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## Interactive Molecular Dynamics

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# Comprehensive Computational Chemistry

## Author Template

### Mandatory Elements

**CHAPTER TITLE:** Interactive Molecular Dynamics

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**ABSTRACT:**

Interactive Molecular Dynamics (IMD) is a real-time simulation technique that allows scientists to interact with virtual molecular systems. Users can observe a simulation in progress in real time and manipulate the motion of individual atoms and molecules by applying forces, and receive feedback on the dynamic response of these systems in interactive time. The development of IMD has been influenced by technological and algorithmic advances in simulation tools as well as advances in human-computer interaction, including haptic devices or augmented and virtual reality approaches, and increasingly affordable devices. Scientific and practical applications include mechanobiology research, determination of experimental structures, and nanoscale property visualization for dissemination. IMD has made significant advances in performance, visualization, and data analysis.

**KEYWORDS:** 10-15 keywords, which will be used for indexing purposes only (listed alphabetically)

Interactive Simulations

Molecular Dynamics

Real-time Visualization

Digital twins

Steered Molecular Dynamics

Simulation steering

Mechanobiology

Human Computer Interaction

Haptic Device

Virtual Reality

**KEY POINTS /OBJECTIVES BOX:**

- Understand what Interactive Molecular Dynamics (IMD) is and how it differs from traditional molecular dynamics simulations.
- Learn about the various technologies that have influenced the development of IMD, including haptic devices, augmented reality approaches, and virtual reality headsets.
- Explore the scientific and practical applications of IMD, including mechanobiology research, determination of experimental structures, and visualization of molecular systems.
- Examine the importance of interactive visualization in IMD simulations and the various techniques and tools used for this purpose.
- Understand the advances and improvements in IMD, including performance, scaling, visualization, and data analysis.

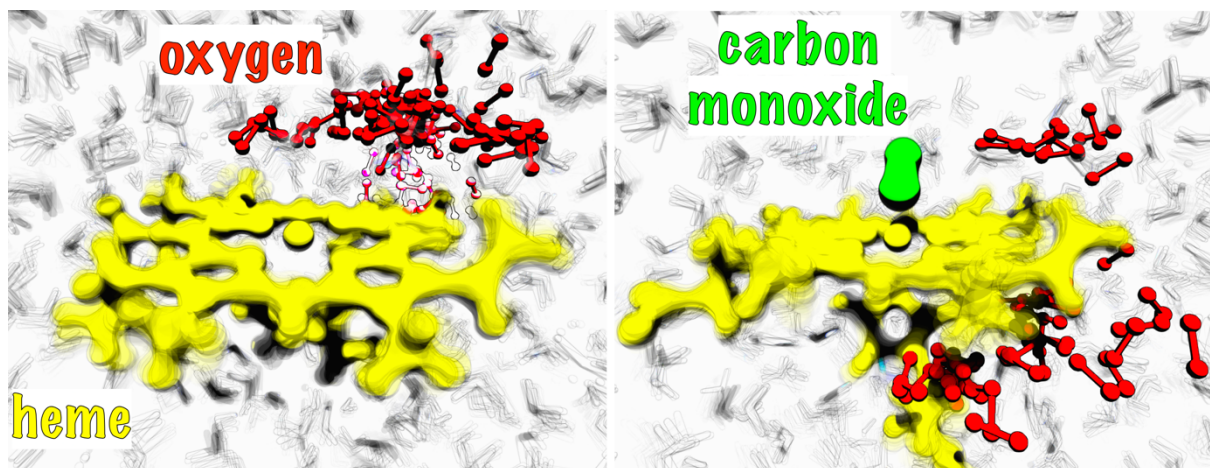
## Section 1: INTRODUCTION:

### Unlocking the Power of Interactivity in Molecular Dynamics

This is an introductory section for the chapter on interactive molecular dynamics (IMD). We begin with a brief introduction to molecular dynamics by giving a simple definition for this simulation approach used to model the behavior of atoms and molecules in motion. We describe the context of molecular dynamics, its importance in scientific research, and the range of applications. These computer simulations use physical laws, in particular building on classical Newtonian dynamics, and mathematical models to calculate the motions of particles over time. This framework allows researchers to study the dynamics of molecular systems with up to millions of atoms.

To quote Nobel Laureate Richard Feynman on this subject, he once said:

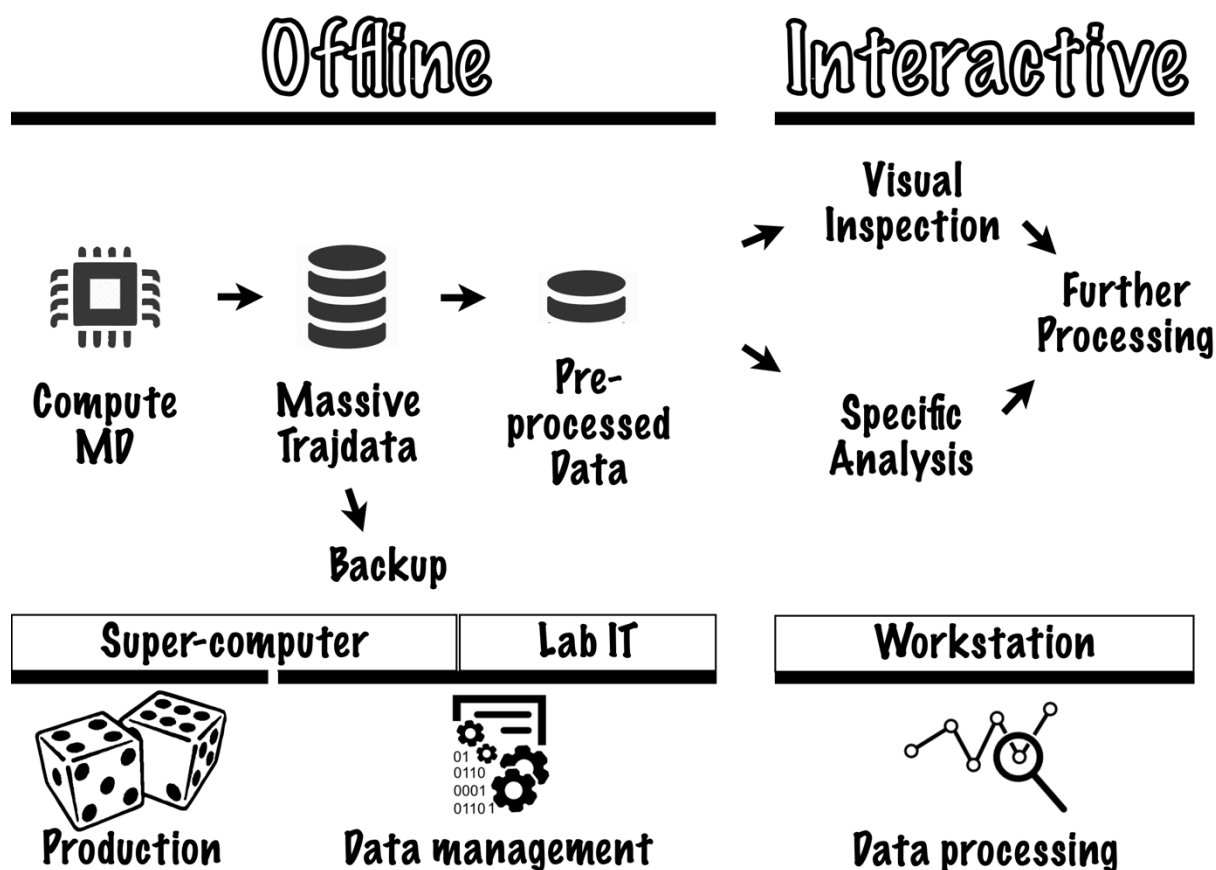
"Everything that living things do can be understood by the jiggling and wiggling of atoms."



**Figure 1.** Oxygen transport in the blood occurs by binding to hemoglobin as a carrier. This process can be disrupted by toxic molecules such as carbon monoxide. The illustration highlights the connection between the wiggling and jiggling of atoms - a quote from Richard Feynman that refers to the concept underlying molecular dynamics simulations - and a process of living things, namely oxygen uptake. Oxygen (red) diffuses freely to the heme binding site (yellow) above the central iron atom when you breathe clean air (left panel). When carbon monoxide (green) is present (right panel), it occupies the exact site where oxygen must bind, blocking oxygen's access to heme. Therefore, oxygen cannot be transported into the bloodstream and poisoning occurs. Image under CC-BY License by Marc Baaden.

This quote illustrates the fundamental importance of understanding the motion of atoms and molecules to the behavior of living systems and is illustrated in Figure 1. Molecular dynamics simulations allow researchers to "see" these jiggling and wiggling motions in action and study how they affect the behavior of complex biological systems, enabling us to understand the world around us and, in particular, the biology of life. Even more, these precise movements can be analyzed in minute detail using a broad arsenal of simulation analysis tools. Through these simulations, scientists can gain a deeper understanding of the physical mechanisms underlying many biological processes, including protein folding, drug binding, and enzyme catalysis. This method has become a reference method in many fields and is routinely used in many areas of biology, chemistry and physics to study processes at the molecular level.

Such MD simulations are very complex and require significant computing power to repeatedly execute and solve a large number of mathematical equations. Because they are very computationally intensive, they can take many days, weeks, or even months to complete. For this reason, researchers typically run MD simulations "offline" on supercomputers that can process large amounts of data quickly. The scientist prepares the simulation by setting the initial conditions and parameters of the simulation, and then sends it to the supercomputer for computation. During this time, the scientist can work on other tasks knowing that the simulation is running independently. Only when the calculation is complete does the scientist retrieve the results and analyze the data to gain insight into the behavior of the molecular system that was simulated. This analysis can include examining the trajectories of individual atoms or molecules, calculating thermodynamic properties such as temperature and pressure, and identifying important interactions between molecules. The discovery process oscillates between visualization, property calculation, and hypothesis generation. This process is illustrated in Figure 2.



**Figure 2.** A typical molecular dynamics workflow in which large portions run offline on a supercomputer or the laboratory system IT without direct intervention by the scientist. Interactive analysis is typically performed post-mortem, i.e., after the simulation is complete and trajectory data, including atomic positions and velocities, have been collected. Therefore, the trajectory data cannot be changed by the scientist. If new ideas emerge during data processing, the whole process of running production simulations, managing the data, and processing them starts all over again. Such a new cycle requires modifying the original input files for the molecular dynamics run and restarting another batch of simulations under the new conditions. Because these input files must be carefully designed, such a process can involve a long trial-and-error iteration. Image under CC-BY License by Marc Baaden.

Interactive Molecular Dynamics (IMD) is an extension of the classical "offline" approach that provides real-time visualization of running molecular dynamics simulations. It describes the visualization and interactivity of these simulations, allowing the simulator to view the system in different ways and to steer the computation in different directions by changing the control parameters. This possibility enhances the simulation experience. IMD opens up exciting possibilities for exploring the dynamic structures of molecular systems by providing this ability to not only observe simulations, but also interactively manipulate them in real time. The ability to intervene in a simulation can be achieved through a variety of methods, including the application of force, modification of biophysical properties, or real-time adjustment of simulation parameters. Several examples will illustrate the potential of IMD.

Interactive molecular dynamics simulations apply control forces to the molecular system in real time, allowing the user to select the direction, amplitude, and point of application. This method allows users to explore the simulation while receiving prompt responses via real-time graphical displays or other sensory aids such as haptic devices. Interactivity means that the user has the ability to change a simulation in real time while it is running, which means that the simulation results must be presented to the user visually and intuitively. The main goal is to allow the user to understand the data in the most efficient way, through intuition rather than numbers. In this approach, the user explores the conformational space, i.e., the range of possible shapes that a molecule can take. Conceptually, the approach is based on a time-dependent model that allows the system to evolve along a low free energy path, resulting in a physically plausible representation of the molecule's behaviour.

To give just one example, before we dive deeper and more systematically into the topic, multiscale simulations, for example, would benefit greatly from interactivity. The biological systems under study are often complicated. Perfecting the associated molecular models requires precise calibration of the interactions. Such fine-tuning of the interactions through non-interactive experiments is difficult to achieve. The use of a variety of modeling scales helps to narrow down the degrees of freedom that are essential for a complex biological system. Focusing on an improved set of such degrees of freedom improves the efficiency of interaction in an IMD simulation.

Interactive molecular dynamics is a textbook example of the broader category of interactive molecular simulation methods. A much more technical and detailed review of this general topic was written by Lanrezac et al.<sup>1</sup> to which we refer the interested reader.

The goal of this chapter on IMD is to provide an understandable and comprehensible reference description with easy to follow examples. Therefore, we will not be exhaustive in our description, but will try to provide a few convincing examples for this encyclopedia. The reader should be aware that this paper is by no means a literature review. Rather, we will attempt to cite only a few

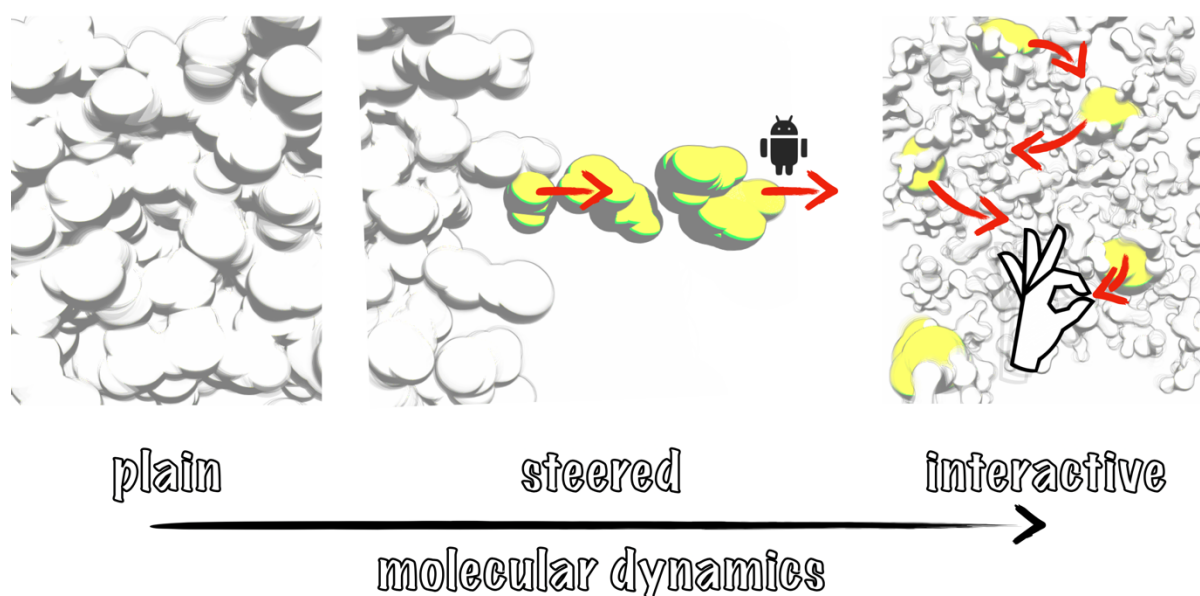
important references at first. Using these references, the reader can then delve further into the literature if they so desire. We will not go into all the details here, but will present from our perspective how to explain this field. This paper is more of a summary, a guide of sorts, to help get started in this field.

## **MAIN TEXT:**

### **Section 2: From traditional Molecular Dynamics to Interactive Simulations.**

We will now examine the evolution of molecular dynamics from its traditional approach, widely known and used, to the introduction of interactivity. This leads us to the concept of interactive molecular dynamics. What is it? In this section, we will give a definition of interactive molecular dynamics and highlight its importance compared to traditional molecular dynamics simulations.

Let us first briefly review the history of molecular dynamics simulations<sup>2</sup> and how they have evolved and become more interactive over time. Molecular dynamics simulations have been used for over half a century to study the behavior of molecules at the atomic level. The first simulations were performed in the 1950s and 1960s by Alder and Wainwright<sup>3</sup>, who used simple models to study the behavior of hard-sphere fluids. Later, molecular dynamics simulations were extended to liquids, membranes, proteins, and many other classes of molecules. Since then, molecular dynamics simulations have become an indispensable tool for understanding a wide range of phenomena in chemistry, materials science, and biology. The continued development of faster computers and more accurate models has led to increasingly sophisticated simulations with increasing predictive power. Interactive molecular dynamics (IMD) research was initiated in the late 1990s. The development of SMD, a steered molecular dynamics tool, was one of the first contributions<sup>4</sup>. This simulation tool has replicated atomic force microscopy (AFM) as a digital twin and uses molecular visualization software to provide graphical insights. Such single-molecule micromanipulation experiments as atomic force microscopy and optical tweezers allow direct investigation of the binding properties of single molecules and their response to mechanical forces. In particular, the idea of digitally reproducing such experiments inspired the subsequent development of interactive molecular dynamics simulation approaches, with the steered molecular dynamics technique being the first step as illustrated in Figure 3. In the original steered molecular dynamics approach, which simulates the effect of external forces on a biomolecule by applying a constant force or displacement to one end and constraining the other end, the direction and magnitude of the force are usually fixed before the simulation begins in batch mode, which can limit the flexibility of the simulation. The next step was to make this control interactive<sup>5,6</sup>. For a variety of biological problems, the addition of such external constraints provides qualitative structural and quantitative energetic insights into protein unfolding, structure refinement, ligand-protein interactions, drug design, etc. From this stage, the approach starts to become known as Interactive Molecular Dynamics, which allows the user to adjust the applied forces during the simulation. This technique provides more flexibility and control over the simulation and makes it easier to study the properties and behavior of biomolecules under different conditions.

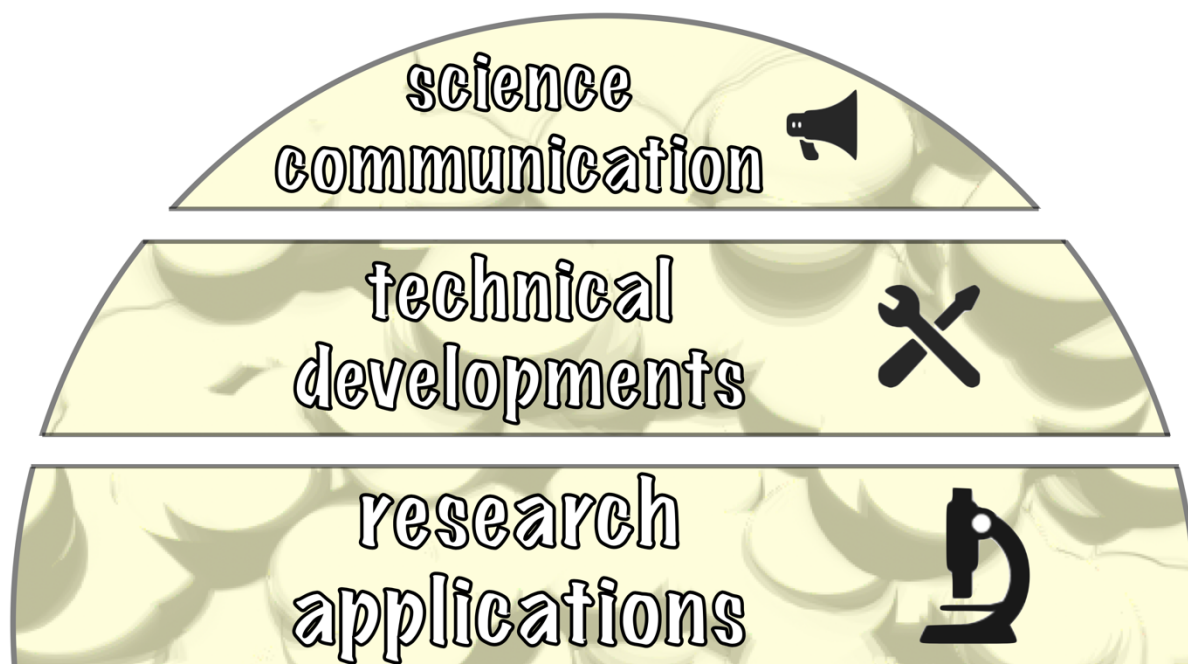


**Figure 3.** A schematic representation of the evolution from plain molecular dynamics to interactive simulations. Steered MD represents a first step that can be automatic or semi-automatic, with forces along the control direction, to fully interactive molecular dynamics with unrestricted choice of forces controlled directly by the human operator. Image under CC-BY License by Marc Baaden.

Let us define interactive molecular dynamics simulations in general terms as a variant of the classical molecular dynamics technique in which the molecular system is manipulated in real time by user-generated forces.

Let us now consider the various motivations for running IMD simulations. These might explain why IMD is becoming more popular and relevant in current scientific research. There are three main motivations that explain why these techniques are so important: First, there are mainly scientific motivations; second, there is an important technical benefit; and third, IMD offers very strong advantages in communication. Because of its origins in SMD, IMD can mimic some experimental conditions and digitally reproduce certain experimental setups. Moreover, and most importantly, IMD provides a very intuitive aspect of the representation of the ongoing simulation, leading to a deeper understanding and facilitating hypothesis generation. IMD informs the individual researcher and allows them to draw from their own human intuition and understanding. The scientist becomes an actor in the simulation process and can manipulate molecules in three dimensions. This capability allows the user to instantly adapt and respond to the behaviour of the molecular system and benefit from human intuition and instant decision making. Thus, it is possible to perform even very complex manipulations. At the same time, however, the IMD approach is limited by simulation speed and human time. Another variation of the approach is human computation, which uses the input of many people. This can be done via IMD simulations, which provide an ensemble of molecular dynamics simulations under human guidance. These can be viewed as a meta-experiment built on many instances of individual IMD simulations. Such an approach makes the most of human visual perception, which offers exceptional capabilities to interpret such complex simulation data. Let us discuss this aspect of human computation in detail. We used it ourselves with a group of students to explore human-directed RNA folding and were able to highlight the differences in the student group's strategy compared to standard automated approaches such as replica exchange MD. This is probably the most original part of such approaches: Access to human strategies that can differ from and complement standard computational methods in the field. It is worth noting that this human-led aspect of working on static molecular structures has been explored many times. The best known

example is Baker Laboratory's FoldIt tool<sup>7</sup>. This has not been explored as much with IMD simulations, but it seems that there is great potential here.



**Figure 4.** Three pillars for the use of interactive molecular dynamics: from research applications for molecular systems, to technical and methodological developments of computational algorithms, to communication of scientific data and educational purposes. Image under CC-BY License by Marc Baaden.

On a more practical level, when developing methods and code, IMD can be a useful tool for debugging. For example, if you are developing a new force field or theoretical representation, interactivity will help you with the trial-and-error phase and speed up debugging and prototyping. This is a more technical facet of IMD used as a tool and illustrates the technical motivations that may exist for IMD implementations.

In addition, IMD is a rich source for illustration and communication in science. The problem is that conveying static images of molecular systems gives a false picture of molecular processes at the nanoscale and does not capture the viewer's attention as efficiently as animated scenes. Therefore, scientists who have created illustrations and movies of such systems have long sought methods to create realistic molecular motion<sup>8</sup>. They have been looking for a way to create motion that is both realistic and impressive, to convey the message of the subtleties of motion at the molecular level, to give a sense of what is going on. MD is the method of choice and, from a theoretical standpoint, the right approach for such a path. IMD offers an even more powerful control for such illustrative purposes.

Let us conclude this section with a reflection on the IMD formalism. The addition of real-time external forces, also known as "tugs," helps overcome energy barriers and achieve desired states quickly. This system has practical applications in the study of proposed new geometric conformations. The ease or difficulty of the computer model to change conformations provides valuable insight into the possible physical pathways and malleable properties of the molecular system. These simulations are inherently non-equilibrium. This characteristic property should be properly accounted for in current IMD workflows, but is often not discussed. For example, when adding user-introduced forces, it could be very informative to analyze where the introduced energies are distributed in the molecular system. There are legitimate concerns about what impact



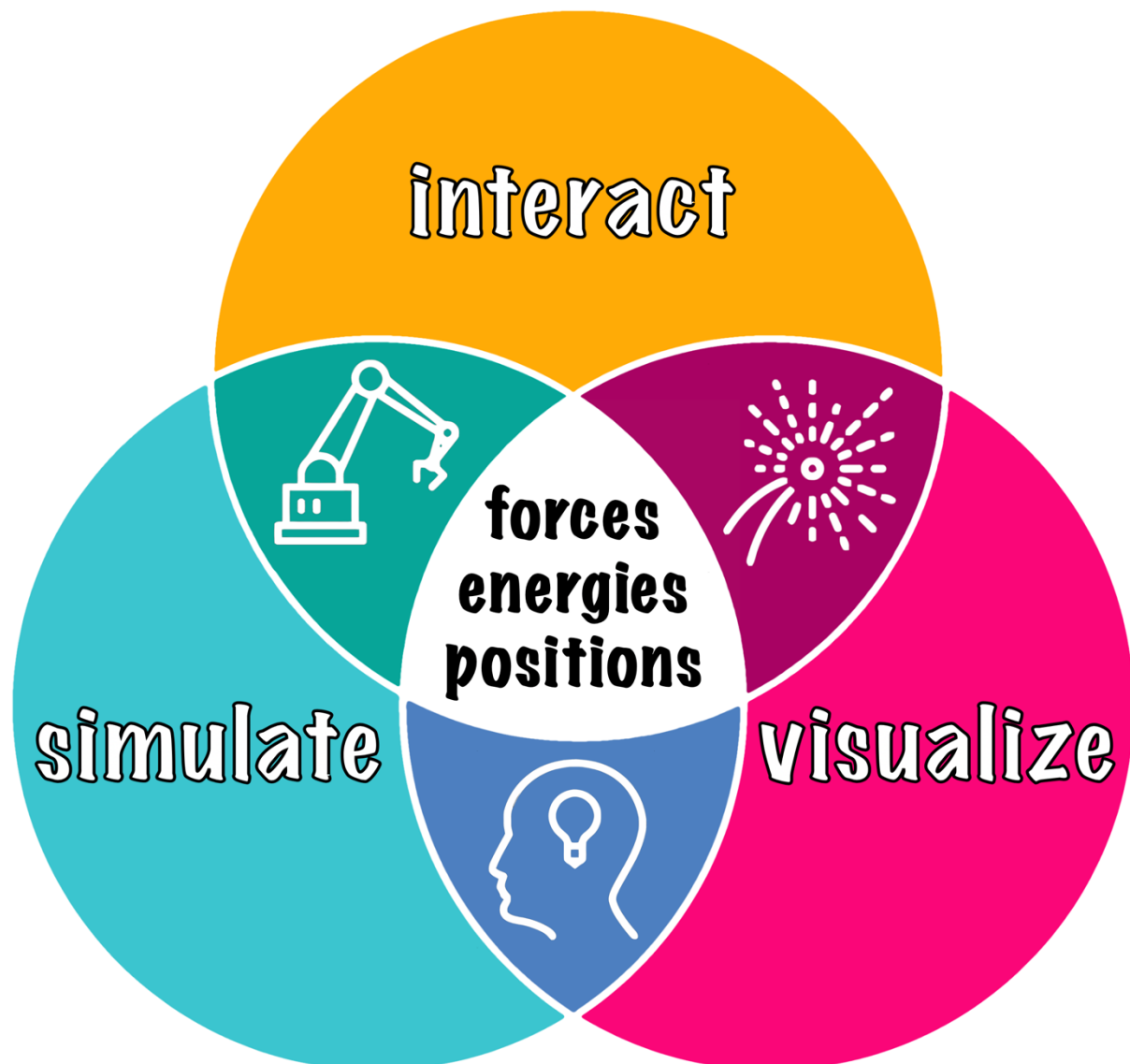
this process might have on the system as a whole. A common argument is that the actual IMD simulation is only a means to explore the properties of the system, and as such should not be considered a valid production simulation. At the same time, common non-interactive approaches such as Umbrella Sampling also add "user" forces to achieve their purpose, but can still be formally analyzed within their theoretical framework. Such a framework has yet to be developed for IMD simulations. The action of external forces on a group of atoms can increase the kinetic energy and temperature of the system. This presents the challenge of scaling these forces appropriately. What impact this has on the energetic balance of the simulation should be investigated further. There are technical implications for how this behavior is affected by, for example, the choice of thermostat and other simulation conditions for the IMD simulation. Another issue that is often not discussed is the sensitivity of simulation codes to external interactive events, not only in terms of physical properties, but also in terms of algorithm and numerical scheme. These considerations lead us naturally to the next section with further technical considerations.

### **Section 3: Enabling Real-time Control: The Technical Underpinnings of Interactive MD**

Here we discuss some technical basics for implementing interactive MD. The purpose of this section on technical basics is to give an overview of the main technical issues that arise when implementing IMD simulations, such as real-time visualization, the interfaces needed to manage inputs and outputs, and the communication between the simulation and the user. Indeed, since there are many technical aspects related to IMD, we will discuss only some essential ones, since the technical features are not the focus of this encyclopedia article. The interested reader may excuse that we only touch on these topics briefly.

An important and key aspect that should be mentioned is the coupling between the elements required for an IMD, in particular the simulation engine, the visualization and the user interaction, and how this coupling is achieved. Is it implemented in memory, via a file, or over the network? This is a particularly interesting aspect and implies design decisions for coupling simulation and interaction codes. A schematic view is given in Figure 5. Several protocols have evolved from early IMD implementations. First, there was MDComm, which had some latency issues and was improved in the IMD protocol, which is still widely used. Instead of hard-coding the protocols into the software, it is possible to use middlewares for such coupling, which is what we are pursuing with the MDDriver middleware. MDDriver is a library for coupling molecular dynamics and molecular user interfaces<sup>9</sup>. In the past, we have also experimented with a dataflow-oriented framework such as FlowVR, which provides finer control and may be a better option for complex setups that require advanced resource and execution control. For simple IMD, an approach such as MDDriver is perfectly adequate today and allows scientists to easily implement the IMD protocol in their simulation engines using our middleware library, which is independent of the simulation engine. The Narupa software suite uses Google's Remote Procedure Call (gRPC) library to provide a more easily customizable and extensible approach. Other technical options can be found in the variety of IMD implementations described in the literature. More recently, work towards standardized protocols for exchanging trajectory data was carried out, such as the MDsrv protocol, which is web-secure and could provide a foundation for alternative web-based IMD implementations. There are some possibilities that arise from the variety of possible approaches. We will mainly discuss aspects related to Stone's original IMD implementation. In general, only a few functions are needed to interface between the molecular dynamics, interaction, and visualization programs. A fundamental question is whether the individual interaction, visualization, and simulation components have interdependent communication schemes and whether they are managed by asynchronous processes. The software components of an IMD simulation must communicate efficiently, and at the same time the communication protocol must balance efficiency with network bandwidth requirements. Special code may need to be developed to improve this communication efficiency. Latency can be a major challenge in IMD when using contention-based networks such as Ethernet,

which can cause unpredictable delays. This limitation is problematic when determining the best route for network communication between the visualization and interaction components and the molecular dynamics backend, especially when dealing with computationally intensive tasks. It is advantageous to have an asynchronous version of the IMD interface for integrating its components so that latency is reduced and the approach can be adapted to different simulation programs. This is an important aspect for a satisfactory user experience as it improves responsiveness. However, depending on the interaction channels chosen - more on this later - such a design can disrupt the haptic experience if, for example, the simulation rate is not consistent and constant. In this context, problems with synchronization have led to the introduction of methods such as the use of a buffer in which data from the simulation is cached before particle positions are updated in the scene. This approach, which separates data reception and particle position updating, has the advantage of decoupling simulation performance from graphics rendering performance so that one is not affected by the other.



**Figure 5.** The three components required for IMD simulations - simulation engine, interaction management, and visualization front end - are coupled together and exchange data such as forces, energies, and positions. The eventual network and adaptation layers required for the coupling are not shown. Image under CC-BY License by Marc Baaden.

A general scheme of coupling could be described as follows. An interface adapts the data flow for IMD to the data structure in the molecular dynamics simulation engine. This adapter is specific to a particular simulation software. The main task of the adaptation layer is to convert physical values into the desired units, but it can also perform complex transformations, such as converting data from one discretization model to another. In a parallel application, the adaptation layer plays a crucial role in the redistribution and acquisition of data. When implementing IMD in a software package, the point in the simulation algorithm where data exchange is required must be identified. This exchange usually includes the transmission of atomic positions, the reception of forces, and the processing of control events for simulation. All this is facilitated by the visualization tool, which usually contains the interaction component. This process can be illustrated as follows: A front-end visualization program and a back-end molecular dynamics program communicate with each other to enable real-time adjustments to the molecular simulations. During each iteration of the event loop, the visualization program checks for updates from the molecular dynamics program and updates the screen representation of the molecular system accordingly. When the user applies a force via an input device, the visualization program passes the force to the molecular dynamics program, which incorporates it into the equations of motion for the molecules. Communication between the visualization and molecular dynamics programs can be facilitated by a communication server that allows efficient network communication. As mentioned earlier, a successful scheme for managing the visualization, molecular dynamics, and input device components is to divide them into three communicating, asynchronous processes. To optimize the performance of interactive molecular dynamics, it is critical to minimize delays and avoid any unnecessary synchronization between the different components. Although IMD is typically divided into these three concurrently communicating processes, including the interaction, visualization, and simulation components, further subdivision using multithreading can help reduce communication delays and remove constraints associated with, for example, synchronizing haptic updates with the visual display, resulting in even better performance. One aspect related to coupling in standard IMD applications relates to *in situ* and *in transit* live simulation analysis<sup>10</sup>, which can be performed with similarly designed modules as in IMD, even if these applications are not strictly speaking IMD implementations. These ideas can be extended to *in situ* control, reporting, and analysis and are very close to the spirit of IMD.

When we talk about technical considerations that relate directly to technology, it is important to keep in mind the required software stack that can limit implementation options if the learning curve is too steep. Here we need to mention game engines as a new type of framework that are on the rise for such developments, allowing a broader audience to experiment with these approaches, not just hardcore computer scientists. Design decisions for implementing an IMD framework inevitably include the choice of this software development environment. In the development of interactive molecular dynamics software, the computational aspects of the actual simulation or, in other words, the underlying physics-based simulation engine, such as the equations of motion, are typically programmed in a standardized language such as C or Fortran. These calculations can be fully transferred between different computer systems. However, the programming required for graphics and interactivity is highly system-dependent, making it challenging for developers to create cross-platform software that can run on different types of hardware and operating systems. This visualization component plays a key role in facilitating user interaction and exploration of the simulation results. An ideal program for such visualization would be capable of working with a broad range of input devices, animating the progress of simulations, and supporting hardware 3D acceleration for real-time rendering. The code structure of such a program should also facilitate extensions for novel input methods and communication with the simulation. To overcome these challenges, developers can use the specialized software frameworks offered by game engines. Here, we will focus specifically on these game engines, which are designed for creating real-time interactive graphics and can help in developing cross-platform interaction and visualization. The

Unity game engine, for example, provides a comprehensive set of tools and APIs for creating interactive and immersive graphical environments that can run on a variety of platforms, including desktop computers, mobile devices, and virtual and augmented reality systems. It is used in the Narupa<sup>11</sup> and UnityMol<sup>12</sup> frameworks for IMD applications, among others. By using software frameworks such as game engines, developers can leverage existing code and graphical assets, which can reduce the development time and cost of creating interactive molecular dynamics simulations. In addition, these frameworks provide a number of features such as physics engines, lighting and shading models, and audio support that can be used to improve the realism and interactivity of the simulation.

IMD has from its beginnings been a **technology testbed**. Initially haptic devices were all the hype and were of course tested with IMD. Then one came to apply this simulation methodology to combine with 3D visualization devices. The next step was to couple IMD as application with augmented reality, for instance demonstrated by Art Olson's pioneering work<sup>13</sup>. Finding technical means to enable multi-user collaboration in an IMD simulation has been explored quite early on. The latest, natural evolution has been to perform IMD using VR headsets<sup>11</sup>. IMD represent an excellent set of tools to test out such technologies, uncover some of its limitations, and understand the general features and relationships in terms of human-computer interaction and human perception of such complex scientific data. Let us look into ways to exploit the simulation feedback. IMD is designed to extend molecular dynamics simulations by providing instant feedback and giving the user direct control over the simulation. Force feedback can greatly enhance the learning experience in interactive simulations by providing additional insight. Haptic feedback provides additional benefits in molecular simulations. It provides proprioceptive feedback about the force controlling the simulation, which in turn can improve the user's interaction with the simulation. The integration of a haptic device together with visual feedback offers a new dimension of user perception. Physical effects such as the viscosity of the solvent and the mechanical resistance can be experienced by the user in a completely new way. This approach is well-suited for teaching purposes and can help to improve user experience and understanding, especially for non-experts. A haptic device with three degrees of freedom is quite intuitive and efficient for interacting with complex molecular models. The hardware requirements for this approach are modest and entry-level solutions are widely available. Research is still ongoing to develop more advanced feedback for instance taking advantage of additional torsion force feedback for a more refined manipulation experience.

An important aspect, to which we have already referred several times, is the way in which the force is applied and distributed to the atoms in the simulation. The force aspect is of key importance and the first question is how to apply and calculate these forces based on the chosen user interaction metaphor. IMD interactions are typically achieved by implementing a feature historically referred to as "Tug Mode". This mode allows the user to move individual atoms or groups of atoms to a desired position at any time. To effectively manipulate particles, two steps are often taken to interactively apply external forces. First, before particles can be moved, they must be manually selected. This is followed by the application of forces. The forces to be applied to the selected particles are calculated based on the user's selection and manipulation. In Tug mode, the user selects the atoms to be moved and specifies the target position. The dragged atoms then progressively move toward the target position as the simulation progresses. This is achieved using linearly moving constraint points that behave like springs and are attached to the atom in question to exert an attractive force toward the target position. Such a spring model is used to control the atoms in order to minimize abrupt perturbations during user interactions. In this approach, the atoms are directed to the equilibrium point where the spring is not under tension. The spring acts as a buffer for the user's interactions rather than using direct position updates. You can specify a scaling factor to control the strength of the attractive force and thus the speed that the moving atoms achieve. However, this method can lead to distortion of the system. To complete an overall manipulation, the atoms may

need to be moved in several steps, with new attractive forces generated at each step. These forces are used both for visual and for sensory feedback. The forces are sent back to the simulation engine. Proper scaling of forces is related to precise and judicious selection of atoms. A fundamental point of discussion is the effect of selecting multiple atoms instead of a single atom to avoid major structural changes in the system. We would like to point out that the adjustment of the simulation system can lead to strong structural distortions and jeopardise the stability of the simulation if the applied forces are not properly calibrated, e.g., if their magnitude is overestimated. The physical simulation engine may simply crash in response to such a situation. The importance of accurately selecting the atoms to be manipulated is illustrated by the potential risks, such as the possibility of a crash, that can occur if the selection is not done accurately. In addition, the selection must be done carefully so that certain structural features such as secondary structure elements are preserved during the manipulation. Especially for small systems, the performance of MD is significantly affected by the time required to manage the user forces. This impact is affected by the ratio of selected particles to the total number of particles in the system. The amount of data to be exchanged depends directly on this ratio. In general, trajectory smoothing or slowing may be required because the inherent jiggling of the atoms can be disruptive and counterproductive to an IMD simulation. The vibrations make force application difficult, which is one reason for using trajectory smoothing methods, of which there are quite a few. This problem can go away if you are working with coarse-grained systems, as we will discuss later, but it is a much bigger problem in all-atom IMD. There are some advanced considerations and methods to distribute the force to all atoms depending on the type of manipulation. This aspect was explored by Jamieson-Binnie in his dissertation. In particular, it should be emphasised that a tricky question is how to implement rotational interactions. This question leads to considerations of how to damp the forces and decompose their various components that contribute to the system changes.

Despite all these technical details, we should emphasize that implementing an interactive MD simulation is still a fairly trivial task. See below a simple pseudocode based on MDDriver to illustrate the approach.

```
# network connection setup
define_interface(port=3000, loglevel=0, client=True, hostname="127.0.0.1")
initialize_imd_interface(wait_for_interaction=True)

# initialize and define important variables
define_imd_variables(nbParticles=0, coordsVectors=NULL, imdEnergies=NULL,
                    nbForces=0, forceParticleIds=0, forceVectors=NULL)

# main loop
do
    IMD_get_coordinates(nbParticles, coordsVectors)
    # user code for visual rendering
    ...
    IMD_get_energies(imdEnergies);
    # user code visual rendering energy
    ...
    # user code for computing user forces to send to simulation
    IMD_send_forces(nbForces, forceParticleIds, forceVectors)
    ...
    # check for any user command to control the IMD simulation
    control_event = get_user_event()
    # handle control events (e.g. pause the simulation, change T, ..)
    ...
```

```

until(control_event == STOP_IMD)

# shut down properly
terminate_imd_interface()

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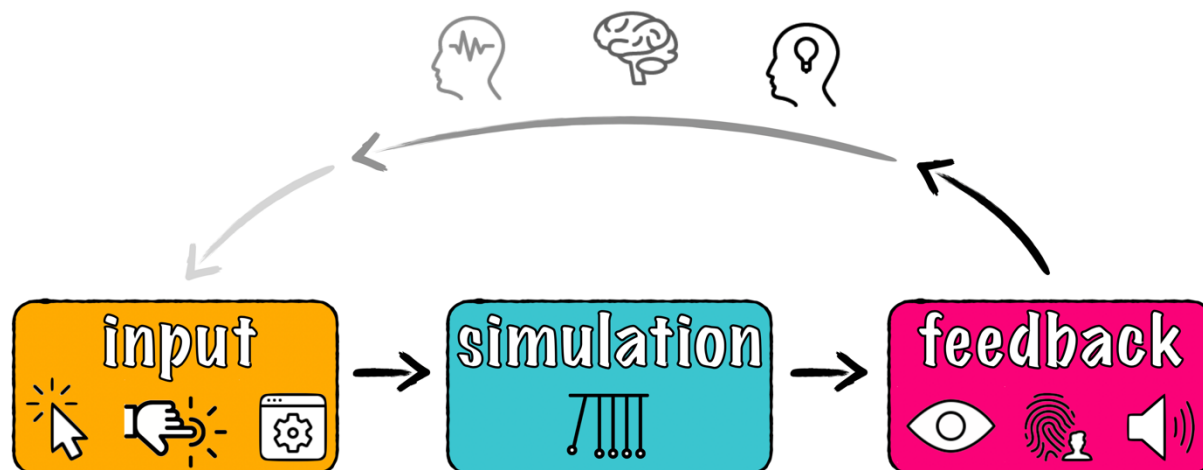
The pseudocode first defines parameters for the connection such as the network port, the role as client or server, the level of logging detail, and the hostname to connect to. The interface is then initialized with the option to wait for an interaction with the server to be established. Next, the relevant variables must be defined, then the main event loop begins. The coordinate vectors of the particles are received to update the rendering of the scene, as well as the energies for possible processing or display. A force vector is then sent back to the simulation based on the user interaction. The final step checks for a user command, such as to pause or stop the interactive simulation. If the simulation continues, the loop is restarted.

To end this technical discussion section, let us emphasize that the visualization engine still deserves attention. One of the pioneers in the field of IMD visualization is the VMD software. In our own work, we developed the UnityMol software from scratch with the particular goal of interactive simulations in mind and as a strong driving force.

#### Section 4: Simulation Methodology for interactive simulations. Innovative Approaches to Simulating the Dynamic World of Molecules

The specific Considerations of Interactive Molecular Dynamics of this chapter aim to provide an Overview of the methodology involved in performing interactive molecular dynamics simulations. This discussion will include the design of the simulation feedback, data collection, data analysis, and visualization techniques employed for that purpose. We further discuss the performance and scaling of IMD simulations over time, and the role of coarse graining in this context.

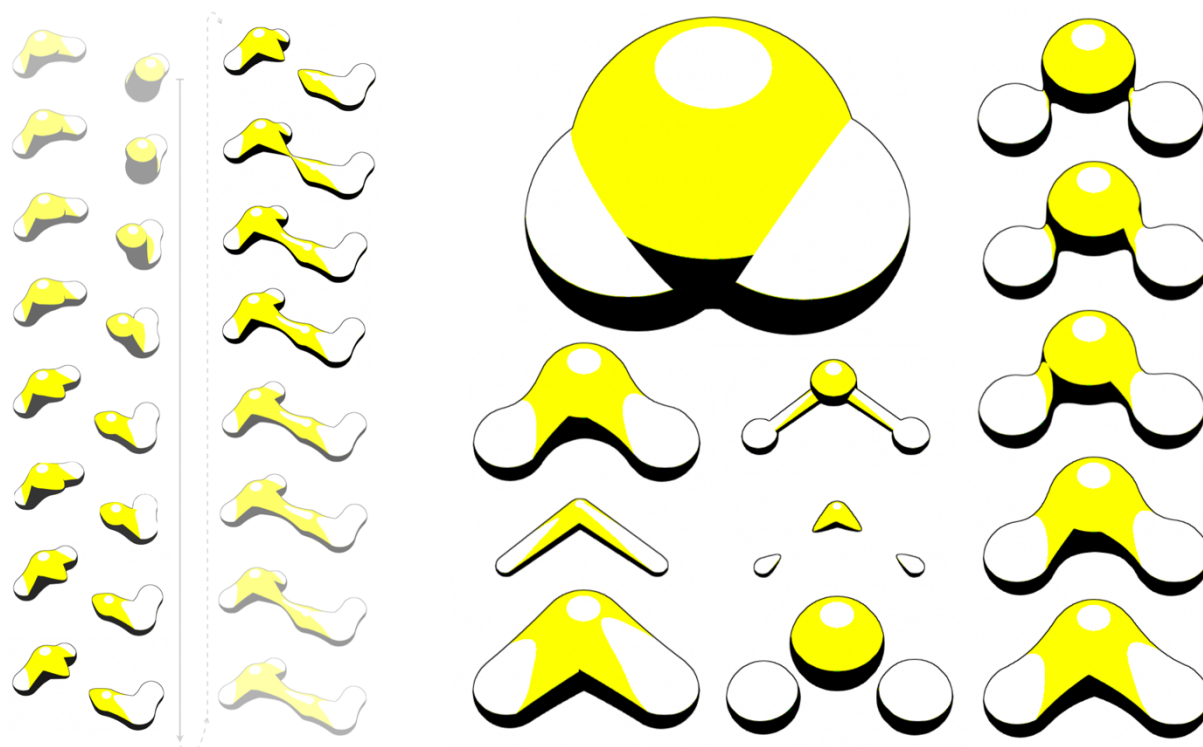
Live simulation feedback is at the heart of IMD simulations. Most often this is visual and tactile feedback, but in a few cases audio feedback may also be of interest. This aspect is formally referred to as multimodal rendering models and includes visual, haptic, and audio rendering. The visual channel is traditionally and by far the most commonly used, which means that visual feedback can be quite overwhelming in an IMD simulation. Therefore, using alternate rendering channels is very beneficial to reduce the load on the visual channel. Let us start with a discussion of the importance of visualization in IMD and a brief description of the different techniques that can be used to visualize the simulations.



**Figure 5.** The IMD simulation event loop: the user generates input to manipulate the simulation system, usually via an input device such as a mouse or joystick, or by changing simulation control

parameters such as temperature. This user input is passed to the simulation engine and processed. The information from the simulation is converted into feedback for the user based on multimodal rendering models, usually for visual, proprioceptive, or auditory channels. Based on this feedback, the user analyzes the situation and responds by adjusting the inputs that are fed into the simulation in the next cycle. Image under CC-BY License by Marc Baaden.

It cannot be overemphasized that visualization is required at multiple levels, from the graphical representation of direct interaction with the simulation to the ability to perform visual trajectory analysis. To cover all facets of such experiments, it may be useful to provide access to multiple interchangeable visualization environments for IMD simulations. More generally, in simple molecular dynamics simulations, visualization is an important tool for understanding how individual particles interact with each other in a system. This relationship allows us to observe the spatial arrangement and cooperative motion or binding between particles. For larger systems, visual abstraction may be required, and direct visualization of the actual molecular system can be complemented by analytical plots. For example, density and velocity fields can be displayed and energies monitored. Another application example is understanding the complex diffusion of lipids in a lipid bilayer, for which there are many visual techniques that can be used to convey the desired information. For such an analytically oriented purpose, real-time plots are very useful. It is then possible to combine different visualization techniques. For example, it is possible to selectively highlight subsets of particles that meet certain criteria, such as those with high potential energy or high velocity. Thus, visualization is not only indispensable, but highly customizable and configurable. It is entirely up to the user to decide what to do. While there is no point in running an IMD simulation if you can not see a minimum amount of information, such as what atoms you are interacting with or a representation of the force acting on the system, its direction, its magnitude, or a coloring of what is happening to that force and how it is being fed into the system, none of this is mandatory. For proper visualization, you need to find a simple way to measure a property of interest to generate data on-the-fly that can be visualized. Without going into details, we would like to mention how open it is in terms of what and how is actually implemented and displayed. With some IMD-specific extensions, it is possible to add a lot of value to IMD through visualization. In our own work, we have explored different approaches, from molecular visualization with VTK, to developing HyperBalls<sup>14</sup> specifically for IMD simulations in OpenGL, to developing visualization capabilities with a game engine that led to UnityMol, but also to using classical tools such as VMD. UnityMol is a molecular visualization tool based on the Unity game engine that allows users to explore and interact with 3D molecules. In particular, it includes features such as the HyperBalls representation, which is beneficial for interactive simulations. HyperBalls are a visual metaphor for representing smooth dynamic bonds. They are implemented as a parametric surface type. Hyperball's graphical rendering can be easily adapted to a variety of representations by setting a number of display parameters and was one of the first methods developed specifically for interactive simulations. In the latest implementation, rendering performance has been significantly improved to allow interactivity for a wide range of applications. The method is implemented with raycasting to enable high-quality rendering in the UnityMol framework. A good IMD setup requires iterations dependent on each specific use case to identify the visualization tools that work well and provide the expected functionality.



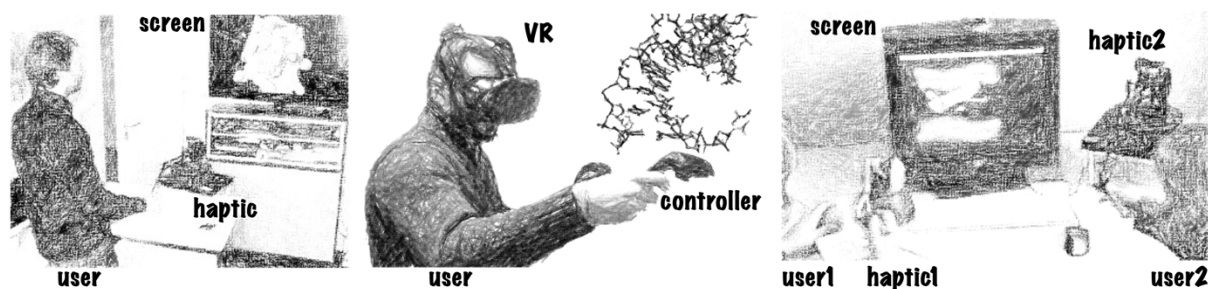
dynamic bonds

scale and shrink factor tuning

**Figure 7.** Illustration of HyperBalls ray-casting technique to display molecular graphics for interactive simulations. One of the IMD features is dynamic visualization of bonds, as shown at left for two water molecules with an oxygen acceptor and a hydrogen donor in yellow. HyperBalls seamlessly makes the hydrogen bonds appear as they form, and indicates their direction through disconnected hyperboloid expansions of the atoms involved. You can use the shrink and scale parameters to seamlessly switch between different common representations, as shown by the comparison at scale for a single water molecule on the right. Image under CC-BY License by Marc Baaden.

Haptic devices are widely used in IMD applications because haptic feedback offers additional advantages over commonly used visual feedback. Haptic feedback technology can be particularly useful when you are dealing with complicated and abstract concepts such as quantum mechanics, as it provides a physical intuition of the subject. A more interactive approach has been shown to effectively integrate the intuitive skills and insights of chemists into the search process, and the proprioceptive feedback provided by haptic devices directly supports the user's intuition by triggering natural reflexes through the forces felt. The use of a haptic pointing device with force feedback allows direct manipulation of three-dimensional structures so that the operator can feel the forces associated with structural changes. This approach offers significant advantages for teaching purposes. As described in the previous section, an important part is to define the interaction models for tugging particles to be used for iMD. More specific implementations are conceivable, e.g., using interaction models to manipulate (some) proteins of a simulation system directly, e.g., as rigid bodies, rather than indirectly by pulling on selected atoms to achieve the same effect. Depending on which physical setup is targeted, the limits of the device's working range both in terms of workspace and force rendering must be considered. Although the precision and intuitive feedback of a haptic device are not required for user interaction, and a simpler interface will suffice for a number of applications, the intuitive nature of touch makes it a method of choice to lower the barrier to adoption of the IMD method.





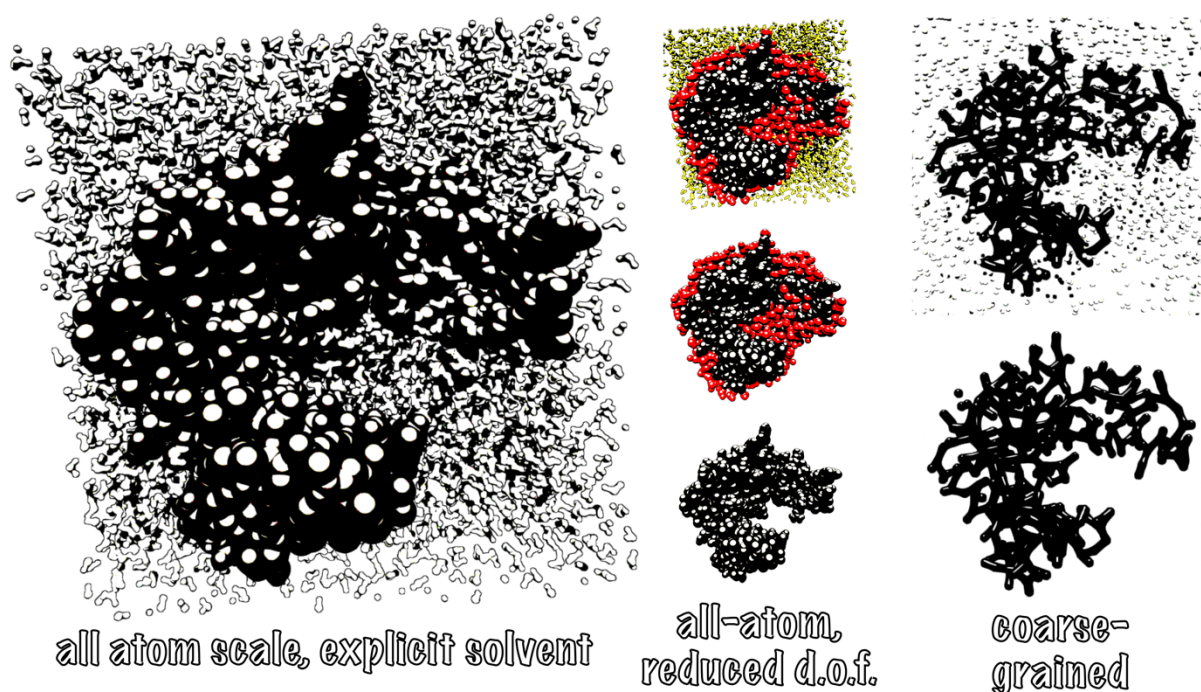
**Figure 8.** Three IMD scenarios. Left: A single user in a desktop environment using a haptic device to interact with the scene displayed on the screen. Middle: an immersive virtual reality (VR) IMD manipulation by a single user wearing a VR headset and using VR controllers for interaction. Right: a semi-immersive collaboration with two users, each using a haptic device and 3D glasses, sharing the central screen for visualization. Navigation devices such as the mouse or the 3D SpaceNavigator mouse are seen in the desktop scenarios, but are not described in detail here. Image under CC-BY License by Marc Baaden.

Interactive molecular simulations were specifically chosen by Rau et al.<sup>15</sup> for sonification experiments. Since an acoustic output for molecular visualizations is not usually available, they experimented with sound to acoustically reproduce selected information from the simulation data. Sound is used to highlight events in molecular dynamics simulations to divert attention from the visual channel and emphasise important phenomena. Sound can provide a more immersive experience and increase teaching effectiveness.

An important requirement for any IMD simulation is performance and scaling. We first discuss some historical developments and use Leech's original performance metric<sup>4</sup>, atomic updates per second, which is the product of system size and time steps per second, to illustrate the fantastic advances in the field. This metric is based on the assumption that simulation speed generally decreases approximately linearly with system size, since MD uses a threshold when calculating non-bonded forces over long distances. In this case, performance can be approximated in terms of atomic updates per second to make predictions given the size of the system being simulated. Compared to the early days of IMD simulations, where typically a few thousand atomic updates per second were achieved on processors such as a SGI MIPS R4400 at 250 MHz and the simulations spanned a few thousand atoms, more recent scaled IMD experiments reported in the literature achieve over 22 million atomic updates on 384 cores of Xeon E5530 CPUs at 2.40 GHz for a system with 1.7 million atoms<sup>16</sup>. A specific issue related to the general performance characteristics is the cost of interactivity of the IMD approach, which has been reported to vary from a negligible impact of about 1% to almost 20%, depending on the conditions under which the simulation is run. A strong impact is for instance seen when many atomic positions are updated in a large simulation system. In general, three regimes can be distinguished. The scalability of the molecular simulation code plays a critical role in IMD performance when studying large simulation systems. However, when the number of particles drops to a medium range, the interactive simulation is slowed down by network and data exchange, graphical rendering, and user interaction alike. For small systems, on the other hand, the interaction component is the main limiting factor, followed by the display component. The exact boundaries between these three areas depend on the software components used and are constantly evolving, so we will not attempt to quantify them.

Molecular dynamics calculations are inherently slow compared to the fast interactions that occur between atoms in real molecules. A limitation arises from the correct modeling of high-frequency vibrations, which requires a simulation time step of about one femtosecond. Since the dynamics of the proteins of interest occur on a much longer time scale, at least thousands to millions of times, the simulation must cover such time scales within the time frame in which the user can perform

interactions. For interactive molecular dynamics to be effective, these user-initiated changes must be made in a reasonable amount of time, typically within seconds to minutes. Often, this boils down to optimizing the critical parts of the interactive time calculation of physicochemical properties and energies. For IMD, these are typically non-bonded van der Waals interactions and electrostatic interactions. To achieve an optimized calculation, there are techniques such as dynamic and static atomic filtering. In the past, there were generally two ways to improve performance: speeding up the computational engine and reducing the "active" system size. To improve performance, parallel versions of MD have been used, which scale well with increasing numbers of processors. To reduce the size of the system, dynamical calculations can be restricted to a specific region of interest in the molecular systems and, for example, to solvent molecules within a certain distance threshold. The other atoms in the system are stationary but act on the forces exerted on the mobile atoms. Such a region is referred to as a molten zone. Although this solution leads to some loss of accuracy in the simulation, it definitely helps to improve performance when resources are limited. Nowadays, with the advances in multiscale representation and coarse graining, these traditional solutions are less necessary.



**Figure 9.** Possible IMD configurations for simulating conformational changes of the enzyme guanylate kinase. The most detailed scale is an all-atom representation of the enzyme with explicit solvent. The number of degrees of freedom in the all-atom simulation can then be gradually reduced by first introducing a molten zone, the enzyme and nearby water molecules in red, surrounded by an immobile solvent environment in yellow. It is possible to consider only the surrounding water layer and omit the more distant solvent molecules. In an implicit solvation treatment, the degrees of freedom of the solvent are completely removed. Alternatively, it is possible to switch to a coarse-grained representation of protein and water. The most approximate representation would be a coarse-grained protein model with implicit solvent or even no solvent at all. The computational cost for the latter option is very low. Image under CC-BY License by Marc Baaden.

Let us emphasise the possibilities offered by coarse graining<sup>9</sup>. Since the speed of the molecular dynamics simulation determines the time frame available for interactive exploration, changing the representation level could be a viable solution for a particular biological problem. This approach implies that it is important to have multiple representation levels to choose from. More generally, coarse-graining provides a better compromise between the time scale of the simulation that can be

covered and the human time scale to which the operator of an IMD is bound. We illustrate this fact with a selection of possible IMD configurations for the enzyme guanylate kinase in water, from a fully explicit representation of all atoms to a coarse-grained representation with implicit solvent, as shown in Figure 9. A good approach to ensure that the user does not have to exert excessive force to achieve the desired manipulation in an interactive simulation is to choose a coarse-grained resolution. As indicated earlier, the problem of redistribution of the applied force and the resulting deformation of the molecule when force is applied is then much less pronounced or may even disappear altogether. This artefact is very present in all atomic setups, but it is a much smaller problem at the CG level. CG simulations provide a good mix of higher computational speed and reasonable modelling accuracy compared to more detailed all-atom simulations. The cost is generally offset by an acceptable loss of precision. Such a setup is particularly useful for initial investigations and hypothesis development for rare molecular interaction events. Multiscale and multiphysics simulation models allow a wide range of fine-tuning of an IMD simulation setup.

Nowadays it is only a small step from simple Interactive MD to immersive (interactive) molecular dynamics, for example in virtual reality environments. One can describe all these possibilities with the term augmented molecular visualization. We have now discussed all the ingredients for a functional problem solving environment and will move on to applications, including immersive applications.

## **Section 5: Unlocking New Frontiers: Applications of Interactive Molecular Dynamics**

The applications of IMD potentially extend to many subfields of molecular systems, from materials science to (bio)chemistry to drug discovery. From a scientific point of view, the most natural connection can be made to the field of mechanobiology, which we will mention as well. This section gives a brief overview of some of these areas where Interactive Molecular Dynamics is used. This area is far too extensive to cover exhaustively. For simplicity, we will illustrate the section mainly with examples from our own research. We will cite some specific applications or case studies to illustrate the impact of IMD.

The application scenarios can be tentatively classified according to their purpose and we will discuss the following aspects. Setting up and tuning simulations is a possible playground for IMD approaches that facilitate the exploration of modelling parameters to improve the method. Model creation and editing benefit greatly from interactivity. It is then natural to explore molecular conformations and, more generally, to explore the phase space interactively. It should be noted that the IMD approach can be used specifically to study molecular properties, such as the mechanical properties of molecular assemblies. We conclude with comments on the playful, educational, and artistic applications of IMD simulations. In all these applications, the perturbation relaxation approach is a common tool of investigation. The response of molecular systems to perturbation by the user offers new insights into a variety of properties. Overall, it is clear that IMD simulations enable exploration of rare events by increasing their probability through user interaction. Interactive simulations of biochemical systems are valuable as they provide intuitive and enhanced perception and can be used for applications such as membrane anchoring, performing interactive docking, and generating new hypotheses, e.g., related to membrane fusion. We can induce large conformational changes, study lipid-protein interactions, and characterize a molecular model in terms of its mechanical properties.

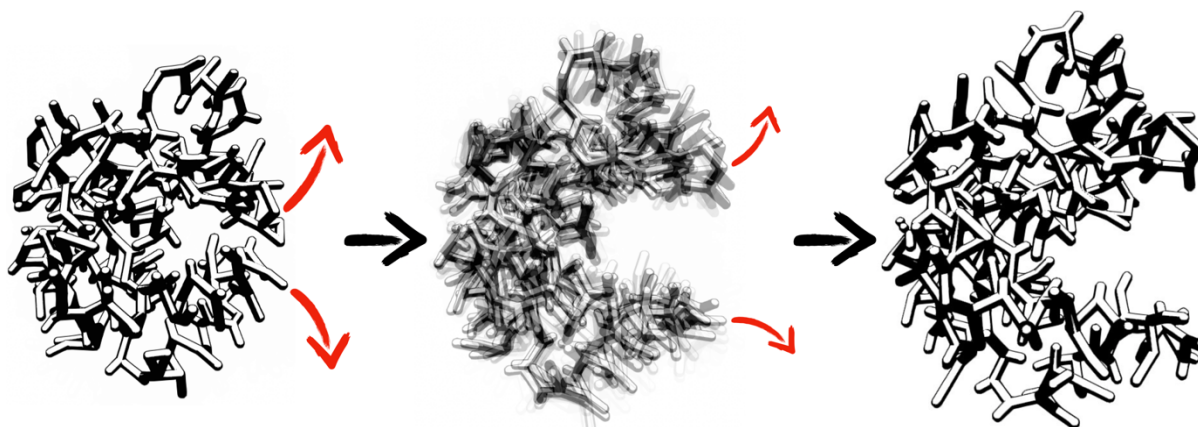
When setting up and tuning simulations, it is very helpful to make the tasks related to simulation tuning and parameter control interactive, as the developer can immediately "see" the effects of changing a particular setting and observe how the molecular simulation responds. This interactivity enables rapid and intuitive prototyping for testing novel modeling methods where the effects of

changes to parameters or simulation algorithms on physicochemical properties and computational exploration can be directly observed. This feature has been little explored in previous studies, which have focused primarily on ways to "control" or "steer" the interactive dynamics for application purposes. The use of interactivity in an exploratory context provides immediate tactile feedback via haptic devices that can be used to enhance known force fields or test for atypical behavior in newly developed parameters. These observations can lead to intuitive perception and better insight into the underlying simulation method through careful post-IMD analysis and quantitative data collection. Live tuning of common simulation parameters offers interesting opportunities. The most basic inherent control is, of course, the scaling of the user force in the IMD. The ability to control the simulation temperature, for example by decreasing it, is very useful for reducing background motion when trying to assemble a particular molecular construct. Such capabilities are being explored by a few packages, often for educational use. Handling temperature changes is a good example, allowing visualization of processes such as crystallization or evaporation in an educational context<sup>17</sup>. More advanced features include the ability to slow down the simulation, which enables more precise interactive manipulations. IMD can be used as an advanced scripting interface to control the simulation in an automated manner, especially during system setup and assembly. Here, direct user interaction is replaced by scripted behavior. We have tested such a scripted setup procedure to model some parts of the flu virus at the coarse-grained level and connect elements that were designed separately. Another key concept is to use a series of IMD simulations setup at different resolutions for comparison in order to improve a particular simulation method and make an informed decision between accuracy and flexibility. Simulation results can be used to identify discrepancies and highlight the strengths and weaknesses of the underlying modeling methods. This information allows the IMD user to choose the best representation for a given molecular system based on specific requirements. The approach provides information on the accuracy and implementation of methods and can validate studies performed at different modeling scales.

Model building and editing is another common scenario for which IMD should be part of every molecular modeler's toolbox. It is of great importance for integrative modeling, for example. Molecular Dynamics Flexible Fitting<sup>18</sup> (MDFF) is based on molecular dynamics and is driven by forces derived from the experimental target data to be fitted. Originally, this computational technique was developed to determine structures using cryo-electron microscopy data over density maps. Although the automatic methods of MDFF work well in most cases, they cannot fully capture the complexity of certain structural regions. Therefore, MDFF refinement can be switched to an interactive mode where the user can manipulate the model in real time and focus on specific regions of interest. In this mode, additional analysis can be provided to the user during the interactive simulation to evaluate the quality of the fit in real time. With this interactive tool for unrefined atomic structures, users can achieve a better fit to low-resolution electron density maps. With iMDFF<sup>19</sup>, They can intuitively explore the intricate structures of large biomolecular complexes through haptics. The immersive Isolde environment<sup>20</sup> was developed based on these principles for experimental structure determination. IMD can be very useful for building models and testing hypotheses. In our own work, we have studied artificial water channels in a membrane environment. A single such channel did not stabilize in the membrane environment and we were able to use IMD to construct a larger artificial water channel assembly. Such an approach can be easily used to construct a variety of supramolecular assemblies and study their stability. Again, the coarse-grained representation offers additional possibilities and a good trade-off between the level of detail of the representation and the complexity of the intermolecular interfaces to create an initial model that can then be refined at the all-atom level.

The study of molecular conformational changes in interactive experiments is very informative, for example, for the study of enzyme systems. It allows to link conformational fluctuations with biological function, for instance when substrate binding clefts close and open. In the case of

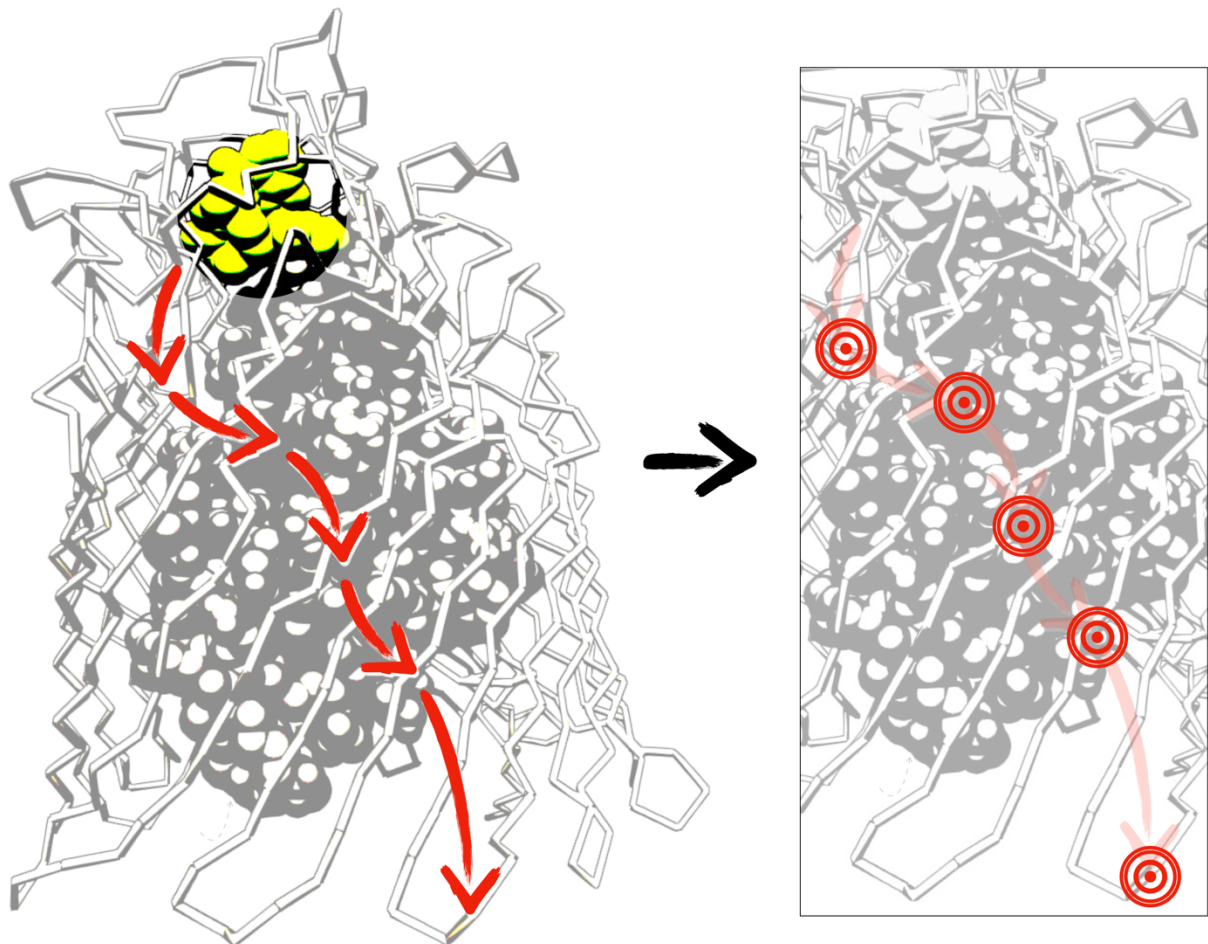
guanylate kinase (GK), we used IMD to study the large conformational changes associated with the enzyme's closing mechanism<sup>9</sup>. Guanylate kinase is a U-shaped molecule whose function is to bring its GMP and ATP binding sites into close contact for the enzymatic reaction. Using IMD simulations, we were able to identify the crucial role of a specific loop region in the closure process. These findings allowed us to propose a new hypothesis on the closure mechanism, where GMP docking could trigger the shift of the loop and drive the process. An interactive approach using IMD simulations provides an innovative and dynamic method for structural exploration that uses computational models to illuminate such important conformational changes. Complementing these experiments, researchers are studying the behavior of the apo enzyme, a form of the enzyme that lacks a substrate. By applying forces to different residues, researchers can induce different conformations of the enzyme and observe hydrogen bond formation and changes in system energy. The immediate visual feedback from the IMD simulation allows them to evaluate the most favorable hypotheses for the enzyme's conformational changes. To generalize, a typical experiment involves inducing changes in the structure of the protein and observing the effects of these changes on its function. The response of the protein allows the identification of key residues and structural elements involved in the conformational changes by observing the movement of atoms and molecules in real time. Consistent with the considerations discussed previously, researchers often use both a coarse-grained and an all-atom representation of the protein to perform IMD simulations for these types of experiments. Coarse-grained simulations allow for efficient exploration of different conformational changes, while all-atom simulations provide a more detailed and accurate picture of the protein's behavior once the range of possibilities has been narrowed down. Therefore, IMD simulations are an exquisite tool to study conformational changes in proteins and to better understand the mechanisms involved.



**Figure 10.** Exploring a large conformational change of the guanylate enzyme by IMD simulations. The U-shaped enzyme is guided repeatedly to open and close its binding cleft where substrates bind. Typically the user would choose interaction points close to the tips of the enzyme (indicated by red arrows) to manipulate the coarse-grained IMD simulation interactively and analyze visual and haptic feedback in real time. Image under CC-BY License by Marc Baaden.

Exploration of phase space and interaction with trajectories is another core function of IMD and leads naturally to the use of rare event sampling. Combined with interactive visual analysis, it provides a powerful means of characterizing the simulation system. In the drug development domain, this leads to an interactive, immersive, intuitive design tool that we previously described as I3 rational design. Phase space exploration can be implemented with varying degrees of interactivity. The automatic control of molecular simulations is an IMD variant. It works by adding to a conventional IMD system the ability to track the position of targets, compare them to an expected trajectory, and deploy new forces accordingly. The bacterial iron transporter FepA is a good example of such SMD live control of a simulation<sup>21</sup>. FepA is an outer membrane protein found in Gram-negative bacteria that transports iron across the bacterial cell membrane. It consists of 22 beta-

strands that form a porin-like structure, with a binding site for iron-containing siderophores in the N-terminal domain. Our goal was to extend previous experiments with the FepA channel that found two possible pathways for iron transport through the channel. However, interactive control along these pathways by a human operator required too much force to be realistic. In this case, the initial IMD explorations provide direction for the simulation, which is more complex than a simple linear motion force normally used in SMD. The method is based on three steps. To begin, the user runs an interactive session to get an overview of the simulation system and rule out some possible paths, and finally decides on one or more paths to be tested automatically. Second, the user defines a set of key points on the chosen path, called targets. Third, the system successively pushes the controlled complex toward the targets in a computer-controlled IMD simulation. The last step can be divided into three main functions: Monitoring the controlled complex, monitoring the location of the targets, and outputting the new forces. The system receives the atomic positions from the simulation at each output step. The current position of the controlled complex and the targets is extracted from the atomic positions. The magnitude and direction of the force acting on the controlled complex depends on the difference between the position of its center of mass and the active target. The system can be run in two ways, either automatically in batch mode, or interactively during a user-controlled session. In batch mode, the rest of the application can be executed without user intervention. The automated sessions provide the user with several metrics that give a quick overview of the status of the control process, including information on the currently applied forces, how far the next target is away, and an estimation of the remaining time to completion. Using these metrics, the user can observe the behavior of the control process and quickly decide if the system should proceed on its own. If not, the user can still intervene by switching to an interactive session if, for example, they determine that the system is stuck. The system was tested on the FepA channel and was able to automatically reproduce the experiments with surprising speed. Such an approach is capable of running large molecular simulations (semi-)interactively and allows for a variety of control scenarios.



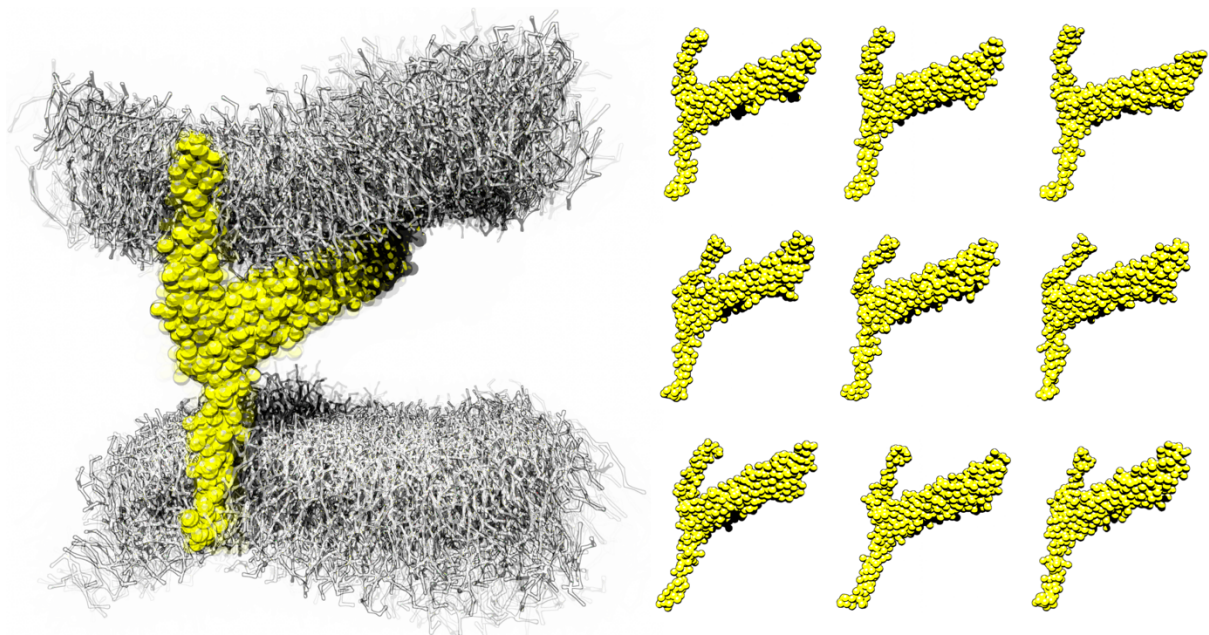
**Figure 11.** Guiding a siderophore through the bacterial iron transporter FepA. The siderophore is shown in yellow, the outer beta barrel is indicated by the trace of carbon alpha atoms, and the inner "plug" domain is shown in space-filling view. A preliminary IMD experiment is used to determine a possible pathway (red arrows). Based on this initial exploration, targets are established as shown in the figure inset. These targets are used in a semi-automatic replica to achieve a similar transport result, but with lower forces to reduce the perturbation of the simulation. Image under CC-BY License by Marc Baaden.

Let us now take a look at another example where fully interactive control was used in relation to OmpT, an outer membrane enzyme<sup>9</sup>. We studied how a small peptide substrate mimetic could be interactively docked to this enzyme. Exploring the dynamic lock-and-key interactions between substrate and receptor is very informative. Interactive molecular dynamics provides real-time insights into the interactions between enzymes and their substrates. By controlling the movement of atoms and molecules in such a simulation, it is possible to observe the effects of these interactions and gain a deeper understanding of how these biochemical catalysts work. In IMD experiments with enzymes and substrates, researchers focus on studying the interactions at the catalytic site, the site where the substrate binds to the enzyme and is converted. One approach is to apply forces to the substrate and observe the response of the active site residues, i.e., the amino acids in the enzyme that are involved in substrate recognition and docking. By observing the relaxation of the active site, researchers can identify the key residues involved in these processes. Researchers can observe the hierarchy of contacts between the substrate and the various catalytic residues, as well as the formation and disruption of hydrogen bonds. By making small shifts in the substrate, researchers can observe changes in the system and assess which interactions are most likely to lead to irreversible changes. Overall, the IMD experiments provide valuable insights into the interactions between

enzymes and their substrates. They give researchers a real-time insight into the behavior of these systems and help them deepen their understanding of how they work.

In mechanobiology, there are quite a few applications that lend themselves to investigation by IMD. From the historical perspective mentioned earlier, we have already discussed that atomic force microscopy provides a clear motivation for developing a digital twin with IMD. In such cases, we have a direct interest in performing IMD simulations with external forces that can be mimicked and explored by the user, who can control and explore every aspect of the virtual experiment. Here we will discuss experiments involving the SNARE complex<sup>9</sup>, which is central to membrane fusion in cells. The SNARE complex consists of a bundle of four protein helices that interact with each other to bring the vesicle and target membranes together so that fusion can occur. Formation of the SNARE complex is critical for neurotransmitter release, hormone secretion, and other membrane trafficking processes. We performed IMD simulations with a force feedback device for two specific studies to investigate the mechanical properties of the protein bundle and lipid-protein interactions. We found that using haptics to probe our model of the SNARE complex significantly improved the intuitive perception of its mechanical behaviour.

This example is well suited for studying the mechanical properties of the molecular assembly of SNARE helices. The aim was to investigate information transfer, in particular the molecular stretching and deformation forces resulting from disruption of the lipid bilayer from a distance by pulling on the hydrophilic and solvent-exposed N-terminal region of the protein bundle. By pulling on this specific part of the molecule, researchers can observe how the structure and overall stability of the system respond to an imposed force. This observation allows for a better understanding of the functional role of the different parts of the molecule and how they interact with each other. For example, in the case of the SNARE complex, pulling on the N-terminal part of the bundle causes the entire protein bundle to stretch. This elasticity demonstrates its structural and mechanical response to the applied force and eventually triggers membrane perturbation at the opposite, membrane-anchored C-terminal end. Further simulations can be used to study the structural integrity of molecular assemblies by testing their self-association through hydrophobic complementarity, e.g., by bringing individual SNARE helices together one-by-one. These interactive simulations provide a powerful tool to gain insight into the mechanical properties of molecular systems and their potential functional role in biological processes.



**Figure 12.** Investigation of the mechanical properties and membrane anchoring of the SNARE complex in a CG IMD simulation. The four-helical protein bundle (yellow) is inserted into a double



bilayer system. The water particles are not shown for clarity. Selected snapshots of the protein are shown to illustrate the exploration of its conformations. Image under CC-BY License by Marc Baaden.

The study of protein-membrane interactions is crucial for understanding cellular processes and can be explored very efficiently using IMD. The anchoring of the transmembrane domains of the SNARE complex in the membrane is a good example for studying the stability of its transmembrane helices and the strength of their incorporation into lipid bilayers. One focus of such studies is the incorporation of the transmembrane domain into a lipid bilayer, and the role of certain residues-in our case, for example, two consecutive tryptophan residues-in helical anchoring was investigated. These residues were found to play a key role in anchoring in the membrane and to maintain a stable position in the membrane despite various perturbation and relaxation attempts. Another focus was on the realignment and repositioning of certain residues, either within the membrane environment or in the interfacial region next to the aqueous solution. The results of such simulations provide intuitive clues to the balance of different forces in the system, e.g., between lipids and between the protein and lipids, which is crucial for understanding protein-membrane interactions. Such interactive molecular dynamics simulations of protein-membrane interactions and protein anchoring in biological membranes are first steps towards a more comprehensive insight into the structure and behavior of proteins in cellular environments in general.

Gamification and the use of human input for scientific purposes is another application area that could build on IMD in the future. Experiments in this direction can be achieved through an interactive-intuitive learning process. They can be considered as a new trend in structural biology moving towards human computing. In our own activities, we were able to set up an RNA folding task as an early form of such an interactive experiment<sup>22</sup>. Participants predicted a significant amount of native folds. This shows how interactive simulations can help laypersons accurately predict the structures of RNA molecules. It appears that humans explore the phase space, i.e., the set of studied conformations, more comprehensively and rapidly than a computer. They propose plausible alternative conformations and have been shown to be able to visually acquire trajectory information and assess the stability of simulated molecules. By linking the results of a large number of IMD simulations performed by many individual users, IMD could enable large-scale and intelligently controlled sampling of protein conformations beyond the capabilities of existing brute-force computational methods. For an experiment of this scale, it is also worthwhile to investigate and optimize the intrinsic robustness of the underlying MD setup. Since human problem-solving strategies differ from and complement existing purely computational methods, such approaches open up new possibilities to be explored.



**Figure 13.** IMD simulations in the classroom. Left: RNA folding is taught using IMD approaches in which students "compete" against each other to achieve the most accurate fold. Right: "BioArcade," an IMD arcade machine that playfully introduces students to IMD simulations and scientific fields such as chemistry and biology. Image under CC-BY License by Marc Baaden.

Last but not least, let us point out the enormous potential of these methods for educational and artistic use. In an IMD study of interactive teaching of enzyme catalysis<sup>23</sup>, most students found this method more engaging and effective than the traditional approach. They reported better understanding and increased interest in continuing their studies. Students were similarly positive about an interdisciplinary biology curriculum that emphasized molecular modeling and IMD<sup>24</sup>. Even younger students at school age who got to see an IMD setup "disguised" as an arcade machine found that the moving molecules that responded to user input attracted more attention. Artistic applications offer many possibilities as well, but querying the scientific literature reveals that they are rarely documented.

Using a wide range of applications, we have shown the potential of IMD approaches for many different use cases. Let us now consider some of the limitations and challenges that interactive simulations bring.

## **Section 6: Overcoming Limitations, facing challenges and Charting New Paths for Interactive Molecular Dynamics.**

We discuss the limitations and challenges associated with performing interactive molecular dynamics simulations. First, we raise the question of the intrinsic validity of such simulations, addressing the limits of accuracy and stability of such simulations. One particular challenge is the reproducibility of IMD experiments. Further limitations arise from computational resources and visualisation artefacts. We conclude with considerations on how to improve the acceptance of the IMD method.

A difficult question to answer, but one that is necessary to make IMD a widely accepted scientific approach, is the validity of interactive simulations. The changes operated on the system by the manipulations may raise questions about the validity of the simulation. The effects of manipulations may strongly alter the course of the simulation. This issue is, of course, related to the challenges of provenance and reproducibility of such experiments, discussed below. Human interventions lead to changes in the simulation system by adding uncontrolled constraints to the simulation. These experiments typically involve a brief interactive session in which IMD scenarios are created that are not in equilibrium. These scenarios may lack appropriate controls or constraints on interactive actions. Therefore, from a statistical mechanics perspective, such scenarios may not represent a realistic state. Applied external forces can help a system overcome potential energy barriers between desired states, but they may negatively impact the validity of the simulation. The addition of constraints increases the total kinetic energy and temperature of the system and can disrupt the simulation if the manipulations occur faster than the system can respond. This situation can be mitigated by a temperature bath, but if a strong attractive force is applied to an atom, energy can be added faster than it is removed, resulting in a significant temperature increase. This increase can be especially problematic in the hot region near the manipulated atom. To mitigate this situation, the hot region can be specially treated by a separate temperature bath. This observation raises an important general question, namely whether the interactive simulation itself is the intended outcome - and therefore should be well-behaved to some degree - or used exclusively for the development and evaluation of hypotheses or new ideas. In some cases, existing data, such as experimental information, may allow IMD simulations to be kept within reasonable bounds, such as in model building and refinement applications. With the constraint imposed by the experimental data, the interactive manipulation is guided towards valid conformations. Another potential problem is that IMD exploration is rarely exhaustive and depends largely on the user's knowledge.

Another limiting factor is that human intervention is difficult to replicate. Since the human element in an IMD simulation is unpredictable, one must develop a strategy to deal with the randomness of

such experiments. This raises the question of how reproducible a particular experiment is and how to create controlled conditions. Reproducibility can therefore be difficult to manage, but is achieved to some extent by recording all user interactions in a file for later replay and analysis. To obtain more reliable results, a simple method is repetition, where the same operator runs the same experiment several times. The results of all simulations are then evaluated together. This strategy helps to collect a statistically significant sample. The recorded user data allows comparison of forces in separate simulations by repeating user interactions from the stored data. With such recordings, you can use a computer to repeat the experiment. The set of user interactions is replayed multiple times to analyze the simulation's response to those interactions statistically. This approach can be extended along the lines described in the Applications section to circumvent the time constraint of a human manipulator mentioned above: One way to reduce the gap between the two characteristic time frames of the human interaction and the actual physical simulation is based on reproducing the human interaction pattern that was previously recorded by the computer, but over a longer period of time. Another approach to achieve reproducibility in the future could be the use of neural networks trained on the operator's input to enable autonomous and intelligent replication of such experiments. It should be noted, however, that reproducibility is not always necessary, especially in interactive experiments where the goal is to take advantage of human expertise and intuition and enhance the spontaneous and unpredictable aspects of the approach.

The crux of performance is a difficulty you should keep in mind for IMD approaches. As mentioned earlier, IMD's technology-driven progress has been marked by significant milestones, particularly in the area of interactive visualization and manipulation. However, it was only in the last two decades that all technological requirements were met, which for a long time limited the application of these simulations in everyday science. Nowadays, this limitation has almost been lifted. However, all-atom molecular dynamics is still not fast enough for an interactive mode. The forces required to generate system feedback in a time frame suitable for a human, typically on the order of minutes, still exceed biologically meaningful force thresholds. The simulation time span that can be explored within minutes provides insufficient sampling of molecular configurations compared to the time frame that is characteristic of biological processes. There is also the problem of excessive forces, which occurs when the discrepancy between the time scale of the simulation and the user's time scale is too large, so that the user exerts an excessive force to observe "something" in the available time. As computational power allows us to span time scales in IMD simulations that we may have only dreamed of a decade ago, our expectations of how much and how long a trajectory should be sampled also increase, so the discrepancy between IMD feasibility and scientists' expectations remains fairly constant. As a result, the interactive MD simulations fall far short of the time scale standards of the non-interactive MD runs.

There are certain IMD challenges that can be related to human challenges. We have already mentioned the importance of visualisation and human capabilities to recognise patterns and interpret the simulation process. However, these human capabilities have a downside: we can be distracted by details. Visual continuity is one such aspect, and it has been argued that visual artefacts in rendering can distract our attention from the core phenomena of a simulation, making it important to correct such situations. Recently, a method has been proposed to preserve visual continuity when depicting protein secondary structures in trajectory visualization and interactive simulations. This method is a good example of this phenomenon.

In addition, it is important to assess what is still missing for widespread application and to make further progress in this area. IMD simulations are not yet widely used in computational biology. There, it is more common to run a series of offline simulations and then visualize and analyze the results. However, interactive molecular simulation tools promise to more efficiently handle time-consuming tasks such as modeling particularly complex biomolecular structures or supporting

approaches such as rational drug design with respect to pharmaceutical applications. To date, interactive molecular simulations are not widely used and only occasionally reported in the literature. In this context, it is worth noting that IMD simulations are potentially invisible to the scientific community. Since a main goal of the IMD may be to define a priori a strategy for a project, to formulate and evaluate initial hypotheses, and to identify the most viable options for using traditional non-interactive simulations, the work done in the exploratory IMD phase is not always cited in later publications after these tasks have been accomplished. Because the main contribution was to formulate preliminary hypotheses that were subsequently tested using conventional methods, such use of IMD for internal purposes may remain largely unknown in the scientific community. Despite the many challenges IMD faces, the future still looks quite bright for this family of approaches, as we will discuss in the next section.

### **Section 7: Where is the future of Interactive Molecular Dynamics heading?**

Let us venture into the future and share some thoughts on what the next frontier in interactive molecular dynamics might be. In this discussion of future trends and advances in interactive molecular dynamics simulations, we will look at developments such as machine learning algorithms and the integration of quantum mechanics.

An anticipated future direction in interactive molecular dynamics is to provide a more solid theoretical basis for studying the effects of human interactions on the simulation. This knowledge could lead to the development of conditions that allow the use of IMD trajectories on thermodynamic grounds. Another development occurring at the same time is the steep increase in computing power. Thus, in the near future, quantum-mechanical interactive simulations for systems that were previously inaccessible may become more and more possible and soon be part of the standard IMD repertoire. Moreover, the constraints imposed by human interactivity continue to motivate new research into the development of ever more efficient simulation codes, as we can observe in other fields. This is true for algorithms such as the Fast Multipole Method or the Lattice-Boltzmann Method, as well as for new numerical schemes such as asynchronous parallel computational models. Other results of interactive molecular simulations that are more fundamental in the field of human-machine interaction, in particular to understand why it is difficult to catch moving targets, an important problem that arises directly from the complex activity of selecting atoms to control during an ongoing simulation.

As we discussed in the previous sections, humans have been shown to be able to explore phase space more comprehensively than automated approaches. This human capability raises the prospect of collaborative and quantitative IMD simulations. Both have been little explored and show great promise. Collaborative approaches have proven very successful in structural studies, e.g., with FoldIt. Their extension and generalization to IMD-based experiments could unlock much further potential. It may be possible to combine this with the implementation of some concepts such as the Jarzynski inequality to arrive at quantitatively useful IMD simulation protocols. Jarzynski showed a way to analyze the total work of irreversible processes in molecular simulations<sup>25</sup>. By averaging the exponential value of the non-quasistatic work, the difference in free energy between two states of the simulation system can be characterized. An interesting application for such collaborative and quantitative IMD simulations is cooperative IMD simulations. Multiple users would interact with the simulation system simultaneously, each acting on one of its parts. With two haptic devices, such exploratory experiments on collaborative work can be performed already. In this chapter, we have focused mainly on the added value of intuition and the generation of qualitative data. It is important to note that it is possible to reconstruct fairly reliable quantitative information from IMD simulations. For this purpose, trajectories, energy terms, and applied forces are recorded in addition to simulation parameters and data. These can then be analyzed after the simulation. From such

simulations, the user can calculate, for example, a potential of the average force as described for SMD simulations.

A much more speculative but intellectually challenging question is how artificial intelligence and machine learning will impact the future of IMD simulations. Machine learning may be able to learn the predictive capabilities of key physical simulation engines, replacing the very computationally intensive current calculations required for interactive molecular dynamics. Scripting approaches could then be used to implement simulations via IMD, with an AI performing the manipulations based on a precise prompt from the user, similar to what ChatGPT currently enables for conversational applications<sup>26</sup>. Of course, any manipulation that can be clearly formulated a priori could one day be machine-translated into simulation instructions for performing the intended task. AI technology can potentially become a powerful "superuser" that can replace the need for a human operator for interactive manipulations. It will be much more difficult to mimic the input of specific human expertise and intuition to develop new hypotheses based on what can be observed and explored in an AI simulation.

Regarding simulation feedback, much research has already been done for haptic and visual feedback. On the other hand, audio feedback is still largely unexplored in the field of interactive molecular dynamics. As for the visual modality, its analytical aspect could be further exploited in conjunction with machine-driven approaches using, for example, semantics and machine-interpretable - or in the future AI-based - knowledge systems. These are particularly promising for an immersive context and possibly in the wake of science in the metaverse.

## **Section 8: Drawing Conclusions and Paving the Way for Further Advancements**

**CONCLUSION/SUMMARY/OUTLOOK:** In this concluding paragraph, we summarize the main points discussed in this chapter, including the importance of interactive molecular dynamics simulations and their potential for further research and development in this area. Emphasis is placed on the intuitive and enhanced perception of molecular systems enabled by IMD. Specific advantages of IMD simulations include the ease of specifying complex, time-varying conditions, the valuable continuous perceptual feedback during a simulation, and the ability to study mechanical properties and structural deformations of molecular systems.

We have seen that IMD is an innovative approach to computational biology that combines the power of computer simulations with the intuition and creativity of human users. IMD allows scientists to directly control simulated biomolecules, visualize the results in real time, and adjust their behavior based on their observations. The IMD approach is based on the idea that the computer is not only a tool for performing simulations, but an assistant to the scientist, helping him or her explore the complex molecular energy landscape and gain valuable insights into the system under study. IMD takes advantage of human visual perception and provides the scientist with a set of interactive visualization tools to create their own representations of the system and understand it in a more holistic way.

Despite some performance challenges and limitations, such as the stability of the simulated systems and the choice of interaction parameters, IMD represents a powerful and complementary tool to improve our understanding of biological systems. IMD provides the ability to combine classical molecular dynamics simulations with human intuition and creativity, making it a valuable tool for solving complex biological problems. IMD has been integrated into immersive environments such as virtual reality and haptic devices to enhance the understanding of simulated systems by using multiple senses and engaging the whole body. Additionally, IMD was successful in tackling challenging biological issues such as helping with discovering new drugs and formulating new mechanistic theories. The IMD approach has democratized science by enabling laypeople to

experience scientific research in computational biology and chemistry firsthand. This opens new opportunities for public engagement and education in these fields.

In summary, Interactive Molecular Dynamics is a powerful and innovative approach to the study of biological systems that combines the strengths of computer simulations and human intuition. IMD has the potential to provide new insights and solutions to some of the most challenging problems in computational biology and opens new opportunities for public engagement and education in the field. As in other application areas such as object manufacturing or architecture, where computational design tools are widely used, Interactive Molecular Dynamics opens the door to rational and user-centred design approaches for new molecules in the next generation of interactive software that could be used for both synthetic biology and rational drug design. Let us conclude with these apt words from Richard Feynman: "The world is a dynamic mess of jiggling things".

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- <https://www.youtube.com/watch?v=e1GcLwMAC7A> .. IMD in VR
- <https://www.youtube.com/watch?v=gH4zuBWFNpo> .. RNA folding in coarse grained IMD
- <https://www.youtube.com/watch?v=AGi2PM0R2JI> .. IMD on an arcade machine for school kids
- [https://www.youtube.com/watch?v=\\_EvS2jCgdKU](https://www.youtube.com/watch?v=_EvS2jCgdKU) .. IMD of a short peptide exploring a surface
- <https://www.youtube.com/watch?v=KLQzMh0Wabl> .. IMD semi-automatic steering
- <https://www.youtube.com/watch?v=pBK22hN7cIM> .. HyperBalls visualization adapted to IMD
- <https://www.youtube.com/watch?v=tHGXYcgRqc8> .. IMD examples with haptic devices

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**RELEVANT WEBSITES:** A list websites relevant to the chapter

- <https://physics.weber.edu/schroeder/md/> :: an educational IMD web demo to dive into IMD
- FoldIt : <https://fold.it/> :: an interactive crowdsourcing computer game to fold proteins. Also see <sup>7</sup>.
- Isolde : <https://isolde.cimr.cam.ac.uk/> :: an immersive environment designed for structure determination using IMD. Also see<sup>20</sup>.
- Narupa : <https://narupa.readthedocs.io/> :: a software for virtual reality and steered molecular dynamics simulations. Also see<sup>11</sup>.
- UnityMol : <http://unitymol.sourceforge.net/> :: a molecular visualization software with IMD extensions. Also see<sup>12</sup>.
- VMD : <https://www.ks.uiuc.edu/Research/vmd/imd/> :: a pioneer in IMD simulations. Also see<sup>6</sup>.
- YASARA : <http://www.yasara.org/> :: a complete modeling package with extensive IMD capabilities.