International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1494-1497www.ijprajournal.com ISSN: 2456-4494

Role of Insilico Methods in the pharmaceutical Industry

NAJUMA ANZAR F[1], SANOOJA K[2], NIVYA MOHAN K[3]and ANASWARA R NATH[4]

1-Department of pharmaceutics/Kerala University of Health sciences/KMCT College of pharmaceutical sciences/kerala-6763012
2, 4-Department of pharmacology/KMCT College of pharmaceutical sciences/Kerala-676301
3-Department of pharmaceutical chemistry/KMCT College of pharmaceutical sciences/Kerala-676301

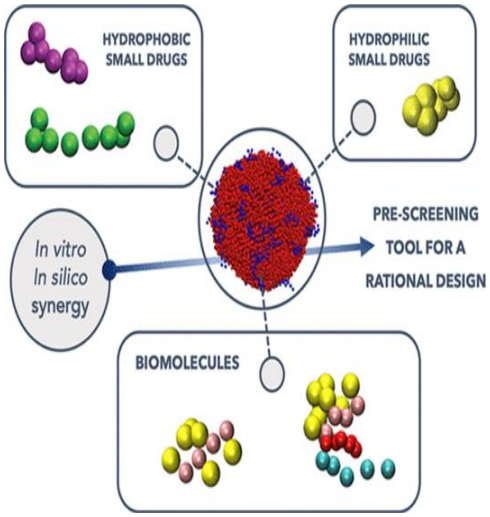
Submitted: 05-08-2022 Accepted: 14-08-2022

ABSTRACT
Drugs were discovered by synthesizing compounds in a time-consuming multi-step processes against a battery of in vivo biological screens and further investigating the promising candidates for their pharmacokinetic properties, metabolism and potential toxicity. Across the spectrum of industrial sectors, including pharmaceuticals, chemicals, personal care products, food additives and their associated regulatory agencies, there is a need to develop robust and reliable methods to reduce or replace animal testing. The main goal of this review is to summarize the insilico methods in the areas of drug discovery process with emphasis on identifying drug targets, pharmacology and pharmacokinetics**.**

Key words: Quantitative structure–activity relationships, Homology models, Pharmacology, Insilicon, In vitro Drug discovery,

I. INTRODUCTION

In silico computational models provide the tools to qualitatively and quantitatively evaluate various treatments on specific diseases and to test a larger set of different conditions (e.g. dosing). These models are abstract representations used to model human diseases, a concept which is often limited by in-vitro/vivo techniques [1].
In comparison to in-vivo techniques, which are performed in whole organisms, in silico modeling offers more practical, economical experiments. Furthermore, computational methods limit the use of animal models in research which supports the rationale in designing novel, safe drug candidates [2].



The pharmaceutical industry has a growing and pressing need for accurate and economical methods to identify new lead candidates and to optimize lead compounds during drug development [3]. In silico methods play an important role in this process. Common in silico methods include, but are not limited to, pharmacophore identification followed by searching against three-dimension (3D) structure database [4], virtual screening by docking small molecules into target enzyme for lead discovery, and quantitative structure activity relationship (QSAR) methods for lead optimization and absorption, distribution, metabolism, excretion and toxicity (ADME/Tox) prediction.
The use of complementary experimental and informatics techniques increases the chance of success in many stages of the discovery process, from the identification of novel targets and elucidation of their functions to the discovery and development of lead compounds with desired properties

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1494-1497www.ijprajournal.com ISSN: 2456-4494

HISTORY OF INSILICO MODEL

Drug design and related disciplines in drug discovery did not wait for the advent of informatics to be born and to grow as sciences. As masterfully summarized byAlbert (1971,1985), the earliest intuitions and insights in structure–activity relations can be traced to the nineteenth century. A relation between activity and a physicochemical property was firmly established byMeyer (1899) andOverton (1901), who proposed a 'Lipoid theory of cellular depression' such that the higher the partition coefficient between a lipid solvent and water, the greater the depressant action. Such papers paved the way for the recognition of lipophilicity and electronic properties as major determinants of PD and PK responses, as best illustrated by the epoch-making and still ongoing work of Corwin Hansch(Hansch and Fujita, 1964;Hansch, 1972), a founding father of drug design.Other pioneers (for example, Crum Brown and Fraser; reviewed by (Albert, 1971)) saw that chemical structure (that is, the nature and connectivity of atoms in a molecule, in fact the two-dimensional structure (2D) of compounds) also played an essential role in pharmacological activity[4].

The conceptual jump from 2D to three-dimensional (3D) structure owes much to the work ofCushny (1926), whose book summarizes a life dedicated to relations between enantiomerism and bioactivity. This vision was expanded in the mid-twentieth century by the discovery of conformational effects on bioactivity (Burgen, 1981[3].

In parallel with our growing understanding of the concept of molecular structure, a few visionary investigators in the late nineteenth and early twentieth centuries (for example, John Langley, Paul Ehrlich and Alfred Clark; reviewed by (Arïens, 1979;Parascandola, 1980) developed the concept of receptors, namely the targets of drug action. The analogies between receptors and enzymes were outlined byAlbert (1971).

The birth of quantitative structure–activity relationships (QSARs), followed in the 1980s and 1990s by computer graphics and molecular modeling. However, computer sciences rapidly ceased to be a simple tool in drug discovery and pharmacology and became a major contributor to progress.

ADVANTAGESOF INSILICO METHODS

- In silico methods have the advantage that they can make fast predictions for a large set of compounds in a high-throughput mode.
- In silico methods make their prediction based on the structure of a compound even before it has been synthesized
- Good predictivity of an in silico method is crucial if the method is to be introduced into the drug development process

APPLICATION OF IN SILICO METHODS

- **Drug Discovery**

Drug discovery and development is an intense, lengthy and an interdisciplinary endeavor. Drug discovery is mostly portrayed as a linear, consecutive process that starts with target and lead discovery, followed by lead optimization and pre-clinical in vitro and in vivo studies to determine if such compounds satisfy a number of pre-set criteria for initiating clinical development. Insilico approach has been of great importance to develop fast and accurate target identification and prediction method for the discovery[5].

There are five insilico methods in drug discovery. They are Molecular docking, Virtual High through put screening, QSAR (Quantitative structure-activity relationship), Pharmacophore mapping, Fragment based screening and which are discussed below.

- **Molecular docking**

Docking is the computational determination of binding affinity between molecules (protein structure and ligand). Given a protein and a ligand find out the binding free energy of the complex formed by docking them. Docking or Computer aided drug designing can be broadly classified as "Receptor based methods" which make use of the structure of the target protein and "Ligand based methods" which is based on the known inhibitors[4].

- **QSAR (Quantitative structure-activity relationship)**

QSAR is statistical approach that attempts to relate physical and chemical properties of molecules to their biological activities. The aim of QSAR is the prediction of molecular properties from their structure without the need to perform the experiment using invitro orinvivo. It saves times and resources [5]. Various descriptors like molecular weight, number of rotatable bonds Log P etc. are commonly used. Many QSAR approaches are in practice based on the data dimensions. It

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1494-1497www.ijprajournal.com ISSN: 2456-4494

ranges from 1D QSAR to 6D QSAR. The methods called quantitative structure-activity relationship (QSAR) are based on the assumption that the activity of a certain chemical compound is related to its structure.

Sometimes it is said that QSAR models represent a way for industry to spend less for toxicological research, or can be used to save animals to be used for experiments. The real challenge is not to identify the best method to protect human beings and environment [9].

- **Pharmacophore mapping**

It is the process of deriving a 3D pharmacophore. A pharmacophore is a set of features together with their relative spatial orientation that are thought to be capable of interaction with a particular biological target such as Hydrogen bond donors and acceptors, positively and negatively charged groups, hydrophobic regions and aromatic ring[10].

A Pharmacophore map can be generated by superposition of active compounds to identify their common features. Based on the pharmacophore map either de novo design or 3D database searching can be carried out. Frequently small molecules with very different 2D structures displace each other from a binding site on macromolecules. The goal of pharmacophore mapping is to transform such 2D structure-activity information into the 3D requirements for binding to the target biomolecule. A pharmacophore features include hydrogen bond acceptor atoms, hydrogen bond donor atoms, hydrogen bond donor site, hydrogen bond acceptor site, and hydrophobic centers.

- **Virtual High Throughput Screening**

Virtual screening is a computational method where large libraries of compounds are assessed for their potential to bind specific sites on target molecules such as proteins, and well-matched compounds tested. Virtual screening (VS) is a computational technique used in drug discovery research. By using computers, it deals with the quick search of large libraries of chemical structures in order to identify those structures which are most likely to bind to a drug target, typically a protein receptor or enzyme [6].

Walters, et al. define virtual screening as "automatically evaluating very large libraries of compounds" using computer program [7]. As this definition suggests, VS has largely been a numbers game focusing on questions like how can we filter down the enormous chemical space of over 1060 conceivable compounds [8] to a manageable number that can be synthesized, purchased, and tested. It is less expensive than High Throughput Screening, Faster than conventional screening, scanning a large number of potential drugs like molecules in very less time.

- **Drug repurposing**

In addition to optimizing drug design, in silico models have been used in drug repurposing. An example of computational biology in drug development is network-based drug-repurposing (NB-DRP). In NB-DRP, the relationships between biological compounds are organized into networks in order to identify emerging properties at a network level. The network allows users to examine how cellular systems undergo different biological phenotypes under various conditions.

In terms of structure, a network is created as a connected graph, in which each node represents a drug or biological target within a target pathway. The benefit of this network brings a perspective to complex diseases which arise from the interaction of many biological networks[6].

The study created a network using ‘claims data’ which includes diagnostic history of genetic and non-genetic diseases, in addition to risk factors. Claims data also provides chronological medical histories of patients. The constructed network allowed a large-scale analysis of associations between diagnoses, and a better understanding of the relationship across multiple diseases.

In silico imaging in clinical trials

While conventional clinical trials can inform whether a product/technology is unsafe or ineffective, they often fail to explain why or how to improve it.In silico clinical trials utilize computer simulation in the development or evaluation of a medical device, intervention or product. This overcomes the challenges of conventional clinical trials by creating algorithms that identify an error or simulating potential improvements[7].

Imaging in silico clinical trials is a prime example of using computational modeling in biological science. In silico imaging is described as the computational simulation for an entire imaging system. The simulation creates the source, the objection, detection and interpretation that are typically used to evaluate new technologies. The primary endpoint of these clinical trials is to determine the scientific value of imaging technology in comparison to the standard of care. The evaluation of imaging techniques is conducted

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1494-1497www.ijprajournal.com ISSN: 2456-4494

across three main categories: detection, diagnosis, and guiding/monitoring of disease treatment.

II. CONCLUSION

In silico methods are steadily providing economic and ethical benefits as an alternative to the traditional animal models in drug development. In silico methods is effective for the simple assessment of the toxic effects of a drug, while complex molecular interactions require advanced deep learning networks with multiple sequence alignment such as the new AlphaFold system that accurately elucidates the 3D structure of proteins. Further highlighting the extensive economic and ethical contributions of in silico tools in promoting drug safety is needed.

REFERENCES:

[1]. https://www.prescouter.com/2022/02/advantages-of-in-silico-toxicology-in-drug-development/
[2]. https://proventainternational.com/a-critical-evaluation-of-the-advantages-and-limitations-of-in-silico-methods-in-clinical-
[3]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1978274/#__sec2title
[4]. Pugazhendhi et al. Insilico Methods in Drug Discovery - A Review. Int J Adv Res Comp Sci Software Engg. 2013;3(5):680-683.
[5]. Bohacek RS, Mc Martin C, Guida WC. The art and practice of structure-based drug design: a molecular modeling perspective. Med Res Rev. 1996;16:3–50.
[6]. Walters WP, Stahl MT, Murcko MA. Virtual screening – an overview. Drug Discov Today. 1998;3(4):160– 178.
[7]. https://journals.sagepub.com/home/atl
[8]. http://en.wikipedia.org/wiki/Virtual_high_throughput_screening
[9]. S Ekins, J Mestres, B Testa. In silico pharmacology for drug discovery: methods for virtual ligand screening and profiling. British J Pharmacol. 2007;152:9–20.
[10]. Di Masi JA, Hansen RW, Grabowsk HG. The price of innovation: new estimates of drug development costs. J Health Econ. 2003;22:151–185.