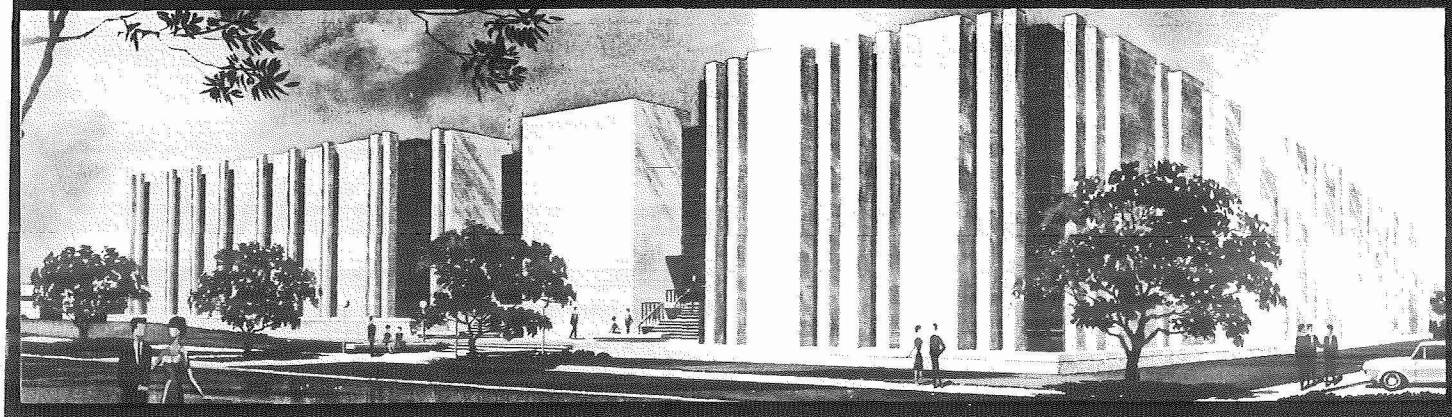
AN EXAMPLE OF AGE DEPENDENCY IN COMPARTMENTAL ANALYSIS

by

J. H. Matis

TRAINING & RESEARCH

GRADUATE INSTITUTE OF STATISTICS



TEXAS A&M UNIVERSITY · COLLEGE STATION

AN EXAMPLE OF AGE DEPENDENCY IN COMPARTMENTAL ANALYSIS

J. H. Matis

Institute of Statistics
Texas A&M University

Technical Report #6
National Aeronautics and Space Administration
Research Grant NGR 44-001-097

March 1971

AN EXAMPLE OF AGE DEPENDENCY IN COMPARTMENTAL ANALYSIS

by

J. H. Matis
Institute of Statistics
Texas A&M University

Summary

Although it has been widely recognized that many compartmental systems are not "in steady state", the lack of such assumption leads to mathematical difficulties in the solution of the model. Such models are studied by numerical methods, for example by the analog computer, but closed solutions to the differential equations which would then permit parameter estimation are rare.

The present report contains a compact analytic solution to the distribution theory of a particular nonsteady state model. The application of the solution is then illustrated with biological data.

1. Introduction

The concept of steady state compartmental analysis has gained wide acceptance in the modelling of biological passage or "clearance". Compartmental analysis proposes that many biological systems may be divided into "compartments" through which materials are transferred, and the steady state provision specifies that this transfer process is characterized by linear kinetics (see e.g. Sheppard [1962]). The rate of flow between any two compartments is described by an unknown transfer rate coefficient which according to linear kinetics is constant over time. These coefficients combine into a sums of exponentials function which then describe passage through the whole system. Data fitted to the sums of exponentials function estimate the rate parameters of a compartmental model.

The lack of a detailed causative mechanism of transfer motivated the "more realistic" incorporation of stochastic behavior to the above steady state analysis (Matis and Hartley [1971]). The probabilistic considerations produced the same sums of exponentials "regression" function as before for the mean value function, but a new estimation procedure was suggested in light of the structure of stochastic error.

The present paper contributes a generalization of a stochastic compartmental model by including a form of nonlinear flow kinetics. Whereas steady state analysis specifies a constant rate coefficient, or equivalently that the lifetimes of particles within compartments follow a negative exponential distribution, the subsequent sections introduce the more general gamma distribution of lifetimes. The report contains the explicit solution of only a particular two compartment model with such lifetimes as an answer to a practical problem; a later report will spell out the complete generalization to an arbitrary n compartment system and will show its relationship to other biomathematical models.

A biological example is included to demonstrate vividly the requirement for nonlinear analysis on the basis of a priori physiological considerations. Moreover, subsequent analysis of the data also illustrates the recognition of such a non-steady state phenomenon.

2. Application

Physiologically, the assumption necessary for linear kinetics, or the constant rate coefficient, is the "random appearance and disappearance of molecules" within the compartments (Zilversmit, et al. [1945]). Although some compartmental systems

have been found to closely satisfy this stipulation (most notably the flow of potassium, K^{42}, between blood plasma and red blood cells), probably the majority do not, either because of incomplete mixing within the compartments or as a result of "age" dependency of the particles. Hence the application of such a non-steady state model would seemingly be as widespread as the use of the usual compartmental analysis which already encompasses a host of bio-medical fields (see e.g. Shepard [1962]).

Consider, for example, the flow of iron in the body. Iron, as well as many other elements, is incorporated into the red blood cell "compartment" and thereby does not "disappear" in a "random" fashion but rather its disappearance is related to the lifetime of the red blood cell. Passage through membranes or orifices are typically time dependent also. This is illustrated at some length in this report by the example of passage through the gastro-intestinal tract of ruminants. Data is conveniently available for this latter application but the techniques, of course, would apply to all similar time dependent systems in any field.

Blaxter [1956] proposed a two compartment model for the passage of particles through the gastro-intestinal tract of ruminants, and the stochastic modelling of Matis and Hartley [1971] (henceforth denoted MH) also confirms the adequacy of the two compartments. The rate coefficients for the passage of many substances, e.g. water soluble isotopes and small indigestible plastic beads used as roughage substitute, are readily accepted to be independent of time with resultant steady state conditions.

It is hypothesized, however, that the passage of hay particles proceeds quite differently inasmuch as such particles undergo physical alteration associated with digestion in the rumen. Since the probability of passage through the rumen orifice increases as the particle's size decreases, and its size is in turn a function of its

"age" in the rumen, age dependency of rate coefficients arises in a natural manner through digestion. The incomplete mixing in the rumen due to the elongated particle size is also thought to contribute to time dependency.

This report assumes that the lifetimes in the rumen follow a gamma probability distribution. Not only is the gamma distribution a rich family of curves with the desired range but its choice will be supported experimentally in subsequent considerations.

In summary, the physiology of the gastro-intestinal tract suggests the study of a two compartment model where gamma time dependency is incorporated into the first compartment. The following section contains the full statistical solution of the above model, and the last section analyzes data from a passage experiment.

3. Solution of Stochastic Model

3.1 Partial Differential Equation for the Generating Function

Consider the two compartment model of Figure 1, where the lifetimes in the first compartment are distributed according to the gamma law $\Gamma(n, \lambda_1)$ and in the second according to the exponential law $E(\lambda_2)$. Let $\eta_i(0)$ be the known number of "labelled" particles introduced into compartment i at time 0 and let $\eta_i(t)$ be the random variable specifying the number of particles in compartment i at time t. The statistical problem is to

$$\boxed{\Gamma(n, \lambda_1)} \rightarrow \boxed{E(\lambda_2)} \rightarrow$$

Figure 1

determine the probability distribution over time of $\eta_i(t)$ for $i = 1, 2$.

According to well-known theory (see e.g. Parzan [1962]), a necessary and sufficient condition for a random variable to be exponentially distributed is the stipulation that the random variable "lacks a memory", i.e. X is exponentially distributed if and only if the conditional probability $P(X > t + \Delta t \mid X > t)$ equals the unconditional probability $P(X > \Delta t)$. This property enables one to treat all particles in compartment 2 alike regardless of their "time of arrival". The transfer probabilities are thus independent of time and the same for each of the $\eta_2(t)$ particles.

The gamma distribution of compartment 1 does not follow the above steady state theory, yet $\Gamma(n, \lambda_1)$ lifetimes may be generated by summing n independent exponential random variables, each with parameter λ_1. This artifice transforms the system of Figure 1 to that of Figure 2, where n exponential subcompartments are embedded in compartment 1, and thus much of the previous stochastic steady state formulation and some of the solution are applicable to the present problem.

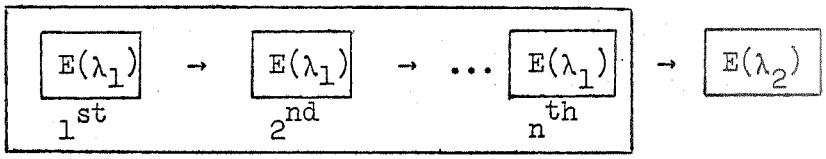


Figure 2

It should be noted that often, as in the present application, the original compartments have a physiological interpretation but the n pseudo-compartments merely generate desired liftime distributions.

It is now convenient to define n + 1 random variables so that at time t the number in compartment 2 is $N_1(t)$, the number in subcompartment n is $N_2(t)$, and so forth until the number in subcompartment 1 is $N_{n+1}(t)$. Let $K(\theta_1, \theta_2, \ldots, \theta_{n+1}, t)$ be the cumulant generating function of these random variables. Either the application of rules-of-thumb developed by Bailey

[1964] or reference to a detailed derivation by MH indicates the following equation for the present model,

$$\frac{\partial K(\theta_1, \theta_2 \cdots \theta_{n+1}, t)}{\partial t} = \lambda_1 \sum_{i=2}^{n+1} (e^{-\theta_i + \theta_{i-1}} - 1) \frac{\partial K}{\partial \theta_i} + \lambda_2 (e^{-\theta_1} - 1) \frac{\partial K}{\partial \theta_1} \tag{1}$$

with the initial condition

$$K(\theta_1, \theta_2, \ldots, \theta_{n+1}, 0) = \eta_1(0)\theta_{n+1} + \eta_2(0)\theta_1 . \tag{2}$$

3.2 Solution for the Generating Function

The linear partial differential equation (1) subject to constraint (2) will now be solved via characteristic theory (see e.g. Ford [1955]) to establish the stochastic model. According to the theory, the n+2 characteristic differential equations of (1), which are

$$\frac{d\theta_1}{dt} = \lambda_2(1 - e^{-\theta_1}) ,$$

$$\frac{d\theta_i}{dt} = \lambda_1(1 - e^{-\theta_i + \theta_{i-1}}) \quad \text{for } i = 2, \ldots, n+1, \tag{3}$$

and

$$\frac{\partial K(\theta_1, \ldots, \theta_{n+1}, t)}{dt} = 0 ,$$

must first be solved in terms of n+2 independent integrals or "characteristic curves", say $\mu_i(\theta_1, \theta_2, \ldots, \theta_{n+1}, t) = c_i$ where c_i is a constant. The relation $\Gamma(\mu_1, \mu_2, \ldots, \mu_{n+2}) = 0$, or equivalently $\mu_{n+2} = \varphi(\mu_1, \mu_2, \ldots, \mu_{n+1})$, where Γ and φ are arbitrary functions is then true and determines the function $K(\theta_1, \theta_2, \ldots, \theta_{n+1}, t)$ when investigated in light of the initial condition $K(\theta_1, \theta_2, \ldots, \theta_{n+1}, 0)$.

The last equation of (3) has solution $K = c_{n+2} = \mu_{n+2}(\theta_1, \theta_2, \ldots, \theta_{n+1}, t)$, and the first n+1 may be transformed to a system of non-homogeneous linear equations by the relation $v_i = e^{\theta_i}$. These transformed equations are

$$\frac{dv_1}{dt} = \lambda_2 v_1 - \lambda_2 \tag{4}$$

and

$$\frac{dv_i}{dt} = \lambda_1(v_i - v_{i-1}) \quad \text{for } i = 2, \ldots, n+1 .$$

Note that the particular solution $v_i = 1$, for $i = 1, \ldots, n+1$, satisfies the above equations.

In the previous work of MH the coefficient matrix of the complimentary homogeneous system was assumed to have unequal eigenvalues. Since these eigenvalues are functions of the data, the assumption holds with probability 1. The present system, however, differs in that n eigenvalues are known equal by design.

The complete solution to equations (4) is found by successive integration to be

$$v_1 = e^{\theta_1} = c_1 e^{\lambda_2 t} + 1$$

and

$$v_i = e^{\theta_i} = e^{\lambda_2 t} c_1 \left(\frac{-\lambda_1}{\lambda_2 - \lambda_1}\right)^{i-1} + e^{\lambda_1 t} \sum_{j=0}^{i-2} c_{i-j} \frac{(-\lambda_1 t)^j}{j!} + 1 \tag{5}$$

$$\text{for } 2 \leq i \leq n+1 .$$

The n+2 independent integrals are equated now by the functional relationship

$$K(\theta_1, \theta_2, \ldots, \theta_{n+1}, t) = u_{n+2} = \varphi[u_1, u_2, \ldots, u_{n+1}] \tag{6}$$

from whence the function φ may be identified by the initial condition. Solving for θ_i in equations (5) when $t = 0$, and substituting into initial condition (2), one has

$$K(\theta_1, \theta_2, \ldots, \theta_{n+1}, 0) = \eta_1(0) \ln[c_1(\frac{-\lambda_1}{\lambda_2 - \lambda_1})^n + c_{n+1} + 1] + \eta_2(0) \ln [c_1 + 1] . \tag{7}$$

Comparing equations (6) and (7) shows that the arguments θ_1 through θ_{n+1} and t enter only through the $u_i(\theta_{ij}, \ldots, \theta_{n+1}, t) = c_i$ curves, hence equations (5) must be solved for c_1 and c_{n+1} in terms of an arbitrary t.

The equation

$$c_1 = (e^{\theta_1} - 1)\, e^{-\lambda_2 t} \tag{8}$$

is immediate, and Cramer's Rule yields $c_{n+1} = e^{-\lambda_1 t} \det A$, where $A = (a_{ij})$ is the matrix defined as

$$a_{i1} = (\frac{-\lambda_1}{\lambda_2 - \lambda_1}) \qquad \text{where } 1 \leq i \leq n+1 ,$$

$$a_{ij} = \begin{cases} 0 & \text{for } i < j \\ \dfrac{(-\lambda_1 t)^{i-j}}{(i-j)!} & \text{for } i \geq j \end{cases} \qquad \text{where } 1 \leq i \leq n+1 \text{ and } 2 \leq j \leq n ,$$

$$a_{i,\, n+1} = (e^{\theta_i} - 1) \qquad \text{where } 1 \leq i \leq n+1 .$$

Thus defining $A_{i,j}$ to be the cofactors of the A matrix, it follows that

$$c_{n+1} = e^{-\lambda_1 t} \sum_{i=1}^{n+1} (e^{\theta_i} - 1) A_{i,\, n+1} \,. \tag{9}$$

In solving for these $A_{i,\, n+1}$ cofactors explicitly, it is immediately clear that

$$A_{n+1,n+1} = 1 \,,$$

$$A_{n,\, n+1} = \lambda_1 t \,,$$

and

$$A_{n-1,n+1} = (\lambda_1 t)^2 / 2 .$$

A generalization by induction shows that

$$A_{j,\, n+1} = \frac{(\lambda_1 t)^{n+1-j}}{(n+1-j)!} \tag{10}$$

for $2 \leq j \leq n + 1$, and the $A_{1,\, n+1}$ cofactor is solved by expanding on its first column to yield

$$A_{1,\, n+1} = (-1) \sum_{i=1}^{n} \left(\frac{-\lambda_1}{\lambda_2 - \lambda_1}\right)^i A_{i+1,\, n+1} \,. \tag{11}$$

The combining of equations (9), (10), and (11) results in

$$c_{n+1} = e^{-\lambda_1 t} \left\{ (e^{\theta_1} - 1)(-1) \sum_{i=1}^{n} \left(\frac{-\lambda_t}{\lambda_2 - \lambda_1}\right)^i \frac{(\lambda_1 t)^{n-i}}{(n-i)!} + \sum_{j=2}^{n+1} (e^{\theta_i} - 1) \frac{(\lambda_i t)^{n+1-j}}{(n+1-j)!} \right\} \tag{12}$$

The cumulant generating function, then, for the series of n + 1 subcompartments at time t is found from (6), (7), (8) and (12) to be

$$K(\theta_1, \theta_2, \ldots, \theta_{n+1}, t) = \eta_1(0) \ln \left[1 + \sum_{k=1}^{n+1} (e^{\theta_k} - 1) \cdot p_{1k}(t)\right] \tag{13}$$

$$+ \eta_2(0) \ln \left[1 + (e^{\theta_1} - 1)\, p_{21}(t)\right]$$

where

$$p_{11}(t) = e^{-\lambda_1 t} (-1) \sum_{i=1}^{n} \left(\frac{-\lambda_1}{\lambda_2 - \lambda_1}\right)^i \frac{(\lambda_1 t)^{n-i}}{(n-i)!} + e^{-\lambda_2 t} \left(\frac{-\lambda_1}{\lambda_2 - \lambda_1}\right)^n ,$$

$$p_{1k}(t) = e^{-\lambda_1 t} \frac{(\lambda_1 t)^{n+1-j}}{(n+1-j)!} \qquad \text{for } 2 \le k \le n+1 , \text{ and}$$

$$p_{21}(t) = e^{-\lambda_2 t} \left(\frac{-\lambda_1}{\lambda_2 - \lambda_1}\right)^n .$$

3.3 Resultant Probability Distribution

This section shows that the c.g.f. in equation (13) characterizes a multinomial distribution. The mean and variance of the number of particles in any subcompartment, say the k^{th}, are determined by first finding the k^{th} marginal c.g.f., or $K(0, \ldots, \theta_k, \ldots, 0, t)$, and then expanding and differentiating the marginal c.g.f. with respect to θ_k. The above operations show that the mean and variance of $N_k(t)$, are

$$E[N_k(t)] = \sum_{i=1}^{2} \eta_i(0)\, p_{ik}(t) \quad \text{and}$$

$$V[N_k(t)] = \sum_{i=1}^{2} \eta_i(0)\, p_{ik}(t)\, [1 - p_{ik}(t)]$$

where $p_{2j}(t) = 0$ for $2 \le j \le n+1$. Inasmuch as these hold for all k and any t, it is apparent that

$$0 \le p_{ij}(t) \le 1$$

for all i, j, and t. A similar argument where only a single $\eta_i(0)$ is non-zero verifies that the sum

$$p_{i.}(t) = \sum_{k=1}^{n+1} p_{ik}(t)$$

is also bound between 0 and 1 inclusive.

Let the number of particles departed from the system, i.e. $\eta_1(0) + \eta_2(0) - \sum_{i=1}^{n+1} N_i(t)$, be denoted $N_o(t)$ and let $p_{io}(t) = 1 - \sum_{j=1}^{n+1} p_{ij}(t)$. Note then that each term of the c.g.f. (13) has the form of a multinomial and that the $p_{ij}(t)$ parameters satisfy the multinomial restrictions. Moreover since the uniqueness property follows from the finite range (see e.g. Kendall and Stuart [1963]), the following proposition holds:

Proposition. Let an (n+2)-vector, $\Delta(t)$, represent the number of particles observed in the exterior and in each of the n+1 subcompartments, i.e. $\Delta^T(t) = [N_o(t), N_1(t), N_2(t), \ldots, N_{n+1}(t)]$. Then $\Delta(t)$ is distributed as the sum of two independent multinomial vectors, say $\Gamma_1(t)$ and $\Gamma_2(t)$, where $\Gamma_i(t)$ has parameters $\eta_i(0)$, and $p_{io}(t)$ through $p_{i,n+1}(t)$.

From the above proposition, one may determine the distribution of the number of particles in each of the two original (physiological) compartments. Recall that $\eta_1(t) = \sum_{i=2}^{n+1} N_i(t)$, $\eta_2(t) = N_1(t)$, and $\eta_o(t) = N_o(t)$. The following corollary is then clear:

Corollary. The vector $[\eta_o(t), \eta_1(t), \eta_2(t)]$ is distributed as the sum of two independent trinomials, the first with parameters $\eta_1(0)$, $p_{1o}(t)$, $\sum_{j=2}^{n+1} p_{ij}(t)$, and $p_{11}(t)$ and the second with parameters $\eta_2(0)$, $p_{2o}(t)$, $\sum_{j=2}^{n+1} p_{2j}(t)$, and $p_{21}(t)$.

The corollary supplies the mean value function and the covariance kernel of the observations over time. These in turn form the basis for estimating the unknown λ_1 and λ_2 parameters by least squares along the lines of MH. Such an example is provided in the next section.

3.4 Illustration for $\Gamma(2, \lambda_1)$ Lifetimes in Compartment 1

The results of Section 3 are illustrated for the compartmental model represented by Figure 3. Suppose further that $\eta_2(0) = 0$. Then the

$$\boxed{\Gamma(2, \lambda_1)} \rightarrow \boxed{E(\lambda_2)} \rightarrow$$

Figure 3

generating function from (13) is

$$K(\theta_1, \theta_2, \theta_3, t) = \eta_1(0) \ln \left[1 + \sum_{k=1}^{3} (e^{\theta_i} - 1)\, p_{1k}(t)\right]$$

where $p_{11}(t) = -e^{-\lambda_1 t}\left[\left(\frac{-\lambda_1}{\lambda_2 - \lambda_1}\right)\lambda_1 t + \left(\frac{\lambda_1}{\lambda_2 - \lambda_1}\right)^2\right] + e^{-\lambda_2 t}\left(\frac{-\lambda_1}{\lambda_2 - \lambda_1}\right)^2$,

$p_{12}(t) = e^{-\lambda_1 t}\lambda_1 t$, and

$p_{13}(t) = e^{-\lambda_1 t}$.

Hence the vector $[\eta_0(t), \eta_1(t), \text{ and } \eta_2(t)]$ is distributed as a trinomial with with parameters $\eta_1(0)$, $p_{10}(t)$, $\sum_{i=2}^{3} p_{1i}(t)$, and $p_{11}(t)$. Moreover, defining $T_n(t)$ to be the number of particles in either compartment 1 with $\Gamma(n, \lambda_1)$ lifetimes or in compartment 2, i.e. $T_n(t) = \sum_{i=1}^{n+1} N_i(t)$ the expected value of $T_2(t)$ is clearly $\sum_{k=1}^{3} E[N_k(t)]$, or

$$E[T_2(t)] = \eta_1(0)\left[e^{-\lambda_1 t}\left\{1 + \lambda_1 t + \left(\frac{\lambda_1}{\lambda_2 - \lambda_1}\right)\lambda_1 t - \left(\frac{\lambda_1}{\lambda_2 - \lambda_1}\right)^2\right\} + e^{-\lambda_2 t}\left(\frac{\lambda_1}{\lambda_2 - \lambda_1}\right)^2\right].$$

(14)

In general, if $\eta_2(0) = 0$ and the first compartment has $\Gamma(n, \lambda_1)$ lifetimes, it can be shown from (13) that

$$E[T_n(t)] = \eta_1(0)\left[e^{-\lambda_2 t}\left(\frac{-\lambda_1}{\lambda_2-\lambda_1}\right)^n + e^{-\lambda_1 t}\left\{\sum_{i=0}^{n-1}\frac{(\lambda_1 t)^i}{i!} - \sum_{j=1}^{n}\left(\frac{-\lambda_1}{\lambda_2-\lambda_1}\right)^j \frac{(\lambda_1 t)^{n-j}}{(n-j)!}\right\}\right]. \tag{15}$$

4. Analysis of Experimental Data

This section applies the time dependent compartmental model of Section 3 to the application described in Section 2 and analyses data from a typical experiment. Inasmuch as this section is intended to suggest a procedure which could be broadly applied, the physiological arguments which support the work below but are unique to this application only will be virtually omitted.

Consider the data of Table I obtained from a passage experiment conducted as follows. A sheep was dosed at time 0 with a radioactive tracer absorbed onto hay particles. The feces were collected at approximately 6 hour intervals and the excreted radioactivity was measured. Standardizing the total label at time 0 to 1.0, the residual in the sheep at time t, denoted $T(t)$, was determined as recorded in Table 1.

t	T(t)	t	T(t)	t	T(t)
0	1.000	66	.134	132	.008
6	1.000	71	.101	138	.008
13	1.000	78	.074	144	.007
18	.987	84	.053	150	.005
24	.913	90	.036	156	.004
37	.578	96	.028	162	.003
42	.459	102	.022	168	.003
48	.349	108	.018	181	.002
54	.252	114	.014	186	.002
61	.195	120	.011	192	.000
		126	.009		

Table 1
Time vs. Fraction of Radioactivity Unrecovered.

These data were first fitted to the model originally suggested by Blaxter et al. [1956] which in addition to two sequential steady state compartments also contains a time delay parameter denoted by τ. Letting $f(t)$ represent the predicted residual amount in the sheep at time t, one may write, in terms of the previous discussion,

$$f(t) = 1.0 \qquad \text{for } t \leq \tau$$

and

$$f(t) = E[T_n(t-\tau)] \qquad \text{for } t > \tau .$$

In the present steady state model, the absence of time dependent flow rates is reflected by $n = 1$.

Although the observations are known to be interdependent and heteroskedastic, these phenomena are not sizeable in light of the number of hay particles fed. The largest source of error in this experiment was thought to be the error of measurement and since such errors are independent, the ordinary least squares estimation procedure for nonlinear models of Hartley [1961] was employed.

The parameter estimates of the above data were $\lambda_1 = .1068$, $\lambda_2 = .0544$, $\tau = 17.5$, and a mean square error, s^2, of 0.236×10^{-4}. Though the overall fit, as measured by s^2, is well within acceptable limits for such experiments in the past, the theoretical discussion of Section 2 suggests the search for an even better model.

For this reason, and other physiological reasons not here considered (e.g. the excessive time delay estimate), the model with $\Gamma(2, \lambda_1)$ time dependency in compartment 1 was considered. The data were fitted to equation (14), where $\eta_1(0) = 1$, by ordinary least squares with resulting estimates $\lambda_1 = .1751$, $\lambda_2 = .0521$, $\tau = 14.6$, and $s^2 = 0.190 \times 10^{-4}$. Note that this model, in addition to satisfying the theoretical considerations, fits better statistically as well.

This success led to the investigation of other members of the $\Gamma(n, \lambda_1)$ family, which results are tabulated in Table 2.

Gamma Function	λ_1	λ_2	τ	$s^2 \times 10^4$
$\Gamma(1, \lambda_1)$	.1068	.0544	17.5	.236
$\Gamma(2, \lambda_1)$	.1751	.0521	14.6	.190
$\Gamma(3, \lambda_1)$	.2268	.0513	12.6	.185
$\Gamma(4, \lambda_1)$	.2696	.0510	10.9	.186
$\Gamma(5, \lambda_1)$	.3070	.0508	9.3	.188
$\Gamma(6, \lambda_1)$	.3405	.0506	7.9	.190
$\Gamma(7, \lambda_1)$	.3713	.0505	6.7	.193

Table 2
Gamma Functions vs. Parameter Estimates.

Note that $\Gamma(3, \lambda_1)$ minimizes s^2 for this isotope, and thus is accepted to describe the passage. The estimated standard errors of its parameters are $s_{\lambda_1} = 0.0106$, $s_{\lambda_2} = 0.0008$, and $s_T = 0.467$ indicating high precision.

The incorporation of time dependency, in addition to minimizing s^2, may also contribute to the identification of the abstract compartments. In the present case, for example, the expected lifetime in the first compartment is changed measurably. It may be shown that since the lifetimes, X, in said compartment are distributed

$$f(X;\ n,\ \lambda_1) = \frac{\lambda_1^n}{(n-1)!}\, X^{n-1}\, e^{-X\lambda_1},$$

the expected value of X is

$$\mu(X) = \frac{n}{\lambda_1} \quad .$$

The mean lifetime in compartment 1 increases from 9.36 under the steady state model to 13.23 for the present model. This change generally becomes more marked as the time dependency phenomenon increases. Of course other moments and indeed the whole distribution are often revealing.

In other applications where the system is not sufficiently well understood to establish time dependency a priori, one can often indicate its presence by the following procedure. The data is fitted to a model containing at least two consecutive and irreversible compartments by the previous theory of MH. Although such theory guarantees that the final λ_i estimates for these compartments are unequal, gamma time dependency will cause them to approach one another. Of course, strict equality is avoided since it would cause degeneracy of the MH models with a resultant inflation in error mean square.

To illustrate this, the data of Table 1 was fitted to a three irreversible compartment model with time delay. The parameter estimates were $\lambda_1 = .1767$, $\lambda_2 = .1734$, $\lambda_3 = .0521$, $\tau = 14.6$, and $s^2 = .198 \times 10^{-4}$. On the surface, this model seems to be an acceptable alternative to $\Gamma(2, \lambda_1)$ above, however the estimated standard deviations of the parameters, which are $s_{\lambda_1} = .9793$, $s_{\lambda_2} = .9437$, $s_{\lambda_2} = .0011$, and $s_\tau = .422$, rule out the acceptance of the first two compartments. Thus, though not acceptable in its own right, the three compartment model strongly suggests the $\Gamma(2, \lambda_1)$ model.

In summary, the data of Table 1 is best described by a two compartment model with $\Gamma(3, .2268)$ lifetimes in compartment 1, $\Gamma(1, .0513)$ lifetimes in compartment 2, and a time delay of 12.6. It is hypothesized that the models of Section 3, with possible minor modifications, could be used profitably in many different applications.

Acknowledgements

The author is indebted to Drs. M. W. Carter and W. B. Smith for their encouragement and interest in this project. Dr. W. C. Ellis and Mr. Bob Goodell supplied the data and guided the physiological aspects of the paper.

References

[1] Bailey, N. T. J. [1964]. The Elements of Stochastic Processes with Applications to the Natural Sciences. Wiley, New York.

[2] Blaxter, K. L., Graham, N. M., and Wainman, F. W. [1956]. "Some Observations on the Digestibility of Food by Sheep, and on Related Problems". Brit. J. Nutr. 10, 69-91.

[3] Ford, L. R. [1955]. Differential Equations. McGraw-Hill, New York.

[4] Hartley, H. O. [1961]. "The Modified Gauss-Newton Method for the Fitting of Nonlinear Regression Functions by Least Squares". Technometrics 3, 269-80.

[5] Kendall, J. H. and Stuart, A. [1963]. The Advanced Theory of Statistics. Vol. 1 2nd Ed. Griffin, London.

[6] Matis, J. H. and Hartley, H. O. [1971]. "Stochastic Compartmental Analysis: Model and Least Squares Estimation from Time Series Data". Biometrics 27.

[7] Parzan, E. [1962]. Stochastic Processes. Holden-Day, San Francisco.

[8] Sheppard, C. W. [1962]. Basic Principles of the Tracer Method. Wiley, New York.

[9] Zilversmit, D. B., Entenman, C., and Fishler, M. C. [1943]. "On the Calculation of Turnover Time and Turnover Rate for Experiments Involving the Use of Labeling Agents". J. Gen. Physiol. 26, 325-331.