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STOCHASTIC MODEL APPLIED IN CHRONIC KIDNEY DISEASE

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ABSTRACT

Multistate Markov models are well-established methods for estimating rates of transition between stages of chronic diseases. The objective of this study is to propose a stochastic model that describes the progression process of chronic kidney disease; CKD, estimate the mean time spent in each stage of disease stages that precedes developing end-stage renal failure and to estimate the life expectancy of a CKD patient. Continuous time Markov Chain is appropriate to model CKD. Explicit expressions of transition probability functions are derived by solving system of forward Kolmogorov differential equations. Besides, the mean sojourn time, the state probability distribution, life expectancy of a CKD patient and expected number of patients in each state of the system are presented in the study. A numerical example is provided. Finally, concluding remarks and discussion are presented. Keywords-Chronic Kidney Disease, Continuous-Time Markov Chain , Kolmogorov Differential Equations , Expected Time to Absorption, Stochastic Processes.

1. INTRODUCTION

Multistate Markov models are well-established methods for estimating rates of transition between stages of chronic diseases. The objective of this dissertation is to study the stochastic model applied in the progression process of chronic kidney disease (CKD) and to estimate the mean time spent in each stage of disease stages that precedes developing end-stage renal failure and to estimate the life expectancy of a CKD patient. Continuous-time Markov Chain is appropriate to model CKD. Explicit expressions of transition probability functions are derived by solving system of forward Kolmogorov differential equations. Besides, the mean sojourn time, the state probability distribution, life expectancy of a CKD patient and expected number of patients in each state of the system are presented in the study.

2. CHRONIC KIDNEY DISEASE:

Chronic kidney disease, or CKD, is a condition that affects the function of the kidneys, and that may progress over time to kidney failure. When the kidneys fail, dialysis or a kidney transplant is needed to support life and people can live for decades with dialysis and/or kidney transplants. Many diseases can cause CKD. Some of them are

i. Diabetes, High blood pressure, hypertension and blood blockage,
ii. Over use of painkiller and allergic reaction to antibiotic,
iii. Sometimes trauma / accident. Other disease like systemic lupus erythematosus tissue disease. Sickle cell anaemia and hepatitisc.
iv. HIV / AIDS and Congestive heart failure.

Some terms explained:

- **Chronic** means ongoing (persistent or long-term). It does not mean 'severe' as some people think. You can have a mild chronic disease. Many people have mild CKD.

- **Renal** means 'relating to the kidney'.
- **Chronic renal failure** is a term that is sometimes used but means much the same as chronic kidney disease. Chronic kidney disease (CKD) is a better term as 'failure' implies that the kidneys have totally 'packed in'.

3. STOCHASTIC MODEL APPLIED IN CHRONIC KIDNEY DISEASE:

A multistate model is a stochastic model based on Markov process which is a solid method for estimating rates of transition between stages of chronic kidney diseases. Covariates like age, sex, occupation, previous residence, other chronic diseases, effect of a given intervention …etc. can be fitted to the transition rates. The output of the models helps in enhancing the national health policies and forming any preventative strategies of CKD and exploring it in earlier stages where the development of the disease can be revised or prevented. Applications of stochastic processes in medicine and their use in controlling disease-related morbidity and mortality are high. It was used in controlling Cancer-related mortality and for estimating progression of a chronic disease with multistate markov models in stochastic process.

4. PURPOSE AND SIGNIFICANCE OF THE STUDY:

Stochastic models play a significant and vital role in various fields like science, engineering, and medicine, environmental and climatic changes. Multistate Markov models are applied in chronic kidney disease and helped in understanding the mechanism of chronic kidney diseases in terms of explaining relationships between developing and progressing in disease stages and other relevant covariates. The objectives of stochastic modelling of chronic kidney diseases are to assess the cost-effectiveness of a new intervention or new technology and to calculate disease progression and use them in controlling diseases-related mortality. The main goal of this study is to propose a stochastic model that describes the progression process of CKD, to estimate the mean time spent in each stage of the disease stages and to estimate the life expectancy of a CKD patient. One of the important significance of the study is to give strategies for defeating any chronic disease is to detect it early side by side with the national planning for insuring sufficient treatment of patients.

Definition 1

Random Variables: A random variable *X* with values in the set *E* is a function which assigns a value X(m) in *E* to each outcome m in Ω.

Definition 1

Stochastic process is just a collection (usually infinite) of random variables, denoted X_t or X(t); where parameter t often represents time. State space of a stochastic process consists of all realizations x of X_t, i.e. $X_t = x$ says the random process is in state x at time t.

5. MODELING

Modelling is the process of producing a model; a model is a representation of the construction and working of some system of interest. A model is similar to but simpler than the system it represents. One purpose of a model is to enable the analyst to predict the effect of changes to the system. On the one hand, a model should be a close approximation to the real system and incorporate most of its salient features. A good model is a judicious trade off between realism and simplicity. Generally, a model intended for a simulation study is a mathematical model developed with the help of simulation software. Mathematical model classifications include, they are

i. Deterministic (input and output variables are fixed values),
ii. Stochastic (at least one of the input or output variables is probabilistic),

iii. Static (time is not taken into account),
iv. Dynamic (time-varying interactions among variables are taken into account).

STOCHASTIC MODELING

Stochastic modeling concerns the use of probability to model real-world situations in which un- certainty is present. Since uncertainty is pervasive, this means that the tools of this course can potentially prove useful in almost all facets of one's professional life (and sometimes even in one's personal life):

i. Gambling
ii. Personal Finances
iii. Disease Treatment Options
iv. Economic Forecasting
v. Product Demand
vi. Call Centre Provisioning
vii. Product Reliability and Warranty Analysis, etc.

The use of a stochastic model does not imply that the modeller fundamentally believes that the system under consideration behaves "randomly".

THE BASIC STEPS OF STOCHASTIC MODELING

The essential steps in building stochastic models are:

i) Identifying the sample space;
ii) Assigning probabilities to the elements of the sample space;
iii) Identifying the events of interest;
iv) Computing the desired probabilities.

MARKOV PROCESSES

Markov analysis considers a set of states or events and analyzes the tendency of one event to be followed by another. There are two different methods for Markov analysis: Markov Chain and Markov Process. The Markov Chain assumes discrete states and a discrete time parameter; with the Markov Process, states are continuous. Markov modelling offers several advantages.

TYPES OF STOCHASTIC MODELS

The most common structures used in health care simulation modelling are

1) Markov modelling
2) Monte carlo simulation
3) Discrete-event simulation:

STAGES OF MULTI STATE MORKOV MODEL IN CKD

We discussed stages of multi state markov model in CKD, CKD progression model, glomerular filtration rate, transition probability matrix for multi-state markov model and derivation of Kolmogorov's differential equations.

MULTI STATE MORKOV MODEL:

Stochastic processes modeling approach is utilized to develop a model of the progression of CKD. The model allows for moving progressively from milder to more severe disease stages and vice versa. At the same time it allows moving from any of the disease stage to an absorbing stage. The progression of CKD which is defined, according to the Kidney Disease Outcomes Quality Initiative (KDOQI) classification for CKD, in terms of staged progressive irreversible deterioration of kidney function and from the definition of CKD as a staged progressive irreversible disease that the state space of the progression process is discrete, but the process is continuous with respect to time.

CONTINUOUS-TIME MARKOV CHAIN:

Continuous-time Markov chain, "CTMC" is appropriate to model CKD since the patient condition deterioration is continuous in time. A CTMC is said to be homogenous in time if the probability of going from one state to another is independent of the time on which the transition occurs. Homogeneity in time holds true for the process of CKD. Hence, one can assume that the finite homogenous continuous-time Markov chain may be an appropriate model of CKD.

CKD PROGRESSION MODEL:

Depending on the general illustrative model of CKD progression presented, then the transition rate matrix of the CKD Progression Model is as follows:

$$V = \begin{pmatrix} -\lambda_{12}-\lambda_{15} & \lambda_{12} & 0 & 0 & \lambda_{15} \\ 0 & -\lambda_{23}-\lambda_{25} & \lambda_{23} & 0 & \lambda_{25} \\ 0 & 0 & -\lambda_{34}-\lambda_{35} & \lambda_{34} & \lambda_{35} \\ 0 & 0 & 0 & -\lambda_{45} & \lambda_{45} \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

V is a 5×5 matrix, its elements λij are the instantaneous rates of transition from one state to another. It can be noticed that λij is independent of time because the CKD process is homogenous with respect to time. Sometimes matrix V is called the generator matrix or the infinitesimal matrix. The elements of V are the model parameters which are population-specific and should be estimated when data is available using the appropriate method of estimation. The initial state probability is given by

$$\pi_{0i}\ (t=0) = p\ (X_0 = S_i)$$

This can be written as a vector:

$$\Pi\ (0) = (\pi_{01}\ \pi_{02}\ \pi_{03}\ \ \pi_{04}\ 0)$$

This probability defines the probability of being in one of the states of the process at the beginning of the study.

Using the analogy of CKD progression process, the initial vector indicates the initial condition of the CKD patients defined as the proportions of patients in each state of the process at the beginning of the study. Entries of initial vector should be non negative and their sum should equal to one.

DISCUSSION:

Chronic diseases represent a major concern to health policy makers, especially in developing countries. When a disease is detected at an early stage, it may be more amenable to treatment. Knowledge about the progression of chronic diseases is important because it may help health policy makers to evaluate expected burden of disease in future and to evaluate cost effectiveness of competing interventions. The Markov chain approach is often used for analyzing progression of diseases by describing the time evolution of an individual in the multistate model.

CTMC is more appropriate than discrete-time Markov chain for studying patient progression through successive stages of a chronic disease where transitions may be slow, therefore have small probabilities and cannot be described accurately in discrete time units. Kolmogorov's differential equation plays a key role in defining uniquely CTMC. The solution of Kolmogorov's differential equation depends on the form of the generator matrix of the model. For simpler forms of the generator matrix, the analytical solution of Kolmogorov's forward system of differential equation is achievable. The resulting Mathematical relations between the probability of transition and rate of transition can be used to formulate a likelihood function of transitions, then estimating the elements of the generator function which is the model parameters. One should take into consideration some important precautions when estimating the model parameters.

CONCLUSION

Thus preliminary concepts of continuous time Marko chain (CTMC) in stochastic processes that were continuous in both time and space, and the concept of Chapman-Kolmogorov equations, Sojourn time in a state are discussed. Thus, we discussed stages of multi state markov model in CKD, CKD progression model, glomerular filtration rate, transition probability matrix for multi-state markov model and derivation of Kolmogorov's differential equations. The main objective of this study is to present a solution of the system of forward Kolmogorov equation of CKD process. Then presenting forms of some extractor functions that may be of great importance for the clinicians and health policy makers.

Thus, from the CKD model we calculated an analytic expression for each element of P (τ, t) by solving the forward Kolmogorov differential equations in using Transition Probability Functions and we discussed about the State Probability Distribution, Mean sojourn time, life expectancy of a CKD Patient and Numerical Example.

We have presented an explicit form of the transition probability matrix of CKD process with 5 states, the first four of them represent the 2nd, 3rd, 4th , and ESRD of CKD according to the KDOQI classification, and the last state is death. Besides, we presented also explicit forms for some important extractor functions which depend primarily on the transition instantaneous rates.

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