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MINI REVIEW

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

In-Silico Analytical Chemistry Contributions to Analytical and Bio-Analytical Applications in Spectroscopic and Chromatographic Techniques: Molecular, Mechanical and Quantum insights

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Abstract

In-silico analytical chemistry is an emerging field that tends to provide the analyst with a profound perspective on the molecular and sub-atomic interactions occurring on different analytical platforms upon encountering analytes in their various matrices. Investigating the interactions between the analyte and the analytical platforms became essential in their design and optimizing their analytical performance regarding selectivity and sensitivity. Molecular mechanical simulations were extensively utilized through various analytical techniques such as; spectroscopic, chromatographic and electro-analytical techniques and in the design of their related analytical platforms. Also, Quantum mechanical calculations were essentially useful in illustrating several analytical events as vertical electronic excitation transitions in UV and IR spectroscopy to interpret and predict their experimentally obtained spectra. Besides, the molecular reactivity of some molecules can be simulated towards complex formation which can be beneficial in comparing their stability and electro-paramagnetic properties. This review presents a critical discussion on some in-silico analytical chemistry principles, simulations and their related applications in the recently reported pharmaceutical research.

Keywords: In-silico analytical chemistry, Molecular mechanical simulations, Quantum mechanical simulations, Pharmaceutical analysis applications.

1. Introduction

Research in analytical chemistry has various aims with a great focus to control the quality levels imposed by the relevant authorities in both food and drug products. Various analytical methodologies are continuously developed to control many issues regarding human, animal and environmental activities. Some of these methodologies are controlling the active pharmaceutical ingredient levels in many different dosage forms (Stone *et al.*, 2010; Elsonbaty and Attala, 2021) others are detecting toxicants (Panter and James, 1990), residual drugs (Pan, Liu and Motto, 2011) and pesticides (LeDoux, 2011), pollutants in a vast array of foods and environmental resources (water, air and soil) (Milovanovic, 2007; Ceriani *et al.*, 2018).

The advancements in both computer hardware and software with collaboration between physical, chemical and mathematical knowledge molecular modeling software came to use in the research field (Sanz-Casado *et al.*, 2004). Molecular modeling is considered the first wave that smoothed for many further applications in computational chemistry (Gubbins and Moore, 2010). The ability to comprehend the molecules constituting our live in their 3D spatial environment empowered the analysts imagination to simulate their interactions in the in-silico mode.

Computational chemistry and simulations found their way in pharmaceutical analysis as tools of trade for their successful roles in eliminating waste in time, chemicals, and hazardous solvents in in-vitro experimentations. Computational simulations aided in aiding the laboratory in-vitro experimentations with in-silico environment simulations which is a time saver and environment friendly (Hanai, 2016). In-silico computational simulations are not per se a replacement for in-vitro experimentations but in the analytical methodology development phase it serves as a downsizing approach to reduce the required in-vitro trials to the most promising candidate conditions (solvents, pH, interacting molecules and ionophores). Docking (D) and molecular dynamic (MD) simulations are identified as the most popular computational approaches based on the typical laws of mechanics to simulate molecular interactions in vacuum and solvated environment without considering the surrounding electrons. Several spectroscopic, chromatographic and electrochemical analytical methodologies were optimized utilizing one or more of these approaches. Moreover, the study of binding and interaction energies and many other material characteristics on the subatomic level is made possible by involving the quantum mechanical (QM) laws of physics. QM calculations enabled us to investigate molecules on the sub atomic level to predict several energetic and vibrational behavior of the matter (Noé *et al.*, 2020).

Through this review article several molecular modeling concepts and techniques will be illustrated. Also, applications of different computational approaches will be presented through a presentation of the latest reported articles in different analytical activities.

1.1. In-silico analytical chemistry

The application of computational simulations besides experimental techniques to investigate and

interpret the interacting molecules in different analytical methodologies led to the development of the in-silico analytical chemistry concept (Hanai, 2016).

In-silico quantitative chemistry aims to present the molecular systems of the analytical experiment in a 3D-environment to study their intermolecular interactions with their developed analytical platforms to achieve several goals. The ultimate goal of the in-silico simulations in the analytical process is to efficiently optimize analytical platform under development to achieve optimal selectivity towards the analytes under investigation. This goal can only be achieved by using computer software loaded by several algorisms that retrieve the knowledge from the laws of mechanics in physics to simulate the random motion of the molecules which is classified under molecular mechanics simulations as D and MD.

Applying the equations of molecular mechanics (MM) in different computer software enabled the researchers to build several molecular models simulating their complex experimental analytical systems as a beginning to further study their motions and interactions (MD), and calculating many important chemical descriptors.

Every atom in the process is viewed by MM-based methodologies as an object whose position and movements are anticipated and stored in a sequence of data bundles called forcefield. When we run a simulation based on MM, the pre-stored data in the forcefield is summoned to control the motion of each single atom in the process. Alternatively, QM calculations can be designated as ab-intio processes because it does not require any pre-stored data of the chemical systems instead calculations are done from scratch. For example; density functional theory (DFT) based calculations are intended to find a suitable approximate solution of the Schrödinger equation of the electrons composing the system under investigation to calculate several energetic descriptors as; dipole moments, molecular orbital energies, bond dissociation energies, heat of formation of a complex, and the electrostatic potentials.

Unfortunately, these ab-intio methods are time consuming and require powerful hardware capabilities so they are only feasible for smaller systems. An alternative semi-empirical method as; the tight-binding method (DFTB) which emerged to compromise the time of calculations with the accuracy. These methods depend partially on forcefields so they are characterized by higher speed and the ability to handle larger systems. Unluckily, these methods suffer from the lowered accuracy and transferability (Bannwarth, Ehlert and Grimme, 2019).

In the later; sections tools of investigating molecular interactions as D and MD will be presented besides the most common QM approaches and finally applications of these approaches in spectroscopy and chromatographic separations will be discussed.

1.2. Molecular mechanical insights

To bring a molecule into the in-silico interface there are several ways. One way; if the molecule is very small and easy to draw then it is the preferred choice, most of the molecular modeling software contains a builder application which enables the users to draw structures directly into the software. This method will result in a 2-D structure that is needs to be

converted into 3-D. after 3-D rendering of the structure torsional angels require modifications to the correct values according to the loaded forcefield.

The loaded forcefield is applied to correct for bond angles, length, torsional angels and recalculates the total system potential energy after each deliberate change. These corrections result in the relaxation of the system total energy which is known as energy minimization (Lewis-Atwell, Townsend and Grayson, 2021). Forcefield equations are varied in agreement to the category of the atoms admitted to the system (Groenhof, 2013). For example; molecules as DNA, enzymes, RNA, proteins and aptamer are comprised of atoms that achieve more complex connections on subsequent levels to acquire their primary, secondary and tertiary structures which necessitated the requirement of a special set of forcefield as; AMBER, GROMOS, and CHARM families.

While other inorganic and organic small molecules utilizes much simpler forcefields as; PEF95SAC, MMFF, and TAFF (González, 2011). There is also the universal forcefield (UFF), whose parameterization is much more flexible and can be used with nearly all atoms defined in the periodic table. However, it is thought of as a confined category of forcefields because it designates the molecules in the system as non-reactive, making it impossible to use it in simulations of reactive molecules. Recently, modifications to the UFF were established to involve the forcefield in molecular reactive simulations involving bonds breaking and formations (Jaillet, Artemova and Redon, 2017).

1.2.1. Molecular conformations and energy minima

Obtaining the lowest energy conformer of the investigated molecule or molecules is necessary for running simulations based on MM. The lowest potential energy conformer represents the most stable one, increasing the odds of its existence in the native form to provide some realism to the MM simulation (Marinova *et al.*, 2021; Soulère, 2021). Most of MM based simulations require preparatory steps before being run as reduction of the system's potential energy. The minimization process results in conformers of lowered potential energy but not always the lowest energy conformer of the investigated molecules. This is due to the technique by which minimization is engaged which is not capable of passing through some energy barriers and ends up with a regional energy minimum conformer. Alternatively, the lowest energy conformer may lay beyond that at a universal energy minimum which necessitates passing through an energy barrier which is not feasible for the MM software and requires special approach as shown in **Figure 1**.

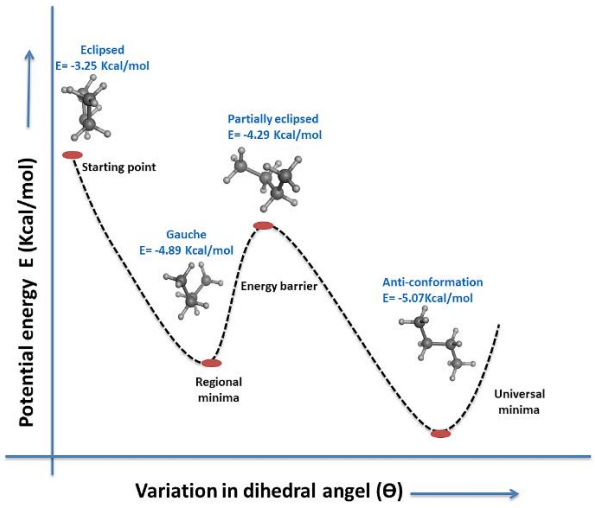

Figure 1: The difference between the local and global energy minima and the stable conformer

Running a conformational search means performing deliberate changes in the bond angels and lengths of the molecule(s) and recording the overall energy of the system at each step. To do that several techniques are available as; Monte-Carlo (MC) simulations, stepwise bond rotation and Low mode MD which is considered as the most abundant due to its speed and accuracy.

1.2.2. Molecular mechanical simulations of non-covalent interactions

Non-covalent interactions (NCI) are the interactions occurring among molecules in a certain chemical system. They can be sub-categorized to different types according to the dominating forces in the interaction. Examples of NCI interactions that should be found in any chemical system are hydrogen bonds and van der Waals forces (H-arene, arene-arene, and arene-cation). A variety of MM simulations with different objectives were required to examine the types and abundance of these NCIs in different chemical systems. Sometimes the main goal of the study is investigating the possibility of fitting a series of smaller molecules into the pockets of a macromolecule so D is the most suitable MM tool for that task. Other times the interaction of small molecules with surrounding molecules is the main goal of the study then MD is the most reasonable MM simulation choice. Comparing the binding energies and abundance of the investigated NCI over different designs of an analytical platform provide the analyst with a conclusive overview about the most suitable conditions to optimize the design of a platform with ultimate analytical performance.

1.2.3. Molecular docking (D)

D is investigating the degree of fitting between two or more molecules (a drug and a macromolecular target) by estimating the generated complex regarding its stability, as shown in **Figure 2**. It is considered one of the most common MM based computational simulations which originated at first for virtual screening of molecular libraries against potential biological targets. Recently, D was intensively applied in analytical chemistry research to investigate several issues regarding analytical methodologies development. The most frequent application of D in-silico analytical chemistry is the evaluation of the analytical platform's selectivity to the target analyte without the inclusion of other potential interfering agents. The earliest task in D process is the binding site perimeter identification which can be achieved using another assessing software as Q-site finder (Laurie and Jackson, 2005). The grid forcefield protocol is used by this software to map the potential binding site interactions (Carosati, Sciabola and Cruciani, 2004).

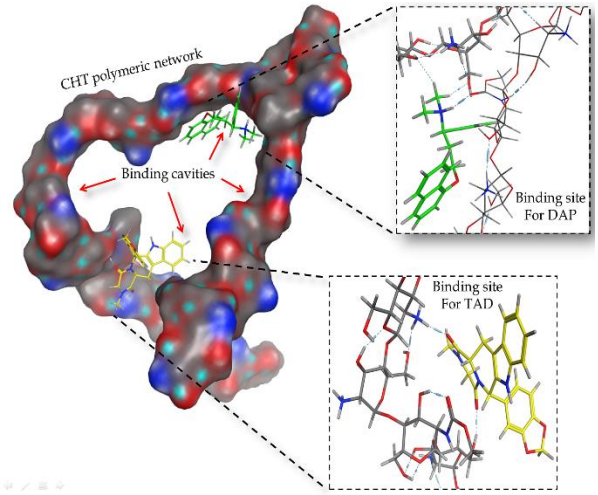

Figure 2: Fitting of both tadalafil (yellow) and dapoxetine (green) to chitosan (CHT) polymeric chains pocket to form a stable complex.

D can be divided into three levels depending on the degree of the flexibility obtained in the sample methodology (Jones *et al.*, 1997; Sierra *et al.*, 2011). In one level, both the macromolecular target and its ligand can be rigidified and a simple fitting is accomplished, the ligand conformation is just varied to suit the rigid target, or both the macromolecular target and its ligand conformations are changed concurrently for optimal fitting. Although flexible docking is thought to be the most accurate method, it has the drawback of requiring a lot of simulation time and computer power (Vieira, Magalhaes and Sousa, 2019).

The poses that results are then arranged using a suitable scoring algorithm based on how well they fit and bind to the macromolecular target. Consensus scoring, which consists of several parallel scoring procedures can do rescoring to provide more accurate scores to avoid decoys.

1.2.4. MD simulations

In order to investigate any potential interactions with their surrounding environment, MD is another MM-based methodology that replicates the random motion of atoms in the simulation environment by implementing deliberate changes to their bond angles, lengths, and torsional angles in accordance with the MM equations (Labute, 2010; Patrick, 2013).

Several motion algorisms are engaged in MD simulations which are accountable for detecting atoms velocities, positions and the affecting forces. One of the most prevalent and precise motion algorithms is the Nose-Poincare Andersen (NPA) equation (Sturgeon and Laird, 2000).

The goals of performing MD simulations are various, one objective is to study the possibility of interactions between molecules which are small enough to have a specified binding site and fail to be studied by the regular D simulation as shown in **Figure 3** (Elgazzar *et al.*, 2022). Another objective is to test the stability of interaction between any interacting molecules which is also considered as a validation for the highly scored docking poses to identify any possible decoys in the D simulation (Ma *et al.*, 2020). Also, the investigation of the effect of solvated environment on the binding between molecules whose simulation is not possible by D can be achieved in solvated modes of MD.

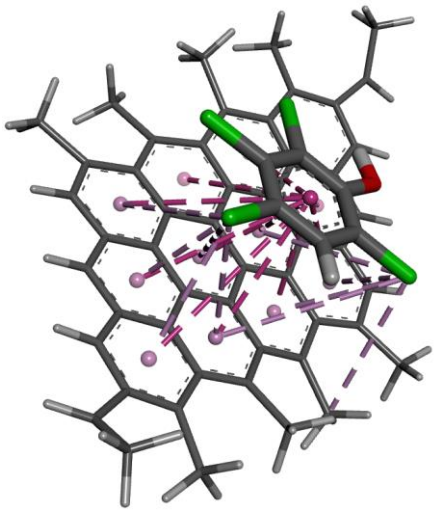

Figure 3: The 3-D structure of the complex between trichlorophenol and graphite stationary phase from MD simulation trajectories showing multiple pi-alkyl interactions with the stationary phase.

1.2.5. Flexible molecular similarity screening

The pharmaceutical compounds arsenal is rich in many different compounds; sometimes there are similarities between these compounds that may be

beneficial in many applications in chemical synthesis and analysis.

Dummy molecular imprinting (DMIP) is a molecular imprinting technique that made use of the molecular similarity between compounds. In the DMIP the original target analyte is not used in the imprinting process per se but another molecule of a similar scaffold is used instead which is called a dummy molecule. After that, the synthesized DMIP is ready to bind to the target analyte. The reason behind the success of such an imprinting technique is the scaffold similarity between two unrelated molecules (the analyte and the dummy molecules) which can be detected by screening the molecular libraries regarding the calculated similarity index. For example; a DMIP polymer for acrylamide was synthesized utilizing Propionamide as a dummy template **Figure 4**. The reasons for utilizing a Dummy template is the elevated toxicity of the original target (acrylamide) and its ability to be covalently attached to the cross linker during radical polymerization process which hinders it removal after the completeness of the imprinting process and causes failure to the imprinting process (Bagheri *et al.*, 2019; Chen *et al.*, 2020).

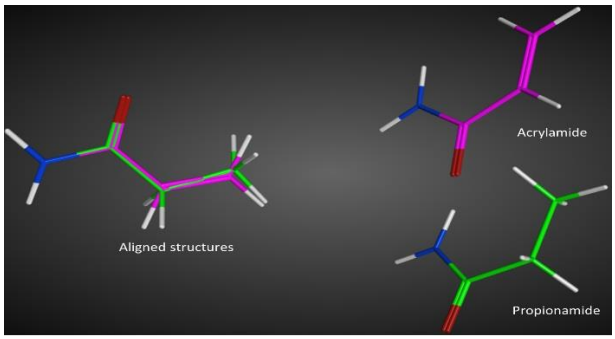

Figure 4: A flexible alignment representation performed between acrylamide and its dummy template propionamide to observe their structural scaffold resemblance.

1.2.6. QM calculations and their applications in-silico analytical activities

Quantum mechanics (QM), as mentioned earlier, are based on applying the quantum physics laws on the subatomic particles like electrons to study their inter-particulate interaction with each other and the surrounding nuclei in a molecule which is reflected on many molecular properties. Therefore, studying the behavior of the electrons making up a molecule can provide us information about its structure as; atomic positions, lattice constants in crystalline substances, bond character, charge distribution, and bond orders. Furthermore, it gives information about molecular energies such as; the total or minimum energy of the system, solvation energy for a substance in different solvents, binding and interaction energies between molecules, and relative energies between phases or compositions (Laird, Ross and Ziegler, 1996; Pahlavani, 2012).

The electrons are considered to have the characteristics of waves in addition to being a particle; thus, the mathematical equations derived by Schrödinger are dubbed wave equations (Luis Levada *et al.*, 2018). The permitted energy state of any system is precisely determined by QM calculations, which are based on approximating a suitable solution to the Schrödinger equation to determine the system's wave function. Finding the exact solution of the Schrödinger equation is only possible for one electron system as a hydrogen atom. However, the situation is further complicated with (n) electrons systems, which is known as the many-body enigma (Lee and Yang, 1957; Szasz, 1963). An approximation is needed for such electronic systems to compensate for their complexity and find an approximate solution for their wave functions.

The earliest attempts for an approximation were set by Born and Oppenheimer (BO) (McNab, 2016) when they assumed that electrons movement is very fast so that nuclei are considered motionless, which allows discriminating energy of nucleus from the electronic energy. Also, the electronic movement is deemed independent, with the effect of other electrons, and nuclei are considered as an average. The BO approximation could isolate the electronic terms from the Schrödinger equation to obtain an approximate solution for the system's electronic energy. Still, the major drawback of this approximation is that when there is more than one electron in the system (many-body system), the wave function will be of 3N variables where (N) is the number of electrons. The number 3 correlates to the spatial positioning of the electron in the three dimensions x, y, and z. the considerable number of variables in this approach made it impractical to be used for many-body systems.

The Hartree-Folk (HF) approximation (Saha and Sengupta, 1980) is another approximation to the many-body enigma; it assumes the many-body system is composed of many single body systems where the effect of sum electron-electron interactions is compensated by an average effective field that is iteratively refined. Each electron (single body) in the system sees the impact of the remaining other electrons and the nuclei as an averaged potential, and from that comes the term self-consistent field (SCF). HF theorem is the most basic ab initio approach and one of the initial principles of quantum-chemical theories derived directly from the Schrodinger-wave equation without any practical considerations.

Afterward, the Hohenberg-Kohn (HK) theorem (Englisch and Englisch, 1983) came through with a more pragmatic solution of the many-body system, assuming the actual ground state energy of the system is provided by a distinctive function of the electron density paving the way to the most common ab initio technique which is known nowadays as; DFT. DFT does not calculate the conventional wave function of the system like the earlier approximations, but instead, it derives the electronic density as a function of the electronic energy. The way DFT works made any many-body system expressed by its electronic density **Figure 5,** a function of the electron in the space (x, y, and z) and time. Consequently, DFT compensates for the complexity of the many-electron systems by decreasing the degrees of freedom in any system for the sake of computational feasibility (Chen, Xu and Chen, 2020).

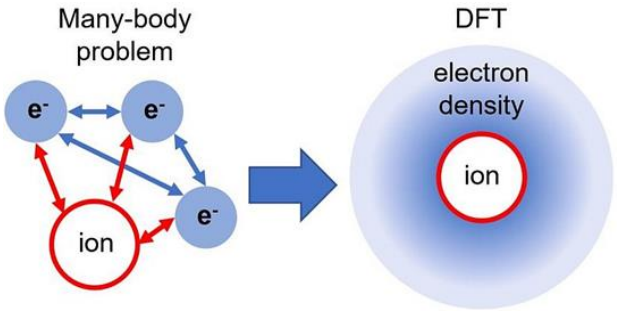

Figure 5: An illustrative scheme representing the main concept of the density functional theory

Another subtype of QM calculations is the semi-empirical methods that simplify the utilized equations to facilitate and reduce the required computational work. Semi-empirical approaches rely on the same theoretical foundation as ab initio MO theory; however, they minimize computing costs by ignoring or approximating time-consuming two-electron integrals. These integrals can be fitted to

experimental data or replaced with analytical but imprecise formulas. In contrast to ab initio approaches, semi-empirical calculations necessitate the parameterization of all constituents in the molecular system relying on force field pre-stored data (Orville-Thomas, 1986).

The optimization and design of specific MIP materials was a perfect example of the many practical applications of QM computations in pharmaceutical analytical research. These MIP are then used as a solid phase for the selective extraction of a broad category of pharmaceutical compounds preliminary to their analysis using different analytical platforms (Bagdžiūnas, 2020; Suryana *et al.*, 2021). Also, QM calculations provide a way to predict UV and NMR spectra of interacting compounds in various solvents(Chen *et al.*, 2014; Altaf, Kausar and Badshah, 2018) and many wide applications in the pharmaceutical field (Mazurek, Szeleszczuk and Pisklak, 2020).

1.2.7. Analytical methodologies applying different computational approaches

1.2.7.1. Aptamer based analytical techniques

Aptamers are single stranded DNA or RNA molecules with the tendency to bind to a wide range of targets ranging from small to macromolecular targets (proteins, cells, viruses and nucleic acid sequences). Aptamers are superior to other traditional bioanalytical platforms (e.g. antibodies) regarding their lowered synthesis cost and their wide thermal and pH stabilities (Ruscito and DeRosa, 2016).

The incorporation of aptamers in biosensors (aptasensors) had the advantages of enhancing the selectivity and sensitivity of the designed analytical platforms due to their unique structural properties. The computational prediction of the sequences comprising the aptasensors depends on the evolution of the appropriate sequences from random nucleic acid libraries based on those sequences whose secondary structures are capable of binding efficiently to the predetermined target molecules. The process of sequence selection is designated the systematic evolution of ligands by exponential enrichment (SELEX) (Liu *et al.*, 2020).

SELEX is an experimental protocol that decides the sequences of the highest affinity towards the selected analyte (Sefah *et al.*, 2010). In this process the desired target is fixed onto a solid support and the nucleic acid library is passed through in several repetitive cycles of binding-wash-release infiltrated by amplification of each yield by Polymerase chain reaction (PCR) (Iliuk, Hu and Tao, 2011). The potential sequences extracted from the SELEX process can be numerous which evoked the development of computer aided approaches that support the selection and optimally design the aptamer sequence that achieve the desired affinity and selectivity towards its targets (Biosensors *et al.*, 2022).

After SELEX process the resulting sequences candidates are 3-D rendered into their final tertiary structures then are tested regarding their affinity and selectivity by various computational approaches as D and MD simulations. The binding energies and their poses are tested in D simulations while the stability of these interactions is tested under MD simulations. Comparisons of the stability and the binding energies are held for the different candidate sequences to extract the most promising candidate for the aptasensor. Aptamer nucleotide mutations can be

performed as an optimization step to enhance the binding of the aptamer towards its target by replacing some weakly interacting nucleotides with those of higher binding potential as inferred from the data gathered from prior MD simulations (Housaindokht, Bozorgmehr and Bahrololoom, 2008).

Aptasensors have a wide range of applications in various analytical and bio-analytical techniques, **Table (1)** summarize some of these recently reported researches involving aptamers as bio-analytical platforms to their sensors.

Table 1: computationally designed aptasensors utilized in various analytical applications

Target analyte	Aptasensor	Computational approach	Ref.
Ofloxacin	72-mer ssDNA taged with fluorescene and the fluorescence intensity was proportional to the bound ofloxacin content based on Fluorescence resonance energy transfer (FRET) concept	Molecular Docking	(Aissa et al., 2020)
Angiotensin II	ssDNA optimized to interact with the target followed by surface plasmon resonance spectroscopic determination of the peptide target	Molecular Docking	(Heiat et al., 2016)
Tobramycin	A liquid crystal based aptasensor was designed to bind and detect tobramycin based on polarized optical microscopy	MD	(Zahraee et al., 2022)
Tetracyclin	40-mer ssDNA aptamer coated Au-nanoparticles for the colorimetric deterction of tetracyclin in honey samples	Molecular Docking	(Wang et al., 2016)
Okadaic acid	A FRET based fluorescent aptasensor was designed for the fluorescence determination of the acid in shellfish	Molecular Docking	(Yan et al., 2022)

1.2.7.2. Spectroscopic methods

In-silico analytical applications in spectroscopic techniques aim to study the excitation behavior of various compounds under electromagnetic ration exposure and predict their resulting transition states (Spectra) or investigate the binding between the analyte in the sample and another bound macromolecule in the matrix as; hemoglobin, serum albumin or nucleic acid molecules.

Besides, computational applications were utilized to interpret the effect of some added compounds (fluorescence enhancers and charge transfer agents) on the analyte interaction with the electromagnetic radiation (absorption or emission mode).

Tables 2 and 3 summarize the most recently reported spectroscopic techniques applying versatile computer aided methodologies to interpret the obtained experimental data.

Table 2: Applying MD and docking simulations to some reported spectroscopic techniques

Pharmaceutical compound	Macromolecular target	Computational approach	Software	Ref.
Roflumilast	BSA[1]	Molecular docking	MOE	(Wani *et al.*, 2018)
Alprazolam, And Fluoxetine Hydrochloride	HSA[2]	Molecular docking	AutoDock	(Dangkoob *et al.*, 2015)
Ledipasvir, And Sofosbuvir	2,3-dichloro-5,6-dicyano-1,4-benzoquinone, and chloranilic acid	MD	MOE	(Elsonbaty *et al.*, 2022)
Astaxanthin and 5-Fluorouracil	Whey protein of β-lactoglobulin	Molecular docking	MOE	(Gholami *et al.*, 2021)
Voriconazole	2-O-methyl-beta-cyclodextrin	Molecular docking	AutoDock	(Miletic *et al.*, 2013)
Levamlodipine	Hemoglobin	Molecular docking	AutoDock	(Xu *et al.*, 2019)
Ciprofloxacin and Sparfloxacin	DNA, RNA, and BSA	Molecular docking	AutoDock	(Rajendiran and Suresh, 2018)
Dimetridazole	HSA	Molecular docking	Surflex-Dock	(Zhang *et al.*, 2013)
Coptisine	ctDNA[3]	Molecular docking	Surflex-Dock	(Mi *et al.*, 2015)
Amlodipine and Celecoxib	Sodium dodecyl sulfate	Molecular docking	MOE	(Attala *et al.*, 2020)
Omeprazole and Esomeprazole	HSA	Molecular docking	AutoDock	(Pawar *et al.*, 2017)

[1] Bovine Serum Albumin; [2] Human Serum Albumin; [3]Circulating tumor DNA

Table 3: applying various QM calculations to some reported spectroscopic techniques

Pharmaceutical compound	Interacting molecules	Computational approach	Software	Ref.
Gliclazide	2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) & tetracyanoethylene (TCNE)	TD-DFT/B3LYP	Gaussian 09	(Soltani *et al.*, 2019)
Amphetamine	$Al_{24}N_{24}$ nanocluster	DFT/TD-DFT/ B3LYP	GAMESS	(Nayini *et al.*, 2020)
pyrene-sulfathiazole-based compounds	–	TD-DFT/B3LYP	Gaussian 09	(Erdoğan and Serdaroğlu, 2021)
Methotrexate	tetramethylsilane	DFT/B3LYP	Gaussian 03	(Ayyappan *et al.*, 2010)

1.2.7.3. Chromatographic methods

Chromatographic analysis is the most frequent and robust analytical technique for the separation and analysis of different compound mixtures in different matrices preliminary to the quantitative determination of these components. Computational modeling of different stationary phases besides the simulation of different interacting compounds is performed to predict the interactive nature of these compounds and their separation order. Hanai presented several models of different stationary phases including silica-based phases, molecular docking simulation of various organic compounds on these phases illustrating their interaction behavior besides various energetic parameters calculations that fully describe the retention behavior of different array of compounds on the molecular level (Carbon, 2014; Graphite and Phases, 2014). Also, in-silico applications were extended towards the separation of chiral compounds using polysaccharide based stationary phases. In such cases, D was performed for the estimation of the elution order and binding nature for each chiral compound. Tailor made stationary phases as those comprising a molecularly imprinted polymer selective to one analyte in the mixture were utilized for the selective extraction and quantitation of an analyte in complex matrices. The design and synthesis of these selective polymers is guided by several computational activities for example; D, MD, and QM calculations that decide the conditions applied through chemical synthesis for optimal selectivity to the target analyte. Some other activities were devoted for the investigation of the liability of several drug compounds, impurities, and drug related substances to interact to specific enzymes or receptors that may cause toxicities to the consuming organism. **Table 4** summarizes some of the recently reported separative techniques making use of computational activities.

1.2.7.4. Quantitative structure retention relationship in chromatography

The in-silico modeling of chemical systems became possible by designing models describing and also predicting a wide array of physicochemical features. Quantitative structure property relationship (QSPR) is a hybrid computational/chemometric approach that aims to collect a bundle of chemical descriptors related to a set of compounds to describe their behavior in a defined chemical environment and also predict the behavior of other new compounds (Seybold, 2012). Applying the concepts of QSPR in the field of analytical chemistry led to the development of the quantitative structure retention relationship (QSRR) to computationally model the chromatographic experiments based on MM chemical descriptors. The QSRR models aim to design mathematical models that describe the retention behavior of compounds towards various stationary / mobile phases' combinations as in **Figure 6**. QSRR was extensively applied in the screening of a wide array of compounds as metabolites and doping agents with the purpose of revealing their identity based on their retention behavior on a specific chromatographic system (Goryński *et al.*, 2013). In another context, two separate QSRR predictive models describing the retention factors of a wide series of quinolones and sulfonamides to facilitate the prediction their identity (Fouad *et al.*, 2022). **Table 5** summarizes some of the recent research activities in analysis involving QSRR models into their chromatographic methodologies.

Table 4: Recently reported chromatographic techniques applying various computational approaches for the determination of different pharmaceutical compounds

Pharmaceutical compound	Macromolecular target	Computational approach	Software	Ref.
Metformin, Canagliflozin, and Dapagliflozin	Amylose tris (3-chloro-5methylphenyl carbamate)	Molecular docking	Schrödinger suite program	(Pandya, Shah and Shrivastav, 2020)
Colchicine	Tubulin	Molecular docking	MOE	(Abdelwahab, et al., 2020)
Anagliptin	Human dipeptidyl peptidase IV	Molecular docking	Schrödinger suite program	(Baira *et al.*, 2018)
4-Methyl acetophenone	Human carbonyl reeducates complexed with hydroxy-PP	Molecular docking	MOE	(Attala *et al.*, 2021)
Paroxetine hydrochloride	Cellulose tris (3-chloro-4-methylphenylcarbamate	Molecular docking	AutoDock	(Qiu *et al.*, 2022)
Levetiracetam	MAA	Stochastic sampling and ab-intio (HF)	MOE	(Attallah *et al.*, 2018)
Anticonvulsant compounds	3,5-dimethylphenylcarbamate derivative of cellulose chiral stationary phase	Semi-emprical, Molecular dynamic / docking	Gaussian 09, and AutoDock	(Barfeii, Garkani-Nejad et al, 2019)

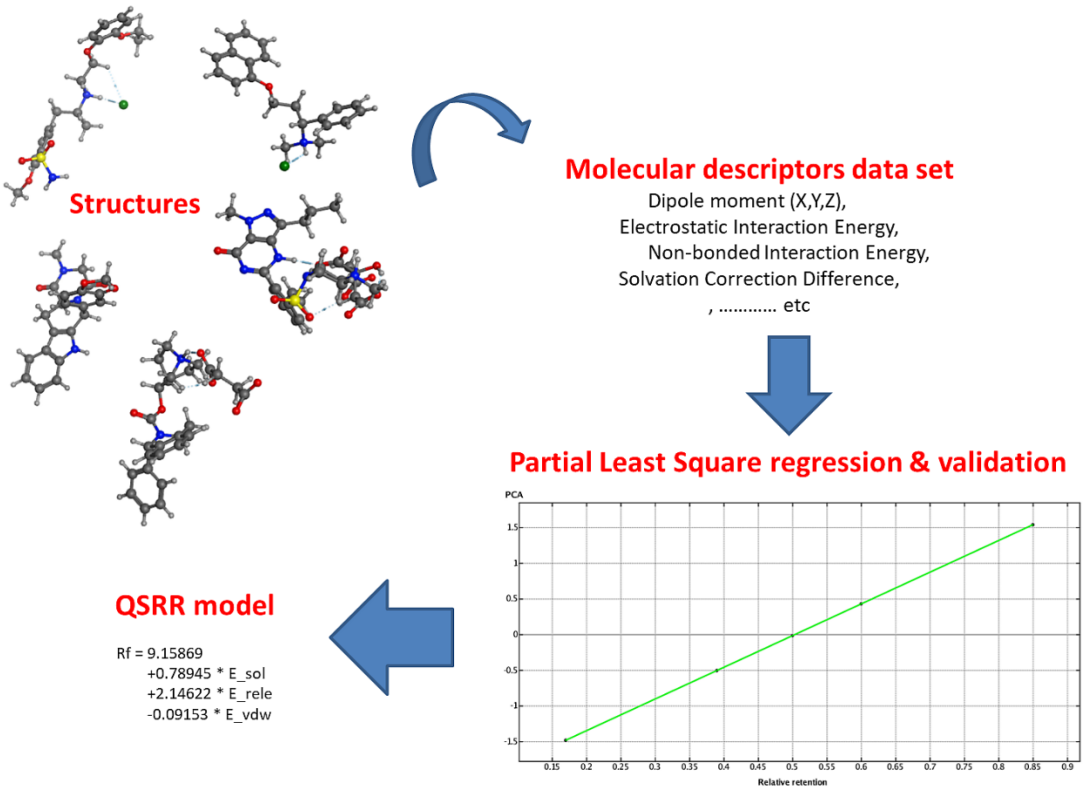

Figure 6: schematic representation of the workflow followed in building predictive QSRR models

Table 5: Some recently reported chromatographic techniques involving different algorithms to build predictive QSRR models for a wide array of pharmaceutical compounds

Pharmaceutical compounds	Chromatographic technique	Stationary phase	Mobile phase	Algorithm	Ref.
2-(dimethyl amino)ethyl esters (DPCA) and 2-pyrrolidine-1-yl-ethyl esters of alkoxyphenylcarbamic acid [1]	LC/UV diode array detector	YMC-Triart C18 (150 × 4.6 mm; 5 μm) Nucleodur Sphinx C18 (150 × 4.6 mm; 5 μm)	ammonium acetate (pH = 7.1)/ methanol (65/35 v/v) ammonium acetate (pH = 7.1)/ acetonitrile (65/35 v/v)	Artificial neural networks	(Ranušová *et al.*, 2021)
Polypropylene, LDPE, HDPE, PVC, PET, and PS [2].	LC/MS-(TOF) [3]	C18 - phenylhexyl, pentafluorophenyl, and cyano (CN) columns	methanol/acetonitrile 50/50 (v/v) and ammonium acetate	Machine learning random forest and support vector machines	(Xu *et al.*, 2023)
62 pain killer drugs as; haloperidol, haloxazolam, alprazolam, …..etc	LC/UV	FineSIL C18T (25 cm × 4.0 mm i.d.)	HClO4+NaClO4/ acetonitrile (70/30) (v/v)	Stepwise model building techniques for regression designs	(Ghasemi and Saaidpour, 2009)
43 pesticides as; fenoxycarb, metolachlor, cyprodinil, …… etc	LC-MS-MS	Atlantis, C 18 column, (150 mm×2.1 mm, 3 μm)	N/A [4]	Genetic algorithm and artificial neural networks	(Khodadoust, 2012)
17α-picolyl and 17(E)-picolinylidene based anticancer drugs.	LC/UV diode array detector	ZORBAX Eclipse XDB-C18 column (4.6 × 50 mm, 1.8 μm)	Methanol/water mixtures (70/30) and (90/10) (v/v)	Artificial neural networks regression	(Kovačević *et al.*, 2016)

[1] The mentioned series of compounds are medically important as potential anesthetic reagents; [2] These abbreviations point to; low-density polyethylene, high-density polyethylene, polyvinyl chloride, polyethylene terephthalate, and polystyrene, respectively; [3] (TOF); time of flight mass analyzer; [4] Non-available data

2. Conclusion

Applying the theories of QM and MM molecular simulations to the realm of analytical analysis is the goal of in-silico analytical chemistry. The results from the experimental investigation can be illustrated and interpreted using such simulations. The knowledge needed to examine the many methodologies and associated activities based on both MM and QM simulations is delivered to the reader by this in-depth critical review. Additionally, the current work offers certain computationally based pharmaceutical analysis applications in the disciplines of spectroscopy and chromatography.

Conflict of Interest

Authors declare that they have no known competing financial interests or personal relationship that could

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