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Find the Serum Cortisol levels with the Help of Classical Markovian Methods Using Normal Distribution

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Abstract
Hypercortisolism is common in stroke patients. The aim of this study was to investigate possible disturbances at different sites within the hypothalamic-pituitary-adrenal axis. We also studied possible serum cortisol levels with the help of classical Markovian methods in the case of symmetrical M/G/S queue.

Keywords: Cortisol, M/G/S Queue, Markovian Methods & Normal Distribution.

1. Introduction
Many patients with acute stroke show a pronounced hypercortisolism [2, 8-10]. Increased plasma and urinary cortisol levels are associated with greater mortality and a poorer functional outcome after stroke [2, 8, 10]. This association has also been demonstrated in other types of brain injury. Theoretically, dysregulation at several sites within the hypothalamic-pituitary-adrenocortical axis may contribute. This includes an increased production rate of cortisol, a change in metabolism and/or clearance rate of cortisol, an increased sensitivity to stimulation of the adrenal glands, and a decreased "shut-off" mechanism of the cortisol axis. In patients with chronic degenerative cerebral disease such as Alzheimer's disease a correlation between cognitive disturbances and hypercortisolism has been demonstrated. It has been hypothesized that hypercortisolism per se may contribute to cognitive disturbances [12]. The acute confusional state commonly occurs in elderly hospitalized patients [6] and may be particularly frequent among stroke patients [3]. It is therefore of interest to study in more detail the different sites within the cortisol axis where possible abnormalities can lead to hypercortisolism early after stroke. Furthermore, we wanted to examine whether there was an association between cortisol levels and acute confusional state and/or motor impairment in these patients.

In a recent paper [5], we studied the stationary G/G/S queue by means of a new factorization method more general than a Wiener Hopf type of decomposition. In this paper, we show that the serum cortisol levels with the help of classical Markovian methods in the case of symmetrical M/G/S queue. The effect of the busy period can be combined with that of the partial occupancies to evaluate the probability of delay. We apply the results successively to the stationary GI/G/S queue and the M/G/S queue. Next section, we defining notation and assumptions and by outlining the recently derived preliminary results for the case of the symmetrical G/G/S queue.

2. Notations and Basic Results for the Symmetric G/G/S Queue
2.1 Notation and Assumptions
Except for the service time distribution, different for each server, the notations and assumptions will be the same as in Le Gall [5]. We consider a queue handled by a multi-server of s non identical servers.

The Arrival Process: We assume metrically transitive, strictly stationary processes of successive non negative inter arrival times. Let $N(t)$ denote the random number of arrivals in the interval$(0, t]$. We write $dN(t) = 1$ or 0 depending on whether or not there is an arrival in the elementary interval $(t, t+dr)$. We exclude the possibility of simultaneous arrivals. We can then write

$$E\{dN(t_0).dN(t_0+t)\} = E[dN(t_0)].\rho(t)dt$$

where $\rho(t)$ is the arrival rate at time $t+t_0$ if an arbitrary arrival occurred at time t_0. We let

$$\int_0^\infty e^{xt}.\rho(t).dt = \alpha_1(z) = \sum_{x=1}^\infty \varphi_{0,x}(z), Re(z) < 0 \quad (1)$$

where $\varphi_{0,x}(z)$ corresponds to the x^{th} arrival following the epoch t_0. However, the stationary assumption and the Abelian theorem give that $\lim_{z \to 0} z\alpha_1(z) = \Lambda$, where $\Lambda$is the mean arrival rate. In a more general way, we may write for $j = 1,2,\ldots$

$$E\{dN(t_0).dN(t_0+t)\ldots dN(t_0+t_1+\cdots+t_{j-1}+t_j)\} = [dN(t_0)].f_j(t_1\ldots t_j).dt_1\ldots dt_j$$

and for $Re(z_j) < 0$ and $j = 1,2,\ldots$

$$\int_0^\infty e^{z_1 t_1}dt_1 \ldots \int_0^\infty e^{z_j t_j}dt_j.f_j(t_1\ldots t_j) = \alpha_j(z_1\ldots z_j) \quad (2)$$

In the case of a renewal process, the successive arrival intervals Y_n are mutually independent and identically distributed, and we let $\varphi_0(z) = E[e^{zY_n}]$, for $Re(z) < 0$.
Expression (1) becomes

$$\alpha_1(z) = \frac{\varphi_0(z)}{1-\varphi_0(z)}$$

and expression (2) becomes

$$\alpha_j(z_1\ldots z_j) = \alpha_1(z_1)\ldots\alpha_1(z_j) \quad (3)$$

In fact, we assume $\varphi_0(z)$to be holomorphic at the origin. From Paul Levy's theorem, we deduce that $\varphi_0(z)$ exists for $Re(z) < \delta$ where δ is a positive real number.

The Service Times: The successive service times T_n are mutually independent and independent of the arrival process. For server j $(j = 1,\ldots,s)$ the service times $T_n(j)$ are identically distributed with a distribution function$F_1(t;j)$; and we let $\varphi_1(z;j) = E[e^{zT_n(j)}]$, for $Re(z) < 0$. We exclude the possibility of batch service and, consequently,

$$F_1(0;\ j) = F_1(+0;j) = 0$$

We assume $\varphi_1(z;j)$ to be holomorphic at the origin. From Paul Levy's theorem, we deduce that $\varphi_1(z;j)$exists for $Re(z) < \delta$, where δ is a real positive number.

The Service Discipline: The servers are supposed to be non identical with different service time distributions. But they are indistinguishable for the service discipline which is "first come first served."

The Traffic Handled: Loynes [7] demonstrated the existence of the stationary regime. The non identical servers are equivalent to different single servers handling the same value y for the traffic intensity per server with the necessary and sufficient condition:

$$\eta < 1$$

Queueing Delay: Since the term "waiting time" means "sojourn time" in Little's formula, for clarity we prefer to use the term "queueing delay" $\tau$for the queueing process only and for an arbitrary customer.

Contour Integrals: In this paper we use Cauchy contour integrals along the imaginary axis in the complex plane. If the contour (followed from the bottom to the top) is to the right of the imaginary axis (the contour being closed at infinity to the right), we write $\int_{+0}$. If the contour is to the left of the imaginary axis, we write $\int_{-0}$.Unless it is necessary to specify whether the contour is to the right or to the left of the imaginary axis, we write $\int_0$.

2.2 Preliminary Results for the Symmetrical G/G/S Queue

Now, we outline the recent results that were presented in [5] for the case of the symmetrical G/G/S queue in equilibrium. To avoid very complicated calculations, Le Gall defined the singular points of the function $E[e^{-q\tau}]$, with $Re(q) > 0$, relating to the queueing delay τ for an arbitrary delayed customer. Secondly, Le Gall established conditions, under which this function is holomorphic, these conditions being satisfied by a more general factorization method than the Wiener Hopf type of decomposition. The results will very easily enable one to tackle the difficult case of non identical servers for the evaluation of the queueing delays of delayed customers.

The Singular Points: For a delayed customer, the queueing delay in server j is denoted $w(j)$. The queueing delay τ of this customer is

$$\tau = Min^+[\omega(1),\ldots,\omega(s)] = Max[0, Min(\omega(1),\ldots,\omega(s))]$$

From an expression given by [11], we may write for $Re(q) \geq 0$

$$e^{-q\tau} = 1 - \frac{1}{(2\pi i)^s}\int_{+0}^{\square} exp(z_1.\omega(1))\frac{dz_1}{z_1}\ldots\int_{+0}^{\square} exp(z_s.\omega(s))\frac{dz_s}{z_s}.\frac{q}{q+\sum_{v=1}^s z_v}$$

with $Re(q+\sum_{v=1}^s z_v) > 0$.

In Le Gall [5], for the symmetrical case gives the singular points of the function $E[e^{-q\tau}]$. These are the singular points of the following function with $Re(q) < 0$, not holomorphic for $Re(q) > 0$:

$$G_s(q) = 1 - \frac{1}{(2\pi i)^s}.\int_{+0}\frac{dz_1}{z_1}\ldots\int_{+0}\frac{dz_S}{z_S}.\frac{q}{q+\sum_{v=1}^S z_v}.\frac{1}{R_S(z_1,\ldots,z_S,q)} \quad (4)$$

with $Re(q+\sum_{v=1}^s z_v) > 0$ and

$$R_s(z_1,\ldots,z_s;q) = 1 + \sum_{\lambda=0}^{s-1}\binom{S}{\lambda}.(-1)^{s-\lambda}.\alpha_{s-\lambda}(q\ldots q).\prod_{j=\lambda+1}^s[\varphi_1(z_j)-1] \quad (5)$$

where $\alpha_{s-\lambda}(q\ldots q)$ is defined by expression (2). The physical meaning may be perceived in the GI/G/S case, where, due to expression (3), we may write

$$R_s(z_1,\ldots,z_s;q) = 1 + \sum_{\lambda=0}^{s-1}\binom{S}{\lambda}.(-1)^{s-\lambda}.[\alpha_1(q)]^{s-\lambda}.\prod_{j=\lambda+1}^s[\varphi_1(z_j)-1]$$

or more simply

$$R_s(z_1, \ldots, z_s; q) = \prod_{j=1}^{s} [1 - \alpha_1(q).(\varphi_1(z_j) - 1)]$$

The case j corresponds to the server$j$, assumed to be in isolation with an arrival process corresponding to $\alpha_1(q)$. For the G/G/S queue, instead ofR_s, we want to define a holomorphic function $V_s(z_1, \ldots, z_s; q)$ for $Re(z_j) \geq 0$ ($j = 1, \ldots, s$) and $Re(q) \geq 0$, so that $V_s(0\ldots0; q)$ has the same singular points as the function $G_s(q)$ given by expressions (4) and (5).

The Factorization Method: Let $V_s(z_1, \ldots, z_s; q) = 1 - U_s(z_1, \ldots, z_s; q)$

In Le Gall [5] for the symmetrical case, we proved that the function U_s has to satisfy the following conditions of factorization: We set

$$U_s(z_1, \ldots, z_s; q) = \frac{(-1)^s.\alpha_s(q \ldots q).\prod_{j=1}^{s}[\varphi_1(z_j)-1]}{R_s(z_1, \ldots, z_s; q)} . \prod_{i=1}^{s} M_i(z_1, \ldots, z_s; q)$$

where R_s, is defined by expression (5) and U_s is holomorphic for $Re(z_i) \geq 0, (i = 1,2, \ldots, s)$and $Re(q) \geq 0$, with the following conditions forM_i:

(a) $M_i$is holomorphic for $Re(z_i) < 0, (i = 1,2, \ldots, s)$

(b) $M_i\left(z_1 \ldots z_{i-1}, -q - \sum_{v=1}^{i-1} z_v, z_{i+1} \ldots z_s; q\right) \equiv 1$

Then, we have

$$V_s(0, \ldots, 0; q) = G_s(q)$$

where $G_s(q)$ is given by expressions (4) and (5).

The Function U_s: For the symmetrical G/G/S queue, the function U_s has been defined in Le Gall [5]:

$$U_s(z_1, \ldots, z_s; q) = Exp\left\{\frac{-1}{(2\pi i)^s} . \int_{-0} \left[\frac{1}{q + \xi_1} + \frac{1}{z_1 - \xi_1}\right] d\xi_1 \ldots \int_{-0} \left[\frac{1}{q + \sum_{v=1}^{s-1} z_v + \xi_s} + \frac{1}{z_s - \xi_s}\right] d\xi_s . logN_s\{\xi_1, \ldots, \xi_s\}\right\}$$

With

$$R\left(q + \sum_{v=1}^{i-1} z_v + \xi_i\right) > 0, i = 1,2, \ldots, s$$

The function N_s is given by

$$\frac{1}{N_s(z_1, \ldots, z_s)} = \frac{A_s(z_1, \ldots, z_s)}{B_s(z_1, \ldots, z_s)}$$

With

$$A_s(z_1, \ldots, z_s) = (-1)^s\{\prod_{j=1}^{s}[\varphi_1(z_j) - 1]\}.\alpha_s\{-z_1, -z_2, \ldots, -\sum_{v=1}^{s} z_v\}$$

and

$$A_s(z_1, \ldots, z_s) = 1 + \sum_{\lambda=0}^{s-1} \binom{s}{\lambda} . (-1)^{s-\lambda} . \left\{\prod_{j=\lambda+1}^{s} [\varphi_1(z_j) - 1]\right\} . \alpha_{s-\lambda}\left\{-\sum_{v=1}^{\lambda+1} z_v, \ldots, -\sum_{v=1}^{s} z_v\right\}$$

where $\alpha_j(z_1, \ldots, z_j)$ is defined by expression (2).

3. The Probability of Delay

During the busy period (congestion state), servers behavior has been defined in a way quite independent of partial occupancy states. For these states, it follows that a busy period appears exactly as a unique congestion state in the lost call model, with n successive service times handled as if there were a unique arrival, with n being the mean value of the busy period size, i.e., of the number of customers served during this busy period. This fact could not be observed with the classical Markovian methods, and it has not been noted in equation of [11].With the lost call model in a stationary mode, let $P_i = P_0.h(i)$ denote the probability that i servers are busy upon the arrival of an arbitrary customer. The probability of loss is $P_\alpha = P_s$ with

$$\frac{1}{P_\alpha} = \frac{1}{P_s} = 1 + \frac{1 + \cdots + h(s-1)}{h(s)}$$

due to the normalizing condition $\sum_{i=0}^{s} P_i = 1$.

With our preceding remark to evaluate the probability of delay P, we have to substitute

$n.h(s)$ for $h(s)$

We may now conclude.

Property (The probability of delay): For a non symmetrical G/G/S queue in a stationary regime the probability of delay is

$$P = \frac{n.P_\alpha}{1 + (n-1).P_\alpha}$$

where P_α is the probability of loss in the lost call model and n is the mean value of the busy period size as defined by previous expression.As already seen in [4], we know that the evaluation of P_α is extremely difficult except in two symmetrical cases: The GI/M/S and M/G/S queues. In particular, for the M/G/S queue we conclude that the delay Erlang formula may be extended for a general service time distribution. In that case, expressiongives $n = [1/(1-\eta)]$. We know that the M/G/S queue has to be excluded; however, it has already been noted by C. Palm that the delay Erlang formula gives still an excellent approximation.

4. Example

Sixteen patients (11 men, five women; mean ± SD age, 71 ±11 years) with an acute brain infarction were selected for this study from our stroke unit. The median delay from onset until admission was 11 hours (range, 1-100 hours). Based on clinical judgement and on the results of computed tomographic (CT) scans, performed in all patients, 14 patients had a supratentorial brain infarction and two patients had a cerebellar infarction. In the supratentorial brain infarction group, eight patients had a probable nonembolic brain infarction, five patients had an embolic brain infarction, and one patient had a lacunar infarction. Six of the patients in this group had right-sided and eight had left-sided brain lesions. These patients all had an extremity paresis afflicting the contralateral arm or leg at admission. Three patients with left-sided brain lesions also had a slight-to-moderate dysphasia at admission. Both patients with cerebellar infarctions had vertigo, one of them having a right-sided arm paresis as well. None of the patients had a pronounced decrease in consciousness, i.e., more than drowsiness, high fever (>38.5°C), renal failure (plasma creatinine level >200 /xmol/1), known extensive weight loss or malnutrition, hypothyroidism/ hyperthyroidism, pituitary insufficiency, uncontrolled diabetes mellitus, obvious abstinence reactions from alcohol or other central nervous stimulants, or epilepsy. None was treated with medications known to interfere with the test results such as glucocorticoids, estrogens, anticonvulsants, high-dose benzodiazepines, or ephedrine. Two of the patients had non-insulin dependent diabetes mellitus.

As control subjects, nine healthy elderly people were selected from an ongoing study of hormone changes in the elderly (six men, three women; mean ± SD age, 71 ± 9 years). All were thoroughly investigated by a resident in geriatric medicine. CT scan of the brain was normal in all individuals, and none were taking drugs. The patients were examined between the third and seventh day after admission. They were investigated in a standardized manner, with repeated clinical assessments. The extent of extremity paresis was quantified using a four point scale [9]. Acute confusional state was diagnosed using criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) [3].A diagnosis of a major depressive episode was based on criteria from DSM-III-R [3]. All tests and interviews with patients, relatives, and staff regarding the diagnoses of acute confusional state and major depression were made by one of the authors.

A short adrenocorticotropic hormone (ACTH) stimulation test was performed in the fasting state between 8 and 9 AM. In this test 0.25 mg ACTH (1-24 ACTH; Synacthen, CIBA-Geigy) was administered slowly intravenously as a bolus dose. Blood was collected for cortisol analyses before the injection and 30 and 60 minutes after the injection. This was followed by an overnight dexamethasone suppression test in which 1mg dexamethasone was given orally at 11 PM. Blood was drawn on the following day at 8 AM for serum cortisol analysis. Serum cortisol was analyzed with a radioimmunoassay kit with an inter assay coefficient variation <8% for the analysis. The area under the curve for the cortisol response to ACTH was calculated by the trapezium rule [1]. The centered cumulative cortisol response to ACTH was calculated using the following formula: area under the curve [1].Differences in cortisol levels between groups were analyzed with the Mann-Whitney Utest. Spearman correlation coefficients were used for the calculation of correlations.

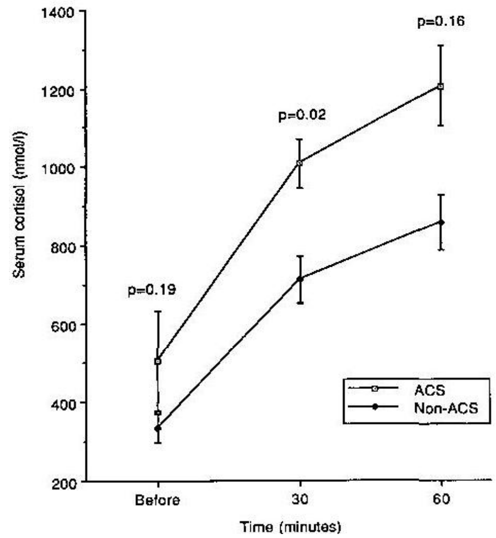

Fig 1: Line graph of Serum Cortisol Before and After the Administration of Adrenocorticotropic Hormone to Stroke Patients

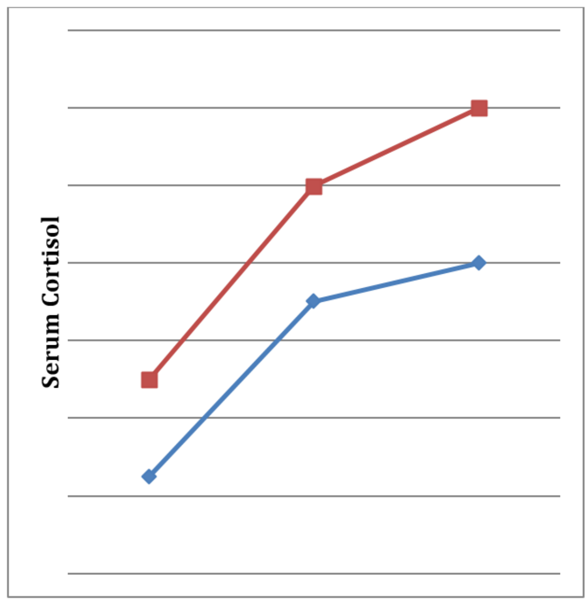

Fig 2: Line graph of Serum Cortisol Before and After the Administration of Adrenocorticotropic Hormone to Stroke Patients (Using Normal Distribution)

5. Conclusion

There are abnormalities in the cortisol axis both at the central level and at the adrenal level early after stroke. Hypercortisolism is closely associated with cognitive disturbances and extensive motor impairment. The serum cortisol levels with the help of classical Markovian methods in the case of symmetrical M/G/S queue are same in both medical and mathematical results. 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 coincide with the medical report {Figure (1)}.

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