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Bivariate Stochastic Simultaneous Differential Equation Model for Heart Failure

Tirupathi Rao Padi [a], P. T. Sakkeel [a*] and V. Kanimozhi [a]

[a] *Department of Statistics, Pondicherry University, Puducherry-605014, India.*

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Abstract

Heart failure is one of the significant public health burdens in the world. According to WHO, 2 million people suffer heart failure worldwide. In this study, we propose a bivariate stochastic model for heart failure disease progression and recovery process, which helps to understand the underlying mechanisms of the recovery process and suggests strategies to improve the performance of the public health system. Sensitivity analysis is carried out to understand the model behavior.

Keywords: Heart failure; stochastic modelling; bivariate poisson process; differential equations.

2010 Mathematics Subject Classification: 60H10; 60J27; 60J28.

1 Introduction

Heart failure is a chronic, progressive condition in which the heart muscle is unable to pump enough blood to meet the body's needs for blood and oxygen. The heart can't keep up with its workload. Heart failure is a significant public health burden, with an estimated 2 million people suffering from heart failure worldwide. Such patients are at high risk of death without advanced therapies like ventricular assist devices, heart transplantation, etc [1, 2, 3, 4]. So, the modeling the heart failure remains an important field of research that helps to understand the underlying mechanisms of the disease progression and recovery process [5].

Compartmental models are the commonly used tool in disease progression. There are two approaches: deterministic and stochastic models. Deterministic models are appropriate for a large population,

Corresponding author: E-mail: sakkeelptnkt@gmail.com;

and stochastic models are suitable for a small population which captures the randomness associated with the system. The basic compartmental models for disease progression were introduced by W.O. Kermack and A.G. McKendrick in 1927 [6, 7, 8]. The statistical perspective of the Kermack - McKendrick model was contributed by J. Bartlett in 1949 [9, 7]. The recent developments in the field of stochastic disease progression models are contributed by Linda J. S. Allen [10, 11, 12, 13, 14]. This paper aims to model how the disease progression could evolve in time under various assumptions. In our model, time t is the independent variable, and the number of individuals in a state is a differentiable function of time. The rates of transition between states are determined stochastically as derivatives of the sizes of the states with respect to time. As a result, our model is formulated as differential equations, and we deduce the probability generating function as well as different statistical measures. The model is derived in Section 2, and its behavior is studied in Section 3.

2 Stochastic Model

Let $P(t)$ and $R(t)$ be the number of heart failure patients and the number of recovered individuals from heart failure at time t, respectively. Let $P(t), R(t); t \geq 0$ be a continuous time Markov chain having a joint probability function given by

$$P_{n_1,n_2}(t) = Prob.\{P(t) = n_1, R(t) = n_2\} \tag{2.1}$$

where t is the continuous parameter of the process and n_1 and n_2 are population sizes of diseased state and recovered state at time t respectively. The schematic diagram of the model is shown in Fig. 1.

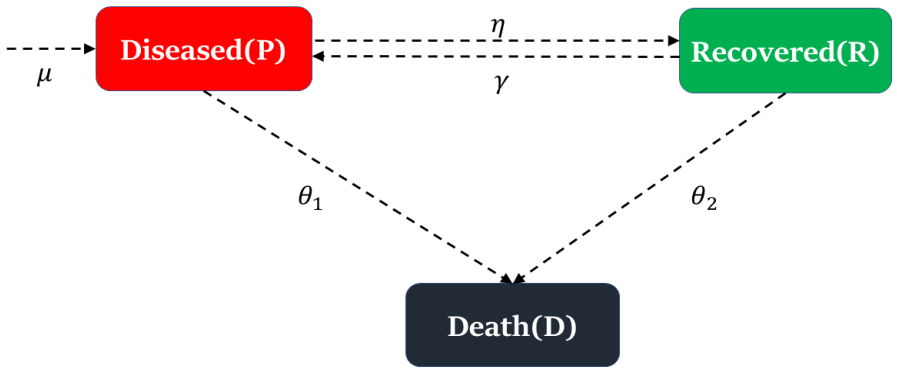

Fig. 1. Schematic diagram for heart failure recovery process

2.1 Assumptions and postulates

We make the following assumptions to construct a model for the heart failure recovery process:

1. Let n_1 be the number of patients suffering from heart failure at a point of time t and n_2 be the number of individuals who recovered from heart failure at a point in time t.

2. Let μ be the incidence rate of heart failure, η be the recovery rate of individuals from heart failure, and γ be the recurring rate of heart failure.
3. Let θ_1 and θ_2 be the death rates per unit time from diseased and recovered states, respectively.
4. Let Δt be an epoch of time during which one transition will occur, and the events that occurred in non-overlapping intervals are statistically independent.

Based on these assumptions, we defined the postulates as follows:

1. The probability of a heart failure patient become recovered during Δt is $n_1\eta\Delta t + o(\Delta t)$.
2. The probability of a new heart failure case happening during Δt is $\mu\Delta t + o(\Delta t)$.
3. The probability of a recurring heart failure among recovered individuals during Δt is $n_2\gamma\Delta t + o(\Delta t)$.
4. The probability of a death occurred among the diseased individuals during Δt is $n_1\theta_1\Delta t + o(\Delta t)$.
5. The probability of a death occurred among the recovered individuals during Δt is $n_2\theta_2\Delta t + o(\Delta t)$.
6. The probability of no event happened during Δt is $1-(\mu+n_1(\eta+\theta_1)+n_2(\gamma+\theta_2))\Delta t+o(\Delta t)$.
7. The probability of occurrence of more than one event during Δt is $o(\Delta t)^2$.

Let $P_{n_1,n_2}(t+\Delta t)$ be the probability of an event occurred during an infinitesimal time interval Δt given that n_1 number of diseased individuals and n_2 number of recovered individuals in the system during $(0,t)$. Then, we defined $P_{n_1,n_2}(t+\Delta t)$ based on the assumptions and postulates of the model as follows:

$$\begin{aligned} P_{n_1,n_2}(t+\Delta t) &= P_{n_1,n_2}(t)[1-(\mu+n_1(\eta+\theta_1)+n_2(\gamma+\theta_2))\Delta t + o(\Delta t)] \\ &+ P_{n_1-1,n_2}(t)[\mu\Delta t + o(\Delta t)] \\ &+ P_{n_1+1,n_2-1}(t)[(n_1+1)\eta\Delta t + o(\Delta t)] \\ &+ P_{n_1-1,n_2+1}(t)[(n_2+1)\gamma\Delta t + o(\Delta t)] \\ &+ P_{n_1+1,n_2}(t)[(n_1+1)\theta_1\Delta t + o(\Delta t)] \\ &+ P_{n_1,n_2+1}(t)[(n_2+1)\theta_2\Delta t + o(\Delta t)] \\ &+ P_{n_1\pm i,n_2\pm j}(t)[o(\Delta t)^2]; i \geq 1; j \geq 1. \end{aligned} \tag{2.2}$$

The differential equation derived from equation (2.2) is

$$\begin{aligned} \frac{d}{dt}P_{n_1,n_2}(t) &= -[\mu+n_1(\eta+\theta_1)+n_2(\gamma+\theta_2)]P_{n_1,n_2}(t) \\ &+ \mu P_{n_1-1,n_2}(t) + (n_1+1)\eta P_{n_1+1,n_2-1}(t) \\ &+ (n_2+1)\gamma P_{n_1-1,n_2+1}(t) + (n_1+1)\theta_1 P_{n_1+1,n_2}(t) \\ &+ (n_2+1)\theta_2 P_{n_1,n_2+1}(t); n_1 \geq 1; n_2 \geq 1. \end{aligned} \tag{2.3}$$

The equation (2.3) can be simplified with the help of the following probability generating function [15, 16, 17, 18, 19, 20]:

$$P(u,v;t) = \sum_{n_1=0}^{\infty}\sum_{n_2=0}^{\infty} u^{n_1}v^{n_2}P_{n_1,n_2}(t) \tag{2.4}$$

and the initial condition:

$$P_{n_1,n_2}(0) = \begin{cases} 1 & if\ n_1 = N_0\ and\ n_2 = M_0 \\ 0 & otherwise \end{cases} \tag{2.5}$$

where N_0 and M_0 are the initial sizes of diseased state and recovered state respectively.

Multiplying the equations (2.3) with $u^{n_1}v^{n_2}$ and summing over all n_1 and n_2, and after simplification we obtain

$$\begin{aligned}\frac{\partial P(u,v;t)}{\partial t} &= \mu(u-1)P(u,v;t) + [\eta(v-u)+\theta_1(1-u)]\frac{\partial P(u,v;t)}{\partial u} \\ &\quad + [\gamma(u-v)+\theta_2(1-v)]\frac{\partial P(u,v;t)}{\partial v}\end{aligned} \tag{2.6}$$

The basic stochastic partial differential equation represented in equation (2.6) can be transformed into a simultaneous system of ordinary differential equations for the model's means, variances, and covariance by differentiating equation (2.6) with respect to u and v respectively and setting $u = v = 1$. Then, we obtain the differential equations of different statistical measures as follows:

$$\frac{dE_u(t)}{dt} = \mu - (\eta+\theta_1)E_u(t) + \gamma E_v(t) \tag{2.7}$$

$$\frac{dE_v(t)}{dt} = \eta E_u(t) - (\gamma+\theta_2)E_v(t) \tag{2.8}$$

$$\frac{dV_u(t)}{dt} = 2[\mu E_u(t) + \gamma E_{uv}(t) - (\eta+\theta_1)V_u(t)] \tag{2.9}$$

$$\frac{dV_v(t)}{dt} = 2[\eta E_{uv}(t) - (\gamma+\theta_2)V_v(t)] \tag{2.10}$$

$$\frac{dE_{uv}(t)}{dt} = \mu E_v(t) + \eta V_u(t) + \gamma V_v(t) - (\eta+\gamma+\theta_1+\theta_2)E_{uv}(t) \tag{2.11}$$

3 Results and Discussion

Since it is difficult to analytically solve the simultaneous system of ordinary differential equations (2.7) to (2.11), it has been solved numerically using R software. The Runge-Kutta method has been used to get the approximate solution for various statistical measures. We fixed the death rates θ_1 and θ_2 as 0.0027 and 0.06, respectively, based on the Report on medical certification of cause of death in 2019, India [21]. The datasets are simulated for changing values of parameters such as recovery rate (η) and recurring rate (γ) to understand the behavior of the diseased state and recovered state. The mean number of individuals in the diseased state and recovered state for different combinations of parameters are shown in Fig. 2.

Fig. 2 shows the mean number of individuals in the diseased state and recovered state for changing values (0.1, 0.5, and 0.9) of parameters such as recovery rate (η) and recurring rate (γ). When the recurring rate (γ) is the same as the recovery rate (η), the mean number of individuals in the diseased state decreases to half of the population, and the mean number of individuals in the recovered state reaches the maximum (40-50) within initial ten months. Then, both are decreasing at almost the same rate. When the recovery rate (η) is greater than the recurring rate (γ), the diseased population decreases abruptly within the initial ten months, and the mean number of recovered individuals attains its maximum (80) when $\eta = 0.9$ (Case 7).

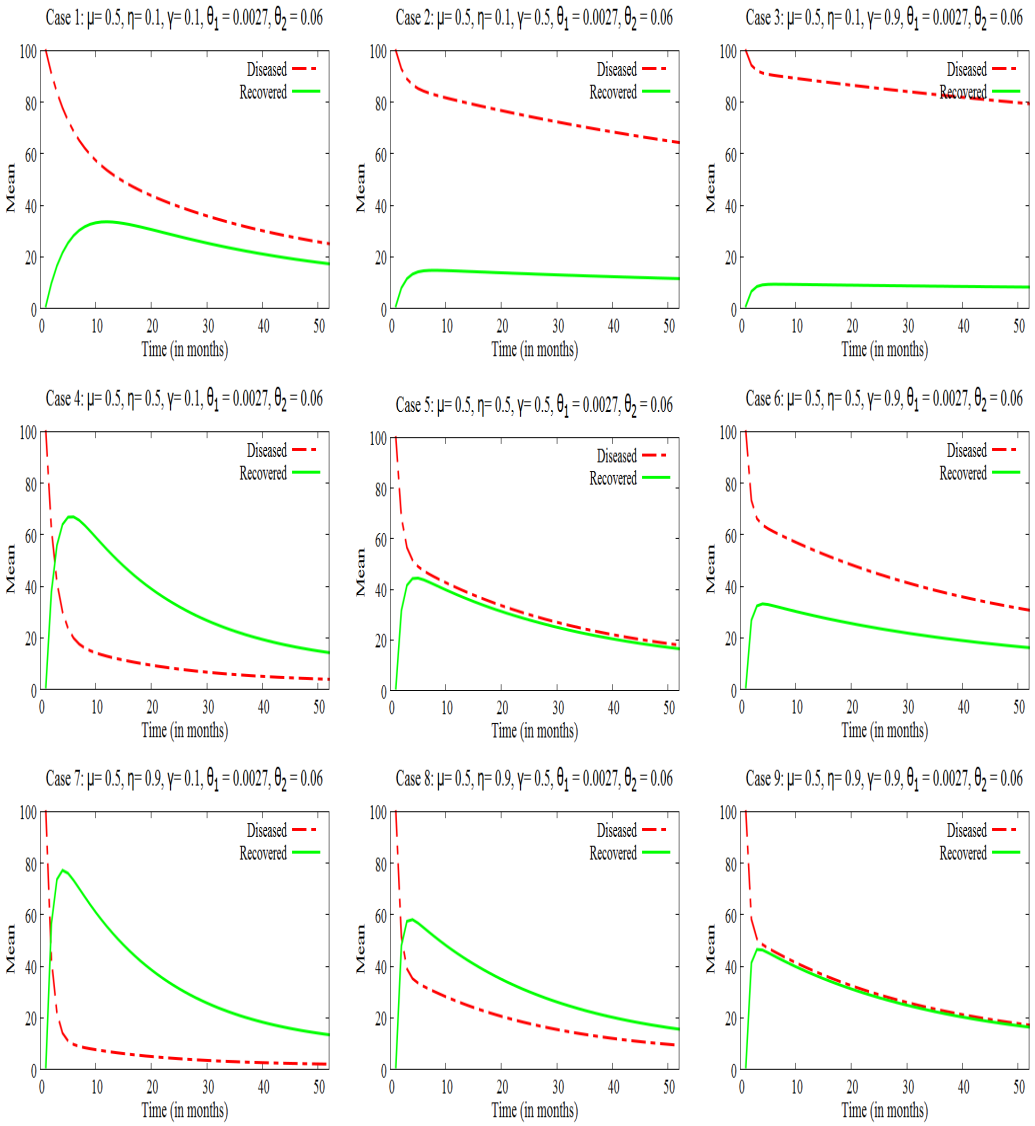

Fig. 2. Mean number of individuals in Diseased state and Recovered state with respect to time (in months)

The mean number of individuals in the diseased state always shows a decreasing trend with respect to time. The mean number of individuals in the recovered state shows an increasing trend in the initial months, then decreases slowly as time progresses. The variability in the sizes of diseased state and recovered state for different combinations of parameters is shown in Fig. 3.

Fig. 3 shows the variance of diseased state and recovered state with respect to time for changing values (0.1, 0.5, and 0.9) of parameters such as recovery rate (η) and recurring rate (γ). Figure 3 indicates that the variance of the diseased state is determined by the recurring rate (γ). The variance

of the diseased state becomes greater than the recovered state as the recurring rate increases. When the recovery rate is at its lowest level (η=0.1), and the recurring rate is higher than the recovery rate, then the variance of the recovered state with respect to time is homogeneous. When the recurring rate is at its lowest level (γ=0.1), and the recovery rate is higher than the recurring rate, then the variance of the diseased state with respect to time is homogeneous. The variance of the recovered state becomes higher than the diseased state when the recovery rate is greater than the recurring rate. The variance of diseased and recovered states changes with time at the same rate for equal and higher values (0.5, 0.9) of recovery rate and recurring rate.

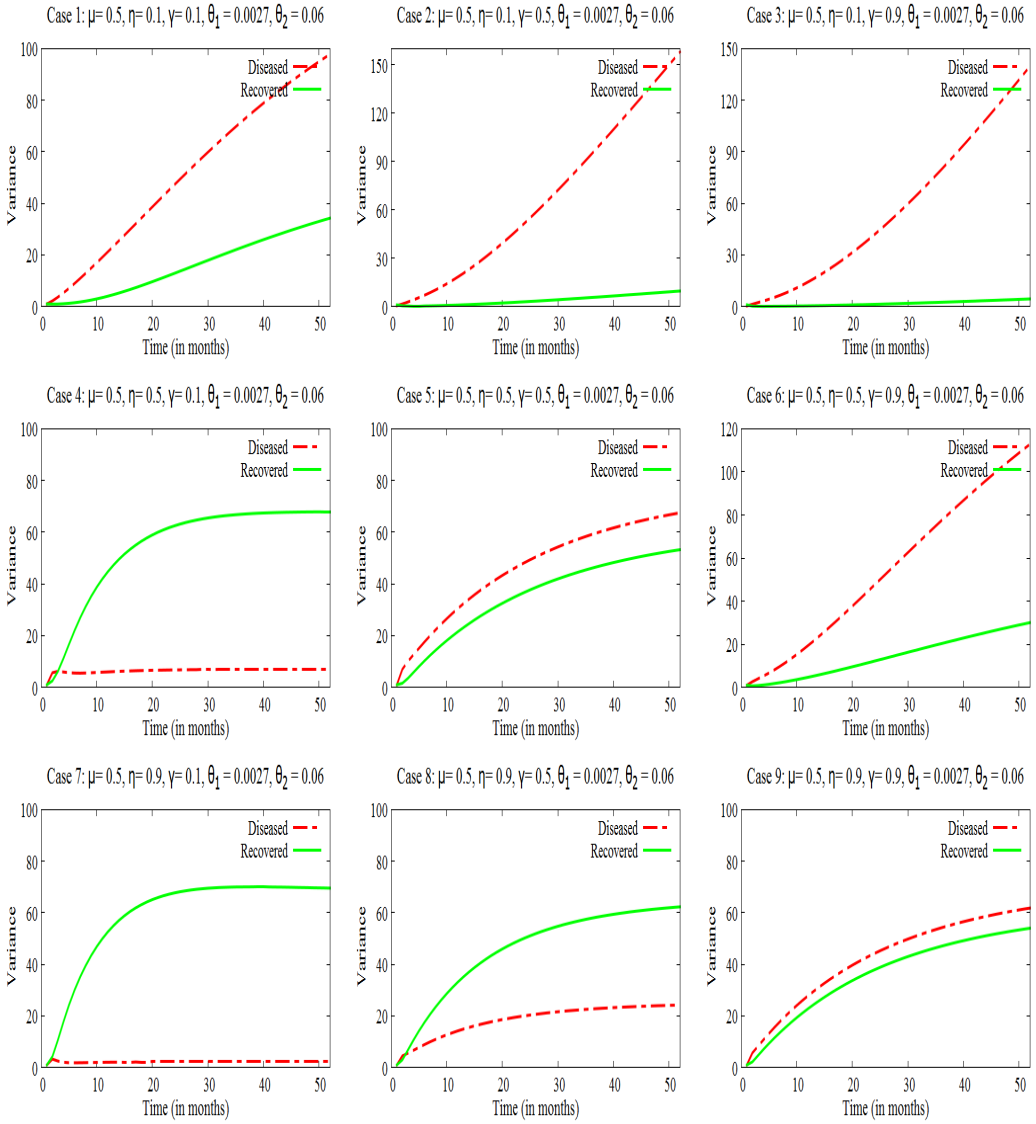

Fig. 3. Variance of Diseased state and Recovered state with respect to time (in months)

4 Conclusion

In this study, we modeled the recovery process of heart failure using a continuous time Markov chain (CTMC). The proposed model has two states: The diseased state and the Recovered state. The different statistical measures have been derived and solved numerically using R software. The model behavior has been studied for various combinations of parameters. Figure 2 indicates that the mean of the diseased state shows a decreasing trend, and the mean of the recovered state increases in the initial months, then decreases gradually. Figure 3 indicates that the variance of diseased and recovered states increases uniformly with respect to time for equal and higher values of parameters. The number of individuals in the recovered state attains its maximum in the initial months and decreases gradually as time progresses. The initial months have a crucial role in the population sizes of the diseased state and recovered state. So, the government should ensure the readiness of the health care system by improving the primary healthcare centers to identify the symptoms of heart failure in the early stage.

Competing Interests

Authors have declared that no competing interests exist.

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