INFERENCE IN STOCHASTIC COMPARTMENT MODELS

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(Received : November, 1975)

1. INTRODUCTION

Recently a new branch of biomathematical modelling called compartment analysis has been developed. The concept of compartment analysis assumes that a system may be divided into homogeneous components, or compartments. Various characteristics of the system are determined by observing the movement of tracer material.

Usually the theory is applied to describe the movement of a population of tracer molecules, *e.g.*, the flow of iron molecules within sheep. Possibly since the individual molecules are infinitesimal in size, nearly all the previous literature has made the implicit assumption of a deterministic flow pattern. In this paper we consider a discreat population of practicles in a steady state compartment system where the transitions are stochastic. The importance of the study of stochastic compartment models have been stressed by many authors, for a recent development, *see* Rustagi (1964, 1965). Cornfield *et al.* (1960) also poiuted out that the stochastic compartment model is more realistic and should be investigated. Matis and Hartley (1971) considered probability distribution theory of a general p-compartments and its implimentation into an estimation procedure.

Compartment analysis finds application in many diverse areas of biomedical science. Also animal nutritionists identify a great variety of materials for which the stochastic model describing the passage of a given material through the gastrointestinal tract of ruminants,

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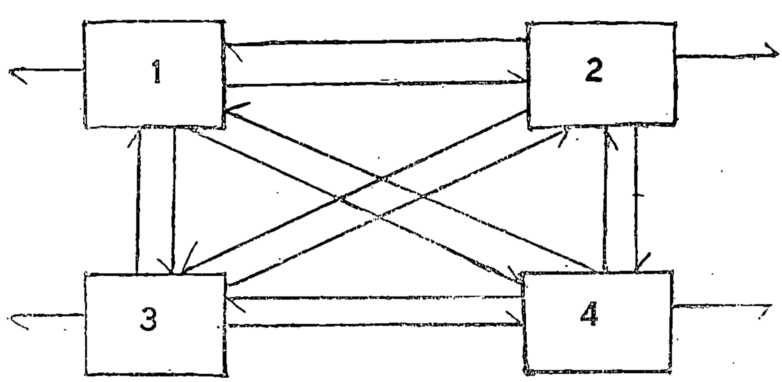
e.g. cattle and sheep, is useful. One particular substance of interest to animal nutritionists consists of indigestible plastic beads used as roughage substitute.

In this paper the stochastic compartment model is developed. The probability generating function for the p random variables specifying the number of tracer particles is derived. Also the results obtained by Matis and Hartley (1971) are obtained through a direct and simplified approach and the probability meanings of the functions defined by them are provided. Some fallacies in the non-linear least squares estimation of the parameters from time-series data on fecal output are pointed out.

2. Derivation of p-Compartment Stochastic Model

Consider a general p-compartment system, where each compartment is connected to each other and to the system exterior. In this system, there are p^2 parameters. Figure (2.1) represents a general $p=4$ compartment system with $p^2=16$ paramaters



A4-Compartment System.

Let v_{ji} be the transitson intensity or 'turnover rate' from compartment i to compartment j, where v_{oi} represents an excretion from compartment i. Then, by definition, $v_{ji}\triangle t$ is the probability that a particular unit migrates from compartment i to compartment j in the time interval $\triangle t$,

For $0<\tau<t$, let

$$v_{ji}\triangle + 0(\triangle) = P_{ji}(\tau, \tau+\triangle)$$

$$= P_r[\text{an individual in compartment } i \text{ at time } \tau \text{ will be in compartment } j \text{ at time } \tau+\triangle],\ i\neq j \qquad \text{...(1)}$$

$$1+v_{ii}\triangle+0(\triangle) = P_{ii}(\tau, \tau+\triangle),\ i=1, 2, \ldots, p. \qquad \text{...(2)}$$

$v_{oi}\triangle+0(\triangle)=P_{oi}\,(\tau,\,\tau+\triangle),$

$=P_r$ [an individual in compartment i at time τ will be in exterior of the system at time $\tau+\triangle$], ...(3)

where $v_{ii}=-\sum_{j\neq i}^{P} v_{ji}$, a linear combination of all rates leaving compartment i,

and $0\,(\triangle)$ represents any function such than $\lim_{\triangle\to 0}\left[\frac{0(\triangle)}{\triangle}\right]=0$

The probability of more than one migration in time $\triangle$ is $0(\triangle)$.

For convenience we introduce the transition intensity matrix

$$\underset{\sim}{V}=\begin{bmatrix} v_{11} & v_{21} & \cdots & v_{p1} \\ v_{21} & v_{22} & \cdots & v_{p2} \\ - & - & \cdots & - \\ - & - & \cdots & - \\ - & - & \cdots & - \\ v_{1p} & v_{2p} & \cdots & v_{pp} \end{bmatrix} \qquad \ldots(4)$$

and

$$\underset{\sim}{U}=(v_{o1},\,v_{o2},\,\ldots,\,v_{op})' \qquad \ldots(5)$$

For a time interval $(0,\,t)$, $0\leq t<\infty$, let

$$P_{ji}\,(t)=P_{ji}\,(0,\,t),\; i, j=1,\,2,\ldots,\,p$$

$$P_{oi}\,(t)=P_{oi}\,(0,\,t),\; i=1,\,2,\cdots,\,p,$$

with $\quad P_{ii}\,(0)=1,\; P_{oi}\,(0)=0,\; P_{ji}\,(0)=0,$

and further let

$$\underset{\sim}{P}(t)=\begin{bmatrix} P_{11}(t) & P_{21}(t) & \cdots & P_{p1}(t) \\ P_{12}(t) & P_{22}(t) & \cdots & P_{p2}(t) \\ - & - & \cdots & - \\ - & - & \cdots & - \\ - & - & \cdots & - \\ P_{1p}(t) & P_{2p}(t) & & P_{pp}(t) \end{bmatrix} \qquad \ldots(6)$$

$$\underset{\sim}{P_o}(t)=[P_{o1}(t),\;P_{o2}(t),\ldots,\;P_{op}(t)] \qquad \ldots(7)$$

with $\quad \underset{\sim}{P}(0)=\underset{\sim}{I}$ and $\underset{\sim}{P_o}\,(0)=\underset{\sim}{0}.$

The following assumptions are made :

Assumption 1. v_{ij} are independent of time.

Assumption 2. The system is elosed:

Whatever may be $t \geq 0$ and for every i, we have

$$\sum_{j=0}^{P} P_{ji}(t)=1, \qquad \ldots(8)$$

so that the intensities and the transition probabilities have the relations :

$$v_{ji} = \frac{d}{dt} P_{ji}(t)\Big|_{t=0}, \quad i, j=1, 2, \ldots, p.$$

$$v_{oi} = \frac{d}{dt} P_{oi}(t)\Big|_{t=0}$$

Assumption 3. The matrix $\underset{\sim}{V}$ is of full rank and the matrix $\underset{\sim}{U}$ is not a zero matrix.

Therefore none of the compartments i is an absorbing compartment, and there is excretion to the system exterior.

Now consider $\tau < t < t+\triangle$,

then,

$$P_{ki}(\tau, t+\triangle)=P_{ki}(\tau, t)\, P_{kk}(t, t+\triangle)+\sum_{j\neq k} P_{ji}(\tau, t)\, P_{kj}(t, t+\triangle) \qquad \ldots(9)$$

Using (2), the equation (9) can be expressed as

$$\frac{P_{ki}(\tau, t+\triangle)-P_{ki}(\tau, t)}{\triangle}$$

$$=P_{ki}(\tau, t)\, v_{kk}+\sum_{j\neq k} P_{ji}(\tau, t) . \frac{P_{kj}(t, t+\triangle)}{\triangle}+\frac{0(\triangle)}{\triangle} \qquad \ldots(10)$$

Taking limit as $\triangle \to 0$, we have

$$\frac{\partial}{\partial t} P_{ki}(\tau, t)=\sum_{j=1}^{p} P_{ji}\, v_{kj} \qquad \ldots(11)$$

since v_{ji} are assumed to be independent of time, the system of differential equations (11) are

$$\frac{d}{dt} P_{ki}(t)=\sum_{j} P_{ji}(t)\, v_{kj} \qquad \ldots(12)$$

These equations are known as Kolmogorov forward differential equations. The corresponding matrix equation describing the p-compartment stochastic model is

$$\underset{\sim}{D}\ \underset{\sim}{P}\ (t)=\underset{\sim}{P}(t)\ \underset{\sim}{V},$$

or

$$(\underset{\sim}{D}-V')\ \underset{\sim}{P}\ (t)=\underset{\sim}{Q}, \qquad ...(13)$$

where

$$\underset{\sim}{D}=\begin{bmatrix} \frac{d}{dt} & 0 & \cdots & 0 \\ 0 & \frac{d}{dt} & \cdots & 0 \\ - & - & \cdots & - \\ - & - & \cdots & - \\ - & - & \cdots & - \\ 0 & 0 & & \frac{d}{dt} \end{bmatrix}$$

and $\underset{\sim}{P}'(t)$ and V' are the transposed matrices of $\underset{\sim}{P}(t)$ and $\underset{\sim}{V}$ respectively.

3. Solution of Stochastic Model

The stochastic model for the p-compartmental system is given in (13). In case $p=1$, the differential equation

$$\underset{\sim}{D}\ \underset{\sim}{P}(t)=\underset{\sim}{P}(t)\ \underset{\sim}{V}$$

is an ordinary first order differential equation with a constant coefficient. Formally, the solution of it is given by

$$\underset{\sim}{P}(t)=e^{\underset{\sim}{V}t}\ P(0) \qquad ...(14)$$

Defining the matrix exponential

$$e^{\underset{\sim}{V}t}=\sum_{n=0}^{\infty} \frac{\underset{\sim}{V}^n . t^n}{n!}, \qquad ...(15)$$

equation (14) provides a solution of the matrix differential equation (13) as

$$\underset{\sim}{P}(t)=e^{\underset{\sim}{V}t} . \underset{\sim}{P}(0). \qquad ...(16)$$

The formal solution (16), however, is not very useful from a practical point of view. For the purpose of application we need explicit functions for the individual transition probabilities $P_{ji}(t)$ that will satisfy the differential equation. Such functions depend on the eigen values of $\underset{\sim}{V}$. Let $\delta_1, \delta_2, \ldots, \delta_p$ be the eigen values of $\underset{\sim}{V}$ and let A_{ij} be the cofactor of (i, j)th element of the matrix $\underset{\sim}{A}(l)=(\delta_l \underset{\sim}{I}-\underset{\sim}{V})$. Let $\underset{\sim}{T}_l\ (k)=[A_{k1}\ (l),\ A_{k2}\ (l)\ \ldots,\ A_{kp}\ (l)]'$ be an eigen vector of $\underset{\sim}{V}$ corresponding to δ_l. The matrix of eigen vectors,

$$\underset{\sim}{T}(k)=[T_1\ (k),\ T_2\ (k),\ \ldots,\ T_p\ (k)]=(T_{jl}{}^{(k)})$$

diagonalizes $\underset{\sim}{V}$. The determinant of $\underset{\sim}{T}(k)$ is denoted by $|\ \underset{\sim}{T}(k)\ |$.

Then following the approach of Chiang (1968) for 'illness-death' process, it can be seen that the explicit solution for the transition probabilities is given by

$$P_{ji}(t)=\sum_{l=1}^{p} A_{ki}\ (l)\ \frac{T_{jl}\ (k)}{|\ \underset{\sim}{T}(k)\ |}\ e^{\delta_l\ t}, \qquad \ldots(17)$$

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

Equation (17) holds true whatever may be $k=1,\ 2,\ \ldots,\ p$. Chiang [1968, pp 138-140] considers equation (15) and expresses $\underset{\sim}{V}$ and its various powers in terms of the matrix of eigen vectors $\underset{\sim}{T}(k)$, its inverse $T^{-1}(k)$ and the diagonal matrix of eigen values. Then expending the solution of $\underset{\sim}{P}(t)$ is obtained the explicit solution for the transition probabilities as given in equation (17).

The transition probabilities $P_{0i}(t)$ and the corresponding transition matrix $P_0(t)$ is derived utilizing probabilities $P_{ji}(t)$. An individual in compartment i may reach the exterior of the system directly from compartment i or by way of some other compartment $j,\ j\neq i$. Since an individual in exit at time t may have reached that state at any time prior to t, let us consider an infinitesimal time interval $(\tau,\ \tau+d\tau)$ for a fixed $\tau,\ 0<\tau\leq t$. The probability of an event A_i, where A_i is such that an individual in compartment i at time zero will reach out of the system in the interval $(\tau,\ \tau+d\tau)$ is given by

$$P\,(A_i)=P_{ii}(\tau)\ \nu_{0i}\ \ d\tau+\sum_{\substack{j=1\\ j\neq i}}^{p} P_{ji}\ (\tau)\ \nu_{0j}\ d\tau$$

As τ varies over the interval (0, t) the events A_i, are mutually exclusive. Hence

$$P_{0i}(t)=\int_0^t \left(\sum_{j=1}^{p} P_{ji}(\tau)\, v_{0j} \right) d\tau$$

The individual transition probability $P_{0i}(t)$ can be obtained from above expression in the form given below; see Singh [1975],

$$P_{0i}(t)=\sum_{l=1}^{p}\sum_{j=1}^{p} A_{ki}(l)\, \frac{T_{jl}(k)}{|\underset{\sim}{T}(k)|}\, \delta_l^{-1}\, (e^{\delta_l t}-1)\, v_{0j} \quad \ldots(18)$$

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

4. Population Sizes and Associated Probability Distribution

An individual in compartment i at time 0 must be either in one of the compartments or in the exterior of the system at time t. Consequently the corresponding transition probabilities add to one, so that

$$\sum_{j=1}^{p} P_{ji}(t)+P_{0i}(t)=1. \quad \ldots(19)$$

Equation (19) may be used to derive the probability distribution of population sizes in p-compartments at any time t. Let $N_i(0)$ denote the number of individuals in compartment i at time 0. Let $N_i(t)$ be a random variable specifying the number of individuals in compartment i at time t. The initial size of the population is

$$N(0)=\sum_{i=1}^{p} N_i(0).$$

$N_j(t)$ can be characterized according to their states at time 0. This is expressed by the formula

$$N_i(t)=N_{i1}(t)+N_{i2}(t)+\ldots+N_{ip}(t),$$

where $N_{ij}(t)$ is the number of individuals in compartment i who were in compartment j at time 0. On the other hand, each of the $N_i(0)$ individuals in compartment i at time 0 must be in one of the compartments or in the exterior of the system at time 0. That is, at any instant t,

$$N_i(0)=\sum_{j=1}^{p} N_{ji}(t)+N_{0i}(t). \quad \ldots(20)$$

Therefore given N_i (0), the random variables on the right side of (20) have joint multinomial distribution.

The following assumption is made :

The behaviour of the $N_i(0)$ individuals in distributing themselves among the various compartments is independent of $N_j(0)$ individuals originating in compartment $j, j \neq i$. It is to be noted that the random variables $N_i(t)$, $i=0, 1, 2, \ldots, p$ are not independently distributed.

For each i the random variable $N_{ji}(t)$, $j=0, 1, 2, \ldots, p$ have a multinomial distribution and their probability generating function (pgf) is given by

$$E\left[s_1^{N_{1i}(t)} s_2^{N_{2i}(t)} \ldots s_p^{N_{pi}(t)} s_o^{N_{oi}(t)} \mid N_i(0)\right]$$
$$=[P_{1i}(t)s_1+P_{2i}(t)s_2+ \ldots +P_{pi}(t)s_p+P_{oi}(t)s_o]^{N_i(0)} \quad \ldots(21)$$

Therefore the pgf of the joint probability distribution for the population sizes of all the compartments at time t is

$$E\left[s_1^{N_1(t)} s_2^{N_2(t)} \ldots s_p^{N_p(t)} s_o^{N_o(t)} \mid N_1(0), N_2(0), \ldots N_p(0)\right]$$
$$=\prod_{i=1}^{P} [P_{1i}(t)\, s_1+P_{2i}(t)\, s_2+ \ldots +P_{pi}(t)\, s_p+P_{oi}(t)\, s_o]^{N_i(0)}$$
$$=\mathrm{P}\,[s_1, s_2, \ldots, s_p, s_o], \text{ say} \quad \ldots(22)$$

The joint probability distribution is then given by

$$P\,[N_1(t)=n_1, N_2(t)=n_2, \ldots, N_p(t)=n_p, N_o(t)=n_o \mid N_1(0), N_2(0), \ldots, N_p(0)]$$
$$=\sum \prod_{i=1}^{P} \frac{N_i(0)\,!}{n_{1i}\,!\; n_{2i}\,! \ldots n_{pi}\,!\; n_{oi}\,!}$$
$$P_{1i}^{n_{1i}}(t)\, P_{2i}^{n_{2i}}(t) \ldots P_{pi}^{n_{pi}}(t)\, P_{oi}^{n_{oi}}(t)$$

where the summation is taken over all possible values of n_{ji}, i, $j=1, 2, \ldots, p$, such that

$$n_{ij}+n_{2j}+ \ldots +n_{pj}=n_j, \; j=0, 1, 2, \ldots, p$$

The cumulant generating function, using $s_i=e^{\theta_i}$, is given by

$$k(\theta_1, \theta_2, \ldots, \theta_p\,;\, t)=\log P\,(e^{\theta_1}, e^{\theta_2}, \ldots, e^{\theta_p}, e^{\theta_o})$$
$$= \sum_{i=1}^{P} N_i(0) \log\left[\sum_{j=0}^{P} P_{ji}(t)\, e^{\theta_j}\right] \quad \ldots(23)$$

Noting that $s_o=1$ and consquently $\theta_o=0$, result in (23)is equivalent to

$$k\ (\theta_1, \theta_2, \ldots, \theta_p\,; t)=\sum_{i=1}^{P} N_i(0) \log\left[\sum_{j=1}^{P} (e^{\theta_j}-1)\, P_{ji}\,(t)+1\right] \quad \ldots(24)$$

The expression in (24) turns out the same as obtained by Matis and Hartley [1971]. Their approach, of course, is lengthy and much involved.

The first moments of the compartments, $\mu_i(t)=E[N_i\,(t)]$, are particularly interesting. These can be computed directly from (21). Clearly

$$\mu_i(t)=\sum_{j=1}^{P} N_j\,(0)\, P_{ij}(t),\ i=1, 2, \ldots\ P \qquad (25)$$

Letting

$$\underset{\sim}{M}(t)=[\mu_1(t), \mu_2(t), \ldots, \mu_p(t)],$$

equations in (25) can be expressed in matrix notation as

$$\underset{\sim}{M}(t)=\underset{\sim}{P}'\,(t)\,\underset{\sim}{M}(0) \qquad \ldots(26)$$

Differentiating both sides of (26) with respect to t, we get

$$\frac{d}{dt}\,\underset{\sim}{M}(t)=\underset{\sim}{D}\,\underset{\sim}{P}'\,(i)\,\underset{\sim}{M}(0)$$

$$=\underset{\sim}{V}'\,\underset{\sim}{P}'(t)\,\underset{\sim}{M}(0)$$

$$=\underset{\sim}{V}'\,\underset{\sim}{M}(t) \qquad \ldots(27)$$

Equation (27) is identical to the deterministic equations of a general p-compartment system. That is, when $N_i(0)$, $i=1, 2, \ldots, p$, are given constants and the probabilities are intensities, the stochastic mode is the deterministic one.

The corresponding variances and covariances are

$$\sigma^2_{N_i}\,(t)=\sum_{j=1}^{P} N_j\,(0)\,P_{ij}\,(i)\,[1-P_{ij}\,(t)],$$

$$i=0,\ 1, 2, \ldots, P.$$

$$\sigma_{N_i(t),\,N_k(t)}=-\sum_{j=1}^{P} N_j(0)\,P_{kj}(t)\,P_{ij}(t).$$

In practical situations, one observes the number of individuals excreted to the exterior of the system as observations on individual compartments are either impossible or difficult. Let $N_T(t)$ denote the number individuals remaining in the system at time t. Clearly

$$N_T(t) = \sum_{i=1}^{P} N_i(t)$$

and

$$E[N_T(t)] = \mu_T(t) = \sum_{j=1}^{P} \sum_{i=1}^{P} N_i(0)\, P_{ji}(t)$$

$$= N(0) - \sum_{i=1}^{P} N_i(0)\, P_{oi}(t)$$

5. Joint Probability Distribution of the Numbers in the System at Different Times

Let, for a given u,

$$\underset{\sim}{N}'_T = [N_T(t_1), N_T(t_2), \ldots, N_T(t_u)]$$

be the number of individuals in the system at time $t_1, t_2, \ldots, t_u$ respectively. The pgf of the joint probability distribution of $\underset{\sim}{N_T}$ is given by

$$G_{\underset{\sim}{N_T}} \Big| N(0)\, (s_1, s_2, \cdots, s_u) = E[s_1^{N_T(t_1)} s_2^{N_T(t_2)} s_u^{N_T(t_u)} \Big| N(0)], \quad \ldots (28)$$

where $|s_i| \leq 1$ for $i = 1, 2, \ldots, u$.

To derive an explicit formula for the pgf (28), we use the identity

$$E[s_1^{N_T(t_1)} s_2^{N_T(t_2)} \ldots s_u^{N_T(t_u)} \mid N(0)]$$

$$= E\, [s_1^{N_T(t_1)} \ldots s_{u-1}^{N_T(t_{u-1})} E\{s_u^{N_T(t_u)} \mid N(t_1), \ldots, N(t_{u-1})\}] \mid N(0)]. \quad \ldots (29)$$

Using the Markov property, equation (28) becomes

$$= E\, [s_1^{N_T(t_1)} \ldots s_{u-1}^{N_T(t_{u-1})} E\, \{s_u^{N_T(t_u)} \mid N_T(t_{u-1})\} \mid N(0)].$$

Repeated application of the same process gives

$$G_{\underset{\sim}{N_T}} \Big| N(0)\, (s_1, s_2, \ldots, s_u) = [1 - \{(1-P_{01})(1-s_1) + (1-P_{02})\, s_1 (1-s_2)$$

$$+ (1-P_{03})\, s_1 s_2 (1-s_3) + \ldots + (1-P_{0u})(s_1 s_2 \ldots s_{u-1})(1-s_u)\}]^{N(0)} \ldots (30)$$

Here P_{0i} is defined to be the probability that the individual in the system moves out of the system in the interval

$$(0, t_i),\ i = 1, 2, \ldots, u.$$

Expression in (30) is then used for deriving the joint probability function $\underset{\sim}{N}_T$ and their moments are given below.

$$\sigma_i^2 = \text{Var}\,[N_T(t_i)] = \text{Var}\left[\sum_{k=1}^{P} N_k(t_i)\right]$$

$$= \text{Var}\,[N(0) - N_o(t_i)]$$

$$= \sum_{k=1}^{P} N_k(0) P_{ok}(t_i)\,[1 - P_{ok}(t_i)]. \qquad ...(31)$$

The covariance σ_{ij} of the process at two different times, t_i and t_j is obtained as usual and is given by

$$\sigma_{ij} = \sum_{k=1}^{P} N_k(0) P_{ok}(t_j)\,[1 - P_{ok}(t_i)] \qquad ...(32)$$

These results show that for a given u, $N_T(t_1)$, ..., $N_T(t_u)$ for the process form a chain of binomial distributions. For a given t, $N_k(t)$ can be regarded as a mixture of multinomial distributions. Indeed, $N_T(t_i)$—$N_T(t_j)$ for various intervals of t may also be regarded as a mixture of mutinomial distributions, where the *kth* component results from the $N_k(0)$ units placed in the *kth* compartment. Equations (31) and (32) may be combined into the following result:

Proposition 1. Let σ_{ij}=Cov $[N_T(t_i), N_T(t_j)]$ be covariance kernel of the process describing the total number of individuals in the system at times t_j and t_i such that $t_j \geqslant t_i$. Then

$$\sigma_{ij} = \sum_{k=1}^{P} N_k(0) P_{ok}(t_j)\,[1 - P_{ok}(t_i)].$$

SUMMARY

This paper is conerned with a finite tracer population in a steady state compartmental system with probabilistic flow. The system is considered to have p compartments. The differential equations describing p compartment stochastic model are derived. This paper advances the distribution theory considerably by providing a compact analytic solution of the stochastic differential equations for giving transition probabilities, population sizes.

Methods presented here provide an alternative set of procedures to those of Matis and Hartley [1971] which are based on lengthy and unnecessarily complicated approach through cumulant generating

function. This approach has the advantage of giving the analyst the direct probabilistic interpretations of various functions utilized in deriving the probability distributions.

ACKNOWLEDGEMENT

The author is grateful to the refrees for their valuable comments in improving the paper to its present form.

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