

# Lecture 10

## More about proteins

Today we're going to extend our discussion of protein structure. This may seem far-removed from gene cloning, but it is the path to understanding the genes that we are cloning.

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*Continued discussion on structure* In the last lecture, I discussed the structures and properties of the 20 amino acids, and introduced the basic structures (such as alpha helices) found in proteins. I'm going to extend that discussion today, focusing on the surface and internal characteristics of proteins.

Once again, the [CHIME plug-in](#) module is essential if you want to be able to view and manipulate the chemical models at your own computer.

Let us begin by reviewing the three sites I recommended at the last lecture:

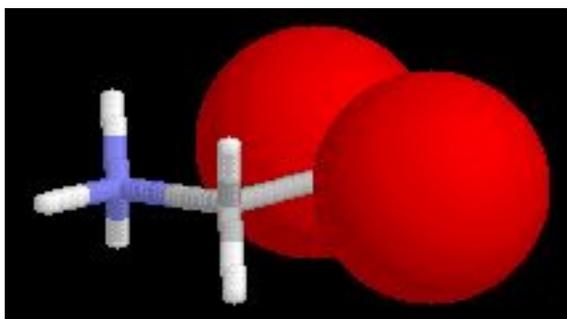
The U.Mass hemoglobin site, cited earlier, illustrates these structural elements nicely in a [continuous animation](#). You can just sit back and watch the show! I would like you also to study each aspect of the model, and for that it would be best to [go to the menu and work through each section](#). You may need to click the "Back" button on the frame on the right to get the menu, and I've indicated below what you should study in each section:

## Protein Structure

### Glycine Representations

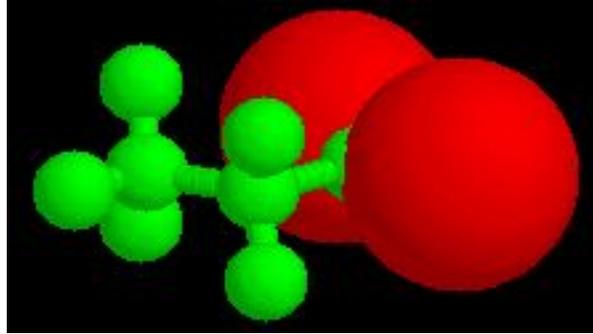
You should familiarize yourself with the three methods of representing simple molecules: Ball and stick, spacefilling, and stick models. If you click and hold your mouse on the "MDL" logo in the frame on the left, you can pull down a menu that includes an entry "Display", which gives you independent control.

An exercise to try: Starting with a representation of glycine in "stick" model, click on the MDL to get your menu, and go to the "Select" menu. Choose the entry "Atom", and within that, choose the entry "O". You have now selected the oxygen atoms in the glycine, and can modify their appearance independently. Go to the "Display" menu item and set "Space filling" and "Van der Waals radii". It should look like this:



You see that we have set two different types of representation in the same molecule. Now try this: Go to "Select" and choose "invert selection". You have now selected everything in the molecule except for the part that was selected before. Go to "Display" and choose "Ball and stick" and then go to "Select" and choose "Change color" to green. Now it should

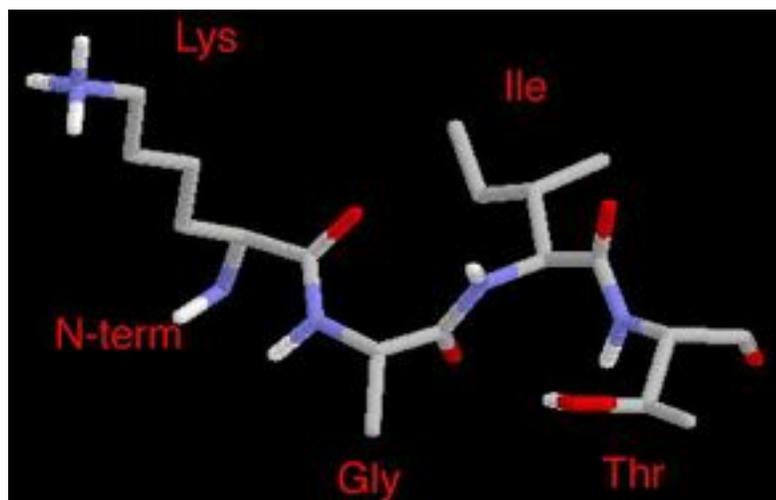
look like this:



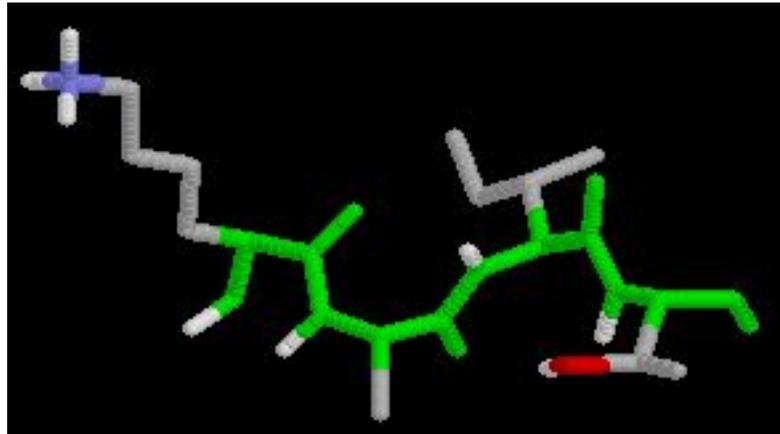
This is just a simple example of how you can control the appearance of a molecule. You should practice on your own, because when we go to look at larger molecules like proteins, we are going to want to be able to select individual residues and change their appearance for study.

### Peptides and Backbones

You can now click on "Back" to get back to the main menu and select "Peptides and Backbones" to continue. Select the first menu item, which gives a model of just the backbone of a single L-amino acid. The R group is not shown. What happens if you select the entire molecule "Select"/"select all" and then set the display to "stick"? You see a glorious tetrapeptide, which looks something like this:



I've taken the liberty of putting in a few annotations, such as the names of the R groups and the location of the N terminus. Can you trace the backbone through this molecule? If not, you can go to "Select"/"Protein"/"Backbone" and then "Select"/"Change color" to green. It will look like this, perhaps:



Now, to learn about secondary structure, let's switch to McClure's [Protein G primer](#) which is an outstanding site.

Choose "alpha helix" from the menu at the top, and study the structure.

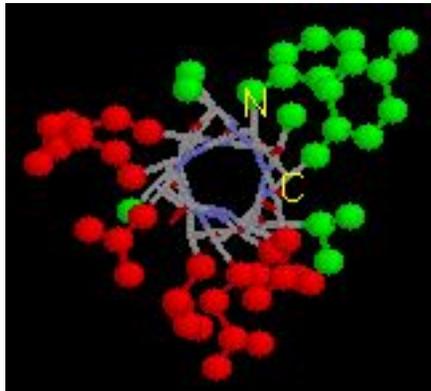
How many residues are there per turn of an alpha helix?

Where do the hydrogen bonds form that hold the helix together?

What is a typical bond distance for the H bonds across the helix?

What is meant by an "amphipathic" helix?

Try going through the exercise in which you color the hydrophobic residues green and the hydrophilic ones red. Turn the molecule so you are looking down the axis of the helix, and it will look something like this:



This may give you an idea about how proteins are assembled beyond a secondary structure, for if the hydrophobic residues can become clustered on one face of a helix, they can be pushed into the interior of the protein as it folds into a tertiary structure.

You may also imagine what might be the consequences of a mutation from, say, a phenylalanine (one of the green hydrophobic residues shown above) to an aspartic acid (one of the polar charged amino acids). It might destabilize the structure of the protein to have a "red" in the middle of the "green".

Now go on to click on the next structural feature in the menu at the top - the beta hairpin.

What is a beta hairpin?

What is a typical bond distance for the H bonds across the sheet?

What is meant by "pleated" sheet?

Look at the Gly-14, and study the phi and psi bond angles on an "edge on" view. Do you see the effect that these angles have on the structure?

Now go to the second example of a beta hairpin, and study the dihedral angles of the Lysine 50. Alpha helices in proteins are right handed, but if you look at the phi and psi angles in turn, you can see that this individual residue provides a left handed helical structure.

What do we mean by right and left handed?  
Which is Phi and which is Psi?

In that example, try setting the display and color of the hydrophobic residues to green ("Select"/"Protein"/"Hydrophobic") then ("Display"/"Sticks") then ("Select"/"Change color"), and the hydrophilic residues to red, as before. Do you see any clustering of types of R groups?

Now go to the full beta sheet example.

What are the typical orientations of H bonds across the antiparallel beta sheet?

What do we mean by antiparallel vs. parallel beta sheet? (If you set the display to Ribbons this may be easier to see)

After coloring the hydrophobic and hydrophilic residues differently, can you see which is the solvent exposed surface?

Now go to the two examples of Type 1 turns, and look at the H bond distances across the backbone.

How far apart in the backbone are the H bond donor and acceptor?

Did you see a Type 1 turn in either of the previous two examples of beta turns?

Now go to the Patterns of Tertiary Folding link, and look at the packing example. Look at the van der Waals radii

representation showing the buried tyrosines, leucines, tryptophans, and phenylalanines. Look at the representation of a "pocket" for the Phe30, noticing the atoms that are in close proximity to the phenyl ring.

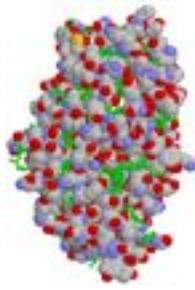
Finally, go to the water hydrogen bonds example, and see how a single water molecule can act as a bridging unit in a protein crystallographic structure.

[Protein Explorer](#) is a program you can use to download and inspect proteins from the Brookhaven crystallographic database.

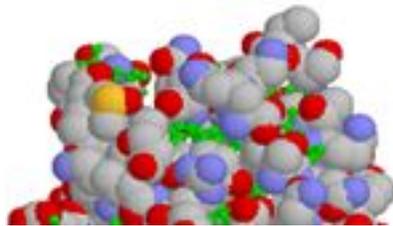
*What's inside,  
what's outside*

One important concept is that proteins fold themselves so that hydrophobic residues tend to be buried in the interior of the protein. Does that mean there can never be an exposed phenylalanine or isoleucine? No, they can certainly be on the surface, but there is an energetic cost associated with having them exposed to the water solvent. The water must "organize" around the hydrophobic residues, and that organization bears the cost of being a decrease in disorder or entropy.

Let's look at a typical example, the protease thermolysin, using Protein Explorer. The protein databank code for this molecule is 1LNF, and I encourage you to view it and isolate the elements I describe below.

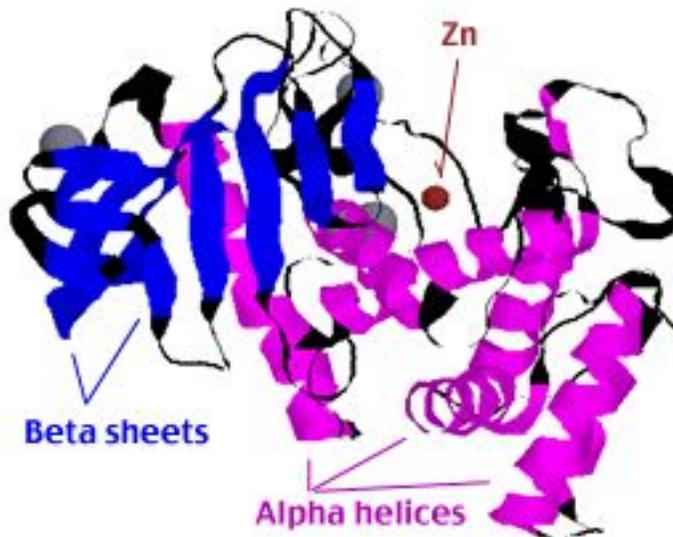


Here is an image of the thermolysin protease, with hydrophobic side chains (phenylalanine, isoleucine, leucine and valine) colored green and represented in "ball and sticks" format. The other residues in the protein are represented in "space-filling" format. It is evident that very little green shows through the cracks!



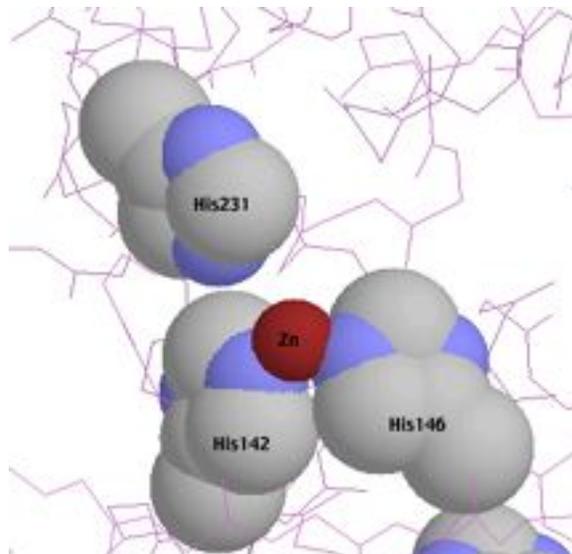
Looking more closely at just one section of the model, we can see that only a few "green" atoms (part of these hydrophobic residues) are visible on the surface. There is a considerable amount of oxygen (red) and nitrogen (blue), which tend to participate in hydrogen bonding with the solvent.

Here is an image of thermolysin, with the alpha helices colored magenta, the beta sheets colored blue, and the remaining structures colored black. The zinc ion is indicated with an arrow. There are also three visible calcium ions (gray) in the upper-left quadrant of the image.



This allows us to review these structures that we had studied using the protein G1 ([see McClure's page](#))

We are particularly interested in how the zinc ion is chelated in the protein. If we set the histidines in space-filling format and the rest of the protein in wire-frame format, it is easy to represent the structure:



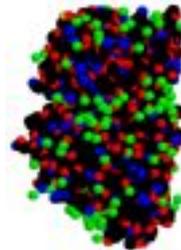
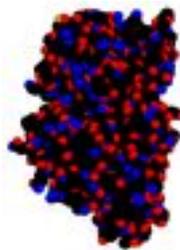
Note that there are three histidines in the vicinity, and that the Zn ion is nestled between two nitrogens from his142 and his146.

How do we get this type of control of individual residues from Protein Explorer? You choose "Explore More" as an

option from the menu on the left, then select "Advanced Explorer" from the new page frame, then select "Seq 3D". You will get a new page with the primary sequence, and from this you can select individual residues or groups of residues for special handling.

I recommend that you repeat this exercise with the molecule 1LNF so that you can turn the model on your computer. You may also be interested in looking at the chelation of the calcium ions around residues 195-205 of thermolysin.

Finally, here is a representation of thermolysin, with the carbon atoms colored black, the oxygen colored red, the nitrogen colored blue. Notice how the water molecules are distributed in the co-crystal (as shown on right in green). The surface of the protein in solution would be covered with water, acting as hydrogen bond donors and acceptors with the oxygen and nitrogens of the amino acids.



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