

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE 03/15/99	3. REPORT TYPE AND DATES COVERED Final; 12/01/97 - 05/31/98	
4. TITLE AND SUBTITLE Inverse Protein Folding		5. FUNDING NUMBERS N00014-92-J-1240	
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9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) Office of Naval Research, Code 341MCE Molecular, Cellular, and Environmental Biology Program 800 North Quincy Street Arlington, VA 22217-5680		10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES			
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited		12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words) We have developed Geocore, a computer algorithm that aims to predict the 3D structures of foldable polymers from their monomer sequences. Our first work was on foundations in simplified models, and most recently we have completed tests in which we found the method is successful in 18 peptides and small proteins. Our continuing efforts will be to speed it up and extend it to larger proteins.			
14. SUBJECT TERMS Protein folding, polymer design, computer algorithm, peptide modeling			15. NUMBER OF PAGES 3
17. SECURITY CLASSIFICATION OF REPORT Unclassified			16. PRICE CODE
			20. LIMITATION OF ABSTRACT UL
18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified		

19990323 042

GRANT #: N00014-92-J-1240

PRINCIPAL INVESTIGATOR: Dr. Ken A. Dill

INSTITUTION: University of California, San Francisco

GRANT TITLE: Inverse Protein Folding

AWARD PERIOD: 12/01/97 - 05/31/98

OBJECTIVE: To develop a model, called Geocore, for protein and polymer folding.

APPROACH: The model is united atom, with 3-6 discrete phi psi backbone options per amino acid and sidechains are fixed in their predominant rotameric state, chosen according to the relative populations in the Protein Databank. There is one hydrophobicity and one H bond parameter, steric violations are not allowed, and the conformations are searched by an extensive branch-and-bound method.

ACCOMPLISHMENTS: We used lattice models first to explore principles of fast conformational search processes and simple energy functions. We developed theory for inverse folding, on sequence design, that showed that this problem is in a much simpler class of computational difficulty than protein folding. We developed a very fast lattice-based search methodology that finds globally optimal conformations of the longest chains yet found by any method.

We then incorporated some of the same conformational search principles into an off-lattice method, called Geocore. We have tested Geocore now on 18 peptides - all the peptides having known structure (i.e., in the PDB) shorter than 31 amino acids (the limit of the current search method). Eleven of these peptides are water soluble. Geocore does well as a filtering algorithm, meaning that keeping the 400 lowest-energy configurations out of more than 10^9 explored per typical peptide, is sufficient to retain a conformation that is native-like by the criteria that the secondary structures are similar and RMSD errors are less than about 5 angstroms, often about 3 angstroms.

The limitations of the method are in the limited phi psi options and the slow search speeds. We currently have independent funding to pursue improvements in these areas.

CONCLUSIONS: We have found that branch-and-bound search methods are competitive in speed with standard methods, like Monte Carlo, for models having discrete phi psi options. The advantage of the Geocore search is that we can be assured of global minima, and this gives a deep test of the energy function. A main conclusion from this work is that simple

energy functions, with few parameters, are arguably no worse than more complex ones. We believe Geocore is a viable early-stage peptide folding model.

SIGNIFICANCE: This work takes steps toward a computer algorithm that can compute the structures of peptides and proteins, ab initio, from their monomer sequences.

PATENT INFORMATION: No patents.

AWARD INFORMATION: President, Biophysical Society, 1998-1999; First Hans Neurath Award, Protein Society, 1998; member BBCA Study Section, NIH.

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