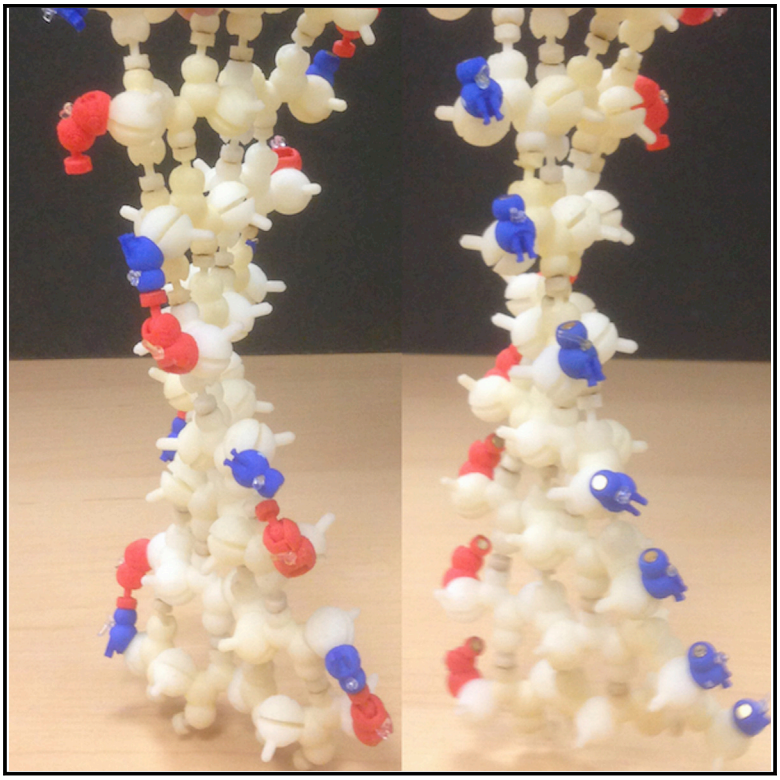
Resource

Structure

A Self-Assisting Protein Folding Model for Teaching Structural Molecular Biology

Graphical Abstract



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In Brief

A new physical polypeptide folding model kit produced with 3D printing is described, which forms magnetic backbone hydrogen bond interactions and secondary structure formation and displays emergent tertiary structural properties as the protein model is assembled.

Highlights

- A new self-assisting physical assembly kit of protein backbone structure is described
- The model demonstrates emergent properties during the formation of protein structure
- The use of the model for teaching principles of protein structure is described
- Electronic files for creating the model components for 3D printing are made available

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A Self-Assisting Protein Folding Model for Teaching Structural Molecular Biology

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SUMMARY

Structural molecular biology is now becoming part of high school science curriculum thus posing a challenge for teachers who need to convey three-dimensional (3D) structures with conventional text and pictures. In many cases even interactive computer graphics does not go far enough to address these challenges. We have developed a flexible model of the polypeptide backbone using 3D printing technology. With this model we have produced a polypeptide assembly kit to create an idealized model of the Triosephosphate isomerase mutase enzyme (TIM), which forms a structure known as TIM barrel. This kit has been used in a laboratory practical where students perform a step-by-step investigation into the nature of protein folding, starting with the handedness of amino acids to the formation of secondary and tertiary structure. Based on the classroom evidence we collected, we conclude that these models are valuable and inexpensive resource for teaching structural molecular biology.

INTRODUCTION

It has been over half a century since the first protein structures were determined using X-ray crystallography. Although lacking the anticipated symmetry and elegance of the earlier Watson and Crick model of DNA (Watson and Crick, 1953), they revealed that proteins folded into intricate and consistent three-dimensional (3D) arrangements made up of fundamental structural motifs, alpha helices and beta sheets, which had been previously predicted based upon polypeptide backbone hydrogen bonding patterns (Pauling and Corey, 1950; Pauling, 2015). Those earliest structures of myoglobin and hemoglobin were visualized by stacked contours of balsa wood derived from the 3D electron density maps computed from the crystal diffraction patterns (Figure 1) (Kendrew et al., 1958; Perutz et al., 1960).

Over the following decade, a number of protein structures were determined. Atomic detail models were built using brass Kendrew model parts fit by hand into a transparent 3D stacked image of the electron density map integrated by a clever construction called a Richards Box using selective lighting and a half silvered mirror (Richards, 1968) (Figure 2). These physical models gave the first clear picture of the spatial atomic arrangements and relationships of the component parts. However, to quantify these structures, the coordinate positions of all of the atoms in the built brass model had to be measured – typically using projected sight lines (for x and y) and plumb lines (for z). Needless to say, this was a tedious and error-prone process.

In the late 1970s physical models gave way to virtual with the advent of interactive 3D computer graphics. Computers were quickly applied to the task of fitting atomic structures into computed electron density maps, and a number of electronic Richards Box programs were developed to accomplish this. Protein crystallographers were some of the earliest adopters of these new and expensive 3D interactive display systems – making protein structure visualization one of the early killer apps that drove development of the technology (Olson and Goodsell, 1992).

The building and use of physical protein models quickly disappeared. By the 1980s most of the Kendrew models of protein structures were abandoned – with only a few preserved as historic artifacts. Although the transition to computer-based protein structure building and visualization had numerous advantages, some of the characteristics of physical model visualization were lost. Physical models can convey spatial relationships and mechanisms in ways that images alone cannot. They engage perceptual and cognitive processes that go beyond the visual and bring a sense of reality and natural interaction into the process of exploration and understanding. Physical molecular models can also serve as analog computers where spatial relationships between components in complex molecular interactions can be explored and manipulated. For instance, in the discovery of the structure of DNA, Watson and Crick manipulated physical models of the nucleotide bases, whose structures and dimensions were known from chemistry, to develop the double helical model of base-pair complementarity that explained the molecular mechanism of genetic inheritance underlying all of biology (Watson, 1968; Crick, 2008).

In the late 1980s, a new rapid prototyping using additive manufacturing technology introduced the concept of computer autofabrication, or 3D printing, of physical objects. Originally

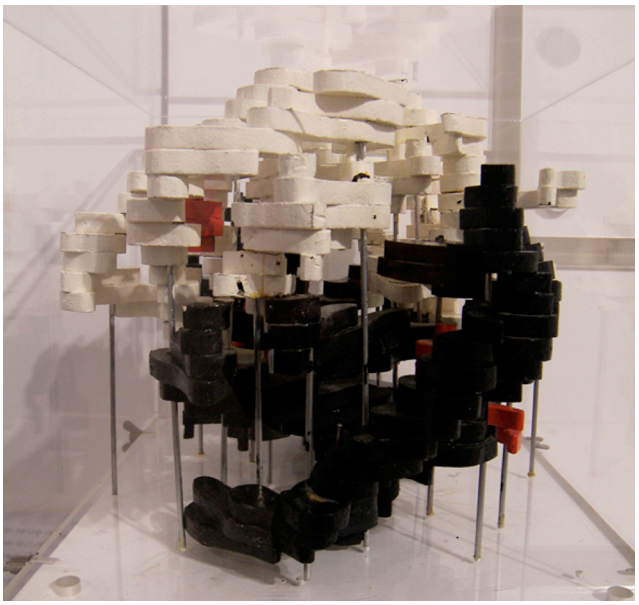

Figure 1. Balsa Wood Model of Hemoglobin
Some of the earliest protein structures solved were visualized using stacked contours of balsa wood, which represent electron density maps computed from the crystal diffraction patterns.

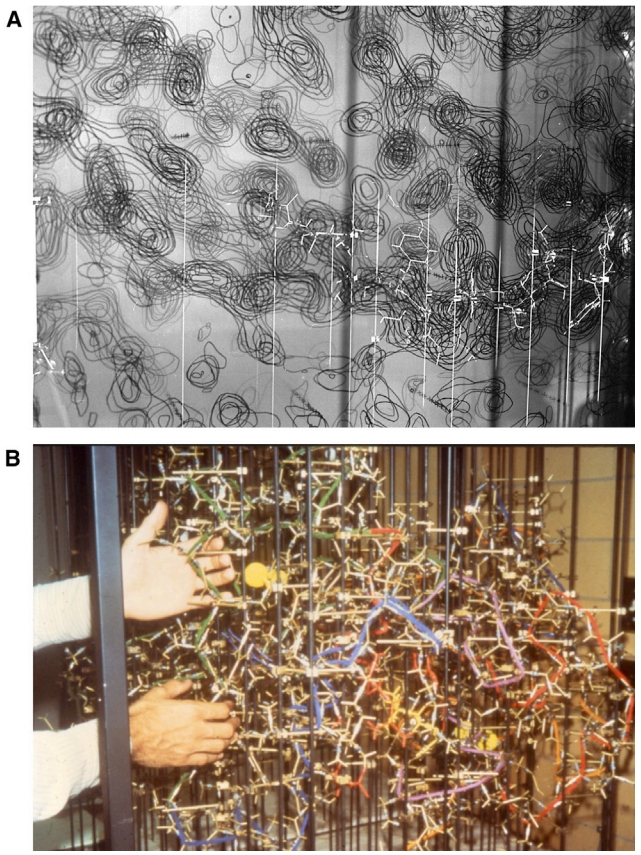

Figure 2. Protein Structure Model Building and Visualization in 1960s
Physical models of protein structures gained in importance in 1960s as the number of structures solved increased.
(A) Stacked electron density used to generate a protein structure model.
(B) Brass Kendrew protein model built by hand in Richards Box that used selective lighting and a half silvered mirror to integrate stacked images of electron density map into a protein structure model.

conceived as a way to quickly produce and test physical models of designed objects before committing to the expense of machining, the technology also became a way to produce custom fabricated objects as the end product in itself. One of the earliest models of a natural object to be produced on a 3D printer was of the enzyme superoxide dismutase in 1991 (Roberts, 1993) (Figure 3). We and others have since explored the utility and special capabilities of 3D printing as applied to molecular models (Fjeld and Voegtli, 2002; Gillet et al., 2004; Bailey, 2005; Gillet et al., 2005; Herman et al., 2006), and have produced a wide variety of molecular representations.

Although 3D printed rigid molecular models have proven widely useful, we have also explored and developed a number of articulated models that demonstrate flexibility and operational characteristics such as assembly. In 2005 we used 3D printing and embedded magnets to produce a self-assembling model of poliovirus (Olson et al., 2007; Olson, 2015). In 2002 we started to design a polypeptide folding and assembly model. Our first attempt printed the specific configurations of each beta strand of a beta barrel of the retinol binding protein, connected by flexible wire loops, in which embedded magnets of complementary polarity represented the peptide backbone hydrogen bond donors and acceptors. This model revealed that even using the known conformations of each strand of the beta barrel, small misalignments in magnet positioning or other structural elements resulted in larger, accumulating errors during the assembly process The complete beta barrel was difficult to assemble and not very strong (Figure 4A).

In 2004 we developed a flexible model of the polypeptide backbone using plastic extrusion 3D printing technology (fused deposition modeling – FDM) (Figure 4B), which enables the printing of robust multi-component objects. We used the known geometry of the peptide backbone to print a set of parts to be assembled into a chain that folds into a given protein shape. We used the Python Molecular Viewer (PMV) (Sanner, 1999) to establish the geometries and FormZ software (www.formZ.com) to develop the geometry of the mechanical aspects of the model parts (Figure 5A). Again, we embedded magnets into the peptide unit to mimic the backbone hydrogen bonding interactions. However this time, we imparted geometric flexibility to the hydrogen bonding by in situ printing of a ball and socket joint for the hydrogen bond acceptor to reflect its known 120° angular interaction range. The orientation of each amino acid in the polypeptide chain is related by two rotational angles (phi and psi) to its two adjacent amino acids. We encoded these angles into the alpha carbon of each by specifying a keyed fit of the preferred angle to each flanking peptide unit. The peptide units and the chain's alpha carbons are strung successively on an elastic monofilament, such that the tension on the filament drives the chain into the preferred specific folding configuration. Thus, while the polypeptide chain is free to rotate at each amino acid, there is a tangible fit when the angle of rotation is at the specific value. The alpha carbons have a slot that allows them to be removed

Figure 3. Stereolithography Model of the Enzyme Superoxide Dismutase Generated in 1991

Computer autofabrication, or 3D printing, of physical objects that developed in the 1980s opened opportunities for using this technology in structural biology to visualize shape and features of protein structure, such as the enzyme superoxide dismutase.

and replaced with those of different phi/psi specifications. Each alpha carbon has a stub that enables physical or virtual side chains to attach to the model (see below). The peptide units are of two types. In the middle of a strand the peptide units contain carboxyl and amino groups together as a single object. At the two ends of each strand separate amino and carboxyl units can snap together to form a new peptide bond and elongate the chain. Since the major structural motifs of proteins consist of alpha helices and beta sheets, with canonical phi-psi angles, we have made units of such motifs along with loop structures with no preferred phi-psi angles that can be snapped together to make a generic protein folding kit. Any specific protein structure can be printed with standard peptide units and custom printed alpha carbons keyed and labeled with the sequence numbers and phi/psi angle encoded. The scale of the model was set to .375 cm/Å, which makes the model of a folded 200 amino acid protein small enough to handle (about the size of a football), but large enough to assemble part by part. A larger CPK scale (1 cm/Å) polypeptide model that also uses magnets for hydrogen bonds, as well as for simulating phi/psi energy barriers was developed by Zuckermann and Chakraborty in 2013 (Chakraborty and Zuckermann, 2013), however the larger scale makes building a full protein model more difficult and costly.

In this resource, we discuss different types of polypeptide and proteins models, describe methods to generate them, and highlight how we have been using them to teach basic biochemistry and structural biology. We hope that this will stimulate their uptake as a useful teaching aid at different levels of science classes.

RESULTS AND DISCUSSION

Use of the Flexible Polypeptide Model for Teaching

To evaluate the utility of the model, two identical chains of 99 peptide units each were strung with the alpha carbons coded in sequence for the phi/psi angles of the HIV protease homodimer (Figure 5B). The backbone hydrogen bonding interactions were made from each linear chain according to the known secondary structural elements of the structure. For all of the known intrachain hydrogen bonds to form, the tertiary structure of the protein had to be folded up by a specific set of sequential interactions of the secondary structure elements. This process itself was highly instructive with regard to the order of the interactions that needed to take place. Since no side chains were represented in the model, a piece of soft black foam was inserted into the beta sheet structure that forms the core of the tertiary fold. Finally, the two folded chains were joined by the dimer interface, which consists of a four-stranded interleaved beta sheet and interactions of the two flap regions. A polypeptide ligand was placed into the active site of the protease enzyme, making stabilizing hydrogen bonds with the flaps from both chains and demonstrating the mode of binding of substrate prior to proteolysis.

Triosephosphate Isomerase Mutase Protein Model

The polypeptide assembly kit was also used to create an idealized model of the Triosephosphate isomerase mutase enzyme (TIM), which forms a structure known as TIM barrel (Figure 6). The folding motif of the TIM barrel consists of eight alpha helices and eight parallel beta strands alternating along the linear sequence, and connected by 15 polypeptide loops. The linear secondary structure folds into a superhelix with an eight-stranded beta barrel at the center, flanked by eight alpha helices around the periphery. The model kit for TIM has been used over the past 10 years to teach hands-on protein folding to students who range from high school to graduate school.

The plastic components used in the TIM barrel kit were printed on an in-house FDM solid printer (Stratasys Dimension); the magnets and elastic filament were purchased from commercial sources. To replicate the TIM barrel kit using a commercial 3D printing service, the cost for the unassembled kit parts would be about $360 (see Table S1). This number does not include the human labor time and costs of inserting the 240 cylindrical magnets and stringing each sub assembled component (beta sheet, alpha helix, and peptide loop). An experienced person can accomplish the task in about 5 hr. The kits described here are prototypes, and a commercially available kit could be redesigned to reduce the part and labor costs.

As described above, structural protein models have played essential roles in scientific discovery, and they also have strong advantages for helping students and scientists learn and explore new structures. While many students understand the relationship between the DNA sequence and the amino acid sequence of the protein that it encodes, it is challenging for them to understand the process by which a linear chain of amino acids folds into a 3D structure. For molecular biology students to understand concepts such as protein conformation, protein evolution, and structure-based drug design they must know how primary structure gives rise to secondary and tertiary structures.

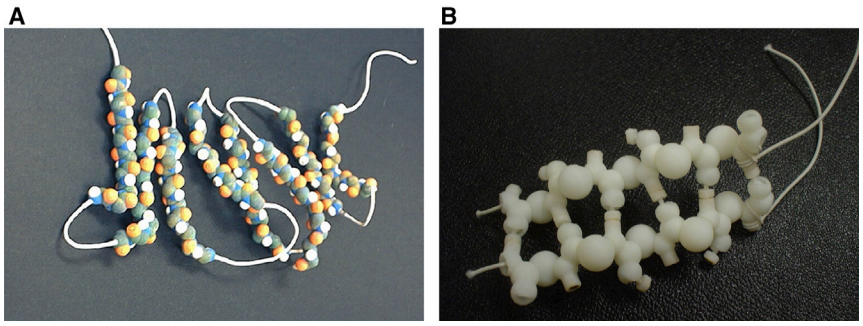

Figure 4. Evolution of Approaches in Building Realistic and Informative Peptide Model

(A) Model of retinol binding protein polypeptide was built using rigid configurations of each beta strand of a beta barrel connected by flexible wire loops. Beta strands contained embedded magnets of complementary polarity to represent the peptide backbone hydrogen bond donors and acceptors. The strand rigidity introduced tension into the physical model as even a small misalignment of magnets resulted in large problems with the model. (B) Flexible two stranded beta sheet that uses plastic extrusion 3D printing technology, embedded magnets, and the knowledge of the peptide backbone geometry to impart geometric flexibility to the hydrogen bonding patterns. In these models each amino acids can rotate freely within the polypeptide chain, but there is a specific fit position that is defined based on physicochemical reality of bond angles.

The modular polypeptide molecular models described here have numerous advantages over existing ball-and-stick model kits that are currently used for in many science courses. Existing models that are completely rigid cannot be easily used to represent dynamic processes such as protein folding. In contrast, the polypeptide folding modeling kit is created with structures that realistically model molecular dimensions and shape, degrees of freedom for bond formation, and which parts are flexible versus rigid. Existing static models have no affordances that assist in assembling correct molecules. Typically kits have generic slots for fitting together atoms and molecules; allowing students to create erroneous models as easily as correct models. Because the polypeptide folding model uses magnets to represent the polar nature of hydrogen bond interactions of the peptide backbone, it enables students to actively engage in the protein folding process. The successive build-up of interactions allows students to feel how hydrogen bonds give rise to stability as secondary structures form. Previous protein structure models have required students to carefully follow assembly instructions. These new models enable exploration and assist in their own assembly by allowing students to create and evaluate correct models versus incorrect ones. That is, students can feel the twist of a beta sheet and feel how there is greater resistance to folding in one direction over another. The built-in tactility created by the interplay of the variety of materials (plastic parts, stretchy monofilament, and magnets) and the realistic constraints on the geometry provide formative feedback to the students about what kinds of interactions or structures are possible. Students are able to observe the assembly process in ways that are not available with static physical models or virtual ones, deepening their understanding of molecular biology.

As with any instructional tool, for student learning to occur the model must be used in the context of an instructional activity. Over a three-year period, an activity using the protein folding kit was studied and iteratively developed as a laboratory practical in a graduate level structural biology class. The aims of the activity were threefold: (1) for students to explore how the chirality of naturally occurring amino acids dictates the resulting handedness of the folded polypeptide chain, (2) to explore structural properties of common secondary structures in proteins (beta sheets and alpha helices), and 3) for students to gain a hands-on experience of how linear primary structures form secondary and tertiary structures. Researchers from the educational research institute WestEd videotaped the implementation of the activities and researchers and instructors used the information from the observations to refine the activities.

In early implementations of the lab practical, multiple students made comments that the model helped them learn. In particular, one student mentioned previous trying (and failing) to make sense of the helices by building them using a traditional ball-and-stick model and stating how the new model helped him understand the spatial relationship in new ways. Students were very enthusiastic about the model use and made comments such as "why don't we do this more often in class? It's fun!" However, during early implementations, many students were extremely quiet while interacting with the models and it was unclear whether they were making connections between the model and concepts in structural biology.

Based on observations of successful students, researchers developed the Label-Build-Explain framework to capture the steps necessary for using the models to lead to a deeper scientific understanding. First, students needed to label the parts of the model with what they represented. For instance, students had to recognize which part of the model represented an alpha carbon or that the small sticks standing out from the model represented where the amino acid side chains would be. Second, students had to build the secondary structures such as the beta sheets and helices so they could understand the spatial relationships of the parts. Finally, to make sure students connect the structure they build with biological concepts they had to generate explanations for how stability and chirality emerges at higher orders of structure and the implications of the structures in natural contexts.

In fall of 2014, we observed and video-recorded 19 students participating in the lab practical as part of a structural biology course at The Scripps Research Institute with the aim of documenting student learning from the models. We looked for verification of students learning as demonstrated by making statements that incorporated prior knowledge with new knowledge from the activity, explaining concepts to other students, and overcoming misconceptions. We also looked for patterns related to what types of interactions with the models led to these learning events. We found that most learning was demonstrated immediately following an attempt to address a prompt on the activity handout or when an instructor would ask a leading question. Further, realizations and understanding often came directly after students struggled or experimented with the physical model. Although the physical assembly of the model was

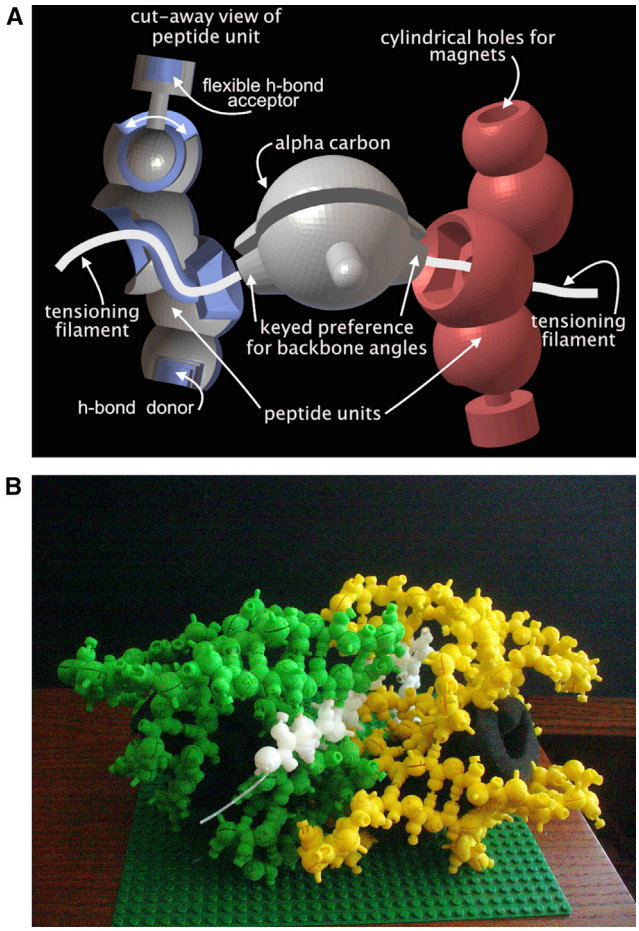

Figure 5. Polypeptide Model Components and Assembly

(A) Computer model showing individual components with flexible ball-socket H-bond acceptor and preference keyed phi/psi sockets.

(B) Complete folded model of HIV protease backbone with two protein chains (yellow and green) and peptide substrate (white).

time-consuming, the construction stage allowed students to refer back to the actual process of folding and use that understanding to make predictions and generate explanations about higher-order structures.

Unique Aspects of the Models for Exploring Chirality and Structure

To more effectively prompt students to explicitly label, build, and explain, researchers and instructors collaborated to create a revised handout that guided students through the activity and included specific questions for them to discuss in their groups. The activity included six major sections: handedness of amino acids, beta sheets, beta barrel formation, helices, TIM barrel, and amino acid sequence and protein structure. For each of these sections students were asked to label structures (e.g., the N and C termini of polypeptides, the handedness of a strand), build structures (e.g., moving from beta strands to beta sheets, beta sheets to beta barrels, and from strands to helices), and create explanations (e.g., how do differences in the arrangement of strands in beta sheets affect its stability? Does the twist of a beta sheet change if the strands are parallel or anti-parallel, why or why not?)

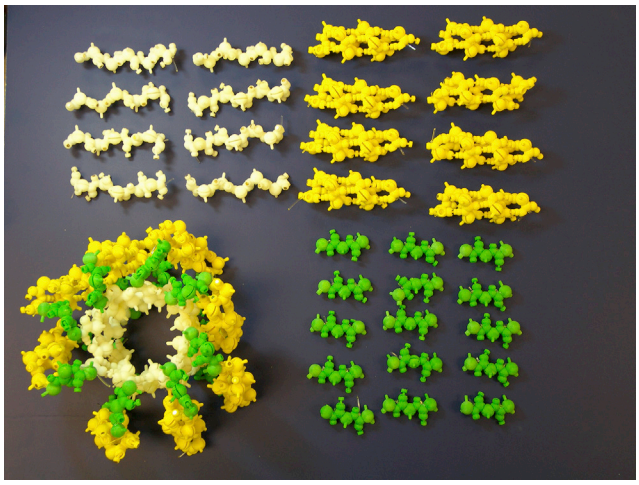

Figure 6. TIM Barrel Polypeptide Assembly Kit and Assembled Protein

Beta strands in white, alpha helices in yellow, and connecting peptide loops in green. All components are initially unfolded prior to assembly. The model contains 353 separately printed plastic parts and 31 strands of flexible filament.

Handedness of Amino Acids

Students were prompted to first explore the amino acid strands and identify which end represented the N terminus, which end represented the C terminus, and the overall handedness of the amino acid. Students determined the overall handedness by using the CORN crib mnemonic (Figure 7). That is, looking down from the position of the alpha carbons hydrogen, the molecule is left handed if, moving clockwise, the carbonyl-oxygen (CO), the amino acid (R) and nitrogen atom (N) are in order. Although students had little trouble determining the handedness of the molecule from diagrams showing the molecule in proper alignment, some students struggled to determine the handedness using the 3D model, suggesting their knowledge from the diagram alone may not have been robust.

Parallel and Anti-parallel Beta Sheets

The next series of activities were to join the strands of amino acids to form parallel and anti-parallel beta sheets. Students were prompted to discuss which ways the side chains pointed when they were joined parallel versus anti-parallel, and how the side chains may affect the formation of beta sheets. Even for graduate students, using the models gave them a deeper understanding of the protein structure. For example, one student said, "We talked about alpha helices and beta sheets a lot, but [this is] a lot more useful … When you [see a diagram of] an anti-parallel sheet, it's not obvious that the R-groups face out and in and out and in (making pleating motion with hands)." Another student noted the models helped him understand the difference in the orientation of the hydrogen bonds and amino acid side chains between the parallel and anti-parallel sheets in ways not possible with 2D diagrams, "When it's anti-parallel it's straight and when it's parallel its [angled] - the hydrogen bonds are different, but because it's not 3D you never see what the effect of this is on the R-group."

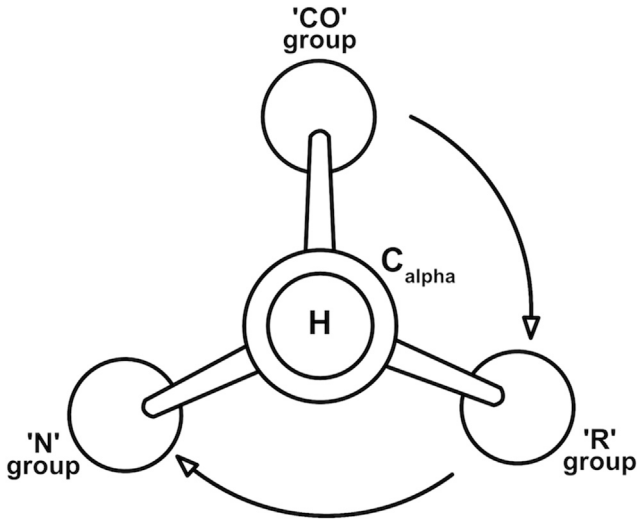

Figure 7. CORN Crib Mnemonic for Amino Acid Chirality
CORN is a useful way of determining the handedness of a molecule by establishing whether the carbonyl-oxygen (CO), the amino acid (R) and nitrogen atom (N) are moving clockwise or not when looked down from the position of the alpha carbon's hydrogen.

Students then determined the overall handedness of the twist of the sheet and used the models to explore whether the handedness or stability changed when the strands were joined in parallel versus anti-parallel (Figure 8). Many students initially had incorrect intuitions about whether parallel and anti-parallel sheets would have the same twist or chirality, e.g., ''My guess is they'll probably twist opposite,'' and ''They must be opposite, right?'' Explorations with the model helped them see that the handedness remained the same in both cases, and generating explanations led them to understand that the twist of the beta sheet, resulted from the chirality of the individual strands of amino acids – which does not change with strand orientation.

Beta Barrel Formation

Following the formation of beta sheets, students joined the open sides of the beta sheet to form a beta barrel. Because of the twist of the sheet, the strands must be tilted relative to the axis of the barrel to form a stable structure (Figure 9A). If they are not staggered, the barrel does not fold easily and is not stable. Further, the twist gives the sheet a directional preference defining which amino acids point inside and which outside the barrel. The models allowed students to feel which arrangements led to barrel formation and which did not. ''If you try to push it the other way it will be restrained, that's cool!'' After staggering anti-parallel strands students successfully built a beta barrel, students expressed an understanding of the stability of the barrel structure compared with the sheet, ''It actually seems to be stable, wow.''

3/10, Alpha, and Pi Helices

Next students used amino acid strands to form helices. Here they needed to distinguish between a right-handed and left handed helix. Students started with a 3/10 helix, and then successively shifted successive hydrogen bonds (magnetic contacts) by one amino acid residue to form an alpha helix, they then optionally shifted them again to form a pi helix. The new models allowed students to see and feel the overall shapes of

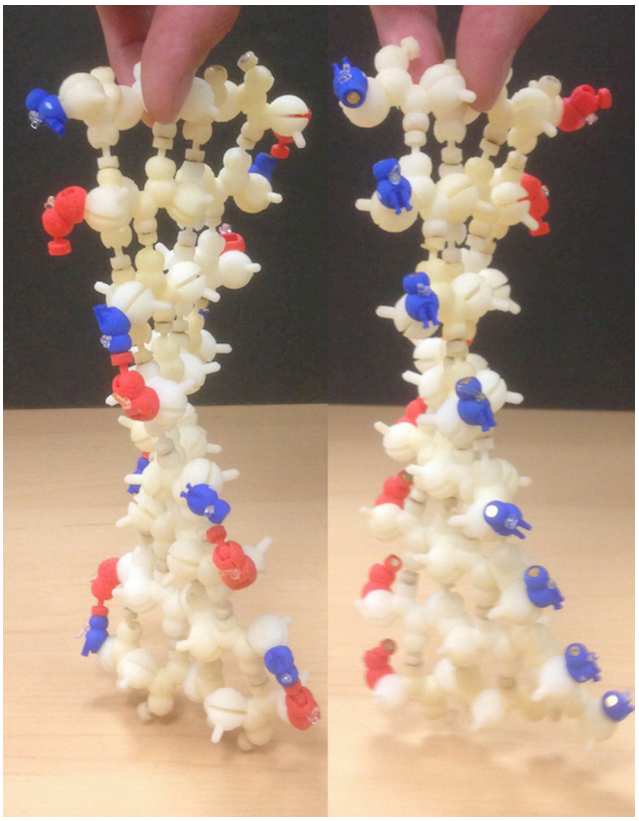

Figure 8. Twist of Anti-Parallel, on the Left, and Parallel Beta Sheets

the different helices and make predictions about their utility. Students noted that the 3/10 helix had a triangular shape, the alpha helix had a square shape and the pi helix had a near-pentagon shape. Students noticed that the helices were increasingly stable as they moved from 3/10 to alpha to the pi helix. Students were able to use the models to compare the relative flexibility and stability between different types of helices and made predictions about what types of helices would be the most useful in building proteins. One student described the alpha helix, ''Maybe that's a compromise here between flexibility and stability, because here (the pi helix) all the bonds are lining up, but it's not flexible at all.'' The other student states, ''This is too rigid (the pi), but this one is too loose (the 3/10). Another student reflected on how traditional models failed to show the differences between the types of helices, ''They gave us the ball and stick types of things and I tried to make these two helices in class and I couldn't.'' Students also expressed the advantages of the polypeptide folding model ''These kind of help you cheat in the sense that they just snap together,'' and ''I just started turning it… and without me even trying it formed an alpha helix [and I thought] I guess that's how it works.''

TIM Barrel Formation

Finally, students attached the beta strands and alpha helices to form a full linear polypeptide chain and fold it into a superhelix (Figures 9B and 9C). In this last part of the activity, students are able to participate in the process of folding a long strand into the TIM barrel. Students start at the amino terminus and

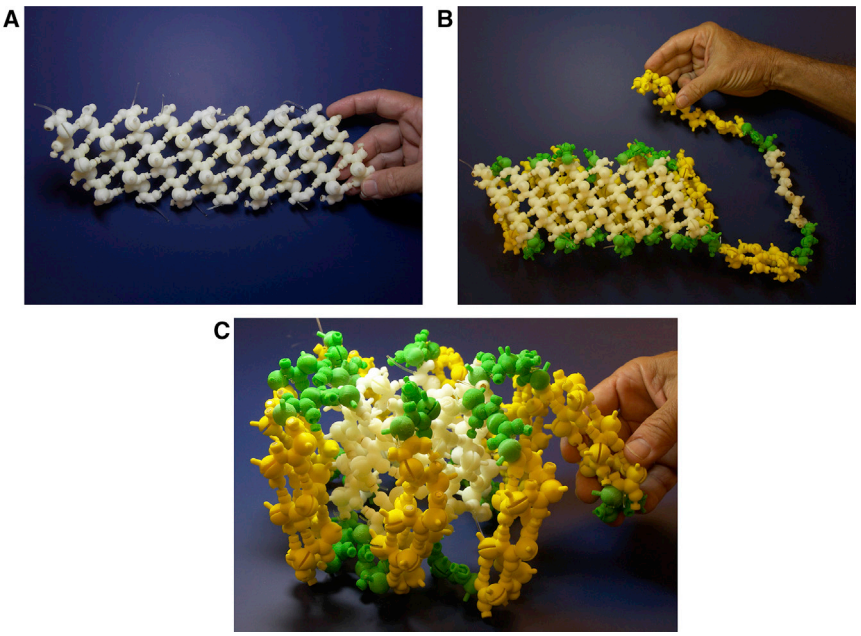

Figure 9. Assembling the TIM Barrel Protein

(A) Folding eight five amino acid beta strands (white) and assembling them into an 8-stranded parallel beta sheet.

(B) Folding eight ten amino acid polypeptide chains (yellow) into alpha helices, connecting them with the beta strands and loops (green) into a linear chain and wrapping them into a right-handed superhelix.

(C) Connecting the interior beta sheet into a beta barrel to make the tertiary structure of the idealized TIM barrel protein.

begin folding the alternating strands and helices to form a right-handed superhelix. As they fold the helix, students must make sure the beta strands bond to forma staggered parallel beta sheet. Once the superhelix is complete, students fold the entire TIM barrel by ensuring the internal beta barrel is attached properly and by connecting the carboxy terminal helix against the beta barrel in the same orientation as the other helices. Building the entire TIM barrel allows students to feel differences in stability between correct and incorrect configurations. When the correct bonds were not formed, stability was compromised, "We got it into one, but it was really fragile." Completing the full TIM barrel was very motivating for students and appeared to provide an appreciation for the complexity of the structures, "Look at it. It's beautiful! And, it's amazing!"

Conclusion

These unique tangible models provided students with new ways of thinking about protein structure and function and have much promise for building deeper understanding of core concepts such as chirality structural stability and emergent properties. They engage perceptual and cognitive processes that go beyond the visual and bring a sense of reality and natural interaction into the process of exploration and understanding. In the context of molecular science, they create a human-scale tangible representation to objects that are too small to be directly perceived. Physical molecular models can also serve as analog computers where spatial relationships between components in complex molecular interactions can be explored and manipulated. The advent of 3D printing has opened up new opportunities to design and prototype novel tools to aid in the understanding of complex biomolecular structures and their mechanisms. With the current and future advances of both 3D printing and the use of mixed or augmented reality (Gillet et al., 2005) (Figure 10), we envision new ways to experience the unseen world of molecular biology.

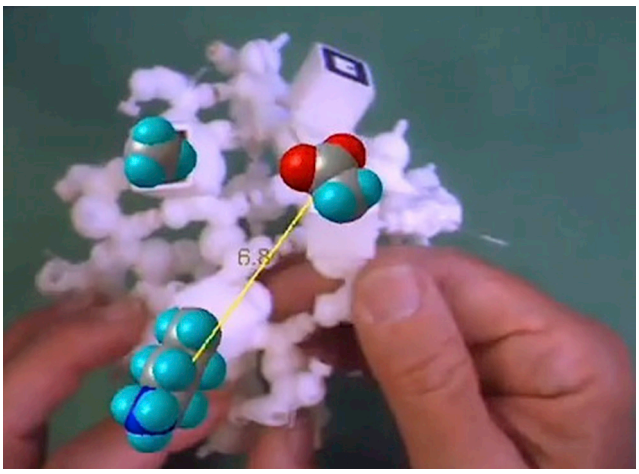

Figure 10. 3D Printing and Mixed or Augmented Reality

Tangible molecular interface comprised of 3D printed polypeptide backbone model of a beta barrel augmented with virtual amino acid side chains and showing interactive distance computation between two amino acids.

Protocol Availability

3D printable .stl files for all components of the polypeptide model have been deposited in the NIH 3D Print Exchange and are available under a Creative Commons License (Attribution-NonCommercial-NoDerivatives 4.0 International).

SUPPLEMENTAL INFORMATION

Supplemental Information includes one table and can be found with this article online at http://dx.doi.org/10.1016/j.str.2017.03.001.

AUTHOR CONTRIBUTIONS

A.O. developed the concept and design of the models, helped develop the lesson with the TIM barrel, and wrote the paper. J.D. helped develop the lessons, videotaped and developed build and observe questions, interviewed the students, and helped write the paper. E.G. developed the original TIM barrel lesson, ran the graduate student practical, and assisted in the development of the TIM barrel kit. M.P. developed student instructions and visual aids and handouts for the TIM barrel lesson, assisted in guiding the students during the lessons, and helped in the design of the TIM barrel kit. J.H. worked on the fabrication and assembly of the polypeptide-folding model and developed the assembly pipeline for the model. A.G. worked on improvements in the design and production of the polypeptide model and assisted in guiding the students during the lessons.

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