How Good Do We Have to be to Solve the Protein Folding and Protein-ligand Scoring Problems?

Professor Kenneth M. Merz Jr.
Colonel Allan R. and Margaret G. Crow Term Professor
University of Florida
Department of Chemistry
Quantum Theory Project
2328 New Physics Building
P.O. Box 118435
Gainesville, Florida 32611-8435
merz@qtp.ufl.edu

Computational Chemistry/Biology is now a well-established field with numerous significant successes to show for several decades of effort. Nonetheless, several challenges remain both from the computational/theoretical and experimental perspective. This talk will touch on several of these challenges and suggest ways in which to overcome them in the coming years. In particular, we will touch on the establishment of error bounds in computational prediction of the free energy of binding of a ligand for a protein target and the folding free energy of a protein and how this affects the outcome of absolute *versus* relative energy computations. Through the formation of probability distribution functions based on CCSD(T)/CBS reference energies we show that computed interaction energies, by multiple methods, typically have significant systematic as well as random errors. Detailed analyses of NDDO based methods, force fields, density functional theory, Hartree-Fock and correlated methods will be presented. Based on these insights we will discuss what future research directions will have the most impact in ultimately leading to the solution of the *ab initio* protein folding and *in silico* drug design problems.