On the origin of symmetry in biological macromolecules

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The high symmetry of protein-protein interactions has fascinated biologist since it's was first inferred by Watson and Crick from the x-ray scattering of icosahedral viruses. There are two levels of preference: homo-polymers may be preferred over hetero-polymers and among homo-polymers symmetric forms may be preferred over asymmetric forms. Proposed explanations of this anecdotal preference for homo polymer symmetric complexes include parsimony, symmetric force fields, and greater surface area remaining for active sites. Those explanations either presuppose symmetry from the start, or impose it as a consequence of biological imperatives. Recently it has been suggested thermodynamics and kinetics alone might prefer homo-dimers over hetero-dimers.

Our hypothesis is that the origin of both homo-polymer preference and symmetry preference may be simple consequence of energy-based selection and thus a universal phenomenon. Here we use quantitative protein modeling to investigate the energetics of docking in homo-dimers and show that the population of low energy dimers is almost entirely symmetric. Hence selection for function in primordial protein complexes should give rise to dominantly symmetric species.

This is an elegant example of theory development from quantitative modeling since experimental observation of the symmetry of fleeting interactions of proteins in conformations above their binding energy is not possible. Instead computational protein structure modeling allows us to quantitatively determine the energy of interaction of proteins in arbitrary orientations and thus by simulation find the energy distribution as a function of symmetry.

We also reduce the anecdotal preference for symmetry to quantitative fact. Here we invent a measure of partial symmetry--the degree of deviation from perfect symmetry-- and compare the degree of symmetry in natural protein homo-dimers to the expected degree of symmetry in random homo-dimer complexes.