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MINI REVIEW

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Current advances in computer-aided design of electrochemical sensors: An analytical review

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Abstract

Electrochemical sensors are situated as effective tools for the sensitive and selective determination of several heavy metal traces, pesticides, and a vast diversity of pharmaceuticals in different matrices. The development of advanced electrochemical sensors requires the collaboration of all scientific knowledge especially; computational chemistry, mathematics, and classical and quantum physics. This interdisciplinary in analytical chemistry made it possible to get benefits from molecular modeling, and simulations to develop more selective and sensitive electro-analytical platforms with lowered cost, time, and effort. Recently, the optimization of sensor design was more practical and robust in the light of computational simulation techniques such as molecular docking, dynamics simulation, and quantum calculations. Molecular modeling approaches (MMA) enabled the analyst to explore unrelenting molecular systems ranging from small chemical systems to massive biological molecules and material assemblies in the fields of computational chemistry. Furthermore, MAA has been recently used in the optimization of the design of different electrochemical sensors. Thus, in this review, we went over the different ap-plications of MMA and demonstrate these techniques on both the molecular and quantum levels. Moreover, we focused on the benefits of bringing such innovative techniques to the field of electro-analytical chemistry and highlighted some of the recently reported electrochemical sensors.

Keywords: Molecular modeling, Molecular mechanics, Quantum mechanics, Electrochemical sensors applications, Molecular imprinting.

1. Introduction

The quality of human life has been far improved by advanced medical care and the newly developed pharmaceuticals (Petrova, 2014). Pharmaceutical products have a significant impact on public health; hence, the quality of these products must be monitored carefully through all of their manufacturing processes (Haleem *et al.*, 2015). Pharmaceutical analysis research provided the regulatory authorities with various analytical techniques that competed to selectively determine the active pharmaceutical ingredients with higher sensitivities (Elsonbaty, Hassan, *et al.*, 2022). Other research activities identified and quantitated hazardous impurities that have a tremendous negative impact on patients' health (Daoudy *et al.*, 2018). Recently, regulatory authorities have applied stringent control on food safety and the quality of nutritional products to protect consumers' health (Lehotay, 2018). This stringent control necessitated the development of various analytical methods to detect residuals and traces of pesticides, veterinary drugs, pollutants, toxins, and industrial byproducts in different food products to guarantee their suitability for use (Cannavan and Maestroni, 2010). Electrochemical sensors provide a perfect tool for the determination of various analytes in different matrices (Naresh and Lee, 2021). The development of several designs of sensors by incorporating advanced materials (nano metal-composites and/or ionophoric substances) enhanced their sensitivity and selectivity (Abdel-Raoof *et al.*, 2021). Moreover, the development of biosensors paved the way to more selective determination of different biological targets as catecholamine neurotransmitters (Ribeiro *et al.*, 2016), peptides (Khatayevich *et al.*, 2014) and some pharmaceuticals (Soomro, 2020). Biosensors are mainly formed of two parts; the bio-sensing platform which can be an enzyme, DNA, RNA, antibodies or drug receptors and the transducer portion as; graphite, graphene or a conductive metal which can be decorated by various nano metal composites to enhance their electrochemical conductivity and so their sensitivity (Zhang, 2015).

Thus, most research activities in pharmaceutical analysis aim to achieve the accepted quality levels in both drug and food products. This goal would not have been possible without achieving the interdisciplinary in pharmaceutical analysis research with mathematics, biostatistics, chemometrics, and physical and computational chemistry (Elsonbaty, Hasan, et al., 2021). One example of the achieved interdisciplinary in the pharmaceutical analysis is shown in the previously reported papers, describing the design and optimization of selective electrochemical sensors for drug(s) quantification relying on computational chemistry approaches.

Computational chemistry and molecular simulations found significant opportunities to serve in pharmaceutical analysis research (Lin, Li and Lin, 2020; Elsonbaty, Madkour, et al., 2022). Many reasons urged the pharmaceutical analysis community to use computational chemistry applications through their research activities intensively. The most obvious reason is the need to validate their experimental work that tests the selectivity of the developed analytical platforms. Practical approaches to test the selectivity are time-consuming, especially in the screening and developmental stages (Taylor, 1983; Dadgar and

Burnett, 1995; Rahman and Khan, 2018). Furthermore, experimental methods suffer from burden errors and require several validations to confirm their results (Ortiz, Sarabia and Sánchez, 2010). Molecular modeling (MM) and simulation approaches were intensively used to study the interaction between these platforms and analytes; moreover, they can validate the adopted experimental approach. Computational simulations help save time and effort to screen different macromolecules versus the analyte to discover the most promising candidates for further downstream development (Kontoyianni, 2017; Yu and Mackerell, 2017).

Nowadays, computers are essential tools in each field of chemistry, and their use urged the development of several software applications that perform different simulation and calculation tasks in chemistry (Kokalj, 2003; Cristea, Nagy and Agachi, 2005; Tetko et al., 2005; Plass et al., 2012). Structural elucidation techniques such as NMR, X-ray crystallography, and the recent cryoelectro microscopy were developed to explore the structural geometry of the biologically active molecules; enzymes, proteins, and nucleic acids. Then were handled by computer software to build a 3-D model of these structures in a process known as MM (Billeter, 1992; Garmann et al., 2015; Fernandez-Leiro and Scheres, 2016).

The ability of a chemist to quickly comprehend and intellectually process structures should not be un-derestimated. Hence, molecular visualization software was first developed to allow scientists to visualize the 3-D structure of the biologically active molecules that are targets for different therapeutic molecules treating various diseases (Tetko et al., 2005; Goddard et al., 2018). The thorough under-standing of the relation between the structures and functions of these biological molecules paved the way for drug discovery and development activities. Some other computational activities were pointed towards calculating different molecular properties such as; partial charges, charge distribution, electrostatic potentials, strain, solvation, and binding energies. These properties are essential to be defined for a molecule to aid in searching molecular conformations, energy minimization, predicting molecular behavior in various chemical systems like the ability to bind to specific functional groups on macro-molecular targets or stability of some interactions in gas and solvated media, and in calculating the molecular orbitals that are essential in calculating the infrared or ultraviolet transitions for a molecule (Neese, 2009; Rasheed and Ahmad, 2011).

The accelerating development in computers hardware led to the emergence of simulations software interested in studying the nature of the interaction between the molecular entities of a chemical system (Martin, 2013; Jurij and Per, 2015; Stone et al., 2016; Guzman et al., 2019). To simulate molecular systems, specific algorithms were developed to define the classical laws of physics to simulate molecular mechanics and predict atoms' motion in space. These algorithms that manage molecular signals and define their structural geometry are collectively known as forcefields. They store the governing parameters for each different molecular system to make further simulation activities such as; molecular docking and dynamic simulations feasible. Molecular docking is an early developed approach to study such

interaction by fitting smaller molecules into a macromolecule's spatial spaces (binding sites) as a part of an enzyme or a nucleic acid sequence. The importance of docking lies in its ability to predict and compare the favorability of a small molecule or a group of small molecules to a specific macromolecule binding site. It is considered an effective tool for the virtual screening of combinatorial databases (Agarwal and Mehrotra, 2016; Fan, Fu and Zhang, 2019). Molecular dynamic simulations (MD) also gave the chance to explore the dynamic interactions of molecules in a chemical system within a predefined time frame predicting the different modes of interactions responsible for the stability of a chemical system. In addition, dynamic simulations studied the effect of solvation on the strength of binding between some small molecules in different solvents (Schneider, Sharma and Abha Rai, 2008; Sharma, Kumar and Chandra, 2019).

The prediction of the interactive behavior of electrons with their counterparts and their nuclei in a molecule was made possible by engaging the quantum mechanics (QM) equations (Alireza Lashkaripour, 2021). The density functional theory (DFT) is an approximation to solve the Schrödinger equation to simulate the wave function of the investigated system, which describes the probability of finding the electron in a given position (orbital) to signify the density of electrons in their orbital then one can determine the allowed energy states of the system. DFT aids in calculating important molecular properties such as charge distributions, total electronic energy, and dipole moment, which are essential to study the behavior of molecules in vacuum and solution media without relying on predetermined parameters (force fields) (Sholl and Steckel, 2009). DFT has many applications in the field of molecular simulations as the determination of the solvation energy of molecules in differ-ent solvents, investigating the spectral characteristics of molecules, optimizing structures of coordi-nate compounds, and predicting the reactivity of various molecules in vacuum and solution (Platas-Iglesias et al., 2011; Chatterjee, 2012; Van Mourik, Bühl and Gaigeot, 2014).

This review presents the basic science behind some of the MM approaches as; molecular and quantum calculations, molecular docking, and dynamic simulations. Also, it gives some insights about the molecular selectivity of some reported electrochemical sensors that use advanced and macromolecular substances or imprinted polymeric networks illustrated by applying some quantum and molecular simulations. Moreover, we demonstrate some reported work studying molecular interactions between pharmaceutical targets and their selective electrochemical sensors utilizing various computational approaches.

2. Molecular modeling (MM); fundamentals and functions

MM techniques serve in aiding drug discovery research. Thanks to the human genome project, differ-ent biological targets' vast discovery was achieved. These extensive data extended our knowledge about the function of other genes and the interplay roles of various proteins and enzymes in various diseases. The advances in computational chemistry enabled us to use these big data to provide on-demand therapies based on knowledge about the different biological targets.

Due to the advancement in computational platforms, several software and algorithms were developed to study molecules and their interactions with biological targets. Molecular mechanics algorithms study different molecular interactions and calculate different energies by applying equations that follow the classical laws of physics to nuclei without considering their surrounding electrons. Torsional points, bond stretching, and non-bonded interactions were calculated and predicted by molecular mechanics. These predictions were based on parameters that define the interactions between different sets of atoms. These data were pre-stored in the utilized software. They were collectively known as force fields in biological systems simulations (Jorgensen and Tirado-Rives, 2005) or as interatomic potentials for the simulation of materials systems (Becker et al., 2013). Applying molecular mechanics equations achieved several essential functions such as; energy minimization, conformational search and identifying stable conformation, studying molecular motions and dynamics simulations, and calculating molecular properties.

Both molecular and quantum mechanics were essential to develop the advanced software involved in MM. On the other hand, quantum mechanics equations were also designed to deal with interactions between electrons and nuclei based on the laws of quantum physics. These equations aid in calculating molecular orbital energies, specific conformation heat of formation, bond dissociation energies, dipole moments, and electrostatic potentials based on an ab-intio as DFT, which relays on solving the Schrödinger equation for electronic structures or a semi-empirical method as density-functional tight-binding (DFTB) (Bannwarth, Ehlert and Grimme, 2019). The ab-intio (DFT) method tends to be more accurate in the predictions that require no stored force field parameters; however, it consumes more time; thus, it is implied in cases of small systems composed of hundreds of atoms. While the semi-empirical (DFTB) method uses the stored force field parameters to perform its predictions, it reduces the computation times and can deal with large systems such as; protein. Nevertheless, this comes with the cost of its lower accuracy and transferability.

Regardless of the utilized computational method or software, several steps must be performed to pre-pare molecules for downstream processing and become compatible with this software's quantum and molecular mechanics laws. First, the small molecules are drawn in a 2D-view, then using the molecular mechanics; they are converted to the 3D view. Finally, crucial steps are performed to prepare the molecules (ligands) for the primary operations.

2.1. Energy minimization and atomic clashes correction

Molecular mechanics identify the attractive and repulsive forces between the individual nuclei of each parameterized atom in the molecular structure. Studying the molecules and their interactions begins withdrawing their structures in a 2-D manner then being visualized into their 3-D form. However, the drawn designs are always energetically unfavored; hence, they need to be actively adjusted. Energy minimization is a critical step in which the energy of molecules is brought to a minimum where the bond lengths and angles are adjusted so that any clashes between atoms are re-corrected and any adverse While MMFF, PEF95SAC, and TAFF force fields

non-bonded interactions are neglected. Then, the initial potential energy of the 3-D system is calculated as the sum of all repulsive and attractive forces between its particles as described by the following equation:

$$E\ (\text{total}) = \sum E\ (bending) + \sum E\ (streching) + \sum E\ (Van\ der\ Waals) + \sum E(torsion) + \sum E\ (coluombic)$$

Molecular mechanics software is applied for changing each bond length, angle, and torsion angels and calculates the total energy of the molecule after each change. By comparing the energies of the emerged structures, the software will finally hit the structure of the lowest energy and shows it as the final 3D structure.

As discussed above, the energy minimization task is solely performed by molecular mechanics equations so that it will depend on the pre-stored force field data. Working with the appropriate force field data is very important in this step because specific force field data should be used in energy calculations according to the type of molecules to be handled. A force field is a set of mathematical equations that can describe the energy of a system based on the coordinates of its particles but with-out consideration of electrons (Lewis-Atwell, Townsend and Grayson, 2021). Each force field contains the parameters that define atom types, bond stretching, bending, and torsion; thus, these parameters will change by changes in the kind of atoms of the admitted molecules. Several force fields are available for different types of molecules, for example, CHARM, AMBE, and GROMOS, which are responsible for simulations related to biomolecules such as proteins, DNA, RNA, and enzymes.

are parameterized for small organic molecules. In addition, these force fields have different versions, for example, CHARMM22, CHARMM27, GROMOS96, GROMOS45A3, GROMOS53A5, GROMOS53A6, AMBER91, AMBER94, AMBER96, AMBER99, MMFF94x, MMFF94s, and MMFF94.

Further details about each force field type are supplied in **Table (1)**. After minimizing the 3-D structure, several structural properties can be calculated. This process can aid in the further downstream processes, such as; the steric energy of the molecule is intrinsically calculated during the minimization process and is responsible for predicting the various strain energies within the molecule. Strain energies consider all bond compressions, bending, deformed torsions, non-bonded atomic interactions leading to atom clashes, and unfavorable dipole-dipole interactions. Steric energy calculations are helpful in comparisons of different conformations of the same molecules. Other molecular properties can be beneficial as partial charges, molecular electrostatic potentials, and molecular orbitals.

2.2. Partial charges calculation

Electrostatic interaction is an essential type of non-bonded intermolecular binding forces between molecules, and it plays a vital role in the biological and chemical environment. Valence electrons in an atom are those involved in electrostatic interactions. The classical view about valence electrons being localized upon specific atoms is not truly accurate as these electrons form a cloud delocalized around the whole atoms in the molecule. However, it spends

Table 1. Summary of recently reported force field protocols utilized in molecular mechanical simulations

Title	Description	Ref.
Amber12:EHT	All-atom forcefield combining Extended Hueckel Theory (EHT) and Amber12. Parameterized for proteins and nucleic acids using Amber 12, and parameterized for small molecules using 2D EHT. This forcefield is suitable for small molecules, macromolecules, or both.	(Gerber and Müller, 1995; Salomon-Ferrer, Case and Walker, 2013)
Amber10:EHT	Parameterized for proteins and nucleic acids using Amber, and parameterized for small molecules using EHT. The Amber10: EHT forcefield is more validated for proteins and nucleic acids than the Amber12: EHT forcefield.	(Gerber and Müller, 1995)
Amber94	This forcefield parameterized for proteins and nucleic acids, however, it is not suitable for most small organic molecules	(Darian and Gannett, 2005)
Amber99	An all-atom forcefield parameterized for proteins and nucleic acids. This forcefield is not suitable for most small organic molecules.	(Wang, Cieplak and Kollman, 2000)
CHARMM27	This forcefield parameterized for proteins, DNA and RNA, however, it is not suitable for most small organic molecules.	(Mackerell, Feig and Brooks, 2004)
Engh-Huber	A united atom forcefield parameterized for crystallographic refinement of proteins. Explicit hydrogens are required for polar atoms (N and O). This forcefield is not suitable for most small organic molecules or DNA.	(Engh and Huber, 1991)
MMFF94	An all-atom forcefield parameterized for small organic molecules. Partial charges are based on bond-charge increments. Suitable for use with Generalized Born solvation models.	(Halgren, 1996)
OPLS-AA	An all-atom forcefield parameterized for proteins and some small organic molecules. Partial charges are based on bond-charge increments that reproduce the original dictionary charges. Polar hydrogens have zero van der Waals radii.	(Jorgensen, Maxwell and Tirado-Rives, 1996)
PFROSST	An all-atom forcefield parameterized for proteins, nucleic acids and small molecules. AMBER parameters are used for macromolecules and parmFrosst parameters are used for small molecules.	(Pérez *et al.*, 2007; Bayly and Mckay, 2010; Sanchez, 2013)

more time around these more electronegative atoms, creating a non-evenly distributed electronic cloud, as shown in Figure 1a. Studying charge distribution and calculating partial charges (PC) are essential for predicting electrostatic binding with many targets by dipole-dipole, hydrogen bonding, and Van der Waal interactions (Peerless *et al.*, 2021).

It is crucial to investigate the charge distribution of a molecule in its native environment. For example, a hydrophilic environment as water will mask the electrostatic interactions between molecules and their targets, while a hydrophobic or less polar hydrophilic environment may enhance the electrostatic interactions. The reason behind that is referred to the non-linear structure of water molecules. The charge distribution in water molecules tends to be shifted towards oxygen atoms Figure 1b, thus, forming a dipole.

(a) **(b)**

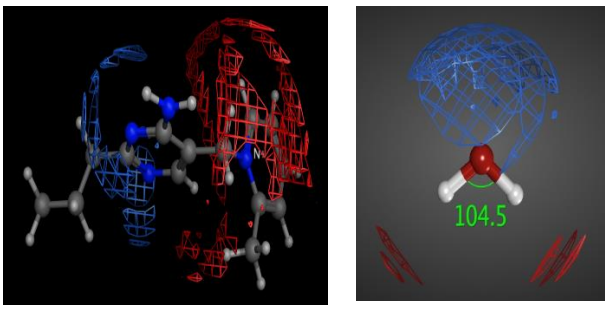


Figure 1: Electrostatic potential mapping of (a) amprolium ion; (b) water molecule generated by molecular operating environment (MOE) software. Electrostatic mapping of water molecule showing bond angel to illustrate the effect of molecular geometry to electronic distribution and polarization.

Moreover, the high polarity of water molecules made them create a strong hydrogen bonding network. Due to the previous characteristics of water molecules, they can completely solvate any polar molecules or even the ions which masks their ability to form strong electrostatic intermolecular interactions (Berg, Tymoczko and Stryer, 2002). An example of the importance of studying partial charges of molecules in their native environment is the dynamic simulation conducted on a system formed of amlodipine and sodium dodecyl sulfate (SDS) to study the complex formation between both of them in a different solvent environment (Attala *et al.*, 2020). In water, it was noticed that AML could not achieve any interactions with SDS due to the effect of the 3-D hydrogen bonding network of water molecules, which buffers the partial charges of both molecules and solvates them completely isolating them from each other, as shown in Figure 2a. While in the case of the Methanol environment, methanol is less polar than water, so it solvated both molecules Figure 2b. However, it did not hinder their binding and complex formation due to its inability to completely buffer the partial charges on both molecules.

(a) **(b)**

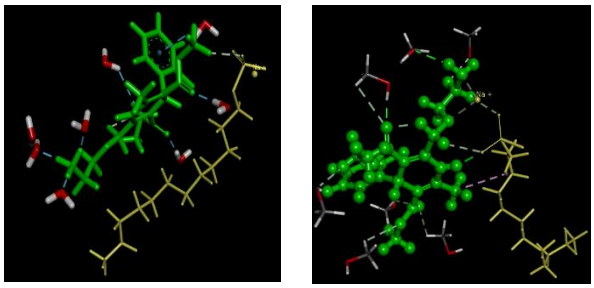


Figure 2: The effect of the (a) aqueous; (b) methanol environments on amlodipine partial charges and its interactions with sur-rounding SDS molecules illustrated by dynamics simulation conducted by MOE Poincare Andreasen algorithm.

2.3. Molecular electrostatic potentials

Charge distribution can be visualized over the whole molecule rather than on each separate atom as in partial charges (Reid and Collins, 2013). This can be done by quantum mechanical software considering the molecular orbitals using the semi-empirical method (DFTB) to view the electronic distribution over the whole molecule, which can help detect the electron-rich or poor positions to describe the molecular reactivity computationally and to predict modes of binding between different molecules and their targets (Murray and Politzer, 2017).

2.4. Machine learning and the prediction of molecular properties

Machine learning (ML) advances have invaded all aspects of life sciences due to their ability to perform large-scale explorations in the chemical environments based on quantum mechanics calculations which are essential in many processes of MM. ML is a category of artificial intelligence based on extensive databases to create a wide variety of training sets based on these data and then create rules to extract knowledge from these data sets (Remington *et al.*, 2020). ML today has reached deep in quantum chemistry and molecular simulations; thus, it learns more and more from quantum mechanics to build models capable of predicting molecular properties (Schütt *et al.*, 2019). Calculations of PC and potential surface energies (PSE), forms of mathematical equations that describe the energy of a single molecule based on its geometry (Unke *et al.*, 2020), are essential for many MM processes. Most of these calculations are based on the electrostatic aspect of energy, as in free energy calculations, molecular docking, and dynamic simulations. PC and PES calculations can be performed with the highest accuracy using quantum mechanics. However, this approach is very time-consuming for systems, including an increased number of molecules. Several machine learning (ML) approaches perform PC and PES calculations with less time and acceptable accuracy. Artificial neural networks (ANNs) have been developed for such tasks using an ML approach called transfer learning which begins with a training model based on a set of data of general quantum mechanics calculations. Then, one can use this model to be retrained for other related calculations (Noé *et al.*, 2020). Figure 3 illustrates the summary of these processes based on ANNs. A recently developed approach that was found effective in predicting PC and PES is the Atom-Path-Descriptor (APD), a molecular descriptor. First, the APD algorism assigns the chemical environment of the 3-D chemical structures. Then, based on the APDs, an ensemble of ML algorisms called extreme gradient boosting and the random forest are used to build regression models for PC/PES predictions (Wang *et al.*, 2020).

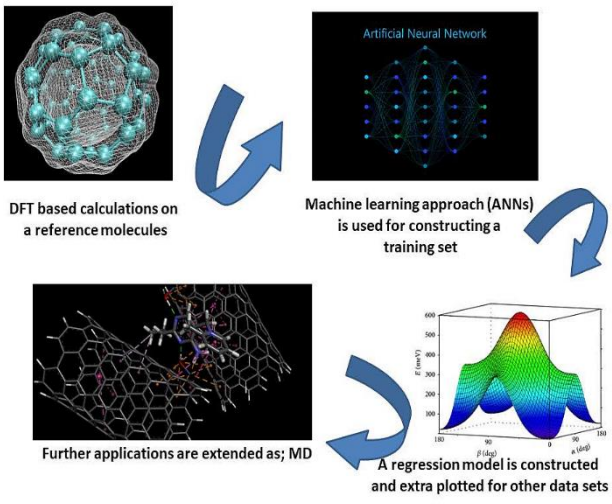


Figure 3: Summary of machine learning approaches utilized to predict molecular properties

3. Conformational search and identification of the most stable conformer

In most MM activities, the most stable conformation of the molecule under study is always used as the primary representative conformation due to its theoretical stability. Unfortunately, in some cases, the active conformation or the conformation that will achieve the most effective binding to its target may not be the most stable one. Hence, a representative ensemble of conformations should be used through most MM activities, especially during molecular docking (Balaban, 1997). While searching for the most stable conformation for a small molecule, the previously discussed steps in structure preparation, including the energy minimization, must be fulfilled. The net result by the end of energy minimization is a specific conformation to be displayed as the one of lowest potential energy. However, unfortunately, it is not the actual most stable conformation.

The energy minimization software can only vary bond angles and lengths to decrease potential energy to a point beyond which these changes have no significant effect on reducing the potential energy. Thus, the MM software will eventually choose a lower energy conformation but closest to the initial conformation. Any changes in bond angles or lengths beyond that local energy minimum conformation require an elevation in the system's energy, which is not a part of the MM software programming. The most stable conformation can be beyond that local energy minimum conformation chosen by the energy minimization MM software but require some additional energy to cross the energy barrier. Hence, specific algorisms were designed to cross that energy barrier by increasing the strain energy of the local energy minimum conformer until it reaches the global minimum of the potential energy Figure 4, and there will be the most stable conformation. Several methods are available for conducting conformational searches. Low mode MD, Monte-Carlo (MC) simulations, Metropolis, and stepwise bond rotation, are the most common methods.

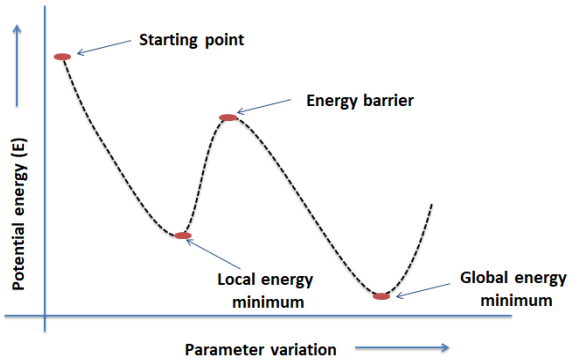


Figure 4: Energy changes during conformational search showing both local and global energy minima

Low mode MD, where heating is offered to the molecule, provides the energy required to overcome the energy barrier to undergo bond stretching, which was not possible during energy minimization. The low mode vibrational MD generates its conformations by operating MD simulation for 1 Ps periods followed by energy minimization (Labute, 2010). This mode is used in significant, disconnected, and macro-cyclic systems where stepwise bond rotation fails to operate. However, it can be used efficiently to generate conformations of small molecules. This method provides realistic results which come from the way it works. In this mode, random kinetic energy is provided to the system, causing more realistic and rapid conformational torsions.

For example, n-butane was sketched and energy

minimized, and after energy minimization, the conformation obtained was as shown in Figure 5a. Then, a low mode MD algorism was used to regenerate conformations which eventually gave two main conformations, as seen in Figure 5b. The gauche conformation had an energy value of (-4.289 Kcal/mol), and a dihedral angle of 65.3 ˚A Figure 5c. On the other hand, the staggered anti-conformation had an energy of (-5.070 Kcal/mol) and a dihedral angle of 180 ˚A showing itself as the most stable conformation Figure 5d.

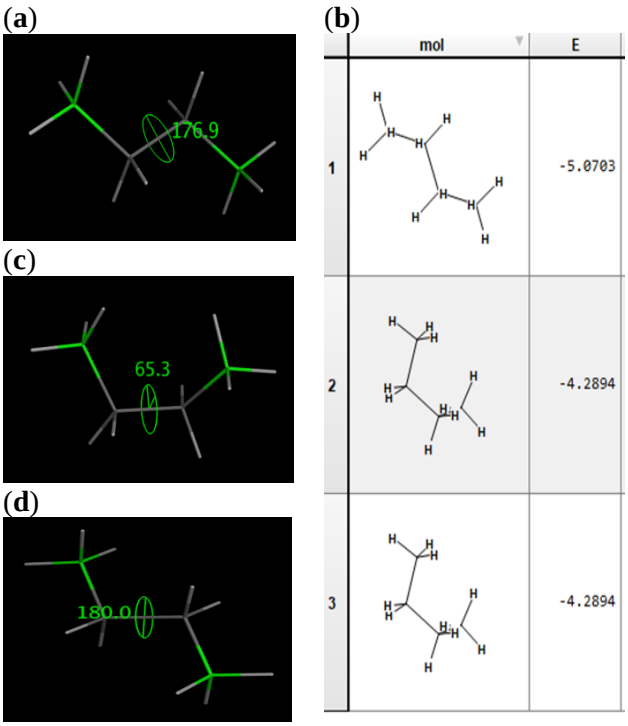


Figure 5: Conformational search by MOE. (a) n-butane conformation obtained after energy minimization showing dihedral angel; (b) Conformational database generated by low mode MD arranged by their energy; (c) n-butane gauche conformation obtained by low mode MD showing the dihedral angel; (d) n-butane staggered conformation obtained by low mode MD showing the dihedral angel.

Comparing the dihedral angles of the local minimum conformer resulting from the energy minimization step (176.9˚A) and that resulting from the MD simulation in low mode (180˚A) proves that energy minimization cannot predict the most stable conformation.

Stepwise bond rotation mode; is also called the systematic search because this mode uses a more systematic process to find more conformations. Unlike low mode MD, this method rotates every bond in the molecule; all bonds are candidates for rotations except ring and terminal bonds, by a constant magnitude till a new conformation is generated each time and without conducting energy minimization after each step. The main aim of this method is to discover all possible conformations for a molecule regardless of its energetic state (Duhé, 2014). A serious problem facing this mode is the combinatorial explosions (CE). CE is a term used to describe the massive number of possible conformations that can be generated from the systematic approach. This approach can yield a considerable number of conformations because every bond is rotated individually, which means the number of conformations will increase exponentially with the size of the molecule, making this approach only suitable for small linear and continuous systems.

Lately, a new approach based on principal component analysis (PCA) associated with quantum mechanical calculations have decreased the system's dimensionality, which provided a solution to the limited applications of the systematic method. This chemometric approach was applied successfully for several drugs such as lansoprazole, pantoprazole, and

omeprazole. The relation between molecular size (the number of freely rotatable bonds) and the generated conformations showed a quadratic growth behavior hindering the combinatorial explosions in the traditional approach (Bruni, Leite and Ferreira, 2002).

Monte Carlo (MC) and Metropolis methods, unlike MD, are biased towards the more stable conformations by spending most of the analysis time on these. MD works by generating random conformations via shifting atoms in space. At the same time, MC functions by executing random bond rotations in the molecule (Patrick, 2013). In MD, the same time of analysis is spent equally for all random conformations, while in MC, after generating each confirmation, it is energy minimized, and its steric energy is compared with each other. The algorism chooses one of the lowest steric energy to complete further random bond rotations and generates lower energy conformations until reaching the global minimum conformation (Paquet and Viktor, 2015). Metropolis method relies on MC algorithm; however, it uses lower temperature in each successive cycle, which increases the probability of hitting the global minimum. This approach of the Metropolis method tends to generate conformations with a specific or common conformational space (Landau, 2003).

In the following sections, we will discuss some utilized MM activities such as molecular docking and MD simulation, which gained significant attention from researchers in pharmaceutical analysis and advanced formulations.

4. Molecular docking

This simulation aims to study the fitting and binding forces of an ensemble of different ligand molecules to functional groups inside the binding site in its target Figure 6. It is defined as a simulation of fitting the ligand within a cavity of its target macromolecule (protein pockets, DNA, RNA loops, imprinted polymeric network, cyclodextrin, or calix cavity). Also, docking can predict the ligand macromolecule complex structure using a computational approach.

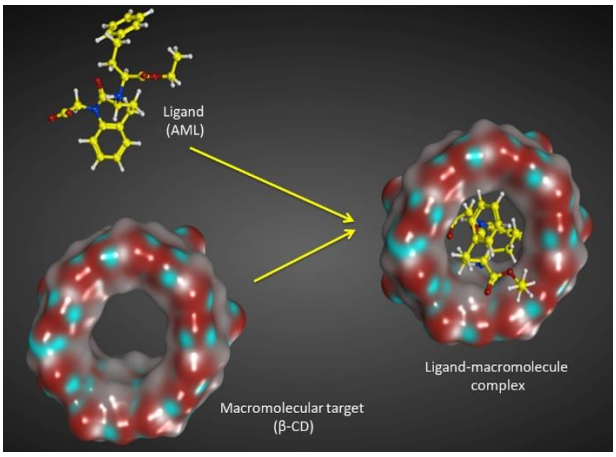


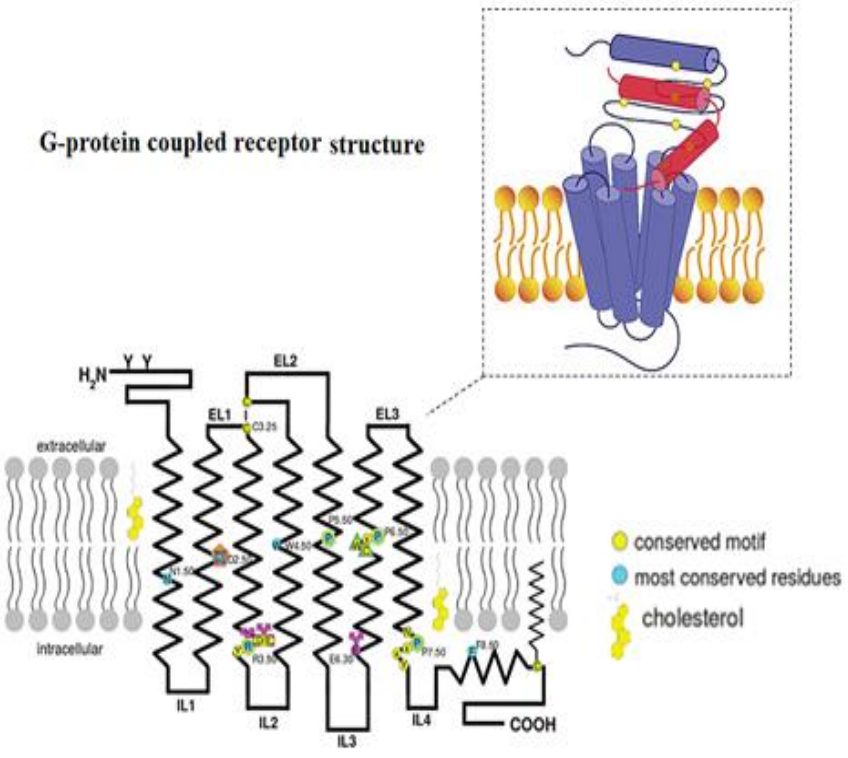
Figure 6: Fitting of amlodipine into β-cyclodextrin target pocket to form an inclusion complex.

4.1. Binding site mining

Before starting docking, there must be a way for operating software to recognize binding sites on the target. Different algorithms have been developed for such tasks, and they can be summarized according to the technique they used to identify sites on a target. The literature found three main methods: sequence-based, geometric, or energy-based methods. The sequence-based method depends on the concept of multiple sequence alignment that superimposes different proteins to discover conserved sequences involved in various binding ligands. This technique is based on the idea that some arrangements involved in binding are not varied during the evolution of other proteins in the same family. For example, in the g protein-coupled receptor family, regardless of the variation in receptor type, there are still some structurally reserved sequences Figure 7a. Thus,

there can be similarities in these sequences at different proteins due to their essential roles in binding. Geometric-based methods assume that a protein is composed of pockets or clefts. A cleft detection algorithm called pocket uses the 3D lattice model for a protein and assigns dots representing either a protein or a solvent. The pocket algorism identifies the binding site as a solvent dot surrounded by protein dots. Other developed algorisms used another approach that applied spheres between all atoms so that no two atoms are contained in a sphere. The clustered spheres that occupy the most significant volume represent a possible pocket or binding site Figure 7b. The energy-based approach depends on the energetic properties of the site rather than surface topology as in geometric approaches. The algorithm applies several functional probes to simulate different atoms and residues in most pharmaceutical and biological compounds. The calculated data can be used as a mapping guide for possible interactions with all potential binding sites in the target. Q-site finder (Laurie and Jackson, 2005) is a software used to perform binding site molecular interaction mapping based on Grid forcefield protocol (Carosati, Sciabola and Cruciani, 2004). Software (CH_3) probes are used to map molecular interactions and then perform clustering analysis to predict positions of binding based on the highest interaction energy calculated from (CH_3) probes.

(**a**)



(**b**)

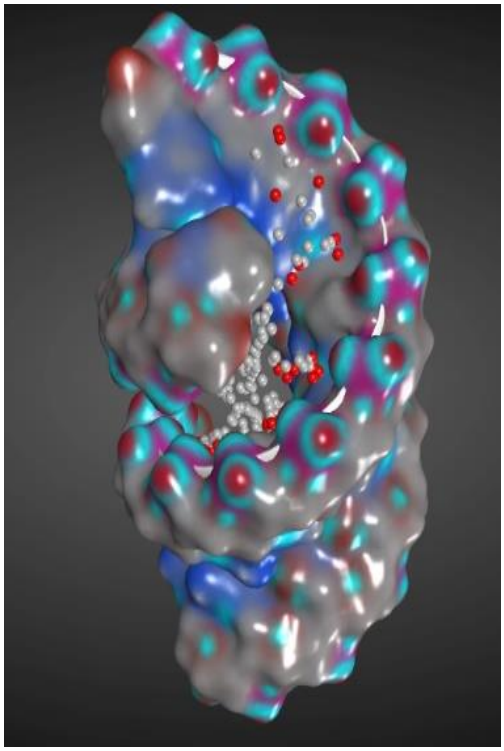


Figure 7: Diagram for how MM software identifies macromolecules. (a) Diagrammatic structure of G-protein coupled receptors super family showing conserved motifs as an example to illustrate how MM software identify possible binding sites; (b) Molecular 3-D surface structure of a DNA sequence 3-ccgatagatacca-5 applying dummy spheres to signify vacant spaces identified as possible binding sites on the DNA molecule.

4.2. Sampling approach in molecular docking

Docking is a two-step process that begins with a sampling of different conformations of each ligand then each conformation (pose) is positioned in the predefined binding site. The final step is applying a scoring function that arranges all the generated poses according to their favorability to the binding site. In addition, docking can be categorized according to the degree of flexibility in the utilized sampling algorism into rigid, semi-flexible, and flexible.

Rigid docking is a model in which the algorism considers both the ligand and the target as rigid entities. Only axial rotations are allowed; therefore, the ligand fits the target in a lock-key like the model. Geometrical and chemical algorithms are used to fit ligands, and different ligands are scored based on steric fit and functional groups similarity to the binding site. Ligand flexibility can be enhanced in rigid docking by supplying a conformational database for the ligand instead of the ligand alone. This approach forces the algorism to test all the supplied conformations for fitting within the binding site. While in the semi-flexible and flexible approaches, a degree of flexibility in the ligand only or both of the ligand and its target, respectively, is offered to increase the ligand's conformational space or the macromolecular target in order to predict the most accurate approximation of the ligand macromolecule complex. The flexibility of both ligand and target is essential to mimic the induced fit nature of some macromolecular targets where the ligands induce some conformational changes upon approaching the binding site. Much computational time and effort will be consumed to accomplish higher degrees of flexibility. According to the aim and nature of binding sites, a compromise between accuracy and computational time is achieved so that a semi-flexible approach can be enough in some cases, and others may require total flexibility. In semi-flexible docking, many approaches are used to ensure flexibility of the ligand while holding the target rigid. A systematic approach, which uses an exhaustive searching technique, discovers all possible poses resulting from alternating every rotatable bond in a combinatorial systemic manner. To avoid combinatorial explosions, several constraints are set to limit the acceptance of search iterations. A fragmentation-based approach is used to offer stability in the ligand molecules by fragmentation of the molecule in positions of rotatable bonds, then a rigid docking of these fragments is implemented. Then finally, linking of the fragments is achieved, which provides partial flexibility of the docked ligands; FlexX (Moustakas *et al.*, 2006; Pagadala, Syed and Tuszynski, 2017) is an example of sampling algorism based on fragmentation. Another approach based on fragmentation is the incremental construction where the central fragment of the molecule is docked then the rest of the fragments are added incrementally.

A stochastic technique is another sampling approach that searches ligand conformations in binding sites by varying the system degrees of freedom in a random manner rather than systematic, which saves time and computational efforts. The main disadvantage of this approach is the decreased search's conformational space, which may lead to missing the actual binder. This drawback can be compromised by increasing the system searching iterations. The most common techniques in the stochastic method are the Mote Carlo (MC) method and the genetic algorism (GA) method. MC method uses the metropolis method in offering limiting parameters (energy constrains) during

sampling of conformations so that the random changes in the ligand must end up with favorable changes in its energy. Autodock Vina is an example of sampling algorisms using the MC method (Tang *et al.*, 2022). GA is considered an evolutionary conformational search method where the idea of biological evolution is inspired. Each conformation (pose) is regarded as a result of changes in several degrees of freedom in the system. Consequently, a single conformation may be imagined as a whole chromosome that is further divided into several genes holding several degrees of freedom that comprise a specific conformation. GA is a method that enables operations as mutations and crossovers that occur naturally between chromosomes to generate new and different conformational spaces. These approaches suffer from the inability to reach the actual experimental binding conditions due to the rigidity of the target binding site.

Several methods are used to perform flexible simulations. One example is the MD simulation which can test the most available degrees of freedom in the ligand–macromolecule complex system. The main disadvantage of using MD in flexible docking is the inadequacy of its sampling. In MD, some energy barriers cannot be passed, resulting in discovering only a narrower conformational space of both the target and the ligand. Furthermore, MD consumes appreciable computational time and effort in analysis, making it a strenuous technique in screening several ligands simultaneously. On the other hand, flexible docking approaches provide total flexibility of both the ligand and target macromolecules to achieve induced conformational changes in the binding site upon positioning of the ligand.

Soft docking is the first and most straightforward approach to provide overall flexibility as applied in Gold software (Jones *et al.*, 1997). It functions by decreasing or adjusting the Van der Waal repulsion energy in the utilized force field parameters between atoms in the system to allow closer movements of both ligand and target atoms (minor clashes) inside the binding site (Sierra *et al.*, 2011). This approach has advantages of simplicity and decreasing computational time but lacks adequate flexibility.

Another approach called target ensembles is functioning by using different conformations of the target itself, then each ligand is docked separately into each target confirmation, afterward the results are merged to give a complete picture; Dock and FlexE (Claußen *et al.*, 2001; Kim, Park and Chong, 2007) are flexible docking software that operates by target ensembles concept.

4.3. Scoring functions for docking: categories and advances

The sole of the docking procedure is the scoring of generated poses to identify binders from decoys quickly. Several scoring functions are used to arrange the different ligand poses or ligands according to their favorability to bind to their targets. The major categories of the scoring functions are forcefield-based, empirical, and knowledge-based. The force field-based functions, from nomenclature, use classical force field parameters to calculate the binding energy of each generated pose based on the sum of all non-bonded interactions as Van der Waal forces and electrostatic interactions. Then, the generated poses are arranged according to their binding energies with the target. This kind of scoring function suffers from slowness in their computations which can be handled by applying cut-off

distances for each type of non-bonded interaction (Salmaso and Moro, 2018). This approach lacks accuracy due to the inability to involve the long-range non-bonded interactions. Their calculated values of binding energies are far from the actual experimental values; thus, they can only be used as a guide to arrange ligand poses in their binding site.

Empirical scoring functions use simple energy terms to decompose the binding energy into ionic critical forces, hydrogen bonding, hydrophobic bonding, and binding entropy. Each term is multiplied by a coefficient and compiled to obtain the total binding energy value. The coefficients are determined from regression analysis performed on a ligand-macromolecular target complex test set, which had previously determined affinities (experimentally). This approach lacks accuracy due to the differences between different software, which may deal with each term differently, and due to differences in the number of terms involved in various software (Guedes, Pereira and Dardenne, 2018). LUDI is an example of software that uses empirical scoring functions in calculating binding energies (Böhm, 1992). A knowledge-based scoring function depends on databases of ligand-target complexes from which statistical analysis is performed to discover the frequency of each type of interaction. The most frequent interactions mean they are the most favorable. The ligand-target atom pairs contacts are then converted into energy components, summed, and used to indicate the overall affinity. Gold/ASP (Jones *et al.*, 1997; Mooij and Verdonk, 2005) is an example of docking software that applies the knowledge-based scoring functions. This approach is simple and suitable for extensive computations as in screening applications.

A particular type of scoring technique is called consensus scoring. This technique depends on the collaboration between various scoring functions to increase the accuracy of hitting the bound pose that represents the actual conformation of the ligand-target complex and increases the chance to avoid decoys (Palacio-Rodríguez *et al.*, 2019; Vieira, Magalhaes and Sousa, 2019).

4.4. Ligand binding affinity calculations: compromising accuracy and speed

Experimental methods such as x-ray diffraction, nuclear magnetic resonance (NMR), cryo-electron microscopy (Billeter, 1992; Fernandez-Leiro and Scheres, 2016), and isothermal titration calorimetry (Duff, Grubbs and Howell, 2011) are the most accurate to determine binding affinity. However, unfortunately, they are not suitable for virtual screening activities, which require faster techniques to reduce handling time. Computational methods based on molecular docking and scoring function achieved the compromise between accuracy and speed of determination. The accuracy of predicting the ligand affinity using the current scoring functions is questionable and maybe not be close enough to the real environment. One reason behind the lack of accuracy of earlier scoring functions is missing the ligand solvation effect, which is a factor that was very difficult to predict or to compensate using current scoring functions. This led to evolution of the physical-based scoring functions, which can expect solvation and binding entropy of ligand.

The most common and successful physical-based scoring functions are the molecular mechanics combined Generalized Born and solvent accessible surface area (MM/GBSA) and molecular mechanics-based Poison-Boltzman coupled with solvent

accessible surface area (MM/PBSA) (Genheden and Ryde, 2015).

Determining the binding affinity of the ligand is tricky as it should consider several complex interactions between the ligand and its surroundings in the system, including the solvent. Additionally, some thermodynamic parameters should be considered as the changes in the entropy of the ligand due to its binding as the binding decreases the degree of flexibility of the ligand. All these considerations are essential for the accurate determination of ligand-target binding affinity. The early discussed scoring functions failed to compensate for such complex interactions of the ligand with its system surroundings; accordingly, they failed to determine the binding affinity accurately. Both MM/GBSA and MM/PBSA could give accurate estimates about binding affinity and be fast enough to be used in virtual screening research activities.

5. MD simulation: theory and applications

MD is the study of the system's flexibility by applying the molecular mechanics' equations (Newton's equation of motion) to move each atom in the system in a time window of femtosecond (fs = 10^{-5} sec). The simulation is run in a time step manner where each atom in the system is allowed to move freely in a time frame range of (1-2) fs (Patrick, 2013). Using the fs time frame is essential because 1fs is less than the time required for a bond stretching vibrational movements in a molecule. If a higher time frame is allowed, two atoms may occupy the same position creating clashes in the system. After each time step (1-2 fs), the position and velocity of each atom is recorded, and the forces acting on each atom are calculated based on force field stored data. The system is forced to move forward in a time steps manner. Each movement for each atom is recorded in a trajectory describing all degrees of design flexibility.

A single simulation may last for several Femto, Nano, or Microseconds according to the aim of the simulation and the type of molecules involved in the system. The more complex the chemical system under investigation, the slower the movement of molecules will be, and a longer simulation time is needed (ns to µs) (Hansson, Oostenbrink and Van Gunsteren, 2002). Recent hardware advancements enabled MD simulations for more extended periods to simulate actions that were impossible to simulate before, for example, simulating the folding process of some protein fragments. Graphical processing unit (GPUs) developments made it easier to perform longer MD simulations due to their rapid performance than the regular central processing units (CPUs). GPUs use a different coding system that takes advantage of the parallel computations (Rovigatti *et al.*, 2015), enabling the MD algorithms to run faster than usual CPUs. Modern computer workstations contain CPU and GPU, which operate simultaneously, but GPUs will have the upper hand when it comes to simulations (Hospital *et al.*, 2015).

To illustrate the different ways both CPU and GPU functions, imagine a complex mathematical problem to be solved was admitted to a group of non-experienced students (GPU) and also to an experienced mathematician (CPU). Then, the predicted result is that the experienced mathematician will be able to solve the problem efficiently regardless of the time consumed; on the other hand, the student group may fail to solve the problem. Consequently, CPUs are more efficient in

handling complex computations but may suffer from time lags. Another example is when clusters of simple calculations are admitted to the last two groups. The student group will show upper supremacy compared to the mathematician alone due to their collaborative efforts. Accordingly, they succeed in reaching the same results quickly, which is the same concept GPU uses to function in parallel form Figure 8.

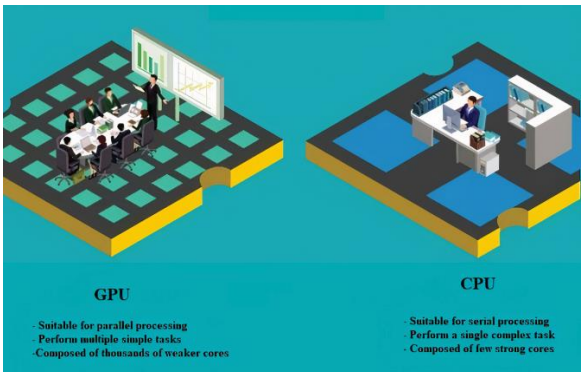


Figure 8: The major differences between GPU and CPU computing.

Applications of MD simulations are extensive and range from assessing the flexibility of the chemical system to illustrating the favorability of interaction between small molecules that do not have any defined binding site or pockets; hence, molecular docking is not applicable (Tian, 2008). MD can also be used to refine the docking scores to examine the stability of the highly ranked poses to detect any decoys (Guterres and Im, 2020). The poses of highest scores are subjected to MD simulation to further discover the target molecules for different binding sites which were not tested during docking, resulting in refining the binding modes of the subjected poses. In addition, MD trajectories can be considered as a conformational database for ligands or targets of polycyclic nature where conventional conformational search approaches failed to discover their entire conformational space (Jørgensen and Christensen, 1995).

Before starting a simulation, one must optimize the chemical system under investigation by correcting any defects in the crystal structures, such as missing hydrogen atoms, because x-ray diffraction does not resolve hydrogen atoms due to their tiny sizes. Before engaging the simulation, energy minimization, assigning the appropriate force field, protonation state (pH) adjustment, solvation, salt ions, and applying potential charges are adjusted. The selection of the type of motion equation is also an important parameter. Several motion equations are available to calculate the system's velocity, position, and forces; the Nose-Poincare Andersen (NPA) extension to the Hamiltonian equation is considered the most accurate and sensitive (Sturgeon and Laird, 2000).

Analyzing the MD trajectories is extremely complex due to the massive number of variables measured for each atom at each time step in the system. The positional distance-based methods to assess and analyze computational models are the most popular and straightforward to perform. Root-mean square deviation (RMSD) is one of the global measures for the conformational stability of the ligand-target complex, and it examines the changes in the dynamics of the natively un-bound macromolecular target. RMSD versus time is the most common indicator for assessing the ligand-target complex stability. The ideal situation across the simulation is some fluctuations in RMSD that occur due to changes in the ligand and target conformations, and by comparing the RMSD plots of the bound (in the complex) and unbound target, it shows the stability indices of the formed complex (Abdelrheem *et al.*, 2020). The radius of gyration (R_g)

is another positional distance-based parameter that measures the distribution of the atoms of a macromolecular target around its axis (Lobanov, Bogatyreva and Galzitskaya, 2008; Sneha and Priya Doss, 2016). R_g versus time is another indicator for the compactness of the target macromolecule. Through the simulation, the fluctuation pattern in the R_g for both the bound and unbound target should be close to each other to guarantee the stability of the ligand-target complex (Wani *et al.*, 2021). Another interesting way to interpret the molecular interactions throughout the simulation is to investigate hydrogen bond formations through time, representing the frequency of hydrogen bonding between different molecules in the system. The most critical achievement gained from the information extracted from the MD simulation is estimating the stability of a ligand-target complex in its native environment (solvated system).

6. Privilege of using molecular modelling approaches within electrochemical sensors

All the previously discussed approaches have gained attention towards application in the optimization and development of the electrochemical and bio sensing. Molecular docking and dynamics simulations are pharmaceutical analysts' most efficient MM activities. A publication survey was implemented to investigate the publication efforts in pharmaceutical analysis, molecular simulations, and applications of MM and simulations in analysis Figure 9 in 2015 to 2023 based on Scopus database. It was evident from the presented data that despite the thriving research activities in the fields of molecular simulations and pharmaceutical research, there was a modest research activity regarding the applications of molecular simulations in pharmaceutical analysis, which urged us to present the current work to point to the importance of applying the knowledge of MM in different pharmaceutical analysis activities.

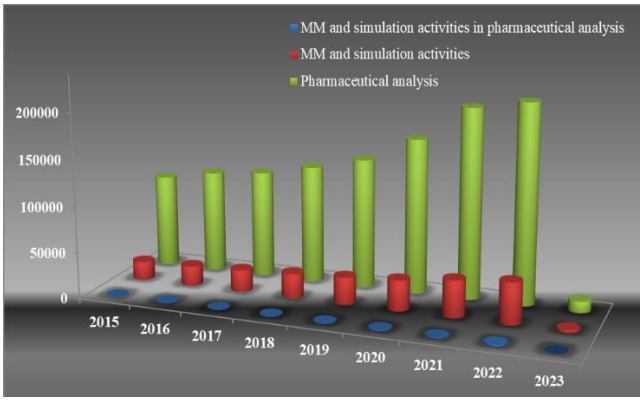


Figure 9: A publication survey investigating the publication efforts in pharmaceutical analysis, molecular simulations, and applications of MM and simulations in analysis from 2015 to 2023 based on Scopus database,

A significant challenge facing any pharmaceutical analytical technique is achieving higher degrees of selectivity and sensitivity towards the desired analyte(s). Electrochemical sensors tend to provide a sensitive and selective technique for quantitation of different analytes. These techniques gained attention due to their dependence on electron flow as a signal carrier which represent cleanest analytical platform ever encountered also, due to their suitability for miniaturization, to decrease the required sample volume to few microliters, they led to a decrement in their waste. Besides, low fabrication cost and less time for sample analysis made these techniques the favorable choice for real time analysis (AlRabiah *et al.*, 2018).

Selectivity of the electrochemical sensors is an important parameter that must be built into its design during the development phase. Selectivity can be achieved by incorporating different types of macromolecules to the electrode sensing part. For example; ionophores are added to the sensing part of the sensor to act by enhancing the sensor's selectivity towards the targeted analyte (Bakker, 2004; Amemiya, 2007). Different arrays of ionophores were reported (Bakker, 2004) as a series of macromolecular compounds of both hydrophilic/lipophilic characters as; (α, β, and γ) – cyclodextrins, Calix [4, 6, and 8] arenes, functionalized cyclodextrins (methyl and hydroxypropyl β-CDs), and others.

Molecular docking is extensively used to screen the selectivity of these ionophores towards the target analyte. The aim of performing molecular docking can be variable. The analyst may use it for choosing the most selective and suitable ionophore for the analyte before conducting any experimental work so decreasing the time of experimenting different sensor designs (Almalik *et al.*, 2018) . Also, one may perform molecular docking to interpret the experimental results obtained from various sensor designs to compare their performance in the light of binding energies of the analyte poses within the pocket of each ionophore (Alrabiah, Homoda, *et al.*, 2019).

Moreover, molecular docking can be performed to confirm selectivity of the chosen ionophore in the presence of other interfering compounds as co-formulated drugs or organic compounds in a dosage form acting as excipients.

Another interesting example for incorporating functional macromolecules is the molecularly imprinted polymers formed of a polymeric network of monomers cross-linked together in a specific arrangement; thus, several gaps in the polymeric network are left behind. These gaps permit selective identification for a particular template molecular geometry (Sajini and Mathew, 2021).

This design is only possible upon optimizing two essential factors; type of progenic solvent in which polymerization reaction takes place and monomer structure capable of interacting with the template molecule. MD and QM calculations were utilized effectively to screen the suitability of a wide variety of monomers to test their binding to the template molecule (analyte) in different solvents (Elsonbaty and Attala, 2021; Liu *et al.*, 2021).

Researches have learnt that optimizing the design of an electrochemical sensor became an easy task in the light of MMA. For example; the sensitivity of a solid contact electrochemical sensor has been always depending on the transducer used in its design(Heli *et al.*, 2010) . Recently, several works reported the use of different nano metal oxide composites to decorate graphite or graphene based sensors (Oghli and Soleymanpour, 2020) . Several attempts were made to explain the interaction between these decorated sensors and their analytes on the quantum and molecular levels using different MM approaches.

Researchers could determine the effect of a nano material added to the sensor composition on the sensor ability to interact with the analyte. So, they became able to investigate various arrays of different sensor designs and compare their performance. Biosensors had also a

great attention to be simulated using computational methods. Since their sensing parts are mainly composed of a biological material which interacts more selectively to its target, their selectivity can be assessed also using techniques as molecular docking and dynamic simulations (Elsonbaty, Abdel-Raoof, *et al.*, 2021).

7. Practical insights for docking and dynamic simulations of small molecules

The Major challenge facing running docking simulations for relatively small organic molecules and some metals is selecting the appropriate force field that parameterizes all of the atom types in the system. This challenge has been tackled by engaging the appropriate force field that parameterizes almost all tiny organic molecules and some metal atoms such as MMFF94X, Amber10: EHT, and universal force field (UFF) (González, 2011; Becker *et al.*, 2013; Coupry, Addicoat and Heine, 2016).

Another problem is the inability of some MM software to identify some interacting molecules as a target or receptor due to its non-protein structural nature and limited geometrical characteristics. Most of the targets used in simulating events in traditional electrochemical sensors are organic molecules rather than proteins or nucleic acids in biosensors, so the software system may not identify the target molecule as the receptor. Due to this drawback, molecular docking is not feasible in most cases, and to study the nature of interactions between these molecules, MD is the only way to do so.

Also, solvation must be considered to simulate these interactions in the chemical system due to a solvent's critical effects on the interaction between molecules, as discussed earlier. Because these simulations do not represent a biological system, many solvents beyond water are available to simulate different chemical systems in vitro as chloroform, dimethyl sulfoxide (DMSO), Methanol, ethanol, and (Hezaveh *et al.*, 2012; Zhang and Lazim, 2017).

It is noticed that the relatively small organic molecular systems are more straightforward than their biological counterparts, so these systems use minimum computational efforts. MD simulations for these systems are simpler and require short times in the ps frame, which is enough to study events as conformational changes and interactions.

MD simulations are the most useful to study such small molecules interactions, and there are three scenarios for the use of MD. First, we can use MD to confirm the obtained experimental work results. Second, we can start with MD simulation and use their results to determine a specific experimental pathway. In the last scenario, we may use MD simulations besides docking study to confirm the validity of the selected poses. Then, experimental work is performed to verify the computational speculations.

8. Applications in pharmaceutical analysis

Several electrochemical sensors and biosensors were reported using different computational approaches to assist their design and performance optimization. Electrochemical sensors are composed of a transducer;

responsible for signal transduction and the sensing part as polymeric membrane, graphite or graphene oxide; accountable for interactions with the external environment and analyte quantitation.

To study the selectivity of the ionophore macromolecule towards an analyte, a molecular docking study can be performed to compare the affinity of the analyte to each of the ionophores. Based on the data extracted from the docking study (docking poses) and binding energies between the analyte (guest) and the ionophore (host), the most stable complex is identified, and the ionophore best candidate can be chosen to achieve the optimal sensor selectivity. Also, the interfering effect of different molecules accompanying the analyte in its matrix can be studied by docking these possible interfering molecules against the sensor ionophore macromolecule. Table 2 epitomizes the most recently reported works that implement the computational activities in designing their electrochemical sensors utilized for a broad spectrum of applications.

In another context, the design of molecularly imprinted polymers for the selective solid-phase extraction of pharmaceutical molecules can be optimized by the Insilco methods besides or instead of the time-consuming in-vitro approaches. MD simulations were reported as the most beneficial tool for simulating the critical steps in designing the polymer as; the selection of the suitable monomer and pyrogenic solvent (Olsson, Wiklander and Nicholls, 2021).

MD simulation is a time-saving approach with minimal computational cost. MD is suitable for screening purposes to select the most favorable candidate monomer(s) for the template molecule in the presence of different organic solvents. Analysis of MD simulation data gives speculations about the stability of the formed interactions between the monomer and the template molecules; moreover, they assist the selection of the best solvent which enforces these interactions. Table 3 displays some of the recently reported research efforts that apply different computational approaches to optimize selective imprinted polymers for various pharmaceutical compounds.

Also, QM calculations based on DFT or semi-empirical methods were reported to optimize the structural geometries of monomer-template complexes. These QM approaches were found helpful in investigating the effect of different solvents on the electronic energies of the monomer-template system.

Table 2: summarizes the most recently reported works that implement the computational activities in designing their electrochemical sensors utilized for a broad spectrum of applications

Transducer	Ionophore (if exists)	Analytical technique	Computational approach	Software	Application	Ref.
GO[a]	-	Potentiometry	Molecular docking was implemented to prove that GO binds to the enzyme at a different pocket rather than the one for D-glucose	AutoDock Vina	Molecular interaction analysis for the immobilization of glucose oxidase enzyme on GO surface to design a glucose biosensor system	(Sumaryada *et al.*, 2019)
Ag/AgCl internal electrode	α, β and γ-CD ionophores	Potentiometry	studying the interaction modes of the drug ion to ionophore by molecular docking	MOE 2010	Molecular docking of different ionophores for the determination of solifenacin in dosage form	(Eissa *et al.*, 2020)
Ag/AgCl internal electrode	β-CD, γ-CD and 4-tert-butyl calix [8] arene	Potentiometry	Molecular docking was implemented to compare the selectivity of each ionophore towards trazodone	MOE 2015	Design and optimization of a PVC based potentiometric sensor for trazodone quantitation	(Alrabiah, Aljohar, *et al.*, 2019)
Ag/AgCl internal electrode	α, β and γ-CD ionophores	Potentiometry	Investigating selectivity of different ionophores towards the drug ion preliminary to optimizing the most suitable candidate by experimental design	MOE 2014	Experimental design aided by molecular docking for design and optimization of benazepril PVC-base sensor	(Elsonbaty and Attala, 2021)
Graphite/ epoxy resin composite	cucurbit[6]uril hydrate	Potentiometry	Molecular docking simulation was implemented to illustrate the interaction mode of the host molecule into its guest	AutoDock Vina, PyMol 1.3 and HyperChem 7.5	Selective quantitation of atropine in hospital settings to assess its shelf life while decreasing its flushing rates and remedy cost	(Ferreira *et al.*, 2021)
Ag/AgCl internal electrode	α, β and γ-CD ionophores	Potentiometry	Molecular docking and dynamic simulation to investigate binding modes of the drug target to each of the ionophores	MOE 2015	Design of cyclodextrin potentiometric sensors for the selective quantitation of procainamide in dosage form	(Alrabiah, Homoda, *et al.*, 2019)

Table 2; Cont.

Unmodified GCE	-	Cyclic voltammetry	Molecular docking was utilized for the identification of drug binding modes to DNA, RNA and BSA	AutoDock v 4.2.6	Studying the interaction of both ciprofloxacin and sparfloxacin with different biological molecules using various analytical techniques	(Rajendiran and Suresh, 2018)
PVC-coated wire of platinumor glassy carbon	Undecyl calix[4] resorcinarene, tert butyl calix[6]arene hexaethyl ester and calix[6]arene hexaethyl ester	Potentiometry	Molecular docking was utilized for comparing selectivity of each ionophre twowards each drug ion	HyperChem v.6.0	Designing potentiometric sensors for the determination of some organic acids, beta blockers and other organic ionizable compounds	(Nagels, Bazylak and Zielinska, 2003)
Ag/AgCl internal electrode	β-CD, and calix [4], [6], and [8]arene	Potentiometry	Molecular docking was conducted to test the fitting of the guest molecule into each different ionophore host pocket	MOE 2015	Determination of levamisole in different livestock products using a PVC membrane based sensor	(Draz, Naguib and Saad, 2021)
Ag/AgCl internal electrode	α, β and γ-CD ionophores	Potentiometry	Investigating binding forces between the guest molecule and each different ionophore host to identify the optimum sensor	MOE 2014	Electrochemical quantitation of Amprolium Hydrochloride in poultry products to assess food safety	(Elsonbaty, Abdel-Raoof, *et al.*, 2021)
GCE/MW-CNT[b]	-	Differential pulse voltammetry and UV-vis spectrophotometry	Molecular docking was utilized to study the binding mode of the dsDNA to the 5-DDMP[c]	Schrodinger Small-Molecule Drug Discovery Suite	DNA based biosensor for the determination of the anticancer 5-DDMP	(Munir *et al.*, 2021)
Ag/AgCl internal electrode	α, β and γ-CD ionophores	Potentiometry	Molecular docking was applied to compare the selectivity of each ionophore towards mebeverine	MOE 2015	Design and fabrication of a PVC relied potentiometric electrodes for Mebeverine analysis	(Abdel-Raoof *et al.*, 2023)

[a] Graphene Oxide

[b] Glassy Carbon Electrode/ Multi Walled Carbon Nanotubes

[c] 5-(diethylamino)-2-((2,6-diethylphenylimino)methyl)phenol

Table 3: shows some of the recently reported research efforts that apply different computational approaches to optimize selective imprinted polymers for various compounds

Monomer	Template	Progenic solvent	Computational approach	Software	Ref.
AAM[a]	Hydrochlorothiazide	THF[d]	DFT calculations	Gaussian 09	(Barros, Custodio and Rath, 2016)
MAA[b]	Levetiracetam	Chloroform	Ab intio (HF)	MOE and Gaussian 09	(Attallah *et al.*, 2018)
MAA	Propranolol and dibenzylamine	Acetonitrile	DFT calculations	Gaussian 09	(Nagy-Szakolczai *et al.*, 2020)
MAA	Caffeine	Acetonitrile and toluene	DFT calculations	Gaussian 09	(Mehamod *et al.*, 2015)
HEMA[c]	Atorvastatin	Hydrogel solution	Lamarckian genetic algorithm	AutoDock Tools version 4.2.6 software	(Pereira-Da-mota *et al.*, 2021)

[a] Acrylamide

[b] Methacrylic acid

[c] 2-Hydroxyethyl methacrylate

[d] Tetrahydrofuran

9. Conclusion

The applications of MM and molecular simulations in the field of pharmaceutical analysis motivated the analyst thinking to the molecular level and aided in the understanding of different events regarding molecules' behavior on the molecular and quantum levels. This comprehensive review provides the reader with the basic knowledge required to understand various techniques and related activities based on MM. In addition, the current work provides some pharmaceutical analysis applications that use different MM approaches.

Conflict of Interest

Authors declare that they have no known competing financial interests or personal relationship that could have appeared to influence the work reported in this paper.

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