Review Article

Artificial Intelligence Meets Computational Chemistry in Drug Discovery

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Abstract

The integration of artificial intelligence (AI) with computational chemistry has opened new frontiers in drug discovery. This systematic review explores recent advances in the convergence of AI-driven approaches with molecular dynamics (MD), quantum machine learning (QML), and physiologically based pharmacokinetic (PBPK) modeling. These tools enhance predictive accuracy, reduce experimental workload, and facilitate the discovery of novel drug candidates. We systematically analyze peer-reviewed literature from ScienceDirect and Scopus-indexed journals from 2020 to 2025, providing an overview of emerging methodologies and their applications. Key findings highlight the synergistic impact of integrating machine learning algorithms with physical and chemical modeling to predict drug–target interactions, optimize pharmacokinetics, and model complex biological systems.

Keywords

Artificial intelligence, Molecular dynamics, Quantum machine learning, PBPK modeling, Drug discovery, Computational chemistry

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1. Introduction

Artificial intelligence (AI) has rapidly transformed many scientific domains, and its integration with computational chemistry offers promising advancements in early-stage drug discovery [1]. Molecular dynamics (MD), quantum machine learning (QML), and physiologically based pharmacokinetic (PBPK) modeling are now increasingly leveraged through AI algorithms to better predict drug behavior, improve virtual screening, and model complex biological interactions [2]. This review focuses on the intersection of these technologies and their applications in pharmaceutical chemistry. Artificial intelligence (AI) has emerged as a transformative force across scientific disciplines, particularly in pharmaceutical chemistry, where early-stage drug discovery demands high precision, large-scale data analysis, and time efficiency. Traditionally, drug development relied on experimental methods that were time-consuming and costly. The convergence of AI with computational chemistry—specifically molecular dynamics (MD), quantum machine learning (QML), and physiologically based pharmacokinetic (PBPK) modeling—has led to a new paradigm in predictive drug modeling. These technologies allow for efficient virtual screening, accurate property prediction, and simulation of human biological systems. This review aims to highlight how AI augments each of these computational methods to improve drug discovery outcomes.

2. Molecular Dynamics and AI Integration

Molecular dynamics simulations model the movement of atoms and molecules over time. AI can significantly enhance MD by predicting simulation outcomes, reducing computational cost, and improving force field accuracy [3]. Deep learning models can be trained on MD trajectories to detect conformational changes, protein folding mechanisms, and ligand interactions with greater efficiency [4]. Molecular dynamics (MD) simulations allow the modeling of atomic movements over time, providing insight into the behavior of complex biomolecular systems. Despite their value, MD simulations are limited by high computational costs. AI, particularly deep learning, has been employed to enhance these simulations by predicting conformational changes and developing surrogate force fields like ANI and DeepMD. This integration reduces simulation time while maintaining or even improving predictive accuracy. AI-driven MD is revolutionizing how researchers understand ligand binding, protein folding, and membrane interactions.

3. Quantum Machine Learning in Drug Discovery

Quantum machine learning (QML) combines quantum computing with AI, allowing faster resolution of chemical simulations involving electron interactions and complex quantum states [5]. Although still nascent, QML has shown promise in predicting molecular properties and simulating reactions that are otherwise computationally intensive [6]. Quantum machine learning (QML) combines quantum computing with artificial intelligence to solve problems that are infeasible for classical computers. It offers advantages in calculating molecular energies, electronic structures, and chemical reactivity,

making it idealfor early-stage drug discovery. Algorithms such as Variational Quantum Eigensolver (VQE) and Quantum Support Vector

Table 1. Applications of AI in Molecular Dynamics Simulations

MD Application Area	AI/ML Technique Used	Purpose	Example Reference
Force Field Development	Neural Networks	Predict potential energy surfaces	[7]
Accelerated Sampling	Reinforcement Learning	Identify rare event transitions	[4]
Conformational State Prediction	Deep Learning (Autoencoders)	Reduce dimensionality and cluster states	[4], [6]
Protein Folding Simulations	AlphaFold + MD	Predict structure, validate via dynamics	[2]
Solvent Interaction Modeling	Graph Neural Networks (GNNs)	Represent atomic environments dynamically	[27]

Machines (QSVM) are currently being explored for drug design. QML is particularly valuable for modeling systems with strong electron correlation, and although it remains an emerging field, its potential for breakthroughs is significant.

4. AI-Augmented PBPK Modeling

Physiologically based pharmacokinetic (PBPK) models simulate drug absorption, distribution, metabolism, and excretion. By incorporating AI, these models can be personalized using patient-specific data, leading to better predictions of therapeutic windows and dosing strategies [7]. Machine learning algorithms such as random forests and neural networks enhance PBPK parameter estimation and sensitivity analysis [8]. Physiologically based pharmacokinetic (PBPK)models simulate drug behavior across human tissues and organs. Traditional PBPK models depend on precise physiological data and complex parameter estimation. By incorporating AI—especially machine learning models like neural networks and decision trees—PBPK modeling becomes more adaptable and predictive. AI helps individualize PBPK models by learning patterns from real-world data and clinical studies, which enhances their utility in regulatory settings and personalized medicine.

Table 2: Comparative analysis of classical ML and quantum ML for applications in drug discovery.

Feature	Classical Machine Learning	Quantum Machine Learning (QML)
Data Encoding	Uses fixed vector representations	Uses quantum states (amplitudes/phases)
Computational Scaling	Polynomial	Potential exponential speedup
Feature Space	Fixed	Can explore high-dimensional Hilbert space
Noise Sensitivity	Robust to noise	Prone to decoherence
Hardware Maturity	Fully developed (CPUs/GPUs)	Still developing (Quantum processors)
Current Drug Discovery Use Case	ADME/Tox prediction, docking	QSAR modeling, protein folding, retrosynthesis
Example Algorithms	Random Forest, CNN, GNN	VQE, QNN, Quantum SVM

Table 3. Comparison of Traditional vs AI-Augmented PBPK Modeling Approaches[13, 14]

Feature	Traditional PBPK Modeling	AI-Augmented PBPK Modeling
Parameter Estimation	Mechanistic, time-consuming	Fast, data-driven using ML/AI algorithms
Data Requirements	Requires extensive preclinical data	Can work with sparse/heterogeneous datasets
Model Flexibility	Rigid structure, difficult to scale	Adaptable, can learn nonlinear relationships
Predictive Accuracy	Moderate	High (depending on data quality)
Extrapolation to Special Populations	Complex and limited	AI can infer and adjust models dynamically
Use in Early Drug Discovery	Limited	Highly suitable for early screening

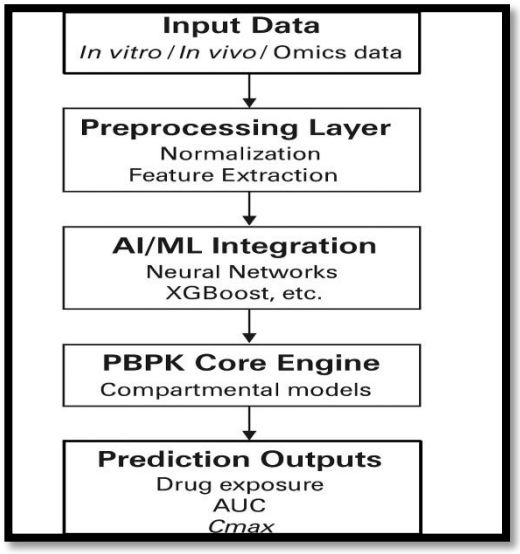

Figure 1. Schematic workflow of AI-augmented physiologically based pharmacokinetic (PBPK) modeling.The process integrates traditional PBPK compartmental models with artificial intelligence and machine learning tools—such as neural networks and gradient boosting methods (e.g., XGBoost)—to enhance parameter estimation, handle complex biological data, and improve prediction accuracy for pharmacokinetic outcomes like drug exposure, AUC, and C_{max}[32, 33].

5. Applications and Case Studies

Recent studies have shown the efficacy of AI-augmented MD and PBPK models in predicting drug toxicity, bioavailability, and blood–brain barrier penetration [9]. QML has been used to simulate potential inhibitors for key disease targets, including kinases and viral proteins [10, 28]. These tools have improved compound prioritization and reduced reliance on costly wet-lab experiments. AI-integrated computational chemistry is being applied in various real-world contexts. For example, AlphaFold has transformed protein structure prediction. AI-enhanced MD simulations have guided the design of HIV-1 protease inhibitors. QML approaches have been used to simulate drug interactions for COVID-19 targets. PBPK models augmented with AI have supported pediatric dosing and prediction of brain drug penetration. These case studies illustrate the potential of AI-driven computational tools to streamline drug discovery and reduce development timelines [10, 22-26].

6. Challenges and Future Perspectives

Despite their advantages, challenges such as data scarcity, model interpretability, and the requirement for quantum hardware limit current applications [11-17]. Collaborative efforts between computational chemists, AI experts, and pharmaceutical scientists are essential to unlock the full potential of these technologies [12, 31]. Despite their benefits, integrating AI with computational chemistry presents challenges. Data quality, interpretability, and model validation remain key obstacles. The “black box” nature of deep learning raises issues for regulatory approval. Quantum computing, while promising, still faces hardware and scalability limitations. Ethical concerns related to data use, reproducibility, and fairness must also be addressed. The future lies in developing hybrid AI-physics models, creating standardized datasets, and advancing explainable AI frameworks to foster greater adoption in pharmaceutical research.

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