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Classics and Hybrids - Approaches to Modeling the Dynamics of Biomolecules

Wolfgang B Fischer*

Institute of Biophotonics, School of Biomedical Science and Engineering, National Yang-Ming University & Biophotonics and Molecular Imaging Research Center (BMIRC), National Yang-Ming University, Taipei 112, Taiwan

The definition of biological molecules usually comprises proteins, lipids and DNA/RNA as well as their building blocks as individual entities. Organic molecules, which are very much smaller than the biomolecules mentioned are usually considered as ligands which modulate these very big molecules. Thus, in terms of size, the Ångstrom level is a dimension which counts for the small ligands, the nano meter and even micro meter level can hold for the biomacromolecules.

Physiological interesting events are investigated on either of these levels: which conformation does a ligand adopt in its active state at a protein? How are the dynamical properties of a macromolecule adopting a mega structure of a liposome or a fibril changing during events like fusion or cell division. In this respect, static and dynamic information is requested.

Starting on the small scale, static information can be obtained from quantum mechanical calculation using respective software. With software performing quantum mechanical calculations low-energy structures and with this the most likely conformation of molecules can be derived. Since these calculations are seen as obtaining energies from very basic assumptions about atoms and molecules, they are called "*ab initio*" calculations.

Introducing the time domain into the *ab initio* calculations, *ab initio* molecular dynamics (aiMD) simulations are developed. In a specific method, called Car-Parinello molecular dynamics (CPMD) [1], the technique lives with the compromise of using spherical representations of the atom with its inner electrons which are not involved in chemical reactions. The outer electrons are handled explicitly. This means, the outer electrons are considered to be involved in chemical bonding and thus, are dealt with on a quantum mechanical level. With this consideration the method already comprises a hybrid method between the pure quantum mechanical calculations and the calculations using the concept of a mechanical force field (ff).

Nevertheless, aiMD is a method with which time resolved data of atomistic dynamics can be achieved. Molecular dynamics (MD) simulations are comprised of two steps, one in which the interaction energy between the atoms is calculated and the respective forces and velocities deduced and another one in which the atoms are moved to the respective new positions based on these calculations. The energy calculations, the first step mentioned above, is quite time consuming. As a rule of thumb, as more atoms the system consists of the more calculations have to be done. The calculations can be expressed in clock-time that means the physical time the computer needs to do all these calculations. Of course, if calculations can be done in parallel then the waiting time for the results can be reduced, or in other words, if I am still willing to wait for e.g. 1 week I can cover longer time spans. At this scale mentioned, usually the resulting time frame covered by these aiMD simulations is in the pico second range. So how big can such a system be so that I can handle it? The answer is, not very big. Usually the number of operations, the number of energy calculations, which need to be done are scaling as $O(N^3)$ where N represents the number of atoms in the system. In summary, I will get high precision information about a rather small system.

Now let's leap frog. The next level of compromise is to skip all the electrons and instead represent the atoms and their electrons by spheres. This approach has the big advantage that one can use Newtonian laws of motion to derive energies and to move atoms and molecules, therewith performing MD simulations. These type of simulations are here referred to as classical MD simulations. In some cases depending on the applied ff all atoms are represented and dealt with in the simulations. Some ffs allow a speed-up of the simulation by presenting parameters for 'united atom' types. The united atoms represent e.g. carbon atoms with their respective hydrogen, so called non titrable atoms, as one 'united' system. With appropriate parameters (see previous editorial [2]) specific conditions of biomacromolecules can readily be covered. At this stage of course some detailed information about the individual atoms is lost. In return, larger systems over a larger time frame can be simulated. Now it is possible to cover the nano second range. With this technique also in combination with improved hardware power even the micro and milli second range is covered [3,4].

QM/MM calculations comprise a compromise between high level quantum mechanical (QM) calculations and molecular mechanical (MM) calculations. In the latter calculations, atoms are parameterized as mentioned for MD simulations. The QM calculations are limited to particular regions of the protein while the MM calculations are used for the rest of the protein [5]. However, the principle of the simulation is that of a time independent analysis of conformational flexibility. Latest QM/MM software scales as $O(N^2)$. In biological systems which process chemical reactions such as enzymes or convert light into mechanical energy the photoreceptors are suitable candidates for the application of QM/MM methods [6]. It is the method of choice when chemical reactions in enzymes are investigated which take place within the protein. Merging with aiMD [7,8] the hybrid method can now also be used to simulate time dependent QM/MM molecular dynamics simulation (QM/MM MD) [6].

Towards the other end, going larger and longer, coarse grained (CG) techniques are available. Classical MD simulations can also be adapted to investigations of large scales and long time frames. Currently available techniques such as coarse grained molecular dynamics (CGMD) simulations unify four of the classical united atoms used

***Corresponding author:** Wolfgang B Fischer, Institute of Biophotonics, School of Biomedical Science and Engineering, National Yang-Ming University and Biophotonics and Molecular Imaging Research Center (BMIRC), National Yang-Ming University, Taipei 112, Taiwan, Tel: +886-2-2826-7394; Fax: +886-2-2823-5460; E-mail: wfischer@ym.edu.tw

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in classical MD simulations into a single sphere which itself is newly parameterized [9,10]. Due to the up-scaling, the type of interactions can be minimized. The amount of parameters of the ff shrinks to oversee able numbers. An elastic network model (EM) is superimposed on the molecule to remain the overall shape of the protein. EM imposes constraints on the software and therefore the analysis of dynamics of the protein internal dynamics needs to be considered with some care. Nevertheless, larger scale dynamics on the tertiary level of proteins can be readily investigated. Long range dynamics, like undulation of lipid membranes or oscillations in the low frequency range of large scale structure can be monitored (vesicles, DNA strains). Per definition the software of this method is not a hybrid method such as QM/MM. It is developed as stand-alone technique. All components of the simulation are coarse grained. It is rather the coarse graining on a structural level which makes the method very attractive. Hybrid systems in which parts of the system are differently grained are developed for investigations of solid-liquid flow [11].

When the frequency of dynamics, such as protein internal dynamics, are considered as irrelevant for the type of experiment so called meso-scale simulation approaches can be used. The approach is especially suitable for a protein or any other systems consisting of many repeating units which itself can be seen as a 'rigid' unit within the time frame of the overall simulation. Therefore these systems can be simplified and represented as spheres which are connected by springs. The dynamics of such systems can be handled either with the concepts of MD simulations or on the basis of Monte Carlo (MC) simulations. MC simulations screen low energy configurations of the system in a time independent fashion. Putative positions of the spheres are adapted and the consequent energy of the system computed. Low energy conformations of the system are kept and high energy conformations are discarded on a random bases (hence MC in reference to the city Monte Carlo with its famous Casino) Over many calculation steps, low energy conformation of the system is obtained.

The bond fluctuation method (BFM) is based on such a simplified representation of the system. The system is are allowed to take positions on a defined grid or lattice points, a so called 'lattice model' [12]. The method is used in theoretical physics to predict principles of polymer assembly and dynamics. In BFM the spheres are connected by bond vectors, allowing to simulate, e.g. long polymer chains. The occupation of lattice points by individual spheres of the chain is screened in a MC approach [12,13]. By seeing a protein as a folded biopolymer attempts have been done to apply BFM for globular protein folding [14]. In addition, the technique is probed to evaluate its predictive power to the folding of membrane proteins such as rhodopsin [15] and the transition of prion protein turning from a healthy to a diseased conformation [16]. In these simulations, the spheres are parameterized so that they embed specific characteristics of the amino acids they represent. What is the advantage of such kind of simulations? They are especially suitable for dense systems where only a very limited set of parameters, such as, e.g. a lattice point cannot be occupied by two spheres, define the condition of the system. This technique has the power to define 'approximate' results in, e.g. protein folding, which can be further used in ff-based methods.

There can be two hybrid states. One is between quantum mechanical calculations and classical MD, a state which is already eagerly in use. The other is between structure based classical MD and any kind of CGMD or even BFM type calculations which possibly will appear on the horizon. As a general outlook, the future could see a race towards simulations of the system at the small scale supported by increasing performance power of the hardware, or the development of multi potent hybrid methods which 'transform' smoothly between time scales.

References

1. Car R, Parrinello M (1985) Unified approach for molecular dynamics and density-functional theory. Phys Rev Lett 55: 2471-2474.
2. Fischer WB (2013) The force field cachet of structure based computer simulations. J Bioanal Biomed 5: e123.
3. Shaw DE, Maragakis P, Lindorff Larsen K, Piana S, Dror RO, et al. (2010) Atomic-level characterization of the structural dynamics of proteins. Science 330.
4. Pierce LCT, Ferrer RS, De Oliveira CAF, McCammon JA, Walker RC (2012) Routine access to millisecond time scale events with accelerated molecular dynamics. J Chem Theory Comput 8: 2997-3002.
5. Warshel A, Levitt M (1976) Theoretical studies of enzymic reactions: Dielectric, electrostatic and steric stabilization of the carbonium ion in the reaction of lysozyme. J Mol Biol 103: 227-249.
6. Brunk E, Rothlisberger U (2015) Mixed quantum mechanical/molecular mechanical molecular dynamics simulations of biological systems in ground and electronically excited states. Chem Rev 115: 6217-6263.
7. Colombo MC, Guidoni L, Laio A, Magistrato A, Maurer P, et al. (2002) Hybrid QM/MM Car-Parrinello simulations of catalytic and enzymatic reactions. Chimia 56: 11-17.
8. Warshel A (2003) Computer simulations of enzyme catalysis: methods, progress and insights. Annu Rev Biophys Biomol Struct 32: 425-443.
9. Marrink SJ, Risselada HJ, Yefimov S, Tieleman DP, De Vries AH (2007) The MARTINI force field: coarse grained model for biomolecular simulations. J Phys Chem B 111: 7812-7824.
10. De Jong DH, Singh G, Bennett WFD, Arnarez C, Wassenaar TA, et al. (2013) Improved parameters for the Martini coarse-grained protein force field. J Comp Theory Comput 9: 687-697.
11. Alexiadis A (2015) The discrete multi-hybrid system for the simulation of solid-liquid flows. PloS ONE 10: e0124678.
12. Carmesin I, Kremer K (1988) The bond fluctuation method: a new effective algorithm for the dynamics of polymers in all spatial dimensions. Macromolecules 21: 2819-2823.
13. Schaffer S (1994) Effects of chain topology on polymer dynamics: bulk melts. J Chem Phys 101: 4205.
14. Zhang L, Zhao D (2001) Folding lattice HP model of proteins using the bond-fluctuation model. Macromol Theory Simul 10: 518-522.
15. Chen CM, Chen CC (2003) Computer simulations of membrane protein folding: structure and dynamics. Biophys J 84: 1902-1908.
16. Ou DM, Chen CC, Chen CM (2007) Contact-induced structure transformation in transmembrane prion propagation. Biophys J 92: 2704-2710.