Proteins with Novel Structure, Function and Dynamics

Andrew Pohorille
Exobiology Branch, NASA Ames Research Center

Recently, a small enzyme that ligates two RNA fragments with the rate of 10^6 above background was evolved *in vitro* (Seelig and Szostak, Nature 448:828-831, 2007). This enzyme does not resemble any contemporary protein (Chao et al., Nature Chem. Biol. 9:81-83, 2013). It consists of a dynamic, catalytic loop, a small, rigid core containing two zinc ions coordinated by neighboring amino acids, and two highly flexible tails that might be unimportant for protein function. In contrast to other proteins, this enzyme does not contain ordered secondary structure elements, such as α-helix or β-sheet. The loop is kept together by just two interactions of a charged residue and a histidine with a zinc ion, which they coordinate on the opposite side of the loop. Such structure appears to be very fragile. Surprisingly, computer simulations indicate otherwise. As the coordinating, charged residue is mutated to alanine, another, nearby charged residue takes its place, thus keeping the structure nearly intact. If this residue is also substituted by alanine a salt bridge involving two other, charged residues on the opposite sides of the loop keeps the loop in place. These adjustments are facilitated by high flexibility of the protein. Computational predictions have been confirmed experimentally, as both mutants retain full activity and overall structure. These results challenge our notions about what is required for protein activity and about the relationship between protein dynamics, stability and robustness. We hypothesize that small, highly dynamic proteins could be both active and fault tolerant in ways that many other proteins are not, i.e. they can adjust to retain their structure and activity even if subjected to mutations in structurally critical regions. This opens the doors for designing proteins with novel functions, structures and dynamics that have not been yet considered.