Reading Assignments:

*Chapter 4: Protein Structure and Function*

Pg 150-153 on allostery

Examine the regulation of the citric acid cycle at these web sites:

http://www.wiley.com/legacy/college/boyer/0470003790/animations/tca/tca.htm

http://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/krebscyc/krebscyc.htm
Control of Metabolic Processes in the Cell

Figure 13–24 Glycolysis and the citric acid cycle lie at the center of metabolism. Some 500 metabolic reactions of a typical cell are shown schematically with the reactions of glycolysis and the citric acid cycle in red. Other reactions either lead into these two central pathways—delivering small molecules to be catabolized with production of energy—or they lead outward and thereby supply carbon compounds for the purpose of biosynthesis.
How do cells regulate these complex reaction sequences?
The cell controls its metabolic activities by controlling the
• The activity of enzymes catalyzing key reactions
• the transport of molecules from one cellular compartment to another

How could the activity of an enzyme be modulated upwards or downwards?

Many possibilities here
**Allosteric Interaction:**
a regulatory mechanism in which a small molecule binds noncovalently to a protein and alters its activity by altering its shape

**Important points:**
- the small molecule is called an effector or a modulator or a ligand
- if the allosteric interaction involves an enzyme the modulator binds at a site other than the active site
- the modulator can activate or inactivate a protein

\[ allo = \text{other} \quad \text{stere} = \text{solid or shape} \]
Allosteric regulation

C = catalytic subunit
R = regulatory subunit

Whether a positive modulator occupies the regulatory pocket on the protein depends on two factors:

- concentration of M
- affinity of binding (M to pocket)
End product inhibition is one example of allostery

- Feedback inhibition regulates the flow through this metabolic pathway. The end product Z binds to and inhibits (lowers the activity of) the enzyme that catalyses the B to X reaction. In this way Z controls its own concentration.
- Thus when quantities of the final product of a metabolic pathway begin to accumulate, the product binds to the first enzyme (unique to its synthesis) and slows down its catalytic action.
- This is called **negative regulation**
The cell has an elaborate interlocking system of feedback controls that coordinate the rates of glycolysis, fatty acid breakdown, the Krebs (citric acid cycle) and electron transport.

As a result of many control mechanisms, the body oxidizes fats and sugars 5-10 times more rapidly during a period of strenuous exercise than during a period of rest.

Examine the regulation of the citric acid cycle at these web sites:
http://www.wiley.com/legacy/college/boyer/0470003790/animations/tca/tca.htm
http://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/krebscyc/krebscyc.htm

Which reactions are regulated?
Look at isocitrate dehydrogenase and α ketoglutarate dehydrogenase
What compounds act as negative regulators?

Enzymes are also subject to positive regulation whereby the enzyme's catalytic rate is increased rather than decreased by the regulatory molecule.
What compounds act as positive regulators?
How else could the activity of an enzyme be regulated?

- In bacteria, the **trp repressor protein** inhibits the transcription of a suite of genes coding for enzymes required for the synthesis of the amino acid tryptophan.
- In the absence of tryptophan, the recognition helices are not in the proper orientation to contact the promoter DNA; no repressor binds and the genes coding for the enzymes are transcribed.
- If tryptophan levels are high, it binds to the repressor protein and causes a subtle shift in the orientation of the recognition helices; now the protein binds the promoter DNA with high affinity.

NOTE: this regulatory circuitry involves allosteric regulation of a regulatory protein (trp repressor) that controls **tryptophan biosynthesis by controlling the level of production of the enzymes required for the biosynthesis of this amino acid.**