Terms you should know: mechanistic explanation, teleological explanation, correlation, necessity, sufficiency, "milieu interior," homeostasis, allostasis, input signal, output signal, independent variable, dependent variable, feedback system, negative feedback, controlled variable, sensor, set point, comparing unit, controller, neutral (dead) zone, high-gain, low-gain, positive feedback, perturbation, indirectly controlled component, control, regulation.

I. Physiology as a science.
   A. Physiology is the study of the function of organ systems and how they interact.
      1. It depends on knowing molecular and cell biology, as well as physics and chemistry.
      2. It emphasizes the interactions among cells, tissues, and organs.
   B. Like any science, Physiology can explain how things happen, not why they happen.
      1. **Mechanistic explanation**: addresses mechanisms that cause the effect. It answers questions that ask “How....”
          a. These explanations discuss events that happened before the observation being explained.
          b. Here are two examples:
             i. The mammalian heart rate increases when sympathetic neurons innervating heart muscle fibers increase their firing rate.
             ii. A neuron produces an action potential when voltage-gated sodium channels open.
      2. **Teleological explanation**: addresses the consequences of an event. (Telos means "end," and a teleological explanation is based on the ends--or effects--of the event). These explanations answer “Why....” questions.
          a. This kind of explanation focuses on events that follow in time the thing you are explaining.
          b. Here are two examples:
             i. Running makes your heart rate increase because your muscles need more oxygen.
             ii. Neurons produce action potentials because they need to send signals over long distances.
      3. Be sure to give mechanistic explanations, not teleological ones, in this course!
   D. Experimental science looks for causal relationships: does A cause B? It uses 3 major approaches:
      1. **Correlation**: A and B occur in a particular order (A then B) under many conditions; for example:
          a. The light switch is up whenever the light is on.
          b. Whenever there is electrical activity in the PBN in a rat’s brain, the rat inhales.
      2. **Necessity** (or “inhibition” or “ablation” or “knock out”): when A is eliminated, B never occurs.
          a. If you disable the light switch with the light off, the light never goes on.
          b. If you anesthetize the PBN in a rat’s brain, the rat stops inhaling.
      3. **Sufficiency** (or “activation”): with everything else held constant, turning on A produces B.
          a. Flipping the light switch up and down turns the light on and off.
          b. If you electrically stimulate the rat’s PBN at a faster rate, it inhales at the faster rate.
      4. From these experiments, we conclude: the light switch turns on the light the rat’s PBN controls inhalation.
      5. Further experiments could show that these conclusions are incomplete, or even wrong, either because the experiment was done badly or because of incomplete information.
II. The focus of this class will be on physiological systems—that is, how different parts of the body work together to regulate normal function.

A. **Rene Descartes** (17th century French mathematician, philosopher, and physiologist), explained reflexes (e.g., pulling one’s finger away from a flame, **Fig. 1.1**) as mechanisms to control the body’s well-being.

- the mechanism was wrong, but the concept was right.

B. A 19th century, French physiologist named **Claude Bernard** found evidence that conditions inside an animal’s body are often quite different from conditions outside the body. He wrote, “The constancy of the internal environment ("milieu intérieur") is required for a free and independent life”
  - Example: the temperature inside your body is currently ~25-30°F higher than the room air.
  - Another example: your blood [Na⁺] is nearly the same whether you drink distilled or salty water.

C. A 20th century American physiologist named **Walter Cannon** studied many complex mechanisms that animals use to maintain the inside of their bodies in a different state from the external world.
  1. He called the maintenance of relatively constant internal conditions **homeostasis**.
     (from Latin “homeo” meaning “alike”, or “same” and Greek “stasis” meaning “remains in place”.)
  2. In fact, there normally are variations in all physiological measures over time, but in a healthy animal, the variations are relatively small and the average value remains constant.

D. Today, physiologists also talk about **allostasis**, because physiological values can change as conditions change
   a. For example, heart rate and body temperature go up during vigorous exercise.
   b. The new value is still very much under control; it is controlled around this new value.

E. The major mechanism for maintaining a variable at a nearly constant value is **negative feedback**.

III. Feedback systems allow the output of a system to control its own state.

A. **Feedback system**: the interacting components of a system are arranged in a closed loop (**Fig. 1.2**).

1. The *direction* of the arrows indicates causality. For example, the value of Component #1 affects the value of Component #2, but Component #2 does not affect Component #1 directly.

2. The sign on each arrow tells whether one component increases or decreases the next one.
   a. A + sign indicates that the two components change in the same direction: if #1 decreases, #2 also decreases; if #1 goes up, #2 goes up. In other words, #1 turns on #2.
b. A - sign indicates that the two components change in opposite directions: if #3 decreases, #1 increases; if #3 goes down, #1 goes up. In other words, #3 turns off #1.

3. What the signs on each arrow really means (Fig. 1.3):
   a. The arrow pointing into the box is the input signal.
   b. The line coming out of a box is the output signal.
   c. Graphically, the input is an independent variable, and is plotted along the X axis, and the output is a dependent variable, and is plotted along the Y axis.

   ![Fig. 1.3](image)

   d. A + sign on the input arrow means a positive slope: increasing I increases O
      decreasing I decreases O

   ![Fig. 1.4](image)

   e. A – sign on the input arrow means a negative slope: increasing I decreases O
      decreasing I increases O

   ![Fig. 1.5](image)

   f. In fact, most plots of biological systems are actually sigmoids rather than straight lines; mostly, for convenience, we approximate the relationships as straight lines.

   g. A positive sign on the input arrow keeps the sign of the output signal the same as the input signal, whereas a negative sign on the input arrow inverts the sign of the signal.
B. Variables in a loop remain at nearly constant values if they form a **negative feedback loop**.
   1. All negative feedback loops have an odd number of negative signs (also called “signal inversions”).
   2. One familiar example of a negative feedback loop is the thermostat on the furnace in your house, which illustrates many aspects of negative feedback (Fig. 1.6).

![Diagram of a negative feedback loop]

3. Components of a negative feedback system:
   a. **Controlled variable** (e.g., air temperature)
   b. **Sensor** (e.g., thermometer)
   c. **Comparing unit**, which compares the output of the sensor to a **set point** (e.g., together, these two elements—the set point and the comparing unit—are a thermostat).
   d. **Controller** (e.g., the furnace) is affected by the output of the comparing unit in two ways:
      i. If the set point is higher than the thermometer reading (i.e., the room is cooler than the thermostat setting), the comparing unit provides positive input to the controller (the furnace), which turns it on.
         --when the controlled variable (the air temperature) is **too low**, the system increases it.
      ii. The furnace (controller) generates heat until the sensed temperature is higher than the set point (i.e., the air is warmer than the thermostat setting) so that the output of the comparing unit provides negative input to the controller and turns off the furnace.
         --when the temperature is **too high**, the feedback loop no longer functions, unless the air temperature once again cools down to a temperature that is lower than the set point.
4. However, we can keep a room cool, too, by using an air conditioner (Fig. 1.7)

![Diagram of air conditioning system](image)

- A major difference between the air conditioning system and the furnace system is that turning on the air conditioner decreases the air temperature, rather than increasing it.

- In addition, the logic of turning on the air conditioner is the reverse of the furnace system:
  - if the sensed temperature is higher than the set point, the air conditioner turns on;
  - if the sensed temperature is lower than the set point, the air conditioner turns off.

5. The furnace and air conditioner loops can be combined in a single diagram (Fig. 1.8).

![Diagram of combined furnace and air conditioner system](image)

- The loops are analyzed by following the arrows around from any point back to the same point.

- **Neutral zone** (or **dead zone**): a maintained, narrow range of the controlled variable (in this case, the room temperature) produced by adjusting the comparing units properly (e.g., there could be a gap between the set point for the furnace and the set point for the air conditioner).
6. Our bodies have a similar kind of control: we shiver when our body temperature is too low, and we sweat when our body temperature is too warm (Fig. 1.9):

- The nervous system forms the sensor, the comparing unit, the set point, and the output to the controllers.
- The controlled variable is the temperature of the body, not the environmental temperature.

7. Some general conclusions about negative feedback systems:
   a. Major importance: they resist changes of the controlled variable.
   b. How to identify the controlled variable
      i. It tends to have the smallest change in value.
      ii. It usually has a specialized sensor.

8. The set point is not always constant.
   a. If you turn up the thermostat (i.e., you increase the value of the set point), the system will generate heat to bring the room temperature to the new set point value.
   b. Fever works the same way: bacterial or viral toxins reset the set point to a higher level.
      i. Physiological mechanisms (like shivering) then hold the body temperature at the higher level.
      ii. That’s why you shiver when you get a fever—your body is adjusting to the higher set point.
   c. **Allostasis**: physiological variation in set points.
      An example: our body temperature increases during exercise; if we try to cool off too fast, we might start shivering at what previously was the normal body temperature, because the set point (the comfortable body temperature) has gone up.

9. **Feedback loops** can vary in their **effectiveness** (also called their **gain**):
   • **low-gain** loops (imagine a room heater in a gym) only weakly affect the value of the controlled variable.
   • **high-gain** loops (imagine a huge furnace providing heat to a small office) very strongly control the value of the controlled variable.
   • In most physiological systems, multiple feedback loops usually act on the same physiological variable: usually, some are faster than others and some have higher gain.
C. Positive feedback loops drive the value of the controlled variable to its highest or lowest extreme. In physiological systems, either positive feedback is controlled by some other variable or it is pathological.

1. In a positive feedback loop there are either no negative signs (Fig. 1.10),

2. or there are an even number of negative signs (Fig. 1.11):

   This one has two negative signs that effectively cancel each other:

3. A real-world example: what if an electrician replaced the thermostat in Fig. 1.11, but got the wires to the furnace and the air conditioner backward:

4. In all the examples of positive feedback systems so far, if one of the components changes, all of the components change in the same direction until they reach a limiting value.
   a. Normally, positive feedback is dangerous (heat stroke is an example).
   b. We will run into a couple of cases, later in the course, where positive feedback is beneficial.

5. Perturbation: a signal that is not part of the loop but affects a loop component (Fig. 1.12).
a. You can use perturbations to test for positive and negative feedback loops:
   (1) Perturb one component; e.g., increase component #3.
   (2) Follow the arrows around the loop, counting up the negative signs.
      • if there are 0 or an even number of negative signs, it is a positive feedback loop.
      • if there are an odd number of negative signs, it is a negative feedback loop.

b. Because perturbations are outside the loop, they are not affected by feedback.

5. Indirectly controlled component: a component that is affected by a signal in the loop but does not provide feedback; therefore, it is not part of the loop itself.

   • An example of an indirectly controlled component (Fig. 1.13). The value of Component #4 in this diagram changes if the value of #3 changes, but the value of #4 has no effect on any component in the loop.

IV. Some generalities about physiological control systems.

A. The difference between control and regulation
   • control: if A causes B to do something, we say that “A controls B”.
   • regulation: the property of a system to keep its parameters within bounds.
     means the same as “homeostasis”.

A. By having multiple controllers, under the influence of different comparing units, many physiological variables (e.g., blood pressure, carbon dioxide levels in the blood, body weight) are maintained relatively constant in the face of large changes in the environment.

B. In most physiological systems, the components (i.e., the boxes) in the loops are organs or parts of organs, and the signals (i.e., the arrows) are carried by nerves or by blood (either hormones or some other component of blood; sometimes it is the blood temperature, pH, or concentration of ions or metabolites that constitute the signal).

C. The signals vary greatly in how fast they act. In general, the rate of their action depends on how the signals are carried:
• nervous system = tens to hundreds of milliseconds.
• peptide hormones = minutes to hours
• steroid hormones = hours to days