

Structural Defects as Signals for Molecular Disease**Fernandez, Ariel****Institute for Biophysical Dynamics, University of Chicago, Chicago, IL, USA; Indiana University School of Informatics, INGEN-Center for Computational Biology and Bioinformatics, Indianapolis, IN, USA**

Biology's sustaining matrix is essentially water. Being a formidable hydrogen-bond former, water is also an "unforgiving" solvent: It attacks overexposed intramolecular hydrogen bonds of protein structure. For intramolecular hydrogen bonds to be primary determinants of structure, as Pauling first noticed, they must be well protected from water attack, and that protection may be achieved intramolecularly, or intermolecularly through complexation or association with ligands (1). In fact, a poor over-all fulfillment of this building constraint has proved to be a clear signal guiding a structure-based diagnosis of propensity for aberrant or amyloidogenic aggregation (2,3). Thus, this picture imposes a severe constraint on biologically admissible structures. At the same time, it is enriched by a crucial fact: under-protected (or under-desolvated) hydrogen bonds are actually *adhesive*: they favor removal of surrounding water as a means to enhance the amide-carbonyl electrostatic interaction, and thus may drive ligand binding or protein-protein association (4). A systematic study of this building constraint, and its role in biological function and molecular disease constitutes the main thrust of my research. Accordingly, I introduced a new category, the *wrapping*, which is built upon protein structure but differs from it. The wrapping assesses the extent of intramolecular desolvation of backbone hydrogen bonds in protein structure and, based on statistical regularities in the PDB, identifies under-wrapped - inherently adhesive - hydrogen bonds, now termed *dehydrons*. The adherence of dehydrons opens up an entire avenue to understand and predict disease-related mutations from a structural biology perspective: The key to success in such an endeavor lies in relating mutations in sequence to the formation or suppression of dehydrons in the structure. Because dehydrons are easily identified from structural databases (1-3), the wrapping concept is ideally suited to be investigated within a "structural bioinformatics" endeavor. Specifically, to deal with the molecular basis of disease from a structural biology perspective, I am investigating the "derivative" of wrapping with respect to mutation. The main question I am currently addressing is: *Where is the wrapping of soluble protein structure most affected by a point mutation in the sequence?* This problem prompted me to introduce a "wrapping susceptibility", a quantifiable measure of the functional consequences of mutation stemming from a dramatic alteration in the level of exposure of intramolecular hydrogen bonds. An extreme susceptibility of wrapping to genetic accident may be a signature for cancer, as my recent preliminary investigation of HCAP (human cancer-associated protein database) suggests, while p53 appears to be the molecule with the highest wrapping susceptibility in the entire PDB. The "extreme susceptibility hypothesis" paves the way to investigate cancer from a structural biology perspective.

References

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