Mathematical Modelling in PET Studies

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Introduction

In biomedical studies, a knowledge of the physiology and biochemistry of what is going on in a given volume of tissue, in some increment of time, for a given situation; or the change in total activity in that volume element (often called region of interest, ROI) as a function of time is desired. A safe approach to take is to formulate a theory or a hypothesis that one can test with appropriate technology, in this case POSITRON EMISSION TOMOGRAPHY, PET. The hypothesis is then cast into a set of mathematical relationships that relate certain variables such as concentrations, the kinetic exchange of molecules, e.g. between blood and tissue, the distribution space clearance and/or washout of certain precursors ... etc. These variables must be related by equations based on a kinetic model of the processes under study. The model assumptions, on which the formulation of the mathematical equations are based, must be founded on the valid principles of thermodynamics, biochemistry, and biophysics. This means that PET work is centered for the most part around physiological modelling such as models of cerebral utilization of glucose[1], regional blood flow models in humans[2,3], neuroreceptor ligand models[4,5], and other models relative to actual physiology that we understand to exist.

Based on the biochemistry of the tissue under study, we then develop a suitable radiopharmaceutical that, via its emitted radiation, give us in vivo qualitative images, and quantitative informations on the distribution of the labelled compound introduced in that tissue. This capability is useful when the isotope used for labelling is confined to a defined chemical species, or its degradation products, and/or their paths in the body are known, hence the judicious choice of the radiopharmaceutical used.

We may ask the question: Why PET? In comparison to other scanners PET has two advantages:

i) High spatial resolution, hence sharp images and accurate localization of the position of the activity;

ii) Temporal information, i.e. sequential isotope distribution as a function of time in the localized volume.

System Identification and the Inverse Problem

The important task for the researcher is that of deriving an appropriate model from the data and informations available in the field. This, in its various aspects, is the inverse problem. In general, once a model is fully specified, at least conceptually, it is easy to solve. At times there are difficulties in obtaining analytical solutions, but then one can generally obtain numerical slutions; however, the two are not entirely independent.

The design of an experiment, and the choice of data to be collected is determined in part by implicit as well as explicit models current at the time, by prior knowledge, and by the viewpoint of the investigator. The important point is that "there is constant interaction between the models current in the area, and the experiments conducted, and the type of data collected". Thus there is no experiment without theory, and there is no meaningful theory without experiment. This is one of the reasons the inverse problem in general is so difficult.

The inverse problem presents itself at many levels of complexity. If one has some information that specifies the model, say an n-compartment system, then the inverse problem is one of model parameter estimation. At the other end of the spectrum, one may know very little about the structure of the system, and the problem then becomes one of system identification or specification. At times the problem lies between these extremes, and the inverse problem becomes a mixture of parameter estimation, and system identification.

It should be obvious from the above, that the general inverse problem includes the problems of experimental design, theory of estimation, and statistical analysis.

Modelling

As discussed above, theory attempts to predict the specific from the general, it establishes functional relationships; it identifies variables, material properties, and the physical, the chemical, and biological constants involved in a state or process. Once thermodynamically valid assumptions of the theory are made, a conceptual framework is established. This is then followed by casting the hypothesis into a set of fucntional mathematical relationships. These equations relate the various variables - dependent and independent - generally in time and/or space. These quantitative relationships are called models.

Uniqueness

The question of uniqueness is very important for the problem of system identification. Clearly the model cannot be so complex that the resultant parameters might not be uniquely qualified by the available data. In the general sense there is rarely any way of knowing how good the solution is to a

problem involving system identification because we seldom have available for us the full set of possible alternatives for comparison. Furthermore, it is often possible to find a compartmental description for a system. Whether not a compartmental description is reasonable or useful can only be decided in terms of other information available on the system.

Compartmental Models

One of the most useful and widely used representations of biological systems is based on the notion of a compartment. Very often we choose to model our biological system as a system of compartments because of the conceptual simplicity, as well as the feasibility of mathematical description. A compartment generally represents a quantity of a substance within the organism, which has uniform and distinguishable kinetics of transformation or transport. Such compartments may represent volumes which are clearly identifiable, and localized, e.g. lungs, or may be non-contiguous and highly distributed, such as the capillary bed, the red blood cells, or a chemical species.

The most widely used models of biological systems consist of compartments represented by a system of linear-first order differential equations. Thus an n-compartment system could be represented by eq. (1), and depicted in Fig. 1.,

$$\dot{\vec{C}}(t) = F\,\vec{C}(t) + \vec{I}(t) \qquad (1)$$

where $\vec{C}(t)$ is an n-vector representing the concentration of a particular material (e.g. the tracer) in each of the n compartments. $\vec{I}(t)$ is an r-vector representing the inputs into the various compartments. F is a matrix of constants, the rate constants, or the fractional transfer constants, f.t.c., from compartment i to compartment j, as shown in Fig. 1. It is typical in problems of this type that concentrations of a particular substance are measured in several of the compartments, but the f.t.c., i.e. the elements of the F matrix are unknown. We should remember that:

i) the elements of the F matrix determine the system's kinetics; and

ii) the functional form of the elements of the input vector $\vec{I}(t)$ will determine the shape, or the functional form of the system's response.

Since the system is assumed to be linear, i.e. it is described by a linear compartmental system, l.c.s., the elements of the F matrix are time-invariant. In addition, the inputs are often into one compartment, and are either constant in time, or take simple functional form, e.g. bolus or delta function.

Data Analysis

Exponential fitting: Extensive work has gone on in the determination of techniques for identifying the elements of the matrix F. Provided all the

eigenvalues of F are distinct, the solutions of the system of eq. (1), i.e. the values of the concentrations of tracers or any other substance in any compartment will be represented by a sum of exponentials, e.g.

$$C_j(t) = \sum_{i=1}^{n} a_0 + a_i \, e^{-k_i t} \qquad j = 1, 2 \ldots n \qquad (2)$$

where a_0 and a_i are real, and k_i is real and positive. Frequently the problem includes that of estimating the number of compartments in the system, i.e. the number of exponential terms in eq. (2). This is the problem of system identification. The obvious approach is to try a number of models with 1, 2, and more exponential terms to see which gives the "best fit". However, it should be apparent that the more parameters available to us, the better fit. One might hope that if a curve actually consists of n exponential components plus some error, then n exponential terms will give a good fit to the data, and the addition of more components will not greatly improve the fit. It should also be noted that, in general the number of data points needed to obtain good fits for sums of exponentials increases markedly as the number of exponentials increases. This is in itself is a serious limitation in data acquisition of the present generation of tomographs. However, there is an alternative method by which n can be determined from washout curves, or the time course of changes in one or more compartments using the Fourier Transform methods, as will be discussed later.

A number of graphical and computational techniques have been developed for identifying the exponents k_i , and the coefficients a_i of eq. (2).[6-10] Since such techniques are useful in systems involving radioactive tracers, such as PET, it is not surprising that formal parameter estimation techniques have been applied to this problem.[11-14]

Other fitting techniques: Other fitting techniques such as fitting the rate equations directly, fitting the smoothed rate equation, fitting the integrated rate equation, or fitting the rate equation by integration could be useful though unpopular.

Biological and Physiological Considerations of the F.T.C.

There is good reason to believe that the f.t.c. are not always constant, or have the same value in health as in disease. Although we are treating biological systems as linear systems in order to simplify the modelling, and the data analysis, yet this provides an incomplete base for the interpretations of long term experiments with intact animals. As we characterize the dynamics of biological systems with the f.t.c., we must consider other linear compartmental systems in which some variences of the f.t.c. are included. The following may serve as examples to be considered.

i) Circadian Changes[15,16]: Many body functions vary periodically with a circadian period, so we must consider linear systems which have periodic

fractional exchange coefficients, i.e. eq. (1) will have a matrix F which has a periodic component, e.g.

$$\dot{\vec{C}}(t) = -(\alpha + \beta \sin \omega t)\, \vec{C}(t) + \vec{I}(t) \ . \qquad (3)$$

Urine output is low at night and rises to a peak at mid day. The urinary excretion of sodium, potassium, chloride and other salts follow a similar period. Phosphate excretion is at a minimum early in the morning, and rises to a peak in the early evening. ACTH secretion by the anterior pituitary gland follows a 24 hr cycle which drives the secretion of adrenal steroids, so there is a peak in plasma levels of adrenal steroids near 8 am, and a minimum at 8 pm. Miotic activity in the tissues of the body follow a 24 hr cycle, believed to be driven by the diurnal cycle of levels of epinephrine, and norepinephrine in the body fluids. Many of these important circadian rythems either reflect changes in, or affect the fractional transfer coefficients between compartments.

ii) Stochastic Behaviour[17-19]: There are good reasons to believe that the f.t.c. often have random components because they must be subject to fluctuations in living things, and if so, we need some theory of linear stochastic compartmental systems. Renal excretion of most materials depends on renal blood flow, and the latter shows variations with changes in position, activity, emotional state ... etc., let alone effects of disease, particularly tumors, more importantly, active transport of many solutes is affected by hormones. Glucose transport in some tissues is affected by insulin, growth hormone, glucagon, and epinephrine. Growth hormone affects amino acid transport. Furthermore there are fluctuations in hormone levels, so we expect to see fluctuations in many f.t.c. which we can treat as random fluctuations.

A linear stochastic compartmental system can be thought of as one which can be obtained by taking a linear compartmental system and adding random components to the f.t.c., such that eq. (1) becomes

$$\dot{\vec{C}}(t) = A\, \vec{C} + \vec{I}(t) \qquad (4)$$

where A = F + E, E being a random matrix, while F remains the same as before.

iii) Control[20-24]: The most important consideration is the fact that biological systems are control systems, and when described as compartmental systems it appears that control is exerted through the f.t.c. Therefore we need to consider control in the context of linear compartmental systems. Metabolic pathways are controlled in two ways: a) slow control via the enzymes which, being proteins that mediate the reaction steps, are synthesized and broken down in living cells. The rate of synthesis of the enzymes is controlled by the rate of formation of the mRNA at the genes; b) fast control which involves the modification of the enzymes which have already been synthesized by the binding of some compounds to the enzymes.

Another method of control is illustrated by the action of a number of hormones, insulin for example, which at least exert their effects in living things, in part, by affecting the transport of specific compounds across the cell membranes of various cell types. These act by controlling the rates of exchange of specific compounds between extracellular and intracellular phases. Thus insulin increases the transport of glucose across cell membranes of the muscle and other tissues, but not the brain. One of the effects of growth hormone is to increase active transport of amino acids in many celltypes. Other examples are found in the oxygen extraction fraction variation with cerebral blood flow, and oxygen levels in the plasma. LCMRGlu changes with disease, emotions ... etc., as reflected in the variations in the k's of Sokoloff's model.[25] The changes of brain permeabilities to oxygen, glucose, amino acids ... etc., with age is another important example of control.[26] We can see that for compartmental representation of living systems, the f.t.c. are functions of permeabilities or transport rates of materials across cell membrane, or the reaction rates of metabolic pathways. Thus we expect to see control exerted via the f.t.c.. Two examples of feed back control are studied in detail; plasma-glucose control systems[26-31], and control of the adrenal cortisol secretion.[32-34]

In practice we expect to run into difficulties because more data points are needed in order to extract the parameters of the various matrices of the three cases discussed above, as well as others. The logistics of instrumentation sensitivity, speed of data acquisition, dose limitations, isotope and biological half-lives, and patient's endurance with prolonged measurements with PET, may add another dimension of difficulty in attempting to resolve some of the variances of the f.t.c.

Inputs

The term I(t) in eq. (1) is the vector of inputs into the system's compartments. In PET work, as in many other investigations involving radioactive tracers, the elements of this vector give the functional expression of the quantity and manner of introduction of these inputs into the system. In general it is one input introduced into one compartment of the system, and very often it has a simple functional form, e.g. unit impulse or constant infusion. However the shape of the input determines the functional form of the response (Fig. 2).

i) Unit Impulse Response: For the analysis of the response of linear systems it is useful to define a formal function which has the following properties:

$$u(t-t_0) = \begin{cases} h & t_0 < t \leq t_0 + 1/h \\ 0 & \text{otherwise} \end{cases} . \qquad (5)$$

Then the Dirac delta function is defined as (and depicted in Fig. 3):

$$\delta(t-t_0) = \lim_{h\to\infty} u(t-t_0) \ . \tag{6}$$

Thus the delta function can be thought of intuitively as a unit impulse delivered instantaneously, i.e.

$$\int_0^\infty \delta(t-t_0) = 1 \ . \tag{7}$$

In practice the closest we get to a unit impulse is the administration of a bolus of radiopharmaceutical over a very short period of time. The response of a linear system to this unit impulse input is called the Unit Impulse Response, U.I.R. This unit impulse response of the system is of great importance because i) the U.I.R., often called the transfer function, T.R., of the system, h(t), characterizes the system, i.e. it acts as a fingerprint of the system, ii) it can be used via the convolution integral, C.I., to calculate the response of the system to any other input, e.g. if the input is described by I(t), then the response of the system, R(t), is given by

$$R(t) = \int_0^t I(\tau)\ H(t-\tau)\ d\tau = \int_0^t I(t-\tau)\ h(\tau)\ d\tau \tag{8}$$

called the convolution integral and often written in the form

$$R(t) = I(t) * h(t) = h(t) * I(t) \ . \tag{9}$$

Though many workers in PET studies use bolus inputs routinely[35], few characterize the systems under study with their transfer functions per se. The concept of the T.F. finds most of its applications in linear flow systems, particularly for the calculations of transit times. Recall that for many living flow systems, the only quantities available for direct experimental measurements are the concentrations in the inflow, e.g. arterial blood concentration of glucose of FDG, C_a , and venous blood concentrations of these species, C_v , and the total activity in the ROI, C_i . This is a general method of analysis that does not depend on the detailed structure of the system. This is essentially a stochastic description of the transfer of the injected material from inflow to outflow. In simple language, the T.F. tells us what happened to the system input between the time of administration and the time of outflow, or the time of observation. If the flow rate is constant, the concentration at the outflow is given by the C.I.

$$C_o(t) = \int_0^t C_i(\tau)\ h(t-\tau)\ d\tau \tag{10}$$

where $C_i(\tau)$, $C_o(t)$, are the input and output concentrations respectively, h(t) is the T.F., and τ is a dummy variable.

Since h(t) is the probability density function of transit times, then the mean transit time of the flow in the system is given by

$$\bar{t} = \int_0^\infty t\ h(t)\ dt\ . \tag{11}$$

ii) Step Function Input: Recently there has been a growing interest in using the technique of constant infusion of short-lived isotopes for the measurement of systems dynamic parameters with PET such as regional blood flow.[36-40] In general, in work with radioactive tracers the label is added to the input of a steady state system (s.s.) at constant level until a steady state in the tracer is achieved, then stopping the infusion of the isotope. The time course of the activity in the system is followed from the instance of administration. In this technique the decrease in the isotope concentration due to its physical decay, and clearance from the ROI is compensated for by the constant infusion of the isotope. In order to understand the important implications of the constant infusion in determining the dynamic parameters of the system, a formal description of the term "constant infusion", and the system's response to it is very useful.

Constant infusion is mathematically represented with what is called Unit Step Function (note that the step function can take any height but it is convenient to normalize it). By definition the U.S.F. is given by

$$S(t-t_0) = \begin{cases} 0 & t<t_0 \\ 1 & t\geq t_0 \end{cases} \tag{12}$$

and schematically represented by Fig. 3.

The response of a linear compartmental system to such input is shown in Fig. 4b. It represents the build up of the labelled material in the system till it reaches static equilibrium, i.e. a constant level of the isotope. Static equilibrium means that the rate of input into the system is equal to the rate of loss of the isotope by decay and washout.

Since we cannot introduce the isotope indefinitely, e.g. because of dose limitations, we stop the constant infusion at an appropriate time when the system has reached isotope steady state. Mathematically, and schematically, the response of the system throughout the observation will look like the difference between two functions, F(t), and the same function displaced in the time scale by θ, i.e. $F(t-\theta)$, as shown in Fig. 5a and b. The net result will look like Fig. 5c. If we examine Fig. 5c carefully we notice that it is made of three parts. Part (1) represents the dynamic build up of the activity in the system, part (2) represents the steady state level of activity, while part (3) gives the washout behaviour of the system after stopping the

administration of the isotope.

The analysis of part (1) of Fig. 5c using one of the methods discussed earlier, e.g. fitting sums of exponentials, should provide informations on the dynamic parameters of the system, e.g. the elements of the matrix F. Part (2) of the same figure simplifies the analysis since the differential equations of eq. (1), and their sum will be equal to zero at steady state. Observations at the steady state have been used extensively in calculating Cerebral Blood Flow, CBF, in PET work because of its simplicity.[36-40] Extensive analysis of the sensitivity of the values of the calculated CBF by this method to experimental and statistical errors especially at low count rates was done, as well as the dependence of the usefulness of the method on the isotope half life.[36-40,41]

The analysis of the washout curve, part (3) of Fig. 5c, using curve fitting will give informations on the elements of the matrix F, as in the analysis of the dynamic build up part. However, this will not uniquely quality the system, i.e. n will not be uniquely determined. This problem can be resolved by using the Fourier Transform to transform the washout curve from the time domain to the frequency domain as shown in Fig. 6, and described by many authors.[42,43] The number of peaks in Fig. 6b determines the number of components in the system, and the value of λ_i gives the biological time constant of the ith compartment i. Because experimental measurements are subject to noise, and statistical fluctuations, the transformed spectrum will look like the dashed curves of Fig. 6b. However, we should note that A_i is proportional to a_i , and $\lambda_i = k_i$ of eq. (2).

Very often measurements in PET work are stopped at the time of stopping the infusion of the isotope, i.e. at time, without following the washout curve except in few cases.[44] This is done for many reasons, not the least of them being the patients' emotional state, the high data noise due to low count rates. These problems should be overcome with the new fast and more sensitive generation of tomographs. Yamamoto et al.[40] did a beautiful study with continuous inhalation of $C^{15}O_2$ which they call "dynamic plus equilibrium imaging", as illustrated in Fig. 7. The fact that the transformation of the washout curve to the frequency domain can uniquely specify the system is worth applying in many more studies with PET, particularly with very short-lived isotopes because the measurement time can be shortened considerably.

iii) Other Types of Inputs: Haung et al., and Selikon and Eichling[41] and others argue that high count rates, and the use of isotopes that are neither of too short nor too long half-lives are needed to reduce the fluctuations in the data obtained in the constant infusion method. They argue that a modification of the constant infusion method to exponentially increasing infusion rate, as suggested by Hack et al.[45], will maintain a constant rate of tracer. An exponential infusion is simply achieved by varying the rate at which material is infused as Exp(pt), where $p>s$, p being the rate of infusion, and s the isotope decay constant. An exponentially

increasing infusion will reach equilibrium faster than constant infusion. The important point is that with exponential infusion one has the flexibility to pick a value for p which will optimize the outcome of the method. What may prove to be an even more significant aspect of exponential infusion is the possibility of using several different rates of delivery on the same subject, which could mean that several unknowns could be solved for simultaneously.

Infusion Schedules

Patlack and Pettigrew[46] devised an elegant method for obtaining infusion schedules for blood concentration-time courses. Following an approach based on unit impulse response analysis, eq. (8), via Laplace Transformation techniques, a general method for an input injection schedules which will achieve this goal were derived. Specific infusion schedules which attain blood levels that are constant, increase linearly, decrease exponentially, and increase exponentially were obtained and illustrated experimentally. Approximate infusion schedules of the above were also obtained and illustrated experimentally. As discussed earlier, the equation that relates the output function, R(t), of any input function, I(t), is the convolution integral via the T.F., h(t) of eq. (8 or 9). The Laplace Transform of eq. (8) is

$$R(S) = I(S)\, H(S) \tag{13}$$

where R(S), I(S), and H(S) are the Laplace Transforms of the output, the input, and the transfer function respectively. Thus, if the T.F. h(t) is known analytically or numerically for any system, then I(t) may be determined for any specific output function, R(t), via the Laplace Transform methods.

As explained above, if a unit impulse input (bolus) is introduced in the system, then the system response will be the T.F., i.e. R(t) = h(t), and if R(t) is described by an appropriate fit of sum of exponentials to the output data, for example, then

$$h(t) = R(t) = \sum_{i=1}^{N} A_i\, e^{-\lambda_i t} . \tag{14}$$

From eq. (14), I(t) can be calculated from the inverse of the Laplace transformation of

$$I(S) = \frac{R(S)}{\sum_{i=1}^{N} A_i/(s+\alpha_i)} \tag{15}$$

where $A_i/(s+\alpha_i)$ is the Laplace Transform of the sum of exponentials, eq. (14).

Input-Output and Discrete-Time Methods

When a system's input and output can be isolated, and the system in

question is approximately linear, discrete-time methods of analysis of the system's response, have been applied with considerable success.[47]

The independent variable of the mathematical representation of an observation may be either continuous or discrete. However, even in the case of a continuous function, in analyzing such function with digital computers, it is necessary to represent the data as a series of discrete numeric values, i.e. sequences of numbers.

By using the definition of a discrete system as a transformation of an input sequence u(k) into an output sequence y(k), as shown in Fig. 8, which obey the superposition, and shift invariance principles, it follows that the definition of the unit impulse sequence (similar to the unit impulse in the time continuum domain) is given by

$$\delta(k) = \begin{cases} 1 & k=0 \\ c & k\neq 0 \end{cases} \tag{16}$$

then we also have

$$u(k-n) = \begin{cases} 1 & k=n \\ 0 & \text{all other discrete values of } k \end{cases} . \tag{17}$$

We can also define the Convolution Summation, which is equivalent to the C.I., of eq. (8), by

$$y(k) = \sum_{i=0}^{\infty} h(k)\, u(k-i) \tag{18}$$

and the linear constant coefficient difference equation as,

$$\begin{aligned} y(k) = {} & b_0u(k)+b_1u(k-1)+....b_Mu(k-M) \\ & -a_1y(k-1)-....a_Ny(k-N) . \end{aligned} \tag{19}$$

Equation (19) tells us that the kth value of the output can be computed from the kth input value, and the Nth and Mth past values of the output and input respectively, provided eq. (19) satisfies the boundary conditions and gives unique solution to the constant coefficients, the a's and the b's. The sequence h(0), h(1), ... of eq. (18) is called system weighting sequence or the system T.F., which is completely equivalent to h(t) in the continuum domain, and is often written in the same format as

$$y(k) = u(k) * h(k) . \tag{20}$$

Bolus inputs can be approximated by a unit impulse sequence, $\delta(k)$, and continuous infusion with a unit step sequence. In the first case u(k-i) in eq. (18) will be $\delta(k-i)$ and will be equal to zero for all i in the summation

range except at i=k, it is equal to zero, i.e.

$$Y(k) = h(k) \qquad \text{for } k = 0, 1, 2. \tag{21}$$

Linear discrete systems are said to be stable if and only if the weighting sequence goes to zero at large discrete times, i.e. h(i) = 0 as i goes to infinity. Similarly, for a unit step sequence u(k) = 0 for k<0, then from eq. (18) the response to such input will be

$$y(k) = \sum_{i=0}^{k} h(i) \tag{22}$$

i.e. the response to the unit step sequence input is the first k+1 terms of the system's weighting sequence. It can be shown that the response of linear systems to such input is steplike in nature and approaches a steady state value, y_{ss}, after an initial transit period as i increases as shown in Fig. 9, and Fig. 4b, and represented by

$$y_{ss}(k) = \sum_{i=0}^{k} h(i) \ . \tag{23}$$

The same result can be obtained from the linear difference equation. Bolus injections of FDG in RCMGlu studies, and continuous inhalation studies of $^{15}O_2$, $C^{15}O_2$ ... etc. are examples where discrete-time methods are of great importance in yielding transfer functions of linear systems. Figure (7) of Yamamoto et al.[40] is an excellent example to illustrate this point.

Transit Times with Discrete-Time Methods: Equation (19) is nothing but a model that relates the output of a linear system to the history of its past and present input sequences, and its past outputs. If in a flow study we obtain data on the discrete sequences of inputs and outputs of the system and fit the data with a model like that of eq. (19), then we can evaluate the constants a_0, a_1, ..., and b_1, b_2, ... Once a stable relationship is obtained, the model is used to calculate the transfer function of the system using a unit impulse sequence. The mean transit time $\bar{t}$ is given by

$$\bar{t} = \sum_{i=0}^{\infty} t_i \, h(i) \Big/ \sum_{i=0}^{\infty} h(i) \tag{24}$$

where t_i is the time interval between observations, and eq. (24) is the ratio of the first to the zeroth moments of distribution of transit times, and it is equivalent to eq. (11).

Conclusions

Models used in describing biological systems' behaviour should be based on sound thermodynamical, biochemical, and biophysical assumptions; should be

as simple as the above requirements dictate, but able to determine the system's parameters uniquely.

Though linear compartmental models are conceptually clear, and often described by simple mathematical relationships that make the task of data analysis feasible, variances in the fractional transfer coefficients should be included in the mathematical formulation to account for the nature of living systems' dynamics. It is the F.T.C. that characterize the system's kinetics, and we do not expect them to be the same in health as in desease, for example.

The shape of the input function that describes the manner of delivery of the radiopharmaceutical into the system under study, and upon which the system's response function depends, should be carefully described and planned. The deciding factor on that shape should be: what kind of information, and parameters are we looking for?

Finally, discrete-time methods of analysis, should be used more often in data analysis in PET studies, as they are simpler and can provide insight into the system under study.

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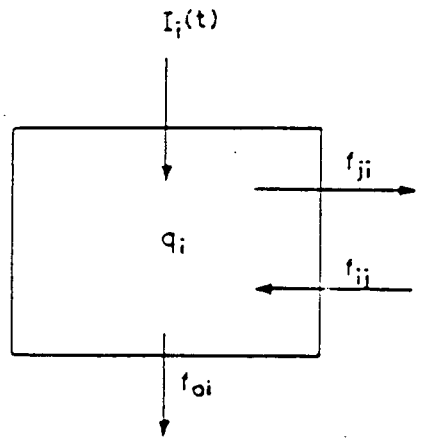

Fig. 1. N-compartment system. The F.T.C. f_{ji} is from comp. i to comp. j.

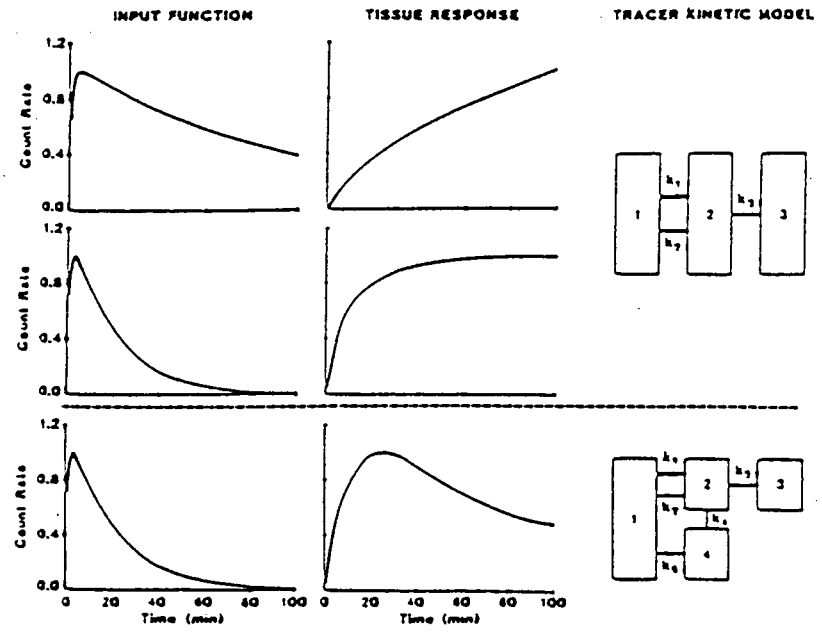

Fig. 2. Tissue response curves of different models to the same input and of the same model to different inputs (Phelps et al.[35]).

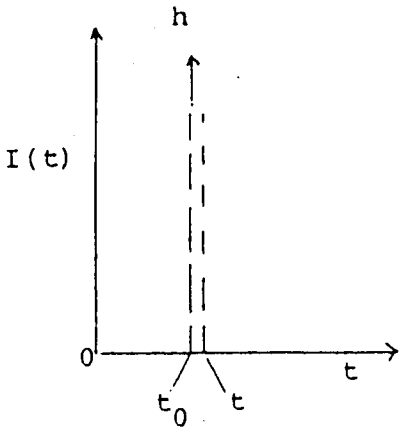

Fig. 3. Dirac delta function.

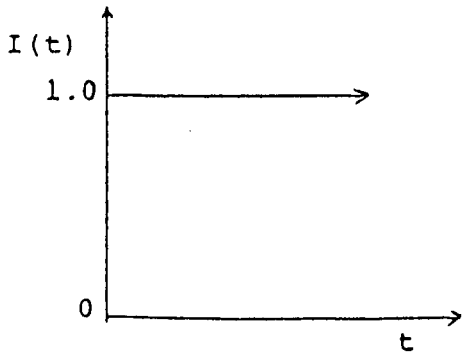

Fig. 4a. Unit step input function.

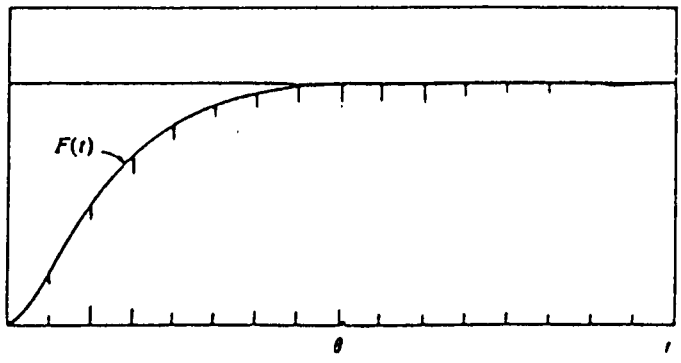

Fig. 4b. Response of a linear compartmental system to a unit step input of Fig. 4a.

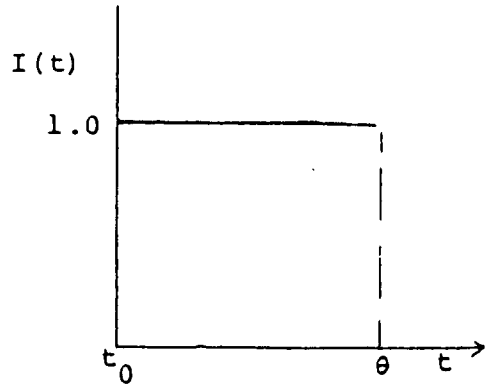

Fig. 5a. Unit step input function terminated at time t=θ.

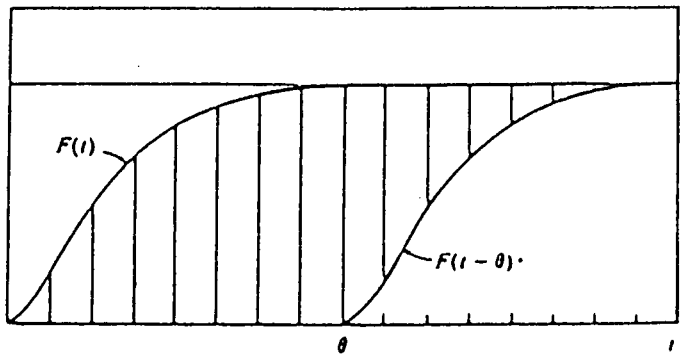

Fig. 5b. The difference between F(T) and F(T-θ) gives the linear compartmental response to the input of Fig. 5a.

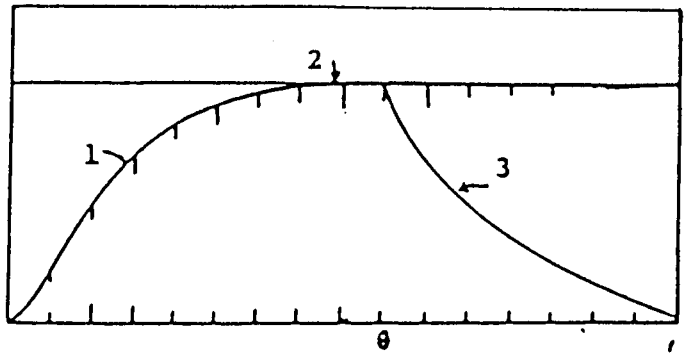

Fig. 5c. Net response of a linear compartmental system to the input of Fig. 5a. Part 1 the dynamic build up, part 2 the steady-state and part 3 the washout of the system.

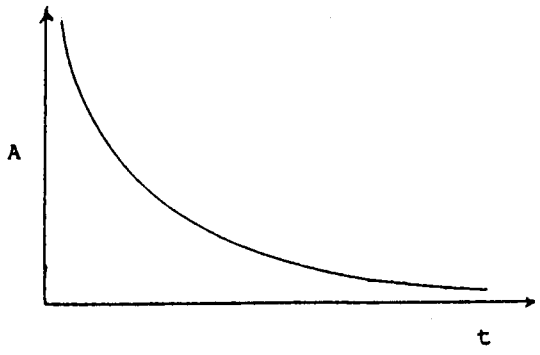

Fig. 6a. Activity-time curve.

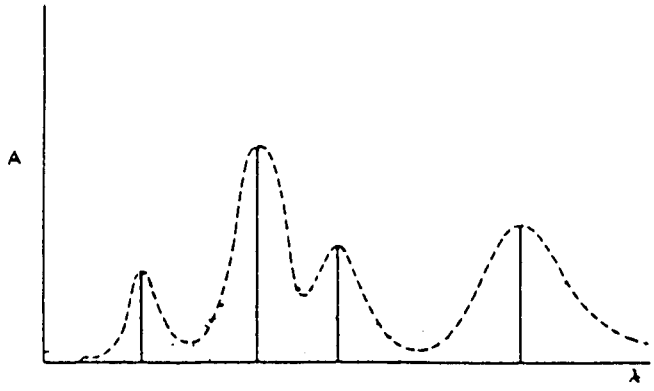

Fig. 6b. The fourier transformation of Fig. 6a into the frequency domain. The peaks give the system's comp. number, λ_i and A_i give the time constant and size of comp. i respectively.

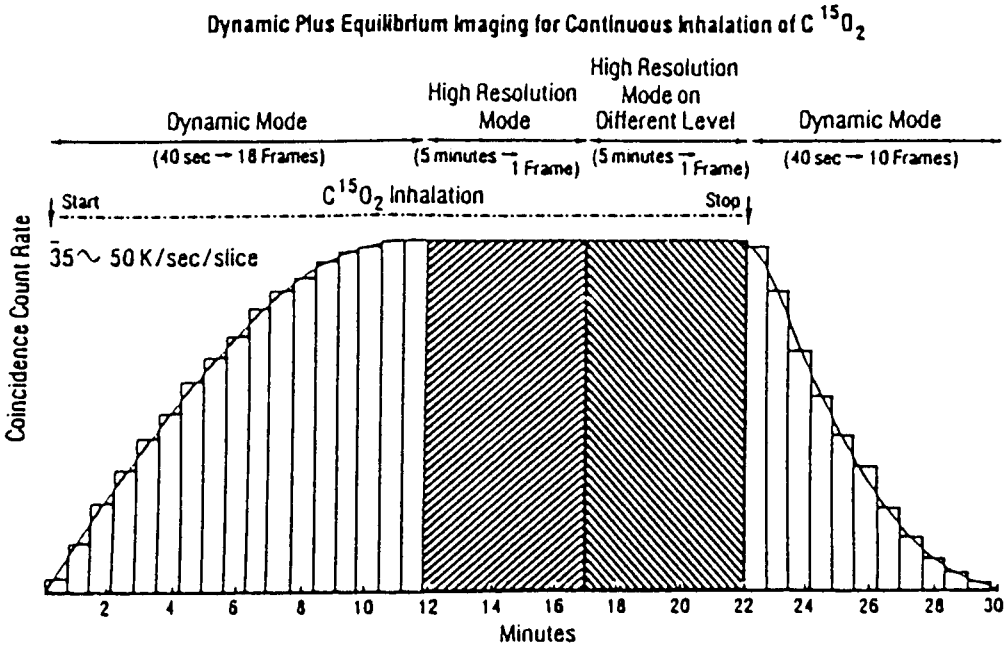

Fig. 7. Dynamic activity build up, equilibrium, plus washout imaging of continuous inhalation of $C^{15}O_2$, an experimental realization of Fig. 5c. (Yamomoto et al.[40])

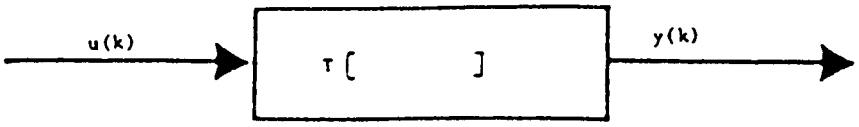

Fig. 8. Definition of a system in discrete-time methods.

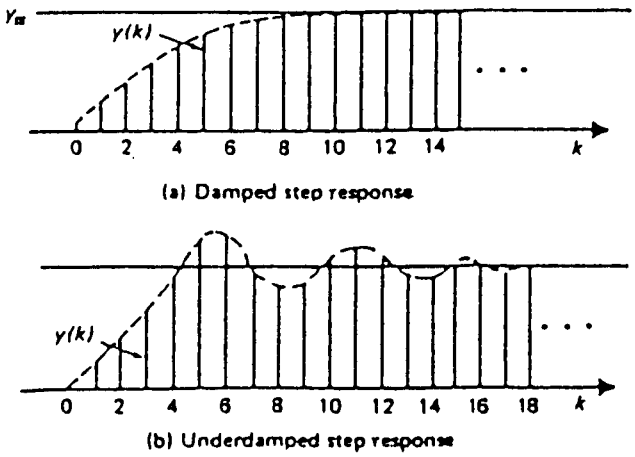

Fig. 9. A linear system's response to a unit step sequence input.