Editorial

A Conversation on Protein Folding

http://www.jbsdonline.com

When the paper on stoichiometry-driven protein folding by Mittal et al. (1) was published, I knew that it would become a controversial publication, bordering on revolutionary. The ideas, such as (i) no preferences are related to side-chain chemistry and (ii) notwithstanding size and 3D fold, the probability that two amino acids will be close together depends mainly on their percent populations, go against what is being currently practised and taught in biochemistry and molecular biology. Preferential interaction between amino acids is the basis of the development of knowledge-based potentials, which in turn form the underpinning of protein structure prediction by modeling and simulation, now routinely performed in many laboratories across the globe (2-5 and references therein).

It was very obvious that I should invite protein structural chemists to comment on the claims of Mittal et al. In my letter of invitation, I made it explicitly clear that their comments would not be subject to the normal peer review so that they could express their personal points, views, and evaluation of Mittal et al. without interference from the referees. This is perfectly fine because the comments themselves are not research articles which require mandatory peer evaluations, but just pure comments, and referees inserting moderation and balance into the comments is not right. These comments are brief items without abstracts, contain only a short list of references, and do not contain original research data. They are essentially open referee reports on Mittal et al. As Editor-in-Chief of the Journal, I thoroughly read each one of the comments; it was necessary to make certain minor editorial changes in a few of them so that all the comments were in resonance with the Journal format and mission. The comments are published without dates received and without the name of the Communicating Editor because they are not regular research articles. Finally this Journal is publishing the section consisting of this editorial, the 29 comments and the author response as Open Access. This is because this Journal strongly believes that doctoral students in biochemistry and molecular biology will benefit a great deal from a study of these comments; and Open Access publication enables this.

I have received comments from 29 laboratories across the globe. I thank all of them for reading Mittal et al. and expressing their opinion. I am particularly grateful to the senior and highly respected investigators in the discipline, Harold Scheraga, Cornell Univ., Brian Matthews, Univ. of Oregon, Alexei Finkelstein, RAS, Pushchino, Russia and Herman Berendes, Univ. of Groningen, The Netherlands for participating in this Conversation and providing their comments within the deadline.

Mittal et al. have written a single collective response to the 29 comments so as to avoid redundancy and to provide the response in a clear well structured setting. There is very little one could do about the repetition of a few items from comment

Corresponding Author:
Ramaswamy H. Sarma
Phone: 518-456-9362
Fax: 518-452-4955
E-mail: rhs07@albany.edu

Ramaswamy H. Sarma
Department of Chemistry, State University of New York at Albany, Albany NY 12222, USA
to comment. Nevertheless, the collection of comments and the author response form an engaging Conversation. Many of the commentators in their presentation have visited the literature on how protein folding evolved over the last 70 years. There have been interesting incidents in which a commentator answers certain questions raised by another commentator, even though commentators themselves had no previous notion of who was writing what. While several people were very critical of the Mittal et al. thesis of protein folding, to others it appeared like a fresh breeze with a novel perspective; even there were young investigators excited about potential development of biologically meaningful ab initio modeling, based on universal principle of stoichiometry. There were discussions of the evolution of the amino acids, a few evolving earlier than others, and how this might have influenced their distribution in the proteins. There was also the question of whether there was any relationship between the proportions of amino acids and their proportions in the codons. There are also people who believe that the organization and the hierarchical structure of the living system makes the living system unique, and that the molecular biology at the lowest level does not dictate the terms and conditions for the higher level.

References