

## Supplement: Review of Negative Feedback Regulation and Water Tank Analogy to Visualize the Regulation of Amounts in Biological Systems

Last semester, you should have learned about regulation and control. These will be major themes this semester and we will begin using these concepts in the first class. These notes present a quick review of important concepts (we will visit all of these ideas within the first week of class) and then presents a useful conceptual model of regulation.

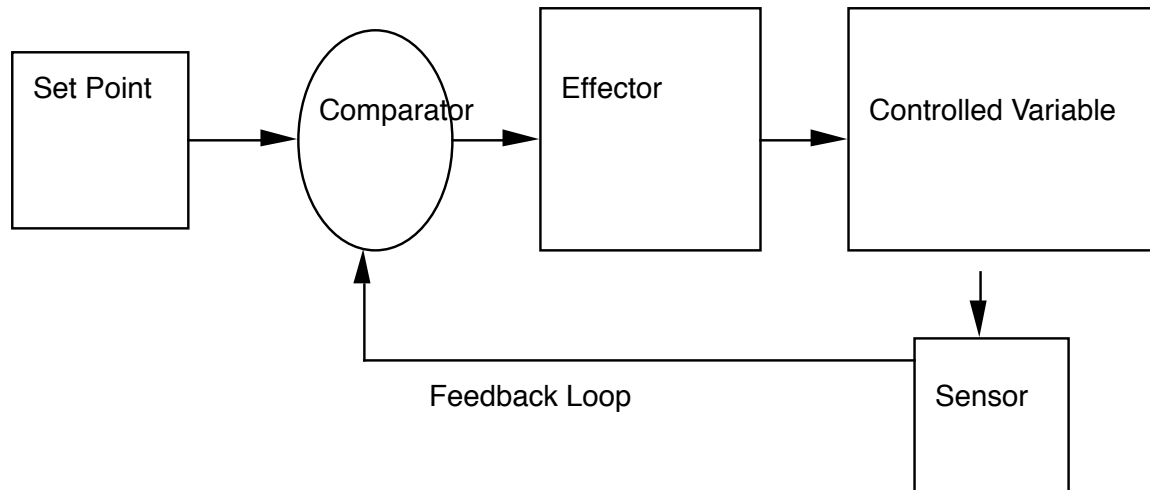
### Review

You have certainly encountered the term **homeostasis** in your previous studies of biology. Recall that the term itself means constant conditions. The physiologist Walter Cannon coined the term in about 1920 and what he had in mind was the ability of animals to, in some cases, precisely control their internal environments in the face of factors that should cause large changes. In fact, no organism is absolutely homeostatic in regards to any important variable but in some cases organisms are quite exacting in their ability to regulate important factors. Although we will not cover it, in other cases organisms simply do not possess the ability to regulate variables, either because they don't need to, because it is expensive metabolically, or because it might actually be better for them not to regulate. So when we consider different species and different physiological factors, we find a continuum from **conformers** who don't regulate at all through all degrees of precision of **regulation** to something that approaches homeostasis. There are advantages to each level of regulation or lack thereof and it is a mistake to always regard homeostasis as the best possible state.

We will see that regulation is achieved using a variety of mechanisms. Chief among these are:

- buffers (this may or may not have to do with  $pH$  -- there are all kinds of buffers);
- chemical and physical equilibria; and
- metabolic pathway regulation where the ability of certain proteins to catalyze crucial reactions is increased or decreased. We will especially focus on this one.

**Regulation and Negative Feedback:** A negative feedback control process is one that **tends to maintain some regulated variable at a more or less preset constant value**. The preset value or range is set by natural selection. Anytime a disturbance occurs to the value, a negative feedback system takes action to return the value to the set point. Here is a schematic of how an engineer would envision negative feedback:



This diagram is quite useful. Let's understand what each of the boxes does:

- **Set Point:** this simply the ideal value for the controlled variable. Its actual value depends on conditions and so it is possible for it change. For example, during exercise we regulate our body temperature at a higher point then when we rest and so the set point changes.
- **Controlled variable:** This is whatever it is that we are regulating. It could be something like the [ATP], body temperature, or blood glucose concentration.
- **Sensor:** something that senses the present value of the controlled variable.
- **Feedback loop:** a pathway to transmit the output of the sensor to the comparator (see next). For example it could relay the present body temperature as detected by neurons in the skin and hypothalamus to the temperature control centers in the brain.
- **Comparator:** something that detects any difference between the set point and the sensed value of the controlled variable. **If there is a difference, an error signal is produced.** This error signal operates the next step in the chain:
- **Effector:** The processes or whatever that change the present value of the controlled variable back towards the set point value. In the case of core body temperature, the effectors include skeletal muscles for shivering, smooth muscles to regulate blood flow, sweat glands, etc.

### The Water Tank Analogy

Above we considered negative feedback during our discussions of the regulation of metabolic pathways (glycolysis). We used an "engineering diagram" to envision how the process works. This short supplement builds on this with a schema for envisioning the regulation of a population of protein or mRNA molecules (or just about anything). This schema incorporates negative feedback but goes beyond that and also shows how total amounts of something can be changed by altering the relative rates of the input process (for example,

synthesis of a protein) and the removal process (breakdown or export). It can easily be expanded and made more complex.

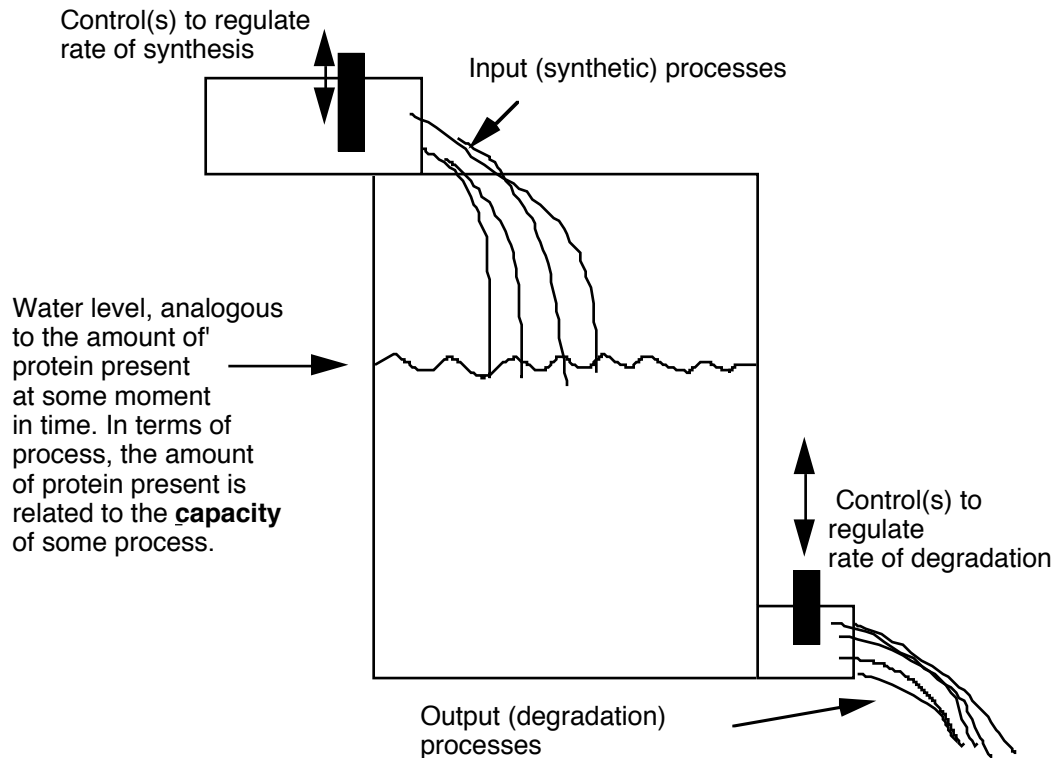
### **The Scheme (Model)**

Proteins are not only be made, but they are also destroyed – no protein in a cell is eternal. The same is true of mRNA. Thus, any specific type of protein and mRNA has a finite lifetime (by contrast, DNA lasts as long as the cell). Thus, the diagram above indicates the processes whereby the number of protein and mRNA molecules can increase but you should also be aware that there are processes that cause both of these to decrease.

Proteins are constantly being broken down into their constituent amino acids. These amino acids are generally used over again to make new proteins, maybe the same type, but more likely, a different type. A number of factors determine how long a protein molecule lasts -- they have to do with the condition of the cell, the type of protein, and the nutritional state of the person (recall that only when someone is starving will they breakdown their own protein molecules to use energy). Messenger RNA molecules tend to last an even shorter period of time. After being used for periods of minutes to several days, they are broken back down to nucleotides and then re-used in the synthesis of new RNA molecules, most likely different from the one they were last in.

A useful analogy for both proteins and mRNA is to think of Gutenberg's invention of moveable type. When a page is type set, we have the analog to a protein or mRNA. When the typeset is broken down, all of the letters (the analogs to amino acids or nucleotides) can be recombined and recycled to produce a new page (new protein or mRNA molecule).

Thus, the amount of a protein that is present in a cell (and for that matter, the amount of mRNA present) is the result of the interplay between synthesis and degradation (just like the relative rates of synthesis and degradation of ATP by demand and supply processes determined how much ATP is in a cell at any moment). The following model is useful:



Notice that as long as the **input rate** equals the **output rate**, that the level (analogous to the number of a particular type of protein molecules in a cell) will remain constant. This model depicts a situation that is termed a **dynamic steady-state**. Dynamic steady-states are characterized by **changing inflows and outflows** but that tend to be matched such that the level remains roughly constant. Thus, in the diagram above, the level will remain constant when the inflow (synthesis) increases provided the outflow also increases by a similar amount.

Dynamic steady -states are very common in the body but we should make one small modification. In the body, dynamic steady-states often involve long term shifts in the level of whatever is under consideration. For instance, training for anaerobic performance will result in increases in the concentration of a number of enzymes such as PFK, LDH, and glycogen synthetase in the trained cells (we'll talk about these soon). The new level is reached by increasing rates of synthesis compared to degradation. A new level is maintained when the rates of synthesis and degradation are once again equal. Detraining (most commonly by reduced activity) will cause the rate of synthesis to decrease compared to degradation; the result is the concentrations of all of these enzymes will decrease (like a decrease in water level in the model just covered). Notice that the usual way that increases or decreases in the level are achieved are by increasing or decreasing the rate of synthesis. Thus, we will focus on what controls protein synthesis but we will keep in mind that there are occasions where the rate of protein degradation can be changed (for example, during calorie starvation -- which will ultimately increase protein degradation).