Zahra Khoshbin ORCID iD: 0000-0002-6939-2036

Recent Advances in Computational Methods for Biosensor Design

Zahra Khoshbin[a,*], Mohammad Reza Housaindokht[a,*], Mohammad Izadyar[a], Mohammad Reza Bozorgmehr[b], Asma Verdian[c]

[a]Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran

[b]Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran

[c]Department of Food Safety and Quality Control, Research Institute of Food Science and Technology (RIFST), Mashhad, Iran

Abstract

Biosensors are analytical tools with a great application in healthcare, food quality control, and environmental monitoring. They are of considerable interest to be designed by using cost-effective and efficient approaches. Designing biosensors with improved functionality or application in new target detection has been converted to a fast-growing field of biomedicine and biotechnology branches. Experimental efforts have led to valuable successes in the field of biosensor design; however, some deficiencies restrict their utilization for this purpose. Computational design of biosensors is introduced as a promising key to eliminate the gap. A set of the reliable structure prediction of the biosensor segments, their stability, and accurate descriptors

* Corresponding authors:

Prof. Mohammad Reza Housaindokht; E-mail address: housain@um.ac.ir, Tel.: +985138805550.

Dr. Zahra Khoshbin; E-mail address: Z.Khoshbin@yahoo.com, Zahra.khoshbin@mail.um.ac.ir, Tel.: +985138804082.

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of molecular interactions are required to computationally design of biosensors. In this review, we provide a comprehensive insight into the progress of computational methods to guide the design and development of biosensors, including molecular dynamics (MD) simulation, quantum mechanics (QM) calculations, molecular docking, virtual screening, and a combination of them as the hybrid methodologies. With relying on the recent advances in the computational methods, an opportunity is emerged for them to be a complementary or an alternative to the experimental methods in the field of biosensor design.

Keywords: Aptasensor; Biosensor design; MD simulation; QM calculation; Virtual screening.

1. Introduction

Biosensors are defined as the analytical tools that have an extensive application in the diverse scientific fields, such as healthcare, clinical diagnostics, pharmaceuticals, food quality control, and environmental monitoring (Bahadır & Sezgintürk, 2015; Cao, Sun, & Grattan, 2014; Kaçar, Erden, & Kılıç, 2017; Mundaca-Uribe et al., 2017). A biosensor comprises three basic components, including the bioreceptor, transducer, and signal processing segments. Bioreceptors are generally included enzymes, proteins, peptides, antibodies, nucleic acids, and aptamers that capture their specific target. The target interaction with its bioreceptor induces the biochemical signals that are converted into a detectable electrical signal via transducer. The electrical signal is amplified and converted to a measurable signal by using a signal processing system (Tereshchenko et al., 2016).

The enzyme-based biosensors are considered as one of the most applicable analytical tools with the ability to recognize the diverse targets through the catalytic alteration of the intended target by the enzyme or the inhibition of the enzyme catalytic activity by the target (Songa & Okonkwo, 2016; Q. Wang et al., 2016). The enzyme-based biosensors have the unique advantages, such as high specificity, good selectivity, reusability, low-cost, facile preparation, and easy miniaturization. However, they suffer from some deficiencies, including instability, limited lifetime, irretrievable enzyme denaturation under the harsh experimental conditions, difficulties in storage, susceptibility to the sample matrix, and sensitivity to the

temperature and pH variations (Ge, Wang, Hou, & Li, 2016; Y. Han, Zheng, & Dong, 2013; Othman, Karimi, & Andreescu, 2016; Rodríguez-Delgado et al., 2015; Syshchyk, Skryshevsky, Soldatkin, & Soldatkin, 2015).

Proteins and peptides are remarkable biomolecules to develop the biosensors, because of their tremendous ability to form the diverse tertiary structures through the interaction with the different targets. Peptide-based biosensors utilize peptides with wonderful water solubility and biological compatibility, which enable them to detect the various targets. Nevertheless, some deficiencies restrict their utilization, such as low durability, limited sensitivity, and degradation under the harsh conditions (Neupane & Lee, 2013; J. Park, In, & Lee, 2015; Puiu & Bala, 2018; Su, Cho, Nam, Choe, & Lee, 2013). The antibody-based biosensors are utilized commonly to detect the diverse targets with the high sensitivity. Unfortunately, antibodies are susceptible to the temperature changes that makes them prone to the degradation and denaturation. Besides, the antibodies possess high molecular weight causing their synthesis and modification to be time-consuming processes. The laboratory animals are required to generate the antibodies that increase their production cost. So, it is an essential need to provide the condition for reducing the time and cost for the generation of the antibody-based biosensors (Y. S. Kim, Raston, & Gu, 2016; M. K. Park et al., 2013; Zhou, Huang, Ding, & Liu, 2014).

As the potential alternative to the antibodies, aptamers are applied extremely to design the aptamer-based biosensors (aptasensors). Aptamers are known as the synthetic single strands of oligonucleotides that possess a great affinity to the vast range of targets, including the small size species e.g. metal ions and the large biomolecules e.g. proteins (Y. Chen et al., 2019; Kanwar, Roy, & Kanwar, 2011; Zhao, Zhuo, Chai, & Yuan, 2015). A comparison with antibodies illustrates that aptamers possess some remarkable advantages that turn them to the impressive recognition parts. For example, the aptamers are synthesized through an in-vitro process with no need for any laboratory animals. A low molecular weight of aptamers makes their production and modification processes to be facile. Aptamers can sustain their durability over the broad pH and temperature ranges. Frequently, aptamers can refold to their native structures after changing the denaturing conditions to the natural ones. Besides, they can maintain their functionality under some denaturing conditions,

such as urine (M. Jafari et al., 2018; Khoshbin, Housaindokht, Verdian, & Bozorgmehr, 2018; Khoshbin, Verdian, Housaindokht, Izadyar, & Rouhbakhsh, 2018; Y. Li, Sun, & Zhao, 2018; J. Liu et al., 2014; Verdian, 2018).

Aptamers are obtained from the random oligonucleotide libraries through the Systematic Evolution of Ligands by the Exponential Enrichment (SELEX) process including the repetitive processes of binding, selection, and amplification of oligonucleotides (Bai, Wang, & Zhao, 2017; Bostan et al., 2017; M. Jafari et al., 2018; Khoshbin, Housaindokht, Izadyar, Verdian, & Bozorgmehr, 2019; S.-e. Wang & Si, 2013). The SELEX technique is applied extensively as an efficient method to generate diverse aptamers; however, some deficiencies restrict its application. For instance, the production, selection, and amplification processes of oligonucleotides require several weeks or some months that make the processes to be time-consuming. Moreover, a large number of the selection and purification rounds causes that the SELEX method to be a complicated and costly approach. In some cases, the post-SELEX modifications are required to improve the SELEX efficiency. Besides, a large number of target species are needed to obtain an efficient SELEX outcome. Type and purity of the targets are also effective subjects on the SELEX outcome. The accuracy of the method is dependent on the election of the initial libraries so that the incomplete libraries cause the loss of the aptamers with the highest target specificity (Blind & Blank, 2015; Darmostuk, Rimpelova, Gbelcova, & Ruml, 2015; D.-K. Yang, Chen, Lee, Hsu, & Chen, 2014; Yazdian-Robati et al., 2019; C. Zhang et al., 2014).

Consequently, the experimentally design of the biosensors and study of their functionality encounter some difficulties. Moreover, the various experimental techniques accompanied by the biosensors to produce a measurable signal as a sign for the presence of the target. Some of the techniques are surface plasmon resonance (SPR), fluorescence resonance energy transfer (FRET), small-angle X-ray scattering (SAXS), electrochemiluminescence (ECL), surface-enhanced Raman spectroscopy (SERS), and photoelectrochemical (PEC) that enhance the cost of the biosensor fabrication (Acquah, Danquah, Yon, Sidhu, & Ongkudon, 2015; Grytz, Marko, Cekan, Sigurdsson, & Prisner, 2016; Kikuchi, Sakai, Teshima, Nemoto, & Akiyama, 2017; Szameit et al., 2016).

Over the past decade, liquid crystals (LCs) have been extremely applied in the field of the material, chemical, and biological sciences, because of their unique physical and optical advantages, such as long-range orientational order, elastic strain, responsiveness to external stimuli, sensitive orientation response, and optical anisotropy (Noonan, Roberts, & Schwartz, 2013; Qi, Hu, Kang, & Yu, 2019). Structurally, LCs are aromatic molecules containing some side chains and terminal groups with a decisive role in their physical and optical properties. The weak intermolecular interactions between the LCs cause that their orientation order to be sensitive to the partial chemical or physical changes at the interface. Besides, their orientation response can be amplified to their bulk. Based on their unique long-range orientation and optical anisotropy, the disturbed LC orientations can be magnified and converted into the optical signals, and finally, can be in situ visualized by using polarized optical microscopy (POM) (Hussain, Pina, & Roque, 2009; Jang et al., 2005; Z. Rouhbakhsh, A. Verdian, & G. Rajabzadeh, 2020; Y. Wang, Hu, Tian, Gao, & Yu, 2016). Hence, LCs can be efficient for the naked-eye target detection with no need for the complicated laboratory-based equipment. Compared to the analytical methods, the LC-based biosensors are label-free and portable that converts them to the well-suited monitoring assays (H. Kim, An, & Jang, 2018; Verdian, Rouhbakhsh, & Fooladi, 2020; Y. Wang, B. Wang, X. Xiong, & S. Deng, 2019). Recently, the LC-based biosensors have gained the great attention as the new candidates for the optical target monitoring, due to the special properties including simple fabrication, great sensitivity, cost-effectiveness, high response speed, and additional labeling step (Hong & Jang, 2020; H. J. Kim, Jang, & Chemical, 2019; Z. Rouhbakhsh, A. Verdian, & G. J. T. Rajabzadeh, 2020). They are attractive to monitor a wide range of analytes, such as proteins, enzymes, lipids, nucleic acids, bacteria, heavy metal ions, and small molecules (Y. Wang, B. Wang, X. Xiong, & S. J. M. A. Deng, 2019; D. Zhao et al., 2015). Although the LC-based biosensors are undoubtedly noteworthy, they possess some deficiencies. The performance of the LC biosensors is impaired at high temperatures because LCs lose their contrast at these conditions. Also, they are not proper to be applied in the conditions with too much light, because of their bright texture (O'Neill & Kelly, 2003; Pagano-Stauffer, Johnson, Clark, & Handschy, 1986). So, it is a necessity requirement to introduce and develop the approaches with the ability to overcome the problems and drawbacks in the field of biosensor design. The computational methodologies are introduced as the efficient strategy to be a

complement or a replacement of the experimental techniques for designing and engineering of the biosensors. The present study provides a comprehensive review with an emphasis on the represented guidelines by the computational methods in the field of biosensor design.

2. Computational Methods for Biosensor Design

Several computational methods are utilized to theoretically design of the biosensors and to investigate the different effective parameters on their functionality. They can be divided into molecular dynamics (MD) simulation, quantum mechanics (QM) calculations, molecular docking, virtual screening, and combinational methods (Scheme 1). The recent achievements of the computational methods for the biosensor design are summarized in the following sections; and finally, some results are achieved based on the studied approaches.

2.1. Molecular Dynamics Simulation

MD simulation is a computational method to inquire the location of atoms constituting a molecular system in space by studying their time-dependent behavior. In MD simulation, a dynamic model is applied that forces the particles to motion. The calculated forces acting on the particles, as the derivative of potentials, are substituted into Newton's equation of motion that yields a description of the positions, velocities, and also, accelerations of the particles with passing time. By knowing the positions and velocities of the atoms, the state of the molecular system can be estimated at any time in the past or future. MD simulation can be performed by using several program packages, such as CHARMM, GROMACS, NAMD, AMBER, LAMMPS, and GROMOS. Typically, GROMACS computes the MD parameters 3-10 times more rapid than other programs. NAMD can efficiently run on parallel machines to study large molecules. Besides, it is compatible with other MD softwares, due to the same force field formats (Allen, 2004; X. Han et al., 2019; Hollingsworth & Dror, 2018; Polanski, 2019). MD simulation is a potent method to study the structure, dynamics, and energetics of the biological systems in the diverse experimental (pressure, temperature, and pH) conditions (Johnson, Kohlmeyer, Johnson, & Klein, 2009; B. Li, Fooksa, Heinze, & Meiler, 2018; Moradi, Shareghi, Saboury, & Farhadian, 2020; Schröder, 2017). Precisely designed MD simulations can frequently intercept the

wrong interpretations of the obtained experimental results. Moreover, MD simulation can provide key information at the atomistic levels when the experimental methods have some limitations or are incapable (Masic et al., 2015; Rigoldi et al., 2016; Tokareva, Jacobsen, Buehler, Wong, & Kaplan, 2014). Therefore, it can be extremely advantageous in providing physical and chemical intuition to design the biosensors with the highest efficiency.

Penchovsky (Penchovsky, 2013) introduced the efficient computational approaches to design small molecule biosensors that act as the Boolean logic functions. Two models were utilized to result in the theophylline and purine sensing ribozymes. A hammerhead ribozyme is the catalytic RNA motif with the ability to catalyze the ligation and cleavage reactions at a special site within the RNA molecule (Hammann, Luptak, Perreault, & de La Peña, 2012). The biosensing system was designed by applying a hammerhead ribozyme in the two models. The first model was based on fusing the theophylline specific aptamer with an expanded version of the hammerhead ribozyme by modeling 2D structures. The second model was designed by fusing the guanine or adenine aptamers with a minimal version of the hammerhead ribozyme by modeling 3D interactions. Figure 1 illustrates the designing scheme for the theophylline sensing ribozymes. Briefly, an extended version of hammerhead ribozyme was considered as a basic construction with a tertiary structure between the loop segment of stem II and a bulge loop within stem I. A random search algorithm was applied in combination with the partition function for the ribozyme folding to produce the theophylline-sensing ribozyme through computing the secondary structures. The theophylline specific aptamer was embedded into stem III that obtained the structures with NOT gate function. All stems were formed properly in the absence of theophylline that induced a self-cleavage state (ON). The theophylline presence caused the ribozyme switching into an inactive state through altering stem III to stem IV (OFF). The proposed computational method is time-efficient and valuable to design molecule-sensing ribozymes with the diverse in vivo and in vitro applications.

Feng et al. (T. Feng, Zhang, Ding, Fan, & Han, 2015) studied the binding of the macrolide biosensor protein MphR(A) and its mutant toward macrolide antibiotic erythromycin (Ery) to specify the most target-specific bioreceptor. The calculated

binding free energies by the MM-GBSA method proved that the mutant possessed a less binding affinity to Ery in comparison with MphR(A) protein. Besides, the binding energy analysis clarified that the reduction in the binding affinity of the V66L/V126L-MphR(A) mutant to Ery was extensively attributed to the electrostatic energies. The MD simulation highlighted the residues with a great influence on the binding affinity of MphR(A) and its mutant to Ery. The Ramachandran diagrams were applied to determine the distribution and percentage of the residues in the different bins, which clarified the conformational changes and the structural transitions in the residues of MphR(A) protein and its mutants. Hence, MD simulation can be an advantageous method to investigate the effect of the changes of bioreceptor components on the target binding affinity. MD simulation can be applied to determine the segments of the bioreceptors with shorter distances, and consequently, higher binding affinity to a special target. A replacement of the bioreceptor components containing the residues with a greater binding tendency to the desired target can result in designing a biosensor with an improved functionality. Moreover, the potential mean force (PMF) is introduced as a proper parameter for the biosensor design through investigation of the target-bioreceptor interaction pathways (W. Zhang, Du, Cranford, & Wang, 2016).

Distributional molecular dynamics (DMD) is the approach to reproduce the distribution of trajectories of the molecular system from MD simulation that enables the simulations to be 2-3 times faster than classical MD simulations. First, MD simulation is utilized to measure the free energy profile for the desired system. Then, the distribution of the random and frictional forces is calculated over the discrete segments; and the simulation is performed through solving the nonlinear generalized Langevin equation (Gordon, Krishnamurthy, & Chung, 2008, 2009; T. A. Hilder & Chung, 2011; T. A. Hilder, Gordon, & Chung, 2010). DMD simulation is considered as a proper method to determine the current-voltage profiles in the carbon-based biosensor (T. Hilder, Pace, & Chung, 2012). This method can be applied in the electrochemical biosensors to elect the most specific bioreceptor toward a target among the various designed bioreceptors. A comparison between the current-voltage profiles of the various bioreceptors attached on a carbon-based substrate in the absence or presence of the intended target clarifies the most efficient designed bioreceptor.

The structural and the configurational parameters have significant effects on its diagnostic ability of a biosensor. Comprehending the effect of such parameters can be achieved by the computational methods, especially in the cases where the use of experimental techniques is limited. Hoshyarmanesh et al. (Hoshyarmanesh, Bahrami, & Kalantarinejad, 2014) studied effect of the substrate material type on the performance of the micro cantilever beam as a biosensor for the prostate specific antigen. Besides, the geometrical configurations of the receptors and the target molecules were investigated to result in the highest biosensor efficiency. The Gibbs free energy difference (ΔG) was calculated for the sensing systems including the diverse substrate materials, such as silicon, silicon oxide, and silicon nitrate (Figure 2). Based on the obtained ΔG values, the most suitable material could be obtained to construct the biosensor substrate. The ΔG values were also calculated for the systems with the different geometrical configuration of receptors and various types of target, distributed on the biosensor surface. The ΔG values were the same for the different target distributions on the biosensor surface, which proved its negligible effect on the biosensor efficiency. In the case of the receptors, the ΔG values were the same for the different configurations that made it difficult to have a decisive decision about the effectiveness of the receptor configurations. So, a statistical approach (the zero assumption) was used according to the following equation:

$$Z = \frac{\overline{X_1} - \overline{X_2}}{\sqrt{\sigma_1^2 / n_1 + \sigma_2^2 / n_2}}$$

where $\overline{X}$, σ, and n are average of the two configurational society, standard deviations of the curves, and the sample number. The zero assumption clarified that the receptor configurations on the biosensor surface were a significant parameter. As a consequence, MD simulation can be applied in the biosensor design to determine the highest efficient substrate, consisting of a pure matter or even a combination of the different materials. MD simulation is also capable to determine the proper electrical content of the substrate material that results in the most biosensor functionality. Yang et al. (G. Yang, Kang, Ye, Wu, & Zhu, 2012) studied the flavin adenine dinucleotide functionalized on the differently charged single-walled carbon nanotubes (FAD-SWNT systems) to determine the best electrical properties of the SWNT substrate for

designing an apo-glucose oxidase (apo-GOx) biosensor. The results clarified that the various conformations of the attached FAD were induced by changing the electrical status of the SWNT substrate. The positively charged and uncharged SWNTs altered the FAD conformation so that prevented the reconstitution of apo-GOx units on the FAD-SWNT system. The conformation changes of the attached FAD on the negatively charged SWNT were the least that facilitated the apo-GOx reconstitution. So, MD simulation could be advantageous to understand the role of the FAD functionalized on the variously charged SWNTs as a critical parameter for designing the GOx biosensor. Hence, MD simulation is a complement for the experimental techniques in the biosensor design through providing the best choice for the electrical status of biomaterials.

The bioreceptor orientation is another effective parameter on the biosensor ability to recognize a target. MD simulation provides a precise insight into the bioreceptor orientation and introduces the strategies to control its rotation for designing the efficient biosensors. Feng et al. (C. Feng, Ding, Ren, & Ma, 2015) introduced a new strategy to control the orientation of the DNA fragment through the DNA copolymerization with the responsive polymers. The polymers undergone the swelling-deswelling transitions with altering the external motives. A thermo-responsive polymer was applied as an example in the study. The DNA orientation could be controlled by utilizing a temperature stimulus as an effective approach. Dissipative particle dynamics (DPD) is a popular simulation method for simulating the rheological and dynamic features of the simple and complicated fluids in the conditions with the critical role of the hydrodynamics and thermal fluctuations. DPD involves the mobile particles, including fluid regions and whole molecules, in a continuous space and distinct time. DPD considers the particles interacting with each other through three types of forces: dissipative force to decrease radial velocity variations between the particles, conservative force obtained from a potential component, and stochastic force along the line connecting the center of the particles. A longer time steps accompanied by a larger particle size causes DPD simulation to be more practical for simulating the hydrodynamics in comparison with conventional MD simulation. Besides, its algorithmic simplicity and great versatility make DPD method an advantageous tool for simulating the complex liquids, e.g. colloids, gels, polymer suspensions, and so on (Espanol & Warren, 2017; M. Liu, Liu, Zhou, &

Chang, 2015; Moeendarbary, Ng, & Zangeneh, 2009). After performing DPD simulations, the order parameter (S) was calculated by considering the DNA orientation relative to the z direction. In the low temperatures, the polymers were hydrophilic that caused their end-grafted DNA fragments were distributed randomly. Besides, the high polymer length in the z direction induced an extensive space for the DNA fragments, resulting in the negligible repulsive electrostatic interactions between the fragments. The DNA orientation was approximately random with a little S parameter in this conditions. An increase in the temperature led to the weak hydrophobicity of the polymers, which reduced the spaces between the DNA fragments. So, the uniformly oriented fragments minimized the electrostatic repulsion that obtained the high S parameter. Consequently, MD simulation can result in the greatest biosensor functionality by using the thermo-responsive polymers. Moreover, the other stimuli-responsive polymers can control the DNA that makes the proposed strategy to be beneficial in the field of biosensor design.

MD simulation can be efficient to design the fluorescent biosensors based on the Förster resonance energy transfer (FRET) process. In the FRET-based biosensors, an energy transfer between donor-acceptor molecules (chromophores) causes a change in fluorescence spectrum that clarifies the target presence (G. Chen, Song, Xiong, & Peng, 2013). The energy transfer can be effectively influenced by the chromophores distance. Since the FRET process is a greatly distance-dependent phenomenon, identifying the best locations of the chromophores is essential to have the most efficient biosensor. Mitchell et al. (Mitchell et al., 2016) described a computational method to specify the chromophore-attachment sites in some ligand-binding proteins. Rangefinder algorithm was utilized as a straightforward approach that led to the FRET-based biosensors for maltose, arginine, and N-acetylneuraminic acid. Based on the proposed approach, the mass center of the binding protein was determined; and the fluorophore was embedded away from the mass center at a specified distance. Applying such an approximate location enabled Rangefinder to obtain the results immediately with no requirement for the comprehensive MD simulations and high efficient computing resources. The dynamic range could be calculated as a Rangefinder output through considering the FRET efficiencies. Relying on the dynamic range results, the accurate sites were determined for attachment of the chromophores to the ligand-binding proteins, resulting in the efficient biosensors for

the targets. Consequently, Rangefinder can be an appropriate computational design approach to develop FRET-based biosensors for diverse targets. The orientation of the chromophores is another effective parameter on the energy transfer efficiency that can be optimized by using MD simulation (Hoefling et al., 2011).

To now, the different combinational methods have been applied to compute the binding energies in the biological systems. A combination of Poisson-Boltzmann Surface Area (PBSA) or generalized Born Surface Area (GBSA) methods with MD simulation (MM-PBSA or MM-GBSA) can be beneficial to compute the binding energies between the bioreceptor and target. After running a standard MD simulation and striping off the solvent, the solvation free-energy terms are added by using the continuum solvent model to generate the MM-PBSA and MM-GBSA energies (Kollman et al., 2000; Zhuang et al., 2016). MM-PBSA and MM-GBSA have emerged as reliable methods to model biomolecular recognition (Jawad, Poudel, Podgornik, Steinmetz, & Ching, 2019). Khoshbin et al. (Khoshbin, Housaindokht, Izadyar, Bozorgmehr, & Verdian, 2019) developed a theoretical design of new aptamers (mutants) with an increased target-affinity by MD simulation. Figure 3 indicates the representation of the screening method, which included three steps. First, the target specific aptamers were collected based on the experimental studies. MD simulation was performed for the aptamers in the presence of the target. Then, binding energies (ΔG_{Bind}) as a criterion of the aptamer specificity were computed by using MM-PBSA method that clarified the aptamer with the greatest affinity to the target. To design the aptamers with an increased specificity to the target, all mutants were obtained by substituting the nucleotides of the selected aptamer. The MD simulations were applied for the mutants that highlighted the mutants with greater specificity based on the calculated ΔG_{Bind} values. For more examination of the validity of the proposed method, a facile colorimetric assay was applied finally. As an efficient strategy, the screening method by MD simulation can be a complement for SELEX process to introduce new aptamers for a wide variety of targets. Recently, Khoshbin and Housaindokht (Khoshbin & Housaindokht, 2020) designed another theoretical mutation method to introduce a mutant aptamer with the improved affinity to sulfadimethoxine antibiotic. Based on Figure 4, MD simulation was performed for the SELEX-introduced (native) aptamer in the presence of the target. Then, the conformational factor (P_i) was calculated for the system that obtained the affinity of

the aptamer residues to the target. The aptamer residue with the least P_i parameter was exchanged to the nucleotide with the highest P_i that resulted in a mutant aptamer. The target-mutant complex was simulated, and P_i values were calculated for each residue. The nucleotide exchange was done similarly, and the designing process was proceeded repeatedly that achieved a mutant with an improved target specificity.

There are some advanced classical MD simulation methods that are helpful for designing the diverse biosensors, such as the Langevin dynamics (LD), temperature-replica-exchange MD (T-REMD), steered MD (SMD), and metadynamics (MTD) (Mollaamin, Najafi, Khaleghian, Hadad, & Monajjemi, 2011; Sponer et al., 2018). The LD simulation method estimates the effects of ignored degrees of freedom through adding two force terms to the Newton's second law. A force term considers a random force to model the effect of collisions and the other adds a frictional force to model dissipative losses. Hence, the impression of the molecular collisions and energy dissipation can be considered by LD simulation. The method is also efficient to study the diffusion of polymer coils in the solutions (Kronfeld, 1993; Pastor, 1994; Rudin, 2013). Hence, LD simulation can be a promising method to design the polymeric biosensors. The principle of T-REMD simulation is to keep the molecular system at a higher temperature making it more easily cross the energy barriers. Since crossing a free-energy barrier is exponentially dependent on the height of the enthalpic part of the barrier, exploring the conformational space at a higher temperature requires less time in comparison with what is at a low temperature. Hence, the faster conformational transitions are yielded by using T-REMD simulation (L.-C. Liu & Kuo, 2015; Sponer et al., 2018). SMD simulation forces molecular system to take away from its initial equilibrium condition with inspiration from the experiments based on single-molecule pulling. Hence, it accelerates the transitions between the various energy minima of the system. SMD simulation is a popular method to study the diverse biological processes, e.g. the protein folding mechanism, ion transportation through membrane channels, drug discovery, and so on. Besides, SMD is a promising tool to obtain the affinity of a bioreceptor to its target (Izrailev et al., 1999; Patel, Berteotti, Ronsisvalle, Rocchia, & Cavalli, 2014; Suan Li & Khanh Mai, 2012). MTD simulation facilitates sampling in molecular dynamics simulations through introducing an additional bias potential, which operates on a number of freedom degrees, referred to as collective variables (CVs). Besides, MTD helps the

systems to get rid of their local minima and assesses the free energy surface as a function of a chosen set of reaction coordinates. Some methods can belong to MTD class, such as local elevation, umbrella sampling, conformational flooding, adaptive force bias, and self-healing umbrella sampling (Barducci, Bonomi, & Parrinello, 2011; Tiwary & Parrinello, 2013). MTD simulation approach can be beneficial to design peptide-based biosensors for mycotoxins that possess a large number of freedom degrees. Thyparambil et al. (Thyparambil, Abramyan, Bazin, & Guiseppi-Elie, 2017; Thyparambil, Bazin, & Guiseppi-Elie, 2017) applied the biased exchange metadynamics (BEMD) method to develop the peptide-based bioreceptors. In this method, same temperature conditions were applied for the conformational sampling. The conformational biomolecule landscapes were studied through a time-dependent bias potential. Besides, the effect of the bioreceptor modification and the interference of the solid substrates on the sensing efficiency of the peptide-based biosensors, and also, in-solution recognition of the mycotoxins by the biosensors can be clarified through BEMD method.

Application of the computational methodologies can provide a new insight to design LC-based biosensors. Liu et al. (Qingyu Liu, Zuo, Zhao, Chen, & Xu, 2017) investigated a LC biosensor based on the inclusion effects of β-cyclodextrin (β-CD) by using MD simulation. The binding affinity of β-CD to sodium dodecyl sulfate (SDS) as the indicator and methylene blue (MB) as the target was clarified through the investigation of the calculated binding energies. The MD simulation study could completely explained the competitive inclusion between SDS and MB by β-CD that indicated the changes in the optical properties of the LC molecules during the sensing process. The MM-GBSA results proved that the higher stability of the complex between β-CD and MB in comparison with that is between β-CD and SDS. Hence, SDS molecule was released after the introduction of MB molecule to the β-CD/SDS complex that altered the optical color of the LC molecules as a sign for the MB monitoring. Consequently, MD simulation can be benefit to study the orientation, ordering, and also, anchoring of the LC molecules in the presence of the different biomolecules. It may provide more exact insight to study the LC-based biosensors in comparison with QM calculations, due to the dramatically weakened intermolecular hydrogen bonds in these systems. Besides, MD simulation can be applied to specify the best conditions in which the LC-based biosensor possesses the highest efficiency.

2.2. Quantum Mechanics Calculations

QM is a suitable method to understand the electronic structure of the different chemical compounds, and also, the thermodynamics, kinetics, and mechanism of chemical reactions at the theoretical level. The method can be divided into ab initio, semi-empirical, and density functional theory (DFT). The Ab initio method requires no empirical information about the molecular system under studying. However, the several approximations are utilized to solve Schrödinger's equation. The Semi-empirical method applies similar computational technique only for the valence electrons; hence, reduces the cost of the computational calculations. DFT method is based on the electron density of the molecular system; hence, it is considered as a greatly rigorous method (Atkins & Friedman, 2011; Gupta, 2015; Latour, 2011). The QM calculations are extensively applied to study the bond-rearrangements of the bioreceptors in the presence of intended target. Besides, changes in the electronic structures and the charge transfers between the bioreceptor and target can be obtained by using the QM calculations (Bykhovski, Zhang, Jensen, & Woolard, 2012; J. Wang, Bai, Xia, Sun, & Zhang, 2011). Such information gives an understanding about the greatest favorable conditions to design biosensors with the highest functionality.

The quantum conductance can be considered as an advantageous parameter to estimate the biosensor selectivity toward a target. Paulla et al. (Paulla & Farajian, 2013) calculated the quantum conductance of armchair graphene nanoribbons (AGNR) to detect CO and CO_2 molecules. The TARABORD program was utilized to calculate the conductance parameter. The required input information for the conductance calculation was provided by the second-order Møller-Plesset (MP2) and density functional theory (DFT) methods. The quantum conductance (C(E)) of the AGNR platform was obtained through the equation:

$$C(E) = \frac{2q^2}{h} T(E)$$

where q, h, and T(E) are the carrier charge, Planck constant, and transmission probability for a charge carrier. A comparison between the values of the calculated conductance for the AGNR-based nanosensor in the absence and presence of the target can be a criterion of the target detection. Also, Kumar et al. (Kumar &

Seminario, 2013) theoretically designed a nanosensor to detect uranium and plutonium ions by using graphene and graphene oxide (GO) as the sensing templates. The current-voltage curves were calculated for the templates and the target-template conjugates by applying the GENIP program, which is based on a combination of Green's functions and density functional theories. Two metallic contacts were modeled through binding the gold atoms to the target-template conjugates to provide the source for electrons based on the DOS of the nonometallic contacts. The current-voltage curves illustrated a significant reduction of the conductance of the functionalized GO with the carbonyl groups in the presence of the targets. Hence, the CO-functionalized GO was considered as a promising sensing template to efficiently detect uranium and plutonium ions. As an idea, conductance changes between the carbon-based platform in the presence of a bioreceptor and its value after introducing a target can be applied to design biosensors theoretically.

Wang et al. (H. Wang et al., 2017) utilized the QM calculation to computationally design the boron-embedded duplex molecularly imprinted hybrid membrane (B-DMIHM) for the detection of lamotrigine (LMT) as an antiepileptic agent. The biding energies of LMT with PAPTMS, APBA, and APTMS monomers were calculated that proved a ternary combination of all monomers could be suitable for the preparation of the B-DMIHM template. Hence, the QM calculations can be applied to provide an accurate measurement of the target tendency to the different biosensing templates. As a consequence, the most appropriate biosensing platform can be determined for intended target through the QM calculations to result in the highest efficiency of the designed biosensor. Besides, the type of the applied solvent for the biosensor preparation can have some effects on the bioreceptor-target interactions. The QM calculation can be utilized to obtain the bioreceptor-target interaction energies to select the most desirable solvent. Nezhadali et al. (Nezhadali & Mojarrab, 2014) chose ethanol as the greatest favorable solvent among water, acetonitrile, methanol, and dimethyl sulfoxide to develop the electrochemical sensor based on carbon nanotube/polypyrrole film by the QM calculation.

2.3. Molecular Docking

Molecular docking is a method to predict the most probable matching mode of a ligand to a bioreceptor through examining the possible conformations and orientations

of the ligand within the bioreceptor binding site. It can be utilized to predict the available potential interactions between a bioreceptor and target as the beneficial information for improving the accuracy and specificity of the biosensors (Salmaso, Sturlese, Cuzzolin, & Moro, 2018). Liu et al. (Qingjun Liu et al., 2013) explored the molecular recognition process of the olfactory biosensor by using the molecular docking technique. The configuration and physiological function of AcASP3 chemosensory protein was studied to identify the optimum conditions for the biosensor design. The results clarified that AcASP3 protein possessed some conserved amino acids including Cys 60 and Gln 64 that played a critical role in the binding interactions, and therefore, the bioreceptor functionality. Moreover, the Ac-ASP3 interactions with the various targets were evaluated through the structure assessment of the protein-target complexes. The improper targets could be eliminated relying the conformations of the complex segments, reducing the experimental cost for the biosensor design. Besides, molecular docking can be applied to consider the interaction of the different parts of a biosensor together in the presence or absence of target to design an efficient biosensor. Jafari et al. (S. Jafari et al., 2015) studied the interaction of $[Ru(bpy)_3]^{2+/3+}$ with a single stranded DNA before and after the hybridization to construct a biosensor for *Aeromonas hydrophila* DNA oligonucleotide.

Bick et al. (Abolhasan, Mehdizadeh, Rashidi, Aghebati-Maleki, & Yousefi, 2019) computationally designed the proteins as the bioreceptors for fentanyl by using molecular docking method through specifying the target attachment sites to the protein scaffolds. Besides, some surrounding residues were designed to achieve the highest bioreceptor affinity to fentanyl. Some fentanyl conformers and a hydrated model were considered based on its different rotatable bonds. Also, a large number of complementary placements for fentanyl in term of shape was embedded within the protein scaffolds. The fentanyl status was controlled precisely through considering only one single conformer per each protein scaffold. Among the designed conformers, Fen49 binder was considered as the strongest ones. The site-saturation mutagenesis (SSM) was applied to obtain an accurate vision of the sequence determinants of binding and folding. Fen49* was introduced as a SSM output with more binding affinity. Finally, the most efficient design was chosen for the further experimental analysis based on the shape complementarity, solvent-accessible-surface-area, and

binding energies. So, molecular docking technique can be useful for selecting the best status of target and bioreceptor among the diverse conformers or mutants to achieve efficient biosensors.

2.4. Virtual Screening

Virtual screening method including ligand-based and receptor-based approaches (LBVS and RBVS, respectively) is routinely utilized to study the different biological systems (Cross, Baroni, Carosati, Benedetti, & Clementi, 2010). It is an economical candidate for identification of promising bioreceptor scaffolds for the diverse targets. The method involves docking of a library containing a large number of compounds against a three-dimensional model of a target. According to the hypothetical binding state of target in the binding site, the binding energy or stability is estimated through considering the bonding interactions. The collected structures are then screened in silico, and the compounds with the great binding affinity to the target are selected for the biosensor design (Ma, Chan, Lee, Kwan, & Leung, 2011).

Pizzoni et al. (Pizzoni, Mascini, Compagnone, Perez, & Di Natale, 2015) presented a strategy to select peptides for designing the gas sensors through applying the virtual screening approach. After the geometry optimization, a maximum number of representative conformers was chosen for further docking simulation. A tetra-peptide library was generated from the starting tri-peptide library with the ability to discriminate between the diverse molecules. Some effective parameters were considered during the selection process, such as the unselective amino acids and the peptides with the ability to give various scores with the most natural/synthetic molecules. As a result, some tetra-peptides were introduced to be efficient candidates for the gas sensor arrays. Besides, Mascini et al. (Mascini et al., 2017) applied a similar approach to present the gas sensor arrays through designing the peptide sequences.

2.5. Combination of Different Computational Methods

Since each available computational method provides own unique information, utilizing their combination can be efficient in designing biosensors. An impressive set of the hybrid methods is developed for this purpose that are as follows:

2.5.1. Molecular Dynamics Simulation-Molecular Docking

Franca et al. (Franca, Leite, Cunha, Oliveira Jr, & Freitas, 2011) designed an enzyme-based nanobiosensor to detect herbicides. The nanobiosensor was constructed through the functionalization of the atomic force microscopy (AFM) tips, covered by a biomolecule with ability to interact with the target (Figure 5). The detection process was performed through evaluating the force between the target and immobilized biomolecule. The MD simulation study confirmed that a dimeric form of acetyl co-enzyme A carboxylase (ACC) was more appropriate for the immobilization on the tips in comparison with the monomeric ones. The obtained results proved that the surface of the ACC active sites and its reminder possessed the positive and negative charges, respectively. Hence, the functionalized AFM tip with the definite positively charged groups was applied to construct the optimized nanobiosensor. Molecular docking method was applied to determine the superior orientation of diclofop and atrazine herbicides with the ACC sites by computing the inhibition coefficients. According to the theoretical results, the nanobiosensor could be designed successfully to detect the diclofop herbicides with the high selectivity.

Replica exchange Monte Carlo (REMC) is an appropriate method to simulate a system containing uneven energy landscape in the situations where it may get stuck in the metastable structures away from the equilibrium state. The method is based on performing independent simulations simultaneously for the N parallel replicas of the system by considering an index parameter (e.g. pressure, temperature, and chemical potential) for the replica. The exchanges are performed during the certain periods of the simulation steps, resulting in the configuration trapped on the local minimum will surmount the potential barrier, and will arrive at the global minimum. The technique enhances the efficiency of the sampling near the equilibrium state by allowing the system to escape from metastable minima (Mignon & Simonson, 2016; Mitsutake, Sugita, & Okamoto, 2003; Okabe, Kawata, Okamoto, & Mikami, 2001).

Enriquez et al. (Hong Enriquez et al., 2012) introduced the short peptides with the ability to sense efavirenz as a potent reverse transcriptase inhibitor with the widespread application in HIV therapy. A combination of the different theoretical methods including MD simulation, molecular docking, and REMC simulation was applied to investigate the flexibility of the mutated peptides and maximize the target-

peptides binding affinity (Figure 6). In the designed method, the peptides flexibility was restricted to the mutated segment and its adjacent Ramachandran angles. The application of MD simulation was efficient to relax the designed mutated peptides before introducing to the molecular docking step. Trapping in a fixed configuration was a significant problem that monitored for a high number of the mutations. Hence, REMC was applied to avoid the traps and improve the efficiency of the designed procedure. The shape and electrostatic complementarity scores were applied to investigate the contact surface between the peptides and efavirenz, and also, to obtain the electrostatic potential values. Relying on the theoretical results, a decapeptide was introduced as a new sensing fragment with an improved affinity for efavirenz.

Herpoldt et al. (Herpoldt et al., 2015) applied molecular docking and MD simulation to study the interactions between the peptides and HIV-1 protease for designing the fluorescent peptide-based biosensors. Molecular docking results specified the most efficient binding sequence of the peptides as the greatest energetically favorable structures for starting MD simulation study. The binding mechanism of two peptide sensors to the protease was investigated by MD simulation. A model for the simultaneous binding of the peptides to the target could be developed successfully. The MM-PBSA approach was applied to calculate the binding energies of the protease-peptides complexes that resulted in the greatest favorable binding energies. The theoretical study provided an efficient approach to design the peptide-based biosensors with no requirement for the high-cost antibody development.

Shcherbinin et al. (Shcherbinin et al., 2015) developed an in-silico selection approach to design a specific aptamer for cytochrome p450 51A1 as the crucial enzyme for the sterol biosynthesis. The designed approach included the several steps. The type of the binding sites of the aptamer was determined by using molecular docking. Then, the oligonucleotides that acted as the recognition segment of the aptamer were chosen to be the starting point to design the aptamers. The structural segment of the aptamer was designed as a part with the ability to sustain the conformation of the recognition part. The binding energies of the target-aptamers complexes were calculated that resulted in selecting the most efficient designed aptamer.

Prandi et al. (Prandi, Ramalho, & França, 2019) designed an enzyme-based fluorescent biosensor to detect the organophosphorus compounds (OPs) as the agricultural pesticides by using molecular docking and MD simulation. Enzyme Esterase 2 (AaEST2) was considered as the biorecognition element, and its residues with ability to bind OPs were specified by the molecular docking study. Moreover, the orientation of OPs inside the active site of AaEST2 was identified by using molecular docking. The best pose of each OP within AaEST2 was obtained from the docking studies, subsequently applied for the MD simulation study. To study the FRET process in the designed biosensor, the coupling between the acceptor (OPs) and donor (Trp85 of AaEST2) was examined, which was dependent on the distance of their center of mass and orientation. The theoretical results proved that all OPs could quench the Trp85 of AaEST2 that triggered the fluorescence response. As a consequence, a combination of molecular docking and MD simulation methods can be efficient to design the diverse biosensors including peptide-based biosensors, enzymatic ones, and aptasensors (Jokar, Safaralizadeh, Hadizadeh, Rahmani, & Kalani, 2016; Shahbaaz, Kanchi, Sabela, & Bisetty, 2018).

2.5.2. Quantum Mechanics-Molecular Dynamics Simulation

Wong et al. (Wong, Xie, & Kwa, 2013) theoretically designed the urea-based chromogenic sensor to selectivity detect $H_2PO_4^-$ anion. The binding affinities of the thiourea-based receptors towards the different anions were obtained by QM calculations. The results clarified that the binding energies were influenced by the solvation effect, dielectric medium, anion basicity, and number of the available proton acceptors. The MD simulation results also proved that the receptors were strongly bound to $H_2PO_4^-$ in comparison with the other anions. Hence, QM/MD studies can be effectively applied to design biosensors for the various targets such as ions.

Khavani et al. (Khavani, Izadyar, & Housaindokht, 2015) specified the selective cyclic nanopeptides (CPs) toward the alkaline earth metal ions. The various cyclic peptides, including glycine (CP1), alanine (CP2), and glycine-valine (CP3) sequences, were selected to have a complexation with the different metal ions. The structural analysis, binding energies, charge transfer interactions, and topological results proved that the CPs formed the greatest stable complexes with Be^{2+} ion among the others. MD simulation was also applied to study the complexes. The electrostatic interaction

energy analysis demonstrated that CP2 peptide was the most efficient receptor for Be^{2+} ion. So, QM/MD studies can be beneficial to develop selective peptide receptors for a specific target.

Khavani et al. (Khavani, Izadyar, & Housaindokht, 2019a) theoretically designed the gold nanoparticles (AuNPs) functionalized RNA aptasensor to detect neomycin B. MD simulations were performed for the aptamer (AP1), aptamer-$S(CH_2)_6$- linker attachment (AP2), and the immobilized aptamer on AuNPs (AP3) in the presence of the different targets (Figure 7). The MD simulation results highlighted that the linker molecule possessed no perturbation effect on the aptamer structure. Based on the QM calculations, neomycin B possessed the highest interaction with the aptamer binding sites. The QM/MD study revealed that the proposed aptasensor was an efficient candidate for the target detection. Consequently, a coupling of the QM calculations with MD simulation analyses can be extremely applied to design the aptasensors functionalized with the diverse NPs, such as AuNPs, AgNPs, magnetic NPs, and carbon-based NPs (graphene, graphene oxide, quantum dots) for a wide range of targets. Also, the QM/MD studies can be applicable for designing biosensors by exploring conformational motions and allosteric regulation of a target and its biorecognition element (Chakravorty et al., 2012; Qin, Li, Bian, Fan, & Qi, 2010).

2.5.3. Quantum Mechanics-Molecular Mechanics

Molecular mechanics (MM) is one of the preferred approaches to study multi-component biological systems through precise evaluating the interactions. The MM method is based on the principles of vibrational spectroscopy, which assumes the positions of nuclei of the atoms constructing a molecular structure as a function of repulsive and attractive forces. In the MM method, molecules are considered as the balls linking together by springs, ignoring electrons. Besides, the energy of a molecular system is expressed as a function of the resistance of its components toward atom crowding, bond stretching, and bond bending. Then, the obtained energy equation is utilized to determine the bond lengths, angles, and dihedrals of the diverse possible potential energy surface minima (GUND, 1996; Lewars, 2016; Tokura & Tamura, 2007; Vanommeslaeghe & Guvench, 2014). Recent decades have witnessed the integration of the MM method with QM calculations as the hybrid QM/MM methodology for studying the biomolecules embedded in a complicated environment

and characterization of the molecular transition states. The basis for integrating both computational methods is to exactly compute the changes of the electronic structure, not considered by MM method. The realistic potential energy surfaces can be generated through the QM calculations that include the charge transfer interactions and environment-dependent polarization effects. In QM/MM, the region of the system, in which the chemical process occurs, is treated at an appropriate level of QM theory, and the remainder is examined by MM that applies the classical mechanics rules. Hence, the cost of the QM calculations reduces by using the hybrid method. The main purpose of the QM/MM approach is to highlight the interaction between a ligand molecule and its receptor and assess their binding affinity together (Groenhof, 2013; Karabencheva-Christova, 2015; Papamichael, Stamatis, Stergiou, Foukis, & Gkini, 2019; Ryde, 2016). The application of QM/MM method can be a promising strategy to study the biological systems containing several thousands of atoms, due to overcome the requirement for the prohibitively immense computational resources (Kraus et al., 2018; Lu et al., 2016).

Goryashchenko et al. (Goryashchenko, Khrenova, & Savitsky, 2018) applied the QM/MM calculations to detect the protease activity by using the fluorescent protein sensors through FRET process. The chromophore and its nearest environment were described by using the QM methods, while the rest of the protein system accompanied by the solvation sphere was described by using the classical force fields. The orientation factor κ^2 was obtained as an effective parameter to select the conditions with the highest FRET efficiency. Hence, QM/MM combination approach can be applied for the computational design of the FRET-based biosensor through considering the optimum structural directions of the biosensor components. Besides, QM/MM approach is advantageous to study the interface of the NPs-bioreceptor molecule to computationally design the diverse biosensors (Charchar, Christofferson, Todorova, & Yarovsky, 2016). However, the uncertainty in definition of the regions for QM and MM calculations is a challenge that ultimately affects the precision of the obtained results.

2.5.4. Molecular Docking-Virtual Screening-Quantitative Structure Activity Relationship

QSAR is an efficient computational method to predict the biological role of the chemicals relying on the statistical and mathematical relations. QSAR is based on the principle that the biological activity of a compound is correlated to the arrangement of the atoms forming its molecular structure. A series of parameters is applied to define the structural information that called molecular descriptors. A combination of theoretical calculations and statistical analysis are utilized based on QSAR model to identify the relationship between molecular descriptors and biological activities or physicochemical features of compounds. OSAR method can be generally classified based on the dimensions of the molecular descriptors, and also, type of the predicted biological activity (Y. Liu, Zhang, Zhang, & Hu, 2019; Peter et al., 2019; Roy, Kar, & Das, 2015).

Huang et al. (Huang, Chen, Chen, Tsai, & Chen, 2010) applied molecular docking and virtual screening methods accompanied with QSAR analysis to design the AMP-activated protein kinase (AMPK) agonist. Virtual screening was applied to select the suitable phenylamide compounds for designing the new AMPK ligands. Molecular docking was used to clarify the ability of the designed ligands to dock into the AMPK binding sites. 3D-QSAR methods, including comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA), could be beneficial to analyze the pharmacophore features of the designed ligands through aligning the structures with the same scaffolds and clarifying the interaction of the molecules. CoMFA was used to quantitatively analyze the correlation between the biological activity of a group of the compounds with the specific alignment and their steric and electronic features. CoMSIA was applied to specify the effect of the electronic and structural properties on the biological activity by studying the ligand-probe interaction. The applied methods highlighted the potent agonists for AMPK.

3. Computational Methods as a Complement of Experimental Techniques for Biosensor Design

The computational methods are the efficient strategy as a complement of the experimental techniques to design biosensors. Guida et al. (Guida et al., 2018) developed a peptide-based biosensor to detect anticancer drug irinotecan (CPT-11) by using surface plasmon resonance and fluorescence spectroscopy. MD simulation was applied to design the short peptides as the artificial bioreceptors through the in silico

mutation process. To decrease the entropic penalty in the unbound state, some cyclic peptides were designed with the property of keeping a disulfide bridge between the first and the last cysteine residues of the ring. To obtain the optimal peptide sequence, CPT-11 was inserted in a cyclic peptide of 12 VAL closed at the end by a disulfide bridge between two cysteines. One amino acid of the peptide was selected and replaced with a different one, except for the two terminal cysteines connected with a disulfide bridge to preserve the cyclic geometry of the peptide. The stability of the target-peptide complex was estimated after each mutation step by calculating the mean value E_i of Vina21 function from the MD trajectory. The new-designed peptide was rejected or accepted based on the Metropolis criterion. The mutation cycle was repeated several times until the binding affinity reached a plateau. Five peptides higher binding affinity and thermal stability were selected for further experimental validation through designing a peptide-based biosensor. The experimental results were accordance with the MD ones. Hence, in silico design of artificial peptides by using MD simulation can be a valuable method to design the different biosensing units with a wide range application in diagnostic area.

Zhu et al. (Zhu et al., 2019) applied single step capillary electrophoresis-based systematic evolution of ligands by exponential enrichment (ssCE-SELEX) process, as the high-efficient technique for the aptamer selection, to obtain the specific aptamer against bovine lactoferrin (BLF) with the high affinity. MD simulation was also utilized as a complementary tool for the experimental method to assess the affinity of the ten proposed aptamers to BLF by analyzing the interaction forces, binding sites, and binding energies. The MD results highlighted that the BLF-aptamer binding was attributed to the hydrogen bonding interactions between the amino acids of BLF and nucleobases of the aptamer. Finally, the BLF detection in milk samples was completed successfully by using the optimized aptasensor based on the selected aptamer with the highest affinity. Besides, MD simulation can be a supplementary for the experimentally biosensor design through specifying bioreceptor elements interacting with target (Hashemian, Khayamian, Saraji, & Shirani, 2016; Saberi, Rezaei, & Khayamian, 2018; Yazdanparast, Benvidi, Azimzadeh, Tezerjani, & Ghaani, 2020).

Toomjeen et al. (Toomjeen et al., 2019) theoretically designed an aptasensor to monitor 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG), as a disease biomarker,

based on the aptamer-induced aggregation of cysteamine-capped AuNPs. The MD results illustrated that the positively charged cysteamine on the AuNPs surface adopted two conformers, including trans and gauche. The trans conformer was the dominant species on the AuNPs surface that stabilized AuNPs in the solution, even in the presence of 8-oxo-dG. Based on the MD results, the target could bind to cysteamine-capped AuNPs through the noncovalent interactions. The 8-oxo-dG recognition by the aptasensor was proved through complex formation of 8-oxo-dG with C10, G11, G18, T24, C30, C36, G38, A47, A56, and T57 nucleobases of the aptamer strand. The van der Waals stacking interactions of the target played an important role in the binding stability. The accuracy of the computational design of the proposed aptasensor was also confirmed by the colorimetric experiment assessment.

Rezaei et al. (Rezaei, Shahshahanipour, Ensafi, & Farrokhpour, 2017) experimentally developed a highly sensitive aptasensor to monitor Hg^{2+} ion based on the CdTe/ZnS quantum dots. Some physical parameters of ion affect the folding tendency of the aptamer, including its radius, charge density, and intrinsic strength to receive charge from a donor atom. Hence, the QM calculations were performed to investigate the interaction of the specific aptamer containing T-T base pairs with the different metal ions that theoretically highlighted the selectivity of the aptamer to Hg^{2+}.

Ha et al. (Ha, Jung, La, Jung, & Yoon, 2017) designed an aptasensor for the kanamycin detection by using aptamer and graphene oxide as the biorecognition element and quencher segment, respectively. The specific aptamer was truncated to the segments as the new shortened aptamers. The truncated aptamers were then analyzed to obtain the minimal sequence for the kanamycin binding. The binding sites of the aptamers were estimated by molecular docking analysis. The results revealed that kanamycin bound to the guanidine or cytidine of the stem-like part in the truncated KBA 3-1 aptamer. Hence, the KBA 3-1 aptamer was applied to experimentally design of the aptasensor.

Zhang et al. (Y. Zhang et al., 2018) constructed a label-free aptasensor for the visual detection of zearalenone. After eight rounds of the SELEX process, the Z100 aptamer was obtained high target binding affinity. The molecular docking analysis

was applied to specify the binding mode between the designed aptamers and zearalenone.

Yarizadeh et al. (Yarizadeh, Behbahani, Mohabatkar, & Noorbakhsh, 2019) applied the computational methods to obtain the carcinoembryonic antigen (CEA) specific aptamers with higher specificity. Twelve CEA-specific aptamers were gathered from the literature. After their structure modeling, the complexes of the aptamers with CEA were simulated by using the ZDOCK server. Two aptamers were chosen based on the docking scores to create a new aptamer library. The different mutations were utilized for the library creation, including truncation, duplication, loop translocation, and four-based segment translocation. In the truncation process, two-five bases were eliminated in two directions of the aptamers (from 3′ to 5′ end, and also, from 5′ to 3′end). In the duplication and translocation processes, each aptamer was divided into four-based segments. Each segment was duplicated and translocated instead of the others in two directions. Molecular docking was conducted for the complexes of the obtained aptamers with the target. Relying on the steric hindrance as a criterion for the aptamer selection, seventeen aptamer sequences with higher binding scores were obtained among the reported sequences. Finally, two aptamers were selected as the elements with greater affinity to CEA, based on ZDOCK scores, the interaction domain of CEA, and steric hindrance. The chosen aptamer were applied as the biorecognition elements to experimentally design of an impedimetric aptasensor for the CEA detection. The results clarified that the CEA detection was improved about 13.5 fold higher in comparison with the constructed aptasensor by the control aptamer.

Yang et al. (L. Yang et al., 2019) developed a sensitive chemiluminescence aptasensor to detect sulfamethazine based on in vitro selected aptamers. Four selected specific aptamers were analyzed by using the computational hybrid method, including MD simulation and molecular docking, to clarify the aptamer binding sites and target recognition mechanism. The theoretical results specified that several aptamer sites could bind sulfamethazine through the hydrophobic, electrostatic, and hydrogen binding interactions, generally consistent with the experimental results.

Khavani et al. (Khavani, Izadyar, & Housaindokht, 2019b) applied a joint theoretical and experimental study to introduce a colorimetric aptasensor for neomycin

B. First, all possible mutant aptamers were theoretically designed by using MD simulation. The binding affinity of the designed aptamers toward the target were examined as a criterion for their sensing ability from the theoretical point of view. The geometrical and energetic parameters proved a greater affinity of two mutants toward neomycin B in comparison with the initial aptamer. An experimental colorimetric method was applied that highlighted the ability of MD simulation to introduce the new aptamers for further experimental application. QM calculations clarified the van der Waals and electrostatic interactions as the driving force for the aptamer complexation with the target (Figure 8).

He et al. (He et al., 2020) introduced an electrochemical aptasensor for the sensitive monitoring of L-arginine by using the hybrid method, including MD simulation and molecular docking. The potential interaction between the peptide aptamers and L-arginine was predicted by using molecular docking. The MD simulation results highlighted that four aptamers were outstanding in terms of the binding energy, clarifying their great specificity to interact with the target. Finally, the potential aptamers were utilized for further experimental verification.

A summary of the application of the computational methods for designing the biosensors is represented in Table 1. Based on Table 1, MD simulation method is an approach with a great application in the field of biosensor design. A significant attention can be focused on the other methods as the supplements for the MD simulation method to represent some new strategies. So, the hybrid methodologies can be the novel approaches with a great potential to provide the precise information for facilitating the experimentally design of biosensors. In spite of their supreme advantages to design biosensors, the computational methods possess some limitations, as illustrated in Table 2 (Al Adeh, 2017; Allen, 2004; Cheatham III & Kollman, 2000; Drummond, 2019; Ellis, 2012; Frenkel, Smit, Tobochnik, McKay, & Christian, 1997; Ghasemi, Abdolmaleki, & Shiri, 2017; Hutter, 2018; Klebe, 2006; Lavecchia & Di Giovanni, 2013; Pons, Grosdidier, Solernou, Pérez-Cano, & Fernández-Recio, 2010; Prieto-Martínez, Arciniega, & Medina-Franco, 2019; Sethi, Joshi, Sasikala, & Alvala, 2019).

4. Conclusions and Future Perspectives

Designing efficient biosensors with great functionality has led to the major developments in the diverse scientific fields. However, experimental designing of biosensors is faced with some difficulties that highlights the urgent requirement for the approaches to overcome the drawbacks. Hence, the computational methods are introduced as the promising candidate to be a complement or a replacement for the experimental techniques to engineer biosensors. The present study provides a comprehensive review with an emphasis on the represented guidelines by the computational methods in the field of biosensor design. The successful computational design of the biosensors is dependent on the precise structural modeling, high biosensing components stability, and optimizing the molecular interactions. MD simulation provides the molecular-level insights and represents the geometries, energies, and many physicochemical properties of the biosensor components. It can be applied to optimize the conditions to achieve the highest biosensor performance. As a consequence, MD simulation method possesses a great potential to reduce the cost of the biosensor development processes and to introduce the conditions in which the biosensor functionality is the highest. Besides, MD simulation can be advantageous to design new bioreceptor segments with an improved sensitivity toward a desired target through the mutation process. According to the prominent advantages of aptasensors in comparison with the other biosensors and relying on the MD simulation method capabilities, new aptasensors with the ability of the multi-target detection can be designed by using MD simulation. As a perspective, designing the multi-functional aptasensors can be promising for the simultaneous detection of a collection of the hazardous targets, e.g. toxins, pesticides, heavy metals, and so on.

The screening method by MD simulation possesses the great potential to design the new bioreceptors with an improved target-binding affinity. As a perspective, the MD screening method can be applied to design the new specific aptamers for a target with no relying on the SELEX results. The MD screening method can be initiated from a comprehensive library containing all possible hypothetical mutants and progresses to obtain the new aptamer with the highest target affinity. The advanced classical MD simulation methods can be a promising candidate to design a wide variety of the biosensors, such as colorimetric ones based on the AuNPs aggregation, fluorescent biosensors based on the FRET process, etc. There are the different platforms that can be applied as the quencher in the FRET-based biosensors. The

computational methods can be efficient in designing or selecting the platform for resulting in the FRET-based biosensors with the highest efficiency. Besides, the utility of the advanced simulation methods can be advantageous to exactly obtain the conditions with the highest bioreceptor efficiency for the target recognition.

QM calculations promote quantificational insight to biosensor components by providing precise bioreceptor-target binding energy. QM method is appeared very capable in designing electrochemical biosensors by introducing the quantum conductance parameter. However, the application of QM calculations is restricted for the biological systems containing thousands of atoms, due to the impractical calculation of the shielding tensor. Hence, hybrid QM/MM method is developed to overcome the restriction. Molecular docking is another computational method with simplicity to use and comprehensible concept that facilitates the identification of the bioreceptor-target binding sites. Based on the determined binding sites by the method, the bioreceptor can be modified to improve the target binding affinity. Also, molecular docking can be efficiently applied to eliminate the improper and non-specific parts of the bioreceptor that results in a shortened residue of the bioreceptor. This issue will be especially substantial when the bioreceptor segment is massive so that the proposed technique reduces the cost and time of the subsequent experimental analysis. Virtual screening possesses a great potential to screen the large library containing the various designed bioreceptors that results the efficient bioreceptor and decreases the number of the suggested candidates for the experimental tests. Since biosensors can be designed through the investigation of the unique parameters by the computational methods, a combination of them can promote the computational progress for this purpose by studying a complete set of the impressive parameters. Besides, a combination of the computational methods can be beneficial to design the LC-based aptasensors as the high-throughput biosensors. Finally, the diverse screening methods can be developed for designing biosensors by a combination of the available computational methods as the promising newly introduced approaches.

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Conflict of interest

The authors declare that they have no conflicts of interest with the contents of this article.

Author contributions

Mohammad Reza Housaindokht and Mohammad Izadyar conceived the ideas, designed, and supervised the study. Mohammad Reza Housaindokht obtained funding. Zahra Khoshbin wrote the manuscript, drafted the figures, and adjusted the tables. Mohammad Reza Bozorgmehr and Asma Verdian advised the study. All authors revised the manuscript and proved the final version.

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Figures

Scheme 1. Representation of computational methods for theoretical design of different types of biosensors.

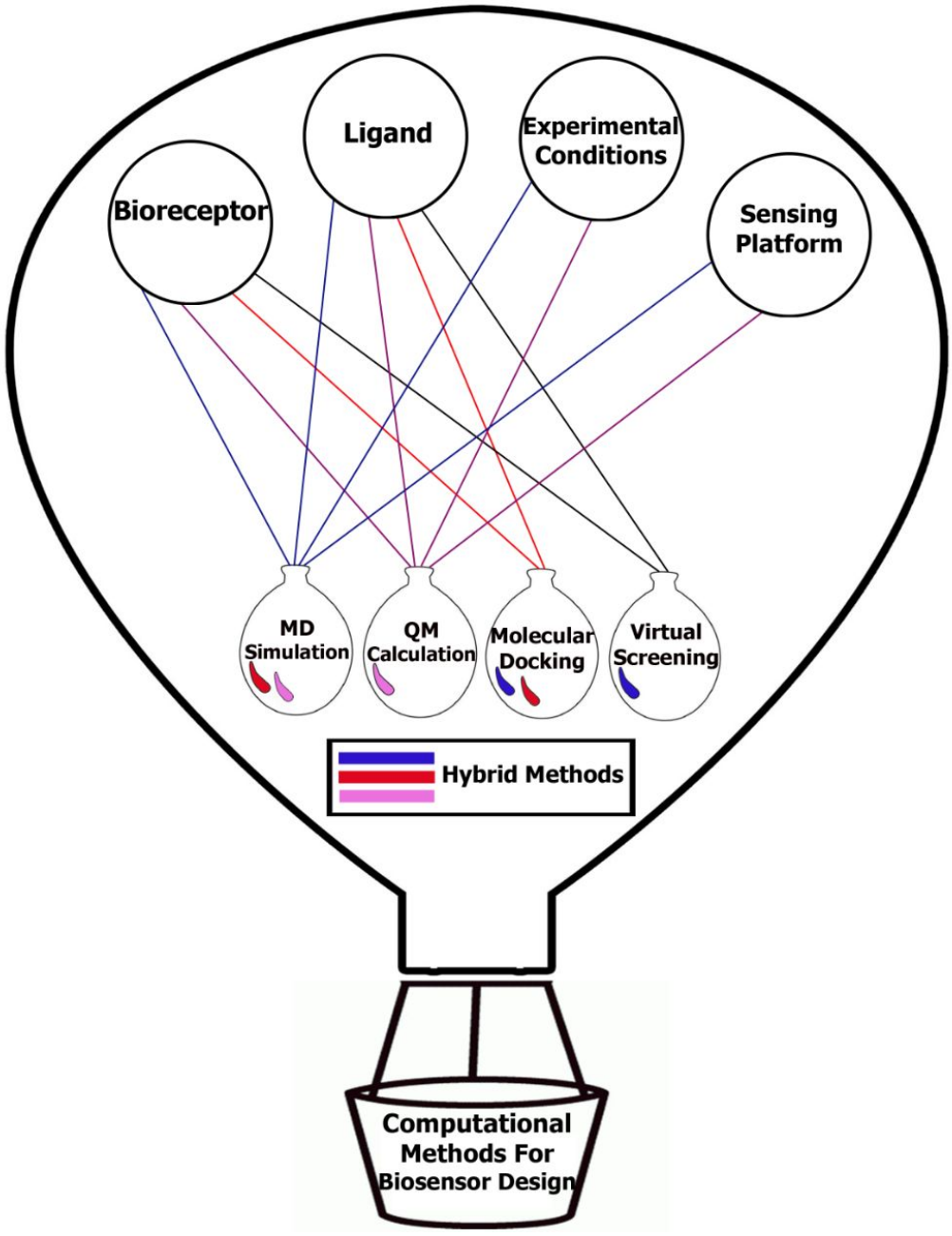

Figure 1. Schematic for theophylline-sensing hammerhead ribozymes. a) The extended hammerhead ribozyme sequence applied for designing theophylline ribozymes. The canonical and non-canonical tertiary interactions of the ribozyme are illustrated by solid and dashed lines, respectively. b) The secondary structure of the theophylline specific aptamer. c) The applied algorithm for designing the theophylline biosensors. Red and black arrows depict the successful and unsuccessful fulfilling of the computational step, respectively. Blue arrows show the unconditional passing to the subsequent step. Hexagons are decision-making steps. d) The theophylline specific aptamer embedded into stem III of the ribozyme. The random nucleotides are indicated as N symptom. All stems have been formed correctly in the absence of theophylline, inducing a self-cleavage state (ON) at the position illustrated by the arrowhead. The theophylline-aptamer interaction has caused the ribozyme switching into an inactive state through stem III distraction and stem IV formation. Reproduced from Ref. Penchovsky (2013).

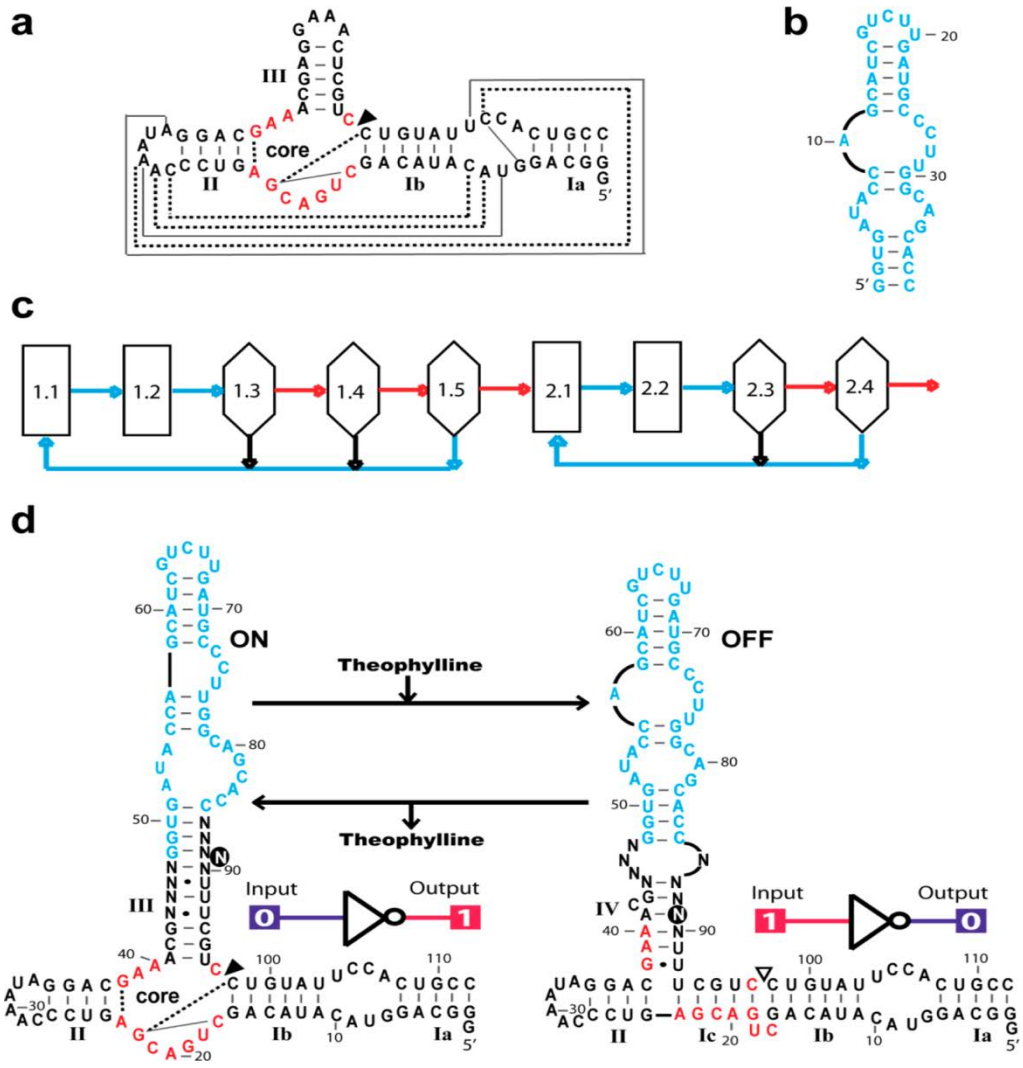

Figure 2. The MD simulated micro cantilever beam with the different substrate materials, including silicon, silicon oxide, and silicon nitrate (A-C). Reproduced from Ref. Hoshyarmanesh et al. (2014).

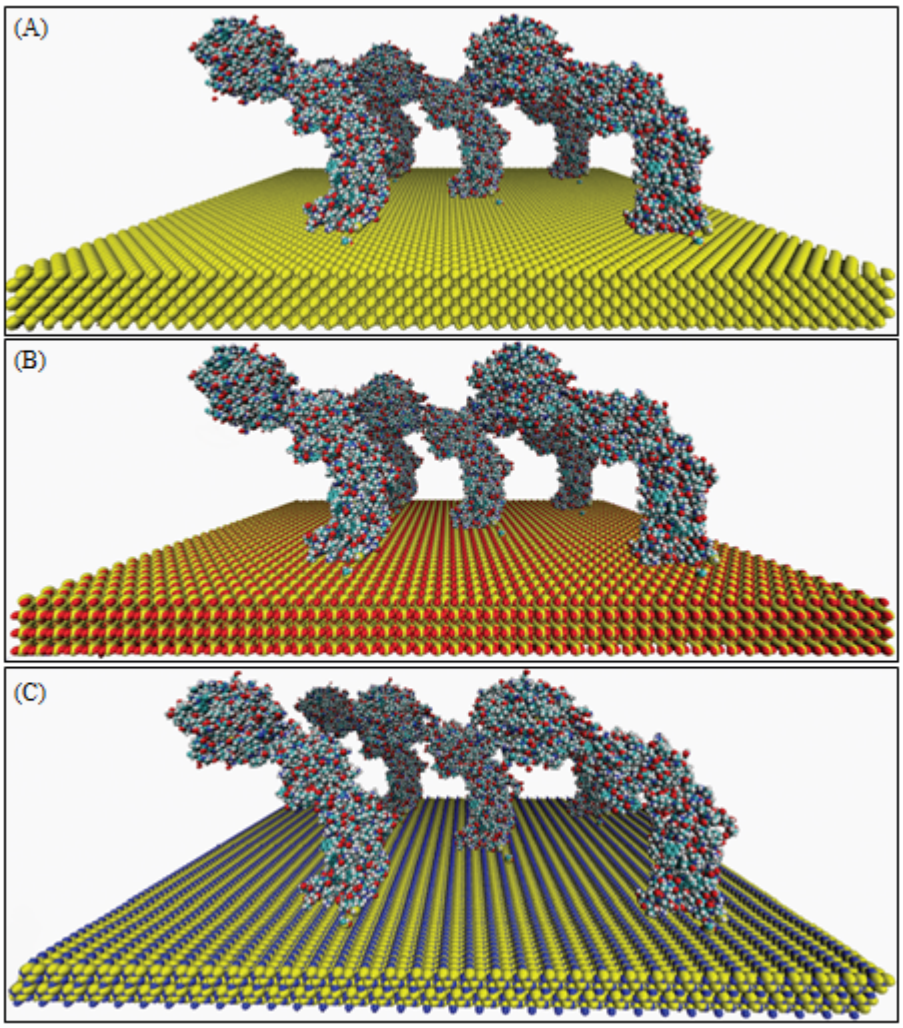

Figure 3. Schematic for designing aptamer through the screening by MD simulation. First, the aptamer with the greatest target specificity is selected among the available aptamers through the screening by MD simulation. Then, the mutants are designed by altering the aptamer nucleotides. Finally, the mutants with the greater specificity toward the target are chosen by the screening by MD simulation. For more confirmation, the specificity of the mutants can be examined by using an experimental method. Reproduced from Ref. Khoshbin et al. (2019).

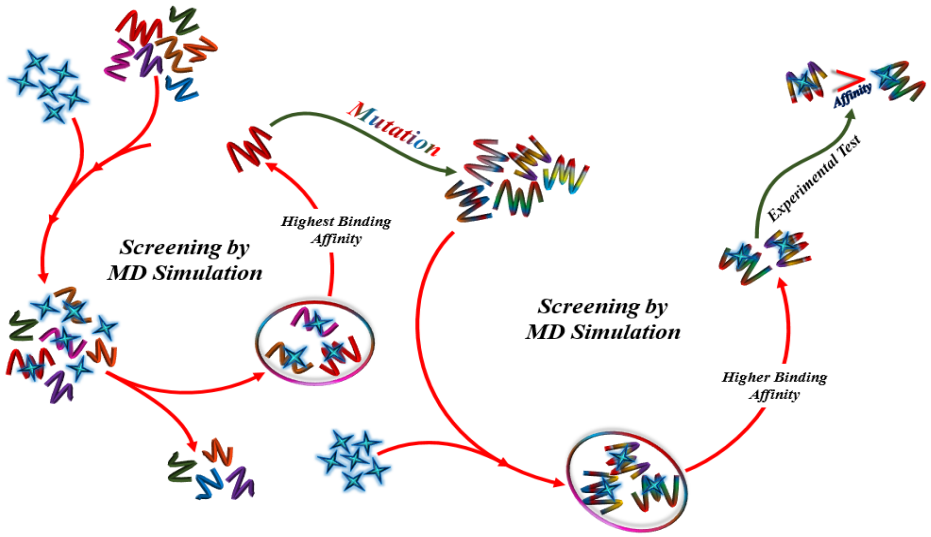

Figure 4. Schematic for designing aptamer through the step by step mutation based on MD simulation. MD simulation was performed for the native aptamer in the presence of the target. The aptamer residue with the least Pi parameter was exchanged to the nucleotide with the highest one, resulting in a mutant aptamer. The MD simulation was performed for the target-mutant complex. The nucleotide exchange was done similarly, and the designing process was proceeded repeatedly that achieved a mutant with an improved target specificity. Reproduced from Ref. Khoshbin and Housaindokht (2020).

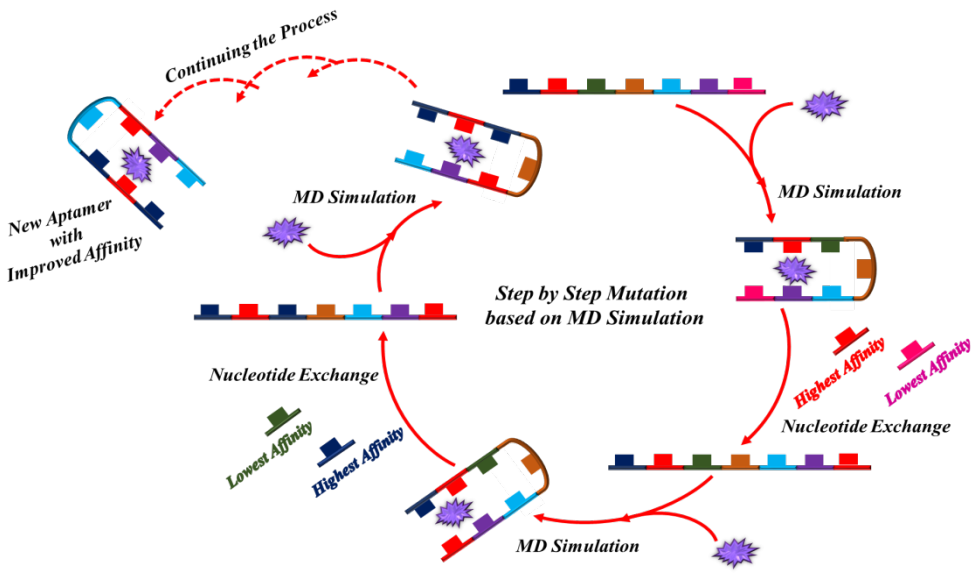

Figure 5. Schematic representation of the theoretically designed nanobiosensor. A) The ACC biomolecules are adsorbed on the AFM tip from an aqueous solution by the electrostatic interactions. The interactions between ACC biomolecules and diclofop and atrazine herbicides can be obtained through computing the required force for withdrawing the herbicides from the solid support. B) The immobilized ACC biomolecules possess the different orientations on the surface of the functionalized AFM tip. Reproduced from Ref. Franca et al. (2011).

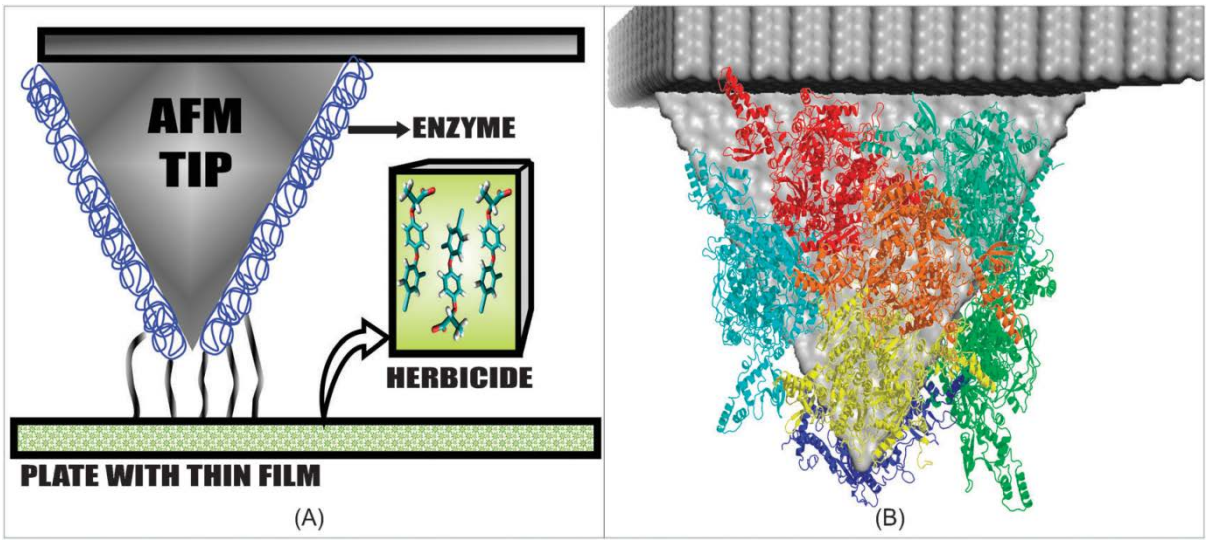

Figure 6. Designing the new peptides (mutants) with the ability to sense efavirenz by using a combination of molecular docking-MD simulation-REMC method. a) The calculated binding energy versus the number of the designed mutations at the different temperatures. b) The calculated binding energy versus the number of the mutations at the lowest temperature. The peptide sequences and the structures of the corresponding complexes are also demonstrated. c) The shape and electrostatic complementarity scores of the accepted peptides from the results of the panel (b). Reproduced from Ref. Enriquez et al. (2012).

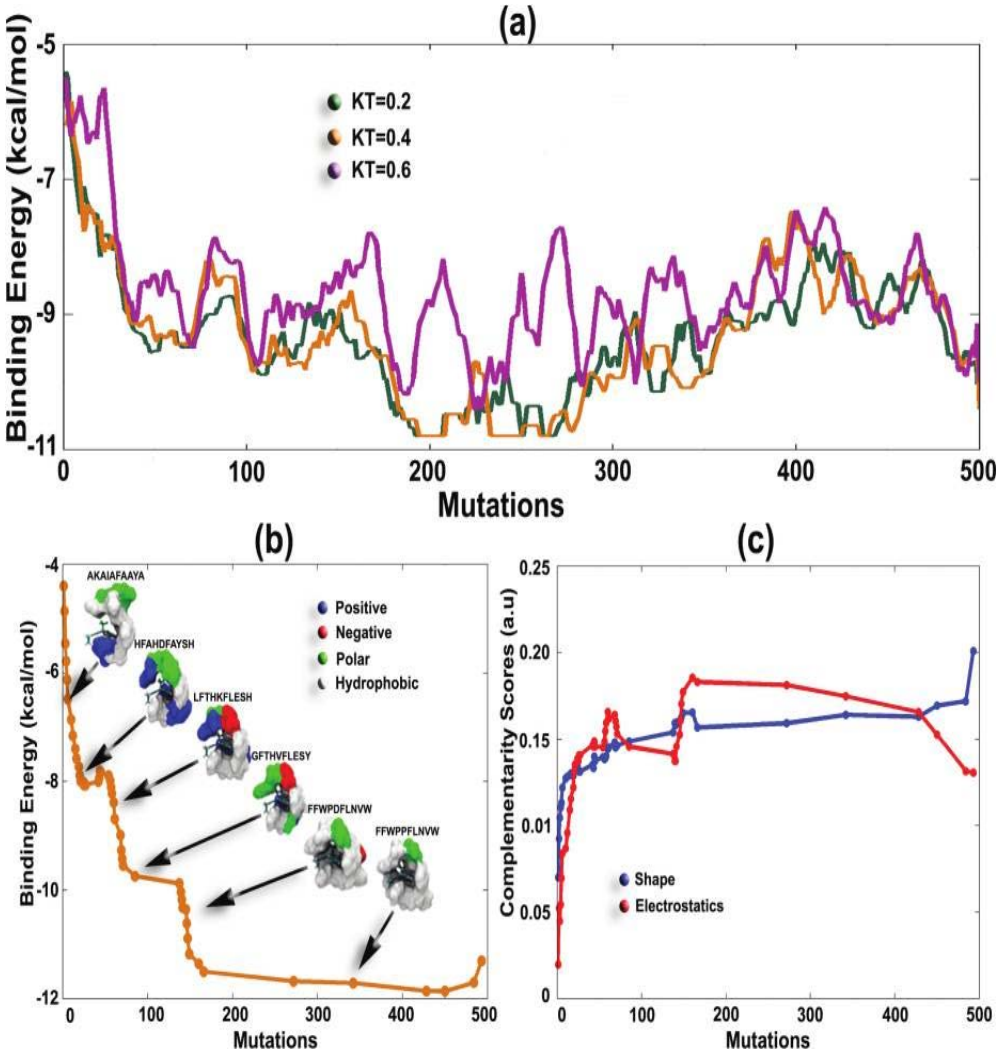

Figure 7. Schematic representation of the designed the AuNPs-functionalized RNA aptasensor in the presence of neomycin B, neomycin C, and paromomycin (NB, NC, and PM, respectively). RMSD, Rg, RMSF, number of H-bonds, distances between the aptamer and AuNPs, and the related EIE (A-F) are illustrated for the different systems. Reproduced from Ref. Khavani et al. (2019).

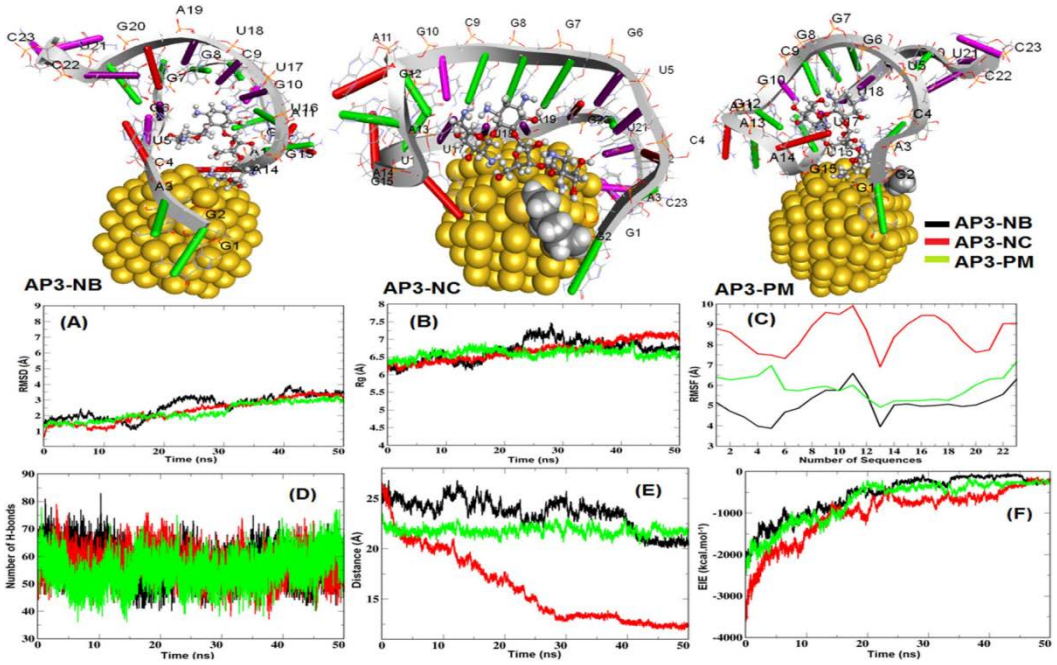

Figure 8. The 3D non-covalent interaction (NCI) analysis for the wild type aptamer (AP-W) and two designed aptamers (AP-M18 and AP-M20) with neomycin B. The color-filled isosurfaces are repulsive, H-bond, and vdW interactions (red, blue, and green, respectively). 3D NCI plots indicate the considerable vdW interactions between the aptamer and target. Based on the NCI analysis, vdW and electrostatic interactions are the driving force for the formation of the aptamer-neomycin B complex. Reproduced from Ref. Khavani et al. (2019).

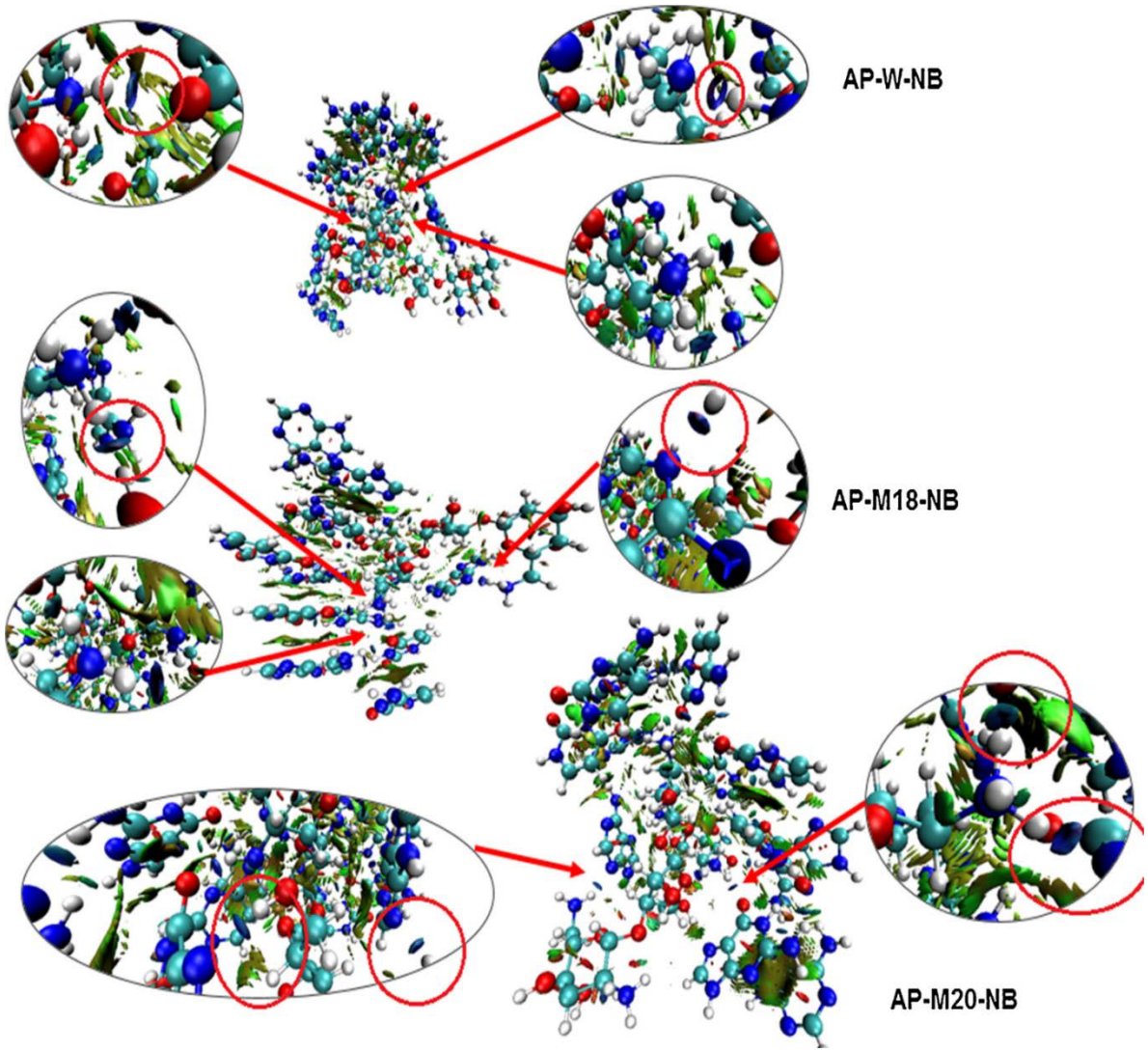

Table 1. Application of the computational methods in the field of biosensor design.

Computational Method	Applications in the Field of Biosensor Design
MD Simulation	1) Determining the conditions (pressure, temperature, and pH) in which the efficiency of the biosensor is the highest

	2) Modifying the biorecognition segment of the bioreceptor through changing the effective parameters in bioreceptor efficiency such as structure, orientation, etc.
	3) Finding the highest effective sites of the biorecognition strand for attaching to electrodes to achieve the best strand folding for designing electrochemical biosensors
	4) Providing the precise information through studying the current-voltage profiles to design efficient electrochemical carbon-based biosensors
	5) Choosing the best platform among the carbon or silicon based materials to obtain the highest efficiency of the biosensor by using Umbrella Sampling approach or Metadynamics simulation
	6) Determining the best composition of the different materials to improve the proper electrical content of the designed biosensor
	7) Determining the best type and composition of the polymeric substrate and the orientation of its constructing units to achieve the highest efficiency of the polymer-based biosensors
	8) Determining the best chromophore-attachment sites to design the efficient FRET-based biosensors
	9) Introducing the screening methods for selecting or designing the bioreceptors with the highest affinity to the desired target
	10) Introducing the new methods such as the mutation approach based on nucleotide exchange for designing novel biosensors
	11) Studying the fusion of two or more bioreceptors and finding their best attachment position to design the hybrid bioreceptors as the new introduced segments for multiple targets detection
	12) Changing the residue of the proteins by using FoldX or Rosetta software to design the efficient new protein-based bioreceptors
QM Calculation	1) Understanding the greatest favorable solvation conditions to design biosensors with the highest functionality
	2) Investigating the biosensor efficiency through calculating the quantum conductance parameter
	3) Designing molecularly imprinted hybrid membranes for biosensors
Molecular Docking	1) Predicting the most probable matching mode of a ligand to a bioreceptor for improvement of the biosensor functionality

	2) Examining the possible conformations and orientations of the desired target within the bioreceptor binding site
	3) Determining the conditions with the greatest potential interactions between a bioreceptor and target to improve the biosensor efficiency
Virtual Screening	1) Identifying the best bioreceptor scaffolds for the target
	2) Selecting the highest efficient bioreceptor for the multiple target detection among the diverse designed species
Hybrid Methodologies	1) Finding the best position for the bioreceptor immobilization on the biosensor platform such as electrode, AFM tip, nano-based substrates, and so on
	2) Determining the best orientation of the segments of the biosensor with respect to the target to obtain the most efficient response
	3) Designing the screening methods including a combination of two or more computational methods to results in high efficient biosensors
	4) Improving efficiency of step by step mutation methods to results in a bioreceptor with the highest efficiency
	5) Clarifying the folding regions of the bioreceptor and position of its constructing units to modify the nonspecific units to the specific ones

Table 2. Some limitations of the computational methods in the field of biosensor design.

Computational Method	**Limitations**
MD Simulation	1) Results are dependent to the chosen interaction potential parameters.
	2) It requires supercomputers for studying very large biological systems, making it to be computationally intensive and time-consuming.
	3) It incorporates the redistribution of electrons in an approximate manner at best.
	4) Intramolecular hydrogen bonds are not explicitly included in modern force fields but described as Coulomb interactions of atomic point charges.
	5) Van der Waals interactions are usually described by Lennard-Jones potential theory that is only applicable in a vacuum.
QM Calculation	1) It is too slow for the complex biological sensing systems.

	2) It is restricted for the biological systems containing thousands of atoms. 3) It requires supercomputers for studying very large biological systems, making it to be computationally intensive and time-consuming. 4) There are too many approximations in some cases, failures for strongly correlated systems, and too slow for liquids.
Molecular Docking	1) There is a lack of confidence in the ability of scoring functions to give accurate binding energies. 2) It is restricted to medium sized ligands and is not feasible for large size ligands. 3) Some intermolecular interaction terms are hardly predicted, such as the solvation effect and entropy change. 4) Some intermolecular interactions are rarely considered in scoring functions. 5) It is a problem to accurately deal with the water molecules in the binding pocket during the docking process. 6) Conformational flexibility upon binding is dissembled during the study by using rigid-body molecular docking approaches.
Virtual Screening	1) A large library containing a wide range of molecules is required accurately. 2) Resolution of the crystal structure may be limited by the experimental x-ray crystallographic procedure. 3) Lack of sufficient experimental data covering the chemical space restricts the applicability of the method for some compounds. 4) Scoring functions are limited by the accurate representation of the underlying interactions between receptor and ligand. 5) Crystallographic structures may not show certain pockets that are subject to dynamic changes upon target-receptor interaction. 6) Time-consuming computation of entropic terms (loss of rotational degrees of freedom and desolvation effects) for the accurate prediction of binding constants.