Recent Advances in Computational Methods for Biosensor Design

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Abstract

Biosensors are the analytical tools with great application in healthcare, food quality control, and environmental monitoring. They are of considerable interest to be designed by using cost-effective and high 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 biosensor designing; however, some deficiencies limit their utilization for this purpose. Computational design of biosensors has been introduced as a promising key to eliminate the gap. A set of reliable structure prediction of the biosensor segments, their stability, and accurate descriptors 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 biosensor design, 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 computational methods, an opportunity has been emerged for them to be complementary or alternative to the experimental methods in the field of biosensor design.

1. Introduction

Biosensors are defined as 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 bioreceptor, transducer, and signal processing segments. Bioreceptors are generally enzymes, proteins, peptides, antibodies, nucleic acids, and aptamers that capture their own specific target. The interaction between a target and 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 have been considered as one of the most applicable analytical tools that are able to recognize 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 and 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 sample matrix, and sensitivity to the temperature and pH variations (Ge, Wang, Hou, & Li, 2016; Han, Zheng, & Dong, 2013; Othman, Karimi, & Andreescu, 2016; Rodriguez-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 diverse tertiary structures through the interaction with different targets. Peptide-based biosensors apply peptides with wonderful water solubility and biological compatibility, which enable them to detect different targets. Nevertheless, some deficiencies restrict their utilization, such as low durability, limited sensitivity, and degradation under harsh conditions (Neupane & Lee, 2013; J. Park, In, & Lee, 2015; Puiu & Bala, 2018; Su, Cho, Nam, Choe, & Lee, 2013).

The antibody-based biosensors have been utilized commonly to detect various targets with high sensitivity. Unfortunately, antibodies are susceptible to 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. 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 of 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 a potential alternative to the antibodies, aptamers have been applied extremely to design the aptamer-based biosensors (aptasensors). Aptamers are the synthetic single strands of oligonucleotides that possess the great affinity to a vast range of different 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 are also can sustain their durability over 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 has been 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 process 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 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).

As a consequence, 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 of the presence of the target. Some of these 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). So, it is a necessity requirement to develop and apply the approaches with the ability

to overcome the problems and drawbacks in the field of the biosensor design. The computational methods have been introduced as an efficient strategy to be a complement or a replacement for the experimental techniques for designing and engineering of diverse biosensors. The present study provides a comprehensive review with an emphasis on the represented guidelines by the computational methods in the field of the biosensor design.

2. Computational Methods for Biosensor Design

Several computational methods have been utilized to theoretically design the biosensors and to investigate the different effective parameters on their functionality, which 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 have been 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 potent computational method to investigate 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; Schroder, 2017). Precisely designed MD simulation can frequently intercept the wrong interpretations of the obtained experimental results. Moreover, MD simulation can obtain 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). Hence, it can be extremely advantageous in providing physical and chemical intuition for designing 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. 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 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 the 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. Besides, the MD simulation highlighted the residues that had 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 that 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 with the residues that have a greater tendency to bind to the target can result in designing a biosensor with improved functionality. Besides, the potential mean force (PMF) has been introduced as a proper parameter to biosensor design through the investigation of the target-bioreceptor interaction pathways (W. Zhang, Du, Cranford, & Wang, 2016).

Distributional molecular dynamics (DMD) simulation is considered as a proper approach to determine the current-voltage profiles in the carbon-based biosensor (Hilder, Pace, & Chung, 2012). This method can be applied in 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 the presence of the intended target clarifies the most efficient designed bioreceptor.

The biosensor structure and the configurational parameters have significant effects on the diagnostic ability of a biosensor. Comprehending the effect of such parameters on the biosensor performance can be achieved by the computational methods, especially in cases where the use of experimental techniques has limitations. 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 the various types of the target distribution on the biosensor surface. The obtained ΔG values were the same for the different target distributions on the biosensor surface that 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:

where 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. Besides, MD simulation is capable to determine the proper electrical content of 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 differently charged single-walled carbon nanotubes (FAD-SWNT systems) to determine the best electrical properties of SWNT substrate for designing a apo-glucose oxidase (apo-GOx) biosensor. The MD results clarified that the various conformations of the attached FAD were induced by changing the electrical status of SWNT. 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 FAD functionalized variously charged SWNTs as a critical parameter for designing the glucose oxidase biosensors. Hence, MD simulation is a complement for the experimental techniques in the biosensor design through providing the best choice for electrical status of biomaterials.

Moreover, the bioreceptor orientation is another effective parameter on biosensor potential to recognize target. MD simulation provides a precise insight into the bioreceptor orientation and introduces the strategies to control its rotation for designing 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 with applying a temperature stimulus as an effective approach. After performing

Dissipative particle dynamics (DPD) simulations, the order parameter (S) was calculated by considering the DNA orientation relative to the z direction. In 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 that caused 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 temperature led to the weak hydrophobicity of the polymers, which reduced the spaces between the DNA fragments. So, the fragments oriented uniformly that minimized the electrostatic repulsion and the high S parameter was obtained. Consequently, MD simulation can result in the greatest biosensor functionality through applying the thermo-responsive polymers. Moreover, the other stimuli-responsive polymers can control the DNA orientation that makes the proposed strategy to be beneficial in the field of biosensor design.

MD simulation can be efficient in designing 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 presence of the target (G. Chen, Song, Xiong, & Peng, 2013). The energy transfer can be 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 leads 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, the and 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 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 for the attachment of chromophores to the ligand-binding proteins were determined that obtained the efficient biosensors for the targets. So, 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).

Up 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). Recently, Khoshbin et al. (Khoshbin, Housaindokht, Izadyar, Bozorgmehr, & Verdian, 2019) developed the 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 target. Then, binding energies (ΔG_{Bind}) as a criterion of the aptamer specificity were computed by using the 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 the SELEX process to introduce new aptamers for a wide variety of targets.

There are some advanced classical MD simulation methods that are helpful for designing the diverse biosensors, such as the Langevin dynamics (LD), replica-exchange MD (REMD), steered MD (SMD), metadynam-

ics (MTD), and so on (Mollaamin, Najafi, Khaleghian, Hadad, & Monajjemi, 2011; Sponer et al., 2018). Metadynamics 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 conformational sampling. The conformational biomolecule landscapes were studied through a time-dependent bias potential. Besides, effect of bioreceptor modification and interference of 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.

Over the past decade, liquid crystals (LCs) have been extremely applied in the field of 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). Recently, the LC-based biosensors have gained the great attention as the new candidates for the label-free optical target monitoring, due to the special properties including simple fabrication, great sensitivity, cost-effectiveness, high response speed, and no need for laborious processes, additional labeling step, and complex instruments (Hong & Jang, 2020; H. J. Kim, Jang, & Chemical, 2019; Rouhbakhsh, Verdian, & 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, Wang, Xiong, & Deng, 2019; D. Zhao et al., 2015). Hence, 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-based sensor 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

The QM calculations have been applied extensively 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:

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 method can 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 a combination of them can be efficient in designing biosensors. An impressive set of the hybrid methods has been 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 functionalization of atomic force microscopy (AFM) tips, covered by a biomolecule that was able to interact with the target (Figure 4). 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 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 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 high selectivity.

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 replica exchange Monte Carlo (REMC) was applied to investigate the flexibility of the mutated peptides and maximize the target-peptides binding affinity (Figure 5). 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 to improve the efficiency of the designed procedure. The shape and electrostatic complementarity scores were used 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 HIV-1 protease and the peptides 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. Therefore, 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 51A1as a crucial enzyme for the sterol biosynthesis. The designed approach included 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 for the aptamers design. 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.

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 introduced a urea-based chromogenic sensors to selectivity detect $H_2PO_4^-$ anion. The binding affinities of thiourea-based receptors towards the different anions were obtained by the QM calculations. The results clarified that the binding energies were influenced by the solvation effect, dielectric medium, anion basicity, and number of 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. So, 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, constructed of glycine (CP1), alanine (CP2), and glycine-valine (CP3) sequences, were selected to have complexation with the different metal ions. The structural analysis, binding energies, charge transfer interactions, and topological results proved that the CPs possessed the greatest stable complexes with Be^{2+}. MD simulation was also applied to study the complexes, and the electrostatic interaction energy analysis demonstrated that CP2 cyclic peptide was the most efficient receptor for Be^{2+} ion. Hence, QM/MD studies can be beneficial to design 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 6). 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 interactions with the aptamer binding sites. The QM/ MD study revealed that the proposed aptasensor was an efficient candidate for the neomycin B detection. Consequently, a coupling of QM calculations with MD simulation analyses can be extremely applied to design the aptasensors functionalized with the diverse nanoparticles including AuNPs, AgNPs, magnetic NPs, carbon-based NPs (graphene, graphene oxide, quantum dots, and so on) for a wide range of targets.

Besides, they (Khavani, Izadyar, & Housaindokht, 2019b) applied a joint theoretical and experimental study to design novel 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, as a criterion for their sensing ability, were examined from the theoretical point of view. The geometrical and energetic parameters proved the greater affinity of two mutants toward neomycin B in comparison with the initial aptamer. A colorimetric method was applied that highlighted the ability of the MD simulation to introduce new aptamers for further experimental application. QM calculations clarified the van der Waals and electrostatic interactions as the driving force of the aptamer complexation with the target (Figure 7). Also, the QM/ MD studies can be applicable for designing biosensors through exploring conformational motions and allosteric regulation of the target and biorecognition elements (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. MM methodology applies the classical mechanics rules to reduce the cost of the QM calculations. The application of hybrid QM/ MM methodology 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 $\varkappa^2$ 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 affect the precision of the obtained results.

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

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 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 quantitatively was used to 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 effective electronic and structural properties on the biological activity through studying the ligand-probe interaction. The applied methods highlighted the potent agonists for AMPK.

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. Therefore, the hybrid methodologies can be the novel approaches with a great potential to provide the precise information for facilitating the experimentally design of biosensors.

3. Conclusions and Future Perspectives

Designing the efficient biosensors with the highest 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 requirement for the approaches to overcome the drawbacks. Hence, the computational methods have been 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. Successful computational design of biosensors is dependent on the precise structure modeling, high biosensing components stability, and optimizing the molecular interactions. MD simulation provides molecular-level insights and represents geometries, energies, and many physicochemical properties of the biosensor components. Besides, it can be applied for optimizing the conditions to achieve the highest biosensor performance. So, MD simulation method possesses the 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 applied to design new bioreceptor segments with an improved sensitivity toward a desired target through 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 method. As a perspective, designing multi-functional aptasensors can be promising for simultaneous detection of a collection of 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 binding affinity to a target. As a perspective, the MD screening method can be applied to design new specific aptamers for a target with no relying on the initial SELEX results. Indeed, 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 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 the biosensor components through providing precise bioreceptor-target binding energy. QM method has appeared very capable in designing electrochemical biosensors by introducing the quantum conductance parameter. However, the application of QM calculations has been restricted for the biological systems containing thousands of atoms, due to impractical calculation of the shielding tensor. Hence, hybrid QM/ MM method has been developed to overcome the restriction. Molecular docking is another computational method with simplicity to use and comprehensible concept that facilitate the identification of 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 highest efficient designed bioreceptor and decreases the number of the suggested candidates for experimental test. However, it has recently emerged in the field of biosensor design. Since biosensors can be designed by the investigation of the unique parameters of the computational methods, a combination of them can promote the computational progress for this purpose through 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 using 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.

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Figure Legends

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 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 5. 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 6. 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 7. 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).

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