American Journal of Botany and Bioengineering
https://biojournals.us/index.php/AJBB
ISSN: 2997-9331

Molecular Simulation Techniques in Protein-Drug Interactions for Neurodegenerative Diseases

Mohammed Nooruldeen Mohammed, Abdullah Hussein Ali, Aqel Jasim Mohammed
Alkitab University, Medical Instrumentation Techniques Engineering

Received: 2025 19, Feb
Accepted: 2025 28, Mar
Published: 2025 08, Apr

Annotation: Neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's continue to pose major global health challenges, with treatment efficacy remaining limited. Although protein-drug interactions are central to therapeutic development, current experimental methods often lack the resolution to capture dynamic molecular behaviors. This study explores advanced molecular simulation techniques—including molecular dynamics (MD), Monte Carlo simulations, docking methods, and free energy calculations—to investigate protein-drug interactions at atomic precision. These simulations provide critical insights into protein folding, binding affinities, and aggregation behaviors associated with neurodegeneration. By simulating complex molecular systems and drug-target interactions, the study underscores the potential of computational modeling to enhance drug discovery pipelines, optimize therapeutic targeting, and contribute to the development of personalized medicine in neurology.

Keywords: molecular simulation, neurodegenerative diseases, protein-drug interaction, molecular dynamics, docking, Alzheimer’s, Parkinson’s, drug discovery, computational biology.

1. Introduction

Presently, the neurodegenerative diseases affecting the population are Parkinson's Disease (PD), Alzheimer's Disease (AD), Huntington's Disease (HD), Prion diseases and many more. These ailments emerge due to a loss or damage of neurons attack the motor system. Mutations in the intron region of a gene (ATXN7), results in the formation a protein known a ataxin-7, are the etiological factor of the neurodegenerative disease; Spinocerebellar Ataxia Type 7 (SCA7) [1]. When ataxin-7 starts to aggregate, a protein-protein action occurs; on the other hand, gene silencing is the action in which mRNA reduces its expression. The gene silencing agent; siRNA will hybridize with mRNA this action leads to blocking the translation process so it reduces the expression of the ataxin-7 protein and decreasing the production of ataxin-7. In the same direction, the anti-sense therapy is induced with the help of antisense molecules which act as a silencer to the ataxin-7 gene.

The biophysical methods such as ensemble and single-molecule fluorescence, X-ray crystallography and NMR, among others, have been utilized during the last decades to dissect the intricacies of these heterogeneous interactions, leading to a better understanding of their role in the mechanisms underlying biological processes and diseases. A set of computational modeling and molecular simulation techniques, based mostly on the physical principles of statistical mechanics, have added valuable, complementary insights to advance the current knowledge of protein-drug, protein-protein and protein-nucleotide interactions, shedding some light on their atomistic detail and dynamics that are often imperceptible to most experimental approaches. In this review, an up-to-date account of the latest computational and theoretical approaches to the study of the interaction of proteins with drugs, proteins, nucleic acids and biomembranes and of some cutting-edge, emerging services regarding the in silico prediction of biophysical and physiological interactions, as well as the determination of the biological function of proteins of yet unknown structure is provided. [2][3][4]

2. Overview of Neurodegenerative Diseases

Neurodegenerative diseases (NDDs) are caused by the loss and/or death of neuronal cells. Many NDDs are related to protein aggregates. In the process of misfolding, abnormal proteins are aggregated into a β-sheet structure consisting of hydrogen bonds between the main chains of neighboring monomers, and toxic protein aggregates can promote the misfolding and aggregation of native proteins. To achieve this, cells have two main defense systems. First, misfolded proteins are maintained in their original functional conformation via molecular chaperones, preventing the aggregation of non-native proteins. Second, cells degrade the aggregated pathogenic protein via the ubiquitin proteasome system (UPS) or autophagy. When these normal systems do not work properly due to mutations, post-translational modifications, aging, etc., the deposition of aggregates tends to increase, which is phenomenologically associated with neurodegenerative diseases [5]. In general, the interaction environment of drugs is similar to that of substrates or other internal common molecules in living cells. As a result, drug molecules interfere with normal protein activity, cause off-target toxicity, and increase protein aggregation. In addition, NDDs can occur in other near-native misfolded forms with small differences from the original conformation, not just in aggregate forms. However, the current drug design method is based on the three-dimensional conformation of the folded protein. As a result, only the specific interaction of the functional native conformation is intentionally considered in the design of the drug molecule, but the interaction with other near-native conformations is not considered. However, the commercially available chemical drug involves many off-target proteins for protein degradation. In the case of neurodegenerative diseases, the success rate of drugs is lower than other diseases, so efforts have been made to improve the protein-degradation system.

2.1. Types of Neurodegenerative Diseases

Neurodegenerative diseases are disorders of the nervous system characterized by the progressive

loss of neuronal structure or function. As the average lifespan increases, the incidence and spread of neurodegenerative diseases become problematic. Many research groups are therefore trying to discover efficacious therapeutic agents for various neurodegenerative disorders. The processes of drug discovery involve various stages, including initial compound testing and lead optimization [5].

Most neurodegenerative diseases are associated with protein aggregates or are characterized by them. Misfolded proteins aggregate into a β-sheet structure, a major phenomenon of protein-misfolding diseases (PMDs). Many active research programs have been conducted to discover small molecules, as they have powerful effects as therapeutic agents. Despite the considerable efforts and achievements, there is a challenge involving the identification of drugs with high efficiency and safety. Among various targets for neurodegenerative diseases, molecular simulation techniques have been employed and applied in the study of protein-drug interactions.

β-sheet formation is an intermediary phenomenon of protein folding. Although the β-sheet structure is necessary for normal protein folding, it is also a structural basis for the aggregation of misfolded proteins having other secondary structures. These misfolded proteins are oligomerized into protofibrils, which lead to the formation of insoluble fibrils or fibers. This β-sheet aggregation process is popularly observed for many proteins, which seems to be the origin of many PMDs. As a defense mechanism against the exponential growth of misfolded protein aggregates, cells maintain proteostasis (a balance between protein synthesis, folding, aggregation, and degradation) through two main types of actions, also known as protein quality control (PQC) networks—(i) refolding of misfolded proteins under the assistance of various molecular chaperones, and (ii) the elimination of aggregated forms of pathogenic proteins by either proteasomal activity or lysosomal degradation. In PMDs, however, the declined function of chaperones and/or the increase of aggregation-prone proteins originating from cellular stresses (aging, genetic mutations, endocytosis, etc.) decrease the PQC systems, which leads to an accumulation of protein aggregates triggering neurodegenerative diseases. [6][7][8]

2.2. Current Treatment Approaches

Neurodegenerative diseases have become one of the most widespread non-communicable diseases that impose heavy burdens on healthcare systems. The disorders share common features of fast progressive neuronal death and subsequent loss of activities. With the growth of aging population, AD acts as the most prevalent cause of dementia and brings challenges for governments and families.

The exact mechanism of AD pathology is highly complex and far from thoroughly understood. The postmortem investigations reveal the features of AD, such as plaques due to β-amyloid aggregates and tangles resulting from the accumulation of hyperphosphorylated τ protein and granulovacuolar degeneration with intraneuronal vacuoles in the brain [9]. The occurrences of tangles are commonly connected with synaptic disfunction. The toxicity and pathogenicity associated with β-amyloid species are the reasons underlying the cascade, including overproduction of Aβ peptides and their values (42-43 aa), aggregation of Aβ into protofibrils, appearance of early neurofibrillary alterations, appearance of neuritic dystrophy, loss of the synapse and extensive neuronal. In this cycle, neuronal cell death can further promote β-amyloid formation, including the release of BSPs and CTFs to the extracellular space. The extracellular BSPs can act by promoting neuropeptide and spine toxicity to contribute to neurodegeneration in AD [5]. The therapeutic strategies available for participants are shown in Figure 1 and are explained as follows.

Firstly, anti-amyloidogenic therapy intended to avoid Aβ aggregates is probably the most comprehensive and well-studied method, including the inhibition of Aβ fibrillogenesis, solubilizing of amyloid fibrils, and β- and γ-secretase inhibitory. AD can be established through removing the amount of Aβ from the brain. The Aβ clearance mechanism could be achieved pharmacologically, mechanically, or therapeutically applied to some specific agents that can

promote Aβ efflux through the BBB. On the other hand, necessity for researching the development of drugs indirectly affecting CSPs stimulates numerous studies of active and passive immunization against CSPs and APP to obtain antibodies controlling the physiological handling of APP. Another pivotal point is to inhibit, by chemical or biological compounds, APP processing, thereby avoiding the formation of CSPs.

The β-folding up field increases the α destruction by E3 ligase. On the top of page 2, oxygen control is required to bring the ER α-degeneration to succeed. The small molecule possesses E3 ligase ability. In other words, because G100 treats oregon through an unknown event, "hypoxia" environment is required in order to enable the mode of action on the mechanism: in general, this necessitates an "oxygen deprivation" situation.

3. Molecular Simulation Techniques

Recent years have seen a rise in the number of studies on neurodegenerative disorders, focusing mainly on understanding Alzheimer's disease as well as the discovery of drug candidates for its treatment. Currently, there is no cure for Alzheimer's, and the existing drugs offer modest symptomatic benefits, thus a major endeavor has been exploring strategies that will change the course of the disease [10]. With the rapid growth of the aging population, the urgency of this task will continue to rise. Compound CID 9998128 binds to BACE1, Aβ42_fld, A60I-Aβ42_fld, and B27E_Aβ40_fld with high binding energies, and the predicted binding mode explains the high binding promiscuity of CID 9998128, showing the capability of CADD methodologies for hit identification. Among these hit compounds, twelve are selected for experimental validation and it is confirmed that CID 9998128 inhibits Aβ fibril and total Aβ formation. This chemical proteomics study successfully revealed the CID 9998128 target proteins with a wide range of binding promiscuity, and remarkably two pan-assay interference compounds (PAINS) aggregators were suggested by the modeling study with BACE1, suggesting the in silico hit identification can also suggest toxicity.

3.1. Molecular Dynamics Simulations

Molecular dynamics (MD) simulations are playing an increasingly important role to study protein-drug interactions in the frame of neurodegenerative diseases. At this regard, the aim of this chapter is to present the most common simulation techniques to perform MD investigations about the way to drug proteins. The interplay of these investigations with experimental techniques and computational methods will be widely discussed. Non-equilibrium processes as the binding-unbinding events between macromolecules, and/or among macromolecules and small ligands is commonly encountered during their dynamics. They are ordinary events, characterizing the interaction among a ligand with the specific site of a protein, without to be sequestered, so quickly detached from the small ligand. The necrotizing molecules, for example, used as therapeutic drugs, are able to kill the propriety of cancer cells blocking specific binding sites of structural proteins.

Molecular dynamics (MDs) simulation is being used for biocombination about thirty years, this technology is very effective for understanding bio-molecular processes in their atomistic detail. A long time ago assembly processes like molecular encounter have been addressed through MD simulations. Biological substrates like proteins have native moments with large surface areas which are generally used as binding sites for drugs or other substrates. Recognition and following complex-formation between two bio molecules mostly occurs with the association of their certain binding sites too. This association is the result of long sequence of capture events, consisting of several semiotic non-specific contacts and of longer specific ones. The time scale required for this kind of events largely relies from the physical chemical atmospheric and plenty of theoretical size depotent models have been proposed to describe this situation, however, the correct treatment of several thousand molecules, such as proteins which are estimated. [11][12][13]

3.2. Monte Carlo Simulations

Proteins are vital cellular macromolecules involved in nearly every aspect of a living organism. Changes in the interactions of a protein with other molecules or its environment can have severe consequences in the cell or in the organism as a whole. In particular, mutations and unbalanced regulation in their interactions can lead to a loss of function or to the gain of a new, sometimes toxic function of the protein causing a series of neurodegenerative diseases. Moreover, protein misfolding due to aging, chemical toxins or wrong interactions can provoke a cascade of misfolded proteins and damage the cells. In this context, the search for drugs to avoid or alleviate these problems is an active field of research. Computational techniques based on molecular simulations can be a valuable help to shed some light on these interactions. Particularly, MC simulations are more focused on the exploration of the phase space of the system. If well designed, can be extremely selective in the sampling of specific regions of the phase space. Regarding the PDIs and the study of drug binding, the ligand must find the pockets with stronger ligand-receptor interactions, indicative of a high binding energy. In the case of exploring the protein stability against a non-nearest neighbor mutation, the neighbors of the mutation are the pockets that will change their binding energy. [14][15][16]

3.3. Docking Simulations

Due to the astronomical number of possible ligand binding positions and the heavy computational demands of evaluating all potential interactions, inviting tools have been developed to perform those calculations in silico. Simple early approaches to docking, sometimes referred to as “lock-and-key” due to the analogy to a physical mechanism. By far the most successful programs employing more precisely and accurately match the ligand to the pocket and also take conformational changes in the receptor due to ligand binding. With the addition of heavy empirical corrections to the van der Waals energy, a program has often been the top ranked program in structure-based docking contests. Despite it having been on the market for nearly two decades, it was found that up to 75% of the individual docking tasks were ranked better by this program than by another.

Covalent docking has emerged as an alternative tool for the accurate prediction of the binding mode of ligands that establish a covalent bond with their target protein. Covalent docking was built into a program and applied for the first time to the elucidation of the binding mode of new peptidyl and peptidomimetic inhibitors of a hepatitis C virus helicase. Recently, a new approach to covalent docking included in a program was developed. This program was tested and validated experimentally on a large number of diverse systems. It was found that the new approach is automatic, fast, robust, easy to use, and computationally efficient. Unprecedented in the field of covalent docking, the approach allows variation of the position of the atom forming a covalent bond without reparameterization. This feature allows docking with unconstrained bond orientations or geometrical restraints on the bond formation site, which represents a bibliographic first in the area of covalent docking. [17][18][19]

3.4. Free Energy Calculations

Understanding binding free energy is critically important for the design of drugs and other chemicals that can affect biological mechanisms in vivo. Free energy via Molecular Simulation has a long history in the simulation of chemical and biomolecular systems, including liquids, amorphous solids and polymers, as well as solvated proteins, nucleic acids, and sugars. The calculation of protein-ligand binding affinities with free energy methods is particularly important for drug lead discovery and optimization. Medicinal chemist often need to select compounds with significantly different structures, so blind tests show that people have a very hard time judging the relative ligand binding affinity of different compound series. Those findings suggest that they should not use docking scores to rank the affinity of different molecules, at least not in a literal sense. Among the seven programs, DOCK and Surflex-Dock are somewhat better than the others, finding ligands with binding affinities within ~ -1.5 log-units of the target, which

would be helpful if the goal were to find multiple chemical series within a known range of affinity, as is sometimes true. Among the four, Surflex-Dock does the best job of ranking affinity in the tests, with an overall 62% success rate. Autodock and FlexX are inconsistent, and DOCK is poor at ranking, with only one of the seven datasets finding the high-scoring compound at or near the top as ranked by affinity [20]. On the whole, this domain analysis suggests that people should not have empirical expectations of docking programs to match SIE/GAFF conformational sampling results in a quantitative sense.

4. Protein-Drug Interactions

Molecular Simulation Techniques in Protein-Drug Interactions Applied to Neurodegenerative Diseases: Protein-Drug Interactions

The term ‘proteoform’ designates all of the different molecular forms in which the protein product of a single gene can be found, including changes due to genetic variations, alternatively spliced mRNA, and post-translational modifications (PTMs), either co- or post-translationally added. The enormous number of different proteoforms far exceeds the gene products coded by the estimated number of genes of an organism. Disordered proteins or proteins with very long intrinsically disordered protein regions often resulting in proteins only marginally well structured are frequently implicated in serious diseases. Targeting these indistinguishable proteins or proteoforms is particularly challenging as they do not have a well defined structure under physiological conditions and even when they bind to a partner form a relatively minor, induced fit structure. Due to their structural plasticity they do not have well defined or have multiple cellular functions.

A rather small number of drugs acting on IDPs and their modulators, including proteins, peptides, small molecules and RNAs, have been discovered compared to the thousands of known compounds targeting ordered proteins. Computational methods have the potential to play an important role in the discovery of drugs that target disordered proteins. Therefore, an introductory brief mathematical representation stresses how molecular modeling can be used to predict disorder propensity of proteins, or to explore their interactions with binding partners, small molecules or drugs. [21]

4.1. Mechanisms of Interaction

The mechanisms of these interactions may consist of a great variety of processes, including changes in the protein conformational equilibrium with profound physiological implications. This is also achieved by a variety of pathogenic factors affecting the native state of proteins, which include heat, chemicals, osmotic pressure, and shearing forces. Would it be possible to understand the universal features of these interactions? In order to gain some insight into this fundamental question, the problem is explored through the analysis of high-performance molecular dynamics computer simulation of a small hydrated protein.

Beginning with classical work, a detailed understanding of protein folding has been gained through computer simulation techniques. More recently, formalisms have been developed allowing to relate characteristic time scales observed in simulations to the genuine folding dynamics of proteins. This progress has been greatly helped by the development of secondary analysis techniques of the conformational space explored during the simulation. Such techniques, amongst others, include principal component analysis and data clustering. Interestingly most of these rapidly interconverting states, so called microstates, are already in local free energy minima.

Such insight has not been translated to the understanding of proteins interacting with other molecules at the microscopic level. Most experimental studies characterize the affinity of the drug to the intact protein, determining the drug association constant. This technique, however, provides little information on the precise nature of the interaction. What is reported is the heat exchanged with the environment during the physical process of the drug binding to the protein.

Due to the intrinsic averaging character of experiments, it is very difficult, and perhaps not possible at all, to deduce the geometrical constrains of the interaction, the way the native state of the protein is modified by the drug, and the sequence of events which lead to this equilibrium state. Over the last decade, molecular simulation techniques have achieved a high level of sophistication and are nowadays routinely employed to investigate problems that are much more complex than making the drug and the protein interact. The experimental setup used in simulations is implemented through a computational program. [22][23][24]

4.2. Importance in Drug Design

Molecular simulation techniques including docking simulation, molecular dynamics (MD), and binding free energy calculation by MM-PBSA of the protein-drug interactions have been successfully applied in exploring the interactions of druggable target proteins with new compounds in development of new drugs for neurodegenerative diseases [10]. There are seven common neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), spinocerebellar ataxias (SCA), pantothenate kinase (PKAN), and prion diseases. The common point of these diseases is the pathology aggregates or inclusions of abnormal protein. This article provides an overview of the molecular simulation techniques in the study of protein-drug interactions that contain the methodologies, helpful tips for users, and some cautions to be considered. At the end, some cases of the application in the study of AD are described.

In the literature, there are many interesting works. Some landmarks are the development of positron emission tomography/single photon emission computed tomography probes targeting Aβ, the rational design of anti-Aβ antibodies, small molecule inhibitors targeting Aβ fibrils, the designing the β-sheet breaker peptides to interfere with amyloid fibril assembly, and the structural modeling of aspartyl protease γ-secretase in complex with one or two Aβ peptides. These studies were established on fulfilling FEP/λ-REMD calculations as well as the assistance of the Site-Identification by Ligand Saturation technique to enhance the FEP calculations for the set of ten α-ketoamides.

5. Case Studies

To perform the computational study of some case studies featuring three complexes that integrate the structural and biological networks responsible for receiving and transmitting neurotrophin signaling. The analysis of the essential dynamics of the molecular dynamics simulations of the protein-protein complexes is used to rationalize the role of some key regions in favoring the binding process. The last two decades have seen an increasing interest in the biological functions and structures of neurotrophin ligands and their transmembrane Trk receptors. Neurotrophins are growth factors found in the brain and peripheric ganglia [25]. Their specific receptors are proteins with tyrosine kinase activity (Trk), coded in the human genome by three genes, TrkA, TrkB and TrkC. TrkA is involved in the connection between nociceptive neurons and central synapsis centers, and a mutation of its gene can cause a large decrease in the pain perception levels, i.e. congenital insensitivity to pain with anhidrosis [26]. TrkA, TrkB and TrkC receptors bind to NGF, BDNF and NT-3/4 respectively. In a complex but clear pattern of coevolution, their neurotrophin ligands have a high aminoacidic sequence similarity without a sequence identity. These molecules have shown to be involved in long distance signaling in a variety of cellular functions, like axon surviving or targeting (by their retrograde signaling in the synapses), but the detailed molecular comprehension is still scarcely defined. After the discovery of NGF in 1950s and the identification of its function in 1970s and 1980s by the Nobel Prize laureates, the X-ray crystallography analysis of the dimmer BDNF in 1990s allowed the identification of an active site not far from the dimerization area. This biomedical interest in these systems was then followed by a boom of biomedical structures: the first structure of neurotrophin (NGF), dimers TrkA, TrkB and TrkC, and more in general of protein-protein complexes involving these high sequences similarity complements structures. In Table 1 some

complexes signaling neurotrophin ligand interactions are displayed. In this table, Sc is the experimental biological interactors localization, while the four potentials implement a multidisciplinary knowledge of these systems.

5.1. Alzheimer's Disease

Introduction: Alzheimer’s Disease (AD) is a progressive and chronic condition, narrowly associated with cognitive dysfunction and memory loss. Development of Alzheimer’s Disease is characterized by the formation of amyloid-β (Aβ) deposits and fibril plaques in human brains, thereby damaging synapse and causing cell death. Neurofibrillary tangles composed of hyperphosphorylated tau protein is another hallmark of AD. Sequential proteolytic cleavage of Amyloid precursor protein results in the formation of Aβ peptides. Formation of Aβ plaques has a direct or indirect implication in neurodegeneration, culminating in Alzheimer’s pathogenesis [9]. Methodology: A fully atomistic molecular simulation was performed to get an insight into the biophysical events underlying the aggregation and oligomerization of Aβ. A novel therapeutics platform to explore the potential synergistic relationship with respect to Aβ hepameric oligomerization was devised. Combination strategies were therefore primarily focused on natural bioactive and by biogenic molecules where the lower doses can effectively modulate the aggregation and oligomerization of Aβ, making it a potent neuroprotective and Aβ helix stabilizing additive. Discussion: The propensity of unbounded Aβ was monitored by a series of 1 μs independent production runs. A condensed environment led to more pronounced alpha-helical formation of Aβ peptides. Detailed β-hairpin arrangements were observed for Aβ-f treated hexamers. PbA and CDSA methodologies were employed for in silico prediction of the potential synergism of all possible combinations of ethyl-iriflophenone, Curdlan-NH2, and Laropiprant. Only combination of Curdlan-NH2 and Laropiprant at 1:2.14 molar ratio exhibited a substantial reduction of more than 50% in proportion with the safety of glucose and leucine enkephalinergic neuronal cells.

5.2. Parkinson's Disease

Molecular modelling simulations are commonly conducted to reveal hidden molecular insights of protein-drug interactions. Since pharmaceutical therapy for neurodegenerative diseases is a challenging task, with the increase of elderly populations worldwide, many research efforts using a variety of computational methods, including molecular simulations, have been conducted to understand pathological molecular mechanisms of neurodegenerative diseases and to discover or develop new potential drugs. Currently, there are no effective drugs that can deter progression of neurodegenerative diseases. Early diagnosis before the onset of symptoms and the ability to stop the development of their related pathology are needed to treat these diseases effectively. Applications from molecular modelling simulations may be an advantageous approach to achieve these unmet needs. In addition, other problems need to be addressed. The blood–brain barrier (BBB) limits transportation of drugs into the brain. Researchers are actively working to overcome this limitation and develop new drugs which can get through the BBB. Researchers are also making a significant effort to identify biomarkers or sedimentary bodies that can be readily assessed from biological fluid or tissue, to diagnose diseases before symptoms occur [27]. Molecular insights relevant to such problems may have been obtained but remain unobserved in published research using molecular simulations. The author expect that this work will contribute to the creativity of various medicinal applications or discoveries related to neurodegenerative diseases, from results obtained by molecular modeling simulations.

5.3. Huntington's Disease

Huntington's Disease (HD) is the most heritable type of neurodegenerative disorder and it occurs globally in all racial groups. The typical occurrence shows the onset in middle age and until now, no treatment is possible that can slow down the progressive neuronal damage initiated by the expansion of CAG trinucleotide present in the gene, HTT. It has been the main focus of intensive basic and preclinical research with the intention of understanding its genetic aspects and the

neurobiological and molecular effects of the disturbance.

Huntingtin is a huge protein located in various cellular parts and is implicated with various proteins; however, its function remains largely unknown. A possible connection among the characteristics of huntingtin may be the deregulation of the axonal transportation of HTT binding proteins with the surface of the oil droplet in neurons. This complex regulatory process might be deregulated by the existence of expanded CAG repeats in the HTT gene. The characterization of protein-protein interactions on a big scale is not feasible either experimentally or computationally. Computational methods capable of prediction of the sub-spaces of all likely interactions could assist to select more promising protein-protein interaction casings for experimental certification. As a result, it is vital to gather data on current computational methods of that prediction, as well as provide an experimentally validated in silico approach to the identification of probable casings of protein-protein interactions [28].

Huntington's Disease (HD) is an autosomal devastating pathology of the central nervous system, hereditary and neurodegenerative, especially characterized by choreiform movements or other extrapyramidal signs, in addition to progressive dementia and mental derangements. The ETNK - RHES - RGS - RAS - PI3K - AKT sign cascade, a signaling path provoked artificially by the huntingtin and blocked by the RAS. Silencing the rhvonal activity of the mutant huntingtin protein with similar huntingtin-related protein-RNAI conjugated polymers. Efficacy of siRNA mediated blockade and partial suppression of huntingtin incessantly with adjustable silencing grades with chemically safe siRNA. Absence of ETA signaling, slow striatum and cortex neurodegeneration lessened by 40–60%. Efficacy of similar performances in an acute huntinian pathology post-onset cat model with confirmations 4 and 7 days post-transdermal siRNA shots. The rhvonal amalgamation between similar huntingtins. Future creation of imaging drugs for extra exploration of ETA signaling in model animals and Huntington's disease patients [29].

6. Data Analysis and Interpretation

Section 6

Biological processes are orchestrated by the interplay of various biomolecules which are dynamically changing their conformations on short time scales of femtoseconds to seconds or even longer. Novel experimental methods, in particular fast structural biology methods, may be able to capture the molecular states transitions. For biomolecules, and in particular for intrinsically disordered proteins (IDPs), states are frequently not only represented by a unique molecular conformation but by a cluster of conformations. Beside the intrinsic experimental difficulties of monitoring conformational dynamics, also the analysis of such data is nontrivial. Molecular simulation is a versatile computational method increasingly filling some of the gaps left by experiments. However, it enables generally only a smaller-scale representation of the system, making comparison of simulation and experimental results difficult [30].

Molecular dynamics simulations of biological macromolecules have developed rapidly over the last few decades. Many early molecular dynamics simulations of biological macromolecules could often be understood qualitatively, but such understanding is rarely productive for analyzing simulation trajectories. Simulations are often carried out with a specific scientific question in mind, but large-scale simulations of complex biological systems allow scientific discovery beyond the initial motivating questions. One approach to such discovery is to carry out a battery of standard analyses to characterize structural and dynamic features of macromolecules. Results of such analyses are typically used to frame hypotheses as to the behavior of the system that can then be validated experimentally or explored further through simulation. However, beyond these well-established analyses, it is difficult to explore and analyze large-scale simulation data. Reduced trajectories do not provide enough information and rely on a priori hypotheses concerning the type and time scale of the important events that occur in a macromolecule. More elaborate clustering analysis and inference of master equation models require additional assumptions concerning the separability of the macromolecular configuration

space, assumptions that are challenged by the molecular topology of many systems. Furthermore, such analyses cannot always provide the detailed, atomic-level understanding of important conformational changes that form the basis for follow-up experimental investigations. Post hoc explanation is also questioned by the "many analysts, many (often conflicting) interpretations" problem [26].

6.1. Analyzing Simulation Data

Early molecular dynamics simulations of biological macromolecules could often be understood qualitatively by inspecting molecular movies generated from the trajectories [30], but nowadays this is rarely a productive approach for fully analyzing simulation trajectories. Simulations are often carried out with a specific scientific question in mind and one way to navigate the large amount of information is to only focus on that question during the analysis, discarding the wealth of other data generated during the simulation. However, there is clearly potential for scientific discovery beyond the motivating question(s) that led to the simulations. Large-scale simulations of very complex biological systems already start providing insights beyond the answer to their motivating questions. One approach to attempt such discovery is to carry out a battery of standard analyses to characterize many different structural and dynamic features, but even the huge amount of data generated might not be enough to capture the relevant phenomena. A more advanced approach is automated feature analysis whose application here is illustrated for the temperature unfolding of a peptide. For example, a distance analysis reveals that the secondary structure in a given peptide is lost compared to an experimental ensemble when the temperature is increased beyond a certain point, showing that the analysis would be particularly well suited for identifying freak occurrences in long simulations. More intricate effects like the secondary structure shift are not recognized by the automated analysis although different experimental observables hint that it might be happening, which indicates a significant fundamental gap despite the complexity of the analyses already performed.

It is difficult to provide suggestions to other researchers when most questions do not indicate the nature of the simulation being analyzed or the goal of the analysis. Common types of analysis include structural analysis (root-mean-square deviation and similar metrics, secondary structure, solvent accessible surface area), dynamics analysis (mean squared fluctuations or covariance as a function of residue number, various ways to characterize essential dynamics), analysis of bond and/or dihedral angles, energetics analysis, analysis of radial distribution functions, and visual inspection. It is recommended for researchers to consider this work a practical reference to which it is referred later in this diving section if also time is spent discussing the results of the structural and dynamical analyses. Also realizing that it is better to be succinct if the secondary focus is on localized effects due to the loss of water. However, researchers should feel free to reach out for further help with the analysis. It is not knowing what to focus on a priori when considering correlations and then causal connections in a system with as many as 100 M atoms that is the main issue presented here. Efforts have been made to extract some potential insights utilizing simulations to that end or in a complementary experimental endeavor, but this proof-of-principle project would investigate the physiological conditions in greater detail. So far there are no MDs of copolymers under tensile loading: previous simulations are on homopolymers, and show no "plasticity." [31][32]

6.2. Visualization Techniques

The representation of the protein with van der Waals and space-fill drawings emphasizes the complexity and tens of thousands interacting atoms of the simulation. The drug is shown in ball-and-sticks with elements color code showing the bond order: nitrogen blue, oxygen red, hydrogen white and carbons grey [33]. There is a strong brightness / outline effect for a clearer distinction between the molecules. The background (simulation) will be shown using the standardized DNA strands. The wireless VR motion controllers represent the "hands". In future projects, to increase a more intuitive handling of protein and drug simulation geometry, simple

physical interactions may become possible, where the user could, for example, bend the protein's secondary structure or add new functional groups to the ligand and while the background simulations would calculate in real-time whether such changes are mechanically stable (intra- and intermolecular forces) or energetically favorable (binding energy). Harmonic constraints would be applied to bond lengths and angles to minimize disruptive geometric deformations. When the user gave the correct vibrational stimulus, further ultrasonic forces could dislodge small molecule within the protein's active site.

Visualization of the geometry of drug binding in the dynamic picture can guide the manipulations of the protein and ligand structure in the process of improving an inhibitor [34]. This project is aimed at lowering the threshold to fully immersive VR scene creation by facilitating the experimental design of the required 3D printed equipment and making the spectroVRscopy software for protein viewer scenes easily available. This would greatly assist research groups that do not have in-house expertise in electromechanics and VR software, resulting in more productive collaborations, particularly with VR facilities at large scientific institutions. In addition to traditional research usage, the software has great potential for outreach and engagement with the general public.

7. Challenges in Molecular Simulations

Introduction

Molecular simulation provides detailed information on the interactions of proteins with one another and with small-molecule ligands. Many biophysical techniques, including atomic force microscopy, electron paramagnetic resonance, and mass spectrometry, are well-suited to examine protein structure and protein-protein interactions. However, information on ligand binding sites from such studies is generally, highly obtuse and often indirect [35]. Other techniques, such as nuclear magnetic resonance, x-ray crystallography, and isothermal titration calorimetry, more directly observe the ligand itself. These latter methods, however, can have difficulty in directly probing high-affinity, low-solubility ligands, such as many drug leads. In the following study, a timely place for a review of molecular simulation methods applied to protein-drug systems for neurodegenerative diseases is provided [10]. The range of molecular simulation techniques examined is broad, from simple Brownian dynamics simulations to all-atom molecular dynamics simulations with explicit solvent, and covers an equally broad range of target proteins. Nonetheless, several consistent themes arise, which may shape the drug discovery scientist's view of how computational results can be used for this particular subset of protein-ligand systems.

Challenges in Molecular Simulations

There is an obvious need for an improved atomic-resolution description of the mode of action of antibody therapeutics. As all putative epitopes are linear stretches of protein sequence within the antigen, it follows that an antibody therapeutic cannot recognize a conformation-based epitope; its target must be a region of the native 3D-structure accessible or mimicable by a linear fragment. A DNA sequence, prokaryote-derived protein, metabolite, lipid, or nucleotide is likely to provide a peptide-based epitope isolatable via phage display or other library-type technology, from which vaccines would require a positive immune response. However, meaningful definitions of functional or mimotope epitopes are ill developed. ProProEP is a high-performance protein epigraph tool. Recent improvements to ProProEP are comprised in the incorporation of eigenpeptide scaling, making its performance competitive with, or other times superior to, current state-of-the-art commercial alternatives. Considering, the future development and health-economy feasibility of complex vaccine strategies, there is an essential need for an improved atomic-resolution description of the mode of action of antibody therapeutics. Nonequilibrium molecular dynamics simulations in Pull code are used to quantify elemental ions transport through the nuclear pore, a key factor in tumorigenesis. Efflux and influx of a range of biologically and environmentally relevant ions are characterized, revealing a profound difference

in transport rate between singly charged monovalent ions on the one hand and doubly and triply charged model trivalent and tetravalent cations on the other. Such observations validate previous but much cruder coarse-grained assertions derived purely from GROMACS simulation studies. It should be possible to observe the entry/exclusion of individual cargo proteins as they transit through the nuclear pore. Model predictions of ions transport can be subjected to validation by upcoming wet experiments with promising techniques. Opportunistically induced mis-assembly of nuclear pore complexes represents a paradigm-altering vulnerability of disease-relevant cells, presenting numerous nascent opportunities in the tight targeting of new drugs. As such, a multi-disciplinary "team" approach is necessitated seeking a modicum of modern-day understanding of such detailed biophysics. Gatherings of participants from the fields of (nano-) medicine, biophysics, high-performance computing, and systems administration provide an amenable environment for facilitating such, perhaps the success of this proposal. As such, a symposium workshop on present results and other literature in the area is proposed as a tentative means of immediate introduction to poorly physicists within the "team". A set of rather ambitious future interdisciplinary research agenda is simultaneously proposed, reconciling the research methodologies of said fundamentals and seeking high-resolution experimental support, standards, and verification. As such, a tricky dose of biophysics is intended, seeking to illuminate the brief history of nucleoporins, the formation, and role nuclear pore complexes play in selective macromolecular transport within the eukaryotic cell, as well as the measures necessary to chemically modulate them. In light of this, a preliminary extensive background in current models, medically relevant transport studies, and methodology in said area is herein provided, with anticipated future directions in modeling efforts iterated and further unified with current understanding. Intentional mis-assembly of these complexes represents a paradigm-altering vulnerability of disease-relevant mechanistic cells; hence the subsequent transport of biologically inadequate ions provides both a tightly targeted hit for putative therapeutics, as well as a means for monitoring and/or validation of predictions. [36][37][38]

7.1. Computational Limitations

One important aspect of molecular modeling of protein-drug interactions is the prediction of small molecule binding affinities to protein targets, which can facilitate drug development. However, computational limitations still constrain the scale and accuracy of these potential future therapies [10]. Many studies have been performed and published on neurodegenerative disorders, focusing primarily on understanding Alzheimer's disease. A search of Pubmed with the term "Alzheimer" yielded over 100 cooking asthears published annually in 2014. More recent modeling works include the prediction of likely aggregation sites on Aβ peptides to help identify alternative targets for drug development, and characteristics of the borinic ester of Bortezomib as a potent, reversible, and exquisitely Zn(II)-selective proteasome inhibitor.

In this dissertation work, both the protein and peptide-ligands exhibit flexibility, and the peptide is considered at an extended state. The MM-PBSA method is used in conjunction with the AMBER package to compute the post-processing binding free energy. This is applied to the neocuproine Cc7 chelator binding to the Aβ40 monomer and dimer. The reversible covalent maturity model is developed mainly for structure-based virtual screening studies in which many compounds are scored multiple times to identify likely binders. A fully-flexible model is introduced that includes hard and soft recrossing in the semiclassical quantum transition state theory limit. An extended Lagrangian microcanonical algorithm is applied to enable and enhance kinetic sampling of the recrossing trajectories. Mixture density neural network regression is evaluated for the self-consistent potential set to increase the efficiency of solving the energy eigenvalue stochastic differential equation. Finally, the accuracy of a simplified membrane potential is assessed for use in BD studies that treat the protein as a permeable hydrophobic membrane.

7.2. Modeling Complex Systems

Molecular Systems Biology has brought together multidisciplinary research teams combining scientists working in the life sciences with physics, mathematics, and computational science to study how the complex interplay of biomolecular events gives rise to the cell's life cycle. The fast advances in the technology of molecular biology and biotechnological methods provide a comprehensive description of the genome, transcriptome, proteome, and metabolome of an organism. In silico based methods play an important role in interpreting and validating the data obtained with the new technologies. Computer assisted modeling methods are used in order to investigate complex biological systems. The building and validation of qualitative and quantitative models of complex biological systems is a challenging task that involves the development and integration of algorithms and statistical methods from mathematics, computational sciences, theoretical physics, and bioinformatics.

The prediction of the three-dimensional structure of a protein has become a central problem in molecular biology, as protein structure is key to understanding its function and stability. This importance has been further emphasized by the growth of structural genomics, where the number of protein sequences far outstrips the number of experimentally determined structures. An initial approach towards this goal was the assembly of homology or comparative models, which can be built when a significant fraction of the protein sequence shares relatively high sequence identity with a protein of known structure. Although this approach was successful in the early stages of structure prediction, its utility decreased with the exponential growth of sequencing projects. Efforts to address this issue have led to the development of a variety of methods to predict a protein's features, which go beyond the exact atomic coordinates. Additionally, the structures of many difficult protein targets have been solved without the aid of comparative modeling.

8. Future Directions

Modeling of protein-drug interactions using molecular simulation techniques has made significant progress over the past decade. This is due to development of more accurate and detailed molecular mechanics force fields for biomolecules, an increased understanding how to sufficiently sample the configurational space of biological macromolecules, and the availability of more powerful computer hardware. The next decade is likely to see further improvements in force fields, and better methods for conformational sampling, such as faster and more sophisticated free energy techniques. However, even with these advances, the full quantitative prediction of microscopically detailed binding modes and affinities over timescales accessible to drug discovery using fully atomistic models is projected to remain out of reach. The main role of such models is therefore expected to be the qualitative interpretation of experiments, facilitating the generation of hypotheses for further testing. For example, these simulations can discern energetically favorable ‘binding modes’ and then allow the design of mutants or analogs that selectively perturb these modes, but not others. If selected types of perturbations lead to specifically attenuated biological activity, then valuable information might be gleaned about the structure-function relationships of the system being studied. Another expectation is that the ability to perform a wide variety of model studies should improve general physical understanding, and hence the quality of model predictions. Of particular importance, increasing the basic understanding of the major physical forces that contribute to binding and specificity in molecular recognition reactions should permit those effects to be exploited more effectively. Moreover, the experimental validation of these kinetic models requires access to specific microscopic details of the binding process that are not usually obtainable by traditional experimental means. These may include, for example, the conformational fluctuations of the interacting species, the vibrational states they explore, or the detailed structures of encounter complexes in solution. With the many independent pieces of direct atomic-level information they can provide, molecular models are well-suited to filling this gap. [39][40][41]

8.1. Advancements in Simulation Techniques

Research and development of effective therapeutics for the treatment of neurodegenerative diseases are areas of active interest and great importance to the global population. Annually, there are over 500 billion US dollars spent by the global population for the detection, treatment, and care of neurodegenerative diseases [10], which are irreversible and continually worsen by slowly deteriorating the structure of the brain and eventually death. Alzheimer's disease (AD) is one such neurodegenerative disease which is considered the worst form among others. With regard to the development and regulation of effective therapeutics, a greater knowledge of the molecular interactions between the drug molecule and the affecting protein is required for the identification of sites to which the drug molecule can specifically and stably bind.

There is a variety of computational techniques available for the study of molecular models including electrostatic field techniques and molecular dynamics simulations. In recent years many sites have been dedicated for the generation of molecular fields and surfaces for the later use of pharmacophore searching. Another powerful computational toolbox for the study of molecular interaction between drug molecule and surface protein is molecular dynamics simulation. In the field of molecular modeling, numerous simulation packages are available and are always being developed and updated. Gromacs and NAMD are of most note due to the efficiency and scalability of the algorithm design architecture but less computational demands are required by LAMMPS, which still allows unprecedentedly large systems to be studied. Dfg is a notable tool in terms of force field creation for molecular dynamics simulation but full knowledge of the system chemistry is required. To complement molecular dynamics simulation and to approach the issue of time scale, umbrella sampling and metadynamics can be utilized. It is not necessary to produce these potential surfaces and sampling functions by hand, softwares are available to calculate potential of mean force from a single molecular dynamics simulation and to find sampling functions which allows the system to proceed over energy barriers.

8.2. Integrating AI in Drug Discovery

Artificial intelligence (AI) is a major breakthrough in today’s world and it has transformed the way of working in various fields. Currently, the whole drug discovery cycle is revolutionized by AI and has improved the novel drug discovery rate, reduced drug discovery costs as well as patient risk by combining high-efficiency, low-cost, and accelerated drug discovery methods. The elemental knowledge of the drug discovery process is essential to develop a deep learning model to predict the drug-protein interactions. AI has attracted the interest of a large number of researchers owing to its rapid development and good prospects. This can replace some labor-intensive, time-consuming work of early drug design and shorten the process from drug search to production, so drugs can be put on the market earlier. The development of a new drug that complies with the specifications of the chemical structure of the drug is called "rational drug design" while the opposite side of this process is called "reverse rational drug design." MDN-Assisted DTIP is characterized as a progressive step for the reverse rational drug design process in which important drug-target interaction points are revealed by assisting Molecular Dynamic Networks (MDNs). These experimental results prove the significance demonstration of the assistant MDN step in identifying actual drug-protein interactions. This is considered a kind of mutual auxiliary framework comprising both wet laboratories as well as in silico techniques. MD simulation has broadly been applied in the exploration of drug-protein dynamics. The dynamics of any drug molecule wins over nearly the thermodynamic success because when drugs bind with a target protein, it generates an extraordinary complex and the affinity and stability of that effectively rely on the dynamics behavior. [42][43][44]

9. Ethical Considerations

Despite the continuous advancement in technology, there are limitations of understanding biological processes due to the intricacies involved that are difficult to obtain and measure under controlled laboratory set-ups, and hence it becomes crucial to model and simulate such processes

with new approaches. Predicting protein–protein interactions (PPIs) is an important aspect of understanding disease mechanisms and for developing therapeutic targets for small molecule drugs. Currently, there are only a limited number of approaches to detect PPIs. However, these approaches have limited sensitivity and are further restricted to interactions between two or at most three proteins [1]. With the continuous development and optimization of molecular simulation techniques, it's become an important technology of molecular science.

There is apprehension about the ever-increasing requirement to obtain large quantity of data for the molecular simulation technique, especially for investigating complex biological systems, such as protein–drug interactions on a genomic scale. Therefore, a new approach has been developed to investigate the interaction between a protein and a set of drugs from a low content of data that is few binding-affinities available for the investigated system. A simulation-based optimization technique is incorporated to evolve sets of multiple mutation-favorable residues on the protein surface. It is suggested that the optimization technique can largely facilitate finding drug compounds with high binding affinities to a target protein.

10. Conclusion

The prediction development and reliability of molecular simulation techniques in determining molecular recognition of low molecular weight substrates or drugs to high molecular weight receptors or enzymes are reviewed. The success and basic requirements for methodology and proper experimental conditions are discussed. Some promising methods including force-field and Quantum Mechanics based simulations, and practical examples are described [1].

Genetic and environmental factors may lead to protein misfolding and aggregation. This growth in proteotoxic oligomers with a high inclination to self-assemble into fibrillar constructions and their deposition is the primary pathological feature of many neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and Creutzfeldt–Jakob disease. Compounds whose molecular shape and composition allow them to interact with the protein monomers and/or proteotoxic oligomers are known as shape and charge complementary molecules. Compounds able to destabilize Aβ, a rich inhibition of its aggregation, an elevation in the production of non-toxic Aβ fibrils or a rich increment in the formation of a population of Aβ fibril constructions that are non-neurotoxic are good candidates to be drug candidates for treating AD.

References:

1. A. M. I. T. KUMAR, "Computational Modeling and Simulations of Protein-Drug and Protein-Protein Complexes: as potential target for therapeutics development," 2018. [PDF]
2. R. Friedman, "Computational studies of protein–drug binding affinity changes upon mutations in the drug target," Reviews: Computational Molecular Science, vol. 2022, Wiley Online Library. wiley.com
3. R. Qureshi, B. Zou, T. Alam, J. Wu, "Computational methods for the analysis and prediction of egfr-mutated lung cancer drug resistance: Recent advances in drug design, challenges and future prospects," in *Proceedings of the IEEE Conference on Computational*, 2022. qnl.qa
4. V. Poongavanam and V. Ramaswamy, "Computational drug discovery: methods and applications," 2024. [HTML]
5. S. Hyun and D. Shin, "Chemical-Mediated Targeted Protein Degradation in Neurodegenerative Diseases," 2021. ncbi.nlm.nih.gov
6. N. Louros, J. Schymkowitz, and F. Rousseau, "Mechanisms and pathology of protein misfolding and aggregation," *Nature Reviews Molecular Cell Biology*, vol. 2023. kuleuven.be
7. M. R. Ajmal, "Protein misfolding and aggregation in proteinopathies: causes, mechanism and cellular response," Diseases, 2023. mdpi.com

8. A. Bigi, R. Cascella, F. Chiti, and C. Cecchi, "Amyloid fibrils act as a reservoir of soluble oligomers, the main culprits in protein deposition diseases," BioEssays, 2022. wiley.com
9. P. Kumar, V. Pillay, Y. E. Choonara, G. Modi et al., "In Silico Theoretical Molecular Modeling for Alzheimer's Disease: The Nicotine-Curcumin Paradigm in Neuroprotection and Neurotherapy," 2011. ncbi.nlm.nih.gov
10. E. King, E. Aitchison, H. Li, and R. Luo, "Recent Developments in Free Energy Calculations for Drug Discovery," 2021. ncbi.nlm.nih.gov
11. M. Post, "Dynamical models of bio-molecular systems from constrained molecular dynamics simulations," 2022. d-nb.info
12. W. F. van Gunsteren, X. Daura, and P. F. J. Fuchs, "On the effect of the various assumptions and approximations used in molecular simulations on the properties of bio-molecular systems: overview and perspective on …," 2021. uq.edu.au
13. J. P. Bittner, I. Smirnova, and S. Jakobtorweihen, "Investigating biomolecules in deep eutectic solvents with molecular dynamics simulations: current state, challenges and future perspectives," Molecules, 2024. mdpi.com
14. F. Di Domenico and C. Lanzillotta, "The disturbance of protein synthesis/degradation homeostasis is a common trait of age-related neurodegenerative disorders," Advances in Protein Chemistry and Structural Biology, vol. 2022, Elsevier. [HTML]
15. N. Mandel and N. Agarwal, "Role of SUMOylation in neurodegenerative diseases," Cells, 2022. mdpi.com
16. J. Sinsky, K. Pichlerova, and J. Hanes, "Tau protein interaction partners and their roles in Alzheimer's disease and other tauopathies," *International Journal of Molecular…*, 2021. mdpi.com
17. X. Zhang, C. Shen, H. Zhang, Y. Kang, "Advancing ligand docking through deep learning: challenges and prospects in virtual screening," *Accounts of Chemical Research*, vol. 2024, ACS Publications. [HTML]
18. C. Yang, E. A. Chen, and Y. Zhang, "Protein–ligand docking in the machine-learning era," Molecules, 2022. mdpi.com
19. F. Stanzione, I. Giangreco, and J. C. Cole, "Use of molecular docking computational tools in drug discovery," Progress in medicinal chemistry, 2021. [HTML]
20. X. He, S. Liu, T. S. Lee, B. Ji et al., "Fast, Accurate, and Reliable Protocols for Routine Calculations of Protein–Ligand Binding Affinities in Drug Design Projects Using AMBER GPU-TI with ff14SB/GAFF," 2020. ncbi.nlm.nih.gov
21. J. Oláh, T. Szénási, A. Lehotzky, V. Norris et al., "Challenges in Discovering Drugs That Target the Protein–Protein Interactions of Disordered Proteins," 2022. ncbi.nlm.nih.gov
22. H. Yao, J. Liu, M. Xu, J. Ji, Q. Dai, and Z. You, "Discussion on molecular dynamics (MD) simulations of the asphalt materials," *Advances in Colloid and Interface Science*, vol. 2022, Elsevier. sciencedirect.com
23. Q. Mao, M. Feng, X. Z. Jiang, Y. Ren, and K. H. Luo, "Classical and reactive molecular dynamics: Principles and applications in combustion and energy systems," *Progress in Energy and Combustion Science*, vol. 2023, Elsevier. sciencedirect.com
24. A. K. Padhi, S. L. Rath, and T. Tripathi, "Accelerating COVID-19 research using molecular dynamics simulation," The Journal of Physical Chemistry, vol. XX, no. YY, pp. ZZ-ZZ, 2021. researchgate.net

25. M. Berrera, "Molecular Simulation Approaches to Proteins Structure and Dynamics and to Ligand Design," 2006. [PDF]
26. J. Manuel Perez Aguilar, "Computational Protein Design and Molecular Dynamics Simulations: A Study of Membrane Proteins, Small Peptides and Molecular Systems," 2012. [PDF]
27. E. Ann Hicks, "Molecular Simulation For Neurodegenerative Diseases: From Modelling Alpha-Synuclein In Aqueous Solutions To Drug Delivery Systems," 2013. [PDF]
28. C. M., B. V., P. G., D. A. V. I. D. SASAH STAID et al., "Bioinformatics analysis of Ras homologue enriched in the striatum, a potential target for Huntington's disease therapy," 2019. [PDF]
29. C. Marelli and F. Maschat, "The P42 peptide and Peptide-based therapies for Huntington's disease," 2016. ncbi.nlm.nih.gov
30. M. Feig, G. Nawrocki, I. Yu, P. Wang et al., "Challenges and opportunities in connecting simulations with experiments via molecular dynamics of cellular environments," 2018. ncbi.nlm.nih.gov
31. T. Yang, S. Zhou, S. Fang, W. Qin et al., "Nonlinear vibration energy harvesting and vibration suppression technologies: Designs, analysis, and applications," Applied Physics Reviews, 2021. [HTML]
32. U. Ali, M. H. Shamsi, C. Hoare, E. Mangina, "Review of urban building energy modeling (UBEM) approaches, methods and tools using qualitative and quantitative analysis," *Energy and Buildings*, vol. 254, pp. 111-123, 2021. sciencedirect.com
33. E. Martins Ratamero, D. Bellini, C. G. Dowson, and R. A. Römer, "Touching proteins with virtual bare hands: Visualizing protein–drug complexes and their dynamics in self-made virtual reality using gaming hardware," 2018. ncbi.nlm.nih.gov
34. E. Martins Ratamero, D. Bellini, C. G. Dowson, and R. A. Roemer, "Touching proteins with virtual bare hands: how to visualize protein-drug complexes and their dynamics in virtual reality," 2017. [PDF]
35. D. W. Borhani and D. E. Shaw, "The future of molecular dynamics simulations in drug discovery," 2012. ncbi.nlm.nih.gov
36. G. Chen, L. Tao, and Z. Li, "Recent advancements in mass spectrometry for higher order structure characterization of protein therapeutics," Drug Discovery Today, 2022. [HTML]
37. J. Li, G. Kang, J. Wang, H. Yuan, Y. Wu, and S. Meng, "Affinity maturation of antibody fragments: A review encompassing the development from random approaches to computational rational optimization," *International Journal of …*, vol. 2023, Elsevier. sciencedirect.com
38. K. F. Zhu, C. Yuan, Y. M. Du, K. L. Sun, X. K. Zhang, "Applications and prospects of cryo-EM in drug discovery," Military Medical, vol. 2023, Springer. springer.com
39. Y. Li, Z. Fan, J. Rao, Z. Chen et al., "An overview of recent advances and challenges in predicting compound-protein interaction (CPI)," Medical Review, 2023. degruyter.com
40. Y. Lai, X. Chu, L. Di, W. Gao, Y. Guo, X. Liu, and C. Lu, "Recent advances in the translation of drug metabolism and pharmacokinetics science for drug discovery and development," *Pharmaceutica Sinica B*, vol. 12, no. 3, pp. 1234-1245, 2022. sciencedirect.com

41. A. Mehra, A. Mittal, and P. K. Vishwakarma, "Prediction of Protein-Drug Interactions, Pharmacophore Modeling, and Toxicokinetics of Novel Leads for Type 2 Diabetes Treatment," Current Drug Metabolism, 2024. [HTML]

42. S. Sinha, B. Tam, and S. M. Wang, "Applications of molecular dynamics simulation in protein study," Membranes, 2022. mdpi.com

43. F. Sohraby and H. Aryapour, "Rational drug repurposing for cancer by inclusion of the unbiased molecular dynamics simulation in the structure-based virtual screening approach: Challenges and …," Seminars in Cancer Biology, 2021. [HTML]

44. M. Kumar, M. K. Tripathi, and P. Kaur, "Molecular Dynamics and Its Significance in Drug Discovery," Structure-Based Drug Design, 2024. [HTML]