Overview
Students explore protein molecules’ physical and chemical characteristics and learn that these unique characteristics enable other molecules to recognize them. They explore the stability of a molecular complex (a stable association between two or more molecules) by experimenting with how complementary shapes can lead to attractions between molecules. They identify the properties of amino acids that cause the shapes and charges on protein surfaces. They predict which molecules will be able to form a complex through molecular recognition. Finally, students explore a real receptor protein and a small molecule that recognizes and activates it.

Learning Objectives
Students will be able to:
• Identify the amino acids on the surface of a protein as responsible for the characteristics of the surface.
• Predict the relative strengths of molecular interactions based on the degree of charge and surface complementarity (“good fit”).
• Predict the characteristics of a ligand (“partner molecule”) based on its binding site.
• Make a connection between the surface characteristics of a protein and the protein’s function.

Possible Student Pre/Misconceptions
• Molecules are collections of atoms and bonds that do not have surfaces (like ball and stick models).
• Proteins are uniform “blobs” without distinguishing characteristics.
• Strong bonds hold a molecular complex together.

Models to Highlight and Possible Discussion Questions
Page 1 – “Life-size” Molecules
Model: Small Molecules vs. Large Molecules
• Highlight the greater surface area of large molecules, allowing more possibilities for interactions with other molecules.
• Zoom in to the “landscape” of a large protein to explore the variety of shapes. To focus on particular peaks and valleys, you can translate (move in x or y dimension) the structure by holding down the shift key and double-clicking on the structure (hold down the second click), then dragging.
• Note the very distinct shapes of large molecules.
Possible Discussion Questions:
• How does temperature affect molecules? What particular effect might temperature have on proteins?
• Why is it important that biological molecules have a variety of sizes, shapes, and surfaces?

Page 2 – A Good Fit
Model: Making Protein Complexes
• Review intermolecular attractions (van der Waals forces) and note that they only work at very small distances.
• Point out how the small molecules often fit better after a short initial run of the model. This is because molecules are somewhat flexible and can adjust to each other’s shapes, allowing for a closer fit.

Possible Discussion Questions:
• What is the difference between a molecule and a molecular complex? What are examples of each? What is the advantage of a molecular complex in a biological system? (It is temporary, made and unmade quickly in response to varying conditions.)

Page 3 – Molecular Surface Charge
Model: Surface Charge on Small Molecules
• Encourage students to view the different substitutions with the molecular surface turned on to opaque, to emphasize that each has a different surface, both shape and charge. Review how differing electronegativities create charge separation.
• Emphasize the difference between “charged” (a full + or – due to gain or loss of a proton) and “polar” (a separation of + and -) amino acids side chains.

Page 4 – Protein Surface Charge
Model: Surface Charge on a Protein
• Point out that the complexity of the surface coupled with the pattern of charge across the surface gives the molecule a unique character.
• Remind students that intermolecular attractions also occur when uncharged regions approach each other very closely.
• If you use the term “R group” with your students, make sure they know that “side chain” is an alternative term, useful when the amino acid is part of a protein (i.e., main polypeptide chain vs. side chain).
Possible Discussion Questions:
• How might a mutation that changes the identity of an amino acid affect the function of a protein? Is it possible for such a mutation to have no effect?

Page 5 – Protein “Landscapes”
Model: Receptor Protein
• Highlight the complementary shape and charge of the binding site and ligand (“partner molecule”).
• Use the three different ligands shown to explain that molecules constantly bump into each other, and that the attractive forces are only strong enough to keep them together when shape and charges are complementary.

Possible Discussion Questions:
• How is molecular recognition important to function?
• What are the potential consequences of the loss of function or the reduced function of a protein?
• Is it possible for a surface to be “too charged” or “too uncharged?”

Page 6 – Response to Adrenaline
Model: Adrenaline Receptor
• Explain that the adrenaline receptor is located in the cell’s plasma membrane, where it can encounter adrenaline that has been released into the bloodstream as a signal of danger.
• Show the membrane view, and explain that only a small “plug” or section of the cell membrane surrounding the structure is shown.

Possible Discussion Questions:
• Drugs are often molecular mimics. The slightly different shape and charge of a drug can cause a different response than the biological partner molecule. For example, the drug may not allow a signal to be passed along into the cell. What effects on behavior might a drug that mimics adrenaline have?
This activity is supported by many activities that deal with the attractions between atoms and molecules. **Atomic Structure** is fundamental to understanding the structure of atoms, including protons and electrons, which are essential for bonding. **Electrostatics** focuses on the attraction of positive and negative charges. The **Intermolecular Attractions** activity highlights the forces of attraction that are at work in helping a molecule “feel” the charges of a partner molecule. **Chemical Bonds** allows students to make connections between the polar and non-polar nature of bonds and how one part of a molecule could be partially positive or negative due to the uneven sharing of electrons. **Molecular Geometry** explains the specific orientation of atoms within larger molecules.

This activity supports three other SAM activities. First, **Four Levels of Protein Structure** builds on student understanding of why structure is so important in protein function. This activity also supports **Diffusion, Osmosis, and Active Transport** and **Cellular Respiration** because there are references in both of these activities to larger scale protein complexes.
Activity Answer Guide

Page 1:

1. Check all of the structural shapes that BOTH macromolecules and small molecules can have.
   (a)(b)(c)(d)

2. Place your protein snapshot here. Use the annotation tool to point to peaks and valleys on the surface of the protein.

   ![Sample snapshot](image)
   Sample snapshot. Students’ snapshots will vary.

3. What ideas do you have about why it is important for biological molecules to have a great variety of sizes, shapes, and surfaces?

   Answers will vary. This question is intended to help elicit students’ current ideas about biological molecules, not to be scored as correct or incorrect.

Page 2:

1. Place snapshot #1 here showing the three partner molecules in place on the protein.

   ![Sample snapshot](image)
   Sample snapshot. Students’ snapshots will vary.

2. Place snapshot #2 here showing whether any partners moved away from the protein when you ran the model.

   ![Sample snapshot](image)
   In this case, the small round molecule did not have enough attractions and at high temperature separated.

3. After raising the temperature, place snapshot #3 here showing the partner that stayed with the protein longest.

   ![Sample snapshot](image)
   Sample snapshot. Students’ snapshots will vary.

4. Why does raising the temperature increase the rate at which the partners separate?

   Increasing the temperature increases the rate of movement (kinetic motion).

5. Describe what factors help small molecules to stick to the protein better.

   One factor is shape. The more intermolecular attractions that form, the better molecules stick to each other. When the shape of a small molecule matches well with the shape of the protein, it brings them close enough for intermolecular attractions to form. If the small molecule does not fit well, the surfaces are too far apart for attractions to occur.
1. How do oxygen and nitrogen affect the sharing of electrons with nearby carbon and hydrogen atoms?

Oxygen and nitrogen are more electronegative than hydrogen or carbon. Because they have a higher attraction for the electrons in a bond, the electrons will tend to spend more time around the oxygen and nitrogen atoms, and less time around the carbon or hydrogen atom.

2. Imagine you are a carbon atom in a molecule composed entirely of carbon and hydrogen. One of the atoms you are bonded to is changed to an oxygen. Describe how the electron cloud around you is affected, and the resulting change in surface charge.

The oxygen attracts the electrons away from me more than either hydrogen or another carbon would. So, the electron cloud around me shifts toward the oxygen. As a result, the surface near the oxygen is negative, and near me, positive.

(Note that if we were looking at a protein that was mostly neutral on the outside, we would surmise that the protein occurs in a lipid-rich environment, such as the cell membrane.)

4. Imagine that the region shown here could bind strongly to another protein. Describe the shape and charge of the part of the other protein that binds here.

The other molecule would have a cavity or pocket that would be complementary in shape to this "knob". Inside the pocket it would be polar, with areas of positive and negative charge that would align opposite to the charges on the knob. Both these factors increase the intermolecular attractions between the knob and the pocket.

Page 4:

1. Which word best describes the character of the amino acid under the protein surface here? (Click to see it in the model.) Choose the BEST answer:
   (c)

2. Which word best describes the character of the amino acid under the protein surface here? (Click to see it in the model.) Select the BEST answer:
   (a)

3. Areas of neutral charge are hydrophobic. Why do you think we don't see much in the way of neutral areas on the surface of this protein? Hint

In the mostly watery environment of a cell, the attractions between water and polar/charged amino acids are much stronger than between water and hydrophobic side chains. As a result, hydrophobic amino acid side chains mostly fold up on the inside of a protein, and polar and charged parts of the protein are on the outside.
1. Use your knowledge of shape, intermolecular attractions, and charge to predict which small molecule the protein in the model above will recognize. Hint (a)

2. After using the new model above, return to your snapshots and place the one with the real partner molecule in the binding site here. Use the circle tool to circle the partner molecule.

3. Explain how the partner molecule recognizes the protein while the other two small molecules do not.

Small molecule #1 recognizes the protein's binding site by its close fit (shape) and opposing charges. The good fit brings the atoms close together because many intermolecular attractions can form. In addition, the areas of charge line up opposite to each other — wherever there is a positive area on the protein, the corresponding part of the partner is negative and vice versa. (The observant student may note that a neutral area is also matched on the partner.) Small molecule #3 has the wrong charges to stay in the site, whereas small molecule #2 has the wrong shape.

1. Do you think adrenaline is a charged molecule? How can you tell?

The surface of adrenaline's binding site is red, indicating that it is positively charged. Therefore, adrenaline must be negatively charged, or it would not be attracted to the site.

2. Why is it important that adrenaline fits closely inside its binding site?

A close fit allows for intermolecular attractions to form so that adrenaline can be held securely by its receptor. Since a small increase in temperature can disrupt molecules that are binding to each other, a close fit means the two molecules are more likely to recognize each other and remain associated long enough to have the desired effect.

1. Describe the features of proteins that allow them to be recognized (or not) by other molecules.

The surface of a protein has a particular shape created by the underlying amino acids, and across the surface there are charges that vary, from neutral to positive or negative. The combination of shape and charge make each protein unique. A molecule that has a complementary shape and opposite charge can, therefore, fit closely with the protein, recognizing and binding to it. Molecules with shapes that don't "match" like this will bounce off, not recognizing the protein.

2. The surface of a protein...

(c)

3. Which of the following changes in a protein would be likely to interfere with molecular recognition?

(e)
4. Some complexes between two molecules stay together only at low temperatures, but when the temperature is raised, they come apart. Use what you have learned about intermolecular attractions to explain how this could happen.

When two molecules don't fit closely together, the complex between two molecules involves only a few intermolecular attractions. At low temperature, those attractions are strong enough to hold the complex together. As the temperature increases, the molecules' energy increases and they vibrate more, breaking the few intermolecular attractions that held the complexes together.

5. A mutant receptor protein is found to be defective and is no longer recognized by its partner molecule. The identity of a single amino acid in the protein was changed by the mutation. Where in the protein would this amino acid most likely be found? (More than one answer may be correct - choose the best answer.)
(a)
1. What makes a protein surface “recognizable” to other molecules?

2. Draw a protein and a small molecule in a complex. Label your drawing so that someone would understand why these two molecules would form a complex.

3. How does electronegativity cause differences in charge across the regions of a protein’s surface?

4. How do intermolecular attractions play a role in the binding of a partner molecule to a receptor?
5. How could a mutation that changes an amino acid from polar to non-polar affect the function of a protein?

6. Career connection: One of the most important aspects of drug design is creating molecules that interact with proteins (receptors, enzymes, etc.) in our bodies. Explain what a person working for a pharmaceutical company would need to know about a protein in order to design another molecule that will stick to it.
SAM HOMEWORK QUESTIONS
Protein Partnering and Function – With Suggested Answers for Teachers

1. What makes a protein surface “recognizable” to other molecules?

Molecules “feel” each other’s shape and charges on their surfaces to recognize a partner molecule.

2. Draw a protein and a small molecule in a complex. Label your drawing so that someone would understand why these two molecules would form a complex.

Student answers may vary. This image from the activity is a good reminder for the concepts that are being addressed in this review question.

3. How can differing electronegativities cause differences in charge across the regions of a protein’s surface?

Electronegativity can be defined as an atom’s ability to attract another atom’s electrons. If electrons are not evenly shared across a protein’s surface, parts of the protein will be partially positive and others will be partially negative. This will cause different characteristics in the protein’s function and structure.

4. How do intermolecular attractions play a role in the binding of a partner molecule to a receptor?

Molecules are in constant motion. If they bump into each other and there is an attraction, the molecules can “stick” together. When the fit between molecules is better, greater intermolecular attractions occur. Charges play an important role in intermolecular attractions, too.

5. How could a mutation that changes an amino acid from polar to non-polar affect the function of a protein?

Changing the polarity of an amino acid will affect the protein structure. How a protein folds is dependent upon its polarity, including regions that are hydrophilic versus those that are hydrophobic. It will also affect how the protein behaves in water or interacts with other molecules.

6. Career connection: You would need to know the shape of the target protein and the charges on its surface where you want your drug to interact or bind to.