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A New Diffusion Model to Estimate the Triiodothyronine Repletion in Infants During Cardiopulmonary Bypass For Congenital Heart Disease Using Stochastic Analysis

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Abstract

Cardiopulmonary bypass suppresses circulating thyroid hormone levels. We hypothesized that triiodothyronine deficiency in the developing heart after bypass may adversely affect cardiac function reserve postoperatively. We consider two identical, parallel M/M/1 queues. Both queues are fed by a Poisson arrival stream of rate λ and have service rates equal to μ. When both queues are non empty, the two systems behave independently of each other. However, when one of the queues becomes empty, the corresponding server helps in the other queue. This is called head of the line processor sharing. We study this model in the heavy traffic limit, where $\rho = \lambda/\mu \to 1$. For, Cardiopulmonary bypass we use the formula that the heavy traffic diffusion approximation and the time dependent probability of the diffusion approximation to the joint queue length process.

Keywords: Cardiopulmonary Bypass, Diffusion Model, Congenital Heart Disease, Stochastic Analysis & Normal Distribution.

Introduction

Circulating levels of the thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4), decrease substantially during and after cardiopulmonary bypass (CPB) [9]. Possible responsible mechanisms include blood dilution during CPB, alterations in peripheral T_3 metabolism, and central disruption of hypothalamic pituitary thyroid control included by nonpulsatile flow [16]. Regardless of the operative mechanisms, depression of serum T_3 and T_4 levels persists for several days after CPB in both adults and children. Several investigators have postulated that thyroid hormone deficiencies can contribute to myocardial depression observed after cardiac surgery and CPB T_3 or T_4 supplementation after coronary artery bypass provides short term increases in cardiac performance in adults, which result from a direct inotropic effect on the heart and decrease in systemic vascular resistance.

The developing heart normally undergoes thyroid promoted maturation of physiologic and metabolic processes, which can increase cardiac contractile function and reserve [18] & [21]. However, operation for congenital heart disease accompanied by CPB can theoretically disturb this maturation at least temporarily by decreasing circulating thyroid hormone levels. Thus, depression of thyroid hormone levels could limit cardiac contractile responses during the vulnerable postoperative period. Accordingly, we postulated that T_3 repletion in the immediate postoperative period should improve hemodynamic parameters in infants undergoing cardiac surgery with CPB. This current study represents the initial phase in evaluation of T_3 repletion in infants undergoing CPB.

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Queuing systems are used in a wide variety of applications, such as computer and communications networks and manufacturing systems. In analyzing such models, one typically wishes to compute the probability distribution of some stochastic process. Obtaining the full time dependent distribution is a difficult task for all but simple models. Here we consider the following model, which is sometimes referred to as head of the line processor sharing of parallel queues. There are two parallel M/M/1 queues, each fed by independent Poisson arrival streams with rate λ. Each of the two servers works at rate μ. When both queues are non empty, each server tends to its own queue. However, if the first queue becomes empty, the first server helps the server in the other queue (same as for second), thereby providing a service rate of 2μ during the idle period.

A Diffusion Model

The steady state joint queue length distribution for this model was analyzed by [8] and a more general model which allows, e.g., for different service rates was analyzed. In [8], the authors obtained an expression for the two dimensional generating function of the joint queue length distribution in terms of elliptic integrals.

The inherent complexity of the solutions in [8] led other authors to investigate asymptotic properties of these solutions, in order to gain more qualitative insights.

The heavy traffic limit is defined as $\rho = \lambda/_{\mu} \to 1$. In this limit, the joint queue length process may be approximated by a diffusion process, whose analysis proves to be simpler than that of the discrete model. In particular, [7] and [10] obtained a relatively simple answer for the steady state distribution of the diffusion approximation. Also, some exact [10] and asymptotic [7] results were obtained for more general models, which allow different service rates and discriminatory processor sharing. Diffusion approximations were also used by [5] to treat more complicated models, with more than two queues. Related models with finite capacity were analyzed by [10]. Applications of these models include the buffering of channels in wide area data networks [10].

In this paper we compute the time dependent distribution for the heavy traffic diffusion model, thereby obtaining information on how steady state is achieved, and other transient phenomena. Denoting by $p(m,n,t)$ the joint probability that $N_1(t) = m$ and $N_2(t) = n$ we obtain the approximation $p(m,n,t) \sim \epsilon^2 P(x,y,T)$, where $\epsilon = 1 - \rho$ and $(x,y,T) = (\epsilon m, \epsilon n, \mu\epsilon^2 t)$ are scaled space and time variables. We shall obtain explicit, albeit complicated, expressions for P and then evaluate these asymptotically for various ranges of space and time. This leads to very simple formulas that clearly show the basic qualitative structure of the joint density function.

In particular, we show that there is a surface $T = T_*(x,y)$ in the (x,y,T) space so that for $T > T_*$, the process has settled to its steady state distribution, while for $T > T_*$, the probability distribution depends upon time as well as on the initial conditions. We shall also consider the unstable case where $\rho > 1$ in the heavy traffic limit. Here the process is transient and the queue lengths tend to grow without bound. We shall show that the two queues are nevertheless coupled in this limit, and obtain a simple quantitative measure of this interaction.

In the asymptotic analysis, we shall allow for space (x,y) to be large as well as time T. We contrast this to relaxation rate asymptotics, which are discussed in the book of [4] for single server queues and by [1] for two tandem M/M/1 queues. These asymptotics would assume that the space variables are held fixed and use the approach to equilibrium in the form $P(x,yT) - P_{eq}(x,y) \sim T^v e^{-\alpha T} \beta(x,y)$, where $\alpha =$ relaxation rate and $t =$ constants. Here P_{eq} is the equilibrium density, which is non zero only if $\rho < 1$. We believe that the asymptotics presented here give a more global description of the transient distribution. We have previously obtained analogous asymptotic results for various models with one space dimension [7] and [23]. In the probability literature, these types of asymptotics are sometimes referred to as large deviations theory. However, such theory generally only gives the exponential rate of growth or decay of the desired quantity. In contrast, here we give very precise results and also indicate how to obtain full asymptotic series. We obtain the results by the saddle point and related methods for evaluating integrals [3].

We also mention related work on the M/M/1-PS queue and more general models by [3], [19], [17], and [22]. These authors consider single queues with the processor sharing service discipline. The main focus in these papers is the calculation of the sojourn time distribution of a tagged customer, as well as its moments. The queue length distribution in the M/M/1-PS model is the same for the PS and FIFO service disciplines. It is the sojourn time distribution that is very different for PS and FIFO service. If we condition the sojourn time on the total service that the tagged customer must receive, then the PS discipline is much more efficient at servicing shorter jobs. In [3], the M/M/1-PS model and computed the Laplace transform of the sojourn time distribution, conditioned on the job **size.** In [19], the GI/M/1-PS model is analyzed. In particular, simple expressions are given for the first two sojourn time moments. The M/G/1-PS model was analyzed by [17]. The response time distribution is computed in [17], the transient distribution of the number of customers present is analyzed a good survey of work on processor shared queues appears. In [17], the author extended the results to calculate the joint distribution of the sojourn time and of the number of customers present upon the departure of the tagged customer. Some approximations for the more difficult GI/G/1-PS model are given in [22].

We believe that the structure of $P(x,y,T)$ revealed here will also arise in other diffusion models corresponding to two or more coupled queues. Other explicit solutions to diffusion models arising in queueing network**s** are given in [15], [6] and [23]. The steady state densities of a large class of two dimensional diffusion models according to their tail behaviors as x and/or $y \to \infty$. We believe that such a classification should also be possible for the transient behavior, and this work may be viewed as a first step in that direction. We also mention that the diffusion approximation analysis presented here should be extendible to problems with general arrivals and/or service. However, these generalizations are likely to lead to somewhat more complicated PDEs and boundary conditions, then those in (10)-(12).

Formation of Model

We let $N_1(t)$ and $N_2(t)$ be the number of customers in the first and second queue. We define the transition probability distribution by

$$p(m,n,t) = p(m,n,t;m_0,n_0) = Prob[N_1(t) = m, N_2(t) = n | N_1(0) = m_0, N_1(0) = n_0] \quad (1)$$

In terms of (m,n), the distribution (1) satisfies the forward equation

$$p_t(m,n,t) = \lambda[p(m-1,n,t) + p(m,n-1,t) - 2p(m,n,t)]$$
$$+\mu[p(m+1,n,t) +$$

$p(m,n+1,t)-2p(m,n,t)]$ (2)
with the boundary conditions

$$p_t(m,0,t)=\lambda[p(m-1,0,t)-2p(m,0,t)] +2\mu[p(m+1,0,t)-p(m,0,t)]+\mu p(m,1,t) \quad (3)$$

$$p_t(0,n,t)=\lambda[p(0,n-1,t)-2p(0,n,t)] +2\mu[p(0,n+1,t)-p(0,n,t)]+\mu p(1,n,t) \quad (4)$$

the corner condition

$$p_t(0,0,t)=2\mu[p(1,0,t)+p(0,1,t)]-2\lambda p(0,0,t) \quad (5)$$

and the initial condition

$$p(m,n,t)=\delta(m,m_0)\delta(n,n_0) \quad (6)$$

Here subscripts denote partial derivatives and δ is the Kronecker delta symbol.

We study the model in the heavy traffic limit, where $\rho = {}^{\lambda}/_{\mu} \to 1$. Formally, we define the small positive parameter ϵ by

$$1-\rho = 1-\frac{\lambda}{\mu} = \epsilon\alpha \quad (7)$$

and scale space and time by ϵ as follows

$$m=\frac{x}{\epsilon}, n=\frac{y}{\epsilon}, t=\frac{T}{\mu\epsilon^2}, m_0=\frac{x_0}{\epsilon}, n_0=\frac{y_0}{\epsilon} \quad (8)$$

Note that this means that the initial queue lengths are assumed to be large, of the order $O(\epsilon^{-1})$.

If the queue is stable (i.e., $\rho<1$), we will set $\alpha=\pm 1$, and then (7) defines in terms of ρ. In the unstable case ($\rho>1$), we will set $\alpha=-1$. If $\rho=1$, we take $\alpha=0$ and then (8) corresponds to viewing $p(m,n,t)$ on large space/time scales, with $m,n,t\to\infty$ and $m/\sqrt{t}, n/\sqrt{t}$ fixed.
With (8), we expand the probability distribution as

$$p(m,n,t)=\epsilon^2\left[P(x,y,T)+\epsilon P^{(1)}(x,y,T)+\cdots\right] \quad (9)$$

From (2) - (4) and (6), we find that the leading term P satisfies the PDE

$$P_T = P_{xx}+P_{yy}+\alpha\left(P_x+P_y\right); x,y,T>0 \quad (10)$$

the boundary conditions

$$P_x(0,y,T)+P_y(0,y,T)+\alpha P(0,y,T)=0; y,T>0 \quad (11)$$

$$P_x(x,0,T)+P_y(x,0,T)+\alpha P(x,0,T)=0; x,T>0 \quad (12)$$

and the initial condition

$$P(x,y,0)=\delta(x-x_0)\delta(y-y_0) \quad (13)$$

We also have the normalization condition

$$\int_0^\infty\int_0^\infty P(x,y,T)dxdy = 1 \text{ for all } T\geq 0 \quad (14)$$

We do not consider the corner condition (5) in formulating the heavy traffic diffusion model. We will show that $P(x,y,T)$ becomes infinite near the origin $x=y=0$, and hence (9) cannot be the correct asymptotic approximation to the discrete probabilities $p(m,n,t)$ for small values of x and y. A proper analysis of the corner region would involve analyzing the discrete model (2)-(5), with $\mu=\lambda+\mu\epsilon\alpha$. However, we will show that such a detailed treatment is not necessary to determine $P(x,y,T)$, which is the heavy traffic diffusion approximation valid away from the corner. The total probability mass in the corner region is asymptotically smaller than that on the (x,y) scale. However, calculating the higher order terms in the series (9) would necessitate a careful treatment of the corner region. We shall obtain an explicit solution for the leading order diffusion approximation $P(x,y,T)$. Then we shall obtain detailed asymptotic results for this limiting density, that apply for x and/or y and/or T large.

Note

With the help of the equations (10) – (14), we get the following results

(a) $x,y,T\to\infty$ then $P(x,y,T)\sim\frac{\sqrt{2}}{\pi}\frac{xy}{T(x+y)}\frac{1}{\sqrt{x^2+y^2}}exp\left(-\frac{x^2+y^2}{4T}\right)$

(b) $y=O(1); x,T\to\infty$ then $P(x,y,T)\sim exp\left(-\frac{x^2}{4T}\right)\frac{\sqrt{2}}{\pi T_x}\left(y+\frac{2T}{x}\right)$

(c) $x=O(1); y,T\to\infty$ then $P(x,y,T)\sim exp\left(-\frac{y^2}{4T}\right)\frac{\sqrt{2}}{\pi T_y}\left(x+\frac{2T}{y}\right)$

(d) $x,y=O(1); T\to\infty$ then $P(x,y,T)\sim\frac{\sqrt{2}}{\pi^{3}/_{2}\sqrt{T}}\ \frac{x+y}{x^2+y^2}$

(e) $x^2+y^2=O(T); T\to\infty$ then

$$P(x,y,T)\sim\frac{\sqrt{2}}{4\pi^{3}/_{2}T^{5}/_{2}}\int_0^\infty\int_0^1\frac{(x+u)(y+u)}{\eta^3\sqrt{1-\eta}}\ exp\left[-\frac{(x+u)^2(y+u)^2}{4T\eta}\right]d\eta du$$

We observe that if $\rho\geq 1, \rho\to 0$ as $T\to\infty$ for any fixed x,y. The expression in part (e) is in fact the exact result for $P=P_{II}$ when $\alpha=0$; for $T\to\infty$ with $x,y=O\left(\sqrt{T}\right)$, this cannot be simplified any further. If we specialize the result to $x-T=O\left(\sqrt{T}\right)$ and $y-T=O\left(\sqrt{T}\right)$, we obtain

$$Lexp\Phi\sim\frac{1}{4\pi T}exp\left[-\frac{\left(x^{'}\right)^2}{4T}-\frac{\left(y^{'}\right)^2}{4T}\right];\ x^{'}=x-T, y^{'}=y-T \quad (15)$$

This is similar to the diffusion approximation for the standard M/M/1 queue for $p>1$ and shows that the two queues decouple in this limit.

Example

Infants less than 1 year old undergoing ventricular septal defect or tetralogy of Fallot repair were randomized into 2 groups. Group T $(n=7)$ received triiodothyronine ($0.4\ \mu g/kg$) immediately before the start of cardiopulmonary bypass and again with myocardial reperfusion. Control $(NT, n=7)$ patients received saline solution placebo or no treatment. Heart rate, systolic and diastolic blood pressure and peak pressure rate product (PRP) were generally maintained at steady levels in the control group over the first 24 hours postoperatively. In our study heart rate is examined first 24 hours. Times in hours are taken as x axis and the heart rate in beats/min as y axis. Heart rate after CPB for the patients receiving $T_3(T)$ and control patients (NT). Time indices hours after termination of CPB. There are significant differences between groups occur at 1 and 3 hours after CPB [11-14], [20] and [24-26].

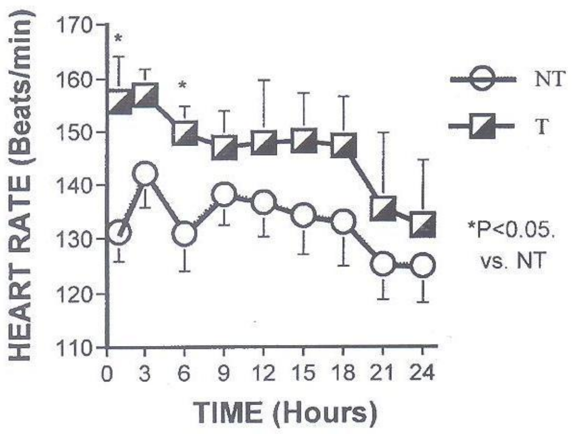

Figure I. Heart rate after CPB for the patients receiving $T_3(T)$ and control patients (NT). Time indicates hours after termination of CPB. Significant differences between groups occur at 1 and 3 hours after CPB.

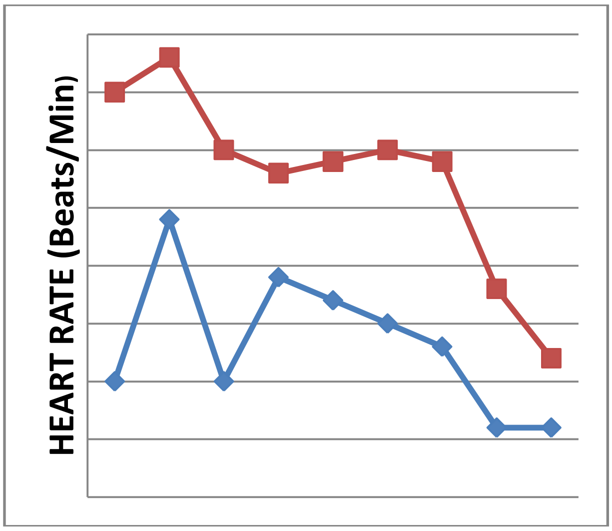

Figure II. Heart rate after CPB for the patients receiving $T_3(T)$ and control patients (NT). Time indicates hours after termination of CPB. Significant differences between groups occur at 1 and 3 hours after CPB (Using Normal Distribution)

Conclusion

These data imply that (1) triiodothyronine in the prescribed dose prevents circulating triiodothyronine deficiencies and (2) triiodothyronine repletion promotes elevation in heart rate without concomitant decrease in systemic blood pressure. The diffusion approximation for the standard M/M/1 queue for $\rho > 1$ also gives the same results as above. By using normal distribution (ND) the mathematical model gives the result as same as the medical report. The medical reports {Figure (1)} are beautifully fitted with the mathematical model {Figure (2)}; $(i.e)$ the results coincide with the mathematical and medical report.

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