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Find the Androgen Deprivation Therapy and Congestive Heart Failure Results Using Stochastic Model

[1]R. Vijayakumar, [2]Dr. A. Muthaiyan, [3]G. Vijayaprabha

[1]Assistant Professor, Department of Mathematics, Srinivasan Engineering College, Perambalur, Tamilnadu, India, *mathsphd1@gmail.com*
[2]Assistant Professor, PG Research & Department of Mathematics, Government Arts College, Ariyalur, Tamilnadu, India, *mathsphd1@gmail.com*
[3]Assistant Professor, Department of Mathematics, Dhanalakshmi Srinivasan Engineering College, Perambalur, Tamilnadu, India, *mathsphd1@gmail.com*

Abstract: *Androgen deprivation therapy (ADT) in nonmetastatic prostate cancer is unclear. Recent data suggests possible increase in the cardiovascular risks receiving ADT. The aim of the study was to investigate the cardiovascular outcomes in a cohort of nonmetastatic prostate cancer patients with no previously documented cardiovascular disease. The purpose of this study was to examine the androgen deprivation therapy results using the stochastic analysis of the departure and quasi input processes of a Markovian single server queue with negative exponential arrivals and repeated attempts.*

Keywords: *Androgen Deprivation Therapy, Cardiovascular Disease, Congestive Heart Failure, Markovian Single Server Queue, Uniform Distribution.*

1. Introduction

Carcinoma of prostate is the most common malignancy in men and the incidence has been increasing during the past two decades [6] & [8]. Androgen deprivation therapy (ADT) in form of bilateral orchiectomy and medical castration has been the mainstay systemic treatment in patients with metastatic disease because of the androgen dependence of the disease [6]. On the other hand, the role of ADT in localized disease remains to be defined, as many patients with localized disease often have a favorable prognosis and may live up to a near normal lifespan. Thus, treatments aiming to further improve the long term outcomes in these patients should outweigh any potential treatment associated adverse effects.

In recent years, the metabolic effects as well as the cardiovascular consequences of ADT had been increasingly recognized. However, clinical data concerning ADT related adverse metabolic and cardiovascular effects remain conflicting. There have been studies demonstrating that patients receiving ADT may have a higher incidence of diabetes mellitus [7], coronary artery disease [7], stroke and even cardiovascular death [11] & [12], but other studies failed to show such associations [1] & [10].This may be due to the fact that, in these studies, the presence of preexisting metabolic condition and other cardiovascular diseases (CD) had not been adequately characterized and controlled.

Our queueing system is characterized by the phenomenon that a customer who finds the server busy upon arrival joins an orbit of unsatisfied customers. The orbiting customers form a queue such that only a customer selected according to a certain rule can reapply for service. The intervals separating two successive repeated attempts are exponentially distributed with rate $\alpha + j\mu$, when the orbit size is $j \geq 1$. Negative arrivals have the effect of killing some customer in the orbit, if one is present, and they have no effect otherwise. Since customers can leave the system without service, the structural form of type M/G/1 is not preserved. We study the Markov chain with transitions occurring at epochs of service completions or negative arrivals. Then we find and use the moments of the random variable i.e., the first two moments under ergodicity are used to investigate the androgen deprivation therapy and congestive heart failure outcomes in a cohort of nonmetastatic prostate cancer patients.

2. Description of the Mathematical Model

Queueing systems with repeated attempts have wide practical use in designing packet switching networks and telecommunication systems. The main characteristic of a single server queue with repeated attempts is that a customer who finds the server busy upon arrival is obliged to leave the service area, but some time later he comes back to reinitiate his demand. Between trials a customer is said to be "in orbit". Most papers assume that each orbiting customer has probability $\mu dt + o(dt)$ of reapplying for service in $(t, t + dt)$, independently of each other customer in orbit at time t. In what follows, we call this retrial policy as classical retrial discipline. For a review of the literature on this topic see [2]. Nevertheless, there are other types of queueing situations, in which the retrial rate is independent of the number of customers in orbit i.e., the retrial rate is α if the orbit is not empty at time t and zero if the orbit is empty. This second retrial policy will be called constant retrial discipline. A detailed discussion of situations where such discipline arises can be found in [3]. In related work [9] examined the $M/G/1$ with two types of customers and constant retrial discipline.

Recently, [5] studied an $M/M/1$ queue with "negative" arrivals. Any arriving customer joins the system with the intention of getting served and then leaving the system. They are treated in the normal way by the server and are taken from the queue according to a specified queueing discipline. At a negative arrival epoch, the system is only affected if customers are present. Then, a customer is removed from the system i.e., each negative arrival reduces the total customers count by one unit. Several practical applications justify the study of these queueing models. In multiprocessor computer systems, negative arrivals represent commands to delete some transaction. In neural networks, primary and negative arrivals represent excitatory and inhibitory signals, respectively.

The purpose of the present work is to study the departure and quasi input processes of a versatile single server queue allowing the simultaneous presence of classical and constant repeated attempts, and negative arrivals. Our queueing model was introduced in [4], where the classification of states, stationary distribution, waiting time and busy period were studied. Thus, this paper completes the investigation initialed in [4].

To allow the presence of both types of repeated attempts we will assume that intervals between two successive repeated attempts are exponentially distributed with rate $\alpha\left(1-\delta_{o_j}\right)+j\mu$, when the orbit size is j. δ_{o_j} denotes Kronecker's function. This retrial policy will be called linear retrial discipline. The main characteristic of our model is its versatility so, in this section, we discuss concrete interpretations of the systems associated with some specific choices of the parameters. Nevertheless, the queueing system under consideration has also an intrinsic interest to model some situations in packet switching networks. Consider a computer network which consists of a group of processors connected with a central transmission unit (CTU). If a processor wishes to send a message it first sends the message to the CTU. If the transmission medium is available, the CTU sends immediately the message; otherwise the message will be stored in a buffer and the CTU must retry the transmission some time later. For mathematical convenience we assume that this random time is exponentially distributed; then we construct a retrial rate of the simplest possible type by assuming that there are two contributions to the retrial intensity. The first one α is fixed and intrinsic with the network design, whereas the second one $j\mu$ depends on the number of units in the buffer. In addition, the CTU sends negative signals to the buffer in order to remove one of the unsatisfied units. This mechanism guarantees a moderate level of internal congestion in the buffer.

It should be pointed out that the presence of a stream of negative arrivals has a profound influence on the system. This is revealed by the fact that the structural form of the $M/G/1$ queue is not preserved. We also observe that, due to the existence of negative arrivals, the limiting probability distribution of the continuous time process describing the number of customers in the system is not equal to the distribution of the embedded process describing the state of the system just after service completion epochs. The rest of the paper is organized as follows. In this section we describe the mathematical model. The study of the embedded Markov chains at service completion and killing epochs and their corresponding factorial moments are carried out in next section. In last section, we obtain the Laplace Stieltjes Transform (LST) of the interdeparture times and its factorial moments.

We consider a single server queueing system with two independent Poisson streams with rates $\lambda > 0$ and $\delta \geq 0$, corresponding to primary and negative arrivals, respectively. If the server is free, an arriving primary customer begins to be served and leaves the system after service completion. Any primary customer finding the server busy upon arrival must leave the service area immediately and seek service again at subsequent epochs until he finds the server free. He is then said to be "in orbit". These unsatisfied customers form a pool such that only one customer selected according to a certain rule can access to the server. The time intervals describing the repeated attempts are assumed to be independent and exponentially distributed with rate $\alpha\left(1-\delta_{o_j}\right)+j\mu$, when there are j customers in orbit. Negative arrivals have the effect of deleting one customer of the orbit, if there are any, who is selected according to some specified killing strategy. Service times are independent exponential random variables with rate$v$. The streams of primary and negative arrivals, intervals separating successive repeated attempts and service times are assumed to be mutually independent.

We now discuss some particularizations which can be obtained with specific choices of the parameters α, μ and δ. First, the case $\delta = 0$ leads to a retrial queue with linear retrial discipline which generalizes the classical and constant retrial queues described in the literature. The case $\mu = 0$ and $\delta = (1-H)\alpha, H \in (0,1)$, corresponds to the constant retrial queue where the customer at the head of the orbit is nonpersistent. Finally, the single server Markovian queue with classical waiting line and negative arrivals is obtained by letting $\alpha \to +\infty$ and $\mu \to +\infty$.

The state of the system at time t can be described by the bivariate process $X = \{X(t), t \geq 0\} = \{(C(t), Q(t)), t \geq 0\}$, where $Q(t)$ represents the number of customers in orbit and $C(t)$ is equal to 1 or 0 according as the server is busy or free, respectively. Note that the process X takes values on the semi strip $S = \{0,1\} \times N$.

We shall consider that the process X is in the ergodic case, which exists if and only if one of the following conditions is verified

(i) $\mu = 0$ and $\gamma < 1$

(ii) $\mu > 0$ and $\rho < 1$

Where $\gamma = \frac{(\lambda-\delta)(\lambda+\alpha)}{v\alpha}$ and $\rho = \frac{\lambda}{\delta+v}$

We also define the limiting probabilities

$$P_{ij} = \lim_{t\to+\infty} P\{C(t) = i, Q(t) = j\}, (i,j) \in S$$

Which are positive if and only if (i) or (ii) is satisfied.. The probabilities P_{ij} and the partial generating functions defined as $P_i(z) = \sum_{j=0}^{\infty} P_{ij} z^j$, for $i \in \{0,1\}$, can be expressed in terms of hyper geometric series. Since our model has a Poisson input, the stationary distribution is equal to the equilibrium state distribution just prior to arrival epochs.

Finally, we introduce some notation used in the rest of the paper. Let us consider the generalized hyper geometric series defined as follows

$$F_k\begin{pmatrix} a_1, a_2, \dots, a_{k+1}; z \\ b_1, b_2, \dots, b_k \end{pmatrix} = \sum_{n=0}^{\infty} \frac{(a_1)_n (a_2)_n \dots (a_{k+1})_n}{(b_1)_n (b_2)_n \dots (b_k)_n} \frac{z^n}{n!}$$

Where $(x)_n$ is the Pochhammer symbol

$$(x)_n = \begin{cases} 1, & n = 0 \\ x(x+1)\dots(x+n-1), & n \geq 1 \end{cases}$$

As is usual, we denote $F_1\begin{pmatrix} a_1, a_2; z \\ b_1 \end{pmatrix}$ by $F(a_1, a_2; b_1 z)$

3. Embedded Markov Chain at Service Completion and Killing Epochs

In this section, we consider the system at epochs /n of service completion or negative arrival. Our purpose is to study the Markov chain with transitions occurring at these instants.

First, we define

$$\Pi_j = \lim_{n\to+\infty} P\{C(\eta_n + 0) + Q(\eta_n + 0) = j\}, j \geq 0$$

The above probabilities can be expressed as

$$\Pi_j = \begin{cases} \overline{\Pi}_0, & j = 0 \\ \overline{\Pi}_j + \widetilde{\Pi}_j, & j \geq 1 \end{cases}$$

Where

$$\overline{\Pi}_j = \lim_{n \to +\infty} P\{X(\eta_n + 0) = (0, j)\}, j \geq 0$$

$$\widetilde{\Pi}_j = \lim_{n \to +\infty} P\{X(\eta_n + 0) = (1, j-1)\}, j \geq 1$$

Note that with the help of $\overline{\Pi}_j$ and $\widetilde{\Pi}_j$, we can distinguish if a transition of our Markov chain corresponds to a service completion or a negative arrival.

It is well known that any stochastic process whose sample functions are step functions with unit jumps has the same limiting distribution just prior to its points of increase as it does just after its points of decrease, when this limiting distribution exists. Thus, the limiting probabilities P_j associated with the total number of customers in the system satisfy

$$P_j = P_{0,j} + P_{1,j-1}\left(1 - \delta_{0,j}\right) = \Pi_j, j \geq 0$$

We assume in the rest of this section that at epoch $t = 0$, the system is in state $(0, 0)$. We define a busy period, L as the period that starts at epoch when a primary customer enters an empty system and ends at the next service completion epoch at which the system becomes empty. A regeneration cycle, T is defined as the first passage time from state $(0, 0)$ to state $(0, 0)$. It should be noted that the continuous time process $\{X(t), t \geq 0\}$ is a regenerative process with embedded renewal process $\{T_1, T_2, \ldots\}$, where T_i denotes the ith cycle. Moreover, $\{X_n\}_{n\geq 0} = \{C(\eta_n + 0), Q(\eta_n + 0)\}_{n \geq 0}$ is a discrete time regenerative process with renewal sequence $\{N_1, N_2, \ldots\}$, where N_i is the number of generalized departures during the ith cycle, T_i. For convenience of notation, we shall denote $T = T_1$ and $N = N_1$.

With these preliminaries we are ready to state the following result in which we study the distributions of the embedded Markov chains at service completion and killing epochs.

Theorem3.1

If the process $\{X(t), \geq 0\}$ is ergodic, then

(i) The probability distribution of the number of customers in orbit just after a service completion epoch is given by

$$\bar{\pi}_0 = \left(F\left(1, 1 + \frac{\lambda+\alpha}{\mu}; 1 + \frac{\alpha+\delta\rho}{\mu}; \rho\right)\right)^{-1} \tag{1}$$

$$\bar{\pi}_j = \bar{\pi}_0 \frac{\left(1+\frac{\lambda+\alpha}{\mu}\right)}{\left(1+\frac{\alpha+\delta\rho}{\mu}\right)} \rho^j, j \geq 1 \tag{2}$$

(ii)If $\delta > 0$, the probability distribution of the number of customers in the system just after a killing epoch is given by

$$\bar{\pi}_j = A \frac{\delta\left(1+\frac{\lambda+\alpha}{\mu}\right)_j}{v\left(1+\frac{\alpha+\delta\rho}{\mu}\right)_j} \rho^j, j \geq 1 \tag{3}$$

Where $A = \left(\frac{\delta(\lambda+\alpha+\mu)}{v(\alpha+\mu+\delta\rho)} \rho F\left(1, 2 + \frac{\lambda+\alpha}{\mu}; 2 + \frac{\alpha+\delta\rho}{\mu};\ \rho\right)\right)^{-1}$

Proof.

By a basic result in the theory of regenerative processes, we have that the probabilities

$$\overline{\Pi}_j = \frac{E[\bar{N}^j]}{E[N]}, j \geq 0 \tag{4}$$

$$\widetilde{\Pi}_j = \frac{E[\tilde{N}^j]}{E[N]}, j \geq 1 \tag{5}$$

Where $\bar{N}^j$ (respectively $\tilde{N}^j$) is the number of service completion epochs at which j customers are left behind in the system during the first regenerative cycle $(0,T]$. Since $\bar{N}^0 1$, then $\bar{\Pi}_0 = 1/E[N]$.

For convenience we denote $(0,j)$ by A_j and (l,j) by B_j, for $j > 0$. We also consider $\bar{N}^j_{ab}$ (respectively $\tilde{N}^j_{ab}$) as the number of service completion epochs at which j customers are left behind in the system during the first passage time, T_{ab} from state a to state b. Then, $\bar{N}^j = \bar{N}^j_{B_0A_0}$ and $\tilde{N}^j = \tilde{N}^j_{B_0A_0}$ for $j \geq 1$.

Let $\Phi^j_{ab}(x,y)$ be the generating function of the pair $(\bar{N}^j_{ab}, \tilde{N}^j_{ab})$ defined by

$$\Phi^j_{ab}(x,y) = E\left[x^{\bar{N}^j_{ab}} y^{\tilde{N}^j_{ab}}\right], j \geq 1, |x| \leq 1 \ \& \ |y| \leq 1$$

Taking into account that a direct transition from the state B_0 to state A_0 (respectively from B_0 to B_1) occurs with probability $v(\lambda+v)^{-1}$ (respectively $\lambda(\lambda+v)^{-1}$), we get that $\Phi^j_{B_0A_0}(x,y)$ can be written as follows

$$\Phi^j_{B_0A_0}(x,y) = \frac{v}{\lambda+v} + \frac{\lambda}{\lambda+v}\Phi^j_{B_1A_0}(x,y) \tag{6}$$

These arguments can be extended to derive the following set of equations

$$\Phi^j_{B_1A_0}(x,y) = \Phi^j_{B_1B_0}(x,y)\, \Phi^j_{B_0A_0}(x,y) \tag{7}$$

$$\Phi^j_{B_iB_{i-1}}(x,y) = \frac{\delta}{\lambda+\delta+v}\left(1-\delta_{ij}+y\delta_{ij}\right) + \frac{\lambda}{\lambda+\delta+v}\Phi^j_{B_{i+1}B_{i-1}}(x,y)$$

$$+\frac{v}{\lambda+\delta+v}\left(1-\delta_{ij}+x\delta_{ij}\right)\Phi^j_{A_iB_{i-1}}(x,y) \tag{8}$$

$$\Phi^j_{B_{i+1}B_{i-1}}(x,y) = \Phi^j_{B_{i+1}B_i}(x,y)\Phi^j_{B_iB_{i-1}}(x,y) \tag{9}$$

$$\Phi^j_{A_iB_{i-1}}(x,y) = \frac{\alpha+i\mu}{\lambda+\alpha+i\mu} + \frac{\lambda}{\lambda+\alpha+i\mu}\Phi^j_{B_iB_{i-1}}(x,y) \tag{10}$$

For $i \geq 1, j \geq 1, |x| \leq 1 \ \& \ |y| \leq 1$

Differentiating the set of equations (6) to (10) with respect to x and setting $x = y = 1$ we obtain

$$E\left[\bar{N}^j_{B_0A_0}\right] = \frac{\lambda}{\lambda+v}E\left[\bar{N}^j_{B_1A_0}\right] \tag{11}$$

$$E\left[\bar{N}^j_{B_1A_0}\right] = E\left[\bar{N}^j_{B_1B_0}\right] + E\left[\bar{N}^j_{B_0A_0}\right] \tag{12}$$

$$E\left[\bar{N}^j_{B_iB_{i-1}}\right] = \frac{\lambda}{\lambda+\delta+v}E\left[\bar{N}^j_{B_{i+1}B_{i-1}}\right] + \frac{v}{\lambda+\delta+v}\left(\delta_{ij} + E\left[\bar{N}^j_{A_iB_{i-1}}\right]\right) \tag{13}$$

$$E\left[\bar{N}^j_{B_{i+1}B_{i-1}}\right] = E\left[\bar{N}^j_{B_{i+1}B_i}\right] + E\left[\bar{N}^j_{B_iB_{i-1}}\right] \tag{14}$$

$$E\left[\bar{N}^j_{A_iB_{i-1}}\right] = \frac{\lambda}{\lambda+\alpha+i\mu}E\left[\bar{N}^j_{B_iB_{i-1}}\right] \tag{15}$$

for $i \geq 1, j \geq 1$. From (11) and (12) we find that

$$E\left[\bar{N}^j\right] = \frac{\lambda}{v}E\left[\bar{N}^j_{B_1B_0}\right] \text{ for } j \geq 1$$

Analogously, from (13) to (15) we get

$$E\left[\bar{N}^j_{B_iB_{i-1}}\right] = \frac{\lambda\left(i+\dfrac{\lambda+\alpha}{\mu}\right)}{(\delta+v)\left(i+\dfrac{\alpha+\delta\rho}{\mu}\right)}\left(\frac{v}{\lambda}\delta_{ij} + E\left[\bar{N}^j_{B_{i+1}B_i}\right]\right), i \geq 1, j \geq 1$$

Thus the following expression for $E\left[\bar{N}^j\right]$ is easily obtained

$$E\left[\bar{N}^j\right] = \frac{\left(1+\frac{\lambda+\alpha}{\mu}\right)_j}{\left(1+\frac{\alpha+\delta\rho}{\mu}\right)_j}\rho^j, j \geq 1 \tag{16}$$

Then the expected number of service completions occurring during a cycle is given by

$$E[\bar{N}] = F\left(1,1+\frac{\lambda+\alpha}{\mu};1+\frac{\alpha+\delta\rho}{\mu};\ \rho\right)$$

Applying a similar scheme for the expected number of customers deleted during $(0,T]$, we deduce the following expressions

$$E\left[\tilde{N}^j\right] = \frac{\delta\left(1+\frac{\lambda+\alpha}{\mu}\right)_j}{v\left(1+\frac{\alpha+\delta\rho}{\mu}\right)_j}\rho^j, j \geq 1 \tag{17}$$

Taking into account that the expected number of killing customers in a cycle can be expressed as $E\left[\tilde{N}\right] = \sum_{j=1}^{\infty} E\left[\tilde{N}^j\right]$, it follows from (17) that

$$E\left[\tilde{N}\right] = \frac{\delta(\lambda+\alpha+\mu)}{v(\alpha+\mu+\delta\rho)}\rho F\left(1,2+\frac{\lambda+\alpha}{\mu};2+\frac{\alpha+\delta\rho}{\mu};\ \rho\right) \tag{18}$$

Thus, $E[N]$ is

$$E[N] = 1+\frac{\lambda(\lambda+\alpha+\mu)}{v(\alpha+\mu+\delta\rho)}F\left(1,2+\frac{\lambda+\alpha}{\mu};2+\frac{\alpha+\delta\rho}{\mu};\ \rho\right) \tag{19}$$

Since

$$\bar{\pi}_j = \frac{\bar{\Pi}_j}{\sum_{k=0}^{\infty}\bar{\Pi}_k}, j \geq 0 \tag{20}$$

$$\tilde{\pi}_j = \frac{\tilde{\Pi}_j}{\sum_{k=1}^{\infty}\tilde{\Pi}_k}, j \geq 1 \tag{21}$$

It follows from (4), (5), (16), (17) and (19) to (21) that formulae (1) to (3) are correct.

To conclude, we observe that the convergence of the series involved in this theorem follows from an easy application of Ratio test and Raabe's test. Our second goal in this section is to find the factorial moments of the sequences $\{\bar{\pi}_j\}_{j\geq 0}$ and $\{\tilde{\pi}_j\}_{j\geq 1}$

Theorem3.2.

If the process $\{X(t), t \geq 0\}$ is ergodic, then

(i) The k$^{\text{th}}$ factorial moment of the embedded Markov chain at service completion epochs $\bar{M}_k$, is given by

$$\bar{M}_k = \bar{\pi}_0\frac{\left(1+\frac{\lambda+\alpha}{\mu}\right)_k}{\left(1+\frac{\alpha+\delta\rho}{\mu}\right)_k}\rho^k k!\, F\left(k+1,k+1+\frac{\lambda+\alpha}{\mu};k+1+\frac{\alpha+\delta\rho}{\mu};\rho\right), k \geq 0 \tag{22}$$

where $\bar{\pi}_0$ was given in equation (1).

(ii) The kth factorial moment of the embedded Markov chain at killing epochs $\tilde{M}_k$, is given by

$$\tilde{M}_k = \frac{\delta}{vE(\tilde{N})}\left(\frac{\left(1+\frac{\lambda+\alpha}{\mu}\right)_k}{\left(1+\frac{\alpha+\delta\rho}{\mu}\right)_k}\rho^k k!\, F\left(k+1,k+1+\frac{\lambda+\alpha}{\mu};k+1+\frac{\alpha+\delta\rho}{\mu};\rho\right)-\delta_{0k}\right), k \geq 0 \tag{23}$$

Where $E\left[\tilde{N}\right]$ was given in equation (18).

Proof.

From (1) to (3) we get the following expressions for the generating functions of $\{\bar{\pi}_j\}_{j\geq 0}$ and $\{\tilde{\pi}_j\}_{j\geq 1}$

$$\bar{\Pi}(z) = \sum_{j=0}^{\infty}\bar{\pi}_j z^j = \bar{\pi}_0 F\left(1,1+\frac{\lambda+\alpha}{\mu};1+\frac{\alpha+\delta\rho}{\mu};\rho z\right) \tag{24}$$

$$\tilde{\Pi}(z) = \sum_{j=1}^{\infty}\tilde{\pi}_j z^j = \frac{\delta(\lambda+\alpha+\mu)}{v(\alpha+\mu+\delta\rho)E(\tilde{N})}\rho z F\left(1,2+\frac{\lambda+\alpha}{\mu};2+\frac{\alpha+\delta\rho}{\mu};\ \rho z\right)$$

Since$(z+1)^n = \sum_{k=0}^{n}\binom{n}{k} z^k$, we obtain that $\overline{\Pi}(z+1) = \sum_{k=0}^{\infty} \overline{M}_k z^k (k!)^{-1}$, and therefore $\overline{M}_k$ can be obtained by a direct identification for the kth coefficient of the series $\overline{\Pi}(z+1)$. Thus, we have from the definition of hyper geometric series and (24) that $\overline{M}_k$, for $k \geq 1$, is given by

$$\overline{M}_k = \bar{\pi}_0 \sum_{j=k}^{\infty} \frac{\left(1+\frac{\lambda+\alpha}{\mu}\right)_j}{\left(1+\frac{\alpha+\delta\rho}{\mu}\right)_j} \rho^j \frac{j!}{(j-k)!}$$

By noting that $(1)_{j+k} = (j+k)!$ and $(a)_{j+k} = (a)_k (a+k)_j$, it follows that $\overline{M}_k$, for $k \geq 1$, is given by (22).

Expression (23) for $\overline{M}_k$, for $k \geq 0$, can be obtained alon the same arguments. By using again the Ratio test and Raabe's test it is verified that $\overline{M}_k$ and $\widetilde{M}_k$ exist for every k. To conclude this section, we summarize in the following corollary some explicit results for the case of constant retrial discipline.

Corollary3.1.

If $\mu = 0, \alpha > 0$ and $\gamma < 1$, then

(i) The probability distribution of the embedded Markov chain a service completion epochs is given by

$$\bar{\pi}_j = \left(1 - \frac{\lambda(\lambda+\alpha)}{v\alpha + \delta(\lambda+\alpha)}\right)\left(\frac{\lambda(\lambda+\alpha)}{v\alpha+\delta(\lambda+\alpha)}\right)^j, j \geq 0$$

And is corresponding kth factorial moment is

$$\overline{M}_k = k!\left(\frac{\lambda(\lambda+\alpha)}{v\alpha + (\delta-\lambda)(\lambda+\alpha)}\right)^k, k \geq 0$$

(ii) If $\delta > 0$, the probability distribution of the embedded Markov chain at killing epochs is given by

$$\tilde{\pi}_j = \left(1 - \frac{\lambda(\lambda+\alpha)}{v\alpha + \delta(\lambda+\alpha)}\right)\left(\frac{\lambda(\lambda+\alpha)}{v\alpha+\delta(\lambda+\alpha)}\right)^{j-1}, j \geq 1$$

And its corresponding kth factorial moment is

$$\widetilde{M}_k = \frac{v\alpha + (\delta-\lambda)(\lambda+\alpha)}{\lambda(\lambda+\alpha)}\left(\frac{v\alpha+\delta(\lambda+\alpha)}{v\alpha+(\delta-\lambda)(\lambda+\alpha)}\left(\frac{\lambda(\lambda+\alpha)}{v\alpha+(\delta-\lambda)(\lambda+\alpha)}\right)^k k! - \delta_{0k}\right), k \geq 0$$

The proof of this result is trivial from theorems 3.1 and 3.2 and thus omitted. However, it

Should be noted that $\bar{\pi}_j = \tilde{\pi}_{j+1}, j \geq 0$=

4. THE DEPARTURE PROCESS

The departure process is defined as the sequence of the times $\{\eta_i\}_{i\geq 0}$ at which customers leave the queueing system after their service completion epochs. The study of $\{\eta_i\}_{i\geq 0}$ is equivalent to the study of $\{\tau_i = \eta_i - \eta_{i-1}\}_{i\geq 1}$ It should be noted that the interval τ_i can be expressed as $\tau_i = R_i + S_i$ for $i \geq 1$, where R_i is defined as the server idle period until the arrival of the ith customer and S_i is the corresponding service time.

We assume that the system is stable, consequently $\tau_1, \tau_2, \ldots$ are identically distributed random variables. For convenience of notation we will denote the interval under consideration as τ_1. We next give the joint distribution of (R_1, S_1) in terms of its Laplace Stieltjes transform (LST).

Theorem4.1

If the queueing system is ergodic, then the Laplace Stieltjes transform

$\varphi(\theta,\omega) = E[exp\{-\theta R_1 - \omega S_1\}]$ is given by

$$\varphi(\theta,\omega)=\frac{v}{\omega+v}\left(1-\frac{\theta}{\theta+\lambda+\alpha}\bar{\pi}_0\left(\frac{\alpha}{\theta+\lambda}+F_2\left(\begin{matrix}1,1+\frac{\lambda+\alpha}{\mu},\frac{\theta+\lambda+\alpha}{\mu};\rho\\ 1+\frac{\alpha+\delta\rho}{\mu},1+\frac{\theta+\lambda+\alpha}{\mu}\end{matrix}\right)\right)\right) \tag{25}$$

For $Re(\theta)\geq 0, Re(\omega)\geq 0$ where $\bar{\pi}_0$ was given in (1).

Proof.

Since the length of service time S_1, is independent of all the events occurred before its commencement, the random variables R_1 and S_1 are independent. Thus,

$\varphi(\theta,\omega)=E[exp\{-\theta R_1\}]E[exp\{-\omega S_1\}]$

Where $E[exp\{-\omega S_1\}]=v(\omega+v)^{-1}$

In order to find the LST of R_1, we condition on the number of customers present in the system at the previous service completion epoch to get

$$E[exp\{-\theta R_1\}]=\frac{\lambda}{\theta+\lambda}\bar{\pi}_0+\sum_{n=1}^{\infty}\frac{\lambda+\alpha+n\mu}{\theta+\lambda+\alpha+n\mu}\bar{\pi}_n$$

Note that

$$\sum_{n=0}^{\infty}\frac{\bar{\pi}_n}{\theta+\lambda+\alpha+n\mu}=\frac{1}{\theta+\lambda+\alpha}\int_0^1\bar{\Pi}\left(\frac{\mu}{x^{\theta+\lambda+\alpha}}\right)dx$$

Thus

$$\sum_{n=1}^{\infty}\frac{\lambda+\alpha+n\mu}{\theta+\lambda+\alpha+n\mu}\bar{\pi}_n=1-\frac{\lambda+\alpha}{\theta+\lambda+\alpha}\bar{\pi}_0-\frac{\theta}{\mu}\int_0^1 t^{\frac{\theta+\lambda+\alpha}{\mu}}\bar{\Pi}(t)dt \tag{26}$$

Substitution of (24) into (26) leads, after some algebraic manipulations to (25).

Note that the generalized hyper geometric series in (25) is convergent if and only if the process $\{X(t),t\geq 0\}$ is ergodic. In the particular case $\mu=0$ and $\alpha>0$, the above result is reduced to a more explicit expression.

Corollary4.1.

If $\mu=0,\alpha>0$ and $\gamma<1$, then the LST of (R_1,S_1) given by

$$\varphi(\theta,\omega)=\frac{v}{(\omega+v)(\theta+\lambda+\alpha)}\left(\lambda+\alpha\left(1-\frac{\theta}{\theta+\lambda}\bar{\pi}_0\right)\right) \tag{27}$$

For $Re(\theta)\geq 0, Re(\omega)\geq 0$ where $\bar{\pi}_0$ was given in corollary 3.1

The LST of the pair (R_1,S_1) can be inverted by inspection. This yields the following result.

Corollary4.2.

If the process $\{X(t),t\geq 0\}$ is ergodic, then

(i) If $\mu=0$ and $\alpha>0$,

$$f_{(R_1,S_1)}(x,y)=ve^{-vy}\left(\lambda e^{-\lambda x}\bar{\pi}_0+(\lambda+\alpha)e^{-(\lambda+\alpha)x}(1-\bar{\pi}_0)\right)\delta(x)\delta(y)$$

Where $\bar{\pi}_0$ was given in corollary 4.1

(ii) If $\mu>0$,

$f_{(R_1,S_1)}(x,y)=\bar{\pi}_0 ve^{-vy}\left(\lambda e^{-\lambda x}+\frac{\lambda+\alpha+\mu}{\alpha+\mu+\delta\rho}\rho e^{-(\lambda+\alpha+\mu)x}\right)\times\left((\lambda+\alpha)F\left(1,2+\frac{\lambda+\alpha}{\mu};2+\right.\right.$

$\alpha+\delta\rho\mu;\rho e-\mu x+\mu F2, 2+\lambda+\alpha\mu;2+\alpha+\delta\rho\mu;\rho e-\mu x\delta x\delta y$

Where $\bar{\pi}_0$ was given in (1).

Our next objective is to obtain formulae for the moments of random variable R_1. $M_k^{R_1} = E\left(R_1^k\right), k \geq 0$

Theorem4.2

Under ergodicity, the moments of R_1 are given by

(i) If $\mu = 0$ and $\alpha > 0$, then

$$M_k^{R_1} = k!\left(\frac{1-\bar{\pi}_0}{(\lambda+\alpha)^k} + \frac{\bar{\pi}_0}{(\lambda)^k}\right), k \geq 0 \tag{28}$$

Where $\bar{\pi}_0$ was given in corollary 3.1.

(ii) If $\mu > 0$, then

$$M_k^{R_1} = k!\,\bar{\pi}_0\left(\frac{1}{(\lambda)^k} + \frac{1}{(\lambda+\alpha)^k}\left(F_k\left(\begin{matrix}1, \frac{\lambda+\alpha}{\mu}, \dots, \frac{\lambda+\alpha}{\mu}; \rho \\ 1+\frac{\alpha+\delta\rho}{\mu}, 1+\frac{\lambda+\alpha}{\mu}, \dots, 1+\frac{\lambda+\alpha}{\mu}\end{matrix}\right) - 1\right)\right) \tag{29}$$

For$k \geq 1$, where $\bar{\pi}_0$ was given in (1).

Proof.

With the help of (27) we easily obtain the expression (28). Upon differentiation of (25) we also obtain

$$M_k^{R_1} = k!\left(\frac{1}{(\lambda)^k} + \frac{1}{(\lambda+\alpha)^k}\right)\bar{\pi}_0 - (-1)^k \frac{1}{\mu} I_k(\theta) \tag{30}$$

Where

$$I_k(\theta) = \frac{d^k}{d\theta^k}\left(\theta \int_0^1 t^{\frac{\theta+\lambda+\alpha}{\mu}-1}\,\overline{\Pi}(t)dt\right) = \theta J(\theta,k) + kJ(\theta,k-1) \tag{31}$$

And $J(\theta,k) = \frac{d^k}{d\theta^k}\left(\theta \int_0^1 t^{\frac{\theta+\lambda+\alpha}{\mu}-1}\,\overline{\Pi}(t)dt\right)$

After some algebraic manipulations we find that

$$J(\theta,k) = (-1)^k k!\,\frac{\mu}{(\theta+\lambda+\alpha)^{k+1}}\bar{\pi}_0 F_{k+2}\left(\begin{matrix}1,1+\frac{\lambda+\alpha}{\mu}, \frac{\theta+\lambda+\alpha}{\mu}, \dots, \frac{\theta+\lambda+\alpha}{\mu}; \rho \\ 1+\frac{\alpha+\delta\rho}{\mu}, 1+\frac{\theta+\lambda+\alpha}{\mu}, \dots, 1+\frac{\theta+\lambda+\alpha}{\mu}\end{matrix}\right) \tag{32}$$

Substituting (31) and (32) into (30), we derive (29). Finally, an application of Ratio test and Raabe's test guarantees again that the series in (29) is convergent if and only if the process $\{X(t), t \geq 0\}$ is ergodic.

To find the k[th] moment of the inter departure time τ_1, $M_k^{\tau_1} = E\left[\tau_1^k\right]$ for $k \geq 0$, we use the simple observation that R_1 and S_1 are independent random variables. We thus obtain $M_k^{\tau_1} = \sum_{j=0}^{k}\binom{k}{j} M_j^{R_1} M_{k-j}^{S_1}$

Where $M_j^{S_1} = j!\,v^{-j}$ for $j \geq 0$.

In applications, the mean and variance of any performance measure are perhaps the most important quantities. Thus, we give these quantities in the following.

Corollary4.3.

(i) If $\mu > 0$ and $\rho < 1$, then

$$E[\tau_1] = \frac{1}{v} + \bar{\pi}_0\left(\frac{1}{\lambda} + \frac{\rho}{\alpha+\mu+\delta\rho} F\left(1,1+\frac{\lambda+\alpha}{\mu}; 2+\frac{\alpha+\delta\rho}{\mu}; \rho\right)\right)$$

$$Var[\tau_1] = \frac{1}{v^2} + 2\bar{\pi}_0\left(\frac{1}{\lambda^2} + \frac{\rho}{(\lambda+\alpha+\mu)(\alpha+\mu+\delta\rho)^3} F_2\left(\begin{matrix}1,1+\frac{\lambda+\alpha}{\mu}; 1+\frac{\lambda+\alpha}{\mu}; \rho \\ 2+\frac{\alpha+\delta\rho}{\mu}; 2+\frac{\alpha+\delta\rho}{\mu}\end{matrix}\right)\right)$$

$$-\left(\bar{\pi}_0\left(\frac{1}{\lambda} + \frac{\rho}{\alpha+\mu+\delta\rho} F\left(1,1+\frac{\lambda+\alpha}{\mu}; 2+\frac{\alpha+\delta\rho}{\mu}; \rho\right)\right)\right)^2$$

Where $\bar{\pi}_0$ was given in equation (1).

(ii) If $\mu = 0, \alpha > 0$ and $\gamma < 1$, then

$$E[\tau_1] = \frac{v^2\alpha + \delta(\lambda+\alpha)(\lambda+v)}{\lambda v(v\alpha + \delta(\lambda+\alpha))}$$

$$Var[\tau_1] = \frac{1}{v^2} + \frac{1}{\lambda^2} + \frac{1}{(\lambda+\alpha)^2}\left(1 - \left(\frac{v\alpha+(\lambda+\alpha)(\delta+\alpha)}{v\alpha+\delta(\lambda+\alpha)}\right)^2\right) \quad (33)$$

5. EXAMPLE

745 patients with no previously documented cardiovascular disease and diabetes mellitus diagnosed to have nonmetastatic prostate cancer were recruited. Of these, 517 patients received ADT and the remaining 228 did not. After a mean follow up of 5.3 years, 60 patients developed primary composite endpoint including (1) coronary artery disease, (2) congestive heart failure, and (3) ischemic stroke. Higher proportion of patients on ADT (51 patients, 9.9%) developed composite endpoint compared with those not on ADT (9 patients, 3.9%) with hazard ratio (HR) of 2.06 (95% confidence interval (CI): 1.03–3.24, P = 0.04). Furthermore, Cox regression analysis revealed that only the use of ADT (HR: 2.1, 95% CI: 1.03–4.25, P = 0.04) and hypertension (HR: 2.0, 95% CI: 1.21–3.33, P < 0.01) were independent predictors for primary composite endpoint [6-7] & [10-12].

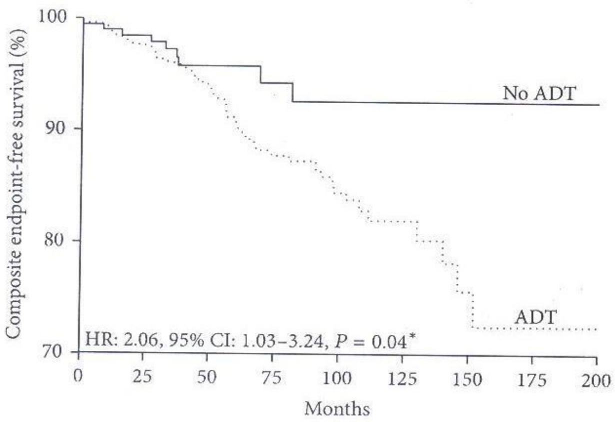
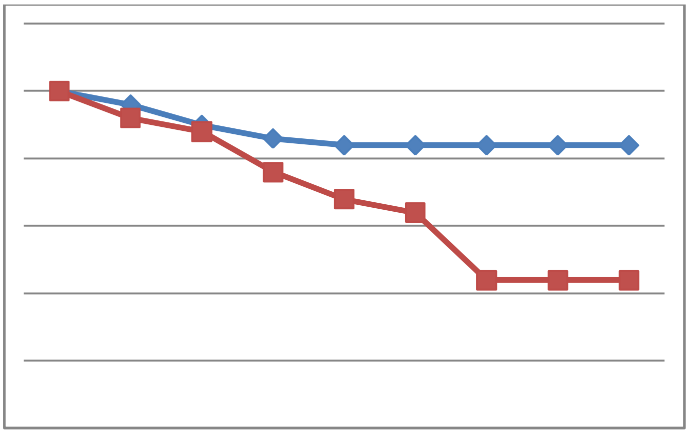


Fig1. *Kaplan Meier curve of primary composite endpoint (Coronary Artery Disease, Congestive Heart Failure and Ischemic Stroke) in patients on ADT and those not on ADT.*



Blue Line: *No* ADT **Red Line:** *ADT*

Fig2.*Kaplan Meier curve of primary composite endpoint (Coronary Artery Disease, Congestive Heart Failure and Ischemic Stroke) in patients on ADT and those not on ADT using Uniform Distribution.*

6. CONCLUSION

ADT in patients with nonmetastatic prostate cancer with no previously documented cardiovascular disease was associated with subsequent development of cardiovascular events. Androgen deprivation therapy and the mean and variance of the departure process in stochastic analysis give the same result. By using uniform distribution 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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