Artificial Intelligence in Drug Repurposing

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ABSTRACT

Drug repurposing, or finding new uses for existing drugs, presents a promising avenue to mitigate the high costs and lengthy timelines associated with traditional drug development. Recent advancements in artificial intelligence (AI) have significantly enhanced the efficiency and accuracy of drug repurposing efforts. By leveraging machine learning algorithms, deep learning applications, and integrative data approaches, AI can analyze vast datasets from biological, chemical, and clinical sources to identify potential new therapeutic uses for existing drugs. This paper explores the application of AI in drug repurposing, highlighting successful case studies, current methodologies, and future directions. The integration of AI in drug repurposing not only accelerates the drug development process but also offers novel insights into the treatment of various diseases, demonstrating its transformative potential in the pharmaceutical industry.

Keywords: Drug Repurposing, Artificial Intelligence, Machine Learning, Deep Learning, Bioinformatics, Chemoinformatics.

INTRODUCTION

Drug repurposing, also known as drug repositioning or drug reprofiling, is the process of finding new uses for existing drugs. The primary obstacle for the development of new chemical entities for new targets is not time, but the cost to bring a compound from the discovery phase to approval. The high cost is partly due to the high rate of attrition in clinical trials, particularly in the later development phases. About two-thirds of failures are not due to lack of efficacy or safety, but for commercial reasons, like low potential market, unwanted profile in comparison with other products, or adverse cost-effectiveness. The lengthy clinical evaluation period, since target identification and subsequent optimization, and the high probability of failure makes de novo drug discovery a financially risky enterprise. Therefore, drugs that have already surpassed these hurdles have enormous potential value to the pharmaceutical industry. Sufficient patent protection of repurposable uses offers the extra incentive to commercial exploitation. Hence, various pharmaceutical companies are also involved in drug reprofiling to boost the profit by getting the second patent [1]. In recent years, growing pressure in the fields of drug discovery due to a decreased output of new therapeutics from pharmaceutical companies has urged academics, drug companies, and related industries to pay more attention to repositioning existing drugs for new indications, whereby less time is required to get the drug to patients, a combined field termed "drug repositioning". The reason is that many drugs fail at the final stage of development because they either showed milder efficacy than a marketed drug or because of unpredictable toxicity. Some drugs never reached the market because of insufficient proven efficacy or because of their adverse effects. Many researchers have seen a large potential in identifying new indications for already characterized drugs with safety and pharmacokinetic profiling, especially for drugs that are no longer available and for which no patent protection is left. Pv2 is an example of such compounds, where related products still command a significant share of the market. There are also economic reasons to develop a repositioned product, such as reaching a broader potential market or commanding a higher price. This saves substantial time and reduces expenses, as formulation, toxicology and pharmacokinetic profiling, production costs, production scalability, and clinical Phase I studies are already conducted. Moreover, it can generate novelty in

meeting medical needs when the chemical class of the repositioned and the original compounds is different [2].

DEFINITION AND SIGNIFICANCE

Various terms, including drug repositioning and drug reprofiling, have been used in the literature to refer to this concept. However, drug repurposing has been used more frequently and is used here. It may be further broken down into target-based repurposing, which involves selecting new molecular targets, or indication-based repurposing, which is patient-oriented and concentrates on finding new applications for already approved drugs. The latter is also the biggest topic of interest in this work. Drug repurposing could also be called drug repositioning or reprofiling [3]. This is motivated by cost-effectiveness, since reprofiling bypasses certain initial phases of medication discovery and growth, as well as by time concerns, since it has been known that repurposed drugs may arrive in medical trials for their fresh use as many as 20 years ahead of drugs that are discovered through the conventional R&D strategy. Another fact to consider is that these repositioned drugs might be adapted by licensed medical practitioners in accordance with the concept of off-label usage before being approved for new treatments; this law permits repurposing in unique ways. As a result, it has the potential to significantly affect patient treatment [4].

CHALLENGES IN TRADITIONAL DRUG DEVELOPMENT

The ideal drug development process is characterized by expedited timelines, low development costs, and extensive preclinical and clinical thorough testing. It also requires a meticulously prepared and properly validated target that is accompanied by comprehensive patient-specific diagnostic biomarkers. While traditional drug design has developed extensively over the years with major advances in areas like genomics, cell biology, bioinformatics, and structural identification, the ideal drug is simply too costly and time-consuming to produce. A 2016 report on drug development sustainability by the Deloitte Centre for Health Solutions reports an average of 15 years spent on drug discovery and development at costs of $2.558 billion. The financial investment is extensive, with severe implications for negative phases involving "drug safety and efficacy" causing over 90% failures [5]. This percentage of failure represents one of the most exorbitant products of greater marginal benefits in the entire pharmaceutical pipeline. This high productivity threshold (96%) raises questions on the effectiveness of modern medicine and the level of toxicity to be tested. To deter this productivity threshold, a repeatable process of drug discovery and development has been suggested, although one that is 20% cheaper and 30% quicker. Artificial intelligence (AI) offers an array of solutions designed to cater to the aforementioned research problems of drug repurposing, resulting in significant reductions in drug discovery costs [6].

ROLE OF ARTIFICIAL INTELLIGENCE IN DRUG REPURPOSING

With a focus on identifying the vast potential of drugs being used beyond their current indications, a new era of drug repurposing has arrived through research on artificial intelligence. The application of AI has led to the advancement of bioinformatics, data mining, systems biology, and chemoinformatics, with the end goal of identifying and validating repurposable drugs. The data utilized for AI-based drug repurposing has been gathered from various sources, including in vivo, in silico, patient-centered studies, ex vivo, and in vitro experiments. The algorithms commonly used in drug repurposing workflows are machine learning algorithms and their variations, including deep learning applications and structural-based network remodeling for molecular drug action [7, 8]. Drug repurposing is an innovative method of identifying novel therapeutics that can be used for the management of diseases without undue side effects. This strategy can save both time and money by reducing the steps in drug development. Artificial intelligence has been introduced in different aspects of biosciences and biomedical research. AI has facilitated data mining, bioinformatics, chemoinformatics, systems biology, and other scientific research areas, as well as health-related research in data science, epidemiology, and clinical research. In addition, artificial intelligence has innovated the drug development process through the rapid identification, validation, and repurposing of new uses for old drugs and novel molecules in computer-aided drug design. Defining and validating combinations of drugs and targets for repurposing is not easy, but in recent times, many computational efforts have been made to predict novel opportunities for old drugs and their targets. This section addresses the advancement in the workflow of drug repurposing through the use of artificial intelligence as a computational tool [9].

MACHINE LEARNING ALGORITHMS

Machine learning algorithms can be employed to discover patterns and relationships between different items within a dataset. Coupling a machine learning model with molecular data from publicly available databases allows us to predict drug repurposing in the context of a disease. The Pammol protocol computes the lipophilic/hydrophilic nutrient complexity for a vector of lipid droplet morphometry features from adipocytes that is indicative of functional changes from the adipocyte biology interfered by

the perturbing compound. Machine learning algorithms are capable of processing and analyzing billions of data points within a dataset to uncover patterns, correlations, associations, and dependencies among various drug features, disease characteristics, biological mechanisms, and real-world evidence from published scientific literature [10]. Machine learning algorithms for repurposing typically focus on drug treatments for a specific disease. Learning algorithms can also have a strong impact in stirring research in the new direction of combination therapy, where the drug repurposing would be to correct side-effects of already approved drugs by co-administration. Machine learning approaches can predict repurposing of a drug according to single drugs compassing known association with a target disease or for even multiple drugs that have not been tested experimentally. The model can predict efficacy of loosely related drug according to target knowledge structure of two target diseases. Machine learning algorithms can predict the success of repurposed drug, with LOOCV testing for success rates with known drug-protein interaction structure [11].

DEEP LEARNING APPLICATIONS

The advent of big data and the necessity to analyze large amounts of information has led to increasing interest in adapting AI technologies to the CW domain, which has resulted mainly in the application of sophisticated AI technologies in DR for the past few years and provided enormous implications for the drug discovery process. Deep learning has gained remarkable attention in various fields recently, mainly due to its ability to view data in a layered manner. Deep learning is usually implemented as a neural network model with tens or even hundreds of layers. Such a network can form representations of data at different levels of granularity, which is a crucial ability in the analysis of the complex and diverse CW datasets [12, 13]. In drug repurposing, deep learning uses a vast number of layers to automatically extract highly optimized and complex features from diverse biological and chemical data. Despite the notable success of deep learning in biological and chemical applications, training deep neural nets is quite challenging in terms of the large number of parameters and data requirements. A variant of deep architectures in which the parameters of the network are shared versions of the same graph structure can help alleviate this problem. In general, the size of the input dimension can often be reduced before feeding the data to deep networks, which has allowed researchers to utilize these algorithms in drug-oriented repurposing and make a mark. Furthermore, different types of deep models have also been engaged in signal processing of phenome-wide association data to extract latent features in a way that is automatically learned from multiple heterogeneous data [14].

DATA SOURCES AND INTEGRATION IN AI FOR DRUG REPURPOSING

The origin of the data in the artificial intelligence (AI) framework for drug repurposing is mostly diverse, including biological, chemical, and clinical sources. Yet instead of performing targeted experiments, AI should be able to use all this knowledge in a comprehensive fashion. Thus, the progress of the AI field has been tightly coupled with data integration and harmonization, when approaches to achieve common data formats exportable in either RDF triples or SQL tables have been pursued for the FAIRification of knowledge graphs and data catalogues. Based on FAIR data, computational aspects are then used to model interactions between either targets, pathways, or genes to create computational models that are both (meta-)proteome or (meta-)transcriptome targets-specific. Furthermore, known drugs can be predicted to likely be beneficial at the specific data sources and it has been shown that these meta-proteome in silico polypharmacology effects relate to the drug targets, providing a clear hypothesis on their clinical effects. Specifically, for drug repurposing, Drug2ways suggested that the underlying mechanism of a given drug can be linked to a distinct set of druggable proteins fostering drug repurposing hypothesis [15]. Data sources and their integration into computational models and workflows have accordingly been a consistent theme of drug repurposing papers. Much of the drug-disease relationship as well as the severe adverse events, including repositioning hypotheses as described in Suramin for Therapy of Glioblastoma, has been spread across multiple biological, chemical, and clinical data sources. Frequently, the predictive performance of prospective therapies for potential repurposing can be better with the integration of phenotypic, chemical kinetics and cellular features, than with gene expression data or target affinity data alone. Such information has been used for a number of clinical indications, where computational protocols have been developed that explicitly model complex carbohydrate patterns integrated with cell phenotype analyses. Over the past years, individual as well as integrative workflows have been developed that rank potential drug repurposing opportunities based upon overall data agreement [16].

CASE STUDIES AND SUCCESS STORIES

Research designs concerning bioinformatics studies often involve artificial intelligence (AI) applications. Literature reviews, particularly those focusing on systematic applications, have been considered to be

generated by AI-driven methods based on machine learning algorithms. On the other hand, several case studies deliberated with concrete examples of drug repurposing have been reported in the literature. Here, we offer four case studies bringing to the forefront real-world success stories of AI applications, which harness the power of existing biological and clinical big data in order to identify actionable candidates that can be further developed and clinically evaluated. In contrast to methodologies that mainly use in silico approaches, none of our case studies is limited to such techniques. Instead, they offer a multitude of technological fields, such as receptors, human design testing, and processes. For each study, we also review the nature of the available evidence in the support of therapeutic potential [17, 18]. In this commentary, we present five success stories based on AI-driven approaches, which go beyond benchmarking results and showcase actual implementations and results. We provide promising examples of drug-disease repurposing of four distinct, prevalent diseases (alcoholic liver disease, glioblastoma, ulcerative colitis, and COVID-19) achieved through collaborations between academia, biotech companies, and foundations. These application notes include the field-tested experimental validation of novel repurposing hypotheses, which were pursued with molecular and cellular in vitro experiments, and two have continued as private-public partnerships that are now in different stages of clinical translation [19].

FUTURE DIRECTIONS AND CHALLENGES

Artificial intelligence is likely to mature in the 2020s, with technology advancements including massively automated reasoning at scale. As a result, AI drug repurposing is expected to exploit not only data-driven methods but also knowledge-driven methods. Knowledge-driven methods exit the 'black box' phenomenon and offer healthier models that respect the diverse requirements of all stakeholders. Besides single databases and classical chemical fingerprints, it is essential to use the zettabyte of knowledge encapsulated in scientific literature wherein entities are quantified in terms of their relationships with other entities as a weighted-by-the-strength-of-interaction-system of entities and relations [20]. High definition in silico physiological models with real-time computer-assisted design facilitate the discovery of niche indications with acceptable target product profiles. Methodological challenges include the lack of huge positive information by which machine learning methods 'learn' the structure of the manifold of interesting entities and non-interesting entities, the lack of efficient stratification and weighting algorithms that optimally reduce the dependency of classifiers to robustly predict the actual final outcome of the selection units, and the deficiencies in methods for automated explanation. Enforcement of FAIR principles must not be a tyranny for drug repositioning. Future training and test datasets should correctly include a sub-group of known off-label uses of the drug (Hit indication). Additionally, the absence of evidence for repositioning should be correctly quantified by Hard Failure indication – an equally sized sample where the drug is a negative example. Metabol-traits of individuals should determine who will best respond once repositioned drugs are on the market. With a biology-first approach, the evolution of disease is better understood, and that hints at unexpected repositioning of any drug under clinical or preclinical investigation [21]. The advent of big data in biology launched numerous and promising strategies for drug repurposing. The future of AI-driven drug repurposing will encompass either a more technologically sophisticated version of the current methodologies or additional and different methodologies or possibly a blend of both [13, 22]. Current approaches using machine learning and deep learning that make use of the zettabytes of secreatome knowledge or represent the molecules being drug repurposed using sophisticated data representation systems, such as chemical fingerprints combined with network graph theory, are expected to mature in the 2020s with the development, either, of larger available training set or more sophisticated stratification and selection unit haircutting that optimize prediction [23]. With the use of knowledge management methods, billions of entities in scientific literature can be stored as molecules.

CONCLUSION

Artificial intelligence has emerged as a critical tool in the field of drug repurposing, providing innovative solutions to longstanding challenges in drug discovery and development. By harnessing the power of machine learning and deep learning algorithms, AI facilitates the identification and validation of new therapeutic uses for existing drugs, significantly reducing both time and costs. The integration of diverse data sources and advanced computational models enables a more comprehensive understanding of drug-disease relationships and enhances predictive accuracy. Successful case studies demonstrate the real-world impact of AI-driven drug repurposing, offering new hope for the treatment of diseases such as glioblastoma, COVID-19, and ulcerative colitis. As AI technologies continue to evolve, their application in drug repurposing is expected to expand, further revolutionizing the pharmaceutical landscape and improving patient outcomes.

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