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# MolPlay: Democratizing Interactive Molecular Simulations and Analyses with a Portable, Turnkey Platform

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Interactive molecular simulations, visual analysis, molecular dynamics, molecular interactions, real-time simulations

Interactive molecular simulations and analyses (IMSA) hold immense potential for accelerating research and improving education, but are only used to a limited extent. This paper explores the possibilities of these powerful techniques and presents a taxonomy of common interactive modeling tasks, such as assembly, deformation, sampling of rare events, along with relevant use cases, especially for the study of membranes and membrane proteins. I introduce MolPlay – a bootable USB platform that provides a turnkey environment with a curated set of hands-on examples to democratize access to IMSA research tools. The portable, self-contained nature of MolPlay enables versatile deployment scenarios ranging from outreach to teaching in computer

labs to facilitating the distribution of research software. Initial tests at an international workshop have shown that MolPlay appeals to different target groups and lowers the access barriers to IMSA. By consolidating more than a decade of expertise into one accessible platform, MolPlay represents a significant step towards broader adoption of these underutilized but powerful computational techniques in education and research.

## Introduction

Studying the dynamics of membranes and membrane proteins at the molecular level is of central importance as it provides crucial insights into cell function, supports the development of new therapeutic strategies for membrane-associated diseases and contributes to advances in areas such as drug delivery and biomaterial design. Interactive molecular simulations and analyses (IMSA) are powerful computational techniques that allow researchers to visualize and manipulate digital representations of such molecular systems in real time<sup>1</sup>. Unlike conventional molecular simulations that run unsupervised, as batch processes, these interactive simulations allow for real-time interventions, the application of external forces, and on-the-fly adjustment of biophysical properties and parameters. Adapted visualization and visual analyses enrich such calculations with crucial information about the molecular systems and their response to the manipulations. These approaches bridge the gap between computational modeling and intuitive exploration by using the researchers' expertise and intuition to guide the simulation process. Through real-time visual and possibly sensory feedback, interactive simulations promote an intuitive understanding of complex molecular phenomena such as membrane incorporation, permeation and aggregation, supporting hypothesis generation and accelerating research. Furthermore, on the level of optimizing resource consumption, they offer the prospect of improved energy efficiency by allowing researchers to make more informed decisions, for

instance as a preliminary assessment before running computationally intensive molecular dynamics simulations with long time scales on supercomputers. By using IMSA in a preliminary stage of a study, scientists can explore different scenarios and refine their experimental design to ultimately select the most promising simulations for full-scale production runs thereby reducing unproductive runs.

Interactive molecular dynamics<sup>2</sup> is the most common variant of IMSA, in which the integration of forces resulting from the pairwise force field potential is supplemented by user forces. Such a simulation is coupled with a real-time visualization, possibly in three dimensions, for live monitoring and user intervention, and with a mechanism that enables user interaction, in the simplest case by a mouse or even more efficiently by a 3D input device. More in-depth background on interactive molecular dynamics is provided in a dedicated encyclopedia article <sup>3</sup>. Although this approach has been around for more than 20 years, its potential is still largely untapped and offers exciting opportunities for further research and innovation in various application areas. My conviction that further dissemination would enable significant new research is based on the extensive use of these approaches in research and teaching, see e.g. Ref. <sup>4</sup> and Ref. <sup>5</sup> as examples. The approach has long been limited by the extent of computation that could be performed in the amount of time a human operator is able to control such an experiment. Recent advances in computational power and optimized coarse-grained or multiscale molecular representations now provide researchers with a dynamic view on simulations of large biomolecular structures in interactive time, even with modest computational resources. A scientist can intervene and manipulate these models during IMSA calculations. This interactive approach offers new opportunities to understand biomolecular phenomena and develop valuable hypotheses for further experimental validation. IMSA remains a niche application that is not

widely known and the motivation for this manuscript and associated tools is to help its broader adoption.

To facilitate the wider dissemination of these techniques, I present a tool that lowers the technical and technological barriers to accessing this methodology. By enabling everyone to experiment with these approaches and explore a range of common use cases, I aim to accelerate the adoption of IMSA. These efforts are in line with another synergistic trend: the increasing availability of publicly accessible molecular simulation datasets through various repositories. Given the inherent potential of IMSA to visually explore simulation data interactively, this technology provides an opportunity to address the data dimension by visualizing and analyzing these shared datasets. MDverse had previously been introduced as a central search engine to access such datasets and enable their visualization and analysis<sup>6</sup>. Interesting recent examples illustrating the upsurge in simulation data exploration are the ABC consortium<sup>7</sup> and COVID-19<sup>8</sup>. With the ambition of extending the IMSA approach to include visual analysis and access to shared molecular simulation datasets in line with FAIR principles, I aim to leverage the visual experience associated with the raw data, unlocking significant potential to optimize the use of these resources<sup>9</sup>.

Here I present MolPlay - a bootable USB platform that provides a turnkey environment with a curated set of practical IMSA examples. MolPlay serves as a playground for users to experiment with different interactive simulation and analysis approaches, lowering the barrier to entry for this methodology. In the longer term, MolPlay aims to democratize access to IMSA techniques by bringing together a variety of use cases and tools in a portable, self-contained package. This accessible solution will enable researchers, educators and students alike to explore the potential of interactive simulations, foster innovation and accelerate the adoption of these computational

approaches across all areas of education and research domains. Notably, it offers guided access to a technology not yet widely adopted, while simultaneously providing rich educational and outreach opportunities. The initial prototype presented here focuses on making the user experience as smooth as possible, with multiple levels of guidance. MolPlay consolidates interactive simulations and analyses into one accessible platform, bridging the gap between technical complexity and expertise to foster broader adoption of these powerful yet underutilized computational approaches for different audiences. The examples discussed in this manuscript largely relate to my own research, as MolPlay was developed based on these examples. However, it is important to point out that many research groups have been active in this field, and a detailed account of their contributions can be found in Ref.<sup>1</sup>.

There have been similar projects with related names in the past, notably the Molecular Playground<sup>10</sup>, an earlier initiative that focused on engaging the public with the beauty of molecular structures through large-scale, interactive installations in physical spaces. In contrast, MolPlay takes a distinctly virtual approach. It serves as a self-contained, portable platform - a *virtual* molecular playground - for interactive molecular simulations and analyses. In terms of bootable operating systems, from the early 2000s, it was common to develop fully-fledged Linux environments with domain-specific software packages, e.g. for bioinformatics. A few such examples are BioconductorBuntu<sup>11</sup>, BioSMACK<sup>12</sup>, birgHPC<sup>13</sup>, DNALinux<sup>14</sup>, Open Discovery<sup>15</sup> and PhyLIS<sup>16</sup>. However, only a few of these projects have survived. MolPlay differs from these projects in that it does not attempt to provide a complete operating system and computing environment, but rather a focused entry point suitable for exploration by non-experts. Mola<sup>17</sup> is similar in spirit to MolPlay. It provided a user-friendly interface for performing virtual screening and molecule docking. Specifically designed for virtual screening tasks with AutoDock4<sup>18</sup> and

Vina<sup>19,20</sup>, Mola automated the processes of ligand preparation, task distribution and result analysis in a bootable Linux environment. It is no longer available. While the focus of these examples was clearly research-oriented, MolPlay, with its playful and interactive nature, naturally encompasses the dimensions of outreach and public engagement. Web-based resources could potentially provide an alternative approach in the future, offering excellent accessibility and platform independence. A prime example is the PhET Interactive Simulations project (<https://phet.colorado.edu/>), which provides numerous interactive online simulations for science and mathematics education. At present, however, web-based implementations can only make limited use of the processing power and hardware acceleration of local computers, which is a severe limitation in view of the scope and scale of the IMSA applications MolPlay is aiming for. Web technologies such as WebAssembly<sup>21</sup>, a binary instruction format, and WebGPU<sup>22</sup>, a low-level graphics API, aim to bridge this gap. An additional effort for such an implementation is that the scientific software stack would have to be ported to the web platform.

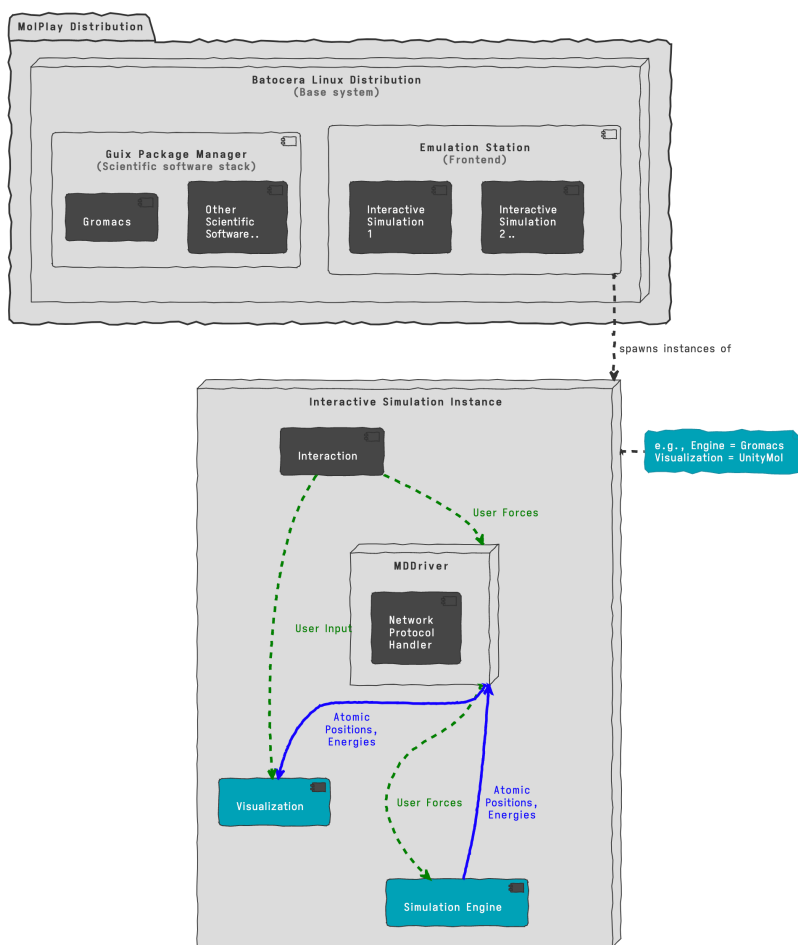
A key question I hope to answer through the wider application of MolPlay is whether the academic community is ready to adopt such an innovative tool and develop further relevant use cases that fully exploit the potential of these interactive simulation and analysis approaches.

## Methods and Computational Details

### **Basics of interactive molecular simulations and analyses**

Interactive Molecular Simulations and Analyses (IMSA) consist of three core components: simulation, visualization and interaction as illustrated schematically in Figure 1. These components are often combined in a specialized software framework to facilitate the exchange of atomic positions, forces and eventually energies or even certain properties between them. In the present work, I employ a network protocol that enables the distribution of tasks to appropriate

hardware resources. Specifically, I build on the MDDriver library, a middleware solution that facilitates the connection between simulation and visualization/interaction components<sup>23</sup>. It is derived from and compatible with the original IMD protocol by Stone and colleagues<sup>2</sup>, to which my team added some extensions for specific applications, without breaking backwards compatibility.



**Figure 1.** Schematic view of an interactive simulation with interaction, visualization and simulation components interconnected through the MDDriver network protocol. Such a simulation is spawned through the MolPlay distribution's menu system. The MolPlay software stack is



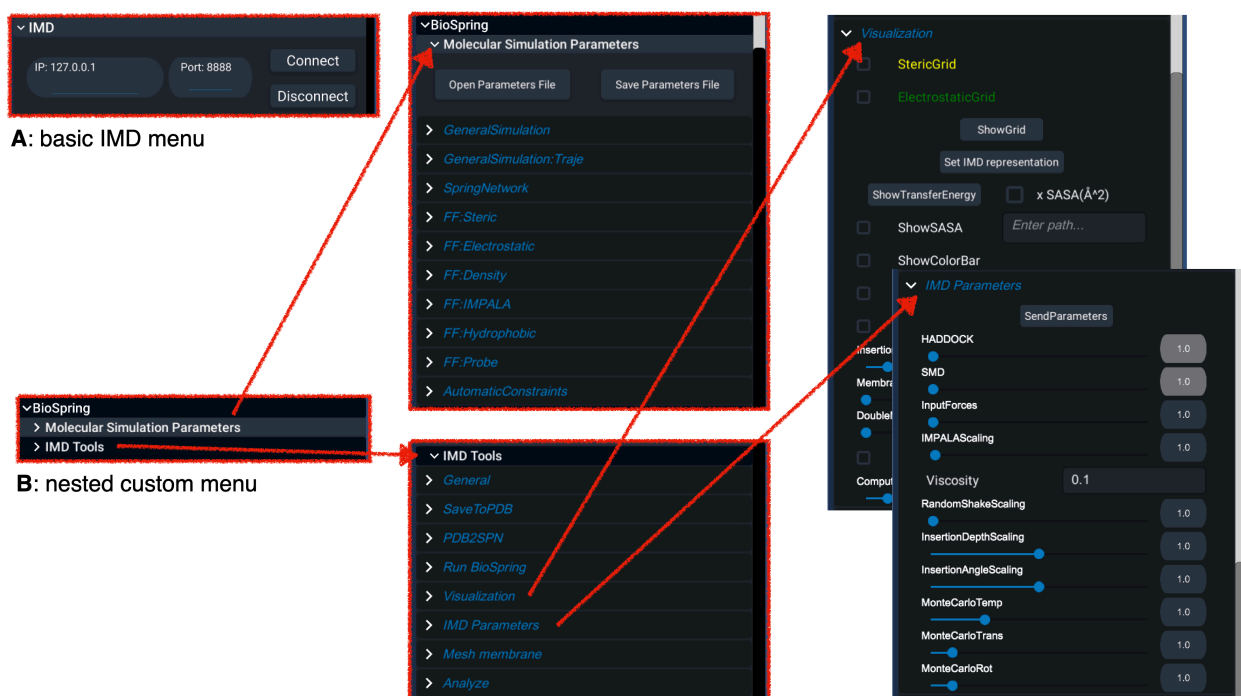
depicted, building on top of Batocera Linux and extended through the Guix package manager and the Emulation station frontend. Image under CC-BY License by Marc Baaden.

For visualization and interaction, I use UnityMol, a visualization prototyping software platform developed from the ground up to support interactive molecular simulations<sup>24</sup>. There is no limitation to add other visualization tools in the future. The computational engine is by design also interchangeable, allowing users to customize this module to their needs and preferences. For example, molecular dynamics (MD) simulations can be performed interactively with widely used packages such as NAMD<sup>25</sup>, LAMMPS<sup>26</sup>, HOOMD<sup>27</sup> or Gromacs<sup>28</sup>, ready to use. MDDriver simplifies the integration of such functions into any MD code, and even more generally into any particle-based simulation approach. For more specialized IMSA applications, my team has developed BioSpring<sup>29</sup>, which uses elastic network models that can be extended with non-bonded interactions and combined with implicit membrane representations<sup>30,31</sup>. With BioSpring, it is possible to fine-tune a specific interactive experience and explicitly control the degrees of freedom to be included in the experiment. It should be noted that applications that focus heavily on the analysis part can be seen as a borderline case where a 'simulation' could be interpreted as merely the computation required to generate the data necessary for the analysis, such as the computation of a property field.

All input files and parameters for the experiments included in MolPlay are provided by an ISO image that can be put on an USB stick to ensure seamless and consistent use on different systems. This modular approach combines a flexible computational engine with dedicated visualization and interaction components and easily accessible examples, creating a versatile, extensible and practical framework for interactive molecular simulation and analysis (IMSA).

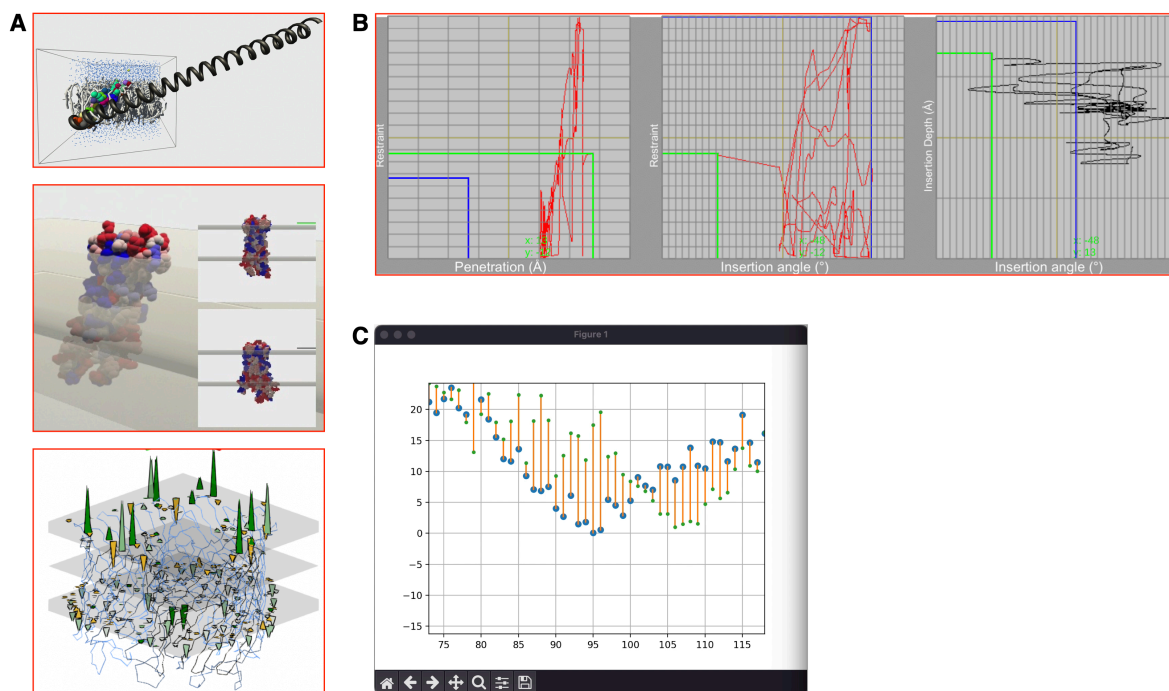
## Case-specific adjustments to the user interface and visual analyses

The user interface (UI) and visual analysis (VA) are customizable. A simple base layer is provided for each IMSA application that is compatible with the original protocol designed by Stone et al.<sup>2</sup>. Two user interface examples implemented in UnityMol are shown in Figure 2.



**Figure 2.** Examples of the user interface implemented in UnityMol. Panel **A** shows the basic interface for connecting to a simulation using the IMD protocol. This part of the user interface is always present. Panel **B** illustrates specific user interface enhancements that have been added to finely control interactive experiments using the BioSpring software. These include a submenu that specifically controls the simulation parameters and another nested menu item related to the interactive manipulations. Here you can see the submenus for the visualization and the IMD parameters. Image under CC-BY License by Marc Baaden.

Basic user interface functions include connecting to and disconnecting from a simulation, which is shown in Figure 2A by a minimal, generic connection interface to attach to a running simulation via the network address of the computer hosting the calculation. This UI interface is functional for any interactive simulation engine. The example in Figure 2B illustrates a more complete and finetuned hierarchy of UI elements to steer an interactive simulation remotely, but will only work properly for the targeted simulation engine it was designed for, here BioSpring. Similar customizations can be applied to the visual analysis features as illustrated in Figure 3. For this purpose, the visual elements within the scene can be customized (Fig. 3A), graphs of desired quantities can be added within UnityMol (Fig. 3B), or external, user-desired visualization facilities can be leveraged (Fig. 3C). Basic visual analysis functions include the visualisation of essential system properties, especially energy time series.



**Figure 3.** Examples of the visual analysis implemented in UnityMol. Panel A shows 3 examples of specific visual representations. Top: a spring indicating the direction of the forces applied. In the center: Simultaneous projection along two axes onto the 3D view for visual assessment of

membrane insertion angles. Bottom: Superimposition of the force vectors acting on the particles in the lipid headgroup region during interactive insertion into the membrane. Panel B shows diagrams implemented directly in the UnityMol environment, plotting membrane penetration depth, angle and energy. Panel C shows an external diagram with live updating, updated by UnityMol and drawn using the matplotlib library with a Python script. Image under CC-BY License by Marc Baaden.

The basic UI and VA functions are typically used for performing interactive molecular dynamics. For the BioSpring simulation engine, which was designed from the ground up for interactive experiments, my team implemented the more comprehensive simulation control UI as well as the specialised VA functions depicted in Figures 2 and 3. For this purpose, Stone's original IMD protocol was extended with custom data structures and additional command types as discussed in Refs.<sup>30,31</sup>.

### **Implementation of a live USB stick**

To facilitate access to and experimentation with IMSA, I have implemented MolPlay as a live environment that can be booted on many recent PCs from a USB stick. This approach allows me to create a comprehensive catalogue of IMSA tools, examples and use cases that enables users to seamlessly explore and implement these approaches without the need for complex installations or configurations.

At the heart of the MolPlay implementation is the Linux distribution Batocera (<https://batocera.org/>), which serves as the base operating system. It provides a lightweight and efficient runtime environment. Batocera is originally designed for the creation of live USB systems in the context of gaming and emulation. It is in its 39th version and has been actively

maintained for the last 8 years. Table 1 describes Batocera hardware compatibility. To meet the diverse software requirements of IMSA applications, I have integrated the Guix linux package manager (<https://guix.gnu.org/>) into the Batocera/MolPlay environment. Guix provides a robust and reproducible solution for the management and distribution of scientific software<sup>32</sup> and ensures that all necessary dependencies and libraries are consistently available. The full software stack necessary to deploy the required codes and libraries can be accessed through Guix. Gromacs for instance, is a native package provided by Guix. Other scientific software packages such as BioSpring can be compiled in a Guix build environment or imported as a runtime environment including dependencies such as specific libraries.

**Table 1.** Hardware compatibility overview

Computer part	Supported hardware *	Comment
<b>Graphics card (GPU) family</b> NVIDIA GeForce NVIDIA Other AMD Radeon RX AMD Radeon Vega AMD Integrated AMD RDNA Intel HD Graphics Intel Iris Plus Graphics Intel UHD Graphics Intel Other	<b>GPUs</b> GTX 750 Ti, GTX 1050, GTX 1050 Ti GTX 750 Ti 550, 6500 XT 3, Vega 3 Radeon (3GB VRAM) 2 Bay Trail, Haswell, Sandy Bridge, 500, 510, 515, 520, 530, 2500, 3000, 4000, 4400, 4600, 5000 655 770, Xe 24EUs 750MHz HD Graphics 4600	
<b>CPU Family</b> AMD Athlon AMD Ryzen AMD Custom Intel Celeron Intel Core i3 Intel Core i5 Intel Core i7 Intel Core m7 Intel Other Beelink	<b>CPUs</b> 3000G, Silver 3050e 7 5800H Aerith APU Zen 2 1037U, G1610, G1610T, N2830, N3450 4130T, 4350, 4360, 8109U 2415M, 3427U, 4250U, 4440, 4570, 4670, 6200U, 12500T 4770T, 4790, 4790K 6Y75 N100, Pentium 4405U, B960, G3220, G4500, Xeon E3-1246 v3 SER5 MAX	Minimum 32-bit x86 processor  Recommended 64-bit x86_64 CPU
RAM	1 Gb minimum	2 Gb recommended

\* Hardware compatibility information is taken from the Batocera wiki website at [https://wiki.batocera.org/supported\\_pc\\_hardware](https://wiki.batocera.org/supported_pc_hardware). CPU and GPU models were constituted from reported working benchmark configurations. Table under CC-BY License by Marc Baaden.

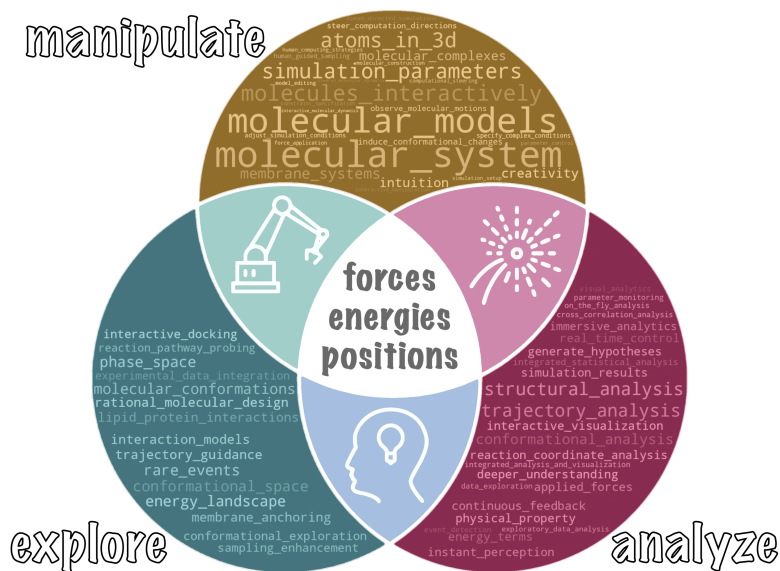
The user experience within MolPlay is customised through the Emulation Station front-end, which is a central element of Batocera and provides a consistent and intuitive menu interface for

accessing, launching and navigating the various IMSA tools, examples and documentation. The user-friendly design of the Emulation Station front-end ensures seamless interaction with the MolPlay environment, regardless of the user's technical knowledge. The user can simply boot from the MolPlay USB stick and immediately start exploring IMSA on their own, guided by easy-to-follow on-screen instructions. This set-up can be used as a stand-alone activity in educational environments such as science fairs or museum exhibitions.

## Results and Discussion

### A tentative task taxonomy for Interactive Simulations

IMSA enables researchers to perform a variety of tasks. For a more structured and systematic discussion it is useful to attempt to categorize them. Tasks can broadly be divided into three main activities: *Manipulate*, i.e. model construction and manipulation, *Explore*, for guiding conformational sampling through phase space, and *Analyze* for analysis and visualization. These actions are not mutually exclusive and can be combined in a particular experiment. Figure 4 provides a schematic view of the taxonomy as well as typical usage examples.



**Figure 4.** Taxonomy of interactive simulation and analysis tasks with selected application examples. Image under CC-BY License by Marc Baaden.

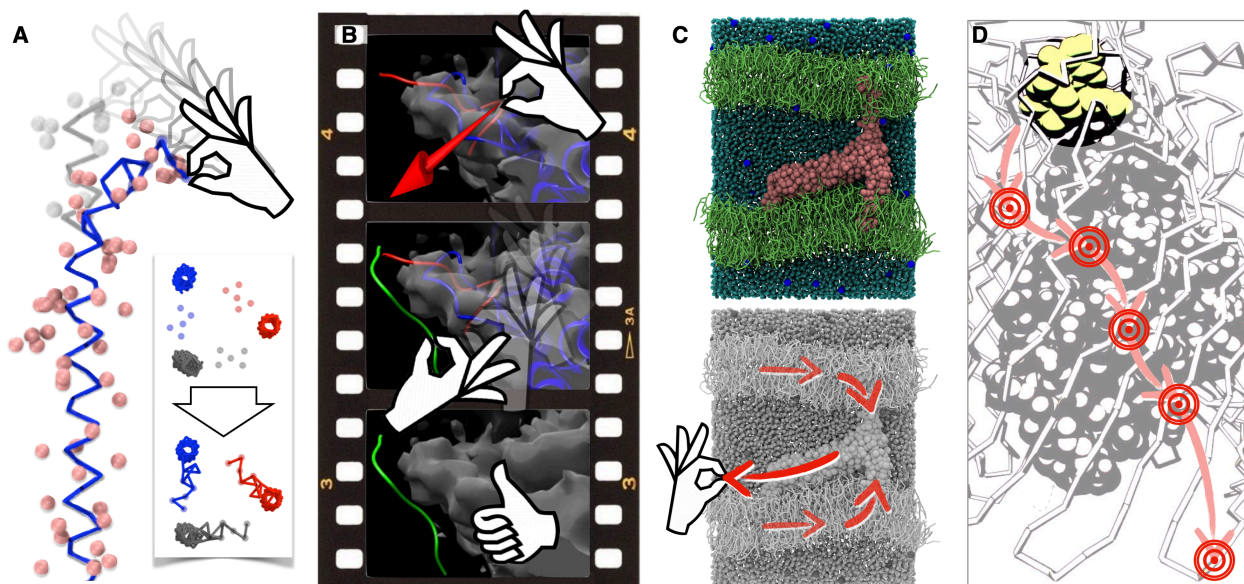
I will briefly describe these tasks and provide more detailed use cases in the next section. Common tasks within the *Manipulate* action include constructing and assembling molecular systems, deforming and manipulating molecular structures, tuning and calibrating molecular models, and applying external forces or constraints, for instance in the context of integrative modeling under experimentally derived constraints. A specific example in this category is probing membrane protein insertion depth and angle interactively. This example can be extended in the context of membrane fusion, where it is of direct biological interest to mechanically induce forces to assess how a macromolecular assembly such as the SNARE complex, a key player in membrane fusion, transduces such force onto apposing membranes. The *Explore* action is aimed at conformation sampling tasks. These include exploring the conformational spaces and energy landscapes of molecular systems, running simulations along specific reaction pathways to investigate particular processes or mechanisms, triggering and investigating rare events that are difficult to observe in conventional simulations. In addition, researchers can apply collective variable biases or impose reaction coordinates to improve sampling efficiency and guide the exploration towards relevant regions of conformational space. A good example for this task may be guiding a membrane-permeating substrate such as a siderophore through its transporter protein to interactively define a specific transport pathway for further sampling, as will be described below. The *Analyze* action enables real-time visualization and analysis, for example by measuring and analyzing forces, deformations and propagation patterns as they occur, providing insights into the underlying molecular mechanisms. One of the simplest applications is merely to monitor simulations by connecting to a running simulation to check nothing unexpected has

happened. In addition, IMSA enables the scrutiny and visualization of interactions and binding events, so that important molecular recognition processes can be investigated. These analysis functions are often combined with the *Manipulate* and *Explore* actions to analyze the resulting dynamics and interactions simultaneously, scrutinizing the response to a given stimulus. IMSA supports collaborative analysis and knowledge sharing, promotes interdisciplinary collaboration and facilitates the communication of results within research teams or educational institutions. The above list of tasks is not exhaustive. The IMSA field is constantly evolving. New tasks and applications continue to emerge that expand the scope of this preliminary taxonomy.

### **Selected examples of use cases**

To illustrate the practical applications and advantages of IMSA techniques, especially in the context of membranes and membrane protein systems, I briefly present a selection of representative use cases from my research to date. These examples show the versatility of such approaches and illustrate concrete tasks in line with the previous taxonomy. However, it is important to note that this selection is by no means exhaustive or a systematic representation of all possible applications.





**Figure 5.** Illustration of four interactive molecular simulation and analysis use cases. A: Preparing a simulation, here by interactively bending transmembrane helices to match a model of the extracellular domain of hemagglutinin (pale spheres in the inset). B: Integrative modeling of the ryanodine receptor, removing a redundant loop during model reconstruction from cryo-EM maps. C: Investigation of the mechanical properties of a double-membrane bilayer system with incorporated SNARE complex. D: Guiding a siderophore probe (light yellow) through the bacterial iron transporter protein FepA along an interactively predetermined pathway. Image under CC-BY License by Marc Baaden.

Preparing for a simulation (*Manipulate*) : IMSA are precious in the early steps of setting up a full-fledged simulation of a complex membrane system. I used it to assemble artificial waterchannel compounds into a multimeric aggregate to improve its membrane stability. For example in the study of metallomacrocyclic pores<sup>33</sup>, I set up a 7-mer aggregate in the membrane using UnityMol in virtual reality to assemble a tight initial complex from a pre-equilibrated monomer following the protocol described in Ref. <sup>34</sup>. For an influenza virion model at the

coarse-grained level, my team used IMSA to match two separately modeled parts of the hemagglutinin membrane protein to assemble them into a unified model<sup>34</sup>. In both cases, the IMSA result served as starting point for extensive production simulations.

Matching models and experiment (*Manipulate, Analyze*): combining experimental boundary conditions with human expertise and intuition to drive IMSA simulations is a precious approach for integrative modeling. My team leveraged cryo-electron microscopy (cryo-EM) data to build models of five functional states of the Ryanodine receptor, using interactive refinement for particularly challenging segments such as loops<sup>35</sup>. For the SNARE complex involved in membrane fusion, my team set up a toolchain to interactively insert the two transmembrane domains of a flexible model of the full four-helical bundle within two bilayers whose spacing can simultaneously be varied<sup>31</sup>. As this model is manipulated, its match with experimental data derived from EPR experiments is monitored to guide the modeling process. Here, the interactively built models are of immediate interest as they represent plausible solutions compatible with known experimental data.

Probing the propagation of forces (*Manipulate, Analyze*): The already mentioned SNARE complex was modeled at the coarse grained level in a fully hydrated double bilayer system to study mechanical properties. By interactive manipulation of the four-helical bundle, forces were transmitted through the transmembrane domains to the two lipid bilayers<sup>23</sup>. The induced deformations could be monitored, providing an intuitive link between the direction of force application and the mechanical effect transferred to the membranes. These simulations provided insights into the mechanical properties and behavior of the SNARE structure, such as the potential mechanical role of the N-terminal bundle in catalyzing fusion events, as evidenced by membrane perturbations upon force application. Furthermore, the transmembrane helix insertion

strengths of the syntaxin and synaptobrevin proteins involved in the bundle differed, with synaptobrevin exhibiting higher stability in its membrane.

Guiding the exploration of phase space (*Explore*): My team investigated the bacterial iron transporter FepA, an outer membrane protein that facilitates the transport of iron-containing siderophores across the outer bacterial membrane. Through an initial interactive molecular simulation session, we identified a potential pathway for iron transport through the FepA channel. However, interactive control of this pathway required unrealistically high forces. Based on these results, we established a set of key target points along the pathway. An automated interactive simulation then more gently guided the siderophore through the conformational landscape of the receptor, passing the target points along the pathway<sup>36</sup>. This approach showed a path towards efficient sampling while maintaining the physical plausibility of the system. The interactive simulations facilitated real-time monitoring and allowed the operator to intervene and override the automatic control when necessary, such as when the system was trapped in local energy minima.

### **First MolPlay prototype for Interactive Molecular Simulations and Analyses**

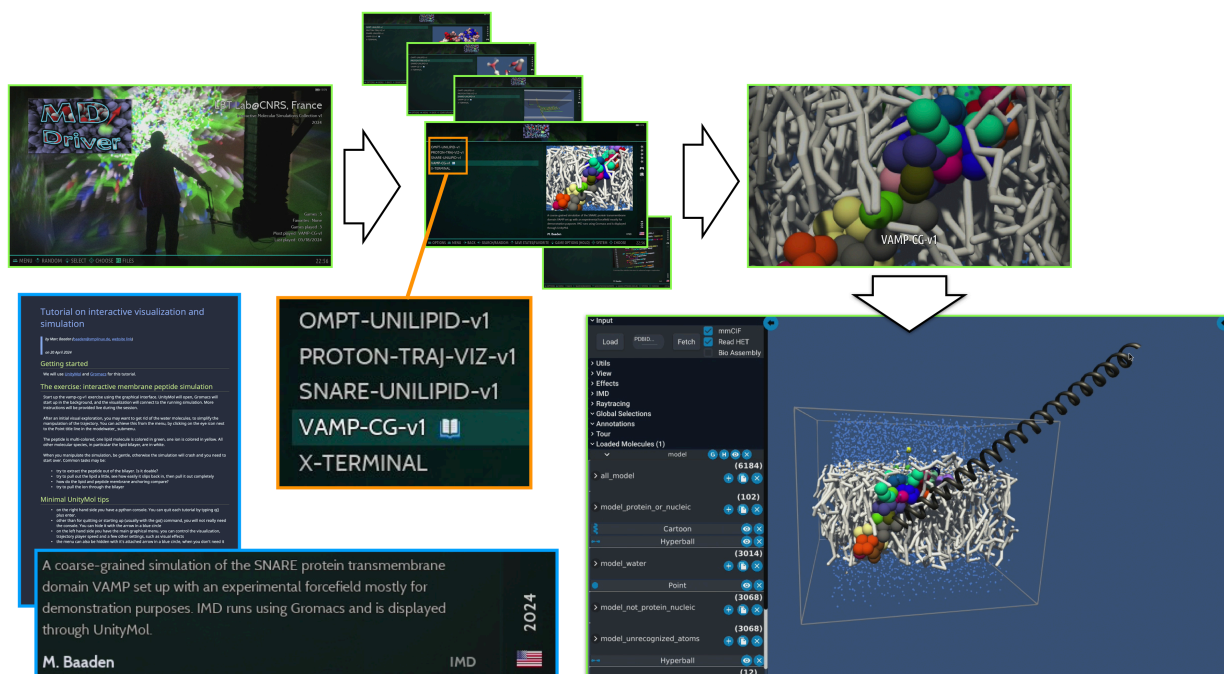
MolPlay is an interactive molecular simulation environment that can be started from a USB stick on a variety of standard hardware. MolPlay is derived from the Linux distribution Batocera, which was originally developed for emulating computer games on many devices. For this research prototype, I used Batocera's capabilities to create an intuitive environment that can be explored in a natural and autonomous way. MolPlay automatically boots into the Emulation Station, a menu-driven tool where each "game" platform is defined by file extensions, with a generic definition for handling such files. I have configured MolPlay with a Python scripting approach, where all commands to launch a particular experience are encoded in a Python script.

These scripts typically position the relevant directories and execute system calls to the corresponding executables and input files. For each "script", a short description, an image, a video and some documentation can be linked together and made visible in the user interface. Additional metadata, such as the language of the instructions (displayed as a country flag), can be provided. Once all the executed programs of an experiment have been completed, the system returns to the menu so that the user can select another experiment. The catalog of experiments, e.g. "Scripts", can easily be expanded. The menu system manages the configuration of input devices, including graphics card setup, sound configuration, network settings and Wi-Fi connectivity to ensure a seamless user experience across different hardware platforms. I have tested MolPlay internally in a research lab environment and at an international training workshop with around 30 participants. Informal positive feedback was received. A more formal evaluation may follow at future events. Here I make the first research prototype available for anyone to try out. This technical solution includes a handful of selected examples of interactive simulations. The catalog of examples will be expanded soon. More details are provided at the project website: <https://molplay.mol3d.tech>.

### **IMSA examples included with MolPlay**

Molplay currently ships with 9 example systems, 4 of which are specifically related to membranes and membrane proteins. All examples are described in detail on the website and in the live MolPlay environment. The range of examples is constantly expanding. A selection of interactive molecular dynamics setups, interactive elastic network simulations and visualization demonstrators is provided, ranging from very simple systems such as a deca-alanine helix in water to a coarse-grained double bilayer system with an interconnecting protein bundle. All chosen examples run fluidly on recent hardware. They were tested extensively on a laptop with

Intel Core i7 processors and Nvidia RTX3070m graphics chip. These examples were selected for their educative value and to span a diversity of use cases for illustration. Each example is described in the live system with a few lines of synopsis, a more detailed 1-2 page document and a commented video walkthrough, such that a user has everything at hand to navigate these examples and experiment with the interactive simulations. Figure 6 depicts a preview of the menu selection system and a few of the help options presented to the user. A series of walkthrough videos are both available online and through the live USB stick.



**Figure 6.** Example MolPlay menu walkthrough. Screenshots are bordered in green, starting from the initial landing page, moving to a first submenu enabling to select the experiment to run. In the selection, the example entitled "VAMP-CG-v1" is chosen. This is highlighted in the orange bordered inset. Once confirmed, a screen is shown during the loading phase before the actual final screen appears and the interactive experiment is ready. The two blue bordered insets show help

documentation available for this example: a short synopsis with some metadata and a more detailed tutorial description. Image under CC-BY License by Marc Baaden.

An advanced option is available for expert users, to open a command line terminal and launch, conceive, test or debug the examples individually. For simplicity, no window manager is pre-installed such that the graphical interface takes over the full screen and the user is not confused with the various modules running in the background. Keyboard hotkeys provide important general operations, for example to enable the user to quit the running example and return to the main menu. Detailed information to guide the user and document all MolPlay features is provided via the MolPlay website. Summary sheets are available on the website to be printed and displayed when MolPlay is set up in kiosk mode, as an autonomous attraction for visitors, for instance in the case of open science fairs or museum exhibits.

### **Extending MolPlay and assessing challenges and limitations**

The MolPlay USB stick enables a variety of application scenarios for different target groups and environments, from public relations and education to research applications in laboratories. One possible use case is the autonomous operation of MolPlay at science fairs, museums or public events to inspire visitors, students and the general public with interactive molecular simulations and analyses. The stand-alone nature of the USB stick allows seamless operation without complex installations or configurations. In education, MolPlay's portability makes it well suited for teaching and training purposes in classrooms or computer labs. Educators can use the pre-configured environment to introduce students to the principles and applications of interactive molecular simulations to promote hands-on learning experiences. In research laboratories, MolPlay serves as a valuable tool for exploring and validating hypotheses and conducting preliminary investigations before embarking on more computationally intensive simulations. The

ability to interactively manipulate and analyze molecular systems can provide researchers with valuable insights and guide their research direction. In addition, MolPlay's modular design facilitates potential future integration with different hardware configurations. While some integrations require additional configuration or compatibility considerations, the inherent modularity of interactive simulations enables the separation of computational tasks from visualization and interaction. Consequently, the actual simulations can be run from the USB stick, while the visualization and interaction components can be offloaded to dedicated hardware installations, such as virtual reality (VR) environments or large-scale display walls. Although MolPlay aims to lower the barriers to entry for interactive molecular simulations, certain challenges and limitations are inherent to these advanced techniques. Integrating specific hardware components such as for instance a variety of input devices, or implementing cross-platform compatibility can lead to complexity, especially when it comes to distribution restrictions or specific hardware requirements. Despite these challenges, MolPlay represents an opportunity to foster collaboration and build a community around interactive molecular simulations and analyses. By providing a common platform and accessible resources, researchers, educators and enthusiasts can share their experiences, contribute new use cases and advance the field together. These collaborative efforts can drive the development of new methods, techniques and best practices.

## Conclusion

Interactive molecular simulations are a powerful but underutilized approach to studying the dynamics and mechanisms of molecular systems such as membranes and membrane proteins. By combining real-time visualization with the ability to manipulate and control simulations, IMSA enable an intuitive understanding of complex phenomena and accelerate hypothesis

generation. This paper introduces MolPlay, a portable USB platform that provides turnkey access to a curated set of IMSA tools and examples. MolPlay lowers the technical barriers to IMSA and facilitates wider application in research and education. MolPlay's key strengths include its self-contained nature that does not require complex installation, its user-friendly interface for navigating the examples, and its consolidation of more than a decade of IMSA expertise into an accessible format. Initial tests have shown that MolPlay has the potential to appeal to different target groups and encourage interactive exploration. By democratizing access to these techniques, MolPlay represents a significant step towards unleashing the full potential of IMSA to drive innovation in computational modeling, analysis and simulations of molecular systems.

## Supporting Information

All relevant complementary information is provided through the MolPlay website

<https://molplay.mol3d.tech>. These include instructions and ISO images to deploy MolPlay through a bootable USB stick.

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### Author Contributions

The manuscript was fully designed and written by M.B. The MolPlay prototype described was conceived by M.B, building on prior published work performed under his supervision, in particular on the MDDriver, BioSpring and UnityMol tools.

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## Notes

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## ABBREVIATIONS

FAIR, findable accessible interoperable reusable; FepA, Ferric enterobactin protein A; IMD, interactive molecular dynamics; IMSA, interactive molecular simulations and analyses; ISO, International Organization for Standardization; MD, molecular dynamics; SNARE, Soluble NSF Attachment Protein Receptor; UI, user interface; USB, Universal Serial Bus; VA visual analysis.

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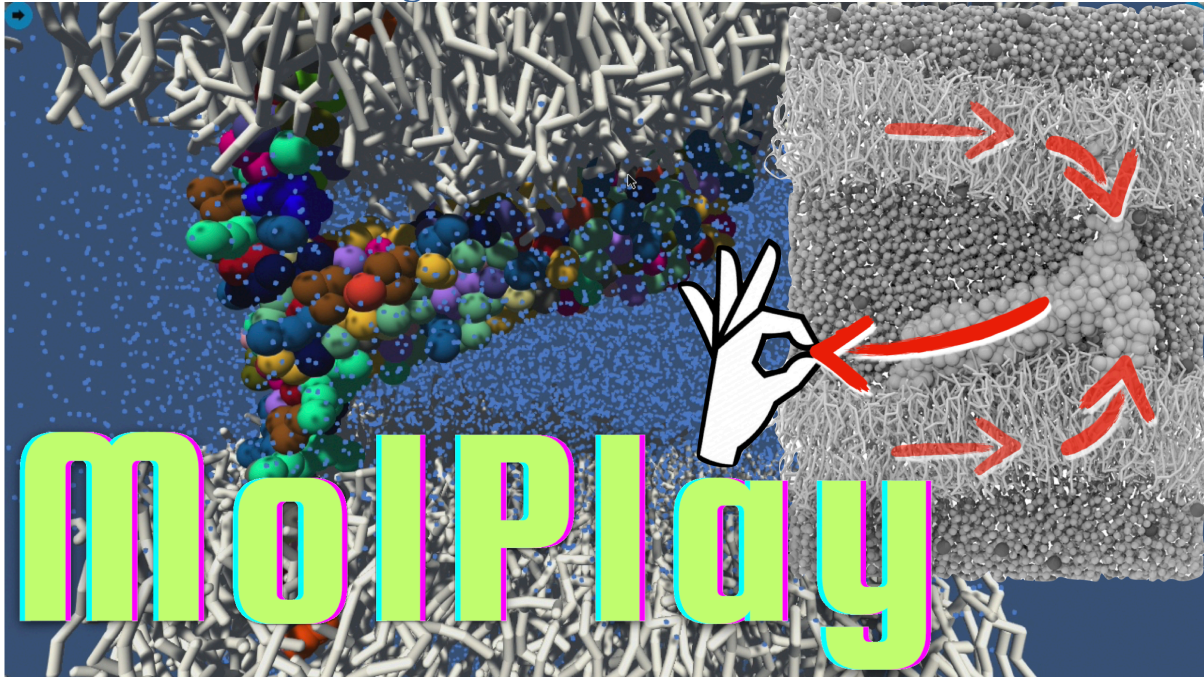
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## Table of Contents Image



Interactive molecular simulation to study the SNARE complex in a double bilayer, a MolPlay example.