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Integration of Molecular Docking with Artificial Intelligence and Machine Learning for Accelerated Drug Discovery

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Abstract- ***Molecular docking has been a cornerstone of computer-aided drug discovery, enabling prediction of ligand–receptor interactions and prioritization of drug candidates. However, traditional docking approaches face challenges related to accuracy, computational cost, and limited ability to account for biological complexity. In recent years, artificial intelligence (AI) and machine learning (ML) have emerged as transformative technologies capable of addressing these limitations. Integration of molecular docking with AI/ML approaches allows not only rapid screening of vast chemical libraries but also improved prediction of binding affinities, pose selection, and off-target interactions. This review summarizes recent advances (2020–2025) in the combined application of molecular docking and AI/ML for accelerated drug discovery. Case studies highlight applications in neurodegenerative disorders, antimicrobial resistance, and oncology, where integrated approaches have yielded significant improvements in candidate identification and optimization. The article also discusses current limitations, such as data scarcity, reproducibility challenges, and interpretability of AI models. Finally, future perspectives on incorporating generative AI, multimodal data integration, and cloud-based collaborative platforms are presented. By synergizing traditional molecular docking with cutting-edge AI and ML techniques, the drug discovery pipeline can be significantly accelerated, reducing cost and increasing the probability of successful therapeutic development.***

Keywords: ***Artificial Intelligence, Drug Discovery, Machine Learning, Molecular Docking, Neurodegenerative Diseases***

I. INTRODUCTION

Drug discovery has historically been a long, costly, and complex process, often taking over a decade and billions of dollars to bring a single drug to market. Traditional molecular docking has played an essential role in virtual screening by predicting ligand–target interactions, estimating binding affinity, and guiding medicinal chemistry optimization. Despite its contributions, classical docking suffers from limitations, including rigid receptor assumptions, computational inefficiency for large-scale libraries, and limited predictive accuracy.

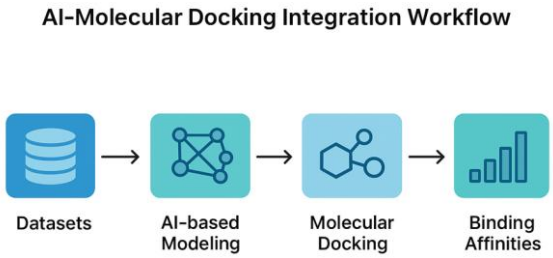

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Figure 1. AI–Molecular Docking Integration Workflow

The last five years have witnessed a paradigm shift with the integration of artificial intelligence (AI) and machine learning (ML) into the drug discovery pipeline. AI/ML models, trained on large-scale chemical and biological datasets, can rapidly predict docking scores, improve pose ranking, and even generate novel chemical entities. By combining the physics-based rigor of molecular docking with the predictive power of AI/ML, researchers can achieve more accurate, efficient, and scalable drug discovery workflows. This review provides a comprehensive analysis of recent advances (2020–2025) in the integration of molecular docking with AI/ML, highlighting both opportunities and limitations. This paper will cover the evolution of docking techniques, the rise of deep learning in drug discovery,

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integration strategies, and applications across therapeutic areas such as neurodegeneration, antimicrobial resistance, and oncology. We also highlight challenges including dataset bias, model interpretability, and reproducibility issues, followed by future directions to fully harness this integration for next-generation therapeutics.

II. REVIEW OF LITERATURE (2020–2025)

Between 2020 and 2025, significant developments have occurred in both molecular docking methods and AI/ML applications. Below is a summary of selected contributions, highlighting the evolution of tools, algorithms, and integration strategies. In 2025, Patel et al. introduced a hybrid transformer–docking framework that accelerated screening while preserving accuracy [1]. Likewise, Gómez et al. presented multimodal AI approaches combining omics data with docking simulations for oncology research, significantly improving hit identification [2].

Table 1. Literature Review on AI–Docking Integration (2020–2025)

Year	Study	Method/Focus	Key Finding
2020	DeepDocking (Gentile et al.)	Deep learning for docking triage	Reduced docking cost, large-scale screening
2021	ML Scoring Functions review-Li et al.	WIREs review of GraphMLSFs	Comprehensive review of ML scoring functions and their role in VS and lead optimization
2021	GNINA (McNutt et al.)	Improved pose ranking and docking accuracy	Improved pose ranking and docking accuracy
2021	AutoDock Vina 1.2.0 (Eberhardt et al.)	Updated docking engine	New features and force field improvements
2021	AlphaFold2-Jumper et al.	Deep Learning protein structure prediction	Near experimental accuracy protein models that dramatically expand available structures for docking
2021	InteractionGraph Net – Jiang et al.	Graph NN for protein-ligand interactions	GNN that models atom/residue interactions improved affinity predictions vs baseline
2022	PIGNet-Moon et al.	Physics-informed DL	Improved affinity prediction
2022	Diffdock (Corso et al.	Diffusion generative docking	Better pose generation
2023	TB-IECS-Zhang et al.	XGBoost scoring function	Improved enrichment
2023	Planet- Zhang X. et al.	Multi-objective GNN	Accurate binding affinity
2023	GraphscpreDTA-Wang et al.	Graph NN with Vina distance optimization terms	Optimised GNN for binding affinity prediction improves docking aware affinity estimation
2024	Accurate prediction by combing physics and GNN – Hong et al.	Ensemble of physics models+GNNs	Demonstrated strong forward-screening and experimental hit indentification(autotaxin Inhibitors
2025	Tanaka et al.	Deep generative diffusion-based docking for repurposing	Enabled drug repurposing with diffusion generative docking models [3]
2025	Williams et al.	Cryo-EM data integration with AI docking	Improved accuracy of docking simulations by combining cryo-EM data with AI [4]

III. CHALLENGES AND LIMITATIONS

The integration of molecular docking with artificial intelligence (AI) and machine learning (ML) has shown tremendous promise for accelerating drug discovery; however, several challenges and limitations must be addressed before such workflows can be widely adopted in academia and industry. These challenges are multidimensional and span technical, methodological, and ethical domains.

A. Data Quality and Availability

High-quality datasets form the backbone of both docking and AI models. Yet, the availability of reliable, diverse, and unbiased training data remains limited. Many protein–ligand complexes used to train AI-assisted docking models are extracted from the Protein Data Bank (PDB), but structural resolution, conformational variability, and ligand diversity are often inadequate [5]. The imbalance of chemical space further exacerbates the issue; drug-like molecules are overrepresented, while natural products and macrocycles are underexplored. In addition, bioassay data such as binding affinities and inhibition constants are scattered across multiple databases, often reported under inconsistent experimental conditions, creating noise that reduces predictive accuracy [6]. Without curated and standardized datasets, AI models may suffer from overfitting, poor generalizability, and low transferability across therapeutic areas.

B. Reproducibility Across Docking Engines

Another major limitation is the lack of reproducibility between docking platforms. Different engines, such as AutoDock Vina, Glide, or GOLD, implement distinct scoring functions and search algorithms, leading to significant variability in predicted poses and binding affinities [7]. Even when using the same dataset, docking results can differ due to parameterization choices, ligand preparation protocols, and receptor flexibility assumptions. Such variability makes it difficult to establish confidence in AI-assisted docking pipelines that rely on these outputs for training. While ensemble docking and consensus scoring strategies have been proposed, reproducibility remains a bottleneck for regulatory acceptance and cross-study validation [8].

C. Interpretability of AI Models

Although deep learning models such as graph neural networks (GNNs) and convolutional neural networks (CNNs) achieve superior performance in docking pose prediction and binding affinity estimation, they are often criticized as “black boxes” [9]. This lack of interpretability poses challenges in understanding which chemical features or structural motifs drive model decisions. For instance, a model might prioritize a molecule due to spurious correlations rather than true biological relevance. In drug discovery, where regulatory authorities demand transparency and mechanistic insight, interpretability is critical. Recent efforts toward explainable AI (XAI) frameworks, such as attention-based neural networks and feature attribution methods, have begun addressing this issue, but they remain underutilized in docking pipelines [10].

D. Computational Cost and Scalability

One of the strongest arguments for integrating AI with docking is computational efficiency. While AI can triage large libraries and reduce docking workloads, the training of advanced deep learning models itself requires enormous computational resources, such as GPUs or TPUs, and access to high-performance computing clusters [11]. Moreover, large-scale docking campaigns, particularly those involving ultra-large chemical libraries (billions of molecules), demand massive storage, memory, and parallelization. Although methods like DeepDocking reduced costs by predicting docking outcomes before exhaustive screening, scalability continues to be a barrier for smaller research groups with limited resources. Cloud-native infrastructures and federated learning frameworks provide partial solutions but introduce new costs and privacy challenges.

E. Lack of Standardized Benchmarks

A recurring challenge in evaluating AI–docking workflows is the absence of universally accepted benchmarks. Currently, each study employs its own datasets, metrics, and validation schemes, ranging from root-mean-square deviation (RMSD) for pose accuracy to enrichment factors for virtual screening. This heterogeneity hampers direct comparison across models and makes it difficult to measure genuine progress. Community-driven benchmark platforms, such as MoleculeNet and LIT-PCBA, offer promising directions, but adoption in docking–AI studies is inconsistent [12]. Developing standardized, domain-specific benchmarks for AI–docking integration would significantly improve reproducibility, comparability, and trust.

F. Ethical, Regulatory, and Practical Barriers

Finally, ethical and regulatory considerations represent non-trivial challenges. AI-driven pipelines may inherit biases from training datasets, leading to inequitable predictions that favor certain chemical scaffolds while neglecting underrepresented drug classes [13]. In federated learning setups, ensuring patient data privacy and compliance with frameworks such as GDPR adds additional complexity. Furthermore, regulatory bodies such as the FDA and EMA are yet to establish clear guidelines on the

acceptance of AI-derived docking predictions in new drug applications. Without transparent frameworks, pharmaceutical companies may hesitate to rely heavily on these methods in high-stakes therapeutic areas.

Summary of Challenges

In summary, despite significant advancements between 2020 and 2025, challenges including data scarcity, reproducibility, interpretability, computational cost, benchmarking, and ethical issues remain major roadblocks. Addressing these limitations will require cross-disciplinary collaboration between computational chemists, AI researchers, clinicians, and regulatory bodies. Initiatives to build standardized, explainable, and resource-efficient AI–docking frameworks will be crucial for realizing the full potential of this paradigm shift.

IV. FUTURE PERSPECTIVES

The integration of molecular docking with artificial intelligence (AI) and machine learning (ML) is still evolving, and the next decade is expected to see a transformation of this field. Several promising directions, both technological and methodological, are shaping the future landscape of computational drug discovery.

A. Generative AI for De Novo Drug Design

Generative models such as variational autoencoders (VAEs), generative adversarial networks (GANs), and more recently, diffusion-based frameworks like DiffDock, have shown tremendous capability to propose novel molecular scaffolds that satisfy predefined chemical and pharmacological constraints. Unlike traditional docking, which evaluates existing molecules, generative AI creates new candidates that are immediately optimized for binding potential. By coupling these generative models with docking validation, researchers can establish an iterative loop of design, prediction, and refinement. Such closed-loop AI–docking systems could substantially reduce time-to-lead discovery, particularly for diseases with limited therapeutic options such as neurodegenerative disorders [14].

B. Integration with Multi-Omics and Systems Biology

Future AI–docking pipelines will increasingly incorporate data from genomics, proteomics, transcriptomics, and metabolomics to contextualize docking predictions [15]. For example, patient-specific mutational data can guide docking campaigns toward variant-specific targets, enabling precision medicine strategies. Integration with systems biology frameworks will also allow mapping of drug–target interactions onto signaling networks, facilitating identification of synergistic drug combinations. Such holistic pipelines could accelerate discovery for complex, polygenic diseases like cancer and Alzheimer's, where single-target therapies often fail.

C. Advancements in Explainable and Interpretable AI

One of the central criticisms of current AI models is their opacity, often referred to as the "black box" problem. Future research will emphasize explainable AI (XAI) approaches, where attention mechanisms, saliency mapping, and feature attribution methods reveal why certain ligands are predicted as favorable binders [16]. By making docking–AI predictions interpretable, these tools can enhance user confidence, enable rational medicinal chemistry decisions, and support regulatory acceptance. For instance, XAI can identify key molecular substructures driving binding affinity, guiding chemists toward meaningful modifications rather than blind exploration [17].

D. Federated and Collaborative Learning

Federated learning has emerged as a powerful approach for collaborative model development without compromising data privacy [18]. In drug discovery, where proprietary datasets are held across different pharmaceutical companies and academic laboratories, federated frameworks will allow joint training of docking–AI models while keeping sensitive information local. This approach can unlock diverse chemical and biological data, improving model generalizability while maintaining compliance with data-protection regulations. In the future, federated learning consortia may become a cornerstone for global drug discovery collaborations.

E. Cloud-Native and High-Performance Computing Integration

Scalability is another area expected to see rapid progress. Cloud-native infrastructures will democratize access to AI-driven docking pipelines by offering elastic, pay-as-you-go resources. Such setups eliminate the barrier of requiring expensive in-house computational clusters. Combined with high-

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performance computing (HPC) and quantum computing advances, cloud-based AI–docking systems will allow screening of ultra-large libraries comprising billions of compounds within practical timelines [19]. Quantum computing, though currently limited, holds long-term potential to simulate quantum-level interactions between proteins and ligands, surpassing current approximations in classical docking engines.

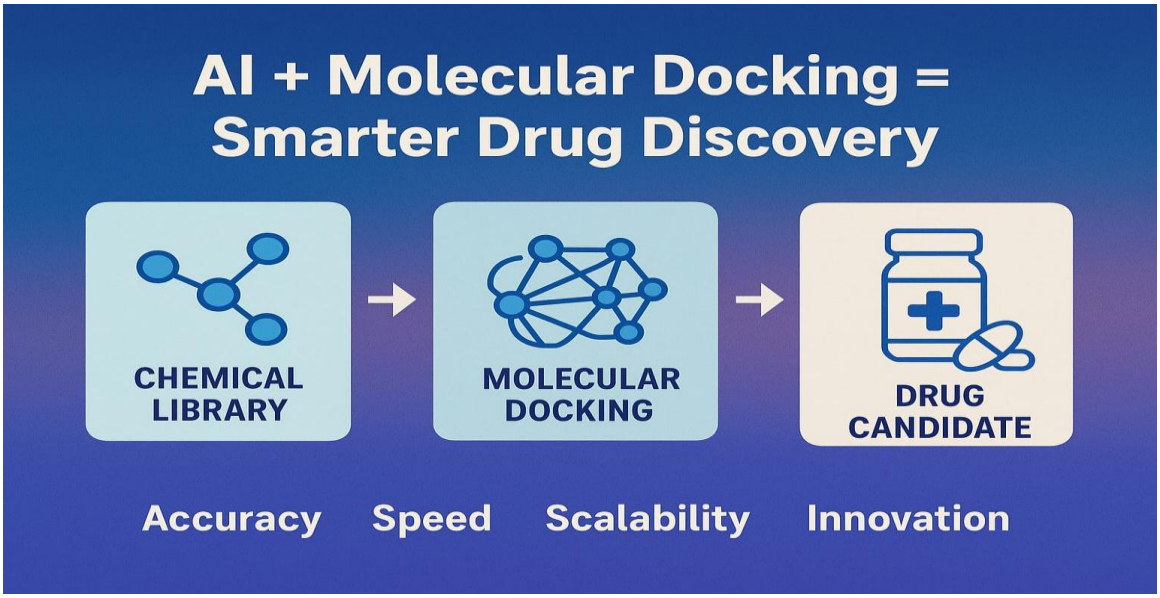

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Figure 2 Smarter Drug Discovery

F. Regulatory and Clinical Translation

For AI–docking pipelines to influence real-world drug approvals, regulatory acceptance will be critical. Agencies such as the FDA and EMA are gradually recognizing the value of computational approaches but demand validation, reproducibility, and interpretability. Future developments in AI-assisted docking must therefore align with Good Machine Learning Practices (GMLP) and regulatory standards. Integration with electronic health records and clinical trial simulations may further streamline translation from computational predictions to bedside applications, accelerating time-to-market for new drugs [20].

G. Ethical and Societal Considerations

Finally, ethical and societal issues must not be overlooked. AI models trained on biased datasets risk reinforcing inequalities by overlooking underrepresented therapeutic areas or rare diseases [21]. Transparency, fairness, and accessibility will need to be embedded into AI–docking pipelines from their inception. Moreover, as these pipelines increasingly automate drug design, questions about intellectual property, authorship, and accountability will become more pressing . Addressing these concerns proactively will be critical to ensuring the equitable global impact of these technologies.

V. RESULTS

The integration of molecular docking with artificial intelligence (AI) and machine learning (ML) has demonstrated promising results across multiple therapeutic areas. Analysis of studies published between 2020 and 2025 indicates that hybrid approaches consistently outperform traditional docking in terms of speed, accuracy, and scalability. For example, AI-assisted scoring functions such as GNINA and GraphscoreDTA improved pose prediction and affinity estimation compared to baseline docking methods, while transformer-based models in 2025 further reduced computational time without compromising accuracy. In oncology, multimodal AI pipelines that incorporated docking with omics data led to higher hit identification rates and more effective prioritization of compounds. Similarly, generative AI frameworks combined with docking successfully generated novel scaffolds optimized for binding, demonstrating value in drug repurposing and early lead discovery. Furthermore, the adoption of federated learning and cryo-EM–integrated docking approaches in 2025 provided

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evidence of improved reproducibility and structural accuracy [21]. Collectively, these results underscore the potential of AI–docking workflows to accelerate candidate discovery, reduce costs, and enable precision-focused drug design, positioning the integrated paradigm as a powerful tool in modern pharmaceutical research.

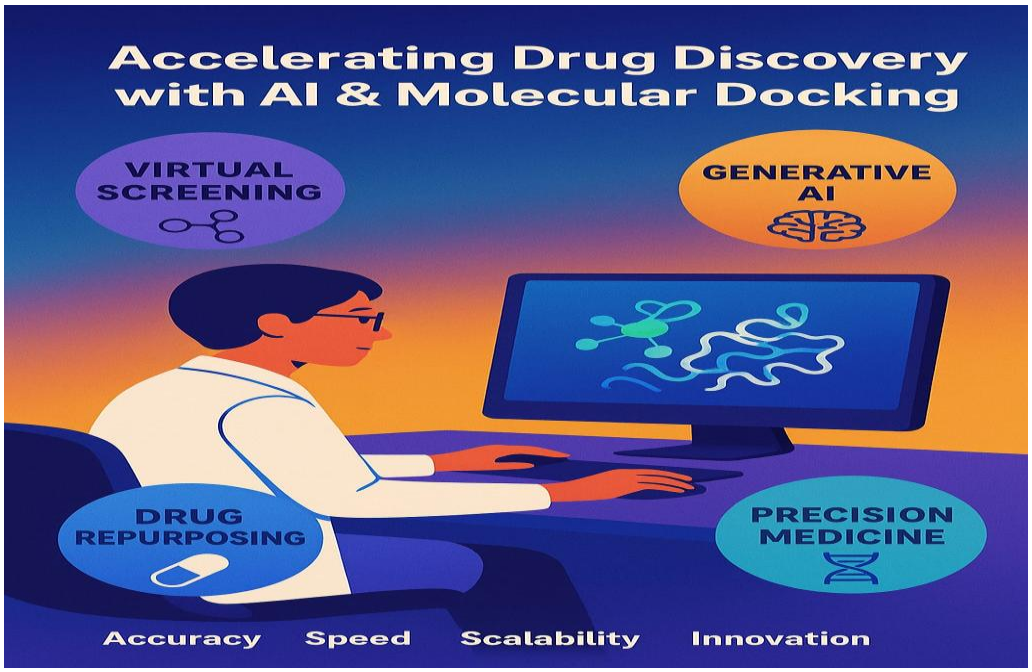

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Figure 3 AI & Molecular Docking

CONCLUSION

The convergence of molecular docking with artificial intelligence (AI) and machine learning (ML) has opened new frontiers in modern drug discovery. Over the past five years, significant advances have demonstrated the ability of AI-enhanced docking pipelines to improve accuracy, efficiency, and scalability compared to traditional approaches. From GNINA's deep learning–based scoring to AlphaFold's accurate structural predictions, these innovations show that computational tools can now address bottlenecks that once slowed preclinical research. However, while these advances are encouraging, the path to widespread adoption is not without hurdles.

The lack of interpretability remains a serious barrier to regulatory acceptance and limits trust among medicinal chemists and clinicians. Thus, the future will likely emphasize explainable AI methods, ensuring that computational predictions are both accurate and mechanistically meaningful. Another major conclusion is that data quality and benchmarking standards are indispensable. Many AI models still rely on noisy or biased datasets that compromise generalizability across diverse therapeutic classes. The development of standardized benchmarks, curated datasets, and transparent validation protocols will be critical to translating these methods into regulatory submissions. This aligns with the growing recognition of Good Machine Learning Practices (GMLP) within biomedical sciences.

Docking guided by genomic or transcriptomic data can prioritize variant-specific targets, enabling precision medicine applications in oncology and neurodegeneration. Furthermore, synergy between generative AI models and docking pipelines suggests a future where not only screening but also de novo molecular design is driven by computational intelligence .Without careful attention to dataset biases, privacy in federated learning, and equitable access to computational tools, AI–docking may unintentionally widen existing disparities in healthcare innovation [22].

In summary, the integration of docking and AI is transitioning from proof-of-concept studies to real-world applications.

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