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Technology Report

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

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ABSTRACT: Visualization can be a motivating way to teach students about molecules. Nowadays, the available experimental data and accurate computational results allow students to build realistic and accurate molecular models. These models include the representation of complex systems such as proteins, membranes, or nanotubes. However, the visualization of these three-dimensional (3D) structures can be challenging, complex, or even abstract for most people. To make the visualization easier and more motivating, BioSIM Augmented Reality (BioSIM^{AR}) was developed as a free online software program to provide a new way to visualize and interact with 3D molecular models in a virtual environment. Using augmented reality (AR) and quick response code technologies, BioSIM^{AR} provides tangible models of molecules to help illustrate chemical concepts. BioSIM^{AR} runs on any electronic device, including mobile phones, tablets, laptops, or desktop computers with a camera and an internet connection, without requiring the installation of additional software. This software program helps people visualize and understand concepts about atoms and molecules, and their characteristics. BioSIM^{AR} is freely available at https://ar.biosim.pt/.

KEYWORDS: *General Public, Elementary/Middle School Science, High School/Introductory Chemistry, First-Year Undergraduate/General, Demonstrations, Computer-Based Learning, Distance Learning/Self Instruction, Hands-On Learning/Manipulatives, Inquiry-Based/Discovery Learning, Molecular Properties/Structure*

Learning chemistry involves, to a very significant extent, understanding the relationship between the properties of molecules and their three-dimensional (3D) structure.[1,2] The molecular structure is dependent on the atoms that are present in the molecule, their spatial rearrangement, and how the atoms are connected to each other.

A large set of molecular properties are a consequence or are related to the 3D arrangement of their atoms, including the melting and boiling temperatures, density, solubility, stability, and type of reaction in which the molecule can participate. Concepts such as stereoisomerism, chirality, chemical bonding, hybridization, molecular symmetry, intra- and intermolecular interactions, and conformational stability also require a good perception of the 3D shape of molecules.[3−5] For these reasons, an important share of many chemical courses involves developing in the student the ability to see, think, and relate the structures of molecules with their properties.[1,2] Usually, this is not an easy task.

Through the years, a variety of alternatives to ease this process has been developed, implemented, and used with success. Notable examples include the Fisher projection for general organic chemistry,[6] the Haworth projection[7] for monosaccharides and cyclic molecules, the Newman projections for alkane stereochemistry,[7,8] and the popular wedge-and-dash notation[8] and Natta projection. These two-dimensional representation schemes try to capture part of the 3D structural features of the molecules. They are quite effective in introducing concepts but are not always intuitive to the mind of the student.[9−15] Furthermore, these representations are normally limited to specific sets of molecules of limited size.

Physical molecular models have traditionally played an important role in developing in students an intuitive understanding of the molecular structure and associated concepts. However, the need for acquisition and/or assembly of the models or building blocks also makes them of limited applicability.[16,17]

A wide range of software applications has been developed to make the visualization of these molecular models easier, such as Avogadro,[18,19] Molekel,[20] Molden,[21] Rasmol,[22,23] VMD,[24] PyMOL,[25] and Chimera,[26] among many others. Today, with the current computational power behind any personal computer, these molecular models can be visually inspected in an intuitive manner. What needs to be improved is how the users interact with them and how users can extract useful information from them. This is important for students and teachers in high school, at universities, or in more advanced

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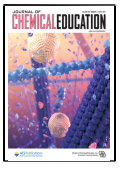

programs, but also for scientists that require this sort of information to perform their research.

The interaction with the molecular models is essential to overcome difficulties associated with the terms and concepts related to the 3D structure of molecules. Several studies have already made conclusions about the advantages of using molecular models when teaching molecular structure.[27−29] For example, 3D printing models can be used to generate real molecular models that can be handled by hand. However, the models are not perfect, are difficult to build, are expensive, and are static.[16,17] Even though 3D printing is becoming cheaper and accessible to the general consumer, it is not as ubiquitous as a smartphone. In 2018, 1.42 million 3D printers were sold worldwide,[30] about 1000 times less than the number of smartphones (1,556.27 million).[31]

Virtual reality devices are glasses that provide an immersive 3D experience, allowing a close interaction between the users and the 3D models. Some devices, e.g., Oculus Rift, PlayStation VR, and HTC Vive, can cost hundreds of dollars and require complex adjustments to work properly on each setup. Regardless, some related approaches have been described in the literature.[32−36] In spite of the number of features available through this kind of approach, they are considerably more expensive and are difficult to operate for nonexpert users. Additionally, they are definitely far from reaching the classrooms of most students and teachers.

Augmented reality (AR) has also been used to provide 3D models of molecules.[10,29,37−39] This approach is considerably cheaper, but usually, it relies on the installation of specific software that sometimes has compatibility issues or may require special graphical resources that are often not available. BiochemAR[40] is an example of a recent AR software program for molecular representation. However, so far it is limited to compatible iOS and Android devices, making it incompatible with computers and non-iOS and non-Android devices. In addition, BiochemAR presently only holds a potassium channel structure available, providing no way to compare multiple structures or ask for more structures to be included. Similarly, MoleculAR[10] was also developed and published as a framework to create and use AR applications for chemistry teaching. However, the application is presently only available for Android devices, and it involves a time-demanding process to prepare the application and make it suitable for use with students in classes. Augmented Chemical Reactions[41] is another AR software program for molecular visualization using AR technology, but currently, it lacks support for different devices, since it only works on computers running Windows. The main advantage of BioSIM^{AR} over these similar applications is the simplicity in starting to use it, since no software installation is required, and even low-budget devices can handle it.

In this paper, the BioSIM Augmented Reality (BioSIM^{AR}) application is presented. This open-source application was developed with the aim of providing an interactive platform to explore a molecular model in a versatile, powerful, and easy to set up technology (Figure 1).

This technology just requires a laptop, a tablet, a smartphone, or a similar device with an integrated camera and an internet connection. No software installation is required. Users only need to download, free of charge, a set of 2D custom cards (Figure 2) that include a specific pattern. When this pattern is recognized by the device's camera, it will provide a 3D image of the molecular model instantaneously.

Figure 1. Three-dimensional representation of the structure of a DNA sequence in augmented reality using BioSIM^{AR}.

Figure 2. Example of a printed card showing the pattern code to observe the 3D structure of an RNA molecule using BioSIM^{AR}.

The rotation of the molecular model is possible at any angle, as long as the camera can detect the code. This allows the users to overcome one of the major difficulties in seeing and analyzing molecular models in computers: the users can interact with it as a real object and not in a less intuitive way that is commonly used through the use of a mouse and a computer screen.

BioSIM^{AR} is available free of charge at https://ar.biosim.pt.

MATERIALS

Development

The development of BioSIM^{AR} kept its application in the classroom of science-related subjects in mind. Therefore, BioSIM^{AR} was coded to run directly on every device with a camera, an internet connection, and a web browser. The restrictions regarding the type of device or operating system are waived by the approach assumed in the development of this software.

Regarding the internet connection requirement, BioSIM^{AR} was developed to avoid possible bad performance in poor-quality connections. When the web page is accessed, all of the required data is downloaded (about 50 MB) and stored in the browser's cache. Then, the camera becomes active, and the users can interact with the cards. From this moment, all the

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visualization and interaction occur locally in the user's device. This strategy ensures the best possible performance independent of internet connection quality. Therefore, the internet connection only affects the loading time with no impact on subsequent usage. The structure files are also kept in the browser's cache for a month, avoiding repetitive downloads for each time that page is reloaded during that time range.

From our experience in teaching in classes and workshops, ease of use is essential to make a particular technology useful and applicable in the classroom context. If a specific educational asset is too difficult or time-demanding to be prepared, teachers usually avoid their use due to the scarcity of time.[42,43] Consequently, the compatibility with most of the devices is also an important aspect to avoid issues and delays using BioSIM^{AR}. Therefore, BioSIM^{AR} was tested in the top 6 most used web browsers (Google Chrome, Safari, Mozilla Firefox, Samsung Internet, Edge, and Opera), representing more than 95% of the total market share.[44] The tests were conducted using Android, iOS, Microsoft Windows, and macOS operating systems. According to those tests, Samsung Browser for Android showed poor performance when used in portrait mode since the camera image did not fit properly on the screen. Table 1 summarizes all of the compatible tests conducted, showing that BioSIM^{AR} is fully compatible with all main operating systems and web browsers.

As shown, BioSIM^{AR} is compatible with a panoply of different combinations of operating systems and web browsers. The compatibility of BioSIM^{AR} with so many different platforms reduces the possibility of issues during its usage.

Table 1. Compatibility Analysis for BioSIM^{AR} Running in the Different Web Browsers and Operating Systems

Operating System (OS)	OS Version	Web Browser	Web Browser Version	Compatibility
Android	8.0.0	Edge	45.11.2.5118	Full
		Google Chrome	87.0.4280.101	Full
		Mozilla Firefox	82.1.3	Full
		Opera	61.1.3076.56625	Full
		Samsung Browser	13.0.2.9	Bad performance (portrait)
iOS/iPadOS	14.3	Edge	45.11.11	Full
		Google Chrome	87.0.4280.77	Full
		Mozilla Firefox	29.2	Full
		Opera	2.5.3	Full
		Safari	14	Full
Microsoft Windows	10	Edge	87.0664.60	Full
		Google Chrome	87.04280.88	Full
		Mozilla Firefox	84.0	Full
		Opera	73.0.3850.284	Full
macOS	11.1	Edge	87.0.664.60	Full
		Google Chrome	87.0.4280.88	Full
		Mozilla Firefox	84.0	Full
		Opera	73.0.3856.284	Full
		Safari	14.0.2	Full

BioSIM^{AR} was coded on the basis of two already available open-source projects: A-FRAME (https://aframe.io/) and AR.js (https://github.com/AR-js-org/AR.js). On the basis of those, BioSIM^{AR} was prepared to show 3D representations of molecules in an augmented reality interface (Figure 3). The

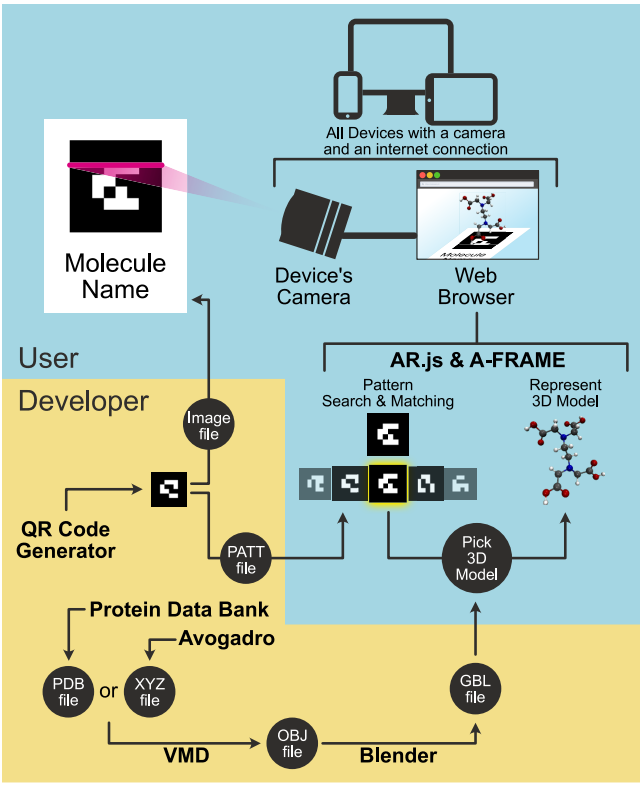

Figure 3. Overview of the workflow involved in the (yellow) development of BioSIM^{AR}, and the processes taken when users point their devices' cameras to a 2D pattern (blue).

interactivity was enhanced by using cards with the molecule's name and a bidimensional code (QR code) (Figure 2). The QR code on the card is recognized by the device's camera and integrated by the software to present the corresponding molecule. In addition, the pattern code provides spatial information about where the molecule must be placed in order to provide a real augmented reality experience. This particular feature allows users to rotate the card and/or the device's camera to inspect the shown molecule from different angles.

The molecules used in this project were obtained from the (Protein Data Bank) PDB repository[45] or manually drawn and optimized using Avogadro 1.2.0[18,19] (Figure 3). The resulting structures, saved as a PDB or an XYZ file, were loaded on VMD[24] in order to prepare their molecular representations. Then, the 3D model of each molecule was exported as a Wavefront OBJ file using the render option of VMD. Subsequently, each Wavefront OBJ file was imported on the 3D model software Blender 2.83.1.[46] Using Blender, the files were adjusted, and in some cases, additional tags were included, such as information about bond lengths, angle amplitudes, dihedral torsions, etc. Finally, a GBL file of the 3D model was exported using Blender. The GBL file contains all of the data required by BioSIM^{AR} to show each of the 3D molecular representations.

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For each molecule that is generated for BioSIM^{AR}, it is also required to design a 2D pattern that is used to identify the molecule. The QR codes were chosen because they provide a unique form to identify different types of data, and they can be easily generated online with tools like "QR Code Generator" (https://www.the-qrcode-generator.com/). Hence, a QR code was generated for each molecule on the basis of its name or internal identification code. Afterward, all of the QR codes were converted into a PATT file according to the AR.js requirements. In the end, three different files are available for each molecule: a GBL file containing the 3D structure of the molecule, a picture of the associated QR code, and a PATT file with the pattern associated with the molecule. In this way, when the device's camera identifies a pattern code, the code is compared with all the PATT patterns available on BioSIM^{AR}, and if it matches, the corresponding molecular representation is loaded from the GBL file and shown (Figure 3).

BioSIM^{AR} can be easily assessed from the following hyperlink (https://biosim.pt/AR/) that opens a webpage and requires access to the device's camera. At this point, users are capable of pointing the camera to one or more cards containing the pattern code. Automatically, the software will show the 3D representation of the molecule, and the users can interact with it. Regarding privacy, BioSIM does not receive or handle the images captured with the camera. The models and patterns are delivered to the browser, and all the processing and analyses occur on the device with no communication with the server. No data is collected apart from the page views statistics collected by Google Analytics.

At this moment, 70 different cards are available for free download at https://ar.biosim.pt/. All of the cards are available in English and Portuguese, but users can easily adapt them to other languages since the recognition patterns are also available. Those cards include simple molecules such as water, ammonia, or ethane, and more complex ones like RNA and DNA fragments. These cards have been developed progressively on the basis of the requests of Portuguese and Brazilian high school teachers. BioSIM^{AR} is prepared to scale up with more structures to shelter different chemical aspects. In addition, due to the open-source nature of this project and of the software involved, users can develop their own sets of molecules and make them available to the community. Currently, there is no automatic process for users to add more molecules to BioSIM^{AR}. The process involves a contact (email), and then the suggestions are analyzed, prepared, and added by us. In the long term, BioSIM^{AR} could be improved to support the creation of custom subsets of molecules, where users upload their own molecules.

IMPLEMENTATION

This project has been used in computational-chemistry-related workshops and classes, as well as by high school teachers in science-related courses. In particular, the BioSIM^{AR} was used in a chemistry class about the geometry of molecules. A total of 26 high school students (10th grade of the Portuguese School System) attended the class and were asked to answer a survey about their opinion on BioSIM^{AR} anonymously. The students were invited to classify, from 1 to 5 (strongly disagree to strongly agree), seven statements about BioSIM^{AR} (Figure 4). All 26 students answered all mandatory questions of the survey. The optional comment/suggestion field was answered by 10 students.

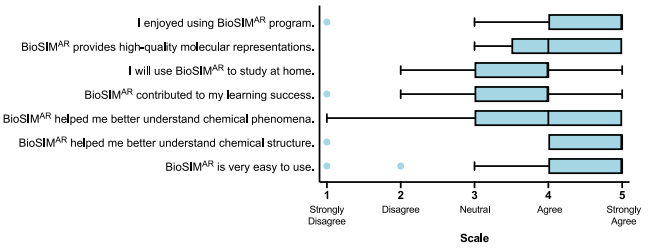

Figure 4. Tukey test results for student responses regarding the use of BioSIM^{AR} (n = 26). Scores on the scale have a range of 1−5. The boxes correspond to the first quartile (left), median (center), and third quartile (right). The whiskers correspond to the lowest (left) and maximum (right) values observed. The blue dots represent outliers. (Statements for response were presented to students in Portuguese and are translated into English here by the authors.)

The first question ("I enjoyed using BioSIM^{AR}") intends to get an overall opinion of the students regarding the experience of using this technology. Although no information about previous experience with other molecular representation technologies was collected, the students considered BioSIM^{AR} easy to use. They also agreed that BioSIM^{AR} provides high-quality molecular representations. When asked about the intention of using BioSIM^{AR} during their study at home, most of them manifested a strong interest. Although most of the students thought that BioSIM^{AR} helps in their learning process, BioSIM^{AR} seems to be more useful to assist students in understanding chemical structure rather than chemical phenomena. This was expected since the molecules available on BioSIM^{AR} are static and were prepared to show structural differences between molecules. In the future, we intend to include dynamics simulations to show chemical reactions and other dynamics phenomena. The helpfulness of BioSIM^{AR} in terms of learning success was only assessed through the opinion of the involved students. In a future workshop or class, it would be valuable to measure the actual impact of BioSIM^{AR} in terms of learning about chemical structure. In this case, students need to be split into groups, and only one group would use BioSIM^{AR} to answer a set of questions about chemical structure. The other group will only have access to the textbook.

In addition to these seven statements to classify, students had the opportunity to share custom feedback or suggestions. One student strongly disagreed with most of the statements because he/she was unable to use BioSIM^{AR} on his/her device ("I was unable to load the site, so I cannot evaluate its quality"). Although a bug report section is available on the BioSIM^{AR} website, this issue was not reported. Therefore, we do not have further information about what causes such an incompatibility. Three other students suggest that the quality of the molecules could be improved, and another student suggests the inclusion of a button to show/hide further information about the shown molecule. Improving the quality of the models makes the related files considerably bigger, which deeply affects the loading time. However, we are working on strategies to dynamically adjust the quality of the models based on the internet connection speed. The suggestion about adding buttons to the interface was already on our road map for future development.

This practical case supports BioSIM^{AR} as a potentially valuable asset in understanding chemical structure using a cheaper and more accessible technology. Moreover, the results

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of this survey agree with the comments we have received from other teachers and students. However, further real case scenarios need to be conducted to assess the real impact of BioSIM^{AR} on the learning process. Different students with and without access to BioSIM^{AR} could be asked to answer the same test about chemical structure. Alternatively, the same group of students could be asked to solve a test before and after using BioSIM^{AR}.

The popularity of BioSIM^{AR} is corroborated by the number of users that access the online platform. Since the release of BioSIM^{AR} in November 2018, our platform was accessed more than 12,000 times, according to the Google Analytics Report.

CONCLUSION

BioSIM^{AR} offers a free and interactive alternative to explain a panoply of different chemical concepts. For example, it can be useful to provide a spatial comparison between L- and D-isomers of alanine (Figure 5). BioSIM^{AR} delivers an interactive tool to represent a difference between the two possible conformers of a chiral carbon.

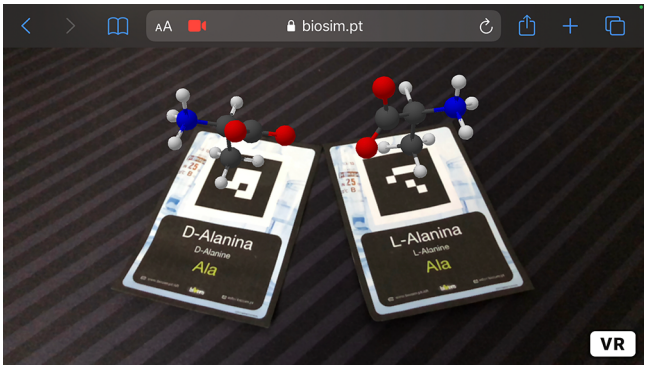

Figure 5. Comparing the structure of (left) D-alanine and (right) L-alanine, highlighting the chiral α-carbon.

In sum, BioSIM^{AR} ensures that more students, teachers, and schools have access to high-end technology without the requirement of expensive hardware or time-consuming and complex setups. Since students can easily use BioSIM^{AR} at home, it also offers an excellent complement to other 3D representation technologies only available at school. Therefore, they can continue to interact with 3D molecular representations during their study sessions at home.

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Notes

The authors declare no competing financial interest. BioSIM^{AR} is available at https://ar.biosim.pt/.

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