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A Stochastic Model for Metabolizing Systems with Computer Simulation

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A stochastic model for a first-order metabolizing system which was studied in the deterministic sense by Branson and others is formulated and a detailed study of the random integral equation arising in the probabilistic model is presented. The equation is used to describe the evolution in time of the amount of metabolite present in the system. Specifically we present a study of the random integral equation of the Volterra type given by

$$M(t;\omega) = M(0;\omega)\,e^{-ct} + \int_0^t R(\tau;\omega)\,e^{-c(t-\tau)}\,d\tau, \qquad t \geqslant 0$$

where $M(t;\omega)$ is an unknown random function giving the amount of metabolite in the system at time $t \geqslant 0$. This equation can be expressed in the general form

$$x(t;\omega) = h(t;\omega) + \int_0^t k(t,\tau;\omega) f(\tau, x(\tau;\omega))\,d\tau, \qquad t \geqslant 0$$

which is of a type whose theoretical aspects have recently been studied by the present authors using as a basis the techniques of probabilistic functional analysis. Conditions are derived under which there exists a unique random solution to the above equation. The usefulness of the model is illustrated using computer simulation by considering a one–organ model, an organ–heart model, and a multicompartment model.

KEY WORDS: Stochastic integral equation; metabolizing system; multicompartment model; chemotherapy; lymphatics; diffusion processes; Volterra; random solution; Lebesgue space; probability measure space; Banach space; Banach's fixed-point theorem; linear operator.

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1. INTRODUCTION

In endeavoring to study any biological or biochemical system, whether it be relatively simple in nature or extremely complex, scientific thought is ceaselessly forging new tools and constructing new models. The aim is always to create more efficient techniques and more realistic models better suited to deal with the problem under consideration than those currently in use. The development of these techniques, of course, owes much to various disciplines but the contribution of probability theory and statistics is particularly important. The scope and applicability of probabilistic models is extremely wide and their use continues to develop rapidly. The purpose of this paper is therefore fourfold:

1. To consider a model of a general metabolizing system which has previously been treated by Branson,[2,3] Wijsman,[12] and Hearon,[4] from a strictly deterministic view point using integral equation techniques.

2. To formulate a random model of the system which we believe to be a more realistic description of the metabolizing process than that offered by the deterministic model.

3. To apply some theoretical techniques pertaining to random Volterra integral equations recently developed by the authors to obtain information concerning the existence and uniqueness of a random solution to the random integral equation which arises in the probabilistic formulation of the model.

4. To illustrate the usefulness of the formulated model using computer simulation by considering a one-organ model, an organ–heart model, and a multicompartment model.

This type of approach has proved successful in the study of similar problems arising in the fields of chemotherapy,[7,8] turbulence theory,[9] and telephone traffic theory.[6]

In Section 2 we shall give a deterministic description of the model and indicate some of the recent effort in the subject area. The proposed stochastic model, the theoretical preliminaries, and main results are given in Sections 3, 4, and 5, respectively. The usefulness of the proposed stochastic model is illustrated by a computer simulation of three basic models, namely a one-organ model, an organ–heart model, and a multicompartment model, in Section 6. In Section 7 we summarize our findings and state certain concluding remarks on the proposed model.

2. THE DETERMINISTIC MODEL

The study of metabolizing systems is of vital concern to biochemists, who have made repeated attempts to describe these systems mathematically. In very general terms, a metabolizing system can be considered as an irregularly shaped region of complex structure where a substance, called the metabolite, is being produced, consumed, transported, modified, or stored.[2] This process involves the synthesis of various compounds which are passed directly or via the lymphatics into the blood stream, in which they are rapidly mixed and then passed either through the capillaries to enter the tissue fluids or to the breakdown sites. The metabolic rates vary greatly, with some molecules traversing the circuit quite rapidly and others more slowly. Thus the multitude and complexity of these diffusion processes, along with fluctuating rates of the molecules, which take place simultaneously in this biological system make a deterministic mathematical description of the metabolizing process virtually impossible and at best highly speculative. Biochemists have, however, made various attempts to describe these reaction systems and have in many instances used as their mathematical models deterministic integral equations.[2–4,12] Integral equation descriptions seem to be especially suited to biological models in that they are well able to handle situations in which the state of the system depends not only on the immediately preceding states but also on all previous states.

Branson[2,3] describes a general metabolizing system using a deterministic integral equation of the Volterra type. The process of interest is the evolution in time of the amount of metabolite in the system. The function of time which describes this evolution shall be denoted by M. Also associated with any metabolizing system will be two functions F and R which we shall call the metabolizing functions. Physically these functions have the following interpretation: $M(t)$ is the amount of metabolite present in the system at time t; $R(t)$ is the rate at which the metabolite is entering the system from the outside at time t; and $F(t - \tau, M(\tau))$ is the fraction left at time t of any amount of metabolite which entered the system at time $0 \leqslant \tau \leqslant t$.

The essential idea in the integral equation description is that the amount of metabolite present in the system at time t is attributable to two sources: the amount remaining from the initial amount present and the amount remaining from that which has entered the system from outside sources at any time $\tau \leqslant t$. Under the assumption that the above is an adequate description of the metabolizing system under study, the following deterministic integral equation was proposed by Branson[2]:

$$M(t) = M(0)F(t, M(0)) + \int_0^t R(\tau)F(t - \tau, M(\tau))\, d\tau, \qquad t \geqslant 0 \qquad (1)$$

The unknown function is M and the equation is of the Volterra type. There has been some question raised as to the general validity of Eq. (1) as a description of an arbitrary metabolizing system,[4,12] but there does seem to be general agreement that it is valid in the case of a first-order reaction. We shall therefore consider this special case in detail.

In the case of a first-order reaction the metabolizing function $F(t-\tau, M(\tau))$ reduces to an exponential function, namely

$$F(t - \tau, M(\tau)) = e^{-c(t-\tau)}, \qquad c > 0$$

In this case Eq. (1) can be written as

$$M(t) = M(0)\, e^{-ct} + \int_0^t R(\tau)\, e^{-c(t-\tau)}\, d\tau, \qquad t \geqslant 0 \tag{2}$$

We shall investigate the random analog to the above equation.

3. THE RANDOM MODEL

The deterministic approach to a metabolizing system essentially assumes that there is one rate function and one metabolizing function associated with the system which together with the initial condition $M(0)$ strictly determine how the metabolite evolves in time. That is, these entities determine a function $M(t)$ and, *ideally speaking*, there is no deviation from this function. The researcher then attempts from experimental data to determine the "true" form for these functions. The usual technique is to obtain at various times of interest several observations on the values of the function $R(t)$, then use as the "true" value some estimate based on these observations, usually the mean. In this way a single approximating curve for $R(t)$ is obtained. This approximation is then used as the true form for $R(t)$ in subsequent work with the model.

The stochastic approach to the problem assumes that if the above procedure were repeated many times, then corresponding to each replication there would arise an approximation for $R(t)$. However, due to the complex and inherently random nature of the metabolizing process, in light of diffusion processes and varying metabolic rates, it is highly likely that the approximating curves so obtained will differ *significantly* from one another *even under the most carefully controlled experimental conditions*. If indeed the variation is large, then there is evidence that there is more than just experimental error entering into the picture and that in fact we are not dealing with a deterministic function but rather with a random one. In this case the use of an approximation for $R(t)$ in the deterministic mathematical model could yield quite unstatisfactory results. Thus it is more realistic and accurate to assume *in the model itself* that the functions involved are indeed random

and search for a random solution to the random integral equation obtained and study its statistical properties.

With this in mind we shall formulate the random analog of equation (2) as follows:

$$M(t;\omega) = M(0;\omega)\, e^{-ct} + \int_0^t R(\tau;\omega)\, e^{-c(t-\tau)}\, d\tau, \qquad t \geqslant 0 \tag{3}$$

where $M(t;\omega)$ is the random function describing the evolution of the system in time and $R(\tau;\omega)$ is the random rate function.

Note that we are actually saying here that for *fixed* t, $M(t;\omega)$ and $R(t;\omega)$ are random variables defined on some underlying complete probability measure space (Ω, A, μ). We shall be interested in determining conditions under which there exists a unique *random solution* to Eq. (3), where by a random solution we mean the following:

Definition 3.1. By a random solution of Eq. (3) we mean a random function $M(t;\omega)$ where for each $t \geqslant 0$, $M(t:\omega)$ has $E\,|\,M(t;\omega)|^2 < \infty$ and satisfies (3) μ-a.e.

With respect to the functions appearing in Eq. (3), we shall make the following assumptions. For each $t \geqslant 0$ the random variable $M(t;\omega)$ has finite variance and there exists a constant Q independent of τ such that $|\,R(\tau;\omega)| \leqslant Q$ μ-a.e. These restrictions are necessary for our theoretical development. Their validity in the physical sense will be commented on later.

4. THEORETICAL PRELIMINARIES

In order to investigate the question of the existence and uniqueness of a random solution to Eq. (3) we shall need to call upon some of the theoretical results pertaining to random integral equations of the Volterra type recently obtained by Tsokos.[11] We shall state here a few pertinent definitions and a theorem relevant to the present problem. For a more complete discussion of the theoretical framework underlying this type of equation the reader is referred to the above-mentioned work.

We shall be concerned with a random integral equation of the Volterra type of the form

$$x(t;\omega) = h(t;\omega) + \int_0^t k(t,\tau;\omega) f(\tau, x(\tau;\omega))\, d\tau, \qquad t \geqslant 0 \tag{4}$$

where (i) $t \to x(t;\omega)$ is a map from R_+, the nonnegative real numbers, into $L_2(\Omega, A, \mu)$, the usual Lebesgue space with respect to the complete probability measure space (Ω, A, μ); (ii) $t \to f(t, x(t;\omega))$ is a map from R_+ into $L_2(\Omega, A, \mu)$;

(iii) $t \to h(t; \omega)$ is a map from R_+ into $L_2(\Omega, A, \mu)$; (iv) $(t, \tau) \to k(t, \tau; \omega)$ is a continuous map from

$$\Delta = \{(t, \tau): \quad 0 \leqslant \tau \leqslant t < \infty\}$$

into $L_\infty(\Omega, A, \mu)$. Note that $L_\infty(\Omega, A, \mu)$ is the usual Lebesgue space of μ essentially bounded functions with respect to (Ω, A, μ). We denote the norm in $L_\infty(\Omega, A, \mu)$ by $|||\cdot|||$.

Definition 4.1. We shall denote by C the Banach space of all continuous and bounded $x(t; \omega)$ from R_+ into $L_2(\Omega, A, \mu)$.

Note that the norm in the space C is defined by

$$\| x(t; \omega)\|_C = \sup_{0 \leqslant t} \{\| x(t; \omega)\|\}$$

where $\|\cdot\| = \|\cdot\|_{L_2(\Omega, A, \mu)}$.

Definition 4.2. We call $x(t; \omega)$ a random solution of Eq. (4) if for each $t \in R_+$, $x(t; \omega)$ is an element of $L_2(\Omega, A, \mu)$ and satisfies (4) μ-a.e.

Definition 4.3. A function $z(t, x)$ mapping $R_+ \times R \to R$ (the reals) is said to be continuous in t uniformly in x if given $t_n \to t$ in R_+ and $\epsilon > 0$, there exists a natural number N_ϵ such that for $n > N_\epsilon$, $| z(t_n, x) - z(t, x)| < \epsilon$ for every $x \in R$.

We now state the following theorem, which will be applicable to our study of Eq. (3). The proof is based on Banach's fixed-point theorem and may be found in the work by Tsokos.[11]

Theorem 4.1. If Eq. (4) satisfies the conditions: (i) there exists a number $A > 0$ such that

$$\int_0^t |||\, k(t, \tau; \omega)|||\, d\tau \leqslant A \qquad \text{for} \quad t \in R_+$$

(ii) $f(t, x)$ is continuous in t uniformly in x from $R_+ \times R \to R$; there exists a constant B such that $|f(t, 0)| \leqslant B$ for $t \in R_+$; and

$$|f(t, x) - f(t, y)| \leqslant \lambda\, |x - y| \qquad \text{for some} \quad \lambda > 0$$

and (iii) $h(t; \omega) \in C$; then there exists a unique random solution $x(t; \omega) \in C$ such that $\| x(t; \omega)\|_C \leqslant \rho$ provided $\| h(t; \omega)\|_C$, λ, and $\| f(t, 0)\|_C$ are sufficiently small.

Note that when we say "sufficiently small" we mean small in the sense that

$$\lambda K < 1 \qquad \text{and} \qquad \| h(t; \omega)\|_C + K \| f(t, 0)\|_C \leqslant \rho(1 - \lambda K)$$

where K is the norm of the linear operator T given by

$$(Tx)(t; \omega) = \int_0^t k(t, \tau; \omega) x(\tau; \omega)\, d\tau$$

5. EXISTENCE OF A RANDOM SOLUTION

In order to use the theoretical results of Section 4 we shall make the following identifications:

$$x(t; \omega) \equiv M(t; \omega), \qquad h(t; \omega) \equiv M(0; \omega)\, e^{-ct}$$
$$k(t, \tau; \omega) \equiv R(\tau; \omega)\, e^{-c(t-\tau)}, \qquad f(\tau, x(\tau; \omega)) \equiv 1$$

In this manner Eq. (3) takes the familiar form

$$x(t; \omega) = h(t; \omega) + \int_0^t k(t, \tau; \omega) f(\tau, x(\tau; \omega))\, d\tau, \qquad t \geqslant 0$$

In order to then apply theorem 4.1 to obtain information concerning the existence and uniqueness of a random solution to Eq. (3) it is necessary to derive conditions under which the basic assumptions of Section 4 and the hypothesis of theorem 4.1 are met. To this end we state the following definition:

Definition 5.1. Let G be a family of functions from a topological space (X, τ) into a metric space (Y, σ). The family is said to be equicontinuous on X if given any $p \in X$, $p_n \to p$, and $\epsilon > 0$, there exists a positive number $N_{\epsilon,p}$ such that $n > N_{\epsilon,p}$ implies that $\sigma[\, g(\, p_n), g(\, p)] < \epsilon$ for all $g \in G$.

Theorem 5.1. If $G = \{e^{-c(t-\tau)} R(\tau; \omega)\colon \omega \in \Omega\}$ is an equicontinuous family of functions from Δ into R, then there exists a unique random solution of Eq. (3) provided $\| M(0; \omega)\, e^{-ct} \|_C$, λ, and $\| f(t, 0)\|_C$ are sufficiently small.

Proof. Fix $t \in R_+$. By assumption $M(t; \omega)$ has finite variance, which implies that for each t, $M(t; \omega) \in L_2(\Omega, A, \mu)$. Since $f(t, x(t; \omega)) \equiv 1$ and (Ω, A, μ) is a probability space and hence a finite measure space, $f(t, x(t; \omega)) \in L_2(\Omega, A, \mu)$ for each $t \in R_+$. Since for fixed t, e^{-ct} is a constant and since $M(0; \omega)$ has finite variance, we can conclude that for each t, $h(t; \omega) \in L_2(\Omega, A, \mu)$

Hence the first three conditions of our theoretical framework are met by the functions of Eq. (3). Now fix $(t, \tau) \in \Delta$.

Recall that $k(t, \tau; \omega) \equiv R(\tau; \omega)\, e^{-c(t-\tau)}$. Since by assumption

$$| R(\tau; \omega)| \leqslant Q, \qquad \mu\text{-a.e.}$$

we have

$$| k(t, \tau; \omega)| = | R(\tau; \omega)\, e^{-c(t-\tau)} | \leqslant Qe^{-c(t-\tau)}, \qquad \mu\text{-a.e.}$$

This implies that $(t, \tau) \to k(t, \tau; \omega)$ is indeed a map from Δ into $L_\infty(\Omega, A, \mu)$. To show that this map is continuous, let $(t_n, \tau_n) \to (t, \tau)$. Choose $\epsilon > 0$. By the equicontinuity condition, there exists an N_ϵ such that $n > N_\epsilon$ implies

$$| e^{-c(t_n-\tau_n)}R(\tau_n ; \omega) - e^{-c(t-\tau)}R(\tau; \omega)| < \epsilon, \qquad \text{each} \quad \omega$$

Thus by definition of the infinity norm, for $n > N_\epsilon$

$$|||\, e^{-c(t_n-\tau_n)}R(\tau_n ; \omega) - e^{-c(t-\tau)}R(\tau; \omega)|||\, < \epsilon$$

However, this simply implies that for $n > N_\epsilon$

$$|||\, k(t_n , \tau_n; \omega) - k(t, \tau; \omega)|||\, < \epsilon$$

as was to be shown.

To show that the hypothesis of theorem 4.1 is satisfied, consider

$$\begin{aligned}
\int_0^t |||\, k(t, \tau; \omega)|||\, d\tau &= \int_0^t |||\, e^{-c(t-\tau)}R(\tau; \omega)|||\, d\tau \\
&= \int_0^t e^{-ct}e^{c\tau}\, |||\, R(\tau; \omega)|||\, d\tau \\
&\leqslant Qe^{-ct} \int_0^t e^{c\tau}\, d\tau = (Qe/c)^{-ct}(e^{ct} - 1) \\
&= (Q/c)(1 - e^{-ct}) \leqslant Q/c
\end{aligned}$$

Since $f(t, x) \equiv 1$, $f(t, x)$ is trivially continuous in t uniformly in x; $B = 1$ will suffice to satisfy the second condition of hypothesis (ii) of theorem 4.1 and

$$| f(t, x) - f(t, y)| = | 1 - 1 | = 0 \leqslant \lambda\, | x - y | \qquad \text{for any} \quad \lambda > 0$$

To see that $h(t;\omega) \in C$, let $t_n \to t$ in R_+ and choose $\epsilon > 0$. If $\| M(0;\omega)\| \neq 0$, choose N such that $n > N$ implies

$$| e^{-ct_n} - e^{ct} | < \epsilon / \| M(0;\omega)\|$$

Then for $n > N$ we have

$$\begin{aligned} \| M(0;\omega)\, e^{-ct_n} - M(0;\omega)\, e^{-ct} \| &= | e^{-ct_n} - e^{-ct} | \, \| M(0;\omega)\| \\ &\leqslant [\epsilon / \| M(0;\omega)\|] \, \| M(0;\omega)\| = \epsilon \end{aligned}$$

If $\| M(0;\omega)\| = 0$, then trivially

$$\| M(0;\omega)e - M(0;\omega)\, e^{-ct} \| < \epsilon$$

Thus $t \to h(t;\omega)$ is continuous from R_+ into $L_2(\Omega, A, \mu)$. To see that the map is bounded, consider

$$\| M(0;\omega)\, e^{-ct} \| = e^{-ct} \| M(0;\omega)\| \leqslant \| M(0;\omega)\|$$

Thus the conditions of theorem 4.1 are satisfied by the functions of Eq. (3) and we can conclude that there exists a unique random solution of Eq. (3) provided $\| h(t;\omega)\|_C = \| M(0;\omega)\, e^{-ct} \|_C$, λ, and $\|f(t,0)\|_C$ are sufficiently small.

Note that when we say that the above quantities are "sufficiently small" we mean small in the sense that

$$\lambda K < 1 \qquad \text{and} \qquad \| M(0;\omega)\, e^{-ct} \|_C + K \|f(t,0)\|_C \leqslant \rho(1 - \lambda K)$$

Note also that

$$\| M(0;\omega)\, e^{-ct} \|_C = \sup_{0 \leqslant t} e^{-ct} \| M(0;\omega)\| = \| M(0;\omega)\|$$

and that $\|f(t,0)\|_C = 1$. Hence we are actually requiring that

$$\lambda K < 1 \qquad \text{and} \qquad \| M(0;\omega)\| + K \leqslant \rho(1 - \lambda K)$$

Since in this case λ can be any positive number, the first condition can easily be satisfied. Hence we will have a unique random solution $M(t;\omega)$ such that for each t

$$E \, | M(t;\omega)|^2 \leqslant \rho$$

provided that

$$E \, | M(0;\omega)|^2 \quad \text{sufficiently small}$$

6. COMPUTER SIMULATION

In order to obtain graphical representations for this biochemical process utilizing its stochastic implications, data have been generated through random simulations. Three basic models, each successively more general, were employed to depict various aspects of the physical system.

Case 1. A one-organ system (Fig. 1), whose input was subjected to an internal exponential diffusion process, is investigated. The input concentration $Ke^{-\alpha t}$ with K the initial metabolite level is shown by Fig. 2; the concentration rate of change, that is, the input minus the output with respect to time is depicted by Fig. 3; and the organ's emission is given by Fig. 4. Finally, the metabolite concentration is shown in Fig. 5.

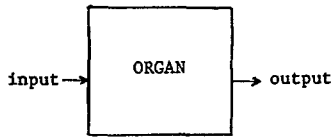

Fig. 1. One-organ model.

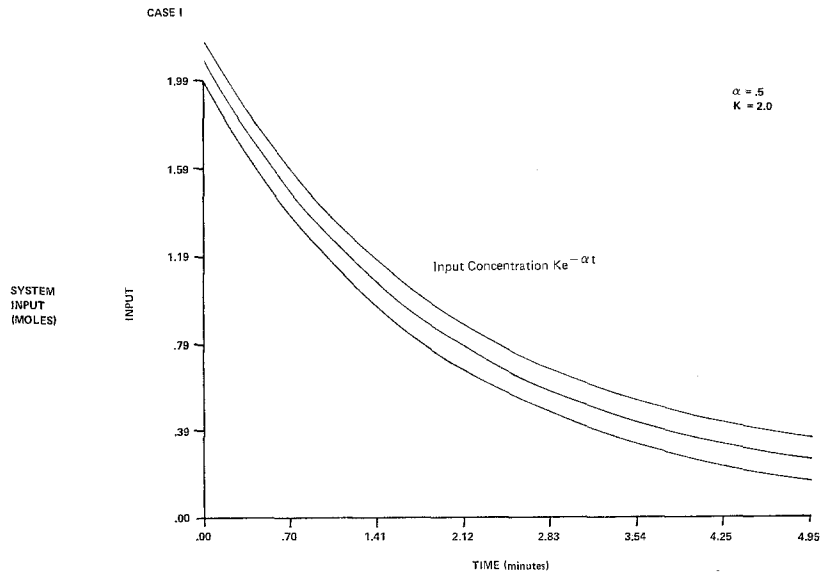

Fig. 2. Input concentration $Ke^{-\alpha t}$ with $K = 2.0$, $\alpha = 0.50$.

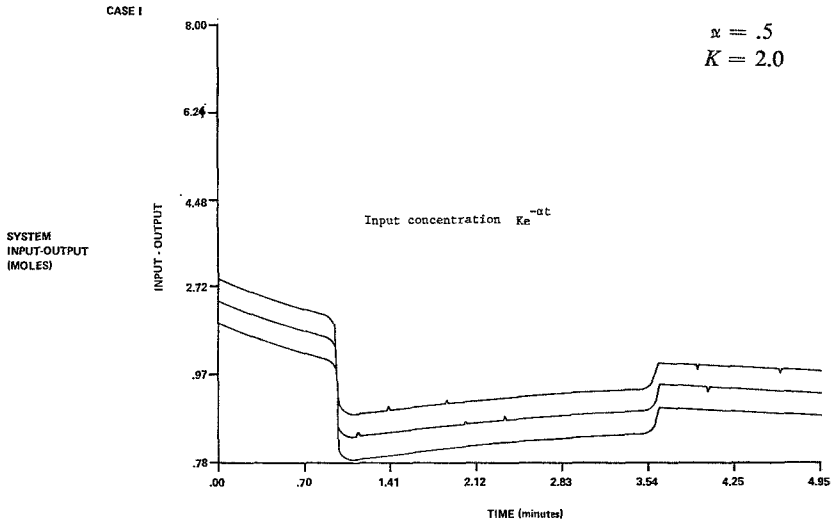

Fig. 3. Rate of change of metabolite for single-organ model.

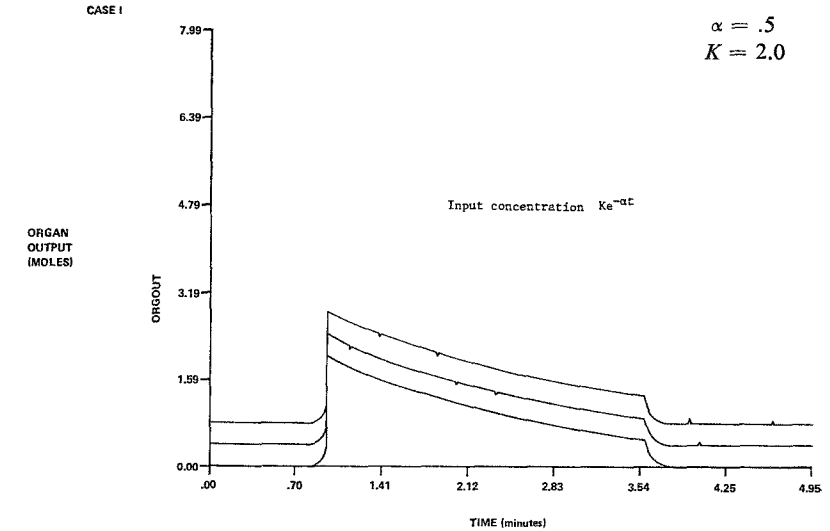

Fig. 4. Organ output with respect to time for one-organ model.

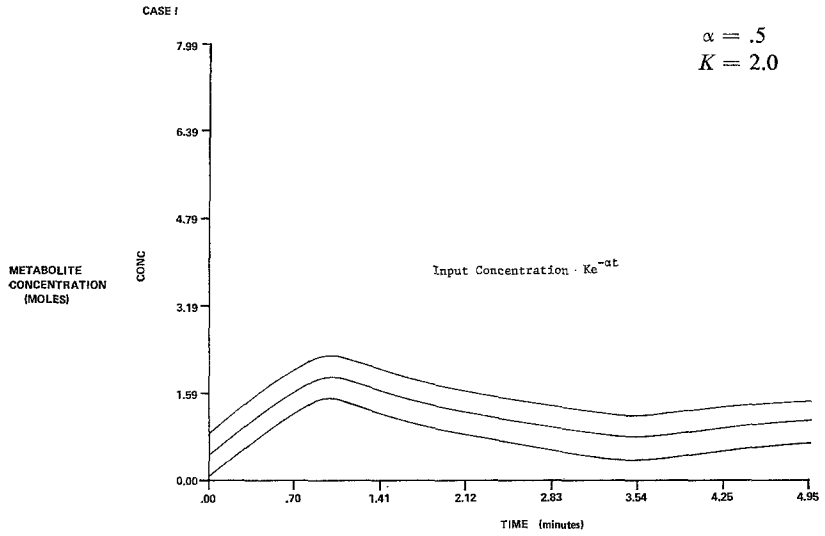

Fig. 5. Metabolite concentration for one-organ system.

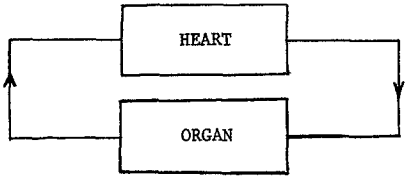

Fig. 6. Organ–heart model.

Case II. An extension of the one-organ model includes the heart as a pumping station (Fig. 6), along with a time lag effect between heart and organ. Two variations of this model are studied depending on the time interval of the initial injection. At first the injection is administered for a short, specified interval, and second, it is administered continuously throughout the period of observation. In the former case the concentration rate of change, organ output, and metabolite concentration are shown by Figs. 7, 8, and 9, respectively, and in the latter instance, in Figs. 10, 11, and 12, respectively.

Case III. A more sophisticated and biologically accurate model is schematically given by Fig. 13. The metabolite is synthesized in the liver and passed into plasma from which it either is excreted or continues to the interstitial sites, the tissue fluids. In the latter instance the metabolite returns to plasma and is recirculated. In each of the above compartments a Brownian-type diffusion process occurs. That is, the metabolite in each compartment

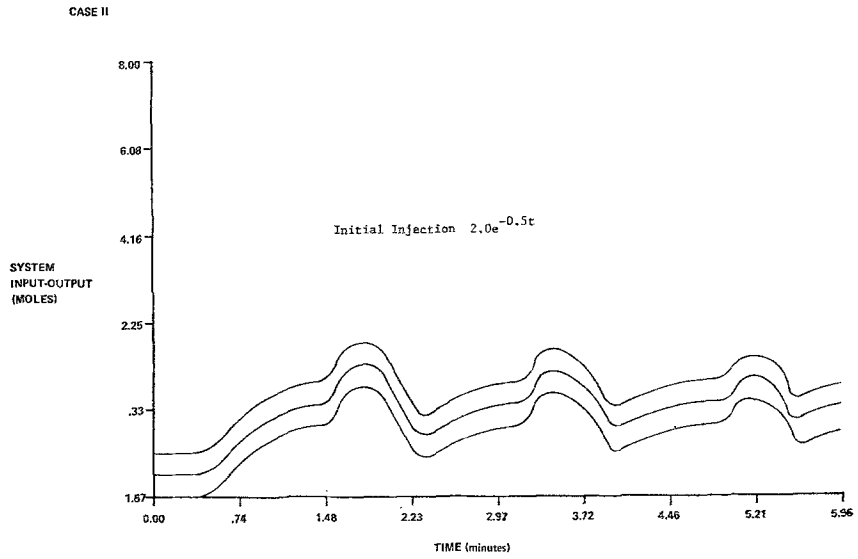

Fig. 7. Rate of change of metabolite for heart–organ model with initial injection of 2.0 moles for 0.50 min.

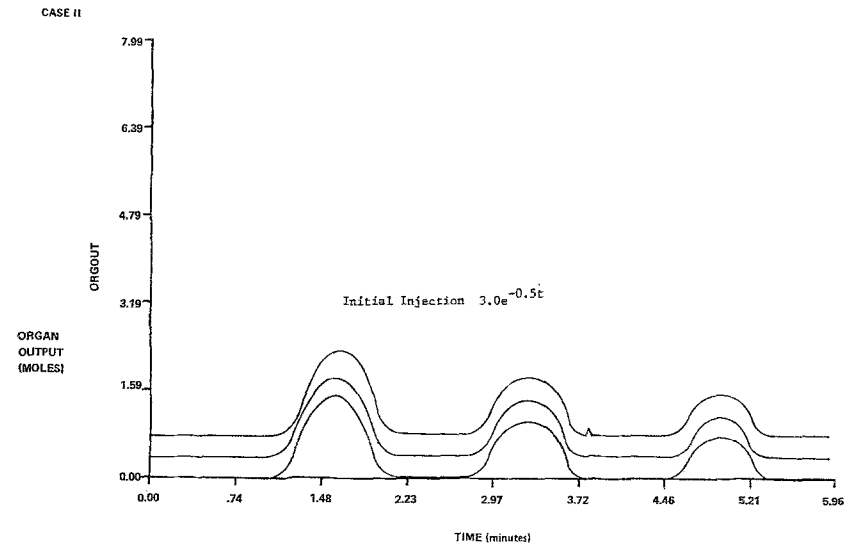

Fig. 8. Organ emission with respect to time for heart–organ system with initial injection of 2.0 moles for 0.50 min.

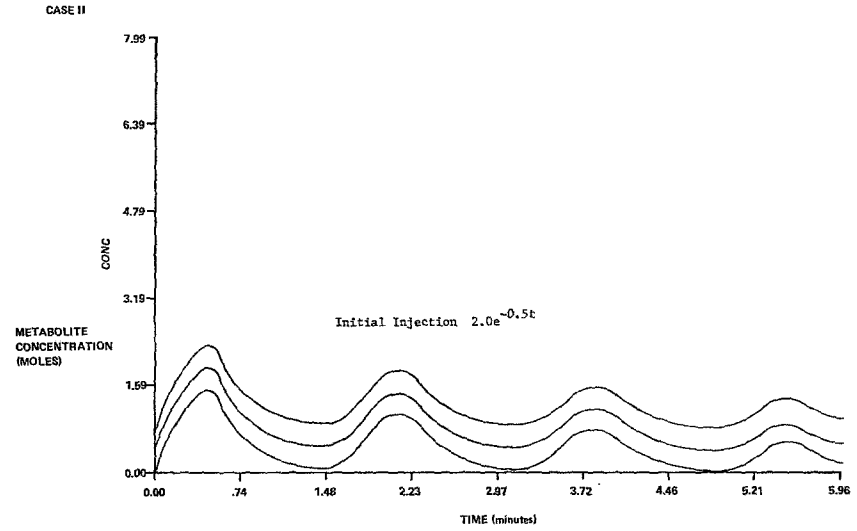

Fig. 9. Metabolite concentration for heart–organ model with initial injection of 2.0 moles for 0.50 min.

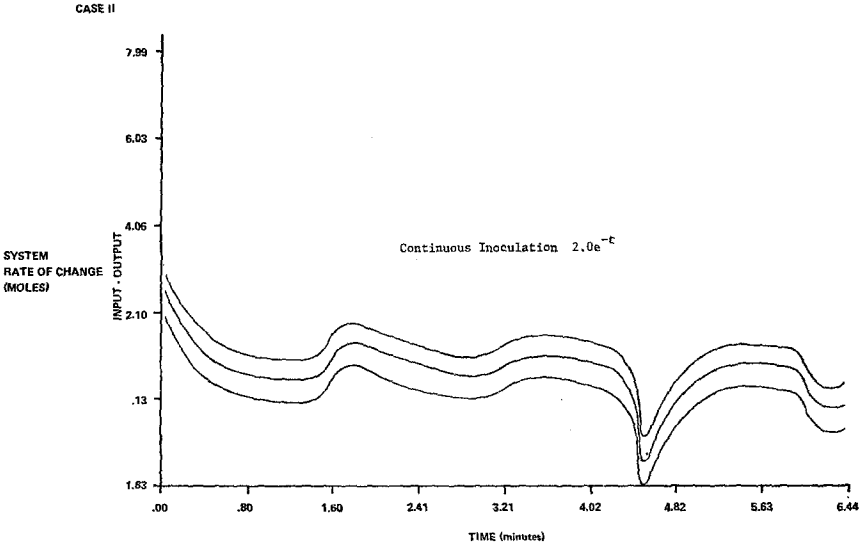

Fig. 10. Rate of change of concentration for heart–organ model with continuous inoculation.

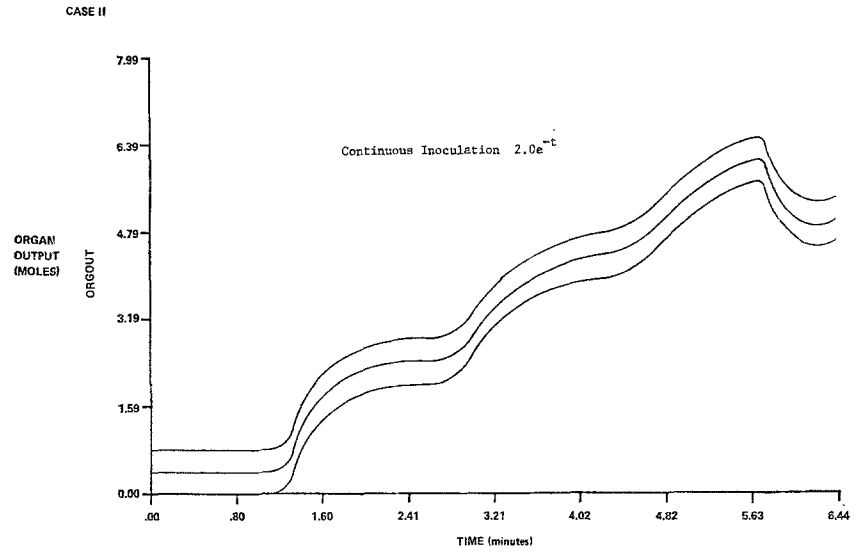

Fig. 11. Organ emission for heart–organ system with continuous inoculation.

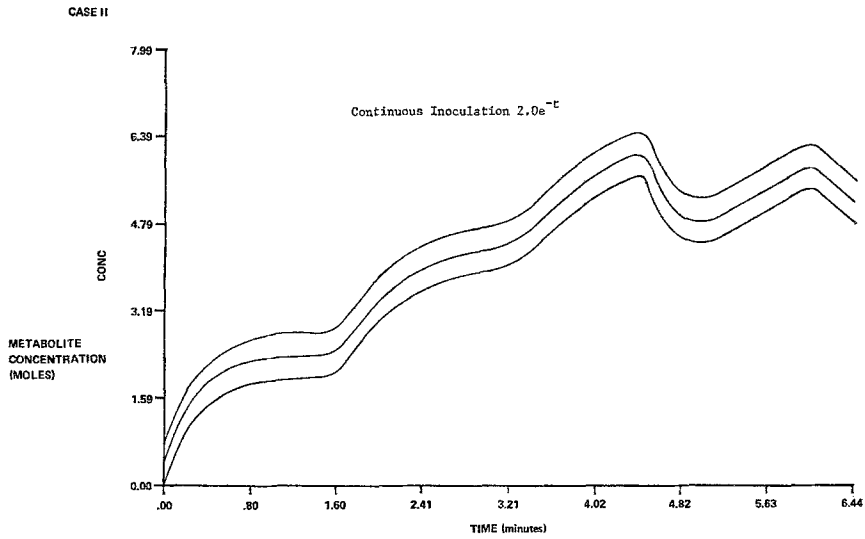

Fig. 12. Metabolite concentration for heart–organ system with continuous inoculation.

undergoes an exponential diffusion process. The input to the liver, plasma, and tissue fluids is depicted by Figs. 14, 15, and 16, respectively, while the output from these chambers is shown by Figs. 17–19. The metabolite concentration is given by Fig. 20 and the various rates of change for each compartment are shown in Figs. 21–23.

7. SUMMARY AND CONCLUDING REMARKS

We have been forced due to mathematical considerations to make several assumptions concerning the random functions $M(t; \omega)$ and $R(t; \omega)$. Namely we assume that $\{M(t; \omega): t \in R_+\}$ is a second-order stochastic process and that for each t, $R(t; \omega)$ is μ-essentially bounded and furthermore that the bound is uniform over R_+. These restrictions make our particular approach to the problem possible. Although these restrictions appear on the surface

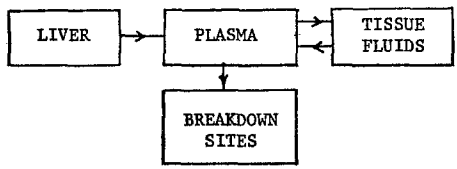

Fig. 13. Multicompartment model.

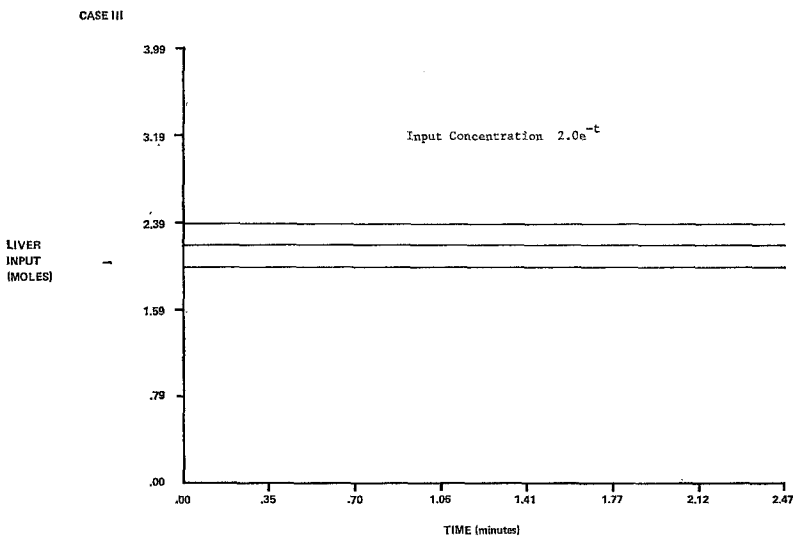

Fig. 14. Input to liver using 2.0 moles concentration in multicompartment model.

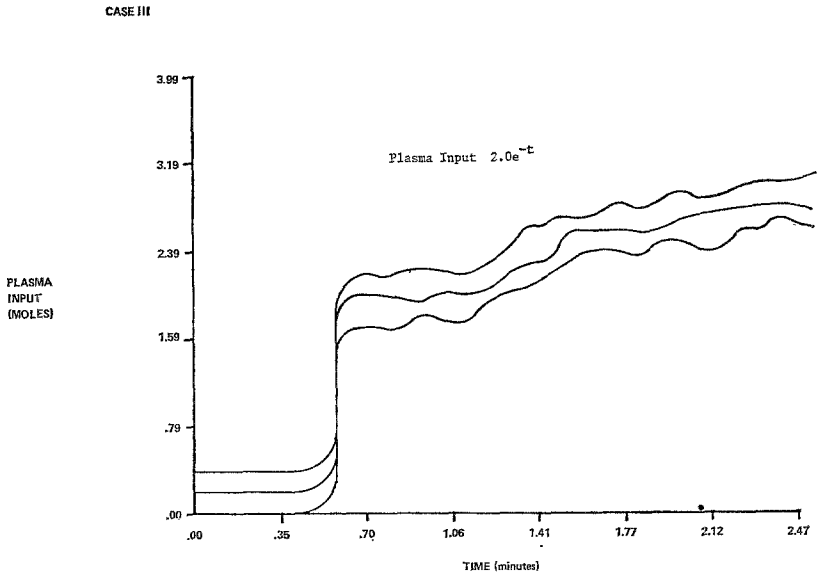

Fig. 15. Plasma input for multicompartment model.

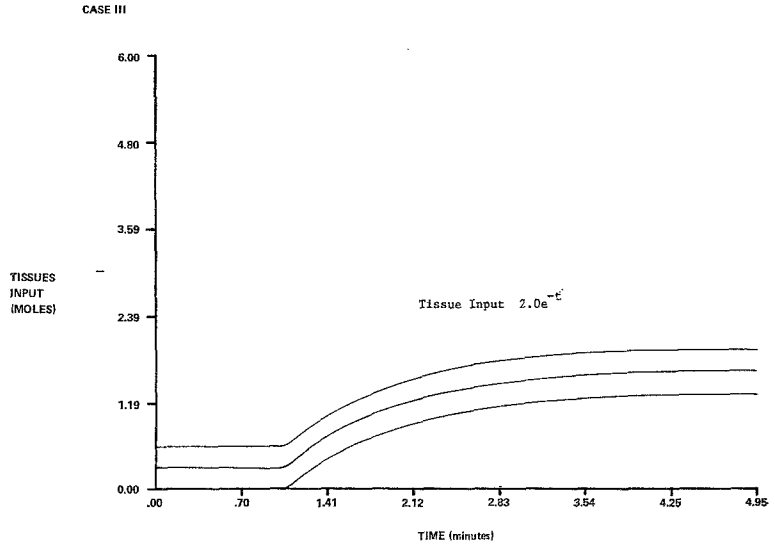

Fig. 16. Tissue input for multicompartment model.

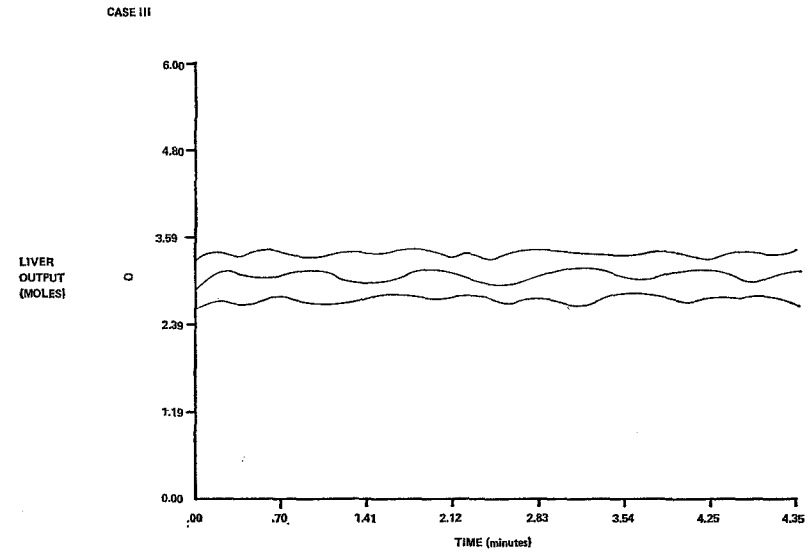

Fig. 17. Liver output for multicompartment model.

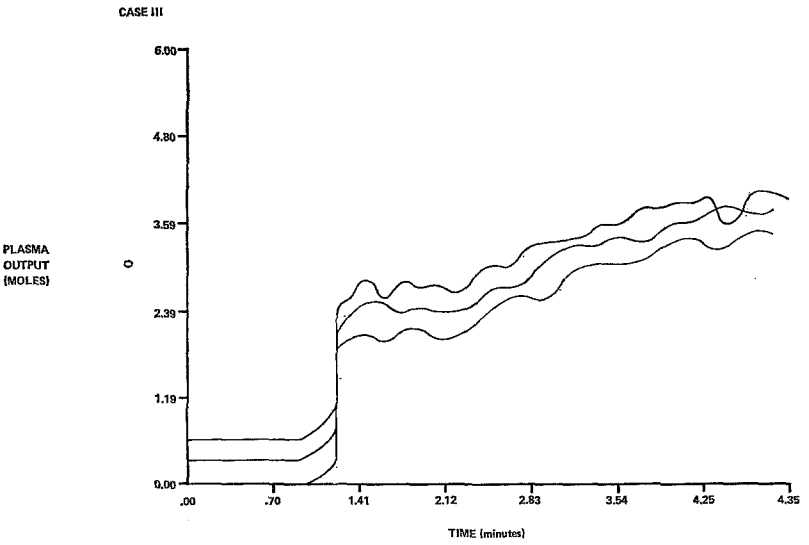

Fig. 18. Plasma output for multicompartment model.

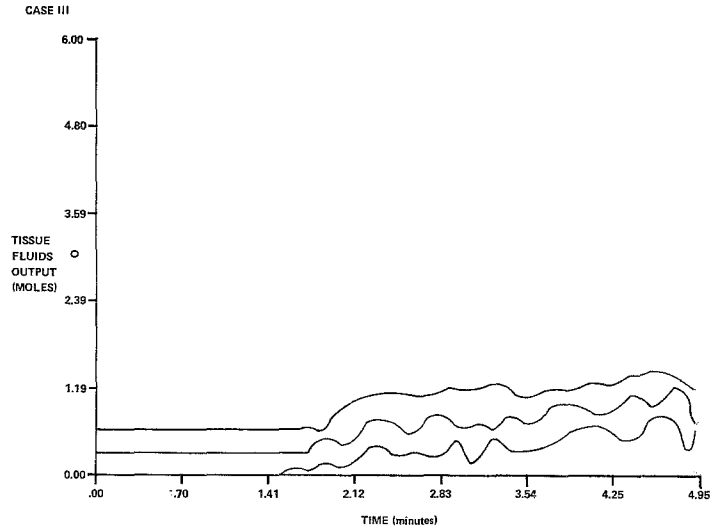

Fig. 19. Tissue output for multicompartment model.

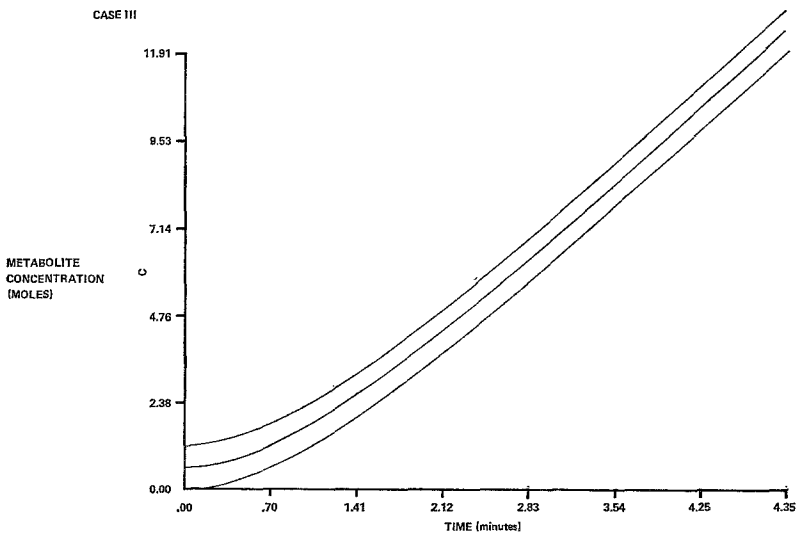

Fig. 20. Cumulative metabolite concentration in multichamber system.

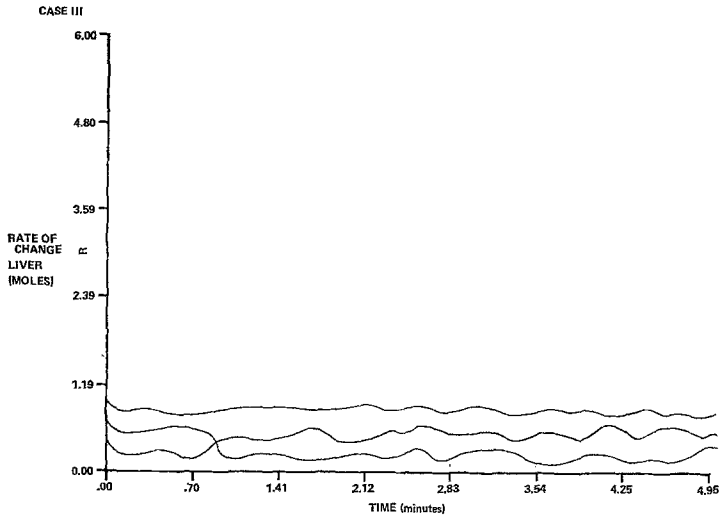

Fig. 21. Concentration rate of change with respect to the liver.

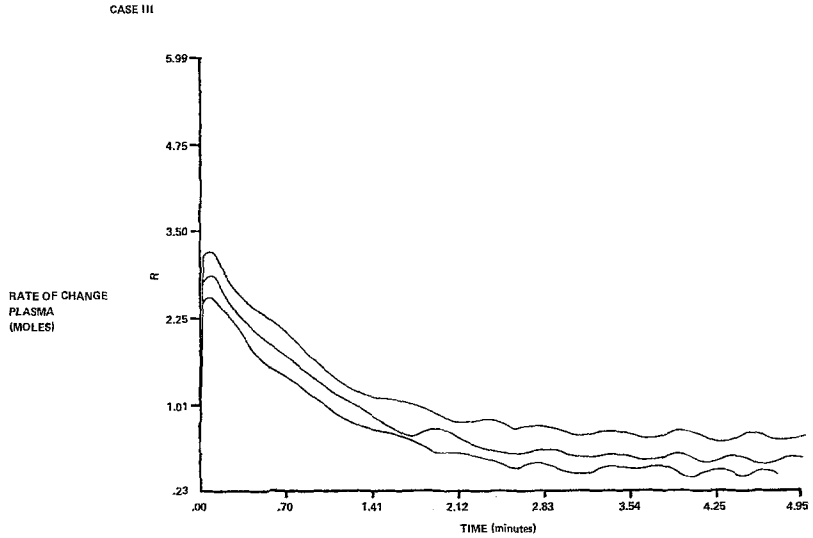

Fig. 22. Concentration rate of change with respect to the plasma.

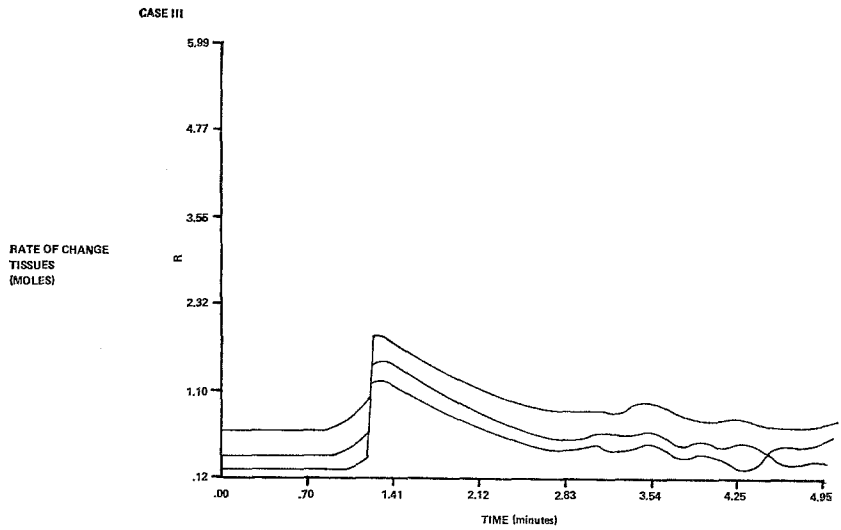

Fig. 23. Concentration rate of change with respect to the tissue fluids.

to be quite strong, in practice they are in many cases easily satisfied due to the physical or chemical characteristics of the system under study. The assumption that $M(t; \omega) \in L_2(\Omega, A, \mu)$ for each $t \in R_+$ is implied by the biological limitations of the physical metabolic process. Also, within a given system the metabolic rate is bounded for each $t \in R_+$ as a result of the occurring physical and chemical reactions.

To demonstrate the accuracy and usefulness of our procedure, we have investigated several models through the utilization of random computer simulations. Graphs were presented depicting the various resultant phenomena using different random generators.

Figure 2 depicts the input concentration $Ke^{-\alpha t}$ with $K = 2.0$ moles and $\alpha = 0.5$. The concentration rate of change, given by Fig. 3, and the organ output, given by Fig. 4, result from the exponential nature of the injected metabolite. After an initial interval, dependent upon the organ length, the graphs demonstrate the anticipated exponential characteristics. That is, the organ emission commences following a small delay due to the metabolite's passage through the organ and then declines gradually indicating the decreasing exponential form of the input concentration. The metabolite concentration, Fig. 5, starts at the origin and increases to a peak which runs at approximately the same time as the organ output commences. At this moment, due to the decreasing functional input, the concentration begins to taper with a small trough occurring at the end of the output interval from which the graph, again, tends to zero.

Varying the model to include the heart as the pumping agent within a one-organ cycle, Fig. 6, the effect of two types of input concentration were investigated. First, the injection was administered for a time interval less than that required to complete the system cycle in order to depict the long-range diffusion behavior of a single inoculation. The graphs (Figs. 7–9) demonstrate the involved diffusion process through the observed dampening effect upon the metabolite concentration allowing for the cycle time lag. The final concentration, Fig. 9, slowly tends toward zero with respect to time, showing the physical and biological utilization of the metabolite by the body. This effect is clearly indicated by examining Fig. 8, the metabolite concentration leaving the organ, which exhibits a gradual decline adjusted for cycle length.

In order to study the continuing aspects of this biological process, the initial infusion was considered to occur for several transversals of the heart–organ cycle with termination prior to the end of observation time. Figures 10–12 depict at equal intervals the concentration increase due to the continued injection of metabolite. After terminating the inoculation period it is seen that the process reverts to that investigated prior in Figs. 7–9. Again the inherent diffusion process is observable in the dampening nature of the metabolite found in the various parts of the biochemical system.

Finally, a more general model was studied, Fig. 13, in an attempt to consider a more complete biological setting. We investigated the interchange of metabolite between the blood and tissue fluids. The metabolite was injected into the system on a continuous basis and the concentration at various positions in the model tabulated graphically. These graphs (Figs. 14–23) depict the inherent physical and biochemical characteristics of metabolic distribution processes as seen above and thus the scientist is permitted to extend the system to include more relevant details without the loss of any pertinent results.

In conclusion let us say that the proposed random model is, we believe, a more realistic description of a general first-order metabolizing system than is the deterministic formulation and should be used whenever possible. A major point to be made is that if a deterministic model is used when in fact the functions involved are random, then the results obtained could be quite unrealistic; however, if a stochastic model is used when a deterministic model would suffice, then nothing is lost.

The scope of the model is not restricted to the study of metabolizing systems; it can be very easily adopted to be applicable to many other problems—for example, it can be used to study pollution in a lake.

REFERENCES

1. R. Bartle, *The Elements of Integration*, Wiley, New York (1966).
2. H. Branson, The use of isotopes in an integral equation description of metabolizing systems, *Cold Spring Harbor Symp. Quant. Biol.* **XIII**:35–42 (1948).
3. H. Branson, The kinetics of reactions in biological systems, *Arch. Biochem. Biophys.* **1952**:36.
4. J. Hearon, A note on the integral equation description of metabolizing systems, *Bull. Math. Biophys.* **1953**:15.
5. J. Horváth, *Topological Vector Spaces and Distributions*, Addison-Wesley, Reading, Massachusetts (1966).
6. W. J. Padgett and C. P. Tsokos, On a stochastic integral equation of the Volterra type in telephone traffic theory, *J. Appl. Probability* **1971** (June).
7. W. J. Padgett and C. P. Tsokos, On a semi-stochastic model arising in biological systems, *Int. J. Math. Biosci.* **1971** (February).
8. W. J. Padgett and C. P. Tsokos, Stochastic model for chemotherapy: computer simulation, *Int. J. Math. Biosci.* **1971** (April).
9. W. J. Padgett and C. P. Tsokos, On the existence of a solution of a stochastic integral equation in turbulence theory, *J. Math. Phys.* **1971** (February).
10. H. L. Royden, *Real Analysis*, Macmillan, New York (1963).
11. C. P. Tsokos, On a stochastic integral equation of the Volterra type, *Math. Systems Theory* **1969**:3.
12. R. Wijsman, A critical investigation of the integral description of metabolizing systems, *Bull. Math. Biophys.* **1953**:15.
13. K. Yosida, *Functional Analysis*, Springer-Verlag, Berlin–Heidelberg–New York (1965).