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MolecularWebXR: Multiuser discussions in chemistry and biology through immersive and inclusive augmented and virtual reality

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ABSTRACT

MolecularWebXR is a new web-based platform for education, science communication and scientific peer discussion in chemistry and biology, based on modern web-based Virtual Reality (VR) and Augmented Reality (AR). With no installs as it is all web-served, MolecularWebXR enables multiple users to simultaneously explore, communicate and discuss concepts about chemistry and biology in immersive 3D environments, by manipulating and passing around objects with their bare hands and pointing at different elements with natural hand gestures. Users may either be present in the same physical space or distributed around the world, in the latter case talking naturally with each other thanks to built-in audio. While MolecularWebXR offers the most immersive experience on high-end AR/VR headsets, its WebXR core also supports participation on consumer devices such as smartphones (with optional cardboard goggles for enhanced immersion), computers, and tablets. MolecularWebXR includes preset VR rooms covering topics in general, inorganic, and organic chemistry, as well as biophysics, structural biology, and general biology. Users can also add new content via the PDB2AR tool. We demonstrate MolecularWebXR's versatility and ease of use across a wide age range (12–80) in fully virtual and mixed real-virtual sessions at science outreach events, undergraduate and graduate courses, scientific collaborations, and conference presentations. MolecularWebXR is available for free use without registration at https://molecularwebxr.org. A blog post version of this preprint with embedded videos is available at https://go.epfl.ch/molecularwebxr-blog-post.

1. Introduction

In education and daily work in the chemical and biological sciences, the ability to visually comprehend and communicate details of inherently three-dimensional objects is essential. However, most formats used to present and manipulate 3D information remain intrinsically two-dimensional [1]. In fact, today most of molecular visualization and manipulation takes place through two-dimensional interfaces and representations such as pictures, diagrams and flat-screen computer graphics. Even the most advanced molecular graphics programs typically display molecules on flat 2D screens, limiting user interaction with atoms, molecules, and structural data to one-handed mouse and keyboard actions. This restricts natural interactivity and prevents concurrent multiuser interactions. To address these drawbacks, over various "waves of hype" on virtual reality (VR) most classical programs for molecular modeling and graphics introduced VR extensions that provide immersive visualization and spatial control on manual operations [2–4]. In addition, various programs have been developed specifically for visualizing and manipulating molecules in VR, often with limited functionalities compared to the VR versions of more complete molecular graphics software but with the benefit of being much simpler to deploy and utilize.

Over the past few decades, immersive and interactive molecular graphics have evolved alongside advances in computer hardware, as extensively reviewed by others and summarized here for context [2] and elaborated briefly here to provide context. By the late 1990s, VR-like applications already existed but immersive experiences were constrained by the limited rendering power of the time, which could not

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meet the demands of real-time stereoscopic 3D environments [5]. Besides, hardware was certainly neither widely available nor affordable. Rapid improvements in GPU speed and memory soon enabled real-time rendering at high frame rates, reaching the 90 frames per second per eye needed to prevent motion sickness and ensure stable, immersive 3D visualization—crucial for the adoption of VR in scientific fields [5,6]. Soon after, a first wave of software exploiting VR for molecular graphics emerged, either as stand-alone programs, in many cases limited in functionalities when compared to regular molecular graphics software, or as plugins that ported existing software into immersive 3D and even interactive molecular manipulation. Among the latter, the popular Visual Molecular Dynamics (VMD) software could be interfaced with VR devices via a separate, dedicated piece of software, and also to the MD engine NAMD to drive MD simulations interactively and in an immersive fashion [7,8]. From the team developing the Chimera programs for molecular graphics, VR capabilities were also integrated until a redesign and rebuild of the modern ChimeraX version which allows native visualization in VR headsets. In parallel to the above developments, older technologies like the CAVE (Cave Automatic Virtual Environment) systems also played a role in shaping the field, offering kind of immersive, room-scale visualization of molecular structures before consumer VR devices were available [9,10].

Despite the growing capabilities of VR platforms, the adoption of immersive molecular visualization tools has been quite limited. This likely stems from at least three factors: the substantial usage barrier around VR hardware as well as its cost, although both are slowly improving as we will develop below; the fact that 2D molecular visualization tools are extremely powerful and well-understood by scientists and students, making them a comfortable choice for research and education despite limited in the various ways introduced above; and that there remains a lack of compelling scientific evidence that the uptake of these immersive tools results in tangible, quantitative benefits for education or for scientific discovery, with some positive [11,12] and other negative [13] reports. We note though that these factors are intertwined in a circular fashion: the current set of tools for immersive molecular graphics and modeling, while promising, does not yet match the feature richness and established workflows of the more traditional 2D platforms, resulting in a reluctance to adopt VR tools which leads to slower developments despite the quickly growing capabilities of the devices.

Nevertheless, VR and AR technology continues to advance, driven primarily by the entertainment industry and hopingly with benefits for the field of molecular graphics and modeling too. Clearly, the most significant leaps in the last decade have been in the increased accessibility and usability of VR headsets in general, facilitated by consumer-level headsets like the Oculus Rift and HTC Vive and all the subsequent generations of devices. The modern VMD and ChimeraX versions described above are supported on some of these devices, as are two AR/VR-specific software for immersive, multiuser molecular graphics and modeling: the commercial-license Nanome, and the open-source software Narupa, the latter described in a variety of applications involving single- and multiuser interactive simulation [8,11,14,15].

1.1. Modern AR/VR and its modern applications to the molecular sciences

Since around year 2020, a new wave of VR and also AR technologies has opened up new frontiers for immersive and interactive learning experiences, with these technologies evolving faster than ever in the consumer market [16]. Following the emergence of compact, head-mounted VR devices tethered to computers and external cameras in the 2010s, renewed interest in VR and AR—driven by the idea of building a 'Metaverse'—led to substantial investments. This spurred the development of more wearable and user-friendly VR and AR devices through the late 2010s and early 2020s. This was achieved through more compact designs and more powerful hardware that incorporated all the functionalities required for an immersive experience into the headset itself, including those for ambient and controller tracking, eliminating the need to connect to external computers and cameras. Starting with the Oculus Quest 2, hand tracking was also possible, thus even making it possible to dispense with handheld controllers altogether. Pass-through technology in these and other devices enabled immersive AR experiences with hand tracking, without the need for specialized equipment. Later models, like the Quest 3 and Apple Vision Pro, even support color views of the real world, producing very realistic AR experiences. While some of these devices remain very niche and expensive, others are affordable, in the range of a low-to-mid class smartphone yet very powerful (examples in the Discussion).

Together with the advent of new AR and VR hardware, new programming standards have also been evolving with the coordination of major vendors, and new software tools have emerged in the last years that allow users to teach, self-learn and work in immersive environments [17]. In the specific context of chemistry and biology [18], stand-alone programs for AR/VR and modules that extend the capabilities of regular computer graphics programs into AR-VR have emerged [19–24]. Importantly, the most advanced of these AR/VR programs are starting to support multiuser sessions, with O'Connor et al. having shown up to six users manipulating a molecular dynamics simulation inside VR using Narupa [11]. Multiuser capabilities are important to enable virtual human interactions and collaborations as required for teaching, collaborative work and discussions, etc.

In recent years, VR tools for molecular graphics and modeling have demonstrated that they can actually help with important applications in advancing scientific discovery in the molecular sciences [19]. For example, researchers have employed VR to interactively explore free energy landscapes along drug-protein binding pathways, revealing mechanisms that can inform drug design strategies [25]; to empower citizen scientists exploring reaction networks interactively to propose reaction pathways and test hypotheses using interactive simulations [26]; to assist molecular docking and starting states for regular molecular simulations [27,28]; and even to help generate training datasets for machine learning models applied to chemical systems in at least two studies [29,30]. These examples and other studies discussed in recent reviews [19] underscore the versatility of VR in enhancing work in the molecular sciences by integrating intuitive, hands-on exploration with various advanced computational tools.

1.2. Client-side web-based AR/VR, and the WebXR standard

However, despite the recent emergence of several new programs for immersive molecular visualization and modeling in VR/AR, their adoption still seems very limited. We argue that the main limitation is not only the cost of the AR and/or VR headsets, which has lowered but is still substantial, but also involves the complex nature of the setups involved and the limited cross-device compatibility of the existing programs. This is why over the last 5 years we have advocated for and built purely web-based solutions for molecular graphics [31], meant to work "out of the box" without installation, recently capitalizing on the WebXR standard and API [32]. WebXR-based solutions bring two advantages of unparalleled relevance to adoption and inclusive access to immersive content: (i) high portability across devices and operating systems, from laptops and smartphones to high-end AR/VR headsets; and (ii) low barriers to deployment and availability as all content runs inside web browsers hence requires no installs or updates and is instantly available upon internet connection [32–34]. Notably, despite being served through web pages, much of the web-based AR and VR content itself runs on the clients, allowing the web apps to preserve privacy and avoid leaking of sensitive data.

For molecular graphics in particular, we discussed in 2020 the building blocks for commodity AR/VR-based molecular visualization and modeling using client-side web-based programming of AR and VR applications [31], and around the same time two such tools emerged. VRmol [35], which offers immersive molecular visualization integrated with genomic variation and drug docking information, and ProteinVR [36], which allows users to explore protein structures in 3D environments. Both tools support single-user experiences, working fully on the clients. As of writing of this article, both web apps work out of the box in all kinds of browser-enabled devices, even in the most modern VR headsets available today, thanks to how the underlying graphics libraries (Babylon.js and Three.js) work and handle the available hardware through the WebXR API.

Motivated by the flexibility and extremely easy deployment of web-based apps, three years ago we released moleculARweb, a free platform that offers several activities and playgrounds for chemistry and structural biology education in commodity AR, that is AR that runs on non-specialized devices such as smartphones, computers, and laptops [12, 37,38]. Next, building on the WebXR standard we extended moleculARweb with PDB2AR, a web tool that allows users to create web-based AR and VR sessions for any kind of consumer device, including basic forms of WebXR-based display. In PDB2AR the virtual objects are generated with VMD [39], and as such it supports all its “representations” from simple ball-and-stick models and cartoons to isosurfaces useful to represent electronic orbitals or cryo-electron maps [40].

2. MolecularWebXR

Here we introduce MolecularWebXR (Fig. 1A), a new multiuser AR/

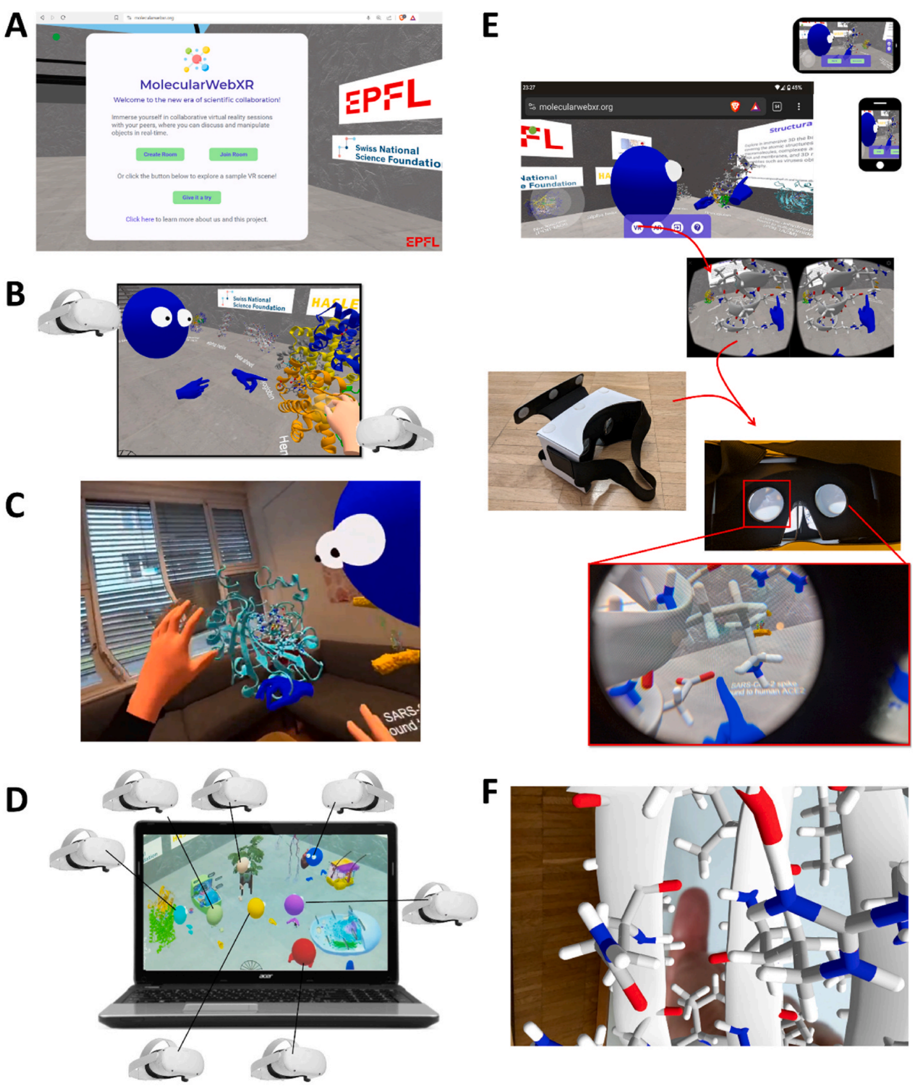

Fig. 1. MolecularWebXR as seen in web browsers on various WebXR-capable devices. (A) Welcome page as seen in a laptop. (B) In VR headsets, the 6 degrees of freedom allow users to explore the VR scene simply by walking around and moving their heads and limbs naturally. In addition, users can translate, rotate and scale objects via natural manual operations with their hands or by using the device’s handheld controllers. The hands/controls and the heads of participants using VR headsets are broadcast to all other users as simplified avatars. If audio is on, these users can naturally talk to each other and with guests who follow the session from any device can listen to the users in VR. (C) A two-user session seen from the view cast by a user wearing an Oculus Quest 3 (orange hands) while another user (blue avatar) follows closely, both in AR wearing Meta Quest 3 headsets. (D) A VR session featuring seven speakers wearing Meta Quest 2 VR headsets as seen from a laptop (looks similar on a tablet). Users can move around the scenes by using the W, A, S and D or the arrow keys if the keyboard (in computers) or a virtual joystick (in smartphones and tablets), and they can direct their looks by using the mouse (computers) or *via* touch gestures (tablets). (E–F) A session with a user in VR mode accessing through a headset (blue avatar) as seen by a user accessing the session with a smartphone. Outside of VR (top) users accessing via smartphones can move around the scene with a virtual joystick and they can gaze *via* touch gestures. In smartphones supporting WebXR (going down through the panel), users can enter WebXR mode and either insert the phone into cardboard goggles to explore the scene via 3 degrees of freedom at the entry point in VR (panel E, without the ability to move around the session but with the option to move their heads to look around naturally) or simply see through the phone for AR (panel F, with six degrees of freedom). For more on how to use MolecularWebXR, see Figs. S1–S3. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

VR platform meant for education, science communication, and possibly for scientific peer discussion, in topics of chemistry and (mainly structural) biology. Leveraging immersive VR and AR as supported by the WebXR standard, and being fully web-served hence not requiring any installations or additional software and being free to use without registration, MolecularWebXR enables multiple users to simultaneously explore, communicate and discuss concepts about chemistry and biology in immersive 3D environments by manipulating and passing around objects with their bare hands and pointing at their features with natural hand gestures. Users can be present in the same physical space or distributed around the world, in the latter case talking naturally through the device thanks to built-in audio features. Inside the AR/VR environment, users can move around and manipulate 3D objects, which consist in GLB-format files prepared from VMD exports or obtained from public repositories. The website comes with various rooms containing pre-built material about topics for chemistry and (structural) biology education, including 3D labels that annotate the material. An empty room is also available for users to populate with custom objects created using moleculARweb's PDB2AR app, enabling personalized VR sessions.

In MolecularWebXR sessions, users with AR/VR headsets are represented by avatars with head and hand movements reflecting their natural poses. They can grab objects using handheld controllers or by pinching their thumb and index fingers if hand tracking is available (and once an object has been grabbed, attempts to grab it by other user will not work). Objects can be moved and resized at will, and users can point naturally with hand tracking. Communication is facilitated through the headset's microphone for seamless interaction. Each user can independently experience the session in VR (Fig. 1B) or AR (Fig. 1C). Users without specialized VR hardware can still participate using laptops, tablets, or smartphones (Fig. 1D–F). On smartphones, the website supports immersive VR with 3 degrees of freedom (head rotations) using cardboard goggles (Fig. 1E), and through-screen AR with 6 degrees of freedom (Fig. 1F).

Throughout the article and its various figures we showcase example applications of MolecularWebXR as either entirely virtual sessions or mixed real-virtual sessions, in VR and in AR, deployed in science outreach days at our institutions, student instruction at courses of varied levels, scientific collaboration, and conference lectures.

2.1. System

As explained above, MolecularWebXR relies on WebXR [32]. This API automatically parses the device's input capabilities into standardized events and mechanisms that are fed into the web browser, for which the software is written in JavaScript at the core. The Three.js library powers in-browser 3D visualization and handles the WebXR interfacing for controller tracking, hand tracking, and AR/VR experience generation. A server, running in Node.js, centralizes the creation and management of rooms where VR sessions take place, and also manages audio via MediaSoup. Rooms with preset content were built from GLB objects recycled from moleculARweb's static content [12,41] and by creating new material in GLB format with VMD and PDB2AR, adding also free 3D GLB objects from Sketchfab.com and labels created in GLB format with the Text-To-STL tool at https://imagetostl.com/.

The VR devices used in the experiences presented throughout the figures of this article were the Oculus Quest 2, Meta Quest 3 and Meta Quest Pro, all with the hand tracking feature enabled. Object manipulation can also be achieved with handheld controllers when users choose to use them (or when hand tracking simply is not available in the device). In addition to the Quest 2, 3 and Pro, we verified proper working of the website in the App Vision Pro, Pico 4, Oculus Quest 1 and HTC Vive Pro, the latter two only with handheld controllers.

MolecularWebXR is designed for broad accessibility, working seamlessly in web browsers on various devices, from high-end VR headsets to smartphones, tablets, and computers, as demonstrated in the figures. Of note regarding this, ProteinVR, VRmol and Narupa all allow sharing VR experiences through smartphones and tablets as well. With MolecularWebXR accessed through high-end VR headsets, users can grab objects and pass them around with their hands or controls, zoom them in or out with natural gestures, use their hands to point at objects, and freely move around scenes, in AR or VR (Fig. 1B–D). Users accessing with headsets are displayed as hands-and-head avatars that all other users can see. On modern smartphones, users can navigate the scene with a joystick on the bottom left and control their gaze by touching the screen (Fig. 1E top, where the joystick is the grey circle on the bottom left). They can also access sessions in immersive VR by using cardboard goggles, without the ability to grab objects as smartphones do not offer built-in hand tracking but with full capability to see the scene and the other users as well as hearing the conversations and talking. A limitation of smartphones in the goggle-assisted VR mode is that they only provide 3 degrees of freedom, allowing 360° visualization but not displacements around the scene, which can only be achieved outside of VR mode by using the joystick shown on the bottom left. However, modern smartphones allow look-through AR with 6 degrees of freedom, as shown in Fig. 1F. Last, on tablets, laptops and other kinds of computers there is naturally no immersive AR or VR of any type (other than with the WebXR emulator plugin if installed); however, users can move around the VR scenes by using the arrow (or W, A, S and D) keys and mouse or touch gestures and they can see and hear all users who are inside AR or VR.

2.2. Using MolecularWebXR

To access MolecularWebXR, users simply visit https://molecularwebxr.org/on their device's browser. On first use, audio permissions must be granted for internet communication. Webcam feed must be allowed in smartphones, tablets and computers as well. No login or registration is needed. For usage details, see Figs. S1–S3.

Once in the main hall (Fig. 1A), the user can create a new room or join an existing one by using a unique code provided by the person who created it, whom we refer to as the *Admin*. When a user creates a new room, s/he becomes its *Admin* and obtains codes to invite *VR-active* and other users who can act as guests, *i.e.* who can follow the presentation but only passively. *VR-active* users with WebXR-capable devices can enter VR and grab virtual objects by pinching their index and thumb (triggering the 'pinch' WebXR event) or pressing a button on their handheld controllers. Object grabbing is only available if the user is in VR and the *Admin* has enabled this feature. Once an object is grabbed, it can't be taken by another user until it's released or the user disconnects.

VR-active users can also talk with each other and with the *Admin* directly through the device, if the *Admin* has enabled audio features (Fig. S2). All users can move around the VR scene and listen to the *Admin* and *VR-active* users, but those in passive mode cannot grab objects or talk. This distinction between user roles allows flexible session formats. For example, *VR-active* users can present and discuss while passive users observe, or sessions can be set up as lectures or presentations led by the *Admin* or a *VR-active* user.

Importantly, VR sessions running in MolecularWebXR can accommodate users located in the same physical space or accessing from remote locations (Fig. 2A and B). In the latter case, the audio features are essential to allow for natural conversation and discussion. However, if all users are located in the same physical space, the audio features should rather be disabled to avoid feedback loops and echo. For mixed-location sessions, the Admin can manage audio settings, but users in the same physical space should disable all but one audio input to avoid interference.

When a session consists of users sharing a session in the same physical space, it is important that the boundaries of all VR devices (the "guardians" or "boundaries" in the jargon of Oculus/Meta products) be setup starting from the same point and orientation in real space. Only in this way will the relative positions of different users match in the physical and virtual worlds. With the right setup, users can feel their

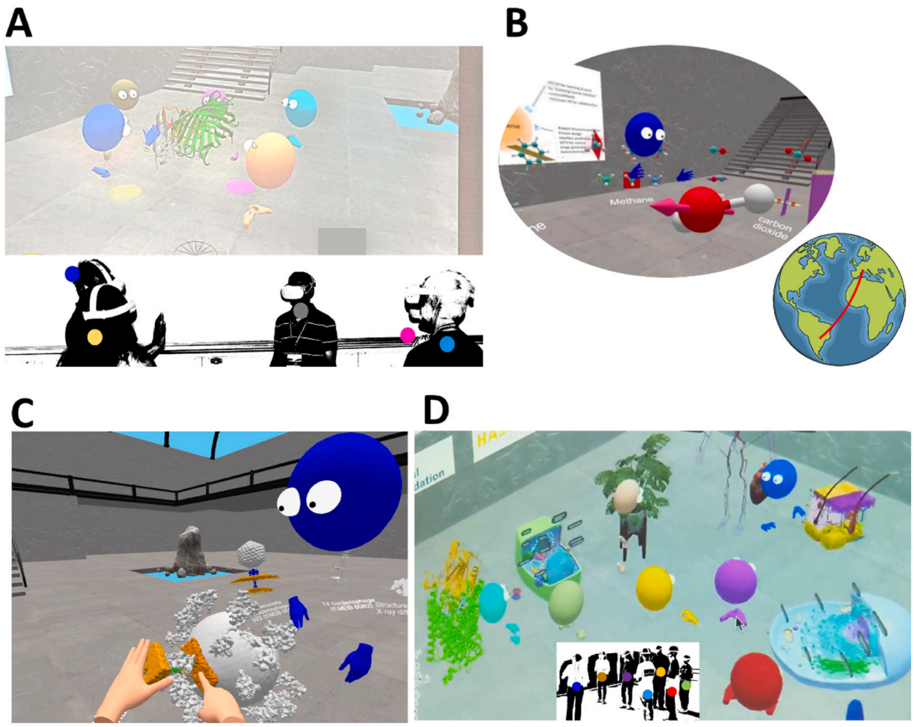

Fig. 2. Real vs. virtual presence in MolecularWebXR, and example content. (A) Five users attending a VR session where the avatar in blue is describing the structure of a protein complex. Example taken from an application of the website to a subset of talks during a structural biology conference. The guardians/boundaries of the 5 headsets were setup as described in the text, to overlay the real and virtual worlds as well as possible. Audio features were off for these activities. Other attendees of the conference could follow the talks by projecting the view of a sixth user accessing through a laptop. (B) A teacher in Rosario, Argentina (blue avatar) teaching his students from inside a room populated with VR content about the symmetry elements of molecules, as seen by a visitor accessing in a VR headset from Lausanne, Switzerland, over 11,000 km away. Students in this case followed the teacher's presentation through the view of a third user who accessed the session with a laptop and projected its view on a widescreen. (C) Two users inside the same VR session, as seen from the viewpoint of the orange avatar as she/he is aligning a model of the SARS-CoV2 Spike protein bound to an ACE2 receptor to the electron density of a Spike protein protruding from the viral particle reported from cryo-electron tomography and subtomogram averaging deposited as EMDB 30430 [42]. (D) A session deployed over an open science day at EPFL using MolecularWebXR with seven people in the VR room, on content prepared by combining custom representations of molecules created by PDB2AR with models obtained from Sketchfab.com in free or paid forms (this room is not available on the website as it contains purchased objects). For photographs in C and D, colors on the users were removed to mask their identities, and we overlaid circles whose colors match the corresponding avatars as seen in the projected views. All the VR headsets involved in these examples were Meta Quest 2 and Meta Quest Pro devices. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

physical proximity and talk directly to each other in a very natural way, in the same real space but handling the virtual objects and not seeing their real bodies but their avatars.

Bandwidth usage is high during the initial download of VR objects when users enter a room. However, once the room is loaded, a stable internet connection is more important than high-speed Wi-Fi to ensure smooth updates as users move objects and navigate the virtual space. We note that no video is transmitted between users but just the quaternions that describe object positions, orientations and scales of the VR objects and of the hands and head avatars of all users inside VR. We've successfully run sessions with up to 8 VR-active users, an Admin on a laptop, and two passive online users, all on the same Wi-Fi network, without major lag.

2.3. Content and example applications

When an Admin creates a session, they can choose a preset room with content designed for specific chemistry and structural biology topics that benefit from 3D visualization, or they can opt for an empty room where objects can be freely added (Fig. 3). Custom content can be created using PDB2AR (https://molecularweb.epfl.ch/pages/pdb2ar.html) (Fig. 3A). The preset content covers topics on molecular structure (Fig. 3B–F), atomic and molecular electronic orbitals (Fig. 3C), symmetry elements in molecules of the main point groups (Fig. 3B), crystal latices and atomic arrangements in simple materials (Fig. 3D), introductory structural biology (Fig. 3F), and 3D views of cellular compartments and viruses obtained by cryo-electron tomography (Fig. 3G–I).

Along the lines of general chemistry, we incorporated rooms specifically designed for lessons on atomic orbitals and molecular structures (VSEPR theory), used in practical sessions for undergraduate science majors at Mahidol University. During the 4-h session, instructors guided first-year students through the rooms. Students inserted VR room images into a two-page lab report, filling in blank tables with names of structures (e.g., trigonal planar or octahedral) and orbitals (e.g., dz [2] or HOMO). Reports were printed and graded like other practical sessions involving wet lab experiments. A survey at the end of the class showed most students were highly satisfied and inspired by the virtual sessions. Details of class activities, including student worksheets, the instructor manual, and student feedback, are available in a separate paper [43] (Fig. 4A). Additionally, we plan to add a room featuring a periodic table of chemical elements (draft version is shown in Fig. 4B) for activities similar to chemistry-related puzzle games [44] but in a more engaging fashion. According to previous studies [43,44], these activities effectively engage high school and early undergraduate students with fundamental chemistry concepts. Note that the system does not automatically evaluate students' actions; instead, teachers oversee and assess their progress during the sessions.

In addition to the standard room for structural biology, MolecularWebXR includes a specialized room for MSc/early PhD-level courses

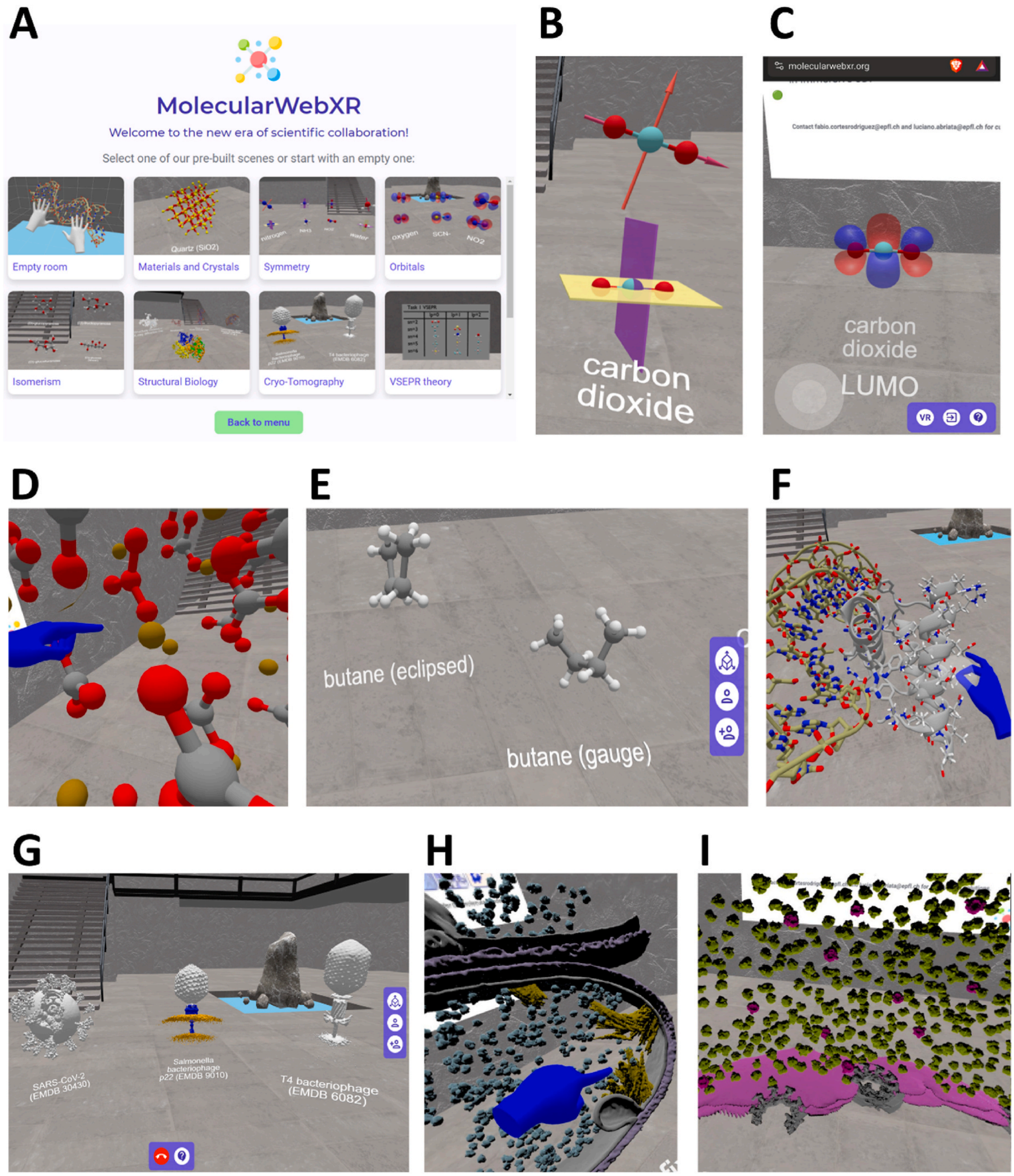

Fig. 3. Examples of 3D content running in VR sessions inside MolecularWebXR. (A) All the rooms and pre-built content available at MolecularWebXR at launch. Besides the empty room to be populated with objects from PDB2AR, we offer rooms displaying the symmetry elements of molecules from the main point groups, the frontier molecular orbitals most widely studied at university level, examples on isomerism, example structures of materials and crystalline arrangements, example structures of biological macromolecules, and examples of subcellular structures imaged in 3D through cryo-electron tomography. (B) Small cut from a laptop screen around CO_2's symmetry elements, from the room on molecular geometry. (C) Screenshot from a smartphone in portrait orientation showing O_2's LUMO, from the room on molecular orbitals. (D) Zoom inside VR on the local geometry around Ca^{2+} ions in calcite, $CaCO_3$, with the viewer's index finger pointing at a Ca^{2+} ion. (E) Models of butane in eclipsed and gauge conformations, from the room on isomerism. (F) Superimposing by hand an atomically detailed model of an alpha helix onto a helix in a cartoon-only representation of a transcription factor bound to DNA. (G) A SARS-CoV-2 particle, a *Salmonella* bacteriophage punching through the two bacterial membranes (orange) with its needle (blue), and a T4 bacteriophage, all retrieved from the indicated the EMDB entries displayed in the labels, as seen in the room about cryo-tomography for biology. (H) Also from the room on cryo-tomography for biology, cut of *Thermoanaerobacter kivui* cell showing the carbon-fixing organelles in yellow, the membrane and some of its invaginations in grey, and the S-layer in purple (Model from Ref. [48]). (I) Another object in the room on cryo-tomography for biology: 3D landscape around the nuclear envelope for a *S. pombe* cell. The model was obtained from Ref. [49] as detailed in Ref. [50] and shows the nuclear envelope (purple) with some nuclear pore complex subunits (grey), 80S ribosomes (green) and fatty acid synthases (magenta). The examples were produced with Meta Quest 2 and Meta Quest 3 headsets. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

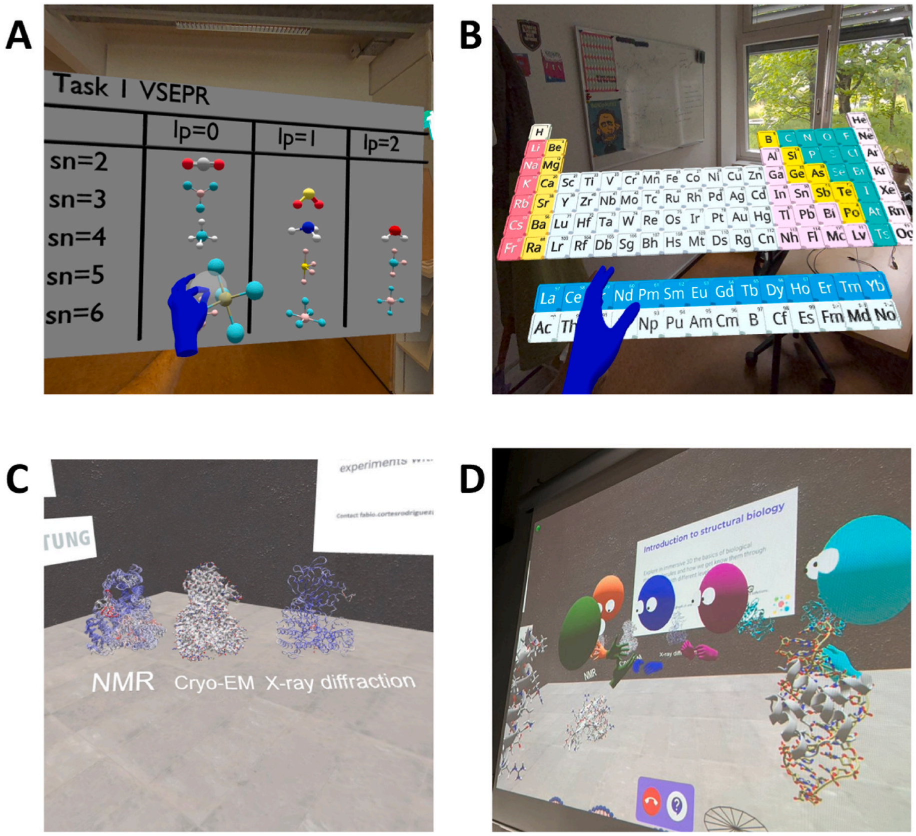

Fig. 4. Some of the VR rooms built specifically for deployment in courses. (A) VSEPR theory for undergraduate students, utilized for lessons at Mahidol University as described in Ref. [43] as seen on a Meta Quest 3 headset in passthrough (AR) mode. (B) A virtual periodic table of the elements, in preparation for future deployment in class, also as seen on a Meta Quest 3 headset in passthrough (AR) mode. (C) Structure of Malate Synthase G as determined by NMR spectroscopy, cryo-electron microscopy and X-ray diffraction, used in a MSc/PhD level course on integrative structural biology, in VR. (D) Four students (red, blue, magenta and cyan avatars) following inside VR the explanations of an instructor (green avatar). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

in integrative structural biology, focusing on the key techniques for determining protein structures. Likewise, besides a standard room for structural biology, MolecularWebXR includes a room specifically tailored to a MSc/early PhD-level course in integrative structural biology that covers the main techniques used to determine protein structures. At the University of Copenhagen, we used this room to show malate synthase G's 3D structure as solved by NMR, X-ray and Cryo-EM [45–47]. By showing these structures and some of the experimental data used to derive them, we illustrated the strengths, limitations and complementarity of the three main techniques for biomolecular atomic structure determination (Fig. 4C–D).

Immersive 3D visualizations are particularly well suited for analyzing *in situ* cryo-electron tomography. Some groups have contributed with cellular 3D reconstructions, and we are open to add more material on request. Fig. 3H shows a map of *T. kivui* cells, as a model depicts the plasma membrane, S-layer, and the unusual filamentous enzyme that drives CO_2 fixation [48]. Fig. 3I shows a 3D landscape around the nuclear envelope of *S. pombe* cells, as seen inside VR. The model was generated from a public dataset (EMPIAR: 10988) [49] as described in Ref. [50] and displays ribosomes, nuclear pore complexes, fatty acid synthases and the nuclear envelope. Other content in the same room includes models of three different viruses and bacteriophages, with their identifying EMDB codes provided in labels (Fig. 3G).

Besides accessing the preset content, users can create with our PDB2AR tool [40] *ad hoc* content for their presentations starting from either raw PDB files (uploaded locally or fetched from the PDB or the AlphaFold-EBI database) or from VMD-generated wavefront objects. In this case, users must follow the procedures described in our previous work [40], and then copy-paste the link to the GLB file obtained via email. An example application of custom-generated content is shown in Fig. 2A for which the users had to prepare virtual representations of the structures they presented as part of a series of scientific talks during a conference.

Furthermore, starting from the empty room and by leveraging content created in-house with PDB2AR and downloaded or purchased from the 3D art platform Sketchfab.com, we have held sessions designed specifically for certain science communication events and school visits where we show not only molecules but also models. For example, Fig. 2D is a snapshot from a 15 min long VR session where a presenter tells an engaging story that connects physics with chemistry and biology attempting to demonstrate the continuous nature of science, with all participants inside VR.

As described throughout the paper, we have successfully applied MolecularWebXR in various formats at scientific presentations in conferences, science outreach events, and for teaching, including combinations where users wore VR headsets or employed other kinds of devices. Importantly, we have had almost 150 people trying the 15 min long VR presentation from Fig. 2D (in groups of 4–7 people plus a presenter) and none of the participants had to quit the experience prematurely due to VR sickness or other problems. Furthermore, users who tried the experiences inside VR headsets spanned an age range from 12 to 80 years old, and all of them could seamlessly manipulate objects with their hands, even when they had absolutely no previous experience utilizing VR headsets (>80 % of the participants).

3. Discussion

Modern VR and AR headsets allow users to visualize and manipulate 3D models with a level of depth and realism that was unattainable just 5 years ago. Unfortunately, multiple factors hinder widespread access to the technology, leaving out a large proportion of the population as compared to solutions based on regular consumer devices. Our previous release, MoleculARweb, tackled the need for more immersive visualization and more intuitive object control for chemistry and structural biology education through web-based but only partially WebXR-based activities and playgrounds. With a steady base of 2500 users per month and almost 120,000 users since its launch, MoleculARweb is widely employed at schools. Now, based on similar core concepts and material but building on WebXR and with the aim of achieving more immersive sessions, we hope the new MolecularWebXR will be welcomed for education, science outreach, and scientific discussions. We note that the device we used most for development, testing and application on users, Meta's Oculus Quest 2 with 128 GB of memory, costs under USD 300 as of June 2024, which is around that of a mid-range smartphone. In October 2023, the Meta Quest 3 device (which has color cameras and thus allows for vivid AR experiences) was launched for under USD 600, and other companies have their own WebXR-supporting VR devices with prices starting around similar values. While these costs might still be prohibitive for individual users in low-income countries, they bring an option for VR/AR at institutions, and will likely come further down in the future (for reference on revision of this paper, Meta announced the Quest 3S product, also with color camera, for USD 300 in October 2024).

As prices keep droping we expect in general wider adoption of AR/VR headsets and apps; and in particular as the WebXR standard keeps developing, with the unmatched possibilities it offers regarding deployment and compatibility, we expect to see more scientific applications and content coming up directly on the web. Web apps like ProteinVR [36], VRmol [35] and HandMol [51] already handle various flavors of molecular graphics and modeling, and MolecularWebXR now adds wider content to 3D visualization at the expense of models being static only (discussed next). A growing universe of tools based on WebXR has the potential to transform the way how chemistry and biology, and science in general, are taught, learned, communicated and discussed, leaving no one behind.

3.1. MolecularWebXR and a discussion of its pros and cons

Profiting from the lower costs and building on web standards with cross-device/cross-OS compatibility and seamless deployment as our flagships, we envision that MolecularWebXR can gain substantial traction just like our moleculARweb did but now providing much more immersive and natural, and thus more engaging, experiences while staying affordable. This, in an inclusive way that does not leave low-resource institutions out, thanks to WebXR running similarly on so many devices. Attesting to its wide reach, we have hit in one year since the release of the MolecularWebXR preprint in October 2023 over 10,000 accesses from around the world (tracked at https://clustrmaps.com/site/1bwmt). Additionally, drawing from our own experiences at our four institutions and at the various activities exemplified in the figures of this article, we have seen how well-funded educational institutions can afford multiple VR headsets to do concurrent multiuser collaboration or teaching with several users inside immersive VR, while institutions with more limited funding can still have one or two users wearing VR headsets to manipulate objects while other users participate from other devices.

An important point to highlight is that MolecularWebXR is not a molecular graphics nor modeling program, as it serves ready-made 3D objects. This is handy in that the system can display absolutely any kind of content for which 3D objects can be prepared in suitable format (mainly GLB). That is how in the outreach sessions connecting biology with chemistry and physics we can display models of tissues, organs, and cells together with molecular structures (as in Fig. 2C), profiting from the large array of models available at websites like SketchFab.com. Using ready 3D objects also allows seamless display of tags and labels as those used to describe the content in all the sessions, or to build the periodic table shown in Fig. 4B.

The big disadvantage of MolecularWebXR serving ready-made 3D objects is that they cannot be changed interactively, meaning that, for example, users cannot change the relative positions of atoms in a molecule or the representations (shapes, colors, etc.) used to display them; likewise, users cannot dynamically change the thresholds for the density values used to visualize electron maps in cryo-EM structures, cryo-tomography models or orbitals. Of course, then, our website cannot replace or even compete in terms of versatility with software such VMD or ChimeraX for the full exploration of density maps, or with other WebXR-based tools like ProteinVR and VRmol to visualize proteins with dynamically changing representations. Coming next from our lab, our HandMol [51] prototype (available at https://go.epfl.ch/handmol) is not as flexible as ProteinVR or VRmol for visualization, but it is to our knowledge the only web-based program that incorporates some form of molecular mechanics with which users can alter molecular structure, even using an AMBER forcefield and the DFT-trained neural network ANI [52,53]. Indeed, we developed HandMol as the WebXR-based, immersive AR/VR counterpart of moleculARweb's virtual modeling kits [37] where molecules are loaded from PDB coordinates, but in two-user, immersive VR that runs, like all of MolecularWebXR's content, on VR and non-VR capable devices.

3.2. Reflecting on the future of immersive molecular graphics

We acknowledge that immersive molecular visualization tools, including our own, face challenges in widespread adoption even considering the recent developments in hardware and standards presented in the Introduction. The powerful and well-established nature of 2D tools makes them the go-to option for most scientists, and the perceived lack of significant quantitative benefits from VR-based tools adds to this hesitation. However, we are optimistic that the current circular situation (where VR tools lack adoption because they are not as feature-rich as 2D tools, and development is slow due to limited usage) will be resolved through continued incremental improvements along the hardware and programming ends, and as the community proposes new tools of actual use. Last regarding this, some concrete applications where AR/VR graphics and modeling make a difference are now emerging, as described in the introduction and in references [19–30].

In particular, recent advances in hardware, such as more wearable and user-friendly headsets, wider cross-device compatibility, more natural interaction through hand tracking, color AR, and the ability to interact with virtual objects without the users having to leave their desks and walk to a specific location where to use the headset (especially with the boundless AR features recently introduced in the standards) will further narrow these obstacles. Moreover, developments in human-computer interaction based on gesture recognition and integrated speech recognition powered by large language models to cast natural requests into commands, as we have advanced in our HandMol [51] prototype, promise to make VR tools even more intuitive and easier to use. In light of these technological advances, we believe that immersive molecular graphics will gradually gain more traction, with each new development bringing us closer to the enticing future that Goddard et al. dubbed "Molecular Visualization in the Holodeck" [2].

CRediT authorship contribution statement

Fabio J. Cortés Rodríguez: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Gianfranco Frattini:** Resources, Methodology, Investigation. **Sittha Phloi-Montri:** Resources, Methodology. **Fernando Teixeira Pinto Meireles:** Resources, Methodology. **Danaé A. Terrien:** Resources, Methodology, Investigation. **Sergio Cruz-León:** Writing – original draft, Validation, Resources, Methodology. **Matteo Dal Peraro:** Validation, Project administration. **Eva Schier:** Validation, Supervision, Resources, Project administration, Investigation, Conceptualization. **Kresten Lindorff-Larsen:** Writing – original draft, Visualization, Validation, Resources, Methodology. **Taweetham Limpanuparb:** Writing – original draft, Visualization, Validation, Resources, Investigation. **Diego M. Moreno:** Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation. **Luciano A. Abriata:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

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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.2024.108932.

Data availability

No data was used for the research described in the article.

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