Tips & Tools
DOI: https://doi.org/10.1128/jmbe.v20i3.1797
JMBE Journal of Microbiology & Biology Education

Minds at Play: Using an Online Protein Folding Game, FoldIt, To Support Student Learning about Protein Folding, Structure, and the Scientific Process †

Rebecca Rashid Achterman
Bastyr University, Kenmore, WA 98028

Structure-function relationships of biological molecules are foundational to undergraduate biology education. In this article and supplemental information, an in-class activity is presented that uses a freely available online game to visualize the nature of chemical bonds as they relate to protein folding and structure. Activity questions and discussion guide students through a consideration of common structural elements as well as the nature of the scientific process. The activity was used in a lab section but could also work as a homework assignment. Student comments from a survey at the end of the course were overwhelmingly positive and indicated the activity helped them appreciate the complexity of protein folding as well as the scientific processes used to solve protein structures.

INTRODUCTION

The relationship between the structure and function of biological molecules has been identified as a core concept common to biochemistry and molecular biology (1). Understanding the three-dimensional (3D) nature of proteins and visualizing the chemical bonds involved in protein folding is crucial for students to be able to consider structure–function relationships, visualize protein–ligand interactions, and predict the effect of mutations. However, students consistently demonstrate misconceptions related to protein structure and folding (2). Textbook images alone can lead to a misrepresentation of protein folding as a transition from a long amino acid sequence to a 3D folded structure (3).

The ability to visualize rotation of a 3D image in space begins in infancy, continues to develop in adolescence, and improves with practice (4). The 3D structures of many proteins are now available as teaching aids, including animations of rotating protein structures that accompany some textbooks. Furthermore, an online protein folding game, FoldIt, uses principles of protein folding to allow players to solve 3D protein structures (https://fold.it/portal/). The FoldIt website includes resources for educators and students related to constructing a classroom group or getting started playing the game; however, it does not directly connect students with questions that tie the game to course learning outcomes.

Educators themselves must take a lead role in generating meaningful activities that incorporate the FoldIt game and are more directly connected to learning outcomes. Franco has published homework activity targeted at general chemistry, organic chemistry, and biochemistry students (5). Franco's activity requires students to access the FoldIt game outside of class and complete enough tutorial puzzles to be able to start the beginner puzzles. Activity questions guide students toward learning outcomes geared toward chemical concepts such as the types of bonds that participate in protein folding, as well as broader questions, such as why programs like FoldIt are useful. Although data are not presented, the activity is described as having improved student comprehension about secondary structures, noncovalent interactions, and structure–function relationships (5). Similarly, Farley provides a worksheet to go along with the tutorial puzzles and reports student perceptions indicating the game was fun to play (94% of students surveyed) and improved understanding of protein structure (100% of students surveyed) (6). Use of "custom contests" has been described for upper-level biochemistry courses, in which educators can create puzzles that fit their curriculum (7).

It is valuable for instructors to have multiple resources to fit the needs of their students. Here, we present an in-class activity that makes use of the FoldIt program. Like the Franco and Farley activities, it has questions that guide the students to connect concepts from the game to learning objectives. However, this activity does not require progression beyond the tutorial puzzles, and it allows students to work in pairs, alleviating some of the technical challenges students experienced. Additionally, this activity includes questions about the process of science. The activity was used in the

---

*Corresponding author. Mailing address: 14500 Juanita Drive NE, Bastyr University, Kenmore, WA 98028. Phone: 425-896-6829. E-mail: rachterman@bastyr.edu.

Received: 27 March 2019, Accepted: 16 September 2019, Published: 18 December 2019.

†Supplemental materials available at http://asmscience.org/jmbe

lab section of an undergraduate course, "Integrated Biochemistry and Cell Biology," during the protein structure topic. Student comments from a survey at the end of the course were overwhelmingly positive, with particular notes made of the ability to rotate proteins, an appreciation of the complexity of protein folding, and improved understanding of the scientific processes used to solve protein structures.

PROCEDURE

Materials and preparation

Computers with the "FoldIt" program downloaded are required. It is recommended that students work in pairs during the activity. Although students could work individually in a small class or parts of the activity could be assigned as homework, some students expressed frustration with the mechanics of the game. Working in pairs allows students to help each other with these technical aspects and focus on scientific learning.

Students should learn the following terms at a basic level before beginning the activity: protein primary structure, secondary structure (*alpha*-helices and *beta*-sheets), tertiary structure, quaternary structure, and amino acids (general structure and side chain), polypeptides (note the backbone and side chains). For a flipped classroom, it would be possible to assign a reading assignment such as the protein structure chapter of their textbook, along with a short quiz over definitions of important terms listed above, and do the activity during the class period.

The activity can be used as a worksheet that is turned in for a grade, and/or used to prepare students for group discussion. A two-hour class period is sufficient to complete the activity and spend time discussing a subset of the questions in detail.

Learning goals

The activity is designed to supplement student learning of scientific principles involved in protein structure and protein folding, which can be challenging to visualize, by using a game that allows users to manipulate a polypeptide in three-dimensional space to create a final folded protein. During the activity, students are led through some of the introductory puzzles and answer questions about how different parts of the protein are behaving, or why they think the designers made a feature work a certain way. The learning goals for the activity are:

- Conceptualize the three-dimensional nature of proteins
- Discuss the role of hydrogen bond formation in secondary structure
- Discuss the role of amino acid side chains in protein folding
- Consider difficulties in predicting protein structure, and how scientists may address these problems

Some activity questions are straightforward and highlight structural aspects of proteins. For example, students are asked to note the orientation of amino acid side chains on *alpha*-helices and *beta*-sheets. Students rotate images of the indicated proteins to identify the spatial location of the side chains.

Other questions are intended to stimulate deeper comparison thinking. For example, students are asked what the "shake" feature does and whether proteins have a built-in "shake" feature when they fold *in vivo*. In the game, the "shake" feature automatically moves side chains to the most thermodynamically stable position. This can lead to a discussion of the observation that proteins spontaneously fold into their most thermodynamically stable configuration, either alone or with assistance from chaperone and chaperonin proteins. This can be used as a tie-in to the Anfinson experiment with RNaseA, which is included in many introductory molecular biology and biochemistry textbooks (8).

Finally, some questions relate to the nature of the scientific process. The final three activity questions ask students to consider the purpose of FoldIt as a scientific endeavor to improve protein structure prediction.

Safety issues

None.

Student survey data

This study (18-1626) has been reviewed by the chair of the Institutional Review Board at Bastyr University and found to meet the exemption criterion listed under 45 CFR 46.101(b)(3).

CONCLUSIONS

Students completed this activity in the lab section of an Integrated Biochemistry and Cell Biology course. Two hours were allotted to complete the activity in pairs and discuss most activity questions as a group. In a survey at the end of the course, all students (100%) responded and had positive comments about the activity (Table 1). Some additionally noted a challenge or negative comment about the activity, usually having to do with how the FoldIt program works. This challenge can be reduced by allowing students to work together in pairs during class and making it clear that it's ok for teams to help each other. Positive themes noted in the survey responses included the ability to rotate proteins in the game and an appreciation of the complexity of protein folding and the scientific processes to solve protein structures. Several general comments related the activity to overall learning about proteins.

While using ball and stick models to "build" amino acids is helpful, FoldIt allows for an interactive experience that helps to develop an understanding not only of optimal protein folding, but

TABLE 1.
Responses to survey question about FoldIt[a].

Response (*n*=15 students)	**Sample student comment**
Activity was helpful or enjoyable (15/15)	
• Appreciated ability to rotate protein structure (6/15)	*The FoldIt program allowed me to see [protein structure] in a more 3D picture where I could twist and turn the protein to see all the important structures discussed in class.*
• Activity helped appreciate the complexity of protein folding (3/15)	*It was helpful because it helped me realize how complex protein folding is! Now, when I hear or read that a protein structure has been solved, I have a deeper appreciation for what that means. I also enjoyed experiencing a program that crowd-sources creative thinkers to be involved in science—I think that's so cool!*
• Activity helped appreciate the complexity of the scientific process related to solving protein structures (6/15)	*The program was really interesting in that it showed how solving protein structure is something that's still very much in the works, and something that we can all contribute to!*
Downside was noted even though the activity was found to be helpful overall (6/15)	
• Downside related to technical aspect of using the program (5/6)	*As we moved further along within the game it became harder to keep up with all of the tricks to get the protein properly aligned and folded.*

[a] Survey question: In the lab section for this class, you used the FoldIt computer program to deepen your understanding of protein structure. In what ways was it (or was it not) useful in visualizing the three-dimensional structure of proteins? Are there any things that stood out about the activity for you that were helpful or harmful to your learning?

also (importantly) of the potential obstacles that can disrupt or derail proper folding. For me, it created a helpful reference point for remembering protein-folding details.

It was useful in visualizing the 3D structure of proteins just by seeing them in 3D (by moving and turning them), but the most impressive is that each protein may only have one ideal way to fold based on its primary structure. The takeaway from that is that the 3D structure of a protein is very specific. One thing that stood out that was helpful was the levels of the game … it impressed in me that protein folding has many rules that build on each other.

In conclusion, the activity described here engages students in learning about protein folding, protein structure, and the scientific process in a way that students find useful and memorable. More research is needed to measure the efficacy of the activity more robustly.

SUPPLEMENTAL MATERIALS

Appendix 1: In-class activity

ACKNOWLEDGMENT

The author does not have any conflicts of interest to declare.

REFERENCES

1. Tansey JT, Baird T Jr, Cox MM, Fox KM, Knight J, Sears D, Bell E. 2013. Foundational concepts and underlying theories for majors in "biochemistry and molecular biology." Biochem Mol Biol Educ 41(5):289–296.
2. Robic S. 2010. Mathematics, thermodynamics, and modeling to address ten common misconceptions about protein structure, folding, and stability. CBE Life Sci Educ 9(3):189–195.
3. Glykos NM. 2011. The 11th misconception? CBE Life Sci Educ 10(1):1–2.
4. Kail R. 1986. The impact of extended practice on rate of mental rotation. J Exp Child Psychol 42(3):378–391.
5. Franco J. 2012. Online gaming for understanding folding, interactions, and structure. J Chem Educ 89(12):1543–1546.
6. Farley PC. 2013. Using the computer game "FoldIt" to entice students to explore external representations of protein structure in a biochemistry course for nonmajors. Biochem Mol Biol Ed 41(1):56–57.
7. Dsilva L, Mittal S, Koepnick B, Flatten J, Cooper S, Horowitz S. 2019. Creating custom FoldIt puzzles for teaching biochemistry. Biochem Mol Biol Ed 47(2):133–139.
8. Anfinson CB, Redfield RR, Choate WL, Page J, Carroll WR. 1954. Studies on the gross structure, cross-linkages, and terminal sequences in ribonuclease. J Biol Chem 207(1):201–210.