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- (88) **Date of publication of the international search report:**
27 November 2008



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(54) **Title:** A METHOD FOR DETERMINING AND PREDICTING PROTEIN AUTONOMOUS FOLDING

(57) **Abstract:** Techniques for determining an equilibrium structure of a protein in a predetermined environment, the protein having Ramachandran angles and a known denatured structure, are disclosed. In a preferred embodiment, a method is presented which involves determining a maximum RMS volume of the known denatured structure of the protein and calculating at least one force on the protein in its current structure in the predetermined environment. The net torque resulting from the at least one force for each of the Ramachandran angles of the protein is then determined. Then at least one section of the protein structure on a side of a Ramachandran angle with greatest torque is rotated to form a new structure. A new RMS volume for the new structure is then calculated, and the method is repeated using the new structure. The method ceases when the new RMS volume of the new protein structure is not less than the RMS volume of the starting structure.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/67639

A. CLASSIFICATION OF SUBJECT MATTER
 IPC: **G06F 19/00(2006.01)**

USPC: 702/27;703/2,11;530/300,350
 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)
 U.S. : 702/27;703/2,11; 530/300, 350

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 practicable, search terms used)
 Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KARPLUS, P.A. Experimentally observed conformation-dependent geometry and hidden strain in proteins. <i>Protein Science</i> . 1996, Volume 6, pages 1406-1420.	1-18
A	DORUKER et al. Role of Water on Unfolding Kinetics of Helical Peptides Studied by Molecular Dynamics Simulations. <i>Biophysical Journal</i> . June 1997, Volume 27, pages 2445-2456.	1-18
A	KRIMM et al. Free-Energy Calculations of the Interactions of Helical Poly (L-Proline) with Water. <i>Proceedings of the National Academy of Sciences</i> . October 1971, Volume 68, Number 10, pages 2468-2471.	1-18
A	SHORTLE, D. Propensities, probabilities, and the Boltzmann hypothesis. <i>Protein Science</i> . 2003, Volume 12, pages 1298-1302.	1-18
A	US 2005/0004766 A1 (RAMNARAYAN et al.) 06 January 2003 (06.01.2003), see Detailed Description of the Invention.	1-18

Further documents are listed in the continuation of Box C. 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	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search: 20 August 2008 (20.08.2008)
 Date of mailing of the international search report: 22 SEP 2008

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Marjorie Moran <i>Lydia Delle For</i> Telephone No. 571-272-1600
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/67639

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. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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:
Please See Continuation Sheet

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 additional fees, this Authority did not invite payment of any additional fees.
 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 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

International application No.
PCT/US07/67639

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/0158672 A1 (RAMNARAYAN et al.) 21 August 2003 (21.08.2003), see Detailed Description of the Invention.	1-18

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

- I. Claims 1-11, drawn to first method for determining equilibrium structure of a protein.
- II. Claims 12-17, drawn to a synthetic protein.
- III. Claim 18, drawn to a second method of determining global energy change.

The inventions listed as Groups II and Groups I or III do not relate to a single general inventive concept under PCT Rule 13.1 because there is no "special technical feature" linking product of Group I and method of determining structure of protein of Group I or determining global energy change of Group III. The product of Group II can be obtained by any number of methods of protein synthesis unrelated to methods of determining of Groups I or III.

With regard to methods of Groups I and III, the methods require different steps: method of Group I requires repeating steps until the new protein structure is not less than the RMS volume of the structure of protein at (b), whereas the method of Group III requires repeating steps using different values for global energy.

Continuation of B. FIELDS SEARCHED Item 3:

WEST, PUBMED, EMBASE, MEDLINE, BIOSIS, SCISEARCH searching terms equilibrium, protein, environment, ramachandran angle, RMS, volume, force, torque, iterate, electrostatic, themal, hydrophobic, bubble, global energy, density, mobility, rotation