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The application of molecular dynamic simulations

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Abstract. Molecular dynamic(MD) simulations have been developed into a mature tool for researchers and have had a huge impact on the aspects of drug discovery, molecular biology, and prediction of specific structures and related functions of macromolecules in recent years. The aim of this article is to provide some essential knowledge about the theories and applications of this useful technology. This introduction to molecular dynamics starts from the definition of some basic concepts, including the molecular mechanics force fields and how they are applied to the motion systems of molecular dynamics simulations and their developments recently. Also, the outstanding strengths and limitations of the MD simulations are discussed, as are some possible solutions to them. This article shows the wide applications of MD simulations, including drug discovery, prediction of structure, and allostery. Due to the growing power of computational calculations and its important role in simulating the biological process between receptors and ligands like allosteric binding sites, MD simulations are thought to be more and more important in the near future.

Keywords: molecular dynamics simulations, materials, allostery, drug discovery.

1. Introduction

The molecular dynamics (MD) simulations have not been developed recently. The start of using computers to understand the structures of condensed materials can be traced back to the 1950s of last century, and MD simulations were first developed by Alder and Wainwright at that time[1]. From that time, the MD simulations, which attempt to simulate atomic motions based on Newton's laws, have experienced a continuous improvement in technology and have become a very useful tool in various fields of science. In particular, the MD technique can be applied to many scientific areas, including the study of ionic solutions, electrochemistry, trubology, and cluster science[2]. MD simulations has been more and more popular in recent years as it can predict the motion and intermolecular force of each atom in the system[3]. As a result, in the first part of this overview, this paper will give a brief introduction of the basic mechanism of the molecular dynamics (MD) simulations information provided by it with some definitions and crucial terms. Then, this article will point out the main strengths and current limitations of the MD simulations and the methods scientists applied to solve the problems. For example, the inaccuracy can be arisen from the approximations of force fields and how researchers manage to overcome it and also the problems caused by the scale of time steps. Finally, the applications of the MD simulations in different areas of scinece are listed which are drug discovery, allostery and structure predictions of some macromolecules. It is discussed how MD simulations are

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used to investigate the structures and future properties of macromolecules, as well as how this is applied to practical applications.

2. MD simulations

The underlying concept behind MD simulations is the force field. The forces acting on each single atom by other atoms can be calculated if the positions of all of the atoms in that system are known. As a result, Newton's law can be applied to calculate the forces exerted on each atom, and their accelerations, velocities, and positions in space can be obtained in further calculations. By repeatedly calculating the forces and positions of the atoms in that system for billions of times, the function related to time is available to simulate the whole motion of the system in three dimensions as long as 1 femtosecond or even longer.The method used to calculate the trajectory is named as a molecular mechanics force field, which is used extensively for the measurements of experiments. In detail, most of the force fields contains several terms which can test Coulombic interactions, simulate the length of covalent bonds and so on. The calculations of the simulations are fairly easy although these equations of force fields are complicated. Some terms and concepts such as Lennard-Jones potentials, Coulomb's law for van der waals and bond length and angles speed up the calculations of the whole simulations[4]. Compare to the classical MD simulations where the covalent bonds are not supposed to be broken, the molecular mechanics simulations mentioned before are applied to study the broken down and formation of covalent bonds or the reactions with the presence of light.

To make sure the figures of integration of the motion are numerically stable, the time step should be short enough that it is supposed to be shorter than the fastest movement in that molecule which might be about 1 to 2 femtoseconds for each in the atom-level simulation. The majority of biochemical reactions such as reactions of proteins requires much longer time than a time step for about nanoseconds or microseconds. As a result, a huge amount of time steps as many as billions are necessary for a whole simulation. As a result, computer clusters or supercomputers are required for the calculations of MD simulations with the performance of a great quantity of processors in parallel. Several studies which compare and analysis the data obtained from the MD simulations have been applied to the area of computers[5]. MD simulations can be used in nuclear magnetic resonance (NMR) because the MD simulations can take the samples of receptors and ligand conformations for NMR measurements such as spin relaxation[6].

3. Limitations and strengths of MD simulations

Although the MD simulations are considered to be a very successful model in many areas especially in the biochemistry, there are still several limitations which restrict the utility of MD simulations and its future development. In particular, MD simulations are limited by two main problems which are force fields which still need further improvement and time step longer than a microsecond which is restricted by existing computational conditions. This results in a serious consequence that the MD simulations are not able to take enough samples under the conformational states during the time steps.

3.1. Limitations and causes

The degree of accuracy of the measurements obtained from the MD simulations is not high enough because the force fields are just approximate values of quantum mechanics at the atomic level. Although MD simulations can be applied for the prediction of most of the motions of particles, some changes in systems with quantum effects can not be simulated due to the approximations.

Aside from the effects of quantum mechanics, the second limitation, as we mentioned before, is that the scale of the time step is too short for understanding the whole reaction. In the case of drug discovery, it is required to explore all the possibilities of conformational states of the protein by using the MD simulations if the researchers aim to produce more accurate figures about the thermodynamic properties and other related configurations which play an important role in the drug industry. As we known that the time step of the MD simulations are currently only in the scale of a millionth of a second which is much shorter than time scales of most biochemical reactions. This results in high

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demand of computational ability and inaccuracy as the sacrifice of numerical stability. In reality, in the past 25 years, the computer power has seen a huge increase and tailored hardwares can be applied to the MD simulations that the speed of calculations can be amplified by Anton supercomputers by about two orders of magnitudes [7]. So the lack of computational ability may not be a problem any more in the future.Also, the MD simulations can be quite sensitive to the algorithms and protocol when assessing the reactions with longer time steps such as protein folding. This proves the importance of analysing and avoiding some approximations[8]. Also, the effectiveness of the MD simulations depends on the accuracy and availability of the macromolecular structures. For example, an accurate homologous model or a protein structure can be quite helpful in running the MD simulations[9].

In reality, MD simulations are facing a huge challenge in this century, which will have a profound impact on the whole area. The calculations of free energy are extremely significant for the simulations of the macromolecule ligand and the intermolecular interactions or forces. The free energy determines the strength of intermolecular interactions, conformational transitions, and binding. To ensure accuracy, it is necessary to correct to within two factors. However, there are two main problems that need to be solved, which are the lack of space and force fields, which are dependent on each other. If free energy can be calculated accurately, it can make a remarkable contribution to drug design because the design of a ligand can be obtained.

3.2. Strengths and future development

In fact, there are several factors which lead to the wide application of MD simulations. The most important two potantial causes are that the increased focus on the field of biochemistry and the advanced technology which has been developed to support the operation of MD simulations. Especially for the area of neuroscience, the experiments set for some specific biochemical molecules such as the G protein-coupled receptors (GPCRs) , ion channels and neurotransmitter transporters and so on all experience a dramatic growth because of the wide space and range and huge resolutions. MD simulations are able to provide variaty of information so as to answer a lot of kinds of questions. For example,the functions of protein when designing the drugs and the mechanism of the aggregation of these proteins in some cases. In addition, the MD simulations are frequently used in the evaluation of properties including stability and mobility of some biochemical molecules. It is only required to assess the simulation of the sturcture generated by using X-ray or cryo-EM so as to obtain the movement range of molecules at equilibrium states. These functions of the MD simulations are critically important for the exploration of the dynamics of specific molecules and ions in the solutions in the drug design.

Fortunately, due to the development of computational ability in the recent decades, both the speed and accuracy of the MD simulations have been improved although the speed is optimized first rather than accuracy. Some advanced technologies have been already applied into this simulations which are integration, single-step perturbation and free energy perturbation.

4. The drug discovery

MD simulations are so widely used in drug discovery that they are almost universally applied to all macromolecular research, including proteins and carbohydrates. MD simulations play an extremely important role in biochemical experiments to explore the dynamic properties of proteins and design drugs based on structures. Compared to the MD simulations, some conventional experimental tools such as X-ray crystallography and NMR can only provide static models, which are different from the true ligands bonded to receptor configurations. These non-dynamic models depending on a single receptor structure can only bring researchers information about the overview of microstructure. But these information is not sufficient for exploring the detailed dynamic motions of smaller molecules for example it is a dynamic process when ligand getting close to the receptor. Moreover, the MD simulations are especially important due to its contribution in simulating the molecule properties which are quite difficult to be detected especially in the experiments under other conditions. Referring

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to the experiments done for the design of ligand and protein in drug discovery, by using the MD simulations, the molecules with a large quantity tested in the experiment can be filtered into a smaller group according to their binding energy levels and stability. The MD simulations have the use to calculate the free energy of ligand and receptor binding. Positions of potential ligand and the binding on the drug target can be probed. In particular, only the pairs of ligand and receptors which are closely bonded can be left after this filtration of simulations after the target being soaked in the small ligands completely.

The MD simulations can be very helpful in discovering the agonist which have the several functions including stimulating the receptors until activation, acting as a partial agonist to signal at a smaller extent or an inverse agonist which lowers the strength of signal on the base if it is unliganded. At present, the realm of designing the biased ligand worths exploration because these ligands have the ability to stimulate specific signal path instead of other routes with the same receptors. The MD simulations are thought to be very powerful in this area because this drug-related design is far more challenging that a in-depth insight of conformations of receptors is necessary.

5. Allostery

The researchers put more focus on the conformational transitions which is also called allostery, a phenomenon related to protein. This is the process which shows one of the most valuable properties of protein that these biomolecules can transfer the effect of a ligand-binder stimulus to another spot[9]. Some methods such as NMR and X-ray crystallography are able to show the figures of binding pockets with endogenous ligands in it. However, these technologies are not inadequate to reveal all the targeted sites in some cases. Compared with them, the MD simulations are proved to be extremely effective in this area by demonstration of Nobel prize in 2013. These kinds of simulations are more useful to identify these potential sites which can be very obscure by using NMR and X-ray. In additional, the allostery sites can also be found by the MD simulations such as the binding sites and allosteric sites on the human beta1 and beta2 receptors.

The MD simulations have two particularly outstanding strengths of simulating the allostery in fact. The first one is that a detailed description about the behaviors of protein can be provided even in relatively high resolution in the two spaces. The second one is said to be the special control system of the simulations that the researchers are able to add extra well-designed perturbations into the closed system. Take an example that the external forces can be exerted on the part of molecules and also extra receptors and ligands can be introduced to explore their impact on the whole process and motions[9].

However, the MD simulations also have some limitations especially for the research of allostery. It is mentioned before that there are inaccuracies caused by the approximations of force fields or quantum mechanics. The scale of the time step is also too short for the critical biochemical reactions like conformational transitions in allostery. Apart from these, also, the algorithm of stomistic simulations are still not capable for a full process of conformational transition. It takes a long time to analyze the complete path of known transitions without having detailed information about one of the ends. The current MD simulations are still too unstable to use conformational ensembles straightforwardly.

6. Conclusion

This overview introduces the basic mechanism and applications of molecular dynamics simulations briefly. This methodology is an extremely valuable tool for researchers to explore the depth of biochemistry. In the recent future of about thirty years, it is predicted that the computational power of computers is likely to be a million times greater than present. According to Moore's law, the quantity of transistors on a microchip increases two times every two years. So, with the weakness of low calculation ability eliminated, some of the thorny problems can be solved. Larger simulations and larger scales of time steps are achievable for the increase in the quantity of samples of conformational space. Also, the simulations can get rid of the boxes with a scale of one cubic micrometer on the edges.In fact, there are several limitations to my overview of the MD simulations. This overview only

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mentions some general strengths and weaknesses of the MD simulations without adequate detailed examples. It is supposed that it is not enough to just cite the data from experiments from other researchers, so it is necessary to use the MD simulations to explore the properties of materials in the future after entering the university if possible. Also, in the general introduction of the MD simulations in this overview, more detailed explanations and elaborations about how the mathematical expressions are applied are required.

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References

[1] B. J. Alder and T. E. Wainwright. 1957 Phase transition for a hard sphere system. J. Chem. Phys., 27:1208–1209, .

[2] Mark E. Tuckerman, P. Jeffrey Ungar 1996 Molecular Dynamics Simulations J. Phys. Chem. , 100, 12878-12887

[3] Karplus, M., McCammon, J. Molecular (2002)dynamics simulations of biomolecules. Nat Struct Mol Biol 9, 646–652.

[4] Adam Hospital1 Josep Ramon Goñi2,3 2015 Molecular dynamics simulations: advances and applications Advances and Applications in Bioinformatics and Chemistry 37-47

[5] van Gunsteren WF, Dolenc J, Mark AE 2008 Molecular simulation as an aid to experimentalists. Curr Opin Struc Biol , 18:149-153.

[6] Jacob D Durrant and J Andrew 2011 McCammon Molecular dynamics simulations and drug discovery. Durrant and McCammon BMC Biology 9-19

[7] David W. Borhani • David E. Shaw 2011 The future of molecular dynamics simulations in drug discovery. Perspective 16-26 DOI 10.1007/s10822-011-9517-y

[8] Elmar Krieger* and Gert Vriend 2015 New Ways to Boost Molecular Dynamics Simulations Journal of Compu- tational Chemistry 996-1007

[9] Hertig S, Latorraca NR, Dror RO (2016) Revealing Atomic-Level Mechanisms of Protein Allostery with Molecular Dynamics Simulations. PLoS Comput Biol 107-130