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A virtual and mixed reality platform for molecular design & drug discovery - Nanome version 1.24

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Abstract

The success of the design and improvement of nanoscale biomolecules like proteins and small molecule drugs relies on a proper understanding of their three-dimensional structures. Nanome's virtual reality/mixed reality (VR/MR) platform provides an immersive and collaborative environment that offers a unique view into the nanoscale world. The platform enables faster and more effective ideation, improved communication of scientific concepts, and multiple tools for lead optimization of molecules. The latest 1.24 version of the Nanome platform integrates multi-user collaboration, mixed reality, enhanced avatars, and a flexible Python API for easy integration with various modeling techniques. We describe key elements of this state-of-the-art framework and how it can accelerate the pace of discovery through empowering industry-standard algorithms across domains of digital science. Nanome is available for download at https://home.nanome.ai/setup.

CCS Concepts

• ***Computing methodologies*** → ***Mixed / augmented reality; Virtual reality;*** • ***Applied computing*** → *Molecular structural biology;* • ***Human-centered computing*** → ***Scientific visualization;*** *Visualization design and evaluation methods;*

1. Introduction

The molecular structure of both endogenous and exogenous bioactive compounds, ranging from small to large molecules, as well as the spatial arrangement of compounds commonly studied in materials science, such as zeolites and Metal-Organic Frameworks (MOFs), is determined by a complex interplay between molecular physicochemical properties and 3D/4D interconnections. For scientists to successfully optimize molecules, it's crucial to have a precise understanding of the structure. This often requires a perspective that can accurately display key features of the molecule and its surface, along with metadata, such as charges, residue IDs, or binding scores.

Within the scientific community, there has been a growing trend toward using Pythonic interfaces for unified user-friendly access to complex code written in C/C++/Fortran. Traditional 2D tools for molecular structure visualization, such as Pymol, can now be easily augmented with open-source resources made available by the research communities to make digital experimentation easier, however, most of these tools are hampered by interface restrictions that make human guidance harder.

Over the past three decades, scientists have increasingly relied on computer graphics to rationalize molecular structures [Fra02]. Historically, the molecular visualization field has been an early adopter of sophisticated lighting and shading techniques such as ray tracing, ambient occlusion, depth-of-field focal blur, motion blur, and translucency [SSS16]. A multitude of molecular graphical approaches have been developed over the years, but despite several applications with rich toolboxes and advanced graphics, mainstream tools are still commonly bound to flat 2D views [CDA22]. Conventional 2D digital interfaces such as computer monitors can only represent molecular structures with a pseudo-3D projection, which leads to a loss of visual information and an obscured perspective as elements overlap in the representation. To compensate, scientists rotate structures to build a mental picture of the true 3D space or gain a visual perspective that allows them to see overlaid metadata; this limits the capacity for interaction and the ability to modify such structures. 2D interfaces such as touchscreen tablets provide a greater degree of co-location for 2D operations [ODD*18], as users directly operate on the interface (i.e., they are not mentally mapping mouse movements onto a screen).

The human mind evolved to understand and operate in 3D space, although lower dimensionality representations (i.e., 2D drawings and 2D screens) can be utilized to convey abstracted molecular information, only 3D representations can fully connect the human experience to the molecular world. Currently only immersive head-mounted displays provide for true 3D representation along with co-located interaction with 3D objects such as molecular structures. Cave systems [CNSD*92] represented one of the first attempts to achieve stereoscopic visualization of molecular structures, leading the way to the exploration of immersive visualization approaches to compare protein structures [MM04], analyze

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binding pockets interactions [FNM*09, KKL*16], docking experiments [AW99, KPL*04], interact with molecular dynamics simulations [AF98, BTM*19, SFMS*21] or NMR [BZC*09] and even interactive analysis of high-throughput screenings [SUS*21].

Over the last seven years, the introduction of affordable commodity Virtual Reality (VR) hardware, such as the HTC Vive and Meta Quest headsets, induced a seminal change in molecular visualization. These headsets offer truly immersive environments that give scientists a complete and natural 3D understanding of nanoscale structures, by allowing them to share a space with biomolecular objects directly. The primary advantages of these head-mounted displays are full 6 degrees of freedom tracking, a high resolution, portability, and, most importantly, the capability for users to interact with digital structures in real-time, either alone or with others.

With fully immersive 3D environments, researchers can experience more accurate digital representations of chemical, biomolecular, and materials structures, without losing any visual data in the process, by placing them in the natural 3D spatial environment needed for interaction with these structures [Ols18]. VR/MR environments allow users to easily manipulate the structures as if they were handling physical objects. Users can also take advantage of the advanced tools embedded into the software for fast experimentation and idea generation. The power of such environments is further enhanced with the utilization of low-latency networking that provides for multiple local or remote researchers to join the same virtual space to observe, collaborate and modify in real-time biomolecular structures. Because of these advantages, common programs for molecular visualization like Chimera X or Coot underwent re-writing into VR-compatible versions [GBS*18, TE21]. Other platforms have been developed from scratch to support VR, such as Nanome [KBL*19], MolecularRift [NGEB15], UnityMol [LaEOE*20], iMD-VR [OBD*19], Peppy [DDG*20] or web applications with VR support like VRmol [XLX*20], ProteinVR [CvR*20] or moleculARweb [CFK*21].

Despite the growing interest in the field of molecular VR/MR, it is still important to acknowledge current limitations associated with the system: hardware accessibility, practicality, and computational power. Headsets have become more affordable, but are still not widespread as 2D monitors. For some individuals, HMDs can feel intrusive to wear, and extended use can rarely cause visual fatigue [FPFVC22, GBS*18, Ols18]. The utility of abstracted chemical representations should also be acknowledged such as in the case of projections into 2D stick drawings where the loss of structural information can be helpful in condensing some aspects of information for easy visual digestion on 2D screens. Such projections start to lose value as molecular structures grow in size and intra/intermolecular interactions necessitate full 3D visualization, such as in the case of proteins and other biologics.

In this paper, we discuss Nanome 1.24 and the advancements in Virtual and Mixed Reality which have enabled Nanome to establish the roots for a scientific metaverse, where complex scientific workflows and innovative visualization techniques can be explored by collaborators with diverse skill sets for research and development purposes in the field of drug discovery and beyond.

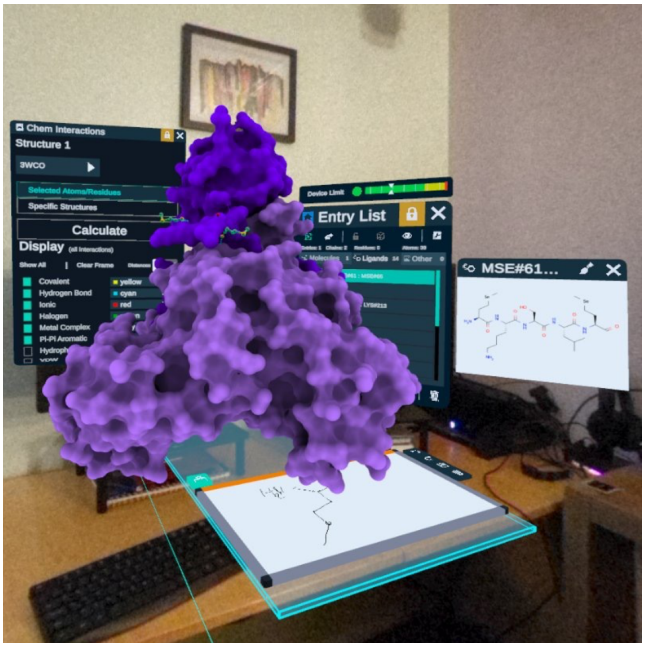

Figure 1: *Mixed Reality. User's view while using mixed reality passthrough mode. The user can see virtual objects, such as protein structures, menus, whiteboards, as well as the physical surroundings. Nanome workspace captured through a Meta Quest Pro headset.*

2. Software Overview

The Nanome platform was developed as a flexible tool to intuitively explore structures, access computational algorithms, and work collaboratively in a molecular virtual environment. Built using the Unity 3D game engine and the object-oriented programming language, C# [KBL*19], Nanome is compatible with several commercial headsets (HTC Vive, Meta Quest, Pico, etc.) and can also run on Windows PCs both as a linked VR application or a 2D interface. The flexible component of Nanome's infrastructure is a Python-based API plugin system, designed to allow the platform to communicate with virtually any scientific algorithm. Several computational tools have already been integrated into the Nanome API server and can securely communicate bi-directionally with active Nanome VR/MR sessions, eliminating the need for scientists to learn C# or a graphical engine like Unity3D to benefit from VR/MR. This API includes examples of several open-source and proprietary tools, made available as "Stacks," which allow for direct scientific experimentation in VR and facilitate rapid ideation and lead improvement. Nanome's API makes traditional applications and algorithms capable of utilizing the improved user control and understanding that naturally emerges from VR/MR technology and can change the user experience of digital science both in individual lab environments and in collaborative sessions.

2.1. Advances in the features and capabilities of Nanome

Over the past five years, the Nanome platform has undergone significant development, enhancing its usability, flexibility, and gen-

Table 1: *List of the major improvements Nanome has undergone from the original version 1.0 (described in [KBL*19]) up to the latest version Nanome 1.24.*

Usability/Flexibility	**Small-molecules**	**Large-molecules**
○ Plugin System & Python integration ○ Whiteboard tool ○ Spatial Recording ○ Nanome Vault ○ In-VR browser (private & shareable) ○ In-VR notepad ○ External software file compatibility (.pse, .mae, .moe) ○ Mixed Reality color passthrough ○ Support for images (.png, .jpg, .jpeg), .pdf and .obj files ○ Meta avatar integration ○ Macros system for commands customization ○ Calendar Invite system ○ Teleportation control, options for skyboxes ○ Image exporting improvements, transparencies, saving locally or sending via email ○ Export molecules modified in Nanome as .pdb, SMILES, .mmcif, .sdf	○ Measure distances, angles and dihedrals. Rotate bonds, build/edit small ligands, chemical groups library, clashes calculations (MedChem tool) ○ Ligand minimization with force field selection (Minimization Plugin) ○ Molecular docking (Smina Docking Plugin) ○ Real-time protein-ligand binding scores (Real-time Atom Scoring Plugin) ○ 2D molecular viewer using RDKit (2D Chemical Preview Plugin) ○ Intermolecular contact/bonding calculations (Chemical Interactions Plugin) ○ Evaluate Lipinski's "Rule of 5" and solubility predictors (Chemical Properties) ○ Conformer generation (Conformers Generator Plugin) ○ Visualization of multi-frame structure metadata in a table/graph (Data Table Plugin) ○ Adding/Removing Hydrogens from structures (Hydrogen Plugin) ○ Multi-model SDF file creation (Merge as Frames Plugin) ○ Load 3D structures from a SMILES strings (SMILES Loader) ○ Support for file types: .mol, .xyz, .mol2, .pqr	○ X-ray and CryoEM Electron Density Map support (.ccp4, .dsn6, .dcd) ○ Conformers and trajectories support (.gro, .trr, .xtc, .psf) ○ Electrostatic Potential Maps generation (Electrostatic Potential Plugin) ○ Improved surface visualization (Solvent Accessible Surfaces, High-Quality Surfaces Plugin) ○ Pairwise protein sequence alignment ○ Protein coloring options (B-factor, Kabat, etc.) ○ Automatic toggling alternative residue conformations ○ Identification of Complementarity-determining region (CDRs) in antibody structures (Antibody Plugin) ○ Protein Chain/Selection superposition (Superimpose Plugin, RMSD Plugin)

eral utility compared to Nanome 1.0 [KBL*19]. Nanome 1.08 introduced the Python API Plugin System, streamlining the integration of popular drug discovery tools like RDKit [RDK], Arpeggio [JHn*17], AutoDock Smina [KBC13], MSMS [SOS96], and Adaptive Poisson-Boltzmann Solver [JES*18]. A comprehensive list is available at https://nanome.ai/stacks.

Additionally improvement in the user experience has been a priority, with features such as the in-VR web browser (section 2.4), Spatial Recordings (section 2.3), Nanome Vault (section 2.3), and compatibility with various file types. For a complete list of updates since 2019, visit https://home.nanome.ai/setup. A summary of major changes up to Nanome 1.24 is presented in Table 1.

2.2. Mixed reality

Recent iterations of VR hardware have coalesced to use "inside-out tracking", often via a number of cameras built into the headset to track the environment and process the relative positions of controllers without the need for wall-mounted infrared transmitters. This approach has allowed VR headsets to be compatible with mixed reality (MR) experiences by utilizing a passthrough mechanism that blends the real and virtual environments by leveraging the embedded cameras. Unlike augmented reality (AR), which superimposes a 3D digital image onto reality [FPFVC22], MR allows the virtual and real environments to coexist, where the user can interact with both the digital and physical elements. Nanome 1.24 introduces passthrough capability for several headsets, including Meta Quest 2, Meta Quest Pro, Varjo XR 3, Vive Focus 3, and Pico Neo 3 headsets, giving users the ability to toggle between VR and MR environments depending on preference and allowing users to manipulate bio-molecular structures as if they were in the room with them. This offers several advantages both in terms of comfort and rooting to real space, allowing for easier communication with colleagues, outside the virtual space as well as the coupling of digital assets to real-world anchors (Figure 1).

The MR implementation in Nanome allows for private or shared sketch boards to be pinned to walls or tables making these real-world surfaces gain a digital function and providing a melding of the digital and real world. Note that although Nanome 1.24 supports MR passthrough on different devices, the user experience can vary depending on the hardware. Specifically, the resolution of built-in cameras and the availability of color passthrough only on specific devices (Quest Pro, Pico Neo 4, and Varjo XR3).

Figure 2: *In-VR web browser. The user has access to a fully functional web browser in VR. Specialized buttons on the browser window open panels that allow the user to navigate through different tabs, save bookmarks, retrieve browsing history, share URLs, launch downloads, and open downloaded files.*

2.3. Collaborative by Design

As science is inherently collaborative, Nanome is designed to provide a digital space where users can work together on molecular designs. Several features have been developed to fulfill this purpose, starting with the possibility of having multi-user sessions with up to 20 participants. The 1.24 version of Nanome enables users to utilize personalizable avatars both in MR and VR, and the built-in face tracking of some headsets makes it possible for users to emote and have a fuller connection to colleagues in multiuser Nanome sessions. Beyond the improved ability for users to represent themselves as they wish, lip and eye tracking aids communication so users can recognize colleagues and observe their facial expressions as they talk.

Nanome 1.24 has the capacity for customized VR/MR workspaces to be saved on local devices or in an online repository called the "Nanome Vault". Users can use this repository to easily upload and download files and access them during a Nanome session or from local devices. The Vault enables users within an organization to effortlessly share and asynchronously work on documents and workspaces. Nanome also has a "Spatial Recording" feature that allows users to record individual and group sessions in Nanome and play them back later while watching with their colleagues whilst in VR/MR. These sessions include spatial positions of users' bodies, molecular representations, and audio. Spatial Recordings can be rewound, paused, fast-forward, as well as stopped for the active manipulation of molecular structures at any point, similar to an immersive and interactive movie. Users can utilize this feature to collaborate asynchronously and develop content for research or education purposes.

2.4. In-VR/MR Web browser

A core feature built into Nanome is the web browser (Figure 2). Each user has a private web browser session that they can share with others in the workspace. Nanome's web browser allows users to navigate websites, view research papers, and easily import files into the workspace. Examples include coordinate files (.pdb, .mmcif, .cif), electron density maps (.ccp4, .dsn6) from the RCSB, the EMDB, and AlphaFoldDB [DITS22] or chemical structures (.sdf, .mol, .xyz) from PubChem and DrugBank databases. This enables scientists to quickly load new targets or candidates for analysis or compare multiple proteins. For users accessing Nanome behind a firewall, such as companies or national laboratories, the web browser also provides for access to internal databases, enabling secure viewing of proprietary structures and associated metadata.

The built-in web browser also serves as an in-VR interface to work on web-based applications, such as MolView [Smi95], SwissADME [DMZ17], or BLAST [JZR*08]. Users' access to web apps ensures continuity during a work session, providing easy access to tools that they would use while working on a traditional 2D

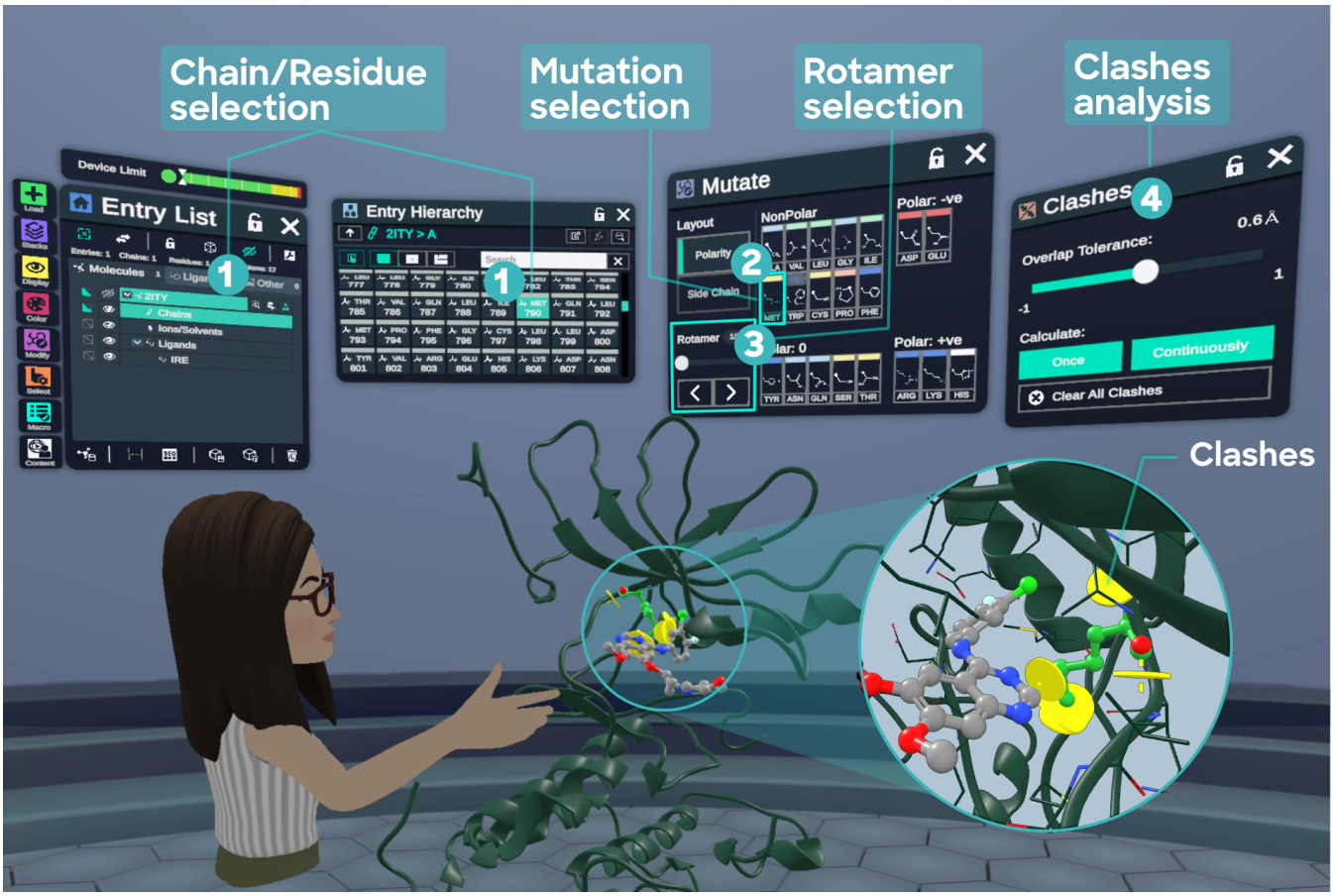

Figure 3: *Amino acid mutations in Nanome. In the example, the user is testing the structural effects of the T790M mutation on EGFR kinase domain structure (PDB 2ITY). The mutated residue is highlighted in bright green. The user (1) selects the protein chain and the residue of interest (T790) from the sequence panel, (2) activates the "Modify" menu from the entry list and chooses the amino acid modification (T to M), (3) scrolls through possible rotamers while (4) getting visual feedback on which ones would create clashes (represented by yellow discs) with the surroundings.*

screen. Finally, similarly to a typical web-browser window, the web browser offers the possibility to save bookmarks, retrieve browsing history, switch between multiple tabs, and share URLs with users in the same work session.

2.5. Mutation and molecular design

Despite the rise of computer-aided drug discovery (CADD) and more recently AI-assisted drug discovery, human evaluation remains an obligatory step in the optimization process and visualization is an essential tool to guide rational structure-based drug design. With these reasons in mind, Nanome has developed several tools for protein and small molecule manipulation and modification.

The selection tool in Nanome allows for the selection of single or multiple residues that can then be instantly mutated to other standard amino acids, and a number of rotamers can be quickly toggled through in order to refine residue side chain orientation. Clash analysis provides real-time visual feedback during protein structure editing (Figure 3). With this toolkit, the user can quickly create structural models that recapitulate specific phenotypes. For example, the user can generate structural models of mutations associated with drug resistance and inspect in VR the structural determinants leading to that effect. A demonstration of a possible design and mutation workflow can be found here: `https://bit.ly/nanome-mutation`.

Building and modifying chemical structures in Nanome is possible through the "MedChem tool", which allows for atomic construction or alteration (Figure 4). The MedChem tool allows for atomic substitution by intersecting the tool's highlighter point with an existing atom, or extension by dragging new connections.

Similarly, tools like the "Torsion" and "Measure" tools help the user to fine-tune molecular edits, enabling bond rotation and the calculation of distances/angles in real-time, both for statical and dynamic molecular structures. Newly generated structures are auto-minimized using a choice of force fields, including General Amber [WWC*04] or MMFF94s [Hal99], allowing for real-time opti-

mization as users iterate through structural modifications. The effects of changes on a molecular design can be assessed instantly by calculating the electrostatic interaction network and clashes surrounding a specific molecule. The combination of these tools is particularly effective when optimizing lead compounds and generating design ideas during collaborative sessions.

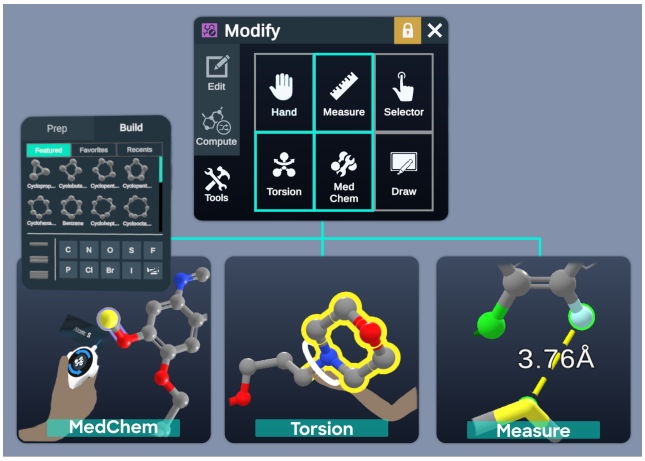

Figure 4: *Modifying chemical structures in Nanome. The Modify Menu (top) enables access to some key tools designed for working with small molecules and ligands in Nanome. The "MedChem tool" (bottom left) opens a secondary panel where the user can choose chemical groups, single atoms, or bonds to substitute/add to a chemical design. In the example, the user is replacing a carbon atom with a sulfur atom. The "Torsion" tool (bottom middle) lets the user rotate chemical bonds visually. It comes with a safety mechanism that signals with the appearance of a white ring whether the bond can be rotated from a chemical standpoint or not. The "Measure" tool (bottom right) enables the user to calculate distances between atoms as well as bond angles.*

2.6. Docking plugin

Nanome's docking stack is a prime example of the algorithmic enhancements achievable with VR/MR applications by leveraging better human decision-making and control. The stack interfaces with Smina docking through a Python API, enabling easy selection of a receptor site, ligand, and docking site, along with adjustment of generated poses and docking site size. The immersive environment users share with proteins makes docking setup as intuitive as touching the desired target location on the protein. This allows for quick iteration through multiple sites, as well as the use of surface rendering to evaluate potential binding pockets and test them (Figure 5).

Scientists are thus less hampered than by a traditional 2D interface's obscured perspective or the forced abstraction of navigating the space and setting the dock parameters using a poorly co-located mouse interface. When combined with the MedChem tool, users can also modify the ligand structure on a promising candidate site while receiving rapid feedback and iterating toward better leads. The real-time atom scoring plugin dynamically scores these structures, offering an intuitive method for generating new structures while measuring the success of iterations and identifying improved candidates.

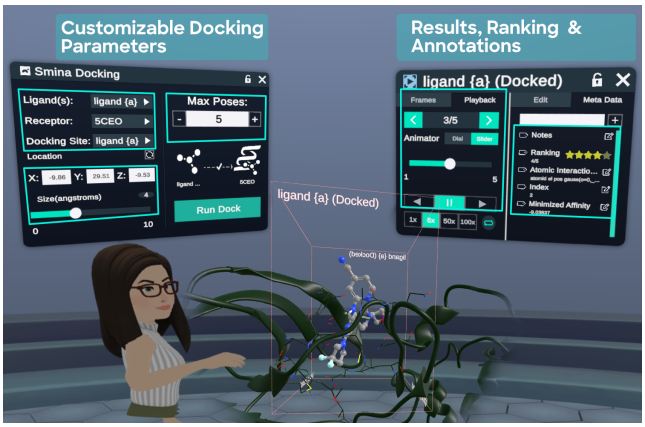

Figure 5: *Docking in VR. The user can run docking calculations in the virtual environment by activating the Smina Docking plugin (left panel), and editing desired parameters including the docking location and radius and the number of iterations. Once the calculations are complete, the docking results menu (right panel) is displayed and the user can circle through the results as well as add notes, rank the results, and visualize the minimization affinity value calculated by Smina.*

3. Applications

In recent years, an increasing number of organizations have paired computational methods with VR/MR to carry out structure-based projects. Over half of the world's top pharmaceutical companies use Nanome for crystal structure analysis, in-silico screening visualization, and small molecule optimization. It has also shown promise in the education landscape, where teachers and professors use the platform to engage in effective collaborations on projects and for lecturing purposes.

Virtual reality assisted the structure-guided rational design of a library of compounds to treat nerve agent poisoning. Scientists used VR in different stages of the design process, from the visual inspection of X-ray structures to the validation and lead optimization of novel chemical entities [GGK*20]. Nanome has also been used to compare different crystal structures of human acetylcholinesterase (AChE) and analyze the results of pairwise computational alignment of ligand-free and ligand-bound macromolecular structures [LBL*21].

In a separate study, compounds obtained from virtual screenings were optimized by scientists inside a virtual reality environment, leading to the design of a completely novel COVID-19 Mpro inhibitor [KLG*21]. Built-in tools provided real-time feedback on ligand minimization, potential clashes, and protein-ligand interactions, speeding up their ideation. A discussion about these molecular designs with the authors can be found here: https://bit.ly/nanome-mpro.

Nanome's VR environment enabled medicinal chemistry analysis on AI-generated compounds for designing COVID-19 Mpro inhibitors. VR enabled medicinal chemists to collaboratively and creatively look at molecular designs and improve them on the fly [ZZZ*20]. A recording of the collaborative compound analysis in VR is available at https://bit.ly/nanome-AI-generative-chem.

The intuitive and interactive nature of the virtual environment makes it also an excellent tool for teaching biochemistry and chemistry classes. Several colleges and universities have introduced VR in their curriculums as valuable support for educators to provide students with a better understanding of 3D structures and engage them in interactive learning experiences.

4. Conclusion and Future Works

In conclusion, Nanome has made significant strides in the field of structure-based design by enhancing existing algorithms used in scientists' workflows and making them VR/MR enabled. The platform's integration of 3D virtual reality viewing and molecular interaction in a collaborative team environment sets it apart and provides a unique solution to the challenges faced by scientists working with structure-enabled projects. As the application of virtual reality continues to evolve, Nanome's platform has the potential to play an increasingly important role in the way scientists approach their work, leading to faster and more effective results. The upcoming release of Nanome 2.0 promises to bring even greater performance, customizability, and user experience to the platform. We anticipate that Nanome's impact in the field of drug discovery will continue to grow and evolve in the coming years.

5. Conflict of Interest Disclosure

S.J.B., M.M., J.G., M.L., D.G., R.B., S.H., E.L. and S.M. are employees of Nanome Inc. and as such have a financial interest in the software.

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