PHYSICS AND RADIATION BIOLOGY

The Derivation of the Gamma-Variate Relationship for Tracer Dilution Curves

Robertson Davenport

University of Michigan Medical Center, Ann Arbor, Michigan

Tracer dilution curves are useful for describing blood flow through vessels and organs. Empirically determined curves for flow through nonbranching vessels have been shown to correspond to a mathematical function called the gamma variate. This paper presents a derivation of the gamma-variate relationship, discusses some of the properties of the gamma variate and its use in problems involving organ blood flow and recirculation.

J Nucl Med 24: 945–948, 1983

The gamma variate is a mathematical function that can be used to describe tracer dilution curves. The expression for a gamma variate is

$$f(t) = \frac{t^{\alpha}e^{-t/\beta}}{\beta^{(\alpha+1)}\Gamma(\alpha+1)} \quad (1)$$

where α and β are parameters ($\alpha > -1$), t is the independent variable, and $\Gamma(\alpha + 1)$ is the gamma function defined by

$$\Gamma(\alpha + 1) = \int_0^{\infty} x^{\alpha}e^{-x}dx \quad (2)$$

(The gamma variate should not be confused with the gamma function, though the two are closely related, as will be shown). Thompson et al. (*1*) showed that gamma variates could be fitted to measured tracer dilution curves with very good agreement, either by the method of least squares or by the method of moments. A family of gamma-variate curves is shown in Fig. 1.

The gamma variate is a well-known function of probability theory. A stochastic model has been proposed to account for its relationship to tracer dilution curves (*2*). The purpose of this paper is to present a deterministic theoretical model from which the gamma-variate relationship is derived. This model allows for a physiological interpretation of the parameters of the function. In addition, it suggests an application to the measurement of organ blood flow.

Received July 13, 1982; revision accepted June 1, 1983.

For reprints contact: Robertson Davenport, Div. of Nucl. Med., University of Michigan Medical Center, Ann Arbor, MI 48109.

DERIVATION

We will begin by assuming that flow in a blood vessel can be modeled as a series of mixing chambers, each completely stirred and of equal volume, V. Let Q be the rate of flow through the vessel. The amount of tracer in a chamber after a small time, Δt, has passed will be equal to the amount in the chamber at time t plus the amount that enters from the previous chamber, minus the amount that flows into the next chamber. If we let D_i designate the amount of tracer in chamber i we then have

$$D_i(t + \Delta t) = D_i(t) + \frac{Q}{V}D_{i-1}(t)\Delta t - \frac{Q}{V}D_i(t)\Delta t. \quad (3)$$

Dividing this equation by V and letting C_i designate the concentration of tracer in chamber i, we have

$$C_i(t + \Delta t) = C_i(t) + \frac{Q}{V}C_{i-1}(t)\Delta t - \frac{Q}{V}C_i(t)\Delta t. \quad (4)$$

This equation may be rearranged to give

$$\frac{C_i(t + \Delta t) - C_i(t)}{\Delta t} = \frac{Q}{V}C_{i-1}(t) - \frac{Q}{V}C_i(t). \quad (5)$$

By taking the limit of Eq. (5) as Δt approaches zero, we have

$$\frac{d}{dt}C_i(t) = \frac{Q}{V}C_{i-1}(t) - \frac{Q}{V}C_i(t) \quad (6)$$

This relationship holds for all chambers but the first. We will assume that the concentration of tracer in the blood flowing into the first chamber is zero. Later the case of

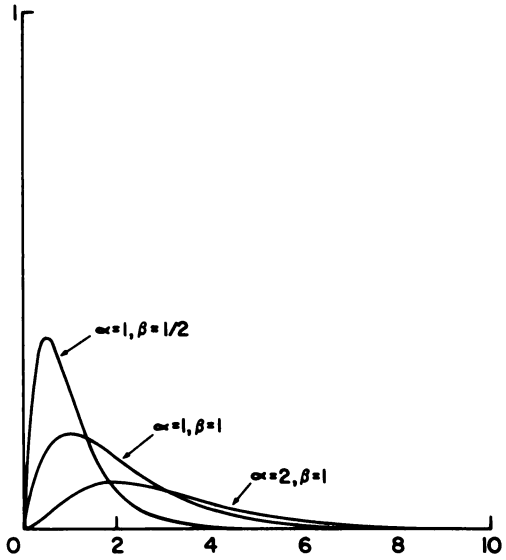

FIG. 1. Family of gamma-variate curves with different values of parameters.

recirculation can be dealt with. For the first chamber we have

$$\frac{d}{dt}C_1(t) = \frac{-Q}{V}C_1(t). \tag{7}$$

The solution to Eq. (7) is

$$C_1(t) = C_0e^{-Qt/V}, \tag{8}$$

where C_0 is an arbitrary constant that will later be determined by normalization. Equation (6) can now be solved iteratively. By substituting the expression for C_1 in the equation for C_2, we have

$$\frac{d}{dt}C_2(t) = \frac{Q}{V}C_0e^{-Qt/V} - \frac{Q}{V}C_2(t). \tag{9}$$

The solution to this is

$$C_2(t) = C_0\frac{Q}{V}te^{-Qt/V}, \tag{10}$$

where C_0 is again an arbitrary constant to be determined by normalization. Using this expression in the equation for C_3, we have

$$\frac{d}{dt}C_3(t) = \frac{Q}{V}C_0\frac{Q}{V}te^{-Qt/V} - \frac{Q}{V}C_3(t), \tag{11}$$

which has the solution

$$C_3(t) = \frac{C_0}{2}\left(\frac{Q}{V}t\right)^2e^{-Qt/V}. \tag{12}$$

This process may be continued. The general pattern that emerges from the above is

$$C_n(t) = \frac{C}{(n-1)!}\left(\frac{Q}{V}t\right)^{n-1}e^{-Qt/V}. \tag{13}$$

It can be verified by direct substitution that Eq. (13) is the solution of Eq. (6).

We can now pass from the discrete case to the continuous case. We will define the continuous parameters α and β to be

$$\alpha = n - 1 \tag{14}$$

$$\frac{1}{\beta} = \frac{Q}{V} \tag{15}$$

The gamma function of Eq. (2) is the continuous analog of the factorial. It can easily be shown through integration by parts that, for integral values n,

$$\Gamma(n) = (n-1)! \tag{16}$$

Making these substitutions in Eq. (13), we have

$$C(\alpha, \beta, t) = \frac{C_0t^\alpha e^{-t/\beta}}{\beta^\alpha\Gamma(\alpha)}. \tag{17}$$

C_0 now can be determined. Since the total amount of tracer injected at the beginning of the vessel is assumed to be unity, we must have

$$\int_0^\infty C(\alpha, \beta, t)dt = 1, \text{ and} \tag{18}$$

by substituting from Eq. (17) we can solve the integral:

$$\begin{aligned}\int_0^\infty C(\alpha, \beta, t)dt &= \frac{C_0}{\beta^\alpha\Gamma(\alpha)}\int_0^\infty t^\alpha e^{-t/\beta}dt \\ &= \frac{C_0\beta}{\Gamma(\alpha)}\int_0^\infty t^\alpha e^{-t}dt = \frac{C_0\beta\Gamma(\alpha+1)}{\Gamma(\alpha)}\end{aligned} \tag{19}$$

Therefore

$$C_0 = \frac{\Gamma(\alpha)}{\beta\Gamma(\alpha+1)}. \tag{20}$$

The final expression is then

$$C(\alpha, \beta, t) = \frac{1}{\beta^{(\alpha+1)}\Gamma(\alpha+1)}t^\alpha e^{-t/\beta}. \tag{21}$$

This is the expression for the gamma variate, which concludes the derivation.

DISCUSSION

Other authors have obtained similar results. Newman (*3*) derived an expression for tracer dilution in a model of central circulation with two mixing chambers, which can be reduced to Eq. (*13*) for the case of n = 2. Sheppard (*2*) has suggested a stochastic model to account for the gamma-variate relationship. In this model the tracer particles are assumed to follow a one-dimensional random walk process through a series of identical mixing chambers. The distribution of tracer can then be shown to satisfy a Poisson distribution

$$C(t) = \frac{t^{n-1}e^{-nt}}{(1/n)^n(n-1)!}, \quad (22)$$

where n is the number of mixing chambers. By making the substitutions

$$\alpha = n - 1, \quad (23)$$

and

$$\beta = 1/n, \quad (24)$$

Eq. (22) can be reduced to a gamma variate. However, this presents a problem with the interpretation of the parameter β. Thompson (*1*) showed that values of β obtained by curve-fitting were all greater than 1, whereas the stochastic model necessitates that they be less than 1, since n is always greater than unity.

The principal advantage of the derivation presented in this paper is the physiologic interpretation of the parameters α and β. From Eq. (14) we see that α designates the number of theoretical mixing chambers, which in turn reflects the degree of turbulance in the flow. It has dimensions of time, and can be thought of as the time required to empty a theoretical mixing chamber at the given flow rate. From Eq. (15) we see that β is the ratio of the volume of a theoretical mixing chamber to the rate of flow. There is no theoretical reason why this value should not be greater than unity, thus obviating the problem of Sheppard.

The parameters α and β are in a sense antagonistic. At a given flow rate, Q, when α is large—meaning that there are relatively more theoretical mixing chambers—β would be expected to be small, since the volume of each chamber relative to the flow would be less. Similarly when α is small, β would be expected to be increased. The tendency for α and β to vary in this inverse way was in fact observed by Thompson et al. (*1*).

Gamma variates probably have their most important use in the interpretation of organ blood-flow studies.

Suppose that a radioactive tracer were injected as a bolus directly into an organ's arterial blood supply. Then a time-activity curve for the organ, f(t), could be generated. In many situations, direct arterial injection is impossible. Instead the tracer is injected somewhere upstream so that the distribution reaching the organ would be described by a gamma variate. The time-activity curve for the organ would then be given by the convolution product

$$f*C = \int_0^t f(t-\tau)C(\alpha, \beta, \tau)d\tau. \quad (25)$$

The time-activity curve can be recovered using the convolution theorem for Laplace transforms. The Laplace transform is defined to be

$$L[f(s)] = \int_0^\infty e^{-st}f(t)dt. \quad (26)$$

The original function, f(t), may be recovered from the L[f(s)] by the inverse Laplace transform

$$f(t) = \int_{C-i\infty}^{C+i\infty} L[f(s)]ds, \quad (27)$$

where the constant C is selected so that the path of integration is to the right of all singularities of L[f] within the complex plane. The convolution theorem states that

$$L[f]L[g] = L[f*g]; \quad (28)$$

therefore

$$f(t) = L^{-1}\left[\frac{L[f*C]}{L[C]}\right], \quad (29)$$

where $L^{-1}[\ ]$ designates the inverse Laplace transform. Since the Laplace transform is closely related to the Fourier transform, an algorithm for evaluating Eq. (29) can readily be implemented on a digital computer. It would enable the measurement of organ's time-activity curves without the distortion caused by dispersion of the tracer bolus in passing through the circulation.

The Laplace transform of a gamma variate can be calculated by

$$\begin{aligned} &L[C(\alpha, \beta, t)] \\ &= \int_0^\infty e^{-st}C(\alpha, \beta, t)dt \\ &= \frac{1}{\beta^{\alpha+1}\Gamma(\alpha+1)}\int_0^\infty e^{-st}t^\alpha e^{-t/\beta}dt \\ &= \frac{1}{\beta^{\alpha+1}\Gamma(\alpha+1)(s+1/\beta)^{\alpha+1}}\int_0^\infty t^\alpha e^{-t}dt \\ &= \frac{1}{(s\beta+1)^{\alpha+1}}. \end{aligned} \quad (30)$$

A consequence of this is that the convolution of two gamma variates with the same β parameter yields another gamma variate. For generality, we will let one of the functions be shifted to the right by a constant T. This corresponds to the situation of two vessels in series. We will make use of the shift property of the Laplace transform. It can be shown by a change of variables that for any function f(t) such that f(t) = 0 for t < 0:

$$L[f(t-T)] = e^{-sT}L[f(t)] \quad (31)$$

for any constant T > 0. Using this and the convolution theorem we have

$$\begin{aligned} &L[(C(\alpha_1, \beta, t)*C(\alpha_2, \beta, t-T))] \\ &\quad = L[C(\alpha_1, \beta, t)]L[C(\alpha_2, \beta, t)]e^{-sT} \\ &\quad = \frac{1}{(s\beta+1)^{\alpha_1+1}}\frac{1}{(s\beta+1)^{\alpha_2+1}}e^{-sT} \\ &\quad = \frac{1}{(s\beta+1)^{(\alpha_1+\alpha_2+1)}}e^{-sT} \\ &\quad = L[C(\alpha_1+\alpha_2+1, \beta, t-T)]. \end{aligned} \quad (32)$$

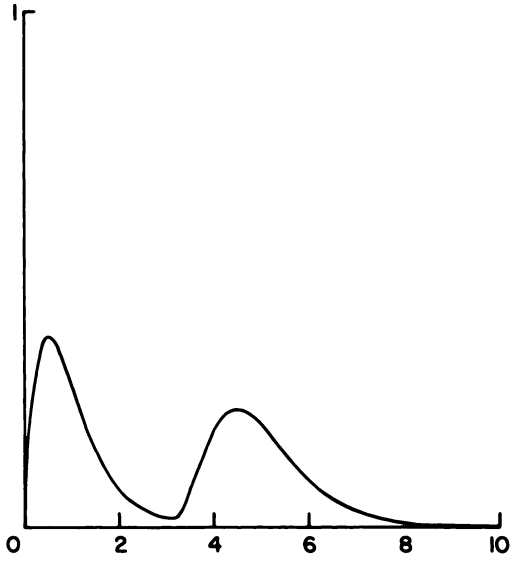

FIG. 2. Illustration of recirculation given by Eq. 36. $\alpha = 1, \beta = 1/2, T = 3$.

Therefore by taking inverse Laplace transforms of both sides of Eq. (32) we have

$$C(\alpha_1, \beta, t)*C(\alpha_2\beta, t - T) = C(\alpha_1 + \alpha_2 + 1, \beta, t - T). \quad (33)$$

This result is just what one would expect intuitively. If we had two vessels in series with the same flow parameter, β, the distribution of tracer at the end of the combined vessel should be described by a gamma variate with an α parameter equal to the sum of those of the two vessels. The fact that the α parameter turns out to be $\alpha_1 + \alpha_2 + 1$ simply indicates that the junction between the two vessels accounts for an additional theoretical mixing chamber.

We can now discuss the effect of recirculation. Suppose that a closed circulatory system is modeled by a single loop with a time delay. The delay, T, represents the transit time for the fluid to make one complete circuit under laminar flow conditions. If a single bolus of tracer were injected into the system, then after one circuit the distribution, D(t), would be given by a gamma variate

$$D(t) = C(\alpha, \beta, t) \quad (34)$$

After two circuits (that is, one recirculation), the distribution would be

$$D(t) = C(\alpha, \beta, t) + C(\alpha, \beta, t)*C(\alpha, \beta, t - T). \quad (35)$$

The first term represents the original bolus. The second term represents the output of the first circuit with delay feeding back into the input of the system. Since the system is linear, the output of a sum of two inputs is just the sum of the individual outputs. Using the convolution relation for gamma variates [Eq. (33)], Eq. (35) reduces to

$$D(t) = C(\alpha, \beta, t) + C(2\alpha + 1, \beta, t - T). \quad (36)$$

This is illustrated in Fig. 2. Similarly, two recirculations would give

$$D(t) = C(\alpha, \beta, t) + C(2\alpha + 1, \beta, t - T) + C(3\alpha + 2, \beta, t - 2T). \quad (37)$$

The general expression for any number of recirculations is clearly apparent.

CONCLUSIONS

The gamma-variate relationship for tracer dilution curves can be derived from a simple deterministic model of flow through a series of mixing chambers. This model gives a physiological interpretation of the two parameters of the gamma variate.

The gamma variate is useful when transform techniques are applied to problems of organ blood flow and recirculation. These theoretical relationships should make the analysis and interpretation of results obtained from tracer dilution methods easier and more rigorous.

ACKNOWLEDGMENTS

The author was supported by a Student Research Fellowship from the Michigan Heart Association. Many thanks to Diane Vecellio for secretarial assistance.

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