Molecular-dynamics Simulations of Biological Systems

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One of the main tools for studying biological molecules is the method of computer modelling based on molecular dynamics (MD)[1, 2, 3]. MD simulations provide detailed information about the fluctuations and conformational changes of proteins and nucleic acids. This method is routinely used for investigations of the structure, dynamics and thermodynamics of biological molecules and their complexes. In the literature, results of MD simulation of proteins dissolved in water, protein–DNA complexes and lipid systems, dealing with various aspects of the thermodynamics of ligand binding and folding and packaging of relatively small (short) proteins are continually published. Nowadays, there are many specialized techniques for solving particular problems, including those listed above, which take into account quantum-mechanical effects as well. The MD modelling technique is also widely used for determining the spatial structure of biological molecules by analyzing the information obtained by means of X-ray diffraction and nuclear magnetic resonance.

With the help of computer simulations usually two classes of problems are addressed. The first one is constructing a computer model of the behaviour of a given protein in order to study its interactions with other proteins, RNA or DNA. These models provide valuable information about vital processes occurring in the cells or in the inter-cellular space. The second class of problems is studying the interaction of a protein with small molecules (ligands) that are able to block its biological activity when bound to it in a stable complex. This is the classic situation in the search of new drugs.

Quantum mechanics describes atomic and molecular systems with high accuracy, if the Schrödinger equation can be solved. Unfortunately, this is only possible under significant simplifications and for systems with a small number of atoms. Biological molecules do not fall in this category – they are extremely complex and consist of huge number of atoms that makes their exact treatment at quantum level practically impossible. Certain approximations are indispensable in studying biomolecules and their dynamics.

Since the mass of the atom is practically concentrated in its nucleus, it is assumed that the nucleus motion complies with the laws of classical physics, while the electrons follow it almost instantly (within times of the order of attosecondes). This permits a classical treatment of the problem provided covalent bonds in the molecules are properly parametrized.

Molecular mechanics describes atoms (nucleus and electrons around it) as point charges with masses, proportional to their atomic number. To each atom are attributed radius (Van-der-Waals radius), polarizability and electric charge, determined by quantum-mechanical calculations or based on measurements. Interactions between atoms (covalent chemical bonds and electrostatic interactions) are represented as $V = \sum_j V_b + \sum_j V_a + \sum_j V_d + \sum_{i,j} V_{i,j} + \sum_{i,j} V_c$, where V_b, V_a, V_d parametrize the chemical bonds (strength, angels and torsions between bonds) with oscillator-like (harmonic) potentials which allow oscillations of the atoms around their equilibrium states. Non-covalent interactions are described by two two-body potential terms — $V_{i,j}$ and V_c, taking into account Van-der-Waals and Coulomb interactions.

In order to track the dynamics of the bonding processes of the biological molecules and the behaviour of proteins under certain conditions (folding, changes in the conformation, etc.) it is necessary to know the time evolution of coordinates and velocities of all atoms in the system. For this purpose, with a given potential (force field) and initial positions and velocities of the atoms, we have to solve numerically the equations of motion (Newton's equations) for the system $m\frac{v(t)}{dt} = -\frac{dV(x)}{dx}$ and $\frac{x(t)}{dt} = v(t)$, where x and v are coordinates and velocities of the atoms. Solutions give us the values of the coordinates and the velocities at discrete times. The time step in most of the calculations is of the order of 1-2 femtoseconds. Thus the trajectory of the system is built. Since the processes of formation of bound states of molecules or the change in their conformation happen relatively fast, in most cases it is sufficient to build trajectories from a few tens of nanoseconds. For large systems (e.g., in studying protein binding in water solution i.e. hundreds of thousands of atoms) the construction of such trajectories takes days or weeks using the most powerful supercomputers. The same applies for studying slow processes, which span over micro- or miliseconds, even for small molecules.

The only way for verifying molecular-dynamics simulations is the comparison with the experiment. In the experiments, we can measure macroscopic thermodynamic characteristics of the system — energy, temperature,

pressure, etc. Thus, it is necessary to compute these characteristics from the microscopic data obtained in the simulations. These calculations are subject to statistical mechanics and are based on the assumption that the time average of the physical variables coincide with the values obtained by averaging over the corresponding statistical ensemble (the ensemble average).

One of the main problems, which is solved by molecular mechanics, is calculation of the free energy of the system and its minimization. This allows to determine the stable conformations of the system, potential binding centers (they correspond to local potential minima) and to assess the probability of binding two molecules into a stable complex. While exploring the conformation space, the system can be trapped in a local minimum and it takes long time to get out of it. Special methods for enhanced sampling of the conformation space have been developed, metadynamics [4,5] and replica exchange MD [6] among them, that help solving this problem.

In the case of slow or with a low probability processes, a speed-up of the computations can be achieved by the so-called coarse-grain simulations [7], where a simplified physical model is built by grouping certain atoms and treating them as a single effective object. This method is highly efficient in building long MD trajectories.

In this talk, the physics basics of MD simulations will be presented. The power of the method will be demonstrated on the example of investigation of human interferon-gamma interactions with its extracellular receptors [8]. The advantage of the enhanced sampling methods will be illustrated with the investigation of artificially mutated interferon-gamma variants [9] (metadynamics) and prion folding (replica exchange MD). The investigation of the mechanism of cellular membrane penetration by antimicrobial peptides will be used as a test bed for the effectiveness and reliability of the coarse-grain MD simulations.

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