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REVIEW ARTICLE

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Comparison between molecular dynamics potentials for simulation of graphene-based nanomaterials for biomedical applications

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ABSTRACT

Objective: This article provides a substantial review of recent research and comparison on molecular dynamics potentials to determine which are most suitable for simulating the phenomena in graphene-based nanomaterials (GBNs).

Significance: GBNs gain significant attention due to their remarkable properties and potential applications, notably in nanomedicine. However, the physical and chemical characteristics toward macromolecules that justify their nanomedical applications are not yet fully understood. The molecular interaction through molecular dynamic simulation offers the benefits for simulating inorganic molecules like GBNs, with necessary adjustments to account for physical and chemical interactions, or thermodynamic conditions.

Method: In this review, we explore various molecular dynamics potentials (force fields) used to simulate interactions and phenomena in graphene-based nanomaterials. Additionally, we offer a brief overview of the benefits and drawbacks of each force fields that available for analysis to assess which one is suitable to study the molecular interaction of graphene-based nanomaterials.

Result: We identify and compare various molecular dynamics potentials that available for analyzing GBNs, providing insights into their suitability for simulating specific phenomena in graphene-based nanomaterials. The specification of each force fields and its purpose can be used for further application of molecular dynamics simulation on GBNs.

Conclusion: GBNs hold significant promise for applications like nanomedicine, but their physical and chemical properties must be thoroughly studied for safe clinical use. Molecular dynamics simulations, using either reactive or non-reactive MD potentials depending on the expected chemical changes, are essential for accurately modeling these properties, requiring careful selection based on the specific application.

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Introduction

Graphene is a type of nanomaterial formed by sheets of sp^2-hybridized carbon atoms that is revealed to be honeycomb-shaped [1]. Extensive research has led to the development of a diverse family of graphene-based nanomaterials (GBNs), including hydrogenated graphene (graphane), fluorinated graphene (fluorographene), oxidized graphene (graphene oxide), and acetylated graphene (graphyne and graphdiyne), among others [2]. Graphene-based nanomaterials have garnered significant attention in the biomedical field due to their remarkable physical, chemical, and biological properties. Graphene exhibits exceptional mechanical strength, high electrical conductivity, and biocompatibility, making it an ideal candidate for various biomedical applications. Graphene oxide possesses tunable surface chemistry, which enhances its interactions with biological systems and enables controlled drug delivery, gene therapy, and imaging applications. Additionally, the large surface area of graphene materials allows for the efficient adsorption of biomolecules, making them useful in biosensing [3], tissue engineering [4], and anticancer therapies. These properties have led to extensive research exploring the potential of graphene-based nanomaterials in diagnostics, therapeutics, and regenerative medicine [5].

In recent years, integrating graphene with other materials has expanded its applicability in biomedicine. Graphene-based nanocomposites, for example, combine the strengths of graphene with other nanomaterials such as gold, silver, and polymeric nanoparticles, enhancing their functionality and biocompatibility. These hybrid materials have been explored in various biomedical contexts, from targeted drug delivery [6,7] to biosensing. The versatility of graphene-based nanomaterials, coupled with their potential for functionalization, positions them as promising candidates for advancing modern biomedical technologies, offering innovative solutions in the areas of biomedicines [7], personalized medicine, and regenerative therapies [5].

Despite its promising applications in nanomedicine, some critical possible molecular phenomena are yet to be explored and understood, such as how GBNs interact with various drugs and macromolecules in the human body and the mechanism of potential toxicity of GBNs. For example, a study by Alimohammadi et al.

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[8] reported that GBNs are predicted as promising to be used in treating Parkinson's disease through the disruption of α-synuclein aggregate formation. However, another study by Zou et al. reported that fluorinated graphene has a toxicity potential through the unfolding and denaturation process of HP35 protein [9]. These conflicting studies justify running molecular dynamics (MD) simulations to study the molecular characteristics of GBNs for biomedical applications to ensure safety before any clinical use.

To facilitate cost-effective and accurate investigations into the physical and chemical properties of GBNs, computational technologies and simulations are employed to support and enhance their characterization. Among these techniques, the molecular dynamics-based approach stands out for its ability to accurately characterize nanomaterials at the molecular scale while maintaining optimal computational efficiency [10]. This simulation is one of the computational methods that could be used to understand the phenomena that occur in molecules. Although most of the recent applications of MD simulations involve biomolecules and organic molecules such as proteins [11] and lipid bilayer membranes [12], molecular dynamics is also valuable for simulating inorganic molecules such as GBNs with some modifications related to the physical and chemical interactions (reactive or non-reactive) [13], thermodynamic conditions [14] and states of matter that need to be considered [15,16]. Molecular dynamic simulations of nanomaterials, including GBNs, become important where experimental techniques may struggle to capture the complexities of nanoscale phenomena due to size limitations and the inherent difficulties in manipulating such small structures [17]. For instance, studies have utilized MD simulations to explore the mechanical properties of graphene and its derivatives, enabling researchers to predict behaviors such as fracture strength and thermal conductivity under various conditions [18,19]. Molecular dynamics simulations are crucial in understanding the interactions between nanomaterials and biological systems in biomedical applications. For example, Gholami et al. [20] employed atomistic MD simulations to investigate how graphene nano-vehicle interacts with cell membranes, providing insights into cellular uptake mechanisms and potential cytotoxicity. The development of bi-crystalline graphene-based polymers can also be evaluated through predictive interactions involving carbon in graphene, with reactive force field (ReaxFF) parameters selected due to their validation in similar simulations [21]. Such simulations allow for the exploration of the effects of surface modifications on the biocompatibility of nanomaterials, which is essential for their safe application in drug delivery and other therapeutic strategies [22]. Overall, MD simulations are an indispensable tool in nanomaterials research, bridging the gap between theoretical predictions and experimental observations and facilitating the design of advanced materials for various applications. Still, there are also differences from the simulation of biomolecules compared to inorganic substances (in this case, GBNs) because of the presence of many-body effects that require potentials (or force fields) that are already programmed to recognize many-body potentials when the simulation of biomolecules, usually only needed potentials that recognize pair-body effects [23]. Hence, we will focus on how molecular dynamic simulations can be used in the simulations of GBNs for nanomedical applications, contrary to the industrial and other than nanomedicine applications, such as water desalination [24], anti-corrosion coatings [25], and gas sensing [26].

Verma et al. [10] previously reviewed modeling techniques for graphene polymers and nanocomposites based on classical mechanics approaches. Building on this foundation, our review delves into the molecular dynamics potential fields frequently used in dynamic simulations for graphene, offering a comprehensive analysis of their applications. By comparing and evaluating these potentials, we aim to provide valuable insights into selecting the molecular dynamics potential for studying graphene-based nanomaterials, paving the way for more accurate and efficient simulations in this rapidly evolving field.

An overview of graphene-based nanomaterials in biomedical applications

Graphene-based nanomaterials have emerged as a revolutionary class of biomedical materials due to their unique properties, such as high electrical conductivity, mechanical strength, and large surface area. These characteristics make GBNs particularly suitable for various applications, including drug delivery systems, biosensors, bioimaging, tissue engineering, gene therapy, and treatments for anticancer therapies **(**Figure 1**)**. In drug delivery systems, graphene and its derivatives (graphene oxide and reduced graphene oxide) are chosen due to their ability to encapsulate therapeutic agents effectively. Their large surface area allows for a high loading capacity of drugs, while their biocompatibility ensures minimal toxicity to surrounding tissues [27]. In addition, GBNs can be functionalized with targeting ligands to enhance the specificity of drug delivery, thus improving therapeutic efficacy and reducing side effects [28]. For instance, studies have demonstrated that graphene-based carriers can facilitate the controlled release of anticancer drugs, leading to enhanced treatment outcomes in cancer therapy [29].

One notable advancement in this field involves the use of graphene oxide (GO) functionalized with cationic polymers such as polyethyleneimine (PEI) to facilitate the condensation of plasmid DNA due to electrostatic interactions, resulting in stable constructs that enhance transfection efficiency while minimizing cytotoxicity [30]. Applying PEI-GO complexes extends to gene silencing, where small interfering RNA (siRNA) can be delivered to cells. For instance, research by Zhang et al. [31] demonstrated the sequential delivery of Bcl-2 targeted siRNA alongside the chemotherapeutic drug doxorubicin (DOX), leading to increased cytotoxicity through a synergistic effect. Additionally, modifications to GO, such as incorporating polyethylene glycol (PEG) and branched PEI, have shown improved transfection efficiency under mild laser irradiation, which disrupts endosomal membranes and enhances the release of genetic material. Beyond gene therapy, graphene-based materials serve as effective nano-carriers for the intracellular delivery of therapeutic proteins [32]. Bone morphogenetic protein (BMP), known for its role in bone regeneration, can be delivered using GO-coated titanium implants. This method allows for sustained release of BMP at targeted sites, promoting the recruitment of mesenchymal stem cells and enhancing bone formation in experimental models [33]. Moreover, the development of chitosan-modified GO (GO-CS) has shown promise as a therapeutic nanocarrier for proteins such as bovine serum albumin (BSA) and collagenase. This approach protects BSA from proteolytic degradation and preserves the enzymatic activity of collagenase [34]. The protective mechanism is attributed to the steric hindrance provided by GO and the reducing properties of BSA, which collectively prevent the interaction between BSA and proteolytic enzymes.

Biosensors represent another significant application of graphene-based materials. The exceptional electrical properties of graphene enable the development of highly sensitive electrochemical sensors capable of detecting biomolecules at low concentrations [35]. These sensors can be employed for real-time monitoring of various biological markers, making them invaluable in diagnostics and disease

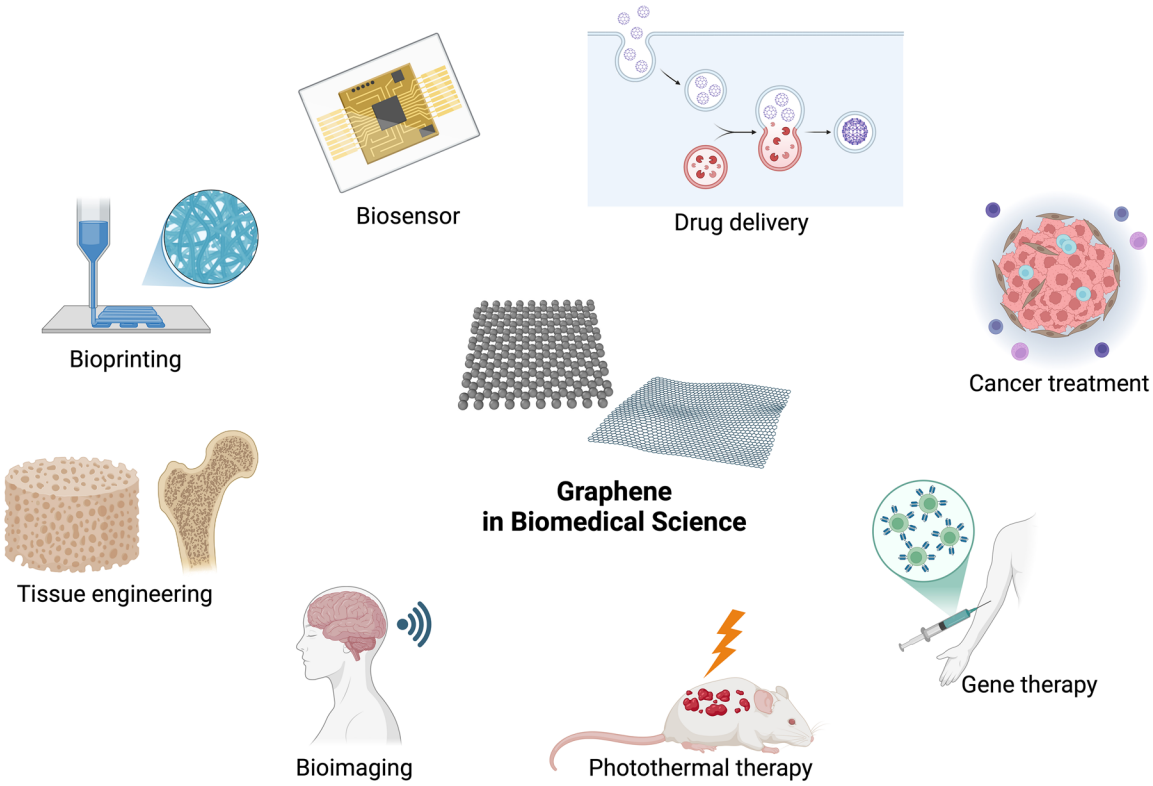

Figure 1. The utilization of graphene in biomedical sciences. Graphene and its derivatives are widely applied in biomedical fields, showcasing their roles in drug delivery, bioimaging, biosensing, tissue engineering, and photothermal therapy. The versatile functionalization capabilities and exceptional physicochemical properties of graphene-based materials enable their integration into diverse theranostic-based technologies (Created in Biorender).

management. For example, graphene-based biosensors have been successfully used to detect glucose levels, cancer biomarkers, and pathogens, showcasing their versatility and effectiveness in clinical settings [27]. A study by Ye et al. [36] used molecular docking and molecular dynamics simulation to predict the interaction and bioactivity properties of the graphene oxide toward RNAse and exonuclease III as the rational protein targets for identifying favorable binding characteristics. This approach is believed to predict how the biomolecules interact with nanomaterials, which can be instrumental in developing biosensors.

In addition, thanks to their versatile surface functionalization and exceptionally high surface area, graphene and its derivatives can be readily modified with small molecular dyes, polymers, nanoparticles, drugs, or biomolecules, enabling the creation of graphene-based nanomaterials for various bioimaging applications [32]. For instance, graphene quantum dots (GQDs) have shown promise due to their excellent photoluminescence and biocompatibility, making them suitable for both *in vitro* and *in vivo* imaging applications [37,38]. These properties enable GQDs to be utilized in various imaging modalities, including fluorescence and photoacoustic imaging, which are critical for early disease detection and monitoring treatment responses [39,40]. Moreover, the integration of graphene with other nanomaterials, such as metal nanoparticles, has been reported to enhance imaging capabilities further by improving signal intensity and stability [41].

Furthermore, graphene and its derivatives are also being explored for 3D-printed scaffolds for application in tissue engineering and regenerative medicines due to high biocompatibility [42]. Their mechanical properties and conductivity can promote cell adhesion, proliferation, and differentiation, making them suitable for bone, nerve, and muscle tissue engineering applications [43–45]. Research indicates that graphene-enhanced scaffolds can support osteogenic differentiation of stem cells, thereby facilitating bone regeneration [46]. Moreover, incorporating graphene into polymer matrices has been shown to improve scaffolds' mechanical strength and bioactivity, which is crucial for successful tissue engineering applications [47,48].

Anticancer treatments utilizing graphene-based materials have garnered significant attention due to their inherent properties. Furthermore, the photothermal properties of graphene allow for its use in photothermal therapy, where localized heating induced by laser irradiation can selectively destroy cancer cells while sparing healthy tissues [29]. Another example is electrochemical immunosensors utilizing graphene, which have been developed to detect prostate-specific antigen (PSA) and carcinoembryonic antigen (CEA), both critical biomarkers for various cancers [49,50]. Graphene-enhanced electrochemical genosensors have shown the ability to detect cancer-associated DNA mutations, including those in the BRAF [51], EGFR [52], and KRAS [53] in patient tissue samples [54]. A graphene-based biosensor demonstrated high sensitivity in detecting ovarian cancer cells, providing a rapid and cost-effective method for cancer diagnosis [55]. Recent breakthroughs demonstrate GBNs are being explored for their potential in targeted cancer therapies, such as hyaluronic acid-modified graphene, which has been designed to selectively target drug-resistant lung cancer cells, overcoming the challenges associated with multidrug resistance [56].

Photodynamic therapy (PDT) is an advanced cancer treatment that employs photosensitizer molecules to selectively target and destroy cancer cells by generating reactive oxygen species (ROS) upon light activation. Chlorin 6, incorporated into folic acid-conjugated graphene oxide *via* hydrophobic and π–π stacking

interactions, has shown significant effectiveness in eradicating cancer cells under irradiation. Similarly, porphyrin-functionalized GO nanosheets stabilized through π–π interactions have demonstrated potential for treating tumors in hypoxic conditions and deep-seated solid tumors, such as glioblastoma multiforme. More recently, Sahu et al. [57] developed a novel nanographene oxide (NGO)-methylene blue conjugated system, stabilized with Pluronic F127, to effectively treat breast cancer cells using an affordable FDA-approved methylene blue dye. These findings demonstrate the potential of this system to achieve complete tumor ablation and prevent metastasis. Targeted approaches like this enhance treatment efficacy while minimizing the systemic toxicity typically associated with conventional chemotherapy [58].

Together, graphene-based nanomaterials hold great promise in the biomedical field, with applications spanning drug delivery systems, biosensors, tissue engineering, and treatments for bacterial infections and cancer. Their unique properties enhance the efficacy of existing therapies and pave the way for innovative approaches in medical science. As research advances, integrating GBNs into clinical practice may significantly improve patient outcomes and revolutionize treatment paradigms.

Molecular dynamics simulation as tool for analysis of complex materials at atomic level

Over the past few decades, molecular simulations have emerged as a powerful tool for elucidating the microscopic mechanisms underlying the macroscopic properties of complex materials [59]. They also serve as a bridge between the predictions of theoretical models and experimentally observed properties [60]. The ability to predict key material properties directly from the chemical composition and molecular architecture of a formulation is of critical importance, as it informs design strategies both for material synthesis and processing. With their capacity to derive essential physical properties from atomistic structures, molecular simulations are increasingly regarded as valuable virtual experiments, often as substitutes for existing laboratory measurements [61,62].

Molecular dynamics simulation is one of the most widely used methods to simulate atomistic phenomena of liquids and solids [63]. It is mainly used to study the properties of polymers and biological macromolecules due to the implications of the complex conformation and configuration of such systems on their behavior. These simulations predict how every atom in a macromolecular system will move over time based on the general model of physics that governs interatomic interactions [64,65]. In molecular dynamic simulations, these governing models of physics are referred to as either 'MD potentials' or 'force fields,' which are represented in a mathematical formula, often derived from the first principle (*ab initio*) or semi-empirical quantum mechanical calculations [66], or by benchmarking of experimental data, such as NMR measurement results [67]. Many MD potentials available in the literature are built for specific molecular systems with different complexity ranges. Typically, these potentials usually represent two terms of interaction, namely bonded and non-bonded interactions. Terms that represent bonded interactions usually capture the local contributions of the molecular interaction, e.g. bond stretching, angle bending, and the molecule torsions, while the non-bonded interactions terms are represented by Van der Waals (12-6 Lennard-Jones potential) and electrostatic interactions [68].

Ideally, these kinds of interactions can be captured directly using *ab initio* calculations, e.g. Hartree-Fock or density functional theory [69], which can help calculate and comprehensively describe the electronic structure of molecules. However, these advantages do not have drawbacks that need to be considered, and one of them is the significant computational resources that would be required to calculate the electronic structures of molecules feasibly [70]. Contrary to that, classical MD simulation can describe the dynamic behaviors of the system empirically, without the need to solve the Schrodinger equation, which plays a large part in *ab initio* calculations [23]. Because of these reasons, MD simulation can be considered a more feasible option to simulate large macromolecular systems (including GBNs) due to its accurate results without extensive computational resources and time.

As mentioned above, MD potentials are essential in MD simulation to move the atoms or molecules over time and to predict these movements. Herewith is a brief overview of widely used MD potentials in macromolecule simulations and the comparison between MD potentials, as seen in Table 1, with a specific interest in the dynamic simulation of GBNs.

CHARMM potential

CHARMM (abbreviated from Chemistry at Harvard Molecular Mechanics) is one of the most widely used MD potentials for molecular dynamics simulations. It is the force field that was applied for the first MD simulation of bovine pancreatic trypsin inhibitor, in which its potential energy was represented using empirical function consisting of bond angles, bond lengths,

Table 1. The specification of the molecular dynamic force fields that widely selected for GBNs.

	Force field / potential				
Characteristics	CHARMM	AMBER	SMTB-Q	AIREBO	ReaxFF
Chemical systems facilitated in the force field	Proteins and small molecules	Proteins and small molecules	Atomistic behavior between metals and oxygen	non-bonded and four-body torsional interactions	Various atomistic systems with various behavior
Basis of the potential	ab initio, using density functional theory (DFT)	ab initio, using density functional theory (DFT)	ab initio, using density functional theory (DFT)	ab initio, using density functional theory (DFT)	ab initio, using density functional theory (DFT)
Rigidity	Rigid	Rigid	Not rigid, any constraints must be provided externally	Not rigid, any constraints must be provided externally	Not rigid, any constraints must be provided externally
Reactivity	No	No	Yes	Yes	Yes
Terms included in energy calculation	Bonds, angles, dihedrals, improper, and nonbonded	Bonds, angles, dihedrals, nonbonded	Ionization, electrostatics, repulsive, covalent	Local coordination, bond angles, conjugated system, van der Waals dispersion interactions, torsion potential	Bonds, over-coordination, under-coordination, lone pair, valence, torsions, van der Waals, electrostatics

dihedral angles, improper, and non-bonded, which also consists of van der Waals and electrostatics terms [71]. Those terms can be expressed as:

$$U = \Sigma_{bond} + \Sigma_{UB} + \Sigma_{angle} + \Sigma_{dihedral} + \Sigma_{improper} + \Sigma_{nonbonded} \quad (1)$$

Although CHARMM potential is an integral part of MD simulation software with the same name, it is already ported, making it compatible with other MD simulation software such as GROMACS [72,73], NAMD [74], and AMBER [75], which contributes to its popularity as one of the most widely used MD potentials.

CHARMM is also popular because of the broad kinds of molecular systems that can be simulated, especially biomolecules. Initially, CHARMM is developed to simulate the dynamics of protein, contributing to the inception of CHARMM22 potential [76]. It was also reworked and optimized to simulate other kinds of biomolecular systems, such as nucleic acids (CHARMM27) [77] and lipids (CHARMM22 and CHARMM27) [78,79]. The separate versions are already optimized into one version, CHARMM36, that can be used to simulate proteins [80,81], nucleic acids [82,83], and lipids [84]. CHARMM also has a separate version which is primarily used to simulate small drug-like molecules called CGenFF (CHARMM General Force Field), which is compatible with biomolecular versions of CHARMM [85]. All of the versions are based on empirical crystallography data, combined and optimized with other simulations, such as quantum mechanical (*ab initio*) and Monte-Carlo simulations [86].

One of the practical uses of CHARMM's potential lies in its role in investigating the various dynamic behaviors of macromolecules. For instance, Sarzynska and coworkers use the CHARMM27 force field to study the kissing loop interaction contributing to the dimerization of HIV-1 genomic RNA, which occurred at the dimerization initiation site (DIS). The study reports that the purines are inclined to move to bulged-in conformation [87], which plays a part in the infectivity of HIV-1 [88]. Moreover, studies of HIV-1 dimerization also give a new perspective of targeted HIV infection treatment, in which DIS can be used as a target [89]. The molecule of drug candidates can be simulated with biomolecular versions of CHARMM, in tandem with CGenFF, which is used to simulate small drug-like molecules that target DIS molecules or any receptors that play a part in diseases.

Other reports study the interaction between biological macromolecules and graphene-based nanomaterials, which use CHARMM as one of the MD potentials in the simulations. For instance, Dasetty and coworkers study the adsorption of amino acids on graphene using varying non-polarizable MD potential, namely CHARMM36, Amberff99SB-ILDN, OPLS-AA, and Amber03w [90]. The study reports that all MD potentials are favorable for the simulation of graphene-amino acid adsorption and complex formation, although CHARMM has less favorable adsorption energy compared with other MD potentials used in the study. CHARMM is also not a reactive MD potential, so its uses may be limited by the chemical phenomena that can be studied.

Despite being suited more for proteins and other biomolecules, CHARMM is also used for graphene-based nanomaterials for biomedical applications. For example, Hashemzadeh and Raissi studied the possibility of graphene and graphene oxide being loaded with doxorubicin (DOX) and paclitaxel (PTX), both are anticancer drugs, using the molecular dynamics simulation method and CHARMM potential. From the simulation, it can be predicted that both GOX and PTX are spontaneously adsorbed into the graphene and graphene oxide surfaces, in which the aromatic rings from both drug molecules are forming π – π interactions with the carrier surface, with both drugs having weaker interactions with graphene oxide, due to the different surface characteristics [91]. Zaboli and coworkers also studied the possibility of graphene oxide that has been functionalized using dopamine to be used in the delivery of cytarabine, also an anticancer drug, using the combined methods of density functional theory *ab initio* calculations and MD simulations. From the simulations, it can be predicted that dopamine-functionalized graphene oxide nanosheet strongly interacts with cytarabine [92].

AMBER potential

AMBER can be described as a collection of tools and programs that work together to do various tasks in MD simulations, including the preparation of necessary input files, production of the MD simulation, and trajectory analysis of MD simulation results [93]. Initially, it was developed by the Kollman group in 1984, to simulate molecular models with an emphasis on the importance of explicit hydrogen in the representations of hydrogen bonding [94]. It was later extended in 1986 by the same group to simulate an all-atom model, in which all atoms and bonds are represented explicitly, not only hydrogen bonds. The group also tested the MD potential in various biomolecular systems, such as amino acids and nucleobases of RNA and DNA [95]. Both initial developments were done to simulate molecules in gas phases using quantum mechanical calculations, along with experimental data such as amide crystal data from Lifson et al. [96,97], and liquid-phase simulation data from Jorgensen [98]. AMBER usually consists of several energy functions, which consists of several terms such as bonds, angles, dihedrals, and non-bonded which can be formulated as below [99]:

$$E = E_{bond} + E_{angles} + E_{dihedrals} + E_{nonbonded} \quad (2)$$

The improvements in computational technology and increasing computational speed have led the same group to develop a whole new version of AMBER potential. The development is done to produce MD potentials suitable for condensed phase simulations, ince preceding works concentrated on simulations in the gas phase. The updated MD potential was derived from quantum mechanical data, along with crystallographic data of analogous nitroxides available at the time. It was later known as ff94 potential [100].

Since then, AMBER potentials have been reworked and parameterized, to simulate molecules other than proteins. There are already several versions of AMBER, with different applications that are useful in the simulations of various kinds of biomolecules. That includes the ff99SB and ff14SB which are the improved versions of ff94 potential [101,102]; Glycam for the simulations and modeling of carbohydrates [103], which later extended into Glycam06 [104] that can also simulate lipids and nucleic acids; Lipid11 and GAFFlipid that specifically parameterized to simulate lipids and phospholipids [105,106]; and GAFF (General Amber Force Field) which simulate small molecules such as drug-like molecules [107].

Because of the wide community of developers, AMBER has become one of the mostly used MD potentials, especially for biomolecular MD simulations. One of the fascinating applications of AMBER potential is the study of new anticancer drugs through enzyme inhibition. A study by Dewaker et al. [108] uses ff14SB in order to investigate the inhibitory activity of seven compounds on histone deacetylase 8 (HDAC8). The study indicates that the proposed drug molecules have encouraging energy profiles, which

suggests their thermodynamic stability and good binding affinity. Another study done by Latallo et al. [109] also uses AMBER potential to predict how allosteric mutations of β-lactamase enzyme contribute to development of drug resistance of gram-negative bacteria against β-lactam antibiotics. Through MD simulations combined with machine learning methods, the study predicts that the catalytic activity of β-lactamase against antibacterial drugs could be increased by several-fold without significant conformational change of the active sites.

In other applications, AMBER-family potentials are also used to simulate graphene-based nanomaterials. A work by Singham et al. uses GAFF and CGenFF to simulate the thermodynamical aspects of adsorption on graphene surfaces in an aqueous environment using propylbenzene and 4-nitrotoluene. The study shows that GAFF and CGenFF can predict similar trends of the relationship between the chemical nature of the solute and adsorption thermodynamics on graphene surfaces, while also showing good agreement with experimental data [110]. However, because AMBER potentials are non-reactive, it has limited capability to simulate graphene, especially if chemical phenomena that involve chemical reactions are accounted for.

However, despite its limitations, AMBER potential is also used in some MD simulation in the biomedical field. For example, Zhu and coworkers investigate the ability of graphene affects the misfolding of human prion protein, which can leads into serious prion disease, using AMBER potential. The simulations results indicating that graphene can adsorb the prion protein quickly, potentially induced partial misfolding of human prion protein [5].

SMTB-Q potential

SMBT-Q (Second Moment Tight-Binding Charge Equilibrium) can be described as a novel variable-charge model [111], which is based on the charge equilibrium (QEq) formalism of Rappe and Goddard [112]. SMTB-Q is an improvement of other QEq-based potentials, such as models proposed by Swamy and Gale [113], Streitz and Mitmire [114], and Demiralp and coworkers [115]. In these three previous models, ionic and covalent contributions of bonds are calculated separately, in which the ionic parts are calculated through charge equilibrium (QEq) and covalent parts are calculated through short-range interatomic potentials. In SMTB-Q models, anion-cation bonding energy is calculated by tight-binding analytical expression, which was proposed by Goniakowski and Noguera [116,117]. SMBT-Q and the previous potentials that it was based on were developed to simulate metal oxides, especially silica and titanium oxide-containing materials. The general SMBT-Q model consists of several terms, such as ionization energy, electrostatics energy, repulsive energy, and covalent energy. These terms combined into the total of cohesive energy, which can be expressed as below [118]:

$$E_{cohesive} = E_{ionization} + E_{electrostatics} + E_{repulsive} + E_{covalent} \tag{3}$$

Since then, SMTB-Q has been reworked and optimized to perform large-scale simulations of bulk, surface, and interfaces of different kinds of metal oxides, such as alumina [119], strontium titanium oxides [120], and uranium oxides [121]. SMTB-Q and previous versions of charge equilibrium-based potentials show good agreement with experimental data and ab initio calculations, especially in describing phase transitions. However, despite the good performance of SMTB-Q and other charge equilibrium potentials, there are still no versions that depict carbon atoms, which are the major building blocks of GBNs. Thus, the use of SMTB-Q potentials is not recommended, unless any atomic metal-oxygen interactions are expected.

AIREBO potential

The Adaptive Intermolecular Reactive Empirical Bond-Order (AIREBO) potential has become a significant force field in molecular dynamics simulations [122], especially for carbon-based materials such as graphene [123–125]. AIREBO is particularly effective for modeling reactive systems due to its ability to account for bond formation and breaking, making it suitable for simulating complex chemical processes in hydrocarbons [126]. It is an extension of the Reactive Empirical Bond-Order (REBO) potential, incorporating both bond-order and van der Waals interactions to capture the behavior of carbon and hydrogen systems effectively [122]. This capability makes AIREBO adept at modeling the mechanical properties of carbon structures, such as graphene and carbon nanotubes, due to its dynamic representation of bond formation and breaking [123,127].

The approach involves effectively integrating three distinct potential functions: the REBO potential, the Lennard-Jones (LJ) potential, and a torsional potential. The LJ potential accounts for non-bonded interactions, while the torsional potential addresses torsional effects within the system, which the REBO formulation does not cover adequately. However, this integration is more complex than merely summing the three potentials. Stuart et al. [122] propose a strategy that adaptively adjusts the relative weighting of each term for every specific two-term interaction.

$$E = E^{REBO} + E^{LJ} + E^{torsion} \tag{4}$$

Furthermore, AIREBO has been shown to provide reliable predictions for the structural and dynamical properties of carbon-based nanomaterials, making it a popular choice for studies involving graphene. For instance, studies have demonstrated that AIREBO can accurately model the bending and fracture behavior of graphene sheets under various conditions, including high-velocity impacts [128]. This makes it particularly valuable in applications involving nanocomposites and structural materials, where understanding mechanical integrity is essential [129]. Additionally, AIREBO has been employed to investigate the effects of point defects in graphene, which are critical for tailoring the material's properties for specific applications [130]. Despite its advantages, AIREBO is not without limitations. Its computational intensity can be prohibitive for large-scale simulations, and the potential may exhibit nonphysical behaviors under certain conditions, such as post-hardening effects, if not carefully parameterized. Another drawback of AIREBO is its relatively higher computational cost than other potentials, such as REBO, which reduces its computational efficiency [123]. These drawbacks necessitate a thorough understanding of the limitations and careful calibration to ensure accurate simulation results involving complex interactions.

In the context of graphene-based nanomaterials, the AIREBO potential has played a crucial role in advancing the understanding of their properties and applications. Those exceptional attributes of graphene, such as high electrical conductivity, outstanding mechanical strength, and extensive surface area, have positioned it as a central focus across diverse fields, including biomedical applications, environmental remediation, and energy storage [125, 131]. Notably, its use in environmental science underscores the potential of graphene-based materials for water treatment and

pollutant removal [132,133]. However, limited studies have explored the interaction of graphene with biological systems, which are critical for the development of drug delivery systems and biosensors leveraging the AIREBO potential [134]. Nevertheless, these studies highlight the versatility of AIREBO in addressing contemporary scientific and technological challenges.

ReaxFF potential

Reactive Force Field (ReaxFF) is a molecular dynamics (MD) potential widely used for simulating large chemical systems, typically consisting of 1000 atoms or more. ReaxFF leverages the relationship between bond distances, bond order, and bond energy, enabling the dissociation of bonds between atoms that are far apart [135]. Initially developed in 2001 by van Duin and coworkers, ReaxFF was designed to simulate the dynamic properties of hydrocarbons. Their work demonstrated its ability to predict the stability and geometry of nonconjugated, conjugated, and radical-containing compounds while describing the dissociation and formation of chemical bonds in hydrocarbon systems [136,137]. The most recent functional form of ReaxFF expresses the total energy of a chemical system as the sum of various contributing factors, such as bond energy, over-coordination penalties, under-coordination stability, lone pair interactions, valence terms, torsions, van der Waals forces, and Coulombic interactions. These contributions are calculated separately for bonded and non-bonded interactions [138]. Similar to other MD potentials, most ReaxFF implementations are based on ab initio calculations, providing a balance between computational efficiency and accuracy.

$$E = E_{bond} + E_{over} + E_{under} + E_{lone} + E_{valence} + E_{torsions} + E_{vdWaals} + E_{electrostatics} \quad (5)$$

Since its inception, ReaxFF has undergone significant optimization and expansion to accommodate a broader range of chemical systems and applications. For instance, it has been parameterized to model the dynamic behavior of shocked hydrocarbon polymers [139], oxidative dehydrogenation of vanadium oxide catalysts [140], and dehydrogenation and combustion of ammonia borane [141]. ReaxFF has consistently demonstrated good agreement with theoretical data, such as ab initio simulations, further solidifying its reliability in various contexts.

ReaxFF has also gained prominence in the study of complex systems, particularly graphene-based nanomaterials. It is uniquely suited for modeling chemical reactions by dynamically allowing bond formation and breaking. This capability is crucial for accurately simulating materials undergoing significant structural changes. Consequently, ReaxFF is highly beneficial in materials science and biomedical applications, where understanding nanomaterial reactivity and interactions with biological systems is essential. For example, ReaxFF has been successfully employed to simulate interactions between graphene oxide and biological molecules, offering valuable insights into the biocompatibility and potential toxicity of these nanomaterials [142]. Additionally, it has been used to explore how graphene-based materials interact with biomolecules like proteins and nucleic acids under realistic conditions [143]. One notable advantage of ReaxFF is its scalability. Although its computational cost is higher than that of conventional non-reactive force fields, it remains feasible for large-scale simulations involving thousands of atoms [56]. This scalability enables researchers to study intricate systems, such as graphene's behavior in biological environments or during drug delivery processes, without sacrificing accuracy. Furthermore, ReaxFF can be integrated with other computational methods, such as density functional theory (DFT), to improve the reliability of simulation results [144].

Despite its advantages, ReaxFF has certain limitations. The accuracy of its force field parameters remains a primary concern. Although parameterization is based on quantum mechanical calculations, the quality of results can vary depending on the system being studied and the accuracy of the underlying data used for parameterization [145]. Discrepancies between ReaxFF predictions and experimental observations have been reported, particularly in complex reactions or systems with significant electronic effects [146]. Therefore, careful validation of ReaxFF parameters is essential for each specific application. Additionally, while ReaxFF excels in simulating bond formation and breaking, it may not fully capture the subtle electronic structure changes occurring during chemical reactions. This limitation can impact the accuracy of simulations involving highly reactive species or systems where electronic effects play a pivotal role [145], thus, researchers must exercise caution when interpreting ReaxFF results in contexts where electronic interactions are critical.

ReaxFF was reported as having a version that simulates chemical systems containing graphene [147]. Singh et al. [148] developed a version of ReaxFF that could describe the properties of graphene, especially its thermomechanical properties. The version of ReaxFF is designed to simulate the dynamics of fluorinated graphene, compared with other forms of graphene, such as pristine graphene, graphane, and hexagonal boron nitride sheet. The work shows that fluorinated graphene remains flat during simulation, and the MD potential is in agreement with quantum mechanical calculations. From this point of development, it is suggested that ReaxFF is suitable for the simulation of graphene-based nanomaterials and has enough capabilities to describe the physical and chemical properties of graphene-based nanomaterials. Kowalik et al. [149] also provide the parameters that can be used to study the chemical and mechanical properties of carbon-based polymers, including graphene-based nanomaterials.

The ReaxFF has emerged as a powerful computational tool for simulating the behavior of graphene-based nanomaterials in various biomedical applications. Unlike traditional force fields, which typically treat atomic interactions as fixed, ReaxFF allows for the dynamic formation and breaking of chemical bonds. It is particularly suitable for studying reactive systems and complex interactions at the molecular level. This capability is crucial for understanding how graphene interacts with biological molecules, essential for its application in drug delivery, biosensing, and tissue engineering [135]. Another significant advantage of ReaxFF is its ability to model the interactions between graphene and biomolecules, such as proteins and nucleic acids, realistically. For instance, studies have shown that ReaxFF can effectively simulate the binding of proteins to graphene surfaces, providing insights into the biocompatibility of these nanomaterials [150,151]. ReaxFF can be instrumental in predicting how modifications to graphene surfaces, such as functionalization with polyethylene glycol (PEG) or other biocompatible materials, enhance their compatibility with biological systems [150,151].

For example, Deshmukh et al. [152] utilized the ReaxFF method within the LAMMPS program to explore the application of laser-induced MXene-functionalized graphene as supercapacitors for health monitoring devices. Additionally, other studies have employed ReaxFF to investigate laser-induced graphene (LIG) derived from lignin and cellulose [153,154]. These findings suggest the potential for developing biosensors using eco-friendly substrates and using these modeling approach to get understanding about the molecular interactions, opening new avenues for

sustainable and versatile biomedical applications. These findings demonstrate that ReaxFF is a valuable tool for simulating graphene-based materials, as it effectively captures the dynamics of bond formation and breaking. This capability is crucial for designing graphene-based drug delivery systems that minimize cytotoxicity while optimizing therapeutic efficacy.

Advancements and challenges in force field development for molecular dynamics simulations of graphene-based materials

Over time, graphene research has expanded to address increasingly complex systems, prompting the development of more versatile force fields. Notable examples as presented in Table 2 include the Dreiding force field, which provides parameters for all elements in the periodic table. Other widely used force fields include CHARMM, AMBER, GROMOS, OPLS, and COMPASS. While these force fields are quite general in application, CHARMM, AMBER, and GROMOS are primarily used for biomolecular simulations, whereas OPLS and COMPASS were originally designed for condensed matter systems. It is important to note that many of these force fields are continually evolving, with multiple versions available, each offering improvements and adjustments for specific applications. Examples include CHARMM36, CHARMM27, GROMOS53A6, as well as AMBER03 and AMBER02 were also used for simulations of graphene.

The development and refinement of the force fields are essential for improving the fidelity of MD simulations. For instance, recent studies have shown that modifications to backbone torsion parameters in force fields can significantly enhance the accuracy of DNA simulations, allowing for better representation of structural fluctuations [172]. Despite advancements, challenges remain regarding the accuracy of current force fields, particularly in complex environments. For example, Petrov and Žagrović [173] highlighted that existing atomistic force fields may not adequately describe protein behavior in crowded biological settings, which can lead to discrepancies between simulation outcomes and experimental observations. This limitation underscores the necessity for continuous validation and refinement of force fields through synergistic efforts between experimental data and computational modeling [173,174]. Moreover, the choice of force field can significantly affect the simulation's results, as demonstrated in studies comparing different force fields for protein interactions. Variations in the strength of salt bridges, for instance, were observed when different force fields were employed, indicating that the selection of an appropriate force field is critical for accurate modeling of biomolecular interactions [175]. Additionally, the CHARMM36 force field has been validated against experimental NMR data, showcasing its effectiveness in capturing the dynamics of proteins [176]. However, even well-established force fields can exhibit limitations, as seen with the AMBER03 force field, which was found to misrepresent the thermal stability of certain proteins [177]. The integration of machine learning techniques into force field development represents a promising avenue for enhancing the accuracy of MD simulations. Recent studies have explored the use of fragment-based approaches and transfer learning to create more precise force fields tailored to specific protein systems [178].

Table 2. The use of molecular dynamics programs and force fields for graphene simulations in biomedical applications.

No	The type of graphene	Force field / potential used	Tools for molecular dynamics simulation	Application in biomedical-related fields	Reference
1	n-Graphene	OPLS-AA	GROMACS	prevent amyloid fibrillation	[8]
2	Graphene oxide	GROMOS53a6	GROMACS	Lipid membrane	[155]
3	Graphene oxide	Martini 2.2	GROMACS	Biosensor	[156]
4	Graphene	COMPASS	Discover and Amorphous cell modules of Materials Studio	Drug loading (for doxorubicin)	[157]
5	Baghdadite-polycaprolactone-graphene	CHARMM and Dreiding	LAMMPS	Bone regeneration	[158]
6	Graphene oxide	CHARMM27	GROMACS	Drug loading (for paclitaxel)	[159]
7	Graphene	Not informed	Spartan14	Biosensor (for COVID-19)	[160]
8	Graphene nanosheets	Amber and FF14SB	AMBER	Biosensor (RBD in SARS-Cov-2)	[161]
9	Graphene	AMBER ff03	AMBER	Protein misfolding and aggregation (amyloid-related proteins)	[5]
10	Graphene oxide	OPLS	GROMACS	Protein – Graphene interaction	[162]
11	Graphene	OPLS-AA	GROMACS	Therapy for HIV	[163]
12	Graphene	OPLS-AA	GROMACS	Protein – Graphene interaction (α-helical ovispirin-1)	[164]
13	Pristine graphene Graphene (carboxyl and amine-functionalized)	CHARMM36	GROMACS	Nanovehicle	[20]
14	Graphene Pristine graphene	CHARMM36	GROMACS	Protein adsorption – Graphene interaction	[165]
15	Graphene oxide	CHARMM27 and Dreiding	NAMD	inhibitor for α-chymotrypsin	[166]
16	Graphite	GROMACS 53a6	GROMACS	Drug loading (Rifampicin and Isoniazid)	[167]
17	Graphene oxide	CHARRM27	GROMACS	Drug loading (5-fluorouracil)	[168]
18	Graphene	OPLS-AA	GROMACS	Antibody-based biosensor	[169]
19	Pristine graphene Carboxylic-functionalized graphene	OPLS-AA	GROMACS	Enzyme inhibitor (lactate dehydrogenase)	[170]
20	PEGylated graphene oxide	Dreiding	Materials Studio	Drug loading (Doxorubicin, Methotrexate)	[171]
21	MXene-Functionalized Graphene	ReaxFF	LAMMPS	Biosensor	[152]

This innovative approach aims to address the inherent limitations of classical force fields by leveraging data-driven methodologies to refine parameterization and improve predictive capabilities. Thus, the role of force fields become pivotal in ensuring the accuracy of molecular dynamics simulations. The ongoing refinement and validation of these models are essential for advancing our understanding of biomolecular systems and their interactions. As computational techniques evolve, the integration of experimental data and machine learning strategies will likely lead to significant improvements in the accuracy and applicability of MD simulations in various fields, including drug discovery and materials science [174,179,180].

The molecular dynamics simulation for GBNs: Choosing the suitable force fields for analysis

In the modeling of any chemical system, two factors need to be considered. These factors are (1) The type of chemical species and (2) the chemical phenomena that will be studied. Because of MD potentials are usually built for specific chemical systems and specific use; it is important to choose which MD potentials are suitable to simulate the specific chemical systems and the phenomena that will be studied in the MD simulations.

In most simulations of biological macromolecules (e.g. proteins, lipids, carbohydrates), the molecular structures are expected to remain intact throughout the simulation. Atomistic behaviors such as ion exchange, bond formation, and bond breaking are generally not anticipated. As a result, these simulations typically employ non-reactive MD potentials, which are simpler and fixed, such as CHARMM and AMBER. Similarly, graphene-based nanomaterials can also be simulated using these non-reactive potentials, provided no atomistic or reactive behavior is expected within the system. However, it is important to note that these potentials are not capable of modeling phenomena like bond breaking in graphene.

In contrast, when atomistic and reactive behavior is expected within a system, the use of reactive MD potentials is recommended. These potentials can accurately capture important phenomena occurring in reactive chemical systems and simulate chemical changes over time. For instance, graphene can be modeled using reactive MD potentials when alterations in chemical structure and properties are anticipated. However, reactive MD potentials are available in multiple versions, each tailored to specific chemical systems and behaviors. Therefore, careful selection and application are essential to ensure accurate representation of the system being studied. To further improve the accuracy of MD-based simulations for graphene, researchers have developed potentials such as Tersoff, REBO, and AIREBO. Among these, AIREBO is widely regarded as the most accurate interatomic potential for simulating graphene's mechanical, fracture, and thermal properties. As an enhanced version of REBO, AIREBO includes additional energy terms to account for non-bonded interactions and torsional effects, making it particularly well-suited for comprehensive modeling of graphene systems.

In contrast to AIREBO, ReaxFF is designed to handle a broader range of chemical systems, including those involving metals oxides and hydrocarbons [152,181]. ReaxFF employs a bond-order concept similar to AIREBO but integrates a more comprehensive energy expression that accounts for valence, Coulomb, and van der Waals forces [135]. This flexibility allows ReaxFF to simulate complex chemical reactions, such as combustion and catalysis, by dynamically adjusting bond orders as bonds form and break [136]. As a result, ReaxFF is suitable for a wide array of applications, from studying polymer cross-linking to investigating catalytic processes on metal oxide.

Each MD potential mentioned earlier has different use cases and instructions, and each must be carefully considered to suit the system to be simulated perfectly. For instance, GROMACS excels in modeling soft matter and biological systems, such as proteins and lipid bilayers, whereas LAMMPS offers distinct advantages for simulating hard matter, including graphene [182]. It is recommended that LAMMPS be used as software because it is available for free and customizable. Its customizability allows one to run various simulation tasks of different molecular systems (Thompson et al. 2022) [183]. It is important to note that LAMMPS requires specific molecular files to indicate the contents of the molecular systems, in this case GBNs; an input file that contains all simulation commands is also needed (Figure 2). LAMMPS is also more suitable for simulating the atomistic behavior of each atom, which is essential in studying the mechanical and chemical properties of graphene-based nanomaterials for nanomedical applications. This is contrary to how other MD simulation packages, such as GROMACS and AMBER, are more suitable to simulate protein and other biomolecules. However, GROMACS and AMBER are still being used for the simulations of GBNs for now.

First, to generate a model of GBNs, several free software and web-based services can be used, such as GOPY [184] and make-graphitics [185] which are built specifically to build graphene-based nanostructures. Proprietary software can also be used, such as Materials Studio, to make a graphene model [186].

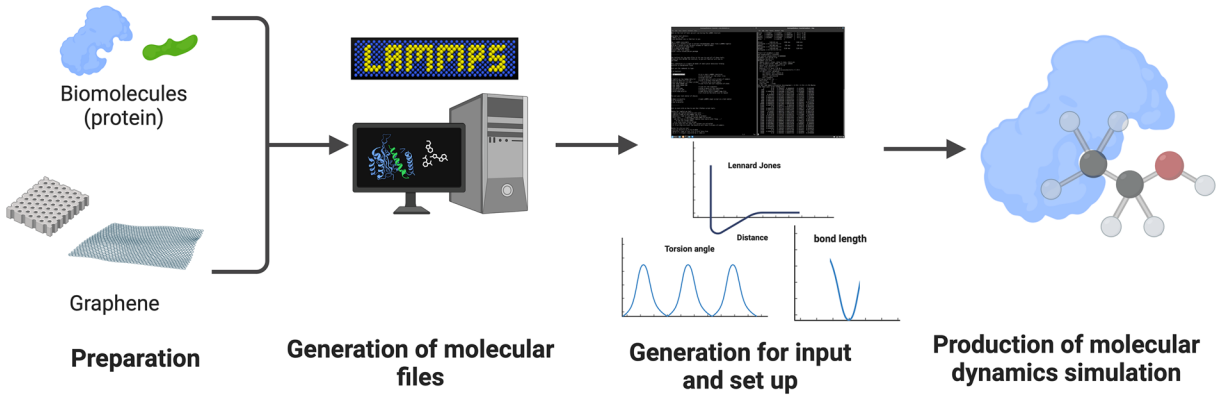

Figure 2. Workflow of molecular dynamics potential implementation in LAMMPS. LAMMPS is a widely used open-source program known for its flexibility and functionality, often applied to simulations of graphene and its derivatives.

These molecular files also need to be changed into file formats that LAMMPS can understand as a molecular data file, and in this case, OVITO (Stukowski, 2009) [187] can be used. Once the molecular file is prepared, the input file can be made manually or automatically generated by third-party software or web-based services, such as CHARMM-GUI [188] and Avogadro [189]. Additional simulation settings can also be added in these input files, including simulation temperature and ensembles; additional constraint algorithms such as SHAKE [190] and RATTLE [191] (available in LAMMPS with additional package installation) and energy minimization settings; among others. Once the input files are appropriately set, the MD simulation can run smoothly and provide the intended simulation results.

Conclusion and future perspective

Graphene-based nanomaterials are among the most studied due to their promising applications, such as in biomedicine. However, their physical and chemical properties need to be examined to ensure safe clinical applications, with both the benefits and risks of using graphene-based nanomaterials in biomedical settings more well understood. One of the methods that can be used to study these properties is molecular dynamics (MD) simulation, which uses force fields or potentials to simulate and calculate the properties of graphene-based nanomaterials.

In this review, we compare several MD potentials with different specifications to provide an understanding of how MD potentials serve various purposes in simulations and offer distinct insights into the interactions between graphene-based nanomaterials and a wide range of biomolecules, such as drugs and proteins. These interactions span diverse physical and chemical properties, which are crucial for understanding their behavior in biomedical environments.

However, MD potentials vary in their specifications and suitability for different use cases. Non-reactive MD potentials are generally sufficient for simulating graphene-based nanomaterials, as they can accurately model their physical and chemical properties. Conversely, when chemical changes or reactions are anticipated in a simulation, reactive MD potentials are more appropriate, as they can capture the dynamics of bond formation and breakage. Therefore, it is essential for researchers to carefully identify the objectives of their MD simulations to select the most suitable type of MD potential for their specific applications.

Looking ahead, developing more advanced MD potentials and hybrid approaches may enable researchers to achieve higher accuracy in modeling complex interactions and reactions involving graphene-based nanomaterials. By leveraging these advancements, the full potential of molecular dynamics simulations in understanding and predicting the behavior of graphene-based nanomaterials in biomedical applications can be realized, further bridging the gap between theoretical studies and practical, safe clinical use.

Authors' contribution

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Data availability statement

All data are provided within the manuscript.

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