From Molecules to Cells – Whole Cell Simulations

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One of the outstanding problems in biology is the elucidation of the relationship between the structure and function of individual molecules and the emergent properties characteristic of cells. We explore these issues on three levels: First, the nature and completeness of protein structure space is examined, and we show that the space of single domain protein structures is likely complete, highly connected and above the percolation threshold. Similarly, we show that the space of protein-protein interfaces is comprised of ~1000 statistically distinct interfaces and is almost complete. These features of protein structures emerge due to the packing of compact hydrogen bonded secondary structural elements and do not require evolution. Next, we describe FINDSITE/FINDSITE^{LHM} a threading based method for the prediction of protein function including binding site identification and virtual small molecule ligand screening that generalizes homology modeling ideas to ligand screening and the use of conserved side chain heavy atoms in contact with the conserved ligand substructure for protein binding site refinement. We then apply the resulting methodology to the human kinome and describe results for the prediction of off-target interactions that are significantly correlated with experiment. Finally, we describe schematic molecular simulations of a model of an *E. coli* cell designed to elucidate qualitative aspects of the nature of intermolecular interactions describing the diffusive behavior of macromolecules in the cellular milieu.