The Journal of Chemical Physics

Bringing chemical structures to life with augmented reality, machine learning, and quantum chemistry

Cite as: J. Chem. Phys. **156**, 204801 (2022); https://doi.org/10.1063/5.0090482
Submitted: 07 March 2022 • Accepted: 04 May 2022 • Accepted Manuscript Online: 05 May 2022 • Published Online: 27 May 2022

Sukolsak Sakshuwong, Hayley Weir, Umberto Raucci, et al.

AIP Publishing

The Journal of Chemical Physics ARTICLE scitation.org/journal/jcp

Bringing chemical structures to life with augmented reality, machine learning, and quantum chemistry

Cite as: J. Chem. Phys. 156, 204801 (2022); doi: 10.1063/5.0090482
Submitted: 7 March 2022 • Accepted: 4 May 2022 •
Published Online: 27 May 2022

Sukolsak Sakshuwong,[1] Hayley Weir,[2,3] Umberto Raucci,[2,3,a)] and Todd J. Martínez[2,3,b)]

AFFILIATIONS

[1] Department of Management Science and Engineering, Stanford University, Stanford, California 94305, USA
[2] Stanford PULSE Institute, SLAC National Accelerator Laboratory, Menlo Park, California 94025, USA
[3] Department of Chemistry, Stanford University, Stanford, California 94305, USA

Note: This paper is part of the JCP Special Topic on Chemical Design by Artificial Intelligence.
[a)] **Present address:** Italian Institute of Technology, Genova GE, Italy.
[b)] **Author to whom correspondence should be addressed:** toddjmartinez@gmail.com

ABSTRACT

Visualizing 3D molecular structures is crucial to understanding and predicting their chemical behavior. However, static 2D hand-drawn skeletal structures remain the preferred method of chemical communication. Here, we combine cutting-edge technologies in augmented reality (AR), machine learning, and computational chemistry to develop MolAR, an open-source mobile application for visualizing molecules in AR directly from their hand-drawn chemical structures. Users can also visualize any molecule or protein directly from its name or protein data bank ID and compute chemical properties in real time via quantum chemistry cloud computing. MolAR provides an easily accessible platform for the scientific community to visualize and interact with 3D molecular structures in an immersive and engaging way.

INTRODUCTION

In 1953, James Watson and Francis Crick proposed the double-helix model as the three-dimensional structure of DNA. They assembled a structure using a set of cardboard cutouts representing the different chemical components.[1] Although quite rudimentary, this visualization tool allowed them to observe how the complementary base pairs fit together to form the structure of a double helix.

This example showcases the importance of visualizing the 3D spatial arrangement of molecules in understanding their chemical behavior. Since Watson and Crick's discovery, 3D visualization tools have made giant strides driven by technological advances. Soon, chemistry modeling kits were widespread in schools and laboratories; this allowed chemists to build molecules with spheres and sticks (see the bond angles and molecular shape and feel which bonds can bend or twist).[2] Nevertheless, building a molecule from scratch during a short lecture can be impractical, while building a biomolecule requires specialized skills. The emergence of graphical modeling software allowed scientists to image and interact with the 3D arrangement of atoms within molecules.[3] Visualization of dynamic trajectories offered a further advance, allowing the evolution of chemical mechanisms to be observed at an atomistic level.

The growing development of extended reality technologies promises a new era for highly immersive molecular visualization.[4] Augmented reality (AR), which superimposes computer-generated content onto real-world scenes, has become popular in a wide range of applications. It is now supported by most smartphones and tablets and soon will be supported natively in web browsers.[5] Chemistry students and researchers can also benefit from the realistic and immersive nature of this tool to visualize 3D molecular structures and their chemical properties.[6,7]

Recently, a number of applications have been developed for viewing molecules in AR,[8–18] primarily for chemical education, and a comprehensive overview of the latest applications has been provided.[19] Currently, some of these applications require the use of fiducial markers, such as QR code or specific patterns printed on a card, in order to place the 3D model and track its location[6,20–28] or

the use of specialized hardware, such as AR glasses or head-mounted displays.[29–32] Others require the 3D model files of the molecules to be created and pre-loaded into the app prior to the recognition, thus limiting the generalizability of the tools.[16] Coster developed an app that can recognize a limited number of chemical structures on which it had been previously trained.[33] MoleculARweb[17] offers a web-based app that can display the chemical structure of a built molecule in AR, whereas Mo-Cubed[34] allows users to build molecular structures and compute their chemical properties via semiempirical calculations, but it cannot display them in AR. Other apps have been developed for protein visualization, for example, Sung *et al.* developed BiochemAR[12] to visualize and manipulate potassium channels, while CRISPR-3D allows some CRISPR-Cas models to be visualized in AR.[35]

Here, we combine cutting-edge technologies in machine learning, augmented reality, and computational chemistry to develop MolAR, a mobile application that allows molecules to be directly visualized in AR together with their electronic features from their hand-drawn structure. The app does not require the use of markers, printouts, or specialized hardware, and there is no need to prepare 3D model files or pre-register molecules. Molecules can be input from their common/IUPAC name, SMILES string, protein data bank (PDB) ID or directly from a picture of their chemical structure. Indeed, skeletal chemical structures continue to be the primary language for chemical communication due to their simple and intuitive nature. Once a molecule is displayed, its chemical properties, such as frontier molecular orbitals and dipole moment, can be calculated and visualized in real time. The combination of these technologies allows chemists to visualize and interact with molecules and their properties in a uniquely immersive and user-friendly way, taking a further step toward the modernization of scientific education.

RESULTS AND DISCUSSION

MolAR is an iOS open source application that can be downloaded for free from Apple's App Store.[36] Figure 1 outlines the main functionality of the app, showing the structure and object recognition, connection to public databases for protein and molecule visualization, and calculation of quantum mechanical properties. In the following, we outline each of the app's functionalities and their significance in research and educational settings.

Building upon the field of optical chemical structure recognition, we recently developed ChemPix, a software package to recognize hand-drawn hydrocarbon structures using deep learning.[37] The algorithm handles structures with wobbly lines, gaps, uneven bond angles, background noise, and shadows. More recently, Mathpix released a hand-drawn chemical structure recognition tool that can digitize molecules with heteroatoms.[38] MolAR employs Mathpix, allowing users to photograph a chemical structure on a piece of paper or a whiteboard and bring it to life in AR. The 3D molecule appears above the structure, and users can perform the pinch gesture on the phone to scale it up or down or use touch and drag to rotate and translate the model. This allows users, for example, to take a picture of a 2D chemical structure in the textbook they are reading and visualize it as a 3D model in a matter of seconds. Chemical structures can also be drawn

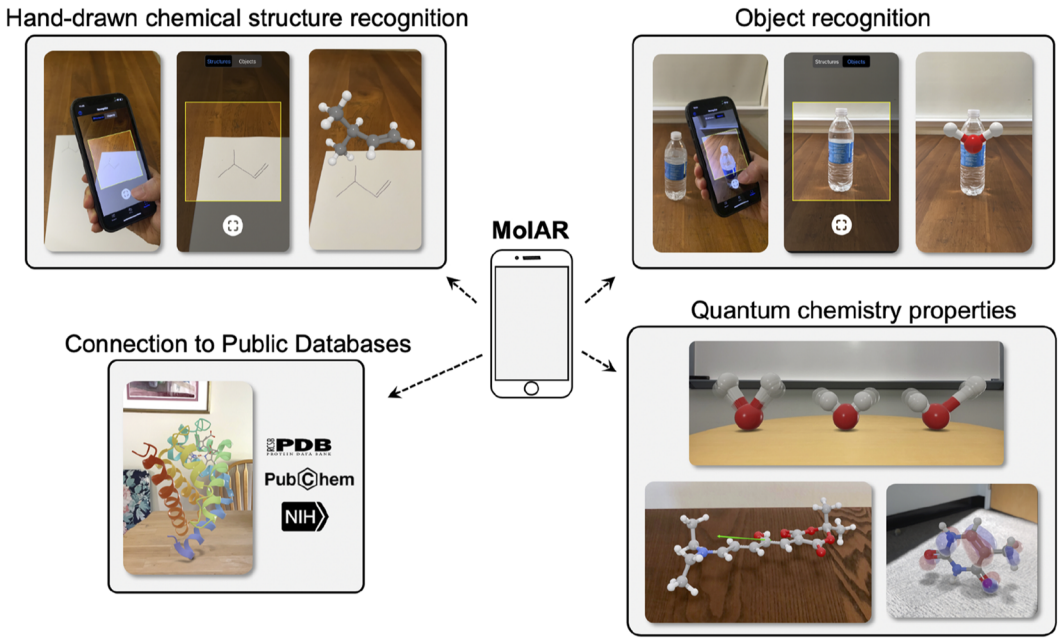

FIG. 1. Outline of MolAR functionalities, including hand-drawn chemical structure recognition, recognition of molecules in objects, visualization of molecules and biomolecules from public databases, visualization of vibrational normal modes of select molecules, and calculation of electronic properties (including dipole moment and molecular orbitals). See the app in action at https://youtu.be/bLqkzz1vZL4.

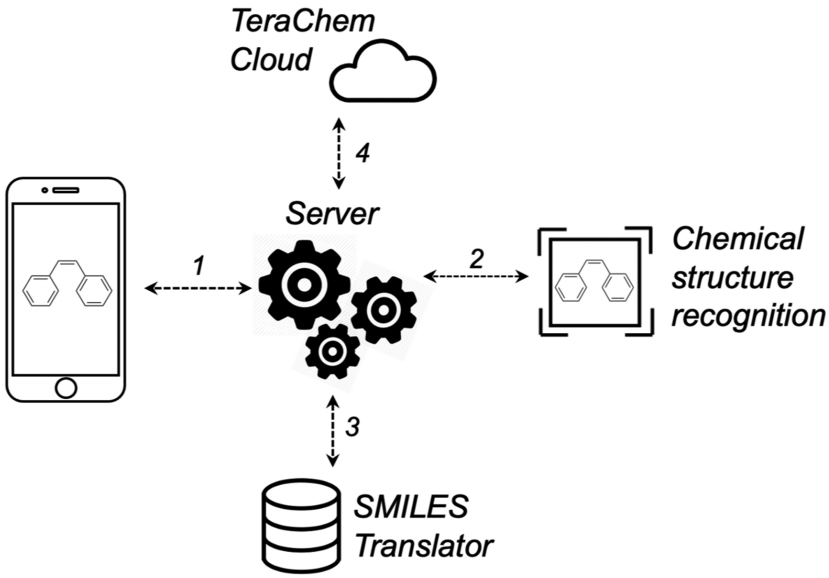

FIG. 2. The MolAR workflow for transforming a hand-drawn chemical structure into a 3D AR model. (1) The app sends the image of the structure to the server, which then (2) feeds the image to Mathpix[38] to predict the SMILES representation. (3) The SMILES is sent to the Online SMILES Translator by the National Cancer Institute to obtain the SDF data. (4) If requested, the server sends the SDF to TeraChem Cloud[39] to compute its chemical properties. Finally, the server returns the SDF and calculation results to the app.

directly in the app for instances when pen and paper are not handy (Fig. S1).

Users also have the option to "hunt" for molecules in common household objects. Objects are mapped to a characteristic molecule responsible for its flavor, color, or smell. For example, when users take a picture of coffee, the 3D model of caffeine appears above it. This can serve to gamify the app, allowing interested users to grasp that objects in the real world are composed of molecules that determine their properties. The feature is designed to develop their scientific curiosity by actively learning about chemicals in a fun and engaging way.

Furthermore, users can view in AR any molecule on PubChem by typing its name or SMILES and any of the 180 000 + proteins and biomolecules in the Protein Data Bank by entering its PDB ID. The immersive interaction with a 3D life-size protein offers a unique way to inspect the structural elements, the active site, and the solvent accessible channels, helping us to unveil the complex structure–function relationships occurring in large biomolecules. In addition to research applications, making visualization of molecule and protein structures accessible to the general public could aid in effectively communicating scientific viewpoints. To help users who are unfamiliar with chemical structures learn about molecules, the app also has a gallery section where users can browse molecules and proteins of interest and visualize them in AR (Fig. S1).

In addition to structural visualization, MolAR allows users to compute and visualize a selection of electronic properties arising from a particular molecular arrangement. Those can be computed in real time through quantum mechanical calculations on TeraChem Cloud, a cloud-based, graphical processing unit (GPU) accelerated electronic structure package.[39] This allows users to visualize the frontier orbitals and the dipole moment vector for the chosen molecule in a matter of seconds. The ability to readily visualize molecular orbitals in AR directly from a hand-drawn structure is a powerful learning tool, particularly when teaching molecular orbital theory. It is also useful in a research context when trying to understand the electronic properties of a molecule and how it will interact with light. Additionally, MolAR allows users to visualize vibrational normal modes for a selection of molecules of educational interest. Through this feature, users can learn about vibrational motion by watching atoms animating in a real-world scene. Students can become familiar with the symmetry features of the vibrational modes, for example, distinguishing between symmetric and asymmetric stretching or understanding motions that induce a change in dipole in the context of spectroscopy. Most importantly, it helps students to understand that molecules are not static but dynamic, three-dimensional objects.

The MolAR workflow is summarized in Fig. 2. When the user takes a picture of a chemical structure, the app starts tracking the position of the structure so that it can place the model there later. The picture is sent to a server that feeds the image to Mathpix[38] to predict the SMILES representation of the structure. The server then sends the SMILES to the National Cancer Institute's Online SMILES Translator to obtain an SDF file with the molecular structure.[40] The server returns the SDF to the app. Finally, the app converts the SDF to a USDZ file, a format for AR models on iOS devices, and places the molecular structure above the hand-drawn image. If the user goes on to request computational chemistry properties, the SDF is sent to TeraChem Cloud[39] that returns the requested properties. An equivalent workflow is used for object recognition. Further technical details are provided in the Methods section and the supplementary material.

CONCLUSIONS AND OUTLOOK

In conclusion, we developed MolAR, a mobile application that employs augmented reality, computational chemistry, and machine learning to transform images of hand-drawn chemical structures into 3D molecules in AR and compute their quantum mechanical

properties. It does not require specialized hardware or even a desktop computer/laptop, making it easily accessible and convenient for users. MolAR is an immersive training application to help students master mental visualization of the 3D structures of molecules. In addition, it provides researchers a platform for barrierless visualization of protein structures and analysis of molecular properties to aid in the understanding of chemical behavior.

The app serves as a building block that can be directly connected to a whole host of additional tools. In the future, we plan to incorporate dynamic motion, chemical reactions, and computation of more quantum mechanical properties, such as the excitation energy. We also plan to link MolAR to our recently reported ChemVox application that performs voice-activated quantum chemistry.[41]

Overall, MolAR is the latest example of how technological progress can enhance scientific research and education, offering another valuable tool in the scientist's current arsenal.

METHODS

The MolAR app is written using the Swift programming language and Apple's iOS SDK, a software development kit for iPhone and iPad. It uses ARKit,[42] part of the iOS SDK, to implement augmented reality. ARKit has features for AR, such as device motion tracking and scene processing. The app communicates with a web server whose main functionality is to recognize objects or chemical structures in an image. The server is written in Node.js. We describe the method in detail below.

AR tracking

When the user takes a picture of an object or a chemical structure, the app places a virtual anchor at the target. The virtual anchor allows the app to track the location of the target as the user moves while the app is processing the picture. Once the app receives the 3D structure from the server, the app places it at the anchor.

Image to SMILES

The server feeds the image it receives to Mathpix[38] to predict the SMILES representation.

SMILES to SDF

We use the Online SMILES Translator by the National Cancer Institute to convert SMILES to SDF. The SDF data of a molecule contain the 3D coordinates of each atom in the molecule and the type of the bond between pairs of atoms.

SDF to geometric primitives

In this step, atoms and bonds in the SDF data are converted to spheres and cylinders. Atoms are represented by spheres, colored according to the CPK coloring scheme and sized according to a scaled van der Waals radius. Bonds are represented by cylinders, colored according to the atoms they connect.

Geometric primitives to USDZ

USDZ is a file format created by Pixar for interchange of 3D models.[43] iOS has a built-in viewer that can show USDZ files in AR. The app generates USDZ files from geometric primitives according to the file format specification. We choose to generate USDZ files on the device rather than on the server because the USDZ file size is much larger than that of the geometric primitives.

Visualizing molecular vibrations

The USDZ file format supports keyframe animations. Each geometric object can be translated, rotated, or scaled by specifying the transformation matrices at different points in time. To visualize molecular vibrations, we animate atoms and bonds separately. The sphere for each atom is translated according to its trajectory. The cylinder for each bond is translated, rotated, and scaled to maintain the connection between the atoms.

Visualizing proteins

When visualizing a protein, the app fetches the CIF data from the Protein Data Bank and then uses Mol*,[44] an open-source macromolecular toolkit, to generate 3D coordinates of the protein. We use the cartoon representation for small or medium proteins and the Gaussian surface representation for large proteins to improve the display performance.

Object recognition

The workflow for object recognition is similar to that of Image-to-SMILES described above. When the user takes a picture of an object, the app also sends the picture to the server. The server uses *Google Cloud Vision API* and *Amazon Rekognition* for object detection.[45,46] We have developed a database that maps common objects to molecules, for example, coffee is mapped to caffeine and carrots are mapped to carotene (Table S1). The server then sends the chemical name of a representative molecule of the photographed object to the app. As in the hand-drawn chemical structure workflow, the app tracks the object during the computation and renders the 3D chemical structure above it.

Quantum chemistry calculation

The electronic structure calculations were performed using TeraChem Cloud[39] with a PBE0/3-21G level of theory in the gas phase.

SUPPLEMENTARY MATERIAL

See the supplementary material for implementation details.

ACKNOWLEDGMENTS

This work was supported by the Office of Naval Research (Grant Nos. N00014-18-1-2659 and N00014-18-1-2624).

AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

DATA AVAILABILITY

The MolAR program can be downloaded from the Apple App Store. The source code of MolAR can be found at https://github.com/mtzgroup/molar.

REFERENCES

[1] L. Pray, "Discovery of DNA structure and function: Watson and Crick," Nat. Educ. **1**, 100 (2008), available at https://www.nature.com/scitable/topicpage/discovery-of-dna-structure-and-function-watson-397/.

[2] E. Francoeur, "The forgotten tool: The design and use of molecular models," Soc. Stud. Sci. **27**, 7–40 (1997).

[3] A. J. Olson, "Perspectives on structural molecular biology visualization: From past to present," J. Mol. Biol. **430**, 3997–4012 (2018).

[4] R. Skibba, "Virtual reality comes of age," Nature **553**, 402–404 (2018).

[5] F. C. Rodríguez, M. Dal Peraro, and L. A. Abriata, "Democratizing interactive, immersive experiences for science education with WebXR," Nat. Comput. Sci. **1**, 631–632 (2021).

[6] S. Singhal, S. Bagga, P. Goyal, and V. Saxena, "Augmented chemistry: Interactive education system," Int. J. Comput. Appl. **49**, 1 (2012).

[7] H.-K. Wu, S. W.-Y. Lee, H.-Y. Chang, and J.-C. Liang, "Current status, opportunities and challenges of augmented reality in education," Comput. Educ. **62**, 41–49 (2013).

[8] H. S. Fernandes, N. M. F. S. A. Cerqueira, and S. F. Sousa, "Developing and using BioSIM^{AR}, an augmented reality program to visualize and learn about chemical structures in a virtual environment on any internet-connected device," J. Chem. Educ. **98**, 1789–1794 (2021).

[9] J. R. Schmid, M. J. Ernst, and G. Thiele, "Structural chemistry 2.0: Combining augmented reality and 3D online models," J. Chem. Educ. **97**, 4515–4519 (2020).

[10] K. Eriksen, B. E. Nielsen, and M. Pittelkow, "Visualizing 3D molecular structures using an augmented reality app," J. Chem. Educ. **97**, 1487–1490 (2020).

[11] S. Yang, B. Mei, and X. Yue, "Mobile augmented reality assisted chemical education: Insights from elements 4D," J. Chem. Educ. **95**, 1060–1062 (2018).

[12] R.-J. Sung, A. T. Wilson, S. M. Lo, L. M. Crowl, J. Nardi, K. St. Clair, and J. M. Liu, "BiochemAR: An augmented reality educational tool for teaching macromolecular structure and function," J. Chem. Educ. **97**, 147–153 (2020).

[13] P. Wolle, M. P. Müller, and D. Rauh, "Augmented reality in scientific publications—Taking the visualization of 3D structures to the next level," ACS Chem. Biol. **13**, 496–499 (2018).

[14] J. M. Argüello and R. E. Dempski, "Fast, simple, student generated augmented reality approach for protein visualization in the classroom and home study," J. Chem. Educ. **97**, 2327–2331 (2020).

[15] J. K. Aw, K. C. Boellaard, T. K. Tan, J. Yap, Y. P. Loh, B. Colasson, É. Blanc, Y. Lam, and F. M. Fung, "Interacting with three-dimensional molecular structures using an augmented reality mobile app," J. Chem. Educ. **97**, 3877–3881 (2020).

[16] B. Sanii, "Creating augmented reality USDZ files to visualize 3D objects on student phones in the classroom," J. Chem. Educ. **97**, 253–257 (2020).

[17] F. C. Rodríguez, G. Frattini, L. F. Krapp, H. Martinez-Hung, D. M. Moreno, M. Roldán, J. Salomón, L. Stemkoski, S. Traeger, M. Dal Peraro, and L. A. Abriata, "MoleculARweb: A web site for chemistry and structural biology education through interactive augmented reality out of the box in commodity devices," J. Chem. Educ. **98**, 2243–2255 (2021).

[18] J. D. Hirst, D. R. Glowacki, and M. Baaden, "Molecular simulations and visualization: Introduction and overview," Faraday Discuss. **169**, 9–22 (2014).

[19] Z. A. Jiménez, "Teaching and learning chemistry via augmented and immersive virtual reality," in *Technology Integration in Chemistry Education and Research (TICER)* (American Chemical Society, 2019), Vol. 1318, pp. 31–52.

[20] S. Cai, X. Wang, and F.-K. Chiang, "A case study of augmented reality simulation system application in a chemistry course," Comput. Human Behav. **37**, 31–40 (2014).

[21] M. Chen and B. Liao, "Augmented reality laboratory for high school electrochemistry course," in *2015 IEEE 15th International Conference on Advanced Learning Technologies, 6–9 July 2015* (IEEE, 2015), pp. 132–136.

[22] H. Hou and Y. Lin, "The development and evaluation of an educational game integrated with augmented reality and virtual laboratory for chemistry experiment learning," in *2017 6th IIAI International Congress on Advanced Applied Informatics (IIAI-AAI), 9–13 July 2017* (IEEE, 2017), pp. 1005–1006.

[23] D. D. Iordache, C. Pribeanu, and A. Balog, "Influence of specific AR capabilities on the learning effectiveness and efficiency," Stud. Inf. Control **21**, 233–240 (2012).

[24] K. L. Narasimha Swamy, P. S. Chavan, and S. Murthy, "StereoChem: Augmented reality 3D molecular model visualization app for teaching and learning stereochemistry," in *2018 IEEE 18th International Conference on Advanced Learning Technologies (ICALT), 9–13 July 2018* (IEEE, 2018), pp. 252–256.

[25] P. Maier and G. Klinker, "Augmented chemical reactions: An augmented reality tool to support chemistry teaching," in *2013 2nd Experiment@ International Conference (exp.At'13), 18–20 September 2013* (IEEE, 2013), pp. 164–165.

[26] A. Nachairit and N. Srisawasdi, "Using mobile augmented reality for chemistry learning of acid-base titration: Correlation between motivation and perception," in *Proceedings of the 23rd International Conference on Computers in Education* (Asia-Pacific Society for Computers in Education, Hangzhou, 2015), pp. 519–528.

[27] K. N. Plunkett, "A simple and practical method for incorporating augmented reality into the classroom and laboratory," J. Chem. Educ. **96**, 2628–2631 (2019).

[28] L. M. M. S. A. Qassem, H. A. Hawai, S. AlShehhi, M. J. Zemerly, and J. W. P. Ng, "AIR-EDUTECH: Augmented immersive reality (AIR) technology for high school chemistry education," in *2016 IEEE Global Engineering Education Conference (EDUCON), 10–13 April 2016* (IEEE, 2016), pp. 842–847.

[29] C. N. Peterson, S. Z. Tavana, O. P. Akinleye, W. H. Johnson, and M. B. Berkmen, "An idea to explore: Use of augmented reality for teaching three-dimensional biomolecular structures," Biochem. Mol. Biol. Educ. **48**, 276–282 (2020).

[30] M. Uselton, "MoleculAR geometry: Chemical visualizations in augmented reality," Honors College of Middle Tennessee State University, 2020.

[31] M. Zheng and M. P. Waller, "ChemPreview: An augmented reality-based molecular interface," J. Mol. Graphics Modell. **73**, 18–23 (2017).

[32] B. Zhu, M. Feng, H. Lowe, J. Kesselman, L. Harrison, and R. E. Dempski, "Increasing enthusiasm and enhancing learning for biochemistry-laboratory safety with an augmented-reality program," J. Chem. Educ. **95**, 1747–1754 (2018).

[33] M. Coster, "MoleculAR: An augmented reality app for organic chemistry," https://organicchemexplained.com/molecular-augmented-reality-app/; accessed 24 November 2021.

[34] See https://play.google.com/store/apps/details?id=club.amase.mocubed for MO-cubed.

[35] CRISPR-3D. See https://innovativegenomics.org/crispr-3d

[36] See https://apps.apple.com/us/app/molar-augmented-reality/id1559504847 to download the MolAR app for iOS devices; accessed 24 November 2021.

[37] H. Weir, K. Thompson, A. Woodward, B. Choi, A. Braun, and T. J. Martínez, "ChemPix: Automated recognition of hand-drawn hydrocarbon structures using deep learning," Chem. Sci. **12**, 10622–10633 (2021).

[38] K. Cunningham, "Convert printed and handwritten chemical diagrams to SMILES," https://mathpix.com/blog/handwritten-chem-diagrams; accessed 24 November 2021.

[39] S. Seritan, K. Thompson, and T. J. Martínez, "TeraChem cloud: A high-performance computing service for scalable distributed GPU-accelerated electronic structure calculations," J. Chem. Inf. Model. **60**, 2126–2137 (2020).

[40]National Cancer Institute, Online SMILES Translator, https://cactus.nci.nih.gov/translate/index.html; accessed 16 August 2021.
[41]U. Raucci, A. Valentini, E. Pieri, H. Weir, S. Seritan, and T. J. Martínez, "Voice-controlled quantum chemistry," Nat. Comput. Sci. **1**, 42–45 (2021).
[42]Apple ARKit, https://developer.apple.com/documentation/arkit; accessed 16 August 2021.
[43]Pixar Animation Studios, Introduction to USD, https://graphics.pixar.com/usd/docs/Introduction-to-USD.html; accessed 16 August 2021.
[44]D. Sehnal, S. Bittrich, M. Deshpande, R. Svobodová, K. Berka, V. Bazgier, S. Velankar, S. K. Burley, J. Koča, and A. S. Rose, "Mol* viewer: Modern web app for 3D visualization and analysis of large biomolecular structures," Nucleic Acids Res. **49**, W431–W437 (2021).
[45]Amazon Web Services. Detecting labels, https://docs.aws.amazon.com/rekognition/latest/dg/labels.html; accessed 16 August 2021.
[46]Google,Detect Labels, https://cloud.google.com/vision/docs/labels; accessed 16 August 2021.