A. Introduction to Molecular Mechanics and Molecular Dynamics

Modeling and computational chemistry are important parts of modern biochemistry. Modeling is important to display in a meaningful and instructive fashion the large amounts of data produced when x-ray crystallography and NMR are used to determine the structure of large biological molecules and complexes. Remember, however, that primary x-ray crystal data (in the form of electron density maps) are just that, and the data must be interpreted like any other type of data. Structures need to be refined and energy minimized to produce more realistic structures (without van der Waals overlap or missing atoms, for example). In addition, atoms within any molecule are not static, but move as bonds vibrate, angles bend, etc. This implies that large biomolecules could adopt many possible conformations of different energies. For proteins, some of these conformations might center around a few average conformations situated at a local or global energy minimum separated from each other by activation energy barriers.

In contrast to small molecules whose structure can be minimized using ab initio or semi-empirical quantum mechanics (using programs such as Spartan), large molecular structures (like DNA, RNA, proteins and their complexes) must be minimized using molecular mechanics, based on Newton's laws. Atoms are treated as masses, and bonds as springs with appropriate force constants. A force field, containing all the relevant parameters for given atom (for example sp3, sp2, sp2 aromatic, and sp C) and bond types is used to solve energy equations which sum all energies over all atoms and bonds in the molecule. These energies include interactions among bonded atoms (stretching, bending, torsion, wagging) and those among nonbonded atoms (electrostatic and van der Waals). For minimizations calculations, the positions of the atoms within a molecule must be systematically or randomly moved and the energy recalculated with the goal of finding a lower energy and hence more stable molecule. Minimization calculations can not probe all conformational space and can not easily move a structure from a local minimum to a global minimum if two are separated by a large energy barrier. Energy minimizations are usually done in the absence of solvent. A common force fields used for macromolecules is CHARMM, AMBER, and GROMOS. Parameters for specific atom type in a given bond include atomic mass, van der Waals radius, partial charge for atoms (from quantum mechanics) and bond length (from electron diffraction data), angles, and force constants for bonds (modeled as springs, obtained from IR).
parameters are derived from experiments and theoretical (usually quantum mechanical) calculations on small organic molecules. A potential energy equation comprised of terms from bond stretching, angle bending, and torsion angle changes (bonded interactions) as well as electrostatic and van der Waals interactions (nonbonded) is then solved (described below).

The goal of molecular dynamics is to simulate the actual changes in a molecule as a function of time after an energy input (heat application at a higher temperature) is added to a molecule at equilibrium. To make the simulation realistic, the structure is placed in a "bath" of thousands of water molecules. As is described below, if the energies of atoms in a large molecule are known, the forces acting on those atoms can be deduced. From Newton's Second Law (F=ma), the velocity or change of position of an atom in the structure with time can be determined. If the dynamic simulation can be run for a long enough period of time, alternate conformations (perhaps those centered around a global minimum as well as those nearby in energy space - a local minimum) may be sampled. By determining what fraction of the simulated conformations resemble the two alternative conformations, the ΔG for the interconversion of the two states can be calculated. As you can imagine, these calculations require large amounts of computer time. They give very important information, however, since protein conformational changes are often, if not always associated with binding of a biological molecule to a binding partner. In silico experiments offer important clues and support to results obtained using other methods of study.

Molecular mechanics (MM) and molecular dynamics (MD) has become a powerful tool in analyzes and predicting properties of complex biological structures. The Noble Prize in Chemistry in 2013 was awarded to Martin Karplus, Michael Levitt and Arieh Warshel "for the development of multiscale models for complex chemical systems". Karplus in particular developed much of the present basis for MD simulations.

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