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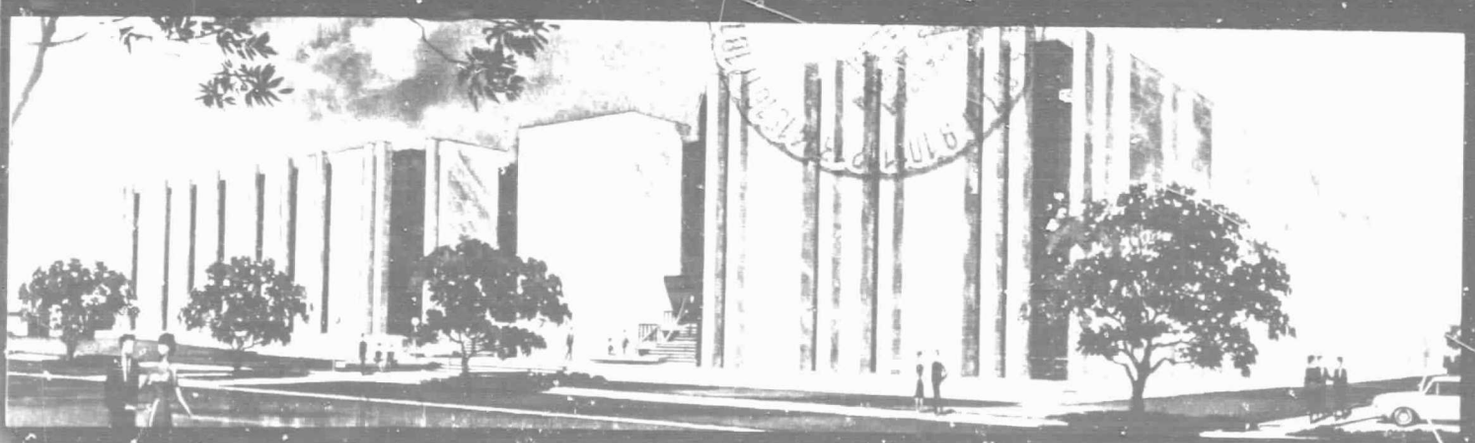

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# STOCHASTIC COMPARTMENTAL ANALYSIS: SOME APPLICATIONS AND EXAMPLES OF ESTIMATION IN A PULSE LABELLED SYSTEM

by

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## Summary

Compartmental analysis, though previously applied mainly to the biomedical sciences, provides a model pertinent to a wide variety of other areas of endeavor. This report illustrates the flexibility of application by citing models from diverse fields which are compartmental in nature.

The stochastic behavior of the above models is outlined and subsequently used to develop an estimation procedure. Two examples illustrate the application of the estimation technique. The first example, a simulation, demonstrates the weakness of ordinary least squares estimation, which is heretofore used, in stochastic compartmental models. A biological experiment forms the second example and it also confirms the above conclusion.

## 1. Introduction

As reported in a former paper (Matis and Hartley [1969]), several previous authors have recognized the need to incorporate stochastic considerations into compartmental analysis. The above paper contributes to that objective by introducing probabilistic behavior to the compart-

mental system most frequently encountered in the literature; i.e. a system that has

(1) a discrete sample space,

(2) steady state conditions,

(3) pulse labelling, and

(4) data available only on the passage of material to the system exterior.

The distribution theory of such a system is solved in general for m compartments and an estimation procedure which utilizes that distribution theory is recommended. In short, the previous report contains a complete solution to the specific theoretical problem above.

The present paper addresses itself to one who would use the theory to analyze data; from the viewpoint of a user, it attempts to breathe life into the mathematical theory. Several diverse applications are sketched in section 2 to illustrate the breadth of possible usage of compartmental analysis. Section 3 briefly reviews the theoretical results of the previous paper and extends the theory slightly along some lines of practical interest. These concepts are elucidated in section 4 by solving examples of both simulated and biological data. Also the examples clearly demonstrate the merits of the estimation procedure.

## 2. Some Applications

Sheppard [1962], Rescigno and Segre [1965], and Whipple and Hart [1963] provide comprehensive reviews of deterministic compartmental analysis and partial bibliographies of its previous use in the literature. As apparent in these reviews, compartmental analysis has application in many diverse areas of bio-medical science. This section will illustrate these traditional applications and also show the relevancy of the technique to other areas of endeavor. It is imperative to recognize that the term "compartment", defined as a homogenous component of a larger system, has broader application in the present considerations than just defining physical location. "Compartments may have a real existence, and well-defined boundaries, as in the cells of plants or animals. More often the compartments are logical abstractions, and may stand for chemical compounds, states of valency, or other homogenous phases in a system." (Whitehouse and Putnam [1953] p. 291). Indeed the socio-economic example below evidences the great flexibility of application. And by no means should the following list be considered exhaustive, but rather as a sample of a much larger population of possibilities.

### 2.1 Pharmacokinetic application

Pharmacokinetics is one traditional subscriber of compartmental analysis. Riegelman, et al. [1968] persuasively argue the usefulness of a two-compartment model in drug studies. They propose that in the study of drug passage the human body may be modelled as in Figure 1. The central

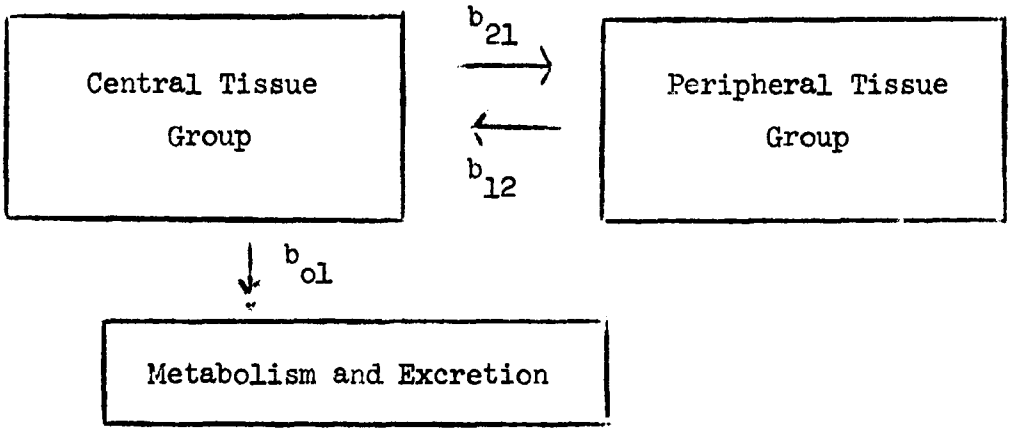


Figure 1

Human Body as a Compartmental System

tissue group and the peripheral tissue group form the first and second compartments of interest in the human body, respectively; the excreted and the metabolized drug is considered the system exterior. The compartmental problem in pharmacokinetics is the estimation of the $b_{ji}$ transition intensity coefficients, also called the "turnover rate" parameters, from data on the passage of a tracer drug.

## 2.2 Animal science application

The passage of material through the gastrointestinal tract of ruminants, e.g. cattle and sheep, constitutes a pertinent problem from animal science. Previous biological evidence suggests that compartmental analysis is applicable to the problem. The gastrointestinal tract may be conceptualized as a series of "vats" (see e.g. Hungate [1966], Chapter V) and indeed Blaxter, et al. [1956], by assuming deterministic behavior, have

obtained "good" fits of experimental data to a compartmental model. They suggest the compartments might be identified by Figure 2.

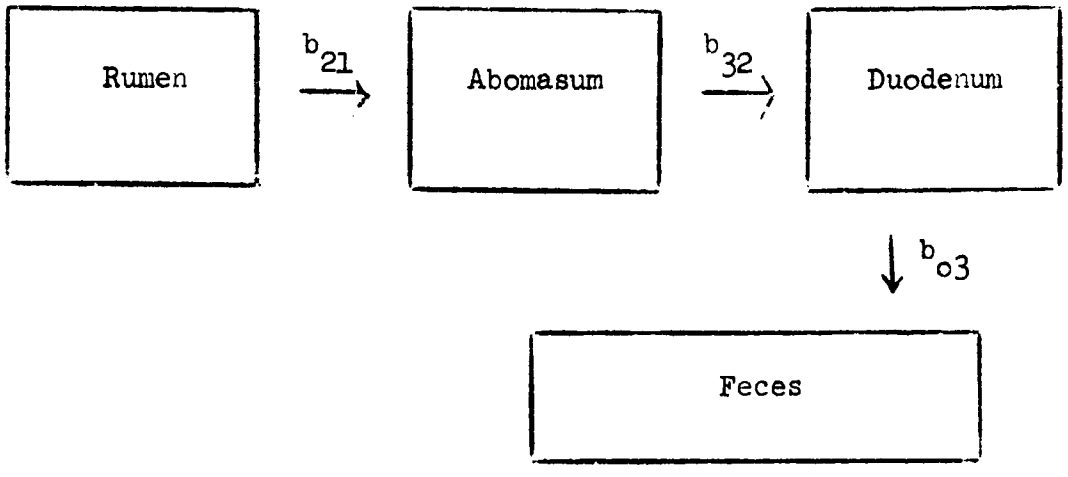


Figure 2

Ruminant Gastrointestinal Tract as a Compartmental System

Animal nutritionists identify a great variety of materials for which the above modelling is useful; for example, one particular substance of interest consists of indigestible, plastic beads used as roughage substitute. Suppose N(0) beads are introduced into the rumen at time 0, and let N(t) be the random variable specifying the number of these beads remaining in the gastrointestinal tract at time t. The compartmental problem in an animal science context is the estimation of the $b_{ji}$ turnover rates from time series data of the random variable N(t).

## 2.3 Sociological application

Bartholomay [1967] discusses a sociological model representing organizational commitment. The model, as diagrammed in Figure 3, was developed by Herbst [1963] to explain the process which new initiates undergo before either leaving an organization or becoming permanently

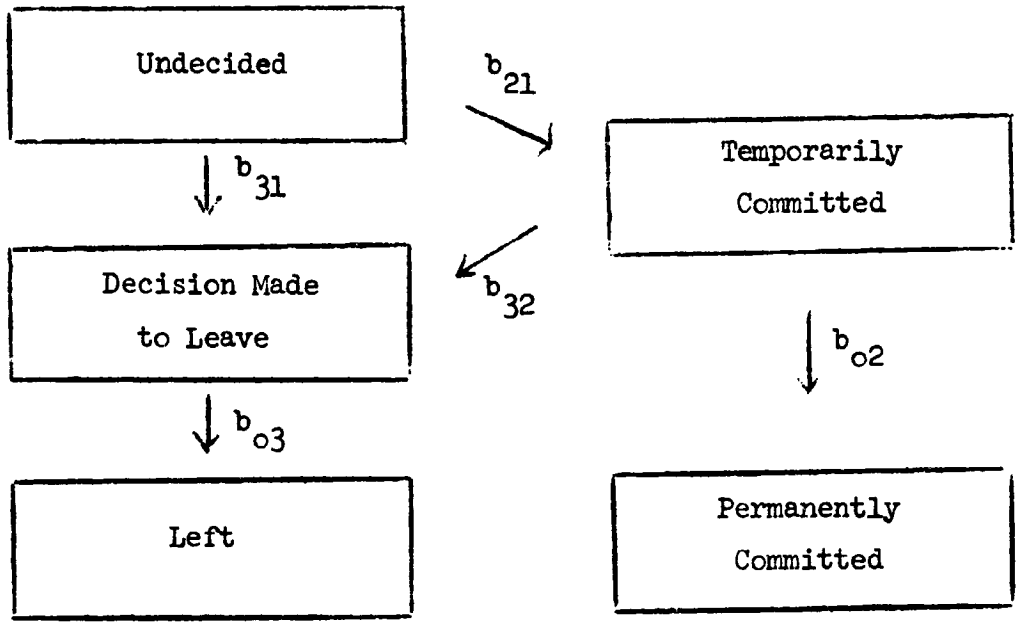


Figure 3
Organizational Commitment Model as a Compartmental System

attached to it. Typically time series data is available only on the number of individuals leaving the organization. Herbst estimated the turnover rate parameters from such data for several different firms by using essentially deterministic procedures, and he obtained "extremely good" fits. The more realistic stochastic model remains to be considered.

## 2.4 Public Health Application

As a final example, consider the illness-death model used extensively in public health. The model as first proposed by Fix and Neyman [1951] is diagrammed by Figure 4. The model has subsequently been refined and most recently is discussed by Chiang [1968]. The general model of Chiang has s "illness states" and r "death states." "An illness state may be broadly defined to include the absence of illness (a health state), a physical impairment, a single specific disease or stage of disease, or any combination of diseases" (Chiang [1968], p. 151), and the death states are similarly defined terminal compartments.

An ultimate objective of such public health models is the estimation of the improvement in the overall survival rate incurred by the successful treatment of an illness state. But a first objective is common to all previous examples, i.e. the estimation of all transition rates from time series data.

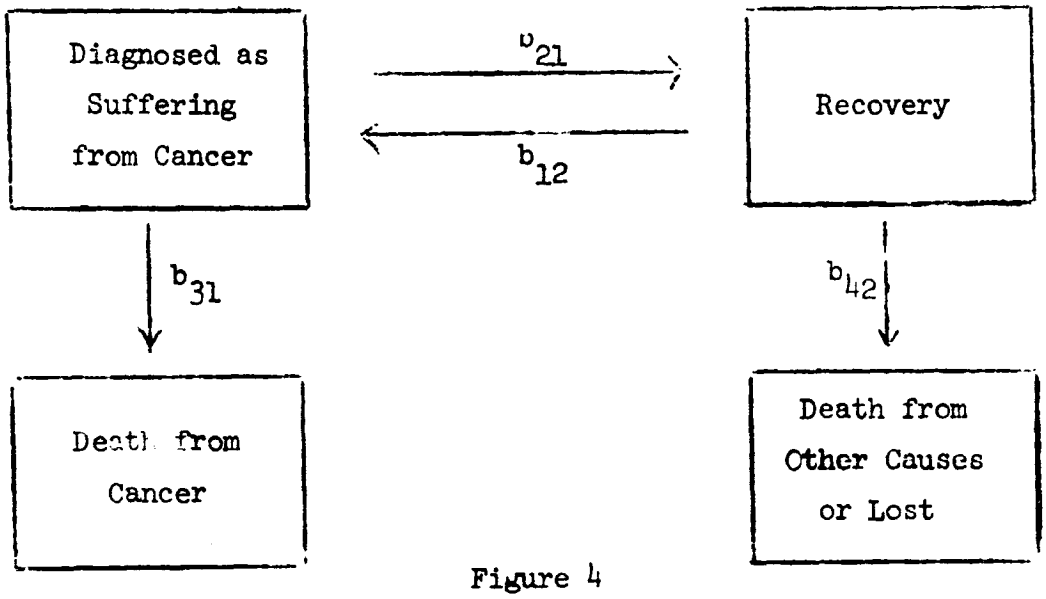


Figure 4

A Particular Illness-Death Model

## 3. Outline of Distribution Theory and Estimation Procedure

Rather than consider the particular models in section 2 separately, this section outlines the distribution theory and estimation procedure of a general m-compartment system where each compartment is connected to each other and to the system exterior. It follows that a general system has $m^2$ parameters and that the models discussed in section 2 are special cases of this general system.

Let $N_i(0)$ be the known number of labelled units introduced into compartment i at time 0, and let $N_i(t)$ be a random variable specifying the number of units in compartment i at time t. Let $b_{ji}$ be the transition intensity or "turnover rate" from compartment i to compartment j, where $b_{oi}$ represents exit from compartment i. Then by definition, $b_{ji}\Delta t$ is the probability that a particular unit migrates from compartment i to compartment j in the time interval $\Delta t$. Figure 5 represents a general m = 2 compartment system with $m^2 = 4$ $b_{ji}$ parameters.

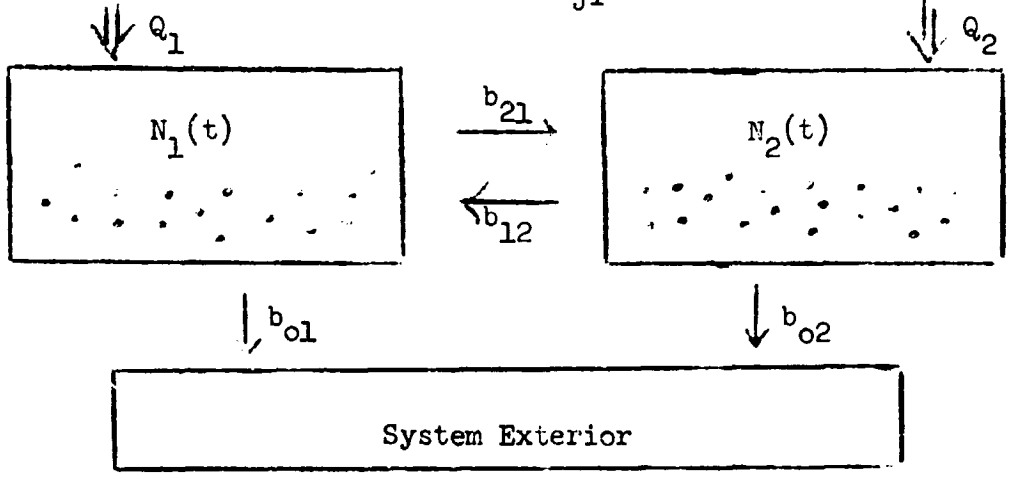


Figure 5
General Two Compartment System

The following definitions are now necessary to present the probability theory. Define an m x m matrix $\beta = (B_{ij})$ such that for $i \neq j$ the element $B_{ij}$ is the negative of the transition intensity to j from i, and the diagonal element $B_{ii}$ is the sum of all intensities leaving compartment i. One

$$\beta = \begin{bmatrix} \sum_{\substack{j=0 \\ j\neq 1}}^{m} b_{j1} & -b_{21} & \cdots & -b_{m1} \\ -b_{12} & \sum_{\substack{j=0 \\ j\neq 2}}^{m} b_{j2} & \cdots & -b_{m2} \\ \vdots & \vdots & & \vdots \\ -b_{1m} & -b_{2m} & \cdots & \sum_{j=0}^{m-1} b_{jm} \end{bmatrix}$$

Let the roots of $\beta$ be $\alpha_i$, i = 1, ..., m; and assume that the complex numbers $\alpha_i$ are distinct. Corresponding to each $\alpha_i$, a latent m-vector, say $F^i$, may be found where the first element is either 0 or is standardized to 1. Let $F = (f_{ij})$ be the matrix of these latent vectors, i.e.

$$F = [F^1, F^2, \ldots, F^m] = \begin{bmatrix} f_{11} & f_{12} & \cdots & f_{1m} \\ f_{21} & f_{22} & \cdots & f_{2m} \\ \vdots & \vdots & & \vdots \\ f_{m1} & f_{m2} & & f_{mm} \end{bmatrix} .$$

The determinant of F is denoted $|F|$, and the cofactor of $f_{ij}$ by $F_{ij}$. Then the parameter of interest, $p_{ik}(t)$, is defined as

$$p_{ik}(t) = \frac{1}{|F|} \sum_{j=1}^{m} f_{ij} F_{kj} e^{-\alpha_j t} . \qquad (1)$$

The following result, which is proven in our previous report, may now be presented.

Result 1: Let $\Gamma_i(t)$, where $\Gamma_i^T(t) = [\gamma_{i1}(t), \gamma_{i2}(t), \ldots, \gamma_{im}(t)]$ for $i = 1, 2, \ldots, m$, be distributed as a multinomial distribution with parameters $N_i(0)$, $p_{i1}(t)$, $p_{i2}(t)$, $\ldots$, $p_{im}(t)$; i.e.

$$\text{Prob}[\gamma_{i1}(t), \gamma_{i2}(t), \ldots, \gamma_{im}(t)] = \frac{N_i(0)! \prod_{j=1}^{m} p_{ij}^{\gamma_{ij}} [1 - \sum_{j=1}^{m} p_{ij}]^{N_i(0) - \sum_{j=1}^{m} \gamma_{ij}}}{\prod_{j=1}^{m} \gamma_{ij}! [N_i(0) - \sum_{j=1}^{m} \gamma_{ij}]!}$$

Also let the vector $\Delta(t)$ be defined by $\Delta^T(t) = [N_1(t), N_2(t), \ldots, N_m(t)]$. If the compartmental system receives tracer only at $t = 0$, then $\Delta(t)$ is distributed as the sum of the m independent $\Gamma_i(t)$, i.e.

$$\Delta(t) = \sum_{i=1}^{m} \Gamma_i(t) .$$

A physical interpretation may be attached to the $\Gamma_i(t)$ vectors. As apparent from its $N_i(0)$ parameter, the $\Gamma_i(t)$ vector characterizes the dispersion throughout the compartments of the $N_i(0)$ units which originated in compartment i. Logically the behavior of these $N_i(0)$ units is independent of the, say, $N_i'(0)$ units originating in compartment $i' (\neq i)$. Indeed, result 1 establishes this assertion and thus the rows of Figure 6 are independent.

| Compartment at time 0 | Compartment at time t: 1 | ... | j | ... | m | Vector Notation |
|---|---|---|---|---|---|---|
| 1 | $\gamma_{11}(t)$ | .. | $\gamma_{1j}(t)$ | .. | $\gamma_{1m}(t)$ | $\Gamma_1(t)$ |
| i | $\gamma_{i1}(t)$ | .. | $\gamma_{ij}(t)$ | .. | $\gamma_{im}(t)$ | $\Gamma_i(t)$ |
| m | $\gamma_{m1}(t)$ | .. | $\gamma_{mj}(t)$ | .. | $\gamma_{mm}(t)$ | $\Gamma_m(t)$ |
| Total | $N_1(t)$ | | $N_j(t)$ | | $N_m(t)$ | $\Delta(t)$ |

Figure 6

Two-way Layout of $\gamma_{ij}(t)$ numbers

However the total (over all m origins) number of units in compartment j, $N_j(t)$, is the $j^{th}$ marginal of $\Delta(t)$ and is not independent of the other marginals. In other words, the columns of Figure 6 are dependent. If u and v are different compartments, the covariance of $\gamma_{iu}$ and $\gamma_{iv}$ is determined by properties of the multinomial distribution to be

$$\mathrm{Cov}[\gamma_{iu}(t),\ \gamma_{iv}(t)] = -N_i(0)p_{iv}(t)p_{iu}(t).$$

Similarly, since $N_j(t) = \sum_{i=1}^{m} \gamma_{ij}$ and by virtue of the independency of the $\Gamma_i(t)$, it follows that

$$\mathrm{Cov}[N_u(t),\ N_v(t)] = -\sum_{i=1}^{m} N_i(0)p_{iv}(t)p_{iu}(t)\ .$$

The distribution within the compartments is thus identified for any particular time. However recall that the data consist of the total number of units in the system at various times, i.e. $N_T(t_i)$ for

$i = 1, \ldots, z$; hence the first and second moments of the $N_T(t_i)$ time series are presently required. Result 2 solves this problem and may be proven using Result 1.

Result 2: Let

$$a_s(t) = \sum_{k=1}^{m} p_{sk}(t) \ . \tag{2}$$

Then the mean value function of $N_T(t)$, say $\mu(t)$, is

$$\mu(t) = \sum_{i=1}^{m} N_i(0)a_i(t), \tag{3}$$

and the covariance kernel of $N_T(t_a)$ and $N_T(t_b)$ where $t_b \geq t_a$, say $\sigma_{ab}$, is

$$\sigma_{ab} = \sum_{i=1}^{m} N_i(0)a_i(t_b)[1 - a_i(t_a)] \ . \tag{4}$$

Result 2 contains the "regression" function, $\mu(t)$, and the z x z variance-covariance matrix $\Sigma = (\sigma_{ij})$. These may be used to estimate the (at most) $m^2$ $b_{ji}$ parameters by an iterative non-linear least squares procedure. The modified Gauss-Newton algorithm of Hartley (1961) is extended in Result 3 to minimize the generalized sum of squared deviations, $\epsilon^T\Sigma^{-1}\epsilon$, by the Aitken generalized least squares theorem (see e.g. Goldberger [1964], p. 233). One then has the following:

Result 3: Let ${}_i\Sigma$ be the $i^{th}$ estimate of $\Sigma$ with ${}_o\Sigma = I$. Let $\Omega$ be the vector of parameters $[b_{o1}, b_{21}, \ldots, b_{m-1,m}]$, and let ${}_i\Omega$ be the $i^{th}$ estimate of $\Omega$. Then $\Omega$ may be estimated as follows:

(1) Holding ${}_{o}\Sigma$ fixed, iterate for the parameter estimates ${}_{1}\Omega$ by the modified Gauss-Newton algorithm.

(2) Substitute the ${}_{1}\Omega({}_{k}\Omega)$ estimates into the matrix $\beta$ and

(a) find its latent roots, $\alpha_i$, and vectors, $F^i$,

(b) using (a), find the $p_{ij}(t)$ and $a_i(t)$ parameters from equations (1) and (2) respectively, and

(c) using (b), find the new estimated variance-covariance matrix ${}_{1}\Sigma({}_{k}\Sigma)$ according to (4).

(3) Iterate for new parameter estimates ${}_{2}\Omega({}_{k+1}\Omega)$ using ${}_{1}\Sigma({}_{k}\Sigma)$ in the Aitken formula with ${}_{1}\Omega({}_{k}\Omega)$ as the initial values.

(4) Repeat steps 2 and 3 obtaining ${}_{i}\Sigma$ and ${}_{i}\Omega$ estimates successively until the process converges.

A full account of the two stage procedure of Result 3, as well as the preceding results, is contained in the previous report (Matis and Hartley [1969]). An additional result is useful in practice. Although Result 2 identifies the variance-covariance matrix $\Sigma$ the ultimate requirement is the information matrix $\Sigma^{-1}$. Fortunately subsequent usage requires the inversion only for given parameter values, hence the inversion need only be done numerically on a computer. Yet an explicit solution for $\Sigma^{-1}$ would obviously save both accuracy and computer time.

Indeed, an explicit inverse of $\Sigma$ is available for the class of problems most frequently encountered. Typically in a pulse labelled experiment, just one compartment, say the $k^{th}$, is initially labelled. The prevalence of the one compartment introduction is partially due both to the simplicity of initiating the experiment as well as the frequent physical inaccessibility of multiple compartments.

In the special case, then, where only compartment k is pulsed, the element of $\Sigma$ in equation (4) reduces to

$$\sigma_{ab} = N_k(0)\, a_k(t_b)[1 - a_k(t_a)] \quad \text{for} \quad 1 \leq a, b \leq z \ .$$

The elements of the information matrix may be derived from the system of equations $\Sigma\, \Sigma^{-1} = I$. The following result is thus derived.

Result 4: Let the information matrix be $\Sigma^{-1} = (\sigma^{ab})$. If only the $k^{th}$ compartment is labelled, the elements of $\Sigma^{-1}$ are

$$N_k(0)\sigma^{bb} = \frac{a_k(t_{b-1}) - a_k(t_{b+1})}{[a_k(t_{b-1}) - a_k(t_b)]\,[a_k(t_b) - a_k(t_{b+1})]} \quad \text{for} \quad 1 \leq b \leq z$$

$$\text{where} \quad a_k(t_o) \equiv 1 \quad \text{and} \quad a_k(t_{z+1}) \equiv 0,$$

$$N_k(0)\sigma^{b+1,b} = N_k(0)\sigma^{b,b+1} = \frac{-1}{a_k(t_b) - a_k(t_{b+1})} \quad \text{for } 1 \leq b \leq z-1 \ ,$$

and

$$\sigma^{ab} = 0 \qquad \text{for} \quad |a - b| > 1 \ .$$

The above solution may be verified by the $\Sigma\, \Sigma^{-1}$ product. Note that since $z^2 - 3z + 2$ elements are 0, the result contributes facility in handling in addition to accuracy.

## 4. Examples of Estimation Procedures

The estimation procedure is illustrated in this section with two examples. One is a simulation with known parameter values and the other consists of data from the application described in section 2.2.

### 4.1 Example of Simulated Data

Consider first simulated data from the compartmental system represented by Figure 7. Data from this system were generated by choosing parameter values $b_{21} = 0.125$ and $b_{02} = 0.250$, and initializing $N_1(0) = 4000$

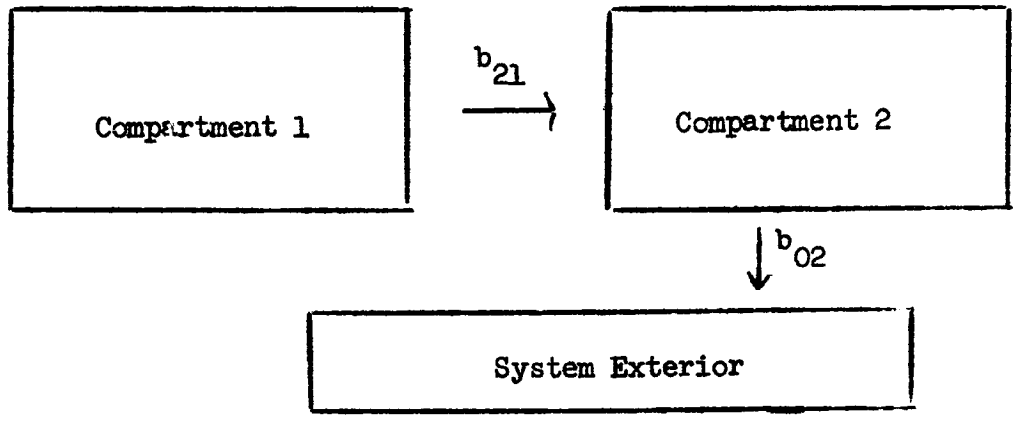


Figure 7

Two Compartment Model of Simulation and Gastrointestinal Tract

and $N_2(0) = 0$. Negative exponential sojourn times were generated to produce a realization of the stochastic process. Table 1 contains this particular realization at $z = 40$ time points defined by $t_i = i$.

In order to estimate the parameters from these 40 data, one proceeds to find the $\rho$ matrix of the compartmental model. The $\beta$ matrix corresponding to Figure 7 is

$$\beta = \begin{bmatrix} b_{21} & -b_{21} \\ 0 & b_{02} \end{bmatrix} .$$

Simple matrix algebra reveals that

$$\alpha_1 = b_{21} \qquad \alpha_2 = b_{02}$$

$$f_{11} = f_{12} = F_{22} = -F_{21} = 1$$

$$f_{21} = F_{12} = 0$$

$$f_{22} = F_{11} = |F| = \frac{b_{21} - b_{02}}{b_{21}} .$$

Substituting the above into (1) and (2), it follows that

$$a(t) = [b_{02} - b_{21}]^{-1} [b_{02}e^{-b_{21}t} - b_{21}e^{-b_{02}t}],$$

from whence the mean and covariance kernel of the random variable $N_T(t)$ are given by

$$\mu_T(t_a) = 4000\, a(t_a)$$

$$\sigma_{ab} = 4000\, a(t_b)\, [1 - a(t_a)] .$$

TABLE 1

Data of Simulation

| t | $N_T(t)$ | t | $N_T(t)$ | t | $N_T(t)$ | t | $N_T(t)$ | t | $N_T(t)$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 3949 | 9 | 2175 | 17 | 917 | 25 | 335 | 33 | 127 |
| 2 | 3799 | 10 | 1968 | 18 | 819 | 26 | 288 | 34 | 112 |
| 3 | 3618 | 11 | 1771 | 19 | 729 | 27 | 258 | 35 | 102 |
| 4 | 3399 | 12 | 1591 | 20 | 643 | 28 | 232 | 36 | 92 |
| 5 | 3147 | 13 | 1448 | 21 | 562 | 29 | 219 | 37 | 81 |
| 6 | 2883 | 14 | 1303 | 22 | 509 | 30 | 185 | 38 | 70 |
| 7 | 2653 | 15 | 1147 | 23 | 441 | 31 | 161 | 39 | 62 |
| 8 | 2418 | 16 | 1012 | 24 | 386 | 32 | 147 | 40 | 55 |

Assuming now that the parameters are unknown, we judiciously select initial parameter estimates, ${}_0b_{21} = 0.125$ and ${}_0b_{02} = 0.250$, and iterate for the least squares estimates (step 1 of the estimation procedure). The derived estimates, ${}_1b_{21}$ and ${}_1b_{02}$, are then substituted into the variance-covariance matrix (step 2) from whence subsequent estimates, ${}_2b_{21}$ and ${}_2b_{02}$, are again obtained by Gauss-Newton iteration (step 3). The procedure is repeated until these estimates converge.

Table 2 summarizes the results of the estimation procedure. Note the very rapid convergence of the ${}_ib$ estimates. The procedure also provides an indicator of goodness-of-fit. Assuming the model to be true, the random variable $s^2$ is distributed as $\chi^2/n$; hence $s^2 = 1.063$ indicates an acceptable fit.

Another noteworthy fact is the difference in the standard deviations. As previously observed, the Aitken estimates are BLUE for a linear model with known covariance matrix. In the present simulation, with the parameters and hence the covariance matrix determined, the standard deviations of the Aitken estimates are determined by

$$\Sigma_{\Omega\Omega} = [G^T\Sigma^{-1}G]^{-1}$$

to be $\sigma_{b_{21}} = .00488$ and $\sigma_{b_{02}} = .01806$. As expected, any other unbiased estimates have a greater variance; in particular the variability of the ordinary least squares (OLS) estimates, $\tilde{\Omega}$, is calculated from

$$\Sigma_{\tilde{\Omega}\tilde{\Omega}} = [G^TG]^{-1}G^T\Sigma G[G^TG]^{-1}$$

to be $\sigma_{b_{21}}^{\sim} = .00528$ and $\sigma_{b_{02}}^{\sim} = .02407$. Note from Table 2 that the recommended estimation procedure estimates the standard deviations of

TABLE 2

Parameter Estimation of Simulation

| Iteration | $_{i}b_{21} \pm$ estimated std. dev. | $_{i}b_{02} \pm$ estimated std. dev. | $s^2$ |
|---|---|---|---|
| 0 | 0.12500 | 0.25000 | |
| 1 | 0.12547 $\pm$ .00092 | 0.24454 $\pm$ .00312 | |
| 2 | 0.12561 $\pm$ .00527 | 0.24419 $\pm$ .01851 | 1.063 |
| 3 | 0.12561 $\pm$ .00527 | 0.24419 $\pm$ .01851 | 1.063 |

the parameters to be $S_{b_{21}} = .00527$ and $S_{b_{02}} = .01851$ which are close to the above $\sigma_{b_{21}}$ and $\sigma_{b_{02}}$. However the OLS estimates of the standard deviations, by failing to recognize the interdependence of the observations, use the improper law

$$\Sigma_{\tilde{\theta}\tilde{\theta}} = \sigma^2[G^TG]^{-1}$$

and thereby seriously underestimate the variability. Iteration 1 of Table 2 gives these improper OLS estimates as $S_{\tilde{b}_{21}} = .00092$ and $S_{\tilde{b}_{02}} = .00312$. In summary, experimenters who use ordinary least squares estimation in stochastic compartmental problems are lead to believe such estimates are exceptionally significant when in fact such estimates may be shown inferior to those of the recommended iterative estimation.

## 4.2 Animal Science Application

As a second example, Table 3 contains data on the passage of beads through the gastrointestinal tract of a sheep. Similar experiments have been conducted by Blaxter, et al. [1956] whose findings are well-received among animal scientists and, indeed, constitute the state-of-the-art in the above mentioned modelling. At time $t' = 0$, 4000 indigestible plastic beads were placed into the rumen of the sheep. The sheep was fed every six hours and her feces were also collected then and analyzed for bead passage. The transformed argument t of Table 2 represents the argument $t'$ in days less a four day fixed transit time or "time delay," i.e. $t = t' - 4$. The four day length of the period was immediately determined from the data since only a few (possibly extraneous) beads had been recovered prior to that time.

TABLE 3

Data on Bead Retention in Sheep 148

| t | $N_T(t)$ | t | $N_T(t)$ | t | $N_T(t)$ | t | $N_T(t)$ | t | $N_T(t)$ | t | $N_T(t)$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.25 | 3989 | 2.75 | 3826 | 3.25 | 3589 | 7.75 | 3374 | 10.50 | 3011 | 14.00 | 2774 |
| 0.50 | 3970 | 3.00 | 3813 | 5.50 | 3570 | 8.00 | 3347 | 10.75 | 2976 | 14.25 | 2766 |
| 0.75 | 3954 | 3.25 | 3795 | 5.75 | 3563 | 8.25 | 3318 | 11.25 | 2941 | 14.50 | 2758 |
| 1.00 | 3935 | 3.50 | 3778 | 6.00 | 3556 | 8.50 | 3250 | 11.50 | 2930 | 14.75 | 2744 |
| 1.25 | 3931 | 3.75 | 3761 | 6.25 | 3542 | 8.75 | 3228 | 12.25 | 2911 | 15.00 | 2736 |
| 1.50 | 3905 | 4.00 | 3705 | 6.50 | 3531 | 9.00 | 3202 | 12.50 | 2891 | 15.25 | 2727 |
| 1.75 | 3888 | 4.25 | 3662 | 6.75 | 3503 | 9.25 | 3179 | 12.75 | 2866 | 15.50 | 2714 |
| 2.00 | 3872 | 4.50 | 3629 | 7.00 | 3473 | 9.75 | 3127 | 13.00 | 2839 | 16.00 | 2701 |
| 2.25 | 3864 | 4.75 | 3622 | 7.25 | 3450 | 10.00 | 3105 | 13.25 | 2821 | 16.25 | 2696 |
| 2.50 | 3832 | 5.00 | 3599 | 7.50 | 3391 | 10.24 | 3062 | 13.75 | 2796 | | |

4.2.1 Two Compartment model

Assuming initially the model of Figure 7 for the data, the mean value function and compartmental covariance kernel, say $\Sigma_c$, are given above in section 4.1. The complete variance-covariance matrix of $N_T(t)$, however, includes two other kernels in addition to the compartmental kernel; one is due to the "end-period" error recognized by Blaxter, et al., and the other is due to some unfortunate mastication of the beads by the sheep. Subsequent experimentation will be designed to practically eliminate both of these latter errors. Hence their form is not presented in this report although, for the sake of completeness, the formulations of the end-period error, $\Sigma_e$, and of the mastication error, $\Sigma_m$, are available in Matis [1970]. For the present data then, the complete variance-covariance matrix, $\Sigma_T$ is the sum of the three components which are assumed independent, i.e.

$$\Sigma_T = \Sigma_c + \Sigma_e + \Sigma_m .$$

The estimation procedure of Result 3 is now employed using the matrix $\Sigma_T$ in the place of the previous $\Sigma$.

Table 4 lists the cycles of the procedure. The fit is not exceptional ($s^2 = 1.6$) but it is within reason for biological data. Inasmuch as current methodology uses ordinary least squares estimates, the fact that the final estimates differ considerably from the OLS estimates is noteworthy. The OLS estimates are 0.0290 and 0.6580 while the terminal estimates of the above procedure are approximately (by extrapolation) 0.0234 and 3.07; in another light one parameter estimate decreased by

TABLE 4

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| Iteration | $_ib_{21} \pm$ estimated std. dev. | $_ib_{22} \pm$ estimated std. dev. | $s^2$ |
|---|---|---|---|
| 1 | .0290 ± .0005 | 0.6580 ± 0.0654 | |
| 2 | .0218 ± .0015 | 5.5656 ± 1.8699 | 1.523 |
| 3 | .0239 ± .0018 | 2.1988 ± 0.9871 | 1.708 |
| 4 | .0231 ± .0017 | 3.6266 ± 1.6228 | 1.615 |
| 5 | .0235 ± .0017 | 2.8129 ± 1.2981 | 1.636 |
| 6 | .0234 ± .0017 | 3.1611 ± 1.4416 | 1.623 |

19% and the other increased by an incredible 370%. In the event one used the compartmental covariance kernel $\Sigma_c$ alone, the final parameter estimates $\hat{b}_{21} = 0.0244$ and $\hat{b}_{02} = 2.552$ are close to the above terminal estimates but again far apart from the OLS estimates.

Also, as in the simulated data example, the estimated standard deviations are deceptively low in OLS estimation. The coefficients of variation for the parameters in OLS are 0.017 and 0.099 compared to 0.073 and 0.456 in the recommended procedure.

### 4.2.2 Three compartment model

The three compartment system of Figure 8 was considered as an

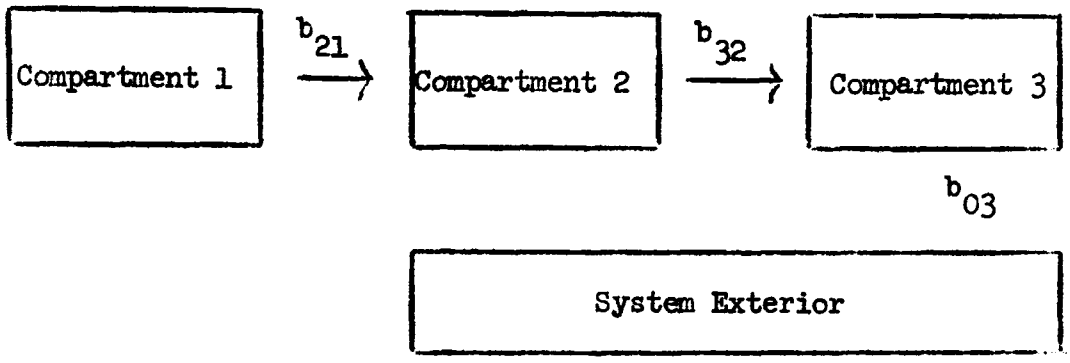


Figure 8

Three Compartment Model of Gastrointestinal Tract

alternative to the previous two compartment model. Its $\beta$ matrix is

$$\beta = \begin{bmatrix} b_{21} & -b_{21} & 0 \\ 0 & b_{32} & -b_{32} \\ 0 & 0 & b_{03} \end{bmatrix},$$

and matrix algebra identifies the mean value function and compartmental covariance kernel as

$$\mu_T(t) = 4000\, a(t)$$

$$\sigma_{ab} = 4000\, a(t_b)[1 - a(t_a)]$$

where now

$$a(t) = [z_1 + z_2 + z_3]^{-1}[z_1 e^{-b_{21}t} + z_2 e^{-b_{32}t} + z_3 e^{-b_{03}t}]$$

with

$$z_1 = b_{32}b_{03}(b_{32} - b_{03})$$

$$z_2 = b_{21}b_{03}(b_{03} - b_{21})$$

$$z_3 = b_{21}b_{32}(b_{21} - b_{32}) \,.$$

This regression model was fit to the data of Table 3 by ordinary least squares with resulting parameter estimates

$$\hat{b}_{21} = 0.0294 \pm .0005$$

$$\hat{b}_{32} = 0.6265 \pm .0673$$

$$\hat{b}_{03} = 16{,}384. \pm 3.401 \times 10^{7}$$

and with no appreciable reduction in the error mean square. Clearly the astronomical turnover of the third compartment indicates the absence of such compartment; the model was thus rejected in favor of the previous two compartment system.

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