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The never-ending quest to understand the shapes and motions of molecules

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Why is it so important to know the shape of molecules? How can virtual reality and advances in scientific visualization help? These are recurrent questions about the importance of understanding molecular shapes and molecular motions. In this brief feature article some background is provided to better understand the central role played by visual and computational analysis of molecular structures. The role of hardware devices and software tools to assist scientists in this quest is pointed out, along with challenges to share visual experiences more broadly. These topics touch upon many current questions in research. Examples related to biological membranes, molecular medicine, -omics data and SARS-Cov-2 structural data are provided to illustrate convincing use cases.

Recently, my lab showcased our latest molecular visualization platform at my research institute's open house. A visitor then asked us, "But why do you actually want to see the shape of molecules, what's so important about that?" Even though this point is obvious to researchers dedicated to this field of research, it deserves to be highlighted for a wider audience.

Recognizing the shape of molecules is a fundamental principle in chemistry and biology. We often talk about the lock-and-key model proposed in 1894 by Emil Fischer, which describes how a molecule designated as a substrate (the key) triggers a so-called enzymatic reaction (e.g., digestion) whereby the substrate is converted to the product of the reaction by complementing the shape of a partner protein (the lock). Complementarity of shapes is common in biology: Many molecules recognize each other and spontaneously join together to form a complex, which then plays a specific role in our bodies. Therefore, in order to understand how our organisms function, researchers must have tools such as special visualization platforms (see [Figure 1](#) for an illustration) to visualize and manipulate the shape of these 3D structures, which have nothing in common with the objects we see with the naked eye in everyday life. The goal of such tools is to make these molecules tangible, real, to examine them, turn around and – why not – poke your head in.

This need to see the 3D shape of molecules in space goes back to Louis Pasteur, who in 1849 had shown an effect of tartaric acid that was due to this molecule being chiral. That is, this molecule exists in two forms with identical structure, one being the mirror image of the other. Stereochemistry was born and with it the need to study this 3D aspect of molecules.

Tartaric acid has only 16 atoms, but most biological molecules, such as the molecular machines that drive many of life's processes, are infinitely more complex, consisting of hundreds of thousands of atoms whose 3D structure must be understood. Usually, scientific and medical illustrators help us make such a connection between the overwhelming complexity of molecular reality and an understandable visual conceptualization. This process is illustrated by the example of biological membranes that inspired a healthy dialogue between raw scientific progress and conceptual illustrations. As scientists who want to capture all the details of the raw data, we have to go to a whole new level if we want to study the machines working in our cells. The mechanisms of these machines are often determined by the shape complementarity between the interacting molecules. This is the case, for example, with the mechanisms that enable the copying or repairing of the genetic code. These machines achieve a learned balance between attraction and repulsion, as if tiny magnets had been placed in just the right places to make all the cogs mesh in the image of a Swiss watch.

Apart from the shape itself, the properties of these molecular objects, such as their deformability, are equally important: Does the molecule behave more like a plush toy, a piece of wood, a block of steel? Does it deform more in some places than in others? Molecules are by no means static. Their dynamics are manifold and take place at different levels of time and space. Among molecules themselves, some open or close. On a larger scale, some molecules dynamically transport 'packages' through the cell or transmit messages. Even more extensive deformations and dynamics occur in the so-called

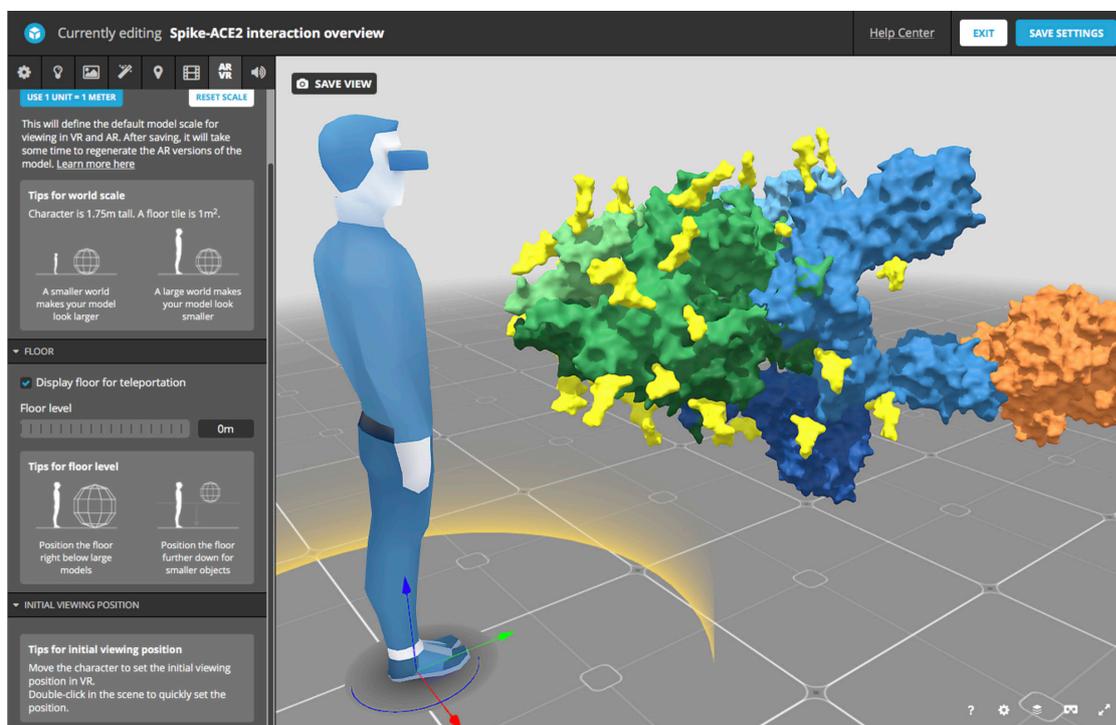


Figure 1. Immersive visualization of molecular shapes and interactions

building molecules that are constantly changing areas of the cell, such as in the mitochondria. These are just a few examples of the essential role played by the dynamics of molecules.

These conformational dynamics remain misunderstood in part because they are difficult to observe. Only through numerical computations will it be possible to interpret experimental data or even predict these behaviours of molecular dynamics using computer simulations. Computer simulations, e.g., provide crucial insights and arguments for the design of molecular approaches in medicine, where dynamics plays a key role. Nowadays, these simulations can be interactive, and the scientist can manipulate, deform and arrange molecules according to current ideas and hypotheses, while tangibly perceiving the forces acting between the molecules. Often, simplified – the so-called coarse-grained – models are particularly well suited to such an approach because they allow us to extend the time and length scales on which objects can be studied. In practice, we particularly use haptic arms – a remote-controlled arm with a device on the end that can be used to touch and feel virtual objects – that are motorized and can exert resistance to deformation. With such a device, it is quite natural to tug on a molecule and study its response to the stimulus.

Clearly, all of these operations, whether simply looking at molecules or controlling their motions and shaping them in time, require state-of-the-art tools. The

3D vision has long been part of the arsenal of chemists and biologists. Back in the 1980s, long before 3D televisions, stereoscopic slideshow devices were used to convey the shape of molecules. Nowadays, it's possible to visualize these objects on your smartphone or print them out in 3D, like jigsaw puzzles that are real puzzles. A serious game called 'FoldIt' has made this its trademark. We experimented with different visualization modalities to make sense of the combined structural and -omics data in an integrated platform called MinOmics, which includes both a high-resolution display wall and virtual reality headsets.

On our visualization platform, researchers gather to immerse themselves in the world of molecules with virtual reality helmets on their heads or converse in front of a giant high-resolution 3D screen showing detailed views of molecular objects. This immersion in the magical world of molecules leads to a more intuitive understanding of the properties of these objects through the unique sensory experience it provides. Since such visual experiences are very rich and insightful, it is also desirable to be able to share them with other scientists, funders and the general public. How the so-called FAIR principles – standing for findable, accessible, interoperable and Reusable – can enable the sharing of such experiences has been illustrated for instance using recent SARS-Cov-2 structural data as example. A number of available software tools for such purposes exist and have recently been reviewed.

Further Reading and Viewing

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- Martinez, X., Chavent, M. and Baaden, M. (2020) Visualizing protein structures — tools and trends. *Biochem. Soc. Trans.* **48**, 499–506. DOI: 10.1042/BST20190621
- The last phrase of the article was loosely adapted from the quote "The purpose of visualization is insight, not pictures" by Ben Shneiderman, who produced many wonderful essays on visualization that are recommended for further reading.

This search quest for molecular forms has an even deeper reason. Scientific thinking is largely based on visual processing of information. This processing ranges from the visualization of initial raw data that stimulates thought, to the formation of hypotheses that are often supported by reasoning about a molecular model, to the communication of ideas in the form of images that summarize the essentials. Visual representations are an extension of our brains, an extension of our working office that allows us to share and represent our ideas together. The main purpose of these visualizations is not to produce beautiful images, but to feed the clairvoyance of scientists. ■

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Dr. Marc Baaden is a computational chemist modeling biological systems and processes at the nanoscale. Topics include application of existing modeling tools but also development of novel software and exploration of innovative methods (such as virtual reality and haptics). The UnityMol software is a key achievement in molecular visualization. A broad range of methods is used, including interactive minimization, coarse grained modeling, molecular membrane dynamics and docking approaches. A recent orientation concerns the FAIR sharing of such data and experiences. Active collaboration with experimental groups to link and validate computational observations is a hallmark. Twitter handle: @baam93