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Stochastic Modelling of Physiologic Processes with Radiotracers and Positron Emission Tomography*

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1. Introduction

Most experimental workers first define a qualitative model, then use experimental data to compute the parameters of that model. For instance the model appropriate to dilution phenomena is a set of ordinary differential equations with constant coefficients, while for diffusion phenomena partial differential equations are to be used, for delay phenomena finite difference equations, etc. Of course, the gnosiological value of the parameters computed in this way depends on the chosen model. An ideal situation would be to define parameters that are independent, or almost independent, of the chosen model.

The compartment model, so often used in nuclear medicine and in pharmacokinetics, is formed by a set of linear differential equations of order one with constant coefficients; its validity depends upon the hypothesis that the system described contains a finite number of

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components, and that each component is homogeneous. These hypotheses exclude the presence of diffusion and of age-dependent processes, or in general of transport of a non-Markovian nature. The fact that frequently the experimental data agree with this model does not necessarily prove the model is appropriate, but only that it is flexible.[1]

In fact any number of classes of functions and an infinity of functions within each class will fit any contiguous single-valued correspondence with time to an arbitrary closeness. Among the most well known demonstrations are those for polynomials[2] and for trigonometric functions.[3] In the specific case of n compartments, the model is a set of n first order linear differential equations in n state variables; they contain n^2 parameters. With n large enough, this model can be made consistent with many experimental data, but at the price of a considerable complexity of the model itself. Frequently, many coefficients of the differential equations are set equal to zero, thus simplifying the differential equations of the model and the fitting of the data. The price paid for this simplification is a reduced flexibility of the model. In addition to the consistency with the experimental data, an obvious conceptual requirement of the model is that its parameters could be interpreted in terms of perceivable physical properties.

All this considered, we shall try to show how the experimental data can be examined in terms of a model making a minimum number of assumptions and giving the best physical interpretations to the parameters involved.

2. Stochastic transport

Consider the transport of a particle through a living system as a stochastic process, i.e. as a random phenomenon that arises through a process controlled by probabilistic rather than deterministic laws. The only requirement we need is that the particle itself behaves in a way independent on its past history, but depending only on its actual location and chemical association.

Many papers have been published recently on stochastic compartments,[4] where the number of particles present in a compartment is a time-dependent random variable; those models require the same general assumptions made with the ordinary compartments, and

in most cases lead to distributions with very small relative variances.[5)]

As an alternative model, consider as random variable the time a given particle reaches a certain state in the system, or the interval of time it takes to move from one state to another; the distribution of this random variable can be analyzed and compared with the experimental data available.

With the hypotheses made, call $A(t)$ the probability density function of the time a given particle is present in a certain state, $B(t)$ the probability density function of the interval of time for the transition from that state to another specified state, and finally $C(t)$ the probability density function of the time the same particle is present in this last state. More precisely,

$A(t)dt$ = probability that a given particle is in the first state at a time between t and $t + dt$,

$B(t)dt$ = probability that a given particle takes a length of time from t to $t + dt$ to move from the first to the second state,

$C(t)dt$ = probability that a given particle is in the second state at a time between t and $t + dt$.

Then, ignoring infinitesimals of order higher than one,

$$A(\tau)d\tau \cdot B(t-\tau)dt$$

is the probability that a given particle left in first state during the interval $\tau, \tau+d\tau$ will be in the second state during the interval $t, t+dt$. Taking the integral of the expression above for all values of τ from 0 to t, one gets the probability that that particle is in the second state at a time between t and $t+dt$ if it was in the first state at any time from 0 to t, i.e.,

$$\int_0^t A(\tau)B(t-\tau)d\tau = C(t). \tag{1}$$

This is the well known convolution integral representing a linear, invariant system, without invoking the properties of homogeneous, well-mixed compartments.

3. Definition of the moments

Many properties of the convolution integral in (1) can be analyzed by first defining the moments of the functions in it.

Given a generic function F(t) defined for all values of t from 0 to $+\infty$, call the moments,

$$F_i = \int_0^\infty \frac{t^i}{i!} F(t)dt \quad (i=0,1,2,\ldots), \tag{2}$$

the relative moments,

$$f_i = \int_0^\infty \frac{t^i}{i!} F(t)dt/F_o, \ (i=1,2,3,\ldots) \tag{3}$$

and the central moments,

$$\phi_i = \int_0^\infty \frac{(t-f_1)^i}{i!} F(t)dt/F_o, \ (i=2,3,4,\ldots) \tag{4}$$

provided that the integrals above converge.

A few comments are necessary. First, the definition of moment in (2) differs from the usual definition by a factor i ; we have introduced this factor because it considerably simplifies many expressions we shall find later on. We shall not discuss the general conditions necessary for the convergence of the integrals in (2), (3), (4), but section 8 shows what can be done when one of those integrals does not converge. Finally, definition (4) applies only to values of i larger than one; for convenience we complete that definition with

$$\phi_1 = f_1, \tag{5}$$

so that in the following pages we shall use central moments for any positive integer i.

To express a central moment in terms of the relative moments, expand the binomial in (4),

$$\phi_i = \sum_{j=0}^{i} \int_0^\infty (-1)^j \frac{t^{i-j} f_1{}^j}{(i-j)!j!} F(t)dt/F_o$$

$$\phi_i = \sum_{j=0}^{i-2} (-1)^j \frac{f_1{}^j}{j!} f_{i-j} + (-1)^{i-1} \frac{f_1{}^{i-1}}{(i-1)!} f_1 + (-1)^i \frac{f_1{}^i}{i!}$$

$$\phi_i = \sum_{j=0}^{i-2} (-1)^j \frac{f_1{}^j f_{i-j}}{j!} + (-1)^{i-1} \frac{i-1}{i!} f_1{}^i. \tag{6}$$

In particular we can write

$$\phi_1 = f_1$$

$$\phi_2 = f_2 - \frac{f_1{}^2}{2}$$

$$\phi_3 = f_3 - f_1 f_2 + \frac{2}{3!} f_1{}^3$$

$$\phi_4 = f_4 - f_1 f_3 + \frac{1}{2!} f_1{}^2 f_2 - \frac{3}{4!} f_1{}^4$$

and so on.

4. Properties of the convolution

Multiply both sides of equation (1) by $t^i/i!$ and integrate from 0 to ∞,

$$\int_0^\infty \frac{t^i}{i!} \int_0^t A(\tau)B(t-\tau)d\tau \cdot dt = \int_0^\infty \frac{t^i}{i!} C(t)dt,$$

where $\underline{i}$ is any non-negative integer; change the order of integration,

$$\int_0^\infty A(\tau) \int_\tau^\infty \frac{t^i}{i!} B(t-\tau)dt \cdot d\tau = C_i;$$

change the variable of the inner integral,

$$\int_0^\infty A(\tau) \int_0^\infty \frac{(t+\tau)^i}{i!} B(t)dt \cdot d\tau = C_i,$$

$$\int_0^\infty A(\tau) \int_0^\infty \sum_{j=0}^{i} \frac{t^j \tau^{i-j}}{j!(i-j)!} B(t)dt \cdot d\tau = C_i,$$

$$\sum_{j=0}^{i} \int_0^\infty \frac{\tau^{i-j}}{(i-j)!} A(\tau) \int_0^\infty \frac{t^j}{j!} B(t)dt \cdot d\tau = C_i,$$

$$\sum_{j=0}^{i} A_{i-j} \cdot B_j = C_i; \quad (i=0,1,2,\ldots) \tag{7}$$

in particular,

$$A_0B_0 = C_0$$

$$A_1B_0 + A_0B_1 = C_1$$

$$A_2B_0 + A_1B_1 + A_0B_2 = C_2$$

$$A_3B_0 + A_2B_1 + A_1B_2 + A_0B_3 = C_3$$

and so on.

Dividing both sides of equation (7) by $A_0 \cdot B_0$ we get

$$\sum_{j=0}^{i} a_{i-j} \cdot b_j = c_i, \quad (i=1,2,3,\ldots). \tag{8}$$

From equation (1) again we get

$$\int_0^\infty \frac{(t-\gamma_1)^i}{i!} \int_0^t A(\tau)B(t-\tau)d\tau \cdot dt = \int_0^\infty \frac{(t-\gamma_1)^i}{i!} C(t)dt,$$

where $\underline{i}$ is any integer larger than one; proceeding as before,

$$\int_0^\infty A(\tau) \int_\tau^\infty \frac{(t-\alpha_1-\beta_1)^i}{i!} B(t-\tau)dt \cdot d\tau = \gamma_i C_0,$$

$$\int_0^\infty A(\tau) \int_0^\infty \frac{[(t-\beta_1)+(\tau-\alpha_1)]^i}{i!} B(t)dt \cdot d\tau = \gamma_i C_0,$$

$$\int_0^\infty A(\tau) \int_0^\infty \sum_{j=0}^{i} \frac{(t-\beta_1)^j(\tau-\alpha_1)^{i-j}}{j!\,(i-j)!} B(t)dt \cdot d\tau = \gamma_i C_0,$$

$$\sum_{j=0}^{i} \int_0^\infty \frac{(\tau-\alpha_1)^{i-j}}{(i-j)!} A(\tau)d\tau \cdot \int_0^\infty \frac{(t-\beta_1)^j}{j!} B(t)dt = \gamma_i C_0;$$

observing that

$$\int_0^\infty (\tau-\alpha_1)A(\tau)d\tau = \int_0^\infty (t-\beta_1)B(t)dt = 0$$

we get finally

$$\alpha_i + \sum_{j=2}^{i-2} \alpha_{i-j}\beta_j + \beta_i = \gamma_i, \tag{9}$$

and in particular from definition (5),

$$\alpha_1 + \beta_1 = \gamma_1$$

and from equation (9),

$$\alpha_2 + \beta_2 = \gamma_2$$

$$\alpha_3 + \beta_3 = \gamma_3$$

$$\alpha_4 + \alpha_2\beta_2 + \beta_4 = \gamma_4$$

$$\alpha_5 + \alpha_3\beta_2 + \alpha_2\beta_3 + \beta_5 = \gamma_5$$

and so on.

In general the number of particles in a given state is very large, and if it can be observed as a function of time it is a very good approximation of the probability density function defined in Section 2. This means that the functions A(t) and C(t) corresponding to two given states can be measured, their moments computed, and finally the moments of the unknown function B(t) obtained using

equations (7), (8), or (9).

These last moments can be given a clear physical meaning; for instance B_0 is the fraction of particles leaving the first state that actually reach the second state, b_1 is the expected interval of time for a particle to move from the first to the second state, β_2 is twice the variance of the above time, etc.

5. A simple compartment

It may be interesting to compare the actual values of the moments of a specific system. Take for instance a single compartment, i.e. a well mixed pool of homogeneous particles, all with the same probability μdt of leaving in the interval from t to t+dt, where μ is a constant; in other words the probability of leaving the compartment does not depend on the absolute time or on the time when a particle entered it. If A(t) is the probability density function characteristic of the compartment, i.e., the probability that a particle is in the compartment at time t, then

$$A(t+dt) = A(t)\cdot(1-\mu dt)$$

is the probability that the given particle present in the compartment at time t is still there at time t+dt; rearranging this equation,

$$dA/dt = -\mu A(t),$$

and integrating,

$$A(t) = A(0)\cdot e^{-\mu t},$$

where A(0), the constant of integration, is the probability that a given particle is present in the compartment at the initial time. Using the definitions (2), (3) and (4) we get for a simple compartment,

$$A_i = A(0)/\mu^{i+1}, \quad i=0,1,2,\ldots$$

$$a_i = 1/\mu^i, \quad i=1,2,3,\ldots$$

$$\alpha_1 = 1/\mu$$

$$\alpha_2 = 1/2\mu^2$$

$$\alpha_3 = 1/3\mu^3$$

$$\alpha_4 = 3/8\mu^4$$

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6. Synthesis

Consider two systems in series, that is two systems such that all particles entering the second of them are originating from the first; the first system is called the unique precursor of the second.[6] If

$A(t)dt$ = probability that a particle entering the first system at time 0 leaves it in the interval $t, t+dt$,

$B(t)dt$ = probability that a particle entering the second system at time 0 leaves it in the interval $t, t+dt$,

then, ignoring infinitesimels of order higher than one,

$$A(\tau)d\tau \cdot B(t-\tau)dt$$

is the probability that a particle entering the first system at time 0 moves to the second in the interval $\tau, \tau+d\tau$ and leaves this one in the interval $t, t+dt$. Taking the integral of the expression above for all values of τ from 0 to t, one gets the probability that a particle that entered the first system at time 0 leaves the second at a time between t and t+dt, no matter when it moved from the first to the second, i.e. the convolution

$$\int_0^t A(\tau)B(t-\tau)d\tau$$

is the probability density function characteristic of the system formed by two systems in series.

Obviously the properties of the convolution described in section 4 apply in this case also.

If two systems are in parallel, i.e. a particle can enter either system and be detected when it leaves either of them, then calling A(t) and B(t) the probability density functions of the two separate systems, the probability density function of the two systems taken globally is A(t) + B(t). Obviously in this case the moments of the resulting system are

A_0+B_0

A_1+B_1

A_2+B_2

For the relative moments we have

$$\frac{A_i+B_i}{A_0+B_0} = \frac{A_i}{A_0}\frac{A_0}{A_0+B_0} + \frac{B_i}{B_0}\frac{B_0}{A_0+B_0} \tag{10}$$

$$= a_i\omega_a + b_i\omega_b,$$

where i is any positive integer and

$$\omega_a = \frac{A_0}{A_0+B_0}, \qquad \omega_b = \frac{B_0}{A_0+B_0},$$

called the weight[7] of the two systems, are factors representing the

probability that a particle goes through one rather than the other system.

If a system forms a loop, i.e. a particle can reenter it immediately after leaving it, put

$A(t)dt$ = probability that a particle that entered the system at time 0 leaves it for the first time in the interval $t, t+dt$;

$M(t)dt$ = probability that a particle that entered the system at time 0 leaves it in the interval $t, t+dt$, irrespective of the number of passages through it.

The convolution $\int_0^t M(\tau)A(t-\tau)d\tau$ is the probability density function corresponding to a particle going through that system two or more times; by adding to that convolution the probability density function corresponding to just one passage, we should get again the function $M(t)$, i.e.,

$$M(t) = \int_0^\infty M(\tau)A(t-\tau)d\tau + A(t);$$

taking the moments of the functions above, using equation (7),

$$M_0 = M_0A_0+A_0$$
$$M_1 = M_0A_1+M_1A_0+A_1$$
$$M_2 = M_0A_2+M_1A_1+M_2A_0+A_2$$
$$M_3 = M_0A_3+M_1A_2+M_2A_1+M_3A_0+A_3$$
$$M_4 = M_0A_4+M_1A_3+M_2A_2+M_3A_1+M_4A_0+A_4$$

hence

$$M_0 = \frac{A_0}{1-A_0} \tag{11}$$

$$M_1 = \frac{1}{1-A_0}[A_1(M_0+1)]$$

$$M_2 = \frac{1}{1-A_0}[A_2(M_0+1)+A_1M_1]$$

$$M_3 = \frac{1}{1-A_0}[A_3(M_0+1)+A_2M_1+A_1M_2]$$

$$M_4 = \frac{1}{1-A_0}[A_4(M_0+1)+A_3M_1+A_2M_2+A_1M_3]$$

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and

$$m_1 = a_1(M_0+1)$$
$$m_2 = a_2(M_0+1)+a_1M_1$$
$$m_3 = a_3(M_0+1)+a_2M_1+a_1M_2$$
$$m_4 = a_4(M_0+1)+a_3M_1+a_2M_2+a_1M_3$$

$$m_i = a_i(M_0+1) + \sum_{j=1}^{i-1} a_jM_{i-j}. \tag{12}$$

7. Analysis

The formulas of the previous section can be inverted to compute the moments of separate subsystems if enough data are available. At this point it is convenient to introduce a new notation. Call $F_n{}^{ij}$ the n-th moment of the transport of a particle from state i to state j, and $F_n{}^{ii}$ the n-th moment of the transport through a cycle beginning and ending in state i. Also call $F_n{}^{ii*}$ the n-th moment of the one-time transport through the cycle around i, and $F_n{}^{ij(\ell,m,\ldots)}$ the n-th moment of the transport from i to j excluding the particles that are going through the states $\ell,m,\ldots$, indicated in parenthesis. Furthermore, if j is one of the superscripts in parenthesis, then from that moment the transport along a cycle through j is excluded.

With this notation equation (11) for instance becomes

$$F_0{}^{jj} = \frac{F_0{}^{jj*}}{1-F_0{}^{jj*}} \tag{13}$$

and equation (12)

$$f_n{}^{jj} = f_n{}^{jj*}(F_0{}^{jj}+1) + \sum_{\ell=1}^{n-1} f_\ell{}^{jj*}\, F_{n-\ell}; \tag{14}$$

by inversion,

$$F_0{}^{jj*} = \frac{F_0{}^{jj}}{1+F_0{}^{jj}},$$

$$f_n{}^{jj*} = \frac{1}{F_0{}^{jj}+1}\left(f_n{}^{jj} - \sum_{\ell=1}^{n-1} f_\ell^{jj*}\, F_{n-\ell}^{jj}\right).$$

Suppose now that two states, i and j have been observed, and from experimental data the moments $F_n{}^{ij}$ have been computed for a sufficient number of values of n. From section 6, remembering equation (7),

$$F_0{}^{ij} = F_0{}^{ij(j)}\cdot F_0{}^{jj}$$

and remembering equation (8),

$$f_n^{ij} = \sum_{\ell=0}^{n} f_{n-\ell}^{ij(j)} \cdot f_\ell^{jj}, \quad n=1,2,\ldots$$

because the direct transfer of a particle from state i to state j is followed by an indeterminate number of recyclings of that particle around state j. If in the two equations above we substitute the values of F_0^{jj} and f_n^{jj} given by equations (13) and (14), we have a number of equations giving the relationship between the moments $F_0^{ij(j)}$, $f_n^{ij(j)}$ of the direct transfer from i to j, and F_0^{jj*}, f_n^{jj*} of a single recycling around j, on one side, and the moments F_0^{ij}, f_n^{ij} of the global transfer from i to j, as observed experimentally. By inversion of those equations, the moments of the subsystems can be computed; they describe the behavior of a particle during transfers not directly observable.

8. Non-converging moments

The definitions given in section 3 required the convergence of certain integrals, in particular of

$$\int_0^\infty \frac{t^i}{i!} F(t)dt; \tag{15}$$

this requires that function F(t) decreases fast enough when t approaches infinity. It is a known fact[8] that most functions found in biological modelling are of exponential order, i.e. they have the property that a constant $\alpha > 0$ exists such that the product

$$e^{-\alpha t}F(t)$$

is bounded for all values of t larger than some finite value T; for a function of exponential order the integral (15) always converges, no matter how large i is. A notable exception is given by a closed system, i.e. a system from where not all particles are eventually lost; in this case

$$\lim_{t\to\infty} F(t) = 0,$$

and the integral (15) does not converge for any non-negative value of i. Obviously the expected time spent by a particle in such a system is infinite. We shall not consider this case, but the more interesting case when function B(t), as defined in section 2, is of exponential order, while function A(t) is bounded but does not approach zero as t approaches infinity. This corresponds to feeding a "regular" system with an endless stream of particles. Equation (1)

shows that function C(t) also will have a non-zero limit, therefore neither the moments of A(t) and of C(t) are defined, while B(t) has defined, but unknown moments.

From the hypothesis that A(t) is bounded, it follows that

$$e^{-\delta t}A(t)$$

is of exponential order for any $\delta > 0$; the convolution integral in (1) can be rewritten as

$$\int_0^t e^{-\delta\tau}A(\tau)\cdot e^{-\delta(t-\tau)}B(t-\tau)d\tau = e^{-\delta t}C(t),$$

showing that the multiplication of both A(t) and C(t) by $e^{-\delta t}$ is equivalent to the multiplication of B(t) by the same exponential function. The new functions $e^{-\delta t}A(t)$ and $e^{-\delta t}C(t)$ have finite moments, and using equations (7), (8), (9) we can compute the moments of $e^{-\delta t}B(t)$; calling B_i^* the moments of this last function, then

$$B_i^* = \int_0^\infty \frac{t^i}{i!} e^{-\delta t}B(t)dt$$

$$= \int_0^\infty \sum_{j=0}^\infty \frac{(-\delta t)^j}{j!} \frac{t^i}{i!} B(t)dt$$

$$= \sum_{j=0}^\infty (-1)^j \delta^j \binom{i+j}{i} B_{i+j}, \quad i=0,1,2,\ldots$$

and by inversion

$$B_i = \sum_{j=0}^\infty \delta^j \binom{i+j}{i} B^*_{i+j}, \quad i=0,1,2,\ldots \tag{16}$$

Incidentally, if the functions A(t) and C(t) are evaluated by measuring the activity of a radioactive tracer in two states of the system, then the "true" probability density functions are multiplied by the exponential function $e^{-\delta t}$, where δ is the decay constant of the nuclide used. If the true functions A(t) and C(t) are not corrected for the radioactive decay, then the moments B_i^* should be corrected using equations (16); these last corrections are frequently easier than the correction of A(t) and C(t) because in general the infinite series in (16) converges very rapidly.

9. Blood flow measurement

Most local blood flow measurement methods relate back to the original Kety-Schmidt equation[9]:

$$dQ_S/dt = F(C_A - C_V), \tag{17}$$

where

Q_S = amount of tracer present in the organ,

C_A, C_V = arterial and venous concentrations of tracer, respectively,

F = flow rate of blood through the organ;

this equation states simply that the amount of tracer circulating through an organ is conserved. An additional assumption is usually made, i.e.,

$$Q_S = \lambda W C_V \tag{18}$$

where

W = volume of the organ,

λ = partition coefficient between organ and blood.

This assumption implies that the amount of tracer present in the organ is simply proportional to the venous concentration. From the assumption follows

$$dQ_S/dt + \frac{F}{\lambda W} Q_S = FC_A.$$

Calling C_B the concentration of the tracer in the organ, and f the blood flow rate per unit volume of tissue,

$C_B = Q_S/W$,

$f = F/W$,

the differential equation above becomes

$$dC_B/dt + \frac{f}{\lambda} C_B = fC_A. \tag{19}$$

Supposing $C_B = 0$ at $t = 0$ and f constant, then

$$C_B(t) = f \int_0^t C_A(\tau) e^{-(f/\lambda)(t-\tau)} d\tau. \tag{20}$$

By using an infusion pump and a servo amplifier[10] we were able to produce a linearly increasing arterial concentration of radiotracer in experimental animals. In this case

$C_A(t) = \alpha t$

with α constant, and equation (20) becomes

$$C_B(t) = \alpha\lambda(t - \frac{\lambda}{f} + \frac{\lambda}{f} e^{-ft/\lambda});$$

the last term in parenthesis becomes negligible after a very short time, therefore

$$C_B(t) = \alpha\lambda(t - \lambda/f). \tag{21}$$

If the values of C_B versus t are plotted, one gets, after a short transient, a straight line of slope $\alpha\lambda$; by extrapolation this straight line intersects the t-axis at a point equal to λ/f. Because α is known, λ and f can be computed. We were in fact able to verify the model in cats and to determine how the brain partition coefficient λ of 4-^{18}F-fluoroantipyrene, and the brain blood flow rate f changed in the same animal by changing the arterial concentration of CO_2 during an experiment.

By observing that equation (20) is a special case of equation (1), using equation (7) and the results of section 5 we get

$$B_0 = \lambda A_0$$

$$B_1 = \lambda A_1 + \lambda^2/f\ A_0$$

$$B_2 = \lambda A_2 + \lambda^2/f\ A_1 + \lambda^3/f^2\ A_0$$

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where $A_0, A_1, A_2, \ldots$, $B_0, B_1, B_2, \ldots$ are the moments of the functions $C_A(t)$ and $C_B(t)$, respectively.

In particular these last equations show that λ is the zeroth moment, λ/f the first relative moment, and $(\lambda/f)^2$ the second relative moment of the function describing the blood flow through the organ. Of course the equations above are redundant; only A_0, A_1, B_0, B_1 are necessary to compute λ and f, nevertheless the higher moments may be useful to check the validity of the assumptions made, i.e. the correctness of equation (20). The mainpoint here is that by using the moments, the arterial concentration function does not need to have a special form, as was required for the validity of equation (21), but can be any function with converging moments.

10. Positron emission tomography

Equation (17) is based on the principle of conservation of mass and is therefore valid in general, provided that both C_A and C_V are uniform throughout the whole organ considered, or if not uniform that an appropriate average value is used for them. On the other hand equation (18) requires an instantaneous equilibration between the concentration in the organ and in the venous blood, i.e. it requires that the organ behave like a perfect compartment.

From the results of section 5 we can say that the probability density function of the organ described by equations (17) and (18) is $fe^{-ft/\lambda}$. Other hypotheses are possible; for instance different parts of the organ may have different partition coefficients, or blood

may diffuse without mixing through the organ or through some parts of it; in all these cases the probability density function of the particles moving through the organ is of course not a simple exponential function as before. If its moments are computed from the experimental results, then the zeroth moment is not the partition coefficient λ as defined by equation (18), but is the fraction of tracer particles that are transferred from the arterial blood to the organ; the first relative moment is the average time spent by a tracer particle in the organ; the second central moment divided by two is the variance of that time, and so forth.

We intend to use a high resolution positron emission tomograph (PETT VI)[11] to determine the successive moments describing the blood circulation through different sections of the brain, for example. Wherever the relative moments form a geometric progression, the circulation in that section follows the rules of a perfect compartment; if this is not the case, the method of section 7 can be used to describe the behavior of a tracer particle in that part of the organ.

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