Tracer Kinetic Methods in Medical Physiology

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chapter 6

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1 Constant Infusion Method (The Stewart Principle)

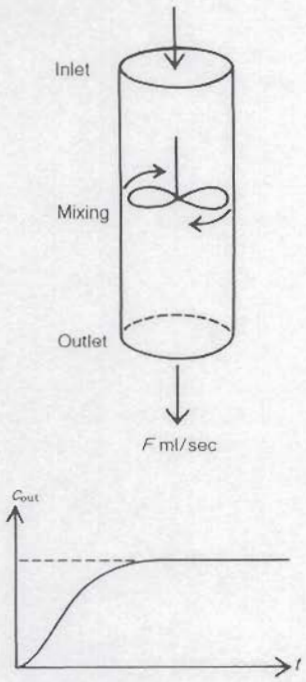
1.1 Introduction

Stewart, G. N. (1897): *J. Physiol.* 22:159.

The *constant infusion* of an indicator and downstream measurement of the dilution constitutes the first and most obvious approach to measuring flow with a foreign substance. But, as will be shown in this chapter, this simple infusion method (steady-state method) is beset with the same difficulties regarding sampling, recirculation of indicator and so forth as the formally rather different *bolus injection method* (impulse response method) to be discussed in subsequent chapters. Indeed, to perceive the close relationship between the two methods as mathematically expressed in the "stimulus response theorem" in Chapters 4 and 6 is a key to understanding indicator methods in general.

Another general point that is emphasized is the formal identity between the concept of a flow (fluid transport) and a flux (mass transport). This theme will be discussed in some detail in the first chapter and repeated in subsequent chapters. We have found it so useful to juxtapose flow and flux that we have chosen to give both terms the same meaning—total flow, and respectively, total flux over a given cross section or membrane surface. According to this terminology the flow or flux per unit area of cross section or membrane surface may be designated the flow density, and respectively, the flux density.

Next we will discuss methods of performing the infusion experiment. No lengthy preambulatory theoretical chapters on matrices, exponentials, transforms, and so forth will be given. Instead, we shall develop the mathematical complexity in each chapter as the need arises in the context of actual experimental situations. Thus we hope to better convey the fact that the simpler methods require only the most elementary algebraic operations, and that the understanding of all the methods depends more on understanding their limitations (e.g., nature of the indicator, mixing, recirculation) than on the mathematical derivations.



1.2 The Experiment

Consider a fluid flowing through a tube at the constant rate F ml/sec. To measure F, one proceeds as follows. At a certain site within the tube, it is possible to induce cross-stream mixing (e.g., using a magnetic stirrer). An indicator i is infused upstream of this site in a solution of concentration c_i mg/ml at the rate F_i ml/sec, so that the *influx* of indicator j_{in} mg/sec is constant at the value

$$j_{in} = F_i\, c_i \qquad [1.1]$$

At a downstream site fluid samples are collected for measuring the outlet concentration that, at some time after the onset of infusion, reaches a constant maximum value c_{out}. Assume that the outlet concentration is the same wherever a sample is taken in the outlet cross section because of the mixing. Hence, after the initial rise in concentration ceases, the *outflux* j_{out} of the indicator can be expressed as

$$j_{out} = (F + F_i)\, c_{out} \qquad [1.2]$$

since the total outflow during the infusion is equal to the throughflow F through the tube plus the rate of infusion F_i. The constant maximal level of the outlet concentration is considered an indication that the amount and spatial distribution of indicator inside the system is also constant from that time. This condition is known as the *indicator steady state*. Since there is neither production nor loss of indicator anywhere in the tube downstream of the inlet, the indicator influx through the inlet must equal the indicator outflux through the outlet; that is, $j_{in} = j_{out}$. Thus Eqs. [1.1] and [1.2] show that

Mass balance of indicator; you "must" be able to write down this equation directly.

$$\begin{aligned} \text{Influx} &= \text{Outflux} \\ F_i\, c_i &= (F + F_i)\, c_{out} \end{aligned} \qquad [1.3]$$

Because the indicator can be measured at much greater dilutions than the infusate, it is possible to keep the rate of infusion much smaller than the throughflow. This means that $F + F_i \simeq F$. In this situation, when Eq. [1.3] is solved for throughflow using this approximation it yields

Stewart principle

$$F \simeq F_i \left(\frac{c_i}{c_{out}}\right) \text{ml/sec} \qquad [1.4]$$

Equation [1.4] demonstrates the dilution principle, basis of the indicator dilution method.

In other words, for sufficiently small infusion rates, the flow is as many times greater than the infusion flow (which equals the infusion rate) as the *dilution factor;* that is, the infusate concentration divided by the outlet concentration. This equation was applied by G. N. Stewart in 1897 for blood flow measurement. He used NaCl as the indicator and conductivity as a measure of concentration. This was the first practical application of indicators for flow measurement in biological systems.

1.3 Analysis of the Constant Infusion Experiment

The system considered has a flow of carrier fluid. A fluid is a substance for which we can conveniently use a volumetric measure V to indicate amount. We shall employ the milliliters unit throughout the text to stress the fluid nature of this type of carrier substance, although cubic centimeters (cm^3) is dimensionally the more correct mode of expressing the unit. According to this definition, the flow F of a fluid across a boundary surface is the volume crossing the surface per unit time (e.g., ml/sec).

V ml
F ml/sec

For any substance in general we will use mass M as the unit designating amount. Often the mass is measured in milligrams, but other units such as milliequivalents can also be used. The rate at which a substance crosses a boundary surface is denoted by the flux J, which is the mass crossing the surface per unit time. J can be measured using units such as mg/sec.

M mg
J mg/sec

The concentration c of a substance in a fluid is the amount per unit volume of fluid; that is, $C = \Delta M/\Delta V$ where Δ denotes that we are (usually) concerned with that small amount of substance ΔM contained in the small volume of fluid ΔV sampled. In a tissue we customarily measure the concentration of a substance in amount per unit weight of the tissue (see also Chapter 5). Lowercase letters are generally used for indicators to denote concentrations, amounts, and fluxes, whereas systemic parameters are indicated by capital letters.

$C = \Delta M/\Delta V$ mg/ml
$c = \Delta m/\Delta V$ mg/ml

Influx of indicator

As expressed in Eq. [1.1], it appears obvious that the influx of indicator j_{in} is the product of infusate concentration c_i and the rate of infusion (inflow of infusate) F_i. However, the simple equation, $j_{in} = F_i\, c_i$, is valid only under special conditions. The conditions at the tip of the catheter through which indicator enters the system both by fluid flow (convection) and by diffusion are complex. Nevertheless, when the concentration profile at the tip of the catheter is constant, the total indicator flux out of the catheter must equal the flux from the injection syringe, $F_i\, c_i$.

General flux equation:

$$j = Fc - DS\, dc/dx$$

where D is the diffusion coefficient, S the cross-sectional area of outlet surface, and dc/dx the concentration gradient at the outlet in the axial or flow direction, x.

Outflux of indicator

The problem of convective mass transport (by fluid flow alone) must be discussed in terms of any effects superimposed on the outflux of indicator from the system by diffusive transport during the indicator steady state. Because of the mixing upstream of the outlet, the axial concentration gradient of indicator at the outlet boundary surface is 0. Since there is no axial concentration gradient, that is, $dc/dx = 0$, the net diffusive flux along the direction of flow is 0. It is for this reason that the outflux is given by the convective flux alone as $j_{out} = (F + F_i)\, c_{out}$.

Outflux is often called efflux.

Mass balance

Indicator outflux equals indicator influx only if the indicator neither disappears nor is produced inside the system. When observing a dye such as Evans Blue in a stream of water flowing in a tube, this is perhaps self-evident. But, for example, when heat is used as the indicator in blood flowing through an organ, these conditions may not hold. In each valid application of the indicator dilution method, one must know the behavior of the indicator in order that the Law of Conservation of Mass be correctly applied.

1.4 Flux by Constant Infusion

A systemic substance is a substance belonging to the system.

If we have measured the fluid flow F by techniques such as total outlet collection or by the constant infusion indicator dilution method, then we can compute the flux J of a systemic substance carried by this fluid using the convective flux equation

$$\text{Flux} = \text{Flow} \times \text{Concentration}$$
$$J = FC \qquad [1.5]$$

Equation [1.5] is valid provided that the axial and transverse concentration gradients of the systemic substance be neglected at the outlet surface. This will be so if the abovementioned cross-stream mixing site of the systemic substance with the carrier fluid is complete, and if no systemic substance is added to the system distal to the mixing site.

The term "flux" denotes the net transport of a substance across a boundary surface (mg/sec); we do not, as some texts do, employ the term to mean transport rate per unit area of the boundary surface.

But the flux J can also be calculated for cases in which there is no flow of a carrier fluid. Consider the constant appearance (influx) of serum albumin in the blood plasma and its constant breakdown (outflux). These processes occur by cellular mechanisms that do not involve convection (flow) of blood or plasma. In this case, J can be calculated if the indicator used is a *tracer* for the systemic substance. Such a tracer could be radioactive iodine-labeled albumin in the example given. The systemic substance is called the *mother substance* and it acts as the carrier substance for the tracer. The amount of tracer per unit amount of mother substance is termed the specific activity s; that is,

H_2O and THO are another example of a mothersubstance–tracer pair.

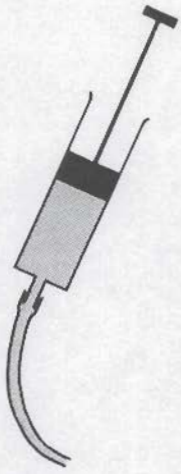
Specific activity is defined as a mass ratio or as a concentration ratio.

$$s = \frac{\Delta m}{\Delta M} = \frac{\Delta m/\Delta V}{\Delta M/\Delta V} = \frac{c}{C} \qquad [1.6]$$

In Eq. [1.6], the amount of mother substance ΔM or its concentration C is taken to *include* the (usually quite negligible) mass of tracer molecules measured in the same units as the unlabeled substance (e.g., mg or millimoles for ΔM, and mg/ml or millimoles/ml for C).

As an example illustrating the concept of specific activity, consider an experiment where the constant influx of tracer is by infusion via a syringe. In this case the influx of tracer $\dot{A}$

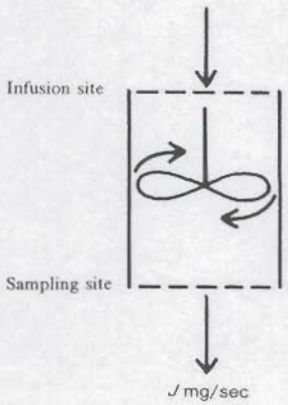
Infusion of F_i ml/sec gives an influx of mother substance of $J_i = F_i C_i$ mg/sec, and an influx of tracer of $j_i = F_i c_i$ mg/sec.



Concentration of mother substance is C_i and of tracer is c_i.

Mass balance of tracer:

$$j_{in} = j_{out}$$



Comparison with Eq. [1.4] shows that:

F corresponds to J
F_i corresponds to J_i
c_i corresponds to s_i
c_{out} corresponds to s_{out}.

and of mother substance J_i occurs in the same ratio s_i as in the syringe fluid.

Hence,

$$\begin{Bmatrix}\text{Influx}\\ \text{of}\\ \text{tracer}\end{Bmatrix} = \begin{Bmatrix}\text{Influx of mother}\\ \text{substance by}\\ \text{infusion}\end{Bmatrix} \times \begin{Bmatrix}\text{Specific}\\ \text{activity of}\\ \text{infusate}\end{Bmatrix} \qquad [1.7]$$

$$j_{in} = J_i s_i$$

Distal to the mixing site we collect samples from the system so that the specific activity can be measured. The samples may be fluid samples (or, in other applications, they may be samples of the solid tissue that constitutes the system). After a certain time, the indicator steady state is reached, as indicated by the specific activity reaching its constant maximum value s_{out}. This value is uniform on the outlet cross section, as well as on sections just proximal and distal to it. The indicator outflux can then be expressed in the simple form

$$j_{out} = (J + J_i)\, s_{out} \qquad [1.8]$$

Equation [1.8] is true because tracer and mother substance move together; independent net diffusion of tracer (called interdiffusion) does not occur because of the mixing; we see that the total outflux of mother substance is equal to the preinfusion outflux plus the amount added by the infusion. The assumption that no destruction or production of tracer occurs inside the system allows us to combine Eqs. [1.7] and [1.8] to obtain

$$\begin{aligned}\text{Influx} &= \text{Outflux}\\ J_i s_i &= (J + J_i)\, s_{out}\end{aligned} \qquad [1.9]$$

Note that the inlet is usually a diffusely distributed "source" (synthetic site) and the outlet a diffusely distributed "sink" (metabolic or "catabolic" site). However, by definition, neither of these belongs to the system proper because, as just stated, *inside* the system neither the tracer nor the mother substance is destroyed or produced.

Because the indicator (tracer) can be measured at much greater dilutions than the infusate, we can keep the rate of infusion of mother substance J_i small compared to the systemic flux J of that substance; that is $J + J_i \simeq J$. In this situation we can solve Eq. [1.9] for flux and obtain

$$J = J_i \left(\frac{s_i}{s_{out}}\right) \text{mg/sec} \qquad [1.10]$$

We derived Eqs. [1.7] to [1.10] in complete analogy to Eqs. [1.1] to [1.4] to emphasize the formal identity of the two conceptual approaches described. The correlations are as follows:

Indicator substance that follows a systemic carrier fluid is called a foreign indicator.	↔	Indicator substance that follows a systemic mother substance is called a tracer.
Flow of carrier fluid, F	↔	Flux of mother substance, J
Concentration of foreign indicator, c	↔	Specific activity of tracer, s

This implies that all the tracer–mother substance equations can be written directly by "translating" from the corresponding indicator–carrier fluid equations. Thus, the flow and flux equations, [1.4] and [1.10] respectively, can be written

In Chapter 1, it is sufficient to memorize only Eq. [1.11].

$$\{F \text{ or } J\} = \frac{\text{Indicator infusion rate}}{\{c_{out} \text{ or } s_{out}\}} \qquad [1.11]$$

since the infusion rates of foreign indicator or of tracer are j_i (indicator) $= F_i\, c_i$ and j_i (tracer) $= J_i\, s_i$, respectively.

1.5 Flow or Flux Equal Dose over Area

Flow or flux equal dose over area is a useful mode of expressing the equations for calculating flow or flux that will be considered in its more conventional form in the context of the bolus injection experiment discussed in Chapters 3 and 4. Operationally speaking, the steady-state indicator outlet concentration c_{out} (or for the flux case, the corresponding specific activity s_{out}) is measured by collecting a sample over a given time interval Δt. The amount of indicator entering (and therefore leaving) the system in this time interval can be considered the indicator dose m_0 administered to the system in that interval.

Operational means "what we actually measure experimentally."

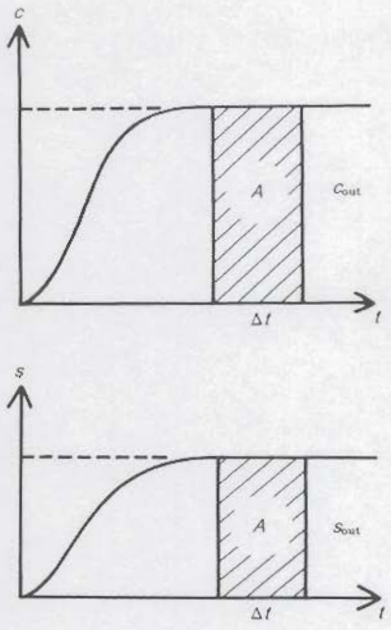
Thus $m_0 = j_{in}\Delta t$ or

$$\text{Dose} = m_0 = \begin{cases} F_i\, c_i\, \Delta t\text{: Dose of indicator.} \\ J_i\, s_i\, \Delta t\text{: Dose of tracer.} \end{cases} \qquad [1.12]$$

Here, as previously, F_i is the inflow of carrier fluid and J_i the influx of mother substance via constant infusion.

The area A under the respective outlet curves during the time interval Δt is

$$\text{Area} = A = \begin{cases} c_{out}\, \Delta t\text{: Area under outlet concentration curve} \\ s_{out}\, \Delta t\text{: Area under outlet specific activity curve} \end{cases} \qquad [1.13]$$



Flow or flux equal dose over area.

Comparison of Eqs. [1.12] and [1.13] to the flow and flux equations, [1.4] and [1.10], shows that we can write both as

$$\left.\begin{matrix} \text{Flow, } F \\ \text{Flux, } J \end{matrix}\right\} = \frac{m_0}{A} = \frac{\text{Dose}}{\text{Area}} \qquad [1.14]$$

In Eq. [1.14], the flow or flux calculations in the continuous infusion method respectively take the same form that will be seen in Chapters 3 and 4 for the bolus injection method. In fact, since the Fick principle discussed in Chapter 2 may be considered a special case of the continuous infusion method for which Eq. [1.14] also holds, *it can be said that the first four chapters in this volume are concerned solely with a single equation: flow or flux equals dose divided by area.*

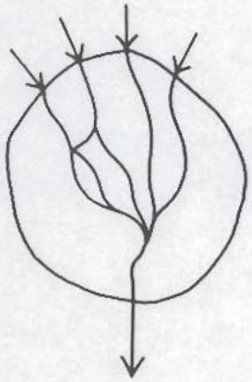
1.6 Mixing

We shall now consider an arbitrary system taken as any well-defined region of the body (e.g., the kidney, the blood volume, the entire body, or a single cell). The system considered is, as was tacitly assumed in the previous sections, to be in a *systemic steady state.* This means that all concentrations, flows, masses, and so forth, of systemic substances of interest are constant in time during the experiment. But concentrations, flows, and so forth, may vary in space.

The system makes a transition from a zero indicator steady state to a nonzero indicator steady state; the *systemic* steady state, however, is unchanged throughout.

The indicator is introduced into the system without appreciably disturbing the systemic steady state; this is the minimal perturbation principle underlying all indicator methods. We have already made use of this principle when arguing that the infusion rate of foreign indicator or fluid of mother substance, respectively, could be kept small compared to the systemic flow or flux we wished to study. Infusing the indicator means that, with respect to the indicator, the system is temporarily in a nonsteady state, but after a transient period, the *indicator steady state* is regained.

In the constant infusion method, the outlet concentration in the indicator steady state is the basic observation. We presented just one special model—a tube with cross sectional mixing between inlet and outlet—as it was argued that the mixing meant that this concentration was the same regardless of where in the outlet we sample. This important point will be discussed next in some detail.



Multiple-inlet, single-outlet system

The single-outlet system

If the system has only a single outlet, then adequate mixing (same concentration at any site in outlet) automatically obtains because we define *a single outlet* as an outlet at which, at any arbitrary time—and not only in the indicator steady state—the concentration is the same at every point in the system. Note in this connection that a laminarly flowing stream of blood leaving an organ cannot be considered a single outlet because the indicator concentration is generally not precisely the same over a cross section of the vein; the outflow in the different streams constitutes infinitely many outlets.

Three terms for same concept:

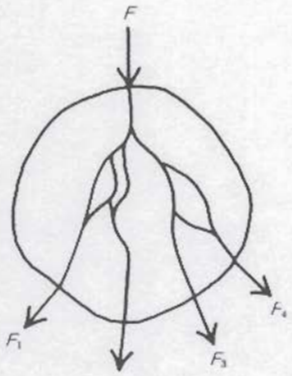
[single outlet =
well mixed outlet =
or equivalent exit]

similarly,

[single inlet =
well mixed inlet =
or equivalent entry]

A single outlet is also called a well-mixed outlet even though, physically speaking, no mixing need occur. In the case of a tracer–mother substance system we use the term single outlet to refer to the fact that the *ratio* of the amounts of both substances (the specific activity) leaving is constant. This is called equivalent exit of tracer and mother substance.

The single-inlet system



$c_{out_1} = c_{out_2} = c_{out_3} = c_{out_4}$

in indicator steady state (for the indicator–carrier fluid situation)

$s_{out_1} = s_{out_2} = s_{out_3} = s_{out_4}$

in indicator steady state (for the tracer–mother substance situation)

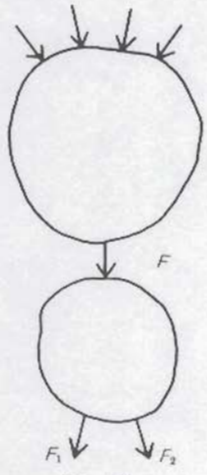
In this system, mixing is by definition confined to the inlet. The systemic carrier fluid (e.g., blood) flows through a system of pathways and leaves the system via the outlets. The indicator concentration in the *indicator steady state* is then constant at all outlets and may be used to calculate the total flow F according to Eqs. [1.4] and [1.14]. This must be so if the indicator is not moved by active cellular forces from one stream of blood to another in the system of continuous connected pathways running from inlet to outlet. In addition, our indicator must behave in this manner in order to be used as indicator of blood flow in the system.

These remarks are easier to follow when considering the tracer–mother substance situation. Because, by definition, the two substances are treated in the same way by the system it follows that after a sufficiently long time of infusion via the single well-mixed inlet the system's specific activity at any point must equal that of the inlet.

Cross-stream mixing

We can combine the two above-mentioned systems in a series so that the single-outlet system feeds into the single-inlet system. The constant infusion of indicator made at any of the combined system's multiple inlets will then (after a time) lead to a constant and identical outlet concentration at any of the combined system's multiple outlets. That this is so can be seen by focusing attention on the "second" subsystem with its well-mixed single inlet for which the relation holds.

The connection between the two subsystems constitutes the site of cross-stream mixing.



$c_{out_1} = c_{out_2}$

in indicator steady state

The general multiple inlet–multiple outlet system

If such a system has no cross-stream mixing site, as determined experimentally by measuring different steady-state concentrations at different outlets, then the indicator dilution method fails. Only if the indicator can be introduced in the various inlets in proportion to flow (flux) of carrier substance can the indicator dilution method be applied. However, this approach, which in essence changes the system to a single-inlet system, is usually not feasible.

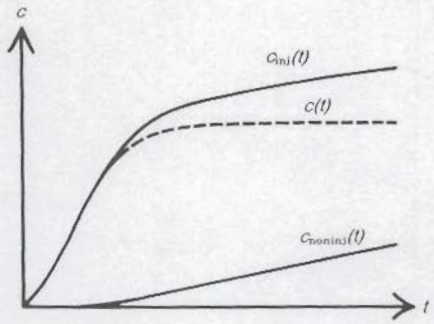
1.7 Recirculation

A major problem in applying the continuous infusion and other indicator dilution methods for circulation studies arises from recirculation of indicator. Before the indicator steady state has been reached, blood containing indicator has already made a complete circuit and is adding to the infusion influx of indicator passing the sampling site. In this situation a constant indicator concentration is not reached. Instead, a continuously rising curve is seen. If all indicator does not recirculate, then $c(t)$ may reach a plateau, although at a higher level than in the absence of recirculation. A method of approximately correcting for recirculation is available if bilaterally symmetrical organs, such as the kidneys or the forearms, are studied. Then, sampling from the venous outflow on the noninjected side gives the concentration to be subtracted from that of the injected side; that is,

$$c(t) \simeq c_{\text{inj}}(t) - c_{\text{noninj}}(t) \qquad [1.15]$$

Thus, the steady-state outlet concentration to be used is obtained as the difference of the two concentrations measured after the initial transient.

Other more precise means of correcting for recirculation are discussed later. We stress here only that one should strive to minimize recirculation as much as possible. This can be done by (a) infusion as close to the mixing site as possible; (b) using an indicator that recirculates only minimally or not at all;[1] and (c) using an indicator for which the time to the indicator steady state is short. If the system studied is an organ with a microcirculation, then the most suitable indicator is (from this point of view) an indicator that does not leave the vascular bed in amounts significant in the context of the experiment. Examples of such indicators are labeled red cells, plasma protein labeled with Evans blue dye (T-1824), or radioactively labeled plasma albumin. As red cells usually traverse a tissue somewhat more rapidly than plasma, labeled cells would theoretically be best for rapid attainment of steady-state conditions. But the practical advantages of a protein label make this the indicator of choice.



We distinguish between vascular and extravascular indicators; some of the extravascular indicators diffuse freely into all cells and these are usually called the freely diffusible indicators.

1.8 Flow of What? Comment on Measurement of Flow of a Two-Component Carrier Fluid Such as Blood

In order to minimize systematic analytical errors that occur at high blood concentrations, it is usually preferable to

[1] Heat is the only indicator for which recirculation can be ignored. Inert gases of low solubility, such as helium or hydrogen, may also be mentioned as they leave the circulation both at the level of the microvasculature and, more completely via the lungs. Indicators such as *p*-aminohippurate or indocyanine green that are taken up (by kidney and liver respectively) also offer some advantages.

dilute the indicator so as to obtain a *standard* having approximately the concentration that the blood sample is going to have when it is collected at the outlet. The diluent used to make up the standard is commonly *blank blood,* that is, blood collected at the outlet just prior to starting the indicator infusion. According to this procedure, the flow equation becomes

B is the dilution factor of the "standard."

$$F = F_i \frac{C_i}{C_{out}} = F_i B \frac{C_{standard}}{C_{out}} \qquad [1.16]$$

where

$$B = \frac{\left[\begin{array}{l}\text{Volume of blank}\\ \text{blood used to}\\ \text{make up standard}\end{array}\right] + \left[\begin{array}{l}\text{Volume of infusate}\\ \text{used to make}\\ \text{up standard}\end{array}\right]}{\left[\begin{array}{l}\text{Volume of infusate used}\\ \text{to make up standard}\end{array}\right]} \qquad [1.17]$$

Typically we would dilute 0.100 ml of infusate with 10.0 ml of blank blood, and in this case the value of the dilution factor would be 101.

According to this procedure, and assuming the volume of blank blood is much larger than the volume of infusate used to make up the standard, the flow calculated by using Eq. [1.16] is the *blood flow* and not the *plasma flow* regardless of how the indicator concentrations are measured in the standard and in the sample. To be explicit, this means that even if we measure both these concentrations in the plasma (assume we used Evans blue dye, T-1824), then the flow obtained is the blood flow. If we had instead made up the standard by diluting the infusate with plasma, then, since the tracer mentioned does not enter red cells, the flow obtained would have been the plasma flow.

We discussed this point in some detail in order to answer some puzzling questions:

Blood flow × Plasmatocrit = Plasma flow, where plasmatocrit is fractional volume of plasma in whole blood: $Ptc = (1 - Hct)$

1. Why is it that T-1824, which does not enter red cells and is analyzed in plasma, yields blood flow and not plasma flow? This is, as stated, due to the dilution by whole blood in making up the standard.

2. Would tritiated water (THO), which equilibrates rapidly with red cell water, yield the same F as T-1824? The answer is again yes, because whole blood is used to dilute the standard.

Closed system

Open system

1.9 Summary

The system considered in indicator methodology is any well-defined region of the body (e.g., the kidney, the brain, all red blood cells, or the total body). It can also be a less tangible "region," such as for example, the entire mass of serum albumin in the body. This system is biochemically well defined and hence is separate from the rest of the body's substances.

Indicator parameters are denoted by lowercase letters: *c, j, m,* and so forth; systemic parameters, by the corresponding capital letters: *C, J, M,* and so forth.

$c = \Delta m/\Delta V$
(Indicator)
$C = \Delta M/\Delta V$
(Systemic substance)
$s = \Delta m/\Delta M$
Hence, it is also true that
$s = c/C$

Flux = Convective flux + Diffusive flux

Convective flux
$j = Fc$

An indicator is used to study certain properties of the system. In this chapter we described a method for measuring flow of a fluid or flux of a substance through the system. The indicator is a substance that is indicative of the parameter to be measured; it must follow the fluid or the substance of interest. The indicator is neither produced nor destroyed inside the system; the system thus obeys the Law of Conservation of Mass.

For the case in which hydrodynamic flow is to be measured the concentration C is the fundamental quantity relating indicator to substance of interest (the fluid). Concentration is defined as the amount of the substance per unit volume of fluid solution. When the flux of a substance is of interest, the corresponding term is the specific activity s, which is defined as the amount of tracer per unit amount of mother substance (the mother substance includes both the labeled and the unlabeled molecules measured in the same units). To review, a tracer is an indicator that follows (i.e., traces) a certain systemic substance called the mother substance.

The net transport of substance across a plane is termed flux. The flux equation will in general have two terms, a convective term and a diffusive term. Convection is the bulk transport process we encounter in the form of fluid flow. Diffusion is transport due to concentration differences of diffusing substance. It arises as the net result of individual random thermal movements of single molecules of the substance considered.

The indicator method discussed in this chapter requires a constant infusion of indicator and it is valid as long as the rate of infusion and the spatial distribution of indicator are constant; that is, as long as the indicator steady state obtains. In the general case in which we infuse indicator at one of many inlets (upstream of a mixing site), the indicator steady state does not require diffusion equilibrium in the entire system. However, below the mixing site, and therefore also just upstream of and just downstream of the outlet, we do have diffusion equilibrium of indicator and carrier substance. Thus, in the indicator steady state, there is no concentration gradient at the outlet. *Hence the diffusive flux across the outlet is 0 in the steady state.* Therefore, in the indicator steady state, the outflux is solely convective.

The systems considered in this volume are all assumed to be in systemic steady state throughout the measurement. That is, we assume that all the parameters we are interested in measuring (e.g., flow F or the flux J) remain constant in time. In particular, we assume that we can introduce (infuse) the indicator without measurably upsetting the system's systemic steady state. This assumption is denoted the "small perturbation assumption."

The basic concept used for deriving the equations is *mass balance,* and application of the Law of Conservation of Mass. In the present context, this simply means that

Law of Conservation of Mass applied to mass transport in open system.

Rate of entrance of indicator	=	Rate of accumulation of indicator inside system	+	Rate of exit of indicator

But, as we assume that we have reached the indicator steady state, that is, there is no further accumulation within the system, the above mass balance reduces to

$$\text{Rate of entrance} = \text{Rate of exit}$$

At the tip of the infusion catheter diffusion also occurs; this can be disregarded, however, by considering the syringe of infusion from which indicator is lost solely by flow convection.

Now we can consider the flux through inlet i (usually one of many) where we infuse at a rate equal to the rate at which the indicator leaves the syringe $j_{in} = F_i c_i$ = infusion rate × concentration in infusate and, correspondingly for the outflux.

We have shown that $F \simeq (c_i/c_{out})\, F_i$ since $F_i \ll F$ (the small perturbation assumption). Also, in the preceding sections we derived the corresponding flux expression so that Eq. [1.11] can be expressed: *Flow or flux equals infusion rate over outlet concentration respectively specific activity.*[2]

Equatio
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$F = j/c$

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14:63.

EXERCISES

1.1 (Flux).

At the aortic value the blood flow (cardiac output) is 6,000 ml/min and the blood concentration of oxygen is 20 ml/100 ml (20 volume %) and that of carbon dioxide is 50 ml/100 ml (50 volume %). Calculate the outflux from the heart of O_2 and CO_2 in ml/sec and in millimoles/sec, noting that the volumes of gas are given in ml STP [Standard Temperature (0°C) and Pressure (atmospheric, dry)] and that 22.4 liters (STPD) = 1 mole.

1.2 (Flux between body and surroundings).

For convenience, assume a ventilation of 8.064 liters/min, taking the ventilation to be the volume of inspired dry air measured at 0°C. Calculate J_{O_2} noting that inspired air has 21% O_2, the expired air has 16% O_2.

J_{O_2} = mmole/sec
J_{H_2O} = mmole/sec

Water turnover is dominated by water ingestion (drink, food) and urinary excretion. Assuming a diuresis of 1.55 liters/24 hr calculate J_{H_2O} in mmole/sec noting that mol wt (H_2O) = 18 g/mole. Are there other loses of H_2O from the body?

The mode of infusion secures mixing at site of injection. *Wahren, J.* (1970): *Acta Physiol. Scand.* Suppl. 269.

1.3 (Forearm blood flow, constant infusion).

Radioactive ^{131}I-labeled human serum albumin (RHISA) is infused in the brachial artery at a rate of 10,000 cpm per minute. At steady state, the downstream concentration is 100 cpm/ml of whole blood. Calculate forearm blood flow, and, using

[2] This summary takes the more usual step-by-step approach and ends with the flow-flux equations; in the main sections the order was reversed as the basic equation was outlined in the beginning. Is this not the way the mind best perceives a topic?

a hematocrit of 0.40, forearm plasma flow. How do we measure forearm glucose uptake?

1.4 (Cardiac output, constant infusion).

A solution of ^{85}Kr gas in sterile saline is infused in the superior vena cava at a constant rate of approximately 1 ml/min and blood samples are collected from a catheter placed in the pulmonary artery.

In order to measure the infusion rate of ^{85}Kr we let the infusion pump infuse the same solution for precisely 1.00 min into a "standard" syringe containing 99 ml of water; after the infusion for 1.00 min the volume of the standard V_{st} is 100 ml. In this way the infusion rate corresponds to the infusion of one standard syringe per minute.

An aliquot of the standard (the contents are first mixed anaerobically using a drop of mercury) has a counting rate of 5,070 cpm and the background is 70 cpm. Denoting by X the factor converting cpm/aliquot to μc/ml, what is the influx of ^{85}Kr, j_{in}?

Using the same counting geometry and the same size aliquots of the blood samples we record over a period of 10 min of counting 1,530, 1,690, 1,710, and 1,700 counts in the samples taken at 0 to 2 min, 2 to 4 min, 4 to 6 min, and 6 to 8 min of infusion. Neglecting recirculation, calculate c_{blood} in μc/ml as the mean of the last three samples. Now calculate cardiac output (c.o.).

Equation for continuous infusion experiment.

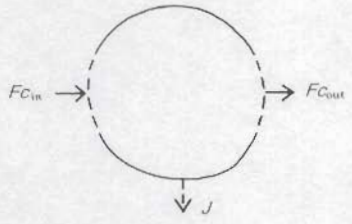
$$F = j/c$$

^{85}Kr is largely exhaled from the lungs so that recirculation effects are quite small, normally less than 10%. See Chidsey, C. A. III et al. (1959): *J. Appl. Physiol.* 14:63.

2 Flow or Flux by Constant Infusion and Constant Nonconvective Outflux (The Fick Principle)

2.1 The Experiment

Fick, A. (1870): Sitzungsb. der Phys.-Med. Ges. zu Würzburg, p. 36.



A negative value for J would represent a constant supply of indicator at the nonconvective opening of the system.

Consider a system with a flow F ml/sec of a fluid entering through a single well-mixed convective inlet and leaving through a single well-mixed convective outlet. The system has, in addition, a nonconvective outlet to the surroundings. The indicator is first considered to be a systemic substance. It enters at the constant rate FC_{in} and leaves through the convective outlet at the constant rate FC_{out}, but it also leaves through the nonconvective outlet at the constant rate J. The amount of indicator inside the system is constant because the indicator is a systemic substance for which the system by definition is in steady state. Indicator mass balance gives

$$\begin{array}{ccccc} \text{Convective} & - & \text{Convective} & = & \text{Nonconvective} \\ \text{influx} & & \text{outflux} & & \text{outflux} \\ FC_{in} & - & FC_{out} & = & J \end{array} \qquad [2.1]$$

The flow of fluid through the system can therefore be measured if the inlet and outlet concentrations C_{in} and C_{out}, can be measured as well as the uptake. This was the method proposed by Fick for determining cardiac output from a measurement of total body oxygen uptake $\dot{V}O_2$ and of the arterial (CaO_2) and mixed venous $C\bar{v}O_2$ oxygen concentrations.

$$F = \frac{\dot{V}O_2}{CaO_2 - C\bar{v}O_2}$$

In this case O_2 is the indicator for flow measurement.

Equation [2.1] can also be used for measuring the nonconvective outflux (the uptake) J of a substance from a system. Consider the example of the measurement of the forearm blood flow F and the arterial and venous glucose concentration C_{in} and C_{out}. Then $F(C_{in} - C_{out})$ is the forearm tissue's glucose uptake J from the blood.

Fick principle

It may be noted that in this mode of presenting the Fick principle we allow no change in mass to take place inside the system: indicator is neither broken down nor produced within the system's interior. This is a so-called conservative system, one in which the conservation of mass is respected. This defini-

tion is applied to all systems used in this volume, as they are alike in this respect.

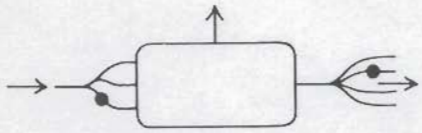
According to this concept one cannot strictly speaking consider the total kidney as the system and then determine the kidney's oxygen uptake as $F(Ca_{O_2} - C\bar{v}_{O_2})$. In doing so one expresses that the indicator (O_2) is continuously consumed inside the system. We must instead consider the mitochondria as diffusely dispersed outlets (a sink) for O_2. Nevertheless, in practice we shall use $[J]_{O_2}$ to denote the renal oxygen uptake.

J is positive if this nonconvective flux is directed toward the exterior as in the case of the oxygen uptake of the kidney. In other situations J is negative, as when we consider carbon dioxide in relation to the kidney; this negative uptake is called the production.

2.2 Mixing

The measured concentrations must be representative; that is, we must be sure that regardless of where in the inlet or in the outlet we sample these concentrations do not vary.

If both sampling sites are well mixed then this holds. But, referring to the discussion on mixing in Chapter 1 (sec. 1.6), it also holds even if cross-stream mixing only exists proximal (upstream) of the sampling sites. The importance of this point is perhaps best appreciated by reference to the use of Fick's method for determining cardiac output in man. Let us assume that samples of the convective inlet of oxygen to the body are obtained by collecting arterial blood from the brachial artery. Because of the mixing of blood in the left side of the heart (in the atrium and the ventricle) it does not matter which one of the larger systemic arteries we sample from; C_{in} is the same throughout. It also does not matter from where in the cross section of the artery we sample. We can also allow the sampling catheter to move from one laminarly flowing stream to another during the sampling. The same applies for sampling of the mixed venous blood where we can sample from the pulmonary artery or any one of its major branches.



• = sampling sites for measurement of C_{in} and C_{out}

$Ca - Cv$

The AV concentration difference

2.3 Errors

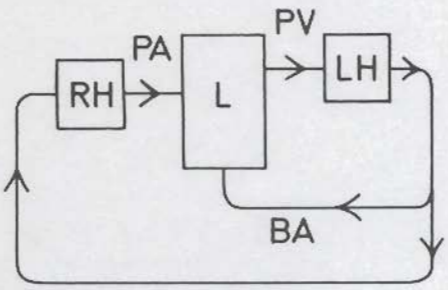
An important aspect of the practical application of Fick's principle is that it depends on measuring the difference between C_{in} and C_{out}. Usually this difference is the arteriovenous difference across an organ. Considerable errors will arise if the two concentrations are almost the same. In such cases great care must be taken to reduce the experimental error of the concentration determination.

If a foreign substance is used as the indicator, then we must be certain that the indicator steady state has been reached, as otherwise the amount of indicator inside the system $m(t)$

has not reached its constant value m. This point can be made clearer by recognizing that the left side of the Fick Eq. [2.1] is the net-convective influx. This balances the net nonconvective outflux J (the uptake) denoted on the right side when, and only when, the amount of the substance inside the system is constant.

The net uptake is usually a metabolic uptake, often designated as $\dot{Q}$. Thus, the Fick equation is written $F(C_{in} - C_{out}) = \dot{Q}$. Referring to the measurement of cardiac output by the Fick principle we see that it is not significant that oxygen diffuses bidirectionally across the blood vessels: it is the net diffusive outflux into the tissues that must be known. This parameter is assessed by measuring the uptake of oxygen at the mouth assuming that O_2 consumption in airways, lung, and circulating blood is negligible.

Effect of bronchial circulation on cardiac output determination (lack of outlet mixing)



In many cases the nonconvective outflux J is nevertheless convective.

The Fick principle is valid even if there are physically speaking many inlets or outlets provided that the concentration is the same at all inlets, and, respectively, at all outlets. Small errors arise in determining the cardiac output, which is defined as the amount of blood leaving the left side of the heart per unit time. Approximately 1% of this blood normally reaches the lung via the bronchial arteries and is not mixed with the venous blood sampled from the pulmonary artery. This means that the value determined for cardiac output is actually the output of the right side of the heart—a trivial difference in normal man.

Another small source of error in applying the Fick principle stems from the fact that in many cases the metabolic uptake J has the form of a small flow of fluid in which the substance is highly concentrated (such as urine or bile). Thus F_{in} slightly exceeds F_{out}. We should also mention that the flow of lymph and the metabolic production of water in the tissues is generally neglected.

The errors in the Fick method, some of which we have discussed, can be perceived quite readily. "What if C_{out} is not the same at all sites?," "What if the system is not in the steady state to a sufficient degree—after all the blood does not flow from the heart in a constant stream?," "Can the oxygen uptake of the lung be neglected?." The emphasis here is on recognizing the fact that in certain applications the Fick principle is quite valid but in others not nearly as much. Underlying the simple formal expression of the Fick equation are many physiological problems that constitute the essence of the method—which is *not* the idealized mass balance Eq. [2.1].

Actual mass balance compared to the "idealized" mass balance concept

2.4 Extraction *E* and clearance *Cl* of a substance

The extraction is defined for the system with a single convective inlet and a single convective outlet by dividing both sides in Eq. [2.1] by the convective influx, FC_{in}

The extraction

$$E = \frac{C_{in} - C_{out}}{C_{in}}$$

is often given i

$$E = \frac{Ca - Cv}{Ca}$$

and correspon

$$1 - E = T$$

The transmiss

$$T = \frac{C_{out}}{C_{in}}$$

often in the f

$$T = \frac{C_v}{C_a}$$

$$J = Cl \times C$$
$$= "F" \times C$$
$$j = Cl \times c$$
$$= "F" \times c$$

Extraction ×

The extraction

$$E = \frac{C_{in} - C_{out}}{C_{in}}$$

is often given in the form of

$$E = \frac{Ca - Cv}{Ca}$$

and correspondingly for the indicator

$$1 - E = T$$

The transmission

$$T = \frac{C_{out}}{C_{in}}$$

often in the form of

$$T = \frac{C_v}{C_a}$$

$$J = Cl \times C$$
$$= \text{"}F\text{"} \times C$$
$$j = Cl \times c$$
$$= \text{"}F\text{"} \times c$$

Extraction × Flow = Clearance

$$E \equiv \frac{FC_{in} - FC_{out}}{FC_{in}} \quad \text{For systemic substance}$$
$$E \equiv \frac{Fc_{in} - Fc_{out}}{Fc_{in}} \quad \text{For foreign indicator in steady state} \qquad [2.2]$$

E is thus the fraction of the inflowing substance of interest that does not leave the system via the outflow. We say that the corresponding molecules have become extracted or cleared from the fluid (blood). Sometimes one also makes use of the complement of E, that is $1 - E$ which correspondingly is defined as the fraction of the inflowing molecules of the substance studied that leaves the system via the outflow; this fraction is said to be transmitted through the system by the fluid stream and hence $1 - E$ is sometimes called the throughput or transmission T.

A useful, or at least often used, concept for describing a nonconvective outflux J is that of the clearance Cl. It is defined as *the flux divided by a reference fluid's concentration of that substance.*

$$Cl \equiv \frac{J}{C} \quad \text{ml/sec for systemic substance}$$
$$Cl \equiv \frac{j}{c} \quad \text{ml/sec for foreign indicator in steady state} \qquad [2.3]$$

The unit of the clearance is seen to be (mg/sec)/(mg/ml) = ml/sec, that is, milliliters of reference fluid per unit time. Thus the clearance has the same unit as the flow in the convective case and the clearance may be considered as the "equivalent" convective flow "F" that, had it occurred, would have resulted in the flux J, and, respectively, j.

Using the inflowing fluid as reference fluid we obtain, by inserting the clearance definition [Eq. 2.3] into the extraction definition [Eq. 2.2], $E = Cl/F$. Hence it follows that

$$EF = Cl \qquad [2.4]$$

Thus the clearance is obtained as the fractional loss of substance via the nonconvective outlet E multiplied by the throughflow F.

In defining the extraction and clearance of a foreign indicator capital rather than lowercase letters were used because the symbols refer to the indicator steady state. Thus if the indicator is a tracer of a systemic substance, tracer and mother substance have the same extraction and clearance. This is true because the specific activity in the steady state is the same at any site of the system after mixing at (or upstream of) the inlet.

The definition of clearance has a physical meaning only if one has reasons to believe that the flux, although unassociated with a fluid flow, is nevertheless caused by a substance being

removed from the reference fluid chosen. As an example consider the creatinine clearance in the glomeruli. The urinary outflux $J_{creat.}$ is here the result of ultrafiltration of renal arterial plasma which is an actual convective flux of creatinine. Hence, taking renal arterial plasma or plasma with the same concentration of creatinine as the reference for measurement of $C_{creat.}$, the clearance $Cl_{creat.}$ corresponds to that plasma flow from which the flow of glomerular ultrafiltrate is actually made, and $E_{creat.}$ is the fraction of renal plasma from which creatinine is removed by filtration flow (the filtration fraction).

But in many cases Cl cannot be given such a concrete physical interpretation. In such cases the term may yet be used operationally to the measurement of flow $FE = Cl \rightarrow F = Cl/E$. As an example of the use of these concepts, consider the calculation of kidney blood flow by measurement of the clearance and the extraction of the indicator *p*-aminohippurate (PAH). The renal clearance of PAH is the ratio of the steady-state urinary excretion rate of PAH, J_{urine}, and the steady state arterial concentration of PAH measured in plasma c_a. To express this plasma clearance as a whole blood clearance we must divide by $(1 - Htc)$ as human red blood cells contain no PAH. The extraction E is $(c_a - c_v)/c_a$ where c_v is the renal venous plasma concentration.

c_a can be measured in venous blood collected from the anticubital vein as the arm does not extract PAH in the indicator steady state

Rearranging Eq. [2.4] we obtain

$$\text{Flow} = \frac{\left[\begin{matrix}\text{Whole blood}\\ \text{Clearance}\end{matrix}\right]}{[\text{Extraction}]} = \begin{matrix}\text{Plasma}\\ \text{clearance}\end{matrix} \times \frac{1}{\text{Extraction}} \times \begin{matrix}\text{Conversion}\\ \text{to blood}\\ \text{flow}\end{matrix}$$

$$F = \frac{Cl}{E} = \frac{J_{urine}}{C_a} \times \frac{c_a}{(c_a - c_v)} \times \frac{1}{(1 - Htc)} \qquad [2.5]$$

which, by cancellation of c_a, shows the equivalence of Eq. [2.5] to the Fick principle, Eq. [2.1]. A further comment regarding this equation might be the following. Because in the normal kidney and at low PAH concentrations the extraction of PAH is almost complete ($E_{PAH} \simeq 1.0$), then the whole blood clearance of PAH is almost equal to the renal blood flow F. Correspondingly, it follows that the renal plasma clearance of PAH in normal subjects (and at low PAH concentrations) almost equals the renal plasma flow. But this has given rise to gross mistakes when, by using the term effective renal blood flow for J/c_{blood}, one has inferred renal circulatory alteration in diseases. This is so because E_{PAH} is not unity in most renal diseases. To explicitly illustrate what is meant by gross error we may consider acute anuria, an acute renal disease where practically no urine is being formed. In this disease the whole blood PAH clearance via the urine is reduced to as low as 1% of the normal value or even less. By taking too literally the concept "effective renal blood flow," that is by forgetting that perhaps E_{PAH} was no

longer close to 1.0, it was concluded that renal blood flow was also reduced to 1% (or less) than normal—a condition of extreme reduction in flow (renal ischemia). It was subsequently found that in this disease E_{PAH} is reduced to a few percent and that renal blood flow was actually only moderately reduced (between approximately 25 and 75% of normal). This example stresses that in general cases the clearance *Cl does not have a precise physical meaning but is merely a tool that one may use to calculate flow or flux.*

2.5 Comments on the Fick Principle

Note that we assume that in the indicator steady state there are no concentration gradients at inlet or outlet; that is the basic equation of the Fick principle contains no term for diffusive fluxes

This principle, which constitutes an application of the Law of Conservation of Mass, states that in the steady state the uptake (nonconvective outflow) equals the difference between the amount entering and leaving by fluid flow. The mass balance concept involved is actually the same as that used in the constant infusion method.

To illustrate this, consider the Fick principle for measurement of cardiac output by measurement of $J =$ (total body O_2 uptake, $\dot{V}O_2$) and $C_{in} - C_{out} = (CaO_2 - C\bar{v}O_2)$. In terms of the constant infusion method the system considered is the lung. Into this system a constant "infusion" of the indicator (O_2) is made at the rate $J = \dot{V}O_2$, CaO_2 is here the *outlet concentration,* and $C\bar{v}O_2$ is the *recirculation* (this can be seen by imagining that suddenly no more O_2 was taken up at the lungs; then during a brief interval the mixed venous O_2 concentration would be found in the arterial blood).

These considerations show that the arteriovenous difference $CaO_2 - C\bar{v}O_2$ is in terms of the constant infusion method *the outlet concentration as corrected for indicator recirculation* [Eq. 1.8] and consequently

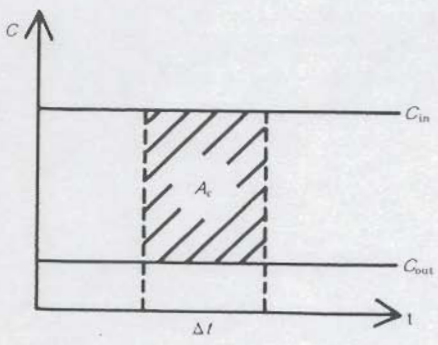
$$\begin{aligned} \text{Influx} &= \quad \text{Outflux} \\ \dot{V}O_2 &= F(CaO_2 - C\bar{v}O_2) \end{aligned}$$

Thus the Fick principle is the constant infusion method in the special case where the recirculation can be corrected for because the recirculation is convective and occurs via a well-mixed inlet that can be sampled.

The Fick equation for flow $F = J/(C_{in} - C_{out})$ can be changed to the dose over area formulation by multiplying both numerator and denominator by the sampling time Δt; the dose in Δt *is* $m_0 = J\Delta t$, the area under the outlet curve in the same interval is $A_c = (C_{in} - C_{out})\Delta t$ after correction for recirculation. Hence $F = J/(C_{in} - C_{out}) = m_0/A_c$.

The Fick principle is strictly an indicator steady-state method just as the constant infusion is. Hence it is not quite correct to use the term for the nonsteady state condition of inert gas uptake (Kety's method), a situation where cross-stream mixing must exist at the inlet and at the outlet. Despite

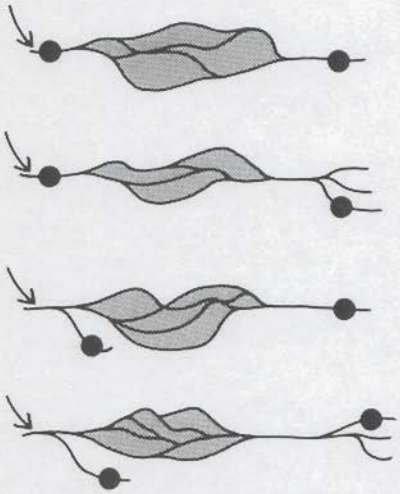
Flow-Dose/Area



the similarity of the basic equations the Kety method is fundamentally different from the Fick principle because Kety's method is a *transit time* method as discussed in Chapter 6; that is, it is based on following a transient indicator nonsteady state.

We stressed the mixing conditions "at site of sampling or upstream thereof" because this is exactly the situation encountered in the most widely used application of the Fick principle—cardiac output determination. The sampling of the arterial blood for oxygen concentration determination, C_{in} in Eq. [2.1], is downstream of the left heart mixing chamber. But this means that we can sample from any artery, from any site in the cross section of the artery, and that this site may even vary during the sampling (such movement of the sampling catheter cannot be allowed in the bolus injection method discussed in Chapters

Arrow is the infusion site; dot is the sampling site.



Four systems with cross-stream mixing at sites of sampling or upstream thereof for which the Fick principle is valid. Only the first system (single inlet—single outlet) is valid for Kety's inert gas uptake method.

EXERCISES

2.1 Give examples of the units for clearance Cl for measurement of glomerular filtration rate GFR, and list three indicators that can be used to measure GFR.

2.2 Given the Cl_{inulin} of the kidney and the extraction E can one then calculate renal blood flow RBF? Inulin is infused at the rate of 4.2 mg/min; after 3 hr the plasma concentration is constant at 0.035 mg/ml. Calculate Cl and, assuming the filtration fraction E is 0.20, calculate renal plasma flow. Assuming the hematocrit is 0.40, calculate the renal blood flow.

2.3 (Calculation of liver blood flow by clearance and extraction of BSP).

Bromsulphthalein (BSP) is infused at a constant rate J_{in} (15 mg/min) intravenously. After an appropriate time interval of approximately 1 hr, the inflow concentration to the liver, that is the concentration in arterial blood or in peripheral venous blood, is found to have reached a constant value c_a (0.02/ml plasma). The indicator steady state has been reached, in which the removal rate equals the infusion rate. The clearance of BSP is then

$$Cl = \text{ml/min}$$

No BSP in red cells: eliminated BSP from plasma = eliminated BSP from blood

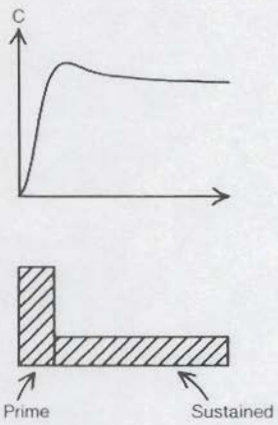
To interpret the clearance in terms of an actual flow rate in the system, it is assumed that this clearance occurs only in the liver. The extraction E of BSP is determined as $(c_a - c_v)/c_a$ is 0.5, where c_v is obtained by a catheter placed in a hepatic vein. Calculate liver blood flow. If the concentration c_a has been determined as amount of BSP per ml of plasma, then the calculated flow is the _____ F flow.

How, in case of plasma analysis, does one calculate liver blood flow? Does the liver blood flow calculated above include hepatic arterial blood flow? Give a reason for your answer.

Absolute temperature 273° + degree Celsius

(No decimals)

To measure $\dot{V}O_2$ is not all that simple!



$$EF = Cl$$

2.4 (Calculation of cardiac output by Fick principle.)

The inspired air volume measured as dry air is 12.0 liters/min and temperature is 25°C. Calculate the inspired air volume per minute as it would have been at 0°C (standard temperature).

The inspired dry air has the normal composition of air, that is: ____% N_2, ____% O_2, ____% CO_2.

The expired air was analyzed and contained in the dry state 80% N_2, 16% O_2, and 4% CO_2. Assuming that N_2 is not taken up or given off, write the mass balance equation in order to calculate the expired volume of dry air (at 0°C):

$$\text{Inspired } N_2 = \text{Expired } N_2$$

Next calculate the per minute expired volume of air expressed as dry air 0°C, the expired volume of O_2/min, that for CO_2, the respiratory quotient (CO_2/O_2), and the oxygen uptake.

With the measured arterial-mixed venous O_2 concentration difference of 57.2 ml O_2 per liter of blood calculate cardiac output. Is the subject at rest?

2.5 (Clearance and extraction of inulin and PAH by the kidney; kidney blood flow by Fick principle.)

A priming bolus and a sustained constant infusion of a solution containing both substances is made intravenously. Blood is collected from the anticubital vein after 30, 60, 90, and 120 min. When constancy of concentrations is observed (indicator steady state for both substances) then the clearances could be obtained as j_{infus}/c.

However, it is more precise to measure the amount of indicator excreted by the urine because even minor variations in the content of indicator in the body will mean that $j_{infus} \neq j_{out}$. Hence the more precise expression is $Cl = j_{out}/c$.

Use the inulin concentration values in Example 2.2. Calculate clearance of inulin. With a measured extraction $E_{in} = (c_a - c_v)/c_a = 0.22$, calculate renal plasma flow ____ml/min. Using a hematocrit value of 0.41 calculate renal blood flow. Indicate also the rate of formation of glomerular ultrafiltrate (the true glomerular filtration rate) assuming that the fractional volume of ultrafiltrate in plasma is 0.93.

As $E_{in} = 0.22$ and $E_{PAH} = 0.92$, why do we preferably use PAH to obtain RBF?

The Correction for Urinary Flow of Water. This is usually a minor correction. However, since it was not mentioned in the text, we felt it would be of interest to include it in this example.

Because of the urinary flow, the blood flow in and out of the kidney is not quite the same (here the still smaller secondary factors, lymph flow and metabolically produced water, are neglected). Hence the extraction measured as $E' = (c_a - c_v)/c_a$ is not an exact measure of the fractional extraction of indicator E from blood traversing the kidney.

The mass balance equation is

$$J_{artery} = J_{vein} + J_{urine} \qquad [1]$$
$$F_a c_a = F_v c_v + F_u c_u$$

Where we can write, if we neglect the quite minimal red cell volume changes and renal lymph

$$F_a = F_v + F_u \qquad [2]$$

Inserting this and noting that $F_u c_u = j_u = Cl\ c_a$ Eq. [1] becomes

$$F_a c_a = (F_a - F_u)c_v + Cl\ c_a \qquad [3]$$

or, solving for the renal plasma inflow F_a, and inserting $E' = (c_a - c_v)/c_a$

$$F_a = \frac{Clc_a - F_u c_v}{c_a - c_v} = \frac{Cl}{E'} - F_u \frac{1 - E'}{E'} \qquad [4]$$

Inserting normal values and using the case of inulin, $Cl = 100$ ml/min, $E' = 0.25$, $Cl/E' = 400$ ml/min, $F_u = 2$ ml/min, $(1 - E')/E' = 0.75/0.25 = 3$, $F_u \cdot (1 - E')/E' = 6$ ml/min. $F_a = 400 - 6 = 394$ ml/min, $F_v = 394 - 2 = 392$ ml/min. Hence we only overestimate F_a and F_v by 1.5% by neglecting the correction term $F_u \cdot (1 - E')/E'$. But, if E decreases to, for instance, 0.01, then $(1 - E')/E'$ increases to 99, or if the urinary flow F_u increases relative to Cl, then the correction may become important.

Wolf, A. W. (1941): *Am. J. Physiol.* 133:496.

This calculation shows clearly that $E' = (c_a - c_v)/c_a$ is an approximation that holds *strictly* only when the substance leaves the system at the nonconvective outlet *without any water*. The correct E in the general case when fluid is lost at a nonconvective outlet u, is

$$E \equiv \frac{J_u}{J_a} = \frac{F_a c_a - F_v c_v}{F_a c_a} \qquad [5]$$

This E gives, as $Cl \equiv J_u/c_a$ or $J_u = Cl\ c_a$, that

$$F_a c_a = J_a = J_u/E = Cl\ c_a/E \qquad [6]$$

Thus $F_a E = Cl$ holds strictly as it must if the definitions are adhered to. We can calculate the correct extraction E using Eq. [5] and inserting $F_v = F_a - F_u$

$$E = \frac{F_a c_a - F_a c_v + F_u c_v}{F_a c_a} = E' + \frac{F_u}{F_a}\frac{c_v}{c_a}$$
$$= E' + \frac{F_u}{F_a}(1 - E') \qquad [7]$$

$$\frac{E}{Cl} = \frac{c_a}{J_a} = \frac{1}{F_a}$$

or

$$EF_a = Cl$$

2.6 (Transcapillary exchange of sucrose.)

During the passage through the muscle capillary no measurable net loss of the indicator sucrose occurs over the capillary membrane when measured in the steady state (prolonged infusion with constant concentration). This means that in this situation the sucrose outflux j_{out} from capillary lumen to interstitium equals the sucrose influx j_{in} over the same membrane (lymph flow is here disregarded).

In a brief injection experiment, however, the dilution of sucrose in the interstitial fluid is so great that the influx (backdiffusion) can be neglected. Suppose that the muscle blood flow is 12.6 ml/100 g/min, and the flow of plasma one-half that amount, the sucrose concentration is 0.10 mg/ml of plasma and that the brief injection indicated that 50% of the sucrose mole-

cules leave the capillary blood initially [i.e., during the first (single) passage through the capillary]. Calculate the initial outflux j_{out} for sucrose expressed in mg/100 g/min. With the mean intracapillary sucrose concentration $\bar{c}$ taken as the mean between c_a and c_v calculate the muscle capillary's *permeability surface area product PS* for sucrose when we define *PS* as the flux per unit concentration gradient across the capillary membrane in 100 g of muscle (with the time unit expressed as minutes). With the surface area taken as 7,000 cm^2/100 g, calculate P = flux per unit concentration difference, per cm^2, and per second = cm/sec.

Note that this example is beyond the immediate scope of Chapters 1 through 8. See Chapter 11.