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Molecular Dynamics Simulations: A Systematic Review of Techniques and Applications in Biochemistry

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Abstract Molecular dynamics (MD) simulations have become a pivotal tool in biochemical research, providing profound insights into molecular interactions and dynamic behaviors at the atomic level. This study comprehensively reviews the historical development, fundamental theories, and key techniques of MD simulations, including all-atom simulations, coarse-grained simulations, and hybrid quantum mechanics/molecular mechanics (QM/MM) simulations. Enhanced sampling techniques, such as metadynamics, replica exchange molecular dynamics (REMD), and adaptive biasing force (ABF) methods, are discussed, with a focus on their roles in overcoming energy barriers and sampling rare events. Advanced analysis methods, including trajectory visualization, energy decomposition analysis, and principal component analysis (PCA), are also reviewed, with an emphasis on their applications in protein conformational studies. This study aims to highlight the central role of MD simulations in elucidating biomolecular behaviors and to provide guidance for their future research and technological development.

Keywords Molecular dynamics simulations; Biochemical research; Enhanced sampling techniques; Protein conformational studies; Drug design

1 Introduction

Molecular dynamics (MD) simulation, which was first applied to study the photoisomerization of rhodopsin in the 1970s, has evolved from a conceptual computational method to a fundamental tool in biochemical research (Sinha et al., 2022). Back then, it was first used in protein research despite the limited computing power available. Nowadays, with more powerful computing devices and more efficient algorithms, MD has been widely applied in various fields and is no longer merely a theoretical tool (Xu, 2023).

In simple terms, MD simulation is to "virtually" reproduce the movement process of molecules in a computer, especially for large biological molecules like proteins. It can record the behavior of molecules at the atomic level with extremely small time steps - a level of detail that many experimental methods find difficult to achieve (Hollingsworth and Dror, 2018; Wu et al., 2022). Therefore, many scientists use it to observe how molecules move, change, and even interact with other molecules. More specifically, this technology is very useful in understanding the changing patterns of proteins. For instance, it is often used to study the binding process between small molecule drugs and proteins, how two proteins recognize each other, or how the structure of a protein changes after mutation (Liu et al., 2018; Lazim et al., 2020). Through these simulations, researchers can obtain detailed information on energy changes and structural changes, which are crucial for understanding the functional relationships of molecules. Processes such as new drug design and target optimization also frequently rely on the reference data provided by MD simulations (Salo-Ahen et al., 2020).

This study will systematically review the technological development and practical applications of MD simulation. The focus will be on some of the latest technical improvements, including the optimization of force fields (i.e., mathematical models used to calculate the forces between atoms), more powerful sampling methods, and the integration with other computational techniques. The application section will mainly concentrate on protein dynamics analysis, drug screening, and research related to membrane proteins, hoping to provide some ideas and inspirations for subsequent biochemical research.

2 Molecular Dynamics Simulation Basics

2.1 How force fields work

In MD simulations, force fields are like rulebooks that tell atoms how to interact. Popular ones like AMBER, CHARMM, and GROMOS use real-world experimental data and some quantum math to predict how molecules will behave (Conde et al., 2022). These rules need to be accurate but not too complicated, otherwise the computer takes forever to run the simulation. Some scientists are now using AI to improve these force fields, especially for tricky quantum effects, making the results more trustworthy.

2.2 Newton's laws drive the simulation

MD simulations basically work by applying Newton's physics over and over to track how particles move. At every tiny step, the computer calculates where atoms should go next, kind of like making a stop-motion movie of molecules (Arya and Bhatt, 2021). This works great for watching big molecules like proteins do their thing inside cells (Hollingsworth and Dror, 2018). But you've got to be careful with settings like boundary conditions and math formulas – get these wrong and your simulation goes off track.

2.3 Timing matters: fast vs. slow motion

Picking the right time step is key in MD. Usually, updates happen every 1-2 femtoseconds (that's super fast!) to catch quick movements like hydrogen bonds shaking (Pan et al., 2022). But there are tricks to speed this up, like tweaking hydrogen atom weights (HMR method) or swapping hydrogen isotopes (HIE trick), letting you use 5-7 fs steps without losing much accuracy. There are two main approaches: equilibrium simulations (studying stable systems) and non-equilibrium ones (watching systems react to changes), both super useful for studying protein folding and shape-shifting (Habasaki et al., 2017).

3 Key Methods of Molecular Dynamics Simulation

3.1 Atomic-level simulation: seeing the details

In molecular dynamics research, atomic-level simulation (all-atom simulations) is the most common approach. It involves directly modeling every atom in the system, leaving no detail unaccounted for. This simulation method provides relatively precise feedback on the interactions between molecules and is particularly useful in studying complex biological structures such as proteins, DNA, or cell membranes. Through this method, researchers can observe minute changes at the atomic level, such as conformational changes, which are crucial for understanding key biochemical reaction processes (Li, 2024). Although the computational load is considerable, with powerful enough equipment, many microscopic changes can be captured.

3.2 Coarse-grained simulations: focus on the whole rather than the details

When the system to be simulated becomes large or the simulation time is extended, the atomic level may become "unmanageable". At this point, a different approach can be adopted - coarse-grained simulations. This method involves combining a group of atoms into a "particle" (or "bead"), which simplifies the molecular structure to a certain extent. Although the specific movements of each atom cannot be observed, the overall dynamic characteristics remain. The greatest advantage of the CG method is that it can save a significant amount of computing power, and it is often used to study the movement of large molecular systems, such as membrane structures or protein aggregation processes (Sokkar et al., 2015).

3.3 QM/MM hybrid simulation: balancing accuracy and efficiency

When the research objective involves electronic behavior, such as reactions at the active sites of enzymes or the process of molecular binding, traditional molecular mechanics methods alone are insufficient. This is where "QM/MM hybrid simulation" comes into play. The idea behind this approach is to "break through the key points": the reaction center is treated with quantum mechanics to obtain a true depiction of the electronic structure, while the rest of the system is still modeled using molecular mechanics to simplify the computational load. This way, the accuracy of the critical regions is maintained without making the entire simulation overly burdensome (Brunk and Rothlisberger, 2015; Kulkarni et al., 2021; Chow et al., 2023). At present, this hybrid approach has been widely applied in fields such as molecular reaction dynamics, research on biological enzyme catalysis, and new drug screening. In recent years, new techniques like "adaptive partitioning" and "introduction of machine learning

models" have also been integrated, further enhancing the efficiency and stability of QM/MM simulations (Duster et al., 2019).

4 The Application of Enhanced Sampling Technology in Molecular Dynamics

4.1 Metadynamics method driven by free energy

4.1.1 Construction of bias potential energy and its role in sampling

Metadynamics is a molecular simulation strategy that can significantly improve sampling efficiency. By introducing a bias potential related to the simulation history, it helps the system break away from the local energy minimum region that is prone to fall into in traditional molecular dynamics (MD). Specifically, this bias potential energy is gradually added over several ** collective variables (CVs) ** - these variables reflect the slowest moving but most critical degrees of freedom for conformational changes in the system. By continuously superimposing small amounts of repulsive Gaussian functions on these CVs, Metadynamics can effectively "fill in" the low valleys on the free energy surface, thereby guiding the system out of the local stable state and accessing a richer conformational space (Pfaendtner, 2019).

4.1.2 Enhance the efficiency across energy barriers and the sampling capability for rare events

One of the most prominent advantages of Metadynamics over traditional MDS is its ability to traverse high-energy barrier regions, making it particularly suitable for capturing low-frequency but critical molecular events such as protein folding and ligand recognition. Because these events often occur on a nanosecond or even millisecond time scale, conventional simulation methods find it difficult to observe them within a reasonable time frame. Metadynamics significantly compressed the required sampling time by applying dynamic bias to CVs, enabling researchers to reveal the transition path and the underlying free energy structure (Zhang, 2024).

4.1.3 Case study: from folding paths to the application of combining mechanisms

Metadynamics has been widely used to analyze dynamic behaviors in various biological systems, such as protein conformational changes and small molecule binding mechanisms. In the study of Aib9 helical peptides, this technique was used to generate the initial conformation set, and then combined with the Markov state model for analysis, thereby characterizing the dynamic characteristics between peptide chain folding and unfolding (Biswas et al., 2018). Furthermore, in exploring the binding energy of flexible protein-ligand complexes, Metadynamics has demonstrated a powerful ability to capture the enthalpy-entropy co-changes during the binding process (Wingbermuhle and Schafer, 2020).

4.2 Multi-temperature exchange: replica exchange molecular dynamics (REMD)

Replica Exchange Molecular Dynamics (REMD) provides another efficient method for exploring complex free energy surfaces. Unlike single-trajectory simulation, REMD operates replicas of the system simultaneously at multiple different temperature points. These replicas attempt to exchange conformations within a set period, thereby enhancing the system's ability to break through energy barriers. This temperature exchange strategy enables the system to rapidly traverse multiple conformational states, and is particularly suitable for systems with rough free energy surfaces and dense local minima, such as the folding paths of proteins or conformational rearrangements of biological macromolecules (Bernardi et al., 2015; Kamberaj, 2018).

4.3 Adaptive offset force (ABF) method

This ABF method is actually quite interesting. It mainly addresses the issue of low sampling efficiency in molecular simulation. In simple terms, it is to dynamically adjust the applied bias force during the simulation process. This force will counteract the free energy gradient of the system (the free energy gradient can be understood as the energy barrier encountered by molecules during movement).

Unlike traditional methods, the uniqueness of ABF lies in the fact that its bias force constantly self-updates during the simulation process. In this way, the system can more smoothly explore the changes in free energy under different states. For instance, when studying the binding of drug molecules to proteins (Yang et al., 2019), or observing conformational changes in proteins (Lazim et al., 2020), this method is particularly effective.

5 Analytical Methods in Molecular Dynamics Simulation

5.1 Trajectory analysis and visualization

In Molecular Dynamics (MD for short) simulations, trajectory analysis and visualization are important ways to understand the evolution of systems over time. With the help of these technical means, researchers can visually observe the structural changes of molecules during the simulation process. Tools like PathReducer can compress the molecular conformational trajectories originally in high-dimensional Spaces to be presented in lower dimensions, while retaining their core geometric variation information as much as possible, thereby helping to analyze complex conformational movements and reaction pathways. Especially for reaction trajectories or large-scale dynamic processes, PathReducer will extract the principal components that best reflect the geometric changes through principal component analysis (PCA), thereby achieving the visualization and dimensionality reduction reconstruction of structural changes (Figure 1) (Hare et al., 2019). Furthermore, Sliding Window Principal Component Analysis (sw-PCA) can be used to capture instantaneous cooperative motion in long-term scale simulations, providing assistance for detecting key events such as conformation transitions (LeVine et al., 2015).

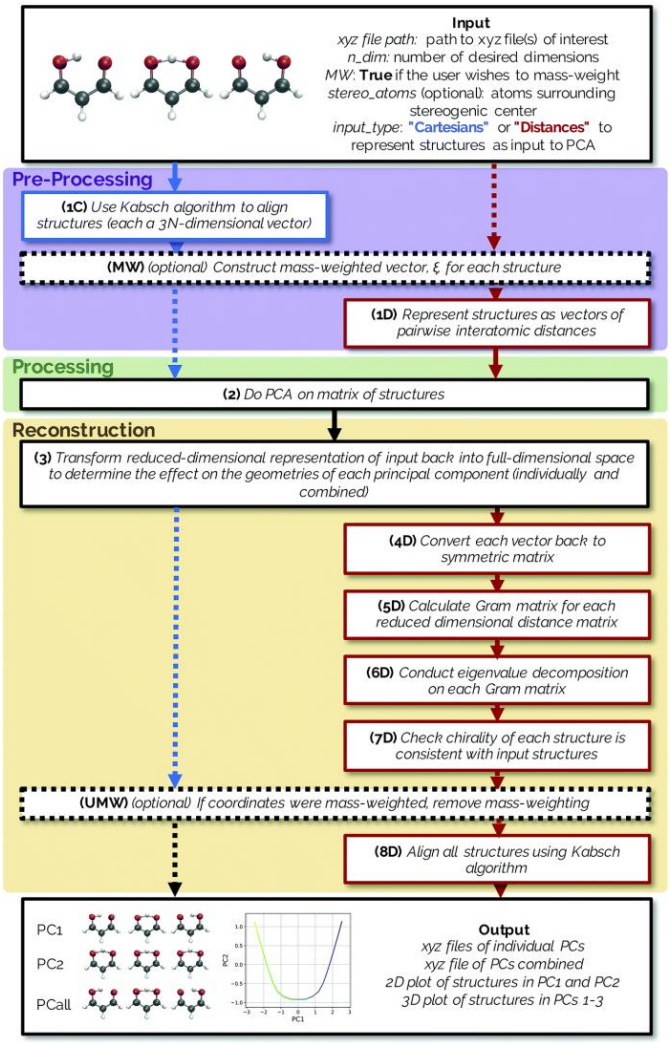

Figure 1 A flowchart indicating how PathReducer works. The blue arrows/boxes represent the procedure used if the user specifies a "Cartesians" input to PCA and the red arrows/boxes represent the path taken with a "Distances" input specified. Black arrows/boxes are parts of the method shared by both input types (Adopted from Hare et al., 2019)

5.2 Energy decomposition method

Energy Decomposition Analysis (EDA for short) is a technique that divides the total energy of a system into different components, including kinetic energy, potential energy, and intermolecular interaction energy, etc.

Through this method, it is possible to more clearly identify which energy components play a major role in the stability or dynamic behavior of the system. In simulations such as Replica Exchange molecular dynamics (MD), this method can also be combined with the probabilistic framework to analyze the energy landscape, thereby identifying the metastable regions of the system (Palma and Pierdominici-Sottile, 2022). This approach is particularly important for understanding the distribution pattern of free energy in complex systems.

5.3 Principal component analysis and clustering methods

5.3.1 The principle and practical application of PCA

Principal Component Analysis (PCA) is a common method for processing high-dimensional information in MD trajectory data, which can help researchers identify the covariate that contributes the most to system changes. It makes the interpretation of complex molecular motion more operable by compressing the original multi-dimensional data to a few main axes (Post et al., 2019; Morishita, 2021. PCA can not only be used for equilibrium state simulation, but also has certain adaptability to non-equilibrium processes (such as conformational transformation). Furthermore, time-dependent PCA analysis can also reveal the phased evolution of structural changes, thereby providing a more detailed dynamic explanation.

5.3.2 The role of clustering methods in conformational space analysis

Cluster analysis is indispensable in the study of the conformational space of molecular systems. Like density-based clustering algorithms, they can effectively identify conformational clusters that exhibit local stability on the Potential Energy Surface, namely the so-called metastable state. This is particularly important in the study of dynamic processes such as protein folding and unfolding. Furthermore, the clustering method combined with correlation feature screening can better distinguish the real cooperative motion from the background noise, which is conducive to improving the recognition accuracy of functional motion (Diez et al., 2022). This strategy is often adopted when analyzing signal paths and structural adjustment mechanisms in complex biological systems.

5.3.3 The combined application of PCA and clustering in the study of protein conformational changes

The combined use of PCA and clustering methods can more comprehensively depict the conformational transformation that proteins undergo during the simulation process. For instance, the PCA-driven Parallel Cascaded selective Molecular dynamics (PaCS-MD) approach successfully captured rare large-scale structural changes occurring in certain proteins by screening conformations with high transition potential and conducting short-term simulations (Yasuda et al., 2020). This technology is applicable to the study of rare events that are not easily observed through traditional methods. In addition, by projecting the simulated trajectories into the dimensionality reduction space, researchers can also more clearly compare the differences between different paths and the path with the lowest energy, thereby gaining a more intuitive understanding of the conformational channels.

6 The Application of Molecular Dynamics Simulation in Protein Structure Research

6.1 Exploration of conformational changes and dynamic behaviors of proteins

Molecular dynamics (MD) simulation, as a computational method, has been widely applied in analyzing the conformational changes and dynamic behaviors of proteins. Proteins themselves are not static; they possess strong structural plasticity, which is crucial for them to perform biological functions such as allosteric regulation and ligand binding. The full-atom explicit solvent simulation study through enhanced sampling technology shows that the current force field model and sampling strategy can reasonably reproduce the slow structural transformation of proteins from the primary state to the secondary state. In addition, such simulations also reveal the structure and biophysical properties of those intermediate states that exist instantaneously and are difficult to capture experimentally. With the aid of these simulation methods, researchers were able to depict the movement trajectories of proteins in the free energy space and further reveal the coupling relationship between conformational changes and molecular recognition processes. For example, this was verified in the study of ribose-binding proteins (Ren et al., 2021).

6.2 Protein-ligand interaction and prediction of binding free energy

In addition to conformational studies, MD simulations have also demonstrated significant value in elucidation of protein-ligand interaction mechanisms and prediction of binding free energy. By simulating the dynamic changes during the ligand binding process, researchers can observe the conformational rearrangements that proteins undergo during the binding process. For example, coarse-grained simulation methods have been used to analyze the coupling mechanism between protein conformational changes and ligand binding, and several key links of this process have been successfully reproduced (Negami et al., 2020). To further enhance the sampling efficiency and accuracy, researchers have also developed enhanced sampling techniques including solute tempering generalized copy exchange, etc., to explore conformational changes induced by ligands. These methods not only draw a complete free energy map, but also enhance the quantitative predictive ability of binding affinity. Overall, the computational framework based on MD is of great significance for revealing the molecular mechanism of ligand recognition and improving the accuracy of binding free energy prediction (Kukol, 2015).

6.3 Case analysis: structural dynamic simulation study of GPCR

G protein-coupled receptors (GPCRS) are a class of important transmembrane proteins, and the process of regulating their activity often involves obvious conformational transitions. In recent years, MD simulation technology has played a key role in explaining the structure-function relationship of GPCRS. Existing studies have shown that MD simulation can accurately reproduce the overall conformational reconstruction process experienced by GPCRS before and after ligand binding, provide the ability to analyze the transition path at the atomic level, and reveal the association between local binding events and overall conformational changes (Tamura and Hayashi, 2015). These simulation results not only deepen our understanding of the functional mechanisms of GPCRS, but also provide strong theoretical support for structure-oriented drug design.

7 The Practical Application of Molecular Dynamics Simulation in Enzyme Catalysis and Drug Design

7.1 Dynamic analysis of enzyme active sites and research on catalytic mechanisms

When it comes to how enzymes work, molecular dynamics simulation (MD) has really been of great help. It can not only clearly see how the active site moves around, but also explain the specific steps of the catalytic reaction. For instance, by using the QM/MM mixed method or ordinary MD simulation, scientists can now figure out why certain amino acids are particularly important and how the protein environment affects the entire reaction. However, it should be noted that these simulation results still need to be combined with experimental data. By tracking how substrates enter and exit, how reactions occur, and how products leave, our understanding of enzymes has indeed deepened significantly (Zhao et al., 2016). What is particularly practical is that this simulation can also demonstrate the influence of factors such as temperature changes and solvent molecules on the binding of proteins and ligands - which is especially crucial for modifying enzymes or designing new catalysts.

7.2 Application of molecular simulation in virtual screening

When looking for new drugs, MD simulation has now become a standard tool. Compared with traditional methods, its greatest advantage is that it can take into account the flexibility of protein structure. By calculating the energy changes and movement trajectories between drug molecules and target proteins, researchers can predict the binding effects more accurately. Some studies have found that after considering the entropy change effect, the consistency between the simulation results and the experimental results can be increased by about 30% (Vivo et al., 2016). Although the computational load is a bit large, the binding conformation obtained in this way is more reliable. Even those binding postures that are prone to errors in traditional molecular docking can now be predicted more accurately.

7.3 Practical case: predicting the mode of action of anti-cancer drugs through simulation

For instance, recently, someone used MD simulation to study the interaction between the breast cancer target MTDH and SND1 proteins. Through an extremely long simulation period (it is said to have taken nearly three months)" They not only identified potential drug binding sites but also screened out a batch of promising inhibitors (Figure 2) (Xu et al., 2023). Interestingly, these simulation results match the subsequent cell experiment

data. Another case is the drug design targeting PKC - because this protein is particularly difficult to handle when staying on the cell membrane, but by simulating the membrane environment, researchers still successfully optimized several candidate drugs (Lautala et al., 2023). These examples demonstrate that although MD simulation is not omnipotent, as long as it is applied in the right place, it can indeed significantly accelerate the development of new drugs.

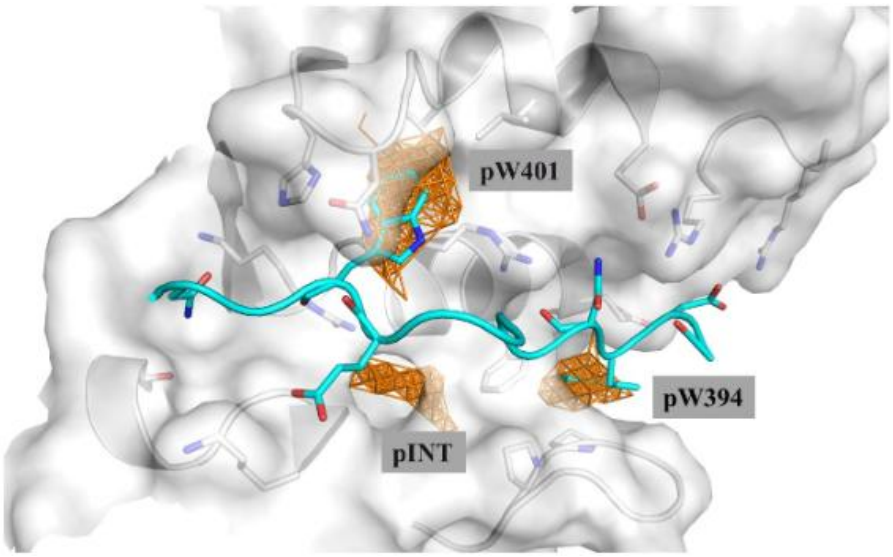

Figure 2 The corresponding pockets pW401, pINT, and pW394 generated based on MTDH-SND1 co-crystal structure 4QMG.The pockets were represented by the frequency grid (brown meshes) with a cut-off of 0.5 using Fpocket (Adopted from Xu et al., 2023)

8 Summary

Molecular dynamics (MD) simulation has become an important tool in modern biochemical research, enabling scientists to observe the movement and interaction of biological macromolecules at the atomic level. By capturing dynamic behaviors such as conformational changes in proteins, molecular recognition processes, and structural changes related to diseases, MD has become indispensable in mechanism research and early drug development. Especially in the simulation of super-large molecular structures such as viral capsid or ribosome complexes, it fills many knowledge gaps that are difficult to solve by traditional experimental methods.

One of the greatest advantages of MD is its ability to analyze the subtle fluctuations and transient interaction patterns of molecules, which are crucial in the target validation, lead compound optimization, and even formulation adjustment stages of drug development. It is particularly worth mentioning that the improvement of the enhanced sampling algorithm (these techniques can capture rare biologically related states more quickly) has greatly enhanced the efficiency and predictive ability of the simulation. However, MD simulation still requires a large amount of computing resources, especially when simulating macromolecular systems or long-duration processes at the microsecond or millisecond level.

Although the classic MD force field (the set of parameters that control atomic interactions) has achieved great success over the past few decades, they usually ignore the polarization effect (the response ability of the electron cloud to the external environment), which can affect the authenticity of the simulation results. Recently developed polarizable force fields are attempting to address this issue, making the simulation of electrostatic interactions in complex systems more accurate.

The large amount of structural dynamic data generated by MD simulation also brings challenges in storage, pattern recognition and data analysis. For this reason, researchers have begun to introduce artificial intelligence, especially machine learning techniques, to optimize data processing procedures and automatically extract key features. Despite the promising prospects, these calculation methods are still in their infancy and need further improvement.

In the future, continuously optimizing force field parameters (especially models with adaptive polarization) is crucial for enhancing the authenticity of MD simulations. At the same time, it is equally important to rationally apply AI tools to improve sampling strategies and analyze massive amounts of data. These advancements can not only enhance the simulation accuracy but also shorten the analysis time for complex biochemical research. Furthermore, expanding the popularization of high-performance computing resources is crucial for supporting large-scale MD projects. Finally, strengthening the cooperation between computational model researchers and experimental scientists can ensure that simulation hypotheses are always based on experimental facts, forming a virtuous cycle and promoting the progress of innovation and drug development.

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

References

Arya H., and Bhatt T., 2021, Molecular dynamics simulations, The Design and Development of Novel Drugs and Vaccines, 12(2): 190-196.
https://doi.org/10.1016/B978-0-12-821471-8.00005-2

Bernardi R., Melo M., and Schulten K., 2015, Enhanced sampling techniques in molecular dynamics simulations of biological systems, Biochimica et Biophysica Acta, 1850(5): 872-877.
https://doi.org/10.1016/j.bbagen.2014.10.019

Biswas M., Lickert B., and Stock G., 2018, Metadynamics enhanced markov modeling of protein dynamics, The Journal of Physical Chemistry, 122(21): 5508-5514.
https://doi.org/10.1021/acs.jpcb.7b11800

Brunk E., and Rothlisberger U., 2015, Mixed quantum mechanical/molecular mechanical molecular dynamics simulations of biological systems in ground and electronically excited states, Chemical Reviews, 115(12): 6217-6263.
https://doi.org/10.1021/cr500628b

Chow M., Lambros E., Li X., and Hammes-Schiffer S., 2023, Nuclear-electronic orbital QM/MM approach: geometry optimizations and molecular dynamics, Journal of Chemical Theory and Computation, 19(13): 3839-3848.
https://doi.org/10.1021/acs.jctc.3c00361

Conde D., Garrido P.F., Calvelo M., Piñeiro Á., and García-Fandiño R., 2022, Molecular dynamics simulations of transmembrane cyclic peptide nanotubes using classical force fields hydrogen mass repartitioning and hydrogen isotope exchange methods: a critical comparison, International Journal of Molecular Sciences, 23(6): 3158.
https://doi.org/10.3390/ijms23063158

Diez G., Nagel D., and Stock G., 2022, Correlation-based feature selection to identify functional dynamics in proteins, Journal of Chemical Theory and Computation, 18(8): 5079-5088.
https://doi.org/10.1021/acs.jctc.2c00337

Duster A., Garza C., Aydintug B., Negussie M., and Lin H., 2019, Adaptive partitioning QM/MM for molecular dynamics simulations: 6, proton transport through a biological channel, Journal of Chemical Theory and Computation, 15(2): 892-905.
https://doi.org/10.1021/acs.jctc.8b01128

Habasaki J., León C., and Ngai K., 2017, Molecular dynamics simulations, Topics in Applied Physics, 132: 355-414.
https://doi.org/10.1007/978-3-319-42391-3_8

Hare S., Bratholm L., Glowacki D., and Carpenter B., 2019, Low dimensional representations along intrinsic reaction coordinates and molecular dynamics trajectories using interatomic distance matrices, Chemical Science, 10: 9954-9968.
https://doi.org/10.1039/C9SC02742D.

Hollingsworth S., and Dror R., 2018, Molecular dynamics simulation for all, Neuron, 99: 1129-1143.
https://doi.org/10.1016/j.neuron.2018.08.011

Kamberaj H., 2018, Faster protein folding using enhanced conformational sampling of molecular dynamics simulation, Journal of Molecular Graphics and Modelling, 81: 32-49.
https://doi.org/10.1016/j.jmgm.2018.02.008

Kukol A., 2015, Molecular Modeling of Proteins, Humana Press, 443.
https://doi.org/10.1007/978-1-4939-1465-4

Kulkarni P.U., Shah H., and Vyas V.K., 2021, Hybrid quantum mechanics/molecular mechanics (QM/MM) simulation: a tool for structure-based drug design and discovery, Mini Reviews in Medicinal Chemistry, 22(8): 1096-1107.
https://doi.org/10.2174/1389557521666211007115250

Lautala S., Provenzani R., Tarvainen I., Sirna K., Karhu S., Grazhdankin E., Lehtinen A., Sa'd H., Koivuniemi A., Xhaard H., Tuominen R., Talman V., Bunker A., and Yli-Kauhaluoma J., 2023, Expanding the paradigm of structure-based drug design: molecular dynamics simulations support the development of new pyridine-based protein kinase c-targeted agonists, Journal of Medicinal Chemistry, 66(7): 4588-4602.
https://doi.org/10.1021/acs.jmedchem.2c01448

Lazim R., Suh D., and Choi S., 2020, Advances in molecular dynamics simulations and enhanced sampling methods for the study of protein systems, International Journal of Molecular Sciences, 21(17): 6339.
https://doi.org/10.3390/ijms21176339

LeVine M.V., Khelashvili G., and Weinstein H., 2015, Simultaneous identification visualization and comparison of complex events in molecular dynamics simulations, Biophysical Journal, 108(2): 379a-380a.
https://doi.org/10.1016/J.BPJ.2014.11.2082

Li M.M., 2024, Molecular mechanisms underlying the diversification of aquatic life forms, International Journal of Aquaculture, 14(4): 184-194.
https://doi.org/10.5376/ija.2024.14.0019

Liu X., Shi D., Zhou S., Liu H., Liu H., and Yao X., 2018, Molecular dynamics simulations and novel drug discovery, Expert Opinion on Drug Discovery, 13: 23-37.
https://doi.org/10.1080/17460441.2018.1403419

Morishita T., 2021, Time-dependent principal component analysis: a unified approach to high-dimensional data reduction using adiabatic dynamics, The Journal of Chemical Physics, 155(13): 134114.
https://doi.org/10.1063/5.0061874

Negami T., Shimizu K., and Terada T., 2020, Coarse-grained molecular dynamics simulation of protein conformational change coupled to ligand binding, Chemical Physics Letters, 742 (2020): 137144.
https://doi.org/10.1016/j.cplett.2020.137144

Palma J., and Pierdominici-Sottile G., 2022, On the uses of PCA to characterise molecular dynamics simulations of biological macromolecules: basics and tips for an effective use, Chemphyschem : a European Journal of Chemical Physics and Physical Chemistry, 24(2): e202200491.
https://doi.org/10.1002/cphc.202200491

Pan X., Van R., Epifanovsky E., Liu J., Pu J., Nam K., and Shao Y., 2022, Accelerating Ab initio quantum mechanical and molecular mechanical (QM/MM) molecular dynamics simulations with multiple time step integration and a recalibrated semiempirical QM/MM hamiltonian, The Journal of Physical Chemistry B, 126(23): 4226-4235.
https://doi.org/10.1021/acs.jpcb.2c02262

Pfaendtner J., 2019, Metadynamics to enhance sampling in biomolecular simulations, Methods in Molecular Biology, 2019: 179-200.
https://doi.org/10.1007/978-1-4939-9608-7_8

Post M., Wolf S., and Stock G., 2019, Principal component analysis of nonequilibrium molecular dynamics simulations, The Journal of Chemical Physics, 150(20): 204110.
https://doi.org/10.1063/1.5089636

Ren W., Dokainish H., Shinobu A., Oshima H.M., and Sugita Y., 2021, Unraveling the coupling between conformational changes and ligand binding in ribose binding protein using multiscale molecular dynamics and free-energy calculations, The Journal of Physical Chemistry B, 125(11), 2898-2909.
https://doi.org/10.1021/acs.jpcb.0c11600

Salo-Ahen O., Alanko I., Bhadane R., Bonvin A., Honorato R., Hossain S., Juffer A., Kabedev A., Lahtela-Kakkonen M., Larsen A., Lescrinier E., Marimuthu P., Mirza M., Mustafa G., Nunes-Alves A., Pantsar T., Saadabadi A., Singaravelu K., and Vanmeert M., 2020, Molecular dynamics simulations in drug discovery and pharmaceutical development, Processes, 9(1): 71.
https://doi.org/10.3390/pr9010071

Sinha S., Tam B., and Wang S.M., 2022, Applications of molecular dynamics simulation in protein study, Membranes, 12(9): 844.
https://doi.org/10.3390/membranes12090844

Sokkar P., Boulanger E., Thiel W., and Sánchez-García E., 2015, Hybrid quantum mechanics/molecular mechanics/coarse grained modeling: a triple-resolution approach for biomolecular systems, Journal of Chemical Theory and Computation, 11(4): 1809-1818.
https://doi.org/10.1021/ct500956u

Tamura K., and Hayashi S., 2015, Linear response path following: a molecular dynamics method to simulate global conformational changes of protein upon ligand binding, Journal of Chemical Theory and Computation, 11(7): 2900-2917.
https://doi.org/10.1021/acs.jctc.5b00120

Vivo M., Masetti M., Bottegoni G., and Cavalli A., 2016, Role of molecular dynamics and related methods in drug discovery, Journal of Medicinal Chemistry, 59(9): 4035-4061.
https://doi.org/10.1021/acs.jmedchem.5b01684

Wingbermühle S., and Schäfer L.V., 2020, Capturing the flexibility of a protein-ligand complex: binding free energies from different enhanced sampling techniques, Journal of Chemical Theory and Computation, 16(7): 4615-4630.
https://doi.org/10.26434/chemrxiv.11106806.v2

Wu X., Xu L., Li E., and Dong G., 2022, Application of molecular dynamics simulation in biomedicine, Chemical Biology and Drug Design, 99: 789-800.
https://doi.org/10.1111/cbdd.14038

Xu B., 2023, The application of molecular dynamic simulations, Applied and Computational Engineering, 7(1): 147-151.
https://doi.org/10.54254/2755-2721/7/20230416

Xu Y., Guo X., Yan D., Dang X., Guo L., Jia T., and Wang Q., 2023, Molecular dynamics simulation-driven focused virtual screening and experimental validation of inhibitors for MTDH-SND1 protein-protein interaction, Journal of Chemical Information and Modeling, 63(11): 3614-3627.
https://doi.org/10.1021/acs.jcim.3c00310

Yang Y., Shao Q., Zhang J., Yang L., and Gao Y., 2019, Enhanced sampling in molecular dynamics, The Journal of Chemical Physics, 151(7): 070902.
https://doi.org/10.1063/1.5109531

Yasuda T., Shigeta Y., and Harada R., 2020, Efficient conformational sampling of collective motions of proteins with principal component analysis-based parallel cascade selection molecular dynamics, Journal of Chemical Information and Modeling, 60(8): 4021-4029.
https://doi.org/10.1021/acs.jcim.0c00580

Zhang J., 2024, New methods for predicting drug molecule activity using deep learning, Bioscience Method, 15(1): 28-36.
https://doi.org/10.5376/bm.2024.15.0004

Zhao Y., and Cao Z., 2016, Global simulations of enzymatic catalysis, Acta Physico-chimica Sinica, 33: 691-708.
https://doi.org/10.3866/PKU.WHXB201612191