Molecular Docking Improved With Human Spatial Perception Using Virtual Reality

Shivam Mishra, Missael Corro-Flores, David Krum, Negin Forouzesh

Abstract—Adaptive steered molecular dynamics (ASMD) is a computational biophysics method in which an external force is applied to a selected set of atoms or a specific reaction coordinate to induce a particular molecular motion. Virtual reality (VR) based methods for protein-ligand docking are beneficial for visualizing on-the-fly interactive molecular dynamics and performing promising docking trajectories. In this paper, we propose a novel method to guide ASMD with optimal trajectories collected from human experiences using interactive molecular dynamics in virtual reality (iMD-VR). We also explain the benefits of using VR as a tool for expediting the process of ligand binding, outlining an experimental protocol that enables iMD-VR users to guide Amprenavir into and out of the binding pockets of HIV-1 protease and recreate their respective crystallographic binding poses within 5 minutes. Later, we discuss our analysis of the results from iMD-VR-assisted ASMD simulation and assess its performance compared to a standard ASMD simulation. From the accuracy point of view, our proposed method calculates higher Potential Mean Force (PMF) values consistently relative to a standard ASMD simulation with an almost twofold increase in all the experiments. Finally, we describe the novelty of the research and discuss results showcasing a faster and more effective convergence of the ligand to the protein's binding site as compared to a standard molecular dynamics simulation, proving the effectiveness of VR in the field of drug discovery. Future work includes the development of an artificial intelligence algorithm capable of predicting optimal binding trajectories for many protein-ligand pairs, as well as the required force needed to steer the ligand to follow the said trajectory.

Index Terms—Molecular Dynamics Simulation, Molecular Docking, Virtual Reality.

1 Introduction

Protein-ligand interactions play a fundamental role in drug discovery, structural biology, and molecular pharmacology [19]. Understanding the binding mechanisms between proteins and ligands is of paramount importance for the design of novel therapeutic agents and the optimization of existing drugs [8]. Over the years, computational techniques have emerged as powerful tools for probing these intricate interactions, offering valuable insights into binding affinity, kinetics, and structural stability [12]. Molecular dynamics (MD) simulations [26] have been at the forefront of computational approaches for the study of protein-ligand interactions, providing atomistic-level insights into the dynamic behavior of these complexes. While conventional MD simulations offer a detailed view of protein-ligand systems, they often struggle to capture rare and biologically significant events, such as ligand binding and unbinding, due to the inherent time scale limitations of MD [24].

In recent years, Adaptive Steered Molecular Dynamics (ASMD) [22] has emerged as a transformative approach to address the challenges associated with rare event sampling in protein-ligand docking studies. ASMD combines the principles of Steered Molecular Dynamics (SMD) with adaptive sampling techniques to systematically guide ligands into binding sites, enhancing the exploration of binding pathways and affording a more comprehensive understanding of the binding process. While this approach represents a significant breakthrough, it does carry limitations inherited from conventional MD. These include computational intensity, convergence difficulties arising from random initialization, and the demand for a high level of expertise due to sensitivity to simulation parameters.

Human perception, intuition, creativity, and expertise are crucial in computer-aided drug discovery and design (CADD) [1, 7]. The display of 3D structures of intricate molecules enhances human cognition, as the human mind has naturally evolved to comprehend and interact with 3D spaces. This capability allows researchers to interact with and manipulate objects within such environments, thereby expediting the drug discovery and design process. Virtual reality (VR) can thus serve as a platform for real-time visualization of complex biomolecular structures and their dynamic behavior in a 3D format. By incorporating interactive elements, such as 3DOF controllers and direct manipulation, VR facilitates user engagement, enabling real-time modifications of structures and the steering of simulations toward solutions that are perceptible to humans [27]. In the process of protein-ligand docking, the naturalistic interactions possible in VR can help empower users to concentrate on optimal trajectories and initialization points within the simulations. Thus, the use of interactive molecular dynamics in virtual reality (iMD-VR) [10] can help overcome the inherent drawbacks of ASMD. In this paper, we introduce a novel experimental protocol that leverages iMD-VR based protein-ligand docking experiences to facilitate more rapid convergence in ASMD simulations with enhanced docking outcomes.

2 Related Work

Human perception, intuition, creativity, and expertise are central to CADD. However, many CADD applications that involve molecular models provide 2D interfaces using traditional monitors to display structures or simulations of 3D biomolecules and traditional controls, such as a mouse, for modification of structures. Such interfaces make it difficult to fully utilize human skills for understanding, manipulating, and solving 3D problems.

The human mind has evolved to visualize and understand 3D space and to interact with and manipulate objects within that 3D space [7]. VR provides a platform for 3D visualization of complex biomolecular structures and their dynamics. With the addition of interactivity via using human hands and fine motor control to manipulate objects directly, VR provides ways to interact, such as modifying structures "on the fly" (e.g., chemical changes) or directing simulations toward a solution visible to a human [7]. Interactive VR provides a variety of affordances that enable humans to focus on the areas of the drug discovery process that benefit from human knowledge and perception, e.g., chemical intuition, visualizing chirality, predicting how proteins and ligands fit together, the effects of a conformational change, or determining which alterations to the chemical structure might improve affinity or specificity. These benefits have significant potential to accelerate drug

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Manuscript received xx xxx. 201x; accepted xx xxx. 201x. Date of Publication xx xxx. 201x; date of current version xx xxx. 201x. For information on obtaining reprints of this article, please send e-mail to: reprints@ieee.org. Digital Object Identifier: xx.xxxx/TVCG.201x.xxxxxxx

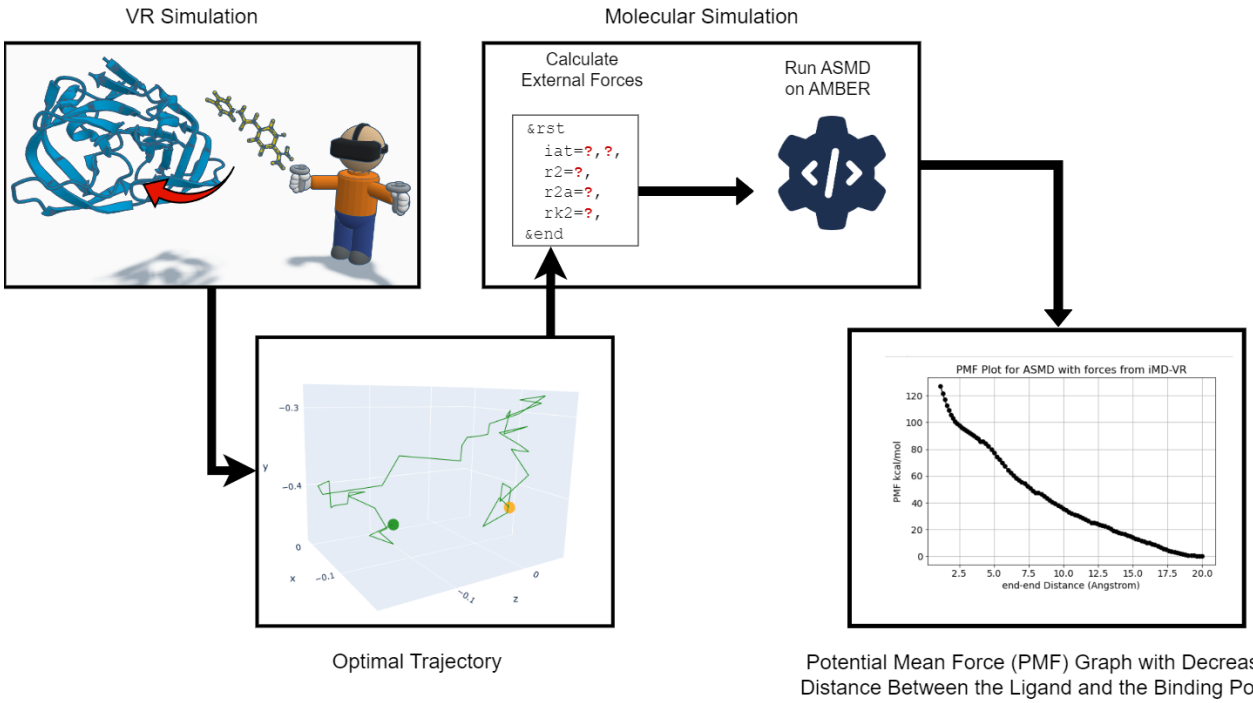


Fig. 1: Stage-wise representation of the i-MDVR Pipeline. (I) Running iMD-VR simulations on Narupa for protein-ligand docking. (II) Obtaining the optimal binding trajectory and forces from iMD-VR. (III) Calculating the Jarzynski constant to run an ASMD simulation. (IV) Analysis of results indicating the effectiveness of iMD-VR in expediting the MD process.

design and development [27].

With the recent advancements in computer technology, such as low cost, high resolution, fast refresh screens, fast GPUs, high-level 3D graphics engines, etc. [7], VR is not just viewed as a source of entertainment but as a technology capable of widespread scientific use. Some examples of using VR in science and engineering for 3D visualization are virtual restoration of archaeological finds [25], viewing the sea bed [15], virtual exploration and cartography [16], safety training in chemical manufacturing [23], sport psychology [2], telepresence for clinicians, teaching anatomy [9], among others. However, even though VR is impacting a variety of other research domains, it is still a new and emerging tool in the molecular science domains. While research has been limited, there have been promising applications, such as investigating the molecular structures related to the SARS-CoV-2 virus [4].

The potential of VR in drug discovery is now beginning to be realized. VR offers several benefits over traditional molecular visualization tools and over traditional interfaces for interacting with biomolecular simulations and molecular modeling. First, VR allows the researcher to visualize drug molecules and their macromolecular targets in full stereoscopic 3D, which allows more detailed perception and deeper understanding of these complex systems and can inform the design and modification of ligands in the process of structure-based design and development [14, 29]. Second, VR allows interaction with molecules, primarily through VR controllers. The controllers can be thought of as a "virtual pair of hands," allowing the user to grasp parts of a molecule or molecules as easily as if they were tangible, real-world objects. Third, recent developments of interactive VR permit users to interact with a real-time MD simulation at the atomic level [20], allowing users to manipulate the molecular system, modifying its structure and interactions "on the fly". In other words, modern VR technology (hardware and software) is not merely an update with better graphics. This ability to manipulate molecules and modify molecular structures under simulation, together with the ability for multiple users to simultaneously collaborate [10], transforms VR from a visualization method to a scientific research tool.

3 Materials and Methods

Figure 1 demonstrates the novel computational pipeline introduced in this paper. In this section, each step of the pipeline is explained in detail.

3.1 Molecular System

HIV-1 protease is a viral aspartyl protease essential to the life cycle of HIV, responsible for cleaving precursor polypeptides into functional proteins, making it an attractive drug target for preventing HIV maturation. Structurally, HIV-1 protease is a homodimer that shares a single active site between two protein subunits, each of which contributes a catalytic aspartic acid [3]. Sulfonamides are a class of drugs licensed for the treatment of HIV that hydrogen bond to the catalytic aspartic residues and thus block protease activity, an example of which is Amprenavir [13]. The HIV-1 protease active site is gated by two beta-hairpin flaps that shift through a series of different conformational states before ligand binding [17].

Unbinding Amprenavir from HIV-1 protease necessitates shifting the two beta-hairpin flaps to an open stance in order to direct Amprenavir outward. Afterward, the flaps must be meticulously returned to their original position without altering their secondary structure. Given the movement of these flaps and the rotational adaptability of Amprenavir, this binding activity is notably demanding from an iMD-VR viewpoint as the user would have to perform several steps such as opening and closing the flaps, to dock, undock the ligand, and place the ligand in the correct conformation which makes this protein-ligand pair a good candidate for testing the abilities of VR [7].

3.2 VR Simulation

The processes of binding and unbinding can be showcased to users through an interactive molecular simulation using Narupa, a VR application that displays molecular models and runs molecular dynamics simulations in an interactive manner. [10]. Users can manipulate Amprenavir as well as the HIV-1 protease, including the flaps, to examine and drive the binding and unbinding processes. Narupa is a flexible, open-source, multi-user iMD-VR software framework that enables mul-

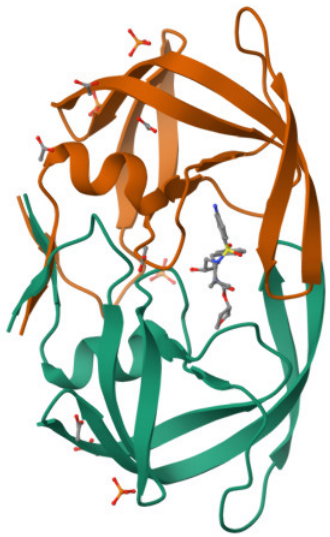


Fig. 2: Amprenavir (small gray compound) docked inside the HIV-1 Protease binding pocket. The virus flaps are shown in brown and green.

tiple researchers to simultaneously cohabit with real-time simulation environments to interactively visualize and manipulate the dynamics of molecular structures with atomic-level precision in ways that were previously unimaginable. Narupa can load PDB files to visualize molecular structures in the VR environment. The parameters of the virtual reality visualization and simulation are characterized by .XML and .json files. It is written using the Unity game engine and supports both desktop and VR displays. Since it is a networked multi-user application, multiple clients (both desktop and VR) can view and interact with the simulation simultaneously. Narupa relies on AMBER [6], a package of molecular simulation programs, to perform real-time MD simulations. We used different modules and tools within AMBER to set up, run, and post-process the simulation.

Three PC-based VR systems were utilized to run the Narupa and AMBER software and conduct the docking and undocking experiments. Two of the PCs were equipped with an Intel i7-10700 CPU with 8 cores, 16GB of RAM, and an NVIDIA Quadro RTC 4000 graphics card with 8GB of GPU memory. Two HTC Vive Pro Eye headsets were used, each wired to one of the PCs, providing a 110° field of view, with 1440x1600 pixels per eye and up to a 90 Hz refresh rate. A VR Ready gaming laptop, equipped with a six-core Intel i7-10750 CPU and 32GB of RAM, was used with an HTC Vive headset. Users manipulated the molecular structures and navigated the virtual scene using the two standard Vive controllers.

3.3 Molecular Simulation

Particle Mesh Ewald (PME) Molecular Dynamics and Adaptive Steered Molecular Dynamics (ASMD) are two popular approaches used in molecular dynamics simulations for studying the behavior of molecules and materials at the atomic and molecular level. PMEMD is commonly used for simulating electrostatic interactions in large molecular systems and has accuracy in handling long-range electrostatic forces. ASMD is used for studying the dynamic behavior and response of a molecular system under the influence of external forces, which allows for efficient exploration of energy landscapes and the determination of pathways. ASMD can provide insights into rare events and transitions as it adapts the applied forces to guide the system along a desired reaction coordinate, which makes it particularly useful for studying processes such as ligand binding, conformational changes, and other rare events in molecular systems. A variety of steps are required for setting up parameters for the MD simulation. These steps are described below.

3.3.1 System Parametrization

For performing iMD-VR runs, the protein was parameterized with the AMBER ff14SB force field [18]. Amprenavir was parameterized with GAFF [28] using antechamber. The systems used the GB-OBC2 implicit water model [21]. All systems were energy minimized before being used as the starting coordinates for each bound complex. All iMD-VR simulations were run at 300 K with a timestep of 0.5 femtoseconds (fs). When interacting with atoms, we utilized a Gaussian force, where the amount of force applied depends on the distance between the user's controller and the atom they were selecting. Once users stopped interacting with a selection, the velocities of all atoms in that selection were reinitialized according to a Boltzmann distribution based on the temperature in order to prevent any remaining interaction energy in molecules from propelling them past where the user intends to place them. An 800 kJ/mol/nm2 was applied to all backbone atoms in HIV-1 protease, excluding those that make up the flaps that gate the active site (defined as residues 49 to 55 in chain A and residues 48 to 54 in chain B). A separate force was applied to the HIV-1 flap backbone atoms. The software default value of 2000 kJ/mol/nm2 force constant was used for these restraints. A higher force constant is used compared to the backbone restraints due to their interactive nature. When a user wishes atoms to be held in place, it is expected that they want to be held in place firmly [7].

Binding small molecules to HIV-1 protease requires a significant shift in the backbone atom positions, altering the structure from closed to open. During the simulation, aside from the active site beta-hairpin flaps, which were manipulated by the user during the simulation, the protein backbone atoms were held by backbone restraints. The users were asked to unbind and rebind Amprenavir. All backbone atoms in the protein were positionally restrained. The users were required to open and close the HIV-1 protease flaps to bind Amprenavir in the correct conformation to the binding site of HIV-1 protease using the Vive controllers in iMD-VR.

3.3.2 Energy Minimization

The minimization is performed in two parts: First, minimization of the waters and then minimization of the entire system. We minimized the potential energy of the system using the steepest descent and conjugate gradient algorithms. We performed 20 ps of minimization with restraints on all solute atoms. Equilibration is followed by heating, in which the system is heated from 100 K to 300 K incrementally.

3.3.3 Equilibration

We equilibrated the system at constant temperature and pressure using the Langevin thermostat and Berendsen barostat. We performed 100 ps of equilibration with harmonic restraints on all solute atoms and 100 ps of equilibration without any restraints.

3.3.4 Production Run With PMEMD

We performed a production run of the system for 200 ns without any restraints. We used periodic boundary conditions, the SHAKE algorithm, the Langevin thermostat, the Berendsen barostat, the Particle Mesh Ewald method, and a time step of 2 fs during the simulation [5]. We saved coordinates every 1000 steps for analysis. After completing the equilibration, we performed ASMD simulations on the protein-ligand pair.

3.3.5 Adaptive Steered Molecular Dynamics

ASMD is an enhanced sampling method utilized within the AMBER molecular dynamics software suite. Unlike traditional MD, which simply allows a system to evolve over time according to Newton's equations of motion, ASMD applies a biasing force to drive a system along certain reaction coordinates or pathways. The "adaptive" aspect comes from the method's ability to adjust the magnitude of the steering force based on the instantaneous velocity of the system along the reaction coordinate. We performed an ASMD run of the system for 200 nanoseconds (ns) without any restraints over five stages. The Jarzynski's force constant was set to 9.7, pushing atom number 3159, a nitrogen atom, from the ligand to atom number 439, a carbon atom

located in the protein's binding site in five stages, minimizing the distance between them from 20 Å to 1 Å in equal intervals. We saved coordinates every 1000 steps for analysis.

3.3.6 iMD-VR Assisted ASMD

The primary objective of this research project is to establish an iMD-VR-assisted pipeline capable of producing the optimal external force constant necessary for guiding the ligand to its docking site. The pipeline is facilitated by using the data acquired from the interactive docking-undocking MD simulations in the VR environment of Narupa. The calculated force constant is then given as an input to steer the ligand toward the binding pocket during AMBER's ASMD simulations.

Force calculation. The 3D force vectors exerted by the user on the atoms of the ligand in the system obtained from iMD-VR are added taking their Cosine, Sine and Tangent components of the force vector to calculate the overall effective force on the ligand using $F_x + F_y + F_z$, the magnitude of the resultant effective force is then calculated using the formula $\sqrt{Fx^2 + Fy^2 + Fz^2}$. In our computational workflow, this calculated magnitude serves a specific purpose. It is designated as the input value for Jarzynski's force [11] constant within the AMBER ASMD framework. By setting Jarzynski's force constant to this computed value, we initiate a series of manipulations within the system.

Our manipulation entails the sequential displacement of atom number 3159, identified as a Nitrogen atom within the ligand, towards atom number 439, a Carbon atom situated within the protein's binding site. This displacement is executed in a controlled manner, employing five distinct stages. The objective in each stage is to gradually reduce the distance between these two atoms, initially starting at a separation of 20Å and progressively approaching a final distance of 1Å. This incremental reduction in distance is achieved through equal intervals. As this manipulation occurs, we judiciously record the coordinates of the system at regular intervals, specifically every 1000 steps, in order to facilitate subsequent analysis and evaluation. These recorded coordinates provide crucial data for our ongoing investigation.

4 Informal User Evaluation

We conducted an informal user evaluation to examine the ability of MD users to interact with a molecular simulation in VR. The interaction consisted of a task in which the users must dock and undock Amprenavir from the binding pocket of HIV-1. While the HIV-1/Amprenavir system is well-known and well-studied, it provides a useful test case for exploring the potential of VR for incorporating human creativity and problem-solving to understand drug interactions and design new treatments. This experimental interaction provides an opportunity to examine the usability of VR-based MD simulations. It also allows the collection of docking and undocking trajectories generated by experts in MD. Thus, this experimental interaction also provided an opportunity to evaluate the feasibility of collecting and using such data to help train machine learning algorithms with greater insight into molecular interactions.

4.1 Participants

As a part of an NSF-funded workshop, a total of 30 people participated in the informal user evaluation (15 female, 15 male). The user evaluation was one of several activities for participants in the workshop. Demographic data was collected as part of participation in the workshop. The participants were between the age of 20-23, among which 3 had little or no experience playing 3D video games, and 5 reported that they were either experienced or very experienced. They were recruited from undergraduate biochemistry, physics, and biology programs and were offered a stipend for participating in the workshop. Participants were required to have a foundational understanding of protein-ligand docking and protein structure, normal or corrected-to-normal vision, and be able to communicate comfortably in spoken and written English.

Workshop participants first read an instruction sheet describing the workshop activities in detail. After being given an opportunity to ask questions, verbal consent to participate in the workshop was provided. After completing the pre-questionnaires, the workshop participants were divided into three cohorts of 10 each. Each cohort participated in the user evaluation. Each cohort was divided into 3 smaller groups of 3-4 members, and each group was then assigned to one of the three available VR systems where one member of each group operated the VR while the other group members guided them by watching the computer screen mirroring the point of view of the participant in the VR. The binding and unbinding task was explained to each group, and each group member was fitted with the head-mounted display in turn. Over a 30-minute period, each group of 3-4 participants had the opportunity to perform the docking and undocking tasks.

Participants were given a short training session where they practiced walking around an example virtual environment for approximately two minutes. When the participants were ready to continue, the experiment tasks were explained, and they were given an opportunity to ask questions. Then, the virtual environment was loaded. Participants explored the environment by rotating and zooming in and out of the protein and ligand structure. Participants learned how to manipulate the ligand and the flaps surrounding the binding site. It took approximately two minutes to explore and learn to interact with the environment. After the participant undocked and re-docked the ligand with the docking site, the session was concluded for that participant.

4.2 Tasks

4.2.1 Task 1: Exploring the Molecular Environment

Each workshop participant was asked to explore the virtual environment. First, they were instructed to explore the structure of the protein as well as the ligand in the virtual environment and to become familiar with the binding site by rotating, zooming in and out of the molecule, and observing it from all the possible directions. A separate monitor displayed the participant's point of view, which helped the investigators in guiding the participants and providing more details based on their perception of the molecular system.

4.2.2 Task 2: Ligand Undocking

In the second stage, the participants were asked to grab the ligand and unbind it by taking it out from the binding site. This required workshop participants to manipulate the beta-hairpin flaps guarding the binding site. This task requires iMD-VR users to move these flaps into an open position to grab and guide amprenavir out of the binding pocket of HIV-1 Protease and then carefully place the loops back without disrupting their secondary structure. This task, in particular, is a bit challenging because the iMD-VR user not only has to figure out the strategy to perform undocking of the ligand but also has to decide, based on their perception, how much force needs to be applied to open the flaps and how much force is needed to pull the ligand out of the binding pocket. Too little force will prove ineffective whereas too much force if applied, can result in deformation or even breaking of bonds in the molecular structures.

4.2.3 Task 3: Ligand Re-Docking

In the final stage, the workshop participants were asked to re-bind the ligand back to the binding pocket. This again required manipulation of the beta-hairpin flaps with the VR controllers and applying force to the ligand to return it to the binding site in a conformation as similar as possible to the original docked position. This task was reported to be comparatively easier than the un-docking task as the iMD-VR user had developed a basic working understanding of the system, but it was still challenging because the user had to decide the most optimal binding trajectory, and the necessary force required to be exerted on the ligand to carefully move it back to the binding site while painting the molecular structure of both, the ligand and the protein. Figure 3 shows a workshop participant performing the above tasks.

4.3 Task outputs

During the time the participant was in the virtual environment, the system logged information such as 3D coordinates of each atom in the system, velocity vectors, overall effective force on each atom, and overall potential energy of the system was recorded in Narupa's logs. The participants also completed a questionnaire to provide feedback about their experiences in the virtual environment and its effectiveness

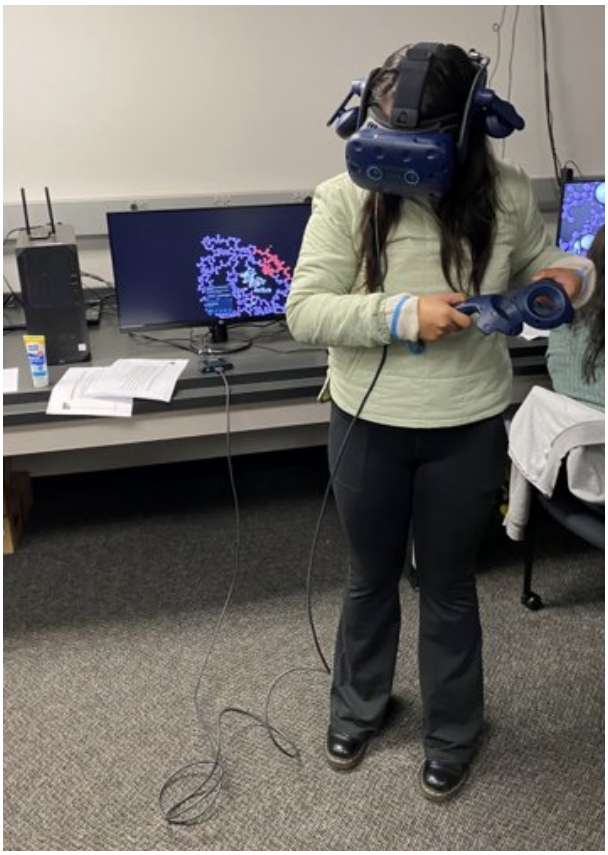


Fig. 3: A participant performing the ligand docking-undocking task in Narupa using an HTC Vive Pro Eye headset.

and ease of use as compared to traditional MD software. The participants were then asked to perform a high-level analysis of information gathered in the logs of their iMD-VR session so that they could go through the physical parameters such as the forces they exerted and the positional changes they made to the atoms in the system thereby demonstrating that iMD-VR is not only efficient as a graphical tool but also has great practical applications in the field of MD analysis.

5 Results And Discussion

In the informal user evaluation, the participants, even without prior knowledge about the binding site of HIV-1 Protease, could easily identify the optimal binding trajectory, typically within a few minutes, thereby enabling the ligand to bind to the designated binding pocket effectively. The trajectory data that were subsequently procured from this process were then used to facilitate the extraction of forces necessary for integration with AMBER ASMD simulations.

Considering the computational time needed to run a PMEMD simulation can be upwards of 8 hours, whereas an ASMD simulation can be completed within 3 hours, which makes ASMD a good candidate for incorporating the human touch via IMD-VR. In the iMD-VR-assisted ASMD simulation, the time required for the ligand to bind to the protein was remarkably short, specifically only 200 picoseconds (ps). This observation suggests a significant advantage in efficiency compared to conventional PMEMD production runs. In this approach, AMBER is spared from the need to spend time extensively sampling molecular space to explore all potential binding paths and select the most optimal one. In contrast, a standard PMEMD production run takes approximately 20 nanoseconds (ns) to accomplish the same sampling and docking processes. In essence, the iMD-VR-assisted ASMD approach proves to be about 100 times faster than the conventional method, presenting a notable improvement in simulation speed and resource allocation.

In comparison to a standard ASMD simulation, the empirical value of Potential Mean Force (PMF) was observed to exhibit oscillations within the range of 120 to 150 kcal/mol in iMD-VR-assisted ASMD simulations. PMF serves as a valuable indicator, offering insights into the free energy landscape of a molecular system. It aids in comprehending the energetics and stability of different states or configurations. This observation specifically pertains to situations where there is a decrease in the end-to-end distance between the ligand and the binding pocket of the protein. Contrasting these findings recorded in the standard ASMD simulations where the PMF values are in the range of 50 Kcal/mol, which reveals a notable difference. The details and visual representations of these comparisons can be found in Figure 6. Essentially, the iMD-VR assisted ASMD simulations provide a nuanced understanding of the molecular system's free energy landscape through the analysis of PMF values.

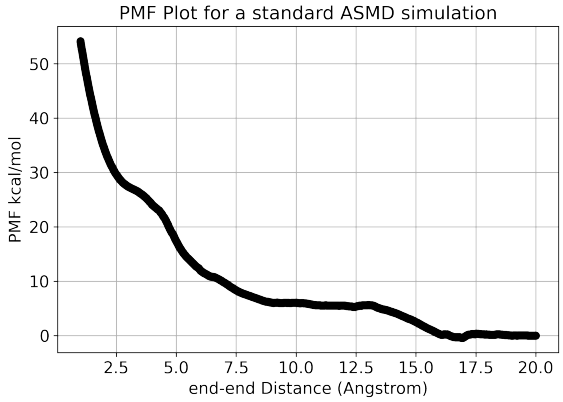
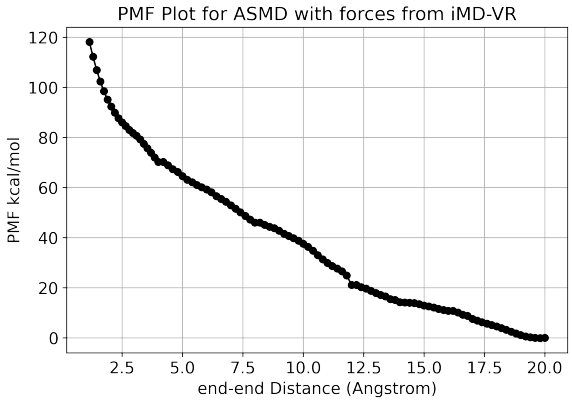


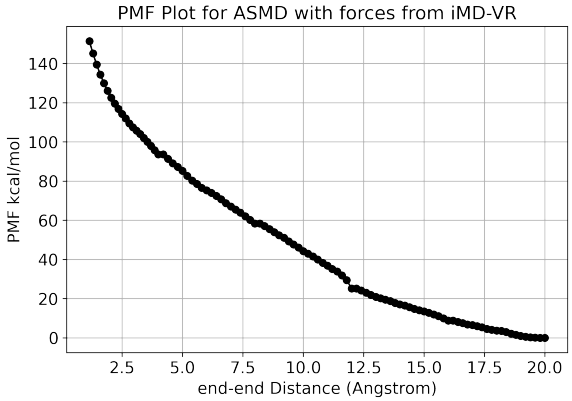
Fig. 4: Schematic of a Potential Mean of Force obtained from the ASMD simulation on the HIV-1 Protease and Amprenavir without i-MDVR component.

A side-by-side comparison of the mean curve of the three graphs presented in Figures 5 and the graph in 4 demonstrates several noteworthy observations: Figure 4, derived from a standard ASMD simulation, provides a baseline for our understanding of the molecular interactions in a typical environment. Figure 5, intriguingly, draws its force data from trajectories recorded during the VR interactions using human visual perception, introducing an innovative approach to the simulation. Upon closer inspection, the PMF values in the VR-informed graph are consistently higher across a range of end-to-end distances. This elevation in PMF is indicative of a stronger, more robust binding affinity in the molecular system under study.

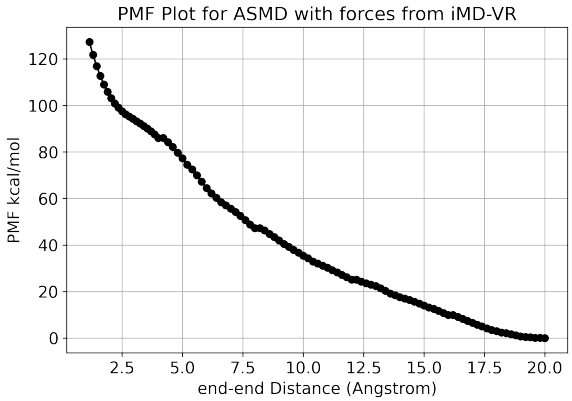
Figure 6 presents comparative analysis of PMF values calculated with a standard ASMD simulation and the mean cure obtained from the three iMD-VR assisted simulations shown in Figure 5. The PMF values associated with the iMD-VR mean curve exhibit a noteworthy increase of more than twofold in comparison to the simple ASMD PMF values. This observation signifies a heightened and robust binding, underscoring the enhanced efficacy of the iMD-VR assisted simulations. Concurrently, the standard deviation of the curve underscores the consistent uniformity of results across the three distinct iMD-VR assisted simulations. In essence, when the forces are sourced from the VR interactions, the system seems to exhibit tighter and more energetically favorable binding interactions. This stark contrast not only highlights the potential advantages of harnessing VR data in ASMD simulations but also opens up avenues for further research into how VR can provide enhanced insights into the intricate world of molecular dynamics.



(a) Schematic of a Potential Mean of Force obtained from a user in cohort 1 on the i-MDVR assisted ASMD simulation on the HIV-1 Protease and Amprenavir.



(b) Schematic of a Potential Mean of Force obtained from a user in cohort 2 on the i-MDVR assisted ASMD simulation on the HIV-1 Protease and Amprenavir.



(c) Schematic of a Potential Mean of Force obtained from a user in cohort 3 on the i-MDVR assisted ASMD simulation on the HIV-1 Protease and Amprenavir.

Fig. 5: Graphs showing the PMF landscape fo iMD-VR assisted ASMD simulations where forces were taken from a participant from each of the three cohorts running iMD-VR

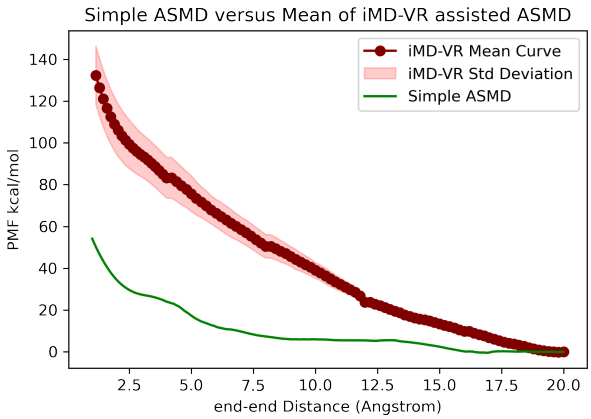


Fig. 6: Comparative Analysis of PMF: The green curve represents the outcomes of a singular ASMD simulation, along with the blue curve that illustrates the mean of three ASMD simulations utilizing forces derived from IMD-VR, while also highlighting the standard deviation across the three iMD-VR simulations.

6 Conclusion

In this paper, we discussed a procedure designed to evaluate the use of VR for MD simulation. The procedure also allows evaluation of the feasibility of collecting molecular trajectories determined interactively by users with the end goal of expediting the process of running MD simulations with human insights. This paper also outlined an experimental protocol for setting up an iMD-VR simulation for the purposes of interactively manipulating a protein-ligand system to obtain the optimal binding trajectory. Utilizing this protocol, we have carried out calculations to derive an optimal force constant for running an ASMD simulation on AMBER. The iMD-VR strategy enables this process to be accelerated compared to the much larger timescales required in unbiased MD simulations, proving iMD-VR is a time-efficient strategy for interactively sampling the unbinding and rebinding of ligands from proteins. We also assessed the extent to which iMD-VR is compatible and helpful with the current state-of-the-art MD tools and software packages. Our results show that in the iMD-VR assisted MD simulation, the ligand was able to reach the binding site in 200 ps (simulation time) as compared to a standard PMEMD simulation where the ligand took 20 ns (simulation time) to dock. This entire protocol enables the users to include an open-source, easy-to-use, and effective tool as a part of the initial step of MD analysis.

From the accuracy point of view, our proposed method calculates higher PMF values consistently relative to a standard ASMD simulation. The mean cure obtained from our novel iMD-VR assisted ASMD simulations, which could be a representative of the multiple simulation executed by different users/cohorts, shows more than twofold increase in estimating PMF values compared to a simple ASMD.

In future work, we intend to carry out more detailed studies on more protein-ligand pairs and develop an artificial intelligence algorithm from the data collected from the iMD-VR sessions to predict the best docking trajectory for a ligand and also to predict the forces needed to recreate that trajectory in an MD simulation. Finally, a more comprehensive study of the iMD-VR assisted ASMD, including the analysis of the ligand's binding modes, conformational flexibility, and configurational entropy, is another future direction that we will pursue in the future.

Acknowledgments

The authors wish to thank Dikshant Sagar, Isabella Apuya Perez, and Deepanker Seth for their assistance in running simulations. This research has been partially funded by NSF 2216858 to N.F.

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