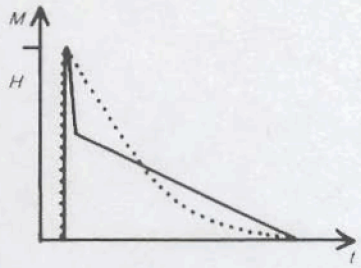
10 Compartmental Analysis



—and . . . have the same H and A but quite different shapes!

10.1 Introduction

The indicator curves contain more information than that derived by black box analysis, in which only four parameters are used (SHAM, see Chapter 8). This can be illustrated, to give one example, by considering the residue curve after bolus injection. Here the black box analysis tells us to measure the area and, in the particular case of a "rapid" bolus, the maximum height. Many curves of the general wash-out (steadily decreasing) type can be drawn so that area and height are the same. In this chapter we enter and survey the black box by making compartmental models of the system's interior. The *Criterion of Usefulness* of these models must, as in any other kind of modeling, be: does the application of compartmental analysis to the experimental data yield useful (i.e., meaningful) physiological information?

10.2 Compartment or Pool

The region R could also be the entire system.

Consider a region R inside a system. Mass balance of indicator for this region is

$$\frac{dm_R(t)}{dt} = j_{R,\text{in}}(t) - j_{R,\text{out}}(t) \qquad [10.1]$$

where $m_R(t)$ is the amount of indicator in region R at time t, and $j_{R,\text{in}}(t)$ and $j_{R,\text{out}}(t)$ are respectively the influx rate (rate of indicator entry at time t) and the outflux rate to and from R. *The region R is defined as a compartment if the outflux is at any time proportional to the amount of indicator in R with the constant of proportionality k being the flux/mass ratio J/M respectively the flow/volume ratio F/Vd of region R:*

Definition of a compartment

Definition of a Compartment

$$j_{R,\text{out}} = k_R m_R(t) \qquad [10.2]$$

where

If a compartment is mixed then both Eqs. [10.2] and [10.3] follow; that is they are no longer the definition.

$$k_R = \begin{cases} J_R/M_R \\ F_R/Vd_R \end{cases} \qquad [10.3]$$

In the systemic steady state the parameter k_R in Eq. [10.2] is constant. Equations [10.2] and [10.3] are, however, sufficiently simple and yet detailed models of the black box so that they can also be solved if $k_R(t)$ is a function of time, as it is under certain conditions.

The single compartment is the only case when systemic steady state need not be maintained. As an example, consider muscle blood flow at rest and exercise.

The relationships shown in Eq. [10.3] are customarily not given as definitions, but are *derived* by defining the compartment as a region throughout which a tracer instantaneously becomes mixed uniformly on injection anywhere within the system. In this "well-mixed case" the specific activity $s_r(t)$ is constant throughout the region at a given time t and equal to that at all outlets. The outflux of indicator from such a well-mixed region is evidently given by

$$j_{R,\text{out}} = J_R s_R(t) = \frac{J_R}{M_R} \cdot m_R(t) \qquad [10.4]$$

which essentially expresses the convective outlet condition.

"Pool" is actually a term that we would not consider very useful, because it stresses the mixing idea that we do not need; it is better to use "compartment."

Our procedure of defining a compartment directly by Eqs. [10.2] and [10.3] rather than by the instantaneous and uniform mixing property is motivated primarily by the *local clearance case* to be discussed in Sec. 10.4. Note that with the definition we employ, a compartment need not involve a mixing or a stirring mechanism. Thus, according to our definition all the red cells of the blood or the entire cerebral cortex can perhaps more readily be accepted as compartments (in specific contexts to be discussed) even though quite obviously no mixing device to distribute indicator exists inside the compartment.

The difference between the conventional definition of a compartment and that given in this section is illustrated by the operational criterion: Conventionally we require that the specific activity is the same at all points (x, y, z) at any time t: $s_R(x, y, z, t)$ is assumed to be constant in space. Our definition does not require a spatially even specific activity. All that is required is *that the local deposition of indicator in any volume element of the region yields the same kinetics (monoexponential) as simultaneous uniform labeling of all parts of R would have yielded.* In terms of the discussion in Chapter 8 a compartment has no "good sites" or "bad sites"; every site is as "good" as any other.

Definition of a nonmixed compartment

Note that both the well-mixed and the "nonwell-mixed" (the nonmixed compartment) are homogeneous (i.e., isotropic); that is they have the same systemic properties throughout.

We might denote a system defined by the well-mixed property a *well-mixed compartment* and a system defined by the local deposition (local clearance experiment) property alluded to above a *nonmixed compartment.* However, the definition by Eqs. [10.2] and [10.3] makes no assumption as to whether mixing does or does not occur; it encompasses both types of systems.

In conclusion, we can therefore answer the question,

"When is a system a compartment?" with, "If the system is well-mixed or if just the washout is monoexponential (this is the meaning of Eq. [10.2], see below) with J/M or F/Vd the exponential coefficient, this latter case encompassing the former."

> *Note:* In Chapter 9 we discussed the impulse labeling of a "generation" of red cells by ^{15}N-glycine. This cohort labeling constitutes a labeling *not* of the red cells in the circulating red cells in the blood but of a certain subfraction (cells of a certain age). Thus in this situation, despite the fact that the red cells are constantly mixed in the blood so that the specific activity is the same throughout, the circulating red cell mass does not constitute a compartment. This is true because the basic tracer condition is not fulfilled: the (average) labeled cell does not have the same chance of destruction as the (average) nonlabeled cell. The example shows that the dictum that "a well-mixed system is a compartment" should be qualified with "for the tracer-mother substance pair." However, as this is generally the case this qualification is not necessary.

10.3 The Washout Curve from a Compartment is Monoexponential

We could have injected indicator rapidly or slowly; but at time 0 (when we start considering the system) the amount m_0 is inside and no further influx occurs; it is a *pure* washout situation.

Consider a situation when an amount m_0 of indicator resides inside a compartment and no additional indicator enters. In this case also no recirculation of indicator occurs. This situation is called the washout or clearance situation (here the word "clearance" simply denotes "washing out").

The mass balance equation for any subsequent time t is given by Eqs. [10.1] and [10.2] as the term for influx is 0. For convenience we will here use the convective terminology and will drop the subscript R. Hence according to our definitions

$$\left.\begin{aligned}\frac{dm(t)}{dt} &= -\frac{F}{Vd}m(t)\\ &= -km(t)\end{aligned}\right\} \qquad [10.5]$$

$dm/dt = j_{in} - j_{out}$

We here show one of the methods of solving Eq. [10.5]; the various steps have been included as an exercise in ln and e functions.

The solution of this differential equation is the monoexponential function because we can rearrange Eq. [10.5] and integrate to obtain (with $dm(t)/dt$ written as $\dot{m}$):

$$\int_0^t \frac{\dot{m}}{m}\,dt = -\int_0^t k\,dt = -kt$$

or

$$\int_{m(0)}^{m(t)} \frac{1}{m}\,dm = -kt$$

$$\ln m(t) - \ln m(0) = -kt$$

$$\ln\left(\frac{m(t)}{m(0)}\right) = -kt \qquad [10.6]$$

$$\frac{m(t)}{m(0)} = e^{-kt}$$

$$\underline{\underline{m(t) = m(0)e^{-kt} = m_0e^{-kt}}}$$

$$\text{with } k = F/Vd$$

$$y' = -ky$$

$$\updownarrow$$

$$y = y_0 e^{-kt}$$

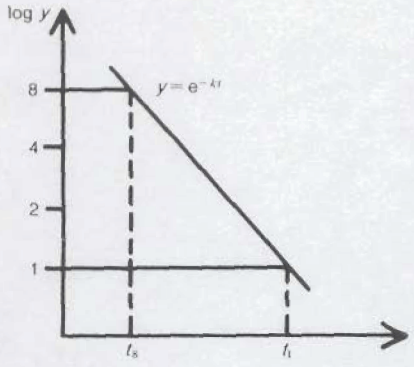
Equation [10.6] is formally identical to Eq. [10.5]: they have precisely the same meaning. To state that the derivative of a curve is at all times proportional to the curve's ordinate is the same as saying that the curve is monoexponential.

The curve described by Eq. [10.6] has the well known characteristic of a *constant half-time* $t_{1/2}$. The relationship between the exponential rate constant k and $t_{1/2}$ is

$$k = \frac{\ln (2)}{t_{1/2}} \approx \frac{0.693}{t_{1/2}} \quad \text{min}^{-1} \qquad [10.7]$$

As an exercise derive Eq. [10.7] from one of the expressions leading to Eq. [10.6] setting $m(t) = 1/2 m_0$ and $t = t_{1/2}$

A practical method of obtaining the rate constant k from a semilog plot of a monoexponential curve is to "count half-lives." A convenient ordinate is chosen that can be divided successively by two several times and still yield integer values. For example, we choose the ordinate 8 (or 80, or 800, etc.), at which the abscissa t_8 is near the left-hand edge of the paper. Divide 8 successively by 2, for example, 3 times, to reach the ordinate 1 (or 10, or 100, etc.), at which the abscissa, near the right-hand edge of the paper, is read off as t_1. The half-life $t_{1/2}$ of the monoexponential curve is then

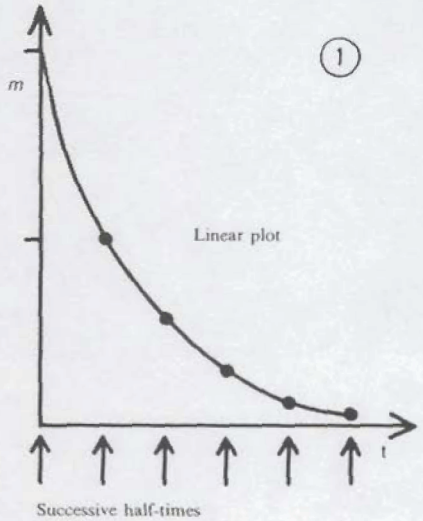


$$t_{1/2} = \frac{t_1 - t_8}{3}$$

Exercise: Half-life $t½$ is defined as the time it takes for the value of a monoexponential decay curve $m(t) = m_0 e^{-kt}$ to decrease to $½\, m(t)$. Prove that $t½$ is independent of the starting value and hence validate the present graphical procedure.

It is important to get "familiarity" with k: it follows from Eq. [10.5] that

$$k = -\frac{dm(t)/dt}{m(t)} \quad \text{min}^{-1} = \frac{\text{Rate of escape}}{\text{Amount}} \quad \text{min}^{-1} \quad \text{at time } t \qquad [10.8]$$

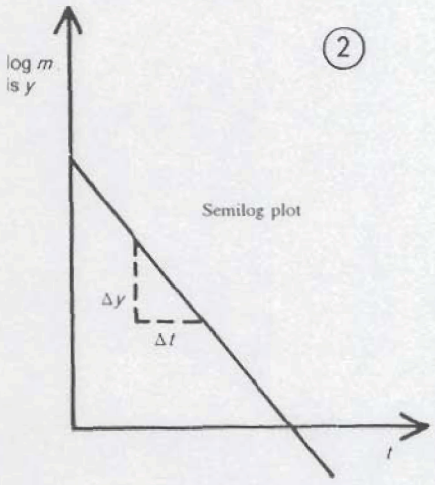


Successive half-times

In other words k is the *fractional escape rate.* A k value of 0.02 min^{-1} means, for example, that 2% of the indicator content in the compartment disappears per minute.

The exponential function has the property that the curvilinear shape can be "straightened out" either by plotting log $m(t)$ against t (semilogarithmic plot), by plotting $m(t)$ against $\dot{m}(t)$ (phase plane method), or by plotting $\dot{m}(t)/m(t)$ against t (fractional escape rate plot).

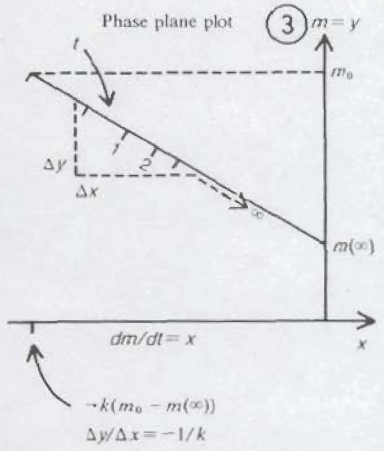
The semilog method is convenient when semilogarithmic graph paper is available. But the method is somewhat insensitive to the data in that it may tend to obscure a minor deviation from the monoexponential curve form. By using decimal logarithms, the equation of the straight line is

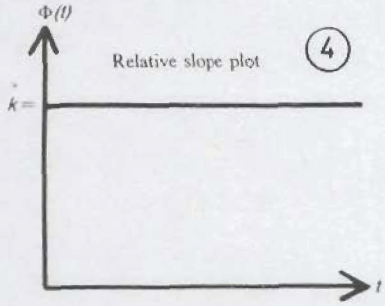


$\Delta y/\Delta t = -D$

where

$\ln(10) \cdot D = k$





Φ is the capital letter for F in the Greek alphabet (Phi)

$$\log_{10} m(t) = \log_{10} m_0 + \log_{10} e^{-kt}$$
$$= \log_{10} m_0 - kt \log_{10} e$$
$$\simeq \log_{10} m_0 - 0.4343\ kt$$

That is, the $\log_{10}$-curve has the 0 time intercept $\log_{10} m_0$ and the slope $-D = -\log_{10}(e)k \simeq -0.4343\ k$. Hence

$$k \simeq \frac{1}{0.4343} D \simeq 2.303\ D \qquad [10.9]$$

[the constant 2.303 is actually $\frac{1}{\log_{10} e} = \ln(10)$]

It should be noted that the infinity value for the residue $m(\infty)$ must be 0 or that it must be known and subtracted before $m(t)$ is plotted on semilogarithmic paper. By this we mean that if the curve form actually is

$$m(t) = m(\infty) + (m_0 - m(\infty))e^{-kt} \qquad [10.10]$$

then the semilogarithmic plot will not give a straight line. This is, however, obtained with the phase plane method of plotting $m(t) = y$ against $m(t)/dt = x$ because differentiation of Eq. [10.10] yields

$$dm(t)/dt = -k(m_0 - m(\infty))e^{-kt} \qquad [10.11]$$

that inserted on the right hand side of Eq. [10.10] gives

$$m(t) = m(\infty) - \frac{1}{k} dm(t)/dt$$
$$y = m(\infty) - 1/kx \qquad [10.12]$$

The phase plane method requires more work to calculate the slopes numerically or to measure them by drawing tangents to $m(t)$ on a linear plot at various times. But it has the advantage of being more sensitive to the data, especially at long time, and of yielding a linear plot even when $m(\infty)$ is not 0.

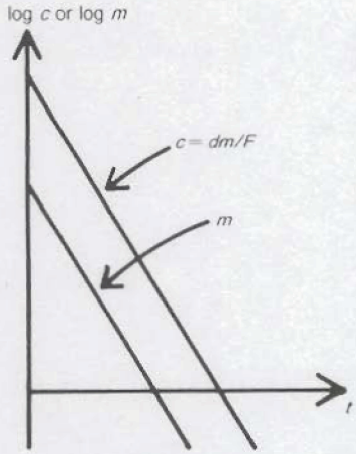
A fourth method of plotting $m(t) = m_0 e^{-kt}$ is to plot the fractional escape rate $\Phi(t) = -\dot{m}/m$ against t. This results in a horizontal line

$$\Phi(t) = k \qquad [10.13]$$

Thus far we have considered the residue curve $m(t)$. But we can also obtain an expression for the outlet concentration $c_{out}(t)$ of a single compartment simply by noting that $j_{out}(t) = -dm(t)/dt = Fc_{out}(t)$. This, as $-dm(t)/dt = F/Vdm(t)$, our basic equation, gives

$$Fc_{out}(t) = \frac{F}{Vd} m(t)$$
$$= \frac{F}{Vd} m_0 e^{-kt} \qquad [10.14]$$

$$c_{out}(t) = \frac{m_0}{Vd} e^{-kt},\ k = \frac{F}{Vd}$$



Note that c is parallel to m; m, that is *only* the case when m is monoexponential.

A monoexponential washout curve is *not per se* evidence of a compartment.

Equation [10.14] shows that the outlet concentration is the same regardless of where we deposit the indicator inside a system with no physical mixing.

We emphasize that a monoexponential curve for residue $m(t)$ or for outlet concentration $c(t)$ in the washout situation is not sufficient to allow one to infer that the system is a compartment. To make this inference it is necessary to show *in addition* that the 0 time intercept (the amplitude) can be interpreted as a meaningful m_0/Vd and that the rate constant K is the F/Vd ratio of the system (this comment refers to the points raised in Sec. 10.7.

As an illustration showing that the presence of a monoexponential washout curve is not sufficient to allow one to infer that a system is a compartment let it be recalled that biological systems generally show a monoexponential washout function after sufficient long time has elapsed (the "final" slope). This holds for very complex systems that are very far from being approximated by a single compartment. And k_n, the exponential coefficient of the final slope, bears no simple relationship to the F/Vd of the entire system or of its slowest compartment.

10.4 The Local Clearance Method, An Example of a System That Is a Compartment and Yet Not Well-mixed

Saline = physiological saline = 0.9% NaCl.

Larsen, O. A. et. al. (1966): *Acta Physiol. Scand.* 66:337.

We have already stressed that it does not matter how the indicator is distributed inside a compartment. Here the important case that results when mixing does not occur shall be further analyzed. Assume that a bolus of about 0.1 ml of sterile saline containing a freely diffusible indicator such as ^{133}Xe (a gamma emitter) is injected at time 0 into a homogeneous tissue such as subcutaneous adipose tissue. A homogeneous tissue has, by definition, the same blood flow per unit volume in all its portions. A portion denotes a volume element of the order of about 1 mm^3, which is so large that in a washout situation diffusion would not (except at extremely slow flow) constitute an adequate mixing factor between portions. Likewise all other relevant physiological parameters are constant throughout the tissue, in particular the volume of distribution per gram of tissue $\lambda = Vd/W$ is the same in all portions. A γ-detector monitors the total amount of ^{133}Xe in the entire volume of tissue (a monitored tissue mass of several grams surrounding the injection site suffices). Assume that one has experimentally found that the rate of disappearance of residue is proportional to the residue; in other words, it has been found experimentally that the washout curve is monoexponential

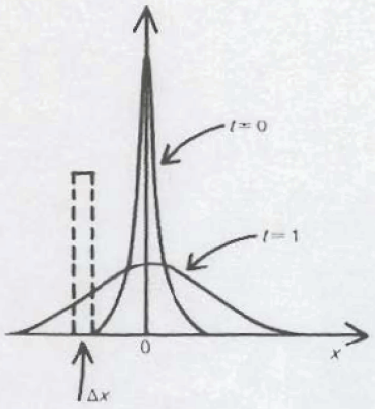
$$m(t) = m_0 e^{-kt} \qquad [10.15]$$

It is experimentally shown, in addition, that

$$k = \frac{F}{Vd} = \frac{F/W}{Vd/W} = \frac{f}{\lambda} \qquad [10.16]$$

Here f is the blood flow per gram of tissue (it could be measured directly by collecting venous effluent blood and by weighing the tissue), and λ is the tissue/blood steady-state concentration ratio (it was calculated according to the rules given in Chapter 5 after measuring the fat content of the tissue). In this way, as both f and λ could be determined, f/λ also could be calculated. It was found to check with k.

Thus, having verified the local clearance method using ^{133}Xe in adipose tissue, one need not go any further. This simple result is, however, quite puzzling. How can it be that the diffusion of ^{133}Xe out of the local tissue, a process that steadily enlarges the size of the depot, does not influence the measurement? A model in which ordinary Fick diffusion as well as washout by perfusion of blood *locally* equilibrated with the tissue can explain this result. Consider for simplicity only the one-dimensional case: The amount m_0 of ^{133}Xe is deposited at time 0 in an infinite plane ($x = 0$ in the sketch). Mass balance in a tissue slab of thickness Δx at the distance x from the plane of deposition gives



Time rate of concentration change	Convection away from local depot	Net diffusion to and from the neighbor slabs	[10.17]

$$\frac{\partial c(x,t)}{\partial t} = -kc(x,t) + D\frac{\partial^2 c(x,t)}{\partial x^2}$$

The detector monitors the total amount of indicator in the tissue; that is

$$m(t) = \int_{-\infty}^{\infty} c(x,t)dx \qquad [10.18]$$

Integrating Eq. [10.17] spatially from $-\infty$ to $+\infty$ and inserting Eq. [10.18] yields

$$\frac{dm(t)}{dt} = -km(t) + D\left[\left(\frac{\partial c}{\partial x}\right)_{\infty} - \left(\frac{\partial c}{\partial x}\right)_{-\infty}\right] \qquad [10.19]$$

The bracketed term is the difference between the indicator gradient at $x = +\infty$ and at $x = -\infty$. Since the indicator never diffuses to infinitely distant regions in appreciable quantity the concentration gradient is 0 in these regions. Hence the bracketed term is 0 and Eq. [10.19] becomes

$$\frac{dm(t)}{dt} = -km(t) \qquad [10.20]$$

The solution of Eq. [10.20] is the observed monoexponential. This means that the decreased local washout from the initially deposited region due to intratissue diffusion is exactly counterbalanced by the increased local washout from more distant regions.

The above argument [Eqs. 10.17 to 10.20] allows one to "explain" the experimental observation of a monoexponential behaviour despite local diffusion processes that spread out the depot. Nevertheless, the significance of this result is the converse; that is, the experimental finding of a monoexponential washout suggests (but does not prove uniquely) that no more than ordinary "millimeter scale" diffusion [Eq. 10.17] goes on in addition to local clearance by blood flow.

10.5 Kety's Local Cerebral Blood Flow Method Based on a Diffusible Tracer and Brain Tissue Sampling

Landau, W. M. et al. (1955): *Trans. Am. Neurol. Assoc.* 80:125.

In this method the cerebral concentration is often measured by a radioautographic technique and hence the method is also called the radioautographic method. It is based on the intravenous infusion over 1 min of a freely diffusible indicator such as $CF_3\ ^{131}I$ (a gas) or [^{131}I]iodoantipyrine. The arterial inflow concentration to the brain is followed by multiple blood samples collected from the femoral artery. Thus $c_a(t)$ is known. After 1 min the animal is decapitated and the brain tissue concentration measured in many small tissue areas.

Remember that $F/Vd = f/\lambda$

The *assumption* is made that the local brain tissue area (about 1 mm^3) constitutes a compartment so that the *unit impulse response function* in terms of the local residue is

$$H^*(t) = e^{-f/\lambda\, t} \qquad [10.21]$$

with f being the blood flow per gram of tissue and λ being the tissue/blood partition coefficient (i.e., volume of distribution per gram of tissue).

The influx of indicator to the tissue area in question is per gram of tissue $fc_a(t)$. Thus the residue per gram of tissue is

$$\begin{aligned} c(t) &= fc_a(t) * e^{-f/\lambda\, t} \\ &= f\int_0^t c_a(u)e^{-f/\lambda\,(u-v}dv\,du \\ &= fe^{f/\lambda\, t}\int_0^t c_a(u)e^{-f/\lambda\, u}du \end{aligned} \qquad [10.22]$$

The blood flow is calculated by computing a family of residue curves for possible values of f (λ is known) and then interpolating at $t = 1$ min to the measured tissue concentration value.

The method depends critically on precise knowledge of λ and on the validity of assuming that the unit impulse response function is monoexponential.

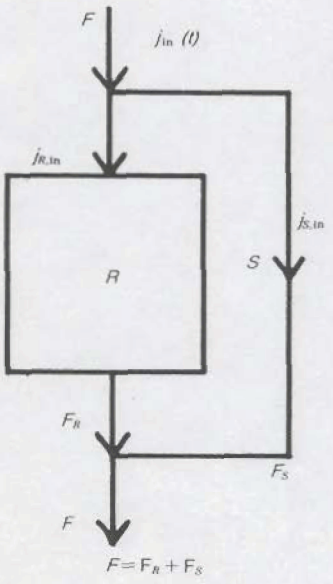
If instead of a freely diffusible indicator one uses *microspheres*, then the unit impulse response function is $H^*(t) = 1$;

that is complete retention. Then the 1-min residue is calculated from

$$\begin{aligned} c(t) &= f c_a(t) * 1 \\ &= f \int_0^t c_a(t)\,dt \\ &= f \cdot [\text{Area}]_{\text{artery}} \end{aligned}$$

This approach, described in Chapter 4 (the bolus fractionation method of Sapirstein), is in principle better than Kety's. However, in using microspheres the problem of equivalent labeling comes in: the microspheres do not quite follow the blood, but to some degree seem to go preferentially to the best perfused areas (they stay in the streaming blood).

Remember that the area is found by sampling femoral blood (see also Ex. 3 in Chapter 8).



10.6 Forward Shunt

Consider that the region R, a single compartment, is bypassed by a forward shunt S, taking the fraction F_S/F of total flow through a pathway of negligible volume of distribution. Let a bolus of ideally brief duration (an impulse) be injected

$$j_{in}(t) = m_0 \delta(t) \qquad [10.23]$$

At the flow branching point the indicator bolus fractionates in proportion to flow so that

$$\left.\begin{aligned} j_{S,in}(t) &= \frac{F_S}{F} m_0 \delta(t) \\ j_{R,in}(t) &= \frac{F_R}{F} m_0 \delta(t) \end{aligned}\right\} \qquad [10.24]$$

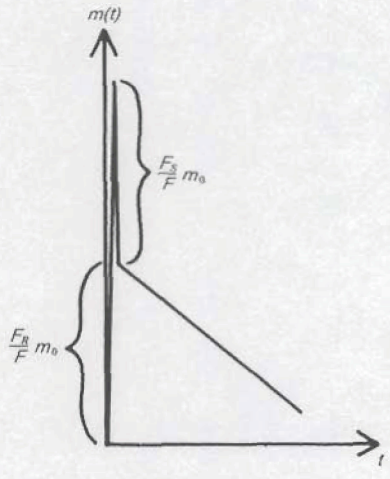
The shunt outflux is the same as the shunt influx $j_S(t)$. The compartment outflux is monoexponential:

$$\left.\begin{aligned} j_{S,out} &= \frac{F_S}{F} m_0 \delta(t) \\ j_{R,out} &= \frac{F_R}{F} \cdot \frac{F_R}{Vd} m_0 e^{-\frac{F_R}{Vd} t} \end{aligned}\right\} \qquad [10.25]$$

The outlet concentration curve of the combined system is thus

$$\begin{aligned} c_{out}(t) &= j_{out}/F \qquad [10.26] \\ &= \frac{F_S}{F} \cdot \frac{m_0}{F} \delta(t) + \frac{F_R}{F} \cdot \frac{m_0}{F} \cdot \frac{F_R}{Vd} e^{-(F_R/Vd)t} \end{aligned}$$

Equation [10.26] thus shows a "spike" contribution (the shunt) followed by a monoexponential curve (the compartment). The shunt dispersion of transit times must be small, as otherwise the spike is smeared out and cannot be seen.



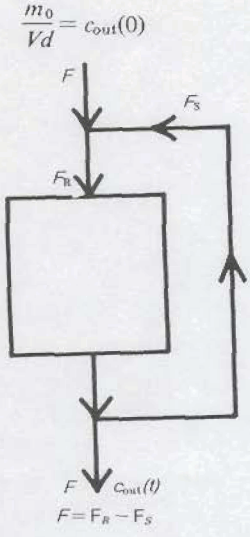
10.7 Feedback Shunting

Now consider that a shunting back from outlet to inlet occurs so that a certain fraction of the outflow from the system

is carried back upstream. The arrangement may be considered as "instant recirculation."

Since F_S essentially functions as an internal mixing device added to the system, which already behaves in a well-mixed manner, it follows that the indicator washout curve following bolus injection has the same form as if no feedback shunting had been present. Hence

$$\left.\begin{aligned} c_{out}(t) &= \frac{m_0}{Vd} e^{-kt} \\ \text{with } k &= F/Vd \end{aligned}\right\} \qquad [10.27]$$



In contrast with the forward shunting case Eq. [10.27] shows *no* spike. The amplitude of the exponential function $c_{out}(0) = m_0/Vd$ represents the full amplitude corresponding to the injected dose.

However, the exponential coefficient $k = F/Vd$ is *not* that of the compartment proper, or $k_R = F_R/VD$. because just as in the feedforward case k is *less by* the factor F_r/F. This shows that even the observation of a monoexponential curve with no spike complications is *insufficient evidence* for deducing the presence of a compartment whose local flow/volume ratio can be measured by

$$k_R = \frac{\text{Compartment throughflow}}{\text{Compartment volume of distribution}} = \frac{F_R}{Vd} \qquad [10.28]$$

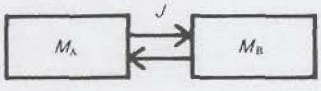
The results here outlined mean that one must somehow be certain, when making the experimental observations, that the outflow from the compartment *itself* is being sampled from; that is, no collateral flow is allowed.

10.8 Two Compartment Systems

Closed system

Suppose we have two well-stirred compartments A and B that continuously exchange a given substance at the rate J mg/sec. We could here think of the red blood cells in plasma exchanging sodium by diffusion and by active cellular forces (the "sodium pump"). A bolus of an amount m_0 of a tracer for the substance is injected into compartment A. What is the time course of the specific activities $s_A(t)$ and $s_B(t)$ in the two compartments?

Two-compartment closed system



$$s = \begin{cases} m/M \\ j/J \end{cases}$$

Influx into A from B is

$j_{B\to A} = Js_B(t)$

same for influx from B to A.

Let M_A and M_B be the amounts of mother substance in the compartments and $m_A(t)$ and $m_B(t)$ the corresponding amounts of the tracer. Mass balance then gives

$$\begin{aligned} \text{Rate of change} &= \text{Influx} - \text{Outflux} \\ dm_A(t)/dt = M_A ds_A(t)/dt &= Js_B(t) - Js_A(t) \\ dm_B(t)/dt = M_B ds_B(t)/dt &= Js_A(t) - Js_B(t) \end{aligned} \qquad [10.29]$$

$$\frac{dy}{dt} = -ky \quad \Rightarrow \quad y = y(0)e^{-kt}$$

Dividing by M_A in the upper equation and by M_B in the lower one and subtracting the two resulting equations gives, with $s_A(t) - s_B(t) = \Delta$,

$$d\Delta/dt = -[J/M_A + J/M_B]\Delta \qquad [10.30]$$

that solved for Δ yields

$$\Delta = \Delta(0)e^{-kt} \qquad [10.31]$$

with

$$k = [J/M_A + J/M_B] \qquad [10.32]$$

Thus Δ, the *difference* in specific activity between the two compartments diminishes monoexponentially:

$$s_A(t) - s_B(t) = [s_A(0) - s_B(0)]e^{-kt} \qquad [10.33]$$

where

$$k = \frac{J}{M_A} + \frac{J}{M_B} \qquad [10.34]$$

The total amount m_0 of tracer in the system is constant and equal to

$$m_0 = m_A(t) + m_B(t) \qquad [10.35]$$

$$= M_A s_A(t) + M_B s_B(t) \qquad [10.36]$$

Equations [10.33] and [10.36] give $s_A(t)$ and $s_B(t)$ as

$$s_A(t) = s(\infty) + [s_A(0) - s(\infty)]e^{-kt} \qquad [10.37]$$

$$s_B(t) = s(\infty)(1 - e^{-kt}) \qquad [10.38]$$

where

$$s_A(0) = \frac{m_0}{M_A} \qquad [10.39]$$

is the initial specific activity in the injected compartment and

$$s(\infty) = \frac{m_0}{M_A + M_B} \qquad [10.40]$$

is the final or equilibrium specific activity throughout the system.

Two independent compartments in parallel

An amount m_0 of indicator is bolus injected into the inflow F which fractionates into an inflow F_G to compartment G and an inflow $F_w = F - F_G$ into the independent compartment w (the gray matter and white matter of the brain approximate this arrangement). By the bolus fractionation principle the amount $m_0 F_G/F$ enters compartment G giving the residue response

$$M_G\ (t) = m_0 \frac{F_G}{F} e^{-k_G t} \qquad [10.41]$$

where

$$k_G = \frac{F_G}{Vd_G} = \frac{F_G}{\lambda_G W_G} = \frac{f_G}{\lambda_G} \qquad [10.42]$$

which defines $f_G = F_G/W_G$. Similarly the amount $m_0 F_w/F$ enters compartment W giving the residue response

$$m_w(t) = m_0 \frac{F_w}{F} e^{-k_w t} \qquad [10.43]$$

where

$$k_w = \frac{F_w}{V d_w} = \frac{F_w}{\lambda_w W_w} = \frac{f_w}{\lambda_w} \qquad [10.44]$$

which defines $f_w = F_w/W_w$. The observed residue $m(t)$ is the sum

$$m(t) = m_G(t) + m_w(t) \qquad [10.45]$$

The exponential amplitudes in Eqs. [10.41] and [10.43] are expressed respectively as

$$\frac{F_G}{F} = \frac{F_G}{W_G}\frac{W_G}{W}\frac{W}{F} = f_G w_G \frac{W}{F} \qquad [10.46]$$

w_G and w_w are the fractional weights.

$$\frac{F_w}{F} = \frac{F_w}{W_w}\frac{W_w}{W}\frac{W}{F} = f_w w_w \frac{W}{F} \qquad [10.47]$$

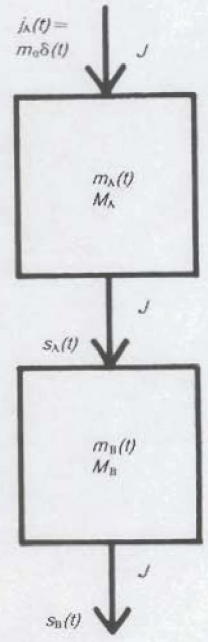
in which are defined $w_G = W_G/W$ and $w_w = W_w/W$. The sum of these equations is

$$1 = (f_G w_G + f_w w_w)\frac{W}{F} \qquad [10.48]$$

which gives

f as a weighted (average flow), the fractional weights being the weighting factors

$$f = \frac{F}{W} = f_G w_G + f_w W_w \qquad [10.49]$$



Substituting Eqs. [10.46], [10.47], and [10.49] into [10.41] and [10.43] and thence into Eq. [10.45] gives

$$\frac{m(t)}{m_0} = a_G e^{-k_G t} + a_w e^{-k_w t} \qquad [10.50]$$

where

$$a_G = 1 - a_w = \frac{f_G w_G}{f_G w_G + f_w w_w} \qquad [10.51]$$

As each compartment has a monoexponential residue the observed total residue is a sum of two exponentials.

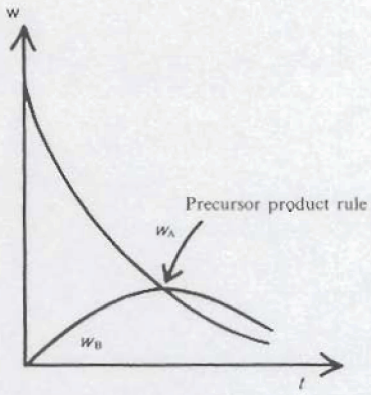
Two compartments in series, one-way flow

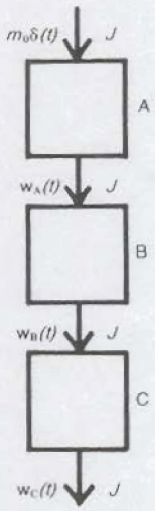
This case is of interest primarily in connection with chemical processes and in describing mother-daughter relationships in radioactive transformations. Tracer-mother substance terminology is used. In the systemic steady state the influx of mother substance into compartment A equals that into B and out of B, it is the throughflux J. A rapid (impulse) injection of the amount m_0 is made into compartment A at $t = 0$.

Mass balance of tracer gives for the two compartments

$$s_A(t) = \frac{m_A(t)}{M_A}$$

$$s_B(t) = \frac{m_B(t)}{M_B}$$





usually
$n \leq 4$

Out In

$$M_A\frac{ds_A}{dt} = -Js_A(t) + m_0\delta(t) \qquad [10.52]$$

$$M_B\frac{ds_B}{dt} = -Js_B(t) + Js_A(t) \qquad [10.53]$$

The solution of Eq. [10.52] for the specific activity per unit dose $w_A(t) = s_A(t)/m_0$ is obtained as in the single compartmental case already discussed [see Eq. 10.6]; thus

$$w_A(t) = \frac{s_A(t)}{m_0} = \frac{1}{M_A}e^{-J/M_A t} \qquad [10.54]$$

Substitution of Eq. [10.54] into [10.53] and solving for $sB(t)$ gives

$$w_B(t) = \frac{s_B(t)}{m_0} = \frac{1}{(M_B - M_A)}(e^{-J/M_B t} - e^{-J/M_A t}) \qquad [10.55]$$

This solution can be obtained by using the convolution integral (Chapter 9).

This system exhibits the precursor-product rule; namely, the maximum of the $w_B(t)$ curve occurs at the point of intersection of $w_A(t)$ and $w_B(t)$. This result is evident from Eq. [10.53], which gives $ds_B(t)/dt = 0$ for $s_A(t) = s_B(t)$. This rule is necessary but not sufficient to identify the present model.

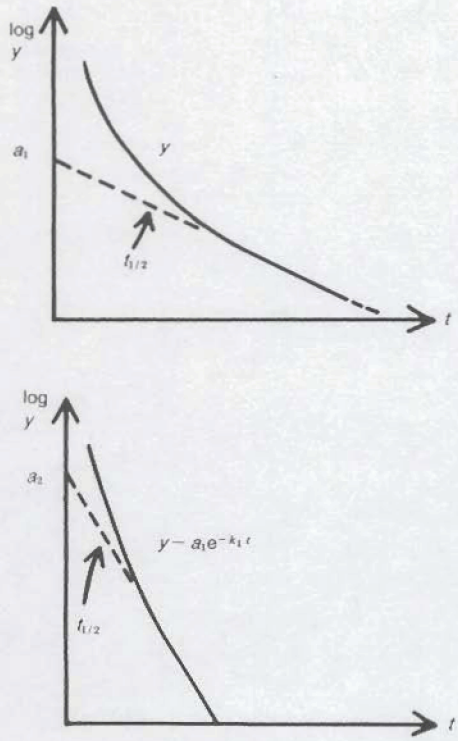
If a third compartment with one-way flow is added to the preceding two, then the precursor-product rule for compartments B and C states that the maximum for the C curve is reached at the intersection of $w_C(t)$ and $w_B(t)$. The intersection of $w_C(t)$ with $w_A(t)$, on the other hand, would occur at a time when $w_C(t)$ was still rising. These statements are proven from the mass balance Eqs. [10.52] and [10.53] and the similar equation for compartment C. Thus the observation of a "specific activity in tissue" curve that continues to rise to its maximum point past the point at which the curve intersects that of the plasma strongly suggests that the tissue measured receives tracer (and hence also systemic substance) not directly from the plasma but from a tissue that in its turn may communicate with the blood.

10.9 Curve-Fitting by Sums of Exponentials

An experimental indicator curve can usually be represented within experimental error by the sum of a small number of exponentials. Thus

$$y(t) = a_\infty + a_1e^{-k_1t} + a_2e^{-k_2t} + \ldots + a_ne^{-k_nt} \qquad [10.56]$$

All of the k's are positive, corresponding to the fact that the curve approaches a_∞ as $t \to \infty$. If all the a's are positive then $y(t)$ "decays" from beginning to end. If some of the a's are negative then $y(t)$ may have an upslope portion. There are



Weighted least squares criterion

$$\sum_{i=t_i} w_i[y_{exp} - y_i]^2$$

must be minimum.

several reasons for the frequent use of Eq. [10.56] to fit experimental data. First, Eq. [10.56] makes it easy to perform various calculations with the data. Second, if a compartmental model is applicable then the a's and k's yield all the physiological information contained in the indicator curve.

How is this curve-fitting accomplished? The oldest, simplest, and still much used method is *curve peeling.* The tail-end portion of the semilog plotted $y(t)$ curve is extrapolated back to $t = 0$ to give a_1. The half-time $(t_{1/2})$ of this straight line gives $k_1 = 0.693/(t_{1/2})$ (if the tail-end portion is curvilinear so as to suggest the presence of $a_\infty \neq 0$ the phase-plane method can be used to find a_∞ and k_1 simultaneously; see Sec. 10.3). The calculated values of $a_1e^{-k_1t}$ are subtracted from $y(t)$ and semilog plotted. The tail-end portion of this plot is extrapolated back to $t = 0$ and the preceding measurements repeated to yield a_2 and k_2. This process is repeated until there are no more points left. The semilog straight line at each stage is drawn by eye to best represent the experimental values that seem to belong to the tail-end portion of that stage.

The modern digital computer has made it possible to conveniently fit sums of exponentials to experimental data by weighted least squares procedures. Manual curve peeling is often used as an initial approximation in such procedures. It has been found that least squares curve fits produced by machine do not produce appreciably better physiological information than manual peeling curve fits. The machine methods are useful, however, as labor-saving devices if a large number of indicator curves are to be processed. The machine methods can also claim a somewhat greater objectivity in the curve-fitting procedure.

Suppose the standard deviation of Eq. [10.56] from the experimental data is satisfactorily small, say 2%. Does this mean that the a_i and k_i of Eq. [10.56] are determined with equal precision? Unfortunately the answer is no, especially if successive k_i are not "well-separated"; that is, if $k_{i+1}/k_i \lesssim 2$ or 3. It becomes quickly evident to anyone using curve peeling that very slight changes in "goodness of fit" (alternative possibilities for drawing semilog straight lines through data points) that are well within experimental error produce very appreciable changes in the a_i and k_i. If a compartmental model is applicable it is essentially the standard deviations of the a_i and k_i that yield the accuracy of the physiological information that can be deduced from the indicator curve. If it is felt that only black box physiological information is obtainable from the indicator curve then it is the standard deviations of the SHAM parameters (see Chapter 8) which tells us the accuracy of the black-box information contained in the indicator curve.

Unfortunately, decay type indicator curves "exhibit" the interesting physiological information (flows, volumes, exchange rates) in a smeared out form, because of the various uninterest-

ing or irrelevant dispersions undergone by the indicator in passing through the system. It is basically for this reason that multiple indicators are used. If two indicators differ in some property of interest but experience similar dispersions in passing through the system, then the "difference" indicator curve will exhibit the property of interest with the dispersion cancelled out.

10.10 Multicompartmental Systems

The indicator mass balance relationships in n-compartmental systems can with matrix notation be written in symmetrical and compart form. The n-compartmental model with n being an arbitrarily large number cannot be solved to yield explicit analytical expressions for the masses and fluxes of the *individual* compartment. But, by using the matrix notation one can as first explicitly noted by Nosslin (1964) and by Bergner (1964) reveal the *general* properties of the system that were expressed in Chapters 1 through 8 by integral equations.

Nosslin, B. (1964): In Metabolism of Human Gamma Globulin, Andersen S. B. Ed., Blackwell, p. 115.

We want to stress this point by deriving the black-box equations from the multicompartmental model. Consider that all n compartments can exchange with all other compartments as well as with the "outside." Mass balance for the rate of change of tracer in all n compartments yields n simultaneous first-order differential equations

Bergner, P.-E. E. (1964): *J. Theor. Biol.*, 6:137.

$$\begin{aligned} M_1 \frac{ds_1}{dt} &= J_{11}s_1 + J_{12}s_2 + \ldots + i_1 \\ M_2 \frac{ds_2}{dt} &= J_{21}s_1 + J_{22}s_2 + \ldots + i_2 \\ &\text{etc.} \end{aligned} \qquad [10.57]$$

s (specific activity) and i (influx from outside) are functions of time.

where the flux of mother substance to compartment 1 from compartment j is J_{1j}, where $-J_{11}$, $-J_{22}$, ... are the *sums* of all outfluxes from the respective compartments (including flux to the outside), and where i_1, i_2, ... are the influxes of tracer from the outside to the respective compartments.

First we derive the stimulus-response theorem for specific activity. Consider a bolus experiment in which a finite amount $\int_0^\infty i_1(t)dt = m_{01}$ of tracer is injected into compartment 1 with no tracer injected into the other compartments. Integration of Eq. [10.57] from $t = 0$ to $t = \infty$ yields, assuming that the system is open so that $s_j(\infty) = 0$ and that the system is empty prior to the injection so that $s_j(0) = 0$, *left hand sides that all are 0.* Rearranging the result thus gives

Note that $\int_0^\infty m_j \frac{ds_j}{dt}\,dt = m_j s_j \int_0^\infty$ is zero for all j.

$$\begin{aligned} J_{11}\int_0^\infty s_1 dt + J_{12}\int_0^\infty s_2 dt + \ldots &= -\int_0^\infty i_1 dt = -m_{01} \\ J_{21}\int_0^\infty s_1 dt + J_{22}\int_0^\infty s_2 dt + \ldots &= 0 \\ &\text{etc.} \end{aligned} \qquad [10.58]$$

Consider next a constant infusion experiment where tracer is infused at the rate $i_1(\infty)$ into compartment 1, and no infusion is made into any other compartment. After long time all the transients have died out. Then all the *ds/dt* values on the left hand sides of Eq. [10.57] *become 0,* giving after rearrangement

$$\left.\begin{array}{l} J_{11}s_1(\infty) + J_{12}s_2(\infty) + \ldots = -i_1(\infty) \\ J_{21}s_1(\infty) + J_{22}s_2(\infty) + \ldots = 0 \\ \text{etc.} \end{array}\right\} \qquad [10.59]$$

Now divide both sides of Eq. [10.58] by m_{01}. Divide likewise both sides of Eq. [10.59] by $i_1(\infty)$. Since the $[J]$ matrix is the same in both sets of equations, Eq. [10.58] is exactly the same set of simultaneous equations for the "unknowns" $\int_0^\infty s_1\, dt/m_{01}$, $\int_0^\infty s_2 dt/m_{01}$, ... as Eq. [10.59] is for its "unknowns" $s_1(\infty)/i_1(\infty)$, $s_2(\infty)/i_1(\infty)$ . . . . Hence corresponding "unknowns" must be equal, or

$$\frac{\int_0^\infty s_j(t)dt}{m_{01}} = \frac{s_j(\infty)}{i_1(\infty)},\ j = 1,2, \ldots . \qquad [10.60]$$

Since compartment 1 can be any compartment, it follows that Eq. [10.60] is the stimulus-response theorem, where the stimulus is an indicator input rate into any one compartment and the response the specific activity measured in any compartment. Multiplying both sides of equations [10.60] by the amount of mother substance M_j for any subset R of the total number of compartments and adding them together we get the regional residue stimulus-response theorem

$$\frac{\int_0^\infty m_R(t)dt}{m_{01}} = \frac{m_R(\infty)}{i_1(\infty)} \qquad [10.61]$$

where

$$m_R(t) = \Sigma_R M_j s_j(t) \qquad [10.62]$$

$$m_R(\infty) = \Sigma_R M_j s_j(\infty) \qquad [10.63]$$

If the subset R is the total number of compartments then the result is the systemic residue theorem.

In order to relate the right side of Eqs. [10.60] and [10.61] to systemic properties the systemic steady state is expressed by the systemic substance (i.e., mother substance) mass balance in each compartment. After proper rearrangement, the result is

$$\left.\begin{array}{l} J_{11} + J_{12} + J_{13} + \ldots = -J_{10} \\ J_{21} + J_{22} + J_{23} + \ldots = -J_{20} \\ \text{etc.} \end{array}\right\} \qquad [10.64]$$

Although Eqs. [10.60] and [10.61] do not require any of the systemic input rates J_{10}, J_{20}, ... to vanish, a simple relation-

ship to these rates holds only in two cases: (a) single systemic input rate and (b) equivalent labeling of multisystemic input rates.

Consider the first case (a) where all systemic input rates but one vanish. For convenience take the nonvanishing input rate as J_{10}. Then $J_{20}, J_{30}, \ldots = 0$ in Eq. [10.64]. Dividing through by J_{10} in Eq. [10.64] and comparing with Eq. [10.59] shows, by the same argument that leads to Eq. [10.60], that

$$\frac{s_1(\infty)}{i_1(\infty)} = \frac{s_2(\infty)}{i_1(\infty)} = \ldots = \frac{1}{J_{10}} \qquad [10.65]$$

And, at long time, $t \to \infty$, s is that of the input as $s_{\text{in}} = i_1(\infty)/J_{10}$.

This expresses the tracer condition of *equal specific activity* throughout the system at long time *if* both tracer and mother substance enter solely via one compartment. Comparing Eq. [10.65] with Eq. [10.60] yields the influx theorem (see Chapter 4) for a bolus injection

$$\left.\begin{aligned} J_{10} = \frac{m_{01}}{\int_0^\infty s_j(t)dt} &= \frac{\text{Dose}}{\text{Area } j} \\ j &= 1,2,\ldots \end{aligned}\right\} \qquad [10.66]$$

This theorem also shows the *equal area of specific activity* property.

Similarly, substituting Eq. [10.65] into [10.63] yields

$$m_R(\infty) = \Sigma_R M_j \frac{i_1(\infty)}{J_{10}} = M_R \frac{i_1(\infty)}{J_{10}} \qquad [10.67]$$

This combined with Eq. [10.61] yields the regional mass theorem

$$\frac{\int_0^\infty m_R(t)dt}{m_{01}} = \frac{M_R}{J_{10}} \qquad [10.68]$$

which becomes the systemic mass theorem (mean transit time theorem) for R = sum of all compartments.

Consider the next case (b), equivalent labeling of multisystemic input systems. All compartments can now have input from the outside. In the bolus injection experiment, inject an amount of indicator into each compartment proportional to the systemic input from outside, or

$$\left.\begin{aligned} m_{01} &= \int_0^\infty i_1 dt = AJ_{10} \\ m_{02} &= \int_0^\infty i_2 dt = AJ_{20} \end{aligned}\right\} \qquad [10.69]$$

etc.

By summing all the equations [10.69] it is seen that the constant A is given by

$$A = \frac{m_{01} + m_{02} + \ldots}{J_{10} + J_{20}} \equiv \frac{m_0}{J} \qquad [10.70]$$

where m_0 is the total dose of indicator and J is the total systemic input from the outside.

Using Eq. [10.69] then the bolus injection equation, instead of Eq. [10.58], becomes

$$\left.\begin{aligned} J_{11}\int_0^\infty s_1\,dt + J_{12}\int_0^\infty s_2\,dt + \ldots = -m_{01} = -\mathrm{A}J_{10} \\ J_{21}\int_0^\infty s_1\,dt + J_{22}\int_0^\infty s_2\,dt + \ldots = -m_{02} = -\mathrm{A}J_{20} \end{aligned}\right\} \quad [10.71]$$

etc.

Dividing Eq. [10.71] by A and deriving the corresponding steps for continuous infusion [cf. Eqs. 10.59 and 10.60] leads to

$$\frac{\int_0^\infty s_1\,dt}{\mathrm{A}} = \frac{\int_0^\infty s_2\,dt}{\mathrm{A}} = \cdots = 1 \quad [10.72]$$

Substituting A from Eq. [10.70] into [10.72] gives

$$J = \frac{m_0}{\int_0^\infty s_1(t)\,dt} = \frac{m_0}{\int_0^\infty s_2(t)\,dt} = \cdots \quad [10.73]$$

which is the influx theorem for a multi-inlet equivalently labeled system. Note that the equivalent labeling equation [10.69] is global (total amount of indicator proportional to systemic input rate), not local (indicator input rate proportional to systemic input rate).

The regional mass theorem for equivalent labeling is obtained by expressing Eq. [10.73] as

$$\left.\begin{aligned} M_1\int_0^\infty s_1(t)\,dt = \int_0^\infty m_1(t)\,dt = M_1\frac{m_0}{J} \\ M_2\int_0^\infty s_2(t)\,dt = \int_0^\infty m_2(t)\,dt = M_2\frac{m_0}{J} \end{aligned}\right\} \quad [10.74]$$

Adding the right-hand parts of Eq. [10.74] for any subset R of the total number of compartments gives

$$\int_0^\infty M_R(t)\,dt = M_R\frac{m_0}{J} \quad [10.75]$$

or

$$\frac{\int_0^\infty m_R(t)\,dt}{m_0} = \frac{M_R}{J} \quad [10.76]$$

which is the regional mass theorem. Summing over the total number of compartments yields the systemic mass theorem [drop subscript R in Eq. (10.76)].

The matrix or compartmental method of proving the stimulus-response, influx, and mass theorems is actually equivalent

to the convolution method we used to prove the black-box theorems by. Indeed, the convolution integral can be regarded as the limiting form of expression of the n-compartment system as $n \to \infty$.

The matrix approach for deriving the general black-box theorems was first used by Nosslin (1964). Although the present approach is somewhat simplified, the simplification is possible because one knows which theorems are to be proved. Without such prior knowledge it is quite difficult to apply the matrix approach!