1

Introduction

1.1 PRELIMINARY CONSIDERATIONS

A *control system* may be defined as a collection of interconnected components that can be made to achieve a desired response in the face of external disturbances. The "desired response" could be the tracking of a specified dynamic trajectory, in which case the control system takes the form of a *servomechanism*. An example of this type of control system is a robot arm that is programmed to grasp some object and to move it to a specified location. There is a second class of control system termed the *regulator*, for which the "desired response" is to maintain a certain physical quantity within specified limits. A simple example of this kind of control system is the thermostat.

There are two basic ways in which a control system can be made to operate. In *open-loop* mode, the response of the system is determined only by the controlling input(s). As an example, let us suppose that we wish to control the temperature of a room in winter with the use of a fan-heater that heats up and circulates the air within the room. By setting the temperature control to "medium," for instance, we should be able to get the room temperature to settle down to an agreeable level during the morning hours. However, as the day progresses and the external environment becomes warmer, the room temperature will also rise, because the rate at which heat is added by the fan-heater exceeds the rate at which heat is dissipated from the room. Conversely, when night sets in and the external temperature falls, the temperature in the room will decrease below the desired level unless the heater setting is raised. This is a fundamental limitation of open-loop control systems. They can perform satisfactorily as long as the external conditions do not affect the system much. The simple example we have described may be considered a physical analog of thermoregulatory control in *poikilothermic* or "cold-blooded" animals. The design of the thermoregulatory processes in these animals does not allow core body temperature to be maintained at a level independent of external conditions; as a consequence, the animal's metabolism also becomes a function of external temperature.

Coming back to the example of the heating system, one way to overcome its limitation might be to anticipate the external changes in temperature and to "preprogram" the temperature setting accordingly. But how would we know what amounts of adjustment are required under the different external temperature conditions? Furthermore, while the external temperature generally varies in a roughly predictable pattern, there will be occasions when this pattern is disrupted. For instance, the appearance of a heavy cloud cover during the day could limit the temperature increase that is generally expected. These problems can be eliminated by making the heater "aware" of changes in the room temperature thereby allowing it to respond accordingly. One possible scheme might be to measure the room temperature, compare the measured temperature with the desired room temperature, and adjust the heater setting in proportion to the difference between these two temperatures. This arrangement is known as *proportional feedback control*. There are, of course, other control strategies that make use of the information derived from measurements of the room temperature. Nevertheless, there is a common feature in all these control schemes: they all employ *feedback*. The great mathematician-engineer, Norbert Wiener, characterized feedback control as "a method of controlling a system by reinserting into it the results of its past performance." In our example, the system *output* (the measured room temperature) is "fed back" and used to adjust the *input* (fan speed). As a consequence, what we now have is a control system that operates in *closed-loop* mode, which also allows the system to be *self-regulatory*. This strategy of control is ubiquitous throughout Nature: the physiological analog of the simple example we have been considering is the thermoregulatory control system of *homeothermic* or "warm-blooded" animals. However, as we will demonstrate throughout this book, the exact means through which closed-loop control is achieved in physiological systems invariably turns out to be considerably more complicated than one might expect.

1.2 HISTORICAL BACKGROUND

The concept of physiological regulation dates back to ancient Greece (~ 500 BC), where the human body was considered a small replica of the Universe. The four basic elements of the Universe—air, water, fire, and earth—were represented in the body by blood, phlegm, yellow bile, and black bile, respectively. The interactions among pairs of these elements produced the four irreducible qualities of wetness, warmth, dryness, and cold. It was the harmonious *balance* among these elements and qualities that led to the proper functioning of the various organ systems. The Greek physician, Galen ($\sim$2nd century AD), consolidated these traditional theories and promoted a physiological theory that was largely held until the end of the 16th century. Similar concepts that developed alongside the Taoist school of thought may be traced back to the 3rd century BC in ancient China. Here, the Universe was composed of five agents (*wuxing*): wood, fire, earth, metal, and water. These elements interacted with one another in two kinds of way. One was a productive relationship, in which one agent would enhance the effects of the other. The other was a limiting or destructive relationship whereby one agent would constrain the effects of the other. As in the Graeco-Roman view, health was maintained by the harmonious balancing of these agents with one another.

The notion of regulatory control clearly persisted in the centuries that followed, as the writings of various notable physiologists such as Boyle, Lavoisier, and Pflüger demonstrate. However, this concept remained somewhat vague until the end of the 19th century when French physiologist Claude Bernard thought about self-regulation in more precise terms. He noted that the cells of higher organisms were always bathed in a fluid medium, e.g., blood or lymph, and that the conditions of this environment were maintained with great stability in the

face of disturbances to the overall physiology of the organism. The maintenance of these relatively constant conditions was achieved by the organism itself. This observation so impressed him that he wrote: "It is the fixity of the '*millieu interieur*' which is the condition of free and independent life." He added further that "all the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment." In the earlier half of this century, Harvard physiologist Walter Cannon refined Bernard's ideas further and demonstrated systematically these concepts in the workings of various physiological processes, such as the regulation of adequate water and food supply through thirst and hunger sensors, the role of the kidneys in regulating excess water and the maintenance of blood acid–base balance. He went on to coin the word *homeostasis* to describe the maintenance of relatively constant physiological conditions. However, he was careful to distinguish the second part of the term, i.e., "stasis", from the word "statics," since he was well aware that although the end result was a relatively unchanging condition, the coordinated physiological processes that produce this state are highly dynamic.

Armed with the tools of mathematics, Wiener in the 1940s explored the notion of feedback to a greater level of detail than had been done previously. Mindful that most physiological systems were nonlinear, he laid the foundation for modeling nonlinear dynamics from a Volterra series perspective. He looked into the problem of instability in neurological control systems and examined the connections between instability and physiological oscillations. He coined the word "cybernetics" to describe the application of control theory to physiology, but with the passage of time this term has come to take on a meaning more closely associated with robotics. The race to develop automatic airplane, radar, and other military control systems in the Second World War provided a tremendous boost to the development of control theory. In the postwar period, an added catalyst for even greater progress was the development of digital computers and the growing availability of facilities for the numerical solution of the complex control problems. Since then, research on physiological control systems has become a field of study in its own, with major contributions coming from a mix of physiologists, mathematicians, and engineers. Pioneering works in "modern" physiological control systems analysis include Grodins (1963), Clynes and Milsum (1970), Milsum (1966), Bayliss (1966), Guyton, Jones and Coleman (1973), Stark (1968) and Milhorn (1966), to name a few.

1.3 SYSTEMS ANALYSIS: FUNDAMENTAL CONCEPTS

Prior to analyzing or designing a control system, it is useful to define explicitly the major variables and structures involved in the problem. One common way of doing this is to construct a *block diagram*. The block diagram captures in schematic form the relationships among the variables and processes that comprise the control system in question. Figure 1.1 shows block diagrams that represent open-loop and closed-loop control systems in canonical form. Consider first the open-loop system (Figure 1.1a). Here, the *controller* component of the system translates the input (r) into a controller action (u), which affects the *controlled system* or "*plant*" thereby influencing the system output (y). At the same time, however, external disturbances (x) also affect plant behavior; thus, any changes in y reflect contributions from both the controller and the external disturbances. If we consider this open-loop system in the context of our previous example of the heating system, the heater would be the controller and the room would represent the plant. Since the function of this control system is to regulate the temperature of the room, it is useful to define a *set-point*, which would
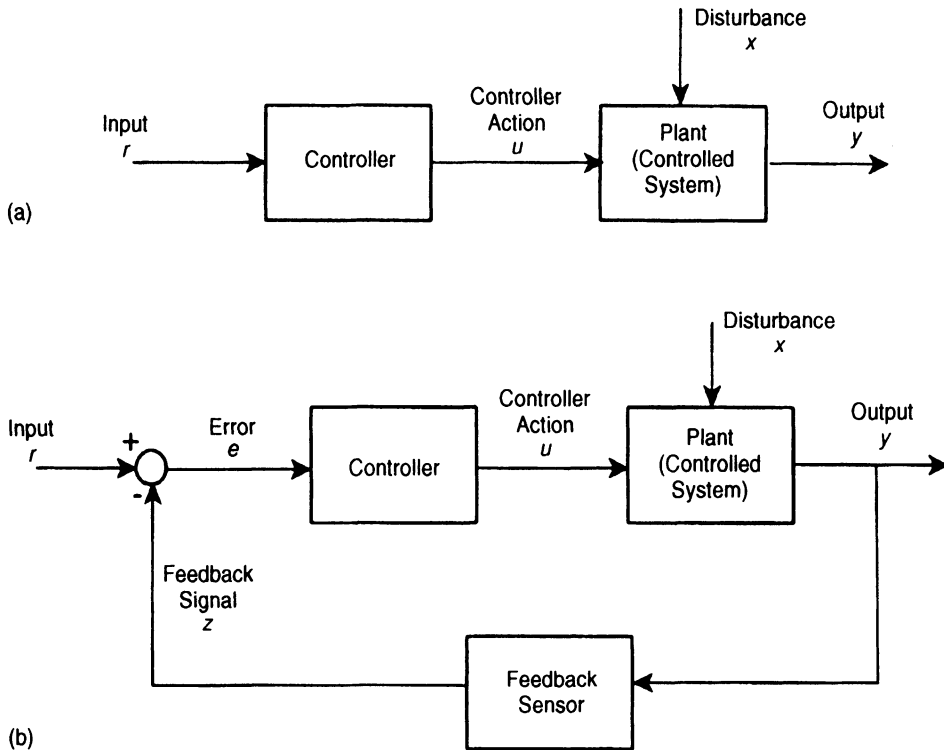
Figure 1.1   Block diagrams of (a) an open-loop control system and a (b) closed-loop control system (bottom).

correspond to the desired room temperature. In the ideal situation of no fluctuations in external temperature (i.e., $x = 0$), a particular input voltage setting would place the room temperature exactly at the set-point. This input level may be referred to as the *reference input value*. In linear control systems analysis, it is useful (and often preferable from a computational viewpoint) to consider the system variables in terms of *changes* from these reference levels instead of their absolute values. Thus, in our example, the input (r) and controller action (u) would represent the deviation from the reference input value and the corresponding change in heat generated by the heater, respectively, while the output (y) would reflect the resulting change in room temperature. Due to the influence of changes in external temperature (x), r must be adjusted continually to offset the effect of these disturbances on y.

As mentioned earlier, we can circumvent this limitation by "closing the loop." Figure 1.1b shows the closed-loop configuration. The change in room temperature (y) is now measured and transduced into the feedback signal (z) by means of a feedback sensor, i.e., the thermostat. The feedback signal is subsequently subtracted from the reference input and the error signal (e) is used to change the controller output. If room temperature falls below the set-point (i.e., y becomes negative), the feedback signal (z) would also be negative. This feedback signal is subtracted from the reference input setting ($r = 0$) at the *mixing point* or *comparator* (shown as the circular object in Figure 1.1b), producing the error signal (e), which is used to adjust the heater setting. Since z is negative, e will be positive. Thus, the heater setting will be raised, increasing the flow of heat to the room and consequently raising the room temperature. Conversely, if room temperature becomes higher than its set-point, the

feedback signal now becomes positive, leading to a negative error signal, which in turn lowers the heater output. This kind of closed-loop system is said to have *negative feedback*, since any changes in system output are compensated for by changes in controller action in the *opposite direction*.

Negative feedback is the key attribute that allows closed-loop control systems to act as regulators. What would happen if, rather than being subtracted, the feedback signal were to be *added* to the input? Going back to our example, if the room temperature were to rise and the feedback signal were to be added at the comparator, the error signal would become positive. The heater setting would be raised and the heat flow into the room would be increased, thereby increasing the room temperature further. This, in turn, would increase the feedback signal and the error signal, and thus produce even further increases in room temperature. This kind of situation represents the *runaway* effect that can result from *positive feedback*. In lay language, one would refer to this as a *vicious cycle* of events. Dangerous as it may seem, positive feedback is actually employed in many physiological processes. However, in these processes, there are constraints built in that limit the extent to which the system variables can change. Nevertheless, there are also many positive feedback processes (e.g., circulatory shock) that in extreme circumstances can lead to the shut-down of various system components, leading eventually to the demise of the organism.

1.4 PHYSIOLOGICAL CONTROL SYSTEMS ANALYSIS: A SIMPLE EXAMPLE

One of the simplest and most fundamental of all physiological control systems is the *muscle stretch reflex*. The most notable example of this kind of reflex is the *knee jerk*, which is used in routine medical examinations as an assessment of the state of the nervous system. A sharp tap to the patellar tendon in the knee leads to an abrupt stretching of the extensor muscle in the thigh to which the tendon is attached. This activates the muscle spindles, which are stretch receptors. Neural impulses, which encode information about the magnitude of the stretch, are sent along afferent nerve fibers to the spinal cord. Since each afferent nerve is synaptically connected with one motorneuron in the spinal cord, the motorneurons get activated and, in turn, send efferent neural impulses back to the same thigh muscle. These produce a contraction of the muscle, which acts to straighten the lower leg. Figure 1.2 shows the basic components of this reflex. A number of important features of this system should be highlighted. First, this and other stretch reflexes involve reflex arcs that are monosynaptic, i.e. only two neurons and one synapse are employed in the reflex. Other reflexes have at least one interneuron connecting the afferent and efferent pathways. Secondly, this closed-loop regulation of muscle length is accomplished in a completely involuntary fashion, as the name "reflex" suggests.

A third important feature of the muscle stretch reflex is that it provides a good example of negative feedback in physiological control systems. Consider the block diagram representation of this reflex, as shown in Figure 1.3. Comparing this configuration with the general closed-loop control system of Figure 1.1, one can see that the thigh muscle now corresponds to the plant or controlled system. The disturbance, x, is the amount of initial stretch produced by the tap to the knee. This produces a proportionate amount of stretch, y, in the muscle spindles, which act as the feedback sensor. The spindles translate this mechanical quantity into an increase in afferent neural traffic (z) sent back to the reflex center in the spinal cord, which corresponds to our controller. In turn, the controller action is an increase in efferent neural traffic (u) directed back to the thigh muscle, which subsequently contracts in order to
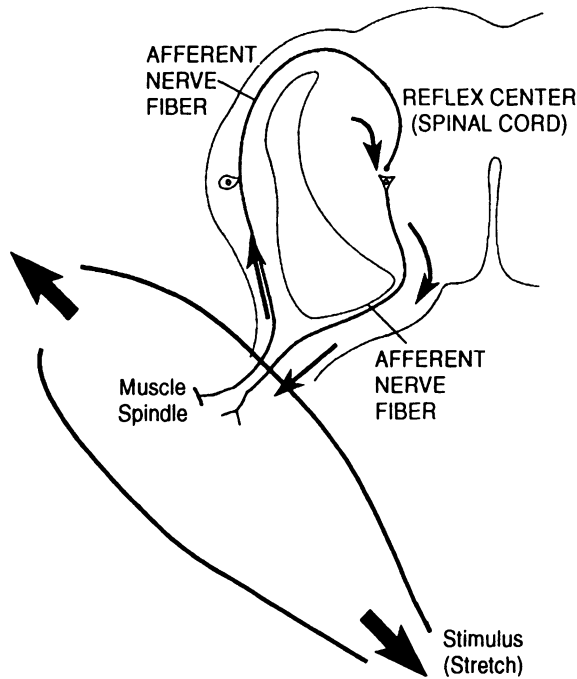
Figure 1.2 Schematic illustration of the muscle stretch reflex. (Adapted from Vander *et al.*, 1997).
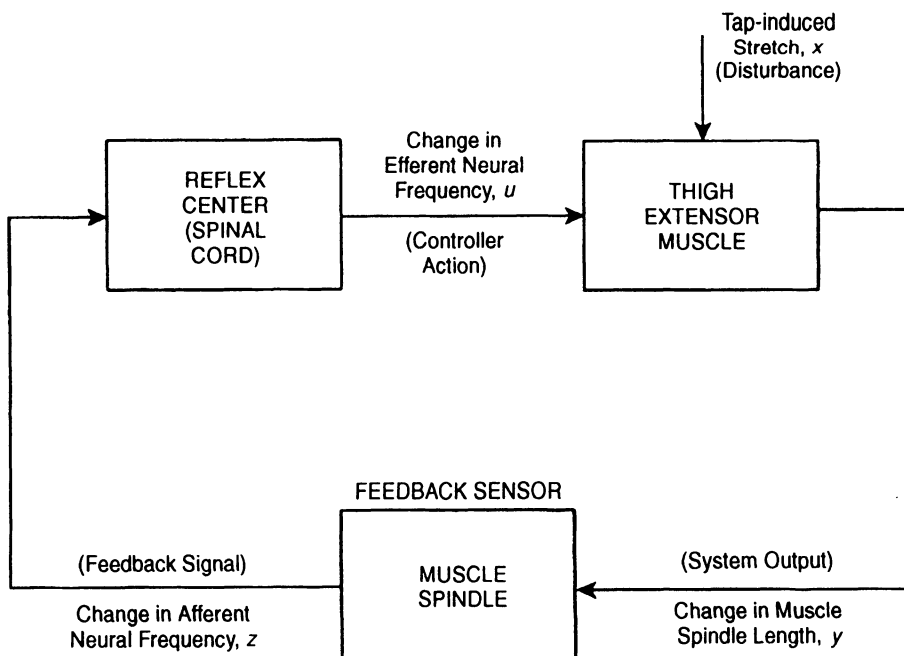
Figure 1.3 Block diagram representation of the muscle stretch reflex.

offset the initial stretch. Although this closed-loop control system differs in some details from the canonical structure shown in Figure 1.1, it is indeed a *negative feedback* system, since the initial disturbance (tap-induced stretch) leads to a controller action that is aimed at *reducing* the effect of the disturbance.

1.5 DIFFERENCES BETWEEN ENGINEERING AND PHYSIOLOGICAL CONTROL SYSTEMS

While the methodology of systems analysis can be applied to both engineering and physiological control systems, it is important to recognize some key differences:

■ An engineering control system is designed to accomplish a defined task, and frequently, the governing parameters have been fine-tuned extensively so that the system will perform its task in an "optimal" manner (at least, under the circumstances in which it is tested). In contrast, physiological control systems are built for versatility and may be capable of serving several different functions. For instance, although the primary purpose of the respiratory system is to provide gas exchange, a secondary but also important function is to facilitate the elimination of heat from the body. Indeed, some of the greatest advances in physiological research have been directed at discovering the functional significance of various biological processes.

■ Since the engineering control system is synthesized by the designer, the characteristics of its various components are generally known. On the other hand, the physiological control system usually consists of components that are unknown and difficult to analyze. Thus, we are confronted with the need to apply system identification techniques to determine how these various subsystems behave before we are able to proceed to analyzing the overall control system.

■ There is an extensive degree of *cross-coupling* or interaction among different physiological control systems. The proper functioning of the cardiovascular system, for instance, is to a large extent dependent on interactions with the respiratory, renal, endocrine, and other organ systems. In the example of the muscle stretch reflex considered earlier, the block diagram shown in Figure 1.3 oversimplifies the actual underlying physiology. There are other factors involved that we omitted and these are shown in the modified block diagram shown in Figure 1.4. First, some branches of the afferent nerves also synapse with the motorneurons that lead to other extensor muscles in the thigh that act synergistically with the primary muscle to straighten the lower leg. Secondly, other branches of the afferent nerves synapse with interneurons which, in turn, synapse with motorneurons that lead to the flexor or antagonist muscles. However, here, the interneurons introduce a polarity change in the signal, so that an increase in afferent neural frequency produces a decrease in the efferent neural traffic that is sent to the flexor muscles. This has the effect of relaxing the flexor muscles so that they do not counteract the activity of the extensor muscles.

■ Physiological control systems, in general, are *adaptive*. This means that the system may be able to offset any change in output not only through feedback but also by allowing the controller or plant characteristics to change. As an example of this type of feature, consider again the operation of the muscle stretch reflex. While this reflex plays a protective role in regulating muscle stretch, it also can hinder the effects of
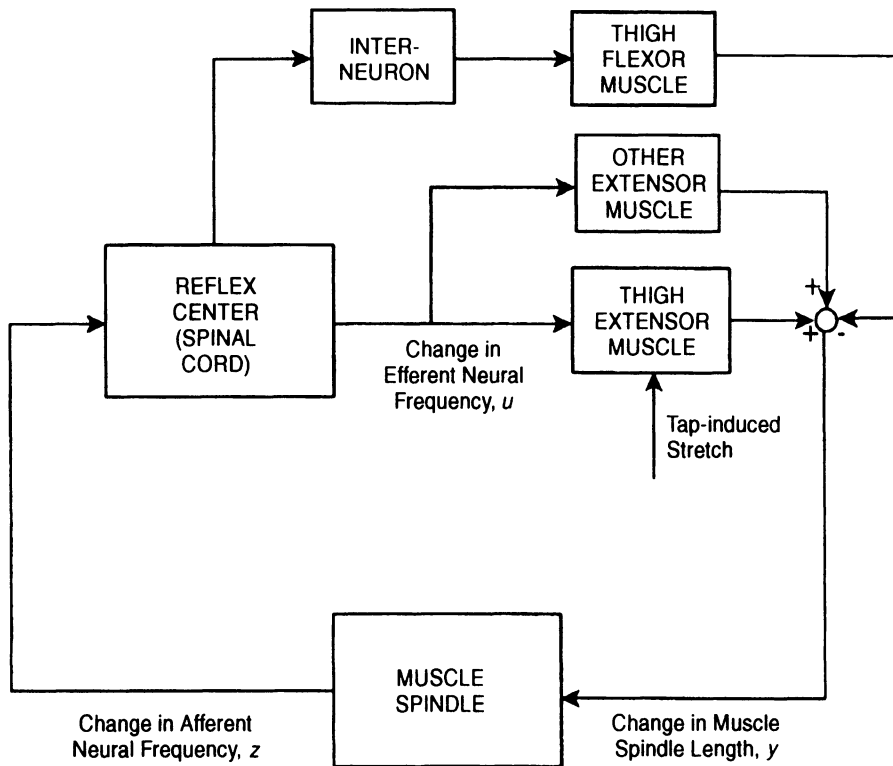
Figure 1.4 Contributions of interrelated systems to the muscle stretch reflex.

voluntary control of the muscles involved. For instance, if one voluntarily flexed the knee, the stretch reflex, if kept unchanged, would come into play and this would produce effects that oppose the intended movement. Figure 1.5 illustrates the solution chosen by Nature to circumvent this problem. When the higher centers send signals down the alpha motorneurons to elicit the contraction of the flexor muscles and the relaxation of the extensor muscle, signals are sent simultaneously down the efferent gamma nerves that innervate the muscle spindles. These gamma signals produce in effect a resetting of the operating lengths of the muscle spindles, so that the voluntarily induced stretch in the extensor muscles is no longer detected by the spindles. Thus, by this clever, adaptive arrangement, the muscle stretch reflex is basically neutralized.

■ At the end of Section 1.4, we alluded to another difference that may be found between physiological control systems and simpler forms of engineering control systems. In Figure 1.1, the feedback signal is explicitly subtracted from the reference input, demonstrating clearly the use of negative feedback. However, in the stretch reflex block diagram of Figure 1.3, the comparator is nowhere to be found. Furthermore, muscle stretch leads to an *increase* in both afferent and efferent neural traffic. So, how is negative feedback achieved? The answer is that negative feedback in this system is "built into" the plant characteristics: increased efferent neural input produces a *contraction* of the extensor muscle, thereby acting to counteract the initial stretch. This kind of *embedded* feedback is highly common in physiological systems.
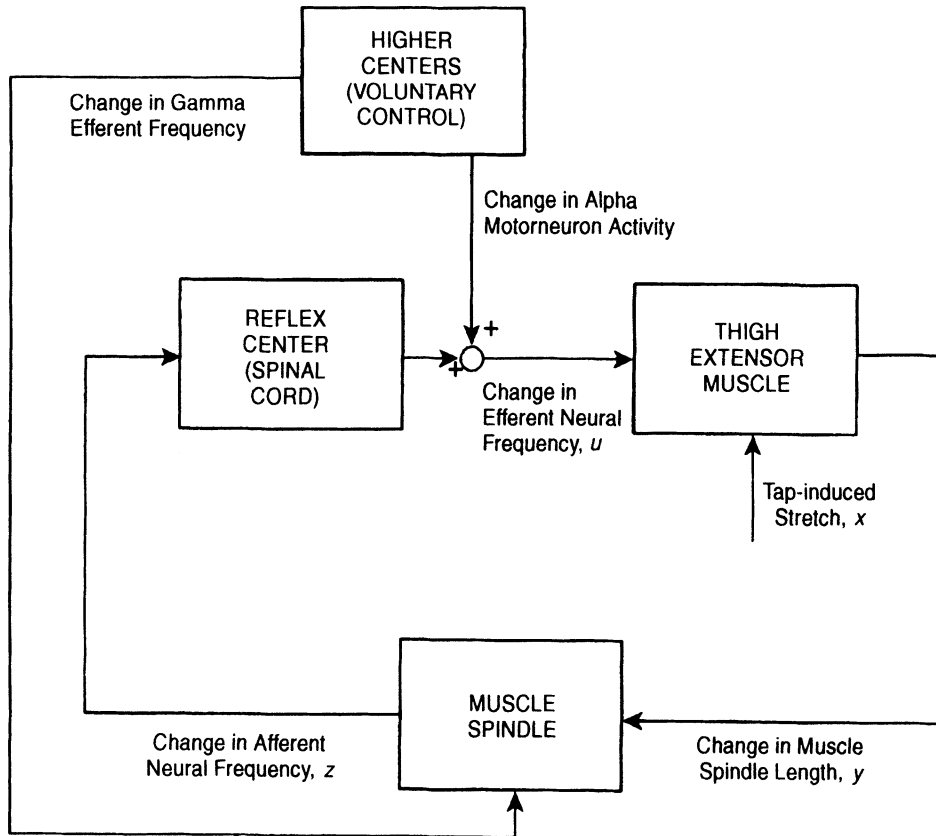
Figure 1.5 Adaptive characteristics of the muscle stretch reflex.

■ One final difference is that physiological systems are generally nonlinear, while engineering control systems can be linear or nonlinear. Frequently, the engineering designer prefers the use of linear system components since they have properties that are well-behaved and easy to predict. This issue will be revisited many times over in the chapters to follow.

1.6 THE SCIENCE (AND ART) OF MODELING

As we have shown, the construction of block diagrams is useful in helping us clarify in our own minds what key variables best represent the system under study. It is also helpful in allowing us to formalize our belief (which is usually based partly on other people's or our own observations and partly on intuition) about how the various processes involved are causally related. The block diagram that emerges from these considerations, therefore, represents a *conceptual model* of the physiological control system under study. However, such a model is limited in its abiliity to enhance our understanding or make predictions, since it only allows qualitative inferences to be made.

To advance the analysis to the next level involves the upgrading of the conceptual model into a *mathematical model*. The mathematical model allows us to make hypotheses

about the contents in each of the "boxes" of the block diagram. For instance, in Figure 1.3, the box labeled "controller" will contain an expression of our belief about how the change in afferent neural frequency may be related to the change in efferent neural frequency. Is the relationship between afferent frequency and efferent frequency linear? If the changes in afferent frequency follow a particular time-course, what will the time-course of the response in efferent frequency be like? One way of answering these questions would be to isolate this part of the physiological control system and perform experiments that would allow us to measure this relationship. In this case, the relationship between the controller input and controller output is derived purely on the basis of observations, and therefore, it may take the form of a table or a curve best-fitted to the data. Alternatively, these data may already have been measured, and one can simply turn to the literature to establish the required input–output relationship. This kind of model assumes no internal structure and has been given a number of labels in the physiological control literature, such as *black-box*, *empirical*, or *nonpara-metric* model. Frequently, on the basis of previous knowledge, we also have some idea of what the underlying physical or chemical processes are likely to be. In such situations, we might propose an hypothesis that reflects this belief. On the basis of the particular physical or chemical laws involved, we would then proceed to derive an algebraic, differential, or integral equation that relates the "input" to the "output" of the system component we are studying. This type of model is said to possess an internal structure, i.e., it places some constraints on how the input may affect the output. As such, we might call this a *structural* or *gray-box* model. In spite of the constraints built into this kind of model, the range of input–output behavior that it is capable of characterizing can still be quite extensive, depending on the number of free parameters (or coefficients) it incorporates. For this reason, this type of model is frequently referred to as a *parametric* model.

Mathematical modeling may be seen as the use of a "language" to elaborate on the details of the conceptual model. However, unlike verbal languages, mathematics provides descriptions that are unambiguous, concise, and self-consistent. By being unambiguous, it enables different researchers to use and test the same model without being confused about the hypotheses built into the model. Since the equations employed in the model are based, at least in large part, on existing knowledge of the physiological processes in question, they also serve the useful purpose of archiving past knowledge and compressing all that information into a compact format. The inherent self-consistency of the model derives from the operational rules of mathematics, which provide a logical accounting system for dealing with the multiple system variables and their interactions with one another. On the other hand, the hypotheses embedded in some components of the model *are* only *hypotheses*, reflecting our best belief regarding the underlying process. More often than not, these are incorrect or oversimplistic. As a consequence, the behavior of the model may not reflect the corresponding reality. Yet, the power of the modeling process lies in its replication of the scientific method: the discrepancy between model prediction and physiological observation can be used as "feed-back" to alert us to the inadequacies of one or more component hypotheses. This allows us to return to the model development stage once again in order to modify our previous assumptions. Subsequently, we would retest the revised model against experimental observa-tions, and so the alternating process of induction and deduction continues until we are satisfied that the model can "explain" most of the observed behavior. Then, having arrived at a "good" model, we could venture to use this model to predict how the system might behave under experimental conditions that have not been employed previously. These predictions would serve as a guide for the planning and design of future experiments.

BIBLIOGRAPHY

Adolph, E. Early concepts in physiological regulation. *Physiol. Rev.* **41**:737–770, 1961.

Bayliss, L.E. *Living Control Systems*. English University Press, London, 1966.

Cannon, W. *The Wisdom of the Body*. Norton, New York, 1939.

Clynes, M., and J.H. Milsum. *Biomedical Engineering Systems*. McGraw-Hill, New York, 1970.

Grodins, F.S. *Control Theory and Biological Systems*. Columbia University Press, New York, 1963.

Guyton, A.C., C.E. Jones, and T.G. Coleman. *Circulatory Physiology: Cardiac Output and Its Regulation*. Saunders, Philadelphia, 1973.

Jones, R.W. *Principles of Biological Regulation*. Academic Press, New York, 1973.

Milhorn, H.T. *The Application of Control Theory to Physiological Systems*. Saunders, Philadelphia, 1966.

Miller, J. *The Body in Question*. Random House, New York, 1978.

Milsum, J.H. *Biological Control Systems Analysis*. McGraw-Hill, New York, 1966.

Riggs, D.S. *Control Theory and Physiological Feedback Mechanisms*. Williams & Wilkins, Baltimore, 1970.

Stark, L. *Neurological Control Systems*. Plenum Press, New York, 1968.

Unschuld, P.U. *Medicine in China: A History of Ideas*. Berkeley, London, 1985.

Vander, A.J., J.H. Sherman, and D.S. Luciano. *Human Physiology: The Mechanisms of Body Function*, 7th ed. McGraw-Hill, New York, 1997.

Wiener, N. *Cybernetics: Control and Communication in the Animal and the Machine*. Wiley, New York, 1961.

PROBLEMS

Based on the verbal descriptions of the following physiological reflex systems, construct block diagrams to represent the major control mechanisms involved. Clearly identify the physiological correlates of the controller, the plant, and the feedback element, as well as the controlling, controlled, and feedback variables. Describe how negative (or positive) feedback is achieved in each case.

P1.1. The Bainbridge reflex is a cardiac reflex that aids in the matching of cardiac output (the flow rate at which blood is pumped out of the heart) to venous return (the flow rate at which blood returns to the heart). Suppose there is a transient increase in the amount of venous blood returning to the right atrium. This increases blood pressure in the right atrium, stimulating the atrial stretch receptors. As a result, neural traffic in the vagal afferents to the medulla is increased. This, in turn, leads to an increase in efferent activity in the cardiac sympathetic nerves as well as a parallel decrease in efferent parasympathetic activity. Consequently, both heart rate and cardiac contractility are increased, raising cardiac output. In this way, the reflex acts like a servomechanism, adjusting cardiac output to track venous return.

P1.2. The pupillary light reflex is another classic example of a negative feedback control system. In response to a decrease in light intensity, receptors in the retina transmit neural impulses at a higher rate to the pretectal nuclei in the midbrain, and subsequently, to the Edinger–Westphal nuclei. From the Edinger–Westphal nuclei, a change in neural traffic down the efferent nerves back to the eyes leads to a relaxation of the sphincter muscles and contraction of the radial dilator muscles that together produce an increase in pupil area, which increases the total flux of light falling on the retina.

P1.3. The regulation of water balance in the body is intimately connected with the control of sodium excretion. One major mechanism of sodium reabsorption involves the renin–angiotensin–aldosterone system. Loss of water and sodium from the body, e.g., due to diarrhea, leads to a drop in plasma volume, which lowers mean systemic blood pressure. This stimulates the venous and arterial baroreflexes, which produce an increase in activity of the renal sympathetic nerves, in turn stimulating the release of renin by the kidneys into the circulation. The increase in plasma renin concentration leads to an increase in plasma angiotensin, which stimulates the release of aldosterone by the adrenal cortex. Subsequently, the increased plasma aldosterone stimulates the reabsorption of sodium by the distal tubules in the kidneys, thereby increasing plasma sodium levels.

P1.4. The control system that regulates water balance is intimately coupled with the control of sodium excretion. When sodium is reabsorbed by the distal tubules of the kidneys, water will also be reabsorbed if the permeability of the tubular epithelium is lowered. This is achieved in the following way. When there is a drop in plasma volume, mean systemic pressure decreases, leading to a change in stimulation of the left atrial pressure receptors. The latter send signals to a group of neurons in the hypothalamus, increasing its production of vasopressin or antidiuretic hormone (ADH). As a result, the ADH concentration in blood plasma increases, which leads to an increase in water permeability of the kidney distal tubules and collecting ducts.

P1.5. Arterial blood pressure is regulated by means of the baroreceptor reflex. Suppose arterial blood pressure falls. This reduces the stimulation of the baroreceptors located in the aortic arch and the carotid sinus, which lowers the rate at which neural impulses are sent along the glossopharyngeal and vagal afferents to the autonomic centers in the medulla. Consequently, sympathetic neural outflow is increased, leading to an increase in heart rate and cardiac contractility, as well as vasoconstriction of the peripheral vascular system. At the same time, a decreased parasympathetic outflow aids in the heart rate increase. These factors together act to raise arterial pressure.

P1.6. A prolonged reduction in blood pressure due to massive loss of blood can lead to "hemorrhagic shock" in which the decreased blood volume lowers mean systemic pressure, venous return and thus, cardiac output. Consequently, arterial blood pressure is also decreased, leading to decreased coronary blood flow, reduction in myocardial oxygenation, loss in the pumping ability of the heart, and therefore, further reduction in cardiac output. The decreased cardiac output also leads to decreased oxygenation of the peripheral tissues, which can increase capillary permeability, thereby allowing fluid to be lost from the blood to the extravascular spaces. This produces further loss of blood volume and mean systemic pressure, and therefore, further reduction in cardiac output.