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A BRIEF OVERVIEW ON MOLECULAR DYNAMICS SIMULATION OF BIOMOLECULAR SYSTEM: PROCEDURE, ALGORITHMS AND APPLICATIONS

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ABSTRACT: Molecular Dynamics (MD) Simulation provides the details explanation of the atomic and molecular interactions that directed by macroscopic and microscopic behaviors of the various systems. This review provides a brief do-how about the theory, procedure, algorithm, and uses of molecular dynamic simulations in different bimolecular systems. An in-depth analysis of different prospects of MD simulation *viz.* procedure of MD simulation, force fields, energy minimization and integration algorithms, concept of ensembles and thermostats with a list of associated software briefly explained. At last discussion of various applications of MD simulation using some recent works, indicates the potential contribution of MD in biological research.

INTRODUCTION: In late 50's, Alder and Wainwright, first time introduced the concept of Molecular Dynamics (MD) to find out the interactions of hard spheres by utilizing Monte Carlo Simulation. This concept further used explored important behavioral insight of simple liquids [1, 2]. In 1964, Rahman carried out another simulation using a realistic potential for liquid Argon [3]. Further, in 1974, Rahman and Stillinger performed the first ever molecular dynamics simulation of a realistic system using liquid water solvent model [4]. Mc-Cammon *et al.,* in 1977 for the first time performed a simulation of the Bovine Pancreatic Trypsin Inhibitor (BPTI).

These days MD simulations are being profoundly used for various purposes such as simulation of dynamic surface exploration of proteins, study of various protein macromolecular complexes (*e.g.* protein-protein, protein-DNA, and protein-ligand interactions) and lipid systems. The MD addresses several of issues such as thermodynamics of protein-ligand complex, proteins folding, umbrella sampling of protein, free energy calculation of molecule, membrane protein simulation and study of ion transport *etc.* [5].

The different simulation methods having searching algorithms and force field parameterizations enabled the users to use different options according to their bimolecular system. These techniques use the principle of classical mechanics, molecular mechanics, and quantum mechanics; for understanding various biochemical systems *viz.* enzymatic reactions, chemical pathways, and thermodynamic study. In addition, simulation techniques are also used to solvate the structure

generated by X-ray crystallography and NMR structure determination [6, 7].

MD can be defined as a plethora of computer simulation techniques for understanding the physical movement and assemblies of atoms for many biologically relevant systems in terms of their structure at the microscopic level over a certain time period. It can also track rapid processes occurring in less than a millisecond.

The aim of MD simulation is to provide an experimental setup to the atoms and molecular interaction to identify the unseen microscopic/ macroscopic details of bio-molecule. In MD simulation real-time environmental conditions are provided to the bio-molecules to identify their behavior. MD simulation the first step is the sample preparation (selection of model systems of N-Particles) as in real experiment where preparation of the material sample is done.

Then Newton's equation of motion is applied to this system until the atoms are permitted to interact for a period of time at a given temperature which follows the law of classical mechanics. On the other hand, in a real experiment, the measure of experimental values of samples through the measuring instruments with respect to time. In the next step, after performing the equilibrium of the system trajectory analysis and measurement is carried out, this is same as the analysis of the sample measurements like statistical analysis of measured reading.

Even though the MD promises reasonably good prediction accuracy, the inclusion of the human error may lead to prediction errors. Similar to the real experiment such as the error in sample preparation and measurement accuracy etc. the computer can also make such mistakes. In addition, simulation also acts as a bridge between theory and the real-life experiment. We may check a theory by conducting a simulation of a particular system model and validate it by performing the real experiments [8].

However, MD simulations with their exclusive features of probing the space and timescales at the same time promoting a potential avenue for the description of different biological reactions in detail. Here, in this review, this discussion about different MD simulation methods, its associated algorithms, force field parameters, software, and the role of molecular dynamics in various biological systems.

Protocol of MD Simulation: MD Simulation procedure includes initialization, force field calculation, calculation of integration of motion equations, ensembles and thermostats selection, equilibrium or production run and analysis. Before MD simulation the selection of structure (*i.e.* NMR or Crystal or Model structure) and initial refinement of the structure is necessary.

The forces between the molecules or atoms are calculated explicitly using required force field (discussed in force field section) of the system and then it is solvated in a different solvent (using different water model *e.g.* SPC SPC/E, TIP3P *etc*). After that, the ions are added to neutralize the system [9, 10].

Moreover, the motion of the molecules or atoms is computed with the suitable numerical integration method on a computer (discussed in details in Classical mechanics and Integration algorithm). In this initialization steps, we allocate initial position (usually by the reading the starting structure) and velocities of particles in the systems.

After the equilibrium process the selection of ensembles and thermostats (given in ensembles and thermostats section), is carried out depending on the experimental choice and system requirements. The production run is performed for a defined time which depends on the bio-molecular system convergence.

Finally, different simulation analysis is performed using various statistical methods and algorithms. If the systems are not optimized, it might take long simulation run or reselection of a different force field may be required. The molecular dynamics simulation procedure in terms of a flowchart is depicted in **Fig. 1**.

The arrows indicate the operations which would be performed with the help of computer program or specified software. The steps are repeated if the desired output is not obtained and the repetition is indicated by the backward flow of the arrows in **Fig. 1**.
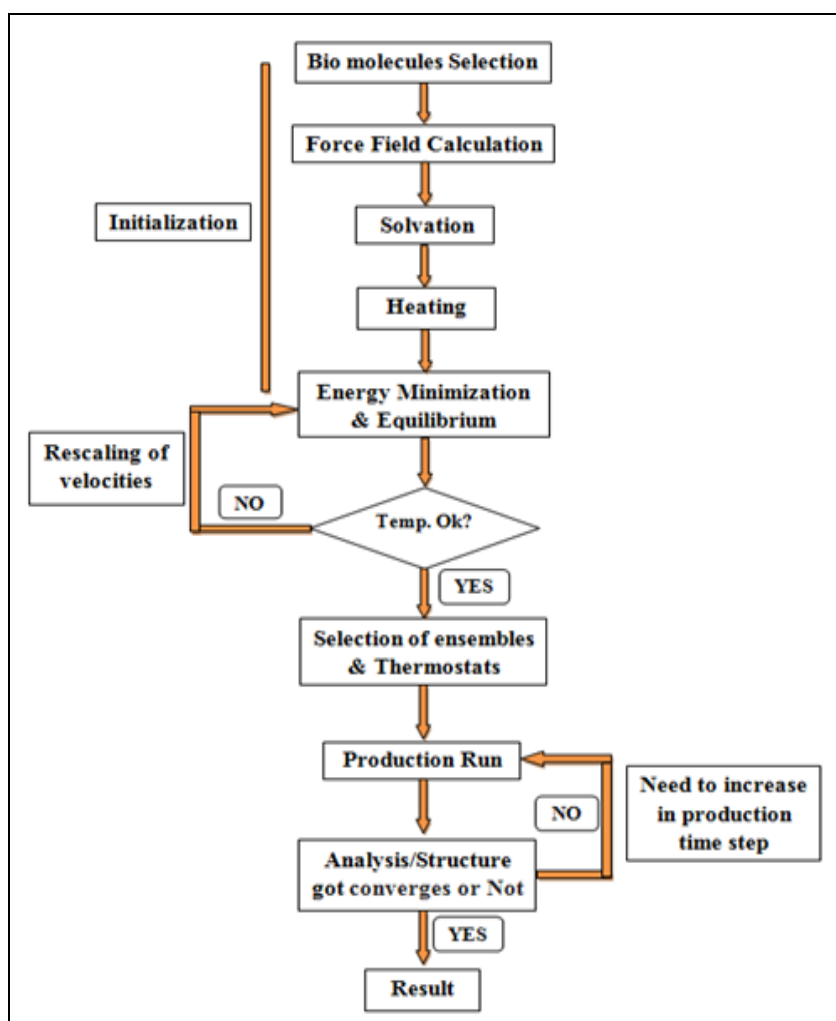
FIG. 1: GENERAL MD SIMULATION FLOWCHART USE FOR A BIO-MOLECULES SIMULATION

Force Field: Force field is the mathematical functions/parameters which are employed to describe the potential energy of the molecules and the atoms in context of molecular modeling. These force field functions and parameters are resultant of experimental and high-level quantum mechanical calculations. Basically, these parameters are designed according to a) 'All-atom', b) 'United-Atom' and c) 'Coarse-grained' force fields. All-atom force fields are used for all type of small atoms in the system together with hydrogen while United-Atom force fields are used for specific large atoms *e.g.* methyl molecule and other molecules. Similarly, the Coarse-gained force-field is frequently used in the long-term simulation of the proteins [11].

Types of Force Fields: The force fields can be broadly classified into five different categories depending on their usage in different systems starting from classical to modern modus operandi.

Starting from classical to second generation force fields, newer dimensions were added later on. For *e.g.* AMBER is generally used for simulating DNA structure to find out the most suitable conformation [12]. Moreover, newly discovered force field named as 'parmbsc1' and SIRAH are very useful for atomistic simulation of almost DNA structure space [13, 14]. The polarizable force fields came up based on the different charges and theories.

As described in the figure, the five bases are given on which the polarizable force fields are classified. Cores grained force field and reactive force fields are generally used for bio-molecular system and reactive chemical system respectively. The **Fig.** includes the name of various force field designed under different categories. The full name of each force field is mentioned below in **Fig. 2** and for more details about the concerned force field, relevant literature may be referred.
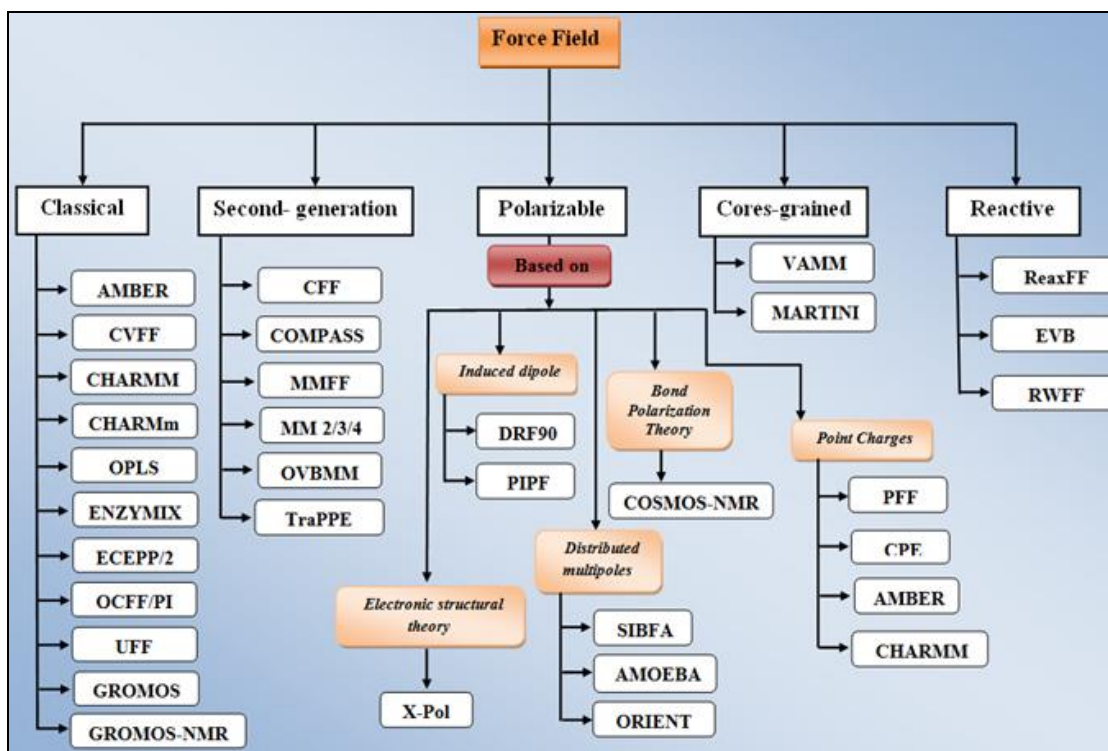
FIG. 2: FORCE FIELD AND THEIR CLASSIFICATION ACCORDING TO DIFFERENT SYSTEMS REQUIREMENT
AMBER (Assisted Model Building and Energy Refinement), CVFF (Consistent Valence Force field), CHARMM (Chemistry at HARvard Molecular Mechanics) CHARMm (commercial version of CHRAMM), COSMOS-NMR (Computer Simulation of Molecular Structures-NMR),GROMOS (GROningen MOlecular Simulation package) OPLS (Optimized Potential for Liquid Simulations), OCFF/PI (Quantum Mechanical Consistent Force Field), UFF (Universal Force Field), CFF (Consistent Force field), COMPASS (Condensed-phase Optimized Molecular Potentials for Atomistic Simulation Studies), MMFF (Merck Molecular Force Field), MM2/3/4 (Molecular Mechanics 2/3/4), QVBMM (Quantized Valence Bonds′ Molecular Mechanics), TraPPE (An Acronym for Transferable Potentials for Phase Equilibria), X-pol (Explicit Polarization theory), DRF90 (Direct Reaction field), PIPF (Polarizable Intermolecular Potential for fluids), VAMM (Virtual Atom Molecular Mechanics), MARTINI (same as name), SIBFA (Sum of Interactions Between Fragments Ab-initio Computed), AMOEBA (Atomic Multipole Optimized Energetic for Bimolecular Applications), ORIENT (same as name), CPE (Chemical Potential Equalization), PFF (Polarizable Force Field), ReaxFF (reactive force field), EVB (Empirical Valance bond) & RWFF (Reactive Water Force Field).

Force Field Function Calculation: The function of the force field can be calculated for bonded and non-bonded molecules and atoms. The precise decomposition of the terms depends on the force field and is defined as the term of the energy of bonded and non-bonded term

$$E_{Total} = E_{bonded} + E_{non-bonded} \qquad (1)$$

The component of bonded and non-bonded depends on the covalent and non-covalent bond interactions expressed by the following equations:

$$E_{bonded} = E_{bond} + E_{angle} + E_{dihedral} \qquad (2)$$

$$E_{non-bonded} = E_{electrostatic} + E_{van\ der\ Walls} \qquad (3)$$

In the presence of force field, the bond and angle term are usually modeled as harmonic oscillators

which prevent them from bond breaking. The Morse potential provides the more practical description for a covalent bond at higher stretching in which the potential energy is written as quadratic forms of internal energy as well as bonding energy modeled by the quantum harmonic oscillator. The non-bonded term includes many more interactions per atom which are computationally intensive. Generally, electrostatic and van der Waal interaction energies are calculated.

The Lennard-Jones potential and Coulomb's law are used to compute the Van der Waal and electrostatic potential respectively [15]. The **Fig. 3** depicts different bonds and stretch term in a continuum solvent model with the different surface area.
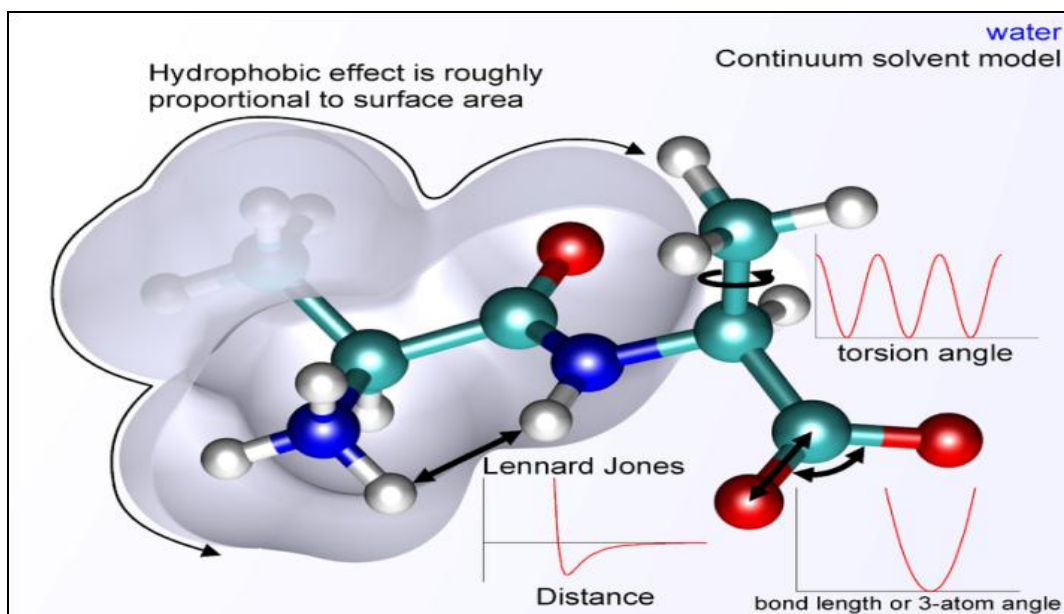
FIG. 3: DIFFERENT FORCES APPLIED TO A MOLECULE WITH CONTINUUM SOLVENT LIKE WATER
http://en.wikipedia.org/wiki/Force_field_%28chemistry%29#mediaviewer/File:MM_PE

Classical Mechanics in MD: MD provides solutions based on classical equations of the atoms and molecules based on the time evolution of the systems. MD is based on Newton's second law of motion and for i^{th} particle of the system can be given as

$$F_i = m_i a_i \qquad (4)$$

Where F_i is the applied force field on mass m_i of particle i and a_i is the acceleration of ith particle. The acceleration of the ith particle in the system can be determined if we know the applied force on particle and expressed as

$$a_i = \frac{dv_i}{dt_i} = \frac{d^2 r_i}{dt^2} \qquad (5)$$

Where v_i is the velocity of the ith particle and it is the second derivative of displacement of the particle with respect to time. Moreover, the acceleration of the particle can be represented as the derivative of the potential energy with respect to the position r_i, of the ith particle in the system

$$a_i = -\frac{1}{m_i} \frac{dE}{d_{r_i}} \qquad (6)$$

The force can expressed as the gradient of the potential energy,

$$F_i = -\nabla_i V \qquad (7)$$

Combining the equation of 1 and 4

$$-\frac{dV}{dr_i} = m_i \frac{d^2 r_i}{dt^2} \qquad (8)$$

Where, V represents the potential energy of systems. This Newton's equation of motion shows the relationship between the derivatives of potential energy to the change in the position of the ith particle as the function of the time in the system.

Initially, allocation of velocities is generally identified from a random distribution and magnitudes provide the required temperature and corrected. Hence there is no overall momentum, *i.e.*

$$P = \sum_{i=1}^{N} m_i v_i = 0 \qquad (9)$$

The velocities v_i are often chosen randomly from a Gaussian distribution or Maxwell-Boltzmann at a certain temperature which provides the probability that an atom i has a velocity v_x in the x direction at a temperature T.

$$p(v_{ix}) = \left(\frac{m_i}{2\pi k_B T} \right)^{1/2} exp \left[-\frac{1}{2} \frac{m_i v_{ix}^2}{k_B T} \right] \qquad (10)$$

The temperature can be calculated from the velocities using the relation.

$$T = \frac{1}{(3N)} \sum_{i=1}^{N} \frac{|p_i|}{2m_i} \qquad (11)$$

Where N is the number of the atoms in the system [15, 16].

Different integration algorithms are used to integrate the motion equations which capture the positions and movements of the particle and noted trajectory files. The trajectory file contains the description of particles positions, particles velocities and particles acceleration, which vary with respect to time. The average values of the particle behavior in the system are also noted the trajectory files. Hence integration algorithms help in the calculation of the positions, velocities of each atom and the state of the system

Integration Algorithms: In a bio-molecular system, the atomic positions (3N) of all atoms, is the function of potential energy. This potential energy function is complicated in nature and there is no analytical solution for the equations of motion, hence the motion equation has to be solved numerically. Many numerical algorithms have been developed for integrating the equations of motion. These algorithms are mainly Beeman's algorithm, Verlet algorithm, Velocity Verlet, and Leap-frog algorithm. Before choosing integration algorithms, it is important that the user must consider the algorithm whether it is computationally efficient, conserve energy & momentum and allow a long time step for integration [17].

Verlet Algorithm: Most commonly used time integration algorithm in MD simulation and computer graphics is Verlet algorithm. Verlet integration is used to integrate Newton's equation of motion and to generate the trajectories of the particle [18]. In 1960s, this algorithm was used by Loup Verlet for MD for the first time. In 1907, Carl Stormer used to study the electrical particles motion in the magnetic field. Later in 1909, Cowell and Crommelin used to calculate the orbit of Halley's Comet. The numerically stable Verlet integrator provides the time reversibility in physical system and prevention of the simplistic form on phase space [19].

Generally, integration algorithms presume the velocities (v_i), positions (r_i) and accelerations (a_i) can be approximated by a Taylor series expansion.

Expanding the position of the ith particle having r_i position at time $t + \Delta t$ and $t - \Delta t$ and b_i as the third derivative of r_i

$$r_i(t+\Delta t) = r_i(t) + v(t)\Delta t + \left(\frac{1}{2}\right)a_i(t)\Delta t^2 + \left(\frac{1}{6}\right)b_i(t)\Delta t^3 + O(\Delta t^4) \qquad (12)$$

$$r_i(t-\Delta t) = r_i(t) - v(t)\Delta t + \left(\frac{1}{2}\right)a_i(t)\Delta t^2 - \left(\frac{1}{6}\right)b_i(t)\Delta t^3 + O(\Delta t^4) \qquad (13)$$

$O(\Delta t^4)$ is local error in position of Verlet integrator. Adding the expression (12) and (13)

$$r_i(t+\Delta t) + r_i(t-\Delta t) = 2\,r(t) + a_i(t)\Delta t^2 + O(\Delta t^4) \qquad (14)$$

Equate equation (14) by putting $a_i = F_i / m_i$

$$r_i(t+\Delta t) = 2\,r(t) - r_i(t-\Delta t) + \frac{F_i}{m_i}(t)\Delta t^2 + O(\Delta t^4) \qquad (15)$$

The equation (12) and (13) constitute the basic form of the Verlet algorithm. As we are integrating Newton's equation, $a_i = F_i / m_i$ x (t), the force is in turn a function of the positions $r_i(t:)$

$$a(t) = -\left(\frac{1}{m_i}\right)\nabla V\big(r_i(t)\big) \qquad (16)$$

This version of Verlet algorithm has a problem, in directly generating the velocities. At the same time as they are not required for the time evolution, their information is sometimes necessary. In addition, they are necessary to calculate the kinetic energy K, whose assessment is essential to test the conservation of the total energy $E=K+V$. From this assessment, one can validate that a MD simulation is taking place correctly. One could compute the velocities from i^{th} positions by using

$$v_i(t) = r_i(t+\Delta t) - r_i(t-\Delta t)/2\Delta t \qquad (17)$$

Still, the fault linked to this expression is the order of Δt^2 rather than $\Delta 4^2$. To come out this complexity, some alternatives have been developed and described in next section [18].

Leapfrog Algorithm: This algorithm is also known as Verlet leapfrog algorithm and is developed to correct some disadvantage associated with the original Verlet algorithm. The Verlet algorithm associates the lack of an explicit velocity term and in reality, the velocities are not available until the positions have been calculated at the subsequent step. To overcome this leap-frog

algorithm use an approximation for derivative, one should consider the velocity v_i at the midpoint between times *(t)* and *(t + Δt)* and express as:

$$v_i(t + \Delta t/2) = r_i(t + \Delta t) - r_i(t)/\Delta t \tag{18}$$

The equation (18) can be solved in term of r_i *(t + Δt)* and yield

$$r_i(t + \Delta t) = r_i(t) + \Delta t v_i(t + \Delta t/2) \tag{19}$$

In the same way, the velocity can also define in the midpoint of *(t - Δt)* and *(t)* as given below

$$v_i(t - \Delta t/2) = r_i(t)/\Delta t - r_i(t - \Delta t) \tag{20}$$

The acceleration a_i at time *(t)* can be defined using appropriate formula for the derivative,

$$a_i(t) = v_i(t + \Delta t/2) - v_i(t - \Delta t/2)/\Delta t \tag{21}$$

By means of Newton's equation for the acceleration $a_i(t) = F_i(t) / m_i$ and putting the value to equation (21) yields

$$v_i(t + \Delta t/2) - v_i(t - \Delta t/2)/\Delta t = \frac{F_i(t)}{m_i} \tag{22}$$

Equation (22) can be solved for v_i *(t + Δt / 2)*,

$$v_i(t + \Delta t/2) = v_i(t - \Delta t/2) + \frac{\Delta t \, F_i(t)}{m_i} \tag{23}$$

Equations (16) and (20) comprise the equations of *Verlet leapfrog algorithm.* It has mainly two advantages which are not present in the original Verlet algorithm (11). (I) in original Verlet algorithm the loss of accuracy due to round-off error is resolved. (II) The original Verlet algorithm does not comprise of the explicit velocities which are included in Verlet leapfrog algorithm. The algorithm still has associated problems like it is still not self-starting. This problem can be solved as in the original Verlet method by implementing one step of the Euler method first and then switching to the Leapfrog algorithm for subsequent steps [20 - 21].

Velocity Verlet: The Velocity Verlet was developed to overcome the associated problem related to

Verlet algorithm. This algorithm is analogous to *leapfrog* method apart from that the velocity and position are calculated at the same time interval while the *leapfrog* method does not perform same. The Velocity Verlet's different form can be obtained from the original Verlet algorithms in which positions r_i, velocities v_i and acceleration a_i at the time *(t + Δt)*.

$$r_i(t + \Delta t) = r_i(t) + v_i(t) + (1/2)a_i(t)\Delta t^2 \tag{24}$$

$$v_i(t - \Delta t/2) = r_i(t) + (1/2)a_i(t)\Delta t \tag{25}$$

$$a_i(t + \Delta t) = -(1/m_i)\nabla V\big(r_i(t + \Delta t)\big) \tag{26}$$

$$v_i(t + \Delta t) = v_i(t + \Delta t/2) + (1/2)a_i(t + \Delta t)\Delta t \tag{27}$$

Note that long-term outcome of Velocity Verlet and Leapfrog is one order better than the semi-implicit Euler method. These algorithms are almost identical up to half velocity time step. The Velocity Verlet differs only while considering midpoint velocity as the final velocity in semi-implicit Euler method. The method has the error of order two which is similar to the midpoint method [22].

Beeman's Algorithm: Beeman's Algorithm is the method that provides the numerical integration of ordinary differential equation of order two, more distinctively Newton's equation of motion. The algorithm is designed in such a way that allows high numbers of particles in MD simulation. It uses a direct or explicit and an implicit variant of the method. In 1973 the Schofield published the direct variant which is commonly known as Beeman's method [23]. This is alternative of the Verlet integration method and creates identical position but uses a different formula for the velocity calculation.

Later in 1976, Beeman published a class of implicit (predictor-corrector) multi-step methods in which the Beeman's methods itself is a variant of the third order method in this class [24]. The full predictor-corrector computes the position r_i of particle at time *(t + Δt)* form data at times *t* and *(t - Δt)*

$$r_i(t + \Delta t) = r_i(t) + v(t)\Delta t + \frac{1}{6}\big(4a_i(t) - a_i(t - \Delta t)\big)\Delta t^2 + O(\Delta t^4) \tag{28}$$

$$r_i(t+\Delta t) = r_i(t) + v(t)\Delta t + \frac{1}{6}\big(a_i(t+\Delta t) - 2a_i(t)\big)\Delta t^2 + O(\Delta t^4)$$

(29)

$$v_i(t+\Delta t)\Delta t = r_i(t+\Delta t) - r_i(t) + \frac{1}{6}\big(2a_i(t+\Delta t) + a_i(t)\big)\Delta t^2 + O(\Delta t^4)$$

(30)

The equation (30) can be represented as an alternative by updating the velocity using second-order Admas-Moulton Method

$$v_i(t+\Delta t) = v_i(t) + \frac{1}{12}\big(5a_i(t+\Delta t) + 8a_i(t) - a(t-\Delta t)\big)\Delta t + O(\Delta t^3)$$

(31)

Ensembles: An ensemble is a large group of microscopically described states of a system with certain constant macroscopic properties. In MD simulations it is used to achieve quantitative outcome under various thermodynamic conditions for realistic models which are parameterized to study a specific molecular or atomic system with a certain degree of realism. It consists of transferable parameters for molecular sub-units usually at the atomistic level. Generally, Microcanonical ensemble (NVE), Isothermal-isobaric ensemble (NPT) Canonical ensemble (NVT), and some other generalized ensembles are used in MD simulation [25].

Microcanonical Ensemble (NVE): A system (solid, liquid or gas) is completely isolated from changes in volume (V) having the constant number of particles (N) and Energy (E). An adiabatic process with no heat exchange is similar the NVE ensemble. In the ensemble, the exchange of kinetic and potential energy with total energy may be seen. A system of particles N with X coordinate and velocities V having potential energy U, the following pair may be expressed in terms of first order differential equation of Newton's notation as

$$F(X) = -\nabla U(X) = MV(t)$$

(32)

$$V(t) = X(t)$$

(33)

Where *U(X)* is the potential energy function of system. The force *F* acting on each particle of the system can be calculated as the negative gradient of *U(X)* [26, 27].

Canonical Ensemble (NVT): Canonical ensemble has volume (V), particles (N) with a contact of heat bath with constant temperature (T). Hence, it is also referred as Constant Temperature Molecular Dynamics (CTMD). The energy of exothermic and endothermic processes is exchanged with a thermo-stat (discussed in next section) in canonical ensemble [26, 27].

Isothermal-isobaric Ensemble (NPT): Isothermal-isobaric ensemble is a statistical mechanical ensemble having (N) particle with constant temperature (T) and pressure (P).The thermostats and barostat correspond most closely to laboratory conditions with a flask open to ambient temperature and pressure. NPT ensemble plays an important role in chemistry as chemical reactions are regularly carried out under constant pressure condition. For simulation of biological membranes, isotropic pressure control is not appropriate. Hence in the simulation of lipid bilayers, pressure control under constant membrane area (NPAT) and the constant surface tension "gamma" (NPγT) ensemble is generally recommended [27].

Generalized Ensemble: The best method of a generalized ensemble is replica exchange and was created to handle the slow dynamics of the disordered spin system. It is also known as parallel tempering. To overcome, the multiple-minima problem the replica exchange MD formulation is used and obtained by exchanging the temperature of non-interacting replicas of the system running at several temperatures.

Thermostats: A thermostat is a modification of the Newtonian MD system with the purpose of generating a statistical ensemble at a constant temperature. It can match experimental conditions and manipulate temperature in the algorithms such as in simulated annealing. In addition, it avoids energy drifts caused by accumulation of numerical errors [28]. Generally, thermostats can follow either canonical or stochastic, a brief summary of different thermostats are described in **Table 1**.

TABLE 1: LIST OF DIFFERENT THERMOSTATS AND THEIR BRIEF DESCRIPTION ARE USED IN MD SIMULATIONS

Thermostat	Description	Canonical?	Stochastic?	Advantages	Disadvantages
Velocity rescaling	• Rescaling of the velocity performs at every time steps by fixing kinetic energy (KE) to match the Temperature of MD. • The desired temperature obtained by multiplying each atomic velocity by factor.	No	No	• Straight-forward to code. • Good for use in initialization step.	• Results do not correspond to any ensemble; while in practice the amount they deviate from canonical is quite small and not permit the correct temperature fluctuation. • Not advised to employ in production MD runs. Since they do not strictly conform to the canonical ensemble, but fine to use during equilibration. • Unwanted or localized correlation motion not removed.
Berendsen	• Another popular velocity rescaling method. • The scaling is obtained as $$\frac{d_v}{d_t} = \frac{f}{m} + \frac{1}{2r}\left(\frac{T_{md}}{T(t)} - 1\right)v$$ where, r is 'rise time' of thermostat. It explain power of the coupling of the to a hypothetical heat bath.	No	No	• Straight-forward to implement. • Method is robust	• Results do not correspond to any ensemble, while in practice; the amount they deviate from canonical is quite small. • Not advised for use in production MD runs since they do not strictly conform to the canonical ensemble, but fine to use during equilibration. • Localized or unwanted correlation motion not removed.
Nose-Hoover chain	• Based on extended Lagrangian formalism. • Based on elegant formalism proposed by Nosé (1984), in which micro-canonical dynamics on this extended system is revealed to give canonical properties. • Deterministic and time reversible. • Hamiltonian is given as $$H = \sum_{i=1}^{N} \frac{p_i^2}{2m_i s^2} + V(q) + \frac{Q s^2}{2} + (3N+1)k_b T \ln s$$ • Logarithmic term required for proper time scaling: canonical ensemble. • Effective mass Q associated with S, if Q too small: system not canonical or Q too large: temperature control inefficient. • Micro-canonical dynamics on extended system give canonical properties	Yes	No	• Easy to implement and use. This implements as chain and each link apply the thermo stating to the previous thermo-stat variable. • Deterministic and time reversible. • Increasing Q lengthens decay time in response to instantaneous temperature jump.	• Extended system not sure to be ergodic. • Becoming trapped in subspace– thus dangerous as a thermostat
Langevin	• Consider the motion of large particles through a continuum of smaller particles $$\frac{dq_i}{dt} = \frac{p_i}{m_i}$$ $$\frac{dp_i}{dt} = -\frac{\delta V(q)}{\delta q_i} - \gamma p_i + \sigma G_i$$ ➢ Viscous drag force proportional to velocity γP_i ➢ Smaller particles give random pushes to large particle. • Fluctuation –dissipation relation. $$\sigma^2 = 2\,\gamma m_i k_B T$$	Yes	Yes	• The behavior of dynamics samples from canonical ensemble is properly thermal for temperature T. • Shown as ergodic. • Local heat bath coupled on each particle. This process removes heat trapped in localized modes. • Accord to use a larger time step compared to non-stochastic thermostats.	• Momentum transfer is destroyed cannot compute diffusion coefficients. • Difficult to implement drag for non-spherical particles.
Andersen	• Possibly the easier thermostat which having correctly sample of the NVT ensemble. • Couple a system to a heat bath to impose desired temperature. • Equations of motion are Hamiltonian with stochastic collision term. • Strength of coupling specified by v, the stochastic collision frequency. • When particle has collision, new velocity is sampled from $N(O,\sqrt{T})$	Yes	Yes	• Samples are from canonical ensemble. • While a Langevin trajectory, over time, drifts away from the 'perfect' (energy conserving) path due to noise and drag, the Andersen trajectory is perfectly energy conserving.	• The mixing of Newtonian dynamics with stochastic collisions turns the MD simulation into a Markov process. • It destroys momentum transport since of the random velocities; therefore, there is no continuity of momentum and cannot be used to compute diffusion coefficients.

Limitation of MD Simulation: There are mainly three limitations are observed when MD simulation was carried out. The limitations are force field dependency, Neglect of Electronic motion and critical frequencies and how they affect the simulation results described below.

Force Field Dependency: The various force fields are designed for the different bio molecules systems like for protein GROMOS and for DNA it is AMBER. The MD simulation can only provide good results if the force field is applied in accordance with the relevant bio molecules otherwise the results will get affected.

Neglect of Electronic Motion: The classical MD follows only the particle nuclear motion while the electronic motion and quantum effects are ignored. Hence, the classical MD is unsuitable for chemical bonding of metal ions and chemical reactions. Quantum dynamics approaches are used for this purpose which is very typical and complex to design as such programs also need high computational power and efficiency.

Critical frequencies: There is a considerable amount of evidence found when we apply the forces and thermostats in the bio-molecular system. One of the most important evidence is the critical frequency of the bonded atom. In general, the critical frequency is the spontaneous oscillation of connected atoms of the system. The classical MD is inappropriate to calculate such vibration at low temperatures where the quantum effects are more suitable. Generally, the quantum effect calculates on the basis of $h\upsilon = k_B T$ .Whenever $h\upsilon > k_B T$, then we should be concerned about the quantum effect. There is some ratio of high-frequency vibrations at T=300K listed in **Table 2**. The $h\upsilon / k_B T$ ratio >1 shows such high frequency vibrational modes are not handled by the classical physics. Moreover, the Newtonian physics calculation shows that energy is equally distributed among the vibrational modes if $h\upsilon / k_B T$ ratio~1. Hence, picoseconds range and longer timeframes time scales are reasonably treated by the classical physics. The **Table 3** showing the broad spectrum of characteristic time scales in bio-molecules which is generally required to simulates a bio molecules.

TABLE 2: THE CALCULATED FREQUENCY, WAVE NUMBER AND THEIR RATIO ARE GENERATED BY DIFFERENT VIBRATIONAL MODE

Vibrational mode	Frequency $\upsilon[s^{-1}]$	Wave number $(1/\lambda)$ [cm^{-1}]	Ratio $h\upsilon / k_B T$
O-C-O bend	2.1×10^{13}	700	3
C-N stretch (amines)	3.8×10^{13}	1250	6
C=O stretch(carbonyl)	5.1×10^{13}	1700	8
O-C-O asymmetric stretch	7.2×10^{13}	2400	12
C-H stretch	9.0×10^{13}	3000	14
O-H stretch	1.1×10^{14}	3600	17

TABLE 3: DIFFERENT TYPES OF BIMOLECULAR MOTION AND THEIR TIME SCALE ARE OBSERVED IN CLASSICAL PHYSICS

S. no.	Internal motion	Timescale [s]
1	Protein folding	$10^{-5} - 10^{-1}$
2	Interior-sidechain rotation (proteins)	$10^{-4} - 10^{0}$
3	Site-juxtaposition (super helical DNA)	$10^{-6} - 10^{0}$
4	Collective subgroup motion for e.g.	
	For hinge bending-	$10^{-11} - 10^{-7}$
	For allosteric transitions Global DNA bending-	$10^{-10} - 10^{-7}$
5	Surface-side chain rotation (Protein)	$10^{-11} - 10^{-10}$
6	Sugar puckering (Nucleic acids)	$10^{-12} - 10^{-9}$
7	Global DNA twisting	10^{-12}
8	Heavy atom angle bend	5×10^{-14}
9	Heavy atom bond stretch	3×10^{-14}
10	Light atom angle bend	2×10^{-14}
11	Double bond stretch	2×10^{-14}
12	Light atom bond stretch	10^{-14}

Other Bimolecular Simulation Methods: This section explains about other simulation methods

(*i.e.* Monte Carlo, Brownian Dynamics) which are broadly used for MD Simulation.

Monte Carlo Method: The Monte Carlo method is a stochastic simulation technique which approximates the probabilities of large numbers of microstates or configurations of equilibrated systems generated by random sampling using Monte Carlo integration and statistical tests. In the 1930s, first time Enrico Femi used Monte Carlo method to study the neutron diffusion and that experiment was not published anywhere. Later on, in the late 1940s, Stanislaw Ulam discovered modern version of Monte Carlo method while working on nuclear weapons project at the Los Alamos National Laboratory. The name Monte Carlo comes from the similar technique playing and recording results in a real gambling casino. The method is frequently utilized in the problems of physics and mathematics and is most useful when it is difficult to achieve a closed-form expression, or infeasible to apply a deterministic algorithm. Generally, the Monte Carlo methods are used in three diverse classes of problems which are optimization, numerical integration and probability distribution [29].

Brownian Dynamics: Brownian Dynamics is an efficient mesoscopic simulation method for bio-molecules in which explicit solvent molecules are reinstated as an alternative of stochastic forces. This approach uses viscous continuum/more sluggish motion colloides or polymer as a solvent, which allows one to simulate in long time scale. The stochastic force applied to the macromolecules which initiate random collusion in the solvent molecules in this way Brownian motion in the system initiate and changes in different time scale. Further in a schismatic differential equation integrates forward in time and generates the trajectory of molecules. Brownian dynamics includes the simulation of particles that undergo Brownian motion and follows the simplified version of Langevin dynamics (LD) [30].

Let us consider the particles having a small mass and it is common to neglect the inertia of these particles. By applying the second law of Newton's for particles i, $F_i^{tot} = m_i a_i$, Here inertia was ignored since the total force is always approximately zero. The total force on a particle consists of drag force F_i^d, Brownian force F_i^B, and all non-hydrodynamic forces F_i^{nh}. The F_i^d due to particle motion through viscous solvent, F_i^B generates due to random collisions of the solvent with the particle while F_i^{nh} includes any external body forces any spring forces and any excluded volume interactions.

$$F_i^{tot} = F_i^B + F_i^d + F_i^{nh} \sim 0 \tag{34}$$

In a crawling flow and neglecting hydrodynamic interactions, the drag force is taken as Stokes drag on a sphere and it can be defined as

$$F_i^d = -\zeta(\frac{dr_i}{d_i} - u^\infty(r_i)) \tag{35}$$

Where $\sum$ is the dog coefficient and $u^\infty(ri)$ is the unperturbed velocity of the solvent evaluated at the position of the particle. The motion governing differential equation of the particle becomes as

$$\frac{dr_i}{d_i} = u^\infty(r_i) + \frac{1}{\zeta}(F_i^{nh}(\{r_j\}) + F_i^B(t)) \tag{36}$$

and is known as Langevin equation, where {ri} is the set of all partials positions on which non-hydrodynamic force depends. This equation is also called stochastic differential equation because the Brownian force is taken from random distribution [31].

Different Algorithms and Software: Various algorithms and software were devolved to perform the bimolecular simulations are listed in **Table 4**, describe their name, functions, dependency on GUP and web link of availability.

TABLE 4: LIST OF FREELY AND COMMERCIALLY AVAILABLE SOFTWARE FOR BIMOLECULAR SIMULATION WHICH USES CLASSICAL MECHANICS AND QUANTUM MECHANICS PROPERTIES

S. no.	Name	Description	GPU	License	Web-references
1	Abalone	• Provides the platform for molecular modeling and MD simulation of bio-molecules especially for biopolymers. • Use AMBER and OPLS force field.	Yes	Free	http://www.biomolecular-modeling.com/Abalone/index.html
2	ACEMD	• Production-class bio-molecular dynamics engine uses CHARMM and AMBER force field. • Running on NVDIA GPUs (Graphics processing unit) and heavily optimized with CUIDA. • Specially designed for GPU and have ability to	Yes	Basic version free Commercial version also available	http://www.acellera.com/products/molecular-dynamics-software-GPU-acemd/

3	ADUN	accomplish supercomputing performance of 40ns/day for all-atom protein system with over 23000 atoms. • Includes tools for the calculation and analysis of several dynamical properties of macromolecules. • User specified CHARMM; AMBER forced field implemented using Force field markup language (FFML). • Empirical valence Bond (EVB) used for the calculation QM and MM.	Yes	Free	http://adun.imim.es/
4	AMBER	• Assisted Model Building with Energy Refinement (AMBER) is a family of force field used for MD of Bio-molecules and also known as software package. • Tools use all AMBER force field only.	Yes	Paid	http://ambermd.org/
5	Ascalaph Designer	• A general purpose tool for molecule design and MD simulation. • Provides the graphical environment to molecular molding and MD program like ORCA, NWChem, CP2K, Firefly, MDynaMix and GAMESS.	Yes	Free (GNU GPL) & Commercial	http://www.biomolecular-modeling.com/Products.html
6	CHARMM	• Chemistry at HARvard Macromolecular Mechanics (CHARMM) is a flexible and widely used MD Simulation program for bio-molecules. • Commercially available in the Discovery Studio for MD.	Yes	Paid	http://www.charmm.org/
7	COSMOS	• Provides MM and MD simulation through Quantum chemistry calculation of chemical shifts and atomic charges with an accuracy that compares to ab initio calculations.	No	Free (Without GUI)	http://www.cosmos-software.de/ce_intro.html
8	CP2K	• CP2K can execute atomistic, molecular simulations of solid state, liquid and biological systems.	Yes	Free for GNU	http://cp2k.org/
9	Culgi	• Provides atomistic and mesoscale MD Simulation.	No	Paid	https://culgi.com/
10	Desmond	• A tool developed at D.E. Shaw Research Foundation to perform high speed MD simulation of Bio-molecules and commercially available in Schrodinger. • The CHARMM (22,27,32,36), AMBER (94,96,99,03) and OPLS (2001, 2005) as well as other in house developed force field variant is suppurated by Desmond.	Yes	Free and Commercial	http://www.deshawresearch.com or http://www.schrodinger.com/Desmond
11	Discovery Studio	• A well known software package provides major solution of Structural Biology focused on the optimization of drug discovery process. • Provides Small molecule simulation as well as large bio molecules MD simulation using CHARMM, MMFF, MOL3, QUANTUMM and CFF.	No	Commercial and trail is available	http://accelrys.com/
12	GROMACS	• GROningen MAchine for Chemical Simulations (GROMCS) is a MD simulation packages for protein, lipids and Nucleic acid and developed at University of Groningen, Netherlands. • Available for CPU and Normal system user and provides all version GROMOES, AMBER and CHARMM fold field parameter. • Most preferable worldwide used software for MD Simulation.	Yes	Free	http://www.gromacs.org/
13	HOOMD-blue	• Uses various pair potentials i.e. dissipative particle dynamics, Brownian dynamics, rigid body constraints, energy minimization, etc. • General-purpose simulation tool highly optimized for GPUs.	Yes	Free	http://codeblue.umich.edu/hoomd-blue/index.html
14	LAMMPS	• Large-scale Atomic/Molecular Massively Parallel Simulator (LAMMPS) is MD simulation program developed by Sandia National laboratories.	Yes	Free	http://lammps.sandia.gov/
15	Macro-Model	• A classical mechanics based program used for molecular modeling and also carry out simulations. • Use stohastics dynamics and mixed Mante Carlo algorithms to perform MD at finite temperature.	No	Paid	http://www.schrodinger.com/MacroModel
16	MAPS	• Materials Processes and Simulations (MAPS) provide the visualization and analysis with multiple simulation engines.	Yes	Closed source/Trial available	http://www.scienomics.com/products/molecular-modeling-platform/
17	MedeA	• Combines computational programs like Vienna. • A-Initio Simulation Package (VASP) LAMMPS, GIBBS for material MD simulations.	No	Paid/Trial available	http://www.materialsdesign.com/

18	Q	• Designed for special kinds of free energy calculation which are free energy Perturbation (FEP) simulation, Empirical valence bond (EVB) calculates the reaction free energy and linear interaction energy used for protein ligand binding affinities. • The available force field are GROMOS87/96, AMBER95, OPLS and CHARMM22	No	Free for non-commercial use	http://xray.bmc.uu.se/~aqwww/q/
19	RedMD	• Provides the MD simulations in a microcanonical ensemble, with Berendsen and Langevin thermostats, and with Brownian dynamic.	No	Free on GNU License	https://bionano.cent.uw.edu.pl/software/redmd
20	SCIGRESS	• Best use for MM calculations on the organic and inorganic molecules containing all elements of the periodic table using verity of force field.	No	Paid	http://www.fqs.pl/Chemistry_Materials_Life_Science/products/scigress
21	TeraChem	• First computational chemistry software enabling quantum chemistry and first principles dynamics for molecular materials and biological molecules. • Designed algorithms exploit massive Parallelism of CUDA-enabled NVIDIA GPUs.	Yes	Paid	http://petachem.com/
22	TINKER	• Provides the molecular mechanics (MM) and MD for bio molecules with some special features for the biopolymer.	No	Free	http://dasher.wustl.edu/tinker/
23	Termolo-X	• Generally used for the numerical simulation of interactions between atoms and molecules.	No	Paid	http://www.tremolo-x.com/overview.html
24	NAMD	• NAnoscale Molecular Dynamic Program (NAMD) for MD simulation developed in the Charm++ parallel programming model. • The parallel molecular dynamic code allowing the interactive simulation in the platform of VMD.	Yes	Free for academics	http://www.ks.uiuc.edu/Research/namd/
25	YASARA	• Yet Another Scientific Artificial Reality Application (YASARA) is a molecular visualization, modeling and MD simulation tool. • Powered by Portable Language (PVL)	No	Paid	http://yasara.org/

Application of MD Simulation: MD simulation is used to explore the complex biochemical processes such as: (I) study of protein folding and mutation analysis, (II) exploration of protein motion as essential for the identification of the protein function, (III) Study of DNA, RNA folding and opening process, (IV) Elucidation of bimolecular complex stability (Protein-protein, Protein-DNA, Protein-RNA, Protein-ligand), (VI) treat collision cascades in the heat spike regime and (VII) Explore the role of temperature in various thermodynamics studies. Indeed various works have been performed to explain these applications of molecular dynamics simulation some of them are explain in subsection.

Study of Protein Folding and Mutation Analysis: Recently, Gupta *et al*., 2015 explored the protein folding and interdomain communication event of heat shock protein 70 (HSP70) through MD simulation. The study explains how the confirmation of HSP70 proteins changes from open state to close state. The results also provide a mechanistic representation of the communication between nucleotide binding domain (NBD) and substrate binding domain SBD. This identifies the different role of subdomains in conformational change mechanism, which leads the chaperone cycle of cHSP70 [32]. **Fig. 4** explains how the HSP70 obtained

open to close states during the different time of simulations. Hernandez *et al*., 2017 studied the mutational analysis of cyclin-dependent kinases (CDKs) 4 and 6, which impede cells from toward the inside of synthesis phase of the cell cycle. Therefore CDK4 and 6 in drug targets in different cancers. Further, they have interactions of palbociclib (a known drug) with already known two mutations of D163G and H100L in CDK6 as well as altering their best substitutes using MD simulations [33]. Indeed these recent studies explain how MD simulation helps in proteins folding and mutational analysis to explore their functions.

Elucidation of Bio-molecular Complex Stability: The bio-molecular complexes such as Protein-protein, Protein-DNA, Protein-RNA, and Protein-ligand are playing the crucial role in the different biological process and molecular functions. Indeed, various studies have explained the role of MD simulation to check the stability of biomolecular interactions in defined environmental conditions on the systems [34 - 42]. Protein-protein interactions play important roles in Vertebrates, plants and other species. Plants produce defense proteins such as proteinase inhibitors (PIs), Heat Shock Proteins (HSPs), Ser/Thr kinase proteins Transcription factors (TFs) *etc* in response to biotic and abiotic

stress. PIs produce by the plant during pests attack and function as pseudosubstrates for the digestive protein of pests. As a result inhibition of proteolysis process in pests occurs, this leads towards amino acid-based mortality. Further, the structural interaction analysis of serine proteinase of

Heterodera glycines (SPHG) with Vigna mungo proteinase inhibitor (VMPI) though Protein-protein docking followed by MD simulation. Study mimics the protein-protein interactions affinity through MD simulation [34].
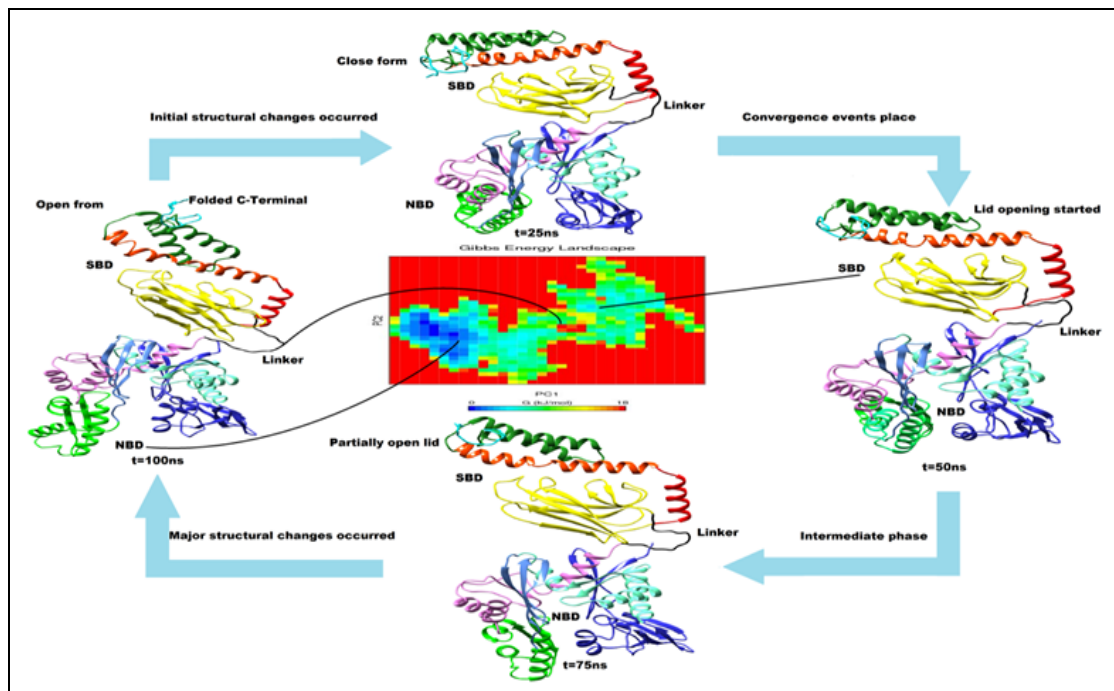
FIG. 4: THE STRUCTURAL AND FOLDING EVOLUTION OF CAMEL HSP70 PROTEIN CALCULATED DURING 100 NS OF MD SIMULATION.
The averaged structure of 25 ns interval is depicting their different folding sate. Gibbs free energy landscape stand for the frequency of subunit folding identified via Principal Component I and II Analysis (PCA). The minimum Gibbs free energy (blue color spot) shows minimum folding rates in domains while the intermediate and higher energy (green and yellow spots) shows intermediate and higher folding rate in subunit of HSP70 whole simulation is performed by Gupta *et al*., 2015(adapted with permission from [30])

The post-transcriptional gene regulation depends not only on the mRNAs sequence but also on their folding into complex secondary structures and chemical modifications of RNA bases. These features of RNA are highly dynamic and independent and having their direct control in the transcriptome, which leads changes in several functions of the cell [35]. Hence, it is important to analyze the coupling of RNA structures and its modifications and RNA–protein interactions at different steps of the gene expression process [36].

Recently, Chhaya *et al*., 2017 performed the MD simulation using AMBER tool to mimic various isoforms of preE-let7 in complex with LIN28 protein which inhibits the biogenesis miRNAs of let-7 family. Further, they also identified structural features and key specificity determining residues (SDR) crucial for the inhibitory role of LIN28 [37].

Similarly, exploration of interaction analysis between protein-DNA complexes through simulation is also helpful to elucidate DNA-binding specificities a gene expression process. For example to analyze stimulus-specific responses of conserved WRKY DNA-binding domain (DBD) completely recognize the 'TTGACY' W-box consensus. We speculated that the W-box consensus might be more degenerate and yet undetected differences in the W-box consensus of WRKYs of different evolutionary descent exist. Simulation analysis was performed to explore differences in DNA-binding specificities [38].

Indeed different studies have been explored protein-ligand complex stability through different dynamics simulation methods and software [39 - 43]. Generally, protein-ligand complex stability is crucial for identification of inhibition or activation

of proteins responsible for various phenotypic and genotypic changes. Gupta *et al*., 2015 explained the protein-ligand complex stability in context to identify the suitable lead compounds for the

treatment of malaria [39]. **Fig. 5** indicating interaction energy and folding rate plot of top five complexes during 25 ns of MD simulation.
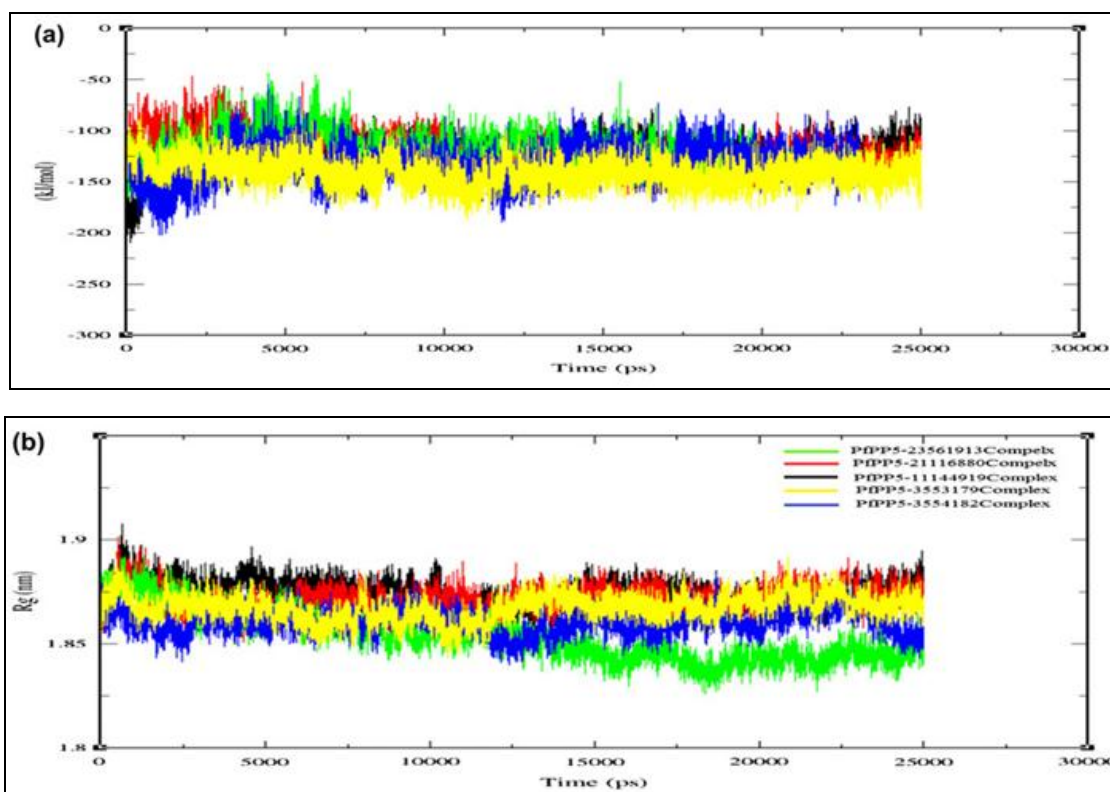
FIG. 5: THE INTERACTION ENERGY AND FOLDING RATE OF PROTEIN-LIGAND COMPLEX STRUCTURES OF STUDY PERFORMED BY GUPTA *et al.*, 2015
(a) The LJ-SR protein–ligand interaction energy graph and (b) radius of gyration (Rg) plot of each complex during 25 ns simulation (adapted with permission from [37])

Study of DNA, RNA Folding, and Opening Process: DNA and RNA are involved in the processing of genetic information at different levels of the cell. To address, how DNA, RNA molecules performed their functions, it is required to understand the structure and dynamics of DNA/RNA at the atomistic level. This can be feasible to analyses them through MD simulation with experiment. Different types of simulations are performed to identify the details DNA, RNA molecules and their interactions with systems solvent, ions and peptides/proteins. Further, it describes structural and dynamical insights of these biomolecules and explains its transition from one state to another state [44 - 48].

Recently, Dens *et al*., reviewed the multiscale simulation of DNA and discussing most recent theoretical methods used to study DNA and classified these methods into four groups as per their level of resolution (**Fig. 6**): (i) electronic, (II)

atomistic, (III), coarse-grained, and (IV) mesoscopic. It is not true that if we are moving words resolution space that means moving also in methodological space. **Fig. 6 a, 6b, 6c** and **6d** highlighting different methods based DNA/RNA simulation: (a) the joint QM/MM work from the Magistrato's group, explaining the atomistic and energetic variations of human Flap endo-nucleases (FENs) with DNA and RNA complex using mixed quantum-classical (QM/MM) meta-dynamics and umbrella sampling free energy calculations [49]. (b) Explains how DNA Holliday-junction simulated with the new force parmBSC1 [13]. (c) An implementation of new force SIRAH force field into LacI–DNA system using twofold resolution treatment of the solute and solvent without compromising the AA region [14]. (d) The model from Schlick and coworkers was used to study the chromatin fiber dynamics [50]. Apart from above-discussed application many other studies

also performed using MD simulation and we recommend researcher to read specific articles to execute and understand deeper MD simulation analysis.
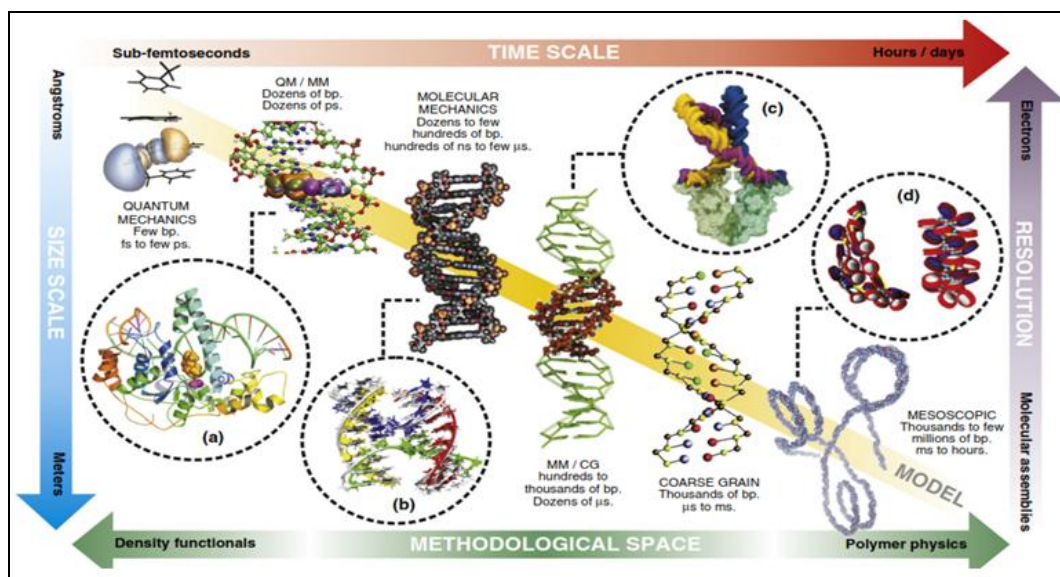
FIG. 6: SCHEME ILLUSTRATING THE INTRINSIC MULTISCALE NATURE OF DNA
The models and applications are sorted in this scheme according to five dimensions *i.e.* time scale, size scale, methodological space, models and resolution (adapted with the permission from, [46]). They have highlighted four applications of MD simulation (a) the combined QM/MM work from the Magistrato's group, were a protein-DNA complex with a DNA lesion is studied in detail [18]. (b) Holliday-junction simulated with the new parmBSC1 refined force-field for DNA simulations, adapted from [13]. (c) LacI-DNA dynamics by multiscale simulations using the SIRAH force-field from Pantano's group [14]. (d) The model from Schlick and coworkers was used to study the chromatin fiber dynamics. Chromatin fibers in the canonical and hairpin-like conformations are depicted (adapted with permission from [50].

CONCLUSION: In this review, a brief outline has been given emphasizing the key elements which are essential to carry out a molecular dynamics simulation, with special emphasis on bio-molecular systems. We have discussed different steps involved in the MD simulation with the necessity of each of them. Also, MD applications and MD limitations were described with assumptions of classical mechanics, molecular mechanics, force fields and integration algorithms.

Moreover, we have briefly described the concept of ensembles and thermostats and its practical use in certain simulation. Bio-molecular simulation methods and various MD simulation programs and software tools available as open source and commercial domain were explained. Finally, different applications of MD simulation with recent work is discussed, indicates their role to understand bio-molecules functions.

CONFLICT OF INTEREST: Authors affirm that they do not have any conflict of interest.

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