CEREBRAL BLOOD FLOW

Mathematical Models, Instrumentation, and Imaging Techniques

Edited by
Aldo Rescigno and
Andrea Boicelli

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PREFACE

The NATO Advanced Study Institute on "Cerebral Blood Flow: Mathematical Models, Instrumentation, and Imaging Techniques" was held in L'Aquila, Italy, June 2-13, 1986. Contributions to this program were received from the University of L'Aquila, Consiglio Nazionale delle Ricerche, Siemens Elettra S.p.A., and Bracco S.p.A.

Recent studies of the cerebral blood circulation have lagged behind analysis of other parameters such as glucose utilization, transmitter distribution, and precursors. This Advanced Study Institute tried to fill this gap by analyzing in detail different physical techniques such as Autoradiography (including Double-Tracer Autoradiography and highly specific tracers as Iodoantipyrine, Microspheres), Single Photon Emission Computed Tomography, Nuclear Magnetic Resonance. Each method was analyzed in regards to its precision, resolution, response time.

A considerable part of this Institute was devoted to the mathematics of CBF measurement, in its two aspects, i.e. the modeling of the underlying kinetic system and the statistical analysis of the data. The modeling methods proposed included the development of a differential algebra whereby the differential and integral equations involved could be solved by simple algebraic methods, including graph-theoretical ones; the statistical methods proposed included the illustration of different parametrizations of possible use in the interpretation of experimental results.

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CONTENTS

MATHEMATICAL MODELS

STOCHASTIC MODELS AND LINEAR TRACER KINETICS

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1. MEANING OF A MODEL

The purpose of a model is to verify whether some hypotheses made on a real system are valid (Rescigno and Beck, 1987), and subordinately to determine the values of some of the parameters that represent specific properties of the system under study (Zierler, 1981). For instance the model commonly used when dilution phenomena are expected, is a set of ordinary differential equations with constant coefficients, while when diffusion phenomena are the case, partial differential equations are to be used, finite difference equations for delay phenomena, etc.

In Nuclear Medicine and in Pharmacokinetics the compartment model is often used (Rescigno and Segre, 1964); it consists of a set of linear differential equations of order one with constant coefficients, and it implies the hypotheses that the system described contains a finite number of 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 parameters computed from the experimental data using this model are the transfer rates between compartments and the turnover rates of compartments; they have a defined physical meaning only if the model is appropriate (Beck and Rescigno, 1970).

With n compartments the number of parameters necessary to characterize the equations is n^2, therefore, ignoring all experimental errors, only n^2 measurements are needed completely to describe the system under observation. With the presence of experimental errors this number should be increased to improve the reliability of the computed parameters. The cost of the measurements may be a factor of importance. The strategy of the measurements may also be important, i.e. measurements made at certain times may carry more information than if made at other times. Some of the parameters may be more "important" than others, i.e. their

information may be more "valuable". Above all, other parametrizations besides the classical one of the transfer rates and turnover rates, may be more valuable in the sense that they may be more directly connected to some externally measurable or physically well-defined quantities, or they may be more sensitive to specific treatments (Matis, Wehrly and Gerald, 1983).

Of course if the hypotheses incorporated into the model are not appropriate, the computed parameters have no gnoseological value. If we make some weaker hypotheses there is a lesser chance of rejection of the model, but the real system will not be described as fully as with a stronger model, i.e. we will be able to determine fewer parameters; those parameters though are more reliable and may even be more "valuable" in the sense hinted above.

The ideal situation would be to define parameters that depend on the smallest possible number of hypotheses, but that still have a physically meaningful interpretation.

One such example is given by Rescigno and Gurpide (1973). While that approach is not completely "model-free", it is certainly very "robust", i.e. it allows to compute parameters that are not very dependent of the assumptions of a specific model. All this considered, we think that the experimental data available to the investigator should be examined in terms of a model implying a minimum number of assumptions and giving the best physical interpretation to the parameters involved.

2. LINEAR STOCHASTIC KINETICS

Consider a particle in a living system and suppose that that particle can be recognized in two different states of the system, where by state we mean a particular location or a particular chemical form, or both. If one state is the precursor of the other (not necessarily the immediate precursor), then we can study the relationship among event A (presence of the particle in the precursor state), event B (transition from precursor to successor state), and event C (presence of the particle in the successor state).

For any t and τ such that $0 < \tau < t$, call $f(\tau)$ the probability of A at time τ and $h(t)$ the probability of C at time t; the range of both functions is 0, 1. Suppose now that B depends only on the interval of time separating A and C, so that we can call now $g(t-\tau)d\tau$ the conditional probability that the particle is in C at time t if it left A in the interval from τ to $\tau+d\tau$.

The product

$$f(\tau).g(t-\tau)d\tau$$

therefore is the absolute probability of A at time τ and of C at time t.

By integration of the above product we must obtain the probability of C at time t irrespective of A, i.e.

$$(1) \qquad \int_0^t f(\tau)g(t-\tau)d\tau = h(t).$$

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

By linear system is meant that two different solutions of equation (1) can be added to give a new solution; in fact if a solution of equation (1) is given by $f_1(t)$, $h_1(t)$, and another one by $f_2(t)$, $h_2(t)$, then a third solution of equation (1) is $f_1(t)+f_2(t)$, $h_1(t)+h_2(t)$, as can be easily verified.

By invariant system I mean that a solution does not change if the time origin is changed. In fact suppose that f(t), h(t) is a solution of equation (1), and consider the new function

$$\begin{aligned} f_1(t) &= 0 && \text{for } 0 \leq t < t_o \\ &= f(t-t_o) && \text{for } t \geq t_o. \end{aligned}$$

For this function

$$\int_o^t f_1(\tau)\, g(t-\tau)\, d\tau = \int_{t_o}^t f(\tau-t_o)\, g(t-\tau)\, d\tau$$
$$= \int_o^{t-t_o} f(\tau)\, g(t-t_o-\tau)\, d\tau;$$

using now equation (1),

$$\int_o^t f_1(\tau)\, g(t-\tau)\, d\tau = 0 \qquad \text{for } 0 \leq t < t_o$$
$$= h(t-t_o) \qquad \text{for } t \geq t_o,$$

i.e. f(t) and h(t) are shifted along the time axis by the same quantity.

If we think of an experiment where a very large number of identical particles is used, then the number of particles in A and in C are good estimators of functions f(t) and h(t) respectively. Function g(t) represents the probability that a particle that left A at time zero will still be in C at time t; therefore in a hypothetical experiment where all identical particles left the precursor at time zero, the number of particles found in the successor will be given by g(t).

In the following pages I shall try to show a number of properties of equation (1) and how to use those properties to interpret the results of some experiments.

3. DEFINITION OF MOMENTS

Given a generic function f(t) defined for all values of t from 0 to $+\infty$, define the <u>moments</u>,

$$(2) \qquad F_i = \int_o^\infty t^i/i!\; f(t)\, dt, \quad i=0,1,2,\ldots$$

and the <u>relative moments</u>,

$$(3) \qquad f_i = \int_o^\infty t^i/i!\; f(t)\, dt/F_o, \quad i=1,2,3,\ldots$$

provided that the integrals above converge.

I shall show in section 6 what can be done when one of those integrals does not converge; for the time being we suppose that all those moments do exist.

Definition (3) applies only to values of <u>i</u> larger than zero; for convenience we complete that definition with

$$f_o = 1.$$

Frequently the moments of a function are defined without the factor 1/i! shown in (2); I prefer to use this factor

because the moment generating functions defined in section 8 actually generate the moments as in (2) and (3) rather than the moments defined without the factor 1/i!, and because the expressions we shall find later on will be considerably simpler. Observe also that these moments are just integral transforms of function f(t) with kernel $t^i/i!$, very similar to the Mellin transform, whose kernel is t^{i-1}; even though in the Mellin transform i is a complex variable while in these moments it is a non-negative integer, they have many interesting properties in common. For more details see for instance Bateman (1954).

4. PROPERTIES OF THE CONVOLUTION

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

$$\int_0^\infty t^i/i! \int_0^t f(\tau)g(t-\tau)d\tau\,dt = \int_0^\infty t^i/i!\; h(t)dt,$$

where i is any non-negative integer; change the order of integration,

$$\int_0^\infty f(\tau)\int_\tau^\infty t^i/i!\; g(t-\tau)dt.d\tau = h_i;$$

change the variable of the inner integral,

$$\int_0^\infty f(\tau)\int_0^\infty (t+\tau)^i/i!\; g(t)dt.d\tau = h_i;$$

after expanding the binomial we obtain finally,

$$\sum_{j=0}^{i} F_{i-j}.G_j = H_i; \quad i=0,1,2,... \tag{4}$$

in particular,

$$F_oG_o = H_o$$

$$F_1G_o + F_oG_1 = H_1$$

$$F_2G_o + F_1G_1 + F_oG_2 = H_2$$

If we divide both sides of equation (4) by F_oG_o we get

$$\sum_{j=0}^{i} f_{i-j}g_j = h_i. \quad i=1,2,3,... \tag{5}$$

The number of particles in a given state is in general very large; if it can be observed as a function of time it represents a very good approximation of the probability density function defined in section 2. This means that if the functions f(t), h(t) corresponding to two given states can be measured, then their moments can be computed and the moments of the unknown function g(t) calculated using equations (4) or (5).

These last moments can be given a clear physical meaning; for instance G_o is the fraction of particles leaving the first state that actually reach the second state (a quantity analogous to the Bioavailability as defined in Pharmacokinetics), g_1 is the expected interval of time for a particle to move from the first to the second state, $g_2-f_1/2$ is the variance of this time divided by two, etc. (Rescigno and Michels, 1973).

5. MOMENTS OF A COMPARTMENT

As an example we can evaluate the moments of a specific system. Take a single compartment, i.e. a well mixed pool of homogeneous particles, all with the same probability m.dt of leaving it in the interval from t to t+dt, where m 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 x(t) is the characteristic function of that compartment, i.e. the probability that a particle is in the compartment at time t, then

$$x(t+dt) = x(t).(1-m.dt)$$

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

$$dx/dt = -m.x(t),$$

and integrating,

$$x(t) = x(0).e^{-mt},$$

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

$$X_i = X(0)/m^{i+1}, \quad i=0,1,2,...$$

$$x_i = 1/m^i. \quad i=1,2,3,...$$

6. NON-CONVERGING MOMENTS

In section 3 the moments and relative moments were defined subject to the condition that the integral

$$(6) \qquad \int_0^\infty t^i/i!\ f(t)dt$$

converges; this requires that function f(t) decreases fast enough when t increases. It is well known that most functions used to describe biological systems are of exponential order, i.e. they have the property that a constant c>0 exists such that the product $e^{-ct}f(t)$ is bounded for all values of t larger than some finite value; for a function of exponential order the integral (6) always converges, no matter how large i is. An exception is given by the functions describing a closed system, i.e. a system from where not all particles are eventually lost; in this case

$$\lim_{t\to\infty} f(t) \neq 0,$$

and the integral (6) does not converge for any non-negative value of i. This is an obvious consequence of the fact that the average time spent by a particle in such a system is infinite. We shall not consider this case, but the more interesting case when function g(t), as defined in section 2, is of exponential order, while function f(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 if function f(t) does not approach zero when t goes to infinity, neither function h(t) will; therefore both f(t) and h(t) have undefined moments, while the moments of g(t) are defined, but unknown.

From the hypothesis that f(t) is bounded, it follows that $e^{-ct}f(t)$ is of exponential order for any c>0; equation (1) can be rewritten

$$\int_0^t e^{-c\tau} f(\tau) . e^{-c(t-\tau)} g(t-\tau) d\tau = e^{-ct} h(t),$$

showing that multiplying both f(t) and h(t) by e^{-ct} is equivalent to multiplying g(t) by the same exponential. The new functions $e^{-ct}f(t)$ and $e^{-ct}h(t)$ have finite moments; they can be used to compute the moments of the modified function $e^{-ct}g(t)$; calling G_i^* the moments of this last function, then

$$G_i^* = \int_0^\infty t^i/i! . e^{-ct} g(t) dt$$

$$= \int_0^\infty \sum_{j=0}^\infty (-ct)^j/j! . t^i/i! . g(t) dt$$

$$G_i^* = \sum_{j=0}^\infty (-1)^j c^j (i+j)!/i!j! . G_{i+j}, \qquad i=0,1,2,...$$

and by inversion

$$G_i = \sum_{j=0}^\infty c^j (i+j)!/i!j! . G_{i+j}^*, \quad i=0,1,2,... \tag{7}$$

In the frequent case when the functions f(t) and h(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^{-ct}, where c is the decay constant of the nuclide used. If the "measured" functions f(t) and h(t) are not corrected for the radioactive decay, then the moments G_i^* should be corrected using equations (7); these last corrections are frequently easy because in general the infinite series in (7) converges very rapidly. More important is the fact that the direct correction of f(t) and h(t) for the disintegration rate of the nuclide involves a non-negligible error when that rate is very high (Rescigno and Lambrecht, 1985), as shown in section 7.

7. RECORDING THE MOMENTS

If the functions f(t) and h(t) are known, their moments can be computed using the definitions given in section 3. However, the integrations required for the computation of the moments of any function introduce some errors that are added to the errors intrinsic to the measurement of the original function.

Furthermore, any particle counter has a finite integration time, therefore it does not measure the exact number of particles present at time t, but the average number of particles present in a certain interval of time; this implies a non negligible error when the rate of change of the number of particles to be counted is large compared to the integration time of the counter (Duncan et al., 1983). To have an idea of the errors involved, consider the simple function

$$f(t) = e^{-mt} ;$$

its average value over the interval of time t_1, t_2 is

$$\int_{t_1}^{t_2} e^{-mt} dt/(t_2-t_1),$$

while its value at the center of the interval is

$$\exp[-m(t2-t1)/2];$$

a simple computation shows that the error committed when taking the former expression for the latter is larger than 10% if $t_2-t_1 = 1.6/m$, and is larger than 100% if $t_2-t_1 = 4.4/m$. With tracers having a physical half-life of less than a minute, the acquisition time of a typical tomograph will cause an excessive error in the determination of the true values of the activity.

Both errors can be eliminated if the transformation function ---> moment is bypassed and the moments are recorded directly at the source, i.e. if the detector itself acts as an encoder.

Call X(t) the number of radioactive particles present in a voxel; the probability that an event will be recorded by an appropriate detector in the interval of time from t to t+dt is kX(t), where k is a constant depending upon the efficiency of the detector and upon the disintegration rate of the radiotracer used; the probability of a double event in the infinitesimal time interval dt is an infinitesimal of order higher than dt and can be neglected. The constant k can be determined by measuring for a sufficiently long interval of time a calibrated source.

I shall ignore here the effect of the finite resolving time of the detector, negligible if the counting rate is not too fast.

Define the random variable N(t) equal to the number of events recorded in the interval of time from 0 to t, with distribution

$$p(r,t) = \text{Prob}\{N(t)=r\}.$$

Note that if X(t) is the number of radioactive particles present in a voxel, then X(t) itself is a random variable, because that number depends not only on the macro-processes taking place in that voxel, but also on the number of disintegrations having taken place in the preceding time interval 0, t.

The counter reads zero at the beginning of an experiment; then, each time an event is recorded, the value of the random variable N(t) increases by one unit; it does not change if no events are recorded; therefore

$$p(0,0) = 1$$

$$p(0,t+dt) = [1-kX(t)dt].p(0,t)$$

$$p(r,t+dt) = kX(t)dt.p(r-1,t) + [1-kX(t)dt].p(r,t), \quad r>0$$

Divide by dt,

$$\partial p(0,t)/\partial t = -kX(t).p(0,t)$$