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New Method Utilizing Continuous Time Markov Chains to Analyze Evolution in the Nine States Model of Non-Alcoholic Fatty Liver Disease

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Abstract
Global increase in prevalence of obesity and type 2 Diabetes is strongly connected to increase prevalence of non-alcoholic fatty liver disease (NAFLD) worldwide. In the present paper, progression of (NAFLD)process is modeled by Continuous time Markov chains(CTMC) with 9states. Maximum likelihood is used to estimate the transition intensities among the states. Once the transition intensities are obtained the mean sojourn time and its variance are estimated as well as the state probability distribution and its asymptotic covariance matrix. A hypothetical example based on longitudinal study assessing patients with NAFLD in various stages is discussed .The mean time to absorption is estimated as well as the other above mentioned statistical indices are examined . In this paper MLE is utilized in a new approach to compensate for the missing values in the follow up period of patients evaluated in longitudinal studies.
Classification code : 60J27 , 60J35
***Key words**: Continuous time Markov chains, Life expectancy, Maximum Likelihood estimation, MeanSojourn Time, Non-Alcoholic Fatty Liver Disease,Panel Data.*

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I. INTRODUCTION

CTMC is commonly used to model data obtained from longitudinal studies in medical research and to investigate the evolution and progression of the diseases over time. Estes et al. [1]used multistate Markov chains to model the epidemic of nonalcoholic fatty liver disease.Younossi et al.[2] used the multistate Markov chains to demonstrate the economic and clinical burden of nonalcoholic fatty liver disease in United States and Europe.

According to American Association for Study of Liver Disease , American College of Gastroenterology, and the American Gastroenterological Association, NAFLD to be defined requires (a) there is evidence of hepatic steatosis (HS) either by imaging or by histology and (b)there are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medications or hereditary disorders [3].This is the same definition established by European Association for the Study of the Liver (EASL),European Association for the Study of Diabetes (EASD)and European Association for the Study of Obesity(EASO)[4].NAFLD can be categorized histologically into nonalcoholic fatty liver (NAFL) or nonalcoholic steato-hepatitis (NASH). NALF is defined as the presence of $\geq$ 5% (HS) without evidence of hepatocellular injury in the form of hepatocyte ballooning .NASH is defined as the presence of $\geq$ 5 % HS and inflammation with hepatocyte injury (ballooning), with or without any fibrosis.

NAFLD is a multistage disease process consisting of 9 stages as depicted in figure1[2]. As shown in the figure; the patient can move across the stages of the disease process.While the remission rates are allowed from stage 4 (compensated liver cirrhosis) to the earlier stages, patient progresses to HCC and liver transplantation once he arrives to stage 5(decompensated liver cirrhosis) and remission rates are not allowed. Death state can be reached from any state. The patient can move from the first 5 stages to stage 8 (HCC) with higher rate of progression from stage 4(CC) or stage 5 (DCC) to stage 8(HCC) compared to first 3 stages.A brief definition of each stage is illustrated in the figure (1).

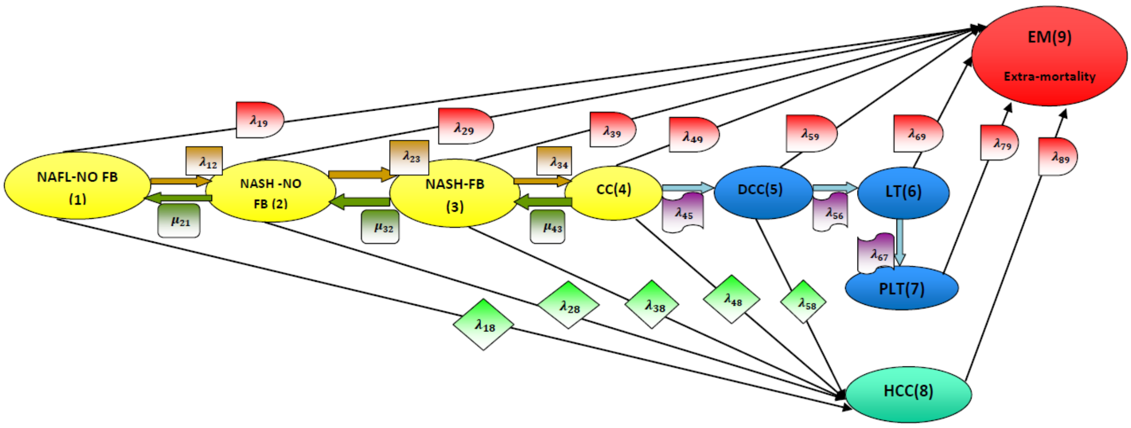

Figure 1: disease model structure :

NAFLD-NO FB= nonalcoholic fatty liver disease with no fibrosis (stage1).NASH-NO FB = nonalcoholic steato-hepatitis with no fibrosis (stage 2).NASH-FB = nonalcoholicsteato-hepatitis with fibrosis (stage 3).CC= compensated cirrhosis (stage 4).DCC= de-compensated cirrhosis (stage 5).LT= liver transplant(stage 6).PLT =post liver transplant (stage 7).HCC =hepato-cellular carcinoma (stage 8).EM= extra-mortality (stage 9).[2]

NAFLD stages are modeled as time homogenous CTMC , that is to 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 Poisson distribution. The states are finite and can be defined or identified based on various aspects such as clinical symptoms and invasive or noninvasive investigations. The gold standard method for classification of histopatholgical changes in the liver is the invasive liver biopsy. It is presently the most trustworthy procedure for diagnosing the presence of steatohepatitis (HS) and fibrosis in NAFLD patients[5]. The limitations of this procedure are cost, sampling error, and procedure-related morbidity and mortality. MR imaging, by spectroscopy[6] or by proton density fat fraction[7], is an excellent noninvasive technique for quantifying HS and is being widely used in NAFLD clinical trials[8] .The use of transient elastrography (TE) to obtain continuous attenuation parameters is a promising tool for quantifying hepatic fat in an ambulatory setting[9]. However, quantifying noninvasively HS in patients with NAFLD is limited in routine clinical care. Also one of the most recent biological markers are the keratin(K18) and its caspase-cleaved fragments(cK18).There are many scoring systems that can identify the stages of the disease process[10].NAFLD has higher prevalence rate in individuals with risk factors such as visceral obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, older age , male sex and being of Hispanic ethnicity[11].

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 time interval between measurements.

The paper is divided into 7 sections. In section 1 the transition probabilities and transition rates are thoroughly discussed. In section 2 mean sojourn time and its variance are reviewed. In section 3 state probability distribution and its covariance matrix are discussed. While in section 4 the life expectancy of the patients are considered. In section 5 expected numbers of patients in each state is obtain .A hypothetical numerical example is used in section 6 to illustrate the above concepts. Lastly a brief summary is comprehended in section 7.

1.TransitionRates And Probabilities

NAFLD is modeled by a multistate Markov chains which define a stochastic process

$[(X(t)\,, t \in \;T\,)]\; over\; a\; finite\; state\; space\;\; S = \{\,1,2,3,4\}\; and\; T = [0, t\,]\; and\; t\; < \infty$

The transitions can occur at any point in time and hence called continuous time Markov chains in contrast to the discrete time Markov chains in which transitions occur at fixed points in time. The rates at which these transitions occur are constant over time and thus are independent of t thatis 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 $\theta_{ij}\;(t) = \lim_{\Delta t \to 0} \frac{P_{ij}(\Delta t) - I}{\Delta t}$ or the Q matrix.

For the above multistate Markov model demonstrating the NAFLD disease process; the forward Kolomogrov differential equations are the following:

$$\frac{d}{dt} P_{ij}(t) =$$

$$\begin{bmatrix} P_{11} & P_{12} & P_{13} & P_{14} & P_{15} & P_{16} & P_{17} & P_{18} & P_{19} \\ P_{21} & P_{22} & P_{23} & P_{24} & P_{25} & P_{26} & P_{27} & P_{18} & P_{29} \\ P_{31} & P_{32} & P_{33} & P_{34} & P_{35} & P_{36} & P_{37} & P_{18} & P_{39} \\ P_{41} & P_{42} & P_{43} & P_{44} & P_{45} & P_{46} & P_{47} & P_{18} & P_{49} \\ 0 & 0 & 0 & 0 & P_{55} & P_{56} & P_{57} & P_{18} & P_{59} \\ 0 & 0 & 0 & 0 & 0 & P_{66} & P_{67} & 0 & P_{69} \\ 0 & 0 & 0 & 0 & 0 & 0 & P_{77} & 0 & P_{79} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & P_{18} & P_{89} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & P_{99} \end{bmatrix} \begin{bmatrix} -\gamma_1 & \lambda_{12} & 0 & 0 & 0 & 0 & 0 & \lambda_{18} & \lambda_{19} \\ \mu_{21} & -\gamma_2 & \lambda_{23} & 0 & 0 & 0 & 0 & \lambda_{28} & \lambda_{29} \\ 0 & \mu_{32} & -\gamma_3 & \lambda_{34} & 0 & 0 & 0 & \lambda_{38} & \lambda_{39} \\ 0 & 0 & \mu_{43} & -\gamma_4 & \lambda_{45} & 0 & 0 & \lambda_{48} & \lambda_{49} \\ 0 & 0 & 0 & 0 & -\gamma_5 & \lambda_{56} & 0 & \lambda_{58} & \lambda_{59} \\ 0 & 0 & 0 & 0 & 0 & -\gamma_6 & \lambda_{67} & 0 & \lambda_{69} \\ 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{79} & 0 & \lambda_{79} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{89} & \lambda_{89} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

Solving the Kolmogorov differential equations will give the transition probability matrix

$P_{ij}(t)(see\ suppl.Info.section\ 1)$

$P_{ij}(t)$satisfies the following properties :

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

While the Q matrix satisfies the following conditions:

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

Where the q_{ij} is the $(i, j)\ th$ entry in the Q matrix emphasizing that the P_{ij} depends only on the interval between t_1 and t_2 not on t_1 .

1.1 Maximum Likelihood Estimation of the Q Matrix

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

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

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

According toKalbfleish and Lawless[12], applying Quasi-Newton method to estimate the rates mandates calculating the score function which is a vector –valued function for the required rates and it's the first derivative of the probability transition function with respect to θ.The second derivative is assumed to be zero .

$$S(\theta) = \frac{\partial}{\partial \theta_h} \log L\ (\theta) = \sum_{r=1}^{\tau} \sum_{i,j=1}^{k} n_{ijr} \frac{\partial P_{ij}(\tau)/\partial \theta_h}{P_{ij}(\tau)}, h = 1, \ldots, 22 \ \ while\ P_{ij}(\tau) = \frac{n_{ijr}}{n_{i+}}$$

$$\frac{n_{ijr}}{P_{ij}(\tau)} =\ n_{i+} \ \ , \qquad such\ that \ \ n_{i+} = \sum_{j=1}^{k} n_{ijr}$$

$S(\theta) = \tau\ e^{\Lambda \tau} d\Lambda$

$\Lambda$is the eigenvalues for each Q matrix in each τ*(see suppl. Info. Esp. excel sheet)*

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

Assuming the second derivative is zero and $\frac{n_{ijr}}{P_{ij}(\tau)} =\ n_{i+}$ then

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

The Quasi-Newton formula is

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

According to Klotz &Sharples[13] the initial $\theta_0 = \frac{n_{ijr}}{n_{i+}}\ for\ \Delta t = 1$

For this NAFLD process $(see\ suppl.info.section\ 1.1)$

2. 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 $\lambda_i = -\lambda_{ii}\ ;\ \ i = 1, \dots, 8$.

According toKalbfleisch& lawless[12]the asymptotic variance of this time is calculated by applying multivariate delta method:

$$var(s_i) = \left[\left(q_{ii}(\hat{\theta})\right)^{-2}\right]^2 \sum_{h=1}^{22}\sum_{g=1}^{22} \frac{\partial q_{ii}}{\partial\theta_g}\frac{\partial q_{ii}}{\partial\theta_h}[\mathrm{M}(\theta)]^{-1}|_{\theta=\hat{\theta}}$$

For this NAFLD process $(see\ suppl.info\ section\ 2)$

3. State Probability Distribution

According toCassandras&Lafortune[14] 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:

$\pi(t) = \pi(0)P(t)$

Stationary probability distribution when t goes to infinity or in other words when the process does not depend on time is obtained by differentiating both sides of the following equation:

$\pi(t) = \pi(0)P(t) = \pi(0)e^{Qt}$

$$differentiate\ \ both\ sides\ to\ obtain\quad \frac{d}{dt}\pi(t)\Big|_{t=0} = \pi(0)Q$$

$$\frac{d}{dt}\pi_i(t)\Big|_{t=0} = [\pi_{0(1)}\quad \pi_{0(2)}\quad \pi_{0(3)}\quad \pi_{0(4)}\quad \pi_{0(5)}\quad \pi_{0(6)}\quad \pi_{0(7)}\quad \pi_{0(8)}\quad \pi_{0(9)}] \times$$

$$\begin{bmatrix} -\gamma_1 & \lambda_{12} & 0 & 0 & 0 & 0 & 0 & \lambda_{18} & \lambda_{19} \\ \mu_{21} & -\gamma_2 & \lambda_{23} & 0 & 0 & 0 & 0 & \lambda_{28} & \lambda_{29} \\ 0 & \mu_{32} & -\gamma_3 & \lambda_{34} & 0 & 0 & 0 & \lambda_{38} & \lambda_{39} \\ 0 & 0 & \mu_{43} & -\gamma_4 & \lambda_{45} & 0 & 0 & \lambda_{48} & \lambda_{49} \\ 0 & 0 & 0 & 0 & -\gamma_5 & \lambda_{56} & 0 & \lambda_{58} & \lambda_{59} \\ 0 & 0 & 0 & 0 & 0 & -\gamma_6 & \lambda_{67} & 0 & \lambda_{69} \\ 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{79} & 0 & \lambda_{79} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{89} & \lambda_{89} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$[\pi_1\quad \pi_2\quad \pi_3\quad \pi_4\quad \pi_5\quad \pi_6\quad \pi_7\quad \pi_8\quad \pi_9]$at specific time point is obtained by solving this system of differential equations. Solving these differential equations for this complex chain is not a trivial matter.

If the limitof $\pi_z = \lim_{t\to\infty}\pi_z(t)$exists , so there is a stationary or steady state distribution andas $t \to \infty$, the $\frac{d}{dt}\pi_j(t) = 0$, since $\pi_z(t)$does not depend on time .Therefore $\frac{d}{dt}\pi(t) = \pi(t)Q$ will reduce to $\pi(t)Q = 0$.

The stationary state probability distribution is obtained by solving $\pi Q = 0$ subject to $\sum_{all\ z}\pi_z = 1$

For this NAFLD process $(see\ suppl.info\ section\ 3)$

3.1Asymptotic Covariance of the State Probability Distribution:

Multivariate delta method is applied to following function $Q'\pi = F(\theta_h, \pi_i) = 0$to obtain asymptotic covariance matrix of the state probability distribution, as π is not a simple function of .

Differentiating$F(\theta_h, \pi_i)$ implicitly with respect to $\theta_h$is used in the following manner:

$$\frac{\partial}{\partial\theta_h}F(\theta_h, \pi_i) = \frac{\partial}{\partial\theta_h}Q'\pi_i = 0$$

$$\frac{\partial}{\partial\theta_h}Q'\pi_i = [Q']\left[\frac{\partial}{\partial\theta_h}\pi_i\right] + \pi_i\left[\frac{\partial}{\partial\theta_h}Q'\right]^T = 0 \quad ,let's\ call\quad \pi_i\left[\frac{\partial}{\partial\theta_h}Q'\right]^T = C(\theta)$$

$$[Q']\left[\frac{\partial}{\partial\theta_h}\pi_i\right] + C(\theta) = 0$$

$$solving\ for\ \left[\frac{\partial}{\partial\theta_h}\pi_i\right]$$

$$\left[\frac{\partial}{\partial\theta_h}\pi_i\right] = -[Q']^{-1}C(\theta)$$

$Let\ \left[\frac{\partial}{\partial \theta_h}\pi_i\right] = A(\theta)$

By multivariate delta method

$var(\pi) = A(\theta)var(\theta)A(\theta)' \quad , \quad where\ var(\theta) = [M(\theta)]^{-1}$

For this NAFLD process: $(see\ suppl.info\ section\ 3.1)$

4. Life Expectancy of Patient in NAFLD Disease Process:

The disease process is composed of 8 transient states and one absorbing (death state). Sothe Q matrix is partitioned into 4sets :

$$Q = \begin{bmatrix} B & A \\ 0 & 0 \end{bmatrix}, \quad where\ B = \begin{bmatrix} -\gamma_1 & \lambda_{12} & 0 & 0 & 0 & 0 & 0 & \lambda_{18} \\ \mu_{21} & -\gamma_2 & \lambda_{23} & 0 & 0 & 0 & 0 & \lambda_{28} \\ 0 & \mu_{32} & -\gamma_3 & \lambda_{34} & 0 & 0 & 0 & \lambda_{38} \\ 0 & 0 & \mu_{43} & -\gamma_4 & \lambda_{45} & 0 & 0 & \lambda_{48} \\ 0 & 0 & 0 & 0 & -\gamma_5 & \lambda_{56} & 0 & \lambda_{58} \\ 0 & 0 & 0 & 0 & 0 & -\gamma_6 & \lambda_{67} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{79} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{89} \end{bmatrix}$$

Also the differential equations can be partitioned into the following:

$[\acute{P}(t) \quad \acute{P}_k(t)] = [P(t) \quad P_k(t)]\begin{bmatrix} B & A \\ 0 & 0 \end{bmatrix}$

B is the transition rate matrix among the transient states and the column vector A is the transition rate from each transient state to the absorbing (death) state.

$A = -B1^T \quad such\ that\ 1^T\ is\ a\ column\ vector\ of\ (k-1) \times 1\ with\ all\ its\ elements\ equal\ to\ one$

$[\acute{P}(t) \quad \acute{P}_k(t)] = [P(t) \quad P_k(t)]\begin{bmatrix} B & A \\ 0 & 0 \end{bmatrix}\ can\ be\ written\ as$

$\acute{P}(t) = P(t)B \quad and\ \acute{P}_k(t) = P(t)A$

$The\ solution\ to\ \ \acute{}P(t) = P(t)B \quad is \quad P(t) = P(0)e^{BT} \quad then \quad \acute{P}_k(t) = P(0)e^{BT}A$

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

$If\ \ \tau_k \quad is\ the\ time\ taken\ from\ state\ i\ to\ reach\ the\ absorbing\ death\ state\ from\ the\ initil\ time$

$F_k(t) = pr[\tau_k \le t] = pr[X(t) = k] = P_k(t) = 1 - P(t)1^t = 1 - P(0)e^{BT}1^t$

The moment theory for 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 such that :

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

$\therefore\ sP^*(s) - P(0) = P^*(s)B\ \ and\ sP^*{}_k(s) = P^*(s)A$

Rearrange :

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

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

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

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

$f^*{}_k(s) = s\,F^*{}_k(s) = \ P(0)[sI - B]^{-1}A \quad ; \quad where \quad A = -B1^T$

Mean time to absorption:

$$E(\tau_k) = (-1)\left.\frac{df^*{}_k(s)}{ds}\right|_{s=0} = (-1)P(0)[sI - B]^{-2}A|_{s=0} = P(0)[-B]^{-1}1^T$$

For this NAFLD process: $(see\ suppl.info\ section\ 4\ )$

5. 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 $u(0) = \sum_{j=1}^{8} u_j\ (0)$, as there are 8 transient states and 1 absorbing states, where $u_j\,(0)$is the initial size or number of patients in state j at time $t = 0$ given that $u_9(0) = 0$i.e initial size of patients in state 9(absorbing death state) is 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[15], there will be $u_j\,(t)$ patients in the transient states at time t, also there will be $u_9(t)$patients in state 9 (death state) at time t.

$$E\left[u_j(t)|u_j(0)\right] = \sum_{j=1,i=1}^{9} u_i(0)P_{ij}(t) \quad , \qquad i\&\,j = 1,\dots,9$$

For this NAFLD process: $(see\ suppl.info\ section\ 5\ )$

6.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.*(see suppl. Info. Section 6)*

A study was conducted over 15 years on 1050 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 (see supplementary material).

The estimated transition rate matrix Q is:

$$\hat{Q} = \begin{bmatrix} -.397 & .39 & 0 & 0 & 0 & 0 & 0 & 0 & .007 \\ .02 & -.281 & .25 & 0 & 0 & 0 & 0 & 0 & .011 \\ 0 & .05 & -.365 & .225 & 0 & 0 & 0 & .047 & .043 \\ 0 & 0 & .041 & -.538 & .281 & 0 & 0 & .109 & .107 \\ 0 & 0 & 0 & 0 & -.348 & .19 & 0 & .059 & .099 \\ 0 & 0 & 0 & 0 & 0 & -.934 & .767 & 0 & .167 \\ 0 & 0 & 0 & 0 & 0 & 0 & -.421 & 0 & .421 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -.745 & .745 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$var(\hat{\theta}) = 1 \times 10^{-13} \begin{bmatrix} v_1 & v_2 \\ v_3 & v_4 \end{bmatrix}$where

Where

$$v_1 = \begin{bmatrix} .3292 & .0327 & .4414 & .0827 & .4004 & .0268 & .2540 & .1517 \\ .0327 & .0064 & .0428 & .0108 & .0385 & .0053 & .0268 & .0159 \\ .4414 & .0428 & .5922 & .1100 & .5373 & .0350 & .3400 & .2032 \\ .0827 & .0108 & .1100 & .0228 & .0995 & .0088 & .0650 & .0387 \\ .4004 & .0385 & .5373 & .0995 & .4876 & .0315 & .3082 & .1843 \\ .0268 & .0053 & .0350 & .0088 & .0315 & .0044 & .0219 & .0130 \\ .2540 & .0268 & .3400 & .0650 & .3082 & .0219 & .1967 & .1174 \\ .1517 & .0159 & .2032 & .0387 & .1843 & .0130 & .1174 & .0702 \end{bmatrix}$$

v_2 , v_3 and $v_4$are all zero matrices of size (8 by 14) , (14 by 8) and (14 by 14) respectively.

Transition probability matrix at 1 year:

$$P(1) = \begin{bmatrix} .6751 & .279 & .0345 & .0024 & 0 & 0 & 0 & .0006 & .0082 \\ .0143 & .7625 & .1819 & .0188 & .0019 & 0 & 0 & .0044 & .016 \\ .0004 & .0364 & .7017 & .1439 & .0206 & .0012 & .0002 & .0346 & .0604 \\ 0 & .0007 & .0262 & .5868 & .1800 & .0145 & .0039 & .0616 & .1215 \\ 0 & 0 & 0 & 0 & .7061 & .1015 & .0416 & .0344 & .1163 \\ 0 & 0 & 0 & 0 & 0 & .3930 & .3938 & 0 & .2132 \\ 0 & 0 & 0 & 0 & 0 & 0 & .6564 & 0 & .3436 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & .4747 & .5253 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

Mean time spent by the patient in state 1 is approximately 2years and 6 months, in state2 the mean sojourn time is approximately 3 years and 6 months , in state 3 it is approximately 2 years and 9 months , in state 4 it is approximately 1 years and 10 months , in state 5 it is approximately 2 years and 10 months, in state 6 it is approximately 1 years and 1 month, in state 7 it is approximately 2 years and 5 months and lastly in state 8 the mean sojourn time is approximately 1 years and 4 months.

If a cohort of 5000 NAFLD patients have initial distribution of$[.62 \quad .22 \quad .081 \quad .03 \quad .028 \quad .005 \quad .007 \quad .009 \quad 0]$ and initial counts of patients in each state are$[3100 \quad 1100 \quad 405 \quad 150 \quad 140 \quad 25 \quad 35 \quad 45 \quad 0]$then at 1 year the state probability distribution is$[.4217 \quad .3437 \quad .1191 \quad .035 \quad .0274 \quad .0054 \quad .0079 \quad .0111 \quad .0287]$ and the expected counts of patients are$[2109 \quad 1718 \quad 595 \quad 175 \quad 137 \quad 27 \quad 39 \quad 56 \quad 144]$.

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

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 $P_{ij}\,(\Delta t = 1)$

$$P_{ij}\,(\Delta t = 1) = \begin{bmatrix} .6751 & .279 & .0345 & .0024 & .0002 & .0000 & .0000 & .0006 & .0082 \\ .0143 & .7625 & .1819 & .0188 & .0018 & .0001 & .0000 & .0044 & .016 \\ .0004 & .0364 & .7017 & .1409 & .0206 & .0012 & .0002 & .0346 & .0604 \\ 0 & .0007 & .0257 & .561 & .1771 & .0145 & .0039 & .0616 & .1215 \\ 0 & 0 & 0 & 0 & .7061 & .1015 & .0416 & .0344 & .1163 \\ 0 & 0 & 0 & 0 & 0 & .3930 & .3938 & 0 & .2132 \\ 0 & 0 & 0 & 0 & 0 & 0 & .6564 & 0 & .3436 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & .4747 & .5253 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

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

	State1	State2	State3	State4	State5	State6	State7	State8	State9	total
State1	1000.5	413.5	51.13	3.6	.3	0	0	.8892	12.15	1482
State2	7.4074	394.97	94.22	9.738	.9324	.0518	0	2.2792	8.288	517.89
State3	.08	7.28	140.34	28.18	4.12	.24	.04	6.92	12.08	199.28
State4	0	.0511	1.8761	40.953	12.9283	1.0585	.2847	4.4968	8.8695	70.518
State5	0	0	0	0	47.3087	6.8005	2.7872	2.3048	7.7921	66.9933
State6	0	0	0	0	0	3.93	3.938	0	2.132	10
State7	0	0	0	0	0	0	11.1588	0	5.8412	17
State8	0	0	0	0	0	0	0	9.494	10.506	20
State9	0	0	0	0	0	0	0	0	0	0

Step 4: apply $\sum_{i=1}^{9}\sum_{j=1}^{9}\frac{\left(O_{ij}-E_{ij}\right)^2}{E_{ij}} = 2226.362 \sim \chi^2_{(9-1)(9-1)(.05)}$

The same steps are used for the observed transition counts in the $\Delta t = 2\ and\ \Delta t = 3$ with the following results:

$$P_{ij}\,(\Delta t = 2) = \begin{bmatrix} .4597 & .4023 & .0983 & .0131 & .0019 & .0001 & .0000 & .0032 & .0209 \\ .0206 & .5920 & .2673 & .0505 & .0097 & .0007 & .0002 & .0129 & .0441 \\ .001 & .0535 & .5026 & .1786 & .054 & .0054 & .0022 & .0503 & .1414 \\ 0 & .0018 & .0325 & .3183 & .2249 & .0318 & .0178 & .0708 & .2486 \\ 0 & 0 & 0 & 0 & .4986 & .1116 & .0967 & .0406 & .2525 \\ 0 & 0 & 0 & 0 & 0 & .1544 & .4133 & 0 & .4323 \\ 0 & 0 & 0 & 0 & 0 & 0 & .4308 & 0 & .5692 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & .2254 & .7746 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

The expected counts

	State1	State2	State3	State4	State5	State6	State7	State8	State9	total
State1	272.6	238.56	58.292	7.7683	1.1267	.0593	0	1.8976	12.394	592.704
State2	4.2642	122.54	55.33	10.454	2.0079	.1449	.0414	2.6703	9.129	206.59
State3	.08	4.28	40.208	14.288	4.32	.432	.176	4.024	11.312	79.12
State4	0	.0522	.9425	9.231	6.5221	.922	.5162	2.0532	7.209	27.45
State5	0	0	0	0	13.462	3.013	2.6109	1.0962	6.818	27
State6	0	0	0	0	0	.6176	1.6532	0	1.729	4
State7	0	0	0	0	0	0	3.0156	0	3.984	7
State8	0	0	0	0	0	0	0	1.8032	6.197	8
State9	0	0	0	0	0	0	0	0	0	0

$$\sum_{i=1}^{9}\sum_{j=1}^{9}\frac{\left(O_{ij}-E_{ij}\right)^2}{E_{ij}} = 160.115 \sim \chi^2_{(9-1)(9-1)(.05)}$$

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

$$P_{ij}\,(\Delta t = 3) = \begin{bmatrix} .3161 & .4386 & .1584 & .0299 & .0065 & .0006 & .0002 & .0078 & .0406 \\ .0225 & .4669 & .2973 & .0771 & .0223 & .0024 & .0011 & .0214 & .0842 \\ .0016 & .0595 & .367 & .172 & .0802 & .0108 & .0066 & .0544 & .2289 \\ .0001 & .0028 & .0313 & .1832 & .2159 & .0400 & .0348 & .0621 & .3655 \\ 0 & 0 & 0 & 0 & .352 & .0945 & .1282 & .0364 & .3889 \\ 0 & 0 & 0 & 0 & 0 & .0607 & .3321 & 0 & .6072 \\ 0 & 0 & 0 & 0 & 0 & 0 & .2828 & 0 & .7172 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & .107 & .893 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

The expected counts

	State1	State2	State3	State4	State5	State6	State7	State8	State9	total
State1	46.783	64.913	23.443	4.4252	.962	.0888	.0296	1.1544	6.0088	147.81
State2	1.148	23.812	15.162	3.9321	1.1373	.1224	.0561	1.3914	4.2942	50.76
State3	.0288	1.071	6.606	3.096	1.4436	.1944	.1188	.9792	4.1202	17.66
State4	.0007	.0196	.2191	1.2824	1.5113	.28	.2436	.4347	2.5585	6.55
State5	0	0	0	0	2.464	.6615	.8974	.2548	2.7223	7
State6	0	0	0	0	0	.1214	.6642	0	1.2144	2
State7	0	0	0	0	0	0	.5656	0	1.4344	2
State8	0	0	0	0	0	0	0	.321	2.679	3
State9	0	0	0	0	0	0	0	0	0	0

$$\sum_{i=1}^{9}\sum_{j=1}^{9}\frac{\left(O_{ij}-E_{ij}\right)^2}{E_{ij}} = 69.778\sim\chi^2_{(9-1)(9-1)(.05)}$$

Step 5: sum up the above results to get:

$$\sum_{i=1}^{9}\sum_{j=1}^{9}\sum_{l=1}^{t=3}\frac{\left(O_{ijl}-E_{ijl}\right)^2}{E_{ijl}} = 2456.255\sim\chi^2_{(df=192)(.05)}$$

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.

7.Conclusion and Summary

Continuous time Markov chains are suitable mathematical and statistical tools to be used for analysis of disease evolution over time. CTMCs being a type of multistate models are utilized to study this evolution in NAFLD patients, with its main phenotypes NAFLD and NASH, as well as the associated presence of fibrosis and its stages. The prevalence of NAFLD is rapidly increasing worldwide, and parallels the epidemics of obesity and type 2 diabetes. Metabolic syndrome is a well-known risk factor.

In the present study, NAFLD is modeled in more elaborative expanded form, which includes nine states: the first eight states are the states of disease progression as time elapses; while, the ninth state is the death state. The importance of such analysis is that the health policy makers can predict the number of affected patients at each stage, the needed investigations and medications for each of them, and the costs and budgets that the medical insurance should assign to this disease burden. This analysis is of great value and benefit to the physicians, as they can conduct longitudinal studies to explore further investigations that better define each stage specifically and efficiently, as well as to explore further treatment needed for each stage. An example of the non-invasive diagnostic tools is the circulating level of cytokeratin-18 fragments, although promising it is not available in a clinical care setting and there is not an established cut-off value for identifying steato-hepatitis (NASH)[16]**.** A genetic polymorphism of patatin-like phospholipase domain-containing protein 3 gene variants (PNPLA-3) are associated with NASH and advanced fibrosis, however testing for these variants in routine clinical care is not supported and needs further studies.

The hypothetical examples of factitious non-real data is used to emphasize the attributes need to be estimated:

- ❖ Transition rate matrix among the various states.
- ❖ Transition probability matrix among states.
- ❖ Mean sojourn time in each state.
- ❖ Life expectancy in each state; in other words, mean time to absorption (death state).
- ❖ Expected number of patients in each state.
- ❖ State probability distribution at specific time point in the future.

Such analysis may give better insights to physicians, especially when new drug classes will soon be released in the market. What drug classes are to be used first? How to monitor the disease throughout the journey of treatment? What investigations to be used in such monitoring? How to modify the drug treatment? What is the target that needs to be achieved and how to maintain this target? And what is more to be said; that in late stage of the disease, when patients suffer from decompensated liver cirrhosis; liver transplantation is the treatment of choice to such patients, which increases the economic burden of NAFLD as was the disease course during treatment in early stages. Also, the load of what are the best economic noninvasive tests to be used in primary health care units for stratification and identification of high risk patients, whether to do genetic tests in health insurance setting, and when to refer for liver biopsy in secondary or special clinics. All these questions can be answered from such longitudinal studies conducted on susceptible individuals. Over and above, some of the recently investigated noninvasive scoring systems of fibrosis need further external validation so as to be generalized in ethnicities other than the one tested upon. There are some controversies of cutoff points of these scoring systems among countries, and among ethnicities within the same country. Although liver biopsy is considered the standard method for diagnosis of NAFLD and staging it; its limitations encourage the development of various noninvasive tests, which necessitate better correlation between the findings obtained from the biopsy and the results of these tests to minimize the misclassification errors, which hamper good diagnosis and prognosis of the patient. These tests should be easy, feasible, convenient and with high safety profile to be used repeatedly in patients for follow up in such longitudinal studies.

Multistate model represented by CTMC is a valuable statistical methodology, for longitudinal studies in medical researches to better comprehend and understand the pathophysiology, or the mechanism of the NAFLD process, and the interactions between the different modifiers either the external, or the internal modifiers. The external modifiers reside in bad dietary habits with excessive fat and carbohydrate ingestion, as well as sedentary life; while, the internal modifiers are represented in genetic factors affecting the metabolism of the food stuff (fat and carbohydrates) and other cellular functions such as risk factors for fibro-genesis (formation of fibrous tissue); as, fibrosis is a detrimental predictor factor for disease progression to liver cirrhosis and its complications. The importance of such understanding has a great impact to reveal the genes that must be tested if ever needed, for whom to do such a test, and should it be in the utilities or services offered by the medical insurance. Moreover, should the degradation byproducts resulting from extracellular matrix destruction be used in routine clinical practice to mirror the fibrosis stages?

In Egypt, there are scare data, or may be no available data, about the prevalence of NAFLD and its phenotypes. Guidelines for risk stratification and identification are also lacking. Thus, more longitudinal studies are needed to cover these issues.

Multistate models can also be used for analysis of competing risks to death in such patients, as the first and second most common causes of death in NAFLD patients are the cardiovascular diseases (CVD) and kidney diseases, while the liver-related mortality is the third common cause of death.

Some other statistical methodologies, like : semi Markov and hidden Markov chains can be used to model NAFLD, especially hidden Markov CTMC can be used to model misclassification errors encountered in studies conducted by time homogenous CTMC.

Hint: A Matlab code is edited to calculate the statistical indices in the hypothetical example. The code can be found published in code ocean site with the following URL:

codeocean.com/capsule/7628018/tree/v1

Abbreviations :

CC: compensated cirrhosis (stage 4),CTMC: continuous time Markov chains, CVS: cardiovascular disease, DCC: de-compensated cirrhosis (stage 5),EASD: European Association for the Study of diabetes, EASL: European Association for the Study of liver, EASO: European Association for the Study of obesity, EM= extra-mortality (stage 9),HCC :hepato-cellular carcinoma (stage 8),HS: hepatic steatosis, LT= liver transplant(stage 6),NAFLD: non-alcoholic fatty liver disease, NAFLD-NO FB: nonalcoholic fatty liver disease with no fibrosis (stage 1),NASH: non-alcoholic steatohepatitis, NASH-NO FB : nonalcoholic steato-hepatitis with no fibrosis (stage 2),NASH-FB : nonalcoholic steato-hepatitis with fibrosis (stage 3),PLT : post liver transplant (stage 7),PNPLA-3: patatin-like phospholipase domain-containing protein 3 gene variants, TE: transient elastography,T2DM: type 2 diabetes mellitus.

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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Appendix:

1.Probability transition matrix:

For the multistate Markov model demonstrating the NAFLD disease process; the forward Kolomogrov differential equations are the following:

$$\frac{d}{dt}P_{ij}(t) =$$

$$\begin{bmatrix} P_{11} & P_{12} & P_{13} & P_{14} & P_{15} & P_{16} & P_{17} & P_{18} & P_{19} \\ P_{21} & P_{22} & P_{23} & P_{24} & P_{25} & P_{26} & P_{27} & P_{28} & P_{29} \\ P_{31} & P_{32} & P_{33} & P_{34} & P_{35} & P_{36} & P_{37} & P_{38} & P_{39} \\ P_{41} & P_{42} & P_{43} & P_{44} & P_{45} & P_{46} & P_{47} & P_{48} & P_{49} \\ 0 & 0 & 0 & 0 & P_{55} & P_{56} & P_{57} & P_{58} & P_{59} \\ 0 & 0 & 0 & 0 & 0 & P_{66} & P_{67} & 0 & P_{69} \\ 0 & 0 & 0 & 0 & 0 & 0 & P_{77} & 0 & P_{79} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & P_{88} & P_{89} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & P_{99} \end{bmatrix} \begin{bmatrix} -\gamma_1 & \lambda_{12} & 0 & 0 & 0 & 0 & 0 & \lambda_{18} & \lambda_{19} \\ \mu_{21} & -\gamma_2 & \lambda_{23} & 0 & 0 & 0 & 0 & \lambda_{28} & \lambda_{29} \\ 0 & \mu_{32} & -\gamma_3 & \lambda_{34} & 0 & 0 & 0 & \lambda_{38} & \lambda_{39} \\ 0 & 0 & \mu_{43} & -\gamma_4 & \lambda_{45} & 0 & 0 & \lambda_{48} & \lambda_{49} \\ 0 & 0 & 0 & 0 & -\gamma_5 & \lambda_{56} & 0 & \lambda_{58} & \lambda_{59} \\ 0 & 0 & 0 & 0 & 0 & -\gamma_6 & \lambda_{67} & 0 & \lambda_{69} \\ 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{79} & 0 & \lambda_{79} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{89} & \lambda_{89} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

The Kolmogrov differential equations are:

The set of equations of the first row:

$$\frac{dP_{11}(t)}{dt} = -(\lambda_{12} + \lambda_{18} + \lambda_{19})P_{11}(t) + \mu_{21}P_{12}(t), \frac{dP_{12}(t)}{dt} = \lambda_{12}P_{11}(t) - (\lambda_{23} + \lambda_{28} + \lambda_{29} + \mu_{21})P_{12}(t) + \mu_{32}P_{13}(t)$$

$$\frac{dP_{13}(t)}{dt} = \lambda_{23}P_{12}(t) - (\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32})P_{13}(t) + \mu_{43}P_{14}(t), \frac{dP_{14}(t)}{dt} = \lambda_{34}P_{13}(t) - (\lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43})P_{14}(t)$$

$$\frac{dP_{15}(t)}{dt} = \lambda_{45}P_{14}(t) - (\lambda_{56} + \lambda_{58} + \lambda_{59})P_{15}(t), \frac{dP_{16}(t)}{dt} = \lambda_{56}P_{15}(t) - (\lambda_{67} + \lambda_{69})P_{16}(t), \frac{dP_{17}(t)}{dt} = \lambda_{67}P_{16}(t) - \lambda_{79}P_{17}(t)$$

$$\frac{dP_{18}(t)}{dt} = \lambda_{18}P_{11}(t) + \lambda_{28}P_{12}(t) + \lambda_{38}P_{13}(t) + \lambda_{48}P_{14}(t) + \lambda_{58}P_{15}(t) - \lambda_{89}P_{18}(t)$$

$$\frac{dP_{19}(t)}{dt} = \lambda_{19}P_{11}(t) + \lambda_{29}P_{12}(t) + \lambda_{39}P_{13}(t) + \lambda_{49}P_{14}(t) + \lambda_{59}P_{15}(t) + \lambda_{69}P_{16}(t) + \lambda_{79}P_{17}(t) + \lambda_{89}P_{18}(t)$$

The set of equations of the second row:

$$\frac{d\,P_{21}(t)}{dt} = -(\lambda_{12} + \lambda_{18} + \lambda_{19})P_{21}(t) + \mu_{21}P_{22}(t), \frac{d\,P_{22}(t)}{dt} = \lambda_{12}P_{21}(t) - (\lambda_{23} + \lambda_{28} + \lambda_{29} + \mu_{21})P_{22}(t) + \mu_{32}P_{23}(t)$$

$$\frac{d\,P_{23}(t)}{dt} = \lambda_{23}P_{22}(t) - (\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32})P_{23}(t) + \mu_{43}P_{24}(t), \frac{d\,P_{24}(t)}{dt} = \lambda_{34}P_{23}(t) - (\lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43})P_{24}(t)$$

$$\frac{d\,P_{25}(t)}{dt} = \lambda_{45}P_{24}(t) - (\lambda_{56} + \lambda_{58} + \lambda_{59})P_{25}(t), \frac{d\,P_{26}(t)}{dt} = \lambda_{56}P_{25}(t) - (\lambda_{67} + \lambda_{69})P_{26}(t), \frac{d\,P_{27}(t)}{dt} = \lambda_{67}P_{26}(t) - \lambda_{79}P_{27}(t)$$

$$\frac{d\,P_{28}(t)}{dt} = \lambda_{18}P_{21}(t) + \lambda_{28}P_{22}(t) + \lambda_{38}P_{23}(t) + \lambda_{48}P_{24}(t) + \lambda_{58}P_{25}(t) - \lambda_{89}P_{28}(t)$$

$$\frac{d\,P_{29}(t)}{dt} = \lambda_{19}P_{21}(t) + \lambda_{29}P_{22}(t) + \lambda_{39}P_{23}(t) + \lambda_{49}P_{24}(t) + \lambda_{59}P_{25}(t) + \lambda_{69}P_{26}(t) + \lambda_{79}P_{27}(t) + \lambda_{89}P_{28}(t)$$

The set of equations of the third row:

$$\frac{d\,P_{31}(t)}{dt} = -(\lambda_{12} + \lambda_{18} + \lambda_{19})P_{31}(t) + \mu_{21}P_{32}(t), \frac{d\,P_{32}(t)}{dt} = \lambda_{12}P_{31}(t) - (\lambda_{23} + \lambda_{28} + \lambda_{29} + \mu_{21})P_{32}(t) + \mu_{32}P_{33}(t)$$

$$\frac{d\,P_{33}(t)}{dt} = \lambda_{23}P_{32}(t) - (\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32})P_{33}(t) + \mu_{43}P_{34}(t), \frac{d\,P_{34}(t)}{dt} = \lambda_{34}P_{33}(t) - (\lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43})P_{34}(t)$$

$$\frac{d\,P_{35}(t)}{dt} = \lambda_{45}P_{34}(t) - (\lambda_{56} + \lambda_{58} + \lambda_{59})P_{35}(t), \frac{d\,P_{36}(t)}{dt} = \lambda_{56}P_{35}(t) - (\lambda_{67} + \lambda_{69})P_{36}(t), \frac{d\,P_{37}(t)}{dt} = \lambda_{67}P_{36}(t) - \lambda_{79}P_{37}(t)$$

$$\frac{d\,P_{38}(t)}{dt} = \lambda_{18}P_{31}(t) + \lambda_{28}P_{32}(t) + \lambda_{38}P_{33}(t) + \lambda_{48}P_{34}(t) + \lambda_{58}P_{35}(t) - \lambda_{89}P_{38}(t)$$

$$\frac{d\,P_{39}(t)}{dt} = \lambda_{19}P_{31}(t) + \lambda_{29}P_{32}(t) + \lambda_{39}P_{33}(t) + \lambda_{49}P_{34}(t) + \lambda_{59}P_{35}(t) + \lambda_{69}P_{36}(t) + \lambda_{79}P_{37}(t) + \lambda_{89}P_{38}(t)$$

The set of equations of the fourth row:

$$\frac{d\,P_{41}(t)}{dt} = -(\lambda_{12} + \lambda_{18} + \lambda_{19})P_{41}(t) + \mu_{21}P_{42}(t), \frac{d\,P_{42}(t)}{dt} = \lambda_{12}P_{41}(t) - (\lambda_{23} + \lambda_{28} + \lambda_{29} + \mu_{21})P_{42}(t) + \mu_{32}P_{43}(t)$$

$$\frac{d\,P_{43}(t)}{dt} = \lambda_{23}P_{42}(t) - (\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32})P_{43}(t) + \mu_{43}P_{44}(t), \frac{d\,P_{44}(t)}{dt} = \lambda_{34}P_{43}(t) - (\lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43})P_{44}(t)$$

$$\frac{d\,P_{45}(t)}{dt} = \lambda_{45}P_{44}(t) - (\lambda_{56} + \lambda_{58} + \lambda_{59})P_{45}(t), \frac{d\,P_{46}(t)}{dt} = \lambda_{56}P_{45}(t) - (\lambda_{67} + \lambda_{69})P_{46}(t), \frac{d\,P_{47}(t)}{dt} = \lambda_{67}P_{46}(t) - \lambda_{79}P_{47}(t)$$

$$\frac{d\,P_{48}(t)}{dt} = \lambda_{18}P_{41}(t) + \lambda_{28}P_{42}(t) + \lambda_{38}P_{43}(t) + \lambda_{48}P_{44}(t) + \lambda_{58}P_{45}(t) - \lambda_{89}P_{48}(t)$$

$$\frac{d\,P_{49}(t)}{dt} = \lambda_{19}P_{41}(t) + \lambda_{29}P_{42}(t) + \lambda_{39}P_{43}(t) + \lambda_{49}P_{44}(t) + \lambda_{59}P_{45}(t) + \lambda_{69}P_{46}(t) + \lambda_{79}P_{47}(t) + \lambda_{89}P_{48}(t)$$

Last 13 equations :

$$\frac{d\,P_{55}(t)}{dt} = -(\lambda_{56} + \lambda_{58} + \lambda_{59})P_{55}(t), \frac{d\,P_{56}(t)}{dt} = \lambda_{56}P_{55}(t) - (\lambda_{67} + \lambda_{69})P_{56}(t), \frac{d\,P_{57}(t)}{dt} = \lambda_{67}P_{56}(t) - \lambda_{79}P_{57}(t)$$

$$\frac{d\,P_{58}(t)}{dt} = \lambda_{58}P_{55}(t) - \lambda_{89}P_{58}(t), \frac{d\,P_{59}(t)}{dt} = \lambda_{59}P_{55}(t) + \lambda_{69}P_{56}(t) + \lambda_{79}P_{57}(t) + \lambda_{89}P_{58}(t), \frac{d\,P_{66}(t)}{dt} = -(\lambda_{67} + \lambda_{69})P_{66}(t)$$

$$\frac{d\,P_{67}(t)}{dt} = \lambda_{67}P_{66}(t) - \lambda_{79}P_{67}(t), \frac{d\,P_{69}(t)}{dt} = \lambda_{69}P_{66}(t) + \lambda_{79}P_{67}(t), \frac{d\,P_{77}(t)}{dt} = -\lambda_{79}P_{77}(t), \frac{d\,P_{79}(t)}{dt} = \lambda_{79}P_{77}(t), \frac{d\,P_{88}(t)}{dt} = -\lambda_{89}P_{88}(t)$$

$$\frac{d\,P_{89}(t)}{dt} = \lambda_{89}P_{88}(t), P_{99}(t) = 1$$

The Kolmogrov Differential Equations For The First 4 Probabilities In The First 4 Rows Are:

$$\frac{d\,P_{ij}(t)}{dt} = P(t)Q(t) = \begin{bmatrix} P_{11} & P_{12} & P_{13} & P_{14} \\ P_{21} & P_{22} & P_{23} & P_{24} \\ P_{31} & P_{32} & P_{33} & P_{34} \\ P_{41} & P_{42} & P_{43} & P_{44} \end{bmatrix} \begin{bmatrix} -\gamma_1 & \lambda_{12} & 0 & 0 \\ \mu_{21} & -\gamma_2 & \lambda_{23} & 0 \\ 0 & \mu_{32} & -\gamma_3 & \lambda_{34} \\ 0 & 0 & \mu_{43} & -\gamma_4 \end{bmatrix}$$

$let's\ call\quad (\lambda_{12} + \lambda_{18} + \lambda_{19}) = \gamma_1 \quad , \qquad (\lambda_{23} + \lambda_{28} + \lambda_{29} + \mu_{21}) = \gamma_2$

$(\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32}) = \gamma_3 \quad , \qquad (\lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43}) = \gamma_4$

The set of equations of the first row: (first 4 probabilities)

The differential equations for the first 4 PDFs' as stated previously solved using Laplace method :

$\mathcal{L}\{P_{ij}(t)\}\ \ is\ presented\ as\ \ P_{ij}^*(s)\ \ , \mathcal{L}\{P_{ij}'(t)\} = s\mathcal{L}\{P_{ij}(t)\} - P_{ij}(0) = s\,P_{ij}^*(s) - P_{ij}(0)$

$$\frac{d\,P_{11}(t)}{dt} = -\gamma_1 P_{11}(t) + \mu_{21}P_{12}(t)$$

$s\,P_{11}^*(s) - P_{11}(0) = -\gamma_1 P_{11}^*(s) + \mu_{21}P_{12}^*(s) \quad \rightarrow \qquad s\,P_{11}^*(s) - 1 = -\gamma_1 P_{11}^*(s) + \mu_{21}P_{12}^*(s)$

$(s + \gamma_1)P_{11}^*(s) - \mu_{21}P_{12}^*(s) = 1$ ……………………………………… (1)

$$\frac{d\,P_{12}(t)}{dt} = \lambda_{12}P_{11}(t) - (\lambda_{23} + \lambda_{28} + \lambda_{29} + \mu_{21})P_{12}(t) + \mu_{32}P_{13}(t)$$

$s\,P_{12}^*(s) - P_{12}(0) = \lambda_{12}P_{11}^*(s) - \gamma_2 P_{12}^*(s) + \mu_{32}P_{13}^*(s) \rightarrow s\,P_{12}^*(s) - 0 - \lambda_{12}P_{11}^*(s) + \gamma_2 P_{12}^*(s) - \mu_{32}P_{13}^*(s) = 0$

$(s + \gamma_2)P_{12}^*(s) - \lambda_{12}P_{11}^*(s) - \mu_{32}P_{13}^*(s) = 0$ ……………….. (2)

$$\frac{d\,P_{13}(t)}{dt} = \lambda_{23}P_{12}(t) - (\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32})P_{13}(t) + \mu_{43}P_{14}(t)$$

$s\,P_{13}^*(s) - P_{13}(0) = \lambda_{23}P_{12}^*(s) - \gamma_3 P_{13}^*(s) + \mu_{43}P_{14}^*(s) \rightarrow\ s\,P_{13}^*(s) - 0 = \lambda_{23}P_{12}^*(s) - \gamma_3 P_{13}^*(s) + \mu_{43}P_{14}^*(s)$

$(s + \gamma_3)P_{13}^*(s) - \lambda_{23}P_{12}^*(s) - \mu_{43}P_{14}^*(s) = 0$ …………………………. (3)

$$\frac{d\,P_{14}(t)}{dt} = \lambda_{34}P_{13}(t) - (\lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43})P_{14}(t)$$

$s\,P_{14}^*(s) - P_{14}(0) = \lambda_{34}P_{13}^*(s) - \gamma_4 P_{14}^*(s) \quad \rightarrow \quad s\,P_{14}^*(s) - 0 = \lambda_{34}P_{13}^*(s) - \gamma_4 P_{14}^*(s)$

$(s + \gamma_4)P_{14}^*(s) - \lambda_{34}P_{13}^*(s) = 0$ ……………………….. (4)

Putting these equations (1,2,3,4) in matrix notation : $MP_{ij}^*(s) = Z$

$$\begin{bmatrix} (s+\gamma_1) & -\mu_{21} & 0 & 0 \\ -\lambda_{12} & (s+\gamma_2) & -\mu_{32} & 0 \\ 0 & -\lambda_{23} & (s+\gamma_3) & -\mu_{43} \\ 0 & 0 & -\lambda_{34} & (s+\gamma_4) \end{bmatrix} \begin{bmatrix} P_{11}^*(s) \\ P_{12}^*(s) \\ P_{13}^*(s) \\ P_{14}^*(s) \end{bmatrix} = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}\ .\ Then\ apply\ Cramer\ rule\ to\ solve\ for\ P_{ij}^*(s) = \frac{D_{P_{ij}^*(s)}}{D}$$

The determinant in the denominator :

$To\ solve\ for\ \ P_{ij}^*(s)\ using\ cramer\ rule\ , the\ determinanat\ \ is\ calculated\ for$

$: D\ \ ,\ \ D_{P_{11}^*(s)},\ \ D_{P_{12}^*(s)},\ \ D_{P_{13}^*(s)},\ \ D_{P_{14}^*(s)}$

$Put\ M\ in\ the\ form \begin{bmatrix} A & B \\ 0 & C \end{bmatrix}\ to\ calculate\ the\ determinant\ in\ a\ blocked\ partition\ matrix$

$$\left\| \begin{bmatrix} (s+\gamma_1) & -\mu_{21} & 0 & 0 \\ -\lambda_{12} & (s+\gamma_2) & -\mu_{32} & 0 \\ 0 & -\lambda_{23} & (s+\gamma_3) & -\mu_{43} \\ 0 & 0 & -\lambda_{34} & (s+\gamma_4) \end{bmatrix} \right\|$$

$$D = [(s+\gamma_1)(s+\gamma_2) - \lambda_{12}\,\mu_{21}] \times \left[\left(\frac{-\lambda_{23}\,\mu_{32}(s+\gamma_1) - \lambda_{12}\,\mu_{21}(s+\gamma_3) + (s+\gamma_1)(s+\gamma_2)(s+\gamma_3)}{(s+\gamma_1)(s+\gamma_2) - \lambda_{12}\,\mu_{21}} \right)(s+\gamma_4) - \lambda_{34}\,\mu_{43} \right]$$

$$D = [(s+\gamma_1)(s+\gamma_2) - \lambda_{12}\,\mu_{21}][(s+\gamma_3)(s+\gamma_4) - \lambda_{34}\,\mu_{43}] - \lambda_{23}\,\mu_{32}(s+\gamma_1)(s+\gamma_4)$$

$$D = s^4 + (w_1 + w_3)s^3 + (w_2 + w_4 + w_1w_3 - \lambda_{23}\,\mu_{32})s^2 + (w_2w_3 + w_1w_4 - w_5)s + (w_2w_4 - w_6)\ \ ,$$

$where:$

$w_1 = \gamma_1 + \gamma_2 = (\lambda_{12} + \lambda_{18} + \lambda_{19}) + (\lambda_{23} + \lambda_{28} + \lambda_{29} + \mu_{21})\ ,$

$w_2 = \gamma_1(\lambda_{23} + \lambda_{28} + \lambda_{29}) + \mu_{21}(\lambda_{18} + \lambda_{19})$

$w_3 = \gamma_3 + \gamma_4 = (\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32}) + (\lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43}),\quad w_4 = \gamma_3(\lambda_{45} + \lambda_{48} + \lambda_{49}) + \mu_{43}(\lambda_{38} + \lambda_{39} + \mu_{32})$

$w_5 = \lambda_{23}\,\mu_{32}(\gamma_1 + \gamma_4)\ \ ,\qquad w_6 = \lambda_{23}\,\mu_{32}\gamma_1\gamma_4 = \lambda_{23}\,\mu_{32}[(\lambda_{12} + \lambda_{18} + \lambda_{19})(\lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43})]$

Determinant in the denominator is a polynomial of the 4 th degree with the following roots: r_1, r_2, r_3, r_4

$D = (s-r_1)(s-r_2)(s-r_3)(s-r_4)$, Then

- ***expand through first column to get*:**

$$D_{P_{11}^*(s)} = \left\|\begin{bmatrix}1 & -\mu_{21} & 0 & 0\\ 0 & (s+\gamma_2) & -\mu_{32} & 0\\ 0 & -\lambda_{23} & (s+\gamma_3) & -\mu_{43}\\ 0 & 0 & -\lambda_{34} & (s+\gamma_4)\end{bmatrix}\right\| = ([s+\gamma_2][(s+\gamma_3)(s+\gamma_4)-\lambda_{34}\,\mu_{43}]) - \lambda_{23}\,\mu_{32}(s+\gamma_4)$$

$$D_{P_{11}^*(s)} = s^3 + (\gamma_2+\gamma_3+\gamma_4)s^2 + (\gamma_2\gamma_3+\gamma_2\gamma_4+\gamma_3\gamma_4-\lambda_{34}\,\mu_{43} - \lambda_{23}\,\mu_{32})\,s - \lambda_{23}\,\mu_{32}\gamma_4 - \lambda_{34}\mu_{43}\gamma_2 + \gamma_2\gamma_3\gamma_4$$

- ***expand through second column to get* :**

$$D_{P_{12}^*(s)} = \left\|\begin{bmatrix}(s+\gamma_1) & 1 & 0 & 0\\ -\lambda_{12} & 0 & -\mu_{32} & 0\\ 0 & 0 & (s+\gamma_3) & -\mu_{43}\\ 0 & 0 & -\lambda_{34} & (s+\gamma_4)\end{bmatrix}\right\| = \lambda_{12}[(s+\gamma_3)(s+\gamma_4)-\lambda_{34}\,\mu_{43}]$$

$$D_{P_{12}^*(s)} = \lambda_{12}s^2 + \lambda_{12}(\gamma_3+\gamma_4)s + \lambda_{12}\gamma_3\gamma_4 - \lambda_{12}\lambda_{34}\,\mu_{43}$$

- ***expand through the third column to get* :**

$$D_{P_{13}^*(s)} = \left\|\begin{bmatrix}(s+\gamma_1) & -\mu_{21} & 1 & 0\\ -\lambda_{12} & (s+\gamma_2) & 0 & 0\\ 0 & -\lambda_{23} & 0 & -\mu_{43}\\ 0 & 0 & 0 & (s+\gamma_4)\end{bmatrix}\right\| = \lambda_{12}\lambda_{23}\ s + \lambda_{12}\lambda_{23}\gamma_4$$

- ***expand through fourth column to get* :**

$$D_{P_{14}^*(s)} = \left\|\begin{bmatrix}(s+\gamma_1) & -\mu_{21} & 0 & 1\\ -\lambda_{12} & (s+\gamma_2) & -\mu_{32} & 0\\ 0 & -\lambda_{23} & (s+\gamma_3) & 0\\ 0 & 0 & -\lambda_{34} & 0\end{bmatrix}\right\| = \lambda_{12}\lambda_{23}\lambda_{34}$$

Using the above technique for the set of equations of the second row (first 4 probabilities) gives the following matrix:

$$\begin{bmatrix}(s+\gamma_1) & -\mu_{21} & 0 & 0\\ -\lambda_{12} & (s+\gamma_2) & -\mu_{32} & 0\\ 0 & -\lambda_{23} & (s+\gamma_3) & -\mu_{43}\\ 0 & 0 & -\lambda_{34} & (s+\gamma_4)\end{bmatrix}\begin{bmatrix}P_{21}^*(s)\\ P_{22}^*(s)\\ P_{23}^*(s)\\ P_{24}^*(s)\end{bmatrix}$$

$$= \begin{bmatrix}0\\1\\0\\0\end{bmatrix}, \textit{then solve for} P_{ij}^*(s) \textit{ by calculating } \ D_{P_{21}^*(s)},\ D_{P_{22}^*(s)},\ D_{P_{23}^*(s)},\ D_{P_{24}^*(s)}$$

- ***expand through first column to get*:**

$$D_{P_{21}^*(s)} = \left\|\begin{bmatrix}0 & -\mu_{21} & 0 & 0\\ 1 & (s+\gamma_2) & -\mu_{32} & 0\\ 0 & -\lambda_{23} & (s+\gamma_3) & -\mu_{43}\\ 0 & 0 & -\lambda_{34} & (s+\gamma_4)\end{bmatrix}\right\| = \mu_{21}[(s+\gamma_3)(s+\gamma_4)-\lambda_{34}\,\mu_{43}]$$

$$D_{P_{21}^*(s)} = \mu_{21}s^2 + (\mu_{21}\gamma_3 + \mu_{21}\gamma_4)\,s + \mu_{21}\gamma_3\gamma_4 - \mu_{21}\lambda_{34}\,\mu_{43}$$

- ***expand through second column to get* :**

$$D_{P_{22}^*(s)} = \left\|\begin{bmatrix}(s+\gamma_1) & 0 & 0 & 0\\ -\lambda_{12} & 1 & -\mu_{32} & 0\\ 0 & 0 & (s+\gamma_3) & -\mu_{43}\\ 0 & 0 & -\lambda_{34} & (s+\gamma_4)\end{bmatrix}\right\| = (s+\gamma_1)[(s+\gamma_3)(s+\gamma_4)-\lambda_{34}\,\mu_{43}]$$

$$D_{P_{22}^*(s)} = s^3 + (\gamma_1+\gamma_3+\gamma_4)s^2 + (\gamma_1\gamma_3+\gamma_1\gamma_4+\gamma_3\gamma_4-\lambda_{34}\,\mu_{43})s - \lambda_{34}\,\mu_{43}\gamma_1 + \gamma_1\gamma_3\gamma_4$$

- ***expand through third column to get* :**

$$D_{P_{23}^*(s)} = \left\|\begin{bmatrix}(s+\gamma_1) & -\mu_{21} & 0 & 0\\ -\lambda_{12} & (s+\gamma_2) & 1 & 0\\ 0 & -\lambda_{23} & 0 & -\mu_{43}\\ 0 & 0 & 0 & (s+\gamma_4)\end{bmatrix}\right\| = \lambda_{23}(s+\gamma_4)(s+\gamma_1)$$

$$= \lambda_{23}s^2 + (\lambda_{23}\gamma_1 + \lambda_{23}\gamma_4)s + \lambda_{23}\gamma_1\gamma_4$$

- ***expand through fourth column to get* :**

$$D_{P_{24}^*(s)} = \left\|\begin{bmatrix}(s+\gamma_1) & -\mu_{21} & 0 & 0\\ -\lambda_{12} & (s+\gamma_2) & -\mu_{32} & 1\\ 0 & -\lambda_{23} & (s+\gamma_3) & 0\\ 0 & 0 & -\lambda_{34} & 0\end{bmatrix}\right\| = \lambda_{23}\lambda_{34}(s+\gamma_1) = \lambda_{23}\lambda_{34}\ s + \lambda_{23}\lambda_{34}\gamma_1$$

Using the above technique for the set of equations of the third row (first 4 probabilities) gives the following matrix:

$$\begin{bmatrix} (s+\gamma_1) & -\mu_{21} & 0 & 0 \\ -\lambda_{12} & (s+\gamma_2) & -\mu_{32} & 0 \\ 0 & -\lambda_{23} & (s+\gamma_3) & -\mu_{43} \\ 0 & 0 & -\lambda_{34} & (s+\gamma_4) \end{bmatrix} \begin{bmatrix} P^*_{31}(s) \\ P^*_{32}(s) \\ P^*_{33}(s) \\ P^*_{34}(s) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 1 \\ 0 \end{bmatrix}, \textit{then solve for } P^*_{ij}(s) \textit{ by calculating } \; D_{P^*_{31}(s)},\; D_{P^*_{32}(s)},\; D_{P^*_{33}(s)},\; D_{P^*_{34}(s)}$$

- ***expand through first column to get***:

$$D_{P^*_{31}(s)} = \left\| \begin{bmatrix} 0 & -\mu_{21} & 0 & 0 \\ 0 & (s+\gamma_2) & -\mu_{32} & 0 \\ 1 & -\lambda_{23} & (s+\gamma_3) & -\mu_{43} \\ 0 & 0 & -\lambda_{34} & (s+\gamma_4) \end{bmatrix} \right\| = \mu_{21}\,\mu_{32}(s+\gamma_4) = \mu_{21}\,\mu_{32}\,s + \mu_{21}\,\mu_{32}\gamma_4$$

- ***expand through second column to get*** :

$$D_{P^*_{32}(s)} = \left\| \begin{bmatrix} (s+\gamma_1) & 0 & 0 & 0 \\ -\lambda_{12} & 0 & -\mu_{32} & 0 \\ 0 & 1 & (s+\gamma_3) & -\mu_{43} \\ 0 & 0 & -\lambda_{34} & (s+\gamma_4) \end{bmatrix} \right\| = \mu_{32}(s+\gamma_1)(s+\gamma_4)$$

$$= \mu_{32}s^2 + (\gamma_1\,\mu_{32} + \gamma_4\,\mu_{32})s + \mu_{32}\gamma_1\gamma_4$$

- ***expand through third column to get*** :

$$D_{P^*_{33}(s)} = \left\| \begin{bmatrix} (s+\gamma_1) & -\mu_{21} & 0 & 0 \\ -\lambda_{12} & (s+\gamma_2) & 0 & 0 \\ 0 & -\lambda_{23} & 1 & -\mu_{43} \\ 0 & 0 & 0 & (s+\gamma_4) \end{bmatrix} \right\| = (s+\gamma_4)[(s+\gamma_1)(s+\gamma_2) - \mu_{21}\lambda_{12}]$$

$$D_{P^*_{33}(s)} = s^3 + (\gamma_1+\gamma_2+\gamma_4)s^2 + (\gamma_1\gamma_2+\gamma_1\gamma_4+\gamma_2\,\gamma_4 - \mu_{21}\lambda_{12})s - \mu_{21}\lambda_{12}\gamma_4 + \gamma_1\gamma_2\gamma_4$$

- ***expand through fourth column to get*** :

$$D_{P^*_{34}(s)} = \left\| \begin{bmatrix} (s+\gamma_1) & -\mu_{21} & 0 & 0 \\ -\lambda_{12} & (s+\gamma_2) & -\mu_{32} & 0 \\ 0 & -\lambda_{23} & (s+\gamma_3) & 1 \\ 0 & 0 & -\lambda_{34} & 0 \end{bmatrix} \right\|$$

$$D_{P^*_{34}(s)} = \lambda_{34}[(s+\gamma_1)(s+\gamma_2) - \mu_{21}\lambda_{12}] = \lambda_{34}s^2 + (\lambda_{34}\gamma_1 + \lambda_{34}\gamma_2)s + \lambda_{34}\gamma_1\gamma_2 - \lambda_{12}\lambda_{34}\mu_{21}$$

Using the above technique for the set of equations of the third row (first 4 probabilities) gives the following matrix:

$$\begin{bmatrix} (s+\gamma_1) & -\mu_{21} & 0 & 0 \\ -\lambda_{12} & (s+\gamma_2) & -\mu_{32} & 0 \\ 0 & -\lambda_{23} & (s+\gamma_3) & -\mu_{43} \\ 0 & 0 & -\lambda_{34} & (s+\gamma_4) \end{bmatrix} \begin{bmatrix} P^*_{41}(s) \\ P^*_{42}(s) \\ P^*_{43}(s) \\ P^*_{44}(s) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \end{bmatrix}, \textit{then solve for } P^*_{ij}(s) \textit{ by calculating } \; D_{P^*_{41}(s)},\; D_{P^*_{42}(s)},\; D_{P^*_{43}(s)},\; D_{P^*_{44}(s)}$$

- ***expand through first column to get***:

$$D_{P^*_{41}(s)} = \left\| \begin{bmatrix} 0 & -\mu_{21} & 0 & 0 \\ 0 & (s+\gamma_2) & -\mu_{32} & 0 \\ 0 & -\lambda_{23} & (s+\gamma_3) & -\mu_{43} \\ 1 & 0 & -\lambda_{34} & (s+\gamma_4) \end{bmatrix} \right\| = \mu_{21}\,\mu_{32}\,\mu_{43}$$

- ***expand through second column to get*** :

$$D_{P^*_{42}(s)} = \left\| \begin{bmatrix} (s+\gamma_1) & 0 & 0 & 0 \\ -\lambda_{12} & 0 & -\mu_{32} & 0 \\ 0 & 0 & (s+\gamma_3) & -\mu_{43} \\ 0 & 1 & -\lambda_{34} & (s+\gamma_4) \end{bmatrix} \right\| = \mu_{32}\,\mu_{43}\,(s+\gamma_1) = \mu_{32}\,\mu_{43}\,s + \mu_{32}\,\mu_{43}\,\gamma_1$$

- ***expand through third column to get*** :

$$D_{P^*_{43}(s)} = \left\| \begin{bmatrix} (s+\gamma_1) & -\mu_{21} & 0 & 0 \\ -\lambda_{12} & (s+\gamma_2) & 0 & 0 \\ 0 & -\lambda_{23} & 0 & -\mu_{43} \\ 0 & 0 & 1 & (s+\gamma_4) \end{bmatrix} \right\| = \mu_{43}[(s+\gamma_1)(s+\gamma_2) - \mu_{21}\lambda_{12}]$$

$D_{P_{43}^*(s)} = \ \mu_{43} s^2 + (\gamma_1\mu_{43} + \gamma_2\mu_{43})s + \gamma_2\gamma_1\mu_{43} - \lambda_{12}\mu_{21}\mu_{43}$

- $\underline{\boldsymbol{expand\ through\ fourth\ column\ to\ get}:}$

$$D_{P_{44}^*(s)} = \left\| \begin{bmatrix} (s+\gamma_1) & -\mu_{21} & 0 & 0 \\ -\lambda_{12} & (s+\gamma_2) & -\mu_{32} & 0 \\ 0 & -\lambda_{23} & (s+\gamma_3) & 0 \\ 0 & 0 & -\lambda_{34} & 1 \end{bmatrix} \right\| = -\lambda_{23}\mu_{32}(s+\gamma_1) + (s+\gamma_3)[(s+\gamma_1)(s+\gamma_2) - \mu_{21}\lambda_{12}]$$

$$D_{P_{44}^*(s)} = s^3 + (\gamma_1+\gamma_2+\gamma_3)s^2 + (\gamma_1\gamma_2 + \gamma_1\gamma_3 + \gamma_2\gamma_3 - \mu_{21}\lambda_{12} - \lambda_{23}\mu_{32})s - \lambda_{23}\mu_{32}\gamma_1 - \mu_{21}\lambda_{12}\gamma_3 + \gamma_1\gamma_2\gamma_3$$

Then Using partial fraction to get inverse laplace:

$$D_{P_{11}^*(s)} = s^3 + (\gamma_2+\gamma_3+\gamma_4)s^2 + (\gamma_2\gamma_3 + \gamma_2\gamma_4 + \gamma_3\gamma_4 - \lambda_{34}\,\mu_{43} - \lambda_{23}\,\mu_{32})\,s - \lambda_{23}\,\mu_{32}\gamma_4 - \lambda_{34}\mu_{43}\gamma_2 + \gamma_2\gamma_3\gamma_4$$

$$P_{11}^*(s) = \frac{D_{P_{11}^*(s)}}{D} = \frac{A_{11}}{(s-r_1)} + \frac{B_{11}}{(s-r_2)} + \frac{C_{11}}{(s-r_3)} + \frac{D_{11}}{(s-r_4)}$$

$$D_{P_{11}^*(s)} = A_{11}(s-r_2)(s-r_3)(s-r_4) + B_{11}(s-r_1)(s-r_3)(s-r_4) + C_{11}(s-r_1)(s-r_2)(s-r_4) + D_{11}(s-r_1)(s-r_2)(s-r_3)$$

$$R.H.S. = [A_{11}(s-r_2)(s^2-(r_3+r_4)s+r_3r_4)] + [B_{11}(s-r_1)(s^2-(r_3+r_4)s+r_3r_4)] + [C_{11}(s-r_1)(s^2-(r_2+r_4)s+r_2r_4)] + [D_{11}(s-r_1)(s^2-(r_2+r_3)s+r_2r_3)]$$

$$R.H.S. = A_{11}\{s^3-(r_2+r_3+r_4)s^2+(r_2r_3+r_2r_4+r_3r_4)s-r_2r_3r_4\} +$$
$$B_{11}\{s^3-(r_1+r_3+r_4)s^2+(r_1r_3+r_1r_4+r_3r_4)s-r_1r_3r_4\} +$$
$$C_{11}\{s^3-(r_1+r_2+r_4)s^2+(r_1r_2+r_1r_4+r_2r_4)s-r_1r_2r_4\} +$$
$$D_{11}\{s^3-(r_1+r_2+r_3)s^2+(r_1r_2+r_1r_3+r_2r_3)s-r_1r_2r_3\}$$

$$R.H.S. = [A_{11}+B_{11}+C_{11}+D_{11}]s^3 +$$
$$[-(r_2+r_3+r_4)A_{11} - (r_1+r_3+r_4)B_{11} - (r_1+r_2+r_4)C_{11} - (r_1+r_2+r_3)D_{11}]s^2 +$$
$$[(r_2r_3+r_2r_4+r_3r_4)A_{11} + (r_1r_3+r_1r_4+r_3r_4)B_{11} + (r_1r_2+r_1r_4+r_2r_4)C_{11} + (r_1r_2+r_1r_3+r_2r_3)D_{11}]s +$$
$$[-r_2r_3r_4A_{11} - r_1r_3r_4B_{11} - r_1r_2r_4C_{11} - r_1r_2r_3D_{11}]$$

$$\because\ D_{P_{11}^*(s)} = s^3 + (\gamma_2+\gamma_3+\gamma_4)s^2 + (\gamma_2\gamma_3+\gamma_2\gamma_4+\gamma_3\gamma_4 - \lambda_{34}\,\mu_{43} - \lambda_{23}\,\mu_{32})\,s - \lambda_{23}\,\mu_{32}\gamma_4 - \lambda_{34}\mu_{43}\gamma_2 + \gamma_2\gamma_3\gamma_4$$

$$\therefore\ D_{P_{11}^*(s)} = R.H.S.$$

EquatingR.H.S.with L.H.S.:

$$[A_{11}+B_{11}+C_{11}+D_{11}]s^3 = s^3$$
$$[-(r_2+r_3+r_4)A_{11} - (r_1+r_3+r_4)B_{11} - (r_1+r_2+r_4)C_{11} - (r_1+r_2+r_3)D_{11}]s^2 = (\gamma_2+\gamma_3+\gamma_4)s^2$$
$$[(r_2r_3+r_2r_4+r_3r_4)A_{11} + (r_1r_3+r_1r_4+r_3r_4)B_{11} + (r_1r_2+r_1r_4+r_2r_4)C_{11} + (r_1r_2+r_1r_3+r_2r_3)D_{11}]s = (\gamma_2\gamma_3+\gamma_2\gamma_4+\gamma_3\gamma_4 - \lambda_{34}\,\mu_{43} - \lambda_{23}\,\mu_{32})\,s$$
$$[-r_2r_3r_4A_{11} - r_1r_3r_4B_{11} - r_1r_2r_4C_{11} - r_1r_2r_3D_{11}] = -\lambda_{23}\,\mu_{32}\gamma_4 - \lambda_{34}\mu_{43}\gamma_2 + \gamma_2\gamma_3\gamma_4$$
$$A_{11}+B_{11}+C_{11}+D_{11} = 1$$
$$-(r_2+r_3+r_4)A_{11} - (r_1+r_3+r_4)B_{11} - (r_1+r_2+r_4)C_{11} - (r_1+r_2+r_3)D_{11} = \gamma_2+\gamma_3+\gamma_4$$
$$(r_2r_3+r_2r_4+r_3r_4)A_{11} + (r_1r_3+r_1r_4+r_3r_4)B_{11} + (r_1r_2+r_1r_4+r_2r_4)C_{11} + (r_1r_2+r_1r_3+r_2r_3)D_{11} = \gamma_2\gamma_3+\gamma_2\gamma_4+\gamma_3\gamma_4 - \lambda_{34}\,\mu_{43} - \lambda_{23}\,\mu_{32}$$
$$-r_2r_3r_4A_{11} - r_1r_3r_4B_{11} - r_1r_2r_4C_{11} - r_1r_2r_3D_{11} = -\lambda_{23}\,\mu_{32}\gamma_4 - \lambda_{34}\mu_{43}\gamma_2 + \gamma_2\gamma_3\gamma_4$$

This set of the four equations will be used repeatedly to calculate the inverse Laplace transform for the first four probabilities in the first four rows, the difference will be in the resultant vector for each $D_{P_{ij}^*(s)}$: in matrix notation

$$\begin{bmatrix} 1 & 1 & 1 & 1 \\ -(r_2+r_3+r_4) & -(r_1+r_3+r_4) & -(r_1+r_2+r_4) & -(r_1+r_2+r_3) \\ (r_2r_3+r_2r_4+r_3r_4) & (r_1r_3+r_1r_4+r_3r_4) & (r_1r_2+r_1r_4+r_2r_4) & (r_1r_2+r_1r_3+r_2r_3) \\ -r_2r_3r_4 & -r_1r_3r_4 & -r_1r_2r_4 & -r_1r_2r_3 \end{bmatrix} \begin{bmatrix} A_{11} \\ B_{11} \\ C_{11} \\ D_{11} \end{bmatrix} = \begin{bmatrix} 1 \\ \gamma_2+\gamma_3+\gamma_4 \\ \gamma_2\gamma_3+\gamma_2\gamma_4+\gamma_3\gamma_4 - \lambda_{34}\,\mu_{43} - \lambda_{23}\,\mu_{32} \\ -\lambda_{23}\,\mu_{32}\gamma_4 - \lambda_{34}\mu_{43}\gamma_2 + \gamma_2\gamma_3\gamma_4 \end{bmatrix}$$

$$let\ \begin{bmatrix} 1 & 1 & 1 & 1 \\ -(r_2+r_3+r_4) & -(r_1+r_3+r_4) & -(r_1+r_2+r_4) & -(r_1+r_2+r_3) \\ (r_2\,r_3+r_2\,r_4+r_3\,r_4) & (r_1\,r_3+r_1\,r_4+r_3\,r_4) & (r_1\,r_2+r_1\,r_4+r_2\,r_4) & (r_1\,r_2+r_1\,r_3+r_2\,r_3) \\ -r_2\,r_3\,r_4 & -r_1\,r_3\,r_4 & -r_1\,r_2\,r_4 & -r_1\,r_2\,r_3 \end{bmatrix} = K(r)$$

$$\begin{bmatrix} A_{11} \\ B_{11} \\ C_{11} \\ D_{11} \end{bmatrix} = \begin{bmatrix} 1 & 1 & 1 & 1 \\ -(r_2+r_3+r_4) & -(r_1+r_3+r_4) & -(r_1+r_2+r_4) & -(r_1+r_2+r_3) \\ (r_2\,r_3+r_2\,r_4+r_3\,r_4) & (r_1\,r_3+r_1\,r_4+r_3\,r_4) & (r_1\,r_2+r_1\,r_4+r_2\,r_4) & (r_1\,r_2+r_1\,r_3+r_2\,r_3) \\ -r_2\,r_3\,r_4 & -r_1\,r_3\,r_4 & -r_1\,r_2\,r_4 & -r_1\,r_2\,r_3 \end{bmatrix}^{-1} \begin{bmatrix} \\ \gamma_2 \\ \gamma_2\gamma_3+\gamma_2\gamma_4+\gamma \\ -\lambda_{23}\,\mu_{32}\gamma_4 \end{bmatrix}$$

$$\begin{bmatrix} A_{11} \\ B_{11} \\ C_{11} \\ D_{11} \end{bmatrix} = [K(r)]^{-1} \begin{bmatrix} 1 \\ \gamma_2+\gamma_3+\gamma_4 \\ \gamma_2\gamma_3+\gamma_2\gamma_4+\gamma_3\gamma_4-\lambda_{34}\,\mu_{43}\ -\lambda_{23}\,\mu_{32} \\ -\lambda_{23}\,\mu_{32}\gamma_4-\lambda_{34}\mu_{43}\gamma_2+\gamma_2\gamma_3\gamma_4 \end{bmatrix}$$

$[K(r)]^{-1}$ *is used repeatedly in the calculations of the first 4 PDF′s in the first 4 rows of the probability matrix*

$$P_{11}^{*}(s) = \frac{D_{P_{11}^{*}(s)}}{D} = \frac{A_{11}}{(s-r_1)} + \frac{B_{11}}{(s-r_2)} + \frac{C_{11}}{(s-r_3)} + \frac{D_{11}}{(s-r_4)}\ ,use\ inverse\ laplace\ of\ both\ sides$$

$$\therefore P_{11}(t) = A_{11}e^{r_1 t} + B_{11}e^{r_2 t} + C_{11}e^{r_3 t} + D_{11}e^{r_4 t}$$

$$For\ \ P_{12}^{*}(s)\ :\frac{\lambda_{12}s^2+\lambda_{12}(\gamma_3+\gamma_4)s+\lambda_{12}\gamma_3\gamma_4\ -\ \lambda_{12}\lambda_{34}\,\mu_{43}}{D} = \frac{A_{12}}{(s-r_1)} + \frac{B_{12}}{(s-r_2)} + \frac{C_{12}}{(s-r_3)} + \frac{D_{12}}{(s-r_4)}$$

The same procedure is used to solve the following PDFs' ; what differs is the numerator of both sides, but the denominators on both sides are the same for all upcoming equations. In matrix notation :

$$\begin{bmatrix} A_{12} \\ B_{12} \\ C_{12} \\ D_{12} \end{bmatrix} = [K(r)]^{-1} \begin{bmatrix} 0 \\ \lambda_{12} \\ \lambda_{12}(\gamma_3+\gamma_4) \\ \lambda_{12}\gamma_3\gamma_4\ -\ \lambda_{12}\lambda_{34}\,\mu_{43} \end{bmatrix}$$

$$\therefore P_{12}^{*}(s) = \frac{D_{P_{12}^{*}(s)}}{D} = \frac{A_{12}}{(s-r_1)} + \frac{B_{12}}{(s-r_2)} + \frac{C_{12}}{(s-r_3)} + \frac{D_{12}}{(s-r_4)},$$

$$so\ \ P_{12}(t) = A_{12}e^{r_1 t} + B_{12}e^{r_2 t} + C_{12}e^{r_3 t} + D_{12}e^{r_4 t}$$

$$For\ \ P_{13}^{*}(s):$$

$$\frac{\lambda_{12}\lambda_{23}\ \ s+\lambda_{12}\lambda_{23}\gamma_4}{D} = \frac{A_{13}}{(s-r_1)} + \frac{B_{13}}{(s-r_2)} + \frac{C_{13}}{(s-r_3)} + \frac{D_{13}}{(s-r_4)}\ \ ,\ \ In\ matrix\ notation:$$

$$\begin{bmatrix} A_{13} \\ B_{13} \\ C_{13} \\ D_{13} \end{bmatrix} = [K(r)]^{-1} \begin{bmatrix} 0 \\ 0 \\ \lambda_{12}\lambda_{23} \\ \lambda_{12}\lambda_{23}\gamma_4 \end{bmatrix}$$

$$\therefore P_{13}^{*}(s) = \frac{D_{P_{13}^{*}(s)}}{D} = \frac{A_{13}}{(s-r_1)} + \frac{B_{13}}{(s-r_2)} + \frac{C_{13}}{(s-r_3)} + \frac{D_{13}}{(s-r_4)}\ ,so\ P_{13}(t)$$

$$= A_{13}e^{r_1 t} + B_{13}e^{r_2 t} + C_{13}e^{r_3 t} + D_{13}e^{r_4 t}$$

$$For\ \ P_{14}^{*}(s)\ :\frac{\lambda_{12}\lambda_{23}\lambda_{34}}{D} = \frac{A_{14}}{(s-r_1)} + \frac{B_{14}}{(s-r_2)} + \frac{C_{14}}{(s-r_3)} + \frac{D_{14}}{(s-r_4)}\quad ,\ \ In\ matrix\ notation:$$

$$\begin{bmatrix} A_{14} \\ B_{14} \\ C_{14} \\ D_{14} \end{bmatrix} = [K(r)]^{-1} \begin{bmatrix} 0 \\ 0 \\ 0 \\ \lambda_{12}\lambda_{23}\lambda_{34} \end{bmatrix}$$

$$\therefore P_{14}^{*}(s) = \frac{D_{P_{14}^{*}(s)}}{D} = \frac{A_{14}}{(s-r_1)} + \frac{B_{14}}{(s-r_2)} + \frac{C_{14}}{(s-r_3)} + \frac{D_{14}}{(s-r_4)}\ ,$$

$$so\ \ P_{14}(t) = A_{14}e^{r_1 t} + B_{14}e^{r_2 t} + C_{14}e^{r_3 t} + D_{14}e^{r_4 t}$$

$$For\ \ P_{21}^{*}(s):\rightarrow\ \begin{bmatrix} A_{21} \\ B_{21} \\ C_{21} \\ D_{21} \end{bmatrix} = [K(r)]^{-1} \begin{bmatrix} 0 \\ \mu_{21} \\ \mu_{21}\gamma_3+\ \mu_{21}\gamma_4 \\ \mu_{21}\gamma_3\gamma_4\ -\ \mu_{21}\lambda_{34}\,\mu_{43} \end{bmatrix}$$

$$\therefore P_{21}^*(s) = \frac{D_{P_{21}^*(s)}}{D} = \frac{A_{21}}{(s-r_1)} + \frac{B_{21}}{(s-r_2)} + \frac{C_{21}}{(s-r_3)} + \frac{D_{21}}{(s-r_4)},$$
$$so\ P_{21}(t) = A_{21}e^{r_1t} + B_{21}e^{r_2t} + C_{21}e^{r_3t} + D_{21}e^{r_4t}$$

$$For\ \ P_{22}^*(s): \rightarrow \begin{bmatrix} A_{22} \\ B_{22} \\ C_{22} \\ D_{22} \end{bmatrix} = [K(r)]^{-1} \begin{bmatrix} 1 \\ \gamma_1 + \gamma_3 + \gamma_4 \\ \gamma_1\gamma_3 + \gamma_1\gamma_4 + \gamma_3\gamma_4 - \lambda_{34}\,\mu_{43} \\ -\lambda_{34}\,\mu_{43}\gamma_1 + \gamma_1\gamma_3\gamma_4 \end{bmatrix}$$

$$\therefore\ \ P_{22}^*(s) = \frac{D_{P_{22}^*(s)}}{D} = \frac{A_{22}}{(s-r_1)} + \frac{B_{22}}{(s-r_2)} + \frac{C_{22}}{(s-r_3)} + \frac{D_{22}}{(s-r_4)},\ so\ P_{22}(t)$$
$$= A_{22}e^{r_1t} + B_{22}e^{r_2t} + C_{22}e^{r_3t} + D_{22}e^{r_4t}$$

$$For\ \ P_{23}^*(s): \rightarrow \begin{bmatrix} A_{23} \\ B_{23} \\ C_{23} \\ D_{23} \end{bmatrix} = [K(r)]^{-1} \begin{bmatrix} 0 \\ \lambda_{23} \\ \lambda_{23}(\gamma_1 + \gamma_4) \\ \lambda_{23}\gamma_1\gamma_4 \end{bmatrix}$$

$$\therefore P_{23}^*(s) = \frac{D_{P_{23}^*(s)}}{D} = \frac{A_{23}}{(s-r_1)} + \frac{B_{23}}{(s-r_2)} + \frac{C_{23}}{(s-r_3)} + \frac{D_{23}}{(s-r_4)},\ so\ P_{23}(t)$$
$$= A_{23}e^{r_1t} + B_{23}e^{r_2t} + C_{23}e^{r_3t} + D_{23}e^{r_4t}$$

$$For\ \ P_{24}^*(s): \rightarrow \begin{bmatrix} A_{24} \\ B_{24} \\ C_{24} \\ D_{24} \end{bmatrix} = [K(r)]^{-1} \begin{bmatrix} 0 \\ 0 \\ \lambda_{23}\lambda_{34} \\ \lambda_{23}\lambda_{34}\gamma_1 \end{bmatrix}$$

$$\therefore\ \ P_{24}^*(s) = \frac{D_{P_{24}^*(s)}}{D} = \frac{A_{24}}{(s-r_1)} + \frac{B_{24}}{(s-r_2)} + \frac{C_{24}}{(s-r_3)} + \frac{D_{24}}{(s-r_4)},\ so\ P_{24}(t)$$
$$= A_{24}e^{r_1t} + B_{24}e^{r_2t} + C_{24}e^{r_3t} + D_{24}e^{r_4t}$$

$$For\ \ P_{31}^*(s) :\rightarrow \begin{bmatrix} A_{31} \\ B_{31} \\ C_{31} \\ D_{31} \end{bmatrix} = [K(r)]^{-1} \begin{bmatrix} 0 \\ 0 \\ \mu_{21}\,\mu_{32} \\ \mu_{21}\,\mu_{32}\gamma_4 \end{bmatrix}$$

$$\therefore P_{31}^*(s) = \frac{D_{P_{31}^*(s)}}{D} = \frac{A_{31}}{(s-r_1)} + \frac{B_{31}}{(s-r_2)} + \frac{C_{31}}{(s-r_3)} + \frac{D_{31}}{(s-r_4)},\ P_{31}(t)$$
$$= A_{31}e^{r_1t} + B_{31}e^{r_2t} + C_{31}e^{r_3t} + D_{31}e^{r_4t}$$

$$For\ \ P_{32}^*(s): \rightarrow \begin{bmatrix} A_{32} \\ B_{32} \\ C_{32} \\ D_{32} \end{bmatrix} = [K(r)]^{-1} \begin{bmatrix} 0 \\ \mu_{32} \\ \mu_{32}(\gamma_1 + \gamma_4) \\ \mu_{32}\gamma_1\gamma_4 \end{bmatrix}$$

$$\therefore P_{32}^*(s) = \frac{D_{P_{32}^*(s)}}{D} = \frac{A_{32}}{(s-r_1)} + \frac{B_{32}}{(s-r_2)} + \frac{C_{32}}{(s-r_3)} + \frac{D_{32}}{(s-r_4)},\ so\ P_{32}(t)$$
$$= A_{32}e^{r_1t} + B_{32}e^{r_2t} + C_{32}e^{r_3t} + D_{32}e^{r_4t}$$

$$For\ \ P_{33}^*(s): \rightarrow \begin{bmatrix} A_{33} \\ B_{33} \\ C_{33} \\ D_{33} \end{bmatrix} = [K(r)]^{-1} \begin{bmatrix} 1 \\ \gamma_1 + \gamma_2 + \gamma_4 \\ \gamma_1\gamma_2 + \gamma_1\gamma_4 + \gamma_2\,\gamma_4 - \ \mu_{21}\lambda_{12} \\ \gamma_1\gamma_2\gamma_4 - \ \mu_{21}\lambda_{12}\gamma_4 \end{bmatrix}$$

$$\therefore P_{33}^*(s) = \frac{D_{P_{33}^*(s)}}{D} = \frac{A_{33}}{(s-r_1)} + \frac{B_{33}}{(s-r_2)} + \frac{C_{33}}{(s-r_3)} + \frac{D_{33}}{(s-r_4)},\quad so\ P_{33}(t)$$
$$= A_{33}e^{r_1t} + B_{33}e^{r_2t} + C_{33}e^{r_3t} + D_{33}e^{r_4t}$$

$$For\ \ P_{34}^*(s): \rightarrow \begin{bmatrix} A_{34} \\ B_{34} \\ C_{34} \\ D_{34} \end{bmatrix} = [K(r)]^{-1} \begin{bmatrix} 0 \\ \lambda_{34} \\ \lambda_{34}(\gamma_1 + \gamma_2) \\ \lambda_{34}\gamma_1\gamma_2 - \lambda_{12}\lambda_{34}\mu_{21} \end{bmatrix}$$

$$\therefore P_{34}^*(s) = \frac{D_{P_{34}^*(s)}}{D} = \frac{A_{34}}{(s-r_1)} + \frac{B_{34}}{(s-r_2)} + \frac{C_{34}}{(s-r_3)} + \frac{D_{34}}{(s-r_4)},\ so\ P_{34}(t)$$
$$= A_{34}e^{r_1t} + B_{34}e^{r_2t} + C_{34}e^{r_3t} + D_{34}e^{r_4t}$$

$$For\ \ P_{41}^*(s): \rightarrow \begin{bmatrix} A_{41} \\ B_{41} \\ C_{41} \\ D_{41} \end{bmatrix} = [K(r)]^{-1} \begin{bmatrix} 0 \\ 0 \\ 0 \\ \mu_{21}\,\mu_{32}\,\mu_{43} \end{bmatrix}$$

$$\therefore\ P_{41}^{*}(s)=\frac{D_{P_{41}^{*}(s)}}{D}=\frac{A_{41}}{(s-r_1)}+\frac{B_{41}}{(s-r_2)}+\frac{C_{41}}{(s-r_3)}+\frac{D_{41}}{(s-r_4)}\ \ , so\ P_{41}(t)$$
$$=A_{41}e^{r_1t}+B_{41}e^{r_2t}+C_{41}e^{r_3t}+D_{41}e^{r_4t}$$

$$For\ \ P_{42}^{*}(s):\rightarrow\begin{bmatrix}A_{42}\\B_{42}\\C_{42}\\D_{42}\end{bmatrix}=[K(r)]^{-1}\begin{bmatrix}0\\0\\\mu_{32}\,\mu_{43}\\\mu_{32}\,\mu_{43}\,\gamma_1\end{bmatrix}$$

$$\therefore P_{42}^{*}(s)=\frac{D_{P_{42}^{*}(s)}}{D}=\frac{A_{42}}{(s-r_1)}+\frac{B_{42}}{(s-r_2)}+\frac{C_{42}}{(s-r_3)}+\frac{D_{42}}{(s-r_4)}\ \ , so\ \ P_{42}(t)$$
$$=A_{42}e^{r_1t}+B_{42}e^{r_2t}+C_{42}e^{r_3t}+D_{42}e^{r_4t}$$

$$For\ \ P_{43}^{*}(s):\rightarrow\begin{bmatrix}A_{43}\\B_{43}\\C_{43}\\D_{43}\end{bmatrix}=[K(r)]^{-1}\begin{bmatrix}0\\\mu_{43}\\\mu_{43}(\gamma_1+\gamma_2)\\\gamma_2\gamma_1\mu_{43}-\lambda_{12}\mu_{21}\mu_{43}\end{bmatrix}$$

$$\therefore P_{43}^{*}(s)=\frac{D_{P_{43}^{*}(s)}}{D}=\frac{A_{43}}{(s-r_1)}+\frac{B_{43}}{(s-r_2)}+\frac{C_{43}}{(s-r_3)}+\frac{D_{43}}{(s-r_4)}\ , so\ P_{43}(t)$$
$$=A_{43}e^{r_1t}+B_{43}e^{r_2t}+C_{43}e^{r_3t}+D_{43}e^{r_4t}$$

$$For\ \ P_{44}^{*}(s):\rightarrow\begin{bmatrix}A_{44}\\B_{44}\\C_{44}\\D_{44}\end{bmatrix}=[K(r)]^{-1}\begin{bmatrix}1\\\gamma_1+\gamma_2+\gamma_3\\\gamma_1\gamma_2+\gamma_1\gamma_3+\ \gamma_2\gamma_3-\mu_{21}\lambda_{12}-\lambda_{23}\mu_{32}\\-\lambda_{23}\mu_{32}\gamma_1-\ \mu_{21}\lambda_{12}\gamma_3+\gamma_1\gamma_2\gamma_3\end{bmatrix}$$

$$\therefore\ P_{44}^{*}(s)=\frac{D_{P_{44}^{*}(s)}}{D}=\frac{A_{44}}{(s-r_1)}+\frac{B_{44}}{(s-r_2)}+\frac{C_{44}}{(s-r_3)}+\frac{D_{44}}{(s-r_4)}\ , so\ P_{44}(t)$$
$$=A_{44}e^{r_1t}+B_{44}e^{r_2t}+C_{44}e^{r_3t}+D_{44}e^{r_4t}$$

Solving the Last 5 Probabilities in the First Row by Using the Method of Integrating Factor

$$\frac{dP_{15}(t)}{dt}=\lambda_{45}P_{14}(t)-(\lambda_{56}+\lambda_{58}+\lambda_{59})P_{15}(t)\,,\ \ let\ \ (\lambda_{56}+\lambda_{58}+\lambda_{59})=w$$

$$\frac{dP_{15}(t)}{dt}=\lambda_{45}P_{14}(t)-wP_{15}(t)\ \ , so\ \frac{d\,P_{15}(t)}{dt}\ +wP_{15}(t)$$
$$=\lambda_{45}P_{14}(t)\ , multiply\ both\ sides\ by\ integrating\ factor\ e^{wt}$$

$$e^{wt}\,\frac{d\,P_{15}(t)}{dt}\ +w\,e^{wt}P_{15}(t)=\lambda_{45}e^{wt}P_{14}(t)\quad,\qquad substitute\ for\ \ P_{14}(t)$$

$$e^{wt}\,\frac{d\,P_{15}(t)}{dt}\ +w\,e^{wt}P_{15}(t)=\lambda_{45}e^{wt}[A_{14}e^{r_1t}+B_{14}e^{r_2t}+C_{14}e^{r_3t}+D_{14}e^{r_4t}]$$

$$\frac{d}{dt}e^{wt}P_{15}(t)\ =\lambda_{45}A_{14}e^{(w+r_1)t}+\lambda_{45}B_{14}e^{(w+r_2)t}+\lambda_{45}C_{14}e^{(w+r_3)t}+\lambda_{45}D_{14}e^{(w+r_4)t}$$

$$let\ \ \ \lambda_{45}A_{14}=G_1\ \ ,\ \lambda_{45}B_{14}=G_2\ \ ,\ \ \lambda_{45}C_{14}=G_3\ \ ,\ \lambda_{45}D_{14}$$
$$=G_4\ \ and\ \ integrate\ both\ sides\ from\ (0\ to\ t)$$

$$e^{wt}P_{15}(t)\ =G_1\left[\frac{e^{(w+r_1)t}}{w+r_1}-\frac{1}{w+r_1}\right]+G_2\left[\frac{e^{(w+r_2)t}}{w+r_2}-\frac{1}{w+r_2}\right]+G_3\left[\frac{e^{(w+r_3)t}}{w+r_3}-\frac{1}{w+r_3}\right]$$
$$+G_4\left[\frac{e^{(w+r_4)t}}{w+r_4}-\frac{1}{w+r_4}\right]$$

$$multiply\ both\ sides\ by\ e^{-wt}$$

$$P_{15}(t)\ =\frac{G_1}{w+r_1}[e^{r_1t}-e^{-wt}]+\frac{G_2}{w+r_2}[e^{r_2t}-e^{-wt}]+\frac{G_3}{w+r_3}[e^{r_3t}-e^{-wt}]+\frac{G_4}{w+r_4}[e^{r_4t}-e^{-wt}]$$

$$P_{15}(t)\ =\frac{G_1}{w+r_1}e^{r_1t}+\frac{G_2}{w+r_2}e^{r_2t}\ +\frac{G_3}{w+r_3}e^{r_3t}+\frac{G_4}{w+r_4}e^{r_4t}-\left[\frac{G_1}{w+r_1}+\frac{G_2}{w+r_2}+\frac{G_3}{w+r_3}+\frac{G_4}{w+r_4}\right]e^{-wt}$$

$$let\ \frac{G_1}{w+r_1}=F_1\ \ ,\qquad\frac{G_2}{w+r_2}=\ F_2\ \ ,\qquad\frac{G_3}{w+r_3}=F_3\ \ ,\frac{G_4}{w+r_4}=F_4\ ,$$
$$-\left[\frac{G_1}{w+r_1}+\frac{G_2}{w+r_2}+\frac{G_3}{w+r_3}+\frac{G_4}{w+r_4}\right]=\ F_5$$

$$P_{15}(t)\ =F_1e^{r_1t}+F_2e^{r_2t}\ +F_3e^{r_3t}+F_4e^{r_4t}+\ F_5e^{-wt}$$

$$\frac{dP_{16}(t)}{dt}=\lambda_{56}P_{15}(t)-(\lambda_{67}+\lambda_{69})P_{16}(t)\ \ ,\qquad let\ \ (\lambda_{67}+\lambda_{69})=u$$

$$\frac{dP_{16}(t)}{dt}=\lambda_{56}P_{15}(t)-uP_{16}(t)\ , so\ \ \frac{d\,P_{16}(t)}{dt}\ +uP_{16}(t)$$
$$=\lambda_{56}P_{15}(t)\ , multiply\ both\ sides\ by\ integrating\ factor\ e^{ut}$$

$$e^{ut}\frac{d\,P_{16}(t)}{dt}+u\,e^{ut}P_{16}(t)=\lambda_{56}e^{ut}P_{15}(t)\quad,\qquad substitute\ for\ \ P_{15}(t)$$
$$e^{ut}\frac{d\,P_{16}(t)}{dt}+u\,e^{ut}P_{16}(t)=\lambda_{56}e^{ut}[F_1e^{r_1t}+F_2e^{r_2t}+F_3e^{r_3t}+F_4e^{r_4t}+F_5e^{-wt}]$$
$$\frac{d}{dt}e^{ut}P_{16}(t)=\lambda_{56}F_1e^{(u+r_1)t}+\lambda_{56}F_2e^{(u+r_2)t}+\lambda_{56}F_3e^{(u+r_3)t}+\lambda_{56}F_4e^{(u+r_4)t}+\lambda_{56}F_5e^{(u-w)t}$$
$$let\quad \lambda_{56}F_1=G_5\ ,\ \lambda_{56}F_2=G_6\ ,\ \lambda_{56}F_3=G_7\ ,\ \lambda_{56}F_4=G_8\ ,\lambda_{56}F_5=G_9\ \ and\ \ integrate\ both\ sides\ from\ (0\ to\ t)$$
$$\frac{d}{dt}e^{ut}P_{16}(t)=G_5e^{(u+r_1)t}+G_6e^{(u+r_2)t}+G_7e^{(u+r_3)t}+G_8e^{(u+r_4)t}+G_9e^{(u-w)t}$$
$$e^{ut}P_{16}(t)=G_5\left[\frac{e^{(u+r_1)t}}{u+r_1}-\frac{1}{u+r_1}\right]+G_6\left[\frac{e^{(u+r_2)t}}{u+r_2}-\frac{1}{u+r_2}\right]+G_7\left[\frac{e^{(u+r_3)t}}{u+r_3}-\frac{1}{u+r_3}\right]+G_8\left[\frac{e^{(u+r_4)t}}{u+r_4}-\frac{1}{u+r_4}\right]+G_9\left[\frac{e^{(u-w)t}}{u-w}-\frac{1}{u-w}\right]$$
$multiply\ both\ sides\ by\ e^{-ut}$
$$P_{16}(t)=\frac{G_5}{u+r_1}[e^{r_1t}-e^{-ut}]+\frac{G_6}{u+r_2}[e^{r_2t}-e^{-ut}]+\frac{G_7}{u+r_3}[e^{r_3t}-e^{-ut}]+\frac{G_8}{u+r_4}[e^{r_4t}-e^{-ut}]+\frac{G_9}{u-w}[e^{-wt}-e^{-ut}]$$
$$P_{16}(t)=\frac{G_5}{u+r_1}e^{r_1t}+\frac{G_6}{u+r_2}e^{r_2t}+\frac{G_7}{u+r_3}e^{r_3t}+\frac{G_8}{u+r_4}e^{r_4t}+\frac{G_9}{u-w}e^{-wt}-\left[\frac{G_5}{u+r_1}+\frac{G_6}{u+r_2}+\frac{G_7}{u+r_3}+\frac{G_8}{u+r_4}+\frac{G_9}{u-w}\right]e^{-ut}$$
$$let\ \frac{G_5}{u+r_1}=F_6\ ,\ \frac{G_6}{u+r_2}=F_7\ ,\frac{G_7}{u+r_3}=F_8\ ,\frac{G_8}{u+r_4}=F_9,\frac{G_9}{u-w}=F_{10}\ ,-\left[\frac{G_5}{u+r_1}+\frac{G_6}{u+r_2}+\frac{G_7}{u+r_3}+\frac{G_8}{u+r_4}+\frac{G_9}{u-w}\right]=F_{11}$$
$$P_{16}(t)=F_6e^{r_1t}+F_7e^{r_2t}+F_8e^{r_3t}+F_9e^{r_4t}+F_{10}e^{-wt}+F_{11}e^{-ut}$$
$$\frac{dP_{17}(t)}{dt}=\lambda_{67}P_{16}(t)-\lambda_{79}P_{17}(t)\ ,$$
$$so\ \ \frac{dP_{17}(t)}{dt}+\lambda_{79}P_{17}(t)=\lambda_{67}P_{16}(t)\quad,\ multiply\ both\ sides\ by\ e^{\lambda_{79}t}$$
$$e^{\lambda_{79}t}\frac{dP_{17}(t)}{dt}+\lambda_{79}e^{\lambda_{79}t}P_{17}(t)=\lambda_{67}e^{\lambda_{79}t}P_{16}(t)\quad,\ \ substitute\ \ for\ P_{16}(t)$$
$$\frac{d}{dt}e^{\lambda_{79}t}P_{17}(t)=\lambda_{67}e^{\lambda_{79}t}[F_6e^{r_1t}+F_7e^{r_2t}+F_8e^{r_3t}+F_9e^{r_4t}+F_{10}e^{-wt}+F_{11}e^{-ut}]$$
$$\frac{d}{dt}e^{\lambda_{79}t}P_{17}(t)=\lambda_{67}F_6e^{(\lambda_{79}+r_1)t}+\lambda_{67}F_7e^{(\lambda_{79}+r_2)t}+\lambda_{67}F_8e^{(\lambda_{79}+r_3)t}+\lambda_{67}F_9e^{(\lambda_{79}+r_4)t}+\lambda_{67}F_{10}e^{(\lambda_{79}-w)t}+\lambda_{67}F_{11}e^{(\lambda_{79}-u)t}$$
$$let\quad \lambda_{67}F_6=G_{10}\ ,\quad \lambda_{67}F_7=G_{11},\quad \lambda_{67}F_8=G_{12}\ ,\quad \lambda_{67}F_9=G_{13},\quad \lambda_{67}F_{10}=G_{14}\ ,\ \lambda_{67}F_{11}=G_{15}$$
$$e^{\lambda_{79}t}P_{17}(t)=G_{10}\left[\frac{e^{(\lambda_{79}+r_1)t}}{\lambda_{79}+r_1}-\frac{1}{\lambda_{79}+r_1}\right]+G_{11}\left[\frac{e^{(\lambda_{79}+r_2)t}}{\lambda_{79}+r_2}-\frac{1}{\lambda_{79}+r_2}\right]+G_{12}\left[\frac{e^{(\lambda_{79}+r_3)t}}{\lambda_{79}+r_3}-\frac{1}{\lambda_{79}+r_3}\right]+G_{13}\left[\frac{e^{(\lambda_{79}+r_4)t}}{\lambda_{79}+r_4}-\frac{1}{\lambda_{79}+r_4}\right]+G_{14}\left[\frac{e^{(\lambda_{79}-w)t}}{\lambda_{79}-w}-\frac{1}{\lambda_{79}-w}\right]+G_{15}\left[\frac{e^{(\lambda_{79}-u)t}}{\lambda_{79}-u}-\frac{1}{\lambda_{79}-u}\right]$$
$multiply\ both\ sides\ by\ e^{-\lambda_{79}t}$
$$P_{17}(t)=\frac{G_{10}}{\lambda_{79}+r_1}\left[e^{r_1t}-e^{-\lambda_{79}t}\right]+\frac{G_{11}}{\lambda_{79}+r_2}\left[e^{r_2t}-e^{-\lambda_{79}t}\right]+\frac{G_{12}}{\lambda_{79}+r_3}\left[e^{r_3t}-e^{-\lambda_{79}t}\right]+\frac{G_{13}}{\lambda_{79}+r_4}\left[e^{r_4t}-e^{-\lambda_{79}t}\right]+\frac{G_{14}}{\lambda_{79}-w}\left[e^{-wt}-e^{-\lambda_{79}t}\right]+\frac{G_{15}}{\lambda_{79}-u}\left[e^{-ut}-e^{-\lambda_{79}t}\right]$$
$$P_{17}(t)=\frac{G_{10}}{\lambda_{79}+r_1}e^{r_1t}+\frac{G_{11}}{\lambda_{79}+r_2}e^{r_2t}+\frac{G_{12}}{\lambda_{79}+r_3}e^{r_3t}+\frac{G_{13}}{\lambda_{79}+r_4}e^{r_4t}+\frac{G_{14}}{\lambda_{79}-w}e^{-wt}+\frac{G_{15}}{\lambda_{79}-u}e^{-ut}-\left[\frac{G_{10}}{\lambda_{79}+r_1}+\frac{G_{11}}{\lambda_{79}+r_2}+\frac{G_{12}}{\lambda_{79}+r_3}+\frac{G_{13}}{\lambda_{79}+r_4}+\frac{G_{14}}{\lambda_{79}-w}+\frac{G_{15}}{\lambda_{79}-u}\right]e^{-\lambda_{79}t}$$
$$let\quad \frac{G_{10}}{\lambda_{79}+r_1}=F_{12}\ ,\frac{G_{11}}{\lambda_{79}+r_2}=F_{13}\ ,\frac{G_{12}}{\lambda_{79}+r_3}=F_{14}\ \ ,\frac{G_{13}}{\lambda_{79}+r_4}=F_{15}\ \ ,\frac{G_{14}}{\lambda_{79}-w}=F_{16}\ \ ,\frac{G_{15}}{\lambda_{79}-u}=F_{17},$$

$$-\left[\frac{G_{10}}{\lambda_{79}+r_1}+\frac{G_{11}}{\lambda_{79}+r_2}+\frac{G_{12}}{\lambda_{79}+r_3}+\frac{G_{13}}{\lambda_{79}+r_4}+\frac{G_{14}}{\lambda_{79}-w}+\frac{G_{15}}{\lambda_{79}-u}\right]=F_{18}$$

$$P_{17}(t)\ =F_{12}e^{r_1t}+F_{13}e^{r_2t}+F_{14}e^{r_3t}+F_{15}e^{r_4t}+F_{16}e^{-wt}+F_{17}e^{-ut}+F_{18}e^{-\lambda_{79}t}$$

$$\frac{dP_{18}(t)}{dt}=\lambda_{18}P_{11}(t)+\lambda_{28}P_{12}(t)+\lambda_{38}P_{13}(t)+\lambda_{48}P_{14}(t)+\lambda_{58}P_{15}(t)-\lambda_{89}P_{18}(t)\ , rearrange:$$

$$\frac{dP_{18}(t)}{dt}+\lambda_{89}P_{18}(t)=\lambda_{18}P_{11}(t)+\lambda_{28}P_{12}(t)+\lambda_{38}P_{13}(t)+\lambda_{48}P_{14}(t)+\lambda_{58}P_{15}(t)$$

multiply both sides by $e^{\lambda_{89}t}$ *and substitute for* $P_{11}(t), P_{12}(t), P_{13}(t)\ , P_{14}(t), P_{15}(t)$

$$e^{\lambda_{89}t}\frac{dP_{18}(t)}{dt}+\lambda_{89}e^{\lambda_{89}t}P_{18}(t)$$
$$=\lambda_{18}e^{\lambda_{89}t}P_{11}(t)+\lambda_{28}e^{\lambda_{89}t}P_{12}(t)+\lambda_{38}e^{\lambda_{89}t}P_{13}(t)+\lambda_{48}e^{\lambda_{89}t}P_{14}(t)+\lambda_{58}e^{\lambda_{89}t}P_{15}(t)$$

$$\frac{d}{dt}\ e^{\lambda_{89}t}P_{18}(t)=\lambda_{18}e^{\lambda_{89}t}P_{11}(t)+\lambda_{28}e^{\lambda_{89}t}P_{12}(t)+\lambda_{38}e^{\lambda_{89}t}P_{13}(t)+\lambda_{48}e^{\lambda_{89}t}P_{14}(t)+\lambda_{58}e^{\lambda_{89}t}P_{15}(t)$$

$$\because\ \lambda_{18}e^{\lambda_{89}t}P_{11}(t)=\lambda_{18}e^{\lambda_{89}t}[A_{11}e^{r_1t}+\ B_{11}e^{r_2t}+C_{11}e^{r_3t}\ +\ D_{11}e^{r_4t}]$$
$$=\lambda_{18}A_{11}e^{(\lambda_{89}+r_1)t}+\lambda_{18}B_{11}e^{(\lambda_{89}+r_2)t}+\lambda_{18}C_{11}e^{(\lambda_{89}+r_3)t}+\lambda_{18}D_{11}e^{(\lambda_{89}+r_4)t}$$

$$\because\ \lambda_{28}e^{\lambda_{89}t}P_{12}(t)=\lambda_{28}e^{\lambda_{89}t}[A_{12}e^{r_1t}+\ B_{12}e^{r_2t}+C_{12}e^{r_3t}\ +\ D_{12}e^{r_4t}]$$
$$=\lambda_{28}A_{12}e^{(\lambda_{89}+r_1)t}+\lambda_{28}B_{12}e^{(\lambda_{89}+r_2)t}+\lambda_{28}C_{12}e^{(\lambda_{89}+r_3)t}\ +\lambda_{28}D_{12}e^{(\lambda_{89}+r_4)t}$$

$$\because\ \lambda_{38}e^{\lambda_{89}t}P_{13}(t)=\lambda_{38}e^{\lambda_{89}t}[A_{13}e^{r_1t}+\ B_{13}e^{r_2t}+C_{13}e^{r_3t}\ +\ D_{13}e^{r_4t}]$$
$$=\lambda_{38}A_{13}e^{(\lambda_{89}+r_1)t}+\lambda_{38}B_{13}e^{(\lambda_{89}+r_2)t}+\lambda_{38}C_{13}e^{(\lambda_{89}+r_3)t}\ +\lambda_{38}D_{13}e^{(\lambda_{89}+r_4)t}$$

$$\because\ \lambda_{48}e^{\lambda_{89}t}P_{14}(t)=\lambda_{48}e^{\lambda_{89}t}[A_{14}e^{r_1t}+\ B_{14}e^{r_2t}+C_{14}e^{r_3t}\ +\ D_{14}e^{r_4t}]$$
$$=\lambda_{48}A_{14}e^{(\lambda_{89}+r_1)t}+\lambda_{48}B_{14}e^{(\lambda_{89}+r_2)t}+\lambda_{48}C_{14}e^{(\lambda_{89}+r_3)t}\ +\lambda_{48}D_{14}e^{(\lambda_{89}+r_4)t}$$

$$\because\ \lambda_{58}e^{\lambda_{89}t}P_{15}(t)=\lambda_{58}e^{\lambda_{89}t}[\ F_1e^{r_1t}+F_2e^{r_2t}\ +F_3e^{r_3t}+F_4e^{r_4t}+\ F_5e^{-wt}]$$
$$=\lambda_{58}F_1e^{(\lambda_{89}+r_1)t}+\lambda_{58}F_2e^{(\lambda_{89}+r_2)t}\ +\lambda_{58}F_3e^{(\lambda_{89}+r_3)t}+\lambda_{58}F_4e^{(\lambda_{89}+r_4)t}+\ \lambda_{58}F_5e^{(\lambda_{89}-w)t}$$

$$\frac{d}{dt}\ e^{\lambda_{89}t}P_{18}(t)=[\lambda_{18}A_{11}+\lambda_{28}A_{12}+\lambda_{38}A_{13}+\lambda_{48}A_{14}+\lambda_{58}F_1]e^{(\lambda_{89}+r_1)t}$$
$$+[\lambda_{18}B_{11}+\lambda_{28}B_{12}+\lambda_{38}B_{13}+\lambda_{48}B_{14}+\lambda_{58}F_2]e^{(\lambda_{89}+r_2)t}$$
$$+[\lambda_{18}C_{11}+\lambda_{28}C_{12}+\lambda_{38}C_{13}+\lambda_{48}C_{14}+\lambda_{58}F_3]e^{(\lambda_{89}+r_3)t}$$
$$+[\lambda_{18}D_{11}+\lambda_{28}D_{12}+\lambda_{38}D_{13}+\lambda_{48}D_{14}+\lambda_{58}F_4]e^{(\lambda_{89}+r_4)t}+\lambda_{58}F_5e^{(\lambda_{89}-w)t}$$

let $[\lambda_{18}A_{11}+\lambda_{28}A_{12}+\lambda_{38}A_{13}+\lambda_{48}A_{14}+\lambda_{58}F_1]=G_{16}\ ,[\lambda_{18}B_{11}+\lambda_{28}B_{12}+\lambda_{38}B_{13}+\lambda_{48}B_{14}+\lambda_{58}F_2]=G_{17}$

$[\lambda_{18}C_{11}+\lambda_{28}C_{12}+\lambda_{38}C_{13}+\lambda_{48}C_{14}+\lambda_{58}F_3]=G_{18}\ ,[\lambda_{18}D_{11}+\lambda_{28}D_{12}+\lambda_{38}D_{13}+\lambda_{48}D_{14}+\lambda_{58}F_4]=G_{19}\ ,\lambda_{58}F_5=G_{20}$

$$\frac{d}{dt}\ e^{\lambda_{89}t}P_{18}(t)=G_{16}e^{(\lambda_{89}+r_1)t}+G_{17}e^{(\lambda_{89}+r_2)t}+G_{18}e^{(\lambda_{89}+r_3)t}+G_{19}e^{(\lambda_{89}+r_4)t}$$
$$+G_{20}e^{(\lambda_{89}-w)t}\ , integrate\ both\ sides:$$

$$e^{\lambda_{89}t}P_{18}(t)=G_{16}\left[\frac{e^{(\lambda_{89}+r_1)t}}{\lambda_{89}+r_1}-\frac{1}{\lambda_{89}+r_1}\right]+G_{17}\left[\frac{e^{(\lambda_{89}+r_2)t}}{\lambda_{89}+r_2}-\frac{1}{\lambda_{89}+r_2}\right]+G_{18}\left[\frac{e^{(\lambda_{89}+r_3)t}}{\lambda_{89}+r_3}-\frac{1}{\lambda_{89}+r_3}\right]$$
$$+G_{19}\left[\frac{e^{(\lambda_{89}+r_4)t}}{\lambda_{89}+r_4}-\frac{1}{\lambda_{89}+r_4}\right]+G_{20}\left[\frac{e^{(\lambda_{89}-w)t}}{\lambda_{89}-w}-\frac{1}{\lambda_{89}-w}\right]$$

multiply both sides by $e^{-\lambda_{89}t}$

$$P_{18}(t)=\frac{G_{16}}{\lambda_{89}+r_1}\left[e^{r_1t}-e^{-\lambda_{89}t}\right]+\frac{G_{17}}{\lambda_{89}+r_2}\left[e^{r_2t}-e^{-\lambda_{89}t}\right]+\frac{G_{18}}{\lambda_{89}+r_3}\left[e^{r_3t}-e^{-\lambda_{89}t}\right]$$
$$+\frac{G_{19}}{\lambda_{89}+r_4}\left[e^{r_4t}-e^{-\lambda_{89}t}\right]+\frac{G_{20}}{\lambda_{89}-w}\left[e^{-wt}-e^{-\lambda_{89}t}\right]$$

$$P_{18}(t)=\frac{G_{16}}{\lambda_{89}+r_1}e^{r_1t}+\frac{G_{17}}{\lambda_{89}+r_2}e^{r_2t}+\frac{G_{18}}{\lambda_{89}+r_3}e^{r_3t}+\frac{G_{19}}{\lambda_{89}+r_4}e^{r_4t}+\frac{G_{20}}{\lambda_{89}-w}e^{-wt}$$
$$-\left[\frac{G_{16}}{\lambda_{89}+r_1}+\frac{G_{17}}{\lambda_{89}+r_2}+\frac{G_{18}}{\lambda_{89}+r_3}+\frac{G_{19}}{\lambda_{89}+r_4}+\frac{G_{20}}{\lambda_{89}-w}\right]e^{-\lambda_{89}t}$$

let $\frac{G_{16}}{\lambda_{89}+r_1}=F_{19}\ ,\frac{G_{17}}{\lambda_{89}+r_2}=F_{20}\ ,\frac{G_{18}}{\lambda_{89}+r_3}=F_{21}\ ,\frac{G_{19}}{\lambda_{89}+r_4}=F_{22}\ ,\frac{G_{20}}{\lambda_{89}-w}$

$$=F_{23}-\left[\frac{G_{16}}{\lambda_{89}+r_1}+\frac{G_{17}}{\lambda_{89}+r_2}+\frac{G_{18}}{\lambda_{89}+r_3}+\frac{G_{19}}{\lambda_{89}+r_4}+\frac{G_{20}}{\lambda_{89}-w}\right]=F_{24}$$

$$P_{18}(t)=F_{19}e^{r_1t}+F_{20}e^{r_2t}+F_{21}e^{r_3t}+F_{22}e^{r_4t}+F_{23}e^{-wt}+F_{24}e^{-\lambda_{89}t}$$

$$\frac{dP_{19}(t)}{dt}=\lambda_{19}P_{11}(t)+\lambda_{29}P_{12}(t)+\lambda_{39}P_{13}(t)+\lambda_{49}P_{14}(t)+\lambda_{59}P_{15}(t)+\lambda_{69}P_{16}(t)+\lambda_{79}P_{17}(t)+\lambda_{89}P_{18}(t)$$

Substitute for each $P_{ij}\ (t)$ then integrate both sides:

$$\frac{dP_{19}(t)}{dt} = \lambda_{19}P_{11}(t) + \lambda_{29}P_{12}(t) + \lambda_{39}P_{13}(t) + \lambda_{49}P_{14}(t) + \lambda_{59}P_{15}(t) + \lambda_{69}P_{16}(t) + \lambda_{79}P_{17}(t) + \lambda_{89}P_{18}(t)$$

$$\because \lambda_{19}P_{11}(t) = \lambda_{19}[A_{11}e^{r_1t} + B_{11}e^{r_2t} + C_{11}e^{r_3t} + D_{11}e^{r_4t}]$$
$$= \lambda_{19}A_{11}e^{r_1t} + \lambda_{19}B_{11}e^{r_2t} + \lambda_{19}C_{11}e^{r_3t} + \lambda_{19}D_{11}e^{r_4t}$$
$$\because \lambda_{29}P_{12}(t) = \lambda_{29}[A_{12}e^{r_1t} + B_{12}e^{r_2t} + C_{12}e^{r_3t} + D_{12}e^{r_4t}]$$
$$= \lambda_{29}A_{12}e^{r_1t} + \lambda_{29}B_{12}e^{r_2t} + \lambda_{29}C_{12}e^{r_3t} + \lambda_{29}D_{12}e^{r_4t}$$
$$\because \lambda_{39}P_{13}(t) = \lambda_{39}[A_{13}e^{r_1t} + B_{13}e^{r_2t} + C_{13}e^{r_3t} + D_{13}e^{r_4t}]$$
$$= \lambda_{39}A_{13}e^{r_1t} + \lambda_{39}B_{13}e^{r_2t} + \lambda_{39}C_{13}e^{r_3t} + \lambda_{39}D_{13}e^{r_4t}$$
$$\because \lambda_{49}P_{14}(t) = \lambda_{49}[A_{14}e^{r_1t} + B_{14}e^{r_2t} + C_{14}e^{r_3t} + D_{14}e^{r_4t}]$$
$$= \lambda_{49}A_{14}e^{r_1t} + \lambda_{49}B_{14}e^{r_2t} + \lambda_{49}C_{14}e^{r_3t} + \lambda_{49}D_{14}e^{r_4t}$$
$$\because \lambda_{59}P_{15}(t) = \lambda_{59}[F_1e^{r_1t} + F_2e^{r_2t} + F_3e^{r_3t} + F_4e^{r_4t} + F_5e^{-wt}]$$
$$= \lambda_{59}F_1e^{r_1t} + \lambda_{59}F_2e^{r_2t} + \lambda_{59}F_3e^{r_3t} + \lambda_{59}F_4e^{r_4t} + \lambda_{59}F_5e^{-wt}$$
$$\because \lambda_{69}P_{16}(t) = \lambda_{69}[F_6e^{r_1t} + F_7e^{r_2t} + F_8e^{r_3t} + F_9e^{r_4t} + F_{10}e^{-wt} + F_{11}e^{-ut}]$$
$$= \lambda_{69}F_6e^{r_1t} + \lambda_{69}F_7e^{r_2t} + \lambda_{69}F_8e^{r_3t} + \lambda_{69}F_9e^{r_4t} + \lambda_{69}F_{10}e^{-wt} + \lambda_{69}F_{11}e^{-ut}$$
$$\because \lambda_{79}P_{17}(t) = \lambda_{79}\left[F_{12}e^{r_1t} + F_{13}e^{r_2t} + F_{14}e^{r_3t} + F_{15}e^{r_4t} + F_{16}e^{-wt} + F_{17}e^{-ut} + F_{18}e^{-\lambda_{79}t}\right]$$
$$= \lambda_{79}F_{12}e^{r_1t} + \lambda_{79}F_{13}e^{r_2t} + \lambda_{79}F_{14}e^{r_3t} + \lambda_{79}F_{15}e^{r_4t} + \lambda_{79}F_{16}e^{-wt} + \lambda_{79}F_{17}e^{-ut} + \lambda_{79}F_{18}e^{-\lambda_{79}t}$$
$$\because \lambda_{89}P_{18}(t) = \lambda_{89}\left[F_{19}e^{r_1t} + F_{20}e^{r_2t} + F_{21}e^{r_3t} + F_{22}e^{r_4t} + F_{23}e^{-wt} + F_{24}e^{-\lambda_{89}t}\right]$$
$$= \lambda_{89}F_{19}e^{r_1t} + \lambda_{89}F_{20}e^{r_2t} + \lambda_{89}F_{21}e^{r_3t} + \lambda_{89}F_{22}e^{r_4t} + \lambda_{89}F_{23}e^{-wt} + \lambda_{89}F_{24}e^{-\lambda_{89}t}$$

$$\frac{dP_{19}(t)}{dt} =$$
$$= (\lambda_{19}A_{11} + \lambda_{29}A_{12} + \lambda_{39}A_{13} + \lambda_{49}A_{14} + \lambda_{59}F_1 + \lambda_{69}F_6 + \lambda_{79}F_{12} + \lambda_{89}F_{19})e^{r_1t} +$$
$$(\lambda_{19}B_{11} + \lambda_{29}B_{12} + \lambda_{39}B_{13} + \lambda_{49}B_{14} + \lambda_{59}F_2 + \lambda_{69}F_7 + \lambda_{79}F_{13} + \lambda_{89}F_{20})e^{r_2t} +$$
$$(\lambda_{19}C_{11} + \lambda_{29}C_{12} + \lambda_{39}C_{13} + \lambda_{49}C_{14} + \lambda_{59}F_3 + \lambda_{69}F_8 + \lambda_{79}F_{14} + \lambda_{89}F_{21})e^{r_3t} +$$
$$(\lambda_{19}D_{11} + \lambda_{29}D_{12} + \lambda_{39}D_{13} + \lambda_{49}D_{14} + \lambda_{59}F_4 + \lambda_{69}F_9 + \lambda_{79}F_{15} + \lambda_{89}F_{22})e^{r_4t} +$$
$$(\lambda_{59}F_5 + \lambda_{69}F_{10} + \lambda_{79}F_{16} + \lambda_{89}F_{23})e^{-wt} + (\lambda_{69}F_{11} + \lambda_{79}F_{17})e^{-ut} + \lambda_{79}F_{18}e^{-\lambda_{79}t} + \lambda_{89}F_{24}e^{-\lambda_{89}t}$$

$Let \quad (\lambda_{19}A_{11} + \lambda_{29}A_{12} + \lambda_{39}A_{13} + \lambda_{49}A_{14} + \lambda_{59}F_1 + \lambda_{69}F_6 + \lambda_{79}F_{12} + \lambda_{89}F_{19}) = G_{21}$
$(\lambda_{19}B_{11} + \lambda_{29}B_{12} + \lambda_{39}B_{13} + \lambda_{49}B_{14} + \lambda_{59}F_2 + \lambda_{69}F_7 + \lambda_{79}F_{13} + \lambda_{89}F_{20}) = G_{22}$
$(\lambda_{19}C_{11} + \lambda_{29}C_{12} + \lambda_{39}C_{13} + \lambda_{49}C_{14} + \lambda_{59}F_3 + \lambda_{69}F_8 + \lambda_{79}F_{14} + \lambda_{89}F_{21}) = G_{23}$
$(\lambda_{19}D_{11} + \lambda_{29}D_{12} + \lambda_{39}D_{13} + \lambda_{49}D_{14} + \lambda_{59}F_4 + \lambda_{69}F_9 + \lambda_{79}F_{15} + \lambda_{89}F_{22})$
$= G_{24}$, $(\lambda_{59}F_5 + \lambda_{69}F_{10} + \lambda_{79}F_{16} + \lambda_{89}F_{23}) = G_{25}$
, $(\lambda_{69}F_{11} + \lambda_{79}F_{17}) = G_{26}$, $\lambda_{79}F_{18} = G_{27}$, $\lambda_{89}F_{24} = G_{28}$

$$\frac{dP_{19}(t)}{dt} = G_{21}e^{r_1t} + G_{22}e^{r_2t} + G_{23}e^{r_3t} + G_{24}e^{r_4t} + G_{25}e^{-wt} + G_{26}e^{-ut} + G_{27}e^{-\lambda_{79}t} + G_{28}e^{-\lambda_{89}t}$$

$$P_{19}(t) = G_{21}\left[\frac{e^{r_1t}}{r_1} - \frac{1}{r_1}\right] + G_{22}\left[\frac{e^{r_2t}}{r_2} - \frac{1}{r_2}\right] + G_{23}\left[\frac{e^{r_3t}}{r_3} - \frac{1}{r_3}\right] + G_{24}\left[\frac{e^{r_4t}}{r_4} - \frac{1}{r_4}\right] + G_{25}\left[\frac{e^{-wt}}{-w} - \frac{1}{-w}\right]$$
$$+ G_{26}\left[\frac{e^{-ut}}{-u} - \frac{1}{-u}\right] + G_{27}\left[\frac{e^{-\lambda_{79}t}}{-\lambda_{79}} - \frac{1}{-\lambda_{79}}\right] + G_{28}\left[\frac{e^{-\lambda_{89}t}}{-\lambda_{89}} - \frac{1}{-\lambda_{89}}\right]$$

$$P_{19}(t) = \frac{G_{21}}{r_1}[e^{r_1t} - 1] + \frac{G_{22}}{r_2}[e^{r_2t} - 1] + \frac{G_{23}}{r_3}[e^{r_3t} - 1] + \frac{G_{24}}{r_4}[e^{r_4t} - 1] + \frac{G_{25}}{w}[1 - e^{-wt}] + \frac{G_{26}}{u}[1 - e^{-ut}]$$
$$+ \frac{G_{27}}{\lambda_{79}}\left[1 - e^{-\lambda_{79}t}\right] + \frac{G_{28}}{\lambda_{89}}\left[1 - e^{-\lambda_{89}t}\right]$$

$$P_{19}(t) = \frac{G_{21}}{r_1}e^{r_1t} + \frac{G_{22}}{r_2}e^{r_2t} + \frac{G_{23}}{r_3}e^{r_3t} + \frac{G_{24}}{r_4}e^{r_4t} - \frac{G_{25}}{w}e^{-wt} - \frac{G_{26}}{u}e^{-ut} - \frac{G_{27}}{\lambda_{79}}e^{-\lambda_{79}t} - \frac{G_{28}}{\lambda_{89}}e^{-\lambda_{89}t}$$
$$+ \left[-\frac{G_{21}}{r_1} - \frac{G_{22}}{r_2} - \frac{G_{23}}{r_3} - \frac{G_{24}}{r_4} + \frac{G_{25}}{w} + \frac{G_{26}}{u} + \frac{G_{27}}{\lambda_{79}} + \frac{G_{28}}{\lambda_{89}}\right]$$

$let \quad \frac{G_{21}}{r_1} = F_{25}$, $\frac{G_{22}}{r_2} = F_{26}$, $\frac{G_{23}}{r_3} = F_{27}$, $\frac{G_{24}}{r_4} = F_{28}$, $-\frac{G_{25}}{w} = F_{29}$, $-\frac{G_{26}}{u} = F_{30}$, $-\frac{G_{27}}{\lambda_{79}} = F_{31}$, $-\frac{G_{28}}{\lambda_{89}} = F_{32}$,

$$\left[-\frac{G_{21}}{r_1} - \frac{G_{22}}{r_2} - \frac{G_{23}}{r_3} - \frac{G_{24}}{r_4} + \frac{G_{25}}{w} + \frac{G_{26}}{u} + \frac{G_{27}}{\lambda_{79}} + \frac{G_{28}}{\lambda_{89}}\right] = F_{33}$$

$$P_{19}(t) = F_{25}e^{r_1t} + F_{26}e^{r_2t} + F_{27}e^{r_3t} + F_{28}e^{r_4t} + F_{29}e^{-wt} + F_{30}e^{-ut} + F_{31}e^{-\lambda_{79}t} + F_{32}e^{-\lambda_{89}t} + F_{33}$$

Solving The Last 5 Probabilities In The second Row By Using The Method Of Integrating Factor

Using the same procedure as in the last 5 probabilities in the first row, but what differ are the coefficients for each PDFs':

$for \ \ P_{25}(t)$: $\lambda_{45}A_{24} = H_1$, $\lambda_{45}B_{24} = H_2$, $\lambda_{45}C_{24} = H_3$, $\lambda_{45}D_{24} = H_4$

$$and \quad \frac{H_1}{w+r_1} = K_1 \ , \quad \frac{H_2}{w+r_2} = K_2 \ , \quad \frac{H_3}{w+r_3} = K_3 \ , \frac{H_4}{w+r_4} = K_4,$$
$$-\left[\frac{H_1}{w+r_1} + \frac{H_2}{w+r_2} + \frac{H_3}{w+r_3} + \frac{H_4}{w+r_4}\right] = K_5$$
$P_{25}(t) = K_1 e^{r_1 t} + K_2 e^{r_2 t} + K_3 e^{r_3 t} + K_4 e^{r_4 t} + K_5 e^{-wt}$

$for \ P_{26}(t)$: $\lambda_{56} K_1 = H_5$, $\lambda_{56} K_2 = H_6$, $\lambda_{56} K_3 = H_7$, $\lambda_{56} K_4 = H_8$, $\lambda_{56} K_5 = H_9$

$$and \quad \frac{H_5}{u+r_1} = K_6 , \frac{H_6}{u+r_2} = K_7 , \frac{H_7}{u+r_3} = K_8 , \frac{H_8}{u+r_4} = K_9 , \frac{H_9}{u-w}$$
$$= K_{10} , -\left[\frac{H_5}{u+r_1} + \frac{H_6}{u+r_2} + \frac{H_7}{u+r_3} + \frac{H_8}{u+r_4} + \frac{H_9}{u-w}\right] = K_{11}$$
$P_{26}(t) = K_6 e^{r_1 t} + K_7 e^{r_2 t} + K_8 e^{r_3 t} + K_9 e^{r_4 t} + K_{10} e^{-wt} + K_{11} e^{-ut}$

$for \ P_{27}(t)$: $\lambda_{67} K_6 = H_{10}$, $\lambda_{67} K_7 = H_{11}$, $\lambda_{67} K_8 = H_{12}$, $\lambda_{67} K_9 = H_{13}$, $\lambda_{67} K_{10} = H_{14}$, $\lambda_{67} K_{11} = H_{15}$

$$and \quad \frac{H_{10}}{\lambda_{79}+r_1} = K_{12} , \quad \frac{H_{11}}{\lambda_{79}+r_2} = K_{13} , \quad \frac{H_{12}}{\lambda_{79}+r_3} = K_{14} , \quad \frac{H_{13}}{\lambda_{79}+r_4} = K_{15} , \quad \frac{H_{14}}{\lambda_{79}-w} = K_{16} ,$$
$$\frac{H_{15}}{\lambda_{79}-u} = K_{17}$$
$$-\left[\frac{H_{10}}{\lambda_{79}+r_1} + \frac{H_{11}}{\lambda_{79}+r_2} + \frac{H_{12}}{\lambda_{79}+r_3} + \frac{H_{13}}{\lambda_{79}+r_4} + \frac{H_{14}}{\lambda_{79}-w} + \frac{H_{15}}{\lambda_{79}-u}\right] = K_{18}$$
$P_{27}(t) = K_{12} e^{r_1 t} + K_{13} e^{r_2 t} + K_{14} e^{r_3 t} + K_{15} e^{r_4 t} + K_{16} e^{-wt} + K_{17} e^{-ut} + K_{18} e^{-\lambda_{79} t}$

$for \ P_{28}(t)$: $[\lambda_{18} A_{21} + \lambda_{28} A_{22} + \lambda_{38} A_{23} + \lambda_{48} A_{24} + \lambda_{58} K_1]$
$= H_{16}$, $[\lambda_{18} B_{21} + \lambda_{28} B_{22} + \lambda_{38} B_{23} + \lambda_{48} B_{24} + \lambda_{58} K_2] = H_{17}$
$[\lambda_{18} C_{21} + \lambda_{28} C_{22} + \lambda_{38} C_{23} + \lambda_{48} C_{24} + \lambda_{58} K_3] = H_{18}$, $[\lambda_{18} D_{21} + \lambda_{28} D_{22} + \lambda_{38} D_{23} + \lambda_{48} D_{24} + \lambda_{58} K_4]$
$= H_{19}$, $\lambda_{58} K_5 = H_{20}$

$$and \quad \frac{H_{16}}{\lambda_{89}+r_1} = K_{19} , \frac{H_{17}}{\lambda_{89}+r_2} = K_{20} , \frac{H_{18}}{\lambda_{89}+r_3} = K_{21} , \frac{H_{19}}{\lambda_{89}+r_4} = K_{22} , \frac{H_{20}}{\lambda_{89}-w} = K_{23}$$
$$, -\left[\frac{H_{16}}{\lambda_{89}+r_1} + \frac{H_{17}}{\lambda_{89}+r_2} + \frac{H_{18}}{\lambda_{89}+r_3} + \frac{H_{19}}{\lambda_{89}+r_4} + \frac{H_{20}}{\lambda_{89}-w}\right] = K_{24}$$
$P_{28}(t) = K_{19} e^{r_1 t} + K_{20} e^{r_2 t} + K_{21} e^{r_3 t} + K_{22} e^{r_4 t} + K_{23} e^{-wt} + K_{24} e^{-\lambda_{89} t}$

$for \ P_{29}(t)$: $(\lambda_{19} A_{21} + \lambda_{29} A_{22} + \lambda_{39} A_{23} + \lambda_{49} A_{24} + \lambda_{59} K_1 + \lambda_{69} K_6 + \lambda_{79} K_{12} + \lambda_{89} K_{19}) = H_{21}$
$(\lambda_{19} B_{21} + \lambda_{29} B_{22} + \lambda_{39} B_{23} + \lambda_{49} B_{24} + \lambda_{59} K_2 + \lambda_{69} K_7 + \lambda_{79} K_{13} + \lambda_{89} K_{20}) = H_{22}$
$(\lambda_{19} C_{21} + \lambda_{29} C_{22} + \lambda_{39} C_{23} + \lambda_{49} C_{24} + \lambda_{59} K_3 + \lambda_{69} K_8 + \lambda_{79} K_{14} + \lambda_{89} K_{21}) = H_{23}$
$(\lambda_{19} D_{21} + \lambda_{29} D_{22} + \lambda_{39} D_{23} + \lambda_{49} D_{24} + \lambda_{59} K_4 + \lambda_{69} K_9 + \lambda_{79} K_{15} + \lambda_{89} K_{22})$
$= H_{24}$, $(\lambda_{59} K_5 + \lambda_{69} K_{10} + \lambda_{79} K_{16} + \lambda_{89} K_{23}) = H_{25}$, $(\lambda_{69} K_{11} + \lambda_{79} K_{17}) = H_{26}$
$\lambda_{79} K_{18} = H_{27}$, $\lambda_{89} K_{24} = H_{28}$

$$and \quad \frac{H_{21}}{r_1} = K_{25} \ , \frac{H_{22}}{r_2} = K_{26} , \frac{H_{23}}{r_3} = K_{27} \ , \frac{H_{24}}{r_4} = K_{28} \ , \ -\frac{H_{25}}{w} = K_{29} \ , -\frac{H_{26}}{u} = K_{30} \ , \ -\frac{H_{27}}{\lambda_{79}} = K_{31} ,$$
$$-\frac{H_{28}}{\lambda_{89}} = K_{32},$$
$$+\left[-\frac{H_{21}}{r_1} - \frac{H_{22}}{r_2} - \frac{H_{23}}{r_3} - \frac{H_{24}}{r_4} + \frac{H_{25}}{w} + \frac{H_{26}}{u} + \frac{H_{27}}{\lambda_{79}} + \frac{H_{28}}{\lambda_{89}}\right] = K_{33}$$
$P_{29}(t) = K_{25} e^{r_1 t} + K_{26} e^{r_2 t} + K_{27} e^{r_3 t} + K_{28} e^{r_4 t} + K_{29} e^{-wt} + K_{30} e^{-ut} + K_{31} e^{-\lambda_{79} t} + K_{32} e^{-\lambda_{89} t} + K_{33}$

Solving The Last 5 Probabilities In The third Row By Using The Method Of Integrating Factor

Using the same procedure as in the last 5 probabilities in the first row, but what differ are the coefficients for each PDFs':

$for \ P_{35}(t)$: $\lambda_{45} A_{34} = L_1$, $\lambda_{45} B_{34} = L_2$, $\lambda_{45} C_{34} = L_3$, $\lambda_{45} D_{34} = L_4$,

$$and \quad \frac{L_1}{w+r_1} = M_1 \ , \quad \frac{L_2}{w+r_2} = M_2 \ , \quad \frac{L_3}{w+r_3} = M_3 \ , \frac{L_4}{w+r_4} = M_4,$$
$$-\left[\frac{L_1}{w+r_1} + \frac{L_2}{w+r_2} + \frac{L_3}{w+r_3} + \frac{L_4}{w+r_4}\right] = M_5$$
$P_{35}(t) = M_1 e^{r_1 t} + M_2 e^{r_2 t} + M_3 e^{r_3 t} + M_4 e^{r_4 t} + M_5 e^{-wt}$

$for \ P_{36}(t)$: $\lambda_{56} M_1 = L_5$, $\lambda_{56} M_2 = L_6$, $\lambda_{56} M_3 = L_7$, $\lambda_{56} M_4 = L_8$, $\lambda_{56} M_5 = L_9$,

$$and \quad \frac{L_5}{u+r_1} = M_6 \ , \ \frac{L_6}{u+r_2} = M_7 , \frac{L_7}{u+r_3} = M_8 , \frac{L_8}{u+r_4} = M_9 , \frac{L_9}{u-w}$$
$$= M_{10} \ , -\left[\frac{L_5}{u+r_1} + \frac{L_6}{u+r_2} + \frac{L_7}{u+r_3} + \frac{L_8}{u+r_4} + \frac{L_9}{u-w}\right] = M_{11}$$
$P_{36}(t) = M_6 e^{r_1 t} + M_7 e^{r_2 t} + M_8 e^{r_3 t} + M_9 e^{r_4 t} + M_{10} e^{-wt} + M_{11} e^{-ut}$

$for\ \ P_{37}(t)$: $\lambda_{67}M_6 = L_{10}$, $\lambda_{67}M_7 = L_{11}$, $\lambda_{67}M_8 = L_{12}$, $\lambda_{67}M_9 = L_{13}$, $\lambda_{67}M_{10} = L_{14}$, $\lambda_{67}M_{11} = L_{15}$

$and\ \ \frac{L_{10}}{\lambda_{79}+r_1} = M_{12}$, $\frac{L_{11}}{\lambda_{79}+r_2} = M_{13}$, $\frac{L_{12}}{\lambda_{79}+r_3} = M_{14}$, $\frac{L_{13}}{\lambda_{79}+r_4} = M_{15}$, $\frac{L_{14}}{\lambda_{79}-w} = M_{16}$, $\frac{L_{15}}{\lambda_{79}-u} = M_{17}$,

$-\left[\frac{L_{10}}{\lambda_{79}+r_1} + \frac{L_{11}}{\lambda_{79}+r_2} + \frac{L_{12}}{\lambda_{79}+r_3} + \frac{L_{13}}{\lambda_{79}+r_4} + \frac{L_{14}}{\lambda_{79}-w} + \frac{L_{15}}{\lambda_{79}-u}\right] = M_{18}$

$P_{37}(t) = M_{12}e^{r_1 t} + M_{13}e^{r_2 t} + M_{14}e^{r_3 t} + M_{15}e^{r_4 t} + M_{16}e^{-wt} + M_{17}e^{-ut} + M_{18}e^{-\lambda_{79}t}$

$for\ \ P_{38}(t)$: $[\lambda_{18}A_{31} + \lambda_{28}A_{32} + \lambda_{38}A_{33} + \lambda_{48}A_{34} + \lambda_{58}M_1] = L_{16}$, $[\lambda_{18}B_{31} + \lambda_{28}B_{32} + \lambda_{38}B_{33} + \lambda_{48}B_{34} + \lambda_{58}M_2] = L_{17}$

$[\lambda_{18}C_{31} + \lambda_{28}C_{32} + \lambda_{38}C_{33} + \lambda_{48}C_{34} + \lambda_{58}M_3] = L_{18}$, $[\lambda_{18}D_{31} + \lambda_{28}D_{32} + \lambda_{38}D_{33} + \lambda_{48}D_{34} + \lambda_{58}M_4] = L_{19}$, $\lambda_{58}M_5 = L_{20}$

$and\ \ \frac{L_{16}}{\lambda_{89}+r_1} = M_{19}$, $\frac{L_{17}}{\lambda_{89}+r_2} = M_{20}$, $\frac{L_{18}}{\lambda_{89}+r_3} = M_{21}$, $\frac{L_{19}}{\lambda_{89}+r_4} = M_{22}$, $\frac{L_{20}}{\lambda_{89}-w} = M_{23}$,

$-\left[\frac{L_{16}}{\lambda_{89}+r_1} + \frac{L_{17}}{\lambda_{89}+r_2} + \frac{L_{18}}{\lambda_{89}+r_3} + \frac{L_{19}}{\lambda_{89}+r_4} + \frac{L_{20}}{\lambda_{89}-w}\right] = M_{24}$

$P_{38}(t) = M_{19}e^{r_1 t} + M_{20}e^{r_2 t} + M_{21}e^{r_3 t} + M_{22}e^{r_4 t} + M_{23}e^{-wt} + M_{24}e^{-\lambda_{89}t}$

$for\ \ P_{39}(t)$: $(\lambda_{19}A_{31} + \lambda_{29}A_{32} + \lambda_{39}A_{33} + \lambda_{49}A_{34} + \lambda_{59}M_1 + \lambda_{69}M_6 + \lambda_{79}M_{12} + \lambda_{89}M_{19}) = L_{21}$

$(\lambda_{19}B_{31} + \lambda_{29}B_{32} + \lambda_{39}B_{33} + \lambda_{49}B_{34} + \lambda_{59}M_2 + \lambda_{69}M_7 + \lambda_{79}M_{13} + \lambda_{89}M_{20}) = L_{22}$

$(\lambda_{19}C_{31} + \lambda_{29}C_{32} + \lambda_{39}C_{33} + \lambda_{49}C_{34} + \lambda_{59}M_3 + \lambda_{69}M_8 + \lambda_{79}M_{14} + \lambda_{89}M_{21}) = L_{23}$

$(\lambda_{19}D_{31} + \lambda_{29}D_{32} + \lambda_{39}D_{33} + \lambda_{49}D_{34} + \lambda_{59}M_4 + \lambda_{69}M_9 + \lambda_{79}M_{15} + \lambda_{89}M_{22}) = L_{24}$

$(\lambda_{59}M_5 + \lambda_{69}M_{10} + \lambda_{79}M_{16} + \lambda_{89}M_{23}) = L_{25}$, $(\lambda_{69}M_{11} + \lambda_{79}M_{17}) = L_{26}$, $\lambda_{79}M_{18} = L_{27}$, $\lambda_{89}M_{24} = L_{28}$

$and\ \ \frac{L_{21}}{r_1} = M_{25}$, $\frac{L_{22}}{r_2} = M_{26}$, $\frac{L_{23}}{r_3} = M_{27}$, $\frac{L_{24}}{r_4} = M_{28}$, $-\frac{L_{25}}{w} = M_{29}$, $-\frac{L_{26}}{u} = M_{30}$, $-\frac{L_{27}}{\lambda_{79}} = M_{31}$, $-\frac{L_{28}}{\lambda_{89}} = M_{32}$

$, + \left[-\frac{L_{21}}{r_1} - \frac{L_{22}}{r_2} - \frac{L_{23}}{r_3} - \frac{L_{24}}{r_4} + \frac{L_{25}}{w} + \frac{L_{26}}{u} + \frac{L_{27}}{\lambda_{79}} + \frac{L_{28}}{\lambda_{89}}\right] = M_{33}$

$P_{39}(t) = M_{25}e^{r_1 t} + M_{26}e^{r_2 t} + M_{27}e^{r_3 t} + M_{28}e^{r_4 t} + M_{29}e^{-wt} + M_{30}e^{-ut} + M_{31}e^{-\lambda_{79}t} + M_{32}e^{-\lambda_{89}t} + M_{33}$

Solving The Last 5 Probabilities In The fourth Row By Using The Method Of Integrating Factor

Using the same procedure as in the last 5 probabilities in the first row, but what differ are the coefficients for each PDFs':

$for\ P_{45}(t)\lambda_{45}A_{44} = Y_1$, $\lambda_{45}B_{44} = Y_2$, $\lambda_{45}C_{44} = Y_3$, $\lambda_{45}D_{44} = Y_4$,

$and\ \ \frac{Y_1}{w+r_1} = R_1$, $\frac{Y_2}{w+r_2} = R_2$, $\frac{Y_3}{w+r_3} = R_3$, $\frac{Y_4}{w+r_4} = R_4$,

$-\left[\frac{Y_1}{w+r_1} + \frac{Y_2}{w+r_2} + \frac{Y_3}{w+r_3} + \frac{Y_4}{w+r_4}\right] = R_5$

$P_{45}(t) = R_1e^{r_1 t} + R_2e^{r_2 t} + R_3e^{r_3 t} + R_4e^{r_4 t} + R_5e^{-wt}$

$for\ \ P_{46}(t)$: $\lambda_{56}R_1 = Y_5$, $\lambda_{56}R_2 = Y_6$, $\lambda_{56}R_3 = Y_7$, $\lambda_{56}R_4 = Y_8$, $\lambda_{56}R_5 = Y_9$, $integrate\ both\ sides\ from\ (0\ to\ t)$

$and\ \ \frac{Y_5}{u+r_1} = R_6$, $\frac{Y_6}{u+r_2} = R_7$, $\frac{Y_7}{u+r_2} = R_8$, $\frac{Y_8}{u+r_2} = R_9$, $\frac{Y_9}{u-w} = R_{10}$, $-\left[\frac{Y_5}{u+r_1} + \frac{Y_6}{u+r_1} + \frac{Y_7}{u+r_1} + \frac{Y_8}{u+r_1} + \frac{Y_9}{u-w}\right] = R_{11}$

$P_{46}(t) = R_6e^{r_1 t} + R_7e^{r_2 t} + R_8e^{r_3 t} + R_9e^{r_4 t} + R_{10}e^{-wt} + R_{11}e^{-ut}$

$for\ \ P_{47}(t)$: $\lambda_{67}R_6 = Y_{10}$, $\lambda_{67}R_7 = Y_{11}$, $\lambda_{67}R_8 = Y_{12}$, $\lambda_{67}R_9 = Y_{13}$, $\lambda_{67}R_{10} = Y_{14}$, $\lambda_{67}R_{11} = Y_{15}$

$and\ \ \frac{Y_{10}}{\lambda_{79}+r_1} = R_{12}$, $\frac{Y_{11}}{\lambda_{79}+r_2} = R_{13}$, $\frac{Y_{12}}{\lambda_{79}+r_3} = R_{14}$, $\frac{Y_{13}}{\lambda_{79}+r_4} = R_{15}$, $\frac{Y_{14}}{\lambda_{79}-w} = R_{16}$, $\frac{Y_{15}}{\lambda_{79}-u} = R_{17}$,

$-\left[\frac{Y_{10}}{\lambda_{79}+r_1} + \frac{Y_{11}}{\lambda_{79}+r_2} + \frac{Y_{12}}{\lambda_{79}+r_3} + \frac{Y_{13}}{\lambda_{79}+r_4} + \frac{Y_{14}}{\lambda_{79}-w} + \frac{Y_{15}}{\lambda_{79}-u}\right] = R_{18}$

$P_{47}(t) = R_{12}e^{r_1 t} + R_{13}e^{r_2 t} + R_{14}e^{r_3 t} + R_{15}e^{r_4 t} + R_{16}e^{-wt} + R_{17}e^{-ut} + R_{18}e^{-\lambda_{79}t}$

$for\ \ P_{48}(t)$: $[\lambda_{18}A_{41}+\lambda_{28}A_{42}+\lambda_{38}A_{43}+\lambda_{48}A_{44}+\lambda_{58}R_1]$
$=Y_{16}\ ,[\lambda_{18}B_{41}+\lambda_{28}B_{42}+\lambda_{38}B_{43}+\lambda_{48}B_{44}+\lambda_{58}R_2]=Y_{17}$
$[\lambda_{18}C_{41}+\lambda_{28}C_{42}+\lambda_{38}C_{43}+\lambda_{48}C_{44}+\lambda_{58}R_3]=Y_{18}\ ,[\lambda_{18}D_{41}+\lambda_{28}D_{42}+\lambda_{38}D_{43}+\lambda_{48}D_{44}+\lambda_{58}R_4]=Y_{19}\ ,$
$\lambda_{58}R_5=Y_{20}$

$and\quad \frac{Y_{16}}{\lambda_{89}+r_1}=R_{19}\ ,\frac{Y_{17}}{\lambda_{89}+r_2}=R_{20}\ ,\frac{Y_{18}}{\lambda_{89}+r_3}=R_{21}\ ,\frac{Y_{19}}{\lambda_{89}+r_4}=R_{22}\ ,\qquad \frac{Y_{20}}{\lambda_{89}-w}=R_{23}$

$$-\left[\frac{Y_{16}}{\lambda_{89}+r_1}+\frac{Y_{17}}{\lambda_{89}+r_2}+\frac{Y_{18}}{\lambda_{89}+r_3}+\frac{Y_{19}}{\lambda_{89}+r_4}+\frac{Y_{20}}{\lambda_{89}-w}\right]=R_{24}$$

$$P_{48}(t)=R_{19}e^{r_1t}+R_{20}e^{r_2t}+R_{21}e^{r_3t}+R_{22}e^{r_4t}+R_{23}e^{-wt}+R_{24}e^{-\lambda_{89}t}$$

$for\ P_{49}(t)$: $(\lambda_{19}A_{41}+\lambda_{29}A_{42}+\lambda_{39}A_{43}+\lambda_{49}A_{44}+\lambda_{59}\ R_1+\lambda_{69}R_6+\lambda_{79}R_{12}+\lambda_{89}R_{19})=Y_{21}$
$(\lambda_{19}B_{41}+\lambda_{29}B_{42}+\lambda_{39}B_{43}+\lambda_{49}B_{44}+\lambda_{59}\ R_2+\lambda_{69}R_7+\lambda_{79}R_{13}+\lambda_{89}R_{20})=Y_{22}$
$(\lambda_{19}C_{41}+\lambda_{29}C_{42}+\lambda_{39}C_{43}+\lambda_{49}C_{44}+\lambda_{59}\ R_3+\lambda_{69}R_8+\lambda_{79}R_{14}+\lambda_{89}R_{21})=Y_{23}$
$(\lambda_{19}D_{41}+\lambda_{29}D_{42}+\lambda_{39}D_{43}+\lambda_{49}D_{44}+\lambda_{59}\ R_4+\lambda_{69}R_9+\lambda_{79}R_{15}+\lambda_{89}R_{22})$
$=Y_{24}\ \ ,(\lambda_{59}R_5+\lambda_{69}R_{10}+\lambda_{79}R_{16}\ +\lambda_{89}R_{23})=Y_{25}$
$(\lambda_{69}R_{11}+\lambda_{79}R_{17})=Y_{26}\quad ,\ \ \lambda_{79}R_{18}=Y_{27}\quad ,\ \ \lambda_{89}R_{24}=Y_{28}$

$and\quad \frac{Y_{21}}{r_1}=R_{25}\quad ,$

$\frac{Y_{22}}{r_2}=R_{26}\ ,\frac{Y_{23}}{r_3}=R_{27}\ \ ,\frac{Y_{24}}{r_4}=R_{28}\ \ ,\ \ -\frac{Y_{25}}{w}=R_{29}\ \ ,-\frac{Y_{26}}{u}=R_{30}\ \ ,\ \ -\frac{Y_{27}}{\lambda_{79}}=R_{31}\ ,-\frac{Y_{28}}{\lambda_{89}}$
$=R_{32}$

$$,+\left[-\frac{Y_{21}}{r_1}-\frac{Y_{22}}{r_2}-\frac{Y_{23}}{r_3}-\frac{Y_{24}}{r_4}+\frac{Y_{25}}{w}+\frac{Y_{26}}{u}+\frac{Y_{27}}{\lambda_{79}}+\frac{Y_{28}}{\lambda_{89}}\right]=R_{33}$$

$$P_{49}(t)=R_{25}e^{r_1t}+R_{26}e^{r_2t}+R_{27}e^{r_3t}+R_{28}e^{r_4t}+R_{29}e^{-wt}+R_{30}e^{-ut}+R_{31}e^{-\lambda_{79}t}+R_{32}e^{-\lambda_{89}t}+R_{33}$$

Solving the last 12 equations in the system by integrating factor:

$$\frac{d\,P_{55}(t)}{dt}=-(\lambda_{56}+\lambda_{58}+\lambda_{59})P_{55}(t)\quad ,\quad let\ \ (\lambda_{56}+\lambda_{58}+\lambda_{59})=w\quad \to so\quad P_{55}(t)=e^{-wt}\quad ,$$

$$\frac{d\,P_{56}(t)}{dt}=\lambda_{56}P_{55}(t)-(\lambda_{67}+\lambda_{69})P_{56}(t)\ ,\qquad let\ (\ \lambda_{67}+\lambda_{69})=u$$

$$\therefore\ P_{56}(t)==\frac{\lambda_{56}}{u-w}[e^{-wt}-e^{-ut}]\ \ ,\ and\quad let\ \ \frac{\lambda_{56}}{u-w}=\ v_1\quad so\ \ P_{56}(t)=v_1(e^{-wt}-e^{-ut})$$

$$\frac{d\,P_{57}(t)}{dt}=\lambda_{67}P_{56}(t)-\lambda_{79}P_{57}(t)\quad\to\quad \frac{d}{dt}e^{\lambda_{79}t}\,P_{57}(t)=\ \ \lambda_{67}v_1e^{(\lambda_{79}-w)t}-\ \lambda_{67}v_1e^{(\lambda_{79}-u)t}$$

$$e^{\lambda_{79}t}\,P_{57}(t)=\quad \lambda_{67}v_1\left[\frac{e^{(\lambda_{79}-w)t}}{\lambda_{79}-w}-\frac{1}{\lambda_{79}-w}\right]-\ \lambda_{67}v_1\left[\frac{e^{(\lambda_{79}-u)t}}{\lambda_{79}-u}-\ \frac{1}{\lambda_{79}-u}\right]$$

$$P_{57}(t)=\quad \frac{\lambda_{67}v_1}{\lambda_{79}-w}\left[e^{-wt}-e^{-\lambda_{79}t}\right]-\frac{\lambda_{67}v_1}{\lambda_{79}-u}\left[e^{-ut}-\ e^{-\lambda_{79}t}\right]$$

$$=\quad \frac{\lambda_{67}v_1}{\lambda_{79}-w}e^{-wt}-\frac{\lambda_{67}v_1}{\lambda_{79}-u}e^{-ut}+\left(\frac{\lambda_{67}v_1}{\lambda_{79}-u}-\frac{\lambda_{67}v_1}{\lambda_{79}-w}\right)e^{-\lambda_{79}t}$$

$$let\quad \frac{\lambda_{67}v_1}{\lambda_{79}-w}=v_2\ \ ,\qquad -\frac{\lambda_{67}v_1}{\lambda_{79}-u}=v_3\quad ,$$

$$\left(\frac{\lambda_{67}v_1}{\lambda_{79}-u}-\frac{\lambda_{67}v_1}{\lambda_{79}-w}\right)=v_4\ \ ,so\ \ P_{57}(t)=\quad v_2\,e^{-wt}+\ v_3e^{-ut}+\ v_4e^{-\lambda_{79}t}$$

$$\frac{d\,P_{58}(t)}{dt}=\lambda_{58}P_{55}(t)-\lambda_{89}P_{58}(t)\ ,\qquad so\quad e^{\lambda_{89}t}\frac{d\,P_{58}(t)}{dt}+\lambda_{89}e^{\lambda_{89}t}P_{58}(t)\ =e^{\lambda_{89}t}\lambda_{58}e^{-wt}$$

$$\frac{d}{dt}e^{\lambda_{89}t}P_{58}(t)\ =\ \lambda_{58}e^{(\lambda_{89}-w)t}\ \ ,\qquad then\quad e^{\lambda_{89}t}P_{58}(t)\ =\ \lambda_{58}\left[\frac{e^{(\lambda_{89}-w)t}}{\lambda_{89}-w}-\frac{1}{\lambda_{89}-w}\right]$$

$$P_{58}(t)\ =\ \frac{\lambda_{58}}{\lambda_{89}-w}\left[e^{-wt}\ \ -e^{-\lambda_{89}t}\right]\ \ ,\ let:\quad \frac{\lambda_{58}}{\lambda_{89}-w}\ =v_5\quad ,\quad so\ P_{58}(t)\ =\ v_5\left(e^{-wt}\ \ -e^{-\lambda_{89}t}\right)$$

$$\frac{d\,P_{59}(t)}{dt}=\lambda_{59}P_{55}(t)+\lambda_{69}P_{56}(t)+\lambda_{79}P_{57}(t)+\lambda_{89}P_{58}(t)$$

$$\frac{d\,P_{59}(t)}{dt}=\lambda_{59}e^{-wt}+\lambda_{69}v_1[e^{-wt}-e^{-ut}]+\lambda_{79}\left[v_2\,e^{-wt}+\ v_3e^{-ut}+\ v_4e^{-\lambda_{79}t}\right]+\lambda_{89}v_5\left[e^{-wt}\ \ -e^{-\lambda_{89}t}\right]$$

$let\ :\ (\lambda_{59}\ +\ \lambda_{69}v_1+\ \ \lambda_{79}v_2\ +\lambda_{89}v_5)=v_6\ \ ,\ (\lambda_{79}v_3\ -\ \lambda_{69}v_1)=v_7\ ,\qquad \lambda_{79}v_4=v_8\ ,\qquad -\lambda_{89}v_5=v_9$

$$\frac{d\,P_{59}(t)}{dt}\ =v_6e^{-wt}+\ v_7e^{-ut}+v_8e^{-\lambda_{79}t}+\ v_9e^{-\lambda_{89}t}$$

$$P_{59}(t) = v_6\left[\frac{e^{-wt}}{-w}-\frac{1}{-w}\right]+ v_7\left[\frac{e^{-ut}}{-u}-\frac{1}{-u}\right]+v_8\left[\frac{e^{-\lambda_{79}t}}{-\lambda_{79}}-\frac{1}{-\lambda_{79}}\right]+ v_9\left[\frac{e^{-\lambda_{89}t}}{-\lambda_{89}}-\frac{1}{-\lambda_{89}}\right]$$

$$P_{59}(t) = \frac{-v_6}{w}e^{-wt} - \frac{v_7}{u}e^{-ut} - \frac{v_8}{\lambda_{79}}e^{-\lambda_{79}t} - \frac{v_9}{\lambda_{89}}e^{-\lambda_{89}t} + \left(\frac{v_6}{w}+\frac{v_7}{u}+\frac{v_8}{\lambda_{79}}+\frac{v_9}{\lambda_{58}}\right)$$

$$let:\ \frac{-v_6}{w}=v_{10}\ ,\ \frac{-v_7}{u}=v_{11}\ ,\ \frac{-v_8}{\lambda_{79}}=v_{12}\ ,\ \frac{-v_9}{\lambda_{89}}=v_{13}\ ,\ \left(\frac{v_6}{w}+\frac{v_7}{u}+\frac{v_8}{\lambda_{79}}+\frac{v_9}{\lambda_{58}}\right)=v_{14}$$

$$P_{59}(t) = v_{10}e^{-wt} + v_{11}e^{-ut} + v_{12}e^{-\lambda_{79}t} + v_{13}e^{-\lambda_{89}t} + v_{14}$$

$$\frac{d\,P_{66}(t)}{dt} = -(\lambda_{67}+\lambda_{69})P_{66}(t)\ ,let\quad (\lambda_{67}+\lambda_{69})=u\ ,\quad so\ \frac{d\,P_{66}(t)}{dt} = -u\,P_{66}(t)\quad and\ P_{66}(t) = e^{-ut}$$

$$\frac{d\,P_{67}(t)}{dt} = \lambda_{67}P_{66}(t) - \lambda_{79}P_{67}(t)\ ,\quad so\quad e^{\lambda_{79}t}\frac{d\,P_{67}(t)}{dt} + \lambda_{79}e^{\lambda_{79}t}P_{67}(t) = e^{\lambda_{79}t}\lambda_{67}e^{-ut} = \lambda_{67}e^{(\lambda_{79}-u)t}$$

$$\frac{d}{dt}e^{\lambda_{79}t}P_{67}(t) = \lambda_{67}e^{(\lambda_{79}-u)t}$$

$$e^{\lambda_{79}t}P_{67}(t) = \lambda_{67}\left[\frac{e^{(\lambda_{79}-u)t}}{\lambda_{79}-u}-\frac{1}{\lambda_{79}-u}\right] = \frac{\lambda_{67}}{\lambda_{79}-u}\left[e^{(\lambda_{79}-u)t} - 1\right]\quad ,so\ P_{67}(t) = \frac{\lambda_{67}}{\lambda_{79}-u}\left[e^{-ut} - e^{-\lambda_{79}t}\right]$$

$$Let\quad \frac{\lambda_{67}}{\lambda_{79}-u} = z_1\quad ,\qquad \text{so}\quad P_{67}(t) = z_1\left(e^{-ut} - e^{-\lambda_{79}t}\right)$$

$$\frac{d\,P_{69}(t)}{dt} = \lambda_{69}P_{66}(t) + \lambda_{79}P_{67}(t)$$

$$\frac{d\,P_{69}(t)}{dt} = \lambda_{69}e^{-ut} + \lambda_{79}z_1\left(e^{-ut} - e^{-\lambda_{79}t}\right) = \lambda_{69}e^{-ut} + \lambda_{79}z_1e^{-ut} - \lambda_{79}z_1e^{-\lambda_{79}t}$$

$$= (\lambda_{69} + \lambda_{79}z_1)e^{-ut} - \lambda_{79}z_1e^{-\lambda_{79}t}$$

$$P_{69}(t) = (\lambda_{69} + \lambda_{79}z_1)\left[\frac{e^{-ut}}{-u}-\frac{1}{-u}\right] - \lambda_{79}z_1\left[\frac{e^{-\lambda_{79}t}}{-\lambda_{79}}-\frac{1}{-\lambda_{79}}\right]$$

$$= \frac{(\lambda_{69} + \lambda_{79}z_1)}{-u}\left[e^{-ut} - 1\right] - \frac{\lambda_{79}z_1}{-\lambda_{79}}\left[e^{-\lambda_{79}t} - 1\right]$$

$$let:\ \frac{(\lambda_{69} + \lambda_{79}z_1)}{-u} = z_2\quad ,-\frac{\lambda_{79}z_1}{-\lambda_{79}} = z_3\ ,\ so\quad P_{69}(t) = z_2(e^{-ut} - 1) + z_3\left(e^{-\lambda_{79}t} - 1\right)$$

$$= z_2e^{-ut} + z_3e^{-\lambda_{79}t} - z_2 - z_3$$

$$\frac{d\,P_{77}(t)}{dt} = -\lambda_{79}P_{77}(t)\quad ,\ so\ P_{77}(t) = e^{-\lambda_{79}t}$$

$$\frac{d\,P_{79}(t)}{dt} = \lambda_{79}P_{77}(t) = \lambda_{79}e^{-\lambda_{79}t}\ \ so\ P_{79}(t) = \lambda_{79}\left[\frac{e^{-\lambda_{79}t}}{-\lambda_{79}}-\frac{1}{-\lambda_{79}}\right] = \frac{\lambda_{79}}{-\lambda_{79}}\left[e^{-\lambda_{79}t} - 1\right] = 1 - e^{-\lambda_{79}t}$$

$$\frac{d\,P_{88}(t)}{dt} = -\lambda_{89}P_{88}(t)\ ,\ so\quad P_{88}(t) = e^{-\lambda_{89}t}$$

$$\frac{d\,P_{89}(t)}{dt} = \lambda_{89}P_{88}(t)\quad ,\rightarrow\quad P_{89}(t) = \lambda_{89}\left[\frac{e^{-\lambda_{89}t}}{-\lambda_{89}}-\frac{1}{-\lambda_{89}}\right] = \frac{\lambda_{89}}{-\lambda_{89}}\left[e^{-\lambda_{89}t} - 1\right]$$

$$= 1 - e^{-\lambda_{89}t}\ \ and\ finaly\ P_{99}(t) = 1$$

2. Estimation Of The Q Ratetransiiton Matrix:

The Q matrix

$$Q = \begin{bmatrix} -\gamma_1 & \lambda_{12} & 0 & 0 & 0 & 0 & 0 & \lambda_{18} & \lambda_{19} \\ \mu_{21} & -\gamma_2 & \lambda_{23} & 0 & 0 & 0 & 0 & \lambda_{28} & \lambda_{29} \\ 0 & \mu_{32} & -\gamma_3 & \lambda_{34} & 0 & 0 & 0 & \lambda_{38} & \lambda_{39} \\ 0 & 0 & \mu_{43} & -\gamma_4 & \lambda_{45} & 0 & 0 & \lambda_{48} & \lambda_{49} \\ 0 & 0 & 0 & 0 & -\gamma_5 & \lambda_{56} & 0 & \lambda_{58} & \lambda_{59} \\ 0 & 0 & 0 & 0 & 0 & -\gamma_6 & \lambda_{67} & 0 & \lambda_{69} \\ 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{79} & 0 & \lambda_{79} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{89} & \lambda_{89} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

let: $(\lambda_{12}+\lambda_{18}+\lambda_{19}) = \gamma_1$, $-\gamma_1 - \rho = r$

$(\lambda_{23}+\lambda_{28}+\lambda_{29}+\mu_{21}) = \gamma_2$, $-\gamma_2 - \rho = x$

$(\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32}) = \gamma_3$, $-\gamma_3 - \rho = y$

$(\lambda_{45}+\lambda_{48}+\lambda_{49}+\mu_{43}) = \gamma_4$, $-\gamma_4 - \rho = z$

$(\lambda_{56}+\lambda_{58}+\lambda_{59}) = \gamma_5$, $(\lambda_{67}+\lambda_{69}) = \gamma_6$

The eigen-values of this matrix are obtained by finding the zeros of the characteristic polynomial (polynomial of the 9 th degree) ,this is achieved by solving the following equation $|Q - \rho I| = 0$,

$the\ following\ is\ the\ determinant\ of\ this\ (Q-\rho I)$

$$[-\mu_{32}\lambda_{23}rz + (-\mu_{21}\lambda_{12}+rx)(yz-\mu_{43}\lambda_{34})](-\gamma_5-\rho)(-\gamma_6-\rho)(-\lambda_{79}-\rho)(-\lambda_{89}-\rho)(-\rho)=0$$

$$-[-\mu_{32}\lambda_{23}rz + (-\mu_{21}\lambda_{12}+rx)(yz-\mu_{43}\lambda_{34})](\gamma_5+\rho)(\gamma_6+\rho)(\lambda_{79}+\rho)(\lambda_{89}+\rho)(\rho)=0$$

As obviously seen this 9th degree polynomial has 9 eigen-values and the full model has 22 transition rates.

$\rho_i = \{\,0\,, zeros\ of\ \ both\ \ quadratics\ \ (\gamma_5+\rho)(\gamma_6+\rho)\ \ and\ \ (\lambda_{79}+\rho)(\lambda_{89}+\rho)$
$and\ zeros\ of\ the\ \ 4th\ degree\ polynomial\ \ [-\mu_{32}\lambda_{23}rz + (-\mu_{21}\lambda_{12}+rx)(yz-\mu_{43}\lambda_{34})]\,\}$
$to\ obtain\ \ the\ \ zeros\ of\ the\ \ 4th\ degree\ polynomial\ \ [-\mu_{32}\lambda_{23}rz + (-\mu_{21}\lambda_{12}+rx)(yz-\mu_{43}\lambda_{34})]$:
$rearrange\ the\ polynomial\ \ and\ substitute\ for\ (\,r,x,y,z)\ \ to\ have\ the\ expanded\ form\ of\ the\ polynomial\ \ which\ is\ the$
$f(\rho)=\rho^4+(w_1+w_3)\rho^3+(w_2+w_4+\ w_1w_3-\lambda_{23}\,\mu_{32})\rho^2+(w_2w_3+w_1w_4-\ w_5)\rho+\ (w_2w_4-\ w_6)\,,$
$where\ \ all\ \ ws'\ \ are\ \ as\ previously\ \ defined$
$The\ quartic\ polynomial\ in\ the\ form\ of\ \ \ (a\,x^4+b\,x^3+c\,x^2+dx+\ e\ \ )\ has\ four\ roots:$

$$\rho_1=-\frac{b}{4a}-S+\frac{1}{2}\sqrt{-4S^2-2p+\frac{q}{S}}\qquad,\qquad \rho_2=-\frac{b}{4a}-S-\frac{1}{2}\sqrt{-4S^2-2p+\frac{q}{S}}$$

$$\rho_3=-\frac{b}{4a}+S+\frac{1}{2}\sqrt{-4S^2-2p-\frac{q}{S}}\qquad,\qquad \rho_4=-\frac{b}{4a}+S-\frac{1}{2}\sqrt{-4S^2-2p-\frac{q}{S}}$$

$$p=\frac{8ac-3b^2}{8a^2}\quad,\quad q=\frac{b^3-4abc+8a^2d}{8a^3}\quad,\quad S=\frac{1}{2}\sqrt{\frac{-2p}{3}+\frac{2}{3a}\sqrt{\Delta_0}\,cos\frac{\emptyset}{3}}\quad,\quad \emptyset$$

$$=arccos\left(\frac{\Delta_1}{(2)\sqrt{\Delta_0^3}}\right)\quad,\quad \frac{d}{dx}[cos^{-1}u]=\frac{-1}{\sqrt{1-u^2}}\frac{du}{dx}\quad,$$

$\Delta_0 = c^2-3bd+12ae\ ,\qquad \Delta_1 = 2c^3-9bcd+27b^2e+27ad^2-72ace$

The other roots:

The zeros for quadratic $(\gamma_5+\rho)(\gamma_6+\rho)$:

$$\rho_5=\frac{-(\gamma_5+\gamma_6)+\sqrt{(\gamma_5+\gamma_6)^2-4\gamma_5\gamma_6}}{2}=\frac{-(\gamma_5+\gamma_6)+\sqrt{.}}{2}$$

$$=\frac{-(\lambda_{56}+\lambda_{58}+\lambda_{59}+\lambda_{67}+\lambda_{69})+(\lambda_{56}^2+\lambda_{58}^2+\lambda_{59}^2+\lambda_{67}^2+\lambda_{69}^2+2\lambda_{56}\lambda_{58}+2\lambda_{56}\lambda_{59}+2\lambda_{58}\lambda_{59}+2\lambda_{67}\lambda_{69}-2\lambda_{56}\lambda_{67}-2\lambda_5}{2}$$

$$\rho_6=\frac{-(\gamma_5+\gamma_6)-\sqrt{(\gamma_5+\gamma_6)^2-4\gamma_5\gamma_6}}{2}=\frac{-(\gamma_5+\gamma_6)-\sqrt{.}}{2}$$

$$=\frac{-(\lambda_{56}+\lambda_{58}+\lambda_{59}+\lambda_{67}+\lambda_{69})-(\lambda_{56}^2+\lambda_{58}^2+\lambda_{59}^2+\lambda_{67}^2+\lambda_{69}^2+2\lambda_{56}\lambda_{58}+2\lambda_{56}\lambda_{59}+2\lambda_{58}\lambda_{59}+2\lambda_{67}\lambda_{69}-2\lambda_{56}\lambda_{67}-2\lambda_5}{2}$$

The zeros for quadratic $(\lambda_{79}+\rho)(\lambda_{89}+\rho)$:

$$\rho_7=\frac{-(\lambda_{79}+\lambda_{89})+\sqrt{(\lambda_{79}+\lambda_{89})^2-4\lambda_{79}\lambda_{89}}}{2}=\frac{-(\lambda_{79}+\lambda_{89})+\sqrt{..}}{2}$$

$$=\frac{-(\lambda_{79}+\lambda_{89})+(\lambda_{79}^2+\lambda_{89}^2-2\lambda_{79}\lambda_{89})^{.5}}{2}$$

$$\rho_8=\frac{-(\lambda_{79}+\lambda_{89})-\sqrt{(\lambda_{79}+\lambda_{89})^2-4\lambda_{79}\lambda_{89}}}{2}=\frac{-(\lambda_{79}+\lambda_{89})-\sqrt{..}}{2}$$

$$=\frac{-(\lambda_{79}+\lambda_{89})-(\lambda_{79}^2+\lambda_{89}^2-2\lambda_{79}\lambda_{89})^{.5}}{2}$$

Now differentiating each eigenvalue with respect to the rates forming this eigenvalue:

Starting with the last 4 roots or eigenvalues because they are simpler than the first 4 eigenvalues:

$$\frac{\partial}{\partial\lambda_{56}}\rho_5=\frac{-1}{2}+\frac{1}{2}\frac{1}{2}(.)^{-.5}(2\lambda_{56}+2\lambda_{58}+2\lambda_{59}-2\lambda_{67}-2\lambda_{69})=\frac{-1}{2}+\frac{1}{2}(.)^{-.5}(\lambda_{56}+\lambda_{58}+\lambda_{59}-\lambda_{67}-\lambda_{69})$$

$$\frac{\partial}{\partial\lambda_{58}}\rho_5=\frac{-1}{2}+\frac{1}{2}\frac{1}{2}(.)^{-.5}(2\lambda_{58}+2\lambda_{56}+2\lambda_{59}-2\lambda_{67}-2\lambda_{69})$$

$$=\frac{-1}{2}+\frac{1}{2}(.)^{-.5}(\lambda_{58}+\lambda_{56}+\lambda_{59}-\lambda_{67}-\lambda_{69})$$

$$\frac{\partial}{\partial\lambda_{59}}\rho_5=\frac{-1}{2}+\frac{1}{2}\frac{1}{2}(.)^{-.5}(2\lambda_{59}+2\lambda_{56}+2\lambda_{58}-2\lambda_{67}-2\lambda_{69})=\frac{-1}{2}+\frac{1}{2}(.)^{-.5}(\lambda_{59}+\lambda_{56}+\lambda_{58}-\lambda_{67}-\lambda_{69})$$

$$\frac{\partial}{\partial\lambda_{67}}\rho_5=\frac{-1}{2}+\frac{1}{2}\frac{1}{2}(.)^{-.5}(2\lambda_{67}+2\lambda_{69}-2\lambda_{56}-2\lambda_{58}-2\lambda_{59})$$

$$=\frac{-1}{2}+\frac{1}{2}(.)^{-.5}(\lambda_{67}+\lambda_{69}-\lambda_{56}-\lambda_{58}-\lambda_{59})$$

$$\frac{\partial}{\partial\lambda_{69}}\rho_5=\frac{-1}{2}+\frac{1}{2}\frac{1}{2}(.)^{-.5}(2\lambda_{69}+2\lambda_{67}-2\lambda_{56}-2\lambda_{58}-2\lambda_{59})=\frac{-1}{2}+\frac{1}{2}(.)^{-.5}(\lambda_{69}+\lambda_{67}-\lambda_{56}-\lambda_{58}-\lambda_{59})$$

$$\frac{\partial}{\partial\lambda_{56}}\rho_6=\frac{-1}{2}-\frac{1}{2}\frac{1}{2}(.)^{-.5}(2\lambda_{56}+2\lambda_{58}+2\lambda_{59}-2\lambda_{67}-2\lambda_{69})=\frac{-1}{2}-\frac{1}{2}(.)^{-.5}(\lambda_{56}+\lambda_{58}+\lambda_{59}-\lambda_{67}-\lambda_{69})$$

$$\frac{\partial}{\partial\lambda_{58}}\rho_6=\frac{-1}{2}-\frac{1}{2}\frac{1}{2}(.)^{-.5}(2\lambda_{58}+2\lambda_{56}+2\lambda_{59}-2\lambda_{67}-2\lambda_{69})$$

$$=\frac{-1}{2}-\frac{1}{2}(.)^{-.5}(\lambda_{58}+\lambda_{56}+\lambda_{59}-\lambda_{67}-\lambda_{69})$$

$$\frac{\partial}{\partial\lambda_{59}}\rho_6=\frac{-1}{2}-\frac{1}{2}\frac{1}{2}(.)^{-.5}(2\lambda_{59}+2\lambda_{56}+2\lambda_{58}-2\lambda_{67}-2\lambda_{69})=\frac{-1}{2}-\frac{1}{2}(.)^{-.5}(\lambda_{59}+\lambda_{56}+\lambda_{58}-\lambda_{67}-\lambda_{69})$$

$$\frac{\partial}{\partial\lambda_{67}}\rho_6=\frac{-1}{2}-\frac{1}{2}\frac{1}{2}(.)^{-.5}(2\lambda_{67}+2\lambda_{69}-2\lambda_{56}-2\lambda_{58}-2\lambda_{59})$$

$$=\frac{-1}{2}-\frac{1}{2}(.)^{-.5}(\lambda_{67}+\lambda_{69}-\lambda_{56}-\lambda_{58}-\lambda_{59})$$

$$\frac{\partial}{\partial\lambda_{69}}\rho_6=\frac{-1}{2}-\frac{1}{2}\frac{1}{2}(.)^{-.5}(2\lambda_{69}+2\lambda_{67}-2\lambda_{56}-2\lambda_{58}-2\lambda_{59})=\frac{-1}{2}-\frac{1}{2}(.)^{-.5}(\lambda_{69}+\lambda_{67}-\lambda_{56}-\lambda_{58}-\lambda_{59})$$

$$\frac{\partial}{\partial\lambda_{79}}\rho_7=\frac{-1}{2}+\frac{1}{2}\frac{1}{2}(.)^{-.5}(2\lambda_{79}-2\lambda_{89})=\frac{-1}{2}+\frac{1}{2}(.)^{-.5}(\lambda_{79}-\lambda_{89})$$

$$\frac{\partial}{\partial\lambda_{89}}\rho_7=\frac{-1}{2}+\frac{1}{2}\frac{1}{2}(.)^{-.5}(2\lambda_{89}-2\lambda_{79})=\frac{-1}{2}+\frac{1}{2}(.)^{-.5}(\lambda_{89}-\lambda_{79})$$

$$\frac{\partial}{\partial\lambda_{79}}\rho_8=\frac{-1}{2}-\frac{1}{2}\frac{1}{2}(.)^{-.5}(2\lambda_{79}-2\lambda_{89})=\frac{-1}{2}-\frac{1}{2}(.)^{-.5}(\lambda_{79}-\lambda_{89})$$

$$\frac{\partial}{\partial\lambda_{89}}\rho_8=\frac{-1}{2}-\frac{1}{2}\frac{1}{2}(.)^{-.5}(2\lambda_{89}-2\lambda_{79})=\frac{-1}{2}-\frac{1}{2}(.)^{-.5}(\lambda_{89}-\lambda_{79})$$

The first 4 roots or eigenvalues will be discussed as follows :

$$\rho_1'=-\frac{b'}{4}-S'+\frac{1}{2}\frac{1}{2}\left(-4S^2-2p+\frac{q}{S}\right)^{-.5}\left(-8SS'-2p'+\frac{q'S-S'q}{S^2}\right)$$

$$\rho_2'=-\frac{b'}{4}-S'-\frac{1}{2}\frac{1}{2}\left(-4S^2-2p+\frac{q}{S}\right)^{-.5}\left(-8SS'-2p'+\frac{q'S-S'q}{S^2}\right)$$

$$\rho_3'=-\frac{b'}{4}+S'+\frac{1}{2}\frac{1}{2}\left(-4S^2-2p-\frac{q}{S}\right)^{-.5}\left(-8SS'-2p'-\frac{q'S-S'q}{S^2}\right),$$

$$\rho_4'=-\frac{b'}{4}+S'-\frac{1}{2}\frac{1}{2}\left(-4S^2-2p-\frac{q}{S}\right)^{-.5}\left(-8SS'-2p'-\frac{q'S-S'q}{S^2}\right)$$

$\because a=1$

$$p=\frac{8ac-3b^2}{8a^2}=\frac{8c-3b^2}{8}\qquad\rightarrow\qquad p'=\frac{1}{8}(8c'-6bb')$$

$$q=\frac{b^3-4abc+8a^2d}{8a^3}=\frac{b^3-4bc+8d}{8}\qquad\rightarrow\qquad q'=\frac{1}{8}(3\,b^2b'-4b'c-4bc'+8d')$$

$$S=\frac{1}{2}\sqrt{\frac{-2p}{3}+\frac{2}{3a}\sqrt{\Delta_0}\,cos\frac{\emptyset}{3}}=\frac{1}{2}\sqrt{\frac{-2p}{3}+\frac{2}{3}\sqrt{\Delta_0}\,cos\frac{\emptyset}{3}}\ \rightarrow$$

$$S'=\frac{1}{2}\frac{1}{2}\left(\frac{-2p}{3}+\frac{2}{3}\sqrt{\Delta_0}\,cos\frac{\emptyset}{3}\right)^{-.5}\left(\frac{-2p'}{3}+\frac{2}{3}\left(\sqrt{\Delta_0}\right)'cos\frac{\emptyset}{3}+\frac{2}{3}\sqrt{\Delta_0}\left(cos\frac{\emptyset}{3}\right)'\right)$$

$$\sqrt{\Delta_0}=\sqrt{c^2-3bd+12e}\ \rightarrow\ \left(\sqrt{\Delta_0}\right)'=\frac{1}{2}(c^2-3bd+12e)^{-.5}(2cc'-3b'd-3bd'+12e')$$

$$\frac{2}{3}\left(\sqrt{\Delta_0}\right)'cos\frac{\emptyset}{3}=\frac{2}{3}\frac{1}{2}(c^2-3bd+12e)^{-.5}(2cc'-3b'd-3bd'+12e')cos\frac{\emptyset}{3}$$

$$=\frac{1}{3}(c^2-3bd+12e)^{-.5}(2cc'-3b'd-3bd'+12e')cos\frac{\emptyset}{3}$$

$$\frac{2}{3}\sqrt{\Delta_0}\left[\left(cos\frac{\emptyset}{3}\right)'\right]=\frac{2}{3}\sqrt{\Delta_0}\left[\left(-sin\frac{\emptyset}{3}\right)\frac{1}{3}(\emptyset')\right]\quad,\emptyset=arccos\left(\frac{\Delta_1}{(2)\sqrt{\Delta_0^3}}\right)=cos^{-1}\left(\frac{\Delta_1}{(2)\sqrt{\Delta_0^3}}\right)$$

$$\rightarrow\quad hint:\ \frac{d}{dx}[cos^{-1}u]=\frac{-1}{\sqrt{1-u^2}}\frac{du}{dx}$$

$$\emptyset^{'} = \frac{\partial}{\partial\theta_i}\left[cos^{-1}\left(\frac{\Delta_1}{(2)\sqrt{\Delta_0^3}}\right)\right] = \frac{-1}{\sqrt{1-\left(\frac{\Delta_1}{(2)\sqrt{\Delta_0^3}}\right)^2}}\frac{\partial}{\partial\theta_i}\left(\frac{\Delta_1}{(2)\sqrt{\Delta_0^3}}\right), \frac{\partial}{\partial\theta_i}\left(\frac{\Delta_1}{(2)\sqrt{\Delta_0^3}}\right) = \frac{1}{2}\left(\frac{\Delta_1^{'}\sqrt{\Delta_0^3} - \Delta_1\left(\sqrt{\Delta_0^3}\right)^{'}}{\left(\sqrt{\Delta_0^3}\right)^2}\right)$$

$$= \frac{1}{2}\left(\frac{\Delta_1^{'}\sqrt{\Delta_0^3} - \Delta_1\left(\sqrt{\Delta_0^3}\right)^{'}}{\Delta_0^3}\right)$$

$$\frac{2}{9}\sqrt{\Delta_0}\left[\left(-sin\frac{\emptyset}{3}\right)(\emptyset^{'})\right] = \frac{2}{9}\sqrt{\Delta_0}\left(-sin\frac{\emptyset}{3}\right)\frac{-1}{\sqrt{1-\left(\frac{\Delta_1}{(2)\sqrt{\Delta_0^3}}\right)^2}}\frac{1}{2}\left(\frac{\Delta_1^{'}\sqrt{\Delta_0^3} - \Delta_1\left(\sqrt{\Delta_0^3}\right)^{'}}{\Delta_0^3}\right)$$

$$= \frac{-1}{9}\frac{\sqrt{\Delta_0}\left(-sin\frac{\emptyset}{3}\right)}{\sqrt{1-\left(\frac{\Delta_1}{(2)\sqrt{\Delta_0^3}}\right)^2}}\left(\frac{\Delta_1^{'}\sqrt{\Delta_0^3} - \Delta_1\left(\sqrt{\Delta_0^3}\right)^{'}}{\Delta_0^3}\right)$$

$$\left(\Delta_0{}^{3/2}\right)^{'} = \frac{3}{2}(c^2 - 3bd + 12e)^{.5}(2cc^{'} - 3b^{'}d - 3bd^{'} + 12e^{'})$$

$$(\Delta_1)^{'} = 6c^2c^{'} - 9b^{'}cd - 9bc^{'}d - 9bcd^{'} + 54bb^{'}e + 27b^2e^{'} + 54dd^{'} - 72c^{'}e - 72ce^{'}$$

$$\frac{\partial}{\partial\lambda_{12}}b = 1\ , \frac{\partial}{\partial\lambda_{12}}c = \{(\lambda_{23} + \lambda_{28} + \lambda_{29})\} + \{\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32} + \lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43}\}$$

$$\frac{\partial}{\partial\lambda_{12}}d = \{(\lambda_{23} + \lambda_{28} + \lambda_{29})\}\{\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32} + \lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43}\}$$
$$+ \{(\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32})(\lambda_{45} + \lambda_{48} + \lambda_{49}) + \mu_{43}(\lambda_{38} + \lambda_{39} + \mu_{32})\} - \lambda_{23}\,\mu_{32}$$

$$\frac{\partial}{\partial\lambda_{12}}e = (\lambda_{23} + \lambda_{28} + \lambda_{29})\{(\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32})(\lambda_{45} + \lambda_{48} + \lambda_{49}) + \mu_{43}(\lambda_{38} + \lambda_{39} + \mu_{32})\}$$
$$- \{\lambda_{23}\,\mu_{32}(\lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43})\}$$

$$\frac{\partial}{\partial\lambda_{18}}b = 1\ ,\quad \frac{\partial}{\partial\lambda_{18}}c = (\lambda_{23} + \lambda_{28} + \lambda_{29}) + \mu_{21} + \{\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32} + \lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43}\}$$

$$\frac{\partial}{\partial\lambda_{18}}d = \{(\lambda_{23} + \lambda_{28} + \lambda_{29}) + \mu_{21}\}\{\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32} + \lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43}\}$$
$$+ \{(\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32})(\lambda_{45} + \lambda_{48} + \lambda_{49}) + \mu_{43}(\lambda_{38} + \lambda_{39} + \mu_{32})\}$$
$$-\lambda_{23}\,\mu_{32}$$

$$\frac{\partial}{\partial\lambda_{18}}e = \{(\lambda_{23} + \lambda_{28} + \lambda_{29}) + \mu_{21}\}\{(\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32})(\lambda_{45} + \lambda_{48} + \lambda_{49}) + \mu_{43}(\lambda_{38} + \lambda_{39} + \mu_{32})\}$$
$$- \{\lambda_{23}\,\mu_{32}(\lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43})\}$$

$$\frac{\partial}{\partial\lambda_{19}}b = 1\ ,\quad \frac{\partial}{\partial\lambda_{19}}c = (\lambda_{23} + \lambda_{28} + \lambda_{29}) + \mu_{21} + \{\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32} + \lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43}\}$$

$$\frac{\partial}{\partial\lambda_{19}}d = \{(\lambda_{23} + \lambda_{28} + \lambda_{29}) + \mu_{21}\}\{\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32} + \lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43}\}$$
$$+ \{(\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32})(\lambda_{45} + \lambda_{48} + \lambda_{49}) + \mu_{43}(\lambda_{38} + \lambda_{39} + \mu_{32})\}$$
$$-\lambda_{23}\,\mu_{32}$$

$$\frac{\partial}{\partial\lambda_{19}}e = \{(\lambda_{23} + \lambda_{28} + \lambda_{29}) + \mu_{21}\}\{(\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32})(\lambda_{45} + \lambda_{48} + \lambda_{49}) + \mu_{43}(\lambda_{38} + \lambda_{39} + \mu_{32})\}$$
$$- \{\lambda_{23}\,\mu_{32}(\lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43})\}$$

$$\frac{\partial}{\partial\lambda_{23}}b = 1\ ,\quad \frac{\partial}{\partial\lambda_{23}}c = \{(\lambda_{12} + \lambda_{18} + \lambda_{19})\} + \{\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32} + \lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43}\} - \mu_{32}$$

$$\frac{\partial}{\partial\lambda_{23}}d = (\lambda_{12} + \lambda_{18} + \lambda_{19})\{\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32} + \lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43}\}$$
$$+ \{(\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32})(\lambda_{45} + \lambda_{48} + \lambda_{49}) + \mu_{43}(\lambda_{38} + \lambda_{39} + \mu_{32})\}$$
$$- \mu_{32}(\lambda_{12} + \lambda_{18} + \lambda_{19} + \lambda_{45} + \lambda_{48} + \lambda_{49} + \mu_{43})$$

$$\frac{\partial}{\partial\lambda_{23}}e = (\lambda_{12}+\lambda_{18}+\lambda_{19})\{(\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32})(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}(\lambda_{38}+\lambda_{39}+\mu_{32})\} - \mu_{32}(\lambda_{12}+\lambda_{18}+\lambda_{19})(\lambda_{45}+\lambda_{48}+\lambda_{49}+\mu_{43})$$

$$\frac{\partial}{\partial\lambda_{28}}b = 1, \quad \frac{\partial}{\partial\lambda_{28}}c = \{(\lambda_{12}+\lambda_{18}+\lambda_{19})\}+\{\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32}+\lambda_{45}+\lambda_{48}+\lambda_{49}+\mu_{43}\}$$

$$\frac{\partial}{\partial\lambda_{28}}d = (\lambda_{12}+\lambda_{18}+\lambda_{19})\{\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32}+\lambda_{45}+\lambda_{48}+\lambda_{49}+\mu_{43}\} + \{(\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32})(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}(\lambda_{38}+\lambda_{39}+\mu_{32})\}$$

$$\frac{\partial}{\partial\lambda_{28}}e = (\lambda_{12}+\lambda_{18}+\lambda_{19})\{(\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32})(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}(\lambda_{38}+\lambda_{39}+\mu_{32})\}$$

$$\frac{\partial}{\partial\lambda_{29}}b = 1, \quad \frac{\partial}{\partial\lambda_{29}}c = \{(\lambda_{12}+\lambda_{18}+\lambda_{19})\}+\{\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32}+\lambda_{45}+\lambda_{48}+\lambda_{49}+\mu_{43}\}$$

$$\frac{\partial}{\partial\lambda_{29}}d = (\lambda_{12}+\lambda_{18}+\lambda_{19})\{\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32}+\lambda_{45}+\lambda_{48}+\lambda_{49}+\mu_{43}\} + \{(\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32})(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}(\lambda_{38}+\lambda_{39}+\mu_{32})\}$$

$$\frac{\partial}{\partial\lambda_{29}}e = (\lambda_{12}+\lambda_{18}+\lambda_{19})\{(\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32})(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}(\lambda_{38}+\lambda_{39}+\mu_{32})\}$$

$$\frac{\partial}{\partial\mu_{21}}b = 1, \frac{\partial}{\partial\mu_{21}}c = (\lambda_{18}+\lambda_{19})+\{\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32}+\lambda_{45}+\lambda_{48}+\lambda_{49}+\mu_{43}\}$$

$$\frac{\partial}{\partial\mu_{21}}d = (\lambda_{18}+\lambda_{19})\{\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32}+\lambda_{45}+\lambda_{48}+\lambda_{49}+\mu_{43}\} + \{(\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32})(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}(\lambda_{38}+\lambda_{39}+\mu_{32})\}$$

$$\frac{\partial}{\partial\mu_{21}}e = (\lambda_{18}+\lambda_{19})\{(\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32})(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}(\lambda_{38}+\lambda_{39}+\mu_{32})\}$$

$$\frac{\partial}{\partial\lambda_{34}}b = 1, \quad \frac{\partial}{\partial\lambda_{34}}c = (\lambda_{45}+\lambda_{48}+\lambda_{49})+\{\lambda_{12}+\lambda_{18}+\lambda_{19}+\lambda_{23}+\lambda_{28}+\lambda_{29}+\mu_{21}\}$$

$$\frac{\partial}{\partial\lambda_{34}}d = \{(\lambda_{12}+\lambda_{18}+\lambda_{19})(\lambda_{23}+\lambda_{28}+\lambda_{29})+\mu_{21}(\lambda_{18}+\lambda_{19})\} + \{\lambda_{12}+\lambda_{18}+\lambda_{19}+\lambda_{23}+\lambda_{28}+\lambda_{29}+\mu_{21}\}(\lambda_{45}+\lambda_{48}+\lambda_{49})$$

$$\frac{\partial}{\partial\lambda_{34}}e = \{(\lambda_{12}+\lambda_{18}+\lambda_{19})(\lambda_{23}+\lambda_{28}+\lambda_{29})+\mu_{21}(\lambda_{18}+\lambda_{19})\}(\lambda_{45}+\lambda_{48}+\lambda_{49})$$

$$\frac{\partial}{\partial\lambda_{38}}b = 1, \quad \frac{\partial}{\partial\lambda_{38}}c = \{(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}\}+\{\lambda_{12}+\lambda_{18}+\lambda_{19}+\lambda_{23}+\lambda_{28}+\lambda_{29}+\mu_{21}\}$$

$$\frac{\partial}{\partial\lambda_{38}}d = \{(\lambda_{12}+\lambda_{18}+\lambda_{19})(\lambda_{23}+\lambda_{28}+\lambda_{29})+\mu_{21}(\lambda_{18}+\lambda_{19})\} + \{\lambda_{12}+\lambda_{18}+\lambda_{19}+\lambda_{23}+\lambda_{28}+\lambda_{29}+\mu_{21}\}\{(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}\}$$

$$\frac{\partial}{\partial\lambda_{38}}e = \{(\lambda_{12}+\lambda_{18}+\lambda_{19})(\lambda_{23}+\lambda_{28}+\lambda_{29})+\mu_{21}(\lambda_{18}+\lambda_{19})\}\{(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}\}$$

$$\frac{\partial}{\partial\lambda_{39}}b = 1, \quad \frac{\partial}{\partial\lambda_{39}}c = \{(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}\}+\{\lambda_{12}+\lambda_{18}+\lambda_{19}+\lambda_{23}+\lambda_{28}+\lambda_{29}+\mu_{21}\}$$

$$\frac{\partial}{\partial\lambda_{39}}d = \{(\lambda_{12}+\lambda_{18}+\lambda_{19})(\lambda_{23}+\lambda_{28}+\lambda_{29})+\mu_{21}(\lambda_{18}+\lambda_{19})\} + \{\lambda_{12}+\lambda_{18}+\lambda_{19}+\lambda_{23}+\lambda_{28}+\lambda_{29}+\mu_{21}\}\{(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}\}$$

$$\frac{\partial}{\partial\lambda_{39}}e = \{(\lambda_{12}+\lambda_{18}+\lambda_{19})(\lambda_{23}+\lambda_{28}+\lambda_{29})+\mu_{21}(\lambda_{18}+\lambda_{19})\}\{(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}\}$$

$$\frac{\partial}{\partial\mu_{32}}b = 1, \quad \frac{\partial}{\partial\mu_{32}}c = \{(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}\}+\{\lambda_{12}+\lambda_{18}+\lambda_{19}+\lambda_{23}+\lambda_{28}+\lambda_{29}+\mu_{21}\}-\lambda_{23}$$

$$\frac{\partial}{\partial\mu_{32}}d = \{(\lambda_{12}+\lambda_{18}+\lambda_{19})(\lambda_{23}+\lambda_{28}+\lambda_{29})+\mu_{21}(\lambda_{18}+\lambda_{19})\} + \{\lambda_{12}+\lambda_{18}+\lambda_{19}+\lambda_{23}+\lambda_{28}+\lambda_{29}+\mu_{21}\}\{(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}\} - \lambda_{23}(\lambda_{12}+\lambda_{18}+\lambda_{19}+\lambda_{45}+\lambda_{48}+\lambda_{49}+\mu_{43})$$

$$\frac{\partial}{\partial\mu_{32}}e = \{(\lambda_{12}+\lambda_{18}+\lambda_{19})(\lambda_{23}+\lambda_{28}+\lambda_{29})+\mu_{21}(\lambda_{18}+\lambda_{19})\}\{(\lambda_{45}+\lambda_{48}+\lambda_{49})+\mu_{43}\} - \lambda_{23}(\lambda_{12}+\lambda_{18}+\lambda_{19})(\lambda_{45}+\lambda_{48}+\lambda_{49}+\mu_{43})$$

$$\frac{\partial}{\partial\lambda_{45}}b = 1, \quad \frac{\partial}{\partial\lambda_{45}}c = (\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32})+\{\lambda_{12}+\lambda_{18}+\lambda_{19}+\lambda_{23}+\lambda_{28}+\lambda_{29}+\mu_{21}\}$$

$$\frac{\partial}{\partial \lambda_{45}} d = \{(\lambda_{12} + \lambda_{18} + \lambda_{19})(\lambda_{23} + \lambda_{28} + \lambda_{29}) + \mu_{21}(\lambda_{18} + \lambda_{19})\} + \{\lambda_{12} + \lambda_{18} + \lambda_{19} + \lambda_{23} + \lambda_{28} + \lambda_{29} + \mu_{21}\}(\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32}) - \lambda_{23}\,\mu_{32}$$

$$\frac{\partial}{\partial \lambda_{45}} e = \{(\lambda_{12} + \lambda_{18} + \lambda_{19})(\lambda_{23} + \lambda_{28} + \lambda_{29}) + \mu_{21}(\lambda_{18} + \lambda_{19})\}(\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32}) - \{\lambda_{23}\,\mu_{32}(\lambda_{12} + \lambda_{18} + \lambda_{19})\}$$

$$\frac{\partial}{\partial \lambda_{48}} b = 1, \quad \frac{\partial}{\partial \lambda_{48}} c = (\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32}) + \{\lambda_{12} + \lambda_{18} + \lambda_{19} + \lambda_{23} + \lambda_{28} + \lambda_{29} + \mu_{21}\}$$

$$\frac{\partial}{\partial \lambda_{48}} d = \{(\lambda_{12} + \lambda_{18} + \lambda_{19})(\lambda_{23} + \lambda_{28} + \lambda_{29}) + \mu_{21}(\lambda_{18} + \lambda_{19})\} + \{\lambda_{12} + \lambda_{18} + \lambda_{19} + \lambda_{23} + \lambda_{28} + \lambda_{29} + \mu_{21}\}(\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32}) - \lambda_{23}\,\mu_{32}$$

$$\frac{\partial}{\partial \lambda_{48}} e = \{(\lambda_{12} + \lambda_{18} + \lambda_{19})(\lambda_{23} + \lambda_{28} + \lambda_{29}) + \mu_{21}(\lambda_{18} + \lambda_{19})\}(\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32}) - \{\lambda_{23}\,\mu_{32}(\lambda_{12} + \lambda_{18} + \lambda_{19})\}$$

$$\frac{\partial}{\partial \lambda_{49}} b = 1\ , \quad \frac{\partial}{\partial \lambda_{49}} c = (\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32}) + \{\lambda_{12} + \lambda_{18} + \lambda_{19} + \lambda_{23} + \lambda_{28} + \lambda_{29} + \mu_{21}\}$$

$$\frac{\partial}{\partial \lambda_{49}} d = \{(\lambda_{12} + \lambda_{18} + \lambda_{19})(\lambda_{23} + \lambda_{28} + \lambda_{29}) + \mu_{21}(\lambda_{18} + \lambda_{19})\} + \{\lambda_{12} + \lambda_{18} + \lambda_{19} + \lambda_{23} + \lambda_{28} + \lambda_{29} + \mu_{21}\}(\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32}) - \lambda_{23}\,\mu_{32}$$

$$\frac{\partial}{\partial \lambda_{49}} e = \{(\lambda_{12} + \lambda_{18} + \lambda_{19})(\lambda_{23} + \lambda_{28} + \lambda_{29}) + \mu_{21}(\lambda_{18} + \lambda_{19})\}(\lambda_{34} + \lambda_{38} + \lambda_{39} + \mu_{32}) - \{\lambda_{23}\,\mu_{32}(\lambda_{12} + \lambda_{18} + \lambda_{19})\}$$

$$\frac{\partial}{\partial \mu_{43}} b = 1\ , \quad \frac{\partial}{\partial \mu_{43}} c = (\lambda_{38} + \lambda_{39} + \mu_{32}) + \{\lambda_{12} + \lambda_{18} + \lambda_{19} + \lambda_{23} + \lambda_{28} + \lambda_{29} + \mu_{21}\}$$

$$\frac{\partial}{\partial \mu_{43}} d = \{(\lambda_{12} + \lambda_{18} + \lambda_{19})(\lambda_{23} + \lambda_{28} + \lambda_{29}) + \mu_{21}(\lambda_{18} + \lambda_{19})\} + \{\lambda_{12} + \lambda_{18} + \lambda_{19} + \lambda_{23} + \lambda_{28} + \lambda_{29} + \mu_{21}\}(\lambda_{38} + \lambda_{39} + \mu_{32}) - \lambda_{23}\,\mu_{32}$$

$$\frac{\partial}{\partial \mu_{43}} e = \{(\lambda_{12} + \lambda_{18} + \lambda_{19})(\lambda_{23} + \lambda_{28} + \lambda_{29}) + \mu_{21}(\lambda_{18} + \lambda_{19})\}(\lambda_{38} + \lambda_{39} + \mu_{32}) - \lambda_{23}\,\mu_{32}(\lambda_{12} + \lambda_{18} + \lambda_{19})$$

$\frac{\partial}{\partial \theta_k} P_{ij}\ (t) = te^{\Lambda t} d\Lambda$, where t = ΔtandΛ $are\ eigenvalues\ \rho_i$, to construct the score vector

$$te^{\Lambda t} d\,\Lambda = te^{\rho_1 t}\begin{bmatrix} \frac{\partial}{\partial \boldsymbol{\lambda}_{12}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{18}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{19}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{23}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{28}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{29}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{21}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{34}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{38}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{39}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{32}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{45}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{48}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{49}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{43}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{56}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{58}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{59}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{67}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{69}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{79}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{89}}\rho_1 \end{bmatrix} + te^{\rho_2 t}\begin{bmatrix} \frac{\partial}{\partial \boldsymbol{\lambda}_{12}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{18}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{19}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{23}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{28}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{29}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{21}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{34}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{38}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{39}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{32}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{45}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{48}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{49}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{43}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{56}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{58}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{59}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{67}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{69}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{79}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{89}}\rho_2 \end{bmatrix} + te^{\rho_3 t}\begin{bmatrix} \frac{\partial}{\partial \boldsymbol{\lambda}_{12}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{18}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{19}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{23}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{28}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{29}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{21}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{34}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{38}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{39}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{32}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{45}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{48}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{49}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{43}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{56}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{58}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{59}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{67}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{69}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{79}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{89}}\rho_3 \end{bmatrix} + te^{\rho_4 t}\begin{bmatrix} \frac{\partial}{\partial \boldsymbol{\lambda}_{12}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{18}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{19}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{23}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{28}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{29}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{21}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{34}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{38}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{39}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{32}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{45}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{48}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{49}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{43}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{56}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{58}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{59}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{67}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{69}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{79}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{89}}\rho_4 \end{bmatrix} + te^{\rho_5 t}\begin{bmatrix} \frac{\partial}{\partial \boldsymbol{\lambda}_{12}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{18}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{19}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{23}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{28}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{29}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{21}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{34}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{38}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{39}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{32}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{45}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{48}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{49}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{43}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{56}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{58}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{59}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{67}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{69}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{79}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{89}}\rho_5 \end{bmatrix}$$

$$+ te^{\rho_6 t}\begin{bmatrix} \frac{\partial}{\partial \boldsymbol{\lambda_{12}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{18}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{19}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{23}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{28}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{29}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\mu_{21}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{34}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{38}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{39}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\mu_{32}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{45}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{48}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{49}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\mu_{43}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{56}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{58}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{59}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{67}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{69}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{79}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{89}}}\rho_6 \end{bmatrix} + te^{\rho_7 t}\begin{bmatrix} \frac{\partial}{\partial \boldsymbol{\lambda_{12}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{18}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{19}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{23}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{28}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{29}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\mu_{21}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{34}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{38}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{39}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\mu_{32}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{45}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{48}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{49}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\mu_{43}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{56}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{58}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{59}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{67}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{69}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{79}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{89}}}\rho_7 \end{bmatrix} + te^{\rho_8 t}\begin{bmatrix} \frac{\partial}{\partial \boldsymbol{\lambda_{12}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{18}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{19}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{23}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{28}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{29}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\mu_{21}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{34}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{38}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{39}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\mu_{32}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{45}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{48}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{49}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\mu_{43}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{56}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{58}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{59}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{67}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{69}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{79}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda_{89}}}\rho_8 \end{bmatrix}$$

$$te^{\Lambda t}d\,\Lambda = te^{\rho_1 t}\begin{bmatrix} \frac{\partial}{\partial \boldsymbol{\lambda}_{12}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{18}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{19}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{23}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{28}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{29}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{21}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{34}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{38}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{39}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{32}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{45}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{48}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{49}}\rho_1 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{43}}\rho_1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} + te^{\rho_2 t}\begin{bmatrix} \frac{\partial}{\partial \boldsymbol{\lambda}_{12}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{18}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{19}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{23}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{28}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{29}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{21}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{34}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{38}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{39}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{32}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{45}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{48}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{49}}\rho_2 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{43}}\rho_2 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} + te^{\rho_3 t}\begin{bmatrix} \frac{\partial}{\partial \boldsymbol{\lambda}_{12}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{18}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{19}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{23}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{28}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{29}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{21}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{34}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{38}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{39}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{32}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{45}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{48}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{49}}\rho_3 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{43}}\rho_3 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} + te^{\rho_4 t}\begin{bmatrix} \frac{\partial}{\partial \boldsymbol{\lambda}_{12}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{18}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{19}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{23}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{28}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{29}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{21}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{34}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{38}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{39}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{32}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{45}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{48}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{49}}\rho_4 \\ \frac{\partial}{\partial \boldsymbol{\mu}_{43}}\rho_4 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} + te^{\rho_5 t}\begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{56}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{58}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{59}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{67}}\rho_5 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{69}}\rho_5 \\ 0 \\ 0 \end{bmatrix}$$

$$+ te^{\rho_6 t}\begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{\mathbf{56}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{\mathbf{58}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{\mathbf{59}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{\mathbf{67}}}\rho_6 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{\mathbf{69}}}\rho_6 \\ 0 \\ 0 \end{bmatrix} + te^{\rho_7 t}\begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{\mathbf{79}}}\rho_7 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{\mathbf{89}}}\rho_7 \end{bmatrix} + te^{\rho_8 t}\begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{\mathbf{79}}}\rho_8 \\ \frac{\partial}{\partial \boldsymbol{\lambda}_{\mathbf{89}}}\rho_8 \end{bmatrix}$$

$$te^{\Lambda t} d\,\Lambda = \begin{bmatrix} te^{\rho_1 t}\frac{\partial}{\partial \boldsymbol{\lambda_{12}}}\rho_1 + te^{\rho_2 t}\frac{\partial}{\partial \boldsymbol{\lambda_{12}}}\rho_2 + te^{\rho_3 t}\frac{\partial}{\partial \boldsymbol{\lambda_{12}}}\rho_3 + te^{\rho_4 t}\frac{\partial}{\partial \boldsymbol{\lambda_{12}}}\rho_4 \\ te^{\rho_1 t}\frac{\partial}{\partial \boldsymbol{\lambda_{18}}}\rho_1 + te^{\rho_2 t}\frac{\partial}{\partial \boldsymbol{\lambda_{18}}}\rho_2 + te^{\rho_3 t}\frac{\partial}{\partial \boldsymbol{\lambda_{18}}}\rho_3 + te^{\rho_4 t}\frac{\partial}{\partial \boldsymbol{\lambda_{18}}}\rho_4 \\ te^{\rho_1 t}\frac{\partial}{\partial \boldsymbol{\lambda_{19}}}\rho_1 + te^{\rho_2 t}\frac{\partial}{\partial \boldsymbol{\lambda_{19}}}\rho_2 + te^{\rho_3 t}\frac{\partial}{\partial \boldsymbol{\lambda_{19}}}\rho_3 + te^{\rho_4 t}\frac{\partial}{\partial \boldsymbol{\lambda_{19}}}\rho_4 \\ te^{\rho_1 t}\frac{\partial}{\partial \boldsymbol{\lambda_{23}}}\rho_1 + te^{\rho_2 t}\frac{\partial}{\partial \boldsymbol{\lambda_{23}}}\rho_2 + te^{\rho_3 t}\frac{\partial}{\partial \boldsymbol{\lambda_{23}}}\rho_3 + te^{\rho_4 t}\frac{\partial}{\partial \boldsymbol{\lambda_{23}}}\rho_4 \\ te^{\rho_1 t}\frac{\partial}{\partial \boldsymbol{\lambda_{28}}}\rho_1 + te^{\rho_2 t}\frac{\partial}{\partial \boldsymbol{\lambda_{28}}}\rho_2 + te^{\rho_3 t}\frac{\partial}{\partial \boldsymbol{\lambda_{28}}}\rho_3 + te^{\rho_4 t}\frac{\partial}{\partial \boldsymbol{\lambda_{28}}}\rho_4 \\ te^{\rho_1 t}\frac{\partial}{\partial \boldsymbol{\lambda_{29}}}\rho_1 + te^{\rho_2 t}\frac{\partial}{\partial \boldsymbol{\lambda_{29}}}\rho_2 + te^{\rho_3 t}\frac{\partial}{\partial \boldsymbol{\lambda_{29}}}\rho_3 + te^{\rho_4 t}\frac{\partial}{\partial \boldsymbol{\lambda_{29}}}\rho_4 \\ te^{\rho_1 t}\frac{\partial}{\partial \boldsymbol{\mu_{21}}}\rho_1 + te^{\rho_2 t}\frac{\partial}{\partial \boldsymbol{\mu_{21}}}\rho_2 + te^{\rho_3 t}\frac{\partial}{\partial \boldsymbol{\mu_{21}}}\rho_3 + te^{\rho_4 t}\frac{\partial}{\partial \boldsymbol{\mu_{21}}}\rho_4 \\ te^{\rho_1 t}\frac{\partial}{\partial \boldsymbol{\lambda_{34}}}\rho_1 + te^{\rho_2 t}\frac{\partial}{\partial \boldsymbol{\lambda_{34}}}\rho_2 + te^{\rho_3 t}\frac{\partial}{\partial \boldsymbol{\lambda_{34}}}\rho_3 + te^{\rho_4 t}\frac{\partial}{\partial \boldsymbol{\lambda_{34}}}\rho_4 \\ te^{\rho_1 t}\frac{\partial}{\partial \boldsymbol{\lambda_{38}}}\rho_1 + te^{\rho_2 t}\frac{\partial}{\partial \boldsymbol{\lambda_{38}}}\rho_2 + te^{\rho_3 t}\frac{\partial}{\partial \boldsymbol{\lambda_{38}}}\rho_3 + te^{\rho_4 t}\frac{\partial}{\partial \boldsymbol{\lambda_{38}}}\rho_4 \\ te^{\rho_1 t}\frac{\partial}{\partial \boldsymbol{\lambda_{39}}}\rho_1 + te^{\rho_2 t}\frac{\partial}{\partial \boldsymbol{\lambda_{39}}}\rho_2 + te^{\rho_3 t}\frac{\partial}{\partial \boldsymbol{\lambda_{39}}}\rho_3 + te^{\rho_4 t}\frac{\partial}{\partial \boldsymbol{\lambda_{39}}}\rho_4 \\ te^{\rho_1 t}\frac{\partial}{\partial \boldsymbol{\mu_{32}}}\rho_1 + te^{\rho_2 t}\frac{\partial}{\partial \boldsymbol{\mu_{32}}}\rho_2 + te^{\rho_3 t}\frac{\partial}{\partial \boldsymbol{\mu_{32}}}\rho_3 + te^{\rho_4 t}\frac{\partial}{\partial \boldsymbol{\mu_{32}}}\rho_4 \\ te^{\rho_1 t}\frac{\partial}{\partial \boldsymbol{\lambda_{45}}}\rho_1 + te^{\rho_2 t}\frac{\partial}{\partial \boldsymbol{\lambda_{45}}}\rho_2 + te^{\rho_3 t}\frac{\partial}{\partial \boldsymbol{\lambda_{45}}}\rho_3 + te^{\rho_4 t}\frac{\partial}{\partial \boldsymbol{\lambda_{45}}}\rho_4 \\ te^{\rho_1 t}\frac{\partial}{\partial \boldsymbol{\lambda_{48}}}\rho_1 + te^{\rho_2 t}\frac{\partial}{\partial \boldsymbol{\lambda_{48}}}\rho_2 + te^{\rho_3 t}\frac{\partial}{\partial \boldsymbol{\lambda_{48}}}\rho_3 + te^{\rho_4 t}\frac{\partial}{\partial \boldsymbol{\lambda_{48}}}\rho_4 \\ te^{\rho_1 t}\frac{\partial}{\partial \boldsymbol{\lambda_{49}}}\rho_1 + te^{\rho_2 t}\frac{\partial}{\partial \boldsymbol{\lambda_{49}}}\rho_2 + te^{\rho_3 t}\frac{\partial}{\partial \boldsymbol{\lambda_{49}}}\rho_3 + te^{\rho_4 t}\frac{\partial}{\partial \boldsymbol{\lambda_{49}}}\rho_4 \\ te^{\rho_1 t}\frac{\partial}{\partial \boldsymbol{\mu_{43}}}\rho_1 + te^{\rho_2 t}\frac{\partial}{\partial \boldsymbol{\mu_{43}}}\rho_2 + te^{\rho_3 t}\frac{\partial}{\partial \boldsymbol{\mu_{43}}}\rho_3 + te^{\rho_4 t}\frac{\partial}{\partial \boldsymbol{\mu_{43}}}\rho_4 \\ te^{\rho_5 t}\frac{\partial}{\partial \boldsymbol{\lambda_{56}}}\rho_5 + te^{\rho_6 t}\frac{\partial}{\partial \boldsymbol{\lambda_{56}}}\rho_6 \\ te^{\rho_5 t}\frac{\partial}{\partial \boldsymbol{\lambda_{58}}}\rho_5 + te^{\rho_6 t}\frac{\partial}{\partial \boldsymbol{\lambda_{58}}}\rho_6 \\ te^{\rho_5 t}\frac{\partial}{\partial \boldsymbol{\lambda_{59}}}\rho_5 + te^{\rho_6 t}\frac{\partial}{\partial \boldsymbol{\lambda_{59}}}\rho_6 \\ te^{\rho_5 t}\frac{\partial}{\partial \boldsymbol{\lambda_{67}}}\rho_5 + te^{\rho_6 t}\frac{\partial}{\partial \boldsymbol{\lambda_{67}}}\rho_6 \\ te^{\rho_5 t}\frac{\partial}{\partial \boldsymbol{\lambda_{69}}}\rho_5 + te^{\rho_6 t}\frac{\partial}{\partial \boldsymbol{\lambda_{69}}}\rho_6 \\ te^{\rho_7 t}\frac{\partial}{\partial \boldsymbol{\lambda_{79}}}\rho_7 + te^{\rho_8 t}\frac{\partial}{\partial \boldsymbol{\lambda_{79}}}\rho_8 \\ te^{\rho_7 t}\frac{\partial}{\partial \boldsymbol{\lambda_{89}}}\rho_7 + te^{\rho_8 t}\frac{\partial}{\partial \boldsymbol{\lambda_{89}}}\rho_8 \end{bmatrix}$$

$the\ vectort(te^{\Lambda t} d\,\Lambda)\ is\ scaled\ by\ a\ factor$

$$= \left(\frac{n_{ij}\,(\Delta t)}{P_{ij}\,(\Delta t)}\right)\ according\ to\ counts\ in\ each\ cell\,;the\ followings\ \ are\ the\ scalars:$$

$$i.e\ \ \frac{n_{11}}{p_{11}} = n_{1+}, \frac{n_{12}}{p_{12}} = n_{1+}, \frac{n_{13}}{p_{13}} = n_{1+}, \frac{n_{14}}{p_{14}} = n_{1+}, \frac{n_{15}}{p_{15}} = n_{1+}, \frac{n_{16}}{p_{16}} = n_{1+}, \frac{n_{17}}{p_{17}} = n_{1+}, \frac{n_{18}}{p_{18}} = n_{1+}, \frac{n_{19}}{p_{19}} = n_{1+}$$

$$\frac{n_{21}}{p_{21}} = n_{2+}, \frac{n_{22}}{p_{22}} = n_{2+}, \frac{n_{23}}{p_{23}} = n_{2+}, \frac{n_{24}}{p_{24}} = n_{2+}, \frac{n_{25}}{p_{25}} = n_{2+}, \frac{n_{26}}{p_{26}} = n_{2+}, \frac{n_{27}}{p_{27}} = n_{2+}, \frac{n_{28}}{p_{28}} = n_{2+}, \frac{n_{29}}{p_{29}} = n_{2+}$$

$\frac{n_{31}}{p_{31}}=n_{3+},\frac{n_{32}}{p_{32}}=n_{3+},\frac{n_{33}}{p_{33}}=n_{3+},\frac{n_{34}}{p_{34}}=n_{3+},\frac{n_{35}}{p_{35}}=n_{3+},\frac{n_{36}}{p_{36}}=n_{3+},\frac{n_{37}}{p_{37}}=n_{3+},\frac{n_{38}}{p_{38}}=n_{3+},\frac{n_{39}}{p_{39}}=n_{3+}$

$\frac{n_{41}}{p_{41}}=n_{4+},\frac{n_{42}}{p_{42}}=n_{4+},\frac{n_{43}}{p_{43}}=n_{4+},\frac{n_{44}}{p_{44}}=n_{4+},\frac{n_{45}}{p_{45}}=n_{4+},\frac{n_{46}}{p_{46}}=n_{4+},\frac{n_{47}}{p_{47}}=n_{4+},\frac{n_{48}}{p_{48}}=n_{4+},\frac{n_{49}}{p_{49}}=n_{4+}$

$\frac{n_{55}}{p_{55}}=n_{5+},\frac{n_{56}}{p_{56}}=n_{5+},\frac{n_{57}}{p_{57}}=n_{5+},\frac{n_{58}}{p_{58}}=n_{5+},\frac{n_{59}}{p_{59}}=n_{5+}$

$,\frac{n_{66}}{p_{66}}=n_{6+},\frac{n_{67}}{p_{67}}=n_{6+},\frac{n_{69}}{p_{69}}=n_{6+}$

$\frac{n_{77}}{p_{77}}=n_{7+},\frac{n_{79}}{p_{79}}=n_{7+}\ ,\quad \frac{n_{88}}{p_{88}}=n_{8+}\ ,\quad \frac{n_{89}}{p_{89}}=n_{8+}$

$then\ the\ scaled\ vectors\ are\ summed\ up\ \ to\ get\ the\ score\ function$

Hint: if the cell does not have counts, so the scalar corresponding to this cell is dropped.

$S(\theta)=[9(n_{1+}+n_{2+}+n_{3+}+n_{4+})+5n_{5+}+3n_{6+}+2(n_{7+}+n_{8+})]te^{\Lambda t}d\ \Lambda$

The scaled score function is cross product with itself i.e

$M(\theta)=scaled\ S(\theta)\times[scaled\ S(\theta)]^T$

$This\ score\ function\ is\ 22\ by\ 1\ vector\ and\ it\ is\ \ used\ in\ quasi-Newton\ Raphson\ method$

According to Kalbfliesch and Lawless (1985) the second derivative is assumed to be zero , the score function is crossed product and scaled for each pdf with the scalars (hint if the cell does not have counts, so the scalar of this cell is dropped) :

$i.e\ \ \frac{n_{1+}}{p_{11}},\frac{n_{1+}}{p_{12}},\dots,\frac{n_{1+}}{p_{19}},\frac{n_{2+}}{p_{21}},\frac{n_{2+}}{p_{22}}\ ,\dots,\frac{n_{2+}}{p_{29}},\frac{n_{3+}}{p_{31}},\frac{n_{3+}}{p_{32}},\dots,\frac{n_{3+}}{p_{39}},\frac{n_{4+}}{p_{41}},\frac{n_{4+}}{p_{42}},\dots,\frac{n_{4+}}{p_{49}},\frac{n_{5+}}{p_{55}},\frac{n_{5+}}{p_{56}}\ ,\dots\ ,\frac{n_{5+}}{p_{59}},\frac{n_{6+}}{p_{66}},\frac{n_{6+}}{p_{67}}\ ,\frac{n_{6+}}{p_{69}},\frac{n_{7+}}{p_{77}},\frac{n_{7+}}{p_{79}}\ ,\frac{n_{8+}}{p_{88}}$

The scaled matrices are summed up to get the scaled hessian matrix $M(\theta_0)$

$$\frac{\partial^2 Log\ L}{\partial\theta_g\partial\theta_h}=\sum_{\Delta t\geq 1}^{3}\sum_{i,j}^{k=9}n_{ij}\left[\frac{\partial^2 P_{ij}(\Delta t)/\partial\theta_g\partial\theta_h}{P_{ij}(\Delta t)}-\frac{\partial P_{ij}(\Delta t)/\partial\theta_g\partial P_{ij}(\Delta t)/\partial\theta_h}{P_{ij}^2(\Delta t)}\right],k\ is\ index\ of\ states\ ,\quad where\ \ P_{ij}\ =\frac{n_{ij}}{n_{i+}}$$

$$\frac{\partial^2 Log\ L}{\partial\theta_g\partial\theta_h}=\sum_{\Delta t\geq 1}^{3}\sum_{i,j}^{k=9}(P_{ij}\,n_{i+})\left[\frac{\partial^2 P_{ij}(\Delta t)/\partial\theta_g\partial\theta_h}{P_{ij}(\Delta t)}-\frac{\partial P_{ij}(\Delta t)/\partial\theta_g\partial P_{ij}(\Delta t)/\partial\theta_h}{P_{ij}^2(\Delta t)}\right]$$

$$\frac{\partial^2 Log\ L}{\partial\theta_g\partial\theta_h}=\sum_{\Delta t\geq 1}^{3}\sum_{i,j}^{k=9}(P_{ij}\,n_{i+})\left[\frac{0}{P_{ij}(\Delta t)}-\frac{\partial P_{ij}(\Delta t)/\partial\theta_g\partial P_{ij}(\Delta t)/\partial\theta_h}{P_{ij}^2(\Delta t)}\right]$$

$$=-\sum_{\Delta t\geq 1}^{3}\sum_{i,j}^{k=9}n_{i+}\frac{\partial P_{ij}(\Delta t)/\partial\theta_g\partial P_{ij}(\Delta t)/\partial\theta_h}{P_{ij}(\Delta t)}$$

$Applying\quad Quasi-Newton\ Raphson\ method\ formula:\theta_1=\theta_0+M(\theta_0)^{-1}S(\theta_0)$

with initial theta according to Klotz and Sharples (1994); the initial θ is $P_{ij}\ =\frac{n_{ij}}{n_{i+}}\,in\ the\ interval\ \Delta\ \mathrm{t}=1$

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

$M(\theta)=[scaled\ S(\theta)][scaled\ S(\theta)]^T\ ,\ \ it\ is\ (22\ by\ 22)\ matrix$

$scaled\ M(\theta)\ \ will\ \ be\ inverted\ to\ be\ used\ \ in\ \ Quasi-Newton\ formula$

3. Mean Sojourn Time

These times are independent so covariance between them is zero

$$var(s_i)=\left[\left(q_{ii}(\hat\theta)\right)^{-2}\right]^2\sum_{h=1}^{22}\sum_{g=1}^{22}\frac{\partial q_{ii}}{\partial\theta_g}\frac{\partial q_{ii}}{\partial\theta_h}[\mathrm{M}(\theta)]^{-1}|_{\theta=\hat\theta}$$

$$var(s_i)=\left[\left(q_{ii}(\hat\theta)\right)^{-2}\right]^2\sum_{h=1}^{22}\sum_{g=1}^{22}\left[\frac{\partial q_{ii}}{\partial\theta_h}\right]^T[\mathrm{M}(\theta)]^{-1}|_{\theta=\hat\theta}\frac{\partial q_{ii}}{\partial\theta_g}$$

$\left[\frac{\partial q_{ii}}{\partial\theta_h}\right]$ $is\ a\ vector\ of\ size\ 22\ by\ 1\ and\ obtained\ by\ differentiating\ the\ diagonal\ elements\ of\ the\ Q\ matrix\ with\ respect\ to\ each\ rate.$

$$var(s_i)=\left[\left(q_{ii}(\hat\theta)\right)^{-2}\right]^2\sum_{h=1}^{22}\sum_{g=1}^{22}\left[\frac{\partial q_{ii}}{\partial\theta_h}\right]^T[\mathrm{M}(\theta)]^{-1}|_{\theta=\hat\theta}\frac{\partial q_{ii}}{\partial\theta_g}$$

$$var(s_1) = \frac{1}{(\lambda_{12}+\lambda_{18}+\lambda_{19})^4}\begin{bmatrix}-1 & -1 & \cdots & -1 & -1\end{bmatrix}[\mathrm{M}(\theta)]^{-1}|_{\theta=\hat{\theta}}\begin{bmatrix}-1\\-1\\\vdots\\-1\\-1\end{bmatrix}$$

The same procedure is applied to obtain the sojourn time for the other states and $[\mathrm{M}(\theta)]^{-1}|_{\theta=\hat{\theta}}$ *as calculated before*

4. State Probability Distribution:

To get the probability distribution of the states after a certain period of time the following equation should be solved:

$\pi = \pi(0)P_{ij}(t)$

$$[\pi_{01} \quad \pi_{02} \quad \pi_{03} \quad \pi_{04} \quad \pi_{05} \quad \pi_{06} \quad \pi_{07} \quad \pi_{08} \quad \pi_{09}] \times \begin{bmatrix} P_{11} & P_{12} & P_{13} & P_{14} & P_{15} & P_{16} & P_{17} & P_{18} & P_{19} \\ P_{21} & P_{22} & P_{23} & P_{24} & P_{25} & P_{26} & P_{27} & P_{28} & P_{29} \\ P_{31} & P_{32} & P_{33} & P_{34} & P_{35} & P_{36} & P_{37} & P_{38} & P_{39} \\ P_{41} & P_{42} & P_{43} & P_{44} & P_{45} & P_{46} & P_{47} & P_{48} & P_{49} \\ 0 & 0 & 0 & 0 & P_{55} & P_{56} & P_{57} & P_{58} & P_{59} \\ 0 & 0 & 0 & 0 & 0 & P_{66} & P_{67} & 0 & P_{69} \\ 0 & 0 & 0 & 0 & 0 & 0 & P_{77} & 0 & P_{79} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & P_{88} & P_{89} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & P_{99} \end{bmatrix}$$
$$= [\pi_1 \quad \pi_2 \quad \pi_3 \quad \pi_4 \quad \pi_5 \quad \pi_6 \quad \pi_7 \quad \pi_8 \quad \pi_9]$$

4.1. Asymptotic Covariance of the Stationary Distribution

To obtain stationary probability distribution when t goes to infinity or in other words when the process does not depend on time the following equation is solved for π , *once the Q matrix is estimated*

$$\pi Q = 0 \text{ with the following constraint } \sum_{allz} \pi_z = 1$$

$$Q = \begin{bmatrix} -\gamma_1 & \lambda_{12} & 0 & 0 & 0 & 0 & 0 & \lambda_{18} & \lambda_{19} \\ \mu_{21} & -\gamma_2 & \lambda_{23} & 0 & 0 & 0 & 0 & \lambda_{28} & \lambda_{29} \\ 0 & \mu_{32} & -\gamma_3 & \lambda_{34} & 0 & 0 & 0 & \lambda_{38} & \lambda_{39} \\ 0 & 0 & \mu_{43} & -\gamma_4 & \lambda_{45} & 0 & 0 & \lambda_{48} & \lambda_{49} \\ 0 & 0 & 0 & 0 & -\gamma_5 & \lambda_{56} & 0 & \lambda_{58} & \lambda_{59} \\ 0 & 0 & 0 & 0 & 0 & -\gamma_6 & \lambda_{67} & 0 & \lambda_{69} \\ 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{79} & 0 & \lambda_{79} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{89} & \lambda_{89} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

let: $(\lambda_{12}+\lambda_{18}+\lambda_{19}) = \gamma_1$, $(\lambda_{23}+\lambda_{28}+\lambda_{29}+\mu_{21}) = \gamma_2$, $(\lambda_{34}+\lambda_{38}+\lambda_{39}+\mu_{32}) = \gamma_3$, $(\lambda_{45}+\lambda_{48}+\lambda_{49}+\mu_{43}) = \gamma_4$,
$(\lambda_{56}+\lambda_{58}+\lambda_{59}) = \gamma_5$, $(\lambda_{67}+\lambda_{69}) = \gamma_6$

$$[\pi_1 \quad \pi_2 \quad \pi_3 \quad \pi_4 \quad \pi_5 \quad \pi_6 \quad \pi_7 \quad \pi_8 \quad \pi_9]\begin{bmatrix} -\gamma_1 & \lambda_{12} & 0 & 0 & 0 & 0 & 0 & \lambda_{18} & \lambda_{19} \\ \mu_{21} & -\gamma_2 & \lambda_{23} & 0 & 0 & 0 & 0 & \lambda_{28} & \lambda_{29} \\ 0 & \mu_{32} & -\gamma_3 & \lambda_{34} & 0 & 0 & 0 & \lambda_{38} & \lambda_{39} \\ 0 & 0 & \mu_{43} & -\gamma_4 & \lambda_{45} & 0 & 0 & \lambda_{48} & \lambda_{49} \\ 0 & 0 & 0 & 0 & -\gamma_5 & \lambda_{56} & 0 & \lambda_{58} & \lambda_{59} \\ 0 & 0 & 0 & 0 & 0 & -\gamma_6 & \lambda_{67} & 0 & \lambda_{69} \\ 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{79} & 0 & \lambda_{79} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{89} & \lambda_{89} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$
$$= [0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0]$$

That is to mean solve the following system of equations:

$-\pi_1\gamma_1 + \pi_2\mu_{21} = 0$, $\pi_1\lambda_{12} - \pi_2\,\gamma_2 + \pi_3\mu_{32} = 0$, $\pi_2\lambda_{23} - \pi_3\,\gamma_3 + \pi_4\mu_{43} = 0$, $\pi_3\lambda_{34} - \pi_4\,\gamma_4 = 0$, $\pi_4\lambda_{45} - \pi_5\,\gamma_5 = 0$

$\pi_5\lambda_{56} - \pi_6\,\gamma_6 = 0$, $\pi_6\lambda_{67} - \pi_7\,\lambda_{79} = 0$, $\pi_1\lambda_{18} + \pi_2\lambda_{28} + \pi_3\lambda_{38} + \pi_4\lambda_{48} + \pi_5\lambda_{58} - \pi_8\lambda_{89} = 0$

$\pi_1\lambda_{19} + \pi_2\lambda_{29} + \pi_3\lambda_{39} + \pi_4\lambda_{49} + \pi_5\lambda_{59} + \pi_6\lambda_{69} + \pi_7\lambda_{79} + \pi_8\lambda_{89} = 0$

subject to : $\pi_1 + \pi_2 + \pi_3 + \pi_4 + \pi_5 + \pi_6 + \pi_7 + \pi_8 + \pi_9 = 1$,

In matrix notation: $X\pi = y$

$$\begin{bmatrix} -\gamma_1 & \mu_{21} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \lambda_{12} & -\gamma_2 & \mu_{32} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \lambda_{23} & -\gamma_3 & \mu_{43} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \lambda_{34} & -\gamma_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \lambda_{45} & -\gamma_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \lambda_{56} & -\gamma_6 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \lambda_{67} & -\lambda_{79} & 0 & 0 \\ \lambda_{18} & \lambda_{28} & \lambda_{38} & \lambda_{48} & \lambda_{58} & 0 & 0 & -\lambda_{89} & 0 \\ \lambda_{19} & \lambda_{29} & \lambda_{39} & \lambda_{49} & \lambda_{59} & \lambda_{69} & \lambda_{79} & \lambda_{89} & 0 \\ 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \end{bmatrix} \begin{bmatrix} \pi_1 \\ \pi_2 \\ \pi_3 \\ \pi_4 \\ \pi_5 \\ \pi_6 \\ \pi_7 \\ \pi_8 \\ \pi_9 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix}$$

$$where \quad X = \begin{bmatrix} -\gamma_1 & \mu_{21} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \lambda_{12} & -\gamma_2 & \mu_{32} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \lambda_{23} & -\gamma_3 & \mu_{43} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \lambda_{34} & -\gamma_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \lambda_{45} & -\gamma_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \lambda_{56} & -\gamma_6 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \lambda_{67} & -\lambda_{79} & 0 & 0 \\ \lambda_{18} & \lambda_{28} & \lambda_{38} & \lambda_{48} & \lambda_{58} & 0 & 0 & -\lambda_{89} & 0 \\ \lambda_{19} & \lambda_{29} & \lambda_{39} & \lambda_{49} & \lambda_{59} & \lambda_{69} & \lambda_{79} & \lambda_{89} & 0 \\ 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \end{bmatrix} \quad and \quad y = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix}$$

$$X\pi = y \qquad \rightarrow \quad \pi = (X^T X)^{-1} X^T y$$

To get the asymptotic covariance matrix of the state probability distribution, the derivative of the state probability distribution with respect to each parameter rate θ should be calculated as following:

$$F(\theta_h, \pi_i) = Q^{'}\pi_i = 0$$

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

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

$$= C(\theta)\ \ is\ a\ matrix$$

$$\left[\frac{\partial}{\partial\theta_h}\pi\right] this\ is\ a\ matrix\ that\ gives\ all\ derivatives\ of\ \pi_1, \pi_2, \pi_3, \pi_4, \pi_5, \pi_6, \pi_7, \pi_8, \pi_9\ with\ respect\ to\ each\ of\ the\ 22\ \theta^{'}s$$

$$\left[\frac{\partial}{\partial\theta_h}\pi\right] = -[Q^{'}]^{-1}C(\theta)\,, \quad \pi(\theta) = \begin{bmatrix} \pi_1 \\ \pi_2 \\ \pi_3 \\ \pi_4 \\ \pi_5 \\ \pi_6 \\ \pi_7 \\ \pi_8 \\ \pi_9 \end{bmatrix} is\ a\ column\ vector\ , and\ \ when\ t\ goes\ to\ infinity\ this\ vector$$

$$= \pi(\theta) = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix}$$

$$C(\theta) = \pi(\theta)\left[\frac{\partial}{\partial\theta_h}Q'\right]^T$$

$$= \begin{bmatrix}\pi_1\\ \pi_2\\ \pi_3\\ \pi_4\\ \pi_5\\ \pi_6\\ \pi_7\\ \pi_8\\ \pi_9\end{bmatrix}[1 \quad 1 \quad \cdots \quad 1 \quad 1]\ , where\ [1 \quad 1 \quad \cdots \quad 1 \quad 1]\ is\ a\ row\ vector\ of\ size\ \ (1 \times 22)$$

$$\pi(\theta)\left[\frac{\partial}{\partial\theta_h}Q'\right]^T = C(\theta)\ \ is\ a\ matrix\ of\ \ size\ \ (9\ \times\ 22)$$

Q' $is\ a\ singular\ matrix\ , and\ its\ inverse\ requires\ \ calculating\ the\ pseudoinverse\ using\ SVD$
$[Q']^{-1}$ $obtained\ by\ \ pseudoinverse\ \ is\ 9\ by\ 9\ matrix$

$$let: \quad A(\theta) = \left[\frac{\partial}{\partial\theta_h}\pi_i\right] = -[Q']^{-1}C(\theta)\ \ \ is\ \ (9\ \times\ 22)\ matrix$$

$$A(\theta) = \begin{bmatrix}
\frac{\partial\pi_1}{\partial\lambda_{12}} & \frac{\partial\pi_1}{\partial\lambda_{18}} & \frac{\partial\pi_1}{\partial\lambda_{19}} & \frac{\partial\pi_1}{\partial\lambda_{23}} & \frac{\partial\pi_1}{\partial\lambda_{28}} & \frac{\partial\pi_1}{\partial\lambda_{29}} & \frac{\partial\pi_1}{\partial\mu_{21}} & \frac{\partial\pi_1}{\partial\lambda_{34}} & \frac{\partial\pi_1}{\partial\lambda_{38}} & \frac{\partial\pi_1}{\partial\lambda_{39}} & \frac{\partial\pi_1}{\partial\mu_{32}} & \frac{\partial\pi_1}{\partial\lambda_{45}} & \frac{\partial\pi_1}{\partial\lambda_{48}} & \frac{\partial\pi_1}{\partial\lambda_{49}} & \frac{\partial\pi_1}{\partial\mu_{43}} & \frac{\partial\pi_1}{\partial\lambda_{56}} & \frac{\partial\pi_1}{\partial\lambda_{58}} \\
\frac{\partial\pi_2}{\partial\lambda_{12}} & \frac{\partial\pi_2}{\partial\lambda_{18}} & \frac{\partial\pi_2}{\partial\lambda_{19}} & \frac{\partial\pi_2}{\partial\lambda_{23}} & \frac{\partial\pi_2}{\partial\lambda_{28}} & \frac{\partial\pi_2}{\partial\lambda_{29}} & \frac{\partial\pi_2}{\partial\mu_{21}} & \frac{\partial\pi_2}{\partial\lambda_{34}} & \frac{\partial\pi_2}{\partial\lambda_{38}} & \frac{\partial\pi_2}{\partial\lambda_{39}} & \frac{\partial\pi_2}{\partial\mu_{32}} & \frac{\partial\pi_2}{\partial\lambda_{45}} & \frac{\partial\pi_2}{\partial\lambda_{48}} & \frac{\partial\pi_2}{\partial\lambda_{49}} & \frac{\partial\pi_2}{\partial\mu_{43}} & \frac{\partial\pi_2}{\partial\lambda_{56}} & \frac{\partial\pi_2}{\partial\lambda_{58}} \\
\frac{\partial\pi_3}{\partial\lambda_{12}} & \frac{\partial\pi_3}{\partial\lambda_{18}} & \frac{\partial\pi_3}{\partial\lambda_{19}} & \frac{\partial\pi_3}{\partial\lambda_{23}} & \frac{\partial\pi_3}{\partial\lambda_{28}} & \frac{\partial\pi_3}{\partial\lambda_{29}} & \frac{\partial\pi_3}{\partial\mu_{21}} & \frac{\partial\pi_3}{\partial\lambda_{34}} & \frac{\partial\pi_3}{\partial\lambda_{38}} & \frac{\partial\pi_3}{\partial\lambda_{39}} & \frac{\partial\pi_3}{\partial\mu_{32}} & \frac{\partial\pi_3}{\partial\lambda_{45}} & \frac{\partial\pi_3}{\partial\lambda_{48}} & \frac{\partial\pi_3}{\partial\lambda_{49}} & \frac{\partial\pi_3}{\partial\mu_{43}} & \frac{\partial\pi_3}{\partial\lambda_{56}} & \frac{\partial\pi_3}{\partial\lambda_{58}} \\
\frac{\partial\pi_4}{\partial\lambda_{12}} & \frac{\partial\pi_4}{\partial\lambda_{18}} & \frac{\partial\pi_4}{\partial\lambda_{19}} & \frac{\partial\pi_4}{\partial\lambda_{23}} & \frac{\partial\pi_4}{\partial\lambda_{28}} & \frac{\partial\pi_4}{\partial\lambda_{29}} & \frac{\partial\pi_4}{\partial\mu_{21}} & \frac{\partial\pi_4}{\partial\lambda_{34}} & \frac{\partial\pi_4}{\partial\lambda_{38}} & \frac{\partial\pi_4}{\partial\lambda_{39}} & \frac{\partial\pi_4}{\partial\mu_{32}} & \frac{\partial\pi_4}{\partial\lambda_{45}} & \frac{\partial\pi_4}{\partial\lambda_{48}} & \frac{\partial\pi_4}{\partial\lambda_{49}} & \frac{\partial\pi_4}{\partial\mu_{43}} & \frac{\partial\pi_4}{\partial\lambda_{56}} & \frac{\partial\pi_4}{\partial\lambda_{58}} \\
\frac{\partial\pi_5}{\partial\lambda_{12}} & \frac{\partial\pi_5}{\partial\lambda_{18}} & \frac{\partial\pi_5}{\partial\lambda_{19}} & \frac{\partial\pi_5}{\partial\lambda_{23}} & \frac{\partial\pi_5}{\partial\lambda_{28}} & \frac{\partial\pi_5}{\partial\lambda_{29}} & \frac{\partial\pi_5}{\partial\mu_{21}} & \frac{\partial\pi_5}{\partial\lambda_{34}} & \frac{\partial\pi_5}{\partial\lambda_{38}} & \frac{\partial\pi_5}{\partial\lambda_{39}} & \frac{\partial\pi_5}{\partial\mu_{32}} & \frac{\partial\pi_5}{\partial\lambda_{45}} & \frac{\partial\pi_5}{\partial\lambda_{48}} & \frac{\partial\pi_5}{\partial\lambda_{49}} & \frac{\partial\pi_5}{\partial\mu_{43}} & \frac{\partial\pi_5}{\partial\lambda_{56}} & \frac{\partial\pi_5}{\partial\lambda_{58}} \\
\frac{\partial\pi_6}{\partial\lambda_{12}} & \frac{\partial\pi_6}{\partial\lambda_{18}} & \frac{\partial\pi_6}{\partial\lambda_{19}} & \frac{\partial\pi_6}{\partial\lambda_{23}} & \frac{\partial\pi_6}{\partial\lambda_{28}} & \frac{\partial\pi_6}{\partial\lambda_{29}} & \frac{\partial\pi_6}{\partial\mu_{21}} & \frac{\partial\pi_6}{\partial\lambda_{34}} & \frac{\partial\pi_6}{\partial\lambda_{38}} & \frac{\partial\pi_6}{\partial\lambda_{39}} & \frac{\partial\pi_6}{\partial\mu_{32}} & \frac{\partial\pi_6}{\partial\lambda_{45}} & \frac{\partial\pi_6}{\partial\lambda_{48}} & \frac{\partial\pi_6}{\partial\lambda_{49}} & \frac{\partial\pi_6}{\partial\mu_{43}} & \frac{\partial\pi_6}{\partial\lambda_{56}} & \frac{\partial\pi_6}{\partial\lambda_{58}} \\
\frac{\partial\pi_7}{\partial\lambda_{12}} & \frac{\partial\pi_7}{\partial\lambda_{18}} & \frac{\partial\pi_7}{\partial\lambda_{19}} & \frac{\partial\pi_7}{\partial\lambda_{23}} & \frac{\partial\pi_7}{\partial\lambda_{28}} & \frac{\partial\pi_7}{\partial\lambda_{29}} & \frac{\partial\pi_7}{\partial\mu_{21}} & \frac{\partial\pi_7}{\partial\lambda_{34}} & \frac{\partial\pi_7}{\partial\lambda_{38}} & \frac{\partial\pi_7}{\partial\lambda_{39}} & \frac{\partial\pi_7}{\partial\mu_{32}} & \frac{\partial\pi_7}{\partial\lambda_{45}} & \frac{\partial\pi_7}{\partial\lambda_{48}} & \frac{\partial\pi_7}{\partial\lambda_{49}} & \frac{\partial\pi_7}{\partial\mu_{43}} & \frac{\partial\pi_7}{\partial\lambda_{56}} & \frac{\partial\pi_7}{\partial\lambda_{58}} \\
\frac{\partial\pi_8}{\partial\lambda_{12}} & \frac{\partial\pi_8}{\partial\lambda_{18}} & \frac{\partial\pi_8}{\partial\lambda_{19}} & \frac{\partial\pi_8}{\partial\lambda_{23}} & \frac{\partial\pi_8}{\partial\lambda_{28}} & \frac{\partial\pi_8}{\partial\lambda_{29}} & \frac{\partial\pi_8}{\partial\mu_{21}} & \frac{\partial\pi_8}{\partial\lambda_{34}} & \frac{\partial\pi_8}{\partial\lambda_{38}} & \frac{\partial\pi_8}{\partial\lambda_{39}} & \frac{\partial\pi_8}{\partial\mu_{32}} & \frac{\partial\pi_8}{\partial\lambda_{45}} & \frac{\partial\pi_8}{\partial\lambda_{48}} & \frac{\partial\pi_8}{\partial\lambda_{49}} & \frac{\partial\pi_8}{\partial\mu_{43}} & \frac{\partial\pi_8}{\partial\lambda_{56}} & \frac{\partial\pi_8}{\partial\lambda_{58}} \\
\frac{\partial\pi_9}{\partial\lambda_{12}} & \frac{\partial\pi_9}{\partial\lambda_{18}} & \frac{\partial\pi_9}{\partial\lambda_{19}} & \frac{\partial\pi_9}{\partial\lambda_{23}} & \frac{\partial\pi_9}{\partial\lambda_{28}} & \frac{\partial\pi_9}{\partial\lambda_{29}} & \frac{\partial\pi_9}{\partial\mu_{21}} & \frac{\partial\pi_9}{\partial\lambda_{34}} & \frac{\partial\pi_9}{\partial\lambda_{38}} & \frac{\partial\pi_9}{\partial\lambda_{39}} & \frac{\partial\pi_9}{\partial\mu_{32}} & \frac{\partial\pi_9}{\partial\lambda_{45}} & \frac{\partial\pi_9}{\partial\lambda_{48}} & \frac{\partial\pi_9}{\partial\lambda_{49}} & \frac{\partial\pi_9}{\partial\mu_{43}} & \frac{\partial\pi_9}{\partial\lambda_{56}} & \frac{\partial\pi_9}{\partial\lambda_{58}}
\end{bmatrix}$$

Using multivariate delta method

$$var(\pi_i) = A(\theta)var(\theta)A(\theta)' \quad , \qquad wherevar(\theta) = [M(\theta)]^{-1} andi = 1,2,\cdots,9.$$

5. Expected Number of Patients in Each State:

$$[m_1(0) \quad m_2(0) \quad m_3(0) \quad m_4(0) \quad m_5(0) \quad m_6(0) \quad m_7(0) \quad m_8(0) \quad m_9(0)]\begin{bmatrix}
P_{11} & P_{12} & P_{13} & P_{14} & P_{15} & P_{16} & P_{17} & P_{18} \\
P_{21} & P_{22} & P_{23} & P_{24} & P_{25} & P_{26} & P_{27} & P_{28} \\
P_{31} & P_{32} & P_{33} & P_{34} & P_{35} & P_{36} & P_{37} & P_{38} \\
P_{41} & P_{42} & P_{43} & P_{44} & P_{45} & P_{46} & P_{47} & P_{48} \\
0 & 0 & 0 & 0 & P_{55} & P_{56} & P_{57} & P_{58} \\
0 & 0 & 0 & 0 & 0 & P_{66} & P_{67} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & P_{77} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & P_{88} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix}$$

$$= [m_1(t) \quad m_2(t) \quad m_3(t) \quad m_4(t) \quad m_5(t) \quad m_6(t) \quad m_7(t) \quad m_8(t) \quad m_9(t)]$$

6. Life Expectancy of a Patient Suffering from NAFLD in Various Stages:

The same procedure used in the previous chapter is used in this chapter.

Partitioning the differential equation into the following :

$$[\acute{P}(t) \quad \acute{P}_k(t)] = [P(t) \quad P_k(t)]\begin{bmatrix}B & A\\ 0 & 0\end{bmatrix}$$

B is the transition rate matrix among the transient states and the column vector A is the transition rate from each transient state to the absorbing (death) state .

$A = -B1^T \quad such\ that\ 1^T\ is\ a\ column\ vector\ of\ k-1\ \times 1\ with\ all\ its\ elements\ equal\ to\ one$

$$Mean\ time\ to\ absorption:\ E(\tau_k) = (-1)\frac{df^*{}_k(s)}{ds}\bigg|_{s=0} = (-1)P(0)[sI-B]^{-2}A|_{s=0} = P(0)[-B]^{-1}1^T$$

$$B = \begin{bmatrix} -\gamma_1 & \lambda_{12} & 0 & 0 & 0 & 0 & 0 & \lambda_{18} \\ \mu_{21} & -\gamma_2 & \lambda_{23} & 0 & 0 & 0 & 0 & \lambda_{28} \\ 0 & \mu_{32} & -\gamma_3 & \lambda_{34} & 0 & 0 & 0 & \lambda_{38} \\ 0 & 0 & \mu_{43} & -\gamma_4 & \lambda_{45} & 0 & 0 & \lambda_{48} \\ 0 & 0 & 0 & 0 & -\gamma_5 & \lambda_{56} & 0 & \lambda_{58} \\ 0 & 0 & 0 & 0 & 0 & -\gamma_6 & \lambda_{67} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{79} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_{89} \end{bmatrix}$$

Steps:

1. First: specify the Q matrix
2. Second: remove the last column and the last row from Q matrix to obtain B matrix
3. Third: get the inverse of the B matrix
4. Forth: multiply the inverse by -1
5. Lastly and fifth: Apply the following formula of mean time to absorption

7. Hypothetical Model:

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 15 years on 1050 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 with different intervals. The following is the final estimated rate matrix and its variance , this is followed by elaborate discussion of the steps; the estimated final transition rate matrix “Q” is :

$$\hat{Q} = \begin{bmatrix} -.397 & .39 & 0 & 0 & 0 & 0 & 0 & 0 & .007 \\ .02 & -.281 & .25 & 0 & 0 & 0 & 0 & 0 & .011 \\ 0 & .05 & -.365 & .225 & 0 & 0 & 0 & .047 & .043 \\ 0 & 0 & .041 & -.538 & .281 & 0 & 0 & .109 & .107 \\ 0 & 0 & 0 & 0 & -.348 & .19 & 0 & .059 & .099 \\ 0 & 0 & 0 & 0 & 0 & -.934 & .767 & 0 & .167 \\ 0 & 0 & 0 & 0 & 0 & 0 & -.421 & 0 & .421 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -.745 & .745 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$var(\hat{\theta}) = 1 \times 10^{-13} \begin{bmatrix} v_1 & v_2 \\ v_3 & v_4 \end{bmatrix}$where

$$v_1 = \begin{bmatrix} .3292 & .0327 & .4414 & .0827 & .4004 & .0268 & .2540 & .1517 \\ .0327 & .0064 & .0428 & .0108 & .0385 & .0053 & .0268 & .0159 \\ .4414 & .0428 & .5922 & .1100 & .5373 & .0350 & .3400 & .2032 \\ .0827 & .0108 & .1100 & .0228 & .0995 & .0088 & .0650 & .0387 \\ .4004 & .0385 & .5373 & .0995 & .4876 & .0315 & .3082 & .1843 \\ .0268 & .0053 & .0350 & .0088 & .0315 & .0044 & .0219 & .0130 \\ .2540 & .0268 & .3400 & .0650 & .3082 & .0219 & .1967 & .1174 \\ .1517 & .0159 & .2032 & .0387 & .1843 & .0130 & .1174 & .0702 \end{bmatrix}$$

v_2 , v_3 and $v_4$are all zero matrices of size (8 by 14) , (14 by 8) and (14 by 14) respectively.

The estimated transition rate matrix Q is calculated utilizing procedure that is similar to the one used in the small model, as shown below in the following steps:

For each Δt , the observed transition counts in this interval are obtained, then applying the successive steps to get the estimated rate matrix:

Step 1: calculate the eigenvalues for the initial Q matrix obtained from the observed transition counts in this interval.

Step 2: calculate $te^{\Lambda t}d\,\Lambda$= t * e^(eigenvalue *t)* partial derivative of each eigenvalues with each rate or theta to get score function.

Step 3: rearrange the score function, then scale it .

Step 4: multiply the rearranged scaled scored function with the transposed rearranged scaled score function to get the hessian matrix (22 by 22 matrix).

Step 5: scale the above hessian matrix, then resultant matrix can be partitioned into 4 matrices.

Step 6: invert the scaled hessian matrix (only the upper left is invertible).

Step 7: multiply the inverted scaled hessian matrix by the scaled score function.

Step 8: apply quasi-newton formula.

Observed counts of transitions during time interval Δt=1										
	State 1	**State 2**	**State3**	**State 4**	**State 5**	**State 6**	**State 7**	**State 8**	**State 9**	**total**
State 1	784	573	74	21	20	0	0	0	10	1482
State 2	9	333	130	21	19	0	0	0	6	518
State 3	4	11	103	44	19	0	0	10	9	200
State 4	0	0	4	33	21	0	0	8	7	73
State 5	0	0	0	0	35	12	10	4	6	67
State 6	0	0	0	0	0	1	8	0	1	10
State 7	0	0	0	0	0	0	10	0	7	17
State 8	0	0	0	0	0	0	0	5	15	20
State 9	0	0	0	0	0	0	0	0	0	0
										2387

Initial Q matrix :									Step 1 : calculate eigenvalues for this Q matrix :	
-.397	.39	0	0	0	0	0	0	.007	**Eigenvalue 1**	-.45792
.02	-.28	.25	0	0	0	0	0	.01	**Eigenvalue 2**	-.58993
0	.05	-.36	.22	0	0	0	.05	.04	**Eigenvalue 3**	-.16836
0	0	.05	-.53	.28	0	0	.11	.09	**Eigenvalue 4**	-.35079
0	0	0	0	-.33	.18	0	.06	.09	**Eigenvalue 5**	-.33
0	0	0	0	0	-.9	.8	0	.1	**Eigenvalue 6**	-.9
0	0	0	0	0	0	-.41	0	.41	**Eigenvalue 7**	-.41
0	0	0	0	0	0	0	-.75	.75	**Eigenvalue 8**	-.75
0	0	0	0	0	0	0	0	0	**Eigenvalue 9**	0

Step 2 : calculate $te^{\Lambda t} d\,\Lambda$		Step 3 : rearrange the score function then scale it by a factor =14204		
Lambda 12	-.6608	**Lambda 12**	-.6608	-9385
Lambda 18	-.6751	**Mu 21**	-.4841	-6876
Lambda 19	-.6751	**Lambda 23**	-.7267	-10323
Lambda 23	-.7267	**Mu 32**	-.5233	-7433
Lambda 28	-.7632	**Lambda 34**	-.6736	-9568
Lambda 29	-.7632	**Mu 43**	-.4503	-6396
Mu 21	-.4841	**Lambda 79**	-.6637	-9426
Lambda 34	-.6736	**Lambda 89**	-.4724	-6709
Lambda 38	-.7058	**Lambda 18**	-.6751	-9589
Lambda 39	-.7058	**Lambda 19**	-.6751	-9589
Mu 32	-.5233	**Lambda 28**	-.7632	-10841
Lambda 45	-.592	**Lambda 29**	-.7632	-10841
Lambda 48	-.592	**Lambda 38**	-.7058	-10025
Lambda 49	-.592	**Lambda 39**	-.7058	-10025
Mu 43	-.4503	**Lambda 45**	-.5920	-8409
Lambda 56	-.7189	**Lambda 48**	-.5920	-8409
Lambda 58	-.7189	**Lambda 49**	-.5920	-8409
Lambda 59	-.7189	**Lambda 56**	-.7189	-10212
Lambda 67	-.4066	**Lambda 58**	-.7189	-10212
Lambda 69	-.4066	**Lambda 59**	-.7189	-10212
Lambda 79	-.6637	**Lambda 67**	-.4066	-5775
Lambda 89	-.4724	**Lambda 69**	-.4066	-5775

Step 4: multiply the rearranged scaled scored function with the transposed rearranged scaled score function to get the hessian matrix (22 by 22 matrix)

Step 5: scale the above hessian matrix by a factor of 606523.3, the resultant matrix can be partitioned into 4 matrices, the upper left matrix of size (8 by 8) is the matrix needs to be inverted but it may be singular or close to be singular so the pseudo-inverse using singular value decomposition is applied. The lower right matrix is (14 by 14) has repeated rows. The matrices on the secondary diagonal, the upper right (8 by 14) and the lower left (14 by 8) have repeated rows so the only invertible matrix is the upper left.

Step 6: invert the scaled hessian matrix (only the upper left is invertible)							
$10^{-15}\times$							
.4574	.3351	.503	.3622	.4663	.3117	.4594	.327
.3351	.2455	.3686	.2654	.3416	.2284	.3366	.2396
.503	.3686	.5533	.3984	.5128	.3428	.5052	.3596
.3622	.2654	.3984	.2869	.3693	.2469	.3638	.2589
.4663	.3416	.5128	.3693	.4753	.3178	.4683	.3333
.3117	.2284	.3428	.2469	.3178	.2124	.3131	.2228
.4594	.3366	.5052	.3638	.4683	.3131	.4614	.3284
.327	.2396	.3596	.2589	.3333	.2228	.3284	.2337

Step 7 : multiply inverted hessian matrix by scaled score function	**Step 8: apply quasi-Newton formula to get the estimated rates in Δt=1**	
-.2746 $*10^{-10}$	**Lambda 12**	.39
-.2012 $*10^{-10}$	**Mu 21**	.02
-.3020 $*10^{-10}$	**Lambda 23**	.25
-.2175 $*10^{-10}$	**Mu 32**	.05
-.2799 $*10^{-10}$	**Lambda 34**	.22
-.1871 $*10^{-10}$	**Mu 43**	.05
-.2758 $*10^{-10}$	**Lambda 79**	.41
-.1963 $*10^{-10}$	**Lambda 89**	.75
0	**Lambda 18**	0
0	**Lambda 19**	.007
0	**Lambda 28**	0
0	**Lambda 29**	.01
0	**Lambda 38**	.05
0	**Lambda 39**	.04
0	**Lambda 45**	.28
0	**Lambda 48**	.11
0	**Lambda 49**	.09
0	**Lambda 56**	.18
0	**Lambda 58**	.06
0	**Lambda 59**	.09
0	**Lambda 67**	.8
0	**Lambda 69**	.1

The same steps are performed for the transitions occurred in time interval =2 :

Observed counts of transitions during time interval Δt=2										
	State 1	**State 2**	**State3**	**State 4**	**State 5**	**State 6**	**State 7**	**State 8**	**State 9**	**total**
State 1	313	229	30	9	8	0	0	0	4	593
State 2	4	133	52	8	7	0	0	0	3	207
State 3	2	4	40	19	8	0	0	3	4	80
State 4	0	0	1	13	8	0	0	3	4	29
State 5	0	0	0	0	13	5	4	2	3	27
State 6	0	0	0	0	0	0	3	0	1	4
State 7	0	0	0	0	0	0	4	0	3	7
State 8	0	0	0	0	0	0	0	2	6	8
State 9	0	0	0	0	0	0	0	0	0	0
										955

Initial Q matrix :									Step 1 : calculate eigenvalues for this Q matrix :	
-.397	.39	0	0	0	0	0	0	.007	**Eigenvalue 1**	-.46595
.02	-.28	.25	0	0	0	0	0	.01	**Eigenvalue 2**	-.59304
0	.05	-.38	.24	0	0	0	.04	.05	**Eigenvalue 3**	-.17668
0	0	.03	-.55	.28	0	0	.1	.14	**Eigenvalue 4**	-.37133
0	0	0	0	-.37	.19	0	.07	.11	**Eigenvalue 5**	-.37
0	0	0	0	0	-1	.75	0	.25	**Eigenvalue 6**	-1
0	0	0	0	0	0	-.43	0	.43	**Eigenvalue 7**	-.43
0	0	0	0	0	0	0	-.75	.75	**Eigenvalue 8**	-.75
0	0	0	0	0	0	0	0	0	**Eigenvalue 9**	0

Step 2 : calculate $\mathbf{te^{\Lambda t} d\,\Lambda}$		Step 3 : rearrange the score function then scale it by a factor =5678		
Lambda 12	-.8781	**Lambda 12**	-.8781	-4986.1
Lambda 18	-.9194	**Mu 21**	-.3807	-2161.4
Lambda 19	-.9194	**Lambda 23**	-1.0806	-6135.9
Lambda 23	-1.0806	**Mu 32**	-.4458	-2531.3
Lambda 28	-1.186	**Lambda 34**	-.9245	-5249.1
Lambda 29	-1.186	**Mu 43**	-.2905	-1649.6
Mu 21	-.3807	**Lambda 79**	-.8463	-4805.4
Lambda 34	-.9245	**Lambda 89**	-.4463	-2533.9
Lambda 38	-.9727	**Lambda 18**	-.9194	-5220.6
Lambda 39	-.9727	**Lambda 19**	-.9194	-5220.6
Mu 32	-.4458	**Lambda 28**	-1.186	-6734.2
Lambda 45	-.6766	**Lambda 29**	-1.186	-6734.2
Lambda 48	-.6766	**Lambda 38**	-.9727	-5523.2
Lambda 49	-.6766	**Lambda 39**	-.9727	-5523.2
Mu 43	-.2905	**Lambda 45**	-.6766	-3841.7
Lambda 56	-.9542	**Lambda 48**	-.6766	-3841.7
Lambda 58	-.9542	**Lambda 49**	-.6766	-3841.7
Lambda 59	-.9542	**Lambda 56**	-.9542	-5418.1
Lambda 67	-.2707	**Lambda 58**	-.9542	-5418.1
Lambda 69	-.2707	**Lambda 59**	-.9542	-5418.1
Lambda 79	-.8463	**Lambda 67**	-.2707	-1536.9
Lambda 89	-.4463	**Lambda 69**	-.2707	-1536.9

Step 4: multiply the rearranged scaled scored function with the transposed rearranged scaled score function to get the hessian matrix (22 by 22 matrix)

Step 5: scale the above hessian matrix by a factor of 235355.8, the resultant matrix can be partitioned into 4 matrices, the upper left matrix of size (8 by 8) is the matrix needs to be inverted but it may be singular or close to be singular so the pseudo-inverse using singular value decomposition is applied. The lower right matrix is (14 by 14) has repeated rows. The matrices on the secondary diagonal, the upper right (8 by 14) and the lower left (14 by 8) have repeated rows so the only invertible matrix is the upper left.

Step 6: invert the scaled hessian matrix (only the upper left is invertible)							
$\mathbf{10^{-14}} \times$							
.5938	.2574	.7307	.3015	.6251	.1964	.5723	.3018
.2574	.1116	.3168	.1307	.271	.0852	.2481	.1308
.7307	.3168	.8992	.371	.7693	.2417	.7042	.3713
.3015	.1307	.371	.153	.3174	.0997	.2905	.1532
.6251	.271	.7693	.3174	.6581	.2068	.6025	.3177

.1964	.0852	.2417	.0997	.2068	.065	.1893	.0998
.5723	.2481	.7042	.2905	.6025	.1893	.5515	.2908
.3018	.1308	.3713	.1532	.3177	.0998	.2908	.1533

Step 7 : multiply inverted hessian matrix by scaled score function	**Step 8: apply quasi-Newton formula to get the estimated rates in Δt=2**	
$-.1588 * 10^{-9}$	**Lambda 12**	.39
$-.0689 * 10^{-9}$	**Mu 21**	.02
$-.1955 * 10^{-9}$	**Lambda 23**	.25
$-.0806 * 10^{-9}$	**Mu 32**	.05
$-.1672 * 10^{-9}$	**Lambda 34**	.24
$-.0525 * 10^{-9}$	**Mu 43**	.03
$-.1531 * 10^{-9}$	**Lambda 79**	.43
$-.0807 * 10^{-9}$	**Lambda 89**	.75
0	**Lambda 18**	0
0	**Lambda 19**	.007
0	**Lambda 28**	0
0	**Lambda 29**	.01
0	**Lambda 38**	.04
0	**Lambda 39**	.05
0	**Lambda 45**	.28
0	**Lambda 48**	.1
0	**Lambda 49**	.14
0	**Lambda 56**	.19
0	**Lambda 58**	.07
0	**Lambda 59**	.11
0	**Lambda 67**	.75
0	**Lambda 69**	.25

The same steps are performed for transitions occurred in time interval =3

Observed counts of transitions during time interval Δ t=3										
	State 1	**State 2**	**State3**	**State 4**	**State 5**	**State 6**	**State 7**	**State 8**	**State 9**	**total**
State 1	78	57	8	2	2	0	0	0	1	148
State 2	1	32	13	2	2	0	0	0	1	51
State 3	0	0	9	4	2	0	0	2	1	18
State 4	0	0	0	3	2	0	0	1	1	7
State 5	0	0	0	0	3	2	1	0	1	7
State 6	0	0	0	0	0	0	1	0	1	2
State 7	0	0	0	0	0	0	1	0	1	2
State 8	0	0	0	0	0	0	0	1	2	3
State 9	0	0	0	0	0	0	0	0	0	0
										238

Initial Q matrix :									**Step 1 : calculate eigenvalues for this Q matrix :**	
-.397	.39	0	0	0	0	0	0	.007	**Eigenvalue 1**	-.48277
.02	-.29	.25	0	0	0	0	0	.02	**Eigenvalue 2**	-.57
0	.05	-.36	.21	0	0	0	.05	.05	**Eigenvalue 3**	-.18296
0	0	0	-.57	.29	0	0	.14	.14	**Eigenvalue 4**	-.38128
0	0	0	0	-.43	.29	0	0	.14	**Eigenvalue 5**	-.43
0	0	0	0	0	-1	.5	0	.5	**Eigenvalue 6**	-1
0	0	0	0	0	0	-.5	0	.5	**Eigenvalue 7**	-.5
0	0	0	0	0	0	0	-.67	.67	**Eigenvalue 8**	-.67
0	0	0	0	0	0	0	0	0	**Eigenvalue 9**	0

Step 2 : calculate $\mathbf{te^{\Lambda t}d\,\Lambda}$		Step 3 : rearrange the score function then scale it by a factor =1354		
Lambda 12	-.8815	**Lambda 12**	-.8815	-1193.6
Lambda 18	-.9480	**Mu 21**	-.0671	-90.9
Lambda 19	-.9480	**Lambda 23**	-1.189	-1609.9
Lambda 23	-1.189	**Mu 32**	-.2052	-277.8
Lambda 28	-1.3642	**Lambda 34**	-1.0813	-1464
Lambda 29	-1.3642	**Mu 43**	-.0554	-75
Mu 21	-.0671	**Lambda 79**	-.6694	-906.4
Lambda 34	-1.0813	**Lambda 89**	-.4020	-544.3
Lambda 38	-1.0813	**Lambda 18**	-.9480	-1283.6
Lambda 39	-1.0813	**Lambda 19**	-.9480	-1283.6
Mu 32	-.2052	**Lambda 28**	-1.3642	-1847.1
Lambda 45	-.5426	**Lambda 29**	-1.3642	-1847.1
Lambda 48	-.5426	**Lambda 38**	-1.0813	-1464
Lambda 49	-.5426	**Lambda 39**	-1.0813	-1464
Mu 43	-.0554	**Lambda 45**	-.5426	-734.7
Lambda 56	-.8258	**Lambda 48**	-.5426	-734.7
Lambda 58	-.8258	**Lambda 49**	-.5426	-734.7
Lambda 59	-.8258	**Lambda 56**	-.8258	-1118.1
Lambda 67	-.1494	**Lambda 58**	-.8258	-1118.1
Lambda 69	-.1494	**Lambda 59**	-.8258	-1118.1
Lambda 79	-.6694	**Lambda 67**	-.1494	-202.2
Lambda 89	-.4020	**Lambda 69**	-.1494	-202.2

Step 4: multiply the rearranged scaled scored function with the transposed rearranged scaled score function to get the hessian matrix (22 by 22 matrix)

Step 5: scale the above hessian matrix by a factor of 56367.63, the resultant matrix can be partitioned into 4 matrices, the upper left matrix of size (8 by 8) is the matrix needs to be inverted but it may be singular or close to be singular so the pseudo-inverse using singular value decomposition is applied. The lower right matrix is (14 by 14) has repeated rows. The matrices on the secondary diagonal, the upper right (8 by 14) and the lower left (14 by 8) have repeated rows so the only invertible matrix is the upper left.

Step 6: invert the scaled hessian matrix (only the upper left is invertible)							
$\mathbf{10^{-12}} \times$							
.4655	.0354	.6278	.1084	.571	.0292	.3535	.2123
.0354	.0027	.0478	.0082	.0435	.0022	.0269	.0162
.6278	.0478	.8468	.1461	.7701	.0394	.4768	.2863
.1084	.0082	.1461	.0252	.1329	.0068	.0823	.0494
.571	.0435	.7701	.1329	.7004	.0359	.4336	.2604
.0292	.0022	.0394	.0068	.0359	.0018	.0222	.0133
.3535	.0269	.4768	.0823	.4336	.0222	.2684	.1612
.2123	.0162	.2863	.0494	.2604	.0133	.1612	.0968

Step 7 : multiply inverted hessian matrix by scaled score function	Step 8: apply quasi-Newton formula to get the estimated rates in Δt=3	
$-.2874 *10^{-8}$	**Lambda 12**	.39
$-.0219 *10^{-8}$	**Mu 21**	.02
$-.3876 *10^{-8}$	**Lambda 23**	.25
$-.0669 *10^{-8}$	**Mu 32**	.05
$-.3525 *10^{-8}$	**Lambda 34**	.21
$-.0180 *10^{-8}$	**Mu 43**	0
$-.2182 *10^{-8}$	**Lambda 79**	.5
$-.1310*10^{-8}$	**Lambda 89**	.67
0	**Lambda 18**	0

0	**Lambda 19**	.007
0	**Lambda 28**	0
0	**Lambda 29**	.02
0	**Lambda 38**	.05
0	**Lambda 39**	.05
0	**Lambda 45**	.29
0	**Lambda 48**	.14
0	**Lambda 49**	.14
0	**Lambda 56**	.29
0	**Lambda 58**	0
0	**Lambda 59**	.14
0	**Lambda 67**	.5
0	**Lambda 69**	.5

Number of transitions observed in first interval corresponds to (2/3) of the total 3580 transitions while the number of transitions observed in the second interval corresponds to (4/15) of the total 3580 transitions and the number of transitions observed in the third interval corresponds to (1/15) of the total 3580 transitions.
Scaling the vector of theta or rates estimated in each interval by these correspondent weights in each interval and then summing up the weighted vectors, the final vector of rates or thetas is obtained which is:

λ_{12}	μ_{21}	λ_{23}	μ_{32}	λ_{34}	μ_{43}	λ_{79}	λ_{89}	λ_{18}	λ_{19}	λ_{28}
0.39	0.02	0.25	0.05	0.225	0.041	0.421	0.745	0	.007	0

λ_{29}	λ_{38}	λ_{39}	λ_{45}	λ_{48}	λ_{49}	λ_{56}	λ_{58}	λ_{59}	λ_{67}	λ_{69}
0.011	0.047	0.043	0.281	0.109	0.107	0.19	0.059	0.099	0.767	0.167

Doing the same procedure for the inverted scaled hessian matrix the final matrix which is the estimated variance of the rates:

$\mathbf{10^{-13}} \times$							
.3293	.0327	.4414	.0827	.4004	.0268	.2540	.1517
.0327	.0064	.0428	.0108	.0385	.0053	.0268	.0159
.4414	.0428	.5922	.1100	.5373	.0350	.3400	.2032
.0827	.0108	.1100	.0228	.0995	.0088	.0650	.0387
.4004	.0385	.5373	.0995	.4876	.0315	.3082	.1843
.0268	.0053	.0350	.0088	.0315	.0044	.0219	.0130
.254	.0268	.3400	.0650	.3082	.0219	.1967	.1174
.1517	.0159	.2032	.0387	.1843	.0130	.1174	.0702

Mean sojourn time for each state:

For state 1	For state 2	For state 3	For state 4	For state 5	For state 6	For state 7	For state 8
2.5189 years	3.5587 years	2.7397 years	1.8587 years	2.8736 years	1.0707 years	2.3753 years	1.3423 years

Mean time spent by the patient in state 1 is approximately 2 years and 6 months, in state 2 the mean sojourn time is approximately 3 years and 6 months , in state 3 it is approximately 2 years and 9 months , in state 4 it is approximately 1 years and 10 months , in state 5 it is approximately 2 years and 10 months, in state 6 it is approximately 1 years and 1 month , in state 7 it is approximately 2 years and 5 months and lastly in state 8 the mean sojourn time is approximately 1 years and 4 months.

Variance of the sojourn time

For state 1	For state 2	For state 3	For state 4	For state 5	For state 6	For state 7	For state 8
$\mathbf{.0362 \times 10^{-9}}$	$\mathbf{.1443 \times 10^{-9}}$	$\mathbf{.0507 \times 10^{-9}}$	$\mathbf{.0107 \times 10^{-9}}$	$\mathbf{.0613 \times 10^{-9}}$	$\mathbf{.0012 \times 10^{-9}}$	$\mathbf{.0286 \times 10^{-9}}$	$\mathbf{.0029 \times 10^{-9}}$

The life expectancy of NAFLD patient or the mean time to absorption:

From state 1	From state 2	From state 3	From state 4	From state 5	From state 6	From state 7	From state 8
13.6762 years	11.3576 years	7.6718 years	5.1966 years	4.7507 years	3.0213 years	2.3753 years	1.3423 years

Mean time for a patient in state 1 to absorption or death is approximately 13 years and 8 month, for a patient in state 2 it is approximately 11 years and 4 months, for a patient in state 3 it is approximately 7 years and 2 months, for a patient is state 4 it is approximately 5 years and 2 months ,for a patient is state 5 it is approximately 4 years and 9 months, for a patient is state 6 it is approximately 3 years, for a patient in state 7 it is approximately 2 years and 4 and a half months, for patient in state 8 it is approximately 1 year and 4 months.

Transition probability matrix at 1 year:

$$P(1) = \begin{bmatrix} .6751 & .279 & .0345 & .0024 & .0002 & .0000 & .0000 & .0006 & .0082 \\ .0143 & .7625 & .1819 & .0188 & .0019 & .0000 & .0000 & .0044 & .016 \\ .0004 & .0364 & .7017 & .1439 & .0206 & .0012 & .0002 & .0346 & .0604 \\ 0 & .0007 & .0262 & .5868 & .1800 & .0145 & .0039 & .0616 & .1215 \\ 0 & 0 & 0 & 0 & .7061 & .1015 & .0416 & .0344 & .1163 \\ 0 & 0 & 0 & 0 & 0 & .3930 & .3938 & 0 & .2132 \\ 0 & 0 & 0 & 0 & 0 & 0 & .6564 & 0 & .3436 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & .4747 & .5253 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

If a cohort of 5000 NAFLD patients have initial distribution of $[.62 \quad .22 \quad .081 \quad .03 \quad .028 \quad .005 \quad .007 \quad .009 \quad 0]$ and initial counts of patients in each state are $[3100 \quad 1100 \quad 405 \quad 150 \quad 140 \quad 25 \quad 35 \quad 45 \quad 0]$ then at 1 year the state probability distribution is $[.4217 \quad .3437 \quad .1191 \quad .035 \quad .0274 \quad .0054 \quad .0079 \quad .0111 \quad .0287]$ and the expected counts of patients are $[2109 \quad 1718 \quad 595 \quad 175 \quad 137 \quad 27 \quad 39 \quad 56 \quad 144]$.

Transition probability matrix at 50 year:

$$P(50) = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

For the above same cohort of 5000 NAFLD patients, at 50 year the state probability distribution is $[0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 1]$, and the estimated variance of this distribution is

$\mathbf{10^{-11}} \times$								
.01	.0316	.033	.02	.0257	.0088	.0239	.0115	0
.0316	.0998	.1043	.0632	.0813	.0278	.0757	.0364	0
.0330	.1043	.1090	.0661	.0850	.0291	.0791	.0380	0
.02	.0632	.0661	.0400	.0515	.0176	.0479	.0230	0
.0257	.0813	.0850	.0515	.0662	.0226	.0616	.0296	0
.0088	.0278	.0291	.0176	.0226	.0077	.0211	.0101	0
.0239	.0757	.0791	.0479	.0616	.0211	.0574	.0276	0
.0115	.0364	.0380	.0230	.0296	.0101	.0276	.0133	0
0	0	0	0	0	0	0	0	0

steps for evaluation of the transition probabilities are demonstrated and as explained in the text :

Step 1: Laplace transform method is applied to solve the 4 differential equations in the first four rows along with Cramer rule using initial value , the determinant is a 4th degree polynomial which has 4 roots equal to the first four eigenvalues of the Q transition rate matrix. So once the Q rate matrix is estimated, the 4th degree polynomial can be solved for its

$r_1 = -.4609, r_2 = -.5898, r_3 = -.1719 \ , r_4 = -.3584$, $using \ \ Cramer \ rule \ P_{ij}^*(s) = \frac{D_{P_{ij}^*(s)}}{D}$,

Step2: the numerator for each probability is given by substitution for $D_{P_{ij}^*(s)}$ as illustrated in the discussion in text, this can be summarized in the following table:

	Coefficient of s^3	Coefficient of s^2	Coefficient of s	Constant
$DP^*(s)_{11}$	1	1.184	.428388	.045862745
$DP^*(s)_{12}$	0	.39	.35217	.07298655
$DP^*(s)_{13}$	0	0	.0975	.052455
$DP^*(s)_{14}$	0	0	0	.0219375

$DP^*(s)_{21}$	0	.02	.01806	.0037429
$DP^*(s)_{22}$	1	1.3	.545636	.074296565
$DP^*(s)_{23}$	0	.25	.23375	.0533965
$DP^*(s)_{24}$	0	0	.05625	.02233125
$DP^*(s)_{31}$	0	0	.001	.000538
$DP^*(s)_{32}$	0	.05	.04675	.0106793
$DP^*(s)_{33}$	1	1.216	.468521	.055821266
$DP^*(s)_{34}$	0	.225	.15255	.023345325
$DP^*(s)_{41}$	0	0	0	.000041
$DP^*(s)_{42}$	0	0	.00205	.00081385
$DP^*(s)_{43}$	0	.041	.027798	.004254037
$DP^*(s)_{44}$	1	1.043	.338727	.032908805

To get the inverse Laplace, partial fraction method is used and this needs the following calculations :

Step 3 : construct (K) matrix			
1	1	1	1
1.12005634	.991227769	1.409099675	1.222616213
.37435313	.306037387	.648411308	.452470172
.03633368	.028397028	.097427266	.046731407

Step 4 : invert (K) matrix			
-22.644304	55.6343565	-120.696652	261.84686
16.4685712	-22.92361	47.346434	-80.27918609
-.2255193	1.311918	-7.631857	44.39699213
10.4012519	-19.02266	80.9820756	-225.9646

Step 5: calculate the coefficient of the first four $P_{ij}(t)$ in the first four rows; let them be called A_{ij}, B_{ij}, C_{ij}, D_{ij}, it is calculated by multiplying the inverted K matrix by the $D_{P_{ij}^*(s)}$

Coefficient of P_{11}	**Coefficient of P_{12}**	**Coefficient of P_{13}**	**Coefficient of P_{14}**
A_{11}= .5307928	A_{12}= -1.69704167	A_{13} = 1.9672538	A_{14}= 5.74426567
B_{11}= .00784714	B_{12}= -.07551577	B_{13}= .40523268	B_{14}= -1.7611246
C_{11}= .094564365	C_{12}= 1.06432039	C_{13}= 1.58473813	C_{14}= .97395901
D_{11}= .366808118	D_{12}= .70823704	D_{13}= -3.95722461	D_{14}= -4.9571
Coefficient of P_{21}	**Coefficient of P_{22}**	**Coefficient of P_{23}**	**Coefficient of P_{24}**
A_{21} = -.0870278	A_{22} = .2782437	A_{23} = -.322547186	A_{24} = -.9418189
B_{21} = -.0038726	B_{22} = .0373265	B_{23} = -.200301556	B_{24} = .87050238
C_{21} = .0545805	C_{22} = .614303	C_{23} = .914677019	C_{24} = .56214835
D_{21} = .0363198	D_{22} = .0701267	D_{23} = -.391828278	D_{24} = -.4908319
Coefficient of P_{31}	**Coefficient of P_{32}**	**Coefficient of P_{33}**	**Coefficient of P_{34}**
A_{31} = .020176962	A_{32} = -.06450944	A_{33} = .07478098	A_{34} = .21835606
B_{31} = .004156233	B_{32} = -.04006031	B_{33} = .21497162	B_{34} = -.9342579
C_{31} = .016253724	C_{32} = .1829354	C_{33} = .27238481	C_{34} = .16740409
D_{31} = -.04058692	D_{32} = -.07836566	D_{33} = .43786259	D_{34} = .54849772
Coefficient of P_{41}	**Coefficient of P_{42}**	**Coefficient of P_{43}**	**Coefficient of P_{44}**
A_{41} = .0107357	A_{42} = -.0343241	A_{43} = .0397889327	A_{44} = .1161825
B_{41} = -.0032914	B_{42} = .031725	B_{43} = -.17024246	B_{44} = .73986714
C_{41} = .0018203	C_{42} = .02204872	C_{43} = .030504745	C_{44} = .01874781

D_{41} = -.0092646	**D_{42} =** -.0178881	**D_{43} =** .099948473	**D_{44} =** .12520254

Step 6: calculate the inverse Laplace for each PDF, which equals:

$$A_{ij}\, e^{(r_1 t)} + B_{ij}\, e^{(r_2 t)} + C_{ij}\, e^{(r_3 t)} + D_{ij}\, e^{(r_4 t)}\ , \qquad t = 1$$

P_{11} =.675065196	**P_{12}** =.27897024	**P_{13} =** .03452831	**P_{14} =** .00246831
P_{21} = .0143062	**P_{22} =** .7624677	**P_{23} =** .181919657	**P_{24} =** .01902779
P_{31} = .000354137	**P_{32} =** .03638393	**P_{33} =** .70170095	**P_{34} =** .14396966
P_{41} = 4.61E-06	**P_{42} =** .0006935	**P_{43} =** .026234471	**P_{44} =** .58677589

Step 7: calculation of the last four probabilities in the first row:

For P_{15}:			
$G_1=\lambda_{45}*A_{14}$	1.6141387	$G_1/(w+r_1)=F_1$	-14.29154
$G_2=\lambda_{45}*B_{14}$	-.494876	$G_2/(w+r_2)=F_2$	2.04686
$G_3=\lambda_{45}*C_{14}$	.2736825	$G_3/(w+r_3)=F_3$	1.5541339
$G_4=\lambda_{45}*D_{14}$	-1.392945	$G_4/(w+r_4)=F_4$	134.14616
		$F_5=-(F_1+F_2+F_3+F_4)$	-1234556

$$P_{15} = F_1 e^{(r_1 t)} + F_2 e^{(r_2 t)} + F_3 e^{(r_3 t)} + F_4 e^{(r_4 t)} + F_5 e^{(-wt)} = .00017491$$

For P_{16}:			
$G_5=\lambda_{56}*F_1$	-2.715392	$G_5/(u+r_1)=F_6$	-5.740103
$G_6=\lambda_{56}*F_2$	.3889051	$G_6/(u+r_2)=F_7$	1.1297899
$G_7=\lambda_{56}*F_3$	.2952855	$G_7/(u+r_3)=F_8$	.387463
$G_8=\lambda_{56}*F_4$	25.48777	$G_8/(u+r_4)=F_9$	44.279103
$G_9=\lambda_{56}*F_5$	-23.45657	$G_9/(u-w)=F_{10}$	-40.02827
		$F_{11}=-(F_6+F_7+F_8+F_9+F_{10})$	-.02798

$$P_{16} = F_6 e^{(r_1 t)} + F_7 e^{(r_2 t)} + F_8 e^{(r_3 t)} + F_9 e^{(r_4 t)} + F_{10} e^{(-wt)} + F_{11} e^{(-ut)} = 6.0813E-6$$

For P_{17}:			
$G_{10}=\lambda_{67}*F_6$	-4.402659	$G_{10}/(\lambda_{79}+r_1)=F_{12}$	110.2217
$G_{11}=\lambda_{67}*F_7$	.86654887	$G_{11}/(\lambda_{79}+r_2)=F_{13}$	-5.134428
$G_{12}=\lambda_{67}*F_8$	.29718414	$G_{12}/(\lambda_{79}+r_3)=F_{14}$	1.193033
$G_{13}=\lambda_{67}*F_9$	33.9620721	$G_{13}/(\lambda_{79}+r_4)=F_{15}$	542.38463
$G_{14}=\lambda_{67}*F_{10}$	-30.701685	$G_{14}/(\lambda_{79}-w)=F_{16}$	-420.57103
$G_{15}=\lambda_{67}*F_{11}$	-.0214606	$G_{15}/(\lambda_{79}-u)=F_{17}$	.04183347
		$F_{18}=-(F_{12}+F_{13}+F_{14}+F_{15}+F_{16}+F_{17})$	-228.13579

$$P_{17} = F_{12} e^{(r_1 t)} + F_{13} e^{(r_2 t)} + F_{14} e^{(r_3 t)} + F_{15} e^{(r_4 t)} + F_{16} e^{(-wt)} + F_{17} e^{(-ut)} + F_{18} e^{(-\lambda_{79} t)} = 7.828E-7$$

For P_{18}:			
$G_{16}=\lambda_{18}*A_{11}+\lambda_{28}*A_{12}+\lambda_{38}*A_{13}+\lambda_{48}*A_{14}+\lambda_{58}*F_1$	-.1246149	$G_{10}/(\lambda_{89}+r_1)=F_{19}$	-.438697828
$G_{17}=\lambda_{18}*B_{11}+\lambda_{28}*B_{12}+\lambda_{38}*B_{13}+\lambda_{48}*B_{14}+\lambda_{58}*F_2$	-.0521514	$G_{10}/(\lambda_{89}+r_2)=F_{20}$	-.335966911
$G_{18}=\lambda_{18}*C_{11}+\lambda_{28}*C_{12}+\lambda_{38}*C_{13}+\lambda_{48}*C_{14}+\lambda_{58}*F_3$	.2723381	$G_{10}/(\lambda_{89}+r_3)=F_{21}$	.475202028
$G_{19}=\lambda_{18}*D_{11}+\lambda_{28}*D_{12}+\lambda_{38}*D_{13}+\lambda_{48}*D_{14}+\lambda_{58}*F_4$	7.1883097	$G_{10}/(\lambda_{89}+r_4)=F_{22}$	18.5928823
$G_{20}=\lambda_{58}*F_5$	-7.2838816	$G_{10}/(\lambda_{89}-w)=F_{23}$	-18.34730875
		$F_{24}=-(F_{19}+F_{20}+F_{21}+F_{22}+F_{23})$	.0538892

$$P_{18} = F_{19} e^{(r_1 t)} + F_{20} e^{(r_2 t)} + F_{21} e^{(r_3 t)} + F_{22} e^{(r_4 t)} + F_{23} e^{(-wt)} + F_{24} e^{(-\lambda_{89} t)} = .00055542$$

for P19:			
$G_{21}=\lambda_{19}*A_{11}+\lambda_{29}*A_{12}+\lambda_{39}*A_{13}+\lambda_{49}*A_{14}+\lambda_{59}*F_1+\lambda_{69}*F_6+\lambda_{79}*F_{12}+\lambda$	44.38733	G_{21}/r_1=F25	-

$_{89}*F_{19}$	9		96.296671
$G_{22}=\lambda_{19}*B_{11}+\lambda_{29}*B_{12}+\lambda_{39}*B_{13}+\lambda_{49}*B_{14}+\lambda_{59}*F_2+\lambda_{69}*F_7+\lambda_{79}*F_{13}+\lambda_{89}*F_{20}$	-2.1923658	G_{22}/r_2=F26	3.71730926
$G_{23}=\lambda_{19}*C_{11}+\lambda_{29}*C_{12}+\lambda_{39}*C_{13}+\lambda_{49}*C_{14}+\lambda_{59}*F_3+\lambda_{69}*F_8+\lambda_{79}*F_{14}+\lambda_{89}*F_{21}$	1.2595848	G_{23}/r_3=F27	-7.327414
$G_{24}=\lambda_{19}*D_{11}+\lambda_{29}*D_{12}+\lambda_{39}*D_{13}+\lambda_{49}*D_{14}+\lambda_{59}*F_4+\lambda_{69}*F_9+\lambda_{79}*F_{15}+\lambda_{89}*F_{22}$	262.1805	G_{24}/r4=F28	-731.5635
$G_{25}=\lambda_{59}*F_5+\lambda_{69}*F10+\lambda_{79}*F_{16}+\lambda_{89}*F_{23}$	-209.63598	$F_{29}=-G_{25}/w$	602.402231
$G_{26}=\lambda_{69}*F_{11}+\lambda_{79}*F_{17}$	0.0129392	$F_{30}=-G_{26}/u$	-0.0138536
$G_{27}=\lambda_{79}*F_{18}$	-96.045167	$F_{31}=-G_{27}/\lambda_{79}$	228.135788
$G_{28}=\lambda_{89}*F_{24}$	0.0401474	$F_{32}=-G_{28}/\lambda_{89}$	-0.0538892
		$F_{33}=-F_{25}-F_{26}-F_{27}-F_{28}+F_{29}+F_{30}+F_{31}+F_{32}$	1

$$P_{19} = F_{25}e^{(r_1t)} + F_{26}e^{(r_2t)} + F_{27}e^{(r_3t)} + F_{28}e^{(r_4t)} + F_{29}e^{(-wt)} + F_{30}e^{(-ut)} + F_{31}e^{(-\lambda_{79}t)} + F_{32}e^{(-\lambda_{89}t)} + F_{33} = .008230754$$

The same substitution is used to calculate the last 5 probabilities in 2nd , 3rd , 4th rows as demonstrated in text .
The same is true for the last 12 PDFs' in the subsequent 4 rows while $P_{99}=1$
The transition probability matrix at 1 year is

$$P_{ij}(t=1) = \begin{bmatrix} .6751 & .279 & .0345 & .0024 & .0002 & .0000 & .0000 & .0006 & .0082 \\ .0143 & .7625 & .1819 & .0188 & .0019 & .0000 & .0000 & .0044 & .016 \\ .0004 & .0364 & .7017 & .1439 & .0206 & .0012 & .0002 & .0346 & .0604 \\ 0 & .0007 & .0262 & .5868 & .1800 & .0145 & .0039 & .0616 & .1215 \\ 0 & 0 & 0 & 0 & .7061 & .1015 & .0416 & .0344 & .1163 \\ 0 & 0 & 0 & 0 & 0 & .3930 & .3938 & 0 & .2132 \\ 0 & 0 & 0 & 0 & 0 & 0 & .6564 & 0 & .3436 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & .4747 & .5253 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

Of those patients (patients with susceptible risk factors) starting at stage S1 (NAFLD with no fibrosis), that is to mean only steatosis, about 30 % of them will move to S2 (NASH with no fibrosis), 3.5% will move to S3 (NASH with fibrosis whether F1, F2 or F3). They are less likely to develop liver cirrhosis whether compensated or decompensated (S4 and S5 respectively), as only; 0.24% of them will get S4 and 0.02% will get S5. Less than 1% of them, about 0.06% will develop HCC (S8=hepatocellular carcinoma) and 0.82% will die (S9). While the majority, about 67.51 % will remain stable in S1. These patients are not candidate for liver transplantation.
Once the patient starts to develop S2 (NASH with no fibrosis), 18.2% of those patients will progress to develop S3 and about 2% will develop S4 (compensated liver cirrhosis), while; they are less likely to get S5 as only 0.19% will get S5 (decompensated liver cirrhosis).They are more likely to develop S8 (0.44% v.s. 0.06% for those starting at S1) and 1.6% will die, however; only 1.4% will regress to S1. 76.25 % will remain stable is S2. These patients are also not candidate for liver transplantation.
Those patients at S3, about 14.39% will progress to S4 (compensated liver cirrhosis), while 2.1% will develop S5 (decompensated liver cirrhosis). Because they are not highly recommended for liver transplantation, only 0.12% of them will survive the first year after liver transplantation (S6) and 0.02% will survive longer than the first year after liver transplantation (S7), however about 3.5% of them will get HCC (S8) and 6.04% will die. Only 0.04 % of them will regress to S1, 3.64% will regress to S2, and 70.17 % will remain stable is S3.
Of the compensated liver cirrhosis patients (S4), about 18% will be decompensated (S5) and because they are putting on waiting list for liver transplantation, so; 1.5% of them will survive the first year after liver transplantation (S6) and 0.39% will survive longer than the first year after liver transplantation (S7), however about 6.16 % of them will get HCC (S8) and 12.15% will die, no one will regress to S1, 0.07% will regress to S2, 2.62% will regress to S3 and 58.68 % will remain stable is S4.

Once the patient develops decompensated liver cirrhosis (S5), they are highly candidate for liver transplantation, thus; 10.15% of them will survive the first year after liver transplantation (S6) and 4.16% will survive longer than the first year after liver transplantation (S7), however about 3.44% of them will get HCC (S8) and 11.63% will die, and 70.61 % will remain stable is S5, but no regression to previous stages (S1, S2, S3, S4).
Of the patients who had survived the first year, 39.38 % of them would be surviving after this year and 21.32% would die.
The patients who had survived for more than one year after liver transplantation, 34.36 % of them would die. And 52.53 % of patients with HCC (S8) will die.

Hint: AMatlab code is edited to calculate the statistical indices in the hypothetical example. The code can be found published in code ocean site with the following URL:

codeocean.com/capsule/7628018/tree/v1