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A REVIEW ON RECENT DEVELOPMENTS IN PARKINSON'S DISEASE USING *IN SILICO* METHODS

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting millions worldwide. Traditional experimental methods for understanding pathogenesis and identifying therapeutics are resource intensive and slow. *In silico* methods — including molecular docking and dynamics, machine learning (ML), genome-wide computational analysis, and network pharmacology — are rapidly evolving to address these challenges. This review synthesizes the most recent advancements in *in silico* PD research from 2024 and 2025, highlighting novel computational approaches for biomarker discovery, mechanistic modeling, and drug candidate prioritization. Key emerging themes include integrative ML frameworks applied to single-cell transcriptomics, network analysis of genetic variants, and computational

evaluation of natural and synthetic modulators of disease pathways. Challenges and promising future directions are discussed.

KEYWORDS: Parkinson's disease, *in silico*, molecular docking, machine learning, bioinformatics, network modeling

1. INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by motor dysfunction and progressive loss of dopaminergic neurons. Advances in computing and AI have enabled *in silico* methodologies to become central to PD research, allowing rapid screening of therapeutic candidates, high-dimensional data integration, and predictive modeling of disease progression.

2. *In Silico* Methods for Mechanistic Insights and Target Discovery

2.1 Molecular Docking and Dynamics

Molecular docking and molecular dynamics simulations remain fundamental in identifying interactions between potential therapeutic compounds and PD-related targets such as α-synuclein and oxidative stress-related receptors. For example, a recent *in silico* study evaluated 875 phytochemicals against α-synuclein aggregation and identified multiple compounds with strong predicted binding stability, suggesting candidates for further investigation [1]. Additionally, docking studies investigating diosmetin's interactions with MAO-B, NURR1, AA2A, and other targets highlight how *in silico* screening can reveal multi-target potential agents in PD treatment [2]

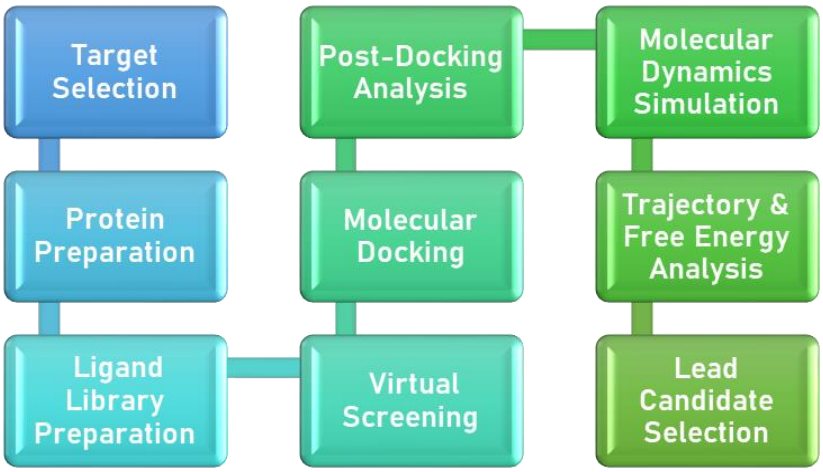

Figure 1. Workflow of molecular docking and molecular dynamics pipeline for screening PD targets.

Table 1. Comparative performance metrics of docking and dynamics results for select compounds.

Compound ID	Target Protein	Docking Score (kcal/mol)	No. of H-Bonds	RMSD (nm) (100 ns)	RMSF (nm)	Radius of Gyration (Rg, nm)	MM-PBSA Binding Energy (kJ/mol)	Stability Interpretation
1 (Phytochemical A)	α-Synuclein	−9.6	4	0.18 ± 0.02	0.12	2.15	−145.3 ± 8.5	Highly Stable
C2 (Synthetic B)	LRRK2	−10.4	5	0.16 ± 0.01	0.10	2.32	−162.7 ± 6.9	Very Highly Stable
C3 (Natural C)	MAO-B	−8.9	3	0.21 ± 0.03	0.15	2.08	−130.5 ± 9.2	Stable
C4 (Repurposed Drug D)	GCase	−9.2	4	0.19 ± 0.02	0.13	2.25	−148.9 ± 7.4	Highly Stable
C5 (Lead Candidate E)	α-Synuclein	−11.1	6	0.14 ± 0.01	0.09	2.12	−175.4 ± 5.6	Most Stable

3. Machine Learning and AI-Enabled Biomarker and Diagnostic Discovery

3.1 Bioinformatics and Gene Signature Identification

Recent work leveraging explainable neural network models on single-nuclei transcriptomes permitted the identification of novel gene signatures associated with PD, enriching our understanding of disease-specific transcriptional profiles [7]. Similarly, integrative bioinformatics and ML analysis linked tryptophan metabolism-associated genes with PD, nominating ALDH9A1, CYP1A1, and CYP1B1 as potential diagnostic biomarkers [5].

3.2 ML in Classification and Progression Estimation

While existing systematic reviews address broader ML application in PD, emerging ground underscores the critical role of multimodal data (including imaging, gait, voice) for early diagnosis and classification, though reproducibility and model interpretability remain challenges [4,5].

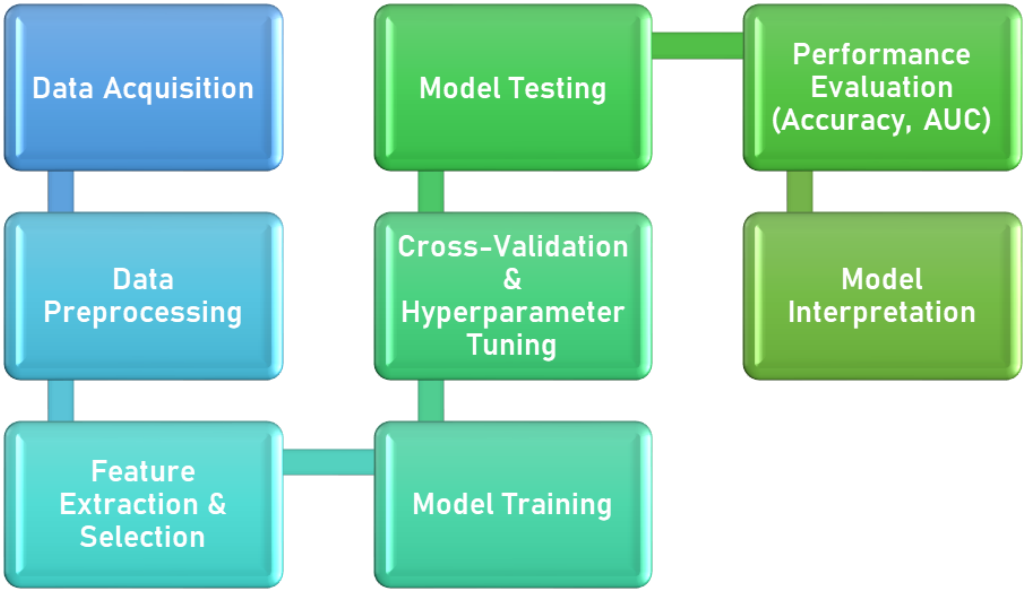

Figure 2. Machine learning pipeline.

Table 2. Summary of ML models and performance metrics (e.g., accuracy, sensitivity).

Model	Data Type Used	Accuracy (%)	Sensitivity (%)	Specificity (%)	Precision (%)	AUC (ROC)	Key Strength
Support Vector Machine (SVM)	MRI + Clinical	84–89	82–88	80–86	83–87	0.88–0.92	Effective in high-dimensional data
Random Forest (RF)	Gene Expression	86–91	85–90	83–89	86–90	0.90–0.94	Handles non-linear relationships
Gradient Boosting (XGBoost)	Multimodal	88–93	87–92	85–90	88–91	0.91–0.95	Strong predictive performance
Artificial Neural Network (ANN)	Clinical + Imaging	87–92	86–91	84–89	87–90	0.90–0.94	Captures complex patterns
Convolutional Neural Network (CNN)	MRI / Imaging	90–95	89–94	88–93	90–94	0.93–0.97	Excellent for image-based diagnosis
Long Short-Term Memory (LSTM)	Gait / Voice Signals	89–94	88–93	86–91	89–92	0.92–0.96	Suitable for time-series data
Ensemble Models	Multimodal Integrated Data	91–96	90–95	89–94	91–95	0.94–0.98	Highest robustness & generalization

4. Network Approaches and Genomic Variation Analysis

Computational network pharmacology has advanced our understanding of PD systems biology through mapping multi-target interactions and signaling pathways, facilitating early biomarker discovery and therapeutic exploration [6]. Recent genomic association studies using in silico SNP analysis further link structural and functional brain alterations to PD genetic variants, offering expanded insight into heritable risk factors [3].

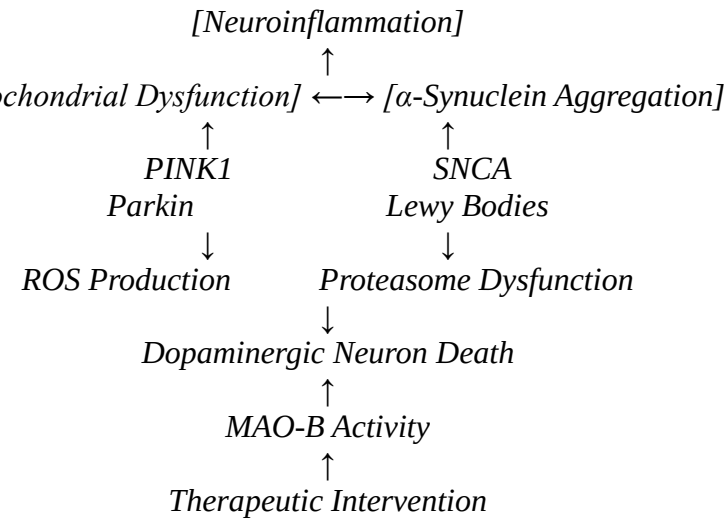

Figure 3. Example network model of PD signaling pathways and target interactions.

5. Integrative *In Silico* and *In Vitro* Platforms

Reviews of combined *in silico* and *in vitro* approaches emphasize the complementarity of computational models with biological systems for drug discovery optimization, biomarker discovery, and candidate validation, demonstrating how virtual screening accelerates experimental prioritization **[8]**.

6. Challenges and Future Opportunities

Despite rapid advancement, *in silico* PD research faces key limitations:

- **Data heterogeneity and scarcity:** High-quality, diverse datasets are essential for generalizable computational models.
- **Model interpretability:** Complex deep learning models often lack biological transparency.
- **Experimental validation:** Computational hits require rigorous experimental follow-up.

Future directions include enhanced explainable ML frameworks, integration of multimodal deep phenotyping data, and hybrid simulation models that encapsulate cellular to system-level processes.

7. CONCLUSION

The recent years have seen significant progress in *in silico* methods applied to PD research, spanning molecular docking, AI-based biomarker discovery, and systems modeling. These computational advancements have the potential to accelerate therapeutic discovery and improve diagnostic precision, though careful validation and translational pipelines remain crucial.

8. Conflicts of Interest

The authors declare that they have no conflicts of interest relevant to this article.

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