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6. AUTHOR(S) Shalom R. Rackovsky		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Dept. Of Biomathematical Sciences Mount Sinai School Of Medicine One Gustave L. Levy Place, Box 1023 New York, NY 10029		8. PERFORMING ORGANIZATION REPORT NUMBER
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13. ABSTRACT (Maximum 200 words)

The characteristics of the inverse protein folding code, specifying the sequences which can be associated with a particular local fold, have been investigated. Methods development continues on the use of amino acid clustering for data compression. We are also investigating the relationship between protein structural symmetry and the distribution of amino acid properties along sequences.

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Final Report

The principal thrust of the research funded by this award was continued elucidation of characteristics of the protein folding code. In work supported by another ONR award (N00014-91-J-1943) it was demonstrated that there exists a short-range folding code in proteins, and the characteristics of that code were investigated. In the present work, we have explored the possibility that there exists an inverse folding code in proteins. This is the code which determines which sequence fragments can be accommodated by a given local chain fold.

We have demonstrated¹ that an inverse folding code indeed exists, and that it has the same characteristics as the direct folding code (which addresses the structures permitted by a given sequence). In particular, it was shown that ~73% of four-residue structure fragments show a preference for particular distributions of sequences, and that the remainder do not. Rather, we suggest that these non-coding structure elements act as hot spots in which mutations are tolerated with no cost in *short-range* folding energy.

This is the first study to consider the inverse folding problem from the viewpoint of short-range interactions. All previous studies of this problem have considered the manner in which sequence substitution affects long-range interactions. Combination of our results with those of other workers, in a study of mutation frequencies in protein sequences, therefore has the potential to show the relative importance of short- and long-range interactions in determining mutation probabilities.

We are also continuing development work on methodology in this area. In recent computations, we have investigated the effect of amino acid clustering methods, useful for sequence data compression, on coding results.

A new area of interest initiated under funding from this award is the investigation of the connection between sequence properties and structural symmetry in proteins. Some protein structures show a high degree of three-dimensional symmetry, and physical intuition suggests that this structural property must be somehow reflected in the distribution of amino acid properties along the chain. We are developing Fourier methods to search for statistically significant periodicities of amino acid properties which may be linked to specific details of protein structure.

Publications

1. S. Rackovsky, On the existence and implications of an inverse folding code in proteins. Proc. Nat. Acad. Sciences USA **92**, 6861 (1995).

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| (a) Dr. Michael Marron
ONR Code 1141
Molecular Biology Program
800 N. Quincy Street
Arlington, VA 22217-5000 | (e) Director
Chemical and Biological Sci Div
Army Research Office
P. O. Box 12211
Research Triangle Park, NC 27709 |
| (b) Administrative Grants Officer
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| (c) Director,
Applied Research Directorate
ONR Code 12
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Naval Research Laboratory
Technical Information Div
Code 2627
Washington, DC 20375 |
| (d) Director
Office of Naval Technology
Code 22
800 N. Quincy Street
Arlington, VA 22217-5000 | |