Our laboratory is using molecular mechanics programs (DISCOVER and INSIGHT) developed by Biosym Technologies, Inc. to simulate the interactions of proteins with polymer surfaces. Biosym's software is installed on the Silicon Graphics 4D/70GT workstation. In the first part of the simulation, crambin (642 atoms) was used to evaluate the performance of DISCOVER and the SGI computer. Hydrogen atoms were included in the molecular models to maximize the effectiveness of the simulation. Consistent valence force field (CVFF) and AMBER force field parameters were compared in the minimization of the crambin model. Several minimizations *in vacuo* were performed with CVFF, and the results were consistent with earlier reports of simulations performed with AMBER force field and united atom models.[1]

Efforts are under way to perform molecular dynamics with crambin in the periodic boundary conditions with water molecules. An important part of the analysis is the examination of the interaction of water molecules with the surface atoms of crambin. Structure and number of water molecules were determined for hydrophobic and hydrophilic surfaces. Solvent-accessible areas were calculated and correlated with experimental results. In the second part of the simulation, individual molecules of alkanes of various lengths were placed in the periodic boundary conditions. It was shown that primary coordination numbers for alkanes were in close agreement with results obtained previously with united atom models.[2] Other published results showed that a water molecule separated two noble gas atoms, and a methane molecule from the hydrophobic surface. Our goal is to demonstrate the hydrophobic effect more definitely with larger nonpolar molecules, such as octadecane. These results will be compared with those obtained for polyethylene oxide, a water-soluble polymer. In the future, we plan to study the solvated protein-polymer system. Although various questions concerning simulation conditions still need to be answered, growing efficiency in computer programming and hardware will make simulation of a complex molecular system practical.

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DNA As a Target for Drug Action

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DNA is a structurally well-characterized molecule, but its large size and seemingly repetitive nature make it an elusive target for selective drug action. However, some of the more clinically important antineoplastic agents (e.g., cisplatin, adriamycin and cyclophosphamide) are thought to exert their toxic effects by reacting with DNA in the tumor cells.

Proteins such as repressors and endonucleases have evolved to attain a remarkable selectivity of binding to predetermined sequences. Likewise, several low-molecular-weight ligands are known to bind to certain regions in DNA in preference to others. But the question remains in this case whether and how the binding is linked to an effective pharmacological (drugs) or toxicological (carcinogens) response.

Interaction of drugs and a target site in DNA can result in chemical cleavage, steric blockage of enzymes, prevention of the conformational changes required for protein binding and/or other long-range effects.

Computer graphics and theoretical calculations are helpful in our understanding of the molecular basis for sequence-specific recognition of DNA by drugs[1,2] and also to explore the ability of DNA to adopt different types of unusual conformations[3] in special circumstances.[4]

Molecular mechanics calculations provide binding enthalpies rather than free energies, and they often ignore solvation effects.[1,2] The problem can sometimes be formulated in terms of differences in free energy of binding, which can be checked against available experimental data[5] (e.g., netropsin binding to poly[d(GC)]·poly[d(GC)] and poly[d(IC)]·poly[d(IC)]). One can slowly mutate the inosine bases into guanine bases in the complex poly[d(IC)]·poly[d(IC)]-netropsin with the solvent molecules explicity considered. By comparing the changes in energy associated with this perturbation with those from the perturbation of the free oligonucleotide in solution, it is possible to derive the difference in free energy of binding to both sequences.

A chemically modified DNA is a potential substrate for DNA repair processes, the best studied of which are those responsible for removal of photoproducts caused by UV light.[6] Questions relating to DNA damage recognition and how to avoid repair will probably become increasingly significant in drug design.

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