# Executive summary of the research work done by TD XAVIER for the period of June 2015 to May 2017

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**Title of research project:**
SEMI–MARKOV MODEL FOR TREATMENT STRATEGY

In most of the medical investigation, state of a patients is decided in the light of a series of medical tests which are subjected to test errors. A modified Markov Decision Process(MDP) called Partially Observed MDP(POMDP) have been developed to deal the data with imperfect information([1],[2]) In these models it is assumed that uncertainty exist, in patient's transition and the state he truly occupies. Therefore the objective is to find an optimal policy based on the observation of the patient and the previous decision rule applied.As reported in [3] a Markov decision approach has been employed for a multi-category patients scheduling decision in computed tomography (CT)and investigated associated tradeoffs from the economic and operational perceptive.

In MDP models the treatment decision are taken at each of a sequence of unit time intervals or fixed epochs and the sojourn time in states has no effect on rewards or incurring costs for patient. However in health-care and other application, decision are taken over continuous time intervals such as varying treatment can be administered. The sojourn time in states may depend on the duration of his/her current health status. The MDP models might not be suitable to model such disease progression instead Semi-Markov Decision Process(SMDP)models are more appropriate. In SMDP models allow patients' state transition to occur in continuous time and allow to assume any probability distribution for sojourn time in a state.

Markov and Semi-Markov process are appropriate model for a multi-state diseases in which the data arises as transition-times and states. Historically it has been difficult to adopt realistic models for biomedical applications since the likelihood turns out to be real complicated. With the progress on numerical method for estimation, problems of tractability can be overcome [6] introduced a k-state Markov model for continuous time processes. Similar models have been applied to AIDS([7]), heart transplantation ([8]), diabetes ([9],[10]), infectious diseases and cancer screening and so on. These models have been further extended to include fixed time and time-varying covariate information. (see for eg: [11],[12]). Methods for estimation of transition rates are generally numerically based and have usual maximum likelihood sampling schemes such as Metroplois-Hasting method([13],[14]), or have used

population-based approaches akin to weighted least squares. These approaches have all concentrated on continuous-time Markov processes usually due to unequally spaced observation times.

I consider a complex survival model that lives in a randomly changing environment which affect model parameters. The term 'environment' is used in the generic sense so that it represents any set of conditions that affect the stochastic structure of the model investigated. The concept of 'environment' process , is one form or another, has been used in the literature for various purpose.The use of environmental process to modulate the deterministic and stochastic parameters of Operation Research models can be seen in reliability, inventory and queueing applications. The problem of optimal replacement of a semi-Markov system under semi-Markov environment is studied by [15] (see also [16],[17]) discuss other applications in inventory and queueing. A comprehensive discussion on Markov modulated queueing system can be found in [19]. These collected observations, *Analysis of Categorical data in medicine* has been presented at **National Seminar on Research Methodlogy & Statistical Analysis Using IBM SPSS** 20– 21 November 2015; St. Thomas College (Autonomous), Thrissur, 680 001, Kerala.

Although the literature cited above illustrate the use of random environment in reliability, inventory and queueing model, the concept is of paramount interest in Survival analysis. It is generally assumed that a patient stays in a given fixed environment. The probability law of his ageing and death process there remain intact throughout his useful life. The life duration and corresponding hazard rate is taken to be the one obtained through statistical life testing procedures that are believed to be under ideal conditions.There has been growing interest in the recent years in lifetime models under random environment.

This is necessitated by the fact that the subject/patient often lives in varying environments during which they are subjected to varying environment conditions with significant effects on performance/health status. During a treatment period whole environment of the patient may change due to occurrence of other contagious diseases, hypertension, high blood pressure, cardiac problems, severe climatic/seasonal changes or adopting entirely new treatment strategy on medical team's advice. When environment changes, the state of patient also changes. The deterioration and failure process therefore depends on the environment. This makes it crucial to identify an optimal treatment strategy especially for a range of multi-state disease process.

The general form of the Semi-Markov model that represents the foregoing situation I proposed, may be stated as follows:

1. The patient is in a semi-Markov environment$\{(J_n, L_n), n \geq 0\}$ on a set K of

countable environment states, where $J_n$is the state of the environment immediately after its nth transition epoch $T_n$, and $0 = T_0 < T_1 < T_2 < \cdots$. $L_n$ is the time duration of the patient in the state $J_n$. Let the state's kernel be

$$G_{kk}(t) = Pr(T_{n-1} - T_n \leq t, J_{n+1} = k'/J_n = k)$$

and let $\psi_{kk'} = G_{kk'}(\infty)$ and $G_k(t) = \sum_{k' \in K} G_{kk'}(t)$.

2. During an environment state k, the patient goes through several states of disease according to a semi-Markov process with a kernel $\{P_{ij}^k(t), i, j \in S\}$ and a set $S = \{0, 1, 2, ...\}$ of countable states, where the state 0 represents disease-free state, and states 1, 2, . . . represent the different adverse disease states of the patient and the bigger the value, the more serious is the condition.
Let $P_{ij}^k = P_{ij}^k(\infty), T_{ij}^k(t) = P_{ij}^k(t)/P_{ij}^k$ and $T_i^k(t) = \sum_{j \in S} P_{ij}^k(t)$

3. Suppose that the patient is in environment k, then one of the following two actions can be chosen if his state transfers to i :
(a) Continue the present treatment strategy (denoted by C) with a cost rate $h^k(i)$;
(b)Initiating a rejuvenating treatment strategy (denoted by R)like chemotherapy, radiation, surgery, organ transplant and/or admission in ICU etc., with a cost rate $c^k(i)$, and the time of action R is assumed to be a random variable with probability distribution function $F^k(t)$, and the state after rejuvenation will be 0, the disease-free state.

4. When the environment state changes from $k$ to $k'$ if action C or R is chosen then the patient's state will change immediately according to a probability $q_{ij}^k$ and an instantaneous cost $R^k(i, C)$occurs; while if action R is chosen then within no time it completed and an instantaneous cost $R^k(i, R)$ occurs.

5. The objective is to minimize the expected discounted total costs with discount factor $\alpha > 0$.

The above treatment strategy can be modeled by a semi-Markov decision process (SMDP) in a semi- Markov environment, presented and studied by Hu (1997), as follows.
During the environment state k, i.e., $J_n = k$ for some $n \geq 0$, it can be modeled by the following SMDP:

$$SMDP_k := \{S, A, p^k(j|i, a), T^k(.|i, a, j), r^k(i, a, j, u)\}$$

where $S$ is the state space and A =$\{$C, R$\}$is the action set. The transition probability $p^k$, the distribution function $T^k$ of the transition time, and the one step cost function

$r^k$ are given, respectively by

$$P^k(j|i,C) = P^k_{ij}\ , \qquad P^k(j|i,R) = \delta_{i0}$$
$$T^k(t|i,C,j) = T^k_{ij}(t)\ , \quad T^k(t|i,R,0) = F^k(t)$$
$$r^k(i,C,j,u) = h^k(i)\int_0^u e^{-\alpha t}dt = h^k(i)\alpha^{-1}(1-e^{-\alpha t})$$
$$r^k(i,R,j,u) = C^k(i)\int_0^u e^{-\alpha t}dt = C^k(i)\alpha^{-1}(1-e^{-\alpha t})$$
$$\delta_{i0} = \begin{cases} 1 & \text{if} \quad j=0, \\ 0 & \text{otherwise} \end{cases}$$

This result *Stochastic Models for Medical Treatments* has been presented at **National Seminar on Recent Advances Of Statistics In Medical Field** 23–24 November 2015; Government Victoria College Palakkad, Kerala.

I proposed an optimal treatment strategy for subject/patient lives in varying random environments, imparting significant effects on performance/health status; using semi-markov decision process. The environment is modelled as a Semi-Markov Process and in each environment state, the patient goes through several states of disease according to a Semi-Markov Process.

The Optimal treatment strategy model with discrete time Markov decision processes (DTMDP), has been considered for a optimality equation with n-horizon state space $\Omega$

$$V^*_n(x) = min\{V^*_n(x,C), V^*_n(x,R)\},\ \text{where}\ \ x=(k,s,i)\in\Omega$$

where $V^*_n(x)$ is the optimal value from state x for n horizons problem, while

$$V^*_n(x,C) = r(x,C) + \sum_{k\in K}\beta(x,C,k')\sum_{j\in S} q^k_{ij}\ V^*_{n-1}(k',0,j)$$
$$+\sum_{j\in S} P^k_{ij}\int_0^\infty e^{-\alpha t}V^*_{n-1}(k,s+t,j)\ dT^k_{ij}(t)$$

$$V^*_n(x,R) = r(x,R) + \sum_{k\in K}\beta(x,R,k')\ V^*_{n-1}(k',0,0)$$
$$+\int_0^\infty e^{-\alpha t}V^*_{n-1}(k,s+t,0)\ dF^k(t)$$

are the values from state $x$ in n horizons if action C or R is used respectively in the first horizon and then an optimal policy in the remaining horizons. The initial conditions are

$$V^*_0(x,C) = V^*_0(x,C) = 0$$

$$Let \quad v_n(x) = V_n^*(x, C) - V_n^*(x, R), \quad v(x) = V^*(x, C) - V^*(x, R)\}$$
$$x = (k, s, i) \in \Omega$$

then it follows from the standard theory of DTMDP that

$$\lim_{n\to\infty} V_n^*(x, a) = V^*(x, a), \quad a = C, R$$
$$\lim_{n\to\infty} v_n(x) = v(x)$$

while the optimal policies can be depicted as $f_n^*(x) = C \iff v_n(x) < 0, f^*(x) = C \iff v(x) < 0$. So,$(f_N^*, f_{N_1}^*, ..., f_0^*)$ is optimal for N-horizon problem; and $f^*$ is optimal for the infinite horizon discounted criterion. A concept of stochastic order between two distribution functions is needed. For two distribution functions F and G, F is said to be smaller stochastically than G, denoted by $F \preceq G$, if $F(t) \geq G(t)$ for each t

*Stochastic Modeling Of Multi-State Disease Dynamics Under Random Environments* Published in **Stochastic Models in Reliability Engineering, Life Science and Operations Management (SMRLO), 2016 IEEE**, Date Of Issue : 10.1109/SMRLO.2016.69 and presented at the **second international symposium on stochastic models in reliability, engineering, life science and operation management**, 15-18 Feb. 2016, Beer-Sheva, Israel

A special case for a Markov environment was discussed. When the control limits are bounded for each environment state, the countable states of patient was simplified equivalently to a finite one.

The Markov Environment environment be

$$G_{kk'}(t) = \psi_{kk'} G_k(t), \quad G_k(t) = 1 - e^{-\lambda_k t}, t \geq 0, k \; and \; k' \; \in \; K.$$

In this case, it will be shown that the variable s in state x = (k, s, i ) can be deleted. Let

$$t_F^k = \int_0^\infty [1 - e^{-(\lambda_k + \alpha)t}] dF^k(t)$$
$$t_{ij}^k = \int_0^\infty [1 - e^{-(\lambda_k + \alpha)t}] dT_{ij}^k(t)]$$
$$t_t^k = \sum_{j\in S} P_{ij}^k t_{ij}^k, \quad \alpha_F^k = 1 - t_F^k, \quad \alpha_{ij}^k = 1 - t_{ij}^k, \quad \alpha_i^k = 1 - t_i^k$$

Then $F^k(t)$ and$T_{ij}^k(t)$ calculated and

$$\begin{aligned} r(x,C) &= r'(k,i,C)e^{-(\lambda_k s)} = \frac{t_i^k}{\lambda_k+\alpha}[h^k(i)+\lambda_k R^k(i,C)]e^{-(\lambda_k s)} \\ r(x,R) &= r'(k,i,R)e^{-(\lambda_k s)} = \frac{t_F^k}{\lambda_k+\alpha}[c^k(i)+\lambda_k R^k(i,R)]e^{-(\lambda_k s)} \qquad (0.1) \\ \beta(x,C,k') &= \frac{\lambda_k t_i^k}{\lambda_k+\alpha}\psi_{kk'}e^{-\lambda_k s} \\ \beta(x,R,k') &= \frac{\lambda_k t_F^k}{\lambda_k+\alpha}\psi_{kk'}e^{-\lambda_k s} \end{aligned}$$

Based on Eqn.( 0.1), it can be shown that $e^{\lambda_k s}V^*(k,s,i)$ and therefore $e^{\lambda_k s}V^*(k,s,i,C)$, $e^{\lambda_k s}V^*(k,s,i,R)$ are independent of $s$ and thus

$$\begin{aligned} e^{\lambda_k s}V^*(k,s,i) &= V^*(k,0,i) \\ e^{\lambda_k s}V^*(k,s,i,C) &= V^*(k,0,i,C) \\ e^{\lambda_k s}V^*(k,s,i,R) &= V^*(k,0,i,R) \end{aligned}$$

We denote by

$$V^*(k,i) := V^*(k,0,i), \quad V^*(k,i,C) := V^*(k,0,i,C), \quad V^*(k,i,R) := V^*(k,0,i,R)$$

and

$$v(k,i) = V^*(k,i,C) - V^*(k,i,R)$$

Then $V^*(k,i)$ is the minimal nonnegative solution of the following optimality equation

$$V^*(k,i) = min\{V^*(k,i,C), \quad V^*(k,i,R)\}$$

The Markov decision processes are simple yet powerful models for sequential decision problems. In the proposed model of optimum treatment strategy,I assume that there is a state space; at each time the system occupies a certain state, and the decision maker, or controller, has a set of feasible actions for that state that can be applied. Semi-Markov stochastic model is a useful tool for predicting the evolution of infection of infectious diseases and the probability of an infected patients survival. In SMDP models allow patients' state transition to occur in continuous time and allow to assume any probability distribution for sojourn time in a state.

The proposed an optimal treatment strategy for subject/patient lives in varying random environments, imparting significant effects on performance/health status; using semi-markov decision process. The environment is modelled as a Semi-Markov Process and in each environment state, the patient goes through several states of

disease according to a Semi-Markov Process. A special case for a Markov environment was discussed. When the control limits are bounded for each environment state, the countable states of patient was simplified equivalently to a finite one.

Also developed a comprehensive **C++ program** to determine optimal treatment strategy of the proposed model. With the help of the program, a numerical example was illustrated to prove the correctness and validity of the analysis.

**Research papers presented /published/**
**Accepted for publication/ Communicated for publication:**

1. *Analysis of Categorical data in medicine* presented at **National Seminar on Research Methodology & Statistical Analysis Using IBM SPSS** 20– 21 November 2015; St. Thomas College (Autonomous), Thrissur, 680 001, Kerala.

2. *Stochastic Models for Medical Treatments* presented at **National Seminar on Recent Advances Of Statistics In Medical Field** 23–24 November 2015; Government Victoria College Palakkad, Kerala.

3. *Stochastic Modeling Of Multi-State Disease Dynamics Under Random Environments* published in **Stochastic Models in Reliability Engineering, Life Science and Operations Management (SMRLO), 2016 IEEE**, Date Of Issue : 10.1109/SMRLO.2016.69

4. Presented at the **second international symposium on stochastic models in reliability, engineering, life science and operation management**, 15-18 Feb. 2016, Beer-Sheva, Israel

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**Research Scope**

Further studies should include the properties of monotone of optimal policies, rejuvenating treatments with varying success rate and so on. It is likely that the semi-Markov models will be more and more applied to epidemiology and this will be facilitated by the development of more flexible estimation methods, increasing power of computing and the availability of data from large cohort studies. A model by means of the backward recurrence time process it is possible to assess different transition probabilities as a function of the duration inside the states. Moreover, it is possible to attach a reward structure to the process that allows the possibility of doing a cost analysis that considers, for example, the cost of antiretroviral treatment and/or other social costs related to the dynamic evolution of the HIV infection. These features will be the object of future research.