Protein Folding Quotes

Prof. Sorin Istrail
CSCI1820
Tues. & Thur. 2:30-3:50p.m.
CIT room 241

"...a very nice step forward in the computerology of proteins"

Ken Dill

Folding proteins fast (editorial on the first approximation algorithm for protein folding). *Science*, 269:1821, 1995.

"The subject of chaos is characterized by an abundance of quantitative data, an unending supply of beautiful pictures, and a shortage of rigorous theorems. Rigorous theorems are the best way to give a subject intellectual depth and precision. Until you can prove rigorous theorems, you do not fully understand the meaning of your concepts."

Freeman Dyson

F. Dyson. Birds and Frogs. *Notics of the American Mathematical Society*, 56:212-223, 2008.

"The most vitally characteristic fact about mathematics is, in my opinion, its quite peculiar relationship to the natural sciences ... In modern empirical sciences it has become more and more a major criterion of success whether they have become accessible to the mathematical method or to the near-mathematical methods of physics. Indeed, throughout the natural sciences an unbroken chain of successive pseudomorphoses, all of them pressing toward mathematics, and almost identified with the idea of scientific progress, has become more and more evident. Biology becomes increasingly pervaded by chemistry and physics, chemistry by experimental and theoretical physics, and physics by very mathematical forms of theoretical physics.

There is a quite peculiar duplicity in the nature of mathematics. One has to realize this duplicity, to accept it, and to assimilate it into one's thinking on the subject. This double face is the face of mathematics, and I do not believe that any simplified, unitarian view of the thing is possible without sacrificing the essence."

John von Neumann

J. v. Neumann. The mathematician. In *"The Works of the Mind*," University of Chicago Press:180-196, 1947.

"[P]rotein folding is a fascinating cross-disciplinary field that attracts scientists with different backgrounds and scientific cultures. They bring to the protein folding field the models and the way of thinking that are accepted of their respective background fields. Such diversity of scientific cultures is a great virtue of the protein folding field, in which physics, chemistry, biology, and mathematics meet. It is important for our cross-disciplinary field to discuss with balance both strong points and limitations of different approaches."

Eugene Shakhnovich

E. Shakhnovich. Modeling protein folding: the beauty and power of simplicity. *Folding and Design*, 1:50-54, 1996.

"The protein folding problem is three different problems: the folding code – the thermodynamic question of how a native structure results from the interatomic forces acting on an amino acid sequence; protein structure prediction – the computational problem of how to predict the native structure of a protein from its amino acid; and the folding speed (Levinthal's paradox) – the kinetic question of how a protein can fold so fast… Current knowledge of the folding code is sufficient to guide the successful design of new proteins and new materials. Current computer algorithms are now predicting the native structures of small simple proteins remarkable accurately, contributing to drug discovery and proteomics. Even once intractable Levinthal 'spuzzle now seems to have a very simple answer…"

Ken Dill

K. A. Dill, S. Banu Ozkan, T. R. Weikl, J. D. Chodera and V. A. Voelz. The protein folding problem: when will it be solved? *Current Opinion in Structural Biology*, 17:2342-346, 2007.

"The failure of protein-folding processes, both within cells (in vivo) and within test tubes or industrial vats (in vitro), causes serious difficulties both for biomedical research and for biotechnology industry. Protein chains that fail to fold properly aggregate into an insoluble and inactive state… There is increased recognition that some human diseases are associated with aberrations or defects in protein chain folding. These include Alzheimer's and Huntington's and cystic fibrosis."

Jonathan King

J. King, C. Haase-Pettingell, and D. Gossard. Protein folding and misfolding. *American Scientist*, 90:445-453, 2002.

"Understanding the mechanism of protein folding is often called the "second half" of genetics. Computational approaches have been instrumental in the efforts. Simplified models have been applied to understand the physical principles governing the folding process and will continue to play important roles in the endeavor."

Peter Kollman

Y. Duan and P.A. Kollman. Computational protein folding: From lattice to all-atom. *IBM Systems Journal*, 40:297-309, 2001.

"We must emphasize a statement which I am sure you have heard before, but which must be repeated again and again. It is that the sciences do not try to explain, they hardly even try to interpret, they mainly make models. By a model is meant a mathematical construct which, with the addition of certain verbal interpretations, describes the observed phenomena. Furthermore, it must satisfy certain esthetic criteria, that is, in relation to how much it describes, it must be rather simple. Since one cannot tell exactly how 'simple' simple is … Simplicity is largely a matter of historical background, of previous conditioning, of antecedents, of customary procedures, and it is very much a function of what is explained by it."

John von Neumann

J. v. Neumann. Method in physical sciences. In *"The Unity of Knowledge"* ed. L. Leary, pages 157-164, 1955.

"[We] take as our premise that proteins are chain molecules that have specific monomer sequences and are driven to fold mainly by nonlocal interactions subject to steric constraints. There is currently no accurate analytical theory that can account for chain connectivity, excluded volume in the compact states, and specific sequences of monomer units. Simple exact models have been developed to explore such properties."

Ken Dill

K. A. Dill, S. Bromberg, K. Yue, K. M. Fiebig, D. P. Yee, P. D. Thomas and H. S. Chan. Principles of protein folding: A perspective from simple exact models. *Protein Science*, 4:561-602, 1995.

"It seems remarkable that so simple a model based on time averaged forces can account for the stability and folding of a molecule as complicated as a protein. Looking at known protein conformations closely, one is struck by the precise geometry of the interatomic contacts that stabilise the molecule: all possible interior hydrogen bonds are well formed, and many of the nonpolar side chains interlock to form a close packed interior. . . . [T]he forces responsible for this precise geometry ... cause the chain to fold into the approximate shape rapidly and without having to pass through many local minima ... Although calculating the energy of the all atom molecule would be time consuming, one would have the great advantage of starting close to the right conformation ... The general concept of using a simple model . . . when the detailed forces are too complicated has many potential applications . . . Such a hierarchical approach might eventually lead to an understanding and simulation of very complicated biological assembly processes. "

Michael Levitt and Arieh Warshel

M. Levitt and A. Warshel. Computer simulation of protein folding. *Nature*, 253:694-698, 1975.

"[F]olding is an intrinsically statistical phenomenon and no conclusion can be derived from a single folding or unfolding trajectory. . . . Lattice and other simplified analytical models are the statistical mechanician's contribution to the protein folding . . . their intimate connection with statistical mechanics . . . is very important as it often allows us to compare simulation with statistical-mechanical analytical theories."

Eugene Shakhnovich

E. Shakhnovich. Modeling protein folding: the beauty and power of simplicity. *Folding and Design*, 1:50-54, 1996.

"The central question addressed in this review is this: Is there some clever algorithm, yet to be invented, that can find the global minimum of a protein's potential-energy function reliably and reasonably quickly? Or is there something intrinsic to the problem that prevents such a solution from existing? … Is there an approximation algorithm for global potential-energy minimization? … To our knowledge, the possible existence of an approximation algorithm for protein structure prediction has not been addressed … Such an approximation algorithm might be of significant practical use in protein-structure prediction, because exactness is not a central issue."

Martin Karplus

J. T. Ngo, J. Marks and M. Karplus. Computational complexity, protein structure prediction, and the Levinthal paradox. *In K. Merz, Jr. and S. Le Grant, editors, The Protein Folding Problem and Tertiary Structure Prediction,* chapter 14, Birkhauser, Boston, MA, pages 435-508, 1994.

"It is the mark of an instructed mind to rest satisfied with the degree of precision which the nature of the subjects permits and not seek an exactness where only an approximation of the truth is possible."

Aristotle 319 BC

Aristotle. In nichomachean ethics. *Oxford University Press*, B15-20:1112, 1959

"The exactness of mathematics is well illustrated by proofs of impossibility. When asserting that doubling the cube … is impossible, the statement does not merely refer to a temporary limitation of human ability to perform this feat. It goes far beyond this, for it proclaims that never, no matter what, will anybody ever be able to [double the cube]. No other science, or for that matter no other discipline of human endeavor, can even contemplate anything of such finality."

Mark Kak and Stan Ulam 1968

"For a quarter of a century now NP-completeness has been computer science's favorite paradigm, fad, punching bag, buzzword, alibi, and intellectual export… pervasive and contagious."

Christos Papadimitriou 1995

"[T]he true elegance of this consequence of natural selection was dramatized by the ribonuclease work since the refolding of this molecule after full denaturation by reductive cleavage of its four disulfide bonds ... required that only 1 of 105 possible pairings of eight sulfhyryl groups to form four disulfide linkages take place. ... to establish ... the "thermodynamic hypothesis." This hypothesis states that the three-dimensional structure of a native protein in its normal physiological milieu (solvent, pH, ionic strength, presence of other components such as metal ions or prosthetic groups, temperature, and other) is the one in which the Gibbs free energy of the whole system is lowest; that is, that the native conformation is determined by its totality of interatomic interactions and hence by the amino acid sequence, in a given environment."

Christian Anfinsen

C. B. Anfinsen. Principles that govern the folding of protein chains. *Science*, 181:223-230, 1973.