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Stochastic Model to Find the Testosterone Therapy on Functional Capacity in CHF Patients Using Stochastic Analysis

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Abstract: Heart failure is a serious cardiovascular condition leading to life threatening events, poor prognosis, and degradation of quality of life. According to the present evidences suggesting association between low testosterone level and prediction of reduced exercise capacity as well as poor clinical outcome in patients with heart failure, we sought to determine if testosterone therapy improves clinical and cardiovascular conditions as well as quality of life status in patients with stable chronic heart failure. The purpose of this study was to examine the testosterone therapy on functional capacity in congestive heart failure patients using the stochastic analysis of the departure and quasi input processes of a Markovian single server queue with negative exponential arrivals and repeated attempts.

Key Words: Testosterone Therapy, Congestive Heart Failure, Markovian Single Server Queue, Departure Process, Normal Distribution.

I. INTRODUCTION

A noticeable evolution of therapeutic concepts has taken place with a variety of cardiac and hormonal drugs with the aim of improving patient's survival, preventing sudden death, and improving quality of life [7] & [9]. In a significant proportion of heart failure patients, testosterone deficiency as an anabolic hormonal defect has been proven and identified even in both genders [5]. This metabolic and endocrinological abnormality is frequently associated with impaired exercise tolerance and reduced cardiac function [16]. For this reason, combination therapy with booster cardiovascular drugs and testosterone replacement therapy might be very beneficial in heart failure patients. The physiological pathways involved in these therapeutic processes have been recently examined. First, elevated level of testosterone following replacement therapy is major indicator for increase of peak VO_2 in affected men with heart failure explaining improvement of exercise tolerance in these patients [6]. Furthermore, testosterone replacement therapy can reduce circulating levels of inflammatory mediators including tumor necrosis factor α ($TNF - \alpha$) and interleukin (IL) $- 1\beta$, as well as total cholesterol in patients with established simultaneous coronary artery disease and testosterone deficiency. According to the present evidences suggesting association between low testosterone level and prediction of reduced exercise capacity as well as poor clinical outcome in patients with heart failure, we sought to determine if testosterone therapy improves clinical and cardiovascular conditions as well as quality of life status in patients with stable chronic heart failure.

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 non metastatic prostate cancer patients.

II. 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

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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 [1]. 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 [2]. In related work [8] examined the $M/G/1$ with two types of customers and constant retrial discipline.

Recently, [4] 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 [3], where the classification of states, stationary distribution, waiting time and busy period were studied. Thus, this paper completes the investigation initiated in [3].

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 $\alpha(1 - \delta_{o_j}) + j\mu$, 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 $\alpha(1 - \delta_{o_j}) + j\mu$, 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 ν . 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

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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 non persistent. Finally, the single server Markovian queue with classical waiting line and negative arrivals is obtained by letting $\alpha \rightarrow +\infty$ and $\mu \rightarrow +\infty$.

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

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

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

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

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 $F_1 \left(\begin{matrix} a_1, a_2; Z \\ b_1 \end{matrix} \right)$ by $F(a_1, a_2; b_1 z)$

III. 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 i^{th} customer and S_i is the corresponding service time. We assume that the system is stable, consequently τ_1, τ_2, \dots 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).

A. Theorem

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

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

$$\text{For } \text{Re}(\theta) \geq 0, \text{Re}(\omega) \geq 0 \text{ where } \bar{\pi}_0 = \left(F \left(1, 1 + \frac{\lambda + \alpha}{\mu}; 1 + \frac{\alpha + \delta \rho}{\mu}; \rho \right) \right)^{-1} \quad (2)$$

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

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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

$$\sum_{n=1}^{\infty} \frac{\lambda + \alpha + n\mu}{\theta + \lambda + \alpha + n\mu} \bar{\pi}_n = 1 - \frac{\lambda + \alpha}{\theta + \lambda + \alpha} \bar{\pi}_0 - \frac{\theta}{\mu} \int_0^1 t^{\frac{\theta + \lambda + \alpha}{\mu}} \bar{\Pi}(t) dt \quad (3)$$

Substitution into (3) leads, after some algebraic manipulations to (1).

Note that the generalized hyper geometric series in (1) 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.

B. Corollary

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

$$\varphi(\theta, \omega) = \frac{v}{(\omega + v)(\theta + \lambda + \alpha)} \left(\lambda + \alpha \left(1 - \frac{\theta}{\theta + \lambda} \bar{\pi}_0 \right) \right) \quad (4)$$

for $Re(\theta) \geq 0, Re(\omega) \geq 0$ where $\bar{\pi}_0$ was given in (2)

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

C. Corollary

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

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

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

Where $\bar{\pi}_0$ was given in (2)

(ii) If $\mu > 0$,

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

Where $\bar{\pi}_0$ was given in (2).

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

D. Theorem

Under ergodicity, the moments of R_1 are given by

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

$$M_k^{R_1} = k! \left(\frac{1 - \bar{\pi}_0}{(\lambda + \alpha)^k} + \frac{\bar{\pi}_0}{(\lambda)^k} \right), k \geq 0 \quad (5)$$

Where $\bar{\pi}_0$ was given in (2).

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

$$M_k^{R_1} = k! \bar{\pi}_0 \left(\frac{1}{(\lambda)^k} + \frac{1}{(\lambda + \alpha)^k} \left(F_k \left(1, \frac{\lambda + \alpha}{\mu}, \dots, \frac{\lambda + \alpha}{\mu}; \rho \right) - 1 \right) \right) \quad (6)$$

for $k \geq 1$, where $\bar{\pi}_0$ was given in (2).

Proof:

With the help of (4) we easily obtain the expression (5). Upon differentiation of (1) we also obtain

$$M_k^{R_1} = k! \left(\frac{1}{(\lambda)^k} + \frac{1}{(\lambda + \alpha)^k} \right) \bar{\pi}_0 - (-1)^k \frac{1}{\mu} I_k(\theta) \quad (7)$$

$$\text{Where } I_k(\theta) = \frac{d^k}{d\theta^k} \left(\theta \int_0^1 t^{\frac{\theta + \lambda + \alpha}{\mu} - 1} \bar{\Pi}(t) dt \right) = \theta J(\theta, k) + k J(\theta, k - 1) \quad (8)$$

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

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After some algebraic manipulations we find that

$$J(\theta, k) = (-1)^k k! \frac{\mu}{(\theta + \lambda + \alpha)^{k+1}} \bar{\pi}_0 F_{k+2} \left(\begin{matrix} 1, 1 + \frac{\lambda + \alpha}{\mu}, \frac{\theta + \lambda + \alpha}{\mu}, \dots, \frac{\theta + \lambda + \alpha}{\mu}; \rho \\ 1 + \frac{\alpha + \delta \rho}{\mu}, 1 + \frac{\theta + \lambda + \alpha}{\mu}, \dots, 1 + \frac{\theta + \lambda + \alpha}{\mu} \end{matrix} \right) \quad (9)$$

Substituting (8) and (9) into (7), we derive (6). Finally, an application of Ratio test and Raabe's test guarantees again that the series in (6) 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 , $M_k^{\tau_1} = E[\tau_1^k]$ 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.

E. Corollary

(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 (2).

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

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

$$Var[\tau_1] = \frac{1}{v^2} + \frac{1}{\lambda^2} + \frac{1}{(\lambda + \alpha)^2} \left(1 - \left(\frac{v\alpha + (\lambda + \alpha)(\delta + \alpha)}{v\alpha + \delta(\lambda + \alpha)} \right)^2 \right) \quad (10)$$

IV. EXAMPLE

A total of 50 male patients who suffered from congestive heart failure were recruited in a double blind, placebo controlled trial and randomized to receive an intramuscular (gluteal) long acting androgen injection (1ml of testosterone enanthate 250mg/ml) once every four weeks for 12 weeks or receive intramuscular injections of saline (1ml of 0.9% wt/vol NaCl) with the same protocol. Comparing baseline variables and clinical parameters across the two groups who received testosterone or placebo did not show any significant difference, except for 6MWD that was higher in the testosterone group. During the 12 week study period, no significant differences were revealed in the trend of the changes in hemodynamic parameters including systolic and diastolic blood pressures as well as heart rate between the two groups. Also, the changes in body weight were comparable between the groups, while, unlike the group received placebo, those who received testosterone had a significant increasing trend in 6MWD parameter within the study period (6MWD at baseline was $407.44 \pm 100.23m$ and after 12 weeks of follow up reached $491.65 \pm 112.88m$ following testosterone therapy, $P = 0.019$). According to post hoc analysis, the mean 6 walk distance parameter was improved at three time points of 4 weeks, 8 weeks, and 12 weeks after intervention compared with baseline; however no differences were found in this parameter at three post intervention time points. The discrepancy in the trends of changes in 6MWD between study groups remained significant after adjusting baseline variables (*mean square* = 243.262, *F - index* = 4.402 and $P = 0.045$) [5], [7] & [9-15].

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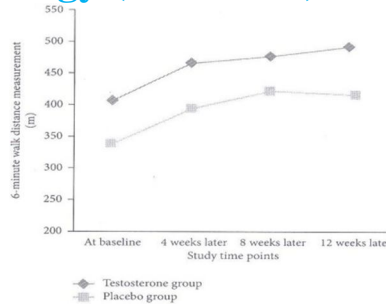


Figure 1: Trend of the changes in 6 minute walk distance parameter in intervention and placebo groups

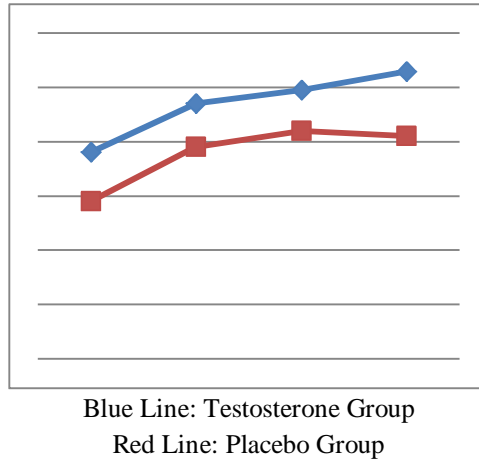


Figure 2: Trend of the changes in 6 minute walk distance parameter in intervention and placebo groups using Gamma Distribution

V. CONCLUSION

The changes in body weight, hemodynamic parameters, and left ventricular dimensional echocardiographic indices were all comparable between the two groups. Regarding changes in diastolic functional state and using Tei index, this parameter was significantly improved. Unlike the group received placebo, those who received testosterone had a significant increasing trend in 6 walk mean distance (6MWD) parameter within the study period ($P = 0.019$). The discrepancy in the trends of changes in 6MWD between study groups remained significant after adjusting baseline variables ($mean\ square = 243.262, F\ index = 4.402$ and $P = 0.045$). Our study strengthens insights into the beneficial role of testosterone in improvement of functional capacity and quality of life in heart failure patients. This results while using motion on Departure Process also gives the same result by using uniform distribution. 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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