MATHEMATICAL MODELS IN DRUG TARGET ANALYSIS: PHARMACOKINETIC AND PHARMACODYNAMIC APPROACH

Abstract

Accurate prediction of drug targets is essential for successful drug design and optimization in the drug discovery and development realm. Various mathematical models have been developed to aid in drug target prediction, incorporating different data types and techniques. One approach is to identify and quantify the protein pathway that is important to the development of diseases or affected by drug therapy with proteome data. This approach involves the construction of quantitative system pharmaceutical models of a disease scale that can predict the therapeutic or side effects of drugs.

Another approach to drug target prediction is the pharmacokinetic and pharmacodynamic (PK/PD) profiling. The PK/PD approach involves the study of how drugs interact with their target proteins and the subsequent effects on pharmacokinetics and pharmacodynamics. By understanding the thermodynamic and kinetic information of drug- target interactions, researchers can gain insights into how drugs bind to their targets and how to optimize their efficacy and minimize potential side effects. These models rely on the integration of genomic, proteomic, and metabolomic data, allowing for a more comprehensive understanding of disease pathology and drug response. By incorporating large-scale data sets and using mathematical algorithms, these models can identify key mechanisms underlying disease pathology and predict potential therapeutic targets. Additionally, mathematical algorithms can also be used to predict the "drug target-likeness" of a protein. Furthermore, mathematical models can aid in predicting the binding affinity between drugs

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and their targets.

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I. INTRODUCTION

Dynamic mathematical models play a crucial role in drug target prediction by providing a systematic framework to study the interactions between drugs and their targets within a biological system. These models include mathematical equations to simulate and predict the dynamics of interaction between drugs and targets, helping to identify and validate potential drugs. Dynamic mathematical models are being used to predict drug targets in a number of ways. One of the recommended ways is to use these mathematical models to stimulate drug binding to a receptor protein. This can be done by modeling the interactions between the drug and the receptor protein at the molecular level. Another way to account for a dynamic model of a biological system is a time-dependent variation in the parameters. These models are usually expressed by differential equations.

Dynamic mathematical models are still under development, but they have the potential to revolutionize the way that drug targets are predicted. By providing a more detailed understanding of how drugs interact with receptors and signaling pathways, these models can help identify new drugs targeted for the most effective treatment of diseases. In this review chapter, some key aspects of dynamic mathematical models will be discussed in drug target analysis in various therapeutic system.

1. **Pharmacokinetic Models**: In order to understand Pharmacokinetic models (PKs) clinical data must be analyzed in terms of ADME (absorption, distribution, metabolism, and excretion) of drugs with response to the body. These models consider factors such as drug concentration, tissue distribution, and clearance rates to predict how a drug interacts with its target over time. Pharmacokinetic models provide insights into drug exposure levels, optimal dosing regimens, and potential drug-drug interactions, aiding in target selection. Relative to dynamic systems, mathematical modeling (linear) takes account of both the drug administration and the body's response to it. Primarily, kinetic models estimate and depict the amount of drug 'D' from the solid form as a function of time t, or f=D(t). Since the underlying mechanism is mostly unclear in practice, semi-empirical equations using basic functions (exponentials, polynomials, etc.) have been proposed. Tonge has described a time-dependent target occupancy model which converts drug-target kinetics into a time-dependent drug activity in the disease state. [1] Another approach is the pharmacokinetic model of drug-drug interactions that occurs when a drug alters the disposition (absorption, distribution, elimination) of a co-administered drug. Pharmacokinetics interactions are mediated by drug metabolizing enzymes and receptor molecules that control gene expression of proteins. [2]

    - **Mathematical Models:** Mathematical models play a crucial role in characterizing drug release from pharmaceutical formulations. These models provide insights into the mechanisms and kinetics of drug release, allowing for a better understanding of how drugs are released from various dosage forms. This information is essential in the development and optimization of pharmaceutical products. One commonly used mathematical model is the Peppas equation, also known as the power law. It describes the kinetics of drug release by considering factors such as formulation type, drug properties, and transport processes involved in drug release from a dosage form to a receiving body fluid. Mathematical models can also include purely mathematical descriptions unrelated to physical, chemical, or biological processes. These models

were developed through integral analysis of various factors. Several mathematical models have been proposed to describe the kinetics of drug release in pharmaceutics. These models comprise the Peppas equation or power law model, zero-order kinetics model, first-order kinetics model, Higuchi model, Hixson-Crowell model, Korsmeyer-Peppas model, and Hopfenberg model. Each has its own set of assumptions and mathematical equations employed to explain the drug release process. Here, summarize the six renowned models which have been studied in various papers. [3-5]

- **Zero-order model:**

  $D(t) = a+ct$, ----------{1} [two parameters a and c]

- **First-Order Model:**

  $D(t) = D_0 \exp(kt/2.303)$,-------{2} [two parameters D_0 and k]

- **Higuchi Model (6):**

  $D(t) = k(t)^{1/2}$,----------{3} [single free parameter k]

- **Hixson-Crowell Model [7]:**

  $D(t) = (a+ct)^3$,----------{4} [two parameters a and c]

- **Korsmeyer-Peppas Model (or power-law model) [8]:**

  $D(t) = (at)^n$,----------{5} [two parameters a and n]

- **Hopfenberg Model for the n=1 flat Geometry [9]:**

  $D(t) = kt$,----------{6} [single parameter k]

These models provide a quantitative framework for understanding and predicting the release kinetics of drugs. By utilizing mathematical models, researchers can analyze and interpret drug release data to determine the underlying mechanisms and kinetics of release. This interaction plays a crucial role in determining the pharmacokinetic profile of drugs, as it can strongly affect important parameters such as clearance and volume of distribution. [10] The strength and characteristics of drug binding to various molecules, particularly serum albumin, are key factors that influence the availability and distribution of a drug within the body. Serum albumin is an abundant protein found in blood plasma that has high affinity for many drugs. Its binding capacity allows it to transport and distribute drugs throughout the circulatory system. The binding affinity between a drug and serum albumin determines how tightly they interact with each other.

2. **Pharmacodynamic Models**: The Pharmacodynamic (PD) model defines the relationship between drug concentrations and effects on downstream biological pathways or targets. These models help in understanding the dose-response relationship, drug potency, and

drug efficacy. By simulating the drug-target interaction dynamics, pharmacodynamic models can predict the impact of different drug-target interactions on therapeutic outcomes and identify potential targets with desired effects. Hedges has done pioneering work on mechanistic PD models on antibacterial action. [11] He expounded the adsorption kinetics of a lethal amount of the bacterial toxin. The model consists of two parts, in the first part, the colicin istaken up by receptors, and after the completion of the second phase, the lethal outcome occurs. [12]

Drug-target binding modelling is an integral element of drug discovery and development. This includes predicting and understanding the connection between a drug molecule and its proposed target, such as a protein or enzyme in the body. For the purpose of modeling drug-target binding, multiple techniques can be utilized, for example molecular docking, and molecular dynamics simulations. In particular, molecular docking is a computational technique used in drug development to predict the orientation and shape of a ligand in the active site of a protein. Another approach is to run a molecular dynamics simulation, which simulates the motion and behavior of atoms and molecules over time. By applying Newton's laws of motion and considering interatomic forces, MD simulations can provide insights into the dynamic behavior of drug-target complexes.

Zou et al. [13] has described the (PK/PD) models have emerged as powerful tools in drug delivery research, offering a comprehensive understanding of drug dynamics and the body's response to the drug. In this review, they have demonstrated hypothetical minimal threshold value in relation to drug exposure-response relationship using primary data on PD models. Currently, modeling techniques are commonly applied to drug delivery systems and large modification molecules, such as liposome, nanoparticles and nanoemulsion. The integration of PK and PD models with statistical modeling allows for individual dose optimization, improving the efficacy of drug therapy. [14,15]

3. **Systems Biology Models**: Systems biology (SB) models integrate molecular data, such as gene expression, protein-protein interactions, and signaling pathways, to create a holistic representation of the biological system. These models simulate the dynamic behavior of biological networks and enable the identification of key regulatory nodes or potential drug targets. Systems biology models provide insights into the complex interactions between drugs, targets, and cellular processes, aiding in target prediction and drug discovery.

System biology models are crucial in pharmaceutical research for recognizing and authenticating possible drug targets. By utilizing computational and mathematical models, system biology tries to replicate and analyze the action of biological systems at a molecular level. These efforts enable researchers to build mechanistic connections between multiple individual molecules that form larger systems of cells, tissues, and organs. This integration of molecular data helps in generating predictive models of patho- physiological processes and anticipating intervention outcomes. SB models can analyze disease-corrupted networks and identify key molecules or pathways that contribute to disease progression.

In recent years, interest in computational and system biology has increased considerably, particularly in mathematical modeling and simulation. This approach

allows researchers to create models that capture the complex dynamics of molecular regulatory systems found within living organisms. By integrating information from various levels such as genetics, transcriptomics, proteomics, and metabolomics, these models provide valuable insights into the behavior of biological systems. The process of building these models typically follows a bottom-up approach. Researchers propose hypothetical networks of biochemical reactions between genes, proteins, and metabolites as a starting point. Here are some examples of SB models:

- **The Boolean Network of the Yeast Cell:** This network was developed in the early 1990s and uses a set of Boolean variables to encode the different stages of the cell cycle. The model was used to study the effects of mutations on the cell cycle and to identify potential drug targets. Recently, Kotiang and Eslami (2022) [15] devised a computational framework for combining Boolean networks and factor diagrams to study the global dynamical properties of biological systems. Furthermore, the mathematical formulation allows us to analyze the dynamics and behavior of error propagation in gene regulatory networks by performing a density evolution (DE) analysis.

  In 2004, Chen et al. presented a highly detailed nonlinear ordinary differential equations model that could illustrate the synthesis, degradation and modification of proteins in the cell-cycle pathway. This model accounted for key elements of the budding yeast cell-cycle control system witnessed in wild-type and more than one hundred mutants.[16]

  Zhou et al. described the logic operations performed by the enzymes. The enzyme logic systems and the bioelectrocatalytic interface were attained by pH Changes Due To Protonation. Molecular Computing Systems, Within The Purview Of unconventional computing, have seen much attention and have led to a quick development of molecules which can be managed by signals and are capable to do Boolean logic operations and basic arithmetic functions. [17]

  DNA-generated computer systems offer faster computing power than enzyme-generated logic systems. Nonetheless, they offer novel biosensing and bioactivation features that operate in a binary mode. Katz in 2018 has examined distinct kinds of enzyme logic gates demonstrated with designated enzymatic responses/cascades. By extending this research to include biomolecular systems, complex computational functions became much easier to execute than with synthetic molecules, thus enhancing their functional complexity. [18]

- **The metabolic network of Escherichia Coli:** The model was used to study the effects of changes in nutrient availability on cell metabolism. The computer modeling of bacterial metabolism provides an optimistic method for anticipating variations in the microbial abilities and tactics used in the host relationship from strain to strain. By combining computational and experimental techniques, systems biology attempts to analyze the complexity of biological networks in a system-based manner, taking into account the interaction of cellular components and complex cellular behavior. [19]

Genome-scale biological networks have been shown to be beneficial in the decoding of high-throughput data and the formation of computational models. Mathematical models are created from network reconstructions, and contain variables, parameters, and equations to show the potential behavior of these networks.
[20] Genome-scale metabolic models are advantageous for the investigation of cellular metabolism. These models have revolutionized the field of systems biology, elucidating cellular phenotypes and linking annotated genome sequences to physiological functions. One of the major applications of genome-scale metabolic reconstructions is in predicting and understanding cellular phenotypes. [21]

4. **Network-Based Models:** Network-based models utilize network theory to represent the interactions between drug targets, genes, proteins, and other biological entities. These models provide a comprehensive framework for understanding the complex relationships and interactions within biological systems. By analyzing the intricate connections within these networks, network-based models can uncover important insights into the mechanisms of diseases and identify potential drug targets. In these models, biological entities are represented as nodes or vertices, and the interactions between them are represented as edges or links. The resulting network provides a graphical representation of the relationships and connections between different components of the system. [22,23]

Network-based approaches can be created using various types of biological data, such as PPI (protein-protein interactions), gene regulatory networks, metabolic pathways, and drug-receptor interactions. By integrating and analyzing these data sets, researchers can gain insights into the structure and functional relationship between biological entity. These models can be used to study a variety of biological phenomena, including disease mechanisms, drug discovery, and biomarker identification. For example, in the context of drug discovery, network-based models can help identify potential drug targets by analyzing the connectivity and centrality of nodes in a network representing disease-related biological processes. Network analysis techniques, such as network topology analysis, clustering algorithms, and network propagation methods, can be applied to interpret the network structure and dynamics. These methods can identify key nodes or modules within the network that play crucial roles in the overall system behavior. [24]

5. **Machine Learning and Data-Driven Models**: Machine learning and data-driven models have become invaluable tools in the field of biomedical research. These models leverage computational algorithms to analyze large-scale biological data, including genomic, proteomic, and clinical data. By training ML algorithms with annotated datasets, these models can find patterns, relationships, and associations within the data that can be used to predict the interactions between drugs and targets and prioritize potential targets for further experimental validation. [25]

Machine learning approaches have gained popularity in drug discovery and modeling drug-target interactions. ML models can learn patterns and relationships from large datasets comprising known drug-target pairs and their experimental binding affinities. [26] By using a variety of ML algorithms such as random forests, support vector machines, and deep learning neural networks, predictive models can be built that estimate the binding affinity of new drug-target pairs. [27] Dynamic mathematical models in drug target prediction provide a quantitative framework for understanding the complex

interactions between drugs and their targets. By integrating biological knowledge, experimental data, and computational approaches, these models help guide the selection of potential drug targets, optimize drug discovery processes, and accelerate the development of new therapeutic interventions.[28]

II. SURVEY: MATHEMATICAL MODELS IN DRUG TAREGT ANALYSIS

Mathematical models are abstract representations of biological systems and allow us to understand biological behavior and its fundamental dynamics. [29] In many cases, the mathematical modeling of drug behavior is based only on the measured concentration-time profiles of drugs administered in plasma or blood. By integrating PK and PD models into statistical analysis, PK/PD analysis aims to better understand the relationship between drug exposure and therapeutic response. Mathematical modeling approaches link drug-dependent dynamics with downstream effects at different scales for various purposes, such as treating various diseases such as bacteria, viruses, tumors, hypertension and mental illness. Existing models require prospective validation given the complexity of the model, which can vary significantly depending on existing knowledge.

The field of drug discovery has largely benefited from the inclusion of computational approaches along with traditional methods. Through the use of mathematical modeling and computational drug design approaches, the limitations of the traditional drug development process, including its high cost and time commitment, have been significantly alleviated. [30] Mathematical models are used not only in drug design, but also in some important scientific fields such as climate modeling, aerospace, space technology, manufacturing and design, seismics, environment, economics, materials research, water resources, drug design, population dynamics and combat and war problems, medicine and Biology. In the table-1 below, various PK-PD profiles have been illustrated with drug-target implications.

III. CONCLUSION

The development of mechanistic pharmacodynamic modeling has revolutionized the field of drug action, allowing for a deeper understanding of the mechanisms underlying drug response. This approach, commonly referred to as systems pharmacology, combines the use of mathematical models with a clear biological interpretation to gain mechanistic insights into drug actions and their effects on the body. [39] Through the integration of pharmacokinetic and pharmacodynamic data, mechanistic PD modeling offers a comprehensive framework for studying drug-receptor binding and optimizing drug doses for various applications. A possible future mechanistic application of PD modeling is the development of antiviral drugs. By modeling the interactions between viral targets and potential antiviral compounds, researchers can gain insights into drug efficacy, identify optimal dosing regimens, and explore the potential for combination therapy to enhance antiviral activity. Furthermore, these models can also be applied to the development of antibiotics. Understanding antibiotic action mechanisms and their interactions with bacterial targets, mechanistic PK-PD models can guide the development of more effective drugs and optimize dosing strategies to combat antibiotic resistance.

Table 1: PK-PD Profiles with Drug-Target Implications

S. No.	Models	Drug-target implications	References
1.	Pharmacokinetic	E2072-GCP-II Inhibitor.	[31]
2.	Pharmacokinetic	Nutlin-3a is an MDM2-p53 antagonist.	[32]
3.	Pharmacokinetic and pharmacodynamic profiles	Daiaza, and triazafluorenone series of metabotropic glutamate receptor antagonists.	[33]
4.	Pharmacokinetic	4-[3-aryl-2,2-dioxido-2,1,3-benzothiadiazol-1(3H)-yl]-1-(methylamino)butan-2-ols used as potent nor-epinephrine re-uptake inhibitor.	[34]
5.	Pharmacodynamic profiles	Serotonin 4 receptor (5-HT(4)) agonists are potent neurotransmitter.	[35]
6.	PK-PD models	In-vitro anti fungal activity of fluconazole and caspofungin.	[36]
7.	Pharmacodynamic profiles	Dalbavancin.	[37]
8.	Pharmacokinetic	Anaplastic lymphoma kinase (ALK) inhibits the growth of non-small-cell lung cancer (NSCLC).	[38]

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