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STOCHASTIC ANALYSIS WITH SIMULATION OF TIME TO HOSPITALIZATION AND HOSPITALIZATION TIME FOR DIABETES WHEN TWO ORGANS FAIL WITH COXIAN-2 OBSERVATION TIME FOR PROPHYLACTIC TREATMENT

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ABSTRACT

T*his paper assumes one organ A of a diabetic person is exposed to organ failure due to a two phase risk process and another organ B has a random failure time. Prophylactic treatment starts after one or two observations following Coxian-2 distribution. In the model, the hospitalization for diabetes starts when both the organs A and B are in failed state or when the prophylactic treatment starts. The joint Laplace transform of the distribution of time to hospitalization for treatment and hospital treatment time are presented along with their expectations. The expected time to hospitalization for treatment and expected treatment time are obtained for numerical Studies. Simulation studies are under taken using linear congruential generators. EC distribution is considered for the general distribution of life time of organ B since it is the best approximation for a general distribution. Erlang and phase type distributions are considered for hospital stage treatment times. Random values of all the variables are generated to present simulated values of time to hospitalization and hospitalization times for various parameter values of Coxian time to prophylactic treatment.*

Keywords: *Diabetic mellitus, Prophylactic treatment, PH phase2 distribution, Erlang-Coxian2 distribution, Simulation study, Linear congruential generator.*

I. INTRODUCTION

Prevention of the disease is always given much importance as that would safe guard the patient. Risk factors of diabetes mellitus have been presented by Bhattacharya, Biswas, Ghosh and Banerjee in [1]. Foster, Fauci, Braunward, Isselbacher, Wilson, Mortin and Kasper have studied diabetes mellitus in [2]. Kannell and McGee [3] have analyzed Diabetes and Cardiovascular Risk Factors. King, Aubert and Herman in [4] have listed the global burden of diabetes during the period 1995-2025. King and Rewers [5] have estimates for the prevalence of diabetes mellitus and impaired glucose tolerance in adults. Usha and Eswariprem in [6] have focused their discussions on the models with metabolic disorder. Eswariprem, Ramanarayanan and Usha [7] have analyzed such models with prophylactic treatment to avoid the disease. Mathematical models and assumptions play a great and distinctive role in this area. Any study with prophylactic treatment will be very beneficial to the society. Moreover cure from the disease after treatment is time consuming and above all is seldom achieved in many cases. This paper concentrates on situations of prophylactic treatment to prevent the disease when one organ A of a person is exposed to failure due to a two phase failure process and another organ B fails after a random time. Rajkumar, Gajivaradhan and Ramanarayanan [8] have treated recently a diabetic model where time to admit for prophylactic treatment has exponential distribution and have also discussed the effect of prophylactic treatment. Since exponential random variable has constant hazard rate, it may be useful if the hazard rate changes to some higher level after a random time so that mean of the time to admit for prophylactic treatment decreases. Such varying rates models are named as switching the clock back to zero (SCBZ) models and they are treated in various other contexts and areas by Raja Rao [9], Murthy and Ramanarayanan [10] and Snehalatha, Sekar and Ramanarayanan [11] to name a few of them. In this paper the time to admit for prophylactic treatment has SCBZ property and this has been identified in order to make admission early for treatment. Recent advancements in

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Probability, Operations Research and Simulation methods are utilized for the presentation of the results here. Analyzing real life stochastic models researchers collect data directly from the source/ hospitals (primary data) or use secondary data from research organizations or use simulated data for studies. Simulation studies are more suitable in this area since in most of the cases in general, hospitable real life data may not be sufficiently available and at times they may heavily depend on the biased nature of the data collectors. They may vary hospital to hospital and they may not be genuine enough for the study since many other factors such as the quality of nursing and medical treatments provided to the patients by hospitals are involved. The alertness of the patients in expressing the symptoms and timely assistance of insurance and finance agencies involved may play always the leading role in providing proper treatment. These are necessary to generate perfect and genuine data. Since the reputation of many connected organizations are involved, there may not be anybody to take the responsibility of the perfectness of the data provided. In this area not much of significant simulation studies are available or taken up so far at any depth. For simulation analysis, models with general random variables present the real life-like situations and results. It is well known that any general distribution may be well approximated by Erlang-Coxian 2 (EC) Phase type distribution and the details of the same are presented by T. Osogami and M. H.Balter [12] using the first three moments comparison method. For the simulation analysis here, Martin Haugh [13] results and Law and Kelton methods using Hull and Dobell results [14] are utilized to generate uniform random values and all other random values required. In the model treated here, a person with two defective organs A and B is considered. He is provided hospital treatment when both the organs are in failed state or when he is admitted for prophylactic treatment. In real life situations, it is often seen that the failure of organ A producing insulin (pancreatic failure) is not noticed by many patients until organ B fails (say, kidney or some other failure) similarly organ B failure (say, kidney failure) may not be noticed until organ A also fails (pancreatic failure). In such situations treatment begins when two organs A and B are in failed state. This arises when the patient is unable to identify and reveal promptly the symptoms on time for treatment. Depending on the values of the parameter of time to prophylactic treatment two sub-cases namely case (i) of a coxian type and case (ii) of a generalized Erlang with failure in all phases are noticed and studied. The joint Laplace-Stieltjes transform of time to hospitalization for treatment and hospital treatment time, the expected time to hospitalization for treatment and expected treatment time for the model are derived. Numerical examples are studied assuming exponential life time for organ B. Simulation studies are provided considering Erlang-Coxian 2 life time for organ B and considering the sum of Erlang and phase-two for hospital treatment times for the two cases. Varying the parameter of time to prophylactic treatment several simulated values are generated for time to hospitalization and hospitalization times.

II MODEL: BOTH ORGANS FAILURE AND PROPHYLACTIC TREATMENT

The general assumptions of the model studied here are given below. In real life situations and in many cases it may be seen that due to ignorance and negligence, the patient with two defective organs may not be sent for hospitalization unless both organs become failed. It is very common in many cases that the pancreas failed patients may not be aware of the lower insulin level / higher sugar level until another organ also fails.

Assumptions

(1) Defective organ A producing insulin functions in two phases of damaged levels namely level 1 (phase 1) and level 2 (phase 2) where level 1 is considered to be a better level of the two with lesser failure rate. Due to negligence and carelessness, the organ A may move to level 2 from level 1 and due to pre-hospital medication the organ A may move to level 1 from level 2. The failed level of the organ A is level 3. The transition rates of the organ A to the failed level 3 from level 1 and from level 2 are respectively $\lambda_1 and\ \lambda_2\ with\ \lambda_2 > \lambda_1$. The transition rates from level 1 to level 2 is μ_1 and from level 2 to level 1 is μ_2. At time 0 the organ A level is 1 and let F_A denote the life time (time to failure) of organ A.

(2) Defective organ B has a general life time F_B with Cumulative distribution function (Cdf) F_B(x) and probability density function (pdf) f_B(x).

(3) Irrespective of the status of the organs the patient is observed for a random time F_P with Coxian 2 distribution. The observation time F_P has exponential distribution with parameter α with probability q (one observation only) and with probability p =1 - q, the observation time is the sum of two random times (two observations) with exponential distributions with parameters α and β.

(4) The hospital treatment begins when the two organs are in failed state or when the prophylactic treatment starts whichever occurs first.

(5) The hospital treatment time for the failure of the organs is a random variable H_1 with Cdf $H_1(x)$ and pdf $h_1(x)$. The prophylactic treatment time in the hospital is a random variable H_2 with Cdf $H_2(x)$ and pdf $h_2(x)$.

Analysis

To study the above model two probability distributions, namely, $F_A(x)$ and $F_P(x)$, of time to failure of the organ A from the level 1 at time 0 and of time to admit the person for prophylactic treatment are to be obtained.

Derivation of the Cdf $F_A(x)$ of Time to Failure of Organ A from the Level 1 at Time 0

Levels 1 and 2 of the organ A may be considered as phases 1 and 2 respectively of PH phase 2 distribution.

Considering the failed state as absorbing state 3, $Q = \begin{bmatrix} -(\lambda_1+\mu_1) & \mu_1 & \lambda_1 \\ \mu_2 & -(\lambda_2+\mu_2) & \lambda_2 \\ 0 & 0 & 0 \end{bmatrix}$ (1)

is the infinitesimal generator describing the transitions. The pdf $f_A(t)$ and the Cdf $F_A(t)$ of the time to absorption starting from state 1 at time zero are derived here. Various transition probabilities may be derived as follows.

Let $P_{i,j}(t)$ = P (At time t the organ A is in level j and it has not failed during (0, t) | at time 0 it is in level i) (2)

for i, j = 1, 2. The probability $P_{1,1}(t)$ may be written considering the two possibilities that (i) the organ A may remain in level 1 during (0, t) without a failure or (ii) it moves to level 2 at time u for u ϵ (0, t) and it is in level 1 at time t without a failure . It may be seen that $P_{1,1}(t) = e^{-(\lambda_1+\mu_1)t} + \int_0^t \mu_1 e^{-(\lambda_1+\mu_1)u} P_{2,1}(t-u)\,du$ (3)

Using similar arguments it may be seen that $P_{2,1}(t) = \int_0^t \mu_2 e^{-(\lambda_2+\mu_2)u} P_{1,1}(t-u)\,du$, (4)

$P_{1,2}(t) = \int_0^t \mu_1 e^{-(\lambda_1+\mu_1)u} P_{2,2}(t-u)\,du$ (5)

and $P_{2,2}(t) = e^{-(\lambda_2+\mu_2)t} + \int_0^t \mu_2 e^{-(\lambda_2+\mu_2)u} P_{1,2}(t-u)\,du$. (6)

The above four equations (3) to (6) may be solved using Laplace transform method to obtain results as follows.

$P_{1,1}(t) = (\frac{1}{2})\, e^{-at}(e^{bt} + e^{-bt}) + (\frac{1}{4b})(\lambda_2 - \lambda_1 + \mu_2 - \mu_1)\, e^{-at}(e^{bt} - e^{-bt})$ (7)

$P_{1,2}(t) = (\frac{\mu_1}{2b})\, e^{-at}(e^{bt} - e^{-bt})$ (8)

$P_{2,2}(t) = (\frac{1}{2})\, e^{-at}(e^{bt} + e^{-bt}) + (\frac{1}{4b})(\lambda_1 - \lambda_2 + \mu_1 - \mu_2)\, e^{-at}(e^{bt} - e^{-bt})$ (9)

$P_{2,1}(t) = (\frac{\mu_2}{2b})\, e^{-at}(e^{bt} - e^{-bt})$ (10)

Here $a = (\frac{1}{2})(\lambda_1 + \lambda_2 + \mu_1 + \mu_2)$ and $b = (\frac{1}{2})\sqrt{(\lambda_1 - \lambda_2 + \mu_1 - \mu_2)^2 + 4\mu_1\mu_2}$. (11)

It can be seen that $a^2 - b^2 = \lambda_1\lambda_2 + \lambda_1\mu_2 + \lambda_2\mu_1$; $(\frac{a+b-\lambda_1}{2b})$ (a - b) = $\left(\frac{a^2-b^2-a\lambda_1}{2b}\right) + \frac{\lambda_1}{2}$

= $\frac{\lambda_1}{2} + \frac{\lambda_1}{4b}(\lambda_2 - \lambda_1 + \mu_2 - \mu_1) + (\frac{\lambda_2\mu_1}{2b})$ and $(\frac{a-b-\lambda_1}{2b})$ (a + b) = $-\frac{\lambda_1}{2} + \frac{\lambda_1}{4b}(\lambda_2 - \lambda_1 + \mu_2 - \mu_1) + (\frac{\lambda_2\mu_1}{2b})$ (12)

The absorption to state 3 can occur from any phase 1 or 2 since the organ A may fail from level 1 or level 2. The probability density function (pdf) $p_{1,3}(t)$ of time to failure of the organ A, starting from level 1 at time 0 is written using the absorption rates from levels 1 and 2 as follows. For notational convenience let $p_{1,3}(t) = f_A(t)$.

Using above results

$p_{1,3}(t) = \lambda_1 P_{1,1}(t) + \lambda_2 P_{1,2}(t) = f_A(t) = k_1(a - b)\, e^{-(a-b)t} - k_2(a + b)\, e^{-(a+b)t}$ (13)

where $k_1 = \frac{a+b-\lambda_1}{2b}$ and $k_2 = \frac{a-b-\lambda_1}{2b}$. Its Cdf is $F_A(t) = \int_0^t f_A(u)du = 1 - k_1 e^{-(a-b)t} + k_2 e^{-(a+b)t}$. (14)

Derivation of Cdf $F_P(x)$ of Time to Admit the Person for Prophylactic Treatment

Noting the first observation time (state 1 holding time) has exponential distribution with parameter α, noting with probability p the second observation is provided to the patient where the observation time (state 2 holding time) has exponential distribution with parameter β and considering the admission in hospital as absorption in state 3, the infinitesimal generator describing the various transitions is given by $Q' = \begin{bmatrix} -\alpha & p\alpha & q\alpha \\ 0 & -\beta & \beta \\ 0 & 0 & 0 \end{bmatrix}$. (15)

The pdf of time to hospitalization for prophylactic treatment starting from state 1 is

$f_P(t) = q\alpha e^{-\alpha t} + \int_0^t p\alpha\, e^{-\alpha u}\, \beta e^{-\beta(t-u)} du$. On simplification and integration, two types are noticed, namely, type (i) unequal holding rates $\alpha \neq \beta$ and type (ii) equal holding rates $\alpha = \beta$.

$$f_P(t) = \begin{cases} k_1'\beta e^{-\beta t} + k_2'\alpha e^{-\alpha t}, & if\ \alpha \neq \beta \quad \text{type (i)} \\ q\beta e^{-\beta t} + p\beta^2 t\, e^{-\beta t}, & if\ \alpha = \beta \quad type\ (ii) \end{cases} \quad (16)$$

where $k_1' = \frac{p\alpha}{(\alpha-\beta)}$ and $k_2' = \frac{(q\alpha-\beta)}{(\alpha-\beta)}$ and the Cdf after simplification is

$$F_P(t) = \begin{cases} 1 - k_1' e^{-\beta t} - k_2' e^{-\alpha t}, & if \ \alpha \neq \beta \quad type\ (i) \\ 1 - e^{-\beta t} - p\beta\, t\, e^{-\beta t}, & if \ \alpha = \beta \quad type\ (ii) \end{cases} . \tag{17}$$

To study the model, the joint pdf of two variables (T, H) where T is the time to hospitalization and H is the hospitalization time is required. Here variable T = Minimum {Maximum of the life times of the two organs (A, B), the time to prophylactic treatment} and variable H is the hospitalization time = H_1 *or* H_2 according as the hospitalization begins when the two organs are in failed state or the patient is admitted for prophylactic treatment.

The joint pdf of (T, H) is f (x, y) = $[F_A(x)f_B(x) + f_A(x)F_B(x)]\,\overline{F_P}\,(x)\,h_1(y) + (1 - F_A(x)F_B(x))f_P(x)\,h_2(y)$. (18)

The first term (with the square bracket) of the RHS of (18) is the pdf-part that the two organs A and B fail before the completion of the time to prophylactic treatment and the hospitalization is provided for the failure of the organs. The second term is the pdf-part that the patient is admitted for prophylactic treatment before the failures of the both organs A and B and the hospitalization for the prophylactic treatment is provided. The double Laplace transform of the pdf of (T, H) is given by $f^*(\xi, \eta) = \int_0^\infty \int_0^\infty e^{-\xi x - \eta y} f(x, y)\, dx\, dy$. (19)

The equation (19) using the structure of the equation (18) becomes a single integral.

$f^*(\xi, \eta) = \int_0^\infty e^{-\xi x}\{[F_A(x)f_B(x) + f_A(x)F_B(x)]\,\overline{F_P}\,(x)h_1^*(\eta) + (1 - F_A(x)F_B(x))\,f_P(x)h_2^*(\eta)\}\,dx.$ (20)

Using (13), (14), (16) and (17) equation (20) has to be written for $\alpha \neq \beta$ and $\alpha = \beta$.

Results for Type (i) $\alpha \neq \beta$

The Cdf and the pdf of organ A life time $F_A(x)$ and $f_A(x)$ are presented in (14) and (13). Using them in (20) for $\alpha \neq \beta$, equation (20) becomes after simplification using the fact $f_B^*(s) = s\,F_B^*(s)$ as follows.

$$\begin{aligned} f^*(\xi, \eta) = {} & \xi\, h_1^*(\eta)\{k_1'[F_B^*(\xi + \beta) - k_1F_B^*(\xi + \beta + a - b) + k_2 F_B^*(\xi + \beta + a + b)] + k_2'[F_B^*(\xi + \alpha) - k_1F_B^*(\xi + \alpha + a - b) \\ & + k_2F_B^*(\xi + \alpha + a + b)]\} + [h_1^*(\eta) - h_2^*(\eta)]\ \{\beta k_1'[F_B^*(\xi + \beta) - k_1F_B^*(\xi + \beta + a - b) + k_2 F_B^*(\xi + \beta + a + b)] \\ & + \alpha\, k_2'[F_B^*(\xi + \alpha) - k_1F_B^*(\xi + \alpha + a - b) + k_2F_B^*(\xi + \alpha + a + b)]\} + h_2^*(\eta)\,[\frac{\beta\, k_1'}{\xi + \beta} + \frac{\alpha\, k_2'}{\xi + \alpha}]. \end{aligned} \tag{21}$$

The Laplace transform of the pdf of the time to hospitalization T is seen after simplification by taking $\eta = 0$ in (21).

$$\begin{aligned} f^*(\xi, 0) = {} & \xi\ \{\ k_1'[F_B^*(\xi + \beta) - k_1F_B^*(\xi + \beta + a - b) + k_2\ F_B^*(\xi + \beta + a + b)] \\ & + k_2'\ [F_B^*(\xi + \alpha) - k_1F_B^*(\xi + \alpha + a - b) + k_2F_B^*(\xi + \alpha + a + b)]\} + [\frac{\beta\, k_1'}{\xi + \beta} + \frac{\alpha\, k_2'}{\xi + \alpha}]. \end{aligned} \tag{22}$$

Now $E(T) = -\frac{d}{d\xi} f^*(\xi, 0)\,|_{\xi=0}$ gives

$$E(T) = k_1'[\frac{1}{\beta} - F_B^*(\beta) + k_1F_B^*(\beta + a - b) - k_2\ F_B^*(\beta + a + b)] + k_2'\,[\frac{1}{\alpha} - F_B^*(\alpha) + k_1F_B^*(\alpha + a - b) - k_2F_B^*(\alpha + a + b)] \tag{23}$$

Using equation (21) the Laplace transform of the pdf of the hospitalization time H may be obtained by taking $\xi = 0$.

$$\begin{aligned} f^*(0, \eta) = {} & (h_1^*(\eta) - h_2^*(\eta))\{\beta k_1'[F_B^*(\beta) - k_1F_B^*(\beta + a - b) + k_2\ F_B^*(\beta + a + b)] \\ & + \alpha\, k_2'[F_B^*(\alpha) - k_1F_B^*(\alpha + a - b) + k_2F_B^*(\alpha + a + b)]\} + h_2^*(\eta) \end{aligned} \tag{24}$$

Since $E(H) = -\frac{d}{d\eta} f^*(0, \eta)\,|_{\eta=0}$, $E(H) = [E(H_1) - E(H_2)]\{\beta k_1'[F_B^*(\beta) - k_1F_B^*(\beta + a - b) + k_2\ F_B^*(\beta + a + b)]$

$$+ \alpha\, k_2'[F_B^*(\alpha) - k_1F_B^*(\alpha + a - b) + k_2F_B^*(\alpha + a + b)]\} + E(H_2) \tag{25}$$

Inversion of Laplace transform of (22) and (24) are straight forward. Noting $P(T \leq t) = L^{-1}\,(\frac{f^*(\xi,0)}{\xi})$, the Cdf of the time to hospitalization T and the Cdf of the hospitalization time H are given below.

$$\begin{aligned} P(T \leq t) = F_T(t) = 1 - {} & k_1'\, e^{-\beta t} - k_2' e^{-\alpha t} + k_1'[F_B(t)\, e^{-\beta t} - k_1F_B(t)\, e^{-(\beta + a - b)t} + k_2F_B(t)\, e^{-(\beta + a + b)t}] \\ & + k_2'[F_B(t)\, e^{-\alpha t} - k_1F_B(t)\, e^{-(\alpha + a - b)t} + k_2F_B(t)\, e^{-(\alpha + a + b)t}]. \end{aligned} \tag{26}$$

$$\begin{aligned} P(H \leq t) = F_H(t) = {} & [H_1(t) - H_2(t)]\ \{\beta k_1'[F_B^*(\beta) - k_1F_B^*(\beta + a - b) + k_2\ F_B^*(\beta + a + b)] \\ & + \alpha\, k_2'[F_B^*(\alpha) - k_1F_B^*(\alpha + a - b) + k_2F_B^*(\alpha + a + b)]\} + H_2(t) \end{aligned} \tag{27}$$

Results for Type (ii) α = β

The Cdf and the pdf of organ A life time $F_A(x)$ and $f_A(x)$ are presented in (14) and (13). Using them in (20) for α = β, f*(ξ, η) becomes as follows, after simplification using the fact f_B^*(s) = s F_B^*(s) and f_B^* ' (s) = F_B^*(s) + s F_B^* ' (s).

f*(ξ, η) = h_1*(η)[(ξ+ q β) F_B^*(ξ +β) - k_1(ξ + q β) F_B^*(ξ + β + a - b) + k_2 (ξ + q β) F_B^*(ξ +β + a + b)
- p β (ξ + β) F_B^* ' (ξ +β) +k_1p β (ξ + β) F_B^* ' (ξ +β+ a – b) - k_2 p β (ξ + β) F_B^* ' (ξ +β + a + b)]
+ h_2*(η) [$\frac{q\beta}{\xi+\beta}$ +p $(\frac{\beta}{\xi+\beta})^2$ - q β F_B^*(ξ + β) + $k_1 q$ β F_B^*(ξ +β+ a – b) - $k_2 q$ β F_B^*(ξ +β + a + b) + p β^2 F_B^* ' (ξ + β)
- k_1p $\beta^2 F_B^*$ ' (ξ +β+ a – b) + k_2p β^2 F_B^* ' (ξ +β + a + b)]. (28)

The Laplace transform of the pdf of the time to hospitalization T is seen after simplification by taking η = 0 in (28).

f*(ξ, 0) = $\frac{q\beta}{\xi+\beta}$ +p $(\frac{\beta}{\xi+\beta})^2$ + ξ { F_B^*(ξ +β) - $k_1 F_B^*$(ξ + β + a - b) + k_2 F_B^*(ξ +β + a + b) - p β F_B^* ' (ξ +β)
+k_1p β F_B^* ' (ξ +β+ a – b) - k_2 p β F_B^* ' (ξ +β + a + b) }. (29)

Now E (T) = $-\frac{d}{d\xi}$ f*(ξ, 0) $|_{\xi=0}$ gives E (T) = $\frac{1+p}{\beta}$ - { F_B^*(β) - $k_1 F_B^*$(β + a - b) + k_2 F_B^*(β + a + b) - p β F_B^* ' (β)
+ k_1p β F_B^* ' (β+ a – b) - k_2 p β F_B^* ' (β + a + b) } (30)

Using equation (28), the Laplace transform of the pdf of the hospitalization time H may be obtained by taking ξ = 0.

f*(0, η) = (h_1*(η) - h_2*(η)) [q β F_B^*(β) - k_1 q β F_B^*(β + a - b) + k_2 q β F_B^*(β + a + b)
- p β^2 F_B^* ' (β) +k_1p β^2 F_B^* ' (β+ a – b) - k_2 p β^2 F_B^* ' (β + a + b)] + h_2*(η). (31)

Since E (H) = $-\frac{d}{d\eta}$ f*(0, η) $|_{\eta=0}$, E (H) = [E(H_1) - E(H_2)] [q β F_B^*(β) - k_1 q β F_B^*(β + a - b) + k_2 q β F_B^*(β + a + b)
- p β^2 F_B^* ' (β) +k_1p β^2 F_B^* ' (β+ a – b) - k_2 p β^2 F_B^* ' (β + a + b)] + E(H_2). (32)

Inversion of Laplace transform of (29) and (31) are straight forward. The Cdf of T and Cdf of H are

P (T ≤ t) = F_T (t) =1 - $e^{-\beta t}$ - p β t $e^{-\beta t}$ +$e^{-\beta t}$ F_B(t) - k_1 $e^{-(\beta+a-b)t}$ F_B(t) + $k_2 e^{-(\beta+a+b)t}$ F_B(t) + p β t $e^{-\beta t}$ F_B(t)
- k_1p β t $e^{-(\beta+a-b)t}$ F_B(t) +$k_2 p\beta$ t $e^{-(\beta+a+b)t}$ F_B(t). (33)

P (H ≤ t) = F_H(t) = [H_1(t) - H_2(t)] [q β F_B^*(β) - k_1 q β F_B^*(β + a - b) + k_2 q β F_B^*(β + a + b)
- p β^2 F_B^* ' (β) +k_1p β^2 F_B^* ' (β+ a – b) - k_2 p β^2 F_B^* ' (β + a + b)] + H_2(t). (34)

Special Cases of Life Times of Organ B:

Two special cases, namely, organ B with exponential life time and with EC life time distributions are treated below.

Special Case (1): Exponential Life Time for Organ B

When the life time of the organ B has exponential distribution with parameter θ then F_B(x) = 1-$e^{-\theta x}$. E(T) and E(H) can be written using (23), (30), (25) and (32) for the two types (i) and (ii) by substituting $\frac{\theta}{s(\theta+s)}$ for F_B*(s) and its derivatives for various values of s present there.

Special Case (2): Erlang-Coxian 2 (EC) Life Time for Organ B

Let the life time of the organ B have EC distribution with parameter set (k, θ, θ_1, p_1, θ_2) which is the Cdf of the sum of Erlang (k, θ) and Coxian-2 (θ_1, p_1, θ_2) random variables where the Erlang part has k phases with parameter θ and the Coxian 2 has the infinitesimal generator describing the transition as Q''=$\begin{bmatrix} -\theta_1 & p_1\theta_1 & q_1\theta_1 \\ 0 & -\theta_2 & \theta_2 \\ 0 & 0 & 0 \end{bmatrix}$ (35)

for p_1 + q_1 = 1 with starting phase 1. By comparing Q'' with Q' in (15) the pdf of Coxian 2 may be written as $g_1(x) = (\frac{q_1\theta_1-\theta_2}{\theta_1-\theta_2})\ \theta_1 e^{-\theta_1 x} + (\frac{p_1\theta_1}{\theta_1-\theta_2})\theta_2 e^{-\theta_2 x}$ and $G_1(x)$ = 1- $(\frac{q_1\theta_1-\theta_2}{\theta_1-\theta_2})\ e^{-\theta_1 x}$ - $(\frac{p_1\theta_1}{\theta_1-\theta_2})e^{-\theta_2 x}$. The Laplace transform of the Coxian 2 is $g_1^*(s) = (\frac{q_1\theta_1-\theta_2}{\theta_1-\theta_2})(\frac{\theta_1}{\theta_1+s})+(\frac{p_1\theta_1}{\theta_1-\theta_2})(\frac{\theta_2}{\theta_2+s})$. (36)

The pdf f_B(x) being the pdf of the sum of Erlang and Coxian 2, its Laplace transform is f_B*(s) = $(\frac{\theta}{\theta+s})^k g_1^*(s)$. (37)

Laplace transform of $Cdf\ F_B(x)$ is F_B*(s) = $\frac{f_B^*(s)}{s}$ = $\frac{(\frac{\theta}{\theta+s})^k[(\frac{q_1\theta_1-\theta_2}{\theta_1-\theta_2})(\frac{\theta_1}{\theta_1+s})+(\frac{p_1\theta_1}{\theta_1-\theta_2})(\frac{\theta_2}{\theta_2+s})]}{s}$. (38)

The expected time to hospitalization and expected (treatment) hospitalization time respectively, E(T) and E(H) may be written considering equation (38) and its derivative and using (23),(30),(25) and (32) for the two types (i) and (ii).

Numerical and Simulation Studies:

(I). Numerical Studies:

As an application of the results obtained numerical study is taken up to present the expected times E(T) and E(H) for various values of the parameters introduced for the two types (i) and (ii) assuming $\lambda_1 = .3,\ \lambda_2 = .35,\ \mu_1 = .4, \mu_2 = .5$.

From (11), a=0.775; b=0.45345893; a + b = 1.228458929; a - b = 0.321541071 which gives the life time of organ A has Cdf, F_A (t) =1 - 1.02375195 $e^{-(0.321541071)t}$+ 0.02375195$e^{-(1.228458929)t}$ with pdf f_A (t) = (0.3291783001) $e^{-(0.3215410713)t}$- (0.291783001)$e^{-(1.228458929)t}$. Let the Cdf of organ B life time be F_B(t) = 1-$e^{-\theta t}$ with values for θ =0.4, 0.5, 0.6 and 0.7. Let the parameter of the Coxian time to prophylactic treatment for type (i) be with parameters α = 0.05, p= 0.2, 0.4, 0.6, 0.8 and β =0.1. Let the parameters for type (ii) be α = β = 0.1 with same values for p = 0.2, 0.4, 0.6, 0.8. Fixing p = 0.2 calculations are done by varying θ as =0.4, 0.5, 0.6 and 0.7. Fixing θ = 0.4 calculations are done by varying p as =0.2, 0.4, 0.6 and 0.8. Let the expected values of various treatment times be E(H_1)=0.1 and E(H_2)=0.05.

Table 1: Fixing p = 0.2 & Varying θ

θ	E(T) type (i)	E(H) type (i)	E(T) type (ii)	E(H) type (ii)
0.4	3.739923634	0.092239351	3.343097733	0.086462831
0.5	3.4765887	0.092798257	3.126001208	0.087349452
0.6	3.311161704	0.093146815	2.985716781	0.087920854
0.7	3.200211978	0.093379278	2.889658443	0.088311323

Table 2: Fixing p = 0.2 & Varying θ

p	E(T) type (i)	E(H) type (i)	E(T) type (ii)	E(H) type (ii)
0.2	3.739923634	0.092239351	3.343097733	0.086462831
0.4	3.833524253	0.093594509	3.507875546	0.088817262
0.6	3.927124872	0.094949668	3.672653359	0.091171693
0.8	4.020725491	0.096304826	3.837431172	0.093526124

For the two types (i) and (ii), E (T), E (H) values are presented in tables 1 and 2. Results for the two types (i) α≠ β and (ii) α = β are presented using equations (23), (25), (30) and (32). The variations of them on varying the parameters are clearly exhibited. The parameter values are substituted to obtain the statistical estimates. They present exact values of the estimates but they do not present any sample-runs or real life-like situations. Although θ and p cause variations in the values of E(T) and E(H) as seen above, the effects of the life times of organs A, B and the time to prophylactic treatment and the effects of various treatments provided in the hospital can be studied only by simulating and analyzing them. In simulation studies one may find real life like situations.

(II). Simulation Studies:

(i) Organ A

The simulated values of the life times of organ A, organ B and the time to prophylactic treatment are required for the study. They are generated using the methods presented by Martin Haugh [13] by generating uniform random values u using Linear Congruential Generator (LCG). The random values for the life time of the organ A may be generated noting that the two-phase life time distribution of organ A given in (14) derived using the (cyclic) infinitesimal generator Q of (1) is same as the coxian-2 distribution function of the absorption time with starting phase 1 of the continuous time Markov chain whose infinitesimal generator is Q''' given by (39). This may be seen as follows. Using the arguments given for (15), (16) and (17) for the Cdf of time to prophylactic treatment, it may be noted that

the infinitesimal generator which starts in (phase) level 1 given by Q'''=$\begin{bmatrix} -(a+b) & a+b-\lambda_1 & \lambda_1 \\ 0 & -(a-b) & (a-b) \\ 0 & 0 & 0 \end{bmatrix}$ (39)

has the absorption time distribution same as $F_A(x)$ given in (14) where a, b and λ_1 are as defined for the life time of the organ A. This makes the replacement of the generator (1) of the cyclic type by the generator (39) which is of acyclic type for simulation studies. The Cdf $F_A(x)$ is coxian with parameters (a + b) and (a - b) for holding exponential times in level 1 and level 2 respectively with probability p' = $\frac{(a+b-\lambda_1)}{(a+b)}$ for transition to level 2 from level 1 and with probability q' = 1- p' for absorption from level 1 when the holding time is over in level 1 for organ A. There is no transition from level 2 to level 1 and (there is no loop-like) no cyclic formation of transitions from level 1→level 2 → level l before absorptions. From level 2 absorption alone occurs after the holding time there. As in the numerical case-study the same values for the organ A transition rates are assumed, namely, $\lambda_1 = 0.3, \lambda_2 = 0.35,\ \mu_1 = 0.4,\ \mu_2 = 0.5$. Then from (11), a = 0.775; b = 0.453458929; a + b = 1.228458929; a - b = 0.3215410713 and p' = 0.755791591 which gives the life time of organ A has Coxian-2 Cdf, F_A (t) =1 - 1.02375195 $e^{-(0.3215410713)t}$+ 0.02375195$e^{-(1.228458929)t}$ with pdf f_A (t)= (0.3291783) $e^{-(0.3215410713)t}$- (0.0291783) $e^{-(1.228458929)t}$. The first and second exponential random time values of Coxian 2 time part of life time of the organ A can be generated by x'_A= - ($\frac{1}{1.228458929}$)ln u and x''_A = - ($\frac{1}{0.321541071}$) ln u (40)

where ln is natural logarithm and the random uniform values for the two are generated by two different LCGs. Considering third uniform random value u generated by another LCG, the Coxian life time of the organ A becomes $x_A = x'_A + x''_A$ if u ≤ p' = 0.755791591 and the Coxian time x_A becomes $x_A = x'_A$ if u > p' = 0.755791591.

So the simulated random time values for life time of the organ A is $x_A = \begin{cases} x'_A + x''_A & if\ u \le p' = 0.755791591 \\ x'_A & if\ u > p' = 0.755791591 \end{cases}$ (41)

So, for the life time of the organ A three random values are required to be simulated by three different LCGs.

(ii) Organ B

In the numerical study the general life time of the organ B is assumed to follow an exponential distribution. When it has some unknown distribution the researcher has to fit the distribution of it using the data available (primary / secondary). The method is to find the first three moments from the available data. When the first three moments are available, it has been established that the EC distribution with parameter set $(\tilde{p}, k, \theta, \theta_1, p_1, \theta_2)$ is an excellent and more suitable approximation for any general distribution function using the method of comparison of first three moments by T. Osogamy and M.H.Balter [12] where the details for finding the exact EC distribution with its parameter values are also available. EC $(\tilde{p}, k, \theta, \theta_1, p_1, \theta_2)$ has probability mass 1 - $\tilde{p}$ at time zero, where $0 < \tilde{p} \le 1$ and with probability $\tilde{p}$ its distribution is the Cdf of the sum of Erlang (k, θ) and Coxian $(\theta_1, p_1, \theta_2)$ random variables. So the assumption and consideration of an EC distribution for the life time of the organ B is ideal for simulation studies. Further such a study with EC distribution is almost a study on any general distribution. Accordingly it is assumed that the organ B has EC life time distribution with parameters set $\{\tilde{p}, k, \theta, \theta_1, p_1, \theta_2\}$ with respective values {1, 5, 2.5, 20, 0.5, 30} to study the Special case (2). Simulation study for the case of EC life distribution with $\tilde{p} < 1$ is similar. The method and study taken up here is valid for any set of values of the EC parameter set for the organ B.

For the Special case (2), the life time of the organ B is the sum of Erlang and Coxian random times. Its Erlang random time part is generated by considering $y = -\frac{1}{2.5} \ln \prod_{i=1}^{5} u_i$ (42)
and u_i are generated by different LCGs for i=1 to 5. Its first and second exponential random values of Coxian random part of the organ B are generated by $z = -\frac{1}{20} \ln u$ and $w = -\frac{1}{30} \ln u$ (43)
by two different LCGs. Considering third uniform random value u generated by another LCG, the Coxian time becomes z + w if $u \le p_1 = 0.5$ and if $u > p_1 = 0.5$ the Coxian time becomes z . So the simulated random time values for the life time of the organ B is $x' = \begin{cases} y + z + w & if\ u \le p_1 = 0.5 \\ y + z & if\ u > p_1 = 0.5 \end{cases}$. (44)

For the EC life time of the organ B, eight random values are required to be simulated by eight different LCGs.

(iii) Time to Prophylactic Treatment

Type (i) of Unequal Holding Rates α ≠ β
Let the parameters of the Coxian time to prophylactic treatment be α, p and β with values α = 0.5, p = 0.2, 0.4, 0.6, 0.8 and β = 1. Simulated uniform random values v', w' and v'' are required to decide the time to hospitalization for prophylactic treatment for simulating (exponential) observation times and to decide whether second opinion is required. Observation times are simulated by considering
$v' = -\frac{1}{0.5} \ln u$, and $v'' = -\frac{1}{1} \ln u$. (45)

The requirement of second observation is decided by w'. This gives the simulated time to prophylactic treatment is as follows for type (i). $x'' = \begin{cases} v' + v'' & if\ w' \le p \\ v' & if\ w' > p \end{cases}$ (46)

Four values of p = 0.2, 0.4, 0.6 and 0.8 are considered to study the variations using w'. This makes for the simulation of time to prophylactic treatment six uniform random values are required to be simulated by six different LCGs two for α, β and four for p for type (i)

Type (ii) Equal Holding Rates α = β
Let the parameters of the Coxian time to prophylactic treatment be α, p and β with values for α = β = 1 and p = 0.2, 0.4, 0.6, 0.8. Simulated uniform random values v''', w'' and v'''' are required for generating the time to hospitalization for prophylactic treatment two for simulating (exponential) observation times and four to decide whether second opinion is required. Observation times are simulated by considering $v''' = -\frac{1}{1} \ln u$, and $v'''' = -\frac{1}{1} \ln u$. (47)

The requirement of second observation is decided by w''. This gives the simulated time to prophylactic treatment is as follows for Model type (ii). $x''' = \begin{cases} v''' + v'''' & if\ w'' \le p \\ v''' & if\ w'' > p \end{cases}$ (48)

One uniform random value is required to be simulated for the first observation time for α = 1. For other random variables simulated values of type (i) may be used here for both p and the second exponential time. This means for the simulation of time to prophylactic treatment for the types (i) and (ii) seven uniform random values are required to be simulated by six different LCGs for values of α, β and p for type (i) and by one LCG for α for type (ii).

(iv) Time to Hospitalization

The simulated time to hospitalization for treatment is T = min {max{x_A, x'}, x"} for the type (i) and is T= min {max{x_A, x'}, x'"} for the type (ii). It may be noted that for the types (i) and (ii) 18 uniform random values three for the simulation of x_A, eight for the simulation of x', six for the simulations of x" and one for the simulation of x'" are to be generated to simulate the time to hospitalization for the Special case (2).

(v) Hospital Treatment Time

In the parametric model one can assume the expected values of various treatment (hospitalization) times. Exact structures of the distribution functions may not be required and the values of expectations alone are sufficient. Simulation studies are different. One has to study the types and stages of treatments as explained by Mark Fackrell [15] to get simulated hospital treatment times.

Two types of treatments H_1 *and* H_2 are considered here. Let five and three stages of treatments one by one respectively for them be assumed as follows.

- Treatment H_1 : Emergency Department (ED)→ Operation Theatre (OPT) → Intensive Care Unit (ICU) ↔ High Dependency Ward (HDW) → Ward (W) → Discharge
- Treatment H_2 : ED → ICU → W → Discharge.

In the treatment H_1, loop like treatments, namely, ICU→ HDW → ICU are also assumed to study the repetition of treatment at a stage. Let transitions from ED→OPT and OPT→ICU occur following exponential distributions with rate 60. From ICU let the patient move to HDW in an exponential time with rate 60. From HDW let the patient move to W in an exponential time with rate 60 or let the patient move back to ICU in an exponential time with rate 40 so that the total holding time at HDW may be exponential with rate 100. Let the holding time at W be exponential with rate 60 for the discharge of the patient. The infinitesimal generator which is a 6 by 6 matrix with states for H_1 is presented as

$$Q'''' = \begin{bmatrix} States & ED & OPT & ICU & HDW & W & D \\ ED & -60 & 60 & 0 & 0 & 0 & 0 \\ OPT & 0 & -60 & 60 & 0 & 0 & 0 \\ ICU & 0 & 0 & -60 & 60 & 0 & 0 \\ HDW & 0 & 0 & 40 & -100 & 60 & 0 \\ W & 0 & 0 & 0 & 0 & -60 & 60 \\ D & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

The sub matrix describing the cyclic formation is

$$Q^v = \begin{bmatrix} States & ICU & HDW & W \\ ICW & -60 & 60 & 0 \\ HDW & 40 & -100 & 60 \end{bmatrix}.$$

This may be compared with cyclic Q in (1) which has been replaced by acyclic Q'" in (39).

Using (39) and taking $\lambda_1 = 0,\ \lambda_2 = 60,\ \mu_1 = 60,\ \mu_2 = 40$, it can be seen that a = 80, b = 52.9150262213,
a + b =132.9150262213 = c (say), a - b = 27.0849737787 = d (say) (49)
the sub matrix Q^v gets the replacement by $\begin{bmatrix} -c & c & 0 \\ 0 & -d & d \end{bmatrix}$. Replacing this for Q^v in Q'''' the acyclic infinitesimal generator obtained for treatment H_1 is seen as below.

$$Q^{vi} = \begin{bmatrix} States & ED & OPT & ICU & HDW & W & D \\ ED & -60 & 60 & 0 & 0 & 0 & 0 \\ OPT & 0 & -60 & 60 & 0 & 0 & 0 \\ ICU & 0 & 0 & -c & c & 0 & 0 \\ HDW & 0 & 0 & 0 & -d & d & 0 \\ W & 0 & 0 & 0 & 0 & -60 & 60 \\ D & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \quad (50)$$

The random hospitalization times H_2 and H_3 are assumed to have Erlang distributions E(3, 60) and E(2, 60) respectively. Assuming the treatment patterns are same for the two types (i) and (ii), it may be noted that the simulated hospitalization times for treatments H_1, H_2 and H_3 are respectively

H_1 = - $(\frac{1}{60}) \ln \prod_{i=1}^{3} u_i$ - $(\frac{1}{c}) \ln u_5$ - $(\frac{1}{d})u_6$; H_2= - $(\frac{1}{60}) \ln \prod_{i=1}^{3} u_i$ and H_3 = - $(\frac{1}{60}) \ln \prod_{i=1}^{2} u_i$. (51)

The random values u_i appearing on the right side of H_j for j= 1, 2 are to be generated by different LCGs for various values of i. It may be noted that 8 random variables are considered for hospitalization treatment times, namely, 5 random variables with exponential distribution for H_1 and 3 random variables with exponential distributions for H_2.

(vi) Generating Random Values Using LCG

The total number of uniform random values for the two types (i) and (ii) of the Special case (2) are 26, namely, 18 for the time to hospitalization and 8 for hospital treatment times. These 26 uniform random u_i for i=1 to 26 values are generated by linear congruential generators Z_{n+1}= (a$Z_n + c$)mod 16 with seed value Z_0 whose short form representation is given by LCG (a, c, 16, Z_0) for different values of a, c and Z_0. This generates all the sixteen remainder values of division by 16 in random manner so that sixteen uniform random values u = $\frac{z}{16}$ given by {0.0625, 0.375, 0.9375, 0.75, 0.8125, 0.125, 0.6875, 0.5, 0.5625, 0.875, 0.4375, 0.25, 0.3125, 0.625, 0.1875, 0} are obtained in some order. It may be noted that for uniform distribution it is known that E(U) =.5 and Variance =1/12=.08333. They are comparable with average simulated value 0.46875 and its variance 0.083 of the data. The value u = 0 in the above gives extreme value of the simulated random value since natural logarithm of u, namely, ln (u) is required for simulation. When u = 0 is deleted the average becomes .5 = E(U).

The LCGs used for Special case (2) are listed here.

- For simulation of the life time of the organ A, LCG (5, 1, 16, 1), LCG (9, 1, 16, 2) and LCG (13, 1, 16, 3) are used.
- For organ B the following LCGs used are as follows. Erlang with phase 5 and parameter 2.5 life part of the organ B, LCG(1, 3,16, 4), LCG(5, 3,16, 5), LCG(9, 3,16, 6), LCG(13, 3,16, 7) and LCG(1, 5,16, 8) are used; for the Coxian life part with parameter 20 of exponential time of the organ B, LCG(5, 5,16, 9) is used; LCG (9, 5, 16, 10) is used for the probability p_1 = 0.5 to decide the occurrence of the second exponential treatment time and LCG(13,5,16,11) is used for the second coxian exponential time with parameter 30.
- For the type (i) of the prophylactic treatment, six LCGs are used, namely, LCG(1,7,16,12) for the parameter α =0.5 of the first exponential time, LCG(5,7,16,13), LCG(9,7,16,14) , LCG(13,7,16,15) and LCG(1,9,16,1) for the probability p = 0.2, 0.4, 0.6, 0.8 and LCG(5,9,16,2) for the parameter β = 1 of the second exponential time.
- For the type (ii) of the prophylactic treatment, one LCG is used, namely, LCG(9,9,16,3) for the parameter α = 1 of the first exponential time. As type (ii) differs from type (i) in that part only, other simulated values of p and β of type (i) are used.
- For the first and second exponential times of hospitalization time of H_1, LCG(13,9,16,4) and LCG(1,11,16, 5) are used; for the acyclic first and second parts (exponentials) LCG(5,11,16,6) and LCG(9,11,16,7) are used and for the last exponential time LCG(13,11,16,8) is used.
- For the Erlang phase 3 hospitalization time of H_2, LCG(1,13,16,9), LCG(5,13,16,10), and LCG(9,13,16,11) are used.

All the 26 LCGs' used above namely, the LCG (a, c, m, Z_0) for a = 1, 5, 9, 13; c= 1, 3, 5, 7, 9, 11, 13, 15; m =16; Z_0= 1 to 15 have full period of length 16. The values of a, c mentioned here with Z_0= 1 to 15 and m = 16 satisfy the Hull and Dobell theorem [14] which guarantees the LCGs to have full period.

(vii) Results for Special case (2):

The following table 5 gives the failure times of the organ A in fifth column. Exponential random times are simulated using inverse method described earlier. The Organ A failure time is simulated using (40) and (41). It may be noted that the second exponential simulated value in column 4 is added to the first exponential simulated value in column 2 when u value in column 3 is u ≤ p' = 0.755791591 presented in **red** color.

Table 5: Life Time of Organ A

Organ A	a + b= 1.228458929	U for p'= 0.755791591	a-b= 0.3215410713	Life time of organ A
Simulation 1	2.256964931	0.125	5.206104548	7.463069479
Simulation 2	0.798422503	0.1875	2.1557034	2.954125903
Simulation 3	0.052536165	0.75	1.789395496	1.841931662
Simulation 4	0.23418127	0.8125	3.050401148	0.23418127
Simulation 5	0.169024263	0.375	0.20071626	0.369740522
Simulation 6	1.692723698	0.4375	4.311406799	6.004130498
Simulation 7	0.30501097	0.0625	3.617425311	3.922436281
Simulation 8	0.564241233	0.625	6.467110199	7.031351432
Simulation 9	0.468362541	0.6875	1.165305097	1.633667638
Simulation 10	0.108698296	0.25	8.622813599	8.731511895

Simulation 11	0.672939529	0.3125	0.415285649	1.088225179
Simulation 12	1.128482466	0.875	2.570989049	1.128482466
Simulation 13	0.94683736	0.9375	0.894697748	0.94683736
Simulation 14	0.382596128	0.5	0.645763118	1.028359246
Simulation 15	1.362663736	0.5625	1.461721911	2.824385647

Failure time of the Organ B is given in Table 6 column 6 using the equations in (42), (43) and (44). Coxian simulated second exponential time in column 5 of table 6 is to be added with the sum of the terms of second and third columns when u value for p_1 is $u \leq 0.5$ which is marked in red color. The maximum of the life time of the organ A (listed in table 5 column 5) and of the life time of the organ B (presented in column 6 table 6) may be seen in column 7 table 6 in **red** color to indicate the maximum of the failure times of organ A and organ B.

Table 6: Life Time of Organ B and Maximum of Life Times of A and B

Organ B	Erlang(5,2.5)	Coxian Exp 1	U for p_1=0.5	Coxian Exp 2	Life time of B	Max(A,B)
Simulation 1	2.020040071	0.028768207	0.625	0.012489782	2.048808278	7.463069479
Simulation 2	0.812358219	0.103972077	0.9375	0.046209812	0.916330296	2.954125903
Simulation 3	1.830256879	0.003226926	0.75	0.019178805	1.833483805	1.841931662
Simulation 4	1.075070034	0.05815754	0.0625	0.015666788	1.148894362	1.148894362
Simulation 5	1.996463057	0.00667657	0.875	0.027555952	2.003139626	2.003139626
Simulation 6	3.467994704	0.018734672	0.1875	0.038771694	3.52550107	6.004130498
Simulation 7	2.206900295	0.014384104	0.3125	0.032694308	2.253978707	3.922436281
Simulation 8	0.516491341	0.138629436	0.125	0.055799214	0.710919991	7.031351432
Simulation 9	2.180444374	0.023500181	0.4375	0.009589402	2.213533958	2.213533958
Simulation 10	1.857854028	0.041333929	0.25	0.092419624	1.991607581	8.731511895
Simulation 11	2.018258331	0.034657359	0.5625	0.069314718	2.05291569	2.05291569
Simulation 12	2.798404131	0.010381968	0.375	0.002151284	2.810937383	2.810937383
Simulation 13	0.928339108	0.049041463	0.6875	0.023104906	0.97738057	0.97738057
Simulation 14	0.99922169	0.083698822	0.5	0.006921312	1.089841824	1.089841824
Simulation 15	2.671022638	0.069314718	0.8125	0.004451046	2.740337356	2.824385647

Time to Prophylactic treatment for the type (i) when $\alpha = 0.5 \neq \beta = 1$ using (45) and (46) for Coxian exponential times 1 and 2 are presented in columns 2 and 7 of table 7. The column 7 of table 7 is added with column 2 when u values in the columns 3 to 6 are not greater than p = 0.2, 0.4, 0.6, 0.8 by **purple color**.

Table 7: Simulated Random Values for Components of Time to Prophylactic Treatment for Type (i)

$\alpha = 0.5, \beta = 1$	Cox 1 (Para 0.5)	U for p =0.2	U for p=0.4	U for p=0.6	U for p=0.8	Cox 2 (Para 1)
Simulation 1	0.575364145	0.8125	0.875	0.9375	0.0625	2.079441542
Simulation 2	3.347952867	0.5	0.3125	0.625	0.625	1.673976434
Simulation 3	0.940007258	0.9375	0.25	0.5625	0.1875	0.693147181
Simulation 4	5.545177444	0.125	0.6875	0.75	0.75	2.772588722
Simulation 5	1.386294361	0.0625	0.625	0.1875	0.3125	0.133531393
Simulation 6	0.129077042	0.75	0.0625	0.875	0.875	0.064538521
Simulation 7	1.961658506	0.1875	0.4375	0.8125	0.4375	1.386294361
Simulation 8	0.41527873	0.375	0.375	0.4375	0.5625	0.207639365
Simulation 9	2.772588722	0.3125	0.8125	0.125	0.125	0.470003629
Simulation 10	0.749386899	0.4375	0.75	0.0625	0.6875	0.374693449
Simulation 11	4.158883083	0.625	0.1875	0.25	0.25	0.575364145
Simulation 12	1.15072829	0.5625	0.125	0.6875	0.8125	0.980829253
Simulation 13	1.653357146	0.25	0.5625	0.375	0.375	0.826678573
Simulation 14	0.267062785	0.6875	0.5	0.3125	0.9375	0.287682072
Simulation 15	2.32630162	0.875	0.9375	0.5	0.5	1.16315081

Using table 7, simulated times for prophylactic treatment are presented below in table 8 considering addition where ever second observations are required for type (i). Time to hospitalization for treatment is presented below for $\alpha = 0.5$ and $\beta = 1$ in table 9. The **Red color** indicates the patient is admitted due to failure of organs A and B and **the purple color** indicates he is admitted for prophylactic treatment.

Table 8: Simulated Times for Prophylactic Treatment (PT) for Type (i) for Values of p

α = 0.5, β = 1	PT for p=0.2	PT for p=0.4	PT for p=0.6	PT for p=0.8
Simulation 1	0.575364145	0.575364145	0.575364145	2.654805687
Simulation 2	3.347952867	5.021929301	3.347952867	5.021929301
Simulation 3	0.940007258	1.633154439	0.940007258	0.940007258
Simulation 4	8.317766167	5.545177444	5.545177444	8.317766167
Simulation 5	1.519825754	1.386294361	1.519825754	1.519825754
Simulation 6	0.129077042	0.129077042	0.129077042	0.193615563
Simulation 7	3.347952867	1.961658506	1.961658506	3.347952867
Simulation 8	0.41527873	0.622918094	0.622918094	0.622918094
Simulation 9	2.772588722	2.772588722	3.242592351	3.242592351
Simulation 10	0.749386899	0.749386899	1.124080348	1.124080348
Simulation 11	4.158883083	4.734247228	4.734247228	4.734247228
Simulation 12	1.15072829	2.131557543	1.15072829	1.15072829
Simulation 13	1.653357146	1.653357146	2.48003572	2.48003572
Simulation 14	0.267062785	0.267062785	0.554744858	0.267062785
Simulation 15	2.32630162	2.32630162	3.489452429	3.489452429

Table 9: Time to Hospitalization T for different p values for Type (i)

(α, β) = (0.5, 1)	T for p =0.2	T for p=0.4	T for p=0.6	T for p=0.8
Simulation 1	0.575364145	0.575364145	0.575364145	2.654805687
Simulation 2	2.954125903	2.954125903	2.954125903	2.954125903
Simulation 3	0.940007258	1.633154439	0.940007258	0.940007258
Simulation 4	1.148894362	1.148894362	1.148894362	1.148894362
Simulation 5	1.519825754	1.386294361	1.519825754	1.519825754
Simulation 6	0.129077042	0.129077042	0.129077042	0.193615563
Simulation 7	3.347952867	1.961658506	1.961658506	3.347952867
Simulation 8	0.41527873	0.622918094	0.622918094	0.622918094
Simulation 9	2.213533958	2.213533958	2.213533958	2.213533958
Simulation 10	0.749386899	0.749386899	1.124080348	1.124080348
Simulation 11	2.05291569	2.05291569	2.05291569	2.05291569
Simulation 12	1.15072829	2.131557543	1.15072829	1.15072829
Simulation 13	0.97738057	0.97738057	0.97738057	0.97738057
Simulation 14	0.267062785	0.267062785	0.554744858	0.267062785
Simulation 15	2.32630162	2.32630162	2.824385647	2.824385647

Time to Prophylactic treatment for the type (ii) when α = β = 1 using (47) and (48) for Coxian exponential times 1 and 2 are presented in columns 2 and 7 of table 10. The column 7 is considered for addition when u values in the columns 3 to 6 are not greater than p = 0.2, 0.4, 0.6 and 0.8 by **purple color**.

Table 10: Simulated Values for the Components of Time to Prophylactic Treatment for Type (ii) and u values

α = 1, β = 1	Cox 1 (Para 1)	U for p =0.2	U for p=0.4	U for p=0.6	U for p=0.8	Cox 2 (Para 1)
Simulation 1	1.673976434	0.8125	0.875	0.9375	0.0625	2.079441542
Simulation 2	1.386294361	0.5	0.3125	0.625	0.625	1.673976434
Simulation 3	0.207639365	0.9375	0.25	0.5625	0.1875	0.693147181
Simulation 4	0.133531393	0.125	0.6875	0.75	0.75	2.772588722
Simulation 5	0.826678573	0.0625	0.625	0.1875	0.3125	0.133531393
Simulation 6	0.693147181	0.75	0.0625	0.875	0.875	0.064538521
Simulation 7	2.772588722	0.1875	0.4375	0.8125	0.4375	1.386294361
Simulation 8	2.079441542	0.375	0.375	0.4375	0.5625	0.207639365
Simulation 9	0.374693449	0.3125	0.8125	0.125	0.125	0.470003629
Simulation 10	0.287682072	0.4375	0.75	0.0625	0.6875	0.374693449
Simulation 11	1.16315081	0.625	0.1875	0.25	0.25	0.575364145
Simulation 12	0.980829253	0.5625	0.125	0.6875	0.8125	0.980829253
Simulation 13	0.064538521	0.25	0.5625	0.375	0.375	0.826678573
Simulation 14	0.575364145	0.6875	0.5	0.3125	0.9375	0.287682072
Simulation 15	0.470003629	0.875	0.9375	0.5	0.5	1.16315081

Using table 10, simulated times for prophylactic treatment are presented below in table 11 considering addition where ever second observations are required for type (ii). Time to hospitalization for treatment is presented below for $\alpha = 1 = \beta$ in table 12. The **Red color** indicates the patient is admitted due to the failures of organs A and B. **The purple color** is for prophylactic treatment. The hospital treatment times may be simulated as follows. Since the treatment time H_1 is the sum of Erlang random variable with parameter set (2,60) and three exponential random variables with parameters c, d and 60 where c=132.9150262213 and d =27.0849737787 by equation (49), the simulated H_1 values are presented as follows in table 13. The total treatment time for H_1 is given in column 6 table 13 by adding the columns 2 to 5 in table 13. The treatment times H_2 is generated by LCGs as mentioned in (vi) earlier and presented in column 7 of table 13. The **red** and **purple** colors indicate the treatment times are for the **organs** A and B and for **prophylactic** treatment respectively.

Table 11: Simulated Times for Prophylactic Treatment (PT) for Type (ii) for Values of p

$\alpha = 1, \beta = 1$	PT for p=0.2	PT for p=0.4	PT for p=0.6	PT for p=0.8
Simulation 1	1.673976434	1.673976434	1.673976434	3.753417975
Simulation 2	1.386294361	3.060270795	1.386294361	3.060270795
Simulation 3	0.207639365	0.900786545	0.900786545	0.900786545
Simulation 4	2.906120115	0.133531393	0.133531393	2.906120115
Simulation 5	0.960209966	0.826678573	0.960209966	0.960209966
Simulation 6	0.693147181	0.757685702	0.693147181	0.693147181
Simulation 7	4.158883083	2.772588722	2.772588722	4.158883083
Simulation 8	2.079441542	2.287080906	2.287080906	2.287080906
Simulation 9	0.374693449	0.374693449	0.844697079	0.844697079
Simulation 10	0.287682072	0.287682072	0.662375522	0.662375522
Simulation 11	1.16315081	1.738514955	1.738514955	1.738514955
Simulation 12	0.980829253	1.961658506	0.980829253	0.980829253
Simulation 13	0.064538521	0.064538521	0.891217094	0.891217094
Simulation 14	0.575364145	0.575364145	0.863046217	0.575364145
Simulation 15	0.470003629	0.470003629	1.633154439	1.633154439

Table 12: Simulated Times for Time to Hospitalization T for Type (ii)

$\alpha = 1, \beta = 1$	T for p = 0.2	T for p=0.4	T for p=0.6	T for p=0.8
Simulation 1	1.673976434	1.673976434	1.673976434	3.753417975
Simulation 2	1.386294361	2.954125903	1.386294361	2.954125903
Simulation 3	0.207639365	0.900786545	0.900786545	0.900786545
Simulation 4	1.148894362	0.133531393	0.133531393	1.148894362
Simulation 5	0.960209966	0.826678573	0.960209966	0.960209966
Simulation 6	0.693147181	0.757685702	0.693147181	0.693147181
Simulation 7	3.922436281	2.772588722	2.772588722	3.922436281
Simulation 8	2.079441542	2.287080906	2.287080906	2.287080906
Simulation 9	0.374693449	0.374693449	0.844697079	0.844697079
Simulation 10	0.287682072	0.287682072	0.662375522	0.662375522
Simulation 11	1.16315081	1.738514955	1.738514955	1.738514955
Simulation 12	0.980829253	1.961658506	0.980829253	0.980829253
Simulation 13	0.064538521	0.064538521	0.891217094	0.891217094
Simulation 14	0.575364145	0.575364145	0.863046217	0.575364145
Simulation 15	0.470003629	0.470003629	1.633154439	1.633154439

Table 13: Hospital Treatment Times for Stage Treatments Type H_1,Total of H_1 and H_2

	H1 Erlang(2 ,60)	H1 exp(c)	H1 exp(d)	H1 exp(60)	H1 Total time	H2 Erlang(3,60)
Simulation1	0.042490753	0.007379371	0.030521668	0.011552453	0.091944244	0.023667687
Simulation 2	0.009705547	0.004328812	0.017352929	0.027899607	0.059286895	0.020883452
Simulation 3	0.051004513	0.005214965	0.042944506	0.034657359	0.133821343	0.074109419
Simulation 4	0.074109419	0.012594336	0.025591577	0.019385847	0.131681178	0.023922145
Simulation 5	0.014384104	0.003536121	0.061804617	0.004794701	0.084519543	0.047285454
Simulation 6	0.016003499	0.001562196	0.036213041	0.013777976	0.067556712	0.066232679
Simulation 7	0.035733001	0.002164406	0.102366306	0.016347154	0.156610868	0.062556966
Simulation 8	0.008255357	0.006219602	0.051183153	0.009589402	0.075247515	0.120319231
Simulation 9	0.0309383	0.001004637	0.002382816	0.006244891	0.040570644	0.048435335
Simulation 10	0.035733001	0.020859859	0.07677473	0.007833394	0.141200984	0.039408714
Simulation 11	0.008470414	0.002819045	0.00766622	0.003460656	0.022416335	0.022846503

Simulation 12	0.021141855	0.015644894	0.013833997	0.023104906	0.073725653	0.035389346
Simulation 13	0.069314718	0.008751086	0.004930091	0.001075642	0.084071537	0.067351667
Simulation 14	0.017422796	0.01042993	0.021242928	0.002225523	0.051321177	0.015459746
Simulation 15	0.02161137	0.000485562	0.010621464	0.046209812	0.078928208	0.016609627

The simulated values in table 13 are common for the two types (i) and (ii). They are to be linked to table 9 and table 12 for the types (i) and (ii). For example in table 9 type (i), the patient is admitted for prophylactic treatment for p=0.2 in simulation 1 at time **0.575364145** and he is to be provided treatment H_2 for time **0.023667687** given for simulation 1 column 7 in table 13. Similarly in simulation 4 for p = 0.2 in table 12 the organs A and B are in failed state at time **1.148894362** and his hospital treatment time for $H_1$is to be **0.131681178.** For the fifteen simulations of time to hospitalization T in table 9 for various values of p the corresponding treatment types and times are listed in table 14. **Purple** color indicates the **prophylactic** treatment and **red** color indicates the treatment times of **organs** A and B. The simulated values of table 13 are to be linked to table 12 for type (ii). For example in table 12 simulation 7 for p = 0.2 , the patient is admitted for hospitalization due to the failure of the organs at time **3.922436281** and he is to be provided treatment H_1 for time **0.156610868** which is placed in table 13 simulation 7 column 6. In similar manner all the fifteen simulations of table 12 for various values of p may be linked with corresponding simulated treatment times in table 13. They are presented in table 15 for type (ii).

Table 14: Hospital treatment times H for Type (i)-Unequal rates (α, β) = (0.5, 1)

(α, β) = (0.5, 1)	H time p=0.2	H time p=0.4	H time p=0.6	H time p=0.8
Simulation 1	0.023667687	0.023667687	0.023667687	0.023667687
Simulation 2	0.059286895	0.059286895	0.059286895	0.059286895
Simulation 3	0.074109419	0.074109419	0.074109419	0.074109419
Simulation 4	0.131681178	0.131681178	0.131681178	0.131681178
Simulation 5	0.047285454	0.047285454	0.047285454	0.047285454
Simulation 6	0.066232679	0.066232679	0.066232679	0.066232679
Simulation 7	0.062556966	0.062556966	0.062556966	0.062556966
Simulation 8	0.120319231	0.120319231	0.120319231	0.120319231
Simulation 9	0.040570644	0.040570644	0.040570644	0.040570644
Simulation 10	0.039408714	0.039408714	0.039408714	0.039408714
Simulation 11	0.022416335	0.022416335	0.022416335	0.022416335
Simulation 12	0.035389346	0.035389346	0.035389346	0.035389346
Simulation 13	0.084071537	0.084071537	0.084071537	0.084071537
Simulation 14	0.015459746	0.015459746	0.015459746	0.015459746
Simulation 15	0.016609627	0.016609627	0.078928208	0.078928208

Table 15: Hospital treatment times for Type (ii)-Equal rates (α, β) = (1, 1)

(α, β) = (1, 1)	H time p=0.2	H time p=0.4	H time p=o.6	H time p=0.8
Simulation 1	0.023667687	0.023667687	0.023667687	0.023667687
Simulation 2	0.020883452	0.059286895	0.020883452	0.059286895
Simulation 3	0.074109419	0.074109419	0.074109419	0.074109419
Simulation 4	0.131681178	0.023922145	0.023922145	0.131681178
Simulation 5	0.047285454	0.047285454	0.047285454	0.047285454
Simulation 6	0.066232679	0.066232679	0.066232679	0.066232679
Simulation 7	0.156610868	0.062556966	0.062556966	0.156610868
Simulation 8	0.120319231	0.120319231	0.120319231	0.120319231
Simulation 9	0.048435335	0.048435335	0.048435335	0.048435335
Simulation 10	0.039408714	0.039408714	0.039408714	0.039408714
Simulation 11	0.022846503	0.022846503	0.022846503	0.022846503
Simulation 12	0.035389346	0.035389346	0.035389346	0.035389346
Simulation 13	0.067351667	0.067351667	0.067351667	0.067351667
Simulation 14	0.015459746	0.015459746	0.015459746	0.015459746
Simulation 15	0.016609627	0.016609627	0.016609627	0.016609627

The average values of simulated values of T and H for types (i) and (ii) listed in tables (9), (12), (15) and (16) are presented in table (17) for various values of p which is the probability required for second observation. The following figures 1 and 2 present the graphical representation of table 17. Figures 1 and 2 present the effect of p on the averages of simulated values of T and H for various values of p for the two cases.

Table 17: Averages of T and H for Special case (2) - Type (i) and Type (ii) for values of p

Special case (2)	p = 0.2	p = 0.4	p = 0.6	p = 0.8
Average T; for (0.5, 1)	1.384522392	1.408641728	1.383309362	1.599482185
Average H; for (0.5, 1)	0.055937697	0.055937697	0.060092269	0.060092269
Average T; for (1, 1)	1.065886758	1.18526063	1.228096671	1.596416774
Average H; for (1, 1)	0.05908606	0.048192094	0.045631865	0.06164629

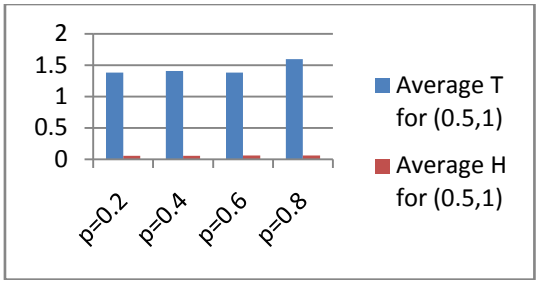

Figure 1: Averages of T and H: α=0.5 & β=1.

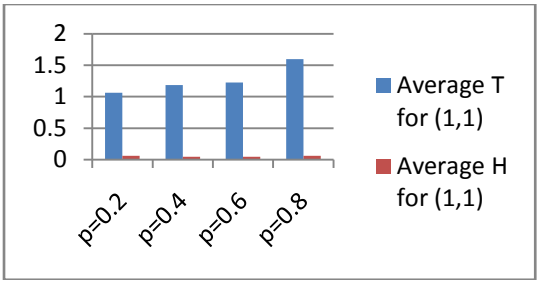

Figure 2: Averages of T and H: α=1 & β=1

In the type (i) and type (ii), the only difference is in the value of the parameter α where in type (i) α = 0.5 and in type (ii) α =1. The effect of the change of α, the parameter of the first exponential observation time, may be seen on comparing figures (1) and (2) for averages. The variations of average of simulated values are comparatively high for p = 0.8 when the second prophylactic observation is taken up in 80% of the cases. Both the averages T and H are more for p = 0.8 compared to p = 0.6. In the last column of table 15, corresponding to simulations 2, 4 and 7, it may be noted that the two organs fail before the completion of second observation time calling for treatment of type H_1. Possibly the second observation may not be required in those cases. This actually increases both the averages of T and H for p = 0.8 which is exhibited in figure 2. In the other figure also variations of E(T) and E(H) can be noted.

CONCLUSION

Diabetic models with two observation times including one for second opinion for prophylactic treatment have been studied with two defective organs exposed to failures. Two types have come up depending on whether the observation holding time rates are equal or not equal. In the model the patient has been sent for hospitalization when both organs have failed or when prophylactic treatment has started. The organ A of the patient has two phase PH life distribution and his organ B has general life time. The time to prophylactic treatment has Coxian 2 distribution. The hospital treatment times for the organs A and B and for prophylactic treatments have distinct distributions H_i for i=1 and 2 respectively. The joint Laplace Stieltjes transform of the joint distribution of time to hospitalization and hospitalization time have been obtained. Individual distributions are also presented. The expected time to hospitalization and the expected hospitalization times are derived. Numerical studies are presented for the two models assuming exponential life time distribution for organ B by fixing and varying parameter values. Simulation study has been taken up in this area considering a set of parameter values of two phase life distribution of the organ A. EC distribution is the closed form approximation for the general life time distribution of the organ B. Different parameter values of Coxian time to prophylactic treatment, Erlang and cyclic phase type distributions for hospitalization times for the two cases of the model are taken up for simulation. Cyclic type treatment in the hospital for H_1 has been identified as acyclic type using equality of distributions so that simulation can be performed easily. All the results are tabulated and graphical presentation are provided. Since not much of simulation analysis are available in literature for diabetic models, this study opens up a real life like study in this area. Various other distributions if used for simulation studies may also produce more interesting results.

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