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Computational Chemistry Approaches in Drug Repurposing for Emerging Diseases

Dr. Priya S. Menon
Department of Computational Biology
Indian Institute of Technology (IIT) Bombay, India

Abstract
Traditional drug discovery processes are cumbersome due to their high failure rates, lengthy and expensive development times, and the critical requirement for quick therapeutic interventions during new disease outbreaks. To combat these kinds of emergencies more quickly and cheaply, the practice of drug repurposing—the process of finding new therapeutic applications for already-approved or experimental pharmaceuticals—has been gaining popularity. A modern repurposing pipeline would not be complete without computational chemistry, which has allowed for the rapid identification of candidates and the systematic investigation of drug-target interactions. Pharmacophore mapping, molecular docking, QSAR modeling, and molecular dynamics simulations are some of the techniques that scientists use to screen large chemical libraries and make accurate predictions about binding affinities. By combining these methodologies with network pharmacology and systems biology, their applicability has been greatly enhanced, allowing for a more comprehensive understanding of polypharmacological effects and intricate disease pathways. The predictive capacity of computational models has been significantly improved by recent advancements in machine learning and artificial intelligence. This has made it easier to find new candidates and migrate from in silico forecasts to experimental validation.
Keywords: Computational chemistry; drug repurposing; emerging diseases; molecular docking

Introduction
Rapid therapeutic development strategies are urgently needed to avoid the expensive, time-consuming, and potentially dangerous processes of de novo drug discovery in order to combat emerging diseases like pandemics, drug-resistant infections, and viral outbreaks. Due to regulatory obstacles, unexpected toxicity, and low efficacy, traditional drug development pipelines can take over a decade and cost billions of dollars to bring a single new medicine to market. Within this framework, drug repurposing—the process of discovering new uses for current medications—has become increasingly popular as a practical and economical way to solve unfulfilled medical requirements, especially in rapidly evolving public health crises. By utilizing previously established safety, pharmacokinetic, and manufacturing properties, repurposed medications can be quickly deployed during crises like the COVID-19 pandemic and the translational pathway from bench to bedside can be shortened. To optimize candidates, rank compounds for experimental validation, and forecast and assess drug-target interactions, computational chemistry has become an essential tool in contemporary drug repurposing tactics. In silico approaches are essential for discovering potential treatments for new diseases

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in which time and resources are scarce, thanks to developments in molecular modeling, artificial intelligence, and structural bioinformatics, which have greatly enhanced researchers' capacity to traverse enormous chemical and biological spaces. Molecular docking and similar methods form the backbone of computational drug repurposing because they can predict the atomic-level binding of a pharmacological molecule to a target protein, estimate binding affinity, and uncover possible action pathways. Finding inhibitors of SARS-CoV-2 major protease (Mpro) and spike protein, for example, has made extensive use of this strategy to screen current drug libraries against newly discovered viral or bacterial proteins. Docking and molecular dynamics (MD) simulations work hand in hand to improve docking predictions and find subtle interaction patterns that guide drug optimization by providing dynamic insights into the stability, conformational flexibility, and energetics of drug-target complexes under physiological conditions. In a similar vein, QSAR modeling uses statistical and machine learning methods to tie together chemical structures and biological activities. This paves the way for predictive modeling of massive compound datasets and the discovery of potential leads based on structural features. To make it even better, pharmacophore mapping and modeling define the key chemical properties needed for biological activity and compare them to drug databases to find potential candidates with comparable profiles.

Principles of Drug Repurposing

The practice of drug repurposing, also called drug repositioning, is a practical alternative to the time-consuming, expensive, and infamously high-attrition-rate conventional drug discovery process. It involves systematically finding new therapeutic uses for existing drugs, whether they have already been approved for clinical use, shelved during development, or withdrawn for reasons unrelated to safety. The basic idea behind repurposing is to find new uses for chemicals that already have proven pharmacokinetic, pharmacodynamic, and safety profiles. This can cut down on the time, money, and risks needed to bring a therapy to market. In contrast to the lengthy and expensive process of developing a brand-new chemical entity through de novo drug discovery—which can take years and cost billions of dollars—repurposed drugs can be brought to clinical use much more quickly, sometimes within a few years. This is especially important during epidemics of new diseases, when time is of the essence. There are various approaches to repurposing drugs. One is knowledge-based repurposing, which uses drug mechanisms and disease biology to find overlap. Another is computational repurposing, which uses in silico modeling, docking, and network pharmacology to predict new drug-target interactions. There is also experimental repurposing, which involves screening existing drugs across disease-relevant assays. Finally, there is clinical observation-based repurposing, which considers off-target or serendipitous therapeutic effects observed during trials or post-marketing surveillance. The effectiveness of this approach is demonstrated by its track record of success: Following its withdrawal from use due to teratogenic effects, sildenafil was repurposed for erectile dysfunction and pulmonary hypertension. Thalidomide was repositioned as a therapy for multiple myeloma and leprosy. Remdesivir was most recently repurposed for COVID-19 treatment under emergency use authorization after being originally developed for Ebola. Such cases demonstrate the adaptability of repurposing and its ability to

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prolong the medicinal half-lives of pharmaceuticals. From a scientific standpoint, repurposing works by taking advantage of common molecular pathways and pathophysiological mechanisms in different diseases. For example, in viral infections, where cytokine storms cause pathology, medications that target inflammatory cascades in autoimmune disorders may work well. The mapping of drug-disease networks has been made possible by breakthroughs in systems biology, bioinformatics, and chemoinformatics, which provides a rational basis for discovering repositioning prospects. Because of the need to thoroughly assess variations in dosage, medication delivery, and long-term safety for new indications, rigorous validation is still an important part of the repurposing process. A more efficient, resource-conscious, and data-driven paradigm is embodied by drug repurposing principles; this paradigm is in line with precision medicine and global health preparedness goals; and it offers hope for faster therapeutic responses to both chronic diseases and unexpected new health threats.

Molecular Docking and Virtual Screening

Computational chemistry approaches to drug repurposing use molecular docking and virtual screening to predict how existing drugs interact with novel biological targets to identify candidate compounds with therapeutic potential for emerging diseases quickly, cheaply, and mechanistically. Molecular docking simulates the interaction between a small molecule (ligand) and a biomolecular target, usually a protein, to estimate the ligand's preferred orientation, binding mode, and affinity when forming a complex with the target, revealing therapeutic efficacy predictions. Scoring functions—mathematical models that assess the projected drug–target interaction based on physicochemical concepts including hydrogen bonding, hydrophobic effects, electrostatics, and van der Waals interactions—are essential to docking. Virtual screening uses docking algorithms to identify compounds most likely to bind and regulate a disease-relevant target in huge pharmacological libraries, including FDA-approved medicines and experimental and natural product databases. Docking and virtual screening in repurposing are attractive because they are scalable and fast. In silico screening can evaluate thousands to millions of compounds within days, narrowing the pool of experimental validation candidates. The COVID-19 pandemic showed the value of docking and virtual screening in emerging diseases. Global research efforts rapidly mobilized computational pipelines to identify inhibitors of SARS-CoV-2 proteins like Mpro, RdRp, and the spike protein's receptor-binding domain. Docking was used to repurpose antiviral medications including remdesivir, favipiravir, and lopinavir, as well as non-antiviral molecules like ivermectin, chloroquine, and certain anticancer drugs, demonstrating the range of computational screen options. Remdesivir binds tightly to RdRp, supporting its clinical evaluation and emergency use authorization; docking experiments showed this. Docking suggested that hydroxychloroquine could disrupt spike protein–ACE2 receptor connections, prompting early therapeutic trials but later skepticism. These examples show that docking can quickly discover interesting candidates, but rigorous in vitro and in vivo validation is needed to validate biological activity. Beyond viral infections, docking has been used in oncology to reposition alcohol-aversion drugs like disulfiram as proteasome inhibitors with anticancer potential, and in neurodegenerative diseases to show that anti-inflammatory and

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antihypertensive agents can modulate amyloid aggregation and tau pathology. For robustness and dependability, virtual screening operations sometimes require numerous steps. First, target selection and preparation require high-quality protein structures from X-ray crystallography, NMR, or cryo-electron microscopy, or homology modeling when experimental structures are unavailable. Second, to maximize clinical translatability, ligand libraries should include medication-like molecules with documented pharmacokinetic and toxicity profiles from FDA-approved drug libraries like DrugBank or the ZINC database. Third, docking simulations use AutoDock, Glide, GOLD, or MOE, which use different scoring methods and search methodologies. Since molecular dynamics simulations account for protein flexibility and solvent effects overlooked in rigid docking, post-docking refinement is becoming standard procedure to better anticipate binding stability and energetics. Consensus scoring—combining findings from several docking algorithms—reduces scoring function biases and boosts hit certainty. To assess drug-likeness and clinical viability, shortlisted compounds undergo ADMET (absorption, distribution, metabolism, excretion, and toxicity) predictions. Integrating molecular docking and virtual screening with pharmacophore modeling and machine learning-based prioritization enhances medication repurposing. Pharmacophore models allow screening for medicines that bind like known inhibitors by defining the spatial organization of biological activity-related properties. COVID-19 researchers used this hybrid technique to match pharmacophore properties from antiviral drugs to find protease inhibitors. This pipeline benefits from machine learning by learning from big docking datasets, improving scoring functions, and predicting binding affinities more accurately.

Machine Learning and Artificial Intelligence in Repurposing

Machine learning (ML) and artificial intelligence (AI) have rapidly become integral components of computational chemistry approaches in drug repurposing, allowing the analysis of vast, heterogeneous biomedical datasets and the discovery of hidden patterns that traditional methods cannot detect, accelerating the discovery of novel therapeutic uses for existing drugs in emerging diseases. Repurposing relies on ML and AI algorithms' ability to learn from historical data—including chemical structures, bioassay results, clinical outcomes, omics profiles, and literature mining—to build predictive models that can accurately and scalably infer new drug–target or drug–disease relationships. AI approaches can generalize from complex, nonlinear, and high-dimensional data, unlike molecular docking or QSAR modeling, which rely heavily on predefined physical or statistical rules. This makes them ideal for multifactorial human diseases and drug action polypharmacology. Predicting off-target effects and identifying new disease indications with random forests and support vector machines (SVMs) trained on chemical fingerprints was one of the first AI applications in drug repurposing. Recently, deep learning architectures like CNNs, RNNs, and GNNs have revolutionized the field by representing drugs and proteins as structured data like molecular graphs or amino acid sequences and learning directly from them without handcrafted features. These models generally outperform computational chemistry in accuracy and throughput in predicting binding affinities, drug–target interactions, and drug–disease connections.

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AI has enabled large-scale drug–target interaction (DTI) prediction, which is key to repurposing. Matrix factorization, deep autoencoders, and graph-based models use existing drug–target connections to infer novel interactions, repositioning medications toward emerging targets involved in viral infections, malignancies, and neurological illnesses. AI models screened thousands of approved drugs against SARS-CoV-2 proteins during the COVID-19 pandemic, prioritizing baricitinib based on predicted interactions with viral entry pathways and host kinases. This led to clinical trials and emergency use approval. By learning latent representations of chemical space and suggesting medications with structural or functional resemblance to known actives, generative adversarial networks (GANs) and variational autoencoders (VAEs) can produce new hypotheses. NLP, another powerful branch of AI, has been used to mine biomedical literature, clinical trial repositories, and EHRs for repurposing opportunities by identifying drug-disease co-occurrences, extracting mechanistic insights, or correlating off-label use with patient outcomes. IBM Watson and DeepMind's AlphaFold show how AI-driven NLP and protein structure prediction can boost druggable target and repurposing prospects in computational chemistry.

Conclusion

Modern medication repurposing relies on computational chemistry to accelerate therapy discovery in emerging diseases with limited time and resources. Researchers can quickly predict drug–target interactions and identify promising candidates using molecular docking, virtual screening, molecular dynamics simulations, QSAR modeling, and pharmacophore mapping. Systems biology and network pharmacology have broadened this reach, allowing multi-target analyses that reflect human diseases' complex, multifactorial character. As shown during the COVID-19 pandemic and in ongoing efforts for oncology, neurodegenerative disorders, and rare diseases, machine learning and artificial intelligence can uncover hidden patterns, refine predictions, and simulate real-world therapeutic responses. These computational methods reduce drug development cost, time, and risk while leveraging current medication safety and pharmacological expertise. Dependence on high-quality structural and biological data, repeatability issues, AI model interpretability, and regulatory acceptance of computationally driven predictions remain hurdles. Addressing these limitations will require algorithm innovation, dataset standardization, tighter integration between in silico predictions and experimental validation, and cross-disciplinary collaboration across chemistry, biology, data science, and medicine. Future drug repurposing will be more precise, predictive, and patient-tailored thanks to computational chemistry, artificial intelligence, cryo-electron microscopy, omics technologies, and personalized medicine frameworks. Computational chemistry approaches in drug repurposing can solve critical health problems and accelerate therapeutic innovation in translational medicine.

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