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Molecular Graphics: Bridging Structural Biologists and Computer Scientists

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Abstract

Visualization of molecular structures is one of the most common tasks carried out by structural biologists, yet the technical details and advances required to efficiently display molecular structures are often hidden from the end user. During decades molecular viewer software such as Chimera, COOT, PyMOL, or VMD provided the most common solutions to quickly visualize structures. Nowadays, new and efficient ways to depict molecular objects are changing how structural biologists interact with their data. Such novelties are often driven by advances made by computer scientists, but an important gap remains between this community and the final users such as structural and computational biologists. In this perspective article, we clarify how developments from computer graphics and data visualization have led to novel ways of understanding protein structure. We present future developments from computer science that will be beneficial for structural biology. By pointing to canonical papers and explaining technical progress underlying new graphical developments in simple terms, we hope to promote communication between the different communities to shape future developments in molecular graphics.

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11 **1. Introduction and Motivation**

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14 Molecular graphics tools and methods has been actively developed for over
15 50 years, always tightly linked to advances in computer hardware [1]. Early on,
16 key developments in molecular graphics attracted interest from a broad range
17 of scientists — hence, some were published in journals such as Science [2]. To-
18 5 day, however, the field has fragmented into two main communities: advances
19 in computer graphics are almost always reported in publications aimed at com-
20 puter scientists, while applications of these methods that uncover new biological
21 insights are reported in journals aimed at structural biologists. One key issue
22 caused by this fragmentation is that publications are often difficult to access
23 for scientists outside of the respective sub-field — fortunately, this situation
24 is slowly improving due to the increase in open-access publication. A related
25 issue is that interaction between the two communities is low as they rarely at-
26 tend common meetings. As a result of these issues, many structural biologists
27 10 are unaware of interesting advances in molecular graphics methods; conversely,
28 computer scientists working in molecular graphics are not always aware of or
29 focused on the most interesting visualization challenges raised by cutting edge
30 experimental methods.
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41 This perspective article aims to help address some of these issues result-
42 20 ing from the fragmentation of these communities. We begin by briefly review-
43 ing highlights in the history of molecular graphics. We then outline some of
44 core computational visualization methods currently used in molecular graph-
45 ics tools, and explain how they help advance our understanding of biomolecu-
46 lar structures. We also discuss methods currently being developed to address
47 emerging challenges, such as structures derived from cryo-electron microscopy
48 (cryo-EM) [3, 4].
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2. A Brief History of Molecular Graphics

Some key moments in molecular graphics are summarized in figure 1, which also lists several recent review articles.

As described in the review from Jane and David Richardson [13], the earliest molecular graphics were drawings and physical models created by hand. As these began to be replaced by computer graphics, a key initial focus was on inventing novel visual representations that help push forward the understanding of biomolecular function by emphasising important structures features. Two striking examples were: (1) the ribbon representation developed by Jane Richardson, published in *Nature* in 1977 [5] and (2) the molecular surface representation developed by Michael Connolly, published in *Science* in 1983 [14]. Such developments profoundly transformed the practise 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 *et al.* [15], O'Donoghue *et al.* [16], and Johnson and Hertig [17] each give a guide to the available tools and help identify the best visualization methods for addressing specific biological questions. Johnson and Hertig [17] further present visual tools and methods for 3D animations and describe how these can be effectively combined with visual metaphors to create visual narratives that explain complex, biomolecular mechanisms, either to other scientists or to the general public.

In recent years, as described in the review from Im *et al.* [18], structural biology has become increasingly interconnected with many other kinds of data, and the visualization challenges have moved from the static views of single molecules toward dynamics views of much larger scales, such as whole viruses, subcellular organelles, or even entire cells.

These challenges have inspired intense research within the computer graphics community, aimed at creating solutions that take advantage of advances in GPU capabilities (described by Chavent *et al.* [19]), as well as new analysis and im-

mersive approaches (described by Hirst *et al.* [20]). These recent developments are summarized in three recent *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 from Kozlikova *et al.* [21] details algorithms that can be used to render small molecules up to large macromolecular assemblies, such as microtubules. The reviews from Krone *et al.* [22] and Simoes *et al.* [23] focus on detection of cavities on protein surfaces and their rendering.

Mostly, these developments in computer graphics have been first created as research prototypes, rather than as usable implementations, and have been reported in computer science publications. As a result, while some of these advances have been incorporated in widely-used molecular graphics tools (e.g., VMD [24, 25], Chimera [26]), unfortunately — as noted by Goddard *et al.* 10 years ago [15] — many developments in computer graphics are still not visible to, or accessible 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).

Thus, one of our goals for this work is to highlight recent computer graphics advances that have not yet been implemented in broadly accessible molecular viewers, but have potential to help address the emerging challenges in molecular graphics.

3. Advanced Lighting and Shading Effects

Many advances have been made in lighting and shading effects applied to molecular graphics that can, in turn, help users understand the overall spatial organization of complex biomolecules (figure 2).

Blinn-Phong lighting and real-time shadows: Currently, most molecular graphics tools use an approximation of physically based lighting called the Blinn-Phong model [27, 28], composed of three terms: (1) an ambient term that models incident light coming equally from all directions; (2) a diffuse term; and

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8 (3) a specular term that models surface reflections. Together, these three terms
9 give a fairly realistic approximation of the local lighting and shading condi-
10 tions at the surface of smooth 3D objects (figure 2). However, the Blinn-Phong
11 model has key limitations; for example, it cannot convey shadows cast between
12 objects. A range of computational strategies have been developed to overcomes
13 these limitations; for example, Krone *et al.* [29] recently presented a strategy
14 that can efficiently compute shadows for large scale molecular systems, such as
15 virus capsids with up to 1 million atoms.
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20 **Ambient occlusion:** Ambient occlusion (AO) is a shading and rendering
21 technique that adds depth cues which, in turn, can greatly help in revealing
22 detailed features for complex, 3D objects [30, 31] (see figure 2). For static 3D
23 molecules, AO has been available for many years via the QuteMol viewer from
24 Tarini *et al.* [8]. AO effects has also become available in more popular molecular
25 graphics tools, such as VMD [32] and, more recently, ChimeraX [26].
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29 Ambient occlusion darkens buried parts of a structure — mostly cavities
30 and crevices — to approximate non-directional lighting effects. AO relies on a
31 depth-map, computed for each point-of-view around the molecule; this is then
32 used to determine and store the visibility of each atom in a texture map. If
33 the atoms are hidden from the camera, the texel (one element of the texture
34 map) of the corresponding part of this atom is darkened. These occlusion maps
35 are computed once on the GPU; the effect is then very fast to render as long
36 as the molecule is static. For dynamic molecular data, a fast approximation of
37 AO was proposed by Grottel *et al.* [33] that allows for interactively rendering
38 of dynamics systems composed of millions of atoms.
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42 **Ray-tracing:** Ray tracing methods provide a much more realistic simula-
43 tion of lighting by computing the paths and reflections that photons would travel
44 from each light source to the view point. This produces photorealistic rendering
45 that can be very helpful in conveying complex, 3D molecular structures (see
46 figure 2). However, as these calculations require much computing power, many
47 users only use ray tracing when finalizing high-quality, static images for pub-
48 lication. Two available tools that can be used in this way are ePMV [34] and
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7 BioBlender [35]; both these tools use the open-source 3D modelling software
8 Blender on their backend for ray tracing.

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10 The VMD tool [7] includes the **Tachyon** ray-tracer for computing static im-
11 ages, and further offers real-time ray-tracing via highly efficient CPU (OSPRay)
12 and GPU (OPTIX-CUDA) methods [32]. This approach was recently used to
13 interactively display very large, dynamic molecular systems containing dozens
14 of millions of atoms, such as chromatophores [25].
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18 In summary, thanks to recent advances in both hardware and software,
19 molecular graphics tools can now feasibly combine real-time global illumination
20 with a range of non-photorealistic rendering methods; this provide high-quality
21 depth cues that can greatly help users with the challenging task of understand-
22 ing complex, 3D molecular structures [16].
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27 4. Molecular Surface Rendering

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30 Visualizing molecular surfaces has proven to be very useful representations
31 for revealing functional aspects of biomolecules, such as proteins and nucleic
32 acids. Thus, as described in the review from Kozlíková *et al.* [21], many different
33 methods have been proposed to calculate molecular surfaces, each designed to
34 highlight specific biomolecular properties. In this section, we briefly mention the
35 methods that are most commonly used, as well as a few of the more promising
36 methods that have recently been proposed.
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40 One of the most commonly used molecular surface methods is to simply
41 represent each atom as a sphere with corresponding **van der Waals (vdW)**
42 radius (figure 2). In addition to being quick to compute, this method has the
43 advantage that it automatically conveys a sense of spatial scale, since atoms
44 are directly visualized; however, a limitation of the vdW surface is that it is
45 often difficult to see where other molecules (e.g., **ligands**) are likely to interact
46 favourably.
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51 To address this limitation, the **Solvent Accessible Surface (SAS)** was
52 proposed [36]. This is calculated using a spherical probe with a radius set to
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150 SAS is significantly larger than the true molecular volume.

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155 This limitation is mostly overcome by the **Solvent Excluded Surface** (SES), which is also known as the Smooth Molecular Surface, or the Connolly Surface [6, 14]. The SES is defined similarly to the SAS, but uses the probe contact surface instead of the probe center, thereby closing gaps that are inaccessible to the probe while also giving a better approximation to the true molecular volume. Over the past decade, many fast methods to compute and render the SES have been proposed: Krone *et al.* [37] used shader-based ray casting to render with high image quality. Lindow *et al.* [38] accelerated the computation on multi-core CPUs, while Krone *et al.* [39] presented a GPU-based algorithm
160 to compute the surface interactively. Jurcik *et al.* [40] developed a method based on the work of Krone *et al.* [37, 39] to render the SES semi-transparently. Hermosilla *et al.* [41] computed the SES progressively on a 3D grid and rendered the results using volume rendering.

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170 In addition to the commonly used SES, a range of additional molecular surface definitions have been proposed: (1) The **Ligand Excluded Surface** by Lindow *et al.* [42] uses the actual ligand instead of a spherical probe to carve out the surface; (2) **Gaussian Surfaces** can be related to the electron density cloud of a molecule, modelled by radially symmetric Gaussian density kernels for each atom. Krone *et al.* [24] presented the fast**Quicksurf** algorithm to compute
175 such surfaces on the GPU, available in VMD. (3) The smooth **Molecular Skin Surface** [43] can approximate the SES and may be rendered using shader-based ray casting (see work by Chavent *et al.* [11] and figure 1, 2008). Later, Lindow *et al.* [38] refined their approach and presented a fast, CPU-parallelized computation. (4) Cipriano and Gleicher [9] presented an SES-based **Molecular Surface Abstraction**, which smoothens areas of high frequency (see figure 1, 2007).

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8 In summary, molecular surface rendering methods, such as SES, remain very
9 common in molecular graphics; however, these methods are not well suited for
10 all kinds of structural data.
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12 13 14 180 **5. Volume Rendering**

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16 Volume rendering methods are used to visualize density maps from X-ray
17 crystallography or from cryo-EM (Figure 3). A commonly used method is **direct**
18 **volume rendering** (DVR), in which the density map is shown as a fog of vary-
19 ing opacity and color. DVR is often implemented via GPU-based ray marching.
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21 Figure 3 (top left) shows a direct volume rendering of a cryo-EM map in combi-
22 185 nation with a fitted protein structure. For some tasks, users might be interested
23 in a certain interface of the volumetric data; in such cases, visualizing an iso-
24 surface is a feasible approach (see Figure 3 top right).
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28 Volume rendering methods are also used for a range of other kinds of molecu-
29 lar data. For example, electrostatic fields are often visualized with either isosur-
30 190 faces or field lines (Figure 3, bottom left and right, respectively). Additionally,
31 volume rendering methods has been used to show uncertainty in biomolecular
32 structures.
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36 With modern GPUs, volume rendering can be done interactively [44]. Al-
37 ternatively, interactivity can also be achieved with CPU-based methods. For
38 195 example, Knoll *et al.* [45] recently presented a CPU-based volume rendering
39 method for interactive ray tracing. They approximated the electron density
40 field using radial basis functions for each atom to visualize molecular data,
41 similar to the Gaussian surfaces mentioned in Section 4, which are isosurfaces
42 extracted from the Gaussian volume.
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47 48 **6. Dynamics and Flexibility**

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50 Biomolecules are often intrinsically very dynamic and flexible, leading to po-
51 sitional uncertainty in experimentally derived models. Many of these dynamic
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7 properties can be experimentally measured [46] and modeled in molecular sim-
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9 205 ulations [47]. In any case, it is still challenging to clearly convey dynamic
10 properties visually.

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12 One approach is to replace precisely defined atomic positions by probability
13 distributions [48], another to accumulate sampled conformations on a grid and
14 depict an isosurface or a volume rendering [49]. Alternatively, a given graphical
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16 210 representation can be made thicker or more fuzzy when positional uncertainty is
17 observed, versus making it thinner and well defined for precise conformations, as
18 is commonly applied to tubular 'sausage plot' representation of a protein back-
19 bone [50, 51]. Other options are to depict thermal vibrations of atoms through
20 multi-layered semi-transparent surfaces [52] or to use voxel maps for selected
21 flexible elements such as loops or domains in proteins [53]. Recently, Schulz *et*
22 *al.* [54] presented approaches to map uncertainty values like positional uncer-
23 tainty or flexibility to the cartoon representation of a protein using geometric
24 215 distortion and transparency. Figure 4 depicts flexibility using a motion blur
25 effect.

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32 220 Another approach is to enrich common representations by adding cues in-
33 dicating flexibility. Bryden *et al.* [55] used glyphs combining arcs and arrows
34 to illustrate directional molecular flexibility for clusters of atoms that exhibit a
35 synchronized rotational motion. Fioravante *et al.* [56] used color or cone glyphs
36 to depict motional correlations in proteins, based on principal component anal-
37 ysis and covariance clustering.
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41 Yet another approach is to use abstractions to recapitulate the observed
42 motion. Dabdoub *et al.* [57] draw pathlines of selected atoms to visualize the
43 dynamics of a molecule and add more visual cues through semi-transparent
44 ribbons displaying the movement of bonds. This approach allows the viewer to
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46 230 follow short parts of a trajectory, yet the visual representation might quickly
47 get confusing for very complex movements.
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7. Multi-scale Visualization

Driven by advances in experimental methods [4], in computational modeling [18], and in integrative approaches [58], the size and complexity of molecular systems amenable to structural biology is rapidly increasing. This, in turn, is creating new visualization challenges.

Inspired by David Goodsell’s pioneering depictions of biomolecular landscapes [59], several recent initiatives in computer graphics have taken on the challenge of constructing such models [12]. These models can be useful both for research [60, 61] as well as communication [62].

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.* [63]. A key method is to automatically adapt the level of molecular detail, depending on the proximity of the camera. Thus, Parulek *et al.* proposed a continuous and visual abstraction to pass from a very precise protein surface to a simple vdW representation as a function of the distance between the scene and the user’s point of view [64] (see figure 4). A similar approach was used to represent DNA origami structures at different scales [65] (see figure 4). Such seamless transformations can also be applied to pass efficiently from one protein depiction to another for illustrative purposes [10] (see figure 1).

These developments pave the way towards systems that enable interactive exploration of molecular-scale models of entire cells [66, 67] (see figure 4).

8. New Software Platforms for Molecular Graphics

Currently, most molecular graphics tools that structural biologists use as a mainstay are implemented as dedicated, stand-alone applications. However, this is set to change.

Recent advances in web technology are driving rapid developments in web-based molecular graphics tools, as outlined in several recent reviews [69, 70, 71]. One of the main drivers has been the WebGL API, which gives native support

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8 for GPU hardware-acceleration for molecular graphics web-apps, such as NGL
9 Viewer [72], LiteMol [73], and Jolecule [74]. Other driving technologies include
10 WebWorkers (e.g., used in NGL Viewer to calculate molecular surfaces off the
11 main thread), WebSockets (e.g., used to facilitate interactive visualization of
12 molecular dynamics trajectories [75]), and WebVR. In turn, this new genera-
13 265 tion of molecular graphics web-apps are being re-deployed as components on
14 many other web sites. For example, they are used by the world-wide Protein
15 Data Bank [76] on each of its three web sites (rcsb.org, pdbe.org, pdbj.org). Ad-
16 ditionally, they are used by the SwissModel [77] and Aquaria [78] resources to
17 facilitate access to millions of 3D structures derived from large-scale modeling.
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23 Currently, however, most web-based molecular graphics tools do not yet offer
24 the full range of functionality available with more established, stand-alone tools
25 (e.g., Chimera, VMD, etc.). This may soon change, driven by open-source, col-
26 laborative projects such as the recently launched Mol* initiative (molstar.org),
27 aimed at developing a common framework for web molecular graphics.
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31 Another relatively new software platform for molecular graphics is the Unity
32 3D game engine, which has been used to create the molecular editor Unity-
33 Mol [68] and MolecularRift [79], a tool for drug design. Developing in Unity
34 can greatly simplify deployment to AR and VR devices (e.g., Oculus Rift,
35 Hololens) [80].
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38 Finally, molecular graphics is increasingly being used within professional
39 animation software platforms. For the open-source, 3D modeling tool Blender,
40 the plugin BioBlender facilitates use of biomolecular structures [81], while the
41 Pyrite plugin facilitates use of molecular dynamics simulations [82]. For the
42 commercial 3D modeling tool Autodesk Maya, the plugin Molecular Maya ([83])
43 285 facilitates use of biomolecules.
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48 9. Conclusion

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51 We believe that increased adoption of some of these promising methods has
52 significant potential to advance structural biology by improving how structural
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290 biologists see and think about their data.

By covering references to state of the art surveys written by well recognized teams in the field, the perspective may further provide an entry point to contact computer graphics researchers to implement new rendering techniques which will definitely benefit structural biology.

295 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 in computer graphics — meetings such as VIZBI [84], BioVis [85], and MolVA [86].

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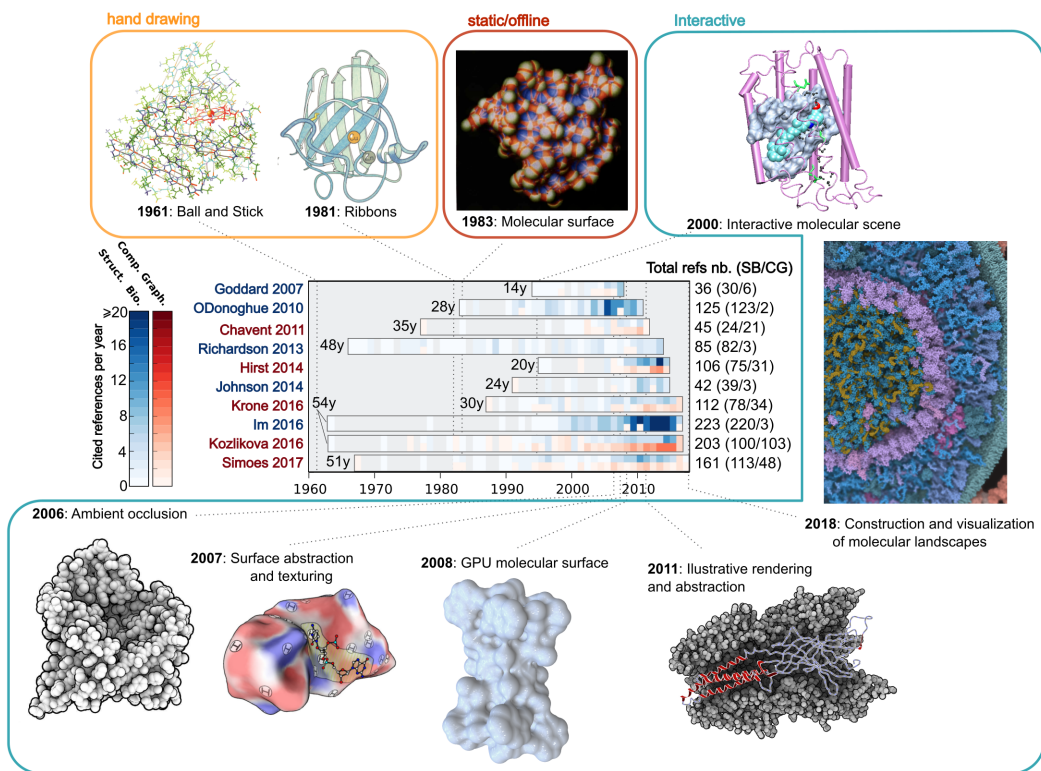


Figure 1: List of surveys presented in this article indicating their time span, number of cited references per year, total number of references, and the ratio of papers coming from the structural biology and computer graphics and visualization fields, respectively. If an article refers to both types of references for the same year, the cell is divided in two rows of different color. Blue color refers to articles oriented towards a more general (structural biology) audience while red color 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 Martin 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 [5] to more sophisticated representations like molecular surfaces. This surface was first processed as a static image [6]. During the early 90s to 2000s, with the advent of molecular viewers such as VMD, PyMOL or UCSF Chimera, it was possible to display all these representations interactively (here, a scene rendered with VMD [7]). From mid-2000s, technical developments performed in computer graphics labs are changing the way of visualizing molecular structures by better rendering molecular shapes using lighting effects such as Ambient Occlusion [8], developing new ways of rendering molecular structures [9, 10] or efficiently harnessing Graphics Processing Units (GPU) capabilities [11]. Now, it is possible to interactively construct and visualize very crowded and large systems opening the way for mesoscale models (spanning thousands of Angstroms and containing millions of molecules) with a nearly atomic resolution [12]. Unfortunately, these methods are not yet fully available to the end users such as structural biologists.

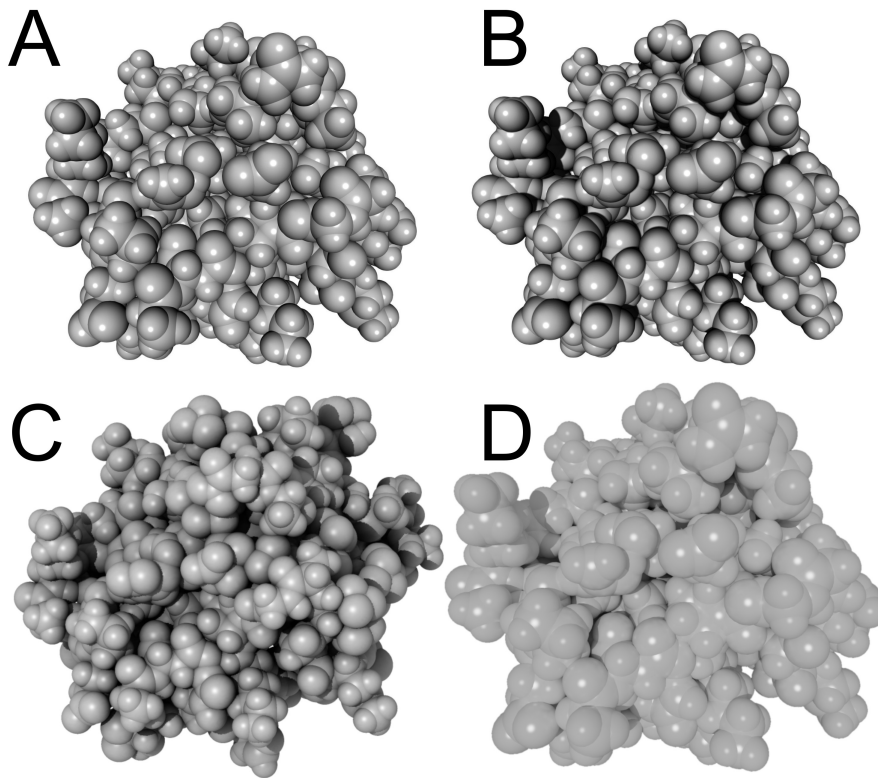


Figure 2: A- Basic Blinn-Phong (BP) rendering. B- Addition of shadows to BP rendering. C- Ambient occlusion lighting added to BP and shadows. D- Photorealistic rendering. While the three first renderings can be performed interactively, the latter still requires costly computation which currently only allows rendering static images.

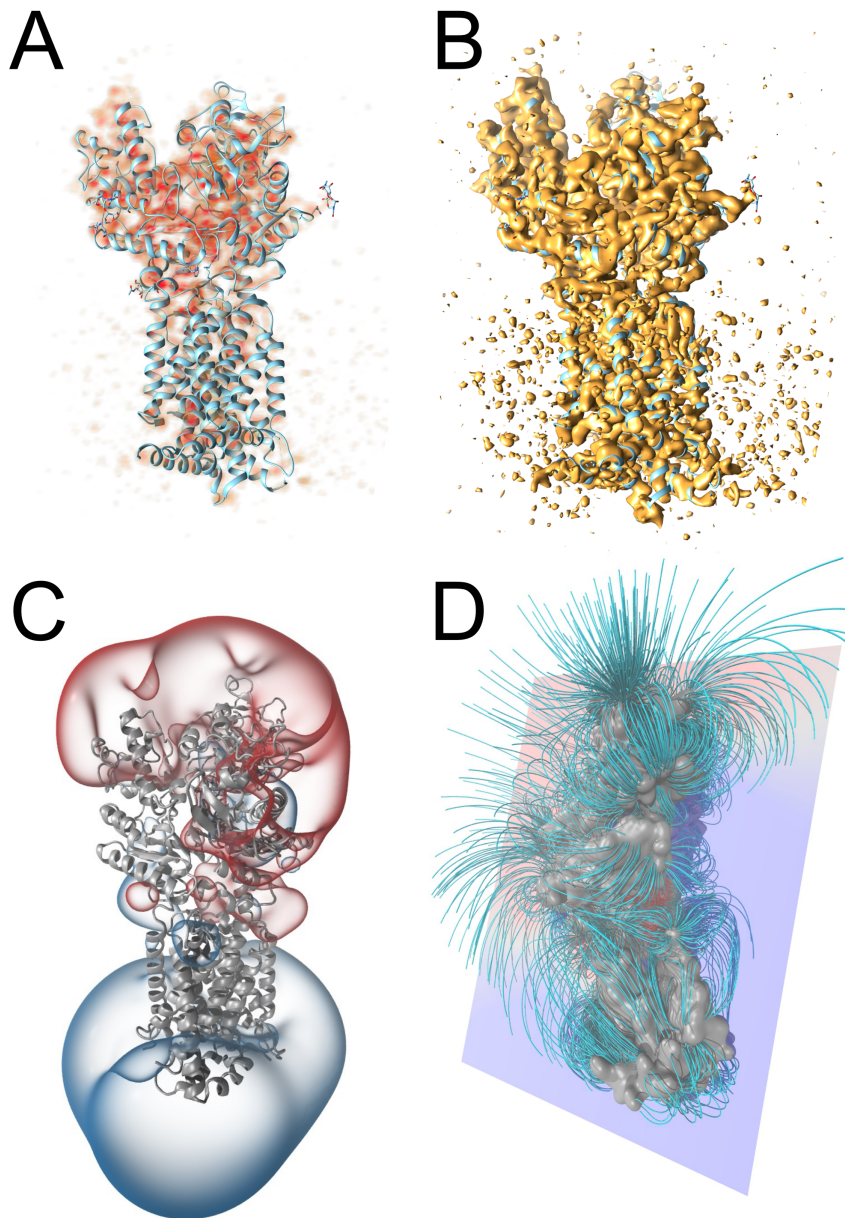


Figure 3: Examples of volume rendering for molecular data. Visualization of the cryo-EM map of a protein (PDB ID: 6D4J; EMD ID: EMD-7796) rendered using direct volume rendering (A) and isosurface (B). Electrostatic field represented as isosurface (C) and as field lines (D).

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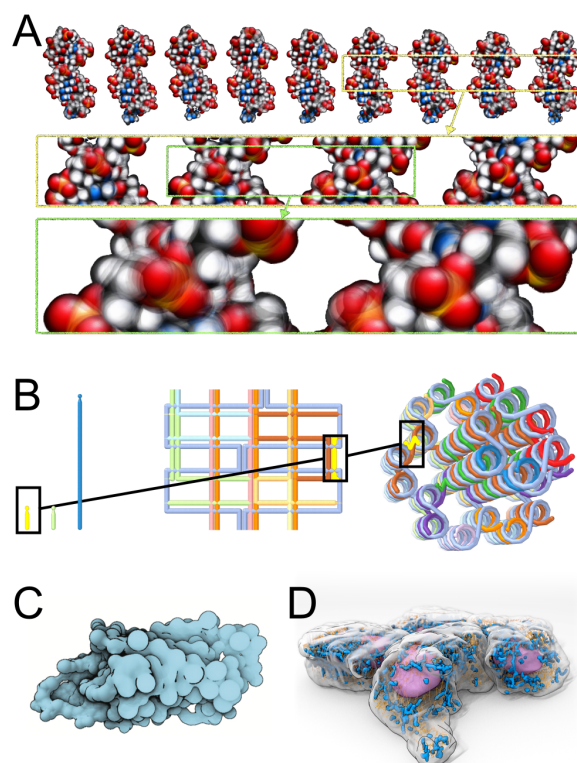


Figure 4: A- DNA dynamics depicted as time lapse-motion blurred rendering of an MD trajectory. Three levels of magnification are provided to depict dynamics at different time- and lengthscales: on the top row overall double helix motion is visible with DNA groove deformations up to the tens of Angstroms scale, in the middle row the local groove dynamics is highlighted leading to Angstrom-scale shape changes and the bottom row depicts very short timescale sub-Angstrom phosphodiester backbone vibrations. Figure generated using UnityMol [68]. B- Abstractions of DNA origami [65]. C- continuous transformation to pass from a very 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 [64]. D- illustrative representation of cell models [66]. 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>