

The use of conformational memories in the study of peptide conformations and peptide-protein interactions

Rob Whitnell  
Professor of Chemistry  
Guilford College

The conformational memories (CM) method of Guarnieri, Weinstein, and Wilson uses a combination of Monte Carlo techniques and simulated annealing to explore completely and efficiently the dihedral conformational space of peptides and small proteins. CM has been shown to be successful in exploring the conformations of peptide hormones such as GnRH and small molecules such as anandamide, an endogenous ligand of the CB1 cannabinoid receptor. CM has also been successfully used to develop models of several G-protein coupled receptors (GPCR), providing structural explanations for the results of experiments on receptor activation and ligand binding. We discuss two extensions of the CM method that we have done in collaboration with Prof. Patti Reggio's group at UNCG. First, we describe varying bond angles in CM in addition to dihedral angles, thereby substantially increasing the conformational space that can be explored without any noticeable loss of efficiency. Second, we describe the extension of CM to use inhomogeneous environments, both implicit environments such as the membrane model of Lazaridis that can model the environment around GPCRs and explicit-atom environments such as in the interaction of a peptide with the surface of an antibody. We present results from the extended CM calculations for several systems: more complete exploration of significant local energy minima in the pentapeptide Met-enkephalin; calculations on helix 7 of CB1 that provide better exploration of intrahelix hydrogen bonding in agreement with experimentally validated conformations; and studies of the binding of the gp41 heptapeptide epitope to the HIV-1 neutralizing antibody 2F5 that give evidence for the role of key water molecules in mediating the epitope-antibody interactions.