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Lesson

Electron Location, Location, Location: Understanding Biological Interactions

Amanda (Mandy) E. Schivell

Department of Biology, University of Washington

Abstract

Introductory Biology courses typically introduce the structure and function of biomolecules such as proteins and nucleic acids. To understand biomolecules fully, students require knowledge of fundamental chemistry concepts such as covalent bonding, intermolecular interactions and hydrophilicity/hydrophobicity (1). Students enter our large (>400 student) course with a notoriously limited conceptual grasp of basic chemistry principles. Our lesson is an activity designed on the principles of POGIL (Process Oriented Guided Inquiry Learning). In 50 minutes, students build their own definitions of the following: polar vs. non-polar covalent bonds, hydrophilicity/hydrophobicity and the nature of hydrogen bonding based simply on the relative electronegativities of oxygen, nitrogen, carbon and hydrogen. We find that this exercise improves students' understanding of these chemical concepts. Since adopting this activity, students have been better able to understand biomolecular structures and predict interactions between molecules.

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Supporting Materials: Supporting Files S1. Understanding Biological Interactions – Activity Student Version; S2. Understanding Biological Interactions – Activity Instructor Version; S3. Understanding Biological Interactions – Reading Quiz Questions; S4. Understanding Biological Interactions – Polling Questions; S5. Understanding Biological Interactions – Answers to Polling Questions; S6. Understanding Biological Interactions – Suggested Lecture Notes; S7. Understanding Biological Interactions – Use of Concepts; S8. Understanding Biological Interactions – Practice Problems and Summative Assessment Examples; and S9. Understanding Biological Interactions – Answers to Practice Problems and Summative Assessment Examples.

Correspondence to: Box 351800, University of Washington, Seattle, WA 98195. Email: schivell@uw.edu

Learning Goals

- What factors contribute to the size and complexity of biological macromolecules?
- What is the role of noncovalent intermolecular interactions?
- How is structure (and hence function) of macromolecules governed by foundational principles of chemistry and physics?

The learning goals listed above are from the Biochemistry and Molecular Biology learning framework foundational concept: Macromolecular structure determines function and regulation.

Learning Objectives

- Students will understand how differences in electronegativity between covalently bonded atoms in a molecule relates to the ability of that molecule to interact with others.
- Students will be able to distinguish between polar and non-polar covalent bonds within the context of biological molecules
- Students will learn the difference between hydrophobic and hydrophilic interactions.
- Students will be able to predict whether a biomolecule is largely hydrophobic or hydrophilic based on its molecular structure.
- Students will create their own definition of "hydrogen bond" in the context of small biological molecules.
- Students will be able to predict whether a hydrogen bond can occur between two molecules.

INTRODUCTION

One of the most important fundamental concepts of biology is understanding how biological molecules interact with each other (1,2). This relies on chemistry, in particular the three most important intermolecular attractions between biomolecules: hydrogen bonds, ionic bonds and hydrophobic interactions. In turn, these three interactions are based on the relative electronegativities and electrostatic charges of the atoms involved. In my and my colleagues' experience teaching thousands of Introductory Biology undergraduates for over 20 years, students struggle to learn these concepts despite the chemistry prerequisite for our course.

Understanding intermolecular attractions, and in particular hydrogen bonding, is crucial to predict which biomolecules are soluble in water or how different proteins might bind to each other, to ligands, or to substrates. Students struggle with the concept of electrostatic interactions, often confusing covalent bonds within a molecule with hydrogen or ionic bonds between parts of a large molecule or between different molecules. Students believe that ionic bonds are stronger than covalent bonds in cells (forgetting the fact that table salt dissolves in water) or that hydrogen in a fatty acid chain can form a hydrogen bond with a nitrogen or oxygen in another molecule.

To investigate this issue, I and my colleagues spoke with Chemistry instructors as well as our students to find the disconnect. The main issue stems from the fact that chemistry courses must focus on the properties of *all* elements, in *all* environments. However, biology is a tiny, very specialized chemical situation, where we focus primarily on a *few* elements (carbon, nitrogen, oxygen and hydrogen) that make up molecules functioning in *aqueous* environments. We wrote this activity to help students build their understanding of the nature of biological molecules from the "ground up." Students need only start with the relative electronegativities of the four key elements to build their own definitions of solubility in water, hydrophobicity/hydrophilicity, polarity and hydrogen bonding.

Other educators have recognized students' need to have a strong understanding of chemical concepts. Sauterer (2011) describes using electronegativity as a framework in lecture to help students understand "chemical bonding, polarity and hydrogen bonding" (1). Werth (2017) has created a lesson for first day Biochemistry courses that requires them to use their knowledge of non-covalent interactions to predict the structure of a serotonin binding pocket (2). Hydrogen bonding, in particular, can be illustrated by demonstrations that require simple household items (3) and has been brilliantly modeled by using Styrofoam balls and Velcro (4). While these last two examples provide excellent ways to demonstrate hydrogen bonding's properties and effects on a larger scale, they do not consider the source of the electrostatic attractions that underlie hydrogen bonding.

Our lesson provides a student-centered, active learning activity that uses electronegativity as a basis for understanding why covalent bonds are polar or non-polar and how that relates to molecular interactions. Our lesson is targeted at Introductory Biology students who are just beginning to explore the structures of biological molecules. Although similar in principle to Sauterer, our lesson is based in active learning. In addition, our lesson could act as "refresher" exercise prior to the more advanced Werth activity in an upper division course.

Our lesson helps build three important concepts: 1) the difference between polar and non-polar covalent bonds; 2) the definitions of hydrophilicity and hydrophobicity; and 3) the nature of hydrogen bonds in biological contexts. Students can then apply these concepts to protein structure (i.e., using the properties of an R-group to determine what interactions it can form), DNA structure (hydrogen bonding between nitrogenous bases), and membrane transport (the hydrophobic barrier created by phospholipids). We use this lesson at the beginning of the course so that we can refer back to this foundational knowledge.

We find that this activity helps reduce students' feelings of overwhelm when faced with the size and complexity of biological macromolecules. For example, when discussing protein structure two days after this lesson, students are asked to predict where hydrogen bonds form based on the atoms and bonds in the backbone of an alpha helix. Later in the course we ask students to predict changes in substrate-enzyme binding based on the atomic structures of R-groups that are mutated in the active site (for examples of both of these, see Supporting File S7. Understanding Biological Interactions – Use of Concepts). Students can always return to the fundamentals learned in this activity to help them with higher-order concepts.

We designed the lesson based on the principles I learned at a workshop for the POGIL initiative. The activity contains a series of simple diagrams that have a small amount of information (referred to as "Models") and we ask students to work in groups to answer highly structured questions that require careful observation of the model. As they answer questions, groups practice problem solving, generate definitions and then apply knowledge to new scenarios. Meta-analyses of active learning in general (5) and POGIL specifically (6) have been shown to significantly reduce failure rates in college courses. More recently, group work on activities in classes has been shown to result in significant learning gains compared to traditional lecture (7). These findings have encouraged us to continue to improve our activity to maximize student learning.

Intended Audience

This lesson is intended for Introductory Biology students at any institution with any class size. We and our peers at nearby institutions have used this lesson in large-lecture classroom environments (>400 students) as well as in small classrooms (~12 students). The vast majority of students have been intended STEM majors.

Required Learning Time

One 50-minute class period.

Prerequisite Student Knowledge

Students will need to know the following: simple atomic structure, valence electrons, and the nature of a covalent bond. It will help if they have some familiarity with common biological atoms - carbon, nitrogen, oxygen and hydrogen. Most of this information is available in early chapters of Introductory Biology textbooks, or in first-year Chemistry textbooks. OpenStax is a free textbook with a lesson that is sufficient for this. Our students have one quarter of Introductory Chemistry as a prerequisite for this course. We teach this on the first content day of the quarter (typically the second day of the course).

Prerequisite Teacher Knowledge

Teachers need to have a basic knowledge of chemistry similar to what is recommended for students. Most of what you need is in the "chemistry" portion of Introductory Biology textbooks.

SCIENTIFIC TEACHING THEMES

Active Learning

- The activity was designed based on the principles of POGIL. Students build conceptual knowledge by working through crafted questions that refer to a Model which contains all the information they need to build the concepts, practice skills and apply their new knowledge.
- Students are encouraged to work in pairs. We print half as many activities as there are students so that they must work together in the classroom. We also post the document electronically for those who require or prefer that format. In our large classrooms we also see groups of three form, however we encourage them to find new partners and work in pairs. This is because we more often observe one student dominating the work when there are three students. This may be due to the linear seating arrangement in our large lecture halls.
- Polling questions engage the students to think further and provide valuable feedback to instructors on how to further discuss material.

Assessment

- Staff circulate through the lecture hall answering student questions throughout the activity for real-time assessment of student success and progress. We use this to fine-tune the timing of polling questions and to gauge whether additional information needs to be provided to the class as a whole.
- We ask polling questions after students complete each Model (Supporting File S4. Understanding Biological Interactions – Polling Questions). For each polling question, students think on their own first and poll in individually, then they discuss their choices with peers and poll in again. We use Poll Everywhere, but other options work as well. Finally, we use random call to select a student to share their group's discussion.
- Students are given chances to practice and self-assess their knowledge of the concepts from this lesson in ungraded practice problems (with keys) that we publish for the students online. For examples, see Supporting File S8. Understanding Biological Interactions – Practice Problems and Summative Assessment Examples.
- Summative assessments include exam questions that rely on the concepts from this activity, but typically in a broader context such as protein structure or enzyme/substrate interactions. For examples, see Supporting File S8. Understanding Biological Interactions – Practice Problems and Summative Assessment Examples.

Inclusive Teaching

- In large classrooms we use random call to help increase inclusivity and belonging. On the first day of the course we discuss why we use this strategy, explicitly referencing the Eddy, Brownell and Wenderoth (8) finding that males volunteer answers more often than females.
- In order to make random call less threatening, we use a highly structured process following many of the principles outlined by Waugh and Andrews (9). Students work on the question once on their own, then with a group so they have had time to think and discuss the question. We use inclusive language by asking about the process, not for the answer: "Student X, what was your group discussing?" or "What were your group's thoughts?" We frame random call on the first day of the course as being the *start of a discussion*, not an assessment of a particular student. Students with extreme anxiety are able to opt-out of the random call list and we do not assign any credit for answering or not answering the call.
- In order to accurately refer to students we have a pre-course survey in which we obtain each student's preferred name and pronoun.
- To support issues of identity and belonging in the classroom, we frequently use short, unscripted statements to reinforce all students' rightful presence in the course and each students' intrinsic value. We openly acknowledge that students frequently feel "imposter" syndrome and encourage them to seek study groups or help from staff.
- On the first day of class, we have shared our own academic stories of "feeling like a failure" to normalize the fact that we all struggle and can still succeed.
- We use positive language to frame student responses and encourage continued discussion.
- Our institution has a service contract with Poll Everywhere so all students have free access to polling software. If an institution does not have this access, an equitable option could be to simply ask students to raise their hands or hand out index cards with letters or that are different colors so that students can raise the card that indicates their selection. One drawback to this method is that it can stigmatize students who have the incorrect selection, so students may lose a sense of belonging.

LESSON PLAN

This lesson is taught in a 50-minute session in a course that typically has more than 400 students. Students work in pairs with one activity worksheet per pair. We emphasize process - students do not have to know anything except what is provided for them in the activity to answer the questions, as long as they have done the relevant preparation. As they work through the models, conceptual understandings are grown, clarified and challenged to achieve high-level, long-term scientific understanding.

Instructor preparation for class:

- Have enough copies of the activity (Supporting File S1. Understanding Biological Interactions – Activity Student Version) for one activity worksheet per pair of students. We also upload the activity online (as a .pdf) for students who prefer to use their digital devices for writing answers or who require a digital format for access.
- Make sure all staff/TAs have worked through the activity themselves and have had their questions answered based on the instructor key (Supporting File S2. Understanding Biological Interactions – Activity Instructor Version). Supporting File S2 also includes common areas of student confusion or misconceptions and how we typically address them.
- Prepare staff to circulate through the classroom to answer questions and report common misconceptions and class progress back to the lead instructor.

Student preparation for class:

- Complete the assigned textbook reading on biological atoms (familiarity with O, N, C and H) and covalent bonds. For an example, see Chapter 2 of Freeman's Biological Science, 7e (11).
- Take the "Reading Quiz" (done online) that consists of 6 questions all answerable using the textbook reading. (Supporting File S3. Understanding Biological Interactions – Reading Quiz Questions)
- Bring to class a polling device and a writing utensil.

The activity is designed to help students with three main concepts. Here is the logic behind each model and the questions for each (Supporting File S1. Understanding Biological Interactions – Activity Student Version).

Model 1: Polar vs Non-polar Bonds

Model 1 shows four simple molecules, some of which have polar covalent bonds, some of which have non-polar covalent bonds. They are drawn with "long" lines to represent the bonds so that it is easy for students to draw in electrons and also the partial charges on the atoms in each molecule. Students use the relative electronegativities of the atoms (shown in the activity) to draw the likely position of the electrons in each covalent bond (Q1) and label each atom that has a partial charge (Q2). Students then label all polar bonds in the diagram (Q3) and generate their own definition of a "polar covalent bond" based on what they have done (Q4). Model 1 teaches students to look at atoms in individual bonds and predict polarity (which they have defined on their own).

After most students complete Model 1 (as judged by staff circulating throughout the room), we ask Polling Question 1 in which students predict whether bonds are polar or non-polar in a novel molecule. See Supporting File S4. Understanding Biological Interactions – Polling Questions and Supporting File S5. Understanding Biological Interactions – Answers to Polling Questions. The latter contains suggestions for follow up questions if students have misconceptions.

Model 2: Life Takes Place in Water

Model 2 shows two mixtures - one of methanol and water, the other of ethane and water. The diagrams are space-filling models to get students used to seeing different depictions of molecules. Students use their definition from Model 1 to predict which of the molecules have polar covalent bonds (Q5), non-polar covalent bonds (Q6), and identify molecules that are hydrophobic (Q7) and hydrophilic (Q8). Students write a description of the relationship between polarity and hydrophobicity (Q9). Question 10 shows four biological molecules (a carbohydrate, an amino acid, a nucleotide and a fatty acid), which the students identify as primarily hydrophobic or hydrophilic.

After most students complete Model 2, we ask Polling Question 2 where students choose which molecule is most hydrophobic.

Model 3: Molecular Interactions

Model 3 shows two small molecules with a labeled hydrogen bond between them. Students draw in the position of electrons based on electronegativity (Q11) and the partial charges of the atoms involved in the hydrogen bond (Q12). Students explain why a weak attraction occurs between the partially charged hydrogen and oxygen of the hydrogen bond in their own words (Q13). Using this definition, they predict a different hydrogen bond that can occur between the molecules in Model 3 (Q14), hydrogen bonds that could be present in Model 2 (Q15), and hydrogen bonds that can form between molecules that they have to draw (Q16). Question 17 shows an alpha helix, DNA base pairing and cellulose strands and students draw in possible hydrogen bonds that hold the molecules together. As students complete the activity, we ask Polling Question 3 that asks students to identify which pair of molecules can interact with a hydrogen bond.

Note that in this section we have not addressed the aspect of hydrogen bonding that requires there to be a lone pair of electrons in the accepting atom. We have done this for two reasons: First, both nitrogen and oxygen have at least one lone pair and they are almost exclusively the hydrogen bond acceptors in biology. Second, we would like to keep the lesson as simple as possible to reduce student anxiety about their chemistry background. In addition, our lesson is consistent with several introductory textbooks that define hydrogen bonding as an attraction between partially charged atoms (10-13).

On Your Own (not necessarily done during the class period)

Question 18 asks for students to consider how hydrogen bonds, which are relatively weak, can be so important for the overall structure of biomolecules.

After class:

- Post answer key to website.
- Answer questions on our student discussion board.

The next class lesson begins with a polling question where students predict the "solubility" of molecules in water using the principles learned in this lesson. We use the idea of solubility as a launching point for the discussion of water as the key biological solvent.

The recommended teaching timeline for the activity is described in Table 1.

TEACHING DISCUSSION

This lesson was first used in 2011 as a way to help introductory students strengthen their understanding of chemistry. In the decade prior, we barely covered the chemical concepts of polar vs non-polar bonds, hydrophobicity/hydrophilicity or hydrogen bonding. We would dive right into the structure and function of carbohydrates, proteins, etc., assuming that the students had a solid foundation from their chemistry course prerequisite. However, over the years it became clear that student understanding was at best "rote" and at worst completely forgotten or misunderstood.

For the past decade, we have taught this lesson on the first day of full instruction, and have observed the following:

1. An overall improvement in the ability of students to predict the behavior of molecules. For example, whether a molecule will be soluble in water, whether a molecule will cross a lipid bilayer, or how an R-group in a protein will interact with other molecules.
2. Better understanding by students that they can predict these things not by memorization, but by analyzing structures of molecules and applying the knowledge from this lesson.
3. We can easily refer students who remain confused about these topics back to the lesson for review, or work with them on it in office hours.

By having this lesson be the first one of the course, and explicitly discussing how it underpins all of the biochemistry they will learn, it becomes the foundation of the class to which we refer back frequently. Interestingly, our graduate student TAs have also appreciated the lesson because it serves as a useful refresher on basic chemistry principles, improving their understanding and subsequently their teaching. This extremely active first day lesson also helps to set a positive tone for activity and engagement for the rest of the course.

In evaluations and discussions with the thousands of students in our course we hear mixed opinions about the POGIL activity approach (we have 8-10 such lessons during the course). Many students ask us to have a second lecture period where we "teach" the same concepts to them after they have completed the lesson. This is in line with wider research findings about student frustrations with active learning in the midst of improved learning (14, 15). Although we consistently message that they are building the concepts *during their work* on the activity, many students feel like they are not sufficiently "taught" unless there is a professor stating facts in front of the class. On the other hand, some students find that the group activities are the best part of our course and want us to design more. In office hours over the decade since we started these lessons, students joke with me that "the answer is always hydrogen bonding!" or "you always ask me to look at the bonds!", even during the last week of the course. Overall, we find that we can ask more in-depth biochemical questions on assessments and students seem to ask fewer low-level definitional questions about chemistry and interactions. For examples of the differences in the types of assessment questions we have used before adopting this activity and after adopting this activity, see Supporting File S8. Understanding Biological Interactions – Practice Problems and Summative Assessment Examples.

Fitting This Lesson into the Course

This lesson is useful for instructors that want students to be able to predict the behavior of biomolecules by using images of structures, not their names. For example, instead of asking students to memorize names or structures of amino acids, we show amino acid structures on assessments and ask them to predict behaviors. We routinely refer back to hydrogen bonding and hydrophobicity in future lectures and lab exercises in order to have students explain the behavior of interacting molecules. (See Supporting File S7. Understanding Biological Interactions – Use of Concepts).

Some topics in which we utilize concepts from this lesson:

- Biomolecular structure of the four main macromolecules
- Enzyme function
- Cellular respiration (energetics of non-polar vs. polar bonds)
- Molecular interactions during transcription and translation, gene expression, signaling, etc.
- Phospholipid and membrane structure and permeability

Possible Extensions/Modifications

Although we use this lesson in a large lecture course (>400 students), colleagues of ours have used it in courses as small as 12 students with reported success. The most important aspects of the lesson are: students working together, having easy access to staff for questions and the intermittent polling questions to reveal and comment on misconceptions.

This year we have moved our course online due to the COVID-19 pandemic. We still use this lesson in an online format (Zoom) with the following modifications:

- Classes that include this activity are *optionally* synchronous. We usually have about one-third of students attend synchronously. We record the activity to ensure that students who have difficulty accessing our class at a specific time can do the work.
- Because most students participate in the lesson asynchronously, we are unable to ensure students work in pairs. Instead, we encourage students to find study partners and watch the recordings together. If students do not know anyone, we put them into study groups based on self-reported availability.
- The activity is available online for students to download before lecture.
- During the recording, we give explicit instructions for when to pause and work on specific models/questions together before starting the recording for polling questions.
- Using our historical knowledge of student misconceptions and common answers, we discuss the logic of the answers to each polling question (if they are not offered by the students present synchronously).

SUPPORTING MATERIALS

- S1. Understanding Biological Interactions – Activity Student Version
- S2. Understanding Biological Interactions – Activity Instructor Version
- S3. Understanding Biological Interactions – Reading Quiz Questions. Given as a pre-class quiz online
- S4. Understanding Biological Interactions – Polling Questions. Used during the activity
- S5. Understanding Biological Interactions – Answers to Polling Questions
- S6. Understanding Biological Interactions – Suggested Lecture Notes
- S7. Understanding Biological Interactions – Use of Concepts
- S8. Understanding Biological Interactions – Practice Problems and Summative Assessment Examples
- S9. Understanding Biological Interactions – Answers to Practice Problems and Summative Assessment Examples

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Table 1. Recommended teaching timeline.

Activity	Description	Estimated Time	Notes
Preparation for Class			
Prepare activities to hand out in class	Photocopy activity so that there are enough for 1 per pair of students in the course.	1-3 hours	Student version of the activity is provided in Supporting File S1. Understanding Biological Interactions – Activity Student Version
Class Session			
Introduction to Activity	Explain to the students that they will be generating useful knowledge by carefully working on this activity. They will NOT need to look anything up and should not have any books or websites open. Hand out activity during discussion - 1 per pair of students	~3 minutes	Suggested Lecture Slides with notes are in Supporting File S6. Understanding Biological Interactions – Suggested Lecture Notes
Introduction of drawing electrons	Draw example of the two electrons in a bond sitting (on average) closer to the more electronegative atom if there is a difference.	~2 minutes	Suggested Lecture Slides with notes are in Supporting File S6. Understanding Biological Interactions – Suggested Lecture Notes
Student work on Model 1	Staff circulate to answer questions, students are encouraged to share their answers with other groups if they finish early. They can also move on to the next Model if they finish early.	~10 minutes	
Polling Question Round 1	First polling question: First, students think on their own and poll in Second, students discuss with their partner and poll in Third, we use random call to have group report out their thoughts	~10 minutes	Polling question 1 in Supporting File S4. Understanding Biological Interactions – Polling Questions. (Answers to polling questions in Supporting File S5. Understanding Biological Interactions – Answers to Polling Questions)
Student work on Model 2	Staff circulates to answer questions, students are encouraged to share their answers with other groups if they finish early. They can also move on to the next Model.	~7 minutes	
Polling Question Round 2	One polling question	~5 minutes	Polling question 2 in Supporting File S4. Understanding Biological Interactions – Polling Questions.
Student work on Model 3	Staff circulates to answer questions, students are encouraged to share their answers with other groups if they finish early. They can also move on to the next Model.	~5 minutes	
Polling Question Round 3	One polling question (and optional open-ended question if time allows)	~7 minutes	Polling question 3 and optional discussion question in Supporting File S4. Understanding Biological Interactions – Polling Questions.
Wrap Up	Ask if there are any last questions from the students	Any time left	