RESEARCH PAPER

Computational challenges and prediction accuracy in molecular simulation

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ABSTRACT
Molecular simulation is a set of modern computational techniques and a powerful tool for understanding the properties of molecules and biological systems at the atomic level. Its aim is to understand and predict the behavior and properties of these complex molecules and systems. The accuracy of the information depends on the quality of the software used, the precision of the computers, and the approximations used, especially Born-Oppenheimer approximation. This article aims to review the developments in molecular modeling and attempt to identify the best and most accurate techniques that provide information comparable to that obtained experimentally. It also summarizes the available literature and identifies the best techniques used to study physical and chemical properties. The article also aimed to highlight future prospects for understanding biological activity, the relationship between the chemical structure of drugs and antibiotic activity and side effects, and to identify gaps in research on this topic and attempt to address them with future research
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INTRODUCTION

Molecular modeling is a computer tool for simulating molecular systems at their interaction level. Its main importance lies in interpreting chemical reactions and arriving at the optimal and most stable form of biological compounds [1]. Quantum mechanics and molecular simulations have revolutionized computational chemistry, enabling the optimization of the structure of many complex biological materials that are difficult to study experimentally. Rapid advancements in computing have transformed molecular simulations into a tool for developing the electronic structures of drugs and some complex biological systems. Molecular simulations rely on a set of fundamental principles in calculations[2]:

1) Physical models (laws of motion):

Classical mechanics, which has existed for many years and for a long time, is based on Newton's laws of motion and uses molecular dynamics **(MD)** Molecular simulations rely on a set of fundamental principles in calculations. Computer simulations are used (MD) to iteratively study the motion of atoms and molecules and physical transformations . Molecular dynamics simulations link the behavior of individual molecules to thermodynamics, where temperature is a measure of the translational motion of molecules**[3]**. Through this, we can determine dynamic properties such as free energy and enthalpy for many protein molecules or complexes. Quantum thermodynamics is a relatively new field that studies uncertainty at the atomic and molecular level. Entropy, the second law of thermodynamics, is rooted in quantum chemistry and changes with Planck's constant and quantum numbers, unlike in classical physics where the total disorder can constant[4] .

2) Monte Cario :

In the 1940s, John von Neumann (physicist, mathematician, computer scientist, and polymath) created the Monte Calroy simulation. Monte Carlo **(MC)** simulation is a mathematical technique that predicts the outcomes of an uncertain event using computer programs and mathematical equations [5]. It is based on probability and incorporates uncertainty and random elements in the results, relying on random groups that obtain different outcomes. The statistical behavior of a moving point in a closed system is used. This point passes through many possible locations in a recurring system where computer programs are used to predict a range of future outcomes. The clearer the results, the more definitive the predictions[6] .

3)Force Fields :

Force fields in molecular simulations are experimental mathematical models used to calculate total energy (bonding and non-bonding energy) based on the molecule's coordinates at the atomic level, including bonds, angles, charges, and their most prominent fields , **AMBER** (Assisted Model Building with Energy Refinement)[7] , **CHARMM** (Chemistry at Harvard Mechanics) , **OPLS** (Optimized Potential For liquid simulations) .

4)Computer Simulation

It is a scientific method that uses computers to model the movement and interactions of atoms and molecules, where it represents molecules as mechanical systems and then determines their interactions and movement based on Newton's laws of motion. This simulation can deal with

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molecules of millions of atoms and can use supercomputers and parallel processing [8]. These simulations deal with molecules of millions of atoms that are not easily detectable; therefore, research has focused on simulating large protein molecules in order to obtain more interactive and effective materials and drugs [9].

Discussion and Application :

Quantum mechanics developed in the early 20th century (1900-1925) as a theoretical tool to explain many phenomena that classical physics could not explain, such as blackbody radiation and the photoelectric effect [10]. Early quantum theory emerged with Max Planck in 1900 in explaining blackbody radiation through the quantization of energy, and later with Einstein in 1905 explaining the photoelectric effect . 1913 Bohr was able to present a quantized atomic model in which electrons revolve in quantized energy orbits . Modern quantum mechanics (1925-1930), as developed by Schrödinger, was able to describe particles as wave functions [11], and Max Born 1926 was able to provide a probabilistic explanation of the wave function, Between 1927 and 1928, the English scientist George introduced a vague concept of quantum tunneling. Later, Dirac [12], Hilbert, and von Neumann developed molecular models that included metalloids and lasers, and the wave function became a tool for describing many physical systems. At the beginning of the 21st century, the second quantum revolution began, moving from an understanding of quantum mechanics to individual quantum states (superposition and entanglement) [13]. This phase focused on quantum computing, sensing, and communications. In the 1970s, John Clauser was able to confirm the phenomenon of quantum entanglement, while in the 1980s, Alain Aspect conducted crucial experiments that demonstrated the instantaneous response of entangled particles, earning them the 2022 Nobel Prize. But they were unable to undo the entanglement, leading to information loss[14] . In 1994 Peter Shor , a mathematician and computer scientist, discovered a quantum algorithm that could analyze large numbers into their elementary components faster than a conventional computer, and was able to solve many complex mathematical problems . between 1984-1985 John Clarke revolutionized quantum mechanics by conducting microscopic quantum tunneling experiments, demonstrating that electrical circuits made of conductive materials can behave like quantum particles. He also succeeded in quantizing energy in electrical circuits and was awarded the Nobel Prize in 2025 for this scientific discovery [15] . In 1990, Peter Schmidt, a mathematician and computer scientist, discovered a quantum algorithm that could analyze large numbers into their constituent elements much faster than a conventional computer. This algorithm enabled him to solve many complex mathematical problems. Researchers (Martin Bojowald at companies like Google and IBM have also contributed to the development of quantum computing, but it is still not possible to unify quantum mechanics with general relativity . The period from 2020 to 2025 witnessed tremendous leaps in quantum mechanics and molecular modeling, with a massive development and transition from research theories to practical applications [16]. Following Google's 2019 announcement of quantum supremacy and quantum computers, research focused on optical quantum computers, quantum sensing, and the quantum internet. Modern Algorithms were able to simulate complex chemical reactions at the molecular level. Research between 2020 - 2026 focused on using molecular modeling and quantum mechanics in drug development and determining the structure of some complex compounds that are difficult to characterize in the laboratory Research focused on using molecular modeling and quantum mechanics in drug development and determining the structure of some complex compounds that are difficult to identify. Scientists David Baker Jhon Jumper and[17] . Demis Hassabis able to decode proteins and predict protein structure through the use of molecular simulations, earning them the 2024 Nobel Prize.. and his research was largely free of errors or flaws. However, some scientists criticized quantum mechanics, arguing that scientific progress must be based on experimentation, NVIDIA , Jensen Companies have also developed hybrid platforms that allow the use of artificial intelligence and quantum processors to accelerate chemical space exploration [18]. The years between 2020 and 2026 witnessed significant leaps in molecular modeling, transforming it from a purely theoretical tool into a practical application and a key to many scientific discoveries, especially in the age of artificial intelligence. It was no longer used solely for predicting protein structure; it evolved to include the design of customized proteins that do not exist in nature for therapeutic and industrial purposes. Scientists successfully developed fluorescent proteins by simulating a process that would have taken 500 million years in just a few days. Molecular modeling also aided in the discovery of many drugs and how they interact with the entire cell, not just a single protein. This was particularly true after the development of numerous high-precision computers, which were used to design treatments tailored to each patient's genetic profile. Many research projects in this field have been awarded Nobel Prizes[19].

Challenges and future Prospects

The challenges in simulating molecules in modern quantum mechanics lie in the computational complexities, the precision of the computers used, and the difficulty of simulating chemical reactions in their real-world environment[20]. Despite improvements in algorithms, simulating molecular dynamics requires significant time and ultra-precise computing. Quantum computers still face errors due to the extreme sensitivity of qubits to environmental interference (loss of coherence) and the need for extreme cooling. Furthermore, the weakness of current encryption systems poses a security challenge that necessitates the use of post-quantum encryption [21], in addition to the limitations of algorithms that are still in their early stages. The future prospects of using quantum computers lie in overcoming the complexity barrier for many complex systems that were previously difficult to challenge experimentally and in revolutionizing medicine and materials science[22]. By simulating highly complex molecular interactions, quantum computers have

accelerated the production of highly effective therapeutic drugs. Moreover, the integration of artificial intelligence with quantum computing has led to significant developments in the world of medicine. Despite these promising prospects, it requires correcting quantum errors, developing a super cooling mechanism for some processors, and increasing research to achieve more comprehensive and accurate algorithms for dealing with complex biological systems[23].

Summary :

This article demonstrates that molecular simulation has transitioned from a simple supplement to a cornerstone of scientific research in protein synthesis and drug discovery. A review of previous literature reveals the remarkable advancements in quantum mechanics and molecular mechanics, enabling the unprecedentedly accurate characterization of biological systems. Current trends in the literature suggest that artificial intelligence will play a pivotal role in the future, both in developing intelligent fields and accelerating computations, thus opening new horizons. The future of molecular simulation lies in its shift towards practical application, accelerating drug discovery and the development of active ingredients, thereby reducing reliance on costly and time-consuming laboratory experiments. Simulation has become an indispensable tool not only for interpreting experimental results but also for predicting the properties of biological systems with microscopic precision.

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