Monday's
Modeling

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It's a fact of life – we all carry around mutations: random changes in the sequence of nucleotides that make up our DNA. While some mutations can cause diseases such as Sickle Cell Anemia, others may simply contribute to the more subtle variations that make each living being unique. Mutations encompass various changes to the DNA sequence caused by substitutions, deletions, and insertions of the nucleotides. DNA determines the sequence of amino acids in proteins. That sequence, in turn, determines the shape of each protein and its biological function. Mutations sometimes change the shape and function of proteins. The molecular basis of this chain of causation is challenging to teach.

Figure 1. A view of the Mutations model. The 20 amino acids in the chain are connected to the genetic "keyboard" below it. Students can change or delete any nucleotide in the keyboard and observe possible changes in the sequence of the amino acids and the changes in the way the chain folds.

An NSF-funded project, the Molecular Workbench, is completing a study (see "Notes from the Molecular Classroom" on page 8) of how a molecular dynamics model, embedded in relevant learning experiences, can help students reason about how changes in DNA might have implications for protein function.

At the heart of this activity lies a computational model. In the smallest fractions of time, the computer makes many millions of calculations prescribed by the model, and displays on the computer screen new configurations of molecules in response to a student's intervention. Contrary to traditional animations whose interactivity is usually lim-ited to pressing the "Start" and "Stop" buttons, dynamic models allow students to conduct experiments at a molecular level and follow their own lines of inquiry.

For this Monday's Lesson we present a short activity in which students use a model to explore interactively the relationship between DNA and the shape of the protein for which it codes. A complete set of activities with lesson plans is available at:

http://workbench.concord.org/web_content/

Launch the Model

To open and run the *Mutations: Substitutions and Deletions* model, go to http://xeon.concord.org:8080/modeler/web-start/protein/mutations.jnlp in your web browser. The software will launch automatically. A simplified two-dimensional molecular dynamics model approximates protein folding in different environments. The white beads represent amino acids connected by peptide bonds and the blue background represents the water in which the polypeptide chain is floating. Connected to the peptide chain is a genetic "keyboard," which allows students to generate mutations in the DNA and thereby affect the sequence of the amino acids in a protein for which this part of the DNA is the genetic code.

With this model, students can control the amino acid sequence by replacing amino acids in the model protein or by altering the sequence of the nucleotides in the corresponding string of DNA. They also can change properties of the surrounding media (from vacuum to water or oil). Working with the model, students learn the correspondence between the sequence of nucleotides in a strand of DNA and the sequence of the amino acids in a protein, and explore in real time how changes they make in the genetic code affect both the sequence of amino acids and the shape of the model protein. See Figure 1.
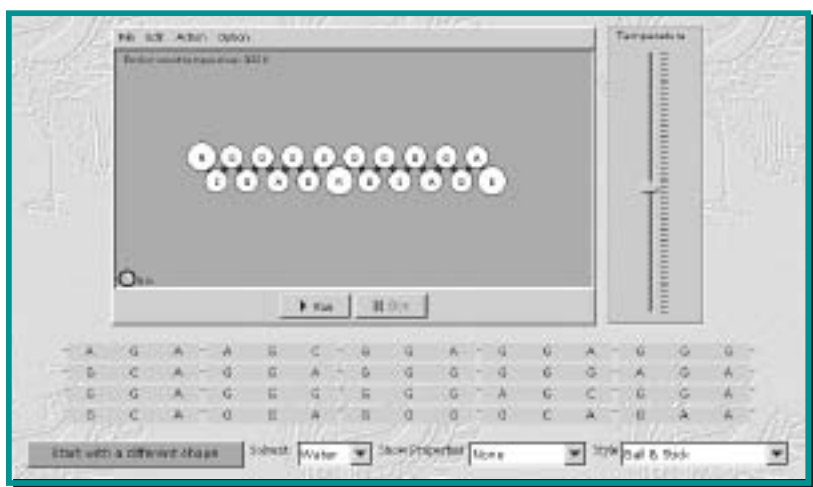
’s Lesson
Mutations

The Activity

A. Substitutions

1. Begin by clicking the cursor on the run button and running the model.
2. Note the model forms a "flying bird" pattern.
3. Change the first G of the third codon (GGA) in DNA to A, making the codon AGA.
   - To change a nucleotide, point the cursor towards it. Now left-click (on a PC) or hold-click (on a Mac) to open a pull-down menu.
   - Select a new nucleotide.
   - When you make a nucleotide mutation, the corresponding amino acid in the protein window will blink in yellow.
   - You can look at the different properties of the new amino acid by selecting "charge" or "hydrophobicity" from the "Show Properties" menu.
   - You can view the name of the amino acid by pointing the cursor to the amino acid and holding the "Alt" (Option key on a Mac) key while left-clicking the mouse. A bullet in front of its name identifies the amino acid.
4. Click "Run." Describe what happens, if anything, to the shape.
5. Now make three changes in the sequence of DNA by randomly substituting any of the nucleotides with another. Record what nucleotide you changed (for example, "In the fifth codon, I changed the first nucleotide from A to T.") and describe how the replacement affected, if at all, the shape of the protein.
6. Explain why some substitutions of nucleotides in the DNA appear to have no effect on the protein.
7. Explain how one critical substitution of the nucleotides in the DNA can have a significant effect on protein shape.
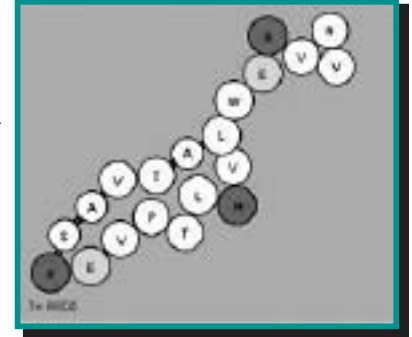
B. Deletions

1. Reload the model by clicking the reload button in the menu bar.
2. Change the sequence of DNA by deleting the third nucleotide. Click "Run."
3. Describe what happens to the shape of the protein.
4. The original protein sequence is:
   R-S-G-G-G-A-G-G-G-R-G-G-G-S-G-R-G-G-R-E
   Record the new protein sequence.
5. What happens to the DNA code after you deleted the third nucleotide?
6. Which type of mutation has the greater effect, substituting a nucleotide or deleting one? What might explain this difference?

Getting at the Root of Sickle Cell Disease

In this activity students work with the critical segment of the hemoglobin's protein to explore the effect of the mutation in the DNA leading to Sickle Cell disease. They generate single point mutations leading to the replacement of the anionic glutamic acid with non-polar valine. This is exactly the amino acid substitution that causes Sickle Cell disease. Students can then learn how such mutation affects the hemoglobin conformation. They also learn how this mutation can help protect a carrier from malaria. Try this yourself at: http://xeon.concord.org:8080/modeler/webstart/protein/hemoglobin.jnlp

Figure 2. The portion of the hemoglobin protein that contains the Sickle Cell mutation, as rendered in the Molecular Workbench model.

Educational Significance

The model cannot predict the actual protein conformations for a large molecule – this is still an open research question – but it does illustrate how changes in temperature, charge, or surrounding medium can change the shape of a protein. It also allows students to explore the relative role of different mutations on the shape of a protein and predict how various mutations (substitutions, deletions, insertions) affect the function of proteins and why, for example, in most cases deletions are lethal for a cell. This model provides students with a manipulative, dynamic tool that could develop their intuition about basic interactions affecting protein folding, and allows students to observe in real time how changes they make in the genetic code affect both the sequence of amino acids and the shape of the model protein. @

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ARTICLE LINKS & NOTES

Molecular Workbench — http://workbench.concord.org

Molecular Workbench activities and lesson plans — http://workbench.concord.org/web_content/

Java Sun Microsystems — http://www.java.com/en/download/manual.jsp