late in advance the most efficient delivery of drug to be administered (including concentration, flow rate, and so forth). This question can never be answered conclusively unless one has detailed information about the tumor growth rate, the extent to which the drug is effective at killing malignant cells, as well as a host of other complicating effects such as geometry, effect on healthy cells, and so on.

However, to gain some practice with continuous modeling, a reasonable first step is to extract the simplest essential features of this complicated system and think of an idealized caricature, such as that shown in Figure 4.5. For example, as a first step we could assume that the pump, liver, and hepatic artery together behave like a system of interconnected chambers or compartments through which the drug can flow. The tumor cells are restricted to the liver. In this idealization we might assume that (1) the blood bathing a tumor is perfectly mixed and (2) all tumor cells are equally exposed to the drug. This, of course, is a major oversimplification. However, it permits us to define and make statements about two variables:

\[ N = \text{the number of tumor cells per unit blood volume,} \]

\[ C = \text{the number of drug units in circulation per unit blood volume.} \]

**Figure 4.5** In modeling continuous-injection chemotherapy, we might idealize the tumor as a collection of \( N \) identical cells that are all equally exposed to \( C \) units of drug.

Several quantities might enter into the formulation of the equations. These include parameters that can be set or varied by the clinician, as well as those that are specific to the patient. We may also wish to define the following:

\[ C_0 = \text{the concentration of drug solution in the chamber (units/volume),} \]

\[ F = \text{the pump flow rate (volume/unit time),} \]

\[ V = \text{volume of the blood in direct contact with tumor area,} \]

\[ u = \text{rate of blood flow away from tumor site,} \]

\[ a = \text{reproductive rate of tumor cells.} \]
red (including con-
sequence), rate, the extent to
host of other com-
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which the drug can
on we might assume
all tumor cells are
implification. How-

l volume.

that are all equally

equations. These in-
well as those that are
g:
units/volume),

\[
\begin{align}
\text{tumor} & \quad \frac{dN}{dt} = \text{growth rate of cells} - \text{death rate} \\
\text{drug} & \quad \frac{dc}{dt} = \text{rate drug infused by cells} - \text{rate of uptake by cells} - \text{rate of removal by circulation}
\end{align}
\]

Clearly this example is a somewhat transparent analog of the chemostat, because in abstraction of the real situation, we made a caricature of the pump-tumor-circulatory system, as shown in Figure 4.5. A few remaining assumptions must still be incorporated in the model which in principle, can now be written fully. Some analysis of this example is suggested in problem 25.

It should be pointed out that this simple model for chemotherapy is somewhat unrealistic, as it treats all tumor cells identically. In most treatments, the drugs administered actually differentiate between cells in different stages of their cell cycle. Models that are of direct clinical applicability must take these features into account.

Further reading on this subject in Swan (1984), Newton (1980), and Arcoesty et al. (1973) is recommended. A more advanced approach based on the cell cycle will be outlined in a later chapter.

**Modeling Glucose-Insulin Kinetics**

A second area to which similar mathematical models can be applied is the physiological control of blood glucose by the pancreatic hormone insulin. Models that lead to a greater understanding of glucose-insulin dynamics are of potential clinical importance for treating the disorder known as diabetes mellitus.

There are two distinct forms of this disease, juvenile-onset (type I) and adult-onset (type II) diabetes. In the former, the pancreatic cells that produce insulin (islets of Langerhans) are destroyed and an insulin deficiency results. In the latter it appears that the fault lies with mechanisms governing the secretion or response to insulin when blood glucose levels are increased (for example, after a meal).

The chief role of insulin is to mediate the uptake of glucose into cells. When the hormone is deficient or defective, an imbalance of glucose results. Because glucose is a key metabolic substrate in many physiological processes, abnormally low or high levels result in severe problems. One way of treating juvenile-onset diabetes is by continually supplying the body with the insulin that it is incapable of making. There are clearly different ways of achieving this; currently the most widely used is a repeated schedule of daily injections. Other ways of delivering the drug are under-
going development. (Sources dating back several years are given in the references.)

Here we explore a simple model for the way insulin regulates blood glucose levels following a disturbance in the mean concentration. The model, due to Bolie (1960), contains four functions (whose exact forms are unspecified). These terms are meant to depict sources and removal rates of glucose, \( y \), and of insulin, \( x \), in the blood. The equations he gives are (see the definitions given in Table 4.3)

\[
\text{Table 4.3 Variables in Bolie's (1960) Model for Insulin-Glucose Regulation}
\]

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Dimensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V )</td>
<td>Extracellular fluid volume</td>
<td>Volume</td>
</tr>
<tr>
<td>( I )</td>
<td>Rate of insulin injection</td>
<td>Units/time</td>
</tr>
<tr>
<td>( G )</td>
<td>Rate of glucose injection</td>
<td>Mass/time</td>
</tr>
<tr>
<td>( X(i) )</td>
<td>Extracellular insulin concentration</td>
<td>Units/volume</td>
</tr>
<tr>
<td>( Y(i) )</td>
<td>Extracellular glucose concentration</td>
<td>Units/volume</td>
</tr>
<tr>
<td>( F_1(X) )</td>
<td>Rate of degradation of insulin</td>
<td>(See problem 26)</td>
</tr>
<tr>
<td>( F_2(Y) )</td>
<td>Rate of production of insulin</td>
<td>&quot;</td>
</tr>
<tr>
<td>( F_3(X, Y) )</td>
<td>Rate of liver accumulation of glucose</td>
<td>&quot;</td>
</tr>
<tr>
<td>( F_4(X, Y) )</td>
<td>Rate of tissue utilization of glucose</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

\[
\text{insulin: } \quad V \frac{dX}{dt} = I - F_1(X) + F_2(Y), \quad (84a)
\]

\[
\text{glucose: } \quad V \frac{dY}{dt} = G - F_3(X, Y) - F_4(X, Y). \quad (84b)
\]

The model is a minimal one that omits many of the complicating features; see the original article for a discussion of the validity of the equations. Although the model's applicability is restricted, it serves well as an example on which to illustrate the ideas and techniques of this chapter. (See problem 26.)

An aspect of this model worth noting is that Bolie does not attempt to use experimental data to deduce the forms of the functions \( F_i, i = 1, 2, 3, 4 \), directly. Rather, he studies the behavior of the system close to the mean steady-state levels when no insulin or glucose is being administered [equations (84a, b) where \( I = G = 0 \) and \( dX/dt = dY/dt = 0 \)]. He deduces values of the coefficients \( a_{11}, a_{12}, a_{21}, a_{22} \) and \( a_{22} \) in a Jacobian of (84) by looking at empirical data for physiological responses to small disturbances. The approach is rather like that of the plant-herbivore model discussed in Section 3.5. His article is particularly suitable for independent reading and class presentation as it combines mathematical ideas with consideration of empirical results.

Equally accessible are contemporary articles by Ackerman et al. (1965, 1969), Gatewood et al. (1970), and Segre et al. (1973) in which linear models of the release of hormone and removal rate of both substances are presented and compared to data. An excellent recent summary of this literature and of the topic in general is given by Swan (1984, Chap. 3) whose approach to the problem is based on optimal control theory.
Aside from a multitude of large-scale simulation models that we will not dwell on here, more recent models have incorporated nonlinear kinetics (Bellomo et al., 1982) and much greater attention to the details of the physiology. Landahl and Grodsky (1982) give a model for insulin release in which they describe the spike-like pattern of insulin secretion in response to a stepped-up glucose concentration stimulus. Their model consists of four coupled ordinary differential equations. The same phenomenon has also been treated elsewhere using a partial differential equation model (for example, Grodsky, 1972; Hagander et al., 1978). These papers would be accessible to somewhat more advanced readers.

### Compartmental Analysis

Physiologists are often interested in following the distribution of biological substances in the body. For clinical medicine the rate of uptake of drugs by different tissues or organs is of great importance in determining an optimal regime of medication. Other substances of natural origin, such as hormones, metabolic substrates, lipoproteins, and peptides, have complex patterns of distribution. These are also studied by related techniques that frequently involve radiolabeled tracers: the substance of interest is radioactively labeled and introduced into the blood (for example, by an injection at $t = 0$). Its concentration in the blood can then be ascertained by withdrawing successive samples at $t = t_1, t_2, \ldots, t_n$; these samples are analyzed for amount of radioactivity remaining. (Generally, it is not possible to measure concentrations in tissues other than blood.)

Questions of interest to a physiologist might be:

1. At what rate is the substance taken up and released by the tissues?
2. At what rate is the substance degraded or eliminated altogether from the circulation (for example, by the kidney) or from tissue (for example, by biochemical degradation)?

A common approach for modeling such processes is compartmental analysis: the body is described as a set of interconnected, well-mixed compartments (see Figure 4.6b) that exchange the substance and degrade it by simple linear kinetics. One of the most elementary models is that of a two-compartment system, where pool 1 is the circulatory system from which measurements are made and pool 2 consists of all other relevant tissues, not necessarily a single organ or physiological entity. The goal is then to use the data from pool 1 to make deductions about the magnitude of the exchange $L_{ij}$ and degradation $D_{i}$ from each pool.

To proceed, we define the following parameters:

- $m_1 =$ mass in pool 1,
- $m_2 =$ mass in pool 2,
- $V_1 =$ volume of pool 1,
- $V_2 =$ volume of pool 2,
- $x_1 =$ mass per unit volume in pool 1,
Figure 4.6 (a) Results of a physiological experiment in which the percentage of tracer remaining in the blood is followed over 300 h and is shown by points marked + on this semilog plot. Using such data one can estimate the quantities $\lambda$, $\alpha$, and $b_i$ in (88a,b) and thus make deductions about the distribution of the substance in the body. Dotted-dashed line: $a_1 e^{-\lambda t}$; dashed line: $a_2 e^{-\lambda t}$; and solid line, $a_1 e^{-\lambda t} + a_2 e^{-\lambda t}$. Here $\lambda_2 < \lambda_1$.

(b) A two-compartment model with exchange rates $L_{12}$, degradation rates $D_i$, and rates of injection $u_1$ and $u_2$, $u_1 = u_2 = 0$ (see text).


\[ x_2 = \text{mass per unit volume in pool 2}, \]
\[ L_{ij} = \text{exchange from pool } i \text{ to pool } j, \]
\[ D_j = \text{degradation from pool } j, \]
\[ u_j = \text{rate of injection of substance into pool } j. \]

Note that \( L_{ij} \) and \( D_j \) have units of \( 1/\text{time} \), while \( u_j \) has units of mass/\( \text{time} \). A linear model would then lead to the following mass balance equations:

\[
\frac{dm_1}{dt} = -L_{12}m_1 + L_{21}m_2 - D_1m_1 + u_1, \quad (85a)
\]
\[
\frac{dm_2}{dt} = L_{12}m_1 - L_{21}m_2 - D_2m_2 + u_2. \quad (85b)
\]

In problem 30 we show that this can be rewritten in the form

\[
\frac{dx_1}{dt} = -K_1x_1 + K_{21}x_2 + w_1, \quad (86a)
\]
\[
\frac{dx_2}{dt} = K_{12}x_1 - K_2x_2 + w_2, \quad (86b)
\]

where

\[
K_1 = L_{12} + D_1, \quad K_2 = L_{21} + D_2, \]
\[
K_{21} = \frac{L_{21}V_2}{V_1}, \quad K_{12} = \frac{L_{12}V_1}{V_2}, \]
\[
w_1 = \frac{u_1}{V_1}, \quad w_2 = \frac{u_2}{V_2}. \]

Note that now coefficients are corrected by terms that account for effects of dilution since compartment sizes are not necessarily the same. This illustrates why equations should proceed from mass balance rather than from concentration balance.

Now suppose that a mass \( M_0 \) of substance is introduced into the bloodstream by a bolus injection (i.e. all at one time, say at \( t = 0 \)). Assuming that it is rapidly mixed in the circulation, we may take

\[
m_1(0) = m_0, \quad m_2(0) = 0, \quad u_1 = u_2 = 0. \quad (87)
\]

Then equations (86a,b) are readily solved since they are linear and we obtain

\[
x = c_1v_1e^{-\lambda_1t} + c_2v_2e^{-\lambda_2t} \quad (88a)
\]

where

\[
x = \begin{pmatrix} x_1(t) \\ x_2(t) \end{pmatrix} \quad \text{and} \quad c_i = \begin{pmatrix} a_i \\ b_i \end{pmatrix}. \quad (88b)
\]

Note that the exponents are negative because substance is being removed. In problems 30 through 32 we discuss how, by fitting such solutions to data for \( x_1(t) \) (concentration in the blood), we can gain appreciation for the rates of exchange and degradation in the body. A thorough treatment of this topic is to be found in Rubinow (1975).