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Review

Exploring the role of receptor flexibility in structure-based drug discovery

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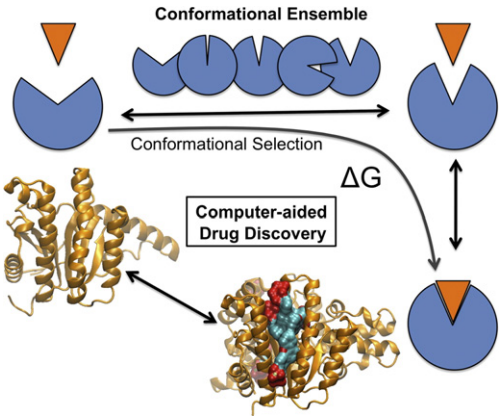
HIGHLIGHTS

- Receptor flexibility plays a key role in structure-based drug design.
- Receptor ensemble-based methods improve predictive power of virtual screening.
- MD and enhanced sampling techniques are useful tools to explore conformational space.

GRAPHICAL ABSTRACT



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ABSTRACT

The proper understanding of biomolecular recognition mechanisms that take place in a drug target is of paramount importance to improve the efficiency of drug discovery and development. The intrinsic dynamic character of proteins has a strong influence on biomolecular recognition mechanisms and models such as conformational selection have been widely used to account for this dynamic association process. However, conformational changes occurring in the receptor prior and upon association with other molecules are diverse and not obvious to predict when only a few structures of the receptor are available. In view of the prominent role of protein flexibility in ligand binding and its implications for drug discovery, it is of great interest to identify receptor conformations that play a major role in biomolecular recognition before starting rational drug design efforts. In this review, we discuss a number of recent advances in computer-aided drug discovery techniques that have been proposed to incorporate receptor flexibility into structure-based drug design. The allowance for receptor flexibility provided by computational techniques such as molecular dynamics simulations or enhanced sampling techniques helps to improve the accuracy of methods used to estimate binding affinities and, thus, such methods can contribute to the discovery of novel drug leads.

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Contents

1. Biomolecular recognition mechanisms

Biomolecular recognition is at the heart of all biological processes that take place in living organisms. Understanding how a ligand binds to a biological receptor, how proteins interact with each other, how lipids and proteins aggregate in the cell membrane, and how these events trigger or block a wide range of biochemical reactions is of paramount importance, not only for the field of biophysics but also for other disciplines such as rational drug design. In the last decades, the interpretation of mechanisms describing biomolecular recognition has been the focus of a passionate debate that has contributed to push forward the research in many fields such as biophysics and pharmacology among others [1–3]. More than 50 years ago, our view of binding events underwent a Copernican turn evolving from an idea based on rigid lock-and-key like models to be described as a dynamic and flexible process [4,5]. All these findings not only served to advance the field towards a better understanding of protein–ligand binding but also introduced an extra degree of complexity to the description of biomolecular recognition processes. Biomolecular recognition is an intricate process of orchestrated and random motions, where the ligand from one side and the receptor from the other seek for complementary conformations to improve the binding affinity with its partner along this fascinating biomolecular dance.

The description of protein–ligand interactions is not a simple task due to the variety of motions and mechanisms interplaying in this complex but vital process. To comprehend how biomolecular recognition occurs, we first need to understand the role of all different partners involved in this association process. One of the main centers of attention has been to elucidate the role played by the ligand during the binding event. In particular, whether it is directly responsible for inducing a conformational change to the biological receptor upon binding or whether it stabilizes specific preexistent conformational states displayed by the dynamic protein. In other words, by which mechanisms do ligands such as substrates or synthetic drugs regulate biochemical reactions? In the last decades, the concepts of induced fit and conformational selection emerged as the most popular mechanisms to explain the intricate biomolecular recognition process. The idea of induced fit, introduced by Koshland more than fifty years ago, relies on the formation of an initial loose ligand–receptor complex that induces a conformational change in the protein, resulting in a series of rearrangements that lead to a complex with tighter binding [4]. This model implies that interacting biomolecules do not necessarily have a complementary shape prior the binding event because it is induced by the ligand. However, experimental evidences based on kinetic studies proved that the induced fit hypothesis was not able to describe all the variety of binding scenarios [6]. In 1999, Nussinov and coworkers coined the term conformational selection, also known as population shift, which is based on the idea that all conformations are present when the ligand is not bound to the receptor and, then, the ligand acts to selectively stabilize specific receptor conformations, causing a shift in the populations observed in the unbound ensemble towards this specific conformational state (see Fig. 1) [7–10]. Both theories, although they appear to be antagonistic, are not necessarily mutually exclusive. Recent studies show that conformational selection is usually followed by a conformational adjustment [11]. In this line, extended models that combine characteristics of conformational selection, induced fit and classical lock-and-key mechanisms have been reported [3]. Despite being often disregarded, water plays a crucial role in molecular association. In the last years, great efforts have been put to determine the nature of the hydrophobic effect and its implications for biomolecular recognition. Experimental and theoretical studies have pointed out the capital importance of both entropic and enthalpic contributions of water networks to the free energy of binding [12–15]. Computer-aided drug design techniques try to incorporate some of the main features of biomolecular recognition process to improve the accuracy and predictive power of these computational methods. For example, a plethora of techniques have been proposed to account for conformational selection and induced fit during the estimation of binding affinities in structure-based virtual screening [16–19].

The debate on mechanisms underlying biomolecular recognition has been always strongly linked to the study of allosteric effects. Allostery is a phenomenon that describes the interaction occurring between a regulatory site, also called allosteric site, and another site of the protein, usually the active site, that gives rise to a functional change on the latter [5,20]. This process is mediated by an effector that binds to the allosteric site, which induces a conformational change to the protein that affects the activity of another site, altering protein function. Thus, the allosteric effector is responsible for regulating the biological activity of the protein. The allosteric term was coined and popularized in the early 1960s by Changeux, Jacob and Monod from their studies of conformational changes mediated by signal transduction in several enzymes, where they tried to initially explain allosteric effects from the induced fit perspective [21,22]. Despite the youth of the term allostery, this concept underwent a rapid revolution when the Monod–Wyman–Changeux (MWC) model was proposed to account for positive cooperativity and allosteric effects of oxygen binding in myoglobin [5]. This model states that when an allosteric binding event occurs, a shift of the equilibrium of two pre-existing conformational states is observed. Consequently, the early works of Changeux and coworkers laid the foundations of some of the ideas that would eventually lead to the introduction of the conformational selection biomolecular recognition mechanism. The MWC theory of allostery was opposed to the Koshland–Némethy–Filmer (KNF) model, which explained the conformational transitions observed as a consequence of allosteric binding, in the same terms as the induced fit theory [23]. The KNF theory also incorporated some of the ideas introduced by Pauling on the study of cooperativity in oxygen binding in hemoglobin [24]. After several years of discussion, the MWC model and its subsequent generalizations [3,25,26] remained as the most widely used theories to account for allosteric effects. A third model of allostery, referred to us as entropic allostery, pictures the remote effects of ligand binding to have a purely