Title

Mathematical Models for Exchange of Substances in Regional Vascular Beds-Measurement of the Rates with in Vivo Counters

Authors

Parker, Howard G
Hippensteele, J Robert

Publication Date

2023-09-06

MATHEMATICAL MODELS FOR EXCHANGE OF SUBSTANCES IN REGIONAL VASCULAR BEDS--MEASUREMENT OF THE RATES WITH IN VIVO COUNTERS

Howard G. Parker, M. D., Ph. D.,
Ernest L. Dobson, Ph. D.
Donner Laboratory and Lawrence Radiation Laboratory,
University of California, Berkeley, California

J. Robert Hippensteele, Ph. D.
Department of Anatomy and Physiology,
University of Indiana, Bloomington, Indiana

Abstract. Sangren and Sheppard developed a mathematical model for first-order processes taking place in the regional circulation, applicable--for example--to tracer studies of potassium transport. It permits calculation of specific activity at any point along a "tube of flow" or in the cuff of tissue surrounding it as a function of time following a spike injection of tracer. In efforts to relate to the exchange rate curves obtained with in vivo counters pointed at the region of interest, we developed a compartment-system model of the process. In investigating the properties of the Sangren and Sheppard model integrated over an entire circulatory bed, as the in vivo counter would see it, we found that when the distribution of transit times of the "tubes of flow" can be approximated by an exponential sum, the solution reduces to that of the compartment system model. This results in an important simplification in the calculation, and insight into the assumptions underlying the two different models. A curve-fitting computer program for the compartment model has been written and applied to double-isotope studies of potassium transport in the hind leg of the dog.

DISCLAIMER

Introduction. In a series of double-isotope experiments involving radioactive sodium and potassium injected simultaneously into the femoral artery of dogs, an effort is being made to interpret data from in vivo counters and femoral venous blood in terms of the kinetics of these ions in the hind leg of the dog (Hippensteele et al., 1969). One line of thought in modeling such a process is that developed by Dobson and Warner (1957), who initiated in vivo monitoring of extremities following intra-arterial injection of radioactive tracers. They fitted exponential sums to such curves, after correction for the recirculated radioactivity, and interpreted them in terms of the size and flow rate of a group of parallel uniformly mixed "compartments," each of which is washed out according to an exponential process. There is evidence that this conception is adequate for sodium, which can leak out of the blood vessels into extracellular space, as well as for materials that cannot leave the blood vessel. This appears to be the case because blood flow is a rate-limiting step, so the effect of diffusion rate cannot be seen in such curves. In working with potassium, however, with the cell membrane known to be a significant diffusion barrier, and active transport of potassium taking place, a further elaboration of such models to account for diffusion or transport seems necessary. The problem of modeling potassium transport in and out of the circulation has been considered by many, but not in a form directly applicable to in vivo counting. A natural elaboration of the Dobson and Warner model that appears to have the requisite properties is a multicompartment system such as that shown in Figs. 1 and 2. In this conception, the sodium can enter only the compartments labeled A, whereas the potassium can enter both A and B. The B compartments can be conceived of as the potassium pool within cells. A single pair of compartments will not suffice to explain the multiexponential curves for the sodium as well as potassium in the dog hind leg. Hence the parallel com-

partment pairs, or parallel "flow beds." The differential equations for this model and their solutions are presented.

One alternative approach involves a modification of the treatment by Sangren and Sheppard (1953) and Sheppard (1962) of a capillary bed as parallel "tubes of flow" from which the ions can leak and return along the length of the tube according to first-order kinetics (see Figs. 3 and 4). They derived an expression for the specific activity of a substance as a function of time and distance along a tube following a spike injection. Their expression can be applied to in vivo counting-rate data by modification to represent the fraction of the injected dose present per unit traversal time, rather than specific activity, followed by integration over tube transit time and over the distribution of transit times in parallel tubes. There is a striking resemblance between the partial differential equations and the ordinary differential equations of the "parallel compartment" model proposed here. If we further assume that the transit time distribution function is an exponential sum, the equations and solutions for the total content of tracer in and surrounding the tubes reduce to those resulting from the parallel-compartment model.

It has been widely appreciated (Zierler, 1962) that for a nondiffusible substance, an exponential distribution of transit times through a circulatory bed is equivalent for some purposes to a well-stirred compartment. The present result extends this notion to another type of substance: one that can leak from and return to the paths followed by nondiffusible substances. This permits an important simplification in calculation of such transport rates, and puts the result in a form directly applicable to fitting curves from in vivo counters. It suggests greater validity of the results of the compartment-system calculation than one might at first expect if thinking in terms of discrete well-mixed gross regions within the circulatory bed.

The equations for a reference tracer (such as radioactive sodium ion) that cannot enter the cells, as well as for the tracer that can "leak" (potassium), are developed here because our interpretation of the in vivo curves requires use of the double-isotope experiment and the particular interrelationship of the kinetics of the two tracers. This is explained in the Discussion. The compartment model is presented first, followed by the "tubes of flow" model.

Either of these models might find application to any substance introduced into the regional circulation that undergoes a first-order process of removal, or removal and return. It has been preferred to present them here, however, in the phraseology of the more restricted case of steady-state exchange or transport of substances and the first-order processes undergone by the tracers used in studying the exchange.

In each model, the reference tracer can be handled simply as a degenerate case of the diffusable tracer, with zero rate of diffusion and return. For purposes of exposition, however, it appears desirable to develop the subject for the simpler case of the reference tracer before taking up the complications of the diffusible one.

I. The Compartment-System Model. The steady-state transport of substances such as sodium and potassium can be conceived as indicated in Figs. 1 and 2. Figure 2 is an arbitrarily chosen pair of compartments, or "flow beds," from the complex of beds with varying volumes and perfusion shown in Fig. 1. The reference tracer (Na^+) enters only the compartments labeled A, directly accessible to the circulation. The "diffusible" tracer (K^+) is being transported from A to a compartment B and back. (For K^+, B is many times as large as A.) It is assumed that the rate constant λ''_i, determined by blood circulation to the ith flow

bed, applies equally to reference and diffusible tracer. Note that λ and λ', the fractional turnover rates indicated, are the same for all flow beds (see Discussion), whereas λ''_i is different in each flow bed. The fraction f_i of the arterial blood flow to each bed is arbitrary and not necessarily related to the volume of the bed.

If $Q_{A,i}$ is the amount of K^+ in the ith A compartment and $Q_{B,i}$ the amount in the corresponding B compartment, the steady-state assumption implies

$$\lambda Q_{A,i} = \lambda' Q_{B,i}.$$

This permits determination of relative compartment sizes from the ratio of the rate constants, or vice versa. We are otherwise not concerned here with the nontracer material, or with specific activities. The equations are presented in terms of quantities q of tracer substances, all as a fraction of the injected dose. A "spike" injection is assumed, where a fraction f_i of the injected dose appears in compartment A_i instantaneously at time zero.

A. The reference tracer. The differential equations for this simpler of the two tracer cases take the form

$$\frac{d\, q_{A,i}}{dt} = -\lambda''_i\, q_{A,i}, \qquad (1)$$

with the boundary conditions

$$q_{A,i}(0) = f_i.$$

The total amount of reference tracer in the system is

$$q_{TOT} = \sum_i q_{A,i}.$$

Although this is a case of simple exponential processes in parallel, the solution is presented in Laplace transforms, for comparison with later results. The equations in transform space are

$$s\,\bar{q}_{A,i} - q_{A,i}(0) = -\lambda''_i\,\bar{q}_{A,i},$$

where s is the variable in transform space corresponding to t, and a symbol with a bar over it indicates the Laplace transform of the corresponding unmarked symbol (Carslaw and Jaeger, 1959; Churchill, 1958). Then

$$(s + \lambda''_i)\,\bar{q}_{A,i} = f_i,$$

$$\bar{q}_{A,i} = \frac{f_i}{s + q''}, \tag{2}$$

$$\bar{q}_{TOT} = \sum_i \frac{f_i}{s + \lambda''_i}.$$

Using a standard inverse transform, we obtains

$$q_{TOT} = \sum_i f_i\, e^{-\lambda_i t}. \tag{3}$$

B. The diffusible tracer. The pair of simultaneous differential equations for each flow bed in this case is

$$\frac{d\,q_{A,i}}{dt} = \lambda' q_{B,i} - (\lambda + \lambda''_i)\,q_{A,i}, \tag{4}$$

$$\frac{d\,q_{B,i}}{dt} = \lambda\, q_{A,i} - \lambda' q_{B,i}, \tag{5}$$

with boundary conditions

$$q_{A,i}(0) = f_i,$$
$$q_{B,i}(0) = 0.$$

The equations in transform space are

$$s\,\bar{q}_{A,i} - q_{A,i}(0) = \lambda'\bar{q}_{B,i} - (\lambda + \lambda''_i)\,\bar{q}_{A,i},$$

$$s\,\bar{q}_{B,i} - q_{B,i}(0) = \lambda\,\bar{q}_{A,i} - \lambda'\bar{q}_{B,i}.$$

Substituting the above boundary conditions and solving for $\bar{q}_{A,i}$ and $\bar{q}_{B,i}$, we let

$$d_i = s^2 + (\lambda + \lambda' + \lambda_i'')\, s + \lambda'\lambda_i'' ;$$

then

$$\bar{q}_{A,i} = \frac{f_i(s+\lambda')}{d_i}, \quad \bar{q}_{B,i} = \frac{f_i \lambda}{d_i}, \quad \bar{q}_{A,i} + q_{B,i} = \frac{f_i(s+\lambda+\lambda')}{d_i}$$

and

$$\bar{q}_{TOT} = \sum_i \frac{f_i (s+\lambda+\lambda')}{d_i} . \tag{6}$$

Factoring d_i by means of the quadratic theorem and using standard inverse transforms, we obtain the following, where b_i and c_i are convenient intermediate variables and $r_{1,i}$ and $r_{2,i}$ are the roots of the auxiliary equation $d_i = 0$:

If we let $\quad b_i = \lambda + \lambda' + \lambda_i'' \quad$ and $\quad c_i = \lambda' \lambda_i'' ,$

the roots are

$$r_{1,i} = \frac{1}{2}\left\{-b_i + \sqrt{b_i^2 - 4c_i}\right\}, \quad r_{2,i} = \frac{1}{2}\left\{-b_i - \sqrt{b_i^2 - 4c_i}\right\},$$

and

$$q_{TOT} = \sum_i \left[\frac{f_i}{r_{1,i} - r_{2,i}} \left\{(\lambda+\lambda'+r_{1,i})\, e^{r_{1,i}t} - (\lambda+\lambda'+r_{2,i})\, e^{r_{2,i}t}\right\}\right]. \tag{7}$$

For purposes of comparison of this result with a later one from the second model, note that if a variable $c(s)$ is defined as

$$c(s) = s + \lambda - \frac{\lambda\lambda'}{s+\lambda'} ,$$

then equation (6) can be changed by algebraic manipulation into the form

$$\bar{q}_{TOT} = \left(1 + \frac{\lambda}{s + \lambda'}\right) \sum_i \frac{f_i}{c + \lambda_i''} \cdot \qquad (8)$$

Inverse transformation of this expression could be done by means of standard transforms, resulting in a very complicated expression in exponentials, Bessel functions, and their integrals, resembling the general result from the "tubes of flow" model. The previous result in closed form, equation (7), is greatly preferable for most purposes.

II. The Model Based on "Tubes of Flow". In this model the exchange process takes place in a regional circulatory bed consisting of "tubes of flow" or trajectories along which the reference tracer (Na^+) can pass, and from which the "diffusible" tracer (K^+) can leak (or be transported) and return. For Na^+ the trajectories are limited to blood and interstitial fluid. Figure 3 indicates a general conception of the multiple trajectories available, and shows that in the case of greatest interest to us, there are many short trajectories and few long ones, such that the ~~transit~~ distribution of transit times might be fitted by an exponential sum. (The identical distribution could be visualized for pathlength only if linear velocity were constant throughout the bed). Figure 4 shows a detailed view of one of the tubes. It indicates that "A" refers to tracer within the tube and "B" to tracer in the cuff of fluid surrounding the tube. Nothing akin to laminar flow takes place in this model, but merely bulk transfer down the tube, with a risk λ of leaking out of the tube per unit time, together with a probability λ' of returning from the surrounding cuff per unit time. An important restriction of this model, in order to obtain any answer with known methods, is that in the cuff around the tube, no diffusion of tracer is allowed in the direction along the axis of the tube. Since most of the space in this cuff consists of many indi-

vidual cells fairly close to one or another capillary, this assumption seems not unreasonable.

Sangren and Sheppard (1953) have treated a single tube from this model in some detail, deriving an expression for specific activity at any length x along the tube with flow having velocity v, as a function of time. They also point out the close relationship of such equations to those for heat transfer in heat exchangers, as presented by Carslaw and Jaeger (1959). For detailed presentation of this model and justification of the assumptions, the papers by Sangren and Sheppard (1953), Sheppard (1962), and Carslaw and Jaeger (1959) should be consulted.

Although the initial part of our derivation is closely patterned on those of Sangren and Sheppard (1953) and Carslaw and Jaeger (1959), it differs in the following respects:

1. A notation more in keeping with one for compartment systems is used, to aid in presenting the parallels between them.

2. We present virtually the same equations, with small but important differences in order to account for the amounts of tracer as the fraction of injected dose per unit tube length, the latter given in units of tube-traversal time. We assume the same relationship between relative size of tube A and B as was assumed in the discussion of Model I for relative compartment size: $\lambda Q_A = \lambda' Q_B$, where Q is the amount of nontracer diffusible substance per unit tube ~~length.~~ traversal time.

3. Since tube length x and velocity v are never measured and need never be explicitly considered in application of the model, we preferred to omit them. This simplifies the appearance of the equations, and emphasizes the fact that one need ~~to~~ not know distances, areas, or velocities. Instead, the model is derived by using tube traversal times and transit time distributions. A variable τ indicates the time to reach any point along a tube, and is related to distance and assumed uniform velocity within that tube

by the equation $\tau = \frac{x}{v}$. The closely related variable T is used for the transit time of any particular tube, the time for complete traversal of its length:

$$T = \frac{\text{tube length}}{v}.$$

A. The reference tracer. With t=time and τ and T defined as above, let $a(t,\tau) \equiv \partial q_A / \partial \tau$, where q_A is the fraction of injected tracer in the tube; a is then the fraction of injected dose traveling at velocity v present per unit tube-traversal time. The partial differential equation governing travel of the reference tracer (Na^+) is

$$\frac{\partial a}{\partial t} = - \frac{\partial a}{\partial \tau}. \tag{9}$$

The boundary condition of interest in the case of spike injection at zero time is

$$\begin{aligned} a(0,\tau) &= 0 \text{ if } \tau > 0 \\ &= 1 \text{ if } \tau = 0. \end{aligned}$$

In transform space,

$$s\bar{a} - a(0,\tau) = - \frac{\partial \bar{a}}{\partial \tau}.$$

Rearranging, we have

$$\frac{\partial \bar{a}}{\partial \tau} + s\bar{a} = a(0,\tau) = \delta(\tau).$$

Integration of this ordinary first-order equation with respect to τ yields

$$\bar{a} = e^{-s\tau}. \tag{10}$$

This is a particular solution that is of interest to us for spike injection at the beginning of the tubes at time zero. (For more detailed consideration of the boundary conditions giving rise to this solution see Sheppard, 1962.) Its inverse transform is

$$\frac{\partial q_A}{\partial \tau} = a = \delta(t - \tau), \tag{11}$$

which represents merely a spike of reference tracer, unattenuated, coursing down a tube. The amount in a whole tube whose transit time is given by the variable T is

$$q_A(t, T) = \int_0^T a\, d\tau \quad \begin{matrix} = 1 \text{ when } T \geq t \\ = 0 \text{ when } T < t, \end{matrix} \tag{12}$$

indicating that a tube contains either all or none of its reference tracer, depending on the position of the wave relative to the length of the tube. The amount in the whole circulatory bed, assuming a distribution of transit time for the tubes F(T), is given by

$$q_{TOT} = \int_0^\infty F(T)\, q_A\, dt.$$

Substituting the results for q_A, we get

$$q_{TOT} = \int_t^\infty F(T)\, dt. \tag{13}$$

In the case of special interest to us when $F(T) = \sum_i \lambda_i'' e^{-\lambda_i'' T}$, a multi-exponential sum for the frequency function of tube transit times for the reference tracer, substitution and integration yield

$$q_{TOT} = \sum_i f_i e^{-\lambda_i'' t}, \tag{14}$$

or, in transform notation,

$$\bar{q}_{TOT} = \sum_i \frac{f_i}{s+\lambda_1''}. \tag{15}$$

These solutions are identical with those obtained from the differential equations of the compartment system model, equations (2) and (3). The correspondence is obvious for the reference tracer, but the result is needed in general form for the double-isotope

comparisons to be made later.

B. The diffusible tracer. Closely following the foregoing exposition, let

$$a(t,\tau) \equiv \frac{\partial q_A}{\partial \tau}$$

and

$$b(t,\tau) \equiv \frac{\partial q_B}{\partial \tau},$$

where A and a refer to diffusible tracer in the tube and B and b refer to diffusible tracer in the cuff around the tube. The partial differential equations for our case are

$$\frac{\partial a}{\partial t} = \lambda' b - \lambda a - \frac{\partial a}{\partial \tau}, \tag{16}$$

$$\frac{\partial b}{\partial t} = \lambda a - \lambda' b; \tag{17}$$

a and b are functions of t and τ.

Boundary conditions are

$$a(0,\tau) = 0 \text{ if } \tau > 0$$
$$= 1 \text{ if } \tau = 0,$$
$$b(0,\tau) = 0 \text{ for all } \tau.$$

Closely following Sangren and Sheppard's solution,

$$s\bar{a} - a(0,\tau) = \lambda'\bar{b} - \lambda\bar{a} - \frac{\partial \bar{a}}{\partial \tau},$$

$$s\bar{b} - b(0,\tau) = \lambda\bar{a} - \lambda'\bar{b}.$$

Eliminating $\bar{b}$, we obtain

$$\frac{\partial \bar{a}}{\partial \tau} + c\bar{a} = a(0,\tau),$$

where

$$c = s + \lambda + \frac{\lambda\lambda'}{s+\lambda'}.$$

A particular solution of this ordinary first-order differential equation that pertains to our problem is

$$\bar{a} = e^{-c\tau}. \tag{18}$$

Consult Sheppard for justification of the use of this particular solution following spike injection. Using standard transforms in the manner indicated by Sangren and Sheppard, and defining two convenient variables $p = \lambda\tau$ and $q = \lambda'(t-\tau)$, we have

$$\frac{\partial q_A}{\partial \tau} = a(t,\tau) = \lambda' e^{-p} \{ \delta(q) + e^{-q} I_1 (2\sqrt{pq}) \sqrt{p/q} \}, \tag{19}$$

where I_1 is a standard Bessel function of imaginary argument.

Following Carslaw and Jaeger (1959), who explicitly considered the case of the B region, but for different boundary conditions, we have

$$\frac{\partial q_B}{\partial \tau} = b(t,\tau) = \lambda e^{-(p+q)} I_0 (2\sqrt{pq}). \tag{20}$$

Then

$$q_{A+B}(t,T) = \int_0^T \frac{\partial q_{A+B}}{\partial \tau} \, d\tau = \int_0^T (a+b)\, d\tau. \tag{21}$$

For computational purposes, a and b as derived above in terms of exponentials and Bessel functions (as series) can be substituted in this expression and integrated by approximate means. If we assume a frequency function of tube transit times $F(T)$, as was done for the reference substance, then

drops "(t)" down on to main line

$$q_{TOT}(t) = \int_0^\infty F(T)\, q_{A+B}\, dt \overset{*}{=} \int_0^\infty F(T) \int_0^T (a+b)\, d\tau\, dT. \tag{22}$$

* = "equals"

This equation can be programmed for an approximate solution with arbitrary $F(T)$. When that is done, a particularly important simplification is possible for the double-isotope case. For all tubes of length T greater than t, q_{A+B} must be equal to 1. This is accomplished by integrating equation (22) from 0 to t instead of 0 to ∞, and letting the integral from t to ∞ be given by the sodium-

retention curve defined by equation (13). Since $\int_0^T (a+b)d\tau$, that is q_{A+B}, must be 1 for all tubes where $T>t$, $\int_t^\infty F(T) \int_0^T (a+b)d\tau dT$ must equal $\int_t^\infty F(T)dT$. The F(T) in question is a distribution that we assume is shared by reference and diffusible tracers. Hence for K^+,

$$q_{TOT,K} = \int_0^t F(T) \int_0^T (a+b)\, d\tau dT + q_{TOT,Na}. \qquad (23)$$

That equation (22) reduces to equation (7) of the compartment-system model when $F(T) = \sum_i \lambda_i'' f_i e^{-\lambda_i'' T}$, the multiexponential frequency function, can be shown with the Laplace transforms of the above solutions:

$$\bar{q}_{TOT} = \int_0^\infty F(T) \int_0^T (\bar{a}+\bar{b})\, d\tau dT. \qquad (24)$$

But $q = e^{-c\tau}$, and it can readily be shown from equation (17) that

$$\bar{b} = \frac{\lambda}{s+\lambda'} \bar{a} = \frac{\lambda e^{-c\tau}}{s+\lambda'}.$$

Substituting the values of $\bar{a}$, $\bar{b}$, and F(T) into equation (24) and evaluating the integrals (now all in terms of simple exponentials), we arrive immediately at the result

$$\bar{q}_{TOT} = \left(1 + \frac{\lambda}{s+\lambda'}\right) \sum_i \frac{f_i}{c + \lambda_i''},$$

which is identical with that for the total quantity in the compartment model, equation (8). The result can readily be shown for the integral of A or B separately, as well as for the total. Therefore, in the "tubes of flow" model (Figs. 3 and 4), when tube length is multiexponential in distribution, total quantities of tracer occupying the sum of all A or of all B portions of the region are described by the ordinary differential equations (1), (4), and (5).

A simplification in computation based on equation (22) could also result if F(T) were a frequency function approximated by sums and differences of exponentials, rather than sums alone, but the ordinary differential equations (1), (4), and (5) and the model visualized in Figs. 1 and 2 would then not retain any physical significance; negative quantities of tracer in some of the compartments would be involved. A group of two-compartment flow beds partly or entirely linked in series rather than parallel can be shown to produce a system of differential equations with appropriate properties, but finding the particular model is irrevelant to the estimate of λ and λ'.

Discussion. Curve fitting with the above equations depends on some further assumptions. Since an in vivo counter records something merely proportional to the amount of radioactive tracer in a region, the fitting can be done by noting that for equations in which we left q refer, for example, to counting rates rather than quantities, we have $\sum_i f_i \neq 1$. The additional degree of freedom thus introduced suffices to make the transition. It must be assumed that the counting efficiency of either of the tracers is unchanged by its being in one or another of the different flow beds, or in the A or B parts of the region, an assumption often easy to make because of the anatomic nature of the region, such as the dog hind leg. The methods of standardization and correction for recirculation in experiments of this type have been presented by Dobson and Warner (1960) and by Hippensteele (1967). In the double-isotope experiment we have not assumed that an adequate standardization can be done to relate counting rate to quantity. Instead it is assumed that the standardization is adequate to correct for the relative counting efficiency of the two tracers. A further reasonable assumption is that the regions occupied by the two tracers are so intermixed anatomically that from the point of view of the counter they occupy essentially the same volume, whatever that may be. Hence, when the reference

tracer curve is multiexponential with n component exponentials, the 2n parameters f_i and λ_i'' are shared by the equations for the two tracers, and the diffusible tracer curve has 2n components, but only two additional degrees of freedom λ and λ'.

A program has been written for the CDC 6600 computer, fitting equation (7) to potassium data. It uses the minimization program "VARMIT" (written by Eric Beals, Lawrence Radiation Laboratory, University of California, Berkeley) to determine a weighted least-squares fit to λ and λ', given the f_i and λ_i'' from a previous weighted sum of exponentials fitted to the sodium data. To do this one supplies the sum of least squares, readily determined from equation (7), together with its partial derivatives with respect to λ and λ'. The calculation of the partial derivatives was programmed in simple piecewise fashion patterned step by step on the programming of equation (7) rather than written as a single expression prior to programming, as this was most economical of effort and easiest to check. Given this information at each step in its search, VARMIT takes a pair of initial estimates for λ and λ' and finds optimum values for them simultaneously.

Simple programming in a few lines of a conversational language "FOCAL" on the PDP-8 computer has provided curves for equations (3) and (7) that have helped verify the calculation. The results obtained for the compartment-model fit have been checked against the FOCAL result and against a program "MIMIC" on the large computer. The latter program provides a language to solve ordinary differential equations directly, but only for given parameters, lacking the "fitting" feature. The FOCAL programming conveniently provides outflow rate for the two tracers as well as quantities present. With this conversational language it is easy to calculate a number of additional results such as ratios of the two isotopes as a function of time.

When equation (23) from the more complicated "tubes of flow"

model is programmed in FOCAL language, with F(T) a multiexponential, it checks against equation (7). It takes a very much longer time to calculate each point, however, and with less accuracy. It does an approximate double integration, and for each step it must calculate Bessel functions and exponential sums for the input.

The models with multiexponential F(T) have been fitted to data for sodium and potassium ions (Fig. 5). The general nature of the fit is satisfactory, giving rise to a potassium leak rate λ of about the same order of magnitude as the average perfusion rate for sodium, and to a cellular potassium space very much larger than the extracellular potassium space, as one would expect. We have not completely worked out all technical problems in standardization, but the general result obtained here would appear to have intrinsic interest and potential applicability to a number of similar problems.

The two models that are presented here share certain assumptions, and not others, as a close review of the differential equations and boundary conditions shows. The fact that the "tubes of flow" model reduces to the compartment model in the circumstances outlined helps complete a clearer picture of what assumptions are made when these models are used, and what alternatives might be considered among their variants. One can consider the use of exponential sums merely an empirical device to approximate transit-time distributions and make the solution more tractable. Existence of discrete anatomic regions with uniform mixing in the ordinary sense is not an assumption essential to employment of the equations of the compartment-system model. The mere existence of trajectories of various lengths through a circulatory bed gives rise to a type of mixing indistinguishable from it for our purposes. In either model, there also remains the assumption that a tracer ion is at a fixed risk of undergoing a first-order process removing

it from the flow while it is in the region, and with a fixed probability of returning to that flow.

In the compartment model, restrictions were placed on λ and λ' more or less arbitrarily at first, in order to keep the number of parameters to a minimum. A number of alternative ways to assign λ and λ' for each flow bed, relate them to perfusion, or give them a distribution of values readily suggest themselves. With the tubes of flow, on the other hand, it is necessary to consider λ and λ' constant along any tube in order to derive the above result. An arbitrary relationship of λ and λ' to tube transit time would not be particularly hard to incorporate. In the simpler case in which λ' is zero (first-order removal without return), Sheppard (1962) has shown that the method gives a mean value for λ even though it may vary along the length of the tube. (Use of this latter model, incidentally, may offer a way to make a simplified fit to only the initial portions of curves, in order to estimate λ alone. We have restricted the presentation here to the more general case. The simplified one should be most applicable when λ' is known to be much smaller than λ, as for potassium transport.) Though the constancy of λ and λ' assumed in these models was arbitrary, and for purposes of simplification, as one thinks about alternatives it soon appears that this simple approach is hard to improve on without further arbitrary assumptions that cannot now be checked. Also, potassium transport may be a function of cell surface or volume, and the ratio of cellular to extracellular potassium can probably best be assumed at present to be constant over the various flow beds. Hence it appears that the particular models presented here, with their restrictions on λ and λ', may presently be the most reasonable approach to finding average values for them.

One further result from the above models: When the reference tracer curve is multiexponential, the probability that a diffusible tracer ion enters a B compartment (enters a cell) one or

INSERT A

page 24

From data of the type shown in ~~Figure~~ 5 the parameter P can be measured. It is the fraction of the diffusible substance entering the cells on passage through the tissue. When the intracellular pool is very large, P corresponds to the approximate notion of the "fraction of the injected tracer trapped in the tissue", which has been of particular interest in the use of radioactive potassium in circulatory studies. In the dog leg it appears that only about one-fourth of the K^+ is so trapped.

more times on single passage through the region of interest is given by

$$P = \sum_i \frac{\lambda f_i}{\lambda + \lambda_i''} .$$

Insert A continues paragraph

Acknowledgment. The authors gratefully acknowledge the expert technical assistance of Mrs. Jean Lynch and Miss Laurie Craise. Also much appreciated are the assistance and consultation of the Mathematics and Computing Group of Lawrence Radiation Laboratory, Berkeley, particularly by Mr. Mark Horovitz, Mr. William Hogan, and Mr. Kenneth Wiley.

This work was done under the auspices of the U. S. Atomic Energy Commission.

BIBLIOGRAPHY

Carslaw, H. S., and J. C. Jaeger. 1959. Conduction of Heat in Solids, 2nd Ed. Oxford, Clarendon. 391-394.

Churchill, R. V. 1958. Operational Mathematics, 2nd Ed. New York, McGraw-Hill, N. Y.

Dobson, E. L., and G. F. Warner. 1957. "Measurement of Regional Sodium Turnover Rates and Their Application to the Estimation of Regional Blood Flow." Am. J. Physiol. 189-276.

Dobson, E. L., and G. F. Warner. 1960. "Clearance Rates Following Intra-Arterial Injections in the Study of Peripheral Vascular Beds." In Methods in Medical Research, Vol. 8, ed. H. D. Bruner, Chicago Year Book Publishers.

Hippensteele, J. R. 1967. "Tracer Kinetic Studies of the Dynamics of the Microcirculation in Peripheral Vascular Beds" (Ph. D. thesis). Lawrence Radiation Laboratory Report UCRL-17774,

Aug. 1967, University of California, Berkeley, California.

Hippensteele, J. R., H. G. Parker, E. L. Dobson, and J. J. Lynch. 1969. "Potassium Exchange from the Sodium Space in the Dog's Leg." Fed. Proc. 28, 824-(abstract).

Sangren, W. C., and C. W. Sheppard. 1953. "A Mathematical Derivation of the Exchange of a Labelled Substance between a Liquid Flowing in a Vessel and an External Compartment." Bull. Math. Biophys. 15, 387-394.

Sheppard, C. W., 1962. Basic Principles of the Tracer Method." New York, Wiley.

Zierler, K. L., 1962. "Circulation Times and the Theory of Indicator-Dilution Methods for Determining Blood Flow and Volume." Handbook of Physiology, Sec. 2; Circulation, Vol. 1 Chapt. 18, p. 585, American Physiological Society.

FIGURE CAPTIONS

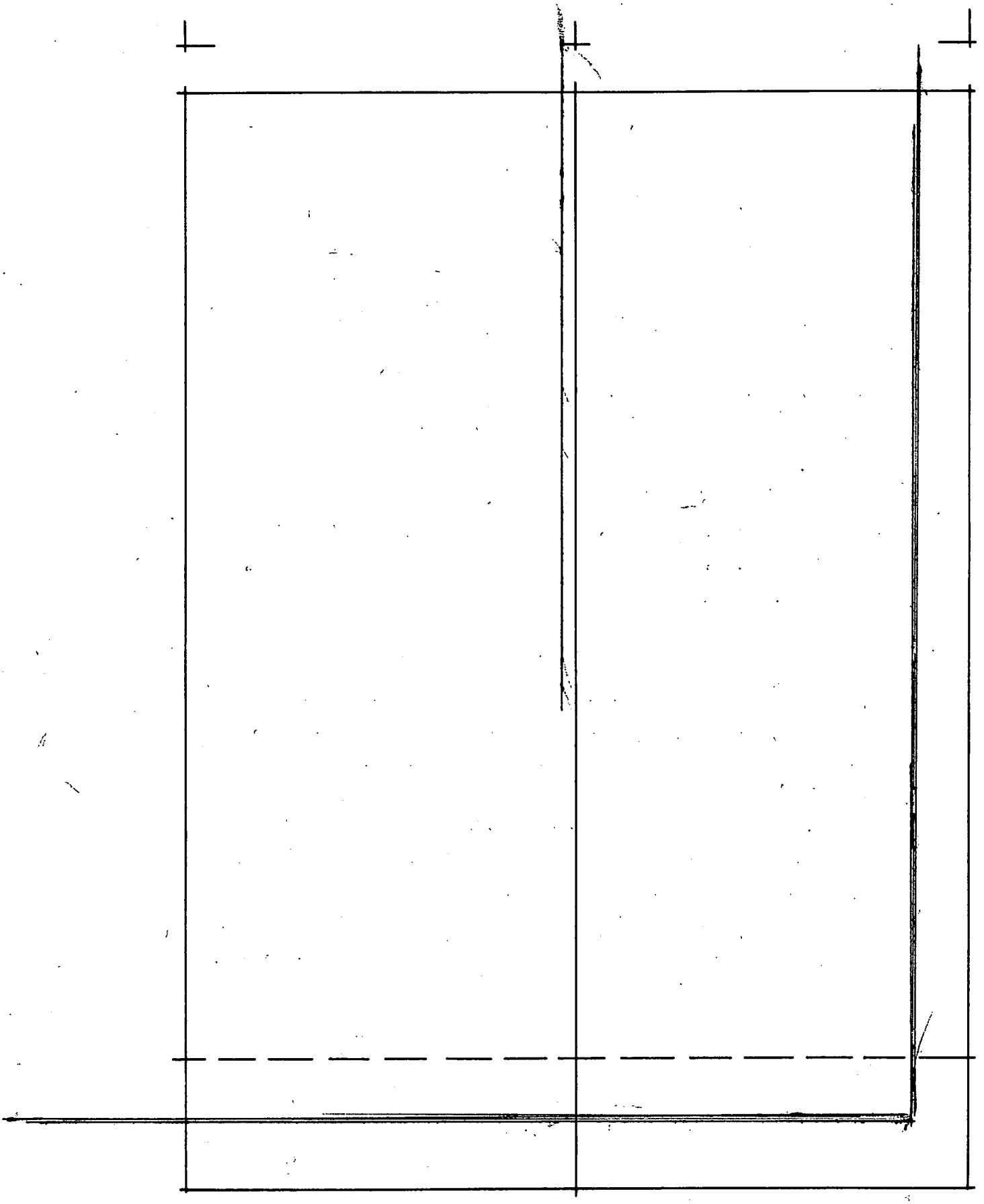
Figure 1. Compartment-system model of a region of the circulation consisting of parallel sets of two-compartment flow beds.

Figure 2. Enlargement of the ith flow bed from Fig. 1, indicating the relationship of the parameters and compartment labels as they appear in the equations. The reference tracer can enter only A, whereas the diffusible tracer enters both A and B.

Figure 3. The regional circulatory bed visualized as compounded of a number of "tubes of flow" of varying length, from each of which "leakage" and return of diffusible tracer are possible along its length.

Figure 4. Enlargement of a portion of one of the "tubes of flow" in Fig. 3, indicating the "A" region within the tube, occupied by both tracers, and the "B" region or cuff of fluid around the tube, into which only diffusible tracer can leak and return.

Figure 5. Equations (3) and (7) fitted by weighted least squares to *in vivo* counter data from the dog hind leg, with radioactive Na^+ and K^+ injected simultaneously in the femoral artery. The counting rate has been corrected for counter cross-talk, radioactive decay, and recirculation, and normalized for injected dose.



Graphic Arts PHOTO REQUEST Berkeley

RL-2499(Rev.5/69)

1 Item	3 ← 4 Type	6 *C	8 ← 9 Size	11 14 No.
N	CT			
	CO			
	LI			
	HT			
P	CT			
	CO			
	LI			
	HT			
S	CT			
	CO			
	LI			
F	CT			
	LI			
D	CT			
	CO			
M				
T	LI			
	HT			

UCRL [illegible] SEND TO: _____

Other _____ Slides _____

Editor _____ Prints [illegible]

Author [illegible] Orig. [illegible]

Date Sent 11-4-70 Neg. _____

Date Shot _____ Pos. _____

Photographer _____

Site _____ Description _____

*Code

E=Enlarge

C=Contact

M=35 mm

L=Lantern

☐ Slides

☐ Film Pos.

☐ Diapos.

☐ D.F. Pos.

☐ D.F. Diapos.

SPECIAL INSTRUCTIONS [illegible]

Negative Number	Fig. No.	Pg. No.	Negatives Size	BW	COL	Line	HT	Prints No.	Glossy Size	No.	Matte Size	Positives No.	Size
[illegible]	5							1	[illegible]	1	[illegible]		
[illegible]													
TOTAL													

16 ← 20 22 ← 28 30

Account No.: [illegible] Bldg. _____ Room _____ Ext. _____

Requester: Due Date RUSH ☐

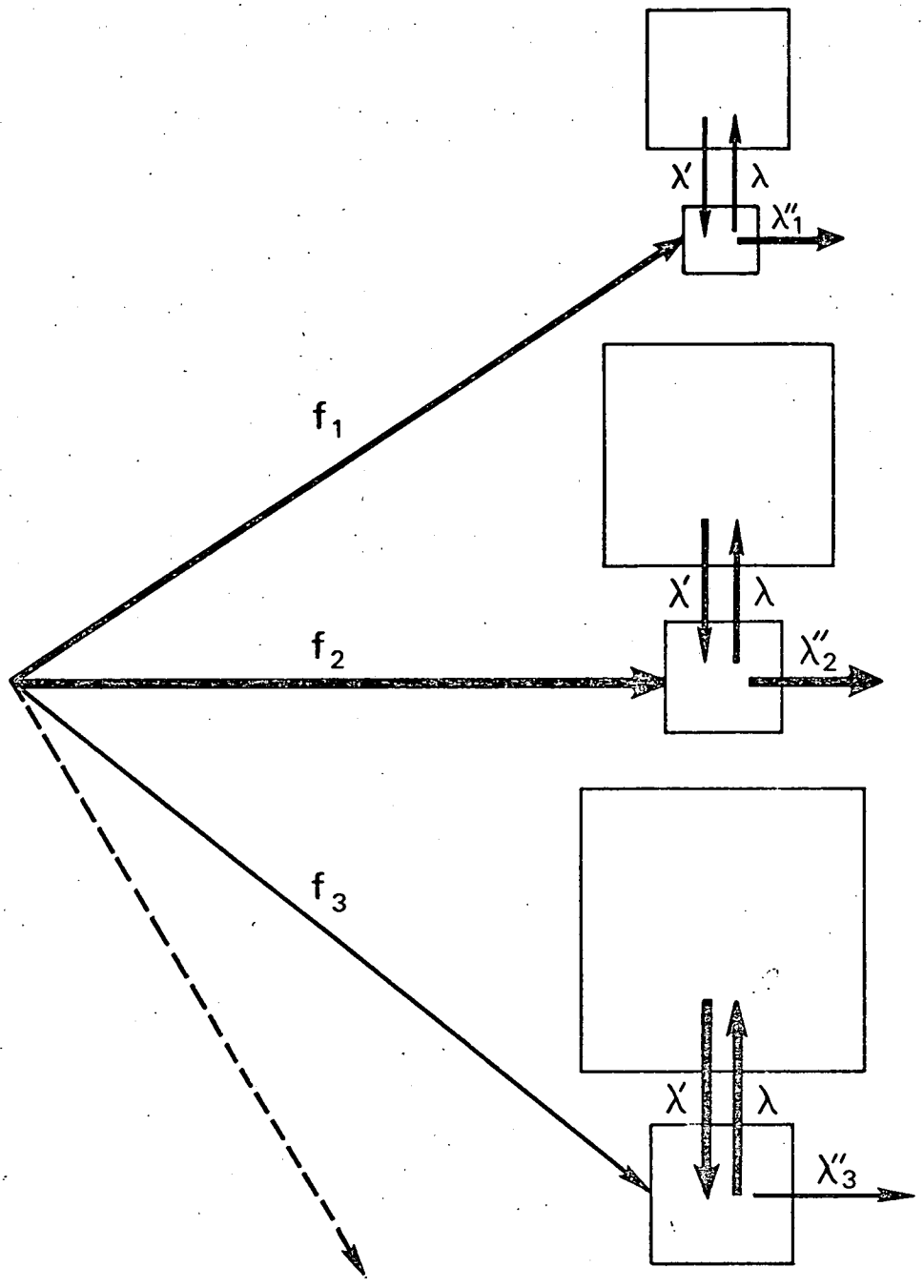
MATHEMATICAL MODELS FOR EXCHANGE OF SUBSTANCES IN REGIONAL VASCULAR BEDS--MEASUREMENT OF THE RATES WITH IN VIVO COUNTERS

Howard G. Parker, M. D., Ph. D.,
Ernest L. Dobson, Ph. D.
Donner Laboratory and Lawrence Radiation Laboratory,
University of California, Berkeley, California

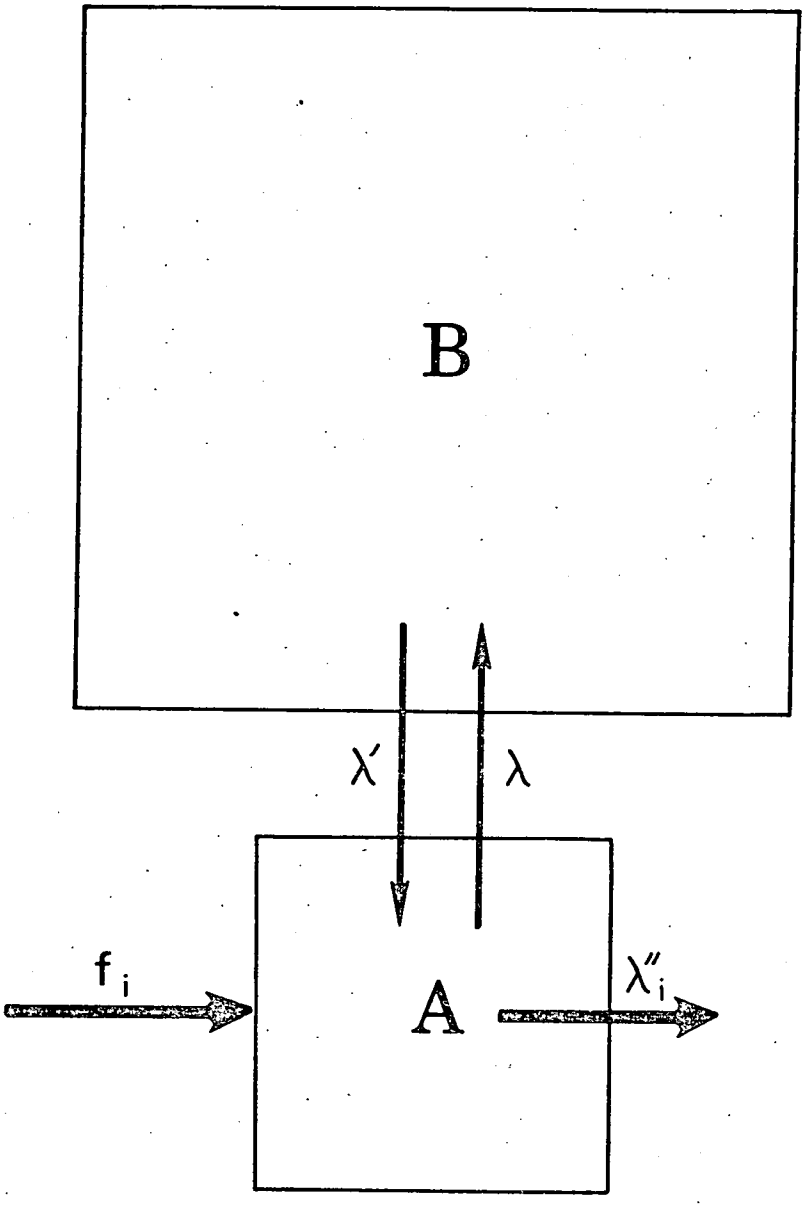
J. Robert Hippensteele, Ph. D.
Department of Anatomy and Physiology,
University of Indiana, Bloomington, Indiana

Abstract. Sangren and Sheppard developed a mathematical model for first-order processes taking place in the regional circulation, applicable--for example--to tracer studies of potassium transport. It permits calculation of specific activity at any point along a "tube of flow" or in the cuff of tissue surrounding it as a function of time following a spike injection of tracer. In efforts to relate to the exchange rate curves obtained with in vivo counters pointed at the region of interest, we developed a compartment-system model of the process. In investigating the properties of the Sangren and Sheppard model integrated over an entire circulatory bed, as the in vivo counter would see it, we found that when the distribution of transit times of the "tubes of flow" can be approximated by an exponential sum, the solution reduces to that of the compartment system model. This results in an important simplification in the calculation, and insight into the assumptions underlying the two different models. A curve-fitting computer program for the compartment model has been written and applied to double-isotope studies of potassium transport in the hind leg of the dog.

Introduction. In a series of double-isotope experiments involving radioactive sodium and potassium injected simultaneously into the femoral artery of dogs, an effort is being made to interpret data from in vivo counters and femoral venous blood in terms of the kinetics of these ions in the hind leg of the dog (Hippensteele et al., 1969). One line of thought in modeling such a process is that developed by Dobson and Warner (1957), who initiated in vivo monitoring of extremities following intra-arterial injection of radioactive tracers. They fitted exponential sums to such curves, after correction for the recirculated radioactivity, and interpreted them in terms of the size and flow rate of a group of parallel uniformly mixed "compartments," each of which is washed out according to an exponential process. There is evidence that this conception is adequate for sodium, which can leak out of the blood vessels into extracellular space, as well as for materials that cannot leave the blood vessel. This appears to be the case because blood flow is a rate-limiting step, so the effect of diffusion rate cannot be seen in such curves. In working with potassium, however, with the cell membrane known to be a significant diffusion barrier, and active transport of potassium taking place, a further elaboration of such models to account for diffusion or transport seems necessary. The problem of modeling potassium transport in and out of the circulation has been considered by many, but not in a form directly applicable to in vivo counting. A natural elaboration of the Dobson and Warner model that appears to have the requisite properties is a multicompartment system such as that shown in Figs. 1 and 2. In this conception, the sodium can enter only the compartments labeled A, whereas the potassium can enter both A and B. The B compartments can be conceived of as the potassium pool within cells. A single pair of compartments will not suffice to explain the multiexponential curves for the sodium as well as potassium in the dog hind leg. Hence the parallel com-



DBL 702 5571

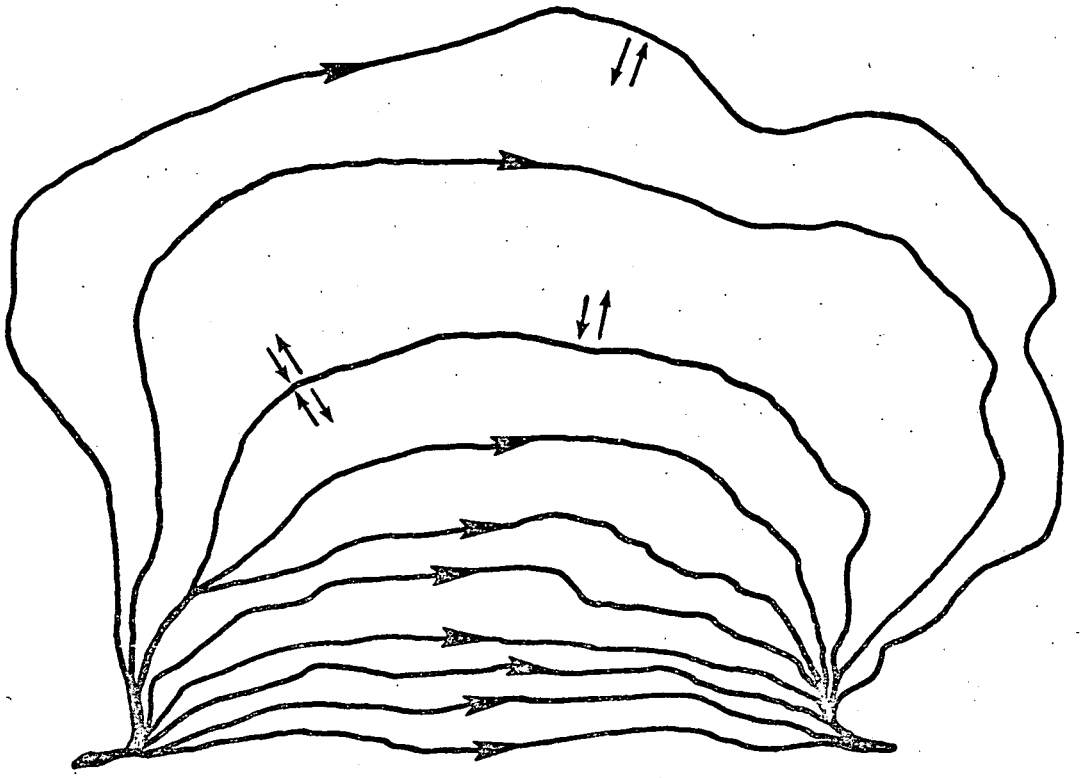


DBL 702 5572

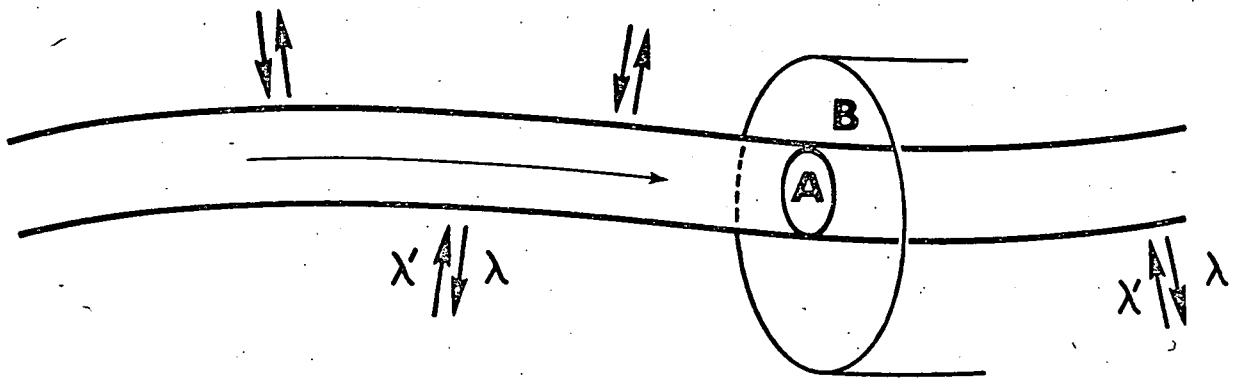
partment pairs, or parallel "flow beds." The differential equations for this model and their solutions are presented.

One alternative approach involves a modification of the treatment by Sangren and Sheppard (1953) and Sheppard (1962) of a capillary bed as parallel "tubes of flow" from which the ions can leak and return along the length of the tube according to first-order kinetics (see Figs. 3 and 4). They derived an expression for the specific activity of a substance as a function of time and distance along a tube following a spike injection. Their expression can be applied to in vivo counting-rate data by modification to represent the fraction of the injected dose present per unit traversal time, rather than specific activity, followed by integration over tube transit time and over the distribution of transit times in parallel tubes. There is a striking resemblance between the partial differential equations and the ordinary differential equations of the "parallel compartment" model proposed here. If we further assume that the transit time distribution function is an exponential sum, the equations and solutions for the total content of tracer in and surrounding the tubes reduce to those resulting from the parallel-compartment model.

It has been widely appreciated (Zierler, 1962) that for a nondiffusible substance, an exponential distribution of transit times through a circulatory bed is equivalent for some purposes to a well-stirred compartment. The present result extends this notion to another type of substance: one that can leak from and return to the paths followed by nondiffusible substances. This permits an important simplification in calculation of such transport rates, and puts the result in a form directly applicable to fitting curves from in vivo counters. It suggests greater validity of the results of the compartment-system calculation than one might at first expect if thinking in terms of discrete well-mixed gross regions within the circulatory bed.



DBL 702 5573


B
A
χ'
λ
χ'
λ

The equations for a reference tracer (such as radioactive sodium ion) that cannot enter the cells, as well as for the tracer that can "leak" (potassium), are developed here because our interpretation of the in vivo curves requires use of the double-isotope experiment and the particular interrelationship of the kinetics of the two tracers. This is explained in the Discussion. The compartment model is presented first, followed by the "tubes of flow" model.

Either of these models might find application to any substance introduced into the regional circulation that undergoes a first-order process of removal, or removal and return. It has been preferred to present them here, however, in the phraseology of the more restricted case of steady-state exchange or transport of substances and the first-order processes undergone by the tracers used in studying the exchange.

In each model, the reference tracer can be handled simply as a degenerate case of the diffusable tracer, with zero rate of diffusion and return. For purposes of exposition, however, it appears desirable to develop the subject for the simpler case of the reference tracer before taking up the complications of the diffusible one.

I. The Compartment-System Model. The steady-state transport of substances such as sodium and potassium can be conceived as indicated in Figs. 1 and 2. Figure 2 is an arbitrarily chosen pair of compartments, or "flow bed," from the complex of beds with varying volumes and perfusion shown in Fig. 1. The reference tracer (Na^+) enters only the compartments labeled A, directly accessible to the circulation. The "diffusible" tracer (K^+) is being transported from A to a compartment B and back. (For K^+, B is many times as large as A.) It is assumed that the rate constant λ'_i, determined by blood circulation to the ith flow

bed, applies equally to reference and diffusible tracer. Note that λ and λ', the fractional turnover rates indicated, are the same for all flow beds (see Discussion), whereas λ''_i is different in each flow bed. The fraction f_i of the arterial blood flow to each bed is arbitrary and not necessarily related to the volume of the bed.

If $Q_{A,i}$ is the amount of K^+ in the ith A compartment and $Q_{B,i}$ the amount in the corresponding B compartment, the steady-state assumption implies

$$\lambda Q_{A,i} = \lambda' Q_{B,i}.$$

This permits determination of relative compartment sizes from the ratio of the rate constants, or vice versa. We are otherwise not concerned here with the nontracer material, or with specific activities. The equations are presented in terms of quantities q of tracer substances, all as a fraction of the injected dose. A "spike" injection is assumed, where a fraction f_i of the injected dose appears in compartment A_i instantaneously at time zero.

A. The reference tracer. The differential equations for this simpler of the two tracer cases take the form

$$\frac{d\, q_{A,i}}{dt} = -\lambda''_i\, q_{A,i}, \qquad (1)$$

with the boundary conditions

$$q_{A,i}(0) = f_i.$$

The total amount of reference tracer in the system is

$$q_{TOT} = \sum_i q_{A,i}.$$

Although this is a case of simple exponential processes in parallel, the solution is presented in Laplace transforms, for comparison with later results. The equations in transform space are

$$s\,\bar{q}_{A,i} - q_{A,i}(0) = -\lambda_i''\,\bar{q}_{A,i},$$

where s is the variable in transform space corresponding to t, and a symbol with a bar over it indicates the Laplace transform of the corresponding unmarked symbol (Carslaw and Jaeger, 1959; Churchill, 1958). Then

$$\begin{aligned} (s + \lambda_i'')\,\bar{q}_{A,i} &= f_i, \\ \bar{q}_{A,i} &= \frac{f_i}{s + q''}, \\ \bar{q}_{TOT} &= \sum_i \frac{f_i}{s + \lambda_i''}. \end{aligned} \tag{2}$$

Using a standard inverse transform, we obtain

$$q_{TOT} = \sum_i f_i\, e^{-\lambda_i t}. \tag{3}$$

B. The diffusible tracer. The pair of simultaneous differential equations for each flow bed in this case is

$$\frac{d\,q_{A,i}}{dt} = \lambda'\,q_{B,i} - (\lambda + \lambda_i'')\,q_{A,i}, \tag{4}$$

$$\frac{d\,q_{B,i}}{dt} = \lambda\,q_{A,i} - \lambda'\,q_{B,i}, \tag{5}$$

with boundary conditions

$$\begin{aligned} q_{A,i}(0) &= f_i, \\ q_{B,i}(0) &= 0. \end{aligned}$$

The equations in transform space are

$$s\,\bar{q}_{A,i} - q_{A,i}(0) = \lambda'\,\bar{q}_{B,i} - (\lambda + \lambda_i'')\,\bar{q}_{A,i},$$

$$s\,\bar{q}_{B,i} - q_{B,i}(0) = \lambda\,\bar{q}_{A,i} - \lambda'\,\bar{q}_{B,i}.$$

Substituting the above boundary conditions and solving for $\bar{q}_{A,i}$ and $\bar{q}_{B,i}$, we let

$$d_i = s^2 + (\lambda + \lambda' + \lambda_i'')\, s + \lambda'\lambda_i'';$$

then

$$\bar{q}_{A,i} = \frac{f_i(s+\lambda')}{d_i}, \quad \bar{q}_{B,i} = \frac{f_i \lambda}{d_i}, \quad \bar{q}_{A,i} + q_{B,i} = \frac{f_i(s+\lambda+\lambda')}{d_i}$$

and

$$\bar{q}_{TOT} = \sum_i \frac{f_i (s+\lambda+\lambda')}{d_i}. \tag{6}$$

Factoring d_i by means of the quadratic theorem and using standard inverse transforms, we obtain the following, where b_i and c_i are convenient intermediate variables and $r_{1,i}$ and $r_{2,i}$ are the roots of the auxiliary equation $d_i = 0$:

If we let $\quad b_i = \lambda + \lambda' + \lambda_i'' \quad$ and $\quad c_i = \lambda' \lambda_i''$,

the roots are

$$r_{1,i} = \frac{1}{2}\left\{-b_i + \sqrt{b_i^2 - 4c_i}\right\}, \quad r_{2,i} = \frac{1}{2}\left\{-b_i - \sqrt{b_i^2 - 4c_i}\right\},$$

and

$$q_{TOT} = \sum_i \left[\frac{f_i}{r_{1,i} - r_{2,i}} \left\{(\lambda+\lambda'+r_{1,i})\, e^{r_{1,i}t} - (\lambda+\lambda'+r_{2,i})\, e^{r_{2,i}t}\right\}\right]. \tag{7}$$

For purposes of comparison of this result with a later one from the second model, note that if a variable $c(s)$ is defined as

$$c(s) = s + \lambda - \frac{\lambda\lambda'}{s+\lambda'},$$

then equation (6) can be changed by algebraic manipulation into the form

$$\bar{q}_{TOT} = \left(1 + \frac{\lambda}{s + \lambda'}\right) \sum_i \frac{f_i}{c + \lambda_i''} \cdot \qquad (8)$$

Inverse transformation of this expression could be done by means of standard transforms, resulting in a very complicated expression in exponentials, Bessel functions, and their integrals, resembling the general result from the "tubes of flow" model. The previous result in closed form, equation (7), is greatly preferable for most purposes.

II. The Model Based on "Tubes of Flow". In this model the exchange process takes place in a regional circulatory bed consisting of "tubes of flow" or trajectories along which the reference tracer (Na^+) can pass, and from which the "diffusible" tracer (K^+) can leak (or be transported) and return. For Na^+ the trajectories are limited to blood and interstitial fluid. Figure 3 indicates a general conception of the multiple trajectories available, and shows that in the case of greatest interest to us, there are many short trajectories and few long ones, such that the distribution of transit times might be fitted by an exponential sum. (The identical distribution could be visualized for path length only if linear velocity were constant throughout the bed). Figure 4 shows a detailed view of one of the tubes. It indicates that "A" refers to tracer within the tube and "B" to tracer in the cuff of fluid surrounding the tube. Nothing akin to laminar flow takes place in this model, but merely bulk transfer down the tube, with a risk λ of leaking out of the tube per unit time, together with a probability λ' of returning from the surrounding cuff per unit time. An important restriction of this model, in order to obtain any answer with known methods, is that in the cuff around the tube, no diffusion of tracer is allowed in the direction along the axis of the tube. Since most of the space in this cuff consists of many indi-

vidual cells fairly close to one or another capillary, this assumption seems not unreasonable.

Sangren and Sheppard (1953) have treated a single tube from this model in some detail, deriving an expression for specific activity at any length x along the tube with flow having velocity v, as a function of time. They also point out the close relationship of such equations to those for heat transfer in heat exchangers, as presented by Carslaw and Jaeger (1959). For detailed presentation of this model and justification of the assumptions, the papers by Sangren and Sheppard (1953), Sheppard (1962), and Carslaw and Jaeger (1959) should be consulted.

Although the initial part of our derivation is closely patterned on those of Sangren and Sheppard (1953) and Carslaw and Jaeger (1959), it differs in the following respects:

1. A notation more in keeping with one for compartment systems is used, to aid in presenting the parallels between them.

2. We present virtually the same equations, with small but important differences in order to account for the amounts of tracer as the fraction of injected dose per unit tube length, the latter given in units of tube-traversal time. We assume the same relationship between relative size of tube A and B as was assumed in the discussion of Model I for relative compartment size: $\lambda Q_A = \lambda' Q_B$, where Q is the amount of nontracer diffusible substance per unit tube traversal time.

3. Since tube length x and velocity v are never measured and need never be explicitly considered in application of the model, we preferred to omit them. This simplifies the appearance of the equations, and emphasizes the fact that one need not know distances, areas, or velocities. Instead, the model is derived by using tube traversal times and transit time distributions. A variable τ indicates the time to reach any point along a tube, and is related to distance and assumed uniform velocity within that tube

by the equation $\tau = \frac{x}{v}$. The closely related variable T is used for the transit time of any particular tube, the time for complete traversal of its length:

$$T = \frac{\text{tube length}}{v}.$$

A. The reference tracer. With t=time and τ and T defined as above, let $a(t,\tau) \equiv \partial q_A / \partial \tau$, where q_A is the fraction of injected tracer in the tube; a is then the fraction of injected dose traveling at velocity v present per unit tube-traversal time. The partial differential equation governing travel of the reference tracer (Na^+) is

$$\frac{\partial a}{\partial t} = - \frac{\partial a}{\partial \tau} . \tag{9}$$

The boundary condition of interest in the case of spike injection at zero time is

$$\begin{aligned} a(0,\tau) &= 0 \text{ if } \tau > 0 \\ &= 1 \text{ if } \tau = 0. \end{aligned}$$

In transform space,

$$s\bar{a} - a(0,\tau) = - \frac{\partial \bar{a}}{\partial \tau}.$$

Rearranging, we have

$$\frac{\partial \bar{a}}{\partial \tau} + s\bar{a} = a(0,\tau) = \delta(\tau).$$

Integration of this ordinary first-order equation with respect to τ yields

$$\bar{a} = e^{-s\tau}. \tag{10}$$

This is a particular solution that is of interest to us for spike injection at the beginning of the tubes at time zero. (For more detailed consideration of the boundary conditions giving rise to this solution see Sheppard, 1962.) Its inverse transform is

$$\frac{\partial q_A}{\partial \tau} = a = \delta(t - \tau), \tag{11}$$

which represents merely a spike of reference tracer, unattenuated, coursing down a tube. The amount in a whole tube whose transit time is given by the variable T is

$$q_A(t, T) = \int_0^T a\, d\tau \quad = 1 \text{ when } T \geq t \qquad = 0 \text{ when } T < t, \tag{12}$$

indicating that a tube contains either all or none of its reference tracer, depending on the position of the wave relative to the length of the tube. The amount in the whole circulatory bed, assuming a distribution of transit time for the tubes F(T), is given by

$$q_{TOT} = \int_0^\infty F(T)\, q_A\, dt.$$

Substituting the results for q_A, we get

$$q_{TOT} = \int_t^\infty F(T)\, dt. \tag{13}$$

In the case of special interest to us when $F(T) = \sum_i \lambda_i'' e^{-\lambda_i'' T}$, a multi-exponential sum for the frequency function of tube transit times for the reference tracer, substitution and integration yield

$$q_{TOT} = \sum_i f_i e^{-\lambda_i'' t}, \tag{14}$$

or, in transform notation,

$$\bar{q}_{TOT} = \sum_i \frac{f_i}{s+\lambda_1''}. \tag{15}$$

These solutions are identical with those obtained from the differential equations of the compartment system model, equations (2) and (3). The correspondence is obvious for the reference tracer, but the result is needed in general form for the double-isotope

comparisons to be made later.

B. The diffusible tracer. Closely following the foregoing exposition, let

$$a(t,\tau) \equiv \frac{\partial q_A}{\partial \tau}$$

and

$$b(t,\tau) \equiv \frac{\partial q_B}{\partial \tau},$$

where A and a refer to diffusible tracer in the tube and B and b refer to diffusible tracer in the cuff around the tube. The partial differential equations for our case are

$$\frac{\partial a}{\partial t} = \lambda' b - \lambda a - \frac{\partial a}{\partial \tau}, \tag{16}$$

$$\frac{\partial b}{\partial t} = \lambda a - \lambda' b; \tag{17}$$

a and b are functions of t and τ.

Boundary conditions are

$$a(0,\tau) = 0 \quad \text{if } \tau > 0$$
$$= 1 \quad \text{if } \tau = 0,$$
$$b(0,\tau) = 0 \quad \text{for all } \tau.$$

Closely following Sangren and Sheppard's solution,

$$s\bar{a} - a(0,\tau) = \lambda'\bar{b} - \lambda\bar{a} - \frac{\partial \bar{a}}{\partial \tau},$$

$$s\bar{b} - b(0,\tau) = \lambda\bar{a} - \lambda'\bar{b}.$$

Eliminating $\bar{b}$, we obtain

$$\frac{\partial \bar{a}}{\partial \tau} + c\bar{a} = a(0,\tau),$$

where

$$c = s + \lambda + \frac{\lambda\lambda'}{s+\lambda'}.$$

A particular solution of this ordinary first-order differential equation that pertains to our problem is

$$\bar{a} = e^{-c\tau}. \tag{18}$$

Consult Sheppard for justification of the use of this particular solution following spike injection. Using standard transforms in the manner indicated by Sangren and Sheppard, and defining two convenient variables $p = \lambda\tau$ and $q = \lambda'(t-\tau)$, we have

$$\frac{\partial q_A}{\partial \tau} = a(t,\tau) = \lambda' e^{-p} \{ \delta(q) + e^{-q} I_1 (2\sqrt{pq}) \sqrt{p/q} \}, \tag{19}$$

where I_1 is a standard Bessel function of imaginary argument.

Following Carslaw and Jaeger (1959), who explicitly considered the case of the B region, but for different boundary conditions, we have

$$\frac{\partial q_B}{\partial \tau} = b(t,\tau) = \lambda e^{-(p+q)} I_0 (2\sqrt{pq}). \tag{20}$$

Then

$$q_{A+B}(t,T) = \int_0^T \frac{\partial q_{A+B}}{\partial \tau} \, d\tau = \int_0^T (a+b)\, d\tau. \tag{21}$$

For computational purposes, a and b as derived above in terms of exponentials and Bessel functions (as series) can be substituted in this expression and integrated by approximate means. If we assume a frequency function of tube transit times F(T), as was done for the reference substance, then

$$q_{TOT}(t) = \int_0^\infty F(T)\, q_{A+B}\, dt = \int_0^\infty F(T) \int_0^T (a+b) d\tau dT. \tag{22}$$

This equation can be programmed for an approximate solution with arbitrary F(T). When that is done, a particularly important simplification is possible for the double-isotope case. For all tubes of length T greater than t, q_{A+B} must be equal to 1. This is accomplished by integrating equation (22) from 0 to t instead of 0 to ∞, and letting the integral from t to ∞ be given by the sodium-

retention curve defined by equation (13). Since $\int_0^T (a+b)d\tau$, that is q_{A+B}, must be 1 for all tubes where $T > t$, $\int_t^\infty F(T) \int_0^T (a+b)d\tau dT$ must equal $\int_t^\infty F(T)dT$. The $F(T)$ in question is a distribution that we assume is shared by reference and diffusible tracers. Hence for K^+,

$$q_{TOT,K} = \int_0^t F(T) \int_0^T (a+b)\, d\tau dT + q_{TOT,Na}. \qquad (23)$$

That equation (22) reduces to equation (7) of the compartment-system model when $F(T) = \sum_i \lambda_i'' f_i e^{-\lambda_i' T}$, the multiexponential frequency function, can be shown with the Laplace transforms of the above solutions:

$$\bar{q}_{TOT} = \int_0^\infty F(T) \int_0^T (\bar{a}+\bar{b})\, d\tau dT. \qquad (24)$$

But $q = e^{-c\tau}$, and it can readily be shown from equation (17) that

$$\bar{b} = \frac{\lambda}{s+\lambda'} \bar{a} = \frac{\lambda e^{-c\tau}}{s+\lambda'}.$$

Substituting the values of $\bar{a}$, $\bar{b}$, and $F(T)$ into equation (24) and evaluating the integrals (now all in terms of simple exponentials), we arrive immediately at the result

$$\bar{q}_{TOT} = \left(1 + \frac{\lambda}{s+\lambda'}\right) \sum_i \frac{f_i}{c + \lambda_i''},$$

which is identical with that for the total quantity in the compartment model, equation (8). The result can readily be shown for the integral of A or B separately, as well as for the total. Therefore, in the "tubes of flow" model (Figs. 3 and 4), when tube length is multiexponential in distribution, total quantities of tracer occupying the sum of all A or of all B portions of the region are described by the ordinary differential equations (1), (4), and (5).

A simplification in computation based on equation (22) could also result if F(T) were a frequency function approximated by sums and differences of exponentials, rather than sums alone, but the ordinary differential equations (1), (4), and (5) and the model visualized in Figs. 1 and 2 would then not retain any physical significance; negative quantities of tracer in some of the compartments would be involved. A group of two-compartment flow beds partly or entirely linked in series rather than parallel can be shown to produce a system of differential equations with appropriate properties, but finding the particular model is irrevelant to the estimate of λ and λ'.

Discussion. Curve fitting with the above equations depends on some further assumptions. Since an in vivo counter records something merely proportional to the amount of radioactive tracer in a region, the fitting can be done by noting that for equations in which we let q refer, for example, to counting rates rather than quantities, we have $\sum_i f_i \neq 1$. The additional degree of freedom thus introduced suffices to make the transition. It must be assumed that the counting efficiency of either of the tracers is unchanged by its being in one or another of the different flow beds, or in the A or B parts of the region, an assumption often easy to make because of the anatomic nature of the region, such as the dog hind leg. The methods of standardization and correction for recirculation in experiments of this type have been presented by Dobson and Warner (1960) and by Hippensteele (1967). In the double-isotope experiment we have not assumed that an adequate standardization can be done to relate counting rate to quantity. Instead it is assumed that the standardization is adequate to correct for the relative counting efficiency of the two tracers. A further reasonable assumption is that the regions occupied by the two tracers are so intermixed anatomically that from the point of view of the counter they occupy essentially the same volume, whatever that may be. Hence, when the reference

tracer curve is multiexponential with n component exponentials, the 2n parameters f_i and λ_i'' are shared by the equations for the two tracers, and the diffusible tracer curve has 2n components, but only two additional degrees of freedom λ and λ'.

A program has been written for the CDC 6600 computer, fitting equation (7) to potassium data. It uses the minimization program "VARMIT" (written by Eric Beals, Lawrence Radiation Laboratory, University of California, Berkeley) to determine a weighted least-squares fit to λ and λ', given the f_i and λ_i'' from a previous weighted sum of exponentials fitted to the sodium data. To do this one supplies the sum of least squares, readily determined from equation (7), together with its partial derivatives with respect to λ and λ'. The calculation of the partial derivatives was programmed in simple piecewise fashion patterned step by step on the programming of equation (7) rather than written as a single expression prior to programming, as this was most economical of effort and easiest to check. Given this information at each step in its search, VARMIT takes a pair of initial estimates for λ and λ' and finds optimum values for them simultaneously.

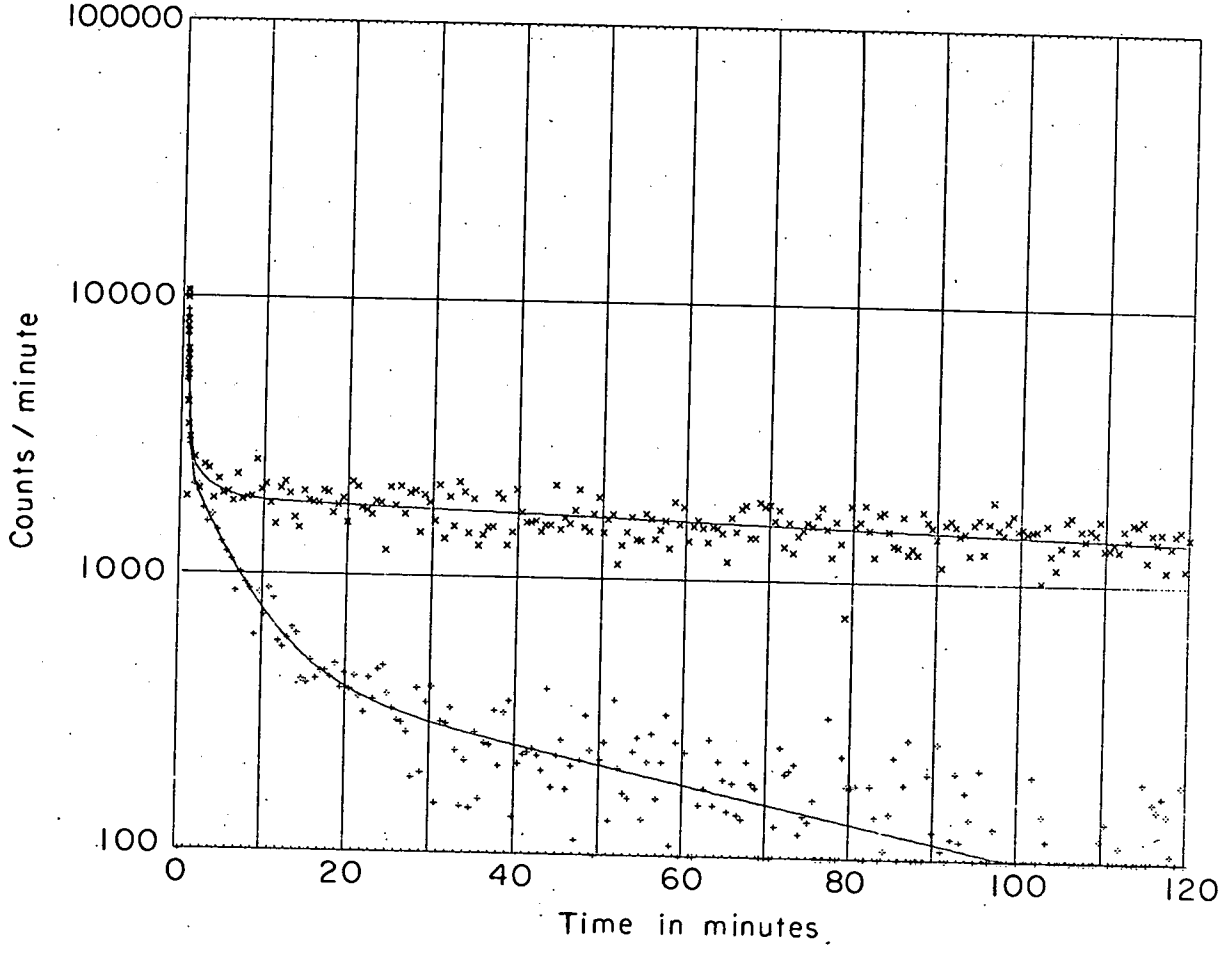
Simple programming in a few lines of a conversational language "FOCAL" on the PDP-8 computer has provided curves for equations (3) and (7) that have helped verify the calculation. The results obtained for the compartment-model fit have been checked against the FOCAL result and against a program "MIMIC" on the large computer. The latter program provides a language to solve ordinary differential equations directly, but only for given parameters, lacking the "fitting" feature. The FOCAL programming conveniently provides outflow rate for the two tracers as well as quantities present. With this conversational language it is easy to calculate a number of additional results such as ratios of the two isotopes as a function of time.

When equation (23) from the more complicated "tubes of flow"

model is programmed in FOCAL language, with F(T) a multiexponential, it checks against equation (7). It takes a very much longer time to calculate each point, however, and with less accuracy. It does an approximate double integration, and for each step it must calculate Bessel functions and exponential sums for the input.

The models with multiexponential F(T) have been fitted to data for sodium and potassium ions (Fig. 5). The general nature of the fit is satisfactory, giving rise to a potassium leak rate λ of about the same order of magnitude as the average perfusion rate for sodium, and to a cellular potassium space very much larger than the extracellular potassium space, as one would expect. We have not completely worked out all technical problems in standardization, but the general result obtained here would appear to have intrinsic interest and potential applicability to a number of similar problems.

The two models that are presented here share certain assumptions, and not others, as a close review of the differential equations and boundary conditions shows. The fact that the "tubes of flow" model reduces to the compartment model in the circumstances outlined helps complete a clearer picture of what assumptions are made when these models are used, and what alternatives might be considered among their variants. One can consider the use of exponential sums merely an empirical device to approximate transit-time distributions and make the solution more tractable. Existence of discrete anatomic regions with uniform mixing in the ordinary sense is not an assumption essential to employment of the equations of the compartment-system model. The mere existence of trajectories of various lengths through a circulatory bed gives rise to a type of mixing indistinguishable from it for our purposes. In either model, there also remains the assumption that a tracer ion is at a fixed risk of undergoing a first-order process removing


100000
10000
1000
100
Counts / minute
0
20
40
60
80
100
120
Time in minutes
DBL 703-5644

it from the flow while it is in the region, and with a fixed probability of returning to that flow.

In the compartment model, restrictions were placed on λ and λ' more or less arbitrarily at first, in order to keep the number of parameters to a minimum. A number of alternative ways to assign λ and λ' for each flow bed, relate them to perfusion, or give them a distribution of values readily suggest themselves. With the tubes of flow, on the other hand, it is necessary to consider λ and λ' constant along any tube in order to derive the above result. An arbitrary relationship of λ and λ' to tube transit time would not be particularly hard to incorporate. In the simpler case in which λ' is zero (first-order removal without return), Sheppard (1962) has shown that the method gives a mean value for λ even though it may vary along the length of the tube. (Use of this latter model, incidentally, may offer a way to make a simplified fit to only the initial portions of curves, in order to estimate λ alone. We have restricted the presentation here to the more general case. The simplified one should be most applicable when λ' is known to be much smaller than λ, as for potassium transport.) Though the constancy of λ and λ' assumed in these models was arbitrary, and for purposes of simplification, as one thinks about alternatives it soon appears that this simple approach is hard to improve on without further arbitrary assumptions that cannot now be checked. Also, potassium transport may be a function of cell surface or volume, and the ratio of cellular to extracellular potassium can probably best be assumed at present to be constant over the various flow beds. Hence it appears that the particular models presented here, with their restrictions on λ and λ', may presently be the most reasonable approach to finding average values for them.

One further result from the above models: When the reference tracer curve is multiexponential, the probability that a diffusible tracer ion enters a B compartment (enters a cell) one or

more times on single passage through the region of interest is given by

$$P = \sum_i \frac{\lambda f_i}{\lambda + \lambda_i''} .$$

From data of the type shown in Fig. 5 the parameter P can be measured. It is the fraction of the diffusible substance entering the cells on passage through the tissue. When the intracellular pool is very large, P corresponds to the approximate notion of the "fraction of the injected tracer trapped in the tissue," which has been of particular interest in the use of radioactive potassium in circulatory studies. In the dog leg it appears that only about one-fourth of the K^+ is so trapped.

Acknowledgment. The authors gratefully acknowledge the expert technical assistance of Mrs. Jean Lynch and Miss Laurie Craise. Also much appreciated are the assistance and consultation of the Mathematics and Computing Group of Lawrence Radiation Laboratory, Berkeley, particularly by Mr. Mark Horovitz, Mr. William Hogan, and Mr. Kenneth Wiley.

This work was done under the auspices of the U. S. Atomic Energy Commission.

BIBLIOGRAPHY

Carslaw, H. S., and J. C. Jaeger. 1959. Conduction of Heat in Solids, 2nd Ed. Oxford, Clarendon. 391-394.

Churchill, R. V. 1958. Operational Mathematics, 2nd Ed. New York, McGraw-Hill, N. Y.

Dobson, E. L., and G. F. Warner. 1957. "Measurement of Regional Sodium Turnover Rates and Their Application to the Estimation of Regional Blood Flow." Am. J. Physiol. 189-276.

Dobson, E. L., and G. F. Warner. 1960. "Clearance Rates Following Intra-Arterial Injections in the Study of Peripheral Vascular Beds." In Methods in Medical Research, Vol. 8, ed. H. D. Bruner, Chicago Year Book Publishers.

Hippensteele, J. R. 1967. "Tracer Kinetic Studies of the Dynamics of the Microcirculation in Peripheral Vascular Beds" (Ph. D. thesis). Lawrence Radiation Laboratory Report UCRL-17774, Aug. 1967, University of California, Berkeley, California.

Hippensteele, J. R., H. G. Parker, E. L. Dobson, and J. J. Lynch. 1969. "Potassium Exchange from the Sodium Space in the Dog's Leg." Fed. Proc. 28, 824-(abstract).

Sangren, W. C., and C. W. Sheppard. 1953. "A Mathematical Derivation of the Exchange of a Labelled Substance between a Liquid Flowing in a Vessel and an External Compartment." Bull. Math. Biophys. 15, 387-394.

Sheppard, C. W., 1962. Basic Principles of the Tracer Method." New York, Wiley.

Zierler, K. L., 1962. "Circulation Times and the Theory of Indicator-Dilution Methods for Determining Blood Flow and Volume." Handbook of Physiology, Sec. 2; Circulation, Vol. 1 Chapt. 18, p. 585, American Physiological Society.

FIGURE CAPTIONS

Figure 1. Compartment-system model of a region of the circulation consisting of parallel sets of two-compartment flow beds.

Figure 2. Enlargement of the ith flow bed from Fig. 1, indicating the relationship of the parameters and compartment labels as they appear in the equations. The reference tracer can enter only A, whereas the diffusible tracer enters both A and B.

Figure 3. The regional circulatory bed visualized as compounded of a number of "tubes of flow" of varying length, from each of which "leakage" and return of diffusible tracer are possible along its length.

Figure 4. Enlargement of a portion of one of the "tubes of flow" in Fig. 3, indicating the "A" region within the tube, occupied by both tracers, and the "B" region or cuff of fluid around the tube, into which only diffusible tracer can leak and return.

Figure 5. Equations (3) and (7) fitted by weighted least squares to *in vivo* counter data from the dog hind leg, with radioactive Na^+ and K^+ injected simultaneously in the femoral artery. The counting rate has been corrected for counter cross-talk, radioactive decay, and recirculation, and normalized for injected dose.