Repurposing antitumoral drugs for multi-resistant infections

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Abstract. The growing global issue of antimicrobial resistance needs the development of new and more rapid treatment techniques. The traditional medication development approach is becoming less sustainable due to high costs and long durations. In this context, drug repurposing is a promising alternative since it offers a faster, cost-effective alternative by identifying new uses for existing drugs. This study applies artificial intelligence-based methods, particularly machine learning and deep learning to explore drug-pathogen interactions using open-access datasets, aiming to enhance specificity and reduce toxicity.

Keywords: Drug Repurposing · Antimicrobial resistance · Artificial intelligence.

1 Introduction

1.1 Context and motivation

Currently, the treatment of choice to combat bacterial infections is the use of antibiotics and other antimicrobial products. The excessive use of these drugs has been contributing to bacteria rise their antimicrobial resistance (AMR)[31]. This recurring problem has become increasingly serious and is now listed by the World Health Organization (WHO) as one of the main global threats to public health, as there is an increase in AMR not only from bacteria, but also from viruses, fungi and parasites[38]; some of these pathogenic organisms are no longer even affected by the available treatments, leaving populations weaker and unprotected in terms of the risk of infection, illness and even death.

To address AMR, two strategies are commonly explored: traditional drug discovery, which is costly and time-consuming, and drug repurposing, which seeks new therapeutic applications for approved drugs, reducing time and cost [28].As a result, drug repurposing has become a reliable tool to identify new drugs and quickly address public health emergencies[2].

The biggest challenge right now is finding new associations between drugs and pathogens/diseases in the middle of an enormous amount of data[4]. Among the various drug repurposing methods, the most efficient is computational drug repurposing, which takes advantage of the recent big generation of free biological and medical data and the use of analytical methods based on Artificial Intelligence (AI), particularly Machine Learning (ML) and Deep Learning (DL)[32].

1.2 Objective

The main objective is to do drug repurposing as a more efficient and economical alternative to conventional drug discovery. Even when identified through in silico methods, repurposed drugs can lack specificity for new targets, leading to off-target effects and reduced efficacy. In addition, the range of possible drug candidates may be limited and additional optimization might be necessary for their new applications. Therefore, the use of computational drug repurposing aims to reduce or even solve all these problems[3,42].

2 Background

2.1 Antimicrobial Resistance

Antimicrobial resistance is a natural process amplified by the misuse of antibiotics, antivirals, antifungals, and antiparasitics. The WHO ranks AMR as one of the top ten global health hazards, citing its rising impact on death and morbidity caused by resistant diseases[38]. According to reports, if adequate measures are not adopted, AMR might kill up to 10 million people each year by 2050, overtaking cancer as the major cause of death[31]. The molecular processes that cause AMR include spontaneous genetic mutations and horizontal gene transfer via plasmids, transposons, and integrons. These conditions promote the transmission of resistance genes among bacterial species, resulting in the development of multidrug-resistant pathogens like those in the ESKAPE group[4,3]. Indeed, the most threatening pathogens, often showing resistance to multiple or all classes of antibiotics, are grouped under the acronym ESKAPE responsible for the majority of nosocomial infections worldwide due to their ability to "escape" conventional antibiotics[33].

The COVID-19 pandemic has exacerbated the AMR situation by encouraging extensive antibiotic usage in hospitalized patients, even without verified bacterial illnesses [33]. This, along with strain on healthcare institutions and disruptions to surveillance efforts, has expedited the development of resistance. Research is investigating solutions such as novel antibiotic classes, phage treatment, and nanotechnology-based antimicrobials [20].

2.2 Drug Repurposing

Cancer remains one of the leading causes of death worldwide, driving continuous efforts to develop more effective therapies [29]. While classical chemotherapeutic agents have long played a central role in treatment, their use is often limited by toxicity, lack of specificity, and drug resistance [40]. Advances such as targeted therapies, immunotherapies, and combination regimens have improved outcomes, yet treating refractory and multidrug-resistant cancers remains a major challenge [40,29].

Drug repurposing is a promising and cost-effective method for finding new therapeutic uses for existing and licensed medications[28]. Unlike traditional

drug discovery, repurposing uses clinically existing medications to drastically reduce development time and failure rates[19]. This strategy has proven effective in severe public health situations, such as the COVID-19 pandemic, where quick treatment deployment was critical[32]. Beyond infectious illnesses, drug repurposing has gained popularity in oncology, where non-cancer therapies such as antimicrobials and cardiovascular medications have been revealed to have surprising anticancer effects[5,43].

The promise of repurposing is not just its efficiency, but also its ability to find unanticipated pharmacological effects, particularly when led by large-scale biological data and computer modeling. The application of AI-driven methods has significantly improved medication repurposing efforts[3]. ML and DL algorithms have been extremely useful in predicting drug-disease interactions, finding off-target effects, providing tools to mine existing datasets, and ranking candidate compounds with high translational potential[41]. The convergence of systems biology, cheminformatics, and omics technology has enabled the creation of computational frameworks for assessing drug-disease interactions beyond their intended applications. This is especially important in the context of AMR and multidrug-resistant diseases, where repurposed antitumoral and non-antibiotic medications may serve as alternative therapeutics[11].

2.3 Bioinformatic approach

AI in drug discovery To analyze the vast number of datasets, including drug-target interactions, genetic sequences and pharmacokinetics, needed to repurpose drugs is still to limited and time-consuming[26]. Thus, there is a need to execute new techniques sell-sufficient to overcome this problem, and that is where AI emerges as a powerful tool to resolve this problem[24]. The application of AI in the drug discovery area allows for the prediction and minimization of potential off-target interactions, analyzing both protein sequences and chemical structures, maximizing efficacy and minimizing toxicity. This helps researchers save time by focusing on drugs with the best chances of success[9].

Machine Learning has emerged as a transformational force in medication repurposing, allowing for predictive modeling, complicated pattern identification, and high-throughput hypothesis development from multidimensional biological data[1,4]. Training on datasets containing molecular structures, gene-disease associations, and pharmacological profiles allows ML algorithms to identify previously unknown therapeutic potentials in existing drugs with greater speed and scalability than traditional experimental pipelines[32].

One of the most significant advantages of machine learning is its ability to manage high-dimensional and diverse data, such as genomes, proteomics, chemical descriptors, and clinical outcomes. Random forests, support vector machines (SVM), and graph-based models have all been used extensively to repurpose frameworks, predict drug-target interactions, and infer mechanisms of action[41,8]. Furthermore, ML has shown to be useful in prioritizing repurposing

options for AMR. As traditional antibiotics lose potency, combining ML models with biological networks and phenotypic screening data aids in identifying non-antibiotic medicines with potential antibacterial properties[2].

Deep Learning allows computational models to learn representations of data that are more abstract. It tries to discover structures in, usually, larger data sets by using backpropagation to show the machine how it should change its own parameters, which are used to compute each layer, from the representations it has learned from previous layers[15].

Deep learning has become popular due to its ability to uncover latent patterns from high-dimensional biological data. Convolutional neural networks (CNNs) and autoencoders can be trained using structured datasets such as ChEMBL and DrugBank[21,35]. These models can anticipate drug-target interactions, toxicity profiles, and synergistic effects in combination therapy. The growing availability of open-access databases such as Drug Repurposing Hub and BindingDB has boosted ML by providing well-annotated training datasets[35]. When combined with unsupervised or semi-supervised learning approaches, these datasets allow for the development of innovative hypotheses in pharmacology with minimum experimental input.

3 Methodology

3.1 Search and Study selection

We conducted our review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) standards[10]. A detailed search was conducted on Google Scholar for full-length research publications published between January 2020 and March 2025 using the keywords: "machine learning", "deep learning", "drug repurposing" and "antimicrobial resistance".

Our search yielded 87 items, which were then narrowed down to 38 relevant research articles after screening for computational drug repurposing and drug data utilization. There were 16 papers found in PubMed, 12 papers found in Nature, and 10 other papers from citation searching, which were chosen for their focus on ML-based AMR prediction. Figure 1 presents an overview of the selection procedure.

3.2 Review of selected literature

In addition, we included publications that apply artificial intelligence models in this context in Table 1. This table summarizes recent machine learning and deep learning models applied to drug repurposing, including model names, publication dates, and links to source code to emphasize reproducibility.

Recent advances in artificial intelligence, particularly deep learning, have significantly impacted drug repurposing. Among these, TxGNN, proposed by

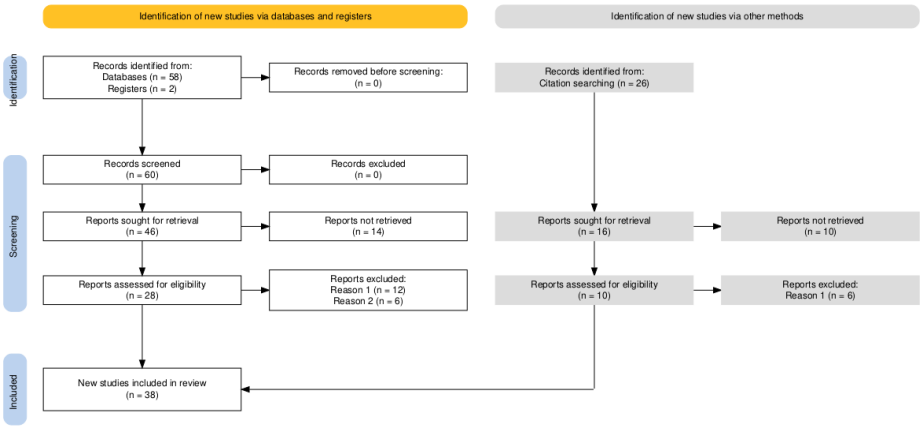

Fig. 1. Flow chart for article selection and filtering

Wang et al., uses Graph Neural Networks to model biomedical knowledge graphs, achieving strong performance in predicting drug–disease associations [35]. Similarly, Shennong, introduced by Zhang et al., combines molecular embeddings with biological data to effectively predict drug–target interactions across multiple tasks [43].

To address interpretability, APEX offers an explainable machine learning pipeline for drug repositioning, integrating predictive modeling with result visualization [34]. VAMPr applies explainable AI to predict antimicrobial resistance from genomic data, delivering accurate and interpretable results [18].

Other neural models include Chemprop, which uses message-passing neural networks to predict molecular properties from SMILE, and Chemformer, a transformer-based model pretrained on chemical data, supporting tasks like molecular translation and bioactivity prediction [30,14].

MARS adopts multi-task learning to identify antimicrobial resistance signatures in genomic data, while CCMDR leverages contrastive learning to distinguish valid drug–indication pairs, improving precision in repositioning [39,36].

MOSES provides a standardized platform to benchmark generative molecular models, and DrugRepo is a curated ML-driven database for predicting new drug indications from pharmacological data [25,2].

MM-RBM applies multimodal restricted Boltzmann machines to integrate diverse biomedical data for repositioning, while DRIAD uses deep learning to infer drug response across diseases by combining transcriptomic and pharmacological profiles [12,27]. Lastly, BacEffluxPred is an SVM-based tool for identifying bacterial efflux pump inhibitors, aiding virtual screening of potential repositioning candidates [23].

Table 1. Summary of predictive models for drug discovery and their associated code. References are listed in the bibliography.

Ref.	Date	Predictive model	Code
[13]	2024	TxGNN	https://github.com/mims-harvard/TxGNN
[43]	2024	Shennong framework	https://github.com/PeijingZhang/Shennong
[23]	2020	BacEffluxPred	http://proteininformatics.org/mkumar/baceffluxpred/
[35]	2022	DrugRepo	https://github.com/futurerepo/drugrepo
[27]	2021	DRIAD	https://github.com/labsyspharm/DRIADrc
[18]	2020	VAMPr	https://github.com/jiwoongbio/VAMPr
[12]	2020	MM-RBM	https://github.com/LBBSoft/Multimodal-Drug-Repurposing.git
[30]	2020	Chemprop	https://github.com/swansonk14/chemprop
[34]	2024	APEX	https://gitlab.com/machine-biology-group-public/apex
[25]	2020	MOSES	https://github.com/molecularsets/moses
[14]	2022	Chemformer	https://github.com/MolecularAI/Chemformer
[39]	2021	MARS	https://github.com/yutxie/mars
[36]	2021	CCMDR	https://github.com/HoytWen/CCMDR

3.3 Data loading and preparation

Data preparation is a fundamental stage in model development, involving the integration, cleaning, and harmonization of heterogeneous datasets [7]. Key preprocessing steps include handling missing data, normalizing values, encoding categorical variables, and aligning temporal features for time-series modeling [17]. Feature engineering transforms raw clinical data into meaningful variables for machine learning, while techniques such as data augmentation and class balancing are employed to mitigate the imbalance typically observed in AMR datasets [22,6]. Various machine learning and deep learning methods have been applied to predict antimicrobial resistance patterns. Traditional classifiers like SVM, random forests, and logistic regression are widely used in supervised settings [41,28], while deep learning models, particularly CNNs and RNNs, excel in capturing complex nonlinear relationships in clinical data [15,12].

Our approach focuses on predicting bacterial responses to antibiotics using multi-class and multi-label classification tasks [42]. Ensemble methods and hybrid models will be used to improve predictive stability [41,28], and time-series architectures will support forecasting future resistance trends from historical data. Some frameworks will also incorporate adaptive early warning systems that update predictions with new patient information [16]. Although regression models will be less frequent, they will be applied to estimate resistance probability or severity using linear models, gradient boosting, or deep regression networks [2]. Performance will be assessed using metrics such as accuracy, precision, and recall. Cross-validation will be implemented to evaluate model generalization, with external validation on independent datasets emphasized to ensure real-world applicability [42,37].

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