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Connecting Protein Structure to Intermolecular Interactions: A Computer Modeling Laboratory

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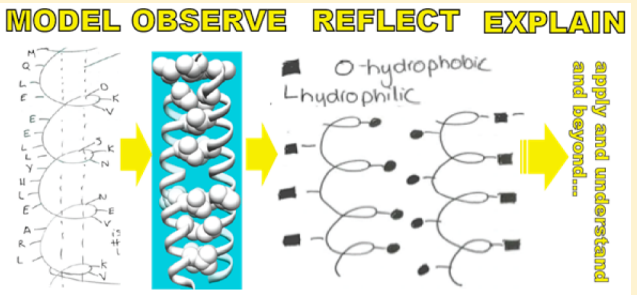
Supporting Information

ABSTRACT: An understanding of protein folding relies on a solid foundation of a number of critical chemical concepts, such as molecular structure, intra-/intermolecular interactions, and relating structure to function. Recent reports show that students struggle on all levels to achieve these understandings and use them in meaningful ways. Further, several reports show that the visualization techniques employed to help students understand protein structure often lead to confusion and propagate further misconceptions. Here, we report on a lab exercise using computer-based modeling to support student proficiency in using and making models and understanding H-bonding and the hydrophobic effect in the context of protein folding. We analyzed student drawings and explanations of protein structure and found significant improvements from pre- to postlab, indicating that students improved their understanding of protein folding. Further, we report on how we systematically refined our laboratory materials based on student work.



KEYWORDS: *First Year Undergraduate/General, Chemical Education Research, Biochemistry, Laboratory Instruction, Interdisciplinary/Multidisciplinary, Computer-Based Learning, Inquiry-Based/Discovery Learning, Hydrogen Bonding, Lewis Structures, Nonmajor Courses, Proteins/Peptides*

FEATURE: Chemical Education Research

BACKGROUND

Many first-year chemistry students fail to understand the concepts related to intermolecular interactions and fail to apply these concepts in a meaningful way.[1] This problem is even more troubling for prehealth students in a one- or two-semester "GOB" (General, Organic, and Biochemistry) course.[2,3] An understanding of molecular interactions is required for understanding protein structure and function and is considered foundational in nursing and other health-related fields.[4−6] Often, these are the last courses these students may take from a chemistry perspective, and therefore these gaps in understanding may never be remediated later on.

To address these concerns, we have developed a computer-based modeling lab that explores the basic concepts of intra-/intermolecular interactions in the context of protein folding. We have implemented and refined this lab in a 100-level organic and biochemistry course, which predominately serves prenursing students. This lab is designed to allow students to discover for themselves the relevant components of protein structure and the role of intra-/intermolecular interactions in protein folding. We have employed UCSF Chimera, a simple, free program that reads Protein Data Bank (PDB) structures and allows for viewing and modification.[7] While this work describes implementation in a 100-level prenursing course, this lab has also been implemented in a 400-level Biochemistry course.

This lab is part of a set of laboratories we are developing to teach fundamental concepts in chemistry that meet the needs of prehealth students using the MORE framework. MORE, developed by Rickey and co-workers,[8,9] asks students to **model** a system of interest in both the macroscopic and molecular level. In lab, students **observe** the system. Based on their observations, students **reflect** on their model, using evidence collected in lab to refine their model. The students then **explain** the model in general terms, or in relation to a similar system. This emphasis on connecting a molecular-level understanding of various phenomena to observations is consistent with many other important curriculum reform efforts.[10,11] Further, MORE emphasizes reasoning with evidence, a component of many science standards and nursing practice.[12,13]

The key concepts that this lab teaches are consistent with comprehensive studies of prenursing programs[4] and even key

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concepts for a traditional general chemistry course. The fundamental concepts students are learning in this lab are that (1) molecular structure leads to function and (2) molecular structure can be used to predict the strength and nature of intra-/intermolecular interactions, which can in turn be used to predict the physical properties of a system. To help students learn these concepts, it is important to understand the breadth and depth of the struggle that students have in relating molecular structure to observations. For example, it has been demonstrated that general and organic chemistry students fail to connect molecular structure, intermolecular interactions, and basic phenomena such as boiling points.[1] It has further been demonstrated that the breakdown occurs at many levels; students struggle to draw Lewis structures, struggle to see that Lewis structures can predict intermolecular interactions, and struggle to see how that relates to macroscopic behaviors. An effective method to overcome this problem is via an iterative series of exercises of increasing complexity by viewing more and more complex Lewis structures, considering different physical phenomena, and making relevant connections.[11] In our work, students follow this trajectory over the course of the semester by considering, for example, boiling points, solubility, and acid−base relationships in a series of laboratories. Protein folding is an excellent culmination of these activities, as self-assembly is dictated by the various intermolecular interactions, which can be viewed in 3D using appropriate software.

This laboratory exercise is also designed to increase student understanding of visual representations of biochemical molecules. The importance of visualization in biochemistry education is well-acknowledged by the education community, with instructors using a variety of visualization methods, particularly in the context of lecture.[14,15] However, it has been shown that students often misinterpret or fail to see the limitations of these visualizations, leading to misconceptions in basic concepts, such as α-helical structure.[16] Recent efforts have been focused on improving student competence in interpreting biomolecular representations, with positive outcomes.[16] These efforts have used POGIL-based, in-class strategies using static images. We offer that this study shares new insights on and provides new methods for improving student understanding of molecular visualization. Further, our laboratory exercise distinguishes itself from other laboratory exercises[17,18] in its focus on H-bonding and the hydrophobic effect and also in its pedagogical approach.

The conceptual framework behind the new laboratory work is associated with two different sources: the constructivist perspective that is embedded in the MORE framework and social theories of learning, especially those related to peer learning. These framework sources also shape our research questions.

The MORE framework is built on an understanding of the role of reflection within the process of constructing knowledge.[9] This, in turn, relies on the idea that learning is supported by (a) asking students to consider prior knowledge, (b) providing opportunities for metacognition, and (c) guiding students to create deep conceptual understandings based on a robust body of facts.[19] The model phase of the MORE framework is a place where students can present their initial understandings, drawn on current knowledge; these are then subject to critique following the observe phase, including the two steps of considering how the new information confirms or refutes prior understandings and how the new information can form the basis of the final explanation. The implementation of the MORE framework in our context includes a specific step where students are prompted to make and discuss their observations in pairs. This draws on the research that indicates how collaboration and peer-to-peer dialogue supports learning, aligning in particular with social constructivist standpoints.[20]

During the course of our work we also engaged in a cycle of revision of our work that incorporated research findings from one semester as the basis of changes for a subsequent semester. In this case, we were following the framework known as design-based research (DBR).[21] A specific design (here, the MORE framework) was applied to learning about molecular interactions using computer modeling. Analysis of student work and reflection on the teaching experience in the first semester provided specific evidence to evaluate the success of the design, and this led to particular changes in the design.

The same theoretical frameworks that guide our implementation and our revision of the experiments are the basis of our research. We have a scaffold on which we are able to study student actions and performance, and then we have results that address research on student outcomes and also directly contribute to both refined design and to our research on the process of revision itself, the latter being essential elements of DBR. Similarly, the MORE framework emphasizes students' explicit description of their understandings, using both words and diagrams. These are then analyzed, following a constructivist paradigm for learning, to allow us to describe how students were or were not able to construct the expected knowledge during their experience.

Continual evaluation and improvement of laboratories can contribute to students learning and also allow for more rapid adoption of best practices.[22] In this work, we report on the specific, incremental changes made to the lab between the Fall 2014 (F14) and Spring 2015 (S15) implementations. Some of the changes include creating a prelab video, asking students to draw and reflect on models during lab, and asking students to compare their work with other groups.

RESEARCH QUESTIONS

In order for students to successfully learn from lab, they need to be engaged in the experience and the content must be taught at the appropriate level. Ideally, students will be able to use and build upon that knowledge. In the course of developing our laboratory materials, we have identified four research questions:

(1) Can we better help students in a 100-level Chemistry course to understand protein structure by revising of our pedagogical approach?

To evaluate our pedagogical approaches and student learning, we used research questions 2, 3, and 4:

(2) Do students *complete* the activity of making and revising models, as indicated by outcome measures to evaluate completion of prelab, during-lab, and postlab activities?

(3) Do students *learn* about protein structure from making and revising their models, as indicated by outcome measures to evaluate correctness of prelab, during-lab, and postlab activities?

(4) What evidence exists in student work to illustrate understanding (or misconceptions) of protein structure, and what evidence exists to illustrate progress in learning?

METHODS AND FRAMEWORKS

Description of Implementation

This laboratory was implemented in a one-semester Survey of Organic and Biochemistry course for predominately prenursing students who have taken one semester of General Chemistry at

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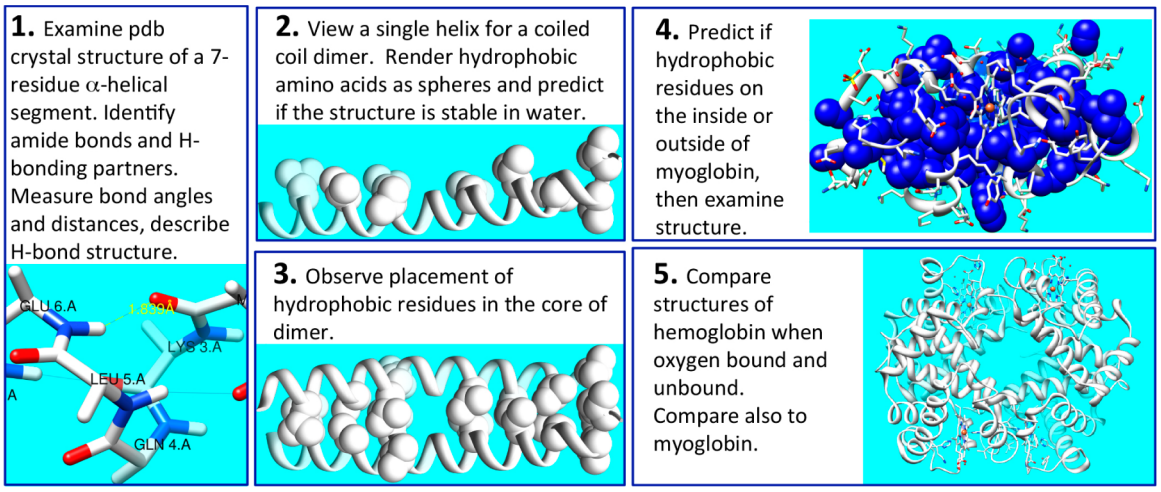

Figure 1. Description of laboratory procedures (parts 1−5) performed by students.

a large, urban, state university in the Midwest United States. The course follows a traditional sequence and is linked to a lecture course that employs a traditional textbook.[23] In each week of the 15 week semester of our course, students attend 2.5 h of lecture, 1 h of discussion with a teaching assistant (TA), and one 3 h lab with a TA. TAs (four for F14 and three for S15) were approximately equivalent in training and experience over the period of this study.

The student population is culturally diverse, and most are preparing to apply to a top-caliber nursing program. The population of students at this University is roughly 40 percent underrepresented minorities, with an average ACT score very close to the U.S. average. Thus, this program should be very appropriate at many other institutions.

We present data from two semesters, Fall 2014 and Spring 2015, when the Computer Modeling of Proteins Lab was implemented in week 12 and week 13 of a 15 week semester, respectively. Students work with lab partners; two students were assigned to each computer. In addition, students were instructed to sit near and communicate with one other group. The relevant exam was implemented in week 14 for both F14 and S15.

Collection of Student Work

In F14, we collected student lab reports for this lab and systematically analyzed student work to evaluate student performance and learning. Based on our analysis in the DBR cycle, we refined the lab and reimplemented in S15, and again systematically evaluated student work. We further analyzed student learning by evaluating student responses to a related exam question. Herein we will report on our methods for analyzing student outcomes, revisions made based on this analysis, and improved student outcomes after revision. Further, we provide specific examples to illustrate changes in student understanding over the course of the activity. Collection and analysis of student work was performed in accordance with a protocol approved by the university institutional review board (IRB).

Analysis of Student Work

In order to examine differences in student outcomes between the F14 and S15 implementations, we developed a detailed coding scheme. To study student completion, we developed outcome measures to assess if students attempted each component of the lab. To evaluate learning, we studied outcome measures for which activities students performed correctly in the prelab and which activities students performed properly during lab or in the postlab. Specifically, we evaluated students' ability to describe the role of intra-/intermolecular interactions in protein folding and stability. In the process of coding student work, we paid particular attention to errors that could be ascribed to misconceptions.

A total of 53 lab reports from F14 and 52 lab reports from S15 were collected. Ten lab reports from F14 and five lab reports from S15 were used for the purpose of developing, testing, and discussing the coding system used to analyze reports (the coding scheme is given in the Supporting Information, Tables S4−S6). Since these laboratories were discussed at length by the coders, they were removed from the analysis to ensure validity of the coding scheme. Two coders evaluated 70% of the S15 student lab reports (n = 47). The coders achieved an inter-rater reliability of 78% for postlab item 5 and an inter-rater reliability of 85% or greater for all other questions. A single coder proceeded to analyze the remaining laboratories from S15 and F14 (n = 43).

Coding was performed using constant comparison, selective coding. Operational definitions of the codes were defined through discussion between coders, resulting in a detailed rubric. The main challenges were interpreting student drawings and words and deciding the threshold for a correct answer.

Differences between the prelab and postlab for each semester and differences between the F14 and S15 implementations were evaluated for significance using a Z-test for two population proportions. Full statistical analysis is included in the Supporting Information (Tables S1 and S2).

Student performance on a related exam question was also analyzed. The rubric used to code the exam response was parallel to the rubric for the laboratory report, and was coded by a single coder (n = 40, F14; n = 41, S15). This exam question had been used in previous semesters by the same instructor, and there is no indication that students misunderstood the question or were confused by the question wording. The rubric used to code exam question 2 was developed using constant comparison, selective coding (see Supporting Information, Table S7).

To evaluate learning by the students, we identified four specific learning objectives related to protein structure for this component of the course, and for this lab exercise in particular. Doing so also allowed us to identify misconceptions as revealed in the prelab and that might be corrected during the

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performance of this laboratory exercise. Examples of student errors, and students' ability to correct these errors over the course of lab, are also provided.

RESULTS

Description of Lab Procedure and Goals

The goal of this laboratory experience was to have students relate their understanding of intermolecular interactions to the basic features of protein folding. Specifically, we wanted students to consider the role of the hydrophobic effect and the role of H-bonding in protein structure and then also to learn the concepts of primary, secondary, tertiary, and quaternary structure. Students were introduced to the lab with a prelab video (S15 only) and written introduction in their lab handout (Supporting Information, page 15). These resources recapped some of the basic ideas of protein folding but did not explicitly state the importance of the hydrophobic effect in driving protein folding or illustrate what was meant by the burial of hydrophobic residues. However, this content was explicitly described during the lecture portion of the course in the week prior to lab and was readily accessible in the course textbook. The model system of a coiled coil that was used in the lab was never discussed in class or the textbook.

In F14 and S15, students followed the same basic procedures and examined PDB protein structures using Chimera.[7] The students downloaded the PDB files from the course Web site and used them during the lab period. The lab can be broken down into five parts, as described below and illustrated in Figure 1. Each part of the lab was developed to help students understand a specific element of protein folding or to address a specific misconception that has been identified in the literature. Briefly, students explored structures of increasing complexity, first exploring H-bonding in a helical segment, then looking at hydrophobic residues in a peptide, and then applying their understanding to larger protein structures (Figure 1).

Our design departs from previous examples of the implementation of the MORE framework through our choice of the phenomenon used during the observe phase. Specifically, previous work with the MORE framework emphasized observation of macroscopic phenomena, typically involving the properties of actual chemical substances. In our case, the phenomenon of interest is also experimental, using evidence from X-ray crystal structures. The experimental evidence is presented to the student by means of a computer modeling exercise. This has a macroscopic aspect in that it is something students observe visually, but it is very different from, for example, watching an actual precipitate form. However, we note that the computer exercise was not a passive experience: it was one in which the students manipulated different objects (on a computer screen) and monitored the outcome. In this way, they extended the experimental evidence from crystal structures into a set of observations. That we were able to observe students providing rich descriptions of what they saw on the screen, and that these descriptions became part of the evidence for their explanations, confirms the integrity of a computer modeling experience as a basis for observation in the MORE framework.

Development and Refinement of Student Prompts, Based on the Analysis of Student Work

Student lab reports for this lab exercise were systematically analyzed from F14 and found to be deficient in several areas, which will be described in detail in the coming sections. Briefly, student models focused on surface features, and it appeared that most students put minimal effort into their initial models. Students often skipped the more difficult, conceptual prompts or provided cursory answers. Many students did not use evidence from lab to refine their models, often stating that their initial model was correct, though initial models were deficient in many ways. Many students persisted in stating that protein folding was driven mainly by H-bonding. Only 14% of students correctly incorporated hydrophobic patterning into their models, and only 5% related hydrophobic partitioning to stability.

To address these problems, first, we wanted to ensure that students are properly guided in their initial thinking about their models.[24] To ensure that all students have relevant background information before coming to lab, a prelab video was created that describes basic features of proteins (for example that proteins are derived from amino acids). The video also familiarizes students with the Chimera software, since demonstrating laboratory techniques by video has been shown to reduce students' cognitive load, allowing them to focus more deeply on chemical concepts.[24] Further, the implementation of prelab videos was expected to reduce the amount of material that must be covered with the TAs, allowing the TAs more time to engage in one-on-one student interactions and group discussions.

We also wanted to ensure that students understood the MORE pedagogy and that our expectations for lab were clear to them. Significant changes were made to several other laboratories in the curriculum, better aligning them with the MORE pedagogy. Prelab videos were introduced in S15 to three other laboratories. In addition, a video to introduce the students to MORE was provided at the beginning of the semester. These changes gave students many opportunities to use MORE and also to obtain feedback from instructors, either informally or using the detailed grading rubrics that were developed for each lab.

Throughout the S15 semester, students were more engaged in lab and better prepared to create their models (data not shown). Lab improvements throughout the semester may have played a significant factor in improving student performance. However, as shown in Table 1, we found that the ACT scores for the S15 students were significantly higher than for the F14 students (p = 0.002). Statistically significant differences were not found in prerequisite Chemistry grades for the two groups of students (Table 1). While there is no established link between ACT score and lab performance, finding any inherent differences between the F14 and S15 students is a limitation of this study.

Table 1. Prerequisite Chemistry Grade, Course Grade, and ACT Scores

Term/p	Av Prerequisite Final Grade[a]	Av Course Final Grade[a]	Av ACT Score
F14[b]	2.70	2.46	23.3
S15[c]	2.71	2.92	24.9
p	0.89	0.12	0.0022

[a]Grade calculation scale: A = 4; B = 3; C = 2; D, F, W = 0. [b]F14, n = 77. [c]S15, n = 99.

For the S15 implementation, significant changes were also made to prelab, during-lab, and postlab questions to focus student attention on the types of interactions that occur in protein folding. The prompts and sample student responses are given in Figures 2−4. Due to space constraints, only the student-

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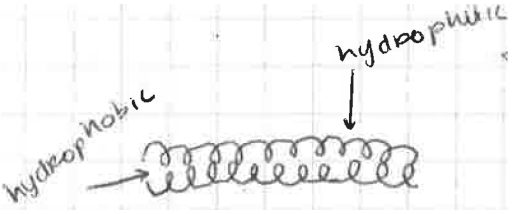
Fall 2014 Pre-Lab:
For this question, you will be graded in completion, rather than correctness of the model. In the post-lab, you will asked to evaluate your original models based on what you experienced in lab. The GCN4-p1 domain (also called the leucine zipper domain) forms an alpha-helix in solution, which matches up with a second peptide to form a dimer. Draw a picture of how you would expect GCN4-p1 domain to fold. What do you think is the driving-force for folding? Be sure to label your model and describe what each representation means.

Fall 2014 Post-lab refined model



Spring 2015 Pre-Lab:
For this question, you will be graded in completion, rather than correctness of the model. In the post-lab, you will asked to evaluate your original models based on what you experienced in lab. The sequence for the GCN4-p1 domain (also called the leucine zipper domain) is given in pre-lab question 1. It forms an alpha-helix in solution, which matches up with a second peptide to form a dimer.

i. Draw a picture of how you would expect GCN4-p1 domain to fold. Be sure to label your model and describe what each representation means.
ii. Indicate in your drawing which amino acids you think will be buried inside the structure. Also indicate where you think H-bonds will form.
iii. Describe the structure you drew and why you drew it that way. What is the energetic driving force for protein folding?

Spring 2015 Post-lab refined model

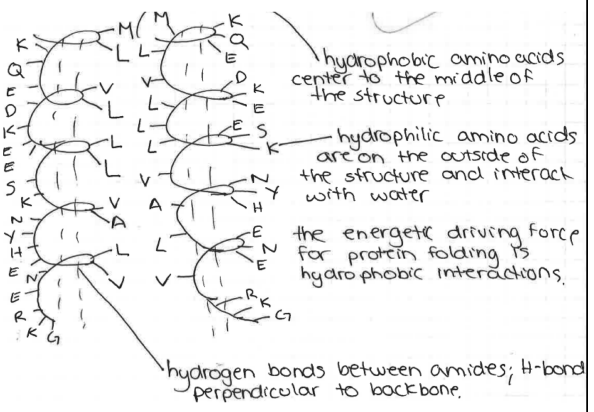


Figure 2. Prelab questions shown for F14 and S15, respectively. Refined postlab models are shown for one student response from each semester. Labels that were written by the student are shown. Initial models and additional text that accompanied student responses are given in the Supporting Information. Student drawings reproduced with permission.

Fall 2014 During Lab: (student response not shown)
Observe: Describe the pattern of hydrophobic/hydrophilic residues.
Reflect: (for post-lab) How does it relate to the stability of the peptide's folded structure?

Spring 2015 During Lab
Observe: Draw a sketch of the peptide, including where you would expect to find H-bonds and the location of the hydrophobic amino acids.
Reflect: How does primary sequence relate to the stability of the peptide's folded structure? In other words, how does the pattern of hydrophobic residues effect protein stability? Briefly examine you prelab model and describe any changes you might make.
Compare: Compare what you drew and predicted with another group of students. You are permitted to change your answers/drawings based on this discussion

Spring 2015 During Lab model

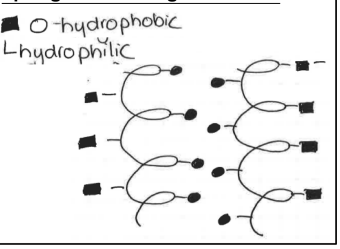


Figure 3. Prompts given during lab in Fall 2014 and Spring 2015, respectively. This prompt is given after students render the coiled coil dimer to highlight the location of hydrophobic residues. Complete examples of student responses are given in the Supporting Information. Student drawings reproduced with permission.

generated drawings are shown in Figures 2−4. The full models, including explanatory text, are provided in the Supporting Information (Figures S2−S8).

In the MORE framework, students are given a prelab question that asks them to model the system of interest based on their own understanding of the material going into lab.[25] After lab, students are asked to refine their initial model based on what they observed in lab. We modified these pre-/postlab questions as shown in Figure 2 to ask explicitly for the driving force of protein folding and for students to draw the location of H-bonds. We also divided the question into subquestions to encourage students to respond to all prompts. Of particular note is the specific direction we gave of what to observe and describe. This simple addition provided scaffolding for students about what experimental evidence from the crystal structures was most important for their work. This deviates somewhat from the "unscaffolded" observations commonly used in MORE laboratories.[25] But, we found it appropriate given that the crystal structures, in their richness, provide so much other information of less importance to the problem for this lab.

A critical component of MORE is that students make observations during lab and reflect on how those observations inform their prelab model. We reasoned that asking students to explicitly draw what they observe,[26] asking them to reflect on

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Fall 2014 "Explain" (prompt given after examination of myoglobin structure)
Reflect: (for post-lab) What are some similarities and differences between the GCN4-p1 structure and the myoglobin structure? What role does H-bonding have in the GCN4-p1? What about in myoglobin?

Spring 2015 "Explain" (prompt given in post-lab)
Describe the similarities and differences between the GCN4-p1 dimer, myoglobin, and hemoglobin. Can you relate these similarities and differences to general principles that describe protein structure?

Figure 4. Prompt given to elicit student's general understanding of protein structure. Complete examples of student responses are given in the Supporting Information.

their models during lab,[25] and asking them to compare their work with other groups[27] would make a significant impact in students' ability to refine their models. Several reflective prompts are given during lab, such as the prompt shown in Figure 3, which is given when students examine the structure of the coiled coil dimer. We modified the prompt from the F14 to S15 implementation as shown in Figure 3.

To probe students' ability to make generalizations about protein folding, we asked an open-ended, postlab question. This task was designed to evaluate students' ability to "explain" what they observed. We wanted to see if students would discuss the hydrophobic effect and the role of H-bonding, as was highlighted in the lab. The explain question was modified slightly and moved from a prompt during lab (F14) to the postlab (S15), as shown in Figure 4.

Student Outcomes

We determined the percentage of students who completed each part of the lab, whether or not it was correct. These results for F14 and the refined implementation in S15 are shown in Table 2. We found that students completed most of the prelab, during-lab, and postlab activities in both implementations. As indicated in Table 2 item 1, most students (approximately 90%) drew a picture for the prelab question shown in Figure 2. They also attempted to draw the amide H-bonding pattern in the prelab (item 4, question shown in Supporting Information). Over 90% of students completed most observations and assignments during lab. For example, they wrote observations and reflections when examining the hydrophobic patterning (item 5; see also Figure 3) and attempted to draw amide H-bonding (item 4). In the F14 implementation, many students did not attempt to answer the more challenging questions. For example, only 45% of students attempted the explain prompt, item 6, which asked students to explain protein folding in general terms (Figure 4). In S15 student focus was directed to this conceptual question by moving it to the postlab, with significantly higher percentage of students (88%, $Z = 6.8$, $p = 0$) completing the explain prompt.

Table 2. Percent of Students Who *Complete* a Particular Prelab, During-Lab, or Postlab Activity

		F14[c]		S15[d]	
Item	Content	Prelab, %	During Lab or Postlab, %	Prelab, %	During Lab or Postlab, %
1	Draw a picture of the model	88	88	92	96
2	Indicate what is "buried"	14	N/D[b]	68	N/D[b]
3	Improve model significantly	N/A[a]	17	N/A[a]	49
4	Draw two amide bonds H-bonding	90	98	90	100
5	Observe hydrophobic amino acids (part 2)	N/A[a]	92	N/A[a]	91
6	Describe protein folding in general terms	N/A[a]	45	N/A[a]	88

[a]Not applicable. [b]Not determined. [c]F14 ($n = 43$). [d]S15 ($n = 47$).

For a model to be considered improved, it must have scored higher in the postlab than on the prelab using the rubric given in Box 1. In alignment with the MORE framework, students were expected to use evidence from lab to improve their models. We reasoned that α-helix and dimer formation are structural features immediately apparent upon viewing the peptide in Chimera. In our view, this learning preceded the more nuanced analysis required to identify the burial of hydrophobic amino acids. Likewise, the ability to illustrate the burial of hydrophobic amino acids preceded a clear understanding of the hydrophobic effect. For this reason we chose to use the linear scoring method presented in Box 1.

Box 1. Measures to evaluate the improvement between pre- and postlab modeling question

0 = Model is not an α-helix and/or dimer.
1 = Model is an α-helix and dimer.
2 = Hydrophobic amino acids drawn/indicated between two helices in the model.
3 = Model correct and burial of hydrophobic amino acids linked to protein stability.

In F14, only 17% of students substantially improved their models (Table 2, item 3) from prelab to postlab. However, F14 student initial models were deficient, with only 14% of students making some indication of what was "buried" in the structure (item 2). In the S15 implementation 49% of students improved their model based on their observations in lab (item 3), which was significantly higher than what we observed for F14 ($Z = 3$, $p = 0.001$). Student pre- and postlab models in S15 included more detail, with 68% of students making some indication of what was buried in the prelab (item 2). Note that, for item 2, a description in words, without indication in the drawing, was considered completion. The response rate on item 2 was an indication that in the F14 implementation students were more likely to ignore the more challenging or detailed components of the question.

Student Understanding

We also examined student work to determine if they were able to better understand protein folding based on their experiences during lab. To measure improvement in pre- and postlab activities, we again used the measures indicated in Box 1. The measures for correctness during lab are given in Table 3. Since the F14 assignment did not specifically ask students to draw the location of the hydrophobic amino acids, a written description was considered sufficient. Importantly, this is a key feature of protein folding that we nevertheless expected students to draw in their postlab models.

We found that student performance improved in S15 with respect to our F14 implementation. Table 4 indicates the

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Table 3. Measures for Evaluating During-Lab Activities

Item	Content	During Lab
1	Indicate that hydrophobic amino acids "buried"	Written description is sufficient.
2	Link stability to burial of hydrophobic groups	Written description is sufficient, but must correctly indicate burial of hydrophobic amino acids.
3	Properly draw two amide bonds H-bonding	Student must draw correct Lewis structures and clearly indicate the H-bond.

percent of students who correctly performed specific tasks in the prelab, during lab, and postlab. For the F14 implementation, postlab responses were not significantly improved for any of the outcomes measured. Conversely, for the S15 implementation, postlab answers were significantly improved for items 1−3 ($p < 0.05$; Supporting Information Table S2). In S15, 40% of students drew an α-helix and dimer in the prelab, whereas 52% of the students drew an α-helix and dimer in the prelab for our F14 implementation. While student initial models in S15 were less likely to include clear representations of these basic structural features, the drawings included more details and explanation (Table 4) even though those details may have been incorrect. In S15, 67% of students created postlab models that clearly included an α-helix and dimer.

During lab, students in the F14 and S15 implementations were equally likely to correctly observe the placement of hydrophobic amino acids (73% of students), but S15 students were significantly more likely to incorporate their observations into their model in S15 ($Z = 4.0$, $p = 0$), with 56% of students incorporating this feature in their postlab models. Further, 50% of students in S15 clearly linked stability to the hydrophobic effect during lab, with 36% of students incorporating the hydrophobic effect into their postlab models.

While these results are quite encouraging, students persist in their struggle to properly draw two amides forming an H-bond (Table 4, item 4). Students also struggle to answer the postlab explain prompt in a way that relates to the learning they achieved during lab (Table 4, item 5). Students tend to classify GCN4, myoglobin, and hemoglobin as having secondary, tertiary, and quaternary structure and comment on function (for example stating that hemoglobin and myoglobin contain heme and bind oxygen). In the S15 implementation, only 12% of students correctly described the role of both H-bonding and the hydrophobic effect in their response.

Learning Objectives and Study of Student Misconceptions

In our refined S15 lab, the richness of student prelab models provided clues as to students misconceptions on protein folding, and we exclusively present student work from the refined S15 implementation. We describe the specific student misconceptions we observed, some of which were anticipated based on a literature review. We illustrate how student misconceptions were revealed in the prelab and how they were (or, in some cases, were not) corrected during the course of performing this laboratory exercise.

Learning Objective 1: Drawing Lewis Structures and H-Bonding Patterns for an Amide

In the prelab students were asked to draw two amides engaged in H-bonding. In part 1 of the lab, students were asked to identify an H-bond between two amides in a seven-residue α-helix. It has been demonstrated that students struggle to draw Lewis structures and hydrogen bonds,[1,26] which is consistent with our observations. While 56% of students drew the amide H-bonding properly during lab, many students persisted in incorrect notions of H-bonding and Lewis structures. For example student A (Figure 5) neglected to draw the carbonyl double bond during lab, perhaps since the program does not indicate double bonds. This student also did not clearly illustrate the distance between two amides. Student B appeared to be seeking a specific covalent bond, indicating how troublesome the term "H-bonding" can be for some students. In lab, the student drew amide bond formation, in spite of significant guidance provided by the lab handout and the availability of a TA. Student C had difficulty drawing the correct Lewis structure in the prelab, and during lab drew H-bonds directly between the N and O.

Learning Objective 2: α-Helical Structure and H-Bonding Pattern

In the prelab, students were asked to draw a model of the GCN4-p1 leucine zipper domain and were told it is an α-helix and dimer. In part 2, students were instructed to observe and draw the H-bonding pattern on an isolated α-helix (students were told it is a fragment of a crystal structure). Indeed, we found that what might appear to be a simple direction to draw an α-helix revealed many student misconceptions, often associated with mistaken understandings of the nature of the structures involved. For example, in the prelab, we observed student D (Figure 6) conflating protein α-helices with B-form DNA structure. Several other students, such as student E, drew an isolated α-helix. Indeed, it was clear that many students believed an α-helix is stable in aqueous solution due to H-bonding. While most students have some concept of backbone H-bonding, many struggled to draw it, or instead drew interactions between two helices (student F, Figure 6). Indeed, the difficulty of this task is supported by work by Harle and Towns, which illustrates that students struggle to properly draw H-bonding patterns in α-helices.[26] Observations by students D, E, and F for part 2 of the lab are provided in the Supporting Information (Figures S6−S8) and show some progression in learning.

Table 4. Percent of Students Who *Are Correct* in Particular Prelab, During-Lab, or Postlab Activity

		F14[c]			S15[d]		
Item	Content	Prelab, %	During Lab, %	Postlab, %	Prelab, %	During Lab, %	Postlab, %
1	Model is an α-helix and dimer	52	N/D[b]	59	40	N/D[b]	67
2	Indicate that hydrophobic amino acids "buried"	5	73	14	17	73	56
3	Link stability to burial of hydrophobic groups	2.4	24	5	12	50	36
4	Properly draw two amide bonds H-bonding	40	60	N/A[a]	48	56	N/A[a]
5	Describe protein folding in general terms	N/A[a]	7	N/A[a]	N/A[a]	N/A[a]	12

[a]Not applicable. [b]Not determined. [c]F14 ($n = 43$). [d]S15 ($n = 47$).

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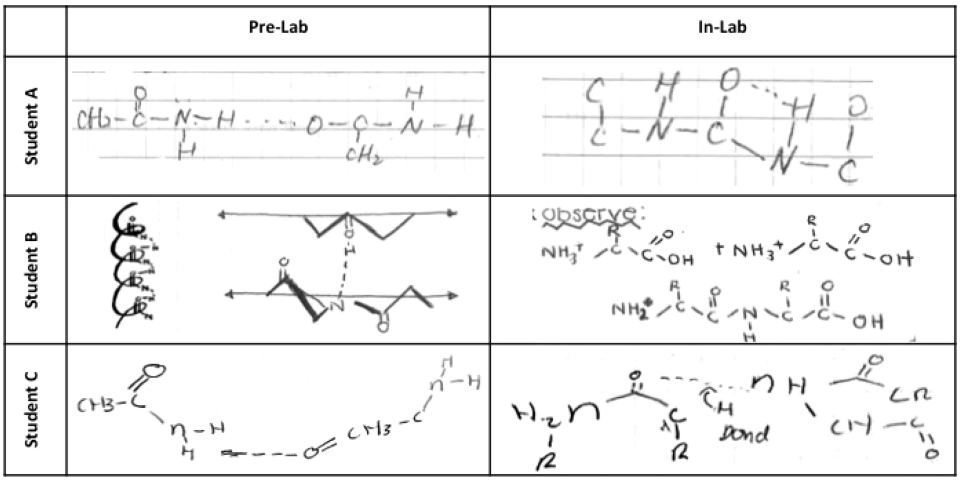

Figure 5. Examples of students' troublesome illustrations of hydrogen bonding. Student drawings reproduced with permission.

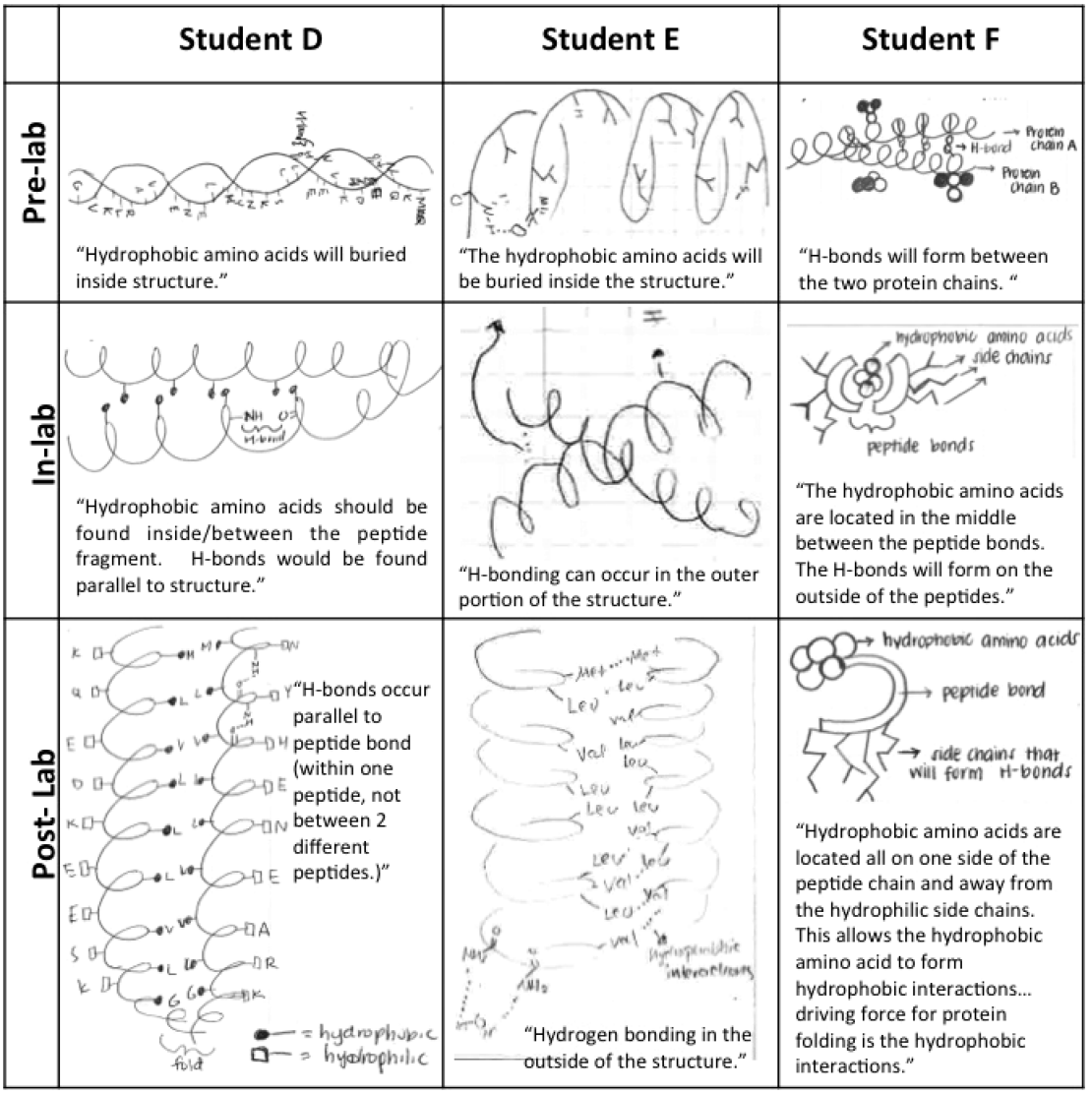

Figure 6. Examples of students' ability to correct common misconceptions during lab. Student drawings reproduced with permission.

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Learning Objective 3: Understanding Dimer Formation, Burial of Hydrophobic Amino Acids, and the Hydrophobic Effect

Building upon the activity in part 2, students observed a coiled coil dimer in part 3. Students rendered the hydrophobic amino acids as spheres to more clearly observe the placement of the hydrophobic amino acid side chains. These observations, in concert with reflective prompts and TA-led discussions, were intended to improve student understanding of the hydrophobic effect.

In the prelab, many students identified the driving force for protein folding as the result of hydrogen bonding between or within helices (for example, Figure S3). However, in lecture, students were taught that the most significant driving force for protein folding in aqueous solution is the burial of hydrophobic amino acids. Since many students did not have a clear conception of what is meant by an α-helix, dimer, or burial of hydrophobic residues, the concept of protein folding being driven by the burial of hydrophobic residues was likely not a meaningful statement. In addition to difficulty in drawing an α-helix and dimer in the prelab, many students incorrectly drew hydrophobic amino acids inside the α-helix backbone (students D and E, Figure 6). Similar misconceptions have been identified in the literature, where the ribbon diagram is partially to blame for students believing that the inside of the α-helix backbone is hollow, allowing for the inclusion of solvent molecules or amino acid side chains.[28]

The laboratory experience provided students with the opportunity, using their observations, to improve their understanding of protein folding. In particular, we demonstrated that students were able to correct their picture of protein folding using the example of a coiled coil dimer. For example, students D and E were able to clearly explain the hydrophobic effect during lab. On the other hand, the postlab did not always show this improvement. For example, nontraditional representations of an α-helix were provided, as exemplified by student F. The development of nontraditional models illustrates the authenticity of the exercise, in that students are presenting models that make sense to them, not models that are constructed by the professor or TA.

Learning Objective 4: Applying Understanding to Larger Protein Structure

After viewing a coiled coil dimer, students move to part 4, where they were first asked to predict if the hydrophobic amino acids will be on the inside or outside of myoglobin. Students then loaded the myoglobin structure and rendered the hydrophobic amino acids as blue spheres. Students were asked to determine if the hydrophobic amino acids are on the inside or outside of the folded protein structure. Interestingly, even at the beginning of the assignment, we found that 73% of students predicted that the hydrophobic amino acids would be on the inside, and retained their prediction upon seeing the structure. An additional 7% of students had incorrect or missing predictions but were able to observe that the hydrophobic amino acids were mainly on the interior portion of myoglobin. Importantly, many students commented on the difficulty of this task, suggesting that the coiled coil exercise trained students' eyes to better observe the more complicated myoglobin structure. For example, one student wrote:

"Predict: in a large protein structure the hydrophobic residues are expected to be on the inside, just as all other proteins. Observe: the placement of hydrophobic residues are mostly on the inside of the structure. Since the structure is very big and disorganized it is hard to tell if all the hydrophobic amino acids are inside but from what it seems like most of the amino acids are centered toward the center of the structure."

Exam Question

Student learning was further evaluated based on response to a related exam question (Box 2). The exam question was

Box 2. Exam Question

GCN4-p1 domain forms an α-helix in solution, which matches up with a second peptide to form a dimer (a coiled coil). Draw a picture of how you would expect the GCN4-p1 to fold. Indicate at least three relevant structural features. What is the driving-force for folding?

evaluated using the same criteria indicated in Box 1 but additionally scored for the inclusion of H-bonding along the α-helix (Supporting Information Table S7). Again, our scoring criteria required students to draw an α-helix and dimer using the traditional representation. Scores may have been much higher using less stringent criteria, as many students made their own representations of an α-helix. (Supporting Information Figure S1). In both implementations, 90% of students answered the question shown in Box 2. As shown in Table 5, we again observed significant gains with students properly drawing important structural features such as the location of hydrophobic amino acids and H-bonding along the helix (see Supporting Information Tables S1 and S2 for the statistical analysis). These results once again demonstrate how learning gains can be achieved with appropriate revision to existing learning materials.

Table 5. Percent of students who are correct in particular exam response

Content	F14, %[a]	S15, %[b]
α-helix and dimer	52	61
Hydrophobic residues drawn "inside"	27	51
Stability linked to hydrophobic effect	19	24
Includes H-bonding along helix	13	50

[a]F14 (n = 43). [b]S15 (n = 47).

DISCUSSION

These results speak to our research questions in several ways. Research question 1 focused on the ways in which systematic revision affected and improved the pedagogical approach. We have shown (especially in Tables 2 and 4) significantly better results for the students after changes that included additional prompts to help them make sense of complicated, authentic computer images. In addition, student initial engagement with the assignment was assisted by the addition of prelab videos that allowed them to begin productive work with the computer models much more quickly and effectively. Much of the scaffolding added to the S15 implementation served to clarify *how* to approach learning and not *what* to learn. For example, we asked students to draw and compare models during lab. The revised prelab modeling question, asking students to draw the location of H-bonds and hydrophobic amino acids, served to clarify expectations, as well as provide structural clues to the students. In our view, students in the F14 implementation put

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minimal effort into making and revising models. In S15, the prompt requested specific details and therefore required more effort, leading to better understanding. In contrast to other reports,[29] we found that students spent more time on their models in the revised implementation, leading to learning gains. In this respect, our results are expected, since spending more time on a concept will likely result in higher gains.

The evaluation of student completion of the assignment (research question 2), particularly with respect to producing complete final models, was also examined. A rubric was implemented to evaluate this, and it provided evidence that, especially with improved scaffolding in the form of new prompts, student completion was higher in Spring, 2015. We chose to focus on H-bonding and the hydrophobic effect, as these concepts are readily found in their chemistry course and students have an appropriate base from which to apply their understanding. Students responded well to this activity, with the majority of students making and revising models to illustrate an understanding of protein folding. We note, though, that very few students clearly expressed these ideas in their response to the postlab question shown in Figure 4. Instead, many students provided a surface description of primary, secondary, and tertiary structure, or referred to either H-bonding or the hydrophobic effect, but not both. As we continue to incorporate MORE throughout the course in a systematic way, students' ability to answer such general questions may improve.

In an assignment such as this, evaluating learning (research questions 3 and 4) is done primarily by examining student responses within their lab reports and by considering work on a related exam question. Throughout, we found that particular misconceptions about the nature of bonding—especially with respect to amides—were persistent. However, especially with directed observations, students' ability to notice the location and the meaning of hydrophobic residues in intra- and interstrand interactions was often improved. Similarly, we demonstrated that students learned important features of protein folding such as α-helix structure, that amino acids are oriented on the outside of the helix, and the role of the hydrophobic effect. For 100-level students, as with all students, it is critical to build learning based upon a student's current understanding and experiences.[24]

Despite our successes, students struggled to properly draw H-bonding patterns in Lewis structures, with only 56% of students generating fully correct drawings in lab. The challenges associated with drawing correct Lewis structures and H-bonding has recently been explored in a series of studies by Cooper and co-workers, and their work included examination of a proposed learning progression.[11] While our results cannot be directly compared, students who were taught using Cooper's learning progression averaged 54−57% correct on questions relating to Lewis structures after one semester.[11] This similarity in student success after an intervention does suggest that our efforts are in line with reforms made by others. Further, in our study, we observed that most students drew two amides to illustrate H-bonding patterns, even in the prelab (data not shown). In contrast, a report shows that only 15% of Organic Chemistry students use two molecules to illustrate H-bonding interactions in an un-reformed course.[1] While again we cannot directly compare studies, our results may reflect learning that occurred earlier in the semester in other MORE laboratories that were focused on these concepts.

CONCLUSIONS AND IMPLICATIONS

The Computer Modeling of Proteins lab reported here provides a unique method for teaching intra-/intermolecular interactions and protein structure. This lab has been and can be directly implemented in the Chemistry curriculum in 100- and 400-level courses. Student outcomes demonstrate that learning takes place during lab, and that students can apply this learning to similar exam problems. Further, we have outlined a number of key features that improved the lab experience for our students, which may aid others in their own lab reforms.

Our report is consistent with many reports demonstrating the importance of having students draw models, provide written explanations, and use evidence to support conclusions.[9,24,26,29] Our TAs report that the modeling laboratories require about as much time to grade as the traditional laboratories. The detailed grading rubric improves consistency and ease of TA grading and feedback. Indeed, high-enrollment courses often have small laboratory sections, presenting an opportunity to draw and revise models, even for courses where all exams are multiple choice. Further, in a single glance the grader can determine if the model is a dimer, α-helix, shows the location of hydrophobic residues, and properly indicates H-bonding in the backbone. The grader is then only required to read a few lines of text related to the implications of the student model. Hence, modeling questions can be graded quickly in lab reports and also on exams and provides insight into student thinking.

This report is in line with other efforts to improve student conceptual understanding of chemistry.[9,24,26,29] Improved student competency with molecular level representations is necessary to help students connect macroscopic observations to the molecular level.[16] Further, laboratory time is an excellent opportunity for active learning, building models, and giving feedback.

The laboratory exercise can be further tuned to the needs of the course by adding or removing activities. For example, it is well-known that students often believe that ions can pass through the center of an α-helix, and this is a stumbling block for understanding ion channel structure and function.[16,26] For a course in which ion channels are taught, an exercise can be added in which students render the seven-residue segment in a space-filling model. With this exercise, students see that the helix is not hollow, and rather the atoms of the backbone occupy the space in the center of the helix. We have incorporated this activity in prior implementations (data not shown), but since students did not learn about ion channels in this course, the exercise did not connect to what they were learning and was extraneous.

For future implementations, we will further modify the lab to prompt students to compare drawings during this H-bonding exercise and to check that their drawings contain proper Lewis structures. We will also modify the TA notes so that TAs guide students more closely through the initial steps in the lab. We conjecture that students' cognitive loads may be overwhelmed at the beginning of the lab, when students are just learning how to use the computer program, interpreting structures, and learning our expectations for this lab. This may contribute to their weak performance on the task of drawing H-bonds. Further, despite the fact that TAs received training with Chimera, their lack of familiarity with the program may make it more difficult to manage the lab, especially for part 1 where students are examining H-bonding. To better facilitate training and ease adoption at other institutions, we have prepared a video for

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instructors and TAs. This improved training may also improve student performance on the H-bonding activity. Importantly, these changes are a reflection of our ongoing effort to improve laboratories, evaluate their effectiveness, and identify best practices.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00910. The prelab and TA training videos and PDB files are available from the corresponding author upon request.

Revised laboratory experiment, TA notes, the coding scheme for laboratory reports, and exam question, complete responses to prompts for students shown in Figures 2−4, and complete exam questions (PDF)

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Notes

The authors declare no competing financial interest.

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