Structure
Perspective

Molecular Graphics: Bridging Structural Biologists and Computer Scientists

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Visualization of molecular structures is one of the most common tasks carried out by structural biologists, typically using software, such as Chimera, COOT, PyMOL, or VMD. In this Perspective article, we outline how past developments in computer graphics and data visualization have expanded the understanding of biomolecular function, and we summarize recent advances that promise to further transform structural biology. We also highlight how progress in molecular graphics has been impeded by communication barriers between two communities: the computer scientists driving these advances, and the structural and computational biologists who stand to benefit. By pointing to canonical papers and explaining technical progress underlying new graphical developments in simple terms, we aim to improve communication between these communities; this, in turn, would help shape future developments in molecular graphics.

Molecular graphics tools and methods have been actively developed for over 50 years, always tightly linked to advances in computer hardware (Levinthal, 1966). Early on, key developments in molecular graphics attracted interest from a broad range of scientists—hence, some were published in generalist journals, such as Science (Langridge et al., 1981). At present, however, the field has fragmented into two main communities: advances in computer graphics are almost always reported in publications aimed at computer scientists, while applications of computer graphics that uncover new biological insights are reported in journals aimed at structural biologists. Two key issues caused by this fragmentation are that publications are often difficult to access for scientists outside of their respective subfields, and interactions between the two communities is low as they rarely attend the same meetings. As a result of these issues, many structural biologists are unaware of recent advances in molecular graphics methods; conversely, computer scientists working in molecular graphics are not always aware of, or focused on, the most important visualization challenges raised by cutting edge experimental methods.

This Perspective article aims to help address some of the above issues. We begin by briefly reviewing highlights in the history of molecular graphics. We then outline how some of the core computational visualization methods currently used in molecular graphics tools can be used to improve understanding of biomolecular structures. Finally, we highlight emerging challenges in structural biology and how they may be addressed by advances in computer graphics and by new software platforms (e.g., augmented reality).

A Brief History of Molecular Graphics

Here we present a brief history of molecular graphics, for interested readers a more extensive review was recently published (Olson, 2018). Some key moments in molecular graphics are summarized in Figure 1, together with recent review articles. The earliest molecular graphics were hand drawings and physical models (Richardson and Richardson, 2013); as these began to be replaced by computer graphics, a key initial focus was on inventing novel visual representations that help in understanding biomolecular function by emphasizing important structural features. Two striking examples were: (1) the ribbon representation developed by Jane Richardson (1977) and (2) the molecular surface representation developed by Michael Connolly (1983a). Such developments profoundly transformed the practice of structural biology, leading to the launch of the *Journal of Molecular Graphics* in 1983, first giving the field its own dedicated journal. Since then, a large number of molecular graphics tools have been developed. The reviews from Goddard and Ferrin (2007), O'Donoghue et al. (2010), and Johnson and Hertig (2014) discuss available tools and help identify the best visualization methods for addressing specific biological questions.

In recent years, structural biology has become increasingly interconnected with many other kinds of data (Im et al., 2016), and the visualization challenges have moved from the static views of single molecules toward dynamic views of much larger scales, such as whole viruses, subcellular organelles, or even entire cells (see also Goodsell et al., 2018). These challenges have inspired intense research within the computer graphics community, aimed at creating solutions that take better advantage of current

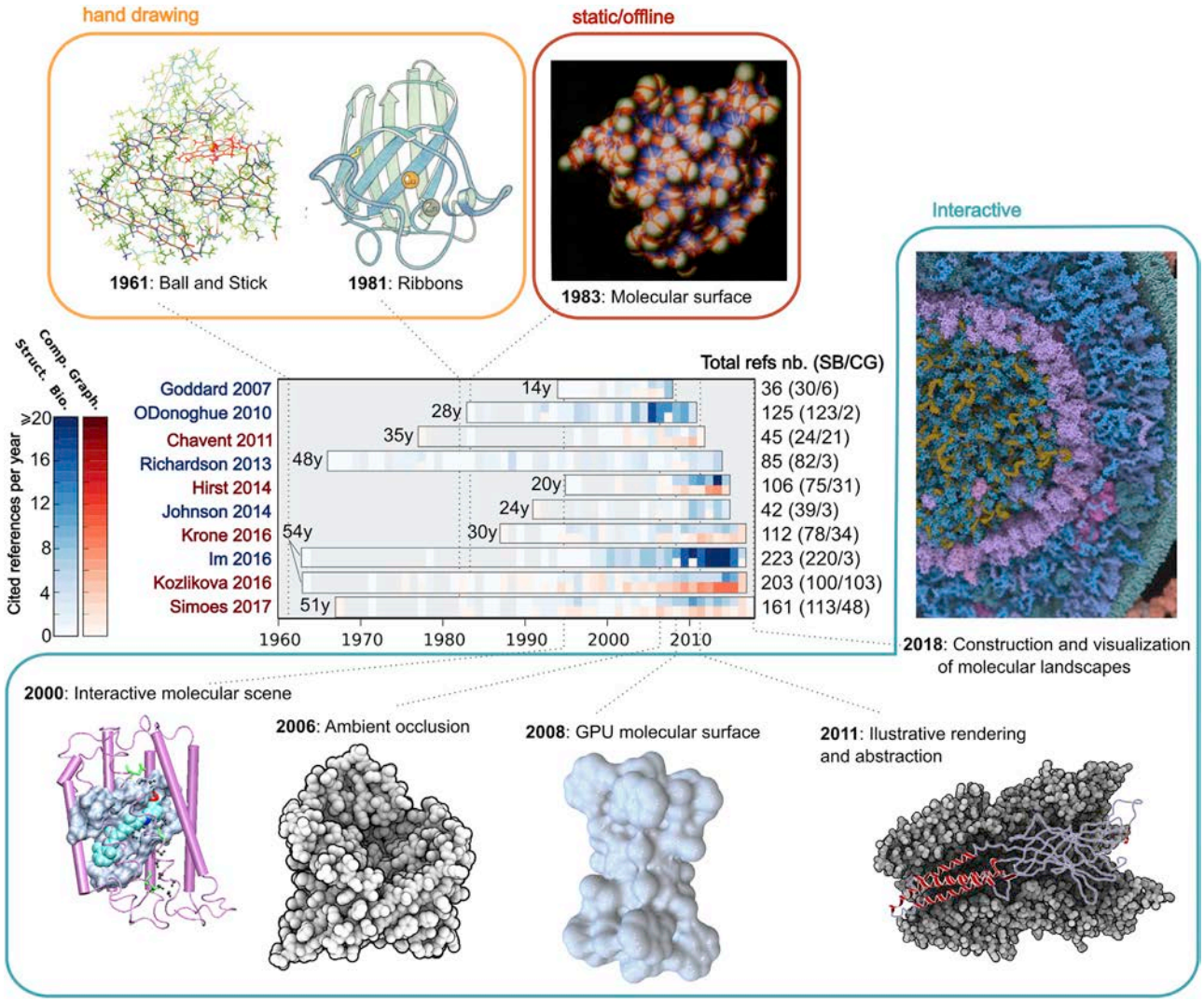

Figure 1. A Brief History of Molecular Graphics

List of surveys indicating their time span, number of cited references per year, total number of references, and the ratio of papers coming from the structural biology and computer graphics and visualization fields, respectively. If an article refers to both types of references for the same year, the cell is divided in two rows of different color. Blue refers to articles oriented toward a more general (structural biology) audience, while red depicts more technical articles generally published in journals and conferences from the computer graphics community. Figures around the diagram present milestones for molecular visualizations: from hand drawings of myoglobin by Irving Geis (Illustration, Irving Geis. Used with permission from the Howard Hughes Medical Institute; www.hhmi.org. All rights reserved) and the ribbons diagram designed by Jane Richardson to more sophisticated representations, such as molecular surfaces. This surface was first processed as a static image. During the early 1990s to the 2000s, with the advent of molecular viewers, it was possible to display all these representations interactively (here, a scene rendered with VMD). From mid-2000s, technical developments performed in computer graphics labs are changing the way of visualizing molecular structures by better rendering molecular shapes. Now, it is possible to interactively construct and visualize crowded and large systems, opening the way for mesoscale models (spanning thousands of Angstroms and containing millions of molecules) with a nearly atomic resolution.

graphic processor unit (GPU) capabilities (Chavent et al., 2011), as well as new analysis and immersive approaches (Hirst et al., 2014). These recent developments are summarized in three state-of-the-art reviews of molecular graphics, each describing technical developments that can help structural biologists choose the best algorithms for a dedicated purpose. The review by Kozlikova et al, (2017) details algorithms that can be used to render from small molecules to large macromolecular assemblies, such as microtubules. Two other reviews (Krone et al., 2016; Simões et al., 2017) focus on detection and visualization of cavities on protein surfaces.

Many of the above developments in computer graphics have been first created as research prototypes, rather than usable implementations, and have been reported in computer science publications. As a result, while some advances are incorporated in widely used molecular graphics tools (e.g., VMD, Krone et al., 2012; Stone et al., 2016; or Chimera, Goddard et al., 2018), unfortunately—as already noted 10 years ago (Goddard and Ferrin, 2007)—many developments remain unused by the structural biology community. This is evident from the very small fraction of computer graphics papers cited in recent reviews published for structural biologists (Figure 1).

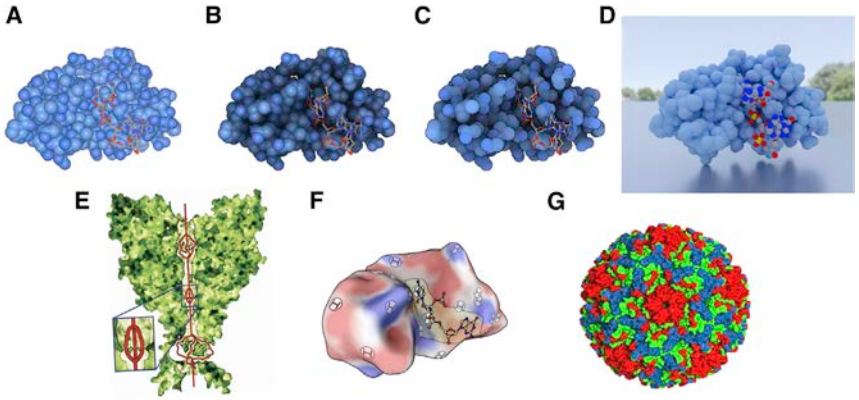

Figure 2. Lighting Effects and Surface Rendering

(A) Basic Blinn-Phong (BP) rendering.

(B) Addition of ambient occlusion (AO) lighting to BP.

(C) Non-photorealistic rendering (flat colors and outlines) with AO. (A–C) Figures rendered with Mol*, 3D visualization available at https://molstar.org/demos/lighting/.

(D) Photorealistic rendering (UnityMol rendering).

(E) Highlighting a molecular path by focusing lights on the path and clipping the surface along the path.

(F) Molecular surface abstraction and addition of markers on the surface.

(G) QuickSurf rendering of a viral capsid. (A–D and F) Ribonuclease with a d(ACGA) molecule (PDB: 1M07).

Thus, one of our goals here is to present some of the key computational methods commonly used for molecular graphics, and highlight how these methods can help address emerging challenges in structural biology. In the Supplemental Information we present some further, more recent, methods not yet implemented in broadly accessible molecular viewers.

Lighting and Shading Effects to Improve 3D Structure Perception

As with almost any complex 3D object, rendering molecular structures in 2D (e.g., on a computer screen or on paper) requires making compromises, distortions, and omissions. To compensate, a variety of visual effects are used to better communicate the true 3D shape. Some of the most common visual effects relate to lighting and shading; for molecular graphics, these effects can help users better understand the overall spatial organization of complex biomolecules (Figure 2).

Currently, most molecular graphics tools use an approximation of physically based lighting called the *Blinn-Phong model* (Blinn, 1977; Phong, 1975). This models light reflection from a 3D surface using three terms (see Figure S1): (1) an ambient term that equally brightens all objects in the scene, thus modeling uniform, global illumination; (2) a diffuse term that models reflection from specific light sources on rough surfaces, thus selectively brightening and darkening parts of the surface; and (3) a specular term that models reflections from specific light sources on shiny surfaces, producing specular highlights. Together, these terms give a fairly realistic lighting model for smooth 3D objects (Figure 2A); however, one key limitation of the model is that it cannot convey shadows cast between objects. To overcome this limitation, a range of computational strategies have been developed (Table S1)—some can efficiently compute shadows for large molecular systems (Krone et al., 2017).

To further enhance 3D structure, the above methods can be combined with *Ambient Occlusion* (AO), a shading effect that darkens buried (or occluded) regions of a structure—mostly cavities and crevices—to approximate non-directional (i.e., global or ambient) lighting (Figure 2B). For static 3D molecules, AO has been available for more than 10 years via the QuteMol (http://qutemol.sourceforge.net) viewer (Tarini et al., 2006). AO is also available in popular molecular graphics tools, such as VMD (examples and tutorial: https://www.ks.uiuc.edu/Research/vmd/minitutorials/tachyonao/) (Humphrey et al., 1996) (Figure 2G), PyMOL (brief tutorial: https://pymol.org/dokuwiki/doku.php?id=media:ambient_occlusion.) and, more recently, ChimeraX (Goddard et al., 2018).

Ray tracing is a method for more realistically simulating lighting by computing the paths that photons would travel from each light source to the view point, accounting for reflections (an easy-to-use ray-tracer available in the web browser can be tested at the address: http://lighttracer.org; see Supplemental Information on how to use it for molecular surfaces). This produces photorealistic rendering (Figure 2D), but usually requires significant computing power. Ray tracing is often used in creating high-quality static images for artwork and cover images. This method can be useful when rendering molecules for virtual reality (VR) and augmented reality (AR), because realistic rendering makes it easier for users to immerse themselves in these environments. Recently, VMD has included CPU-based (https://www.ospray.org) and GPU-based (https://developer.nvidia.com/optix) ray-tracing methods that can interactively display large, dynamic molecular systems (up to tens of millions of atoms; Stone et al., 2016).

Another group of methods, called *non-photorealistic* renderings, aim to highlight selected features while hiding others. One of these methods, known as *cel-shading* ("cel" for celluloid) or toon-shading, reduces shadows and adds thick outlines to highlight the molecular silhouette, thus creating a flattened, cartoon-like rendering. Cel-shading is used by David Goodsell in many of his well-known renderings of crowded biomolecular landscapes (Goodsell et al., 2018). For molecular graphics, non-photorealistic rendering can often be effective in combination with AO (see also cel-shading + AO examples in the Molecule of the Month by D. Goodsell: https://pdb101.rcsb.org/motm/motm-by-date) (Tarini et al., 2006) (Figure 2C). Readers can also check online the differences between standard lighting (with and without AO) and non-photorealistic rendering on different molecules at https://molstar.org/demos/lighting/.

Lighting can also be used to elucidate specific aspects of biomolecular structure: e.g., Lindow et al. (2011) described a compelling way of using lighting to highlight tunnels and channels in large molecules (Figure 2E). Table S1 provides a list of state-of-the-art methods for efficiently implementing the lighting and shading effects presented in this section.

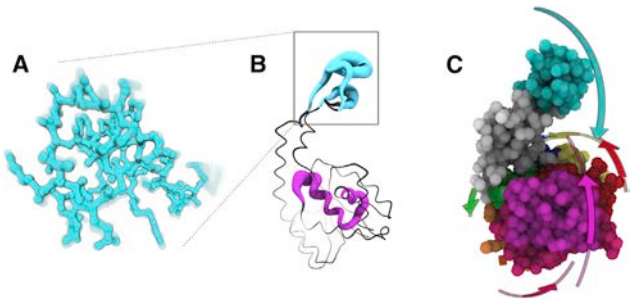

Figure 3. Dynamics and Flexibility
(A) Blurr effect to render the local flexibility of residues (UnityMol rendering).
(B) At a larger scale, it is possible to render flexibility for larger area by using a sausage plot (VMD rendering).
(C) Large rotational and directional movements can be depicted by arrows and arcs (based on Bryden et al., 2012).

Molecular Surface Rendering to Highlight Biomolecular Properties

To better convey 3D shape, a commonly used strategy in molecular graphics is to simplify the representation; instead of showing each atom as a van der Waals (vdW) sphere (Figures 2A–2D), only the overall molecular surface is shown. A recent review exhaustively described available methods for calculating these surfaces (Kozlikova et al., 2017). Below, we present key methods and how they can be used to highlight specific biomolecular properties.

One of the most commonly used molecular surface methods, described by Connolly (1983a, 1983b), is defined by rolling a spherical probe approximately the size of a water molecule. Probes not in contact with atoms remove material, leaving inaccessible gaps filled. Thus, the result is often called the *Solvent Excluded Surface* (SES). Thanks to recent developments with GPU-based calculation, the SES can now often be generated interactively (Krone et al., 2009; Lindow et al., 2010) (more details on recent SES algorithms in Table S2). Replacing the spherical water probe by a larger ligand to carve out the surface, Lindow et al. (2014) proposed the *Ligand Excluded Surface*, which may better describe the surface of a protein accessible to a specific ligand as well as help to focus on cavities more suited for this ligand.

Constructing the SES with a rolling ball can lead to artifacts such as self-intersecting surfaces and sharp points and edges (Bates et al., 2008; Vorobjev and Hermans, 1997), which can result in inaccurate calculation of molecular properties that depend on the surface having a well-defined inside and outside or a smooth boundary (Geng et al., 2007). Several smooth surfaces have been developed. The recent *Molecular Skin Surface* developed by Edelsbrunner (1999) is not yet as common, but has an attractive mathematical definition that guarantees smooth surfaces and supports fast computation on both CPUs and GPUs (Chavent et al., 2008; Lindow et al., 2010) (see Figure 1, 2008). It does use a shrinkage parameter that is not directly tied to the size of the solvent molecule. Cipriano and Gleicher (2007) presented the *Molecular Surface Abstraction*, which is based on SES but smooths areas of high frequency to simplify the representation but keep the overall shape (Figure 2F). By adding markers on the surface, important areas, such as ligand binding pocket, are highlighted. To interactively visualize large systems, such as virus capsids, a smooth *Gaussian Density Surface* can be used. Krone et al. (2012) proposed a fast GPU implementation available in the molecular viewer VMD, the so-called *Quicksurf*. This representation reduces surface details to avoid cluttering the display while accelerating the surface rendering (Figure 2G). Beyond molecular surface representations, computer graphics researches advance on volume rendering to visualize density maps from X-ray crystallography or from cryoelectron microscopy. For interested readers, recent algorithms on volume rendering as well as application cases are available in Supplemental Information.

Conveying Dynamics and Flexibility: From Atoms to Proteins

Biomolecules are intrinsically dynamic and flexible, leading to positional uncertainty. Even if molecular dynamic properties can be measured (Kay, 2016), and modeled in molecular simulations (Bottaro and Lindorff-Larsen, 2018), a clear visualization of such dynamical properties is still a challenge—especially if rendered on a static image.

At near-atomic scales, it is possible to convey fuzziness and flexibility using a *blurring effect* (Figure 3A). Schmidt-Ehrenberg et al. (2002) create such an effect by using volume-rendering techniques. Although it works well for small molecules, this approach cannot be adapted for larger molecular systems because it may introduce too much ambiguity. Alternatively, a given graphical representation can be made thicker when positional uncertainty is observed and thinner when the location is well defined. This is typically applied on the protein backbone using the well-known *sausage plot* representation combined with color clues (Figure 3B). This representation can be performed using molecular viewers such as MOLMOL (https://sourceforge.net/p/molmol/wiki/Home/) (Koradi et al., 1996) or PyMOL (called the "putty" representation: https://pymolwiki.org/index.php/Cartoon). This type of approach was recently updated by Schulz et al. (2018) to map positional and structural uncertainties to the cartoon representation of a protein using geometric distortion and transparency. To display short motions of a group of atoms Dabdoub et al. (2015) drew *pathlines and ribbons* connecting the different positions over time representing the motion of the atoms rather than their coordinates.

These approaches cannot clearly highlight correlated motions of distant groups of atoms which are important to understand allosteric effects taking place in proteins. Fioravante et al. (2013) have proposed addressing this issue via rendering methods that display motional correlations in proteins. For larger directional movements of proteins, such as domain motions observed in Normal Mode Analysis, Bryden et al. (2012) automatically grouped the atoms based on velocity and simplified the motion by displaying *arcs and arrows* assigned to the identified groups (Figure 3C).

Multiscale Visualization: Bridging the Different Scales up to the Entire Cell

Driven by advances in experimental methods (Cheng, 2018), in computational modeling (Im et al., 2016), and in integrative approaches (Sali et al., 2015), the size and complexity of molecular systems amenable to structural biology is rapidly increasing. This, in turn, is creating new visualization challenges.

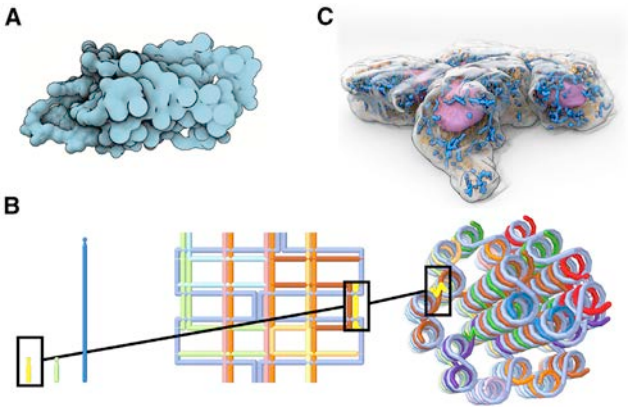

Figure 4. Multiscale Visualization
(A) Continuous transformation to pass from a precise molecular surface (on the left side of the molecule) to a simplified surface representation (center), then to a vdW representation, as a function of the user's point of view.
(B) Abstractions of DNA origami.
(C) Illustrative representation of cell models. Purple, nuclear surface; blue, mitochondria; yellow, microtubules. The cell surface is outlined and semi-transparent. Image from the Allen Cell Explorer: https://www.allencell.org.

Inspired by David Goodsell's pioneering depictions of *biomolecular landscapes* (Goodsell et al., 2018), several recent initiatives in computer graphics have taken on the challenge of constructing such models (Klein et al., 2018) (Figure 1, 2018). These models can be useful for research (Iwasa, 2015; Johnson et al., 2015) as well as communication (Iwasa, 2010).

To facilitate navigation in such complex and crowded landscapes, a range of multiscale molecular visualization techniques have been developed; these are described in a recent survey from Miao et al. (2019). A key method is to automatically *adapt the level of molecular detail*, depending on the proximity of the camera. Parulek et al. (2014) proposed a continuous and visual abstraction to pass from a precise protein surface to a simple vdW representation as a function of the distance between the scene and the user's point of view (Figure 4A). A similar approach was used to represent DNA origami structures at different scales (Miao et al., 2018) (Figure 4B). Such *seamless transformations* can also be applied to pass efficiently from one protein depiction to another for illustrative purposes (van der Zwan et al., 2011) (Figure 1, 2011).

These developments pave the way toward systems that enable interactive exploration of *molecular-scale models of entire cells* (Mindek et al., 2018; Singla et al., 2018) (Figure 4C). These new visual approaches will not only be used for rendering molecular systems on a screen but will be especially useful if applied with new technological advances such as VR (Davison et al., 2019). Indeed, the future of molecular graphics will no longer be limited to computer screens but will adapt to users' visual practices through tablets, smartphones, and VR/AR devices driven by web technologies.

Beyond the Stand-Alone Molecular Viewer: New Software Platforms

Recent advances in web technology are driving rapid developments in *web-based molecular graphics tools*, as outlined in several recent reviews (Mwalongo et al., 2016; Yuan et al., 2017), which are available on desktop computers, tablets, and smartphones alike. One of the main drivers has been the WebGL API, which gives native support for GPU hardware-acceleration for molecular graphics web-apps, such as *NGL Viewer* (Rose and Hildebrand, 2015), *LiteMol* (Sehnal et al., 2017), and *Jolecule* (https://jolecule.appspot.com), which are compatible with use on smartphones and tablets. This new generation of graphics web-apps are being deployed on different projects, such as the worldwide PDB (on each of its three websites; rcsb.org, pdbe.org, and pdbj.org) (Berman et al., 2012), SwissModel (Schwede, 2003), and Aquaria (O'Donoghue et al., 2015), resources used to facilitate access to millions of 3D structures and models. Currently, however, most web-based molecular graphics tools do not yet offer the full range of functionalities available with more established, stand-alone tools (e.g., Chimera, VMD, etc.). This may soon change, driven by open-source, collaborative projects such as the recently launched *Mol* initiative* (https://molstar.org), aimed at developing a common framework for web molecular graphics.

Another alternative is to re-use software platforms that already contain implemented and efficient graphical functions for molecular graphics purpose. Several projects use the Unity (https://unity.com/) 3D game engine for molecular graphics: *UnityMol* (http://unitymol.sourceforge.net) (Lv et al., 2013) to display protein structures, the mesoscale viewer *cellVIEW* (https://www.cg.tuwien.ac.at/cellview/) (Le Muzic et al., 2015), and *MolecularRift* (https://github.com/Magnusnorrby/MolecularRift) (Norrby et al., 2015), a tool for drug design using VR. Molecular graphics is also increasingly being used within professional animation software platforms. *BioBlender* (http://www.bioblender.org) (Andrei et al., 2012), *ePMV* (http://epmv.scripps.edu) (Johnson et al., 2011), and *Pyrite* (https://durrantlab.pitt.edu/pyrite/) (Rajendiran and Durrant, 2018), use the 3D creation suite Blender (https://www.blender.org) to perform high-quality rendering of molecular structures and molecular dynamics simulation data. One can also cite *Molecular Maya* (Molecular Maya: https://clarafi.com/tools/mmaya/, Autodesk Maya: https://www.autodesk.com/products/maya/overview), a plugin for the commercial 3D modeling tool Autodesk Maya to render and animate molecular structures.

AR and VR devices (e.g., Oculus Rift, Hololens) are becoming increasingly affordable, which now allows researchers using them to display molecular systems (Hirst et al., 2014; O'Connor et al., 2018). VR is indeed especially useful to render, manipulate, and explore molecular structures from small molecules (Norrby et al., 2015) to large systems (Stone et al., 2016) up to the cellular level (Johnston et al., 2018). Although VR and AR are now routinely used by a single user, technological developments to allow close collaboration of several users in VR/AR are still subject of ongoing research (Arthur et al., 1998; Chastine et al., 2005).

Find Your Nearest Computer Graphics Researcher

Because of limited space, we unfortunately cannot discuss further how computer graphics can support structural biology. We hope to have convinced you that improving the rendering of molecular structures is not only a matter of esthetics but really helps understanding of molecular functions. For people wanting to start improving their rendering, in addition to consulting the links and references available in this article, we encourage them to read Mura et al. (2010) for an introduction to biomolecular

graphics, and Jenkinson (2018) for an overview on modalities to communicate molecular science. In a more general context, Bang Wong's "Data visualization Points of View" (http://blogs.nature.com/methagora/2013/07/data-visualization-points-of-view.html) is also a good resource to easily guide the readers to understand scientific data visualization and design scientific figures.

We believe that increased adoption of some of these promising methods has significant potential to advance structural biology by improving how structural biologists see and think about their data. By covering references to state-of-the-art surveys written by well-recognized teams in the field, this perspective may further provide an entry point to contact computer graphics researchers to implement new rendering techniques that will definitely benefit structural biology. To further help realizing this goal, we would also encourage readers to consider participating in scientific events that bring structural biologists together with researchers working on computer graphics: meetings, such as VIZBI (Visualizing Biological Data, https://vizbi.org), BioVis (http://biovis.net), and MolVA (Molecular Graphics and Visual Analysis of Molecular Data, http://decibel.fi.muni.cz/~xbyska/molva/).

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.str.2019.09.001.

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AUTHOR CONTRIBUTIONS

The manuscript was written through contributions of all authors.

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