Article

MoleculARweb: A Web Site for Chemistry and Structural Biology Education through Interactive Augmented Reality out of the Box in Commodity Devices

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Cite This: *J. Chem. Educ.* 2021, 98, 2243–2255

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ABSTRACT: Augmented/virtual realities (ARs/VRs) promise to revolutionize STEM education. However, most easy-to-use tools are limited to static visualizations, which limits the approachable content, whereas more interactive and dynamic alternatives require costly hardware, preventing large-scale use and evaluation of pedagogical effects. Here, we introduce https://MoleculARweb.epfl.ch, a free, open-source web site with interactive AR webpage-based apps that work out-of-the-box in laptops, tablets, and smartphones, where students and teachers can naturally handle virtual objects to explore molecular structure, reactivity, dynamics, and interactions, covering topics from inorganic, organic, and biological chemistry. With these web apps, teachers and science communicators can develop interactive material for their lessons and hands-on activities for their students and target public, in person or online, as we exemplify. Thousands of accesses to moleculARweb attest to the ease of use; teacher feedback attests to the utility in online teaching and homework during a pandemic; and in-class plus online surveys show that users find AR engaging and useful for teaching and learning chemistry. These observations support the potential of AR in future education and show the large impact that modern web technologies have in democratizing access to digital learning tools, providing the possibility to mass-test the pedagogical effect of these technologies in STEM education.
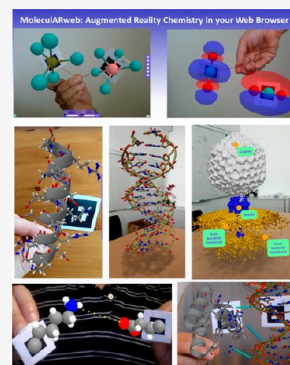
INTRODUCTION

Computer graphics applications for molecular visualization are well-established tools for teaching and self-learning about molecular structures, properties, and reactivity in chemistry and biology courses.[1−3] An important limitation of regular computer graphics programs is the unintuitive link between the six degrees of freedom naturally available to each of the user's limbs, the single-handed 2D nature of mouse-driven operations, and the 3D nature of molecular structures and interactions between pairs of molecules. Human interaction with molecular models is in fact much more fluid with physical molecular models (such as plastic-made kits for small molecules and proteins, 3D-printed models,[4,5] etc.) than with 2D graphics and a mouse, because the tangible model enables the seamless manipulation of the 3D structure and even of its internal flexibility. The user can also more easily compare two tangible molecules by moving them independently with the hands than two molecules handled with a single mouse on a flat screen. On the contrary, physical kits for molecular modeling themselves have several limitations including a restricted number and types of atoms available, the need to manually build each model, and the lack of any augmentation

that computers can offer such as colors, textures, and labels to display surfaces, measurements, or auxiliary information. Besides, physical models are limited to atomic representations of molecules and at most secondary structure representations of proteins. Studies suggest that combining computer graphics and physical models may help to better grasp 3D structures compared to using any of them alone.[6] Here, we report a web site with a large set of webpage-based apps ("web apps") that intend to blend physical and virtual experiences for chemistry and biology education through augmented reality in a format delivered directly through web browsers and operational without any *ad hoc* hardware or software.

Technologies for advanced human–computer interaction using augmented and virtual reality (AR/VR) aim at connecting the physical space around users with simulated
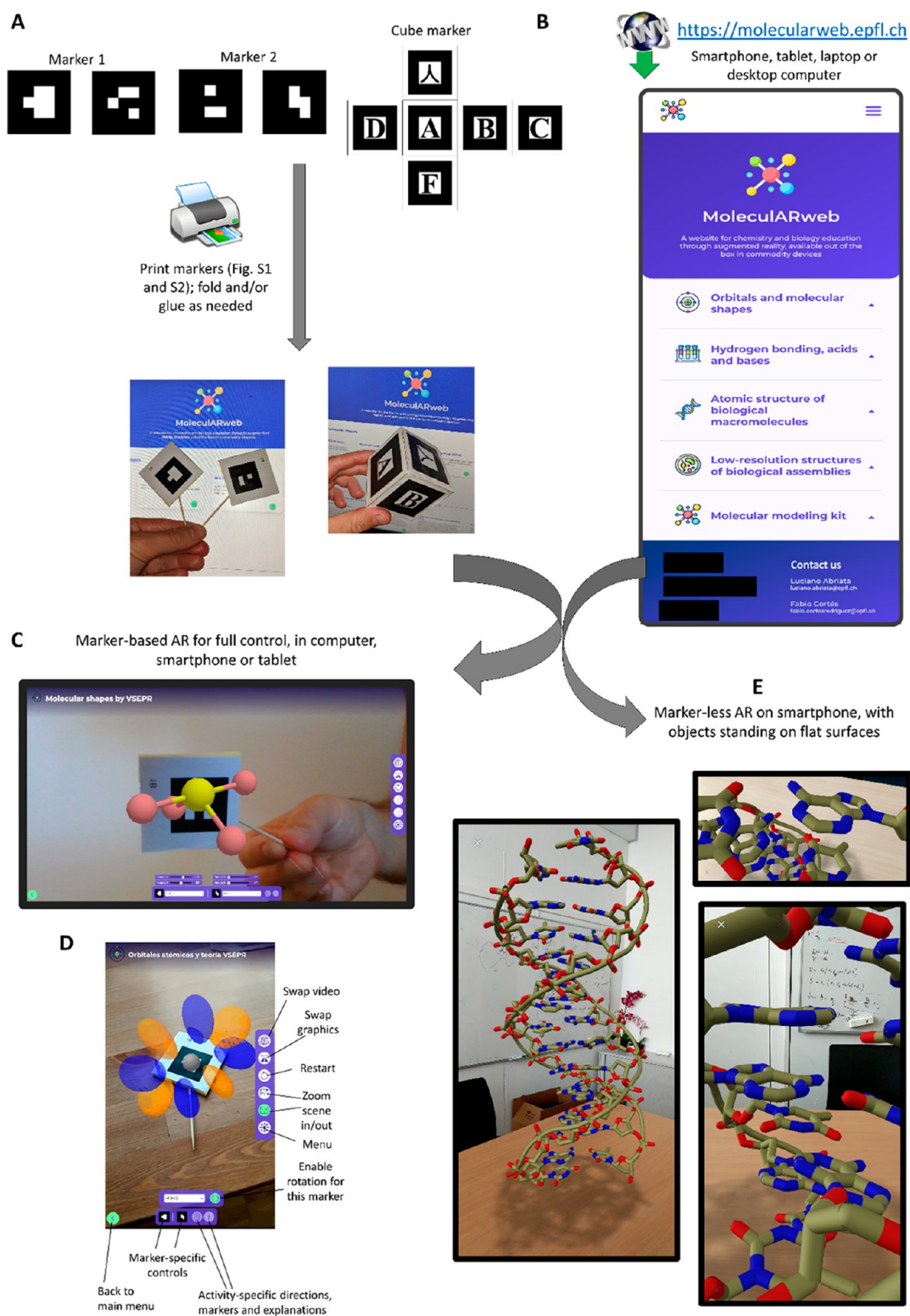
Figure 1. Accessing and using MoleculARweb (most browsers are supported, but Google Chrome is recommended). (A) Users need to print the markers (from Figures S1 and S2), fold and possibly glue them, and set them in a way physically comfortable for handling. Here, the flat markers 1 and 2 are folded in half and glued onto a flat solid support through which toothpicks cross, giving a handle; and the cube marker is folded and glued onto a custom-cut rubber cube. (B) Users then must direct a web browser to https://MoleculARweb.epfl.ch on a smartphone, tablet, or computer, access a web app from the modules, and then enable the webcam when prompted and show it the markers. (C) SF4 molecule from the web app on molecular shapes based on VSEPR theory, displayed on a marker in a laptop screen. (D) Example of controls in one of the web apps, shown in the smartphone layout for the app about atomic orbitals, here showing a 4f orbital. Controls on the right are general across the different web apps and permit controlling general zoom level, restart, an graphics orientation depending on device (for example, using the computer webcam as a mirror or a smartphone for look-through requires opposite video swaps). Controls at the bottom are app-specific, allowing the selection of different examples and tuning marker-specific rotations and zoom level through touch gestures. (E) Some of the visualization-only web apps can also be launched in

Figure 1. continued

the WebXR mode of modern smartphones, which does not use AR markers but rather detects flat surfaces and deposits the models on top of them such that the user can explore them all around, as shown here for a double-stranded DNA molecule. Marker-less AR will not work on older iPhones even with Chrome or on older Android devices without WebXR support. When this mode is available and expected to work, the web app automatically displays a "3D" icon in the bottom right, which opens the marker-less mode after clicking "See in your space".

objects that they can handle in space. In VR, the experience is fully virtual, including a virtual environment, while in AR the users see the virtual objects overlaid onto the physical world. The main advantage of AR/VR tools over regular computer graphics relies in the full 3D control of the visualization, even if actually displayed on a flat screen, which allows for a much more natural interaction with the molecules.[7] Moreover, AR/VR applications typically enable the independent use of two hands to manipulate multiple virtual objects simultaneously. AR and VR thus allow for much more complex operations than standard computer graphics, which has been shown to improve the manipulation of virtual objects including virtual molecules.[8] AR is of special interest, as it keeps the user in view of their limbs, thus further facilitating coordination compared to VR,[9] and of the surroundings, thus not disrupting integration with persons around, important for students in a class.

Chemistry and structural biology have been particularly fruitful niches for AR/VR, with a rapid growth in the number of software tools that implement such technologies both for education and for actual research. Among a much larger collection of works, we highlight selected cases of educational value: the early tangible-virtual models, highly interactive and using regular webcam-equipped computers;[10−13] the many easy-to-use but mostly visualization-only AR systems that run on consumer smartphones, tablets, and computers, introduced recently by several groups;[14−26] the VR-versions of high-end molecular visualization programs,[27−31] all requiring specific costly hardware but implementing advanced features, and even interactive molecular simulations that have been used in the classroom.[32−34] A couple of more global reviews are also recommended for a more complete coverage of the subject.[35,36]

Despite all the purported advantages of AR and VR for molecular modeling in education, several important issues stand. First, the highest-end tools for handling molecules in AR/VR require *ad hoc* hardware such as VR headsets, AR lenses, and user-tracking cameras and hand-held devices that are expensive despite the dropping costs (and often require quite powerful computers), thus precluding one-per-student adoption even in wealthy countries. Second, in many cases, the software setups are often complex for lay users, while the simpler alternatives such as install-use programs for phones are often limited to visualization capabilities; moreover, many of these programs are paid. Third, because these issues strongly limit availability and usability, we lack large-scale testing about the actual pedagogical effects of AR/VR tools over conventional teaching tools. Thus, although AR and VR have attributed large potential in assisting the teaching and learning of STEM (science, technology, engineering, and mathematics), this needs to be further studied.[36,37] Lastly, most of the pedagogical tools with modest hardware requirements, which hence could become widely used, are quite limited to the display of static graphics, certainly insightful but with no interactivity nor any kind of molecular mechanics.

We recently described how tools for programming dynamic content into web pages[38,39] offer a relatively simple way to

encode interactive molecular graphics applications into AR experiences without the need of specialized hardware and running directly inside web browsers on regular computers.[19] Here, we introduce MoleculARweb, a web site that proposes a large number of webpage-based apps for interactive AR-based molecular visualization running in regular web browsers in regular computers, laptops, tablets, and smartphones equipped with a webcam and Internet connection. Users only need to prepare 2D markers (detains in Figures S1 and S2) and show them to the device's webcam. The device then superimposes the virtual objects onto them, allowing the users to manipulate molecules, electronic orbitals, and other virtual objects by moving the AR markers, in an environment that enables the interactive exploration of structure, dynamics, and interactions. The web apps available by the time of first release cover topics about molecular shapes, electronic orbitals, acid−base equilibria, hydrogen bonding, structures of biological macromolecules, X-ray diffraction and electron microscopy, and molecular mechanics. One of the main web apps is a prototype of an AR-based molecular modeling kit where users can build any model and explore its structure and dynamics, resembling the experience of manipulating a plastic-made model but enhanced with some minimal molecular mechanics.

The web site is open source and freely available without registration at https://MoleculARweb.epfl.ch, including at the moment over 20 web apps available in English, Spanish, Italian, French, Portuguese, and German languages. Online surveys and web site usage analytics obtained after thousands of accesses, as well as the direct live tests conducted in chemistry classes, visits to schools, and science outreach activities, all show very good engagement and support the positive pedagogical impact of AR technologies on learning.

■ OVERALL DESCRIPTION OF THE WEB SITE

To use the web apps in MoleculARweb, users must print the AR markers required as shown in Figure 1A (Figures S1 and S2 display the markers ready to print in different sizes). All but the Virtual Modeling Kit require the flat 2-side markers labeled "Marker 1" and "Marker 2" in Figure 1A (Figure S1), while the Virtual Modeling Kit uses the cube marker of Figure 1A (Figure S2). Each web app is accessed directly from the main menu (Figure 1B) or from direct links. Users must enable webcam feed when prompted by the browser to begin the AR experience. Users then move and rotate the AR markers in front of the webcam to drive the position and orientation of the virtual objects (Figure 1C) and thus trigger interactivity for the interactive examples. The web site can be used either in a regular laptop or computer that acts as a mirror where the user sees its reflection with the virtual objects on the markers (Figure 1C) or in either mirror or look-through modes on smartphones and tablets (by swapping front and back webcams, Figure 1D). Modern smartphones further support marker-less visualizations that stand on flat surfaces in AR (Figure 1E), which the web site makes available for certain visualization-only web apps (when this mode is available, a
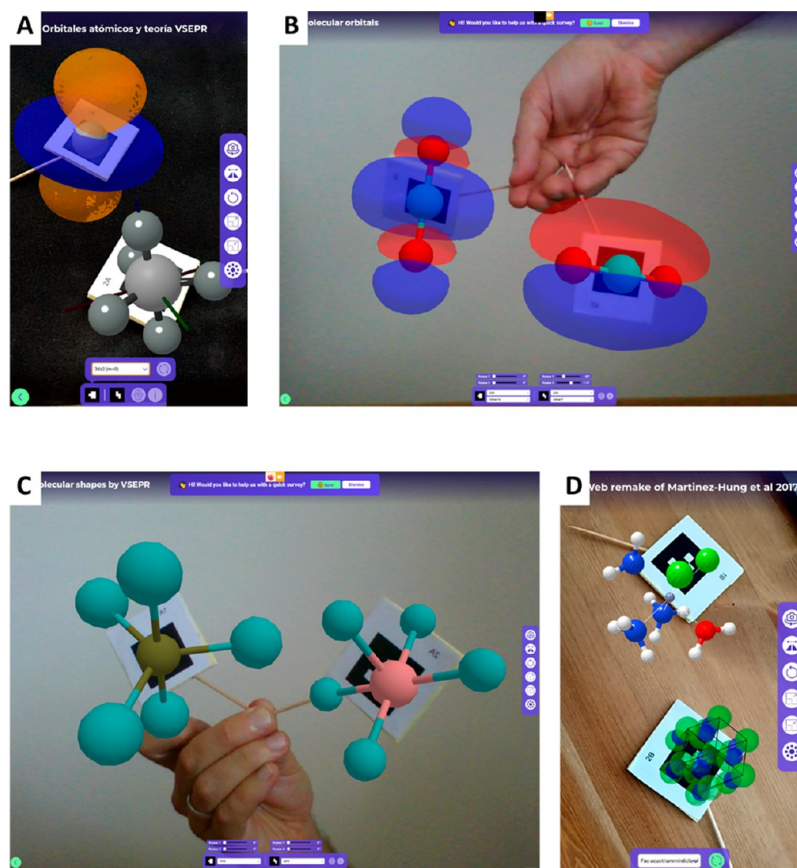
Figure 2. Module on atomic orbitals, molecular orbitals, and molecular shapes. (A) Markers displaying a $3d_{z^2}$ atomic orbital and a trigonal bipyramidal geometry in a smartphone. (B) Markers displaying σ antibonding (left) and π bonding molecular orbitals of CO_2 in a computer. (C) Comparing trigonal bipyramidal (AX_5) and square pyramidal geometries (AX_5E) of PCl_5 and BrF_5, respectively, in a computer. (D) Markers displaying the aquodiaminotrichloroferric complex and the unit cell of ZnS in a smartphone, among other examples from Martinez-Hung et al. from 2017 repurposed for webAR.

"3D" icon is displayed in the bottom left). The different figures in this article exemplify uses in all these modes.

Except for the marker-less mode, which is currently unsupported in Apple devices, all the web site content was verified to work in all AR modes on several brands of smartphones, tablets, and laptop computers using Windows, Linux, Mac, and Android operating systems, with Chrome, Brave, Firefox, Edge, and Safari web browsers updated at least as of April 2021 (Internet Explorer is not supported). We recommend Google Chrome as the best-performing, most-tested browser in all operating systems and devices.

To use the AR web apps described in the next sections, the user needs to access the webpage of interest, enable the webcam when the browser prompts, show the AR marker(s) indicated to the webcam, and follow the instructions. Most web apps employ the flat two-sided markers labeled 1 and 2 in Figure 1A (Figure S1), which need to be folded and glued back-to-back as indicated. Attaching small sticks to the markers as in the figures helps to control them without hiding any part from the webcam. One web app, the Virtual Modeling Kit, employs the cube marker of Figure 1A (printable from Figure S2), also best if folded and glued to a solid cube. Table S1 lists potential problems and solutions; among the key ones are ensuring https URL access without firewalls, enabling the webcam when the web browser prompts, leaving a white space around the printed AR markers, avoiding covering the markers

with the fingers when they are manipulated, and having good lighting but not direct strong light on the AR markers.

Users can directly access all web apps from the main screen (Figure 1B), which also displays on-board instructions in video format and language settings and links to the AR markers, relevant articles, and an online survey for user feedback. The screen of each web app contains general controls to zoom, swap cameras, invert video and graphics, etc. (Figure 1D), plus app-specific controls that enable choosing among systems and provide interactivity. Note that, besides the marker-based handling of virtual objects, most web apps further support zooming and rotations with standard mouse operations or with fingers in touch-enabled devices when the rotation mode is on. This enables the incorporation of fixed markers into documents onto which the apps can directly display the virtual objects and also offers the possibility that multiple users working with the same printed AR marker rotate the virtual objects independently.

■ WEB APPS ACTIVE BY THE TIME OF FIRST RELEASE

The web apps at MoleculARweb are arranged in five main thematic modules: (i) Atomic orbitals, molecular orbitals, and molecular shapes; (ii) hydrogen bonding, acids, and bases; (iii) atomic structure of biological macromolecules; (iv) large biological assemblies; and (v) a virtual-mechanical molecular modeling kit.
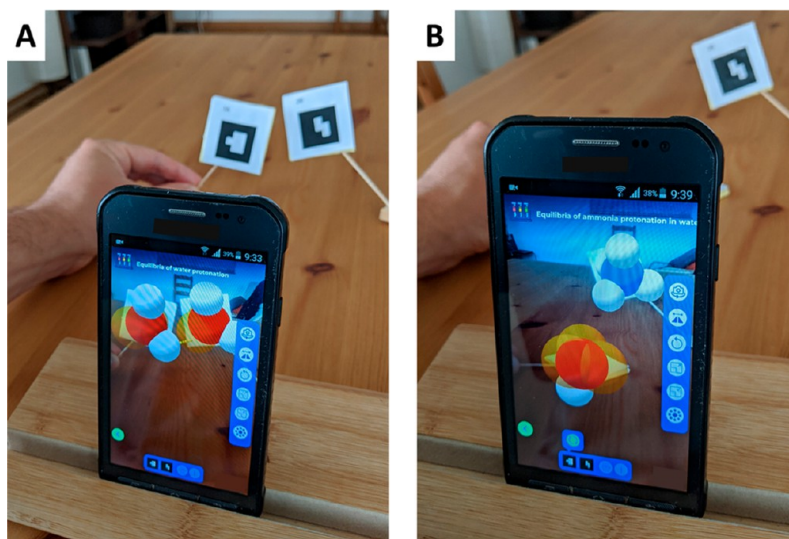
Figure 3. Module on hydrogen bonding, acids, and bases. (A) Two water molecules establishing a hydrogen bond and ready to transfer a H⁺ from the left to the right. (B) Water molecule reacted with ammonia leading to a hydroxide anion and an ammonium cation. The web apps of this module utilize the CPK color scheme for atoms: red for oxygen, blue for nitrogen, gray for carbon, and white for hydrogens, while lone electron clouds are shown in transparent orange. This figure further illustrates a convenient use of smartphones and tablets where they are left standing out on a support, freeing up both hands for molecule handling.

The module on atomic orbitals, molecular orbitals, and molecular shapes includes five web apps. In the first web app, users can inspect the s, p, d, f, and g atomic orbitals, the sp, sp^2, sp^3, sp^3d, and sp^3d^2 hybrid orbitals, and the main ideal VSEPR geometries (Figure 2A, exemplifying a $3dz^2$ atomic orbital and a trigonal planar molecular geometry). Any orbital or molecular shape can be displayed on any of two markers, even simultaneously, which allows for interactive comparison of different objects. The second web app displays all the molecular orbitals precalculated for a list of simple molecules and polyatomic ions: H_2O, O_2, BH_3, CH_4, CO, CO_2, N_2, N_3^-, NH_3, NO_2, BF_3, and SCN^-. After selecting a molecule or ion for a marker, the user can chose to display one of its orbitals (Figure 2B, showing an example of the σ antibonding and π bonding orbitals of CO_2). As in the previous example, each marker can independently handle a different molecule, which is here useful to compare orbitals and assist thinking about reactivity. The third web app contains molecular structures representative of the main kinds of molecular shapes according to VSEPR theory, also handled independently on two markers (Figure 2C). The fourth web app is a web remake of the AR examples employed and tested in a previous work[40] covering key crystalline structures and water complexes (Figure 2D). The fifth web app opens up the modeling kit where users can load and work on any molecule, described later in this article as a separate module.

The module on hydrogen bonding, acids, and bases includes four web apps where teachers can show or students can explore themselves, how hydrogen atoms interact with lone electron pairs of electronegative atoms through hydrogen bonds, how protons can actually "jump" between molecules, thus changing their protonation states, and how this relates to concepts of acids and bases through a very graphical, interactive description of the dynamic equilibria involved. One example displays two water molecules that exchange between hydronium, water, and hydroxide species by exchanging protons when they are close enough (Figure 3A). Another example shows how acetic acid can protonate water to give hydronium

cation plus acetate, and another shows how ammonia can take a proton from water, producing hydroxide anion and ammonium (Figure 3B). The fourth example features an acidic and a basic amino acid reacting directly with each other to change from neutral to oppositely charged species.

The module on the atomic structure of biological macromolecules includes preset examples of static 3D visualizations and some interactive web apps. The static visualizations are all arranged in the "Compilation of . . ." app, in whose dropdown menus users can chose among a set of examples. These currently include short pieces of double-stranded DNA in A, B, and Z forms, a protein–DNA complex, a short peptide, and a drug-bound trimeric protein. These static visualizations can be manipulated either in desktop or laptop computers with the AR markers or placed virtually on top of flat surfaces captured from the real world in the user's space (Figure 1E, exemplifying a dsDNA molecule that the user can walk around, on smartphones or tablets only). The interactive apps include one for inspecting α and β protein secondary structures at atomic resolution while toggling the cartoon representations and the most important interactions that stabilize these structures (Figure 4A), another for docking a DNA-binding protein onto its cognate DNA through its major groove (Figure 4B, exemplifying its use in teaching), and another where students can interactively dock a peptide into an experimental electron density map from an actual X-ray diffraction experiment (Figure S3, introducing how molecular structures are experimentally determined).

A separate module contains static visualization-only material about biological macromolecular assemblies, to be viewed with AR markers in any device or standing on flat surfaces without any markers in smartphones and tablets. This module currently includes an experimental volumetric map of a bacteriophage that has inserted its needle through the two bacterial membranes (EMD-9010, Figure 5A, several marker-less views of the same standing object, with annotations); an integrative model of the SARS-Cov-2 spike protein bound to human ACE2 (PDB IDs: 6VYB, 6M17, and 6M0J); a structure of a
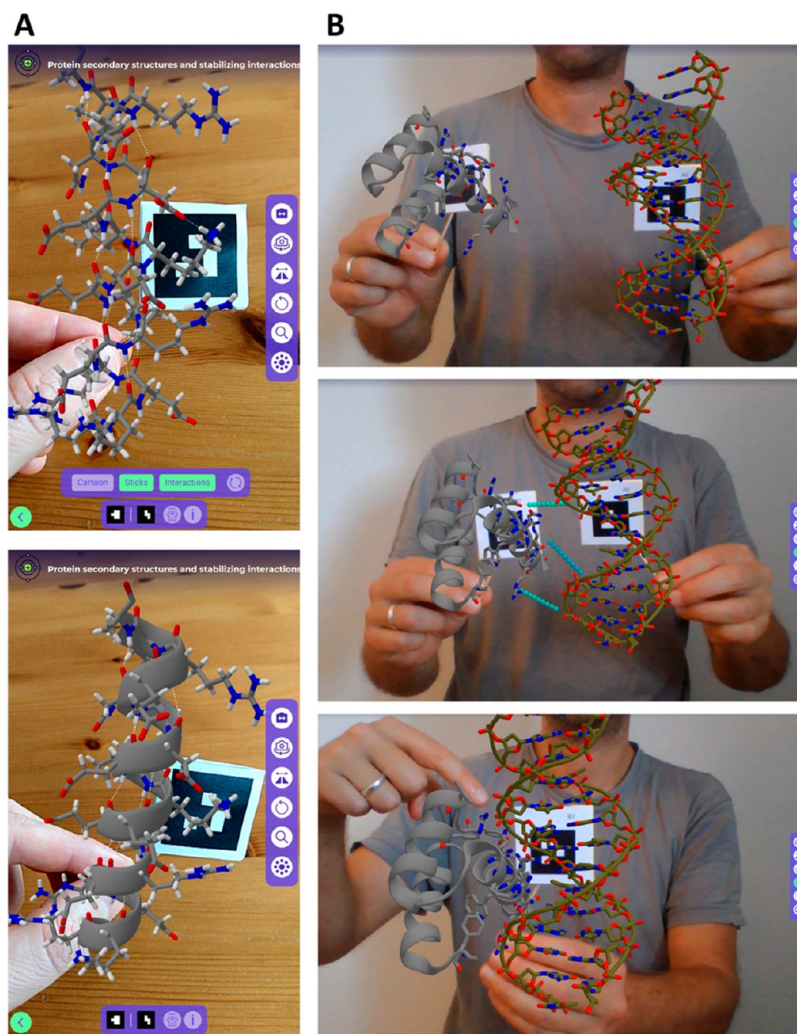
Figure 4. Module on atomistic structure of biological macromolecules. (A) Inspecting a fully atomistic α helical structure on a smartphone, toggling the depiction of interactions (compare left and right). (B) Teaching about DNA structure and protein–DNA interactions during a remote online class on a computer: while both molecules are away (or only one marker is shown to the webcam), each can be inspected individually in detail; then, when they approach, the program highlights interactions that when satisfied lead to the protein–DNA complex. In the complex, the instructor here points with his fingers at the most important interactions, here salt bridges between positively charged side chains of the protein and the negatively backbone phosphates of the double-stranded DNA molecule. This example, from PDB 1FJL intends to aid the understanding of noncovalent interactions, here especially guided by electrostatic complementarity between positively charged amino acids of the protein and phosphate groups of the DNA molecule.

bacterial pilus determined by cryo-electron tomography with X-ray structures fitted inside and including portions of the two cell membranes and the peptidoglycan (PDB: 3JC8 + EMD-3247, Figure 5B, held on a marker and seen on a computer); an X-ray structure of a nucleosome including the 4 histones and 2 rounds of dsDNA wrapped around (PDB ID: 1AOI, Figure 5C, held with marker in a smartphone); a cryo-electron tomography map of the human nuclear pore complex obtained *in situ* (EMDB-3103, Figure 5D, on marker in smartphone); and a cryo-electron microscopy structure of a mammal ribosome with a tRNA in the A/P position paired to a stretch of mRNA and another tRNA in the P/E position (PDB: 6HCJ, Figure 5E).

The last module is a tool where users can view and handle in AR any molecule from its atomic coordinates, as a virtual alternative to a tangible molecular modeling kit (Figure 6A). The molecules are input in PDB format, either loaded from preset examples or pasted from any coordinate file. Current examples range from very small molecules useful for an introduction to molecular shapes and structure to small organic molecules, pharmaceuticals, and metabolites, crystalline arrangements, segments of dsDNA and proteins, nanoparticles and carbon allotropes, among others. Then, any other molecule can be built or retrieved from public databases and copy-pasted into the AR kit by using Prof. Robert Hanson's Hack-a-mol web app at https://chemapps.stolaf.edu/jmol/jsmol/hackamol.htm. The Modeling Kit AR web app displays atoms as either spheres or sticks (Figure 6B) using standard CPK colors, with double and triple bonds shown as thicker sticks. Beyond mere visualization, the app simulates thermal fluctuations, which by coupling throughout multiple atoms give rise to dihedral torsions and thus small conformational transitions. The observed motions are propagated from a very simple rigid-body mechanical force field after connecting atoms with a special set of constraints as described in the Methods section. Of course, such a simple approach cannot accurately describe the full underlying physics, especially nonclassical phenomena, rather being closer to a tangible,
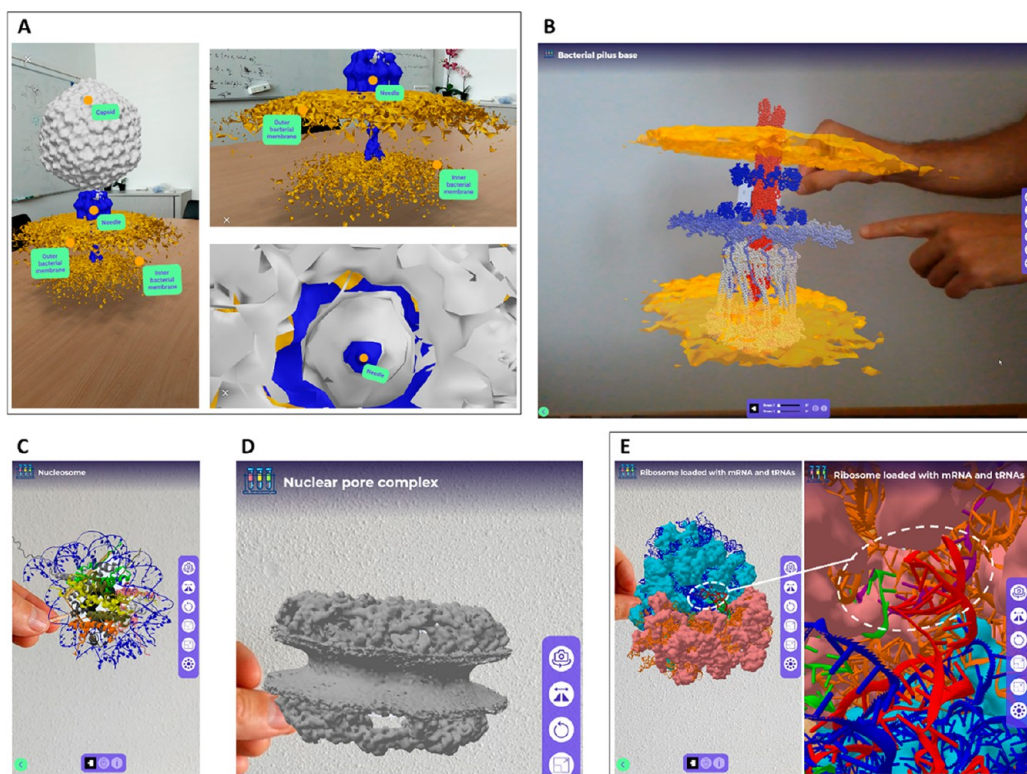
Figure 5. Module on biological macromolecular assemblies. (A) Bacteriophage with its needle punching through the outer and inner membranes of a bacterium as observed by 3D cryo-electron tomography (EMDB-9010), here displayed on marker-less AR on a flat surface with overlaid labels that name the different parts of the virus. Three different views of the same session are shown, two from outside the virus and one from inside the capsid looking down toward the needle. (B) Displayed on a computer, a cryo-electron tomogram of the bacterial pilus machine obtained in intact cells with X-ray structures of proteins fit inside and including portions of the two cell membranes (orange surfaces) and peptidoglycan (pointed at by the finger) (example built from PDB: 3JC8 and EMD-3247). (C) X-ray structure of a nucleosome including the 4 histones and 2 rounds of double-strand DNA wrapped around (PDB ID: 1AOI) held with an AR marker in a smartphone. (D) Cryo-electron tomography of the human nuclear pore complex obtained *in situ* (EMDB-3103, Figure 5D, on marker in smartphone). (E) Mammal ribosome held on a marker (PDB: 6HCJ) seen from far (left) with the large subunit in cyan-blue shades and the small subunits in orange-salmon shades, proteins as surfaces, and RNA molecules as cartoons, and zoomed into the tRNA−mRNA interaction sites (right) where the mRNA is in purple, the tRNA at the A/P position is in green, and the tRNA at the P/E position is in red.

physical molecular modeling kit. Some advantages we expect from this web app over a physical kit are the virtually unlimited number and types of atoms available, the possibility to immediately explore complex molecules without the need to build them, the option to mirror graphical output useful to study chirality, and the communication of the idea that molecules are dynamic rather than static, directly allowing for the visualization of dynamics, dihedral rotations, the rigidity of double bonds and rings, and other concepts about molecular conformations. Example use cases of this web app are inspecting dihedral angles as molecules move, useful to understand for example *cis-/trans-*isomerization and Newman projections in butane (Figure 6B), or chair-boat transitions in 6-member rings like cyclohexane (Figure 6C); also looking at complex molecular geometries and chirality as exemplified for cholesterol (Figure 6D) or the atomic details of any biological molecule or material as in the preset examples shown in Figure 7: proteins, nucleic acids, carbon nanotubes, and crystalline arrangements.

■ USER ADOPTION AND PEDAGOGICAL EFFECTS

We promoted through social media, YouTube videos, press articles, visits to various learning centers, and a preprint at ChemRxiv the prototypes of the first web apps from May 2019 to July 2020 and then the full release version of moleculARweb

during the months of August through to December 2020. During the two periods, we collected automated web site analytics, optional online surveys (fully anonymized) by students and teachers of high-school and university levels, e-mail feedback from interested teachers, live experiences at science outreach events and school visits, and first-hand experiences at chemistry classes.

Considering the prototype version of the web site (which since August 2020 redirects to the formal release version), we received > 14,500 accesses between May 2019 and January 2021, especially from the Americas and Europe, followed by Middle East, Southern Asia, Oceania, and Africa (Figure S4). Detailed Google Analytics applicable only to the formal release version of the web site show 2030 users between August 1st 2020 and January 31st 2021 who viewed almost 15,000 pages and spent up to 30 min in the web site exploring an average of four sessions with an average of ∼ 7.5 min per session (excluding bounces). Users include around 28% people estimated by Google Analytics to be between 18 and 24 years old, followed by 34% of users in the range from 25 to 34 years old, 16% in the range 35−44 years old, and 24% being 45 or older (no data for users under 18 years old are provided). Genders reported by Google Analytics were estimated as 46% females and 54% males.
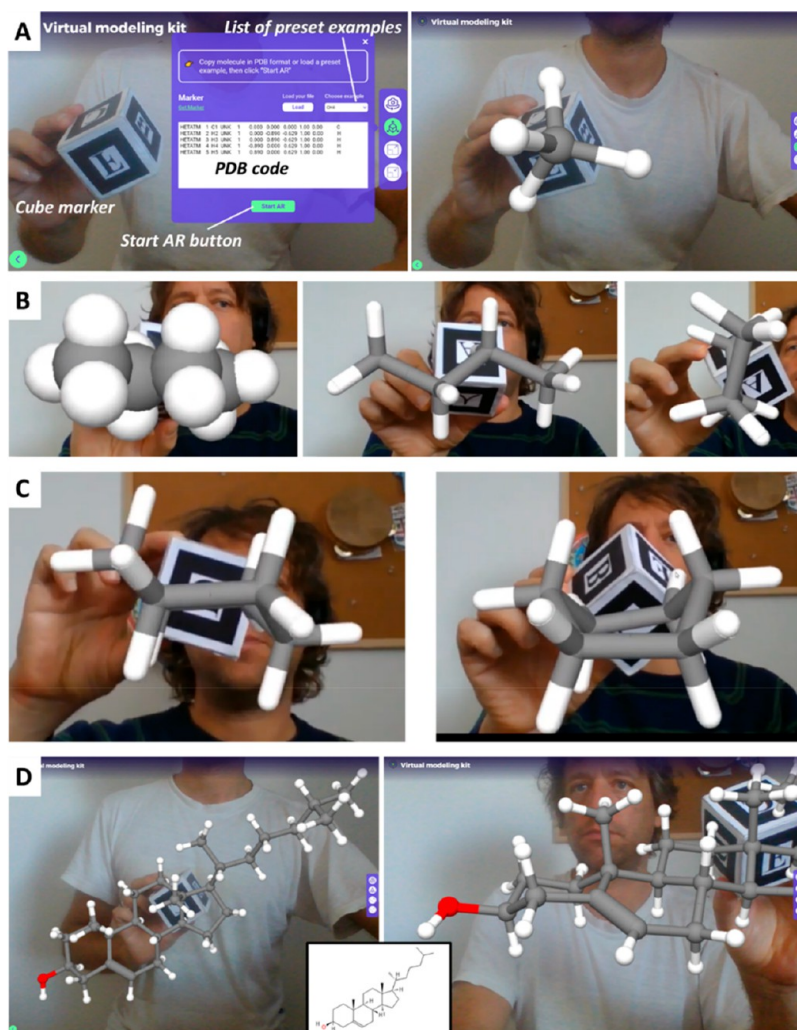
Figure 6. Virtual Molecular Modeling Kit. In this web app, users can load any molecule and then handle them in 3D with a cube marker; furthermore, the web app incorporates rudimentary molecular mechanics that make models flexible, allowing users to study motions. (A) Main interface showing controls to load a molecule in PDB format and start the AR experience, before (left) and after (right) clicking on "Start AR" to display a methane molecule. (B) Starting butane molecule from the preset example in its lowest-energy anti conformation, shown in spacefill representation (left) and as sticks (center) and in the syn conformation observed after the molecule has moved for some time due to thermal fluctuations. (C) Cyclohexane in its chair conformation as in the starting coordinates from the preset example, and then in a boat conformation obtained as the molecule moves due to thermal motions. (D) Molecule of cholesterol (from the NCI database accessed through Prof. Hanson's Hack-A-Mol: https://chemapps.stolaf.edu/jmol/jsmol/hackamol.htm) shown in full on the left and zoomed on the OH side as the instructor comments on the only double bond (thicker bond in front) and the chirality of the OH-bound and methyl-bound carbons.

In the four months previous to submission of this manuscript, i.e., from October 2020 to January 2021, returning users were 25% out of 668 users in October, 37% out of 284 in November, 20% out of 853 in December, and 30% out of 279 in January. Together with the residence times and the total number of entries, these numbers suggest that the web site is indeed being used around the world, which we confirmed by personal emails written to us by teachers especially from the Americas and Europe, plus some from English-speaking parts of Asia and Oceania. in more detail, the accessed locations from Google Analytics on the formal web site are similar to those observed in the prototype web site, i.e., with more accesses from the Americas and Europe followed by parts of Asia, Oceania, and Africa. Language is a possible limitation, as we have focused on the most spoken languages in Switzerland. For example, web site access from Africa is dominated by countries with French-speaking and English-speaking populations. We are working to enable automated web site translation through Google Chrome, to allow using the web apps in virtually any language.

Such large access from all over the world brings the potential to analyze at a large scale how useful the students and teachers perceive the tool for learning and teaching. We set up short, anonymized surveys tailored separately to students and teachers (https://molecularweb.epfl.ch/pages/feedback.html), which are optional but prompted repeatedly in the different web apps until they are filled in. We observed very low participation compared to the thousands of users. As of January 2021, only 32 entries were filled by educators and 99 by students, with the 32 teachers reporting a total of 409 students using the web site for their classes.

The online surveys attest quite good accessibility of the web site. From the data completed by teachers and students together (Figure 8A), we couldd see that 70% of them had no contact with AR before using the web site, 21% had used AR apps a few ($\leq$3) times, and only 9% had already used AR apps
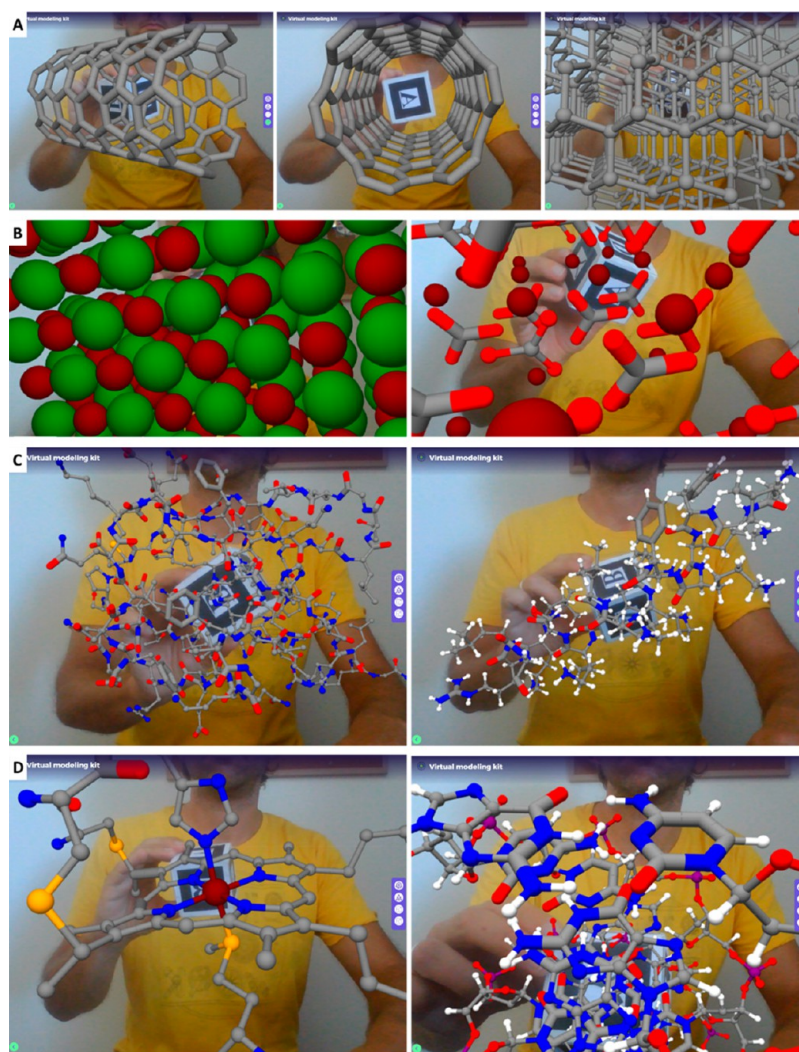
Figure 7. Virtual Molecular Modeling Kit used on larger molecules. (A) Two views of a carbon nanotube (left and center, built with CHARMM-GUI) and a diamond crystal (right) built from a PDB file retrieved at https://preparatorychemistry.com/Jmol_carbon_diamond.htm. (B) Crystal arrangements in sodium chloride (left, sodium and chloride ions shown as red and green spheres, respectively) and calcite ($CaCO_3$, right, with calcium cations as spheres and carbonate anions as sticks) built from PDB files available at https://ww2.chemistry.gatech.edu/~lw26/structure/small_molecules/index.html. (C) Ubiquitin as in the X-ray structure in PDB 2D3G (left) and an α helical antimicrobial peptide solved by NMR in PDB 2RLH (right). Notice the double-bond character of peptide bonds and aromatic rings, also the hydrogen bonding patterns in the helix. (D) NMR structure of a double-strand DNA (PDB 5J3G) seen from far (left) to inspect the overall shape and major and minor grooves and inspected closely for base stacking and hydrogen-bonding patterns (right).

many times. Still, 91% of them could make the web apps work, almost half of whom reported that they worked smoothly right from the first attempt. Differentiating students from teachers, we found that students had less previous experience with AR than teachers yet they seem to have struggled less to run the contents. We highlight that all user access to the formal release of moleculARweb happened during the Covid-19 pandemic, reflected in the very high usage from home as reported by students: 55% indicated using the site only at home, 30% both at home and at their institution, and 15% only at their institution (Figure S5A).

Regarding the evaluation of actual pedagogical effects, the ideal test would be to compare the performance of students on learning a subject either using the AR web site against a control group not using it. This is however difficult to keep under control in a web site with free access, even more so considering that most student users were located at their homes due to the pandemic. However, through the online surveys, we asked the

educators to evaluate their own perception of the pedagogical impact that the web site had on their students. Only 17 of the 32 teachers expressed their evaluation on this, with all of them indicating that they perceived an interest of students in the AR tool (Figure S5B). Of them, 14 (82%) perceived that using the web site helped their students to better grasp the contents they had studied in the lecture assisted by the AR web apps (Figure 8A, bottom right). Two teachers indicated that web site was only a little useful, and one indicated that it was not useful. From the side of the students, all but one replied this question of the survey (Figure 8A, bottom left). Their perception on the utility of the web site was very similar to that of the teachers: 83% of the students indicated that the web site helped them very much to better understand the subject, 13% indicated that the web site was somewhat useful, and 4% indicated that the web site was not useful to them.

Among the educators who filled in the surveys, there were several high school and early university teachers who contacted
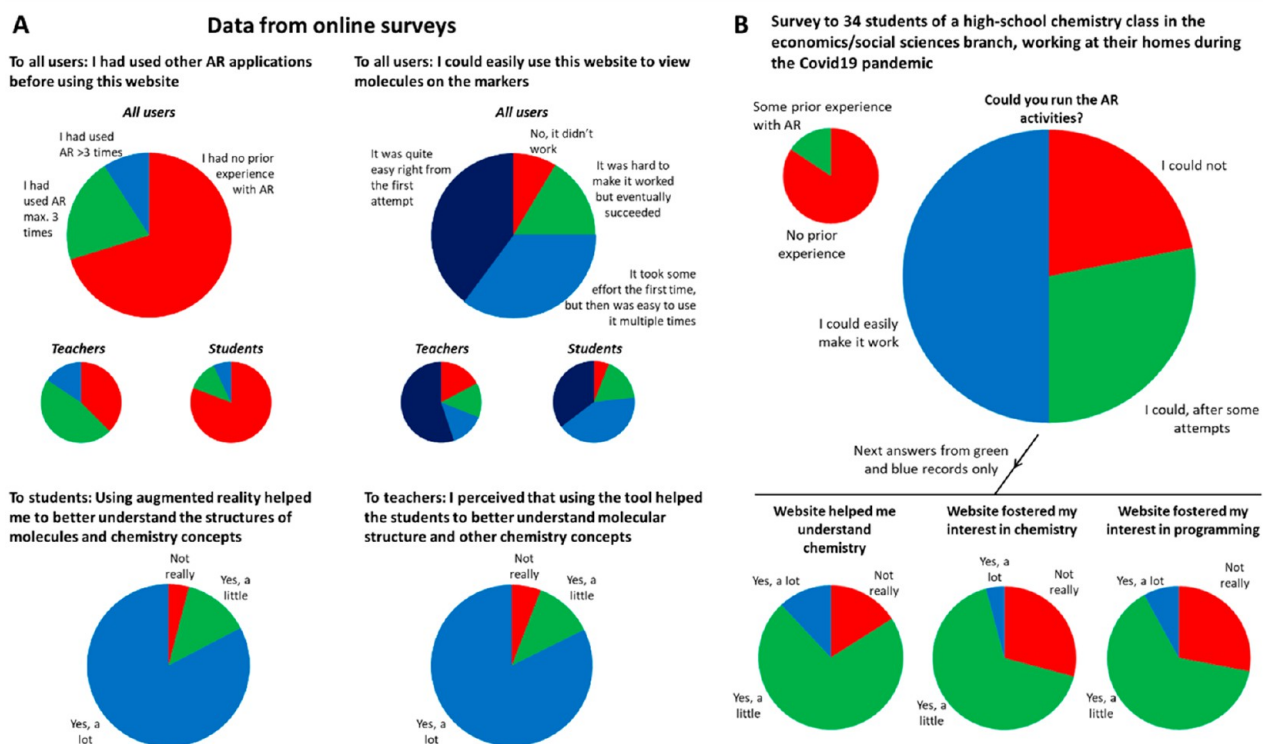
Figure 8. User adoption and pedagogical effects. (A) Results of the optional surveys prompted by the web site, specific for students and educators, designed to quantify how easy it was for them to utilize the AR web apps and how useful they perceive the tool is for learning. The questions are accessible at https://molecularweb.epfl.ch/pages/feedback.html. (B) Survey results on a homogeneous set of 34 students attending the same chemistry class (14−15 years old, economics/social branch of their high-school) at the affiliation of M.R.

us thanking for the availability of the tools, asking questions and proposing several ideas, many of which are now implemented, and attesting utility in their classes. Example comments describing uses were a professor at the leveling entry course of a university who used the virtual modeling kit for the organic chemistry lectures, another professor who used the module on atomic orbitals and molecular shapes in first-year chemistry at the university, a high-school teacher introducing students to basic general chemistry, and the leader of a regional group of students training for the country's chemistry tournament. The free, open availability on the web and its suitability to at-home work during the Covid-19 pandemic were especially acknowledged. Web availability is always very appreciated because it facilitates the deployment and utilization of educational programs,[41−43] even more so if students are forced to study at home as during the Covid-19 pandemic.

On more personal quantitative experiences to evaluate educational impact, we also tested the web site on 34 students of a high-school chemistry class at the affiliation of M.R. As in the previous case, this offers a controlled group of students of similar age and background, here all between 14 and 15 years old and in the economics/social branch of their school. As homework carried out by the students at their homes due to the Covid-19 pandemic but before the release of the formal web site, i.e., on its preliminary version, they were told to visualize different molecules in the virtual modeling kit web app to identify the atoms and shapes around them. From surveys filled out individually by the students of this class (Figure 8B), we found that 78% of the students could effectively run the AR modeling by themselves at their homes. Of them, 73% perceived that the tool was somewhat useful to

their aim, 12% perceived that the tool was very helpful, and 15% indicated that they did not find it useful. Besides, 70% of those who could use the AR web site said that the web apps fostered interest in chemistry, and also 70% said it made them curious about the underlying programming. We in fact also asked these questions in the online surveys, revealing that the web site made 96% of the students gain interest in chemistry and 70% gain interest in the underlying programming (Figure S5C).

The different results between the group of anonymous online students and those from a controlled class is interesting: the former found that the web site helped them "a lot" (Figure 8A), whereas the latter found that it helped them "a little". It is important to note that the controlled group are chemistry students within the social branch of their high school, while the group of online users likely includes actual undergraduate students of chemistry-related careers, given their ages and the comments made by teachers.

Further completing quantitative tests in personal interactions, one of the web apps implemented in the web site (about the shapes of coordination chemistry compounds) consists in a web rewrite of a program by Martinez-Huang et al., which had already proven the pedagogical value in tests with 32 students of an early chemistry university course.[18]

We finally tested, qualitatively without surveys, the user engagement on students and on the general public during a science communication event at EPFL, during EPFL's visit to high schools and other Swiss universities during 2019, and in the 2019 course on Structural Inorganic Chemistry at the affiliation of G.F. and D.M.M. Participants seemed engaged and enthusiastic and definitely interested in trying the experiences. We observed very quick adaptation to the use of

the markers especially by kids, teenagers, and young adults but not much by elder people. Consistent with the interest fostered in the programming aspects observed among student users in the online surveys and in M.R.'s class, some teenagers were particularly interested in the source code behind the AR web apps, especially having realized that they could view and experiment with it directly in their computers.

In the science communication event for the general public at EPFL, each visitor of our stand toured individually through four AR web apps that covered increasingly complex subjects starting from electrostatic interactions between small molecules, then the role of these interactions in biology specifically in protein−DNA binding, then moving on to large assemblies like viruses, and finally to a quick game about how protein structures are determined experimentally, where they docked amino acids to an electron density cloud building up a short peptide. The last web app served as an introduction to a hands-on experiment at the next-door stand, where visitors crystallized lysozyme, looked at the crystals, and then were instructed about how electron densities are determined by X-ray diffraction at the next-door stand of the Protein Structure Facility, closing the demonstration on protein structure determination. Last, the Structural Inorganic Chemistry course taught by G.F. and D.M.M. employed mainly the web app about molecular orbitals, which helped students to inspect the small molecules studied in class in 3D to decide on the plausible reactions and geometries, acting as an extension of the standard on-paper exercises—unfortunately we could not collect statistics on this small group of eight students.

■ METHODS

The MoleculARweb site is based entirely in client-side programming, i.e., technologies for programming dynamic content into web pages, essentially HTML5, CSS, and JavaScript. As such it can be easily copied for reuse from alternative locations and even adapted to run locally instead of online. All code and 3D objects can be consulted and downloaded directly from the web site and at GitHub: https://github.com/fcor/molecular-mirror-app, also backed up at Zenodo (DOI: 10.5281/zenodo.4545690).

Briefly, moleculARweb uses free, open JavaScript implementations of computer vision and graphics libraries to detect the fiducial AR markers printed on regular paper with a standard printer through the webcam and to overlay on top of the markers the atoms, molecules, or other virtual objects needed to render each experience.[19]

Key to the development of MoleculARweb are A-Frame, AR.js, Three.js, jsartoolkit, Cannon.js, and ModelViewer among other libraries, using the methods and technologies described in ref 19. Briefly, A-Frame, AR.js, Three.js, and jsartoolkit were used to build marker-based AR experiences; visualizations standing on flat surfaces were achieved using the ModelViewer web component; and interactivity was handled through *ad hoc* JavaScript code that can be consulted directly from the source code of the web pages. Molecular motions in the virtual molecular modeling kit were handled by the Cannon.js library for rigid-body physics; more specifically, atoms are represented by hard spheres of radii proportional to atomic radii, pairs of atoms within bonding distance are kept at a fixed distance with a strong Cannon constraint, pairs of atoms bonded to the same atom are weakly constrained to the starting distances to maintain angles, and pairs of atoms

bonded to pairs of bonded sp^2 carbons are also constrained to hamper rotations around double C—C bonds.

The 3D objects representing small molecules are built on-the-fly using 3D graphics primitives, while complex 3D objects were exported from VMD (structures, electron maps, orbitals, etc.) or Orbital Viewer version 1.04 (atomic orbitals) and edited as required with Blender. To compute molecular orbitals, the small molecules were built with Molden[44] and then optimized and molecular orbitals were calculated at the HF/STO-3G level with the Gaussian 09 package. Optimized structures and molecular orbitals were rendered in VMD.[45]

■ CLOSING REMARKS

We introduced MoleculARweb with a large set of interactive pedagogical AR web apps for chemistry and structural biology education in a fully web interface accessible for free without registration and in six languages. With these web apps, teachers and science communicators can introduce more interactive ways to communicate knowledge and create engaging activities for students to explore chemistry interactively, as in other software-adaptation articles.[46] We propose multiple ways to use the web site, most illustrated in the examples given throughout the article: (i) teaching students and the public in live presentations and (ii) in online lectures or science communication videos by streaming or recording the browser displays, in both cases with the educator handling the molecules; (iii) by instructing students themselves to explore the models with hand-held markers or even by employing markers inserted in the texts provided to them; and (iv) by setting up visualizations on flat surfaces like floors, tables, or workbenchs. We note that marker-based web apps are suitable for finely handling objects with hands and to trigger interactivity between pairs of objects in the interactive examples; besides, multiple independent users using the same AR marker seen through different devices will display the virtual objects from their respective locations, so they can be applied to collaborative work. On the contrary, models standing on flat surfaces are not locked to any marker, so the views cannot be shared by independent users, but it is more practical to look at very large models as users can easily move to inspect them from any angle and position, even getting inside of them as in the bacteriophage example in Figure 5A.

We strongly encourage educators to test the web site, implement it in their lessons both for direct teaching in person and in online classes, and also by setting students to work by themselves. We further invite educators to contact us to point out bugs, ask for questions and troubleshooting, and to propose new content. Finally, we encourage all users to answer the optional surveys that pop up with distinct questions for students and educators, as they will allow us to improve the web site and maintain it functional for the devices and browsers most widely used. Moreover, the information from the surveys will allow us to deepen the assessment about the utility and effects of webAR technologies on STEM education. The different qualitative and quantitative evaluations presented here support a positive pedagogical effect of AR in teaching and learning chemistry and pave the way for controlled studies at the large-scale approachable with such simple technology, although the exact protocol for such study is not trivial to devise. Furthermore, a study sustained over years could help to discern whether AR brings real, long-lasting engagement, interest and educational value, or it is rather the infatuation with innovative media that creates a motivation that may not

last, especially as future generations of students grow up surrounded by AR and VR media. This would also tell whether engagement and pedagogical effects come together or whether there is an intrinsic pedagogical effect of AR tools independent of the engagement they generate.

■ ASSOCIATED CONTENT

ⓈⒾ Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.1c00179.

Figures of Markers 1 and 2 for all activities except the virtual modeling kit, cube marker required for the Virtual Modeling Kit, end point of an activity, map of activity between May 29 of 2019 and January 31 of 2021, and results from online surveys and table of requirements and troubleshooting for developers and users (PDF, DOCX)

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Notes

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■ ACKNOWLEDGMENTS

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