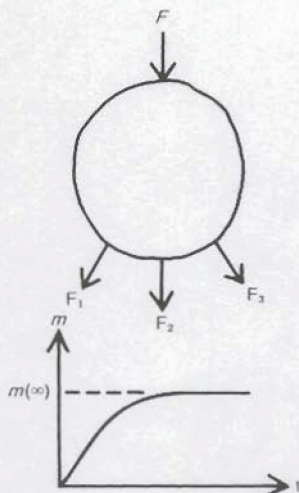# 6 The Volume/Flow and Mass/Flux Ratio of an Open System (Mean Transit Time). I: Constant Infusion Techniques

Note that in many cases $c(\infty)$ is the same at inlet and outlet (s).

A Vd has the unit of ml and F the unit of ml/sec, then Vd/F has the unit of seconds (time).

$s(\infty) =$
$m(\infty)/M =$
$j(\infty)/J$

The unit of M/J is time.

6.1 The Experiment

A continuous infusion of indicator is made into a system with a single convective inlet. After a sufficiently long time, the indicator steady state is reached, so that the mass of indicator inside the system, the residue, is constant at its final value $m(\infty)$. The volume of distribution of the indicator inside the system Vd is defined as in Chapter 5, Eq. [5.1]; that is, $m(\infty)$ is considered as the product $Vd\ c(\infty)$ where $c(\infty)$, generally speaking, is the steady-state concentration in any suitable fluid. Here we chose to let the inflowing fluid be the reference fluid. As $m(\infty) = Vd\ c(\infty)$ then

$$Vd = \frac{m(\infty)}{c(\infty)} = \frac{\text{Residue}}{\text{Inlet concentration}} \quad [6.1]$$

The steady state flux of indicator through the system is $j(\infty) = F\ c(\infty)$ where F is the inflow of carrier fluid. Dividing Eq. [6.1] by F on both sides therefore yields

$$\frac{Vd}{F} = \frac{m(\infty)}{j(\infty)} = \frac{\text{Residue}}{\text{Flux}} \quad [6.2]$$

When the indicator is a tracer for a systemic (mother) substance, the steady state specific activity $s(\infty)$ is the same in the system as a whole as at the single inlet. Hence, as $s(\infty) = m(\infty)/M$

$$M = \frac{m(\infty)}{s(\infty)} = \frac{\text{Residue}}{\text{Specific activity}} \quad [6.3]$$

$s(\infty)$ also equals $j(\infty)/J$; therefore dividing on both sides of Eq. [6.3] by J gives

$$\frac{M}{J} = \frac{m(\infty)}{j(\infty)} = \frac{\text{Mass of indicator}}{\text{Flux of indicator}} \quad [6.4]$$

This basic equation may be written directly, because it follows from the identical behavior of tracer and mother sub-

Flux
un
sion

If 1 ml leaves per sec and the transit time is 6 sec then, with plug flow, the entire tube volume Vd has been displaced into the collecting bucket in 6 sec; that is

$$Vd = F \times \bar{t}$$
$$= 1 \times 6$$
$$= 6 \text{ ml}$$

$\bar{t} = t_{novo}$ is called *turnover time*.

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stance: *The mass/flux ratio of mother substance equals that of the tracer in the steady state.*

If the single inlet is convective then we can combine Eqs. [6.2] and [6.4] to obtain
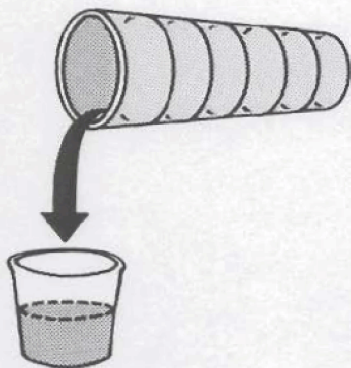
$$\frac{Vd}{F} = \frac{M}{J} = \frac{m(\infty)}{j(\infty)} = \frac{\text{Residue}}{\text{Flux}} \qquad [6.5]$$

But if tracer and mother substance do not enter the system by being carried by a fluid stream (they might enter by diffusion), then Eq. [6.5] has a meaning only if F is considered as an equivalent flow or clearance (expressed in the same volume units as the fluid used for reference when defining Vd).

The important volume/flow or mass/flux ratio has the dimension of *time*. Although it is not strictly needed for our present purpose we shall here mention that this ratio is the system's *mean transit time $\bar{t}$ for that indicator*. When, as in all methods to be discussed in this chapter and in Chapter 7, we determine the $Vd/F = M/J$ ratio, we in essence determine $\bar{t}$.

If the flow F of fluid in a tube of volume Vd is plug flow, then there is one single transit time which is also the system's mean transit time $\bar{t}$ and where $Vd = \bar{t}F$. This is the equation for simple displacement of a fluid. A generalization of this plug flow equation to any arbitrary system can be used to prove that $Vd = F\bar{t}$ and $M = J\bar{t}$ for a single inlet system (see Chapter 7, Sec. 7.2 and 7.10).

Another way of understanding why the ratio $Vd/F = M/J$ is the mean transit time is by considering M/J. For example, let M be 300 g of serum albumin and J 10 g per day (the daily production and breakdown). Then it takes an average of 30 days for a "new" molecule to reach the breakdown site. This example also shows that the mean transit time is the time it takes to renew the mass M, and $\bar{t}$ may consequently also be called t_{novo}.

6.2 Constant Infusion and Inlet–Outlet Detection During Saturation or Desaturation

In this approach the indicator residue/flux ratio in the steady state, $m(\infty)/j(\infty) = M/J = Vd/F$, is obtained from concentration measurements at both the inlet and the outlet of a single-inlet, single-outlet system. The measurements are made during an indicator *transient* during which the system goes from one indicator steady state to another. Often the "first" steady state is that of 0 concentration at inlet and outlet as well as inside the system, and the "second" steady state is that obtained after a sufficient period of constant inlet concentration. This is the simple *saturation* experiment. The mirror image is *desaturation*.

– During the transient the amount of indicator inside the
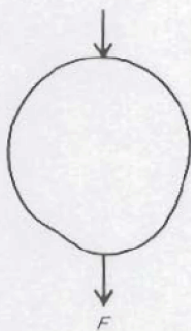
system (the residue) will vary as a function of time $m(t)$ with the rate of change dm/dt being the difference between inflow and outflow rates

$$
\begin{array}{ll}
\text{Rate of change} & = \text{Rate of} & - \text{Rate of} \\
\text{of residue} & \quad\text{inflow} & \quad\text{outflow}
\end{array}
$$

$$
dm/dt = Fc_{\text{in}}(t) - Fc_{\text{out}}(t) \qquad [6.6]
$$

Integrating this equation between the two times indicating the two steady states (0 and ∞) yields

Left side (and hence also right side) becomes 0 if the two steady states are identical.

$$
\int_0^\infty dm = m(t)\Big|_0^\infty = F\int_0^\infty c_{\text{in}}(t)dt - F\int_0^\infty c_{\text{out}}(t)dt \qquad [6.7]
$$

The left side of this equation is the sum of all the increments of residue dm during the experiment; that is, it is the final residue minus the initial residue. If, for simplicity, the initial residue is taken to be 0 then the left side is $m(\infty)$, which according to Eq. [6.1] equals $Vd\,c(\infty)$. Hence Eq. [6.7] becomes

Saturation

$$
\begin{array}{ll}
\text{Cumulative} & = \text{Cumulative} & - \text{Cumulative} \\
\text{residue} & \quad\text{input} & \quad\text{output}
\end{array}
$$

$$
Vd\,c(\infty) = F\int_0^\infty c_{\text{in}}(t)dt - F\int_0^\infty c_{\text{out}}(t)dt \qquad [6.8]
$$

Desaturation

This important equation should, we hope, be immediately acceptable: The cumulative residue is, according to the definitions, equal to the volume of distribution multiplied by the steady state inlet concentration $c(\infty)$ where a subscript (in) or (out) is unnecessary because in the steady state inlet and outlet concentrations are the same; the cumulative input is obtained by summing (integrating) all the inputs $Fc_{\text{in}}(t)dt$; the same applies for the cumulative output. $c(\infty)$ is the *height* of the concentration curves in the steady state and $\int_0^\infty [c_{\text{in}}(t) - c_{\text{out}}(t)]dt$ is the *area* between them. We can therefore rewrite Eq. [6.8] as

Saturation after previous saturation at lower concentration.

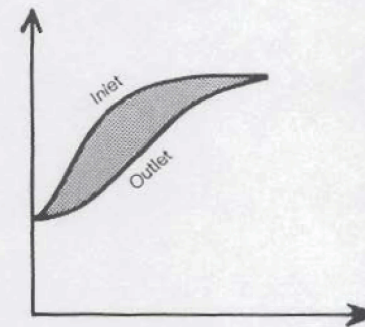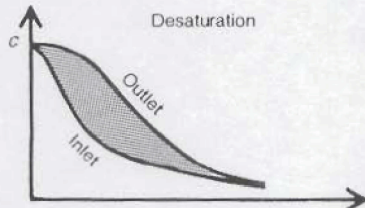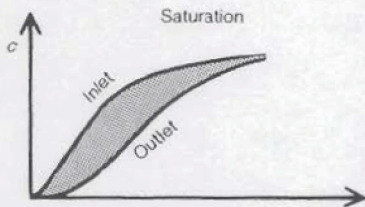### Constant Infusion, Inlet–Outlet Detection

$$
\frac{m(\infty)}{j(\infty)} = \frac{M}{J} = \frac{Vd}{F} = \frac{\int_0^\infty [c_{\text{in}}(t) - c_{\text{out}}(t)]dt}{c(\infty)} = \frac{\text{Area}}{\text{Height}} \qquad [6.9]
$$

This area equals Vd/F and M/J. It is measured in units of time and actually equals the *mean transit time $\bar{t}$*.

Thus it follows that if we scale the concentrations so that all concentrations are divided by $c(\infty)$, that is, if we plot $c_{\text{in}}(t)/c(\infty)$ and $c_{\text{out}}(t)/c(\infty)$ as functions of time, then the area between these normalized curves is the volume/flow and mass/flux ratio of the system for that indicator.

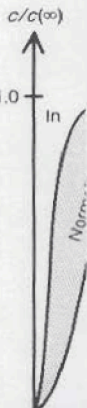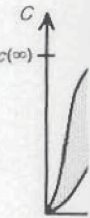### Comments on inlet–outlet detection during saturation or desaturation

We have only to measure the concentration ratios $c_{\text{in}}(t)/c(\infty)$ and $c_{\text{out}}(t)/c(\infty)$. Hence in this method one does not have

S_{in} and S_{out} are the inlet and outlet cross sectional areas.

Bradley S. E. et al. (1953): *Trans. Assoc. Am. Phys.* 66:294.
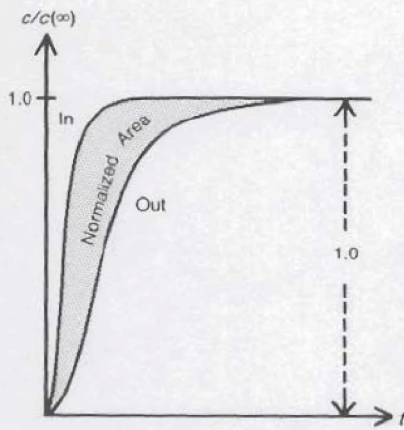
to measure absolute concentrations and the rate of infusion is therefore immaterial and need not be known. In this respect the constant infusion or "saturation" method for measuring Vd/F or M/J differs from the constant infusion method for measurement of flow or flux, Stewart's method, as discussed in Chapter 1. We also note that the models used are different. In the saturation method both inlet and outlet mixing is assumed whereas in Stewart's method only one site of cross-stream mixing—at inlet, outlet or anywhere inside the system—is assumed.

The sampling procedure used in the inlet–outlet detection method must be discussed in relation to the influence of diffusion processes as analyzed in detail in Chapter 3. It will be recalled that in a convective system, where the indicator is carried in a fluid stream, inlet and outlet concentrations can be followed in two basically different ways—as collection of fluid samples (bucket sampling) or as *in situ* sampling at the open boundary surface of the outlet. Because we are concerned with assessing the amounts of indicator entering and leaving the system $j_{in}(t)$ and $j_{out}(t)$ we should in principle be using the bucket sampling procedure in situations where diffusive fluxes in the fluid stream can be quantitatively important. This conclusion is, however, not valid because (just as when calculating flows) *the diffusion terms cancel out:* The correct version of Eq. [6.6] is namely $dm/dt = j_{in}(t) - j_{out}(t)$, or

$$dm/dt = Fc_{in}(t) - DS_{in}\partial c_{in}/\partial x - Fc_{out}(t) + DS_{out}\partial c_{out}/\partial x \qquad [6.10]$$

With constant linear velocity $v = \partial x/dt$ the two derivatives in the direction of flow are proportional to the corresponding time derivatives. Hence, since we wish to integrate Eq. [6.10] from 0 to ∞, the integrals become $- DS_{in}c_{in}(\infty)$ and $+ DS_{out}c_{out}(\infty)$. For equal areas and infinity concentrations it follows that the diffusion terms cancel out.

6.3 Splanchnic Plasma Volume

The equilibration or saturation principle for measuring $Vd/F =$ area/height can be used for calculating Vd if F can be measured simultaneously by an independent method. As an example of this approach we shall describe the technique developed by Bradley and co-workers for measuring the splanchnic plasma volume in man.

A convenient but arbitrary amount of a plasma indicator such as Evans Blue dye (T-1824) or ^{131}I-labeled human serum albumin is injected intravenously as a bolus. The concentration in systemic arterial plasma, as conveniently sampled from the brachial or femoral artery, represents the concentration $c_{in}(t)$ in the blood supplied to the splanchnic area (spleen, intestine, liver). Thus although the splanchnic area has physically speaking many arterial inlets, none of which we sample from, because
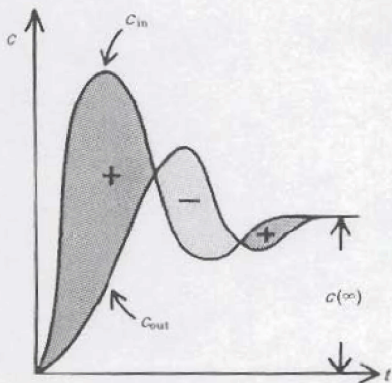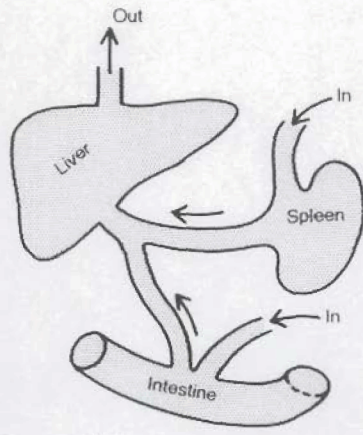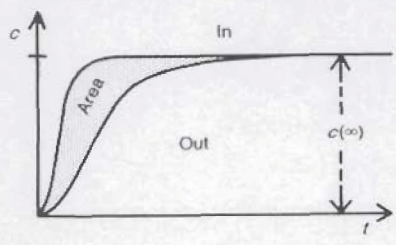
of the mixing in the heart the system is *functionally* speaking a single-inlet system, with the inlet concentration given by the femoral arterial blood. The concentration in venous plasma as obtained from blood sampled by a catheter placed via the arm and the right atrium of the heart into one of the hepatic veins represents the outlet concentration $c_{out}(t)$.

The rapid mixing of the indicator in the intravascular pool (the plasma volume) ensures that $c_{in}(t)$ becomes practically constant after approximately 2 min. It is for this reason that one can consider the experiment as a continuous infusion one. At steady state [that is, when the arterial and venous curves have reached the same constant level $c(\infty)$], we can express the amount of indicator in the system as $m(\infty) = Vd\, c(\infty)$, Vd being the *splanchnic plasma volume*. This equilibrium is reached after approximately 2 to 3 min. We can also obtain $m(\infty)$ as the difference between the cumulative input $F\int_0^\infty c_{in}(t)dt$

$= F\Sigma\, c_{in}(i)\Delta t_i$ and the corresponding cumulative output. Hence, as expressed in Eq. [6.9], Vd/F is calculated as the area/height ratio.

Therefore, if the splanchnic plasma flow F is measured simultaneously by the bromsulphthalein (BSP) or cardiogreen clearance method, Vd can readily be calculated. These clearance methods are based on a constant infusion at a known rate $j(\infty)$ of indicators removed solely by the liver.

The splanchnic plasma volume as determined with the equilibration technique will include all rapidly exchangeable albumin in the liver, spleen, and intestine. Especially in the spleen and in the liver there are reasons to assume that albumin exchanges quite freely across the capillary wall. Hence in these organs Vd also includes the paracapillary albumin space. In brain and also in lung and muscle the capillary permeability to protein is so low that Vd as measured by the same technique is the intravascular volume.

Bradley and co-workers stated that the ratio $Vd/F =$ area/height is the mean transit time of albumin $\bar t$ through the splanchnic bed; the splanchnic mean transit time of albumin $\bar t = Vd/F$ is approximately 20 sec in man.

Anatomy of splanchnic circulation

Note that the clearance is

$$Cl = \frac{j(\infty)}{c_a(\infty)}$$

and the extraction

$$E\frac{c_a(\infty) - c_v(\infty)}{c_a(\infty)}$$

hence $F = Cl/E$

Kety S. S. and Schmidt C. F. (1945): *Am. J. Physiol.*, 143:53.

6.4 Cerebral Blood Flow

In the Kety-Schmidt inert gas inhalation method for the saturation principle, the measurement of $Vd/F =$ area/height is used for calculating the flow per gram of tissue in the human brain. This is possible because independent information is available for the volume of distribution per gram of tissue, λ.

A convenient but arbitrary constant concentration of an inert gas (e.g., nitrous oxide, argon, or radioactive krypton)
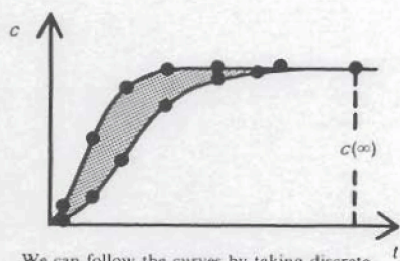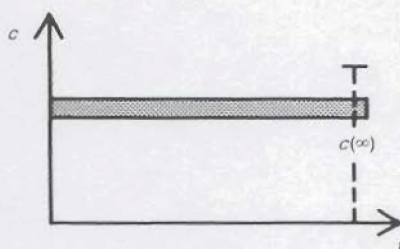
We can follow the curves by taking discrete samples and interpolating
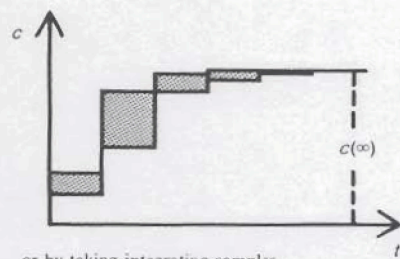
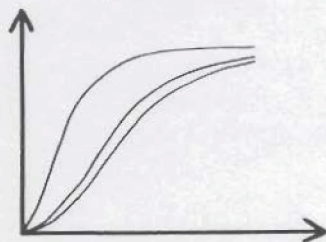or by taking integrating samples

for example, only two samples

$$CBF = 100 \frac{F_{brain}}{W_{brain}}$$

area from t_1 to infinity is

$$\Delta = [c_{in}(t_1) - c_{out}(t_1)]$$

multiplied by

$$t_{1/2}/0.693 = t_{1/e}$$

Lower two curves are, from right to left, internal jugular vein.

is inhaled for approximately 15 min. The concentration in systemic arterial blood as conveniently sampled from the brachial or femoral artery is the same as that going to the brain $c_{in}(t)$. Thus, although the brain has four main arteries, the two internal carotid arteries and the two vertebral arteries, the system is a single-inlet system. The concentration in cerebral venous blood is followed by samples obtained from the superior end of the internal jugular vein of one or both sides of the head. These two veins constitute the main drainage from the brain and the inert gas saturation curves are in most cases almost superposable. However, because side-to-side differences do exist, the system is strictly speaking not a single-outlet system. A way of expressing this point is by stating that with unilateral internal jugular venous sampling one measures the blood flow of that part of the brain draining to the vein from which the sample is taken. This is mainly that half-part of the forebrain lying to the same side (the ipsilateral hemisphere).

At equilibrium the residue of indicator gas in 100 g of tissue is

$$Residue \quad = \quad In \quad - \quad Out$$
$$100c_{brain}(\infty) = CBF\int_0^\infty c_{in}(t)dt - CBF\int_0^\infty c_{out}(t)dt \quad [6.11]$$

where, following conventional usage, we have defined CBF as the blood flow through 100 g of brain "average" tissue.

Because equilibrium has been reached the brain concentration is related to that of the blood by the equilibrium partition coefficient $\lambda = c_{brain}(\infty)/c_{blood}(\infty)$. Hence

$$100c_{brain}(\infty) = 100\lambda c(\infty) \quad [6.12]$$

From Eqs. [6.11] and [6.12] it follows that

Kety-Schmidt Equation for CBF

$$CBF = 100\lambda \frac{c(\infty)}{\int_0^\infty c_{in}(t) - c_{out}(t)dt} = 100\lambda \frac{Height}{Area} \quad [6.13]$$

The use of Eq. [6.12] and hence also the final equation presupposes that the entire area is obtained until full saturation when $c_{in} = c_{out}$. However, this point is not reached within the experimental period. One may then, as originally proposed by Kety and Schmidt (1945), employ a monoexponential extrapolation just as in the Henriques-Hamilton indicator dilution method. But in a subsequent paper Kety and Schmidt proposed that an *approximate* state of diffusion equilibrium between brain and cerebral venous blood could be assumed after 10 min of saturation; that is, they assumed that the ratio $c_{brain}(10)/c_{out}(10)$ could be approximately taken to equal the equilibrium value λ. Hence rewriting Eqs. [6.11], [6.12], and [6.13] for a saturation time of 10 min gives
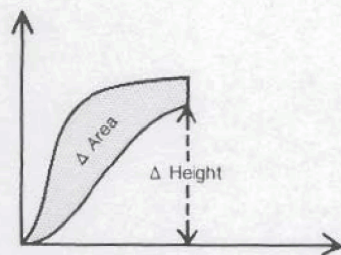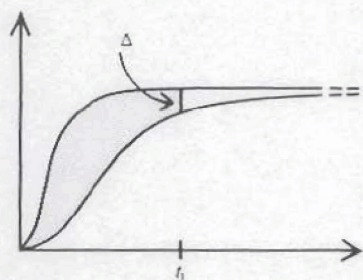
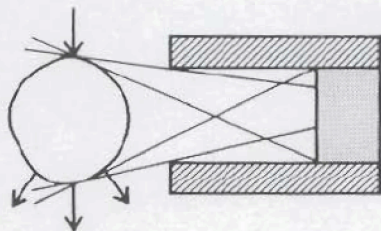The Kety-Schmidt experiment essentially consists of measuring the mean transit time $\bar{t}$ of the inert gas

$$\bar{t} = \frac{\text{Area}}{\text{Height}}$$

$\bar{t}$ is approximately 2 min in normal man using N_2O.

$$CBF = 100f$$

$$\frac{\lambda}{f} = \bar{t}$$

Residue detection by external counting converts system to a single-outlet system.

$$100\, c_{\text{brain}}(10) = CBF \int_0^{10} c_{\text{in}}(t) - c_{\text{out}}(t)dt \qquad [6.14]$$

$$100\, c_{\text{brain}}(10) \approx 100\lambda\, c_{\text{out}}(10) \qquad [6.15]$$

Kety and Schmidt 10-Min Approximation for CBF

$$CBF \approx 100\lambda\, \frac{c_{\text{out}}(10)}{\int_0^{10} c_{\text{in}}(t) - c_{\text{out}}(t)dt} = \frac{\Delta\, \text{Height}}{\Delta\, \text{Area}} \qquad [6.16]$$

In the literature one often sees the notation $CBF(\infty)$ for the value obtained by extrapolation using Eq. [6.13] and $CBF(10)$ when using Eq. [6.16].

It must be emphasized that Eq. [6.16] is theoretically not correct: At no time "before" full saturation can Eq. [6.15] be correct. The normal value of cerebral blood flow in man is for $CBF(\infty)$ of approximately 45 ml/100 g/min whereas the $CBF(10)$ is about 53 ml/100 g/min. Thus there is approximately a 15% overestimation of flow resulting from the 10 min truncation. Nevertheless, the approximation is of considerable value because accurate extrapolation to infinity is usually not possible.

We have in the above followed Kety and Schmidt's original derivation quite closely. Making more use of the concepts developed in this text we would have recalled from Chapter 5 that λ is not only the equilibrium concentration ratio $c_{\text{brain}}/c_{\text{blood}}$ but also (by the same definition), the *volume of distribution per gram of brain tissue.* Hence, denoting the flow per gram of tissue F/W by f we can write

$$\frac{Vd}{F} = \frac{Vd/W}{F/W} = \frac{\lambda}{f} \quad \text{min} \qquad [6.17]$$

As shown in Sec. 6.2 Vd/F is the area/height ratio, and thus the final equation is directly obtained. The Vd/F ratio is the mean transit time $\bar{t}$. For the normal brain $\bar{t}$ is approximately 2 min for inert gas having about the same solubility in brain tissue as in blood, that is, with a λ of approximately 1.0 ml/g. Hence it follows, as $f = \lambda/\bar{t}$, that the blood flow per gram of brain is approximately 0.5 ml/g/min or 50 ml/100 g/min.

The inert gas saturation method of Kety and Schmidt may be used to study flow in any organ from which mixed venous blood can be collected and for which λ can be assumed to be a constant. Myocardium and kidney are such tissues.

6.5 Constant Infusion and Residue Detection During Saturation or Desaturation

In this method the volume/flow or mass/flux ratio is determined from a direct observation of the indicator steady

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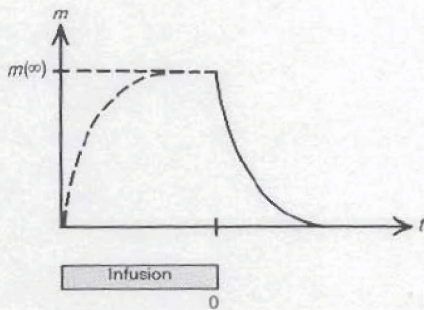
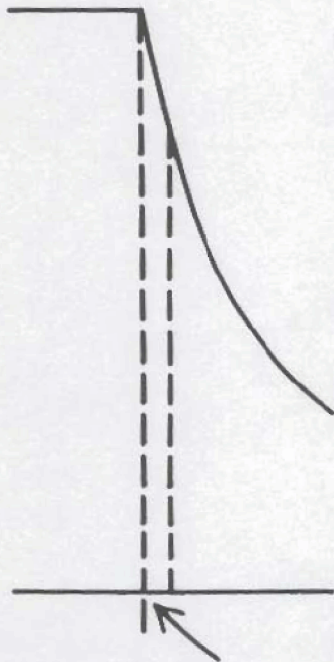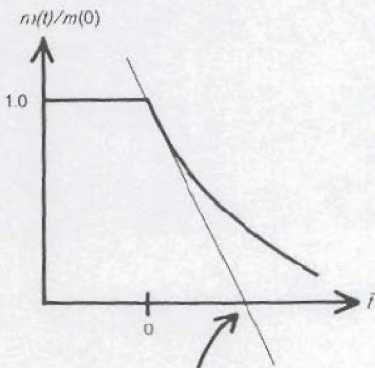Desaturation after full saturation

Blowup of initial part of linear plot of *m(t)*

Brief interval of constant and maximal slope

Relative initial slope is $-1/\bar{t} = J/M$.

state mass/flux ratio $m(\infty)/j(\infty)$. The mass of indicator in the system (the residue) may in some cases be followed by the use of gamma-emitting radioactive tracers allowing external counting over the organ. Because the residue detection must take all outlets into account simultaneously, the use of a direct method of measuring residue may be especially convenient with a multiple-outlet system; still the system can have only one inlet at which the indicator infusion is made. (Compare this to the inlet–outlet detection technique where a single-inlet, single-outlet system must be assumed).

The experimental situation involves a constant infusion of indicator that is continued until complete saturation is reached, that is, until the steady state for the indicator is reached. Following this, the infusion is suddenly stopped and the time at stopping is denoted time 0 with respect to desaturation. The residue is followed as a function of time during the early part of the desaturation. In this situation the steady state residue $m(\infty)$ is equal to the initial residue $m(0)$, and the steady state indicator flux through the system $j(\infty)$ is the initial rate of decrease of residue $-dm(0)/dt = -\dot{m}(0)$. This must be true because during a brief time interval after the infusion has been stopped the outflux continues at unaltered rate (this time interval is the shortest transit time through the system). Hence

Constant Infusion, Residue Detection

$$\frac{Vd}{F} = \frac{M}{J} = \frac{m(\infty)}{j(\infty)} = \frac{m(0)}{-\dot{m}(0)} = -\frac{\text{Initial residue}}{\text{Initial slope of residue}} \quad [6.18]$$

It should be noted that the initial slope is that of a linear plot of the residue *m(t)* versus time. After a short time the outlet concentration starts to decrease and then the slope dm/dt also decreases; that is, the initial constant (steepest) slope is no longer seen.

The initial slope method may also be used in the form of a recording of the saturation curve as the initial rate of residue accumulation is $j(\infty)$ until the time when the indicator also starts to leave the system via the exit (the shortest transit time).

One continues infusion until full saturation has occurred in order to record $m(\infty)$. But this approach is less practical than the desaturation one, because it may be difficult to ensure a completely constant indicator infusion rate from the beginning and throughout the experiment. It is easier just to stop a constant infusion and then to record the initial slope during desaturation.

It follows from Eq. [6.18] that if we scale the residue curve so that all amounts are divided by $m(\infty) = m(0)$; that is, if we plot $m(t)/m(0)$, then the numerical value of the initial slope of this curve is the reciprocal of the volume/flow and mass/flux ratio of the system. Regardless of the scaling factor

used, the initial (steepest) tangent intersects the abscissa at the system's mean transit time $\bar{t}$.

Comments on the residue detection during saturation or desaturation (the initial slope method)

As only the ratio of residue m_0 to residue decrease dm/dt must be measured, the absolute residual amount need not be determined. When external counting is used, we do not need to know the counting geometry. Thus the rate of indicator infusion is also immaterial.

The major difficulty of the initial slope method consists in the possibility that the time during which the outflux continues unaltered (at maximum rate $j(\infty)$) while the influx has completely stopped *may be quite short.* Consider for example that we were to study by external counting the initial rate of decrease of [131]albumin infused at constant rate into the arterial inlet (in well mixed fashion) of an isolated skeletal muscle. Even if one stops the infusion pump abruptly, the influx of indicator does not instantaneously drop to 0 because the indicator concentration in the inflowing artery cannot change stepwise. Perhaps it will take 1 or 2 sec for c_{in} to reach a level that is so low that it can be neglected. Following this, there is probably a brief period, perhaps of 3 to 5 sec, during which the outflux can be assumed to continue at the same (maximum) rate as during the infusion. It is during this brief period that the initial slope must be recorded. Clearly, this slope cannot generally be recorded very accurately in so short a time, especially if the slope is relatively shallow.

This discussion demonstrates that although theoretically the residue detection method is quite analogous to the inlet–outlet detection method, in practice the two methods are quite different. The difficulties of determining the initial *linear* slope of the residue curve is such that to our knowledge the method has never been used. *It is the initial, or, more precisely, steepest slope of a semilogarithmic plot that one employs.*

The justification for making a semilogarithmic plot of the curve is that, initially at least, the system may behave like a well-mixed system, a "compartment," as will be discussed further in Chapter 10. We shall here just mention that if a residue curve is monoexponential between time 0 and time t_1, then it means that until t_1

$$m(t) = m(0)e^{-kt} \qquad [6.19]$$

For this curve the relative slope $\dot{m}/m$ has the numerical value of

$$-\dot{m}(t)/m(t) = k = 1/\bar{t} \qquad [6.20]$$

Hence it follows that if the curve decreases monoexponentially from the start then
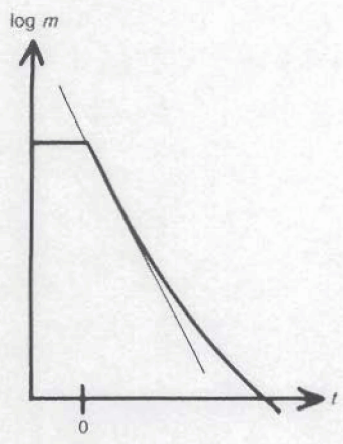
An even greater blowup of initial part of curve

Period during which inflowing concentration reaches 0.

Period of initial steepest slope which equals $j(\infty)$ if outflow concentration remains $c(\infty)$.

Chapter 7
Zeirler & Meier 1954
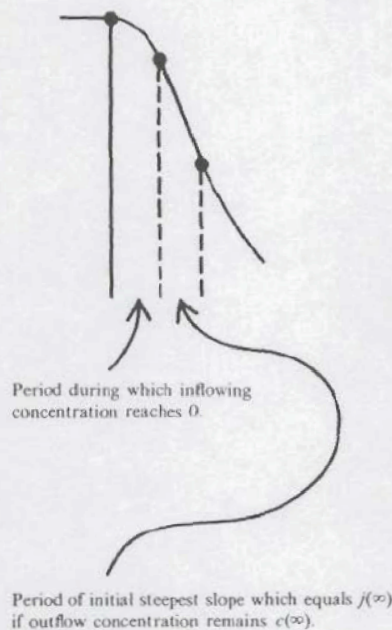
<table>
<tr><td>Fractional initial slope on linear plot may be constant only for a very brief interval of a few seconds.</td><td>Initial slope on semilogarithmic plot may be constant for a considerably longer interval.</td><td>[6.21]</td></tr>
</table>

$$-\dot{m}(0)/m(0) \approx -\dot{m}(t)/m(t)$$

The practical procedure is usually to plot the early part of the curve on semilogarithmic paper and then measure the halftime $t_{1/2}$ of the tangent to the initial steepest part of the curve. Then

$$-\dot{m}(0)/m(0) = k = \frac{\ln_2}{t_{1/2}} \approx \frac{0.693}{t_{1/2}} \qquad [6.22]$$

For further discussion of the well-mixed monoexponentially desaturating system the reader is referred to Chapter 10. It may seem odd that we have discussed an approach (linear slope) that cannot be used in practice. It has been done for the reasons of symmetry, so as to correspond to residue detection after bolus injection mentioned in Chapter 7 and also in order to point out that all one does by the semilogarithmic initial slope is to find an experimentally satisfactory way of determining the initial *linear* slope, which is the kinetically correct parameter $1/\bar{t}$.

6.6 Transcapillary Albumin Flux

The method is based on measuring the albumin mass/flux M/J ratio by observing the initial fractional escape rate $1 - \dot{m}(0)/m(0)$ of tracer albumin injected intravenously. Then, by also measuring the intravascular mass of albumin M the absolute transcapillary escape rate J can be calculated.

In order to calculate the intravascular albumin mass we must know the dose m_0 of tracer injected. Blood samples are collected without stasis with 10-min intervals during the first hour after the injection. In the plasma the concentration of the indicator $c(t)$ and that of albumin C (or total protein) is measured and the ratio gives the specific activity as a function of time $s(t)$. By retrograde monoexponential extrapolation the estimated initial value $s(0)$ is obtained and thus the intravascular mass is obtained from

$$M = \frac{m_0}{s(0)} \qquad [6.23]$$

The halftime of the initial slope on the semilogarithmic curve may be read off the curve. Then

$$M/J = \bar{t} = t_{1/e} = t_{1/2}/\ln 2 \approx t_{1/2}/0.693 \qquad [6.24]$$

For accurate determinations one may use a linear regression of the logarithm of $s(t)$ or of $c(t)$ on time and employ

Due to the rapid mixing the intravenous bolus injection gives an initial state comparable to that of full saturation after prolonged infusion.
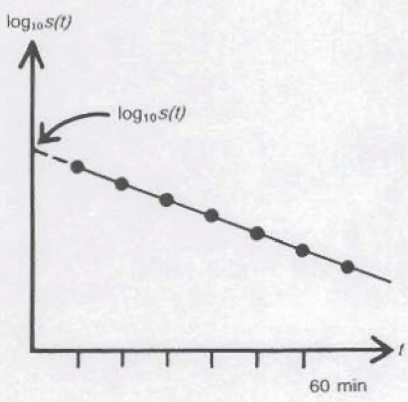
the slope obtained (the use of decade logarithms $\log_{10}$ instead of natural logarithms $\ln = \log_e$ is due merely to convention). For $c(t)$ we use the numerical value of the decade logarithms slope, B; that gives

$$
\begin{aligned}
M/J &= \bar{t} \\
&= -c(t)/(dc(t)/dt) \\
&= -1/(d\ln c(t)/dt) \\
&= -1/(\ln 10)(d\log_{10} c(t)/dt) \\
&= -1/(2.303 \; d\log_{10} c(t)/dt) \\
&= 1/(2.303 \; B) \\
&= 0.4343 \; (1/B) \sec
\end{aligned}
$$

$\ln X = \ln 10 \log_{10} X$
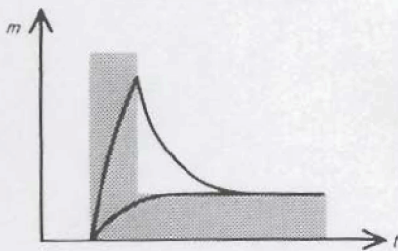 $\simeq 2.303 \log_{10} X$

By using the slope of the tracer curve after 10 min the transcapillary escape measured does not include the exchange of rapidly exchangeable albumin as in spleen and liver. The mixing of the tracer at such sites is probably essentially complete when the mixing with the intravascular albumin pool has taken place.

6.7 Cerebral Cortex Blood Flow

Ingvar D. H. and Lassen N. A. (1962):
Acta Physiol. Scand., 54:325.

This method was designed for measuring the blood flow of the superficial half millimeter of the cerebral cortex in animals. It can also be applied to other tissues. The indicator used is the radioactive inert gas ^{85}Kr dissolved in physiological saline (0.9% NaCl) and infused into a cerebral artery usually via a small catheter placed in a side branch (the lingual artery). ^{85}Kr emits for all practical purposes only β radiation (electrons) with a maximum energy of 0.7 MeV. This means that by using a small Geiger counter placed over the exposed brain surface, indicator may be recorded down to a depth of approximately 0.5 millimeters.

The infusion may be made in the form of a more rapid one for the first minute followed by one-fourth that speed for the following 4 min. This ensures more complete saturation of all cortical tissue phases (layers) during the 5 min than would be obtained had the same infusion speed been used throughout. The absolute amounts being infused are unimportant. One merely infuses an amount such that a suitable plateau counting rate $m(\infty)$ of approximately 3,000 to 6,000 counts per min is reached.

Diagram of two saturation curves in cortex

Upon sudden cessation of the infusion the washout curve is recorded for approximately 1 min using either the cumulative counts obtained in suitable short time intervals (2 sec) or a ratemeter curve with a suitable time constant (3 sec). Transferring the clearance curve to logarithmic paper the $t_{1/2}$ of the initial practically monoexponential part is obtained. Then

$k = f/\lambda$

$$Vd/F = \lambda/f = 1/k = \bar{t} \approx t_{1/2}/0.693 \qquad [6.25]$$

That is, we can calculate the blood flow per 100 g of brain cortex, CBF_{cortex}, as

$\bar{t} = A/H$

$$\text{CBF}_{\text{cortex}} = 100f \approx 100\lambda \frac{0.693}{t_{1/2}} \qquad [6.26]$$

where λ is the cortex:blood partition coefficient of ^{85}Kr.

This description of the ^{85}Kr infusion method does not introduce the multicompartmental model that was employed when first developing the method. In this approach the desaturation curve is considered as the sum of n exponential terms each of the form exp. $[-f_i/\lambda_i)t]$ and with a 0 time value equaling the amount of indicator in that tissue at time 0 $W_i c_i(0) = W_i[c_i(0)/c_b(0)]c_b(0) = W_i\lambda_i c_b$; that is,

$$m(t) = \Sigma\ W_i\lambda_i c_b(0)\ e^{-f_i/\lambda_i\,t} \qquad [6.27]$$

where $c_b(0)$ is the inert gas concentration in the blood at full saturation, W_i is the weight of tissue i, f_i its blood flow per gram of tissue, and λ_i its tissue:blood partition coefficient. The numerical value of the fractional slope (slope in a semilogarithmic system using the natural logarithm) is at time 0

$$k_{t=0} = \left[\frac{-dm(t)/dt}{m(t)}\right]_{t=0} = \frac{\Sigma\ W_i f_i}{\Sigma\ W_i\lambda_i} = \frac{\bar{f}}{\bar{\lambda}} \qquad [6.28]$$

where the mean flow $\bar{f}$ and mean partition $\bar{\lambda}$ coefficients are defined as indicated in the equation. Hence it follows that Eq. [6.26] is obtained by this derivation also. But the concepts behind Eq. [6.27] are quite complex and all that is stated by the multiexponential formulation is that initially the curve becomes practically monoexponential with a slope being equal to the fractional slope in a linear system, a slope that we thus determine *in practice* by the semilogarithmic plotting. This calculation is carried out without ever using or even calculating the flow and weight of the presumed individual components, the number of which is neither known nor must be known in order to calculate the cortical blood flow per unit weight of the tissue.

EXERCISES

6.1 Kidney plasma volume: ^{131}I-labeled human serum albumin is injected intravenously and with catheters of equal volume a continuous sample is withdrawn from an artery and from the renal vein over 1 min (A_I and V_I) followed by another sample collected over the following 15 sec (A_{II} and V_{II}).

The radioactivity measured was

$A_1 = 10,000$ cps sampled 0 → 60 sec
$V_1 = 9,400$ cps sampled 0 → 60 sec
$A_2 = 12,000$ cps sampled 60 → 75 sec
$V_2 = 12,000$ cps sampled 60 → 75 sec

Calculate $Vd/F = \bar{t}$; i.e., the mean transit time of albumin molecules through the kidney is $\bar{t} = $ min = sec.

By para-aminohippurate (PAH) clearance and extraction

Left margin notes (top to bottom):

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arithms

exp. $[-(f_i/\lambda_i)t]$
is just another way of writing
$e^{-f_i/\lambda_i\,t}$

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[6.25]
of brain

$\bar{t} = A/H$

$\bar{t} = Vd/F$

the renal plasma flow has been measured to be 900 ml/min. Assume that the kidneys weigh 300 g and thus calculate the plasma column Vd per 100 g: ____ ml/100 g.

Can one, yes or two, calculate the % renal blood volume accurately if the hematocrit of the arterial blood is 0.40?

With renal hematocrit assumed to be 0.9 × large vessel = ____ calculate the red cell volume of the kidney, Vd_{RBC}:

$$\frac{Vd_{RBC}}{Vd_{RBC} + Vd_{PL}} = 0.36$$

$$\frac{Vd_{RBC}/V_{PL}}{Vd_{RBC}/Vd_{PL} + 1} = 0.36$$

$$Vd_{RBC}/Vd_{PL} = \frac{0.36}{0.64}$$

Note the impracticality of the procedure because $\bar{t}$ is so short that $\bar{C}_a$ is almost the same as $\bar{C}_v$ during the first one minute.

6.2 Myocardial blood flow: ^{133}Xe is inhaled at constant concentration and during the 5 min of inhalation one samples 5 pairs of 1-min samples that are taken continuously and in immediate succession from a peripheral artery and the coronary sinus (the main venous drainage) from the left ventricle. Counting equal volumes in a well counter shows the

CA	0 → 1 min	12,000 cpm
CV	0 → 1 min	8,000 cpm
CA	1 → 2 min	50,000 cpm
CV	1 → 2 min	45,000 cpm
CA	2 → 3 min	58,000 cpm
CV	2 → 3 min	56,000 cpm
CA	3 → 4 min	60,000 cpm
CV	3 → 4 min	59,000 cpm
CA	4 → 5 min	60,000 cpm
CV	4 → 5 min	60,000 cpm

Calculate the mean transit time $\bar{t}$ of ^{133}Xe through the myocardium $\bar{t} \cdot$ = ____ min. Assume that the myocardial/blood partition coefficient for ^{133}Xe is 0.70 ml/g. Calculate $f = \lambda/\bar{t}$ and myocardial blood flow (MBF) = 100 f = ____ ml/100 g/min. Note that in this case with $\bar{t}$ = 30 sec the errors inherent in calculating the A-V differences are not nearly as critical as in Ex. 6.1.

Assume that the mean transit time of an albumin tracer is 6 sec = 0.1 min. Calculate the myocardial plasma volume. ____ ml/100g.

6.3 Escape of labeled albumin from the plasma space. During the first 60 min after intravenous injection of a bolus of ^{131}I-labeled albumin (injected dose $m_0 = 3.0 \times 10^6$ cpm) the following concentrations were measured:

time	log (cpm/ml)
10	2.997
15	2.995
20	2.994
30	2.991

40	2.988
50	2.985
55	2.983
60	2.982

Calculate by retrograde extrapolation $c(0)$ and $Vd = m_0/c(0)$. With an albumin concentration of 4 g/dl calculate intravascular mass of albumin $M =$ ____ g. Then calculate $1/\bar{t} = k = -d \ln c/dt = -2.30 \cdot d \log_{10}c/dt$. $k =$ ____ hr. The mean transite time of an albumin molecule in the plasma space $\bar{t}$ is ____ hr.

The outflux (net loss) of albumin from plasma space J is ____ g/hr or ____ g/24 hr.

6.4 Brain cortex blood flow by β-counting of ^{85}Kr after saturation using Geiger–Müllers counter over exposed cortex.

Use the table in Ex. 6.3 but assume time is measured in units of 1/10 sec, i.e. over a total of 6 sec.

Calculate cortical blood flow assuming λ_{cortex} is 0.8.

$$k = \underline{\hspace{1cm}} \ min^{-1}$$

cortex blood flow $= 100 \cdot f = 100 \cdot \lambda/\bar{t} = \underline{100 \cdot \lambda \cdot k}$ ml/ 100 g/min

Note that in practice one usually records the curve for approximately 30 sec (for as long as it is linear in a semilogarithmic plot) and then measures $t_{1/2} \simeq 0.693/k$ or $t_{1/e} \simeq t_{0.37} \simeq 1/k$ to calculate k and hence $\bar{t}$.