Structure, Vol. 13, 483–491, March, 2005, ©2005 Elsevier Ltd All rights reserved. DOI 10.1016/j.str.2005.01.009

Tangible Interfaces for Structural Molecular Biology

Alexandre Gillet, Michel Sanner, Daniel Stoffler, and Arthur Olson[1,*]
The Scripps Research Institute
La Jolla, California 92037

Summary

The evolving technology of computer autofabrication makes it possible to produce physical models for complex biological molecules and assemblies. Augmented reality has recently developed as a computer interface technology that enables the mixing of real-world objects and computer-generated graphics. We report an application that demonstrates the use of autofabricated tangible models and augmented reality for research and communication in molecular biology. We have extended our molecular modeling environment, PMV, to support the fabrication of a wide variety of physical molecular models, and have adapted an augmented reality system to allow virtual 3D representations to be overlaid onto the tangible molecular models. Users can easily change the overlaid information, switching between different representations of the molecule, displays of molecular properties, or dynamic information. The physical models provide a powerful, intuitive interface for manipulating the computer models, streamlining the interface between human intent, the physical model, and the computational activity.

Introduction

With the prevalence of structural and genomic data, molecular biology has become a human-guided, computer-assisted endeavor. The computer assists the essential human function in two ways: in exploration of scientific data, searching for and testing scientific hypotheses; and in collaboration between two or more scientists, sharing knowledge and expertise. As databases grow, as our structure and process models become more complex, and as software methods become more diverse, access and manipulation of digital information is increasingly a critical issue for research and collaboration in molecular biology.

Currently, exploratory research in structural molecular biology is dominated by 3D representations via computer graphics. Collaboration, both remote and local, is aided by shared viewing of these interactive visual representations of molecular data. Yet, recent advances in the field of human-computer interfaces have not been applied to the technology used by molecular biologists—most work in biomolecular structure, and genomics is performed in front of a workstation display using a mouse and keyboard as input devices.

The tactile and proprioceptive senses provide key perceptual cues to our ability to understand 3D forms, and to perform physical manipulations, but are currently underutilized in most computational activities, including structural molecular biology. Recently, the concept has arisen that the "sixth sense" of body awareness may play a critical role in our fundamental understanding of physical laws (Smetacek and Mechsner, 2004). Thus, physical models may provide an enhanced perceptual experience in our comprehension of molecular structure and interaction. Early structure research relied heavily on physical models: Pauling used his newly-invented space-filling models to depict the molecular structures that he solved by crystallography and to predict the basic folding units of protein structures (Pauling and Corey, 1950). Watson and Crick used brass-wire molecular models to help them devise an atomic model of the of DNA double helix (Watson and Crick, 1953), which reconciled decades of genetic data. These researchers "thought with their hands" by using physical analogs to produce important scientific results. Current research in molecular biology now focuses on larger assemblies and on more complex interactions, for which the traditional atom-based physical models are inadequate.

The evolving technology of computer autofabrication ("3D printing") now makes it possible to produce physical models for complex molecular assemblies (Olson, 2001). Computer autofabrication technology, sometimes called "solid" or 3D printing (Burns, 1993) has evolved over the last decade from a rapid prototyping tool for product design and manufacture to a class of more broadly applied output devices used in many contexts where physical representations are helpful. All of these technologies utilize a layer-by-layer build-up of the physical part with some method of support for overhangs in the vertical build direction. The great advantage of these methods is that nearly any shape can be built—limited only by the imagination and the structural integrity of the building material. A number of different types of solid printers are on the market, utilizing materials ranging from cornstarch to metal and enabling the production of parts with various physical and mechanical properties. Solid printers that can produce full-color parts are now available.

The field of augmented reality (AR) has likewise emerged over the past decade within the computer-human interface community. The "transparent computer interface" is a goal driving development of immersive displays, object tracking, haptics, and numerous other technologies for virtual reality. An important objective of this development is the creation of a sense of user presence in a computational interaction. Much of the research into this subject has been focused on far- and mid-field tasks, such as motion simulation, navigation, and virtual walkthroughs, where the user is immersed in the simulated environment. Near field activities, including such traditional human tasks as tool manipulation, model building, and close inspection have been advanced through the use of 3D computer graphics for over 40 years. Much of the recent work in

*Correspondence: olson@scripps.edu
[1]Lab Address: http://www.scripps.edu/pub/olson-web

near-field object presence (Barfield and Weghorst, 1993) and interaction has focused on improved rendering, stereoscopy, force feedback, and 6D object manipulation techniques (Poupyrev et al., 1997). The application of force-feedback to molecular modeling was pioneered by Brooks and coworkers at the University of North Carolina (Ouh-Young et al., 1988; Taylor et al., 1993). More recent work by Taylor and colleagues has resulted in a haptic interface to scanning probe microscopy, termed "the nanomanipulator" (Taylor et al., 1993). Augmented reality has also been brought to bear on near-field interactions in such applications as diagnostic medicine and surgical planning. More recently, the use of real-world proxies, or physical icons ("phicons") has begun to be explored in augmented reality applications to increase the illusion of real interaction (Ishii and Hau, 1997; Billinghurst, 1999; Underkoffler et al., 1999). Brooks has identified the area of haptics as being critical to the sense of presence for near-field activities (Brooks, 1999) such as the exploration of molecular structure and function.

In this paper, we report on an application that demonstrates the use of autofabricated tangible models and augmented reality for research in molecular biology to enhance the scientific environment for collaboration and exploration. The physical models are produced and integrated into an augmented reality environment to streamline the interface between human intent, the physical model, and the computational activity. We have developed an AR system that allows virtual 3D representations generated by our Python Molecular Viewer (PMV) (Coon et al., 2001) to be overlaid on an autofabricated model of the molecule. The precise registration of the virtual objects with the real world is done using the ARToolKit library developed at the University of Washington (Billinghurst, 1999). While using our tangible interaction environment, users can easily change the representation shown, and, for example, access information about molecular properties of the molecules.

Producing physical molecular models presents both new challenges and opportunities for representing molecular properties and behaviors. Unlike an intangible computer graphic, the physical model can embody not only the visual characteristics of the molecular system, but also analogs of some of its physical features. Merging physical and virtual objects into an AR environment (Milgram and Kishino, 1994) enables new modes of interaction through the manipulation of tangible models and the complex information they represent (Behringer et al., 1999).

We have found that the tangible interfaces that we have produced provide users with both enhanced perception and intuitive manipulation of complex biomolecules and their interactions.

Results and Discussion

Design of Physical Models

We use PMV (Coon et al., 2001) both to create our virtual molecular objects and to design our tangible molecular models, greatly simplifying the integration of the models with the virtual environment. We use our visual programming interface, Vision (formerly called ViPEr) (Sanner et al., 2002; Sanner, 2005, this issue of *Structure*), to integrate nonmolecular features into the virtual and physical models. PMV is a modular software framework for designing and specifying a wide range of molecular models, including molecular surfaces, extruded volumes, backbone ribbons, and atomic ball-and-stick representations. PMV can also handle volumetric data from low-resolution structural information and produce isocontour surfaces for that data. It allows the design of models at different levels of abstraction, resolution, and scale for different needs: using representations that focus on molecular shape when large systems and interactions are presented, and incorporating atomic details when needed to look at function at the atomic level. Vision is a graphical programming environment that allows the integration of computational components as nodes in a visual network editor, enabling rapid prototyping of new applications.

Both PMV and Vision are built within the interpreted language Python, which serves as a glue layer to interconnect different software components at a high level (Sanner, 1999). We have used Python for a number of years in this capacity because of its many desirable characteristics: it is open source and object oriented, platform independent, extensible and efficient, and has excellent introspection capabilities. PMV includes a generic 3D visualization component (DejaVu), which provides a high-level interface to the OpenGL library and its geometry viewing application.

To this, we have added components that provide all manner of molecular modeling and visualization functionality, including MSMS, Maximal Speed Molecular Surface (Sanner et al., 1996) for the calculation of solvent-excluded surfaces, GLE tubing and extrusion library (www.linas.org/gle) for the extrusion of arbitrary 2D shapes along an arbitrary 3D path (as needed for ribbon diagrams), Babel (eyesopen.com/babel.html) for handling molecular files and coordinates, and RAPID Robust and Accurate Polygon Interference Detection System (Gottschalk, Lin et al. 1996) for the fast detection of intersections between polygonal models. New components have also been developed to export the resulting representations from the PMV environment in STL (stereolithography) or VRML (Virtual Reality Modeling Language) format as input to the autofabrication machinery.

Designing a physical visualization utilizing autofabrication necessitates requirements well beyond those of the virtual models seen on the computer screen. First, the model must be a geometrically correct object, with inside and outside well defined. Many computer molecular models produce improper geometries with self-intersections and open edges. Second, the model must be designed to be mechanically feasible—that is, it must hold together (with no "floating" parts), and be strong enough to withstand handling and gravity. Issues of material characteristics such as strength and anisotropy as well as supplementary support structures must be factored into the design of the model. Thus with the components available in PMV and Vision, we are able to create valid solid objects, add additional

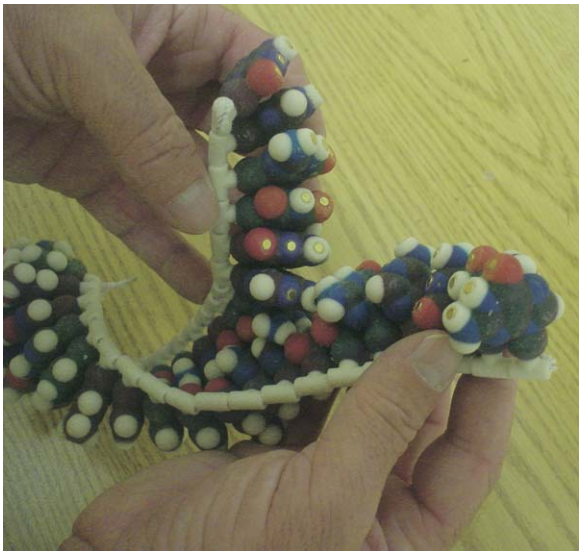

Figure 1. Molecular Modeling Coupled with Computer-Aided Design Software Allows for Design and Exact Placement of Affordances

Here a flexible model of DNA with magnets representing hydrogen bond donors and acceptors gives the feel of double helix base pair recognition.

support structures if necessary, and export the geometries to the autofabrication machinery. Unlike traditional CAD/CAM packages, our environment is tailored to the production of a wide variety of molecular representations, resolutions and scales, utilizing the established visual vocabulary of molecular modeling.

In addition to the constraints of producing a physical model, there are possibilities to enhance its functionality through design of mechanical or other operational features. For more complex representations that incorporate flexibility or other functional characteristics, we rely upon supplementing the design using CAD/CAM approaches. In collaboration with the University of Utah, we have developed a parser to transform atomic coordinates into surface/feature-based representations, for use in extending the functionality and utility of the physical molecular models. Computer aided design (CAD) capabilities, such as constructive solid geometric Boolean operations on objects, enable a wide variety of modeling extensions. Such extensions include the design of affordances into the models to accommodate analog components, such as magnets to represent bonding capacity, such as hydrogen bond donors and acceptors in DNA base pairs (see Figure 1). Other mechanical components such as hinges, flexible linkers, and springs can also be built into the models. While each autofabricated model can be custom built, it is also possible to prototype components that can then be replicated using other, less expensive technologies. The Utah Group has developed software for replication technologies that can fit the atoms to a plane, split the model into halves, and create outer and inner models for injection molding.

Production of Models

We have utilized two autofabrication technologies. In our testing of the methods, we have found that each has definite advantages and disadvantages for the construction of molecular models. The Z-corp process (Zcorp 406 color 3D printer) applies a pigment-binder mixture to powdered gypsum using ink-jet print heads. The parts are finished by infiltrating a strengthening agent into the model after construction. This may be wax or cyanoacrylate glue if rigid models are desired, or an elastomer to produce rubber-like flexible models. The process is relatively fast and the materials are relatively inexpensive. The major advantage is that full-color models may be constructed automatically (see Figure 2). The models, however, can be fragile, and one challenge for our future work is to overcome this fragility.

Stratasys (Stratasys Prodigy Plus) uses a fused deposition method that extrudes a molten ABS plastic filament to form each layer. The process is slower and approximately twice the cost for materials and the models are monochrome. However, they are far more durable, so finer representations, such as ball-and-stick models and preassembled operational mechanical parts can be routinely created.

Augmented Reality Interface

Physical molecular models, while vastly more informative and intuitive than 2D drawing or textual descriptions, are fixed in form and cannot show everything about a structure's properties. We use computer-based spatial tracking and rendering methods to enhance the semantic content of our models and to show dynamic properties. Augmented reality combines real world presence with virtual object presence, giving the illusion of a real interaction by leveraging the natural semantics of physical object manipulation (Fitzmaurice et al., 1995; Ishii and Hau, 1997; Brave et al., 1998; Gorbert et al., 1998; Billinghurst, 1999). Our AR interface combines real-world user and physical model presence with computational models and data. The user manipulates a model, and the model is tracked by a video camera and is displayed on the computer screen. A virtual representation (e.g., another 3D rendering of the same molecule, textual labels, or a 3D animation) is composited with the video display, and spatially registered with the model as the user manipulates and explores the structure. The result is a quite compelling sense of virtual object realism (see Supplemental Data for a video of the system in operation). Our approach is based on the widely-used ARToolKit (Billinghurst, 1999), an open-source software library for developing vision-based AR applications. ARToolKit is a software library that can be used to calculate the real camera position and orientation relative to physical markers in real time, allowing overlay of virtual objects onto the physical markers. Some of the features of the library include use of a single camera for position/orientation tracking, marker tracking code that uses simple black squares and pattern matching software that allows arbitrary patterns to be used, and fast performance for real time AR applications. The video tracking recognizes marker squares. By analyzing the distortion and scale of these

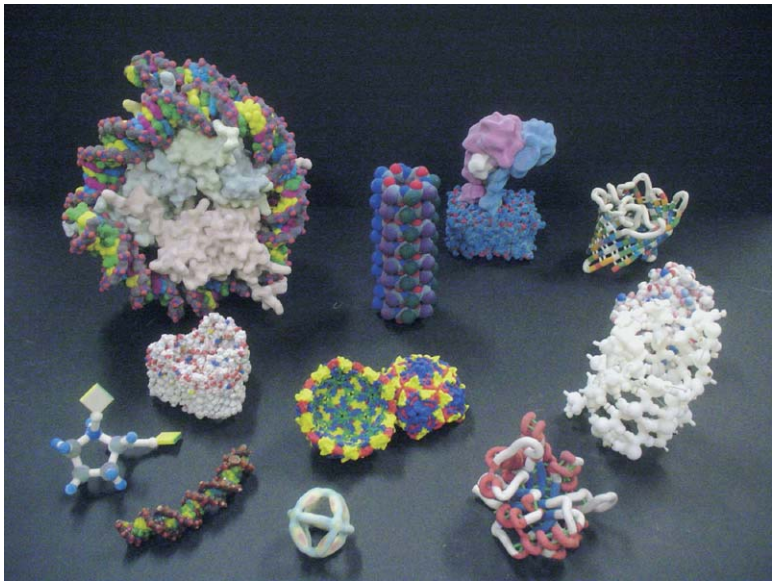

Figure 2. A Number of Molecular Models Built with Different Materials, Showing a Wide Range of Molecular Representations, Scales, and Sizes

squares, the translation and orientation of the marker can be computed. The pattern within each square is recognized and identified with a particular marker placement (see Figure 3).

We have wrapped the ARToolKit in Python to allow integration with PMV, creating PyARTK, a stand-alone Python module that provides a framework to manage markers, displays composite images from video input, and allows access to the functionality of the ARToolKit library. It has been integrated with PMV to streamline both the design and the display of models within the same environment. A geometry manager in PyARTK assigns the geometries, animations, and masks to specific AR markers or sets of markers. Changes can be made interactively as the modeling proceeds. Computer graphic objects, camera operations, and clipping and lighting controls are provided in the interface, along with the video tracking and composite display. PyARTK tracks the embedded markers and then combines the video display of the model with the molecular graphics created by PMV.

We have also added a basic animation facility to PyARTK, which allows run-time paging through different computer-generated representations while manipulating and examining the model. It was apparent in early tests that masking could be used to enhance the perceptual integration of the physical and virtual objects (see Figure 6). The mask is created directly from the geometry used to build the tangible model. It is used to erase portions of the virtual object that should be occluded by the physical model.

The tangible molecular models are recognized and tracked using the square fiducial markers, which are placed on the surface of the model. These markers are used to register the superimposed virtual object with the manipulated real-world object. When designing the model in PMV, we can add one or more small square marker platforms to the model. Once the model is built, printed paper markers are glued onto these platforms. The transformations specifying the relationships between the markers and the models are saved during the design phase, and later used to compute the correct registration to overlap the 3D virtual object with the tangible model. By using several markers, the AR overlay

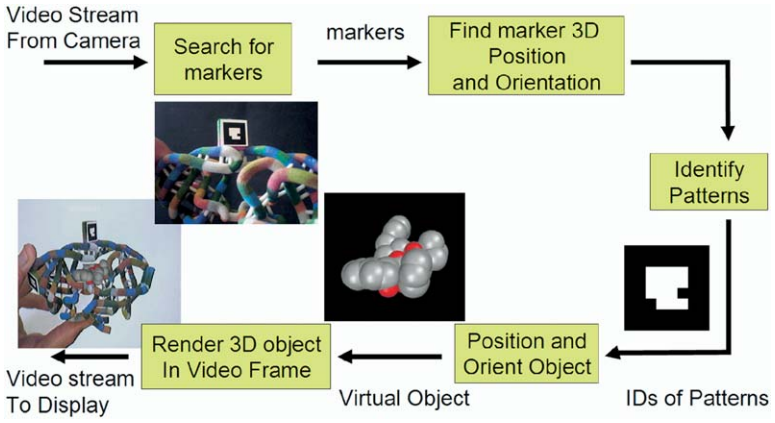

Figure 3. The Image Processing Pipeline Used in ARToolKit

Adapted from the ARToolKit 2.33 manual.

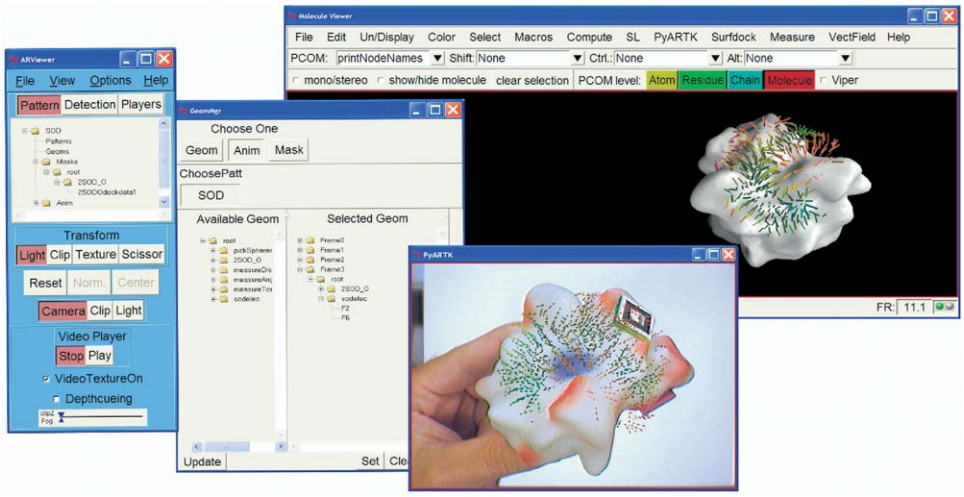

Figure 4. PyARTK and PMV Are Shown Integrated in the Same Process

Different windows and graphical user interfaces control a variety of functions. The ARTViewer window is the interface for managing the patterns, GeomMgr window provides an interface for setting the geometry assigned to a pattern, and finally, the PyARTK window provides the composite graphic and video display. The PMV window is shown with the geometry used to build the tangible model of SOD and the vector field used to augment the tangible model.

can be maintained and appropriately occluded while being arbitrarily manipulated and viewed from all angles. To facilitate this, we have implemented the concept of a group of markers, so that one model can carry several markers that all display the same virtual object but with different orientation depending on the location of the marker on the model.

Integration of the PMV and the PyARTK Applications

PMV and PyARTK are two independent components providing two fundamentally different functionalities. PMV has built-in knowledge of molecules including the ability to compute molecule-specific representations. PyARTK provides a python wrapper to the ARToolKit library for developing computer vision-based AR applications including multiple object tracking and compositing of computer-generated 3D geometries and video.

PyARTK has no knowledge of molecules. This crucial design features make this software component reusable in a much broader context than molecular visualization and modeling. The ability to compute ribbon diagrams or color a molecular geometry according to a given molecular property could in principle be extracted from PMV and added to PyARTK. However, this would duplicate functionality and would require the repetition of this process for a large and increasing number of PMV commands. Instead, we decided to interface PMV and PyARTK in order to (1) allow PyARTK to gain access to PMV's ability to handle and represent molecules, and (2) streamline both the design and the display of models within the same environment. We wrote a new PMV command that creates an instance of a PyARTK object when executed. When PyARTK is started inside the PMV environment, the geometry manager obtains knowledge of the geometries computed in PMV. We also gain access to PMV logging capabilities allowing us to generate scripts that can be rerun later (see Figure 4).

AR Implementation

With a software system in place for autofabrication of tangible molecular models and integration with an AR environment, we could begin to test our hypothesis that the perception of the complex shapes and interactions of biological molecules can be enhanced by the manipulation of augmented physical models. The implementation of a system where we could easily explore its utility dictated some practical design decisions. The integration of the physical models with the virtual augmentation requires the superposition of the two worlds into the same perceptual space. There are a number of ways to achieve this, including use of a head-mounted display where the user sees video of the real world scene and the superimposed computer graphic information. Projection of the computer information onto the physical model could be another approach. The expense and imperfect performance of these technologies at the present time lead us to a simpler "two-view" solution. By placing the video camera on a stalk near the users eyes and positioning a computer screen behind the area where the physical models are manipulated, both the physical model and the computer augmented scene can be viewed. By shifting focus, the user's attention can be directed either to the physical model or to the augmented scene. This configuration has proven to be an effective, inexpensive, and portable solution (see Figure 5). We have demonstrated this implementation utilizing readily available, commodity USB or Firewire cameras attached to laptop computers (Windows, MAC, and Linux). We have found that controlled lighting with USB-powered LED lights helps maintain the video tracking in different physical environments.

Examples

The following examples demonstrate how this application can be useful in a collaborative environment and

Figure 5. Set-Up of Augmented Reality Interface

A Firewire camera can be seen on the stalk above the manipulated model. The combined video and computer augmented images are displayed on the screen of the laptop computer.

also be a powerful tool for communicating key concepts in molecular biology.

HIV Protease

In this first example, we integrated a physical protein backbone representation of HIV protease with a computer graphic display of various inhibitor molecules that are effective in the treatment of AIDS. We built a backbone representation of HIV protease using the Zcorp printer. The geometry is represented by a tube colored by the amino acid sequence along the backbone. To track the model in any position, we placed three markers on the model, so that in any orientation, at least one marker is in the field of view of the video camera. We used AR overlay to show the bound conformation of five inhibitors within the active site of the protease (see Figure 6). Each inhibitor is displayed as a space-filling representation and colored by atom type. Text can also be displayed giving the names of the inhibitors as they are shown. The user can page through each inhibitor by using the animation player built within PyARTK. Notice in the figure that a mask is superimposed on the physical backbone model, providing correct occlusion of the computer graphic with the video texture.

Superoxide Dismutase

This example illustrates the function of superoxide dismutase (SOD), a detoxification enzyme that exhibits a strong electrostatic funneling effect. The user manipulates a tangible model of the SOD molecule built with the Stratasys printer (see Figure 7), and AR enhances the monochrome tangible model with color and shows dynamic properties. The physical model is represented as a spherical harmonic surface, which shows the overall shape of the protein but smoothes out the atomic details (Duncan and Olson, 1993). A real-time volume rendered electrostatic field is displayed around the protein surface, utilizing 3D texture mapping available on modern graphics processing units. A transfer function widget can interactively control its appearance. In addition, animated arrows are displayed in the vicinity of the enzyme's active site, to show the field gradient that depicts the forces a negatively charged superoxide free radical would feel. With this interface, we can also manipulate interactions of two SOD proteins that form a dimeric complex, and thus provide an intuitive way to guide computational exploration.

Ribosome

The ribosome is a complex biomolecular machine composed of two subunits that together build proteins by aligning tRNA molecules along an mRNA strand. We have created a tangible model of the small subunit (see Figure 8) using the Zcorp printer, using a smooth spherical harmonic representation. We augment the physical model with a virtual representation of the large subunit, to show how the two subunits assemble into the functional complex. We also show an animation of the three positions of tRNA at the translation interface of the ribosome.

Evaluation

In collaboration with the Human Interfaces Technology Laboratory at the University of Washington, we are currently testing the efficacy of augmented models in a classroom setting, and their usefulness for basic research by structural molecular biologists.

The first pilot test involved Biotech Academy program high school students in Seattle. The initial lesson was developed around basic protein structure concepts and the structure and function of hemoglobin. We produced an appropriate set of hemoglobin models and we conducted a weeklong technology assessment. The results suggested that the augmented tangible models were quite engaging and instructive, but we needed to have a more comprehensive lesson plan in order to generate quantitative results.

In our second test, we have created models of the twenty naturally occurring amino acids, and designed a short lesson to present their structure and function in proteins. A pilot study with students from a college-

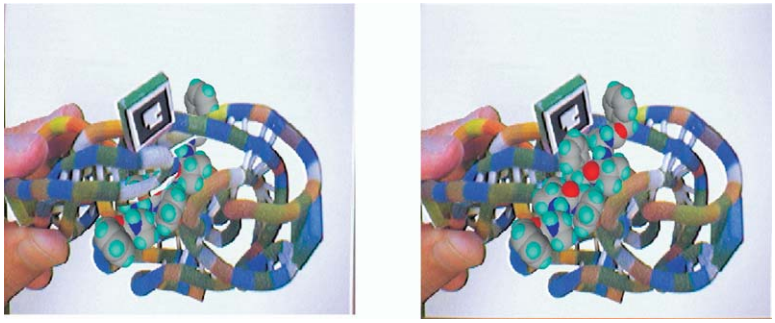

Figure 6. A Three-Dimensional Virtual Object Occluded by the Physical Model

The pictures show the use of masking to give a compelling sense of virtual object realism. The left picture shows the scene with the mask, using the geometry of the tangible model as the mask. The right picture shows the composite image when the masking is not in use. Notice how the three red oxygen atoms appear to be under the protein chain in the left image, while in the unmasked, image the virtual component appears in front of the physical model.

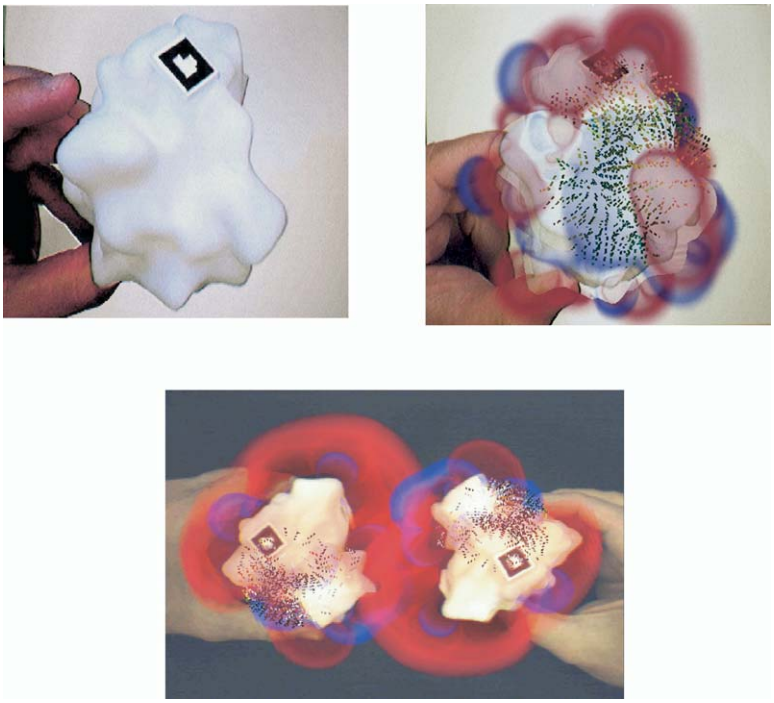

Figure 7. SOD Model with and without AR

The electrostatic field is shown with small arrows that point along the local field vectors (they appear as small dots in this picture), and the potential is shown with volume-rendered clouds, with positive in blue and negative in red. Lower image shows computer augmentation of two subunits of the SOD dimer which are tracked and manipulated independently.

level biochemistry class at the University of Washington is under way. Two students work together on two tasks, guided by a proctor. First, the students examine each amino acid, learning about its structure and chemical properties. In each case, the augmented reality interface helps students identify the side chain and explore different representations. Second, the students explore the context of four functionally different amino acids within a protein structure. The augmented reality interface displays the local environment of the amino acid in the protein, showing the role of the amino acid in the protein structure and function. Finally, the students are tested for understanding of the relationship between structure and function in the amino acids using a simulated mutation experiment. At the time of this writing, the results are not yet available.

We are also evaluating how augmented tangible models can be productively used in basic research by molecular biologists. We have produced a number of models for colleagues in our institute for applications ranging from drug design to assembly of large biomolecular complexes, and have received uniformly positive comments on the value of this approach for enhanced comprehension and communication of structural characteristics.

Conclusions

In our experience, we have found that tangible molecular models may provide several advantages over computer visualizations alone. (1) They produce a multisensory engagement which includes visual, tactile, and proprioceptive perceptual pathways for learning and memory. (2) They provide the capability of analog computation, where physical features such as shape, flexibility, and bonding capacity (e.g., using magnets) represent molecular characteristics. (3) They provide a natural and intuitive mechanism for manipulation and exploration, without the intervention of limited and indirect mechanisms such as the computer mouse. (4) They can provide both overview and detail simultaneously, enhancing contextual observation. (5) They are persistent objects, lending themselves to extended observation and contemplation. And (6), by serving as shared objects between individuals, the physical model tends to enhance social interaction and focus in ways

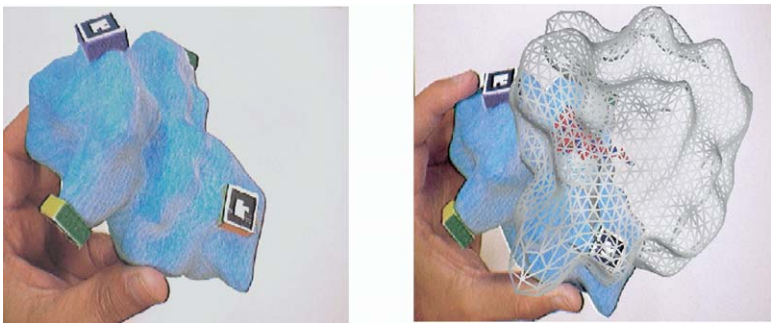

Figure 8. Ribosome without (Left) and with AR (Right)

The large subunit is shown with a wire cage, and one tRNA position is shown in red in a space-filling representation.

that a computer display does not, and thus can enhance collaborative discussion.

Our current approach to tangible computer interfaces for molecular biology has been prototyped in an inexpensive, portable form, using off-the-shelf components. We routinely demonstrate the technology during presentations, at the podium, projecting the composite video and virtual images for the audience to view. It is unfortunate, however, that the true impact of the system is difficult to convey through words and pictures alone. This system may be set up in a classroom at reasonable cost. PyARTK enables facile combination of molecular modeling capabilities with input and output in the AR environment. Using PMV along with our system has proven to be a fast and efficient approach to develop and test new ideas. Other interfaces such as force-feedback devices can be easily added to our existing system by creating appropriate interface modules (Sankaranarayanan et al., 2003). Because model manipulation engages the user's hands, we are exploring speech recognition technology for computer command input.

In our future work, we plan to develop a spatially tracked "data probe" designed to enhance interaction between the physical and virtual models. Users will be able to point to different places on the tangible model and get information from the virtual model. We will further develop our abilities to drive or steer computations of molecular interactions using this interface approach. We also plan to develop new methods for markerless spatial tracking, removing the need for fiducial tracking markers. We plan to extend the use and assessment of our augmented tangible model technologies to a wide range of educational levels and settings, including K–12, undergraduate, graduate, and public science exhibits.

Supplemental Data

A movie showing the production and utilization of autofabricated models of biomolecular structures in an augmented reality environment is available online at http://www.structure.org/cgi/content/full/13/3/483/DC1/.

Acknowledgments

This paper is based upon work first reported at the IEEE Conference Visualization '04 (Gillet et al., 2004). We would like to thank our collaborators E. Cohen, D. Johnson, and R. Reisenfeld at the University of Utah, and S. Weghorst, M. Billingshurst, T. Furness, and B. Winn at the University of Washington. We also acknowledge the National Institutes of Health (NIH BISTI EB00798) and the National Science Foundation (NSF ITR 0121282) for supporting this work. This is publication 17043-MB from the Scripps Research Institute.

Received: November 22, 2004
Revised: January 11, 2005
Accepted: January 12, 2005
Published: March 8, 2005

References

Barfield, W., and Weghorst, S. (1993). The sense of presence within virtual environments: a conceptual framework. 5th International Conference on Human-Computer Interaction, Orlando, FL.

Behringer, R., Klinker, G., Klinker, G.J., and Mizell, D.W. (1999). Augmented Reality: Placing Artificial Objects in Real Scenes (Natick, MA: A.K. Peters Ltd.).

Billinghurst, M.H. (1999). Collaborative mixed reality. International Symposium on Mixed Reality, Yokohama, Japan.

Brave, S., Ishii, H., and Dahley, A. (1998). Tangible interfaces for remote collaboration and communication. Proceedings of CSCW, Seattle, WA.

Brooks, J.F.P. (1999). What's real about virtual reality? IEEE Comput. Graph. Appl. *19*, 16–27.

Burns, M. (1993). Improving Productivity in Manufacturing (Englewood Cliffs, NJ: PTR Prentice Hall).

Coon, S., Sanner, M.F., and Olson, A.J. (2001). Re-usable components for structural bioinformatics. 9th International Python Conference (IPC9), Long Beach, CA.

Duncan, B.S., and Olson, A.J. (1993). Approximation and characterization of molecular surfaces. Biopolymers *33*, 219–229.

Fitzmaurice, G., Ishii, H., and Buxton, W. (1995). Bricks: laying the foundations for graspable user interfaces. CHI'95, Conference on Human Factors in Computing Systems, Chicago, IL.

Gillet, A., Sanner, M., Stoffler, D., Goodsell, D., and Olson, A. (2004). Augmented reality with tangible auto-fabricated models for molecular biology applications. IEEE Visualization 2004, Austin, Texas.

Gorbert, M.G., Orth, M., and Ishii, H. (1998). Triangles: tangible interface for manipulation and exploration of digital information topography. CHI'98, Conference on Human Factors in Computing Systems, Chicago, IL.

Gottschalk, S., Lin, M.C., and Manocha, D. (1996). OBBTree: a hierarchical structure for rapid interface detection. 23rd Annual Conference on Computer Graphics and Interactive Techniques, New Orleans, LA.

Ishii, H., and Hau, B. (1997). Tangible bits: towards seamless interfaces between people, bits and atoms. CHI '97, Conference on Human Factors in Computing Systems, Chicago, IL.

Milgram, P., and Kishino, F. (1994). Taxonomy of mixed reality visual displays. IEICE Trans. Inf. Syst. *E77*, 1321–1329.

Olson, A. (2001). Molecular graphics and animation. In International Tables of Crystallography, Volume F, M. Rossmann and E. Arnold, eds. (Amsterdam: Kluwer International Publishers), pp. 357–368.

Ouh-Young, M.M., Pique, M.E., Hughes, J., Srinivasan, N., and Brooks, F.P., Jr. (1988). Using a manipulator for force display in molecular docking. IEEE Robotics and Automation Conference, Philadelphia, PA.

Pauling, L., and Corey, R.B. (1950). Two hydrogen-bonded spiral configurations of the polypeptide chain. J. Am. Chem. Soc. *72*, 5349.

Poupyrev, I., Weghorst, S., Billinghurst, M., and Ichikawa, T. (1997). A framework and testbed for studying manipulation techniques for immersive VR. In Proceedings of ACM Symposium on Virtual Reality Software and Technology 1997 (VRST), pp. 21-28.

Sankaranarayanan, G., Weghorst, S., Sanner, M., Gillet, A., and Olson, A. (2003). Role of haptics in teaching structural molecular biology. 11th Symposium on Haptic Interfaces for Virtual Environment and Teleoperator Systems, Los Angeles, CA.

Sanner, M.F. (1999). Python: a programming language for software integration and development. J. Mol. Graph. Model. *17*, 57–61.

Sanner, M.F. (2005). A component-based software environment for visualizing large macromolecular assemblies. Structure *13*, this issue, 447–462.

Sanner, M.F., Olson, A.J., and Sphehner, J.C. (1996). Reduced surface: an efficient way to compute molecular surfaces. Biopolymers *38*, 305–320.

Sanner, M.F., Stoffler, D., and Olson, A.J. (2002). ViPEr, a visual programming environment for python. 10th International Python Conference, Alexandria, VA.

Smetacek, V., and Mechsner, F. (2004). Making sense. Nature *432*, 21.

Taylor, R.M., Robinett, W., Chi, V.L., Brooks, F.P., Jr., Wright, W.V., Williams, R.S., and Snyder, E.J. (1993). The nanomanipulator: a virtual reality interface for a scanning tunneling microscope. SIGGRAPH 1993, San Diego, CA.

Underkoffler, J., Ullmer, B., and Ishii, H. (1999). Emancipated pixels: real-world computer graphics in the luminous room. SIGGRAPH 1999, Los Angeles, CA.

Watson, J.D., and Crick, F.H.C. (1953). A structure for deoxyribose nucleic acid. Nature *171*, 737–738.