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(54) Title: A METHOD, APPARATUS, COMPUTER-READABLE MEDIUM AND USE FOR PHARMACOKINETIC MODELING

(57) Abstract: An advantageous method, apparatus, computer-readable medium, and use for improving the estimation of relevant initial parameters for parameter reconstruction processes in molecular imaging are disclosed, resulting in shorter process times and more robust results with small confidence intervals.

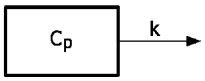

FIG. 1a

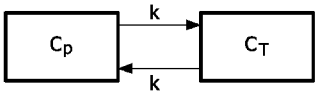

FIG. 1b

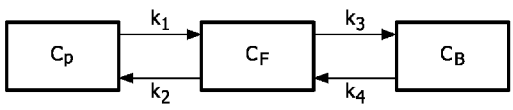

FIG. 1c

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A method, apparatus, computer-readable medium and use for pharmacokinetic modeling

FIELD OF THE INVENTION

This invention pertains in general to the field of molecular imaging. More particularly the invention relates to data-driven adaptation of initial parameters for pharmacokinetic modeling.

BACKGROUND OF THE INVENTION

Molecular imaging is extensively used in medicine as a technique to image various targets or pathways, particularly in vivo. Tracers functioning as probes facilitate the imaging and chemically interact with their surroundings and in turn alter the image according to the molecular changes occurring within the area of interest. Molecular imaging is applied to many different areas of interest, such as determination of a pre-disease state or molecular states that occur prior to the occurrence or detection of typical symptoms of a disease. Other applications comprise the imaging of gene expression in vivo and the development of novel tracers or biomarkers.

In order to implement molecular imaging, there are currently several different molecular imaging systems and devices available, such as SPECT (Single Photon Emission Computed Tomography) systems and PET (Positron Emission Tomography) systems. The latter are important techniques when imaging physiological activities, as for instance in the brain or when determining flow paths *in vivo*.

Pharmacokinetic modeling is a technique to estimate functional or biological parameters from time series of medical imaging data. PET is a common imaging modality to acquire this type of data. A radioactively labeled imaging agent (tracer) is administered and the time course of its distribution is measured. A compartment model describes the biological/chemical/physical behavior of the tracer in the tissue of interest. The parameters of this model are to be estimated and have a direct functional interpretation, such as hypoxia for the PET tracer FMISO that can be of diagnostic value. An integral part of pharmacokinetic modeling is the optimization or reconstruction process, where the model parameters are fitted in such a way to give the best description of the observed data. While the robustness and accuracy of the parameter estimates extracted from the fit are governed mostly by the model

and reconstruction algorithm used, the choice of initial parameters also plays an important role. Initial parameters have a direct impact on the speed of the reconstruction process, as less iteration steps are necessary if "good" initial parameters have been selected which are relatively "close" to the final "true" parameters. Additionally, if the models used are more complex, the cost-function of the reconstruction may exhibit several local minima in the parameter space. In that case, again it is important that the initial parameters are close to the true parameters to avoid that the parameter reconstruction algorithm runs into a local minimum which may even correspond to physiologically or biologically insensible parameters.

When performing reconstruction on a per-voxel basis, i.e. when a complete reconstruction process is started for each individual voxel in the image dataset, the computation speed is of particular interest. In standard reconstruction approaches within the art, the set of initial parameters is the same for each voxel, meaning that the "distance" between initial and true parameters, and as a result both computational speed and robustness of the fits, will vary over the voxels of the analyzed dataset.

When pharmacokinetic modeling is applied to four-dimensional data from medical imaging systems, many individual data-points have to be processed. Typically, particularly for nuclear imaging procedures, this data exhibits a significant noise level. These two facts together imply that the modeling is both time-consuming and modeling results may have large confidence intervals.

Hence, an improved method to achieve shorter computation times as well as more robust and accurate results would be advantageous.

SUMMARY OF THE INVENTION

Accordingly, the present invention preferably seeks to mitigate, alleviate or eliminate one or more of the above-identified deficiencies in the art and disadvantages singly or in any combination and solves at least the above mentioned problems by providing a method, apparatus, computer readable medium, and use according to the appended patent claims.

According to one aspect of the invention, a method is provided for pharmacokinetic modeling of an image dataset comprising a set of volumes of interest having a plurality of volumes, each volume comprising at least one voxel having at least one related data value. The method comprises assigning an initial set of parameter values to initial parameters describing a first type of voxel within said image dataset, calculating a mean

voxel data value for each volume in an initial set of volumes of interest comprised in said set of volumes of interest, reconstructing parameters for each volume in said initial set of volumes of interest, based on said mean voxel data value and said initial set of parameter values, resulting in a subsequent set of parameters, and assigning said subsequent set of parameters as initial parameters to a subsequent set of volumes of interest comprised in said image dataset.

According to another aspect of the invention, an apparatus is provided for pharmacokinetic modeling of an image dataset comprising a set of volumes of interest having a plurality of volumes, each volume comprising at least one voxel having at least one related data value. The apparatus comprises a first assigning unit for assigning an initial set of parameter values to initial parameters describing a first type of voxel within said image dataset, a calculation unit for calculating a mean voxel data value for each volume in an initial set of volumes of interest comprised in said set of volumes of interest, a reconstruction unit for reconstructing parameters for each volume in said initial set of volumes of interest, based on said mean voxel data value and said initial set of parameter values, resulting in a subsequent set of parameters, and a second assigning unit for assigning said subsequent set of parameters as initial parameters to a subsequent set of volumes of interest comprised in said image dataset.

According to another aspect of the invention, a computer-readable medium is provided having embodied thereon a computer program for processing by a computer, for pharmacokinetic modeling of an image dataset comprising a set of volumes of interest having a plurality of volumes, each volume comprising at least one voxel having at least one related data value. The computer program comprises a first assigning code segment for assigning an initial set of parameter values to initial parameters describing a first type of voxel within said image dataset, a calculation code segment for calculating a mean voxel data value for each volume in an initial set of volumes of interest comprised in said set of volumes of interest, a reconstruction code segment for reconstructing parameters for each volume in said initial set of volumes of interest, based on said mean voxel data value and said initial set of parameter values, resulting in a subsequent set of parameters, and a second assigning code segment for assigning said subsequent set of parameters as initial parameters to a subsequent set of volumes of interest comprised in said image dataset.

According to yet another aspect of the invention, a use of the method, apparatus or computer-readable medium according to any of the appended claims 1-18 for diagnosing a disorder or disease in a human is provided.

The present invention is applicable to all cases where data, which represents regional information, is subjected to a reconstruction procedure to extract parametric maps. Another feature of the present invention is the data-driven adaptation of the initial values of successive reconstruction steps.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other aspects, features and advantages of which the invention is capable of will be apparent and elucidated from the following description of embodiments of the present invention, reference being made to the accompanying drawings, in which

Fig. 1 is an illustration showing a one-, two- and three-compartment model;

Fig. 2 is an illustration showing a volume of interest comprising 8 voxels a-h;

Fig. 3 is an illustration showing a method for initial parameter adaptation for reconstruction according to an embodiment;

Fig. 4 is an illustration showing a volume of interest reduction scheme according to an embodiment;

Fig. 5 is an illustration showing a volume of interest reduction scheme according to an embodiment;

Fig. 6 is an illustration showing an apparatus according to an embodiment; and

Fig. 7 is an illustration showing a volume of interest reduction scheme according to an embodiment.

DESCRIPTION OF EMBODIMENTS

Fig. 1 is showing different examples of known pharmacokinetic compartment models. Fig. 1a illustrates a one-compartment model, Fig. 1b illustrates a two-compartment model and Fig. 1c illustrates a three-compartment model. However, higher order compartment models may also be considered. The one-compartment model comprises one compartment, in which the tracer concentration is denoted C_p. k defines the outflow of the tracer from the compartment. In Fig. 1b, C_P denotes the tracer concentration in a blood compartment, whereas C_T specifies the concentration in a tissue compartment. In a pharmacokinetic two-compartment model, the total activity measured, involving a weighted sum of the individual concentrations associated to the compartments for a region of interest or an individual voxel at position x, is described for each point in time t by an activity function $A(x,t) = [1-\beta(x)]\cdot C_P + \beta(x)\cdot C_T$. The activity function $A(x,t)$ hence describes the bio distribution of the tracer. Here, parameter $\beta(x)$ denotes the partition of blood and tissue

compartments at a position x in the region of interest. The region of interest may for instance be a human organ, such as the heart. The concentration in the tissue compartment, C_T, is composed of an inflow from a reservoir with corresponding tracer concentration C_P (specified by the input function) by a rate k and the outflow of tracer by the same rate k. In a three-compartment model the tracer flow between the three compartments is indicated by k_1, k_2, k_3 and k_4.

Nomenclature concerning the number of compartments is sometimes confusing in literature. In some publications the number of compartments are defined as the number of tissue compartments, so that Fig 1a shows a "zero"-compartment model, 1b a one-compartment model and 1c would correspond to a two-compartment model. More exactly one could write n-tissue-compartment model. Hereinafter, the following specification utilizes the latter way of nomenclature describing the number of compartments.

Fig. 2 illustrates an image dataset comprising a volume of interest (hereinafter referred to as VOI, and volumes of interest referred to as VOIs) comprising 8 voxels 21a-21h. In standard reconstruction approaches according within the art the set of initial parameters is the same for each voxel a-h independently of the data in the voxels. If the actual true parameters are far from the initial parameters estimate in a voxel the resolution of said voxel in the resulting visualized image will most likely have a large confidence interval meaning that the resolution of the visualized image may be poor or be very noisy/speckled.

The following description focuses on embodiments of the present invention applicable to molecular imaging and in particular to the adaptation of initial parameters for kinetic modeling. However, it will be appreciated that the invention is not limited to these specific applications or implementations, but may be applied to many other applications within the field of molecular imaging.

Use of the present invention reduces the computation time needed for the reconstruction process. The term reconstruction in this context means subsequent assessment of the parameters, i.e. reconstruction of the kinetic parameters. Moreover the present invention increases the robustness of the parameter estimates, as local minima in the parameter space of the cost-function, which do not represent the true solution, may be avoided. Furthermore the present invention allows the user to interactively control the trade-off between computation time and spatial resolution, if the method based on the iterative reduction of VOIs is applied.

The present invention provides an advantageous way of improving the estimation of relevant initial parameters of reconstruction processes in molecular imaging,

which results in shorter process times and more robust results with small confidence intervals.

Moreover, the present invention provides a convenient way of establishing quality assurance procedures, which take into account the individual investigated volume of interest (VOI) of the image dataset leading to variability of initial parameters between investigated VOIs of the image dataset.

Furthermore, the present invention provides an improved approach of interactively controlling the spatial resolution of the parametric maps created by the reconstruction process before reaching the maximum resolution.

The present invention introduces data-driven adaptation of initial parameters for kinetic modeling, which aims at achieving a distribution of initial parameters adapted to the analyzed dataset by iterative pre-processing steps.

In an embodiment, according to Fig. 3, a method 30 is provided for pharmacokinetic modeling of an image dataset comprising an initial set of volumes of interest $\{V\}^j = V_0^j, V_1^j, ..., V_{n-1}^j$, wherein j illustrates the iteration step number, having a plurality (n) of volumes V_i^j, comprising at least one voxel having at least one related data value. By definition $\{V\}^0$ contains the entire image dataset. The method comprises assigning 31 an initial set of parameters comprising parameter values to initial parameters $\{P\}^j = P_0^j, P_1^j, ..., P_{n-1}^j, j = 0$ describing a first type of voxel within the image dataset. The first type of voxel may be chosen to represent healthy tissue or may by some measure be a mean value of the typical parameter range for the image dataset. Thus, if a parameter in a VOI V_i^0 may take on values between 0 and 1, 0.5 could be used as the initial parameter P_i^0 in the first step. Different parameters for the different volumes of interests within the initial sets of parameters may be used. An example of the initial set of parameters may be $\{P\}^0 = [P_0^0, P_1^0, ..., P_{n-1}^0] = [0.5, 0.3, ..., 0.6]$. Moreover the method comprises calculating 32 a mean voxel data value for each VOI in the initial set of VOIs. Furthermore the method comprises reconstructing within 33 parameters for each volume in the initial set of VOIs, based on the mean voxel data value for each VOI and the first set of initial parameters resulting in a subsequent set of parameters.

There are several known ways of performing parameter reconstruction in order to reconstruct parameter estimates. The reconstructing in this embodiment may e.g. be a non-linear regression using the Levenberg-Marquardt-algorithm. A simplex method or any other

reconstruction procedure could also be used. Here again, reconstruction is used as a synonym for parameter estimation. Another reconstruction that could be used in the method is maximizing a likelihood function $P(\beta(x),k(x)\,|\,D)$, where P denotes the probability distribution for the parameters $\beta(x)$ and $k(x)$ given an observed list mode data, and where $\beta(x)$ and $k(x)$ define the initial parameter estimates is that are denoted by the subsequent set of parameters $\{P\}^j, j=1$.

Moreover the method comprises assigning within 34 the subsequent set of parameters as initial parameters $\{P\}^j, j=1$ to a subsequent set of VOIs $\{V\}^j, j=1$ in the image dataset.

The advantage of this embodiment is that the initial parameters for each new set of VOIs are not the same for all parts of the image dataset but are adapted based on pre-processed sets of VOIs. This means that the initial parameters used to reconstruct the parameters for the entire image dataset are adapted to the content of the image dataset. This drastically reduces the calculation time and flexibility of the reconstruction process.

In an embodiment the method further comprises iteratively repeating within 35 the calculating of 32, reconstructing of 33, and assigning of 34 using the subsequent set of initial parameters (calculated in the j:th iteration) as a new initial set of initial parameters $\{P\}^j, j=j+1$ to a subsequent set of VOIs $\{V\}^j, j=j+1$ in the image dataset.

In an embodiment the method further comprises creating, a parametric map including the reconstructed parameters. The parametric map is continuously updated with the latest reconstructed parameter estimates as the method is iteratively repeated.

The investigated sets of VOIs may be chosen differently in the method depending on the kind of reconstruction process.

In an embodiment, according to Figs. 4a and 4b, a Volume Of Interest (VOI) reduction scheme is provided. The VOI reduction scheme illustrates how successive sets of VOIs are chosen for each successive iteration step of the method. For simplicity Fig. 4a is shown using 2D VOIs, however 3D VOIs, as in Fig. 4b, are naturally equally possible within the scope of the present invention. The first set of VOIs $\{V\}^0$ 41 contains the entire dataset to be analyzed (i.e. not on the per-voxel basis). After the first reconstruction resulting in a second set of initial parameter estimates, the first set of VOIs is divided by a predetermined number N into NxN VOIs $\{V\}^1$, 42a-i for N=3 in Fig. 4a, and NxNxN for 3D VOIs in Fig. 4b. In successive iteration steps, the resulting initial parameter estimates from the

reconstruction are assigned to VOIs, which are indicated by the different gray shadings, that originate from the same super ordinate VOI. This means that the first set of initial parameters $\{P\}^0$ will be used as initial parameters for the first set of VOIs $\{V\}^0$ 41. The second set of initial parameters $\{P\}^1$ will be used as initial parameters for the second set of VOIs $\{V\}^1$ 42a-i, $\{P\}^2$ will be used as initial parameters for the third set of VOIs $\{V\}^2$ 43 etc.

By utilizing the method according to some embodiments, the overall number of reconstruction steps, summed over all iterations, will be reduced for the majority of the individual voxels in the full VOI, since for each iteration, the initial parameters have been adapted to the data in the prior reconstruction step.

Using the above VOI reduction scheme according to some embodiments, the investigated set of VOIs, in the last iteration step, will consist of the individual voxels within the image dataset, which will result in the maximum resolution of the resulting parametric map and hence after rendering maximum resolution of the visualized image.

According to an embodiment the method is repeated until the user decides that the spatial resolution of the parametric map is high enough for his or her purposes (i.e. the sub-volumes are small enough) or until the VOIs in $\{V_j\}$ cannot be divided further (i.e. they already represent single voxels). The final parameter estimates are then given by P_i^{j+1}.

In an embodiment of the invention the predetermined number of sub-VOIs are 3 throughout the entire reconstruction process. In the 3D case, one set of VOIs thus results in 9 (3x3x3) smaller VOIs.

In an embodiment of the invention, according to Fig. 5, the predetermined number of VOIs follows a predetermined partitioning scheme, wherein $N = (N_1, N_2, ...N_{n-1}, N_n)$ is a vector containing the predetermined numbers in the partitioning scheme for the entire reconstruction process, where n is the total number of iterations, such as $N = (3,4,3,...)$ for a reconstruction process wherein the first predetermined number after the first reconstruction is 3.

In another embodiment the partitioning scheme is defined throughout the reconstruction process, e.g. depending on the difference or ratio between two subsequent sets of initial parameters. As an example, if the difference or ratio between two consecutive sets of initial parameters is large (e.g. predetermined threshold) the next element in the N-vector may be chosen to be smaller than if the difference or ratio between two consecutive sets of initial parameters is small. In this way the reconstruction process gives feedback to itself.

Accordingly if two sets of initial parameters are too diverse, the proceeding reconstruction process compensates by changing the partitioning scheme.

According to another embodiment the subsequent set of VOIs $\{V\}^{j}, j = j+1$ is identical to the initial set of VOIs $\{V\}^{j}, j = j$. This embodiment is advantageous, e.g. when the difference or ratio between two consecutive initial parameter estimates $\{P\}^{1}$, $\{P\}^{2}$ is larger than a predetermined threshold. The resulting initial parameters $\{P\}^{2}$ from the last iteration may then be used as initial parameters to the same VOI, i.e. $\{V\}^{1}$, that was used resulting in $\{P\}^{2}$.

In another embodiment the set of VOIs may be a set of voxels. Using the method according to some embodiments, eventually the VOIs will arrive on a voxel basis and hence cannot be subdivided further. Here, the greatest resolution of the parametric maps is achieved, provided that good initial parameter estimates are present.

In an embodiment the iterative reconstruction model complexity is increased in successive iteration steps.

In an embodiment of the invention, the reconstruction utilizes a simple model in the first iteration step, i.e. j=0, e.g. a one-compartment model. The complexity of this model is stepwise increased so as to in the last iteration the original model is obtained again. As an example the original model consists of three compartments. In the first iteration a simplified version of that model is used, that has been reduced to just one compartment. In the next iteration step, an intermediate two-compartment model is used, and in the third step one arrives at the original three-compartment model. For successive model versions, the mathematical relations between the fewer parameters of the simpler reconstruction model to the parameters of the more complex model are established. This really depends on the models used. The inventors of the present invention have e.g. used a special three compartment model for hypoxia imaging and have shown that this model can be transformed under certain assumptions to a two-compartment model. This transformation results in relations for some of the model parameters, e.g. k_2 in the two-compartment model is equal to a function of some other parameters in the three-compartment model. The exact relations are naturally dependent on the specific models. Using these relations, the initial parameters of the more refined versions of the models are calculated from the resulting parameters of the reconstruction of the simpler models. Additional parameters of the complex models, which cannot be related to the simpler models, are assigned with new initial values. The advantage of this embodiment

is that the parameters of the simpler reconstruction models typically can be determined more robustly. Thus, successive iterations begin with already good estimates for the initial parameters, so that the total number of reconstruction steps is reduced.

In another embodiment, the method further utilizes a combination of successively smaller VOIs, according to a partitioning scheme, and more complex reconstruction methods. In each iteration step, both the VOIs and the reconstruction models are successively refined.

Calculation of reconstruction efficiency

Generally, the decreased number of reconstruction steps in each iteration counterbalances the additional iterations of the method according to some embodiments of the invention. It is shown in the following that the reconstruction is performed more efficiently.

The use of the term iteration in this context is used to denote the iterative steps in the method with different sets of VOIs etc. The successive steps during the reconstruction process are referred to as reconstruction steps.

For the method of the invention, using VOI reduction with the same predetermined number in each iteration step, to be less time-consuming than some other less-advantageous methods, the following relation must apply:

$$NI \geq (N + \frac{N}{\Delta} + \frac{N}{\Delta^2} + ... + 1)\bar{I} \qquad \text{(eqn 1)}$$

where N denotes the total number of voxels in the image dataset. The average number of reconstruction steps for some other methods reconstruction models and the method according to an embodiment is defined as I and $\bar{I}$, respectively. The average should be appreciated as the average over all iterations and all VOIs for each iteration. Δ is given by the predetermined number of sub-volumes into which a larger VOI is divided $(\Delta > 1)$. By defining a ratio $m = I / \bar{I}$ eqn 1 may rewritten as

$$\frac{I}{\bar{I}} \geq \frac{(N + \frac{N}{\Delta} + \frac{N}{\Delta^2} + ... + 1)}{N} = m \geq \sum_{j=0}^{k} \frac{1}{\Delta^j} \qquad \text{(eqn 2)}$$

assuming that N, Δ and k are adjusted in such a way to give $\Delta^k = N$, meaning that one reaches single voxels in the k-th iteration step. To estimate the upper bound for which the present method still gives an advantage in terms of speed, the finite may be replaced by the (larger) infinite sum (i.e. $k \to \infty$) and thus

$m \geq \frac{\Delta}{\Delta - 1}$.

If m is larger than this value, i.e. if the average number of iterations is reduced by at least a factor of m, the proposed method is faster. As an example, by setting $\Delta = 3$ and thus each VOI is divided into 3 x 3 x 3 sub-volumes, the corresponding ratio is $m = 27/26 \approx 1.04$, meaning that already a 4% reduction in the average number of reconstruction steps due to the iteratively adapted initial values results in an overall decrease of the computation time.

According to another embodiment, the reconstruction method comprises only two iteration steps (e.g. indicated as j=1, and j=2) by setting the predetermined number such that the second set of VOIs consists of the individual voxels of the image dataset. There are N voxels and I reconstruction steps in the "some other methods" method. In this embodiment, in the first iteration (j=1), an average over the complete dataset is used and in the second and final iteration again the individual voxels are used, i.e. N voxels. Both iterations together consist of $N+1$ voxels with an average number $\bar{I}$ of reconstruction steps. Regarding computation efficiency this means $(N+1)\bar{I}$ iterations will be performed, and hence, in accordance with eqn 1,

$$NI \geq (N+1)\bar{I} \Rightarrow m \geq \frac{N+1}{N}$$

This means that for the typical numbers of voxels analyzed $(N >> 100)$, the iterative method will be more efficient for a sub-percent reduction in the average number of reconstruction steps. As an example, it may take 10 reconstruction steps to calculate the parameters with the "some other methods" method for 100 voxels. In the method according to this embodiment the average over the 100 voxels is first calculated and then reconstructed to get the "improved" starting values and these are used for the second iteration. If m is larger than (100+1)/100, i.e. if the average number of iterations is reduced by at least a factor of m, the method according to this embodiment is faster than some other methods, i.e. it needs a smaller total number of reconstruction steps. This means for the given example above that $\bar{I} \leq 100 * 10/101 \approx 9{,}9$ to be more efficient than the "some other methods" method.

In another embodiment the method is implemented into an analysis workstation that comes with the medical imaging device, e.g. the PET scanner, as a piece of additional software. The method may run on the same processor and use the same memory as the reconstruction software for example.

In an embodiment the image dataset is a 2D, 3D, 4D or higher-dimensional medical image dataset, e.g. created using Computed Tomography, Magnetic Resonance Imaging or Ultrasound Imaging.

In another embodiment, according to Fig. 6, an apparatus 60 for pharmacokinetic modeling of an image dataset comprising a set of VOIs having a plurality of volumes, each volume comprising at least one voxel having at least one related data value. The apparatus comprises at least one unit for performing the method according to embodiments. The apparatus comprises

a first assigning unit 61 for assigning an initial set of parameter values to initial parameters describing a first type of voxel within the image dataset,

a calculation unit 62 for calculating a mean voxel data value for each volume in an initial set of VOIs comprised in the set of VOIs,

a reconstruction unit 63 for reconstructing parameters for each volume in the initial set of VOIs, based on the mean voxel data value and the initial set of parameter values, resulting in a subsequent set of parameters, and

a second assigning unit 64 for assigning the subsequent set of parameters as initial parameters $\{P\}^j, j=1$ to a subsequent set of VOIs $\{V\}^j, j=1$ comprised in the image dataset.

In an embodiment the apparatus 60 further comprises a repeating unit 65 for iteratively repeating the calculating, the reconstructing, and the assigning, using each subsequent set of parameters as the initial parameters and each subsequent VOI as the initial set of VOI until a parametric map having a predetermined resolution is achieved.

In another embodiment the repeating unit 65 may be used by user interaction to interactively control the spatial resolution of the resulting parametric maps. The user may stop the iterative reconstruction process prior to reaching the maximum resolution (i.e. reconstructing single voxels), if the resolution so far reached is considered adequate. This means that the user may stop the iterative reconstruction process independently of the predetermined spatial resolution.

The unit(s) comprised in the apparatus according to some embodiments may be any unit(s) normally used for performing the involved tasks, e.g. a hardware, such as a processor with a memory. The processor may be any of variety of processors, such as Intel or AMD processors, CPUs, microprocessors, Programmable Intelligent Computer (PIC) microcontrollers, Digital Signal Processors (DSP), etc. However, the scope of the invention is not limited to these specific processors. The memory may be any memory capable of storing

information, such as Random Access Memories (RAM) such as, Double Density RAM (DDR, DDR2), Single Density RAM (SDRAM), Static RAM (SRAM), Dynamic RAM (DRAM), Video RAM (VRAM), etc. The memory may also be a FLASH memory such as a USB, Compact Flash, SmartMedia, MMC memory, MemoryStick, SD Card, MiniSD, MicroSD, xD Card, TransFlash, and MicroDrive memory etc. However, the scope of the invention is not limited to these specific memories.

In an embodiment the apparatus is comprised in a medical workstation or medical system, such as a PET Scan System, Computed Tomography (CT) system, Magnetic Resonance Imaging (MRI) System or Ultrasound Imaging (US) system.

In other embodiments the method may be integrated into a stand-alone device, which essentially has processing and memory capability, such as a normal computer that runs the software. However, in clinical practice, it is most convenient to have the analysis tools integrated into as few different workstations as possible to alleviate workflow.

In an embodiment of the invention the apparatus 60 further comprises a render unit 66 for rendering a 2D or 3D visualization of the image dataset based on the resulting parametric map.

In an embodiment the apparatus 60 further comprises a display unit 67 for displaying the rendered 2D or 3D visualization to a user.

In a practical implementation the method according to some embodiments may be used as follows: 1) The user selects the initial set of VOIs that he wants to analyze; 2) The user then sets all options and starts the reconstruction process. 3) On the screen, he would then see in real time the results in each iteration step. That means, that in the first iteration the results would be presented in rather larger VOIs, in the next steps, the VOIs would be more refined (depending on the partitioning scheme), and so on. 4) Once the user decides that the (spatial) resolution is sufficient for the special case he is investigating, he can press a STOP button and the reconstruction is stopped. 5) The results computed so far are then treated as the final ones. As an example, when the user is viewing a suspicious region in the lung and wants to determine if there are subregions with increased metabolism, such as cancerous tissues, he would select a large VOI around these suspicious areas and start the process. Once he sees enough spatial structure to be able to determine between areas of different metabolism, he may stop the process, as more refined results might not provide further details about the disease and would only take more time. As should be appreciated time is always a critical resource in a clinical environment.

In another embodiment, according to Fig. 7, a computer-readable medium 70 having embodied thereon a computer program for processing by a computer is provided, for pharmacokinetic modeling of an image dataset comprising a set of VOIs having a plurality of volumes, each volume comprising at least one voxel having at least one related data value. The computer program comprises a first assigning code segment 71 for assigning an initial set of parameter values to initial parameters describing a first type of voxel within the image dataset, a calculation code segment 72 for calculating a mean voxel data value for each volume in an initial set of VOIs comprised in the set of VOIs, a reconstruction code segment 73 for reconstructing parameters for each volume in the initial set of VOIs, based on the mean voxel data value and the initial set of parameter values, resulting in a subsequent set of parameters, and a second assigning code segment 74 for assigning the subsequent set of parameters as initial parameters to a subsequent set of VOIs comprised in the image dataset.

In an embodiment the computer-readable medium 70 further comprises a repeating code segment 75 for iteratively repeating the calculating, the reconstructing, and the assigning, using each subsequent set of parameters as the initial parameters and each subsequent VOI as the initial set of VOI, until a parametric map having a predetermined resolution is achieved.

In an embodiment of the invention the computer-readable medium 70 further comprises a render code segment 76 for rendering a 2D or 3D visualization of the image dataset based on the resulting parametric map.

In an embodiment the computer-readable medium 70 further comprises a display code segment 77 for displaying the rendered 2D or 3D visualization to a user.

In an embodiment the computer-readable medium, comprising code segments arranged, when run by an apparatus having computer-processing properties, for performing all of the method steps defined in some embodiments.

In an embodiment the method, apparatus, or computer-readable medium is used for diagnosing a disorder or disease, such as cancer, in a human.

According to an embodiment a computer readable medium is provided for performing the method according some embodiments of the invention.

Applications and use of the above-described method, apparatus, computer readable medium, and use according to embodiments of the invention are various and is applicable to all cases where data, which represents regional information, is subjected to a reconstruction procedure to extract parametric maps.

The invention may be implemented in any suitable form including hardware, software, firmware or any combination of these. However, preferably, the invention is implemented as computer software running on one or more data processors and/or digital signal processors. The elements and components of an embodiment of the invention may be physically, functionally and logically implemented in any suitable way. Indeed, the functionality may be implemented in a single unit, in a plurality of units or as part of other functional units. As such, the invention may be implemented in a single unit, or may be physically and functionally distributed between different units and processors.

Although the present invention has been described above with reference to specific embodiments, it is not intended to be limited to the specific form set forth herein. Rather, the invention is limited only by the accompanying claims and, other embodiments than the specific above are equally possible within the scope of these appended claims.

In the claims, the term "comprises/comprising" does not exclude the presence of other elements or steps. Furthermore, although individually listed, a plurality of units, elements or method steps may be implemented by e.g. a single unit or processor. Additionally, although individual features may be included in different claims, these may possibly advantageously be combined, and the inclusion in different claims does not imply that a combination of features is not feasible and/or advantageous. In addition, singular references do not exclude a plurality. The terms "a", "an", “first”, “second” etc do not preclude a plurality. Reference signs in the claims are provided merely as a clarifying example and shall not be construed as limiting the scope of the claims in any way.

CLAIMS:

1. A method for pharmacokinetic modeling of an image dataset comprising a set of volumes of interest having a plurality of volumes, each volume comprising at least one voxel having at least one related data value, said method comprising

assigning an initial set of parameter values to initial parameters describing a first type of voxel within said image dataset,

calculating a mean voxel data value for each volume in an initial set of volumes of interest comprised in said set of volumes of interest,

reconstructing parameters for each volume in said initial set of volumes of interest, based on said mean voxel data value and said initial set of parameter values, resulting in a subsequent set of parameters, and

assigning said subsequent set of parameters as initial parameters to a subsequent set of volumes of interest comprised in said image dataset.

2. The method according to claim 1, comprising creating a parametric map, having a spatial resolution, for said image dataset by iteratively repeating said calculating, said reconstructing, and said assigning, using each subsequent set of parameters as said initial parameters and each subsequent volume of interest as said initial set of volume of interest, resulting in a predetermined spatial resolution of said parametric map.

3. The method according to claim 2, comprising stopping said repeating by user interaction, independently of said predetermined spatial resolution of said parametric map.

4. The method according to claim 1, further comprising iteratively repeating said calculating, said reconstructing, and said assigning, using each subsequent set of parameters as said initial parameters and each subsequent volume of interest as said initial set of volume of interest until the total number of iterations is equal to a predetermined number of iterations.

5. The method according to claim 1, wherein said image dataset is a 2D, 3D, or higher-dimensional medical image dataset.

6. The method according to claim 1, wherein said subsequent set of volumes of interest is a sub-volume of said initial set of volumes of interest according to a partitioning scheme.

7. The method according to claim 6, wherein said partitioning scheme is predetermined.

8. The method according to claim 6, comprising calculating said partitioning scheme based on two subsequent sets of initial parameters.

9. The method according to claim 1, wherein said subsequent volume of interest is identical to said initial set of volumes of interest.

10. The method according to any of the previous claims, wherein at least one of said initial set of volumes of interest and said subsequent set of volumes of interest is a voxel.

11. The method according to any one of the previous claims, said reconstructing of parameters comprising, in successive iteration steps, increasing a reconstruction complexity of said reconstructing of parameters.

12. The method according to any of the previous claims, wherein said reconstructing of parameters is based on a one-compartment model, a two-compartment model or higher order compartment model.

13. The method according to claim 1, wherein said first type of voxel describes healthy tissue.

14. An apparatus (60) for pharmacokinetic modeling of an image dataset comprising a set of volumes of interest having a plurality of volumes, each volume comprising at least one voxel having at least one related data value, said apparatus comprising

a first assigning unit (61) for assigning an initial set of parameter values to initial parameters describing a first type of voxel within said image dataset,

a calculation unit (62) for calculating a mean voxel data value for each volume in an initial set of volumes of interest comprised in said set of volumes of interest,

a reconstruction unit (63) for reconstructing parameters for each volume in said initial set of volumes of interest, based on said mean voxel data value and said initial set of parameter values, resulting in a subsequent set of parameters, and

a second assigning unit (64) for assigning said subsequent set of parameters as initial parameters to a subsequent set of volumes of interest comprised in said image dataset.

15. The apparatus (60) according to claim 14, further comprising a repeating unit (65) for iteratively repeating said calculating, said reconstructing, and said assigning, using each subsequent set of parameters as said initial parameters and each subsequent volume of interest as said initial set of volume of interest until a parametric map having a predetermined resolution is achieved.

16. The apparatus (60) according to claim 15, further comprising a render unit (66) for rendering a 2D or 3D visualization of said image dataset based on said parametric map.

17. The apparatus according to any one of the claims 14-16, being comprised in a medical workstation or a medical imaging system.

18. A computer-readable medium (70) having embodied thereon a computer program for processing by a computer, for pharmacokinetic modeling of an image dataset comprising a set of volumes of interest having a plurality of volumes, each volume comprising at least one voxel having at least one related data value, said computer program comprising

a first assigning code segment (71) for assigning an initial set of parameter values to initial parameters describing a first type of voxel within said image dataset,

a calculation code segment (72) for calculating a mean voxel data value for each volume in an initial set of volumes of interest comprised in said set of volumes of interest,

a reconstruction code segment (73) for reconstructing parameters for each

volume in said initial set of volumes of interest, based on said mean voxel data value and said initial set of parameter values, resulting in a subsequent set of parameters, and

a second assigning code segment (74) for assigning said subsequent set of parameters as initial parameters to a subsequent set of volumes of interest comprised in said image dataset.

19. Use of the method, apparatus or computer-readable medium according to any of the previous claims, for diagnosing a disorder or disease in a human.

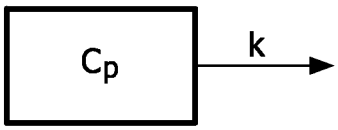

FIG. 1a

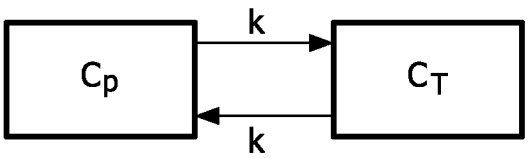

FIG. 1b

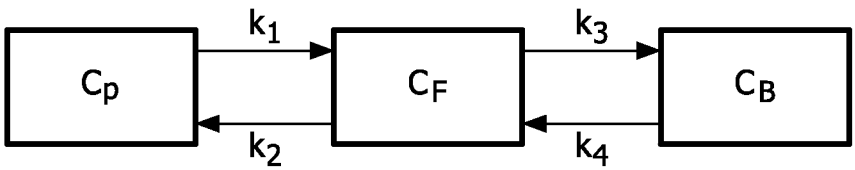

FIG. 1c

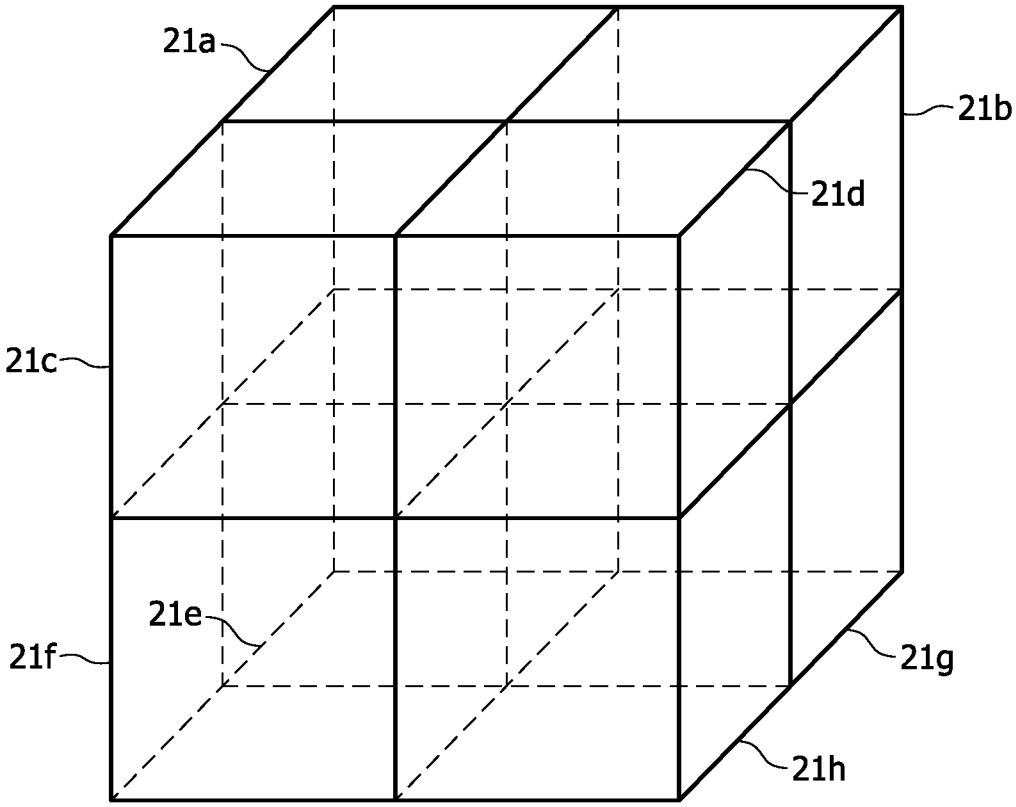

FIG. 2

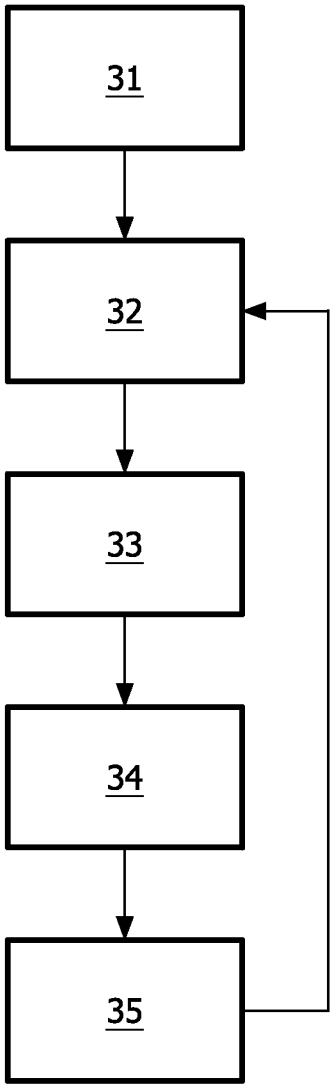

FIG. 3

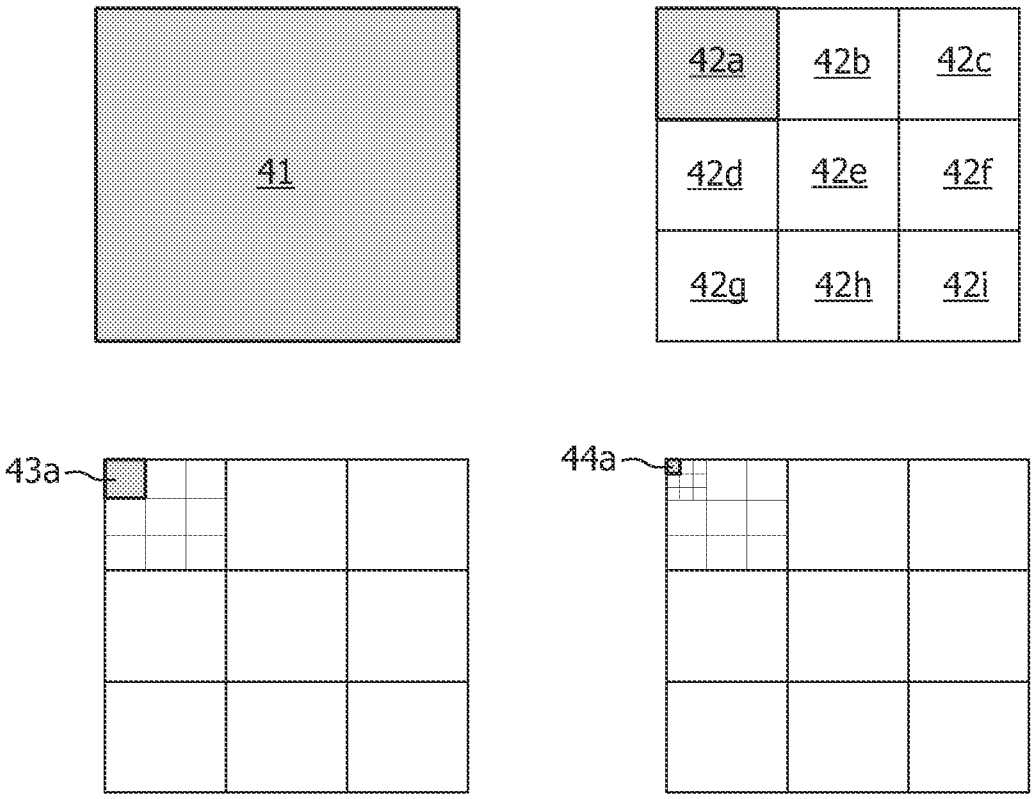

FIG. 4a

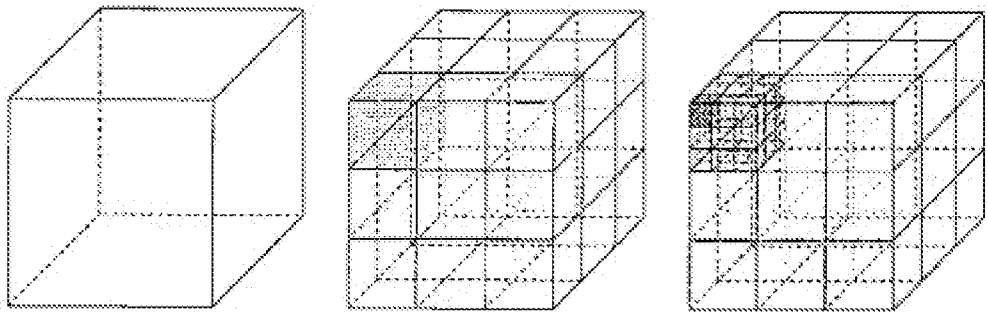

FIG. 4b

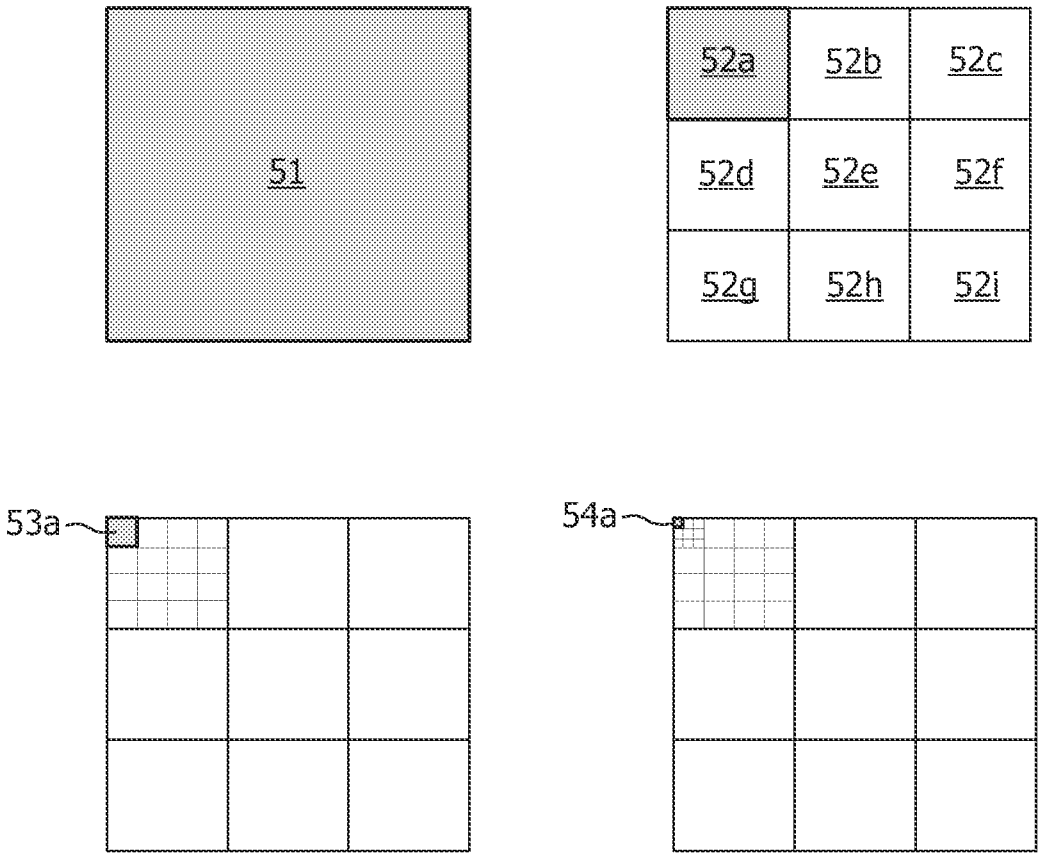

FIG. 5

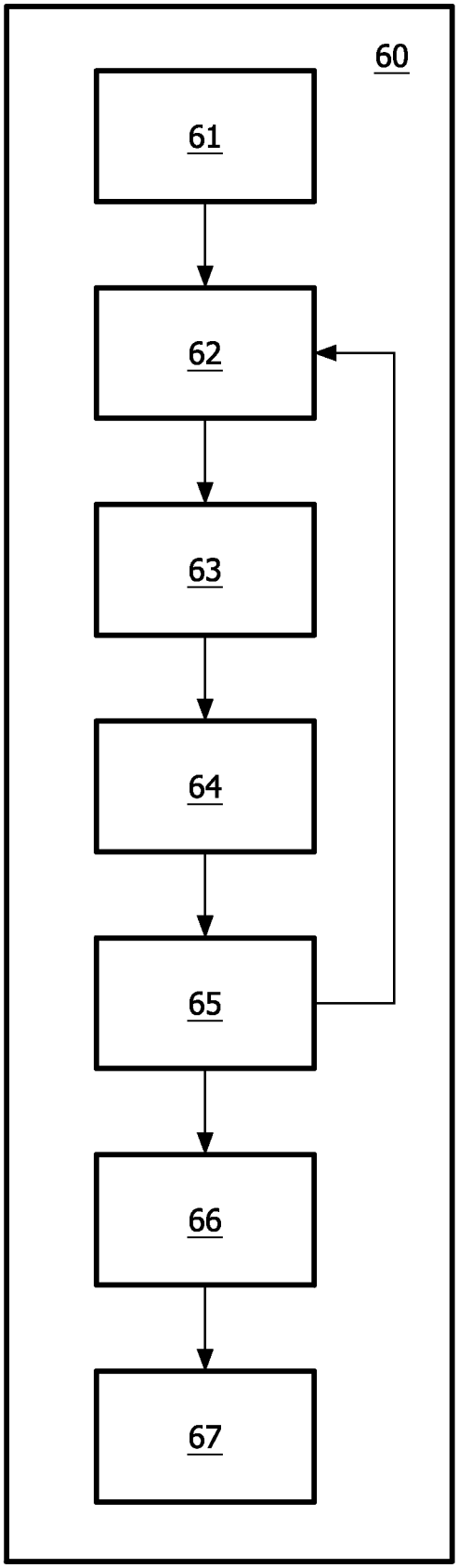

FIG. 6

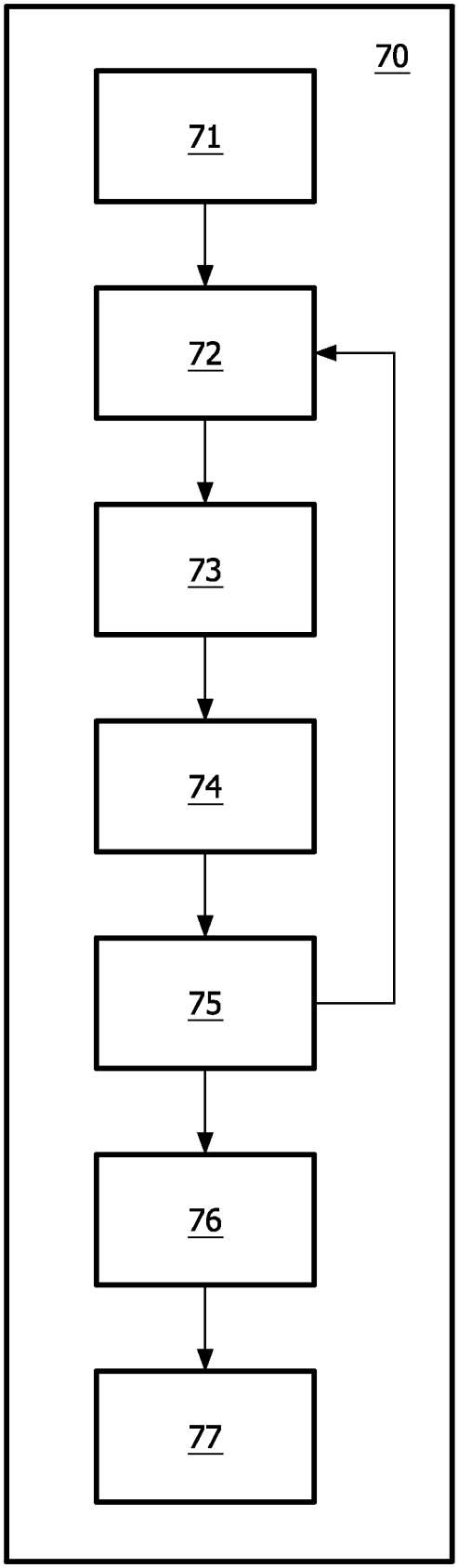

FIG. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/053065

A. CLASSIFICATION OF SUBJECT MATTER
INV. G06T7/00

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)
G06T

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, INSPEC, IBM-TDB

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M.E. KAMASAK, C.A. BOUMAN, E.D. MORRIS, K.D. SAUER: "Parametric reconstruction of kinetic PET data with plasma function estimation" PROCEEDINGS OF SPIE - COMPUTATIONAL IMAGING III, vol. 5674, 2005, pages 293-304, XP002475170 abstract sections 3.2, 3.3, 3.4 figures 3,6,7	1,2, 4-10, 12-18
Y	section 2, paragraph 1; figure 1 section 3.4	3,11

-/--

[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
9 April 2008	21/04/2008

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	Katartzis, Antonios

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/053065

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/109343 A (PHILIPS INTELLECTUAL PROPERTY [DE]; KONINKL PHILIPS ELECTRONICS NV [NL) 17 November 2005 (2005-11-17) page 4, line 22 - line 27	3
A	page 5, line 1 - line 20; figure 1	16,17
Y	F.E. TURKHEIMER, R. HINZ, V.J. CUNNINGHAM: "On the Undecidability Among Kinetic Models: From Model Selection to Model Averaging" JOURNAL OF CELEBRAL BLOOD FLOW & METABOLISM, vol. 23, 2003, pages 490-498, XP002475171 page 497, column 2	11
A	BOUMAN C A ET AL: "Direct Reconstruction of Kinetic Parameter Images From Dynamic PET Data" IEEE TRANSACTIONS ON MEDICAL IMAGING, IEEE SERVICE CENTER, PISCATAWAY, NJ, US, vol. 24, no. 5, May 2005 (2005-05), pages 636-650, XP011131264 ISSN: 0278-0062 the whole document	1,14,18
A	TURKHEIMER ET AL: "Multi-resolution Bayesian regression in PET dynamic studies using wavelets" NEUROIMAGE, ACADEMIC PRESS, ORLANDO, FL, US, vol. 32, no. 1, 20 July 2006 (2006-07-20), pages 111-121, XP005768331 ISSN: 1053-8119 the whole document	1,14,18
A	JONATHAN S MALTZ: "Optimal Time-Activity Basis Selection for Exponential Spectral Analysis: Application to the Solution of Large Dynamic Emission Tomographic Reconstruction Problems" IEEE TRANSACTIONS ON NUCLEAR SCIENCE, IEEE SERVICE CENTER, NEW YORK, NY, US, vol. 49, no. 4, August 2001 (2001-08), pages 1452-1464, XP011042113 ISSN: 0018-9499 the whole document	1,14,18
A	J.B. BASSINGTHWAIGHTE, H.J.CHIZECK, L.E ATLAS: "Strategies and Tactics in Multiscale Modeling of Cell-to-Organ Systems" PROCEEDINGS OF THE IEEE, vol. 94, no. 4, 2006, pages 819-831, XP002475186 the whole document	1,11,14, 18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2007/053065

Box No. 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.: 19
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 19 relates to subject-matter (a diagnostic method and related apparatus or computer-readable medium) considered by this Authority to be covered by the provisions of Rule 39.1(iv) PCT. Consequently, no search is carried out for this claim (Article 17(2)(a)(I) PCT).

2. [ ] Claims Nos.:
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:

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 No. 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 allsearchable claims.

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

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers 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 and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2007/053065

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005109343 A	17-11-2005	CN 1969295 A	23-05-2007
		JP 2007536551 T	13-12-2007
		US 2007165926 A1	19-07-2007