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Articles

Tactile Teaching

EXPLORING PROTEIN STRUCTURE/FUNCTION USING PHYSICAL MODELS*

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Tim Herman‡§, Jennifer Morris‡, Shannon Colton‡, Ann Batiza‡, Michael Patrick¶, Margaret Franzen‖, and David S. Goodsell**

*From the ‡MSOE Center for BioMolecular Modeling, Milwaukee School of Engineering, Milwaukee, Wisconsin 53213, the ¶Department of Medical Genetics, University of Wisconsin-Madison, Wisconsin 53706, ‖Pellissippi State Technical Community College, Knoxville, Tennessee 37933, and **The Scripps Research Institute, La Jolla, California 92037*

The technology now exists to construct physical models of proteins based on atomic coordinates of solved structures. We review here our recent experiences in using physical models to teach concepts of protein structure and function at both the high school and the undergraduate levels. At the high school level, physical models are used in a professional development program targeted to biology and chemistry teachers. This program has recently been expanded to include two student enrichment programs in which high school students participate in physical protein modeling activities. At the undergraduate level, we are currently exploring the usefulness of physical models in communicating concepts of protein structure and function that have been traditionally difficult to teach. We discuss our recent experience with two such examples: the close-packed nature of an enzyme active site and the pH-induced conformational change of the influenza hemagglutinin protein during virus infection.

A common goal of biochemistry educators is to provide students with a deep understanding of fundamental concepts underlying protein structure and function. This is most commonly done by exposing students to stunning two-dimensional color graphics of proteins in textbooks and frequently augmenting these static figures with interactive images that can be rotated in three-dimensional space in a computer environment. Although this approach is successful for those students who are able to infer three-dimensional information from these inherently two-dimensional representations, many other students fail to make this inference. For them, the molecular world of proteins remains an abstraction for which they have little interest. We have found that physical models of proteins (Fig. 1) are amazingly effective tools that initially capture the interest of this larger group of students and motivate them to learn more about this invisible, molecular world. These physical models are synergistic with computer visualization tools, allowing students to generalize their initial understanding of a specific protein to other structures that are explored in a computer environment. We review here our recent experience with the use of physical models to make this molecular world "real" for students at both the high school and the undergraduate levels.

A THEORETICAL BASIS FOR THE VALUE OF PHYSICAL MODELS IN TEACHING ABSTRACT CONCEPTS IN SCIENCE

The value of physical models of small molecules in organic chemistry courses is well known to biochemistry educators. However, these small molecule kits are not practical for modeling the higher order molecular structures of proteins. Experienced researchers have learned to infer three-dimensional information from two-dimensional images of proteins or to manipulate interactive, computer-generated images of proteins. Unfortunately, our current educational practice treats *inexpert* students as though they were *expert* researchers. Students are introduced to proteins through two-dimensional drawings or interactive computer visualizations in which proteins are manipulated in virtual space. We believe that many students fail to become engaged when protein structure is introduced in these ways because they lack the basic understanding to interpret these abstract images.

Lawyers with only 30 minutes to educate a jury about the general concept of a protein machine often choose to initially engage their attention with a physical model. Only after the concept of a protein is made accessible to the jurors through the use of the physical model are diagrams or other representations used to highlight particular aspects of the protein. Some students are like the jurors. They will not be engaged by your discussion of a protein

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§ To whom correspondence should be addressed: MSOE Center for BioMolecular Modeling, Milwaukee School of Engineering, 1025 N. Broadway, Milwaukee, WI 53202. Tel.: 414-277-7529; Fax: 414-277-7486; E-mail: herman@msoe.edu.

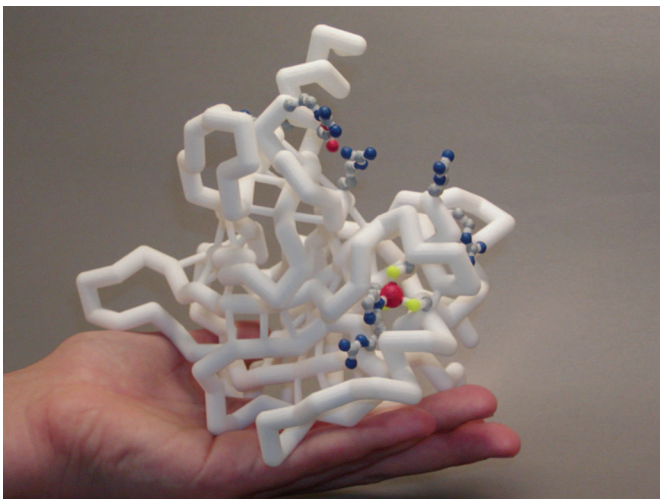

FIG. 1. **A nylon model of the p53 tumor suppressor protein (based on 1tsr.pdb).**

unless they can first identify with the entity being discussed. Our sense is that this is especially true of students for whom the mental rotation of images is difficult, as is documented more often for girls than for boys [1–3]. When such a student rotates a physical model in her hand rather than in her mind, we believe that this experience is more likely to open the door to the molecular world of proteins. In an analysis of visuospatial thinking in chemistry, Hsin-Kai Wu and Priti Shah [4] concluded that adept visuospatial skills correlate with achievement in chemistry and that appropriate instructional representations can help students with poor skills overcome their deficiencies [4]. They reported that "*when visualization tools require a great deal of cognitive resources to mentally keep track of visuospatial information, these tools are likely to only benefit those students who have strong visuospatial skills. When tools are specifically designed to reduce cognitive load, they support learning for low spatial [ability] students.*" [Ref. 4, p. 486]

The study of a "concreteness fading" technique provides a rationale for our best practice regarding physical models. We feel that it is most efficient to first introduce proteins using physical models and then later elaborate and generalize that experience through the synergistic use of interactive computer images. Goldstone and Son [5] explored this fading technique with 84 undergraduates at Indiana University. The students first manipulated a two-dimensional simulation using realistic images. In a later simulation based upon the same principles of operation, the realistic images were replaced with more abstract geometric figures. Goldstone and Son found that persons introduced to the simulation in this way (realistic images first followed by abstract ones) could best transfer their understanding of the simulation process to a new situation. This type of learning outperformed all other possible permutations: consistent use of a realistic image, exclusive use of an abstract image, or a reverse presentation of the images (abstract first and then realistic). Although Goldstone and Son did not employ physical models in their simulations, the fact that they first made the connection to the real world explicit, and then used images that were more abstract and portable, mimics our best practice.

Jiun-Liang Ke *et al.* [6] wrote, "*For some scholars . . . sensori-motor experiences are at the heart of all our thinking*" [Ref. 6., p. 1590]. The power of sensori-motor experiences in stimulating questions was borne out in an experiment by M. Gail Jones *et al.* [7]. Students who were given the opportunity to "touch" viruses using a pressure-sensitive joystick were significantly more interested in the experience than those who used a conventional mouse. The more authentic tactile experience generated significantly richer descriptions of viral characteristics, more questions about the viruses, and the use of more analogies to describe them. This finding mimics our experience that protein models function as "thinking tools" that stimulate discussion because the model itself provides spatial insights that stimulate questions and because participants can clearly articulate their questions in reference to the model.

Finally, Hsin-Kai Wu and Priti Shah [4] distilled five principles for the design of curricular materials based upon their analysis of 135 research papers on the topic of visuospatial thinking in chemistry. Many of these principles address student difficulties in mapping concepts to representations, a problem that is especially difficult for students with low spatial abilities. Wu and Shah [4] cite evidence for the usefulness of students' manipulation of both concrete models and three-dimensional computer-generated images to enhance their understanding of abstract concepts. They conclude that "*manipulating 3D molecular structures created by concrete models or computer-based tools might require less cognitive resources in the spatial domain . . . this type of learning might help low spatial ability students more, when high spatial ability students are already able to create 3D images mentally by viewing 2D representations on paper.*" [Ref. 4, p. 483]. They call for the active manipulation of multiple representations and descriptions whose connections are integrated in an explicit manner. "*It seems that students need to recognize the visual similarities and differences between 2D and 3D models through rotating and comparing these representations.*" [Ref. 4, p. 485] We could not agree more.

In summary, we believe that concrete models of proteins are crucial thinking tools, especially for students for whom the chemical world is the least accessible, intuitive, or interesting. Their subsequent use of interactive computer-generated images, graphic schemata, and animations allow these students to construct abstractions as they wean themselves from more explicit, concrete representations.

PHYSICAL PROTEIN MODELS BY RAPID PROTOTYPING TECHNOLOGY

The MSOE[1] Center for BioMolecular Modeling was created at the Milwaukee School of Engineering (MSOE) to take advantage of the unique technologies in the school's Rapid Prototyping Center. Rapid prototyping is an additive manufacturing technology in which physical models are created in a layer-by-layer process from a variety of ma-

[1] The abbreviations used are: MSOE, Milwaukee School of Engineering; SLS, selective laser sintering; SMART, Students Modeling A Research Topic; HA, hemagglutinin; RP-RasMol, Rapid Prototyping-RasMol.

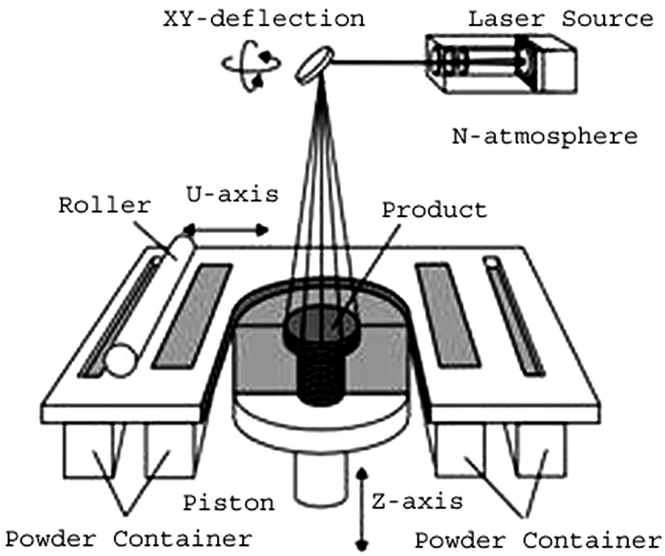

FIG. 2. **Schematic illustration of the SLS process.**

terials including a liquid photoactive polymer, plastic wire, paper, powdered nylon, and plaster (www.rpc.msoe.edu/cbm/technology.php). Protein models were initially designed by loading atomic coordinates of individual atoms from a pdb file into computer-assisted design software. Each atom was then represented by a sphere, and adjacent spheres were connected by cylinders to build up a ball-and-stick representation of the protein. The final model was exported from the computer-assisted design software as an "stl file," a format recognized by automated rapid prototyping machines. More recently, the standard RasMol molecular viewer [8] has been modified to produce Rapid Prototyping-RasMol (RP-RasMol), with the added functionality of directly generating solid modeling files that can be used by rapid prototyping machines. As a result, any virtual image of a protein that can be generated in a RasMol environment can now be easily converted into a physical model using any one of several rapid prototyping technologies. Therefore, anyone with a modest familiarity with the RasMol viewer can now become a model designer. High school teachers and students participating in our summer courses or Students Modeling A Research Topic (SMART) Team program (see below) now routinely use RP-RasMol to create physical models used in their classrooms or models of proteins being investigated in biochemistry research laboratories.

Of the several rapid prototyping technologies that are available, we have found Selective Laser Sintering (SLS) and Z Corporation's three-dimensional printing technology to be most useful for making protein models. SLS uses nylon powder and a CO_2 laser to sinter the powder together to build up the final model in a layer-by-layer process (Fig. 2). These nylon models are somewhat flexible and very durable. However, because they are made of white nylon powder, they must be hand-painted to color-code specific features of the model. In contrast, the Z Corporation three-dimensional color printer uses ink jet printer technology to deposit droplets of pigmented glue on successive layers of plaster powder to build up colored physical models. Although these models are very hard, they are also brittle and can be damaged if dropped on a hard floor. The major advantage of the Z Corporation's technology is that very complex color schemes can be automatically applied to these models.

EXPLORING PROTEIN STRUCTURE, A PROFESSIONAL DEVELOPMENT PROGRAM FOR HIGH SCHOOL SCIENCE TEACHERS

We began our exploration of the power of physical models by creating models of α-helices, β-sheets, and whole proteins to use in our professional development course for high school biology and chemistry teachers, *Genes, Schemes and Molecular Machines* (www.rpc.msoe.edu/cbm). This program is supported by a Science Education Partnership Award (SEPA) grant from the National Center for Research Resources at the NIH. We were immediately struck by how effective these physical models were in engaging teachers in conversations about the underlying chemical principles that determine protein structure. The importance of the tactile nature of these models was repeatedly seen. For example, a teacher excitedly reported that she knew the structure of an amino acid side chain because she remembered holding a physical model of the structure on the previous day. A physical model of the β-globin protein provided a tactile anchor point from which a consideration of other proteins naturally followed. We noted the power of these physical models as thinking tools that allowed teachers to frame additional questions related to protein structure. We also noted that there was a natural transition from the use of a physical model of a specific protein to the use of computer visualization tools such as RasMol to test the generality of features in other proteins found in the Protein Data Bank. These experiences informed our current view of the optimal order for the use of these instructional tools: physical models first followed by computer visualization tools.

Although we were well aware of teachers' enthusiasm for using physical models from our experiences in summer courses, we were nevertheless surprised to see how motivated they were when they began to work with research scientists to use RP-RasMol to design and create models of proteins that were being investigated in the researchers' laboratories. This phase of the program began in the summer of 2001 when a group of six teachers from the previous summer course returned to use RP-RasMol to design and build the first ever physical models of the ribosome based on the coordinates published by the Noller [9] and Steitz laboratories [10]. This motivation stemmed not only from the fact that they were generating physical models of new structures but that they were participating in "real science" as they communicated with researchers and incorporated features of that structure into a physical model that facilitated the telling of a "molecular story" (www.rpc.msoe.edu/sepa/3dt_update.htm).

SMART TEAMS, A HIGH SCHOOL STUDENT-ENRICHMENT PROGRAM

Within months of this initial teacher-based modeling project, we were approached by another teacher who wanted to get his students involved in a project building a physical model of a protein. This occurred immediately after the anthrax-laced letters were mailed in the fall of 2001. We therefore formed our first SMART Team com-

FIG. 3. **Our first SMART Team meets with Wei Jen Tang (University of Chicago) to discuss the edema factor model.**

posed of three high school seniors and began exploring the proteins involved in anthrax pathogenesis. Of the three proteins involved in this process, the structure of only one, the anthrax protective antigen, was known and published [11] at this time. The structure of the second, lethal factor, was about to be published [12], and the structure of the third, edema factor, had just been solved by Wie Jen Tang's group at the University of Chicago [13]. Within four months, this first SMART Team worked closely with the Tang laboratory and designed and built physical models of all three proteins (Fig. 3). During this process, they also visited John Young's laboratory at the University of Wisconsin-Madison, where they learned about a newly identified receptor for the anthrax protective antigen [18]. This first SMART Team later provided Dr. Young with 24 copies of the anthrax protective antigen model, which he distributed to members of a special congressional panel conducting hearings on bioterrorism.

As a result of these first two modeling projects, we realized that we had discovered a powerful way to bridge the gap between high school science classrooms and the *real world of science* as it exists in the research laboratories of neighboring research institutions. Since that time, the SMART Team program has grown to include 10 local Teams operating each year in Wisconsin as well as an equal number of remote Teams spread across the U. S. More recently, SMART Teams have begun to attend national research meetings (Fig. 4), at which they present their modeling projects in poster sessions alongside graduate students and post-docs from around the world. The Pingry School SMART Team (Martinsville, NJ) recently attended the American Society for Biochemistry and Molecular Biology (ASBMB) meeting in San Francisco, where they presented their physical model of an *Escherichia coli* RNA polymerase complex based on their work with the Seth Darst laboratory at Rockefeller University. These SMART Team projects provide ongoing professional development opportunities for teachers and have been instrumental in shaping the career goals of many students. Most importantly, students learn that science is not simply the information found between the covers of their textbook. Instead, science is better represented by the process whereby that information is discovered in basic research laboratories.

FOLDING PROTEINS, FROM ACCURATE PROTOTYPED MODELS TO SCHEMATIC, FREE-FORM MINI-TOOBER MODELS

Although rapid prototyping technology makes it possible to create accurate three-dimensional models of proteins, the cost and limited availability of this technology precludes the widespread dissemination of these models to classrooms. Therefore, we have begun to explore the use of Mini-Toobers (flexible, foam-covered wires) as a less expensive, free-form modeling medium. We began by creating a protein folding activity based on the use of this material as a model of the α-carbon backbone of a protein. A collection of color-coded foam cutouts represents the shapes of the 20 amino acid side chains (Fig. 5). After students position the amino acid side chains in the appropriate category (hydrophobic, hydrophilic, or charged) on a magnetic chart, they will select 15 side chains and randomly distribute them along a Mini-Toober backbone to create a 15-amino acid protein. After reminding students that proteins are synthesized and folded in a polar, aqueous environment, students are instructed to fold their protein, following basic laws of chemistry. Although is it an easy task to fold the Mini-Toober such that all of the hydrophobic (yellow) side chains are clustered together to form a hydrophobic core in the center for a globular structure, it is more difficult (and sometimes impossible) to find one shape that simultaneously maintains (i) a hydrophobic core, (ii) salt bridges between oppositely charged side chains on the surface of the protein, and (iii) a disulfide bond between two cysteine side chains. This activity has proven to be very effective in allowing students to kinesthetically discover how basic principles of chemistry drive the spontaneous folding of proteins. Also, once these general concepts have been established using this physical model, students can then be introduced to the use of

FIG. 4. **The 2006 Pingry School SMART Team at the recent ASBMB meeting in San Francisco.**

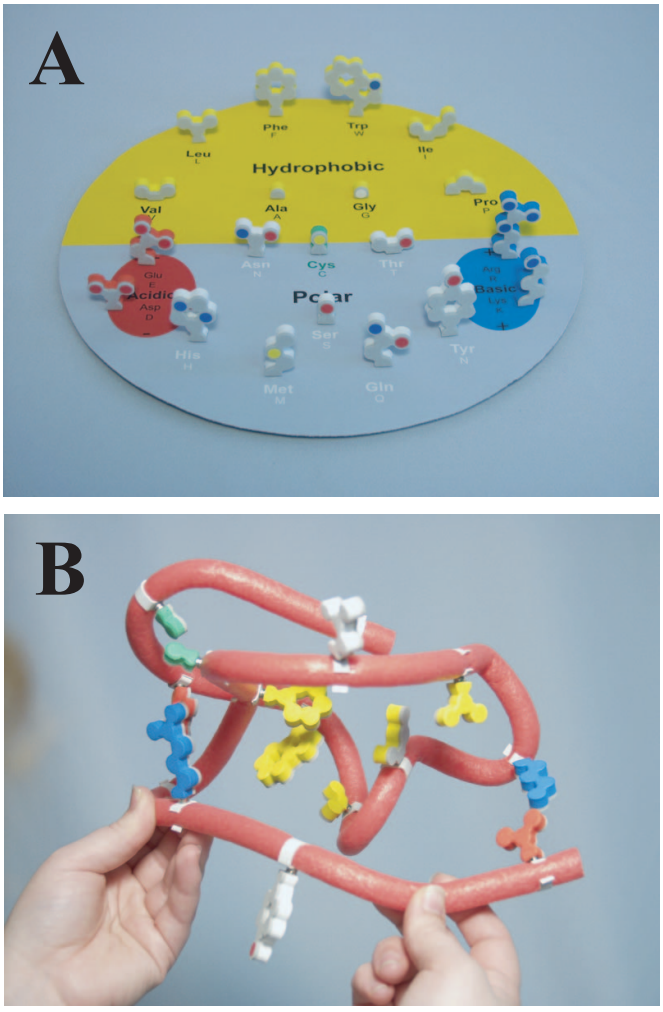

FIG. 5. **Foam cutouts of the 20-amino acid side chains (*A*) are placed on Mini-Toober backbone (*B*) and "folded" following basic laws of chemistry.**

RasMol or other visualization tools to determine how rigorously these rules are recapitulated in the structures of real proteins accessed through the Protein Data Bank.

More recently, we have further developed the use of this Mini-Toober modeling medium for use in a protein modeling event for the Science Olympiad competition. This protein modeling event introduces high school students to the Protein Data Bank, including the Molecule of the Month resource (www.rcsb.org), and the use of computer visualization tools. In a pre-competition phase, teams are provided with Mini-Toobers and instructed to fashion a physical model of a protein previously featured as a Molecule of the Month. To be successful, teams must first learn about basic concepts of protein structure and the use of RasMol to visualize proteins in a computer environment. This is done through a combination of workshops and on-line training resources (www.rpc.msoe.edu/ScienceOlympiad). The pre-built model is brought to the competition, where each team is then required to model a second protein (or protein fragment) during the 50-minute on-site competition (Fig. 6). In addition to fashioning the physical model using a RasMol image as a guide, students must also answer questions about the protein's function and the primary citation that first reported the structure. This protein modeling event was first piloted in the Wisconsin Science Olympiad competition in 2005. Based on the success of that pilot, the event was run in New Jersey (sponsored by the Protein Data Bank), Kansas, and Wisconsin in 2006.

PHYSICAL MODELS IN AN UNDERGRADUATE CURRICULUM

Physical models are very useful in introducing the basic concepts of protein structure to high school students. We have also worked with undergraduate educators to show that they have a similar effect on undergraduate students in a variety of courses ranging from introductory chemistry and biochemistry to upper level courses in biochemistry and cell biology. In every case, we observed the powerful ability of physical models to capture the interest of students and prompt them to ask questions about other structural features related to the models. In a 2-year field test of the use of physical models in a biochemistry course at DePauw University, we documented a dramatic gain in learning that was correlated with the students' rating of

FIG. 6. **A high school student competes in the protein modeling event of Science Olympiad.**

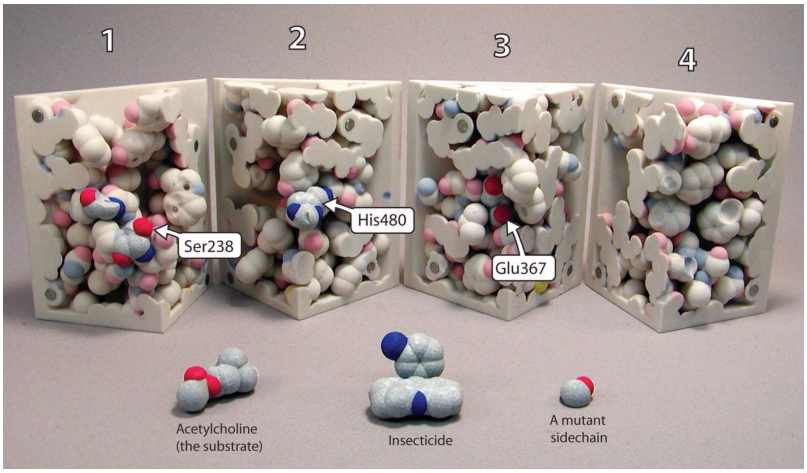

FIG. 7. **A space-filled model of the active site of acetylcholinesterase, based on 1qon.pdb.**

physical models as the most useful learning tool experienced in the course [14]. Similarly, a 3-year field test of the use of physical models in a large freshman chemistry course at the University of Wisconsin-Madison showed that models captured students' interest in the subject of biomolecular structure and bridged the gap between the traditional disciplines of chemistry and biology [15]. Finally, an ongoing field test of the models in an honors cell biology course at the University of Wisconsin-Madison has provided evidence that the use of physical models by students in an active learning setting increases their use of computer visualization tools. This result suggests that when students use physical models and begin to ask questions, they more readily perceive the value of computer visualization tools in pursuing answers to more sophisticated molecular structure/function questions.

In addition to using physical models to teach fundamental concepts of protein structure, we are currently exploring their effectiveness in teaching traditionally difficult concepts in undergraduate biochemistry. Two of these current projects are outlined below.

The Active Site of Acetylcholinesterase, Evolution in Action—One particularly difficult concept to convey to students is the close-packed nature of an enzyme active site. Active sites are often buried at the bottom of clefts or grooves in globular proteins, where the surrounding structures obscure the specific interactions between the substrate and active site residues. A common solution to this problem is to represent the active site in a ball-and-stick format that allows each of the components to be visualized. Unfortunately, this representation often leads to the misconception that proteins are made "mostly of air" and that there is a lot of room for substrates to rattle around in an active site. We have addressed this problem by creating a space-filled physical model of the acetylcholinesterase active site in a cube that was subsequently cross-sectioned into four wedges (Fig. 7). This allows the active site to be "unfolded" to reveal the catalytic triad of Ser-238, His-480, and Glu-367. The cube was initially positioned around the active site in a computer environment such that each member of the triad is revealed on three successive wedges in the unfolded model. As wedges 1, 2, and 3 are folded together, students see how these linearly distant amino acid side chains are positioned next to each other in three-dimensional space to set up the charge-relay system that activates Ser-238 for catalysis. The acetylcholine sub-

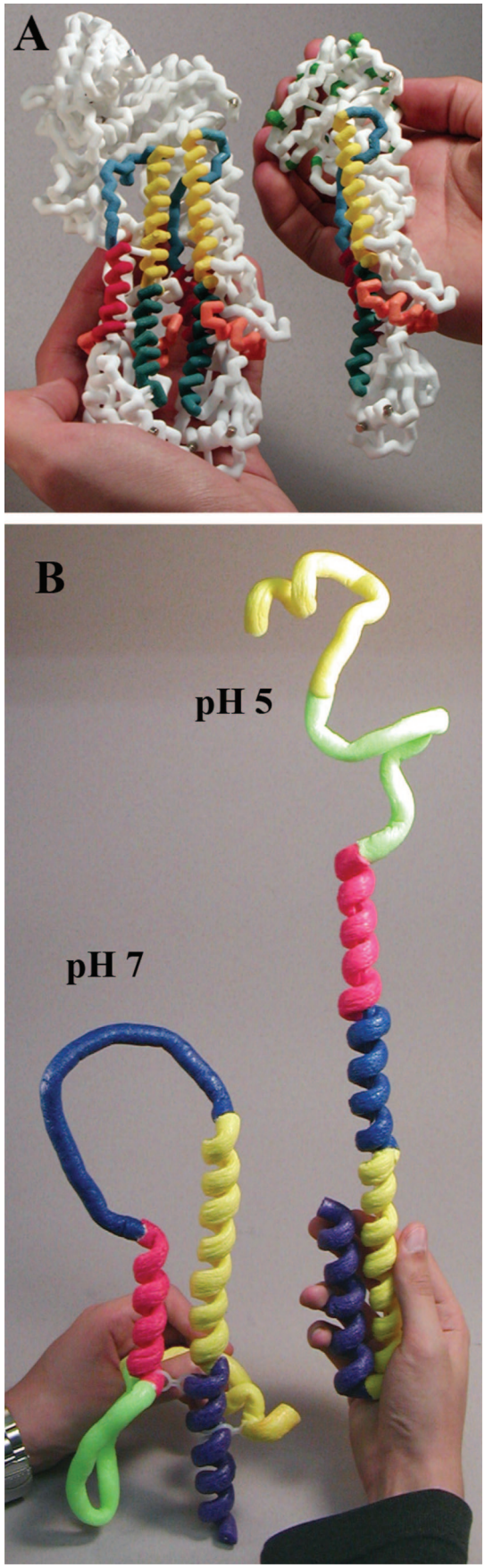

FIG. 8. **Nylon models (*A*) of the three-subunit hemagglutinin protein (based on 5hmg.pdb) and Mini-Toober models (*B*) of the region of HA2 that undergoes a dramatic conformational change from pH 7 (*left*) to pH 5 (*right*).**

strate can be docked into the active site, and students can see that there is just enough room to accommodate this substrate as the model is folded together. Similarly, when an insecticide is docked in the active site, the substrate is no longer able to bind, demonstrating competitive inhibition. Also, finally, when Gly-119 (located immediately adjacent to Ser-238) is mutated to serine, the new carbon and hydroxyl group interferes with binding of the insecticide, without affecting substrate binding. This mutation has been reported as the molecular basis for the emergence of insecticide-resistant strains of mosquitoes in three different geographical areas in response to long term, widespread spraying of the insecticide [16].

The pH-Induced Conformational Change in the Influenza Hemagglutinin Protein—A particularly compelling, but difficult to understand molecular story that has unfolded over the past 20 years is the manner in which the influenza hemagglutinin protein (HA) first binds to receptors on the surface of mammalian cells at neutral pH and then undergoes a dramatic conformational change that leads to fusion of the viral and cellular membranes [17]. This conformational change is triggered by the decrease in the pH of the endosome following receptor-mediated endocytosis. We have constructed a series of physical models that effectively "deconstruct" the trimeric HA protein and make this process understandable to students. In the model shown in Fig. 6*A*, each subunit of the trimer can be "undocked" from the complex. Color coding is then used to highlight the different regions of HA2 that undergo the conformational change. This same region of HA2 has also been modeled with color-coded Mini-Toobers, allowing students to physically interconvert the two alternative conformations of the protein. During this conformational change, a 20-amino acid "loop" in HA2 (colored *blue* in the models shown in Fig. 8) coils up into an α-helix. This results in the movement of the fusion peptide (the *yellow segment* at the N-terminal end of HA2) to a new position over 100 Å away, where it embeds itself in the cellular membrane. At the same time, a 50-amino acid α-helix (Fig. 8*B*, *yellow* plus *purple*) now becomes two discontinuous helices. Since the C-terminal end of HA2 is embedded in the viral membrane, this second conformational change has the effect of moving the viral membrane toward the cellular membrane, leading to membrane fusion. We believe that the opportunity for students to actually model this change with Mini-Toobers will lead to a greater appreciation of the complexity of proteins as molecular machines. Having appreciated the complexity of this conformational change, students are then left to wonder about the molecular basis of this pH-triggered event. Computer visualization tools can then be used to explore the distribution of histidine amino acids in the HA protein and to consider the effect of their protonation on the structure of the protein.

DISSEMINATING PHYSICAL MODELS TO CLASSROOMS

All of the physical models described in this review are available to borrow from the MSOE Model Lending Library. Models are loaned for a two-week period, free of charge except for return postage. Collections of related models that can be used to teach a specific topic are packaged together in suitcases. A listing of model collections that are

available through this Model Lending Library can be found at www.rpc.msoe.edu/lib. Seventy model collections were loaned out to educators in 18 states during the first 5 months of the 2005–2006 academic year. One educator who used the Lending Library commented that the models were *"invaluable to my students as they need concrete images to understand the abstract concepts of protein structure."* Another commented that *"I would almost go so far as to say that models are essential to teaching protein structure. A 2-D representation in a textbook, or even the computer models with a 3-D feel, just cannot adequately convey all aspects of structure."*

CONCLUSIONS

New developments in the molecular biosciences over the past 30 years have resulted in an increasingly detailed description of the molecular mechanisms at work in biological processes. During this time, we have come to appreciate proteins as complex, dynamic machines that often function as components of large multisubunit complexes. As the complexities of the stories have grown, so too have the problems associated with communicating those stories through two-dimensional graphics printed on paper. Experienced researchers now commonly use computer visualization tools while reading papers to more fully understand the nuances of the structures being described. However, inexperienced students are not universally up to the task of using these tools. Instead, many of them benefit from the use of "tactile visualizations" of these structures in the form of physical models. These models provide an entry point into the subject that allows them to initially anchor their understanding of proteins to concrete entities. This foundation can then be used to build up abstract concepts related to how they function. The stories that we would like to share with our students have become complex, compelling, and three-dimensional. The tools we use to communicate these stories to students should possess these same qualities.

Acknowledgments—We thank the many high school teachers with whom we have had the pleasure of working during the development of the programs described here. Their enthusiasm for science and dedication to students has been an inspiration to us all. In addition, we thank the undergraduate educators with whom we have worked to field-test these materials. "Scientific Teaching" is coming [19], and these educators are leading the way.

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