Immersive Examination of the Qualitative Structure of Biomolecules

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Abstract

The geometry of biomolecules dictates their function, but reasoning about that structure is difficult because of their 3D complexity and the range of scales involved. The wooden or plastic ball-and-stick models that are common in high-school chemistry labs help people reason about these issues when the molecules involved are small, but they are useless in the study of large biomolecules. Largely for this reason, 3D computer visualization tools have become essential in this field. However, these tools are limited by their interfaces. Traditional graphics workstations project a 3D model onto 2D screen, and interaction with the 3D model is indirect, using 2D mouse or pointing device. Immersive visualization is a potential solution to this: it allows a user to visualize a biomolecule in 3D and interact with it directly in 3-space. This paper reports upon a pilot study about the effects of immersive visualization upon an expert's reasoning about the qualitative structure of these molecules. We ported a standard visualization application (PyMOL) to a CAVE-like immersive virtual environment (IVE), then invited three separate biochemistry research groups—people who use PyMOL routinely on desktop computers—to examine their favorite molecule in the IVE. Within ninety minutes of immersive investigation, each group reported a new discovery about the qualitative structure of that molecule. We believe that the immersive environment facilitated these discoveries by supporting and facilitating the natural spatial reasoning abilities of its users.

An immersive virtual environment is a combination of hardware and software that provides a psychophysical experience of being surrounded by a computer-generated scene (see Figure 1). Immersive virtual environments provide users with an egocentric three-dimensional perspective: users are immersed in a virtual world, where they can explore complex spatial systems by looking through them, walking around them, and viewing them from different perspectives. Immersive environments may help people see and understand the structure of complex three-dimensional datasets; in contrast to more traditional graphics workstations, these environments allow one to visualize data using the well-practiced, non-concious analysis that automatically accompanies an embodied, egocentric visual perspective. There are several studies that have investigated the added value of immersive environments (Pausch, Proffitt, & Williams 1997; Ruddle, Payne, & Jones 1999; Arns, Cruz-Neira, & Cook 1999; Swan *et al.* 2003; Gruchalla 2004; Schulze *et al.* 2005; Demiralp *et al.* 2006). However, the results of these studies are mixed and the issue is somewhat controversial. There are few studies that clearly demonstrate the effectiveness of immersive environments for real-world problems, and none that approach this issue from the standpoint of qualitative reasoning. Our study does so, and our results indicate that experts understand more about the geometry of biomolecules if they use an immersive environment than if they use the same visualization tools on a standard desktop. Within ninety minutes of immersive investigation, each of the three groups in our study reported a new discovery about the qualitative structure of an important biomolecule—molecules that these groups had been studying for years in with the same software visualization tool on desktop environments.

Immersive visualization has long been proposed as a means to analyze the complex three-dimensional structure of biological molecules (Ihlenfeldt 1997), and it is used by numerous investigators in basic research and industrial settings. Qualitative spatial analysis of the structure of these molecules at a range of scales is essential, because their overall three-dimensional configuration dictates the atomic interactions that are the basis of their function. Understanding the geometry of the building blocks of a biomolecule, and their relationships, is key to many of the grand-challenge problems in biochemistry: the rational design of drugs that enhance or inhibit molecular activity, the understanding of how steps in embryonic development normally proceed or go wrong in the presence of genetic mutations of molecular structure, and so on.

This paper documents a pilot study in which three separate groups of biochemists visualized and interacted with individual biological molecules in a CAVE-like IVE. In each case, the immersive working session yielded new insights that the same biochemists had not previously achieved with their extensive use of the same visualization package on standard desktop computer displays. Large-scale spatial features, such as pockets and ridges, were readily identi-

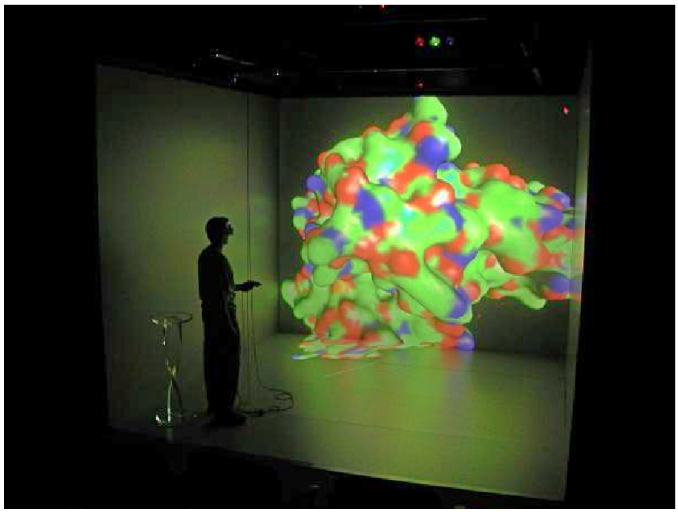

Figure 1: A user interacting with a PyMOL visualization of a molecular surface inside a CAVE-like immersive virtual environment, which provides the opportunity to visualize the molecule using normal, everyday-world perceptual abilities that have been tuned and practiced from birth.

fied when walking around the molecule displayed at human scale.

Methods

Three University of Colorado at Boulder (UCB) biochemistry research groups were invited to study a molecule of their choice—one central to their current research—in a FakeSpace Flex, a CAVE-like immersive virtual environment. The research groups had each intensively studied their chosen molecule using *non-immersive* visualization techniques—the desktop version of PyMOL, a popular open-source molecular visualization system (DeLano 2002)—for at least a year prior to conducting their research in the IVE. We ported this same tool to a stereoscopic, interactive IVE (Gruchalla, Marbach, & Dubin 2007) to provide some informal control in our study.

The Flex is configurable large-screen projection-based 12'x12'x10' theater, consisting of four walls: three rear-projected screens measuring 12'x10' that form the right wall, back wall, and left wall of the IVE. The fourth wall is the 12'x12' floor that is projected from above. A three-dimensional effect is created inside the IVE through active stereo projection and motion parallax. Stereo projection is achieved by projecting two images in sequence on each screen: an image for the viewer's left eye, followed by an image for the viewer's right eye. Viewers wear active stereo LCD shutter glasses to view the stereoscopic images. Infrared emitters synchronize the glasses with the graphics pipes. When the computer renders the image for the left eye, the right eye shutter is closed. Similarly, when the computer renders the image for the right eye, the left eye shutter is closed. This shuttering action creates the illusion of three-dimensional images. A motion parallax is supported by tracking the position and orientation of the viewer's head and using this information to generate an egocentric perspective. Virtual objects can be manipulated inside the IVE using a tracked wand.

PyMOL (DeLano 2002) is a powerful and versatile open-source, cross-platform real-time molecular visualization system that supports standard representations for molecular structures (e.g., wire bonds, cylinders, spheres, ball-and-stick, dot surfaces, solid surfaces, wire meshes, backbone ribbons, and cartoon ribbons). PyMOL's primary interface is an embedded Python interpreter, which is the basis for its sophistication. Our immersive port of PyMOL allows users to view PyMOL visualizations in a head-tracked IVE and manipulate molecular structures using a six-degree-of-freedom input device. Only the visualization and 3D interaction elements of PyMOL were ported to the IVE; its python-based command-line interface ran on a desktop computer. The visualization is *composed* (e.g., loading pdb files, choosing representations, selecting colormaps, ...) using the PyMOL command-line interface on this desktop, then viewed and manipulated in the IVE. Clearly, an IVE is poorly suited to support a command-line interface. Dividing the workflow between the two environments allows all the power and sophistication of the command-line interface to be used to construct the 3D model, while the visualization of the model and the spatial reasoning about its nature can be done in the 3D space of the IVE.

In this environment, three biochemistry groups conducted actual research about how the structure of their molecule relates to its function:

- The laboratory of Professor Arthur Pardi studying the anti-VEGF aptamer (Ruckman *et al.* 1998)
- The laboratory of Professor Natalie Ahn studying the extracellular signal-regulated kinase ERK2 (1erk.pdb) (Zhang *et al.* 1994)
- The laboratory of Professor Shelley Copley studying the enzyme maleylacetoacetate isomerase (1fw1.pdb) (Polekhina *et al.* 2001)

With one exception[1], the participants had no previous experience in viewing or manipulating objects in the IVE. Each group was given a brief introduction to the environment and how to manipulate molecular structures using the wand. Each group worked for about 90 minutes, with three of four members of the team working collaboratively inside the IVE, while one team member controlled the content of the visualization from a desktop computer using the PyMOL command-line and desktop interfaces. This similar to a traditional team working session, in which one member group would control the visualization from a desktop computer using the PyMOL command-line and desktop interface; however, in a traditional working session the rest of the team would gather around the computer to view and try to understand the resulting visualization.

[1]Professor Pardi had toured the immersive facilities and seen several immersive demos prior to the pilot study.

Results

Despite having a long and extensive research history with their respective molecules, all three groups arrived at a new insight from their 90-minute IVE research session. All of these insights were similar, and all involved qualitative reasoning about geometry. Each group became newly aware of a large spatial feature, such as an empty space or ridge, that they had not noticed during their (considerable) previous PyMOL work with the molecule on desktop computer monitors. In each case, the newly recognized feature led to insights about the molecule's function that follow directly from geometry: how its pieces move, for instance, or how they fit together. These are described in the following paragraphs. Each group left with the intention of exploring a new theoretical possibility based on these insights; the Ahn group actually integrated a hypothesis concerning the structure into a new grant proposal.

The Copley group recognized an empty pocket indenting from the surface in the enzyme maleylacetoacetate isomerase (MAAI) (see Figure 2). MAAI is normally a dimer, in which the interface between the dimer molecules blocks this pocket. However, the monomer of MAAI is similar to—and is used by the Copley group as—a model for another molecule, tetrachlorohydroquinone (TCHQ) dehalogenase, which is a monomer. This group is studying how a key component of the molecule's active site, amino acid cysteine at position 16 (cys16), interacts with substrate molecules that must be able to diffuse into TCHQ dehalogenase in order to reach cys16. The pocket represents a large enough opening for such entry, with cys16 lying at its base (darkened area in Figures 2c and 2d). When viewing this molecule on workstations, the researchers had discounted this region as a potential active site of TCHQ dehalogenase because they did not judge it to be spacious enough for the substrate to penetrate to cys16. The immersive visualization gave the researchers the ability to stand inside the pocket, which gave them enough information to reverse their decision.

The Ahn group was interested in a long "ridge" of potentially interacting amino acids that link two important sites of the enzyme ERK2 (see Figure 3). ERK2 is crucial component of the machinery that underlies normal and malignant cell production. Previous experiments had determined that small conformational changes caused by mutations of amino acids in the region shown in orange can cause a change in shape all the way across the molecule, in the region shown in purple. Biochemists are interested in understanding how such conformational changes are transferred across molecules, and the Ahn group used the IVE port of PyMOL to investigate this issue in ERK2. During their immersive investigation, they recognized the "ridge" between these two regions (shown in green in figure 3) as a possible physical linkage. This ridge could "transmit" changes in the orange region across the molecule to the purple region.

The Pardi group was interested in understanding how the complex surface regions of two molecules fit together in a complementary way. They used the IVE's six-degree-of-freedom handheld wand to manipulate the positions and orientations of the regulatory molecule VEGF and the anti-VEGF aptamer. VEGF has been implicated in human macular degeneration, a progressive disease that causes loss of high-acuity, central vision. The synthetic, anti-VEGF aptamer has been shown to be effective in slowing the progression of macular degeneration; however, the ability of anti-VEGF aptamer to inhibit the VEGF molecule is deterimined by the quality of the fit between the two. Using the interactive capabilities of the IVE, the Pardi group discovered a new possible fitting between the two molecules (see Figure 4).

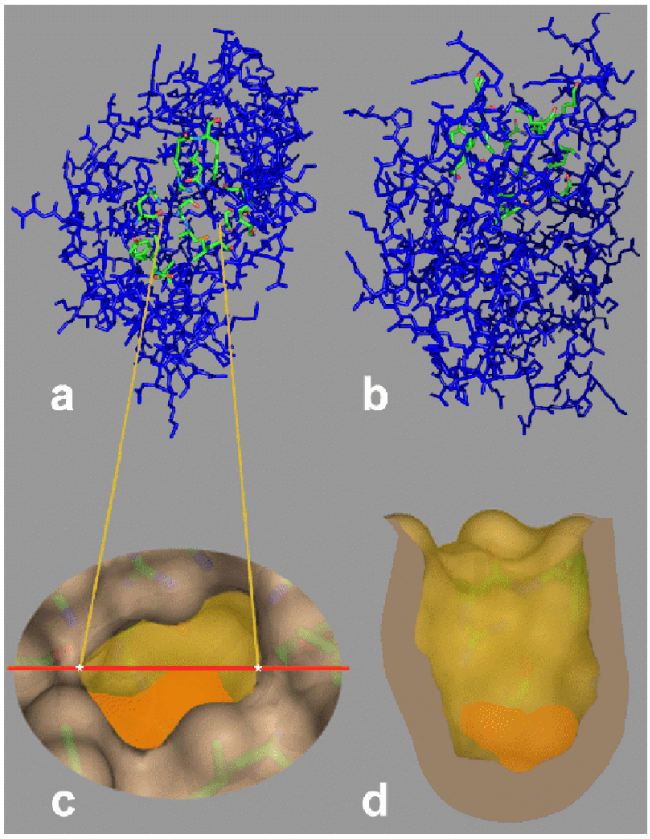

Figure 2: A molecular "pocket" that was discovered in the IVE: At top, the molecule (maleylacetoacetate isomerase) is shown in stick-representation with the region of interest shown with bright, non-dark-blue sticks; (a) is a view looking down into the pocket, (b) is a side view of the molecule at the same scale. The bottom two images show partial surface views of the region of the molecule immediately surrounding the pocket, with the approximate inside "surface" of the pocket in gold, and the amino acid cys16 in orange. (c) is a view looking down into the pocket; the mouth of the pocket corresponds to the region shown in the stick representation, as indicated by the lines. For (d), the pocket was bisected by the plane indicated by the line (x-axis) in (c), and rotated 90 degrees about the x-axis to yield a view of half of the pocket seen in side view, corresponding to the portion of the pocket at the top of (c). Panels (c) and (d) are to the same scale; the width of visible pocket in (c) is approximately 10 angstroms.

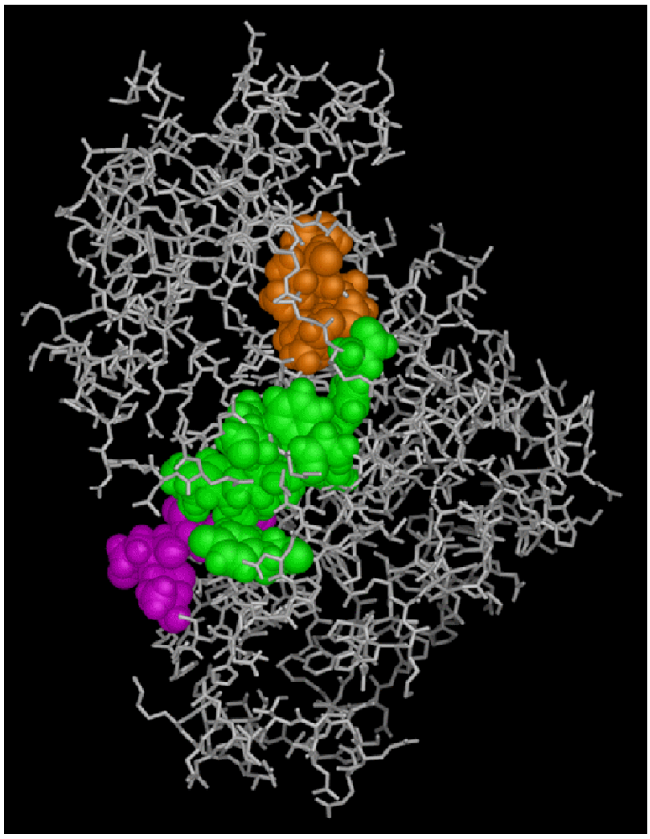

Figure 3: A stick-figure model of ERK2 with regions of interest shown in space-fill representation. Mutations in the orange region are known to cause shape changes in the magenta region. The "ridge" of green colored atoms, recognized by the Ahn group in the IVE, is a possible linkage between these regions.

Discussion

Reasoning about relationally generated space (such as a pocket in a molecule) depends on the scale of presentation, varying points of view, and movement in and around it. Thus, we suggest it is not surprising that the naturalistic IVE display allowed each of the three research groups to recognize important spatial features that they had previously overlooked in small, flat-screen, computer displays that must be indirectly manipulated with a mouse. The importance of naturalistic viewing is supported by numerous elegant experiments involving real-world, normal-size scenes (Purves & Lotto 2003; Yang & Purves 2003). Probabilistic matching of images like this provides a good explanation of numerous visual phenomena. This is not surprising; perceptual experience has molded our genetic makeup and it is tuned by the learning that each of us accumulates as we exist and develop day-to-day (Geary & Huffman 2002). This kind of knowledge is wired—and continuously rewired—in the neural circuitry of our brain, based on polysensory activities. That is, cognitive structures are developed from perception and action, and grounded in the physical interactions with the

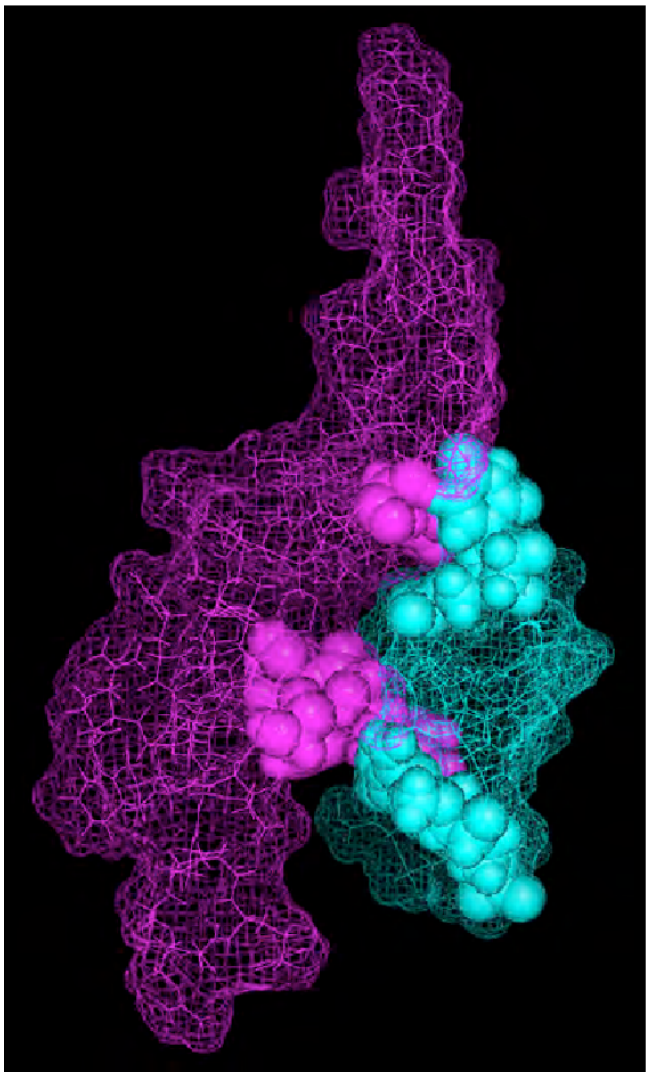

Figure 4: The Pardi group used the 3D interactive wand inside the IVE to investigate how the loop region of anti-VEGF aptamer (cyan) fits to a site on the outside of VEGF (magenta). The surfaces of both regions are show as meshes surrounding stick-figure representations, with atoms considered important shown in space-fill view.

environment (Pecher & Zwaan 2005).

In this context, it makes complete sense that working in an IVE allows people to reason more effectively about the geometry of biomolecules. Studies that demonstrate this effect are surprisingly rare, though, and the added value of immersion is controversial in the visualization community. This study is part of a larger effort that addresses this broader issue: a general definition of conditions under which the use of fully interactive, three-dimensional, immersive visualization adds value to research activities. As indicated in the previous section, our results suggest that short, intense sessions of IVE viewing valuably augment more extensive, non-IVE based research of molecular function. The underlying reasons for this, we believe, are threefold:

- First, spatial judgments are body-relative in everyday activity (Hatfield 2003). It is easier, for example, to judge whether you could crawl through a passageway in a cave if you are in the cave and looking at the passageway than if you are examining a five-inch-tall rendering of it on a flat screen monitor. Our hypothesis is that examining a molecule *at a human scale* made it easier for the biochemists to reason about the different spatial structures. Because the IVE presented the biomolecules at a natural and familiar scale—similar to the way many complex-shaped, everyday objects appear in the world—it facilitated effective reasoning about there shape.
- Second, the egocentric perspective improves spatial reasoning, object recognition, and stresses the role of action in building knowledge. Much of this happens automatically: people do not stop and think about how to move their heads or bodies in order to get a better view of something. The IVE supports this very naturally. Its unique features—natural body movements and well-practiced automatic brain function as the basis for examination of the structure in question—is consistent with recent research on *embodied cognition*, cognition that is based on perceptual knowledge accumulated through what we have encountered and manipulated with our bodies as we move within and examine the world (Wilson 2002; Wolputte 2002).
- Finally, the collaborative nature of the environment facilitates collaborative reasoning about the data. The large scale of the environment allowed multiple biochemistry researchers to gather inside the environment simultaneously. All the groups commented that they found working collaboratively in the IVE to be much easier than crowding around a small computer screen. The large scale made it easy to see what atoms and regions another member of the group was referring to. Often they used bodily references to direct each other, such as, "that group of bonds near your left shoulder."

Reasoning about the geometry of objects has a long and rich history in the qualitative reasoning field, and there are interesting papers about ontologies, paradigms, techniques, and applications for this in every QR workshop—beginning with an augmented version of Hayes's "pieces of stuff" ontology that was presented at QR '87 for reasoning about collections of molecules (Collins 1987). A few QR systems have been built over the years specifically for reasoning about molecular structure (Bandini, Cattaneo, & Stofella 1988). Most of the geometry-related work in the QR community has involved mechanical devices, an application (like biomolecules) where shape and function are intimately inter-related. Iwasaki, Joskowicz, Nielsen, and Faltings have made significant contributions to this over the years (Joskowicz 1987; Iwasaki 1987; Nielsen 1987; 1988; Faltings, Baechler, & Kun 1991; Tessler, Iwasaki, & Law 1993; Faltings 1993; Sun & Faltings 1994; Joskowicz & Sacks 1997). There has also been some work in the QR community that considers the cognitive science perspective along with the representation and the geometry, notably from Ken Forbus's group (Ferguson & Forbus 1999; Forbus, Ferguson, & Usher 2000; Forbus, Tomai, & Usher 2003; 2005; Lovett, Dehghani, & Forbus 2006).

The study reported here has a much more complicated application area than most of these papers, and much less lofty aims. We are not trying to simulate, design, or deduce anything. We rely on the human experts to figure out what's meaningful; we want simply to understand how immersive environments support their reasoning about the geometry that factors into that determination. Because of the comparative nature of our study, the ontology and the model are pre-specified. Our goal is not to figure out whether a better model or ontology exists for these purposes, as in many interesting QR papers, e.g., (Pacheco, Escrig, & Toledo 2002) but rather to study how the presentation & interface affects the spatial reasoning about the molecules. We are not trying to generalize ideas about structure across application domains, as in (Adorni *et al.* 1988) nor are we trying build more-abstract modelling paradigms, as in the elegant work of Escrig (which is concerned with many of the concepts that arise here, like how things fit together) (Museros & Escrig 2004). There are obviously many interesting problems to tackle involving the kinematics & dynamics of the biomolecules in our study, as well as the role of geometry in those processes, but these are "grand-challenge" problems and outside our scope.

Conclusion

This pilot study suggests that immersive environments enhance the ability of human experts to reason about the geometry of complex biomolecules. It also contributes further evidence to the general debate about the added value of large-scale immersive environments in the investigation of complex interactive spatial domains. The small sample size and lack of formal controls, however, mean that the results are only preliminary. The discoveries reported by the scientists in the study may have been facilitated by the opportunity to use embodied perceptual mechanisms afforded by the environment. Comments from the subjects suggest that the environment may have also provided a much improved collaborative atmosphere. Regardless of the specifics mechanisms, the results are very promising: all three user tests in this study generated a new piece of science as a result of their improved geometric reasoning about a complex problem.

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References

Adorni, G.; Burdese, M.; Del Grosso, A.; Loddo, R.; and Zucchini, A. 1988. A qualitative approach to structural mechanics. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Arns, L.; Cruz-Neira, C.; and Cook, D. 1999. The benefits of statistical visualization in an immersive environment. In *VR '99: Proceedings of the IEEE Virtual Reality 1999 (VR'99)*, 88–95.

Bandini, S.; Cattaneo, G.; and Stofella, P. 1988. A theory for molecule structures: The molecular onthology theory. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Collins, J. W. 1987. Reasoning about fluids via molecular collections. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

DeLano, W. 2002. The pymol molecular graphics system. http://www.pymol.org.

Demiralp, C.; Jackson, C.; Karelitz, D.; Zhang, S.; and Laidlaw, D. H. 2006. Cave and fishtank virtual-reality displays: A qualitative and quantitative comparison. *IEEE Transactions on Visualization and Computer Graphics* 12(3):323–330.

Faltings, B.; Baechler, E.; and Kun, S. 1991. Efficient qualitative kinematics. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Faltings, B. 1993. Qualitative structural analysis using diagrammatic reasoning. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Ferguson, R., and Forbus, K. 1999. Georep: A flexible tool for spatial representation of line drawings. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Forbus, K. D.; Ferguson, R. W.; and Usher, J. M. 2000. Towards a computational model of sketching. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Forbus, K. D.; Tomai, E.; and Usher, J. 2003. Qualitative spatial reasoning for visual grouping in sketches. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Forbus, K. D.; Tomai, E.; and Usher, J. 2005. Solving everyday physical reasoning problems by analogy using sketches. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Geary, D., and Huffman, K. 2002. Brain and cognitive evolution: forms of modularity and functions of mind. *Psychol. Bull.* 128(5).

Gruchalla, K.; Marbach, J.; and Dubin, M. 2007. Porting legacy applications to immersive virtual environments: A case study. In *Proceedings of 2007 International Conference on Computer Graphics Theory and Applications*, 179–184.

Gruchalla, K. 2004. Immersive well-path editing: Investigating the added value of immersion. In *VR '04: Proceedings of the IEEE Virtual Reality 2004 (VR'04)*, 157–164.

Hatfield, G. 2003. Representation and constraints: the inverse problem and the structure of visual space. *Acta Psychol. (Amst.)* 114:355–378.

Ihlenfeldt, W. 1997. Virtual reality in chemistry. *Journal of Molecular Modeling* 3:368–402.

Iwasaki, Y. 1987. Generating behavior equations from explicit representation of mechanisms. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Joskowicz, L., and Sacks, E. 1997. Qualitative and quantitative mechanical assembly design. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Joskowicz, L. 1987. Shape and function in mechanical devices. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Lovett, A.; Dehghani, M.; and Forbus, K. 2006. Solving everyday physical reasoning problems by analogy using sketches. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Museros, L., and Escrig, M. T. 2004. A qualitative theory for shape representation and matching. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Nielsen, P. 1987. A qualitative approach to mechanical constraint. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Nielsen, P. 1988. Qualitative mechanics: Envisioning the clock. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Pacheco, J.; Escrig, M. T.; and Toledo, F. 2002. Qualitative spatial reasoning on three-dimensional orientation. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Pausch, R.; Proffitt, D.; and Williams, G. 1997. Quantifying immersion in virtual reality. In *Proceedings of the 24th annual conference on Computer graphics and interactive techniques*, 13–18. ACM Press/Addison-Wesley Publishing Co.

Pecher, D., and Zwaan, R. 2005. Introduction to grounding cognition. In Pecher, D., and Zwaan, R., eds., *Grounding*

cognition, 1–7. Cambridge, England: Cambridge University Press.

Polekhina, G.; Board, P.; Blackburn, A.; and Parker, M. 2001. Crystal structure of maleylacetoacetate isomerase/glutathione transferase zeta reveals the molecular basis for its remarkable catalytic promiscuity. *Biochemistry* 40(6):567–576.

Purves, D., and Lotto, B. 2003. In *Why We See What We Do: An Empirical Theory of Vision*. Sunderland, MA: Sinauer.

Ruckman, J.; Green, L.; Beeson, J.; Waugh, S.; Gillette, W.; Henninger, D.; Claesson-Welsh, L.; and Janjic, N. 1998. 2'-fluoropyrimidine rna-based aptamers to the 165-amino acid form of vascular endothelial growth factor(vegf(165)) - inhibition of receptor binding and vegf-induced vascular permeability through interactions requiring the exon 7-encoded domain. *Journal of Biological Chemistry* 273:20556–20567.

Ruddle, R.; Payne, S.; and Jones, D. 1999. Navigating large-scale virtual enviroments: What differences occur between helmet-mounted and desk-top displays? *Presence: Teleoperators and Virtual Environments* 8:157–168.

Schulze, J.; Forsberg, A.; Kleppe; Zeleznik, R.; and Laidlaw, D. H. 2005. Characterizing the effect of level of immersion on a 3D marking task. In *Proceedings of HCI International*.

Sun, K., and Faltings, B. 1994. Supporting creative mechanical design. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Swan, J. E.; Gabbard, J. L.; Hix, D.; Schulman, R. S.; and Kim, K. P. 2003. A comparative study of user performance in a map-based virtual environment. In *VR '03: Proceedings of IEEE Virtual Reality 2003 (VR'03)*, 259–266.

Tessler, S.; Iwasaki, Y.; and Law, K. 1993. Qualitative structural analysis using diagrammatic reasoning. In *Proceedings of the International Workshop on Qualitative Reasoning about Physical Systems*.

Wilson, M. 2002. Six views of embodied cognition. *Psychon. Bull. Rev.* 9(4):625–636.

Wolputte, S. V. 2002. Hang on to your self: of bodies, embodiment, and selves. *Ann. Rev. Anthropol.* 33:251–269.

Yang, Z., and Purves, D. 2003. A statistical explanation of visual spaces. *Nat. Neurosci.* 6(6):632–640.

Zhang, F.; Strand, A.; Robbins, D.; Cobb, M.; and Goldsmith, E. 1994. Atomic structure of the map kinase erk2 at 2.3 a resolution. *Nature* 367:704–711.