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REVIEW

Molecular Dynamics Simulations and Their Novel Applications in Drug Delivery for Cancer Treatment: A Review

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Abstract

Molecular Dynamics (MD) simulations have emerged as a vital tool in optimizing drug delivery for cancer therapy, offering detailed atomic-level insights into the interactions between drugs and their carriers. Unlike traditional experimental methods, which can be resource-intensive and time-consuming, MD simulations provide a more efficient and precise approach to studying drug encapsulation, stability, and release processes. These simulations are essential for designing effective drug carriers and gaining a deeper understanding of the molecular mechanisms that influence drug behavior in biological systems. Recent research has highlighted the broad applicability of MD simulations in assessing different drug delivery systems, such as functionalized carbon nanotubes (FCNTs), chitosan-based nanoparticles, metal-organic frameworks (MOFs), and human serum albumin (HSA). FCNTs are known for their high drug-loading capacity and stability, while biocompatible carriers like HSA and chitosan are favored for their biodegradability and reduced toxicity. Case studies involving anticancer drugs, including Doxorubicin (DOX), Gemcitabine (GEM), and Paclitaxel (PTX), showcase how MD simulations can improve drug solubility and optimize controlled release mechanisms. Although the computational complexity of these simulations presents challenges, advances in high-performance computing and machine learning techniques are driving significant progress. These innovations are facilitating the development of more targeted and efficient cancer therapies. By combining MD simulations with experimental validation, researchers are enhancing predictive models and accelerating the creation of next-generation drug delivery systems.

Keywords Molecular dynamics · Drug delivery · Cancer treatment · Nanocarriers · Computational biology

Introduction

Cancer is a group of more than 100 different diseases, each characterized by the uncontrolled growth and spread of abnormal cells. Among cancer treatment methods are radiotherapy, surgery, immunotherapy, chemotherapy, hormone therapy, and photodynamic therapy. However, chemotherapy, while widely used, is associated with adverse side effects. These include the drugs not specifically targeting cancer cells and inadvertently destroying healthy cells. Consequently, the quality of life and survival rates of patients undergoing cancer treatment are limited. Hence, the development of new drugs and the improvement of existing treatments are crucial [1].

New drug development faces significant challenges, increasing interest in computer simulation-supported drug design. MDS offer promising applications in cancer treatment by providing molecular-level insights into drug interactions and therapeutic effects [2–5]. Advances in

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computational technology have facilitated structure-based drug design, making it a valuable tool in medical research. Cancer remains a leading cause of death due to its high incidence and mortality rates, and chemotherapy, though common, is often associated with severe side effects. As a result, research efforts focus on developing new anticancer drugs and improving existing treatments. Computer simulations contribute to these efforts by aiding drug design and optimizing therapeutic strategies [6–9].

Molecular dynamics simulations help understand the stability, solubility, and cellular interactions of drugs in biological environments. This data is critical for improving drug formulations and enhancing therapeutic efficacy [10–12]. Molecular dynamics simulations analyze how drugs interact with cell membranes at the atomic level, depending on their hydrophilic or hydrophobic properties. This allows for understanding drug distribution and efficacy, and the design of effective delivery systems that reduce side effects [13–15].

MDS are a method used to examine the structural, dynamic, and thermodynamic properties of molecular systems [16–18]. These simulations typically involve systems containing biomolecules such as proteins, enzymes, or lipids. Since the system is usually in an aqueous solution, accounting for water or electrolytes in simulations is important. Protein Data Bank structures can be used as a starting point for simulations, and different techniques like homology or comparative modeling can be employed when the structure is unavailable [19]. MDS use an "all-atom" approach, representing atoms in detail and following Newton's laws of motion to advance the system's state over a series of time steps [20, 21]. This review comprehensively examines the critical role of molecular dynamics simulations (MDS) in drug delivery strategies in cancer treatment. By studying how drug molecules interact with target proteins, cell membranes, and nanoparticle-based carriers at the atomic level, MDS helps increase therapeutic efficacy while reducing side effects. The effects of factors such as the acidic microenvironment of cancer cells, biological pressure, and pH on the stability and effectiveness of drug carriers can be analyzed in detail using MDS, enabling the development of pH-sensitive and pressure-resistant drug delivery systems. Furthermore, simulations support drug discovery and development by shortening experimental time and reducing costs.

However, MDS faces challenges such as computational complexity and limitations in simulating synthetic membranes. However, innovative approaches such as artificial intelligence and multi-scale models are contributing to overcoming these hurdles by improving the predictive accuracy and efficiency of MDS. These integrations make molecular dynamics simulations an increasingly important and transformative tool in the design of drug delivery systems and the elucidation of molecular mechanisms in cancer treatment. It is expected that MDS will become more widespread in research and applications in these areas in the future [6, 22].

Fundamentals of Molecular Dynamics Simulation

MD simulations are a computational technique that applies Newton's laws of motion to predict the movement of atoms within a biomolecular system over time. By calculating the forces acting on each atom from its neighbors, these simulations allow for the updating of atomic positions and velocities. The result is a trajectory that represents the atomic configuration of the system at each time step. Compared to experimental methods, MD simulations offer several benefits. They provide detailed insights into atomic positions and movements, which can be challenging to observe experimentally. Additionally, simulation conditions can be precisely controlled, such as the initial structure of a protein, the presence of ligands, mutations, modifications, and the surrounding environment. By running simulations under varying conditions, the impacts of different molecular changes can be assessed. Overall, MD simulations are a valuable tool for investigating biomolecular systems and gaining a deeper understanding of their behavior under various circumstances [9].

In MD simulations, forces are computed using a model called a molecular mechanics force field. This model is derived from quantum mechanical principles and is often calibrated to align with experimental data. A typical force field includes components that represent electrostatic (Coulombic) interactions between atoms, spring-like terms that describe the preferred bond lengths, and additional terms to account for other interatomic interactions. However, it's important to recognize that these force fields are inherently approximate. Over the past decade, comparisons between simulations and experimental results have shown significant improvements in the accuracy of these force fields [23]. Despite their usefulness, these models are inherently imperfect, and the uncertainty introduced by these approaches must be taken into account when analyzing simulation results. Additionally, in classical MD simulations, the formation or breaking of covalent bonds is not considered. To address reactions that involve changes in covalent bonds or are driven by light absorption, Quantum Mechanics/Molecular Mechanics (QM/MM) simulations are often used. In these simulations, a portion of the system is modeled using quantum mechanical calculations, while the rest is treated with classical MD techniques [24].

To maintain numerical stability, the time steps in MD simulations must be kept extremely short, usually on the order of femtoseconds (10^-15 s). However, most biochemically significant events, such as important structural changes

in proteins, occur on timescales ranging from nanoseconds to microseconds or even longer. As a result, typical simulations require millions or even billions of time steps to capture these processes. Combined with the large number of interatomic interactions that must be calculated for each time step, this makes MD simulations computationally intensive [9]. Classical molecular dynamics is a computational method used to simulate the movement of atoms and molecules, based on Newton's laws of motion. It examines the system's behavior over time by modeling interactions between atoms through empirical force fields [25].

Despite these limitations, advanced methods such as accelerated molecular dynamics (aMD) have been developed to increase the efficiency of molecular dynamics simulations. Accelerated molecular dynamics (aMD) is an advanced variation of classical molecular dynamics designed to improve conformational sampling by lowering the energy barriers that separate different states of a system. By reducing the effect of these barriers, aMD enables more rapid exploration of a wider conformational space, allowing molecules to transition between states more efficiently. This approach is particularly useful in long simulations and large-scale systems, as it helps reduce computation time while increasing the effectiveness of structural exploration. aMD is especially beneficial in scenarios where energy barriers are significant, such as in the study of biomolecules, chemical reactions, and phase transitions [26]. aMDplays a vital role in drug delivery applications by aiding the binding and interaction of drugs with their targets, overcoming significant energy barriers between biomolecules. By enabling more efficient exploration of drug-target interactions and speeding up the sampling of a wider variety of conformational states, aMD supports the development of more effective and safer drugs.

The methodology employed in this review involved a systematic search and analysis of relevant literature addressing the application of MDS in drug delivery for cancer treatment. The primary objective was to comprehensively investigate recent studies that utilized MDS to gain insights into molecular interactions, structural aspects, and dynamic behaviors governing drug delivery systems. A thorough literature search was conducted using reputable databases, including PubMed, ScienceDirect, and IEEE Xplore. The search strategy encompassed keywords such as "Molecular Dynamics," "Drug Delivery," "Cancer Treatment," and related terms. The inclusion criteria involved studies published in peer-reviewed journals, with a focus on applications of MDS in cancer drug delivery [2, 27–30].

The retrieved articles were screened based on titles and abstracts to identify studies relevant to the review's scope. Full-text articles were then assessed for eligibility, ensuring alignment with the theme of MDS and their novel applications in cancer drug delivery [31–33]. Relevant data from selected studies were systematically extracted, emphasizing details on the types of cancer, drug molecules investigated, and the specific applications of MDS in elucidating drug-carrier interactions. Key findings, methodologies, and outcomes were recorded for comprehensive analysis. The selected literature was critically analyzed to assess the strengths and limitations of MDS in studying drug delivery systems. Emphasis was placed on understanding the methodologies employed in MDS, including force fields, simulation parameters, and validation techniques. The synthesized findings were organized to present a cohesive narrative that highlights the contributions of MDS in designing and optimizing drug delivery systems. Specific attention was given to diverse applications across various cancer types and different drug molecules [34–36].

Explanation of Molecular Dynamics Simulation

The fundamental concept of an MDS is clear-cut. With knowledge of the atom positions in a biomolecular system (like a protein in a watery environment, potentially surrounded by a lipid bilayer), one can compute the force exerted on each atom by all others. Utilizing Newton's laws of motion, the simulation then predicts the spatial coordinates of each atom over time. Essentially, by iteratively calculating forces and updating positions and velocities accordingly, the simulation generates a three-dimensional sequence, akin to a movie, depicting the atomic-level arrangement of the system throughout the simulated time frame [37] (Fig. 1).

In molecular dynamics simulations, force field equations are used to calculate both coupled and independent interactions. Coupled interactions refer to forces that model chemical bonds between atoms, such as bond lengths and bond angles. On the other hand, independent interactions encompass forces like Van der Waals and electrostatic interactions between molecules. The accuracy and efficiency of the simulations depend on how well these interactions are accounted for.In molecular simulations, calculating the forces acting on each particle is often the most computationally demanding task. This is particularly true in systems where particles interact bidirectionally, requiring the consideration of interactions between each particle and its neighbors. To evaluate these interactions, pairwise distances are typically used, and various techniques are applied to speed up the force calculation process. One such technique involves combining short-range and long-range forces to optimize time scaling, which can also be adapted for molecular dynamics simulations.The calculation of distances between particles is carried out using periodic boundary conditions. Intermolecular forces are then determined, with the use of a cut-off distance that is smaller than half the size of the periodic box. The program computes the distances between a particle and its

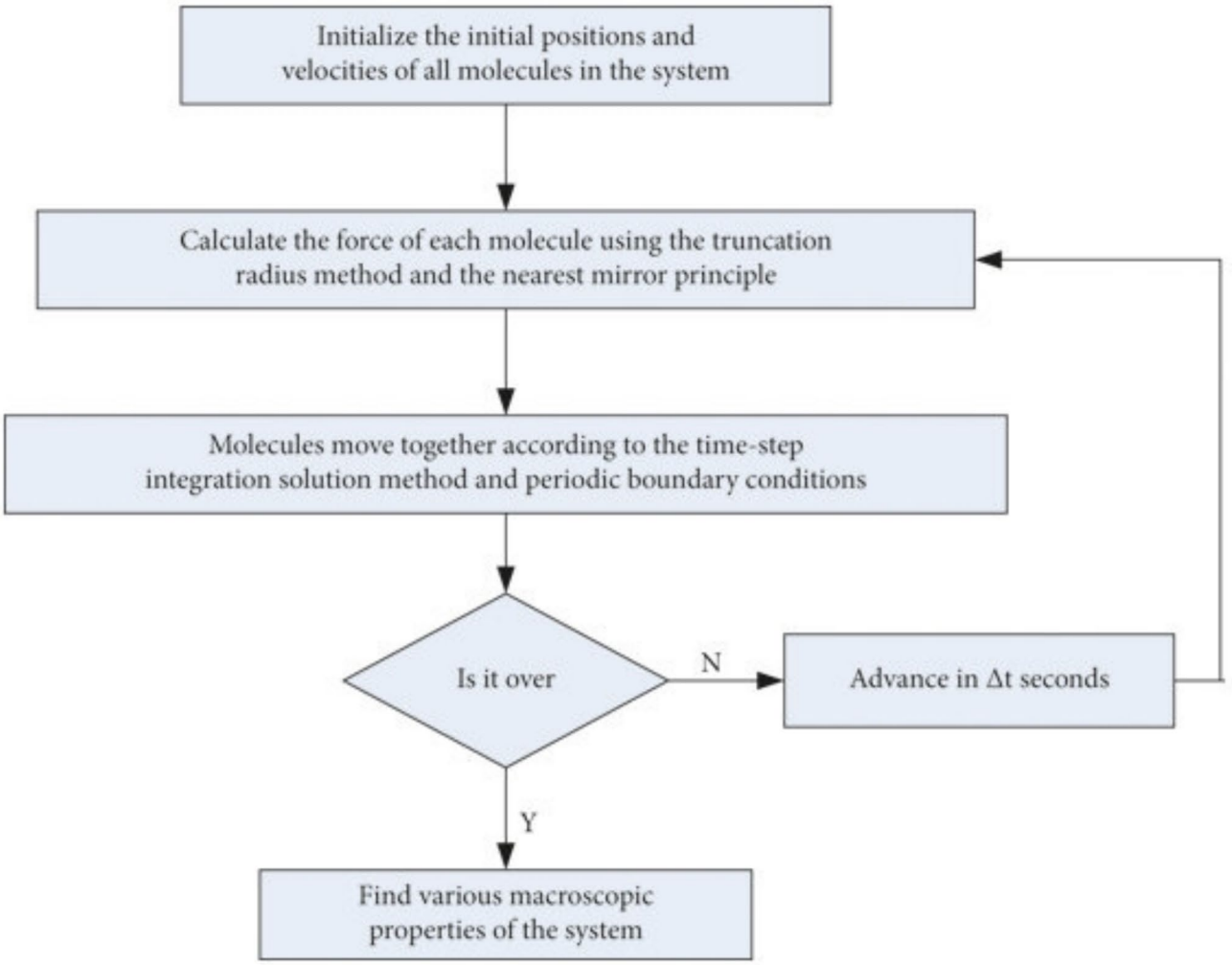


Fig. 1 Flowchart of the molecular dynamics simulation method [38]

nearest periodic image, and if these distances are smaller than the square of the cut-off radius, the interaction is taken into account. A rounding function is used to convert real numbers into integers for these distance calculations. This approach ensures efficient evaluation of interactions during the simulation [39].

The basic theory of MD is mentioned in the working paper of Berendsen and van Gunsteren [40], and it is summarized in the following graph.

MDS is an effective way to explore the interfacial interactions at the atomic and molecular levels. MDS was used to investigate the interactions between different molecules and drugs such as tobramycin or proteins such as fibronectin and bone morphogenetic protein-7 [44–46]. The study of Shang et al [44] aimed to enhance Hydroxyapatite (HAp) as a drug carrier through Zn doping. Molecular simulations revealed increased doxorubicin binding energy with Zn, emphasizing the significance of ion-doped HAp in drug adsorption.

The study of Wang et al investigates the influence of intermolecular interactions on the stability of a carbon nanotube (CNT) capped by functionalized gold nanoparticles (AuNPs), with potential applications as a pH-controlled drug carrier. Initial experimental endeavors demonstrated the feasibility of fabricating such a nanocontainer capable of encapsulating the anticancer drug cisplatin within the CNT's inner space and sealing its ends with functionalized AuNPs. However, the anticipated behavior, namely the detachment of AuNPs at acidic pH leading to the release of cisplatin, was not observed. Conversely, theoretical examinations of a chemically identical system suggested that cisplatin release at acidic pH should occur. Consequently, a comprehensive theoretical analysis was conducted to explore various factors possibly contributing to the disparity between experimental and theoretical findings. The investigation identified a significant disparity in dispersion interaction between the CNT and AuNP in solution as the primary factor influencing the

experimental system. This interaction, however, can be partially regulated by adjusting the system size or modifying the ratio between AuNP diameter and CNT diameter. Therefore, while the concept of a pH-sensitive drug carrier remains promising, precise adjustment of structural parameters is imperative to achieve desired functionality (Fig. 2A) [41].

In this study examines the dispersion of CNTs in different aqueous environments, including water, water/surfactant, and water/polymer systems, providing valuable insights for drug delivery applications. Since CNTs hold promise as drug carriers, ensuring their stable and uniform distribution in biological environments is crucial for efficient drug transport to target sites. The research investigates CNT interactions at the atomic scale and utilizes Monte Carlo simulations at the mesoscale to assess dispersion behavior. Results indicate that surfactants improve dispersion by reducing CNT interactions, while factors such as CNT length, diameter, and orientation play a key role in their distribution. Additionally, the adaptive biasing force method proves effective in optimizing dispersion. By offering a deeper understanding of these factors, the study helps identify suitable components for improving CNT stability in drug delivery systems. The importance of this research lies in addressing challenges associated with inconsistent CNT dispersion, which can hinder drug transport, reduce bioavailability, and increase toxicity risks. The model's findings contribute to the development of optimized formulations, enhancing drug delivery efficiency while minimizing adverse effects [47] . The model explores CNT interactions at the atomistic scale and utilizes Monte Carlo simulations at the mesoscale. Key findings include surfactant-induced weaker CNT interactions, significant impact of CNT orientation, length, and diameter on dispersion, and the effectiveness of the adaptive biasing force method. The model offers insights into the entropic and enthalpic contributions, providing a basis for screening potential components to enhance CNT dispersion in various systems.

In MDS, forces are computed using a molecular mechanic's force field, calibrated based on quantum mechanical calculations and often adjusted to specific experimental

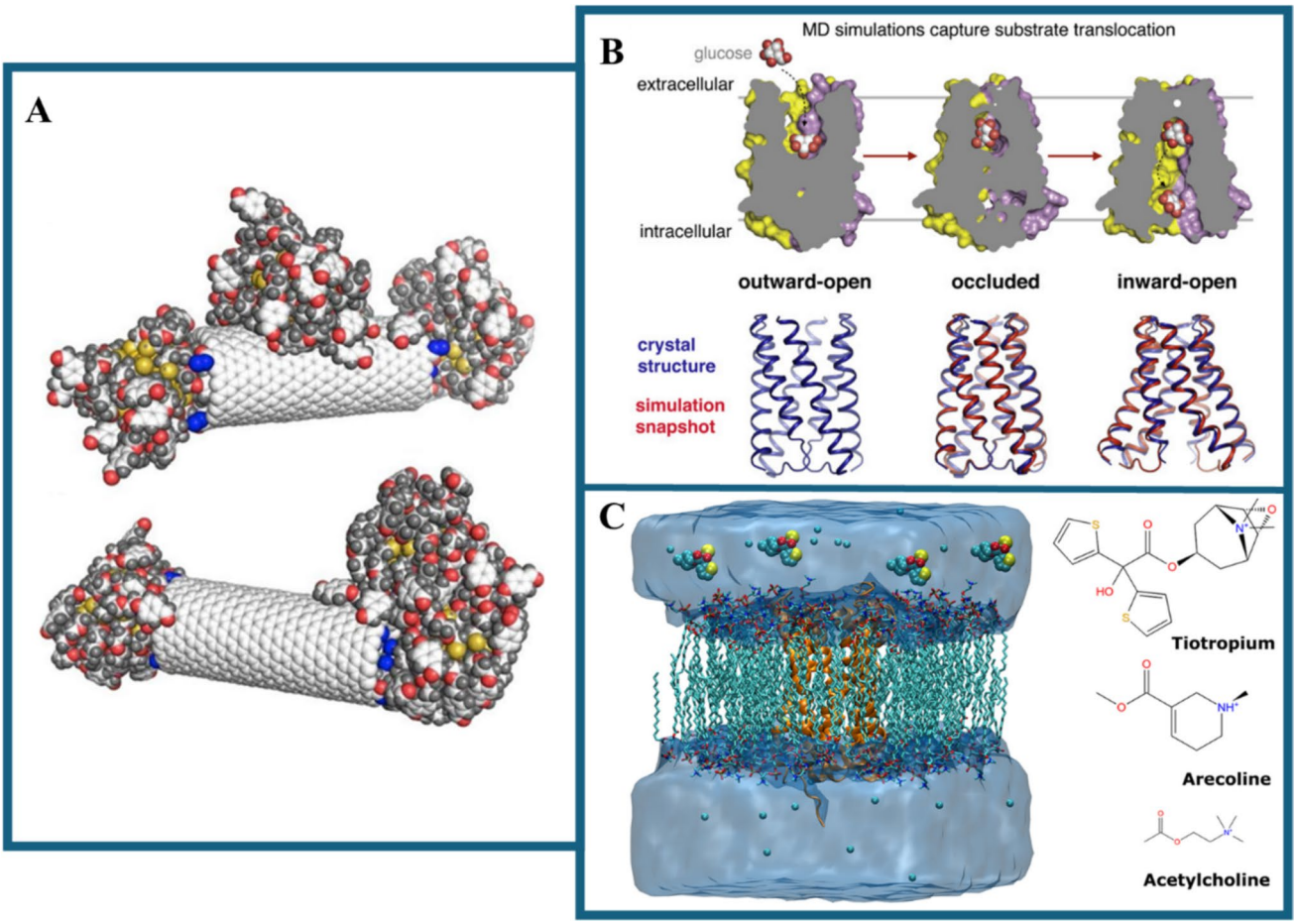


Fig. 2 **A** Simulation snapshots illustrating the pre-collision state of the system [41], **B** Case Study: Atomic-Level Mechanism of an Alternating Access Transporter [42], **C** Schematic representation of the M3 muscarinic receptor–ligand-binding simulation system and three known ligands of the M3 receptor that are selected for aMD simulations: antagonist TTP, partial agonist Arc, and full agonist Ach [43]

data. This force field includes terms representing electrostatic (Coulombic) interactions, spring-like terms modeling covalent bond lengths, and other interatomic interaction terms. While force fields have shown notable improvement over the last decade, they are inherently approximate, and comparisons with diverse experimental data highlight their remaining imperfections [9, 23].

In the study of Aldawood et al, they proposed a model that utilizes the Lennard-Jones (L-J) potential function to calculate the melting points of nanoparticles, taking into account size, shape, atomic volume, and surface packing. The model, particularly for spherical nanoparticles, aligns well with experimental values for AuNPs and lead (Pb) nanoparticles. It also aligns with Qi and Wang's model predicting the Gibbs-Thompson relation. Furthermore, the non-integer L-J potential function in the model proves effective in predicting the melting points (Tm) of nanoparticles [48].

The algorithms used in MDS is summarized as follows [49]:

1. Algorithms for large-scale MD
    a. Short-range interactions
    b. Long-range interactions
    c. Other issues
2. Algorithms for parallel MD
    a. Task queue
    b. Replicated data and systolic loops
    c. Spatial decomposition

More novel articles have researched the optimization of these algorithms to solve the problems related to computing large models. The study of Chen et al, enhances molecular dynamics simulation performance through machine learning and data mining algorithms. Implementing Restricted Boltzmann Machines (RBM) and optimizing with K-Nearest Neighbors (KNN) shows significant improvements, with up to 36.96% efficiency gains in force calculation and trajectory equation running times [50].

Importance of MD Simulation in Studying Molecular Interactions

The importance of MDS lays in forecasting the movements of individual atoms within a molecular system, utilizing a general physics model for interatomic interactions. These simulations provide detailed insights into biomolecular processes like conformational changes, ligand binding, and protein folding, offering atomic-level information with femtosecond temporal resolution. Additionally, MDS can predict the atomic responses of biomolecules to perturbations such as mutations, phosphorylation, protonation, or the introduction/removal of ligands (Fig. 2B) [42].

Understanding the intricate process of ligand binding to receptors holds paramount importance in pharmaceutical research for identifying potential drug targets. Computational methods, with their ability to offer detailed atomic insights, serve as valuable tools in this endeavor. In this context, aMD emerges as a promising approach for simulating the dynamics of ligand binding to G-protein-coupled receptors (GPCRs), such as the M3 muscarinic receptor, which serves as a therapeutic target for various human ailments like cancer, diabetes, and obesity. The study employed long-timescale aMD simulations to investigate the binding mechanisms of three distinct ligand molecules: the antagonist tiotropium (TTP), partial agonist arecoline (ARc), and full agonist acetylcholine (ACh) to the M3 muscarinic receptor. By contrast to previous conventional MD simulations, which typically operate at microsecond timescales, aMD significantly expedited the binding processes. Specifically, aMD facilitated the rapid binding of ACh to the orthosteric ligand-binding site of the receptor and accelerated the binding of TTP to an extracellular vestibule. Moreover, additional aMD simulations successfully captured the binding of ARc to the orthosteric site of the receptor. Notably, the study revealed that all three ligands exhibited binding in the extracellular vestibule at various stages of their binding pathways, suggesting its significance as a metastable binding site. These findings underscore the utility of aMD in elucidating protein-ligand binding dynamics, particularly in the context of drug recognition in GPCRs (Fig. 2C) [43].

The significance of MD simulations in molecular biology and drug discovery has surged in recent years. These simulations offer a detailed view of protein and biomolecule behavior at the atomic level with high temporal resolution. With enhancements in simulation speed, accuracy, and accessibility, alongside the growing availability of experimental structural data, MD simulations have become increasingly appealing to researchers, particularly in fields like neuroscience. They play a crucial role in elucidating functional mechanisms of biomolecules, uncovering the structural underpinnings of diseases, and aiding in the design and refinement of small molecules, peptides, and proteins. This article aims to explore the practical insights provided by MD simulations and how they inspire further experimental investigations [9].

Although MD simulations serve as a crucial tool for studying the behavior of biomolecules and proteins, environmental variables can have a significant influence on the precision of these simulations and the interactions within biomolecular systems. These factors can shape the efficiency of chemical and biological processes by altering the structures, interactions and dynamic behaviour of biomolecules. For example, ın this study examines how temperature fluctuations affect

the microstructure of passive film nanopores in chloride environments through molecular dynamics simulations. The results show that as temperature rises, the hydrogen bond stability between water molecules and the γ-FeOOH substrate decreases, causing ions to occupy oxygen sites. Additionally, higher temperatures destabilize the hydration shell of ions in solution, increasing their thermal motion and leading to a higher likelihood of ion collisions and the formation of ionic pairs. Within the γ-FeOOH substrate, temperature increases reduce the strength of interactions and amplify thermal vibrations, which in turn boosts chemical activity and encourages ion adsorption. As a result, elevated temperatures improve the transport and adsorption efficiency of water and ions in γ-FeOOH nanopores, accelerating the degradation of the passive film. This research provides a detailed understanding of how temperature influences the corrosion resistance of reinforced concrete structures [51].

In this another study highlights the potential for discrepancies in experimental results when examining the scaling mechanism. To address this, the impact of temperature, ion concentration, and substrate material on $CaCO_3$ scaling was investigated using molecular simulations. The molecular dynamics calculations revealed that $CaCO_3$ tends to form in various systems when the temperature exceeds a certain critical threshold. Additionally, the scaling ability of Fe(111), influenced by the interactions between scaling ions and clusters, was observed to initially increase with concentration, before decreasing at higher concentrations. Furthermore, both molecular dynamics and density functional theory findings show that the scaling capacity of Fe(111), Ni(111), and Cu(111) decreases in sequence. This study offers valuable insights into the scaling mechanism within complex environments (Fig. 3A) [52].

In this study utilizing structural analysis and molecular dynamics simulations found that the N-terminal helices of FocA do not effectively block substrate permeation. These residues, which are structurally undefined, form helices under low pH conditions, allowing the pathway to accommodate cytoplasmic entry and seemingly explaining the observed cessation of electrical signaling. Equilibrium simulations and thermodynamic calculations indicate that FocA is permeable to both formate and formic acid. As a result, the conversion from formate to formic acid may disrupt the electric current. The study also explores the mechanism of formate export under physiological pH conditions. This research enhances our understanding of FocA's substrate transport mechanism and provides valuable insights into the function of other transporter family members [54].

In this similarly study explored the impact of different pH levels on the Master Protease (Mpro) of the SARS-CoV-2 virus, which is a key target for therapeutic interventions. Computational methods were used to analyze

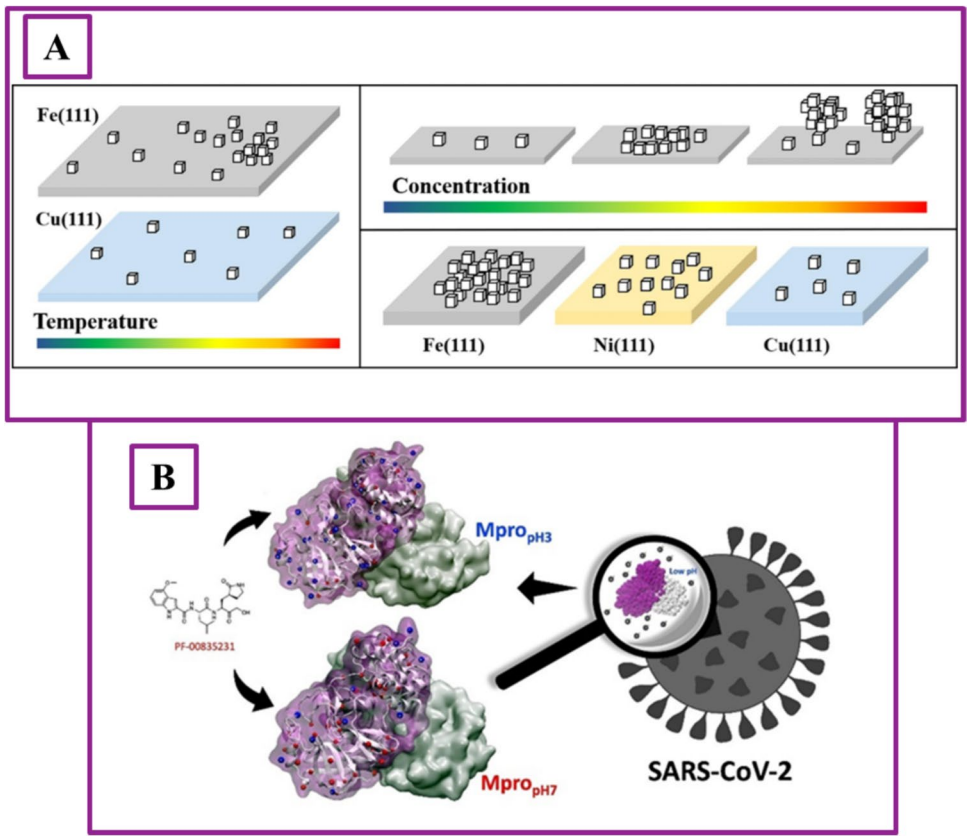


Fig. 3 **A** Schematic overview, molecular simulations illustrate how temperature, ion concentration, and substrate type influence CaCO3 scaling, highlighting a critical temperature threshold and differing scaling behaviors on Fe, Ni, and Cu surfaces [52]. Copyright 2022 Elsevier. **B**. Schematic overview, molecular simulations examined the protonation states of SARS-CoV-2 Mpro across varying pH levels, emphasizing its structural stability and effective inhibitor interaction under acidic conditions [53]. Copyright 2021 MDPI

the protonation and deprotonation states of Mpro at various pH conditions. Molecular Dynamics simulations were performed to evaluate the structural stability of Mpro. The findings revealed that the active site and dimerization residues of Mpro were not significantly affected by pH variations. However, changes in substrate-binding residues were observed at lower pH levels, which led to an expansion of the binding pocket. Additionally, the solvent distribution around the catalytic residues Cys145 and His41 varied with pH, which may have implications for the enzyme's catalytic mechanism. The study also examined the interaction of PF-00835231, a potential therapeutic compound from Pfizer, with Mpro across different pH values, revealing strong binding affinity. In conclusion, the results suggest that pH can influence the catalytic activity of SARS-CoV-2 Mpro, and this factor should be taken into account when developing therapeutic strategies targeting this enzyme (Fig. 3B) [53].

As the field of computerized simulation is expanding, more tools are being developed and integrated into research and studies to provide MDS. Table 1 provides a summary of the main tools that are utilized in different materials and biomaterials simulation.

Molecular Interactions in Drug Delivery

Molecular Aspects of Drug Delivery

In order to talk about the aspects of drug delivery we can start with the types of drug molecules used in cancer treatment and their interactions with biological targets. In order to treat cancer, there are currently four main types of systemic therapy options available: immunotherapy, endocrine therapy, targeted therapy, and chemotherapy. These categories do not always align with one another [57]. To optimize the use of currently available medications, new or improved delivery methods can be designed. The process of finding new therapeutics is still a drawn-out, expensive, challenging, and inefficient one, with a high attrition rate, despite advancements in biotechnology and our understanding of biological systems. Subsequent to preclinical research on animal and cell models, as well as human clinical trials, drug development and discovery culminate in the process of securing regulatory approval to bring the medication to the market [58, 59].

Over the past decade, the biopharmaceutical industry has experienced remarkable growth, particularly in the development of biologics and biotherapeutics. This surge in innovation has seen a notable increase in the proportion of approved new biological entities compared to traditional chemical entities. Alongside this expansion, biopharmaceuticals have become increasingly complex in both their structure and mode of action. Consequently, the interpretation, analysis, and prediction of their quantitative pharmacology have become more challenging.

In response to these complexities, we introduce a modeling and simulation (M&S) framework tailored for the preclinical development of monoclonal antibodies, serving as a representative example of biopharmaceuticals. Within this framework, we discuss M&S strategies aimed at facilitating successful implementation throughout various stages of development, including early discovery, lead optimization, and the selection of initial doses for first-in-human studies. Our exploration reveals that these pivotal stages of preclinical development heavily rely on M&S activities, particularly in the realms of pharmacokinetic-pharmacodynamic (PKPD) modeling. Moreover, we underscore the importance of leveraging systems biology (SB), systems pharmacology (SP), and translational pharmacology (TP) to inform decision-making processes. These methodologies offer an integrated and rationalized framework for navigating preclinical development challenges. They enhance our understanding of targets and systems, facilitate interpretation of data obtained from in vitro and in vivo experiments, enable prediction of human PKPD profiles, and support the design of first-in-human studies through a more systematic approach (Fig. 4A) [60].

The development of venetoclax, the first medication to target a protein-protein interaction, and the recent approval of sotorasib, the first inhibitor to target a mutant form of the KRAS oncogene KRAS G12C, are noteworthy examples of fragment-based drug discovery's notable successes [61, 66, 67]. The discovery of inhibitors that target enzymes involved in DNA damage repair or signaling came about as an advancement over genotoxic chemotherapy techniques. Such methods might be especially effective for tumors that have problems with DNA repair. In 2005, two distinct groups independently observed that poly (ADP-ribose) polymerase inhibitors were more toxic to cancer cells that had either BRCA1 or BRCA2 mutations. This finding is arguably the most exciting one in this regard [67–69]. Today, tumors lacking homologous recombination can benefit from the use of PARP inhibitors, which are a clinical reality (Fig. 4B) [61].

Genomic instability in cancer, caused by defects in DNA repair mechanisms, creates therapeutic vulnerabilities. The 2009 clinical trial of the PARP inhibitor olaparib validated synthetic lethality by targeting PARP1 in BRCA1/BRCA2-deficient tumors. Since then, multiple PARP inhibitors have been developed for breast and ovarian cancers, with growing understanding of their mechanisms and resistance. Current research focuses on expanding patient selection beyond BRCA mutations, applying PARP inhibitors to other cancers like prostate and pancreatic, and exploring combination therapies. This review summarizes these advances and highlights the potential to broaden PARP inhibitor use through precision medicine (Fig. 4C) [62].

Table 1 Brief overview of computational tools used in MDS

Simulation type	Computational tool	Utilization	Force fields used and their typical accuracies	References
Materials related dynamics	MMTools	MMTools is a modular C++ toolkit accessible through a Tcl command language script. Integrated with the NAMD molecular dynamics program, it allows monitoring and analysis. Users can employ MMTools for processing molecular dynamics data from NAMD or other programs using Tcl scripts.	Amber:High, but limited for small molecules Charmm:High Accuracy Gromos:Good, Limited for Chemical Reactions Opls:High Accuracy, Reaxff:Good, Atomic Complexity-Dependent Variable Uff:Low Accuracy	[131]
	Materials Studio	The software is compatible with Windows-based or Linux-based servers and workstations. Materials Studio serves as a comprehensive tool for computational chemistry, bioinformatics, chemoinformatics, molecular dynamics simulations, and quantum mechanics. Predicts the atomic and molecular structures and properties of materials. It is utilized in advanced research on various materials like polymers, nanotubes, and ceramics by universities, research centers, and high-tech companies.	Compass:High Accuracy Dreiding:Medium Accuracy Mmff:High Accuracy Charmm:High Accuracy Uff:Medium Accuracy Reaxff:Good Accuracy, Ecam:High Accuracy	[55]
	LAMMPS	Supports diverse particle interaction models for various materials, adaptable to any platform from single CPUs to supercomputers with accelerators. It grants users substantial control over simulations through input scripts or custom code additions for new features. Utilizing programming languages such as C++, Python, C, and Fortran. LAMMPS employs parallel spatial decomposition and advanced integration algorithms, offering stability and extensive support for interatomic potentials, constraints, diagnostics, and pre/post-processing features.	Reaxff:Good Accuracy Charmm:High Accuracy Amber:High Accuracy Lennard-Jones: Medium Accuracy Eam: High Accuracy Tersoff:Good Accuracy Stillinger Weber: Good Accuracy	[135]

Table 1 (continued)

Simulation type	Computational tool	Utilization	Force fields used and their typical accuracies	References
Biological systems related dynamics	GROMACS	Support all simulation algorithms. Automatically handles biomolecules like proteins, nucleic acids, and lipids, with built-in support for common force fields. It includes various implicit solvent models and advanced free-energy algorithms, utilizing multithreading for parallelization on diverse systems, including Windows workstations. Featuring hand-tuned assembly kernels and efficient parallelization, GROMACS achieves high-performance making it suitable for massively parallel simulations.	Charmm:High Accuracy Amber:High Accuracy Gromos:High Accuracy Opls:High Accuracy Lj(Lennard-Jones): Medium Accuracy	[5, 132]
	Amber	Convenient modeling of new molecules and models. Exceptionally high performance as a result of the quick development of high-performance computing based on GPUs. Writers of science simulations must write their own scripts. Mainly mdin, prmtop, and inpcrd are the input files used by the Amber MD model. It is difficult for users to modify the functions of Ambermdprep because it is a bash script.	Amber Ff14sb: High Accuracy Amber Ff99sb: High Accuracy Amber Parm96: High Accuracy Gaff: High Accuracy Tip3p: High Accuracy	[133, 134]
	NAMD	Compatible with multiple file formats, best parallel processing and high efficiency for large-molecule simulations. The Beowulf-class PC clusters, which are becoming more and more common and resemble the workstation clusters for which NAMD was originally intended, are a particularly good fit for NAMD. Object-oriented design using C++enables extensibility and maintainability. Future iterations of NAMD will also leverage multiprocessor workstation clusters effectively.	Charmm:High Accuracy Amber:High Accuracy Opls: High Accuracy Gromos:High Accuracy Tip3p: High Accuracy	[136]
	CHARMM	Fast updating potential energy model. Greatly versatile used as a molecular simulation program. Its main emphasis being on biologically significant molecules found in solution, crystals, and membrane environments, such as proteins, peptides, lipids, nucleic acids, carbohydrates, and small molecule ligands. It also offers a broad range of computational tools, such as multiple molecular minimization, dynamics, and analysis techniques, free energy estimators, model-building capabilities, and conformational and path sampling methods.	Charmm36:High Accuracy Charmm22:High Accuracy Charmm27:High Accuracy	[37, 133]

Table 1 (continued)

Simulation type	Computational tool	Utilization		Force fields used and their typical accuracies	References
	DESMOND	DESMOND MD is a software tool designed for conducting dynamic simulations of biological systems. It is widely used in areas such as drug development, protein dynamics, biomolecular interactions, lipid-membrane simulations, and nanotechnology. The program supports the optimization of pharmaceuticals by modeling how drugs interact with their target proteins. Additionally, it helps in understanding the roles of biomolecules by analyzing interactions between proteins and protein-DNA/RNA. DESMOND MD is also capable of simulating the interactions between nanoparticles, biomolecules, and solvents.	Opls:High Accuracy Charmm:High Accuracy Amber:High Accuracy Reaxff:Chemical Accuracy	[56]

Disease resistance to specific small-molecule inhibitors or the onset and progression of non-small cell lung cancer are caused by genetic mutations that impact the receptor tyrosine kinases epidermal growth factor receptor (EGFR) and Her2, members of the ErbB receptor tyrosine kinase family. A transmembrane segment, an intracellular tyrosine kinase domain, and an extracellular ligand-binding domain make up these targets. Activating and drug-resistant mutations of Her2 and EGFR were discussed in the article along with their impact on protein structures. The paper emphasized a common mechanism of drug sensitivity resulting from mutations that upset a hydrophobic cluster, an essential property for preserving the C-out conformation of an inactive helix. Nevertheless, the field lacks comprehensive understanding of drug-resistant exon 20 insertion mutations in Her2 and EGFR, despite the fact that drug resistance resulting from steric interference with inhibitors of active sites-directed small molecules can be readily evaluated using presently available crystal structures [70].

Activating mutations in the epidermal growth factor receptor (EGFR) are typically responsive to EGFR tyrosine kinase inhibitors (TKIs) in non-small cell lung cancers (NSCLCs). However, a subset of NSCLCs with mutations in exon 20 of EGFR and HER2 exhibit intrinsic resistance to available therapies. Through a combination of computational, laboratory, and animal model studies, researchers investigated the structural alterations caused by exon 20 mutations and sought effective inhibitors. Their 3D modeling revealed that these mutations constrict the drug-binding pocket, making it challenging for large, rigid inhibitors to bind effectively. However, they found that poziotinib, due to its small size and flexibility, could overcome these steric changes and effectively inhibit the most common EGFR and HER2 exon 20 mutants. In laboratory studies and animal models, poziotinib demonstrated superior activity compared to approved EGFR TKIs in NSCLCs harboring EGFR or HER2 exon 20 mutations. A phase 2 trial involving 11 patients with NSCLC carrying EGFR exon 20 mutations showed promising results, with a confirmed objective response rate of 64% to poziotinib. These findings highlight poziotinib as a potent inhibitor of EGFR and HER2 exon 20 mutations, shedding light on the molecular characteristics of TKIs that can bypass steric changes induced by these mutations (Fig. 4D) [63].

Another type of mutation is the B-type Raf proto-oncogene (BRAF) cause altered BRAF protein, which stimulates the growth of cancer cells, in about half of melanomas14. Some small-molecule targeted therapies that can be effective against cancers that have a BRAF mutation are B-type Raf proto-oncogene protein inhibitors (e.g., vemurafenib, dabrafenib). In addition to BRAF inhibitors, other medications such as trametinib, which is activated by mitogens, can also be used to treat melanomas that have a BRAF mutation [71].

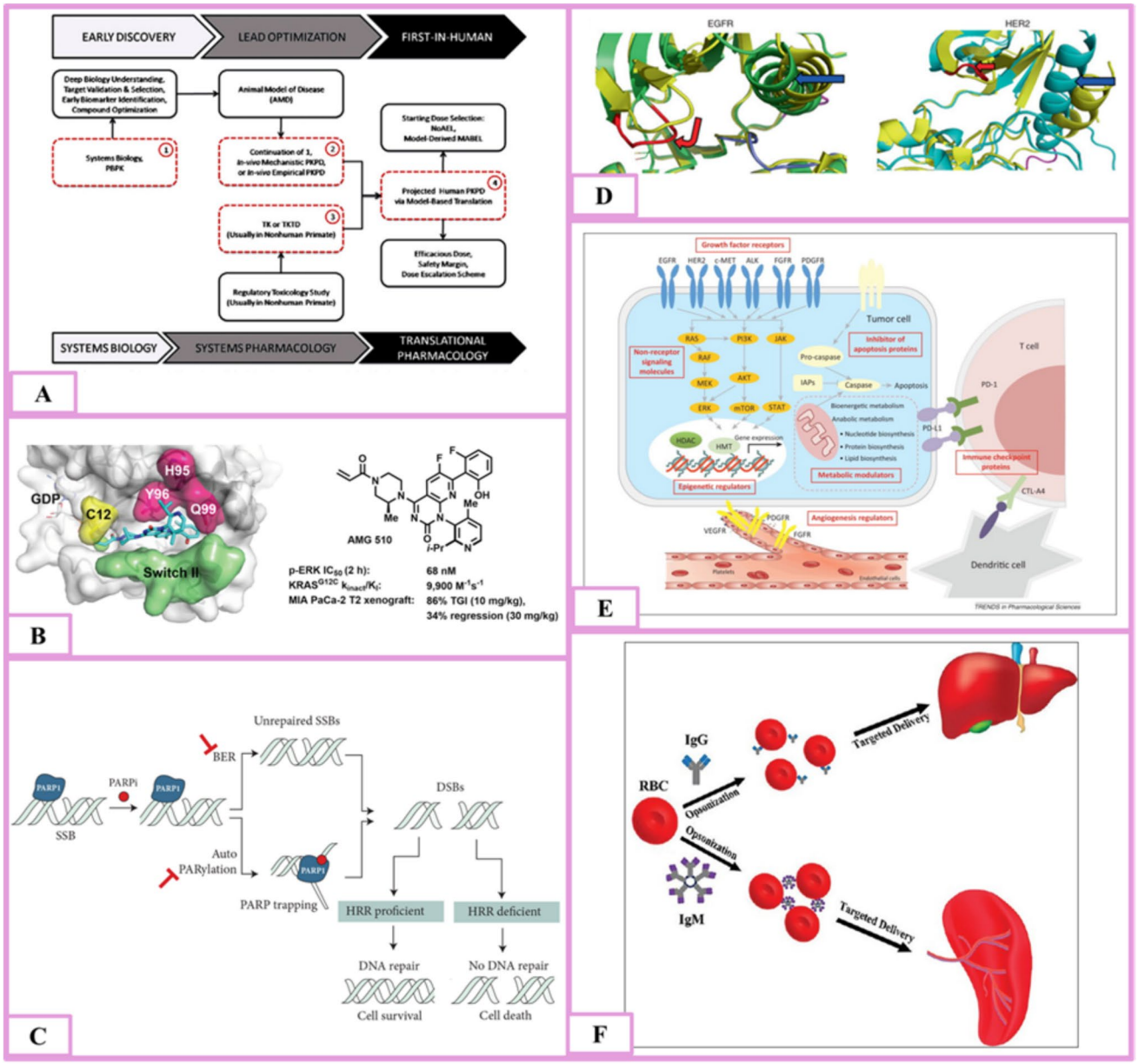


Fig. 4 **A** Summary of the model-based preclinical development framework for biopharmaceuticals [60], **B** Comparison of the GDP-KRASG12C binding modes of ARS-1620 (Graphical abstract) [61], **C** Proposed mechanisms for PARPi activity in HRR-deficient cells. PARP inhibition impairs repair of single strain breaks (SSBs) by disrupting the base excision repair (BER) pathway and also causing PARP1 trapping by inhibiting auto-PARylation and/or PARP release from DNA. These result in unresolved DNA double-strand breaks (DSBs) that in homologous recombination repair (HRR)-deficient cells lead to cell death [62], **D** 3D modeling of EGFR D770insNPG (green) and EGFR T790M (yellow) and 3D modeling of HER2 A775insYVMA (blue) and HER2-WT (yellow) [63], **E**. Targets for molecularly targeted cancer therapy [64], **F**. Targets for molecularly targeted cancer therapy [65]

Other putative molecular targets for non-small cell lung cancers have been identified. Monoclonal antibody bevacizumab binds to vascular endothelial growth factor (VEGF) and prevents tumor blood vessel growth, which is one possible treatment option for colorectal cancer. An additional monoclonal antibody that targets EGFR is panitumumab. Testing for these mutations is recommended since mutations in the Kirsten rat sarcoma virus gene may be linked to decreased panitumumab efficacy (Fig. 4E) [64].

Challenges in Traditional Drug Delivery Methods

The challenges facing the recent advancements in DDSs are presented from studies as follows. A major obstacle is the limited and varied literature, hindering nanomedicine

progress [65, 72–76]. Safety concerns arise regarding nanoparticles' interactions, safety, and their impact on non-target organs. Firstly, the particle size in DDSs is causing a major drawback, causing poor absorption, instability, and adverse effects. Smaller particles offer a solution, overcoming absorption and bioavailability issues associated with larger particles. The second challenge is target-specific delivery complications as they persist due to challenges in reaching the target site effectively. Systemic administration of siRNA faces degradation and absorption issues. Lipid nanoparticles show promise, but reactions with the body and potential toxicity pose challenges. Moreover, the toxicity of nanomaterials, particularly with materials like silver, gold, silica, and titanium, raises health and environmental concerns. Carbon nanotubes, despite their potential, exhibit harmful effects on embryos, genes, and various organs, necessitating thorough toxicity testing. And despite reduced systematic toxicity compared to conventional medicine, these DDSs only marginally enhance therapeutic efficacy. Crucially, the highly abnormal human tumor microenvironment presents challenging barriers to nanomedicine delivery, beyond the capabilities of enhanced penetration and retention effects alone. Biocompatibility and acceptability challenges arise from the body's distinct responses to biological and synthetic materials. The blood-brain barrier poses a hurdle for achieving therapeutic drug concentrations in brain tissues, limiting the efficacy of DDSs. Natural barriers in the body, such as the liver and kidneys, can hinder drug delivery by treating nanoparticles as waste products. Accumulation in the liver's Kupffer cells and renal system considerations highlight challenges in ensuring effective drug delivery. Even though DDSs show potential, addressing literature gaps, ensuring safety, overcoming biocompatibility challenges, and navigating natural barriers are necessary for advancing nanomedicine applications. Further research and development are needed to enhance the effectiveness and safety of DDSs.

Novel drug delivery systems have significantly improved the pharmacokinetics of drugs, reduced undesired side effects and enhanced patient compliance through extended-release periods. While there have been notable advancements in controlled drug release, the utilization of micro- and nano-carriers faces challenges such as rapid clearance and ineffective targeting. As an alternative, cell systems have emerged as promising biological carriers. Cells offer advantages such as stable release into the bloodstream, slow clearance, efficient targeting, and high biocompatibility when used as drug carriers. Notably, cells like erythrocytes, leukocytes, stem cells, and platelets have been employed as release systems. This review article aims to explore the common types of cells utilized in drug delivery systems and their applications (Fig. 4F) [65].

Role of MDS in Developing Molecular Interactions for Drug Delivery

Over the past two decades, extensive research has been directed towards nanotechnology for cancer treatment, focusing particularly on designing nanocarriers for targeted delivery of anticancer drugs. The primary goal has been to create nanocarriers with high drug-loading capacity, ensuring exclusive delivery to solid tumor sites and minimizing unwanted side effects. Drug loading onto nanocarriers involves either physical or chemical bonding to the carrier surface, each presenting unique challenges. Chemically bound drugs offer greater stability in the human body, while physically bound drugs, especially those surface-adsorbed, may face issues such as premature release into the bloodstream due to interactions with blood components. A deeper understanding of drug-nanocarrier interactions is crucial for designing more efficient and resilient DDSs [77]. The potential of MD simulations of intracellular self-assembly for drug delivery is presenting as five functional motifs in the study of [72].

Molecular simulations and experimental studies assessed MDS construction and delivery efficacy. The solvent-exposed surface area of the assembling modular, along with non-covalent interactions, dictated molecule solubility. Peptide backbone forces and side-chain interactions contributed to self-assembly, optimizing the system for hydrophilic and hydrophobic drugs. The predicted drug delivery molecule recognized cancer cell lines, intracellularly forming fibers for prolonged drug retention. Regular prediction and rational molecular design promise improved modulated drug delivery platforms. In the examination conducted by (Eneida [78]), he highlighted the efficacy of utilizing bilayers as models for liposomes, polymersomes, niosomes, and similar nanoparticles to glean insights into their characteristics. This approach establishes a direct link with experimental model bilayers. Through atomistic simulations, one can delve into intricate details, like drug partitioning within distinct bilayer regions. This method allows a deeper exploration of the primary interactions governing the drug's localization. Specific interactions, such as hydrogen bonding, cation-π interactions (pertinent to aromatic molecules), salt bridges, or entropic effects, guide the drug's localization. Notably, hydrophobic drugs tend to partition into the hydrophobic core of the bilayer. Observing the drug release mechanism through conventional MD simulations is often impractical due to lengthy timescales involved. However, valuable insights can be gained by calculating the free energy along a specific pathway as the drug exits the nanostructure. Various methods, including umbrella sampling, adaptive biasing force (ABF), Wang-Landau algorithm, steer molecular dynamics, and metadynamics, have been proposed to enhance configurational space sampling. To study drug release, a

predefined reaction path, such as the z-direction for bilayers or the radius for spherical nanoparticles, is typically chosen.

The utilization of modulated molecular design for intracellular self-assembly presents a promising avenue in drug delivery, offering optimized drug biodistribution and metabolism. This approach, characterized by its modular design concept, imparts multifunctionality to the delivery system, enhancing drug pharmacokinetics through selectivity and versatility. However, precise control over the self-assembling process at desired sites remains a significant challenge for rational molecular design. In this study, we developed a modulated drug-delivery system (MDS) employing intracellular peptide self-assembly to achieve efficient drug delivery [72, 79].

The MDS was crafted based on a modulated molecular design strategy comprising five functional motifs, which undergo caspase3/7 hydrolysis-directed in situ self-assembly into fibrous nanostructures within target cells. Experimental investigations and molecular simulations were conducted to assess the successful construction and delivery efficacy of the MDS. Our findings, corroborated by molecular simulation analysis, elucidate that the solvent-exposed surface area percentage of the assembling modular segment (KLVFFAE), along with its non-covalent interactions with the four other modules, collectively govern the molecule's solubility. The weak intramolecular forces of the peptide backbone, such as hydrogen bonding, as well as multivalent interactions of the side chains like salt bridges and hydrophobic interactions, contribute to the self-assembly process. The structural variances among the delivered molecules optimize the system for accommodating both hydrophilic and hydrophobic drugs. Importantly, the designed drug delivery molecule exhibits specific recognition of targeted cancer cell lines, facilitating intracellular self-assembly into fibers, thereby promoting prolonged drug retention and accumulation. The consistent prediction and rational molecular design strategies outlined in this study hold promise for further advancements in constructing and optimizing modulated drug delivery platforms (Fig. 5A) [72].

Molecular dynamics simulations were utilized to explore the loading and dynamics of doxorubicin (DOX) anticancer drug on graphene oxide (GO) and poly (ethylene glycol) (PEG) decorated GO (PEGGO) nanocarriers in an aqueous environment at human body temperature (310 K) and physiological pH level of 7.4. The mechanisms of DOX adsorption on PEGGO, as influenced by PEG chain length, were elucidated. While the total DOX-nanocarrier interaction energy was statistically similar for the DOX/GO (control), DOX/Sh-PEGGO (short PEG chains with 15 repeat units), and DOX/L-PEGGO (long PEG chains with 30 repeat units) within the margin of error, the interactions between PEG and DOX increased with longer PEG chains. Simultaneously, the solvent-accessible contact area between PEG and DOX nearly doubled when transitioning from short to long PEG chains. PEGylation of GO effectively augmented the average water density around the nanocarrier, acting as a barrier and prompting DOX migration to the solvated PEG-free segment of the GO surface, particularly pronounced with shorter PEG chains. The DOX-DOX solvent-accessible contact area was smaller in the DOX/GO system, indicating reduced drug aggregation compared to PEGGO systems, albeit with slightly higher levels of aggregation. The computational findings in this study illuminate that increasing PEG chain length enhances DOX loading on the nanocarrier, revealing an observation challenging to ascertain through experimental means. Furthermore, a comprehensive understanding is provided for DOX adsorption and retention in PEGGO drug delivery systems, offering insights to enhance the drug's circulation time, delivery, and targeting efficiency for researchers (Fig. 5B) [77].

In this chapter, we delve into the diverse applications of molecular dynamics simulations within the realm of drug delivery systems (DDS) as explored by our research group. DDS, integral to drug development and therapy, involve formulations or devices facilitating the controlled introduction of therapeutic agents into the body, thereby enhancing efficacy and safety by regulating the release rate, timing, and site of drug delivery. Biocompatible nanoparticles, operating at the nanoscale, have emerged as pivotal elements in improving the effectiveness of approved medications. Understanding the molecular intricacies of the encapsulation process holds significant promise in directing nanocarriers to target specific systems effectively. Our discussion encompasses various applications of drug delivery carriers, including liposomes, polymeric micelles, and polymersomes, employing both atomistic and coarse-grained molecular dynamics simulations (Fig. 5C) [78].

Recent molecular dynamics (MD) simulations reveal that interactions like hydrogen bonding, π-π stacking, ionic bonds, and van der Waals forces play key roles in enhancing drug adsorption on carrier surfaces. The chemical composition, surface functional groups, and charge distribution of substrates directly affect adsorption efficiency. These insights from MD studies help optimize drug loading, stability, and controlled release by guiding the design of carriers with improved binding and retention, ultimately leading to more effective drug delivery systems.

Molecular dynamics simulations are a critical method for understanding adsorption processes in drug carrier systems, and examine in detail the influence of solvent molecules, ionic species and carrier materials. The polarity and viscosity of solvents can directly affect the binding of drug molecules to the carrier surface; for example, water generally provides high adsorption efficiency, while solvents such as ethanol and nicotine can alter surface interactions in different ways. Similarly, ionic species can favour or inhibit

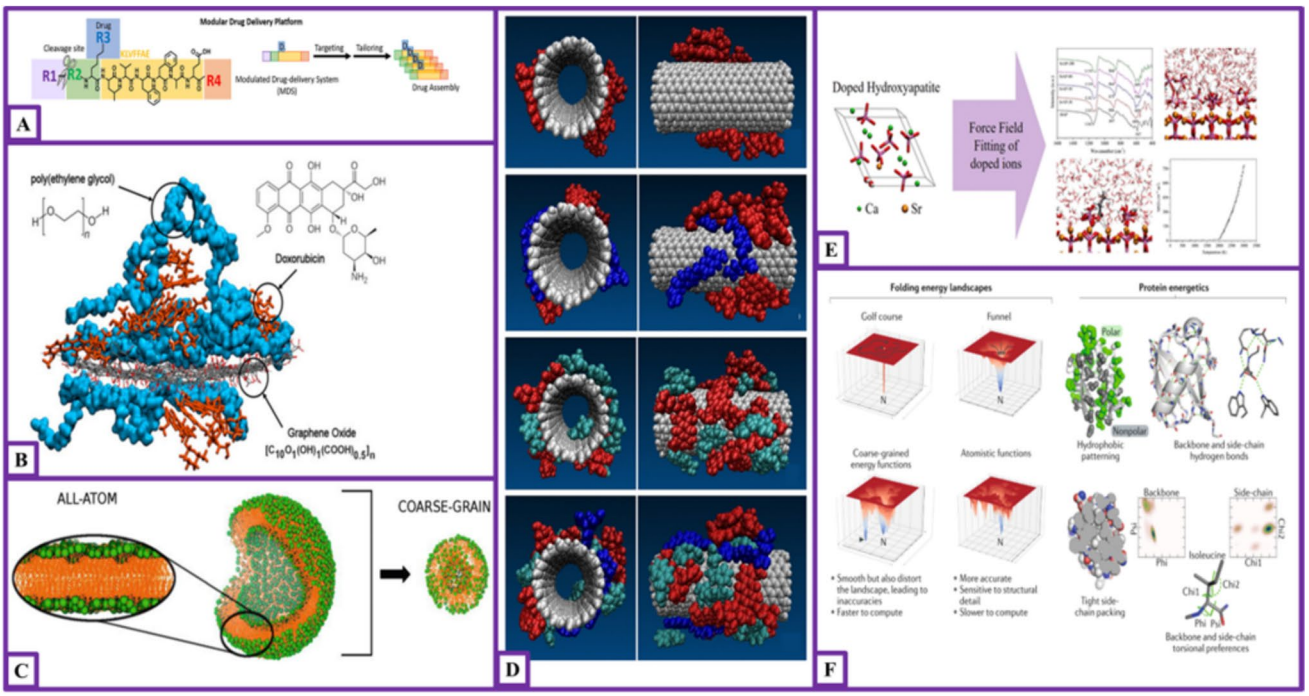


Fig. 5 **A** Illustration of modular designed drug delivery platform [72], **B** Loading of doxorubicin (DOX) anticancer drug onto graphene oxide (GO) and poly(ethylene glycol) (PEG) decorated GO (PEGGO) nanocarriers, molecular dynamics (MD) simulations graphical abstract [77], **C** Schematic representation of the section of the vesicle bilayer and small liposome used as model for atomistic and coarse grain simulations [78], **D** The structures of the functionalized CNTs; DOX (red)-CNT; DOX (red)-Trp (green)-CNT; DOX (red)-FA (blue)-CNT; DOX (red)-Trp (green)-FA (blue)-CNT [80], **E** Graphical abstract of Sr-doped HAP and other biomolecules [81], **F** Protein-folding landscapes and energies [82]

the adsorption process by altering the surface charge distribution. The coexistence of more than one drug molecule can also complicate adsorption dynamics. The structure of the carrier material is also an important factor and different systems such as GO, CNTs and metal-organic frameworks (MOFs) offer various surface interactions. For example, studies with MD simulations show that the adsorption of the drug Thioguanine (TG) on the graphene oxide surface varies depending on the solvent and that water makes this process thermodynamically advantageous. Such simulations provide valuable information for optimising drug adsorption mechanisms and making drug transport systems more efficient. The literature includes significant studies aimed at understanding the mechanisms of drug adsorption and the effects of solvents. For instance, the study by Salo-Ahen et al. demonstrates the applicability of computational approaches in the delivery and adsorption processes of poorly soluble drugs. The objective of this work is to evaluate the effects of different solvents and formulation strategies on drug solubility and adsorption efficiency using MD simulations. The findings provide valuable guidance for optimizing strategies such as co-solvents, surfactants, and amorphous formulations [83].

Similarly, the study by Hasanzade and Raissi investigates the adsorption of the anticancer drug TG on a GO surface using DFT and MD simulations. The main aim of this study is to determine how different solvents (e.g., water, ethanol, nicotine) affect the adsorption process and to elucidate the optimization potential of nanomaterial-based carriers like GO in drug delivery systems. This research highlights the roles of molecular interactions and surface dynamics in solvent effects, thereby identifying key parameters for the efficient delivery of drugs to target sites [84]. Both studies illustrate the significant value of molecular dynamics simulations in developing improved drug adsorption and delivery systems. They also reveal that the properties of solvents, ions, and carrier materials play critical roles in these processes. These insights contribute substantially to research efforts aimed at developing more efficient drug delivery systems and improving clinical outcomes.

MD simulations have been widely utilized to study drug delivery substrates at the atomic level, offering critical insights into their stability, drug adsorption capacity, and controlled release mechanisms. The role of solvents, coexisting ionic species, and molecular interactions significantly affects the adsorption efficiency of drugs on carrier surfaces. Solvents such as water, ethanol, and nicotine influence drug

adsorption processes in various ways. Water, being a polar solvent, facilitates strong interactions between drug molecules and carrier surfaces, often enhancing adsorption efficiency. In contrast, organic solvents like ethanol alter solubility properties, sometimes weakening drug-carrier interactions. Nicotine, although a less common solvent, exhibits a unique adsorption dynamic due to its high solubility potential. Ionic species, such as Na^+ and Cl^-, can modulate drug adsorption by altering the charge distribution on carrier surfaces. Positively charged ions (e.g., Na^+) enhance adsorption by forming strong electrostatic interactions, whereas negatively charged ions (e.g., Cl^-) may disrupt surface charge balance, reducing adsorption efficiency. The presence of multiple drug molecules introduces additional complexity to the adsorption process. While some drugs compete for binding sites, others interact synergistically, promoting adsorption. Molecular properties such as size, charge, and chemical structure play a crucial role in determining adsorption efficiency.

Various nanomaterials have been explored as drug carriers, including:

- **Graphene Oxide (GO):** High surface area and functional groups enable strong drug interactions.
- **Metal-Organic Frameworks (MOFs):** Porous structures allow for high drug-loading capacity.
- **Carbon Nanotubes (CNTs):** Strong interactions with drug molecules facilitate efficient adsorption.

MD simulations have been instrumental in understanding the adsorption mechanisms at the molecular level. For example, studies have demonstrated how water enhances the adsorption of anticancer drugs like TG on graphene oxide surfaces, making the process thermodynamically favorable. Additionally, MD simulations have revealed how solvents, ionic species, and carrier materials influence drug interactions, ultimately aiding in the design of more efficient drug delivery systems (Table 2).

By integrating MD simulations, researchers continue to refine drug delivery technologies, optimizing the efficiency of nanocarriers for targeted therapies. The combination of computational and experimental approaches remains critical in advancing modern nanomedicine.

The reliability and accuracy of MD simulation data play a crucial role in the development of drug delivery systems. Since MD simulations provide theoretical insights into molecular interactions, adsorption mechanisms, and drug release dynamics, their validation against experimental data is essential for ensuring scientific rigor and practical applicability. MD simulations can predict various physicochemical properties of drug carriers, such as drug encapsulation efficiency, stability under physiological conditions, and interaction with biological membranes. However, for these findings to be considered reliable, they must be supported by experimental evidence. Studies should compare MD-generated results with real-world observations, including:

- Spectroscopic data (e.g., FTIR, NMR) to confirm molecular interactions.
- Surface analysis techniques (e.g., SEM, TEM, AFM) to verify adsorption patterns.
- Drug release kinetics obtained from in vitro and in vivo experiments.

Given the importance of validating MD simulation data, researchers must provide scientifically sound explanations based on existing literature and experimental cases reported in previous studies. This approach strengthens the credibility of simulation-based findings and ensures that theoretical predictions align with real-world applications. In drug delivery research, integrating MD simulations with experimental techniques not only enhances the understanding of molecular interactions but also aids in the optimization of nanocarrier systems for targeted therapy. By emphasizing validation, the field of computational drug delivery can advance more effectively, bridging the gap between theoretical models and practical pharmaceutical applications [33].

MD simulations are a crucial tool for understanding and improving the effectiveness of drug carrier systems in cancer treatment. However, although many drugs have been studied both experimentally and through MD simulations in the literature, some have not been included in the current review. In this context, when evaluating various drug types and their carrier systems examined using MD simulations, small-molecule chemotherapeutics, targeted therapies, immunotherapeutics, RNA-based drugs, and natural compounds stand out.

Chemotherapeutics such as doxorubicin (DOX), paclitaxel (PTX), and cisplatin have generally been studied with lipid- and polymer-based carriers. Targeted therapies, including erlotinib, imatinib, and sorafenib, have been modeled with nanocarriers due to their specific effects on cellular targets. Immunotherapy agents, such as pembrolizumab, nivolumab, and bevacizumab, have been investigated with nanocarrier systems to explore their interactions with the immune system. In recent years, siRNA- and mRNA-based drugs have also been modeled within lipid nanoparticles, highlighting the potential of gene-based therapies. Among natural compounds, curcumin and resveratrol are prominent molecules studied through MD simulations due to their biocompatibility.

This review demonstrates that while MD simulations contribute significantly to understanding the effects of drug carrier systems, some drugs remain outside the current scope. Given the broad range of drugs available in the literature, future studies should be designed more comprehensively. In

Table 2 A summary of key insights from MD simulations on different drug carriers

Substrate type	Examples	Key insights from MD simulations	References
Lipid-Based Carriers	Liposomes, SLNs	Drug encapsulation, membrane permeability, stability	[85]
Polymeric Nanoparticles	PLGA, PEGylated systems	Polymer-drug interactions, controlled release	[86]
Dendrimers	PAMAM dendrimers	Drug loading, release kinetics, cytotoxicity	[87]
Carbon-Based Materials	Graphene oxide, CNTs	Drug adsorption, cellular interactions, toxicity	[88]
MOFs	ZIF-8, UiO-66, MIL-101	Drug adsorption, stability, controlled release	[89]

this regard, MD simulations play a critical role in optimizing drug carrier systems for cancer treatment, emphasizing the need for further research on a wider variety of drugs [90] (Table 3).

Applications of Molecular Dynamics Simulation in Cancer Drug Delivery

General Overview of Current DDSs

This overview of [104] covers current DDSs, exploring various administration routes, drug formulations, and devices. However, new DDSs are becoming increasingly popular as substitutes for traditional methods. Lipid nanoparticles, including micelles and liposomes, are actively studied for their potential to deliver drugs to specific tissues. However, challenges persist, including the shortened half-life due to phagocytic absorption and hepatic filtration, as well as concerns regarding targeted release and the potential toxicity of nanoparticles. Nanoparticles play a crucial role in drug delivery and serve as pharmaceuticals and diagnostics. Targeted drug delivery advances, particularly in cancer therapy, are discussed in novel studies, along with challenges in delivering drugs to the brain. Refinements in drug delivery aim to support the development of personalized medicine, addressing commercial aspects, challenges, and the future of DDSs.

In similarly study of [77], they analyzed the GO, a two-dimensional single-layer carbon sheet adorned with oxygen-containing functional groups, has demonstrated its suitability as a carrier for drug molecules. This includes the attachment of drugs on its extended surface as well as at the edges through both covalent and noncovalent interactions.

The study of [72] discusses a molecular design based on intracellular self-assembly for drug delivery, emphasizing optimized biodistribution and metabolism. The modulated drug-delivery system utilizes five functional motifs, transforming into fibrous nanostructures within target cells through caspase 3/7 hydrolysis-directed in situ self-assembly. Experimental studies and molecular simulations confirm successful construction and delivery efficacy. The solvent-exposed surface area and non-covalent interactions determine molecule solubility, utilizing weak intramolecular forces and multivalent interactions. The system accommodates structural differences for both hydrophilic and hydrophobic drugs, showcasing targeted cancer cell recognition and intracellular self-assembly for prolonged drug retention.

Molecular dynamics simulations have emerged as a powerful tool for understanding drug adsorption mechanisms at the molecular level. Lomzov et al. utilized MD simulations to investigate the thermal stability of oligonucleotide duplexes, demonstrating that the enthalpy of DNA/DNA complex formation can be accurately calculated using this approach. Their study explored the impact of various simulation parameters on the secondary structure and hybridization enthalpy of oligonucleotides, identifying optimal conditions for reliable thermodynamic predictions. By comparing MD-based calculations with experimental thermodynamic data from a large set of oligonucleotides, they showed that the stability of DNA complexes could be predicted with high accuracy. These findings underscore the importance of incorporating thermodynamic factors into the study of drug carrier systems [105].

Similarly, Salo-Ahen et al. provided a comprehensive overview of the diverse applications of MD simulations in drug discovery and pharmaceutical development. Their study highlighted the role of MD simulations in evaluating drug-target interactions, understanding membrane protein dynamics, and analyzing nanoparticle-based drug formulations. They particularly emphasized the use of MD simulations for assessing the stability and solubility of amorphous drug formulations, which is crucial for optimizing drug delivery systems [83]. Building upon these insights, MD simulations offer a robust framework for calculating key thermodynamic parameters in drug adsorption processes, including free energy change (ΔG), enthalpy (ΔH), and entropy (ΔS). The effects of solvent interactions, temperature variations, and binding energetics on drug adsorption efficiency need to be further explored through comprehensive simulation studies. In conclusion, integrating MD-based thermodynamic analyses into the development of drug delivery systems for cancer treatment is of paramount importance. Future research should focus on enhancing the accuracy of drug adsorption models by combining MD

Table 3 Overview of various drugs, their types, and the carriers examined using MD simulations

Drug	Drug type	Carriers examined via MD simulations	References
Doxorubicin (DOX)	Chemotherapeutic	Lipid nanoparticles, dendrimers	[91]
Paclitaxel (PTX)	Chemotherapeutic	Polymeric nanoparticles, micelles	[92]
Cisplatin	Chemotherapeutic	Lipid and polymer carriers	[93]
Erlotinib	Targeted therapy (EGFR inhibitor)	Lipid-based nanoparticles	[94]
Imatinib	Targeted therapy (BCR-ABL inhibitor)	Nanocarriers (lipid, polymer)	[95]
Sorafenib	Kinase inhibitor	Polymer-based carriers	[96]
Pembrolizumab	Immunotherapy (PD-1 inhibitor)	Can be modeled with nanoparticle systems	[97]
Nivolumab	Immunotherapy (PD-1 inhibitor)	Nanocarrier systems	[98]
Bevacizumab	Immunotherapy (VEGF inhibitor)	Polymeric carriers in MD simulations	[99]
Patisiran	siRNA-based drug	Lipid nanoparticles (LNP)	[100]
Onpattro	siRNA-based drug	Lipid-based carrier systems	[101]
Curcumin	Natural compound	Lipid nanoparticles, micelles	[102]
Resveratrol	Natural compound	Polymeric carriers, lipid systems	[103]

simulations with experimental validation, ultimately leading to more efficient and targeted drug delivery strategies.

MD simulations are essential for selecting appropriate polymer materials by analyzing their structural, mechanical, and thermal characteristics at the atomic level. This technique is applicable to various polymer types, including thermoplastic, thermoset, natural, nanocomposite, and ionic polymers. By simulating factors such as solubility, diffusion, stability, and surface interactions, MD helps evaluate their suitability for different applications. This approach streamlines experimental processes, enabling the efficient selection and design of polymers with tailored properties.

Thermoplastic Polymers

Thermoplastic polyurethanes (TPUs) are versatile materials known for their excellent flexibility and energy-dissipating capabilities under substantial mechanical deformation. This study explores the molecular basis of TPU's mechanical properties by examining the interactions between its hard and soft segments. Molecular simulations were conducted to analyze the mechanical behavior of TPU, which contains 4,4'-diphenylmethane diisocyanate and n-butanediol (hard segment) as well as poly(tetramethylene oxide) (soft segment), under large tensile deformation. Using the Interphase Monte Carlo method, the simulations revealed the mechanisms responsible for yielding, hardening, and the Mullins effect in TPU. It was observed that these mechanisms varied depending on the chain topology and the direction of the applied load. The findings suggest that TPU's superior flexibility and ability to disperse energy are largely attributed to cyclic loading [106].

Thermoset Polymers

Thermosetting materials, such as cured epoxy resins, are known for their strong chemical bonds, excellent heat and chemical resistance, and the ability to be reinforced with fibers and nanoparticles to improve their toughness. These characteristics make them ideal for various applications in industries like aerospace, electronics, and biomedicine. Traditional methods for developing and testing these materials can be time-consuming and complex. However, with the progress of data-driven computational materials design, the approach to discovering and optimizing new thermosets is evolving. MD simulations are gaining significance in developing new materials without the need for physical synthesis or testing, as well as in understanding interactions with various interfaces and nanofillers. Although MD is not yet the primary validation method for material development, as molecular force fields improve and computational power increases, MD simulations are expected to play an increasingly vital role in generating precise and reliable data [107].

Natural Polymers

Natural rubber (NR), known for its stress-induced crystallization (SIC), demonstrates exceptional mechanical properties compared to other elastomeric materials. Despite its widespread use, a comprehensive understanding of the structure-mechanical property relationship in NR is still lacking. In this study, MD simulations were utilized to explore the influence of various factors such as the mass fraction of phospholipids and proteins (ω), hydrogen-bonding interaction strength (εH), and non-hydrogen-bonding interaction strength (εNH) on the structural morphology, dynamic behavior, and mechanical performance of NR. The results showed that NR tends to form local clusters through

hydrogen bonds between chain ends, which subsequently affect the mobility of the polymer chains and lead to changes in mechanical properties. These fundamental mechanisms have a significant impact on NR's stress-strain behavior [108].

Nanocomposite Polymers

Polymer nanocomposites (PNCs) are materials created by integrating nanoparticles into a polymer matrix, which improves their mechanical, thermal, and electrical properties.This study explores how the morphology of dynamic crosslinking networks affects the properties of self-healing PNCs. The researchers designed modified nanoparticles with varying sphericity to create a supramolecular network within the PNCs. It was found that increasing sphericity led to a more uniform distribution of the supramolecular network. Further analysis of the polymer chain segment dynamics revealed that the integrity of the supramolecular network restricts the mobility of the polymer matrix chains. The mechanical properties of the PNCs were mainly influenced by the supramolecular network, while the efficiency of self-healing was primarily affected by the sphericity changes. The study also identified that an optimal grafting density can improve both the mechanical and self-healing properties of the PNCs. Overall, this research offers valuable insights for the development and production of self-healing PNCs using modified nanoparticles [58, 59].

Ionic Polymers

Ionic polymers are a class of polymers that contain ionic bonds, which enable them to exhibit unique properties such as electrical conductivity and electroactivity. These characteristics make them particularly interesting for a variety of applications, and molecular dynamics simulations have proven to be an effective tool in understanding their behavior at the molecular level. Molecular dynamics simulations employing general bead-spring models have proven effective in revealing molecular behavior and structure-property correlations in various polymeric systems. Although these models do not provide atomic-level detail, they incorporate tunable parameters to represent different types of chemical interactions. This approach not only grants access to larger length and time scales but also provides valuable physical insights relevant to a broad range of materials. In these models, parameters such as the number of links and beads can be adjusted to characterize the essential properties of homopolymers. For systems involving uncharged copolymers or solvents, the strength of interparticle potentials is modulated to represent chemical interactions. However, in ion-containing polymer systems, ions interact more strongly and over longer distances with one another, as well as with solvents and monomers, which adds a layer of complexity to the model. As a result, considerable efforts have been made to better capture and analyze these ion-related phenomena in polymeric systems [109].

Specific Treatments for Different Cancer Types

Doxorubicin (DOX) is a type of chemotherapy medication categorized as an anthracycline, a group of highly prescribed and effective anticancer drugs used to treat various conditions such as breast carcinoma, osteosarcoma, acute leukemia, brain tumors, and more [80, 110]. This study employs molecular dynamics (MD) simulations to investigate the adsorption behavior of DOX, an anticancer drug, onto both pristine and functionalized CNTs immersed in an aqueous solution. Initially, the CNTs undergo functionalization with tryptophan (Trp) and folic acid (FA) before introducing DOX molecules into the system. Results from the simulations reveal robust interactions between the drug molecules and the functionalized CNTs, particularly evident under physiological pH conditions. Moreover, functionalization notably enhances the solubility of CNTs in aqueous environments. The impact of pH variations on drug release from both pristine and functionalized CNTs is also explored. The findings suggest that in acidic conditions, the protonation of functional groups (such as Trp) and the resultant repulsive forces between DOX molecules and functional groups facilitate the release of DOX from the surface of functionalized CNTs. Importantly, drug release is strongly influenced by the pH and the protonation states of both DOX and functionalized CNTs (Fig. 5D) [80].

Gemcitabine is a pyrimidine antimetabolite approved by the Food and Drug Administration (FDA) for cancer treatment. This anticancer drug demonstrates effectiveness against a diverse range of tumors. The cytotoxic effects of gemcitabine are harnessed through its incorporation into DNA, contributing to its therapeutic impact in the treatment of various cancers. The approval by the FDA underscores its recognized efficacy and safety in clinical applications for cancer patients [34, 111]. Paclitaxel (Taxol, PTX) is a prominent anti-mitosis agent with a rich history of research since its discovery in the early 1960 s. Renowned for its therapeutic effectiveness, paclitaxel has demonstrated positive outcomes in treating various cancers, including those affecting the breast, ovaries, prostate, lung, bladder, esophagus, and head and neck [112].

Hydroxyapatite (HAP) stands out as a prominent inorganic constituent found abundantly in human bones and teeth, sparking considerable interest for its potential as an implant material. One effective strategy to enhance its biological properties involves the incorporation of foreign ions

into the HAP lattice structure. uses first-principles calculations and molecular dynamics simulations to investigate strontium (Sr)-doped hydroxyapatite (HAP), an important bone and teeth mineral. It successfully models structural, thermal, and elastic properties across varying Sr concentrations and examines how pH affects Sr-substituted HAP's solubility and surface adsorption. The findings show Sr ions influence biomolecule adsorption differently, weakening Glu but strengthening Lys interactions. The developed force-field parameters offer a useful tool for future research on Sr-doped HAP and biomolecular interactions (Fig. 5E) [81].

The complex process of designing epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors is hindered by insufficient understanding of the dynamic behavior of the EGFR binding site. A study utilizing molecular dynamics simulations analyzed 33 protein-ligand complexes, revealing that the T790M mutation impacts the binding pocket dynamics, the Rg mutation causes a slight compression in the binding region, and Rg is linked to biological activity. This study emphasizes the limitations of traditional scoring functions in recognizing potent inhibitors. The research sheds light on enhancing the efficacy and optimization of EGFR TKIs, identifying ASP800 as the most flexible residue and ALA743 as the most structurally stable. Notably, MET793 and LEU844 are proposed to play crucial roles in ligand recognition, offering insights for the rational design of future EGFR TKIs by incorporating dynamic structural characteristics [113].

Owen et al. [114] aim to investigate the structural, electronic, and biological properties of chlorogenic acid [(Z)− 5-((3-(2,3-dihydroxyphenyl)acryloyl) oxy)− 1,3,4-trihydroxycyclohexa-2,4-diene−1-carboxylic acid], a natural compound. The compound was first characterized using spectroscopic methods such as UV–Vis, ^{1}H NMR, ^{13}C NMR, and FT–IR. Subsequently, molecular stability was analyzed using Density Functional Theory (DFT) calculations; the energy range (HOMO–LUMO gap) calculated using different functionals was found to be 3.7–7.8 eV. This value indicates that the compound is electronically quite stable. The geometrical structure optimized by DFT was found to highly correlate with experimental X-ray crystallography data (in terms of bond lengths and bond angles). The FT-IR spectrum is supported by O–H (3366 cm^{-1}), C=O (1689 cm^{-1}), C–H (1636–1442 cm^{-1}), and C–O (1192, 1122 cm^{-1}) stretching vibrations. The compound's drug potential was evaluated according to Lipinski, Ghose, Veber, and Egan rules, and ADME analyses showed that it has a good oral bioavailability profile. However, toxicological modeling revealed potential hepatotoxic and immunotoxic effects. Molecular docking studies showed that the compound has high affinity for the target protein; binding energies of − 8.30 and − 9.5 kcal/mol were found to be higher than those of the reference drug. Additionally, during molecular dynamics (MD) simulations, the complex.

Mukheerjee et al., in silico methods were employed to discover and assess a possible VEGF inhibitor that could influence the immunosuppressive tumor microenvironment in ovarian cancer. From a selection of 12 inhibitors reported in prior studies, AEE788 was found to have a high binding affinity toward the target protein. This compound served as the basis for structure-based virtual screening, which resulted in the identification of CID 88265020, a molecule showing even greater binding strength. Molecular dynamics simulations, alongside pharmacophore modeling and toxicity assessments, indicated only minor differences between the two candidates. The findings suggest that CID 88265020 holds significant promise as a VEGFR inhibitor and could be a strong candidate for future ovarian cancer treatment development [55].

Jiao et al. a combination of network pharmacology, molecular docking, and molecular dynamics (MD) simulations was employed to explore the breast cancer-fighting potential of *Scutellaria baicalensis*. Out of 25 bioactive compounds and 91 predicted targets, **coptisine** and **stigmasterol** demonstrated strong interactions with the cancer-associated protein **AKT1**. Results from MD simulations indicated that the **coptisine–AKT1 complex** displayed greater structural stability and lower binding energy compared to the stigmasterol complex. These outcomes highlight the multi-target and multi-compound therapeutic potential of *Scutellaria baicalensis* in breast cancer, with **coptisine** standing out as a particularly promising AKT1-targeting agent (Fig. 6A) [115].

Isa et al. explored natural compounds derived from *Musa sapientum* for their ability to target crucial proteins involved in breast cancer, such as ERα, mTOR, EGFR, and PR. An initial screening of twenty-three compounds based on their physicochemical and pharmacokinetic profiles narrowed the selection to five candidates with favorable drug-like properties. Molecular docking analyses identified two compounds, CID_616859 and CID_1742210, as having strong binding affinities to all the target proteins. Further molecular dynamics simulations demonstrated the stability of these protein-ligand complexes, indicating that these compounds may hold promise as multi-target inhibitors in breast cancer therapy pending additional experimental verification (Fig. 6B) [116].

Rashidieh et al. investigates MLN4924, a novel anti-cancer agent targeting the NEDD8-activating enzyme (NAE), a key player in protein degradation processes. MLN4924 has demonstrated effectiveness against multiple cancer types, including lung, colon, melanoma, and lymphoma. Nonetheless, mutations such as A171T, Y352H, and I310N within NAE have been shown to diminish the enzyme's responsiveness to MLN4924, contributing to resistance. Earlier molecular dynamics studies indicated that these mutations

influence the binding interactions between NAE, ATP, and the inhibitor. Expanding upon these findings, the present study utilizes enhanced molecular dynamics simulations via Gromacs software to elucidate the structural mechanisms underlying enzyme mutations and associated drug resistance [117].

Comparative Analysis of MD Simulation-Assisted and Traditional DDSs Across Different Cancer Types

See Table 4.

Challenges and Future Perspectives

Limitations of MD Simulations in Complex Biological Systems

Traditional molecular simulations face the challenge of finding a balance between the high computational cost of ab initio molecular dynamics and the lower precision of empirical force fields [124].

Another study has addressed the issues in the realm of computational efforts that focuses on simulating synthetic membrane substances and aiding in the design of materials. Where limitations arise when analyzing desalination membranes reveals nano-sized physiochemical and morphological heterogeneity in common polyamide membranes. Semipermeable thin film composite models may not effectively capture such heterogeneity, posing challenges. Additionally, computational capacities of current CGUs present barriers, where innovative algorithms for building membrane models aim to enhance experimental-simulation compatibilities. Understanding solute rejection in membranes, influenced by mechanisms like size exclusion, charge exclusion, and interactive interfacial correlations, can benefit from MD simulations [125].

While tools for protein structure prediction and design have made significant advancements, challenges persist. The energy functions guiding these processes, designed for computational efficiency, still face difficulties in accurately balancing polar and nonpolar interactions and solvation effects, especially at interfaces. Consequently, success rates in interface-modelling applications, including protein docking with backbone flexibility, one-sided interface design, and enzyme design, continue to be limited [126]. Another limitation discussed in Ref. [126] is related to the vast conformational space of proteins, and the challenge it poses

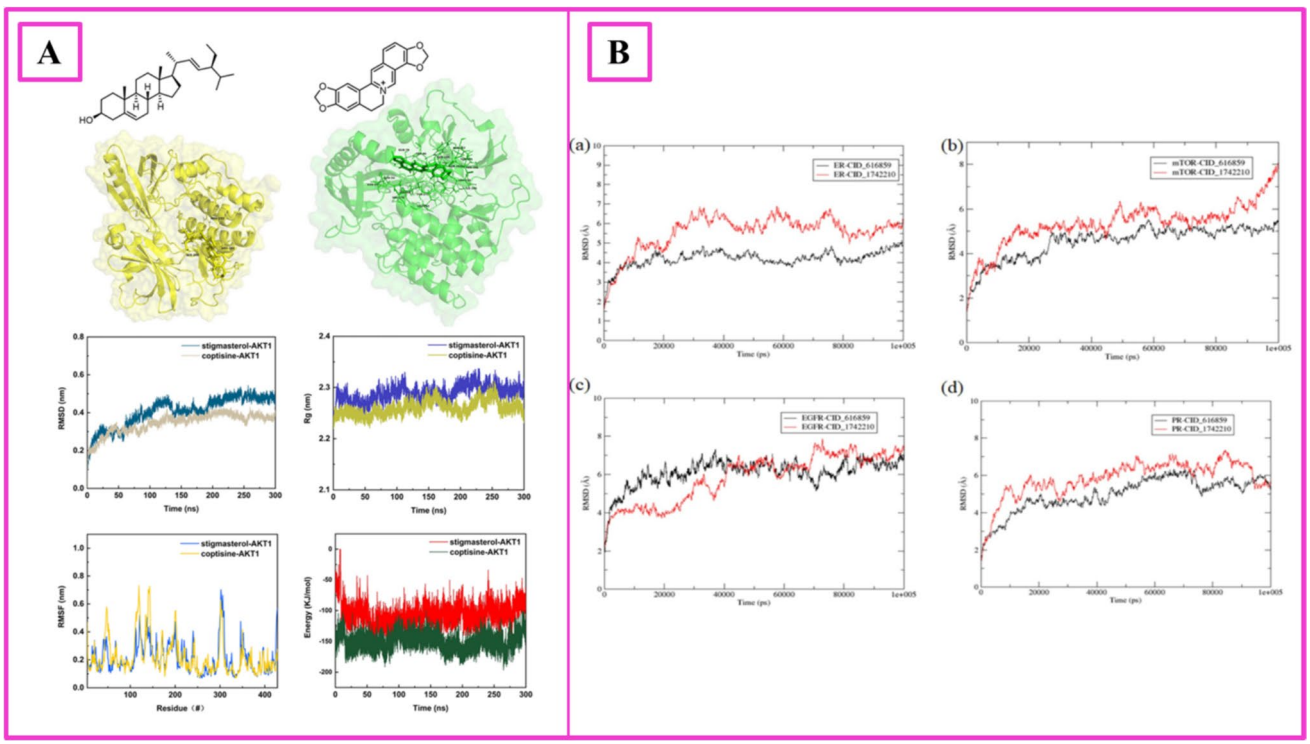


Fig. 6 **A** Schematic summary, 300 ns molecular dynamics simulations were conducted to assess the stability, interaction profiles, and dynamic behavior of stigmasterol- and coptisine-bound AKT1 complexes through multiple analytical approaches [115]. Copyright 2023 MDPI, **B** schematic summary, RMSD analyses highlighted time-dependent backbone fluctuations and structural alterations resulting from ligand binding in complexes of **a** ERα, **b** mTOR, **c** EGFR, and **d** PR with CID_616859 and CID_1742210 [116]. Copyright 2025 SPRINGER NATURE

for structure prediction while simulating the structures. The research highlights the obstacle of searching through an exponentially growing conformational space, making it impractical to explore all possible conformations of a protein within a reasonable timeframe using traditional methods. This limitation is relevant to the challenges faced in simulating complex biological systems, where the sheer complexity and size of molecular structures make exhaustive exploration computationally intensive and often infeasible (Fig. 5F) [82].

The study of Ref. [50] discusses the challenges related to the scale and complexity of molecular dynamics simulations, highlighting the need for optimization and improvement of the calculation process.

The limitation mentioned in this context is the computational complexity associated with the large number of particles in the system to be studied. The scale of calculation and analysis becomes significant, particularly when dealing with tens of thousands of particles. Researchers are focusing on optimizing the calculation process to address this limitation. The paper proposes the integration of machine learning and data mining algorithms to enhance the efficiency of molecular dynamics simulations, aiming to overcome the challenges posed by the scale and complexity of these simulations. At this point, the U.S. Food and Drug Administration (FDA) has not approved CNTs for use in drug delivery due to the lack of sufficient information on their toxicity, biocompatibility, and long-term biological effects. To address this issue, it is vital to conduct comprehensive in vitro and in vivo studies to evaluate the safety and toxicity of CNTs and to apply surface modifications to improve their biocompatibility. Additionally, preclinical studies and pharmacokinetic evaluations should comply with FDA regulatory guidelines. Long-term animal studies should be conducted to assess potential risks before moving on to human trials, and safety data should be thoroughly documented. Once these requirements are met, CNTs can be considered for approval in drug delivery applications [127].

Future Directions and Potential Breakthroughs, Considering Different Cancer Types

The study Ref. [128] of has concluded that synergy of cutting-edge computing hardware and sophisticated software has given rise to a genuine computational microscope. MD simulation stands out as a dependable method for observing the structure and dynamics of substantial protein complexes within authentic cellular settings. While all-atom MD is the benchmark, coarse-grained MD serves as a complementary approach, allowing exploration of extended time and length scales, provided the simplified force field accurately represents the physical and chemical mechanisms involved in the studied process.

A novel study has discussed implementing artificial intelligence and mentioned that generative networks like Boltzmann generators have proven their ability to generate physically realistic one-shot samples of model systems and proteins in implicit solvents. Scaling to larger systems requires incorporating energy invariances, such as the exchange of identical solvent particles, into the transformation, and including parameter sharing. This approach goes beyond sampling the probability density of a specific system and aims to generalize from a dataset of examples within a class of molecules, such as solvated proteins. However, equivariant networks with parameter sharing for generative learning are currently unavailable and need development [129].

Another novel study had aimed to overcome computational challenges in large-scale organic systems by proposing a universal multiscale higher-order equivariant model with active learning techniques. Addressing issues like long-range intermolecular interactions and molecular conformations, the model achieves the highest predictive accuracy, significant improvements in computational speed, and enhanced memory efficiency compared to existing equivariant models. Additionally, a bond length stretching method enhances the stability of long-time molecular simulations. With only 901 samples, the model extends high precision to systems with hundreds of thousands of atoms, ensuring accuracy, speed, efficiency, and stability for long-time molecular simulations in large-scale organic systems [124].

While molecular dynamics (MD) simulations provide atomistic insights into biomolecular behavior, their predictive accuracy critically depends on the underlying force fields and simulation parameters. To ensure reliability, simulation results are often validated against experimental data such as X-ray crystallography, NMR spectroscopy, calorimetric measurements, or single-molecule techniques. For example, structural stability can be assessed using RMSD and RMSF analyses in comparison with crystallographic coordinates, while binding free energy estimates (via MM-PBSA or MM-GBSA methods) can be compared with experimental affinity values. Moreover, quantum mechanical calculations (e.g., DFT) and enhanced sampling methods can complement MD to improve accuracy. Such cross-validation strategies are essential for building confidence in simulation-based findings and ensuring their translational relevance [130].

Conclusion

MDS proves valuable in understanding molecular interactions, drug delivery systems, and material properties. However, challenges remain, particularly in the approximation of

Table 4 Over review of MD simulation on different molecules

Current treatments	Cancer type	Applications of MD simulation in drug delivery		References
Doxorubicin (DOX)	Bone sarcomas, as well as cancers affecting the breast, ovary, bladder, and thyroid. Additionally, it is employed in the treatment of acute lymphoblastic leukemia, acute myeloblastic leukemia, Hodgkin lymphoma, and small cell lung cancer.	Drug Delivery with Functionalized CNTs (FCNTs)	Simulation results revealed strong interactions between drug molecules and FCNTs at physiological pH. Additionally, functionalization led to a notable increase in the solubility of FCNTs in aqueous solutions.	[80, 118]
		Protonated DOX Penetration into Liposome Membranes	Free energy calculations were done to protonate DOX into liposome membranes. Which resulted in the development of optimal formulations for lipid-based carriers, particularly those with pH-responsive membranes.	[80, 110]
Gemcitabine (GEM)	Used to treat several cancer types such as NSCLC, urothelial cancer cells pancreatic, bladder, ovarian and breast cancer.	Chitosan as a Carrier for Gemcitabine	Molecular dynamics simulations investigated the use of the biodegradable biopolymer chitosan as a carrier for the drug gemcitabine. The study explored the impact of different drug concentrations on loading efficiency. Radial distribution function calculations suggested that in the absence of water molecules, drug molecules were closer to chitosan, leading to higher loading efficiency in these systems.	[34, 80]
		Gemcitabine in Metal Organic Frameworks (MOFs)	A multiscale computational study investigated the microscopic behavior of the anti-cancer drug GEM stored in metal organic frameworks IRMOF-74-III and the functionalized OH-IRMOF-74-III. MD simulations revealed slow diffusion of GEM inside the pores of both hosts, crucial for controlled release. The study highlights the biocompatible (OH)-IRMOF-74-III as a promising nanoencapsulator for GEM delivery.	[80, 119]
		Human Serum Albumin (HSA) as a Protein-Based Nanoparticle for Drug Delivery	MD simulations explored HSA the interactions between two Sudlow sites of HSA and GEM, as a cancer treatment. Results indicated that GEM strongly binds to the subdomain IIIA of HSA, with hydrogen bonding being the primary force in the stability of the GEM-HSA complex. The study suggests HSA as a potential drug delivery agent due to its compatibility and binding capacity.	[80, 111]

Table 4 (continued)

Current treatments	Cancer type	Applications of MD simulation in drug delivery		References
Paclitaxel, (PTX)	Research showed that this treatment is used for various cancers including breast, ovaries, prostate, lung, bladder, esophagus, and head and neck.	COS/SA Nanoparticles for Paclitaxel Delivery	MD simulations were conducted to understand the reaction of PTX encapsulated by salicylic acid-grafted chitosan oligosaccharide (COS/SA) nanoparticles. Van der Waals and hydrophobic interactions were identified. Electrostatic and hydrogen-bonding interactions also played supportive roles in COS/SA aggregation. The study revealed that COS/SA nanoparticles are highly hydrosoluble and enhance the aqueous solubility of PTX, a hydrophobic drug. Different drug loading systems were investigated, and the best theoretical drug loading was determined to be 10%.	[120]
		N-Doped Graphene for Paclitaxel Adsorption	MD simulations investigated the adsorption of PTX onto graphene doped with nitrogen atoms (N-doped graphene) in both vacuum and aqueous environments. The adsorption energy was found to decrease with an increase in nitrogen atoms concentration. The surface-PTX average distance, representing the distance between the center of mass of PTX and the surface, indicated weak interactions between the drug molecule and pristine graphene.	[121]
		Triazine Dendrimers with PTX for Prostate Cancer Treatment	The antitumor activities of triazine dendrimers bearing PTX were evaluated in SCID mice with human prostate cancer xenografts. A new construct, prodrug 2, was designed to tether PTX with linkers containing both an ester and disulfide, enhancing its antitumor activity. PEGylation was employed for solubility, biocompatibility, and increased plasma half-life. MD simulations guided the use of a heterogeneous population of PEGylated materials without fractionation, with different PEG chain incorporations. Intravenous delivery of prodrug 2 showed tumor growth arrest and regression over a 10-week treatment period without mortality for mice treated with a 50 mg paclitaxel/kg triple dosing regime.	[112]

Table 4 (continued)

Current treatments	Cancer type	Applications of MD simulation in drug delivery		References
Hydroxyapatite (HAp)	Treatment with HAp resulted in hypodiploid DNA content and DNA fragmentation in lung cancer cells, osteosarcoma cells, breast cancer cells, colon cancer cells, and liver cancer cells, indicating a consistent pattern of responses across various cancer cell types.	Zn-Doped HAp for Enhanced Drug Delivery	MD simulations were conducted to investigate the influence of Zn doping on the crystal structure and adsorption capacity of macromolecular drugs on HAp. Results demonstrated that Zn doping significantly increased the binding energy of DOX on HAp. The interaction between surface Ca ions and carbonyl-O played a crucial role in adsorption. The study also explored the adsorption of tinidazole, revealing a positive correlation between the number of active "O" atoms in the drug and binding stability. These simulations provide valuable insights into drug adsorption on HAp and ion-doped HAp, enhancing their potential as drug carriers.	[44, 122]
		Sr-Doped HAp for Enhanced Biomaterial Properties	First-principles calculations and MD simulations were conducted to investigate the influence of strontium ions substituted in HAp. The study revealed that Sr-substituted HAP exhibited higher solubility with decreasing pH values, and Sr ions tended to adsorb onto the HAP surface, with increased adsorption at higher pH. The substitution of Sr ions also influenced the adsorption of Glu side-chain analogues and Lys side-chain analogues on the HAP surface.	[81, 122]
		HAp Binding with Clathrin-Associated Protein Adaptin-2 (AP2)	MD was utilized on HAp as spherical, rod-shaped, and needle-shaped, with the clathrin-associated AP2 at the atomic level. The study revealed that different nanoparticle morphologies determined their binding specificity through electrostatic interactions. Globular HAp significantly changed the conformation of AP2 protein, while needle-shaped HAp exhibited a more substantial binding energy with AP2. While rising recognition in clathrin-mediated endocytosis, enhancing design principles and potential mechanisms of high-efficiency nano-biomaterials, and establishing a basis for their potential anti-tumor therapeutic effects.	[122, 123]

force fields and the need for further algorithm optimization to enhance computational efficiency.

Understanding molecular interactions in drug delivery is crucial for optimizing therapeutics. Challenges in traditional drug delivery methods underscore the need for advancements, and molecular dynamics simulations play a pivotal role in unraveling complexities, offering insights into drug interactions and release mechanisms. Further research and development are necessary to address challenges and enhance the effectiveness and safety of drug delivery systems. MD simulations play a vital role in understanding and optimizing drug delivery systems across various cancer types. They provide insights into interactions, solubility, loading efficiency, and controlled release mechanisms for different drugs and carriers. MD simulations enhance the precision of targeted cancer therapies, reducing the likelihood of harm to healthy cells. They are particularly valuable in optimizing nanoparticle-based drug delivery systems, ensuring more effective targeting of the tumor microenvironment. This approach improves drug bioavailability while minimizing toxicity, leading to safer and more efficient treatments. By advancing personalized medicine and supporting pharmaceutical research, MD simulations play a crucial role in developing more successful cancer therapies. The studies reviewed demonstrate the potential of MD simulations in guiding the design and development of more effective and targeted drug delivery systems for cancer treatment. This comprehensive overview illustrates the diverse applications of MD simulations in advancing drug delivery strategies for cancer therapy, emphasizing the significance of computational approaches in the development of personalized and efficient treatment modalities. While challenges persist in MD simulations, advancements in computing hardware, software, and innovative methodologies, such as integrating artificial intelligence, hold the potential for breakthroughs in understanding complex biological systems and improving the accuracy and efficiency of simulations. The ongoing synergy between experimental data and computational simulations offers a comprehensive approach to exploring biological phenomena. As comprehended in this review article, the application of MD simulation in cancer drug delivery stands as a transformative tool, providing unprecedented insights into the molecular intricacies of drug interactions. From precise drug design to the optimization of delivery systems, MDS contributes significantly to the advancement of targeted and effective cancer treatments, bringing us closer to realizing the potential of personalized and optimized therapeutic interventions. By uniting our efforts, integrating AI advancements, and collaboratively addressing the complexities inherent in MD simulations, we can usher in a new era of precision and efficiency in cancer drug delivery research. This call to action seeks to inspire researchers, institutions, and organizations to join forces, pushing the boundaries of what is achievable and paving the way for transformative advancements in the fight against cancer.

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Declarations

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