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Computer-Aided Drug Design

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Once, a US General summarized his philosophy on warfare in just four concise statements, "The art of war is simple enough. Find out where your enemy is. Get at him as soon as you can. Strike him as hard as you can, and keep moving." Although these overarching statements formed the basic premise of modern war strategies, the same concepts have been applied in designing new drugs aimed at combating a broad range of diseases. In this context, rational drug design or computer-aided drug design [1-3] has been established as an exciting research approach aimed at developing safer and more efficacious drugs using modern computational tools which are fast and inexpensive compared to traditional methods. The ultimate goal of this research is to design small organic compounds that bind to a specific molecular target, and result in the inhibition (or less frequently, activation) of a particular protein or enzyme involved in a given cellular pathway, i.e. a blockage of a specific protein-protein interaction. The development of such drugs has been recognized early on by the pharmaceutical industry as a principal foundation that provides it with the necessary return on investment to fuel further research and development [4] leading to a discovery and development cycle.

Our understanding of cell mechanisms and pathways at a molecular level becomes deeper and clearer every day. This is largely due to the great efforts and hard work of genomic and proteomic research groups who add novel targets for drug intervention on a regular basis [5-7]. Thus far, several hundred proteins have been synthetically expressed and many of them are currently evaluated for their druggability [5]. These targets involve several families comprised of G-protein coupled receptors (GPCRs), ligand-gated ion channels (LGICs), cytoskeleton proteins, phosphatases, kinases, nuclear receptors (NRs) and DNA repair proteins. The growing list of potential drug targets encourages a bold question if it is in principle possible to restore any diseased cell to a healthy state by uncovering a drug for every potential druggable target? Certainly, if this dream is ever realized, many diseases will be cured and relegated to the dustbin of history in a manner similar to the effect of the discovery of vaccines in the 19th and early 20th century. We think this is most definitely achievable as a result of rapid progress made in the computational drug discovery area.

A typical rational drug design effort involves many tools that can be used either separately or in combination depending on the available structural and kinetic data. Once the structure of a target (typically a protein) is available, docking algorithms can be used to place each ligand (i.e. a molecule or a molecular fragment included in a typical library of compounds) and predict its most probable binding mode within the binding site of the target [8,9]. Moreover, most docking programs can rank the predicted activity of each compound by analyzing the different ligand-target interactions in terms of the estimated binding affinity of the complex. In addition to docking techniques, one can define the essential interactions between the ligand and the binding site of the receptor and translate this information into the formulation of binding-site pharmacophore models [10]. These models can be used to search the available chemical space for compounds that can complement the physicochemical features of the receptor. As these two procedures require a comprehensive understanding of the structural arrangement of the target, they have been commonly termed as structure-based drug design (SBDD). On the other hand, and for most of the cases, the three-dimensional structure of the target, the binding site or even the target itself are not accurately known, although there may be a number of known active compounds that have been identified experimentally. In this case, data mining algorithms can be used to screen for compounds that are structurally similar to the known actives (similarity search) [11] or that comprise the chemical features of these compounds (pharmacophore search) [12], in what is called ligand-based drug design (LBDD). Thus, these two fundamental procedures, SBDD and LBDD, form the general layout of present-day rational drug design protocols.

Despite the recent seminal advances in computer software and hardware combined with the continuous exponential growth of biological information, there are many challenges still to be addressed. The most important challenge is to combine the wealth of knowledge in genomics, proteomics, systems biology, population genetics and pharmacogenomics with the advancements in computer software and hardware to truly mimic biological systems while designing new drugs. This requires more accurate force fields, scoring functions, docking and alignment algorithms in addition to more precise chemoinformatics and bioinformatics tools. Each of these topics is currently considered a rapidly growing field that has branched into subfields with the aim of providing better representations of the interacting biological systems and ultimately designing save and effective drugs [13-18].

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