaric acid, oxalic acid, acetic acid, lactic acid, formic acid, malic acid, maleic acid, malonic acid, citric acid, fumaric acid, itaconic acid, levulinic acid, xylonic acid, aconitic acid, ascorbic acid, kojic acid, and comeric acid; a preferred organic acid is citric acid.

In this document and in its claims, the verb "to comprise" and its conjugations is used in its non-limiting sense to mean that items following the word are included, but items not specifically mentioned are not excluded. In addition, reference to an element by the indefinite article "a" or "an" does not exclude the possibility that more than one of the element is present, unless the context clearly requires that there be one and only one of the elements. The indefinite article "a" or "an" thus usually means "at least one".

Examples

1. Example 1: Analysis of codon pair bias

1.1 Material and methods

1.1.1 Data and software

Codon pair analysis may be performed on coding sequences (CDS) in whole genome sequence data as well as partial groups derived of those (or a partial genome sequence, like for example cDNA/EST libraries, or even partial genome data from multiple genomes from related organisms). The tools used in the present invention read these data using FASTA files as input. The vast majority of all calculations have been performed in MATLAB 7.01 (The MathWorks, Inc., www.mathworks.com), but for some detailed analyses of the obtained results Spotfire DecisionSite 8.0 (Spotfire, Inc., http://www.spotfire.com/products/decisionsite.cfm) was used.

For *A. niger*, a FASTA file with predicted cDNA sequences for the full genome of CBS513.88 (Pel et al., 2007, Nat Biotech. 25: 221-231) and a group of 479 highly expressed genes were used. Furthermore, since usually less than half of the >14,000 genes in *A. niger* are expressed at the same time under pilot-scale fermentation conditions, data from 24 GeneChips obtained using such conditions was used to extract a second set of genes that includes only genes that are actually expressed within various experiments (taking only genes with at least 18 'present' calls into account, using Affymetrix MAS5.0 array analysis software; this set comprised 4,584 genes) and to rank them according to observed mRNA level (since no other data was available at that time), so a set of (presumably) highly expressed genes of any size can be identified easily. This second set was created to be able to rank the data according to their expression level.

For this analysis we have used transcription levels of the genes. Alternatively one can also apply quantitative protein expression data, *e.g.* by two-dimensional gel electrophoresis of the proteins and subsequent identification via mass spectrometry. However, generating protein expression on large sets of proteins is still quite time consuming in comparison with determination of mRNA levels (*e.g.* using genechips). Therefore, what is done here is to study the effect of codon bias on translation *before* translation has actually happened. Gygi *et al.* (Yeast. Mol. Cel. Biol. 19(3):1720-30) actually found a "correlation of protein and mRNA expression levels with codon bias" in *E. coli*, even although the correlation of mRNA and protein expression levels was rather rudimentary only. Hence, the term "expression level" will be used in this text when actually only the effect on the transcription level has been determined.

For *Bacillus subtilis*, an organism containing around 4,000 genes, a group of 300 highly expressed genes was available and has been analyzed. See Table 1.1 for an overview of the

basic properties of the genomes of all organisms that have been taken into account in this study (however, not all of them will be described in detail).

In every analysis, (putative) genes that included one or more stop codons at another position than the end and sequences with a length not divisible by three (i.e. where a frameshift might have occurred during sequencing) have been ignored. Also the first five and the last five codons of every gene have not been taken into account because these sites might be involved in protein binding and releasing efficiency and therefore be subject to different selection pressures than the other parts of the sequence, so codon and codon pair bias there might not be representative. ORFs (ORF = open reading frame) shorter than 20 codons have also been omitted from the analysis. In Table 1.1 this is already taken into account.

Table 1.1 Nucleotide content of several organisms, including number of ORF's and genome size in Megabasepair (Mbp).

name of organism	# of ORFs	Mbp	nucleotide content			
			A	C	G	T
A. nidulans	7,782	10.61	24%	28%	26%	22%
A. niger	13,962	18.41	24%	27%	26%	22%
A. oryzae	12,074	16,29	25%	26%	26%	23%
B. amyloliquefaciens	4,449	3,54	26%	24%	27%	23%
B. subtilis	4,104	3.66	30%	20%	24%	26%
E. coli K12	4,289	4.09	24%	25%	27%	24%
K. lactis	5,336	7.52	32%	19%	21%	28%
P. chrysogenum	13,164	17.54	24%	27%	25%	23%
S. cerevisiae	6,449	9.01	33%	19%	20%	28%
S. coelicolor	7,894	7.62	14%	37%	35%	13%
T. reesei	8,331	11.45	23%	30%	28%	20%

1.1.2 Expected occurrences of codon pairs

In order to analyze codon pair usage, first the occurrences of every single codon and every codon pair have been counted, below denoted by $n_{obs}((c_i, c_j))$, where *obs* stands for *observed.* The double parenthesis are necessary to indicate that "observed number", *i.e.* n_{obs}, is a function with just one argument, which itself is a pair (in that case: a pair of codons, *i.e.* (c_i,c_j)). The same applies to all functions on codon pairs defined below. The indices *i*, *j* and also *k* can be 1 to 64, indicating the number of the codon in the internal representation (according to their alphabetical order). (c_i,c_j) denoting a codon pair with c_i being the left codon (*i.e.* the 5' triplet of the 6-nucleotide sequence) and right c_j one (*i.e.* closer to the 3'-end), as well as the number of

occurrences $n_{sc}^{all}(c_k)$ for every codon c_k (where the subscript *sc* stands for *single codon* and the superscript *all* indicates that the number refers to the full genome, as opposed to $n_{sc}^{g}(c_k)$, which will be used to denote codon ratios in a single gene *g*; functions of codon pairs like $n_{obs}((c_i,c_j))$ always refer to the number in the full genome or a larger group of genes). Single codon ratios (Note that in some papers these ratios are also called frequencies. However, codon frequencies may also refer to the number of occurrences of a codon divided by the total number of all codons) were then calculated

$$r_{sc}^{all}(c_k) = n_{sc}^{all}(c_k) \Big/ \sum_{c_l \in syn(c_k)} n_{sc}^{all}(c_l)$$

where $syn(c_k)$ denotes the set of codons that encode for the same amino acid as c_k and are thus synonymous to c_k. Thus, the value of the sum below the fraction bar equals the number of occurrences of the amino acid encoded by c_i in the whole proteome. See Appendix 1 for a concise list of the most important symbols and formulas used here.

To reveal whether certain alleged codon pair preferences are only the result of preferences of the individual codons, it is necessary to calculate expected values for every codon pair based on individual codon frequencies. These have been calculated using the formula

$$n_{exp}^{own}((c_i,c_j)) = r_{sc}^{all}(c_i) \cdot r_{sc}^{all}(c_j) \cdot \sum_{\substack{c_m \in syn(c_i) \\ c_n \in syn(c_j)}} n_{obs}((c_m,c_n))$$

The superscript *own* is used to distinguish the values from those obtained using other methods mentioned later. In the last factor of this equation, the actual numbers of occurrences of all synonymous codon pairs are summed up. Thus, the expected amount of each codon pair is the product of the individual codon usage ratios and the number of occurrences of the respective amino acid pair.

Gutman and Hatfield (1989, Proc. Natl. Acad. Sci USA 86:3699-3703) proposed another method of calculating expected values. Their initial approach was to calculate the codon frequencies (i.e. the amount of codons in a gene *g* divided by the total number of codons in *g*, denoted |*g*|) for every gene individually, and then multiply these values pair wise and with the number of codon pairs in that sequence (which is |*g*|-1).

$$n_{exp}^{gh1}((c_i,c_j)) = \sum_{g \in ORFs} \frac{n_{sc}^{g}(c_i)}{|g|} \cdot \frac{n_{sc}^{g}(c_j)}{|g|} \cdot (|g|-1) \ .$$

In this equation "*gh1*" denotes Gutman and Hatfield method 1 (1989, *supra*). This results in expected codon pair values for each gene (the part after the sum operator in the equation above), which are then added up, resulting in final expected values that are by definition

adjusted for possible deviations in single codon usage among different genes of the same genome, but do not take a possible bias in amino acid pair usage into account. This means that if certain amino acids tend to be next to each other more often than others, or, in other words, if the numbers of occurrences of the amino acid pairs are not similar to what they would be in randomized sequences with the same amino acid composition, the expected values would also be significantly different in that codon pairs encoding rather rarely used amino acid pairs would have too high expected values and those of more often used amino acid pairs too low ones.

Gutman and Hatfield (1989, *supra*) also proposed a method of normalizing their expected values for amino acid pair bias. Therefore, they simply compared the expected number of amino acid pairs according to their methods with the observed ones and scaled the expected values of all affected codon pairs accordingly to make the former match the latter:

$$n_{exp}^{gh2}((c_i,c_j)) = n_{exp}^{ghl}((c_i,c_j)) \cdot \frac{\sum_{\substack{c_m \in syn(c_i) \\ c_n \in syn(c_j)}} n_{obs}((c_m,c_n))}{\sum_{\substack{c_m \in syn(c_i) \\ c_n \in syn(c_j)}} n_{exp}^{ghl}((c_m,c_n))}$$

In this equation "*gh2*" denotes Gutman and Hatfield method 2 (1989, *supra*).

1.1.3 Calculating codon pair bias

The actual codon pair bias $bias((c_i,c_j))$ should then result from the difference between the expected and actual (observed) numbers of the codon pairs (where any of these methods for the expected values can be used). The initial approach was to calculate it simply by

$$bias_1((c_i,c_j)) = \frac{n_{obs}((c_i,c_j)) - n_{exp}((c_i,c_j))}{n_{exp}((c_i,c_j))}.$$

This way, the bias value would indicate how many percent more or less often than expected the codon pair is actually used (if multiplied by 100%, that is). For amino acid pairs not occurring in an analyzed set of genes, the bias value according to the formula would be 0/0 for all corresponding codon pairs. In that case, it is defined to be 0. The lower limit of the bias values would thus be -1, whereas there is no clear upper limit. This was considered somewhat impractical, so instead

$$bias((c_i,c_j)) = \frac{n_{obs}((c_i,c_j)) - n_{exp}((c_i,c_j))}{\max(n_{obs}((c_i,c_j)), n_{exp}((c_i,c_j)))}$$

was used, where max(a,b) denotes the greater of the two values a and b, which always results in a bias value in (-1,1). This means that the bias value can be -1, but not +1. The former happens when a certain codon pair is not used at all to encode for an amino acid pair that really occurs;

the value +1 can not be reached because $n_{\exp}((c_i,c_j))$ would have to be 0 then, but this is only possible when $n_{obs}((c_i,c_j))$ is 0, too.

The interpretation given above is still valid for bias values <0 (which means that $n_{obs}((c_i,c_j)) < n_{exp}((c_i,c_j))$, so both formulas have the same result). If $n_{obs}((c_i,c_j)) > n_{exp}((c_i,c_j))$, the bias values (which are >0 then) indicate how many percent lower than the observed value the expected value is (i.e. in that case the baseline is changed).

1.1.4 Statistical significance of the bias

Gutman and Hatfield (1989, *supra*) used a χ^2-test to determine the statistical significance of their results. This test is used to check how likely it is that certain observed results occurred by chance under a specific hypothesis. When examining codon pairs, this hypothesis would be that the codon pair usage is the result of a random selection of every codon independently. To test this hypothesis, a χ^2-value is calculated

$$\chi^2 = \sum_{(c_m,c_n)\in CP} \frac{(n_{obs}((c_m,c_n)) - n_{exp}((c_m,c_n)))^2}{n_{exp}((c_m,c_n))}$$

(with CP denoting the set of all codon pairs not including a stop codon). The number of degrees of freedom is then 3720 (61*61-1). If codon pair selection were random, one would expect the χ^2-value to be around 3720 (equal to the number of degrees of freedom) with a standard deviation equal to the square root of 2*degrees of freedom.

This way, the overall statistical significance of the observed bias can be tested. However, one can also deduce the statistical significance of the bias of individual codon pairs. As for the method of calculating expected values proposed earlier, the number of occurrences of a codon pair is considered to be the result of a sequence of independent yes/no experiments (yes: these two codons are selected for encoding the respective amino acid pair; no: another codon pair is selected), so it follows a binomial distribution, which can be approximated by a normal distribution if the set of analyzed genes is sufficiently large. This is considered a good approximation if n*p>4, where n stands for the number of experiments and p for the probability of "yes", which is also the expected value. Therefore, for every codon pair a standard deviation can be calculated according to the formula

$$\sigma((c_i,c_j)) = \sqrt{n_{exp}((c_i,c_j)) \cdot (1 - r_{sc}^{all}(c_i) \cdot r_{sc}^{all}(c_j))}\,.$$

Then, the standard scores, also referred to as z-scores, can be calculated

$$z((c_i,c_j)) = \frac{(n_{obs}((c_i,c_j)) - n_{exp}((c_i,c_j))}{\sigma((c_i,c_j))}.$$

The absolute value of the z-score tells how many standard deviations away from the expected value the actual (observed) value is. Assuming a normal distribution, approximately 95% of all observations should be within two standard deviations from the expected value and >99% within three.

1.2 Results

1.2.1 Existence of codon pair bias

Using the above methods we have found that significant codon pair biases exist. For all investigated organisms, the χ^2-test delivered χ^2-values several times as high as the number of degrees of freedom and thus also many standard deviations above the expected value. As for the bias of individual codon pairs, the finding of Moura et al. that in yeast "about 47% of codon-pair contexts fall within the interval -3 to +3" standard deviations away from the expected values (although they calculated the expected values in a different way), which corresponds to the z-scores in our analysis, could be confirmed. Overall, there are significantly more codon pairs with rather high z-scores than there should be if codon pair usage were random. See Table 1.2: with a random selection, which would result approximately in a normal distribution, for example only about 5% of all codon pairs should have a z-score greater than 2 or less than -2, but in the whole genome of the selected four organisms, this actually applies to more than two thirds.

Table 1.2. Z-scores in different organisms

|z-score|	>1	>2	>3
normal distribution	68.3%	5.0 %	0.3 %

A. nidulans	86.1%	73.7%	60.4%
A. niger	89.2%	79.1%	69.7%
A. oryzae	88.4%	76.7%	65.1%
B. amyloliquefaciens	88.1%	76.4%	64.0%
B. subtilis	86.1%	72.0%	59.3%
E. coli K12	86.1%	74.8%	64.0%
K. lactis	82.6%	67.0%	53.4%
P. chrysogenum	89.3%	79.1%	69.0%
S. cerevisiae	82.7%	67.6%	52.1%
S. coelicolor	82.0%	66.5%	53.5%
T. reesei	89.0%	79.8%	71.0%

Note that these values are somewhat correlated with genome size (see Table 1.1 for a comparison), i.e. organism with larger genomes tend to have codon pairs with more extreme z-scores. Especially when analyzing smaller groups of genes (e.g. 479 highly expressed ones in *A. niger*), the values are lower (for this example: 65.1%, 37.2% and 19.7%, respectively), as smaller numbers of occurrences lead to higher standard deviations (compared to the expected values) and thus to less statistical significance of the results. This leads to the conclusion that codon pair usage is not the result of a random selection of the codons according to the single codon ratios.

The distribution of the bias values themselves differs from one organism to another. This can be explained with reference to Figure 3 which shows the distribution of codon pair bias values for the 3,721 sense:sense codon pairs in different organisms. The numbers in the top right corner of each histogram in Figure 3 are the standard deviations for the observed distribution; the mean values (not shown) are between -0.06 and -0.01 for all organisms. In the histograms shown in Figure 3, one can see that out of the ten tested organisms, the bacteria *E. coli, B. subtilus*, *B. amiloliquefaciens* and *S. coelicolor* have the most extreme codon pair bias, whereas bias in the fungi *A. niger*, *A. oryzae, A. terreus*, *A. nidulans, P. chrysogenum* and yeasts *S. cerevisiae* and *K. lactis*, is less extreme.

Another interesting observation can be made when comparing codon pair bias of different organisms. Bias values from related organisms show a higher correlation than those from unrelated organisms. This is explained with reference to Figure 4. Figure 4 shows correlation in codon pair bias of various organisms. A correlation coefficient is shown in the top right corner

of each subplot. In this analysis, the highest correlations could be observed between *A. niger* vs. *P. chrysogenum*, and *A. niger* vs. *A. oryzae*, the lowest, *i.e.* effectively no correlation could be observed between *B. subtilis* and *S. coelicolor*. Interestingly, no negative correlations have been observed. This means that although organisms with a high GC-content (like *S. coelicolor*) mostly prefer those codons that are the less used ones in AT-rich organisms (like *S. cerevisiae* or, although not extremely AT-rich, *B. subtilis*), there are no two organism where the preferred pairs of one organism were likely to be rejected in the other and vice versa. This could mean that although bias of almost every single codon is organism-dependent, there are several codon pairs that are preferred and/or rejected in almost every organism (*e.g.* because of their likeliness to cause frameshifts or tRNAs with not matching structure).

1.2.2 Patterns in codon pair bias

In order to visualize the observed codon pair bias, so-called maps can be drawn as has been done by Moura et al. (2005) (they refer to these maps as "codon context maps"). This can be most easily explained with reference to colored images that consist of colored rectangles for every codon pair, with the rows representing the first and the columns representing the second codon of the pair. Red colors indicate a negative and green ones a positive bias. White represents codon pairs that really have a bias equal 0 (which is the case for ATG-ATG, for example, since that is the only way to encode the amino acid pair Met-Met) and pairs incorporating a stop codon.

However, colored images cannot be part of the disclosure of a patent application. For black & white visualization, the image will be split in two images in this example. Figure 5A displays the positive codon pairs for *A. niger*, while Figure 5B displays the negative codon pairs for *A. niger* (see also Appendix 3, Table C1). The more biased the codon-pair, the more black the corresponding rectangle. The bias values here range from –0.67 to 0.54, where in other organisms they might even get slightly above +/-0.9 (see also figure 3). The highest intensities of black (original green (top) and black (original red (bottom)) in these diagrams represent values of 0.9 and -0.9, respectively (not reached here; mostly, the absolute values of the maximum bias are slightly lower than those of the minimum bias.

In addition, we refer to CPW matrix-tables in Appendix 3, which contain the numerical values of the bias of the codon pairs and we refer to Figure 5 as a black and white example of the colored image, whereby the skilled person may reconstruct a colored version using the numerical values from the tables in Appendix 3.

The first approach to these codon pair maps was to have the rows and columns sorted according to their alphabetical order (as this is the order of their internal representation). What could be seen in that map was that the diagonals seemed to contain slightly more green than red spots, which indicates that many codons have a preference for the same codon as its neighbor. Furthermore, most neighboring columns were somewhat similar where neighboring rows were mostly not (data not shown) see Figures 5A and 5B and Appendix 3, Table C1. However most rows were similar to a row separated by three others, i.e. there was some similarity of every fourth row.

Since the common property of every fourth row is the last nucleotide of the first codon of the pairs, it is more preferred to sort rows sorted according to the alphabetical order of the third position as first sorting criterion and the middle position as second. What can then be seen in the map for *A. niger* (Figures 5C and D, and Appendix 3, Table C1) is that bias seems to correlate indeed mainly with the last nucleotide of the first (5') and the first nucleotide of the second (3') codon, as most values of the respective blocks of 16*16 codon pairs have the same color. For example, a general rule that can be identified in Aspergillus is that codon pairs like xxT-Axx (x denoting any nucleotide, indicating that the one at the respective position is not important for the specified rule) are rejected (red block in the lower left corner), whereas the pattern xxA-Txx characterizes preferred codons (green block in the top right corner), again indicating that codon pair bias is directional. However, not all bias can be explained just with patterns in the two neighboring nucleotides in the "middle" of the codon pair. xxC-Axx codon pairs, for example (see second block from top on the very left), are not generally preferred or rejected, but there is a clear preference for pairs of the pattern xxC-AAx (note the four green columns on the left of the block just mentioned). Bias can also depend on not neighboring nucleotides (e.g. the strong rejection of CxA-Gxx pairs in *B. subtilis*; see Figures 6A and 6B and Appendix 3, Table C4). Unfortunately, codon pair bias cannot always be attributed to such "simple" patterns (see for example the rather chaotic map for *E. coli* in Figures 7A and B and Appendix 3, Table C5) – even when performing a cluster analysis using Spotfire DecisionSite 8.0 (http://www.spotfire.com/products/decisionsite.cfm) no general properties could be found (data not shown), i.e. the identified clusters consisted mostly of unrelated codons (i.e. no common nucleotides at the same position).

1.2.3 Relation of bias and expression level

Looking at the bias map for the genes with high expression level (or better: presumably high expression level, since they were identified by looking at transcription levels only) of

A. niger (see Figure 8), the existence of larger groups, i.e. blocks in the diagram, is not as obvious (or, in other words, simple rules as described above might not exist at all). Yet since two thirds of all codon pairs occur 36 or less times in this group, and because of the on average much lower z-scores as mentioned above, one can attribute this to a large extent to random fluctuations.

Figure 9 shows a scatter plot of bias in a group of 479 highly expressed genes (vertical axis) versus the bias in all genes (horizontal) of *A. niger*. All 3,721 codon pairs not involving stop codons are shown.

Shading from light gray to black were assigned according to the absolute values of the z-scores in the overall genome, i.e. light dots in the plot do not have a significant bias in all genes), as were sizes according to the absolute z-scores in the highly expressed group, i.e. very small dots do not have a significant bias there (here |z-score|<1.9). The solid black line indicates where both bias values are equal; the dashed black line shows the best linear approximation of the actual correlation (identified by principal component analysis); its slope is around 2.1.

When comparing the two bias values of each codon pair in the highly expressed group and in the full genome (see the scatter plot in Figure 9), one can see that for most pairs the bias in the highly transcribed group is more extreme, i.e. lower if it is below 0 and higher if it is positive, but there are some pairs where the bias values are quite different and even have a different sign. However, these are mostly codon pairs with a small number of occurrences in the top group, and most pairs where the bias is highly significant (blue, large circles) have similar biases in both groups (i.e. they are close to the blue line that indicates where both bias values are equal).

No specific patterns regarding similar bias differences of codons that share two of the three nucleotides could be found (neither for *A. niger* nor for *B. subtilis*), i.e. in plots of the bias difference analogous to the one above there were no larger groups with similar bias difference.

1.3. Details of the identification of codon pair weights for gene adaptation

Codon pair weight for adaptation can be determined now according the described methods (Appendix 1: Codon pair weights – method one sequence group (or genome)):

1. based on the full set of genes; based on a subset of 1.
2. being identified as the fraction of highly expressed genes.

In addition, we started a search to identify codon pair weights that clearly relate to a higher transcription level, which is required for a improved method for adaptation of codon pair usage, the following methods have been applied: In *A. niger*, where a complete ranking

extracted from GeneChip data was available for the aforementioned set of 4,584 actually expressed genes (see "Data" in "Materials and Methods"), the mean codon pair weights of each gene (i.e. the equivalent of the fitcp(g) values) were calculated. Then the genes were sorted according to fitness values (ascending order) and expression level (descending order). Since highly expressed genes are supposed to have low codon pair fitness values, these two rankings would be equal when using ideal codon pair weights, so a comparison of these two rankings can give information about the quality of the weights used in the fitness function (where slightly more attention was given to the "correct" ranking of the highly expressed genes than to the ranking of the mediocre ones). Additionally, the correlation coefficient (covariance divided by the standard deviation of each variable) between ranking and average codon pair weights of the 4,584 genes was calculated.

Several possible sets of weights have been examined, including

i. bias values from the whole genome,
ii. bias values of the highly expressed group,
iii. bias with all the values that do not have a certain minimum z-score set to zero
iv. bias values raised to the power of 2 (and some other values) to give highly preferred or rejected codons a lower/higher influence
v. combinations thereof
vi. z-scores themselves
vii. difference of bias values/z-scores from the highly expressed group and the full genome.

For the genetic algorithm (GA), their negations have been used, since preferred codon pairs had been identified with positive values (rather arbitrarily), but the GA performs minimization. This applies to all weights mentioned.

Out of these, the "best" weight matrix turned out to be a combination of item ii to iv, however, an even better one could be obtained – as described above – by calculating the codon pair "bias" in the highly expressed group using expected values calculated based on the codon ratios of the whole genome. Figure 10 shows the correlation that is observed.

Unlike all other weight sets tested, codon pairs involving codons that are more underrepresented in the highly expressed group get a slight disadvantage here. Thus, these weights are the only ones that also reflect the different single codon bias of the highly expressed group and all genes. Using these weights carries the risk of rejecting some codon pairs that actually have a positive bias in the highly expressed group, but consist of (in the highly

expressed group) rarely used codons. However, since our desired single codon ratios are usually not identical to those in the group of genes with high expression, but more "extreme" than these, single codon optimization would replace these underrepresented anyway, so we can consider the weights described above very convenient for codon pair optimization.

Concluding, a potentially improved codon pair weight matrix for gene adaptation has been identified as described above. The equation is given in Appendix 1: Codon pair weights – method highly expressed group with reference group (or genome).

1.4. Single codon and codon pair optimization *in silico*

1.4.1 Material and methods

The developed MATLAB toolbox for analyzing and optimizing genes consists of several functions that have been organized in different directories according to their capacities. In order to use them, it is therefore necessary to make all of them known to the MATLAB environment. To do this, select "Set Path" from the File menu and then click "Add *with subfolders*" and select the path where the toolbox is installed (usually called "Matlab-bio"). Also add the location of FASTA and other files that should be analyzed. All individual MATLAB functions are briefly described in "contents.m" (type "help Matlab-bio" to display this file in the MATLAB environment and use "help" followed by a function's name to get detailed information about it). For gene optimization focusing on codon pair usage, the two important functions are "`fullanalysis`" and "`geneopt`".

If the full genome of an organism you want to adapt a gene to is located in the file, say, "*Aniger_ORF.fasta*" and the identifiers of its highly expressed genes are in "*an-high.txt*" type "`fullanalysis('Aniger_ORF.fasta','an-high.txt', 'an');`" and you will get (i) a codon pair bias map for the full genome, (ii) a codon pair bias map for the group of genes in the second file and (iii) several variables (*i.e.* sets of temporarily stored data) in the MATLAB workspace for further use. The third parameter of "`fullanalysis`" determines only how these variables are named and can be omitted if only one genome is to be analyzed at the same time. Among the mentioned variables are: (i) codon pair usage and bias data for the full genome (named "*cpan*" in this example), (ii) the same for the special group of genes specified by the second parameter (named "*cpans*") and (iii) structure with target single codon ratios and codon pair weights that can be used for the genetic algorithm. "`fullanalysis('Xyz_ORF.fasta');`" will only show the codon pair bias map and store the bias data for the respective genome.

Although the second parameter may be any file that includes gene identifiers (*e.g.* a set of genes with low expression or genes with a certain common function), it is always treated like a set of highly expressed genes regarding this (potential) parameter (named "*optparamforan*" in the example, which stands for *the optimization parameter for the specified organism*). Note that the single codon ratios here are simply calculated $r_{sc}^{target}(c_k) = 2 \cdot r_{sc}^{high}(c_k) - r_{sc}^{all}(c_k)$, which is an acceptable approximation. Target ratios might be as well identified by other methods that include the details of the single codon distribution (see main text) in order to further improve specification of desired ratios. In addition, target ratios may be left empty when no specific bias is found, in order to give the codon-pair algorithm more freedom in finding solutions with a higher codon-pair fitness. Several of such pre-determined single-codon target vectors are given in Appendix 1, for various host organisms.

To use pre-specified single-codon target ratio's for the genetic algorithm, change the field "*cr*" of the parameter by typing "`optparamforan.cr = [`", then paste the single codon ratios (*e.g.* copied from an Excel sheet; note that they should be in alphabetical order of the codons), type "`];`" if the ratios are available as a 64-element row or "`]';`" if they are copied from a column and press enter (note the additional single quotation mark or apostrophe following the closing bracket in the latter case). Unimportant codon ratios, *i.e.* codons where no specific target ratio is desired, may be assigned the "value" `NaN` (*n*ot *a n*umber) and they will be ignored when single codon fitness is calculated.

To exclude certain short sequences from the optimized gene, set the parameter "*rs*" in the same way, where each sequence must be enclosed by single quotation marks and all sequences together must be enclosed in braces, *e.g.* (without the line break) "`optparamforan.rs = {'CTGCAG' 'GCGGCGCC'};`". Finally, the field *cpi* of the parameter might be changed to give single codon optimization or codon pair optimization a higher importance in the combined fitness function (see the subsection "performing codon pair optimization" in "results and discussion"). The default value is 0.2. Set it to a lower value if the results of the experiments with codon pair optimized genes reveal little improvement of codon pair optimized genes compared to single codon optimized ones; in the opposite case, a higher *cpi* might be better.

The actual optimization of the gene using the genetic algorithm can then be performed using the function `geneopt`. The only parameters needed are the sequence to be optimized and the structure containing codon pair weights, target ratios and restriction sites as described above, so `geneopt('MUVARNEQST*', optparamforan);` could for example be used to optimize the given (rather short) protein sequence for high expression in *A. niger*; the '*' is used

to denote that the resulting genetic sequence should have a stop codon at the end (however, as the optimal stop signal in *A. niger* is believed to be the tetramer TAAA, this is not necessary). Note that the sequence to be optimized must again be enclosed in single quotation marks; if the sequence contains only the letters A, C, G, T or U and its length is a factor of 3, it is automatically regarded a nucleotide sequence. The genetic algorithm then runs for 1000 generations with a population size of 200, of which 80 each are kept for the generation (the 79 best and one randomly picked) and used to generate new individuals, where 40% of the new individuals are generated using crossover and 60% using the mutation operator. These default values turned out to be very convenient for the optimization, *i.e.* changes in these parameters will only, if at all, lead to very slightly "better" genes, but they can be changed as well, for example if significantly more or less calculation time should be spent on the optimization (an average run of `geneopt` with a gene of about 500 codons takes about 15 minutes on a 1.4 GHz Pentium M Processor). `geneopt(seq, optparamforan, [50 750 5 0 0.6])` will, for example, let the genetic algorithm calculate 750 generations of a population where 50 individuals are kept for each new generation and 250 are newly generated (5*50; *i.e.* 300 individuals are examined in each generation), only the best (and no randomly picked) individuals are kept and 60% of the recombinations are performed using the crossover operator. For more details on how to specify these parameters, type `help geneopt` and `help geneticalgorithm`.

Note that although the procedure of generating codon pair weights from analyzing the corresponding FASTA files is shown and described here for *A. niger* and B. subtilis, just for these two organisms this is not necessary because these calculations have already been performed for previous gene optimizations. For easier use, the respective parameters for the genetic algorithms have been stored (type "load gadata_for_an" or "load gadata_for_bs", respectively; note that the parameters there are now just simply called an_param and bs_param.

1.4.2 Results

Figure 11 shows fitness values of five optimized versions each for different values of *cpi* (see legend of the diagram in Figure11). The protein is a fungal α-amylase (FUA; also referred to as AmyB) that was optimized for the host *A. niger* (see Example 2). Additionally, the results of "pure" single codon optimization (black dots on the right) and codon pair optimization are shown (group top left). The optimized versions were obtained by running the genetic algorithm for around 1000 generations with a population size of 400, which took about 17 minutes for

each run on a 1.4 GHz Pentium M. Note that pure single codon optimization and pure codon pair optimization took only about 60% of that time.

In Figure11 the wild type ($fit_{sc}(g_{fua})$=0.165, $fit_{cp}(g_{fua})$=0.033) does not fit on this plot (it would be far to the right and above). The optimal gene is always the one with the lowest values for fit_{sc} and fit_{cp}. Given the position of the dots, it is therefore not clear for which value of *cpi* the most improved gene could be obtained, since we do not know yet whether single codon usage or codon pair usage is more important. However, a fare trade-off seems to appear in case of *cpi* = 0.2.

The improvement in single codon and codon pair usage can be visualized in so-called sequence quality plots proposed in this work. Figure 12 illustrates two diagrams which show the sequence quality of the first 20 (out of 499) codons of the aforementioned FUA (see also Example 2).

Note that these sequence quality diagrams not only depend on the sequence itself, but also on the set of weights and the desired single codon ratios and thus on the organism. Note also that it is possible to define target single codon ratios as "don't care" for those codons with low or no codon bias, i.e. the usage of a certain codon is not considered positive or negative for expression compared to its synonymous codons. In that case, only the blue x-mark is shown for the actual ratio of the respective codon in the gene and that particular position is ignored when calculating single codon fitness (see 1.4. Single codon and codon pair optimization *in silico*).

1.5 Conclusions

A significant correlation of codon pair usage and transcription levels has been established in a wide range of organisms. It was demonstrated that this bias cannot only be explained by dinucleotide bias around the reading frame site. Since possible explanations for preference or rejection of certain codon pairs all focus on the translation, it should be assumed that both are caused by natural selection acting at the same time on characteristics that affect translation and other characteristics that affect transcription in order to minimize the cell's efforts to produce enzymes or at least the more important of them.

Optimizing codon pair usage in polypeptide coding sequences can thus be considered for achieving improved overexpression, in addition to classic single-codon optimization or single codon harmonization, where only single codons frequencies are considered for optimization. Codon pair adaptation and single codon adaptation of the same gene interfere only slightly for the investigated fungal host class and the bacilli in this example, *i.e.* both can be performed at the same time and the result will have "better" single codon usage and "better" codon pair usage

than the wild-type gene, and any of the two aspects can only be improved slightly when ignoring the other one.

To read the FASTA files and perform the analysis and optimization, user-friendly MATLAB functions have been designed. New methods of visualizing codon pair bias and codon pair usage of single genes have been introduced as well, see Example 2 and Example 4. The genetic algorithm designed for the optimization allows effective dealing with the constraints imposed by interdependence of adjacent codon pairs while the specially designed mutation operators that always improve one of the two aspects of sequence quality (single codon an codon pair fitness) help to circumvent the inefficiency usually accompanying genetic algorithms because of their trait of generating many bad possible solutions in the recombination step after the first few generations.

The proper codon pair usage influences enzyme production, which will be shown experimentally in the following examples. Codon pair optimized variants of three genes to be expressed in *B. subtilis* have been prepared, of which one each will be compared to a synthetic gene that has adapted single codon usage only and another one to a synthetic gene that has gone through the optimization process using the negation of the presumably positive weights, but still been optimized for single codon usage the same way as before, see Example 4 and Example 5. This way, the notion of Irwin *et al.* (1995) that underrepresented codons stimulate translation, which was rejected here, will also put to the test. For *A. niger*, a codon pair optimized version of the aforementioned amyB will be tested and compared to the wild-type and synthetic gene with single codon harmonization, see Examples 2 and 3.

2. Example 2: Use of a method of the invention for construction of improved DNA sequences for improving production of the *Aspergillus niger* fungal amylase enzyme in *A. niger*.

Below, the method of the invention is applied to design novel nucleotide sequences for the AmyB (FUA) gene of *A. niger*, which are optimized in single codon and / or codon pair usage for improved expression in *A. niger*. This method can be applied the same way for the improvement of codon use of any nucleotide sequence.

2.1 Introduction

A concept of single-codon optimization by means of codon-harmonization was previously developed by the applicants of this invention and reported in the main text (see also example 3). In this example we show how one applied the method of the invention to design a gene that were optimized for both single codon and codon pair usage. In this specific case weight matrices

are applied that have been created by applying two subsets of 2% and 4% of highly expressed genes of the full *A. niger* genome that contains 14,000 genes. For the single-codon usage the algorithm has driven the solution to a gene with synonymous codon-frequencies as defined by Table B.1 (= column 3 of Table 2.1), while for the codon-pair usage, it will optimized toward an optimal set of codon-pairs with a high frequency of them having associated negative weights (in Table C.2), being the codon-pairs that are overrepresented with respect to its expected values in the set of 4% highly expressed genes. Note that in case one does not have a defined list of highly expressed genes for a specified host, one can also (i) apply the weight matrices of a similar host organism, for example the *P. chrysogenum* matrices can be applied for *A niger*; or (ii) apply the full genome sequence data or a subset of it to derive good, but less optimal weight matrices.

2.2 Materials and Methods

2 .2.1 Wild-type amyB coding sequence encoding *A. niger* alpha-amylase *AmyB*

The DNA sequence of the *amy*B gene encoding the alpha-amylase protein was disclosed in J. Biochem. Mol. Biol. 37(4):429-438(2004) (Matsubara T., Ammar Y.B., Anindyawati T., Yamamoto S., Ito K., Iizuka M., Minamiura N. "Molecular cloning and determination of the nucleotide sequence of raw starch digesting alpha-amylase from *Aspergillus awamori* KT-11.") and also can be retrieved from EMBL Nucleotide Sequence Database (http://www.ebi.ac.uk/embl/index.html) under accession number AB083159. The genomic sequence of the native *A. niger amy*B gene is shown as SEQ ID NO. 1. The corresponding coding or cDNA sequence of *amy*B is shown as SEQ ID NO. 2. The translated sequence of SEQ ID NO. 2 is assigned as the SEQ ID NO. 3, representing the *A. niger* alpha-amylase protein AmyB. This sequence has also a 100% similarity with the *A. oryzae* alpha-amylase protein (Wirsel S., Lachmund A., Wildhardt G., Ruttkowski E., "Three alpha-amylase genes of Aspergillus oryzae exhibit identical intron-exon organization."; Mol. Microbiol. 3:3-14(1989, UniProt accession nr. P10529, P11763 or Q00250). Optimization according a method of the invention has been performed on the amyB cDNA sequence.

2.3 Design procedure

The optimized coding nucleotide sequence SEQ ID NO 6 is the result of a run with the described software method. The applied parameters were: population size = 200; number of iterations = 1000; *cpi* = 0.20, CPW matrix = "Table C.2. CPW: Aspergillus niger – highly expressed sequences" and the CR matrix = "Table B.1 column 4: CR table ANS: Aspergillus

niger – highly expressed sequences". Moreover, a penalty value of +1 is added to fit_{combi} for each occurrence of a *PstI* (CTGCAG) and NotI (GCGGCGCC) site.

Convergence of the solution toward a minimal value for fit_{combi} is shown in Figure 13. The obtained objective values for SEQ ID NO. 6 are given in Table 2.2, together with those for SEQ ID NO. 2 and SEQ ID NO. 5. Figure 14 explains the single codon statistics for these genes as is shown in Figure 15 and 16, and Table 2.2 gives the actual values for the codons in the three sequences. Figure 18-20 show both single-codon and codon pair statistics for the three gene variants. This type of graph is explained in detail in Figure 17 and its description. From these graphs it is clear that single-codon statistics are highly similar for SEQ ID NO. 5 and SEQ ID NO. 6. However, the method of the invention leads to a gene with an improved number of codon pairs with associated negative weights ($w_{cp}(g) \leq 0$), 93% vs. 74%, and also a further reduction in fit_{cp} from -0.18 to -0.34 indicating a more optimal usage of codon pairs having more negative weights associated with them.

Table 2.1 Codon optimization for amyB.

AA	Codon	Optimal codon distribution [%]	amyB w.t. [# codons]	amyB w.t. [% codons / AA]	amyB sc optimized [# codons]	amyB sc & cp optimized [# codons]
A	Ala_GCT	38	5	11.9	16	18
	Ala_GCC	51	15	35.7	21	23
	Ala_GCA	0	12	28.6	0	0
	Ala_GCG	11	10	23.8	5	1
C	Cys_TGT	0	7	77.8	0	0
	Cys_TGC	100	2	22.2	9	9
D	Asp_GAT	36	20	47.6	15	15
	Asp_GAC	64	22	52.4	27	27
E	Glu_GAA	26	5	41.7	3	3
	Glu_GAG	74	7	58.3	9	9
F	Phe_TTT	0	3	20.0	0	0
	Phe_TTC	100	12	80.0	15	15
G	Gly_GGT	49	10	23.3	21	22
	Gly_GGC	35	18	41.9	15	15
	Gly_GGA	16	10	23.3	7	6
	Gly_GGG	0	5	11.6	0	0
H	His_CAT	0	3	42.9	0	0
	His_CAC	100	4	57.1	7	7
I	Ile_ATT	27	7	25.0	7	7
	Ile_ATC	73	19	67.9	21	21
	Ile_ATA	0	2	7.1	0	0
K	Lys_AAA	0	7	35.0	0	0
	Lys_AAG	100	13	65.0	20	20
L	Leu_TTA	0	1	2.7	0	0
	Leu_TTG	13	10	27.0	5	4

	Leu_CTT	17	4	10.8	6	7
	Leu_CTC	38	13	35.1	14	15
	Leu_CTA	0	3	8.1	0	0
	Leu_CTG	32	6	16.2	12	11
M	Met_ATG	100	10	100.0	10	10
N	Asn_AAT	0	3	11.5	0	0
	Asn_AAC	100	23	88.5	26	26
P	Pro_CCT	36	6	27.3	8	8
	Pro_CCC	64	8	36.4	14	14
	Pro_CCA	0	3	13.6	0	0
	Pro_CCG	0	5	22.7	0	0
Q	Gln_CAA	0	5	25.0	0	0
	Gln_CAG	100	15	75.0	20	20
R	Arg_CGT	49	1	10.0	5	5
	Arg_CGC	51	2	20.0	5	5
	Arg_CGA	0	2	20.0	0	0
	Arg_CGG	0	2	20.0	0	0
	Arg_AGA	0	0	0.0	0	0
	Arg_AGG	0	3	8.1	0	0
S	Ser_TCT	21	4	10.8	8	8
	Ser_TCC	44	9	24.3	16	17
	Ser_TCA	0	4	10.8	0	0
	Ser_TCG	14	10	27.0	5	4
	Ser_AGT	0	4	10.8	0	0
	Ser_AGC	21	6	16.2	8	8
T	Thr_ACT	30	9	22.5	12	12
	Thr_ACC	70	13	32.5	28	28
	Thr_ACA	0	10	25.0	0	0
	Thr_ACG	0	8	20.0	0	0
V	Val_GTT	27	5	16.1	8	9

	Val_GTC	54	12	38.7	17	17
	Val_GTA	0	4	12.9	0	0
	Val_GTG	19	10	32.3	6	5
W	Trp_TGG	100	12	100.0	12	12
Y	Tyr_TAT	0	11	31.4	0	0
	Tyr_TAC	100	24	68.6	35	35

Table 2.2 Codon optimization for amyB.

Sequence	Type	fit_{sc}	fit_{cp}	$w_{cp}(g) \leq 0$	fit_{combi} (cpi=0.2)
SEQ ID NO. 2	WT	0.1652	0.0329	37.3%	0.090
SEQ ID NO. 5	sc optimized	0.0046	-0.1765	73.9%	-0.862
SEQ ID NO. 6	sc + cp optimized	0.0109	-0.3420	92.6%	-1.621

All three sequences listed in Table 2.2 are coding sequences of which the translated sequence is assigned as SEQ ID NO. 3.

3. Example 3: Testing of the method of the invention for construction of improved DNA sequences for providing improved production of the *Aspergillus niger* fungal amylase enzyme in *A. niger*.

The method of the invention is below applied to the improvement of single codon and codon pair use of the AmyB gene of *A. niger*. This method can be applied the same way for the improvement of codon use and improved expression of any nucleotide sequence.

3.1 Material and Methods

3.1.1 Strains

WT 1: This *A. niger* strain is used as a wild-type strain. This strain is deposited at the CBS Institute under the deposit number CBS 513.88.

WT 2: This *A. niger* strain is a WT 1 strain comprising a deletion of the gene encoding glucoamylase (*gla*A). WT 2 was constructed by using the "MARKER-GENE FREE" approach as described in EP 0 635 574 B1. In this patent it is extensively described how to delete *gla*A specific DNA sequences in the genome of CBS 513.88. The procedure resulted in a MARKER-

GENE FREE Δ*gla*A recombinant *A. niger* CBS 513.88 strain, possessing finally no foreign DNA sequences at all.

WT 3: This *A. niger* strain is a WT 2 strain comprising a mutation which results in an oxalate deficient *A. niger* strain. WT 3 was constructed by using the method as described in EP1590444. In this patent application, it is extensively described how to screen for an oxalate deficient *A. niger* strain. Strain WT3 was constructed according to the methods of Examples 1 and 2 of EP1590444, strain WT 3 is mutant strain 22 of EP1590444 (designated FINAL in EP1590444).

WT 4: This *A. niger* strain is a WT 3 strain comprising the deletion of three genes encoding alpha-amylases (*amy*B, *amy*BI and *amy*BII) in three subsequent steps. The construction of deletion vectors and genomic deletion of these three genes has been described in detail in WO2005095624. The vectors pDEL-AMYA, pDEL-AMYBI and pDEL-AMYBII, described in WO2005095624, have been used according the "MARKER-GENE FREE" approach as described in EP 0 635 574 B1. The procedure described above resulted in an oxalate deficient, MARKER-GENE FREE Δ*gla*A, Δ*amy*A, Δ*amy*BI and Δ*amy*BII amylase-negative recombinant *A. niger* CBS 513.88 strain, possessing finally no foreign DNA sequences at all. As such, WT 4 is more optimized for alpha-amylase expression compared to WT1.

3.1.2 *A. niger* shake flask fermentations

A. niger strains were pre-cultured in 20 ml pre-culture medium as described in the Examples: "*A. niger* shake flask fermentations" section of WO99/32617. After overnight growth, 10 ml of this culture was transferred to fermentation medium 1 (FM1) for alpha-amylase fermentations. Fermentation is performed in 500 ml flasks with baffle with 100 ml fermentation broth at 34°C and 170 rpm for the number of days indicated, generally as described in WO99/32617.

This FM1 medium contains per liter: 52.570 g glucose, 8.5 g maltose, 25 g Caseinhydrolysate, 12.5 g Yeast extract, 1 g KH2PO4, 2 g K2SO4, 0.5 g MgSO4.7H2O, 0.03 g ZnCl2, 80.02 g CaCl2, 0.01 g MnSO4.4H2O, 0.3 g FeSO4.7H2O, 10 ml Pen-Strep (Invitrogen, cat. nr. 10378-016), 48 g MES, adjusted to pH 5.6 with 4 N H2SO4.

3.1.3 Fungal alpha-amylase activity

To determine the alpha-amylase activity in *A. niger* culture broth, the Megazyme cereal alpha-amylase kit is used (Megazyme, CERALPHA alpha amylase assay kit, catalogue. ref. K-CERA, year 2000-2001), according protocol of the supplier. The measured activity is based on

hydrolysis of non-reducing-end blocked ρ-nitrophenyl maltoheptaoside in the presence of excess glucoamylase and α-glucosidase. The amount of formed ρ-nitrophenol is a measure for alpha-amylase activity present in a sample.

3.2 Construction of an Aspergillus expression construct for the wild-type amyB coding sequence encoding *A. niger* alpha-amylase *AmyB*

The DNA sequence of the wild-type amyB gene have been described under 2.2.1. For expression analysis in *Aspergillus* species of *A. niger amy*B constructs, the strong amyB promoter is applied for over-expression of the alpha amylase enzyme in *A. niger* using pGBFIN-based expression constructs (as described in WO99/32617). The translational initiation sequence of the *amyB* promoter including ATG start codon of PamyB is 5'-GGCATTTATG ATG-3' or 5'-GAAGGCATTT ATG-3', dependent on which ATG is selected as start codon. This translational initiation sequence of PamyB has been modified into 5'-CACCGTCAAA ATG-3' in all subsequent *amyB* expression constructs generated below.

Appropriate restriction sites were introduced at both ends to allow cloning in an expression vector. The native *amy*B gene contains a 'TGA' stop codon. In all *amy*B constructs made below, the 5'-TGA-3' translational termination sequence was replaced by 5'-TAAA-3' followed by the 5'-TTAATTAA-3' of the *Pac*I restriction site. At the 5'-end an *Xho*I site was introduced and at the 3'-end a *Pac*I site. Therefore, a fragment comprising a modified genomic *amy*B promoter and amyB cDNA sequence was completely synthesized, cloned and the sequence was confirmed by sequence analysis.

This fragment comprising the alpha-amylase promoter with modified translational initiation sequence and amyB cDNA sequence with modified translational termination sequence was digested with *Xho*I and *Pac*I and introduced in an *Xho*I and *Pac*I digested pGBFIN-12 vector (construction and layout as described in WO99/32617), generating pGBFINFUA-1 (Figure 21). The sequence of the introduced PCR fragment was confirmed by sequence analysis and its sequence is presented in SEQ ID NO. 4.

3.3 Improvement of the single-codon usage for the alpha-amylase coding sequence amyB for expression in *A. niger*

A method of single-codon optimization is applied below for the improvement of codon use of the amyB gene of *A. niger*. The nucleotide coding sequence of the native amyB is shown as SEQ ID NO. 2.

The codon use of the native *amy*B gene of *A. niger* and the synthetic optimized variant are given in Table 2.1 below. For the native and single-codon optimized synthetic *amy*B gene, the exact numbers for each codon are given as well as the distribution per amino acid. Additionally, the third column provides the proposed optimal distribution, which is the target for optimization.

For the group 1 amino acids, there is only one possibility. Group 1 consists of methionine that is always encoded by ATG and tryptophane that is always encoded by TGG.

The group 2 amino acids are subject to optimization according to the extreme frequency of 0% or 100%, the strategy is clear. All codons for a group 2 AA are specifically changed into the optimal variant of the two possible codons. More specifically for cysteine, a codon, TGT is replaced by TGC; for phenylalanine, TTT by TTC; for histidine, CAT by CAC; for lysine, AAA by AAG, for asparagine, AAT by AAC; for glutamine, CAA by CAG; for tyrosine, TAT by TAC.

The group 3 amino acids can be encoded by several codons as indicated in Table 3.1; each codon being present in a preferred codon frequency: for alanine GCT, GCC, GCA, GCG; for aspartate, GAT, GAC; for glutamate, GAA, GAG; for glycine, GGT, GGC, GGA, GGG; for isoleucine, ATT, ATC, ATA; for leucine, TTA, TTG, CTT, CTC, CTA, CTG; for proline, CCT, CCC, CCA, CCG; for arginine, CGT, CGC, CGA, CGG, AGA, AGG; for serine, TCT, TCC, TCA, TCG, AGT, AGC; for threonine, ACT, ACC, ACA, ACG; for valine, GTT, GTC, GTA, GTG, are optimized according the following methodology:

For the group 3 amino acids (AA) and their encoding codons, the calculation of the optimal occurrence of each possible codon within a given coding sequence is performed according to the following methodology:

i. sum for each of the respective group 3 AA, the total number of residues encoded in the given sequence, see column A1 (Table 3.1),

ii. for each AA and codon encoding that AA, multiply the total number for that AA by the optimal codon distribution in Table 2.1, resulting in a raw codon distribution, which generally may contain decimal numbers, see column A2 (Table 3.2),

iii. round off the values of the raw codon distribution (ii), by removing the digits, resulting in a rounded off codon distribution, see column A3 (Table 3.2),

iv. sum for each of the AA, the total number of AA represented in the rounded off codon distribution (iii), see column A4 (Table 3.1),

v. calculate the total missing number of residues for each of the respective AA in the rounded off codon distribution, by subtracting the total number of residues encoded in

the given sequence (i) with the total number of AA represented in the rounded off codon distribution (iv), see column A5 (Table 3.1),

vi. calculate for each codon, the decimal difference between the raw codon distribution (ii) and the rounded off codon distribution (iii) by subtraction, see column A6 (Table 3.2),

vii. multiply for each codon, the decimal difference (vi) and the optimal codon distribution in table 1, giving a weight value for each codon, see column A7 (Table 3.2),

viii. for each of the respective AA, select for the amount of missing residues (v), the respective amount of codons that have the highest weight value (vii), see column A8 (Table 3.2),

ix. the calculation of the final optimal codon distribution within a given sequence encoding a polypeptide is calculated by summing the rounded off codon distribution (iii) and the selected amount of missing residues (viii) for each codon, see column A9 (Table 3.2).

Table 3.1

AA(i)	I	A1	A4	A5
Ala	1	42	40	2
Asp	2	42	41	1
Glu	3	12	11	1
Gly	4	43	42	1
Ile	5	28	27	1
Leu	6	37	35	2
Pro	7	22	21	1
Arg	8	10	9	1
Ser	9	37	35	2
Thr	10	40	40	0
Val	11	31	29	2

Table 3.2

Codon	A2	A3	A6	A7	A8	A9
Ala_GCT	15.96	15	0.96	0.365	1	16
Ala_GCC	21.42	21	0.42	0.014	1	21
Ala_GCA	0	0	0	0.000	0	0
Ala_GCG	4.62	4	0.62	0.068	0	5
Asp_GAT	15.12	15	0.12	0.043	0	15
Asp_GAC	26.88	26	0.88	0.563	1	27
Glu_GAA	3.12	3	0.12	0.031	0	3
Glu_GAG	8.88	8	0.88	0.651	1	9
Gly_GGT	21.07	21	0.07	0.034	0	21
Gly_GGC	15.05	15	0.05	0.018	0	15
Gly_GGA	6.88	6	0.88	0.141	1	7
Gly_GGG	0	0	0	0.000	0	0
Ile_ATT	7.56	7	0.56	0.151	0	7
Ile_ATC	20.44	20	0.44	0.321	1	21
Ile_ATA	0	0	0	0.000	0	0
Leu_TTA	0	0	0	0.000	0	0

Leu_TTG	4.81	4	0.81	0.105	1	5
Leu_CTT	6.29	6	0.29	0.049	0	6
Leu_CTC	14.06	14	0.06	0.023	0	14
Leu_CTA	0	0	0	0.000	0	0
Leu_CTG	11.84	11	0.84	0.269	1	12
Pro_CCT	7.92	7	0.92	0.331	1	8
Pro_CCC	14.08	14	0.08	0.051	0	14
Pro_CCA	0	0	0	0.000	0	0
Pro_CCG	0	0	0	0.000	0	0
Arg_CGT	4.9	4	0.9	0.441	1	5
Arg_CGC	5.1	5	0.1	0.051	0	5
Arg_CGA	0	0	0	0.000	0	0
Arg_CGG	0	0	0	0.000	0	0
Arg_AGA	0	0	0	0.000	0	0
Arg_AGG	0	0	0	0.000	0	0
Ser_TCT	7.77	7	0.77	0.162	1	8
Ser_TCC	16.28	16	0.28	0.123	0	16
Ser_TCA	0	0	0	0.000	0	0
Ser_TCG	5.18	5	0.18	0.025	0	5
Ser_AGT	0	0	0	0.000	0	0
Ser_AGC	7.77	7	0.77	0.162	1	8
Thr_ACT	12	12	0	0.000	0	12
Thr_ACC	28	28	0	0.000	0	28
Thr_ACA	0	0	0	0.000	0	0
Thr_ACG	0	0	0	0.000	0	0
Val_GTT	8.37	8	0.37	0.100	0	8
Val_GTC	16.74	16	0.74	0.400	1	17
Val_GTA	0	0	0	0.000	0	0
Val_GTG	5.89	5	0.89	0.169	1	6

Subsequently, a completely new nucleotide coding sequence was created by random distribution of the proposed number of synonymous codons (Table 2.1) for each amino acid in the original amyB peptide. The synthetic *amy*B sequence, resulting from the process described above, is indicated in SEQ ID NO. 5. Secondary structures in the modified coding sequence

were checked using the Clone Manager 7 program (Sci. Ed. Central: Scientific & Educational software, version 7.02) for possible occurrence of harmful secondary structures.

3.4 Optimization of the coding sequence according a the combined single-codon and codon-pair method of the invention for the alpha-amylase coding sequence *amy*B for expression in *A. niger*

A method of the invention is applied for the improvement of the coding sequence of the amyB gene of *A. niger*. The optimized *amy*B sequence, resulting from the process described in Example 2, is indicated in SEQ ID NO. 6. Secondary structures in the modified coding sequence were checked using the Clone Manager 7 program (Sci. Ed. Central: Scientific & Educational software, version 7.02) for possible occurrence of harmful secondary structures.

3.5 Construction of modified *amy*B expression vectors for expressing *A. niger* alpha-amylase AmyB encoded by coding sequences described in examples 3.2 and 3.3

The DNA sequence of the *Xho*I - *Pac*I fragment of pGBFINFUA-1 (Figure 21) is shown as SEQ ID NO. 4 and comprises the amyB promoter and wild-type amyB cDNA sequence with a modified translational initiation sequence and modified translation stop sequence. The DNA sequence comprising a variant of the translational initiation sequence of the alpha-amylase promoter combined with a codon optimized coding sequence for the alpha-amylase encoding amyB gene, as described in Example 1.2, is shown as SEQ ID NO. 7. The DNA sequence comprising a variant of the translational initiation sequence of the alpha-amylase promoter combined with an optimized coding sequence according the combined single-codon and codon-pair method of the invention for the alpha-amylase encoding amyB gene, as described in Example 3.3, is shown as SEQ ID NO. 8.

For cloning these modified sequence variants in an expression vector, the two synthetic gene fragments were digested with *Xho*I and *Pac*I and introduced in the large fragment of an *Xho*I and *Pac*I digested pGBFINFUA-1 vector (Figure 21), generating variant expression vectors. After checking the integration of the correct fragment, the variant expression constructs were named pGBFINFUA-2 and pGBFINFUA-3, as described below in Table 3.3.

Table 3.3: Modified expression constructs for alpha-amylase expression in *A. niger*

Plasmid name	SEQ ID NO	Translation initiation sequence	Coding sequence	Translation stop sequence
pGBFINFUA-1	4	Modified	w.t.	Modified

		(CACCGTCAAA ATG)		(TAA ATA)
pGBFINFUA-2	7	Modified (CACCGTCAAA ATG)	Single-codon optimized	Modified (TAA ATA)
pGBFINFUA-3	8	Modified (CACCGTCAAA ATG)	Modified according invention	Modified (TAA ATA)

The translated sequences of the amyB coding sequences of plasmid pGBFINFUA-1 to pGBFINFUA-3 are according to the amino acid sequence as depicted in SEQ ID NO 3, representing the wild-type *A. niger* alpha-amylase enzyme.

3.6 Expression in *A. niger* of modified pGBFINFUA- expression constructs of *A. niger* alpha-amylase

The pGBFINFUA-1, -2 and -3 expression constructs, prepared as described above, were introduced in *A. niger* by transformation as described below and according to the strategy depicted in Figure 22.

In order to introduce the three pGBFINFUA-1, -2 and -3 vectors (Table 3.3) in WT 4, a transformation and subsequent selection of transformants was carried out as described in WO98/46772 and WO99/32617. In brief, linear DNA of the pGBFINFUA- constructs was isolated and used to transform *A. niger*. Transformants were selected on acetamide media and colony purified according standard procedures. Colonies were diagnosed for integration at the glaA locus and for copy number using PCR. Ten independent transformants of each of the pGBFINFUA-1, -2 and -3 constructs with similar estimated copy numbers (low copy: 1-3) were selected and numbered using the name of the transforming plasmid, as for example FUA-1-1 (for the first pGBFINFUA-1 transformant) and FUA-3-1 (for the first pGBFINFUA-3 transformant), respectively.

The selected FUA-strains and *A. niger* WT 4 were used to perform shake flask experiments in 100 ml of the medium and under conditions as described above. After 3 and 4 days of fermentation, samples were taken.

The production of alpha-amylase enzyme was measured in all three different *A. niger* FUA-transformants. As can be learned from Figure 23, optimization of the coding sequence according the method of the invention shows a higher improvement on expression of AmyB compared to the other method tested called single-codon optimization. These figures have been summarized in Table 3.4 below.

Table 3.4. Relative average alpha-amylase activities of transformants with wild-type construct compared to those with modified *amy*B coding sequences (as concluded from Figure 23).

Strain type	SEQ ID NO	Coding sequence	Alpha-amylase activity
FUA-1	4	w.t.	100 %
FUA-2	7	Single-codon optimized	200 %
FUA-3	8	Modified according invention	400 %

These results indicate clearly that the method of the invention can be applied to improve protein expression in a host, although the expression construct and host has already several other optimizations, such as for example a strong promoter, an improved translation initiation sequence, an improved translation stop sequence, an optimal single-codon usage and / or an improved host for protein expression.

4. Example 4: Design of improved DNA sequences for expression of three heterologous enzymes in *Bacillus* species: *Bacillus subtilis* and *Bacillus amiloliquefaciens*.

4.1. Introduction

Example 4 describes the experiment design and application of a method of the invention described in this patent for (improved) expression of heterologous proteins in both *Bacillus* species, more specifically in this example *Bacillus subtilis* and *Bacillus amiloliquefaciens*. A preferred expression host is *Bacillus amiloliquefaciens*.

The *Bacillus subtilis* genome was published in 1997 and other Bacillus species followed (Kunst, F. *et al.* 1997. The complete genome sequence of the Gram-positive bacterium *Bacillus subtilis*. Nature 390:249-56; Rey, M.W. *et al.* (2004). Complete genome sequence of the industrial bacterium *Bacillus licheniformis* and comparisons with closely related *Bacillus* species. Genome Biology 5:R77; Rasko D.A. et al. (2005). Genomics of the *Bacillus cereus* group of organisms. FEMS Microbiology Reviews 29:303-329).

In this example, the full sequence of *B. subtilis* was chosen as the basis for calculating single-codon frequencies and codon-pair weights. Comparison of GC-content and tRNAs provided a similar picture for the *Bacillus* species mentioned (*vide supra*). This is an indication that the same statistics are applicable for other related *Bacillus* species. Moreover, from example 1 (see also Figure 4), it was already clear that related species show similar codon-pair frequencies.

In Figure 4 (see also example 1), a codon-pair comparison plot, based on full genome statistics for *B. subtilis vs. B. amyloliquefaciens* can be found. A good correlation between both data sets is observed. Moreover, it seems that *B. amyloliquefaciens* is more versatile, since there is a subgroup of codon-pair combinations that is well accepted in *B. amiloliquefaciens,* while it has highly negative values for *B. subtilis*; the opposite is not observed.

4.2. Experiment design

Three proteins sequences were selected for expression in both *Bacillus subtilis and Bacillus amiloliquefaciens*:

Protein 1: Xylose (glucose) isomerase xylA (EC.5.3.1.5) from *Bacillus stearothermophilus*;
Protein 2: Xylose (glucose) isomerase xylA (EC.5.3.1.5) from *Streptomyces olivochromogenes*;
Protein 3: L-arabinose isomerase (EC 5.3.1.4) from *Thermoanaerobacter mathranii*.

Table 4.1 Overview gene constructs; Protein 2 was chosen to further explore the codon-pair concept in broader sense.

	Gene	Protein	Single codon-optimization	Single codon & positive codon-pair optimization	Single codon & negative codon-pair optimization
Protein 1		SEQ ID NO. 9	SEQ ID NO. 16	SEQ ID NO. 13	
Protein 2		SEQ ID NO. 10	SEQ ID NO. 17	SEQ ID NO. 14	SEQ ID NO. 18
Protein 3	SEQ ID NO. 11	SEQ ID NO. 12		SEQ ID NO. 15	

Table 4.1 provides an overview of the methods applied to the 3 genes described above. For Protein 1, Protein 2 and Protein 3, the codon-pair optimization of the method of the invention is applied in addition to the single codon optimization developed before.

As a control, the effect of single codon optimization and negative codon pair optimization was tested experimentally by including 2 additional constructs for protein 2. One variant (SEQ.ID. 18) is designed where it is 'optimized' toward bad codon pairs (i.e. negative codon-pair optimization), and a second one with only single-codon optimization (SEQ.ID. 17). Protein 2 was chosen, since *Streptomyces* species show highly different codon-pair bias, see example 1 and Figure 4.

All designed *B. amyloliquefaciens* genes avoided the occurrence of *Nde*I (CATATG) and *Bam*HI (GGATTC) restriction sites. Additionally, they contained a single restriction site for removing the *E. coli* part of the cloning vector pBHA12.

4.3. Single codon optimization

Single-codon optimized variants for Protein 1 and Protein 2 were designed using the method described in Example 3.3 for single-codon optimization, resulting in SEQ ID NO. 16 and SEQ ID NO. 17, respectively. The applied single-codon distribution table (Table 4.2) was determined using the 50 most-highly expressed genes as determined by 24 Affymetrix GeneChips for *B. subtilus* 168 using 6 independent fermentation time-series. All GeneChips were normalized with respect to their arithmetic mean. The expression list excludes those genes that were deliberately over expressed in strain engineering, and hence their measured expression level cannot be correlated with their codon usage.

Determination of single codon distribution table 4.2 is done by visual inspection of codon frequency histograms of 50, 100, 200, 400 highest expressed sequences and of all *B. subtilis* sequences. In case of a clear trend toward either 0% or 100% for the most highly expressed

genes, an assignment of 0% and 100% was made, respectively. For the other codons that were not assigned, the average usage was calculated and normalized to the set of synonymous codons, by leaving out the assigned codons. The resulting target single-codon frequencies are given in Table 4.2, column 3.

Table 4.2 Codon-usage distribution for synthetic gene design on the basis of the 50 most highly-expressed genes and visual inspection of single codon usage histograms, *e.g.* Figure 24; Don' t care terms can be applied during codon-pair optimization to let the choice for those codons free, thus not taking into account single-codon optimization for these codons.

		Single codon distribution %	Don't care = 0 care = 1
A	Ala_GCT	50	0
	Ala_GCC	0	1
	Ala_GCA	50	0
	Ala_GCG	0	1
C	Cys_TGT	51	0
	Cys_TGC	49	0
D	Asp_GAT	63	1
	Asp_GAC	37	1
E	Glu_GAA	100	1
	Glu_GAG	0	1
F	Phe_TTT	55	0
	Phe_TTC	45	0
G	Gly_GGT	31	1
	Gly_GGC	34	1
	Gly_GGA	35	1
	Gly_GGG	0	1

H	His_CAT	71	0
	His_CAC	29	0
I	Ile_ATT	60	0
	Ile_ATC	40	0
	Ile_ATA	0	1
K	Lys_AAA	100	1
	Lys_AAG	0	1
L	Leu_TTA	39	0
	Leu_TTG	24	0
	Leu_CTT	37	0
	Leu_CTC	0	1
	Leu_CTA	0	1
	Leu_CTG	0	1
M	Met_ATG	100	1
N	Asn_AAT	45	0
	Asn_AAC	55	0
P	Pro_CCT	35	0
	Pro_CCC	0	1
	Pro_CCA	22	0
	Pro_CCG	43	0
Q	Gln_CAA	100	1
	Gln_CAG	0	1
R	Arg_CGT	38	0
	Arg_CGC	34	0
	Arg_CGA	0	1
	Arg_CGG	0	1

	Arg_AGA	28	0
	Arg_AGG	0	1
S	Ser_TCT	34	0
	Ser_TCC	0	1
	Ser_TCA	34	0
	Ser_TCG	0	1
	Ser_AGT	0	1
	Ser_AGC	32	0
T	Thr_ACT	33	0
	Thr_ACC	0	1
	Thr_ACA	46	0
	Thr_ACG	22	1
V	Val_GTT	47	1
	Val_GTC	0	1
	Val_GTA	23	1
	Val_GTG	30	1
W	Trp_TGG	100	1
Y	Tyr_TAT	62	0
	Tyr_TAC	38	0
	Stop_TGA	0	1
	Stop_TAG	0	1
	Stop_TAA	100	1

4.4. Codon pair optimization

Codon pair optimization was performed according the method of the invention. The optimized coding nucleotide sequences SEQ ID NO. 13-15 are the result of a run with the described software method. The applied parameters were: population size = 200; number of iterations = 1000; *cpi* = 0.20, CPW matrix = "Table C.4. CPW: *Bacillus subtilis* – highly expressed sequences" and the CR matrix = "Table B.1 column 5: CR table BAS: *Bacillus subtilis* – highly expressed sequences" (also in Table 4.2) and 'don't care elements as in Table 4.2. Moreover, a penalty value of +1 is added to fit_{combi} for each occurrence of a *Nde*I (CATATG) and *Bam*HI (GGATTC) restriction site.

The optimized coding nucleotide sequences SEQ ID NO. 18 is the result of a run with the described software method. The applied parameters were: population size = 200; number of iterations = 1000; *cpi* = 0.20, CPW matrix = -1 times "Table C.4. CPW: *Bacillus subtilis* – highly expressed sequences" (for obtaining codon-pair optimization toward bad codon pairs) and the CR matrix = "Table B.1 column 5: CR table BAS: *Bacillus subtilis* – highly expressed sequences" (also in Table 4.2) and 'don't care elements as in Table 4.2. Moreover, a penalty value of +1 is added to fit_{combi} for each occurrence of a *Nde*I (CATATG) and *Bam*HI (GGATTC) restriction site.

'Don't care' elements in Table 4.2 are chosen for those codons that do not show codon bias. This was done by visual inspection of the single-codon bias graph, see 4.3. The usage of such elements provides additional freedom to the codon-pair part of the optimization.

All optimizations converged toward a minimal value for fit_{combi}. The obtained objective values for SEQ ID NO. 13-15 and SEQ ID NO18 are given in Table 4.2, together with those for SEQ ID NO. 11, SEQ ID NO. 16 and SEQ ID NO. 17. From that data it is clear that single codon statistics are highly similar for SEQ ID NO. 16 and SEQ ID NO. 17 in comparison with SEQ ID NO. 14 and SEQ ID NO. 15. However, the method of the invention leads to a gene with an improved number of codon pairs with associated negative weights, indicating a more optimal usage of codon pairs having more negative weights associated with them, see Table 4.3.

'Optimizing' using maximization of fit_{cp} leads to a gene with an increased number of codon pairs with associated positive weights, indicating an increased usage of codon pairs having more positive weights associated with them, thus bad influence on translation characteristics is expected. For SEQ ID NO. 18 ($w_{cp}(g) \leq 0$) is 24 % vs. 85% for SEQ ID NO. 14, and also fit_{cp} increased from 1.20 to –1.43.

Table 4.3 Codon optimization; objective fitness values for genes for expression in *B. subtilis* and *B. amyloliquefaciens*.

Sequence	Type	fit_{sc}	fit_{cp}	$w_{cp}(g) \leq 0$	fit_{combi} (cpi=0.2)
SEQ ID NO. 11	WT	0.078	0.097	41.1%	0.350
SEQ ID NO. 13	sc + cp optimized	0.004	-0.293	89.1%	-1.439
SEQ ID NO. 14	sc + cp optimized	0.004	-0.292	84.8%	-1.431
SEQ ID NO. 15	sc + cp optimized	0.003	-0.303	89.2%	-1.493
SEQ ID NO. 16	sc optimized	0.002	-0.023	56.9%	-0.114
SEQ ID NO. 17	sc optimized	0.003	0.087	44.3%	0.428
SEQ ID NO. 18	sc + negative cp optimized	0.015	0.257	23.5%	1.196

5. Example 5: Testing the method of the invention for expression of three heterologous enzymes in *Bacillus subtilis* and *Bacillus amyloliquefaciens*.

5.1 Introduction

Example 5 describes the experiment and results of the expression of 3 heterologous genes with sequence variants of these in both *Bacillus subtilis* and *Bacillus amiloliquefaciens* hosts cells. Variants are made according the method of the invention, as described in Example 4.

5.2 Materials and Methods

5.2.1 *Bacillus* growth media

2*TY (per L): tryptone peptone 16 g, yeast extract Difco 10 g, NaCl 5 g.

5.2.2 Transformation of *B. subtilis*

Media

2x Spizizen medium: 28 g K_2HPO_4;12 g KH_2PO_4; 4 g $(NH_4)_2SO_4$; 2.3 g Na_3-citrate.$2H_2O$; 0.4 g $MgSO_4$ .7 H_2O; H_2O to 900 ml and adjust to pH 7.0-7.4 with 4N NaOH. Add H_2O to 1 liter.

Autoclave 20 minutes at 120°C.

1x *Spizizen-plus medium*: add to 50 ml 2x Spizizen medium 50 ml milliQ;1 ml 50% glucose and 100 µl casamino acids (20 µg/ml final concentration).

A single *Bacillus* colony (or an aliquot from a deep freeze vessel) from a non-selective 2xTY agar plate was inoculated in 10 ml 2xTY broth in a 100 ml shake flask. Cells were grown overnight in an incubator shaker at 37°C and ± 250 rpm. The OD was measured at 600 nm and the culture was diluted with 1x Spizizen-plus medium till $OD_{600\approx}0.1$. Cells were grown at 37°C and 250-300 rpm till the culture OD_{600} is 0.4 – 0.6. The culture was diluted 1:1 with 1x Spizizen medium supplemented with 0.5% glucose (starvation medium) and it was incubated for 90 min at 37°C and 250-300 rpm. The culture was centrifuged at 4500 rpm in a tabletop centrifuge for 10 minutes. 90% of the supernatant was removed and pellet was suspended in rest volume. DNA (1 - 5 µg in a maximum of 20 µl) was mixed with 0.5 ml competent cells in a universal and incubated for 1 hour at 37°C in a rotary shaking water bath under firm shaking (≈5/6). Cells

were plated (20 to 200 µl) on selective 2xTY agar plates containing 25-µg/ml kanamycin and incubated over night at 37°C.

5.2.3 Preparation of cell-free extract

The pellet obtained from 1 ml culture was resuspended in buffer A containing 10 mM Thris-HCl (pH 7.5), 10 mM EDTA, F50 mM NaCl, 1mg/ml lysozyme and protease inhibitors (Complete EDTA-free protease inhibitor cocktail, Roche). The resuspended pellets were incubated for 30 min at 37°C, for protoplastation and subsequently sonicated as follows: 30 sec, 10 amplitude microns (3 cycles), with 15 sec. cooling between cycles. After sonification cell debris was spun down by centrifugation (10 min, 13000 rpm at 4°C), and the clear lysates were used for further analysis.

5.2.4 Selection of glucose isomerase and L-arabinose isomerase encoding genes and design of synthetic genes for expression in *Bacillus amyloliquefaciens* and *Bacillus subtilis*

Three enzymes selected are:

1. *Bacillus stearothermophilus* xylose isomerase (P54272 Swissprot); protein sequence SEQ ID NO. 9,
2. *Streptomyces olivochromogenes* xylose isomerase (P15587 Swissprot); protein SEQ ID NO. 10,
3. *Thermoanaerobacter mathranii* L-arabinose isomerase (AJ 582623.1 EMBL, and also US2003/012971A1), protein SEQ ID NO. 11, nucleotide SEQ ID NO. 12.

As seen above the selected enzymes have different microbial origin. With the aim to overproduce these enzymes in *Bacillus subtilis* or *Bacillus amyloliquefaciens* we have optimized the nucleotide sequence for each protein in such a way that it is suitable for expression in *Bacillus* species, see Example 4.

We have optimized the nucleotide sequences that encode the above mentioned enzymes. The sequences are listed in the sequence list under the SEQ ID NO. 13. (*Bacillus stearothermophilus* glucose (xylose) isomerase), SEQ ID NO. 14. (*Streptomyces olivochromogenes* glucose (xylose) isomerase), SEQ ID NO. 15. (*Thermoanaerobacter mathranii* L-arabinose isomerase). As a control, one variant with a single-codon optimization without codon-pair optimization, SEQ ID

NO. 16-17, and one with single-codon optimization with "negative codon-pair optimization" SEQ ID NO. 18, were generated, see example 4 and Table 4.1.

5.3 Cloning of the glucose isomerase and L-arabinose isomerase encoding genes in the *E.coli/Bacillus* shuttle vector and transformation to *Bacilli*

For the expression of the selected genes in *Bacilli* we have used the pBHA12 *E.coli/Bacillus* shuffle vector (Figure 26). This vector is essentially derived from the expression vector pBHA-1 (EP 340878) in which a promoter derived from the *amy*Q gene of *Bacillus amyloliquefaciens* replaced the *Hpa*II promoter. The pBHA12 plasmid contains two multiple cloning sites (Figure 26). All selected and optimized genes were made synthetically (DNA 2.0, Menlo Park, CA, U.S.A.) as two fragments (A and B). The A fragment corresponding to the 5' end of the gene was clone behind the *amy*Q promoter. Both fragments have been extended with specific restriction endonuclease sites in order to allow direct cloning in the multiple cloning sites 1 and 2 (see Figure 27). The 3' end of the fragment A and 5' end of the fragment B overlap by a unique restriction endonuclease site that allows excision of the *E. coli* part of the vector and back ligation prior to the transformation of *Bacillus subtilis* (CBS 363.94). During the procedure of cloning and transformation of *B. subtilis*, *E. coli* was used as an intermediate host. The two-step cloning approach in pBHA12 was chosen in order to avoid possible problems during cloning and propagation of the expression vectors in *E. coli*. In Table 5.1 the restriction enzyme recognition sites added to fragments A and B are listed as well as the unique restriction site that allows back ligation and as such reconstruction of an entire and functional gene. All the 5' ends of the A fragments contain *Nde*I site (recognition sequence CATATG) that allows cloning of genes as a fragment starting exactly at their respective start codon (ATG).

Table 5.1. The summary of the restriction endonuclease (RE) cloning sites that have been added to the gene fragments to facilitate the cloning in pBHA12.

Gene/RE	Fragment A		Fragment B		Unique RE site (position in the gene)
	5' end	3' end	5' end	3' end	
B. stearothermophilus GI	*Nde*I	*Bam*HI	*Sma*I	*Kpn*I	*Pvu*II (496 bp)
S. olivochromogenes GI	*Nde*I	*Mlu*I	*Eco*RV	*Kpn*I	*Cla*I (372 bp)
T. mathranii ARAA	*Nde*I	*Mlu*I	*Sac*I	*Kpn*I	*Cla*I (708 bp)

The A and B fragments of 5 genes have been cloned in two steps in the MCS1 and 2, respectively, as shown for the SEQ ID NO. 13 in Figure 27, using the standard molecular biology methods (Sambrook & Russell, *Molecular Cloning: A Laboratory Manual, 3rd Ed.*, CSHL Press, Cold Spring Harbor, NY, 2001; and Ausubel *et al.*, *Current Protocols in Molecular Biology*, Wiley InterScience, NY, 1995). The transformation was performed in the *E.coli* TOP10 (Invitrogen) or INV110 (Invitrogen) in the case of using methylation sensitive restriction endonucleases in a further step. Several *E. coli* ampicilline resistant transformants for each expression construct were isolated using the mini or midi plasmid isolation kits (Macherey-Nagel and Sigma, respectively). The correct ligation of the corresponding A and B fragments in the pBHA12 vector was confirmed by restriction analysis. In the next step the pBHA12 plasmids that contained the A and B fragments of the genes were digested with the unique restriction endonuclease (see Table 5.1) to excise the *E. coli* part of the vector. The *Bacillus* part of the vector that contained the interrupted gene was isolated from the agarose gel using gel extraction kit (Macherey-Nagel) and back ligated. The ligation mixture was transformed to *B. subtilis* CBS 363.94 strain by competent cell transformation. Several *B. subtilis* kanamycin resistant transformants for each expression construct were isolated using the mini or midi plasmid isolation kits (Macherey-Nagel and Sigma, respectively). The expression constructs were checked by restriction analysis for the correct pattern after the excision of the *E. coli* part and the back ligation of the *Bacillus* part of the pBHA12 vector. For each construct three *B. subtilis* transformants were selected for analysis of the cell free extract.

5.4 Detection of overproduced enzymes in *Bacilli*

Three *B. subtilis* transformants and three *B. amyloliquefaciens* transformants for each construct were used to analyze the cell free extract for the presence of the corresponding protein – glucose or L-arabinose isomerase. The 2xTY fermentation media were used to grow the strains. Samples (1ml) were taken at 24 hours of fermentation (in shake flask) and the cell free extract was prepared including protease inhibitors in the extraction buffer. 13µl of the cell free extract were analyzed on SDS-PAGE (Invitrogen). For several transformants a clear band corresponding to the expected Mw of the overexpressed protein was detected. A visual comparison of the bands is given in Table 5.2. It is clear that the method of the invention improved protein production for *Bacillus stearothermophilus* xylose isomerase, *Streptomyces olivochromogenes* xylose isomerase and *Thermoanaerobacter mathranii* L-arabinose isomerase, by using the codon-pair method, *i.e.* this results in improved protein production in comparison

with either the WT reference gene or the single-codon optimized variants. Moreover, if negative codon-pair optimization was applied together with single-codon optimization, no product was detected.

Table 5.2 Overexpression of three heterologous genes in *Bacilli*. WT: Wild type; sc: single codon optimization; cp: codon pair optimization; cp^-: negative codon pair optimization.

	B. subtilis				*B. amyloliquefaciens*			
	WT	sc	sc & cp	sc & cp^-	WT	sc	sc & cp	sc & cp^-
Bacillus stearothermophilus xylose isomerase (SEQ ID NO. 16, 13)		+	+++			+	+++	
Streptomyces olivochromogenes xylose isomerase (SEQ ID NO. 17, 14, 18)		+	++	0		+	++	0
Thermoanaerobacter mathranii L-arabinose isomerase (SEQ ID 12, 15)	0/+		++		0		++	

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APPENDIX 1: List of symbols and equations

Single codon:

c_i

Codons encoding the same amino acid:

$syn(c_i)$

Number of occurrences of the codon c_i:

$n_{sc}(c_i)$

Ratio of the codon c_k (compared to its synonyms):

$$r_{sc}(c_k) = n_{sc}(c_k) \Big/ \sum_{c_l \in syn(c_k)} n_{sc}(c_l)$$

Codon pair:

(c_i, c_j)

Occurrences (observed number) of codon pair:

$n_{obs}((c_i, c_j))$

Expected number of this codon pair:

$$n_{exp}^{own}((c_i, c_j)) = r_{sc}^{all}(c_i) \cdot r_{sc}^{all}(c_j) \cdot \sum_{\substack{c_m \in syn(c_i) \\ c_n \in syn(c_j)}} n_{obs}((c_m, c_n))$$

Corresponding standard deviation:

$$\sigma((c_i, c_j)) = \sqrt{n_{exp}((c_i, c_j)) \cdot (1 - r_{sc}^{all}(c_i) \cdot r_{sc}^{all}(c_j))}$$

Corresponding standard score (z-score):

$$z((c_i, c_j)) = \frac{(n_{obs}((c_i, c_j)) - n_{\exp}((c_i, c_j))}{\sigma((c_i, c_j))}$$

Bias coefficient for a codon pair:

$$bias((c_i,c_j)) = \frac{n_{obs}((c_i,c_j)) - n_{exp}((c_i,c_j))}{\max(n_{obs}((c_i,c_j)), n_{exp}((c_i,c_j)))}$$

Combined "expected" values (for weights):

$$n_{exp}^{combi}((c_i,c_j)) = r_{sc}^{all}(c_i) \cdot r_{sc}^{all}(c_j) \cdot \sum_{\substack{c_k \in syn(c_i) \\ c_l \in syn(c_j)}} n_{obs}^{high}((c_k,c_l))$$

Codon pair weights – method one sequence group (or genome):

$$w((c_i,c_j)) = \frac{n_{exp}^{all}((c_i,c_j)) - n_{obs}^{all}((c_i,c_j))}{\max(n_{obs}^{all}((c_i,c_j)), n_{exp}^{all}((c_i,c_j)))}$$

Codon pair weights – method highly expressed group with reference group (or genome):

$$w((c_i,c_j)) = \frac{n_{exp}^{combi}((c_i,c_j)) - n_{obs}^{high}((c_i,c_j))}{\max(n_{obs}^{high}((c_i,c_j)), n_{exp}^{combi}((c_i,c_j)))}$$

APPENDIX 2: CR vectors

Table B.1: CR matrix values for the following organisms in columns: (1) AN: *A. niger* full genome - method: statistical distribution; (2) ANS: *A. niger* 250 highly-expressed genes - method: visual inspection, (3) AN_d: *A. niger* care-don't care (0-1) vector; (4) BS: *B. subtilis* full genome - method: statistical distribution; (5) BSS: *B. subtilis* 50 highly-expressed genes - method: visual inspection, (6) BS_d: *B. subtilis* care-don't care (0-1) vector; (7) EC: *E. coli* full genome 4298 seq; - method: statistical distribution; (8) ECS *E. coli* highly expressed group 100 seq from Carbone et al. (2003) - method: visual inspection; (9) EC_d: *E. coli* care-don't care (0-1) vector; (10) BA: *B. amyloliquefaciens* full genome - method: statistical distribution; (11) BAS: *B. amyolliquefaciens* 50 highly-expressed genes - method: visual inspection, (12) BS_d: *B. amyolliquefaciens* care-don't care (0-1) vector; (13) SC: *S. cerevisiae* full genome - method: statistical distribution; (14) SCS: *S. cerevisiae* 200 highly-expressed genes - method: visual inspection, (15) SC_d: *S. cerevisiae* care-don't care (0-1) vector; (16) SCO: *S. coelicolor*A3(2) full genome - method: statistical distribution

.

Note: For fungal microorganisms, and more specific *P. chrysogenum*, *A.* Oryzae, *A. terreus*, *A. nidulans*, *A. fumigatus*, *T. reesei*, *N. fischerii*, the CR vector derived using the *A. niger* sequences applies. For yeast in general, and more specific *K. lactis* and *S. pombe*, the CR vector derived using the *S. cerevisiae* sequences applies. For *Streptomyces* species the CR vector derived using *S. coelicolor* A3(2) applies.

		1	2	3	4	5	6	7	8	9	10	11	12
		AN	ANS	AN_d	BS	BSS	BS_d	EC	ECS	EC_d	BA	BAS	BA_d
1	AAA	33	0	1	71	100	1	75	81	0	69	100	1
2	AAC	58	100	1	43	55	0	73	100	0	66	50	0
3	AAG	67	100	1	29	0	1	25	19	0	31	0	1
4	AAT	42	0	1	57	45	0	66	0	0	76	50	0
5	ACA	21	0	1	41	46	0	14	0	0	29	30	0
6	ACC	35	70	1	16	0	1	42	57	1	21	0	1
7	ACG	22	0	1	26	22	1	26	0	0	38	40	0
8	ACT	23	30	1	17	33	0	18	43	1	13	30	0
9	AGA	13	0	1	27	28	0	5	0	0	14	20	0
10	AGC	18	21	1	22	32	0	27	28	1	22	30	0
11	AGG	12	0	1	10	0	1	3	0	0	7	0	1
12	AGT	13	0	1	11	0	1	16	0	0	9	0	1
13	ATA	14	0	1	14	0	1	9	0	0	15	0	1
14	ATC	52	73	1	35	40	0	41	72	1	42	40	0
15	ATG	100	100	1	100	100	1	100	100	0	100	100	1
16	ATT	34	27	1	51	60	0	51	28	1	44	60	0
17	CAA	40	0	1	53	100	1	36	17	0	42	60	0
18	CAC	51	100	1	32	29	0	42	81	0	41	40	0
19	CAG	60	100	1	47	0	1	64	83	0	58	40	0
20	CAT	49	0	1	68	71	0	58	19	0	59	60	0
21	CCA	22	0	1	20	22	0	20	14	0	11	0	1
22	CCC	29	64	1	10	0	1	13	0	0	17	0	1
23	CCG	24	0	1	41	43	0	49	86	0	52	60	0

24	CCT	25	36	1	29	35	0	17	0	0	20	40	0
25	CGA	15	0	1	10	0	1	7	0	0	12	0	1
26	CGC	25	51	1	19	34	0	38	34	0	32	40	0
27	CGG	18	0	1	15	0	1	10	0	0	20	0	1
28	CGT	16	49	1	18	38	0	36	66	0	15	40	0
29	CTA	10	0	1	5	0	1	4	0	0	4	0	1
30	CTC	24	38	1	11	0	1	10	0	0	17	0	1
31	CTG	25	32	1	23	0	1	47	100	0	28	20	0
32	CTT	17	17	1	23	37	0	11	0	0	21	30	0
33	GAA	42	26	1	69	100	1	69	80	0	66	40	0
34	GAC	49	64	1	36	37	1	37	64	1	44	40	0
35	GAG	58	74	1	31	0	1	31	20	0	34	60	0
36	GAT	51	36	1	64	63	1	63	36	1	56	60	0
37	GCA	21	0	1	29	50	0	22	30	0	18	30	0
38	GCC	32	51	1	20	0	1	27	0	0	26	0	1
39	GCG	21	11	1	25	0	1	34	23	0	38	30	0
40	GCT	26	38	1	26	50	0	17	47	0	18	40	0
41	GGA	24	16	1	32	35	1	12	0	0	26	30	0
42	GGC	32	35	1	33	34	1	39	42	1	41	40	0
43	GGG	19	0	1	16	0	1	15	0	0	17	0	1
44	GGT	25	49	1	19	31	1	34	58	1	16	30	0
45	GTA	11	0	1	21	23	1	16	29	0	16	25	0
46	GTC	35	54	1	24	0	1	21	0	0	32	25	0
47	GTG	30	19	1	26	30	1	36	19	0	28	25	0
48	GTT	24	27	1	29	47	1	26	53	0	23	25	0
49	TAA	27	100	1	62	100	1	59	100	0	41	100	1
50	TAC	58	100	1	34	38	0	42	76	1	59	50	0
51	TAG	31	0	1	22	0	1	32	0	0	21	0	1
52	TAT	42	0	1	66	62	0	58	24	1	16	50	0
53	TCA	13	0	1	24	34	0	13	0	0	16	30	0
54	TCC	23	44	1	12	0	1	14	31	1	16	0	1
55	TCG	17	14	1	10	0	1	14	0	0	61	40	0
56	TCT	17	21	1	21	34	0	15	41	1	100	30	0
57	TGA	42	0	1	16	0	1	9	0	0	39	20	0
58	TGC	59	100	1	54	49	0	55	100	0	17	30	0
59	TGG	100	100	1	100	100	1	100	100	0	41	0	1
60	TGT	41	0	1	46	51	0	45	0	0	14	0	1
61	TTA	6	0	1	21	39	0	14	0	0	59	0	1
62	TTC	65	100	1	30	45	0	41	77	1	69	40	0
63	TTG	18	13	1	16	24	0	13	0	0	66	100	1
64	TTT	35	0	1	70	55	0	59	23	1	31	60	0
		AN	ANS	AN_d	BA	BAS	BA_d	EC	ECS	EC_d	BS	BSS	BS_d
		1	2	3	4	5	6	7	8	9	10	11	12

Table B.1 continued

		13	14	15	16	17	18	19	20	21	22	23	24
		SC	SCS	SC_d	SCO								
1	AAA	59	21	1	5								
2	AAC	40	75	1	96								
3	AAG	41	79	1	95								
4	AAT	60	25	1	4								
5	ACA	31	6	1	2								
6	ACC	21	40	1	65								
7	ACG	14	2	1	31								
8	ACT	34	52	1	2								
9	AGA	47	76	1	1								
10	AGC	11	3	1	25								
11	AGG	21	3	1	4								
12	AGT	16	4	1	3								
13	ATA	28	0	1	2								
14	ATC	26	48	1	96								
15	ATG	100	100	1	100								
16	ATT	46	58	1	2								
17	CAA	69	90	1	5								
18	CAC	36	59	1	93								
19	CAG	31	10	1	95								
20	CAT	64	41	1	7								
21	CCA	41	74	1	2								
22	CCC	16	5	1	41								
23	CCG	13	0	1	54								
24	CCT	31	23	1	2								
25	CGA	7	0	1	3								
26	CGC	6	1	1	47								
27	CGG	4	0	1	39								
28	CGT	14	25	1	6								
29	CTA	14	9	1	0								
30	CTC	6	0	1	36								
31	CTG	11	5	1	60								
32	CTT	13	3	1	2								
33	GAA	70	85	1	15								
34	GAC	35	51	1	95								
35	GAG	30	15	1	85								
36	GAT	65	49	1	5								
37	GCA	30	2	1	4								
38	GCC	22	33	1	58								
39	GCG	11	0	1	36								
40	GCT	37	64	1	2								
41	GGA	23	0	1	7								

42	GGC	20	8	1	64
43	GGG	12	1	1	19
44	GGT	45	95	1	10
45	GTA	22	0	1	3
46	GTC	20	39	1	55
47	GTG	19	8	1	40
48	GTT	39	54	1	2
49	TAA	-	100	1	-
50	TAC	43	74	1	95
51	TAG	-	0	1	-
52	TAT	57	26	1	5
53	TCA	21	8	1	2
54	TCC	16	32	1	41
55	TCG	10	5	1	28
56	TCT	26	48	1	1
57	TGA	-	0	1	-
58	TGC	38	13	1	91
59	TGG	100	100	1	100
60	TGT	62	87	1	9
61	TTA	28	21	1	0
62	TTC	41	71	1	98
63	TTG	28	62	1	2
64	TTT	59	29	1	2

		SC	SCS	1	SCO								
		13	14	15	16	17	18	19	20	21	22	23	24

APPENDIX 3: CPW matrices

Table C.1: CPW matrix *Aspergillus niger* full genome (left codon indicated in column 2, right codon indicated in row 2). Host cell: *A. niger*; Sequence data: full *A. niger* genome.

		1	2	3	4	5	6	7	8	9	10	11	12
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
1	AAA	0.62	0.37	0.38	0.34	-0.16	0.07	0.18	0.29	-0.19	-0.03	-0.14	0.11
2	AAC	-0.17	-0.28	-0.23	-0.05	0.08	-0.25	-0.01	0.03	0.02	-0.30	0.17	-0.04
3	AAG	-0.02	-0.20	-0.24	-0.05	-0.02	-0.04	-0.12	0.03	-0.14	-0.05	-0.18	-0.03
4	AAT	0.24	0.45	0.44	0.22	0.16	0.16	0.15	0.06	0.19	0.17	0.23	0.08
5	ACA	0.00	0.09	0.25	0.04	-0.25	0.04	0.14	0.20	-0.25	-0.01	-0.22	0.10
6	ACC	-0.17	-0.35	-0.28	-0.07	0.11	-0.30	0.17	0.01	-0.08	-0.22	0.07	-0.02
7	ACG	-0.18	0.01	-0.06	-0.05	0.00	0.21	-0.14	0.10	-0.25	0.15	-0.36	0.00
8	ACT	0.36	0.57	0.53	0.40	0.13	0.17	0.17	-0.22	0.03	0.27	0.15	0.20
9	AGA	-0.01	0.05	0.06	-0.08	-0.18	0.19	0.10	0.11	-0.37	-0.17	-0.30	-0.15
10	AGC	-0.28	-0.26	-0.26	-0.25	0.00	-0.06	0.04	0.03	-0.20	-0.31	-0.04	-0.21
11	AGG	-0.31	0.08	-0.22	-0.32	-0.17	0.31	-0.25	0.01	-0.39	0.10	-0.52	-0.18
12	AGT	0.21	0.35	0.47	0.17	0.24	0.37	0.28	0.13	0.21	0.28	0.27	0.05
13	ATA	0.06	0.25	0.38	0.16	-0.21	0.03	0.08	0.04	-0.10	0.07	-0.07	0.17
14	ATC	-0.27	-0.35	-0.31	-0.15	0.03	-0.30	-0.03	-0.04	0.14	-0.10	0.20	0.02
15	ATG	0.02	-0.06	-0.01	0.09	0.05	0.01	-0.10	0.04	-0.13	-0.14	-0.08	0.00
16	ATT	0.50	0.55	0.56	0.45	0.34	0.26	0.26	0.16	0.41	0.44	0.46	0.38
17	CAA	0.27	0.21	0.25	0.10	-0.15	-0.01	0.14	0.20	-0.07	-0.09	0.05	0.03
18	CAC	-0.29	-0.25	-0.26	-0.18	-0.05	-0.22	0.01	-0.03	0.11	-0.25	0.32	-0.09
19	CAG	-0.17	-0.08	-0.13	-0.11	-0.08	0.09	-0.09	-0.06	-0.08	-0.01	0.02	-0.01
20	CAT	0.23	0.44	0.46	0.09	0.08	0.18	0.15	0.04	0.42	0.29	0.50	0.22
21	CCA	0.10	0.16	0.24	0.01	-0.24	0.01	0.12	0.02	-0.12	0.13	-0.11	0.17
22	CCC	-0.28	-0.36	-0.37	-0.15	0.09	-0.15	0.03	-0.04	-0.12	-0.17	0.05	-0.06
23	CCG	-0.14	0.07	0.06	-0.09	-0.12	0.08	-0.14	0.00	-0.04	0.32	-0.06	0.14
24	CCT	0.38	0.46	0.48	0.26	0.09	0.18	0.16	-0.02	0.31	0.38	0.33	0.23
25	CGA	0.17	0.19	0.28	0.12	-0.19	0.06	0.16	0.17	-0.03	-0.14	0.01	0.03
26	CGC	-0.24	-0.25	-0.26	-0.22	-0.07	-0.16	-0.16	0.03	0.01	-0.32	0.18	-0.27
27	CGG	-0.22	0.13	0.01	-0.15	-0.26	0.15	-0.31	-0.11	-0.24	0.07	-0.19	-0.18
28	CGT	0.51	0.45	0.67	0.48	0.29	0.24	0.32	0.17	0.63	0.44	0.58	0.40
29	CTA	0.24	0.26	0.43	0.25	-0.03	0.03	0.33	0.27	0.24	0.12	0.18	0.25
30	CTC	-0.23	-0.30	-0.20	-0.11	0.03	-0.24	0.09	-0.02	0.29	-0.17	0.33	-0.06
31	CTG	-0.16	-0.12	-0.13	0.04	0.12	0.07	0.02	0.09	0.12	0.01	0.04	0.09
32	CTT	0.54	0.52	0.64	0.48	0.19	0.23	0.26	0.11	0.56	0.44	0.55	0.38
33	GAA	0.46	0.27	0.24	0.09	-0.09	0.06	0.09	0.17	-0.23	-0.16	-0.14	-0.12
34	GAC	-0.18	-0.21	-0.28	-0.19	0.01	-0.13	-0.03	0.00	0.01	-0.31	0.05	-0.23
35	GAG	-0.07	-0.07	-0.23	-0.19	-0.05	0.10	-0.22	-0.03	-0.19	-0.09	-0.31	-0.20
36	GAT	0.24	0.34	0.36	0.09	0.06	0.12	0.02	-0.01	0.20	0.19	0.27	0.01
37	GCA	0.08	0.09	0.15	0.00	-0.16	0.07	0.05	0.04	-0.19	0.07	-0.23	0.06
38	GCC	-0.28	-0.36	-0.28	-0.23	0.10	-0.11	-0.04	-0.05	-0.05	-0.25	-0.01	-0.26

39	GCG	-0.07	0.11	-0.06	-0.08	-0.16	0.15	-0.26	0.00	-0.18	0.28	-0.31	0.05
40	GCT	0.38	0.60	0.48	0.38	0.16	0.21	0.10	-0.12	0.18	0.31	0.22	0.13
41	GGA	0.03	-0.09	-0.11	-0.19	-0.21	0.07	-0.09	-0.05	-0.37	-0.20	-0.30	-0.28
42	GGC	-0.12	-0.13	-0.19	-0.04	-0.10	-0.12	-0.11	-0.04	0.10	-0.25	0.15	-0.27
43	GGG	-0.33	0.21	-0.17	-0.29	-0.15	0.34	-0.26	-0.02	-0.31	0.20	-0.52	-0.25
44	GGT	0.34	0.31	0.65	0.32	0.24	0.17	0.38	0.03	0.31	0.21	0.45	-0.02
45	GTA	0.22	0.30	0.38	0.09	-0.13	0.09	0.08	0.12	0.18	0.38	0.07	0.39
46	GTC	-0.20	-0.34	-0.33	-0.24	0.14	-0.18	0.00	-0.18	0.18	-0.19	0.15	-0.11
47	GTG	-0.01	0.03	-0.06	0.06	-0.01	0.09	-0.22	-0.12	0.03	0.16	-0.27	0.24
48	GTT	0.53	0.55	0.50	0.38	0.35	0.31	0.13	-0.03	0.43	0.37	0.24	0.28
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.18	-0.29	-0.24	-0.06	0.13	-0.23	0.00	0.01	0.15	-0.20	0.34	-0.06
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.33	0.44	0.41	0.24	0.18	0.14	0.05	0.05	0.32	0.33	0.31	0.21
53	TCA	0.01	0.22	0.29	-0.03	-0.33	0.02	0.05	-0.09	-0.18	0.11	-0.27	0.14
54	TCC	-0.21	-0.30	-0.30	-0.07	0.07	-0.21	0.10	0.00	-0.01	-0.19	0.08	0.13
55	TCG	-0.14	0.06	-0.02	-0.11	-0.09	0.00	-0.20	-0.09	-0.07	0.21	-0.21	0.10
56	TCT	0.44	0.55	0.56	0.37	0.03	0.15	0.17	-0.13	0.22	0.35	0.30	0.37
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	-0.26	-0.19	-0.25	-0.23	-0.10	-0.10	-0.15	-0.07	-0.09	-0.10	-0.04	-0.26
59	TGG	-0.09	0.02	0.05	-0.03	-0.03	0.15	-0.15	-0.04	-0.28	-0.01	-0.29	-0.22
60	TGT	0.27	0.43	0.61	0.31	0.16	0.25	0.14	0.08	0.39	0.47	0.37	0.32
61	TTA	0.31	0.39	0.41	0.20	-0.05	0.13	0.11	0.09	0.04	0.24	-0.01	0.13
62	TTC	-0.18	-0.30	-0.27	-0.08	0.14	-0.24	0.05	-0.06	0.19	-0.09	0.20	0.02
63	TTG	-0.17	-0.12	-0.26	-0.24	-0.17	-0.08	-0.34	-0.29	-0.08	0.08	-0.35	-0.12
64	TTT	0.54	0.58	0.61	0.46	0.25	0.19	0.09	0.08	0.40	0.41	0.29	0.29
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
		1	2	3	4	5	6	7	8	9	10	11	12

Table C.1 continued

		13	14	15	16	17	18	19	20	21	22	23	24
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
1	AAA	-0.14	0.21	0.19	0.31	-0.14	-0.07	0.16	-0.08	-0.11	-0.04	0.05	0.19
2	AAC	0.24	-0.17	-0.09	0.08	-0.02	-0.18	-0.11	0.10	0.05	-0.19	-0.05	0.08
3	AAG	-0.04	-0.13	-0.08	-0.01	0.06	0.00	-0.06	0.08	0.03	-0.09	0.00	0.05
4	AAT	0.06	0.08	0.14	0.04	0.06	0.16	0.15	0.02	0.07	0.05	0.10	0.05
5	ACA	-0.11	0.20	0.04	0.20	-0.07	0.01	0.05	0.00	-0.22	-0.02	0.00	0.05
6	ACC	0.11	-0.29	-0.14	-0.07	0.09	-0.12	0.08	0.20	0.19	0.02	0.11	0.21
7	ACG	-0.16	0.12	-0.05	0.09	-0.06	-0.02	-0.19	-0.07	-0.03	0.10	-0.15	0.04
8	ACT	0.12	0.18	0.26	0.09	-0.01	-0.01	0.04	-0.02	-0.02	-0.16	-0.07	-0.19
9	AGA	-0.31	0.19	0.06	0.09	-0.14	-0.05	-0.05	-0.15	-0.10	0.15	0.10	0.14
10	AGC	-0.08	-0.09	-0.20	-0.09	0.00	-0.05	-0.09	-0.12	0.13	0.22	0.13	0.16
11	AGG	-0.44	0.19	-0.09	-0.11	0.05	0.20	0.10	0.02	-0.15	0.27	-0.05	0.01
12	AGT	-0.20	0.03	0.11	-0.02	-0.04	0.11	0.07	-0.12	0.04	0.07	-0.05	0.02

13	ATA	-0.34	0.17	0.10	0.21	-0.14	0.11	0.07	-0.07	-0.20	-0.08	-0.02	-0.09
14	ATC	0.21	-0.25	-0.19	0.00	0.04	-0.18	-0.02	0.17	0.16	-0.09	0.21	0.19
15	ATG	-0.09	0.01	0.00	0.03	0.04	-0.04	-0.03	0.04	-0.01	0.01	-0.02	0.02
16	ATT	0.24	0.19	0.32	0.16	-0.03	0.07	0.03	-0.01	0.03	-0.19	-0.03	-0.16
17	CAA	-0.21	0.14	0.15	0.25	-0.16	0.02	0.22	-0.03	-0.15	0.02	0.10	0.14
18	CAC	0.21	-0.16	-0.13	-0.02	-0.14	-0.18	0.00	0.14	0.07	-0.01	0.06	0.15
19	CAG	-0.09	-0.07	-0.09	-0.07	0.01	0.04	-0.06	-0.04	-0.11	0.04	0.00	-0.01
20	CAT	-0.04	0.16	0.15	0.01	-0.06	0.14	0.15	-0.05	-0.07	-0.04	-0.03	-0.11
21	CCA	-0.02	0.24	0.09	0.08	-0.05	0.11	0.21	0.08	-0.30	0.08	-0.03	0.10
22	CCC	-0.06	-0.29	-0.20	-0.12	0.06	0.16	0.02	0.15	0.19	0.56	0.06	0.29
23	CCG	-0.14	0.09	-0.04	0.05	-0.08	0.02	-0.07	-0.10	-0.08	0.18	-0.19	0.01
24	CCT	0.07	0.20	0.26	0.08	-0.12	-0.17	0.01	-0.19	-0.23	-0.17	-0.20	-0.25
25	CGA	0.07	0.28	0.18	0.25	-0.15	-0.11	-0.08	-0.04	-0.27	0.05	-0.23	-0.03
26	CGC	-0.01	-0.23	-0.20	-0.14	0.07	0.07	-0.04	-0.07	0.23	0.20	0.23	0.31
27	CGG	-0.33	0.18	-0.06	-0.03	0.07	0.30	0.17	0.05	-0.23	0.12	-0.14	-0.08
28	CGT	0.11	0.01	0.31	0.19	-0.08	-0.10	0.02	-0.09	-0.13	-0.22	-0.20	-0.20
29	CTA	0.03	0.25	0.24	0.32	-0.19	-0.15	-0.04	-0.10	-0.26	-0.08	-0.05	-0.06
30	CTC	0.06	-0.22	-0.08	-0.03	0.06	-0.03	0.17	0.23	0.14	-0.12	0.31	0.13
31	CTG	0.05	0.00	-0.02	0.06	0.02	-0.06	-0.12	0.05	0.15	0.09	0.15	0.09
32	CTT	0.21	0.25	0.39	0.20	-0.12	-0.13	0.04	-0.18	-0.23	-0.34	-0.04	-0.33
33	GAA	-0.07	0.11	0.13	0.14	-0.05	0.07	0.17	0.00	0.00	0.09	0.10	0.16
34	GAC	0.10	0.00	-0.10	-0.03	-0.04	-0.15	-0.12	-0.03	0.16	-0.12	-0.02	-0.01
35	GAG	-0.05	-0.01	-0.09	-0.14	0.01	0.03	-0.09	-0.07	-0.09	0.02	-0.09	-0.09
36	GAT	-0.01	0.06	0.11	-0.08	0.10	0.22	0.09	-0.02	0.10	-0.02	-0.04	0.02
37	GCA	0.09	0.30	0.18	0.17	0.04	0.10	0.07	-0.02	-0.18	0.10	-0.10	-0.02
38	GCC	0.13	-0.27	-0.24	-0.28	0.21	0.00	0.04	0.14	0.28	0.20	0.15	0.20
39	GCG	0.01	0.23	0.02	0.08	-0.10	0.02	-0.24	-0.23	-0.09	0.06	-0.28	-0.07
40	GCT	0.12	0.18	0.24	-0.07	0.04	0.04	-0.02	-0.06	0.04	-0.13	-0.01	-0.26
41	GGA	-0.11	0.21	0.02	0.07	0.00	0.17	-0.01	-0.01	-0.08	0.16	-0.05	0.04
42	GGC	0.12	-0.04	-0.14	-0.10	-0.05	-0.15	-0.14	-0.12	0.16	0.07	0.09	0.00
43	GGG	-0.30	0.26	-0.08	-0.15	0.16	0.33	0.06	-0.04	-0.15	0.01	-0.20	-0.18
44	GGT	0.15	-0.13	0.26	-0.03	0.04	0.06	0.11	-0.02	0.11	-0.02	0.06	-0.15
45	GTA	-0.04	0.30	0.22	0.20	-0.17	-0.02	-0.04	-0.16	-0.29	-0.04	-0.11	-0.21
46	GTC	0.13	-0.22	-0.18	-0.23	0.23	-0.02	0.10	0.19	0.33	0.11	0.27	0.15
47	GTG	0.02	0.19	-0.01	-0.06	0.01	0.03	-0.21	-0.08	0.14	0.10	-0.15	-0.07
48	GTT	0.14	0.22	0.25	0.00	0.01	0.00	0.04	-0.08	-0.05	-0.21	-0.02	-0.32
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.18	-0.17	-0.11	0.04	0.02	-0.15	-0.05	0.13	0.17	-0.02	0.17	0.15
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.08	0.13	0.18	0.05	-0.01	0.11	0.06	-0.04	-0.06	-0.15	-0.15	-0.15
53	TCA	-0.24	0.20	0.04	0.07	0.00	0.18	0.14	0.12	-0.28	0.00	0.00	-0.02
54	TCC	-0.01	-0.25	-0.11	0.03	0.13	-0.02	0.08	0.16	0.12	0.12	0.09	0.18
55	TCG	-0.14	0.12	0.00	0.15	-0.12	0.05	-0.11	-0.12	-0.04	0.04	-0.14	-0.09
56	TCT	0.08	0.21	0.33	0.21	-0.08	-0.01	0.02	-0.09	-0.15	-0.21	-0.13	-0.27

57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	-0.05	-0.01	-0.14	-0.17	0.04	-0.04	-0.06	-0.05	0.26	0.17	0.06	0.15
59	TGG	-0.09	0.09	0.00	-0.09	0.05	0.00	-0.03	0.00	-0.02	0.06	-0.07	0.02
60	TGT	-0.02	0.16	0.23	0.12	-0.06	0.15	0.09	-0.01	-0.13	-0.11	-0.27	-0.21
61	TTA	-0.25	0.27	0.09	0.18	-0.18	-0.01	0.00	-0.20	-0.32	-0.01	-0.12	-0.15
62	TTC	0.30	-0.21	-0.13	-0.02	0.04	-0.20	-0.14	0.12	0.20	-0.11	0.11	-0.02
63	TTG	-0.23	-0.12	-0.28	-0.26	0.15	0.27	-0.02	0.05	0.21	0.27	0.09	0.08
64	TTT	0.28	0.21	0.29	0.13	0.10	0.17	0.19	0.07	0.00	-0.09	-0.01	-0.07
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
		13	14	15	16	17	18	19	20	21	22	23	24

Table 1 continued

		25	26	27	28	29	30	31	32	33	34	35	36
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
1	AAA	-0.14	0.13	0.00	0.25	-0.12	0.05	0.15	0.18	-0.15	-0.18	0.07	-0.04
2	AAC	0.02	-0.18	-0.06	-0.11	0.11	-0.20	-0.08	0.05	0.11	0.02	0.09	0.29
3	AAG	0.13	0.01	0.08	0.07	0.04	-0.06	-0.10	-0.04	0.10	0.09	-0.04	0.04
4	AAT	-0.02	0.09	-0.06	0.17	-0.10	0.03	-0.01	0.06	-0.12	-0.17	-0.13	-0.20
5	ACA	-0.01	0.23	0.14	0.44	-0.12	0.27	0.14	0.16	-0.10	-0.09	0.05	0.03
6	ACC	0.25	-0.06	0.20	0.08	0.13	-0.23	0.08	0.18	0.09	-0.11	0.11	0.17
7	ACG	-0.01	0.05	-0.04	0.28	-0.07	0.15	-0.11	0.07	-0.06	-0.05	-0.19	-0.13
8	ACT	-0.15	-0.16	-0.07	-0.22	-0.07	-0.10	-0.07	-0.11	0.00	0.15	0.04	0.04
9	AGA	0.00	0.26	-0.16	0.24	-0.18	0.25	0.11	0.06	-0.14	0.01	0.04	-0.04
10	AGC	0.06	0.20	0.02	0.02	0.23	0.30	0.19	0.09	-0.02	-0.05	0.03	0.14
11	AGG	0.19	0.37	0.21	0.37	-0.22	0.36	0.05	-0.09	-0.14	0.18	-0.22	-0.21
12	AGT	-0.21	-0.08	-0.26	-0.05	-0.27	-0.08	-0.20	-0.16	-0.16	-0.14	-0.11	-0.22
13	ATA	-0.12	0.32	0.08	0.17	-0.24	0.13	0.15	-0.06	0.03	0.17	0.25	0.22
14	ATC	0.07	-0.18	-0.01	-0.09	0.12	-0.18	0.08	0.17	0.14	-0.04	0.13	0.25
15	ATG	0.07	-0.01	0.06	0.06	0.00	0.00	-0.09	-0.07	0.03	0.00	-0.02	0.00
16	ATT	-0.16	-0.11	-0.13	-0.11	-0.09	-0.15	-0.09	-0.12	-0.19	-0.21	-0.24	-0.19
17	CAA	-0.03	0.13	0.03	0.15	-0.07	0.08	0.20	0.16	-0.18	-0.06	0.12	-0.08
18	CAC	0.02	-0.14	0.06	-0.23	0.19	-0.07	0.12	0.11	0.03	0.05	0.09	0.17
19	CAG	-0.04	-0.06	0.00	-0.02	-0.04	0.00	-0.15	-0.10	0.01	0.12	0.02	-0.02
20	CAT	-0.12	-0.09	-0.10	-0.14	-0.19	-0.08	-0.07	-0.13	-0.14	-0.02	0.00	-0.17
21	CCA	-0.09	0.26	0.06	0.33	-0.08	0.28	0.13	0.14	-0.11	-0.04	0.06	0.00
22	CCC	0.00	0.08	0.07	-0.12	0.22	-0.05	0.33	0.21	-0.04	-0.09	-0.02	0.07
23	CCG	0.02	0.01	0.00	0.21	-0.09	0.19	-0.11	0.04	-0.03	-0.01	-0.11	-0.09
24	CCT	-0.20	-0.15	-0.07	-0.34	-0.11	-0.12	-0.01	-0.24	0.06	0.15	0.18	0.02
25	CGA	-0.29	0.09	-0.15	0.18	-0.31	0.04	-0.17	0.03	0.04	0.10	0.17	0.13
26	CGC	0.24	0.04	0.13	-0.02	0.25	0.18	0.18	0.27	0.02	-0.04	0.09	0.10
27	CGG	0.08	0.24	0.05	0.26	-0.01	0.33	-0.05	0.09	0.02	0.14	0.00	-0.08
28	CGT	-0.18	-0.31	-0.17	-0.36	-0.29	-0.33	-0.26	-0.24	-0.06	-0.12	0.04	-0.12
29	CTA	-0.32	-0.03	-0.18	0.05	-0.32	0.06	0.16	-0.07	-0.03	0.01	0.15	0.11
30	CTC	0.03	-0.25	0.17	-0.10	0.09	-0.31	0.19	0.09	0.06	-0.09	0.14	0.20

31	CTG	0.02	-0.15	-0.05	-0.04	0.16	0.10	-0.04	0.09	-0.10	-0.10	-0.11	-0.02
32	CTT	-0.19	-0.12	-0.03	-0.25	-0.28	-0.30	-0.11	-0.32	0.00	-0.05	0.09	-0.02
33	GAA	0.07	0.27	0.06	0.26	-0.04	0.16	0.18	0.12	-0.14	-0.14	0.01	-0.10
34	GAC	-0.03	-0.11	-0.09	-0.17	0.17	-0.04	-0.01	-0.02	0.13	0.06	0.08	0.19
35	GAG	0.06	0.07	0.01	0.02	-0.03	0.08	-0.17	-0.12	0.12	0.22	-0.02	-0.02
36	GAT	0.01	0.08	-0.08	0.07	-0.03	0.05	-0.06	-0.03	-0.05	-0.04	-0.12	-0.17
37	GCA	-0.04	0.31	0.04	0.34	0.11	0.39	0.17	0.21	-0.07	-0.12	-0.08	-0.12
38	GCC	0.26	0.02	0.17	-0.06	0.23	0.00	0.08	0.15	0.10	-0.06	0.12	0.09
39	GCG	0.01	-0.05	-0.15	0.08	0.07	0.20	-0.26	0.01	0.00	0.02	-0.21	-0.12
40	GCT	-0.04	-0.03	-0.02	-0.30	0.01	-0.04	-0.08	-0.14	0.05	0.30	0.04	-0.01
41	GGA	-0.08	0.30	-0.08	0.16	0.02	0.39	0.07	0.18	-0.04	0.11	-0.05	0.01
42	GGC	0.12	0.01	0.10	-0.20	0.19	0.14	0.14	0.14	0.12	0.04	0.00	0.11
43	GGG	0.09	0.35	0.15	0.26	-0.12	0.32	-0.10	-0.12	0.02	0.28	-0.19	-0.17
44	GGT	0.07	-0.10	-0.04	-0.22	-0.08	-0.20	-0.16	-0.27	-0.05	-0.10	0.15	-0.19
45	GTA	-0.14	0.21	-0.12	0.26	-0.13	0.21	0.16	-0.05	0.08	0.20	0.20	0.14
46	GTC	0.13	-0.12	0.07	-0.05	0.23	-0.08	0.11	0.06	0.22	-0.05	0.08	0.17
47	GTG	-0.02	-0.13	-0.14	0.16	0.09	0.16	-0.15	-0.03	-0.05	0.07	-0.13	-0.17
48	GTT	-0.06	-0.06	-0.02	-0.14	-0.08	-0.10	-0.10	-0.20	-0.07	-0.01	-0.15	-0.13
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.05	-0.17	0.03	-0.16	0.18	-0.15	0.02	0.12	0.10	-0.03	0.06	0.18
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.10	-0.11	-0.07	-0.02	-0.12	-0.16	-0.10	-0.13	-0.06	-0.05	-0.12	-0.14
53	TCA	-0.07	0.32	-0.01	0.36	-0.11	0.28	0.26	0.10	-0.06	-0.03	0.13	0.12
54	TCC	0.14	-0.02	0.17	0.07	0.14	-0.19	0.16	0.13	0.03	-0.13	0.09	0.17
55	TCG	-0.07	0.00	-0.09	0.15	-0.07	0.15	-0.11	-0.03	-0.06	0.01	-0.12	-0.08
56	TCT	-0.14	-0.12	-0.05	-0.25	-0.16	-0.12	0.02	-0.15	0.02	0.15	0.14	0.05
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.20	0.13	0.12	-0.05	0.29	0.27	0.17	0.17	0.09	0.04	0.03	0.12
59	TGG	0.15	0.08	0.17	0.17	-0.14	0.09	-0.05	-0.07	0.01	0.12	-0.01	-0.10
60	TGT	-0.23	-0.16	-0.29	-0.09	-0.21	-0.16	-0.19	-0.23	-0.11	0.01	-0.04	-0.19
61	TTA	-0.23	0.25	-0.14	0.19	-0.33	-0.01	-0.06	-0.20	0.04	0.13	0.16	0.11
62	TTC	0.01	-0.22	-0.08	-0.20	0.18	-0.21	-0.01	0.01	0.14	0.04	0.11	0.24
63	TTG	0.12	0.20	0.09	0.27	0.16	0.25	0.06	0.04	-0.03	0.14	-0.14	-0.14
64	TTT	-0.07	0.11	0.09	0.18	0.01	0.00	0.11	0.01	-0.13	-0.20	-0.22	-0.21
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
		25	26	27	28	29	30	31	32	33	34	35	36

Table C.1 continued

		37	38	39	40	41	42	43	44	45	46	47	48
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
1	AAA	-0.27	-0.15	-0.04	0.06	-0.15	-0.15	-0.13	0.21	-0.26	-0.12	0.04	0.18
2	AAC	0.31	0.04	0.41	0.39	0.26	0.01	0.31	0.27	0.42	0.09	0.30	0.32
3	AAG	0.16	0.05	0.00	0.04	0.09	0.01	0.10	-0.03	0.22	-0.03	0.02	-0.02
4	AAT	-0.23	-0.26	-0.35	-0.23	-0.23	-0.26	-0.29	-0.02	-0.13	-0.30	-0.23	-0.25

5	ACA	-0.29	-0.07	0.01	0.06	-0.02	0.06	-0.01	0.34	-0.24	0.10	0.06	0.18
6	ACC	0.28	0.16	0.35	0.38	0.25	0.00	0.31	0.11	0.35	-0.07	0.21	0.18
7	ACG	-0.08	0.01	-0.30	-0.01	0.02	0.01	-0.21	0.07	-0.09	0.06	-0.25	0.03
8	ACT	-0.19	-0.17	-0.15	-0.27	-0.23	-0.20	-0.19	-0.28	-0.12	-0.14	-0.02	-0.27
9	AGA	-0.16	0.15	0.01	0.04	-0.22	0.09	-0.19	0.08	-0.35	0.19	0.08	0.14
10	AGC	0.18	0.15	0.31	0.27	0.16	0.08	0.21	0.16	0.27	0.13	0.17	0.20
11	AGG	0.00	0.32	-0.08	-0.03	-0.02	0.28	-0.25	0.08	-0.21	0.25	-0.13	-0.13
12	AGT	-0.09	-0.05	-0.23	-0.17	-0.29	-0.17	-0.32	-0.30	-0.31	-0.16	-0.31	-0.30
13	ATA	-0.16	0.14	0.14	0.13	0.16	0.28	0.12	0.37	-0.28	0.22	0.19	0.22
14	ATC	0.28	0.04	0.33	0.35	0.17	0.06	0.25	0.15	0.43	0.04	0.24	0.35
15	ATG	0.02	0.02	-0.04	-0.01	0.01	-0.05	0.05	0.02	-0.04	0.01	0.00	0.00
16	ATT	-0.23	-0.30	-0.30	-0.28	-0.28	-0.23	-0.28	-0.20	-0.16	-0.32	-0.26	-0.30
17	CAA	-0.23	-0.10	0.04	-0.02	-0.18	-0.20	-0.16	0.11	-0.28	-0.11	0.06	0.08
18	CAC	0.30	0.03	0.33	0.27	0.21	-0.03	0.32	0.15	0.44	0.02	0.48	0.21
19	CAG	0.07	0.14	0.00	0.02	0.08	0.08	0.25	0.00	0.06	0.03	0.03	0.03
20	CAT	-0.22	-0.11	-0.25	-0.16	-0.12	-0.16	-0.16	-0.04	-0.20	-0.23	-0.10	-0.28
21	CCA	-0.25	0.01	0.11	-0.07	-0.11	0.02	-0.03	0.20	-0.27	0.05	0.04	0.12
22	CCC	0.25	0.03	0.28	0.20	0.16	0.04	0.20	-0.02	0.25	-0.09	0.18	0.16
23	CCG	0.03	0.13	-0.13	-0.03	0.00	0.16	-0.12	0.10	-0.07	0.17	-0.13	-0.05
24	CCT	-0.16	0.01	-0.08	-0.28	-0.17	-0.07	-0.11	-0.22	-0.09	-0.06	0.02	-0.25
25	CGA	-0.23	0.08	-0.07	0.08	-0.12	-0.05	-0.01	0.23	-0.25	0.03	0.01	0.16
26	CGC	0.14	-0.06	0.24	0.31	0.16	-0.01	0.21	0.13	0.23	0.11	0.11	0.31
27	CGG	0.02	0.17	-0.24	-0.06	0.06	0.25	0.18	0.14	-0.23	0.19	-0.15	-0.02
28	CGT	-0.05	-0.23	-0.15	-0.26	-0.22	-0.19	-0.01	-0.44	-0.15	-0.28	-0.13	-0.27
29	CTA	-0.26	-0.08	0.11	0.00	-0.19	-0.13	0.06	0.19	-0.25	-0.05	0.18	0.14
30	CTC	0.31	-0.02	0.40	0.29	0.24	0.10	0.35	0.16	0.33	-0.08	0.32	0.24
31	CTG	-0.06	-0.06	-0.13	-0.09	-0.15	-0.05	-0.02	-0.12	-0.04	-0.03	-0.09	-0.01
32	CTT	-0.14	-0.10	-0.13	-0.22	-0.23	0.01	-0.18	-0.23	-0.01	-0.18	0.03	-0.27
33	GAA	-0.21	-0.14	-0.08	-0.06	-0.17	-0.13	-0.22	0.06	-0.26	-0.09	-0.01	0.01
34	GAC	0.32	0.17	0.38	0.39	0.29	0.13	0.21	0.26	0.36	0.28	0.25	0.30
35	GAG	0.14	0.19	-0.04	0.06	0.16	0.17	-0.02	0.04	0.04	0.18	-0.03	-0.02
36	GAT	-0.16	-0.17	-0.34	-0.23	-0.18	-0.15	-0.31	-0.07	-0.19	-0.13	-0.25	-0.29
37	GCA	-0.30	0.05	-0.02	-0.02	-0.11	0.01	0.00	0.17	-0.21	0.19	0.02	0.13
38	GCC	0.30	0.10	0.34	0.28	0.27	0.17	0.27	0.00	0.23	0.01	0.08	0.17
39	GCG	0.13	0.23	-0.23	0.14	0.15	0.14	-0.08	0.07	-0.04	0.26	-0.14	0.09
40	GCT	-0.12	-0.13	-0.18	-0.40	-0.18	-0.11	-0.22	-0.37	-0.11	-0.15	-0.15	-0.30
41	GGA	-0.06	0.23	0.10	0.08	-0.12	0.11	-0.09	0.09	-0.11	0.26	0.07	0.17
42	GGC	0.12	0.09	0.24	0.18	0.25	0.05	0.27	0.14	0.25	0.20	0.15	0.26
43	GGG	0.02	0.33	-0.12	0.01	0.28	0.42	0.28	0.21	-0.23	0.37	-0.20	-0.03
44	GGT	-0.14	-0.27	-0.09	-0.40	-0.22	-0.18	-0.07	-0.54	-0.20	-0.32	-0.18	-0.39
45	GTA	-0.25	-0.04	-0.01	0.00	-0.09	0.16	-0.08	0.37	-0.31	0.13	0.14	0.23
46	GTC	0.25	0.10	0.31	0.22	0.17	0.00	0.18	0.04	0.39	0.09	0.25	0.27
47	GTG	0.03	0.12	-0.08	-0.09	0.04	0.15	0.03	0.16	-0.09	0.15	-0.28	-0.09
48	GTT	-0.15	-0.10	-0.25	-0.32	-0.22	-0.15	-0.31	-0.30	-0.01	-0.17	-0.14	-0.34

49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.35	0.03	0.34	0.33	0.17	-0.07	0.28	0.20	0.42	0.13	0.19	0.30
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.17	-0.24	-0.38	-0.19	-0.17	-0.17	-0.18	-0.03	-0.11	-0.23	-0.26	-0.25
53	TCA	-0.24	0.02	0.14	0.03	0.00	0.17	-0.07	0.31	-0.27	0.09	0.12	0.18
54	TCC	0.17	-0.08	0.32	0.23	0.21	0.00	0.22	0.10	0.28	-0.07	0.19	0.21
55	TCG	0.07	0.09	-0.08	0.03	0.07	0.12	-0.06	0.23	-0.12	0.09	-0.11	0.06
56	TCT	-0.26	-0.18	-0.19	-0.35	-0.24	-0.14	-0.18	-0.20	-0.10	-0.08	-0.05	-0.20
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.18	0.04	0.24	0.20	0.25	0.18	0.14	-0.03	0.19	0.21	0.17	0.29
59	TGG	0.02	0.11	-0.12	-0.04	-0.07	0.07	0.18	-0.14	-0.20	0.24	-0.12	-0.05
60	TGT	-0.06	-0.15	-0.29	-0.22	-0.17	-0.03	-0.21	-0.26	-0.22	-0.21	-0.21	-0.31
61	TTA	-0.11	0.15	0.13	0.03	0.00	0.17	-0.15	0.19	-0.28	0.20	0.11	0.07
62	TTC	0.40	0.12	0.38	0.35	0.30	0.21	0.32	0.16	0.45	0.06	0.30	0.29
63	TTG	0.09	0.17	-0.15	-0.05	-0.01	0.21	-0.16	0.08	-0.01	0.13	-0.14	-0.12
64	TTT	-0.29	-0.33	-0.42	-0.36	-0.29	-0.28	-0.40	-0.27	-0.15	-0.30	-0.33	-0.31
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
		37	38	39	40	41	42	43	44	45	46	47	48

Table C.1 continued

		49	50	51	52	53	54	55	56	57	58	59	60
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
1	AAA	0.00	-0.25	0.00	-0.18	-0.32	-0.22	-0.04	-0.04	0.00	-0.37	-0.34	-0.29
2	AAC	0.00	-0.25	0.00	0.06	0.15	-0.09	-0.11	0.12	0.00	-0.19	-0.12	0.16
3	AAG	0.00	0.14	0.00	0.14	0.11	0.13	0.04	0.13	0.00	0.27	0.24	0.22
4	AAT	0.00	0.30	0.00	0.14	0.04	0.16	0.14	0.10	0.00	0.09	0.19	0.11
5	ACA	0.00	-0.14	0.00	-0.21	-0.25	-0.12	-0.06	-0.18	0.00	-0.14	-0.22	-0.14
6	ACC	0.00	-0.27	0.00	0.17	0.17	-0.22	-0.01	0.12	0.00	-0.23	-0.11	0.12
7	ACG	0.00	0.23	0.00	0.06	0.19	0.36	0.09	0.19	0.00	0.33	0.31	0.34
8	ACT	0.00	0.31	0.00	0.21	-0.07	0.02	-0.04	-0.07	0.00	0.03	0.17	-0.01
9	AGA	0.00	-0.05	0.00	-0.25	-0.05	0.25	0.15	0.09	0.00	-0.18	-0.18	-0.17
10	AGC	0.00	-0.23	0.00	-0.13	0.10	0.08	0.10	0.09	0.00	-0.21	-0.21	-0.14
11	AGG	0.00	0.44	0.00	-0.02	-0.05	0.43	0.12	0.19	0.00	0.39	0.21	0.05
12	AGT	0.00	0.30	0.00	0.02	0.21	0.44	0.38	0.34	0.00	0.15	0.21	0.16
13	ATA	0.00	-0.20	0.00	-0.31	-0.51	-0.32	-0.27	-0.37	0.00	-0.21	-0.26	-0.29
14	ATC	0.00	-0.27	0.00	0.12	0.17	-0.23	0.03	0.10	0.00	-0.10	-0.10	0.10
15	ATG	0.00	-0.01	0.00	0.02	0.08	0.07	0.02	0.00	0.00	-0.01	0.00	0.02
16	ATT	0.00	0.41	0.00	0.38	0.13	0.07	0.20	0.13	0.00	0.20	0.31	0.13
17	CAA	0.00	-0.07	0.00	-0.13	-0.19	-0.10	0.07	0.06	0.00	-0.22	-0.20	-0.24
18	CAC	0.00	-0.21	0.00	-0.02	0.11	-0.15	-0.06	0.05	0.00	-0.21	-0.15	0.08
19	CAG	0.00	0.13	0.00	0.00	-0.08	0.14	0.02	0.06	0.00	0.22	0.16	0.16
20	CAT	0.00	0.29	0.00	0.00	-0.07	0.09	0.02	0.04	0.00	0.17	0.19	0.06
21	CCA	0.00	-0.07	0.00	-0.09	-0.38	-0.15	-0.13	-0.17	0.00	-0.11	-0.18	-0.17
22	CCC	0.00	-0.17	0.00	0.23	0.15	-0.16	0.13	0.04	0.00	-0.08	-0.02	0.10

23	CCG	0.00	0.13	0.00	-0.16	-0.06	0.19	-0.08	0.01	0.00	0.26	0.06	0.21
24	CCT	0.00	0.11	0.00	0.09	-0.11	0.02	0.05	-0.12	0.00	-0.06	0.16	-0.09
25	CGA	0.00	-0.06	0.00	-0.16	-0.33	0.07	-0.17	0.03	0.00	-0.16	-0.16	-0.11
26	CGC	0.00	-0.16	0.00	0.00	0.04	-0.11	0.05	0.06	0.00	-0.14	-0.09	0.07
27	CGG	0.00	0.12	0.00	-0.20	-0.15	0.18	-0.24	-0.01	0.00	0.20	0.09	0.08
28	CGT	0.00	0.32	0.00	0.19	0.19	0.16	0.25	0.09	0.00	0.09	0.26	0.04
29	CTA	0.00	-0.18	0.00	-0.15	-0.34	-0.21	-0.08	-0.17	0.00	-0.14	-0.23	-0.20
30	CTC	0.00	-0.32	0.00	0.08	0.09	-0.34	0.13	-0.01	0.00	-0.23	-0.18	-0.09
31	CTG	0.00	0.13	0.00	0.03	0.07	0.14	0.05	0.12	0.00	0.21	0.15	0.19
32	CTT	0.00	0.19	0.00	0.16	-0.03	-0.06	0.06	-0.14	0.00	-0.10	0.07	-0.06
33	GAA	0.00	-0.12	0.00	-0.12	-0.12	-0.03	0.09	0.01	0.00	-0.17	-0.22	-0.22
34	GAC	0.00	-0.25	0.00	-0.11	0.13	-0.07	-0.23	-0.03	0.00	-0.22	-0.23	-0.15
35	GAG	0.00	0.20	0.00	-0.03	0.15	0.25	-0.01	0.12	0.00	0.23	0.21	0.08
36	GAT	0.00	0.32	0.00	0.12	0.14	0.28	0.12	0.20	0.00	0.29	0.30	0.16
37	GCA	0.00	-0.15	0.00	-0.24	-0.30	-0.07	-0.18	-0.24	0.00	-0.10	-0.09	-0.06
38	GCC	0.00	-0.22	0.00	0.11	0.24	-0.08	-0.03	0.07	0.00	-0.06	-0.11	-0.09
39	GCG	0.00	0.26	0.00	-0.14	0.12	0.31	-0.03	0.14	0.00	0.32	0.07	0.16
40	GCT	0.00	0.38	0.00	0.13	0.03	0.09	0.06	-0.07	0.00	0.06	0.18	-0.14
41	GGA	0.00	-0.14	0.00	-0.23	-0.12	0.17	0.02	-0.02	0.00	-0.02	-0.17	-0.22
42	GGC	0.00	-0.11	0.00	-0.04	0.01	-0.08	0.00	-0.14	0.00	-0.17	-0.16	-0.12
43	GGG	0.00	0.26	0.00	-0.27	0.01	0.38	0.00	0.00	0.00	0.32	0.09	-0.14
44	GGT	0.00	0.36	0.00	0.27	0.28	0.27	0.29	0.15	0.00	0.32	0.37	0.17
45	GTA	0.00	-0.24	0.00	-0.33	-0.43	-0.30	-0.30	-0.43	0.00	-0.29	-0.26	-0.18
46	GTC	0.00	-0.21	0.00	-0.02	0.14	-0.17	0.01	-0.01	0.00	-0.20	-0.12	0.02
47	GTG	0.00	0.28	0.00	-0.05	0.11	0.29	-0.09	-0.02	0.00	0.26	0.18	0.12
48	GTT	0.00	0.33	0.00	0.15	0.03	0.07	0.04	-0.10	0.00	0.17	0.14	0.00
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.00	-0.27	0.00	-0.03	0.22	-0.14	-0.17	-0.01	0.00	-0.17	-0.16	0.01
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.00	0.37	0.00	0.23	0.09	0.14	0.02	0.03	0.00	0.24	0.27	0.05
53	TCA	0.00	-0.13	0.00	-0.11	-0.43	-0.21	-0.15	-0.24	0.00	-0.15	-0.23	-0.18
54	TCC	0.00	-0.21	0.00	0.16	0.16	-0.23	0.10	0.00	0.00	-0.12	-0.01	0.18
55	TCG	0.00	0.20	0.00	-0.01	0.03	0.14	-0.15	0.00	0.00	0.30	0.11	0.23
56	TCT	0.00	0.28	0.00	0.18	-0.12	-0.13	-0.02	-0.25	0.00	0.05	0.26	-0.02
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.00	-0.15	0.00	-0.21	0.07	-0.19	-0.16	-0.09	0.00	-0.13	-0.16	-0.16
59	TGG	0.00	0.08	0.00	-0.10	0.02	0.12	0.04	0.00	0.00	0.08	0.00	-0.10
60	TGT	0.00	0.44	0.00	0.12	0.04	0.20	0.15	0.12	0.00	0.32	0.27	0.10
61	TTA	0.00	0.02	0.00	-0.23	-0.44	-0.13	-0.26	-0.29	0.00	-0.05	-0.26	-0.30
62	TTC	0.00	-0.24	0.00	0.04	0.12	-0.23	-0.04	0.00	0.00	-0.10	-0.12	-0.05
63	TTG	0.00	0.29	0.00	0.04	0.19	0.28	0.03	0.08	0.00	0.38	0.28	0.13
64	TTT	0.00	0.35	0.00	0.25	0.15	0.08	-0.03	-0.03	0.00	0.17	0.24	0.16
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
		49	50	51	52	53	54	55	56	57	58	59	60

Table C.1 continued

		61	62	63	64
		TTA	TTC	TTG	TTT
1	AAA	-0.29	-0.15	-0.09	-0.02
2	AAC	0.33	-0.19	0.14	-0.10
3	AAG	0.24	0.02	0.12	0.14
4	AAT	-0.04	0.21	0.14	0.34
5	ACA	-0.41	-0.04	-0.13	-0.11
6	ACC	0.23	-0.17	0.08	-0.04
7	ACG	0.12	0.26	0.06	0.00
8	ACT	-0.14	0.09	-0.10	0.21
9	AGA	-0.35	0.27	0.01	0.01
10	AGC	-0.16	-0.07	-0.14	-0.16
11	AGG	-0.25	0.28	-0.19	-0.06
12	AGT	-0.11	0.20	-0.07	0.24
13	ATA	-0.42	-0.23	-0.18	-0.33
14	ATC	0.17	-0.21	0.18	0.14
15	ATG	0.22	0.02	0.15	-0.03
16	ATT	0.23	0.27	0.19	0.46
17	CAA	-0.36	-0.11	-0.03	-0.07
18	CAC	0.26	-0.11	0.11	-0.10
19	CAG	0.12	0.06	0.14	0.09
20	CAT	-0.04	0.09	0.04	0.18
21	CCA	-0.32	0.01	-0.20	-0.17
22	CCC	0.04	-0.12	-0.04	0.09
23	CCG	-0.17	0.12	-0.22	-0.09
24	CCT	-0.17	0.06	-0.11	0.13
25	CGA	-0.24	-0.06	-0.02	-0.07
26	CGC	0.03	-0.19	0.16	0.03
27	CGG	-0.27	-0.13	-0.19	-0.20
28	CGT	-0.05	0.14	0.24	0.40
29	CTA	-0.28	-0.04	0.13	-0.14
30	CTC	0.20	-0.29	0.29	-0.01
31	CTG	0.34	0.15	0.23	0.17
32	CTT	0.00	-0.01	0.07	0.23
33	GAA	-0.19	0.00	-0.08	-0.08
34	GAC	0.29	-0.10	-0.08	-0.33
35	GAG	0.23	0.08	-0.03	-0.09
36	GAT	0.10	0.24	0.03	0.25
37	GCA	-0.26	0.02	-0.21	-0.20
38	GCC	0.13	-0.04	-0.08	-0.16
39	GCG	0.12	0.24	-0.23	-0.11
40	GCT	-0.17	0.08	-0.15	0.10

41	GGA	-0.26	0.03	-0.13	-0.15
42	GGC	0.00	-0.10	-0.09	-0.04
43	GGG	-0.33	0.00	-0.37	-0.36
44	GGT	0.12	0.23	0.28	0.43
45	GTA	-0.38	-0.13	-0.13	-0.25
46	GTC	0.23	-0.19	0.04	-0.11
47	GTG	0.26	0.28	-0.10	-0.17
48	GTT	0.22	0.20	0.06	0.34
49	TAA	0.00	0.00	0.00	0.00
50	TAC	0.25	-0.15	0.21	-0.11
51	TAG	0.00	0.00	0.00	0.00
52	TAT	0.18	0.21	0.15	0.25
53	TCA	-0.39	-0.08	-0.13	-0.14
54	TCC	0.05	-0.12	0.08	0.06
55	TCG	-0.01	0.14	-0.02	0.03
56	TCT	-0.13	0.02	-0.05	0.10
57	TGA	0.00	0.00	0.00	0.00
58	TGC	-0.10	-0.07	-0.13	-0.17
59	TGG	0.04	0.04	0.10	-0.06
60	TGT	-0.09	0.19	0.01	0.15
61	TTA	-0.39	-0.03	-0.14	-0.21
62	TTC	0.19	-0.24	0.00	-0.01
63	TTG	0.17	0.23	-0.05	0.03
64	TTT	0.28	0.29	0.15	0.56
		TTA	TTC	TTG	TTT
		61	62	63	64

Table C.2: CPW matrix A. *niger* highly expressed sequences (left codon indicated in column 2, right codon indicated in row 2). Host cell: *A. niger*; Sequence data: full *A. niger* genome; Highly expressed group: 400 seqs.

		1	2	3	4	5	6	7	8	9	10	11	12
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
1	AAA	0.93	0.64	0.65	0.92	0.61	0.65	0.67	0.57	0.07	0.61	-0.09	0.75
2	AAC	0.44	-0.48	-0.42	0.49	0.57	-0.50	0.16	-0.33	0.33	-0.25	0.60	0.13
3	AAG	0.51	-0.42	-0.36	0.48	0.27	-0.46	0.43	-0.18	-0.23	-0.14	0.13	0.23
4	AAT	0.60	0.68	0.75	0.65	0.35	0.63	0.44	0.80	0.75	0.36	0.80	0.31
5	ACA	0.29	0.45	0.56	0.71	0.22	0.43	0.15	0.66	0.33	0.58	-0.14	0.28
6	ACC	0.34	-0.58	-0.53	0.45	0.33	-0.59	0.43	-0.46	0.31	-0.41	-0.20	0.15
7	ACG	0.25	-0.02	0.39	0.16	0.56	0.08	0.52	0.47	0.01	0.59	-0.30	0.57
8	ACT	0.50	0.81	0.48	0.48	0.66	0.10	0.60	0.20	-0.36	0.26	0.64	0.62
9	AGA	0.64	-0.07	0.01	0.27	0.56	0.27	0.63	0.29	-0.32	0.34	0.09	0.27
10	AGC	0.34	-0.39	-0.44	0.08	0.40	-0.34	0.33	-0.38	0.42	-0.39	-0.30	0.20
11	AGG	-0.20	0.24	-0.29	0.17	-0.44	-0.33	-0.44	0.17	-0.04	0.58	0.72	0.33
12	AGT	0.78	0.56	0.79	0.51	0.28	0.58	0.54	0.45	0.49	0.71	0.89	0.75
13	ATA	0.02	0.86	0.62	0.58	0.44	0.61	0.53	0.74	0.41	0.68	0.69	0.50
14	ATC	0.12	-0.53	-0.44	0.29	0.52	-0.58	0.12	-0.03	0.38	-0.14	0.04	0.21
15	ATG	0.41	-0.21	-0.13	0.44	0.56	-0.25	0.28	-0.16	-0.08	-0.36	0.31	0.26
16	ATT	0.63	0.77	0.82	0.82	0.66	0.38	0.61	0.47	0.76	0.61	0.75	0.58
17	CAA	0.70	0.52	0.58	0.01	-0.25	0.44	0.03	0.57	-0.45	0.19	-0.06	0.53
18	CAC	-0.13	-0.47	-0.47	-0.04	0.41	-0.55	-0.29	-0.05	0.02	-0.28	-0.31	0.16
19	CAG	0.29	-0.29	-0.37	0.18	0.45	-0.39	0.49	-0.27	0.15	-0.24	0.22	0.13
20	CAT	0.74	0.74	0.84	0.55	0.49	0.48	0.61	0.70	0.77	0.77	0.84	0.57
21	CCA	0.61	0.76	0.31	0.48	-0.33	0.31	0.04	0.41	0.32	0.29	0.28	0.66
22	CCC	0.57	-0.56	-0.62	0.12	0.38	-0.44	0.25	-0.31	-0.06	-0.51	-0.40	0.28
23	CCG	0.13	0.08	0.59	0.27	0.33	0.36	0.46	0.19	0.19	0.59	0.84	0.61
24	CCT	0.53	0.24	0.55	0.43	-0.13	-0.22	0.51	-0.16	0.80	-0.24	0.57	-0.18
25	CGA	0.73	0.37	0.77	0.77	-0.07	0.38	0.61	0.62	0.72	0.35	0.80	0.52
26	CGC	0.34	-0.49	-0.56	-0.03	0.51	-0.40	0.26	-0.29	-0.36	-0.47	-0.10	-0.08
27	CGG	0.20	0.32	0.58	0.48	0.14	0.48	0.11	0.34	0.58	0.51	0.25	0.40
28	CGT	0.77	-0.21	0.21	0.59	0.11	-0.48	0.09	0.08	0.66	0.48	0.78	0.53
29	CTA	0.80	0.47	0.71	0.91	-0.07	0.19	0.83	0.51	-0.26	0.12	0.45	0.38
30	CTC	0.20	-0.46	-0.49	0.14	0.40	-0.44	0.39	-0.07	0.28	-0.32	0.49	-0.25
31	CTG	0.42	-0.34	-0.22	0.38	0.61	-0.42	0.38	0.08	0.30	-0.24	-0.42	0.24
32	CTT	0.32	0.40	0.74	0.81	0.42	-0.04	0.43	-0.02	0.70	0.48	0.84	0.51
33	GAA	0.79	0.31	0.58	0.58	0.10	0.33	0.47	0.64	0.48	0.34	0.01	0.49
34	GAC	0.37	-0.42	-0.50	0.13	0.34	-0.47	0.46	-0.18	0.23	-0.39	0.50	-0.26
35	GAG	0.52	-0.37	-0.43	0.28	0.54	-0.43	0.33	-0.40	0.06	-0.38	0.22	0.09
36	GAT	0.66	0.42	0.66	0.42	-0.16	0.19	0.57	0.31	0.59	0.52	0.23	0.44
37	GCA	0.24	0.21	0.48	0.42	0.46	0.32	-0.10	0.43	0.20	0.17	-0.35	0.58
38	GCC	0.38	-0.61	-0.54	0.25	0.19	-0.47	0.11	-0.37	-0.08	-0.44	0.52	-0.14
39	GCG	0.66	0.26	0.42	0.30	0.50	0.42	0.54	0.24	0.06	0.53	0.63	0.73
40	GCT	0.38	0.66	0.32	0.78	0.49	-0.20	0.50	-0.27	-0.21	0.19	0.54	0.48
41	GGA	0.67	-0.01	-0.01	0.40	0.33	0.05	-0.03	-0.02	0.11	-0.36	0.53	0.02
42	GGC	0.11	-0.38	-0.51	0.33	0.52	-0.30	0.26	-0.05	-0.13	-0.48	-0.23	-0.13
43	GGG	0.72	0.53	0.61	0.64	0.64	0.44	0.70	0.57	0.83	0.66	0.91	0.57
44	GGT	0.48	-0.29	0.42	0.48	0.62	-0.53	0.57	-0.35	0.58	0.01	0.78	0.15
45	GTA	0.79	0.65	0.64	0.58	0.56	0.50	0.75	0.35	0.70	0.59	0.68	0.34
46	GTC	0.25	-0.60	-0.56	0.39	0.66	-0.55	0.32	-0.22	0.33	-0.33	-0.26	-0.02
47	GTG	0.63	0.21	0.37	0.71	0.32	-0.22	0.19	0.20	0.22	0.22	-0.23	0.67
48	GTT	0.60	0.51	0.54	0.64	0.72	0.01	0.56	0.05	0.83	0.41	0.69	0.75
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.34	-0.49	-0.45	0.39	0.49	-0.52	0.59	-0.31	-0.42	-0.25	0.68	0.08

51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.84	0.72	0.81	0.74	0.52	0.48	0.73	0.22	1.00	0.62	-0.17	0.80
53	TCA	0.40	0.60	0.66	-0.06	-0.64	0.33	-0.43	0.57	0.36	0.33	-0.63	0.36
54	TCC	0.42	-0.55	-0.57	0.35	0.69	-0.47	0.48	-0.28	0.05	-0.30	-0.28	0.13
55	TCG	0.18	-0.02	0.13	-0.09	0.13	0.02	0.29	0.24	0.39	0.30	0.07	0.43
56	TCT	0.70	0.75	0.64	0.74	0.50	0.02	0.21	-0.05	0.22	0.29	0.70	0.82
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.57	-0.33	-0.33	-0.17	0.20	-0.46	0.11	-0.31	-0.05	0.39	-0.52	0.41
59	TGG	0.19	-0.20	-0.06	0.43	0.63	-0.28	0.65	-0.34	-0.50	0.03	0.09	-0.12
60	TGT	0.20	0.74	0.42	0.50	0.67	0.41	0.81	0.64	0.42	0.77	1.00	0.38
61	TTA	0.85	0.85	0.45	0.51	0.49	0.69	0.36	0.69	0.41	0.53	0.16	0.56
62	TTC	0.18	-0.45	-0.35	0.42	0.33	-0.46	0.36	-0.18	0.46	-0.14	0.17	0.09
63	TTG	-0.26	-0.02	0.10	-0.05	0.25	-0.21	-0.06	-0.22	0.42	0.30	0.59	0.17
64	TTT	0.70	0.82	0.82	0.77	0.53	0.49	0.54	0.62	-0.23	0.52	-0.27	0.76
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
		1	2	3	4	5	6	7	8	9	10	11	12

Table C.2 continued

		13	14	15	16	17	18	19	20	21	22	23	24
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
1	AAA	0.11	0.75	0.53	0.32	-0.36	-0.09	0.55	0.56	0.61	0.29	0.53	0.80
2	AAC	0.76	-0.39	-0.10	-0.08	0.35	-0.44	-0.46	0.40	0.62	-0.56	0.04	-0.15
3	AAG	0.63	-0.36	-0.16	0.17	0.47	-0.37	-0.26	0.55	0.53	-0.51	0.23	-0.08
4	AAT	0.18	0.60	0.19	0.53	0.79	0.61	0.63	0.15	0.79	0.55	0.77	0.16
5	ACA	0.70	0.59	0.37	0.47	-0.15	0.35	-0.17	0.49	0.03	0.05	0.73	0.16
6	ACC	0.31	-0.53	-0.41	-0.28	0.37	-0.53	-0.28	0.68	0.62	-0.54	-0.01	0.03
7	ACG	-0.24	0.58	0.52	0.47	0.53	0.27	0.34	0.27	0.61	0.53	0.53	0.39
8	ACT	0.70	0.14	0.37	0.55	0.38	-0.25	-0.22	0.17	0.31	-0.51	0.57	-0.31
9	AGA	0.12	-0.39	0.10	0.62	-0.14	-0.26	0.06	0.25	0.50	0.30	0.31	0.02
10	AGC	0.64	-0.23	-0.26	-0.01	0.43	-0.05	-0.28	0.38	0.58	-0.16	0.15	-0.11
11	AGG	-0.60	0.55	0.05	0.75	0.20	-0.39	0.47	0.65	0.15	0.63	0.76	-0.21
12	AGT	0.55	0.22	0.39	0.45	0.49	0.21	0.23	0.54	0.27	0.29	0.53	0.15
13	ATA	-0.15	0.74	0.56	0.62	0.06	0.74	-0.04	0.84	-0.38	-0.07	0.88	0.46
14	ATC	0.58	-0.43	-0.31	-0.07	0.33	-0.52	-0.29	0.52	0.04	-0.39	0.25	0.09
15	ATG	-0.07	-0.16	0.00	0.33	0.10	-0.26	-0.06	0.41	0.22	-0.41	0.28	0.43
16	ATT	0.84	0.48	0.57	0.28	0.07	0.24	0.34	0.42	0.63	-0.10	0.18	0.01
17	CAA	0.77	0.30	0.25	0.56	0.21	-0.19	0.44	0.28	-0.32	-0.05	-0.13	0.22
18	CAC	0.93	-0.49	-0.20	-0.10	-0.37	-0.52	-0.18	0.57	0.38	-0.55	0.39	-0.26
19	CAG	-0.08	-0.32	-0.12	0.08	0.20	-0.17	-0.30	0.24	0.49	-0.29	0.43	-0.07
20	CAT	0.44	0.53	0.30	0.62	0.09	0.49	0.61	0.25	0.26	0.62	0.62	-0.08
21	CCA	0.62	0.22	0.65	0.57	0.39	0.66	0.68	0.66	0.17	0.26	-0.33	-0.08
22	CCC	0.17	-0.48	-0.42	-0.34	0.40	-0.57	-0.51	0.54	0.37	0.26	-0.08	-0.05
23	CCG	0.20	0.42	0.11	0.23	0.34	0.49	0.35	0.57	0.10	0.52	0.26	0.69
24	CCT	-0.28	0.34	0.32	0.29	0.25	-0.46	-0.22	0.17	-0.45	-0.41	0.14	-0.39
25	CGA	0.66	0.44	0.48	0.57	0.73	0.57	0.49	0.49	0.69	0.64	0.41	-0.25
26	CGC	0.73	-0.09	-0.34	-0.07	0.26	-0.40	-0.45	0.57	0.52	-0.57	0.23	-0.20
27	CGG	0.24	0.40	0.36	0.48	0.46	0.51	0.71	0.71	-0.14	0.50	0.42	0.76
28	CGT	-0.19	-0.61	0.00	-0.01	0.02	-0.55	-0.48	-0.18	0.44	-0.62	0.18	-0.29
29	CTA	0.33	0.80	0.47	0.57	-0.16	-0.38	0.48	0.37	-0.30	-0.21	0.48	0.05
30	CTC	0.65	-0.35	-0.18	-0.08	0.50	-0.38	-0.41	0.62	0.58	-0.48	0.35	-0.01
31	CTG	0.71	-0.40	-0.25	-0.05	0.34	-0.35	-0.20	0.32	0.62	-0.30	0.31	0.20
32	CTT	0.61	0.44	0.56	0.56	-0.24	-0.16	-0.10	0.39	-0.41	-0.46	0.50	-0.37
33	GAA	-0.20	0.25	0.42	0.39	-0.16	-0.22	0.45	0.55	-0.17	0.49	0.73	0.27
34	GAC	0.59	-0.26	-0.31	-0.11	0.34	-0.43	-0.43	0.19	0.53	-0.54	0.27	-0.31
35	GAG	0.59	-0.33	-0.21	0.17	0.32	-0.38	-0.29	0.57	0.35	-0.46	0.29	-0.27

36	GAT	0.01	0.11	0.47	0.36	0.62	0.29	0.20	0.39	0.44	0.23	0.46	0.27
37	GCA	0.75	0.46	0.56	0.50	0.43	0.26	0.49	0.69	-0.08	0.53	0.38	0.41
38	GCC	0.52	-0.49	-0.39	-0.37	0.53	-0.39	-0.33	0.47	0.81	-0.34	0.54	0.01
39	GCG	0.91	0.69	0.47	0.55	0.54	0.05	0.01	0.68	0.25	0.55	0.38	0.30
40	GCT	0.33	-0.10	0.08	0.15	0.41	-0.51	-0.42	0.35	0.57	-0.60	0.40	-0.61
41	GGA	0.71	0.45	0.06	0.36	0.53	-0.03	0.15	0.44	-0.23	0.13	0.40	-0.13
42	GGC	0.63	-0.01	-0.11	0.04	0.24	-0.41	-0.40	0.37	0.05	-0.22	0.50	-0.15
43	GGG	-0.41	0.59	0.72	0.76	0.53	0.34	0.46	0.65	0.40	0.55	0.49	0.37
44	GGT	0.78	-0.58	-0.20	0.00	0.41	-0.37	-0.26	0.42	0.61	-0.51	0.61	-0.42
45	GTA	0.18	0.82	0.78	0.69	0.41	0.34	0.56	0.39	0.44	0.39	0.57	0.61
46	GTC	0.80	-0.52	-0.40	-0.28	0.68	-0.49	-0.32	0.49	0.74	-0.41	0.62	0.13
47	GTG	0.69	0.39	0.30	0.55	0.18	0.05	-0.10	0.66	0.72	-0.05	0.37	-0.01
48	GTT	0.58	0.11	0.37	0.16	-0.19	-0.27	-0.04	0.27	0.39	-0.56	-0.01	-0.47
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.71	-0.34	-0.30	0.03	-0.15	-0.46	-0.21	0.28	0.35	-0.53	0.30	-0.05
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.29	0.48	0.69	0.32	0.24	0.55	0.47	0.53	0.66	0.27	0.41	0.32
53	TCA	0.52	0.09	0.50	0.54	0.42	0.59	0.19	0.33	-0.48	0.66	0.61	0.01
54	TCC	0.44	-0.54	-0.37	-0.23	0.30	-0.45	-0.45	0.09	0.55	-0.46	-0.16	-0.01
55	TCG	0.40	0.16	0.30	0.27	0.29	0.25	0.25	0.27	0.27	0.10	0.41	0.24
56	TCT	0.61	0.22	0.29	0.75	0.32	-0.45	-0.16	0.03	-0.02	-0.42	0.16	-0.35
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.44	0.12	-0.25	-0.36	0.02	-0.46	-0.27	0.43	0.37	-0.56	0.73	0.07
59	TGG	-0.24	0.02	0.00	0.08	0.10	-0.26	-0.05	0.42	-0.12	-0.18	0.23	0.15
60	TGT	0.07	-0.10	0.56	0.52	-0.25	0.27	0.79	0.62	0.53	0.45	-0.07	0.10
61	TTA	0.23	0.90	0.78	0.51	-0.39	0.80	0.74	-0.08	0.48	0.47	-0.16	0.37
62	TTC	0.63	-0.30	-0.24	-0.21	0.41	-0.42	-0.39	0.35	0.17	-0.48	0.31	-0.14
63	TTG	0.50	-0.05	-0.12	-0.31	0.58	0.01	0.34	0.38	0.59	0.38	0.38	0.12
64	TTT	0.75	0.49	0.72	0.68	0.40	0.71	0.69	0.32	0.60	0.39	0.73	0.41
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
		13	14	15	16	17	18	19	20	21	22	23	24

Table C.2 continued

		25	26	27	28	29	30	31	32	33	34	35	36
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
1	AAA	0.29	0.27	0.75	0.72	0.56	0.49	0.73	0.55	0.35	0.35	0.37	0.19
2	AAC	-0.07	-0.52	0.42	-0.45	-0.12	-0.36	-0.36	-0.10	0.19	-0.34	-0.29	0.30
3	AAG	0.60	-0.26	0.35	-0.47	0.09	-0.42	-0.18	-0.09	0.27	-0.24	-0.28	0.12
4	AAT	0.57	0.30	0.75	0.22	0.72	0.41	0.48	0.66	0.42	0.17	0.22	0.22
5	ACA	0.55	-0.33	0.52	0.81	-0.25	0.52	0.53	0.27	0.25	0.37	0.43	0.38
6	ACC	0.69	-0.38	0.27	-0.53	-0.45	-0.52	-0.30	-0.02	0.22	-0.42	-0.30	0.12
7	ACG	0.57	0.63	0.68	0.61	0.61	0.50	0.35	0.27	0.36	0.25	0.13	0.47
8	ACT	0.48	-0.37	0.41	-0.51	0.53	-0.31	-0.21	-0.01	0.39	-0.24	-0.38	0.08
9	AGA	0.63	0.22	0.29	0.45	0.29	-0.11	0.38	-0.30	0.31	0.42	0.46	0.62
10	AGC	0.32	-0.08	0.41	-0.34	0.71	0.18	0.30	-0.05	-0.19	0.02	0.04	0.41
11	AGG	0.70	-0.35	0.55	0.71	0.25	0.47	0.50	-0.17	0.09	-0.40	0.23	0.56
12	AGT	0.38	0.36	0.47	0.32	0.24	-0.07	-0.23	0.20	0.15	0.09	0.00	0.04
13	ATA	0.44	0.78	0.66	-0.20	-0.33	0.38	0.12	0.52	0.26	0.78	0.77	0.81
14	ATC	0.44	-0.37	0.44	-0.61	0.67	-0.33	-0.34	0.02	0.30	-0.10	-0.06	0.14
15	ATG	0.40	-0.26	0.37	-0.19	0.57	-0.18	-0.01	-0.30	0.13	-0.08	-0.08	0.09
16	ATT	0.67	0.02	0.31	0.01	0.36	-0.03	0.14	0.03	0.18	-0.34	-0.39	-0.02
17	CAA	0.59	0.60	0.42	0.06	0.46	0.40	0.37	0.28	0.23	0.31	0.45	0.27
18	CAC	0.60	-0.36	-0.01	-0.66	-0.26	-0.46	-0.41	-0.10	-0.12	-0.43	-0.22	0.35
19	CAG	0.50	-0.33	0.45	-0.51	0.66	-0.44	-0.28	-0.15	0.28	-0.21	-0.35	-0.06
20	CAT	0.65	0.66	0.47	0.23	-0.30	0.60	0.52	0.76	0.24	0.32	0.29	0.19

21	CCA	0.78	0.39	0.33	0.57	0.35	0.65	0.10	0.49	0.19	0.45	0.33	0.50
22	CCC	0.49	-0.31	0.55	-0.69	-0.29	-0.34	0.04	0.09	0.07	-0.32	-0.46	-0.17
23	CCG	0.66	0.42	0.53	0.71	0.50	0.49	0.24	-0.05	0.51	-0.09	0.45	0.45
24	CCT	-0.22	-0.34	0.61	-0.64	0.43	-0.35	-0.41	-0.33	0.14	-0.31	-0.13	0.29
25	CGA	0.64	0.62	0.46	0.69	0.10	0.73	0.45	0.35	0.34	0.30	0.69	0.71
26	CGC	-0.13	-0.45	0.37	-0.62	0.17	-0.30	-0.11	0.35	0.17	0.01	-0.22	0.20
27	CGG	0.19	0.63	0.76	0.60	0.53	0.78	0.62	0.58	0.56	0.36	0.46	0.20
28	CGT	0.48	-0.45	0.21	-0.69	-0.16	-0.63	-0.59	-0.47	0.09	-0.62	-0.64	-0.33
29	CTA	0.45	-0.51	-0.01	-0.25	-0.36	-0.30	0.52	0.55	0.73	0.29	0.39	0.17
30	CTC	0.69	-0.54	0.07	-0.65	0.70	-0.44	-0.18	-0.28	0.14	-0.29	-0.33	0.02
31	CTG	0.54	-0.22	0.52	-0.35	0.69	-0.18	-0.01	0.04	0.13	-0.10	-0.18	0.13
32	CTT	0.58	0.02	0.60	-0.33	0.33	-0.31	-0.24	-0.05	0.26	-0.34	-0.30	0.10
33	GAA	0.14	0.49	0.63	0.22	0.79	0.25	0.49	0.42	0.24	-0.08	0.30	0.22
34	GAC	0.52	-0.44	-0.15	-0.58	-0.09	-0.33	-0.10	-0.26	0.32	-0.05	-0.21	0.34
35	GAG	0.40	-0.32	0.39	-0.58	0.57	-0.42	-0.29	-0.34	0.34	-0.11	-0.34	0.05
36	GAT	-0.09	0.44	0.66	0.30	0.61	0.06	0.02	-0.07	0.50	-0.29	-0.21	0.13
37	GCA	0.39	0.64	0.60	0.67	0.48	0.73	0.52	0.39	0.41	0.35	0.17	0.47
38	GCC	0.72	-0.34	0.49	-0.56	0.72	-0.36	-0.19	-0.23	0.42	-0.38	-0.25	-0.12
39	GCG	0.74	0.65	0.52	0.31	0.23	0.26	0.35	0.44	0.37	-0.08	0.36	0.34
40	GCT	0.59	-0.53	0.48	-0.65	0.62	-0.47	-0.36	-0.37	0.20	0.13	-0.44	0.09
41	GGA	0.71	0.14	0.62	-0.10	0.64	0.56	0.58	0.48	0.48	0.51	0.30	0.25
42	GGC	0.33	-0.35	0.60	-0.60	0.08	0.17	0.08	0.29	0.33	0.17	-0.18	0.37
43	GGG	-0.13	0.81	0.81	0.15	0.45	0.35	0.72	0.62	0.59	0.41	0.64	0.65
44	GGT	0.65	-0.27	0.59	-0.64	-0.11	-0.64	-0.54	-0.47	-0.12	-0.58	-0.47	-0.26
45	GTA	0.77	0.16	0.91	0.66	0.78	0.56	0.62	0.46	0.75	0.71	0.70	0.48
46	GTC	0.57	-0.52	0.25	-0.62	0.28	-0.40	-0.23	-0.31	0.43	-0.28	-0.23	0.15
47	GTG	0.66	-0.03	0.52	0.45	0.78	0.06	0.15	0.07	0.36	0.19	0.15	0.50
48	GTT	0.78	-0.20	0.53	-0.25	-0.07	-0.37	-0.14	-0.10	0.01	-0.48	-0.47	0.07
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.57	-0.42	0.23	-0.54	0.38	-0.36	-0.24	-0.21	0.18	-0.28	-0.33	0.25
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.57	0.63	0.39	0.56	-0.11	0.22	-0.07	0.48	0.50	0.16	0.26	0.09
53	TCA	-0.18	0.68	0.63	0.34	-0.55	0.24	0.46	0.46	0.54	0.27	0.11	-0.03
54	TCC	0.77	-0.48	0.14	-0.52	-0.21	-0.40	-0.30	-0.01	0.34	-0.54	-0.38	0.09
55	TCG	0.49	0.20	0.53	0.55	-0.54	0.34	0.10	0.32	0.42	0.20	0.18	0.19
56	TCT	-0.02	-0.47	0.43	-0.55	0.42	-0.15	-0.30	-0.32	0.14	0.16	-0.20	0.26
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.82	0.05	0.73	-0.59	-0.22	-0.02	-0.04	0.34	0.09	0.02	-0.20	0.13
59	TGG	0.74	-0.28	0.61	-0.02	-0.43	-0.12	0.05	0.17	0.21	0.11	-0.12	-0.10
60	TGT	0.41	0.71	-0.19	-0.46	0.09	-0.05	-0.11	-0.09	0.24	0.32	0.16	-0.37
61	TTA	0.10	0.93	0.43	0.78	-0.05	0.48	0.40	1.00	0.43	0.23	0.85	0.81
62	TTC	0.67	-0.37	0.43	-0.61	0.04	-0.26	-0.35	-0.15	0.31	-0.17	-0.21	0.25
63	TTG	0.56	0.63	0.59	0.30	-0.13	-0.01	0.29	0.01	0.37	0.24	0.08	0.22
64	TTT	0.82	0.64	0.77	0.68	-0.50	0.64	0.68	0.45	0.03	-0.35	0.10	0.45
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
		25	26	27	28	29	30	31	32	33	34	35	36

Table C.2 continued

		37	38	39	40	41	42	43	44	45	46	47	48
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
1	AAA	0.41	0.43	0.35	0.59	-0.15	0.24	0.21	0.76	0.90	0.31	0.57	0.60
2	AAC	0.66	-0.30	0.33	-0.04	0.12	-0.32	0.53	-0.22	0.92	-0.40	0.38	-0.03
3	AAG	0.49	-0.43	0.52	-0.27	0.38	-0.14	0.85	-0.47	0.73	-0.42	0.29	-0.20
4	AAT	-0.06	-0.11	0.24	-0.13	0.34	0.11	0.36	0.27	0.57	-0.07	0.14	0.15
5	ACA	0.53	0.45	0.57	0.54	0.64	0.46	0.45	0.53	0.06	0.55	0.37	0.69

6	ACC	0.30	-0.14	0.53	-0.14	0.19	-0.17	0.69	-0.46	0.77	-0.45	0.29	-0.31
7	ACG	0.24	-0.12	0.50	0.18	0.41	0.41	0.70	0.29	0.04	0.57	0.18	0.12
8	ACT	-0.18	-0.47	0.05	-0.54	-0.03	-0.30	0.55	-0.61	0.24	-0.38	0.25	-0.30
9	AGA	0.16	0.27	0.50	0.47	0.18	0.63	0.82	0.21	0.42	0.54	0.35	0.45
10	AGC	0.59	0.14	0.58	-0.08	0.53	-0.05	0.71	-0.35	0.73	0.05	0.17	-0.12
11	AGG	-0.34	0.09	0.82	0.44	0.57	0.49	0.81	0.39	-0.18	0.21	0.51	0.47
12	AGT	0.46	-0.26	0.24	0.05	0.35	0.16	0.53	-0.32	0.36	-0.16	-0.17	-0.09
13	ATA	0.60	0.70	0.79	0.77	0.16	0.86	0.83	0.83	-0.54	0.73	0.52	0.69
14	ATC	0.61	-0.06	0.62	-0.04	0.40	0.20	0.79	-0.44	0.72	-0.26	0.53	0.15
15	ATG	0.30	-0.24	0.38	-0.08	0.33	0.06	0.36	-0.33	0.58	-0.23	0.30	-0.11
16	ATT	0.29	-0.55	0.02	-0.44	-0.03	-0.21	0.39	-0.47	0.00	-0.45	0.07	-0.23
17	CAA	-0.02	0.24	0.48	0.37	0.08	0.17	0.68	0.03	0.50	0.34	0.54	0.55
18	CAC	0.20	-0.34	0.32	-0.27	-0.04	-0.15	0.80	-0.44	0.45	-0.43	0.71	-0.35
19	CAG	0.33	-0.29	0.27	-0.33	0.32	-0.12	0.75	-0.45	0.57	-0.42	0.16	-0.29
20	CAT	-0.42	0.39	0.43	0.45	0.01	0.16	0.52	0.27	0.92	-0.15	0.48	0.20
21	CCA	0.45	0.57	0.35	0.09	0.35	-0.07	-0.29	0.38	-0.25	0.57	0.54	0.55
22	CCC	0.57	-0.43	0.57	-0.29	0.09	-0.20	0.64	-0.57	0.12	-0.48	-0.08	-0.31
23	CCG	0.14	0.22	0.09	-0.17	0.56	0.49	0.64	0.53	0.68	0.43	0.42	0.12
24	CCT	0.53	-0.26	0.55	-0.44	0.12	0.05	0.60	-0.48	0.59	-0.28	0.11	-0.17
25	CGA	0.68	0.66	0.75	0.60	0.47	-0.17	0.53	0.70	0.78	0.13	0.47	0.58
26	CGC	0.22	-0.15	0.65	-0.15	0.44	0.10	0.60	-0.06	0.09	0.14	0.20	0.12
27	CGG	0.52	0.43	0.39	0.30	0.63	0.58	0.74	0.42	0.25	0.55	0.11	0.27
28	CGT	0.09	-0.69	-0.02	-0.66	-0.35	-0.43	0.45	-0.82	0.51	-0.73	-0.26	-0.46
29	CTA	0.53	-0.13	-0.23	-0.32	-0.39	-0.22	0.66	0.73	0.44	0.56	0.75	-0.22
30	CTC	0.48	-0.22	0.52	-0.07	0.13	0.05	0.78	-0.35	0.67	-0.38	0.38	-0.01
31	CTG	0.24	-0.28	0.20	-0.26	0.07	-0.07	0.65	-0.32	0.35	-0.35	0.11	-0.09
32	CTT	0.34	-0.45	0.45	-0.46	-0.32	-0.26	0.58	-0.58	-0.07	-0.33	0.18	-0.28
33	GAA	0.16	0.03	0.21	0.38	0.30	0.05	0.49	0.31	0.70	-0.16	0.34	0.34
34	GAC	0.60	-0.12	0.49	0.26	0.40	-0.16	0.69	-0.14	0.59	0.06	0.49	0.02
35	GAG	0.51	-0.29	0.44	-0.37	0.34	-0.15	0.77	-0.49	0.69	-0.31	0.37	-0.32
36	GAT	0.53	-0.42	0.09	-0.29	0.04	-0.17	0.06	-0.07	0.36	-0.36	0.15	-0.27
37	GCA	0.29	0.66	0.42	0.51	0.23	0.30	0.39	0.50	-0.22	0.51	0.37	0.53
38	GCC	0.61	-0.28	0.42	-0.06	0.54	0.23	0.75	-0.49	0.59	-0.41	0.34	-0.28
39	GCG	0.46	0.28	0.44	0.48	0.51	0.51	0.74	0.32	0.16	0.45	0.45	0.51
40	GCT	0.31	-0.53	0.12	-0.58	-0.05	-0.35	0.57	-0.64	0.07	-0.40	0.19	-0.36
41	GGA	0.14	0.38	0.50	0.42	0.45	0.46	0.80	0.31	0.78	0.50	0.63	0.23
42	GGC	0.51	0.36	0.75	0.11	0.49	0.28	0.75	0.08	0.64	0.47	0.54	0.28
43	GGG	0.61	0.78	0.84	0.46	0.60	0.83	0.89	0.78	0.73	0.73	0.74	0.77
44	GGT	0.39	-0.66	0.32	-0.67	-0.15	-0.33	0.63	-0.78	0.63	-0.66	-0.22	-0.69
45	GTA	-0.11	-0.05	0.34	0.73	0.51	0.51	-0.21	0.89	0.66	0.39	0.46	0.70
46	GTC	0.43	-0.16	0.66	-0.20	0.22	-0.14	0.47	-0.53	0.67	-0.36	0.41	-0.04
47	GTG	0.59	0.14	0.58	0.21	0.50	0.37	0.71	0.55	0.75	0.22	0.39	0.38
48	GTT	-0.13	-0.47	0.22	-0.53	0.02	-0.17	0.41	-0.56	0.57	-0.51	0.06	-0.50
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.66	-0.32	0.52	-0.24	0.41	-0.22	0.06	-0.22	0.77	-0.16	-0.10	0.15
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.45	-0.26	0.59	-0.13	0.38	-0.14	0.52	0.11	0.36	-0.04	0.20	-0.25
53	TCA	0.55	0.54	0.16	0.31	0.43	0.82	0.62	0.78	0.44	0.22	0.49	0.57
54	TCC	0.10	-0.39	0.53	-0.32	0.00	-0.37	0.52	-0.50	0.47	-0.54	0.10	-0.36
55	TCG	0.21	0.20	0.40	0.13	0.41	0.39	0.66	0.35	0.57	0.37	0.27	0.35
56	TCT	0.20	-0.44	0.26	-0.51	0.08	-0.42	0.06	-0.37	0.33	-0.09	0.33	-0.16
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.63	0.14	0.31	-0.43	0.41	0.26	0.16	-0.43	-0.17	0.35	0.58	0.23
59	TGG	0.35	0.00	0.00	-0.19	0.42	0.12	0.68	-0.45	-0.15	0.49	-0.17	-0.31
60	TGT	0.50	-0.23	0.25	-0.23	0.21	0.31	0.44	-0.40	0.66	-0.58	0.35	-0.46
61	TTA	0.68	0.70	0.70	0.45	0.92	0.95	-0.02	0.81	0.36	0.79	-0.14	1.00

62	TTC	0.77	-0.26	0.66	-0.24	0.46	0.06	0.80	-0.43	0.09	-0.35	0.45	0.01
63	TTG	0.55	0.29	0.45	0.27	0.47	0.47	0.78	0.00	0.23	0.34	0.33	0.01
64	TTT	0.19	-0.27	0.01	-0.17	0.06	-0.02	0.55	-0.29	0.74	-0.14	0.23	0.26
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
		37	38	39	40	41	42	43	44	45	46	47	48

Table C.2 continued

		49	50	51	52	53	54	55	56	57	58	59	60
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
1	AAA	0.00	0.05	0.00	0.44	-0.60	0.47	0.21	0.51	0.00	0.06	-0.07	0.16
2	AAC	0.00	-0.38	0.00	0.11	0.51	-0.47	-0.17	-0.17	0.00	-0.39	-0.30	0.08
3	AAG	0.00	-0.27	0.00	0.43	0.32	-0.38	0.04	0.04	0.00	-0.17	0.03	0.25
4	AAT	0.00	0.47	0.00	0.74	0.47	0.66	0.45	0.43	0.00	0.58	0.72	0.65
5	ACA	0.00	0.10	0.00	0.36	0.29	0.26	0.35	0.18	0.00	0.31	-0.11	0.26
6	ACC	0.00	-0.54	0.00	0.41	0.29	-0.58	-0.30	-0.01	0.00	-0.44	-0.22	0.29
7	ACG	0.00	0.11	0.00	0.59	0.18	0.40	0.22	0.46	0.00	0.52	0.03	0.65
8	ACT	0.00	0.47	0.00	0.54	0.38	-0.12	0.33	-0.22	0.00	-0.19	0.53	-0.02
9	AGA	0.00	-0.27	0.00	-0.51	0.12	-0.31	0.72	-0.19	0.00	0.27	-0.66	-0.17
10	AGC	0.00	-0.45	0.00	0.29	-0.12	-0.28	0.22	-0.22	0.00	-0.11	-0.40	-0.06
11	AGG	0.00	0.71	0.00	0.46	0.18	-0.43	0.56	0.30	0.00	0.87	0.49	0.36
12	AGT	0.00	0.28	0.00	0.33	0.31	0.55	0.70	0.47	0.00	0.30	0.65	0.61
13	ATA	0.00	0.30	0.00	-0.42	-0.84	0.70	0.67	-0.57	0.00	0.40	0.58	-0.54
14	ATC	0.00	-0.41	0.00	0.35	0.64	-0.59	0.23	-0.05	0.00	-0.17	-0.32	-0.17
15	ATG	0.00	-0.22	0.00	0.45	0.34	-0.17	0.39	0.09	0.00	-0.11	0.00	0.21
16	ATT	0.00	0.55	0.00	0.47	0.69	0.41	0.48	0.48	0.00	0.51	0.62	0.25
17	CAA	0.00	0.06	0.00	-0.09	0.59	0.19	0.29	0.40	0.00	0.16	-0.04	-0.42
18	CAC	0.00	-0.47	0.00	0.35	0.17	-0.54	-0.01	-0.33	0.00	-0.50	-0.35	-0.04
19	CAG	0.00	-0.16	0.00	0.32	0.43	-0.42	-0.05	-0.08	0.00	-0.10	0.03	0.45
20	CAT	0.00	0.51	0.00	0.45	0.54	0.42	0.38	0.23	0.00	0.66	0.64	0.89
21	CCA	0.00	0.09	0.00	0.52	0.29	0.25	0.37	-0.05	0.00	0.26	0.45	0.38
22	CCC	0.00	-0.50	0.00	0.51	0.76	-0.59	0.33	-0.17	0.00	-0.42	-0.33	0.37
23	CCG	0.00	-0.02	0.00	0.23	-0.33	0.39	0.37	0.19	0.00	0.64	0.38	1.00
24	CCT	0.00	0.10	0.00	0.52	0.67	-0.12	0.17	-0.06	0.00	-0.45	-0.07	-0.07
25	CGA	0.00	-0.22	0.00	0.71	-0.43	0.17	0.26	0.67	0.00	0.45	0.55	0.08
26	CGC	0.00	-0.35	0.00	0.43	0.26	-0.53	-0.27	-0.36	0.00	-0.61	0.00	0.40
27	CGG	0.00	0.34	0.00	0.56	0.36	0.32	0.56	0.50	0.00	0.51	0.44	0.53
28	CGT	0.00	-0.39	0.00	0.50	0.26	-0.28	0.22	0.14	0.00	-0.08	-0.02	0.43
29	CTA	0.00	-0.15	0.00	0.61	0.59	-0.25	0.54	0.57	0.00	0.47	-0.11	1.00
30	CTC	0.00	-0.41	0.00	0.24	0.11	-0.46	0.27	-0.13	0.00	-0.42	-0.44	-0.11
31	CTG	0.00	-0.28	0.00	0.31	-0.10	-0.21	0.11	-0.15	0.00	-0.01	0.11	0.23
32	CTT	0.00	0.20	0.00	0.59	0.25	-0.18	0.03	-0.30	0.00	-0.51	0.32	0.36
33	GAA	0.00	-0.21	0.00	0.33	0.46	0.07	0.18	0.35	0.00	0.45	-0.13	0.26
34	GAC	0.00	-0.47	0.00	0.42	0.61	-0.44	-0.12	-0.32	0.00	-0.43	-0.33	0.00
35	GAG	0.00	-0.20	0.00	0.48	0.56	-0.40	0.20	-0.09	0.00	-0.38	0.10	0.36
36	GAT	0.00	0.30	0.00	0.56	0.68	0.20	0.44	0.29	0.00	0.62	0.52	0.25
37	GCA	0.00	0.13	0.00	0.38	-0.11	0.03	0.23	0.21	0.00	0.17	0.10	0.45
38	GCC	0.00	-0.59	0.00	0.38	0.57	-0.56	0.17	-0.13	0.00	-0.25	-0.33	-0.23
39	GCG	0.00	0.54	0.00	0.55	0.18	0.52	0.52	0.27	0.00	0.69	0.39	0.68
40	GCT	0.00	0.44	0.00	0.27	0.49	-0.32	0.26	-0.13	0.00	-0.26	0.27	-0.15
41	GGA	0.00	-0.25	0.00	0.03	0.23	-0.15	0.19	0.39	0.00	0.02	0.03	-0.26
42	GGC	0.00	-0.26	0.00	0.31	0.46	-0.37	0.38	-0.28	0.00	-0.22	-0.40	-0.07
43	GGG	0.00	0.56	0.00	0.12	0.33	0.61	0.40	0.37	0.00	0.68	0.70	0.29
44	GGT	0.00	-0.16	0.00	0.49	0.75	-0.32	0.51	0.06	0.00	-0.10	0.42	0.38
45	GTA	0.00	-0.30	0.00	0.58	0.11	0.08	-0.05	-0.52	0.00	0.43	0.45	0.22
46	GTC	0.00	-0.44	0.00	0.25	0.51	-0.55	0.22	-0.30	0.00	-0.50	-0.30	0.26

47	GTG	0.00	0.19	0.00	0.48	0.11	0.39	0.46	0.08	0.00	0.03	0.06	0.70
48	GTT	0.00	0.08	0.00	0.57	0.02	-0.27	0.43	0.16	0.00	0.24	0.42	0.52
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.00	-0.43	0.00	0.18	0.23	-0.40	0.04	-0.50	0.00	-0.43	-0.28	0.13
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.00	0.61	0.00	0.71	0.84	0.43	0.60	0.27	0.00	0.78	0.65	0.57
53	TCA	0.00	0.39	0.00	0.41	-0.19	-0.07	0.58	-0.10	0.00	0.34	0.21	0.32
54	TCC	0.00	-0.47	0.00	0.31	0.27	-0.52	0.47	-0.22	0.00	-0.48	-0.25	0.36
55	TCG	0.00	0.34	0.00	0.52	0.11	0.22	0.11	0.14	0.00	0.38	0.48	0.74
56	TCT	0.00	0.17	0.00	0.14	0.22	-0.48	0.02	-0.34	0.00	-0.40	0.12	0.28
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.00	-0.32	0.00	0.35	0.30	-0.47	-0.45	-0.47	0.00	-0.30	-0.25	-0.08
59	TGG	0.00	-0.19	0.00	0.38	-0.24	-0.13	0.28	0.17	0.00	0.11	0.00	-0.16
60	TGT	0.00	0.34	0.00	0.14	0.61	0.51	0.75	0.49	0.00	0.50	0.56	0.50
61	TTA	0.00	0.54	0.00	0.36	-0.20	0.56	0.41	0.49	0.00	0.83	0.55	0.72
62	TTC	0.00	-0.42	0.00	0.33	0.51	-0.49	0.38	-0.19	0.00	-0.08	-0.21	-0.35
63	TTG	0.00	0.20	0.00	0.09	0.43	0.31	0.43	0.25	0.00	0.79	0.54	0.25
64	TTT	0.00	0.68	0.00	0.77	0.65	0.27	0.43	-0.09	0.00	0.74	0.59	0.30
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
		49	50	51	52	53	54	55	56	57	58	59	60

Table C.2 continued

		61	62	63	64
		TTA	TTC	TTG	TTT
1	AAA	0.72	0.34	0.10	0.50
2	AAC	0.79	-0.39	0.00	0.31
3	AAG	0.15	-0.27	0.34	0.39
4	AAT	0.46	0.65	0.37	0.45
5	ACA	0.00	0.14	0.08	0.37
6	ACC	0.89	-0.37	0.19	0.54
7	ACG	0.81	0.46	0.68	-0.10
8	ACT	0.82	-0.09	0.21	0.15
9	AGA	0.10	0.21	0.18	0.66
10	AGC	0.55	-0.12	-0.01	0.21
11	AGG	0.05	0.52	-0.18	0.71
12	AGT	0.42	0.37	0.20	0.66
13	ATA	0.29	0.42	0.71	0.42
14	ATC	0.50	-0.41	0.24	0.29
15	ATG	0.52	-0.16	0.35	0.45
16	ATT	0.85	0.54	0.20	0.53
17	CAA	0.05	0.11	-0.12	0.34
18	CAC	0.73	-0.37	0.05	0.07
19	CAG	0.70	-0.26	0.51	0.46
20	CAT	0.79	0.34	0.33	0.71
21	CCA	-0.07	0.31	0.36	0.22
22	CCC	0.55	-0.51	-0.32	0.32
23	CCG	0.41	0.39	0.25	0.40
24	CCT	0.57	0.01	0.37	0.66
25	CGA	1.00	0.42	0.54	0.43
26	CGC	-0.29	-0.44	0.11	-0.20
27	CGG	0.61	0.30	0.03	0.57
28	CGT	1.00	-0.37	0.02	0.46
29	CTA	-0.64	-0.19	0.53	0.00
30	CTC	0.65	-0.44	0.10	0.18
31	CTG	0.68	-0.06	0.25	0.25

32	CTT	0.49	0.00	0.07	0.49
33	GAA	0.55	0.13	0.20	0.39
34	GAC	0.71	-0.41	0.19	-0.13
35	GAG	0.78	-0.28	0.22	0.43
36	GAT	0.87	0.44	0.37	0.78
37	GCA	0.50	0.46	0.13	0.26
38	GCC	0.82	-0.17	0.03	0.17
39	GCG	0.46	0.20	0.44	-0.07
40	GCT	0.49	-0.36	0.11	0.46
41	GGA	0.31	-0.14	0.18	0.36
42	GGC	0.76	-0.12	0.12	0.43
43	GGG	0.53	0.63	-0.05	0.35
44	GGT	0.94	-0.44	0.52	0.75
45	GTA	0.57	0.27	0.48	0.63
46	GTC	0.58	-0.43	0.26	0.29
47	GTG	0.93	0.10	0.30	0.35
48	GTT	0.59	0.22	0.39	0.51
49	TAA	0.00	0.00	0.00	0.00
50	TAC	0.87	-0.37	0.27	0.14
51	TAG	0.00	0.00	0.00	0.00
52	TAT	0.79	0.56	0.58	0.65
53	TCA	0.09	0.29	0.12	0.49
54	TCC	0.65	-0.32	0.19	0.39
55	TCG	0.62	-0.11	0.44	0.33
56	TCT	-0.41	-0.32	0.27	0.27
57	TGA	0.00	0.00	0.00	0.00
58	TGC	0.30	-0.28	-0.18	0.20
59	TGG	0.77	-0.14	0.11	0.37
60	TGT	-0.14	0.33	0.44	0.38
61	TTA	0.66	0.79	0.67	0.40
62	TTC	0.75	-0.37	0.13	0.34
63	TTG	0.59	0.40	0.33	0.39
64	TTT	0.77	0.63	0.50	0.80
		TTA	TTC	TTG	TTT
		61	62	63	64

Table C.3: CPW matrix *Bacillus subtilis* full genome (left codon indicated in column 2, right codon indicated in row 2). Host cell: *B. subtilis*; Sequence data: full *B. subtilis* genome.

		1	2	3	4	5	6	7	8	9	10	11	12
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
1	AAA	0.02	-0.28	-0.11	0.04	-0.28	-0.13	-0.23	0.44	0.16	-0.39	-0.02	0.04
2	AAC	-0.04	-0.22	0.01	-0.16	0.09	0.10	0.06	0.10	-0.17	-0.63	-0.38	-0.54
3	AAG	0.00	0.33	0.18	0.36	0.43	0.59	0.38	0.50	0.48	0.22	0.28	0.05
4	AAT	-0.03	0.11	0.13	0.24	-0.08	-0.05	-0.20	0.29	0.61	0.57	0.56	0.32
5	ACA	-0.22	-0.31	-0.27	-0.16	-0.13	-0.24	-0.13	-0.33	-0.45	-0.30	-0.51	-0.25
6	ACC	0.40	0.19	0.43	-0.13	0.42	0.10	0.61	-0.12	0.05	0.37	0.16	0.02
7	ACG	-0.06	0.22	-0.20	0.04	-0.18	0.17	0.01	-0.31	-0.37	0.26	-0.22	-0.02
8	ACT	0.57	0.69	0.54	0.49	0.45	0.53	0.68	0.18	0.36	0.75	0.32	0.46
9	AGA	-0.31	-0.31	-0.32	-0.18	-0.09	-0.30	-0.37	0.22	-0.44	-0.34	-0.59	-0.20
10	AGC	-0.09	0.05	-0.15	-0.14	-0.07	-0.15	-0.10	-0.20	-0.31	-0.32	-0.59	-0.38
11	AGG	0.30	0.52	0.23	0.29	0.35	0.51	0.45	0.43	-0.07	0.44	-0.02	0.26
12	AGT	0.10	0.54	0.28	0.28	0.03	0.52	0.03	0.15	0.71	0.87	0.82	0.80
13	ATA	-0.40	-0.15	-0.37	-0.08	0.24	-0.23	0.12	-0.14	-0.11	0.28	-0.43	0.06
14	ATC	-0.15	-0.17	0.07	-0.29	-0.05	-0.13	0.15	-0.21	-0.44	-0.50	-0.47	-0.48
15	ATG	0.11	0.08	-0.21	-0.06	0.02	0.14	-0.10	-0.01	-0.31	-0.09	-0.32	-0.19
16	ATT	0.20	0.21	0.31	0.31	-0.02	0.03	-0.03	0.18	0.69	0.85	0.66	0.60
17	CAA	-0.27	-0.43	-0.38	-0.26	-0.10	-0.46	-0.26	-0.02	-0.18	-0.40	-0.18	-0.17
18	CAC	0.14	-0.04	-0.04	-0.22	0.26	-0.08	0.10	0.10	-0.32	-0.52	-0.40	-0.44
19	CAG	0.47	0.58	0.40	0.52	0.31	0.41	0.16	0.33	0.50	0.65	0.29	0.63
20	CAT	-0.06	0.01	0.02	0.15	-0.12	0.01	-0.09	0.11	0.61	0.66	0.62	0.47
21	CCA	-0.34	-0.49	-0.45	-0.34	0.09	-0.33	0.11	-0.37	-0.51	-0.48	-0.51	-0.50
22	CCC	0.50	0.35	0.59	-0.09	0.55	0.25	0.69	-0.11	0.14	0.30	0.83	0.11
23	CCG	-0.02	0.18	-0.13	-0.12	-0.31	-0.09	-0.03	-0.51	-0.22	0.37	0.39	0.07
24	CCT	0.31	0.49	0.33	0.39	0.49	0.45	0.67	0.28	0.55	0.80	0.54	0.58
25	CGA	-0.47	-0.52	-0.32	-0.45	-0.08	-0.21	-0.16	0.01	-0.32	-0.55	0.17	-0.22
26	CGC	0.31	0.13	0.10	-0.10	0.15	-0.06	0.14	0.27	-0.13	-0.33	-0.15	-0.31
27	CGG	0.21	0.48	0.21	0.04	-0.25	0.24	-0.43	-0.04	0.38	0.45	0.31	0.46
28	CGT	0.42	0.61	0.51	0.50	0.24	0.59	0.17	0.36	0.89	0.90	0.90	0.85
29	CTA	-0.36	-0.20	-0.43	-0.27	0.29	-0.36	0.28	-0.06	-0.37	-0.31	-0.47	-0.23
30	CTC	0.37	0.34	0.27	-0.02	0.34	-0.09	0.50	-0.11	-0.39	-0.38	-0.04	-0.33
31	CTG	-0.10	0.03	-0.20	-0.13	-0.26	-0.18	-0.23	-0.41	0.09	0.45	0.10	0.39
32	CTT	0.67	0.61	0.68	0.55	0.56	0.44	0.61	0.31	0.54	0.74	0.60	0.68
33	GAA	-0.09	-0.25	-0.06	-0.03	-0.20	-0.16	-0.21	0.28	0.08	-0.37	0.15	-0.15
34	GAC	-0.05	-0.16	-0.05	-0.21	0.13	0.01	0.18	-0.07	-0.35	-0.65	-0.52	-0.58
35	GAG	0.20	0.40	0.17	0.32	0.36	0.57	0.16	0.35	0.34	0.23	0.50	0.14
36	GAT	-0.01	0.07	0.14	0.18	-0.09	0.09	-0.15	0.13	0.72	0.77	0.72	0.56
37	GCA	-0.29	-0.29	-0.24	-0.19	-0.21	-0.32	-0.07	-0.38	-0.46	-0.27	-0.39	-0.35
38	GCC	0.13	-0.10	0.05	-0.35	0.16	0.12	0.44	-0.31	-0.47	-0.23	0.06	-0.25
39	GCG	-0.07	0.30	-0.15	0.04	-0.25	0.21	0.05	-0.26	-0.25	0.44	0.31	0.26
40	GCT	0.43	0.44	0.47	0.50	0.33	0.53	0.56	0.13	0.65	0.87	0.76	0.61
41	GGA	-0.33	-0.38	-0.11	-0.24	-0.21	-0.23	-0.36	-0.14	-0.29	-0.45	-0.20	-0.26

42	GGC	0.30	0.27	0.21	0.11	0.10	0.07	0.14	-0.01	-0.27	-0.30	-0.36	-0.27
43	GGG	-0.24	-0.01	-0.13	-0.16	0.10	0.34	0.10	0.22	0.07	0.10	0.21	-0.02
44	GGT	0.32	0.52	0.51	0.51	0.23	0.62	0.23	0.08	0.81	0.88	0.85	0.84
45	GTA	-0.34	-0.34	-0.37	-0.22	-0.09	-0.23	-0.21	0.05	-0.28	-0.09	-0.40	0.00
46	GTC	0.00	0.01	0.43	-0.26	0.01	-0.26	0.03	-0.19	-0.55	-0.56	-0.38	-0.47
47	GTG	-0.21	0.05	-0.29	-0.16	-0.25	-0.05	-0.17	0.02	0.22	0.55	0.19	0.42
48	GTT	0.56	0.49	0.49	0.53	0.41	0.36	0.41	0.13	0.68	0.87	0.76	0.66
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.01	-0.32	0.10	-0.20	-0.04	-0.03	-0.03	0.02	-0.36	-0.60	-0.49	-0.58
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.06	0.11	0.09	0.24	-0.05	0.20	-0.12	0.24	0.65	0.75	0.68	0.54
53	TCA	-0.19	-0.22	-0.19	-0.22	-0.16	-0.27	-0.04	-0.44	-0.32	-0.23	-0.36	-0.16
54	TCC	0.25	0.06	0.37	-0.26	0.28	0.06	0.45	-0.15	-0.42	-0.22	0.29	-0.30
55	TCG	-0.02	0.32	-0.14	-0.06	-0.05	0.08	0.24	-0.28	-0.03	0.58	0.22	0.20
56	TCT	0.15	0.27	0.24	0.24	0.23	0.31	0.51	-0.13	0.70	0.86	0.56	0.58
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.06	-0.09	-0.14	-0.15	0.21	-0.20	0.05	0.31	0.08	-0.39	-0.34	-0.12
59	TGG	0.13	0.06	-0.23	-0.04	-0.02	0.29	-0.19	0.15	-0.28	-0.20	0.04	-0.13
60	TGT	0.01	0.33	0.02	0.05	0.01	-0.26	-0.30	0.20	0.82	0.91	0.83	0.70
61	TTA	-0.35	-0.36	-0.37	-0.35	-0.17	-0.33	-0.32	-0.33	-0.26	-0.16	-0.19	-0.21
62	TTC	-0.09	0.02	0.02	-0.04	0.12	-0.18	0.29	-0.29	-0.54	-0.49	-0.58	-0.46
63	TTG	-0.08	0.10	-0.22	-0.19	0.15	0.04	0.10	-0.18	0.00	0.43	0.11	0.16
64	TTT	-0.02	0.03	0.14	-0.01	0.02	-0.16	0.00	0.05	0.49	0.80	0.50	0.57
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
		1	2	3	4	5	6	7	8	9	10	11	12

Table C.3 continued

		13	14	15	16	17	18	19	20	21	22	23	24
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
1	AAA	-0.36	-0.29	-0.14	0.22	0.07	0.14	0.15	0.35	0.07	0.35	0.19	0.45
2	AAC	0.17	0.01	0.04	0.06	0.09	0.02	0.32	0.17	0.20	0.17	0.19	0.12
3	AAG	0.01	0.32	0.38	0.29	-0.12	-0.37	-0.28	-0.41	-0.20	-0.31	-0.41	-0.42
4	AAT	-0.25	-0.06	-0.03	0.05	-0.23	0.04	-0.02	-0.14	-0.26	-0.27	-0.11	0.06
5	ACA	0.16	0.23	0.04	0.36	0.02	0.09	-0.05	0.22	0.08	0.27	-0.03	0.05
6	ACC	-0.05	-0.23	0.19	-0.52	0.00	-0.05	0.11	-0.29	0.29	0.40	0.47	0.36
7	ACG	-0.35	-0.19	-0.35	-0.37	0.05	0.18	0.30	0.24	-0.32	0.05	-0.24	-0.33
8	ACT	0.51	0.78	0.64	0.66	-0.34	-0.39	-0.08	-0.33	0.05	0.14	0.29	-0.09
9	AGA	-0.14	-0.09	-0.11	0.11	0.21	0.23	-0.19	0.28	0.44	0.23	0.26	0.36
10	AGC	-0.09	0.06	-0.21	-0.02	-0.20	-0.07	-0.20	-0.13	0.35	0.36	0.10	0.34
11	AGG	-0.14	0.31	0.21	0.25	-0.13	-0.26	-0.40	-0.27	-0.29	-0.02	-0.33	-0.31
12	AGT	-0.22	0.24	-0.06	-0.08	0.08	0.43	0.18	0.01	-0.21	-0.31	0.00	-0.07
13	ATA	0.02	0.68	0.56	0.72	-0.19	0.04	-0.09	0.01	-0.05	-0.13	-0.17	0.05
14	ATC	-0.11	-0.24	-0.19	-0.26	0.31	0.38	0.38	0.24	0.20	0.11	0.28	0.32
15	ATG	0.09	0.02	0.00	-0.04	0.27	-0.04	-0.22	0.02	0.26	0.10	-0.11	-0.02
16	ATT	0.22	0.03	0.03	0.07	-0.23	-0.25	-0.10	-0.13	-0.21	-0.29	-0.12	-0.08

17	CAA	-0.21	-0.33	-0.30	-0.14	0.64	0.76	0.70	0.74	0.69	0.73	0.87	0.81
18	CAC	0.26	0.05	0.05	0.05	0.15	0.00	0.17	0.00	-0.01	0.07	0.17	0.13
19	CAG	0.45	0.42	0.45	0.19	-0.31	-0.44	-0.48	-0.43	-0.40	-0.44	-0.46	-0.47
20	CAT	0.04	-0.03	-0.02	-0.06	-0.05	-0.03	-0.09	0.01	-0.10	-0.26	0.00	-0.02
21	CCA	-0.02	-0.22	-0.32	0.07	0.58	0.54	0.65	0.64	0.40	0.71	0.87	0.65
22	CCC	0.42	0.15	0.36	0.06	-0.03	-0.35	0.34	-0.11	0.13	0.69	0.44	-0.02
23	CCG	0.12	-0.12	-0.18	-0.36	-0.24	-0.09	-0.14	-0.15	-0.40	-0.24	-0.22	-0.35
24	CCT	0.43	0.57	0.52	0.46	-0.08	-0.02	-0.09	-0.12	-0.05	0.08	0.23	0.03
25	CGA	-0.15	-0.37	-0.38	-0.23	0.68	0.60	0.59	0.57	0.64	0.79	0.71	0.85
26	CGC	0.27	-0.05	0.18	0.08	-0.06	-0.29	-0.32	-0.31	0.28	-0.07	-0.12	0.01
27	CGG	-0.05	-0.03	-0.15	-0.30	0.00	-0.14	-0.12	-0.25	0.17	-0.22	-0.23	-0.20
28	CGT	0.33	0.22	0.34	0.21	0.14	0.24	0.32	0.23	-0.24	-0.43	-0.32	-0.28
29	CTA	-0.17	0.20	0.12	0.38	0.54	0.65	0.60	0.48	0.75	0.76	0.80	0.79
30	CTC	-0.04	-0.10	-0.11	-0.24	0.21	0.37	0.44	0.17	0.22	-0.09	0.15	0.10
31	CTG	0.29	-0.25	-0.22	-0.21	-0.23	-0.14	-0.04	0.01	-0.25	-0.12	-0.32	-0.26
32	CTT	0.47	0.53	0.58	0.48	-0.25	-0.42	-0.23	-0.30	-0.20	-0.29	-0.18	-0.32
33	GAA	-0.17	-0.20	-0.10	0.13	0.12	0.28	0.10	0.37	0.25	0.40	0.22	0.51
34	GAC	0.16	0.07	-0.02	-0.06	0.11	0.16	0.16	-0.06	0.32	0.21	0.10	-0.06
35	GAG	0.16	0.22	0.24	0.02	-0.06	-0.33	-0.29	-0.46	-0.37	-0.30	-0.42	-0.44
36	GAT	-0.09	0.02	0.01	0.00	-0.06	0.11	-0.09	-0.06	-0.16	-0.18	-0.01	0.01
37	GCA	0.14	0.17	-0.05	0.32	0.05	0.22	-0.08	0.33	0.09	0.11	0.21	0.14
38	GCC	-0.10	-0.22	-0.06	-0.41	-0.05	-0.08	0.12	-0.28	0.43	0.39	0.52	0.37
39	GCG	-0.09	-0.12	-0.28	-0.34	-0.08	0.09	0.10	0.08	-0.34	-0.17	-0.33	-0.34
40	GCT	0.38	0.57	0.53	0.41	-0.16	-0.20	0.16	-0.12	0.04	-0.29	0.10	-0.16
41	GGA	0.10	0.01	-0.07	0.16	-0.14	0.03	-0.19	0.04	0.29	0.46	0.10	0.22
42	GGC	0.02	-0.07	-0.07	-0.15	0.19	0.10	0.07	0.01	0.41	0.36	0.10	0.11
43	GGG	-0.26	0.17	-0.03	-0.22	-0.18	-0.27	-0.31	-0.39	-0.37	-0.26	-0.44	-0.38
44	GGT	0.13	0.21	0.30	0.13	0.38	0.29	0.38	0.39	0.09	-0.31	-0.10	-0.08
45	GTA	0.40	0.51	0.36	0.66	0.22	0.20	-0.17	0.29	0.43	0.28	0.34	0.38
46	GTC	-0.14	-0.39	-0.37	-0.43	0.42	0.34	0.53	0.16	0.57	0.51	0.48	0.44
47	GTG	0.08	-0.04	-0.14	-0.18	0.17	0.04	-0.16	0.20	-0.03	-0.09	-0.41	-0.28
48	GTT	0.35	0.27	0.43	0.32	-0.32	-0.36	-0.29	-0.33	-0.23	-0.39	-0.12	-0.31
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.39	0.10	0.07	0.17	0.32	0.29	0.39	0.21	0.39	0.41	0.19	0.31
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.18	-0.10	-0.04	0.09	-0.23	-0.20	-0.07	-0.06	-0.23	-0.12	-0.16	0.00
53	TCA	0.05	0.17	0.08	0.22	0.05	0.17	0.17	0.26	-0.13	0.22	0.28	-0.07
54	TCC	-0.09	-0.21	-0.10	-0.36	0.22	-0.12	0.36	0.02	0.17	0.21	0.54	0.32
55	TCG	-0.24	-0.08	0.02	-0.38	0.07	0.17	0.30	-0.02	-0.37	-0.30	-0.18	-0.48
56	TCT	0.19	0.33	0.29	0.18	-0.28	-0.21	0.04	-0.14	-0.39	-0.40	0.03	-0.32
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.09	-0.01	-0.02	0.36	-0.20	-0.37	-0.22	-0.05	0.25	0.43	-0.08	0.31
59	TGG	-0.17	0.09	0.00	-0.01	0.39	-0.06	-0.29	0.03	0.42	0.41	-0.23	0.04
60	TGT	-0.38	-0.24	0.02	-0.07	0.51	0.20	0.13	0.31	-0.04	-0.31	-0.17	-0.10

61	TTA	-0.24	-0.16	-0.22	0.02	0.40	0.51	0.31	0.24	0.69	0.61	0.81	0.64
62	TTC	0.26	0.13	0.25	0.18	-0.08	-0.07	0.28	-0.01	-0.08	-0.08	-0.16	-0.33
63	TTG	-0.01	-0.05	-0.05	-0.28	0.07	0.10	-0.23	0.14	-0.04	0.19	-0.24	-0.14
64	TTT	-0.01	-0.17	-0.10	-0.01	-0.10	0.13	0.02	-0.04	-0.02	-0.02	0.16	0.18
		ATA 13	ATC 14	ATG 15	ATT 16	CAA 17	CAC 18	CAG 19	CAT 20	CCA 21	CCC 22	CCG 23	CCT 24

Table C.3 continued

		25	26	27	28	29	30	31	32	33	34	35	36
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
1	AAA	-0.37	0.05	-0.23	0.30	0.00	0.43	0.29	0.57	-0.09	-0.17	0.04	0.22
2	AAC	-0.36	-0.39	-0.23	-0.43	-0.29	0.17	-0.15	-0.09	0.33	0.28	0.42	0.26
3	AAG	-0.17	0.07	-0.44	-0.06	-0.53	-0.53	-0.69	-0.60	0.03	-0.02	0.29	-0.19
4	AAT	0.01	0.40	0.23	0.25	-0.33	-0.06	0.08	0.13	-0.29	-0.20	0.00	-0.16
5	ACA	0.15	0.29	0.43	0.25	0.27	0.08	0.27	0.21	-0.02	-0.08	-0.16	0.05
6	ACC	-0.05	-0.31	-0.15	-0.32	0.20	0.21	0.33	0.06	0.41	0.39	0.29	0.04
7	ACG	0.45	0.49	0.47	0.55	-0.27	-0.33	-0.41	-0.47	0.27	0.43	0.33	0.12
8	ACT	0.57	0.28	0.47	-0.26	-0.22	0.44	0.62	0.01	-0.42	-0.37	-0.36	-0.35
9	AGA	-0.30	0.06	-0.20	0.22	0.58	0.45	0.33	0.58	-0.13	-0.21	-0.23	0.16
10	AGC	-0.36	-0.37	-0.41	-0.41	0.11	0.11	-0.08	0.14	0.43	0.35	0.25	0.37
11	AGG	-0.27	-0.12	-0.39	0.04	-0.27	-0.55	-0.68	-0.51	0.04	0.15	-0.14	-0.05
12	AGT	0.40	0.84	0.70	0.78	-0.27	0.04	0.17	0.04	-0.52	-0.44	-0.47	-0.44
13	ATA	-0.17	0.15	0.06	0.21	-0.24	0.07	0.26	0.31	-0.24	-0.22	-0.18	-0.13
14	ATC	0.10	-0.42	0.14	-0.26	0.15	0.29	0.37	0.25	0.28	0.31	0.39	0.39
15	ATG	0.45	0.26	0.15	0.21	0.14	-0.22	-0.43	-0.18	0.10	-0.05	-0.18	0.03
16	ATT	0.14	0.08	0.38	0.14	-0.06	-0.12	0.34	0.15	-0.19	-0.10	0.00	-0.21
17	CAA	0.49	0.73	0.68	0.78	0.43	0.81	0.82	0.85	0.14	0.02	-0.11	0.19
18	CAC	-0.19	-0.53	-0.27	-0.46	0.10	0.21	0.31	0.11	0.27	0.36	0.14	0.12
19	CAG	-0.39	-0.43	-0.52	-0.45	-0.36	-0.50	-0.58	-0.58	-0.03	0.04	-0.10	-0.19
20	CAT	0.10	0.25	0.13	0.13	0.03	0.10	0.26	0.26	-0.06	-0.14	-0.17	-0.06
21	CCA	0.60	0.67	0.73	0.60	0.53	0.69	0.77	0.72	0.25	0.07	-0.02	0.25
22	CCC	-0.48	-0.62	-0.11	-0.57	0.21	0.19	0.61	0.40	0.25	0.08	-0.17	-0.17
23	CCG	-0.12	-0.22	-0.15	-0.22	-0.26	-0.55	-0.33	-0.52	0.21	0.36	0.28	0.31
24	CCT	0.45	0.38	0.63	0.04	0.15	0.29	0.65	0.24	-0.33	-0.32	-0.34	-0.40
25	CGA	0.53	0.65	0.68	0.70	0.51	0.64	0.59	0.66	0.36	0.28	0.05	0.30
26	CGC	0.09	-0.51	-0.23	-0.51	0.10	0.09	-0.06	0.14	0.58	0.29	0.24	0.35
27	CGG	-0.01	0.36	0.16	0.21	0.12	-0.37	-0.51	-0.41	-0.04	-0.04	-0.14	-0.06
28	CGT	0.85	0.76	0.85	0.48	-0.03	-0.30	-0.05	-0.11	-0.27	-0.34	-0.17	-0.33
29	CTA	0.85	0.82	0.76	0.72	0.15	0.72	0.78	0.70	0.19	0.24	-0.11	0.16
30	CTC	0.08	-0.32	0.07	-0.30	0.42	0.28	0.49	0.38	0.35	0.10	0.49	-0.06
31	CTG	0.10	-0.12	-0.18	-0.13	0.09	-0.32	-0.44	-0.31	0.30	0.39	0.05	0.27
32	CTT	0.10	-0.31	0.02	-0.21	0.06	-0.14	0.34	0.11	-0.35	-0.09	-0.38	-0.44
33	GAA	-0.23	0.20	-0.11	0.33	0.29	0.48	0.27	0.58	-0.02	-0.07	-0.13	0.16
34	GAC	-0.38	-0.54	-0.45	-0.51	0.27	0.28	0.32	0.25	0.36	0.39	0.25	0.25
35	GAG	-0.13	-0.21	-0.49	-0.34	-0.39	-0.35	-0.60	-0.63	0.10	0.08	0.17	-0.23

36	GAT	0.16	0.49	0.33	0.39	0.04	0.06	0.17	0.10	-0.18	-0.18	-0.09	-0.13
37	GCA	0.17	0.19	0.36	0.26	0.16	0.15	0.24	0.24	0.00	-0.05	-0.02	0.14
38	GCC	-0.01	-0.46	-0.18	-0.38	0.40	0.31	0.47	0.27	0.43	0.37	0.18	0.20
39	GCG	0.10	0.21	0.10	-0.01	-0.11	-0.39	-0.37	-0.48	0.13	0.24	0.14	0.21
40	GCT	0.68	0.64	0.73	0.22	0.03	0.15	0.53	0.03	-0.31	-0.36	-0.29	-0.35
41	GGA	-0.11	-0.05	0.06	0.03	0.25	0.30	0.27	0.27	-0.14	-0.28	-0.04	0.06
42	GGC	0.00	-0.08	-0.16	-0.31	0.33	0.46	0.32	0.14	0.41	0.30	0.18	0.27
43	GGG	-0.09	-0.13	-0.16	0.02	-0.17	-0.36	-0.53	-0.56	0.05	0.21	0.27	0.12
44	GGT	0.71	0.79	0.79	0.67	0.14	0.02	0.34	-0.20	-0.37	-0.38	-0.28	-0.28
45	GTA	0.32	0.32	0.30	0.37	0.14	0.22	0.30	0.51	-0.06	-0.12	-0.18	0.12
46	GTC	0.20	-0.32	0.18	-0.18	0.47	0.45	0.50	0.50	0.49	0.46	0.37	0.18
47	GTG	0.18	0.12	-0.07	0.00	-0.10	-0.37	-0.55	-0.42	0.18	0.27	0.14	0.25
48	GTT	0.21	0.01	0.16	-0.02	-0.05	-0.21	0.18	0.04	-0.35	-0.31	-0.27	-0.35
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.33	-0.42	-0.39	-0.40	0.05	0.34	0.42	0.36	0.29	0.29	0.19	0.16
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.11	0.32	0.08	0.29	-0.12	0.11	0.39	0.36	-0.18	-0.16	0.04	-0.06
53	TCA	0.24	0.28	0.26	0.39	-0.14	0.08	0.34	0.16	0.03	-0.07	-0.14	0.07
54	TCC	-0.07	-0.45	-0.11	-0.41	0.12	0.27	0.51	0.17	0.55	0.46	0.34	0.30
55	TCG	0.39	0.37	0.23	0.10	-0.36	-0.38	-0.31	-0.47	0.26	0.33	0.21	0.18
56	TCT	0.40	0.60	0.65	0.35	-0.19	-0.16	0.41	-0.12	-0.25	-0.20	-0.15	-0.30
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	-0.49	-0.53	-0.45	-0.47	0.13	0.27	-0.02	0.35	0.50	0.43	0.14	0.39
59	TGG	0.22	0.10	-0.08	0.36	-0.04	-0.28	-0.41	-0.17	0.08	0.16	-0.14	-0.08
60	TGT	0.84	0.83	0.64	0.77	-0.31	-0.21	0.00	0.03	-0.29	-0.36	-0.37	-0.31
61	TTA	0.49	0.64	0.43	0.65	0.15	0.55	0.58	0.66	0.03	0.10	-0.10	0.07
62	TTC	-0.33	-0.50	-0.26	-0.53	-0.01	0.24	0.32	0.28	0.44	0.48	0.53	0.44
63	TTG	-0.23	-0.25	-0.26	-0.25	-0.22	-0.32	-0.47	-0.35	0.27	0.23	0.11	0.15
64	TTT	0.43	0.42	0.38	0.43	-0.08	-0.06	0.37	0.39	-0.22	-0.18	-0.07	-0.17
		CGA 25	CGC 26	CGG 27	CGT 28	CTA 29	CTC 30	CTG 31	CTT 32	GAA 33	GAC 34	GAG 35	GAT 36

Table C.3 continued

		37 GCA	38 GCC	39 GCG	40 GCT	41 GGA	42 GGC	43 GGG	44 GGT	45 GTA	46 GTC	47 GTG	48 GTT
1	AAA	-0.18	0.02	-0.30	0.25	-0.07	-0.17	-0.30	0.17	-0.19	0.17	-0.21	0.47
2	AAC	0.15	0.03	0.20	0.26	-0.30	-0.31	-0.21	-0.24	0.09	0.19	0.30	0.33
3	AAG	0.26	0.49	0.08	0.24	0.21	0.37	0.25	0.42	-0.13	0.09	-0.27	-0.12
4	AAT	-0.06	-0.26	-0.17	0.07	0.22	0.37	0.30	0.32	-0.25	-0.21	-0.23	0.09
5	ACA	0.06	0.06	0.07	-0.10	0.02	-0.11	-0.16	-0.11	0.22	0.23	0.26	0.28
6	ACC	0.12	0.20	0.37	-0.20	-0.31	-0.30	-0.27	-0.33	-0.12	-0.03	0.19	-0.34
7	ACG	-0.03	0.40	0.25	-0.12	0.17	0.55	0.39	0.30	0.14	0.17	0.23	-0.20
8	ACT	-0.28	-0.23	0.01	-0.40	0.04	0.16	0.28	-0.19	-0.40	-0.36	-0.15	-0.51
9	AGA	-0.07	-0.01	-0.33	0.28	-0.26	-0.15	-0.38	0.19	0.21	0.19	-0.15	0.49
10	AGC	0.36	0.20	0.35	0.43	-0.38	-0.29	-0.33	-0.28	0.30	0.43	0.30	0.49
11	AGG	-0.03	0.24	-0.22	0.20	-0.34	0.06	0.36	0.54	0.05	0.34	-0.29	0.07
12	AGT	-0.10	-0.09	-0.21	-0.06	0.59	0.82	0.80	0.56	-0.37	-0.28	-0.44	-0.28
13	ATA	0.24	0.20	0.13	0.22	0.28	0.23	0.10	0.13	0.53	0.65	0.68	0.70

14	ATC	0.06	-0.22	0.24	0.05	-0.30	-0.48	-0.39	-0.47	-0.09	-0.11	0.16	-0.09
15	ATG	0.08	0.28	-0.18	-0.08	0.07	0.14	-0.32	0.05	0.13	0.12	-0.18	0.01
16	ATT	0.00	-0.30	0.01	0.05	0.51	0.45	0.51	0.41	-0.10	-0.22	-0.11	-0.01
17	CAA	0.11	0.01	0.02	0.16	-0.15	-0.19	-0.34	-0.17	-0.11	-0.04	-0.24	0.28
18	CAC	0.18	-0.29	0.15	-0.13	-0.32	-0.49	-0.37	-0.38	0.13	0.08	0.23	0.06
19	CAG	-0.13	0.24	-0.17	-0.12	0.11	0.42	0.00	0.47	0.25	0.17	-0.18	-0.02
20	CAT	0.06	-0.13	-0.04	0.15	0.37	0.31	0.32	0.33	-0.11	-0.11	-0.20	0.21
21	CCA	0.36	0.20	0.47	-0.04	0.31	0.12	-0.01	-0.25	0.35	0.16	0.39	0.17
22	CCC	-0.23	-0.27	0.10	-0.58	-0.56	-0.63	-0.31	-0.57	-0.01	-0.22	0.16	-0.31
23	CCG	-0.06	0.36	0.26	-0.14	-0.07	0.21	0.24	0.04	0.35	0.37	0.36	-0.11
24	CCT	-0.08	-0.11	-0.02	-0.28	0.25	0.33	0.43	-0.20	-0.25	-0.37	0.04	-0.47
25	CGA	0.47	0.57	0.20	0.22	0.22	0.12	0.05	0.31	0.47	0.12	-0.22	0.42
26	CGC	0.26	0.04	0.10	0.17	-0.41	-0.45	-0.22	-0.37	0.31	-0.03	0.20	0.29
27	CGG	-0.22	0.18	-0.27	0.05	0.03	0.38	0.32	0.60	-0.05	0.19	-0.29	0.13
28	CGT	-0.02	-0.24	-0.21	0.00	0.69	0.77	0.71	0.68	-0.39	-0.41	-0.39	-0.21
29	CTA	0.42	0.14	0.36	0.13	0.30	-0.09	-0.08	-0.17	0.11	-0.09	0.20	0.15
30	CTC	0.09	-0.22	0.24	-0.13	-0.42	-0.64	-0.48	-0.65	-0.10	-0.49	-0.13	-0.47
31	CTG	0.06	0.20	0.03	0.01	0.52	0.47	0.34	0.54	0.63	0.47	0.45	0.46
32	CTT	-0.14	-0.40	-0.08	-0.29	-0.03	-0.25	0.05	-0.19	-0.26	-0.49	-0.34	-0.35
33	GAA	-0.10	-0.01	-0.32	0.15	-0.09	-0.21	-0.22	0.14	-0.08	0.08	-0.29	0.32
34	GAC	0.18	0.05	0.17	0.13	-0.43	-0.48	-0.40	-0.42	0.27	0.34	0.32	0.26
35	GAG	0.19	0.52	0.14	0.26	0.28	0.31	0.18	0.44	0.09	0.26	-0.05	-0.16
36	GAT	-0.04	-0.19	-0.08	0.03	0.39	0.50	0.50	0.42	-0.23	-0.07	-0.23	-0.05
37	GCA	0.00	-0.09	0.19	0.01	0.06	-0.04	-0.06	-0.16	0.26	0.20	0.26	0.23
38	GCC	0.07	0.17	0.32	-0.19	-0.41	-0.33	-0.24	-0.49	0.16	0.09	0.37	-0.10
39	GCG	-0.19	0.32	0.11	-0.11	-0.01	0.30	0.06	0.13	0.17	0.27	0.21	-0.12
40	GCT	-0.07	-0.17	0.10	-0.23	0.37	0.53	0.52	0.24	-0.36	-0.34	-0.03	-0.46
41	GGA	0.05	0.13	-0.21	0.19	0.17	0.25	0.24	0.56	0.38	0.49	0.41	0.50
42	GGC	0.10	0.03	0.19	-0.02	-0.54	-0.40	-0.38	-0.46	-0.04	0.03	0.08	-0.13
43	GGG	-0.11	0.47	-0.03	0.09	0.17	0.52	0.59	0.79	0.23	0.44	0.38	0.06
44	GGT	-0.22	-0.10	-0.25	-0.19	0.62	0.80	0.70	0.60	-0.51	-0.48	-0.45	-0.51
45	GTA	0.07	-0.08	0.02	0.07	0.21	0.25	-0.12	-0.02	0.43	0.48	0.49	0.58
46	GTC	0.17	0.07	0.46	0.04	-0.42	-0.58	-0.45	-0.61	-0.01	-0.16	-0.05	-0.20
47	GTG	-0.12	0.28	-0.10	0.06	0.63	0.68	0.49	0.72	0.56	0.48	0.31	0.42
48	GTT	0.01	-0.34	-0.11	-0.20	0.30	0.47	0.40	0.12	-0.31	-0.50	-0.32	-0.35
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.10	0.11	0.02	0.00	-0.45	-0.45	-0.43	-0.34	0.25	0.39	0.23	0.44
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.03	-0.13	-0.11	0.18	0.33	0.39	0.47	0.45	-0.30	-0.17	-0.24	0.13
53	TCA	-0.10	-0.14	-0.03	-0.20	-0.07	-0.13	0.00	-0.21	0.22	0.21	0.34	0.14
54	TCC	0.06	-0.14	0.44	-0.31	-0.14	-0.35	-0.12	-0.44	0.26	-0.02	0.54	-0.25
55	TCG	-0.18	0.25	0.16	-0.13	0.11	0.38	0.17	0.09	0.19	0.21	0.21	-0.20
56	TCT	-0.11	-0.16	0.13	-0.31	0.44	0.58	0.56	0.23	-0.31	-0.40	0.09	-0.49
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.23	-0.01	0.00	0.36	-0.49	-0.38	-0.35	-0.17	0.33	0.39	0.37	0.58
59	TGG	-0.06	0.29	-0.19	0.08	-0.23	0.09	0.00	0.32	0.06	0.33	-0.30	0.05
60	TGT	-0.29	-0.05	-0.23	0.08	0.69	0.89	0.80	0.63	-0.46	-0.44	-0.36	-0.02
61	TTA	0.25	0.21	0.26	0.27	0.10	0.12	-0.17	-0.07	0.29	0.34	0.25	0.32
62	TTC	0.20	-0.05	0.45	0.16	-0.33	-0.44	-0.33	-0.40	0.33	0.25	0.56	0.08
63	TTG	-0.15	0.31	-0.03	-0.13	0.39	0.48	0.34	0.57	0.48	0.33	0.05	-0.06
64	TTT	0.01	-0.28	-0.09	0.04	0.35	0.19	0.37	0.33	0.07	-0.31	-0.06	-0.07
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
		37	38	39	40	41	42	43	44	45	46	47	48

Table C.3 continued

		49	50	51	52	53	54	55	56	57	58	59	60
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
1	AAA	0.00	-0.18	0.00	0.06	-0.19	0.23	-0.21	0.40	0.00	-0.09	-0.03	0.08
2	AAC	0.00	-0.08	0.00	-0.09	0.23	0.09	0.31	0.27	0.00	-0.29	-0.25	-0.25
3	AAG	0.00	0.11	0.00	0.08	0.34	0.39	0.18	0.27	0.00	0.17	0.07	-0.10
4	AAT	0.00	0.01	0.00	0.11	0.06	0.27	0.09	0.28	0.00	0.30	0.26	0.30
5	ACA	0.00	0.00	0.00	0.12	-0.12	-0.03	-0.01	0.06	0.00	0.05	0.00	0.00
6	ACC	0.00	0.11	0.00	-0.17	0.30	-0.09	-0.20	-0.13	0.00	-0.14	0.42	-0.01
7	ACG	0.00	-0.03	0.00	-0.07	0.21	0.24	0.39	0.18	0.00	0.05	0.10	0.53
8	ACT	0.00	-0.12	0.00	0.07	-0.32	-0.15	0.02	-0.38	0.00	-0.04	-0.37	-0.48
9	AGA	0.00	0.18	0.00	0.38	0.36	0.45	0.03	0.50	0.00	0.14	-0.16	0.44
10	AGC	0.00	-0.13	0.00	-0.18	0.23	0.24	-0.02	0.18	0.00	-0.31	-0.39	-0.29
11	AGG	0.00	0.23	0.00	0.26	0.25	0.35	-0.17	0.42	0.00	0.19	0.10	0.30
12	AGT	0.00	0.44	0.00	0.16	-0.22	0.21	-0.05	0.14	0.00	0.82	0.48	0.41
13	ATA	0.00	-0.24	0.00	-0.03	-0.12	-0.23	-0.38	-0.06	0.00	-0.30	-0.45	-0.21
14	ATC	0.00	0.38	0.00	0.25	0.35	0.33	0.45	0.40	0.00	0.22	0.28	0.20
15	ATG	0.00	-0.19	0.00	0.12	0.14	0.08	-0.07	0.05	0.00	-0.09	0.00	0.12
16	ATT	0.00	-0.15	0.00	-0.16	-0.16	-0.25	0.00	-0.32	0.00	-0.03	-0.01	-0.09
17	CAA	0.00	-0.27	0.00	-0.21	-0.18	-0.28	-0.39	-0.04	0.00	-0.35	-0.19	-0.21
18	CAC	0.00	0.28	0.00	0.09	0.24	-0.07	0.13	0.10	0.00	-0.21	-0.07	0.07
19	CAG	0.00	0.40	0.00	0.27	0.25	0.13	0.21	0.24	0.00	0.39	0.24	0.47
20	CAT	0.00	-0.08	0.00	-0.07	-0.08	-0.27	-0.02	-0.06	0.00	0.17	0.04	-0.08
21	CCA	0.00	-0.30	0.00	-0.18	-0.28	-0.17	-0.06	-0.39	0.00	-0.36	-0.38	-0.16
22	CCC	0.00	0.42	0.00	0.00	0.13	-0.16	0.28	0.23	0.00	-0.13	0.71	0.22
23	CCG	0.00	0.32	0.00	0.33	0.21	0.30	0.44	0.07	0.00	0.37	0.29	0.43
24	CCT	0.00	-0.15	0.00	-0.30	-0.21	-0.40	-0.24	-0.35	0.00	-0.19	-0.20	-0.33
25	CGA	0.00	-0.16	0.00	-0.20	0.25	0.03	-0.01	0.25	0.00	-0.05	0.15	-0.01
26	CGC	0.00	-0.25	0.00	-0.27	-0.06	-0.28	0.04	0.00	0.00	-0.54	-0.47	-0.56
27	CGG	0.00	0.34	0.00	0.24	0.24	0.51	-0.06	0.43	0.00	0.56	0.59	0.42
28	CGT	0.00	-0.14	0.00	-0.25	-0.42	-0.42	-0.50	-0.45	0.00	0.59	0.63	0.35
29	CTA	0.00	-0.37	0.00	-0.37	-0.28	-0.37	-0.47	-0.20	0.00	-0.50	-0.53	-0.51
30	CTC	0.00	0.26	0.00	0.17	0.22	0.28	0.34	0.21	0.00	0.28	0.28	-0.16
31	CTG	0.00	0.11	0.00	0.11	0.06	-0.05	-0.01	-0.02	0.00	0.29	0.18	0.60
32	CTT	0.00	-0.06	0.00	-0.13	-0.09	-0.29	-0.07	-0.44	0.00	-0.15	0.11	-0.11
33	GAA	0.00	-0.16	0.00	0.05	-0.07	0.08	-0.22	0.28	0.00	-0.15	0.00	-0.03
34	GAC	0.00	0.28	0.00	0.18	0.50	0.34	0.36	0.38	0.00	-0.24	-0.21	-0.11
35	GAG	0.00	0.13	0.00	0.05	0.28	0.50	0.15	0.29	0.00	0.18	0.00	0.29
36	GAT	0.00	-0.08	0.00	-0.12	-0.12	-0.15	-0.11	0.01	0.00	0.20	0.15	0.05
37	GCA	0.00	-0.04	0.00	0.15	0.00	-0.23	-0.08	-0.01	0.00	0.01	-0.11	0.00
38	GCC	0.00	0.08	0.00	-0.08	0.31	0.16	0.33	0.07	0.00	-0.39	0.11	-0.29
39	GCG	0.00	0.29	0.00	0.26	0.39	0.41	0.53	0.29	0.00	0.40	0.35	0.34
40	GCT	0.00	-0.25	0.00	-0.27	-0.41	-0.45	-0.25	-0.48	0.00	0.18	-0.24	-0.10
41	GGA	0.00	0.10	0.00	0.10	-0.05	0.79	0.07	0.42	0.00	0.13	0.27	0.31
42	GGC	0.00	-0.20	0.00	-0.17	0.22	0.11	0.18	0.17	0.00	-0.39	-0.46	-0.47
43	GGG	0.00	0.29	0.00	0.24	0.42	0.60	0.39	0.41	0.00	0.28	0.46	0.47
44	GGT	0.00	0.25	0.00	-0.10	-0.51	-0.11	-0.39	-0.41	0.00	0.76	0.70	0.63
45	GTA	0.00	-0.35	0.00	-0.08	-0.29	-0.32	-0.39	-0.27	0.00	0.01	-0.36	-0.33
46	GTC	0.00	0.48	0.00	0.21	0.41	0.36	0.44	0.44	0.00	-0.04	0.29	0.04
47	GTG	0.00	-0.10	0.00	-0.02	0.23	0.26	0.23	0.21	0.00	0.36	0.11	0.42
48	GTT	0.00	0.07	0.00	-0.12	-0.14	-0.40	-0.01	-0.37	0.00	-0.12	0.03	-0.21
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.00	0.00	0.00	0.05	0.29	0.08	0.05	0.18	0.00	-0.10	-0.05	-0.20
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.00	-0.02	0.00	-0.02	-0.09	-0.14	-0.01	0.09	0.00	0.07	0.03	0.11
53	TCA	0.00	0.18	0.00	0.30	0.08	-0.09	0.13	-0.10	0.00	0.26	0.10	0.32
54	TCC	0.00	-0.10	0.00	-0.29	-0.01	-0.13	0.14	-0.17	0.00	-0.40	0.20	-0.32

55	TCG	0.00	0.24	0.00	0.16	0.29	0.30	0.51	0.14	0.00	0.38	0.25	0.55
56	TCT	0.00	-0.08	0.00	-0.11	-0.30	-0.27	-0.12	-0.40	0.00	0.12	0.10	-0.17
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.00	-0.08	0.00	-0.05	0.09	0.19	-0.28	0.25	0.00	-0.31	-0.32	-0.41
59	TGG	0.00	-0.10	0.00	0.06	0.15	0.32	-0.03	-0.01	0.00	0.06	0.00	-0.07
60	TGT	0.00	0.27	0.00	-0.03	-0.30	-0.17	-0.30	0.07	0.00	0.86	0.56	0.45
61	TTA	0.00	0.03	0.00	-0.15	-0.20	-0.20	-0.21	-0.05	0.00	-0.34	-0.29	-0.10
62	TTC	0.00	0.13	0.00	0.21	0.01	-0.05	0.04	-0.07	0.00	-0.09	-0.09	-0.19
63	TTG	0.00	0.22	0.00	0.17	0.17	0.12	0.27	-0.01	0.00	0.07	0.22	0.49
64	TTT	0.00	-0.06	0.00	-0.09	-0.11	-0.10	-0.05	-0.17	0.00	0.14	0.05	-0.01
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
		49	50	51	52	53	54	55	56	57	58	59	60

Table C.3 continued

		61	62	63	64
		TTA	TTC	TTG	TTT
1	AAA	0.34	-0.27	0.31	0.26
2	AAC	0.22	-0.27	0.24	-0.06
3	AAG	0.63	-0.10	0.72	-0.12
4	AAT	-0.09	-0.13	-0.07	0.25
5	ACA	0.06	0.00	-0.22	0.16
6	ACC	0.12	-0.15	-0.08	-0.30
7	ACG	0.15	0.07	0.58	-0.10
8	ACT	-0.11	0.13	-0.03	0.19
9	AGA	0.48	0.44	0.29	0.48
10	AGC	0.26	0.21	0.10	-0.01
11	AGG	0.46	0.29	0.68	0.29
12	AGT	-0.27	0.38	-0.26	0.10
13	ATA	-0.45	-0.39	-0.48	-0.10
14	ATC	0.35	0.21	0.49	0.28
15	ATG	0.74	-0.02	0.76	0.01
16	ATT	-0.47	-0.32	-0.45	0.04
17	CAA	0.11	-0.12	0.14	-0.17
18	CAC	0.09	0.05	-0.11	0.17
19	CAG	0.66	0.27	0.68	0.16
20	CAT	-0.31	0.02	-0.43	-0.09
21	CCA	-0.22	-0.22	-0.18	-0.28
22	CCC	0.38	0.42	0.10	0.22
23	CCG	0.40	0.23	0.67	-0.04
24	CCT	-0.27	0.15	0.01	0.05
25	CGA	-0.24	-0.34	-0.22	-0.24
26	CGC	0.33	0.04	0.18	0.05
27	CGG	0.41	0.41	0.72	0.00
28	CGT	-0.36	-0.40	-0.37	-0.45
29	CTA	-0.49	-0.30	-0.57	-0.28
30	CTC	0.35	0.32	0.04	0.23
31	CTG	0.19	0.10	0.49	-0.19

32	CTT	-0.05	0.25	-0.33	0.41
33	GAA	0.20	-0.04	0.02	0.03
34	GAC	0.12	0.20	0.07	0.18
35	GAG	0.52	0.22	0.58	-0.11
36	GAT	-0.33	-0.10	-0.40	-0.10
37	GCA	-0.05	0.18	-0.20	-0.02
38	GCC	0.35	0.26	0.14	0.05
39	GCG	0.21	0.34	0.56	-0.09
40	GCT	-0.36	-0.08	-0.32	-0.19
41	GGA	-0.01	0.10	-0.14	0.03
42	GGC	0.27	0.08	0.11	0.13
43	GGG	0.19	0.43	0.40	-0.02
44	GGT	-0.40	-0.13	-0.46	-0.34
45	GTA	-0.24	-0.36	-0.36	-0.25
46	GTC	0.53	0.32	0.42	0.29
47	GTG	0.14	0.17	0.45	-0.15
48	GTT	-0.25	0.00	-0.24	0.09
49	TAA	0.00	0.00	0.00	0.00
50	TAC	-0.07	0.08	-0.05	0.13
51	TAG	0.00	0.00	0.00	0.00
52	TAT	-0.43	-0.21	-0.50	0.03
53	TCA	-0.13	0.02	-0.20	0.01
54	TCC	0.09	-0.11	0.02	-0.24
55	TCG	-0.17	0.10	0.56	-0.28
56	TCT	-0.33	0.09	-0.09	0.09
57	TGA	0.00	0.00	0.00	0.00
58	TGC	0.23	0.13	0.09	0.10
59	TGG	0.70	0.01	0.83	-0.01
60	TGT	-0.31	0.17	-0.33	-0.22
61	TTA	-0.17	-0.09	-0.20	-0.15
62	TTC	-0.22	-0.26	0.15	-0.14
63	TTG	0.24	-0.05	0.58	-0.24
64	TTT	-0.44	-0.25	-0.36	0.30
		TTA	TTC	TTG	TTT
		61	62	63	64

Table C.4: CPW matrix *Bacillus subtilis* highly expressed sequences (left codon indicated in column 2, right codon indicated in row 2). Host cell: *B. subtilus*; Sequence data: full *B. subtilus* genome; Highly expressed group: 415 seqs.

		1	2	3	4	5	6	7	8	9	10	11	12
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
1	AAA	-0.03	-0.38	-0.04	0.19	-0.34	0.00	-0.23	0.22	0.36	-0.17	0.48	0.25
2	AAC	-0.30	-0.53	-0.05	-0.02	-0.18	0.39	0.03	-0.11	0.03	-0.69	0.26	0.06
3	AAG	0.03	0.24	0.17	0.48	0.59	0.79	0.50	0.58	0.82	0.26	0.88	-0.11
4	AAT	0.15	0.27	0.48	0.49	-0.10	0.19	-0.16	0.60	0.87	0.83	0.89	0.27
5	ACA	-0.32	-0.46	-0.18	-0.09	-0.24	0.00	0.24	-0.59	-0.24	-0.49	-0.13	0.11
6	ACC	0.51	0.51	0.75	0.30	0.43	0.64	0.78	-0.31	0.23	0.79	1.00	0.09
7	ACG	0.14	-0.14	-0.14	0.32	-0.12	0.03	-0.08	-0.16	-0.21	0.32	0.25	0.33
8	ACT	0.44	0.35	0.10	0.68	0.50	1.00	0.89	-0.39	0.08	0.48	-0.52	1.00
9	AGA	-0.18	-0.33	-0.19	0.35	-0.12	0.22	-0.28	0.11	0.10	-0.01	-0.25	-0.50
10	AGC	-0.17	-0.10	0.12	0.14	-0.05	0.39	-0.23	-0.18	-0.39	-0.13	-0.36	-0.47
11	AGG	0.88	0.84	0.86	0.49	0.76	1.00	1.00	1.00	0.33	1.00	0.39	0.45
12	AGT	-0.01	0.72	0.68	0.67	-0.20	0.47	0.05	-0.06	0.79	0.84	1.00	0.66
13	ATA	0.01	0.26	0.53	0.43	0.73	0.65	0.17	0.83	0.48	0.67	1.00	0.76
14	ATC	-0.28	-0.44	0.07	-0.20	-0.08	0.29	0.20	-0.48	-0.09	-0.52	-0.30	-0.56
15	ATG	0.13	-0.27	-0.24	0.29	0.25	-0.06	-0.11	-0.27	-0.23	0.17	0.43	-0.25
16	ATT	0.15	0.09	0.12	0.42	-0.30	0.31	0.15	0.01	0.90	0.84	0.91	0.76
17	CAA	-0.32	-0.54	-0.43	-0.08	-0.29	-0.25	-0.42	0.20	0.12	-0.46	0.49	0.33
18	CAC	-0.14	-0.44	0.26	0.35	0.11	0.24	-0.19	-0.34	-0.37	-0.65	-0.31	-0.58
19	CAG	0.57	0.60	0.61	0.56	0.62	0.45	-0.02	0.45	0.61	0.84	0.29	0.88
20	CAT	-0.04	-0.19	0.15	0.31	-0.09	0.35	-0.05	0.16	0.74	0.73	1.00	0.56
21	CCA	-0.31	-0.64	-0.46	-0.17	-0.09	0.00	0.17	-0.64	-0.60	-0.66	-0.41	-0.31
22	CCC	0.69	0.39	1.00	0.84	1.00	0.58	1.00	0.58	0.56	1.00	1.00	0.38
23	CCG	0.07	0.09	-0.17	-0.09	-0.43	0.65	0.13	-0.61	-0.07	0.65	0.75	-0.21
24	CCT	0.06	0.30	0.39	0.51	0.38	0.47	0.77	0.74	0.73	0.47	1.00	0.81
25	CGA	0.16	-0.47	0.74	-0.42	0.20	0.41	0.48	0.71	-0.42	-0.31	1.00	-0.05
26	CGC	-0.36	-0.41	-0.22	0.09	-0.02	0.04	-0.18	-0.08	-0.53	-0.41	0.45	-0.63
27	CGG	0.48	0.61	0.20	0.40	-0.05	0.46	-0.28	1.00	0.74	0.26	1.00	0.35
28	CGT	-0.23	0.24	0.30	-0.20	-0.42	0.69	-0.40	-0.51	1.00	1.00	1.00	1.00
29	CTA	-0.24	-0.30	-0.25	0.01	0.59	0.74	1.00	-0.04	-0.36	-0.52	0.29	0.58
30	CTC	0.47	0.09	0.29	0.35	0.46	0.30	0.31	-0.28	0.08	-0.38	0.37	-0.10
31	CTG	-0.13	-0.29	0.03	-0.05	-0.30	-0.12	-0.31	-0.57	0.25	0.64	-0.03	0.65
32	CTT	0.47	0.54	0.72	0.69	0.49	0.62	0.81	-0.08	0.62	0.72	0.56	0.65
33	GAA	-0.08	-0.35	0.05	0.13	-0.25	-0.09	-0.11	-0.07	0.26	-0.37	0.75	-0.08
34	GAC	-0.23	-0.33	-0.02	-0.14	-0.10	0.29	0.32	-0.37	-0.08	-0.71	-0.04	-0.61
35	GAG	0.09	0.23	0.14	0.42	0.21	0.84	0.53	0.32	0.64	0.25	0.55	0.23
36	GAT	0.00	-0.03	0.41	0.34	-0.12	0.30	-0.01	0.10	0.85	0.78	0.83	0.76
37	GCA	-0.29	-0.44	0.02	0.51	-0.41	-0.06	0.42	-0.57	-0.43	-0.29	0.47	-0.62
38	GCC	0.39	-0.31	0.43	0.04	0.58	0.64	0.72	0.04	-0.24	0.11	0.28	-0.08
39	GCG	-0.23	-0.06	-0.22	-0.01	-0.29	0.15	0.10	-0.52	-0.31	0.39	0.58	0.14
40	GCT	0.19	-0.04	0.54	0.47	0.25	0.80	0.40	-0.17	0.94	0.95	0.85	0.39

41	GGA	-0.14	-0.45	0.24	-0.16	-0.38	0.36	-0.38	-0.24	-0.10	-0.51	0.67	-0.28
42	GGC	0.12	-0.02	0.09	0.31	0.10	0.61	0.25	0.17	-0.05	-0.28	0.40	0.20
43	GGG	-0.13	0.40	0.38	0.12	0.52	0.49	0.76	0.59	0.54	0.62	0.79	0.67
44	GGT	-0.27	-0.19	0.37	0.68	-0.31	0.37	0.09	-0.52	0.93	1.00	1.00	0.70
45	GTA	-0.45	-0.51	-0.19	-0.17	-0.32	-0.14	-0.39	-0.52	-0.30	-0.11	0.78	0.07
46	GTC	0.11	0.12	0.57	-0.11	-0.08	0.37	0.52	-0.24	-0.40	-0.51	0.84	-0.51
47	GTG	-0.20	-0.26	-0.35	0.15	-0.19	0.18	-0.05	-0.01	0.58	0.35	0.51	0.12
48	GTT	0.52	0.20	0.52	0.69	0.46	0.71	0.39	-0.24	0.62	0.82	0.55	0.76
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.21	-0.66	-0.04	0.14	-0.43	0.42	0.23	-0.46	-0.31	-0.51	0.50	-0.68
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.03	0.37	0.28	0.46	0.36	0.54	-0.30	0.31	0.76	1.00	1.00	0.76
53	TCA	-0.24	-0.49	0.29	0.22	0.12	-0.23	-0.11	-0.66	-0.36	-0.32	0.24	-0.53
54	TCC	0.59	-0.03	0.31	-0.34	0.41	0.36	0.49	-0.42	-0.54	-0.34	1.00	-0.28
55	TCG	0.20	0.56	-0.30	0.21	0.36	0.73	0.84	0.46	-0.07	1.00	-0.15	-0.05
56	TCT	-0.15	-0.23	-0.07	0.16	-0.21	0.46	0.52	-0.25	0.79	1.00	1.00	0.31
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	-0.17	-0.18	0.30	0.24	-0.05	1.00	-0.28	0.33	-0.44	-0.38	1.00	0.00
59	TGG	0.18	-0.22	-0.30	0.22	0.13	0.55	-0.33	-0.04	-0.35	-0.47	0.04	-0.31
60	TGT	-0.09	-0.16	0.43	0.07	-0.21	-0.18	0.28	-0.18	1.00	1.00	1.00	1.00
61	TTA	-0.33	-0.52	-0.32	-0.14	-0.19	0.40	-0.32	-0.48	-0.31	-0.11	0.46	0.04
62	TTC	-0.38	-0.39	-0.06	0.49	-0.38	0.33	0.07	-0.19	-0.55	-0.62	-0.46	-0.54
63	TTG	-0.23	-0.12	-0.18	0.00	0.27	0.23	0.09	-0.44	0.33	0.75	0.31	0.46
64	TTT	0.16	-0.12	0.34	0.11	0.13	-0.27	0.31	0.16	0.59	0.88	0.75	0.73
		AAA 1	AAC 2	AAG 3	AAT 4	ACA 5	ACC 6	ACG 7	ACT 8	AGA 9	AGC 10	AGG 11	AGT 12

Table C.4 continued

		13 ATA	14 ATC	15 ATG	16 ATT	17 CAA	18 CAC	19 CAG	20 CAT	21 CCA	22 CCC	23 CCG	24 CCT
1	AAA	0.42	-0.44	-0.15	0.14	-0.04	-0.12	0.37	0.57	0.04	0.46	0.21	0.20
2	AAC	0.66	-0.46	-0.33	0.09	-0.30	-0.15	0.04	-0.14	-0.24	0.53	-0.15	0.13
3	AAG	0.92	0.46	0.39	0.21	-0.19	-0.51	-0.33	-0.39	-0.04	0.84	-0.36	-0.49
4	AAT	0.54	-0.11	0.38	0.24	-0.01	-0.18	0.33	0.30	-0.08	-0.08	-0.08	0.36
5	ACA	0.70	-0.18	-0.12	0.23	-0.14	-0.28	0.06	0.24	-0.34	0.33	-0.11	0.04
6	ACC	0.08	0.08	0.38	-0.32	0.47	-0.33	0.45	0.63	0.51	0.66	0.93	0.68
7	ACG	-0.42	-0.27	-0.26	-0.39	0.31	0.22	0.16	0.40	-0.51	0.59	0.00	-0.34
8	ACT	0.54	0.95	0.58	0.74	-0.47	-0.62	-0.34	-0.36	-0.61	0.66	0.58	0.04
9	AGA	0.41	-0.10	0.39	0.24	0.61	-0.29	0.20	0.15	0.48	1.00	-0.16	0.43
10	AGC	0.37	-0.19	0.01	-0.22	-0.16	-0.36	-0.18	0.36	0.14	0.70	0.07	0.24
11	AGG	0.35	0.57	0.61	0.60	0.70	0.57	0.38	0.16	0.53	1.00	0.18	0.38
12	AGT	0.17	0.54	0.23	0.12	0.73	0.43	0.44	0.30	0.37	0.34	0.32	-0.03
13	ATA	0.81	0.80	0.93	0.71	0.15	0.33	0.05	0.13	0.16	0.64	-0.08	0.11
14	ATC	0.15	-0.51	-0.36	-0.20	0.05	0.26	0.34	0.12	-0.20	0.64	0.07	0.44
15	ATG	0.55	-0.13	0.00	-0.03	0.19	-0.21	-0.17	0.13	-0.11	0.44	0.11	-0.18

16	ATT	0.66	-0.03	0.18	0.21	-0.22	-0.48	-0.04	0.19	-0.25	0.47	-0.19	-0.06
17	CAA	0.21	-0.49	-0.32	-0.14	0.59	0.90	0.82	0.61	0.56	0.81	0.89	0.83
18	CAC	1.00	-0.11	-0.14	-0.33	0.04	-0.57	0.09	-0.05	-0.21	1.00	0.04	-0.04
19	CAG	0.70	0.50	0.49	0.31	-0.26	-0.42	-0.53	-0.42	-0.50	0.04	-0.46	-0.49
20	CAT	0.56	-0.03	0.08	0.05	0.13	0.32	-0.16	0.18	-0.32	0.51	-0.07	0.18
21	CCA	0.75	-0.50	-0.23	0.08	-0.02	-0.37	0.79	0.90	0.12	1.00	1.00	0.13
22	CCC	1.00	1.00	0.63	1.00	0.35	-0.21	1.00	0.17	0.07	1.00	1.00	0.39
23	CCG	0.57	-0.38	-0.28	-0.43	-0.39	0.05	0.50	-0.12	-0.42	-0.17	-0.32	-0.47
24	CCT	1.00	0.56	0.60	0.64	-0.33	0.21	-0.15	-0.26	0.42	1.00	0.50	-0.13
25	CGA	-0.20	-0.20	-0.24	-0.07	0.41	1.00	0.70	0.80	0.54	1.00	0.80	1.00
26	CGC	0.85	0.12	-0.24	-0.20	-0.23	-0.26	-0.43	-0.12	-0.33	0.55	-0.10	-0.11
27	CGG	0.04	0.10	-0.09	-0.27	0.37	0.49	0.26	0.00	0.16	1.00	0.64	0.26
28	CGT	0.67	-0.36	-0.20	-0.24	-0.62	-0.36	0.03	-0.29	-0.55	-0.03	-0.53	-0.63
29	CTA	1.00	0.18	-0.01	-0.01	0.42	1.00	1.00	0.56	0.67	1.00	0.86	1.00
30	CTC	0.46	-0.03	-0.13	-0.20	0.55	0.61	0.60	0.32	0.28	0.69	0.25	0.24
31	CTG	0.24	-0.40	-0.27	-0.22	-0.11	0.54	0.19	0.19	-0.30	0.86	-0.24	0.02
32	CTT	0.75	0.37	0.61	0.65	-0.47	-0.58	-0.22	-0.46	-0.36	0.42	-0.27	-0.60
33	GAA	0.35	-0.34	-0.14	0.10	0.27	0.63	0.13	0.37	0.35	0.91	0.38	0.46
34	GAC	0.53	-0.08	0.08	0.07	-0.29	-0.34	0.38	-0.16	-0.15	0.46	0.23	0.00
35	GAG	0.56	0.22	0.36	0.10	-0.19	-0.58	-0.38	-0.43	-0.28	-0.09	-0.53	-0.56
36	GAT	0.30	-0.07	-0.04	-0.08	0.13	0.23	-0.10	0.14	-0.05	0.49	-0.15	-0.06
37	GCA	0.59	-0.19	-0.22	0.34	-0.15	0.15	-0.25	0.35	-0.17	0.82	-0.07	-0.07
38	GCC	0.45	-0.08	0.23	-0.19	0.23	0.11	0.43	0.07	0.53	0.75	0.50	0.69
39	GCG	0.13	-0.35	-0.25	-0.39	0.02	-0.37	0.51	-0.03	-0.27	0.42	-0.28	-0.25
40	GCT	0.45	0.42	0.49	0.46	-0.42	-0.33	0.22	0.00	-0.15	0.79	0.15	-0.47
41	GGA	0.82	-0.03	0.24	0.15	-0.20	-0.54	-0.05	0.17	0.08	0.41	-0.16	0.09
42	GGC	0.35	-0.19	0.03	-0.02	-0.04	-0.06	0.22	0.13	0.24	0.64	0.01	0.39
43	GGG	0.54	0.39	0.25	-0.13	0.10	-0.33	0.01	0.05	-0.06	0.25	-0.41	-0.47
44	GGT	0.19	-0.43	-0.41	-0.07	0.11	0.08	-0.02	0.61	0.06	0.67	0.12	-0.12
45	GTA	0.62	0.15	0.35	0.74	0.14	-0.19	-0.14	0.29	-0.01	0.52	0.08	-0.04
46	GTC	0.57	-0.37	-0.34	-0.37	0.52	0.61	0.65	0.62	0.83	0.46	0.74	0.44
47	GTG	0.57	-0.11	-0.06	0.14	0.35	0.22	0.02	0.16	-0.02	0.46	-0.46	-0.32
48	GTT	0.35	-0.36	0.28	0.25	-0.44	-0.51	-0.37	-0.40	-0.24	0.18	0.03	-0.39
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.12	-0.43	-0.26	0.32	-0.12	-0.06	0.24	0.04	-0.25	0.37	0.29	0.02
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.30	-0.05	0.19	0.10	-0.04	0.05	-0.01	-0.03	-0.26	0.49	-0.17	0.21
53	TCA	0.76	0.06	-0.21	0.25	-0.21	-0.01	0.13	0.32	-0.20	0.12	0.16	-0.27
54	TCC	0.56	-0.26	-0.20	-0.35	0.78	-0.38	0.43	0.55	0.24	0.46	0.56	0.83
55	TCG	1.00	-0.19	0.37	-0.38	0.02	-0.31	0.28	0.28	0.04	0.32	-0.40	-0.48
56	TCT	0.17	-0.14	0.14	0.31	-0.53	-0.46	0.29	-0.32	-0.61	1.00	0.11	-0.40
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.49	-0.16	0.09	0.63	-0.22	-0.50	-0.37	-0.19	-0.23	0.32	0.16	-0.06
59	TGG	-0.23	0.05	0.00	0.04	0.46	-0.29	-0.32	0.20	0.34	1.00	0.00	-0.35

60	TGT	-0.18	-0.59	-0.10	0.40	0.69	0.39	0.36	0.70	0.61	0.17	-0.01	-0.35
61	TTA	0.90	-0.38	-0.20	0.07	0.37	0.55	0.12	0.22	0.50	0.64	0.78	0.34
62	TTC	0.59	-0.23	-0.16	0.02	-0.51	-0.58	-0.37	-0.41	-0.55	0.27	-0.36	-0.65
63	TTG	0.60	-0.28	0.06	-0.22	0.00	-0.13	-0.15	0.36	0.25	0.10	-0.20	0.23
64	TTT	0.23	0.02	0.09	-0.05	0.31	0.49	0.47	0.41	0.27	0.66	0.37	0.68
		ATA 13	ATC 14	ATG 15	ATT 16	CAA 17	CAC 18	CAG 19	CAT 20	CCA 21	CCC 22	CCG 23	CCT 24

Table C.4 continued

		25 CGA	26 CGC	27 CGG	28 CGT	29 CTA	30 CTC	31 CTG	32 CTT	33 GAA	34 GAC	35 GAG	36 GAT
1	AAA	-0.20	-0.38	-0.04	-0.20	-0.17	0.49	0.50	0.26	-0.13	-0.26	-0.06	0.25
2	AAC	-0.22	-0.55	0.04	-0.70	-0.61	0.17	-0.31	-0.46	0.13	-0.10	0.39	0.18
3	AAG	0.30	-0.03	0.07	-0.50	-0.39	-0.31	-0.66	-0.68	0.25	-0.12	0.38	-0.05
4	AAT	0.33	0.53	0.73	-0.20	0.33	0.29	0.25	0.03	-0.19	-0.27	-0.02	0.12
5	ACA	1.00	0.04	0.42	-0.02	0.36	0.37	0.17	-0.08	-0.20	0.05	0.05	0.20
6	ACC	0.19	0.43	0.75	0.13	0.34	0.56	0.45	-0.14	0.57	0.37	0.33	0.21
7	ACG	0.52	0.44	0.56	0.23	-0.36	-0.17	-0.23	-0.49	0.27	0.55	0.68	0.25
8	ACT	0.19	-0.47	1.00	-0.83	0.02	0.57	0.73	-0.02	-0.42	-0.67	-0.45	-0.43
9	AGA	-0.34	-0.09	0.60	0.19	0.78	0.70	0.35	0.72	-0.07	-0.27	0.03	0.44
10	AGC	0.49	-0.60	-0.08	-0.33	0.09	0.30	-0.04	-0.24	0.34	0.31	0.40	0.50
11	AGG	1.00	0.73	-0.31	0.69	0.39	-0.08	-0.44	0.24	0.53	0.32	0.34	-0.26
12	AGT	0.45	0.49	0.32	0.71	0.01	0.78	0.07	-0.12	-0.51	-0.54	-0.51	-0.44
13	ATA	-0.03	0.36	1.00	0.63	0.61	-0.04	0.59	0.67	0.43	0.56	0.46	0.15
14	ATC	0.07	-0.63	0.36	-0.62	0.07	0.36	0.48	-0.41	-0.10	-0.01	0.31	0.17
15	ATG	0.86	-0.13	0.41	-0.32	0.67	0.18	-0.40	-0.43	0.02	-0.12	-0.04	0.08
16	ATT	0.15	0.01	0.74	-0.39	0.22	-0.14	0.52	-0.02	-0.14	-0.20	-0.04	-0.08
17	CAA	0.34	0.54	0.90	0.38	0.59	0.94	0.91	0.86	0.04	0.21	-0.30	0.18
18	CAC	0.07	-0.54	-0.56	-0.71	0.18	0.82	0.15	-0.38	-0.11	0.23	0.26	0.08
19	CAG	0.32	-0.52	-0.58	-0.54	-0.46	-0.49	-0.44	-0.68	0.05	0.18	0.25	-0.29
20	CAT	0.77	0.36	0.44	0.15	0.40	0.65	0.50	0.46	0.14	-0.21	-0.23	0.05
21	CCA	0.45	-0.02	0.66	-0.32	1.00	0.64	0.58	0.66	0.08	0.05	-0.26	0.13
22	CCC	1.00	-0.77	1.00	0.38	1.00	0.23	0.82	0.64	0.46	0.53	0.32	0.82
23	CCG	-0.30	0.34	0.27	-0.51	-0.43	-0.39	-0.20	-0.62	0.25	0.33	0.51	0.28
24	CCT	1.00	0.33	0.33	-0.35	0.19	0.29	0.61	0.05	-0.40	-0.39	-0.33	-0.45
25	CGA	1.00	0.73	1.00	0.70	0.41	0.74	0.39	0.63	0.54	0.18	0.79	0.44
26	CGC	0.20	-0.66	-0.12	-0.76	-0.27	-0.32	-0.38	-0.08	0.43	-0.13	0.10	0.22
27	CGG	1.00	0.51	0.36	0.81	0.27	0.36	-0.33	-0.22	0.50	0.30	0.34	0.37
28	CGT	1.00	0.29	0.44	-0.64	-0.55	-0.40	-0.05	-0.60	-0.52	-0.62	-0.63	-0.19
29	CTA	1.00	1.00	1.00	1.00	-0.26	0.10	0.86	0.86	0.03	0.33	-0.16	0.02
30	CTC	0.70	-0.11	0.26	-0.23	0.70	0.74	0.57	0.50	0.53	0.11	0.67	-0.12
31	CTG	0.72	-0.11	0.48	-0.27	0.44	-0.27	-0.22	-0.43	0.49	0.45	0.22	0.48
32	CTT	-0.22	-0.72	0.13	-0.60	-0.11	-0.30	0.01	-0.50	-0.53	-0.40	-0.43	-0.54
33	GAA	-0.02	-0.03	0.22	-0.03	0.24	0.33	0.33	0.50	-0.11	-0.27	-0.20	0.08
34	GAC	-0.42	-0.74	-0.37	-0.67	0.23	0.26	0.31	0.02	0.05	0.29	0.24	0.17

35	GAG	0.22	-0.53	-0.21	-0.61	-0.48	-0.46	-0.50	-0.70	0.30	0.22	0.43	0.15
36	GAT	0.59	0.43	0.65	0.57	0.20	0.10	0.23	-0.10	-0.11	-0.31	0.06	0.07
37	GCA	0.87	-0.38	0.61	-0.19	0.26	0.19	0.36	-0.06	0.12	-0.07	0.20	0.20
38	GCC	0.83	0.11	0.47	-0.55	0.67	0.63	0.45	0.59	0.39	0.63	0.43	0.31
39	GCG	0.32	-0.17	0.67	-0.40	-0.04	-0.25	-0.37	-0.59	0.14	0.12	0.19	0.26
40	GCT	0.41	0.32	0.82	-0.54	-0.35	0.38	0.54	-0.16	-0.43	-0.56	-0.31	-0.27
41	GGA	0.26	-0.51	0.42	-0.48	0.61	0.43	0.41	-0.04	-0.11	-0.27	0.15	-0.03
42	GGC	0.33	-0.30	0.05	-0.57	-0.16	0.42	0.34	-0.12	0.34	0.12	0.20	0.35
43	GGG	0.39	0.15	0.26	0.24	0.50	0.23	-0.16	-0.45	0.40	0.33	0.66	0.36
44	GGT	0.82	0.58	0.89	-0.25	-0.35	-0.32	0.63	-0.65	-0.49	-0.59	-0.44	-0.05
45	GTA	0.58	-0.32	0.36	-0.19	-0.43	0.14	0.23	-0.17	-0.11	-0.15	-0.34	0.06
46	GTC	0.68	-0.46	0.81	-0.46	0.56	0.35	0.66	0.54	0.56	0.51	0.60	0.31
47	GTG	0.37	0.04	0.61	-0.09	0.41	-0.43	-0.51	-0.47	0.47	0.28	0.38	0.35
48	GTT	0.28	-0.40	0.47	-0.54	0.06	-0.20	0.58	-0.27	-0.47	-0.43	-0.30	-0.35
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.17	-0.63	-0.25	-0.70	-0.33	0.20	0.19	-0.23	0.16	0.42	0.29	-0.23
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.35	0.22	0.68	0.10	0.20	0.07	0.50	0.30	-0.15	-0.17	0.04	0.14
53	TCA	1.00	0.20	0.85	-0.04	0.34	-0.14	0.18	0.00	0.12	0.14	-0.02	0.21
54	TCC	1.00	-0.60	0.18	-0.40	-0.17	0.65	0.58	0.09	0.69	0.56	0.34	0.26
55	TCG	0.43	0.74	0.65	-0.17	-0.35	-0.11	-0.37	-0.50	0.60	0.89	0.49	0.19
56	TCT	0.72	-0.15	1.00	-0.39	-0.43	0.45	0.43	-0.29	-0.40	-0.49	-0.31	-0.34
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	-0.15	-0.63	-0.30	-0.60	0.21	0.30	-0.32	-0.13	0.61	0.30	-0.19	0.52
59	TGG	0.69	-0.01	0.24	0.17	0.62	-0.41	-0.30	-0.16	0.05	-0.14	-0.09	0.09
60	TGT	1.00	1.00	1.00	1.00	0.04	0.15	0.60	-0.28	-0.20	-0.16	-0.43	-0.42
61	TTA	0.65	0.67	0.68	0.34	0.65	0.47	0.64	0.50	0.07	0.35	0.20	0.40
62	TTC	-0.22	-0.60	-0.29	-0.77	-0.30	0.11	-0.27	-0.44	0.24	-0.15	0.64	0.36
63	TTG	1.00	-0.04	0.04	-0.24	-0.24	-0.31	-0.33	-0.45	0.42	0.30	0.37	0.34
64	TTT	0.64	0.66	0.85	0.61	0.46	0.40	0.58	0.41	-0.27	-0.27	0.23	0.09
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
		25	26	27	28	29	30	31	32	33	34	35	36

Table C.4 continued

		37	38	39	40	41	42	43	44	45	46	47	48
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
1	AAA	-0.24	-0.06	-0.31	0.08	0.09	-0.31	-0.15	-0.16	-0.44	0.20	-0.08	0.24
2	AAC	-0.05	0.57	-0.13	-0.25	-0.42	-0.39	-0.10	-0.50	-0.35	0.11	0.04	-0.11
3	AAG	0.38	0.77	0.32	0.46	0.51	0.34	0.60	0.36	0.11	0.45	0.06	-0.08
4	AAT	-0.08	0.20	-0.22	0.30	0.47	0.55	0.51	0.47	-0.02	0.15	-0.11	0.27
5	ACA	0.25	0.34	0.18	-0.32	0.00	0.00	0.02	-0.36	0.18	0.10	0.28	0.11
6	ACC	0.49	0.62	0.34	-0.09	-0.09	0.04	0.04	-0.41	0.24	0.11	0.55	-0.18
7	ACG	-0.15	0.77	0.39	-0.21	0.38	0.57	0.89	0.29	0.15	0.06	0.55	-0.23
8	ACT	-0.56	-0.31	0.10	-0.59	-0.26	-0.24	0.42	-0.63	-0.56	-0.21	-0.13	-0.58
9	AGA	0.13	0.58	-0.43	0.47	0.11	0.14	0.15	0.08	0.54	0.71	0.30	0.52

10	AGC	0.39	0.47	0.49	0.51	-0.52	-0.35	0.16	0.01	-0.13	0.61	0.47	0.47
11	AGG	0.58	0.43	0.55	0.68	-0.17	0.63	0.48	0.54	0.16	0.52	0.36	0.85
12	AGT	-0.29	-0.13	-0.34	-0.34	0.68	0.78	0.85	0.60	-0.45	-0.05	-0.33	-0.42
13	ATA	0.73	0.46	0.50	0.92	0.81	0.72	0.29	0.79	1.00	0.86	0.78	0.74
14	ATC	-0.18	-0.03	0.21	-0.35	-0.42	-0.51	-0.39	-0.67	-0.44	-0.19	0.12	-0.27
15	ATG	0.03	0.65	-0.05	-0.34	0.23	-0.03	0.10	-0.30	0.09	0.08	0.05	-0.15
16	ATT	-0.15	-0.12	0.16	-0.07	0.70	0.58	0.77	0.33	0.24	-0.07	0.12	-0.16
17	CAA	0.07	0.23	0.01	-0.03	0.13	-0.37	-0.18	-0.50	-0.42	-0.06	-0.14	0.16
18	CAC	0.07	-0.03	0.19	0.04	-0.19	-0.53	0.05	-0.58	-0.29	-0.06	-0.07	-0.42
19	CAG	-0.16	0.43	-0.04	-0.27	0.44	0.52	0.04	0.37	0.25	0.44	-0.06	0.04
20	CAT	0.13	-0.11	-0.16	0.01	0.31	0.26	0.61	0.31	-0.02	0.15	-0.09	0.52
21	CCA	0.09	0.38	0.43	-0.23	0.07	0.21	0.23	-0.56	0.18	0.38	0.31	-0.17
22	CCC	0.03	0.78	-0.03	-0.22	0.15	-0.35	0.73	-0.17	1.00	0.41	0.56	0.47
23	CCG	0.05	0.29	0.34	-0.24	0.05	0.21	0.50	-0.15	0.17	0.40	0.49	-0.19
24	CCT	0.00	-0.13	0.20	-0.53	-0.15	0.28	0.16	-0.50	-0.47	-0.41	0.09	-0.48
25	CGA	0.86	0.63	0.86	0.69	0.48	-0.07	0.75	0.78	0.59	0.85	0.38	0.44
26	CGC	-0.17	0.40	-0.12	-0.07	-0.68	-0.44	0.18	-0.69	-0.38	-0.01	-0.18	-0.31
27	CGG	0.33	0.55	0.20	-0.12	0.92	0.56	0.69	0.86	0.62	0.62	-0.12	0.40
28	CGT	-0.31	-0.21	-0.68	-0.47	0.30	0.62	0.46	-0.30	-0.66	-0.51	-0.55	-0.49
29	CTA	0.48	0.65	-0.19	0.12	0.48	-0.36	-0.21	-0.65	-0.25	0.16	0.15	-0.46
30	CTC	0.14	0.23	0.39	0.02	-0.38	-0.67	0.22	-0.68	-0.37	-0.33	0.55	-0.55
31	CTG	0.28	0.64	0.26	0.08	0.65	0.53	0.74	0.54	0.72	0.76	0.68	0.65
32	CTT	-0.41	-0.45	-0.22	-0.50	-0.21	-0.46	0.27	-0.50	-0.42	-0.52	-0.34	-0.52
33	GAA	-0.27	0.18	-0.33	-0.07	0.07	-0.39	0.18	-0.25	-0.24	0.16	-0.25	0.05
34	GAC	0.26	0.34	0.16	-0.22	-0.50	-0.57	0.00	-0.61	0.28	0.45	0.30	-0.16
35	GAG	0.45	0.78	0.36	0.27	0.42	0.41	0.71	0.49	0.04	0.37	0.46	-0.08
36	GAT	0.07	-0.02	-0.19	-0.08	0.55	0.64	0.79	0.39	-0.40	0.22	-0.12	-0.01
37	GCA	-0.09	0.21	0.15	-0.18	0.18	-0.04	-0.05	-0.15	0.25	0.20	0.45	0.16
38	GCC	0.31	0.40	0.55	0.13	-0.41	-0.27	0.35	-0.54	0.45	0.55	0.58	0.13
39	GCG	-0.04	0.58	0.23	-0.19	0.09	0.47	0.27	-0.17	0.14	0.40	0.19	-0.19
40	GCT	-0.21	0.10	-0.24	-0.53	0.14	0.34	0.68	-0.25	-0.54	-0.38	0.00	-0.58
41	GGA	0.13	0.49	-0.21	0.15	0.50	0.35	0.30	0.64	0.16	0.73	0.66	0.62
42	GGC	0.10	0.07	0.18	-0.07	-0.63	-0.46	0.15	-0.57	-0.17	0.22	0.19	-0.36
43	GGG	0.37	0.70	0.38	0.38	0.37	0.66	0.86	0.68	0.19	0.58	0.62	-0.02
44	GGT	-0.32	0.14	-0.56	-0.51	0.61	0.82	0.75	0.39	-0.59	-0.53	-0.37	-0.57
45	GTA	0.14	0.11	-0.38	-0.19	0.28	0.05	0.07	-0.30	0.38	0.11	0.66	0.46
46	GTC	0.26	0.44	0.50	0.03	-0.46	-0.57	-0.05	-0.64	-0.22	0.55	0.16	-0.34
47	GTG	0.35	0.60	-0.03	0.03	0.67	0.61	0.71	0.64	0.79	0.65	0.55	0.62
48	GTT	-0.21	-0.34	-0.28	-0.26	0.37	0.42	0.73	-0.18	-0.51	-0.40	-0.36	-0.53
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.19	0.05	0.13	-0.32	-0.34	-0.55	-0.25	-0.60	0.12	0.20	0.00	0.03
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.06	0.19	-0.03	0.10	0.47	0.44	0.59	0.51	-0.15	-0.06	-0.15	0.19
53	TCA	0.25	-0.12	0.11	-0.34	0.48	-0.22	0.26	-0.38	-0.05	0.16	0.39	0.15

54	TCC	0.01	0.38	0.68	-0.42	-0.02	-0.45	0.51	-0.42	0.66	0.57	0.91	-0.14
55	TCG	0.42	0.74	0.49	0.23	0.11	0.70	0.53	0.03	0.14	0.78	0.46	-0.08
56	TCT	-0.05	0.03	-0.18	-0.65	0.40	0.45	0.54	-0.45	-0.56	-0.48	0.14	-0.56
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.47	0.28	-0.35	0.24	-0.50	-0.45	-0.03	-0.15	-0.28	0.47	0.47	0.52
59	TGG	-0.18	0.13	-0.10	0.26	0.05	-0.34	0.50	0.41	-0.18	0.54	-0.27	0.00
60	TGT	0.04	-0.23	-0.16	-0.09	1.00	0.74	0.64	0.52	-0.29	-0.48	-0.33	0.22
61	TTA	0.01	0.55	0.19	0.51	0.30	0.26	0.29	-0.07	-0.08	0.18	0.61	0.10
62	TTC	-0.05	0.01	0.16	0.04	-0.38	-0.49	-0.39	-0.65	-0.17	0.04	0.57	-0.36
63	TTG	-0.36	0.49	0.29	-0.05	0.62	0.53	0.75	0.71	0.27	0.62	0.45	0.25
64	TTT	0.11	0.13	-0.22	-0.01	0.44	0.43	0.65	0.35	0.00	-0.12	0.19	0.01
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
		37	38	39	40	41	42	43	44	45	46	47	48

Table C.4 continued

		49	50	51	52	53	54	55	56	57	58	59	60
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
1	AAA	0.00	-0.21	0.00	0.10	-0.35	0.10	-0.04	0.11	0.00	-0.23	-0.06	-0.19
2	AAC	0.00	-0.46	0.00	-0.15	-0.28	-0.12	0.68	-0.45	0.00	-0.52	-0.39	-0.41
3	AAG	0.00	-0.12	0.00	0.17	0.23	0.50	0.62	0.18	0.00	0.66	0.15	0.59
4	AAT	0.00	0.38	0.00	0.28	0.41	0.51	0.50	0.57	0.00	0.73	0.50	0.67
5	ACA	0.00	-0.04	0.00	0.19	-0.32	-0.18	0.18	0.01	0.00	-0.37	0.05	0.05
6	ACC	0.00	0.28	0.00	0.29	0.39	0.63	0.77	0.54	0.00	-0.25	0.40	1.00
7	ACG	0.00	-0.33	0.00	0.00	0.34	0.02	0.31	0.39	0.00	0.01	0.28	1.00
8	ACT	0.00	-0.58	0.00	0.35	-0.38	-0.32	0.07	-0.54	0.00	0.00	-0.50	-0.38
9	AGA	0.00	0.54	0.00	0.69	0.82	0.84	-0.19	0.70	0.00	0.43	-0.10	-0.03
10	AGC	0.00	-0.39	0.00	-0.17	-0.05	0.49	0.52	-0.03	0.00	0.27	-0.32	-0.32
11	AGG	0.00	0.37	0.00	1.00	1.00	1.00	-0.11	0.72	0.00	1.00	0.62	1.00
12	AGT	0.00	0.84	0.00	0.39	-0.18	1.00	-0.53	-0.28	0.00	1.00	0.71	0.35
13	ATA	0.00	0.80	0.00	-0.05	0.57	0.03	0.26	0.27	0.00	0.39	0.55	1.00
14	ATC	0.00	-0.05	0.00	0.33	0.28	0.22	0.25	0.02	0.00	0.59	0.40	-0.11
15	ATG	0.00	-0.21	0.00	0.15	0.03	-0.35	0.32	0.13	0.00	-0.18	0.00	0.26
16	ATT	0.00	-0.47	0.00	0.17	-0.10	-0.23	0.27	-0.44	0.00	-0.34	-0.30	-0.16
17	CAA	0.00	-0.36	0.00	-0.24	-0.09	0.00	-0.46	-0.41	0.00	-0.26	-0.29	-0.39
18	CAC	0.00	-0.01	0.00	-0.20	0.07	0.04	1.00	0.10	0.00	0.45	-0.12	-0.01
19	CAG	0.00	0.29	0.00	0.48	0.49	0.53	0.29	-0.26	0.00	0.54	0.42	0.44
20	CAT	0.00	0.00	0.00	0.12	-0.27	0.17	0.70	-0.10	0.00	-0.18	0.07	0.01
21	CCA	0.00	-0.56	0.00	-0.04	-0.14	0.53	0.70	-0.48	0.00	-0.52	-0.18	-0.40
22	CCC	0.00	0.66	0.00	1.00	0.18	0.50	-0.21	0.69	0.00	1.00	0.57	1.00
23	CCG	0.00	0.09	0.00	0.48	-0.01	0.59	0.35	-0.48	0.00	1.00	0.29	0.64
24	CCT	0.00	-0.53	0.00	-0.12	0.06	0.53	0.41	-0.43	0.00	-0.45	-0.32	-0.55
25	CGA	0.00	0.39	0.00	0.01	0.77	0.15	1.00	0.73	0.00	-0.33	0.27	-0.63
26	CGC	0.00	-0.42	0.00	-0.27	-0.30	1.00	1.00	-0.46	0.00	-0.68	-0.61	-0.53
27	CGG	0.00	0.44	0.00	0.50	0.57	0.48	0.67	0.84	0.00	1.00	0.78	0.44
28	CGT	0.00	-0.59	0.00	-0.53	-0.67	0.09	-0.51	-0.80	0.00	1.00	0.80	1.00

29	CTA	0.00	-0.48	0.00	-0.18	0.26	0.66	-0.41	-0.32	0.00	-0.41	-0.60	-0.51
30	CTC	0.00	0.14	0.00	0.31	0.02	1.00	0.81	0.44	0.00	0.25	0.18	1.00
31	CTG	0.00	0.33	0.00	-0.10	-0.18	0.37	0.65	-0.12	0.00	0.30	0.48	0.79
32	CTT	0.00	-0.59	0.00	-0.16	-0.21	-0.50	-0.19	-0.66	0.00	-0.52	0.23	0.36
33	GAA	0.00	-0.34	0.00	0.32	-0.16	0.21	-0.14	0.14	0.00	0.40	0.13	-0.25
34	GAC	0.00	-0.20	0.00	0.18	0.31	0.31	0.27	0.14	0.00	-0.51	-0.38	0.17
35	GAG	0.00	0.00	0.00	-0.09	0.22	0.47	0.33	0.45	0.00	-0.41	-0.22	0.49
36	GAT	0.00	-0.28	0.00	0.19	-0.06	-0.19	0.59	0.23	0.00	0.38	0.35	0.16
37	GCA	0.00	-0.09	0.00	0.14	0.04	-0.27	0.08	0.09	0.00	-0.41	-0.18	0.21
38	GCC	0.00	0.53	0.00	0.28	0.57	0.71	0.25	0.69	0.00	-0.05	0.28	0.36
39	GCG	0.00	-0.01	0.00	0.34	0.28	0.54	0.61	0.18	0.00	0.31	0.28	0.50
40	GCT	0.00	-0.50	0.00	-0.29	-0.26	-0.53	-0.36	-0.64	0.00	0.41	-0.23	-0.49
41	GGA	0.00	-0.10	0.00	0.12	0.04	0.72	0.38	0.21	0.00	0.48	0.34	0.62
42	GGC	0.00	-0.16	0.00	-0.10	0.47	0.17	0.59	0.08	0.00	-0.42	-0.47	-0.59
43	GGG	0.00	0.26	0.00	0.35	0.63	0.87	0.83	0.49	0.00	0.40	0.58	0.27
44	GGT	0.00	0.34	0.00	-0.24	-0.65	0.17	-0.17	-0.73	0.00	1.00	0.53	0.36
45	GTA	0.00	-0.64	0.00	-0.17	-0.38	-0.18	-0.07	-0.55	0.00	-0.32	-0.11	-0.37
46	GTC	0.00	0.59	0.00	0.53	0.61	0.79	0.28	0.60	0.00	-0.19	0.23	0.10
47	GTG	0.00	-0.08	0.00	0.41	0.18	0.50	0.46	0.29	0.00	0.51	0.15	0.70
48	GTT	0.00	-0.33	0.00	-0.03	-0.12	-0.23	0.26	-0.53	0.00	0.21	-0.21	-0.33
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.00	-0.13	0.00	0.21	0.41	-0.07	0.09	-0.44	0.00	-0.17	-0.09	-0.49
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.00	0.04	0.00	-0.08	-0.06	-0.13	-0.18	0.16	0.00	0.57	0.05	-0.04
53	TCA	0.00	-0.31	0.00	0.57	0.32	0.26	0.38	-0.19	0.00	-0.29	-0.03	0.43
54	TCC	0.00	-0.37	0.00	0.29	0.26	0.33	-0.12	0.02	0.00	0.14	1.00	0.48
55	TCG	0.00	0.50	0.00	0.64	0.69	0.72	0.64	0.29	0.00	0.45	0.40	1.00
56	TCT	0.00	-0.42	0.00	-0.19	-0.38	-0.35	0.47	-0.54	0.00	-0.38	-0.38	-0.49
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.00	0.13	0.00	-0.20	0.11	-0.18	-0.03	-0.01	0.00	-0.55	1.00	-0.26
59	TGG	0.00	0.20	0.00	-0.09	0.89	0.81	0.26	-0.31	0.00	-0.34	0.00	0.63
60	TGT	0.00	0.65	0.00	-0.12	-0.38	0.02	-0.20	0.08	0.00	1.00	-0.55	1.00
61	TTA	0.00	0.34	0.00	0.33	-0.29	-0.27	0.23	-0.31	0.00	-0.54	0.05	1.00
62	TTC	0.00	-0.57	0.00	-0.13	-0.46	0.07	-0.24	-0.57	0.00	-0.18	-0.52	-0.33
63	TTG	0.00	0.16	0.00	0.60	0.34	0.78	0.58	0.11	0.00	-0.27	-0.45	0.33
64	TTT	0.00	0.25	0.00	0.27	0.25	0.35	0.59	0.11	0.00	0.23	0.51	0.07
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
		49	50	51	52	53	54	55	56	57	58	59	60

Table C.4 continued

		61	62	63	64
		TTA	TTC	TTG	TTT
1	AAA	0.32	-0.44	0.42	0.38
2	AAC	0.12	-0.58	0.11	-0.10
3	AAG	0.70	-0.02	0.66	-0.03

4	AAT	0.32	-0.14	0.52	0.66
5	ACA	0.01	-0.33	-0.32	0.04
6	ACC	0.07	-0.04	0.36	0.34
7	ACG	0.30	-0.34	0.43	-0.06
8	ACT	-0.34	0.30	0.04	0.56
9	AGA	0.43	0.31	0.27	0.68
10	AGC	0.42	-0.29	0.33	-0.13
11	AGG	0.53	0.53	1.00	0.67
12	AGT	-0.12	0.36	0.19	0.39
13	ATA	-0.10	-0.41	-0.35	0.42
14	ATC	0.05	-0.36	0.27	0.36
15	ATG	0.80	-0.41	0.86	0.33
16	ATT	-0.41	-0.49	-0.30	0.35
17	CAA	0.16	-0.33	0.10	-0.05
18	CAC	-0.40	-0.43	-0.25	0.18
19	CAG	0.67	0.06	0.63	0.27
20	CAT	-0.37	-0.18	-0.43	0.19
21	CCA	-0.04	-0.60	-0.42	-0.30
22	CCC	0.78	1.00	0.44	0.61
23	CCG	0.32	-0.08	0.71	0.01
24	CCT	-0.09	0.22	0.04	0.35
25	CGA	0.55	-0.37	1.00	-0.15
26	CGC	-0.05	-0.48	-0.30	-0.09
27	CGG	0.63	0.86	0.88	0.15
28	CGT	-0.48	-0.71	-0.51	-0.12
29	CTA	-0.47	-0.69	-0.49	-0.15
30	CTC	0.54	-0.18	-0.14	0.53
31	CTG	0.39	-0.31	0.50	-0.04
32	CTT	-0.22	0.02	-0.19	0.66
33	GAA	0.37	-0.33	0.26	0.16
34	GAC	0.08	-0.38	0.00	0.34
35	GAG	0.46	0.14	0.67	0.09
36	GAT	-0.09	-0.26	-0.41	0.14
37	GCA	-0.09	-0.30	0.04	0.13
38	GCC	0.53	0.15	-0.07	0.20
39	GCG	0.10	-0.05	0.70	-0.16
40	GCT	-0.40	-0.15	-0.12	0.16
41	GGA	0.17	-0.23	-0.01	0.35
42	GGC	0.18	-0.46	0.11	0.25
43	GGG	0.87	0.53	0.59	0.52
44	GGT	-0.37	-0.50	-0.52	-0.23
45	GTA	-0.37	-0.69	-0.34	-0.14
46	GTC	0.74	0.24	0.43	0.29
47	GTG	0.36	0.30	0.62	0.01

48	GTT	-0.14	0.05	-0.15	0.30
49	TAA	0.00	0.00	0.00	0.00
50	TAC	0.08	-0.28	0.03	-0.11
51	TAG	0.00	0.00	0.00	0.00
52	TAT	-0.22	-0.25	-0.50	0.32
53	TCA	-0.43	0.07	0.21	-0.12
54	TCC	0.39	0.09	-0.30	0.51
55	TCG	0.35	0.17	0.50	-0.20
56	TCT	-0.29	-0.49	0.02	0.39
57	TGA	0.00	0.00	0.00	0.00
58	TGC	-0.17	-0.47	0.49	0.11
59	TGG	0.51	-0.18	0.63	0.11
60	TGT	0.51	0.23	-0.36	0.28
61	TTA	0.34	-0.22	0.49	0.16
62	TTC	-0.41	-0.67	-0.23	-0.18
63	TTG	0.33	-0.49	0.71	-0.13
64	TTT	-0.29	-0.05	-0.05	0.58
		TTA	TTC	TTG	TTT
		61	62	63	64

Table C.5: CPW matrix *Escherichia coli* K12 full genome (left codon indicated in column 2, right codon indicated in row 2). Host cell: *E. coli*; Sequence data: full *E. coli* genome.

		1	2	3	4	5	6	7	8	9	10	11	12
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
1	AAA	0.19	0.01	-0.04	-0.10	-0.31	-0.06	-0.24	0.18	-0.03	0.08	0.20	0.07
2	AAC	0.13	0.09	0.01	0.25	0.38	-0.08	0.34	0.18	-0.32	-0.41	-0.33	-0.36
3	AAG	-0.35	0.14	-0.17	0.17	0.15	0.53	0.47	0.58	-0.17	0.14	-0.12	-0.13
4	AAT	-0.13	-0.10	-0.05	-0.24	0.04	-0.23	-0.04	-0.14	0.27	0.16	0.47	0.15
5	ACA	-0.19	0.32	-0.21	-0.05	-0.52	0.20	-0.27	-0.07	-0.37	0.66	-0.54	0.43
6	ACC	-0.21	-0.29	0.08	-0.19	0.01	-0.25	-0.17	-0.26	-0.10	-0.47	-0.06	-0.39
7	ACG	0.41	0.74	0.28	0.55	0.10	0.52	0.23	0.40	0.68	0.91	0.50	0.88
8	ACT	0.01	-0.36	0.20	0.00	0.37	0.11	0.24	0.28	0.83	0.87	0.93	0.85
9	AGA	-0.41	0.01	-0.53	-0.59	-0.74	-0.22	-0.50	0.02	-0.85	0.41	-0.72	-0.59
10	AGC	-0.21	-0.05	-0.22	-0.21	0.24	0.23	0.28	0.33	0.07	-0.10	-0.29	-0.27
11	AGG	0.11	0.43	-0.46	-0.05	-0.49	0.70	0.29	0.11	-0.67	0.51	-0.04	-0.31
12	AGT	-0.28	-0.19	-0.42	-0.41	0.06	0.16	0.03	0.20	0.41	0.05	0.71	0.02
13	ATA	-0.39	0.15	-0.34	-0.35	-0.45	-0.16	-0.23	-0.24	-0.74	-0.13	-0.70	0.02
14	ATC	-0.03	-0.25	-0.12	0.06	0.50	-0.34	0.44	-0.32	0.07	-0.36	-0.46	-0.34
15	ATG	0.11	0.01	-0.27	-0.01	0.22	-0.04	-0.12	0.18	0.62	-0.03	0.28	-0.06
16	ATT	0.16	0.15	0.02	0.16	0.49	-0.02	0.38	-0.05	0.47	0.43	0.86	0.58
17	CAA	-0.34	-0.34	-0.31	-0.35	-0.39	-0.27	-0.37	-0.25	0.08	-0.38	0.04	-0.45
18	CAC	0.17	-0.10	0.13	0.12	0.36	-0.19	0.38	-0.02	0.44	-0.36	0.10	-0.41
19	CAG	0.28	0.22	0.22	0.34	0.04	0.35	0.13	0.25	0.60	0.30	0.52	0.34
20	CAT	-0.12	-0.13	-0.05	0.19	0.20	-0.13	0.10	-0.10	0.16	0.28	0.90	0.47
21	CCA	-0.19	-0.16	0.11	-0.18	-0.56	-0.28	-0.44	-0.12	-0.35	0.25	0.31	0.39
22	CCC	0.13	-0.21	0.47	-0.38	-0.23	-0.04	0.11	-0.01	-0.59	-0.51	-0.52	-0.28
23	CCG	-0.11	0.10	-0.06	0.22	-0.16	0.31	-0.08	0.10	0.72	0.56	0.75	0.59
24	CCT	0.39	-0.04	0.40	0.18	0.19	0.40	0.41	0.29	0.93	0.87	0.88	0.91
25	CGA	-0.08	0.50	0.12	-0.19	-0.42	-0.10	0.03	-0.17	-0.33	0.25	-0.42	0.35
26	CGC	0.18	0.21	-0.07	-0.04	-0.08	-0.01	0.14	0.05	-0.10	-0.33	-0.28	-0.42
27	CGG	0.55	0.79	0.18	0.71	-0.41	0.60	0.20	0.25	0.05	0.79	0.02	0.43
28	CGT	-0.07	-0.20	-0.30	-0.24	0.25	-0.11	0.34	-0.33	0.67	0.06	0.63	0.20
29	CTA	-0.41	-0.01	-0.21	-0.18	-0.38	-0.10	-0.11	0.05	-0.51	-0.27	-0.54	-0.38
30	CTC	0.19	-0.50	-0.11	-0.55	0.25	-0.33	0.32	-0.35	-0.24	-0.06	-0.55	-0.24
31	CTG	-0.09	0.29	0.06	0.14	0.00	0.09	-0.10	0.09	0.75	0.60	0.59	0.56
32	CTT	0.34	-0.26	-0.16	-0.43	0.43	0.22	0.55	0.09	0.39	-0.16	0.65	0.43
33	GAA	0.00	-0.14	0.18	-0.03	-0.21	-0.21	-0.24	0.11	0.09	-0.13	-0.15	-0.17
34	GAC	0.01	-0.03	0.01	0.25	0.21	-0.19	0.12	0.00	-0.68	-0.58	-0.71	-0.52
35	GAG	-0.04	0.25	-0.21	0.20	0.05	0.87	0.03	0.56	0.06	0.07	0.01	-0.05

36	GAT	-0.02	-0.20	0.05	0.18	0.25	-0.13	0.16	0.10	0.53	0.23	0.77	0.51
37	GCA	-0.21	0.18	0.10	0.14	-0.44	-0.02	-0.44	0.01	-0.36	0.34	-0.52	0.27
38	GCC	0.12	-0.23	0.62	-0.26	-0.01	-0.11	-0.11	-0.12	-0.74	-0.65	-0.60	-0.65
39	GCG	-0.09	0.44	-0.27	0.24	-0.19	0.34	-0.07	0.29	0.40	0.67	0.38	0.65
40	GCT	0.14	-0.41	0.37	-0.08	0.27	0.30	0.32	0.22	0.85	0.85	0.91	0.91
41	GGA	-0.15	0.36	0.10	-0.31	-0.62	0.05	-0.54	-0.24	-0.72	-0.01	-0.52	-0.40
42	GGC	0.10	-0.01	0.02	-0.08	-0.01	-0.04	0.04	-0.01	-0.36	-0.31	-0.50	-0.34
43	GGG	0.24	0.72	0.33	0.15	-0.24	0.72	-0.05	0.05	0.07	0.63	0.46	0.16
44	GGT	-0.16	-0.15	-0.11	-0.10	-0.19	0.58	-0.27	-0.25	0.50	0.05	0.76	0.32
45	GTA	-0.27	0.15	0.21	-0.05	-0.22	0.22	-0.33	-0.05	-0.54	0.22	-0.29	0.09
46	GTC	0.29	0.03	0.67	-0.25	-0.03	-0.37	-0.10	-0.47	-0.59	-0.59	-0.68	-0.58
47	GTG	-0.16	0.41	-0.30	0.05	0.10	0.26	-0.16	0.04	0.29	0.43	0.33	0.20
48	GTT	0.25	-0.31	-0.02	-0.08	0.44	0.23	0.44	0.11	0.58	0.46	0.84	0.58
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.11	-0.40	0.02	0.39	0.29	-0.43	0.41	-0.02	0.02	-0.48	0.11	-0.24
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.05	-0.16	0.12	0.55	0.52	-0.20	0.38	0.49	0.65	0.31	0.72	0.67
53	TCA	-0.08	0.36	0.11	0.21	-0.56	-0.08	-0.43	-0.04	-0.23	0.62	-0.47	0.44
54	TCC	0.50	-0.12	0.56	0.25	-0.17	-0.38	-0.16	-0.39	-0.33	-0.58	-0.47	-0.53
55	TCG	0.05	0.53	0.06	0.38	-0.16	0.28	-0.14	0.39	0.67	0.75	0.65	0.70
56	TCT	0.45	-0.24	0.46	0.31	0.18	-0.07	0.28	-0.07	0.83	0.97	0.70	0.92
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.05	0.36	0.49	0.08	0.11	0.02	0.46	0.27	-0.15	0.22	-0.26	0.32
59	TGG	0.06	0.02	-0.16	-0.03	-0.21	0.27	-0.28	0.13	0.57	0.15	0.97	-0.09
60	TGT	-0.14	-0.11	-0.22	-0.33	-0.16	-0.13	-0.24	-0.29	0.51	0.30	0.64	0.23
61	TTA	-0.07	0.42	0.10	-0.15	-0.11	-0.33	-0.40	-0.15	-0.51	-0.47	-0.46	-0.59
62	TTC	0.01	0.03	0.12	0.22	0.49	-0.15	0.44	-0.23	-0.24	-0.25	-0.63	-0.11
63	TTG	0.20	0.55	0.14	0.08	0.30	0.38	0.12	0.31	0.34	0.23	0.23	-0.20
64	TTT	-0.04	-0.10	0.04	-0.05	0.49	-0.25	0.35	-0.22	0.44	0.31	0.83	0.38
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
		1	2	3	4	5	6	7	8	9	10	11	12

Table C.5 continued

		13	14	15	16	17	18	19	20	21	22	23	24
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
1	AAA	-0.42	-0.08	0.05	0.20	0.14	0.12	0.20	0.12	0.16	0.04	0.07	0.10
2	AAC	0.54	0.11	0.22	0.31	0.48	-0.11	-0.02	0.09	0.10	0.30	-0.18	0.29
3	AAG	-0.33	-0.03	-0.14	-0.02	-0.42	-0.26	-0.34	-0.30	-0.41	-0.29	-0.16	-0.11

4	AAT	0.04	-0.26	-0.21	-0.22	-0.08	-0.03	-0.19	0.03	0.01	-0.08	0.05	-0.03
5	ACA	-0.45	0.39	-0.09	0.31	-0.39	0.21	0.12	0.06	-0.49	-0.25	-0.20	-0.38
6	ACC	0.38	-0.29	-0.09	-0.19	0.46	-0.04	0.21	0.24	0.52	0.61	0.68	0.58
7	ACG	-0.01	0.61	-0.04	0.33	-0.45	-0.03	0.04	-0.07	-0.67	-0.29	-0.47	-0.39
8	ACT	0.34	-0.25	0.39	-0.13	0.03	-0.42	-0.29	-0.03	0.52	0.08	0.35	0.34
9	AGA	-0.74	0.38	-0.11	-0.01	-0.12	0.56	0.42	0.02	0.03	-0.33	0.21	-0.14
10	AGC	0.41	0.25	0.31	0.12	0.47	-0.20	-0.40	-0.21	0.35	0.51	0.07	0.53
11	AGG	-0.72	0.24	-0.14	0.28	-0.47	0.40	-0.13	-0.03	-0.51	-0.42	-0.30	-0.19
12	AGT	0.13	0.04	-0.01	-0.13	0.49	0.19	-0.20	0.04	0.48	0.45	0.36	0.42
13	ATA	-0.64	0.32	-0.13	0.30	-0.23	0.18	0.14	0.23	0.07	-0.44	0.23	-0.17
14	ATC	0.68	-0.20	-0.04	0.19	0.66	-0.08	0.12	0.25	0.30	-0.24	0.01	-0.06
15	ATG	0.06	-0.08	0.00	0.07	0.09	-0.12	-0.04	0.10	-0.14	0.06	0.05	-0.02
16	ATT	0.45	-0.14	0.05	-0.02	0.30	-0.10	-0.35	-0.11	0.14	-0.28	0.12	-0.26
17	CAA	-0.48	-0.29	-0.06	-0.21	-0.31	0.07	0.23	-0.12	0.02	-0.23	-0.05	-0.26
18	CAC	0.55	0.15	0.40	0.16	0.68	0.00	0.11	0.09	0.39	0.44	0.22	0.23
19	CAG	-0.08	0.24	0.03	0.20	-0.28	0.15	0.21	-0.07	-0.19	0.35	0.10	0.04
20	CAT	0.26	-0.11	-0.23	-0.17	-0.04	-0.02	-0.25	-0.05	-0.07	-0.21	-0.16	-0.30
21	CCA	-0.35	0.03	-0.22	0.13	-0.45	-0.05	0.04	0.06	-0.37	0.18	-0.15	-0.11
22	CCC	-0.51	-0.35	0.51	-0.28	0.75	0.44	0.59	0.21	0.65	0.16	0.74	0.11
23	CCG	-0.17	0.28	-0.17	-0.08	-0.35	-0.09	-0.10	-0.14	-0.47	0.12	-0.02	0.09
24	CCT	-0.01	0.03	0.63	0.25	0.67	0.41	0.66	0.05	0.18	-0.20	0.53	0.04
25	CGA	-0.57	0.13	-0.47	-0.25	-0.33	0.35	0.29	-0.12	-0.37	-0.24	-0.06	-0.51
26	CGC	0.40	0.14	0.31	-0.03	0.68	0.01	-0.21	-0.10	0.24	0.11	-0.10	0.18
27	CGG	-0.62	0.23	-0.61	-0.10	-0.40	0.39	-0.10	-0.01	0.24	0.40	0.83	0.06
28	CGT	0.46	0.07	0.25	-0.14	0.65	-0.02	-0.24	-0.03	0.13	0.36	-0.23	0.02
29	CTA	-0.25	0.24	0.05	0.07	-0.71	-0.36	-0.29	-0.39	-0.40	-0.60	-0.41	-0.52
30	CTC	0.48	0.17	0.72	0.30	0.81	0.40	0.46	0.42	0.86	-0.10	0.72	0.42
31	CTG	0.13	0.21	-0.09	-0.01	-0.40	0.08	0.71	-0.09	0.06	0.17	0.10	0.17
32	CTT	0.27	-0.21	0.75	0.15	0.70	0.39	0.30	0.08	0.53	-0.30	0.49	-0.20
33	GAA	-0.25	-0.04	0.20	0.18	0.07	0.25	0.33	0.16	0.36	-0.03	0.09	0.02
34	GAC	0.63	0.19	0.29	0.37	0.45	-0.07	-0.08	0.04	0.38	0.35	-0.09	0.42
35	GAG	-0.32	-0.22	-0.31	0.06	-0.43	-0.33	-0.29	-0.29	-0.42	0.65	-0.24	-0.18
36	GAT	0.33	-0.26	-0.15	-0.10	-0.03	-0.19	-0.07	0.19	0.10	-0.23	-0.07	-0.11
37	GCA	-0.33	0.24	-0.13	0.18	-0.32	0.22	0.14	0.14	-0.40	0.07	-0.35	-0.29
38	GCC	0.29	-0.02	0.36	-0.19	0.66	0.17	0.27	0.18	0.54	0.04	0.60	0.33
39	GCG	-0.27	0.36	-0.31	-0.13	-0.42	-0.13	-0.17	-0.18	-0.43	0.31	-0.13	0.03
40	GCT	0.24	-0.27	0.59	0.00	0.57	-0.22	0.09	0.02	0.38	-0.05	0.19	0.28
41	GGA	-0.61	0.61	-0.37	0.02	-0.35	-0.01	0.13	-0.29	-0.33	0.13	-0.20	0.10
42	GGC	0.34	0.27	0.19	0.01	0.82	0.54	0.53	0.53	0.29	0.24	0.01	0.44

43	GGG	-0.47	-0.28	-0.43	-0.28	-0.73	0.10	-0.45	-0.50	-0.67	0.72	-0.52	-0.02
44	GGT	0.43	-0.01	0.30	-0.09	0.40	-0.32	-0.24	-0.19	0.39	0.64	0.10	0.33
45	GTA	-0.04	0.52	-0.11	0.41	-0.34	0.07	-0.33	-0.10	-0.15	-0.09	-0.36	-0.12
46	GTC	0.26	0.02	0.30	-0.13	0.86	0.42	0.45	0.16	0.76	0.18	0.62	0.31
47	GTG	-0.05	-0.01	-0.35	-0.20	-0.13	0.36	-0.20	-0.18	-0.19	0.28	-0.21	-0.01
48	GTT	0.47	-0.22	0.59	0.13	0.59	-0.31	-0.13	-0.07	0.42	-0.27	0.03	-0.30
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.44	-0.20	0.13	0.17	0.65	0.02	0.17	0.24	0.35	0.10	0.15	0.30
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.03	-0.19	-0.09	0.17	-0.03	-0.37	-0.27	0.25	0.18	-0.35	-0.19	-0.03
53	TCA	-0.54	0.28	-0.33	0.17	-0.39	0.13	0.26	0.19	-0.45	-0.38	-0.33	-0.28
54	TCC	0.08	-0.28	0.22	-0.10	0.73	0.22	0.39	0.41	0.35	-0.16	0.42	-0.06
55	TCG	-0.38	0.29	-0.43	-0.17	-0.49	0.11	0.01	-0.01	-0.62	-0.34	-0.31	-0.23
56	TCT	-0.08	-0.21	0.41	-0.12	0.47	-0.32	0.33	0.12	0.14	-0.14	0.07	-0.14
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.13	0.27	0.19	0.10	0.48	-0.19	-0.28	-0.13	-0.02	0.43	-0.35	0.09
59	TGG	-0.49	0.01	0.00	0.12	-0.09	0.08	0.05	-0.06	0.10	0.26	-0.06	-0.09
60	TGT	-0.22	-0.10	-0.19	-0.24	0.71	0.32	-0.16	0.17	0.52	0.62	0.09	0.38
61	TTA	-0.27	-0.06	-0.25	-0.20	-0.31	0.11	-0.24	0.03	0.09	-0.57	-0.21	-0.36
62	TTC	0.68	0.30	0.57	0.53	0.84	-0.35	-0.50	-0.08	0.26	-0.27	-0.45	-0.26
63	TTG	-0.39	-0.05	-0.33	-0.40	-0.45	-0.17	-0.54	-0.27	-0.37	-0.45	-0.27	-0.40
64	TTT	0.18	-0.29	-0.30	-0.25	0.52	0.32	0.15	0.13	0.54	0.02	0.45	0.12
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
		13	14	15	16	17	18	19	20	21	22	23	24

Table C.5 continued

		25	26	27	28	29	30	31	32	33	34	35	36
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
1	AAA	0.27	0.06	0.16	0.21	0.20	-0.06	0.05	0.20	0.14	-0.10	-0.46	-0.14
2	AAC	0.10	-0.17	0.02	-0.16	0.66	-0.15	-0.09	0.00	0.03	-0.14	0.18	0.02
3	AAG	-0.56	-0.25	-0.50	-0.27	-0.51	-0.23	-0.38	-0.06	0.61	0.56	0.41	0.42
4	AAT	0.10	0.12	0.12	0.34	0.04	-0.40	0.07	-0.30	-0.13	-0.13	0.02	0.19
5	ACA	-0.18	0.21	0.02	0.38	-0.47	-0.15	0.25	-0.23	-0.19	0.26	-0.10	0.20
6	ACC	-0.10	-0.12	0.19	0.08	0.53	0.38	0.54	0.46	0.01	-0.24	0.16	-0.15
7	ACG	-0.46	-0.03	-0.30	-0.21	-0.72	-0.42	-0.53	-0.47	0.16	0.54	0.49	0.45
8	ACT	0.49	-0.06	0.81	0.17	0.35	0.14	0.42	0.31	-0.40	-0.49	0.07	0.01
9	AGA	-0.54	0.30	-0.31	0.31	-0.13	0.30	0.43	-0.28	0.05	0.41	0.07	0.28
10	AGC	0.14	-0.09	-0.09	-0.12	0.66	0.16	0.06	0.32	-0.25	-0.16	-0.12	-0.26

11	AGG	-0.63	0.20	-0.30	0.21	-0.70	-0.28	-0.18	-0.62	0.01	0.44	-0.19	-0.12
12	AGT	0.28	0.24	-0.15	0.32	0.62	0.30	0.19	0.18	-0.39	0.01	-0.20	-0.06
13	ATA	-0.23	0.31	0.10	0.20	-0.31	-0.21	0.41	-0.33	0.06	0.47	0.11	0.33
14	ATC	0.69	-0.21	0.55	0.06	0.84	-0.59	0.31	-0.05	0.08	-0.42	0.30	0.15
15	ATG	0.21	-0.08	0.31	-0.09	0.05	-0.17	-0.02	0.19	-0.03	0.02	0.07	-0.01
16	ATT	0.50	-0.19	0.54	-0.08	0.62	-0.44	0.07	-0.30	-0.12	0.25	-0.11	-0.01
17	CAA	-0.38	0.10	-0.31	-0.09	-0.16	-0.30	-0.21	-0.39	0.44	0.59	0.11	0.56
18	CAC	0.10	0.00	0.02	-0.04	0.80	0.29	0.19	0.14	0.13	-0.28	0.14	-0.16
19	CAG	-0.43	0.29	-0.20	-0.09	-0.31	0.16	0.47	-0.32	-0.15	-0.17	-0.15	-0.26
20	CAT	0.24	-0.15	-0.19	0.13	-0.06	-0.26	-0.10	-0.42	-0.12	-0.08	-0.02	0.37
21	CCA	-0.52	-0.20	-0.38	0.20	-0.36	0.21	0.18	0.18	-0.14	-0.06	-0.10	0.28
22	CCC	-0.22	0.25	-0.16	0.31	0.57	0.61	0.74	0.42	0.50	-0.05	0.54	-0.31
23	CCG	-0.11	-0.17	0.55	-0.20	-0.52	-0.06	-0.30	0.10	-0.13	0.16	0.21	0.11
24	CCT	0.50	0.39	0.56	0.35	0.36	0.54	0.61	0.30	-0.15	-0.39	0.10	-0.18
25	CGA	-0.34	-0.05	-0.38	-0.04	-0.53	-0.27	-0.39	-0.30	0.26	0.61	0.27	0.45
26	CGC	0.37	0.02	0.27	0.01	0.81	0.51	0.12	0.45	0.13	-0.21	0.01	-0.22
27	CGG	-0.56	0.21	-0.64	-0.06	-0.56	0.34	-0.25	-0.25	-0.26	0.64	0.08	0.26
28	CGT	0.30	-0.02	-0.10	0.01	0.56	0.25	-0.20	0.01	-0.13	-0.10	0.04	0.17
29	CTA	-0.54	-0.52	-0.54	-0.37	-0.46	-0.41	-0.16	-0.41	0.79	0.92	0.77	0.84
30	CTC	0.68	0.77	0.33	0.79	0.93	0.66	0.81	0.62	0.00	-0.68	0.47	-0.50
31	CTG	0.20	-0.06	0.28	-0.17	0.04	0.15	0.02	0.10	-0.30	0.24	-0.20	-0.12
32	CTT	0.69	0.52	0.58	0.56	0.50	0.22	0.69	0.25	-0.17	-0.01	-0.53	-0.49
33	GAA	0.30	0.24	0.11	0.19	0.29	0.30	-0.01	0.29	0.07	-0.04	-0.49	-0.27
34	GAC	-0.01	-0.13	-0.09	-0.18	0.66	0.05	0.14	0.17	0.08	-0.04	0.15	-0.08
35	GAG	-0.45	-0.19	-0.51	-0.34	-0.49	0.67	-0.31	-0.21	0.59	0.61	0.47	0.53
36	GAT	0.54	-0.05	0.23	0.25	0.28	-0.49	0.15	-0.15	-0.05	-0.14	-0.07	0.16
37	GCA	-0.33	0.27	-0.08	0.27	-0.33	0.31	0.01	0.17	-0.26	0.26	-0.22	0.19
38	GCC	0.06	-0.02	0.02	0.04	0.73	0.52	0.52	0.52	0.17	-0.24	0.14	-0.30
39	GCG	-0.44	0.15	-0.37	-0.20	-0.58	0.08	-0.42	-0.11	0.21	0.57	0.40	0.33
40	GCT	0.55	0.18	0.66	0.21	0.45	0.51	0.47	0.45	-0.39	-0.47	0.05	-0.27
41	GGA	-0.63	-0.34	-0.54	-0.35	-0.29	0.42	0.04	-0.26	0.19	0.51	0.09	0.45
42	GGC	0.61	0.56	0.61	0.55	0.73	0.54	0.25	0.42	-0.07	-0.20	-0.13	-0.35
43	GGG	-0.71	-0.36	-0.59	-0.46	-0.69	0.78	-0.51	-0.52	0.36	0.76	0.31	0.52
44	GGT	0.45	0.01	0.25	-0.17	0.64	0.84	-0.04	0.31	-0.13	0.10	0.05	0.10
45	GTA	-0.08	-0.20	-0.04	-0.34	-0.04	0.00	-0.32	-0.25	-0.03	0.40	0.00	0.30
46	GTC	0.67	0.45	0.43	0.42	0.89	0.55	0.70	0.58	0.13	0.23	-0.01	-0.45
47	GTG	0.06	-0.12	-0.27	-0.25	-0.20	-0.03	-0.40	-0.04	0.25	0.55	0.23	0.23
48	GTT	0.42	0.13	0.58	0.12	0.56	0.17	0.40	0.28	-0.25	-0.11	-0.37	-0.33
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

50	TAC	0.31	-0.02	-0.06	0.10	0.76	0.07	0.22	0.31	0.06	-0.33	0.18	0.02
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.10	-0.26	0.01	0.15	0.15	-0.53	-0.13	-0.33	-0.10	-0.31	0.00	0.47
53	TCA	-0.15	-0.08	-0.29	0.30	-0.57	-0.25	-0.11	-0.28	0.01	0.41	0.28	0.40
54	TCC	-0.15	-0.23	0.04	0.01	0.66	0.38	0.51	0.41	0.48	-0.12	0.38	0.00
55	TCG	-0.28	-0.19	-0.42	-0.07	-0.69	-0.33	-0.53	-0.44	0.42	0.67	0.68	0.62
56	TCT	0.68	0.10	0.75	0.24	0.26	0.22	0.20	-0.09	-0.17	-0.50	0.42	0.00
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.02	-0.13	-0.24	-0.14	0.73	-0.07	-0.24	0.04	0.06	-0.21	0.24	0.00
59	TGG	-0.50	0.22	-0.40	0.00	-0.47	0.57	-0.11	0.22	-0.08	0.26	0.19	-0.13
60	TGT	-0.10	0.42	-0.54	0.35	0.49	0.38	-0.07	0.05	-0.18	0.00	0.02	0.20
61	TTA	0.12	-0.29	-0.12	-0.20	0.00	-0.28	-0.04	-0.21	0.66	0.74	0.62	0.56
62	TTC	0.64	-0.42	0.23	-0.33	0.83	-0.66	-0.12	-0.29	0.26	-0.07	0.30	0.15
63	TTG	-0.28	-0.21	-0.28	-0.28	-0.54	-0.44	-0.49	-0.43	0.84	0.90	0.83	0.69
64	TTT	0.64	0.22	0.54	0.34	0.63	-0.29	0.51	-0.14	-0.19	-0.06	-0.12	-0.04
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
		25	26	27	28	29	30	31	32	33	34	35	36

Table C.5 continued

		37	38	39	40	41	42	43	44	45	46	47	48
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
1	AAA	0.00	-0.15	-0.21	0.31	0.11	-0.16	-0.28	-0.01	0.29	-0.08	-0.22	0.18
2	AAC	0.41	-0.36	0.27	0.14	0.19	-0.21	0.36	-0.20	0.12	-0.36	0.07	-0.10
3	AAG	0.28	0.52	0.18	0.25	-0.05	0.41	0.17	0.68	-0.04	0.19	0.10	0.11
4	AAT	0.20	-0.34	0.13	-0.05	0.35	-0.04	0.56	0.10	0.35	-0.22	0.29	0.13
5	ACA	-0.24	0.28	0.15	0.06	-0.43	0.26	-0.13	0.10	-0.15	0.37	0.25	0.33
6	ACC	0.02	-0.19	0.30	-0.11	-0.40	-0.04	-0.32	-0.20	-0.03	-0.01	0.19	-0.22
7	ACG	-0.32	0.70	-0.19	0.22	0.20	0.48	0.24	0.43	-0.45	0.17	-0.27	0.06
8	ACT	-0.06	-0.25	-0.08	-0.26	0.03	-0.30	0.67	0.11	0.04	-0.03	0.47	0.04
9	AGA	-0.30	0.45	-0.02	0.09	-0.54	0.27	-0.14	0.33	-0.21	-0.02	0.14	0.07
10	AGC	0.17	-0.39	0.34	0.55	-0.15	-0.14	0.10	-0.16	-0.12	-0.16	-0.01	0.01
11	AGG	-0.49	0.51	0.04	-0.23	-0.26	0.51	0.41	0.60	0.17	0.55	-0.10	-0.06
12	AGT	0.12	-0.14	0.03	0.01	0.04	0.20	0.29	0.09	0.45	0.40	0.37	0.37
13	ATA	0.21	0.00	0.40	0.33	0.26	0.39	0.05	0.31	0.40	0.03	0.43	0.19
14	ATC	0.45	-0.43	0.45	-0.19	0.64	-0.13	0.44	-0.13	0.53	-0.38	0.34	-0.13
15	ATG	-0.05	0.52	-0.29	0.12	-0.14	-0.10	-0.36	0.43	0.29	0.08	-0.21	0.14
16	ATT	0.46	-0.41	0.30	-0.26	0.68	-0.22	0.59	-0.24	0.59	-0.39	0.14	-0.21
17	CAA	0.61	0.43	0.54	0.54	-0.04	0.34	-0.27	0.27	0.60	0.61	0.58	0.55

18	CAC	0.21	-0.34	0.14	-0.21	0.16	-0.35	0.05	-0.41	-0.24	-0.33	0.87	-0.36
19	CAG	-0.32	0.21	-0.36	-0.19	-0.31	-0.08	-0.45	0.36	-0.31	-0.01	-0.27	-0.28
20	CAT	0.35	-0.11	0.10	-0.04	0.32	0.29	0.52	0.28	0.25	-0.15	0.04	-0.10
21	CCA	0.01	0.24	0.33	0.19	-0.41	-0.03	-0.09	0.15	-0.07	0.55	0.26	0.44
22	CCC	-0.37	-0.46	0.06	-0.40	-0.47	-0.41	0.34	-0.35	0.05	-0.20	0.30	-0.29
23	CCG	-0.25	0.76	0.09	0.34	-0.04	0.33	0.01	0.35	-0.42	0.31	-0.14	-0.06
24	CCT	-0.29	-0.45	-0.38	-0.46	-0.22	-0.44	0.05	-0.08	-0.06	-0.08	0.40	-0.22
25	CGA	0.09	0.36	0.11	0.11	-0.11	0.57	0.17	0.54	-0.19	0.24	-0.07	0.40
26	CGC	-0.04	-0.28	0.22	-0.07	-0.06	-0.21	0.01	-0.14	-0.27	-0.12	-0.15	-0.13
27	CGG	-0.52	0.23	-0.49	-0.21	-0.45	0.52	0.16	0.55	-0.66	-0.19	-0.55	-0.21
28	CGT	0.25	0.24	0.14	0.00	-0.03	-0.01	0.17	-0.07	0.36	0.43	0.48	0.31
29	CTA	0.76	0.73	0.75	0.78	0.73	0.71	0.59	0.74	0.83	0.72	0.81	0.72
30	CTC	0.43	-0.34	0.42	0.11	-0.20	-0.59	-0.34	-0.54	0.71	0.39	0.75	0.47
31	CTG	-0.43	0.48	-0.46	-0.12	0.01	0.23	-0.27	0.29	-0.29	-0.12	-0.49	-0.15
32	CTT	0.29	-0.33	0.33	-0.21	0.17	-0.39	-0.23	-0.08	0.64	0.31	0.73	0.37
33	GAA	0.02	-0.13	-0.25	0.09	-0.07	-0.13	-0.42	-0.16	0.21	-0.07	-0.33	0.02
34	GAC	0.29	-0.16	0.24	-0.02	0.15	-0.23	0.02	-0.28	0.16	-0.06	0.18	-0.16
35	GAG	0.32	0.51	0.12	0.42	0.45	0.59	0.21	0.67	0.44	0.44	0.25	0.40
36	GAT	0.26	-0.25	0.01	-0.13	0.34	-0.04	0.59	0.10	0.29	-0.19	-0.01	-0.02
37	GCA	-0.13	0.41	0.18	0.10	-0.25	-0.03	-0.21	-0.12	-0.16	0.42	0.25	0.38
38	GCC	-0.17	-0.15	0.28	-0.18	-0.68	0.87	-0.56	-0.09	0.00	0.05	0.31	-0.12
39	GCG	-0.33	0.70	-0.19	0.33	-0.06	0.26	0.05	0.19	-0.50	0.28	-0.32	0.01
40	GCT	-0.20	-0.31	-0.13	-0.30	0.01	-0.15	0.21	-0.02	-0.23	0.08	0.43	-0.11
41	GGA	0.11	0.38	0.26	0.44	-0.01	0.65	0.54	0.71	0.41	0.63	0.63	0.62
42	GGC	-0.46	0.96	-0.28	-0.11	-0.21	-0.38	-0.15	-0.37	-0.42	-0.14	-0.33	-0.27
43	GGG	-0.12	0.44	-0.24	0.23	0.30	0.73	0.67	0.84	-0.03	0.60	0.31	0.32
44	GGT	-0.05	0.04	-0.02	0.01	0.21	0.17	0.21	-0.07	0.13	0.24	0.20	0.12
45	GTA	0.24	0.46	0.14	0.41	0.26	0.42	-0.07	0.20	0.28	0.39	0.07	0.46
46	GTC	0.27	-0.35	0.13	-0.26	-0.04	-0.31	-0.43	-0.44	0.46	0.12	0.30	0.04
47	GTG	-0.03	0.66	-0.34	0.20	0.32	0.46	-0.01	0.36	-0.13	-0.06	-0.48	-0.16
48	GTT	0.21	-0.37	0.23	-0.37	0.44	-0.26	0.06	-0.17	0.45	0.08	0.49	-0.04
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.24	-0.33	0.25	-0.08	0.34	-0.31	0.24	-0.29	0.31	-0.12	0.34	-0.11
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.24	-0.33	0.18	0.16	0.37	0.02	0.60	0.15	0.29	-0.35	0.11	-0.17
53	TCA	-0.17	0.15	0.19	0.35	-0.28	0.41	0.21	0.30	-0.21	0.20	0.27	0.35
54	TCC	-0.16	-0.07	0.38	-0.20	-0.09	-0.39	-0.36	-0.47	-0.20	-0.10	0.30	-0.11
55	TCG	-0.27	0.64	-0.14	0.22	0.45	0.74	0.47	0.61	-0.52	0.02	-0.42	0.03
56	TCT	-0.12	-0.39	-0.16	-0.33	0.41	-0.24	0.76	-0.31	-0.20	-0.07	0.44	-0.31

57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.05	-0.17	0.23	0.09	0.01	-0.04	0.08	-0.13	-0.18	0.02	-0.11	0.18
59	TGG	-0.09	0.46	-0.25	0.10	-0.58	0.01	-0.08	0.46	-0.32	0.33	-0.08	0.12
60	TGT	-0.08	-0.06	-0.04	-0.08	0.16	0.07	0.28	-0.06	0.12	-0.13	0.05	0.11
61	TTA	0.55	0.40	0.45	0.56	0.20	0.19	-0.17	-0.04	0.62	0.20	0.39	0.45
62	TTC	0.60	-0.18	0.56	0.07	0.67	0.13	0.51	-0.06	0.50	0.06	0.51	0.09
63	TTG	0.44	0.78	0.55	0.46	0.01	0.53	-0.06	0.47	0.43	0.46	0.38	0.30
64	TTT	0.44	-0.53	0.31	-0.41	0.65	-0.23	0.62	-0.34	0.32	-0.49	0.11	-0.29
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
		37	38	39	40	41	42	43	44	45	46	47	48

Table C.5 continued

		49	50	51	52	53	54	55	56	57	58	59	60
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
1	AAA	0.00	-0.03	0.00	-0.03	-0.11	0.01	-0.21	0.13	0.00	-0.01	0.05	0.05
2	AAC	0.00	-0.24	0.00	0.06	0.15	-0.17	0.13	0.26	0.00	-0.24	-0.42	-0.17
3	AAG	0.00	0.09	0.00	0.12	-0.08	0.34	-0.26	0.03	0.00	0.08	-0.14	-0.18
4	AAT	0.00	0.03	0.00	0.20	0.15	0.44	0.50	0.37	0.00	0.29	0.90	0.37
5	ACA	0.00	0.38	0.00	0.41	-0.54	0.01	-0.34	0.02	0.00	0.51	0.06	0.15
6	ACC	0.00	-0.17	0.00	-0.07	0.17	0.02	-0.02	-0.08	0.00	-0.36	-0.43	-0.47
7	ACG	0.00	0.75	0.00	0.45	-0.04	0.54	0.05	0.35	0.00	0.88	0.66	0.84
8	ACT	0.00	-0.54	0.00	-0.41	-0.35	-0.46	-0.24	-0.41	0.00	0.19	0.90	0.19
9	AGA	0.00	0.47	0.00	0.16	0.42	0.68	0.24	0.67	0.00	0.44	0.53	0.07
10	AGC	0.00	-0.28	0.00	-0.19	0.58	0.31	0.43	0.55	0.00	0.13	-0.30	0.30
11	AGG	0.00	0.76	0.00	0.40	0.11	0.73	0.39	0.06	0.00	0.57	0.65	0.20
12	AGT	0.00	-0.30	0.00	-0.40	-0.34	-0.05	-0.23	0.00	0.00	-0.22	0.28	0.01
13	ATA	0.00	0.38	0.00	-0.09	-0.36	0.06	-0.09	-0.24	0.00	0.21	0.05	-0.30
14	ATC	0.00	-0.18	0.00	0.22	0.50	-0.36	0.39	-0.13	0.00	0.00	-0.44	0.15
15	ATG	0.00	-0.02	0.00	0.02	0.13	0.25	-0.27	0.16	0.00	0.03	0.00	-0.03
16	ATT	0.00	0.08	0.00	-0.12	0.13	-0.16	0.20	-0.12	0.00	-0.05	0.65	-0.04
17	CAA	0.00	0.01	0.00	-0.24	-0.22	-0.06	-0.01	-0.01	0.00	0.05	0.04	-0.14
18	CAC	0.00	-0.12	0.00	-0.03	-0.01	-0.27	0.12	-0.18	0.00	-0.36	-0.51	-0.11
19	CAG	0.00	0.01	0.00	0.15	-0.06	0.38	-0.20	0.23	0.00	-0.01	-0.02	0.07
20	CAT	0.00	-0.07	0.00	0.16	0.04	0.22	0.25	0.16	0.00	0.24	0.78	0.31
21	CCA	0.00	0.38	0.00	0.49	-0.44	0.05	-0.31	0.15	0.00	0.18	0.51	0.38
22	CCC	0.00	-0.17	0.00	-0.21	-0.22	-0.38	0.04	-0.27	0.00	-0.56	-0.42	-0.51
23	CCG	0.00	0.33	0.00	0.20	-0.20	0.37	0.00	0.16	0.00	0.26	-0.21	0.50
24	CCT	0.00	-0.51	0.00	-0.57	-0.65	-0.65	-0.49	-0.65	0.00	-0.39	0.87	-0.39

25	CGA	0.00	0.48	0.00	0.25	0.42	0.20	0.14	0.36	0.00	0.55	0.38	0.43
26	CGC	0.00	-0.05	0.00	-0.07	0.21	0.21	0.11	0.25	0.00	-0.29	-0.43	-0.14
27	CGG	0.00	0.81	0.00	0.54	0.39	0.85	0.56	0.76	0.00	0.67	0.74	0.61
28	CGT	0.00	-0.05	0.00	-0.25	-0.22	-0.18	-0.08	-0.32	0.00	0.01	0.46	0.03
29	CTA	0.00	0.34	0.00	0.14	0.12	0.31	-0.25	0.31	0.00	0.02	-0.43	-0.14
30	CTC	0.00	-0.56	0.00	-0.53	-0.30	-0.67	-0.19	-0.68	0.00	-0.42	-0.32	-0.36
31	CTG	0.00	0.33	0.00	0.25	0.43	0.82	0.21	0.53	0.00	0.30	0.17	0.37
32	CTT	0.00	-0.43	0.00	-0.55	-0.57	-0.76	-0.52	-0.74	0.00	-0.39	0.41	-0.45
33	GAA	0.00	0.08	0.00	0.05	0.11	0.03	0.32	0.20	0.00	0.29	0.21	0.14
34	GAC	0.00	-0.09	0.00	0.25	0.16	-0.21	0.34	0.14	0.00	-0.36	-0.60	-0.09
35	GAG	0.00	-0.18	0.00	-0.07	-0.16	0.07	-0.24	-0.06	0.00	-0.30	-0.32	-0.37
36	GAT	0.00	-0.20	0.00	0.09	0.25	0.12	0.37	0.32	0.00	0.10	0.90	0.34
37	GCA	0.00	0.53	0.00	0.48	-0.05	0.31	-0.21	0.23	0.00	0.72	-0.02	0.41
38	GCC	0.00	-0.04	0.00	-0.25	0.14	-0.06	-0.13	-0.20	0.00	-0.49	-0.48	-0.60
39	GCG	0.00	0.58	0.00	0.34	0.33	0.69	0.29	0.41	0.00	0.66	0.29	0.55
40	GCT	0.00	-0.56	0.00	-0.56	-0.36	-0.42	-0.27	-0.48	0.00	0.08	0.94	-0.22
41	GGA	0.00	0.31	0.00	-0.15	0.13	0.72	-0.49	0.47	0.00	-0.07	0.21	-0.12
42	GGC	0.00	0.02	0.00	0.04	0.41	0.33	0.38	0.45	0.00	-0.20	-0.44	-0.22
43	GGG	0.00	0.70	0.00	0.31	0.52	0.84	0.42	0.68	0.00	0.79	0.78	0.46
44	GGT	0.00	-0.12	0.00	-0.26	-0.34	-0.30	-0.35	-0.42	0.00	0.15	0.52	-0.04
45	GTA	0.00	0.44	0.00	0.44	0.06	0.17	-0.14	0.18	0.00	0.38	-0.02	-0.04
46	GTC	0.00	-0.08	0.00	-0.22	0.31	-0.13	0.23	-0.16	0.00	-0.35	-0.61	-0.29
47	GTG	0.00	0.67	0.00	0.40	0.59	0.79	0.27	0.61	0.00	0.39	0.37	0.47
48	GTT	0.00	-0.39	0.00	-0.49	-0.28	-0.54	-0.23	-0.58	0.00	-0.26	0.79	-0.22
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.00	-0.30	0.00	0.32	0.29	-0.27	0.23	0.04	0.00	-0.33	-0.51	0.17
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.00	-0.30	0.00	0.33	-0.10	-0.28	0.34	0.31	0.00	0.03	0.78	0.31
53	TCA	0.00	0.59	0.00	0.54	-0.55	0.07	-0.40	-0.17	0.00	0.03	0.00	0.40
54	TCC	0.00	0.11	0.00	0.46	0.04	-0.15	0.27	-0.10	0.00	-0.53	-0.45	-0.50
55	TCG	0.00	0.74	0.00	0.58	-0.05	0.49	0.02	0.38	0.00	0.48	0.40	0.62
56	TCT	0.00	-0.27	0.00	-0.22	-0.51	-0.54	-0.26	-0.53	0.00	0.20	0.96	0.03
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.00	-0.14	0.00	0.09	-0.03	0.13	0.19	-0.04	0.00	-0.15	-0.33	-0.18
59	TGG	0.00	0.10	0.00	-0.07	-0.38	0.49	-0.35	0.40	0.00	0.10	0.00	-0.11
60	TGT	0.00	0.11	0.00	-0.04	-0.50	-0.31	-0.30	-0.26	0.00	0.37	0.61	0.09
61	TTA	0.00	0.62	0.00	0.31	-0.06	0.04	-0.26	0.13	0.00	-0.08	-0.11	-0.13
62	TTC	0.00	-0.13	0.00	0.12	0.02	-0.40	-0.18	-0.24	0.00	-0.25	-0.52	-0.08
63	TTG	0.00	0.38	0.00	0.01	-0.17	0.55	-0.35	0.34	0.00	0.03	-0.21	-0.17

64	TTT	0.00	0.10	0.00	-0.07	0.08	-0.03	0.35	0.08	0.00	0.10	0.80	0.25
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
		49	50	51	52	53	54	55	56	57	58	59	60

Table C.5 continued

		61	62	63	64
		TTA	TTC	TTG	TTT
1	AAA	0.15	-0.03	0.40	0.23
2	AAC	0.46	-0.30	0.58	0.19
3	AAG	-0.02	-0.22	-0.02	-0.31
4	AAT	-0.23	-0.04	0.06	0.20
5	ACA	-0.50	0.16	-0.40	-0.13
6	ACC	0.43	-0.19	0.53	0.01
7	ACG	-0.24	0.41	-0.34	0.27
8	ACT	0.24	-0.34	0.32	-0.09
9	AGA	-0.34	0.66	-0.01	0.30
10	AGC	0.65	0.04	0.67	0.27
11	AGG	-0.24	0.61	-0.44	0.37
12	AGT	0.06	-0.13	-0.27	-0.32
13	ATA	-0.57	-0.25	-0.57	-0.49
14	ATC	0.66	-0.16	0.69	0.37
15	ATG	0.36	-0.15	-0.21	0.13
16	ATT	-0.03	-0.16	-0.35	0.12
17	CAA	-0.11	0.39	0.05	0.05
18	CAC	0.53	-0.16	0.68	0.08
19	CAG	-0.07	-0.16	-0.25	-0.04
20	CAT	-0.24	0.03	-0.21	0.03
21	CCA	-0.32	0.19	-0.26	0.12
22	CCC	0.32	0.02	0.40	0.04
23	CCG	-0.03	-0.09	-0.12	0.00
24	CCT	-0.07	-0.07	0.31	-0.05
25	CGA	-0.47	0.12	-0.44	-0.09
26	CGC	0.38	0.10	0.48	-0.08
27	CGG	-0.36	0.78	-0.44	0.38
28	CGT	0.02	-0.05	-0.13	-0.24
29	CTA	-0.46	0.18	-0.47	-0.33
30	CTC	0.77	0.26	0.85	0.15
31	CTG	0.22	0.09	0.07	-0.08

32	CTT	0.12	0.15	0.30	0.03
33	GAA	0.24	0.51	0.39	0.16
34	GAC	0.39	-0.05	0.59	0.33
35	GAG	-0.25	-0.38	-0.35	-0.42
36	GAT	-0.39	-0.18	-0.18	-0.01
37	GCA	-0.41	0.06	-0.35	-0.19
38	GCC	0.47	0.16	0.57	-0.03
39	GCG	-0.27	0.29	-0.29	-0.07
40	GCT	0.21	-0.04	0.27	-0.17
41	GGA	-0.66	-0.18	-0.45	-0.37
42	GGC	0.32	0.08	0.41	0.03
43	GGG	-0.49	0.57	-0.40	0.34
44	GGT	-0.19	0.12	-0.18	-0.23
45	GTA	-0.48	-0.19	-0.53	-0.27
46	GTC	0.62	-0.10	0.71	-0.15
47	GTG	0.12	0.16	-0.28	0.14
48	GTT	0.16	0.08	0.25	0.11
49	TAA	0.00	0.00	0.00	0.00
50	TAC	0.66	-0.28	0.72	0.28
51	TAG	0.00	0.00	0.00	0.00
52	TAT	-0.10	-0.15	-0.10	0.14
53	TCA	-0.53	0.09	-0.33	-0.18
54	TCC	0.48	0.00	0.58	0.23
55	TCG	-0.23	0.12	-0.39	-0.09
56	TCT	0.14	-0.09	0.01	0.02
57	TGA	0.00	0.00	0.00	0.00
58	TGC	0.41	-0.03	0.55	0.10
59	TGG	0.09	0.22	0.01	-0.14
60	TGT	-0.15	0.13	0.07	-0.16
61	TTA	-0.42	0.19	-0.43	0.00
62	TTC	0.52	-0.39	0.50	-0.15
63	TTG	-0.31	-0.18	-0.54	-0.15
64	TTT	-0.34	0.14	-0.23	0.39
		TTA	TTC	TTG	TTT
		61	62	63	64

Table C.6: CPW matrix *Escherichi coli* K12 highly expressed sequences (left codon indicated in column 2, right codon indicated in row 2). Host cell: *E. coli*; Sequence data: full *E. coli* genome; Highly expressed group: 100 seqs.

		1	2	3	4	5	6	7	8	9	10	11	12
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
1	AAA	0.25	-0.47	0.55	0.83	0.88	-0.33	0.61	-0.59	1.00	0.49	1.00	0.88
2	AAC	-0.40	-0.58	-0.48	0.29	0.78	-0.61	0.68	-0.35	1.00	-0.55	1.00	0.80
3	AAG	-0.59	-0.02	0.25	0.86	0.61	0.43	1.00	0.40	1.00	-0.41	1.00	1.00
4	AAT	0.86	0.60	1.00	1.00	1.00	0.52	1.00	-0.05	1.00	1.00	1.00	1.00
5	ACA	0.79	0.75	1.00	1.00	1.00	1.00	0.70	0.52	1.00	0.64	1.00	1.00
6	ACC	-0.33	-0.65	-0.57	0.55	0.64	-0.43	0.74	-0.69	0.31	-0.41	1.00	1.00
7	ACG	0.90	0.88	0.67	1.00	1.00	0.74	0.57	0.31	1.00	1.00	1.00	1.00
8	ACT	-0.22	-0.36	-0.06	0.52	1.00	-0.56	0.31	-0.62	1.00	1.00	1.00	0.48
9	AGA	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
10	AGC	0.08	-0.35	0.10	0.71	1.00	0.14	0.82	1.00	1.00	0.22	1.00	1.00
11	AGG	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
12	AGT	1.00	0.56	1.00	1.00	1.00	0.80	1.00	1.00	1.00	1.00	1.00	1.00
13	ATA	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
14	ATC	-0.53	-0.72	-0.38	0.55	1.00	-0.58	0.85	-0.77	1.00	-0.20	1.00	0.67
15	ATG	0.12	-0.38	-0.29	0.74	0.64	-0.25	0.48	-0.29	1.00	-0.11	1.00	0.79
16	ATT	0.64	0.73	0.93	0.95	0.87	0.46	0.87	-0.12	1.00	0.93	1.00	1.00
17	CAA	0.71	0.47	1.00	0.68	1.00	0.65	0.81	0.07	1.00	1.00	1.00	0.54
18	CAC	-0.51	-0.65	-0.60	1.00	1.00	-0.65	1.00	-0.72	1.00	-0.63	1.00	-0.10
19	CAG	-0.33	-0.46	-0.11	0.40	0.79	-0.32	1.00	-0.75	1.00	-0.41	1.00	1.00
20	CAT	0.92	0.00	0.73	1.00	1.00	0.57	0.77	0.24	1.00	0.55	1.00	1.00
21	CCA	0.43	0.30	1.00	0.71	1.00	-0.07	1.00	-0.13	1.00	-0.28	1.00	1.00
22	CCC	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
23	CCG	-0.43	-0.64	-0.08	0.79	0.47	-0.52	1.00	-0.71	1.00	0.01	1.00	0.54
24	CCT	0.45	1.00	1.00	0.31	1.00	0.48	1.00	0.31	1.00	1.00	1.00	1.00
25	CGA	1.00	1.00	1.00	1.00	1.00	1.00	1.00	-0.19	1.00	1.00	1.00	1.00
26	CGC	0.43	-0.39	0.17	0.91	1.00	0.42	1.00	-0.14	1.00	0.52	1.00	1.00
27	CGG	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
28	CGT	-0.45	-0.59	-0.59	0.41	0.21	-0.54	0.62	-0.83	1.00	0.23	1.00	0.53
29	CTA	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
30	CTC	0.76	0.38	0.74	1.00	1.00	0.66	1.00	0.55	1.00	0.46	1.00	1.00
31	CTG	-0.53	-0.69	0.02	0.73	0.64	-0.60	0.66	-0.76	1.00	-0.35	1.00	0.90
32	CTT	0.84	0.79	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.73	1.00	1.00
33	GAA	-0.11	-0.45	0.76	0.69	0.89	-0.43	0.63	-0.64	1.00	-0.26	1.00	0.76

34	GAC	-0.51	-0.63	-0.51	0.91	0.76	-0.58	0.66	-0.51	1.00	-0.63	1.00	1.00
35	GAG	-0.15	-0.21	-0.14	1.00	1.00	0.79	1.00	0.24	1.00	0.86	1.00	1.00
36	GAT	0.61	-0.20	0.64	1.00	1.00	-0.22	1.00	0.12	1.00	0.92	1.00	1.00
37	GCA	0.37	-0.45	0.91	1.00	0.24	-0.55	0.88	-0.80	1.00	-0.07	1.00	0.75
38	GCC	0.71	0.49	0.93	0.94	0.80	0.65	0.91	0.39	1.00	0.17	1.00	0.81
39	GCG	-0.18	-0.22	-0.03	0.90	0.85	0.12	0.86	-0.43	1.00	0.76	1.00	0.85
40	GCT	-0.64	-0.79	-0.42	0.68	1.00	-0.55	0.36	-0.61	1.00	0.65	1.00	1.00
41	GGA	0.94	0.68	1.00	1.00	1.00	0.84	1.00	1.00	1.00	0.76	1.00	1.00
42	GGC	0.29	-0.27	0.51	0.64	0.85	-0.04	0.86	-0.21	1.00	0.32	1.00	0.77
43	GGG	0.82	1.00	1.00	1.00	1.00	1.00	1.00	0.69	1.00	1.00	1.00	1.00
44	GGT	-0.57	-0.64	-0.24	0.44	0.64	-0.29	0.32	-0.86	1.00	-0.04	1.00	0.86
45	GTA	-0.15	-0.64	1.00	0.67	0.31	-0.50	-0.13	-0.83	1.00	-0.21	1.00	0.61
46	GTC	0.73	0.25	0.75	1.00	1.00	0.29	1.00	0.25	1.00	0.26	1.00	1.00
47	GTG	0.04	0.23	0.63	0.93	1.00	0.04	0.86	-0.50	1.00	0.83	1.00	0.68
48	GTT	-0.47	-0.70	-0.53	0.90	1.00	-0.38	0.90	-0.47	1.00	0.37	1.00	1.00
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.47	-0.71	-0.29	0.84	1.00	-0.68	1.00	-0.73	1.00	-0.64	1.00	1.00
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.52	0.50	0.82	1.00	1.00	0.47	1.00	0.80	1.00	0.72	1.00	1.00
53	TCA	1.00	0.46	1.00	1.00	1.00	1.00	1.00	-0.24	1.00	1.00	1.00	1.00
54	TCC	-0.63	-0.73	-0.57	0.73	0.31	-0.78	1.00	-0.69	1.00	-0.77	1.00	1.00
55	TCG	0.51	1.00	0.68	1.00	1.00	1.00	1.00	0.49	1.00	1.00	1.00	1.00
56	TCT	-0.56	-0.76	0.31	1.00	0.29	-0.77	1.00	-0.83	1.00	1.00	1.00	1.00
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	-0.22	-0.28	1.00	1.00	1.00	-0.48	1.00	0.27	1.00	-0.23	1.00	0.20
59	TGG	-0.23	-0.37	1.00	0.71	1.00	-0.20	0.32	-0.39	1.00	0.28	1.00	1.00
60	TGT	-0.25	-0.57	1.00	1.00	-0.15	0.66	1.00	-0.78	1.00	1.00	1.00	1.00
61	TTA	0.94	1.00	1.00	1.00	1.00	1.00	1.00	0.64	1.00	0.78	1.00	1.00
62	TTC	-0.49	-0.69	0.14	0.65	0.51	-0.61	1.00	-0.77	1.00	-0.30	1.00	1.00
63	TTG	0.81	0.83	1.00	1.00	0.53	1.00	1.00	0.63	1.00	0.56	1.00	1.00
64	TTT	0.54	0.47	0.49	0.94	0.82	0.73	1.00	0.00	1.00	0.76	1.00	1.00
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
		1	2	3	4	5	6	7	8	9	10	11	12

Table C.6 continued

		13	14	15	16	17	18	19	20	21	22	23	24
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
1	AAA	1.00	-0.36	-0.04	0.44	0.20	-0.51	0.16	1.00	-0.17	1.00	0.05	0.38

2	AAC	1.00	-0.72	-0.41	0.69	0.54	-0.70	-0.56	0.47	0.24	1.00	-0.62	0.82
3	AAG	1.00	-0.49	0.15	0.32	0.24	-0.64	-0.50	0.54	0.71	1.00	-0.61	-0.03
4	AAT	1.00	0.62	0.87	0.94	1.00	0.71	0.70	1.00	0.81	1.00	0.46	1.00
5	ACA	1.00	0.83	1.00	1.00	1.00	1.00	0.76	1.00	1.00	1.00	0.81	1.00
6	ACC	1.00	-0.67	-0.47	0.30	0.19	-0.47	0.01	0.61	0.37	1.00	0.05	0.81
7	ACG	1.00	1.00	0.73	0.80	0.56	0.44	0.88	1.00	0.49	1.00	0.36	0.69
8	ACT	1.00	-0.64	0.35	0.35	-0.44	-0.85	-0.73	1.00	0.58	1.00	-0.82	-0.60
9	AGA	1.00	1.00	1.00	1.00	1.00	1.00	1.00	-0.33	1.00	1.00	1.00	1.00
10	AGC	1.00	-0.37	0.38	0.63	1.00	-0.51	-0.17	0.78	1.00	1.00	-0.29	1.00
11	AGG	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
12	AGT	1.00	0.84	1.00	0.86	0.53	1.00	1.00	1.00	1.00	1.00	0.48	1.00
13	ATA	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
14	ATC	1.00	-0.70	-0.53	0.04	0.45	-0.68	-0.42	0.50	-0.18	0.73	-0.57	-0.31
15	ATG	1.00	-0.48	0.00	0.64	0.33	-0.43	-0.15	0.56	-0.24	1.00	-0.17	0.30
16	ATT	1.00	0.23	0.82	0.88	1.00	-0.09	-0.24	0.72	0.86	1.00	0.02	1.00
17	CAA	1.00	0.32	0.66	0.91	0.82	-0.11	0.81	0.58	1.00	1.00	-0.04	0.00
18	CAC	1.00	-0.73	-0.38	0.27	1.00	-0.72	-0.52	0.55	-0.33	1.00	-0.64	1.00
19	CAG	1.00	-0.58	-0.26	0.31	0.52	-0.58	-0.48	0.78	0.78	1.00	-0.49	0.48
20	CAT	1.00	0.53	0.46	0.76	1.00	0.09	-0.10	1.00	1.00	1.00	0.40	0.33
21	CCA	1.00	-0.61	0.57	0.84	0.37	0.59	0.34	0.69	1.00	1.00	-0.23	1.00
22	CCC	1.00	0.70	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
23	CCG	1.00	-0.58	-0.37	0.24	0.33	-0.70	-0.53	0.56	-0.42	1.00	-0.50	-0.36
24	CCT	1.00	0.53	0.49	1.00	1.00	1.00	0.80	0.63	1.00	1.00	1.00	1.00
25	CGA	1.00	0.58	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
26	CGC	1.00	0.54	0.10	0.35	1.00	0.30	0.44	0.87	0.78	1.00	0.36	0.20
27	CGG	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
28	CGT	1.00	-0.74	-0.40	0.14	0.55	-0.73	-0.69	0.02	0.29	1.00	-0.66	-0.61
29	CTA	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
30	CTC	1.00	0.14	0.81	0.64	0.63	0.47	0.61	1.00	1.00	1.00	0.82	1.00
31	CTG	1.00	-0.71	-0.43	0.25	-0.28	-0.75	-0.54	0.67	-0.48	0.84	-0.60	-0.02
32	CTT	1.00	0.78	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.63	1.00
33	GAA	1.00	-0.56	-0.11	0.66	0.49	-0.28	0.12	0.67	-0.22	1.00	-0.06	-0.02
34	GAC	1.00	-0.66	-0.35	0.38	0.87	-0.66	-0.57	0.34	0.51	1.00	-0.40	1.00
35	GAG	1.00	-0.30	0.27	0.78	0.48	-0.64	-0.52	0.51	1.00	1.00	-0.48	0.62
36	GAT	1.00	-0.30	0.33	0.85	0.68	-0.28	0.16	0.94	0.42	1.00	-0.38	0.65
37	GCA	1.00	-0.56	-0.41	0.47	0.76	-0.47	-0.36	0.69	0.41	0.55	-0.62	-0.06
38	GCC	1.00	0.50	0.60	0.70	1.00	1.00	0.41	0.76	1.00	1.00	0.92	0.45
39	GCG	1.00	0.07	-0.01	0.17	0.72	-0.52	-0.04	0.63	0.65	0.73	-0.27	1.00
40	GCT	1.00	-0.78	-0.07	0.49	0.37	-0.76	-0.70	0.18	0.22	1.00	-0.70	1.00

41	GGA	1.00	1.00	0.88	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.23	1.00
42	GGC	1.00	0.25	0.07	0.58	0.92	-0.39	0.26	0.87	0.43	0.71	-0.13	0.77
43	GGG	1.00	0.71	1.00	0.84	1.00	0.07	0.88	1.00	0.49	1.00	0.27	1.00
44	GGT	1.00	-0.75	-0.45	-0.04	0.80	-0.67	-0.71	-0.01	0.32	1.00	-0.64	0.46
45	GTA	1.00	-0.52	-0.56	0.51	0.31	-0.68	-0.65	0.33	-0.47	1.00	-0.63	-0.55
46	GTC	1.00	0.44	0.77	0.83	1.00	1.00	0.49	0.76	0.21	1.00	0.53	0.37
47	GTG	1.00	-0.10	0.06	0.76	0.71	0.82	0.93	1.00	0.54	1.00	0.56	0.63
48	GTT	1.00	-0.78	0.03	0.61	0.39	-0.80	-0.65	0.20	0.33	1.00	-0.55	-0.53
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	1.00	-0.74	-0.55	0.33	1.00	-0.66	-0.55	-0.02	0.23	1.00	-0.48	1.00
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	1.00	0.57	0.91	0.78	1.00	0.18	0.01	1.00	0.71	1.00	-0.26	0.30
53	TCA	1.00	1.00	0.72	1.00	1.00	1.00	0.69	1.00	1.00	1.00	0.68	1.00
54	TCC	1.00	-0.81	-0.61	0.04	1.00	-0.69	-0.50	0.60	1.00	1.00	-0.62	1.00
55	TCG	1.00	0.84	0.11	0.74	1.00	1.00	1.00	1.00	0.29	1.00	0.75	1.00
56	TCT	1.00	-0.78	-0.47	0.72	1.00	-0.86	-0.82	0.58	1.00	1.00	-0.83	0.09
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	1.00	-0.24	-0.07	1.00	1.00	-0.58	-0.45	0.55	0.05	1.00	-0.58	1.00
59	TGG	1.00	-0.28	0.00	0.18	1.00	-0.57	-0.34	1.00	1.00	1.00	-0.47	1.00
60	TGT	1.00	-0.73	0.10	1.00	-0.54	0.25	1.00	0.44	-0.16	1.00	0.57	1.00
61	TTA	1.00	1.00	1.00	0.85	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
62	TTC	1.00	-0.74	-0.30	0.73	1.00	-0.79	-0.71	0.41	0.23	1.00	-0.73	-0.28
63	TTG	1.00	0.82	0.23	1.00	1.00	1.00	0.84	0.67	0.58	1.00	0.70	1.00
64	TTT	1.00	0.19	0.32	0.86	1.00	1.00	0.90	1.00	1.00	1.00	1.00	1.00
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
		13	14	15	16	17	18	19	20	21	22	23	24

Table C.6 continued

		25	26	27	28	29	30	31	32	33	34	35	36
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
1	AAA	1.00	0.43	1.00	-0.36	1.00	0.76	-0.46	0.84	-0.17	-0.53	-0.32	0.26
2	AAC	1.00	-0.26	1.00	-0.70	0.42	-0.38	-0.66	0.80	-0.47	-0.62	-0.15	0.01
3	AAG	0.33	-0.32	1.00	-0.61	1.00	0.19	-0.41	0.73	0.95	0.82	1.00	0.84
4	AAT	1.00	1.00	1.00	1.00	1.00	1.00	0.74	1.00	0.82	0.59	0.79	0.85
5	ACA	1.00	1.00	1.00	0.34	1.00	1.00	0.86	1.00	0.41	0.41	0.74	1.00
6	ACC	1.00	0.33	1.00	-0.56	1.00	0.62	-0.45	0.61	-0.36	-0.40	0.22	0.31
7	ACG	1.00	0.90	1.00	0.79	1.00	1.00	-0.31	1.00	0.89	1.00	1.00	1.00
8	ACT	1.00	-0.59	1.00	-0.77	-0.32	1.00	-0.75	1.00	-0.61	-0.83	0.18	-0.27

9	AGA	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
10	AGC	1.00	0.07	1.00	-0.69	1.00	1.00	-0.43	0.45	-0.20	-0.19	0.75	0.33
11	AGG	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
12	AGT	1.00	1.00	1.00	1.00	1.00	1.00	0.90	1.00	0.79	0.79	1.00	0.88
13	ATA	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
14	ATC	1.00	-0.34	1.00	-0.63	1.00	-0.67	-0.59	0.13	-0.57	-0.72	-0.08	-0.07
15	ATG	1.00	0.35	1.00	-0.49	1.00	0.27	-0.41	0.85	-0.10	-0.45	0.24	0.49
16	ATT	1.00	0.55	1.00	-0.12	1.00	0.64	-0.13	1.00	0.53	0.57	0.86	0.80
17	CAA	1.00	0.86	1.00	-0.07	1.00	0.71	0.26	0.70	0.65	0.03	-0.14	0.83
18	CAC	-0.27	-0.48	1.00	-0.66	1.00	-0.62	-0.69	0.46	-0.55	-0.70	0.06	0.33
19	CAG	1.00	0.01	1.00	-0.57	0.56	-0.07	-0.53	0.22	-0.36	-0.40	0.60	-0.04
20	CAT	1.00	0.68	1.00	0.66	1.00	1.00	0.58	1.00	0.45	-0.25	1.00	1.00
21	CCA	1.00	0.68	1.00	0.32	1.00	0.33	0.72	1.00	-0.35	-0.53	0.46	0.64
22	CCC	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.88	1.00	1.00	0.73
23	CCG	1.00	-0.58	1.00	-0.45	1.00	0.76	-0.69	0.76	-0.38	-0.51	0.81	0.17
24	CCT	1.00	0.23	1.00	1.00	1.00	1.00	0.66	0.18	0.13	-0.31	0.14	0.78
25	CGA	1.00	1.00	1.00	1.00	1.00	1.00	0.72	1.00	1.00	0.47	1.00	1.00
26	CGC	1.00	0.28	1.00	-0.34	1.00	0.79	-0.02	0.79	-0.05	-0.13	0.63	0.22
27	CGG	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
28	CGT	1.00	-0.34	1.00	-0.65	1.00	0.33	-0.73	0.09	-0.49	-0.68	-0.19	0.28
29	CTA	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.47	1.00	0.68
30	CTC	1.00	1.00	1.00	0.79	1.00	0.37	0.87	0.37	0.08	-0.66	0.31	0.45
31	CTG	1.00	-0.40	1.00	-0.70	1.00	-0.05	-0.69	0.47	-0.52	-0.47	0.32	-0.07
32	CTT	1.00	1.00	1.00	1.00	1.00	1.00	0.73	1.00	0.61	-0.41	-0.28	0.67
33	GAA	0.83	0.51	1.00	-0.38	1.00	0.93	-0.47	0.66	-0.25	-0.57	-0.40	0.08
34	GAC	1.00	-0.37	1.00	-0.72	1.00	-0.15	-0.65	0.32	-0.54	-0.66	-0.20	0.30
35	GAG	1.00	-0.25	1.00	-0.56	1.00	0.85	-0.47	0.70	0.97	1.00	0.93	1.00
36	GAT	1.00	0.48	1.00	0.50	1.00	0.90	-0.07	0.90	0.44	-0.28	0.71	0.73
37	GCA	1.00	0.13	1.00	-0.62	1.00	0.40	-0.58	1.00	-0.37	-0.42	0.10	0.70
38	GCC	1.00	0.63	1.00	0.67	1.00	1.00	0.41	1.00	0.54	-0.05	0.95	0.77
39	GCG	1.00	0.34	1.00	-0.37	1.00	0.52	-0.48	0.52	0.52	0.62	0.92	0.77
40	GCT	0.33	-0.50	1.00	-0.69	1.00	1.00	-0.69	0.20	-0.74	-0.86	-0.27	-0.38
41	GGA	1.00	1.00	1.00	0.65	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.90
42	GGC	1.00	0.29	1.00	-0.39	1.00	0.13	-0.29	0.49	-0.38	-0.62	0.45	0.29
43	GGG	1.00	1.00	1.00	1.00	1.00	1.00	0.93	1.00	0.94	1.00	0.88	0.86
44	GGT	1.00	0.10	1.00	-0.74	1.00	0.85	-0.72	0.24	-0.44	-0.54	0.51	0.43
45	GTA	1.00	-0.25	1.00	-0.76	1.00	0.66	-0.75	0.32	-0.61	-0.52	-0.06	0.44
46	GTC	1.00	1.00	1.00	0.60	1.00	1.00	0.75	1.00	0.76	0.33	0.92	0.92
47	GTG	1.00	0.83	1.00	0.12	1.00	0.72	-0.10	1.00	0.80	0.73	1.00	0.84

48	GTT	0.49	-0.37	1.00	-0.69	1.00	0.00	-0.66	0.80	-0.65	-0.77	-0.01	-0.41
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.26	-0.38	1.00	-0.70	1.00	-0.31	-0.65	0.26	-0.45	-0.61	-0.01	0.00
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	1.00	0.91	1.00	0.35	1.00	0.17	0.19	0.72	0.41	0.10	0.45	0.64
53	TCA	1.00	1.00	1.00	1.00	1.00	1.00	0.87	1.00	0.61	0.74	1.00	1.00
54	TCC	1.00	0.26	1.00	-0.76	1.00	0.50	-0.64	1.00	0.05	-0.60	-0.39	0.50
55	TCG	1.00	1.00	1.00	1.00	1.00	1.00	0.09	1.00	1.00	1.00	1.00	1.00
56	TCT	1.00	-0.22	1.00	-0.72	1.00	1.00	-0.81	0.47	-0.76	-0.86	-0.48	-0.40
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	1.00	0.26	1.00	-0.75	1.00	-0.19	-0.61	1.00	-0.36	-0.41	0.42	1.00
59	TGG	1.00	0.17	1.00	-0.43	1.00	0.40	-0.43	1.00	-0.26	-0.35	0.77	0.32
60	TGT	1.00	1.00	1.00	1.00	1.00	1.00	0.36	-0.36	0.35	-0.65	0.27	0.37
61	TTA	1.00	0.84	1.00	0.83	1.00	1.00	1.00	1.00	1.00	0.70	1.00	0.82
62	TTC	1.00	-0.45	1.00	-0.75	1.00	-0.62	-0.73	-0.35	-0.40	-0.64	-0.09	0.02
63	TTG	1.00	0.84	1.00	1.00	1.00	1.00	0.78	0.48	0.94	0.55	0.86	0.91
64	TTT	1.00	1.00	1.00	0.80	1.00	1.00	0.94	1.00	0.23	-0.05	0.67	0.82
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
		25	26	27	28	29	30	31	32	33	34	35	36

Table C.6 continued

		37	38	39	40	41	42	43	44	45	46	47	48
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
1	AAA	-0.28	0.55	-0.19	-0.59	1.00	-0.35	0.79	-0.41	-0.36	0.58	-0.03	-0.51
2	AAC	-0.49	-0.44	0.30	-0.56	1.00	-0.43	1.00	-0.61	-0.69	0.33	-0.07	-0.59
3	AAG	0.82	1.00	0.84	0.40	1.00	0.68	1.00	0.62	0.64	0.75	0.93	0.79
4	AAT	0.61	0.92	0.66	0.11	1.00	0.62	1.00	0.59	0.85	1.00	0.94	0.48
5	ACA	0.75	0.61	1.00	0.34	1.00	1.00	1.00	0.47	0.59	1.00	1.00	0.75
6	ACC	-0.24	0.66	0.48	-0.59	0.75	0.35	0.91	-0.65	-0.70	0.91	0.50	-0.73
7	ACG	0.76	0.91	0.86	0.84	1.00	0.95	1.00	0.94	0.80	1.00	0.92	0.88
8	ACT	-0.80	-0.45	-0.33	-0.84	1.00	-0.68	1.00	-0.72	-0.61	0.77	0.60	-0.67
9	AGA	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
10	AGC	0.59	0.47	0.51	0.64	1.00	0.45	1.00	-0.06	0.79	0.54	0.38	-0.22
11	AGG	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
12	AGT	0.75	0.80	0.55	1.00	1.00	0.87	1.00	0.85	1.00	1.00	1.00	1.00
13	ATA	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
14	ATC	-0.18	0.01	-0.20	-0.79	0.82	-0.28	0.87	-0.74	-0.34	-0.13	0.19	-0.78
15	ATG	0.08	0.70	0.05	-0.59	1.00	-0.08	0.90	-0.38	-0.28	0.51	0.52	-0.48

16	ATT	0.40	0.50	0.84	-0.25	1.00	0.44	1.00	0.52	0.82	0.62	1.00	0.09
17	CAA	0.85	0.65	0.74	0.22	1.00	0.39	1.00	0.51	0.73	1.00	0.78	0.52
18	CAC	0.25	-0.36	-0.44	-0.75	1.00	-0.41	1.00	-0.72	-0.75	-0.11	0.83	-0.80
19	CAG	-0.28	0.76	-0.05	-0.74	1.00	-0.36	1.00	-0.50	-0.50	0.30	0.30	-0.62
20	CAT	0.62	0.71	0.78	0.26	1.00	0.65	1.00	0.49	1.00	1.00	0.88	0.82
21	CCA	0.29	0.82	0.44	-0.36	0.44	0.41	1.00	-0.19	-0.44	1.00	1.00	-0.05
22	CCC	0.64	1.00	1.00	0.53	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.68
23	CCG	-0.58	0.80	0.45	-0.68	0.80	-0.47	0.43	-0.36	-0.73	0.55	0.58	-0.68
24	CCT	-0.41	0.78	-0.34	-0.46	1.00	-0.37	1.00	0.58	0.57	1.00	1.00	0.75
25	CGA	1.00	1.00	1.00	0.30	1.00	1.00	1.00	1.00	0.25	1.00	1.00	1.00
26	CGC	-0.20	0.68	0.85	-0.57	1.00	0.10	0.87	-0.17	-0.66	0.83	0.42	-0.63
27	CGG	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
28	CGT	-0.37	0.45	-0.34	-0.79	1.00	-0.41	0.86	-0.69	-0.58	0.82	0.54	-0.53
29	CTA	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.37
30	CTC	0.64	0.72	0.57	1.00	1.00	-0.10	1.00	-0.53	0.27	1.00	1.00	0.35
31	CTG	-0.54	0.71	-0.23	-0.79	1.00	-0.37	0.87	-0.62	-0.70	0.19	0.02	-0.68
32	CTT	1.00	0.57	0.78	-0.17	1.00	-0.26	0.70	0.60	1.00	1.00	1.00	0.78
33	GAA	-0.34	0.40	-0.27	-0.65	0.93	-0.39	0.79	-0.52	-0.20	0.37	-0.06	-0.63
34	GAC	-0.54	0.43	-0.08	-0.73	1.00	-0.52	0.79	-0.66	-0.75	0.64	-0.02	-0.73
35	GAG	0.93	1.00	1.00	0.91	1.00	0.96	1.00	0.74	1.00	0.83	0.95	0.93
36	GAT	0.06	0.75	0.63	-0.35	0.91	0.54	1.00	0.17	0.51	0.78	0.67	0.46
37	GCA	-0.31	0.73	0.23	-0.68	1.00	-0.29	0.74	-0.51	-0.70	0.61	0.38	-0.32
38	GCC	0.25	0.96	0.97	-0.41	1.00	0.96	0.90	-0.05	0.36	0.92	0.87	-0.21
39	GCG	0.19	0.94	0.73	0.09	1.00	0.36	0.92	-0.04	-0.49	0.71	0.70	-0.17
40	GCT	-0.75	0.15	-0.43	-0.87	1.00	-0.73	0.65	-0.64	-0.65	0.49	0.25	-0.79
41	GGA	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
42	GGC	-0.39	0.88	-0.01	-0.58	1.00	-0.32	1.00	-0.53	-0.61	0.67	0.03	-0.65
43	GGG	0.86	1.00	0.91	0.81	1.00	1.00	1.00	0.91	1.00	1.00	1.00	0.87
44	GGT	-0.44	0.55	-0.29	-0.72	1.00	0.18	1.00	-0.68	-0.37	0.87	0.46	-0.57
45	GTA	-0.41	0.23	-0.25	-0.46	1.00	0.53	1.00	-0.65	-0.54	1.00	0.55	-0.49
46	GTC	0.80	0.92	0.76	-0.24	0.75	0.40	1.00	-0.34	0.38	1.00	0.74	0.27
47	GTG	0.65	0.91	0.83	0.39	1.00	0.84	1.00	-0.11	0.19	0.74	0.66	-0.51
48	GTT	-0.46	0.09	-0.12	-0.88	1.00	-0.47	1.00	-0.70	-0.36	0.27	0.25	-0.76
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.56	0.53	0.28	-0.67	1.00	-0.56	1.00	-0.64	-0.35	-0.08	0.47	-0.53
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.19	0.73	0.38	-0.40	1.00	0.74	1.00	0.31	0.61	0.32	0.68	-0.49
53	TCA	0.69	1.00	0.81	0.17	1.00	1.00	0.58	0.81	1.00	1.00	0.80	1.00
54	TCC	-0.77	0.80	-0.17	-0.79	0.52	-0.44	1.00	-0.79	-0.83	-0.11	-0.14	-0.75

55	TCG	1.00	1.00	1.00	0.35	1.00	1.00	1.00	0.85	1.00	0.73	1.00	0.77
56	TCT	-0.78	-0.19	-0.62	-0.83	1.00	-0.52	1.00	-0.84	-0.87	-0.14	0.32	-0.74
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	-0.67	0.47	0.40	0.55	1.00	0.41	1.00	-0.60	-0.44	0.36	0.25	-0.07
59	TGG	-0.46	0.80	0.07	-0.28	1.00	-0.26	1.00	-0.26	-0.28	0.67	0.42	-0.48
60	TGT	0.57	0.67	-0.21	-0.41	0.30	0.07	1.00	-0.25	-0.70	1.00	0.06	0.33
61	TTA	0.71	0.77	1.00	0.42	1.00	0.91	0.76	0.68	0.41	1.00	1.00	0.82
62	TTC	-0.37	0.11	0.19	-0.63	0.18	-0.19	0.71	-0.72	-0.70	0.72	0.43	-0.71
63	TTG	1.00	0.88	0.91	0.80	1.00	1.00	1.00	0.89	0.70	1.00	1.00	0.82
64	TTT	0.57	0.54	0.44	-0.55	1.00	0.80	0.89	0.23	0.26	0.79	0.69	0.12
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
		37	38	39	40	41	42	43	44	45	46	47	48

Table C.6 continued

		49	50	51	52	53	54	55	56	57	58	59	60
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
1	AAA	0.00	-0.31	0.00	0.21	1.00	-0.35	0.66	-0.65	0.00	-0.06	0.02	0.20
2	AAC	0.00	-0.71	0.00	0.40	1.00	-0.74	0.81	-0.71	0.00	-0.62	-0.45	0.18
3	AAG	0.00	0.14	0.00	0.35	1.00	0.21	0.24	-0.81	0.00	-0.29	-0.07	0.11
4	AAT	0.00	1.00	0.00	1.00	1.00	0.51	1.00	1.00	0.00	1.00	1.00	1.00
5	ACA	0.00	1.00	0.00	1.00	1.00	1.00	1.00	0.31	0.00	1.00	0.40	1.00
6	ACC	0.00	-0.60	0.00	0.38	1.00	-0.15	0.81	-0.69	0.00	-0.27	-0.53	-0.61
7	ACG	0.00	1.00	0.00	0.85	1.00	1.00	1.00	0.67	0.00	1.00	1.00	1.00
8	ACT	0.00	-0.77	0.00	0.53	0.36	-0.88	0.00	-0.88	0.00	-0.45	1.00	1.00
9	AGA	0.00	1.00	0.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00
10	AGC	0.00	-0.40	0.00	0.49	1.00	-0.54	1.00	-0.47	0.00	-0.28	0.70	0.42
11	AGG	0.00	1.00	0.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00
12	AGT	0.00	0.69	0.00	1.00	1.00	0.32	1.00	0.30	0.00	1.00	1.00	1.00
13	ATA	0.00	1.00	0.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00
14	ATC	0.00	-0.69	0.00	0.28	1.00	-0.84	0.84	-0.64	0.00	-0.41	-0.58	-0.53
15	ATG	0.00	-0.43	0.00	0.56	1.00	-0.60	0.80	-0.42	0.00	0.40	0.00	-0.33
16	ATT	0.00	0.30	0.00	0.70	1.00	0.03	0.87	-0.53	0.00	0.53	1.00	0.70
17	CAA	0.00	0.40	0.00	0.89	1.00	0.54	1.00	1.00	0.00	1.00	0.64	1.00
18	CAC	0.00	-0.77	0.00	0.61	-0.27	-0.40	1.00	-0.83	0.00	-0.60	-0.57	-0.05
19	CAG	0.00	-0.53	0.00	0.23	1.00	-0.31	0.77	-0.80	0.00	-0.51	-0.25	0.14
20	CAT	0.00	1.00	0.00	0.71	1.00	1.00	1.00	1.00	0.00	0.37	1.00	1.00
21	CCA	0.00	0.34	0.00	0.75	1.00	-0.22	1.00	0.34	0.00	-0.74	0.47	1.00
22	CCC	0.00	1.00	0.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00

23	CCG	0.00	-0.44	0.00	0.37	0.44	-0.52	1.00	-0.78	0.00	0.32	-0.41	-0.41
24	CCT	0.00	-0.77	0.00	0.70	0.05	-0.68	1.00	-0.58	0.00	1.00	1.00	1.00
25	CGA	0.00	1.00	0.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00
26	CGC	0.00	0.01	0.00	0.50	1.00	-0.11	1.00	-0.14	0.00	0.36	-0.52	1.00
27	CGG	0.00	1.00	0.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00
28	CGT	0.00	-0.64	0.00	-0.16	0.13	-0.75	0.77	-0.87	0.00	-0.70	0.56	0.15
29	CTA	0.00	1.00	0.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00
30	CTC	0.00	-0.31	0.00	1.00	1.00	-0.50	1.00	-0.36	0.00	1.00	1.00	1.00
31	CTG	0.00	-0.67	0.00	0.24	0.74	-0.60	0.70	-0.80	0.00	-0.48	-0.44	-0.42
32	CTT	0.00	0.02	0.00	1.00	0.37	-0.35	1.00	-0.52	0.00	-0.25	1.00	1.00
33	GAA	0.00	-0.54	0.00	0.64	1.00	-0.56	0.77	-0.57	0.00	0.40	0.28	-0.34
34	GAC	0.00	-0.66	0.00	0.37	0.71	-0.80	0.54	-0.49	0.00	-0.62	-0.61	0.40
35	GAG	0.00	-0.07	0.00	0.65	1.00	-0.53	1.00	-0.60	0.00	-0.25	-0.38	0.44
36	GAT	0.00	-0.18	0.00	0.83	0.83	-0.41	1.00	-0.15	0.00	0.43	0.94	0.46
37	GCA	0.00	-0.42	0.00	0.68	0.69	-0.43	0.76	-0.70	0.00	0.50	-0.62	-0.47
38	GCC	0.00	0.44	0.00	0.08	1.00	0.42	1.00	-0.38	0.00	0.22	-0.02	0.02
39	GCG	0.00	0.41	0.00	1.00	1.00	0.11	0.72	-0.61	0.00	0.41	0.69	-0.10
40	GCT	0.00	-0.83	0.00	0.00	1.00	-0.81	0.37	-0.89	0.00	-0.62	0.65	1.00
41	GGA	0.00	0.73	0.00	1.00	0.46	1.00	1.00	1.00	0.00	1.00	1.00	1.00
42	GGC	0.00	-0.36	0.00	0.57	1.00	-0.33	1.00	0.40	0.00	0.32	-0.50	-0.07
43	GGG	0.00	1.00	0.00	1.00	1.00	1.00	1.00	0.36	0.00	1.00	1.00	1.00
44	GGT	0.00	-0.68	0.00	0.16	0.15	-0.79	0.87	-0.87	0.00	-0.62	0.44	-0.03
45	GTA	0.00	-0.40	0.00	0.64	1.00	-0.82	1.00	-0.84	0.00	-0.46	-0.71	-0.68
46	GTC	0.00	-0.02	0.00	0.87	1.00	0.72	1.00	0.71	0.00	1.00	0.65	1.00
47	GTG	0.00	0.11	0.00	0.77	1.00	0.35	1.00	0.33	0.00	-0.02	0.17	1.00
48	GTT	0.00	-0.71	0.00	-0.16	1.00	-0.81	1.00	-0.85	0.00	-0.61	0.70	0.54
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.00	-0.78	0.00	0.61	1.00	-0.76	0.67	-0.77	0.00	-0.71	-0.57	1.00
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.00	0.81	0.00	1.00	1.00	0.22	1.00	1.00	0.00	1.00	1.00	0.34
53	TCA	0.00	0.24	0.00	1.00	1.00	1.00	1.00	0.14	0.00	1.00	0.32	1.00
54	TCC	0.00	-0.68	0.00	0.53	1.00	-0.63	0.35	-0.52	0.00	-0.71	-0.80	-0.54
55	TCG	0.00	1.00	0.00	1.00	1.00	1.00	1.00	-0.26	0.00	1.00	1.00	1.00
56	TCT	0.00	-0.82	0.00	0.03	0.14	-0.84	-0.63	-0.88	0.00	-0.44	0.43	-0.55
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.00	-0.76	0.00	1.00	1.00	-0.58	0.23	-0.76	0.00	-0.54	-0.44	-0.26
59	TGG	0.00	-0.41	0.00	0.52	1.00	-0.50	1.00	-0.71	0.00	1.00	0.00	-0.56
60	TGT	0.00	1.00	0.00	1.00	1.00	-0.01	1.00	-0.04	0.00	1.00	1.00	1.00
61	TTA	0.00	0.61	0.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00

62	TTC	0.00	-0.74	0.00	0.11	1.00	-0.79	0.72	-0.86	0.00	-0.69	-0.57	-0.15
63	TTG	0.00	1.00	0.00	1.00	1.00	1.00	1.00	0.15	0.00	1.00	0.17	1.00
64	TTT	0.00	0.82	0.00	0.87	1.00	0.56	1.00	1.00	0.00	1.00	1.00	1.00
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
		49	50	51	52	53	54	55	56	57	58	59	60

Table C.6 continued

		61	62	63	64
		TTA	TTC	TTG	TTT
1	AAA	0.87	-0.43	0.87	0.69
2	AAC	1.00	-0.72	0.83	0.57
3	AAG	0.78	-0.53	0.78	0.42
4	AAT	0.80	1.00	1.00	0.93
5	ACA	1.00	1.00	1.00	1.00
6	ACC	0.84	-0.59	1.00	0.28
7	ACG	0.75	0.43	0.74	0.79
8	ACT	1.00	-0.64	0.58	0.31
9	AGA	1.00	1.00	1.00	1.00
10	AGC	1.00	-0.48	0.56	0.88
11	AGG	1.00	1.00	1.00	1.00
12	AGT	1.00	0.40	0.59	1.00
13	ATA	1.00	1.00	1.00	1.00
14	ATC	1.00	-0.69	1.00	0.29
15	ATG	0.76	-0.52	0.76	0.81
16	ATT	1.00	0.05	0.85	0.88
17	CAA	1.00	1.00	1.00	0.88
18	CAC	1.00	-0.77	0.56	0.49
19	CAG	1.00	-0.66	0.75	0.58
20	CAT	1.00	0.74	0.67	1.00
21	CCA	1.00	1.00	1.00	1.00
22	CCC	1.00	1.00	1.00	1.00
23	CCG	0.80	-0.70	0.41	0.40
24	CCT	1.00	0.66	1.00	0.50
25	CGA	1.00	1.00	1.00	1.00
26	CGC	1.00	-0.48	1.00	0.36
27	CGG	1.00	1.00	1.00	1.00
28	CGT	1.00	-0.61	1.00	0.51
29	CTA	1.00	1.00	1.00	1.00

30	CTC	1.00	1.00	1.00	0.73
31	CTG	0.57	-0.72	0.46	0.44
32	CTT	1.00	0.27	1.00	1.00
33	GAA	0.95	-0.35	0.95	0.76
34	GAC	0.86	-0.74	0.58	0.40
35	GAG	0.88	-0.63	1.00	0.46
36	GAT	0.84	0.22	0.84	0.87
37	GCA	1.00	-0.70	0.83	0.29
38	GCC	1.00	-0.06	1.00	0.84
39	GCG	1.00	-0.44	1.00	0.76
40	GCT	0.78	-0.44	1.00	0.73
41	GGA	1.00	1.00	1.00	1.00
42	GGC	1.00	-0.60	0.90	0.33
43	GGG	1.00	0.84	1.00	1.00
44	GGT	0.76	-0.48	0.88	0.36
45	GTA	1.00	-0.63	0.45	0.00
46	GTC	1.00	-0.43	1.00	0.76
47	GTG	1.00	-0.55	0.77	0.72
48	GTT	1.00	-0.06	0.84	0.90
49	TAA	0.00	0.00	0.00	0.00
50	TAC	1.00	-0.75	1.00	0.42
51	TAG	0.00	0.00	0.00	0.00
52	TAT	1.00	0.65	1.00	0.91
53	TCA	1.00	1.00	1.00	1.00
54	TCC	0.59	-0.79	0.59	0.33
55	TCG	1.00	0.42	1.00	0.78
56	TCT	0.58	-0.73	0.57	0.30
57	TGA	0.00	0.00	0.00	0.00
58	TGC	1.00	0.16	1.00	-0.47
59	TGG	0.51	-0.45	1.00	0.61
60	TGT	1.00	-0.05	1.00	1.00
61	TTA	1.00	1.00	1.00	1.00
62	TTC	1.00	-0.76	1.00	0.16
63	TTG	1.00	0.70	0.58	1.00
64	TTT	1.00	1.00	1.00	0.92
		TTA	TTC	TTG	TTT
		61	62	63	64

Table C.7: CPW matrix *Bacillus amyloliquefaciens* full genome (left codon indicated in column 2, right codon indicated in row 2). Host cell: *B. amyloliqueaciens*; Sequence data: full *B. amyloliqueaciens* genome.

		1	2	3	4	5	6	7	8	9	10	11	12
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
1	AAA	-0.05	-0.25	-0.09	0.00	-0.34	-0.02	-0.08	0.42	-0.33	-0.40	-0.31	-0.19
2	AAC	0.05	-0.11	0.11	-0.07	0.21	0.18	0.08	0.18	-0.48	-0.61	-0.54	-0.58
3	AAG	0.12	0.35	0.23	0.38	0.32	0.34	0.20	0.37	0.18	0.20	0.04	0.21
4	AAT	-0.12	0.07	0.10	0.12	-0.23	0.05	-0.15	0.00	0.53	0.79	0.64	0.32
5	ACA	-0.43	-0.44	-0.32	-0.32	-0.20	-0.29	0.02	-0.27	-0.63	-0.38	-0.68	-0.44
6	ACC	0.60	0.33	0.56	-0.01	0.50	0.32	0.64	-0.08	-0.05	0.34	0.45	0.31
7	ACG	0.05	0.24	-0.10	0.11	-0.16	-0.09	-0.28	-0.16	-0.46	0.00	-0.37	0.27
8	ACT	0.48	0.67	0.64	0.51	0.44	0.50	0.71	0.08	0.46	0.90	0.22	0.53
9	AGA	-0.60	-0.52	-0.64	-0.44	-0.42	-0.32	-0.41	-0.29	-0.32	-0.48	-0.38	-0.35
10	AGC	-0.01	0.19	0.08	0.01	0.01	-0.14	-0.10	-0.08	-0.38	-0.30	-0.60	-0.25
11	AGG	-0.06	0.17	-0.24	-0.08	-0.09	0.29	-0.11	0.09	0.23	0.19	0.13	-0.28
12	AGT	-0.08	0.61	0.16	0.12	0.26	0.48	0.32	0.24	0.60	0.89	0.56	0.62
13	ATA	-0.54	-0.26	-0.35	-0.19	-0.27	0.05	0.19	-0.15	-0.45	0.23	-0.40	-0.16
14	ATC	0.24	-0.06	0.16	-0.15	0.16	-0.20	0.25	-0.04	-0.60	-0.45	-0.59	-0.44
15	ATG	0.04	0.06	-0.07	-0.05	0.08	0.05	-0.08	0.04	-0.46	-0.19	-0.37	-0.17
16	ATT	-0.02	0.25	0.18	0.16	-0.20	0.01	-0.05	0.01	0.63	0.91	0.74	0.70
17	CAA	-0.39	-0.46	-0.41	-0.29	0.15	-0.28	-0.02	0.19	-0.22	-0.43	-0.26	-0.23
18	CAC	0.34	0.06	0.17	-0.05	0.29	-0.02	0.27	0.31	0.02	-0.46	-0.21	-0.33
19	CAG	0.48	0.39	0.33	0.43	0.11	0.07	-0.08	0.05	0.67	0.53	0.54	0.54
20	CAT	-0.20	0.02	-0.13	-0.01	-0.22	-0.06	-0.15	-0.02	0.79	0.82	0.76	0.61
21	CCA	-0.26	-0.45	-0.25	-0.20	-0.29	-0.42	0.14	-0.66	-0.47	-0.44	-0.53	-0.47
22	CCC	0.72	0.58	0.53	0.35	0.65	0.27	0.53	0.36	0.61	0.67	0.75	0.50
23	CCG	-0.14	-0.13	-0.29	-0.20	-0.14	-0.18	-0.13	-0.43	0.02	0.05	0.37	0.18
24	CCT	0.30	0.42	0.46	0.56	0.39	0.60	0.74	-0.04	0.75	0.77	0.71	0.58
25	CGA	-0.18	-0.22	-0.11	-0.15	0.04	-0.14	0.01	-0.32	0.48	-0.55	-0.33	-0.56
26	CGC	0.56	0.00	0.00	0.26	0.48	-0.06	-0.18	0.45	0.72	-0.07	0.43	0.22
27	CGG	0.08	0.17	0.19	-0.09	0.24	0.38	-0.19	0.01	0.70	0.48	0.66	0.60
28	CGT	0.42	0.71	0.48	0.48	0.37	0.53	0.29	-0.03	0.97	0.82	0.84	0.74
29	CTA	-0.19	0.20	-0.21	-0.03	0.04	0.07	0.48	-0.36	-0.48	0.14	-0.52	-0.41
30	CTC	0.63	0.54	0.39	0.29	0.51	0.13	0.40	0.23	-0.37	-0.14	-0.34	-0.30
31	CTG	-0.15	-0.18	-0.30	-0.15	-0.24	-0.26	-0.24	-0.29	0.01	0.28	0.02	0.33
32	CTT	0.64	0.59	0.75	0.59	0.49	0.42	0.70	0.16	0.70	0.87	0.56	0.64
33	GAA	-0.16	-0.24	-0.03	0.00	-0.27	-0.18	-0.07	0.34	-0.05	-0.35	0.17	-0.22

34	GAC	0.13	-0.07	-0.17	-0.09	0.32	0.00	0.04	0.18	-0.36	-0.58	-0.49	-0.51
35	GAG	0.29	0.29	0.21	0.30	0.39	0.44	0.04	0.45	0.39	0.21	0.46	0.12
36	GAT	-0.09	0.09	0.16	0.06	-0.13	0.10	-0.17	0.01	0.73	0.83	0.72	0.66
37	GCA	-0.48	-0.50	-0.48	-0.37	-0.34	-0.43	-0.06	-0.53	-0.25	-0.51	-0.41	-0.50
38	GCC	0.25	0.27	0.27	-0.15	0.32	0.14	0.50	0.06	0.11	0.38	0.49	0.17
39	GCG	0.14	-0.08	-0.21	0.21	-0.13	-0.02	-0.31	-0.08	0.30	0.06	0.33	0.45
40	GCT	0.40	0.55	0.61	0.55	0.32	0.45	0.63	0.33	0.89	0.91	0.88	0.84
41	GGA	-0.46	-0.41	-0.25	-0.38	-0.33	-0.21	-0.37	-0.15	-0.35	-0.48	-0.26	-0.30
42	GGC	0.43	0.07	-0.05	0.15	0.19	-0.02	-0.09	0.09	-0.13	-0.31	-0.23	-0.18
43	GGG	-0.04	0.37	0.20	0.00	0.22	0.65	0.24	0.27	0.23	0.37	0.44	0.34
44	GGT	0.23	0.64	0.50	0.40	0.22	0.60	0.13	0.19	0.85	0.92	0.75	0.44
45	GTA	-0.45	-0.39	-0.35	-0.25	-0.19	-0.18	-0.22	-0.22	-0.34	0.04	-0.37	-0.18
46	GTC	0.21	0.06	0.38	-0.16	0.13	-0.18	0.11	-0.07	-0.44	-0.39	-0.31	-0.45
47	GTG	-0.17	0.00	-0.28	-0.10	-0.10	-0.01	-0.32	0.19	0.20	0.31	0.22	0.49
48	GTT	0.40	0.64	0.52	0.40	0.34	0.40	0.48	0.23	0.67	0.94	0.71	0.65
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.12	-0.16	-0.06	-0.17	0.13	0.05	-0.14	0.14	-0.59	-0.55	-0.61	-0.57
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.14	0.14	0.23	0.14	-0.15	0.28	-0.03	0.08	0.50	0.82	0.59	0.70
53	TCA	-0.38	-0.39	-0.19	-0.39	-0.28	-0.36	0.06	-0.58	-0.50	-0.30	-0.42	-0.26
54	TCC	0.29	0.35	0.46	-0.18	0.25	0.11	0.54	-0.33	-0.44	0.35	0.37	-0.08
55	TCG	0.35	-0.06	-0.14	0.22	0.18	-0.26	-0.31	-0.24	0.09	0.00	0.16	0.41
56	TCT	-0.04	0.40	0.33	0.24	0.20	0.49	0.63	-0.01	0.76	0.91	0.75	0.74
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.21	-0.16	-0.17	0.09	0.27	-0.15	-0.10	0.38	0.10	-0.27	-0.39	-0.22
59	TGG	0.05	0.18	-0.10	-0.15	0.16	0.21	-0.21	0.15	-0.32	-0.09	0.01	-0.27
60	TGT	-0.18	0.46	0.00	-0.22	-0.11	0.46	-0.23	0.00	0.77	0.91	0.74	0.59
61	TTA	-0.47	-0.45	-0.45	-0.43	-0.25	-0.32	-0.19	-0.34	-0.52	-0.18	-0.30	-0.33
62	TTC	0.19	-0.01	0.06	0.04	0.25	-0.20	0.20	-0.25	-0.62	-0.45	-0.63	-0.41
63	TTG	-0.25	-0.09	-0.16	-0.28	-0.22	-0.19	-0.13	-0.35	-0.27	0.35	-0.20	0.13
64	TTT	-0.18	0.06	0.13	-0.08	-0.15	-0.06	0.06	-0.04	0.58	0.93	0.67	0.66
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
		1	2	3	4	5	6	7	8	9	10	11	12

Table C.7 continued

		13	14	15	16	17	18	19	20	21	22	23	24
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
1	AAA	-0.41	-0.20	-0.08	0.26	-0.09	0.32	0.26	0.20	0.18	0.45	0.26	0.34

2	AAC	0.24	0.09	0.09	0.15	0.17	0.25	0.32	0.10	0.19	0.40	0.24	0.13
3	AAG	0.14	0.18	0.20	0.20	0.00	-0.28	-0.30	-0.40	-0.30	-0.28	-0.43	-0.37
4	AAT	-0.31	-0.08	-0.08	-0.08	-0.34	-0.06	-0.07	-0.18	-0.11	-0.12	-0.22	-0.18
5	ACA	-0.12	0.34	0.06	0.35	-0.15	0.14	0.05	0.17	0.23	0.11	0.08	0.07
6	ACC	-0.09	-0.04	0.43	-0.39	0.15	0.24	0.30	-0.10	0.22	0.38	0.58	0.29
7	ACG	-0.01	-0.13	-0.30	-0.21	0.25	-0.13	-0.12	0.17	0.03	-0.23	-0.27	-0.16
8	ACT	0.03	0.74	0.57	0.46	-0.53	-0.29	0.02	-0.41	-0.03	0.05	0.14	-0.42
9	AGA	-0.40	-0.21	-0.37	-0.15	-0.10	0.47	-0.27	0.35	0.38	0.49	0.40	0.29
10	AGC	0.12	-0.01	-0.12	-0.11	-0.03	0.10	-0.12	-0.16	0.50	0.16	0.11	0.44
11	AGG	-0.35	0.37	0.01	-0.11	0.00	-0.24	-0.37	-0.25	-0.13	-0.31	-0.24	0.21
12	AGT	-0.21	0.23	-0.14	-0.06	-0.25	0.38	-0.06	-0.26	-0.29	-0.01	-0.03	-0.07
13	ATA	-0.24	0.59	0.42	0.61	-0.37	-0.04	-0.13	-0.12	-0.20	0.12	0.03	-0.20
14	ATC	0.15	-0.11	-0.03	-0.16	0.49	0.49	0.50	0.36	0.38	0.41	0.39	0.39
15	ATG	0.13	0.07	0.00	-0.10	0.43	-0.15	-0.22	0.14	0.49	0.13	-0.09	-0.04
16	ATT	-0.09	0.02	-0.08	-0.01	-0.36	-0.23	-0.25	-0.33	-0.19	-0.35	-0.30	-0.23
17	CAA	-0.31	-0.10	-0.21	0.00	0.55	0.69	0.70	0.72	0.53	0.60	0.82	0.54
18	CAC	0.20	0.15	0.24	0.19	0.42	0.34	0.43	0.15	0.18	0.39	0.28	0.24
19	CAG	0.22	0.00	0.17	0.10	0.07	-0.37	-0.42	-0.27	-0.18	-0.30	-0.32	-0.37
20	CAT	-0.17	-0.05	-0.15	-0.16	-0.20	-0.19	-0.27	-0.11	-0.24	-0.17	-0.17	-0.16
21	CCA	0.00	0.27	0.04	0.39	0.19	0.04	0.36	0.38	-0.39	0.20	0.54	-0.04
22	CCC	0.30	0.50	0.53	0.30	0.47	0.40	0.62	0.23	-0.28	0.53	0.69	0.27
23	CCG	0.17	-0.25	-0.26	-0.32	-0.18	-0.23	-0.12	0.07	-0.25	-0.39	-0.13	-0.07
24	CCT	0.24	0.65	0.60	0.43	-0.22	-0.01	0.02	-0.12	0.21	-0.06	0.33	-0.15
25	CGA	-0.50	-0.20	-0.04	0.31	0.12	-0.38	0.09	0.01	-0.45	0.31	0.41	0.02
26	CGC	0.31	0.01	0.30	0.47	0.56	0.33	0.39	0.40	0.07	0.22	0.33	0.55
27	CGG	-0.33	-0.31	-0.30	-0.27	-0.23	-0.43	-0.39	-0.27	-0.48	-0.48	-0.37	-0.40
28	CGT	0.12	0.31	0.42	0.38	-0.02	-0.23	-0.09	0.05	-0.40	-0.24	-0.07	-0.15
29	CTA	-0.38	0.32	0.38	0.47	-0.29	-0.01	0.66	-0.21	-0.57	-0.09	0.37	-0.44
30	CTC	0.28	0.20	0.39	0.11	0.60	0.67	0.68	0.38	0.49	0.53	0.56	0.31
31	CTG	0.27	-0.29	-0.30	-0.17	-0.25	-0.27	-0.14	-0.01	0.28	-0.34	-0.38	-0.12
32	CTT	0.45	0.55	0.51	0.42	-0.27	-0.36	-0.24	-0.34	-0.03	-0.23	-0.15	-0.40
33	GAA	-0.12	-0.18	-0.09	0.16	0.12	0.34	0.23	0.34	0.26	0.44	0.33	0.38
34	GAC	0.17	-0.04	0.04	0.08	0.31	0.35	0.38	0.23	0.27	0.45	0.28	0.29
35	GAG	0.13	0.05	0.19	0.12	0.10	-0.40	-0.39	-0.39	-0.42	-0.40	-0.40	-0.39
36	GAT	-0.10	0.14	-0.03	-0.16	-0.23	-0.25	-0.22	-0.13	-0.10	0.00	-0.28	-0.12
37	GCA	-0.03	0.11	-0.06	0.21	0.10	0.29	0.19	0.45	-0.03	0.15	0.37	0.34
38	GCC	0.13	-0.02	0.11	-0.25	0.27	0.42	0.52	0.17	0.43	0.39	0.70	0.60
39	GCG	0.19	-0.26	-0.24	-0.10	-0.15	-0.39	-0.28	0.01	-0.30	-0.49	-0.38	-0.08
40	GCT	0.40	0.63	0.60	0.40	-0.33	-0.21	0.11	-0.13	-0.28	0.02	0.18	-0.25

41	GGA	-0.05	-0.08	-0.22	0.00	-0.30	0.16	-0.23	-0.01	0.17	0.51	0.18	0.10
42	GGC	0.21	-0.12	0.07	-0.11	0.44	0.19	0.27	0.07	0.08	0.26	0.23	0.40
43	GGG	-0.05	0.34	0.04	0.05	-0.09	-0.12	-0.35	-0.35	-0.27	-0.27	-0.43	-0.44
44	GGT	0.07	0.26	0.19	-0.04	0.08	0.09	0.09	-0.01	-0.60	-0.18	-0.07	0.12
45	GTA	0.26	0.43	0.26	0.67	0.23	0.14	-0.11	0.17	-0.14	0.56	0.38	0.08
46	GTC	0.11	-0.26	-0.12	-0.37	0.54	0.57	0.66	0.34	0.56	0.61	0.68	0.54
47	GTG	0.24	-0.12	-0.20	0.12	0.18	-0.03	-0.34	-0.04	0.23	-0.25	-0.47	-0.29
48	GTT	0.26	0.29	0.35	0.21	-0.46	-0.35	-0.36	-0.47	-0.21	-0.46	-0.19	-0.43
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.25	0.17	0.11	0.14	0.29	0.29	0.49	0.25	0.48	0.58	0.28	0.37
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.36	0.00	-0.07	0.00	-0.31	-0.06	-0.17	-0.22	-0.02	-0.14	-0.29	-0.05
53	TCA	0.03	0.27	-0.05	0.11	-0.10	0.35	0.23	0.33	-0.04	0.15	0.24	-0.19
54	TCC	0.17	-0.15	-0.02	-0.41	0.28	0.27	0.58	-0.06	0.47	0.43	0.63	0.38
55	TCG	0.15	-0.12	-0.03	0.02	-0.04	-0.21	-0.16	0.05	-0.34	-0.46	-0.41	-0.37
56	TCT	0.08	0.38	0.44	0.12	-0.45	-0.14	0.15	-0.30	-0.38	-0.35	0.03	-0.38
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.07	0.05	0.11	0.38	0.00	-0.09	0.12	0.11	-0.03	0.24	0.02	0.32
59	TGG	-0.15	0.16	0.00	-0.10	0.40	-0.03	-0.21	0.02	0.53	0.15	-0.16	0.18
60	TGT	-0.52	-0.23	-0.17	-0.18	-0.18	0.10	-0.06	-0.13	-0.02	-0.13	-0.14	-0.29
61	TTA	-0.31	-0.18	-0.32	-0.22	0.14	0.50	0.32	0.17	0.28	0.63	0.81	0.46
62	TTC	0.34	0.19	0.23	0.21	0.19	0.24	0.34	0.27	0.16	0.38	0.04	-0.15
63	TTG	0.13	-0.10	0.04	-0.33	0.00	0.13	-0.25	0.24	0.08	0.01	-0.06	0.04
64	TTT	-0.15	-0.16	-0.15	-0.11	-0.31	0.01	-0.05	-0.26	-0.10	-0.17	-0.03	0.07
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
		13	14	15	16	17	18	19	20	21	22	23	24

Table C.7 continued

		25	26	27	28	29	30	31	32	33	34	35	36
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
1	AAA	0.32	0.37	-0.15	0.38	-0.15	0.56	0.31	0.57	-0.16	-0.17	0.08	0.11
2	AAC	0.16	-0.23	-0.23	-0.38	-0.21	0.25	-0.05	0.07	0.32	0.21	0.35	0.24
3	AAG	0.21	-0.16	-0.47	-0.07	-0.08	-0.47	-0.61	-0.59	0.14	0.17	0.36	0.00
4	AAT	0.10	0.54	0.34	0.23	-0.25	-0.01	-0.10	0.12	-0.32	-0.11	-0.02	-0.23
5	ACA	0.45	0.48	0.42	0.10	-0.19	0.40	0.37	0.27	-0.12	-0.03	0.07	0.08
6	ACC	0.27	0.16	0.07	-0.26	0.58	0.44	0.56	0.16	0.17	-0.20	-0.18	-0.11
7	ACG	0.32	-0.16	0.07	0.25	0.19	-0.42	-0.33	-0.28	0.14	0.38	0.28	0.11
8	ACT	0.22	0.46	0.57	-0.19	-0.46	0.38	0.58	-0.23	-0.40	-0.29	-0.32	-0.43

9	AGA	0.62	0.78	0.39	0.64	0.04	0.44	0.27	0.44	-0.27	0.12	-0.19	0.13
10	AGC	-0.02	-0.13	-0.35	-0.24	0.38	0.29	-0.09	0.11	0.35	0.24	0.11	0.24
11	AGG	0.39	0.43	-0.11	0.42	0.03	-0.40	-0.64	-0.52	-0.22	0.28	-0.09	0.05
12	AGT	-0.20	0.72	0.56	0.64	-0.24	-0.13	-0.28	-0.25	-0.56	-0.31	-0.36	-0.53
13	ATA	-0.13	0.30	0.08	-0.02	-0.41	0.22	0.28	0.11	-0.23	-0.02	-0.02	-0.04
14	ATC	0.34	-0.34	-0.14	-0.33	0.35	0.39	0.41	0.44	0.37	0.06	0.15	0.38
15	ATG	0.61	0.10	0.04	0.18	0.28	-0.13	-0.30	-0.17	0.02	0.03	-0.04	-0.02
16	ATT	0.46	0.61	0.51	0.40	0.00	-0.14	0.07	0.00	-0.29	-0.05	0.04	-0.28
17	CAA	0.24	0.57	0.56	0.56	-0.18	0.75	0.64	0.76	0.16	0.09	0.10	0.18
18	CAC	-0.20	-0.32	-0.14	-0.19	0.39	0.20	0.23	0.18	0.24	-0.11	-0.23	0.00
19	CAG	0.01	-0.34	-0.31	-0.35	0.02	-0.38	-0.34	-0.46	-0.14	0.05	0.05	-0.17
20	CAT	-0.14	0.22	0.11	-0.07	-0.19	0.01	-0.08	0.14	-0.07	0.11	0.03	-0.01
21	CCA	-0.14	-0.12	-0.07	-0.21	-0.49	0.44	0.69	0.54	0.30	0.26	0.23	0.35
22	CCC	-0.26	0.04	0.08	-0.16	0.27	0.48	0.66	0.38	0.05	-0.36	-0.36	-0.17
23	CCG	-0.05	-0.22	0.14	0.01	-0.20	-0.43	-0.18	-0.38	0.20	0.27	0.32	0.27
24	CCT	-0.27	0.20	0.34	-0.05	-0.34	0.38	0.51	0.10	-0.44	-0.31	-0.38	-0.45
25	CGA	-0.61	-0.33	-0.22	-0.24	-0.53	0.67	0.59	0.55	0.51	0.38	0.55	0.25
26	CGC	-0.20	-0.11	0.25	0.24	0.41	0.09	0.16	0.42	0.31	-0.35	-0.46	-0.03
27	CGG	-0.36	-0.34	-0.22	-0.28	-0.62	-0.54	-0.45	-0.39	0.23	0.46	0.28	0.23
28	CGT	-0.55	-0.14	0.08	-0.28	-0.42	-0.29	-0.19	-0.19	-0.12	-0.27	-0.25	-0.14
29	CTA	-0.64	-0.16	-0.16	-0.37	-0.70	0.74	0.68	0.32	0.37	0.59	0.49	0.26
30	CTC	0.50	0.35	0.26	-0.10	0.32	0.56	0.71	0.49	0.28	-0.46	-0.30	-0.16
31	CTG	0.45	-0.39	-0.10	-0.04	0.18	-0.40	-0.36	-0.28	0.31	0.49	0.35	0.42
32	CTT	-0.11	-0.03	0.16	-0.25	-0.08	-0.08	0.20	-0.02	-0.42	-0.17	-0.36	-0.45
33	GAA	0.29	0.48	0.02	0.37	0.33	0.60	0.27	0.51	-0.13	-0.06	-0.06	-0.02
34	GAC	-0.01	-0.07	-0.20	-0.27	0.36	0.38	0.32	0.23	0.30	-0.07	-0.13	0.03
35	GAG	-0.11	-0.43	-0.52	-0.36	-0.23	-0.32	-0.54	-0.58	0.22	0.20	0.27	-0.03
36	GAT	-0.26	0.15	0.28	0.09	-0.25	-0.07	-0.12	0.04	-0.19	0.04	0.08	-0.01
37	GCA	0.32	0.47	0.45	0.52	-0.06	0.41	0.46	0.47	0.11	0.09	0.15	0.17
38	GCC	0.07	0.07	0.26	0.01	0.44	0.56	0.61	0.44	0.11	-0.26	-0.41	-0.20
39	GCG	-0.24	-0.34	-0.05	0.04	-0.21	-0.57	-0.37	-0.36	0.22	0.37	0.35	0.32
40	GCT	-0.56	-0.14	-0.05	-0.28	-0.32	0.22	0.45	-0.18	-0.39	-0.19	-0.11	-0.39
41	GGA	0.19	0.44	0.08	0.27	0.09	0.41	0.12	0.04	-0.24	-0.04	0.02	0.07
42	GGC	0.06	-0.10	-0.12	-0.05	0.62	0.31	0.24	0.34	0.32	-0.15	-0.23	0.03
43	GGG	-0.28	-0.20	-0.32	-0.23	-0.04	-0.39	-0.45	-0.53	0.27	0.52	0.42	0.41
44	GGT	-0.12	0.39	0.31	0.15	0.02	0.04	-0.07	-0.39	-0.32	-0.29	-0.21	-0.34
45	GTA	-0.06	0.35	0.15	0.17	0.17	0.46	0.38	0.55	0.13	0.15	0.13	0.32
46	GTC	0.45	0.19	0.10	0.16	0.62	0.66	0.58	0.57	0.29	-0.30	-0.35	-0.11
47	GTG	0.44	-0.36	-0.15	0.13	0.39	-0.52	-0.57	-0.43	0.18	0.52	0.33	0.35

48	GTT	-0.37	0.05	0.07	-0.20	-0.13	-0.11	0.18	-0.14	-0.35	-0.17	-0.12	-0.27
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.20	-0.20	-0.43	-0.44	0.32	0.46	0.24	0.47	0.32	0.05	0.14	0.16
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.39	0.54	0.24	0.41	-0.23	0.05	0.07	0.29	-0.24	-0.06	0.06	-0.09
53	TCA	0.45	0.43	0.43	0.42	-0.09	0.33	0.37	0.20	-0.10	-0.01	0.00	0.15
54	TCC	0.17	0.02	0.07	-0.19	0.50	0.51	0.58	0.32	0.34	0.06	0.14	0.04
55	TCG	-0.24	-0.45	-0.13	0.11	-0.28	-0.50	-0.29	-0.26	0.40	0.36	0.36	0.41
56	TCT	0.12	0.50	0.47	0.22	-0.17	-0.04	0.38	-0.23	-0.38	-0.32	-0.15	-0.34
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	-0.24	-0.27	-0.19	-0.02	0.67	0.09	0.10	0.21	0.47	-0.07	-0.04	0.27
59	TGG	0.41	0.06	-0.04	-0.02	0.01	-0.23	-0.28	0.02	0.06	0.04	-0.11	-0.03
60	TGT	-0.10	0.49	0.53	0.34	-0.04	-0.21	-0.33	-0.14	-0.42	-0.24	-0.15	-0.12
61	TTA	0.63	0.77	0.44	0.60	0.29	0.66	0.63	0.61	-0.02	0.31	0.17	0.12
62	TTC	0.09	-0.30	-0.24	-0.44	0.37	0.37	0.36	0.44	0.46	0.11	-0.05	0.37
63	TTG	0.26	-0.14	-0.13	-0.15	-0.19	-0.05	-0.18	-0.26	0.10	0.43	0.25	0.09
64	TTT	0.38	0.47	0.42	0.34	-0.27	-0.04	0.24	0.16	-0.28	-0.12	0.14	-0.18
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
		25	26	27	28	29	30	31	32	33	34	35	36

Table C.7 continued

		37	38	39	40	41	42	43	44	45	46	47	48
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
1	AAA	-0.23	0.06	-0.16	0.28	-0.29	-0.04	-0.22	0.28	-0.26	0.18	-0.19	0.44
2	AAC	-0.06	-0.08	-0.12	0.17	-0.45	-0.44	-0.12	-0.35	0.03	0.05	0.09	0.32
3	AAG	0.10	0.45	-0.09	0.19	0.21	0.28	0.27	0.47	-0.08	0.14	-0.32	0.07
4	AAT	-0.07	-0.06	0.13	0.20	0.52	0.71	0.60	0.46	-0.34	-0.02	-0.12	0.07
5	ACA	0.05	0.23	0.50	0.15	-0.06	0.20	0.28	-0.09	0.37	0.49	0.52	0.43
6	ACC	-0.24	-0.12	-0.17	-0.28	-0.52	-0.30	-0.12	-0.43	-0.30	-0.41	-0.18	-0.55
7	ACG	-0.25	0.08	-0.01	-0.22	-0.10	0.21	0.26	0.07	0.14	0.20	-0.02	-0.08
8	ACT	-0.12	0.03	0.27	-0.24	-0.10	0.65	0.63	-0.05	-0.41	0.04	0.19	-0.40
9	AGA	0.39	0.47	0.35	0.53	-0.21	0.24	-0.05	0.24	0.32	0.36	0.03	0.47
10	AGC	0.05	-0.16	0.00	0.16	-0.39	-0.34	-0.06	-0.26	0.18	0.13	0.16	0.36
11	AGG	0.33	0.59	0.34	0.29	-0.08	0.51	-0.28	0.44	0.24	0.40	-0.20	0.08
12	AGT	0.04	0.49	0.34	0.11	0.73	0.88	0.77	0.45	-0.41	-0.01	-0.14	-0.18
13	ATA	0.27	0.26	0.45	0.35	0.32	0.57	0.42	0.43	0.49	0.77	0.66	0.52
14	ATC	-0.18	-0.38	-0.10	-0.10	-0.41	-0.54	-0.30	-0.49	-0.18	-0.37	-0.16	-0.17
15	ATG	0.16	0.23	-0.13	-0.15	-0.13	0.10	-0.09	0.08	0.24	0.06	-0.21	0.09

16	ATT	0.23	-0.10	0.35	0.20	0.77	0.89	0.79	0.58	0.09	0.06	0.29	0.24
17	CAA	0.04	0.22	0.29	0.04	-0.20	-0.16	-0.32	-0.36	-0.23	-0.02	-0.23	0.22
18	CAC	0.06	-0.28	-0.25	-0.23	-0.25	-0.54	-0.40	-0.46	-0.19	-0.16	-0.08	-0.07
19	CAG	0.01	0.11	-0.26	-0.07	0.03	0.23	0.10	0.52	0.15	0.18	-0.18	0.15
20	CAT	0.30	0.14	0.22	0.21	0.53	0.70	0.66	0.50	0.17	0.02	0.10	0.20
21	CCA	0.17	-0.08	0.48	-0.06	0.51	0.30	0.13	-0.35	-0.27	0.32	0.55	0.15
22	CCC	-0.31	-0.54	-0.38	-0.48	-0.45	-0.66	-0.35	-0.58	-0.23	-0.52	-0.31	-0.57
23	CCG	0.09	0.19	0.29	-0.06	0.04	0.08	0.22	0.20	0.39	0.36	0.32	0.06
24	CCT	-0.01	0.03	0.30	-0.32	0.63	0.72	0.60	0.38	-0.33	-0.24	0.18	-0.42
25	CGA	-0.20	0.15	0.12	-0.06	0.14	0.14	0.51	0.03	0.37	0.75	0.60	0.40
26	CGC	-0.14	-0.33	-0.36	-0.29	0.04	-0.55	-0.32	-0.42	-0.03	-0.33	-0.35	-0.12
27	CGG	0.36	0.45	0.27	0.18	0.50	0.59	0.23	0.53	0.39	0.38	0.10	0.26
28	CGT	0.24	0.06	0.13	-0.20	0.67	0.71	0.70	0.41	-0.24	-0.31	0.01	-0.30
29	CTA	0.41	0.52	0.84	0.37	0.54	0.52	0.44	0.03	0.27	0.72	0.30	0.36
30	CTC	0.00	-0.53	-0.52	-0.12	-0.50	-0.73	-0.47	-0.67	-0.27	-0.62	-0.44	-0.38
31	CTG	0.31	0.38	0.34	0.19	0.60	0.60	0.53	0.66	0.65	0.54	0.56	0.50
32	CTT	-0.11	-0.39	-0.01	-0.11	0.42	0.47	0.61	0.27	-0.22	-0.41	-0.25	-0.28
33	GAA	-0.16	0.02	-0.19	0.12	-0.28	-0.18	-0.10	0.07	-0.14	0.05	-0.31	0.24
34	GAC	-0.01	-0.14	-0.22	0.04	-0.43	-0.52	-0.34	-0.39	0.09	0.08	-0.13	0.12
35	GAG	0.29	0.35	-0.01	0.25	0.43	0.38	0.27	0.47	0.29	0.37	-0.12	0.10
36	GAT	0.16	0.07	0.09	0.24	0.64	0.81	0.65	0.45	-0.15	0.00	-0.07	0.13
37	GCA	0.08	0.15	0.43	0.16	-0.01	0.04	0.11	-0.15	0.34	0.35	0.51	0.30
38	GCC	-0.19	-0.28	-0.18	-0.25	-0.41	-0.41	-0.25	-0.46	-0.25	-0.37	-0.13	-0.49
39	GCG	0.10	0.18	0.01	0.05	0.08	0.10	0.21	0.24	0.34	0.36	0.06	0.17
40	GCT	-0.08	-0.02	0.23	-0.18	0.70	0.79	0.69	0.44	-0.18	-0.03	0.29	-0.41
41	GGA	0.01	0.21	0.14	0.28	0.37	0.56	0.65	0.66	-0.06	0.53	0.39	0.49
42	GGC	0.01	0.03	-0.31	-0.19	-0.18	-0.25	0.05	-0.13	-0.07	-0.21	-0.23	-0.12
43	GGG	-0.09	0.63	0.29	0.14	0.54	0.51	-0.87	0.81	0.33	0.62	0.42	0.16
44	GGT	-0.14	0.10	0.03	-0.30	0.73	0.83	0.79	0.64	-0.45	-0.30	-0.26	-0.48
45	GTA	0.35	0.13	0.35	0.25	0.30	0.45	0.34	-0.01	0.23	0.52	0.54	0.61
46	GTC	0.07	-0.32	-0.34	-0.09	-0.39	-0.59	-0.35	-0.62	-0.32	-0.44	-0.28	-0.30
47	GTG	0.22	0.37	0.19	0.16	0.61	0.67	0.51	0.62	0.70	0.57	0.43	0.51
48	GTT	0.02	-0.15	0.14	0.03	0.75	0.80	0.73	0.48	-0.18	-0.24	0.03	-0.16
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.14	-0.04	-0.16	0.11	-0.58	-0.50	-0.36	-0.42	0.23	0.07	-0.07	0.40
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.08	0.06	0.06	0.23	0.60	0.80	0.72	0.57	-0.22	-0.03	-0.19	0.13
53	TCA	-0.21	0.01	0.36	-0.05	-0.17	-0.04	0.16	-0.08	0.35	0.41	0.50	0.16
54	TCC	-0.28	-0.27	0.12	-0.44	-0.46	-0.41	0.01	-0.49	-0.40	-0.37	0.12	-0.55

55	TCG	-0.28	0.10	-0.12	-0.03	0.27	0.12	0.22	0.40	0.47	0.07	0.05	0.08
56	TCT	-0.14	0.05	0.50	-0.25	0.66	0.83	0.75	0.53	-0.37	-0.23	0.33	-0.42
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.21	-0.20	-0.27	0.03	-0.28	-0.34	-0.22	-0.33	0.23	-0.07	-0.01	0.37
59	TGG	0.05	0.29	-0.20	0.07	-0.18	0.04	-0.08	0.36	0.27	0.26	-0.37	0.16
60	TGT	0.12	0.42	0.31	0.40	0.78	0.87	0.84	0.67	-0.13	-0.10	-0.17	-0.17
61	TTA	0.37	0.41	0.56	0.29	-0.07	0.26	0.05	0.14	0.28	0.49	0.55	0.41
62	TTC	0.17	-0.26	-0.14	-0.05	-0.45	-0.55	-0.32	-0.54	0.31	-0.23	0.20	0.10
63	TTG	-0.15	0.22	0.09	-0.05	0.16	0.49	0.27	0.27	0.28	0.43	0.25	0.13
64	TTT	-0.04	-0.01	0.23	0.14	0.67	0.77	0.77	0.57	-0.04	-0.16	0.16	0.05
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
		37	38	39	40	41	42	43	44	45	46	47	48

Table C.7 continued

		49	50	51	52	53	54	55	56	57	58	59	60
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
1	AAA	0.00	-0.10	0.00	-0.03	-0.26	0.15	0.23	0.38	0.00	0.00	-0.07	-0.13
2	AAC	0.00	0.10	0.00	0.03	0.38	0.41	0.39	0.27	0.00	-0.21	-0.17	-0.05
3	AAG	0.00	0.12	0.00	0.17	0.26	0.44	0.17	0.32	0.00	0.16	0.16	0.02
4	AAT	0.00	0.03	0.00	-0.11	-0.11	-0.05	0.21	0.05	0.00	0.33	0.19	-0.06
5	ACA	0.00	-0.20	0.00	-0.13	-0.17	-0.18	-0.06	-0.19	0.00	-0.15	-0.38	-0.12
6	ACC	0.00	0.25	0.00	0.05	0.37	0.26	0.19	0.08	0.00	-0.15	0.36	-0.29
7	ACG	0.00	0.22	0.00	0.13	0.26	0.30	0.02	0.32	0.00	0.36	0.33	0.48
8	ACT	0.00	-0.28	0.00	-0.26	-0.50	-0.40	-0.26	-0.58	0.00	-0.13	-0.27	-0.58
9	AGA	0.00	-0.13	0.00	-0.19	-0.03	0.11	-0.06	0.49	0.00	0.34	-0.40	0.08
10	AGC	0.00	0.02	0.00	-0.10	0.35	0.35	0.23	0.40	0.00	-0.03	-0.36	-0.09
11	AGG	0.00	0.49	0.00	0.39	0.01	0.64	0.10	0.19	0.00	0.48	-0.30	0.15
12	AGT	0.00	0.25	0.00	-0.12	-0.35	0.10	-0.10	-0.18	0.00	0.22	0.71	0.38
13	ATA	0.00	-0.29	0.00	-0.06	-0.21	-0.34	-0.17	-0.13	0.00	-0.16	-0.47	-0.47
14	ATC	0.00	0.39	0.00	0.36	0.46	0.34	0.36	0.56	0.00	-0.07	0.08	0.15
15	ATG	0.00	-0.03	0.00	0.03	0.16	0.09	-0.01	0.18	0.00	0.00	0.00	0.00
16	ATT	0.00	-0.18	0.00	-0.30	-0.29	-0.35	0.14	-0.44	0.00	0.35	0.17	-0.24
17	CAA	0.00	-0.37	0.00	-0.35	-0.39	-0.41	-0.35	-0.28	0.00	-0.31	-0.42	-0.26
18	CAC	0.00	0.27	0.00	0.33	0.41	0.21	0.28	0.35	0.00	0.06	0.08	0.06
19	CAG	0.00	0.25	0.00	0.45	0.31	0.40	0.19	0.37	0.00	0.20	0.48	0.41
20	CAT	0.00	-0.21	0.00	-0.17	-0.30	-0.32	-0.23	-0.07	0.00	0.05	-0.06	-0.18
21	CCA	0.00	-0.32	0.00	-0.28	-0.27	-0.54	0.01	-0.54	0.00	-0.57	-0.41	-0.45
22	CCC	0.00	0.56	0.00	0.41	0.49	0.42	0.49	0.46	0.00	0.18	0.49	0.19

23	CCG	0.00	0.17	0.00	0.15	0.08	0.06	-0.11	0.05	0.00	0.19	0.06	0.49
24	CCT	0.00	-0.32	0.00	-0.44	-0.41	-0.40	0.02	-0.54	0.00	-0.22	-0.18	-0.41
25	CGA	0.00	-0.16	0.00	0.22	-0.18	-0.58	-0.49	-0.50	0.00	-0.68	0.38	-0.37
26	CGC	0.00	-0.17	0.00	0.11	0.47	0.33	-0.19	0.52	0.00	-0.08	-0.31	0.26
27	CGG	0.00	0.35	0.00	0.11	0.40	0.62	0.22	0.44	0.00	0.36	0.64	0.51
28	CGT	0.00	-0.15	0.00	-0.26	-0.40	-0.30	-0.46	-0.44	0.00	0.08	0.54	0.53
29	CTA	0.00	-0.41	0.00	-0.44	-0.41	-0.54	-0.48	-0.62	0.00	-0.72	-0.56	-0.68
30	CTC	0.00	0.49	0.00	0.45	0.58	0.48	0.55	0.60	0.00	0.24	0.40	0.35
31	CTG	0.00	-0.10	0.00	0.14	-0.07	-0.01	-0.29	0.00	0.00	0.04	0.07	0.52
32	CTT	0.00	-0.09	0.00	-0.21	-0.16	-0.35	0.07	-0.53	0.00	0.02	0.22	-0.37
33	GAA	0.00	-0.20	0.00	0.00	-0.09	-0.09	-0.17	0.27	0.00	0.01	-0.11	-0.23
34	GAC	0.00	0.35	0.00	0.29	0.52	0.53	0.54	0.45	0.00	-0.10	-0.13	0.04
35	GAG	0.00	0.21	0.00	0.21	0.43	0.50	0.31	0.39	0.00	0.18	0.23	0.21
36	GAT	0.00	-0.21	0.00	-0.20	-0.22	-0.28	-0.22	-0.15	0.00	0.06	0.13	0.03
37	GCA	0.00	-0.35	0.00	-0.07	-0.35	-0.41	-0.40	-0.38	0.00	-0.32	-0.48	-0.14
38	GCC	0.00	0.38	0.00	0.15	0.43	0.36	0.33	0.46	0.00	-0.24	0.28	-0.13
39	GCG	0.00	0.21	0.00	0.40	0.48	0.37	-0.19	0.35	0.00	0.27	0.22	0.55
40	GCT	0.00	-0.45	0.00	-0.47	-0.50	-0.54	-0.33	-0.53	0.00	-0.05	-0.06	-0.11
41	GGA	0.00	0.04	0.00	-0.09	-0.26	0.79	0.04	0.06	0.00	-0.06	0.16	0.16
42	GGC	0.00	-0.11	0.00	0.00	0.24	0.35	-0.10	0.36	0.00	-0.28	-0.35	-0.33
43	GGG	0.00	0.38	0.00	0.29	0.41	0.66	0.59	0.53	0.00	0.56	0.55	0.42
44	GGT	0.00	0.01	0.00	-0.26	-0.60	-0.28	-0.43	-0.50	0.00	0.49	0.55	0.63
45	GTA	0.00	-0.40	0.00	-0.28	-0.42	-0.47	-0.40	-0.42	0.00	-0.35	-0.43	-0.35
46	GTC	0.00	0.44	0.00	0.23	0.55	0.45	0.49	0.48	0.00	-0.08	0.17	0.03
47	GTG	0.00	0.03	0.00	0.12	0.27	0.18	-0.23	0.34	0.00	0.21	0.10	0.51
48	GTT	0.00	-0.14	0.00	-0.24	-0.24	-0.47	-0.02	-0.47	0.00	0.26	0.12	-0.27
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.00	0.23	0.00	0.34	0.35	0.38	0.35	0.28	0.00	-0.14	-0.08	-0.06
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.00	-0.19	0.00	-0.17	-0.25	-0.24	-0.01	-0.08	0.00	0.15	0.06	-0.02
53	TCA	0.00	0.18	0.00	0.25	-0.15	-0.22	0.21	-0.21	0.00	0.11	-0.13	0.09
54	TCC	0.00	0.36	0.00	-0.10	0.31	-0.10	0.45	-0.01	0.00	-0.29	0.25	-0.21
55	TCG	0.00	0.14	0.00	0.45	0.32	0.24	-0.39	0.35	0.00	-0.08	0.11	0.58
56	TCT	0.00	-0.28	0.00	-0.47	-0.41	-0.50	-0.02	-0.55	0.00	0.14	0.27	-0.19
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.00	-0.05	0.00	0.30	0.46	0.29	-0.25	0.26	0.00	-0.08	-0.30	-0.31
59	TGG	0.00	0.01	0.00	-0.01	0.16	0.33	-0.21	0.10	0.00	-0.03	0.00	0.06
60	TGT	0.00	0.02	0.00	-0.34	-0.32	-0.17	-0.29	-0.35	0.00	0.50	0.82	0.26
61	TTA	0.00	-0.26	0.00	-0.27	-0.38	-0.23	0.00	-0.21	0.00	-0.04	-0.44	-0.38

62	TTC	0.00	0.31	0.00	0.42	0.20	0.07	0.06	0.29	0.00	-0.18	-0.05	-0.13
63	TTG	0.00	0.26	0.00	0.06	0.10	-0.14	0.11	0.02	0.00	0.17	0.08	0.41
64	TTT	0.00	-0.18	0.00	-0.24	-0.26	-0.23	0.18	-0.34	0.00	0.27	0.04	-0.08
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
		49	50	51	52	53	54	55	56	57	58	59	60

Table C.7 continued

		61	62	63	64
		TTA	TTC	TTG	TTT
1	AAA	0.10	-0.15	0.17	0.24
2	AAC	0.19	-0.08	0.38	0.11
3	AAG	0.63	-0.11	0.69	-0.14
4	AAT	-0.37	-0.07	-0.02	0.01
5	ACA	-0.23	-0.16	-0.52	-0.12
6	ACC	0.46	0.17	0.16	0.07
7	ACG	0.44	0.03	0.66	0.26
8	ACT	-0.45	-0.10	-0.45	-0.38
9	AGA	0.17	0.30	-0.20	0.34
10	AGC	0.36	0.15	0.25	0.19
11	AGG	0.18	0.19	0.52	0.01
12	AGT	-0.40	0.06	-0.23	-0.28
13	ATA	-0.48	-0.32	-0.61	-0.22
14	ATC	0.37	0.30	0.55	0.40
15	ATG	0.66	0.10	0.81	-0.07
16	ATT	-0.62	-0.26	-0.52	-0.18
17	CAA	-0.14	-0.27	-0.25	-0.32
18	CAC	0.36	0.12	0.20	0.40
19	CAG	0.76	0.19	0.49	0.34
20	CAT	-0.36	-0.14	-0.43	-0.19
21	CCA	-0.29	-0.19	-0.42	-0.19
22	CCC	0.65	0.56	0.43	0.48
23	CCG	0.43	0.07	0.62	-0.13
24	CCT	-0.39	0.12	-0.29	-0.23
25	CGA	0.12	-0.28	-0.18	0.04
26	CGC	0.68	-0.14	0.46	0.39
27	CGG	0.64	0.17	0.64	0.01
28	CGT	-0.10	-0.42	-0.23	-0.38
29	CTA	-0.63	-0.25	-0.66	-0.33

30	CTC	0.58	0.53	0.30	0.46
31	CTG	0.16	-0.16	0.45	-0.20
32	CTT	-0.41	0.24	-0.55	0.27
33	GAA	0.11	-0.02	-0.19	-0.04
34	GAC	0.27	0.29	0.11	0.39
35	GAG	0.65	0.11	0.61	0.03
36	GAT	-0.42	-0.24	-0.34	-0.21
37	GCA	-0.26	-0.31	-0.38	-0.24
38	GCC	0.50	0.35	0.44	0.28
39	GCG	0.59	0.02	0.57	0.23
40	GCT	-0.39	-0.14	-0.47	-0.40
41	GGA	-0.02	0.17	-0.34	-0.22
42	GGC	0.45	0.01	0.33	0.22
43	GGG	0.45	0.53	0.54	0.13
44	GGT	-0.49	-0.27	-0.48	-0.45
45	GTA	-0.40	-0.37	-0.50	-0.38
46	GTC	0.62	0.54	0.70	0.39
47	GTG	0.39	-0.13	0.55	-0.02
48	GTT	-0.41	-0.12	-0.49	-0.18
49	TAA	0.00	0.00	0.00	0.00
50	TAC	-0.05	0.14	0.15	0.31
51	TAG	0.00	0.00	0.00	0.00
52	TAT	-0.52	-0.22	-0.50	-0.08
53	TCA	-0.36	-0.01	-0.37	-0.13
54	TCC	0.16	0.22	0.27	-0.06
55	TCG	0.35	0.09	0.44	0.16
56	TCT	-0.54	-0.08	-0.33	-0.26
57	TGA	0.00	0.00	0.00	0.00
58	TGC	0.37	0.12	0.43	0.37
59	TGG	0.54	0.11	0.76	-0.07
60	TGT	-0.43	-0.19	-0.31	-0.41
61	TTA	-0.36	-0.12	-0.40	-0.34
62	TTC	0.04	0.02	0.43	0.11
63	TTG	0.14	0.22	0.51	-0.27
64	TTT	-0.61	-0.21	-0.47	0.10
		TTA	TTC	TTG	TTT
		61	62	63	64

Table C.8: CPW matrix *Bacillus amyloliqueaciens* K12 highly expressed sequences (left codon indicated in column 2, right codon indicated in row 2). Host cell: *B. amyloliqueaciens*; Sequence data: full *B. amyloliqueaciens* genome; Highly expressed group: 236 seqs.

		1	2	3	4	5	6	7	8	9	10	11	12
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
1	AAA	0.01	-0.27	-0.03	0.08	-0.25	-0.11	-0.16	0.63	-0.32	-0.14	0.09	0.42
2	AAC	0.20	-0.38	0.36	0.17	0.35	-0.26	0.01	0.50	-0.36	-0.55	0.59	-0.73
3	AAG	0.01	0.40	-0.01	0.62	0.31	0.37	0.03	0.65	0.50	-0.01	0.57	0.35
4	AAT	-0.29	0.42	-0.02	0.26	-0.26	0.24	-0.26	0.16	1.00	1.00	0.48	0.48
5	ACA	-0.41	-0.51	-0.36	-0.40	-0.15	-0.08	0.18	-0.17	-0.60	-0.54	-0.76	-0.21
6	ACC	0.52	0.06	0.23	0.32	1.00	-0.17	0.81	-0.25	-0.49	0.00	-0.10	1.00
7	ACG	0.01	0.37	0.19	0.19	-0.19	-0.47	-0.41	-0.20	-0.19	-0.03	-0.62	0.18
8	ACT	0.70	0.85	0.79	1.00	0.76	1.00	0.37	1.00	1.00	1.00	1.00	1.00
9	AGA	-0.47	-0.20	-0.39	-0.18	-0.20	-0.03	-0.17	-0.41	-0.21	-0.34	-0.65	1.00
10	AGC	-0.12	0.39	-0.24	-0.04	-0.11	0.22	-0.09	0.43	-0.51	-0.40	-0.53	-0.11
11	AGG	0.10	0.67	0.49	0.17	1.00	1.00	0.59	1.00	-0.30	1.00	1.00	1.00
12	AGT	-0.02	0.41	0.36	0.62	0.59	-0.34	-0.44	0.17	1.00	1.00	1.00	1.00
13	ATA	-0.51	0.31	-0.27	0.71	0.23	0.53	-0.10	-0.36	-0.22	0.16	-0.77	1.00
14	ATC	0.09	-0.10	0.44	-0.13	0.19	-0.36	0.22	-0.14	-0.30	-0.31	-0.08	-0.59
15	ATG	0.17	0.21	-0.32	-0.21	-0.15	-0.04	0.20	-0.05	-0.39	0.17	-0.35	-0.17
16	ATT	0.01	0.08	-0.09	0.00	0.18	-0.18	-0.16	0.17	0.83	0.94	1.00	0.84
17	CAA	-0.34	-0.46	-0.46	-0.23	0.11	-0.27	0.36	0.24	0.45	0.17	-0.47	-0.38
18	CAC	-0.04	0.45	0.27	-0.39	0.28	0.73	0.12	0.12	0.61	-0.53	-0.75	-0.61
19	CAG	0.42	0.40	0.51	0.47	-0.02	-0.16	-0.24	0.34	0.80	0.70	0.66	0.42
20	CAT	-0.13	-0.23	0.31	0.45	-0.12	0.79	-0.37	-0.39	0.69	0.86	1.00	1.00
21	CCA	0.44	-0.39	-0.68	-0.05	1.00	-0.06	0.50	-0.57	0.00	-0.74	1.00	-0.76
22	CCC	0.85	0.10	1.00	0.71	1.00	1.00	0.59	1.00	1.00	0.61	1.00	-0.12
23	CCG	-0.02	-0.11	-0.40	-0.31	-0.37	-0.23	-0.12	-0.57	0.24	0.05	0.48	0.15
24	CCT	0.14	0.89	0.20	0.33	0.34	0.59	1.00	1.00	1.00	0.45	-0.62	-0.06
25	CGA	-0.18	-0.62	0.32	-0.11	-0.22	1.00	0.44	1.00	-0.66	-0.29	-0.70	1.00
26	CGC	0.41	-0.22	-0.05	-0.04	0.21	-0.21	-0.35	0.40	0.41	-0.51	1.00	-0.36
27	CGG	0.35	0.21	0.18	-0.41	-0.35	0.65	-0.50	0.61	0.42	0.37	-0.66	1.00
28	CGT	0.03	0.90	0.54	0.50	0.29	0.48	0.51	-0.14	1.00	1.00	1.00	0.55
29	CTA	-0.44	-0.21	1.00	0.20	-0.20	-0.13	1.00	1.00	-0.33	0.17	1.00	-0.58
30	CTC	0.60	0.75	0.53	0.06	0.84	-0.16	0.58	0.01	-0.26	-0.22	-0.24	-0.47
31	CTG	-0.19	-0.21	-0.18	-0.20	-0.40	-0.09	-0.36	-0.33	0.12	0.26	-0.33	0.11
32	CTT	0.59	0.54	0.65	0.80	0.50	0.35	0.74	-0.03	0.40	0.66	1.00	1.00
33	GAA	-0.04	-0.22	0.03	-0.05	-0.33	-0.21	0.05	0.46	-0.04	-0.43	0.60	-0.10

34	GAC	-0.12	-0.07	-0.19	0.14	0.54	-0.12	0.07	-0.20	-0.43	-0.64	-0.67	-0.63
35	GAG	0.13	0.41	-0.10	0.48	0.47	0.39	0.26	-0.17	0.71	0.76	0.35	0.66
36	GAT	0.21	-0.02	-0.08	-0.01	-0.03	0.53	-0.34	-0.05	0.92	1.00	1.00	0.62
37	GCA	-0.48	-0.16	-0.42	-0.49	0.02	-0.22	0.27	-0.41	-0.16	-0.49	-0.67	-0.63
38	GCC	0.66	0.17	0.56	-0.17	0.06	0.13	0.49	0.28	-0.39	0.56	-0.54	-0.57
39	GCG	-0.15	0.18	-0.12	-0.13	-0.49	-0.05	0.01	-0.25	-0.05	0.39	-0.16	0.82
40	GCT	0.32	0.24	0.63	0.74	0.04	0.49	0.52	0.44	0.85	1.00	1.00	1.00
41	GGA	-0.35	-0.39	-0.13	-0.23	-0.33	-0.38	-0.15	-0.19	-0.31	-0.44	-0.12	0.55
42	GGC	0.45	0.13	-0.25	0.26	0.14	0.03	-0.20	0.41	0.05	-0.48	-0.07	-0.11
43	GGG	0.08	0.19	0.07	-0.17	0.46	1.00	0.19	1.00	0.34	0.54	1.00	1.00
44	GGT	-0.13	0.10	0.74	0.71	0.33	0.59	-0.14	-0.26	0.82	1.00	1.00	1.00
45	GTA	-0.43	-0.45	-0.33	-0.33	-0.23	-0.16	-0.35	0.01	-0.62	0.14	1.00	0.06
46	GTC	0.25	0.10	0.15	-0.18	0.07	0.01	-0.02	-0.09	-0.54	-0.45	-0.26	-0.24
47	GTG	-0.26	0.11	-0.19	0.01	-0.27	0.16	-0.30	0.19	0.19	-0.06	0.22	0.56
48	GTT	0.49	0.60	0.75	0.28	0.42	0.36	0.65	0.17	0.77	1.00	0.60	0.78
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.06	0.51	0.23	-0.25	-0.10	-0.12	-0.15	-0.01	-0.19	-0.34	-0.17	-0.67
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.22	0.07	0.42	-0.27	-0.17	0.00	0.24	0.55	0.84	0.90	1.00	0.70
53	TCA	-0.10	-0.49	-0.25	-0.05	0.15	0.21	-0.33	-0.31	-0.43	-0.45	-0.08	-0.74
54	TCC	0.33	0.65	0.25	-0.55	0.76	0.12	-0.04	0.02	-0.47	-0.09	1.00	-0.22
55	TCG	0.10	0.41	0.58	0.00	0.19	0.50	-0.15	-0.39	0.09	0.75	-0.51	1.00
56	TCT	-0.02	0.11	0.18	0.35	-0.37	0.03	0.70	-0.07	1.00	1.00	1.00	1.00
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.75	-0.40	0.28	-0.22	1.00	-0.56	-0.44	1.00	0.22	-0.41	-0.63	-0.19
59	TGG	0.11	-0.22	-0.24	0.35	-0.01	0.73	-0.12	-0.32	-0.35	0.11	-0.05	-0.61
60	TGT	-0.55	1.00	-0.04	0.38	0.40	1.00	-0.36	-0.18	1.00	1.00	1.00	1.00
61	TTA	-0.38	-0.24	-0.46	-0.47	0.15	-0.12	-0.35	-0.65	0.08	-0.25	0.37	-0.16
62	TTC	-0.06	-0.08	0.13	0.42	0.22	-0.21	0.55	-0.53	-0.58	-0.44	-0.59	-0.42
63	TTG	-0.27	-0.35	-0.47	-0.36	0.59	-0.33	0.30	-0.39	-0.17	0.46	1.00	0.61
64	TTT	-0.01	-0.02	0.05	-0.18	-0.23	0.04	0.10	0.07	0.64	0.77	1.00	1.00
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
		1	2	3	4	5	6	7	8	9	10	11	12

Table C.8 continued

		13	14	15	16	17	18	19	20	21	22	23	24
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
1	AAA	-0.14	-0.34	-0.02	0.51	-0.07	0.15	0.45	0.25	-0.28	0.09	0.43	0.31

2	AAC	0.43	0.18	-0.04	-0.03	-0.10	-0.05	0.39	0.05	0.02	0.19	0.35	0.50
3	AAG	0.11	0.06	0.06	0.11	0.20	-0.52	-0.56	-0.15	0.22	-0.38	-0.46	-0.56
4	AAT	-0.59	0.05	0.05	-0.07	-0.20	0.43	-0.18	-0.26	-0.40	-0.42	-0.42	0.52
5	ACA	0.51	0.27	-0.22	0.61	-0.42	0.06	-0.11	0.50	0.12	0.28	-0.17	0.50
6	ACC	-0.45	-0.09	0.56	-0.45	0.68	0.42	0.08	0.32	0.20	1.00	0.75	0.38
7	ACG	-0.33	-0.24	-0.28	-0.35	0.40	-0.08	0.24	-0.22	-0.12	-0.20	-0.40	0.27
8	ACT	0.50	0.81	0.84	0.50	0.30	-0.22	-0.44	-0.43	0.11	0.27	0.32	-0.41
9	AGA	-0.19	-0.13	0.01	-0.13	0.46	0.73	-0.07	-0.22	1.00	1.00	-0.24	0.63
10	AGC	-0.01	0.00	0.10	-0.13	0.23	0.21	-0.28	-0.49	0.46	-0.44	0.42	1.00
11	AGG	-0.64	0.48	0.33	0.16	0.08	-0.64	0.67	0.28	1.00	-0.63	-0.33	1.00
12	AGT	0.02	-0.09	0.76	0.02	0.63	0.62	-0.07	0.70	-0.84	-0.23	-0.31	-0.17
13	ATA	0.32	0.50	1.00	0.86	-0.67	0.10	-0.17	-0.07	0.05	-0.57	-0.47	0.64
14	ATC	0.24	-0.28	-0.03	-0.03	0.64	0.24	0.33	0.47	0.30	0.57	0.57	0.19
15	ATG	0.14	-0.06	0.00	0.03	0.47	-0.23	-0.25	0.23	0.14	0.29	0.05	-0.24
16	ATT	-0.18	-0.06	-0.14	0.24	-0.43	-0.31	0.04	-0.26	-0.59	-0.41	-0.21	-0.14
17	CAA	0.15	-0.10	-0.25	-0.03	0.67	1.00	0.60	0.73	0.37	1.00	1.00	0.76
18	CAC	-0.42	0.28	-0.07	-0.11	0.05	0.29	0.54	-0.11	0.55	1.00	0.10	-0.18
19	CAG	0.59	0.12	0.25	-0.14	0.11	-0.52	-0.46	-0.20	0.09	1.00	-0.45	-0.56
20	CAT	0.32	-0.07	0.06	-0.02	-0.11	0.21	-0.27	-0.20	-0.30	-0.15	-0.17	0.18
21	CCA	1.00	0.36	-0.21	-0.52	0.46	0.02	1.00	1.00	1.00	1.00	1.00	1.00
22	CCC	1.00	1.00	1.00	0.72	0.11	0.20	0.68	0.05	1.00	1.00	1.00	-0.12
23	CCG	0.47	-0.32	-0.33	-0.24	-0.19	-0.36	0.16	0.06	-0.09	-0.45	-0.20	-0.21
24	CCT	1.00	0.38	0.88	0.47	-0.52	0.44	-0.05	0.12	1.00	-0.71	0.37	-0.06
25	CGA	1.00	-0.43	-0.63	-0.56	0.38	1.00	0.55	0.02	1.00	1.00	1.00	1.00
26	CGC	0.71	0.03	0.03	0.01	0.15	0.05	-0.03	-0.17	1.00	1.00	0.18	0.48
27	CGG	-0.56	-0.14	-0.18	-0.20	0.26	-0.10	-0.32	0.12	-0.24	-0.77	0.20	-0.34
28	CGT	0.58	0.61	0.39	0.16	-0.39	0.17	-0.09	-0.08	1.00	0.19	-0.49	-0.47
29	CTA	1.00	-0.62	-0.27	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.41	1.00
30	CTC	-0.61	0.10	0.02	-0.04	0.74	0.43	0.54	0.40	1.00	1.00	0.46	0.42
31	CTG	-0.48	-0.25	-0.24	-0.19	-0.02	-0.17	0.10	0.22	-0.42	-0.29	-0.31	-0.09
32	CTT	0.54	0.48	0.28	0.77	-0.30	-0.30	-0.33	-0.38	-0.21	-0.61	-0.23	-0.41
33	GAA	-0.01	-0.12	-0.13	0.04	0.11	0.35	0.19	0.27	0.21	0.22	0.23	0.64
34	GAC	0.38	0.12	0.21	0.13	0.35	0.66	0.29	0.12	0.11	0.51	0.14	0.43
35	GAG	-0.20	0.30	0.38	0.00	-0.25	-0.38	-0.30	-0.47	-0.58	-0.48	-0.44	-0.34
36	GAT	-0.32	0.12	-0.15	-0.24	-0.39	-0.18	0.01	-0.26	0.00	0.39	-0.31	0.04
37	GCA	0.20	-0.08	-0.03	0.36	0.08	0.82	0.04	0.58	-0.50	0.17	0.54	0.42
38	GCC	-0.45	-0.01	-0.27	-0.35	-0.28	0.40	0.25	0.06	1.00	0.30	0.74	0.35
39	GCG	0.53	-0.16	-0.17	-0.20	0.22	-0.12	-0.23	0.02	-0.15	0.03	-0.15	-0.48
40	GCT	0.21	0.56	0.81	0.47	-0.10	-0.48	0.27	-0.44	0.01	-0.51	-0.22	-0.52

41	GGA	0.15	0.08	-0.12	-0.06	-0.44	-0.21	0.02	-0.09	1.00	0.59	0.02	-0.41
42	GGC	0.27	-0.10	0.02	-0.19	0.46	0.18	0.13	0.22	0.30	0.13	0.36	0.60
43	GGG	-0.02	0.68	-0.24	-0.13	0.66	0.08	-0.41	-0.45	1.00	-0.38	-0.49	-0.34
44	GGT	0.16	0.27	0.45	-0.15	-0.49	0.05	0.70	0.25	0.19	0.33	-0.19	-0.54
45	GTA	0.74	0.51	0.30	0.69	0.52	0.57	-0.17	-0.17	0.53	0.62	0.64	-0.07
46	GTC	0.21	-0.38	-0.32	-0.17	0.35	0.60	0.74	0.38	0.72	0.53	0.70	0.78
47	GTG	-0.09	0.01	0.01	-0.09	0.08	0.69	-0.43	-0.17	0.01	-0.47	-0.53	-0.43
48	GTT	0.06	-0.08	0.33	0.17	-0.39	-0.51	-0.10	-0.42	0.66	0.17	-0.25	-0.35
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.62	0.22	0.38	-0.12	0.06	0.52	0.23	-0.13	-0.40	0.66	0.23	0.36
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.40	0.19	-0.25	0.13	-0.13	0.15	-0.12	-0.26	1.00	0.39	-0.41	0.29
53	TCA	-0.27	0.49	-0.13	0.32	-0.30	-0.06	-0.03	0.79	0.45	1.00	0.41	-0.05
54	TCC	-0.13	-0.33	-0.10	-0.54	0.78	0.32	0.68	1.00	0.07	0.24	0.29	0.64
55	TCG	0.35	-0.08	0.06	0.09	0.51	-0.60	-0.20	0.00	-0.04	-0.42	-0.21	-0.58
56	TCT	0.16	0.14	-0.18	0.33	-0.37	-0.45	-0.04	0.09	-0.70	0.44	-0.12	-0.57
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	1.00	-0.44	0.44	0.57	-0.09	-0.37	-0.25	-0.21	-0.01	1.00	0.23	1.00
59	TGG	0.48	0.33	0.00	-0.31	0.63	-0.23	-0.31	0.23	1.00	-0.71	0.13	0.45
60	TGT	-0.35	0.14	-0.39	0.07	-0.05	0.54	0.62	0.64	-0.66	-0.58	0.55	-0.75
61	TTA	-0.43	-0.10	-0.16	-0.06	0.51	0.64	0.03	0.43	0.04	0.61	0.56	0.63
62	TTC	1.00	-0.16	0.15	0.13	0.75	-0.08	-0.20	-0.18	1.00	1.00	0.03	-0.09
63	TTG	0.53	0.05	0.44	-0.28	-0.22	-0.17	-0.34	-0.34	1.00	-0.36	0.61	0.03
64	TTT	0.34	0.06	-0.10	-0.19	0.16	-0.22	-0.26	0.45	-0.23	-0.65	0.01	0.33
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
		13	14	15	16	17	18	19	20	21	22	23	24

Table C.8 continued

		25	26	27	28	29	30	31	32	33	34	35	36
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
1	AAA	-0.56	0.18	-0.22	0.32	-0.17	0.49	0.31	0.39	-0.17	-0.29	0.14	0.27
2	AAC	-0.40	-0.26	-0.39	-0.09	1.00	0.00	-0.17	0.13	0.20	0.50	-0.07	0.33
3	AAG	1.00	-0.13	-0.03	0.36	0.15	-0.52	-0.63	-0.64	0.24	0.01	0.48	0.17
4	AAT	-0.64	0.57	0.58	0.06	1.00	-0.35	-0.47	0.04	-0.18	-0.37	-0.01	-0.31
5	ACA	0.18	0.50	0.76	-0.09	0.21	0.59	0.18	0.10	0.24	0.10	-0.11	0.20
6	ACC	1.00	0.77	1.00	-0.25	1.00	0.24	0.14	-0.06	0.39	-0.31	0.03	0.22
7	ACG	0.29	0.67	-0.21	1.00	1.00	-0.14	-0.21	-0.42	0.00	0.61	0.15	-0.06
8	ACT	1.00	-0.22	0.50	-0.70	-0.79	0.37	0.64	-0.24	-0.38	-0.21	-0.50	-0.55

9	AGA	0.03	-0.16	0.42	0.14	-0.58	0.85	0.56	0.71	-0.20	0.02	-0.22	0.18
10	AGC	-0.31	-0.36	-0.34	0.19	1.00	0.62	-0.07	-0.15	0.61	0.26	0.47	0.57
11	AGG	1.00	-0.01	-0.75	1.00	1.00	-0.36	-0.82	-0.56	-0.43	0.63	-0.54	0.38
12	AGT	1.00	0.68	1.00	1.00	1.00	-0.45	-0.20	0.09	-0.44	-0.53	-0.65	-0.60
13	ATA	-0.49	0.40	-0.43	0.56	1.00	0.63	-0.21	1.00	-0.29	0.57	0.42	-0.08
14	ATC	-0.32	-0.59	0.67	-0.12	-0.37	0.17	0.57	0.22	0.23	0.16	0.31	0.37
15	ATG	0.16	0.36	0.13	0.16	0.46	-0.04	-0.37	-0.23	0.00	0.05	-0.01	-0.04
16	ATT	-0.16	0.58	0.41	0.39	0.43	-0.21	-0.06	0.17	-0.28	-0.02	0.15	-0.38
17	CAA	0.37	0.61	0.43	0.15	0.13	1.00	0.87	0.86	0.21	-0.19	-0.05	0.18
18	CAC	-0.72	-0.27	0.47	-0.50	-0.40	0.78	0.01	0.46	0.11	0.45	0.19	0.38
19	CAG	-0.46	-0.45	-0.39	-0.25	0.37	-0.36	-0.54	-0.47	-0.10	0.04	-0.06	-0.02
20	CAT	-0.29	-0.23	0.58	0.69	-0.24	0.14	0.31	0.25	-0.13	-0.37	-0.01	-0.09
21	CCA	1.00	-0.29	-0.27	1.00	1.00	1.00	1.00	0.24	0.26	0.21	-0.46	1.00
22	CCC	1.00	-0.65	-0.70	1.00	1.00	0.00	0.43	0.37	0.39	-0.42	-0.34	0.10
23	CCG	-0.64	-0.22	-0.04	0.38	0.28	-0.46	0.10	0.19	0.13	0.36	0.36	0.19
24	CCT	1.00	-0.07	0.48	-0.15	1.00	0.53	0.47	-0.32	-0.33	-0.24	-0.38	-0.54
25	CGA	1.00	0.32	-0.25	1.00	1.00	0.29	0.19	0.56	0.80	-0.34	1.00	0.16
26	CGC	0.32	-0.44	-0.18	-0.53	0.17	0.24	0.14	0.26	0.48	0.23	0.25	0.35
27	CGG	1.00	0.59	-0.37	1.00	1.00	-0.66	-0.31	-0.16	0.17	0.40	-0.15	0.25
28	CGT	1.00	0.70	0.70	-0.35	1.00	0.84	0.01	-0.49	-0.13	-0.63	-0.43	-0.18
29	CTA	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.35	1.00	1.00	-0.21	-0.20
30	CTC	-0.44	0.05	0.73	-0.28	1.00	0.32	0.69	0.41	0.41	-0.19	0.27	-0.08
31	CTG	-0.01	-0.41	-0.27	0.10	0.40	-0.52	-0.46	-0.29	0.27	0.41	0.11	0.44
32	CTT	1.00	0.15	0.67	-0.42	0.35	0.49	0.23	-0.10	-0.39	-0.31	-0.46	-0.46
33	GAA	0.29	0.45	-0.22	0.41	0.57	0.50	0.38	0.56	-0.06	0.02	-0.16	0.08
34	GAC	-0.63	-0.34	-0.59	-0.47	-0.02	0.14	0.36	0.01	0.25	0.14	0.03	0.21
35	GAG	-0.25	-0.59	-0.46	-0.40	-0.38	-0.42	-0.55	-0.64	0.25	0.13	0.24	-0.26
36	GAT	0.25	0.88	0.78	0.58	0.15	-0.14	-0.10	0.38	-0.24	0.09	0.26	-0.26
37	GCA	1.00	0.47	0.79	-0.07	0.24	0.12	0.61	0.57	0.28	0.01	0.06	-0.04
38	GCC	0.42	-0.20	-0.28	-0.30	1.00	0.50	0.48	0.53	0.34	0.05	0.01	0.06
39	GCG	0.19	-0.23	-0.36	0.46	0.56	-0.58	-0.29	-0.40	-0.07	0.42	0.12	0.28
40	GCT	1.00	1.00	1.00	-0.53	-0.66	0.71	0.50	-0.17	-0.40	-0.28	0.01	-0.45
41	GGA	0.49	0.22	0.24	-0.20	1.00	0.42	0.20	0.28	-0.25	-0.04	-0.19	0.25
42	GGC	1.00	-0.33	-0.16	-0.23	-0.44	0.01	0.30	0.34	0.27	-0.17	0.16	0.26
43	GGG	-0.01	0.22	-0.63	0.32	1.00	-0.49	-0.49	-0.65	0.39	0.60	0.30	0.01
44	GGT	0.16	0.49	0.50	0.07	-0.52	0.19	0.30	-0.41	-0.22	-0.51	-0.36	-0.09
45	GTA	1.00	0.54	0.55	0.33	-0.67	0.61	0.33	0.35	0.03	0.14	-0.10	0.28
46	GTC	0.54	-0.04	0.18	-0.24	-0.17	0.76	0.51	0.71	0.48	0.05	-0.19	-0.14
47	GTG	0.47	-0.46	-0.37	0.53	-0.29	-0.56	-0.55	-0.47	0.16	0.40	0.54	0.41

48	GTT	-0.38	0.50	0.52	0.28	-0.30	-0.40	0.31	-0.09	-0.39	-0.33	-0.34	-0.33
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.38	0.01	-0.41	-0.72	1.00	0.28	0.10	0.46	0.27	0.36	0.31	0.02
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.54	0.56	0.79	0.84	-0.49	0.11	-0.08	0.45	-0.26	-0.26	0.01	0.00
53	TCA	1.00	-0.31	1.00	0.51	0.02	0.49	0.42	0.37	0.06	-0.04	-0.26	-0.06
54	TCC	1.00	-0.12	0.26	-0.09	-0.39	-0.07	0.51	0.20	0.14	0.37	0.09	-0.14
55	TCG	1.00	-0.06	-0.60	-0.19	-0.73	-0.58	-0.27	-0.17	0.38	0.57	-0.16	0.17
56	TCT	1.00	0.17	1.00	0.00	-0.58	-0.09	0.64	-0.32	-0.25	-0.16	-0.36	-0.14
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	-0.45	-0.60	-0.07	-0.38	1.00	-0.13	-0.08	0.28	0.65	0.35	0.35	0.59
59	TGG	1.00	0.56	-0.21	-0.21	-0.49	0.24	-0.51	0.05	-0.01	0.10	0.03	-0.08
60	TGT	1.00	1.00	1.00	1.00	1.00	0.45	0.05	-0.52	-0.39	-0.46	-0.55	-0.36
61	TTA	0.15	0.48	0.24	0.81	1.00	0.61	0.71	0.76	0.03	0.38	0.30	0.12
62	TTC	-0.70	-0.26	0.34	-0.59	1.00	0.32	0.54	0.43	0.48	0.22	0.04	0.55
63	TTG	1.00	-0.27	-0.62	-0.19	-0.24	-0.16	-0.43	-0.28	0.34	0.59	-0.11	-0.02
64	TTT	1.00	0.75	0.50	0.45	-0.50	-0.39	-0.07	0.57	-0.30	-0.35	0.15	-0.09
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
		25	26	27	28	29	30	31	32	33	34	35	36

Table C.8 continued

		37	38	39	40	41	42	43	44	45	46	47	48
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
1	AAA	-0.13	0.01	-0.16	0.14	-0.21	-0.21	-0.13	0.28	-0.22	0.40	-0.34	0.39
2	AAC	0.30	0.41	-0.38	-0.15	-0.35	-0.39	-0.26	-0.36	0.14	-0.22	0.34	0.21
3	AAG	0.30	0.52	-0.14	0.24	0.42	0.40	0.10	0.79	-0.28	0.03	-0.35	0.43
4	AAT	-0.14	-0.26	0.21	0.74	0.83	0.79	0.65	0.43	-0.17	-0.28	0.01	0.21
5	ACA	0.17	-0.23	0.35	-0.09	0.62	-0.14	0.13	0.28	0.31	0.48	0.57	0.50
6	ACC	-0.13	0.03	-0.11	-0.39	-0.28	-0.28	0.08	-0.52	-0.61	-0.60	-0.11	-0.37
7	ACG	0.04	0.49	0.05	-0.30	-0.12	0.04	0.03	-0.14	0.03	0.41	0.00	-0.07
8	ACT	0.01	-0.07	0.17	-0.28	0.11	0.73	0.49	-0.47	-0.56	0.04	0.13	-0.12
9	AGA	0.33	0.15	-0.27	0.84	0.22	-0.16	-0.22	-0.22	0.20	-0.17	0.16	0.71
10	AGC	0.35	-0.16	-0.18	0.14	-0.51	-0.21	-0.30	-0.49	-0.38	0.51	0.19	0.34
11	AGG	0.43	0.52	1.00	-0.40	-0.24	1.00	1.00	1.00	1.00	0.18	-0.65	-0.59
12	AGT	0.37	0.20	0.26	0.38	0.81	1.00	0.24	1.00	-0.50	0.19	-0.39	0.04
13	ATA	1.00	-0.28	-0.08	0.39	0.62	0.33	0.63	0.07	1.00	0.46	0.79	0.79
14	ATC	-0.16	-0.25	-0.09	-0.22	-0.32	-0.54	-0.50	-0.40	-0.30	-0.29	-0.11	-0.13
15	ATG	0.23	0.09	0.01	-0.26	0.20	-0.09	0.15	-0.19	-0.12	0.19	-0.24	0.19

16	ATT	0.26	-0.15	0.30	0.39	0.85	0.95	0.63	0.75	0.23	-0.07	0.21	0.28
17	CAA	0.18	0.23	0.46	-0.14	-0.24	-0.33	-0.05	-0.43	0.08	-0.17	-0.38	0.45
18	CAC	0.02	-0.10	0.33	0.20	-0.23	-0.53	-0.32	-0.35	-0.13	0.03	-0.12	-0.33
19	CAG	0.14	0.11	-0.22	-0.36	0.17	0.27	0.37	0.58	0.22	0.26	-0.36	0.36
20	CAT	-0.22	-0.46	0.17	0.49	0.34	0.74	0.42	0.52	0.28	0.34	-0.13	0.09
21	CCA	-0.01	0.14	0.70	-0.33	0.05	0.32	1.00	-0.68	0.53	0.71	0.67	-0.02
22	CCC	-0.70	0.30	-0.42	-0.19	-0.23	-0.73	-0.68	0.14	-0.35	-0.57	0.18	-0.78
23	CCG	0.38	-0.27	0.59	-0.12	-0.14	0.21	0.13	-0.22	0.43	0.43	0.29	-0.03
24	CCT	-0.36	-0.24	0.43	-0.35	0.51	0.83	1.00	0.40	-0.38	-0.30	0.49	-0.36
25	CGA	1.00	1.00	1.00	0.24	-0.16	-0.21	1.00	0.02	-0.46	0.44	0.35	-0.49
26	CGC	-0.06	-0.33	-0.28	0.19	-0.27	-0.36	-0.31	-0.26	0.30	-0.10	-0.22	-0.24
27	CGG	0.54	0.61	-0.47	-0.26	-0.20	0.24	-0.53	0.12	0.73	0.00	0.42	0.02
28	CGT	-0.27	0.13	-0.09	0.16	0.47	0.91	1.00	0.13	-0.46	0.14	0.42	0.12
29	CTA	0.24	-0.48	0.11	0.26	0.38	-0.43	1.00	-0.51	-0.56	0.30	0.19	0.18
30	CTC	0.12	-0.57	-0.31	0.32	-0.41	-0.74	-0.63	-0.67	-0.33	-0.60	-0.21	-0.28
31	CTG	0.38	0.15	0.24	0.28	0.72	0.48	0.36	0.77	0.91	0.23	0.58	0.76
32	CTT	-0.35	-0.26	-0.21	-0.08	0.45	0.25	0.90	-0.14	0.07	-0.34	-0.10	-0.40
33	GAA	-0.12	-0.09	-0.22	0.07	-0.04	-0.16	-0.18	0.06	-0.08	-0.08	-0.38	0.22
34	GAC	-0.14	0.19	-0.03	0.06	-0.53	-0.49	-0.20	-0.45	0.12	0.29	0.12	0.31
35	GAG	0.16	0.39	0.19	0.71	0.55	0.16	-0.01	0.35	0.60	0.52	0.16	0.20
36	GAT	0.02	0.25	-0.20	0.04	0.67	0.88	0.61	0.62	-0.35	-0.08	-0.28	0.16
37	GCA	-0.05	0.01	0.35	-0.22	0.10	0.28	0.17	0.01	0.59	0.50	0.37	0.47
38	GCC	-0.32	-0.10	0.08	-0.41	-0.54	-0.37	-0.29	-0.43	0.17	-0.39	0.02	-0.53
39	GCG	0.13	0.32	0.10	-0.04	-0.16	0.20	0.02	0.07	-0.01	0.07	-0.05	-0.07
40	GCT	0.09	0.07	0.21	-0.33	0.82	0.62	0.88	0.22	0.36	0.07	0.38	-0.31
41	GGA	0.07	0.01	-0.17	0.39	0.47	0.48	0.28	0.35	0.18	0.51	0.42	0.31
42	GGC	0.21	-0.13	0.05	-0.23	-0.46	-0.25	0.02	-0.24	0.05	-0.25	-0.16	-0.15
43	GGG	-0.26	0.79	-0.01	0.03	0.15	0.35	-0.88	0.68	0.56	0.29	0.17	0.37
44	GGT	-0.11	0.31	-0.27	0.10	0.84	0.92	1.00	0.91	-0.42	-0.32	-0.11	-0.37
45	GTA	0.42	0.12	0.32	0.54	-0.12	-0.10	0.59	-0.35	0.50	0.54	0.47	0.64
46	GTC	0.09	-0.27	-0.22	-0.34	-0.50	-0.59	-0.11	-0.49	-0.27	-0.20	-0.44	-0.55
47	GTG	-0.36	0.52	0.38	0.28	0.71	0.64	0.27	1.00	0.82	0.78	0.37	0.49
48	GTT	-0.20	0.08	-0.24	0.10	0.55	0.73	0.70	0.51	0.37	-0.21	-0.17	-0.38
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.17	0.03	-0.22	0.07	-0.49	-0.42	-0.42	-0.57	0.84	0.21	0.54	0.18
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.26	-0.15	-0.08	0.27	0.79	0.85	0.86	0.66	-0.31	-0.37	-0.39	0.27
53	TCA	0.23	-0.37	0.22	0.35	-0.16	-0.24	0.34	0.45	-0.04	0.30	0.51	-0.14
54	TCC	-0.23	0.06	0.24	-0.50	-0.51	-0.10	-0.10	-0.40	-0.27	-0.44	0.31	-0.49

55	TCG	-0.40	-0.43	-0.09	-0.03	0.37	-0.07	1.00	0.58	0.78	-0.25	0.69	-0.30
56	TCT	-0.26	0.31	0.52	0.07	0.67	0.65	0.84	0.33	-0.22	0.22	0.50	-0.43
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	-0.50	0.16	0.03	0.02	-0.46	-0.54	0.47	-0.08	0.20	0.27	0.72	1.00
59	TGG	-0.48	0.10	0.25	0.37	-0.19	0.26	-0.51	0.66	-0.19	0.25	-0.18	0.11
60	TGT	1.00	0.59	-0.41	0.53	0.81	1.00	1.00	1.00	-0.66	-0.43	-0.51	0.17
61	TTA	0.16	0.60	0.56	0.36	-0.07	0.02	-0.06	-0.21	-0.36	0.31	0.50	-0.11
62	TTC	0.58	-0.06	0.39	-0.03	-0.59	-0.53	0.06	-0.50	-0.18	0.20	0.22	0.37
63	TTG	-0.19	0.17	0.06	-0.25	0.80	0.71	0.00	0.50	0.81	0.21	0.21	-0.17
64	TTT	0.21	-0.32	-0.20	-0.08	0.85	0.71	1.00	0.58	0.00	-0.45	0.18	0.28
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
		37	38	39	40	41	42	43	44	45	46	47	48

Table C.8 continued

		49	50	51	52	53	54	55	56	57	58	59	60
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
1	AAA	0.00	-0.26	0.00	0.06	-0.31	-0.02	0.08	0.35	0.00	0.02	0.17	0.05
2	AAC	0.00	-0.14	0.00	0.18	0.72	0.76	-0.26	0.30	0.00	0.07	-0.13	-0.40
3	AAG	0.00	0.40	0.00	0.36	0.09	0.62	-0.34	0.16	0.00	0.08	-0.32	-0.25
4	AAT	0.00	-0.08	0.00	0.04	0.10	-0.59	0.31	0.78	0.00	0.41	0.20	0.14
5	ACA	0.00	-0.16	0.00	-0.05	0.02	-0.10	-0.31	0.06	0.00	-0.26	0.15	0.03
6	ACC	0.00	-0.09	0.00	0.17	0.60	1.00	0.24	0.26	0.00	-0.19	0.61	1.00
7	ACG	0.00	0.26	0.00	0.41	0.34	0.36	0.28	-0.14	0.00	-0.14	-0.22	0.16
8	ACT	0.00	-0.42	0.00	-0.35	-0.10	0.25	-0.21	-0.67	0.00	-0.27	-0.23	1.00
9	AGA	0.00	1.00	0.00	0.22	-0.19	-0.23	-0.15	-0.12	0.00	0.22	0.01	-0.41
10	AGC	0.00	-0.15	0.00	0.07	0.35	0.78	-0.19	0.20	0.00	0.43	0.02	0.59
11	AGG	0.00	1.00	0.00	0.34	0.48	1.00	1.00	0.35	0.00	1.00	-0.56	1.00
12	AGT	0.00	0.32	0.00	0.09	-0.34	-0.22	-0.65	-0.28	0.00	1.00	0.05	1.00
13	ATA	0.00	-0.60	0.00	-0.37	-0.11	-0.30	1.00	-0.04	0.00	-0.38	-0.52	1.00
14	ATC	0.00	0.46	0.00	0.40	0.37	0.11	0.50	0.55	0.00	-0.04	-0.13	0.35
15	ATG	0.00	0.18	0.00	-0.14	-0.43	0.72	0.52	-0.04	0.00	0.58	0.00	-0.45
16	ATT	0.00	-0.19	0.00	-0.22	-0.23	-0.54	0.04	-0.42	0.00	0.20	0.38	-0.38
17	CAA	0.00	-0.32	0.00	-0.47	-0.21	-0.47	-0.58	0.14	0.00	-0.17	-0.42	-0.43
18	CAC	0.00	0.46	0.00	-0.30	0.46	0.70	-0.02	0.11	0.00	-0.11	0.18	-0.23
19	CAG	0.00	0.59	0.00	0.42	-0.18	0.32	0.42	0.00	0.00	-0.14	0.53	1.00
20	CAT	0.00	0.47	0.00	-0.29	-0.50	-0.31	0.46	0.47	0.00	0.11	-0.12	0.23
21	CCA	0.00	-0.33	0.00	-0.43	0.03	1.00	-0.46	-0.58	0.00	-0.17	0.05	-0.43
22	CCC	0.00	0.19	0.00	0.64	0.21	0.33	1.00	0.51	0.00	0.01	1.00	1.00

23	CCG	0.00	0.09	0.00	0.07	-0.03	0.50	0.44	0.36	0.00	0.45	-0.31	-0.25
24	CCT	0.00	-0.25	0.00	-0.01	-0.46	-0.36	-0.05	-0.37	0.00	1.00	0.64	-0.70
25	CGA	0.00	-0.51	0.00	-0.44	0.29	-0.17	1.00	0.13	0.00	-0.45	1.00	1.00
26	CGC	0.00	-0.35	0.00	0.04	0.78	0.82	0.18	-0.32	0.00	-0.40	-0.46	-0.64
27	CGG	0.00	0.40	0.00	0.20	0.58	1.00	0.60	0.48	0.00	0.46	0.55	1.00
28	CGT	0.00	-0.44	0.00	-0.16	-0.42	0.20	-0.58	-0.68	0.00	1.00	1.00	1.00
29	CTA	0.00	1.00	0.00	-0.78	-0.60	-0.29	-0.69	-0.03	0.00	1.00	-0.79	-0.82
30	CTC	0.00	0.17	0.00	0.56	0.24	0.63	-0.19	0.73	0.00	0.49	0.37	-0.32
31	CTG	0.00	-0.12	0.00	-0.21	-0.05	0.16	-0.35	0.01	0.00	0.42	-0.08	0.58
32	CTT	0.00	-0.13	0.00	0.45	-0.26	0.31	-0.03	-0.50	0.00	0.04	0.60	-0.57
33	GAA	0.00	-0.08	0.00	-0.06	-0.01	-0.18	0.09	0.29	0.00	-0.11	0.08	0.10
34	GAC	0.00	0.32	0.00	0.51	0.76	0.60	0.40	0.32	0.00	-0.34	-0.09	-0.18
35	GAG	0.00	0.04	0.00	0.32	0.76	-0.29	-0.12	0.26	0.00	-0.19	-0.17	0.55
36	GAT	0.00	-0.35	0.00	-0.16	-0.11	-0.47	0.12	0.10	0.00	0.58	0.08	-0.02
37	GCA	0.00	-0.22	0.00	-0.02	-0.13	-0.06	-0.16	-0.23	0.00	0.28	-0.39	0.48
38	GCC	0.00	0.71	0.00	0.05	0.64	0.55	0.49	0.12	0.00	-0.53	-0.07	-0.55
39	GCG	0.00	0.52	0.00	0.34	0.07	0.58	0.06	0.39	0.00	0.36	0.47	0.69
40	GCT	0.00	-0.49	0.00	-0.51	-0.19	-0.75	-0.15	-0.61	0.00	0.29	-0.07	-0.03
41	GGA	0.00	-0.06	0.00	-0.29	0.45	1.00	0.11	0.13	0.00	0.40	0.41	0.71
42	GGC	0.00	-0.02	0.00	0.29	0.05	-0.04	-0.21	0.52	0.00	-0.45	-0.50	-0.39
43	GGG	0.00	0.70	0.00	-0.16	0.06	1.00	0.11	0.42	0.00	-0.37	1.00	1.00
44	GGT	0.00	-0.11	0.00	-0.09	-0.36	0.34	-0.49	-0.65	0.00	0.67	0.81	1.00
45	GTA	0.00	-0.47	0.00	-0.30	-0.39	-0.58	-0.03	-0.42	0.00	-0.13	-0.45	-0.20
46	GTC	0.00	0.59	0.00	0.27	0.41	0.67	0.50	0.68	0.00	-0.37	0.31	0.49
47	GTG	0.00	-0.25	0.00	0.16	0.39	-0.03	-0.14	0.62	0.00	0.80	0.04	0.71
48	GTT	0.00	0.22	0.00	-0.11	-0.14	-0.52	-0.15	-0.48	0.00	0.17	0.18	-0.58
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.00	0.12	0.00	0.22	0.64	0.20	1.00	0.12	0.00	0.02	0.20	-0.47
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.00	-0.10	0.00	-0.16	-0.32	-0.19	-0.37	-0.30	0.00	0.71	-0.15	-0.20
53	TCA	0.00	0.17	0.00	0.27	0.21	0.33	-0.33	0.84	0.00	0.42	-0.49	0.58
54	TCC	0.00	0.20	0.00	-0.29	0.78	-0.33	0.16	0.73	0.00	-0.59	1.00	-0.29
55	TCG	0.00	0.10	0.00	0.20	0.00	1.00	-0.30	-0.19	0.00	-0.77	-0.20	1.00
56	TCT	0.00	0.12	0.00	-0.41	-0.31	-0.59	0.08	-0.28	0.00	-0.07	0.59	0.48
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.00	-0.51	0.00	0.09	1.00	-0.54	-0.59	1.00	0.00	-0.30	1.00	-0.52
59	TGG	0.00	0.36	0.00	-0.24	0.32	1.00	-0.53	0.17	0.00	-0.32	0.00	0.69
60	TGT	0.00	0.26	0.00	1.00	-0.46	1.00	-0.57	0.24	0.00	1.00	-0.59	1.00
61	TTA	0.00	0.37	0.00	-0.29	-0.46	0.48	0.02	-0.02	0.00	-0.49	-0.29	0.30

62	TTC	0.00	0.10	0.00	0.20	-0.17	-0.16	0.24	0.01	0.00	-0.30	-0.39	0.48
63	TTG	0.00	-0.20	0.00	0.08	0.18	-0.38	0.74	0.16	0.00	1.00	-0.24	0.08
64	TTT	0.00	-0.22	0.00	0.02	-0.27	-0.29	0.42	0.25	0.00	-0.07	0.47	0.22
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
		49	50	51	52	53	54	55	56	57	58	59	60

Table C.8 continued

		61	62	63	64
		TTA	TTC	TTG	TTT
1	AAA	0.29	-0.39	0.07	0.62
2	AAC	0.24	-0.36	0.75	0.37
3	AAG	0.68	-0.10	0.72	-0.24
4	AAT	0.39	-0.29	0.52	0.38
5	ACA	-0.15	-0.31	-0.52	0.20
6	ACC	0.82	0.47	0.52	-0.38
7	ACG	0.41	0.17	0.89	0.06
8	ACT	0.00	-0.15	-0.62	0.26
9	AGA	0.27	0.69	0.61	0.65
10	AGC	0.28	0.25	-0.09	0.03
11	AGG	1.00	0.48	1.00	0.21
12	AGT	-0.28	-0.20	0.08	0.53
13	ATA	-0.72	-0.46	-0.69	-0.29
14	ATC	0.47	0.36	0.48	0.48
15	ATG	0.80	-0.14	0.83	0.12
16	ATT	-0.60	-0.27	-0.33	-0.24
17	CAA	-0.16	-0.33	0.29	-0.23
18	CAC	-0.20	-0.10	-0.39	0.27
19	CAG	0.77	0.33	0.38	0.24
20	CAT	-0.49	-0.09	-0.42	-0.07
21	CCA	-0.43	-0.32	-0.35	0.17
22	CCC	1.00	0.40	-0.21	0.09
23	CCG	-0.25	0.16	0.77	-0.21
24	CCT	-0.63	0.72	-0.43	-0.22
25	CGA	0.33	-0.65	-0.72	-0.07
26	CGC	0.28	0.13	0.05	0.35
27	CGG	1.00	0.37	-0.06	-0.48
28	CGT	-0.26	-0.42	-0.37	-0.40
29	CTA	-0.50	1.00	-0.24	-0.75

30	CTC	0.48	0.73	-0.02	0.59
31	CTG	0.78	0.07	0.32	-0.29
32	CTT	-0.27	0.06	-0.48	0.68
33	GAA	0.18	0.01	-0.32	0.03
34	GAC	0.43	0.33	0.17	0.37
35	GAG	0.41	-0.26	0.74	0.17
36	GAT	-0.35	-0.41	-0.52	0.01
37	GCA	-0.46	-0.33	-0.10	-0.26
38	GCC	0.21	0.66	0.17	0.24
39	GCG	0.29	0.30	0.78	0.17
40	GCT	-0.32	-0.32	-0.59	-0.32
41	GGA	-0.09	0.30	-0.39	-0.18
42	GGC	0.44	0.39	0.49	0.31
43	GGG	0.53	0.68	0.18	-0.05
44	GGT	-0.14	-0.46	-0.51	-0.53
45	GTA	-0.10	-0.23	0.03	-0.40
46	GTC	0.48	0.69	0.80	0.53
47	GTG	0.04	0.36	0.43	-0.24
48	GTT	-0.29	-0.37	-0.22	-0.11
49	TAA	0.00	0.00	0.00	0.00
50	TAC	-0.39	0.31	0.28	0.27
51	TAG	0.00	0.00	0.00	0.00
52	TAT	-0.36	-0.09	-0.48	-0.27
53	TCA	-0.17	-0.08	-0.30	-0.28
54	TCC	0.39	0.82	0.19	0.45
55	TCG	0.54	0.59	1.00	-0.36
56	TCT	-0.66	-0.42	0.02	-0.01
57	TGA	0.00	0.00	0.00	0.00
58	TGC	-0.31	-0.05	1.00	0.80
59	TGG	0.76	0.37	1.00	-0.22
60	TGT	-0.05	-0.12	0.31	-0.50
61	TTA	-0.42	-0.04	-0.23	-0.40
62	TTC	-0.08	-0.01	0.43	-0.10
63	TTG	0.68	-0.03	-0.06	-0.45
64	TTT	-0.59	-0.15	-0.23	0.22
		TTA	TTC	TTG	TTT
		61	62	63	64

Table C.9: CPW matrix *Saccharomyces cerevisiae* full genome (left codon indicated in column 2, right codon indicated in row 2). Host cell: *S.cerevisiae*; Sequence data: full *S. cerevisiae* genome.

		1	2	3	4	5	6	7	8	9	10	11	12
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
1	AAA	0.18	0.05	0.13	-0.05	-0.12	0.12	0.00	0.05	-0.09	-0.24	-0.17	-0.23
2	AAC	-0.12	-0.14	-0.19	-0.03	-0.06	-0.12	0.03	-0.11	-0.16	-0.28	-0.14	-0.17
3	AAG	-0.17	-0.05	-0.20	0.05	-0.06	0.02	-0.08	0.09	-0.04	-0.05	-0.03	0.02
4	AAT	0.06	0.09	0.21	0.04	0.01	0.07	0.04	0.10	0.14	-0.04	0.02	-0.07
5	ACA	0.00	-0.06	-0.10	-0.13	-0.11	0.16	0.06	0.20	-0.33	-0.01	-0.30	-0.11
6	ACC	-0.23	-0.27	-0.33	-0.11	-0.11	-0.31	-0.16	-0.28	-0.09	-0.05	0.05	0.02
7	ACG	-0.10	0.06	0.00	0.01	0.15	0.33	0.19	0.38	-0.09	0.01	-0.19	0.13
8	ACT	0.30	0.31	0.29	0.17	0.12	-0.10	0.12	-0.07	0.26	0.30	0.36	0.12
9	AGA	0.04	-0.16	-0.10	-0.10	-0.11	0.00	0.01	-0.06	-0.25	-0.13	-0.17	-0.13
10	AGC	-0.13	-0.21	0.04	-0.19	-0.08	-0.25	-0.21	-0.14	0.01	-0.31	-0.16	-0.22
11	AGG	-0.24	0.09	-0.06	0.16	-0.07	0.12	-0.03	0.05	0.11	0.02	0.11	0.14
12	AGT	-0.02	0.05	0.28	-0.03	0.02	-0.01	0.00	0.18	0.27	0.00	0.15	0.00
13	ATA	-0.05	-0.08	0.04	-0.12	-0.14	0.19	-0.16	0.06	-0.12	-0.01	-0.17	0.07
14	ATC	-0.35	-0.34	-0.35	-0.24	-0.11	-0.27	-0.05	-0.25	-0.22	-0.04	-0.12	-0.19
15	ATG	-0.05	0.00	0.08	0.00	-0.13	-0.01	-0.09	0.18	-0.09	-0.17	-0.03	-0.14
16	ATT	0.30	0.31	0.34	0.29	0.22	0.12	0.23	0.06	0.25	0.39	0.28	0.31
17	CAA	0.05	0.01	-0.08	-0.06	-0.11	0.06	-0.15	-0.09	-0.07	-0.14	-0.10	-0.28
18	CAC	-0.17	-0.22	-0.27	-0.16	-0.22	-0.09	-0.10	-0.16	-0.09	-0.06	0.16	0.08
19	CAG	-0.05	0.16	0.11	0.01	-0.02	0.31	0.04	0.33	0.28	-0.01	0.10	0.09
20	CAT	0.11	0.17	0.22	0.10	0.05	0.16	0.19	0.09	0.24	0.29	0.27	0.28
21	CCA	0.01	-0.04	-0.18	-0.08	-0.04	0.01	0.07	-0.13	-0.28	0.09	-0.17	0.01
22	CCC	-0.25	-0.12	-0.28	-0.18	-0.24	-0.25	-0.22	-0.15	0.05	-0.15	0.09	-0.11
23	CCG	0.09	0.02	0.05	0.08	0.00	0.53	0.17	0.37	0.20	0.31	0.11	0.28
24	CCT	0.21	0.22	0.34	0.12	0.13	-0.06	0.05	0.19	0.44	0.45	0.41	0.32
25	CGA	0.12	-0.08	0.30	-0.14	0.02	-0.07	-0.24	0.19	0.06	-0.08	-0.03	-0.26
26	CGC	0.05	0.07	0.05	0.07	-0.22	-0.14	-0.08	0.17	0.31	-0.49	0.16	-0.30
27	CGG	-0.10	0.21	0.04	-0.15	-0.07	0.40	0.11	0.52	0.44	0.27	-0.05	-0.06
28	CGT	0.27	0.40	0.29	0.26	0.24	-0.08	0.18	0.12	0.47	0.38	0.45	0.15
29	CTA	0.12	0.05	0.11	-0.02	-0.08	0.11	0.05	0.14	-0.06	-0.05	-0.06	-0.01
30	CTC	-0.02	-0.09	-0.01	-0.15	-0.07	-0.35	-0.21	-0.19	0.32	-0.22	0.19	-0.27
31	CTG	-0.11	-0.08	0.00	-0.01	0.15	0.20	-0.10	0.21	0.22	0.02	0.06	0.16
32	CTT	0.53	0.39	0.59	0.46	0.33	0.24	0.19	0.18	0.54	0.48	0.61	0.53
33	GAA	0.05	0.00	-0.05	-0.05	-0.07	0.05	-0.11	-0.08	-0.10	-0.24	-0.06	-0.31

34	GAC	-0.11	-0.18	-0.24	-0.05	-0.03	-0.17	0.06	-0.19	-0.11	-0.15	-0.11	-0.10
35	GAG	-0.04	0.06	0.02	0.10	0.08	0.19	0.05	0.21	0.18	-0.14	0.09	-0.10
36	GAT	0.04	0.14	0.22	0.02	0.06	0.07	0.06	0.08	0.15	0.12	0.18	0.12
37	GCA	0.05	-0.05	0.03	-0.11	0.05	0.31	0.15	0.21	-0.34	-0.10	-0.29	-0.06
38	GCC	-0.18	-0.18	-0.41	-0.19	-0.10	-0.34	-0.19	-0.32	0.06	-0.08	-0.07	-0.08
39	GCG	0.07	0.01	-0.06	0.17	0.18	0.45	0.08	0.25	0.21	0.25	0.20	0.28
40	GCT	0.22	0.14	0.20	0.21	0.15	-0.04	0.20	-0.19	0.21	0.30	0.33	0.27
41	GGA	-0.12	-0.15	-0.02	-0.26	-0.16	0.14	-0.29	0.05	-0.26	-0.22	-0.24	-0.30
42	GGC	0.10	0.04	0.05	-0.03	0.01	0.03	0.11	-0.03	0.04	-0.24	-0.04	-0.27
43	GGG	-0.19	0.02	-0.13	0.13	-0.01	0.24	-0.06	0.23	0.06	-0.01	0.01	0.21
44	GGT	0.10	0.02	0.02	0.18	0.12	-0.13	0.16	-0.09	0.00	0.12	0.40	0.27
45	GTA	-0.05	-0.02	0.09	-0.10	-0.05	0.14	-0.18	0.11	-0.09	-0.01	-0.16	0.12
46	GTC	-0.19	-0.25	-0.36	-0.16	-0.14	-0.40	0.06	-0.29	-0.11	-0.10	-0.07	-0.16
47	GTG	-0.13	-0.07	-0.13	0.07	0.02	0.07	0.03	0.21	-0.01	0.01	-0.02	0.14
48	GTT	0.26	0.16	0.29	0.17	0.27	0.01	0.29	-0.04	0.26	0.26	0.40	0.28
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.13	-0.18	-0.23	-0.10	-0.14	-0.04	-0.09	-0.10	-0.02	0.11	-0.15	0.04
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.12	0.15	0.22	0.10	0.06	0.13	-0.14	0.17	0.21	0.30	0.07	0.26
53	TCA	0.03	0.04	0.07	-0.05	0.16	0.30	0.06	0.12	-0.27	0.03	-0.27	0.10
54	TCC	-0.28	-0.17	-0.31	-0.13	-0.16	-0.22	-0.12	-0.34	-0.05	-0.14	-0.02	-0.14
55	TCG	-0.15	0.03	-0.14	-0.04	0.12	0.33	0.02	0.30	-0.15	0.07	-0.21	0.21
56	TCT	0.21	0.28	0.27	0.19	0.05	0.03	0.11	-0.07	0.35	0.33	0.24	0.30
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	-0.12	-0.03	-0.14	-0.10	-0.04	-0.11	0.04	-0.02	0.09	-0.15	-0.17	0.00
59	TGG	-0.04	0.02	0.06	-0.01	-0.03	-0.02	-0.11	0.09	-0.17	0.15	-0.15	0.18
60	TGT	0.00	0.00	0.21	0.08	0.13	-0.06	-0.05	0.02	0.30	0.27	0.16	0.36
61	TTA	0.14	0.05	0.06	0.10	-0.12	-0.07	-0.10	-0.06	-0.08	-0.03	-0.09	-0.07
62	TTC	-0.35	-0.32	-0.34	-0.28	0.03	-0.28	-0.07	-0.19	-0.18	-0.17	-0.17	-0.16
63	TTG	-0.28	-0.25	-0.29	-0.15	0.07	-0.18	-0.06	-0.05	-0.13	-0.10	-0.09	-0.07
64	TTT	0.30	0.28	0.44	0.29	0.26	-0.06	0.07	0.11	0.14	0.13	0.15	0.18
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
		1	2	3	4	5	6	7	8	9	10	11	12

Table C.9 continued

		13	14	15	16	17	18	19	20	21	22	23	24
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
1	AAA	-0.16	0.00	-0.10	-0.06	0.10	0.18	0.05	0.13	0.00	0.10	-0.08	-0.01

2	AAC	0.06	-0.05	0.00	0.01	-0.15	-0.07	-0.12	-0.07	0.01	0.06	0.18	-0.02
3	AAG	0.11	0.10	0.15	0.13	-0.12	-0.21	-0.10	-0.15	-0.07	0.03	0.11	0.04
4	AAT	0.05	0.01	0.00	-0.05	0.06	0.11	0.23	0.01	0.03	0.15	-0.15	-0.10
5	ACA	-0.10	0.27	-0.13	0.07	0.09	-0.02	-0.05	-0.13	-0.05	0.04	0.04	-0.17
6	ACC	-0.19	-0.33	-0.15	-0.24	0.04	0.07	0.20	0.21	0.14	0.21	0.35	0.36
7	ACG	-0.16	0.25	-0.05	0.30	-0.12	-0.19	-0.26	-0.23	0.02	-0.28	-0.35	-0.24
8	ACT	0.13	0.04	0.26	0.09	-0.07	0.13	0.11	0.09	-0.11	0.13	0.05	0.09
9	AGA	-0.14	0.03	-0.06	-0.01	0.10	0.05	0.10	0.12	0.04	0.23	0.08	0.04
10	AGC	-0.21	-0.02	0.09	-0.02	0.10	0.05	0.21	0.04	0.36	0.14	0.39	0.23
11	AGG	-0.21	0.27	0.10	0.14	-0.09	0.14	-0.18	-0.02	-0.18	-0.29	-0.32	-0.19
12	AGT	-0.15	0.14	0.24	0.04	0.25	0.21	0.47	0.18	0.42	0.28	0.33	0.30
13	ATA	-0.19	0.17	-0.08	0.18	0.20	-0.08	0.06	0.09	0.05	-0.03	-0.39	0.09
14	ATC	-0.06	-0.30	-0.22	-0.14	0.07	0.18	0.02	0.04	0.10	0.24	0.29	0.30
15	ATG	0.01	0.08	0.00	-0.05	-0.07	0.07	0.16	-0.04	0.07	-0.21	0.07	0.02
16	ATT	0.18	0.01	0.21	0.06	-0.14	-0.08	-0.04	-0.06	-0.07	0.01	-0.19	-0.10
17	CAA	-0.13	0.04	-0.09	-0.01	0.19	0.16	-0.06	0.08	0.00	0.31	-0.21	-0.01
18	CAC	0.03	-0.05	-0.07	-0.06	-0.07	-0.09	-0.09	0.10	0.05	0.19	0.23	0.33
19	CAG	-0.05	0.10	0.22	0.16	-0.05	-0.15	-0.40	-0.22	0.06	-0.03	-0.27	0.01
20	CAT	0.08	-0.09	0.04	0.04	0.02	-0.01	0.11	-0.02	-0.04	0.17	-0.29	-0.16
21	CCA	-0.06	0.14	-0.03	0.03	0.18	0.09	-0.11	0.12	-0.18	0.36	-0.17	0.00
22	CCC	-0.28	-0.29	-0.25	-0.21	0.34	0.26	0.31	0.02	0.33	0.49	0.55	0.38
23	CCG	-0.18	0.13	0.03	0.07	-0.10	-0.11	-0.45	-0.15	-0.08	-0.07	0.05	0.00
24	CCT	0.17	0.09	0.21	0.13	-0.18	-0.10	0.02	-0.13	-0.18	0.00	-0.09	-0.04
25	CGA	-0.32	0.13	-0.24	0.07	0.11	0.25	-0.20	-0.23	0.16	0.12	0.53	0.01
26	CGC	-0.21	0.03	0.05	0.18	-0.09	-0.33	-0.13	-0.30	0.02	-0.25	-0.13	0.04
27	CGG	0.02	0.27	-0.02	0.26	0.10	-0.09	-0.41	0.12	0.09	-0.47	-0.29	-0.11
28	CGT	0.16	0.01	0.20	-0.08	-0.02	-0.08	-0.01	-0.14	0.24	0.05	0.11	0.19
29	CTA	-0.10	0.10	-0.01	0.19	-0.02	0.00	-0.10	-0.03	-0.07	-0.08	-0.25	-0.06
30	CTC	-0.26	-0.24	0.03	-0.16	0.42	0.08	0.25	0.09	0.19	-0.06	0.36	0.19
31	CTG	-0.22	0.03	0.03	0.08	0.01	-0.11	-0.15	-0.05	0.22	-0.28	-0.06	0.19
32	CTT	0.30	0.21	0.42	0.13	0.11	-0.05	0.25	-0.13	-0.09	-0.15	-0.18	-0.08
33	GAA	-0.09	0.03	-0.07	-0.08	0.10	0.10	0.07	0.14	0.14	0.17	0.04	0.03
34	GAC	0.05	-0.05	-0.02	0.03	-0.17	-0.17	-0.22	-0.16	-0.01	-0.05	0.10	-0.10
35	GAG	0.15	0.16	0.18	0.12	-0.16	-0.19	-0.21	-0.25	-0.17	-0.27	0.10	-0.25
36	GAT	0.09	-0.07	0.01	-0.03	0.11	0.11	0.16	0.10	0.10	0.15	-0.11	-0.09
37	GCA	0.14	0.15	-0.09	0.16	0.03	0.12	0.01	-0.08	-0.06	0.01	0.31	-0.16
38	GCC	-0.05	-0.38	-0.22	-0.38	0.10	0.23	0.27	0.13	0.10	0.18	0.54	0.34
39	GCG	0.19	0.33	0.13	0.26	-0.15	-0.12	-0.29	-0.26	-0.15	-0.28	0.00	-0.13
40	GCT	0.32	0.02	0.21	-0.04	-0.11	-0.11	0.18	0.07	-0.13	-0.13	0.27	-0.01

41	GGA	-0.10	0.25	-0.07	0.11	-0.03	-0.17	-0.07	0.14	0.20	-0.13	0.14	-0.07
42	GGC	-0.06	0.14	0.17	0.13	-0.27	-0.31	-0.33	-0.27	-0.10	-0.30	0.38	-0.11
43	GGG	0.10	0.29	0.10	0.33	-0.03	-0.11	-0.10	-0.02	-0.26	-0.52	-0.48	-0.36
44	GGT	0.07	-0.18	-0.06	-0.19	0.09	0.12	0.49	0.22	0.13	0.21	0.45	0.15
45	GTA	-0.11	0.28	-0.04	0.24	0.03	0.22	-0.17	-0.03	-0.10	-0.09	-0.26	-0.04
46	GTC	0.04	-0.35	-0.18	-0.32	0.08	-0.13	0.21	-0.05	0.13	0.15	0.53	0.27
47	GTG	-0.01	0.23	-0.03	0.21	-0.04	0.16	-0.15	0.13	0.14	-0.13	-0.03	0.15
48	GTT	0.19	-0.03	0.15	-0.05	-0.06	-0.05	0.15	-0.06	-0.11	-0.02	0.13	-0.15
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.13	-0.24	-0.09	0.05	-0.11	-0.17	-0.06	-0.01	-0.01	0.27	0.36	0.29
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.15	-0.06	0.07	-0.02	0.02	0.10	0.21	0.03	-0.14	0.09	-0.21	-0.13
53	TCA	-0.05	0.25	-0.08	0.20	-0.01	0.15	-0.18	-0.03	-0.17	-0.15	-0.09	-0.27
54	TCC	-0.19	-0.34	-0.24	-0.26	0.10	0.01	0.17	0.18	0.32	0.21	0.46	0.30
55	TCG	-0.15	0.15	-0.15	0.20	-0.17	-0.36	-0.27	-0.26	-0.16	-0.32	-0.30	-0.17
56	TCT	0.19	0.05	0.14	0.08	-0.20	-0.01	0.03	-0.10	-0.24	-0.23	-0.11	-0.11
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	-0.17	0.02	-0.16	-0.02	-0.20	-0.13	-0.13	-0.07	0.21	-0.17	0.16	0.15
59	TGG	-0.12	0.11	0.00	0.02	-0.04	-0.13	0.09	0.09	-0.02	-0.19	0.14	0.10
60	TGT	0.11	-0.04	0.12	0.04	0.08	-0.03	0.25	0.11	0.14	-0.33	0.14	-0.18
61	TTA	0.00	0.06	-0.07	0.06	-0.15	0.00	-0.14	0.07	-0.09	0.08	-0.25	-0.02
62	TTC	0.09	-0.26	-0.18	-0.16	-0.15	-0.20	-0.16	-0.15	-0.06	-0.37	0.21	-0.04
63	TTG	-0.07	-0.07	-0.12	-0.14	0.05	0.02	0.09	0.04	0.12	-0.10	0.21	0.20
64	TTT	0.27	0.07	0.15	0.02	0.10	0.14	0.19	0.14	0.18	-0.16	0.06	0.06
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
		13	14	15	16	17	18	19	20	21	22	23	24

Table C.9 continued

		25	26	27	28	29	30	31	32	33	34	35	36
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
1	AAA	0.08	0.33	0.01	0.25	-0.27	0.09	-0.20	-0.05	0.08	0.08	0.00	0.04
2	AAC	0.26	-0.17	0.09	-0.13	0.08	-0.11	0.06	-0.06	0.15	0.12	0.20	0.11
3	AAG	0.28	0.22	0.12	0.20	-0.11	0.06	-0.11	0.04	-0.07	-0.14	-0.08	-0.03
4	AAT	-0.02	0.06	0.15	0.09	0.08	-0.04	0.12	0.10	-0.10	-0.11	-0.11	-0.05
5	ACA	0.00	0.04	-0.06	0.12	0.08	0.16	0.13	0.14	-0.05	0.05	-0.06	-0.05
6	ACC	0.46	0.31	0.36	0.14	0.34	0.31	0.23	0.05	0.24	0.19	0.20	0.13
7	ACG	-0.22	0.12	-0.11	0.34	-0.22	-0.11	-0.31	-0.17	0.02	-0.07	-0.13	-0.06
8	ACT	0.32	0.23	0.16	0.21	0.10	0.14	0.23	0.15	-0.11	0.03	0.02	-0.08

9	AGA	0.35	0.34	0.23	0.29	0.01	0.32	0.06	0.29	-0.04	0.03	0.00	-0.04
10	AGC	-0.07	-0.24	-0.12	0.23	0.38	0.25	0.35	0.22	-0.03	-0.13	-0.11	-0.15
11	AGG	-0.14	-0.02	-0.30	0.08	-0.27	-0.20	-0.17	-0.17	0.03	0.01	-0.03	0.11
12	AGT	0.10	0.06	0.13	0.28	0.44	0.22	0.31	0.15	-0.29	-0.28	-0.25	-0.31
13	ATA	-0.46	0.02	-0.53	0.15	-0.12	0.19	-0.18	-0.04	0.15	0.09	0.01	0.12
14	ATC	0.22	-0.08	0.23	0.16	0.09	-0.15	0.15	0.08	0.15	0.06	0.02	0.09
15	ATG	0.26	0.26	0.03	0.11	-0.18	-0.08	-0.29	-0.30	-0.02	-0.07	0.06	0.04
16	ATT	0.08	0.05	0.17	-0.05	0.08	0.00	0.12	-0.20	-0.15	-0.10	-0.01	-0.10
17	CAA	-0.03	0.22	-0.01	0.12	-0.03	0.26	-0.14	0.22	-0.04	0.11	-0.05	-0.03
18	CAC	0.12	-0.20	-0.15	-0.32	0.41	-0.06	0.18	0.02	0.06	-0.04	0.08	0.01
19	CAG	-0.13	-0.26	-0.35	-0.19	-0.13	-0.11	-0.19	-0.04	0.14	-0.10	0.02	0.00
20	CAT	-0.48	-0.19	-0.04	-0.20	0.08	-0.01	0.16	0.01	-0.05	0.00	0.00	0.01
21	CCA	0.16	0.06	0.01	0.09	0.10	0.20	0.12	0.18	-0.02	0.16	-0.09	0.04
22	CCC	0.24	-0.01	0.32	0.09	0.19	-0.11	0.29	0.17	0.27	0.19	0.30	0.20
23	CCG	-0.14	-0.22	-0.34	0.18	-0.45	-0.03	-0.41	-0.17	0.01	-0.08	-0.13	-0.04
24	CCT	-0.38	-0.21	0.06	-0.29	0.20	0.09	0.01	0.01	-0.06	-0.09	-0.08	-0.19
25	CGA	0.30	0.08	0.04	0.36	-0.38	0.07	0.03	-0.07	0.07	-0.16	-0.09	0.00
26	CGC	-0.03	-0.47	-0.49	-0.38	0.15	-0.23	-0.10	-0.01	0.33	0.21	-0.16	0.01
27	CGG	0.16	-0.22	-0.54	0.29	-0.31	-0.42	-0.43	-0.36	0.13	0.14	-0.01	0.22
28	CGT	0.01	-0.32	0.05	-0.48	0.04	-0.11	0.22	0.01	-0.05	-0.11	0.07	-0.09
29	CTA	-0.29	0.10	-0.10	-0.10	-0.20	-0.13	-0.27	0.06	-0.03	0.10	-0.02	0.08
30	CTC	-0.25	-0.22	0.18	0.21	0.19	-0.11	0.15	0.05	0.29	0.09	0.08	-0.08
31	CTG	-0.42	-0.19	-0.39	0.16	-0.16	-0.11	-0.22	-0.01	-0.08	-0.18	-0.14	-0.04
32	CTT	-0.49	0.05	-0.29	-0.04	-0.11	-0.36	-0.03	-0.27	0.15	0.00	0.28	-0.03
33	GAA	0.01	0.21	-0.14	0.08	-0.13	0.11	-0.06	0.11	0.00	0.02	0.01	-0.02
34	GAC	0.05	-0.30	-0.02	-0.42	0.18	0.01	0.06	-0.03	0.11	0.11	0.17	0.13
35	GAG	0.20	-0.16	-0.03	0.07	-0.20	-0.24	-0.30	-0.13	0.04	-0.03	-0.11	0.03
36	GAT	0.07	0.01	0.35	-0.11	0.23	0.01	0.22	0.02	-0.06	-0.05	-0.07	-0.07
37	GCA	0.18	-0.07	0.27	0.03	0.01	0.02	0.05	0.19	-0.15	-0.10	-0.09	-0.13
38	GCC	0.57	0.16	0.43	-0.16	0.13	-0.05	0.21	-0.09	0.33	0.33	0.43	0.30
39	GCG	0.41	-0.19	-0.08	0.18	-0.37	-0.30	-0.36	-0.24	-0.01	-0.15	-0.11	-0.05
40	GCT	0.24	0.02	-0.10	-0.13	0.14	0.12	0.31	-0.09	-0.12	0.00	0.05	-0.07
41	GGA	0.11	-0.17	-0.05	0.16	-0.03	0.01	-0.10	0.02	0.05	0.15	-0.03	0.13
42	GGC	0.29	-0.33	0.03	-0.38	0.05	-0.20	-0.02	-0.05	0.08	0.04	0.11	0.08
43	GGG	-0.16	-0.10	-0.10	-0.17	-0.39	-0.43	-0.42	-0.39	0.18	0.23	0.03	0.33
44	GGT	0.51	0.26	0.63	-0.08	0.04	0.07	0.41	0.08	-0.13	-0.21	0.05	-0.11
45	GTA	-0.51	-0.18	-0.29	-0.27	0.01	-0.12	-0.14	-0.09	0.02	0.02	-0.17	-0.07
46	GTC	0.49	-0.07	0.37	-0.07	0.26	-0.04	0.17	-0.20	0.23	0.04	0.32	0.23
47	GTG	0.13	-0.09	-0.36	0.16	-0.10	-0.13	-0.16	-0.11	-0.26	-0.14	-0.32	-0.10

48	GTT	0.23	-0.11	0.20	-0.31	0.19	-0.17	0.18	-0.25	0.06	0.02	0.15	0.00
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.23	-0.19	-0.05	-0.27	0.06	0.00	-0.05	0.18	0.06	0.02	0.07	0.08
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.04	-0.02	-0.03	-0.18	0.14	-0.02	0.06	0.01	-0.05	-0.10	-0.04	-0.01
53	TCA	-0.37	0.02	-0.01	0.27	-0.11	0.14	-0.11	-0.04	0.02	0.15	0.05	0.05
54	TCC	-0.11	0.02	0.32	-0.05	0.14	0.18	0.17	0.13	0.33	0.36	0.21	0.30
55	TCG	-0.02	-0.22	0.06	0.23	-0.32	-0.10	-0.34	-0.11	0.19	0.27	0.01	0.15
56	TCT	-0.17	-0.30	0.20	-0.18	0.06	0.04	0.13	0.01	-0.01	0.09	0.07	-0.05
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	-0.26	-0.19	-0.46	-0.41	0.16	-0.27	0.01	-0.11	0.23	0.14	0.15	0.17
59	TGG	0.17	0.51	0.36	0.52	-0.09	-0.09	-0.18	0.05	0.04	-0.10	-0.08	0.06
60	TGT	-0.17	-0.15	0.05	-0.23	0.08	-0.19	0.03	-0.03	-0.07	-0.09	-0.20	-0.09
61	TTA	-0.22	-0.19	-0.15	0.01	-0.19	-0.08	-0.19	-0.05	-0.02	0.03	-0.02	0.04
62	TTC	-0.08	-0.22	-0.01	-0.25	0.09	-0.14	0.15	0.06	0.27	0.23	0.28	0.23
63	TTG	0.12	0.08	0.13	0.11	0.14	0.27	0.15	0.27	-0.06	-0.03	-0.04	-0.02
64	TTT	-0.05	0.13	-0.20	0.38	0.21	-0.03	0.19	0.04	-0.19	-0.14	-0.07	-0.13
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
		25	26	27	28	29	30	31	32	33	34	35	36

Table C.9 continued

		37	38	39	40	41	42	43	44	45	46	47	48
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
1	AAA	0.09	0.22	0.20	0.10	0.01	0.10	0.01	0.11	-0.04	-0.01	-0.10	-0.08
2	AAC	0.24	0.19	0.35	0.15	0.19	0.14	0.17	0.18	0.14	-0.14	0.22	0.01
3	AAG	-0.10	-0.13	-0.17	-0.21	-0.07	-0.26	0.10	-0.06	0.14	0.01	0.21	0.05
4	AAT	-0.12	-0.15	-0.21	-0.08	-0.15	-0.21	-0.27	0.05	0.02	-0.08	0.10	-0.09
5	ACA	-0.06	0.25	-0.06	0.30	-0.12	0.06	-0.04	0.13	-0.18	0.24	-0.03	0.24
6	ACC	0.16	0.08	0.21	0.08	0.28	0.27	0.30	-0.08	0.06	-0.09	0.08	0.04
7	ACG	-0.12	0.26	-0.27	0.23	-0.12	-0.09	-0.21	0.24	-0.25	0.12	-0.22	0.22
8	ACT	-0.20	-0.21	-0.10	-0.18	0.03	0.08	-0.12	-0.21	-0.07	-0.03	-0.08	-0.11
9	AGA	0.00	-0.01	0.11	-0.02	-0.03	-0.04	0.23	-0.13	-0.08	0.08	0.13	0.02
10	AGC	0.12	-0.16	0.28	0.05	-0.13	-0.21	-0.16	0.03	-0.10	0.14	0.02	0.14
11	AGG	-0.13	-0.02	-0.18	-0.10	0.19	0.15	0.42	0.39	-0.11	0.12	-0.13	0.22
12	AGT	-0.23	-0.22	-0.29	-0.19	-0.32	-0.22	-0.33	-0.20	-0.16	-0.14	-0.04	-0.08
13	ATA	0.11	0.25	-0.09	0.31	0.14	0.17	0.11	0.40	0.06	0.30	0.00	0.33
14	ATC	0.35	0.26	0.29	0.31	0.21	0.06	0.03	0.07	0.30	0.07	0.24	0.21
15	ATG	-0.05	-0.01	-0.09	0.08	-0.04	-0.03	-0.12	0.07	0.02	-0.01	0.02	-0.02

16	ATT	-0.17	-0.30	-0.22	-0.22	-0.11	-0.09	-0.20	-0.23	-0.09	-0.26	-0.19	-0.21
17	CAA	0.05	0.04	-0.05	-0.04	0.06	-0.04	-0.02	-0.05	-0.10	0.05	-0.17	0.04
18	CAC	0.21	0.15	0.29	0.22	0.23	0.10	0.09	0.06	0.10	-0.01	0.15	-0.09
19	CAG	-0.03	0.00	-0.26	0.12	-0.18	-0.18	0.10	0.29	-0.05	0.17	-0.09	0.21
20	CAT	-0.03	-0.19	-0.20	-0.07	-0.10	0.02	-0.17	-0.03	0.06	0.00	0.02	-0.05
21	CCA	-0.02	0.27	0.16	0.13	0.12	0.00	0.20	-0.06	0.01	0.26	0.15	0.18
22	CCC	0.21	0.25	0.41	0.09	0.22	0.14	0.42	0.20	-0.29	0.07	-0.11	0.04
23	CCG	-0.11	0.29	0.05	0.16	-0.24	-0.26	-0.17	0.47	-0.28	0.17	-0.03	0.15
24	CCT	-0.22	-0.10	-0.24	-0.30	-0.12	-0.11	-0.30	-0.10	-0.25	0.01	-0.15	-0.11
25	CGA	-0.15	0.28	0.25	0.30	-0.23	-0.02	0.17	0.47	-0.16	0.28	-0.04	0.17
26	CGC	0.00	0.40	0.52	0.32	-0.03	-0.12	-0.11	0.31	0.26	0.40	0.15	0.00
27	CGG	0.33	0.12	0.00	0.35	0.04	0.30	0.39	0.62	-0.07	0.28	0.10	0.36
28	CGT	-0.04	-0.18	-0.05	-0.08	-0.16	-0.36	-0.27	-0.40	-0.25	-0.27	-0.18	-0.29
29	CTA	-0.03	0.20	0.01	0.06	-0.04	0.09	0.12	0.18	0.00	0.11	-0.02	0.22
30	CTC	0.34	0.21	0.29	0.30	0.20	0.10	0.06	-0.13	0.02	0.05	0.09	0.14
31	CTG	-0.18	-0.17	-0.32	0.17	-0.21	-0.17	-0.05	0.09	-0.28	-0.08	-0.22	0.13
32	CTT	0.00	-0.08	-0.17	-0.04	-0.26	-0.16	-0.15	-0.09	0.02	-0.04	-0.16	-0.06
33	GAA	0.08	0.11	0.06	-0.02	0.01	0.03	-0.01	-0.07	-0.01	0.02	-0.04	-0.06
34	GAC	0.24	0.13	0.38	0.13	0.25	0.08	0.17	0.08	0.11	0.18	0.15	0.02
35	GAG	-0.25	-0.03	-0.16	0.05	-0.13	-0.12	0.04	0.26	0.03	0.14	-0.03	0.11
36	GAT	-0.02	-0.06	-0.08	-0.16	-0.04	-0.06	-0.13	-0.06	0.08	-0.12	-0.02	-0.09
37	GCA	0.00	0.30	0.26	0.22	-0.08	-0.03	0.16	0.04	-0.11	0.27	0.11	0.26
38	GCC	0.29	0.04	0.49	-0.06	0.43	0.31	0.48	-0.06	0.25	0.03	0.19	-0.04
39	GCG	-0.05	0.14	-0.03	0.13	-0.14	-0.19	0.16	0.31	-0.28	0.25	-0.08	0.21
40	GCT	-0.01	-0.22	0.05	-0.33	0.10	-0.04	0.23	-0.30	0.01	-0.19	-0.13	-0.21
41	GGA	0.11	0.36	0.22	0.33	-0.08	0.18	0.08	0.38	0.22	0.42	0.28	0.37
42	GGC	0.14	-0.05	0.39	-0.06	0.09	-0.05	0.20	0.12	0.18	0.18	0.20	0.12
43	GGG	0.11	0.17	0.16	0.34	0.32	0.21	0.33	0.56	0.15	0.46	0.20	0.38
44	GGT	0.05	-0.29	0.03	-0.27	0.11	-0.02	-0.06	-0.37	-0.04	-0.37	-0.09	-0.31
45	GTA	-0.11	0.26	-0.16	0.27	-0.03	0.09	-0.08	0.32	0.04	0.26	-0.10	0.21
46	GTC	0.13	0.18	0.43	0.16	0.13	0.19	0.13	-0.03	0.28	0.09	0.32	0.07
47	GTG	-0.21	-0.18	-0.13	0.08	-0.11	-0.01	-0.30	0.23	-0.31	0.00	-0.28	0.07
48	GTT	0.02	-0.16	0.04	-0.15	-0.20	0.06	0.02	-0.17	0.18	-0.21	0.11	-0.19
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.30	0.10	0.27	0.12	0.21	0.20	0.15	0.03	0.19	-0.11	0.06	0.02
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.12	-0.11	-0.18	-0.12	-0.09	0.02	-0.14	-0.10	0.26	-0.14	-0.13	-0.06
53	TCA	-0.01	0.42	0.01	0.20	-0.15	0.07	0.03	0.22	-0.11	0.40	0.05	0.27
54	TCC	0.26	0.24	0.35	0.22	0.25	0.29	0.33	0.13	0.07	0.07	0.12	0.03

55	TCG	0.09	0.43	-0.04	0.44	0.24	0.23	0.26	0.48	-0.14	0.39	-0.01	0.20
56	TCT	-0.17	-0.17	-0.20	-0.21	-0.03	0.02	-0.04	-0.13	-0.08	-0.14	-0.24	-0.14
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.26	0.20	0.20	0.33	0.30	0.24	0.00	0.23	-0.03	0.23	0.25	0.17
59	TGG	0.01	0.04	-0.12	0.01	0.18	-0.02	-0.24	0.01	-0.08	0.03	0.21	-0.07
60	TGT	-0.03	-0.13	-0.19	-0.20	0.07	-0.14	-0.18	-0.16	0.08	-0.21	0.05	-0.15
61	TTA	0.06	0.12	-0.04	0.22	-0.02	0.14	0.03	0.08	0.09	0.11	-0.03	0.17
62	TTC	0.45	0.36	0.52	0.46	0.44	0.36	0.47	0.17	0.43	0.16	0.40	0.26
63	TTG	-0.10	-0.17	-0.12	-0.12	0.08	0.05	0.07	-0.08	-0.05	-0.11	-0.13	-0.08
64	TTT	-0.17	-0.36	-0.21	-0.19	-0.16	-0.19	-0.09	-0.19	-0.06	-0.21	0.01	-0.27
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
		37	38	39	40	41	42	43	44	45	46	47	48

Table C.9 continued

		49	50	51	52	53	54	55	56	57	58	59	60
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
1	AAA	0.00	-0.03	0.00	-0.09	-0.17	0.08	-0.13	0.01	0.00	-0.08	-0.15	-0.14
2	AAC	0.00	-0.14	0.00	-0.06	0.15	-0.03	0.10	0.00	0.00	0.00	-0.14	-0.12
3	AAG	0.00	0.01	0.00	0.16	0.22	0.28	0.16	0.30	0.00	0.12	0.26	0.23
4	AAT	0.00	0.09	0.00	0.06	-0.01	0.12	0.03	0.09	0.00	0.07	0.11	0.05
5	ACA	0.00	0.07	0.00	-0.11	-0.05	0.07	0.07	0.04	0.00	-0.17	-0.07	-0.08
6	ACC	0.00	-0.01	0.00	0.12	0.06	0.12	0.20	0.01	0.00	0.13	0.04	0.00
7	ACG	0.00	-0.05	0.00	-0.16	-0.05	0.21	0.07	0.28	0.00	-0.21	0.04	0.05
8	ACT	0.00	0.04	0.00	0.06	-0.16	-0.14	0.01	-0.20	0.00	0.21	0.03	0.07
9	AGA	0.00	0.18	0.00	0.13	-0.04	0.27	-0.01	0.17	0.00	0.27	0.08	0.12
10	AGC	0.00	0.09	0.00	-0.08	0.16	0.19	0.12	0.05	0.00	-0.08	0.03	0.00
11	AGG	0.00	0.06	0.00	0.14	-0.09	0.20	-0.18	0.11	0.00	0.09	0.13	0.35
12	AGT	0.00	0.10	0.00	0.01	0.02	0.23	0.18	0.18	0.00	-0.17	0.01	-0.16
13	ATA	0.00	-0.20	0.00	-0.24	-0.28	-0.12	-0.29	-0.14	0.00	-0.13	-0.18	-0.09
14	ATC	0.00	0.11	0.00	0.27	0.27	0.02	0.29	0.22	0.00	0.06	0.19	0.13
15	ATG	0.00	-0.04	0.00	0.03	0.05	0.05	-0.03	0.13	0.00	-0.07	0.00	0.05
16	ATT	0.00	0.08	0.00	0.04	0.00	-0.13	0.10	-0.11	0.00	-0.07	0.03	0.07
17	CAA	0.00	0.10	0.00	0.08	0.04	0.16	-0.02	0.01	0.00	0.21	-0.06	-0.08
18	CAC	0.00	0.02	0.00	-0.08	-0.03	-0.04	0.15	0.02	0.00	-0.04	-0.01	0.04
19	CAG	0.00	-0.23	0.00	-0.11	-0.01	0.25	-0.09	0.24	0.00	-0.23	0.13	0.09
20	CAT	0.00	0.17	0.00	-0.08	-0.08	-0.05	-0.13	-0.14	0.00	0.14	0.01	-0.08
21	CCA	0.00	0.07	0.00	-0.07	-0.08	0.14	0.04	-0.07	0.00	-0.19	-0.17	0.08
22	CCC	0.00	0.13	0.00	0.20	-0.03	-0.12	-0.02	-0.26	0.00	-0.03	0.17	-0.05

23	CCG	0.00	-0.25	0.00	-0.14	0.07	0.23	0.20	0.28	0.00	0.15	0.20	0.30
24	CCT	0.00	0.11	0.00	-0.04	-0.15	-0.13	-0.13	-0.11	0.00	0.00	0.10	-0.03
25	CGA	0.00	-0.28	0.00	-0.12	0.03	0.32	-0.06	0.06	0.00	-0.45	0.04	-0.09
26	CGC	0.00	-0.45	0.00	-0.17	-0.06	0.03	-0.10	-0.16	0.00	-0.41	-0.34	-0.18
27	CGG	0.00	-0.22	0.00	-0.27	-0.20	-0.11	-0.51	-0.12	0.00	-0.37	0.24	0.04
28	CGT	0.00	-0.23	0.00	-0.16	-0.06	-0.22	0.00	-0.08	0.00	-0.30	-0.25	-0.38
29	CTA	0.00	-0.05	0.00	-0.06	-0.09	-0.22	-0.23	-0.01	0.00	0.03	-0.22	-0.10
30	CTC	0.00	-0.05	0.00	-0.15	0.01	-0.19	-0.19	-0.13	0.00	-0.35	0.00	-0.30
31	CTG	0.00	-0.04	0.00	0.10	0.13	0.25	-0.01	0.34	0.00	0.01	0.19	0.20
32	CTT	0.00	-0.29	0.00	-0.36	-0.29	-0.43	-0.30	-0.33	0.00	-0.31	-0.25	-0.34
33	GAA	0.00	0.06	0.00	0.02	0.10	0.14	0.11	0.06	0.00	0.11	-0.05	-0.09
34	GAC	0.00	-0.13	0.00	-0.06	0.23	-0.01	0.01	-0.10	0.00	-0.07	-0.05	-0.19
35	GAG	0.00	-0.14	0.00	-0.04	0.13	0.30	-0.06	0.21	0.00	-0.11	0.13	0.14
36	GAT	0.00	0.16	0.00	-0.03	0.02	-0.03	-0.01	-0.07	0.00	0.20	0.03	0.03
37	GCA	0.00	-0.04	0.00	-0.10	0.04	0.03	-0.04	0.01	0.00	-0.31	-0.05	-0.05
38	GCC	0.00	0.18	0.00	0.11	0.28	-0.01	0.23	-0.07	0.00	0.17	0.17	-0.14
39	GCG	0.00	-0.19	0.00	-0.23	-0.01	0.10	0.01	0.12	0.00	-0.09	-0.10	0.18
40	GCT	0.00	0.04	0.00	0.09	-0.03	-0.30	-0.02	-0.16	0.00	0.35	-0.02	0.05
41	GGA	0.00	0.11	0.00	-0.15	0.11	0.08	-0.08	0.02	0.00	0.01	-0.08	-0.03
42	GGC	0.00	-0.17	0.00	-0.12	-0.09	-0.20	0.11	-0.12	0.00	-0.07	-0.19	-0.27
43	GGG	0.00	-0.02	0.00	0.15	0.17	-0.11	0.07	-0.02	0.00	0.08	0.22	0.23
44	GGT	0.00	0.00	0.00	0.14	0.11	0.01	0.23	-0.02	0.00	0.08	0.08	0.07
45	GTA	0.00	0.00	0.00	-0.09	-0.11	-0.18	-0.14	0.03	0.00	-0.11	-0.06	0.14
46	GTC	0.00	-0.04	0.00	0.30	0.28	-0.06	0.28	0.07	0.00	0.12	0.10	0.03
47	GTG	0.00	0.15	0.00	0.17	0.23	0.18	0.06	0.31	0.00	0.01	0.16	0.23
48	GTT	0.00	-0.12	0.00	-0.10	-0.13	-0.24	0.00	-0.25	0.00	-0.12	-0.09	-0.11
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.00	-0.14	0.00	0.00	0.10	-0.01	0.15	-0.03	0.00	0.12	-0.10	-0.12
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.00	0.16	0.00	-0.02	-0.05	-0.15	-0.13	-0.18	0.00	0.07	0.09	0.01
53	TCA	0.00	-0.04	0.00	-0.19	-0.18	0.02	-0.17	0.06	0.00	-0.19	-0.13	-0.07
54	TCC	0.00	0.15	0.00	0.21	0.07	-0.02	-0.03	-0.02	0.00	0.14	0.15	0.17
55	TCG	0.00	-0.26	0.00	-0.18	0.05	0.01	-0.17	0.26	0.00	0.00	-0.20	0.08
56	TCT	0.00	0.11	0.00	0.08	-0.14	-0.15	-0.10	-0.20	0.00	0.14	0.11	0.13
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.00	-0.12	0.00	-0.16	0.00	-0.20	0.05	-0.10	0.00	-0.13	-0.06	-0.14
59	TGG	0.00	-0.11	0.00	0.09	-0.15	0.05	-0.08	-0.02	0.00	0.01	0.00	-0.01
60	TGT	0.00	0.17	0.00	0.05	-0.05	-0.04	-0.04	-0.05	0.00	0.09	0.04	0.11
61	TTA	0.00	0.09	0.00	0.08	-0.11	-0.05	-0.15	-0.02	0.00	0.04	-0.16	-0.03

62	TTC	0.00	0.01	0.00	0.22	0.27	0.07	0.23	0.21	0.00	0.02	0.09	0.10
63	TTG	0.00	0.17	0.00	0.22	0.30	0.23	0.37	0.35	0.00	0.27	0.42	0.35
64	TTT	0.00	-0.15	0.00	-0.02	-0.10	-0.15	-0.09	-0.15	0.00	-0.10	-0.06	0.00
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
		49	50	51	52	53	54	55	56	57	58	59	60

Table C.9 continued

		61	62	63	64
		TTA	TTC	TTG	TTT
1	AAA	-0.03	0.00	0.10	-0.08
2	AAC	0.10	-0.01	-0.07	0.03
3	AAG	0.24	0.12	0.16	0.04
4	AAT	-0.07	-0.02	-0.07	0.00
5	ACA	0.00	0.22	0.22	-0.09
6	ACC	0.08	0.05	0.20	0.23
7	ACG	0.05	0.11	0.03	-0.02
8	ACT	-0.30	-0.17	-0.31	-0.09
9	AGA	-0.03	0.14	0.09	-0.09
10	AGC	0.28	0.15	0.31	0.11
11	AGG	0.00	0.01	0.13	-0.21
12	AGT	-0.05	-0.08	-0.02	0.02
13	ATA	-0.05	-0.04	0.10	-0.17
14	ATC	0.21	0.07	0.16	0.24
15	ATG	0.22	0.11	0.29	-0.07
16	ATT	-0.13	-0.12	-0.03	0.07
17	CAA	0.02	0.10	-0.01	0.09
18	CAC	0.25	-0.06	0.04	0.22
19	CAG	0.02	-0.07	0.00	-0.23
20	CAT	-0.20	-0.09	-0.15	-0.03
21	CCA	-0.06	0.08	-0.01	-0.12
22	CCC	-0.07	-0.10	0.11	-0.12
23	CCG	-0.27	0.08	0.05	0.02
24	CCT	-0.06	0.01	0.02	0.19
25	CGA	-0.12	0.14	0.12	-0.12
26	CGC	0.05	0.17	0.30	0.25
27	CGG	-0.12	-0.14	-0.17	-0.34
28	CGT	-0.08	0.17	-0.13	0.34
29	CTA	-0.10	0.09	0.04	0.03

30	CTC	0.15	-0.29	0.08	-0.18
31	CTG	0.21	0.01	0.13	0.11
32	CTT	-0.34	-0.49	-0.32	-0.17
33	GAA	0.10	0.20	0.05	-0.02
34	GAC	0.12	0.05	-0.06	0.13
35	GAG	0.06	0.02	0.08	-0.23
36	GAT	-0.11	-0.05	-0.16	-0.05
37	GCA	-0.01	0.01	0.04	-0.20
38	GCC	0.21	0.00	0.13	0.01
39	GCG	-0.08	-0.11	-0.07	-0.21
40	GCT	-0.04	0.12	-0.18	0.22
41	GGA	-0.06	-0.03	0.11	-0.33
42	GGC	0.16	0.24	0.22	0.18
43	GGG	-0.19	-0.45	-0.27	-0.50
44	GGT	0.05	0.15	0.03	0.44
45	GTA	0.19	0.09	0.08	-0.14
46	GTC	0.20	0.00	-0.01	0.10
47	GTG	0.31	0.21	0.17	0.05
48	GTT	-0.11	-0.22	-0.16	0.10
49	TAA	0.00	0.00	0.00	0.00
50	TAC	0.19	0.01	-0.06	0.15
51	TAG	0.00	0.00	0.00	0.00
52	TAT	-0.06	-0.12	-0.16	-0.02
53	TCA	-0.18	-0.01	-0.03	-0.15
54	TCC	0.05	0.02	0.09	-0.03
55	TCG	-0.14	-0.06	-0.09	-0.14
56	TCT	-0.17	0.07	-0.19	0.13
57	TGA	0.00	0.00	0.00	0.00
58	TGC	0.07	0.04	0.18	-0.18
59	TGG	0.02	0.00	0.11	0.00
60	TGT	0.00	0.04	-0.09	0.08
61	TTA	-0.01	0.06	0.06	0.00
62	TTC	0.09	-0.09	-0.02	0.16
63	TTG	0.34	0.27	0.26	0.21
64	TTT	-0.13	-0.20	-0.15	0.11
		TTA	TTC	TTG	TTT
		61	62	63	64

Table C.10: CPW matrix *Saccaromyces.cerevisiae* highly expressed sequences (left codon indicated in column 2, right codon indicated in row 2). Host cell: *S.cerevisiae*; Sequence data: full *S.cerevisiae* genome; Highly expressed group: 300 seqs.

		1	2	3	4	5	6	7	8	9	10	11	12
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
1	AAA	0.67	0.35	0.49	0.42	0.66	0.30	0.47	0.24	0.43	0.44	0.51	0.55
2	AAC	-0.05	-0.62	-0.63	0.07	0.12	-0.62	-0.11	-0.52	-0.53	-0.26	-0.04	-0.25
3	AAG	-0.10	-0.61	-0.65	0.12	0.21	-0.59	0.26	-0.53	-0.59	-0.16	0.20	0.11
4	AAT	0.61	0.16	0.35	0.58	0.63	0.28	0.62	0.40	0.42	0.44	0.38	0.44
5	ACA	0.49	0.22	0.13	0.28	0.52	0.49	0.78	0.49	-0.19	0.62	-0.07	0.38
6	ACC	-0.13	-0.71	-0.71	-0.18	-0.15	-0.67	0.00	-0.56	-0.54	-0.15	0.12	0.14
7	ACG	0.50	0.37	0.29	0.53	0.57	0.56	0.62	0.61	0.07	0.89	0.17	0.49
8	ACT	0.31	-0.16	0.07	0.61	0.19	-0.34	0.49	-0.34	-0.27	0.48	0.83	0.53
9	AGA	0.25	-0.53	-0.59	0.10	0.03	-0.59	0.27	-0.38	-0.53	0.19	0.24	-0.01
10	AGC	0.54	-0.04	0.21	0.55	0.59	0.17	1.00	0.19	0.38	-0.02	0.31	0.46
11	AGG	0.42	0.44	0.45	0.47	0.68	0.33	0.69	0.71	0.29	0.66	0.56	0.84
12	AGT	0.49	0.04	0.48	0.46	0.72	0.47	0.69	0.31	0.70	0.57	0.39	0.52
13	ATA	0.56	0.50	0.64	0.67	0.53	0.32	0.63	0.47	0.58	0.75	0.58	0.59
14	ATC	-0.31	-0.66	-0.68	-0.28	-0.11	-0.55	0.04	-0.63	-0.67	0.30	0.14	-0.10
15	ATG	0.23	-0.30	-0.25	0.29	0.39	-0.12	0.56	-0.33	-0.30	0.47	0.16	0.20
16	ATT	0.49	-0.20	0.02	0.50	0.55	-0.15	0.49	0.01	-0.07	0.67	0.48	0.64
17	CAA	0.22	-0.40	-0.43	0.25	0.26	-0.48	0.50	-0.29	-0.36	0.00	0.23	-0.16
18	CAC	0.10	-0.55	-0.67	0.07	0.12	-0.62	0.44	-0.53	-0.59	0.31	0.61	-0.02
19	CAG	0.54	0.40	0.20	0.16	0.43	0.35	-0.08	0.60	0.19	0.11	0.62	0.39
20	CAT	0.54	-0.09	0.31	0.50	0.51	0.07	0.45	0.36	0.46	0.74	0.62	0.87
21	CCA	0.20	-0.52	-0.64	-0.15	0.12	-0.54	0.45	-0.53	-0.61	0.13	-0.09	-0.11
22	CCC	0.41	-0.03	-0.07	0.27	0.58	0.09	0.18	-0.08	0.21	0.63	0.65	0.49
23	CCG	0.84	0.75	0.63	0.75	0.80	1.00	0.85	0.94	0.73	0.53	1.00	0.89
24	CCT	0.45	0.10	0.28	0.51	0.71	-0.20	0.22	0.10	0.54	0.81	0.64	0.61
25	CGA	0.83	0.56	0.92	0.70	0.87	0.80	0.40	0.88	0.83	0.67	1.00	0.09
26	CGC	0.46	0.34	0.33	0.65	0.52	-0.14	0.29	0.42	0.80	1.00	1.00	0.19
27	CGG	0.71	0.44	0.73	0.62	0.54	1.00	0.49	1.00	0.86	0.43	0.68	1.00
28	CGT	0.19	-0.25	-0.18	0.13	0.32	-0.44	0.39	-0.23	0.07	0.66	0.53	-0.04
29	CTA	0.39	0.19	0.24	0.47	0.47	0.61	0.41	0.22	-0.39	0.74	0.34	0.41
30	CTC	0.67	0.17	0.03	0.40	0.68	-0.21	-0.29	0.57	0.65	0.69	0.74	0.68
31	CTG	0.42	0.38	0.29	0.35	0.62	0.33	0.72	0.54	0.78	0.50	0.79	0.66
32	CTT	0.78	0.60	0.61	0.71	0.89	0.54	0.61	0.55	0.76	0.72	1.00	0.81
33	GAA	0.22	-0.35	-0.37	0.24	0.28	-0.40	0.28	-0.31	-0.39	-0.03	0.50	0.13

34	GAC	-0.04	-0.57	-0.62	-0.07	0.20	-0.62	0.44	-0.50	-0.44	0.17	0.22	0.02
35	GAG	0.49	-0.03	-0.03	0.30	0.46	0.38	0.47	0.30	0.32	0.19	0.53	0.41
36	GAT	0.44	0.19	0.27	0.40	0.68	-0.05	0.42	0.12	0.34	0.55	0.53	0.78
37	GCA	0.58	0.37	0.27	0.62	0.51	0.40	0.60	0.61	-0.07	0.56	0.22	0.45
38	GCC	-0.02	-0.58	-0.62	-0.07	0.10	-0.57	0.41	-0.53	-0.51	0.51	0.48	0.70
39	GCG	0.83	0.45	0.26	0.56	0.79	0.50	0.71	0.65	0.67	0.81	0.82	0.67
40	GCT	0.26	-0.46	-0.40	0.21	0.35	-0.55	0.38	-0.37	-0.28	0.56	0.52	0.43
41	GGA	0.64	0.46	0.46	0.58	0.69	0.39	0.63	0.50	0.43	0.72	0.89	0.74
42	GGC	0.55	0.00	0.27	0.49	0.68	0.49	0.79	0.02	0.37	0.24	0.27	0.44
43	GGG	0.62	0.55	0.40	0.73	0.49	0.48	0.43	0.30	0.39	0.39	0.61	0.86
44	GGT	0.03	-0.61	-0.60	0.08	0.32	-0.56	0.41	-0.58	-0.55	0.53	0.52	0.55
45	GTA	0.66	0.37	0.47	0.42	0.59	0.53	0.58	0.26	0.54	0.72	0.34	0.69
46	GTC	-0.17	-0.63	-0.70	-0.17	0.27	-0.65	0.67	-0.60	-0.56	-0.36	0.74	0.21
47	GTG	0.51	0.10	0.07	0.64	0.54	0.25	0.52	0.48	-0.20	0.50	0.66	0.57
48	GTT	0.31	-0.27	-0.21	0.21	0.59	-0.45	0.66	-0.37	-0.17	0.56	0.52	0.67
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	-0.09	-0.58	-0.61	0.08	0.04	-0.56	0.42	-0.57	-0.57	0.30	0.52	-0.09
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.60	0.06	0.43	0.61	0.67	0.42	0.66	0.30	0.59	0.52	0.64	0.64
53	TCA	0.69	0.22	0.07	0.48	0.37	0.20	0.29	0.52	-0.29	0.19	0.03	0.39
54	TCC	0.04	-0.68	-0.74	-0.25	-0.17	-0.66	-0.13	-0.59	-0.60	-0.09	0.10	-0.02
55	TCG	-0.01	0.17	-0.05	0.38	0.68	0.80	0.59	0.12	-0.23	0.65	0.22	0.21
56	TCT	0.21	-0.45	-0.36	0.38	0.29	-0.54	0.11	-0.44	0.06	0.67	0.50	0.41
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.26	0.62	0.12	0.42	0.11	0.02	0.50	0.70	0.34	0.29	0.76	0.51
59	TGG	0.15	-0.17	-0.17	0.14	0.59	-0.25	0.16	-0.28	-0.33	0.35	0.17	0.33
60	TGT	0.09	-0.43	-0.30	0.00	0.45	-0.52	0.23	-0.30	-0.26	0.13	0.40	0.70
61	TTA	0.57	-0.21	0.06	0.61	0.25	-0.38	0.58	-0.14	-0.19	0.16	0.18	0.35
62	TTC	-0.20	-0.61	-0.64	-0.13	0.26	-0.60	0.42	-0.51	-0.58	-0.10	0.44	-0.07
63	TTG	-0.27	-0.64	-0.68	-0.28	0.17	-0.65	0.43	-0.59	-0.62	-0.04	0.21	-0.06
64	TTT	0.68	0.33	0.47	0.61	0.54	0.07	0.47	0.34	0.32	0.39	0.43	0.53
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
		1	2	3	4	5	6	7	8	9	10	11	12

Table C.10 continued

		13	14	15	16	17	18	19	20	21	22	23	24
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
1	AAA	0.52	0.14	0.16	0.15	0.22	0.25	0.34	0.54	0.04	0.54	0.59	0.32

2	AAC	0.53	-0.61	-0.24	-0.41	-0.45	-0.53	0.05	-0.33	-0.50	0.40	0.18	-0.19
3	AAG	0.62	-0.56	-0.18	-0.31	-0.41	-0.55	0.35	-0.21	-0.51	0.16	0.57	-0.16
4	AAT	0.71	0.03	0.22	0.39	0.26	0.44	0.63	0.52	0.20	0.09	0.44	0.36
5	ACA	0.68	0.51	0.29	0.41	0.60	0.33	0.41	0.22	0.01	0.50	0.94	0.52
6	ACC	0.44	-0.61	-0.54	-0.59	-0.26	-0.49	0.33	0.08	-0.40	0.13	0.45	0.30
7	ACG	0.54	0.12	0.18	0.63	0.14	0.43	0.34	0.42	0.09	0.00	0.44	0.55
8	ACT	0.38	-0.30	0.41	-0.12	-0.48	-0.44	0.43	0.08	-0.54	0.46	0.60	-0.12
9	AGA	0.47	-0.48	-0.21	-0.32	-0.26	-0.41	0.21	0.06	-0.54	0.44	0.44	-0.11
10	AGC	0.36	0.02	0.59	0.54	0.09	0.13	0.39	0.51	0.54	0.56	1.00	0.10
11	AGG	0.50	0.46	0.28	0.27	0.51	0.25	0.39	0.39	0.19	0.58	0.47	0.50
12	AGT	0.63	0.52	0.54	0.19	0.52	0.63	0.79	0.42	0.61	0.90	0.62	0.48
13	ATA	0.66	0.51	0.37	0.68	0.79	0.78	0.68	0.49	0.53	0.59	0.77	0.65
14	ATC	0.41	-0.64	-0.47	-0.46	-0.44	-0.39	0.38	0.09	-0.39	0.35	0.43	-0.02
15	ATG	0.71	-0.25	0.00	-0.19	-0.05	-0.19	0.11	0.13	-0.33	0.27	0.59	0.26
16	ATT	0.62	-0.24	0.28	-0.13	-0.30	-0.51	0.21	0.17	-0.48	0.30	0.39	-0.02
17	CAA	0.54	-0.50	-0.22	-0.16	-0.19	-0.17	0.26	-0.08	-0.37	0.36	0.42	-0.05
18	CAC	0.69	-0.52	-0.45	-0.46	-0.27	-0.61	-0.17	0.28	-0.21	0.78	0.32	0.12
19	CAG	0.85	0.27	0.60	0.29	0.22	0.37	0.07	0.23	0.45	0.60	0.37	-0.02
20	CAT	0.48	0.09	0.46	0.23	0.07	0.13	0.41	0.26	-0.27	0.58	0.62	-0.19
21	CCA	0.53	-0.52	-0.38	-0.42	-0.12	-0.21	0.02	0.36	-0.47	0.53	0.74	-0.22
22	CCC	0.58	-0.36	0.36	0.19	0.35	0.12	0.09	0.67	0.06	0.65	1.00	0.29
23	CCG	0.69	0.42	0.43	0.62	0.59	0.26	0.49	0.79	0.40	-0.09	0.72	0.78
24	CCT	0.78	0.13	0.45	0.13	-0.33	-0.54	0.28	-0.28	-0.22	0.21	0.10	0.14
25	CGA	0.33	0.76	0.70	0.79	0.90	0.51	0.78	1.00	0.68	1.00	1.00	1.00
26	CGC	0.47	-0.01	0.10	0.75	-0.10	-0.43	-0.38	0.35	0.43	0.51	1.00	0.01
27	CGG	1.00	0.79	1.00	0.53	0.82	1.00	0.62	1.00	1.00	0.30	1.00	1.00
28	CGT	0.43	-0.35	-0.18	-0.32	-0.56	-0.60	0.54	0.03	-0.38	-0.03	0.47	0.05
29	CTA	0.61	0.58	0.45	0.31	0.12	-0.23	0.04	-0.10	-0.28	-0.12	0.90	0.14
30	CTC	0.58	0.46	0.47	0.33	0.74	0.59	0.66	0.89	0.65	0.82	0.77	0.72
31	CTG	0.60	-0.10	0.35	0.12	0.16	-0.17	0.27	-0.04	0.25	-0.20	0.88	0.46
32	CTT	0.85	0.63	0.53	0.54	0.30	0.26	0.69	0.59	0.46	0.27	0.59	0.34
33	GAA	0.60	-0.32	-0.19	-0.29	-0.19	-0.31	0.33	0.34	-0.26	0.53	0.56	-0.11
34	GAC	0.61	-0.40	-0.31	-0.24	-0.47	-0.41	-0.19	-0.21	-0.41	0.43	0.61	-0.23
35	GAG	0.64	0.12	0.54	0.23	0.03	0.15	0.37	-0.22	0.14	0.42	0.26	-0.24
36	GAT	0.69	-0.29	0.24	-0.02	0.27	0.24	0.60	0.22	-0.12	0.36	0.58	0.16
37	GCA	0.82	0.45	0.44	0.58	0.39	0.29	0.69	0.49	0.27	0.76	0.82	0.51
38	GCC	0.40	-0.58	-0.41	-0.58	-0.22	0.11	0.51	0.12	-0.44	0.36	0.76	0.31
39	GCG	0.81	0.59	0.78	0.57	0.46	0.34	0.12	0.41	0.27	0.50	0.84	0.74
40	GCT	0.75	-0.42	-0.15	-0.30	-0.48	-0.59	0.46	-0.03	-0.61	0.46	0.66	-0.10

41	GGA	0.74	0.69	0.63	0.52	0.41	0.48	0.65	0.60	0.52	0.39	0.89	0.33
42	GGC	0.82	0.42	0.52	0.47	-0.32	-0.32	0.14	-0.03	-0.18	0.30	0.87	-0.07
43	GGG	0.81	0.33	0.64	0.79	0.66	0.53	0.51	0.73	0.31	-0.11	0.59	0.01
44	GGT	0.49	-0.62	-0.42	-0.50	-0.41	-0.52	0.60	0.03	-0.53	0.34	0.78	0.01
45	GTA	0.72	0.63	0.67	0.68	0.43	0.48	0.65	0.34	0.27	0.74	0.75	0.54
46	GTC	0.60	-0.70	-0.32	-0.54	-0.46	-0.64	0.57	-0.28	-0.43	0.16	0.91	0.32
47	GTG	0.72	0.40	0.20	0.49	0.16	0.09	0.22	0.54	0.26	-0.19	0.72	0.41
48	GTT	0.76	-0.42	-0.19	-0.26	-0.32	-0.18	0.50	0.20	-0.54	0.34	0.44	-0.06
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.30	-0.57	-0.26	-0.19	-0.27	-0.27	-0.12	-0.32	-0.53	0.48	0.72	-0.09
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.59	0.26	0.26	0.10	0.10	0.18	0.49	0.42	0.01	0.66	0.50	0.25
53	TCA	0.61	0.55	0.04	0.56	0.38	0.38	0.25	0.31	-0.16	0.09	0.61	0.22
54	TCC	0.29	-0.71	-0.59	-0.56	-0.14	-0.52	0.25	0.14	-0.27	0.48	0.61	0.31
55	TCG	0.52	-0.19	0.01	0.41	-0.16	-0.19	-0.17	0.04	-0.19	0.01	1.00	0.15
56	TCT	0.55	-0.49	0.24	-0.29	-0.50	-0.50	0.16	-0.22	-0.62	-0.15	-0.02	-0.10
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.32	0.26	0.19	0.32	-0.27	-0.49	0.84	0.11	-0.25	0.21	1.00	0.60
59	TGG	0.70	-0.33	0.00	-0.13	-0.16	-0.36	0.42	0.31	-0.28	0.40	0.34	0.16
60	TGT	0.43	-0.48	-0.11	-0.13	-0.02	-0.25	0.03	0.46	-0.37	0.35	0.39	0.01
61	TTA	0.62	-0.27	0.07	0.16	-0.20	-0.25	0.14	0.26	-0.14	0.41	0.50	0.00
62	TTC	0.54	-0.55	-0.23	-0.32	-0.55	-0.62	0.04	-0.19	-0.62	-0.37	0.83	-0.35
63	TTG	0.39	-0.58	-0.44	-0.58	-0.34	-0.55	0.00	0.19	-0.56	-0.24	0.65	-0.10
64	TTT	0.79	-0.01	0.21	0.09	0.52	0.32	0.67	0.60	0.54	0.28	0.83	0.59
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
		13	14	15	16	17	18	19	20	21	22	23	24

Table C.10 continued

		25	26	27	28	29	30	31	32	33	34	35	36
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
1	AAA	0.64	0.63	0.82	0.24	0.21	0.83	0.06	0.62	0.33	0.42	0.39	0.33
2	AAC	0.87	-0.17	-0.08	-0.53	0.28	-0.23	-0.17	0.20	-0.30	-0.27	0.03	-0.04
3	AAG	0.85	0.30	0.75	-0.49	-0.12	0.52	-0.02	0.31	-0.40	-0.54	-0.05	-0.14
4	AAT	0.66	0.49	0.85	0.35	0.22	0.56	0.44	0.56	0.15	-0.10	0.30	0.22
5	ACA	0.73	0.35	0.30	0.38	0.69	0.42	0.57	0.64	0.34	0.27	0.29	0.45
6	ACC	0.80	1.00	0.32	-0.01	0.28	0.36	0.77	0.43	-0.23	-0.20	0.25	-0.18
7	ACG	1.00	0.27	1.00	0.38	0.59	0.51	-0.11	0.05	0.47	0.38	0.35	0.56
8	ACT	1.00	0.70	0.79	-0.12	-0.06	0.80	0.44	0.08	-0.36	-0.42	-0.02	-0.20

9	AGA	0.75	0.51	0.29	-0.24	0.06	0.63	0.21	0.31	-0.31	-0.38	0.11	-0.14
10	AGC	0.71	-0.27	0.51	0.41	0.59	0.36	0.91	0.64	0.14	0.33	0.28	0.17
11	AGG	0.45	0.78	0.05	0.53	0.42	0.45	0.20	0.63	0.38	0.33	0.43	0.55
12	AGT	1.00	0.29	0.66	0.30	0.72	0.56	0.76	0.90	0.05	-0.09	0.00	-0.04
13	ATA	0.86	1.00	0.30	0.86	0.46	0.82	0.46	0.71	0.69	0.71	0.55	0.65
14	ATC	1.00	0.29	0.24	-0.49	0.49	0.50	-0.01	0.24	-0.15	-0.26	0.07	-0.08
15	ATG	1.00	0.58	0.80	0.17	0.15	0.50	-0.14	-0.05	-0.17	-0.31	0.49	0.24
16	ATT	0.83	0.60	0.71	-0.27	0.02	0.26	0.24	-0.23	-0.34	-0.44	0.07	-0.05
17	CAA	0.91	0.49	0.85	-0.16	0.18	0.51	0.11	0.56	-0.21	-0.10	0.10	-0.09
18	CAC	1.00	1.00	0.51	-0.54	0.57	0.66	0.46	0.24	-0.27	-0.42	-0.03	0.01
19	CAG	0.44	-0.11	0.04	-0.05	0.24	0.47	0.37	0.71	0.26	-0.07	0.48	0.39
20	CAT	0.68	-0.42	0.72	-0.32	0.32	0.53	0.19	0.32	0.13	-0.17	0.20	0.32
21	CCA	0.73	0.36	0.54	-0.13	-0.08	0.52	0.31	0.31	-0.43	-0.24	0.07	-0.10
22	CCC	1.00	-0.39	0.42	0.65	0.22	0.59	0.56	0.72	0.67	0.29	0.68	0.52
23	CCG	0.57	1.00	0.26	1.00	0.56	-0.04	-0.10	0.18	0.41	0.26	0.43	0.04
24	CCT	0.82	-0.04	0.70	-0.41	-0.10	0.47	0.44	0.81	0.03	0.04	0.45	-0.07
25	CGA	1.00	1.00	1.00	1.00	0.83	0.19	1.00	0.64	0.73	0.88	0.74	0.80
26	CGC	1.00	0.23	-0.09	-0.49	-0.01	0.52	0.49	1.00	0.67	0.71	0.85	0.22
27	CGG	-0.46	1.00	1.00	1.00	0.42	-0.27	-0.09	0.69	0.81	0.58	1.00	0.89
28	CGT	1.00	1.00	1.00	-0.75	-0.11	0.80	-0.39	0.08	-0.48	-0.40	0.15	-0.25
29	CTA	0.84	1.00	0.72	-0.53	-0.05	0.76	-0.07	0.36	0.13	0.03	0.29	0.11
30	CTC	0.62	0.08	1.00	0.80	0.76	1.00	0.85	0.75	0.69	0.04	0.85	0.72
31	CTG	0.38	0.51	0.30	0.27	0.05	-0.17	-0.27	0.39	0.13	-0.26	0.30	0.17
32	CTT	0.83	0.79	-0.32	0.39	0.09	0.24	0.12	0.49	0.42	0.10	0.70	0.50
33	GAA	0.76	0.71	0.42	-0.31	-0.18	0.61	0.16	0.50	-0.20	-0.18	0.18	-0.05
34	GAC	0.57	-0.02	0.51	-0.70	0.42	0.63	0.27	0.55	-0.12	-0.21	0.11	0.15
35	GAG	0.77	-0.08	0.61	0.02	-0.07	0.15	0.21	0.30	0.30	0.16	0.27	0.32
36	GAT	0.92	0.63	0.87	-0.39	0.27	0.53	0.43	0.40	-0.09	-0.21	0.33	0.14
37	GCA	0.79	0.51	0.12	0.00	0.64	0.82	0.67	0.48	0.44	0.18	0.41	0.50
38	GCC	1.00	0.50	0.76	-0.38	0.17	0.34	0.56	-0.03	0.14	-0.12	0.47	0.18
39	GCG	1.00	0.36	1.00	0.18	0.33	-0.10	0.23	0.43	0.57	0.14	0.10	0.45
40	GCT	0.83	0.50	0.86	-0.49	0.02	0.46	0.18	0.20	-0.48	-0.46	0.08	-0.20
41	GGA	0.69	0.82	1.00	0.45	0.57	0.63	0.55	0.71	0.58	0.63	0.60	0.57
42	GGC	0.82	-0.21	1.00	-0.50	0.46	0.36	0.37	0.42	0.36	0.45	0.41	0.27
43	GGG	0.43	0.66	0.51	0.28	-0.08	-0.03	0.08	0.23	0.78	0.74	0.58	0.78
44	GGT	0.84	0.81	0.87	-0.57	-0.27	0.49	0.30	0.14	-0.48	-0.54	-0.05	-0.27
45	GTA	0.82	0.58	0.70	0.02	0.61	0.54	0.56	0.34	0.29	0.36	0.19	0.46
46	GTC	0.81	0.09	1.00	-0.59	0.33	0.60	0.15	-0.03	-0.22	-0.44	0.36	0.04
47	GTG	0.80	0.06	1.00	0.30	0.26	0.59	0.17	0.16	-0.02	-0.09	0.04	0.28

48	GTT	1.00	0.05	0.83	-0.56	0.25	0.27	0.50	0.04	-0.24	-0.41	0.41	0.09
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.29	0.16	0.70	-0.66	0.25	0.25	0.05	0.37	-0.21	-0.33	-0.03	-0.08
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.87	0.84	0.54	-0.02	0.40	0.50	0.24	0.55	0.10	-0.11	0.26	0.34
53	TCA	1.00	0.64	0.23	0.24	0.23	0.50	0.33	0.59	0.32	0.52	0.48	0.36
54	TCC	0.80	0.03	1.00	-0.60	0.19	0.43	0.52	0.29	-0.20	-0.29	-0.06	-0.01
55	TCG	1.00	0.22	1.00	0.34	0.08	0.64	-0.31	0.43	0.54	0.07	0.31	0.28
56	TCT	0.63	-0.02	1.00	-0.63	-0.29	0.32	0.31	0.29	-0.45	-0.48	0.34	-0.09
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	1.00	-0.41	1.00	0.28	0.58	0.34	0.47	-0.04	0.05	0.06	0.70	0.94
59	TGG	1.00	0.42	0.58	0.51	0.23	0.54	-0.18	0.79	-0.15	-0.29	0.41	0.21
60	TGT	1.00	-0.36	1.00	-0.65	0.14	-0.02	-0.29	0.36	-0.20	-0.19	0.09	-0.32
61	TTA	0.75	0.70	0.86	0.07	0.02	0.82	0.28	0.26	0.15	0.25	0.38	0.28
62	TTC	0.67	0.03	1.00	-0.57	0.08	-0.01	0.28	0.21	-0.10	-0.22	0.20	0.03
63	TTG	0.83	0.70	0.72	-0.39	-0.29	0.64	0.19	0.59	-0.52	-0.49	-0.08	-0.28
64	TTT	0.89	0.20	0.81	0.60	0.59	0.83	0.60	0.72	-0.10	-0.17	0.29	0.19
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
		25	26	27	28	29	30	31	32	33	34	35	36

Table C.10 continued

		37	38	39	40	41	42	43	44	45	46	47	48
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
1	AAA	0.64	0.29	0.72	0.30	0.68	0.54	0.46	0.09	0.57	0.10	0.31	0.24
2	AAC	0.43	-0.37	0.73	-0.33	0.52	0.27	0.16	-0.46	0.50	-0.49	0.32	-0.43
3	AAG	0.24	-0.51	0.33	-0.58	0.39	-0.28	0.41	-0.56	0.65	-0.58	0.38	-0.48
4	AAT	0.45	-0.09	0.14	-0.14	0.48	0.26	0.20	-0.11	0.69	0.00	0.27	0.03
5	ACA	0.60	0.51	0.70	0.41	0.44	0.61	0.60	0.32	0.64	0.50	0.40	0.57
6	ACC	0.40	-0.38	0.62	-0.44	0.72	0.27	0.61	-0.57	0.50	-0.60	0.12	-0.39
7	ACG	0.63	0.55	0.42	0.31	0.62	0.26	0.50	0.54	0.19	0.36	0.15	0.63
8	ACT	0.25	-0.45	-0.12	-0.52	0.67	0.47	0.47	-0.61	0.27	-0.49	0.16	-0.42
9	AGA	0.51	-0.33	0.34	-0.48	0.62	0.11	0.63	-0.57	0.55	-0.43	0.25	-0.35
10	AGC	0.54	-0.15	0.89	0.29	0.33	0.23	0.66	0.33	0.26	0.35	0.77	0.43
11	AGG	0.51	0.24	0.72	-0.05	0.72	0.17	0.80	0.44	0.58	0.30	0.33	0.63
12	AGT	0.40	0.19	0.62	0.28	0.46	0.38	0.54	-0.16	0.58	0.10	0.17	0.27
13	ATA	0.70	0.90	0.86	0.75	0.69	0.62	0.64	0.75	0.78	0.58	0.68	0.68
14	ATC	0.58	-0.09	0.42	0.09	0.70	0.27	0.22	-0.49	0.60	-0.10	0.08	-0.18
15	ATG	0.40	-0.23	0.60	-0.25	0.38	0.35	0.36	-0.31	0.55	-0.17	0.30	-0.26

16	ATT	0.18	-0.55	0.32	-0.54	0.37	0.04	0.21	-0.49	0.28	-0.59	0.17	-0.38
17	CAA	0.44	-0.07	0.63	-0.51	0.58	0.09	0.43	-0.52	0.39	-0.41	-0.03	-0.28
18	CAC	0.39	-0.29	0.56	-0.36	0.80	0.14	0.75	-0.58	0.59	-0.48	0.23	-0.32
19	CAG	0.45	0.59	0.36	0.31	0.81	0.45	0.82	0.52	0.43	0.57	0.50	0.40
20	CAT	0.53	-0.11	-0.12	-0.11	0.66	0.43	0.37	-0.18	0.47	-0.13	0.23	-0.02
21	CCA	0.22	-0.30	0.59	-0.52	0.52	0.05	0.30	-0.59	0.43	-0.31	0.36	-0.30
22	CCC	0.40	0.40	0.74	0.32	0.67	0.26	1.00	0.39	0.43	-0.22	0.58	0.50
23	CCG	0.68	0.75	0.67	0.69	0.79	0.17	0.81	0.85	0.52	0.23	0.46	0.55
24	CCT	0.31	-0.11	0.20	-0.22	0.67	-0.09	0.69	-0.23	0.04	-0.42	0.20	-0.26
25	CGA	1.00	0.86	1.00	0.92	1.00	0.81	1.00	1.00	0.83	0.81	1.00	0.70
26	CGC	0.63	0.34	0.68	0.50	0.42	0.55	-0.07	0.22	0.79	0.55	0.53	0.41
27	CGG	1.00	0.76	1.00	0.71	0.16	1.00	-0.35	0.72	0.40	0.68	0.66	0.66
28	CGT	0.37	-0.51	0.59	-0.54	0.67	-0.19	0.08	-0.50	0.12	-0.75	-0.28	-0.41
29	CTA	0.57	0.32	0.65	0.16	0.47	0.14	0.65	-0.13	0.60	0.30	0.23	0.22
30	CTC	0.81	0.32	0.83	0.64	0.73	0.80	0.18	0.28	0.71	0.79	0.46	0.51
31	CTG	0.39	-0.08	0.47	0.26	0.09	0.29	0.56	0.00	0.18	-0.10	0.25	0.24
32	CTT	0.72	0.05	0.55	0.40	0.64	0.45	0.63	0.07	0.87	0.30	0.32	0.22
33	GAA	0.49	-0.25	0.50	-0.38	0.57	0.31	0.52	-0.49	0.54	-0.36	0.13	-0.38
34	GAC	0.72	-0.19	0.35	-0.19	0.67	0.51	0.30	-0.30	0.51	-0.11	0.32	0.02
35	GAG	0.26	0.14	0.22	0.25	0.58	0.34	0.83	0.24	0.74	0.40	0.62	0.30
36	GAT	0.52	-0.22	0.43	-0.36	0.46	0.50	0.05	-0.36	0.58	-0.38	0.24	-0.26
37	GCA	0.53	0.63	0.79	0.53	0.58	0.45	0.67	0.19	0.63	0.53	0.60	0.56
38	GCC	0.42	-0.31	0.79	-0.37	0.68	0.45	0.90	-0.55	0.41	-0.53	0.17	-0.20
39	GCG	0.71	0.50	0.45	0.51	0.64	0.29	0.52	0.48	0.60	0.01	0.55	0.51
40	GCT	0.31	-0.47	0.68	-0.60	0.74	0.19	0.59	-0.58	0.40	-0.60	0.08	-0.42
41	GGA	0.77	0.53	0.95	0.67	0.77	0.61	0.64	0.65	0.78	0.76	0.75	0.84
42	GGC	0.62	0.14	0.75	0.10	0.84	0.67	0.64	0.27	0.78	0.31	0.57	0.47
43	GGG	0.85	0.59	0.80	0.63	0.84	0.82	0.90	0.66	0.85	0.89	0.88	0.71
44	GGT	0.39	-0.54	0.40	-0.62	0.53	0.12	0.17	-0.67	0.37	-0.67	0.35	-0.60
45	GTA	0.66	0.55	0.74	0.58	0.70	0.58	0.69	0.60	0.71	0.63	0.68	0.69
46	GTC	0.49	-0.27	0.44	-0.30	0.42	-0.04	0.53	-0.64	0.60	-0.41	0.41	-0.39
47	GTG	0.40	-0.12	0.77	0.28	0.51	0.65	0.65	0.30	0.29	-0.01	0.20	0.41
48	GTT	0.28	-0.48	0.47	-0.52	0.45	0.28	0.61	-0.51	0.56	-0.60	0.52	-0.47
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.58	-0.34	0.65	-0.45	0.62	0.14	0.41	-0.50	0.28	-0.44	0.37	-0.39
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.45	-0.01	0.47	-0.13	0.72	0.37	0.44	-0.19	0.68	-0.17	0.36	0.07
53	TCA	0.70	0.51	0.60	0.32	0.24	0.53	0.53	0.35	0.41	0.25	0.33	0.52
54	TCC	0.50	-0.41	0.54	-0.48	0.36	0.16	0.53	-0.59	0.05	-0.63	-0.19	-0.40

55	TCG	0.67	0.43	0.14	0.66	0.72	0.53	0.37	0.41	0.62	0.34	0.74	0.66
56	TCT	0.15	-0.61	0.21	-0.59	0.59	0.35	0.43	-0.61	0.34	-0.56	-0.29	-0.41
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.75	0.20	0.56	0.59	0.90	0.33	-0.07	0.22	1.00	0.87	1.00	0.39
59	TGG	0.46	-0.20	0.44	-0.26	0.62	0.48	-0.21	-0.31	0.58	-0.06	0.53	-0.36
60	TGT	0.63	-0.47	-0.48	-0.38	0.76	-0.03	0.23	-0.48	0.19	-0.45	0.01	-0.46
61	TTA	0.49	0.16	0.36	-0.05	0.48	0.29	0.54	-0.25	0.52	-0.22	0.04	0.03
62	TTC	0.47	0.03	0.50	0.20	0.70	0.18	0.63	-0.51	0.73	-0.44	0.17	-0.01
63	TTG	0.18	-0.58	0.08	-0.62	0.48	0.05	0.50	-0.59	0.32	-0.58	-0.16	-0.50
64	TTT	0.20	-0.40	0.25	-0.26	0.73	0.24	0.47	-0.23	0.53	-0.29	0.34	-0.23
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
		37	38	39	40	41	42	43	44	45	46	47	48

Table C.10 continued

		49	50	51	52	53	54	55	56	57	58	59	60
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
1	AAA	0.00	-0.14	0.00	0.31	0.10	0.12	0.26	-0.18	0.00	0.34	-0.03	0.01
2	AAC	0.00	-0.53	0.00	-0.15	-0.03	-0.48	-0.17	-0.40	0.00	0.25	-0.43	-0.57
3	AAG	0.00	-0.43	0.00	0.32	0.35	-0.37	0.07	-0.42	0.00	0.24	0.05	-0.31
4	AAT	0.00	0.34	0.00	0.44	0.46	0.08	0.34	0.11	0.00	0.60	0.51	0.41
5	ACA	0.00	0.31	0.00	0.63	0.41	0.16	0.46	0.19	0.00	0.66	0.27	-0.16
6	ACC	0.00	-0.54	0.00	0.24	0.25	-0.45	-0.15	-0.44	0.00	-0.33	-0.39	-0.42
7	ACG	0.00	-0.02	0.00	0.66	0.56	0.70	0.52	0.46	0.00	0.75	0.57	0.53
8	ACT	0.00	-0.50	0.00	0.11	-0.11	-0.49	-0.11	-0.54	0.00	0.90	-0.08	-0.34
9	AGA	0.00	-0.31	0.00	0.43	0.05	-0.44	0.37	-0.41	0.00	0.46	-0.17	-0.34
10	AGC	0.00	0.23	0.00	0.60	0.39	0.01	0.56	0.17	0.00	0.20	0.10	0.51
11	AGG	0.00	0.23	0.00	0.54	0.00	0.12	0.49	0.19	0.00	1.00	0.61	0.71
12	AGT	0.00	0.14	0.00	0.63	0.41	0.51	0.57	0.47	0.00	0.45	0.44	0.49
13	ATA	0.00	0.25	0.00	0.56	0.43	0.37	0.44	0.50	0.00	0.71	0.76	0.53
14	ATC	0.00	-0.49	0.00	-0.06	-0.06	-0.57	0.03	-0.53	0.00	0.37	-0.44	-0.46
15	ATG	0.00	-0.24	0.00	0.23	0.31	-0.33	0.28	-0.27	0.00	0.29	0.00	-0.15
16	ATT	0.00	-0.21	0.00	0.18	0.34	-0.45	0.14	-0.39	0.00	-0.06	-0.02	-0.17
17	CAA	0.00	-0.27	0.00	0.20	0.36	-0.27	0.59	-0.33	0.00	0.44	-0.20	-0.30
18	CAC	0.00	-0.31	0.00	-0.09	0.52	-0.60	-0.14	-0.60	0.00	0.45	-0.31	-0.32
19	CAG	0.00	-0.21	0.00	0.35	0.13	0.16	0.33	0.08	0.00	0.19	0.55	0.25
20	CAT	0.00	-0.06	0.00	0.29	0.30	0.05	0.42	-0.16	0.00	0.08	0.25	0.06
21	CCA	0.00	-0.45	0.00	0.26	0.15	-0.39	0.24	-0.58	0.00	0.16	-0.48	-0.45
22	CCC	0.00	0.47	0.00	0.14	0.36	0.04	0.30	-0.09	0.00	0.28	0.90	0.12

23	CCG	0.00	0.52	0.00	0.56	0.76	0.78	0.82	0.80	0.00	0.54	0.88	0.44
24	CCT	0.00	-0.36	0.00	0.24	0.34	-0.39	-0.18	-0.09	0.00	-0.09	0.40	0.55
25	CGA	0.00	0.84	0.00	0.63	1.00	1.00	0.63	0.72	0.00	1.00	0.81	1.00
26	CGC	0.00	0.03	0.00	0.41	1.00	-0.28	-0.25	0.16	0.00	0.17	0.54	1.00
27	CGG	0.00	0.44	0.00	0.58	-0.15	0.60	1.00	0.76	0.00	1.00	0.67	0.26
28	CGT	0.00	-0.68	0.00	-0.47	0.30	-0.53	-0.25	-0.50	0.00	-0.44	-0.51	-0.69
29	CTA	0.00	-0.18	0.00	0.08	0.32	0.03	0.04	-0.05	0.00	0.31	-0.38	-0.30
30	CTC	0.00	0.01	0.00	0.55	0.60	-0.35	0.82	0.21	0.00	0.67	0.59	0.00
31	CTG	0.00	0.10	0.00	0.52	0.48	0.41	0.34	0.26	0.00	0.31	0.42	-0.22
32	CTT	0.00	-0.25	0.00	0.15	0.17	-0.39	-0.10	-0.25	0.00	0.56	0.39	-0.07
33	GAA	0.00	-0.26	0.00	0.23	0.55	-0.44	0.53	-0.38	0.00	0.30	-0.12	-0.26
34	GAC	0.00	-0.48	0.00	0.07	0.31	-0.57	0.00	-0.58	0.00	-0.01	-0.25	-0.56
35	GAG	0.00	-0.17	0.00	0.22	0.58	-0.06	0.03	0.13	0.00	0.37	0.32	0.15
36	GAT	0.00	0.09	0.00	0.28	0.39	0.02	-0.11	0.00	0.00	0.70	0.18	0.24
37	GCA	0.00	0.24	0.00	0.59	0.32	-0.12	0.21	0.07	0.00	0.61	0.35	0.33
38	GCC	0.00	-0.24	0.00	0.45	0.06	-0.56	-0.10	-0.40	0.00	0.68	0.08	-0.26
39	GCG	0.00	0.00	0.00	0.34	0.60	0.39	0.57	0.51	0.00	0.39	-0.02	0.75
40	GCT	0.00	-0.55	0.00	0.07	0.29	-0.56	0.30	-0.50	0.00	0.43	-0.24	-0.54
41	GGA	0.00	0.55	0.00	0.53	0.54	0.53	0.88	0.32	0.00	0.72	0.17	0.20
42	GGC	0.00	-0.34	0.00	0.40	0.31	-0.46	0.36	-0.33	0.00	0.14	-0.24	0.01
43	GGG	0.00	0.61	0.00	0.58	0.68	0.00	0.54	-0.07	0.00	0.31	0.47	0.47
44	GGT	0.00	-0.55	0.00	0.14	0.24	-0.59	0.22	-0.57	0.00	0.25	-0.07	-0.41
45	GTA	0.00	0.37	0.00	0.55	0.62	0.25	0.43	0.10	0.00	-0.18	0.54	0.48
46	GTC	0.00	-0.44	0.00	0.10	0.47	-0.60	0.46	-0.49	0.00	0.21	-0.42	-0.44
47	GTG	0.00	0.15	0.00	0.46	0.71	0.11	0.72	0.31	0.00	0.59	0.43	0.24
48	GTT	0.00	-0.41	0.00	0.02	0.06	-0.61	0.39	-0.50	0.00	-0.03	-0.12	-0.13
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.00	-0.54	0.00	0.15	0.11	-0.49	0.14	-0.40	0.00	0.14	-0.39	-0.47
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.00	0.29	0.00	0.35	0.48	-0.05	0.24	-0.21	0.00	0.71	0.48	0.16
53	TCA	0.00	-0.07	0.00	0.21	0.20	0.26	0.54	0.07	0.00	-0.20	0.03	-0.13
54	TCC	0.00	-0.32	0.00	0.11	0.31	-0.45	-0.06	-0.49	0.00	0.29	-0.38	-0.28
55	TCG	0.00	-0.29	0.00	0.14	0.50	0.31	-0.17	0.36	0.00	-0.37	-0.01	0.30
56	TCT	0.00	-0.51	0.00	0.10	-0.15	-0.64	0.21	-0.59	0.00	0.32	0.03	-0.34
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.00	-0.27	0.00	0.26	0.72	-0.20	0.40	0.10	0.00	-0.25	-0.02	0.32
59	TGG	0.00	-0.33	0.00	0.37	0.46	-0.30	0.09	-0.34	0.00	0.47	0.00	-0.23
60	TGT	0.00	-0.21	0.00	0.22	0.38	-0.57	0.51	-0.47	0.00	0.59	0.01	-0.30
61	TTA	0.00	-0.09	0.00	0.37	0.42	-0.20	0.24	-0.26	0.00	0.65	-0.36	-0.15

62	TTC	0.00	-0.48	0.00	0.08	0.22	-0.64	-0.20	-0.40	0.00	0.37	-0.22	-0.40
63	TTG	0.00	-0.50	0.00	0.19	0.20	-0.60	0.39	-0.51	0.00	0.23	0.38	-0.30
64	TTT	0.00	0.05	0.00	0.39	0.27	-0.02	0.36	0.34	0.00	-0.06	0.19	0.34
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
		49	50	51	52	53	54	55	56	57	58	59	60

Table C.10 continued

		61	62	63	64
		TTA	TTC	TTG	TTT
1	AAA	0.15	-0.20	-0.19	0.40
2	AAC	-0.11	-0.53	-0.59	-0.02
3	AAG	0.20	-0.44	-0.53	0.20
4	AAT	0.28	0.16	0.04	0.42
5	ACA	0.42	0.47	0.26	0.34
6	ACC	-0.11	-0.42	-0.42	0.07
7	ACG	0.54	0.52	0.30	0.67
8	ACT	-0.29	-0.52	-0.65	-0.03
9	AGA	-0.21	-0.44	-0.57	0.06
10	AGC	0.65	0.53	0.31	0.46
11	AGG	0.55	0.28	0.26	0.26
12	AGT	0.50	0.28	-0.12	0.48
13	ATA	0.42	0.34	0.38	0.47
14	ATC	-0.13	-0.38	-0.60	-0.05
15	ATG	0.24	-0.17	-0.25	0.14
16	ATT	0.18	-0.35	-0.37	0.21
17	CAA	-0.16	-0.21	-0.48	0.06
18	CAC	0.34	-0.52	-0.51	0.34
19	CAG	0.40	-0.24	0.17	0.47
20	CAT	0.10	-0.27	-0.39	0.48
21	CCA	-0.31	-0.42	-0.60	-0.19
22	CCC	0.15	-0.31	0.29	0.63
23	CCG	0.38	0.62	0.61	0.63
24	CCT	0.34	-0.23	0.00	0.58
25	CGA	1.00	0.60	0.83	0.46
26	CGC	0.79	0.37	0.48	0.79
27	CGG	0.55	0.10	0.26	0.08
28	CGT	-0.06	-0.38	-0.45	0.41
29	CTA	-0.14	0.20	-0.19	0.19

30	CTC	0.57	-0.23	0.03	0.32
31	CTG	0.45	-0.09	0.03	0.39
32	CTT	0.18	-0.54	-0.36	0.41
33	GAA	0.11	-0.22	-0.37	0.17
34	GAC	0.11	-0.40	-0.52	0.27
35	GAG	0.40	-0.11	-0.18	0.15
36	GAT	0.10	-0.23	-0.37	0.31
37	GCA	0.60	0.62	0.32	0.36
38	GCC	-0.03	-0.47	-0.24	-0.19
39	GCG	0.59	-0.05	0.45	0.39
40	GCT	-0.21	-0.48	-0.67	0.39
41	GGA	0.52	0.19	0.46	0.31
42	GGC	0.49	0.65	0.26	0.50
43	GGG	-0.16	-0.58	-0.48	-0.25
44	GGT	-0.08	-0.53	-0.57	0.48
45	GTA	0.56	0.54	0.54	0.43
46	GTC	-0.18	-0.52	-0.65	-0.01
47	GTG	0.39	-0.06	-0.07	0.32
48	GTT	0.08	-0.43	-0.51	0.31
49	TAA	0.00	0.00	0.00	0.00
50	TAC	0.15	-0.32	-0.57	-0.14
51	TAG	0.00	0.00	0.00	0.00
52	TAT	0.22	-0.13	-0.21	0.48
53	TCA	0.13	-0.18	0.03	0.24
54	TCC	-0.05	-0.44	-0.51	0.04
55	TCG	0.02	-0.11	0.14	0.39
56	TCT	-0.29	-0.60	-0.67	0.35
57	TGA	0.00	0.00	0.00	0.00
58	TGC	0.21	0.60	0.57	0.24
59	TGG	-0.24	-0.25	-0.17	0.23
60	TGT	0.08	-0.43	-0.49	0.11
61	TTA	0.27	-0.20	-0.16	0.23
62	TTC	-0.11	-0.54	-0.65	0.03
63	TTG	0.05	-0.27	-0.58	0.06
64	TTT	0.28	0.11	-0.16	0.46
		TTA	TTC	TTG	TTT
		61	62	63	64

Table C.11: CPW matrix *Streptomyces coelicolor* A3(2) full genome (left codon indicated in column 2, right codon indicated in row 2). Host cell: *S. coelicolor*; Sequence data: full *S. coelicilor* genome.

		1	2	3	4	5	6	7	8	9	10	11	12
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
1	AAA	0.00	0.79	0.70	-0.65	-0.60	0.28	0.48	-0.48	-0.86	0.24	-0.66	-0.69
2	AAC	0.44	-0.05	-0.06	0.30	0.52	-0.13	0.15	0.32	0.10	-0.27	0.09	0.36
3	AAG	0.58	-0.05	-0.06	0.45	-0.01	0.03	-0.10	0.15	0.08	-0.03	0.21	0.52
4	AAT	-0.02	0.89	0.87	1.00	0.22	0.80	0.57	-0.63	1.00	0.77	0.62	0.60
5	ACA	1.00	0.83	0.74	-0.23	-0.60	0.71	0.50	-0.58	-0.75	0.30	-0.40	-0.15
6	ACC	0.08	-0.16	-0.11	-0.18	-0.05	-0.03	-0.02	-0.26	0.15	-0.17	-0.34	-0.29
7	ACG	0.19	0.31	0.12	-0.08	-0.39	0.22	-0.30	-0.22	-0.32	0.22	0.00	-0.14
8	ACT	1.00	0.85	0.87	0.40	-0.37	0.69	0.63	-0.61	-0.26	0.88	-0.06	-0.38
9	AGA	-0.47	0.37	0.44	-0.82	-0.80	0.35	-0.03	-0.66	-0.88	-0.26	-0.72	-0.60
10	AGC	-0.23	-0.11	-0.14	-0.47	-0.35	0.05	-0.03	-0.32	-0.62	-0.34	-0.60	-0.58
11	AGG	-0.64	-0.13	-0.27	-0.58	-0.62	0.06	-0.27	-0.35	-0.60	-0.22	-0.22	-0.51
12	AGT	-0.64	0.74	0.87	0.14	0.19	0.51	-0.40	-0.67	0.55	0.74	0.91	-0.47
13	ATA	-0.12	0.91	0.74	0.32	1.00	0.84	0.41	0.02	-0.69	0.46	-0.20	0.14
14	ATC	-0.02	-0.04	-0.03	0.07	0.32	-0.11	0.15	-0.07	-0.05	-0.22	-0.31	-0.19
15	ATG	0.07	-0.01	0.00	0.24	0.01	0.08	-0.14	0.01	0.54	-0.17	0.43	-0.02
16	ATT	0.39	0.85	0.78	-0.54	-0.48	0.77	0.67	-0.36	-0.12	0.95	0.55	-0.27
17	CAA	0.12	0.80	0.62	-0.22	-0.65	0.62	0.59	-0.06	-0.42	0.58	-0.01	0.31
18	CAC	0.05	-0.06	-0.07	0.01	0.08	-0.15	0.19	-0.10	0.51	-0.23	0.54	0.00
19	CAG	-0.01	-0.05	-0.03	0.38	-0.15	-0.03	-0.01	0.13	0.49	-0.07	0.66	0.47
20	CAT	0.66	0.90	0.89	-0.37	0.31	0.90	0.61	-0.39	0.39	0.75	0.82	0.61
21	CCA	-0.34	0.53	0.55	-0.66	-0.65	0.63	0.36	-0.54	-0.75	0.55	-0.41	-0.42
22	CCC	-0.10	-0.11	-0.09	-0.13	-0.13	-0.18	0.05	-0.28	0.23	0.03	-0.38	-0.17
23	CCG	0.00	0.05	0.03	0.15	-0.20	0.20	-0.16	-0.23	-0.12	0.23	-0.22	0.10
24	CCT	-0.40	0.81	0.81	-0.51	-0.27	0.71	0.32	-0.64	0.50	0.83	0.51	1.00
25	CGA	0.07	0.27	0.20	-0.63	-0.43	0.54	0.42	-0.12	-0.79	-0.06	-0.33	-0.41
26	CGC	-0.46	-0.34	-0.34	-0.51	-0.08	-0.28	0.01	-0.23	-0.56	-0.35	-0.58	-0.42
27	CGG	0.21	0.56	0.57	-0.10	-0.11	0.45	0.22	0.29	0.36	0.51	0.54	0.41
28	CGT	0.18	0.79	0.75	-0.36	-0.28	0.01	-0.57	-0.57	0.45	0.75	0.75	0.62
29	CTA	-0.22	0.52	0.67	1.00	0.27	0.81	0.49	-0.83	-0.70	0.81	0.34	-0.70
30	CTC	-0.30	-0.30	-0.23	-0.13	0.29	-0.38	0.28	-0.14	0.04	-0.15	-0.31	-0.03
31	CTG	0.15	0.20	0.17	0.55	0.36	0.10	0.23	0.53	0.31	0.19	0.29	0.43
32	CTT	0.44	0.95	0.94	0.16	0.84	0.79	0.67	-0.62	0.63	0.92	0.78	0.27
33	GAA	0.57	0.82	0.78	0.19	-0.35	0.57	0.46	0.05	-0.06	0.47	0.28	0.52

34	GAC	0.12	-0.05	-0.05	0.18	0.28	-0.09	0.07	0.09	0.34	-0.17	0.40	0.03
35	GAG	0.29	-0.14	-0.14	0.31	-0.14	0.01	-0.24	0.21	0.57	-0.10	0.49	0.36
36	GAT	0.71	0.91	0.89	-0.23	0.19	0.76	0.54	-0.28	0.42	0.80	0.85	0.54
37	GCA	-0.09	0.84	0.75	0.17	-0.50	0.68	0.49	-0.20	-0.20	0.48	-0.06	-0.10
38	GCC	0.14	-0.18	-0.10	-0.22	0.14	-0.12	0.07	-0.01	0.06	0.41	-0.24	-0.02
39	GCG	-0.05	0.20	0.04	0.27	-0.18	0.15	-0.21	0.10	0.17	-0.08	0.20	-0.02
40	GCT	0.29	0.86	0.93	0.50	-0.24	0.72	0.53	-0.52	0.59	0.87	0.72	0.78
41	GGA	-0.40	0.40	0.48	-0.16	-0.49	0.47	0.11	-0.08	-0.61	0.10	-0.28	-0.35
42	GGC	-0.11	-0.20	-0.20	-0.31	-0.05	-0.14	-0.12	-0.03	-0.36	-0.26	-0.42	-0.34
43	GGG	-0.27	0.28	0.24	-0.20	-0.21	0.45	-0.20	0.04	-0.33	0.28	0.15	-0.08
44	GGT	0.66	0.91	0.88	0.64	0.34	0.60	-0.17	0.35	0.44	0.90	0.83	0.58
45	GTA	0.18	0.91	0.90	0.20	0.33	0.92	0.88	0.21	-0.20	0.86	-0.02	0.24
46	GTC	-0.16	-0.19	-0.03	-0.28	0.27	-0.25	0.19	0.06	0.17	-0.13	0.10	0.12
47	GTG	-0.09	0.22	-0.04	0.35	0.11	0.23	-0.14	0.31	0.38	0.06	0.42	0.22
48	GTT	0.39	0.97	0.87	1.00	0.28	0.87	0.71	0.26	0.61	0.88	0.69	0.59
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.47	-0.08	-0.07	0.83	0.20	0.00	-0.16	0.92	0.75	-0.20	0.79	0.70
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	1.00	0.91	0.90	1.00	0.39	0.82	0.71	1.00	0.44	0.74	0.67	0.03
53	TCA	0.12	0.89	0.70	0.38	-0.57	0.73	0.29	-0.50	0.35	0.13	-0.14	-0.54
54	TCC	0.30	-0.17	-0.02	0.28	0.01	-0.07	-0.12	-0.28	0.05	-0.04	-0.04	-0.03
55	TCG	0.03	0.24	0.00	0.21	-0.24	0.32	-0.30	0.27	0.21	0.49	0.38	0.20
56	TCT	1.00	0.91	1.00	-0.05	-0.32	0.62	0.46	1.00	-0.55	0.58	0.78	1.00
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	-0.10	-0.07	-0.07	-0.26	-0.21	0.02	-0.12	0.40	0.04	0.29	0.42	-0.09
59	TGG	-0.36	-0.01	0.03	0.34	-0.20	0.15	-0.23	-0.20	0.47	-0.02	0.51	0.00
60	TGT	-0.46	0.97	0.81	-0.56	1.00	0.51	-0.10	-0.50	0.12	0.92	0.31	0.64
61	TTA	1.00	1.00	1.00	1.00	-0.76	0.84	0.67	1.00	-0.90	0.46	1.00	1.00
62	TTC	-0.20	-0.02	0.00	0.19	0.58	-0.13	0.22	0.28	0.21	-0.01	0.33	0.20
63	TTG	-0.70	0.24	-0.23	-0.60	0.04	0.35	-0.20	-0.32	-0.71	-0.22	-0.49	-0.54
64	TTT	-0.05	0.95	0.73	1.00	-0.07	0.72	0.62	-0.55	-0.41	0.61	0.00	1.00
		AAA	AAC	AAG	AAT	ACA	ACC	ACG	ACT	AGA	AGC	AGG	AGT
		1	2	3	4	5	6	7	8	9	10	11	12

Table C.11 continued

		13	14	15	16	17	18	19	20	21	22	23	24
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
1	AAA	-0.50	0.74	0.22	-0.69	-0.42	-0.21	-0.24	-0.69	-0.67	-0.47	-0.58	-0.57

2	AAC	0.58	-0.05	-0.03	0.21	0.37	-0.02	0.00	0.47	0.55	0.23	-0.03	0.22
3	AAG	0.46	-0.05	-0.01	0.23	0.50	-0.01	-0.01	0.37	0.36	0.06	0.04	0.33
4	AAT	1.00	0.75	0.83	-0.39	-0.74	-0.10	-0.18	-0.74	-0.82	-0.62	-0.72	-0.70
5	ACA	1.00	0.85	0.68	-0.07	-0.67	-0.24	-0.44	-0.76	-0.89	-0.73	-0.75	-0.80
6	ACC	0.59	0.11	0.16	-0.10	0.15	0.09	0.04	-0.21	0.40	0.38	0.18	0.15
7	ACG	0.18	-0.26	-0.30	-0.35	-0.15	-0.05	0.02	-0.27	0.05	-0.15	-0.10	-0.29
8	ACT	0.31	0.82	0.86	-0.32	-0.70	0.13	-0.37	-0.78	-0.87	-0.75	-0.75	-0.90
9	AGA	-0.30	0.39	0.37	-0.67	-0.74	-0.13	-0.13	-0.17	-0.86	-0.19	-0.28	-0.79
10	AGC	1.00	0.13	0.30	-0.17	0.12	-0.12	-0.07	-0.48	0.04	0.08	0.12	-0.37
11	AGG	0.72	0.00	0.06	-0.45	-0.64	0.20	-0.02	-0.30	-0.62	-0.23	-0.10	-0.18
12	AGT	0.51	0.70	0.85	-0.52	-0.33	-0.22	-0.20	-0.69	-0.65	-0.30	-0.37	-0.79
13	ATA	1.00	0.87	0.91	-0.57	0.43	0.12	0.06	-0.25	0.44	-0.67	-0.65	-0.66
14	ATC	0.82	-0.05	-0.04	-0.12	0.44	0.00	-0.01	0.18	0.50	0.18	0.08	0.43
15	ATG	0.97	-0.03	0.00	0.17	0.15	-0.01	-0.01	0.17	0.09	0.07	-0.06	0.07
16	ATT	1.00	0.73	0.80	-0.19	-0.83	-0.44	-0.24	-0.58	-0.91	-0.79	-0.81	-0.91
17	CAA	0.63	0.80	0.77	-0.17	-0.32	0.22	0.02	0.45	-0.19	-0.25	-0.19	-0.72
18	CAC	-0.25	-0.06	-0.05	0.37	0.20	0.01	0.00	0.04	0.28	0.03	0.20	0.14
19	CAG	-0.18	-0.04	-0.04	0.07	0.01	-0.02	0.00	0.12	-0.24	-0.05	0.09	-0.02
20	CAT	0.19	0.79	0.65	0.57	-0.68	-0.08	-0.06	-0.37	-0.59	-0.60	-0.65	-0.67
21	CCA	-0.58	0.96	0.69	-0.83	-0.70	0.03	-0.37	-0.42	-0.93	-0.67	-0.73	-0.87
22	CCC	-0.18	0.30	0.25	-0.28	0.32	0.56	0.44	0.21	0.29	0.82	0.48	0.07
23	CCG	-0.29	-0.21	-0.20	-0.18	-0.18	-0.30	-0.23	0.07	-0.35	-0.28	-0.18	-0.16
24	CCT	0.30	0.84	0.75	-0.78	-0.70	-0.08	-0.23	-0.65	-0.84	-0.60	-0.55	-0.84
25	CGA	-0.60	0.63	0.64	-0.59	-0.60	0.34	-0.18	-0.58	-0.78	-0.06	-0.34	-0.65
26	CGC	-0.09	0.03	0.08	0.05	0.13	0.31	0.24	-0.05	0.28	0.05	0.34	0.39
27	CGG	-0.37	-0.12	-0.21	-0.26	-0.27	-0.29	-0.18	-0.22	-0.01	-0.15	0.08	-0.06
28	CGT	0.35	0.47	0.61	0.11	-0.61	0.21	-0.04	-0.56	-0.67	-0.49	-0.46	-0.71
29	CTA	-0.44	0.75	0.83	-0.48	-0.80	0.14	-0.34	-0.67	-0.88	-0.54	-0.47	-0.82
30	CTC	0.07	0.23	0.30	-0.01	-0.23	0.54	-0.38	0.52	0.56	0.41	0.57	0.54
31	CTG	0.16	-0.14	-0.17	0.28	-0.48	-0.27	0.56	0.32	0.25	-0.32	-0.07	0.19
32	CTT	0.60	0.89	0.85	-0.21	-0.69	0.08	-0.72	-0.39	-0.86	-0.75	-0.64	-0.82
33	GAA	0.50	0.80	0.71	0.40	-0.35	-0.15	-0.15	0.20	-0.64	-0.38	-0.48	-0.43
34	GAC	-0.06	-0.05	-0.04	0.36	0.34	0.04	0.01	0.01	0.46	0.24	0.00	0.37
35	GAG	-0.17	-0.13	-0.11	0.20	0.22	0.01	0.03	0.32	0.26	0.21	0.08	0.42
36	GAT	0.16	0.86	0.75	-0.44	-0.68	-0.36	-0.27	-0.68	-0.80	-0.66	-0.72	-0.74
37	GCA	0.26	0.83	0.81	-0.42	-0.69	-0.33	-0.47	-0.58	-0.84	-0.70	-0.72	-0.78
38	GCC	-0.04	0.22	0.17	0.22	0.20	0.14	0.11	-0.09	0.44	0.33	0.30	0.25
39	GCG	-0.49	-0.32	-0.29	-0.18	0.12	-0.11	-0.03	0.08	0.05	-0.13	0.01	0.08
40	GCT	0.47	0.86	0.85	-0.12	-0.75	-0.03	-0.42	-0.80	-0.85	-0.77	-0.70	-0.86

41	GGA	-0.15	0.54	0.40	-0.49	-0.57	-0.37	-0.32	-0.41	-0.73	-0.33	-0.51	-0.57
42	GGC	-0.13	-0.16	-0.12	0.15	0.41	0.26	0.26	0.25	0.36	0.24	0.29	0.36
43	GGG	-0.22	0.13	-0.02	-0.28	-0.47	-0.36	-0.41	-0.51	-0.38	-0.16	-0.27	-0.42
44	GGT	0.72	0.62	0.68	0.16	-0.06	-0.04	0.01	-0.46	-0.38	-0.30	-0.38	-0.52
45	GTA	0.11	0.88	0.85	-0.40	-0.67	0.21	-0.34	-0.32	-0.47	-0.50	-0.68	-0.53
46	GTC	0.10	0.05	0.15	0.19	0.43	0.25	0.14	0.11	0.71	0.33	0.37	0.54
47	GTG	0.35	-0.16	-0.23	0.21	0.28	-0.27	-0.14	0.27	0.04	-0.18	-0.25	0.30
48	GTT	0.58	0.81	0.70	-0.44	-0.55	-0.17	-0.39	-0.77	-0.86	-0.75	-0.72	-0.85
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.27	-0.05	-0.04	0.40	0.24	-0.05	0.00	0.79	0.33	0.35	0.00	0.63
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.13	0.75	0.80	-0.46	-0.60	-0.22	-0.18	1.00	-0.81	-0.69	-0.80	-0.65
53	TCA	-0.29	0.82	0.87	-0.74	-0.53	0.13	-0.40	-0.56	-0.87	-0.65	-0.74	-0.83
54	TCC	-0.12	0.09	0.11	0.12	0.34	0.23	0.14	0.31	0.28	0.28	0.18	0.20
55	TCG	-0.43	-0.28	-0.38	-0.31	0.19	-0.12	-0.07	0.13	0.04	-0.10	-0.05	0.09
56	TCT	-0.72	0.80	0.87	-0.22	0.40	-0.25	-0.35	-0.79	-0.37	-0.70	-0.62	-0.90
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.22	-0.07	-0.04	-0.45	0.02	0.02	0.00	-0.11	-0.06	0.10	0.04	0.18
59	TGG	-0.18	0.01	0.00	-0.01	0.27	-0.02	-0.01	0.20	0.04	0.00	-0.01	0.19
60	TGT	1.00	0.91	0.41	-0.29	-0.42	0.02	0.01	-0.69	-0.67	-0.31	-0.44	-0.46
61	TTA	1.00	1.00	1.00	-0.91	-0.86	1.00	-0.31	-0.88	-0.91	-0.36	-0.61	1.00
62	TTC	0.41	-0.02	-0.01	0.20	0.47	-0.01	-0.02	0.35	0.70	0.05	0.03	0.33
63	TTG	0.21	-0.05	-0.19	-0.68	-0.44	0.05	-0.60	-0.30	-0.68	-0.01	-0.16	-0.43
64	TTT	1.00	0.72	0.85	-0.84	-0.79	-0.34	-0.21	-0.84	-0.89	-0.83	-0.71	-0.94
		ATA	ATC	ATG	ATT	CAA	CAC	CAG	CAT	CCA	CCC	CCG	CCT
		13	14	15	16	17	18	19	20	21	22	23	24

Table C.11 continued

		25	26	27	28	29	30	31	32	33	34	35	36
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
1	AAA	-0.82	-0.59	-0.56	-0.28	-0.85	-0.65	-0.45	-0.58	0.20	0.67	0.50	0.10
2	AAC	0.02	-0.01	-0.05	0.31	0.60	-0.17	0.15	0.08	0.14	-0.03	-0.04	0.27
3	AAG	0.19	0.12	-0.05	0.34	0.37	-0.07	0.13	0.29	-0.10	-0.05	-0.01	0.38
4	AAT	-0.68	0.03	0.24	-0.43	-0.74	-0.56	-0.38	-0.80	-0.44	0.48	0.46	-0.65
5	ACA	-0.80	-0.08	-0.34	-0.69	-0.63	-0.35	-0.36	-0.68	-0.09	0.57	0.55	-0.07
6	ACC	0.07	-0.09	-0.12	-0.21	0.80	0.00	0.25	0.02	-0.07	-0.05	-0.12	-0.29
7	ACG	0.08	0.43	0.35	0.02	0.44	-0.16	-0.23	-0.27	0.22	0.10	0.20	-0.16
8	ACT	-0.58	-0.18	-0.05	-0.40	-0.59	-0.44	-0.08	-0.86	-0.16	0.50	0.49	-0.49

9	AGA	-0.76	-0.08	-0.12	-0.22	-0.37	-0.39	-0.17	-0.78	-0.40	0.56	0.47	-0.35
10	AGC	-0.41	-0.16	-0.11	-0.42	0.89	0.12	0.23	-0.36	-0.20	-0.13	-0.25	-0.49
11	AGG	-0.44	0.28	0.10	-0.11	-0.21	-0.13	0.01	-0.42	-0.48	0.19	0.23	-0.41
12	AGT	-0.42	0.47	0.53	-0.51	-0.45	0.11	0.02	-0.62	-0.50	-0.03	-0.12	-0.71
13	ATA	-0.75	-0.53	-0.60	-0.72	-0.59	-0.39	-0.15	-0.37	0.21	0.52	0.28	0.28
14	ATC	0.47	-0.06	0.19	0.08	0.66	-0.22	0.18	-0.18	0.22	-0.03	-0.06	0.18
15	ATG	0.10	-0.08	0.02	0.16	0.75	-0.13	0.05	0.28	0.15	-0.01	-0.03	0.23
16	ATT	-0.77	-0.30	0.12	-0.66	1.00	-0.50	-0.38	-0.91	0.36	0.56	0.51	-0.73
17	CAA	-0.73	-0.38	-0.40	-0.36	-0.91	-0.63	-0.67	-0.68	-0.26	0.61	0.49	-0.07
18	CAC	0.09	-0.07	-0.05	0.04	-0.53	-0.02	0.12	0.16	0.00	-0.03	-0.04	-0.01
19	CAG	0.04	-0.06	0.05	0.18	-0.19	-0.13	0.36	0.11	-0.09	-0.04	0.00	0.17
20	CAT	-0.44	0.20	0.52	0.05	-0.76	-0.45	-0.51	-0.71	0.30	0.43	0.47	-0.54
21	CCA	-0.85	-0.47	-0.48	-0.72	-0.78	-0.12	-0.44	-0.60	-0.07	0.73	0.60	-0.27
22	CCC	-0.08	0.06	0.13	-0.05	0.17	0.44	0.48	0.32	-0.18	-0.15	-0.25	-0.22
23	CCG	-0.01	-0.14	0.28	0.08	-0.26	-0.09	-0.29	-0.06	0.25	0.10	0.20	0.18
24	CCT	-0.76	-0.22	-0.11	-0.67	-0.74	-0.10	0.32	-0.82	-0.33	0.27	0.40	-0.74
25	CGA	-0.78	-0.31	-0.38	-0.50	-0.69	-0.20	-0.32	-0.74	0.02	0.57	0.45	-0.57
26	CGC	-0.15	-0.07	0.06	-0.26	0.38	0.29	0.42	0.26	-0.01	-0.04	-0.11	-0.05
27	CGG	0.10	0.09	0.13	0.10	-0.32	-0.25	-0.33	0.00	0.07	0.00	0.12	0.18
28	CGT	-0.36	0.37	0.36	-0.39	-0.40	0.14	0.27	-0.65	-0.38	-0.02	-0.08	-0.61
29	CTA	-0.94	-0.57	-0.67	-0.78	-0.92	-0.43	-0.37	-0.87	-0.18	0.59	0.31	-0.09
30	CTC	0.72	0.65	0.70	0.56	0.34	0.26	0.57	0.36	-0.43	-0.28	0.65	-0.22
31	CTG	0.15	-0.41	-0.06	-0.06	0.38	-0.28	-0.17	0.29	-0.08	0.18	-0.22	0.50
32	CTT	-0.71	-0.01	0.15	-0.26	-0.77	-0.32	0.03	-0.77	-0.37	0.52	-0.04	-0.66
33	GAA	-0.58	-0.45	-0.40	0.02	-0.75	-0.61	-0.56	-0.53	0.12	0.60	0.44	0.10
34	GAC	0.30	0.11	-0.21	0.05	0.22	0.05	0.02	0.17	0.11	-0.03	-0.05	0.07
35	GAG	0.25	0.22	-0.10	0.40	0.23	0.79	-0.04	0.30	-0.06	-0.10	-0.07	0.16
36	GAT	-0.50	0.38	0.55	-0.24	-0.87	-0.50	-0.45	-0.77	0.09	0.50	0.55	-0.39
37	GCA	-0.72	-0.38	-0.54	-0.50	-0.66	-0.38	-0.47	-0.59	0.24	0.64	0.68	-0.23
38	GCC	0.16	-0.15	-0.04	-0.16	0.09	0.24	0.21	0.17	-0.20	-0.15	-0.18	-0.27
39	GCG	-0.05	0.41	0.16	0.26	0.11	-0.08	-0.24	0.25	0.23	0.21	0.26	0.22
40	GCT	-0.58	0.17	0.10	-0.49	-0.80	-0.34	-0.22	-0.74	-0.05	0.53	0.57	-0.61
41	GGA	-0.67	-0.31	-0.37	-0.39	-0.70	-0.40	-0.40	-0.58	0.20	0.49	0.53	-0.06
42	GGC	0.11	0.10	0.03	-0.09	0.25	0.31	0.23	0.22	0.14	-0.06	-0.07	0.12
43	GGG	-0.05	0.05	-0.32	-0.21	-0.39	-0.24	-0.37	-0.27	0.12	0.14	0.10	0.11
44	GGT	0.25	0.67	0.66	0.06	-0.43	-0.20	-0.25	-0.59	-0.32	-0.18	-0.19	-0.58
45	GTA	-0.80	-0.69	-0.83	-0.60	-0.51	-0.45	-0.56	-0.50	0.62	0.88	0.76	0.63
46	GTC	0.46	0.17	0.34	0.22	0.45	0.07	0.28	0.22	-0.01	-0.15	-0.13	-0.12
47	GTG	0.23	-0.13	-0.14	0.19	0.50	-0.13	-0.20	0.29	0.28	0.15	0.07	0.25

48	GTT	-0.73	0.00	0.03	-0.49	-0.78	-0.49	-0.22	-0.83	0.04	0.56	0.48	-0.58
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.15	0.00	-0.18	0.37	0.57	0.01	0.11	0.32	0.26	-0.06	-0.07	0.71
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	-0.59	0.44	0.34	-0.07	-0.87	-0.59	-0.69	-0.67	0.46	0.64	0.63	0.55
53	TCA	-0.75	-0.31	-0.49	-0.55	-0.90	-0.43	-0.55	-0.57	0.35	0.65	0.77	-0.20
54	TCC	0.09	-0.05	-0.01	-0.05	0.11	0.15	0.17	0.24	-0.07	-0.06	-0.03	0.03
55	TCG	0.39	0.31	0.32	0.25	-0.10	-0.11	-0.30	0.02	0.39	0.22	0.28	0.24
56	TCT	-0.81	0.16	0.08	-0.67	-0.78	-0.19	0.08	-0.86	-0.22	0.42	0.59	-0.66
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	-0.27	0.03	-0.10	-0.31	0.46	0.24	-0.04	0.16	0.02	-0.03	-0.04	0.15
59	TGG	0.01	0.12	-0.19	0.13	-0.45	0.16	-0.09	0.34	0.18	-0.02	-0.03	0.39
60	TGT	-0.03	0.53	0.66	-0.32	-0.45	-0.20	-0.53	-0.69	-0.11	0.37	0.40	-0.63
61	TTA	-0.88	-0.58	-0.70	-0.87	1.00	-0.16	-0.48	1.00	0.00	0.68	0.64	1.00
62	TTC	0.37	-0.05	0.01	0.03	0.56	-0.11	0.06	0.30	0.15	-0.03	-0.03	0.39
63	TTG	-0.34	-0.23	-0.36	-0.46	-0.47	-0.03	-0.21	-0.58	-0.20	0.50	-0.11	-0.19
64	TTT	-0.83	-0.33	-0.08	-0.62	-0.84	-0.42	-0.31	-0.50	0.03	0.57	0.52	-0.72
		CGA	CGC	CGG	CGT	CTA	CTC	CTG	CTT	GAA	GAC	GAG	GAT
		25	26	27	28	29	30	31	32	33	34	35	36

Table C.11 continued

		37	38	39	40	41	42	43	44	45	46	47	48
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
1	AAA	-0.31	0.44	0.43	-0.27	-0.23	0.43	0.30	0.30	0.09	0.66	0.57	-0.12
2	AAC	0.40	-0.05	0.01	0.22	0.21	-0.15	0.25	0.31	0.33	-0.10	0.13	0.26
3	AAG	-0.13	0.10	-0.17	0.12	0.29	-0.16	0.23	0.39	0.58	-0.10	0.02	0.23
4	AAT	-0.23	0.13	0.26	-0.48	0.25	0.67	0.45	0.19	0.51	-0.05	0.02	-0.69
5	ACA	-0.61	0.39	0.32	-0.62	-0.29	0.62	0.21	0.20	0.29	0.68	0.56	-0.50
6	ACC	-0.14	0.08	0.07	-0.21	-0.20	-0.15	-0.12	-0.27	0.38	0.02	0.20	-0.12
7	ACG	-0.46	0.05	-0.28	-0.33	0.18	0.40	0.21	0.35	0.43	-0.16	-0.32	0.01
8	ACT	-0.05	0.38	0.16	-0.79	-0.07	0.68	0.52	0.18	0.39	0.49	0.45	-0.51
9	AGA	-0.55	0.21	0.13	-0.47	-0.62	0.47	-0.26	-0.25	0.75	0.35	0.36	-0.58
10	AGC	0.13	0.14	0.03	-0.08	-0.14	-0.07	-0.14	-0.26	0.71	0.13	0.15	-0.31
11	AGG	-0.42	0.09	-0.11	-0.38	-0.14	0.28	0.28	0.42	0.60	0.07	-0.12	-0.62
12	AGT	0.02	-0.09	-0.15	-0.72	-0.27	0.41	-0.05	-0.22	0.68	0.16	-0.15	-0.50
13	ATA	0.36	-0.16	-0.14	0.81	0.04	0.27	-0.10	0.66	1.00	0.54	0.58	-0.42
14	ATC	0.45	-0.12	0.14	0.30	0.37	-0.13	0.21	0.10	0.85	-0.14	0.09	0.03
15	ATG	0.12	0.03	-0.06	0.07	0.33	-0.12	0.21	0.24	0.93	-0.01	-0.06	0.04

16	ATT	-0.02	0.50	0.49	-0.59	0.29	0.74	0.33	0.76	0.75	0.60	0.64	-0.82
17	CAA	-0.49	0.35	0.40	-0.48	-0.62	0.40	-0.43	0.00	0.08	0.55	0.51	-0.23
18	CAC	0.24	-0.05	0.05	0.37	0.08	-0.09	0.00	0.09	-0.11	-0.04	0.18	0.00
19	CAG	-0.29	0.02	-0.02	-0.06	0.10	-0.09	0.14	0.34	0.12	-0.02	-0.04	-0.12
20	CAT	-0.36	-0.06	0.15	-0.63	0.26	0.74	0.61	0.22	-0.52	-0.25	-0.46	-0.74
21	CCA	-0.49	0.50	0.42	-0.60	-0.59	0.47	0.00	-0.19	0.19	0.68	0.44	-0.49
22	CCC	-0.36	-0.14	-0.02	-0.40	-0.29	-0.30	-0.14	-0.33	-0.37	0.09	0.24	-0.13
23	CCG	-0.10	0.11	0.12	-0.09	0.18	0.30	0.17	0.34	0.09	0.00	-0.24	-0.12
24	CCT	-0.17	-0.10	0.14	-0.82	-0.33	0.52	0.15	-0.40	-0.34	0.35	0.51	-0.76
25	CGA	-0.59	0.16	0.14	-0.56	-0.61	0.15	-0.35	-0.36	-0.53	0.53	0.20	-0.60
26	CGC	0.20	0.03	0.22	0.24	-0.18	-0.22	-0.21	-0.28	0.18	0.10	0.41	0.09
27	CGG	-0.13	-0.05	-0.14	0.04	0.27	0.24	0.30	0.42	-0.17	-0.10	-0.40	-0.09
28	CGT	-0.01	-0.24	-0.15	-0.49	0.19	0.48	0.26	-0.23	0.15	0.16	0.38	-0.32
29	CTA	0.18	0.47	0.80	-0.32	-0.07	0.67	0.38	0.03	0.56	0.78	0.49	-0.76
30	CTC	0.24	-0.39	0.05	0.10	0.05	-0.48	-0.16	-0.37	0.01	-0.17	0.39	0.06
31	CTG	0.40	0.09	0.31	0.45	0.52	0.29	0.51	0.57	0.54	-0.07	-0.08	0.47
32	CTT	-0.15	-0.12	0.36	-0.57	0.29	0.61	0.27	0.00	0.41	0.35	0.43	-0.73
33	GAA	-0.24	0.37	0.23	-0.07	-0.36	0.32	-0.23	0.44	-0.13	0.52	0.45	0.42
34	GAC	0.33	0.01	-0.07	0.36	0.01	-0.06	-0.06	0.15	-0.34	0.05	-0.03	0.33
35	GAG	-0.19	0.11	-0.23	0.16	0.14	-0.12	0.06	0.39	0.28	-0.06	-0.13	0.11
36	GAT	0.04	-0.03	0.21	-0.65	0.31	0.76	0.60	0.57	-0.47	-0.06	-0.08	-0.70
37	GCA	-0.51	0.41	0.42	-0.36	-0.35	0.49	0.05	0.16	0.36	0.71	0.53	-0.44
38	GCC	-0.09	-0.04	0.08	-0.12	-0.41	0.33	-0.42	-0.45	-0.50	0.03	0.10	-0.04
39	GCG	-0.23	0.07	-0.16	0.04	0.08	0.01	0.00	0.15	-0.05	0.08	-0.30	0.12
40	GCT	-0.01	0.07	0.14	-0.76	0.05	0.71	0.35	-0.14	-0.19	0.37	0.48	-0.74
41	GGA	-0.52	0.22	-0.05	0.17	0.01	0.52	0.28	0.39	-0.32	0.38	0.09	-0.10
42	GGC	0.26	0.05	0.01	0.27	-0.15	-0.21	-0.19	-0.30	-0.20	0.02	0.14	0.02
43	GGG	-0.19	0.34	-0.27	-0.10	0.18	0.59	0.79	0.54	0.33	0.22	-0.34	-0.12
44	GGT	0.17	-0.29	-0.34	-0.62	0.09	0.39	0.30	-0.29	0.07	-0.27	-0.35	-0.55
45	GTA	0.45	0.73	0.74	0.06	0.38	0.73	0.50	0.54	0.64	0.85	0.80	0.13
46	GTC	0.35	-0.21	0.14	0.21	0.06	-0.30	0.01	-0.14	-0.27	-0.23	0.23	0.29
47	GTG	0.20	0.11	-0.05	0.23	0.37	0.31	0.27	0.45	0.53	0.11	-0.12	0.39
48	GTT	-0.17	0.11	0.39	-0.68	0.60	0.57	0.57	0.15	0.03	0.40	0.47	-0.58
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.37	0.01	-0.10	0.59	0.16	-0.13	-0.02	0.55	0.11	-0.12	0.19	0.28
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.30	0.24	0.17	0.16	0.18	0.76	0.72	0.72	-0.58	0.03	-0.34	0.37
53	TCA	-0.39	0.45	0.34	-0.29	-0.43	0.63	0.33	-0.05	0.38	0.78	0.57	-0.51
54	TCC	-0.14	0.08	0.04	-0.15	-0.15	-0.11	-0.17	-0.22	-0.29	0.11	0.16	-0.05

55	TCG	-0.31	0.07	-0.34	-0.23	0.22	0.31	0.15	0.39	-0.09	-0.09	-0.43	-0.18
56	TCT	-0.37	0.12	0.02	-0.87	-0.48	0.66	0.20	-0.32	-0.05	0.24	0.56	-0.71
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.19	0.12	-0.10	0.06	-0.13	0.05	-0.23	-0.19	-0.06	0.14	-0.04	-0.01
59	TGG	-0.03	0.14	-0.19	0.30	0.05	-0.09	0.20	0.21	0.26	0.16	-0.20	0.24
60	TGT	-0.10	-0.23	-0.32	-0.50	0.05	0.71	0.56	0.37	-0.08	-0.23	-0.49	-0.69
61	TTA	1.00	0.92	0.24	-0.84	-0.51	0.88	-0.16	1.00	-0.61	0.58	0.03	1.00
62	TTC	0.39	-0.09	0.09	0.41	0.31	-0.07	0.08	0.05	0.25	-0.09	0.09	0.16
63	TTG	-0.34	0.43	0.21	-0.36	0.13	0.57	0.28	0.15	0.48	0.48	0.18	-0.18
64	TTT	0.28	0.24	0.48	-0.76	-0.07	0.63	0.68	0.36	-0.32	0.47	0.49	-0.71
		GCA	GCC	GCG	GCT	GGA	GGC	GGG	GGT	GTA	GTC	GTG	GTT
		37	38	39	40	41	42	43	44	45	46	47	48

Table C.11 continued

		49	50	51	52	53	54	55	56	57	58	59	60
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
1	AAA	0.00	0.20	0.00	-0.13	-0.48	0.26	0.57	-0.48	0.00	0.33	-0.35	-0.40
2	AAC	0.00	-0.04	0.00	0.45	0.41	0.02	0.22	0.08	0.00	-0.06	-0.03	0.46
3	AAG	0.00	-0.04	0.00	0.62	0.27	0.01	-0.10	0.26	0.00	-0.05	0.03	0.39
4	AAT	0.00	0.46	0.00	1.00	-0.43	-0.07	-0.07	-0.75	0.00	0.58	0.75	-0.53
5	ACA	0.00	0.57	0.00	-0.37	-0.64	0.13	-0.02	-0.79	0.00	0.15	0.17	-0.59
6	ACC	0.00	0.12	0.00	-0.28	-0.20	0.13	-0.12	-0.17	0.00	-0.17	-0.22	-0.39
7	ACG	0.00	-0.20	0.00	-0.50	-0.16	0.18	0.05	-0.34	0.00	0.55	0.56	-0.07
8	ACT	0.00	0.68	0.00	-0.08	-0.76	-0.22	-0.45	-0.90	0.00	0.39	0.16	1.00
9	AGA	0.00	0.74	0.00	-0.42	-0.86	0.16	-0.31	-0.80	0.00	0.04	0.11	0.12
10	AGC	0.00	0.22	0.00	-0.54	0.35	0.43	0.42	-0.17	0.00	0.05	-0.07	-0.27
11	AGG	0.00	0.39	0.00	-0.37	-0.62	0.15	-0.29	-0.58	0.00	0.24	0.48	-0.18
12	AGT	0.00	0.12	0.00	-0.51	-0.59	-0.27	-0.56	-0.78	0.00	-0.27	0.08	-0.51
13	ATA	0.00	0.51	0.00	0.18	0.38	-0.38	-0.43	-0.76	0.00	0.37	0.22	0.21
14	ATC	0.00	-0.03	0.00	0.18	0.49	0.01	0.24	0.29	0.00	-0.05	-0.01	0.31
15	ATG	0.00	-0.02	0.00	0.39	0.34	0.11	-0.01	-0.03	0.00	-0.03	0.00	0.36
16	ATT	0.00	0.30	0.00	-0.43	-0.75	-0.24	0.02	-0.70	0.00	0.83	0.45	-0.41
17	CAA	0.00	0.80	0.00	-0.13	-0.39	0.47	0.49	1.00	0.00	0.58	0.11	1.00
18	CAC	0.00	-0.05	0.00	-0.05	0.07	-0.02	0.21	0.42	0.00	-0.08	-0.06	0.27
19	CAG	0.00	-0.07	0.00	0.63	0.09	-0.02	-0.06	0.39	0.00	-0.07	-0.01	0.40
20	CAT	0.00	0.64	0.00	0.26	0.15	-0.06	0.24	-0.48	0.00	0.66	0.79	0.69
21	CCA	0.00	0.72	0.00	0.41	-0.75	0.43	0.34	-0.81	0.00	0.11	0.15	-0.72
22	CCC	0.00	0.12	0.00	-0.15	-0.17	0.00	-0.11	-0.51	0.00	-0.29	-0.25	-0.42

23	CCG	0.00	-0.11	0.00	-0.09	-0.08	-0.01	-0.01	0.17	0.00	0.33	0.23	0.40
24	CCT	0.00	0.58	0.00	-0.61	-0.83	-0.53	-0.50	-0.86	0.00	0.13	0.45	-0.76
25	CGA	0.00	0.41	0.00	-0.46	-0.72	0.24	0.14	-0.72	0.00	-0.17	-0.05	-0.65
26	CGC	0.00	-0.19	0.00	-0.43	-0.18	-0.11	0.06	0.05	0.00	-0.21	-0.31	-0.38
27	CGG	0.00	0.19	0.00	-0.02	0.02	0.32	0.17	0.32	0.00	0.33	0.41	0.11
28	CGT	0.00	0.34	0.00	-0.11	-0.66	-0.42	-0.42	-0.64	0.00	0.38	0.58	-0.42
29	CTA	0.00	0.59	0.00	-0.76	-0.72	0.71	0.49	-0.50	0.00	0.68	-0.10	-0.68
30	CTC	0.00	-0.16	0.00	0.04	0.52	-0.23	0.42	0.31	0.00	0.40	0.43	0.37
31	CTG	0.00	0.08	0.00	0.37	0.43	-0.11	0.05	0.52	0.00	-0.23	-0.20	0.27
32	CTT	0.00	0.58	0.00	-0.53	-0.62	-0.37	-0.18	-0.83	0.00	0.72	0.75	0.30
33	GAA	0.00	0.65	0.00	0.45	-0.35	0.44	0.42	0.01	0.00	0.21	0.16	0.75
34	GAC	0.00	-0.05	0.00	0.39	0.33	0.02	0.09	0.51	0.00	-0.06	-0.04	0.27
35	GAG	0.00	-0.13	0.00	0.56	0.15	-0.02	-0.17	0.57	0.00	-0.09	-0.03	0.45
36	GAT	0.00	0.60	0.00	0.37	-0.78	-0.08	-0.17	-0.68	0.00	0.64	0.88	0.59
37	GCA	0.00	0.56	0.00	0.28	-0.53	0.13	-0.10	-0.68	0.00	0.32	0.05	-0.32
38	GCC	0.00	0.00	0.00	-0.16	-0.04	-0.12	-0.11	-0.09	0.00	-0.18	-0.19	-0.41
39	GCG	0.00	-0.07	0.00	-0.10	0.05	0.06	0.03	0.05	0.00	0.38	0.33	0.24
40	GCT	0.00	0.59	0.00	0.00	-0.75	-0.53	-0.52	-0.87	0.00	0.44	0.52	-0.52
41	GGA	0.00	-0.01	0.00	-0.29	-0.47	0.32	-0.09	0.20	0.00	0.22	0.23	-0.46
42	GGC	0.00	0.01	0.00	-0.32	0.13	0.12	0.04	0.24	0.00	-0.11	-0.21	-0.32
43	GGG	0.00	-0.07	0.00	-0.06	-0.07	0.33	0.00	0.15	0.00	0.25	0.38	-0.12
44	GGT	0.00	0.23	0.00	0.26	-0.56	-0.26	-0.49	-0.70	0.00	0.57	0.80	0.01
45	GTA	0.00	0.88	0.00	0.47	0.38	0.55	0.46	-0.46	0.00	0.75	0.35	-0.13
46	GTC	0.00	-0.10	0.00	-0.07	0.40	-0.22	0.16	0.17	0.00	-0.04	0.14	0.21
47	GTG	0.00	0.05	0.00	0.21	0.27	0.19	-0.03	0.47	0.00	-0.07	-0.20	0.24
48	GTT	0.00	0.64	0.00	-0.24	-0.83	-0.22	-0.33	-0.49	0.00	0.68	0.81	0.28
49	TAA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	TAC	0.00	-0.08	0.00	0.94	0.26	0.10	-0.11	0.80	0.00	-0.09	-0.03	0.62
51	TAG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
52	TAT	0.00	0.73	0.00	0.61	-0.46	0.57	0.04	1.00	0.00	0.62	0.64	0.45
53	TCA	0.00	0.78	0.00	1.00	-0.63	0.38	-0.12	-0.85	0.00	0.18	0.07	0.41
54	TCC	0.00	-0.01	0.00	0.28	0.10	-0.07	-0.24	-0.02	0.00	-0.25	-0.22	-0.05
55	TCG	0.00	-0.21	0.00	0.22	0.01	0.10	-0.07	0.07	0.00	0.45	0.45	0.42
56	TCT	0.00	0.76	0.00	-0.46	-0.62	-0.52	-0.55	-0.90	0.00	0.41	0.48	1.00
57	TGA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	TGC	0.00	-0.02	0.00	-0.25	0.03	0.06	-0.20	-0.03	0.00	-0.03	-0.07	-0.08
59	TGG	0.00	-0.01	0.00	0.15	-0.14	0.15	-0.17	0.39	0.00	-0.03	0.00	0.27
60	TGT	0.00	0.43	0.00	-0.26	-0.72	-0.31	-0.45	-0.84	0.00	0.43	0.76	-0.42
61	TTA	0.00	1.00	0.00	-0.94	-0.85	0.67	0.52	-0.91	0.00	-0.45	-0.69	1.00

62	TTC	0.00	-0.02	0.00	0.38	0.40	-0.12	0.14	0.40	0.00	-0.03	-0.01	0.29
63	TTG	0.00	0.08	0.00	-0.55	-0.73	-0.10	-0.27	-0.57	0.00	0.01	-0.44	-0.52
64	TTT	0.00	0.47	0.00	-0.48	-0.48	-0.02	0.11	-0.69	0.00	0.57	0.62	-0.69
		TAA	TAC	TAG	TAT	TCA	TCC	TCG	TCT	TGA	TGC	TGG	TGT
		49	50	51	52	53	54	55	56	57	58	59	60

Table C.11 continued

		61	62	63	64
		TTA	TTC	TTG	TTT
1	AAA	1.00	0.43	-0.28	-0.73
2	AAC	0.08	-0.02	0.78	0.57
3	AAG	1.00	-0.02	0.27	-0.02
4	AAT	1.00	0.35	0.44	-0.65
5	ACA	1.00	0.65	-0.14	-0.51
6	ACC	0.62	-0.12	0.28	0.01
7	ACG	-0.37	0.22	-0.25	-0.01
8	ACT	-0.93	0.25	-0.57	-0.82
9	AGA	1.00	0.48	-0.14	-0.76
10	AGC	1.00	0.18	0.51	-0.41
11	AGG	-0.44	0.13	-0.48	0.20
12	AGT	1.00	0.15	0.60	-0.80
13	ATA	1.00	0.41	-0.05	-0.43
14	ATC	1.00	-0.01	0.76	0.18
15	ATG	1.00	-0.01	0.63	0.38
16	ATT	1.00	0.25	-0.70	-0.91
17	CAA	-0.90	0.77	-0.69	-0.85
18	CAC	-0.19	-0.04	0.49	0.16
19	CAG	-0.46	-0.04	-0.74	0.39
20	CAT	1.00	0.50	-0.31	1.00
21	CCA	-0.84	0.71	-0.64	-0.59
22	CCC	-0.37	-0.15	-0.07	-0.15
23	CCG	0.04	0.09	-0.58	-0.07
24	CCT	1.00	0.34	-0.41	-0.65
25	CGA	-0.88	0.41	-0.39	-0.69
26	CGC	0.51	-0.09	0.64	-0.30
27	CGG	-0.43	0.09	-0.51	0.21
28	CGT	-0.72	-0.05	0.03	-0.56
29	CTA	-0.95	0.56	-0.70	-0.67

30	CTC	0.32	-0.09	0.71	0.04
31	CTG	0.29	0.04	0.02	0.54
32	CTT	-0.94	0.36	-0.56	-0.79
33	GAA	-0.29	0.65	0.19	0.00
34	GAC	1.00	-0.03	0.62	0.38
35	GAG	-0.12	-0.11	-0.52	0.26
36	GAT	-0.57	0.40	-0.39	0.37
37	GCA	-0.59	0.68	-0.52	-0.55
38	GCC	0.26	-0.10	0.47	-0.12
39	GCG	-0.52	0.09	-0.43	-0.20
40	GCT	-0.85	0.36	-0.53	-0.70
41	GGA	-0.50	0.19	0.08	-0.33
42	GGC	0.65	-0.04	0.63	-0.12
43	GGG	-0.48	0.05	-0.43	-0.19
44	GGT	-0.35	0.05	0.31	-0.58
45	GTA	1.00	0.82	-0.21	0.65
46	GTC	0.61	-0.18	0.84	0.57
47	GTG	0.64	0.20	0.32	0.41
48	GTT	1.00	0.26	-0.53	-0.24
49	TAA	0.00	0.00	0.00	0.00
50	TAC	0.65	-0.02	0.60	0.37
51	TAG	0.00	0.00	0.00	0.00
52	TAT	-0.86	0.37	-0.31	-0.41
53	TCA	-0.87	0.65	-0.42	-0.81
54	TCC	0.27	-0.24	0.12	-0.10
55	TCG	-0.06	0.25	-0.52	0.25
56	TCT	-0.92	0.33	-0.72	-0.67
57	TGA	0.00	0.00	0.00	0.00
58	TGC	-0.52	-0.02	0.50	-0.21
59	TGG	-0.17	0.00	-0.01	-0.11
60	TGT	1.00	0.31	-0.25	-0.22
61	TTA	1.00	0.72	-0.82	1.00
62	TTC	0.16	-0.02	0.63	0.51
63	TTG	1.00	0.20	-0.74	-0.55
64	TTT	1.00	0.45	-0.86	-0.47
		TTA	TTC	TTG	TTT
		61	62	63	64

Applicant's or agent's file reference number 25051WO	International application No.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description first mentioned on page 26 line 24

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet [ ]

Name of depositary institution

CENTRAAL BUREAU VOOR SCHIMMELCULTURES

Address of depositary institution *(including postal code and country)*
Uppsalalaan 8
P.O. Box 85167
NL-3508 AD Utrecht
The Netherlands

Date of deposit 10-08-1988	Accession Number CBS 513.88

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet [ ]

We inform you that the availability of the microorganism identified above, referred to Rule 13bis PCT, shall be effected only by issue of a sample to an expert nominated by the requester until the publication of the mention of grant of the national patent or, where applicable, for twenty years from the date of filing if the application has been refused, withdrawn or deemed to be withdrawn.

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description first mentioned on page 26 line 26.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

Name of depositary institution

CENTRAAL BUREAU VOOR SCHIMMELCULTURES

Address of depositary institution *(including postal code and country)*
Uppsalalaan 8
P.O. Box 85167
NL-3508 AD Utrecht
The Netherlands

Date of deposit 02-06-1995	Accession Number CBS 455.95

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

We inform you that the availability of the microorganism identified above, referred to Rule 13bis PCT, shall be effected only by issue of a sample to an expert nominated by the requester until the publication of the mention of grant of the national patent or, where applicable, for twenty years from the date of filing if the application has been refused, withdrawn or deemed to be withdrawn.

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Wallentin, Marko

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Form PCT/RO/134 (July 1992)

Claims

1. A method of optimization of a nucleotide coding sequence coding for a predetermined amino acid sequence, whereby the coding sequence is optimized for expression in a predetermined host cell, the method comprising:

a) generating at least one original coding sequence that codes for the predetermined amino acid sequence;

b) generating at least one newly generated coding sequence from this at least one original coding sequence by replacing in this at least one original coding sequence one or more codons by a synonymous codon;

c) determining a fitness value of said at least one original coding sequence and a fitness value of said at least one newly generated coding sequence while using a fitness function that determines at least one of single codon fitness and codon pair fitness for the predetermined host cell;

d) choosing one or more selected coding sequence amongst said at least one original coding sequence and said at least one newly generated coding sequence in accordance with a predetermined selection criterion such that the higher is said fitness value, the higher is a chance of being chosen;

e) repeating actions b) through d) while treating said one or more selected coding sequence as one or more original coding sequence in actions b) through d) until a predetermined iteration stop criterion is fulfilled.

2. A method according to claim 1, wherein said predetermined selection criterion is such that said one or more selected coding sequence have a best fitness value according to a predetermined criterion.

3. A method according to claim 1 or 2, wherein said method comprises, after action e):

f) selecting a best individual coding sequence amongst said one or more selected coding sequences where said best individual coding sequence has a better fitness value than other selected coding sequences.

4. A method according to any one of claims 1 - 3, wherein said predetermined iteration stop criterion is at least one of:

(a) testing whether at least one of said selected coding sequences have a best fitness value above a predetermined threshold value;

(b) testing whether none of said selected coding sequences has a best fitness value below said predetermined threshold value;

(c) testing whether at least one of said selected coding sequences has at least 30% of the codon pairs with associated positive codon pair weights for the predetermined host cell in said original coding sequence being transformed into codon pairs with associated negative weights; and,

(d) testing whether at least one of said selected coding sequences has at least 30% of the codon pairs with associated positive weights above 0 for the predetermined host cell in said original coding sequence being transformed into codon pairs with associated weights below 0.

5. A method according to any one of claims 1 - 4, wherein said fitness function defines single codon fitness by means of:

$$fit_c(g) = 100 - \frac{1}{|g|} \cdot \sum_{k=1}^{|g|} \left| r_c^{target}(c(k)) - r_c^{g}(c(k)) \right| \cdot 100$$

where g symbolizes a coding sequence, $|g|$ its length, $g(k)$ its k-th codon, $r_c^{target}(c(k))$ is a desired ratio of codon c(k) and $r_c^{g}(c(k))$ an actual ratio in the nucleotide coding sequence g.

6. A method according to any one of claims 1 - 4, wherein said fitness function defines codon pair fitness by means of:

$$fit_{cp}(g) = \frac{1}{|g|-1} \cdot \sum_{k=1}^{|g|-1} w((c(k), c(k+1))$$

where $w((c(k), c(k+1))$ is a weight of a codon pair in a coding sequence g, $|g|$ is length of said nucleotide coding sequence and $c(k)$ is k-th codon in said coding sequence.

7. A method according to any one of claims 1 - 4, wherein said fitness function is defined by means of:

$$fit_{combi}(g) = \frac{fit_{cp}(g)}{cpi + fit_{sc}(g)}$$

where

$$fit_{cp}(g) = \frac{1}{|g|-1} \cdot \sum_{k=1}^{|g|-1} w((c(k), c(k+1))$$

$$fit_{sc}(g) = \frac{1}{|g|} \cdot \sum_{k=1}^{|g|} \left| r_{sc}^{target}(c(k)) - r_{sc}^{g}(c(k)) \right|$$

cpi is a real value greater than zero, $fit_{cp}(g)$ is codon pair fitness function, $fit_{sc}(g)$ is a single codon fitness function, $w((c(k), c(k+1))$ is a weight of a codon pair in a coding sequence g, $|g|$ is length of said coding sequence, c(k) is k-th codon in said sequence of codons, $r_{sc}^{target}(c(k))$ is a desired ratio of codon c(k) and $r_{sc}^{g}(c(k))$ an actual ratio in the coding sequence g.

8. A method according to claim 7, wherein *cpi* is between 10^{-4} and 0.5.

9. A method according to any one of claims 6 - 8, wherein said codon pair weights w are taken from a 61×61 codon pair matrix without stop codons, or a 61 × 64 codon pair matrix that includes stop-codons, and wherein said codon pair weights w are calculated on the basis of a computer-based method, using as input at least one of:

(a) a group of nucleotide sequences consisting of at least 200 coding sequences of a predetermined host;

(b) a group of nucleotide sequences consisting of at least 200 coding sequences of the species to which the predetermined host belongs;

(c) a group of nucleotide sequences consisting of at least 5% of the protein encoding nucleotide sequences in a genome sequence of the predetermined host; and,

(d) a group of nucleotide sequences consisting of at least 5% of the protein encoding nucleotide sequences in a genome sequence of a genus related to the predetermined host.

10. A method according to claim 9, wherein said codon pair weights w are determined for at least 5%, 10%, 20%, 50%, and preferably 100% of the possible 61 × 64 codon pairs including the termination signal as stop codon.

11. A method according to claim 6 – 8, wherein said codon pair weights w are taken from a 61×61 codon pair matrix without stop codons, or a 61 × 64 codon pair matrix that includes stop-codons, and wherein said codon pair weights w are defined by means of:

$$w((c_i,c_j)) = \frac{n_{exp}^{combi}((c_i,c_j)) - n_{obs}^{high}((c_i,c_j))}{\max(n_{obs}^{high}((c_i,c_j)), n_{exp}^{combi}((c_i,c_j)))}$$

where the combined expected values $n_{exp}^{combi}((c_i,c_j))$ are defined by means of:

$$n_{exp}^{combi}((c_i,c_j)) = r_{sc}^{all}(c_i) \cdot r_{sc}^{all}(c_j) \cdot \sum_{\substack{c_k \in syn(c_i) \\ c_l \in syn(c_j)}} n_{obs}^{high}((c_k,c_l))$$

where $r_{sc}^{all}(c_k)$ denote the single codon ratio of c_k in the whole genome data set and $n_{obs}^{high}((c_i,c_j))$ the occurrences of a pair (c_i,c_j) in the highly expressed group, and wherein the highly expressed group are the genes whose mRNA's can be detected at a level of at least 20 copies per cell.

12. A method according any of the preceding claims where said original coding nucleotide sequence coding for predetermined amino acid sequence is selected from:

(a) a wild-type nucleotide sequence coding for said predetermined amino acid sequence

(b) a reverse translation of the predetermined amino acid sequence whereby a codon for an amino acid position in the predetermined amino acid sequence is randomly chosen from the synonymous codons coding for the amino acid; and,

(c) a reverse translation of the predetermined amino acid sequence whereby a codon for an amino acid position in the predetermined amino acid sequence is chosen in accordance with a single-codon bias for the predetermined host cell or a species related to the host cell.

13. A method according to any of claims 1 - 12, wherein said predetermined host cell is a cell of a microorganism, preferably a microorganism of a genus selected from: *Bacillus*, *Actinomycetis*, *Escherichia*, *Streptomyces*, *Aspergillus*, *Penicillium*, *Kluyveromyces*, *Saccharomyces*.

14. A method according to any of claims 1 - 12, wherein said predetermined host cell is a cell of an animal or plant, preferably a cell of a cell line selected from CHO, BHK, NS0, COS, Vero, PER.C6™, HEK-293, Drosophila S2, Spodoptera Sf9 and Spodoptera Sf21.

15. A computer comprising a processor and memory, the processor being arranged to read from said memory and write into said memory, the memory comprising data and instructions arranged to provide said processor with the capacity to perform the method of any of the claims 1 - 14.

16. Computer program product comprising data and instructions and arranged to be loaded in a memory of a computer that also comprises a processor, the processor being arranged to read from said memory and write into said memory, the data and instructions being arranged to provide said processor with the capacity to perform the method of any of the claims 1 - 14.

17. Data carrier provided with a computer program product as claimed in claim 16.

18. A nucleic acid molecule comprising a coding sequence coding for a predetermined amino acid sequence, wherein the coding sequence is not a naturally occurring coding sequence and wherein, the coding sequence has a $fit_{cp}(g)$ of at least below -0.1, and preferably below –0.2, and more preferably below –0.3 for a predetermined host cell.

19. A nucleic acid molecule comprising a coding sequence coding for a predetermined amino acid sequence, wherein the coding sequence is not a naturally occurring coding sequence and wherein, the coding sequence has a $fit_{cp}(g)$ of at least below -0.1, and preferably below –0.2 for a predetermined host cell and a $fit_{sci}(g)$ of at least below 0.1 for a predetermined host cell.

20. A nucleic acid molecule according to claim 18 or 19, wherein the coding sequence is operably linked to expression control sequence that are capable of directing expression of the coding sequence in the predetermined host cell.

21. A host cell comprising a nucleic acid molecule as defined in claim 20.

22. A method for producing a polypeptide having the predetermined amino acid sequence, the method comprising culturing a host cell as defined in claim 21 under conditions conducive to the expression of the polypeptide and, optionally, recovery of the polypeptide.

23. A method for producing at least one of an intracellular and an extracellular metabolite, the method comprising culturing a host cell as defined in claim 21 under conditions conducive to

the production of the metabolite, whereby preferably the polypeptide having the predetermined amino acid sequence is involved in the production of the metabolite.

Fig 1

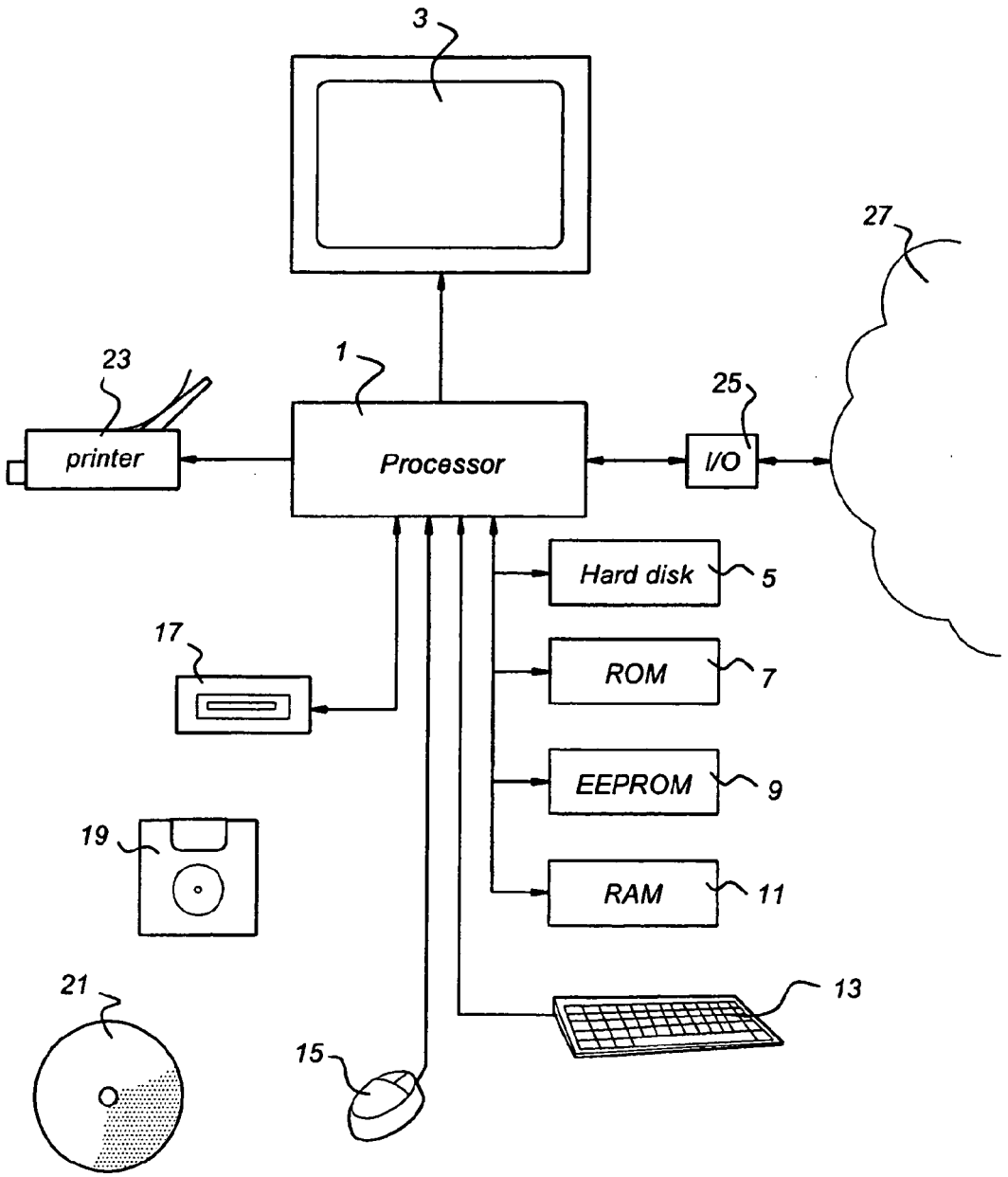

3
27
23
1
25
printer
Processor
I/O
Hard disk
5
17
ROM
7
EEPROM
9
19
RAM
11
21
13
15

Fig 2

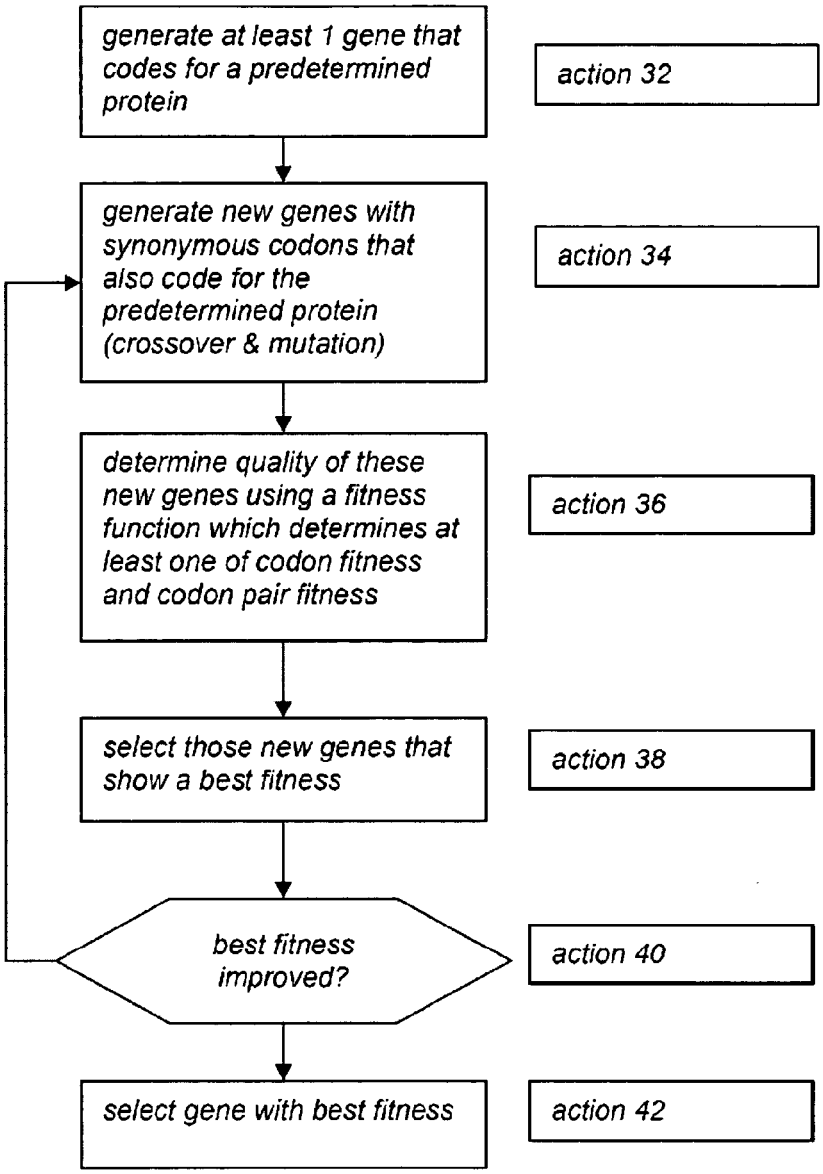

generate at least 1 gene that codes for a predetermined protein
action 32
generate new genes with synonymous codons that also code for the predetermined protein (crossover & mutation)
action 34
determine quality of these new genes using a fitness function which determines at least one of codon fitness and codon pair fitness
action 36
select those new genes that show a best fitness
action 38
best fitness improved?
action 40
select gene with best fitness
action 42

Fig 3

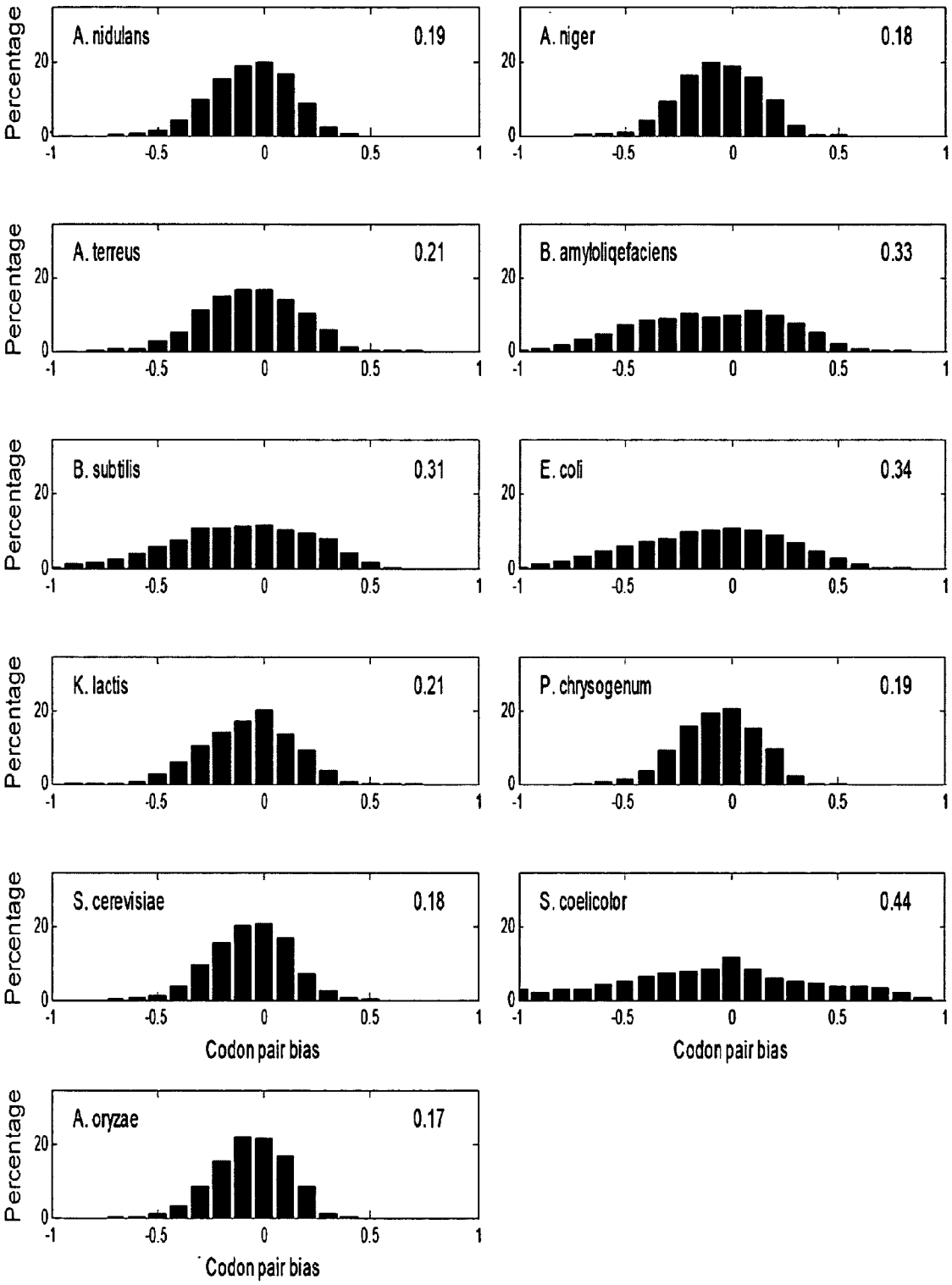

A. nidulans 0.19
A. niger 0.18
A. terreus 0.21
B. amyloliqefaciens 0.33
B. subtilis 0.31
E. coli 0.34
K. lactis 0.21
P. chrysogenum 0.19
S. cerevisiae 0.18
S. coelicolor 0.44
A. oryzae 0.17
Percentage
Codon pair bias

Fig 4

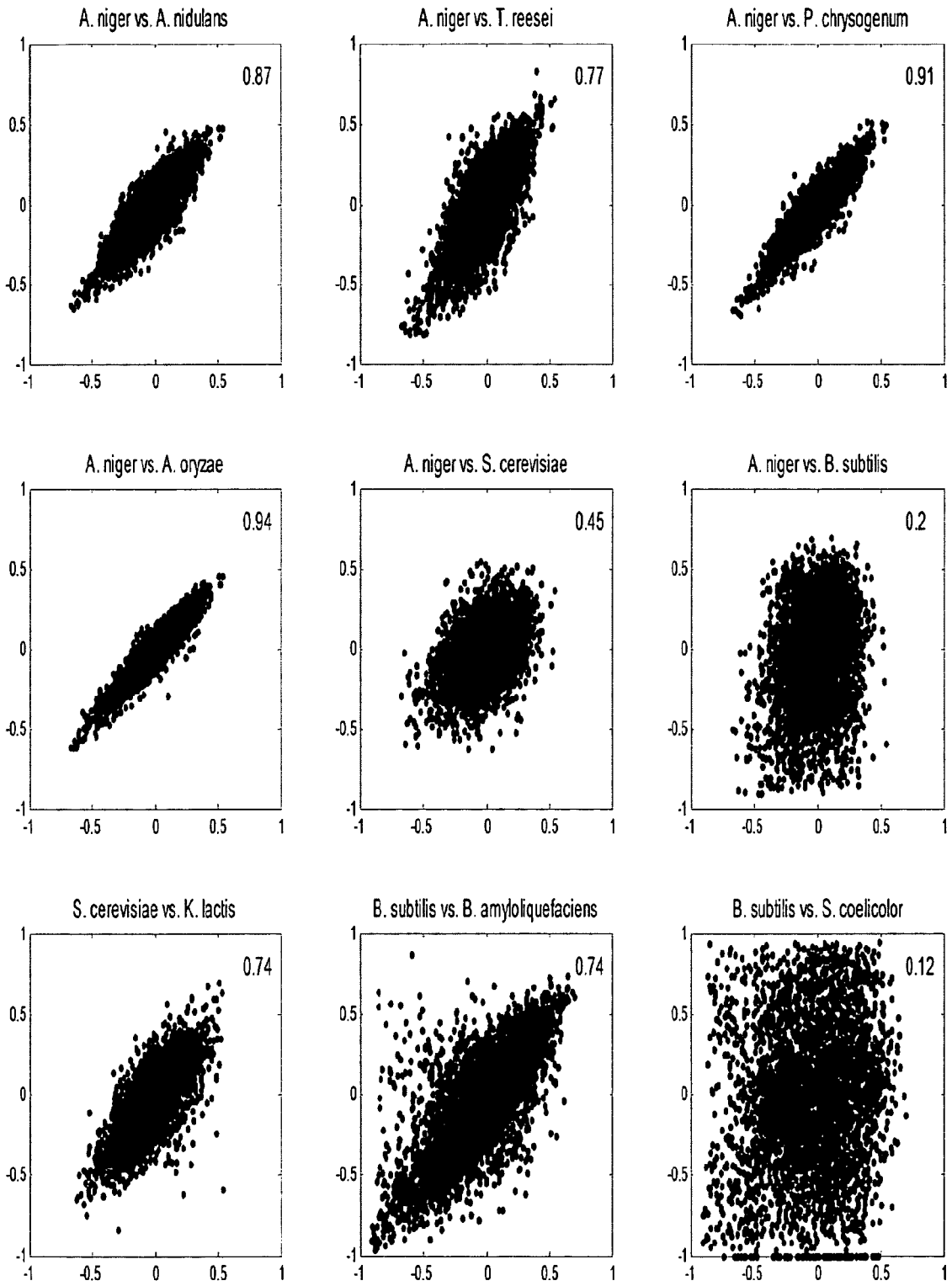

A. niger vs. A. nidulans
0.87
A. niger vs. T. reesei
0.77
A. niger vs. P. chrysogenum
0.91
A. niger vs. A. oryzae
0.94
A. niger vs. S. cerevisiae
0.45
A. niger vs. B. subtilis
0.2
S. cerevisiae vs. K. lactis
0.74
B. subtilis vs. B. amyloliquefaciens
0.74
B. subtilis vs. S. coelicolor
0.12
1
0.5
0
-0.5
-1

Fig 5a

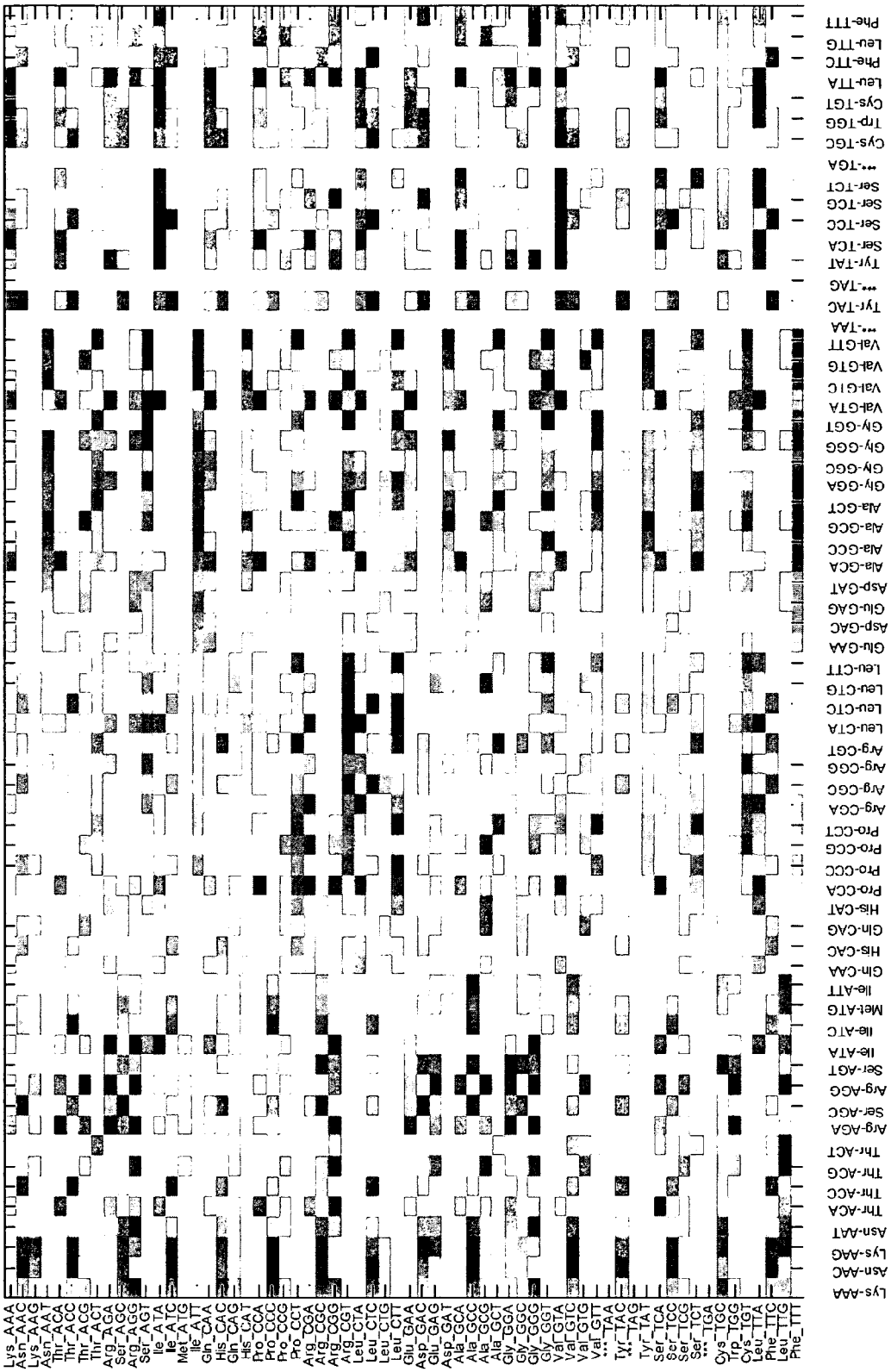
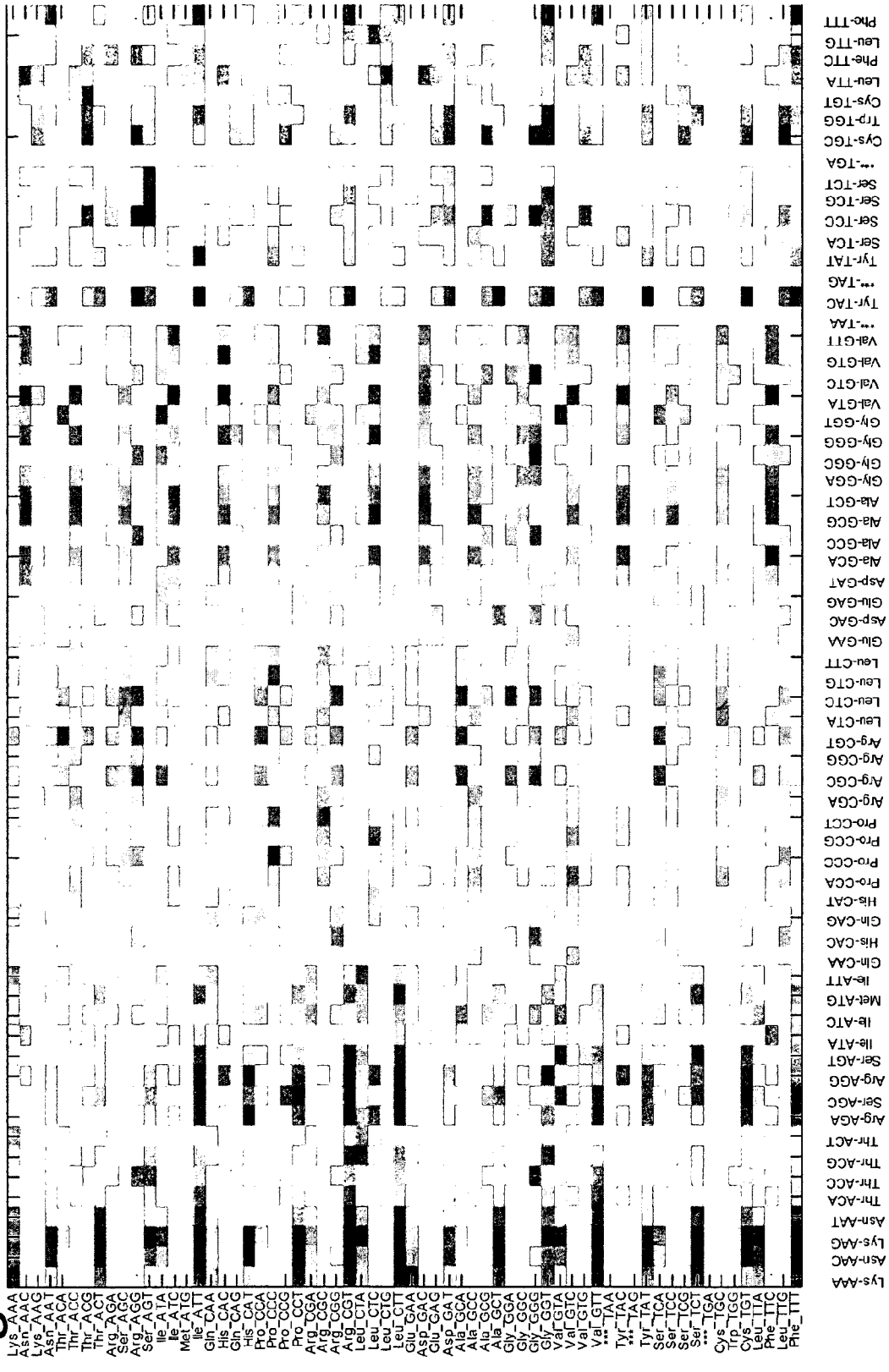

POSITIVE codon pair bias in A. niger (rows and columns sorted alphabetically)
Lys_AAA
Asn_AAC
Lys_AAG
Asn_AAT
Thr_ACA
Thr_ACC
Thr_ACG
Thr_ACT
Arg_AGA
Ser_AGC
Arg_AGG
Ser_AGT
Ile_ATA
Ile_ATC
Met_ATG
Ile_ATT
Gln_CAA
His_CAC
Gln_CAG
His_CAT
Pro_CCA
Pro_CCC
Pro_CCG
Pro_CCT
Arg_CGA
Arg_CGC
Arg_CGG
Arg_CGT
Leu_CTA
Leu_CTC
Leu_CTG
Leu_CTT
Glu_GAA
Asp_GAC
Glu_GAG
Asp_GAT
Ala_GCA
Ala_GCC
Ala_GCG
Ala_GCT
Gly_GGA
Gly_GGC
Gly_GGG
Gly_GGT
Val_GTA
Val_GTC
Val_GTG
Val_GTT
***_TAA
Tyr_TAC
***_TAG
Tyr_TAT
Ser_TCA
Ser_TCC
Ser_TCG
Ser_TCT
***_TGA
Cys_TGC
Trp_TGG
Cys_TGT
Leu_TTA
Phe_TTC
Leu_TTG
Phe_TTT
Lys-AAA
Asn-AAC
Lys-AAG
Asn-AAT
Thr-ACA
Thr-ACC
Thr-ACG
Thr-ACT
Arg-AGA
Ser-AGC
Arg-AGG
Ser-AGT
Ile-ATA
Ile-ATC
Met-ATG
Ile-ATT
Gln-CAA
His-CAC
Gln-CAG
His-CAT
Pro-CCA
Pro-CCC
Pro-CCG
Pro-CCT
Arg-CGA
Arg-CGC
Arg-CGG
Arg-CGT
Leu-CTA
Leu-CTC
Leu-CTG
Leu-CTT
Glu-GAA
Asp-GAC
Glu-GAG
Asp-GAT
Ala-GCA
Ala-GCC
Ala-GCG
Ala-GCT
Gly-GGA
Gly-GGC
Gly-GGG
Gly-GGT
Val-GTA
Val-GTC
Val-GTG
Val-GTT
***-TAA
Tyr-TAC
***-TAG
Tyr-TAT
Ser-TCA
Ser-TCC
Ser-TCG
Ser-TCT
***-TGA
Cys-TGC
Trp-TGG
Cys-TGT
Leu-TTA
Phe-TTC
Leu-TTG
Phe-TTT

Fig 5b


NEGATIVE codon pair bias in A. niger (rows and columns sorted alphabetically)
Lys_AAA
Asn_AAC
Lys_AAG
Asn_AAT
Thr_ACA
Thr_ACC
Thr_ACG
Thr_ACT
Arg_AGA
Ser_AGC
Arg_AGG
Ser_AGT
Ile_ATA
Ile_ATC
Met_ATG
Ile_ATT
Gln_CAA
His_CAC
Gln_CAG
His_CAT
Pro_CCA
Pro_CCC
Pro_CCG
Pro_CCT
Arg_CGA
Arg_CGC
Arg_CGG
Arg_CGT
Leu_CTA
Leu_CTC
Leu_CTG
Leu_CTT
Glu_GAA
Asp_GAC
Glu_GAG
Asp_GAT
Ala_GCA
Ala_GCC
Ala_GCG
Ala_GCT
Gly_GGA
Gly_GGC
Gly_GGG
Gly_GGT
Val_GTA
Val_GTC
Val_GTG
Val_GTT
***_TAA
Tyr_TAC
Tyr_TAT
Ser_TCA
Ser_TCC
Ser_TCG
Ser_TCT
***_TGA
Cys_TGC
Trp_TGG
Cys_TGT
Leu_TTA
Phe_TTC
Leu_TTG
Phe_TTT
Lys-AAA
Asn-AAC
Lys-AAG
Asn-AAT
Thr-ACA
Thr-ACC
Thr-ACG
Thr-ACT
Arg-AGA
Ser-AGC
Arg-AGG
Ser-AGT
Ile-ATA
Ile-ATC
Met-ATG
Ile-ATT
Gln-CAA
His-CAC
Gln-CAG
His-CAT
Pro-CCA
Pro-CCC
Pro-CCG
Pro-CCT
Arg-CGA
Arg-CGC
Arg-CGG
Arg-CGT
Leu-CTA
Leu-CTC
Leu-CTG
Leu-CTT
Glu-GAA
Asp-GAC
Glu-GAG
Asp-GAT
Ala-GCA
Ala-GCC
Ala-GCG
Ala-GCT
Gly-GGA
Gly-GGC
Gly-GGG
Gly-GGT
Val-GTA
Val-GTC
Val-GTG
Val-GTT
***-TAA
Tyr-TAC
***-TAG
Tyr-TAT
Ser-TCA
Ser-TCC
Ser-TCG
Ser-TCT
***-TGA
Cys-TGC
Trp-TGG
Cys-TGT
Leu-TTA
Phe-TTC
Leu-TTG
Phe-TTT

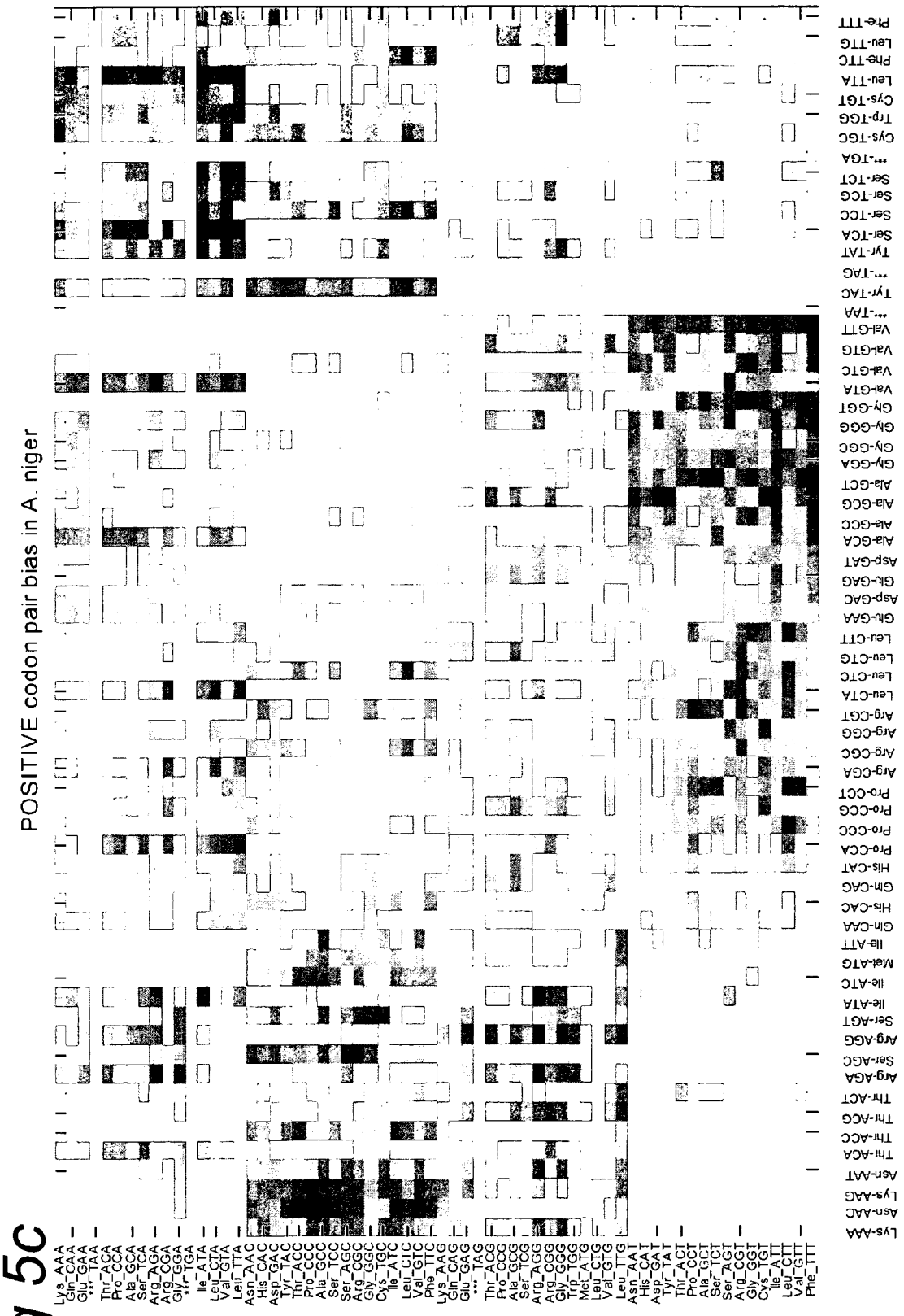
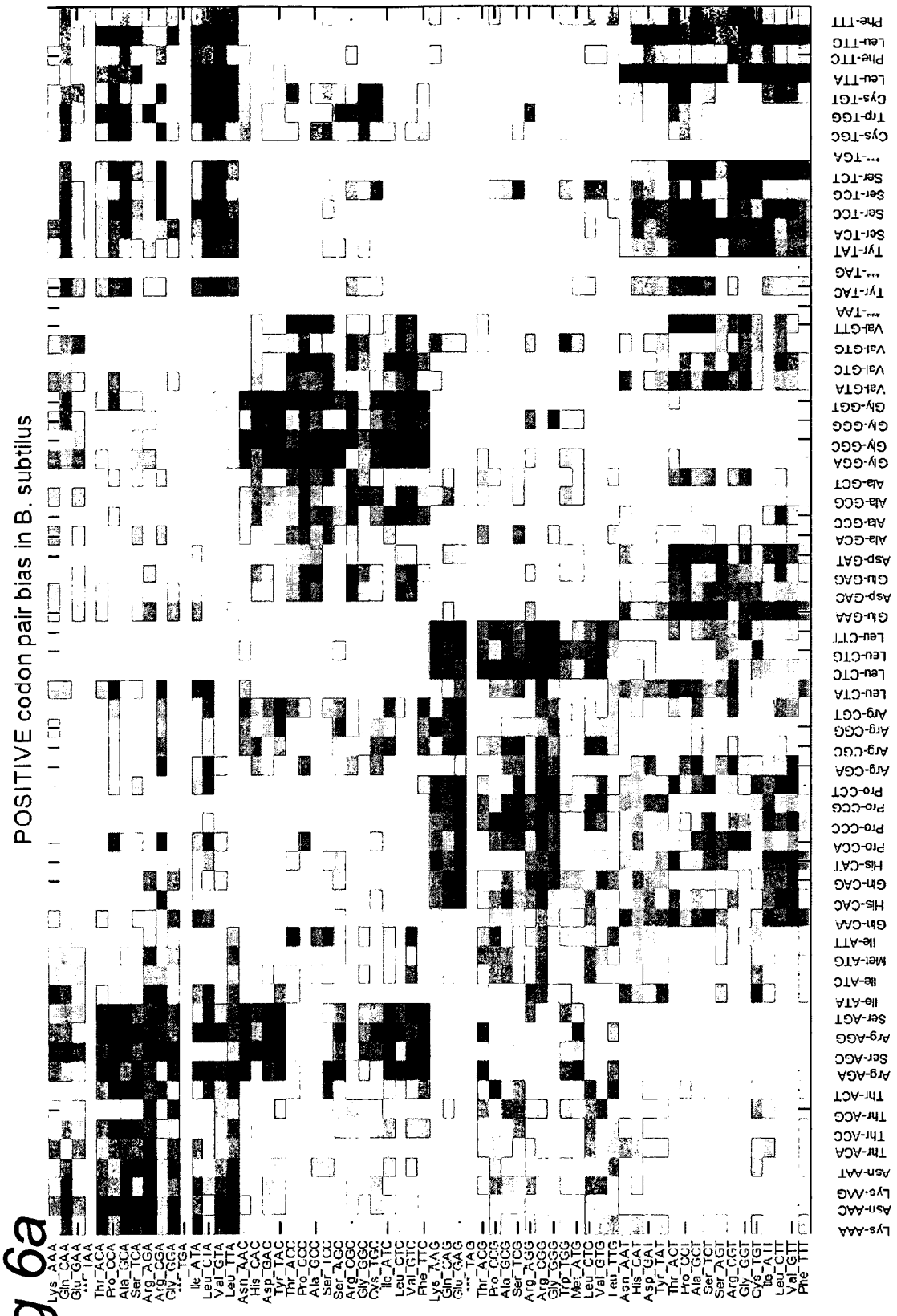

POSITIVE codon pair bias in A. niger
Lys_AAA
Asn_AAC
Lys-AAG
Asn-AAT
Thr-ACA
Thr-ACC
Thr-ACG
Thr-ACT
Arg-AGA
Ser-AGC
Arg-AGG
Ser-AGT
Ile-ATA
Ile-ATC
Met-ATG
Ile-ATT
Gln-CAA
His-CAC
Gln-CAG
His-CAT
Pro-CCA
Pro-CCC
Pro-CCG
Pro-CCT
Arg-CGA
Arg-CGC
Arg-CGG
Arg-CGT
Leu-CTA
Leu-CTC
Leu-CTG
Leu-CTT
Glu-GAA
Asp-GAC
Glu-GAG
Asp-GAT
Ala-GCA
Ala-GCC
Ala-GCG
Ala-GCT
Gly-GGA
Gly-GGC
Gly-GGG
Gly-GGT
Val-GTA
Val-GTC
Val-GTG
Val-GTT
***-TAA
Tyr-TAC
***-TAG
Tyr-TAT
Ser-TCA
Ser-TCC
Ser-TCG
Ser-TCT
***-TGA
Cys-TGC
Trp-TGG
Cys-TGT
Leu-TTA
Phe-TTC
Leu-TTG
Phe-TTT
Lys_AAA
Gln_CAA
Glu_GAA
***_TAA
Thr_ACA
Pro_CCA
Ala_TCA
Ser_AGA
Arg_CGA
Gly_GGA
***_TGA
Ile_ATA
Leu_CTA
Val_GTA
Leu_TTA
Asn_AAC
His_CAC
Asp_GAC
Tyr_TAC
Thr_ACC
Pro_CCC
Ala_TCC
Ser_AGC
Arg_CGC
Gly_GGC
Cys_TGC
Ile_ATC
Leu_CTC
Val_GTC
Phe_TTC
Lys_AAG
Gln_CAG
Glu_GAG
***_TAG
Thr_ACG
Pro_CCG
Ala_TCG
Ser_AGG
Arg_CGG
Gly_GGG
Trp_TGG
Met_ATG
Leu_CTG
Val_GTG
Leu_TTG
Asn_AAT
His_CAT
Asp_GAT
Tyr_TAT
Thr_ACT
Pro_CCT
Ala_TCT
Ser_AGT
Arg_CGT
Gly_GGT
Cys_TGT
Ile_ATT
Leu_CTT
Val_GTT
Phe_TTT

Fig 5c

NEGATIVE codon pair bias in A. niger
Lys_AAA
Asn_AAC
Lys_AAG
Asn_AAT
Thr_ACA
Thr_ACC
Thr_ACG
Thr_ACT
Arg_AGA
Ser_AGC
Arg_AGG
Ser_AGT
Ile_ATA
Ile_ATC
Met_ATG
Ile_ATT
Gln_CAA
His_CAC
Gln_CAG
His_CAT
Pro_CCA
Pro_CCC
Pro_CCG
Pro_CCT
Arg_CGA
Arg_CGC
Arg_CGG
Arg_CGT
Leu_CTA
Leu_CTC
Leu_CTG
Leu_CTT
Glu_GAA
Asp_GAC
Glu_GAG
Asp_GAT
Ala_GCA
Ala_GCC
Ala_GCG
Ala_GCT
Gly_GGA
Gly_GGC
Gly_GGG
Gly_GGT
Val_GTA
Val_GTC
Val_GTG
Val_GTT
***_TAA
Tyr_TAC
***_TAG
Tyr_TAT
Ser_TCA
Ser_TCC
Ser_TCG
Ser_TCT
***_TGA
Cys_TGC
Trp_TGG
Cys_TGT
Leu_TTA
Phe_TTC
Leu_TTG
Phe_TTT
Lys_AAA
Asn_AAC
Lys_AAG
Asn_AAT
Thr_ACA
Thr_ACC
Thr_ACG
Thr_ACT
Arg_AGA
Ser_AGC
Arg_AGG
Ser_AGT
Ile_ATA
Ile_ATC
Met_ATG
Ile_ATT
Gln_CAA
His_CAC
Gln_CAG
His_CAT
Pro_CCA
Pro_CCC
Pro_CCG
Pro_CCT
Arg_CGA
Arg_CGC
Arg_CGG
Arg_CGT
Leu_CTA
Leu_CTC
Leu_CTG
Leu_CTT
Glu_GAA
Asp_GAC
Glu_GAG
Asp_GAT
Ala_GCA
Ala_GCC
Ala_GCG
Ala_GCT
Gly_GGA
Gly_GGC
Gly_GGG
Gly_GGT
Val_GTA
Val_GTC
Val_GTG
Val_GTT
***_TAA
Tyr_TAC
***_TAG
Tyr_TAT
Ser_TCA
Ser_TCC
Ser_TCG
Ser_TCT
***_TGA
Cys_TGC
Trp_TGG
Cys_TGT
Leu_TTA
Phe_TTC
Leu_TTG
Phe_TTT

Fig 5d

Fig 6a


POSITIVE codon pair bias in B. subtilus
Lys-AAA
Asn-AAC
Lys-AAG
Asn-AAT
Thr-ACA
Thr-ACC
Thr-ACG
Thr-ACT
Arg-AGA
Ser-AGC
Arg-AGG
Ser-AGT
Ile-ATA
Ile-ATC
Met-ATG
Ile-ATT
Gln-CAA
His-CAC
Gln-CAG
His-CAT
Pro-CCA
Pro-CCC
Pro-CCG
Pro-CCT
Arg-CGA
Arg-CGC
Arg-CGG
Arg-CGT
Leu-CTA
Leu-CTC
Leu-CTG
Leu-CTT
Glu-GAA
Asp-GAC
Glu-GAG
Asp-GAT
Ala-GCA
Ala-GCC
Ala-GCG
Ala-GCT
Gly-GGA
Gly-GGC
Gly-GGG
Gly-GGT
Val-GTA
Val-GTC
Val-GTG
Val-GTT
***-TAA
Tyr-TAC
***-TAG
Tyr-TAT
Ser-TCA
Ser-TCC
Ser-TCG
Ser-TCT
***-TGA
Cys-TGC
Trp-TGG
Cys-TGT
Leu-TTA
Phe-TTC
Leu-TTG
Phe-TTT
Lys_AAA
Gln_CAA
Glu_GAA
***_TAA
Thr_ACA
Pro_CCA
Ala_GCA
Ser_TCA
Arg_AGA
Arg_CGA
Gly_TGA
Ile_ATA
Leu_CTA
Val_GTA
Leu_TTA
Asn_AAC
His_CAC
Asp_GAC
Tyr_TAC
Thr_ACC
Pro_CCC
Ala_GCC
Ser_TCC
Ser_AGC
Arg_CGC
Gly_GGC
Cys_TGC
Ile_ATC
Leu_CTC
Val_GTC
Phe_TTC
Lys_AAG
Gln_CAG
Glu_GAG
***_TAG
Thr_ACG
Pro_CCG
Ala_GCG
Ser_TCG
Arg_AGG
Arg_CGG
Gly_GGG
Trp_TGG
Met_ATG
Leu_CTG
Val_GTG
Ile_ATT
Asn_AAT
His_CAT
Asp_GAT
Tyr_TAT
Thr_ACT
Pro_CCT
Ala_GCT
Ser_TCT
Ser_AGT
Arg_CGT
Gly_GGT
Cys_TGT
Ile_ATT
Leu_CTT
Val_GTT
Phe_TTT

NEGATIVE codon pair bias in B. subtilus
Lys_AAA
Gln_CAA
Glu_GAA
***_TAA
Thr_ACA
Pro_CCA
Ala_GCA
Ser_TCA
Arg_AGA
Arg_CGA
Cys_TGA
Ile_ATA
Leu_CTA
Val_GTA
Leu_TTA
Asn_AAC
His_CAC
Asp_GAC
Tyr_TAC
Thr_ACC
Pro_CCC
Ala_GCC
Ser_TCC
Ser_AGC
Arg_CGC
Gly_GGC
Cys_TGC
Ile_ATC
Leu_CTC
Val_GTC
Phe_TTC
Lys_AAG
Gln_CAG
Glu_GAG
***_TAG
Thr_ACG
Pro_CCG
Ala_GCG
Ser_TCG
Arg_AGG
Arg_CGG
Gly_GGG
Trp_TGG
Met_ATG
Leu_CTG
Val_GTG
Leu_TTG
Asn_AAT
His_CAT
Asp_GAT
Tyr_TAT
Thr_ACT
Pro_CCT
Ala_GCT
Ser_TCT
Ser_AGT
Arg_CGT
Gly_GGT
Cys_TGT
Ile_ATT
Val_GTT
Phe_TTT
Lys-AAA
Asn-AAC
Lys-AAG
Asn-AAT
Thr-ACA
Thr-ACC
Thr-ACG
Thr-ACT
Arg-AGA
Ser-AGC
Arg-AGG
Ser-AGT
Ile-ATA
Ile-ATC
Met-ATG
Ile-ATT
Gln-CAA
His-CAC
Gln-CAG
His-CAT
Pro-CCA
Pro-CCC
Pro-CCG
Pro-CCT
Arg-CGA
Arg-CGC
Arg-CGG
Arg-CGT
Leu-CTA
Leu-CTC
Leu-CTG
Leu-CTT
Glu-GAA
Asp-GAC
Glu-GAG
Asp-GAT
Ala-GCA
Ala-GCC
Ala-GCG
Ala-GCT
Gly-GGA
Gly-GGC
Gly-GGG
Gly-GGT
Val-GTA
Val-GTC
Val-GTG
Val-GTT
***-TAA
Tyr-TAC
***-TAG
Tyr-TAT
Ser-TCA
Ser-TCC
Ser-TCG
Ser-TCT
***-TGA
Cys-TGC
Trp-TGG
Cys-TGT
Leu-TTA
Phe-TTC
Leu-TTG
Phe-TTT

Fig 6b

POSITIVE codon pair bias in E. coli
Lys_AAA
Gln_CAA
Glu_GAA
***_TAA
Thr_ACA
Pro_CCA
Ala_GCA
Ser_TCA
Arg_AGA
Arg_CGA
Gly_GGA
***_TGA
Ile_ATA
Leu_CTA
Val_GTA
Leu_TTA
Asn_AAC
His_CAC
Asp_GAC
Tyr_TAC
Thr_ACC
Pro_CCC
Ala_GCC
Ser_TCC
Ser_AGC
Arg_CGC
Gly_GGC
Cys_TGC
Ile_ATC
Leu_CTC
Val_GTC
Phe_TTC
Lys_AAG
Gln_CAG
Glu_GAG
***_TAG
Thr_ACG
Pro_CCG
Ala_GCG
Ser_TCG
Arg_AGG
Arg_CGG
Gly_GGG
Trp_TGG
Met_ATG
Leu_CTG
Val_GTG
Leu_TTG
Asn_AAT
His_CAT
Asp_GAT
Tyr_TAT
Thr_ACT
Pro_CCT
Ala_GCT
Ser_TCT
Ser_AGT
Arg_CGT
Gly_GGT
Cys_TGT
Ile_ATT
Leu_CTT
Val_GTT
Phe_TTT
Lys-AAA
Asn-AAC
Lys-AAG
Asn-AAT
Thr-ACA
Thr-ACC
Thr-ACG
Thr-ACT
Arg-AGA
Ser-AGC
Arg-AGG
Ser-AGT
Ile-ATA
Ile-ATC
Met-ATG
Ile-ATT
Gln-CAA
His-CAC
Gln-CAG
His-CAT
Pro-CCA
Pro-CCC
Pro-CCG
Pro-CCT
Arg-CGA
Arg-CGC
Arg-CGG
Arg-CGT
Leu-CTA
Leu-CTC
Leu-CTG
Leu-CTT
Glu-GAA
Asp-GAC
Glu-GAG
Asp-GAT
Ala-GCA
Ala-GCC
Ala-GCG
Ala-GCT
Gly-GGA
Gly-GGC
Gly-GGG
Gly-GGT
Val-GTA
Val-GTC
Val-GTG
Val-GTT
***-TAA
Tyr-TAC
***-TAG
Tyr-TAT
Ser-TCA
Ser-TCC
Ser-TCG
Ser-TCT
***-TGA
Cys-TGC
Trp-TGG
Cys-TGT
Leu-TTA
Phe-TTC
Leu-TTG
Phe-TTT

Fig 7a

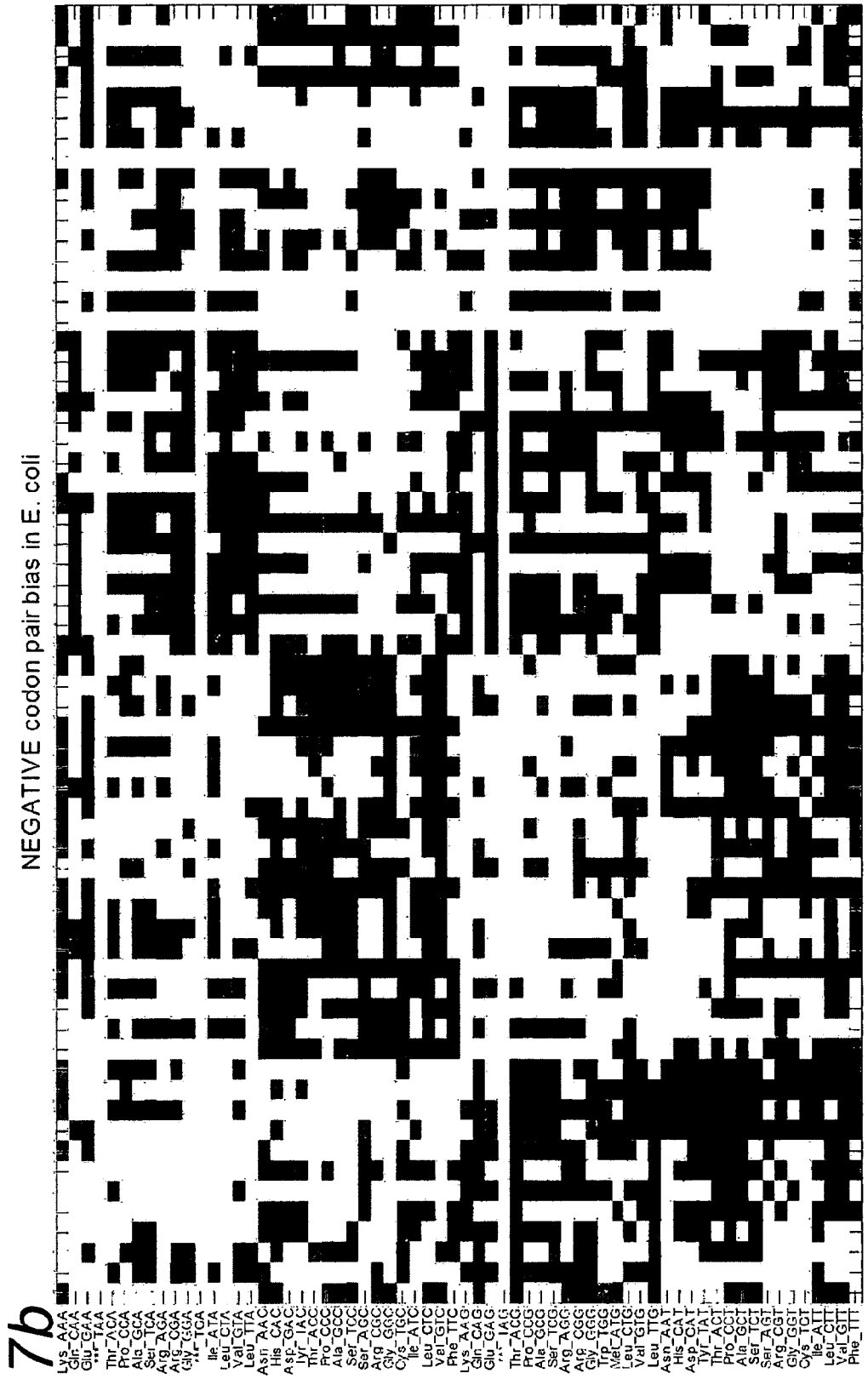

NEGATIVE codon pair bias in E. coli
Lys_AAA
Gln_CAA
Glu_GAA
***_TAA
Thr_ACA
Pro_CCA
Ala_GCA
Ser_TCA
Arg_AGA
Arg_CGA
Gly_GGA
***_TCA
Ile_ATA
Leu_CTA
Val_GTA
Leu_TTA
Asn_AAC
His_CAC
Asp_GAC
Tyr_TAC
Thr_ACC
Pro_CCC
Ala_GCC
Ser_TCC
Ser_AGC
Arg_CGC
Gly_GGC
Cys_TGC
Ile_ATC
Leu_CTC
Val_GTC
Phe_TTC
Lys_AAG
Gln_CAG
Glu_GAG
***_TAG
Thr_ACG
Pro_CCG
Ala_GCG
Ser_TCG
Arg_AGG
Arg_CGG
Gly_GGG
Trp_TGG
Met_ATG
Leu_CTG
Val_GTG
Leu_TTG
Asn_AAT
His_CAT
Asp_GAT
Tyr_TAT
Thr_ACT
Pro_CCT
Ala_GCT
Ser_TCT
Ser_AGT
Arg_CGT
Gly_GGT
Cys_TGT
Ile_ATT
Leu_CTT
Val_GTT
Phe_TTT
Lys-AAA
Asn-AAC
Lys-AAG
Asn-AAT
Thr-ACA
Thr-ACC
Thr-ACG
Thr-ACT
Arg-AGA
Ser-AGC
Arg-AGG
Ser-AGT
Ile-ATA
Ile-ATC
Met-ATG
Ile-ATT
Gln-CAA
His-CAC
Gln-CAG
His-CAT
Pro-CCA
Pro-CCC
Pro-CCG
Pro-CCT
Arg-CGA
Arg-CGC
Arg-CGG
Arg-CGT
Leu-CTA
Leu-CTC
Leu-CTG
Leu-CTT
Glu-GAA
Asp-GAC
Glu-GAG
Asp-GAT
Ala-GCA
Ala-GCC
Ala-GCG
Ala-GCT
Gly-GGA
Gly-GGC
Gly-GGG
Gly-GGT
Val-GTA
Val-GTC
Val-GTG
Val-GTT
***-TAA
Tyr-TAC
***-TAG
Tyr-TAT
Ser-TCA
Ser-TCC
Ser-TCG
Ser-TCT
***-TGA
Cys-TGC
Trp-TGG
Cys-TGT
Leu-TTA
Phe-TTC
Leu-TTG
Phe-TTT

Fig 7b

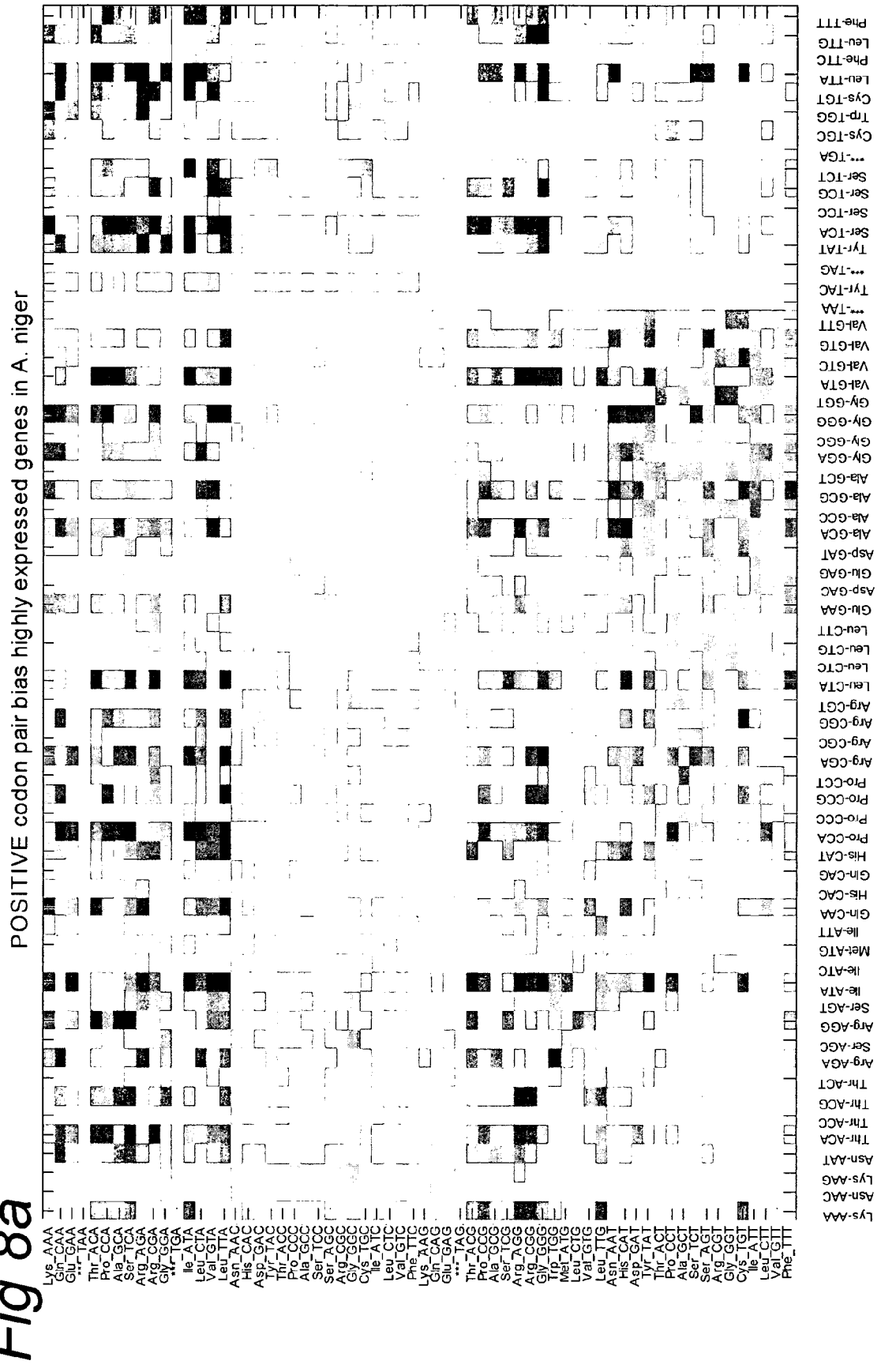

POSITIVE codon pair bias highly expressed genes in A. niger
Lys_AAA
Gln_CAA
Glu_GAA
***_TAA
Thr_ACA
Pro_CCA
Ala_GCA
Ser_TCA
Arg_AGA
Arg_CGA
Gly_GGA
***_TGA
Ile_ATA
Leu_CTA
Val_GTA
Leu_TTA
Asn_AAC
His_CAC
Asp_GAC
Tyr_TAC
Thr_ACC
Pro_CCC
Ala_GCC
Ser_TCC
Ser_AGC
Arg_CGC
Gly_GGC
Cys_TGC
Ile_ATC
Leu_CTC
Val_GTC
Phe_TTC
Lys_AAG
Gln_CAG
Glu_GAG
***_TAG
Thr_ACG
Pro_CCG
Ala_GCG
Ser_TCG
Arg_AGG
Arg_CGG
Gly_GGG
Trp_TGG
Met_ATG
Leu_CTG
Val_GTG
Leu_TTG
Asn_AAT
His_CAT
Asp_GAT
Tyr_TAT
Thr_ACT
Pro_CCT
Ala_GCT
Ser_TCT
Ser_AGT
Arg_CGT
Gly_GGT
Cys_TGT
Ile_ATT
Leu_CTT
Val_GTT
Phe_TTT
Lys-AAA
Asn-AAC
Lys-AAG
Asn-AAT
Thr-ACA
Thr-ACC
Thr-ACG
Thr-ACT
Arg-AGA
Ser-AGC
Arg-AGG
Ser-AGT
Ile-ATA
Ile-ATC
Met-ATG
Ile-ATT
Gln-CAA
His-CAC
Gln-CAG
His-CAT
Pro-CCA
Pro-CCC
Pro-CCG
Pro-CCT
Arg-CGA
Arg-CGC
Arg-CGG
Arg-CGT
Leu-CTA
Leu-CTC
Leu-CTG
Leu-CTT
Glu-GAA
Asp-GAC
Glu-GAG
Asp-GAT
Ala-GCA
Ala-GCC
Ala-GCG
Ala-GCT
Gly-GGA
Gly-GGC
Gly-GGG
Gly-GGT
Val-GTA
Val-GTC
Val-GTG
Val-GTT
***-TAA
Tyr-TAC
***-TAG
Tyr-TAT
Ser-TCA
Ser-TCC
Ser-TCG
Ser-TCT
***-TGA
Cys-TGC
Trp-TGG
Cys-TGT
Leu-TTA
Phe-TTC
Leu-TTG
Phe-TTT

Fig 8a

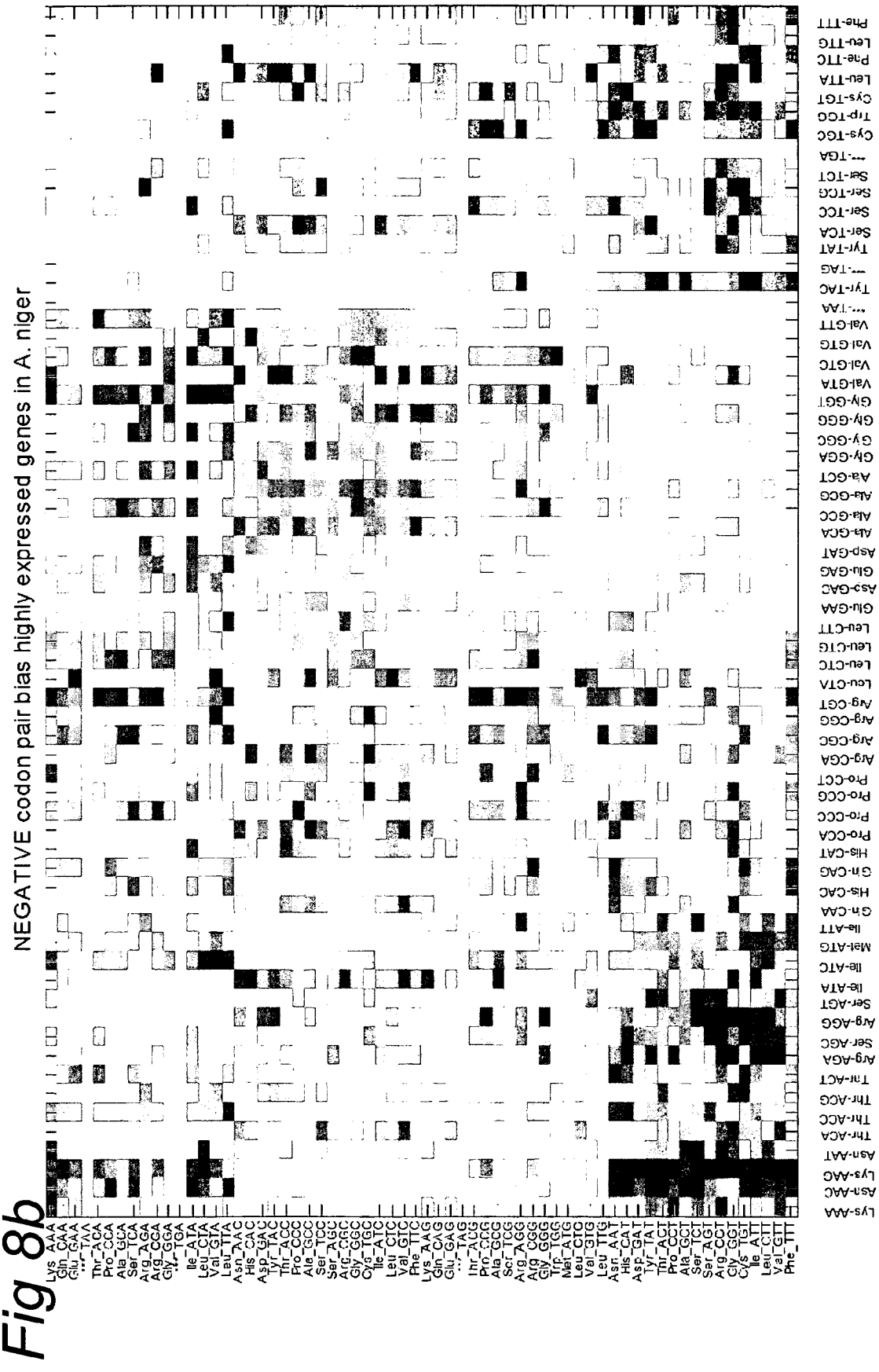

NEGATIVE codon pair bias highly expressed genes in A. niger
Lys_AAA
Asn_AAC
Lys_AAG
Asn_AAT
Thr_ACA
Thr_ACC
Thr_ACG
Thr_ACT
Arg_AGA
Ser_AGC
Arg_AGG
Ser_AGT
Ile_ATA
Ile_ATC
Met_ATG
Ile_ATT
Gln_CAA
His_CAC
Gln_CAG
His_CAT
Pro_CCA
Pro_CCC
Pro_CCG
Pro_CCT
Arg_CGA
Arg_CGC
Arg_CGG
Arg_CGT
Leu_CTA
Leu_CTC
Leu_CTG
Leu_CTT
Glu_GAA
Asp_GAC
Glu_GAG
Asp_GAT
Ala_GCA
Ala_GCC
Ala_GCG
Ala_GCT
Gly_GGA
Gly_GGC
Gly_GGG
Gly_GGT
Val_GTA
Val_GTC
Val_GTG
Val_GTT
***_TAA
Tyr_TAC
***_TAG
Tyr_TAT
Ser_TCA
Ser_TCC
Ser_TCG
Ser_TCT
***_TGA
Cys_TGC
Trp_TGG
Cys_TGT
Leu_TTA
Phe_TTC
Leu_TTG
Phe_TTT
Lys_AAA
Gln_CAA
Glu_GAA
***_TAA
Thr_ACA
Pro_CCA
Ala_GCA
Ser_TCA
Arg_AGA
Arg_CGA
Gly_GGA
***_TGA
Ile_ATA
Leu_CTA
Val_GTA
Leu_TTA
Asn_AAC
His_CAC
Asp_GAC
Tyr_TAC
Thr_ACC
Pro_CCC
Ala_GCC
Ser_TCC
Arg_AGC
Arg_CGC
Gly_GGC
Cys_TGC
Ile_ATC
Leu_CTC
Val_GTC
Phe_TTC
Lys_AAG
Gln_CAG
Glu_GAG
***_TAG
Thr_ACG
Pro_CCG
Ala_GCG
Ser_TCG
Arg_AGG
Arg_CGG
Gly_GGG
Trp_TGG
Met_ATG
Leu_CTG
Val_GTG
Leu_TTG
Asn_AAT
His_CAT
Asp_GAT
Tyr_TAT
Thr_ACT
Pro_CCT
Ala_GCT
Ser_TCT
Arg_AGT
Arg_CGT
Gly_GGT
Cys_TGT
Ile_ATT
Leu_CTT
Val_GTT
Phe_TTT
Lys-AAA
Asn-AAC
Lys-AAG
Asn-AAT
Thr-ACA
Thr-ACC
Thr-ACG
Thr-ACT
Arg-AGA
Ser-AGC
Arg-AGG
Ser-AGT
Ile-ATA
Ile-ATC
Met-ATG
Ile-ATT
Gln-CAA
His-CAC
Gln-CAG
His-CAT
Pro-CCA
Pro-CCC
Pro-CCG
Pro-CCT
Arg-CGA
Arg-CGC
Arg-CGG
Arg-CGT
Leu-CTA
Leu-CTC
Leu-CTG
Leu-CTT
Glu-GAA
Asp-GAC
Glu-GAG
Asp-GAT
Ala-GCA
Ala-GCC
Ala-GCG
Ala-GCT
Gly-GGA
Gly-GGC
Gly-GGG
Gly-GGT
Val-GTA
Val-GTC
Val-GTG
Val-GTT
***-TAA
Tyr-TAC
***-TAG
Tyr-TAT
Ser-TCA
Ser-TCC
Ser-TCG
Ser-TCT
***-TGA
Cys-TGC
Trp-TGG
Cys-TGT
Leu-TTA
Phe-TTC
Leu-TTG
Phe-TTT

Fig 8b

Fig 9

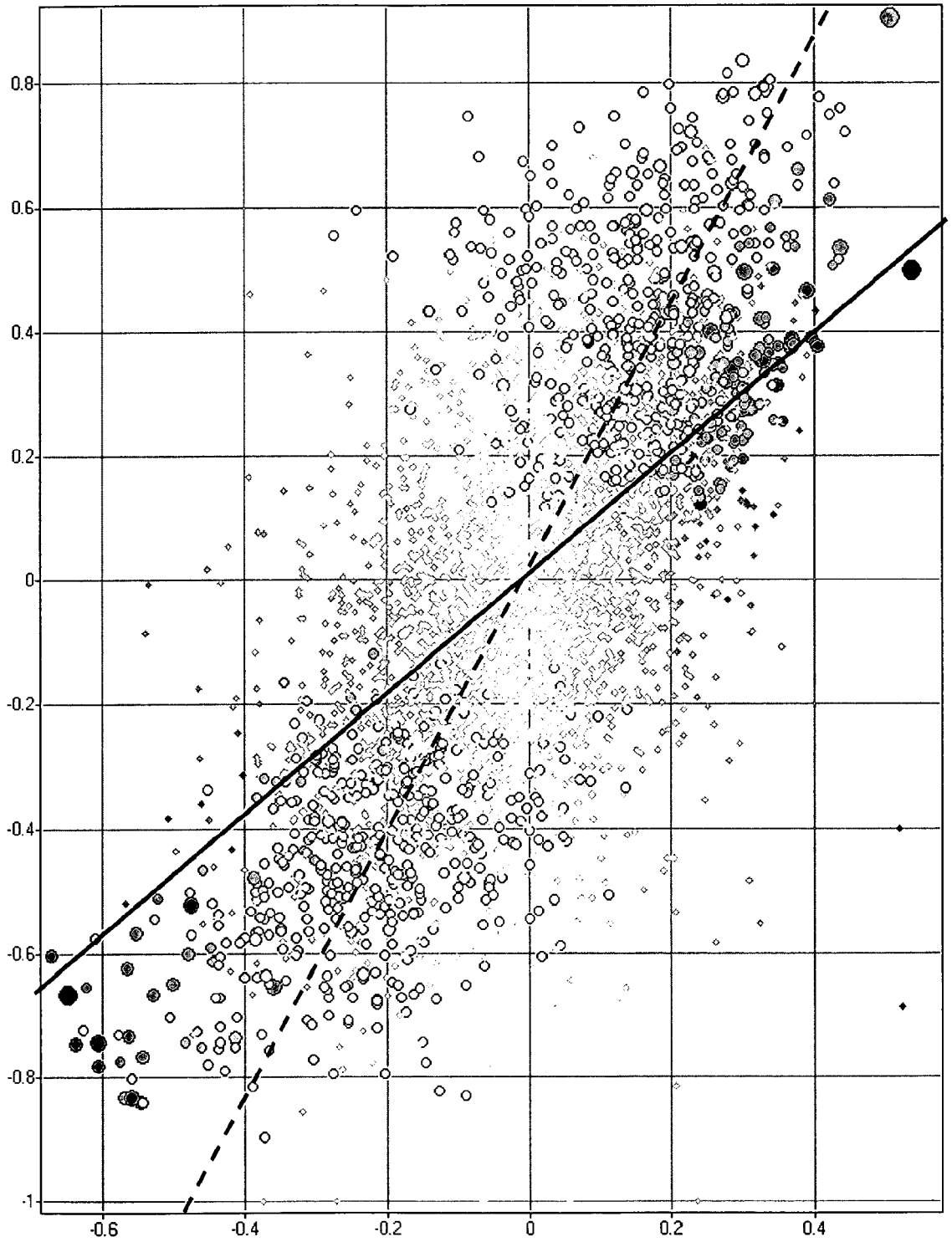


Fig 10

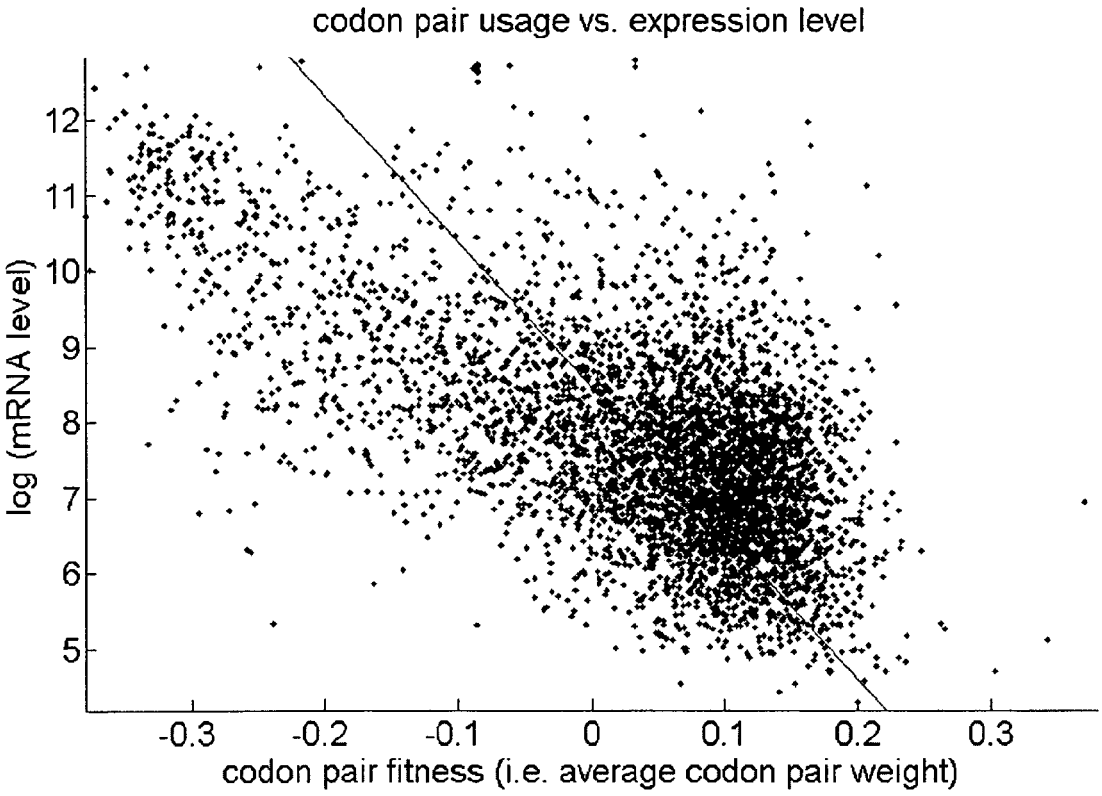

codon pair usage vs. expression level
log (mRNA level)
12
11
10
9
8
7
6
5
-0.3
-0.2
-0.1
0
0.1
0.2
0.3
codon pair fitness (i.e. average codon pair weight)

Fig 11

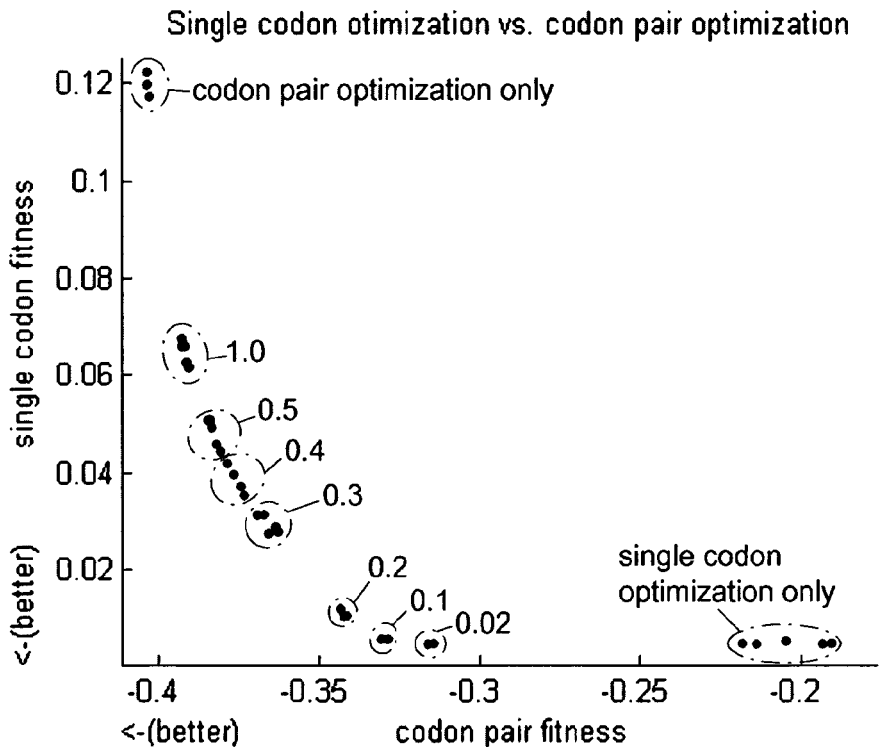

Single codon otimization vs. codon pair optimization
codon pair optimization only
single codon fitness
<-(better)
0.12
0.1
0.08
0.06
0.04
0.02
1.0
0.5
0.4
0.3
0.2
0.1
0.02
single codon
optimization only
-0.4
-0.35
-0.3
-0.25
-0.2
<-(better)
codon pair fitness

Fig 12

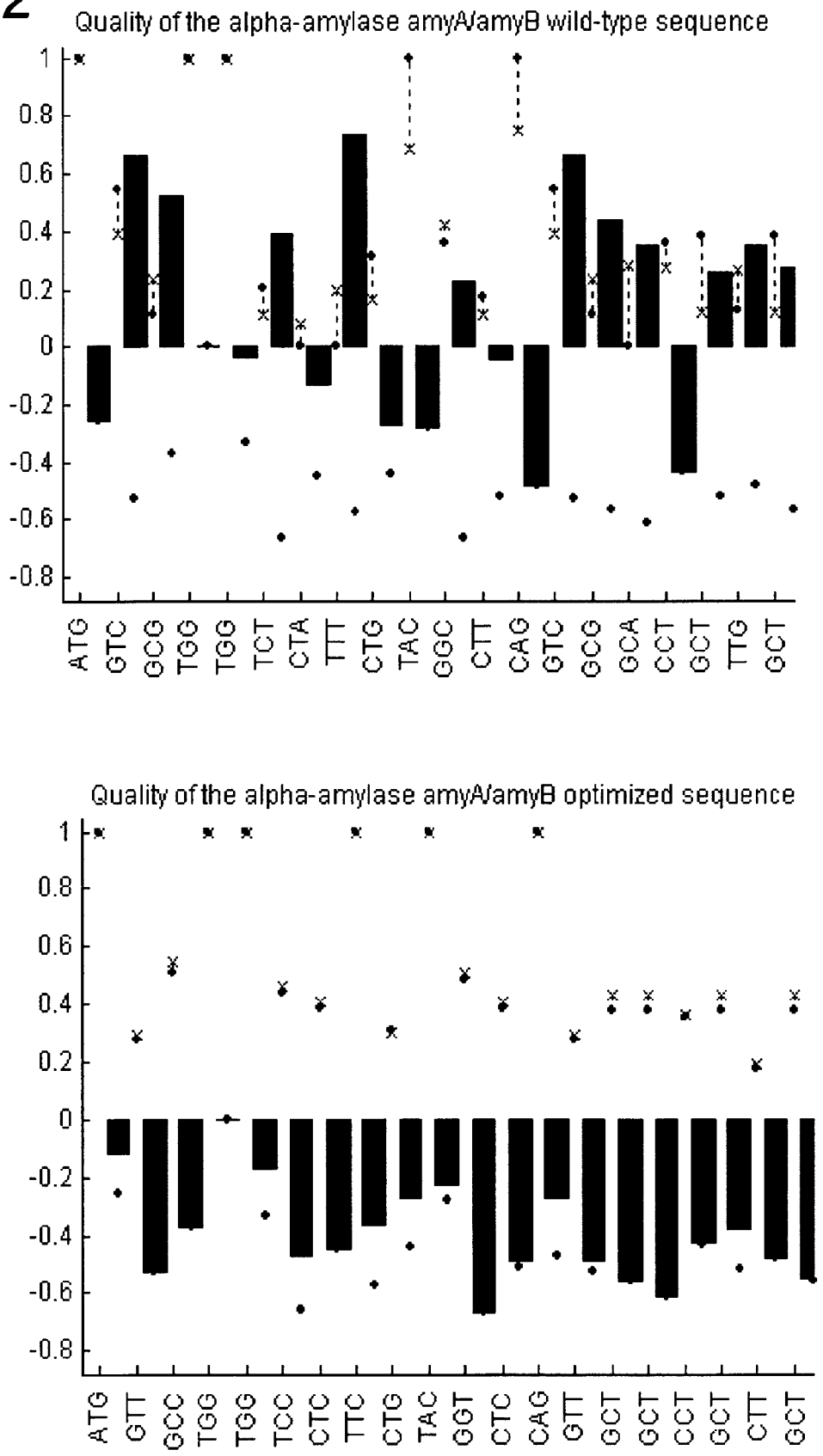

Quality of the alpha-amylase amyA/amyB wild-type sequence
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
ATG GTC GCG TGG TGG TCT CTA TTT CTG TAC GGC CTT CAG GTC GCG GCA CCT GCT TTG GCT
Quality of the alpha-amylase amyA/amyB optimized sequence
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
ATG GTT GCC TGG TGG TCC CTC TTC CTG TAC GGT CTC CAG GTT GCT GCT CCT GCT CTT GCT

Fig 13

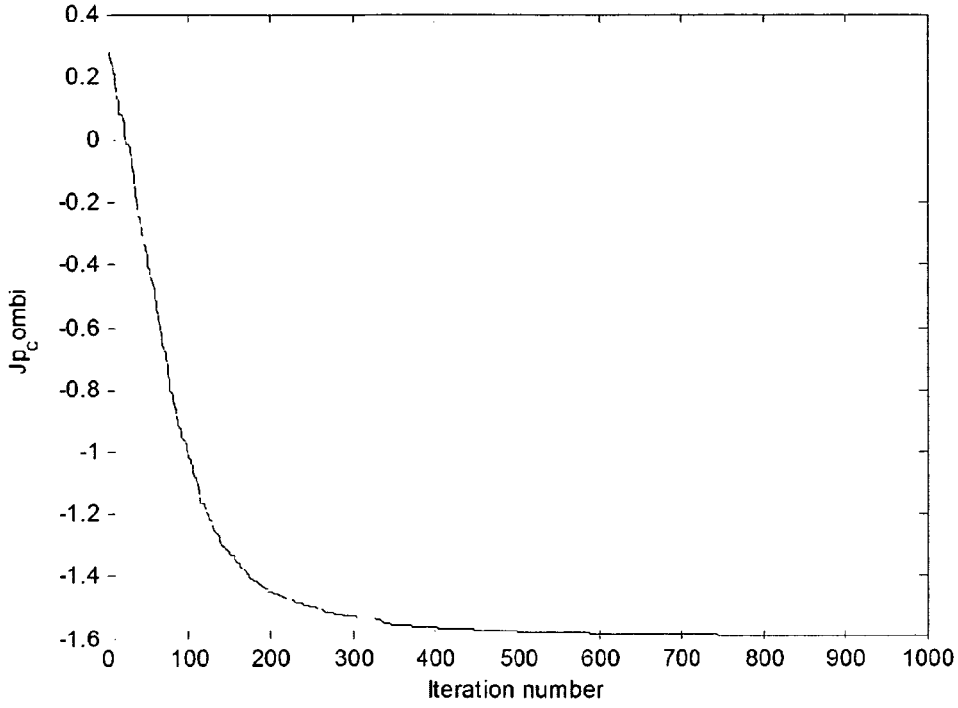

0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4
-1.6
Jp_combi
0
100
200
300
400
500
600
700
800
900
1000
Iteration number

Fig 14

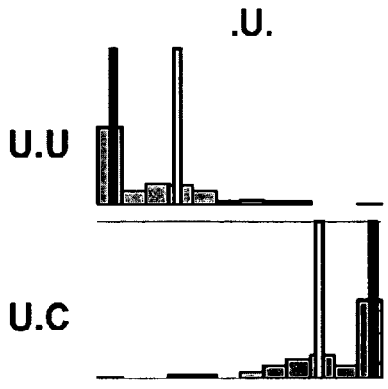

.U.
U.U
U.C

Fig 15(1)

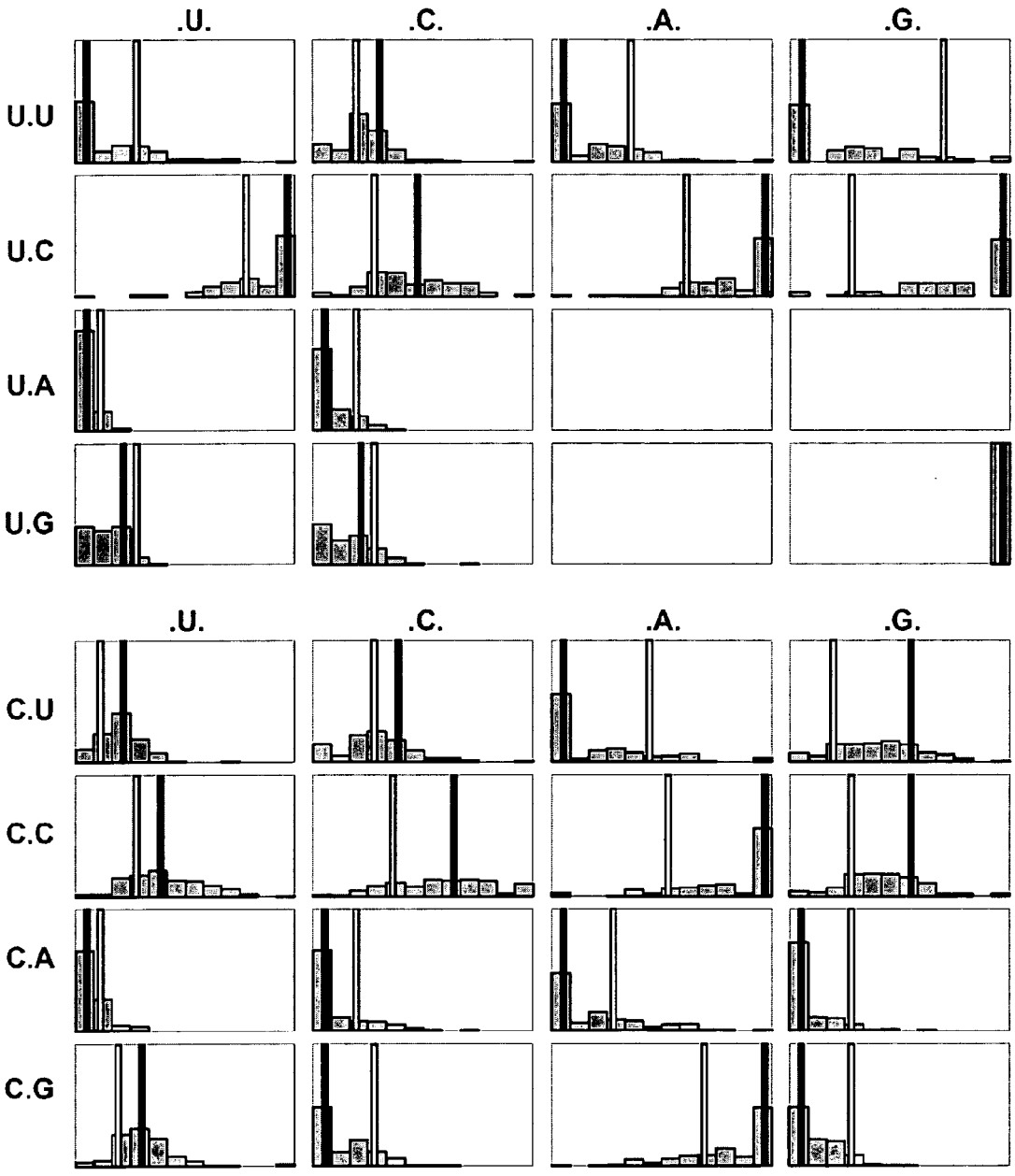


Fig 15(2)

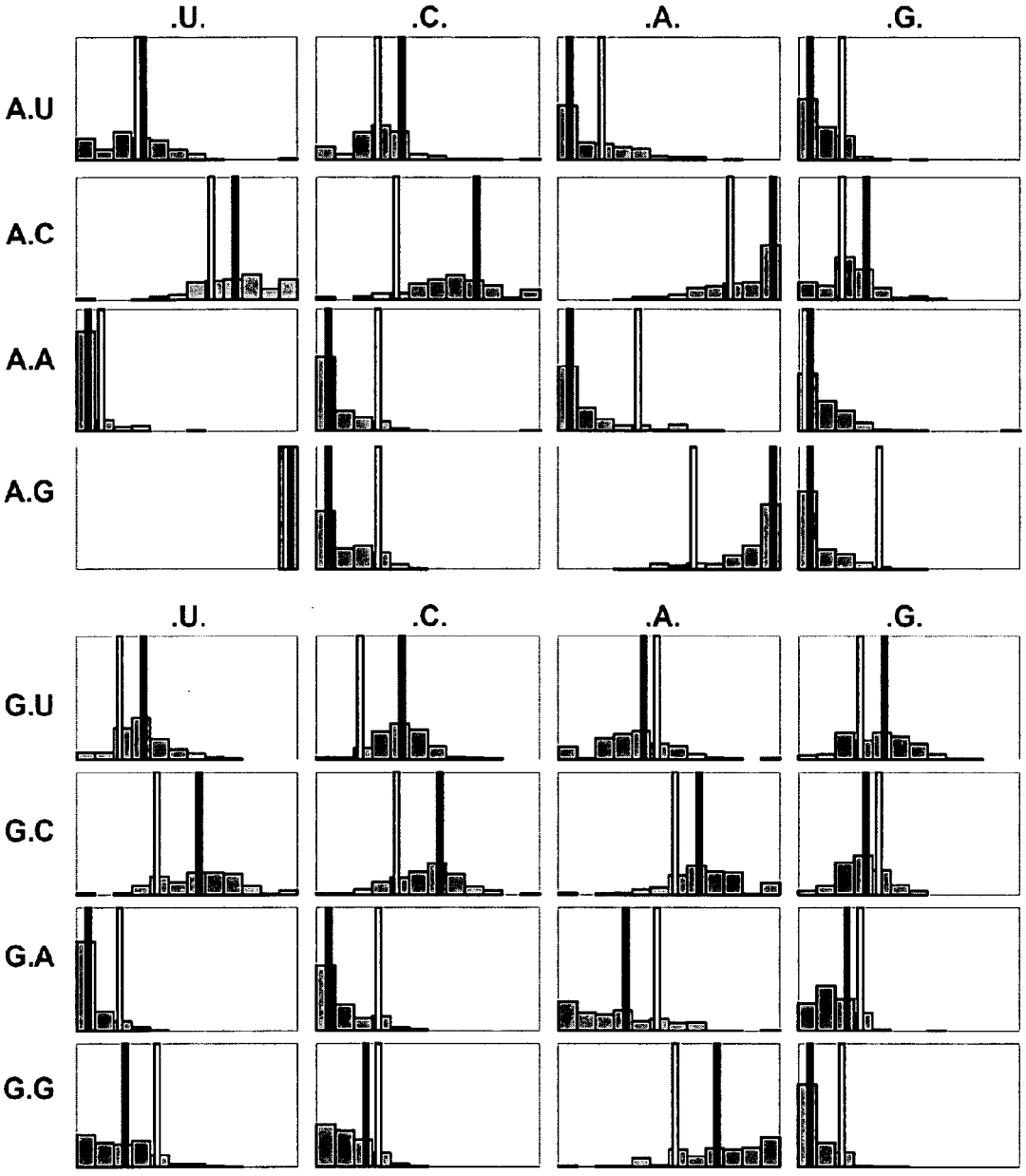


Fig 16(1)

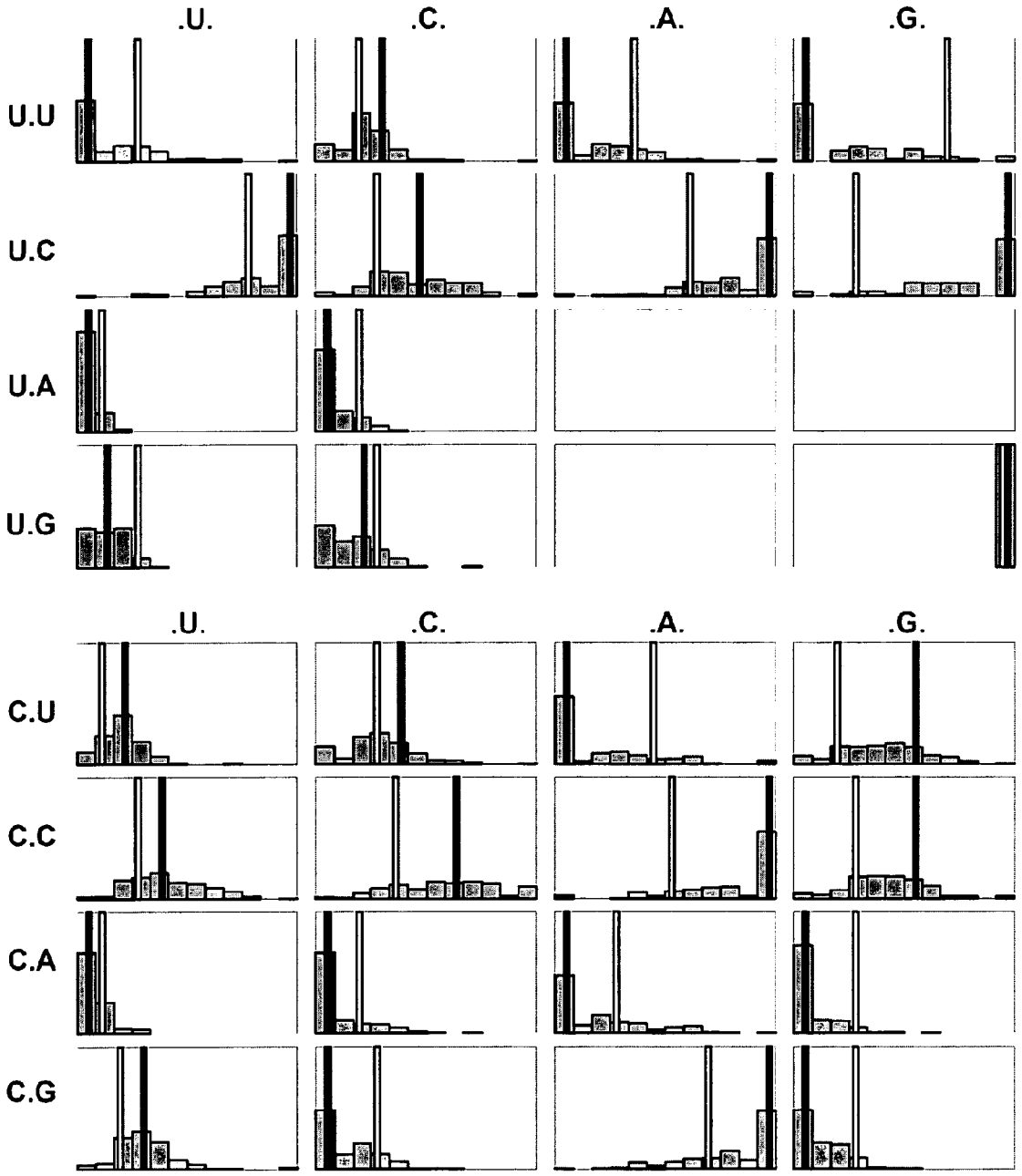


Fig 16(2)

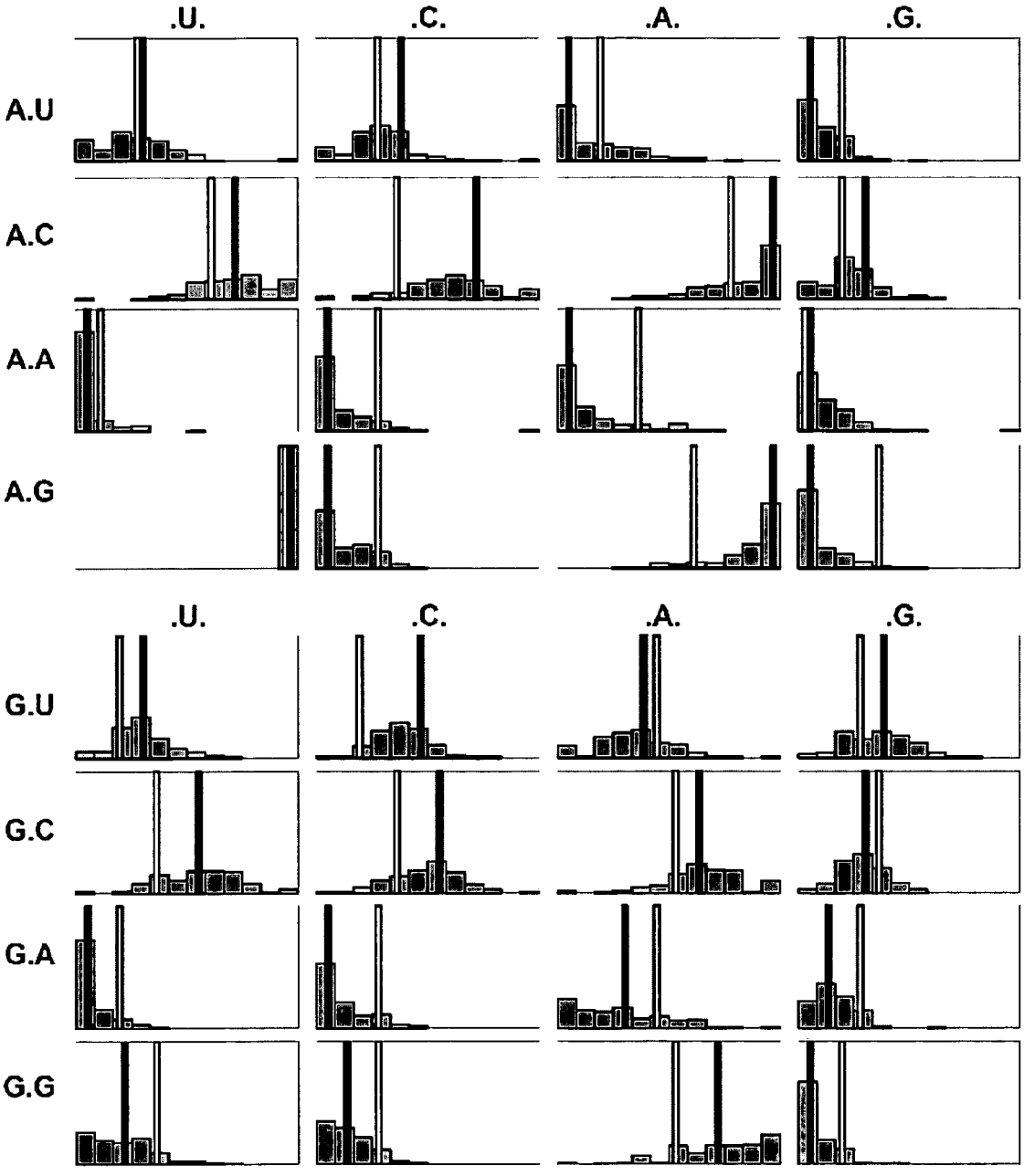


Fig 17

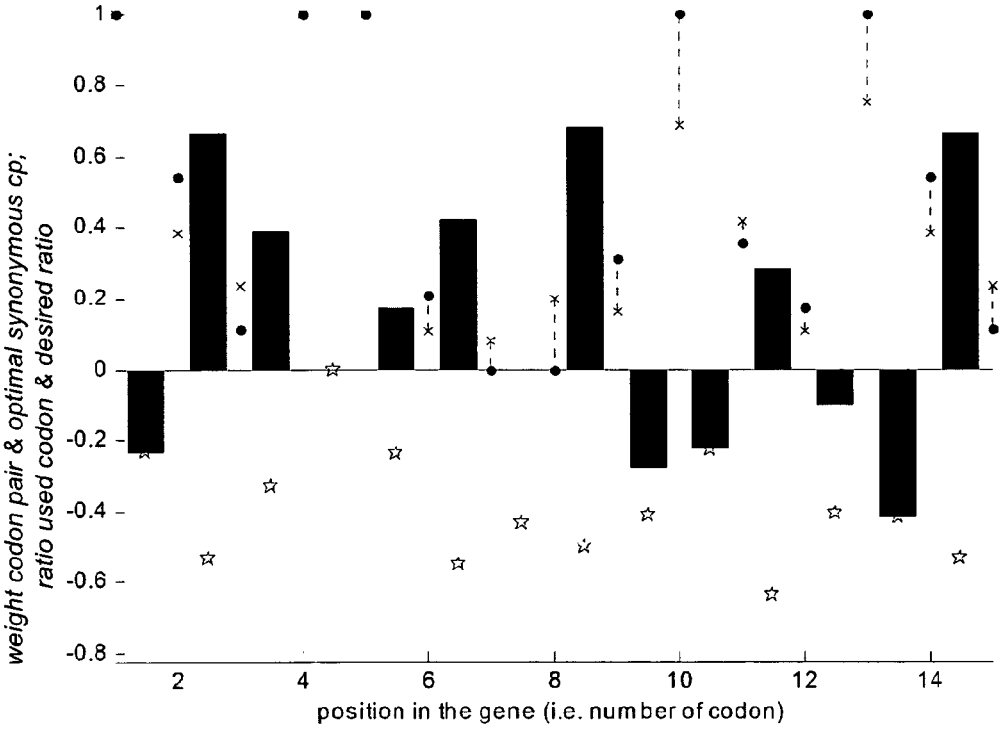

weight codon pair & optimal synonymous cp;
ratio used codon & desired ratio
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
2
4
6
8
10
12
14
position in the gene (i.e. number of codon)

Fig 18

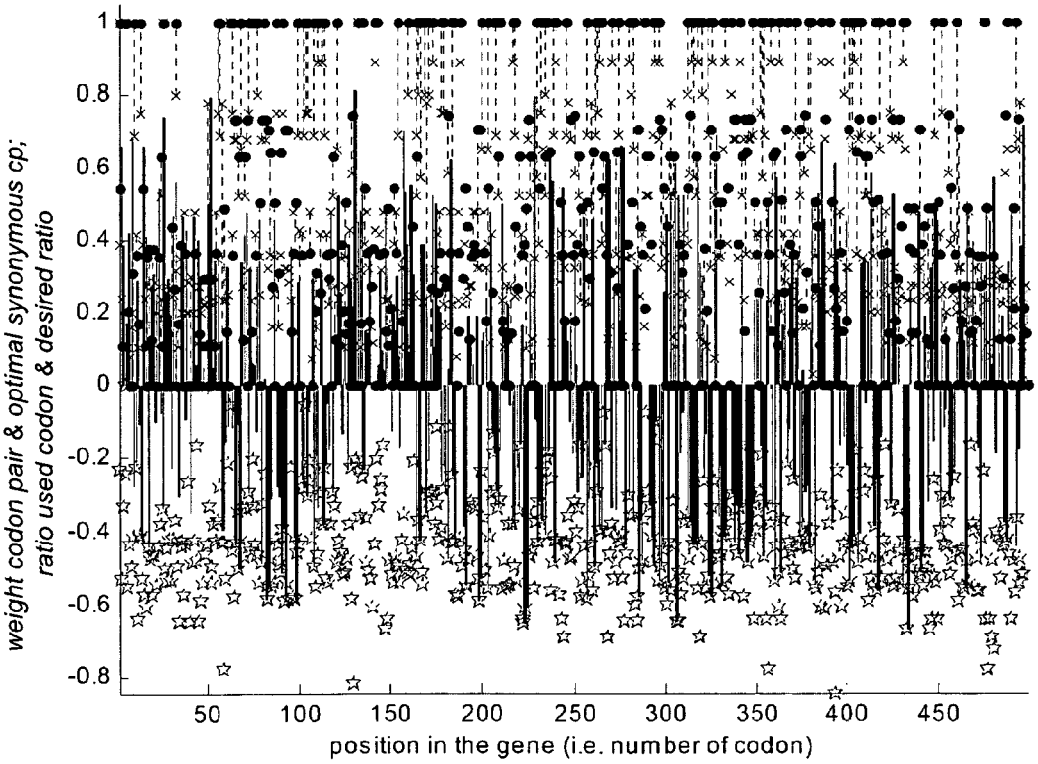

weight codon pair & optimal synonymous cp;
ratio used codon & desired ratio
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
50
100
150
200
250
300
350
400
450
position in the gene (i.e. number of codon)

Fig 19

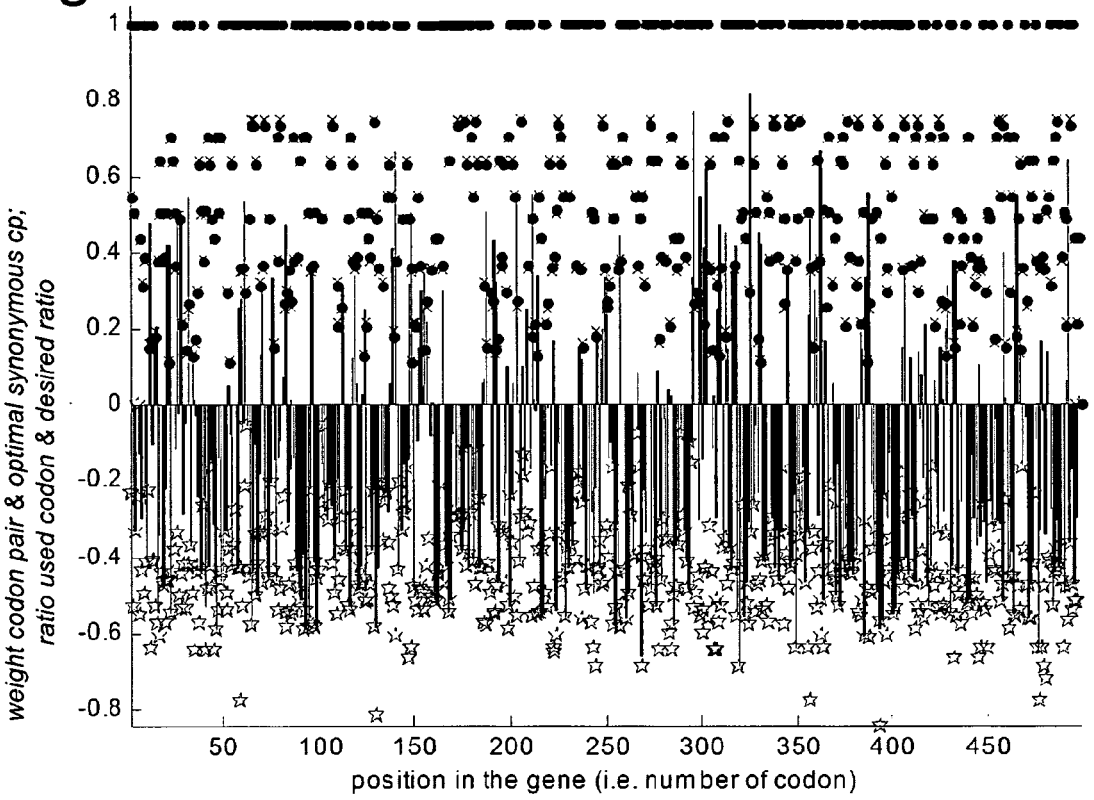

weight codon pair & optimal synonymous cp;
ratio used codon & desired ratio
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
50
100
150
200
250
300
350
400
450
position in the gene (i.e. number of codon)

Fig 20

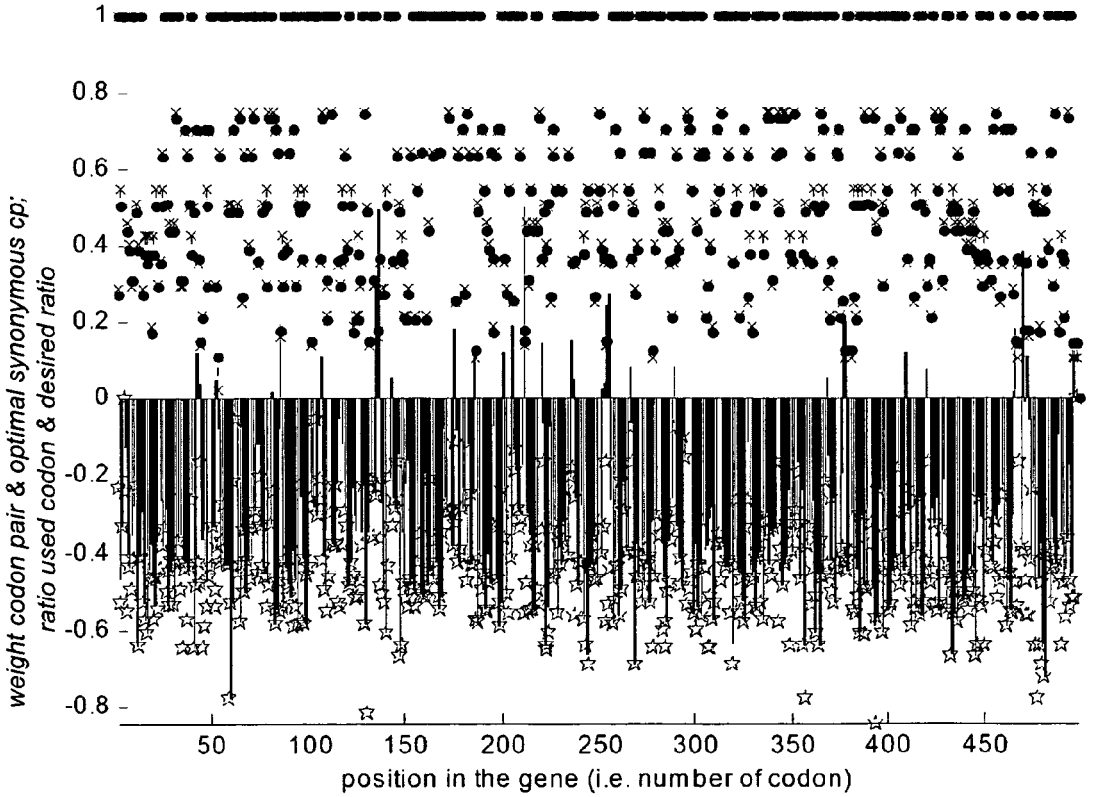

weight codon pair & optimal synonymous cp;
ratio used codon & desired ratio
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
50
100
150
200
250
300
350
400
450
position in the gene (i.e. number of codon)

Fig 21

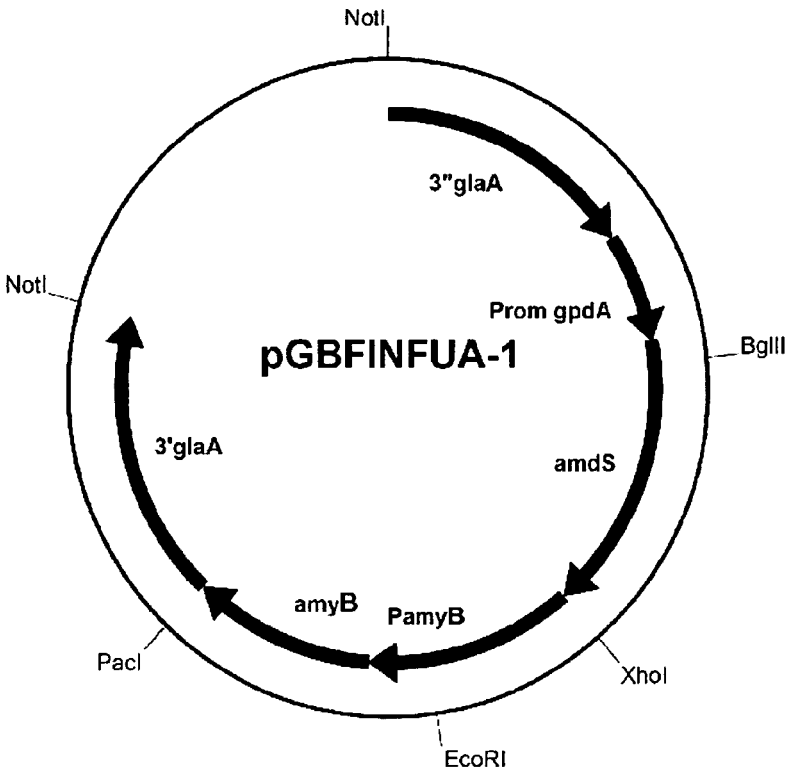

NotI
3"glaA
NotI
Prom gpdA
pGBFINFUA-1
BglII
3'glaA
amdS
amyB
PamyB
PacI
XhoI
EcoRI

Fig 22

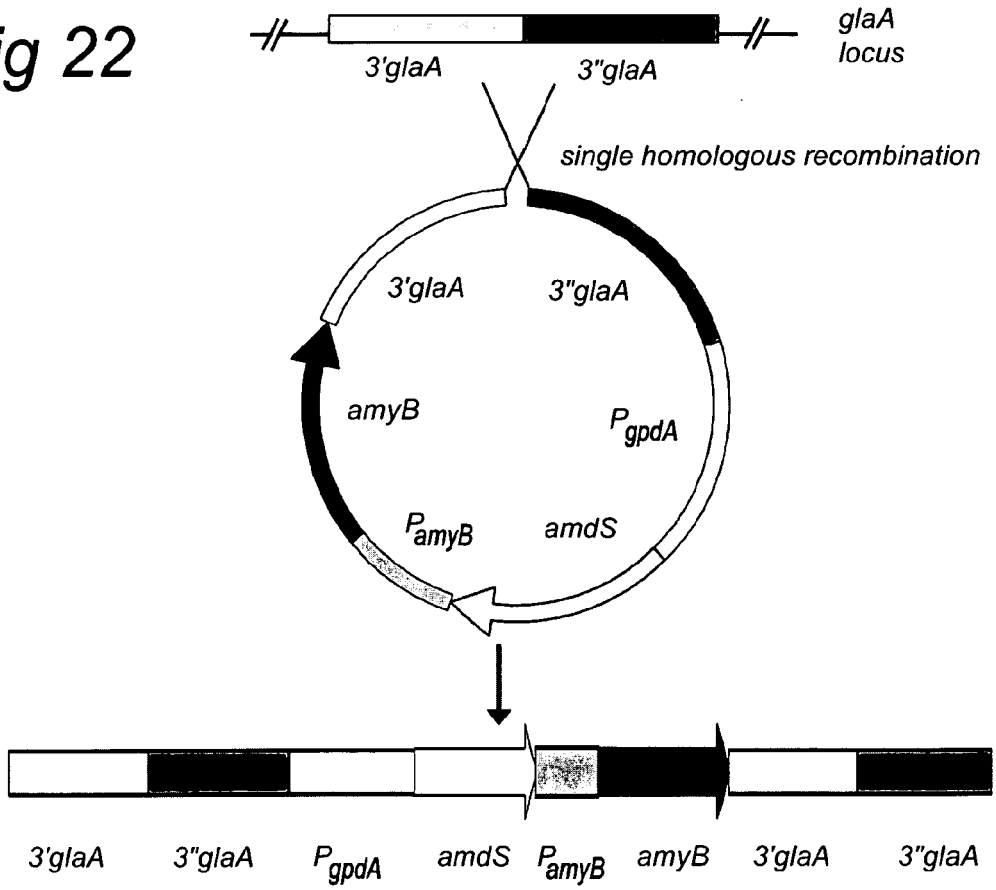

glaA
locus
3'glaA
3"glaA
single homologous recombination
3'glaA
3"glaA
amyB
PgpdA
PamyB
amdS
3'glaA
3"glaA
PgpdA
amdS
PamyB
amyB
3'glaA
3"glaA

Fig 23

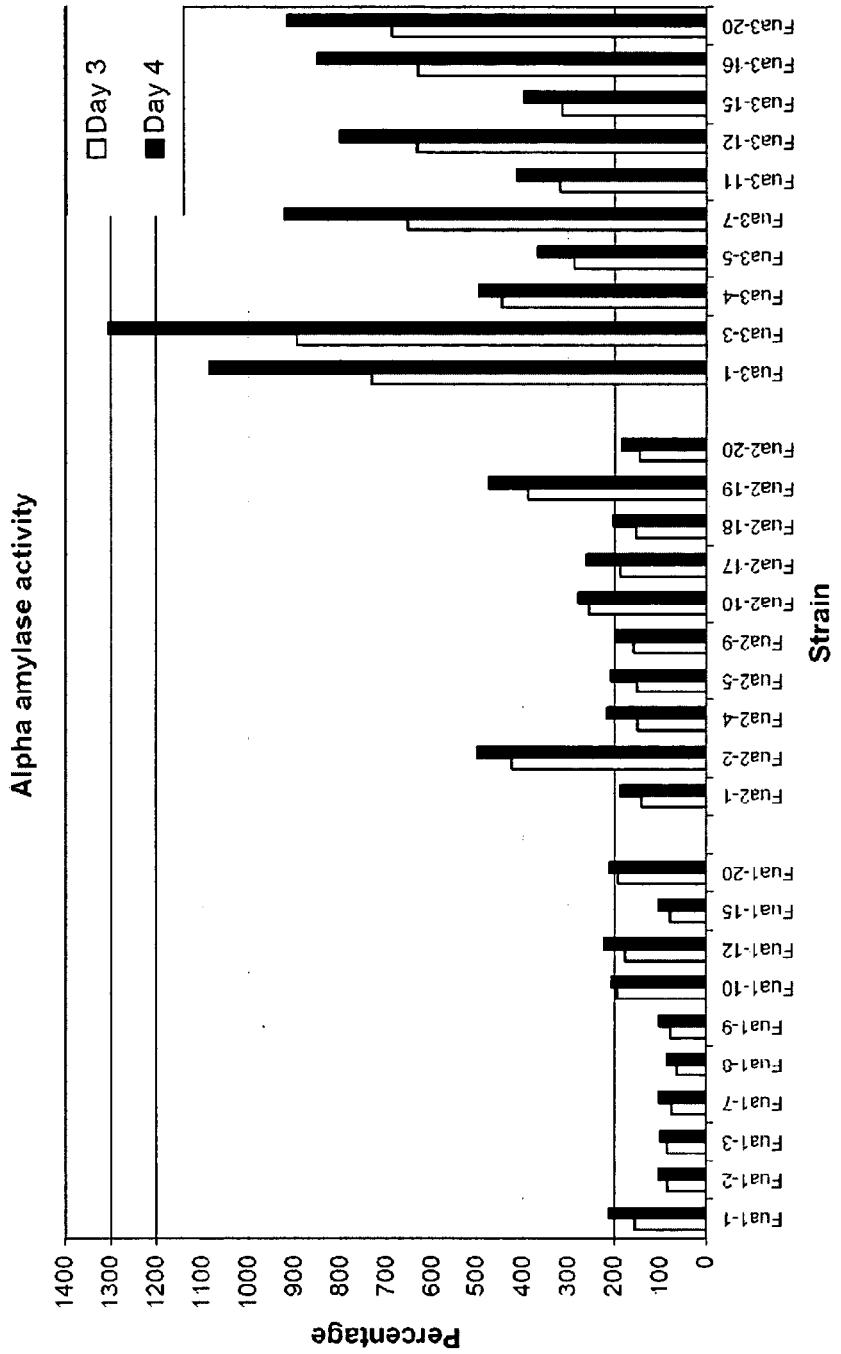

Alpha amylase activity
Day 3
Day 4
Percentage
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
Strain
Fua3-20
Fua3-16
Fua3-15
Fua3-12
Fua3-11
Fua3-7
Fua3-5
Fua3-4
Fua3-3
Fua3-1
Fua2-20
Fua2-19
Fua2-18
Fua2-17
Fua2-10
Fua2-9
Fua2-5
Fua2-4
Fua2-2
Fua2-1
Fua1-20
Fua1-15
Fua1-12
Fua1-10
Fua1-9
Fua1-8
Fua1-7
Fua1-3
Fua1-2
Fua1-1

Fig 24(1)

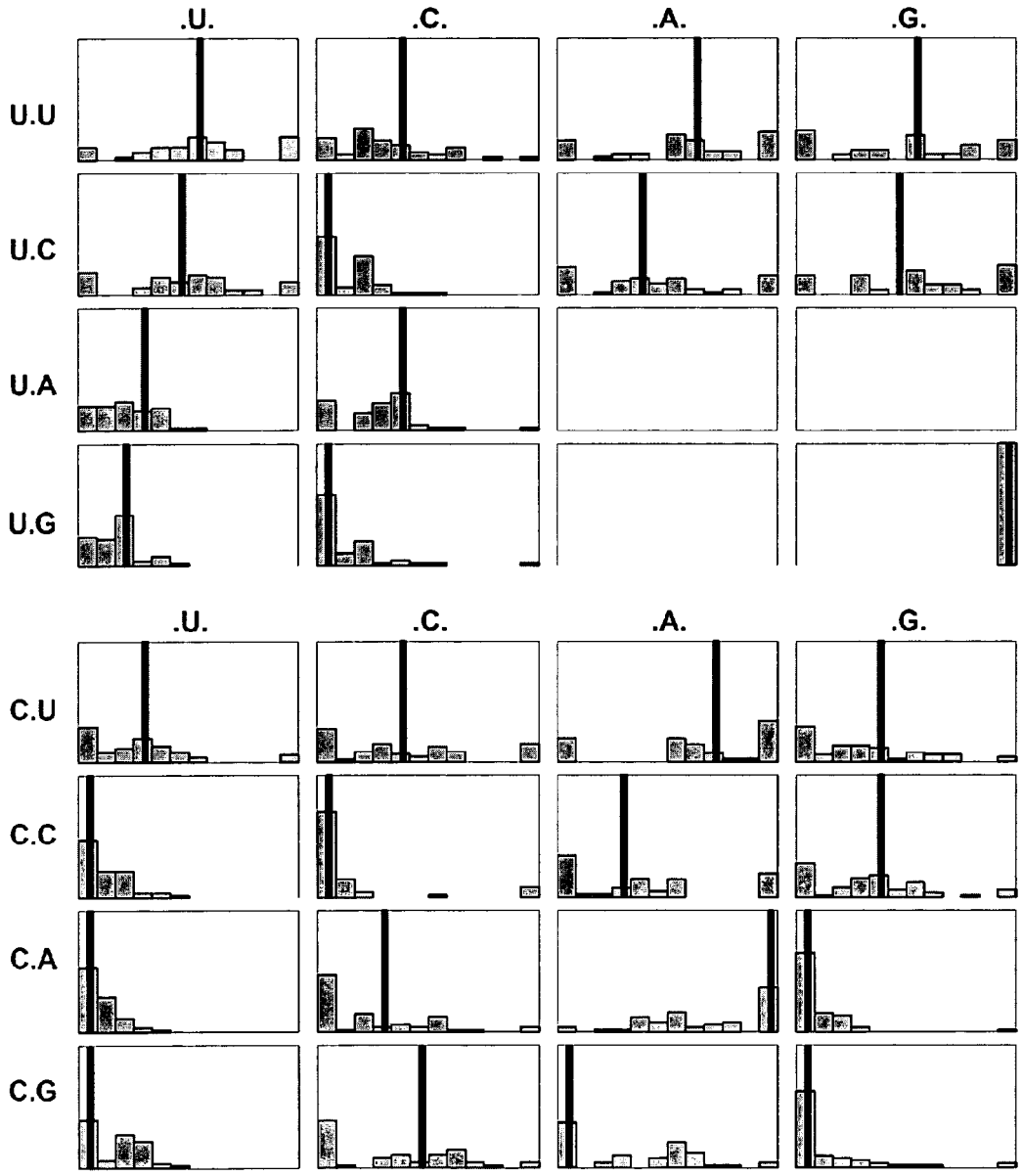


Fig 24(2)

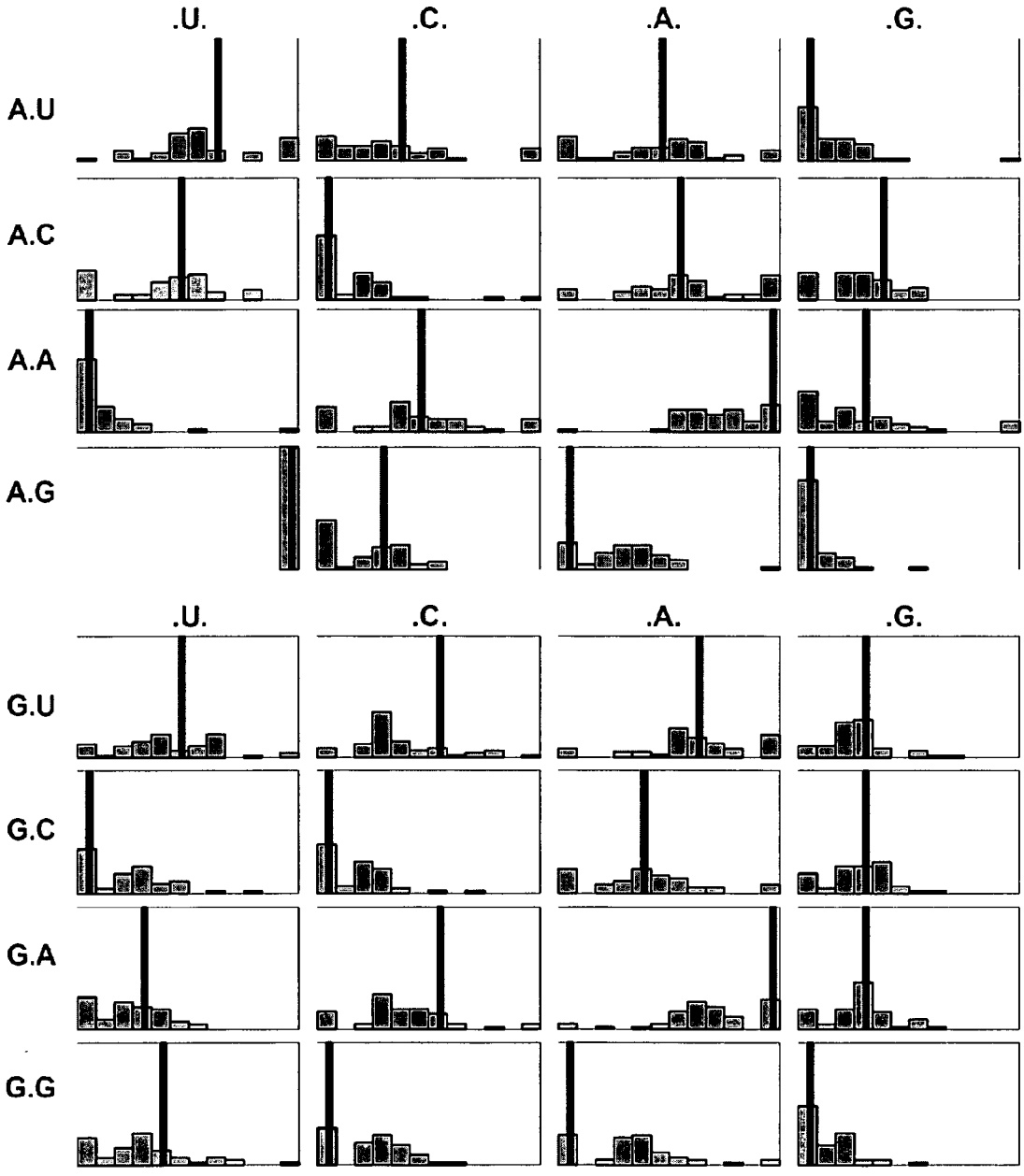


Fig 25a

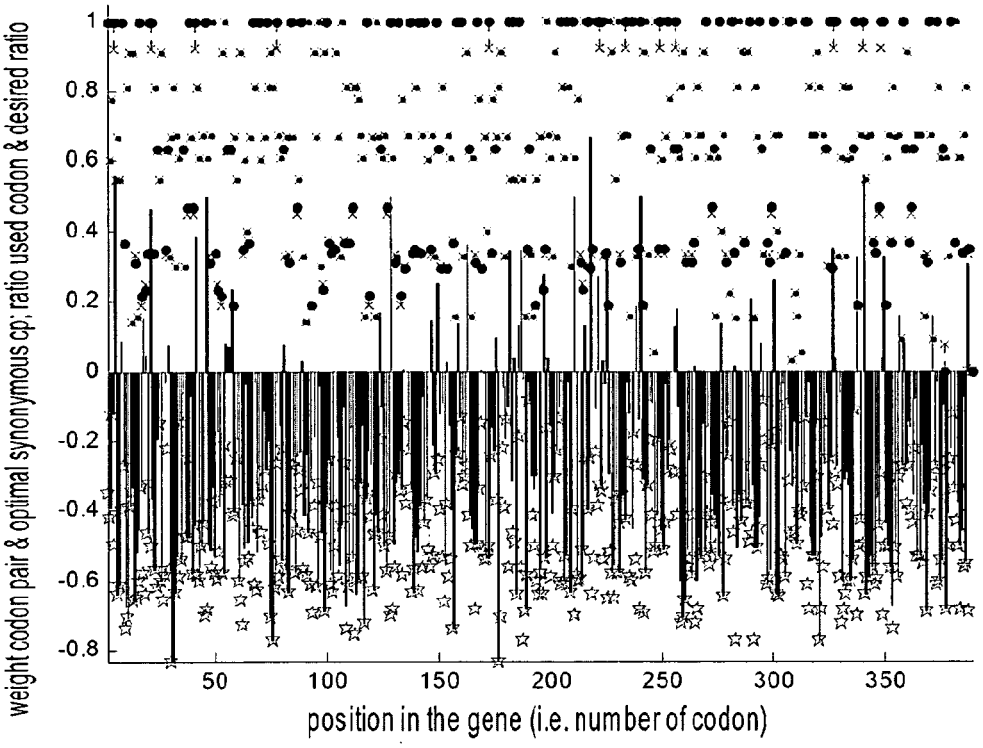


Fig 25b

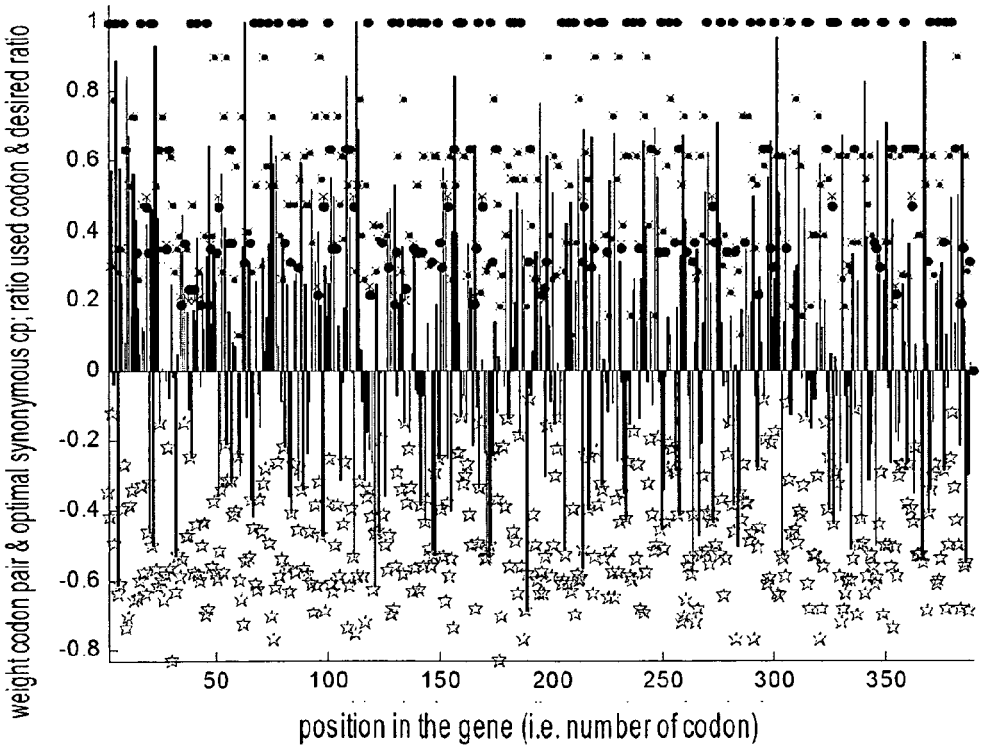


Fig 25c

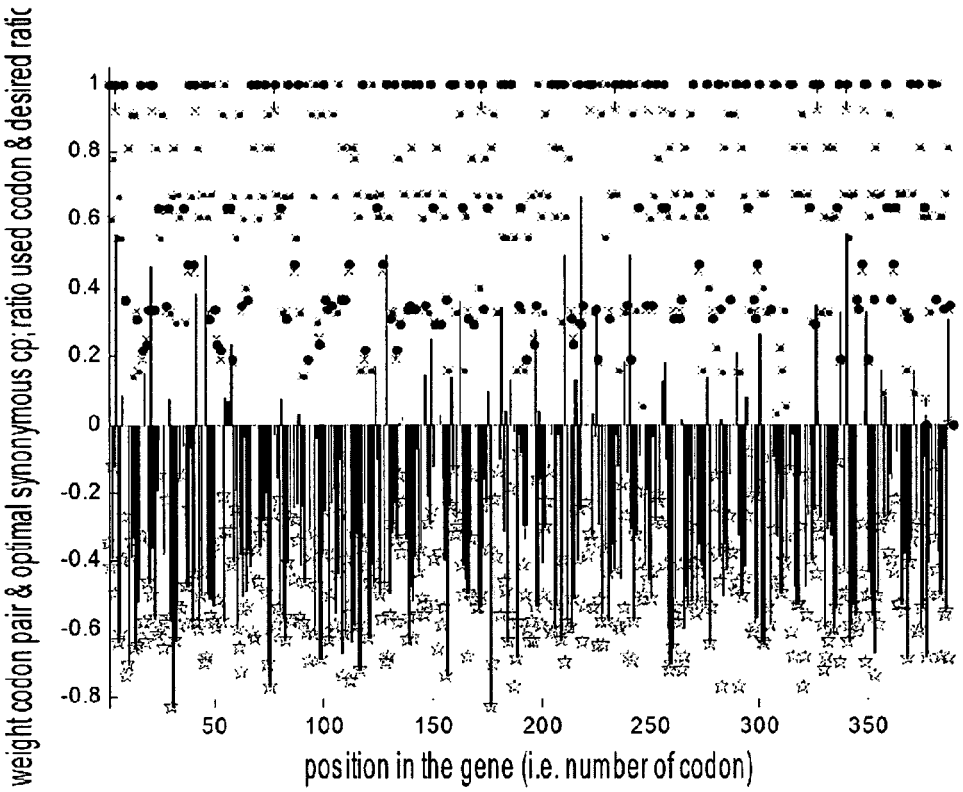

weight codon pair & optimal synonymous cp; ratio used codon & desired ratio
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
50
100
150
200
250
300
350
position in the gene (i.e. number of codon)

Fig 26

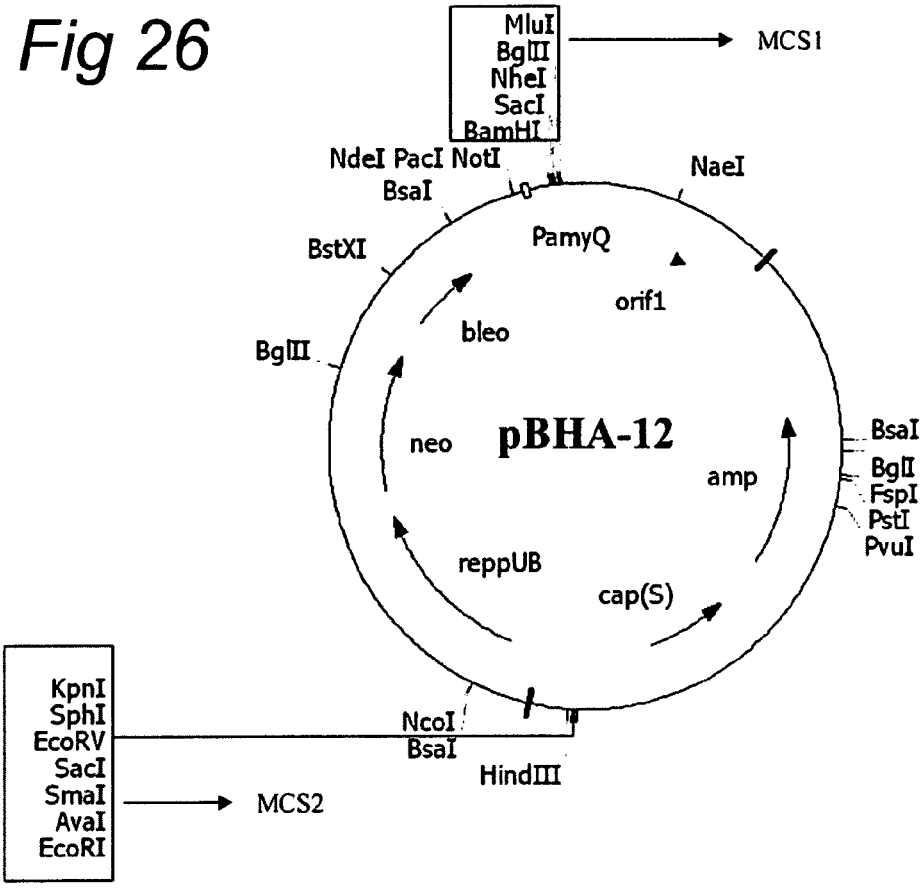
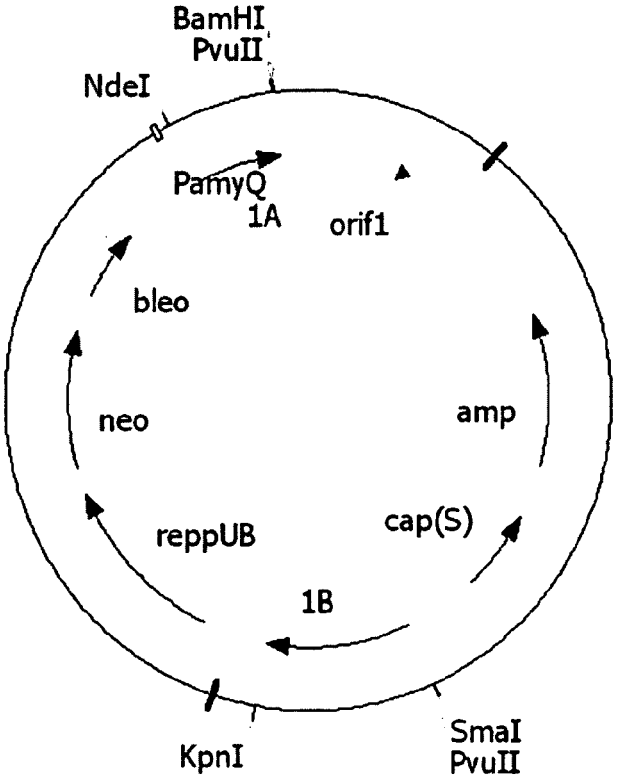

MluI
BglII
NheI
SacI
BamHI
MCS1
NdeI PacI NotI
BsaI
NaeI
BstXI
PamyQ
orif1
bleo
BglII
neo
pBHA-12
amp
BsaI
BglI
FspI
PstI
PvuI
reppUB
cap(S)
KpnI
SphI
EcoRV
SacI
SmaI
AvaI
EcoRI
NcoI
BsaI
HindIII
MCS2

Fig 27


BamHI
PvuII
NdeI
PamyQ
1A
orif1
bleo
neo
amp
reppUB
cap(S)
1B
KpnI
SmaI
PvuII

BUDAPEST TREATY ON THE INTERNATIONAL
RECOGNITION OF THE DEPOSIT OF MICROORGANISMS
FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

TO

Gist-brocades
Wateringseweg 1
Postbus 1
2600 MA DELFT

VIABILITY STATEMENT
issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified on the following page

NAME AND ADDRESS OF THE PARTY TO WHOM THE VIABILITY STATEMENT IS ISSUED

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: Gist-brocades N.V. Address: Wateringseweg 1 Postbus 1 2600 MA DELFT	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: CBS 513.88 Date of the deposit or of the transfer[1]: 10 August 1988

III. VIABILITY STATEMENT

The viability of the microorganism identified under II above was tested on 31 August 1988[2]. On that date, the said microorganism was

[3] [X] viable

[3] [ ] no longer viable

1 Indicate the date of the original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).

2 In the cases referred to in Rule 10.2(a)(ii) and (iii), refer to the most recent viability test.

3 Mark with a cross the applicable box.

IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: Centraalbureau voor Schimmelcultures Address: Oosterstraat 1 Postbus 1 3740 AG BAARN	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): Date: 7 december 1988 drs. G.B.A. van Reenen

[4] Fill in if the information has been requested and if the results of the test were negative.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/055943

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/67

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IRWIN B. ET AL.,: "codon pair utilization biases influence translational elongation step times" J. BIOL. CHEM., vol. 270, no. 39, 29 September 1995 (1995-09-29), pages 22801-22806, XP002406003 cited in the application the whole document	1-14
X	BOYCHEVA S. ET AL.,: "codon pairs in the genome of escherichia coli" BIOINFORMATICS, vol. 19, no. 8, 2003, pages 987-998, XP002406004 cited in the application the whole document	1-14

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 2007	30/10/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mueller, Frank

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/055943

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/02694 A (UNIV QUEENSLAND [AU]; FRAZER IAN [AU]; ZHOU JIAN [AU]) 21 January 1999 (1999-01-21) see whole doc. esp. claims	1-14
X	WO 03/085114 A (WALTER REED ARMY INST OF RES [US]; ANGOV EVELINA [US]; LYON JEFFREY A) 16 October 2003 (2003-10-16) cited in the application see whole doc. esp. claims	1-15
X	US 5 082 767 A (HATFIELD G WESLEY [US] ET AL) 21 January 1992 (1992-01-21) cited in the application see whole doc. esp. claims	1-14
A	MAKRIDES: "Strategies for Achieving High-Level Expression of Genes in Escherichia coli" MICROBIOLOGICAL REVIEWS, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, DC, US, vol. 60, no. 3, September 1996 (1996-09), pages 512-538, XP002095235 ISSN: 0146-0749 see esp. p.524	1-14
P,X	WO 2006/077258 A (DSM IP ASSETS BV [NL]; ROUBOS JOHANNES ANDRIES [NL]; DONKERS SERGE PET) 27 July 2006 (2006-07-27) see whole doc. esp. claims and p.11 ff.	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/055943

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 16,17,18-23
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(v) PCT - Presentation of information (claim 17)

Rule 39.1(vi) PCT - Program for computers (claim 16)

2. [X] Claims Nos.: 18-23
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 16,17,18-23

Rule 39.1(v) PCT - Presentation of information (claim 17)

Rule 39.1(vi) PCT - Program for computers (claim 16)

Continuation of Box II.2

Claims Nos.: 18-23

Present claim 18-23 relate to a/an compound/product/apparatus/method which has a given desired property or effect, namely nucleic acid molecules fullfiling the fitness values as defined in the wording of claim 18. However, the description does not provide support and disclosure in the sense of Article 6 and 5 PCT for any such compound/product/apparatus/method having the said property or effect and there is no common general knowledge of this kind available to the person skilled in the art. This non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of the claim (PCT Guidelines 9.19 and 9.20).

Therefore no search was carried out for claims 18-23.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/055943

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9902694 A	21-01-1999	CA 2296067 A1	21-01-1999
		EP 1002091 A1	24-05-2000
		JP 2001509388 T	24-07-2001
WO 03085114 A	16-10-2003	AU 2003228440 A1	20-10-2003
		CA 2480504 A1	16-10-2003
		EP 1490494 A1	29-12-2004
US 5082767 A	21-01-1992	NONE	
WO 2006077258 A	27-07-2006	AU 2006207463 A1	27-07-2006