## Introduction to Metabolism

### Purpose of metabolism

Processes tend to spontaneously achieve equilibrium states, in which ΔG is zero. Living organisms are far from equilibrium; however, living organisms must obey the laws of thermodynamics, and therefore maintaining this distance from equilibrium requires effort. Organisms represent regions of order in a universe in which order is unstable. Organisms must therefore obtain energy ***in useful form*** from their environment to allow them to maintain their ordered state.

For most organisms, however, collecting energy indiscriminately is a problem. Organisms must also maintain homeostasis[1], in which many physical parameters remain constant. Once a human has reached adulthood, the mass of the individual remains fairly constant over time, in spite of a yearly ingestion of over five hundred kilograms of external materials. Maintaining this homeostatic condition requires a high degree of regulation.

Organisms obtain the energy necessary for survival from their environment. Plants use photons released from the sun as their energy source. Other organisms consume plants, or consume other organisms that have consumed plants, to obtain their energy. The energy is used to maintain the low-entropy, non-equilibrium state, to drive chemical processes and in general, to support life.

Organisms need energy for **chemical synthesis**, because they need to be able to synthesize proteins, lipids, and nucleic acids. All of these are **ordered** molecules; synthesizing large molecules from small ones requires energy to overcome the entropic cost of the process. Organisms also need energy to generate **heat** (room temperature is at least 10°C below human body temperature; ambient temperature may be much lower). Maintaining a body temperature of 37°C may therefore require considerable energy. Finally, animals need energy for **locomotion**, because moving requires energy that must be derived from chemical sources.

In general, heat is not useful energy. A human basking in the sun synthesizes vitamin D, and experiences an increased risk for skin cancer, but does not directly obtain usable energy. The ΔG for the metabolism of a compound is a measure of the usable energy in the compound. The ΔG is the energy available to do work.

Two major types of metabolic processes are used in biological systems: catabolic and anabolic.

### Catabolic processes

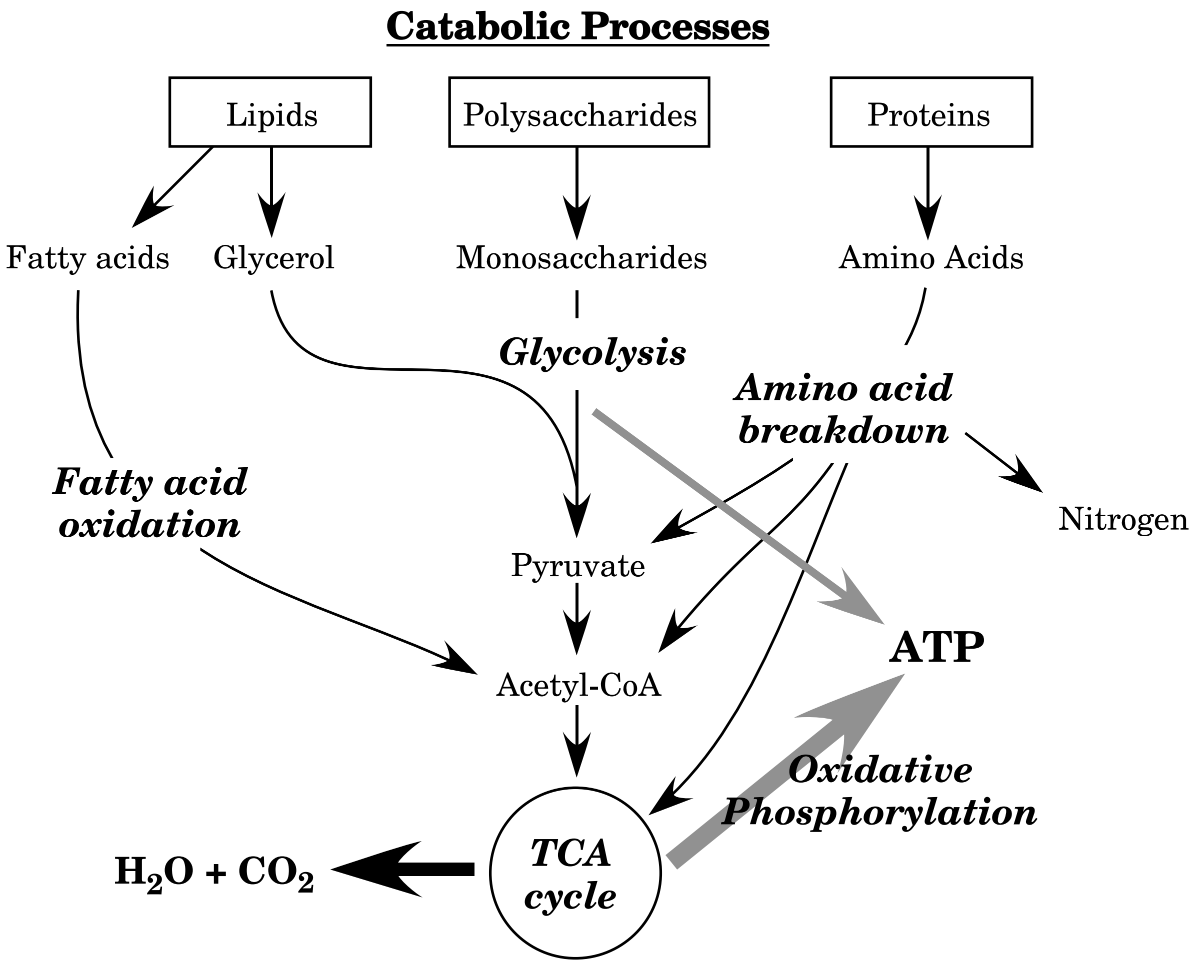
Catabolic processes involve the conversion of large molecules into small ones. Catabolism has two goals: 1) release of the energy required by living organisms in a

---

[1] Homeostatic and equilibrium states are superficially similar, in that the obvious system parameters do not change. However, maintaining a homeostatic state requires control and effort. A river downstream of a dam is homeostatic, in that its water level remains fairly constant, although the water present is in constant flux, and must be continuously replaced. In contrast, a pond is at equilibrium, with the water having no tendency to move in any direction.

usable form, and 2) generation of starting materials for biosynthetic reactions. The diagram below shows the major pathways for the metabolism of dietary components. Each of the three major nutrient types (lipids, carbohydrates, and proteins) can be converted to both energy and to metabolic intermediates.

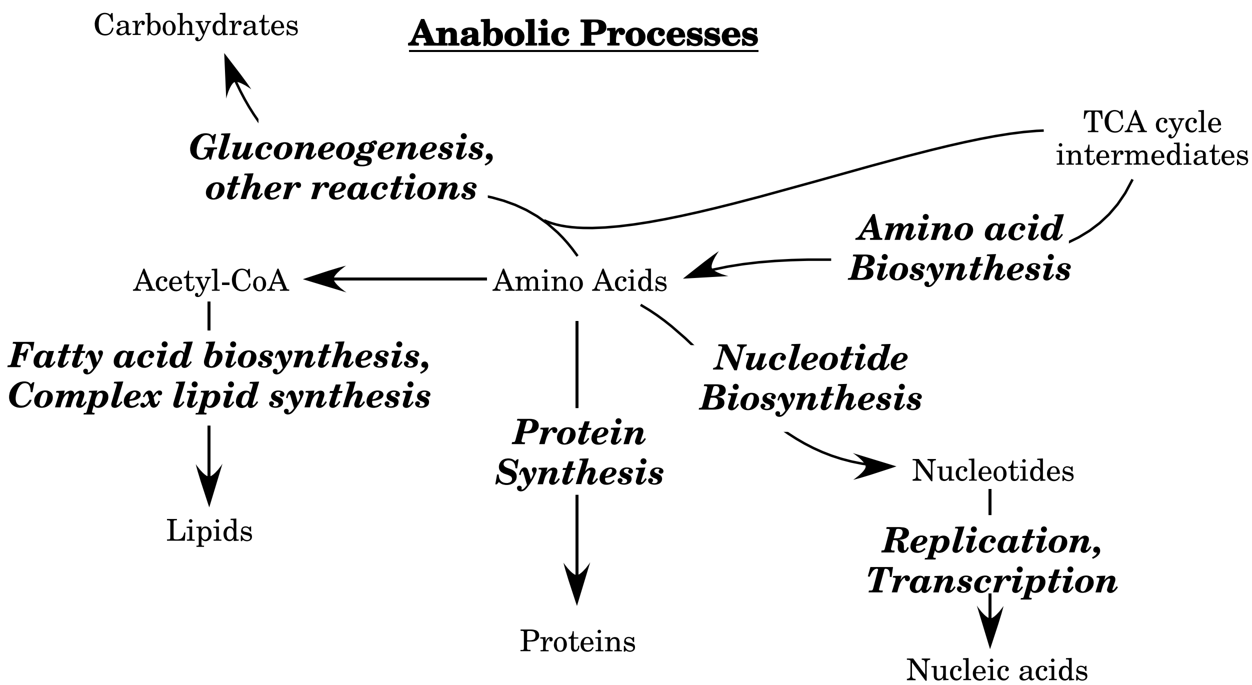
The energy derived from the catabolic processes is usually temporarily conserved in the form of adenosine triphosphate (ATP). This energy can then be used for other processes.




**Anabolic processes**

Anabolism is the reverse of catabolism; it involves the synthesis of useful larger molecules from smaller precursors. The function of catabolism is to convert large molecules into small molecules and into energy in usable form; the function of anabolism is to use the energy provided by catabolism to convert these smaller molecules into larger molecules.

Living organisms have a wide variety of different metabolic pathways that allow the synthesis of most molecules required for the survival of the organism. These include pathways for the synthesis of proteins, lipids, and carbohydrates. In many cases, the processes for breakdown and synthesis of molecules share pathways. These pathways (such as the TCA cycle) are called **amphibolic**, to reflect their involvement in both catabolic and anabolic processes.



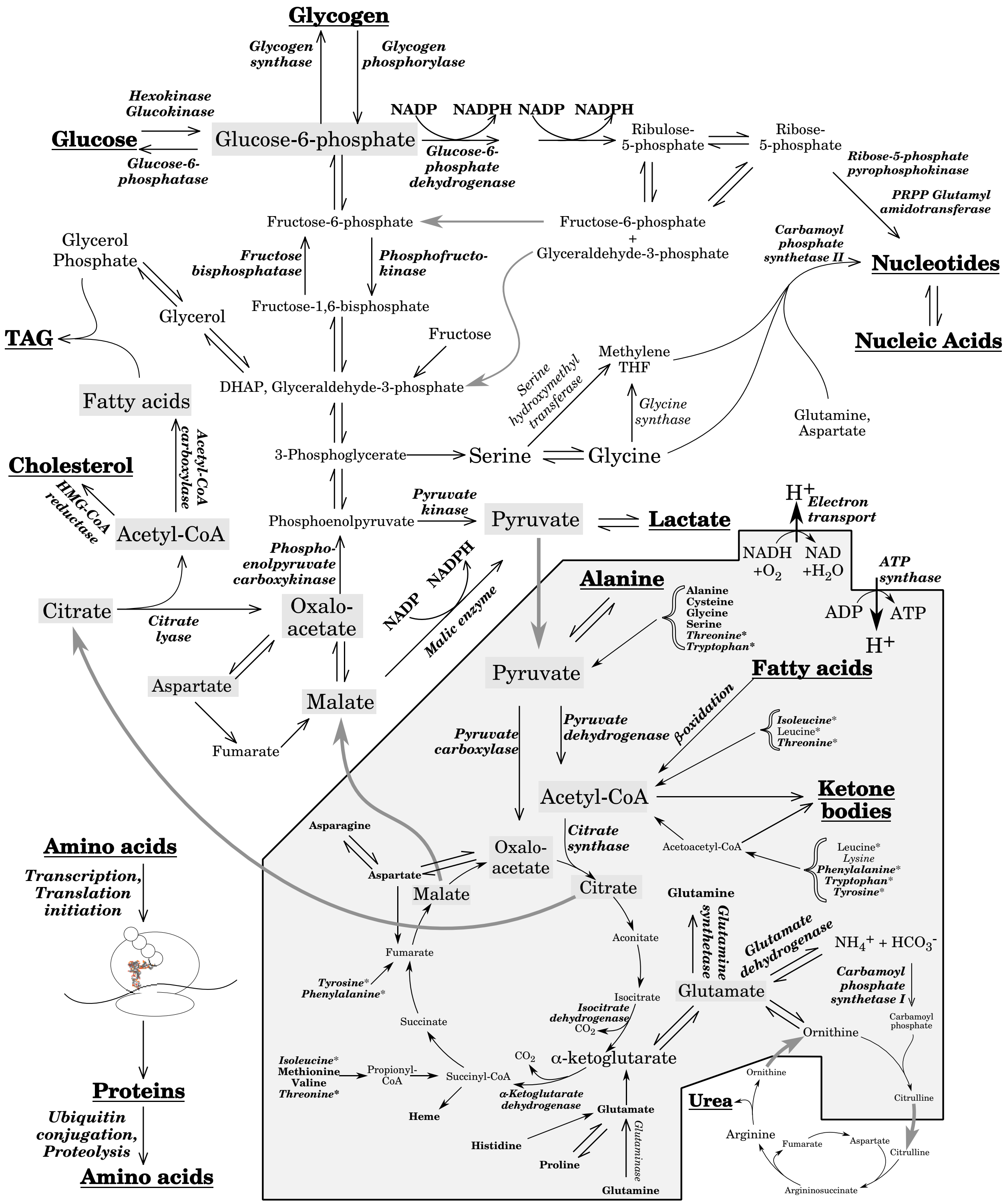

**Metabolic pathways**

Over the first two sections of this course, we have discussed concepts that allow us to understand the general concepts involved in enzymatic reactions. In real cells, however, the enzymatic reactions do not occur in isolation; instead they are grouped together into pathways.

A number of charts have been put together to show the reactions that occur in living organisms. These charts appear somewhat daunting at first; in fact they are quite useful, because they show how the reactions are interrelated. You have probably seen the large version of the biochemical pathways required for living organisms. The chart below shows a simplified version. This version shows the major pathways and highlights the major important compounds and the enzymes that act as control points in the pathways.

A few features of the chart are worth mentioning:
1. The chart lists only selected enzymes; in general, these are the major regulatory control points for each pathway, although some enzymes are important but non-regulated.
2. Compounds highlighted in **grey boxes** are compounds of particular importance; most of these compounds act as branch points, and are involved in more than one pathway.
3. The **black arrows** shown represent reactions catalyzed by one or more enzymes. The **grey arrows** represent translocation of compounds, or point out the fact that the same compound is present in more than one pathway.
4. The irregularly shaped grey box represents the **mitochondrial compartment**

within eukaryotic cells. The mitochondria are somewhat functionally distinct from the remainder of the cell; relatively few molecules can enter or leave a mitochondrion freely.




Relatively few amino acid biosynthetic pathways are shown in this chart. For animals, this is a reasonably accurate representation of events, because most animals completely lack the ability to synthesize eight of the twenty standard amino acids, and have very limited capacity for the synthesis of four others. The pathways for amino acid synthesis from non-amino acid precursors present in humans are shown in the diagram.

### Metabolic processes are highly regulated

We will talk about regulation and regulatory mechanisms for metabolism as we discuss each pathway. Metabolism has several levels of regulation. In some cases, the metabolic process only occurs in some cell types; the other cells lack the required enzymes. In many cases, the pathways are tightly regulated by hormones, which alter either the amount of enzymes or the activity of existing enzymes. In many cases, the pathways are tightly regulated by feedback effectors, which are intermediates from later in the pathway, or from other pathways, alter the rate of reactions in the pathway.

In some cases where it is necessary to keep pathways separated, two pathways exist in different compartments within the cell. The mitochondria are frequently used for keeping some molecules and processes separate from others. We will see examples of all of these concepts during the remainder of the course.

### Thermodynamics of pathways

Biochemical pathways all have large **overall negative ΔG values**. As a result, the pathways are effectively irreversible under physiological conditions. This feature is important for the control of the flow of material through each pathway.

An example of this is the conversion of glucose to pyruvate, and the conversion of pyruvate to glucose. Both pathways have negative ΔG. If the pathways were identical, this would violate the laws of thermodynamics. Clearly, the pathway for glucose synthesis from pyruvate must differ from the pathway for the breakdown of glucose to pyruvate. This is a general principle: the pathway for the synthesis of a compound always differs in at least one step from the pathway for the breakdown of the compound.

### Experimental methods

Metabolic pathways were worked out using a variety of methods. Many of these pathways, such as glycolysis, were worked out using the relatively crude methods available in the 1920s and 1930s.

It is difficult to use purified enzymes to work out a pathway, because it is not always clear what the cellular substrate and product concentrations will be, and in some cases, is not clear what the physiological substrate for a given enzyme actually is. Most studies therefore must be performed in cellular extracts or in tissues, which act as sources of all of the relevant enzymes.

These systems must then be manipulated in various ways to allow the isolation of specific intermediates (as opposed to merely the isolation of the final product of the pathway). In some cases, the manipulation involves the use of normal metabolic regulatory molecules. In most cases, however, the manipulation involves the use of inhibitors of enzymes that catalyze reactions proposed to be involved in pathway. Additional information was derived from studies on naturally occurring mutations in both experimental animals and genetic disorders in humans. More recently, experiments performed in genetically manipulated animals have been used to explore the role of different enzymes in the pathways.

The use of labeled versions of biological molecules has an important role in metabolic studies. The must commonly used labels are radioactive isotopes of hydrogen, carbon, and phosphorus. These isotopes are chemically identical to the normal non-radioactive isotopes of these elements, but are readily detectable in very small amounts. Using synthetic forms of biological molecules with labels at specific locations makes it possible to follow the processes that occur within the pathway.

## Summary

Organisms require energy from their environment to maintain their non-equilibrium state. For animals, this energy must be obtained in the form of molecules that can be oxidized to obtain free energy.

Metabolism has four functions:

1) to obtain chemical energy from food
2) to convert nutrients to the precursors of biologically important molecules
3) to synthesize the biologically important molecules
4) to degrade previously formed molecules no longer needed.

Catabolic processes are the degradative processes. Catabolic processes result in oxidation of the starting material, and result in net release of useful energy.

Anabolic processes are the synthetic processes. Anabolic processes result in reduction of the substrate molecules, and require the input of energy.

In general, catabolic processes start with a wide variety of molecules (many different types of proteins, many different types of carbohydrates, and many different types of lipids), and produce a small number of molecules (water, carbon dioxide, and nitrogen waste products when carried to completion, or free amino acids, glucose, lactate, and acetyl-CoA when the purpose is to produce intermediates).

Anabolic processes, in contrast, begin with a few types of small molecules, and produce the wide variety of biological molecules required by living organisms.

The anabolic and catabolic pathways are tightly regulated; this regulation is in part due to the fact that the pathways all have significant overall negative $\Delta G$ under physiological conditions.