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EDITORIAL

AI Meets Molecular Dynamics - A New Era for Virtual Screening

Dr. Bandoo C. Chatale

MET Institute of Pharmacy (Degree), MET Complex, Bandra Reclamation, Bandra (West),

Mumbai 400050, Maharashtra, India

**Corresponding author: bandooc_iop@met.edu*

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Over the past two decades, Molecular Dynamics (MD) simulations have transitioned from a niche computational tool to a mainstream pillar of modern drug discovery. Today, the accelerating convergence of MD with machine learning, enhanced sampling methods, and experimental structural biology is reshaping the way we identify, refine, and validate drug candidates.

A particularly exciting development is the application of enhanced sampling MD to capture the elusive conformational changes of proteins and ligands. While static crystallographic snapshots provide invaluable insights, they often miss hidden allosteric pockets or transient binding pathways. Approaches such as Gaussian accelerated MD, metadynamics, and adaptive sampling now allow researchers to routinely explore events occurring on millisecond timescales, uncovering cryptic binding sites that could not be revealed otherwise. These hidden sites have become fertile ground for the design of allosteric modulators, a rapidly growing class of drugs offering improved selectivity and reduced resistance.

Equally transformative is the integration of alchemical free energy calculations into drug discovery pipelines. Once considered computationally prohibitive, Free Energy Perturbation (FEP) methods are now being applied at scale to guide medicinal chemistry decisions with near-experimental accuracy. The combination of GPU acceleration and artificial intelligence has dramatically lowered computational barriers, allowing for the systematic evaluation of hundreds of ligands in days rather than months.

MD is also playing a pivotal role in membrane protein drug discovery, particularly for G-protein coupled receptors (GPCRs), which remain the targets of more than one-third of approved drugs. Long-timescale simulations reveal how lipid composition influences ligand binding and receptor activation, offering new routes to rational drug design. Moreover, the synergy between cryo-electron microscopy, AlphaFold-predicted structures, and MD-based refinement is enabling unprecedented resolution in modeling dynamic protein–drug complexes.

Looking forward, the marriage of MD and AI promises to further transform the field. Machine learning–driven force fields, trained on quantum mechanical data, are delivering quantum-level accuracy at classical MD speed. When coupled with AI-guided ligand design, MD simulations are poised to create a feedback loop of prediction, simulation, and optimization that can dramatically shorten the drug discovery cycle.

In sum, MD has moved far beyond its early role as a "visualization tool" and is now a predictive engine driving decision-making in pharma and academia alike. As computational power, algorithms, and AI converge, the vision of fully integrating MD into every stage of drug discovery — from hit identification to clinical candidate optimization — is becoming a tangible reality. The next generation of medicines will not only be tested in laboratories, but also designed, refined, and validated inside the computer.

KEYWORDS: Molecular Dynamics, Drug Discovery, Molecular Modeling

ABOUT THE EDITOR

***Dr. Bandoo Chatale**, Assistant Professor at MET Institute of Pharmacy (Degree), Mumbai, holds an M.S. (Pharm.) in Medicinal Chemistry from NIPER, Mohali, and a Ph.D. (Tech.) from ICT, Mumbai, with prior industry experience at Piramal, Ahmedabad. With expertise in molecular modeling, co-crystallization, and small molecule synthesis, he has authored 8 international publications, 4 reviews, 2 books, and a design patent, while also serving as a peer reviewer for reputed journals. A dedicated mentor, he has guided researcher, conducted 10+ workshops, FDPs, and multiple professional training programs, besides delivering invited talks on AI in pharmaceutical sciences. He is founder of Anandeep Foundation and Springwell Pharma Pvt. Ltd., and recipient of MET GAURAV and MET PRAGNYAVANT Awards, he continues to advance research, innovation, and training in pharmaceutical sciences.*