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Development of a virtual reality platform for effective communication of structural data in drug discovery

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ABSTRACT

In drug discovery, structural knowledge of a target enables structure-based design approaches and thereby reduces the time and labor required to develop a therapy. Whilst molecular graphics frameworks coupled with computational analysis are now ubiquitous tools for the structural and computational biologist, sharing the detailed visualization and derived structural information with non-expert users still presents a challenge. Here we describe an intuitive virtual world for viewing, manipulating, and modifying chemical and macromolecular structures in a fully immersive and collaborative 3D environment. By reducing the barriers to viewing and interacting with structural data, structural analysis can be democratized to a general scientist, which in turn fosters novel collaboration, ideas, and findings in structural biology and structure-based drug discovery.

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1. Introduction

For structural biologists and computational modelers, annotating and manipulating structures with conventional two-dimensional molecular graphics software is routine. However, presenting this data in format suitable to share and engage non-expert scientists is challenging. Yet, with over 140 thousand structures in the PDB [1], the use of structures in drug discovery and structure-based design continues to expand. The emergence of cryo-electron microscopy and the accompanying increase in structure complexity as the field rapidly moves toward the cellular realm [2] only compounds these problems.

To illustrate the risks of information loss in structural analysis, take, for example, typical representations of the ATP binding site of a kinase, in this case RIPK2 (PDB ID: 5W5O) [3] shown in Fig. 1. On the left (Fig. 1a) is a clear representation of specific interactions that contribute to the binding of the compound, yet much of the surrounding information and spatial context is lost. Conversely, Fig. 1b captures the full scope of the binding site, but is difficult to interpret. Both of these representations omit the gross morphological view of the binding site, shown in Fig. 1c. Deciding which molecular depiction(s) to use is often left to the discretion of the presenter and consequently can vary in quality and clarity, and therefore, the collaborating medical chemist or biologist may be left in the dark.

In the five decades that macromolecule structure data has been publicly available [1], these representation problems have not been ignored, and various levels of abstraction, from hand drawn electron clouds, to physical models, to highly stylized cartoons have been used to rationalize and communicate the information [4,5]. Prior to the early 90s, sharing structural data was largely a specialized arena involving costly dedicated graphics workstations. This changed in the early 90s with the introduction of computational rendering on commodity hardware in what has been referred to as the "single most important event in the history of digital molecular visualization" (J.A. Perkins on the release of RasMol in 1992) [5]. For the first time, scientists could visualize molecules from multiple perspectives, in different representations (ribbon, ball-and-stick, etc.) with minimal time and effort. Although revolutionary, the advent of open-source computer graphics tools like PyMOL also added a technical barrier to molecular visualization. As opposed to physical models or cartoon drawings, computerized molecular graphics require a high-level technical know-how to visualize and manipulate. The level of familiarity required to quickly and easily manipulate a structure to convey the appropriate molecular information can be a significant deterrent for those outside the field.

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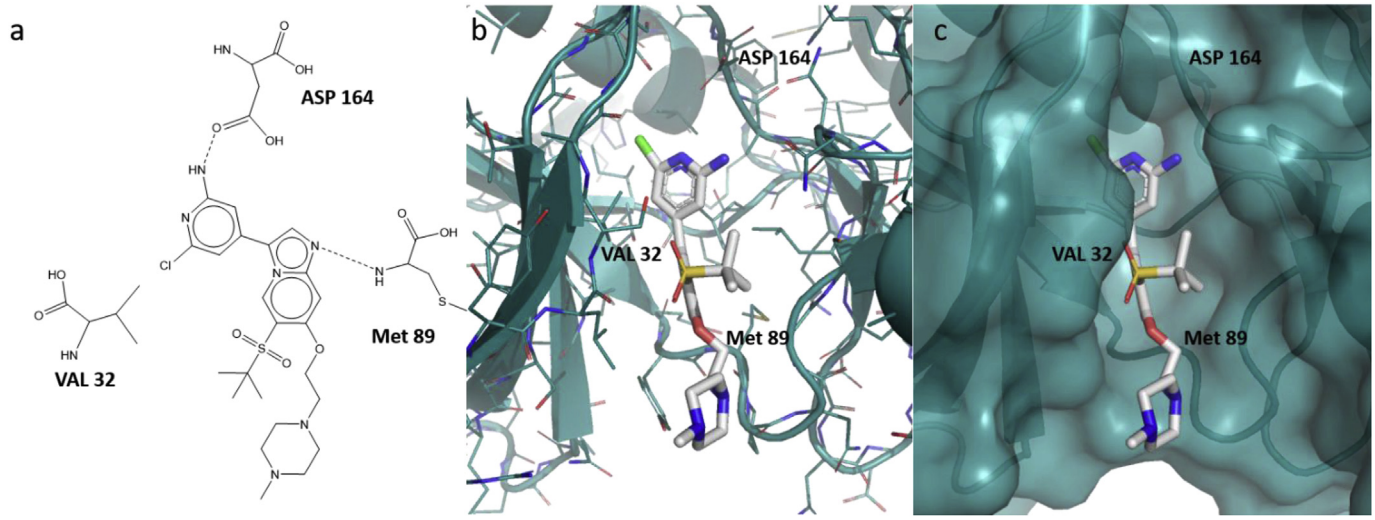


Fig. 1. Alternative depictions of RIPK2 binding site can convey different meanings and information.

The desire to interact with molecules in a way that is intuitive and reflective of their native environment has been clear in the structural community for many years [6–12]. Whilst the resulting technologies, which include CAVE [13] and 3D-displays, extend collaboration capabilities they either, in the case of 3D glasses, do not free the user from the yoke of having an expert system-specific knowledge, or require a very specialized custom-built platform. Although not widely used, 3D viewing with specialized glasses can be implemented to alleviate some loss of spatial information, but still constrains the team to looking in one direction at one view of the molecule (3D non-immersive displays). These barriers have, thus far, prevented the wide adoption of alternative technologies by structural and computational biologists.

In practice, generic presentation methods are typically used for sharing structural data. A common scenario is a single presenter driving the slides or modelling program whilst the other team members participate passively rather than collaboratively. In projecting the 3D coordinates of the molecule onto a two-dimensional screen (e.g. projecting a PyMOL session) or static slide, both of which are herein referred to as 2D-display, much of the structural richness is reduced. In such displays distance and perspective are conveyed by visual effects such as depth cueing (shading), occlusion, and foreshortening, all of which are exemplified in Fig. 1 [14]. In dynamic sessions, these aspects are further enhanced by motion cues that help the user orient themselves [14]. Even with the aide of these visual cues, intuiting distances and angles is still difficult for the majority of viewers which is further exacerbated when information is left out to aide clarity (resecting residues/structures to show a specific point of interest). Despite the loss of information and cumbersome nature inherent to this presentation style, the benefits of having various disciplines such as structural biologists, computer modelers, and medicinal chemists, contribute to the molecular design process are immense, and therefore the practice persists.

The commoditization of Virtual Reality (VR) hardware [15,16], into a relatively low-cost and low-maintenance option for viewing and interacting with structural data offers a solution to these problems. In VR, scientists can physically interact with molecules, in a world that is not restricted by space, allowing users to reach out and touch a molecule as if it were an everyday object, but unlike an everyday object, force fields can be manipulated in the virtual environment effectively bringing atomic level physics to the macroscale. Multiple groups, including ours, have begun experimenting with intuitive on-the-fly molecular and quantum mechanics with VR and have demonstrated improved task completion and positive user experiences in VR for both non-expert and advanced users [17–19]. Others have experimented with interactive modelling with other technologies such as haptic feedback [8] and augmented reality [9].

Which combination of technologies will provide the optimal solution is as yet unknown, but it is clear that the Molecular Graphics field has yet to fully explore the advantages of working collaboratively in a virtual molecular modelling world. Nanome was developed to explore these possibilities with a goal of minimizing the need for technical know-how, and making molecular structure and dynamics more intuitive. This approach should greatly reduce the communication barrier between structural biologists and other disciplines, enhancing idea flow and collaboration within drug-discovery teams. The application is the first collaboration-focused VR platform for visualization, manipulation, simulation, and communication of structural data where all participants in the virtual world can carry an equal weight in the team with the autonomy to individually explore, modify, and manipulate structures in a group setting, without the normal encumbrances of real space (Fig. 2). Developed for use with commodity hardware and incorporating highly efficient, GPU-enabled algorithms for VR applications, Nanome is capable of hosting more than 10 scientists in a virtual molecular world. This work describes the software development, benchmarking, and a sample use case highlighting the utility of this technology in drug-discovery.

2. Methods

2.1. Development process

Nanome was developed by taking advantage of the expertise of two groups of people with orthogonal skill sets; a set of drug discovery experts with varying degrees of knowledge in medicinal chemistry, structural biology, and computational chemistry and a set of programmers with molecular graphics and VR experience. This arrangement allowed a rapid biweekly development cycle where the interaction of scientists within the application were observed by the programming team in real time, allowing key features to be identified by both teams that enhanced interaction

with molecules and communication with collaborators.

2.2. Program

Nanome was built using the Unity 2017.4.3f. game engine and the object-oriented programming language, C# using libraries provided by C#'s.Net framework. Unity's deployment of Nanome is compatible with Windows PCs and provides all of the hardware and physics simulation for the program. The program interface Code management was done using the Agile Scrum project management model on a 2-week cycle. Following implementation of new features, users were provided 2 weeks to test and review before a follow-up meeting with the developers, during which time, developers implemented changes from the prior weeks' cycle. Oculus guidelines and best practices regarding programming were followed to minimize potential motion-sickness and general unease that can be associated with VR.

2.3. Hardware and technical specifications

The Nanome software is compatible with the Oculus Rift, HTC VIVE, and Microsoft Mixed Reality hardware. The work presented here uses the Oculus® Rift [15] in conjunction with Microsoft Windows® 10 Professional operating system. The system includes a headset, left and right-hand controllers, as well as two mountable sensors that detect movement of the headset and controllers. The headset is equipped with speakers and microphone.

A GPU is required to run the headset, with a graphics power equivalent to the NVIDIA GTX 1060 (minimum) or NVIDIA GTX 1080 (recommended). In our VR lab, we have four customized workstations, allowing up to four participants to join a given session from within the physical lab. The workstations are Dell T5810 Precision computers each containing a NVIDIA Titan X GPU with 3584 CUDA cores and 12 GB GDDR5X RAM. Computers are equipped with an Intel Xeon 8 core CPU, 32 GB RAM, 512 GB SSD, a picture of our VR workstations is included in the supplementary information (Supplemental Fig. S1). One notable feature of these workstations is that they are mounted on rolling platforms making them fully portable. They can easily be brought to meeting rooms for convenient transition between VR and projection media.

Multi-user collaboration requires Microsoft Windows Server® version 2012 R2 or higher running as a virtual appliance, which can be hosted either on premise or remotely (e.g. through Amazon AWS). The server software is equipped to adequately host 20 participants.

The software is ready to run out of the box and does not require installation of any additional software programs or features, with the exception of the software needed by the VR hardware, Oculus® software in our case.

3. Results and discussion

3.1. Performance and benchmarking

Nanome was benchmarked on two main features, environment and collaboration capabilities.

3.2. Environment

We compared loading times, surface rendering, and memory usage in Nanome to four widely used freely-available molecular visualization software packages; PyMOL, Discovery Studio, and Chimera, all of which are traditional 2D software, and also to Chimera X, a VR-capable molecular visualizer (Fig. 3). All tests were performed on an Intel Core i5-7400 CPU @ 3.00 GHz, 8.0 GB RAM, with an NVIDIA GTX 1060 3 GB DDR5 VRAM 1152 CUDA cores 1506 MHz GPU. The scripts for all benchmarking tests are available in the Supplemental Information. Regrettably we were unable to test against more VR-enabled packages due to availability and/or lack of appropriate hardware, however, we compared available information of these packages (Supplemental Table 1).

The pdb load times in Nanome are slightly slower, but overall

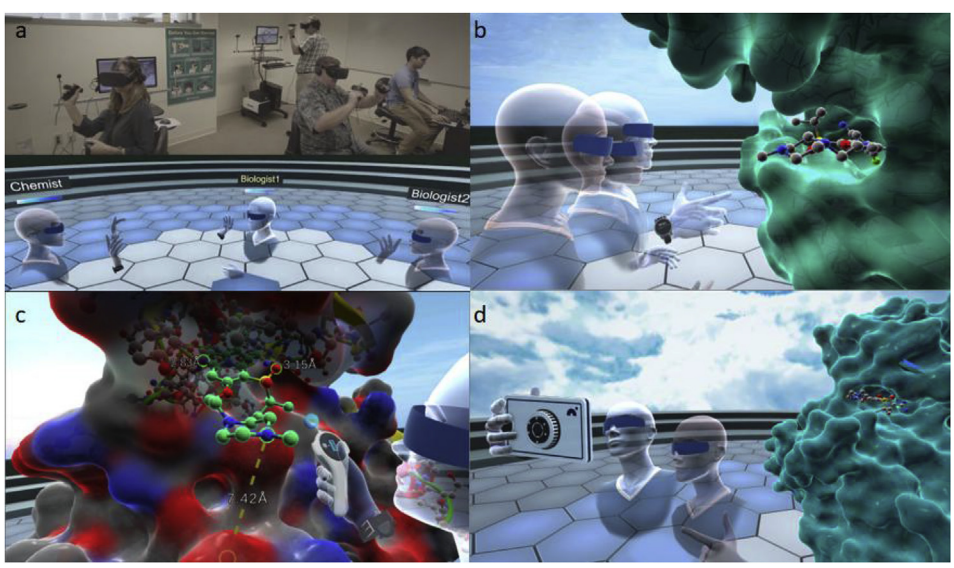


Fig. 2. Nanome environment and VR lab setup. a) The top panel shows the VR physical lab with three participants interacting in the virtual room. The VR Chemist on the far left corresponds to the person sitting at the front, center of the physical room waving both hands, VR Biologist 1 is on the far left and VR Biologist 2 is standing in the back of the physical VR lab. b) Collaboration in VR allows multiple users to occupy the same space and therefore share the same view of the protein or binding pocket. c) Demonstration of the measure tool in Nanome. The user has a small virtual controller that is used to select points to measure between, either protein atoms or a point in space. Measurements are displayed in Angstroms as dotted lines connecting the two selected points d) Camera feature can be used to take pictures of macromolecules or compounds that have been edited (or take selfies). "Photos" are stored as jpegs on the local machine from which the photo was captured. A sample video showing the environment is available in the supplementary information.

comparable to 2D-platforms (Fig. 2a). This is noteworthy given the added level of complexity in 3D-rendering; VR demands rendering at or above 90 frames per second [20] in addition to two "draw" cycles, one per eye, at 1080x1200 pixels each. The cost of two draw cycles is slightly reduced in Unity by traversing the scene only once before rendering, known as single pass stereo rendering [21]. Computing bond information is done using the fast bond generation mode in OpenBabel [22]. These computations were performed on an outside thread (not within Unity) and is one of the largest bottlenecks in structure loading. Load times are greatly improved by loading files in sdf format, a format that contains bond information and therefore avoids on-the-fly bond calculation. Notably, the VR-enabled Chimera X by default loads atoms in van der Waals representation as opposed to including bonding information, this could account for the faster load speeds observed in Chimera X for larger structures.

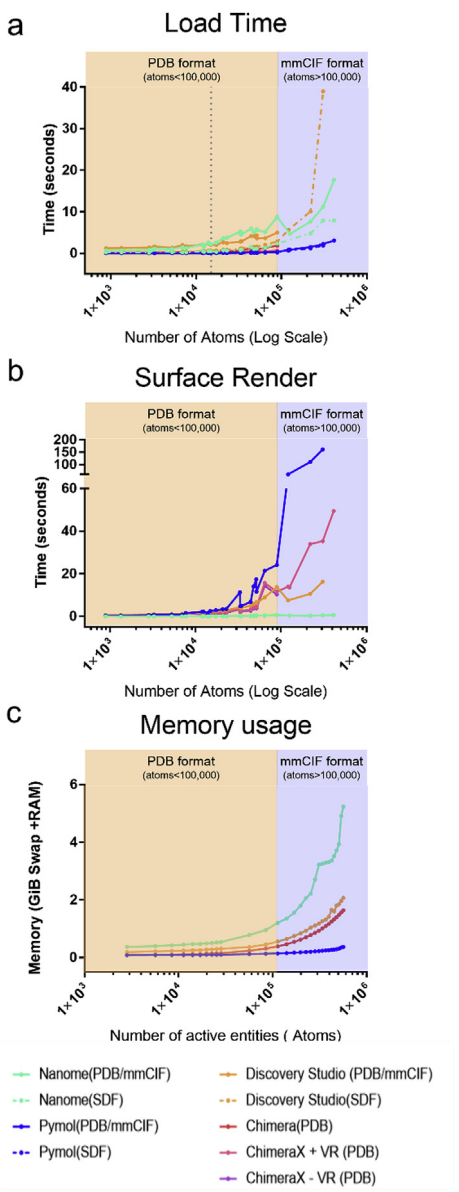


Fig. 3. Load and Render Benchmarking. Nanome 0.8 was compared to four other molecular visualization/modelling softwares; Chimera 1.13.1, PyMOL 2.2.0.0, and Chimera X 0.7, and Discovery Studio 2017 R2 64-bit. Of these, Chimera X and Nanome are VR visualizers and PyMOL, Discovery Studio and Chimera are 2D visualizers.

Surface rendering in Nanome outperforms all other suites tested by several fold (Fig. 3B). The Nanome surface model (Fig. 2b–d) has expected feature list including, transparency, coloring, and cropping (Supplementary Video 1). The surface rendering algorithm in Nanome is based on the rolling method but has been designed specifically for the GPU architecture. Additionally, by default, Nanome calculates the merged surface which is computationally more demanding, as opposed to calculating and displaying surfaces for each individual chain. The details of this algorithm are elaborated in the Supplementary Information.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.jmgm.2019.03.010.

Consistent with the load times, the memory usage is higher in Nanome than in the other software tested (Fig. 3c). As mentioned above this is in part due to the higher computational demand of 3D rendering in VR versus 2D. An additional contributor to higher memory usage in Nanome is the expanded file format required for networking within the program. While the RAM usage would be considered high for a low-mid level consumer grade machine, the minimum RAM requirement, 8.0 GB, for Oculus Rift and most VR-capable workstations easily accommodate higher RAM required for Nanome and other VR applications.

3.3. User capacity

The server software is equipped to host 20 avatar participants. In practice, however, we have found diminishing returns after 6 participants when each user is actively discussing and manipulating the structure. Because there is limited data and availability of VR molecular visualization/manipulation programs that allow multiple, multi-site users, we used Skype (version 12.1815.210.0) with screen share showing Chimera X as our primary comparison metric (Fig. 4a). The Task Manager Process tab was used to monitor the network usage of each program. Nanome is much less taxing on the bandwidth than Skype (Fig. 4a), furthermore the latency is minimal as additional users join (Fig. 4b).

3.4. Program features

3.4.1. Virtual space and navigation

Upon opening the Nanome software, the user is represented as a human avatar with visible hands and head (Fig. 2a). The meeting space is an "open-air" room that has a tiled hexagonal floor (Fig. 2). In the center of the floor is a large blue tile that represents the center of the space (Fig. 2a). Around this tile, are light grey hexagonal tile that indicate areas where users can move to within the space. Users can teleport around the space to different tiles to view the protein/structure from different angles or can share the same tile and interact and collaborate with the structure from the same point of view and occupying the same volume, as shown in Fig. 2b.

Users interact with the environment via a controller in each hand. Each controller is equipped with two triggers, one under the index finger and one under the middle finger, a joystick, and 3 buttons (A, B, and "Oculus"). Each avatar has indicator lasers emanating from each hand visible only to that user. These lasers, in combination with the index finger triggers are used to select various items. For instance, to teleport from one tile to another, users point their laser at the desired location and move via index finger trigger. The teleportation design is such that the user does not experience any simulated rotational or acceleration motion which can be responsible for motion sickness in VR simulations [23].

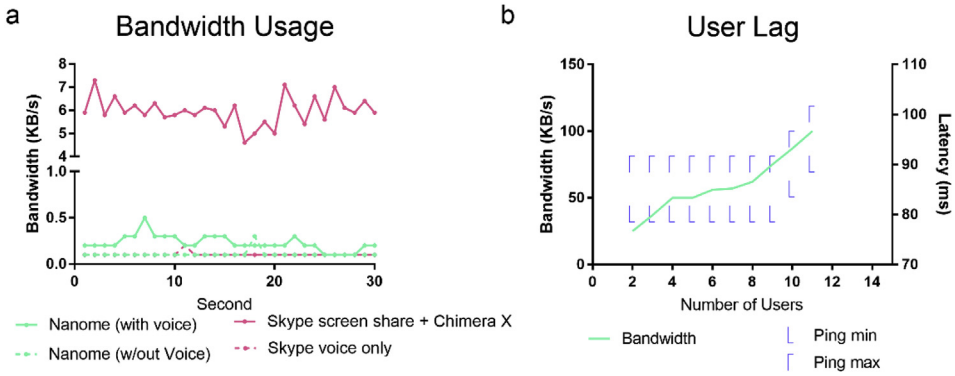


Fig. 4. Collaboration capabilities and resource usage of Nanome compared with Skype.

3.5. Molecular visualization and manipulation

Structures can be imported into the meeting room from the RCSB database, DrugBank, PubChem, or a local database or folder in pdb, mmcif or sdf format. The import panel is automatically opened upon entering the room. The Oculus Rift controllers and Nanome software allow users to intuitively manipulate imported objects as they would objects in real life. Grabbing molecules with one or two hands allows users to rotate/translate and scale molecules, respectively. Beyond moving and scaling the objects, more detailed manipulations are available in the Nanome virtual menus (Box 1). Additionally, the software has Alexa based voice-recognition capabilities, allowing users to issue simple voice commands, such as "Ok Nanome Hide Surface" in place of multiple controller clicks for many features.

The program two main sets of menus; the Molecular Menu which controls the manipulations of loaded molecules and resembles a tablet computer and the Settings Menu which is located on the user's left wrist and controls programmatic settings (Shown in Box 1).

The Molecular Menu can be opened by flicking the left controller inward, as if quickly turning a door knob. From this menu the user can import, select, and modify molecules or parts of molecules using typical molecular viewing options found in most molecular modelling software. A ribbon model, surface view, and full atomistic (both ball-and-stick and stick) representations are available. This menu also displays the molecular sequence allowing the user to display/hide various portions of the molecule or color selections by a given color or scheme (atomic displacement factor, residue, etc.). Molecules can be displayed either individually or together and can be locked such that they can be moved about the scene while their respective locations remain fixed. The user also has the option to split, duplicate, or merge molecular chains. This menu also has a submenu containing tools for making measurements, molecular editing, and minimization (further information available in the Supplemental Information).

The Settings Menu, is always visible on the left wrist and controls various program settings such as the microphone, headset volume, and background music (Box 1: Settings Menu). It also indicates whether the user is in presenter mode (capable of structure manipulation) or in viewer mode (not capable of structure manipulation). This panel also contains a button to teleport all users to the same spot. In addition, this menu allows a user to leave the VR meeting space.

3.6. Virtual collaboration

One of the key features of the Nanome software is the ability to easily communicate and collaborate with fellow scientists, either locally or globally. The platform allows for users to connect to a centralized server from any location and join together in the virtual meeting room in one of three modes, virtual participant, 2D-viewer, or ghost mode. Users may join or exit the meeting room at will, in any mode without disrupting the ongoing session.

In participant mode, the user is visible and audible as a human avatar (Fig. 2) and has full access to menu panels, molecular manipulation and program controls. At a given time one user is designated as the "presenter" and he or she control manipulations of the loaded structures, however other users may still move about the space autonomously and explore structures freely. Avatars may also occupy the same space effectively allowing the same view to be experienced by two participants (Fig. 2b), a feature not available in real-life. In addition, the presenter can teleport all other avatars to his or her location allowing all participants to share the same virtual space and as a result, the same view (Fig. 2b). We have found this to be a very helpful feature for in-depth discussions. The "presenter" designation can be quickly handed off to other participants via a button on the avatar's wrist. Both microphone and headphone capabilities are built into the Oculus, enabling seamless communication and interaction for participants that are not in the same physical location. In our hands, this has been the most used mode of the Nanome setup.

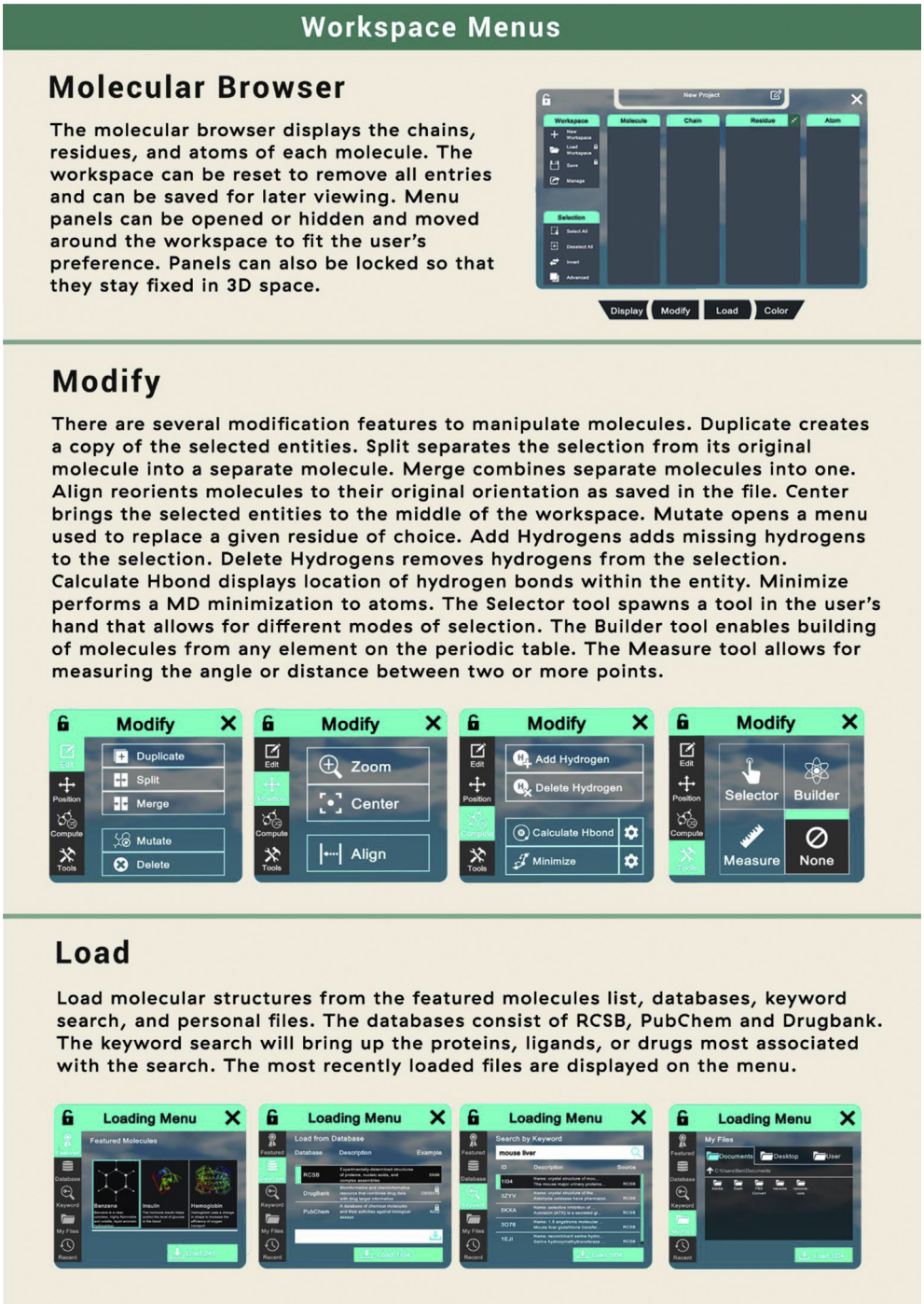
In viewer mode, the user is represented as a video camera visible to other participants. In this mode, the user can view the entire scene, move about the space freely, and hear/speak to other participants, however the user does not have access to molecular manipulation or program controls. Viewer mode is accessed via a keyboard and mouse which enables users that do not have VR hardware to connect and join in on discussions, but also limits the functionality to "viewer only".

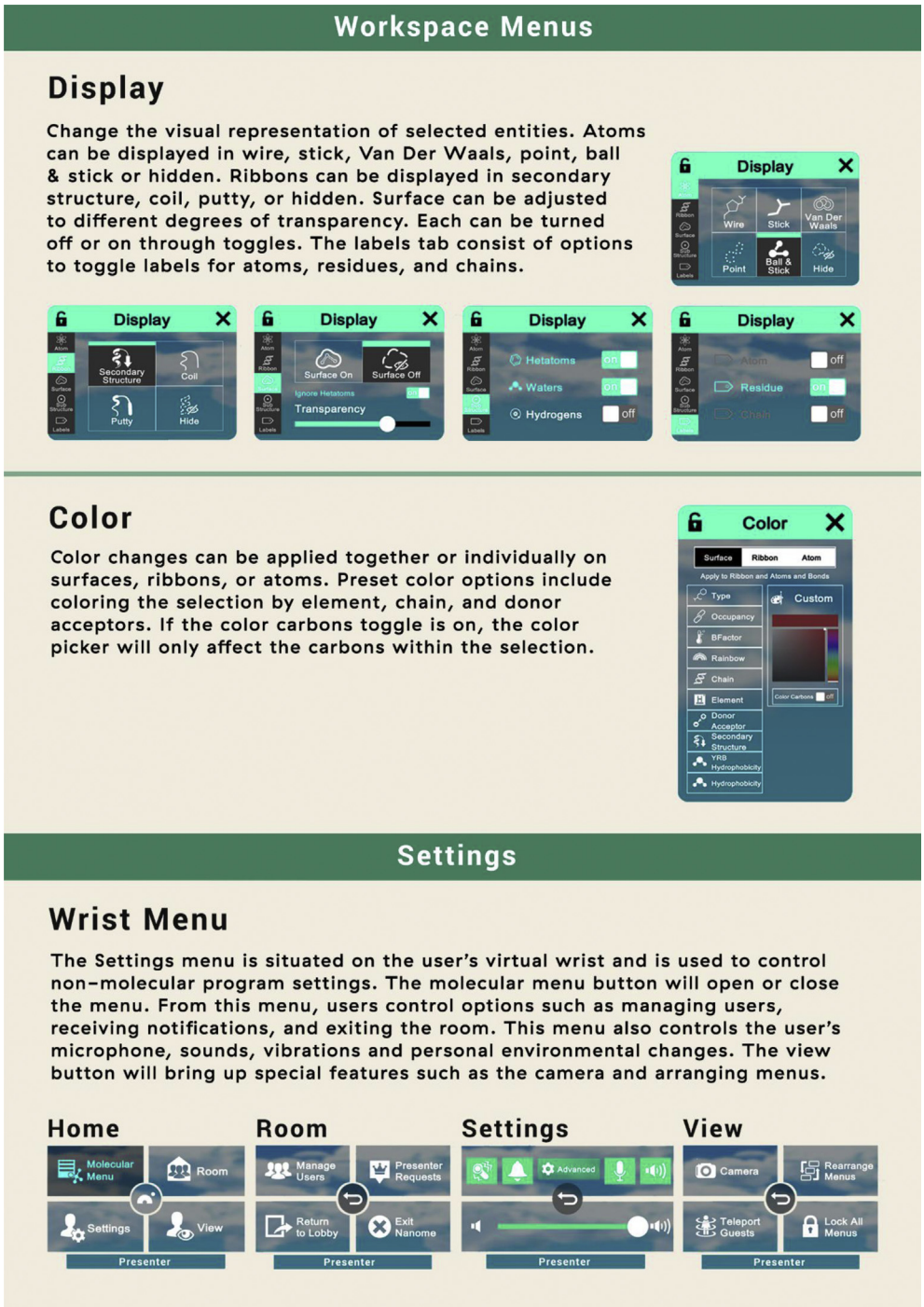
Finally, ghost mode is a passive viewing experience from a fixed position on the presenting avatar. This mode allows a VR session to be streamed to a large audience. In this mode the audience is simply that and cannot communicate with VR participants or manipulate molecules. This feature can be used for large auditorium-style presentations.

3.7. User example: small molecule design

In structure-enabled projects, crystal structures or docked models of the scaffold of interest can inspire design ideas for subsequent compounds in a series. As a proof of concept for small molecule modelling, we rebuilt the RIP2 kinase inhibitor compound in the pocket of 5W5O structure from scratch and achieved an RMSD of 1.8 Å between the modeled compound and the co-crystal compound. As a further test, users were also able to start

Box 1
Tool Menus





(*continued*).

from the crystal structure and model substitutions into pockets adjacent to the pyrazolopyridine group with the idea of picking up additional hydrogen bonds to Asparagine 164 (Fig. 1b and c Supplementary Video One).

Going beyond "proof of concept", in one active, in-house project, the team recognized the potential of designing a macrocyclic version of a given active compound to improve physicochemical properties. In this case, four chemists used the VR suite to explore potential macrocycle options. Within a few minutes, new users were comfortable in the environment and were pointing out potential sites for macrocyclization. Ultimately, the group synthesized a series of macrocycles that retained moderate activity and demonstrated improved PK properties.

4. Conclusions

Enhancing structure-based design is not only a matter of making modelling software more predictive of reality but also allowing the input from various experts to be incorporated in real-time. Nanome achieves this by integrating a 3D virtual reality viewing experience

with molecular interaction and manipulation in a team environment. The collaboration between Nanome and GNF has resulted in software that can be mastered in a matter of minutes, with intuitive controls tailored to the needs of drug discovery scientists from various disciplines and backgrounds, and allows structure-based design collaboration in real-time. Although the application of virtual reality is still in its infancy, it is expanding across various sectors and will play an increasing role in scientific fields where real space access is limited because of scale or complexity. In the biology arena, use-cases for immersive, real-space environments are plentiful and include 3-D cell viewing, mathematical modelling, and imaging. In structural biology, in particular, we anticipate that the use of commodity hardware and intuitive controls within VR environments will increase the spectrum and scope of users and in turn accelerate our understanding and biomolecular modulators.

Further information about the Nanome package can be found here: https://nanome.ai. Nanome is also available via the Oculus store: https://www.oculus.com/experiences/rift/1873145426039242/

At the time of this publication, Nanome is under active development and additional releases are planned.

Conflicts of interest

V.B, S.M., E.L., K.W., and E.D. are employees of Nanome Inc. and as such have a financial interest in the software. L.J.K, G.L., K.M., S.R.F., and G.S. are employees of the Novartis Institute for Biomedical Research and declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmgm.2019.03.010.

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