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Molecular Dynamics: The Computational Molecular Microscope

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Advanced technologies in molecular biology and modern experimental biophysics heavily rely not only on the knowledge of structure of essential proteins but also on their structural dynamics. The function of these bimolecular systems and the pathways along which the biological phenomena take place can be determined based on the knowledge of the molecular structure and behavior. As such, the simple view of rigid biological structures could not adequately describe the intra-molecular motions and their essential role in conformational changes that are critical to the function. Molecular dynamics simulation offers a computational microscope allowing us to visualize the motion of molecular systems at high spatial and temporal resolutions, thereby providing new opportunities for developing a deeper understanding of the dynamics of biological systems at atomic resolution where no experimental microscope is currently applicable.

Keywords: Molecular Dynamics Simulation; Computational Biology; Structural Bioinformatics

1. Introduction

Over the past decades, the structures of a large number of essential proteins have been characterized using advanced molecular biological and biophysical techniques. Various structural biological and imaging techniques including nuclear magnetic resonance (NMR), electron microscopy (EM), and x-ray crystallography have enabled us to obtain the exact position of atoms within a molecule. Among these methods, x-ray crystallography has been most successful in yielding atomic structures of bimolecular systems; however, the functionally relevant structure of molecules may be affected during the crystallization process (1).

While x-ray crystallography can recognize a single structural state of a macromolecule, NMR has the advantage of providing structural information on multiple structural states in solution, with no undesired structural effects. NMR, however, is currently restricted to relatively small biomolecules. Consequently, some of the most physiologically important macromolecules such as membrane proteins remain inaccessible by the method (2). The crystallography techniques help to define the products of bimolecular interactions and conformational states under certain physical and/or chemical conditions. But the mechanistic details of the interactions or the nature of conformational changes involved in the function are still unreachable by the method (1). Several alternative experimental biophysical methods have been developed to determine whether or not a conformational change takes place, however the atomic details of the molecular mechanism are still largely inaccessible experimentally (3, 4).

It is currently widely accepted that characterizing molecular behavior of biological systems is necessary to understand their function. Most areas in biomedical sciences are affected by discoveries of the molecular mechanisms which are keys to control and regulation of the biological phenomena (4). In the absence of experimental methods with sufficiently high resolutions, theoretical methods offer an alternative route to explore molecular systems. Molecular dynamics simulations offer such a technique in which the molecular motion can be characterized at very high temporal and spatial resolutions, simultaneously. Knowing the initial positions, velocities, and interaction forces of all particles (atoms), these properties can be calculated for a later time using essential physics rules (5).

Molecular dynamics can be viewed as a part of an an interdisciplinary field, collectively referred to as computational biology, which has been formed based on theoretical biophysics and biochemistry, extending over the areas of computer science, mathematics, statistics, molecular biology, genetics, evolution, and visualization. Molecular dynamics simulations have been found very effective to investigate various bimolecular systems at an atomic resolution, yielding molecular pathways underlying the events and processes fundamental to biological function. Given the information offered by these technologies, the knowledge acquired by computational studies (so called

in silico studies) is highly complementary to what originating from experimental approaches, together resulting in a more complete picture of the mechanism of function of bimolecular systems (6).

2. Molecular Modeling

Molecular modeling spans a wide spectrum of studies ranging from determination and visualization of atomic coordinates of a molecule, to highly accurate and advanced molecular simulations of complex bimolecular systems using the laws of physics. Prediction of molecular behavior has played a significant role in modern molecular research, such as characterization of biosynthesis pathways, interaction between molecules (e.g. receptor-ligand docking), initiation mechanisms of a biochemical phenomenon and so on.

Molecular modeling techniques allowing one to calculate the atomic coordinates based on the NMR and/or a crystallographic picture are well-established in molecular imaging. A great area known as "molecular simulation" relates to the use of molecular modeling techniques to determine the movements and behavior of the molecules at an atomistic scale (6).

3. Molecular Dynamics Simulation

Molecular dynamics (MD) is a mimic of the physical movements of atoms and molecules, realized by solving the equations of motion for all atoms comprising a molecular system. The three dimensional models of the molecules are constructed considering their physical properties, such as atomic diameters, electric charges, bonds connecting atoms, as well as bond angles and dihedrals. Using potential energy functions derived from classical molecular mechanics, the interaction of atoms and molecules are calculated for a period of time, giving a view of the motion of the atoms (7).

The potential energy of non-bonded interactions between atoms as well as intra-molecular energies including the energies of the bonds, bond angles, and torsion angles are calculated considering the environmental factors such as temperature, pressure, viscosity and the pH. Having specific rules to calculate the potential energy, the next step is to calculate the force vectors that define the direction and distance of movement during a specific time unit referred to as the time step (1). In each time step, all simulated particles move to their new positions, which will be then used as the initial points for the force calculations in the next time step. The paths of the movements of atoms (trajectories) which are resulted by numerically solving the equations of motion will be saved for analysis. Visualizing programs can then be used to display and analyze the trajectory of the simulation (6, 7).

MD simulations allow us to view and study the details of dynamic processes that occur in biological systems on timescales ranging from picoseconds to microseconds (7). MD can be utilized in a variety of biological studies (4, 6, 7), such as:

- Protein structure prediction (*ab initio* prediction)
- Protein conformational changes under specific conditions
- Mechanistic studies of substrate movement in membrane channels, transporters.
- Protein folding kinetics and pathways
- Receptor-ligand interaction
- Molecular interaction between proteins, DNA, membranes.

4. Verification and Analysis of MD Simulations

MD results have been verified for a variety of molecular systems by comparing the detailed experimental measurement of homogeneous systems such as a box of water (8). The final molecular conformation predicted by MD also closely mimics the known crystallographic images. The objectives of the analysis of MD trajectories are to verify if the simulation has run successfully, to measure critical properties of the molecules, and to compare certain changes. In order to perform these analyses, we may apply several methods (1, 6, 7):

- Looking at the trajectory (visualization)
- Evaluation of the structural changes and comparison to the initial situation using root mean square deviations (RMSD) and fluctuations (RMSF)
- Evaluation of folding using radius of gyration (Rg)
- Comparison of the hydrogen bonds, effects and changes during the simulation
- Analysis of the secondary structure changes
- Free energy and interaction energy calculations
- Analysis of the protein backbone PHI/PSI angles (Ramachandran plots).

5. Conclusions

The simple view of rigid molecular structures can not describe the intra-molecular motions and their essential roles in conformational changes and protein function, aspects that are very difficult to characterize on the lab desk using current experimental methods. Dynamic models represent powerful tools for understanding the basis of the function of biological macromolecules which is hard to explore in nature. Making a dynamic image of a molecular system helps to understand the pathway between known molecular conformations. Considering the rapid and continuing improvement of supercomputing facilities, MD simulation, which is viewed as a computational microscope, is expected to reach a more significant position for exploration of larger biological systems and on longer time scales, where no microscope is currently applicable experimentally.

Authors' Contributions

Who was responsible for: study concept and design: Dr. Kalani; acquisition of data: both authors; drafting of the manuscript: Dr. Kalani; critical revision of the manu-

script for important intellectual content: Dr. Tajkhorshid; study supervision: Dr. Tajkhorshid.

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