INTRODUCTION, REGULATION AND CONTROL SYSTEMS[1]

Brief Summary: We start with a brief description of what physiology is and some approaches to its study. We then move on to the central paradigm of physiology -- regulation and learn about the general mechanisms used to achieve regulation -- control (feedback) systems. The concept of homeostasis as one manifestation of regulation is also discussed.

I. INTRODUCTION

Science seeks to explain natural phenomena by framing hypotheses that are predictive, explanatory, and most importantly, testable. In other words, science is the study of **CAUSATION**. There are two ways of looking at causation in biology and with each of these views a certain approach predominates. These have often been termed "proximate and ultimate" but I prefer the more informative terms of **mechanism** (=proximate cause) and **evolutionary history** (= "ultimate cause"). It is useful to know all of these terms.

A. STUDY OF MECHANISM -- PROCESS BIOLOGY -- AND THE USE OF REDUCTIONISM AND EMERGENCE: Studies of **mechanism** seek to elucidate the immediate causes of a process. Accordingly, we also term investigations that look at immediate mechanism as being examples of process biology. These studies describe the events that occur in some process and their relationships one to another and to other processes.

Reductionism is the belief that processes can be explained by reference to more and more "fundamental" processes. For example, a reductionist explains the action of an enzyme by reference to its structure (as with other catalysts). Its structure is in turn determined by specific attractions between molecular groups and by the influences of the physical and chemical environment the enzyme is found in. This in turn can be related to more and more "basic" processes. In the end, an extreme reductionist will claim that all biological phenomena can ultimately be explained by a few basic laws of physics.

Studies of mechanism are usually strongly reductionist, in that they seek explanation and understanding of a process in terms of other immediate processes and in terms of "more fundamental" chemical and physical processes.

EMERGENCE is the belief all of the processes found in a so-called "higher" level of complexity cannot be predicted from an understanding of lower levels of complexity. Some properties "emerge" as a result of increased complexity. Put another way, emergence is the principle that the whole is more than the sum of the parts. We can think of a sort of hard or radical emergence, one that many scientists have trouble accepting and a softer emergence that has many adherents. "Hard emergence" borders on vitalism or mysticism and many seem to understand it as something almost mystical. I would say that the views that some have of the human mind as being more than the sum of the activity of groups of neurons would be "radical emergence". On the

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other hand, the softer version explains that in complex systems many interactions that determine the action of the system are possible; however, only certain ones are realized and it is not evident which ones will be used. This is emergence because the complexity is not easily predictable using a strictly reductionistic approach.

! Whether or not emergence is a real phenomenon (and not simply the result of something we haven't yet noticed) is a hot subject of debate in science, mathematics and philosophy. It is obviously of tremendous theoretical importance for it implies that the radical reductionistic approach favored by many is ultimately limiting.

Process approaches to the phenotype do not answer all questions about the nature of an organism or a biological process. Causation also can be studied at an entirely different level that asks fundamentally different questions:

B. **EVOLUTIONARY HISTORY OF PROCESS:** It is common to see that similar biological problems are solved differently in various organisms. Questions of ultimate causation deal with the reasons for these differences. Particular solutions to physiological problems may be dictated as much by the evolutionary history of a lineage -- the pre-existing structures and processes found in one lineage and not another -- as by the nature of the problem itself. Knowing evolutionary trajectories are often just as important as the laws of physics or chemistry in understanding why structures found in different organisms perform the same functions.

AN ILLUSTRATION OF INVESTIGATION INTO THE PHENOTYPE BY USING PROCESS AND HISTORICAL INVESTIGATIONS: Suppose that we study the coordination of the heart beat. Questions of mechanism would deal with the nature of the action potentials responsible for producing the heart beat -- how they are produced and transmitted.

On the other hand, if we wanted to know why mammals use a myogenic heart (one where the muscle cells of the heart, not the nervous system, produces the coordinating beat) versus the use of a neurogenic heart (where a group of neurons associated with the heart initiate beats), we would be looking at what seems to be primarily a question of history. Both myogenic and neurogenic hearts work well -- it is not a matter of one being inferior compared to the other but instead the result of different evolutionary events in two different lineages. T

II. DEFINITIONS:

A. PHYSIOLOGY DEFINED: establishment of space-time relationships between physical and chemical events within the organism as a response to events both within the organism and in the environment.

? According to this definition, is physiology concerned with the study of mechanism or history?

Notice that physiology is very concerned with examining factors that are readily quantifiable -- degree of perturbation (say the size of some experimental treatment), the magnitude and types of responses, time delays between the stimulus (or perturbation) and response(s). Note also that this approach lends itself strongly to a very quantitative approach. Since we can accurately measure the variables used, we should be able to make very specific predictions as to the outcome of a particular situation. Thus, hypotheses can be tested very rigorously. You will see that physiology is probably the most quantitative area of biology (with the exception of genetics, its equal) you have (or probably will) be exposed to. We will often rely on the construction of **mathematical models** as hypotheses to predict the outcomes of experimental situations. If these models accurately predict the outcome, we will accept them as reasonable tentative working explanations of how things work.

B. MAJOR SUB-DIVISIONS of animal physiology. Let me emphasize that these are very artificial and overlap considerably. One "taxonomy" relies on biological hierarchy of complexity. Thus:

1. CELL PHYSIOLOGY: very self explanatory, it deals with the events that occur within cells and the function of a cell *per se*. It also is concerned with the co-coordinated activities of cells. It tends to be strongly based in biochemistry.

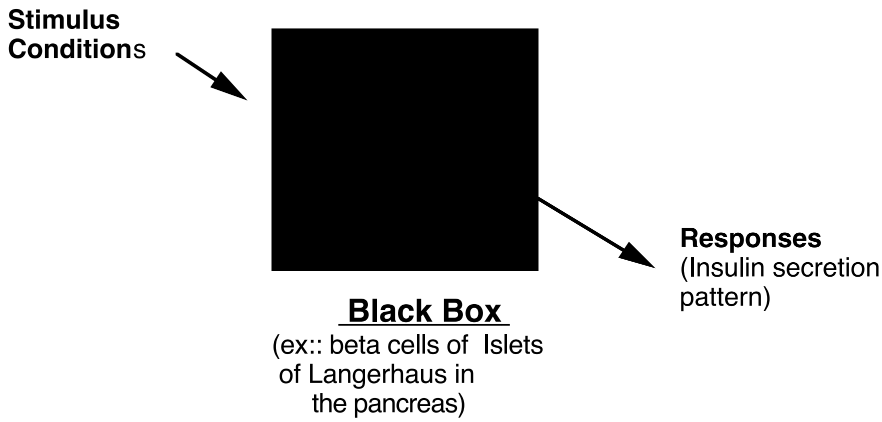
-- The early part of each unit of study in our course will be very much within the realm cell physiology. I am a reductionist at heart. However, we will quickly move from cell to:

2. TISSUE, ORGAN, SYSTEM snd WHOLE ORGANISM PHYSIOLOGY: which deals primarily with the way large groups of different cells (organs) interact with other organs or with how the entire organism behaves a physiological unit. This type of physiology often, but not always, tends towards being highly biophysical in approach and explanation. Whether reference is primarily to chemistry, physics or evolutionary history depends on the system being analyzed and the questions being asked.

a. Due to EMERGENCE (the truth of which we will accept as a working hypothesis for this course) we will be dealing with processes not specifically predicted as a result of cell physiological studies. --

b. In this branch of phys., we tend to treat cells or even organs or organ systems as **BLACK BOXES**.

! A **black box** is something that is only observed on the outside. We know how it responds to a certain set of stimuli, but we do not know (or choose to ignore how) it actually works in producing these responses. A black box is whatever we decide it is -- it may be something that we cannot presently observe due to technical limitations or it could be something that we simply do not wish to investigate in detail at this time -- all we are interested in is its gross behavior and not its inner workings. It may not be important for us to know exactly *how* something happens when we are interested in it as a small part of a larger system. For instance, if I am studying the regulation of plasma glucose in mammals, I may well not be interested in knowing how β-cells of the Islets of Langerhaus of the pancreas actually produce and secrete insulin -- I may instead only be interested in knowing how much insulin is released by the cells in response to some particular set of conditions -- the inner workings of the cell (while important in general) are irrelevant to what I need to know at present (although later it might become very important) and therefore I treat them as a black box:



3. Specific Approaches to Animal Physiology: We will use all of these approaches at different times.

a. Comparative Physiology: studies the underlying physiological similarities and differences of organisms. It is interested in understanding both physiological mechanisms and its practitioners often work strongly within an evolutionary context.

b. Physiological Ecology: primarily concerned with understanding and describing the physiological mechanisms that allow an organism to live in a particular environment -- in other words, the details of physiological systems as adaptations to particular environments.

Our textbook emphasizes both of the approaches above.

c. Mammalian (human) Phys.: emphasis is on medically-related problems, this is the best funded and most workers are in this area. As a result, many of the basic discoveries in physiology occur in this field. It is sometimes derisively called dog, rat and cat physiology since these plus rabbits are the favorite targets of study.

? What types of causation are mammalian phys. and physiological ecology primarily concerned with?
Your textbook is very strongly oriented towards comparative and ecological physiology.

d. **More about approaches to Physiology**: physiology is commonly approached through the eyes of either a chemist or physicist. Most of the biology courses that you have had at Holy Cross have undoubtedly emphasized the chemical approach to understanding life. ***In this course we will use both biochemical and biophysical approaches.***

III.

III. ENGINEERING AND OPTIMALITY

A. We will often tend to take an **engineering viewpoint** towards organisms. However, engineering usually implies some degree of PERFECTION or IDEALITY of design and is OFTEN AIMED AT ONLY ONE PROCESS. While various adaptations may often seem to be excellent, we must remember two things about organisms that reinforce the necessity of taking a whole organism approach:

1. **EVOLUTIONARY HISTORY**: Organisms must use what is already at hand in achieving a physiological adaptation. Structures do not pop out of nothingness. Read the Science article by Jacob about "Evolution and Tinkering" carefully.

2. **Organisms are "MIXED REGIMES"**. Using a structure for one process of necessity may minimize its use for other processes. Thinking of a respiratory organ only in terms of its ability to exchange O_2 may indicate that it is not "perfectly designed" from an engineering standpoint for this function. However, when we realize that this same organ also must exchange CO_2, water and heat or, in the case of some organisms such as clams where it may also be used for feeding, we realize that compromises are required in design. Thus several factors must be considered and weighed in design, or alternatives must be found to avoid negative effects of maximizing one type of function. Thus, evolution appears to **OPTIMIZE** function by weighing these various effects.

IV. The concept of HOMEOSTASIS

A. HISTORY: Observations that organisms were often able to maintain internal states for some variable that were considerably at variance with the environment and further that disease processes were often associated with the lack of an ability to maintain such a difference led the great French physiologist Claude **BERNARD** to state in 1859 that:

"la fixite du milieu interieur est la condition de la vie libre"

roughly, this translates to: "one condition of a free and independent life is a constant internal environment".

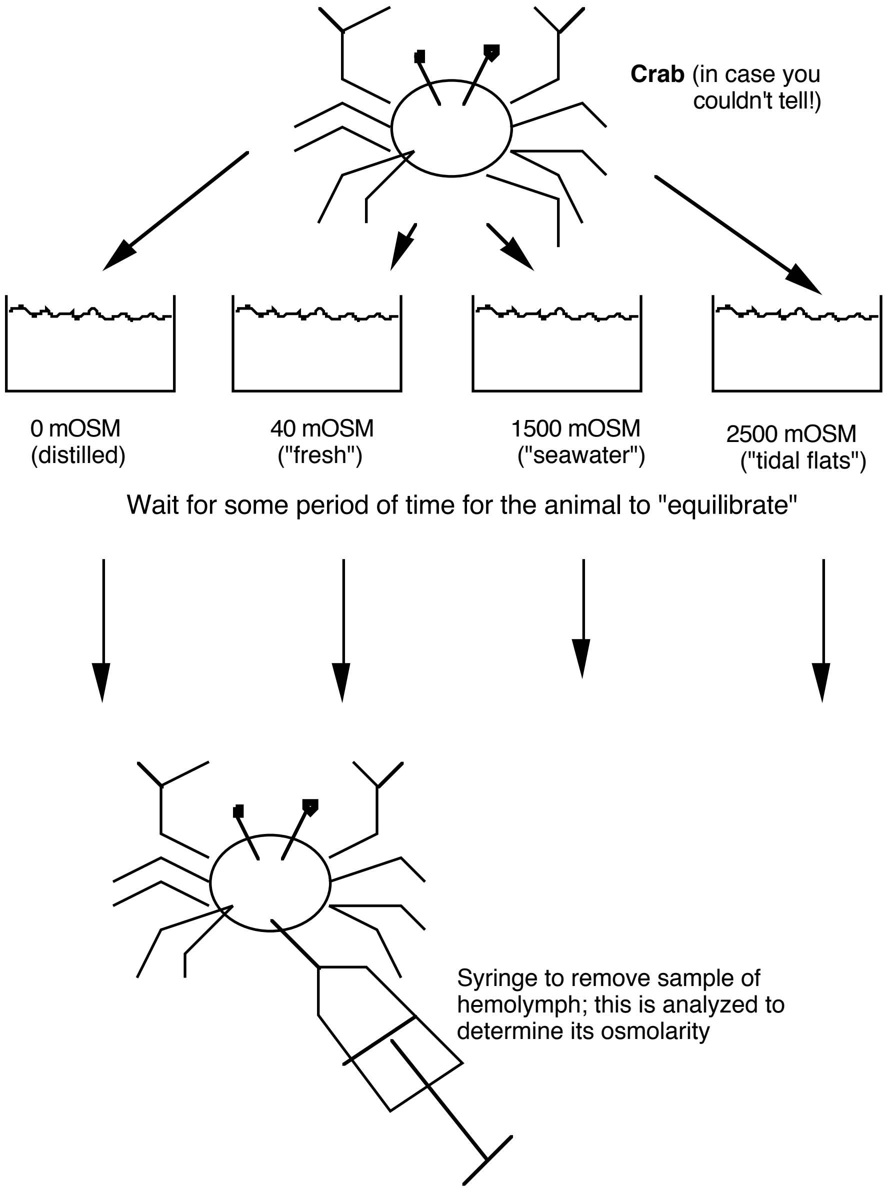
In 1939 **CANNON** coined the term **HOMEOSTASIS** for what Bernard had described. There is a tendency for biologists, especially those trained with a bias towards human biology, to view more precise regulation (true homeostasis) as somehow always better and something indicative of how advanced an organism is. One theme of this course will be to show how foolish this view is -- ***we will learn to view true homeostasis (precise regulation) as one possible solution to the survival game***. Thus, instead of using the term homeostasis, we will talk more often of **REGULATION**. In fact, if there is a central theme in physiology it is the **study of regulatory mechanisms:** that is, the study of the methods an organism uses to produce a certain internal environment.

This earlier belief that perfect homeostasis was the inevitable characteristic of higher organisms owes much to the "ladder of progress" notions of evolution. What do I mean by this?

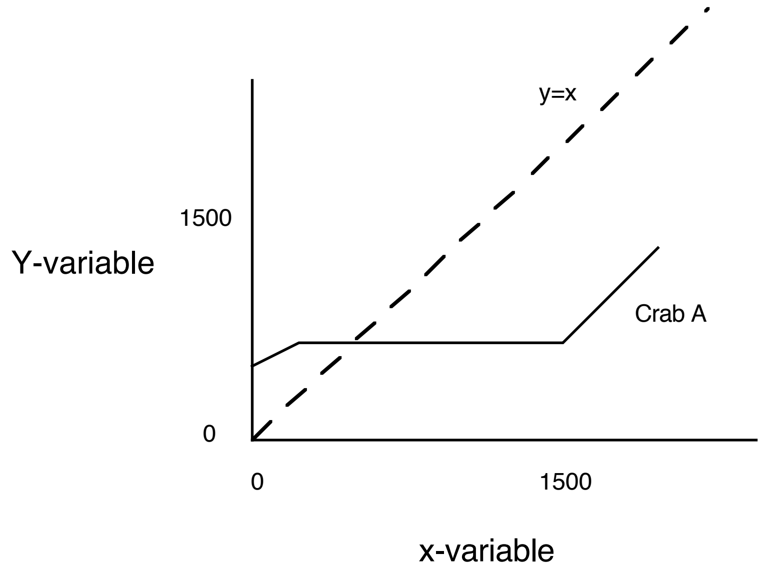
B. AN EXAMPLE: As an example of regulation in different organisms, let's look at the abilities of three different species of crabs to regulate the overall concentration of solutes in their bodies, i.e., their abilities to **OSMOREGULATE**.

Examination of osmoregulatory abilities will require that we put the crabs into a series of different osmotic environments. These will be defined in terms of their concentrations of ions (osmolarity). Since crabs live in or by the sea we will use seawater that has either been diluted or concentrated, much as it would be by rain or evaporation.

We will put the animals into these different water samples and leave them in there long enough for them to reach equilibrium (this may include their reaching the ultimate physiological equilibrium, death). We refer to the time when the animals are being placed in the new environment and when the response is measured as the **EQUILIBRATION TIME**. Conditions to which the animal is exposed are called **AMBIENT CONDITIONS**.

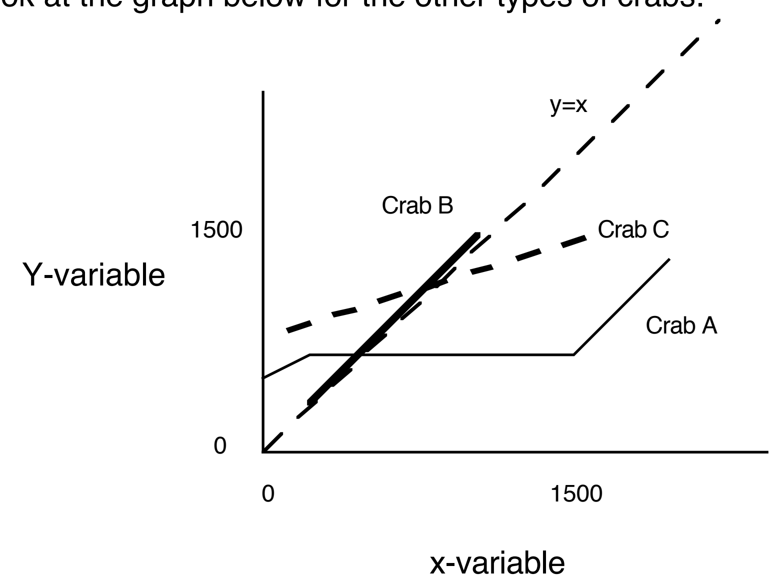


The easiest way to visualize the results of our experiment is to draw a graph that displays the results. Let's suppose that we did this experiment for three different species. Here's the first:



? What are the INDEPENDENT and DEPENDENT VARIABLES in our experiment?

Note the **identity function** where x = y. This is a MODEL FOR THE CASE OF **NO REGULATION**, i.e. **CONFORMITY**. Next look at the graph for species A. Over the range of environmental osmolarity between 40 and 1500 mOSM the concentration of its body fluids remains constant. Thus, over this range it is a **REGULATOR**. Note that outside of this range species A becomes a conformer (its line becomes parallel to the identity line; or in other words, its concentration changes at the same rate as the environment) and that extreme values it dies.
Now look at the graph below for the other types of crabs.



? Are they regulators or conformers?

V. CONTROL SYSTEMS

A. In order to understand regulation, we need to understand control systems. A control system consists of a series of components that work together to control some process. We will identify these components in terms of names commonly applied to them in the specialty of engineering known as control theory. It is important to realize that several components may in some cases reside in a single cell while in other cases many different cells or even tissues may make up one part of a control system.

What is about to follow should not be taken too literally.

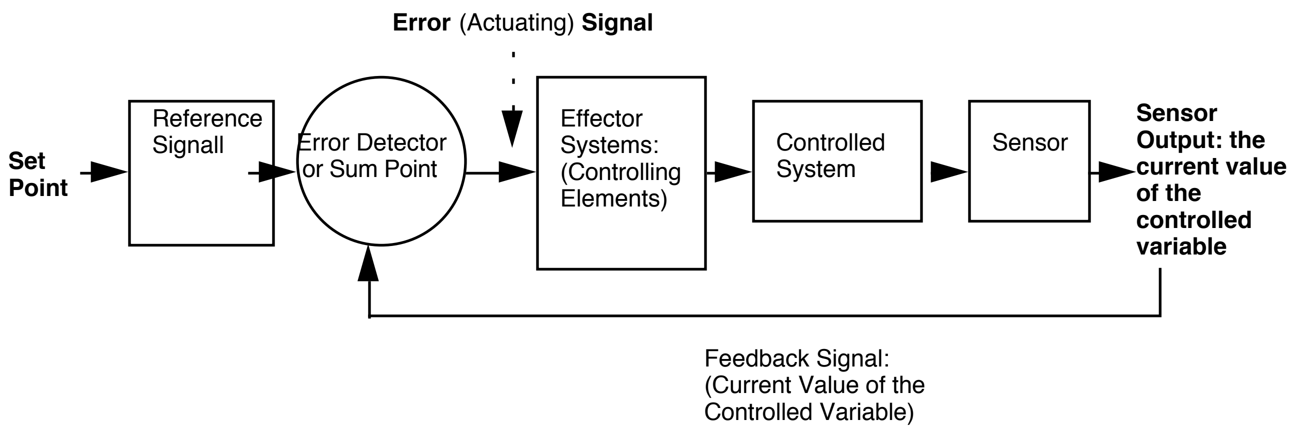
B. Definitions:

1. **CONTROLLED VARIABLE:** the factor that we wish to regulate. In the example above, it would be the osmolarity of the crab's blood. Some type of **SENSOR** monitors the value of the controlled variable and sends this information to an error detector (see below).

2. **SET POINT:** the desired value of the controlled variable. As an example, for alert but not active humans the set point for body temperature is 37º C. The value of the set point is often relayed to a place called the error detector (see below) as a **REFERENCE SIGNAL**.

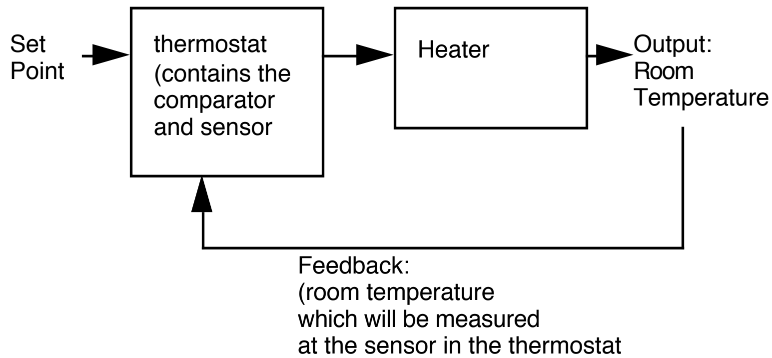
3. **ERROR DETECTOR (COMPARATOR):** a device that compares the value of the controlled variable with the set point. It produces a signal **(ERROR SIGNAL)** that then operates one or more **EFFECTOR SYSTEMS**.

The Elements of a Typical Control System



Now let's use the most common example and easiest for most to understand, heating a house. In this case, the controlled variable is the room temp., the set point is selected by the inhabitants of the room and the comparator is the thermostat. When a difference between the room temp. and the set point is measured an error signal is produced that goes to activate the effector (furnace) and thereby increase the room T. Finally, when the room is back to normal T, the error signal stops. Let's draw the system:

A System forControlling (or simply changing) Room Temperature. It will be a negative feedback system if it keeps temperatures at constant values; positive if it pushes the temerature away from the previous value.



Note how one device (in this case the thermostat) may take on several of the functions outlined in the previous figure. Groups of cells involved in feedback systems in organisms often perform more than one of these system functions.
Normal room temperature control systems such as the one shown above are examples of CLOSED LOOP NEGATIVE FEEDBACK SYSTEMS. Let's define these:

a. **NEGATIVE FEEDBACK SYSTEM:** The control system acts to minimize any deviation of the controlled variable from the set point. Any deviation results in a response that tends to return the system to the set point.

b. **CLOSED LOOP SYSTEM:** A system that monitors and affects the same variable, for example; room temperature is monitored and then increased or decreased. By contrast an OPEN LOOP system monitors a different variable from the one it controls; for instance controlling room temperature by monitoring outside temperature. Open loop systems are not very important in physiology.

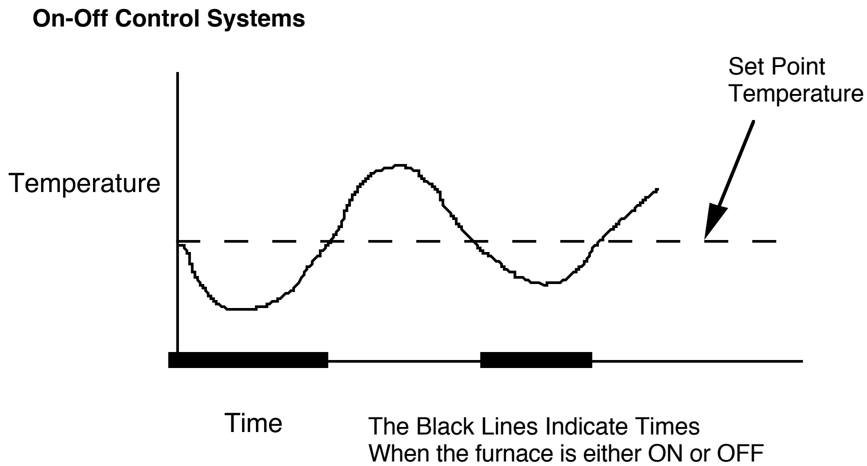
4. An opposite type of control system: **POSITIVE FEEDBACK.** In positive feedback systems a **stimulus tends to push the value of the controlled variable further and further from the original set point**. These systems are less common in physiological systems but are nevertheless quite important. Example: the posterior pituitary hormone of mammals OXYTOCIN. It is involved in two + feedback systems. At birth, a signal that causes initial weak uterine contractions. These contractions cause the baby's head to push against the cervix where stretch receptors send messages to the brain which cause the release of more oxytocin. In response to the oxytocin, stronger contractions occur, causing more stretching and further release of oxytocin. The entire process continues until the child is born. The absence of stretch breaks the positive feedback loop. A similar process occurs during nursing with the LET-DOWN REFLEX in nursing. Here, suckling causes oxytocin to be released. The oxytocin then stimulates contraction of smooth muscles lining the areas where milk is stored and forcing it towards the nipple the process continues until the infant stops feeding.

8. RESPONSE OR SENSING PATTERNS: Positive and negative feedback systems may use a number of different patterns of response or sensing processes to achieve control. **In physiological systems, typically several of these are merged to give precise control over some variable. As always, keep in mind that each of these patterns is a human intellectual construct and any "real" system will probably only have some of its attributes; it might also have some attributes of several different types of sensing patterns**.

For all response types, assume some disturbance has occurred to the regulated variable

a. **ON- OFF:** most like the regulation of room temp, where the furnace is either on or off.

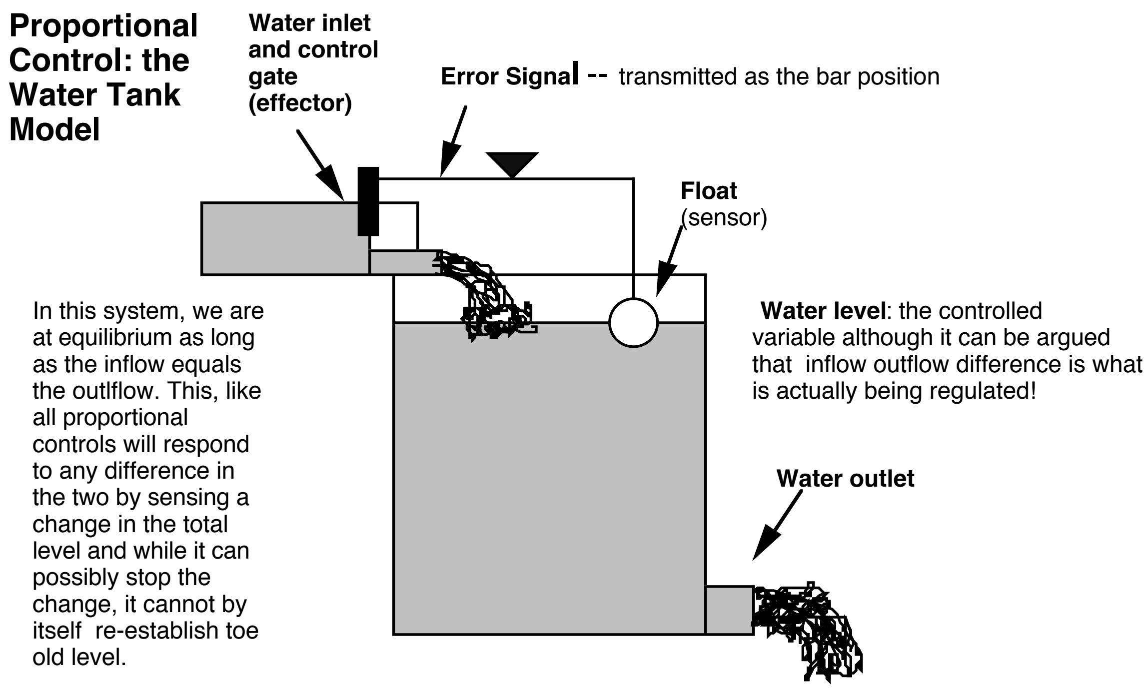
1. Oscillates, does not reach a steady state.
2. Can return the system to the original set point (although usually only momentarily).



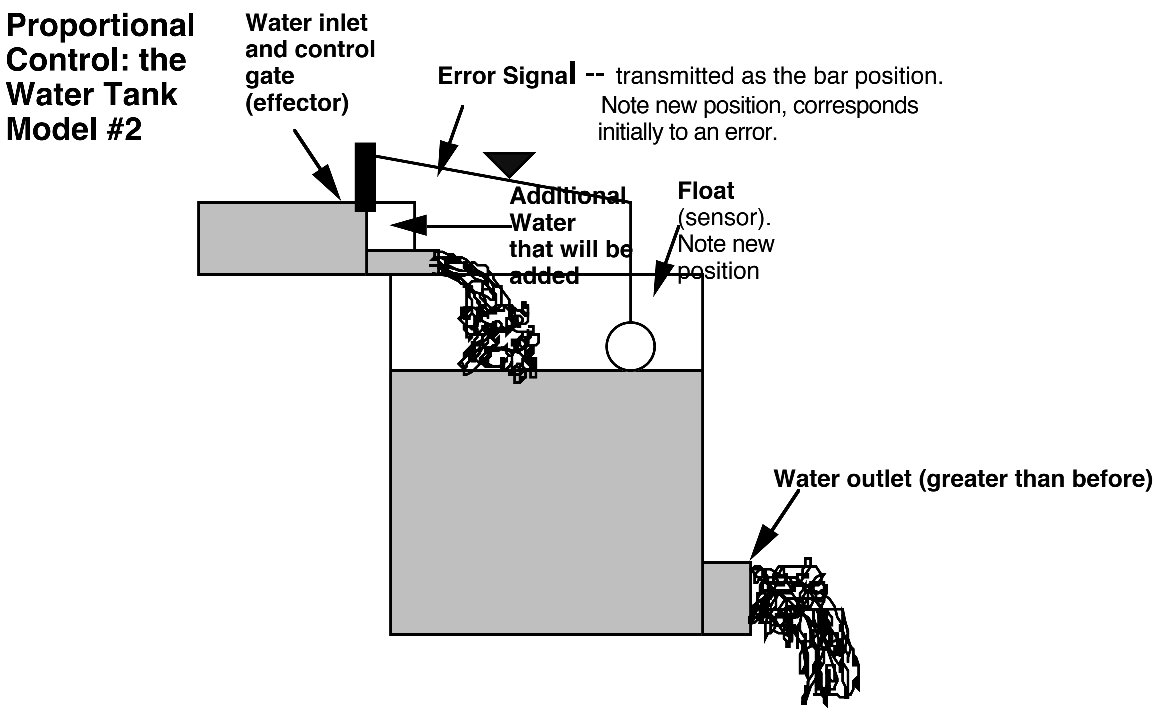
3. The stability of an on - off system (size of oscillations) is a function of the sensitivity of the sensors and fineness of response of the effectors. Stability can be enhanced through the action of **ANTAGONISTIC SYSTEMS** where two systems work in opposition to each other. Ex.: controlling room temperature with air conditioning and a heater.

No system that I can think of works exactly like an on-off system where we go from no response to full response (black bars on x axis of previous graph). However, many systems do have the characteristic of response threshold and saturation -- no response to signals below a certain level and no further response after a certain level is reached (the system has reached its capacity). However, there is a range of responses in between so let's look at the other modes of controls used by engineers as partial analogies to what happens in organisms.

b. **PROPORTIONAL CONTROL:** Where **there is a linear relationship between the degree of the error signal and the size of the response**. Example: a tub full of water controlled by a float: if more water leaves the tub, the float drops further and causes more water to enter via the input:



1. Proportional systems QUICKLY REACH A NEW STEADY-STATE BUT BY THEMSELVES THEY CANNOT BRING THE SYSTEM BACK TO THE ORIGINAL SET POINT. For example: say the water flow increases from the tub (a disturbance). The float drops and water input increases until it equals the outflow. At this point there is a steady-state but no return to the original value (see next page).



2. To actually return the system to the original set point, an even larger error signal is needed, but a proportional controller cannot produce it. So, proportional controllers must operate with another type of system if return to the original set point is required.

c. **INTEGRAL CONTROL SYSTEM:** the response is proportional to the time integral of some variable ($\int X dt$). Thus if a constant very small disturbance (such as an accumulation of a metabolite) is introduced, this system detects the error and adds it over time; if a certain threshold is reached, then the control system is triggered. It is useful for detecting and rectifying small errors that occur over time or it can also be used to time events. For instance, some trees determine when to drop their leaves by slowly manufacturing chemicals each day. These gradually accumulate and when they reach a certain amount, they help to trigger to events associated with the fall.

d. **DERIVATIVE CONTROL ACTION (RATE CONTROL):** responds to the rate of change of the controlled variable (dV/dt). Thus, the faster the change, the greater the response. It is useful in conjunction with some other method of control such as a proportional controller. *Derivative control systems anticipate the size of the response needed but they have a tendency to over or undershoot since their response is based on the rate of change and not the actual deviation from the set point.*

? Blood plasma glucose level is important since its value helps determine the concentration gradient for the entry of glucose into many types of cells. If it is too low, cells cannot get adequate glucose while if it is too high, damage results from a number of causes (to be discussed later in lab).

Given that glucose can be added to the blood from the liver and it can be removed by a number of tissues, primarily the muscles, brain, and fat cells:

Discuss how glucose can be regulated when the demand for it can change rapidly with time. Make your discussion in terms of control systems that could or couldn't be used by the body. Do not look up the types of hormones the body actually uses -- you be the engineer.