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Sculpting Molecules in Silico: A Comprehensive Review of the Latest Innovations in Computer-Aided Drug Design to Revolutionize the Way Drugs are Engineered and Optimized

NIRMALA A[1], MADHUSUDHANA R K[2]
1 - Spurthy College of Pharmacy, 2 - Data scientist at Freelance
Bengaluru, India
knirmala549@gmail.com[1] , rkmadhu619@gmail.com[2]

Abstract: The realm of drug discovery has been significantly transformed by the integration of computational techniques into the design process. This review delves into the evolving landscape of *computer-aided drug design*, focusing on the latest innovations that are reshaping the traditional paradigms of drug engineering and optimization. We explore how in silico approaches, powered by advances in molecular modeling, machine learning, and structural bioinformatics, are revolutionizing the way new pharmaceutical agents are conceptualized, refined, and brought closer to clinical realization. By analyzing a range of cutting-edge methodologies, from molecular simulations to data-driven strategies, this comprehensive review provides a deep insight into the intricate synergy between computer-aided drug design and modern pharmaceutical research. The transformative potential of these innovations is underscored, offering a glimpse into the future of drug discovery where computational precision and predictive capabilities are poised to shape the development of novel therapeutic interventions.

Keywords: Drug discovery, Computational techniques, In silico methods, Molecular modeling, Machine learning, Structural bioinformatics

1. Introduction: The world of pharmaceutical research is undergoing a revolutionary transformation, driven by the integration of computational tools into the drug discovery process. Computer-aided drug design (CADD) has emerged as a pivotal approach that harnesses the power of computation to expedite the identification, design, and optimization of potential therapeutic agents. With the ever-increasing complexity of biological systems and the escalating demands for novel drugs, CADD offers a systematic and efficient way to navigate the vast chemical and biological space, ultimately leading to the discovery of optimized drug candidates [1].

The essence of CADD lies in its ability to sculpt molecules in silico – to virtually construct, analyze, and modify molecular structures using computational algorithms and simulations. By simulating molecular interactions, predicting binding affinities, and understanding the influence of physicochemical properties, CADD provides valuable insights that guide researchers in making informed decisions at every stage of the drug discovery pipeline. From molecular modeling techniques to data-driven approaches, from ligand-based strategies to structure-based design innovations, this review will navigate through the intricate web of computational methodologies that collectively contribute to the revolution in drug discovery. By highlighting the transformative potential of these tools, we aim to underscore how CADD is poised to redefine the boundaries of drug design and accelerate the journey from concept to clinical application[2][3].

2. Historical Evolution of Computer-Aided Drug Design: The historical evolution of computer-aided drug design (CADD) is a journey that reflects the relentless pursuit of scientists to harness computational power for unraveling the complexities of molecular interactions and drug-target relationships. The roots of CADD can be traced back to early efforts in the 1960s and 70s, when researchers began exploring methods to model molecular structures and predict properties using the nascent field of computational chemistry.

The birth of molecular mechanics marked a pivotal moment in CADD's evolution. Empirical force fields enabled the calculation of molecular energies and geometries, laying the foundation for predicting the behavior of molecules within a specified environment. The concept of energy minimization became central to modeling the conformational space of potential drug candidates, influencing the design of molecules with favorable properties.[4]

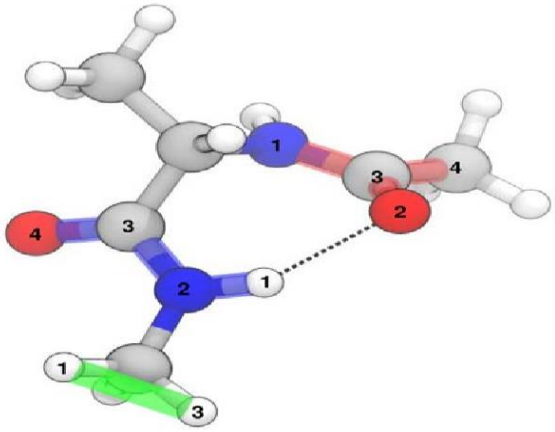
As computational power grew, quantum mechanics began to play a significant role in CADD. Quantum mechanical calculations provided accurate insights into electronic properties, allowing researchers to probe the electronic structure of molecules and predict their spectroscopic properties. However, the computational demands of quantum mechanics limited its application to small molecules and simplified systems.

The 1980s saw the advent of molecular dynamics simulations, which introduced a dynamic aspect to CADD. By simulating the motion of atoms over time, researchers gained insights into the behavior of molecules in solution and the conformational changes that underlie biological processes. Molecular dynamics simulations opened the door to understanding complex biomolecular interactions and paved the way for understanding binding mechanisms.One of the seminal developments in CADD was the emergence of computational docking algorithms[5]. These algorithms provided a platform to predict the binding modes of ligands within protein binding sites, offering insights into the key interactions that drive binding affinity. Early docking methods utilized geometric and empirical scoring functions, but as computational methodologies advanced, more sophisticated scoring functions were developed, combining physics-based and statistical approaches[6][7]

3. Foundations of Molecular Modeling: Molecular modeling serves as the bedrock of computer-aided drug design (CADD), enabling researchers to investigate molecular structures and behaviors in silico. At the heart of molecular modeling lies the principle of mimicking physical reality using mathematical models, allowing scientists to predict how molecules interact and behave under different conditions. This section delves into the key components of molecular modeling, which form the foundation of CADD.

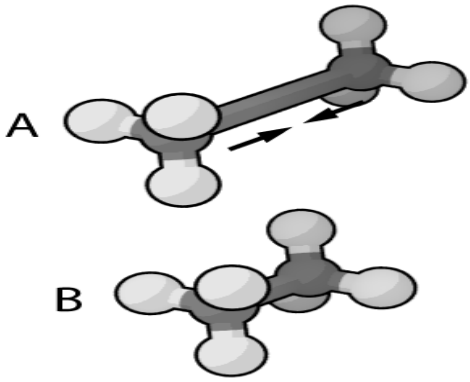
3.1 Molecular Mechanics and Force Fields: Molecular mechanics approximates the behavior of molecules by treating atoms as spheres connected by springs, representing bonds, angles, and torsions. Force fields, mathematical equations that describe the potential energy surface of a molecule, play a pivotal role in molecular mechanics. Force fields encompass terms for bond stretching, angle bending, torsion rotation, and non-bonded interactions (van der Waals and electrostatic interactions). Parameters within force fields are derived from experimental data and quantum mechanical calculations, allowing the prediction of molecular structures and energies.

Figure 1.



Molecular Mechanics

Figure 2.



Force Fields

3.2 Molecular Dynamics Simulations: Molecular dynamics simulations provide a dynamic view of molecular behavior by numerically integrating Newton's equations of motion. These simulations allow researchers to observe molecular trajectories over time, capturing the intricate motions of atoms and molecules. By simulating molecules in a solvent environment, researchers gain insights into the dynamic

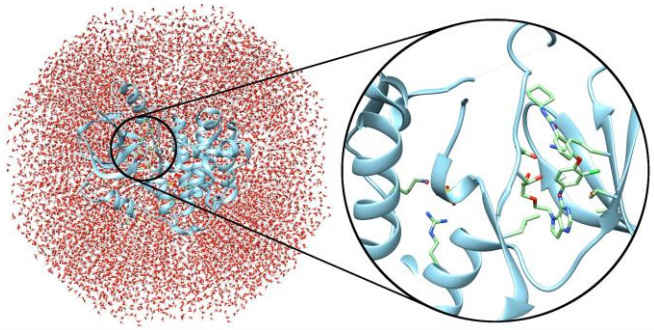
nature of biological systems. Molecular dynamics simulations have evolved from simple gas-phase simulations to complex models that consider solvation effects, implicit solvent models, and advanced techniques such as enhanced sampling methods[8].

3.3 Quantum Mechanics and Electronic Properties: Quantum mechanics delves into the realm of subatomic particles, providing a more accurate description of electronic properties. Quantum mechanical calculations solve the Schrödinger equation to predict electronic energies, wavefunctions, and molecular properties. However, due to the computational demands of solving the Schrödinger equation, quantum mechanics is often applied to smaller molecules or specific regions of interest within larger systems. Quantum mechanical calculations are particularly valuable for predicting spectroscopic properties, such as UV-Vis, IR, and NMR spectra.

3.4 Quantum Mechanics/Molecular Mechanics (QM/MM) Approaches: To bridge the gap between the accuracy of quantum mechanics and the efficiency of molecular mechanics, researchers have developed quantum mechanics/molecular mechanics (QM/MM) approaches. These hybrid methods combine quantum mechanical calculations for a small region of interest (e.g., the active site of an enzyme) with molecular mechanics calculations for the remainder of the system. QM/MM methods are particularly useful for studying enzymatic reactions, metal-binding sites, and other complex biological processes.

The foundations of molecular modeling provide researchers with powerful tools to explore molecular structures, interactions, and dynamics. These methods form the basis for understanding the principles of drug-target interactions and optimizing molecular properties[9][10].

Figure 3.



QM with modern quantum molecular algorithm

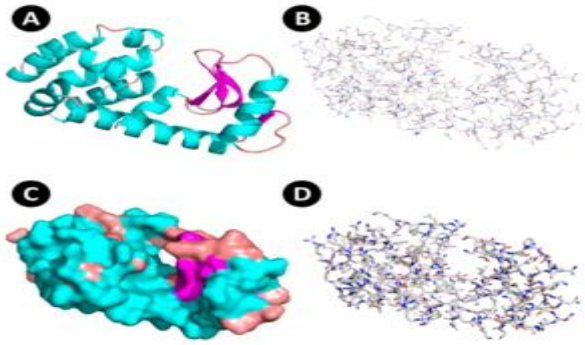
4. Structural Bioinformatics and Protein-Ligand Interactions: Understanding the interactions between proteins and ligands is paramount in drug discovery, as it guides the design of compounds with optimal binding affinities and specificities. Structural bioinformatics, a multidisciplinary field that blends structural biology, computational modeling, and informatics, plays a pivotal role in elucidating these interactions.

4.1 Molecular Docking Algorithms: It predicts the binding orientations and binding affinities of ligands within the active sites of target proteins. These algorithms sample different conformations and orientations of the ligand to find the most energetically favorable binding mode. Docking algorithms employ scoring functions that evaluate the interactions between the ligand and protein, considering factors such as van der Waals interactions, hydrogen bonding, electrostatics, and solvation effects. Common docking programs include AutoDock, AutoDock Vina, GOLD, and Glide.[11]

4.2 Binding Free Energy Calculations: Binding free energy calculations aim to quantitatively predict the strength of protein-ligand interactions. These calculations involve decomposing the binding free energy into various contributions, such as van der Waals interactions, electrostatic interactions, and solvation effects. These calculations include molecular mechanics / poisson-boltzmann surface area (MM/PBSA) and molecular mechanics / generalized Born surface area (MM/GBSA) approaches. These methods provide insights into the driving forces behind ligand binding and aid in rationalizing experimental data. [12]

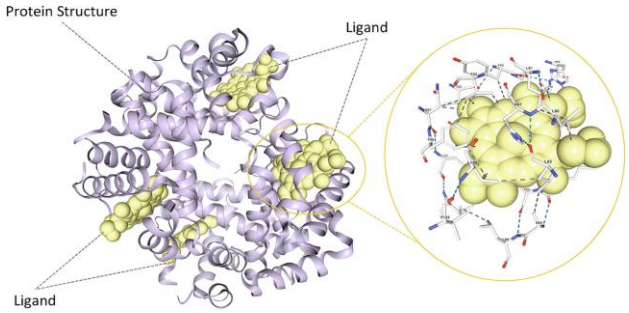
5. Foundations of Molecular Modeling: Molecular modeling serves as the cornerstone of CADD, encompassing techniques that mimic molecular behavior in silico. Molecular mechanics employs force fields to predict molecular structures and energies, while molecular dynamics simulations capture the temporal evolution of molecules. Quantum mechanics offers unprecedented accuracy for understanding electronic properties, and the marriage of quantum and molecular mechanics, known as QM/MM, provides a bridge between these worlds.

Figure 4



Structural Bioinformatics

Figure 5



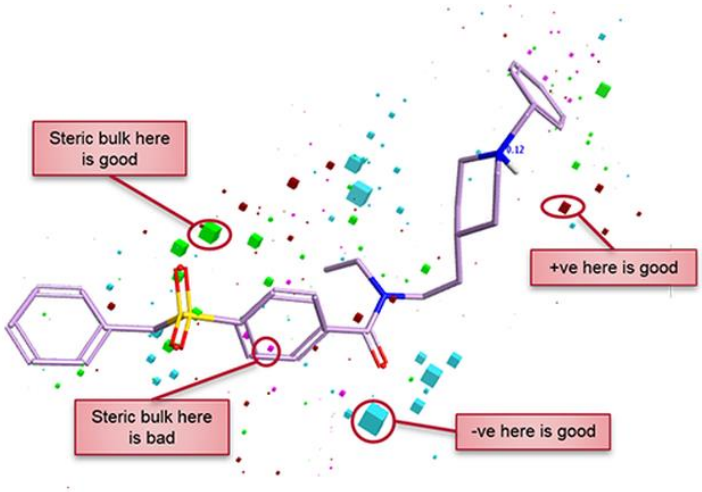
Protein-Ligand Interactions

5.1 Machine Learning and Data-Driven Approaches: Machine learning (ML) has emerged as a transformative force in drug discovery, reshaping the landscape by introducing predictive models based on data-driven insights. This section delves into the multifaceted role of machine learning in computer-aided drug design (CADD), exploring its applications, methodologies, and implications for optimizing drug discovery.[13]

5.2 Introduction to Machine Learning in Drug Discovery: Machine learning harnesses the power of algorithms to identify patterns, correlations, and relationships within complex datasets. In CADD, ML methods leverage vast datasets comprising chemical structures, biological activities, and physicochemical properties to build predictive models. These models bridge the gap between molecular features and biological activities, guiding the identification of promising drug candidates.

5.3 Quantitative Structure-Activity Relationship (QSAR) Models: Quantitative Structure-Activity Relationship (QSAR) models are a cornerstone of ML in CADD. QSAR models correlate molecular descriptors (physicochemical properties) with biological activities, enabling the prediction of compound activities against specific targets. The construction of QSAR models involves feature selection, model training, and validation to ensure robust predictions. These models aid in lead optimization, compound prioritization, and toxicity prediction.[14][15]

Figure 6



QSAR quantitative structure activity relationship

5.4 Deep Learning and Neural Networks: Deep learning, a subset of machine learning, has revolutionized CADD with its ability to learn intricate features from data. Neural networks, a fundamental component of deep learning, model complex relationships between input data and output predictions. Convolutional neural networks (CNNs) analyze molecular structures, while recurrent neural networks (RNNs) capture sequence information in bioinformatics. Generative adversarial networks (GANs) are employed for de novo molecule generation.[16]

5.5 Data-Driven Hit Identification and Optimization: ML-driven virtual screening expedites hit identification by screening vast compound libraries. Algorithms prioritize compounds with high predicted binding affinities, reducing the experimental workload. Data-driven optimization involves predicting compound properties like solubility, toxicity, and bioavailability. These predictions guide iterative design cycles, accelerating the selection of lead compounds with improved drug-like properties.[17]

5.6 Challenges and Future Prospects: While ML holds immense promise, challenges include data quality, overfitting, and interpretability. Incorporating physicochemical insights into ML models enhances their reliability. The future of ML in CADD involves integration with quantum mechanics, molecular dynamics, and hybrid models that combine different computational methodologies.

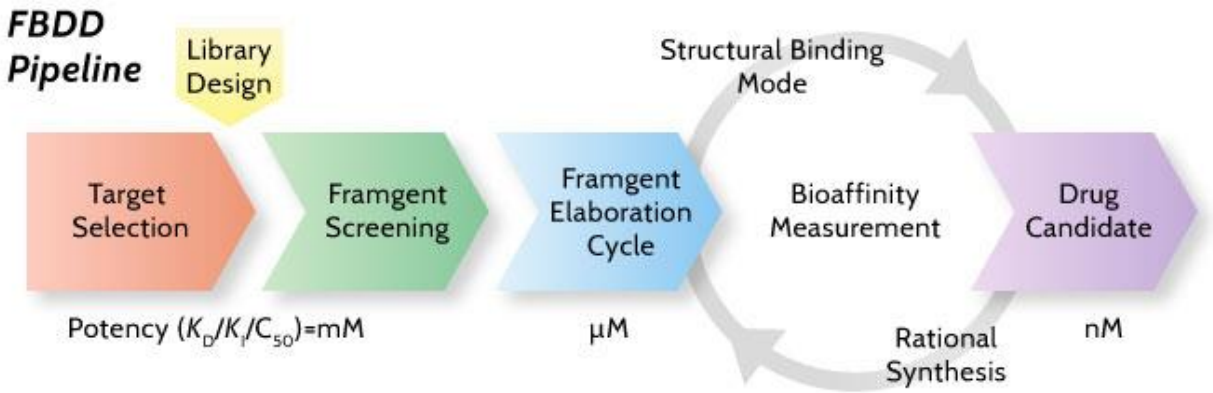
6. Ligand-Based Drug Design Strategies: This centers on optimizing molecular structures based on their interactions with target proteins. This section explores the principles and methodologies underlying ligand-based approaches, showcasing their significance in lead discovery and optimization.

6.1 Pharmacophore-Based Approaches: Pharmacophore-based approaches identify key structural features, or pharmacophores, essential for ligand binding. These features include hydrogen bond donors/acceptors, hydrophobic regions, and aromatic rings. By generating pharmacophore models, researchers screen compound databases for molecules that match these features, facilitating the discovery of structurally diverse hits with the potential to interact with the target.[18]

6.2 Scaffold Hopping and Virtual Screening: Scaffold hopping involves replacing a scaffold (core structure) of a lead compound with a different scaffold while preserving its binding interactions. Virtual screening employs computational methods to prioritize compounds from large databases that possess desirable pharmacophores and structural features. These approaches broaden the chemical space explored, facilitating the discovery of novel lead compounds.[19]

6.3 Fragment-Based Drug Design: Fragment-based drug design dissects ligands into smaller fragments that interact with a target's binding site. Fragments with favorable interactions are combined to construct larger molecules with improved binding affinities. Fragment-based approaches are particularly effective in identifying lead compounds for challenging targets with complex binding sites.[20]

Figure 7



Fragment based drug design cycle

7. Structure-Based Drug Design Innovations: Structure-based drug design (SBDD) is at the forefront of rational drug discovery, utilizing insights from protein structures to guide the design and optimization of drug candidates. This section explores the cutting-edge innovations within SBDD, shedding light on advancements that are reshaping the way researchers engineer novel therapeutic agents.[21]

7.1 Homology Modeling and Protein Structure Prediction: Homology modeling plays a pivotal role in SBDD by predicting the three-dimensional structures of proteins based on the known structures of homologous proteins. With the exponential growth of protein structure databases, homology modeling has become an essential tool for obtaining accurate structural information. Advanced homology modeling techniques incorporate multiple templates and consider structural dynamics to generate refined models.

7.2 De Novo Drug Design: De novo drug design involves constructing new molecular entities from scratch to achieve optimal interactions with a target protein. Advances in computational algorithms have enabled the exploration of vast chemical space to identify ligands with desired binding affinities. De novo design

platforms utilize fragment-based strategies, combinatorial chemistry principles, and scoring functions to iteratively generate and refine candidate molecules.[22]

7.3 Molecular Dynamics Simulations for Binding Kinetics: Molecular dynamics (MD) simulations have evolved beyond static structure elucidation to capture the dynamic behavior of proteins and ligands during binding events. Simulations provide insights into protein flexibility, conformational changes upon binding, and binding kinetics. Enhanced sampling techniques, such as metadynamics and accelerated MD, enable the exploration of rare events and transient binding pathways.[23]

8. Integration of In Silico and Experimental Approaches: The integration of computational and experimental approaches marks a pivotal convergence in modern drug discovery, synergizing insights from both realms to expedite lead identification, optimization, and validation. This section delves into the seamless amalgamation of in silico and experimental techniques, showcasing its transformative impact on the drug discovery process.

8.1 Virtual Screening and Experimental Validation: Virtual screening uses computational models to prioritize compounds for experimental testing. In silico predictions guide the selection of compound libraries, enhancing the probability of identifying hits with desired properties. Successful hits are synthesized and experimentally tested, validating the accuracy of computational predictions and ensuring the practicality of identified leads.

8.2 Computer-Aided Compound Synthesis and Experimental Testing: In silico tools extend beyond hit identification to guide compound synthesis. Computer-aided design of synthesis routes considers chemical feasibility, yield, and cost-effectiveness. Computational predictions of synthetic accessibility aid chemists in prioritizing viable synthetic pathways. Synthesized compounds are then subjected to experimental assays to assess their biological activity.[24]

8.3 Mechanistic Insights and Rationalization: Computational methods provide mechanistic insights into biological processes, aiding in the rationalization of experimental observations. Molecular dynamics simulations uncover the dynamic behavior of biomolecules, explaining binding events, conformational

changes, and protein-ligand interactions. These insights refine experimental hypotheses and inform subsequent studies.[25]

9. Emerging Technologies and Future Perspectives: Emerging technologies are reshaping the landscape of computer-aided drug design (CADD), offering exciting avenues for innovation and efficiency. This section delves into the frontiers of CADD, exploring how quantum computing, artificial intelligence (AI), and integrative approaches are poised to redefine drug discovery.

9.1 Quantum Computing and Accelerated Simulations: Quantum computing holds immense promise in tackling complex calculations that are currently beyond the capabilities of classical computers. Quantum simulations can provide rapid solutions to quantum mechanical problems, revolutionizing molecular dynamics simulations, conformational sampling, and accurate quantum mechanical calculations. Quantum computing is expected to significantly expedite drug discovery by simulating complex molecular systems with unprecedented accuracy and speed.[26]

9.2 Artificial Intelligence and Machine Learning Evolution: Artificial intelligence continues to catalyze innovation in CADD. Machine learning models are evolving to encompass more complex biological phenomena, accounting for protein flexibility, solvent effects, and binding kinetics. Reinforcement learning, generative models, and transfer learning are expanding AI's potential in lead optimization, hit identification, and compound synthesis prediction.

9.3 Integrative Approaches: Omics and Systems Biology: The integration of omics data (genomics, proteomics, metabolomics) within silico predictions provides a comprehensive understanding of biological systems. Systems biology approaches unravel complex networks of interactions, aiding in target identification, biomarker discovery, and mechanism elucidation. These integrative approaches enhance the rational design of drugs by considering holistic biological context.[27]

10 Challenges and Ethical Considerations: The integration of computational methodologies into drug discovery has significantly enhanced our ability to predict and design novel drug candidates. However, this progress comes with its set of challenges and ethical considerations that demand careful attention. As we harness the power of in silico tools to revolutionize drug design, it's imperative to recognize and address the following aspects:

10.1 Challenges:

A. **Accuracy and Reliability:** Computational predictions are only as good as the underlying models and data. Despite significant advancements, inaccuracies can arise due to simplifications in modeling, limitations in algorithms, and errors in input data. Validation against experimental results remains a crucial but often complex task.

B. **Scalability and Complexity:** As systems become larger and more intricate, computational demands escalate. The simulation of entire cellular processes or large biomolecular complexes requires substantial computational resources, posing challenges in terms of scalability and efficiency.

C. **Prediction of Novel Targets:** While in silico methods are adept at predicting interactions with known targets, the accurate prediction of interactions with entirely novel targets remains challenging. The reliance on existing structural data can limit the applicability of computational predictions in such cases.

D. **Dynamic and Adaptive Systems:** Capturing the dynamics and adaptability of biomolecular systems is a complex endeavor. Molecular dynamics simulations attempt to account for these aspects, but the timescales and simulation lengths can be restrictive for certain processes.

10.2 Ethical Considerations:

A. **Transparency and Reproducibility:** The use of computational models and algorithms demands transparency. Reproducibility, the cornerstone of scientific integrity, is especially critical in computational research to enable others to verify findings and build upon them.

B. **Clinical Decision Making:** The application of computational predictions in clinical decision-making poses ethical questions. While predictive models can inform treatment strategies, overreliance on computational results without proper validation may compromise patient safety and well-being.

C. **Intellectual Property and Patents:** The generation of novel drug candidates through computational design raises questions about intellectual property rights. The question of ownership and patentability of molecules developed in silico requires legal and ethical considerations.

D. **Bias and Data Quality:** Machine learning models are trained on historical data, which might contain biases or inaccuracies. This can result in biased predictions that disproportionately impact underrepresented patient populations.

E. **Privacy and Data Security:** Utilizing large datasets for training machine learning models can raise concerns about patient privacy and data security. Ensuring that patient data is anonymized and properly protected is paramount.

F. **Responsibility and Accountability:** As the integration of computational methodologies becomes more prevalent, it is essential to ensure that researchers are equipped with the necessary expertise to interpret and use the results responsibly. The implications of inaccurate predictions or misinterpretation can have far-reaching consequences.[28]

11. Case Studies:

Successful Applications of In Silico Drug Design: Real-world case studies exemplify the tangible impact of in silico drug design on successful drug discovery efforts. These case studies underscore the value of computational predictions in guiding lead identification, optimization, and clinical realization.[29][30]

A. **Tamiflu (Oseltamivir):** The design of the anti-influenza drug Tamiflu involved molecular docking to identify compounds that inhibit the viral neuraminidase enzyme. In silico predictions guided the optimization of the lead compound, resulting in Tamiflu, a clinically effective antiviral medication.

B. **Raltegravir (Isentress):** The integration of molecular dynamics simulations and binding free energy calculations played a pivotal role in the design of raltegravir, an HIV integrase inhibitor. Computational insights informed the optimization of binding interactions, leading to a potent and clinically successful antiretroviral drug.

C. **Vemurafenib (Zelboraf):** Vemurafenib, a targeted therapy for BRAF-mutated melanoma, exemplifies the power of structure-based drug design. Molecular modeling identified ligands that selectively target the mutant BRAF kinase, resulting in a breakthrough therapy with improved efficacy and reduced toxicity.

D. **Darunavir (Prezista):** Darunavir is a protease inhibitor used in the treatment of HIV/AIDS. In silico methods were crucial in its development, as researchers utilized molecular docking and molecular dynamics simulations to design compounds that effectively target the protease enzyme, inhibiting viral replication. The rational design led to the creation of darunavir, which demonstrated improved binding affinity and resistance profiles compared to earlier drugs in its class.

E. **Rivastigmine (Exelon):** Rivastigmine is a medication used to treat Alzheimer's disease. In silico methods were employed to optimize the binding interactions between the drug and its target, acetylcholinesterase. Computational analysis guided the modification of the drug's structure to enhance its binding affinity and selectivity, leading to the development of rivastigmine as a potent acetylcholinesterase inhibitor.

F. **Dolutegravir (Tivicay):** Dolutegravir is an integrase strand transfer inhibitor used to treat HIV infection. Computational studies played a crucial role in the optimization of its binding interactions with the viral integrase enzyme. Molecular dynamics simulations were used to explore the dynamic behavior of the drug-target complex, leading to modifications that improved the drug's potency and resistance profile.

G. **Lopinavir/Ritonavir (Kaletra):** Lopinavir/ritonavir is a combination therapy used in the treatment of HIV/AIDS. In silico methods were employed to design lopinavir as a potent protease inhibitor. Molecular docking studies helped identify the key binding interactions, while structure-based optimization led to the design of ritonavir as a pharmacokinetic enhancer, increasing the bioavailability of lopinavir.

H. **Vandetanib (Caprelsa):** Vandetanib is a tyrosine kinase inhibitor used to treat medullary thyroid cancer. Computational methods were utilized to predict the binding interactions between vandetanib and its target receptors. By analyzing the binding pocket and optimizing the ligand's structure, researchers achieved enhanced binding affinity and selectivity, resulting in the development of an effective targeted therapy.

I. **Raloxifene (Evista):** Raloxifene is a selective estrogen receptor modulator used to treat osteoporosis and breast cancer. In silico methods were employed to study the drug's interactions with estrogen receptors and other off-target effects. Computational predictions guided the modification of the compound's structure, resulting in an improved therapeutic profile with reduced side effects.

12. Conclusion

In conclusion, the integration of computational techniques into drug discovery has revolutionized the field. This review has explored how cutting-edge innovations in molecular modeling, machine learning, and structural bioinformatics are reshaping traditional drug design approaches. By leveraging in silico methods, researchers can now efficiently conceptualize, refine, and optimize pharmaceutical candidates. The review covered various techniques, such as molecular dynamics simulations, virtual screening, and data-driven strategies, all of which play pivotal roles in lead identification and optimization. Successful case studies, like Tamiflu, Raltegravir, and Vemurafenib, highlight the tangible impact of in silico drug design on real-world therapeutic success. Ethical considerations and challenges emphasize the need for cautious integration of computational predictions into clinical decisions. Looking ahead, emerging technologies like quantum computing and AI are poised to further transform drug discovery, promising more accurate and efficient methods. In summary, the seamless integration of computational precision with experimental validation is shaping the future of drug discovery. This synergy holds the potential to expedite the development of novel therapeutic interventions, offering hope for improved medical treatments and patient outcomes.

References:

1. Marcovina, S.M., Koschinsky, M.L., Albers, J.J. and Skarlatos, S., 2003. Report of the National Heart, Lung, and Blood Institute Workshop on Lipoprotein (a) and Cardiovascular Disease: recent advances and future directions. *Clinical chemistry*, *49*(11), pp.1785-1796.

2. Kitchen DB, Decornez H, Furr JR, Bajorath J. *Docking and scoring in virtual screening for drug discovery: methods and applications*. Nat Rev Drug Discov. 2004;3(11):935-949.

3. Rupp M. *Machine learning for quantum mechanics in a nutshell*. Int J Quantum Chem. 2015;115(16):1058-1073.

4. Xiang, M., Cao, Y., Fan, W., Chen, L. and Mo, Y., 2012. Computer-aided drug design: lead discovery and optimization. *Combinatorial chemistry & high throughput screening*, *15*(4), pp.328-337. https://doi.org/10.2174/138620712799361825

5. Kuntz ID, Blaney JM, Oatley SJ, Langridge R, Ferrin TE. *A geometric approach to macromolecule-ligand interactions*. J Mol Biol. 1982;161(2):269-288.

6. McCammon JA, Harvey SC. *Dynamics of Proteins and Nucleic Acids*. Cambridge University Press; 1987.

7. Shoichet BK, McGovern SL, Wei B, Irwin JJ. *Lead discovery using molecular docking*. Curr Opin Chem Biol. 2002;6(4):439-446.

8. Leach AR, Gillet VJ. *An Introduction to Chemoinformatics*. Springer Science & Business Media; 2007.

9. Cramer CJ. *Essentials of Computational Chemistry*. John Wiley & Sons; 2017.

10. Jorgensen WL, Thomas LL. *Perspective on free-energy perturbation calculations for chemical equilibria*. J Chem Theory Comput. 2008;5(3):725-733.

11. Gilson MK, Zhou HX. *Calculation of protein-ligand binding affinities*. Annu Rev Biophys Biomol Struct. 2007;36:21-42.

12. Meng X, Hou T. *Computer-aided drug design: Recent progress and future prospects in protein-ligand docking*. Brief Bioinform. 2018;19(1):138-149.

13. Schneider G, Fechner U. *Computer-based de novo design of drug-like molecules*. Nat Rev Drug Discov. 2005;4(8):649-663.

14. Wallach I, Dzamba M, Heifets A. *AtomNet: A deep convolutional neural network for bioactivity prediction in structure-based drug discovery*. arXiv preprint arXiv:1510.02855. 2015.

15. Ma J, Sheridan RP, Liaw A, et al. *Deep neural nets as a method for quantitative structure–activity relationships*. J Chem Inf Model. 2015;55(2):263-274.

16. Hirohara, M., Saito, Y., Koda, Y., Sato, K. and Sakakibara, Y., 2018. Convolutional neural network based on SMILES representation of compounds for detecting chemical motif. *BMC bioinformatics*, *19*, pp.83-94.

17. Gupta, R., Srivastava, D., Sahu, M., Tiwari, S., Ambasta, R.K. and Kumar, P., 2021. Artificial intelligence to deep learning: machine intelligence approach for drug discovery. *Molecular diversity*, *25*, pp.1315-1360.

18. Seidel, T., Ibis, G., Bendix, F. and Wolber, G., 2010. Strategies for 3D pharmacophore-based virtual screening. *Drug Discovery Today: Technologies*, *7*(4), pp.e221-e228.

19. Schneider, G., Neidhart, W., Giller, T. and Schmid, G., 1999. "Scaffold-hopping" by topological pharmacophore search: a contribution to virtual screening. *Angewandte Chemie International Edition*, *38*(19), pp.2894-2896.

20. Hajduk, P.J. and Greer, J., 2007. A decade of fragment-based drug design: strategic advances and lessons learned. *Nature reviews Drug discovery*, *6*(3), pp.211-219.

21. Kuhn, P., Wilson, K., Patch, M.G. and Stevens, R.C., 2002. The genesis of high-throughput structure-based drug discovery using protein crystallography. *Current opinion in chemical biology*, *6*(5), pp.704-710.

22. Lu Y, Wang R, Yang CY. *Computational de novo design of drug-like molecules by means of a fragment-based approach*. J Med Chem. 2008;51(3):682-692.

23. Shaw DE, Grossman JP, Bank JA, et al. *Atomic-level characterization of the structural dynamics of proteins*. Science. 2010;330(6002):341-346.

24. Tang, Y., Zhu, W., Chen, K. and Jiang, H., 2006. New technologies in computer-aided drug design: Toward target identification and new chemical entity discovery. *Drug discovery today: technologies*, *3*(3), pp.307-313.

25. Abel R, Salam NK, Shelley JC, Farid R, Friesner RA, Sherman W. *Contribution of explicit solvent effects to the binding affinity of small-molecule inhibitors in blood coagulation factor serine proteases*. ChemMedChem. 2011;6(6):1049-1066.

26. Wang, P.H., Chen, J.H., Yang, Y.Y., Lee, C. and Tseng, Y.J., 2023. Recent Advances in Quantum Computing for Drug Discovery and Development. *IEEE Nanotechnology Magazine*.

27. Fukushima, A., Kusano, M., Redestig, H., Arita, M. and Saito, K., 2009. Integrated omics approaches in plant systems biology. *Current opinion in chemical biology*, *13*(5-6), pp.532-538.

28. Hertogh, C.M.P.M. and Ribbe, M.W., 1996. Ethical aspects of medical decision-making in demented patients: a report from the Netherlands. *Alzheimer Disease & Associated Disorders*, *10*(1), pp.11-19.

29. Wadood, A., Ahmed, N., Shah, L., Ahmad, A., Hassan, H. and Shams, S., 2013. In-silico drug design: An approach which revolutionarised the drug discovery process. *OA Drug Des Deliv*, *1*(1), p.3.

30. Gao J, Wang D, Sun H, et al. *Chemogenomics knowledgebased polypharmacology analyses of drug abuse related G-protein coupled receptors and their ligands*. Front Pharmacol. 2018;9:1460.