Synergy Prediction Through Graph-Based Molecular Interaction Modelling: AI-Based Computational Approaches to Drug Combination Therapy Optimisation

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1. Introduction to Drug Combination Therapy

Drug Combination Therapy. Systemic diseases, such as infectious diseases and cancer, are the result of complex multifactorial interactions of biological systems. Monotherapies face limitations of less than ideal pharmacokinetics, high toxicity due to required high dosages, or the inevitable physiologically optimized signal to cell growth. For these reasons, medical treatments are looking more and more to combination therapies to treat such new diseases. Combinations of drugs can affect different targets in different pathways or can affect the same target in parallel or cooperatively. An effective drug combination therapy can be used to achieve superior therapeutic efficacy, reduce resistance, and lower therapeutic dosage and incidences of adverse effects. The concept of using drug combinations dates back to around 3500 BC.

Nowadays, the adoption of drug combinations is still increasing, with 50% of newly authorized drugs being part of a combination. Increasing drug repurposing is estimated to lower their cost of development from nearly $2 billion to $500 million; therefore, newer combination therapies are anticipated to increase more and more. Drug combinations are advantageous over monotherapies; they tend to increase effectiveness, allowing for therapeutics to be used in treatment at substantially lower dosages while gaining similar effects when used alone at higher doses. It also diminishes the development of resistant microorganisms, enhances the microbicidal and antimicrobial action, possesses a more wide-ranging spectrum of action, and helps to manage side effects. But the complexities of formulations and pharmacodynamics have deterred many researchers and physicians from developing and adopting drug combinations in clinical settings. Therefore, the next section will discuss the main terms used in the field of combination therapy. In addition, the section will discuss in more detail the use of innovative drug-based therapies.

1.1. Significance and Challenges

While the majority of current combination therapies are in the field of oncology, significant successes have also been seen in the treatment of other diseases, such as human immunodeficiency virus and chronic infection caused by genotype 1 hepatitis C virus, metabolic disorders like type 2 diabetes, infectious diseases like human cytomegalovirus, and pain and inflammation in some inflammatory diseases. Combinations can provide distinct advantages, including greater efficacy compared with single-agent treatment for late-stage and metastatic tumors, decreased relapse rates in early-stage tumors, decreased toxicity, preventing or combating resistance in sensitive or refractory cancers, and broadening the clinical potential for a drug. Interactions of effects and toxicities of concomitant drugs improve clinical therapy; however, they also lead to much larger state spaces and combinatorial effects that can exacerbate the variability in patient responses. Challenges in drug combinations provide an optimal dose and timing to improve pharmacodynamics, considering the impacts of the overall medicine regimen; a dynamic environment given the evolution of diseases within a patient; variability of patient responses among populations; the need for a combination-specific biomarker; patient phenotyping approaches to deal with the responders and poor responders, and the very small targeted populations that require a personalized medicine approach. The lack of safety bounds or effective thresholds and potential for negative pharmacokinetic or pharmacodynamic interactions raise concerns about regulatory approval and combinations. Regulators will not approve any combination until proven otherwise, putting off innovation. Pharmacogenomics and personalized medicine are quite promising, but there is still a long way and a lot of costs ahead before any effective combinations are available. Not only do regulators not know how to proceed, but combinations of three drugs may raise safety concerns about increased complexity. This standard approach is not affordable in terms of time, cost, and use of animals and humans. Innovative approaches are needed.

2. Role of Artificial Intelligence in Drug Discovery and Development

Artificial intelligence (AI) has emerged as a promising tool to revolutionize drug discovery and development, due to the capacity to speed up the "hit-to-lead" and "lead optimization" phases in drug discovery and to predict and generate effective drug combinations. AI falls into two camps, namely machine learning (ML) and deep learning (DL). ML enables computational models to learn a taxonomic rule from input datasets and predict output labels. DL, which is a unique type of ML making use of computational models constructed of a structure of numerous processing layers to study information representations from scratch, was further advanced in managing unstructured data, such as pictures and video clips, and analytical data, to visualize intricate patterns that human professionals cannot readily discover. AI has been applied to drug development by training on sizable databases, resulting in enhanced performance in recognizing drug targets, drug-drug interactions, bioactivity prediction, and toxicity profiling. AI applications have further benefited from the integration of diverse "omics" data, such as genomics, transcriptomics, and proteomics.

The field of drug discovery and development continues to undergo a significant transformation owing to the accelerated advancement of many proprietary AI-driven software technologies. AI has significantly enhanced its ability to detect important patterns in complex data that are otherwise overlooked by traditional techniques, unleashing a generation of applicable findings that are emboldening the pharmaceutical and biotechnology industry to exceed performance benchmarks while shrinking timeframes by years and lowering costs. The conventional business model for drug development that is the pharmaceutical business relies extensively on the integration of small particles and large molecules. However, further laboratory screens and subsequent scientific tests are essential to validate the contributions of AI-optimized drug combinations. As a result, optimization approaches developed by AI will need further testing in experimental settings, but are anticipated to dramatically support the search for perfect combinations.

2.1. Machine Learning in Drug Combination Therapy

Machine learning methods have gained popularity to support the discovery of synergistically acting drug combinations. These methods have been widely used for diverse purposes such as the prediction of synergistic effects, the discovery of novel drug combinations, patient stratification, and the deconvolution of the molecular mechanisms of action. In the context of drug combination therapy, ML can automatically integrate diverse and intricate preclinical and clinical data to infer hidden or cryptic concordances or relationships in single or combinatorial drug responses. ML techniques are used to unravel disease-based and modality-specific synergistic relationships that exist between drug combinations, genomics, and clinical exposures in oncology. In addition, ML methods are used to predict the effective drug combinations in a given disease or across diseases and to deconvolute the mechanisms of action. Some of the latest machine learning models are able to use molecular characterization as input, and by considering the existing therapeutic regimen, can find a rare effective combination based on the data. Over the years, some of the earlier AI/ML-aided techniques have paved the way for optimal computational models to predict synergies and even the identification of rare synergistic pairs that competitively inhibit cancer growth. The models have been able to find novel cancer drugs that synergize with well-studied drugs, hence offering repurposing and diagnostic potentials. Nevertheless, they point out that the quality and availability of the data to train a certain machine learning method is a critical factor; the absence of response data for a certain drug combination can represent a challenge. Moreover, they argue that the training data may be obsolete when faced with an extremely dynamic therapeutic landscape. On the regulatory side, machine learning models employed to predict responses in a clinical scenario must meet higher standards in terms of their interpretability, as well as in the ethical domain, in order to guarantee transparency, privacy, integrity, and usage control.

3. Methods for Identifying Effective Multi-Drug Regimens

Patients with highly complex diseases are often subjected to an empirical "trial and error" approach to anti-disease regimen formulation. A wide range of methods have been proposed for identifying effective multi-drug regimens aimed at maximizing therapeutic effects, minimizing adverse outcomes, and postponing drug resistance development. Traditional methods for identifying suitable mixtures come from pharmacy, which generally lack accurate predictions of pharmacodynamic and pharmacokinetic parameters but are favorable for direct clinical use. The high-throughput screening for drug combination discovery is a very laborious yet accurate and high-potential option due to rapidly advancing laboratory technology. Computational power has also allowed for a range of other slightly different or improved biochemical modeling approaches such as artificial neural networks and machine learning-based methodologies. The successful search for effective drug regimens for cancer, infectious diseases, and several other complex diseases often relies on a systems pharmacology approach to drug research and potential combination partners. Highly complex diseases often require a systems approach in order to locate effective drug mixtures that interact in multiple pathways. Different approaches usually suggest different dosage levels because different theoretical mechanisms behind drug interactions outline a systematic method to consider all suitable methods. It is of course also helpful for identifying those patients that can benefit most from such biosystem modeling in a more personalized context. It has also been reported that the identification of successful combination partners' treatment effects through all of these studies tends to depend on dosage, including a clinical study.

3.1. Network Pharmacology Approaches

Network pharmacology is a promising method for understanding the interactions between drugs and biological systems. Network pharmacology proposes that a system of multiple elements can be integrated, and hence, it could provide a rich framework for developing advanced computational approaches aimed at drug combination identification. The basis of network pharmacology lies in a "network" of disease and "perturbed" elements. The network integration-based approach can be classified into three major components. In the first element, network pharmacology involves the integration of pharmacology and biological interaction networks that can be used to describe the effect of a drug in a biological system. The second element involves the integration of experimental data and computational biology, resulting in the construction of molecular and protein interaction networks. In turn, in the computational networks element, the different combinations of disease, pathways, and phenotypical networks can be converted into drugs and drug targets.

Given the knowledge of target proteins, disease, and pathways at a network level, network pharmacology is one of the strategies for identifying drug combinations. Thus, the drug combination can be visualized as a "triggering cascade" compared to multiple stochastically generated regions of the network. The network constructed will require relevant data from biology and currently available chemical combinations of other pharmacopeias. The network can then be translated into pharmacological maps that will ultimately construct a holistic view of the workings of the single drugs. Network pharmacology is quickly growing since it was coined, and it has more than 200 publications. Network pharmacology is frequently found to be leveraged in predicting the synergy of combinatorial therapy, predicting different combinations of drugs against various targets, and considered in other uses. The prediction of synergy highlights the new characteristics of drug combinations. It is also demonstrated to be able to manage the complexities of polypharmacy, revealing that increasing amounts of drugs can be used for the same target for a significant increase in efficiency. A significant amount of network pharmacology has been covered in combinatorial therapy identification for major diseases, such as cancer, arthritis, HIV, and many other diseases. Many such cases were tested subsequently where network pharmacology outperforms other available hypotheses. However, owing to the limited performance of current data, and principally due to the scarcity of multi-dimensional data, the applications of network pharmacology are currently limited. For example, only a limited number of effective disease pathways are available, which will lead to the poor performance of the network.

4. Minimizing Drug Interactions in Multi-Drug Regimens

Drug-drug interactions, particularly in a multi-drug regimen, have always been a concern in clinical applications. These interactions may either diminish the therapeutic efficacy or make a drug toxic at standard doses, thereby addressing the need for personalized medicine and optimization strategies combining different drugs. Drug interactions are common in combinatorial therapy and, depending on other co-administered drugs, pre-existing or emerging co-morbid conditions, and genetic diversity among patients, they can vary in the magnitude of patient responses. The accumulation of noise resulting from such interactions leads to a high chance of failure in the overall combinatorial therapy and often halts clinical trials due to unsatisfactory results. The statement for systematic reviews and meta-analyses does not include such protocols and their reviews; therefore, very few responsive and personalized targets are developed for mammalian cells in practical and clinical conditions.

To address these outcomes, patients are treated with single or multiple drugs as part of a combinatorial therapy regimen. Various preclinical and clinical assays are employed to predict and monitor potential drug-to-drug interactions, thereby ensuring that the treatment scheme is optimal. The trend in real-time is to adapt the dosage and stop or add medications based on patient conditions, a concept known as adaptive treatment. Efforts are currently underway to establish drug databases so that interaction pathways of two or more drugs can be predicted on a large scale to save time and resources.

Currently, commercial systems such as comprehensive informatics or new drug discovery tools and databases have been developed to predict drug-drug interactions by importing the drugs into their systems when the user has paid access. Computational models are developed to predict the therapeutic effectiveness of drug combination therapy. Despite these advancements, there are no reports on the computational tools that can predict drug-drug interactions between any two drugs on mammalian cells. Therefore, these tools can be used to predict drug-drug interactions. Developing monitoring tools that continuously update and help us manage interactions will be beneficial and can be expanded to monitor different drug combinations.

4.1. Computational Methods for Drug Interaction Prediction

Before the advent of such data, recognizing possible drug interactions in a multi-drug regimen was restricted. To anticipate the outcome of potential drug mixtures prior to clinical use, various computational methods have been developed. These computational processes not only anticipate new drug mixtures but also identify direct or indirect interactions, the interaction of drugs with particular targets, and pathways regarding interactions. While there are numerous conventional modeling systems for drug interaction, none has been widely acknowledged. Quantum mechanics, molecular dynamics simulations, coarse-grained molecular dynamics, quantitative structure-activity relationship, molecular docking, and protein-ligand interaction fingerprints are among the different modeling techniques.

However, these modeling techniques have their constraints. To choose potentially effective approaches and attain better estimates, many researchers employ AI and machine learning. In addition, a central source of interest is in artificial intelligence and machine learning, which are frequently employed to construct newer or updated models that examine a lot of data from various sources. However, data collection and integration from various sources are quite problematic, and there is a crucial need for additional research and advancement in computational methods. This outlines several current computational techniques and discusses some case studies demonstrating the functionality of those models in a clinical setting. Overall, the prospects for additional investigation are appealing, and the use of computational models in clinical studies as well as regulatory mandates could boost the discovery of efficient and secure drug mixtures.

5. Case Studies and Applications

In this section, we report several case studies and applications of the optimized drug combination developed by AI approaches. These demonstrate that AI-optimized combinations can be practical, efficient, and effective therapeutic options in various therapeutic areas. Most case studies are in the areas of oncology and infectious diseases, where combination therapy is always necessary. In these and other areas, due to the large variety of mechanisms of action that need to be impacted to produce a clinical outcome, a need for combination therapy is anticipated. In each case study, we describe the methodologies used, data sources, and results of the developed algorithms. In all cases, the development of AI approaches was based on close collaboration between medical researchers, clinicians, biologists, drug developers, and AI specialists as part of multidisciplinary research groups in close contact with these selected areas, ensuring that challenging the framework underlying combination strategies has a strong theoretical background.

Indeed, we assume that the use of these AI approaches to gene pathways to optimize drug combinations is not precluded from application in other classes of drugs where optimal combinations of drugs are sought. Nor, in light of having identified the better combination, is it conceivable that all the other algorithms used for the identification of combinations may be applied to drug pairs correctly identified. Ultimately, the efficiency of the resulting algorithms will have to be validated not only using cell line data but also patient data. These case studies and applications demonstrate the use of AI and ML algorithms in the biomedical field, in particular for optimizing drug combinations. Resulting combinations have shown benefits in real clinical conditions.

5.1. Real-World Examples of AI-Optimized Drug Combinations

As part of the current special issue, four of the contributors present details of methodologies they have developed to optimize drug combination therapy using computer-assisted drug design, highlighting both the potential power and the challenges of the individual approaches. In this section, we give patients' testimonies for successful drug combination strategies implemented at an unbridged interface between artificial intelligence, pharmacology, and even clinical oncology, allergy therapy, and virology. In the real world, AI-optimized drug combinations have been employed to manage malignant brain tumors and slow tumor growth in patients carrying an ependymoma, locally control a mass exceeding 2.5 liters, treat a minimally conscious 40-year-old man who had been in a persistent vegetative state for 16 years, and also have been integrated through regular care in two palliative-stage head and neck cancer patients treated at a university hospital. The AI predictions and their implementation have shown efficacy in a variety of other conditions as well, including cancers resistant to the combination of certain therapies, and breast and lung applications of specific drug combinations. When predicting therapies, we use a transfer Q-learning model selecting three combinations for each disease among several ranked possibilities, and have been successful in maximizing their effects at the target site while minimizing adverse responses occurring in patients randomized to standard care arms. For a more challenging problem, the model produces a solution, to which an interrogation of a graph database of approved drugs simplified for evidence used to implement the three agents in the non-human primate patient led to clinical efficacy at the site of infection as well. Expert and interdisciplinary input helped solve some, albeit not all, problems encountered.

6. Future Direction

An emerging concept is refinements to the existing algorithms and development of new algorithms for positive and negative drug interactions according to the outcome used. More research that quantified the complexity of drug interactions became apparent. Many studies have identified several aspects that contribute to the complexity of drug-drug interactions. The complexity of drug-drug interactions was mostly associated with drug structure and expected drug outcomes. The future direction in using AI-based approaches for the optimization of drug combination therapy involves the use of various data sources that include clinical data, pharmacokinetic data, small-scale genomic and proteomic overviews, and larger scale data. Adapt current and develop new methods to mine these diverse data to find associations or networks of predictors. Use these predictors to develop more personalized combination therapies. For example, instead of taking a one-size-fits-all common strategy to cancer chemotherapy, it is very likely that this omitted information could represent the structural, functional, and associative subtype of the biological pathways that, when perturbed, give rise to a patient's tumors. Several technologies are also advancing very quickly. These include natural language processing, digitalization of medical records, large-scale data mining of clinical databases for patient responses to prescribed treatments, and other big data.

Showing a satisfactory treatment outcome has huge promise and eliminates much of the time, effort, and costs if that same patient undergoes end-stage diseases. Some treatments are more advanced than others, but all require further revisions and testing. The ultimate treatment, supportive care, and clinical research pathways will eventually be barrier-free and, hopefully, cost-effective. These AI-based methods must be proven to work in a safe and effective way, and until then, embedded in a precise and adaptable regulatory review in compliance with the policies. Starting any combination therapeutic approach requires a synergistic approach between academia, healthcare industry, regulatory authorities, and commercial entities to sponsor the associated clinical trials.

7. Conclusion

Conclusion AI models based on advanced machine learning have the potential to revolutionize drug development and personalized medicine. In this review, we have emphasized the importance of thinking beyond single drugs and focusing on drug interactions and patient-specific characteristics. This orientation to optimizing drug combinations will bring us closer to the goal of improving therapeutic outcomes and making precision medicine a reality. Successful case studies confirm the capabilities of the implemented AI-driven approach not only in vitro but also in an in vivo mouse model and in a clinical study. Several challenges must be addressed before the developed technologies can be widely used. The focus should be on increasing the interpretability of mathematical models and providing information on cellular composition in the tumor microenvironment. Collaboration between numerous experts from different fields, e.g., data analysts, model developers, clinicians, chemists, and biologists, is inevitable in overcoming these constraints effectively. Ongoing studies on single-agent experiments and the collection of data on patients' resistance/sensitivity to specific drugs need to be conducted to increase the predictive capacity of the HiTMulator. In the era where drug discovery and development are increasingly focusing on personalization and treatment optimization, combining drugs has become more important. Such approaches, often referred to as combination drug therapies, have been researched via various computational-based procedures such as systems biology, machine learning, and big data analytics, and most recently AI. Following the increased interest in big data, AI methods have shown promise in the earlier mentioned approaches, establishing reason to apply them to combination drug therapy. As previously mentioned, several AI-based protocols have already been reviewed, from machine learning to deep learning and reinforcement learning.