A New Mathematical Model to Estimate the Plasma Cortisol Concentration Using Gamma Distribution

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Abstract

The efficacy of the standard high dose ACTH stimulation test (HDT), using a pharmacological 250-mg dose of synthetic ACTH, in the diagnosis of central hypoadrenalism is controversial. The insulin hypoglycemia test is widely regarded as the gold standard dynamic stimulation test of the Hypothalamo-Pituitary-Adrenal (HPA) axis that provides the most reliable assessment of HPA axis integrity and reserve. Alternatively, a prolonged infusion of ACTH causes a continuing rise in plasma cortisol levels that may predict the adrenals' capacity to respond to severe ongoing stress. In this paper, we calculate the plasma cortisol concentration with the help of single buffer multiclass queue.

Key Words: ACTH, HPA, Cortisol, Multiclass Queue & Gamma Distribution

1. Introduction

Hypothalamo-Pituitary-Adrenal (HPA) axis dysfunction is a potentially life threatening condition. It is of paramount importance that safe, reliable diagnostic tests be available to identify patients at risk for adrenal insufficiency. ACTH stimulation testing was originally developed using purified hormone extracted from animal pituitaries [4]. Before reliable ACTH assays were available, performing 8-h infusions of ACTH on 3 consecutive days with measurement of urinary steroid metabolites or plasma 17-hydroxycorticosteroids [3] was established as the best method of differentiating between primary and secondary adrenal insufficiency. More rapid tests were quickly introduced after the development of plasma cortisol assay methods and the synthesis of ACTH [5]. The short ACTH stimulation test, using the standard dose of 250mg ACTH-(1–24) but with varying routes of administration and sampling times, has been widely recommended as a convenient and reliable screening test for the diagnosis of primary or secondary hypoadrenalism [6, 10, 11]. Quantifying the adrenal response to an 8-h infusion of synthetic ACTH, however, remains a valuable test of adrenocortical reserve that may more accurately reflect the degree of cortisol secretion required in response to severe stress [12].

Several recent studies and a review of the performance characteristics of the high dose (250 mg) ACTH stimulation test (HDT) question its efficacy in the setting of secondary adrenal insufficiency. The accepted gold standard test of HPA axis function is the insulin hypoglycemia test (IHT). Inducing hypoglycemia provides a potent stimulus for cortisol secretion via hypothalamic and pituitary activation, mimicking the effects of a major physical or psychological stress. Significant numbers of patients have been described who had a normal cortisol response to a bolus 250-mg dose of ACTH and yet had clearly subnormal responses to either the IHT or other tests designed to assess the integrity of the entire HPA axis, such as the overnight metyrapone test or the glucagon stimulation test.

Peak plasma ACTH concentrations exceed 22,000 pmol/L after the administration of 250 mg synthetic ACTH, levels at least 2 orders of magnitude greater than those measured during major physical stresses such as severe sepsis or multiple trauma or during insulin-induced hypoglycemia. [12] Showed that very much lower doses of exogenous ACTH were sufficient to cause ACTH and cortisol levels similar to those stimulated by insulin hypoglycemia and suggested that administration of more physiological ACTH doses may improve diagnostic accuracy. Maximal short term cortisol secretion can be achieved with ACTH doses much lower than 250 mg; however, the dose suggested has varied in different studies. Low dose ACTH testing (using 1 mg) may be more sensitive than the standard 250-mg test in the detection of HPA axis dysfunction in patients with pituitary disease or using inhaled steroids.

In this paper, we consider a single-buffer multiclass queue. We consider two cases separately: fluid queue and ordinary queue. In the fluid case the input to the queue is fluid that belongs to K different type's modulated K independent Markovian on-off processes. The k^{th} $(k = 1,2, \dots, K)$modulating process on for an exp (μ_k) amount of time and off for an exp (λ_k) amount of time. When it is on, the fluid of type k arrives at rate $r_k > 0$, and no fluid arrives while it is off. Thus the input process of type k is completely described by three parameters: (λ_k, μ_k, r_k). The fluid belonging to all classes accumulates in a single buffer and is removed on a first come first served (FCFS) basis. In a fluid setting, the FCFS discipline is taken to mean that fluid arriving at time t is removed from the buffer only after will be processing fluids of many types simultaneously. The output from such a queue is rather complex. We show that the case of a two-class system. The output processes of different types of fluids are neither independent, nor can be described by three-parameter on-off processes. Our aim is to approximate the output process of type k fluid by three-parameter on-off process with parameters$(\lambda_k^o, \mu_k^o, r_k^o), k = 1,2, \dots K$.

One motivation behind this analysis is in telecommunication networks. The idea of using fluid queues in telecommunications is well established, initiated by the pioneering work by [1]. There is a large literature on fluid queues; wee the survey paper by [1]. Several researchers have also studied networks of fluid queues: see [7] & [8]. Exact analysis of fluid networks is intractable, and hence we need to find methods of approximate analysis. In this regard, earlier work done in queueing networks is a valuable guide. One promising approach is the decomposition approach, as presented by [1] and further refined by [15] in QNA.

A similar approach is also considered by [2] & [9]. The idea is to model the telecommunication network as a network of multiclass fluid queues with FCFS discipline at all nodes. Here we assume that the external fluid inputs to all the nodes in the network are Markovian on-off processes described by three parameters. Then we approximate the output processes from a given node as independent Markovian on-off processes by using the methodology developed here. That is, we think of a node as a non linear mapping of the input to other queues. We seek an equilibrium solution to the nonlinear system where the output parameters are consistent with the input parameters.

It is clear that the results here will be impractical to use for large values of K since the distributions involve matrices of size 2^K. We will develop computationally efficient approximations for computing the output parameters distribution of the input parameters. The results developed here can be used to quantify the case of these approximations. This work is under progress and will be reported at a later case of the ordinary queue is the standard M/G/1 queue with multiple types of customers. Customers belong to K different types and arrive according to K independent Poisson process. The arrival rates and service time distributions are class-dependent. The service time is FCFS. The output analysis of this queue is given in the next section.

2. Output analysis

Accomplish the aim of characterizing the output of fluid type k as a three-parameter on-off times, we define the output process of type k to be 'on' if fluid of type k is emerging from the fluid at a positive rate, and 'off' if no fluid of type k is emerging from the buffer. The distributions of the on and off times of the output process of type k are complicated. Let τ_k^{on} and τ_k^{off} denote their respective means. Then we approximate the output on and off times exponential random variables with parameters

$$\lambda_k^{\mathrm{o}} = \frac{1}{\tau_k^{\mathrm{off}}} \quad (1)$$

$$\mu_k^{\mathrm{o}} = \frac{1}{\tau_k^{\mathrm{on}}} \quad (2)$$

The actual rate at which fluid of type k emerges during the on time of the output process of type differences. The mean input rate of fluid of type k is given by

$$m_k = r_k \frac{\lambda_k}{\lambda_k + \mu_k}$$

It is known that (See [9]) the fluid queue is stable if

$$m = \sum_{k=1}^{K} m_k < c$$

In a stable system, the mean output rate m_k^0 of type k fluid must be the same as its mean input on time. Hence, if we approximate the output rate during the output on time by a constant r_k^0 (which we call the effective peak rate of the output process), we must have

$$m_k^{\mathrm{o}} = r_k^{\mathrm{o}} \frac{\lambda_k^{\mathrm{o}}}{\lambda_k^{\mathrm{o}} + \mu_k^{\mathrm{o}}} = m_k$$

Using (1) and (2) we get

$$r_k^{\mathrm{o}} = r_k \frac{\lambda_k}{\lambda_k + \mu_k} \frac{\tau_k^{\mathrm{on}} + \tau_k^{\mathrm{off}}}{\tau_k^{\mathrm{on}}} \quad (3)$$

Equations (1) to (3) imply that the output process of type k can be approximated by an on-off processes with parameters $(\lambda_k^{\mathrm{o}}, \mu_k^{\mathrm{o}}, r_k^{\mathrm{o}})$ if we know the mean output on time τ_k^{on} and the mean off timeτ_k^{off}.

3. Multiclass M/G/1 Queue

Consider a single server queue with K classes of customer. Customers of class $k(1 \le k \le K)$ arrive according to a Poisson process with rate λ_k and form a single line. They are served by a single server according to a first come first served discipline. The service times of a class k customers are i.i.d with meanν_k. The classes are independent of each other. A multiclass M/G/1 queue with an FCFS service discipline may be regarded as a standard single-class M/G/1 queue arrival rate

$$\lambda = \sum_{k=1}^{K} \lambda_k \quad (4)$$

And mean service time

$$\nu = \sum_{k=1}^{K} \frac{\lambda_k \nu_k}{\lambda} \quad (5)$$

Let $\rho_k = \lambda_k \nu_k$ (6)

The queue is stable if

$$\rho = \sum_{k=1}^{K} \rho_k < 1 \qquad (7)$$

Define $S(t)$ to be the state of he server as follows: $S(t) = 0$ if the server is idle at time t, and $S(t) = k$ if the server is serving a customer of class k at time t. Clearly the $\{S(t), t \geq 0\}$ process is a regenerative process with state space $\{0,1,2, \ldots \ldots, K\}$, and it regenerates whenever a enters state 0. In this section, we compute τ_k, the expected sojourn time in state k, and τ_{kk}, the expected inter visit time to state k. The main result is given in the following theorem.

3.1 Theorem:

Assume that the queue is stable. Then

$$\tau_k = \frac{\lambda \nu_k}{(1-\rho)\lambda_k + (\lambda - \lambda_k)}, \ 1 \leq k \leq K \qquad (8)$$

And

$$\tau_{kk} = \frac{\lambda}{(1-\rho)\lambda_k^2 + \lambda_k(\lambda - \lambda_k)} = \frac{\tau_k}{\rho_k}, 1 \leq k \leq K \qquad (9)$$

Proof:

Since the queue is assumed to be stable, ρ_k is the long-run fraction of the time the server is busy serving customers of class k. Suppose that $S(0) = 0$, and define T to be the first time the S process re-enters state 0. Furthermore, define T_k to be the total time spent in state k of the S process during $(0, T]$, and N_k to be the total number of visits to state k during $(0, T]$. Results from regenerative processes imply that

$$\rho_k = \frac{E(T_k)}{E(T)} \qquad (10)$$

$$\tau_k = \frac{E(T_k)}{E(N_k)} \qquad (11)$$

$$\tau_{kk} = \frac{E(T)}{E(N_k)} \qquad (12)$$

Since $E(T)$ is the expected length of a busy cycle in an M/G/1 queue with arrival rate λ and mean service times ν as given in (4) and (5), we have

$$E(T) = \frac{1}{\lambda} + \frac{\nu}{1-\rho} = \frac{1}{\lambda(1-\rho)}$$

Where ρ is defined in (7). Using (10) we get

$$E(T_k) = \frac{\rho_k}{\lambda(1-\rho)} \qquad (13)$$

Where ρ_k is defined by (6). Next we compute $E(N_k)$. Let N be the total number of customers served during the first busy cycle, and let X_n be the type of the n^{th} customer $(1 \leq n \leq N)$. The FCFS service discipline implies that

$$N_k = I\{X_1 = k\} + \sum_{n=2}^{N} I\{X_{n-1} \neq k, X_n = k\}$$

Hence,

$$E(N_k) = P(X_1 = k) + E\left(\sum_{n=2}^{N} I\{X_{n-1} \neq k, X_n = k\}\right)$$

Using the fact that $\{X_n, n \geq 1\}$ is a sequence of i.i.d random variables with common probability mass function

$$P(X_n = k) = \frac{\lambda_k}{\lambda}, 1 \leq k \leq K$$

We get

$$E(N_k) = \frac{\lambda_k}{\lambda} + \{E(N) \quad 1\}\frac{\lambda_k}{\lambda}\left(1 \quad \frac{\lambda_k}{\lambda}\right)$$

From the results for a standard M/G/1 queue, we know that $E(N) = 1/(1 \quad \rho)$. Using this we get

$$E(N_k) = \frac{\lambda_k^2}{\lambda^2} + \left(\frac{1}{1-\rho}\right)\left(\frac{\lambda_k}{\lambda}\right)\left(1 \quad \frac{\lambda_k}{\lambda}\right) \qquad (14)$$

Using (14) and (13) in (11) and (12) we get (8) and (9).
This completes the proof.

4. Example

Nine healthy subjects, seven males and two females, aged 28–51 yr (mean, 38 yr), participated in this study. The subjects all had normal medical histories and physical examinations, were nonsmokers, and had never received any type of glucocorticoid therapy. No subject had any contraindications to the performance of an IHT, such as a history of cardiovascular or cerebrovascular disease or epilepsy. The oldest subject (51 yr) completed a standard exercise stress test to ensure satisfactory cardiovascular status. Serum chemistries, full blood counts, erythrocyte sedimentation rate, static anterior pituitary function tests, and electrocardiograms were 1.99 m2 (range, 1.83– 2.15 m2). Each subject underwent six tests. The LDTs were performed a minimum of 48 h apart, the 8-h infusions and IHTs were separated from all other tests by a minimum of 5 days.

All tests were performed in a random order and single blinded. The subjects were free of medication for at least 4 weeks and abstained from alcohol and caffeine for at least 24 h before each test. The LDTs and HDTs were performed in the early to late afternoon, a time of low basal secretary activity for ACTH and cortisol. The subjects were fasted for 3 h before the insertion of two forearm venous cannulas, one for drug administration and the other with a three-way tap to allow blood sampling and volume replacement with isotonic saline. An ACTH solution was prepared freshly for each LDT by injecting 250 mg ACTH into a 1000-mL bag of 5% dextrose, resulting in a concentration of 0.25 mg/mL. The appropriate dose was withdrawn shortly before injection. Each subject underwent three separate tests with the following doses: 0.1, 0.5, and 1.0. Blood samples for plasma ACTH and cortisol measurements were collected at 215, 0, 2 (ACTH only), 5, 10, 15, 20, 30, 45, and 60 min. The HDT was performed using a standard protocol; the dose was injected at 0 min, blood sampling was performed at each time point (0, 20, 30, 45, and 60 min) for cortisol measurement by HPLC, separate samples were collected at 0, 30, and 60 min for cortisol measurement by FPIA.

The IHTs were commenced at 08.00 h after an overnight fast with bilateral cannulas insertion as described above. Blood samples for cortisol and ACTH determination were collected at 15-min intervals from 15 min before to 120 min after injection of 0.15 U/kg soluble. Blood glucose was measured at 5-min intervals from 0 min to ensure nadir detection. All of the tests were satisfactory according to standard criteria, with all subjects experiencing hypoglycemic symptoms and achieving blood glucose levels below 1.5 mmol/L (range, 0.4 –1.4 mmol/L; mean nadir, 0.9 mmol/L). No test complications occurred. The ACTH infusion test was also commenced at 0800 h, but no fasting before or during the test was required. ACTH was injected into a 500-mL bag of normal saline and infused at a constant rate over 8 h. Blood sampling was performed hourly for cortisol measurement by HPLC, RIA, and FPIA, with additional samples at 0, 1, 7, and 8 h for plasma ACTH measurements [12-14].

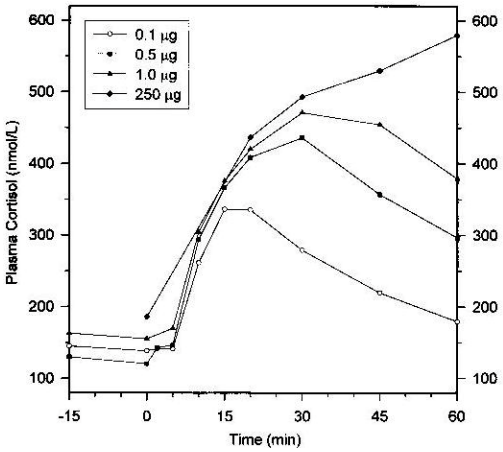

Figure (1): Changes in Plasma Cortisol Concentrations.

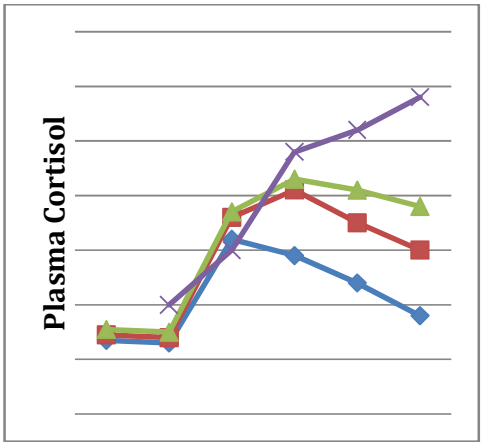

Figure (2): Changes in Plasma Cortisol Concentrations using Gamma Distribution.

5. Conclusion

Single buffer multiclass queue by using gamma distribution gives the same as the medical report. There is no significance difference between medical and mathematical reports. The medical reports are beautifully fitted with the mathematical model. Hence the mathematical report {Figure (2)} is coinciding with the medical report {Figure (1)}.

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