CHAPTER 1

INTRODUCTION

Examples, pertinent to the application of process control in some areas of bioprocessing and drug delivery, are outlined below to underscore the ubiquitous nature of this technology. Concepts of disturbance variables, set points, manipulated variables, and controlled variables are introduced. Block diagrams are drawn to describe processes. A list of hardware and software required to implement control algorithms is also included.

1.1 THE ROLE OF PROCESS DYNAMICS AND CONTROL IN BRANCHES OF BIOLOGY

Biology deals with the study of living organisms and vital processes. A close examination of cellular functions reveals a sophisticated mechanism and a remarkable control system. The cells, fundamental units in all living things, are responsible for growth, maintenance, and reproduction. Branches of biology, such as biotechnology and physiology, have witnessed a substantial growth in the application of control theories to guide research and to promote discovery.

1.1.1 Applications in Biotechnology

The dynamics of bacterial growth, for example, involve *in vivo* and *in vitro* reactions (i.e., bioreactions). A microorganism, inoculated into a sterilized

Control of Biological and Drug-Delivery Systems for Chemical, Biomedical, and Pharmaceutical Engineering, First Edition. Laurent Simon.

medium, undergoes a lag, an exponential growth phase, a stationary phase, and a death phase. Cell proliferation occurs in a bioreactor, a critical unit operation in biopharmaceutical, biochemical, and activated sludge processes, to name a few [1]. In the lag phase, there is little or no evidence of cell division as the bacteria adjust to their new environment. In microbial cell cultivation, the length of the lag phase can be attributed to the type and age of the microorganism, the size of the inoculum, the temperature of the medium, and nutrient concentration. As cells divide in a bioreactor, their number grows in an exponential fashion. An equilibrium phase (i.e., stationary phase) is achieved as the rate at which cells die is equal to the rate at which they divide. For *in vitro* processes, the lack of nutrients, pH changes, and reduced oxygen are among the factors that may explain why some cells enter the stationary phase. In the death phase, the number of viable cells decreases as nutrients deplete and lytic enzymes start to accumulate. Process dynamics and control can be applied, in biotechnology, to identify the factors that influence cell growth and help devise a procedure for maximizing the production of high-valued proteins. An efficient system needs to consider the different growth phases because of the diverse patterns and kinetics exhibited by the cells. Distinct methods are required depending on the production of (1) primary metabolites, excreted in the exponential growth phase, or (2) secondary metabolites, generated as the cells approach the stationary phase.

It is also necessary to regulate the environmental conditions (e.g., temperature, pH, dissolved oxygen [DO], and limiting nutrient) that affect the reactions occurring within the cells in order to achieve a desired outcome (e.g., product yield, cell concentration). The goal of process control is defined in these terms by Boudreau and McMillan [1]:

> Process control attempts to influence the individual sophisticated internal reactions of billions of cells by controlling their extracellular environment.

DO control is crucial in the cultivation of aerobic cells in bioreactors. Oxygen is required in aerobic respiration to produce energy, in the form of adenosine triphosphate (ATP), from glucose or another organic substrate. The energy consumed by the cells helps them to carry reactions, make products, reproduce, transport nutrients, and change locations. The control of DO in bioprocesses requires careful consideration and an understanding of process dynamics. For example, fermentations aimed at producing antibiotics can be highly viscous, which may lead to fluctuation in the DO concentration in the bioreactor [2]. Advanced algorithms, incorporating the kinetic data, were applied in real time to control DO in the production of aminoglycoside antibiotics from *Streptomyces*.

Figure 1.1 shows DO control when a mouse hybridoma cell line was used to produce an antibody against a tissue-type plasminogen activator (t-PA). Only some of the peripherals are shown in the schematic. Sampling and inoculum ports, humidifiers, and moisture traps are usually included. This product

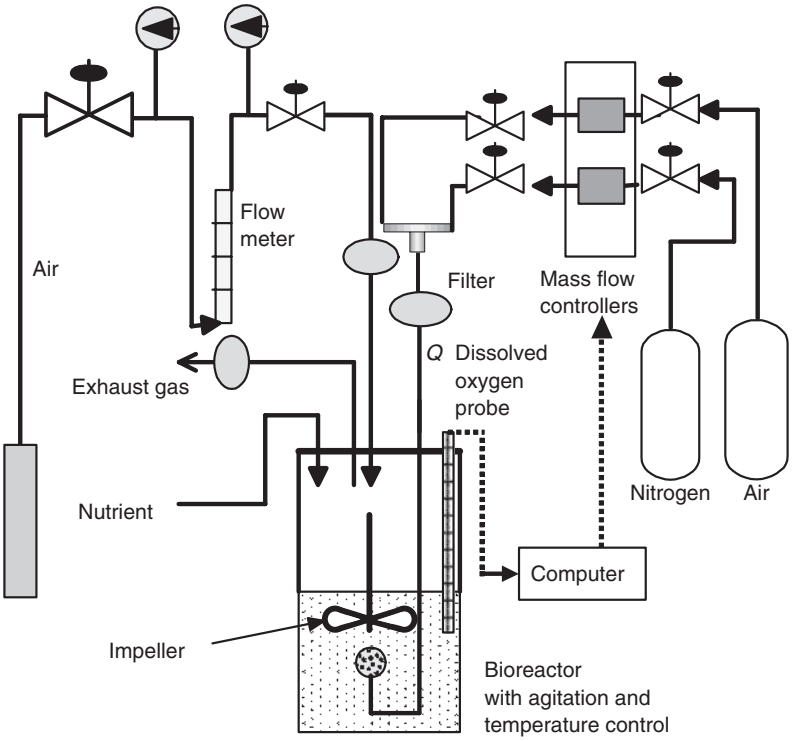

Figure 1.1. Schematic diagram for the control of dissolved oxygen.

(t-PA) has important clinical applications in heart attack research. A control strategy that depends on manipulating the airflow in the sparger, or the agitation, would not work because the hybridoma cells lack a protective cell wall and, as a result, are highly sensitive to shear forces. The basic idea is to disturb the growth environment minimally by keeping the stirring speed and gas flow rate constant. Signals from the DO probe are sent to the computer that stores a control design algorithm (i.e., control law). The computer/controller sends instructions to the mass flow controllers (MFCs) to vary the flow rates of nitrogen (F_{N2}) and air (F_{air}) while keeping a constant total gas flow rate ($Q = F_{N2} + F_{air}$). To design the control law properly, it is important to understand how the hybridoma cells respond to changes in the DO concentration and the dynamics of the DO probe. For these reasons, a fundamental knowledge of process dynamics is a critical step in control design. A *block diagram*, usually drawn to represent the system (Fig. 1.2), is a schematic representation of the interconnections or relationships among variables and processes that make up the control system. The actual DO concentration in the bioreactor is read by the DO probe, which feeds a signal to a *comparator*. The difference between a reference value, set by the operator, and the input signal is

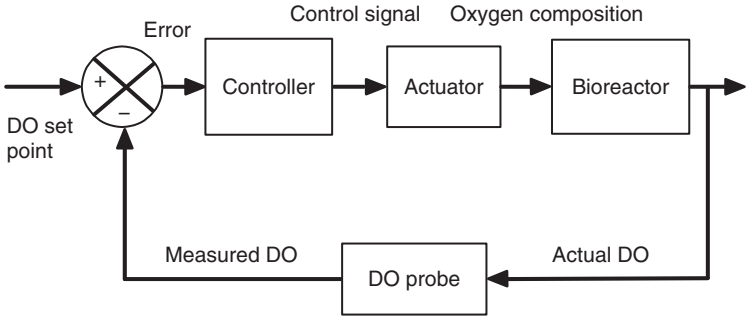

Figure 1.2. Block diagram of the feedback control of dissolved oxygen.

calculated by the comparator. This error is sent to the controller that is linked to actuators, in this case, two MFCs. The MFCs are not only able to measure the flow of gases but can also manipulate the flow rates based on the electric signals received from the computer. Then, the molar fraction of oxygen in Q is adjusted before entering the bioreactor. In this illustration, the combined comparator and controller are represented by the computer.

Also, MFCs can act as stand-alone controllers and are equipped with a mass flow sensor, a control valve, and actuators. More details will be given in the section on instrumentation. For this application, it is sufficient to say that the air and nitrogen flow rates are adjusted by the MFCs.

The *control of pH* is essential in industrial fermentation processes because of the dependence of the cell-specific growth rate and protein production on the pH. An acidic medium may be the result of depletion in the nutrient leading to the production of organic acids (e.g., acetic acids). Bioreactors are usually equipped with pH controllers. In Chinese hamster ovary (CHO) cells, CO_2 tends to accumulate in the bioreactor, especially at a high cell density [3]. The buildup of CO_2 reduces the culture pH (i.e., increase in cations) because of the following equilibrium equation:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \tag{1.1}$$

around a pH of 7.0. The addition of NaOH leads to a rise in HCO_3^- ions via

$$NaOH + H_2CO_3 \leftrightarrow Na^+ + HCO_3^- + H_2O \tag{1.2}$$

and causes the equilibrium reaction (i.e., Eq. 1.1) to shift to the left, increasing the pH. A block diagram of the process is shown in Figure 1.3. In this case, the controller manipulates the flow rates of CO_2 and NaOH in order to hold the pH at a desired value. Buffer solutions, such as bicarbonate, can also be used in the culture system to prevent significant pH changes.

The *addition of nutrient into bioreactors* often provides a way to enhance cell growth or to promote product formation. In the fed-batch mode, limiting

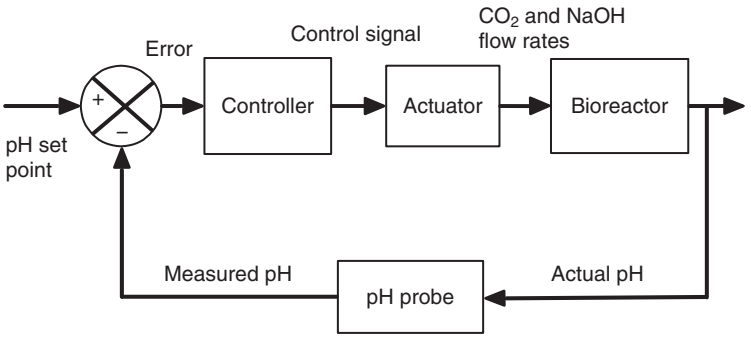

Figure 1.3. Block diagram of the feedback control of pH.

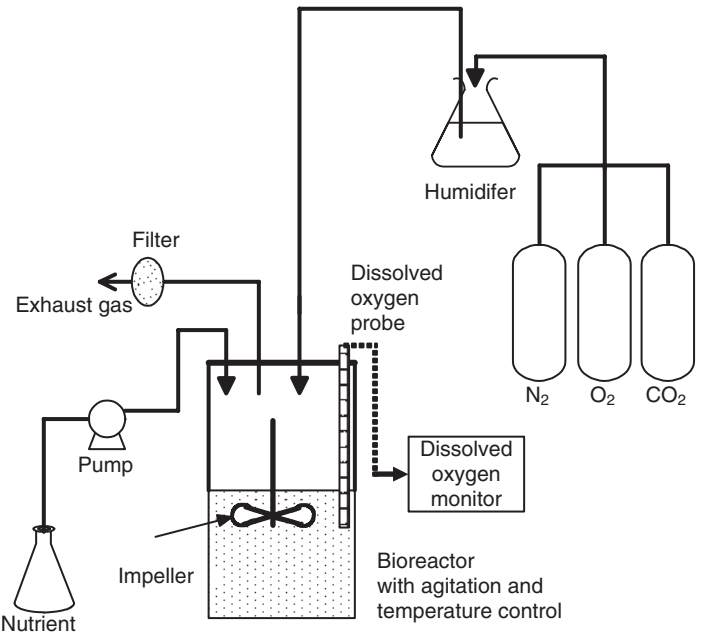

Figure 1.4. Fed-batch operation of a culture of hybridoma cells.

substrates are added to the cultivation vessel. This mode of operation is selected when the microorganism grows to a high cell density. Because the specific growth rate is often a strong function of substrate concentration, tight control of the nutrient is necessary as starvation or overfeeding can easily occur in the absence of accurate feeding protocols. A mathematical description (i.e., differential equations) of the cell culture kinetics is useful to estimate the substrate flow rate that should be added into the vessel to satisfy specified requirements. An example is shown in Figure 1.4 for hybridoma cultures [4].

Equations that represent cell growth, product formation, and nutrient consumption are written when performing a mass balance on the process unit:

$$\text{Accumulation} = \text{Input} + \text{Generation} - \text{Output} - \text{Consumption}. \quad (1.3)$$

For a product that is partially growth and non-growth-associated, the accumulation rate in the bioreactor can be set equal to the generation rate. However, the generation rate includes expressions that capture the two dynamics:

$$\frac{d[P]}{dt} = \alpha \frac{d[X_v]}{dt} + \beta X_v(t), \quad (1.4)$$

where α and β are the growth and non-growth-associated coefficients, respectively. The product P depends on the cell growth rate and the concentration of viable cells X_v. Control can be implemented to make sure that glutamine or glucose is introduced into the bioreactor at a rate that optimizes the production of monoclonal antibodies.

1.1.2 Applications in Physiological Systems

In bioreactors, cells, isolated from animal organs and tissues, are cultivated in culture media for the production of a desired product. For example, CHO cells, derived from the ovaries of Chinese hamsters, have been used for the production of protein with a therapeutic value, such as t-PA. Culture conditions are selected carefully to make sure that the extracellular environment is conducive to growth and product formation. Process control is implemented in such a context to suppress the effects of *disturbances* on key *output variables* (*regulatory control*) or to ensure that if a set point or *reference value* is changed by the operator, the bioreactor has no difficulty tracking the set point (*servo problem*). Because the environmental variables influence the biochemical events occurring within the cell, a fundamental goal of bioreactor process control is to regulate these external factors in order to preserve *homeostasis*—"the maintenance of the steady-state conditions in the internal environment" [5]. A change in metabolic activities is indicated by a decrease in pH, a reduction of glucose level, or an increase in the temperature as a result of a high viable cell concentration. In this case, external controllers are necessary to help each cell perform its metabolic function. Some pertinent questions are the following: How do cells, in their physiological surroundings, preserve metabolic equilibrium in the face of various disturbances or fluctuations? What control mechanisms are involved in the regulation of excess water by the kidneys? How do millions of interconnected neurons control the activities of muscles and allow a person to stand? How does the brain control the inner body temperature?

1.1.2.1 Pupil Light Reflex Is an Example of Physiological Control in the Human Body The pupil automatically constricts when we are exposed

to a bright light. It seems that the body is preprogrammed to let a controlled amount of light enter the eyes. The reflex is so strong that it serves to assess damage to the central nervous system or the level of human consciousness. From the way we instinctively squint when the light gets brighter, it is reasonable to deduce that there is a natural controller behaving like a thermostat that regulates a room temperature. One of the main differences between the two designs is that the inner workings of the human biological device and the control law that directs its behavior are a mystery to us, at least until we study and elucidate the underlying mechanism. In physiological systems, the engineer is being asked to characterize the plant, identify the sensor(s), and infer the type of control strategy being implemented. Goodman summarized the challenging tasks in the following terms [6]:

> These tasks are made especially difficult by the constraint that system viability cannot be threatened by probes required to make necessary interventions and measurements. Nor is one permitted arbitrarily to partition the system into discrete units or assemblies and use "stimulus–response" (input-output) techniques to characterize structure and function, i.e., procedures must be "noninvasive" or as nearly so as possible. One hypothetical analog is that of a control engineer assigned the task of improving the performance of a petrochemical plant by synthesizing an automatic process control system. Detailed design drawings and specifications, the engineer is told, are not complete. Although the plant is partially visible behind a high fence, direct access is denied. Thus, the engineer faces the challenge of determining what is inside the fence on the basis of prior knowledge of how some similar plants operate, and the freedom noninvasively to measure what goes through the wires and pipes that connect the plant to the environment. The engineer, with caution, may be permitted small variations of some input fluxes providing that plant throughput and product quality are not compromised.

There are identification methods, commonly used in control engineering, that can be applied to model how the retina responds to a change in light intensity (Fig. 1.5) [7]. A light flux of a specific intensity (L_c) falls on the retina. The

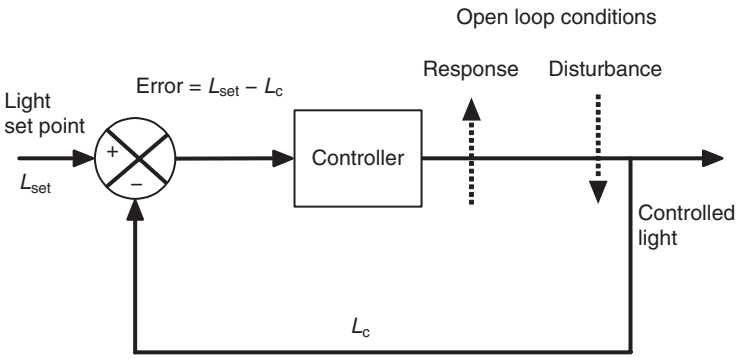

Figure 1.5. Block diagram of the pupillary light reflex system.

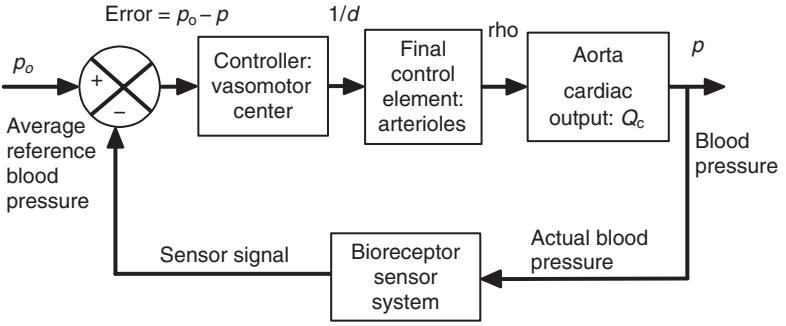

Figure 1.6. Feedback control of blood pressure using the vasomotor center.

difference between the set (or reference) point L_{set} and the controlled variable L_c is fed to the controller (i.e., the pupil neuromuscular apparatus). The latter adjusts the pupil size to drive the error to zero. Experiments were conducted to introduce disturbances to the system (i.e., change in the light flux) and to measure the response (i.e., change in the pupil area) without compromising the system.

1.1.2.2 The Control of Human Arterial Blood Pressure Provides an Illustration of Biological Control In the block diagram shown in Figure 1.6, the aorta represents the *plant* [8]. The cardiac output (Q_c) is defined as the volumetric flow rate of blood from the heart to the aorta. Its value can be calculated by multiplying the stroke volume (i.e., volume of blood pumped with each beat) by the heart rate. The *controlled variable p* (arterial blood pressure: outward force by the blood flow against the arterial walls) is obtained by multiplying Q_c by the peripheral resistance (ρ) imposed by the arterioles. The *output p* is fed to the baroreceptor sensor system, which sends a signal to a comparator where the indicated value (p) is compared to reference p_o. Baroreceptors are pressure sensors found in the blood vessels of some mammals. These devices sense the resistance of blood flow against the vessel walls and send impulses (*action potentials*) to the brain via *glossopharyngeal* and *vagus* nerves. The error is then fed to the cardioregulatory and vasomotor centers (VMC) in the brain (i.e., *controller*). In this example, we consider the VMC as the only controller to simplify the analysis (constant Q_c). An increased activity in the VMC is accompanied by a decrease in the diameter of the arterioles (d) and an increase in the peripheral resistance since $\rho = k(1/d)^4$, where k is a proportionality constant. In reality, the VMC transmits sympathetic stimulations (Act_{VMC}) to the blood vessels. Similarly, as the activity in the VMC is decreased, d is increased, which results in a decrease in ρ [8]. From the equation $p = Q_c\rho$, a probable scenario that explains the regulation of cardiac output can be deduced. For example, if $p > p_0$, as a result of a *disturbance*, $\varepsilon < 0 \Rightarrow Act_{VMC} \downarrow \Rightarrow d \uparrow \Rightarrow \rho \downarrow \Rightarrow p \downarrow$. A similar analysis can be conducted to show how both the VMC and the cardiovascular center—which sends sympa-

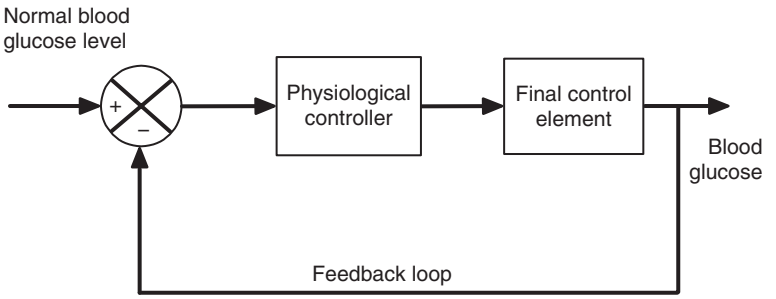

Figure 1.7. Feedback control of blood glucose by insulin in a nondiabetic person.

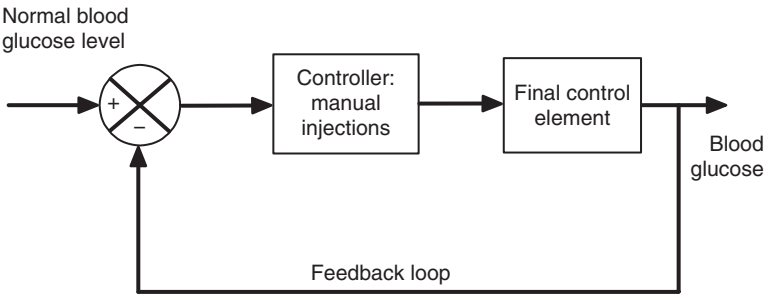

Figure 1.8. Feedback control of blood glucose by insulin in a diabetic person.

thetic stimulations to the heart affecting the heart rate and stroke volume—regulate the blood pressure.

1.1.2.3 Blood Glucose Can Be Controlled by Exogenous Insulin Injections Insulin-dependent diabetes mellitus (IDDM), or type 1 diabetes, is a chronic disease that may lead to blindness, heart disease, and stroke in people afflicted with the illness. In type 1 diabetes, the pancreatic beta cells, responsible for secreting the insulin hormone, have been destroyed as a result of an autoimmune process. In the absence of insulin, the way the body converts sugar (i.e., glucose) in the blood into energy, made available to all the cells in the body, is not well regulated. In other words, the cells either have too much glucose (i.e., hyperglycemia) in the blood plasma or an inadequate amount in the case of hypoglycemia. Under healthy conditions, a physiological regulator, such as the ones described above, makes sure that a constant glucose level is held. A simplified block diagram is provided in Figure 1.7. A more detailed block diagram, similar to Figure 1.6, can be drawn that includes, for example, the stimulation of the beta cells and secretion of insulin.

In type 1 diabetic patients, the control system is replaced by an external mechanism where people monitor their daily glucose concentrations and take insulin shots in order to maintain a constant blood glucose level (Fig. 1.8). In these situations, accurate and timely readings of the glucose are paramount.

1.2 THE ROLE OF PROCESS DYNAMICS AND CONTROL IN DRUG-DELIVERY SYSTEMS

There are several applications of process dynamics and control in drug delivery. The tools applied to understand transient process behaviors (e.g., Laplace transforms) can also be used to track the evolution of drugs in the body. Keeping the pharmaceutical agent at a desired concentration in the blood requires the development of programming tools similar to the optimization of a fed-batch bioreactor. In designing controlled-release devices, it is important to achieve an optimal control of the drug-delivery rate. Modern control theories are applied to optimize treatment strategies.

1.2.1 Applications in Compartmental Models

Drug delivery, using compartmental models, requires a sound understanding of pharmacokinetics, which deals with drug absorption, distribution, metabolism, and excretion (ADME). A therapeutic concentration of the active pharmaceutical ingredient (API) must be able to reach the target site. Knowledge of the transient behaviors of compartment models is therefore necessary.

The one-compartment model is used to describe uniform drug distribution in the body. Based on this representation, the body behaves like a well-stirred vessel (Fig. 1.9). This framework is implemented for intravenous (IV) boluses (i.e., instantaneous delivery) and continuous infusions. After a single dose is administered, the drug is distributed throughout the body and metabolized. If a second dose is not taken on time, the medication may be ineffective as the plasma concentration drops well below a therapeutic level. Pharmacokinetic information helps compute drug-dosing regimens. In the context of IV boluses, several injections must be administered at predetermined times in order to maintain a plasma drug concentration between the toxic and ineffective levels (Fig. 1.10). The time to reach a desired drug concentration can be estimated using dynamic analysis.

Process dynamics plays a major role in analyzing drug administration via constant-rate infusion during hospitalization. One of the main advantages of an IV infusion is the elimination of fluctuations evident in bolus IV dosing. However, the pharmacokinetics must be carefully assessed to make sure that it does not take a long time to establish a steady-state plasma drug concentration. This information can also help decide whether a combination of IV

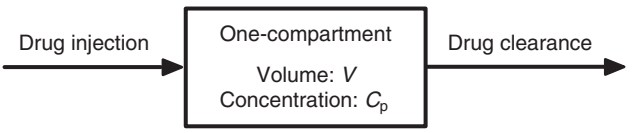

Figure 1.9. Representation of a one-compartment model.

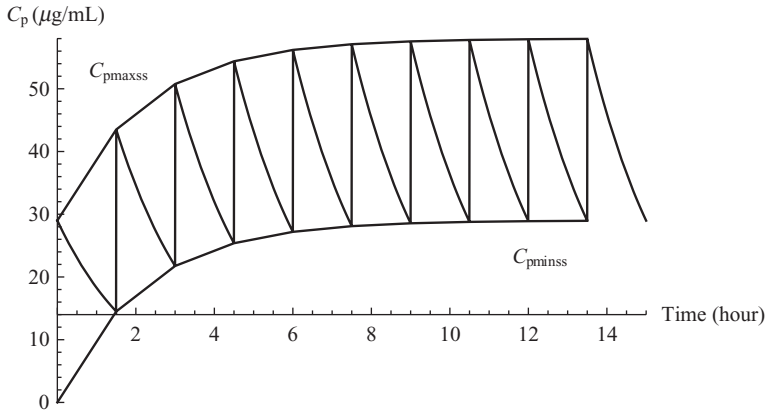

Figure 1.10. Plasma concentration profile for a multiple IV bolus regimen.

boluses and constant-rate infusions is the most appropriate way to administer the medication.

1.2.2 Applications in Controlled-Release Technology

The purpose of controlled drug release is to guarantee that the medicament is delivered at a specified rate and is sustained in the blood at a desired concentration. Unlike IV boluses and continuous infusions, needles are not used. The transdermal route enhances patient compliance, which is essential for therapy to work. A patch is placed on the skin and the medication is released continuously over a period of time. In addition, once the patch is affixed to the skin, it is no longer necessary to remember when to take the medication. *In vitro* drug permeation studies are usually conducted using Franz diffusion cells. In a typical configuration, permeation experiments are performed using excised skins (e.g., full-thickness human skin) or synthetic membranes, such as poly(ethylene-vinyl acetate) (EVA). The membrane is positioned between the donor cell and a receiver compartment, containing a continuously stirred solution (i.e., PermeGear glass diffusion cells, PermeGear, Riegelsville, PA). Drug molecules diffuse across the membrane from the donor cell and into the receiver compartment. By removing the entire receiver volume during sampling and replacing it with a fresh solution at regular intervals, the concentration in the receiver cell remains at zero (i.e., sink condition).

The system, described in Figure 1.11, can be analyzed, using tools learned in process dynamics courses (e.g., Laplace transforms). The findings can serve to inform product designers of the solvent properties and membrane thickness/composition necessary to reach a particular delivery rate or a desired plasma drug concentration, when the patch is applied to the skin. Dynamic system analysis techniques can also be implemented to describe how the transient

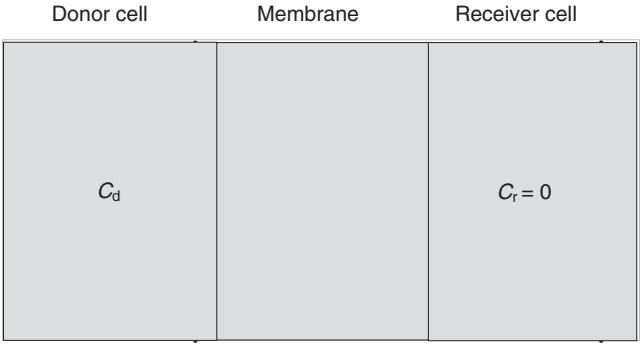

Figure 1.11. Experimental apparatus for Franz diffusion cell experiments.

response (e.g., flux, plasma drug concentration) relates to pertinent design parameters [9].

1.1.2.4 Modern Control Theory Can Be Applied to Calculate a Set of Optimum Loading Doses in a Transdermal Patch These doses need to be administered at regular intervals in order to have a constant delivery rate over a defined period [10]. Once the percutaneous absorption kinetics is known, simulations can be conducted to estimate drug-dosage regimens appropriate for a particular treatment. The methods required in these cases (i.e., *dynamic programming*) are beyond the scope of this textbook. However, they are implemented in several processes in chemical engineering where it is necessary to compute a set of control and state histories that minimize an objective function. A brief description is provided in Chapter 16.

1.3 INSTRUMENTATION

An understanding of the physical elements of the control system is necessary for designing the controller. For example, the time delay, caused by a sensor, of a fluid moving through a pipe or by transmission lines may adversely influence the performance of the controller.

The control system is composed of the *process*, *primary elements*, a *controller*, and the *final control elements*. Figure 1.12 shows the hardware elements in a liquid-level control system. A liquid with flow rate F_i and temperature T_i enters the tank. The liquid level (h) in the tank (i.e., the process) is measured by a level transmitter (LT) such as a differential pressure cell (primary element). Information from the sensor is sent to the level controller (LC) along a transmission line. This reading is compared to the set point (h_{SP}) and the controller calculates a signal based on the error ($h - h_{SP}$) and a control law. The output from the controller adjusts the valve (final control element) in order to get the liquid level as close as possible to the set point.

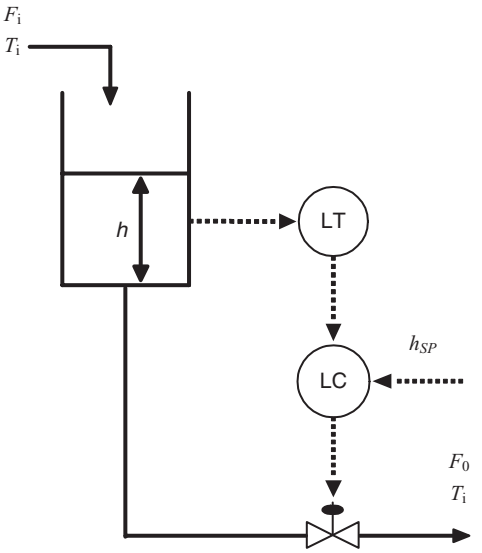

Figure 1.12. Diagram of a liquid-level control system including the hardware elements.

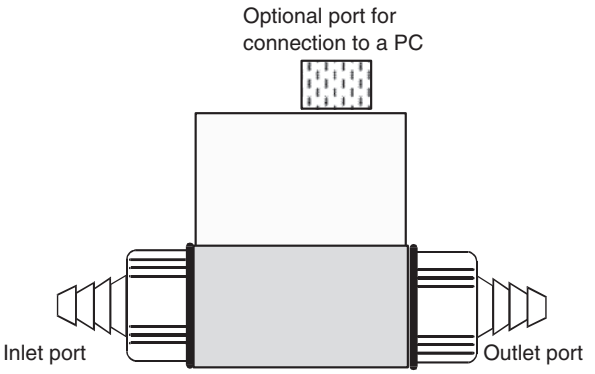

Figure 1.13. Diagram of a typical mass flow controller.

1.3.1 MFCs

MFCs are often used in bioprocess technology to measure and control the gas flow rate into bioreactors. Desired levels of DO and carbon dioxide are achieved during the cultivation of mammalian cells via computer-coupled MFCs (Fig. 1.13). The gas enters the device through the inlet port where it is measured by a *sensor*. Note that only a fraction of the gas goes through the

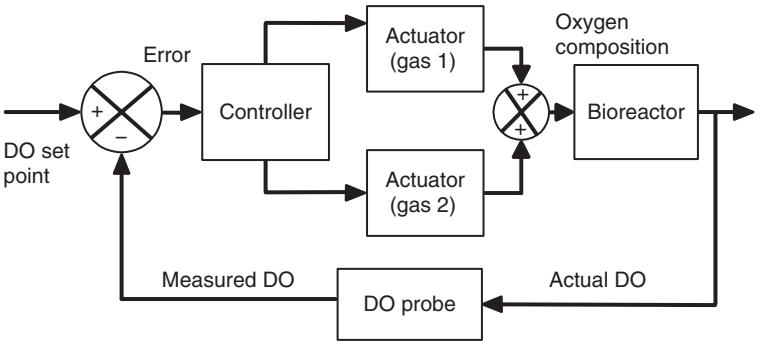

Figure 1.14. Block diagram of the feedback control of the dissolved oxygen using two MFCs.

sensor because of the presence of a *bypass* in the line. The voltage signal from the sensor is transmitted to a controller (built into the device) that compares the sensor output to a set point programmed by an operator or sent to the device by a computer. A proportional valve, placed in the line, receives information from the controller to adjust the outlet flow, following a control law, until it equals the set point. Depending on the model, MFCs are equipped with solenoid, piezoelectric or thermal actuator valves. Data acquisition and interface cards are needed in cases where input signals are sent via a computer [11]. In terms of process dynamics, the *response time* of the MFC is usually determined by how quickly the sensor responds to a change in the flow rate (usually a few seconds). The valve exhibits a very fast response time (less than 2 seconds, depending on the type of control valve). Two MFCs can be used to control the concentration of DO using the molar fraction of oxygen. Note that the *controller block* in Figure 1.14 (programmed in a computer) calculates the set point flow rates that are sent to each MFC. Each *actuator block* is equipped with its control system as described above. This is an example of a *cascade control* where the output of a *primary controller* is used to manipulate the set points of two *secondary controllers* playing the roles of actuators.

1.3.2 DO Probes

The concentration of DO in a bioreactor is measured using a DO probe. For animal cells, the specific rate of oxygen demand is in the range of 0.5–5.0 10^{-10} mmol O_2/cell/h. Culture-DO is generally controlled between 30% and 50% (relative to air saturation). Two types of sensors are the *polarographic* and *galvanic DO electrodes*. In both cases, a membrane (highly permeable to oxygen transport), an anode, cathode, and an electrolyte solution are used. However, an external voltage source is required for polarographic probes contrary to the galvanic DO sensors.

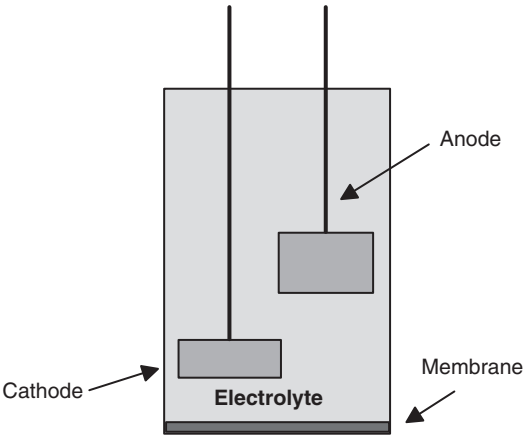

Figure 1.15. Principle of dissolved oxygen measurement.

When the galvanic DO probe is placed in a medium, oxygen diffuses through the membrane and is reduced at the inert cathode (Fig. 1.15):

$$O_2 + 2H_2O + 4e^- \rightarrow 4OH^-. \tag{1.5}$$

At the anode (assuming lead), the following reaction takes place:

$$2Pb + 4OH^- \rightarrow 2Pb(OH)_2 + 4e^-. \tag{1.6}$$

The cathode, usually made of gold or silver, is separated from the external fluid by a semipermeable membrane (e.g., fluorinated ethylene propylene [FEP] Teflon, polyethylene) that allows oxygen to pass through but blocks water and large solute molecules [12]. At steady state, the current signal from the probe is proportional to the flux of oxygen through the membrane and the electrolyte layer located between the membrane and the cathode [12]:

$$I = F \times n \times f, \tag{1.7}$$

where I is the current intensity (amp), F is the Faraday constant (96,500 C/mol), f is the flux of oxygen (mol/s) and n is the number of electrons transferred/mole of O_2 reduced. By considering the oxygen flux from the external phase to cathode Q (g/s), we have

$$Q = \frac{D_m S_m D_e S_e A P_{O2}}{L_m D_e S_e + L_e D_m S_m} \tag{1.8}$$

The parameters of Equation (1.8) are [12]

D_m (cm^2/s):	diffusion coefficient of O_2 in the membrane material
S_m ($g/cm^3/atm$):	solubility of O_2 in the membrane material
D_e (cm^2/s):	diffusion coefficient of O_2 in the electrolyte
S_e ($g/cm^3/atm$):	solubility of O_2 in the electrolyte
A (cm^2):	surface area for both the membrane and electrolyte layer perpendicular to the oxygen flux
P_{O2} (atm):	partial pressure of oxygen in the external phase
L_m (cm):	membrane thickness
L_e (cm):	electrolyte layer thickness.

Since $f = Q/32$, the current intensity is

$$I = \frac{96,500 \times 4}{32} \frac{D_m S_m D_e S_e A P_{O2}}{L_m D_e S_e + L_e D_m S_m} = 12,062 \frac{D_m S_m D_e S_e A P_{O2}}{L_m D_e S_e + L_e D_m S_m}. \quad (1.9)$$

The temperature of the system should be considered when calibrating the device because of the dependence of oxygen partial pressure on temperature. DO probes can be calibrated in nitrogen (zero oxygen) and air-saturated media. These sensors usually exhibit a response time that can be incorporated into the design of the controller.

1.3.3 pH Probes

The pH is another important cell culture environmental parameter that needs to be carefully controlled in industrial fermentation processes. The optimal pH range when growing host mammalian cells, such as hybridoma, CHO, and myeloma, is 7.1–7.4. Production of carbon dioxide (CO_2) and lactic acid ($C_3H_6O_3$) is responsible for the decrease in pH detected during batch cell culture:

$$\begin{aligned} CO_2 + H_2O &\rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^- \\ C_6H_{12}O_6 &\rightleftarrows 2CH_3 - CH_2O - COO^- + 2H^+. \end{aligned} \quad (1.10)$$

In the first reaction, carbon dioxide reacts with water to produce carbonic acid (H_2CO_3), which dissociates into a proton (H^+) and the bicarbonate ion (HCO_3^-). Lactic acid (weak acid), which partially dissociates in water to give lactate ion ($CH_3 - CH_2O - COO^-$) and H^+, is generated from glucose ($C_6H_{12}O_6$) in the second reaction. For control purposes, a calibrated pH glass electrode is routinely used to inform the operator (or a computer) when to introduce CO_2 or HCl into the bioreactor, lowering the pH, or to direct the addition of NaOH and $NaHCO_3$, raising the pH.

pH sensors measure the negative logarithm of the dissolved hydronium ion concentration. In fact, the pH is related to the hydrogen ion activity a_H:

$$a_H = 10^{-pH}; \qquad pH = -\log(a_H). \tag{1.11}$$

Since the hydrogen ion activity is equal to the hydrogen ion concentration (c_H) for dilute solutions, we have

$$pH = -\log(c_H). \tag{1.12}$$

A standard pH sensor used in fermentation processes consists of a glass electrode and a reference electrode. The glass electrode is made up of a glass bulb membrane, an internal solution, and an Ag/AgCl electrode. Protons (H^+) are exchanged between the glass membrane (silicon dioxide and metal oxides) and the investigated solution:

$$Si - O^- + H_3O^+ \rightarrow Si - O - H^+ + H_2O. \tag{1.13}$$

A reference electrode helps complete the circuit (Fig. 1.16). The voltage measured between the electrodes is proportional to the solution's pH:

$$V = V_0 + \frac{RT}{F}\ln(a_H) = V_0 + \frac{2.303RT}{F}\log(a_H) = V_0 - \frac{2.303RT}{F}pH, \tag{1.14}$$

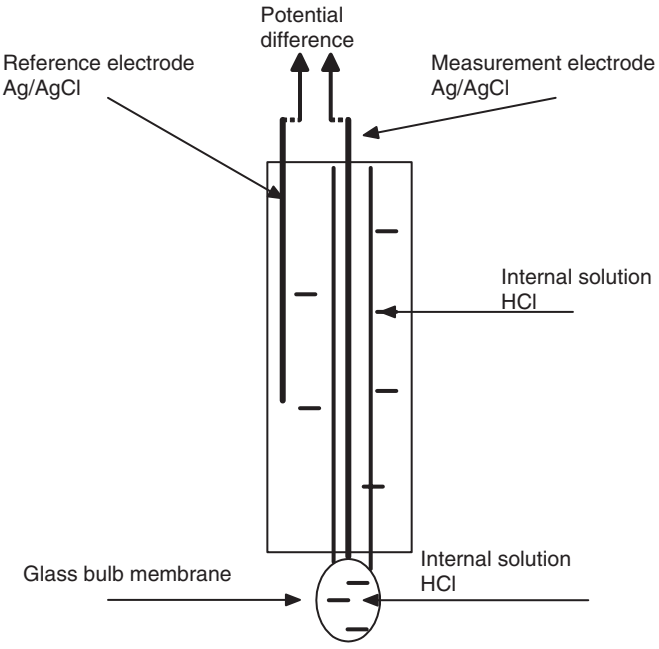

Figure 1.16. pH probe.

where V is the potential of the glass electrode and V_0 is an offset potential. Equation (1.14) reflects equilibrium conditions and does not show how the voltage reading is affected by the pH-response characteristics. Data on the pH response of glass electrodes can be found in Perley [13].

The above online instruments, along with others, such as temperature probes, turbidity meters (for cell mass measurement), and level sensors, affect the performance of the controller. In most cases, their dynamics can be approximated by simple functions that incorporate time-delay phenomena and a time that measures how long it takes to reach an ultimate value (i.e., *time constant*).

1.4 SUMMARY

Applications of process dynamics and control theory extend from biotechnology and physiological systems to drug-delivery processes. In the cases analyzed, an understanding of how the process works and the choices of input variables that have an impact on the controlled variables are important considerations. In addition, a clear statement of the goals of the controller should be included. A good practice is to draw block diagrams to show interconnections among variables and processes involved in the control system. A typical block diagram also includes measuring devices, such as MFCs and DO probes. The operation and dynamics of each piece of equipment must be understood.

PROBLEMS

1.1. Provide two examples of process control applications in biological systems.

1.2. Draw a block diagram of a furnace control system. Identify the main elements (e.g., room, sensor, furnace).

1.3. Provide a block diagram of a feedback control system where the cardiovascular center regulates blood pressure.

1.4. Provide a block diagram of a feedback control system where the vasometer and cardiovascular centers regulate blood pressure.

1.5. Write the ordinary differential equation describing the plasma blood serum concentration for a one-compartment model. Use a single IV bolus dose.

1.6. Solve the following equations governing steady-state oxygen transport across a membrane:

$$D_{\mathrm{m}} \frac{d^2 C_{\mathrm{O_2}}}{dx^2} = 0$$

$$C_{\mathrm{O_2}}(x = 0) = S_{\mathrm{m}} P_{\mathrm{O_2}}$$

$$C_{\mathrm{O_2}}(x = L_{\mathrm{m}}) = 0.$$

1.7. Derive the steady-state flux for diffusive oxygen transport across a membrane. Hint: Use the results from Problem 1.6.

1.8. The dynamics of a turbidity meter (nephelometric turbidity unit) is given by

$$y(t) = a\left(1 - \mathrm{e}^{-6.67(t-0.23)}\right)\psi(t - 0.23),$$

where $\psi(t - t_{\mathrm{d}})$ is the unit step function and t_{d} is the time delay (minute). Calculate $y(1.0)$.

1.9. The dynamics of an analyzer is described by

$$y(t) = a\left(1 - \mathrm{e}^{-6.67t}\right),$$

What is the steady-state value of y?

1.10. The dynamics of an enzyme analyzer (g/L) is described by

$$y(t) = \left(1 - \mathrm{e}^{-1.3(t-3.0)}\right)\psi(t - 3.0),$$

where $\psi(t - t_{\mathrm{d}})$ is the unit step function and t_{d} is the time delay (minute). At what time is $y(t) = 0.98y(t \to \infty)$? Note: $y(t \to \infty)$ represents the steady-state value of y.

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