Creating a Protein Model

Proteins are chains of amino acids (**aa**) that are linked together through covalent peptide bonds. In this model, you will generate a backbone — the peptide bond segment of the protein. You will not visualize the amino acid residues that give the protein its particular structure and chemistry. However, you will get a feel for the different types of structural segments that make up a protein.

- The primary structure is the amino acid sequence.
- Two main secondary structures are alpha α helix and betaβsheet.
- Tertiary structure is how the random coils, helices and sheets interact. Disulfide bonds stabilize tertiary structure.
- Some proteins have quaternary structures because they are made up of identical or different subunits (example: hemoglobin) .

Based on analysis of the crystal structures of hundreds of proteins, scientists have found about 270 motifs or small patterns that are related to the amino acid and structural appearances of short stretches of sequence. Because of this large amount of sequence/structure data, some scientists think that they are getting close to being able to PREDICT the structure of a protein from its **aa** sequence. This information is also enabling scientists to imagine being able soon to rationally design proteins with predictable activities. To do this, scientists will use a DNA synthesizer to prepare DNA segments of defined coding sequence and then clone this sequence into bacteria or eukaryotic cells and translate the sequence into the protein.

Our wire model does NOT resemble protein synthesis. During protein synthesis, individual amino acids (**aa**) are connected to the growing (nascent) protein chain on the ribosome.

We CAN model the end-product (a folded protein) by simply coiling a fine wire around a pencil, pen or applicator stick. You will need only 1 length of wire per protein. Hemoglobin (Hb) would have 4 wires, with 2 wires each formed into Hb-_ and 2 Hb-_ subunits.

Proteins ARE somewhat flexible. Imagine a stapler (bond-maker) or a scissors (bond-breaker). Most proteins are unstable and so care about temperature, pH, salt conditions, presence of detergents or ions, etc. All these conditions bring about subtle or large changes in protein structure. Large changes may be irreversible. The protein forgets how to refold after it has been unfolded or denatured.

Materials:	**Wire (10-20 cm)**	**Pencil, pen or applicator stick (hereafter called "stick")**

Sources for wire:

- Craft store beading wire.
- Phone cable.
- Rolls of twist-tie, available at dollar stores or hardware stores.

- Coil the wire around the pencil. You can make some coils and then leave some wire hanging, then coil some more. The coils can have different numbers of turns. Proteins themselves are NOT symmetrical in general.
- Gently pull off the wire from the pencil.
- Stretch out the non-coiled areas and fold some of them back to form beta-sheets.
- Gently smush the whole thing in your cupped hands.
- When you release your hands you will have a somewhat spherical entity, a model of the backbone of a globular protein.
- If you press OR stretch the model gently, you will notice that it springs back. Native (active state) proteins have some flexibility.
- If you stretch more, which models heat (high temperature) or chemical denaturation like with detergent, the protein can no longer go back to its native conformation (you may not remember how you folded it initially) and it stays denatured and inactive.

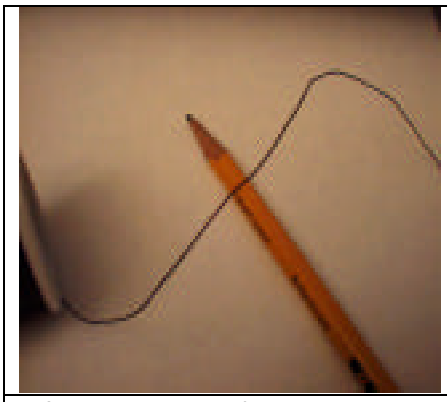
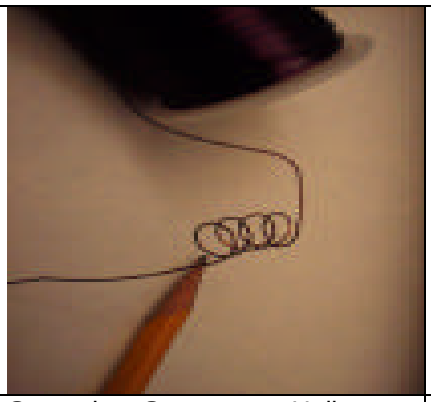
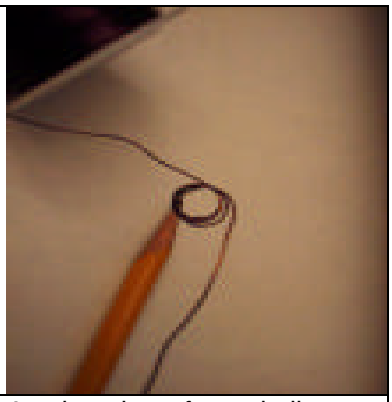
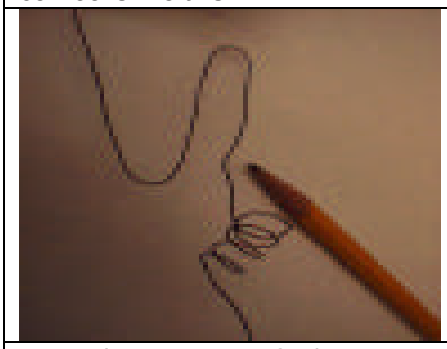
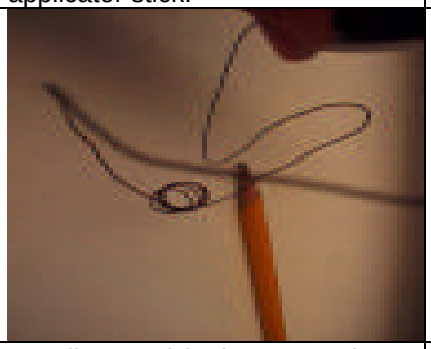
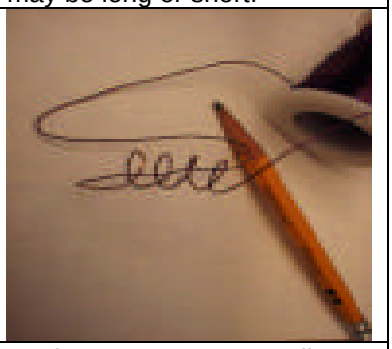
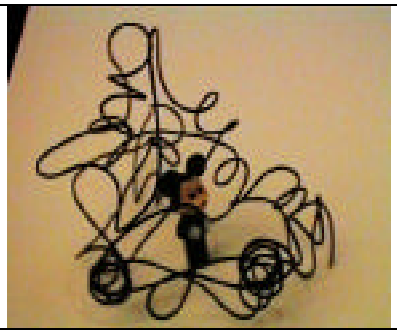
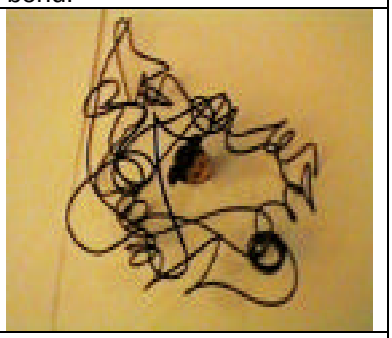
Go to the NIH home page **http://www.ncbi.nlm.nih.gov** Click on **Structure** along the top bar.
This will take you to information about the sequence (GenPept Report) but also Internet link to 3-D structures of various proteins. You will need to download some free software used by professionals such as (Chime, RasMol, Cn3D). **http://www.umass.edu/microbio/rasmol/index.html** has links to the protein structure sites. When you open the protein structure files in these software applications, choose ribbon or cartoon and choose structure. Ribbon will show the backbone more clearly and structure will show the _-helix as pink and the _-sheets as yellow.

Find the structures of insulin and catalase and try to model their 3-D structures.
There will be many entries for insulin (76), insulin hormone (61) and for catalase (18), because these proteins have been isolated from many different organisms, AND because many protein chemists have been studying various conditions and how they affect the structure of these proteins (hemoglobin also!).

If you simply type in insulin, 76 or more structures will come up. For insulin hormone, 61 structures will remain.
Scroll down until the names get simple. Eventually you will find "Structure of Insulin, (1ZEH)

The structure information is stored at the Protein Data Bank **http://www.rscb.org/pdb** and linked to NIH. The Protein Data Bank's home page has links to very helpful background (select **Get Educated**)

Hands-On: Wire Proteins Help Us to Visualize Protein Structure in 3 Dimensions

		
Primary Sequence/Structure The chain of amino acids. Random coil looks like this.	Secondary Structure: α-Helix - Curl wire around a pencil or applicator stick.	Another view of an α-helix, also called a "barrel." Helices may be long or short.
		
Secondary structure: β-Sheet Folded like a switchback path.	α-Helices and β-Sheets may be next to or near each other in the sequence, separated by a small segment of random coil.	Tertiary Structures: α-Helices and β-sheets may be stabilized by disulfide bonds between cysteines. Use a paper clip or staple for the S-S bond.
		
Different views of a protein. The N and C terminal **aa**'s may be nearby or far away.	The substrate helps orient us. Most substrates fit into clefts.	Most active sites have **aa** from different parts of the chain that appear close because of the many structural folds.

Internet Resources

Software
Check with your school systems operator. This software is ALL professional, yet FREE for anyone to use. The programs take up very little memory on the hard drive and CHIME is a Browser Plug-in

Cn3D (see in 3-D!)
http://www.ncbi.nlm.nih.gov
Select "Structure." On the LEFT column, select Cn3D

CHIME and RasMol and Protein Explorer
http://www.umass.edu/microbio/rasmol/index.html

National Center for Biotechnology Information
http://www.ncbi.nlm.nih.gov select STRUCTURE

Protein DataBank
http://www.rscb.org/pdb

Useful structures for school

small molecules (nucleotides and amino acids)
http://chemistry.gsu.edu/glactone/ . Follow the links to pedagogical PDBs
insulin
hemoglobin
catalase
HIV protease
DNA
lysozyme

Standards of Learning Connections:

- Macromolecules
- Enzyme activity
- Structure and Functions of Cells
- Health and Disease
- Science and Technology
- Mutations
- Gene Expression
- Evolutionary relationships
- History of Scientific Discovery
- Computer and Information Technology

Interesting Protein Stories

Dorothy Crowfoot Hodgkin
http://nobelprizes.com/nobel/chemistry/dch.html

Prions
http://www.hhmi.org/news/lindquist3.html

Green Fluorescent Protein
http://pantheon.cis.yale.edu/~wfm5/gfp_gateway.html