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Deep inside molecules — digital twins at the nanoscale

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Abstract: Background Digital twins offer rich potential for exploration in virtual reality (VR). Using interactive molecular simulation approaches, they enable a human operator to access the physical properties of molecular objects and to build, manipulate, and study their assemblies. Integrative modeling and drug design are important applications of this technology. **Methods** In this study, head-mounted virtual reality displays connected to molecular simulation engines were used to create interactive and immersive digital twins. They were used to perform tasks relevant to specific use cases. **Results** Three areas were investigated, including model building, rational design, and tangible models. Here, we report several membrane-embedded systems of ion channels, viral components, and artificial water channels. We were able to improve and create molecular designs based on digital twins. **Conclusions** The molecular application domain offers great opportunities, and most of the technical and technological aspects have been solved. Wider adoption is expected once the onboarding of VR is simplified and the technology gains wider acceptance.

Keywords: Digital twins; Molecular simulation; Virtual reality

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1 Introduction

Digital twins are important emerging computational tools that enable to replicate complex processes. By replicating these processes in real time on a computer, we can create 3D models of certain aspects of the real world that can be used as surrogates for reality. Here, we focus on digital twins at the nanoscale, that is, in molecular systems. One can define such a nanoscale molecular digital twin as a virtual representation of a physical molecule that serves as the real-time digital counterpart of a nanoscale microscopic object. It is scaled up to the human scale so that it can be studied in the same way as macroscopic objects, where molecular properties are calculated on the fly using state-of-the-art computational tools. As illustrated in [Figure 1](#), the Web of Science retrieves over 2000 scientific publications containing “digital twins” in their title, spanning the

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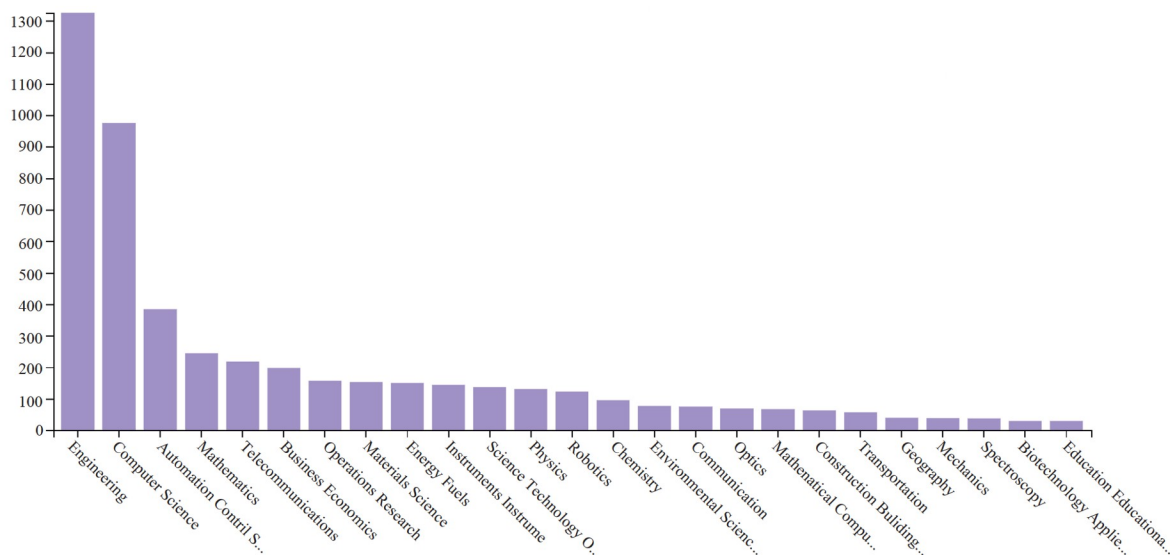


Figure 1 Citation analysis of publications with the keyword “digital twins” in their title, ranked according to citations in a given scientific domain. Source: Web of Science.

main application areas of engineering, computer science, automation control systems, mathematics, and telecommunications. Applications in molecular systems can be found primarily in the materials science field and in relation to energy fuels. Chemistry is only featured in the 14th position in terms of the number of publications, with 95 records, accounting for less than 5%. Biological applications only appear very late on this list. This observation is somewhat reflected in the surveys conducted by Barricelli et al.^[1] and Huang et al.^[2]. The “digital twin” term is largely used in an industrial context, often linked directly to manufacturing and process design; yet, we do not usually describe academic research in these terms.

However, in the field of molecular modeling, digital twins at the nanoscale have been around for many decades, as demonstrated by a handful of use cases, such as by Stavropoulos et al.^[3], who described an example based on molecular dynamics and Vincke et al.^[4], who added interactive manipulation of a digitally replicated real-world molecular model. Perhaps the most emblematic example is the human brain project^[5,6], which attempted to create a model of a functioning brain at the molecular level but still encountered many challenges^[7]. The computational approach to molecular dynamics is a key method that has been used for many decades to represent molecular processes at the nanoscale on computers. Such simulations can be performed interactively, as described in [8], which is the key to implementing a true digital twin. They can also be aimed directly at reproducing real experimental data, as described by Dubois for scanning tunneling microscopy^[9]. Nanoscale haptic control has also been investigated experimentally^[10,11], but these examples lack the aspect of a digital twin, which is a computational representation of the molecular system.

Let us briefly review the field of molecular modeling using digital twins – the focus of this article – by discussing seminal work that has contributed decisively to the current state of the art in this field. Before the term “digital twin” was used, such digital representations were usually referred to in the literature as “simulations” of specific classes of molecules, the most emblematic example of which is liquid water^[12]. Later, more complex molecular objects such as polymer melts were recreated as digital twins^[13]. The development of widely used general-purpose force fields^[14,15] extended this approach. This was followed by studies on membranes^[16] and subsequently, on very complex molecular systems embedded in membranes^[17]. In particular, such digital simulation twins have helped improve our understanding of protein folding^[18,19]. The development of reactive force fields has opened up further possibilities^[20]. A pertinent example of how such digital twins allow the study of specific parameters affecting molecular processes is water conduction through

carbon nanotubes^[21]. Generally, they have become important tools for understanding the physical basis of the structure and function of dynamic models of biological macromolecules^[22]. Another leap was made with the democratization of coarse-graining approaches^[23], extending to longer time scales and larger system sizes. Recent examples include mesoscopic modeling of the extracellular matrix^[24] and other large biological entities^[25]. This might make it possible to model whole cells such as an alga, as described in [26].

Virtual reality (VR) has been an early adopter of molecular systems to inspire usage scenarios for technology. Such nanoscale objects are inherently complex, difficult to understand, and require assistance to gain a deeper insight into their properties. The use of VR combined with advanced molecular visualization opens up a new dimension for these studies and renders such academic capabilities useful to the industry. Hardware has been a limiting factor for a long time. Cave Automatic Virtual Environments, for example, are very bulky, require a lot of space, and are immobile. With the advent of low-cost, high-quality head-mounted displays (HMDs), the situation in this area has changed dramatically^[27]. In addition to hardware, the advent of user-friendly software frameworks built on game engines, for example, has lowered the barrier of technical skills required to experiment with VR approaches and made them accessible to a broader range of academic teams.

Here, we report on the molecular simulations of digital twins in the realm of VR. This includes running simulations, such as molecular dynamics and interactive elastic network models, as well as performing advanced immersive visual analysis. We present three categories of use cases for digital twins by discussing selected proof-of-concept implementations. These can cover a wide range of domains such as drug discovery. In this field, virtual computational approaches are now being routinely used and have shown impressive success^[28]. For example, molecules against HIV have been developed and have reached the clinical stage^[29]. Other academic and technological applications are also discussed. By using generic middleware for our technical implementations that connect both domains, this approach can be easily extended to novel applications. In the following sections, we first present the underlying methods and then discuss the results for these use cases. The discussion following these sections concludes the paper.

2 Methods

We describe a series of experiments with digital twins in VR using prototype software and tools, including molecular modeling steps, simulation coupling, VR manipulation, and visualization. During the VR experiments, the participants wore an HMD and were immersed in a virtual environment. We first describe the methods in terms of molecular modeling and then, in the second subsection, in terms of VR aspects and equipment.

2.1 Molecular modeling

The molecular modeling section informs the digital twin about the intrinsic properties of the molecular object based on physical laws that are processed in a simulation engine depending on the atomic coordinates of the model under study. In most applications, the simulation of molecules is dynamic, that is, it includes a fourth dimension – the temporal dimension – in addition to three spatial dimensions. Therefore, these experiments can be classified as 4D and not merely 3D. The simulation engine is interchangeable in the experiments performed and we provide details of the most common experiments. To couple the simulation engines with the VR part described below, a specific piece of middleware is required to implement an interactive protocol for molecular simulations, MDDriver^[30], which we will also briefly describe. The simulation programs most commonly used for interactive digital twin experiments are an elastic network model, BioSpring^[31], and molecular dynamics simulations using the Gromacs package^[32]. BioSpring was designed for interactivity^[32] and we will describe it first.

The BioSpring software package represents each molecular component through a variable network of harmonic springs, enabling interactive dynamic testing. The extended elastic network model (aENM) combines the usual harmonic spring network functions with unbound force field terms between atoms or pseudoatoms, as described in [33]. aENM supports the use of multiple cutoff distances to determine the final spring network. Thus, more or less weight can be assigned to secondary or tertiary structures as needed. In a typical study, a cutoff distance of 9Å was used for scaffold particles involved in secondary structure elements, whereas it was reduced to 5Å for other particles belonging to loops or side chains. The two resulting spring networks were merged into a final aENM model after the particles of the two previous aENM models were connected by a spring when they were closer than the cutoff distance of 5Å. This approach significantly simplified the creation of multiscale scenarios, providing the ability to combine atomistic and coarse-grained models. Owing to code optimizations that include parallel computing and GPU programming, this approach can be used on desktops or laptops to create molecular assemblies. As part of a digital twin, BioSpring is remarkably efficient in preparing numerical simulations or developing biomolecular models that incorporate qualitative experimental data. For the example concerning the MutS mismatch repair protein, we used a reduced representation of the protein derived from the 1W7A crystal structure. The augmented elastic network representation combines a specific coarse-grained elastic network^[34], an optimized repulsive steric Lennard–Jones term, and a coulombic potential. Springs were generated automatically within a 9Å cutoff, except for connections between the MBD domains and the rest of the complex that were generated with a 4.4Å cutoff to provide sufficient flexibility for the deformations.

When a more detailed representation was required, for instance, when an explicit membrane or solvent representation was involved in the molecular system, molecular dynamics simulations were the method of choice. We performed many digital twin experiments using the Gromacs molecular dynamics software suite. Here, we describe a typical setup, such as that used for the water channel example discussed in Section 3. GROMACS 2019.2 was used to perform the simulations with all atoms with an integration time step of 2fs. Bonds involving hydrogen atoms were constrained using the LINear Constraint Solver algorithm^[35]. Ewald electrostatics with a particle mesh and cutoff of 12Å were used, in addition to the Verlet buffer scheme for nonbonded interactions; the neighbor list was updated once every 20 steps. Three baths (channels, lipids, water, and ions) were coupled to a temperature of 310K using a Nosé–Hoover thermostat^[36] with a time constant $\tau = 1$ ps and chain length of 4. The pressure in the x/y dimensions was isotropically scaled to 1 bar using a Parrinello–Rahman barostat^[37], and the z dimension was independently coupled to a reference pressure of 1 bar, $\tau = 5.0$ ps, and compressibility of $4.5 \times 10^{-5} \text{ bar}^{-1}$. All systems were minimized for 5000 steps using the steepest descent algorithm and equilibrated for 2 ns using decreasing position constraints of 1000, 400, 200, 100, 40 $\text{kJ mol}^{-1} \text{ nm}^{-2}$ for heavy atoms, using the initial structure as a reference. Finally, interactive production runs were performed without position constraints.

To couple such molecular simulation engines within a digital twin scenario to a VR interface enabling interactive molecular simulations, as reviewed in [8], we used the MDDriver middleware^[38] whose application to a broad range of systems is described in [30]. In MDDriver, interactivity is based on a network transmission protocol for the general use of atom positions from the simulation engine and the user's provision of specific force constraints for each atom. The user can then adjust the amplitude and direction of the forces applied to the selected particles according to their requirements. The interactive application of external forces to particles can be viewed as a two-step paradigm. The first step is the manual selection of one or more particles, and the second is the use of a force model^[39] to calculate the forces acting on these selected particles. The forces are used simultaneously for visual and sensory feedback and then sent back to the simulation engine. This approach is fairly ubiquitous and can be adapted to most molecular simulation programs such as BioSpring or Gromacs. This functionality was implemented as an independent software library to provide a TCP/IP network

connection between a graphical molecular representation with a user interface and molecular simulation. The MDDriver library was specifically designed for easy integration into any molecular simulation program that can provide a range of particle positions for each time step.

2.2 VR

To add VR capabilities to our digital twin experiments, we used the open-source software UnityMol^[40] as the basis for development. The molecular graphics and interactive tasks were designed in Unity, and the VR capabilities took advantage of the available vendor SDKs for popular HMD models such as Oculus Rift, Quest, and HTC Vive. For all the experiments described here, we used UnityMol. The software can be downloaded and it works in desktop (2D), display wall (3D), and VR headset (immersive 3D with head-tracking) modes. Special visualization features were added for VR, as described in [41]. UnityMol was connected to the original MDDriver library for interactive simulations and alternatively, to an early prototype of the Artemis software library with equivalent functionality. The rendering performance was so good that no latency was observed in the systems described in this work, and high frame rates, which are required for a good VR experience, were achieved.

The equipment used for most VR experiments was an HTC Vive HMD, either in a wired or wireless setup. All runs were performed on a workstation with an Intel(R) Core(TM) i7-9700K CPU running at 3.60GHz and 32GB of onboard memory using the above simulation programs. Molecular scenes were rendered using an NVIDIA GeForce RTX 2080 Ti graphics card with 11GB GDDR6 memory. User interactions were performed using the native controls of the HMD. RyR ion channel exploration was performed using an Oculus Quest 2 HMD set up in a wired configuration with a high-speed USB-C cable.

3 Results

The results of three types of tasks relevant to digital twins of molecular systems in VR are reported. The first is the creation of molecular models. This is an important step for further studies and requires the satisfaction of several conditions, such as the use of a valid physical representation of the molecular model; satisfaction of all known experimental constraints; and satisfaction of the user's design decisions, typically on how to assemble the parts into an overarching molecular machinery. Second, we discuss the rational design of molecular objects that typically includes a dimension of feedback between the model design and experimental measurements. Experimental observations were used to validate the design and measure its performance. The third use case involves establishing feedback of the digital twin with physical representations. This approach creates a three-way loop among a physical object at the nanoscale, its digital twin, and a tangible representation in the real world.

An overarching question concerns expert and user evaluations, and feedback regarding task implementation. For most applications, we conducted an informal evaluation with selected groups of users (typically between 2 and 10) that directly informed the design. We also conducted a series of guided interviews with researchers from the field of ergonomics. These lasted between 20 and 60 minutes and were thoroughly analyzed. Where appropriate, we used the hierarchical task analysis (HTA)^[42] evaluation method, which is more theoretical than empirical. HTA requires only one expert to compare the different execution times of subtasks determined by subdividing the main task. Each subtask can be subdivided again until the subtasks reach a sufficient level of precision to accurately evaluate their execution times. This method is particularly useful for comparing similar tasks performed under various conditions. It allows one to evaluate both the task methodology with respect to specific conditions and the performance of the conditions for a given task.

3.1 Molecular builder’s workshop: tools for integrative modeling

Integrative modeling is often used to describe the creation of 3D molecular models based on the integration of various experimental data sources, including cryo-Electron Microscopy, Small Angle X-Ray Scattering, Fluorescence Resonance Energy Transfer, mutagenesis, Nuclear Magnetic Resonance, mass spectrometry, and cross-linking experiments. A digital twin provides a useful platform for integrating such diverse information into structural models because the human operator may select the best strategy to evolve the current design. As this building task is intimately linked to the 3D architecture of a molecular object, VR enables an adapted environment for manipulation.

A typical example is shown in Figure 2. The molecular object under study is the MutS protein complex. The first molecular structure can be found in the protein database^[43]; here, the crystal structure 1W7A is described in [44]. This structure does not agree with reported measurements of the active conformation when the complex interacts with partner proteins in a realistic environment. Here, we targeted the distance limits from the FRET fluorescence and crosslinking experiments. Therefore, we explored the possible deformation geometries of the MutS protein complex to generate configurations compatible with these available measurements. Two distances – D1 and D2 – were monitored with the constraint that D1 was larger than 28Å and D2 was smaller than 17Å. Initially, D1 was too small and D2 was too large. The manipulation was delicate because, as shown schematically in Figure 1, the two distances were interconnected and the protein domains were linked in a circular arrangement. These interdependent conditions could, of course, be accommodated by a human operator in a VR environment, simultaneously extending D1 by pulling apart the two green domains and reducing D2 by bringing together the orange and light green domains. We performed approximately 20 interactive runs and generated seven models that were compatible with initial distance constraints. These models can be subsequently evaluated in further experiments by first deriving hypotheses that distinguish them and then testing them. Such hypotheses may involve analyzing distances to predict where cross-connections might form and then testing whether the predicted cross-connections are actually observed to filter out the model that satisfies the most constraints.

Another typical example is the joining of two composite parts of a large molecule. Often, the structures of individual parts can be found in databases or can be predicted quite reliably using tools such as AlphaFold^[45]. However, it is a delicate task to establish a connection between two such parts, as this connection must not stress the molecule or otherwise sabotage its functionality. Immersive digital twins of the individual parts

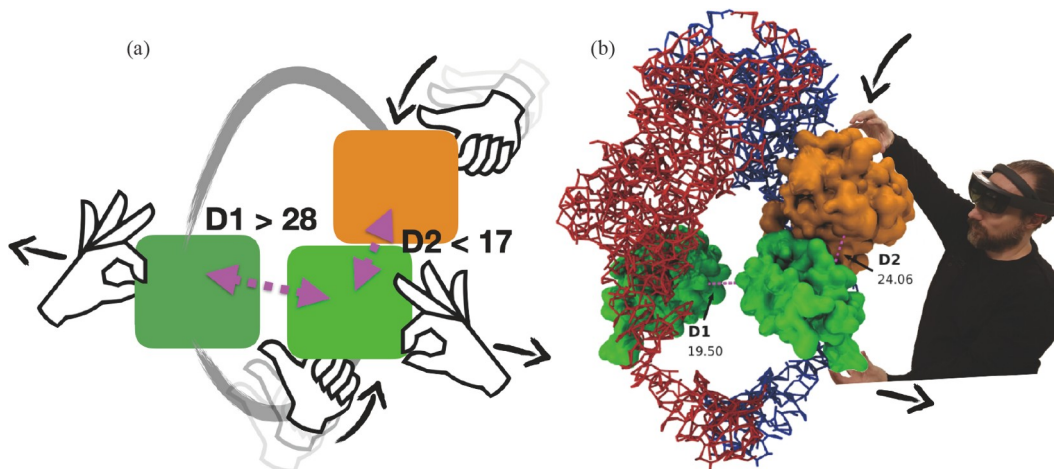


Figure 2 Interactive integrative modeling of a MutS complex satisfying two distance constraints. The left panel schematically shows the experimental goal: increasing D1 — the distance between the two green protein domains, and simultaneously decreasing D2 — the distance between the light green and orange domains. The right panel shows the initial model and the approximate directions of manipulation to fulfill both conditions simultaneously.

assembled in a framework, where they can be carefully connected, are an excellent application for VR. We applied this approach to model the influenza virus^[46] and assembled a hemagglutinin model in which a helical connection had to be made. Hemagglutinin, a trimeric glyco-membrane protein on the outer envelope, is an essential component of the virus. The 1MQM crystal structure contained only the part of the extracellular domain that protruded from the membrane but not the inner half. The inner part, consisting of alpha helices, was modeled and contained four residues that overlapped with the 1MQM part. The task shown in [Figure 3](#) was to create a connection between the overlapping parts that preserved the helical structure. This was achieved through interactive, semi-automatic manipulation using the BioSpring spring network model that was ideal for this type of operation. Linear steric repulsion was used to avoid interpenetration. We used an automatic constraint function to move the first four residues of the TM helices to their positions in the crystallographic structure. We used ghost particles as the final target positions. To avoid pulling the entire helix through imposed shifts, only the first 12 residues (out of 42) remained dynamic. Displacement of the four residues to their target positions could be achieved in only a few seconds. Several tests were required to optimize the forces of the stresses, especially for the residues farthest from the target.

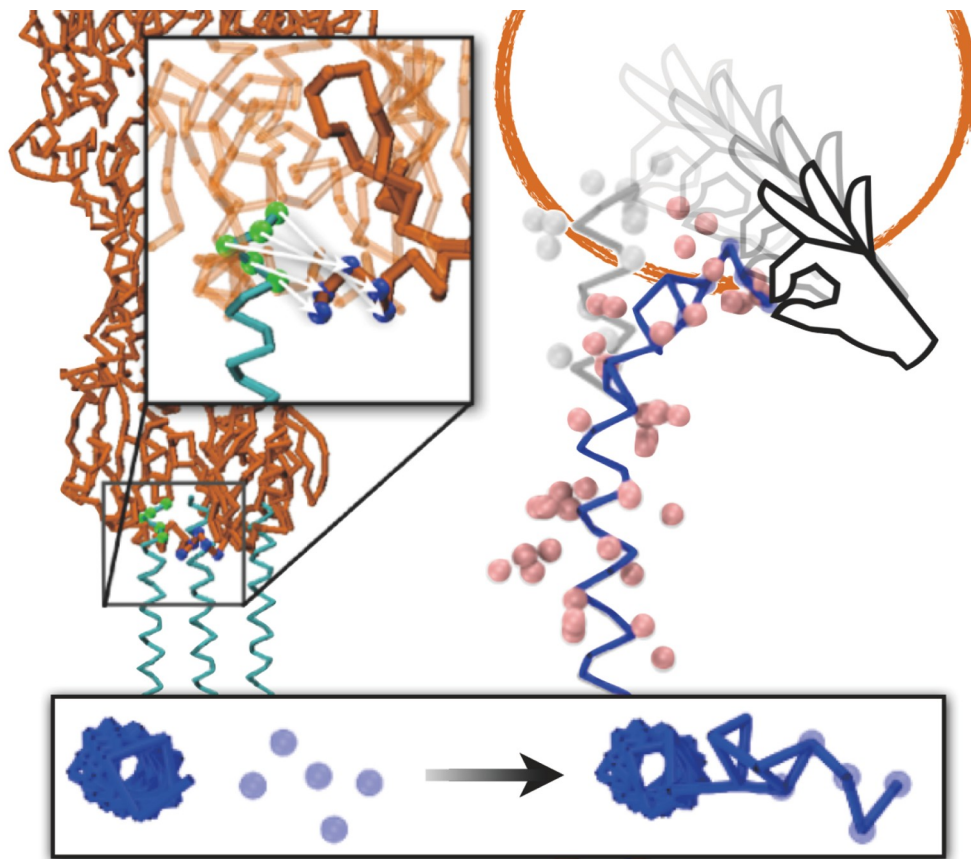


Figure 3 Modeling of influenza virus hemagglutinin by joining two protein domains: the extracellular domain in orange, for which a crystal structure is available, and the helical transmembrane domain in cyan. The overlapping atoms between the two parts are indicated in the insets, as is the direction of manipulative motion. The tip of the transmembrane helix is bent to join the extracellular domain. The lower figure panel illustrates the process as seen from above.

It is also possible to use the work of human operators more actively, particularly through interactive molecular simulations^[8]. We tested this approach in a classroom setting to teach RNA structure and folding, in particular [\[47\]](#). An intuitive study was conducted with 141 students who had virtually no prior information about nucleic acid scaffolds. They were only given a brief description of the major forces that defined RNA structures and were asked to accurately predict 3D RNA constructs of increasing complexity and length (four

RNAs of 22–47 nucleotides). Because the target solution was known, we allowed them to submit their predictions and obtain an Root Mean Square Deviation value for the structural deviation to see how far they were from the correct solution. In addition, we compared their results with those of the full computational refolding of these target structures. This study showed that the human subjects effectively used different and complementary strategies compared to a fully computational algorithm. Interestingly, because of the large number of participants, we were only able to conduct the experiments using a desktop setup. This was sufficient to produce high-quality solutions for simpler target structures. However, the students themselves indicated that, for more complex RNA targets, a more immersive VR setup would have been helpful. Therefore, we implemented the same interactive simulation approach in a VR environment, as shown in [Figure 4](#). We have yet to conduct a new campaign of such folding experiments and are still considering how to best make the technology accessible to a larger group of subjects for transfer to a classroom setting.

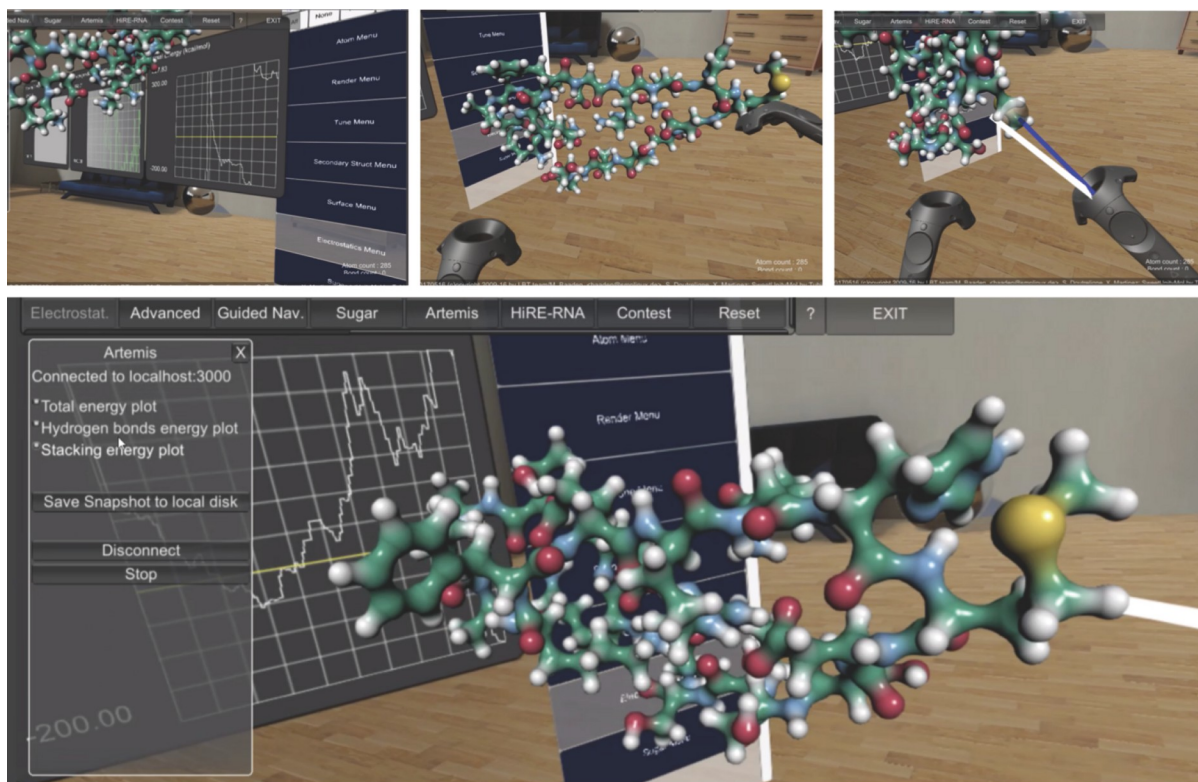


Figure 4 Interactive molecular dynamics in virtual reality. The top row shows the sequential steps of displaying simulation properties such as energy and hydrogen bonding, approaching the molecule with the controllers for manipulation, selecting by a laser pointer metaphor (blue beam), and providing visual feedback on the applied force (white rectangular block). The last image shows how the molecule is stretched as a result of this manipulation. This content is available as Supplementary Movie 1.

After the individual modeling steps of an integrative modeling pipeline have been performed, the final model must be inspected and verified. VR is ideally suited for this purpose. We recently created a complex atomistic model of the largest known ion channel – the ryanodine receptor – with more than 20000 residues and explored the final model in detail using VR. [Figure 5](#) shows part of the exploration process that we performed in UnityMol VR. The exploration of the channel model as a control of our integrative modeling pipeline included an assessment of the overall compactness of the model to identify unphysical gaps, scrutiny of the channel pore to ensure that its opening matched the modeled physiological state, and examination of the transmembrane portion and orientation of the hydrophobic exposure. In terms of scale and complexity, the RyR use case limits the creation of complex models and includes a digital twin of all experimental data collected to support the creation process. Combined with VR, a digital twin provides an exquisite environment

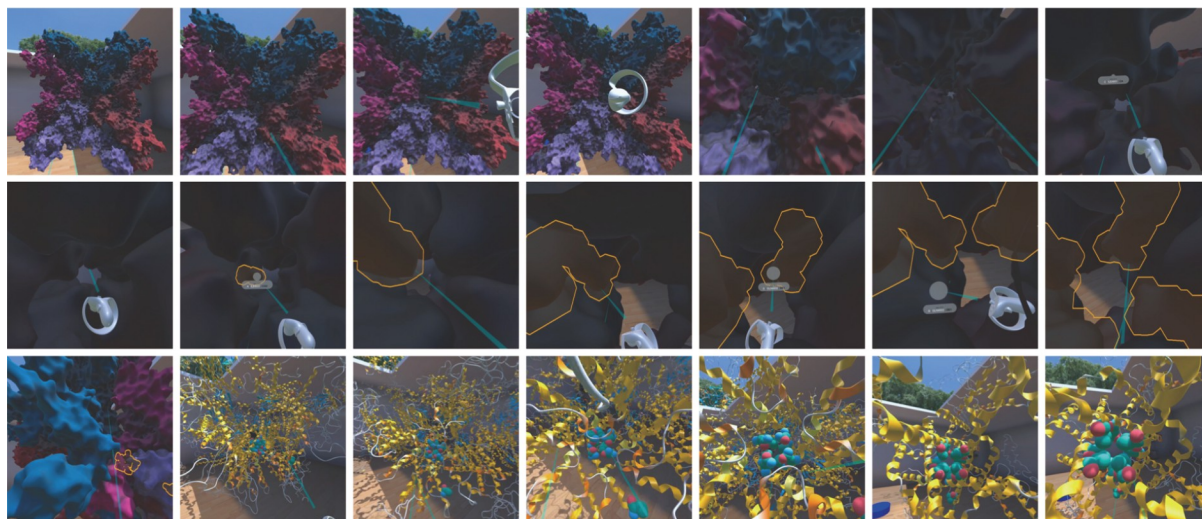


Figure 5 Row of screenshots for visual exploration of an integrative model of the RyR ion channel. The top row shows the full model, followed by a camera pan to look at the central part of the channel and focus on the constriction of this ion channel. The second row shows how the main amino acid residues of the channel constriction are selected. Then the display changes and the last row shows an examination of these key residues of the constriction in the context of the overall structure and in particular, the transmembrane components. This content is available as Supplementary Movie 2.

to explore such a model in detail.

The limits for integrative model-building approaches, as described here, are related to the requirement of interactivity, which is not an issue for simple tasks as described initially, but starts to become more critical when complex models such as RyR are built. These aspects are discussed in more detail in a recent case study^[48].

3.2 I3 rational design: interactive, immersive, intuitive

The modeling described in the previous section was the first step in designing functional molecular constructs that serve real-world purposes, such as drugs for medical treatment^[49], adhesives for gluing objects together, or, as we will see here, compounds for filtering and purifying water. In the design process, digital twin models enabled the prediction and optimization of molecular properties that could then be matched with experimental data. Thus, rational design involved feedback between the model development phase and experimental control measurements. Experimental observations were used in a feedback loop to validate the design, measure its performance, and highlight areas where further improvements were needed. The novelty of combining digital twins and VR in this process was that it became more interactive, immersive, and intuitive, which is why we propose to call it “I3 rational design”. We provide a concrete example that illustrates the process and fits into a general rational design context related to developing better technologies for drinking water.

In biology, water is transported through cell membranes via natural channels and pores. Artificial biomimetic water channels could improve our understanding of the natural functions of these protein channels and provide new strategies for developing highly selective, advanced water purification systems^[50,51]. Inspired by the selective components of natural protein channels and the identification of building blocks for highly selective cross-membrane water transport architectures, fully synthetic biomimetic channels have been developed^[52]. These retain the high conductance activity of natural macromolecules but have a simpler chemical structure. These simplified systems provide an opportunity to understand the mechanistic and structural behavior, and form the basis for developing better artificial water channels. In the example described below, we focus on digital twins as a tool to complement experiments to understand the properties of such systems, with the goal of extracting key concepts and developing and optimizing better compounds. Molecular dynamics simulations combined with VR in a digital twin setup of a membrane-embedded experimental system provide immersive, collaborative insight into the complex mechanisms underlying the function of

artificial water channels.

In collaboration with the experimental teams, we investigated a large number of potential constructs with different chemical scaffolds. We performed I3 rational design with three different setups, comparing a 2D desktop environment, VR headsets for truly immersive and deep exploration of artificial water channels, and a large-scale, high-resolution display wall. We focus here on the VR approach because it immerses the user in the molecular world to perform design work in the most natural and intuitive manner. In comparison, the display wall is better suited for collaborative visual analysis of a complex 3D scene and possibly, for the validation of a final design. In terms of visualizing water channels, the third dimension showed immediate benefits by providing the scientist with a greater depth of field, making it easier to identify the individual channels and highlight the water molecules within a given pore. In particular, when using a surface representation of channels and pores, 3D visualization offers a great advantage by improving the perception of irregularities and cracks. By dividing the channels (arbitrarily and geometrically) in half and representing them as surfaces with different attributes, for example, in terms of color or transparency, visualization is enhanced and identification of differences in stabilization and permeation on each “side” is facilitated, as shown in [Figure 6](#). The VR headset provides the ability to move within the molecule, precisely control and change the viewing angle, and tune it into a specific channel of interest. The visual experience is greatly enhanced and requires less preparation for efficiency when moving from a desktop to a 3D display wall in the VR headset context.

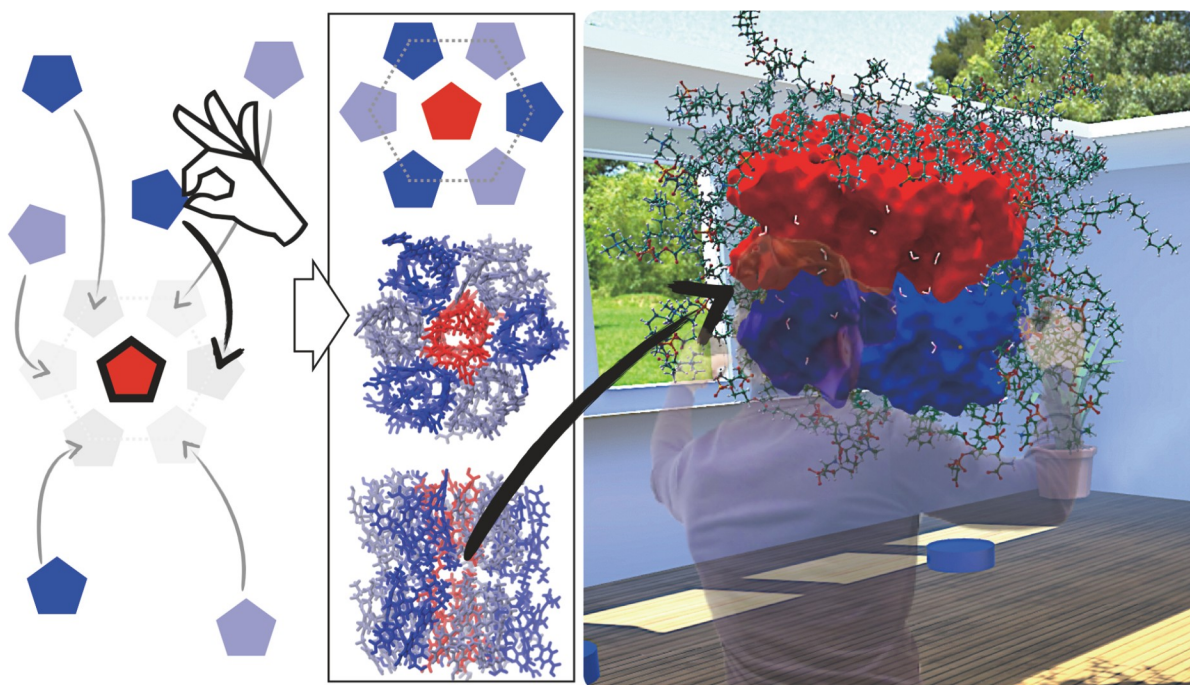


Figure 6 Interactive design of artificial water channels in a membrane environment. The left panel schematically summarizes how to arrange the channel connections in a hexagonal shape around a central channel (red). The resulting model is shown in the middle panel. This model is inserted into a membrane environment and equilibrated. It can then be verified in virtual reality, as shown in the right panel.

A typical design process involves the chemical synthesis of a new set of compounds that may be of interest. Chemical topology is available to construct a model and it is not uncommon to determine the actual 3D structure of a compound in a crystal environment. In modeling, we examined how the compound behaved in a membrane environment and whether it created passageways through the membrane to allow water transport. From these simulations, the water permeation rate could be calculated and matched with the experimental

results. By doing this for a range of compounds and confirming that the same trends were observed as in the experiments, the model was initially validated. In addition, properties such as ion impermeability can be used to further discriminate and confirm the agreement between the digital twin and experimental reality. We attempted to find more direct ways to compare simulations and experiments, but determining the arrangement within the membrane remained a very difficult task for such compounds. Because we do not know how the compound aggregates in the membrane, a recurring problem is to construct a hypothetical aggregate that serves as a starting point for the simulations and observe its stability and agreement with permeation properties. In this context, the digital twin was very helpful.

In the case presented here, we constructed an initial assembly that consisted of two compounds joined head-to-tail in the membrane because they formed a suitable passage in their interior, shielded by the surroundings. However, this aggregate was unstable and we therefore had to improve our design. The hypothesis was that a single pair of compounds in a membrane environment was too fragile because the ratio of lipid-exposed surface area to interaction within the aggregate was unfavorable. Therefore, we attempted to construct larger aggregates in this study. By analyzing the shape and size of the compound, we hypothesized that placing a second layer of compound pairs in a hexagonal shape around the first layer might lead to a better design. As shown in [Figure 6](#), we constructed such an aggregate in VR by placing additional pairs one by one in contact with the first, intuitively optimizing the complementarity of shapes until the entire aggregate was constructed. The aggregate was then placed in a membrane, refined using molecular simulations, and visually inspected. The aggregate proved to be a valid starting point and was injected into the design cycle to examine this compound series further.

We found that the digital VR twin made the design process more efficient than using a desktop environment where there are many more steric clashes that are intuitively avoided in the immersive context because they catch the eye more naturally. Our goal was to make more steps of the process interactive. For example, once the model is created, it needs to be inserted into a membrane environment and the entire system needs to be relaxed so that the lipid–compound interface can optimize its interaction. This step is currently performed offline and only the results are fed back into the digital VR twin. This separation of duties is an important limitation of the current methodology. The next generation of rational I3 design tools should incorporate these modeling aspects into the VR context. The timeframe for some of these steps may be longer than that for a typical interactive manipulation, which presents another challenge.

3.3 From twins to triplets: digital, physical, and tangible siblings using smart hardware

Here, we want to connect virtual drug screening, for which there are digital twins, with a tangible “sibling” in the real world. The goal is to simplify the screening process in which millions of molecules can be considered. To achieve this, a pharmacophore model is needed to assess a large database of molecules. One approach is to use a 3D pharmacophore that is a 3D representation of molecular properties. Pharmacophores can either be ligand-based—derived from a set of known ligands, or structure-based—derived from the information of the target. With an interactive 3D pharmacophore design, the user can take advantage of virtual screening without ignoring the interaction of the drug candidate with its environment. The analysis of the drug’s environment near its target has been shown to be important^[49]. From this point of view, a suitable digital twin allows the combination of the potential of virtual screening without compromising the possibility of using human expert knowledge about the interaction between known ligands and a target. As part of the PIRATE (“Pharmacophore Interactif grace a la Realite AugmenTeE”) project, we are attempting to use a mixed-reality 3D pharmacophore for this process, and we present here some preliminary ideas and prototypes. Combining augmented and virtual reality with tangible artifacts allows an expert to make the 3D pharmacophore interactive, and benefits from the potential of 3D human pattern recognition and novel interaction technology. The underlying concept

is to benefit from human intelligence that is more effective than computer algorithms for certain tasks^[47,53]. The digital triplet described herein is essentially a synergistic collaboration between humans and machines.

A drug discovery tool based on the use of physical molecular models as tangible molecular interfaces^[54] provides an interactive continuum between efficient and intuitive physical manipulation by the user and virtual chemical modeling and simulation using a digital twin. Such a platform would allow users to build molecules using a modular physical model, similar to Lego building blocks. Their virtual counterparts are then constructed using image processing and IoT technologies^[4]. Applied to drug discovery, each user-created physical model could be easily integrated into an interactive molecular simulation of a larger biomolecular environment, with its properties (e.g., favorable and unfavorable interactions with each potential target) calculated and displayed. Based on a representative molecule, the user constructs a real-world representation using physical ball-and-stick models. This molecule forms the framework for the pharmacophore. Our current prototype is designed for amino acids and will be versatile by automatically creating computer-aided design (CAD) files. The tangible interface allows the user to interactively add or remove pharmacophore elements and change their relative positions to optimize favorable interactions. The developed smart devices scan the physical molecular model and bring it back into the virtual world to link it to its digital twin.

A key concept of this framework is the construction of an editable molecule with a tangible interface, the current prototype of which is shown in [Figure 7](#). Based on smart devices, the user constructs a prototype molecule with physical sphere and rod representations. This molecule forms the framework for the pharmacophore. The entire interactive process is driven by underlying molecular simulations, considering the user's interactive manipulation of the physical pharmacophore. The tangible physical twin adds another dimension to classical digital twins. The use of tangible physical models to build and control virtual models in a 3D scene, supported by a virtual screening and molecular modeling approach, can therefore be described as a digital, physical, and tangible triplet. This approach represents a special case because a real molecular object is elusive at the nanoscale. As an alternative to VR representation and to make it more realistic, tangible artifacts provide

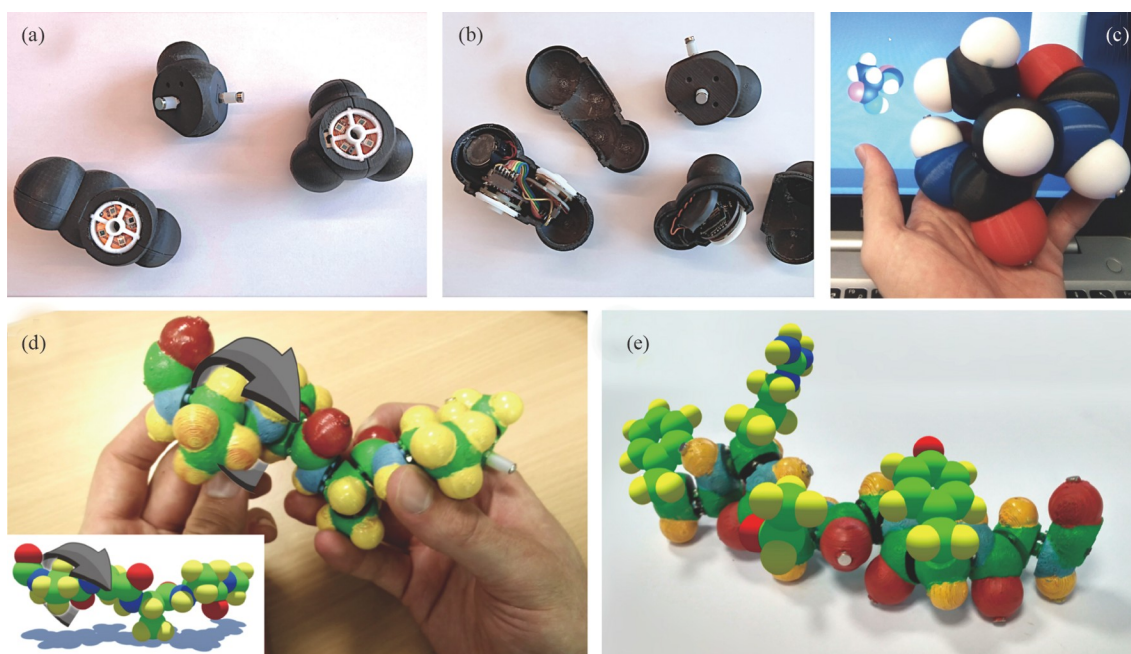


Figure 7 Various aspects of the tangible model are presented. Panel (a) shows 3D-printed elements and the connections used to assemble them. Panel (b) shows the electronics, particularly the power supply. Panel (c) shows the tangible model in the foreground and the reconstruction of the virtual digital twin on the computer screen in the background. Panel (d) shows a typical manipulation — a rotation of a part of the composite model. Panel (e) shows a tangible model of a basic framework extended with virtual side chains. Images courtesy of Xavier Martinez, Nicolas Férey, and Bastien Vincke. A demo video is available as Supplementary Movie 3.

a more accessible molecular input interface because there is no need to wear a VR headset or learn a specific controller functionality to use it.

The flexible and modular physical model of the ligand embeds sensors for model building. We first demonstrated the feasibility of the approach using embedded Hall effect sensors to measure the ϕ and ψ angle series of a flexible physical model of a peptide chain in a tangible interface prototype. We then focused our design on a generic physical IoT module that included rotational and optical sensors with wireless networking capabilities and 4h of autonomy for each component of the physical model to be used as a tangible molecular interface owing to the connected embedded sensors. Using a software tool, we provided CAD files for each component of any ligand from an input file describing the ligand and its degrees of freedom. The CAD files were needed to print a part of the physical model and allow generic sensors to be embedded to provide degrees of freedom in terms of the angles between each component that could be used as a tangible molecular interface. Optical sensors allow us to identify components and detect events that occur between them during the manipulation and construction of the physical model. The sensors embedded in the flexible model allow us to obtain all the information required to create a virtual 3D molecular representation of the physical model in real time. This information is transmitted via a special wireless network protocol. The virtual 3D representation of this molecular physical model can then be visualized using UnityMol software. Once a model is created, its numerical counterpart and thus, the pharmacophore, can be varied by modifying the tangible interface.

Limitations arise from the fact that the tangible parts must be produced using a 3D printing process. This requires a certain amount of preparation time before an experiment can be performed, and thus, thorough planning is necessary to avoid disrupting the creative design process. In addition, drug molecules may contain different chemical functionalities that require appropriate design of modular extensions of the basic molecular framework. Other issues are more technical, such as how to power the device efficiently.

4 Discussion and conclusion

Our results provide guidelines for the design of digital twins and triplets equipped with VR. Globally, molecular simulations provide a mature foundation for the creation of digital twin models. Transferring this experience to the virtual dimension is very easy because of the inherent 3D focus of molecular objects. We present UnityMol as an existing software tool for which VR porting has been successful and experiments can now be routinely performed in VR with enhanced digital twin models. Several use cases were presented to demonstrate this, starting with the creation of molecular models and integrative models in particular. An intuitive VR tool could help this thriving field by bringing molecular simulations to scientists from other fields who are not experts in these methods. This also applies to the I3 rational design of molecular devices, such as the artificial water-filtering channels presented in this work. Another direction has been proposed by physically representing twins with tangible 3D-printed devices to create real-world artifacts. This approach is still in its early stages and we have presented important concepts. In summary, static exploration and molecular assembly have been well developed, and only the usability and number of functions need to be improved. Interactive simulations are also quite advanced in their implementation but still have fundamental problems, such as an inherent barrier on the time scale, which we will discuss below. For molecular triplets, we are still in the early stages. For example, some physical limitations on the fabrication and construction of 3D-printed models are yet to be resolved. The difficulty in using batteries to power the sensors is a particular challenge. We are currently considering several possible improvements to the design, including transmitting power remotely, as in wireless inductive charging, or using a powered base station to position molecules in the workspace.

The time scale is an important issue in molecular modeling. Not all simulations can be performed in an

interactive environment because it would take too long to perform the necessary calculations. The interactive VR experiment with a digital twin is limited by the time a human operator is willing (and able) to control the simulation. This is typically from a few minutes up to half an hour. For example, a molecular dynamics simulation computes only a few nanoseconds or perhaps a microsecond of the dynamics of a molecule. Therefore, the magnitude of the forces that the user applies to the simulation to produce a visible effect is usually too large compared with the forces that occur in real biological systems without causing damage. Even when the simulation is run with massive computational resources, this limitation is severe. A classic solution is to create a simplified system in which the degrees of freedom that are deemed unnecessary are removed. This model simplification—also called coarse-graining—can be achieved by using implicit solvents and membranes or by coarse-graining the representation of atoms by grouping them into larger grains. Such simplification saves significant computational resources and improves operational efficiency. Natural constraints arise from the fact that simulation results must be accurate enough for the relevant application. This requires the identification of degrees of freedom that do not affect the desired property and can be neglected. Another possibility is to perform interactive manipulation with unrealistic forces and then couple it with a longer noninteractive follow-up simulation that allows the use of gentler forces. Such a procedure can be viewed as informed planning and optimization of the simulation process. We experimented with this in the context of the outer membrane protein FepA, where we sought a passage to drive a transport molecule through a narrow inner channel^[55]. Such a passage can be sketched in an interactive simulation, its path recorded, and then replayed in a classical controlled simulation to guide the molecule more smoothly through the system.

An important issue in these experiments is the contribution of the human operator. It has been shown that interactive simulations, such as those discussed for RNA folding in the classroom, also have great potential for research, for example, FoldIt^[56,57]. This project can be viewed as an online 3D puzzle in which players are asked to shake and wiggle the 3D structure of proteins to find the most stable conformations. Such a collaborative puzzle can use the power of the crowd to solve complicated scientific problems; hence, the approach is called “crowdsourcing”. The project has produced remarkable results from a biological perspective, but has also been useful for the collaborative development of new algorithms^[58,59]. The problem addressed by FoldIt is similarly complex, that is, NP complete^[60], as in the drug design example we presented. Similar to our classroom example, the analysis of the tasks performed by the participants showed that the players took a different path from that taken by the computer. The analysis showed that there was no equivalent algorithm for player behavior. This is one of the main reasons for implementing I3 rational design approaches that are intuitive, interactive, and immersive, allowing the use of these “human algorithms”. Generally, interactive simulations and citizen science are areas that are rapidly developing and where the number of projects shows significant growth, including in the field of biochemistry^[61]. Digital twins can eventually be placed in the hands of fellow citizens to provide deeper insights into many processes, whether in nature or in industry.

The concept of using augmented and virtual elements to connect the physical “real” world with the invisible and opaque nanoworld promises highly intuitive interfaces. This is achieved by creating digital, physical, and tangible triplets. This approach is based on intelligent hardware that creates a conduit between the digital model and real tactile manipulation. It borrows heavily from the concept of data physicalization^[62] and extends it to perform live simulations. The current prototype establishes a one-way connection between the physical object and digital domain. In the future, it would be useful to establish feedback communication that connects simulation data to the physical model, possibly in the form of vibrations or other tactile feedback.

Two main themes have emerged regarding future directions and development characteristics. First, the collaborative aspects should be refined so that multiuser scenarios can be implemented in which complex tasks can be completed using digital twins. One particular application area mentioned earlier is integrative mod-

eling, as a number of conditions must frequently be met simultaneously to create a valid model, which may require simultaneous, collaborative control by multiple users. Second, technologies used for interaction and feedback, such as haptics in immersive environments, should be developed beyond the currently supported device capabilities. They do not presently allow the user to “feel” the properties of the molecular materials of the digital twin with sufficient depth, although the mechanical properties are of great importance.

In conclusion, the molecular domain offers tremendous opportunities for digital twins in VR environments if most of the technical and technological hurdles could be overcome. Once the onboarding of VR is simplified and the technology is widely adopted, this approach should find a much wider range of applications.

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Declaration of competing interest

We declare that we have no conflict of interest.

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