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DISORDER AND FLEXIBILITY IN PROTEIN STRUCTURE AND FUNCTION

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In 1894 Fischer[1] wrote (as translated in[2]) "To use a picture, I would like to say that enzyme and glucoside have to fit to each other like a lock and key in order to exert a chemical effect on each other." This lock and key model, which has dominated thinking about interactions between proteins for more than one hundred years, came from the simple observations that invertase from beer yeast hydrolyzed α-glucosides but not β-glucosides, while emulsin hydrolyzed the β- but not the α-glucosides.

By 1936, Mirsky and Pauling[3] had assembled enough information to conclude, "The characteristic specific properties of native proteins we attribute to their uniquely defined configurations. The denatured protein molecule we consider to be characterized by the absence of a uniquely defined configuration." Thus, long before RNase had been renatured in vitro[4] and before the atomic resolution structures of myoglobin[5] and lysozyme[6] had been determined, a well-ordered, highly-specific 3 D structure was already accepted as the necessary prerequisite for protein function. More than 12,000 protein structures have been deposited into the Protein Data Bank[7] by now. These many structures continue to reinforce a rigid view of protein structure.

We are all aware that there has been a recent increase in emphasis in the importance of disorder and flexibility in protein function, but few of us are aware of the length of time these concepts have been incubating in the biochemical literature.

At the time of this writing, we are in the 50th anniversary of the first paper suggesting that an ensemble, rather than a fixed 3D structure, can be important for protein function. In 1950 (!) serum albumin was reported to exhibit competitive binding to many different small, hydrophobic anionic molecules differing markedly in their shapes. By exactly the same logic used for the lock and key, Karush inferred that the protein-ligand interactions stabilized the best-fitting member from an ensemble of structures in equilibrium; he called this phenomenon configurational adaptability[8]. Since 1950, hundreds of papers have been published indicating the importance of disorder and flexibility for protein structure and function, yet these ideas don't appear in any of the current biochemistry texts. We hope that our previous session in PSB'99 and this one in PSB'01 will help draw attention to this old, but now emerging area of research.

A. T. Alexandrescu, in "An NMR-Based Quenched Hydrogen Exchange Investigation of Model Amyloid Fibrils Formed by Cold Shock Protein A", describes a novel method for studying the intrinsic structural stability of model amyloid fibrils formed from acid-denatured cold shock protein A (CspA). The author applies a clever variation of the hydrogen exchange trapping experiment to probe the hydrogen bonding of the fibril aggregates. The results indicate that in the model CspA fibrils, all the amide protons are involved in stable fibril structure. Little information is known about the hydrogen bonding stability of the non-native amyloid fibrils and the new technique offers an important addition to the limited number methods available for investigating the structure and stability of aggregates.

A computational approach to the study of protein flexibility is presented in the paper, "Collective Reorientational Motion and Nuclear Spin Relaxation in Proteins" by J.J. Prompers, S.F. Lienin, and R. Brüschweiler. The authors describe the importance of collective reorientational motional models as they relate to the nuclear magnetic resonance spin relaxation of proteins. Since folded proteins are densely packed, the motions within the protein core are necessarily correlated to a degree, while motional processes within the flexible and surface residues will be impacted to a lesser degree by collective movements. Measures are presented for assessing whether collective motions the motions of a given protein fragment are affected more locally or more globally. Molecular dynamics simulations of the protein ubiquitin are used to illustrate these new measures of collective reorientational motions. This subject if of great interest to the interpretation and analysis of NMR spin relaxation data since the motional processes within proteins significantly impact the nuclear spin relaxation parameters.

The last paper in this session, "The Protein Non-Folding Problem: Amino Acid Determinants of Intrinsic Order and Disorder" by R.M. Williams, Z. Obradovic, V. Mathura, W. Braun, E.C. Garner, J. Young, S. Takayama, C. J. Brown, and A.K. Dunker, reports the compilation of larger databases of structurally characterized, intrinsically disordered proteins than were heretofore available.

These data were used to study correlations between amino acid compositions and attributes with intrinsically ordered and disordered protein. A little-used attribute that is a measure of “side chain packing capacity” turns out to be the best discriminator between ordered and disordered sequences, while the much more widely known hydropathy does only slightly less well.

Overall, this session promises to add to our understanding of intrinsically disordered proteins.

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