CTMC Analyzing NAFLD Progression (Small Model)

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Short Report

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CTMC Analyzing NAFLD Progression (Small Model)

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Abstract:

In this article, I tackle the problem of non-alcoholic fatty liver disease (NAFLD) from a statistical point of view. Using the multistate model, in the form of the continuous-time Markov chains, helps the statistical analysis of the progression of the disease over time. The simplest model of the health-disease-death process is applied to the NAFLD. The model is composed of 8 pdfs and 5 rates that need to be estimated. Maximum likelihood and quasi-Newton methods are applied to estimate the transition rates among states. Exponentiation of this estimated rate matrix yields the transition probability matrix. This transition probability matrix can also be estimated by solving the forward Kolmogorov differential equations. Testing time homogeneity of this CTMC that models the disease process is also discussed by the author. This can be achieved by finding an empirical probability matrix that equates to the exponentiation of the transition rate matrix, which is thoroughly investigated. Also, the embedding problem that may arise when trying to find the transition rate matrix from the transition probability matrix of the corresponding discrete-time model is clarified. Testing Markovian property of the chain is also presented. Some remarks are also highlighted as regards the state probability distribution and the stationary probability distribution.

Key words: continuous time Markov chains, non-alcoholic fatty liver disease, embedding problem, mean sojourn time, stationary probability distribution.

CTMC Analyzing NAFLD Progression (Small Model)

Studying the natural history of disease during which individuals start at one initial state then as time passes the patients move from one state to another, can be investigated by using multistate Markov chains. The evolution of the disease over different phases can be monitored by taking repeated observations of the disease stage at pre-specified time points following entry into the study. The disease stage is recorded at the time of observation while the exact time of state change is unobserved. NAFLD is a multistage disease process; in its simplest form has a general structure model as depicted in Figure (1).

Figure (1): general model structure.(Younossi et al., 2016)

NAFLD stages are modeled as time homogenous CTMC , that is mean $P_{ij}(\Delta t)$ depends on Δt and not on t , with constant transition intensities λ_{ij} over time, exponentially distributed time spent within each state, and patients' events follow the Poisson distribution. The states are one for the susceptible cases (state 1) and one for NAFLD cases (state 2) and two absorbing states ; one for the death due to NAFLD (state 3) and one for death due to any other cause (state 4). The transition rate λ_{12} is the rate of progression from state 1 to state 2, while the transition rate μ_{12} is the regression rate from state 2 to state 1. The transition rate λ_{23} is the progression rate from state 2 to state 3 and λ_{24} is the rate of progression from state 2 to state 4. For simplicity, all individuals are assumed to enter the disease process at stage one and they are all followed up with the same length of the time interval between measurements.

In this article, the transition probabilities and transition rates are thoroughly discussed. Also, mean sojourn time and its variance are reviewed as well as a state probability distribution and its covariance matrix. This is followed by an exploration of the life expectancy of the patients and the expected numbers of patients in each state. Lastly, a hypothetical numerical example is used to illustrate these concepts.

4.1. Transition Probability Matrix

The transitions can occur at any point in time. The rates at which these transitions occur are constant over time and thus are independent of t that is to say the transition of patient from *state i at time t to state j at $t = t + s$ where $s = \Delta t$* depends on difference between two consecutive time points. And it's defined as $\theta_{ij}(t) = \lim_{\Delta t \rightarrow 0} \frac{P_{ij}(\Delta t) - I}{\Delta t}$ or the Q matrix.

For the above multistate Markov model demonstrating the NAFLD disease process; the forward Kolmogorov differential equations is represented by (1)

$$\frac{d}{dt} P_{ij}(t) = \begin{bmatrix} P_{11} & P_{12} & P_{13} & P_{14} \\ P_{21} & P_{22} & P_{23} & P_{24} \\ 0 & 0 & P_{33} & 0 \\ 0 & 0 & 0 & P_{44} \end{bmatrix} \begin{bmatrix} -(\lambda_{12} + \lambda_{14}) & \lambda_{12} & 0 & \lambda_{14} \\ \mu_{21} & -(\mu_{21} + \lambda_{23} + \lambda_{24}) & \lambda_{23} & \lambda_{24} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \quad (1)$$

The Kolmogorov differential equations:

$$\frac{dP_{11}}{dt} = -P_{11}(\lambda_{12} + \lambda_{14}) + P_{12}\mu_{21} \quad (2)$$

$$\frac{dP_{12}}{dt} = P_{11}\lambda_{12} - P_{12}(\mu_{21} + \lambda_{23} + \lambda_{24}) \quad (3)$$

$$\frac{dP_{13}}{dt} = P_{12}\lambda_{23} \quad (4)$$

$$\frac{dP_{14}}{dt} = P_{11}\lambda_{14} + P_{12}\lambda_{24} \quad (5)$$

$$\frac{dP_{21}}{dt} = -P_{21}(\lambda_{12} + \lambda_{14}) + P_{22}\mu_{21} \quad (6)$$

$$\frac{dP_{22}}{dt} = P_{21}\lambda_{12} - P_{22}(\mu_{21} + \lambda_{23} + \lambda_{24}) \quad (7)$$

$$\frac{dP_{23}}{dt} = P_{22}\lambda_{23} \quad (8)$$

$$\frac{dP_{24}}{dt} = P_{21}\lambda_{14} + P_{22}\lambda_{24} \quad (9)$$

$$P_{33} = 1, P_{44} = 1$$

The solution of this system of equations will give the $P_{ij}(t)$

To solve the set of probabilities in the first row:

The first 2 equations are (2) and (3) :

$$\text{let: } \gamma_1 = \lambda_{12} + \lambda_{14} \quad , \quad \gamma_2 = \mu_{21} + \lambda_{23} + \lambda_{24}$$

To get P_{11}

$$DP_{11} + \gamma_1 P_{11} - \mu_{21} P_{12} = 0 \quad (10)$$

$$DP_{12} + \gamma_2 P_{12} - \lambda_{12} P_{11} = 0 \quad (11)$$

$$(D + \gamma_1)P_{11} - \mu_{21} P_{12} = 0 \quad (12)$$

$$-\lambda_{12} P_{11} + (D + \gamma_2)P_{12} = 0 \quad (13)$$

Multiply equation (12) by $(D + \gamma_2)$ and multiply equation (13) by μ_{21}

$$(D + \gamma_1)(D + \gamma_2)P_{11} - (D + \gamma_2)\mu_{21}P_{12} = 0 \quad (14)$$

$$-\lambda_{12} \mu_{21} P_{11} + (D + \gamma_2) \mu_{21} P_{12} = 0 \quad (15)$$

Add the above equations and solve simultaneously to get the roots (value of D), let's call it w_1 & w_2 :

$$[(D + \gamma_1)(D + \gamma_2) - \lambda_{12}\mu_{21}] P_{11} = 0, \quad [D^2 + (\gamma_1 + \gamma_2)D + \gamma_1\gamma_2 - \lambda_{12}\mu_{21}] P_{11} = 0$$

$$w_1 = \frac{-(\gamma_1 + \gamma_2) - \sqrt{(\gamma_1 + \gamma_2)^2 - 4\gamma_1\gamma_2 + 4\lambda_{12}\mu_{21}}}{2}, \quad w_2 = \frac{-(\gamma_1 + \gamma_2) + \sqrt{(\gamma_1 + \gamma_2)^2 - 4\gamma_1\gamma_2 + 4\lambda_{12}\mu_{21}}}{2}$$

$$\text{where : } (\gamma_1 + \gamma_2)^2 - 4\gamma_1\gamma_2 + 4\lambda_{12}\mu_{21} > 0$$

$$P_{11} = c_1 e^{w_1 t} + c_2 e^{w_2 t}$$

To get P_{12}

Multiply equation (12) by λ_{12} and multiply equation (13) by $(D + \gamma_1)$

$$(D + \gamma_1) \lambda_{12} P_{11} - \lambda_{12} \mu_{21} P_{12} = 0 \quad (16)$$

$$-(D + \gamma_1) \lambda_{12} P_{11} + (D + \gamma_1)(D + \gamma_2) P_{12} = 0 \quad (17)$$

Add the above equations and solve simultaneously to get the roots (value of D), let's call it w_1 & w_2 :

$$[(D + \gamma_1)(D + \gamma_2) - \lambda_{12}\mu_{21}] P_{12} = 0, \quad [D^2 + (\gamma_1 + \gamma_2)D + \gamma_1\gamma_2 - \lambda_{12}\mu_{21}] P_{12} = 0$$

$$w_1 = \frac{-(\gamma_1 + \gamma_2) - \sqrt{(\gamma_1 + \gamma_2)^2 - 4\gamma_1\gamma_2 + 4\lambda_{12}\mu_{21}}}{2}, \quad w_2 = \frac{-(\gamma_1 + \gamma_2) + \sqrt{(\gamma_1 + \gamma_2)^2 - 4\gamma_1\gamma_2 + 4\lambda_{12}\mu_{21}}}{2}$$

$$\text{where : } (\gamma_1 + \gamma_2)^2 - 4\gamma_1\gamma_2 + 4\lambda_{12}\mu_{21} > 0$$

$$P_{12} = c_3 e^{w_1 t} + c_4 e^{w_2 t}$$

Substitute in (10) to solve for the constants

$$c_1 w_1 e^{w_1 t} + c_2 w_2 e^{w_2 t} + c_1 \gamma_1 e^{w_1 t} + c_2 \gamma_1 e^{w_2 t} - \mu_{21} c_3 e^{w_1 t} - \mu_{21} c_4 e^{w_2 t} = 0$$

$$(c_1 w_1 + c_1 \gamma_1 - \mu_{21} c_3) e^{w_1 t} + (c_2 w_2 + c_2 \gamma_1 - \mu_{21} c_4) e^{w_2 t} = 0$$

$\begin{aligned} c_1 w_1 + c_1 \gamma_1 - \mu_{21} c_3 &= 0 \\ \mu_{21} c_3 &= c_1 w_1 + c_1 \gamma_1 \\ c_3 &= \frac{c_1}{\mu_{21}} (w_1 + \gamma_1) \end{aligned}$	$\begin{aligned} c_2 w_2 + c_2 \gamma_1 - \mu_{21} c_4 &= 0 \\ \mu_{21} c_4 &= c_2 w_2 + c_2 \gamma_1 \\ c_4 &= \frac{c_2}{\mu_{21}} (w_2 + \gamma_1) \end{aligned}$
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$$P_{11} = c_1 e^{w_1 t} + c_2 e^{w_2 t}, \quad P_{12} = c_3 e^{w_1 t} + c_4 e^{w_2 t} = \frac{c_1}{\mu_{21}} (w_1 + \gamma_1) e^{w_1 t} + \frac{c_2}{\mu_{21}} (w_2 + \gamma_1) e^{w_2 t}$$

Using initial values at :

$$P_{11}(0) = 1 \rightarrow c_1 + c_2 = 1 \rightarrow c_1 = 1 - c_2$$

$$P_{12}(0) = 0 \rightarrow \frac{c_1}{\mu_{21}} (w_1 + \gamma_1) + \frac{c_2}{\mu_{21}} (w_2 + \gamma_1) = 0$$

$$\therefore c_2 = \left(\frac{w_1 + \gamma_1}{w_1 - w_2} \right) \quad \text{and} \quad c_1 = (1 - c_2) = \left(\frac{w_2 + \gamma_1}{w_2 - w_1} \right)$$

$$P_{11} = \left(\frac{w_2 + \gamma_1}{w_2 - w_1} \right) e^{w_1 t} + \left(\frac{w_1 + \gamma_1}{w_1 - w_2} \right) e^{w_2 t}$$

$$P_{12} = \frac{c_1}{\mu_{21}} (w_1 + \gamma_1) e^{w_1 t} + \frac{c_2}{\mu_{21}} (w_2 + \gamma_1) e^{w_2 t} = \left(\frac{w_2 + \gamma_1}{w_2 - w_1} \right) \left(\frac{w_1 + \gamma_1}{\mu_{21}} \right) e^{w_1 t} + \left(\frac{w_1 + \gamma_1}{w_1 - w_2} \right) \left(\frac{w_2 + \gamma_1}{\mu_{21}} \right) e^{w_2 t}$$

$$\text{let : } \left(\frac{w_2 + \gamma_1}{w_2 - w_1} \right) = A_1, \quad \left(\frac{w_1 + \gamma_1}{w_1 - w_2} \right) = A_2, \quad \left(\frac{w_2 + \gamma_1}{w_2 - w_1} \right) \left(\frac{w_1 + \gamma_1}{\mu_{21}} \right) = A_3, \quad \left(\frac{w_1 + \gamma_1}{w_1 - w_2} \right) \left(\frac{w_2 + \gamma_1}{\mu_{21}} \right) = A_4$$

$$\therefore P_{11} = A_1 e^{w_1 t} + A_2 e^{w_2 t} \quad (18)$$

$$\therefore P_{12} = A_3 e^{w_1 t} + A_4 e^{w_2 t} \quad (19)$$

To get P_{13}

$$\frac{dP_{13}}{dt} = P_{12} \lambda_{23} = \lambda_{23} (A_3 e^{w_1 t} + A_4 e^{w_2 t}) = \lambda_{23} A_3 e^{w_1 t} + \lambda_{23} A_4 e^{w_2 t}$$

$$P_{13} = \left[\lambda_{23} A_3 \frac{e^{w_1 t}}{w_1} - \frac{\lambda_{23} A_3}{w_1} \right] + \left[\lambda_{23} A_4 \frac{e^{w_2 t}}{w_2} - \frac{\lambda_{23} A_4}{w_2} \right]$$

$$P_{13} = \frac{\lambda_{23} A_3}{w_1} (e^{w_1 t} - 1) + \frac{\lambda_{23} A_4}{w_2} (e^{w_2 t} - 1)$$

$$\text{let } \frac{\lambda_{23} A_3}{w_1} = A_5, \quad \frac{\lambda_{23} A_4}{w_2} = A_6$$

$$\therefore P_{13} = A_5 (e^{w_1 t} - 1) + A_6 (e^{w_2 t} - 1) \quad (20)$$

To get P_{14}

$$\frac{dP_{14}}{dt} = \lambda_{14} (A_1 e^{w_1 t} + A_2 e^{w_2 t}) + \lambda_{24} (A_3 e^{w_1 t} + A_4 e^{w_2 t}) = (\lambda_{14} A_1 + \lambda_{24} A_3) e^{w_1 t} + (\lambda_{14} A_2 + \lambda_{24} A_4) e^{w_2 t}$$

$$\text{let : } G_1 = (\lambda_{14} A_1 + \lambda_{24} A_3), \quad G_2 = (\lambda_{14} A_2 + \lambda_{24} A_4), \quad \text{thus } \frac{dP_{14}}{dt} = G_1 e^{w_1 t} + G_2 e^{w_2 t}$$

$$P_{14} = \left[G_1 \frac{e^{w_1 t}}{w_1} - \frac{G_1}{w_1} \right] + \left[G_2 \frac{e^{w_2 t}}{w_2} - \frac{G_2}{w_2} \right] = \frac{G_1}{w_1} (e^{w_1 t} - 1) + \frac{G_2}{w_2} (e^{w_2 t} - 1)$$

$$\text{let : } \frac{G_1}{w_1} = A_7, \quad \frac{G_2}{w_2} = A_8$$

$$\therefore P_{14} = A_7(e^{w_1 t} - 1) + A_8(e^{w_2 t} - 1) \quad (21)$$

To solve the set of probabilities in the second row, equations (6) and (7), set of equations are

$$DP_{21} + \gamma_1 P_{21} - \mu_{21} P_{22} = 0 \quad (22)$$

$$DP_{22} + \gamma_2 P_{22} - \lambda_{12} P_{21} = 0 \quad (23)$$

$$(D + \gamma_1)P_{21} - \mu_{21} P_{22} = 0 \quad (24)$$

$$-\lambda_{12} P_{21} + (D + \gamma_2)P_{22} = 0 \quad (25)$$

To get P_{21} using similar steps as for p_{11} , p_{12} where w_1 and w_2 as previously defined

$$\therefore P_{21} = c_5 e^{w_1 t} + c_6 e^{w_2 t} \quad (26)$$

To get P_{22} using similar steps as for p_{11} , p_{12}

$$\therefore P_{22} = c_7 e^{w_1 t} + c_8 e^{w_2 t} \quad (27)$$

Substitute in (4.22) to get the constants

$$c_5 w_1 e^{w_1 t} + c_6 w_2 e^{w_2 t} + c_5 \gamma_1 e^{w_1 t} + c_6 \gamma_1 e^{w_2 t} - \mu_{21} c_7 e^{w_1 t} - \mu_{21} c_8 e^{w_2 t} = 0$$

$$(c_5 w_1 + c_5 \gamma_1 - \mu_{21} c_7) e^{w_1 t} + (c_6 w_2 + c_6 \gamma_1 - \mu_{21} c_8) e^{w_2 t} = 0$$

$c_5 w_1 + c_5 \gamma_1 - \mu_{21} c_7 = 0$ $\mu_{21} c_7 = c_5 w_1 + c_5 \gamma_1$ $c_7 = \frac{c_5}{\mu_{21}} (w_1 + \gamma_1)$	$c_6 w_2 + c_6 \gamma_1 - \mu_{21} c_8 = 0$ $\mu_{21} c_8 = c_6 w_2 + c_6 \gamma_1$ $c_8 = \frac{c_6}{\mu_{21}} (w_2 + \gamma_1)$
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$$P_{21} = c_5 e^{w_1 t} + c_6 e^{w_2 t}, P_{22} = c_7 e^{w_1 t} + c_8 e^{w_2 t} = \frac{c_5}{\mu_{21}} (w_1 + \gamma_1) e^{w_1 t} + \frac{c_6}{\mu_{21}} (w_2 + \gamma_1) e^{w_2 t}$$

Using initial values at :

$$P_{21}(0) = 0 \rightarrow c_5 + c_6 = 0 \rightarrow c_5 = -c_6$$

$$P_{22}(0) = 1 \rightarrow \frac{c_5}{\mu_{21}} (w_1 + \gamma_1) + \frac{c_6}{\mu_{21}} (w_2 + \gamma_1) = 1$$

$$P_{21} = \left(\frac{\mu_{21}}{w_1 - w_2} \right) (e^{w_1 t} - e^{w_2 t}), \quad P_{22} = \left(\frac{w_1 + \gamma_1}{w_1 - w_2} \right) e^{w_1 t} + \left(\frac{w_2 + \gamma_1}{w_2 - w_1} \right) e^{w_2 t}$$

$$\text{let } \left(\frac{\mu_{21}}{w_1 - w_2} \right) = A_9, \quad \left(\frac{w_1 + \gamma_1}{w_1 - w_2} \right) = A_2, \quad \left(\frac{w_2 + \gamma_1}{w_2 - w_1} \right) = A_1$$

$$\therefore P_{21} = A_9 (e^{w_1 t} - e^{w_2 t}) \quad (28)$$

$$\therefore P_{22} = A_2 e^{w_1 t} + A_1 e^{w_2 t} \quad (29)$$

To get P_{23}

$$\frac{dP_{23}}{dt} = P_{22}\lambda_{23} = \lambda_{23}(A_2 e^{w_1 t} + A_1 e^{w_2 t}) = \lambda_{23}A_2 e^{w_1 t} + \lambda_{23}A_1 e^{w_2 t}$$

$$P_{23} = \left[\lambda_{23}A_2 \frac{e^{w_1 t}}{w_1} - \frac{\lambda_{23}A_2}{w_1} \right] + \left[\lambda_{23}A_1 \frac{e^{w_2 t}}{w_2} - \frac{\lambda_{23}A_1}{w_2} \right]$$

$$P_{23} = \frac{\lambda_{23}A_2}{w_1} (e^{w_1 t} - 1) + \frac{\lambda_{23}A_1}{w_2} (e^{w_2 t} - 1)$$

$$\text{let } \frac{\lambda_{23}A_2}{w_1} = A_{10} \quad , \quad \frac{\lambda_{23}A_1}{w_2} = A_{11}$$

$$\therefore P_{23} = A_{10} (e^{w_1 t} - 1) + A_{11} (e^{w_2 t} - 1) \quad (30)$$

To get P_{24}

$$\frac{dP_{24}}{dt} = P_{21}\lambda_{14} + P_{22}\lambda_{24} = (\lambda_{14}A_9 + \lambda_{24}A_2)e^{w_1 t} + (\lambda_{24}A_1 - \lambda_{14}A_9)e^{w_2 t}$$

$$\text{let : } (\lambda_{14}A_9 + \lambda_{24}A_2) = G_3 \quad , \quad (\lambda_{24}A_1 - \lambda_{14}A_9) = G_4, \text{ thus } \frac{dP_{24}}{dt} = G_3 e^{w_1 t} + G_4 e^{w_2 t}$$

$$P_{24} = \left[G_3 \frac{e^{w_1 t}}{w_1} - \frac{G_3}{w_1} \right] + \left[G_4 \frac{e^{w_2 t}}{w_2} - \frac{G_4}{w_2} \right] = \frac{G_3}{w_1} (e^{w_1 t} - 1) + \frac{G_4}{w_2} (e^{w_2 t} - 1)$$

$$\text{let : } \frac{G_3}{w_1} = A_{12} \quad , \quad \frac{G_4}{w_2} = A_{13}$$

$$\therefore P_{24} = A_{12}(e^{w_1 t} - 1) + A_{13}(e^{w_2 t} - 1) \quad (31)$$

$$P_{33} = 1 \quad \text{and} \quad P_{44} = 1$$

4.2. Maximum Likelihood Estimation of the Q Matrix

According to (Kalbfleisch & Lawless, 1985), let n_{ijr} be the number of individuals in state i at t_{r-1} and in state j at time t_r . Conditioning on the distribution of individuals among states at t_0 , then the likelihood function for θ is in (32) and its log likelihood is in (33)

$$L(\theta) = \prod_{r=1}^{\tau} \left\{ \prod_{i,j=1}^k [P_{ij}(t_{r-1}, t_r)]^{n_{ijr}} \right\}, \text{ where } k \text{ is the index of the number of states} \quad (32)$$

$$\log L(\theta) = \sum_{r=1}^{\tau} \sum_{i,j=1}^k n_{ijr} \log P_{ij}(t_{r-1}, t_r), \quad (33)$$

where $\tau = (t_r - t_{r-1}) = \Delta t$, i.e: the difference between 2 consecutive points in time

Applying Quasi-Newton method to estimate the rates mandates calculating the score function which is a vector –valued function for the required rates in (4.34). It's the first derivative of the transition probability function with respect to θ . The second derivative of the transition probability function with respect to θ is assumed to be zero.

$$S(\theta) = \frac{\partial}{\partial \theta_h} \log L(\theta) = \sum_{r=1}^{\tau} \sum_{i,j=1}^k n_{ijr} \frac{\partial P_{ij}(\tau)/\partial \theta_h}{P_{ij}(\tau)}, \quad (35)$$

where: $h = 1, 2, 3, 4, 5$, $P_{ij}(\tau) = \frac{n_{ijr}}{n_{i+}}$ thus $\frac{n_{ijr}}{P_{ij}(\tau)} = n_{i+}$, such that $n_{i+} = \sum_{j=1}^k n_{ijr}$

where: $\theta_1 = \lambda_{12}$, $\theta_2 = \lambda_{14}$, $\theta_3 = \mu_{21}$, $\theta_4 = \lambda_{23}$, $\theta_5 = \lambda_{24}$

Taking the second derivative of $\log L(\theta)$ in (36) to obtain M matrix and substitute in formula (37):

$$\begin{aligned} \frac{\partial^2 \log L(\theta)}{\partial \theta_g \partial \theta_h} &= \sum_{\Delta t=1}^{\tau} \sum_{i,j}^k n_{ij} \left[\frac{\partial^2 P_{ij}(\Delta t)/\partial \theta_g \partial \theta_h}{P_{ij}(\Delta t)} - \frac{\partial P_{ij}(\Delta t)/\partial \theta_g \partial P_{ij}(\Delta t)/\partial \theta_h}{P_{ij}^2(\Delta t)} \right], \text{ where } P_{ij} = \frac{n_{ij}}{n_{i+}} \\ \frac{\partial^2 \log L(\theta)}{\partial \theta_g \partial \theta_h} &= \sum_{\Delta t=1}^{\tau} \sum_{i,j}^k (P_{ij} n_{i+}) \left[\frac{\partial^2 P_{ij}(\Delta t)/\partial \theta_g \partial \theta_h}{P_{ij}(\Delta t)} - \frac{\partial P_{ij}(\Delta t)/\partial \theta_g \partial P_{ij}(\Delta t)/\partial \theta_h}{P_{ij}^2(\Delta t)} \right] \\ \frac{\partial^2 \log L(\theta)}{\partial \theta_g \partial \theta_h} &= \sum_{\Delta t=1}^{\tau} \sum_{i,j}^k (P_{ij} n_{i+}) \left[\frac{0}{P_{ij}(\Delta t)} - \frac{\partial P_{ij}(\Delta t)/\partial \theta_g \partial P_{ij}(\Delta t)/\partial \theta_h}{P_{ij}^2(\Delta t)} \right] \\ \frac{\partial^2 \log L(\theta)}{\partial \theta_g \partial \theta_h} &= - \sum_{\Delta t=1}^{\tau} \sum_{i,j}^k n_{i+} \frac{\partial P_{ij}(\Delta t)/\partial \theta_g \partial P_{ij}(\Delta t)/\partial \theta_h}{P_{ij}(\Delta t)} \\ \frac{\partial^2}{\partial \theta_g \partial \theta_h} \log L(\theta) &= \sum_{r=1}^{\tau} \sum_{i,j=1}^k n_{ijr} \left\{ \frac{\partial^2 P_{ij}(\tau)/\partial \theta_g \partial \theta_h}{P_{ij}(\tau)} - \frac{\partial P_{ij}(\tau)/\partial \theta_g \partial P_{ij}(\tau)/\partial \theta_h}{P_{ij}^2(\tau)} \right\} \end{aligned} \quad (36)$$

Assuming the $\frac{\partial^2 P_{ij}(\tau)}{\partial \theta_g \partial \theta_h} = 0$ is zero and $\frac{n_{ijr}}{P_{ij}(\tau)} = n_{i+}$, thus

$$M_{ij}(\theta) = \frac{\partial^2}{\partial \theta_g \partial \theta_h} \log L(\theta) = - \sum_{r=1}^{\tau} \sum_{i,j=1}^k n_{i+} \frac{\partial P_{ij}(\tau)/\partial \theta_g \partial P_{ij}(\tau)/\partial \theta_h}{P_{ij}(\tau)}$$

The Quasi-Newton formula is

$$\theta_1 = \theta_0 + [M(\theta_0)]^{-1} S(\theta_0) \quad (37)$$

For this simple model of NAFLD:

$$\frac{\partial}{\partial \theta} P_{ij}(t) = S(\theta) = \tau e^{\Lambda \tau} d\Lambda \text{ and it's scaled 4 times by } n_{1+} \text{ and another 4 times by } n_{2+} \text{ for each } \tau$$

where Λ is the eigenvalues for each Q matrix in each τ

According to (Klotz & Sharples, 1994) the initial $\theta_0 = \frac{n_{ijr}}{n_{i+}}$ for $\Delta t = 1$

Applying this to NALFD process:

$$Q = \begin{bmatrix} -(\lambda_{12} + \lambda_{14}) & \lambda_{12} & 0 & \lambda_{14} \\ \mu_{21} & -(\mu_{21} + \lambda_{23} + \lambda_{24}) & \lambda_{23} & \lambda_{24} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

let : $(\lambda_{12} + \lambda_{14}) = \gamma_1$, $(\mu_{21} + \lambda_{23} + \lambda_{24}) = \gamma_2$, to get $d\Lambda$ with respect to each rate:

first : solve for eigenvalues which are the solution of the $|Q - \rho I| = 0$

second : differentaite each value with respect to all rates, as shown below:

$|Q - \rho I|$ gives the characteristic polynomial of this matrix :

$$[-\lambda_{12}\mu_{21} + (\gamma_1 + \rho)(\gamma_2 + \rho)](-\rho)(-\rho) = 0$$

$$[-\lambda_{12}\mu_{21} + (\gamma_1 + \rho)(\gamma_2 + \rho)](-\rho)(-\rho) = \rho^2[\rho^2 + (\gamma_1 + \gamma_2)\rho + \gamma_1\gamma_2 - \lambda_{12}\mu_{21}] = 0$$

$$\rho = \{0, 0, \rho_3, \rho_4\}$$

$$\rho_3 = \frac{-(\gamma_1 + \gamma_2) - \sqrt{[(\gamma_1 + \gamma_2)]^2 - 4\gamma_1\gamma_2 + 4\mu_{21}\lambda_{12}}}{2} = \frac{-(\gamma_1 + \gamma_2) - \sqrt{\cdot}}{2}$$

$$\rho_4 = \frac{-(\gamma_1 + \gamma_2) + \sqrt{[(\gamma_1 + \gamma_2)]^2 - 4\gamma_1\gamma_2 + 4\mu_{21}\lambda_{12}}}{2} = \frac{-(\gamma_1 + \gamma_2) + \sqrt{\cdot}}{2}$$

$$\sqrt{[(\gamma_1 + \gamma_2)]^2 - 4\gamma_1\gamma_2 + 4\mu_{21}\lambda_{12}} = \sqrt{\cdot}$$

$$= (\lambda_{12}^2 + \lambda_{14}^2 + \mu_{21}^2 + \lambda_{23}^2 + \lambda_{24}^2 + 2\lambda_{12}\lambda_{14} + 2\lambda_{12}\mu_{21} + 2\lambda_{23}\mu_{21} + 2\lambda_{24}\mu_{21} + 2\lambda_{23}\lambda_{24} - 2\lambda_{12}\lambda_{23} - 2\lambda_{12}\lambda_{24} - 2\lambda_{14}\mu_{21} - 2\lambda_{14}\lambda_{23} - 2\lambda_{14}\lambda_{24})^{.5}$$

$$\rho_3 = \frac{1}{2} \{-\lambda_{12} - \lambda_{14} - \mu_{21} - \lambda_{23} - \lambda_{24} - (\lambda_{12}^2 + \lambda_{14}^2 + \mu_{21}^2 + \lambda_{23}^2 + \lambda_{24}^2 + 2\lambda_{12}\lambda_{14} + 2\lambda_{12}\mu_{21} + 2\lambda_{23}\mu_{21} + 2\lambda_{24}\mu_{21} + 2\lambda_{23}\lambda_{24} - 2\lambda_{12}\lambda_{23} - 2\lambda_{12}\lambda_{24} - 2\lambda_{14}\mu_{21} - 2\lambda_{14}\lambda_{23} - 2\lambda_{14}\lambda_{24})^{.5}\}$$

$$\rho_4 = \frac{1}{2} \{-\lambda_{12} - \lambda_{14} - \mu_{21} - \lambda_{23} - \lambda_{24} + (\lambda_{12}^2 + \lambda_{14}^2 + \mu_{21}^2 + \lambda_{23}^2 + \lambda_{24}^2 + 2\lambda_{12}\lambda_{14} + 2\lambda_{12}\mu_{21} + 2\lambda_{23}\mu_{21} + 2\lambda_{24}\mu_{21} + 2\lambda_{23}\lambda_{24} - 2\lambda_{12}\lambda_{23} - 2\lambda_{12}\lambda_{24} - 2\lambda_{14}\mu_{21} - 2\lambda_{14}\lambda_{23} - 2\lambda_{14}\lambda_{24})^{.5}\}$$

$$\theta_1 = \lambda_{12}, \quad \theta_2 = \lambda_{14}, \quad \theta_3 = \mu_{21}, \quad \theta_4 = \lambda_{23}, \quad \theta_5 = \lambda_{24}$$

$$\frac{\partial}{\partial \lambda_{12}} \rho_3 = -\frac{1}{2} - \frac{1}{2}(\cdot)^{-.5}(\lambda_{12} + \lambda_{14} + \mu_{21} - \lambda_{23} - \lambda_{24})$$

$$\frac{\partial}{\partial \lambda_{14}} \rho_3 = -\frac{1}{2} - \frac{1}{2}(\cdot)^{-.5}(\lambda_{12} + \lambda_{14} - \mu_{21} - \lambda_{23} - \lambda_{24})$$

$$\frac{\partial}{\partial \mu_{21}} \rho_3 = -\frac{1}{2} - \frac{1}{2} (\cdot)^{-.5} (\mu_{21} + \lambda_{12} + \lambda_{23} + \lambda_{24} - \lambda_{14})$$

$$\frac{\partial}{\partial \lambda_{23}} \rho_3 = -\frac{1}{2} - \frac{1}{2} (\cdot)^{-.5} (\lambda_{23} + \mu_{21} + \lambda_{24} - \lambda_{12} - \lambda_{14})$$

$$\frac{\partial}{\partial \lambda_{24}} \rho_3 = -\frac{1}{2} - \frac{1}{2} (\cdot)^{-.5} (\lambda_{24} + \mu_{21} + \lambda_{23} - \lambda_{12} - \lambda_{14})$$

$$\frac{\partial}{\partial \lambda_{12}} \rho_4 = -\frac{1}{2} + \frac{1}{2} (\cdot)^{-.5} (\lambda_{12} + \lambda_{14} + \mu_{21} - \lambda_{23} - \lambda_{24})$$

$$\frac{\partial}{\partial \lambda_{14}} \rho_4 = -\frac{1}{2} + \frac{1}{2} (\cdot)^{-.5} (\lambda_{12} + \lambda_{14} - \mu_{21} - \lambda_{23} - \lambda_{24})$$

$$\frac{\partial}{\partial \mu_{21}} \rho_4 = -\frac{1}{2} + \frac{1}{2} (\cdot)^{-.5} (\mu_{21} + \lambda_{12} + \lambda_{23} + \lambda_{24} - \lambda_{14})$$

$$\frac{\partial}{\partial \lambda_{23}} \rho_4 = -\frac{1}{2} + \frac{1}{2} (\cdot)^{-.5} (\lambda_{23} + \mu_{21} + \lambda_{24} - \lambda_{12} - \lambda_{14})$$

$$\frac{\partial}{\partial \lambda_{24}} \rho_4 = -\frac{1}{2} + \frac{1}{2} (\cdot)^{-.5} (\lambda_{24} + \mu_{21} + \lambda_{23} - \lambda_{12} - \lambda_{14})$$

To get maximum likelihood, differentiate each P_{ij} with respect to each rate

$$\frac{\partial}{\partial \theta_h} P_{ij}(t) = t e^{\Lambda t} d \Lambda$$

$$t e^{\Lambda t} d \Lambda = t e^{\rho_3 t} \begin{bmatrix} \frac{\partial \rho_3}{\partial \lambda_{12}} \\ \frac{\partial \rho_3}{\partial \rho_3} \\ \frac{\partial \rho_3}{\partial \lambda_{14}} \\ \frac{\partial \rho_3}{\partial \mu_{21}} \\ \frac{\partial \rho_3}{\partial \rho_3} \\ \frac{\partial \rho_3}{\partial \lambda_{23}} \\ \frac{\partial \rho_3}{\partial \rho_3} \\ \frac{\partial \rho_3}{\partial \lambda_{24}} \end{bmatrix} + t e^{\rho_4 t} \begin{bmatrix} \frac{\partial \rho_4}{\partial \lambda_{12}} \\ \frac{\partial \rho_4}{\partial \rho_4} \\ \frac{\partial \rho_4}{\partial \lambda_{14}} \\ \frac{\partial \rho_4}{\partial \mu_{21}} \\ \frac{\partial \rho_4}{\partial \rho_4} \\ \frac{\partial \rho_4}{\partial \lambda_{23}} \\ \frac{\partial \rho_4}{\partial \rho_4} \\ \frac{\partial \rho_4}{\partial \lambda_{24}} \end{bmatrix} = \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix}, \text{ substitute } t = 1$$

$$t e^{\Lambda t} d \Lambda \text{ at } t = 1$$

$$\begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix} = \begin{bmatrix} -\frac{e^{\rho_3}}{2} - \frac{e^{\rho_4}}{2} + (\cdot)^{-.5} (\lambda_{12} + \lambda_{14} + \mu_{21} - \lambda_{23} - \lambda_{24}) \left[\frac{e^{\rho_4}}{2} - \frac{e^{\rho_3}}{2} \right] \\ -\frac{e^{\rho_3}}{2} - \frac{e^{\rho_4}}{2} + (\cdot)^{-.5} (\lambda_{12} + \lambda_{14} - \mu_{21} - \lambda_{23} - \lambda_{24}) \left[\frac{e^{\rho_4}}{2} - \frac{e^{\rho_3}}{2} \right] \\ -\frac{e^{\rho_3}}{2} - \frac{e^{\rho_4}}{2} + (\cdot)^{-.5} (\mu_{21} + \lambda_{12} + \lambda_{23} + \lambda_{24} - \lambda_{14}) \left[\frac{e^{\rho_4}}{2} - \frac{e^{\rho_3}}{2} \right] \\ -\frac{e^{\rho_3}}{2} - \frac{e^{\rho_4}}{2} + (\cdot)^{-.5} (\lambda_{23} + \mu_{21} + \lambda_{24} - \lambda_{12} - \lambda_{14}) \left[\frac{e^{\rho_4}}{2} - \frac{e^{\rho_3}}{2} \right] \\ -\frac{e^{\rho_3}}{2} - \frac{e^{\rho_4}}{2} + (\cdot)^{-.5} (\lambda_{24} + \mu_{21} + \lambda_{23} - \lambda_{12} - \lambda_{14}) \left[\frac{e^{\rho_4}}{2} - \frac{e^{\rho_3}}{2} \right] \end{bmatrix}$$

$$\begin{aligned}
v_1 &= -\frac{e^{\rho_3}}{2} - \frac{e^{\rho_4}}{2} + (.)^{-.5}(\lambda_{12} + \lambda_{14} + \mu_{21} - \lambda_{23} - \lambda_{24}) \left[\frac{e^{\rho_4}}{2} - \frac{e^{\rho_3}}{2} \right] \\
v_2 &= -\frac{e^{\rho_3}}{2} - \frac{e^{\rho_4}}{2} + (.)^{-.5}(\lambda_{12} + \lambda_{14} - \mu_{21} - \lambda_{23} - \lambda_{24}) \left[\frac{e^{\rho_4}}{2} - \frac{e^{\rho_3}}{2} \right] \\
v_3 &= -\frac{e^{\rho_3}}{2} - \frac{e^{\rho_4}}{2} + (.)^{-.5}(\mu_{21} + \lambda_{12} + \lambda_{23} + \lambda_{24} - \lambda_{14}) \left[\frac{e^{\rho_4}}{2} - \frac{e^{\rho_3}}{2} \right] \\
v_4 &= -\frac{e^{\rho_3}}{2} - \frac{e^{\rho_4}}{2} + (.)^{-.5}(\lambda_{23} + \mu_{21} + \lambda_{24} - \lambda_{12} - \lambda_{14}) \left[\frac{e^{\rho_4}}{2} - \frac{e^{\rho_3}}{2} \right] \\
v_5 &= -\frac{e^{\rho_3}}{2} - \frac{e^{\rho_4}}{2} + (.)^{-.5}(\lambda_{24} + \mu_{21} + \lambda_{23} - \lambda_{12} - \lambda_{14}) \left[\frac{e^{\rho_4}}{2} - \frac{e^{\rho_3}}{2} \right]
\end{aligned}$$

$$\begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix} \begin{bmatrix} v_1 & v_2 & v_3 & v_4 & v_5 \end{bmatrix} = \begin{bmatrix} v_1^2 & v_1 v_2 & v_1 v_3 & v_1 v_4 & v_1 v_5 \\ v_2 v_1 & v_2^2 & v_2 v_3 & v_2 v_4 & v_2 v_5 \\ v_3 v_1 & v_3 v_2 & v_3^2 & v_3 v_4 & v_3 v_5 \\ v_4 v_1 & v_4 v_2 & v_4 v_3 & v_4^2 & v_4 v_5 \\ v_5 v_1 & v_5 v_2 & v_5 v_3 & v_5 v_4 & v_5^2 \end{bmatrix} \text{ is used later to construct } M(\theta)$$

According to (Klotz & Sharples, 1994) $\tau = t_r - t_{r-1} = \Delta t$ and $P_{ij} = \frac{n_{ij}}{n_{i+}}$

$$S(\theta) = \frac{\partial \log L}{\partial \theta_h} = \sum_{\Delta t \geq 1}^3 \sum_{i,j=1}^k n_{ij} \frac{\partial P_{ij}(\Delta t) / \partial \theta_h}{P_{ij}(\Delta t)} = \sum_{\Delta t \geq 1}^3 \sum_{i,j=1}^k n_{ij} \frac{\partial P_{ij}(\Delta t) / \partial \theta_h}{n_{ij} / n_{i+}} = \sum_{\Delta t=1}^3 \sum_{i,j=1}^k n_{i+} \frac{\partial P_{ij}(\Delta t)}{\partial \theta_h} = \sum_{\Delta t=1}^3 \sum_{i,j=1}^k n_{i+} t e^{\Delta t} d \Lambda$$

the resulting vectort $(te^{\Delta t} d \Lambda)$ is scaled by a factor $= \left(\frac{n_{ij}(\Delta t)}{P_{ij}(\Delta t)} \right)$ 8 times ; one for each pdf

the followings are the scalars :

$$i.e \frac{n_{11}}{p_{11}} = n_{1+}, \frac{n_{12}}{p_{12}} = n_{1+}, \frac{n_{13}}{p_{13}} = n_{1+}, \frac{n_{14}}{p_{14}} = n_{1+}, \frac{n_{21}}{p_{21}} = n_{2+}, \frac{n_{22}}{p_{22}} = n_{2+}, \frac{n_{23}}{p_{23}} = n_{2+}, \frac{n_{24}}{p_{24}} = n_{2+}, \text{ all at } (\Delta t)$$

then the scaled vectors are summed to get the score function to be used in quasi – Newton Raphson method .

According to (Kalbfleisch & Lawless, 1985), the score function is crossed product with itself and scaled for each pdf with the scalars :

$$i.e \frac{n_{1+}}{p_{11}}, \frac{n_{1+}}{p_{12}}, \frac{n_{1+}}{p_{13}}, \frac{n_{1+}}{p_{14}}, \frac{n_{2+}}{p_{21}}, \frac{n_{2+}}{p_{22}}, \frac{n_{2+}}{p_{23}}, \frac{n_{2+}}{p_{24}}, \text{ the scaled matrices are summed to get the hessian matrix } M(\theta)$$

$$M(\theta) = \frac{\partial^2 \log L}{\partial \theta_g \partial \theta_h} = - \sum_{\Delta t=1}^3 \sum_{i,j}^k n_{i+} \frac{\partial P_{ij}(\Delta t) / \partial \theta_g \partial P_{ij}(\Delta t) / \partial \theta_h}{P_{ij}(\Delta t)}$$

Substituting in Quasi-Newton formula by the initial value, the score and the inverse of the hessian matrix are calculated to give the estimated rates.

$$S(\theta) = (4n_{1+}) \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix} + (4n_{2+}) \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix} = (4n_{1+} + 4n_{2+}) \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix}, \text{ for each } \Delta t$$

$$M(\theta) = \sum_{\Delta t}^3 \sum_{i,j=1}^k \frac{n_{i+}}{p_{ij}} \left\{ (4n_{1+} + 4n_{2+})^2 \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix} [v_1 \ v_2 \ v_3 \ v_4 \ v_5] \right\}$$

$$M(\theta) = \sum_{\Delta t}^3 \sum_{i,j=1}^k \frac{n_{i+}}{p_{ij}} \left\{ (4n_{1+} + 4n_{2+})^2 \begin{bmatrix} v_1^2 & v_1 v_2 & v_1 v_3 & v_1 v_4 & v_1 v_5 \\ v_2 v_1 & v_2^2 & v_2 v_3 & v_2 v_4 & v_2 v_5 \\ v_3 v_1 & v_3 v_2 & v_3^2 & v_3 v_4 & v_3 v_5 \\ v_4 v_1 & v_4 v_2 & v_4 v_3 & v_4^2 & v_4 v_5 \\ v_5 v_1 & v_5 v_2 & v_5 v_3 & v_5 v_4 & v_5^2 \end{bmatrix} \right\} = \begin{bmatrix} O & R \\ X & Y \end{bmatrix}$$

$M(\theta)$ is a singular matrix

where $O = \begin{bmatrix} v_1^2 & v_1 v_2 & v_1 v_3 \\ v_2 v_1 & v_2^2 & v_2 v_3 \\ v_3 v_1 & v_3 v_2 & v_3^2 \end{bmatrix}$ and it has O^{-1} , so $[M(\theta)]^{-1} = \begin{bmatrix} O^{-1} & 0 \\ 0 & 0 \end{bmatrix}$

4.3. Mean Sojourn Time

It is the mean time spent by a patient in a given state i of the process. It is calculated in relations to transition rates $\hat{\theta}$. These times are independent and exponentially distributed random variables with mean $\frac{1}{\lambda_i}$ where $\lambda_i = -\lambda_{ii}$; $i = 1, 2, 3, 4$. Denoting mean sojourn time by s_i for state i at visits $1, 2, \dots$

$$s_1 = \frac{1}{(\lambda_{12} + \lambda_{14})}, \quad \text{and} \quad s_2 = \frac{1}{(\mu_{21} + \lambda_{23} + \lambda_{24})}$$

According to (Kalbfleisch & Lawless, 1985), the asymptotic variance of this time is calculated by applying multivariate delta method to get (38):

$$var(s_i) = \left[\left(q_{ii}(\hat{\theta}) \right)^{-2} \right]^2 \sum_{h=1}^5 \sum_{g=1}^5 \frac{\partial q_{ii}}{\partial \theta_g} \frac{\partial q_{ii}}{\partial \theta_h} [M(\theta)]^{-1} |_{\theta=\hat{\theta}} \quad (38)$$

These times are independent so covariance between them is zero

$$var(s_i) = \left[\left(q_{ii}(\hat{\theta}) \right)^{-2} \right]^2 \sum_{h=1}^5 \sum_{g=1}^5 \frac{\partial q_{ii}}{\partial \theta_g} \frac{\partial q_{ii}}{\partial \theta_h} [M(\theta)]^{-1} |_{\theta=\hat{\theta}}$$

$$var(s_i) = \left[\left(q_{ii}(\hat{\theta}) \right)^{-2} \right]^2 \sum_{h=1}^5 \sum_{g=1}^5 \left[\frac{\partial q_{ii}}{\partial \theta_h} \right]^T [M(\theta)]^{-1} |_{\theta=\hat{\theta}} \frac{\partial q_{ii}}{\partial \theta_g}$$

$[M(\theta)]^{-1} |_{\theta=\hat{\theta}}$ as calculated by MLE of rate matrix .

$$\frac{\partial q_{ii}}{\partial \theta_h} = \begin{bmatrix} \frac{\partial q_{11}}{\partial \lambda_{12}} \\ \frac{\partial q_{11}}{\partial \lambda_{14}} \\ \frac{\partial q_{22}}{\partial \mu_{21}} \\ \frac{\partial q_{22}}{\partial \lambda_{23}} \\ \frac{\partial q_{33}}{\partial \lambda_{24}} \end{bmatrix} = \begin{bmatrix} -1 \\ -1 \\ -1 \\ -1 \\ -1 \end{bmatrix}, \quad \frac{\partial q_{ii}}{\partial \theta_g} = \begin{bmatrix} \frac{\partial q_{11}}{\partial \lambda_{12}} \\ \frac{\partial q_{11}}{\partial \lambda_{14}} \\ \frac{\partial q_{22}}{\partial \mu_{21}} \\ \frac{\partial q_{22}}{\partial \lambda_{23}} \\ \frac{\partial q_{33}}{\partial \lambda_{24}} \end{bmatrix} = \begin{bmatrix} -1 \\ -1 \\ -1 \\ -1 \\ -1 \end{bmatrix}$$

$$var(s_1) = \frac{1}{(\lambda_{12} + \lambda_{14})^4} [-1 \quad -1 \quad -1 \quad -1 \quad -1] [M(\theta)]^{-1} |_{\theta=\hat{\theta}} \begin{bmatrix} -1 \\ -1 \\ -1 \\ -1 \\ -1 \end{bmatrix}$$

$$var(s_2) = \frac{1}{(\mu_{21} + \lambda_{23} + \lambda_{24})^4} [-1 \quad -1 \quad -1 \quad -1 \quad -1] [M(\theta)]^{-1} |_{\theta=\hat{\theta}} \begin{bmatrix} -1 \\ -1 \\ -1 \\ -1 \\ -1 \end{bmatrix}$$

4.4. State Probability Distribution:

It is the probability distribution for each state at a specific time point given the initial probability distribution. Thus using the rule of total probability; a solution describing the transient behavior of a chain characterized by Q and an initial condition $\pi(0)$ is obtained by direct substitution to solve: $(t) = \pi(0)P(t)$, that is to mean to get the probability of distribution in NAFLD system after a certain period of time; the (39) must be solved:

$$[\pi_1 \quad \pi_2 \quad \pi_3 \quad \pi_4] = [\pi_{1(0)} \quad \pi_{2(0)} \quad \pi_{3(0)} \quad \pi_{4(0)}] \begin{bmatrix} P_{11} & P_{12} & P_{13} & P_{14} \\ P_{21} & P_{22} & P_{23} & P_{24} \\ 0 & 0 & P_{33} & 0 \\ 0 & 0 & 0 & P_{44} \end{bmatrix} \quad (39)$$

where $\pi_{3(0)} = \pi_{4(0)} = 0$, as both are death states

$$\pi_1 = \pi_{1(0)}P_{11} + \pi_{2(0)}P_{21} \quad , \quad \pi_2 = \pi_{1(0)}P_{12} + \pi_{2(0)}P_{22}$$

$$\pi_3 = \pi_{1(0)}P_{13} + \pi_{2(0)}P_{23} \quad , \quad \pi_4 = \pi_{1(0)}P_{14} + \pi_{2(0)}P_{24}$$

Thus to obtain stationary probability distribution when t goes to infinity, or in other words, when the process does not depend on time; call $\lambda_{12} + \lambda_{14} = \gamma_1$ and $\mu_{21} + \lambda_{23} + \lambda_{24} = \gamma_2$, differentiate (4.39) to get (4.40)

$$\pi(t) = \pi(0)P(t) = \pi(0)e^{Qt}, \quad \text{differentiating both sides}$$

$$\left. \frac{d}{dt} \pi(t) \right|_{t=0} = \pi(0)Q \quad (40)$$

$$\left. \frac{d}{dt} \pi(t) \right|_{t=0} = [\pi_{0(1)} \quad \pi_{0(2)} \quad \pi_{0(3)} \quad \pi_{0(4)}] \begin{bmatrix} -\gamma_1 & \lambda_{12} & 0 & \lambda_{14} \\ \mu_{21} & -\gamma_2 & \lambda_{23} & \lambda_{24} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\left. \frac{d}{dt} \pi_1(t) \right|_{t=0} = -\pi_{0(1)}\gamma_1 + \pi_{0(2)}\mu_{21} \quad , \quad \left. \frac{d}{dt} \pi_2(t) \right|_{t=0} = \pi_{0(1)}\lambda_{12} - \pi_{0(2)}\gamma_2$$

$$\left. \frac{d}{dt} \pi_3(t) \right|_{t=0} = \pi_{0(2)}\lambda_{23} \quad , \quad \left. \frac{d}{dt} \pi_4(t) \right|_{t=0} = \pi_{0(1)}\lambda_{14} + \pi_{0(2)}\lambda_{24}$$

By solving these equations, the vector $[\pi_1 \quad \pi_2 \quad \pi_3 \quad \pi_4]$ at specific time point is obtained

Solving these differential equations even for simple chains is not a trivial matter.

Thus as $t \rightarrow \infty$, the $\frac{d}{dt} \pi_j(t) = 0$, since $\pi_z(t)$ does not depend on time.

$$\frac{d}{dt} \pi(t) = \pi(t)Q \quad \text{will reduce to} \quad \pi(t)Q = 0$$

By solving $\pi Q = 0$, subject to $\sum_{all \ z} \pi_z = 1$, the state probability distribution is obtained in (41)

$$[\pi_{(1)} \quad \pi_{(2)} \quad \pi_{(3)} \quad \pi_{(4)}] \begin{bmatrix} -\gamma_1 & \lambda_{12} & 0 & \lambda_{14} \\ \mu_{21} & -\gamma_2 & \lambda_{23} & \lambda_{24} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad (41)$$

$$-\pi_{(1)}\gamma_1 + \pi_{(2)}\mu_{21} = 0 \quad , \quad \pi_{(1)}\lambda_{12} - \pi_{(2)}\gamma_2 = 0 \quad , \quad \pi_{(2)}\lambda_{23} = 0 \quad , \quad \pi_{(1)}\lambda_{14} + \pi_{(2)}\lambda_{24} = 0$$

$$1 = \pi_{(1)} + \pi_{(2)} + \pi_{(3)} + \pi_{(4)}$$

The above equations are expressed in matrix notation in (42):

$$\begin{bmatrix} -\gamma_1 & \mu_{21} & 0 & 0 \\ \lambda_{12} & -\gamma_2 & 0 & 0 \\ 0 & \lambda_{23} & 0 & 0 \\ \lambda_{14} & \lambda_{24} & 0 & 0 \\ 1 & 1 & 1 & 1 \end{bmatrix} \begin{bmatrix} \pi_1 \\ \pi_2 \\ \pi_3 \\ \pi_4 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix} \quad (42)$$

$$\begin{bmatrix} \pi_1 \\ \pi_2 \\ \pi_3 \\ \pi_4 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ \pi_3 \\ 1 - \pi_3 \end{bmatrix}$$

4.4.1. Asymptotic Covariance of the Stationary Distribution

To obtain this, multivariate delta method is used as well as the following function of the

$Q'\pi = 0$, as π is not a simple function of θ . Using implicit differentiation in (43) and (44)

$$\frac{\partial}{\partial \theta} F(\theta_h, \pi_i) = \frac{\partial}{\partial \theta_h} (Q'\pi_i) = 0 \quad , \quad \text{with implicit differentiation} \quad (43)$$

$$\frac{\partial}{\partial \theta_h} F(\theta_h, \pi_i) = \frac{\partial}{\partial \theta_h} (Q'\pi_i) = [Q'] \left[\frac{\partial}{\partial \theta_h} \pi_i \right] + \pi_i \left[\frac{\partial}{\partial \theta_h} Q' \right]^T \quad (44)$$

let's call $\pi_i \left[\frac{\partial}{\partial \theta_h} Q' \right]^T = C(\theta)$ is a matrix

$$\left[\frac{\partial}{\partial \theta_h} \pi \right] = -[Q']^{-1} C(\theta), \pi(\theta) = \begin{bmatrix} \pi_1 \\ \pi_2 \\ \pi_3 \\ \pi_4 \end{bmatrix} \text{ is a column vector}$$

$$C(\theta) = \pi(\theta) \left[\frac{\partial}{\partial \theta_h} Q' \right]^T = \begin{bmatrix} 0 \\ 0 \\ \pi_3 \\ 1 - \pi_3 \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 & 1 \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \pi_3 & \pi_3 & \pi_3 & \pi_3 & \pi_3 \\ 1 - \pi_3 & 1 - \pi_3 & 1 - \pi_3 & 1 - \pi_3 & 1 - \pi_3 \end{bmatrix}$$

$\pi(\theta) \left[\frac{\partial}{\partial \theta_h} Q' \right]^T = C(\theta)$ is a matrix of size (4×5)

$$Q' = \begin{bmatrix} -\gamma_1 & \mu_{21} & 0 & 0 \\ \lambda_{12} & -\gamma_2 & 0 & 0 \\ 0 & \lambda_{23} & 0 & 0 \\ \lambda_{14} & \lambda_{24} & 0 & 0 \end{bmatrix} \text{ is a singular matrix, thus}$$

$[Q']^{-1}$ obtained by pseudoinverse using SVD and resulting in 4 by 4 matrix

$$\text{let: } A(\theta) = \left[\frac{\partial}{\partial \theta_h} \pi_i \right] = -[Q']^{-1} C(\theta) = \begin{bmatrix} \frac{\partial \pi_1}{\partial \lambda_{12}} & \frac{\partial \pi_1}{\partial \lambda_{14}} & \frac{\partial \pi_1}{\partial \mu_{21}} & \frac{\partial \pi_1}{\partial \lambda_{23}} & \frac{\partial \pi_1}{\partial \lambda_{24}} \\ \frac{\partial \pi_2}{\partial \lambda_{12}} & \frac{\partial \pi_2}{\partial \lambda_{14}} & \frac{\partial \pi_2}{\partial \mu_{21}} & \frac{\partial \pi_2}{\partial \lambda_{23}} & \frac{\partial \pi_2}{\partial \lambda_{24}} \\ \frac{\partial \pi_3}{\partial \lambda_{12}} & \frac{\partial \pi_3}{\partial \lambda_{14}} & \frac{\partial \pi_3}{\partial \mu_{21}} & \frac{\partial \pi_3}{\partial \lambda_{23}} & \frac{\partial \pi_3}{\partial \lambda_{24}} \\ \frac{\partial \pi_4}{\partial \lambda_{12}} & \frac{\partial \pi_4}{\partial \lambda_{14}} & \frac{\partial \pi_4}{\partial \mu_{21}} & \frac{\partial \pi_4}{\partial \lambda_{23}} & \frac{\partial \pi_4}{\partial \lambda_{24}} \end{bmatrix} \text{ is 4 by 5 matrix}$$

$\left[\frac{\partial}{\partial \theta_h} \pi \right]$ this is a matrix that gives all derivatives of $\pi_1, \pi_2, \pi_3, \pi_4$ with respect to each $\lambda_{12}, \lambda_{14}, \mu_{21}, \lambda_{23}, \lambda_{24}$

Using multivariate delta method

$$\text{var}(\pi_i) = A(\theta) \text{var}(\theta) A(\theta)' \quad , \quad \text{where } \text{var}(\theta) = [M(\theta)]^{-1} \text{ and } i = 1, 2, 3, 4$$

4.5. Life Expectancy of Patient in NAFLD Disease Process:

The disease process is composed of state 1 and state 2 which are transient states, while state 3 and state 4 both are absorbing states. So partitioning the Q matrix into 4 sets in (45)

$$Q = \begin{bmatrix} -(\lambda_{12} + \lambda_{14}) & \lambda_{12} & 0 & \lambda_{14} \\ \mu_{21} & -(\mu_{21} + \lambda_{23} + \lambda_{24}) & \lambda_{23} & \lambda_{24} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} = \begin{bmatrix} B & A \\ 0 & 0 \end{bmatrix} \quad (45)$$

$$\text{Where } B = \begin{bmatrix} -(\lambda_{12} + \lambda_{14}) & \lambda_{12} \\ \mu_{21} & -(\mu_{21} + \lambda_{23} + \lambda_{24}) \end{bmatrix}, \quad A = \begin{bmatrix} 0 & \lambda_{14} \\ \lambda_{23} & \lambda_{24} \end{bmatrix}$$

$$A = BZ$$

$$\text{let } (\lambda_{12} + \lambda_{14}) = \gamma_1 \quad , \quad (\mu_{21} + \lambda_{23} + \lambda_{24}) = \gamma_2$$

$$\text{so } Z = \begin{bmatrix} \frac{\lambda_{12}\lambda_{23}}{\mu_{21}\lambda_{12} - \gamma_1\gamma_2} & \frac{\lambda_{12}(\mu_{21}\lambda_{14} + \lambda_{24}\gamma_1) - \lambda_{14}(\mu_{21}\lambda_{12} - \gamma_1\gamma_2)}{\gamma_1(\mu_{21}\lambda_{12} - \gamma_1\gamma_2)} \\ \frac{\gamma_1\lambda_{23}}{\mu_{21}\lambda_{12} - \gamma_1\gamma_2} & \frac{(\mu_{21}\lambda_{14} + \lambda_{24}\gamma_1)}{\mu_{21}\lambda_{12} - \gamma_1\gamma_2} \end{bmatrix}$$

$$\begin{bmatrix} \dot{P}(t) & \dot{P}_k(t) \end{bmatrix} = \begin{bmatrix} P(t) & P_k(t) \end{bmatrix} \begin{bmatrix} B & A \\ 0 & 0 \end{bmatrix} \text{ can be written in (4.46) and (4.47)}$$

$$\dot{P}(t) = P(t)B \quad (4.46)$$

$$\dot{P}_k(t) = P(t)A \quad (4.47)$$

The solution to (4.46) is $P(t) = P(0)e^{Bt}$ then $\dot{P}_k(t) = P(0)e^{Bt}A$

$$P_k(t) = A \frac{e^{Bt}}{B} \Big|_{t=0}^{t=t} = A \left[\frac{e^{Bt}}{B} - \frac{1}{B} \right] = \frac{A}{B} [e^{Bt} - 1] = \frac{BZ}{B} [e^{Bt} - 1] = Z[e^{Bt} - 1]$$

$$\text{and } e^{Bt} = 1 + Bt + \frac{(Bt)^2}{2!} + \frac{(Bt)^3}{3!} + \frac{(Bt)^4}{4!} + \dots = \sum_{j=0}^{\infty} \frac{(Bt)^j}{j!}$$

If τ_k is the time taken from state i to reach the absorbing death state from the initial time

$$F_k(t) = pr[\tau_k \leq t] = pr[X(t) = k] = P_k(t) = Z[e^{Bt} - 1]$$

The moment theory for the Laplace transform can be used to obtain the mean of the time which has the above cumulative distribution function.

CTMC can be written in a Laplace transform in (48):

$$[sP^*(s) - P(0) \quad sP_k^*(s)] = [P^*(s) \quad P_k^*(s)] \begin{bmatrix} B & A \\ 0 & 0 \end{bmatrix} \quad (48)$$

$$\therefore sP^*(s) - P(0) = P^*(s)B$$

$$\therefore sP_k^*(s) = P^*(s)A$$

Rearrange :

$$\therefore sP^*(s) - P^*(s)B = P(0)$$

$$P^*(s) [sI - B] = P(0) \rightarrow P^*(s) = P(0)[sI - B]^{-1}$$

$$\therefore sP_k^*(s) = P^*(s)A \rightarrow P_k^*(s) = \frac{1}{s} P^*(s)A = \frac{1}{s} P(0)[sI - B]^{-1}A$$

$$F_k^*(s) = \frac{1}{s} P(0)[sI - B]^{-1}A$$

$$f_k^*(s) = sF_k^*(s) = P(0)[sI - B]^{-1}A \quad ; \quad \text{where } A = BZ$$

Mean time to absorption:

$$E(\tau_k) = (-1) \frac{df_k^*(s)}{ds} \Big|_{s=0} = P(0)[sI - B]^{-2} A|_{s=0} = P(0)[B]^{-1} Z = [B]^{-1} Z$$

$E(\tau_k) = [B]^{-1} Z$ solving this equation:

$$E(\tau_{ik}) = \begin{bmatrix} \frac{-\gamma_2}{\gamma_1\gamma_2 - \mu_{21}\lambda_{12}} & \frac{-\lambda_{12}}{\gamma_1\gamma_2 - \mu_{21}\lambda_{12}} \\ \frac{-\mu_{21}}{\gamma_1\gamma_2 - \mu_{21}\lambda_{12}} & \frac{-\gamma_1}{\gamma_1\gamma_2 - \mu_{21}\lambda_{12}} \end{bmatrix} \begin{bmatrix} \frac{\lambda_{12}\lambda_{23}}{\mu_{21}\lambda_{12} - \gamma_1\gamma_2} & \frac{\lambda_{12}(\mu_{21}\lambda_{14} + \lambda_{24}\gamma_1) - \lambda_{14}(\mu_{21}\lambda_{12} - \gamma_1\gamma_2)}{\gamma_1(\mu_{21}\lambda_{12} - \gamma_1\gamma_2)} \\ \frac{\gamma_1\lambda_{23}}{\mu_{21}\lambda_{12} - \gamma_1\gamma_2} & \frac{(\mu_{21}\lambda_{14} + \lambda_{24}\gamma_1)}{\mu_{21}\lambda_{12} - \gamma_1\gamma_2} \end{bmatrix}$$

$$E(\tau_{13}) = \frac{\lambda_{12}\lambda_{23}(\gamma_1 + \gamma_2)}{(\gamma_1\gamma_2 - \mu_{21}\lambda_{12})^2}$$

$$E(\tau_{14}) = \frac{\lambda_{12}(\mu_{21}\lambda_{14} + \lambda_{24}\gamma_1)(\gamma_1 + \gamma_2)}{\gamma_1(\gamma_1\gamma_2 - \mu_{21}\lambda_{12})^2} + \frac{\lambda_{14}\gamma_2}{\gamma_1(\gamma_1\gamma_2 - \mu_{21}\lambda_{12})}$$

$$E(\tau_{23}) = \frac{\lambda_{23}(\mu_{21}\lambda_{12} + \gamma_1^2)}{(\gamma_1\gamma_2 - \mu_{21}\lambda_{12})^2}$$

$$E(\tau_{24}) = \frac{(\mu_{21}\lambda_{14} + \lambda_{24}\gamma_1)(\mu_{21}\lambda_{12} + \gamma_1^2)}{\gamma_1(\gamma_1\gamma_2 - \mu_{21}\lambda_{12})^2} + \frac{\mu_{21}\lambda_{14}}{\gamma_1(\gamma_1\gamma_2 - \mu_{21}\lambda_{12})}$$

4.6. Expected Number of Patients in Each State

Let $u(0)$ be the size of patients in a specific state at specific time $t = 0$. The initial size of patients $u(0) = \sum_{j=1}^2 u_j(0)$, as there are 2 transient states and 2 absorbing states, where $u_j(0)$ is the initial size or number of patients in state j at time $t = 0$ given that $u_3(0) = 0$ and $u_4(0) = 0$ i.e initial size of patients in state 3 and state 4 (both are absorbing death state) are zero at initial time point $t = 0$. As the transition or the movement of the patients among states are independent so at the end of the whole time interval $(0, t)$ and according to (Chiang, 1968), there will be $u_j(t)$ patients in state 1 and in state 2 at time t , also there will be $u_3(t)$ patients in state 3 (death state) at time t and $u_4(t)$ patients in state 4 (death state) at time t , as shown in (49).

$$E[u_j(t)|u_j(0)] = \sum_{j=1, i=1}^4 u_j(0)P_{ij}(t), \quad i \& j = 1, 2, 3, 4 \quad (49)$$

$$E[u_j(t)|u_j(0)] = \begin{bmatrix} u_1(0) & u_2(0) & 0 & 0 \end{bmatrix} \begin{bmatrix} P_{11} & P_{12} & P_{13} & P_{14} \\ P_{21} & P_{22} & P_{23} & P_{24} \\ 0 & 0 & P_{33} & 0 \\ 0 & 0 & 0 & P_{44} \end{bmatrix} = \begin{bmatrix} u_1(t) & u_2(t) & u_3(t) & u_4(t) \end{bmatrix}$$

$$u_1(t) = u_1(0)P_{11} + u_2(0)P_{21}, \quad u_2(t) = u_1(0)P_{12} + u_2(0)P_{22}, \quad u_3(t) = u_1(0)P_{13} + u_2(0)P_{23}, \quad u_4(t) = u_1(0)P_{14} + u_2(0)P_{24}$$

4.7. Hypothetical Numerical Example

To illustrate the above concepts and discussion, a hypothetical numerical example is introduced. It does not represent real data but it is for demonstrative purposes.

A study was conducted over 8 years on 310 patients with risk factors for developing NAFLD such as type 2 diabetes mellitus, obesity, and hypertension acting alone or together as a metabolic syndrome. The patients were decided to be followed up every year by a liver biopsy to identify the NAFLD cases, but the actual observations were recorded as shown in the Table (6). The following 5 successive Tables (1), (2), (3), (4), (5) illustrate a summary for counts of transitions in the whole period of study and in various lengths of time intervals:

Table (1) demonstrates Numbers of observed transitions among states of NAFLD process during different time intervals $\Delta t = 1, 2, 3$ years

Δt	Transitions among states							
	(1,1)	(1,2)	(1,3)	(1,4)	(2,1)	(2,2)	(2,3)	(2,4)
1	330	163	45	12	5	185	45	15
2	70	30	10	1	2	20	13	4
3	21	8	7	3	1	6	3	1
	421	201	62	16	8	211	61	20

Table (2) demonstrates total counts of transitions throughout whole period of the study (8 years)

	State 1	State 2	State 3	State 4	Total counts
State 1	421	201	62	16	700
State 2	8	211	61	20	300
State 3	0	0	0	0	0
State 4	0	0	0	0	0
Total	429	412	123	36	1000

Table (3) demonstrates the observed counts of transitions during time interval $\Delta t = 1$ year

	State 1	State 2	State 3	State 4	Total counts
State 1	330	163	45	12	550
State 2	5	185	45	15	250
State 3	0	0	0	0	0
State 4	0	0	0	0	0
Total	335	348	90	27	800

Table (4) demonstrates the observed counts of transitions during time interval $\Delta t = 2$ years

	State 1	State 2	State 3	State 4	Total counts
State 1	70	30	10	1	111
State 2	2	20	13	4	39
State 3	0	0	0	0	0
State 4	0	0	0	0	0
Total	72	50	23	5	150

Table (5) demonstrates the observed counts of transitions during time interval $\Delta t = 3$ years

	State 1	State 2	State 3	State 4	Total counts
State 1	21	8	7	3	39
State 2	1	6	3	1	11
State 3	0	0	0	0	0
State 4	0	0	0	0	0
Total	22	14	10	4	50

The next table (6) demonstrates the layout of the data for the persons studied over the 8 years:

Patient ID	time									Patient ID										
	0	1	2	3	4	5	6	7	8		0	1	2	3	4	5	6	7	8	
1	1	1	2	2						53	1	1	1	2	2	4				
2	1	1	2	1		2		1		54	1		2		2					
3	1	3								55	1		2		2					
4	1	1	1	1						56	1	1	1	1	2	2	4			
5	1	2	1		2		2			57	1		2		2					
6	1	2	1		2		2			58	1	1	1	1	1	1	2	2	4	
7	1	2	1		2		2			59	1	2	2		2					
8	1	3								60	1	1	1	1	3					
9	1	1	1	2	2	4				61	1	3								
10	1	3								62	1	1	1	2	2	4				
11	1	1	1	2	1					63	1	1	1	1	1	2	2		2	
12	1	3								64	1	1	2	2		2		2		
13	1	1	1							65	1	1	1	1	2	2		2		
14	1	3								66	1	1	2	2		2				
15	1	1	1	1	1					67	1	1	1	1	2	2		2		
16	1	1	1	1	1	1	1	1	2	68	1	2	2		2					
17	1	1	2	2	4					69	1	2	2	4						
18	1	1	1	1	2					70	1	1		1		1		1		
19	1	1	1	1	1		2		1	71	1	1	1	1		1		1		
20	1	1	1	1	1	1	1			72	1	1	1	1	1	1	2	2		
21	1	1								73	1	2	2		2					
22	1	1	2	2	4					74	1	2	2		2					
23	1	3								75	1	1	1	3						
24	1	3								76	1	1	1	3						
25	1	3								77	1	2	2	2	2	2	2		2	
26	1	3								78	1	1	1		1		1		1	
27	1	3								79	1	1	1	1	2	2	2	2		
28	1	1	2	2	4					80	1	3								
29	1	4								81	1	3								
30	1	4								82	1	1	1	2	2					
31	1	4								83	1	1	1	1	1	2	2		2	
32	1	1	2	2	4					84	1	1	1	1	1	2	2			
33	1	2	2	4						85	1	2	2	2	2	2	2		3	
34	1	2	2		2					86	1	2	2	4						
35	1	2	2		2					87	1		1		1		1		1	
36	1	3								88	1		1		1		1		1	
37	1	3								89	1		1		1		1		1	
38	1	1	2	2	4					90	1	1	1	1	2	2		3		
39	1	4								91	1	1	1	1	1	2	2		3	
40	1	4								92	1		1		1		1		1	
41	1	4								93	1		1		1		1		1	
42	1	1	1	2	2	4				94	1	1	1	3						
43	1	4								95	1	1	1	1	2	2		3		
44	1	4								96	1	1	1	1	3					
45	1	4								97	1	1	1	1	1		1		1	
46	1	1	3							98	1	2	2		3					
47	1	4								99	1	1	1	2	2		3			
48	1	4								100	1	1	1	2	2		3			
49	1	1	1	1	1	2	2	4		101	1	1	1	1	2	2		3		
50	1	1	1	1	1	1	2	2		102	1	2	2		3					
51	1	3								103	1	1	1	3						
52	1	3								104	1	1	1	3						

Patient ID	time									Patient ID	time								
	0	1	2	3	4	5	6	7	8		0	1	2	3	4	5	6	7	8
105	1	1	1	3						157	1	1	1	1	1	2	2	3	
106	1	3								158	1	2	2	3					
107	1	1	1	1	1	2	2		3	159	1	2	2						
108	1		1		1		1		1	160	1	1	1	2	2	3			
109	1	1	1	1	2	2		3		161	1	1	1	2	2	3			
110	1	1	1	1	1	3				162	1	1	1	1	1	2	2	3	
111	1	2	2		3					163	1	2	2						
112	1	1	1	1	3					164	1	1	1	2	2				
113	1	2	2		3					165	1	2	2						
114	1	1	1	3						166	1	1	1	2	2	3			
115	1	1	1	3						167	1	2	2						
116	1	2	2		4					168	1	1	1	1	1	1			
117	1	1	1	3						169	1	2	2	2	3				
118	1	1	1	1		1		1		170	1	2	2	2					
119	1	1	1	1	1	2	2			171	1	1	2	2	3				
120	1		1		1		1		1	172	1	2	2	2	2	2			
121	1	1	1		1		1		1	173	1	2	2	3					
122	1	1	1	1	3					174	1	2	2						
123	1	1	1	1	1	1		2		175	1	1	2	2	2	2			
124	1	1	1	1	1	1	2	2		176	1	2	2						
125	1	2	2		4					177	1	2	2	2	2	2			
126	1	2	2		4					178	1	2	2	3					
127	1	1	1	1	1	2	2		4	179	1	1	1	2	2				
128	1	1	1	1	1	2	2			180	1	2	2	2	2	3			
129	1	1	2	2	3					181	1	2	2	3					
130	1	2	2							182	1	3							
131	1	1	1	3						183	1	3							
132	1	2	2							184	1	1	1	1	1	2	2	2	
133	1	1	1	1		1		1		185	1	2	2	2	2	3			
134	1	2	2							186	1	2	2						
135	1	2	2							187	1	1	1	1	2	2	2	2	
136	1	1	1	2	2	3				188	1	2	2						
137	1	2	2							189	1	1	1	2	2	3			
138	1	2	2	2	2	2				190	1	1	1	1	2	2	3		
139	1	1	1	1	1					191	1	2	2	2	3				
140	1	2	2	2	2	2				192	1	2	2						
141	1	1	1	1	1	1	1	2	2	193	1	1	2	2					
142	1		1		1		1		1	194	1	2	2						
143	1	1	1	1	1	3				195	1	1	1	1	2	2	3		
144	1		1		1		1		1	196	1	2	2						
145	1	1	1	2	2	2	2	3		197	1	2	2						
146	1		1							198	1	1	1	2	2	3			
147	1	1	1	2	2	2	2	3		199	1	2	2						
148	1		1		1		1		1	200	1	1	1	2	2	3			
149	1	1	1	1	1	2	2			201	1	2	2						
150	1		1		1		1		1	202	1	1	1	1	3				
151	1		1		1		1		1	203	1	2	2						
152	1	1	1	1	2	2	3			204	1	1	1	1	1	1	3		
153	1	3								205	1	2	2						
154	1	2	2	3						206	1	1	1	1	2	2	3		
155	1	2	2	3						207	1	2	2						
156	1		1		1		1		1	208	1	1	1	1	1	1	1		

Patient ID	time									Patient ID	time								
	0	1	2	3	4	5	6	7	8		0	1	2	3	4	5	6	7	8
209	1	2	2	3						261	1		2			2			
210	1	2	2							262	1		2						
211	1	1	1	1	2	2				263	1		2						
212	1	2	2	3						264	1		2			2			
213	1	1	1	2	2	3				265	1		2						
214	1	2	2							266	1		2						
215	1	1	1	1	2	2	3			267	1		2						
216	1	2	2	3						268	1		2			2			
217	1	2	2	3						269	1		2						
218	1	2	2							270	1		2						
219	1	2	2							271	1		2						
220	1	1	1	2	2	3				272	1		2						
221	1	1	1	1	1	2	2	3		273	1		2						
222	1	2	2	3						274	1		2						
223	1	2	2	3						275	1		2						
224	1	1	2	2	3					276	1		3						
225	1	3								277	1		3						
226	1	1	1	2	2	3				278	1		3						
227	1	3								279	1		3						
228	1	1	1	1	1	2	2	3		280	1		3						
229	1	2	2	3						281	1		3						
230	1	3								282	1		3						
231	1	1	1	1	1	2	2			283	1		3						
232	1	2	2							284	1		3						
233	1	1	1	1	1	1	1	3		285	1		3						
234	1	2	2	3						286	1		4						
235	1	2	2							287	1			1					
236	1	1	1	1	3					288	1			1					
237	1	2	2							289	1			1			1		
238	1	1	1	2	2	3				290	1			1			2		
239	1	2	2							291	1			1			2		
240	1	1	1	1	1	2	2			292	1			1			3		
241	1	2	2							293	1			1			1		
242	1	1	2	2	3					294	1			1			3		
243	1	2	2							295	1			1			2		
244	1	2	2							296	1			1			3		
245	1	1	2			1	1			297	1			1			1		
246	1	2								298	1			1			2		
247	1	1	2	3						299	1			1			3		
248	1	2								300	1			1			1		
249	1	1	2			4				301	1			1			2		
250	1	2			3					302	1			1			3		
251	1	2								303	1			1			3		
252	1	2			3					304	1			2					
253	1	2			3					305	1			2					
254	1	4								306	1			2					
255	1		2			2				307	1			3					
256	1		2			2				308	1			4					
257	1		2			2				309	1			4					
258	1		2							310	1			4					
259	1		2																
260	1		2																

Steps to obtain the statistical indices:

1- Step one: Use the count table in each interval to get estimated rates and variance-covariance matrix in each interval.

Analyzing the rates in first interval $\Delta t = 1$ and the same procedures are repeated for $\Delta t = 2, 3$

$$\rho_3 = -.37443, \quad \rho_4 = -.20757$$

$$\begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix} = \begin{bmatrix} -.7120 \\ -.7269 \\ -.5488 \\ -.7733 \\ -.7733 \end{bmatrix}, \rightarrow 4(550) + 4(250) \begin{bmatrix} -.7120 \\ -.7269 \\ -.5488 \\ -.7733 \\ -.7733 \end{bmatrix} = 1 \times 10^3 \begin{bmatrix} -.22782 \\ -.23261 \\ -.17562 \\ -.24746 \\ -.24746 \end{bmatrix} = \text{scaled } S(\theta)$$

$$\text{scaled } S(\theta) [\text{scaled } S(\theta)]^T = M(\theta)$$

$$M(\theta) = 1 \times 10^6 \begin{bmatrix} 5.1904 & 5.2992 & 4.0010 & 5.6378 & 5.6378 \\ 5.2995 & 5.4109 & 4.0851 & 5.7563 & 5.7563 \\ 4.001 & 4.0851 & 3.0841 & 4.3459 & 4.3459 \\ 5.6378 & 5.7563 & 4.3459 & 6.1237 & 6.1237 \\ 5.6378 & 5.7563 & 4.3459 & 6.1237 & 6.1237 \end{bmatrix}$$

$$M(\theta) \text{ is multiplied by } \left(\frac{550^2}{330} + \frac{550^2}{163} + \frac{550^2}{45} + \frac{550^2}{12} + \frac{250^2}{5} + \frac{250^2}{185} + \frac{250^2}{45} + \frac{250^2}{15} \right) = 53096.45 \cong 53096$$

$$\text{scaled } M(\theta) = 1 \times 10^{11} \begin{bmatrix} 2.7559 & 2.8138 & 2.1244 & 2.9934 & 2.9934 \\ 2.8138 & 2.8730 & 2.1690 & 3.0564 & 3.0564 \\ 2.1244 & 2.1690 & 1.6376 & 2.3075 & 2.3075 \\ 2.9934 & 3.0564 & 2.3075 & 3.2515 & 3.2515 \\ 2.9934 & 3.0564 & 2.3075 & 3.2515 & 3.2515 \end{bmatrix}$$

$$[\text{scaled } M(\theta)]^{-1} = 1 \times 10^{-12} \begin{bmatrix} .1454 & .1484 & .1120 & .1579 & .1579 \\ .1484 & .1515 & .1144 & .1612 & .1612 \\ .1120 & .1144 & .0864 & .1217 & .1217 \\ .1579 & .1612 & .1217 & .1715 & .1715 \\ .1579 & .1612 & .1217 & .1715 & .1715 \end{bmatrix}$$

$$[\text{scaled } M(\theta)]^{-1} \times \text{scaled } S(\theta) = [\text{scaled } M(\theta)]^{-1} \times \text{scaled } S(\theta)$$

$$\theta_1 = \theta_0 + [\text{scaled } M(\theta)]^{-1} \text{scaled } S(\theta) = \begin{bmatrix} .3 \\ .022 \\ .02 \\ .18 \\ .06 \end{bmatrix}$$

Repeating this procedure for $\Delta t = 2$ and $\Delta t = 3$ will give the following vectors respectively (substitute for $t=2$ and $t=3$ in their intervals):

$$\text{for } \Delta t = 2 \rightarrow \hat{\theta} = \begin{bmatrix} .27 \\ .009 \\ .05 \\ .333 \\ .103 \end{bmatrix} \text{ obtained in the first iteration with a difference from the initial values} = 10^{-7} \begin{bmatrix} -.3034 \\ -.33 \\ -.0759 \\ -.2198 \\ -.2198 \end{bmatrix}$$

$$\text{for } \Delta t = 3 \rightarrow \hat{\theta} = \begin{bmatrix} .205 \\ .077 \\ .091 \\ .273 \\ .091 \end{bmatrix} \text{ obtained in first iteration with a difference from the initial values} = 10^{-5} \begin{bmatrix} -.093 \\ -.1168 \\ -.0177 \\ -.0715 \\ -.0715 \end{bmatrix}$$

As noted from this procedure in all time intervals, the initial values are almost the estimated values regardless of the interval.

2-step two: get final rate and variance-covariance matrix

The estimated rate vector in each interval is weighted according to the contribution of the counts of transitions in this interval to the whole number of transitions (1000 transitions) and summed; this will give the final rate vector:

$$(.8) \begin{bmatrix} .3 \\ .022 \\ .02 \\ .18 \\ .06 \end{bmatrix} + (.15) \begin{bmatrix} .27 \\ .009 \\ .05 \\ .333 \\ .103 \end{bmatrix} + (.05) \begin{bmatrix} .205 \\ .077 \\ .091 \\ .273 \\ .091 \end{bmatrix} = \begin{bmatrix} .2907 \\ .0228 \\ .0280 \\ .2076 \\ .068 \end{bmatrix}$$

$$\text{The estimated final } Q \text{ matrix} = \hat{Q} = \begin{bmatrix} -0.3135 & 0.2907 & 0.0 & 0.0228 \\ 0.0280 & -0.3036 & 0.2076 & 0.068 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

For this $\hat{Q}$ matrix : $w1 = -0.3989$ and $w2 = -0.2182$

For this $\hat{Q}$ matrix : the eigenvalues are $\{-0.3989, -0.2182, 0, 0\}$

Also the weighted sum of the inversed scaled hessian matrix should be used as the variance -covariance matrix of parameter θ

$$[\text{scaled } M(\theta)]^{-1} = 1 \times 10^{-10} \begin{bmatrix} .5788 & .7237 & .1116 & .4440 & .4440 \\ .7237 & .9055 & .1394 & .5554 & .5554 \\ .1116 & .1394 & .0216 & .0856 & .0856 \\ .4440 & .5554 & .0856 & .3407 & .3407 \\ .4440 & .5554 & .0856 & .3407 & .3407 \end{bmatrix}$$

3-step three: Calculating the Mean Sojourn Time and its Variance:

$$E(s_1) = \frac{1}{\lambda_{12} + \lambda_{14}} = \frac{1}{.2907 + .0228} = 3.1898 \text{ year, average time spent in susceptible state is about 3 years}$$

$$E(s_2) = \frac{1}{\mu_{21} + \lambda_{23} + \lambda_{24}} = \frac{1}{.0280 + .2076 + .068} = 3.2938 \text{ year, average time spent in susceptible state is about 3 years}$$

$$\text{var}(s_1) = \frac{1}{(.2907 + .0228)^4} [-1 \quad -1 \quad -1 \quad -1 \quad -1] [M(\theta)]^{-1} |_{\theta=\hat{\theta}} \begin{bmatrix} -1 \\ -1 \\ -1 \\ -1 \\ -1 \end{bmatrix} = 9.4815 \times 10^{-8}$$

$$\text{var}(s_2) = \frac{1}{(.02805 + .2076 + .068)^4} [-1 \quad -1 \quad -1 \quad -1 \quad -1] [M(\theta)]^{-1} |_{\theta=\hat{\theta}} \begin{bmatrix} -1 \\ -1 \\ -1 \\ -1 \\ -1 \end{bmatrix} = 1.0780 \times 10^{-7}$$

observed counts of transitions during time interval $\Delta t=1$					
	state 1	state 2	state 3	state 4	total
state 1	330	163	45	12	550
state 2	5	185	45	15	250
state 3	0	0	0	0	0
state 4	0	0	0	0	0
initial rates			initial Q matrix		
lambda12	0.3		-0.322	0.3	0
lambda14	0.022		0.02	-0.26	0.18
mu21	0.02		0	0	0
lambda23	0.18		0	0	0
lambda24	0.06				
step 1: calculate eigenvalues for the above initial Q matrix $\Delta t=1$:					
	-0.3744				
	-0.2076				
step 2: calculate $t \cdot e^{(\text{eigenvalue} \cdot t)}$ * partial differentiation of eigenvalue with respect to specific theta or rate					
	-0.712				
	-0.7269				
	-0.5488				
	-0.7733				
	-0.7733				
step 3: scale the above score function by a factor equals $4(550)+4(250)=3200$					
	-2278.244				
	-2326.141				
	-1756.172				
	-2474.62				
	-2474.62				
step 4: multiply the scaled score function with the transposed scaled score function to get the hessian matrix					
1.0e+06 *	5.1904	5.2995	4.001	5.6378	5.6378
	5.2995	5.4109	4.0851	5.7563	5.7563
	4.001	4.0851	3.0841	4.3459	4.3459
	5.6378	5.7563	4.3459	6.1237	6.1237
	5.6378	5.7563	4.3459	6.1237	6.1237
step 5: scale the above hessian matrix by a factor equals $53096.45 \approx 53096$					
1.0e+11 *	2.7559	2.8138	2.1244	2.9934	2.9934
	2.8138	2.873	2.169	3.0564	3.0564
	2.1244	2.169	1.6376	2.3075	2.3075
	2.9934	3.0564	2.3075	3.2515	3.2515
	2.9934	3.0564	2.3075	3.2515	3.2515
step 6: invert the scaled hessian matrix					
1.0e-12 *	0.1454	0.1484	0.112	0.1579	0.1579
	0.1484	0.1515	0.1144	0.1612	0.1612
	0.112	0.1144	0.0864	0.1217	0.1217
	0.1579	0.1612	0.1217	0.1715	0.1715
	0.1579	0.1612	0.1217	0.1715	0.1715
step 7: multiply the inverted scaled hessian matrix with the scaled score function					
1.0e-08 *	-0.1655				
	-0.1689				
	-0.1275				
	-0.1797				
	-0.1797				
step 8: apply the Quasi-Newton formula(add the vector of initial rate values with the above calculated vector)					
	0.3				
	0.022				
	0.02				
	0.18				
	0.06				

observed counts of transitions during time interval $\Delta t=2$					
	state 1	state 2	state 3	state 4	total
state 1	70	30	10	1	111
state 2	2	20	13	4	39
state 3	0	0	0	0	0
state 4	0	0	0	0	0
initial rates		initial Q matrix			
lambda12	0.27	-0.279	0.27	0	0.009
lambda14	0.009	0.05	-0.486	0.333	0.103
mu21	0.05	0	0	0	0
lambda23	0.333	0	0	0	0
lambda24	0.103				
step 1: calculate eigenvalues for the above initial Q matrix $\Delta t=2$:					
	-0.2269				
	-0.5381				
step 2: calculate $t \cdot e^{(\text{eigenvalue} \cdot t)}$ partial differentiation of eigenvalue with respect to specific theta or rate					
	-1.0773				
	-1.1719				
	-0.2696				
	-0.7803				
	-0.7803				
step 3: scale the above score function by a factor equals $4(111)+4(39)=600$					
	-646.3779				
	-703.1237				
	-161.7689				
	-468.1962				
	-468.1962				
step 4: multiply the scaled score function with the transposed scaled score function to get the hessian matrix					
1.0e+05 *	4.178	4.5448	1.0456	3.0263	3.0263
	4.5448	4.9438	1.1374	3.292	3.292
	1.0456	1.1374	0.2617	0.7574	0.7574
	3.0263	3.292	0.7574	2.1921	2.1921
	3.0263	3.292	0.7574	2.1921	2.1921
step 5: scale the above hessian matrix by a factor equals 15476.614					
1.0e+09 *	6.4651	7.0327	1.618	4.6829	4.6829
	7.0327	7.6501	1.7601	5.094	5.094
	1.618	1.7601	0.4049	1.172	1.172
	4.6829	5.094	1.172	3.392	3.392
	4.6829	5.094	1.172	3.392	3.392
step 6: invert the scaled hessian matrix					
1.0e-10 *	0.1424	0.155	0.0356	0.1032	0.1032
	0.155	0.1686	0.0388	0.1122	0.1122
	0.0356	0.0388	0.0089	0.0258	0.0258
	0.1032	0.1122	0.0258	0.0747	0.0747
	0.1032	0.1122	0.0258	0.0747	0.0747
step 7: multiply the inverted scaled hessian matrix with the scaled score function					
1.0e-07 *	-0.3034				
	-0.33				
	-0.0759				
	-0.2198				
	-0.2198				
step 8: apply the Quasi-Newton formula(add the vector of initial rate values with the above calculated vector)					
	0.27				
	0.009				
	0.05				
	0.333				
	0.103				

observed counts of transitions during time interval $\Delta t=3$					
	state 1	state 2	state 3	state 4	total
state 1	21	8	7	3	39
state 2	1	6	3	1	11
state 3	0	0	0	0	0
state 4	0	0	0	0	0
first iteration :					
initial rates		initial Q matrix			
lambda12	0.205	-0.282	0.205	0	0.077
lambda14	0.077	0.091	-0.455	0.273	0.091
mu21	0.091	0	0	0	0
lambda23	0.273	0	0	0	0
lambda24	0.091				
step 1: calculate eigenvalues for the above initial Q matrix $\Delta t=3$:					
	-0.2068				
	-0.5302				
step 2 : calculate $t \cdot e^{(\text{eigenvalue} \cdot t)}$ * partial differentiation of eigenvalue with respect to specific theta or rate					
	-1.0983				
	-1.3802				
	-0.2093				
	-0.8443				
	-0.8443				
step 3 : scale the above score function by a factor equals $4(39)+4(11)=200$					
	-219.663				
	-276.039				
	-41.8608				
	-168.862				
	-168.862				
step 4 : multiply the scaled score function with the transposed scaled score function to get the hessian matrix					
1.0e+04 *	4.8252	6.0636	0.9195	3.7093	3.7093
	6.0636	7.6198	1.1555	4.6613	4.6613
	0.9195	1.1555	0.1752	0.7069	0.7069
	3.7093	4.6613	0.7069	2.8514	2.8514
	3.7093	4.6613	0.7069	2.8514	2.8514
step 5 : scale the above hessian matrix by a factor equals 1289.338					
1.0e+07 *	6.2213	7.818	1.1856	4.7825	4.7825
	7.818	9.8245	1.4899	6.0099	6.0099
	1.1856	1.4899	0.2259	0.9114	0.9114
	4.7825	6.0099	0.9114	3.6765	3.6765
	4.7825	6.0099	0.9114	3.6765	3.6765
step 6 : invert the scaled hessian matrix					
1.0e-08 *	0.1115	0.1401	0.0212	0.0857	0.0857
	0.1401	0.176	0.0267	0.1077	0.1077
	0.0212	0.0267	0.004	0.0163	0.0163
	0.0857	0.1077	0.0163	0.0659	0.0659
	0.0857	0.1077	0.0163	0.0659	0.0659
step 7 : multiply the inverted scaled hessian matrix with the scaled score function					
1.0e-05 *	-0.093				
	-0.1168				
	-0.0177				
	-0.0715				
	-0.0715				
step 8 : apply the Quasi-Newton formula(add the vector of initial rate values with the above calculated vector)					
	0.205				
	0.077				
	0.091				
	0.273				
	0.091				

4-step four: State Probability Distribution and expected number of patients at specific time point

Once the rate matrix is obtained, these estimated rates are substituted into the calculated PDFs' from the solved differential equations to get the state probability distribution at any point in time as well as the expected number of patients.

Studying a cohort of 3000 patients with the initial distribution $[.7 \ .3 \ 0 \ 0]$, and initial numbers of patients in each state are $[2100 \ 900 \ 0 \ 0]$.

At 1 year the state probability distribution is approximately:

$$P(1) = [.7 \ .3 \ 0 \ 0] \begin{bmatrix} .7339 & .2138 & .0246 & .0277 \\ .0206 & .7412 & .1793 & .0590 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} = [.5199 \ .3720 \ .0710 \ .0371]$$

And the expected numbers of patients in each state is:

$$[2100 \ 900 \ 0 \ 0] \begin{bmatrix} .7339 & .2138 & .0246 & .0277 \\ .0206 & .7412 & .1793 & .0590 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} = [1559 \ 1117 \ 214 \ 110]$$

At 20 years the state probability distribution is approximately:

$$P(20) = [.7 \ .3 \ 0 \ 0] \begin{bmatrix} .0062 & .0199 & .6742 & .2997 \\ .0019 & .0069 & .7413 & .2499 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} = [.0049 \ .0160 \ .6943 \ .2848]$$

And the expected numbers of patients in each state is:

$$[2100 \ 900 \ 0 \ 0] \begin{bmatrix} .0062 & .0199 & .6742 & .2997 \\ .0019 & .0069 & .7413 & .2499 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} = [15 \ 45 \ 2085 \ 855]$$

At 60 years the state probability distribution is approximately:

$$P(60) = [.7 \ .3 \ 0 \ 0] \begin{bmatrix} 0 & 0 & .7 & .3 \\ 0 & 0 & .75 & .25 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} = [0 \ 0 \ .7097 \ .2903]$$

And the expected numbers of patients in each state is:

$$[2100 \ 900 \ 0 \ 0] \begin{bmatrix} 0 & 0 & .7 & .3 \\ 0 & 0 & .75 & .25 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} = [0 \ 0 \ 2145 \ 855]$$

Asymptotic Covariance of the Stationary Distribution : At 60 years the state probability distribution is $[0 \ 0 \ .7097 \ .2903]$, so to calculate the asymptotic covariance of the stationary distribution follow the upcoming steps:

to calculate the asymptotic covariance matrix of the state distribution at specified time point:

step 1 : calculate the state distribution at the prespecified time point :

for this model calculate the probability transition matrix at 60 years:it is approximately

0	0	0.7	0.3
0	0	0.75	0.25
0	0	1	0
0	0	0	1

for a cohort of 3000 patients with 2100 susceptible and 900 affected patients

the initial probability distribution vector is (.7 , .3 , 0 , 0)

multiplying this initial vector with the pdf at this specific time point

the result is this vector (0 , 0 , .7 , .3) which is the state probability distribution at 60 years

0
0
0.7
0.3

step 2 : partially differentiate the transposed rate matrix with respect to each lambda

the result is a vector of five ones (1 , 1 , 1 , 1 , 1)

1	1	1	1	1
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step 3 : multiply the column vector of state probability distribution with the row vector of ones

the result is a matrix, let it be C (Θ) :

0	0	0	0	0
0	0	0	0	0
0.7	0.7	0.7	0.7	0.7
0.3	0.3	0.3	0.3	0.3

step 4 : calculate the pseudoinverse of transposed rate matrix (final estimated rate matrix)

-2.4852	0.7142	1.1891	0.5819
-1.4878	-1.6733	2.2828	0.8783
0	0	0	0
0	0	0	0

then multiply this matrix by -1 to obtain

2.4842	-0.7142	-1.1891	-0.5819
1.4878	1.6733	-2.2828	-0.8783
0	0	0	0
0	0	0	0

step 5 : multiply the matrices from step 3 and step 4 to obtain A(Θ) matrix :

2.4842	-0.7142	-1.1891	-0.5819	0	0	0	0	0
1.4878	1.6733	-2.2828	-0.8783	0	0	0	0	0
0	0	0	0	0.7	0.7	0.7	0.7	0.7
0	0	0	0	0.3	0.3	0.3	0.3	0.3

the result is A(Θ) matrix

-1.0128	-1.0128	-1.0128	-1.0128	-1.0128
-1.875	-1.875	-1.875	-1.875	-1.875
0	0	0	0	0
0	0	0	0	0

step 6 : multiply (A) matrix with inversed hessian matrix (M) with the transposed of (A) matrix :

to obtain the asymptotic covariance matrix :

1.0e-08 *	0.0939	0.1739
	0.1739	0.322

$C(\theta)$ matrix is calculated as in the following steps:

$$C(\theta) = \pi(\theta) \left[\frac{\partial}{\partial \theta_h} Q' \right]^T = \begin{bmatrix} 0 \\ 0 \\ 0.7 \\ 0.3 \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 & 1 \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0.7 & 0.7 & 0.7 & 0.7 & 0.7 \\ 0.3 & 0.3 & 0.3 & 0.3 & 0.3 \end{bmatrix}$$

Then $\left[\frac{\partial}{\partial \theta_h} \pi \right] = -[Q']^{-1} C(\theta)$, $-[Q']^{-1}$ is calculated taking into account that Q' is a singular matrix and its inverse (the pseudoinverse) is obtained via singular value decomposition (SVD).

$$[Q']^+ = \begin{bmatrix} -2.4852 & 0.7142 & 1.1891 & 0.5819 \\ -1.4878 & -1.6733 & 2.2828 & 0.8783 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$A(\theta) = -[Q']^+ C(\theta) = \begin{bmatrix} -1.0128 & -1.0128 & -1.0128 & -1.0128 & -1.0128 \\ -1.875 & -1.875 & -1.875 & -1.875 & -1.875 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$A(\theta)[scaled\ M(\theta)]^{-1}[A(\theta)]^T = 1 \times 10^{-8} \begin{bmatrix} 0.0939 & 0.1739 & 0 & 0 \\ 0.1739 & 0.3220 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

5-step five: Life Expectancy of the Patient (mean time to absorption):

$$E(\tau_{ik}) = [B]^{-1}Z = \begin{bmatrix} -3.48691 & -3.33935 \\ -0.32212 & -3.60174 \end{bmatrix} \begin{bmatrix} -0.69325 & -0.30675 \\ -0.74772 & -0.25228 \end{bmatrix} = \begin{bmatrix} 4.9159 & 1.9121 \\ 2.9163 & 1.0072 \end{bmatrix}$$

$E(\tau_{13}) = 4.9159\ years, E(\tau_{14}) = 1.9121\ years, E(\tau_{23}) = 2.9163\ years, E(\tau_{24}) = 1.0072\ years$

Mean time spent by the susceptible individuals in state 1 is approximately 3 years and 2 months, and in state 2 is approximately 3 years and 3.5 months. According to American Association for the study of Liver Disease (Chalasani et al., 2018), the most common cause of death in patients with NAFLD is cardiovascular disease (CVD) independent of other metabolic comorbidities, whereas the liver-related mortality is the third common cause of death among patients with NAFLD. Cancer-related mortality is among the top three causes of death in subjects with NAFLD. As shown from the calculations; mean time to absorption can be classified into: mean time from state 1 (susceptible individuals with risk factors) to state 3 (liver-related mortality) is approximately 5 years, while the mean time from state 1 to state 4 (for example CVD as an example for causes of death other than liver-related mortality causes) is approximately 2 years. The mean time from state 2 (NAFLD) to state 3 (liver-related mortality) is approximately 3 years while it decreases to approximately 1 year from state 2 (NAFLD) to state 4 (other causes than liver-related mortality).

From Table (2) the observed initial rates or the initial Q matrix is as calculated below:

$$Q = \begin{bmatrix} -0.31 & 0.287 & 0 & 0.023 \\ 0.027 & -0.297 & 0.203 & 0.067 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

The estimated rates calculated using the MLE and Quasi-Newton method is nearly approaching equality with this initial observed rates. Therefore, the advantage of this approach is that the estimated rates can be obtained from the first iteration. However, the limitation with this method is the degree of the polynomial representing the eigenvalue function as a function of rates. The 2nd degree polynomial is present in a formula that is easily differentiated with respects to each of the rates composing this

polynomial. In addition, if the degree of polynomial is a third or fourth degree, the presence of a formula to differentiate this eigenvalue helps to use this method of MLE as illustrated in this paper. The higher degrees of polynomials lacking the presence of such well-formed formula to be differentiated make it difficult to use this method. Although this sounds to be a restriction, by induction, this method can help to estimate the Q rate matrix as approximately approaching equality with the observed initial rates matrix. So the observed initial rate matrix can be used as an approximation to the estimated rate matrix.

To sum up the findings; this general, simple, and abstracted form of the Health-Disease-Death model can be used to obtain the statistical indices for the progression of NAFLD process over time. This necessitates estimation of 5 rates and 8 PDFs'. In this abstracted form, the NAFLD was explained by one state representing the disease without specifying how the disease progresses in the human body. In other words, this simple model does not answer what are the pathophysiological changes occurring in the body due to evolution of this disease over time. These ominous changes can be collectively grouped into specific stages or states that can be defined specifically to tell what happens in each of these states. Thus, this abstracted form do not specify the NAFLD process in a more detailed form, how many states the disease has and the directions of transitions among the different states. The more complicated model specifies the disease in a more expanded and elaborated form with 22 rates and 49 PDFs' that designates the pathological changes through which the disease evolves over time. This gives a more comprehensive insight of what hepatic cells are suffering from through their journey with this illness. The abstracted simple form of the multistate model have 2 competing risk factors for death represented by 2 different states, one for the causes of death due to complications of the NAFLD process and the other death state is for the causes other than complications of NAFLD. While this is true for this simple model, the complicated nature of the expanded model and for the sake of simplicity of the calculations, the death state is represented by one state. The estimated rate matrix is nearly approaching equality with the observed initial rate matrix. Thus, by induction, and as figured out from the simple model, more death states can be added to the model as absorbing states that represent the different causes of death from this disease. According to the American guidelines (Chalasani et al., 2018), the first and second most leading causes of death are due to vascular causes such as myocardial infarction, cerebral infarction and renal failure. While death due to liver cell failure as complications of NAFLD is the third most common cause of death in these patients. So adding these competing risk factors for death represented by these death states is a little bit tedious in calculations and thus the death state is represented by one death state.

A continuous time Markov chains should be tested for time homogeneity and Markovian property, these are discussed in the following paragraphs.

In the next paragraph, a MATLAB code illustrates the presence of empirical transition probability matrix that is equal to the transition probability matrix obtained from exponentiation the estimated transition rate matrix, thus this is a test for the assumption of time homogeneity of the CTMC. The empirical transition probability matrix is obtained from solving the Kolmogorov differential equations as previously illustrated. (Lencastre et al., 2014; Verbyla et al., 2013)

clear

```

clc
close all

Qq = [-0.3135    0.2907    0    0.0228;
      0.0280   -0.3036    0.2076  0.068 ;
      0         0         0         0 ;
      0         0         0         0 ]

% extract the enteries of the matrix
gamma1=-1*Qq(1,1);
gamma2=-1*Qq(2,2);
lam12=Qq(1,2);
lam14=Qq(1,4);
mu21=Qq(2,1);
lam23=Qq(2,3);
lam24=Qq(2,4);

% roots of characterisitic equations
w1=0.5*[-1*(gamma1+gamma2)-sqrt((gamma1+gamma2)^2-4*gamma1*gamma2+4*lam12*mu21)];
w2=0.5*[-1*(gamma1+gamma2)+sqrt((gamma1+gamma2)^2-4*gamma1*gamma2+4*lam12*mu21)];

% eigenvalues or roots of characterisitic equations and exponentiation of the the rate
matrix to obtain the transition probability matrix
A= eig(Qq);
P=expm(Qq*1)

% finding an empirical transition probability matrix that is equal to the
% matrix obtained from exponentiation of the transition rate matrix
A1= (w2+gamma1)/(w2-w1);
A2= (w1+gamma1)/(w1-w2);
A3=[ (w2+gamma1)/(w2-w1)]*[(w1+gamma1)/(mu21)];
A4=[ (w1+gamma1)/(w1-w2)]*[(w2+gamma1)/(mu21)];
A5=(lam23*A3)/w1;
A6=(lam23*A4)/w2;
G1=lam14*A1+lam24*A3;
G2=lam14*A2+lam24*A4;
A7=G1/w1;
A8=G2/w2;
A9=mu21/(w1-w2);
A10=(lam23*A2)/w1;
A11=(lam23*A1)/w2;
G3=lam14*A9+lam24*A2;
G4=lam24*A1-lam14*A9;
A12=G3/w1;
A13=G4/w2;

t=1;
P11=A1*exp(w1*t)+A2*exp(w2*t);
P12=A3*exp(w1*t)+A4*exp(w2*t);
P13=A5*[exp(w1*t)-1]+A6*[exp(w2*t)-1];
P14=A7*[exp(w1*t)-1]+A8*[exp(w2*t)-1];
P21=A9*[exp(w1*t)-exp(w2*t)];
P22=A2*exp(w1*t)+A1*exp(w2*t);
P23=A10*[exp(w1*t)-1]+A11*[exp(w2*t)-1];
P24=A12*[exp(w1*t)-1]+A13*[exp(w2*t)-1];

EmpiricalProbMatrix= [ P11 P12 P13 P14;
                      P21 P22 P23 P24;
                      0    0    1    0;
                      0    0    0    1]

```


The results obtained after running this code is shown below:

A₁	A₂	A₃	A₄	A₅	A₆	G₁	G₂	A₇	A₈
0.5274	0.4726	-1.6086	1.6086	0.8372	-1.5302	-0.0974	0.1202	0.2441	-0.5507
A₉	A₁₀	A₁₁	G₃	G₄	A₁₂	A₁₃			
-0.1549	-0.2460	-0.5018	0.0286	0.0394	-0.0717	-0.1806			

To test the Markovian hypothesis:

The difference between the empirical transition matrix $P_{0t}^{(e)}$ calculated over the time interval $[0,t]$ and the product of the half-period matrices, $P_{0\frac{t}{2}}^{(e)}$ and $P_{\frac{t}{2}t}^{(e)}$, is calculated and compared using the $\{L^2 - norm\}$ as defined in the following equations (50) and (51). If the difference approaches zero, the process is Markovian.

$$\|Z\| = \rho_{max} (Z) \quad (50)$$

the $\{L^2 - norm\}$ of the transition matrix (Z) is the maximum singular value of Z .

The difference is

$$Z = P_{0t}^{(e)} - \left[P_{0\frac{t}{2}}^{(e)} \times P_{\frac{t}{2}t}^{(e)} \right] \quad (51)$$

The following code illustrates the above concepts

```
T=0.5
halfTimeProbMatrix=expm(Qq*T)
Pempirical=[expm(Qq*T)]*[expm(Qq*T)]
Z=EmpiricalProbMatrix-Pempirical
```

The results obtained from running the above piece of code is

$$\begin{bmatrix} 0.7339 & 0.2138 & 0.0246 & 0.0277 \\ 0.0206 & 0.7412 & 0.1793 & 0.059 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} - \begin{bmatrix} 0.8558 & 0.1246 & 0.0068 & 0.0128 \\ 0.0120 & 0.8600 & 0.0963 & 0.0316 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \times \begin{bmatrix} 0.8558 & 0.1246 & 0.0068 & 0.0128 \\ 0.0120 & 0.8600 & 0.0963 & 0.0316 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

$$= 1 \times 10^{-3} \times \begin{bmatrix} 0.0112 & 0.0113 & -0.0184 & 0.0084 \\ 0.0104 & 0.1048 & 0.1004 & 0.0704 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\text{The eigenvalues for } Z = 1 \times 10^{-3} \times \begin{bmatrix} 0.0099 \\ 0.106 \\ 0 \\ 0 \end{bmatrix}$$

The maximum singular value for Z is zero.

So the process obeys the Markovian property or the Chapman-Kolmogorov equations.

Some Remarks:

- A. Treating the process as discrete time Markov chains in attempt to obtain the transition rate matrix for the corresponding CTMC.

If the process is considered a discrete time discrete state Markov chains. According to the data collected in table (6) and table (2), the transition probability matrix in discrete time is:

$$P = \begin{bmatrix} 0.601 & 0.287 & 0.089 & 0.023 \\ 0.027 & 0.703 & 0.203 & 0.067 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

Taking the log for this transition probability matrix to obtain the Q for the corresponding CTMC:

$$\hat{Q} = \begin{bmatrix} -0.5189 & 0.4438 & 0.0626 & 0.0125 \\ 0.0418 & -0.3612 & 0.2400 & 0.0794 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

This Q matrix fulfills the criteria for the Q matrix which are:

1. $\sum_S q_{ij}(t) = 0$
2. $q_{ij}(t) \geq 0, i \neq j$
3. $-\sum_S q_{ij}(t) = q_{ii}, i = j$

So there is no embedding problem or imbedding problem which also supports the time homogeneity of the CTMC. (Verbyla et al., 2013)

Exponentiation of this Q matrix is transition Probability matrix in continuous time:

$$P = \begin{bmatrix} 0.601 & 0.287 & 0.089 & 0.023 \\ 0.027 & 0.703 & 0.203 & 0.067 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix},$$

which is exactly the transition probability matrix in discrete time and it fulfills the following criteria :

1. $P_{ij}(t + s) = \sum_{l \in S} P_{il}(t)P_{lj}(s), \forall t \geq 0, s \geq 0, i, j, l \in S$; obying kolmogrov equations
2. $\sum_S P_{ij}(t) = 1$
3. $P_{ij}(t) \geq 0, \forall t \geq 0$ and $i, j \in S$

The difference between the probability matrix obtained by this way and the method used in this chapter by Maximum likelihood early illustrated in this chapter is

$$\begin{bmatrix} 0.601 & 0.287 & 0.089 & 0.023 \\ 0.027 & 0.703 & 0.203 & 0.067 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} - \begin{bmatrix} .7339 & .2138 & .0246 & .0277 \\ .0206 & .7412 & .1793 & .0590 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} = \begin{bmatrix} -0.1329 & .0732 & .0644 & -0.0047 \\ .0064 & -0.0382 & .0237 & .008 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

The difference is not that big.

B. The Stationary Probability Distribution:

At time $t = 42$ years, the entries of the transition probability matrix will be constant and will not change thereafter. In other words, it will not depend in time.

$$P(t = 42 \text{ years}) = \begin{bmatrix} 0.0000 & 0.0002 & 0.6932 & 0.3066 \\ 0.0000 & 0.0001 & 0.7477 & 0.2522 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

A cohort of individuals initially starting at a specific distribution with non- zero values in state1 and state 2 but with zero value in state 3 and state 4 , i.e. $[\pi_{0(1)} \ \pi_{0(2)} \ \pi_{0(3)} \ \pi_{0(4)}]$ will have positive values in the first 2 entries while zero values in the last 2 entries , will end up after 42 years or more to a stationary distribution with zero entries in the first 2 states and positive entries in the last 2 states, as shown below in the following examples:

Initial probability distribution	State probability distribution at $t=42$ years and thereafter
[0.9 0.1 0 0]	[0.0 0.0002 0.6986 0.3011]
[0.8 0.2 0 0]	[0.0 0.0001 0.7041 0.2957]
[0.7 0.3 0 0]	[0.0 0.0001 0.7095 0.2903]
[0.6 0.4 0 0]	[0.0 0.0001 0.7150 0.2848]
[0.5 0.5 0 0]	[0.0 0.0001 0.7204 0.2794]
[0.4 0.6 0 0]	[0.0 0.0001 0.7259 0.2740]
[0.3 0.7 0 0]	[0.0 0.0001 0.7313 0.2685]
[0.2 0.8 0 0]	[0.0 0.0001 0.7368 0.2631]
[0.1 0.9 0 0]	[0.0 0.0001 0.7422 0.2577]

It is obvious that the final state distribution (second column) has values that are in between the entry values in the first and the second row of the transition probability matrix at $t=42$ years.

C. Goodness of Fit of the Model:

To calculate goodness of fit for multistate model used in the small model, it is like the procedure used in contingency table, and it is calculated in each interval then sum:

Step 1 : $H_0 =$ future state does not depend on the current state. $H_1 =$
future state does depend on the current state

Step 2: calculate the $P_{ij}(\Delta t = 1) = e^{Qt} = \begin{bmatrix} .7339 & .2136 & .0246 & .0277 \\ .0206 & .7412 & .1793 & .059 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$

Step 3: calculate the expected counts in this interval by multiplying each row in the probability matrix with the corresponding total marginal counts in the observed transition counts matrix in the same interval to get the expected counts.

	State 1	State 2	State3	State4	total
State1	403.645	117.59	13.53	15.235	550.
State2	5.15	185.3	44.825	14.75	250.025
State3	0	0	0	0	0
State4	0	0	0	0	0

Step 4: apply $\sum_{i=1}^4 \sum_{j=1}^4 \frac{(O_{ij} - E_{ij})^2}{E_{ij}} = 104.866 \sim \chi_{(4-1)(4-1)(.05)}^2$

The same steps are used for the observed transition counts in the $\Delta t = 2$ with the following results:

$$P_{ij}(\Delta t = 2) = e^{Qt} = \begin{bmatrix} .543 & .3154 & .0811 & .0606 \\ .0304 & .5537 & .3126 & .1033 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

The expected counts:

	State 1	State 2	State3	State4	total
State1	60.273	35.0094	9.0021	6.7266	111
State2	1.1856	21.5943	12.1914	4.0287	39
State3	0	0	0	0	0
State4	0	0	0	0	0

$$\sum_{i=1}^4 \sum_{j=1}^4 \frac{(O_{ij} - E_{ij})^2}{E_{ij}} = 8.003 \sim \chi_{(4-1)(4-1)(.05)}^2$$

The same steps are used for the observed transition counts in $\Delta t = 3$ with the following results:

$$P_{ij}(\Delta t = 3) = \begin{bmatrix} .405 & .3498 & .151 & .0943 \\ .0337 & .4169 & .4127 & .1368 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

The expected counts:

	State 1	State 2	State3	State4	total
State1	15.795	13.6422	5.889	3.6777	39
State2	.3707	4.5859	4.5397	1.5048	11
State3	0	0	0	0	0
State4	0	0	0	0	0

$$\sum_{i=1}^4 \sum_{j=1}^4 \frac{(O_{ij} - E_{ij})^2}{E_{ij}} = 6.579 \sim \chi_{(4-1)(4-1)(.05)}^2$$

Step 5: sum up the above results to get:

$$\sum_{i=1}^4 \sum_{j=1}^4 \sum_{l=1}^{t=3} \frac{(O_{ijl} - E_{ijl})^2}{E_{ijl}} = 119.449 \sim \chi_{(df=27)(.05)}^2$$

So from the above results the null hypothesis is rejected while the alternative hypothesis is accepted and the model fits the data that is to mean the future state depends on the current state with the estimated transition rate and probability matrices as obtained.

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Declarations:

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Availability of data and material

Not applicable. Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests

The author declares that I have no competing interests.

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Authors' contribution

I am the author who has carried the mathematical analysis as well as applying these mathematical statistical concepts on the hypothetical example.

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Not applicable

Appendix:

“CTMC analyzing NAFLD progression (small model)”

The History of this MATLAB code on the site **CODE OCEAN** site, it is titled with **“The Simplest Multistate Model for Analysis Of NAFLD”**:

Published version 1 on 15 December 2021, URL: <https://codeocean.com/capsules/8641183/tree/v1>
DOI: 10.24433/CO.6022979.v1

Published version 2 on 7 February 2022, URL: <https://codeocean.com/capsule/8641183/tree/v2>
DOI: 10.24433/CO. 6022979.v2

Also the last version (v2) code is present with the associated timeline of the patients in excel format sheet at

IEEE Data Port site. The title of the code is **“CTMC analyzing NAFLD progression (small model)”** with the following DOI : (I uploaded on Saturday 5th of March 2022)
DOI: 10.21227/az1b-x326

This is a documentation for calculation of statistical indices of the NAFLD process (big model or expanded model):

First: calculate the probability matrix by solving the Kolmogorov differential equations which will be the same as the exponentiation of the rate matrix .

Second: calculate the rate matrix in each time interval i.e. when $\Delta t=\{1,2,3\}$

Third: calculate the mean sojourn time and its variance and Life expectancy.

Forth: calculate the variance of stationary probability distribution.

MATLAB code for the calculation of the probability matrix at first year:

In this MATLAB code, the rate matrix is the final estimated rate matrix, time is as chosen by the user :

```
clear
clc
close all

Qq = [-.3135    .2907    0    .0228;
      .0280   -.3036    .2076    .068;
      0        0        0        0;
      0        0        0        0];

% extract the entries of the matrix
gamma1=-1*Qq(1,1);
gamma2=-1*Qq(2,2);
lam12=Qq(1,2);
lam14=Qq(1,4);
mu21=Qq(2,1);
lam23=Qq(2,3);
lam24=Qq(2,4);

% roots of characteristic equations
w1=0.5*[-1*(gamma1+gamma2)-sqrt((gamma1+gamma2)^2-4*gamma1*gamma2+4*lam12*mu21)];
w2=0.5*[-1*(gamma1+gamma2)+sqrt((gamma1+gamma2)^2-4*gamma1*gamma2+4*lam12*mu21)];

% eigenvalues or roots of characteristic equations and exponentiation of the
rate matrix
% to obtain the transition probability matrix at t=1

A= eig(Qq);
P=expm(Qq*1)
P1=expm(Qq*1)

% finding an empirical transition probability matrix that is equal to the
% matrix obtained from exponentiation of the transition rate matrix

A1= (w2+gamma1)/(w2-w1)
A2= (w1+gamma1)/(w1-w2)
A3= [(w2+gamma1)/(w2-w1)]*[(w1+gamma1)/(mu21)]
A4= [(w1+gamma1)/(w1-w2)]*[(w2+gamma1)/(mu21)]
A5=(lam23*A3)/w1
A6=(lam23*A4)/w2
G1=lam14*A1+lam24*A3
G2=lam14*A2+lam24*A4
A7=G1/w1
A8=G2/w2
A9=mu21/(w1-w2)
A10=(lam23*A2)/w1
```



```

A11=(lam23*A1)/w2
G3=lam14*A9+lam24*A2
G4=lam24*A1-lam14*A9
A12=G3/w1
A13=G4/w2

t=1;
P11=A1*exp(w1*t)+A2*exp(w2*t);
P12=A3*exp(w1*t)+A4*exp(w2*t);
P13=A5*[exp(w1*t)-1]+A6*[exp(w2*t)-1];
P14=A7*[exp(w1*t)-1]+A8*[exp(w2*t)-1];

P21=A9*[exp(w1*t)-exp(w2*t)]
P22=A2*exp(w1*t)+A1*exp(w2*t)
P23=A10*[exp(w1*t)-1]+A11*[exp(w2*t)-1]
P24=A12*[exp(w1*t)-1]+A13*[exp(w2*t)-1]

EmpiricalProbMatrix= [ P11 P12 P13 P14;
                        P21 P22 P23 P24;
                        0    0    1    0;
                        0    0    0    1]

```

MATLAB code for calculation of the rate matrix at first interval:

```

clear
clc
close all

Q1=[ -.322    .3    0    .022;
      .02    -.26    .18    .06;
      0      0      0      0 ;
      0      0      0      0 ] ;

lam12=Q1(1,2)
lam14=Q1(1,4)
mu21=Q1(2,1)
lam23=Q1(2,3)
lam24=Q1(2,4)

gamma1=-1*Q1(1,1)
gamma2=-1*Q1(2,2)

eig(Q1)

% STEP ONE : calculate the roots of the 2nd degree polynomial= ?^2
[?^2+(?_1+?_2 )?+?_1 ?_2-?_12 ?_21 ]
r3=-.5*(gamma1+gamma2)-.5*sqrt([(gamma1+gamma2)]^2-
(4*gamma1*gamma2)+(4*mu21*lam12))
r4=-.5*(gamma1+gamma2)+.5*sqrt([(gamma1+gamma2)]^2-
(4*gamma1*gamma2)+(4*mu21*lam12))

```

```

dot=sqrt([(gamma1+gamma2)]^2-(4*gamma1*gamma2)+(4*mu21*lam12))
Y=1/dot

% STEP TWO : get MLE , by differentiating each p_ij with respect to rates and
% d/(d_h ) P_ij (t)=t*exp(?*t)*d? in the first interval , this is
accomplished in
% 2 steps , the first is differentiate R3 and R4 with respect to each rate
% the second step is substitute in equation S(theta)=t*exp(?*t)*d? to obtain
the
% score function

% first step :differentiate R3 with respect to each rates
DiffR3wrtlam12=-.5-.5*Y*(lam12+lam14+mu21-lam23-lam24)
DiffR3wrtlam14=-.5-.5*Y*(lam12+lam14-mu21-lam23-lam24)
DiffR3wrtmu21=-.5-.5*Y*(lam12-lam14+mu21+lam23+lam24)
DiffR3wrtlam23=-.5-.5*Y*(lam23+lam24+mu21-lam12-lam14)
DiffR3wrtlam24=-.5-.5*Y*(lam23+lam24+mu21-lam12-lam14)

% differentiate R4 with respect to each rates
DiffR4wrtlam12=-.5+.5*Y*(lam12+lam14+mu21-lam23-lam24)
DiffR4wrtlam14=-.5+.5*Y*(lam12+lam14-mu21-lam23-lam24)
DiffR4wrtmu21=-.5+.5*Y*(lam12-lam14+mu21+lam23+lam24)
DiffR4wrtlam23=-.5+.5*Y*(lam23+lam24+mu21-lam12-lam14)
DiffR4wrtlam24=-.5+.5*Y*(lam23+lam24+mu21-lam12-lam14)

% second step: calculate the score function : d/(d_h ) P_ij (t)=t*exp(?*t)*d?
% in the first interval
t=1
vectorR3=[DiffR3wrtlam12;DiffR3wrtlam14;DiffR3wrtmu21;DiffR3wrtlam23;DiffR3wr
t lam24]
vectorR4=[DiffR4wrtlam12;DiffR4wrtlam14;DiffR4wrtmu21;DiffR4wrtlam23;DiffR4wr
t lam24]

% calculate S(theta)=t*exp(?*t)*d?, where d? are the vectorR3 and vectorR4
% CALCULATED IN THE PREVIOUS COMMANDS

ScoreFunofTheta= [t*exp(r3*t)*vectorR3] + [t*exp(r4*t)*vectorR4]

% //////////////////////////////////////
% In the following few lines , a code to calculate the scalar for score
% function and hessian matrix:
% C1 is the matrix of transition counts among the states,to calculate the
% scalar for the score function it is the total row count for each cell where
the count is nonzero
% scalar for the hessian matrix is the square of the total row divided by
% the cell count where the counts are nonzeros .

C1=[330 163 45 12 ;
5 185 45 15 ;
0 0 0 0 ;
0 0 0 0 ]

% calculate the total for each row let's call it totsum which is a column
vector that contains in each row

```

```

% the total counts of transitions from this state,
% for example 550 is the total number of transitions from state 1 ,
% 250 is the total number of transitions from state 2 ,

totSum=sum(C1') % calculate the sum of each row to get the total sum
n1=totSum(1,1) % extract the total of the first row
n2=totSum(1,2) % extract the total of the second row
n3=totSum(1,3) % extract the total of the third row
n4=totSum(1,4) % extract the total of the fourth row

% NOW calculate the number of cells with nonzero counts in each row

s1=sum(C1(1,:)>0) % count the total number of cells with nonzero counts in
row1
s2=sum(C1(2,:)>0) % count the total number of cells with nonzero counts in
row2
s3=sum(C1(3,:)>0) % count the total number of cells with nonzero counts in
row3
s4=sum(C1(4,:)>0) % count the total number of cells with nonzero counts in
row4

% calculate the scoreScalar value

nVector=[n1 n2 n3 n4] % total marginal for each row sum over j for nij
in each row
sVector=[s1 s2 s3 s4] % number of cells in each row with nonzero counts
scoreScalar=n1*s1+n2*s2+n3*s3+n4*s4

% extract each row from the matrix of the transition counts

v1=C1(1,1:4)
v2=C1(2,1:4)
v3=C1(3,1:4)
v4=C1(4,1:4)

% extract cells with nonzero counts in each row

V1=v1(v1>0)
V2=v2(v2>0)
V3=v3(v3>0)
V4=v4(v4>0)

% calculate the scalar for hessian matrix ; by squaring the total marginal
% for each row and divide this total marginal by each cell count in this
% row and then sum up the results. repeat this procedure in each row and
% sum up the final results in all rows together.
hessianMatrixxscalar=sum(n1^2./V1)+sum(n2^2./V2)+sum(n3^2./V3)+sum(n4^2./V4)

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

% STEP THREE: scale the score function by the scalar=3200 as calculated

```

```

% from the above subroutines

ScaledScoredFun= 3200*ScoreFunofTheta

% STEP FOUR :to get the hessian matrix , multiply or cross product the scaled
scored
% function with its transposed

MofTheta=ScaledScoredFun*ScaledScoredFun'

% STEP FIVE: scale the above hessian matrix MofTheta bt scalar=53096
ScaledMofTheta=53096*MofTheta

% STEP SIX: invert scaled hessian matrix,ScaledMofTheta is singular matrix
% so use pseudoinverse
invertM1=pinv(ScaledMofTheta)

% STEP SEVEN : multiply invertM with the scaled scored function

diffFromInitial=invertM1*ScaledScoredFun

% STEP EIGHT : apply Quasi-Newton formula theta1=theta0+M(theta0)^(-1)*
S(theta0)

initialRateVector1=[ .3 ;.022 ; .02; .18 ; .06]

desiredRateVector1= initialRateVector1 + diffFromInitial
% //////////////////////////////////////
% the same steps are used to calculate the rates in the second and third
% interval .

```

This is the initial Q rate matrix in the second interval :

```

Q2=[ -.279  .27    0    .009;
      .05  -.486  .333  .103;
      0     0     0     0 ;
      0     0     0     0 ] ;

```

Then implement the same code for rate matrix estimation (the code in the first interval).

This is the initial Q rate matrix in the third interval :

```

Q3=[ -.282  .205    0    .077;
      .091  -.455  .273  .091;
      0     0     0     0 ;
      0     0     0     0 ] ;

```

Then implement the same code for rate matrix estimation (the code in the first interval)

Now calculate the final rate vector and its variance :

```
clear
clc
close all

% calculate weighted rate vector ( final vector):
load desiredRateVector1
load desiredRateVector2
load desiredRateVector3
load invertM1
load invertM2
load invertM3

% calculate the weighted sum of rate vectors to obtain the final rate vector
finalRatevectorSMALLmodelNAFLD
=(.8)*desiredRateVector1+(.15)*desiredRateVector2+(.05)*desiredRateVector3

% calculate the weighted sum of the inverted scaled hessian matrix :
finalMatHessianSMALLmodelNAFLD =(.08)*invertM1+(.15)* invertM2 +(.05)*
invertM3
```

Calculate the Estimated Mean Sojourn Time and Life Expectancy :

```
clear
clc
close all

% calculate mean sojourn time for each state
Qq = [-.3135    .2907    0    .0228;
      .0280   -.3036   .2076   .068;
      0        0        0        0;
      0        0        0        0];

g1=Qq(1,1);
g2=Qq(2,2);

% calculate mean sojourn time , it is the reciprocal of the squared values
% on the diagonal of the Qq matrix :
S1=1/(-g1);
S2=1/(-g2);

Svector=[S1;S2]

% calculate variance of the sojourn time USING THE MULTIVARIATE DELTA METHOD
```

```

% variance of the sojourn time= 1/meanSojournTime^4
*(NegativeOnes'*finalMatHessianSMALLmodelNAFLD*NegativeOnes) :
% finalMatHessianSMALLmodelNAFLD is the variance-covariance matrix of thetas

s1=1/(g1^4)
s2=1/(g2^4)

svector=[s1;s2]

% create row vector of -1 ones sized 5 by 1 :
Ones= ones(5,1)
NegativeOnes= -1.*Ones
load finalMatHessianSMALLmodelNAFLD
v=NegativeOnes'*finalMatHessianSMALLmodelNAFLD*NegativeOnes
vars1=s1*v
vars2=s2*v

% calculate life expectancy :
% step 1:partition the Qq matrix into 4 sub matrices: A,B,and
% last row composed of 2 zero matrices
% construct A=BZ
B = Qq(1:2,1:2)
A= Qq(1:2,3:4)
inv(B)
Z= inv(B)*A
% step 2:
LifeExpectancy=inv(B)*Z

```

Calculate The Variance Of The Stationary Distribution:

```

clear
clc
close all

Qq = [-.3135   .2907       0       .0228;
      .0280  -.3036   .2076   .068;
      0       0       0       0;
      0       0       0       0];

% study the stationary probability distribution of initial cohort of 3000
patients
% with initial number of patients in each state being [2100 900 0 0] and
initial probability
% distribution = [.7 .3 0 0], assuming that the stationary probability
distribution is at
% 60 years

initialCohortCount=[2100 900 0 0]
initialCohortDis=[.7 .3 0 0]
P60=expm(Qq*60)

```

```

% step 1: calculate statinary distribution at 60 year
% where the pi is the statinary distribution and Q is the rate matrix
% calculate state probability distribution at 60 years

stateProbDistribAtSIXTYyear=initiaCohortDis*P60

% step 2:differentiate the rate matrix Q with respect to each rate
% this will give row vector of ones sized 5 by 1

diffQmatrix =ones(5,1);
transposedDiffMatrix =diffQmatrix';

% step 3: calculate C of theta ; C(theta); it is (4 by 5 matrix )
C_Theta=stateProbDistribAtSIXTYyear'*transposedDiffMatrix

% step 4: let R=Qqtransposed , calculate pseudoinverse for this R matrix
R=Qq';
R_inverse=pinv(R)

%step 5 : multiply this R_inverse by -1
R_inverseNegation =-1*R_inverse

%step 6 : calculate A of theta ; A(theta): it is (4 by 55 matrix )
A_Theta =R_inverseNegation*C_Theta

% step 7 : apply multivariate delta method=
% A_Theta*finalMatHessianSMALLmodelNAFLD'*A_Theta'
% finalMatHessianSMALLmodelNAFLD' is the weighted sum of the inverted scaled
hessian matrix

```

This is the MATLAB code of how to construct the transition count table in each interval according to the timeline of the patients in the excel sheet :

```

clear
clc
close all

% // this is a code to calculate the observed transition counts in various
% different time interval

% first load excel sheet as a matrix ( remove any vertical or horizontal
% headers ) , then extraxt each row as a vector to count the transitions in
% differnet interval . In the time point where the patient did not show up
% put zeros

data = xlsread('Myfile4.xlsx','Sheet1');
class(data)

```

```

[row,col]=size(data)
x=1:row
y=1:col

count=0
count11=0
count12=0
count13=0
count14=0
count21=0
count22=0
count23=0
count24=0
count31=0
count32=0
count33=0
count34=0
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
//
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
/////
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
///
% Now calcualte the transitions among states in the whole matrix during the
3 years period :
% to overcome the problem of index out of bound , add multiple of -1 and
subtract this multiple as
% shown below

for x=1:row
    count=count+1
    a1=data(x,:)
    i=1:length(a1)
    a11=[a1 -1 -1 -1 ]

for i=1:length(a11)-3
    if a11(i)==1 && a11(i+1)==0 && a11(i+2)==0 && a11(i+3)==1
        count11=count11+1
    end
end
for i=1:length(a11)-3
    if a11(i)==1 && a11(i+1)==0 && a11(i+2)==0 && a11(i+3)==2
        count12=count12+1
    end
end
for i=1:length(a11)-3
    if a11(i)==1 && a11(i+1)==0 && a11(i+2)==0 && a11(i+3)==3
        count13=count13+1
    end
end
end

```



```

for i=1:length(a11)-3
    if a11(i)==1 && a11(i+1)==0 && a11(i+2)==0 && a11(i+3)==4
        count14=count14+1
    end
end

for i=1:length(a11)-3
    if a11(i)==2 && a11(i+1)==0 && a11(i+2)==0 && a11(i+3)==1
        count21=count21+1
    end
end

for i=1:length(a11)-3
    if a11(i)==2 && a11(i+1)==0 && a11(i+2)==0 && a11(i+3)==2
        count22=count22+1
    end
end

for i=1:length(a11)-3
    if a11(i)==2 && a11(i+1)==0 && a11(i+2)==0 && a11(i+3)==3
        count23=count23+1
    end
end

for i=1:length(a11)-3
    if a11(i)==2 && a11(i+1)==0 && a11(i+2)==0 && a11(i+3)==4
        count24=count24+1
    end
end

for i=1:length(a11)-3
    if a11(i)==3 && a11(i+1)==0 && a11(i+2)==0 && a11(i+3)==1
        count31=count31+1
    end
end

for i=1:length(a11)-3
    if a11(i)==3 && a11(i+1)==0 && a11(i+2)==0 && a11(i+3)==2
        count32=count32+1
    end
end

for i=1:length(a11)-3
    if a11(i)==3 && a11(i+1)==0 && a11(i+2)==0 && a11(i+3)==3
        count33=count33+1
    end
end

for i=1:length(a11)-3
    if a11(i)==3 && a11(i+1)==0 && a11(i+2)==0 && a11(i+3)==4
        count34=count34+1
    end
end

```

```

    Ct3=[count11 count12 count13 count14 ; count21 count22 count23 count24;
count31 count32 count33 count34]

end
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
//
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
/////
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
///
% Now calculate the transitions among states in the first row during the 2
years period
% to overcome the problem of index out of bound , add multiple of -1 and
subtract this multiple as
% shown below

Count11=0
Count12=0
Count13=0
Count14=0
Count21=0
Count22=0
Count23=0
Count24=0
Count31=0
Count32=0
Count33=0
Count34=0

for x=1:row
    count=count+1
    a1=data(x,:)
    j=1:length(a1)
    a11=[a1 -1 -1 ]

for j=1:length(a11)-2
    if a11(j)==1 && a11(j+1)==0 && a11(j+2)==1
        Count11=Count11+1
    end
end

for j=1:length(a11)-2
    if a11(j)==1 && a11(j+1)==0 && a11(j+2)==2
        Count12=Count12+1
    end
end

for j=1:length(a11)-2
    if a11(j)==1 && a11(j+1)==0 && a11(j+2)==3
        Count13=Count13+1
    end
end
for j=1:length(a11)-2

```

```

        if a11(j)==1 && a11(j+1)==0 && a11(j+2)==4
            Count14=Count14+1
        end
    end

    for j=1:length(a11)-2
        if a11(j)==2 && a11(j+1)==0 && a11(j+2)==1
            Count21=Count21+1
        end
    end

    for j=1:length(a11)-2
        if a11(j)==2 && a11(j+1)==0 && a11(j+2)==2
            Count22=Count22+1
        end
    end

    for j=1:length(a11)-2
        if a11(j)==2 && a11(j+1)==0 && a11(j+2)==3
            Count23=Count23+1
        end
    end

    for j=1:length(a11)-2
        if a11(j)==2 && a11(j+1)==0 && a11(j+2)==4
            Count24=Count24+1
        end
    end

    for j=1:length(a11)-2
        if a11(j)==3 && a11(j+1)==0 && a11(j+2)==1
            Count31=Count31+1
        end
    end
    for j=1:length(a11)-2
        if a11(j)==3 && a11(j+1)==0 && a11(j+2)==2
            Count32=Count32+1
        end
    end

    for j=1:length(a11)-2
        if a11(j)==3 && a11(j+1)==0 && a11(j+2)==3
            Count33=Count33+1
        end
    end
    for j=1:length(a11)-2
        if a11(j)==3 && a11(j+1)==0 && a11(j+2)==4
            Count34=Count34+1
        end
    end
    Ct2=[Count11 Count12 Count13 Count14;Count21 Count22 Count23
Count24;Count31 Count32 Count33 Count34 ]
    end
end

```

```

%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
//
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
/
% Now calculate the transitions among states in the whole matrix in delta t =
one year interval
% to overcome the problem of index out of bound , add multiple of -1 and
subtract this multiple as
% shown below

C11=0
C12=0
C13=0
C14=0
C21=0
C22=0
C23=0
C24=0
C31=0
C32=0
C33=0
C34=0

for x=1:row
    count=count+1
    a1=data(x,:)
    k=1:length(a1)
    a11=[a1  -1 ]

    for k=1:length(a11)-1
        if a11(k)==1 && a11(k+1)==1
            C11=C11+1
        end
    end

    for k=1:length(a11)-1
        if a11(k)==1 && a11(k+1)==2
            C12=C12+1
        end
    end

    for k=1:length(a11)-1
        if a11(k)==1 && a11(k+1)==3
            C13=C13+1
        end
    end

    for k=1:length(a11)-1
        if a11(k)==1 && a11(k+1)==4
            C14=C14+1
        end
    end
end

```

```

for k=1:length(a11)-1
    if a11(k)==2 && a11(k+1)==1
        C21=C21+1
    end
end

for k=1:length(a11)-1
    if a11(k)==2 && a11(k+1)==2
        C22=C22+1
    end
end

for k=1:length(a11)-1
    if a11(k)==2 && a11(k+1)==3
        C23=C23+1
    end
end

for k=1:length(a11)-1
    if a11(k)==2 && a11(k+1)==4
        C24=C24+1
    end
end

for k=1:length(a11)-1
    if a11(k)==3 && a11(k+1)==1
        C31=C31+1
    end
end

for k=1:length(a11)-1
    if a11(k)==3 && a11(k+1)==2
        C32=C32+1
    end
end

for k=1:length(a11)-1
    if a11(k)==3 && a11(k+1)==3
        C33=C33+1
    end
end

for k=1:length(a11)-1
    if a11(k)==3 && a11(k+1)==4
        C34=C34+1
    end
end

Ct1=[ C11 C12 C13 C14; C21 C22 C23 C24; C31 C32 C33 C34]

end

Ctot=Ct1+Ct2+Ct3
sum(Ct1')
sum(Ct2')
sum(Ct3')

```

Hint in IEEE Data Port : the excel sheet is called {time line (small model)} . you can use this title or you can use the {Myfile4}

Datasets

Standard Dataset

CTMC ANALYZING NAFLD PROGRESSION (SMALL MODEL)

View

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DOI: 10.21227/az1b-x326

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Published The Simplest multistate model for analysis of NAFLD (Iman Mohammed Attia Abd-Elkhalik Abo-Elreesh)

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Files	Core Files	Size	Status
metadata	1.58 KB	✓	
environment	222 B	✓	
code	51.59 KB	✓	
desiredRateVector1.mat	233 B	✓	
desiredRateVector2.mat	233 B	✓	
desiredRateVector3.mat	232 B	✓	
finalMatHessianSMALLmodel...	315 B	✓	
finalRatevectorSMALLmodelN...	246 B	✓	
invertM1.mat	284 B	✓	
invertM2.mat	288 B	✓	
invertM3.mat	288 B	✓	
LICENSE	1.03 KB	✓	
meanSojournTimeAndVarLif...	2.03 KB	✓	
Myfile4.xlsx	19.29 KB	✓	
RateEstInFirstInt.m	5.44 KB	✓	
RateEstInSecondInt.m	5.44 KB	✓	
RateEstInThirdInt.m	5.45 KB	✓	
run	1.25 KB	✓	
TRANSITIONcountsSMALLm...	7.42 KB	✓	
varianceOfStationaryDistribut...	1.6 KB	✓	
weightedRateAndVarMatrixS...	537 B	✓	
data Manage Datasets	0 B	✓	
Results			
results	498.86 KB		
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Metadata

Bioinformatics

The Simplest multistate model for analysis of NAFLD

Iman Mohammed Attia Abd-Elkhalik Abo-Elreesh

Non-Alcoholic Fatty Liver Disease (NAFLD) can be modeled by the simplest form of multistate model for Health-illness-death process. The system is composed of 4 states: state 1 is the individuals with high risk factors like type 2 diabetes, hypercholesterolemia, obesity and hypertension, state 2 is patients suffering from NAFLD, state 3 is the death state as a complication of NAFLD and state 4 is the death state from other causes than complications of NAFLD. For this system, 5 transitions rates among the states and 8 probability density functions are estimated using maximum likelihood function (MLE) and quasi-newton method. Once the transition rate matrix is obtained, exponentiation of this rate matrix will yield the transition probability matrix. The code also calculate the estimated patients counts in each state at specific time point as well as the state probability distribution at this time point. The estimated mean sojourn time in each state is also calculated. The life expectancy of patients in each state is also estimated.

non-alcoholic fatty liver disease continuous time Markov chains maximum likelihood function mean sojourn time life expectancy of patients biostatistics

Capsule

DOI: 10.24433/CO.6022979.v2

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General

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