Review Article

Computer Aided Drug Discovery and Development - An Important Need of the Hour

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ABSTRACT

Discovery of a new drug is a very difficult task. Pharmaceutical and biotechnology companies need to make huge investments in the discovery of a single drug that may cure a disease or simply alleviate the symptoms of another. These are businesses like any other and profits fuel their growth and provide the investments for future discoveries. Most pharmaceutical or biotechnology companies claim that it costs anywhere between $800 million to $900 million and a time span of twelve to fifteen years to discover a new drug. This may be the reason why in most of the countries till this date their pharmaceutical industries could not launch any new drug in the market and they are satisfied with the business of generic drugs only. In silico-chemico-biological approach computer plays very important role in discovery of new dug, not only it can save money but also time, and are believed to offer means of improved efficiency for the industry. CADDD is being utilized to identify hits (active drug candidates), select leads (most likely candidates for further evaluation), and optimize leads i.e. transform biologically active compounds into suitable drugs by improving their physicochemical, pharmaceutical, ADMET/PK (Absorption, Distribution, Metabolism, Excretion and Toxicity/ pharmacokinetic) properties. Virtual screening is used to discover new drug candidates from different chemical scaffolds by searching commercial, public, or private 3-dimensional chemical structure databases.

Keywords: Silico-Chemico-biological approach, virtual screening.

INTRODUCTION

Discovery of a new drug is a very difficult task. Pharmaceutical and biotechnology companies need to make huge investments in the discovery of a single drug that may cure a disease or simply alleviate the symptoms of another. These are businesses like any other and profits fuel their growth and provide the investments for future discoveries. Most pharmaceutical or biotechnology companies claim that it costs anywhere between $800 million to $900 million and a time span of twelve to fifteen years. In silico-chemico-biological approach computer plays very important role in discovery of new dug, not only it can save money but also time. Use of computational techniques in drug discovery and development process is rapidly gaining in popularity, implementation and appreciation..Both computational and experimental techniques have important roles in drug discovery and development and represent complementary approaches. CADDD entails:

1. Use of computing power to streamline drug discovery and development process.
2. Leverage of chemical and biological information about ligands and/or targets to identify and optimize new drugs.
3. Design of in silico filters to eliminate compounds with undesirable properties (poor activity and/or poor Absorption, Distribution, Metabolism, Excretion and Toxicity, ADMET) and select the most promising candidates Fast expansion in this area has been made possible by advances in software and hardware computational power and sophistication, identification of molecular targets, and an increasing database of publicly available target protein structures. CADDD is being utilized to identify hits (active drug candidates), select leads (most likely candidates for further evaluation), and optimize leads i.e. transform biologically active compounds into suitable drugs by improving their physicochemical, pharmaceutical, ADMET/PK (pharmacokinetic) properties. Virtual screening is used to discover new drug candidates from

different chemical scaffolds by searching commercial, public, or private 3-dimensional chemical structure databases. It is intended to reduce the size of chemical space and thereby allow focus on more promising candidates for lead discovery and optimization. The goal is to enrich set of molecules with desirable properties (active, drug-like, lead-like) and eliminate compounds with undesirable properties (inactive, reactive, toxic, poor ADMET/PK). In another words, in silico modelling is used to significantly minimize time and resource requirements of chemical synthesis and biological testing. The rapid growth of virtual screening is evidenced by increase in the number of citations matching keywords "virtual screening" from 4 in 1997 to 302 in 2004[1]. In his 2003 review article, Green of GlaxoSmithKline concluded that: "The future is bright, the future is virtual"[2] Comparison of traditional and virtual screening in terms of expected cost and time requirements. Stressed the reality that pharmaceutical industry needs to find means of improving efficiency and effectiveness of drug discovery and development in order to sustain itself. This was recently echoed in 2006 that the current business model will become fundamentally untenable unless there is a significant improvement in efficiency and effectiveness of the process.

Estimates of time and cost of currently bringing a new drug to market vary, but seven–twelve years and $ 1.2 billion are often cited[3]. Furthermore, five out of forty thousand compounds tested in animals reach human testing and only one of five compounds reaching clinical studies is approved. This represents an enormous investment in terms of time, money and human and other resources. It includes chemical synthesis, purchase, curation, and biological screening of hundreds of thousands of compounds to identify hits followed by their optimization to generate leads which requiring further synthesis. In addition, predictability of animal studies in terms of both efficacy and toxicity is frequently suboptimal. Therefore, new approaches are needed to facilitate, expedite and streamline drug discovery and development, save time, money and resources. It is estimated that computer modelling and simulations account for ~ 10% of pharmaceutical R&D expenditure and that they will rise to 20% by 2016[4]. Role of computational models is to increase prediction based on existing knowledge[5]. Computational methods are playing increasingly larger and more important role in drug discovery and development[5-12] and are believed to offer means of improved efficiency for the industry. They are expected to limit and focus chemical synthesis and biological testing and thereby greatly decrease traditional resource requirements. Modern drug discovery and development process including prominent role of computational modelling. represents a brief overview, rather than an exhaustive review, of CADDD and the following commonly used computational approaches will be discussed: ligand-based design (pharmacophore)[13], structure (target)-based design (docking)[14], and quantitative structure-activity/property relationships (QSAR/QSPR) (computational predictive toxicology)[15]

Designing and Development of Pharmacophore followed by Docking

IUPAC defines pharmacophore as, "The ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response. A pharmacophore does not represent a real molecule or a real association of functional groups, but a purely abstract concept that accounts for the common molecular interaction capacities of a group of compounds towards their target structure. The pharmacophore can be considered as the largest common denominator shared by a set of active molecules". Pharmacophoric descriptors include H-bond donors, H-bond acceptors, hydrophobic, aromatic, positive ionisable groups, negative ionizable groups. They represent chemical feature complimentarily to the receptor in the three-dimensional space. Further enhancement of a pharmacophore can be obtained by combining it with shape and exclusion volumes (steric) constraints[16]. These enhancements decrease likelihood of finding molecules with a suitable three-dimensional arrangement of functional groups but wrong shape that could prevent them from fitting into the receptor binding site. Pharmacophore requires knowledge of active ligands and/or target receptor. They are number of ways to build a pharmacophore. It can be done based on chemical structure of three or four known active

compounds from different chemical scaffolds[17,18]. Applications and benefits of CADDD have been reviewed and demonstrated in growing number of publications and supported by examples of drugs derived from the in silico approach[19–24]. Virtual screening has been shown more efficient than commonly used empirical screening. Shoichet reported that ligand discovery i.e. hit rates (number of compounds binding to a target divided by number of compounds tested) is greater in virtual screening by three or four orders of magnitude than in empirical screening[25]. Others have reported similar results[26–28]. Number of reports citing successful application of CADDD in developing specific drugs in different therapeutic areas is expanding rapidly. Pharmacophore library screening followed by docking represents complimentary screening methods with the combination providing optimum results[29]. Commonly, this screening approach is preceded by a prior filtering of virtual databases (e.g. physicochemical, ADMET/PK, stability, reactivity, toxicity, drug-like properties, etc.)[30–34]. This combination of screening methods has been successfully employed in designing new hits and leads; typically, this approach involves virtual screening (pharmacophore plus docking) of virtual chemical structure libraries containing hundreds of thousands of compounds and necessitating chemical synthesis and biological screening of less than hundred compounds to yield a handful of drug candidates with good receptor affinities. Recently, application and utility of this virtual screening approach in combination with activity-guided fractionation of medicinal plants was also demonstrated and coined “in combo screening”[35–39].

QSAR/QSPR: Quantitative Structure Activity Relationship/Quantitative Structure Property Relationship

QSAR and QSPR are commonly used computational methods in predictive toxicology. In a strict sense, these two terms are not synonymous even though the term QSAR tends to be used for both QSAR and QSPR. The principle behind them is the same, but they have a different context in terms of the dependent variable, biological activity (QSAR) vs. bio-physico-chemical property (QSPR). Independent variables represent molecular descriptors, e.g. electronic, spatial, topological, conformational, thermodynamic, quantum mechanical, etc. The idea of structure-activity relationship dates back to 1868[40] when Crum Brown and Frazer reported on the correlation of paralyzing activity to the nature of quaternary group of a collection of strychnine-like compounds. More recently, studies of Corwin Hansch in the 1960’s demonstrated applicability and usefulness of QSAR/QSPR approach and led to its growing use[41,42]. Interest in the use of QSAR in the regulatory arena has been growing and is being evaluated[43].

CONCLUSION

CADDD is being utilized to identify hits (active drug candidates), select leads (most likely candidates for further evaluation), and optimize leads i.e. transform biologically active compounds into suitable drugs by improving their physicochemical, pharmaceutical, ADMET/PK (Absorption, Distribution, Metabolism, Excretion and Toxicity/ pharmacokinetic) properties. Virtual screening is used to discover new drug candidates from different chemical scaffolds by searching commercial, public, or private 3-dimensional chemical structure databases.

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