# SIMULTANEOUS ESTIMATION BY PARTIAL TOTALS FOR COMPARTMENTAL MODELS

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## 1. INTRODUCTION

In the study of biological systems, many problems require that the system be considered to be composed of several subsystems called compartments. The studies in bioavailability are specially designed so as to determine the rates of exchange of chemical compound or drug among various compartments. In many biological studies, radioactive tracers are used and the study of the system as composed of several compartments become very explicit. Animal nutritionists and Soil Physicists identify a great variety of material for which the compartmental modelling is useful. The gastrointestinal tract may be conceptualized as a series of compartments and indeed Blaxter *et al.* [3], by assuming deterministic behaviour, have obtained 'good' fits of experimental data to a very restricted 4-compartment model.

In this paper we present an estimation procedure which can be used to obtain initial estimates of the parameters present in the following set of p-regression equations:

$$Y_i(t)=\alpha_{io}+\sum_{k=1}^{p}\alpha_{ik}\, e^{-\lambda_k t}+E_i(t) \qquad \ldots(1.1)$$

for $i=1, 2, \ldots, p$ and $t=0, 1, 2, \ldots, N-1$.

In this expression $Y_i(t)$ and $E_i(t)$ represent random variables associated with the $t$th observation on the $i$th compartment. $t$ is a fixed and known independent variable; and $\alpha_{ik}$'s and $\lambda_k$'s are parameters. The estimation procedure developed in Section 3 is for equally spaced values of $t$. In Section 2 we show that certain compartmental models for radioactive tracer experiments give rise to regression equations like (1.1).

For the nonlinear models above, application of the Least Squares method results in equations which are in general soluble only by iteration. The Least Sequares computations have several unusual features when applied to linear combinations of exponentials. The most unusual aspect is the frequent failure of the iterative computation schemes to converge. Secondly, the iterative process converges but the resulting estimators may not be the least squares estimates. These pitfalls of Least Squares computations have been discussed by Confield *et al.* [5]. For successful implementation of iterative procedure, one needs 'good' initial estimates of parameters appearing in a non-linear fashion in these models. Sometimes the initial estimates may provide the most consistent estimates of the parameters if facilities for computation of iterative least squares are not available.

Since the exponential parameters $\lambda_1$, $\lambda_2$, .... $\lambda p$ appear in each of the regression equations of (1.1), we make use simultaneously of all of the observations on all of the equations being studied to estimate these parameters. Beauchamp and Cornell [1], present simultaneous estimation procedure to provide a simple alternative to the least squares procedures or can be used to compute initial estimates for such procedures. Their estimation procedure is a generalization of the partial totals technique given by Cornell [4], who considered the estimation problem for a single regression equation. It has been pointed out by Singh [7] that Cornell's method has several limitations and in some cases does not provide good initial estimates. The estimation procedure presented in section 3 is a generalization of the partial totals techniques given by Singh [7], who considered the estimation problem for a single regression equation that is a linear combination of exponential terms. In section 4 some of the properties of the procedure presented in Section 3 are investigated and some modifications are given which make the procedure more versatile.

## 2. MODELS

The use of radioactive tracers in biological investigations is an example of an experimental situation which yields data that may be reasonably described by a set of regression equations given in (1.1). Berman and Schoenfeld [2] and Sheppard [6] have discussed the formulation of mathematical models for such experiments. It is assumed that there are fixed transition probabilities or turnover rates from one compartment to another, and the whole system is assumed to be in steady state. The turnover rates are assumed to be proportional to the amounts of material in the compartment.

We consider a $p$-compartment system where data are collected from each compartmenl at equi-spaced time intervals. Compartmental models may be described by a system of $p$ linear differential equations with constant coefficients given by

$$\frac{d\,E\,[\underset{\sim}{Y}\,(t)]}{dt} = \underset{\sim}{V}\,E\,[\underset{\sim}{Y}\,(t)] \qquad ...(2.1)$$

Here, $\underset{\sim}{Y}\,(t)$ is an $p\times 1$ matrix and $\underset{\sim}{V}$ is the $p\times p$ matrix of coefficients. Each element of the column Vector $\underset{\sim}{Y}\,(t)$ measures the content of a compartment at time $t$. The matrix $\underset{\sim}{V}$ is defined by

$$\underset{\sim}{V} = \left\{ \begin{array}{ll} v_{ij} & i\neq j \\ -\sum\limits_{\substack{k=0 \\ k\neq j}}^{p} v_{kj} & i=j \end{array} \right\}$$

where $v_{ij}$ is the fractional rate of transfer from compartment $j$ to compartment $i$ and $v_{oj}$ is the fractional rate of transfer from compartment $j$ out of the system. The solution to the equations (2.1) is given by a set of $p$ regression equations.

$$E[y_i(t)] = \alpha_{io} + \sum_{k=1}^{p} \alpha_{ik}\, e^{-\lambda_k t}$$

for $i=1,2,\ldots, p$ and $t=0, 1, 2, \ldots, N-1$.

Constants $\alpha_{ik}$ are functions of the $v_{ij}$ and the initial conditions of the experiment. $\lambda_1, \lambda_2 \ldots, \lambda_p$ are the characteristic roots of $-\underset{\sim}{V}$. Throughout this paper we assume that the characteristic roots of $\underset{\sim}{V}$ are real and distinct.

During the development of the estimation procedure given in the next section, the only assumption that we need to make about the random variables $\epsilon_i(t)$ is that $E[\epsilon_i(t)]=0$ for all $i$ and $t$. However, additional assumptions are needed in order to investigate some of the properties of the estimators found by this procedure and these will be given in Section 4.

## 3. General Estimation Procedure

We consider a $p$-compartment system where data are collected from each compartment. Writing $\rho_k=\exp.\ (-\lambda_k)$, $\lambda_k>0$, the

$p$-compartment system is represented by a set of $p$ regression equations

$$Y_i(t)=\alpha_{io}+\sum_{k=1}^{p}\alpha_{ik}\,\rho_k^t+\epsilon_i(t) \qquad \text{...(3.1)}$$

for $i=1,2,\ldots,p$ and $t=0, 1, 2,\ldots, N-1$.

Since the parameters $\rho_1, \rho_2 \ldots \rho_p$ appear in each one of the regression equations of (3.1), we make use simultaneously of the observations on all the equations being studied to estimate these parameters. In this section we present the partial totals estimation technique for the above model (3.1) in two cases:

**Case I**

When $\alpha_{io}=0$ for all $i$, $i=1, 2,\ldots, p$,

and let $N=(p+1)m$.

**Case II**

When $\alpha_{io}\neq 0$ for $i=1, 2, \ldots, p$

and let $N=(p+2)m$.

We assume that $p$ and $m$ are positive integers. Also to implement the procedure, we assume that the observations are specified at equally spaced values of $t$. First we consider the Case I.

Group the observations from each compartment into $(p+1)$ groups each containing $m$ observations. Then the following partial totals are formed :

$$S_{ih}=\sum_{j=0}^{m-1}y_i[h+(p+1)j], \qquad \text{...(3.2)}$$

$h=0, 1, 2, \ldots, p,$

$i=1,2,\ldots, p.$

These partial sums, $S_{ih}$, have expectation, $S_{ih}$ given by

$$E[s_{ih}]=S_{ih}=\sum_{k=1}^{p}\alpha_{ik}\,\rho_k^h\,\frac{(1-\rho_k^{(p+1)m})}{(1-\rho_k^{(p+1)})} \qquad \text{...(3.3)}$$

Since $\rho_k$ are distinct, it is easy to verify that the polynomials,

$S_{ih}$, satisfied the $p$th order difference equations,

$$\sum_{h=0}^{p}(-1)^{2p-h}\,\Lambda_{p-h}\,S_{ih}=0, \qquad \text{...(3.4)}$$

$i=1, 2,\ldots, p,$

where, for $r=1, 2, \ldots, p$, the elementary symmetric functions equal the sum of all possible products, that is,

$$\Lambda_r = \sum (\rho_{j1}\, \rho_{j2} \cdots \rho_{jr}), \qquad \ldots(3.5)$$

summation is over $\binom{p}{r}$ different combinations $\Lambda_o=1$. Replacing $S_{ih}$ by $s_{ih}$ in (3.4) we obtain estimators $\hat{\Lambda}^r$ of the $\Lambda_r$ from the equations

$$\sum_{h=0}^{p} (-1)^{2p-h}\ \hat{\Lambda}_{p-h}\, s_{ih}=0 \qquad \ldots(3.6)$$

$$t=1, 2, \ldots, p.$$

Let $\underset{\sim}{A}$ be a $p \times p$ matrix whose $j$th column is $(s_{1j}, s_{2j}, \ldots, s_{pj})^T$ and $\underset{\sim}{A}_j$ be a matrix obtained by replacing the $(p-j)$th column of $\underset{\sim}{A}$ by the column vector $(s_{1p}, s_{2p}, \ldots, s_{pp})^T$.

Then by Cramer's rule we have

$$\hat{\Lambda}_r = (-1)^{r+1} \frac{|\underset{\sim}{A}_j|}{|\underset{\sim}{A}|}, \quad r=1, 2, \ldots, p. \qquad \ldots(3.7)$$

Since the $\hat{\Lambda}_r$ estimate the elementary symmetric functions of the $\rho_k$, the estimators $r_k$ of the $\rho_k$ is given by the $p$ roots of the equation

$$x^p - \frac{|\underset{\sim}{A}_1|}{|\underset{\sim}{A}|} x^{p-1} - \frac{|\underset{\sim}{A}_2|}{|\underset{\sim}{A}|} x^{p-2} - \ldots - \frac{|\underset{\sim}{A}_p|}{|\underset{\sim}{A}|} = 0 \qquad \ldots(3.8)$$

For estimators $\hat{\lambda}_k$ of the $\lambda_k$ we take $\hat{\lambda}_k = -\log_e r_k$.

The method of partial sums may similarly be applied in Case II. Here we assume that there are $(p+2)\,m$ observations. We form the partial sums,

$$s^{*\prime}_{ih} = s^{*}_{ih} - s^{*}_{i(h+1)}$$

for

$$i=1, 2, \ldots, p,$$

$$h=0, 1, 2, \ldots, p,$$

where

$$s^{*}_{ih} = \sum_{j=0}^{m-1} y_i\,[h+(p+2)j],$$

clearly,

$$E\left[\; s^{*}_{ih} \;\right] = S^{*}_{ih} = m\,\alpha_{io} + \sum_{k=1}^{p} \alpha_{ik}\,\rho_k^{h}\;\frac{(1-\rho_k^{(p+2)m})}{(1-\rho_k^{(p+2)})}$$

and

$$S^{*\prime}_{ih} = S^{*}_{ih} - S^{*}_{i(h+1)}\;.$$

The following difference equation is satisfied for each $i$ by the $S^{*\prime}_{ih}$ :

$$\sum_{h=0}^{p} (-1)^{2p-h}\;\Lambda_{p-h}\;S^{*\prime}_{ih} = 0 \qquad \ldots(3.10)$$

for $i=1, 2, \ldots, p$.

Equations (3.10) are the same as (3.4) except that $S^{*\prime}_{ih}$'s have been substituted for $S_{ih}$s. As in case I, the estimators $r_k$ of the $\rho_k$'s are obtained using $s^{*\prime}_{ih}$'s instead of the $s_{ih}$s,

$$i=1, 2, \ldots, p \text{ and } h=0, 1, 2, \ldots, p.$$

Now to obtain the estimators for $\alpha_{ik}$'s, $r_k$ are substituted in place of $\rho_k$ in equation (3.1) giving $p$ regression equations. These are linear in the unknown coefficients $\alpha_{ik}$ and give their estimates using the weighted least squares procedure.

There may be situations where exponentials are well separated in time ($t$) that is, when $\lambda_i >> \lambda_j$. ($i > j$, $i$, $j=1, 2, \ldots, p$), yield data known as 'decay type' data. In such situations a modification in forming partial sums is recommended. Partial sums may be sequentially formed with first $2(p+1)$ or $4(p+1)$ observations for case I and with first $2(p+2)$, $3(p+2)$, or $4(p+2)$ observations for case II. The initial estimates based on modified partial sums are likely to be better if error variances are large. In practice it is generally observed that data are not collected at equi-spaced time intervals after certain stage of collection of data. In such situations the modified sequential estimation procedure of partial sums still works.

## 4. Consistency of the Estimators

The partial-totals estimators are not in general unbiased since they are solutions of polymonials, they are consistent estimators. The following assumptions are made :

(*i*) For each value of $i=1, 2,..., p$, the random variables $\epsilon_i(t)$, for all values of $t$, are uncorrelated with $E[\epsilon_i(t)]=0$.

(*ii*) For each value of $i$ and $h$ the random variables $\epsilon_i(t)$ associated with the corresponding observations $y_i(t)$ in $s_{ih}$ or $s_{ih}'$ have common variance.

(*iii*) For each value of $i$ and $h$ the domain of the independent variable is of constant length, $T$, for $s_{ih}$ or $s_{ih}'$ where $i=1, 2, ..., p$ and $h=0, 1, 2,..., p$.

(*iv*) For $\underset{\sim}{\alpha}=(\alpha_{ik})$, a $p\times p$ matrix,

$$|\underset{\sim}{\alpha}| \neq 0.$$

The proof of consistency follows along the lines of Singh [7] and can be easily varified.

## Summary

This paper describes a technique for obtaining the initial estimates of the exponential parameters in a set of regression equations which are linear combinations of the same exponential parameters, and the number of independent regression equations is the same as the number of exponential parameters. The regression models considered are shown to arise from radioactive tracer experiments using compartmental models. The estimation procedure is developed under the assumption of equally spaced values of the independent variable. The method utilizes independent partial totals and provides a direct and simple procedure. Modifications are presented that make the estimation procedure more versatile to decay-type data where exponentidls are well separated.

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