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Wielding the power of interactive molecular simulations

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Abstract: Since the dawn of the computer age, scientists have designed devices to represent molecular structures and developed tools to simulate their dynamic behavior in silico. To this day, these tools remain central to our understanding of biomolecular phenomena. In contrast to other fields such as fluid mechanics or meteorology, the observation of molecular motions at the atomic level remains a major experimental challenge. Continuous advances in computer graphics and numerical computation, combined with the emergence of human-computer interaction approaches, led to the methodology of so-called “interactive molecular simulations”, characterized by two main features. First, the possibility to visualize a running simulation in interactive time, i.e. compatible with human perception. Second, the possibility to manipulate the simulation interactively by imposing a force, changing a biophysical property, or editing runtime parameters on the fly. Such simulations are still little used in computational biology, where 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 handle time-consuming tasks such as the modeling of particularly complex biomolecular structures more efficiently or to support approaches such as Rational Drug Design with regard to pharmaceutical applications.

Keywords: interactive molecular dynamics, steered molecular dynamics, computational steering, interactive molecular simulations, haptic, virtual reality, human-computer

interaction, molecular modeling, virtual environments, interactive visualization, human intuition, collaborative works, user interfaces, ...

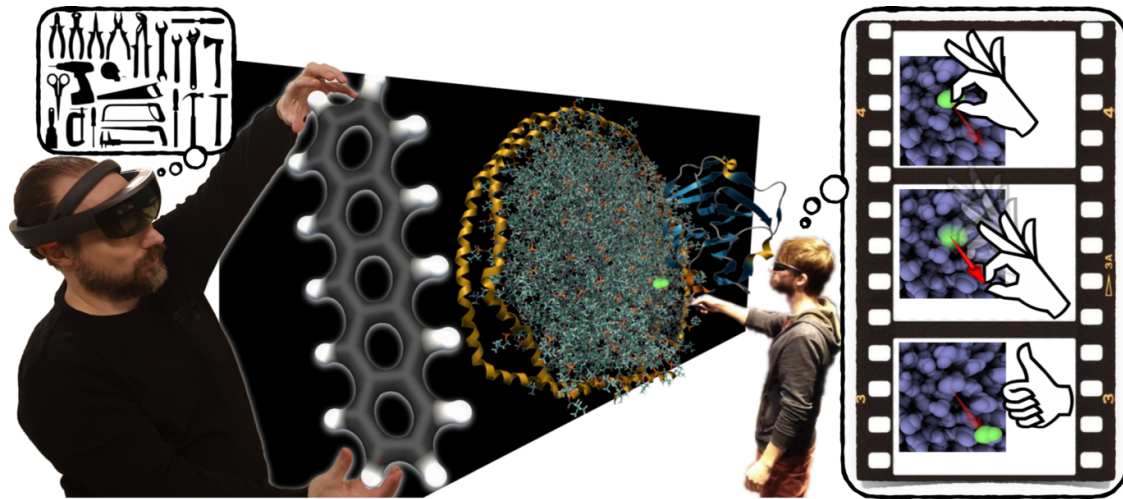


Figure 1: Photomontage illustrating interactive manipulation and building tasks (left) as well as user interaction with a running simulation on a stereoscopic display wall (right). Interactive molecular simulations provide intuitive understanding and allow direct manipulation of the molecular system or a running simulation.

Introduction

The study of nature and technology (industrial, medical, military, etc.) has benefited from the enormous technological breakthrough of the modern computer. The systems studied have become increasingly complex and so have the corresponding simulations and their analysis. Some researchers have looked at integrating computer simulation and visualization, which would allow continuous and interactive control of the ongoing process. Johnson and his team explored the fundamental aspects and issues related to what they defined as *Computational Steering* [1]. Molecules were among the first objects considered to make computer simulations interactively accessible to humans, as shown by the pioneering work of Levinthal to develop new visual interfaces.

“It soon became clear that the new types of visual display that had been developed would permit direct interaction of the investigator and a molecular model that was being constructed by the computer.” [2]

Computer simulation of natural systems has a wide range of applications and uses, such as controlling parameters on the fly. Scientific studies that integrate some degree of interactivity (interactive visualization and / or interactive simulation) can be designed to study medical data [1], serious military training games [3], astrophysics [4], social sciences [5], engineering [6] etc.

Biomolecular sciences have been a pioneer in testing such approaches. This particular review focuses on interactive molecular simulations (IMS) [7]. The use of computer programs to represent and simulate complex (bio)molecular systems has led to a better understanding of the way in which the macroscopic properties of a given system emerge from its behavior at the atomic scale. Molecular dynamics remains an essential method for such studies today.

The design of interfaces to improve human-machine interaction (a concept that has become known in particular as Human-Computer Interaction) is a fundamental area of research. It has led to the development of new technologies, of which the best known are certainly those that we use every day for direct interaction (keyboard input or pointing devices such as the mouse, the touch interfaces of our phones) and the associated graphical applications (text editing, drawing, etc.), as well as software tools dedicated to interface design [8].

In terms of molecular simulations, interactivity has two facets: *interactive visualization*, which studies how the user can explore biological data, and *interactive simulation* (or *computational steering*) [1], which conceptualizes the interactive temporal influence of the user on the ongoing simulation. From a biologist's perspective, this family of approaches might be called *in-silico* experiments on biological phenomena by probing the simulation, and two concepts are depicted in Figure 1.

Figure 2 shows that research in interactive molecular dynamics began in the late 1990s, with one of the pioneering research contributions being the development of a steered molecular simulation tool called *Steered Molecular Dynamics (SMD)* [9], which was designed as a digital twin simulation of atomic force microscopy and used the popular molecular visualization software VMD in its system. The first work on atomic force microscopy experiments that inspired the design of *in silico* models such as SMD dates back several years [10].

We will first introduce the historical context of interactivity in the study of biomolecules to highlight the important issues that we will then address to see how current research has dealt with them. The three main axes of reading are the analysis of interactive environments, computational steering and biological applications documented in the scientific literature. The first part describes all the pieces that need to come together to implement an actual interactive simulation and discusses many facets related to visualization. Because of the many technological hurdles that had to be overcome, this part is quite extensive. The reader more specifically interested in how these pieces enter into synergy and translate into new ways to perform molecular modelling will find these aspects discussed later in the manuscript, in particular starting from section "Interactive molecular simulations extend the modelling repertoire".

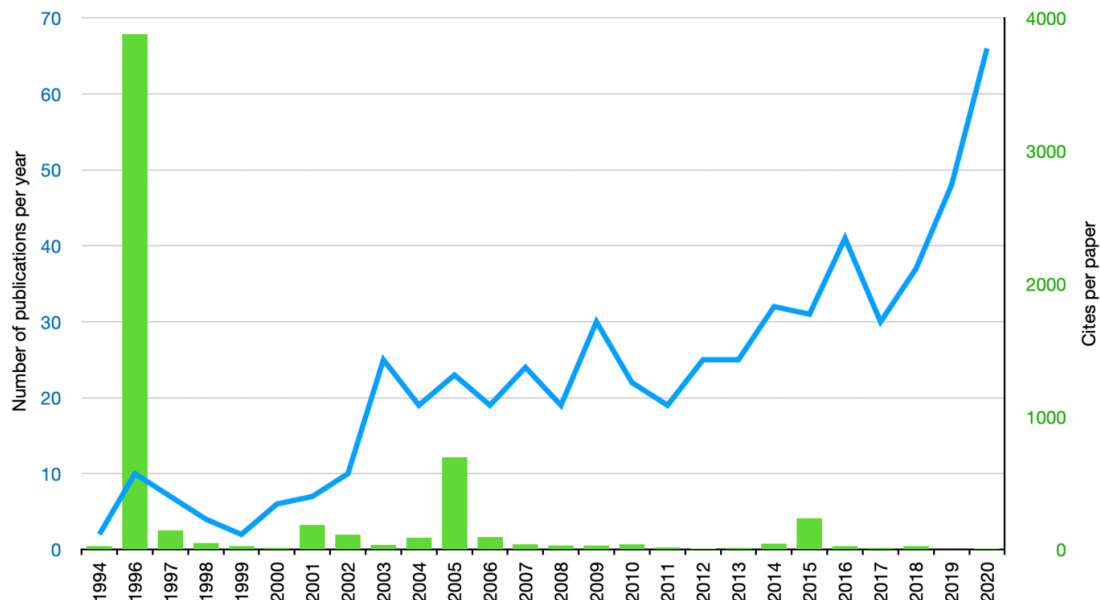


Figure 2. Frequency plot of publications mentioning the keyword “interactive molecular dynamics”. The browsing tool used is PublishOrPerish [11], which uses sources from Google Scholar with a search query for articles published since 1990. The search focuses on the occurrence of keywords in the full data (title, abstract and content) excluding citations and patents. The evolution of the number of publications over time (blue curve) can be read on the left vertical axis, and the number of citations per article per year (green histogram) on the right vertical axis. The three peaks in 1996, 2005, and 2015 can be correlated with the impact of publications on the VMD visualization tool [12], the NAMD [13] and the GROMACS [14] simulation engines, respectively. These metrics provide information on the prevalence of the IMD technique in scientific publications.

Interactive molecular studies – how have they changed science?

In this section we briefly summarize the historical development of molecular simulations from the first designs of modern computers to the first methods of steered molecular simulations. This historical perspective will allow us to shed light on some fundamental aspects of the coupling between human and machine and the original goals for a better understanding of the natural world.

The modalities of this coupling are fast becoming important questions for the future use of modern machines. A historical example is that of Fano and Corbato, who introduced their system of time-sharing on the computers of the Mathematics And Computations project (Project MAC), which allows a larger central computer to be shared by a number of remote individual terminals [15]. Their idea is to see the computer as an extension of the user, as his assistant who maintains a constant dialogue with the machine.

In fact, since the early sixties there have been problems with the practical remoteness of the user from the calculating machines. It soon became clear that an important problem was the time lag between the submission of the program and the generation of the

computational results. The submission of a problem or program by a user could be slowed down in a computing center by the queue created by the organization of the process. This problem ultimately proved to be the limiting factor in the expectation and production of results. However, the machine takes much less time than a human to solve each problem. Also, it is very often necessary to first go through the trial-error loop to calibrate and configure the program. Unfortunately, this process is always a big waste of time in this type of architecture. It is very interesting to note that this problem is still relevant today, even though computing power has increased exponentially. However, one has to see in parallel the fact that problems also increase in complexity, so that for a human user, depending on the system under study, there is still a significant time gap between the moment of entering the problem and obtaining the results, not to mention the fact that the results have to be analyzed afterwards. Therefore, time-sharing on computers was an important issue early on and allowed the computation of a large number of programs by time-slicing [16].

This system was then developed by several teams simultaneously, in particular by the MIT team which developed Project MAC. This project then served as the inspiration for the development of the first interactive molecular visualization and assembly system [2] using a computerized oscilloscope as the display unit (Figure 3), to meet the need for structural information about biological molecules important for understanding their functions and interactions with other molecules [17]; [15]; [2]; [18].



Figure 3. The setup of Levinthal's pioneering machine with the DEC 340 graphics console and a "globe" that controls the direction and speed of image rotation in the foreground. In the back is the PDP-7 minicomputer, and in the centre is the standard remote control console. Reproduced with permission from , image courtesy of Martin Zwick.

In fact, computational techniques for minimizing the energy of the system were not yet sufficiently developed to obtain a comprehensive study of the energy landscape and thus approach the structure with the global energy minimum. Therefore, the implementation of sufficiently sophisticated automatic techniques to obtain structurally relevant results has not been possible. This problem is still relevant in the context of molecular dynamics, and many sampling techniques have been developed to solve it. One research focus is therefore the development of programs that allow a combination of human and computer to capture conformations that neither a human nor a computer alone could sample, as we will also see later on.

The basic idea of interactivity is that the user can make changes during the simulation, and that this control can be done in interactive time. This idea implies that the results of the computer simulation must be presented to a human user and that the operator can grasp the data in the most efficient way, i.e. visually and intuitively more than through numbers. Interactivity is also relevant to the temporal partitioning aspect, which is a form of computational partitioning, because the idea is to be able to quickly retrieve the output data in order to assess the impact of a change in the input variables on the program.

The desire to understand, gain insight into, and become familiar with the behavior of microscopic particles, just as with everyday macroscopic objects, has led researchers to develop and design new methods of digital graphics rendering and devices for human-computer communication [20]. As part of understanding the microscopic world, the display was conceived in terms of interactivity, where the computer model of each particle is graphically represented in an electric field and combined with manual control of its position in space by devices capable of providing sensory feedback to the user. Sutherland's team developed the first augmented reality design between 1965 and 1968, based on the interpretation of head movements and stereoscopic display to surround the user with three-dimensional information and give the impression of immersion in a real environment [21].

During this period, the numerical application of molecular dynamics (MD) was developed, in particular with the development of the numerical integration method of Newton's equations of motion such as the Verlet integration [22] in the 1960s. The numerical formalization contributed to the great success of molecular dynamics and we refer to [23] for a detailed account of this period. Although there are still many limitations, the technique is successfully used to study a wide range of biological models up to huge assemblies. The MD technique was yet to meet interactive visualization.

To return to our discussion of the development of interactive visualization: Levinthal's breakthrough mentioned at the beginning of this paper inspired the GROPE project two years later, in 1967 [24] led by the Brooks team. The project was completed in 1990 and culminated in the first use case for docking molecules to a protein active site with haptic feedback. The final design of their GROPE - III system is shown in Figure 4.

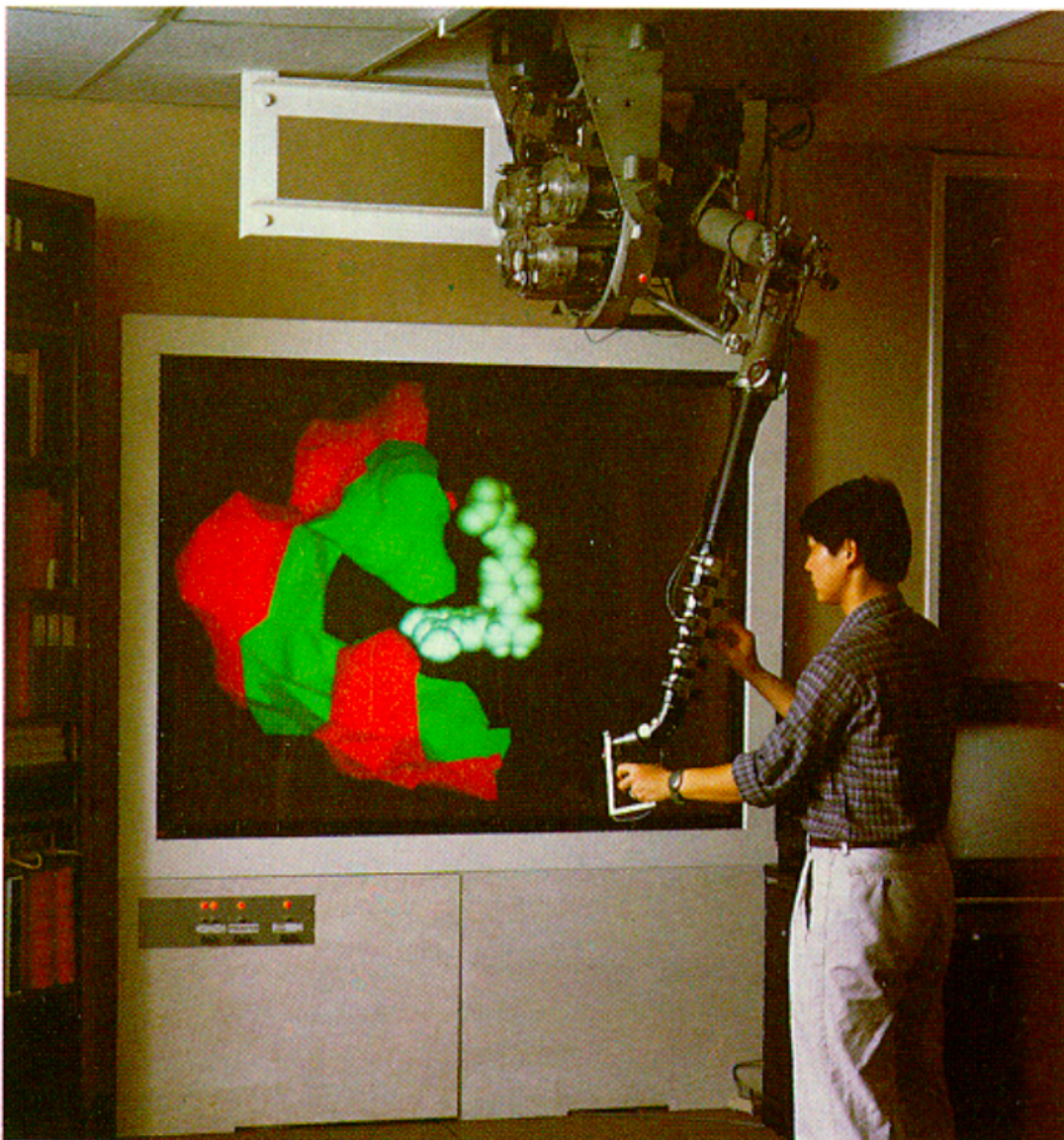


Figure 4. GROPE-III haptic display system in use reproduced with permission from the ACM digital library.

Surles, while working on his dissertation, developed a graphical modeling system called Sculpt [25]; [26] to perform *de novo* design of proteins while maintaining physically valid properties. This program allows the user to interactively move the atoms of the protein system. Figure 5 shows the result of a two-hour Sculpt session that resulted in a *de novo* generated segment with 32 residues (poly-Ala) in which the terminal parts of the two-stranded antiparallel beta ribbon (bottom) are pushed together to form a 6-stranded Greek-Key β -barrel (top).

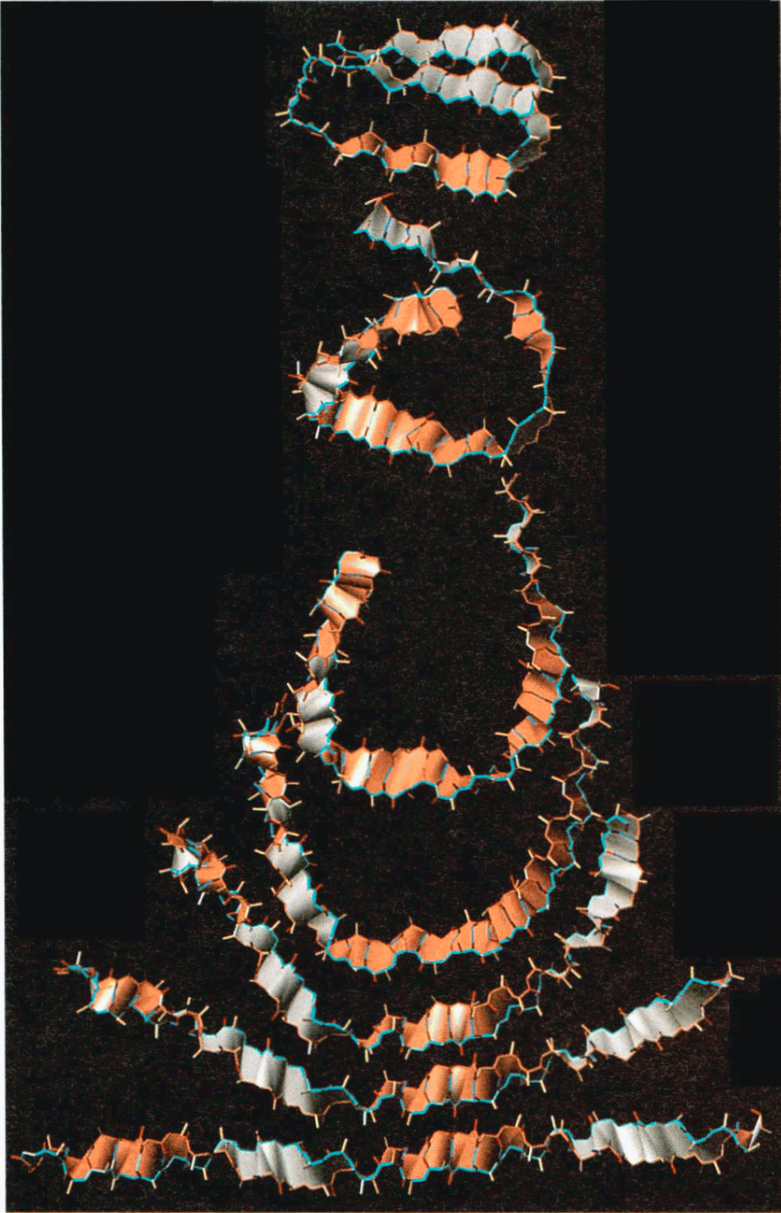


Figure 5. Collage of seven snapshots of a Sculpt session. Reprinted with permission from [26]. Copyright © 1994 The Protein Society

Sculpt finds in interactive time the local minimum of the total energy satisfying a set of constraints by evaluating the gradient of the energy constraints using a method called the augmented Lagrange multiplier method. Such interactive minimization approaches, potentially very powerful, were limited by the computational power available at the time.

The Steered Molecular Dynamics technique [27]; [9] was among the first interactive molecular dynamics frameworks developed to digitally replicate some experimental techniques such as atomic force microscopy (AFM). These techniques date back to the late 80s/early 90s and were developed to study, through simulated manipulation and dragging of small molecules, the binding properties of the (fixed) complex to which they are bound or

the deformation properties arising from the internal mechanical properties of proteins. The method for controlling the atoms is to use a spring model to connect a linearly moving constraint point to the selected atoms. This technique thus cushions the user's interactions by forcing the atoms towards the spring's equilibrium point, rather than through direct position updates that would add too much abrupt disturbance. Obtaining relevant quantitative information about non-bonded interactions from such simulations was promoted by the work of Jarzynski [28] in thermodynamics, who demonstrated that one can obtain information about the difference in the free energy of a system between two states by averaging the exponential of the total work of all non-quasistatic and thus irreversible processes inherent in molecular simulations [27]. SMD research on the application of external forces went a step further towards the development of interactivity by showing that the addition of such external constraints allows for qualitative (structural) and quantitative (energies involved) information on biological problems such as drug design, ligand-protein interaction, protein unfolding, structure refinement, and so on.

In his article on SMD, Leech presents some thoughts on the innovations SMD brings, such as the scientific interpretation of the system being subjected to what he calls "tugs" to denote external forces specified by the user. Indeed, the effects of the manipulations on the system can raise questions about the validity of the simulation by significantly altering its course, which will also be discussed later on. He also designed the architecture of this system. It is interesting to note that his system already allows interactive simulations in two ways: interactive visualization with graphical representations updated at each step of the calculation and control of the parameters and selective manipulation of a group of atoms on the fly.

In their work, Rapaport [29] and Stone [30] extend this system, which can be commonly referred to as Interactive Molecular Dynamics (IMD), to include the use of molecular dynamics, which has made an important complementary contribution to experimental studies in structural biology and biophysics for decades. The goal is not to replace the use of MD, but rather to form a useful and lightweight extension that provides a better understanding of the system under study [29]. Interactive Molecular Simulation (IMS) systems are not limited to the use of a single type of molecular modeling code and can, for example, use approaches other than MD simulations as their underlying physics engine for driving particle motion. Alternative computational modules can be used to overcome certain limitations, such as the computational cost of all-atom MD simulations or the difficulty of setting up such simulations, extending the system to larger scales, etc. We can cite the example of BioSpring [31] which uses a spring network model to simulate interaction between particles to facilitate interactivity and simulations at large scales.

We will discuss these issues in more detail later in this paper, and now turn to a thorough discussion of the components and some of the technical details required for interactive simulations, notably visualization.

Multimodal environments for interactive exploration

Human intuition and understanding

This section on human intuition and understanding serves as an introduction and focuses on the user and his understanding of the results he gets from the machine.

We therefore propose to start from Card's definition of *visualization* [32], which Valle uses in his article whose aim is to reconsider the approach of presenting the results of quantum mechanical computations [33]. Thus, *visualization* is presented as the transformation of computationally generated data into graphical structures. The idea of such graphical information is to use the powerful capabilities of human visual perception to interpret this data. It seems that the mental models associated with high-level processes (cognition) are often visual [33].

It seems that the visual approach to this task is a very exploited research avenue, hence the writing of this section on multimodal environments. Human vision is an extremely powerful tool for information reduction, e.g. pattern recognition, a skill we are trying to automate mainly thanks to the development of machine learning.

As for visualization, at least for molecular simulations, there do not seem to be any frameworks that do not use a visual interface, at least not via a classical screen. The question that arises is mainly in which way one wants to design the representation in the brain to make connections to already acquired abstract concepts. This association is not done by the machine, but by the human being who, thanks to the visualization toolbox that can be considered a mental extension, can shape his own perception and decide to build himself the visual anchors to the mental models that appear to him. The mental reconstruction of the vision or visual perception is all the more efficient because we can view the structural data in 3D, hence the importance of interactive visualization, but the author highlights the fact that the visualization can also be a 2D representation if it brings a new and unexpected information about the data to the eye of the viewer.

In this section, many concepts are worth mentioning, such as the visualization cycle, which allows the user to interact with the data by controlling the visualization parameters. In contrast to the so-called confirmatory data analysis cycle (see Figure 6) where the researcher relies on his or her own hypotheses to use visualization, the use of visualization for data exploration is considered when hypotheses need to be formed [33]. These considerations also raise more fundamental and philosophical questions, but these are beyond the scope of the review.

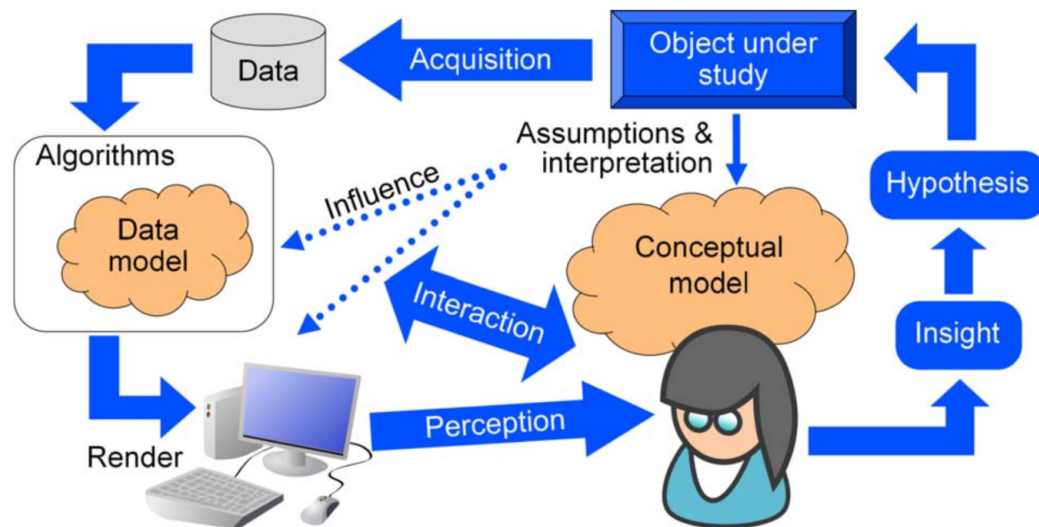


Figure 6. The visualization process model showing the scientific discovery cycle and integrating visualization as an interface between computer results and human perception. Reprinted with permission from [33].

After describing seminal work on early interactive visualization, we will now briefly turn to human intuition in the interactive manipulation of molecular simulations, which is discussed in more detail later in the manuscript. The research of Mazzanti et. al. [34] aims to demonstrate the contribution of interactive simulations to the prediction of RNA structures by non-specialist users. These studies are inspired by the success of FoldIt [35] and EteRNA [36] for the prediction of tertiary protein structures and secondary RNA structures, respectively. Analysis of the results of the experiment shows that humans explore the phase space, i.e. the set of conformations under investigation, more comprehensively and quickly than a computer. They suggest plausible alternative poses, which can be an advantage when the target structure is unknown. It has been shown that humans can visually capture the trajectory and stability of simulated molecules using MD techniques.

2D/3D rendering and visualization techniques

Molecular graphics

The 3D representation of molecular structures allows researchers to gain insight into the purpose of molecular shapes in cells [37]. We will now focus on the different methods used to graphically represent these structures. The preceding part about human intuition and understanding is closely related and complementary. The analysis of different types of biological datasets, not created by direct visualization of structures, will be specifically addressed later on in the manuscript.

Matter at the subatomic level does not behave like the macroscopic objects of daily life, hence we have no ground truth for how to represent them graphically. The atomic radius is used for the three-dimensional representation of the space-filling model, also known as the CPK model [38]. These simplified representations with their color code, such as those of

the ball-and-stick, surface, VDW, licorice, etc., are currently common methods for visualizing atomic positions stored (usually in PDB files) and computed by molecular simulations as coordinates in Euclidean space. These different graphical representations of molecules allow highlighting certain structural features of molecules. However, there is no clear consensus on a general representation method other than maybe the CPK color scheme [39]; [38].

Among these representations, the (molecular) surface is the one that requires the most technical resources, since its computation implies the use of sophisticated algorithms. In the context of interactive visualization, such as the analysis of MD trajectories, the molecular surface is very useful, especially for the analysis of certain phenomena that occur in its vicinity (protein-protein, protein-ligand interaction, binding sites, etc.). To solve this challenge, Krone et al. developed a GPU raycasting-based rendering method to represent the Solvent Excluded Surface (SES) [40]. SES is an implicit mathematical description of the surface whose rendering is similar to the Van der Waals surface, but here adds the real-world context of the presence of the solvent by considering the accessibility of a spherical probe that reflects the average occupation of water molecules at the molecular surface level [41]. Later, an approximation method called Quicksurf was implemented in the VMD software for interactive surface generation during trajectory animation and possibly interactive simulations [42]. More recently a QuickSES implementation followed [43]. For large structures and especially in interactive simulation mode, such surface rendering remains a challenge to find a compromise between sufficient resolution, rich and comprehensive environment for exploration.

In general, the representation with balls and sticks is useful for steered MD, especially for the part of the molecule to be manipulated, since the atoms targeted by the user are uniquely identifiable. This visual representation has been used in a number of publications, including [44]; [45]; [46]; [47], but there are also several examples of surface representations, firstly - in combination with space-filling views - for docking [48], and secondly for the representation of experimental data, such as small-angle X-ray scattering (SAXS)-derived envelopes used as guiding beacon for interactive model building [49]; [31]. These examples of visual representations chosen for interactive processing are by no means exhaustive, and the appropriate choice usually depends on what is best suited to the task at hand.

The increasing amount of data to visualize has led to the development of methods that take advantage of the powerful tools that exist in the video game and cinematic market [50] such as through the use of game engines that integrate key graphics methods for video games such as GPU rendering and ray casting. UnityMol [51] is an example of using a video game engine for molecular visualization and integrating some features that are beneficial for steered simulations, such as the Hyperballs representation [52], a surface type for representing smooth dynamic bonds that can be easily adapted to other representation types by setting a number of parameters [53]. This method is presented in the UnityMol framework and can be rendered by using high-quality raycasting. The latest implementation shows significantly improved rendering performance [51]. For interactivity, this rendering method seems to be acceptable (in terms of number of frames per second), at least up to one hundred thousand atoms. The particle rendering method is

even more efficient in terms of performance and therefore well adapted to the requirements of reactivity for simulation interactivity, as shown in Figure 7 [51]. However, it has several quality limitations.

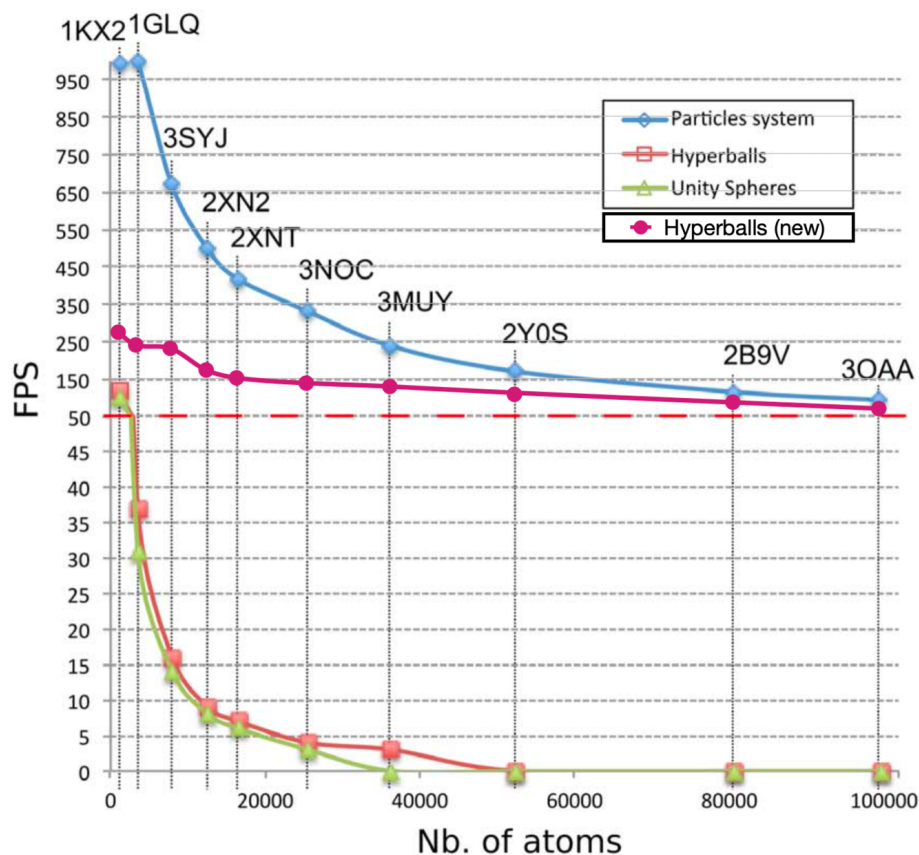


Figure 7. Evaluating the efficiency of various Unity3D features using a wide range of molecule sizes. The display rate (FPS) is measured for the static molecules. This benchmark has been updated for the most recent Hyperballs implementation with a recent hardware configuration (MacOSX 10.15 - 3.1 GHz AMD Radeon Pro 5300). Figure reproduced and adapted from [51]. Image under a CC-BY licence.

Hyperballs was one of the first graphical representations designed specifically for use with interactive simulations. Another pertinent example is the addition of a focused beam of light to guide haptics in the Haptimol tool [54], improving the user experience in such simulations. Very recently, a method to ensure visual continuity of protein secondary structures for trajectories in general and interactive simulations in particular was outlined [55].

Another representation method for steered simulations is the informative visualization of atomic collisions during manipulations developed by Kreylos [56], which allows the user to avoid conformations with steric clashes in favor of other, more plausible conformations.

The overlaps between atoms are calculated in real time during the manipulation and the collisions are visually displayed.

A fundamental concept is that visualization tools should not only be tools for representing raw data, but they should enable the discovery of the meaningful relationships between different structures of a complex and diverse biological datasets through the use of appropriate representations :

The challenge in representing diverse data sets stems from choosing graphical elements that can properly convey the values, properties and relationships to the user [57].

According to Brooks, in his summary of the Faraday discussion in 2014 [58] :

The set of actual visualization techniques for data has not changed much, and there still seems to be no coherent theory for data visualization, the perception thereof, and the comprehension thereof.

Seeing in 3 dimensions : from stereoscopy to immersive virtual and augmented reality environments

Sutherland pioneered the development of a virtual reality headset, which is required for immersive virtual reality. The appropriateness of using the term “Virtual Reality” has been the subject of debate, as the two terms taken together seem contradictory. What is virtual is not in fact unreal, because what is computed by the computer is a particular way of representing an environment that interacts with the abstract mental representation of that environment by humans, just as we can consciously look at a scene in a painting that remains no less real.

What is real and what is not is the subject of a longstanding philosophical debate. It is worth recalling that the immersion associated with virtual reality is something relative. As Freina and Ott explain in their review of immersive virtual reality in education [59], we can distinguish virtual reality in two forms: non-immersive and immersive. The non-immersive VR can be defined as the classical way of interacting with the simulated environment, i.e. with the monitor, keyboard and mouse. In contrast, as Freina explains, the term immersion is used more restrictively in virtual reality and refers to immersion in space:

Spatial immersion into virtual reality is a perception of being physically present in a nonphysical world. The perception is created by surrounding the user of the VR system with images, sound or other stimuli that provide a very absorbing environment.

This definition explains the importance of talking specifically about immersive molecular visualization. The advantages of such an immersive approach have been particularly noted in capturing complex chemical concepts such as electron charge [60], which also lend themselves to collaborative analysis [61].

There are three common display devices for virtual environments that we will introduce in the context of molecular simulations. These devices are head-mounted displays (HMDs), spatially immersive displays (SIDs) such as the CAVE, which we will describe shortly, and the single-screen stereo displays such as the Responsive Workbench [62]; [63].

Not many applications of the virtual workbench to molecular dynamics have been described in the literature. An example of its application has been proposed by Koutek et al. with their tool MolDRIVE [64], a visualization and computer control environment for interactive time MD simulations, in which users can interactively steer particles during an SMD simulation. A unique feature of their system is the implementation of visual feedback of the applied force, replacing the haptic feedback usually used. They thereby demonstrate that visual force feedback may be sufficient to effectively control particles. A more general analysis of interaction visualization was carried out in another study [65]. The authors propose visual representations of interaction forces by considering several variables, such as molecule-ligand distance and energy function, that are essential for understanding binding affinities. They focus on mapping molecular docking pathways through time-dependent visualizations for a variety of energy components and particle resolutions: Atoms, Groups, or Residues. Their visual metaphors help experts to develop drugs or enzymes more efficiently.

Cave Automatic Virtual Environments (CAVE) [66] was developed in the early 1990s and is an immersive virtual reality system in which the user is in a room where the walls, ceiling, and floor form stereoscopic projection surfaces that provide depth rendering using 3D glasses (e.g., stereoscopic shutter glasses). For example, this device was used a few years later to interactively observe the results of molecular dynamics, in which atoms interact with their neighbors, and to verify the accuracy of the interaction decomposition method used here as a parallel computational method for the MD simulation [67]; [68] as illustrated in Figure 8.



Figure 8. User performing an interactive molecular simulation in a CAVE environment that has an advanced haptic device with access to the entire workspace of the immersive system.

The other device we have already talked about is the Head Mounted Displays (HMDs), also known as the Virtual Reality (VR) headset, which has been growing rapidly lately. The device has benefited from hardware improvement and has seen a significant price drop that has allowed for widespread adoption by the general public, especially in the video game industry, which is an emblematic example (e.g. Oculus Rift and HTC Vive released in 2016).

As early as 2010, Stone et. al, who had developed IMD with its VMD visualization software back in 2001, extended the use of their program to include immersive virtual reality displays, taking advantage of the increased capacities of multi-core CPUs and GPUs. One of the challenges cited by Stone is to make the VR technology intuitive and easily configurable so that it is accessible for scientific applications. VMD can thus support VR hardware and software for molecular visualization, analysis, and IMD [69]. A year later, they described their new technique of out-of-core visualization (algorithms using external memory) operating on solid-state disks (SSDs) by taking advantage of their then technological democratization (increase in capacity/price ratio). This technique enables fast writing and reading of large-scale data to obtain trajectory animation of large MD simulations at a stereoscopic display rate high enough for effective immersive visualization and very close to the rate achieved with in-core approaches [70]. Fluid trajectory visualization for large datasets remains a topic of active research [71].

As for user immersion in molecular visualization, technical considerations are currently still a fundamental and limiting aspect, although computational power has improved

significantly and researchers are producing cutting-edge research in this area. A recent example is a study by Deeks et. al showing the development of their open source software framework Narupa, which aims to provide the scientific community and education with a tool that combines interactive molecular dynamics with virtual reality for a wide range of applications. The team has already demonstrated that the application of iMD-VR through their software for predicting protein-ligand interactions is an efficient and potentially useful approach for developing new drug discovery methods [47]. Recently, they described an application with fully flexible docking for generating complexes between some variants of the SARS-CoV-2 main protease (Mpro) and small ligand and oligopeptide substrates [72]. MPro is a widely studied protein as it plays an essential role in the replication cycle of the virus. An important point for a satisfactory user experience is to reduce latency in the system and improve responsiveness. In all iMD-VR simulations, this is achieved by using an implicit solvent model.

In relation to this problem, we can highlight the specific effect of the virtual reality system on the user's sensations, which can lead to a certain discomfort, called cybersickness by Davis et al. in analogy with motion sickness [73]; [74]. It has not been explicitly stated that the iMD-VR system causes such effects, but it may be necessary for broader application to address this issue by identifying the parts of the VR pipeline that contribute most to latency. These parts depend not only on the frame rate of the simulation engines, but also on the image processing [74]. Even less obviously, Weech et. al show that this discomfort could negatively affect the impression of the observer's presence, which is related to the process of sensory integration [75], which in the case of VR is mainly focused on visual integration.

Regarding immersive analysis in the context of VR discussed by [76], we can again cite the Mpro study, where iMD-VR docking is accompanied by visual guidance for the user, manifested in the addition of a trace representation to visually identify the position of a ligand from a known crystal structure (see supplementary video in [77]). Certain variables of the simulations that one wishes to track in real time are naturally represented in 2D (curve, energy information, etc.). Integrating this analysis data into an immersive visualization does not seem trivial, especially when the simulation allows parameters to be manipulated in real time, as is typically the case with IMD. Sommer also describes example use cases of stereoscopic immersive analytics, including interactive building of membrane systems [78]. Bowman's 1999 study shows the integration of a 2D GUI toolkit in VR using a physical tablet and a stylus (to push virtual buttons or drag icons) [79]. Trellet et al. provide a more fundamental study of integrating visualization and analysis of molecular data in an immersive context [80]. There do not seem to be many examples of the use of such 2D interaction metaphors for simulations in VR. Dreher et al. briefly mention one such approach in their study [81]. A similar experiment was conducted with an augmented reality application created with ARToolKit, a dedicated software library for this purpose, which can be opened on a tablet and tracks a 2D physical marker using the camera to overlay the virtual information as a 3D molecular structure [82].

To conclude this part, we will talk about immersion in terms of performance. This topic concerns both visualization and simulation, as it deals with computation in general. Indeed, it seems that performance is still a limiting element that determines the quality of the user's immersion. For example, as mentioned earlier, motion sickness is still a major problem, and

Raaen and Kjellmo point out that the focus in the development of VR is on increasing the frame rate, although this discomfort is the result of a latency problem, the extent of which is difficult to measure [74]. Improving the performance of the simulations themselves naturally employs the strategies of multicore parallelization of CPU and GPU, generally aiming for 60 FPS or more [83]; [84].

Live simulation feedback through multimodal input and output

We will attempt here to summarize the work that has been done to enrich the immersion in the virtual world when working on molecular simulation. We decided to separate and summarize here the interactions (governed by sensory experiences and voluntary control) that go beyond vision and classical devices (keyboard/mouse).

Sensory nervous system modalities specifically process sensory information related to the classical senses (vision, hearing, touch, taste, smell, and the somesthetic senses including proprioception). It has been shown that information is transmitted via the relay of stimuli (action potentials) from sensory cells to specialized areas of the cerebral cortex, where initial processing takes place. We call the processing that then contributes to a broader association of the various specialized areas, each associated with its respective modality, multisensory integration or multimodal integration, the whole providing a perceptual experience with meaning. In turn to this integration, conscious control can be performed to decide, as in the real world, on an active exploration of the system, modifying it through a very precise choice of the pattern and timing at which the motor neurons are activated. There is still a lot of research going on in cognitive science to understand how the brain and nervous system in general process all this information as input and consequently exhibit adapted behavior.

Harley et. al. in their work on sensory VR [85], explain that virtual reality is not just a visual and auditory experience and suggest rethinking the design of system solutions based on non-digital interactions. Their work highlights that even if tangible interaction with real objects is not in synergy with their virtual version, the issue of immersion can be linked to the ambience and atmosphere of the environment, involving all the senses of the user. In their discussion, they showed that an important issue is the position of the body and the physical environment that we consider when developing virtual reality systems. Which parts should be included and which should be omitted to achieve optimal VR immersion? This question seems even more abstract when we try to let the user evolve in an environment where molecular simulations take place, for which there is no equivalent natural environment for humans.

Tactile feedback through haptics

As for interactive simulations, haptic devices, sometimes in conjunction with VR, have been widely used, especially since the second decade of this century, when commercially available hardware could easily be deployed as in VMD through its extended support for multimodal input devices and custom VR systems [69]. Through the development of VMD, Stone et al. attempt to limit the constraints on the technical realization of certain tasks that

can be imposed on users in the realization of their molecular modeling applications, and can therefore focus mainly on scientific problems. Alternative implementations of haptics-based systems were developed at the same time such as in [86] and further extended subsequently [87].

Such touch feedback can be particularly useful when exploring non-intuitive realms such as quantum mechanics. The concept of interactive chemical reactivity exploration is a good example [46], as it remains difficult to grasp due to the high dimensionality of the potential energy surface. An interactive approach effectively brings the chemist's intuition into the search process. By using a haptic pointer with force feedback, the operator can directly manipulate structures in three dimensions and perceive the quantum mechanical response to structural changes as forces. Teaching also immensely benefits from such approaches [88].

The review paper on Haptic-driven Applications to Molecular Modeling provides an overview of haptic-driven molecular modeling software of the last decade that supports IMD and quantum mechanical calculations in addition to molecular docking applications [89]; [90] that the authors expanded later on [91]. In Table 1, we present a similar summary table. The tools were selected based on the arbitrary choice of a Field Citation Ratio higher than 1 of the reference papers. This is not an exhaustive list of haptics-based molecular simulation applications. The goal is to provide some examples of tools whose research has focused on integrating these types of devices.

Systems	Description	Devices	Render	Year Ref.
GROPE-III	Real-time molecular docking system ; 6-DoF drug manipulator and force display interface ; Interaction energy global minimum calculations ; Idea of intelligence augmentation man-machine~	Argonne Remote Manipulators (ARM's)	Picture System PS300 ; Pixel Planes	1990 [23]
Nagata et al system	Protein-ligand docking simulator ; Force between ligand and protein (not global) ; Sense the electrostatic potential field of the protein surface only using a globular probe to find candidate sites	PHANToM	OpenGL	2002 [94]
Yuen et Lee system	Computer-aided molecular design (CAMD) for molecular docking and nanoscale assembly ; ~Haptic force-torque feedback ; Torsional DoF auto-control of the ligand to avoid contact with the receptor ; Intramolecular interaction energy with Lennard-Jones equation	Lab-built 5-DoF device	Lab-built rendering software	2006 [95]
HAMStER	Investigate enthalpic interactions between drugs molecules and its target ; Computer-aided drug design ; combination of tactile and visual force feedback	PHANToM	Qt (Trolltech)	2007 [96]
Chemical Force Feedback	General molecular visualisation ; Adaptable to multiple haptic APIs ; Protein-ligand docking with electrostatic potential grids for the forces feedback calculations	PHANToM	OpenGL	2007 [97]
HMolDock	Biomolecular docking to study helix-helix interactions (Transmembrane α -helices docking) ; e-learning ; Lennard-Jones potential scoring function	PHANToM	OpenGL and ~Virtual Reality Markup Language	2008 [98]
Subasi and Basdogan system	Rigid body ligand-protein docking ; search for binding cavity ; ~Active Haptic Workspace~concept	PHANToM	Unspecified	2008 [99]
Zodiac	Interactive drug design and ligand optimization	PHANToM	Qt4	2008 [100]
HaptiMol	Haptic exploration of the accessible surface of biomolecules : gain insight of the shape and water accessibility	PHANToM	OpenGL	2009 [101]
CoRSAIRe	Immersive and multimodal application with VR, 3D mouse and haptic device ; protein-protein docking	Virtuose (Haption)	OpenGL	2009 [102]
Daunay and Regnier system	Flexible ligand-protein docking ; Design of a particular control scheme for the haptic feedback stability	~Virtuose (Haption)	Molecular Operating Environment (Chemical Computing Group)	2009 [103]
SAMSON	Haptic control of molecular simulator ; quasi-statics method ; flexible molecules simulations ; comparison between position control and force control	PHANToM	Unspecified	2010 [104]
Sourina and Klimenko system	Collaborative haptic-based molecular docking system	PHANToM	CHAI3D	2014 [105]
Haptimol FlexiDocks	Rigid ligand flexible receptor docking to model the conformational receptor response; high frequency haptic updates	PHANToM	Protein Trajectory Viewer (OpenGL)	2019 [106]

Table 1. Haptic-driven applications.

The neglected senses: gesture control and sonification

The use of human gestures as an input modality and the sonification of data as an output modality have been carried out to a lesser extent. A fairly recent and original example is the immersive framework, which uses a set of depth sensors commonly used in the video game industry to capture human shapes that algorithms convert into energy landscapes [83]. These are then used as external boundary conditions (interactivity) for MD simulations. Users can thus directly see and act on the motion of their own field, which is integrated as fluctuations in the energy of the system, giving rise to large variations in the forces acting on the atoms. There are some corrections for excessively high atomic velocities that can affect the stability of the system. Figure 9 shows two users embedded in a 10-ALA peptide MD simulation coordinating through their energy fields to control them.

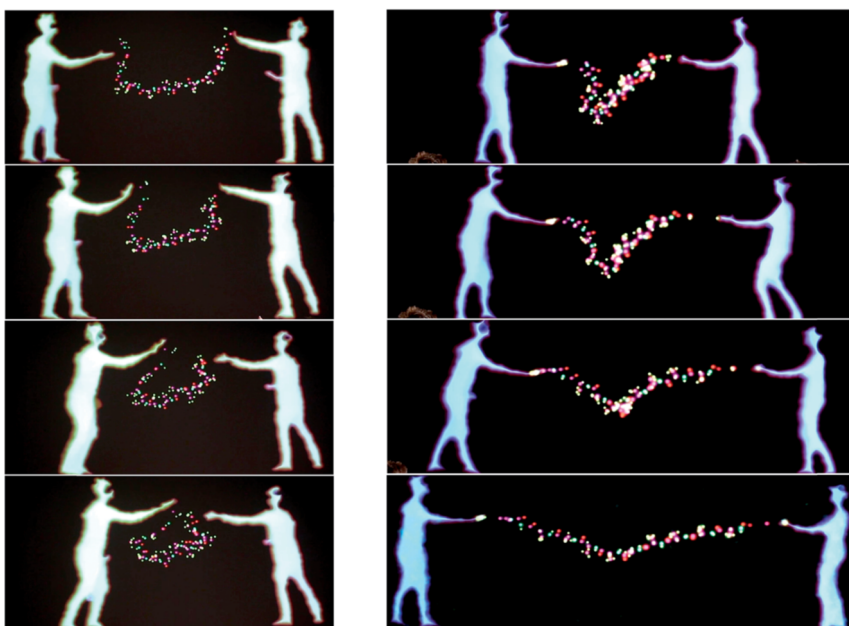


Figure 9. Image sequence showing two users steering a 10-ALA peptide through their corporal gestures. Figure reproduced from [83]. Image under a CC-BY licence.

Graphical feedback has been supplemented by a method of sonifying atomic dynamics. This allows, for example, to distinguish collisions of unbound atoms. However, the authors point out that it is preferable to use a small number of atoms for this purpose, even at the risk of causing a “cacophonous” sound experience for the user. Moreover, real-time Fourier transform calculations add another layer of sonification to hear the variations of the oscillation periods of the whole system (with the influence of the user).

A model for protein surface sonification was tested by Bouchara and Montès [107] as a complement and alternative to visualization. This auditory experiment is immersed in the heart of proteins, so that the “sonicated” surface generates an acoustic environment corresponding to its shape. The user has control over the radius of a spherical filter that has the same origin as the center of the protein, and that accounts for surface areas excluded from the filter area for sonification. The sequence of sound elicitation, its frequency, amplitude, repetition and orientation allows an auditory interpretation of the 3D shape.

Sonification can also be useful to measure changes in one or more parameters over time. The CoRSAIRe protein docking project [101] uses this type of sonification technique based on the parameter mapping of Hermann and Ritter [108], which provides a link between the measured data and the acoustic parameters mentioned earlier. For example, one of the parameters monitored during protein-protein docking tests is a global complementarity score, which is sonified in the form of a prerecorded word with variable intelligibility depending on the score.

Interactive molecular simulations were specifically chosen for sonification by Rau et al. [109]. Since molecular visualizations do not usually have an acoustic output, they experimented with sonification to convey information about the simulation data. They use sound to highlight events from a molecular dynamics simulation. This relieves the visual channel of information and focuses attention on important phenomena. The higher degree of immersion created by sound can be beneficial for teaching purposes.

Other interesting studies and experiments on sonification exist in the literature, such as the one about genes to proteins by Monajjemi [110] but have not been applied to interactive simulations yet.

We have already mentioned several times that interfaces to simulations use at least visual means. Laconsay et. al. have recently investigated what tools and techniques are available to enable people with visual impairments to visualize 2D objects in the context of chemical concepts [111]. This research could help overcome impairments for people pursuing careers in science and further advance research on human-computer interfaces in general.

Putting the pieces together in a functional problem-solving environment

We can, without going into detail, talk about Johnson’s research on a problem-solving environment [1] that allows us to understand the concepts that are useful for developing frameworks such as IMD simulations. For example, the fundamental aspects to consider when adapting molecular simulation codes to computational steering are control structures, data distribution, data presentation, and user interfaces. The latter would leverage a selection of modalities as described hitherto in this section.

The design of such a framework requires the necessary abstraction (e.g., through high-level programming) to enable simulation, visualization and sensory feedback through interaction frameworks. The simulation code is not the most important part of the framework and should be independent and non-specific [29].

In order to create an interactive framework, several issues need to be considered in the existing application or the design of an application aimed at interactivity: What are the biological data and input parameters; how will they be processed by the application; how can the information generated be extracted, analyzed, and presented in a way that provides the user with relevant scientific information. These choices imply decisions related to the modalities, e.g. does a user interaction require the precision and intuitive feedback of a haptic device, or is a simpler interface sufficient? The chosen channels of information would thus use the user's ability to abstract in order to holistically understand the system under study. This analysis, as well as the resulting direct control, aims to bring added value compared to the classical *a posteriori* analysis.

Interactive molecular simulations extend the modelling repertoire

To paraphrase the works of Marchese et al. and Mulder et al., talking about steering a simulation or computational steering in general means that :

[...] a scientist has interactive control over a computational process during its execution. In so doing, the scientist can respond to results as they occur by interactively manipulating parameters to visually explore a what-if analysis, or immediately observe cause-effect relationships among variables [112].

or that

Computational Steering enables the researcher to change parameters of the simulation as the simulation is in progress, while viewing the simulation results simultaneously [113].

In the following, we will describe how these abstract concepts were translated into molecular modelling scenarios by briefly discussing selected examples. These scenarios significantly extend the classical repertoire of molecular modelling with new interactive use cases. Based on the analysis of the literature, we use five categories to structure this discussion. Briefly summarized, these categories include teaching, simulation setup, phase space exploration, visual analysis, and gamification.

Educational and artistic use

The potential of interactive simulations to improve classroom practise has been widely recognised, particularly since the early 2000s [114]; [115]; [116]. The benefits of the 3-dimensional view and immersion are first and foremost lauded [117], dating back even to the 1970s [118]. Of particular importance is the Physics Education Technology (PhET) project, which has developed more than 125 interactive simulations to enhance science education, including quantum mechanics [119] and chemistry [120]. In the context of quantum mechanics and chemical bonding theory, VSEPR theory was the focus of a simulation to construct virtual molecules [121]. Gandhi et al. [122] focused on teaching thermodynamic state variables through real-time simulations. As for interactive and reactive molecular dynamics, the InteraChem Virtual Reality Visualizer is noteworthy [123] as it combines several modern technologies such as virtual reality and speech recognition. In a study teaching enzyme catalysis through interactive MD simulations, most students found the interactive approach more engaging than the traditional approach. They felt that

it improved their understanding and increased their interest in continuing their studies [124]. Similar positive feedback from students was gathered in an interdisciplinary biology curriculum that focused on molecular modelling and IMD [125].

Artistic use is also possible, as exemplified by the work shown in Figure 9 [83], but is rarely documented in the scientific literature.

Setting up and tuning simulations

Simulation tuning through parameter control

There is not much active research to take advantage of the interaction between the user and the programs themselves. Eisenhauer and Gu [126] apply this “interactive program steering” approach to the parallel MD program to directly monitor and control the program’s data decompositions so that the parallel execution threads are fairly distributed. The goal is to gain performance. There are not many such examples in live computational management of molecular simulations. In general, the majority of interaction types in IMS involve the application of forces to atoms, but there has also been some research on direct manipulation of simulation parameters. For example, the visualization package *Java Interactive Molecular Dynamics (JIMD)* [127] can adapt the implementation of parameter manipulation functions to the functions that the simulation engine allows the user to perform, such as handling temperature changes. Of course, new precautions must be taken to avoid read and write conflicts when changing parameter values, as described in this article.

However, Delalande points out that the parameters of the simulations are generally the same for the interactive and the non-interactive simulations, with no possibility of on-the-fly adjustment. On the other hand, certain parameters of the IMD can be changed in interactive time, such as the scaling parameters related to the (haptic) applied force [128], the adjustment of which is used to adapt to the time step variations of the simulation [129]. Narupa similarly allows for interactive and immersive scaling of the interaction strength scale factor parameter within VR [44].

Slowing down the simulation for more precise interactive manipulations is a very useful feature, as is reducing the temperature to reduce background motion. Such principles were applied in Mazzanti’s experiment [34] using the *UnityMol* [51] visualization software. They experimented with changing the system temperature, either by pausing the MD simulation before restarting or on-the-fly. As a future goal, they aim to control the simulation with on-the-fly calculations of experimental target parameters. In the previously mentioned educational work on thermodynamic state variables, temperature is also a key focus [122].

Building and editing models

The initial model used in noninteractive molecular simulations is critical. Interactive approaches offer many advantages in the construction and manipulation of such models. An early example of such molecular construction tasks was developed to study conformational changes and calculate conformational or interaction energies for molecules that were constructed interactively based on a variety of information, including symmetry [130].

Later, the construction of even larger entities was studied, for example supramolecular architectures [131] and DNA nanostructures [132], using a very elegant scale-adaptive approach in the latter case. DNA and RNA nanostructures have also been the subject of recent work combining the levels of design, optimization, and analysis [133]. In this vein, but using simplified models, Indhumathi coined the idea of virtual prototyping of molecules [134].

The interactive molecular building process can also be more closely rooted to experimental structure refinement, as described in several studies [135]; [136]; [137]; [49].

Interactive docking can also be considered a challenging use case of model building and was used early on for rigid [24] or flexible docking [138]. This has led to the development of dedicated interactive software tools such as DockingShop [139] or Haptimol FlexiDock [106] and some success stories [140]; [72].

Exploring phase space and interacting with biomolecular trajectories

Since this is a key application for interactive simulations, we will take a closer look at its origins. An important reference implementation for an interactive simulation architecture is the SMD system developed by the Leech team in 1996 [9], which combines visualization software with a molecular dynamics engine : VMD and the SIGMA molecular dynamics package, respectively. They implemented the communication protocol by modifying Sigma and VMD. Fig. 10 shows the diagram of the system as presented in their original article.

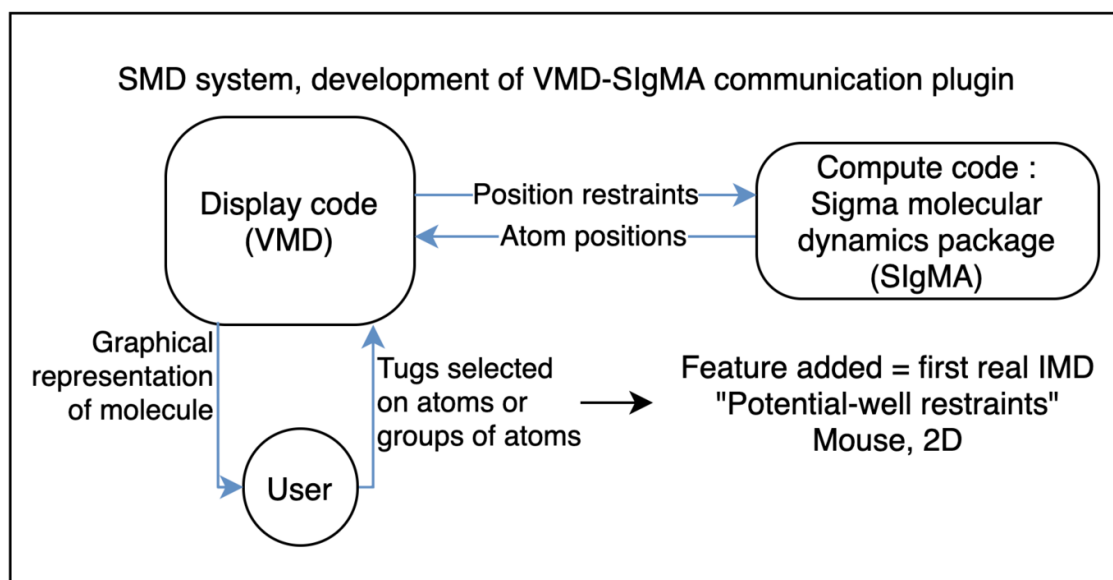


Figure 10. A schematic view of the Steered Molecular System by Leech et al. [9]. The scheme is inspired by Fig. 2 of the original paper.

At each time step of the molecular dynamics simulation, SIGMA sends the calculated atomic positions to update the display in VMD by re-rendering the molecule. At the same time, the visualization interface allows the user to specify new constraints on the atoms that they have specifically selected to affect their dynamics. These constraints on the system are

external forces added to the molecular dynamics simulation, i.e., an approximation of the real physical interactions between atoms (covalent bonds and electrostatic forces). The addition of external forces to the system is not trivial, and apart from opening up new possibilities, such as making it easier to overcome energy barriers, there are legitimate considerations about the perturbations to the system that this process creates. For example, there is the question of the effect of selecting a group of atoms rather than a single atom to avoid significant structural distortions of the system, which demonstrates the importance of selecting which atoms to control, for example, to achieve the preservation of certain secondary structures such as alpha helices during manipulation [9]. Furthermore, the addition of external forces increases the kinetic energy of a group of atoms and the overall temperature of the system [9], which raises the problem of scaling the forces, etc.

In order to produce an effective event on a dynamic molecular structure, it may be necessary to impose an important force beyond the range of pertinent biophysical energies. [141]

For a variety of reasons, external forces affect the validity of the simulation, as the Leech team explained, but perhaps this is not a problem *per se* if we consider that interactive simulation is only an intermediate step in the study of a biological system and its goal is to provide useful information to the user or to prepare subsequent runs. To illustrate this idea, we will discuss, among other things, computational methods for large-scale structural refinement.

The Interactive Molecular Dynamics (IMD) approach initiated by Rapport and Stone [29]; [30] allows for true interactive simulation, unlike the early versions of the SMD system where all boundary conditions are specified prior to simulation. The IMD framework is quite identical to the SMD framework, which uses the VMD visualization tool and, on the other hand, NAMD as the simulation engine. Both tools are extended to use interactivity. The separate haptics, visualization and simulation components are equipped with interdependent communication and asynchronous processes.

Synchronisation problems have necessitated techniques such as introducing a buffer for receiving data from the simulation as an intermediate step to updating the scene with particle positions. This decoupling of received data and particle position updating means that the performance of the simulation is not dependent on or limited by the performance of the graphics rendering. This technique is one way to overcome the performance degradation of a limited data visualisation process [127].

To give an idea of performance, experiments by Dreher et al. with large-scale interactive simulations [142] (on the order of 72k atoms) show that only a few nanoseconds of simulated molecular time can be observed interactively in a 15-minute session, whereas a large number of chemical processes typically require a few microseconds or more. The underlying concept is that the speed at which the simulation runs locks the user into a specific and limited time window that can be explored interactively. Therefore, it may sometimes be necessary to switch simulation methods in order to make the right choice for a particular biological problem. Therefore, it is necessary to have a variety of interactive modeling approaches at one or more scales to choose from.

Interactions to change the trajectory of the system can be used in the form of empirical constraints from experimental data to reproduce specific biological processes. This procedure is particularly useful for the classical MD batch mode, where constraints are added to explore the desired structural dynamics and discover new biological events that would only rarely occur without bias [141]. In interactive mode, this problem does not arise because it is possible to control the combination and timing at which the user decides to apply these constraints, which, however, are still based on *a priori* assumptions.

There are a variety of molecular simulation programs that use a variety of approaches to simulate molecular behaviors. The strength of interactivity lies in the general use of positions and the provision of specific force constraints for each atom. This approach has the advantage of being fairly ubiquitous, as it can be adapted to most molecular simulation programs. It was used in the development of the MDDriver library, an independent library that allows a network to be created between a molecular user interface and a molecular simulation [141]. The MDDriver library was specifically designed for easy integration into any molecular simulation program that can provide a set of particle positions for each time step.

The user can then adjust the amplitude and direction of the forces acting on the selected particles according to his preferences. A haptic device and VR immersion can help enrich the user's perceptions, but the paradigm of interactivity remains the same. The interactive application of external forces to particles is presented by Férey et al. as a two-step paradigm. The first step is the manual selection of one or more particles and the second is the use of the force model described by Stone [30] to calculate the forces acting on these selected particles. These forces are then used simultaneously for visual and sensory feedback and sent back to the simulation engine.

This approach has been tested in several systems. For example, to reproduce the closure mechanism of Guanylate Kinase by increasing the proximity of its two docking sites for GMP and ATP to determine the parts of the system involved in deformation [141]. The tests were performed using *GROMACS* with both all-atom and coarse-grain resolution, and show that the latter primarily allows efficient exploration of the enzyme's closing capabilities. In this way, they were able to propose a new mechanistic hypothesis for the functioning of this enzyme. However, they found that the simulation time scale, especially in VR using IMD, has certain limitations. These limitations, in order to generate significant events on the system, interactively enforce important forces that affect the biophysical relevance of the energies involved.

Another critical point is the way external forces can be applied. The *ab initio* IMD (AI-IMD) system is a method presented by Luehr, Jin, and Martinez [45] for controlling classical *ab initio* MD computations via a haptic device. In general, the principle of the IMD interface used is that the user can control a constraint point connected to the desired atoms by harmonic springs, with the same advantages as previously mentioned.

Although these precautions are taken to tightly control these external perturbations, Luehr et al. explain that the asynchronous implementation of the different components of the IMD interface (which is beneficial for various reasons, such as reducing latency or making it easier to adapt the IMD to different simulation engines) can disrupt the haptic experience

when the simulation rate is not uniform (typically in *ab initio* IMD). For example, when integrating the haptic device into the IMD system, Stone explains that the effective mass (which affects the perception of particle motion in the haptic environment) is highly dependent on the simulation rate [30]. Thus, haptic forces applied over a fixed period of time can be problematic when the simulation speed changes. Another critical problem is that the forces required for AI-IMD simulations can be of considerable magnitude, as the bonds between atoms can be broken, making the integration of haptic forces very difficult, as the MD time step is too long to account for this perturbation. To solve this problem, they used an integrator with multiple time steps to calculate the *ab initio* forces less frequently (in elapsed time) than the haptic forces, since the latter are stronger and require finer integration. There are also issues with resonant oscillations due to latency that can occur when using haptic devices. This fact complicates the calculation of the external forces acting on the selected atoms and forces the calculation of the haptic forces to be integrated directly in the simulation code.

A different approach to render the molecular simulation most efficient was developed by Redon [143]. They proposed the adaptively restrained molecular dynamics (ARMD) approach. The key idea is to turn positional degrees of freedom on and off during the simulation to speed up the computations, allowing users to trade off between precision and speed. In their benchmarks, they were able to speed up simulations by up to an order of magnitude.

The applications in terms of phase space exploration and trajectory interaction span a broad range including enhancing sampling [144], focusing on water molecule dynamics [145], probing drug binding [146] or engineering biomolecules [147]. The exploration can also target specific phenomena such as QM reaction pathways [148] or phase transitions [149].

Interactive visual analysis

Thanks to MD and computational progress, it is possible to simulate increasingly complex systems, but Rapaport noted in the late 20th century that the analysis of these simulations does not scale equally:

While the simulations themselves are becoming increasingly ambitious, considerably less progress has been achieved in terms of the techniques for analyzing the outcomes of these calculations. [29]

We will try to see how research on this topic has developed over the last two decades. This topic deals specifically with interactive time analysis of simulation data outside the scope of the advanced graphical visualization methods of trajectories discussed here. However, there will inevitably be some consideration of visualization, since interactive analysis is generally related to and dependent on visualization.

Currently, powerful structure refinement tools exist to solve very large and complex biomolecular systems. Hybrid methods allow the integration of experimental data from different sources. These hybrid methods are complementary methods that allow the advantages of each method to be exploited. Many computational methods have been developed that combine data from X-ray crystallography (atomic resolution, but limited by

the crystallization step) with cryo-EM data (low resolution, but applicable to very large biomolecular systems). It is important to note that recent developments in cryo-EM detection technology, in particular the use of more sensitive electron cameras since 2013 [150]; [151]; [152], literally make it possible to obtain atomistic models, but that these types of resolved models are still rare, although they have been increasing rapidly recently [153]. Various methods have been developed for combining experimental data with fragment-rigid or flexible fitting. The latter would allow to obtain better trajectories with a better structural fit to the data [154]. One of these complementary fitting methods is based on Molecular Dynamics such as *Molecular Dynamics Flexible Fitting (MDFF)* [155]. This computational method was originally used for structure determination using density maps from cryo-electron microscopy experiments. We will not discuss this method in detail, but in some cases the automatic methods of MDFF are not sufficient to handle some complicated structural regions. It is possible to switch the MDFF refinement to interactive mode and allow the user to manipulate the model to target the desired density region [156]. In this mode, additional information is provided in real time, such as cross-correlation analysis, which allows VMD [12] to provide an estimate of the quality of the fit during the interactive simulation, as used with the *VMD-TimeLine* analysis tool developed by Stone [157]. In fact, there are many tools for model making, such as the Sculptor/Situs tool combination [158]. Gorgon [159] is another interactive toolkit for molecular modeling, focusing in particular on density maps with near atomic to subnanometric resolution (3-10Å).

An important recent advance has been the development of VIA-MD [160], a visual exploration environment for large-scale spatiotemporal MD simulation data. This approach enables interactive 3D exploration and provides integrated statistical analysis, such as visual information on events related to molecular structures and monitoring of parameters to detect events over time and reveal their nature. The figure shows an overview of this analysis environment.

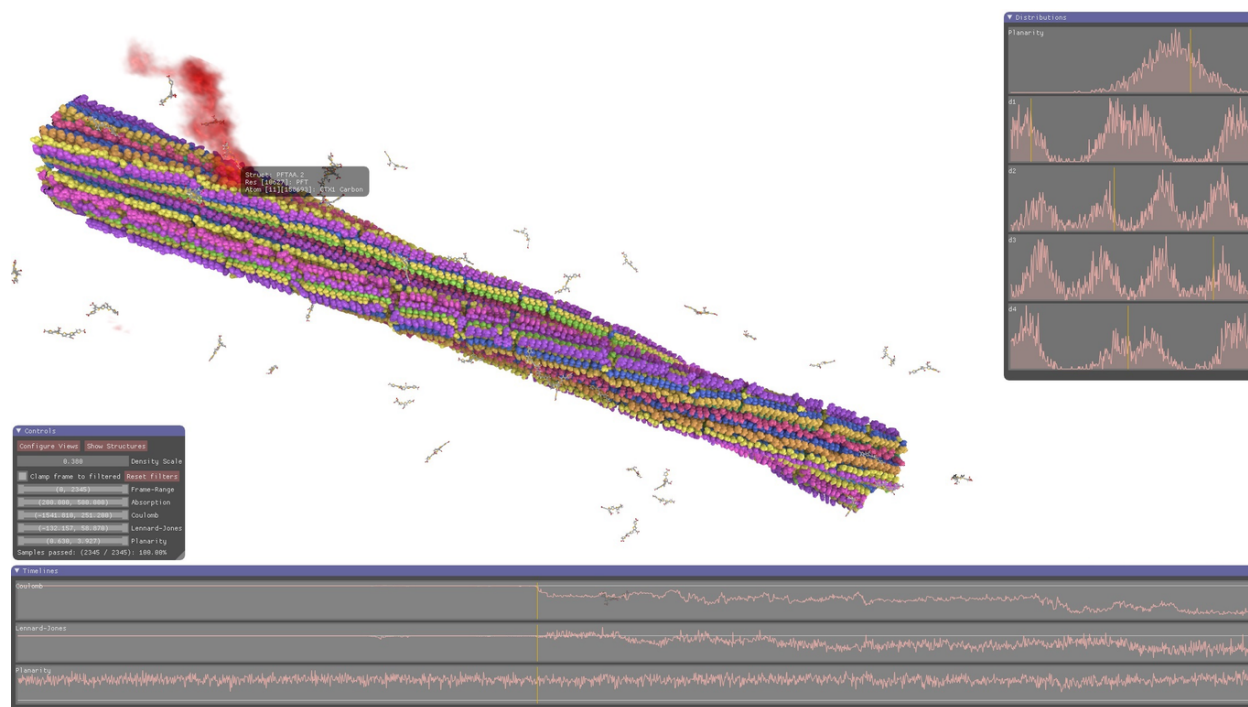


Figure 11. Screen capture of the VIA -MD environment showing an amyloid fibril structure and the corresponding analysis for finding and analyzing events of interest in the simulation. Image kindly provided by the authors with permission.

For large systems, Rapaport pointed out that the simultaneous presence of many particles may prevent observation of what is actually happening. In this case, averaging calculations (e.g., density and velocity fields) should be performed and presented in the form of additional graphs, or allow the use of selective visualization filters according to specific criteria [29].

As explained in the works of Dreher [161] and Rizzi [162], storing a large amount of result data (e.g., handling trajectory files) requires extensive I/O operations that reduce the performance of post-processing analysis. Recently, efforts have been made to perform petascale analyzes [163]. One solution is to run the analysis concurrently with the simulation to avoid full storage of all results. This method is called *in-transit* visualization, the goal of which is to free oneself from the limitation of the transfer rate on the hard disks and to use the computational power of the supercomputer in an unrestrained way. Concurrent analysis acts as a mediator, holding data in buffer memory to perform calculations of analysis and visualization of that data “in transit” before writing it to disk, the whole in parallel with the simulation.

The ExaViz project [81] allows direct or *in situ* analysis even in the context of directed simulations. The difference between “*in transit*” and “*in situ*” is the use of the same computational node as the simulation or not. Another example is the coupling of interactive visualization with the analysis of plasma-surface interactions [164].

The analysis of the action sequences of the user interacting with the simulations, which would serve to correlate the effect of some external forces with some dynamics of the system, implies an open problem of recording all the interactive inputs of the user during the simulation: the problem of reproducibility is crucial to confirm the scientific results. This includes synchronizing the timing of the inputs with the simulation time step, considering and selecting the interactive user inputs that allow robust reproducibility (e.g. convergence of several different trajectories to a common stability state).

Gamification and harnessing human input

The examples described so far focus on enhancing ground truth modelling approaches with a little bit of human interaction. In this section, we present applications that go further by placing human input at the centre of the investigation. This step can be achieved, for example, through crowdsourcing, citizen science, or gamification. In the latter case, scientific problems are reformulated as playful activities, games, or puzzles to leverage human problem-solving capacity. This approach has already been applied to remote optimization of an experiment with ultracold atoms [165], IMD exploration of chemical reaction networks [166], molecular docking [167], RNA folding [34], computational enzyme design [168], and protein structure prediction [35]; [169].

The approach can be taken a step further by attempting to discover the underlying algorithms used by humans in interactive simulations in order to incorporate them into novel modelling algorithms, as described by Khatib et al. [170]. Similarly, data harvested from reactive potential energy surface IMD have been used to train neural networks [171].

Interactive tools and applications for biology

Many of the original applications came from the Schulten group at the University Illinois Urbana-Champaign in the United States. Grayson applied IMD to study the selectivity and regulation of the GIPF membrane channel protein and glycerol kinase enzyme [172]. Their paper also contains detailed information on the IMD communication protocol. The VMD and NAMD tools facilitated the creation of IMD simulations, including haptic devices, and a few years later enabled coarse-grained, low-resolution IMD simulations for the first time [129] for a wide range of systems, including double-membrane/transmembrane protein constructs. They attempted to find a compromise between speed gain and limiting loss of accuracy that allowed application to a range of molecular assemblies from 1900 to 300k particles. This work builds on the MDDriver library mentioned above. It addresses the problem mentioned in the introduction to Chapter 4, where Johnson states that it is sometimes difficult to adapt scientific codes that have taken many years to develop to interactivity [1].

Another example of the use of MDDriver is Molecular scrutiny of PotentiAls (MyPal), which uses a targeted manipulation of charged ions in a precomputed electrostatic potential map that serves as input to the MyPal simulation and corresponds to the potential induced by the macromolecule of interest [173]. Then, the non-pairwise interactions between the ion probes and a limited number of target particles are calculated, as well as

the steric constraints imposed by the shape of the target molecule. The user can thus passively observe the evolution of the probe trajectory or voluntarily apply external forces to it to explore the potential and find docking sites. This method was tested on the DNase I/DNA complex to show the importance of the presence of two cations for electrostatic matching between the DNA and the enzyme, which was independently confirmed [174].

More recently, a study on amyloid fibril formation is worth mentioning, using the special coarse-grained protein model OPEP (Optimized Potential for Efficient protein structure Prediction), which tested interactive simulations for folding peptides from the extended state, among other types of molecular simulation methods [175]. Their work on this topic departs from the standard IMD application by using the aforementioned human ability to sample phase space in a complementary way to fully automated computational approaches [176]. Such tools for interactive protein structure generation have been around for a long time, one example being ProteinShop [177].

Molecular dynamics is widely used and several of the common software packages support interactive simulations. Historically, NAMD - as already mentioned - was among the first programs to support it. Protomol [178], a high-performance framework in C++ for rapid prototyping of novel algorithms for molecular dynamics and related applications, also implemented the IMD approach early on. More recently the method was implemented in the Gromacs simulation engine [14]. The LAMMPS software [179] has also been reported to support interactive simulations.

The particular method of molecular dynamics flexible fitting that we mentioned in connexion with the analysis of results in interactive time was also taken up by the Schulten group and extended to the use of cryo-EM maps to obtain the conformational states of the associated atomic models [155]. The application of this method has been successfully performed in combination with IMD by implementing it in NAMD and VMD for configuration and analysis. These authors mentioned that they are considering future extensions of MDFF, such as the use of implicit solvent models [154]; [180] or sampling techniques based on normal mode dynamics [49]. Beyond these aspects of MDFF, they mention the use of *a posteriori* MD simulations to test their hypotheses about the results of atomic models obtained after MDFF of macromolecular complexes and in agreement with the EM data.

An example of recent MDFF research is Vermaas' study of the refined atomic structure of the EmrE transporter of *E. coli* (known for its link to multidrug resistance through the export of drug-like molecules), based on cryo-EM data to determine the overall atomic model structure of EmrE and computationally investigate its dynamics in different configurations representing the intermediate stages of its transport cycle [135]. The atomic model was refined in an explicit membrane environment using MDFF and interactive molecular dynamics from Stone's implementation in VMD through NAMD simulations [30].

There is also a new open research field of the MDFF method extended to interaction, the interactive MDFF (iMDFF). The initiators of this strategy are Croll et al. whose goal is to allow the user to interactively fit unrefined atomic structures to low-resolution electron density maps. Their iMDFF approach is to use haptics with VMD in the context of an interactive implementation and, in particular, to propose the combination with xMDFF, an

MDFFF method whose goal is to overcome the limitations of using low-resolution data in the study of the structures of large biomolecular complexes. The xMDFFF method allows the computation of low resolution structures obtained by X-ray crystallography and uses a modified MDFFF protocol to compute specific and biased density maps, as it is iteratively determined and thus regenerated at each step from a fitted preliminary model [181]. The method was applied to the insulin receptor, for which only a low-resolution structure of its ectodomain exists [182] and to three structures of complement C4, a protein that plays a crucial role in immune system functions [136].

Focht et. al. including Croll also worked with this system on *Arabidopsis thaliana*, a reference plant organism in research whose plasma membrane H⁺-ATPase 2 (AHA2) structure had been determined ten years earlier from low-resolution crystallographic data. The original model remains controversial, so it was decided to revise the reconstruction and attempt to improve its quality [137].

Flores addressed this problem with an alternative approach called Internal Coordinate Flexible Fitting (ICFF), which is computationally less expensive than MDFFF. His method is presented as a multi-resolution modeling method that consists in building a system by distinguishing different regions according to the level of resolution (coarse-grained or atomistic), in order to balance the coarse-grained approximation with the computational cost of the fine-grained approximation. Thus, there is a predefined set of regions that are considered to be fully flexible, such as certain important regions like the hinge zones and other rigid regions like the domains, and in which the dynamics are computed accordingly, resulting in a large reduction in the degrees of freedom compared to the MDFFF. Similarly, these computational savings apply to the atomic force field due to the addition of various knowledge-based force constraints and the ability to use variable time steps depending on the oscillation frequency of the system [183]. These performance aspects are crucial for the integration of the interaction. Some methods such as ICFF show that it is possible to find optimization strategies, but this choice imposes constraints in advance to limit the number of degrees of freedom, which makes the preparation of the system even more critical.

For this reason, sometimes tools are developed from scratch to efficiently solve a well-designed problem, as in the BioSpring simulation engine, which uses the spring network model to connect particles according to an arbitrary distance criterion and was developed with very low inherent computational costs. As an application example, the interactive flexible molecular fitting method of Molza et al. is discussed, which: (1) is based on the elastic network model and (2) is somewhat similar to the ICFF method of Flores [183] but differs in its preliminary method for defining flexible regions. Namely, it allows for full flexibility whose local amplitude depends on the corresponding particle density [49].

In the application context of creating a model of the dystrophin filament, they developed an interactive docking method based on the BioSpring software that allows the design of models that integrate qualitative experimental data that serve as constraints for simulations (or guides). Specifically for modelling the protein whose mutation is involved in the genetic disease Duchenne muscular dystrophy, the approach combines SAXS data with interactive simulations. The application of their research focused on the dystrophin model,

for which they proposed a hypothesis about its macromolecular complex association with partner molecules ActinF (a type of filamentous actin) and Nitric Oxide Synthase (nNOS).

Their approach is based on the concept of interactive docking [184], which was originally used for low-resolution interactive docking simulations using haptics to reproduce a homologous recombination process. In terms of its implementation, the BioSpring program was intended as an interactive tool for manipulating macromolecules. This is made possible by the extended elastic network model (aENM) and the use of coarse-grained representations combined with or without atomic particles. The aENM is described as a combination of the elastic network model defined by the harmonic functions and the non-bonding terms whose low-resolution force field is also used in the ATTRACT docking program [185]; [186] from previous work. This force field is composed of Lennard-Jones and electrostatic potential terms.

IMD in conjunction with virtual reality was explored by Deeks based on the observation that MD simulations are always particularly costly due to sampling. They developed their iMD-VR Narupa framework [44] for interactive visualization and interactive manipulation of all-atom MD simulations in a virtual environment. They emphasize the fact that humans are particularly suited to perform tasks that require the use of vision and the integration of information from the 3D world. They used the iMD-VR strategy for flexible protein-ligand docking and applied it to several systems to try to approximate protein-ligand positions obtained by crystallography. They selected their trypsin, neuraminidase, and HIV-1 protease systems based on whether or not they had prior knowledge of the docking method, i.e., different levels of a priori knowledge, and tested them with users with different levels of knowledge, showing binding poses within 5-10 minutes [47]. In their search for drugs to treat COVID-19, they also used their approach to construct substrate and inhibitor complexes of the key SARS-CoV-2 protein Mpro [77]. These interactive tools have also more generally been flagged as useful for the fight against the pandemic [187].

Finally, we can cite examples of serious games that have been used in research, such as the UDock interactive protein docking system for exploring the possible conformations of protein complexes [188] and the well-known online multiplayer game FoldIt, which aims to engage a wide audience in solving difficult problems such as refining protein structures [35]. Recently, attempts have been made to find solutions for designing proteins that can dock to the coronavirus spike protein [189]; [190] as shown in Figure 12. Interactive simulations lend themselves well to serious game design [191].

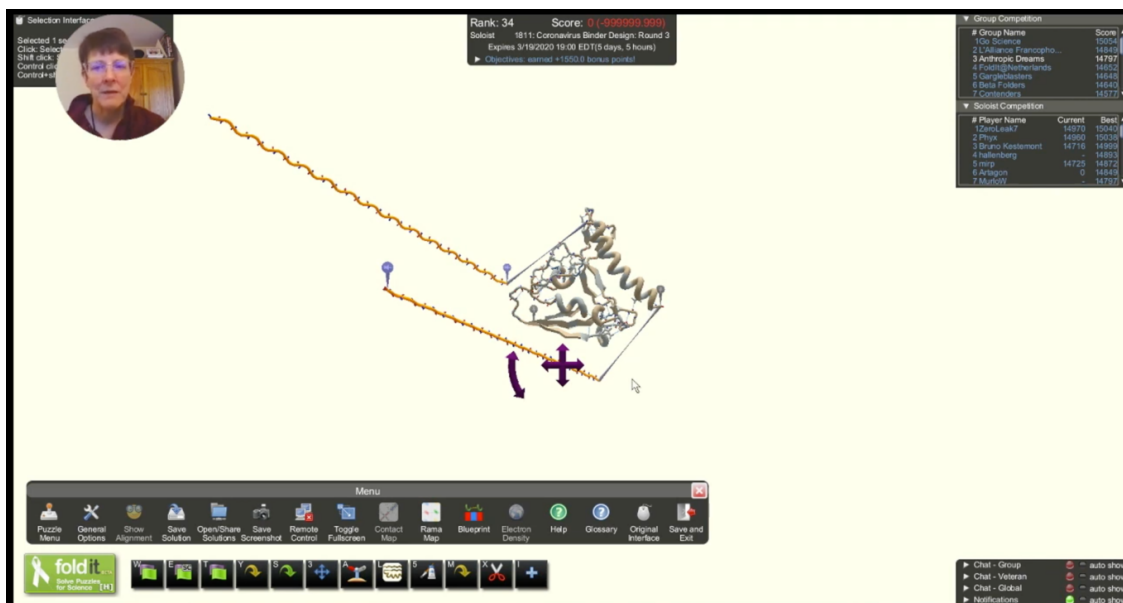


Figure 12. A screen capture of a FoldIt session tutorial showing the design of a protein to be bound to the coronavirus spike protein. Image used with the permission from Center for Game Science, University of Washington.

Evolution of the field and open challenges

Despite the encouraging tendencies observed in Fig. 2, such as the recent surge of IMD-VR and iMDFP applications, to date, interactive molecular simulations largely have been a niche approach that is not widely used and is only occasionally reported in the literature. Here we will try to analyze some of the reasons that contribute to this situation. The development of IMS has been marked by technological milestones over time, many of which were related to the interactive visualization part, as described above. All the technological prerequisites have only really come together in the last two decades, so that for a long time there was only a limited possibility to use these simulations in everyday research to solve scientific questions. Today, this limitation has almost completely disappeared. However, there are still important challenges that give interactive molecular simulations a special status.

What is missing for wide adoption and making further progress?

A closer analysis of the slow progress in recent years suggests the influence of several factors. The inherent multidisciplinary nature that combines computer science and molecular modeling with a number of technical hurdles that must be overcome before a working setup can be achieved represents a practical activation barrier for many traditional modeling laboratories to explore IMS approaches. Issues involve among others the client-server communication protocol and the synchronization of peripherals such as haptic devices with simulation and visualization modules. Another limitation lies in the actual modeling approach, which is made interactive. Many accurate biophysical modeling techniques are not yet fast enough for an interactive mode. This is the case, for example, with all-atom molecular dynamics, where the forces that must be applied to observe the feedback of the

system in a human time frame of minutes often exceed biologically reasonable limits, and the simulation time frame that can be sampled in minutes is too short with respect to the characteristic time frame of biological processes. Performance is specifically addressed in the next subsection. Another important aspect is that the IMS sector has received limited funding compared to, for example, the gaming industry, and therefore implementation of advanced visualization tools has been slow. Hopefully such expertise may transfer back from these industries to the research domain, however intrinsic hurdles may exist [192]. Another peculiarity concerns the way IMS is typically used. It is rarely seen as a new technique that replaces traditional methods, but rather as a complementary tool for developing project strategy, formulating and pre-assessing hypotheses, and identifying the most promising avenues for traditional non-interactive simulations. Thus, when the IMS simulation task is completed, this is not necessarily an aspect that will be mentioned in later publications, as the main contribution was to be able to formulate some hypotheses that were then tested using traditional approaches. Such an internal use of IMS will mostly remain unknown to the community.

The crux of performance

It is undeniable that computer performance has increased significantly in recent years, due in part to the use of graphics processors. This has improved the results of molecular simulations and also raised interactivity to a new level. However, the practical consequence of such an improvement is that routine simulations themselves are now on the order of hundreds of nanoseconds or microseconds, which means days of simulations on large supercomputers. Even if the same technological breakthrough applies to interactivity, the gap between the two approaches seems fairly constant and very difficult to overcome. This situation might also explain why many successful applications of interactive modelling are found in the world of docking, where this time scale problem does not exist, rather than in the world of simulation. For example, it seems to prevent us from considering interactive MD simulations as valid trajectories because they lag too far behind the time scale standards in non-interactive runs. One might think that this situation limits interactivity to the first steps of the modelling process, e.g., in the selection and evaluation of parameters or strategies, or as a means of testing or hypothesising in initial “rough” simulations. However, this boundary is shifting, and one can imagine that IMS approaches could eventually become routine procedures. The main problem is to choose the right application window, where the time frame for human interaction and the limits of computational power meet in a sweet spot. Coarse-grained molecular simulations are definitely a step in this direction, as are hybrid multiscale simulation methods.

How valid are interactive simulations?

Not much attention has been paid to the fact that human intervention can lead to changes (constraints, etc.) in the simulation system. One may wonder how realistic and valid the implicitly out-of-equilibrium IMS scenarios are from a methodological point of view, especially when the experiments are conducted in a short interactive session. To what extent do the methods have controls or constraints on the interactive actions to keep the systems in a reasonably realistic state from a statistical mechanics perspective? This is of

course a valid concern, but it becomes a second-order question when the interactive simulation itself is not the intended outcome, but merely a means of formulating and testing hypotheses, as mentioned above. Similarly, we have seen several model building and refinement applications, where often experimental data is used in conjunction with the IMS and provides a boundary condition that helps to restrict the interactive manipulation to valid conformations.

The challenges of provenance and reproducibility

Interactivity is an attractive strategy to guide the course of a simulation, especially when it has a clear goal (conformational changes, docking), and it is clear that human intuition is a valuable asset. However, human intervention is difficult to reproduce. Strategies to recover human intervention in a reproducible way can involve several approaches. The simplest approach is to repeat each interactive experiment several times with the same operator to statistically analyze the ensemble of simulations. This approach requires saving a record of the user interaction for later analysis. Recording interactive session logs is also the basis for the second approach: although it is unlikely that a human will execute exactly the same moves twice, one can use a computer to replay a recorded set of user interactions multiple times to obtain a statistical analysis of the simulation's response to the interactions. From this strategy, a systematic approach can be derived to translate interactive actions into the design of a simulation strategy that can be used in a conventional way. Such an approach could be a way to circumvent the time constraint mentioned above: the previously recorded human interaction pattern could be reproduced by the computer in a much longer time frame, so that the gap between interaction and simulation becomes smaller. Another variant may be to train neural networks based on the operator input and achieve thereby a different level of reproducibility. On the other hand, it should be made clear that reproducibility is not necessarily essential, depending on the design of an interactive experiment. If the main goal is to involve a human in the simulation loop to benefit from his expertise and intuition, one must necessarily strive to improve the spontaneous and unpredictable/unreproducible aspects of such an approach.

How will artificial intelligence and machine learning affect IMS?

With the advent and tremendous advances of artificial intelligence and machine learning, a legitimate question is how these techniques will affect interactive simulations in the future. Could an AI become a "superuser" with intelligent interaction that significantly reduces the need for human interactivity? Since an AI needs to be trained or programmed, this may only be an option for concepts that are sufficiently well understood or characterized. For example, if the goal is to design a specific conformation, an AI can take control of the simulation once the targeted conformation can be "explained" to the computer. However, when it comes to using specific human expertise and intuition to generate new hypotheses, we are still far from engaging an artificial entity for such tasks. Therefore, we believe that interactive simulations driven by humans still have a bright future ahead of them and will be necessary and very complementary tools to harness human computational power in the near future, as demonstrated by David Baker's group for protein folding or by our group for

interactive RNA folding. They may however provide very high quality data to train AI models and we have seen initial examples in that direction.

Conclusion

Visualization of the result of an ongoing simulation in interactive time and the ability to interactively affect the simulated biomolecules are the two necessary conditions that characterize the interactive molecular simulation approach. The computer was originally conceived as an extension of the user, as his assistant in constant dialog with the machine. Such an assistant can help with complex tasks, such as exploring the molecular energy landscape, which is still the subject of intense research. SMD research has shown that the user can gain valuable information about the system by adding external constraints.

Human visual perception is very powerful and can be used to enhance the understanding of the models under study by promoting interactive visualization. The aim is to provide the scientist with a set of tools that allow him to create his own visual representation of the system from the mental models that occur to him thanks to his intuition and knowledge. Human intuition seems to be able to contribute efficiently to targeted molecular simulations, as shown by the success of FoldIT and EteRNA. The manipulations of users, including non-experts, can be exploited. The idea of interactivity is not to replace existing molecular dynamics simulations, but to complement them as an approach that facilitates communication between human cognition, which interprets information in a holistic manner, and the raw results of the reductionist computations of molecular simulations.

The graphical and structural representation of molecules has benefited from advances in rendering without significant changes in visualization techniques. Interactive simulations use classical representations whose rendering is very fast, such as the VdW, sphere and rod, or particle representations, for computational efficiency. Interactive molecular simulations have been integrated into immersive environments, with research focused on collaborative research in immersion or on the production of educational tools. There are still performance challenges that directly impact the quality of immersion for further use.

Multimodal environments are an active research topic that aims to exploit sensory feedback and voluntary control, with the resulting multisensory integration or multimodal integration being one of the keys to better understanding the systems under study. In the context of this research, the development of haptic devices has undoubtedly contributed most to interactive molecular simulations, although there has been a loss of speed in recent years. The sonification of structural information and measured parameters, as well as the involvement of the human body as a whole, are also remarkable techniques whose exploration allows to refine the understanding of the influence of external contributions on the dynamics of biomolecules *in silico*.

Direct control of the trajectory is, of course, the fundamental interaction in IMS where one can directly observe the effects of manipulations on the simulation. Adapting simulation code for this type of functionality, and for interactive functionality in general (e.g., interactive analysis or control of other parameters) in a rapidly usable framework, is one of

the focuses of larger-scale IMS development. There are still limits to interactivity, such as the relevance of the systems thus perturbed, the maintenance of their stability over the simulation time, the choice of interaction parameters (e.g., the constraint parameters applied to the atoms), the reproducibility of the sequence of application of external forces, etc. The interaction between the user and the operation of the programs themselves or the parameters of the simulations is probably the most complex type of interaction to be realized at present.

Moreover, the increasing complexity of the targeted molecular systems requires advances in the analysis of the results, whether in IMS or in classical MD. Advanced on-the-fly data analysis, while still quite new, is crucial for adapting to big data and integrating ambiguous experimental data.

There are many applications of interactive simulations that show that their use as a complementary technique is relevant to (1) harness human intuition and expertise where classical simulations sometimes reach their limits, such as processes that are too slow to model biomechanical behaviors at achievable simulation times, and (2) develop new mechanistic hypotheses.

Interactivity allows the user to choose the combination of biological constraints in interactive time to limit the addition of arbitrary constraints and thus improve the reproducibility of the experiment. This choice makes it possible, for example, to combine rationality and empiricism in the development of a new drug. The aim is to facilitate the initial stages of modeling before moving on to the lengthy simulations of more complex systems.

As the success of serious games such as FoldIt, UDock, or HireRNA shows, laypeople can also become direct agents of scientific research. They provide the educational world with a means to better understand models of biological systems.

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