

# Chapter 40

## Molecular Dynamics Simulations for Biological Systems

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### ABSTRACT

*Molecular dynamics simulation is an important tool to capture the dynamicity of biological molecule and the atomistic insights. These insights are helpful to explore biological functions. Molecular dynamics simulation from femto seconds to milli seconds scale give a large ensemble of conformations that can reveal many biological mysteries. The main focus of the chapter is to throw light on theories, requirement of molecular dynamics for biological studies and application of molecular dynamics simulations. Molecular dynamics simulations are widely used to study protein-protein interaction, protein-ligand docking, effects of mutation on interactions, protein folding and flexibility of the biological molecules. This chapter also deals with various methods/algorithms of protein tertiary structure prediction, their strengths and weaknesses.*

### INTRODUCTION

It is difficult to perform each and every experiment practically. For example, before going for any mission astronauts are well trained and for that training they are exposed to similar kind of climatic conditions and difficulties that they expect to face on their mission. So, for these kinds of training the spatial conditions were imitated at small scale in the training centre of the space agency. Similarly, imitating conditions of real life is defined as modelling and simulation is used to visualise the operation of the model over time. These techniques give the idea of behaviour of real systems in different scenario and the way they would adapt to these conditions. Here main thrust area of the discussion is computational Molecular Dynamics (MD) Simulation of biological system where large scale computations are used to simulate the biological behaviour.

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MD Simulation is an approach that gives the opportunity to explore the assemblies of molecules at microscopic level and their kinetic behaviour with time which is not possible to decipher from conventional experiments (Alder & Wainright, 1959). Biological systems are very complex and the functions of cells mainly depend on various possible interactions that further depends on its three dimensional structure (Alberts et al., 2002). Being dynamic, the functions of bio-molecules also depend on various kinds of motions (Karplus & McCammon, 2002; Wynsberghe, Van, Chen & Cui, 2008). Biological molecules exhibit a wide range of time scales over which different specific processes occur. Among these atomic fluctuations, side chain motions and loop motions come under local motions (0.01 to 5 Å) which generally takes  $10^{-15}$  to  $10^{-1}$  s to finish. The processes for example, helix motions, domain motions (hinge bending), and subunit motions come under rigid body motions (1 to 10 Å) that generally takes  $10^{-9}$  to 1s. Some other processes, helix coil transitions, dissociation/association and folding/unfolding come under large-scale motions ( $> 5$  Å) that takes  $10^{-7}$  to  $10^4$  s to finish. It is very difficult to visualize most of the changes that take place in very short time span, by macroscopic experiment but by mimicking the *in vivo* conditions computationally and using MD simulation, computer can save these types of changes as different frames or snapshots that can be further visualized and analyzed. Martin Karplus, Yong Duan, Peter Kollman, Arie Warshel, Andrew J McCammon, Wilfred Gunsteren, H J C Berendsen, Andrew Leach, Michael Levitt and C.L. Brooks are the pioneers and major contributors of molecular dynamics simulation of biological molecules. In 2013, Nobel Prize was awarded to pioneers of molecular dynamics simulations: Martin Karplus, Michael Levitt and Arie Warshel that itself said about the recognition and application of molecular dynamics simulation. The objectives of this chapter comprise explanation of the molecular dynamics simulation theories, requirement of molecular dynamics for biological studies and application of molecular dynamics simulations. Moreover this chapter also focuses on various methods/algorithms for tertiary protein structure prediction.

## **BACKGROUND**

Alder and Wainright are pioneers of MD simulation. They introduced these techniques in late 1950's to study the interactions of hard sphere (Alder & Wainright, 1957; Alder & Wainright, 1959). Later in 1964, Rahman carried out first simulation using realistic potential for liquid argon (Rahman, 1964). In 1970s, Rahman and Stillinger used the first realistic system (liquid water) for simulation (Rahman & Stillinger, 1971). However, the first simulation on protein was performed in 1977 (McCammon, Gelin & Karplus, 1977). In 1980s rapid calculations on biomolecules, thermodynamics analyses (free energy calculations) and protein-ligand simulations were added (Wong & McCammon, 1986). In 1990s, Duan and Kollman tried to reveal the folding mechanism of smaller villin protein using molecular dynamics simulation which is considered as land-mark achievement of this field (Duan & Kollman, 1998). The NCBI contains almost 30,000 publications with key-words molecular dynamics simulations. Continuous development of potential and sampling techniques now allow us to perform the simulation to micro-second and even milli-second scale. Here it is noteworthy that in simulation these milli-second scales are supposed to be very large that contradict the real experiment because in simulation co-ordinates are generated at femto-second level. Moving from femto seconds to milli seconds scale give a large ensemble of conformations that can reveal many biological mysteries. Recently quantum mechanics (QM) combined with molecular mechanics (MM) is also being applied rapidly for the molecular interaction. Gaussian is one of the popular software that allows electronic structure modelling of the system. The

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