



Epistruktural Biology

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Editorial

Biological matter is different from other forms of soft matter in at least three main ways: a) The material presents an aqueous (or lipidic) interface, b) It forms complexes but does not “precipitate” or aggregate into homogeneous phases unless it becomes dysfunctional, and c) There is an obvious evolutionary dimension associated with it, as biological matter is so specialized that it cannot be fully understood without taking into account its evolutionary history. These three aspects are intimately interrelated, as we shall presently show, and cannot be overlooked when discussing biological matter because they are inherent to it. Perhaps less obviously, these aspects are also of paramount importance when implementing rational strategies for drug design, as drugs usually take the form of ligands that target soluble proteins or other biological materials blocking their functions. As the interrelations among the three distinctive aspects of biological matter are discussed, unique and insightful approaches will emerge that the physicists and molecular engineers may pursue when exploring the evolutionary dimension [1].

Drug design is often geared at impairing specific dysregulated functions, and therefore, it regards soluble proteins as its primary targets. On the other hand, when examining the evolutionary dimension of biological matter we notice that different cellular functions are often performed by proteins with common ancestry, the so-called paralogs or same-species homologs, whose structural similarity is uncanny. This structural similarity brings about innumerable challenges to the drug designer, especially if he/she adopts the standard structure-based approach to discovery, as undesired cross-reactivity causing side effects are likely to arise. On the other hand, the functional innovation along a given homology resides mainly in the differences in the aqueous interface of paralog proteins, in the so-called epistruktural, rather than in the structure itself. In other words, the epistruktural is the molecular dimension explored by evolution to enable functional innovation and achieve proteomic complexity and the drug designer may target epistruktural differences to control specificity in the therapeutic treatment, telling apart therapeutically relevant targets from those likely to cause side effects.

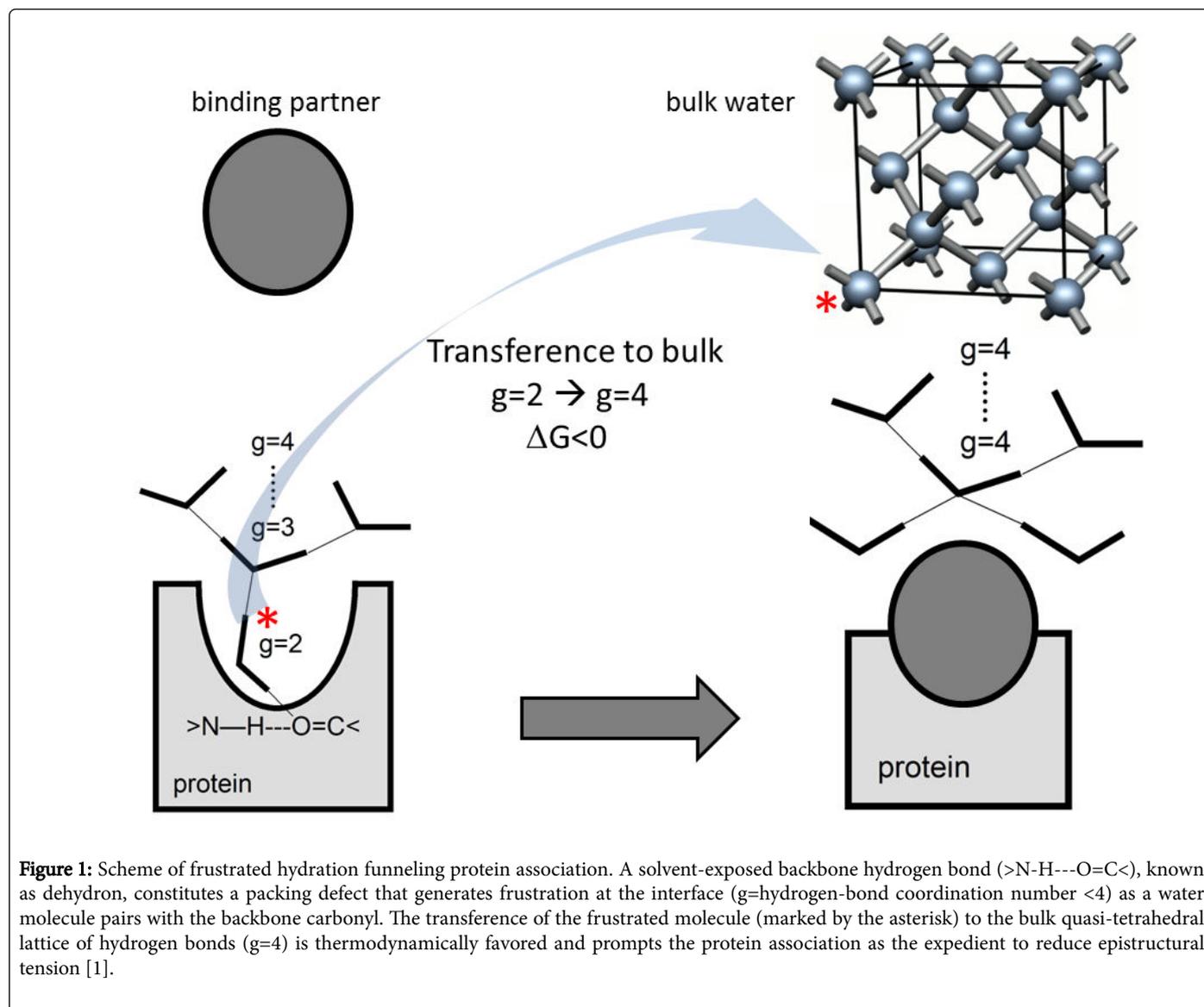
Taken together, these observations seem to be prompting a paradigm shift that would readily supersede the well-established structure-function dichotomy except that the epistruktural is determined by the structure, or rather by the peculiar and poorly understood interrelation between structure and solvent. The epistruktural has an interfacial tension associated with it, i.e., the free energy cost of spanning the protein-water interface per unit surface area. This tension has been shown to be unevenly distributed along the protein surface, creating “hot spots” when water becomes significantly

frustrated in its hydrogen bonding coordination capabilities. These hot spots correspond to packing defects in the protein structure known as dehydrons that provide nanoscale water confinement and therefore become primary promoters of protein associations (Figure 1). Thus, the epistruktural tension is mitigated through protein associations that essentially “correct” the packing defects. In aberrant cases, the epistruktural tension may promote aggregation but this takes place only when the tension is high enough to destabilize any tertiary structure that the protein chain may adopt temporarily.

As stated above, the epistruktural of a protein is not conserved across homologs, notwithstanding the fact that the structure tends to be highly conserved. Furthermore, the dehydrons, the structural features that determine the epistruktural and serve as markers of protein association, are endowed with the potential to functionalize interfacial water, turning it into a chemically competent species capable of acting as a proton acceptor. Thus, the epistruktural plays a crucial role in the mechanisms of enzymatic reaction besides mediating the most elementary molecular processes in biology, i.e., protein associations. These observations suggest that the epistruktural may be the central object from where all three unique attributes of biological matter stem: the epistruktural enshrines the interfacial dielectric structure, is endowed with catalytic functionality, and acts as a marker for molecular evolution, for biomolecular complexation and for aberrant aggregation.

This picture suggests that if the physicist or molecular engineer decides to explore the evolutionary axis, the epistruktural, rather than the structure, may provide the right focus. On the other hand, it is well known that epistruktural differences across paralogous proteins have already been exploited to design safer and more potent drugs with controlled selectivity against therapeutically relevant targets.

Epistruktural biology is thus an emerging discipline that may well revolutionize molecular biophysics and pharmaceuticals, especially if a nanoscale theory of water dielectrics is satisfactorily developed to handle the interrelation between dehydron-induced frustration of water coordination and dielectric modulation. From the informatics perspective, a new “omic” resource, the epiproteome, or universe of protein dehydron patterns associated with a given species, will emerge. The annotations to the epiproteome will depend pivotally on the development of a cogent theory of interfacial dielectrics that captures the interplay between frustration, biomolecular association and biochemical function. Once enriched with interfacial annotation, the epiproteome will become paramount to pursue the biophysical, pharmacological and functional-ontological studies along the evolutionary dimension.



References

1. Fernández A (2016) Physics at the Biomolecular Interface.