Maximum likelihood estimation for a general mixture of Markov jump processes

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Abstract

We estimate a general mixture of Markov jump processes. The key novel feature of the proposed mixture is that the transition intensity matrices of the Markov processes comprising the mixture are entirely unconstrained. The Markov processes are mixed with distributions that depend on the initial state of the mixture process. The new mixture is estimated from its continuously observed realizations using the EM algorithm, which provides the maximum likelihood (ML) estimates of the mixture’s parameters. To obtain the standard errors of the estimates of the mixture’s parameters, we employ Louis’ (1982) general formula for the observed Fisher information matrix. We also derive the asymptotic properties of the ML estimators. Simulation study verifies the estimates’ accuracy and confirms the consistency and asymptotic normality of the estimators. The developed methods are applied to a medical dataset, for which the likelihood ratio test rejects the constrained mixture in favor of the proposed unconstrained one. This application exemplifies the usefulness of a new unconstrained mixture for identification and characterization of homogeneous subpopulations in a heterogeneous population.

keywords: mixture of Markov jump processes, EM algorithm, Fisher information matrix, asymptotic distribution, clustering

1 Introduction

This paper proposes a general mixture of Markov processes. This new mixture is an extension of the model in Frydman (2005), which in turn extends the seminal mover-stayer model presented in Blumen, et al. (1955). The key novel feature of the proposed model is that the transition intensity matrices of the Markov processes comprising the mixture are entirely unconstrained: each homogeneous subpopulation evolves according to a Markov process with its own intensity matrix. The mixture’s regime membership distribution is assumed to depend only on the initial state of the process, and may differ between initial states. Because constraining the transition intensities may obscure the identification of clusters,

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the proposed unconstrained mixture is particularly suitable for identification and characterization of homogeneous subpopulations in a heterogeneous population. This is illustrated with a medical application in which the likelihood ratio test rejects the constrained mixture from Frydman (2005) in favor of the proposed general mixture.

We obtain the maximum likelihood (ML) estimates of a general mixture (g-mixture) from the data consisting of a set of its continuously observed realizations using the EM algorithm of Dempster, et al. (1977). We subsequently develop the estimation of the variances of the estimators of the g-mixture parameters based on Louis’s (1982) general formula for the observed Fisher information matrix. The latter development is challenging but manageable, owing to the explicit form of the observed Fisher information matrix for the g-mixture. We also derive the asymptotic properties of the ML estimators. We show through the simulation study that the estimation is accurate and confirms the asymptotic properties of the estimators. The developed methods are applied to the ventICU dataset from Cook and Lawless (2018).

The g-mixture is different from the mixture of Markov processes recently considered by Jiang and Cook (2019). There, the regime probabilities depend on covariates through the multinomial logistic regression, while the Markov processes in the mixture are assumed to have the same intensity matrices. In the g-mixture, the regime probabilities depend only on an initial state, while the Markov processes have their own intensity matrices. We observe g-mixture continuously, whereas Jiang and Cook (2019) observe the mixture intermittently.

To define the proposed model, let $X = \{X_m, 1 \leq m \leq M\}$ be the mixture of $M$ right-continuous Markov jump processes with the intensity matrices $Q'_m$'s, and transition matrices $P_m(t) = \exp(Q_m t)$ defined on the finite state space $S = E \cup \Delta$, where $E$ is a set of non-absorbing states and $\Delta$ a set of absorbing states. There is a separate mixing distribution for each initial state $i \in E$ of $X$,

$$\phi_{i,m} \equiv P(X = X_m | X_0 = i), \ 1 \leq m \leq M,$$

where $\sum_{m=1}^{M} \phi_{i,m} = 1$. Let $D_m = \text{diag}(\phi_{1,m}, \ldots, \phi_{w,m})$, where $w$ is the cardinality of $E$. Then the transition matrix of a mixture process $X$ is given by

$$P(t) = \sum_{m=1}^{M} D_m P_m(t), \ t \geq 0.$$

Earlier, Frydman (2005) specified the following structure for the intensity matrices of Markov processes comprising the mixture

$$Q_m = \Gamma_m Q \ (1 \leq m \leq M),$$

where $Q$ is a $w \times w$ intensity matrix, $\Gamma_m = \text{diag}(\gamma_{1,m}, \ldots, \gamma_{w,m})$, with $\gamma_{i,m} \geq 0$, for $1 \leq m \leq M - 1$, and $\Gamma_M = I$, an identity matrix. Depending on whether $\gamma_{i,m} = 0$, $0 < \gamma_{i,m} < 1$, $\gamma_{i,m} \geq 1$, the realizations generated by $Q_m$ do not move out of state $i$, or move out of state $i$ at a lower or higher rate than those generated by $Q$, or at an identical rate. This specification, which can be easily extended to include absorbing states, implies that the embedded transition matrices of Markov processes in the mixture are all the same. This mixture may be restrictive in situations in which the population is heterogeneous.
not only with respect to exit rates from states, but also with respect to the direction of movement. However, this mixture has been successfully applied to modeling bond-ratings migration by Frydman and Schuermann (2008)), and to clustering of categorical time series by Pamminger and Fruhwirth-Schnatter (2010). Its distributional properties were studied in Surya (2018).

By setting \( M = 2 \), and \( \gamma_{1,1} = \ldots = \gamma_{w,1} = 0 \) in \( \Gamma_1 \), the transition matrix of \( X \) reduces to \( D_1 I + (I - D_1)P_2(t) \), a transition matrix of a continuous-time mover-stayer (MS) model. The MS model assumes a simple form of population heterogeneity: there are stayers who never leave their initial states, with \( P_1(t) = I \) as their transition matrix, and movers who evolve among the states according to transition matrix \( P_2(t) = \exp(tQ) \). The MS model was the first mixture of Markov chains considered in the literature, and its use in Blumen, et al. (1955) to study labor mobility was the first application of stochastic processes in the social sciences. Frydman (1984) obtained the ML estimators of the discrete-time MS model’s parameters by direct maximization of the observed likelihood function, and Fuchs and Greenhouse (1988) did so by using the expectation-maximization (EM) algorithm. In both cases, estimation used the data on independent realizations of the MS model.

Despite capturing a very simple form of population heterogeneity, the MS mixture’s discrete and continuous-time versions have been widely applied in diverse fields, including medicine (Tabar, et al., 1996), labor economics (Fougere and Kamionka, 2003), large data (Cipollini, et al., 2012), farming (Saint-Cyr and Piet, 2017), and credit risk (Frydman and Kadam, 2004, and Ferreti, et al., 2019). In a continuous-time framework, Yi, et al. (2017) estimated an MS model from panel data in the presence of state misclassification. Cook, et al. (2002) developed a generalized MS model, which allows for subject specific absorbing states, and Shen and Cook (2014) considered a dynamic MS model for recurrent events that can be resolved. In a discrete-time framework, Frydman and Matuszyk (2018, 2019) developed an estimation for a discrete-time MS model with covariate effects on stayers’ probability and movers’ transitions.

The paper is organized as follows. Section 2 sets the notation and derives the observed and complete likelihood functions. Section 3 presents the EM algorithm. Section 4 derives the variances and covariances of the estimators of the g-mixture parameters, and Section 5 presents the asymptotic properties of the estimators. Section 6 is devoted to the simulation study and Section 7 presents the application to ventICU data. Section 8 concludes the paper.

2 The observed and complete likelihood functions

2.1 The observed likelihood function

We consider the general continuous-time mixture \( X \) with \( M \) components defined in the Introduction. Let \( X^k = \{X^k_t, 0 \leq t \leq T\} \) denote the \( k \)'th realization of \( X \) on \([0, T]\) where \( T \) is the end-of-study time, which can be either fixed, or the absorption time of \( X \). Denote by \( X^k− \) that realization without an initial state, that is, \( X^k = (X^k−) \cup X_0 \). And, let \( R^k \) denote the regime label of the \( k \)'th realization. To write the likelihood of \( X^k \), for \( 1 \leq k \leq K \)
and $1 \leq m \leq M$, we define the following quantities associated with $X^k$:

$$
\begin{align*}
\Phi_{k,m} &= I(R_k = m) \\
B^k_i &= I(X^k_0 = i), i \in E, \\
B_i &= \sum_{k=1}^K B^k_i = \# \text{ of realizations with initial state } i, i \in E \\
N^k_{ij} &= \# \text{ of times } X^k \text{ makes an } i \rightarrow j \text{ transition, } i \neq j, i \in E \\
T^k_i &= \int_0^T I(X^k_t = i) du = \text{ total time } X^k \text{ spends in state } i \in E,
\end{align*}
$$

where $\Phi_{k,m}$ is equal to 1 if the $k$'th realization evolves according to the $m$'th Markov process and equal to zero, otherwise. We note that $\Phi_{k,m}$ is unknown, but other quantities in (1) are known. For $1 \leq m \leq M$, let $\theta_m \equiv (q_{ij,m}, i \neq j, \phi_{i,m}, i \in E, j \in S)$ and $\theta = (\theta_m, 1 \leq m \leq M)$ be the mixture’s parameters. The observed likelihood function $L^k(\theta)$ of $X^k, 1 \leq k \leq K$, is

$$
L^k(\theta) = \sum_{m=1}^M L^k_m(\theta) \equiv \sum_{m=1}^M P(X^k, X^k_0 = i, R_k = m)
$$

$$
= \sum_{m=1}^M P(X^k_0 = i)P(R_k = m | X^k_0 = i_k)P(X^k \setminus | X^k_0 = i_k, R_k = m)
$$

$$
= \sum_{m=1}^M \prod_{i \in E} (\pi_i \phi_{i,m}) B^k_i \prod_{i \in E} \left\{ \prod_{j \neq i, j \in S} (q_{ij,m})^{N^k_{ij}} \exp\left( - \sum_{j \neq i, j \in S} q_{ij,m} T^k_i \right) \right\}
$$

$$
= \prod_{i \in E} \pi_i B^k_i \sum_{m=1}^M \prod_{i \in E} (\phi_{i,m})^{B^k_i} \prod_{i \in E} \left\{ \prod_{j \neq i, j \in S} (q_{ij,m})^{N^k_{ij}} \exp\left( - \sum_{j \neq i, j \in S} q_{ij,m} T^k_i \right) \right\}
$$

(2)

where $\pi_i = P(X_0 = i)$ with $\sum_{i \in E} \pi_i = 1$, is an initial distribution of the mixture. Thus, the likelihood function of the $K$ observed sample paths is

$$
\mathcal{L}(\theta) = \prod_{k=1}^K L^k(\theta).
$$

(3)

The likelihood function (3) remains the same when $T$ is a fixed end-of-study time or is the absorption time of the mixture process. Notice that for a fixed $T$, the last state occupation time may be right censored. We will use EM algorithm to obtain the maximum likelihood estimator (mle) of $\theta$ based on $K$ realizations of the mixture process. It follows from (2) and (3) that $\pi_i$ can be easily estimated separately from the other parameters so that if $K$ realizations are available, the mle of $\pi_i$ is

$$
\hat{\pi}_i = \frac{1}{K} \sum_{k=1}^K B^k_i = \frac{B_i}{K}, \text{ for } i \in E.
$$

Therefore, when writing the complete loglikelihood function below, we will omit the factor involving $\pi_i, i \in E$. 

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2.2 The complete loglikelihood function

We now assume that we have the complete information, that is, we also know $\Phi_k,m(1 \leq k \leq K, 1 \leq m \leq M)$. Then the complete loglikelihood of the k\textsuperscript{th} realization $X^k$ is

$$\log L^k_c(\theta) = \sum_{m=1}^{M} \Phi_k,m \log L^k_m(\theta).$$

By (2), the complete loglikelihood of all K realizations is

$$\log L_c(\theta) \sim \sum_{k=1}^{K} \sum_{m=1}^{M} \Phi_k,m \log L^k_m(\theta) = \sum_{m=1}^{M} \Phi_k,m \log \left( \sum_{k=1}^{K} L^k_m(\theta) \right)$$

$$= \sum_{m=1}^{M} \left\{ \sum_{i \in E} B_i,m \log(\phi_i,m) \right\} - \sum_{i \in E} \lambda_i \left( \sum_{m=1}^{M} \phi_i,m - 1 \right)$$

$$+ \sum_{m=1}^{M} \sum_{i \in E} \left\{ \sum_{j \neq i \in S} N_{ij,m} \log q_{ij,m} - \left( \sum_{j \neq i \in S} q_{ij,m} \right) T_{i,m} \right\}$$

where $B_i,m = \sum_{k=1}^{K} \Phi_k,m B^k_i$ = the number of regime $m$ realizations with initial state $i$, $N_{ij,m} = \sum_{k=1}^{K} \Phi_k,m N^k_{ij}$ = the total number of $i \rightarrow j$, ($i \in E, j \in S$) transitions among the m\textsuperscript{th} regime realizations, $T_{i,m} = \sum_{k=1}^{K} \Phi_k,m T_i^k$ = the total waiting time in state $i \in E$ for regime $m$ realizations. And $\lambda_i$ is a Lagrange multiplier. The "wiggle" after $\log L_c(\theta)$ signifies that we omitted the part of $\log L_c(\theta)$ which involves $\pi_i, i \in E$. It can be easily shown by adding up the score equations for $\phi_i,m$ and $q_{ij,m}$, the complete information mles of $\phi_i,m$ and $q_{ij,m}$ are

$$\hat{\phi}^c_{i,m} = \frac{B_i,m}{B_i} \quad (i \in E),$$

$$\hat{q}^c_{ij,m} = \frac{N_{ij,m}}{T_i,m} \quad (j \neq i, i \in E, j \in S).$$

3 The EM algorithm

We now use the EM algorithm to obtain the mle of $\theta_m(1 \leq m \leq M)$ from K realizations. Following Dempster et al. (1977), the mles $\hat{\theta}$ are found iteratively so that the $(p + 1)$-th estimate $\hat{\theta}^{p+1}$ of $\theta$ maximizes

$$\mathbb{E}^p(\log L_c(\theta)|D),$$

where $D = \bigcup_{k=1}^{K} X^k$ denotes the data, $\mathbb{E}^p(\bullet|D)$ refers to the conditional expectation evaluated using the current estimate $\hat{\theta}^p$ after $p$ steps of the algorithm. This is the maximization step (M-step) of the algorithm. The evaluation of the above conditional expectation forms the E-step.
Proposition 1  The EM algorithm for the finite g-mixture of Markov jump processes $X = \{X_m, 1 \leq m \leq M\}$ based on $K$ realizations goes as follows.

Step 1 (Initial step) For $1 \leq m \leq M$, choose initial value $\theta^0_m \equiv (q^0_{ij,m}, i \neq j, \phi^0_{i,m}, i \in E, j \in S)$ of $\theta_m$.

Step 2 (E-step) At the $p$'th iteration ($p = 0, 1, 2, \ldots$), for $1 \leq m \leq M, i \in E, 1 \leq k \leq K$, compute the probability of observing $X^k$ under $\theta^p_m$ 

$$L^k(\theta^p_m) \sim \phi^p_{i,m} \prod_{i \in E} \left( \prod_{j \neq i, j \in S} (q^p_{ij,m})^{N^k_{ij}} \exp\left(-\sum q^p_{ij,m} T^k_i\right) \right), 1 \leq m \leq M.$$ 

and then the probability that the path $X^k$ comes from regime $m$ 

$$\mathbb{E}^p(\Phi_k,m|X^k) = \frac{L^k(\theta^p_m)}{\sum_{\ell=1}^M L^k(\theta^p_\ell)}.$$ 

For $i \in E, j \in S, \text{ and } 1 \leq m \leq M$, compute 

$$\mathbb{E}^p(N_{ij,m}|D) \equiv \sum_{k=1}^K N^k_{ij} \mathbb{E}^p(\Phi_k,m|X^k), \quad j \neq i$$

$$\mathbb{E}^p(T_{i,m}|D) \equiv \sum_{k=1}^K T^k_i \mathbb{E}^p(\Phi_k,m|X^k),$$

$$\mathbb{E}^p(B_{i,m}|D) \equiv \sum_{k=1}^K B^k_i \mathbb{E}^p(\Phi_k,m|X^k).$$

Step 3 (M-step) For $1 \leq m \leq M$, compute, using (5) and (8), the values $\theta^{p+1}_m \equiv (q^{p+1}_{ij,m}, i \neq j, \phi^{p+1}_{i,m}, i \in E, j \in S)$ by 

$$\phi^{p+1}_{i,m} = \frac{\mathbb{E}^{p+1}(B_{i,m}|D)}{B_i}, \quad (7)$$

$$q^{p+1}_{ij,m} = \frac{\mathbb{E}^{p+1}(N_{ij,m}|D)}{\mathbb{E}^{p+1}(T_{i,m}|D)}. \quad (8)$$

Step 4 Stop if convergence criterion is achieved, that is, if the Euclidean norm $||\theta^{p+1} - \theta^p|| < \varepsilon$. Otherwise, return to step 2 and replace $\theta^p_m$ by $\theta^{p+1}_m$.

The EM algorithm described above converges to $\hat{\theta}_m$, the mle of $\theta_m$. We denote by $\infty$ the value of $p$ at which the algorithm converges. At convergence, the equations in (7) and (8) take the form 

$$\hat{\phi}_{i,m} = \frac{\mathbb{E}^{\infty}(B_{i,m}|D)}{B_i},$$

$$\hat{q}_{ij,m} = \frac{\mathbb{E}^{\infty}(N_{ij,m}|D)}{\mathbb{E}^{\infty}(T_{i,m}|D)}.$$
where $\hat{\phi}_{i,m}$ and $\hat{q}_{ij,m}$ are the mles of $\phi_{i,m}$ and $q_{ij,m}$ under incomplete observations. To simplify the notation, in the sequel, we will denote $\mathbb{E}^\infty(Y|D)$ by $\hat{Y}$. Thus, $\hat{\Phi}_{k,m} = \mathbb{E}^\infty(\Phi_{k,m}|D)$ and $\hat{N}_{ij,m} = \mathbb{E}^\infty(N_{ij,m}|D) = \sum_{k=1}^{K} \hat{\Phi}_{k,m} N_{ij}^k$. Similarly, $\hat{T}_{i,m} = \sum_{k=1}^{K} \hat{\Phi}_{k,m} T^k_i$ and $\hat{B}_{i,m} = \sum_{k=1}^{K} \hat{\Phi}_{k,m} B^k_i$.

3.1 Initialization of the EM algorithm

Suppose we have $K$ sample paths from the mixture with $M$ regimes obtained from the simulation or real data. For the initial distribution $\pi_i, i \in E$ of the g-mixture, we use the estimate $\hat{\pi}_i$. For each $i \in E$, we set the initial value of $(\phi_{i,m}, m \in M)$ to be a uniform distribution: $(\phi^0_{i,m}, m \in M) = (1/M, \ldots, 1/M)$. The initial value $Q^0_m$ for the intensity matrix $Q_m$ is obtained by first randomly dividing $K$ sample paths into $M$ subsets with the first $(M - 1)$ subsets having size $[K/M]$ each, and the $M$-th subset being of size $K - (M - 1)(K/M)$. Then, treating the $m$-th subset, $m \in M$, as if it contained realizations from a single Markov process $X_m$ with intensity matrix $Q_m$, $Q^0_m$ was set to be the mle of the intensity matrix $Q_m$.

4 Variances of the mles from the EM algorithm

Let $\phi = (\phi_{i,m}, i \in E, 1 \leq m \leq M)$ and $q = (q_{ij,m}, j \neq i, i \in E, j \in S, 1 \leq m \leq M)$. We will use the following notation for the computation of the estimated variances of $\hat{\phi}$ and $\hat{q}$ in the next section. Define

$$\phi_m = (\phi_{1,m}, \ldots, \phi_{w,m}), \ 1 \leq m \leq M,$$

where $w = |E|$. We form the row vector $\phi$ of dimension $(1 \times Mw)$, which combines the vectors $\phi_m$, i.e., $\phi = (\phi_1, \ldots, \phi_M)$. Similarly, let $q_m$ be a $(1 \times w(w-1))$-vector formed by combining the $E$-row vectors of $Q_m$, with diagonal element $q_{i,i,m}$ removed, i.e.,

$$q_m = (q_{12,m}, \ldots, q_{1w,m}, q_{21,m}, q_{23,m}, \ldots, q_{2w,m}, \ldots, q_{w1,m}, \ldots, q_{w(w-1),m}).$$

Next, we form a row vector $q$ of dimension $(1 \times Mw(w-1))$, when there are no absorbing states, which combines the vectors $q_m$, i.e., $q = (q_1, \ldots, q_M)$. The g-mixture parameters to be estimated are defined by the $(1 \times Mw^2)$-vector

$$\theta = (\phi, q).$$

According to Louis (1982) the variance of $\hat{\theta}$ is given by the inverse of the observed Fisher information matrix $I(\hat{\theta})$ defined by

$$I(\hat{\theta}) = \mathbb{E} \left[ -\frac{\partial^\top}{\partial \theta} \cdot \left( \frac{\partial \log L(\theta)}{\partial \theta} \right) \bigg| D \right] - \mathbb{E} \left[ \left( \frac{\partial \log L(\theta)}{\partial \theta} \right)^\top \cdot \left( \frac{\partial \log L(\theta)}{\partial \theta} \right) \bigg| D \right] \bigg| \hat{\theta} \tag{9}$$

$$= \begin{pmatrix} I(\phi) & I(\hat{\phi}, \hat{q}) \\ I(\hat{q}, \hat{\phi}) & I(\hat{q}) \end{pmatrix},$$
where we use the notation \( \partial \theta = (\partial \phi, \partial q) \) to denote the vector gradient of \( \theta \). The first term is the expected complete data observed information and the second is the variance of complete data score, both conditional on the data \( D \) and evaluated at \( \hat{\theta} \). Below we derive the explicit expressions for \( I(\hat{\phi}), I(\hat{q}) \) and \( I(\hat{q}, \hat{\phi}) \).

### 4.1 Elements of the matrices \( I(\hat{\phi}), I(\hat{q}), \) and \( I(\hat{\phi}, \hat{q}) \)

To derive the expressions for \( I(\hat{\phi}), I(\hat{q}), \) and \( I(\hat{\phi}, \hat{q}) \), we note that the loglikelihood function can be decomposed as

\[
\log L_c(\theta) = \log L_c(\phi) + L_c(q),
\]

where the first term depends only on \( \phi \), while the second term only on \( q \).

\[
\log L_c(\phi) = \sum_{i \in E} \left( \sum_{j \in S} N_{ij,m} \log \phi_{ij,m} \right) - \sum_{i \in E} \left( \sum_{m=1}^{M} \phi_{i,m} - 1 \right),
\]

\[
\log L_c(q) = \sum_{m=1}^{M} \sum_{i \in E} \left( \sum_{j \neq i, j \in S} N_{ij,m} \log q_{ij,m} - \sum_{j \neq i, j \in S} q_{ij,m} T_{i,m} \right).
\]

Also, let \( A_{ij,m} = N_{ij} - q_{ij,m} T_{ij} \), \( A_{ij,m} = \sum_{k=1}^{K} \hat{\Phi}_{k,m} A_{ij,m} \), and

\[
\delta_q(z) = \begin{cases} 1, & q = z \\ 0, & \text{otherwise} \end{cases}
\]

**Proposition 2** For \( (i, r) \in E \), \( (j, v) \in S \), and \( n, m = 1, \ldots, M \),

\[
I(\hat{\phi}_{j,n}, \hat{\phi}_{i,m}) = \frac{\delta_i(j)}{\hat{\phi}_{j,n} \hat{\phi}_{i,m}} \sum_{k=1}^{K} \hat{\Phi}_{k,n} \hat{\Phi}_{k,m} B_{ij}^k
\]

\[
I(\hat{q}_{rv,n}, \hat{q}_{ij,m}) = -\frac{1}{\hat{q}_{rv,n} \hat{q}_{ij,m}} \sum_{k=1}^{K} \hat{\Phi}_{k,n} (\delta_m(n) - \hat{\Phi}_{k,m}) \hat{A}_{ij,m}^k \hat{A}_{ij,m}^k
\]

in particular, the diagonal element \( I(\hat{q}_{ij,m}) := I(\hat{q}_{ij,m}, \hat{q}_{ij,m}) \) is given by

\[
I(\hat{q}_{ij,m}) = \frac{\hat{N}_{ij,m}}{\hat{q}_{ij,m}^2} - \frac{1}{\hat{q}_{ij,m}^2} \sum_{k=1}^{K} \hat{\Phi}_{k,m} (1 - \hat{\Phi}_{k,m}) \left( \hat{A}_{ij,m}^k \right)^2,
\]

and

\[
I(\hat{\phi}_{i,m}, \hat{q}_{rj,n}) = -\frac{1}{\hat{\phi}_{i,m} \hat{q}_{rj,n}} \sum_{k=1}^{K} \hat{\Phi}_{k,n} (\delta_m(n) - \hat{\Phi}_{k,m}) \hat{A}_{rj,n}^k \hat{B}_{ij}^k.
\]

**Proof.** The proofs of above results are provided in part A of Supplementary material. ■

Using the expression (7) on p.12 in Magnus and Neudecker (2007) for inversion of block partitioned matrix, inverting the matrix \( I(\hat{\theta}) \) yields estimated covariance of \( \hat{\theta} \) exhibited in the following proposition.
Proposition 3 The estimated covariance matrix of the mles \( \hat{\theta} \) is given by

\[
\hat{\text{Var}}(\hat{\theta}) = \begin{pmatrix}
\hat{\text{Var}}(\hat{\phi}) & \hat{\text{Cov}}(\hat{\phi}, \hat{q}) \\
\hat{\text{Cov}}^T(\hat{\phi}, \hat{q}) & \hat{\text{Var}}(\hat{q})
\end{pmatrix},
\]

where the estimated variances for \( \hat{q}, \hat{\phi} \), and their covariance are defined by

\[
\hat{\text{Var}}(\hat{q}) = [I(\hat{q}) - I(\hat{q}, \hat{\phi})I^{-1}(\hat{\phi})I(\hat{\phi}, \hat{q})]^{-1},
\]

\[
\hat{\text{Cov}}(\hat{\phi}, \hat{q}) = -I^{-1}(\hat{\phi})I(\hat{\phi}, \hat{q})[I(\hat{q}) - I(\hat{q}, \hat{\phi})I^{-1}(\hat{\phi})I(\hat{\phi}, \hat{q})]^{-1},
\]

\[
\hat{\text{Var}}(\hat{\phi}) = I^{-1}(\hat{\phi}) + \hat{\text{Cov}}(\hat{\phi}, \hat{q})[\hat{\text{Var}}(\hat{q})]^{-1}\hat{\text{Cov}}^T(\hat{\phi}, \hat{q}).
\]

Thus, if \( I(\hat{\phi}, \hat{q}) = 0 \), \( \hat{\text{Cov}}(\hat{\phi}, \hat{q}) = 0 \), \( \hat{\text{Var}}(\hat{\phi}) = I^{-1}(\hat{\phi}) \), and \( \hat{\text{Var}}(\hat{q}) = I^{-1}(\hat{q}) \).

Remark 1 Note that in order to prevent having singularity in estimating the variance of \( \hat{\theta} \) by inverting the information matrix \( I(\hat{\theta}) \), we exclude the estimators \( \hat{\phi}_{i,m} \) and \( \hat{q}_{i,m} \) whose values are (very close) to zero.

4.2 Computation of \( I(\hat{\theta}) \) for a two-regime mixture model

We specialize the general results from Proposition 2 to the case of two-regime mixture model defined on state space \( S = E \cup \Delta \), where \( E = \{1, 2\} \) is a set of transient states and \( \Delta = \{3, 4\} \) is a set of two absorbing states corresponding to the ventICU dataset used in the application section with the state diagram described by Figure 1. Since \( \hat{\phi}_{i,2} = 1 - \hat{\phi}_{i,1} \), we have \( \text{Var}(\hat{\phi}_{i,2}) = \text{Var}(\hat{\phi}_{i,1}) \) for each \( i \in E \), and thus consider only the vector \( \phi = (\phi_{1,1}, \phi_{2,1})^\top \). The \( I(\hat{\phi}) \) is a \((2 \times 2)\)--diagonal matrix with the entries given, using Proposition 2 by

\[
I_{11}(\hat{\phi}) = \sum_{k=1}^{K} \left( \frac{\hat{\Phi}_{k,1}}{\hat{\phi}_{i,1}} \right)^2 B_i^k, \quad i \in E.
\]

To simplify the presentation of the matrix \( I(\hat{q}) \), we split into block partitioned matrix:

\[
I(\hat{q}) = \begin{pmatrix}
I(\hat{q}_1) & I(\hat{q}_1, \hat{q}_2) \\
I(\hat{q}_1, \hat{q}_2) & I(\hat{q}_2)
\end{pmatrix}.
\]

Note that by the symmetry property, \( I(\hat{q}_2, \hat{q}_1) = I^\top(\hat{q}_1, \hat{q}_2) \). To write elements of the matrix \( I(\hat{q}_m)_{6 \times 6} \), with \( m = 1, 2 \), we use the sequence \( \hat{q}_m = (\hat{q}_{12,m}, \hat{q}_{13,m}, \hat{q}_{14,m}, \hat{q}_{21,m}, \hat{q}_{23,m}, \hat{q}_{24,m}) \) and number its components from 1 to 6, so that it is read as \( \hat{q}_m = (\hat{q}_{1,m}, ..., \hat{q}_{6,m}) \). Similarly, we label the \( \ell \)--th component of the vectors \( (\hat{N}_{12,m}, \hat{N}_{13,m}, \hat{N}_{14,m}, \hat{N}_{21,m}, \hat{N}_{23,m}, \hat{N}_{24,m}) \) and \( (\hat{A}_{12,m}, \hat{A}_{13,m}, \hat{A}_{14,m}, \hat{A}_{21,m}, \hat{A}_{23,m}, \hat{A}_{24,m}) \) by \( \hat{N}_{\ell,m} \) and \( \hat{A}_{\ell,m} \).

Then, for \( 1 \leq \ell \leq 6 \), the diagonal elements of the matrix \( I(\hat{q}_m) \) are

\[
I_{\ell\ell}(\hat{q}_m) = \frac{\hat{N}_{\ell,m}}{\hat{q}_{\ell,m}} - \frac{1}{\hat{q}_{\ell,m}} \sum_{k=1}^{K} \hat{\Phi}_{k,m}(1 - \hat{\Phi}_{k,m}) \left( \hat{A}_{\ell,m}^k \right)^2,
\]
while, for $1 \leq \ell \neq \nu \leq 6$, the off-diagonal elements are

$$I_{\ell\nu}(\hat{q}_m) = \frac{1}{q_{\ell,m}q_{\nu,m}} \sum_{k=1}^{K} \hat{\Phi}_{k,m}(1 - \hat{\Phi}_{k,m}) \hat{A}_{\ell,m}^k \hat{A}_{\nu,m}^k.$$  

Moreover, the $(\ell, \nu)$-element of the matrix $I(\hat{q}_1, \hat{q}_2)$ is

$$I_{\ell\nu}(\hat{q}_1, \hat{q}_2) = \frac{1}{q_{\ell,1}q_{\nu,2}} \sum_{k=1}^{K} \hat{\Phi}_{k,1} \hat{\Phi}_{k,2} \hat{A}_{\ell,1}^k \hat{A}_{\nu,2}^k.$$  

For convenience, we write $I(\hat{\phi}, \hat{q}) = [I(\hat{\phi}, \hat{q}_1), I(\hat{\phi}, \hat{q}_2)]$, where for $m = 1, 2$, each $I(\hat{\phi}, \hat{q}_m)$ is a $(2 \times 6)$-matrix whose $(\ell, \nu)$-element is

$$I_{\ell\nu}(\hat{\phi}, \hat{q}_m) = \begin{cases} -\frac{1}{\phi_{\ell,1}q_{\nu,1}} \sum_{k=1}^{K} \hat{\Phi}_{k,1}(1 - \hat{\Phi}_{k,1}) \hat{A}_{\nu,1}^k B_{\ell}^k, & m = 1, \\ -\frac{1}{\phi_{\ell,1}q_{\nu,2}} \sum_{k=1}^{K} \hat{\Phi}_{k,1} \hat{\Phi}_{k,2} \hat{A}_{\nu,2}^k B_{\ell}^k, & m = 2, \end{cases}$$

for $\ell = 1, 2$ and $1 \leq \nu \leq 6$.

### 5 Consistency and asymptotic normality of $\hat{\theta}$.

To show consistency of the mle $\hat{\theta}$, consider a sample average of the expected values of the loglikelihood $\log L_{\ell}^k(\theta)$ given observation of $k$th sample path $X^k$,

$$\mathcal{L}_{c}^K(\theta) = \frac{1}{K} \sum_{k=1}^{K} \mathbb{E}_{\theta_0} \left( \log L_{\ell}^k(\theta) \big| X^k \right),$$

where $\mathbb{E}_{\theta_0}$ is the expectation operator associated with the probability measure $\mathbb{P}_{\theta_0}$ under which $X^k$ was generated. Notice that $\mathcal{L}_{c}^K(\theta)$ is just the D-conditional expected loglikelihood $\mathbb{E}_{\theta_0}(\log L_{\ell}(\theta) | D)$ commonly used in the EM algorithm, normalized by $1/K$. It follows from (4) that the following regularity condition holds for each element $\theta_i$ of $\theta$,

$$\frac{1}{K} \sum_{k=1}^{K} \mathbb{E}_{\theta_0} \left( \left| \frac{\partial}{\partial \theta_i} \log L_{\ell}^k(\theta) \right| X^k \right) < \infty. \quad (10)$$

To be more precise, the average has an upper bound $\frac{1}{\phi_{i,m}}(1 + \phi_{i,m})$ for $\phi_{i,m}$, and $\frac{1}{K} \sum_{k=1}^{K} N_{ij,m}^{k} + T$ for $q_{ij,m}$. Under the regularity condition, the solution $\hat{\theta}_0$ of the equation $0 = \frac{\partial}{\partial \theta} \mathcal{L}_{c}^K(\theta) |_{\theta = \theta_0} = \frac{1}{K} \sum_{k=1}^{K} \mathbb{E}_{\theta_0} \left( \frac{\partial}{\partial \theta} \log L_{\ell}^k(\theta) | X^k \right) |_{\theta = \theta_0}$ corresponds to that given by the EM algorithm at convergence. It follows from the loglikelihood log $L_{\ell}^k(\theta)$ that $\mathbb{E}_{\theta_0}(\log L_{\ell}^k(\theta) | X^k)$ is continuous in both $\theta_0$ and $\theta$ away from zero. In the M-step of each iteration in the EM algorithm, $\theta$ is chosen as such that the function $\mathbb{E}_{\theta_0}(\log L_{\ell}^k(\theta) | X^k)$ is maximized. The latter and the continuity of $\mathbb{E}_{\theta_0}(\log L_{\ell}^k(\theta) | X^k)$ in both $\theta_0$ and $\theta$ are the required conditions for the convergence of EM algorithm to a local maxima $\hat{\theta}_0$, see Theorem 3 in Wu (1983). By independence of all $K$ realizations $\{X^k\}$, $\mathcal{L}_{c}^K(\theta)$ converges in probability as $K \to \infty$ to $\mathcal{L}_{c}(\theta) = \mathbb{E}_{\theta_0}(\log L_{\ell}^k(\theta))$.

Let $\Theta$ denote the set of any possible value, other than zero, of $\theta$. The result below shows that the function $\mathcal{L}_{c}(\theta)$ has a global maximum at $\theta = \theta_0$. 


Proposition 4 For any \( \theta \in \Theta \), \( \mathcal{L}_c(\theta) \leq \mathcal{L}_c(\theta_0) \). Moreover, \( \mathcal{L}_c(\theta) < \mathcal{L}_c(\theta_0) \), unless \( \mathbb{P}_{\theta_0}\{\mathcal{L}_c(\theta) = \mathcal{L}_c(\theta_0)\} = 1 \), and \( \frac{\partial}{\partial \theta} \mathcal{L}_c(\theta) = 0 \) if and only if \( \theta = \theta_0 \).

Proof. See part B in the Supplementary material. ■

Theorem 1 Let condition (10) hold, \( T \) be either a fixed time or the absorption time, and \( \hat{\theta}_0 \) solve equation \( \frac{\partial}{\partial \theta} \mathcal{L}_c^K(\theta_0) = 0 \). Then, \( \hat{\theta}_0 \) converges in probability as \( K \to \infty \) to \( \theta_0 \), and

\[
\sqrt{K}(\hat{\theta}_0 - \theta_0) \sim N(0, \Sigma),
\]

where \( \Sigma := \text{Cov}(\hat{\theta}_0 - \theta_0, \hat{\theta}_0 - \theta_0) \) is a \((Mw^2 \times Mw^2)\) diagonal matrix with

\[
\text{Cov}(\phi_{r,n}^0 - \phi_{r,n}^0, \phi_{i,m}^0 - \phi_{i,m}^0) = \frac{\phi_{r,m}^0}{\pi_r} \delta_i(r)(\delta_m(n) - \delta_{r,n})^2, \\
\text{Cov}(\hat{\phi}_{r,n}^0 - \phi_{r,n}^0, \hat{\phi}_{i,m}^0 - \phi_{i,m}^0) = 0, \\
\text{Cov}(\hat{q}_{r,v,n}^0 - \phi_{r,v,n}^0, q_{i,j,m}^0 - q_{i,j,m}^0) = \frac{q_{r,v,n}^0 \delta_m(n) \delta_i(r) \delta_j(v)}{\mathbb{E}_{\theta_0}(\Phi_{k,n}T_i^k)},
\]

(11)

where for \( D_n^0 = \text{diag}(\phi_{1,n}^0, \cdots, \phi_{w,n}^0) \), \( Q_n^0 = [q_{i,j,n}^0]_{ij} \), and \( \pi = (\pi_1, \cdots, \pi_w) \),

\[
\mathbb{E}_{\theta_0}(\Phi_{k,n}T_i^k) = \begin{cases} 
\int_0^T \pi^\top D_n^0 e^{Q_n e_t} du, & \text{for fixed } T \\
\int_0^\infty \pi^\top D_n^0 e^{Q_n e_t} du, & \text{for absorption time } T.
\end{cases}
\]

Proof. See part C in the Supplementary material. ■

In the absence of heterogeneity \((\delta_m(n) = 1 \text{ and } D_m = I)\), the result in (11) coincides with that of Theorem 6.1 in Albert (1962). In the presence of heterogeneity, estimators of transition rates for different regimes have zero covariances. There is also zero covariance between estimators of regime memberships across different states and transition rates.

6 Simulation Study

We consider a mixture of two continuous-time Markov jump processes \( X_m, m = 1, 2 \), with the intensity matrices \( Q_m, m = 1, 2 \) on state space \( \{1, 2, 3\} \). For the purpose of simulation, we express \( Q_m \) as

\[
Q_m = \text{diag}(q_{1,m}, q_{2,m}, q_{3,m})(P_m - I), m = 1, 2
\]

where \( \text{diag}(q_{1,m}, q_{2,m}, q_{3,m}) \) is the diagonal matrix with \( q_{i,m} = -q_{i,i,m} \) being the exit rate of \( X_m \) from state \( i \), \( P_m \) the transition matrix of a discrete time Markov chain \( Z^m \) embedded in the Markov process \( X_m \) and \( I \) an identity matrix.
For the true values of the mixture’s parameters, we chose uniform initial distribution $\pi = (1/3, 1/3, 1/3)$, and the regime 1 and 2 probabilities as $\phi_1 = (\phi_{1,1}, \phi_{2,1}, \phi_{3,1}) = (0.5, 0.25, 1/5)$ and $\phi_2 = (1, 1, 1) - \phi_1$, respectively. Furthermore, we chose the true transition matrices of the embedded Markov chains $Z^m$, $m = 1, 2$, to be

\[
P_1 = \begin{pmatrix} 0 & 0.6 & 0.4 \\ 0.5 & 0 & 0.5 \\ 0.4 & 0.6 & 0 \end{pmatrix} \quad \text{and} \quad P_2 = \begin{pmatrix} 0 & 0.8 & 0.2 \\ 0.5 & 0 & 0.5 \\ 0.2 & 0.8 & 0 \end{pmatrix}
\]

and the true exit rates from states as $q_1 = (1/3, 2/5, 1/5)$ and $q_2 = (1/2, 1/4, 3/4)$ for regime 1 and 2 respectively. The elements in the true intensity matrices can be found in Table 1 below.

### 6.1 Simulating a sample path of a two-regime mixture

We simulate a sample path of a two-regime mixture on time interval $(0, T) = (0, 30)$. The simulation uses Sigman’s (2017) method for simulating a sample path of a discrete-time Markov chain. In the simulation, $W_i^m$ denotes a waiting time of $X_m$ in state $i$. And we write $W_i^m \sim \exp(q_{i,m})$ to say that $W_i^m$ has an exponential distribution with parameter $q_{i,m}$. We also note that $Z_0^m = X_m(0)$ for $m = 1, 2$.

**Step 1** Draw at random an initial state $i_0$ from a uniform distribution on states $1, 2, 3$.

**Step 2** Given $i_0$, draw the regime indicator $m$ from the Bernoulli distribution with success probability equal to $\phi_{i_0,1}$, where success corresponds to regime $Q_1$.

**Step 3** Set $j = 1$.

**Step 4** For a chosen $m$ in Step 2, set $Z_{j-1}^m = i_{j-1}$, simulate waiting time $W_{i_{j-1}}^m \sim \exp(q_{i_{j-1},m})$ and compute $S_{j-1}^m = \sum_{k=0}^{j-1} W_{i_k}^m$. Stop if $S_{j-1}^m > T$. If not, go to Step 5.

**Step 5** Simulate $Z_j^m = i_j$, conditioning on state $i_{j-1}$

\[
\begin{align*}
\text{if } i_{j-1} &= 1 \text{ and } U_j \leq p_{12,m}, \text{ set } Z_j^m = 2 \\
\text{if } i_{j-1} &= 1 \text{ and } U_j > p_{12,m}, \text{ set } Z_j^m = 3,
\end{align*}
\]

\[
\begin{align*}
\text{if } i_{j-1} &= 2 \text{ and } U_j \leq p_{21,m}, \text{ set } Z_j^m = 1 \\
\text{if } i_{j-1} &= 2 \text{ and } U_j > p_{21,m}, \text{ set } Z_j^m = 3,
\end{align*}
\]

\[
\begin{align*}
\text{if } i_{j-1} &= 3 \text{ and } U_1 \leq p_{31,m}, \text{ set } Z_j^m = 1 \\
\text{if } i_{j-1} &= 3 \text{ and } U_1 > p_{31,m}, \text{ set } Z_j^m = 2,
\end{align*}
\]

where $U_j$ is drawn, independently from previous draws, from $U(0,1)$, a uniform distribution on $[0,1]$. Increase $j$ by one and go to Step 4.

Let $J \equiv \min(j : S_{j-1}^m > T)$. Then $J$ is the iteration at which the simulation stops.

The resulting sample path is $\{Z_0^m = i_0, W_{i_0}^m, Z_1^m = i_1, W_{i_1}^m, \ldots, Z_{J-1}^m = i_{J-1}, W_{i_{J-1}}^m, C\}$, where $W_{i_{J-1}}^m, C$ is a right-censored by $T$ waiting time in state $i_{J-1}$.
Table 1: Bias($\hat{\theta}$)=$\frac{1}{N} \sum_{n=1}^{N} (\hat{\theta}_{n,K} - \theta)$ and RMSE($\hat{\theta}$) =$\left[ \frac{1}{N} \sum_{n=1}^{N} (\hat{\theta}_{n,K} - \theta)^2 \right]^{1/2}$, with fixed $N = 200$, for different number $K$ of sample paths.

| $\theta$ | True Value | Bias ($10^{-2}$) for $K$ = 800 | Bias ($10^{-2}$) for $K$ = 1200 | Bias ($10^{-2}$) for $K$ = 2000 | RMSE ($10^{-2}$) for $K$ = 800 | RMSE ($10^{-2}$) for $K$ = 1200 | RMSE ($10^{-2}$) for $K$ = 2000 |
|---------|-------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| $\phi_{1,1}$ | 0.5 | 2.0787 | 0.8372 | -0.1656 | 7.4662 | 5.1977 | 3.9595 |
| $\phi_{2,1}$ | 0.25 | 1.1391 | 0.5739 | -0.0839 | 6.8112 | 5.6301 | 3.7659 |
| $\phi_{3,1}$ | 0.75 | 0.8329 | 0.2995 | -0.2127 | 6.0929 | 5.0411 | 3.6592 |
| $q_{12.1}$ | 0.2 | 0.1579 | 0.1187 | -0.0432 | 1.1507 | 0.8344 | 0.6330 |
| $q_{13.1}$ | 0.1333 | 0.0951 | 0.0317 | 0.0003 | 0.6299 | 0.5779 | 0.4388 |
| $q_{21.1}$ | 0.2 | -0.0376 | 0.0158 | 0.0005 | 0.8900 | 0.6754 | 0.5373 |
| $q_{23.1}$ | 0.2 | -0.1477 | 0.0950 | -0.0508 | 0.8984 | 0.6626 | 0.5546 |
| $q_{31.1}$ | 0.2 | -0.1477 | -0.0661 | 0.0237 | 1.4041 | 1.1318 | 0.8727 |
| $q_{32.1}$ | 0.3 | 0.1096 | 0.0392 | -0.0025 | 1.1586 | 1.0826 | 0.6792 |
| $q_{12.2}$ | 0.4 | 0.3652 | 0.1250 | -0.0200 | 2.0643 | 1.8367 | 1.3450 |
| $q_{13.2}$ | 0.1 | -0.1462 | -0.0235 | 0.0060 | 0.8862 | 0.6501 | 0.5309 |
| $q_{21.2}$ | 0.2 | 0.0485 | 0.0394 | 0.0097 | 0.7981 | 0.6333 | 0.4349 |
| $q_{23.2}$ | 0.2 | 0.0839 | -0.0486 | -0.0058 | 0.8730 | 0.6035 | 0.4763 |
| $q_{31.2}$ | 0.0667 | -0.1083 | -0.0740 | 0.0189 | 0.7627 | 0.6022 | 0.4026 |
| $q_{32.2}$ | 0.2667 | -0.1751 | -0.1607 | 0.0580 | 1.0573 | 0.9602 | 0.6445 |

6.2 Simulation results

We independently obtained $N = 200$ sets of $K = 800$, 1200 and 2000 sample paths with each sample path generated in the way described in Section 6.1. We chose $\phi^0 = (1/2, 1/2, 1/2)$ to be the initial value of $(\phi_{1,1}, \phi_{2,1}, \phi_{3,1})$, and chose the initial values of $Q_1$ and $Q_2$ as described in Section 3.1. The EM algorithm was run until convergence criterion $||\theta^{p+1} - \theta^p|| < 10^{-4}$ was achieved and was repeated 200 times for each $K$ sample paths.

The simulation results were evaluated using Bias and the Root Mean Squared Error (RMSE) and are reported in Table 1. We observe that as the sample size $K$ increases both Bias and RMSE decrease confirming consistency of the EM estimates. We see from Table 2 that the standard errors obtained from the simulation are close to the theoretical standard errors. We next confirmed that for $K = 2000$ and $N = 200$, the distribution of $\hat{\theta}_K$ is approximately normal using the Kolmogorov-Smirnov (KS) test as follows. For each element of $\theta$, the simulation yields a random sample of 200 biases, with each bias obtained from a set of sample paths of size 2000. We then standardized the biases by dividing them by their standard error. The fit of the standardized biases to the standard normal cdf was assessed using KS test. The p-value of the KS test, reported for each element in Table 2 confirms the large sample normality of its estimator.
Table 2: Estimated standard errors of the mles $\hat{\theta}$ using $\text{Var}(\hat{\theta}) = \text{RMSE}(\hat{\theta})^2 - \text{Bias}(\hat{\theta})^2$ and the inverse of $J(\hat{\theta}_K) = \frac{1}{N} \sum_{n=1}^{N} I(\hat{\theta}_{n,K})$, for $K = 2000$ and $N = 200$. The last column lists the p-value of Kolmogorov-Smirnov statistic for goodness-of-fit between empirical CDF of standardized biases and $N(0,1)$ CDF.

7 Application to ventICU dataset

7.1 Data and the choice of the mixture model

This section applies the methods developed in the paper to the ventICU dataset from Appendix D in Cook and Lawless (2018). The ventICU dataset comes from a prospective cohort study of patients in an intensive care unit (ICU), and contains information on the occurrence of infections and the need for mechanical ventilation along with discharge and death times. Cook and Lawless suggest that the multi-state model in Figure 1 would be suitable for examining the relation between mechanical ventilation status and risk of death or discharge for the sample of 747 patients, but do not provide any analysis of the ventICU dataset. In Figure 1, state $1$ represents being off mechanical ventilator; state $2$ being on mechanical ventilator; state $3$ discharge and state $4$ death. The numbers of transitions between states are exhibited in Table 4 from which we see that at the end of the study 733 patients were either discharged or died, and 14 were still in the hospital. In our analysis, we treat these 14 patients as right-censored observations. The focus of our analysis is on identifying the subgroups of patients characterized by different relations between mechanical ventilation status and risk of death or discharge.

We use Akaike information criterion (AIC), see Akaike (1973), to decide on the choice of the g-mixture for the ventICU data. We estimate six g-mixtures for the ventICU data with the number of regimes $M$ ranging from 1 (single Markov process) to 6. Table 5 shows that
AIC$ _M = 2|\theta _M| - 2\log \mathcal{L}(\hat{\theta} _M)$, where $|\theta _M|$ is the number of parameters in the $M$'th model, is the smallest for $M = 2$, and thus we use the 2-regime mixture in the further analysis of the ventICU data.

| 1  | 2  | 3  | 4  | Censored |
|----|----|----|----|----------|
| 1  | 0  | 75 | 585| 21       | 5        |
| 2  | 319| 0  | 72 | 55       | 9        |

Table 3: Observed transitions among different states and the numbers of patients right-censored in states 1 and 2.

| Model  | AIC       | $\log \mathcal{L}(\hat{\theta})$ |
|--------|-----------|-----------------------------------|
| Markov | 9648.185  | -4817.092                         |
| 2 Mixture | **9611.868** | -4790.934                         |
| 3 Mixture | 9611.991  | -4782.996                         |
| 4 Mixture | 9618.506  | -4778.253                         |
| 5 Mixture | 9628.735  | -4775.367                         |
| 6 Mixture | 9641.453  | -4773.727                         |

Table 4: Summary of model statistics AIC and $\log \mathcal{L}(\hat{\theta})$.

### 7.2 Parameter estimates of the two-regime g-mixture model

From the EM algorithm, the estimated numbers $\hat{B}_{i,m}$ of patients starting in the state $i$ and making transitions according to Markov process $X_m, m = 1, 2$, and the regime probabilities...
\[ \hat{\phi}_{i,m} = \frac{\hat{B}_{i,m}}{B_i} \] with their standard errors are reported in Table 5. We will refer to the

| State(i) | \( B_i \) | \( \hat{B}_{i,1} \) | \( \hat{B}_{i,2} \) | \( \hat{\phi}_{i,1} \) (SE) | \( \hat{\phi}_{i,2} \) (SE) |
|----------|----------|----------------|----------------|----------------|----------------|
| 1        | 367      | 230.75         | 136.25         | 0.6287 (.0504) | 0.3713 (.0504) |
| 2        | 380      | 209.16         | 170.84         | 0.5504 (.0494) | 0.4496 (.0494) |

Table 5: Estimates of \( B_{i,m} \)'s and \( \phi_{i,m} \)'s with their standard errors for the ventICU dataset.

patients estimated to evolve according to \( X_m \) as \( X_m \) patients. We see from Table 5 that initially there were 367 patients in state 1 and 380 in state 2. Using this information together with \( \hat{D}_m = \text{diag}(\hat{\phi}_{1,m}, \hat{\phi}_{2,m}), m = 1, 2 \), we obtain the estimated total number of \( X_1 \) patients, by summing the elements of the vector \( \hat{C}_1 \equiv (367, 380) \hat{D}_1 = (230.75, 209.16) \) to be approximately 440. Similarly summing the elements of \( \hat{C}_2 \equiv (367, 380) \hat{D}_2 = (136.25, 170.84) \), we get the estimated total number of \( X_2 \) patients to be approximately 307. The estimates of the intensity matrices \( Q_1 \) and \( Q_2 \) of the Markov processes \( X_1 \) and \( X_2 \) with the standard errors (in parentheses), computed using the results in Section 4.2, are

\[
\hat{Q}_1 = \frac{1}{2} \begin{pmatrix}
-0.16112 & 0.01657 & 0.14455 & 0.00000 \\
(0.00343) & (0.00973) & (0.01405) & (0.00356) \\
0.12071 & -0.13832 & 0.01405 & 0.00356 \\
(0.01375) & (0.00515) & (0.00973) & (0.00447)
\end{pmatrix},
\]

and

\[
\hat{Q}_2 = \frac{1}{2} \begin{pmatrix}
-0.11594 & 0.01441 & 0.09102 & 0.01051 \\
(0.00425) & (0.00935) & (0.00251) & (0.00324) \\
0.02309 & -0.04550 & 0.01094 & 0.01147 \\
(0.00324) & (0.00248) & (0.00247) & (0.00247)
\end{pmatrix},
\]

respectively, where we omitted the last two rows of zeros, which correspond to the two absorbing states. To prevent having singularity in the inverse of \( I(\hat{\theta}) \), we excluded \( \hat{q}_{14,1} \) from the vector \( \hat{q}_1 \) in the estimation of the standard errors, and assumed that the true value of \( q_{14,1} = 0 \). We see that the regime 2 death intensities are much higher from both initial states than the regime 1 death intensities: in fact regime 1 death intensity for patients who were initially not on ventilator is zero. We also see that regime 1 discharge intensities are higher from both initial states compared to the similar regime 2 intensities. In both regimes, not being initially on ventilator results in a larger discharge intensity compared to the death intensity.

### 7.2.1 Absorption probabilities

To gain a better understanding of the differences between the two regimes, we compare their absorption probabilities \( \hat{f}_{ij,m}, m = 1, 2 \), from state \( i = 1, 2 \) into states \( j = 3, 4 \). The standard equations for these probabilities are derived based on the transition matrices of the discrete time Markov chains embedded into the continuous Markov processes \( X_1 \) and \( X_2 \), and are given in part D of Supplementary material. Here we just state the results: the
absorption probability matrices for the two regimes, denoted by $\hat{F}_1$ and $\hat{F}_2$, with entries $\hat{f}_{ij,1}$ and $\hat{f}_{ij,2}$, $(i = 1, 2), (j = 3, 4)$, are

$$
\hat{F}_1 = \frac{1}{2} \begin{pmatrix} 0.9971 & 0.0029 \\ 0.9717 & 0.0283 \end{pmatrix} \quad \text{and} \quad \hat{F}_2 = \frac{1}{2} \begin{pmatrix} 0.8698 & 0.1302 \\ 0.6818 & 0.3182 \end{pmatrix},
$$

respectively. Comparing $\hat{F}_1$ with $\hat{F}_2$, we see a striking difference in the estimated probability of eventual death in the two regimes. In regime 1, the probability of death for a patient initially in state 1 (not on ventilator) is very small (0.0029), whereas this probability for a patient initially in state 2 (on ventilator), the probability of death is about 11 times larger in regime 2 compared to regime 1. As a result of very large differences in the death probabilities between two regimes, we also observe large differences in their eventual discharge probabilities.

To translate above results into those involving patients’ absorption frequencies in each regime, we would want to pre-multiply $\hat{F}_m$ matrix by the row vector $\hat{C}_m$ to obtain a row vector showing the estimated number of $X_m$ patients who were eventually discharged, or died. But doing so we would overestimate the absorption frequencies by 14 patients who were right-censored at the end of the study. Among those patients, 5 were initially in state 1 and 9 in state 2. To compute absorption frequencies, we have to subtract the 14 patients from the $\hat{C}_m$ vectors, which we do as follows. According to $\hat{D}_m$ matrices, the 5 patients with initial state 1, contribute $5(\hat{\phi}_{11}) = 5(0.6287)$ patients to regime 1 patients and $5(\hat{\phi}_{12}) = 5(0.3713)$ to regime 2 patients. Similarly, the patients initially in state 2, contribute $9(\hat{\phi}_{21}) = 9(0.5504)$ patients to regime 1 patients and $9(\hat{\phi}_{22}) = 9(0.4496)$ to regime 2 patients. Hence, vector $\hat{C}_1 = (230.75, 209.16)$ has to be modified to become vector $\hat{C}_{1,U}$ describing the regime 1 uncensored patients’ absorption frequencies by initial state:

$$
\hat{C}_{1,U} = \hat{C}_1 - [5(0.6287), 9(0.5504)] = (227.6065, 204.2064),
$$

and vector $\hat{C}_2 = (136.25, 170.84)$ has to be modified to become vector $\hat{C}_{2,U}$ describing the regime 2 uncensored patients’ absorption frequencies by initial state:

$$
\hat{C}_{2,U} = \hat{C}_2 - [5(0.3713), 9(0.4496)] = (134.3935, 166.7936).
$$

We can now compute the regime 1 absorption frequencies:

$$
\hat{C}_{1,U} \hat{F}_1 \approx (226.95, 0.66) + (198.43, 5.78) = (425.38, 6.44),
$$

where the first vector in first line shows that absorption frequencies from state 1 and the second those frequencies from state 2 among estimated $X_1$ patients. Summing the two vectors tells us that in regime 1, about 425 patients were eventually discharged and about 6 died. For regime 2, we have

$$
\hat{C}_{2,U} \hat{F}_2 \approx (116.9, 17.5) + (113.72, 53.07) = (230.62, 70.57),
$$

where the interpretation of the vectors is analogous to the one for the regime 1. We see that the estimated total number of deaths is 77.01 $\approx$ 77 which is one more than the observed number of deaths, see Table 5, and the estimated total number of discharges is about 656,
which is one less than the observed number of discharges. This difference is likely due to the rounding errors. The regime 1 death rate is 6.44/431.82 \approx 0.015 or 1.5\% whereas the regime 2 death rate is about 70.57/301.2 = 0.234 or 23.4\%. Consequently, the rate of discharge from both initial states is much larger in regime 1 compared to regime 2. In both regimes most of the patients who died were initially on ventilator (state 2). The proportion of discharges when initially on ventilator is 53.07/70.57 or about 0.75 in regime 2 and 5.78/6.44 \approx 0.9 in regime 1.

Thus, the g-mixture model has identified two regimes corresponding to high risk (regime 2) and low (regime 1) risk of death, with the patients in the high risk regime having about 15 times higher death rate than those in the low risk regime.

### 7.3 The likelihood ratio test of the constrained vs unconstrained mixture

We want to see, if for ventICU data, there is a benefit in using the general mixture proposed in this paper over the constrained mixture considered by Frydman (2005). In the two-regime c-mixture, the two transition intensity matrices $Q_1$ and $Q_2$ are constrained by assuming that $Q_1 = \Gamma Q_2$, where $\Gamma = \text{diag}(\gamma_{1,1}, \gamma_{2,1})$ regulates the speed with which regime 1 subjects move among the states compared to the regime 2 subjects. Hence, the test of c-mixture vs g-mixture can be formulated as $H_0 : Q_1 = \Gamma Q_2$ vs $H_a : Q_1$ and $Q_2$ are unrestricted. To carry out the test, we use the likelihood ratio statistic, $-2 \log \Lambda$:

$$
\Lambda = \frac{L_{c-\text{Mixture}}(\hat{\theta}_c)}{L_{g-\text{Mixture}}(\hat{\theta}_g)},
$$

where $\hat{\theta}_c$ and $\hat{\theta}_g$ are the mles of the vector parameters $\theta_c = \{\phi_{i,1,1}, \phi_{i,2,1}\} \cup \{q_{ij}, i \in E, j \in S, i \neq j\} \cup \{\gamma_{1,1}, \gamma_{2,1}\}$ and $\theta_g = \{\phi_{1,1,1}, \phi_{2,2,1}\} \cup \{q_{ij,m}, 1 \leq m \leq 2, i \in E, j \in S, i \neq j\}$, respectively, where $E = \{1, 2\}$ and $\Delta = \{3, 4\}$. We see that a general mixture has 14 parameters while the constraint one has 10, which means that, under $H_0$, $-2 \log \Lambda$ has $\chi^2$ distribution with 4 degrees of freedom. To evaluate $-2 \log \Lambda$, we note that the likelihood function of a general mixture, $L_{g-\text{Mixture}}(\theta_g)$, is given in (3) and the likelihood function of the constrained mixture is of the form

$$
L_{c-\text{Mixture}}(\theta_c) = \left( \prod_{k=1}^{K} \prod_{i \in E} \pi_i^{B_k} \right) \prod_{k=1}^{K} \prod_{m=1}^{M} \prod_{i \in E} (\phi_{i,m})^{B_k} \times \prod_{i \in E} \left\{ \prod_{j \neq i, j \in S} (\gamma_{i,m} q_{ij})^{N_{ij}} \exp \left( - \sum_{j \neq i, j \in S} \gamma_{i,m} q_{ij} T_i^k \right) \right\},
$$

where the factor in parentheses involving $\pi_i^s$ is the same as the factor involving $\pi_i^s$ in $L_{g-\text{Mixture}}(\theta_c)$ and thus $\pi_i^s$ play no role in the evaluation of $-2 \log \Lambda$. From Table 4, $\log(L_{g-\text{Mixture}}(\hat{\theta}_g)) = -4790.934$, and from the EM algorithm applied to fit the c-mixture to ventICU data, $\log(L_{c-\text{Mixture}}(\hat{\theta}_c)) = -4797.926$. Thus, $-2 \log \Lambda = 13.984$ with the p-value of 0.00735 show that we can reject c-mixture in favor of g-mixture at $\alpha = 0.01$. We further compare the two mixtures in part E of Supplementary material.
8 Concluding remarks

We proposed and estimated a new unconstrained mixture of Markov processes. We showed the consistency and asymptotic normality of the estimators of the mixture’s parameters and obtained the finite sample standard errors of the estimates. The simulation study verified that the estimation was accurate and confirmed the asymptotic properties of the estimators. The application of the proposed mixture to VenICU illustrated its usefulness in identifying subpopulations and its dominance over the constrained mixture. We believe that the unconstrained mixture will dominate the constrained one in many other data sets for which consideration of heterogeneity is relevant. We intend to extend the proposed general mixture in a number of ways which include incorporation of covariates into our continuous observation time framework and developing estimation from observing the mixture at discrete time points in the presence of covariates. The estimation of a discretely observed Markov jump process without covariates has been considered by Bladt and Sørensen (2005, 2009), Inamura (2006), Mostel et al. (2020), and Pfeuffer et al. (2019), among others. The mixture proposed here and the mixtures of finite-state continuous-time Markov processes arising from the above potential extensions should be useful in a variety of contexts in which modeling of the population heterogeneity is important.

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Supplementary material for:
Maximum likelihood estimation for a general mixture of
Markov jump processes

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A Proof of Proposition 2

The proof of Proposition 2 requires the results of Lemma A1 below which presents conditional second moments of $N_{ij,m}$, $T_{i,m}$ and $B_{i,m}$.

A.1 Conditional second moments of $N_{ij,m}$, $T_{i,m}$ and $B_{i,m}$

Lemma A1. For $(i, r) \in E$, $(j, v) \in S$, $1 \leq n, m \leq M$, under the mle $\hat{\theta}$,

\[ \mathbb{E}^\infty(B_{r,n}B_{i,m}|D) = \hat{B}_{r,n}\hat{B}_{i,m} + \delta_i(r) \sum_{k=1}^{K} \hat{\Phi}_{k,n}B_r^k(\delta_m(n) - \hat{\Phi}_{k,m}), \]

\[ \mathbb{E}^\infty(N_{ij,m}N_{rv,n}|D) = \hat{N}_{ij,m}\hat{N}_{rv,n} + \sum_{k=1}^{K} \hat{\Phi}_{k,n}N_{ij}^kN_{rv}^k(\delta_m(n) - \hat{\Phi}_{k,m}), \]

\[ \mathbb{E}^\infty(T_{i,m}T_{r,n}|D) = \hat{T}_{i,m}\hat{T}_{r,n} + \sum_{k=1}^{K} \hat{\Phi}_{k,n}T_i^kT_r^k(\delta_m(n) - \hat{\Phi}_{k,m}), \]

\[ \mathbb{E}^\infty(N_{ij,m}T_{r,n}|D) = \hat{N}_{ij,m}\hat{T}_{r,n} + \sum_{k=1}^{K} \hat{\Phi}_{k,n}N_{ij}^kT_r^k(\delta_m(n) - \hat{\Phi}_{k,m}), \]

\[ \mathbb{E}^\infty[(N_{ij,m} - q_{ij,m}T_{i,m})(N_{rv,n} - q_{rv,n}T_{r,n})|D] \]

\[ = \hat{A}_{ij,m}\hat{A}_{rv,n} + \sum_{k=1}^{K} \hat{\Phi}_{k,n}\hat{A}_{ij,m}^k\hat{A}_{rv,n}^k(\delta_m(n) - \hat{\Phi}_{k,m}), \]

\[ \mathbb{E}^\infty[(N_{ij,m} - q_{ij,m}T_{i,m})B_{r,n}|D] \]

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The proof follows similar arguments to that of used in derivation of the first statement.

Proof of the second statement

which, after rearranging the terms, shows the first statement. ■

Proof of the first statement

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Proof of the second statement

The proof follows similar arguments to that of used in derivation of the first statement.
we compute the first and second order derivatives of log $\Lambda_i^k N_{ij}^k N_{rv}^k$ + \left( \sum_{k=1}^{K} \Phi_{k,m} T_i^k T_r^k \right) \left( \sum_{\ell=1}^{K} \Phi_{\ell,n} T_r^\ell \right)

leading to the claimed second statement after rearranging the terms.

Proof of the third statement

\[ \mathbb{E}^∞(T_i,m T_r,n|D) = \mathbb{E}^∞\left( \left[ \sum_{k=1}^{K} \Phi_{k,m} T_i^k \right] \left[ \sum_{\ell=1}^{K} \Phi_{\ell,n} T_r^\ell \right] |D \right) \]

\[ = \mathbb{E}^∞\left( \sum_{k=1}^{K} \Phi_{k,m} T_i^k T_r^k + \sum_{k=1}^{K} \sum_{k \neq \ell, \ell=1}^{K} \Phi_{k,m} \Phi_{\ell,n} T_i^k T_r^\ell |D \right) \]

\[ = \sum_{k=1}^{K} \delta_m(n) \hat{\Phi}_{k,n} T_i^k T_r^k + \sum_{k=1}^{K} \Phi_{k,m} T_i^k \left( \sum_{\ell=1}^{K} \Phi_{\ell,n} T_r^\ell - \hat{\Phi}_{k,n} T_r^k \right) \]

leading to the claimed third statement after rearranging the terms. The assertion of the last three statements follow similarly to the first three.

A.2 Proof of Proposition 2

Elements of the intensity matrix $I(\phi_{j,n}, \phi_{i,m})$

Following the first statement of Lemma A1 to obtain the elements $I(\phi_{j,n}, \phi_{i,m})$ of $I(\hat{\phi})$, we compute the first and second order derivatives of log $L_c(\phi)$:

\[ \mathbb{E}^∞\left( \frac{\partial^2 \log L_c(\phi)}{\partial \phi_{j,n} \partial \phi_{i,m}} |D \right) \bigg|_{\hat{\theta}} = -\frac{\delta_m(n)\delta_i(j)}{\hat{\phi}_{j,n}^2} \mathbb{E}^∞(B_{j,n}|D) \bigg|_{\hat{\theta}} \]

\[ = -\frac{\delta_m(n)\delta_i(j)}{\hat{\phi}_{j,n}^2} \hat{B}_{j,n}. \tag{1} \]

Since $B_j = \sum_{k=1}^{K} B_j^k \in D, j \in S$, we have $\mathbb{E}^∞(B_j B_i|D) = B_j B_i$. Thus,

\[ \mathbb{E}^∞\left( \frac{\partial \log L_c(\phi)}{\partial \phi_{j,n}} \left[ \frac{\partial \log L_c(\phi)}{\partial \phi_{i,m}} |D \right) \bigg|_{\hat{\theta}} \right. \]
where in the last equality we used \( \hat{\phi}_{j,n} = \frac{\hat{B}_{j,n}}{B_j} \) and the first statement in Lemma A1. Combining (1) with (2) gives the claimed result:

\[
I(\phi_{j,n}, \phi_{t,m}) = \frac{\delta_{ij}(j)}{\phi_{j,n} \phi_{t,m}} \sum_{k=1}^{K} \Phi_{k,n} \delta_{k,j}(\delta_{m}(n) - \Phi_{k,m}).
\]

**Elements of the intensity matrix** \( I(\hat{q}_{rv,n}, \hat{q}_{ij,m}) \)

**Proof.** Since the first order partial derivative of the log-likelihood \( \log L_c(q) \) w.r.t the parameter \( q_{ij,m} \) is given by

\[
\frac{\partial \log L_c(q)}{\partial q_{rv,n}} = \frac{N_{rv,n,T_v,n} - T_v,n}{q_{rv,n}},
\]

we have

\[
\mathbb{E}^{\infty}\left( \frac{\partial^2 \log L_c(q)}{\partial q_{rv,n} \partial q_{ij,m}} \right) = 0.
\]

Furthermore, on account that \( A_{rv,n} := N_{rv,n} - q_{rv,n}T_v,n \) for \((r,v) \in S, 1 \leq n \leq M\), and that \( \tilde{A}_{rv,n} := \mathbb{E}^{\infty}(A_{rv,n}|D)\hat{\theta} = 0 \) the fifth statement of Lemma A1 yields

\[
\mathbb{E}^{\infty}\left( \left[ \frac{\partial L_c(q)}{\partial q_{rv,n}} \right] \left[ \frac{\partial L_c(q)}{\partial q_{ij,m}} \right] \right) \bigg|_{\hat{\theta}}
= \frac{1}{q_{rv,n} \hat{q}_{ij,m}} \mathbb{E}^{\infty}\left( [N_{rv,n} - q_{rv,n}T_v,n][N_{ij,m} - q_{ij,m}T_j,m]\right) \bigg|_{\hat{\theta}}
= \frac{1}{q_{rv,n} \hat{q}_{ij,m}} \mathbb{E}^{\infty}(A_{rv,n}A_{ij,m}|D)\bigg|_{\hat{\theta}}
= \frac{1}{q_{rv,n} \hat{q}_{ij,m}} \sum_{k=1}^{K} \Phi_{k,n} A_{rv,n} \Phi_{k,m}(\delta_{m}(n) - \Phi_{k,m})
\]

from which the elements of information matrix \( I(\hat{q}_{rv,n}, \hat{q}_{ij,m}) \) is obtained.

Moreover, for the diagonal element \( I(q_{ij,m}) := I(q_{ij,m}, q_{ij,m}) \),

\[
\mathbb{E}^{\infty}\left( \frac{\partial^2 \log L_c(q)}{\partial q_{ij,m}^2} \right) \bigg|_{\hat{\theta}} = -\frac{1}{\hat{q}_{ij,m}^2} \mathbb{E}^{\infty}(N_{ij,m}|D)\bigg|_{\hat{\theta}} = -\frac{\hat{N}_{ij,m}}{\hat{q}_{ij,m}},
\]

leading to the diagonal element \( I(q_{ij,m}) \) on account of (3).
Elements of the intensity matrix $I(\hat{\phi}_{i,m}, \hat{q}_{r,j,n})$

**Proof.** It is straightforward to check that $\frac{\partial \log L_c(\theta)}{\partial \phi_{i,m} \partial q_{r,j,n}} = 0$ which in turn yields

$$\mathbb{E}^\infty \left( \frac{\partial \log L_c(\theta)}{\partial \phi_{i,m} \partial q_{r,j,n}} | D \right) |_{\hat{\theta}} = 0.$$

Furthermore, on recalling that $B_i \in S$ and that $\mathbb{E}^\infty (A_{r,j,n}|D) |_{\hat{\theta}} = 0$,

$$\mathbb{E}^\infty \left( \left[ \frac{\partial \log L_c(\theta)}{\partial \phi_{i,m}} \right] \left[ \frac{\partial \log L_c(\theta)}{\partial q_{r,j,n}} \right] | D \right) |_{\hat{\theta}} = \frac{1}{\phi_{i,m} \hat{q}_{r,j,n}} \mathbb{E}^\infty \left( \left[ B_i - \phi_{i,m} B_i \right] \left[ N_{r,j,n} - q_{r,j,n} T_{r,n} \right] | D \right) |_{\hat{\theta}}$$

$$= \frac{1}{\phi_{i,m} \hat{q}_{r,j,n}} \mathbb{E}^\infty \left( B_i - \phi_{i,m} B_i | D \right) |_{\hat{\theta}}$$

$$= \frac{1}{\phi_{i,m} \hat{q}_{r,j,n}} \left( \mathbb{E}^\infty (B_i A_{r,j,n}|D) |_{\hat{\theta}} - \phi_{i,m} B_i \mathbb{E}^\infty (A_{r,j,n}|D) |_{\hat{\theta}} \right)$$

$$= \frac{1}{\phi_{i,m} \hat{q}_{r,j,n}} \sum_{k=1}^{K} \hat{\Phi}_{k,n} A_{r,j,n} B_i^k (\delta_m(n) - \hat{\Phi}_{k,m}),$$

where we have used the last statement of Lemma A1 in the last equality. This completes the assertion of the element $I(\phi_{i,m}, q_{r,j,n})$ of the matrix $I(\hat{\theta})$. \[\blacksquare\]

**B Proof of Proposition 4**

By concavity of the logarithmic function, it follows by Jensen’s inequality,

$$L_c(\theta) - L_c(\theta_0) = \mathbb{E}_{\theta_0} \left( \log \left[ \frac{L_c^k(\theta)}{L_c^k(\theta_0)} \right] \right) \leq \log \mathbb{E}_{\theta_0} \left( \frac{L_c^k(\theta)}{L_c^k(\theta_0)} \right) = 0,$$

where the last equality holds since $\frac{L_c^k(\theta)}{L_c^k(\theta_0)}$ is the Radon–Nikodym derivative associated with changing the underlying probability measure from $P_{\theta_0}$ to $P_\theta$. As a result, $\mathbb{E}_{\theta_0} \left( \frac{L_c^k(\theta)}{L_c^k(\theta_0)} \right) = 1$. It is clear that the equality $L_c(\theta) = L_c(\theta_0)$ holds if $\mathbb{P}_{\theta_0} \{ L_c^k(\theta) = L_c^k(\theta_0) \} = 1$. Furthermore, to show uniqueness of solution to the equation $0 = \frac{\partial}{\partial \theta} L_c(\theta)$, recall following the regularity condition (10) that

$$0 = \frac{\partial}{\partial \theta} L_c(\theta) = \mathbb{E}_{\theta_0} \left( \frac{\partial}{\partial \theta} \log L_c^k(\theta) \right).$$

For $\phi_{i,m}$, we have following the decomposition of the loglikelihood that

$$0 = \frac{\partial}{\partial \phi_{i,m}} L_c(\theta) = \frac{\mathbb{E}_{\theta_0}(B_{i,m})}{\phi_{i,m}} - \mathbb{E}_{\theta_0}(B_i),$$
from which we obtain $\phi_{i,m} = \mathbb{E}_{\theta_0}(B_{i,m})/\mathbb{E}_{\theta_0}(B_i) = \phi_{i,m}^0$. The last equality follows as $\mathbb{E}_{\theta_0}(B_{i,m}) = K \mathbb{E}_{\theta_0}(\Phi_{k,m}B_k^i) = K \pi_i \phi_{i,m}^0$ and $\mathbb{E}_{\theta_0}(B_i) = K \mathbb{E}_{\theta_0}(B_k^i) = K \pi_i$. Similarly, for the derivative w.r.t $q_{ij,m}$, we have

$$0 = \frac{\partial}{\partial q_{ij,m}} L_c(\theta) = \frac{\mathbb{E}_{\theta_0}(N_{ij,m})}{q_{ij,m}} - \mathbb{E}_{\theta_0}(T_{i,m}).$$

The proof is complete once we show that the following result holds.

**Lemma B2.** For $i \in E$, $j \in S$, and $1 \leq m \leq M$, we have for a fixed $T > 0$,

$$\mathbb{E}_{\theta}(\Phi_{k,m}N_{ij}^k) = q_{ij,m} \int_0^T \pi^\top D_m e^{Q_m u} e_i du,$$

$$\mathbb{E}_{\theta}(\Phi_{k,m}T_{i,m}^k) = \int_0^T \pi^\top D_m e^{Q_m u} e_i du,$$

while for $T$ being the absorption time of $X$,

$$\mathbb{E}_{\theta}(\Phi_{k,m}N_{ij}^k) = q_{ij,m} \int_0^\infty \pi^\top D_m e^{Q_m u} e_i du,$$

$$\mathbb{E}_{\theta}(\Phi_{k,m}T_{i,m}^k) = \int_0^\infty \pi^\top D_m e^{Q_m u} e_i du.$$

**For a fixed time $T > 0$**

**Proof.** The proofs are based on adapting similar arguments to the proof of Theorem 5.1 in Albert (1962) by dividing the interval $[0, T]$ into $n$ equal parts of length $h = T/n$. Then, by dominated convergence theorem,

$$\mathbb{E}_{\theta}(\Phi_{k,m}N_{ij}^k) = \mathbb{E}_{\theta}\left( \sum_{\ell=0}^{\infty} 1_{\{\Phi_{k,m}=1, X_{\ell h}^k=i, X_{(\ell+1)h}^k=j, (\ell+1)h \leq T\}} \right)$$

$$= \sum_{\ell=0}^{n-1} \sum_{v \in S} \mathbb{P}_{\theta}\{X_{\ell h}^k = i, X_{(\ell+1)h}^k = j, \Phi_{k,m} = 1, X_0^k = v\}$$

$$= \sum_{\ell=0}^{n-1} \sum_{v \in S} \mathbb{P}_{\theta}\{X_{\ell h}^k = v\} \mathbb{P}_{\theta}\{\Phi_{k,m} = 1|X_0^k = v\}$$

$$\times \mathbb{P}_{\theta}\{X_{(\ell+1)h}^k = i|\Phi_{k,m} = 1, X_0^k = v\}$$

$$\times \mathbb{P}_{\theta}\{X_{(\ell+1)h}^k = j|\Phi_{k,m} = 1, X_0^k = i, X_{\ell h}^k = v\}$$

$$= \sum_{\ell=0}^{n-1} \sum_{v \in S} \pi_v \phi_{v,m} e_v e_{Q_m \ell h} e_i q_{ij,m} h$$

$$= \sum_{\ell=0}^{n-1} \pi^\top D_m e^{Q_m \ell h} e_i q_{ij,m} h \rightarrow q_{ij,m} \int_0^T \pi^\top D_m e^{Q_m u} e_i du.$$
For the second statement, let $Y^k_i(u) = 1_{\{X^k_u = i\}}$. Then by Fubini’s theorem,

\[
\mathbb{E}_\theta(\Phi_{k,m}^T) = \mathbb{E}_\theta\left( \int_0^T \Phi_{k,m}Y^k_i(u)du \right) \\
= \int_0^T \mathbb{P}_\theta\{X^k_u = i, \Phi_{k,m} = 1\}du \\
= \int_0^T \sum_{v \in S} \mathbb{P}_\theta\{X^k_u = i, X^k_0 = v\} \mathbb{P}_\theta\{\Phi_{k,m} = 1|X^k_0 = v\} \\
= \int_0^T \sum_{v \in S} \pi_{v}\phi_{v,m}e^\top_v eQ^m u e_i du \\
= \int_0^T \pi^\top D_m eQ^m u e_i du,
\]

which completes the proof of the claim for fixed $T > 0$. ■

For an absorption time $T$

**Proof.** Since $T$ is the absorption time of $X$, there are no $i \rightarrow j$ transitions from state $i \in E$ to $j \in S$ after $T$. Therefore, for a given $h > 0$, we have

\[
\mathbb{E}_\theta(\Phi_{k,m}N^k_{ij}) = \mathbb{E}_\theta\left( \sum_{\ell=0}^{\lfloor T/h \rfloor - 1} \Phi_{k,m}X^k_\ell(i,j) \right) \\
= \mathbb{E}_\theta\left( \sum_{\ell=0}^{\lfloor T/h \rfloor - 1} \Phi_{k,m}X^k_\ell(i,j) \right) + \mathbb{E}_\theta\left( \sum_{\ell=\lfloor T/h \rfloor}^\infty \Phi_{k,m}X^k_\ell(i,j) \right) \\
= \mathbb{E}_\theta\left( \sum_{\ell=0}^\infty \Phi_{k,m}X^k_\ell(i,j) \right) \\
= \sum_{\ell=0}^\infty \mathbb{P}_\theta\{\Phi_{k,m} = 1, X^k_\ell = i, X^k_{\ell+1} = j\} \\
= \sum_{\ell=0}^\infty \sum_{v \in S} \mathbb{P}_\theta\{X^k_0 = v, \Phi_{k,m} = 1, X^k_\ell = i, X^k_{\ell+1} = j\} \\
= \sum_{\ell=0}^\infty \sum_{v \in S} \mathbb{P}_\theta\{X^k_0 = v\} \mathbb{P}_\theta\{\Phi_{k,m} = 1|X^k_0 = v\} \\
\times \mathbb{P}_\theta\{X^k_{\ell} = i|\Phi_{k,m} = 1, X^k_0 = v\} \\
\times \mathbb{P}_\theta\{X^k_{\ell+1} = j|\Phi_{k,m} = 1, X^k_\ell = i, X^k_0 = v\}
\]
\[
= \sum_{\ell=0}^{\infty} \sum_{v \in S} \pi_v \phi_{v,m} e_v^\top e Q_{m} h e_i q_{ij,m} h
\]
\[
= q_{ij,m} \sum_{\ell=0}^{\infty} \pi^\top D_m e Q_{m} h e_i h \to 0 \int_0^{\infty} \pi^\top D_m e Q_{m} u e_i du,
\]
which in turn establishes the assertion of the first statement. ■

Proof. To prove the second statement, recall that since \( T \) is the absorption time, there is zero total occupation time of \( X \) in state \( i \in E \) after \( T \). Thus,

\[
\mathbb{E}_\theta (\Phi_{k,m}^{T_k}) = \mathbb{E}_\theta \left( \int_0^T 1\{\Phi_{k,m}^{T_k}=1, X_k^0=i\} du \right)
\]
\[
= \mathbb{E}_\theta \left( \int_0^T 1\{\Phi_{k,m}^{T_k}=1, X_k^0=i\} du + \int_T^{\infty} 1\{\Phi_{k,m}^{T_k}=1, X_k^0=i\} du \right)
\]
\[
= \mathbb{E}_\theta \left( \int_0^{\infty} 1\{\Phi_{k,m}^{T_k}=1, X_k^0=i\} du \right)
\]
\[
= \int_0^{\infty} \mathbb{P}_\theta (\Phi_{k,m} = 1, X_k^0 = i) du
\]
\[
= \int_0^{\infty} \sum_{v \in S} \mathbb{P}_\theta (X_k^0 = v, \Phi_{k,m} = 1, X_k^0 = i) du
\]
\[
= \int_0^{\infty} \sum_{v \in S} \mathbb{P}_\theta (X_k^0 = v) \mathbb{P}_\theta (\Phi_{k,m} = 1 | X_k^0 = v)
\]
\[
\times \mathbb{P}_\theta (X_k^0 = i | \Phi_{k,m} = 1, X_k^0 = v) du
\]
\[
= \int_0^{\infty} \pi^\top D_m e Q_{m} u e_i du,
\]
which in turn establishes the second claim for absorption time. ■

C Proof of Theorem 1

C.1 Proof of consistency

It is important to note that due to the presence of the term \( \hat{\Phi}_{k,m} = \mathbb{E}_{\hat{\theta}_0} (\Phi_{k,m} | X^k) \) in the estimator \( \hat{\theta}_0 \), one can not directly use the law of large number and the results of Lemma B2 to prove the consistency of \( \hat{\theta}_0 \). To be more precise, let us consider the estimator \( \hat{q}_{ij,m} = \frac{\sum_{k=1}^{K} \hat{\Phi}_{k,m} N_{ij}^k}{\sum_{k=1}^{K} \hat{\Phi}_{k,m} T_i^k} \) of \( q_{ij,m} \). By independence of all \( K \) realizations \( \{X^k\} \), which were generated under the probability measure \( \mathbb{P}_{\theta_0} \), \( \hat{q}_{ij,m} \) converges as \( K \to \infty \) to \( \frac{\mathbb{E}_{\theta_0} (\hat{q}_{ij,m} | X^k)}{\mathbb{E}_{\theta_0} (\hat{q}_{ij,m} | T_i^k)} \).

The law of iterated expectation does not simplify the latter into \( \frac{\mathbb{E}_{\theta_0} (\Phi_{k,m} N_{ij}^k | X^k)}{\mathbb{E}_{\theta_0} (\Phi_{k,m} T_i^k | X^k)} \), which by Lemma B2 is equal to \( a_{ij,m}^0 \), unless \( \hat{\theta}_0 \) converges to \( \theta_0 \). It works for the Markov process, see Albert (1962). For the mixture process, we propose a slightly different approach.
Proof. On account that the mle $\hat{\theta}$ solves the equation $\frac{\partial}{\partial \theta} \mathcal{L}_c^K(\theta) = 0$ for all $K \geq 1$, i.e., $\frac{\partial}{\partial \theta} \mathcal{L}_c^K(\hat{\theta}) = 0$, the consistency of $\hat{\theta}$ goes as follows. Given that $\theta_0$ is the maximizer of the function $\mathcal{L}_c(\theta)$ satisfying the equation $\frac{\partial}{\partial \theta} \mathcal{L}_c(\theta) = 0$, the consistency of $\hat{\theta}$ follows from independence of all $K$ realizations $\{X^k\}$ since by the law of large number, $\mathcal{L}_c^K(\theta) \xrightarrow{P} \mathcal{L}_c(\theta)$ for any $\theta \in \Theta$ as $K \to \infty$. From the latter we deduce that as the two functions $\mathcal{L}_c^K(\theta)$ and $\mathcal{L}_c(\theta)$ are getting closer with probability increasing to one as $K \to \infty$ and by Proposition 4 the equation $\frac{\partial}{\partial \theta} \mathcal{L}_c^K(\theta) = 0$ has the unique solution $\theta = \theta_0$, the maximum points of the two functions must also get closer which implies that $\hat{\theta}$ converges to $\theta_0$ as $K \to \infty$. ■

C.2 Proof of asymptotic normality

Proof. If the EM estimator $\hat{\theta}$ converges to the true value $\theta$, it follows from Chernoff (1956) and Cramer (1946) p. 254 that for each $(i, j) \in S$ and $1 \leq m \leq M$ the random variable $\tilde{N}_{ij,m}/K - N_{ij,m}/K$, which is equal to $\frac{1}{K} \sum_{k=1}^{K} (\hat{\Phi}_{k,m} N_{ij}^k - \frac{1}{K} \sum_{k=1}^{K} \Phi_{k,m} N_{ij}^k)$, converges to zero in probability as $K \to \infty$. Indeed, by independence of $\{X^k\}$, it follows by the above references, $\frac{1}{K} \sum_{k=1}^{K} \mathbb{E}_\theta(\Phi_{k,m} X^k) N_{ij}^k = \frac{1}{K} \sum_{k=1}^{K} \mathbb{E}_\theta(\Phi_{k,m} N_{ij}^k X^k) \xrightarrow{P} \mathbb{E}_\theta(\Phi_{k,m} N_{ij}^k)$ which is the same convergence as $\frac{1}{K} \sum_{k=1}^{K} \Phi_{k,m} N_{ij}^k$. This would imply that $\tilde{N}_{ij,m}/K$ and $N_{ij,m}/K$ have the same distributional convergence. See van der Vaart (2000), Ch. 2 on stochastic convergence of random variables. Similarly, the same reasoning applies to $T_{i,m}/K - T_{i,m}/K$ and $B_{i,m}/K - B_{i,m}/K$ as $\theta \to \theta$, it follows from the statement above that

$$\sqrt{K}(\tilde{q}_{ij,m} - q_{ij,m}) = \frac{\sqrt{K}}{T_{i,m}/K} \left( \tilde{N}_{ij,m}/K - q_{ij,m} \tilde{T}_{i,m}/K \right)$$

has the same asymptotic distribution as the random variable

$$\frac{\sqrt{K}}{\mathbb{E}_\theta(\Phi_{k,m} T_{i,m}^k)} \left( N_{ij,m}/K - q_{ij,m} T_{i,m}/K \right).$$

By the multivariate central limit theorem, the above has asymptotic multivariate normal distribution with mean zero and the covariance matrix

$$\mathbb{E}_\theta \left( (\Phi_{k,n} N_{ij}^k - q_{ij,m} \Phi_{k,n} T_{i,m}^k) (\Phi_{k,m} N_{ij}^k - q_{ij,m} \Phi_{k,m} T_{i,m}^k) \right) \mathbb{E}_\theta(\Phi_{k,n} T_{i,m}^k) \mathbb{E}_\theta(\Phi_{k,m} T_{i,m}^k).$$

Notice that we have used the fact that $\mathbb{E}_\theta \left( \Phi_{k,n} N_{ij}^k - q_{ij,m} \Phi_{k,n} T_{i,m}^k \right) = 0$. See Lemma [B2] By applying Proposition [C1] (see Section [C.3] below) we have

$$\mathbb{E}_\theta \left( (\Phi_{k,n} N_{ij}^k - q_{ij,m} \Phi_{k,n} T_{i,m}^k) (\Phi_{k,m} N_{ij}^k - q_{ij,m} \Phi_{k,m} T_{i,m}^k) \right)$$

$$= \delta_m(n) \mathbb{E}_\theta(\Phi_{k,n} N_{ij}^k \Phi_{k,m} N_{ij}^k) - \delta_m(n) q_{ij,m} \mathbb{E}_\theta(\Phi_{k,n} N_{ij}^k T_{i,m}^k)$$

$$+ \delta_m(n) q_{ij,m} \mathbb{E}_\theta(\Phi_{k,n} N_{ij}^k T_{i,m}^k) + q_{ij,m} q_{ij,m} \delta_m(n) \mathbb{E}_\theta(\Phi_{k,n} T_{i,m}^k T_{i,m}^k)$$

$$= \delta_m(n) \delta_i(i') \delta_j(j') q_{ij,m} \int_0^T \mathbf{1}^T D_n e^{Q_n u} e_j du.$$
which establishes the assertion of $\text{Cov}(\hat{q}_{i',j',n} - q_{i',j',n}, \hat{q}_{ij,m} - q_{ij,m})$ given that

$$\mathbb{E}_\theta(\Phi_{k,n}T_i^k) = \int_0^T \pi^\top D_n e^{Q_m u} e_i du.$$

By similar arguments, one can show subsequently using Proposition C1.

$$\text{Cov}(\hat{\phi}_{i',n} - \phi_{i',n}, \hat{q}_{ij,m} - q_{ij,m}) = \frac{\mathbb{E}_\theta((\Phi_{k,n}B_{i'}^k - \phi_{i',n}B_{i'}^k)(\Phi_{k,m}N_{ij}^k - q_{ij,m}\Phi_{k,m}T_i^k))}{\mathbb{E}_\theta(B_{i'}^k)\mathbb{E}_\theta(\Phi_{k,m}T_i^k)} = 0,$$

and

$$\text{Cov}(\hat{\phi}_{i',n} - \phi_{i',n}, \hat{\phi}_{i,m} - \phi_{i,m}) = \frac{\mathbb{E}_\theta((\Phi_{k,n}B_{i'}^k - \phi_{i',n}B_{i'}^k)((\Phi_{k,m}B_{i'}^k - \phi_{i,m}B_{i'}^k))}{\mathbb{E}_\theta(B_{i'}^k)\mathbb{E}_\theta(B_{k}^k)} = \frac{\phi_{i',n}}{\pi_i} \delta_i(i')(\delta_m(n) - \phi_{i,m}),$$

which complete the proof of the theorem. ■

### C.3 Unconditional second moments of $N_{ij,m}$, $T_{i,m}$ and $B_{i,m}$

This part will have a proposition with its proof. It generalizes the results of Theorem 5.1 of Albert (1962) for a mixture of Markov jump processes.

**Proposition C1.** Let $D_m$ be a $(w \times w)$ diagonal matrix with diagonal elements $\phi_{i,m}$, $i \in E$. The unconditional moments of $B_i^k$, $N_{ij}$, and $T_i^k$ are

$$\mathbb{E}_\theta(\Phi_{k,n}B_{i'}^k N_{ij}^k) = q_{ij,m} \pi_{i'} \phi_{i',m} e_i^\top \int_0^T e^{Q_m u} e_i du,$$

$$\mathbb{E}_\theta(\Phi_{k,m}B_{i'}^k T_i^k) = \pi_{i'} \phi_{i',m} e_i^\top \int_0^T e^{Q_m u} e_i du,$$

$$\mathbb{E}_\theta(\Phi_{k,m}N_{ij}^k N_{i'j}^k) = q_{ij,m} \delta_i(i') \delta_j(j') \pi^\top D_m \left( \int_0^T e^{Q_m u} du \right) e_i + q_{ij,m} q_{i'j,m} \pi^\top D_m \left[ \int_0^T \int_0^u e^{Q_m t} e_i e_j^\top e^{Q_m(u-t)} e_i du \right],$$

$$\mathbb{E}_\theta(\Phi_{k,m}T_i^k T_{i'}^k) = \pi^\top D_m \left[ \int_0^T \int_0^u e^{Q_m t} e_i e_j^\top e^{Q_m(u-t)} e_i du \right] + \int_0^T \int_0^u e^{Q_m t} e_i e_j^\top e^{Q_m(u-t)} e_i du.$$
\[ E_\theta (\Phi_{k,m} N^k_{ij} T^k_i) = q_{ij,m} \pi^\top D_m \left[ \int_0^T \int_0^u e^{Q_m t} e^\top_{i'} e e^{Q_m (u-t)} e_i dt du \right. \\
\left. + \int_0^T \int_0^u e^{Q_m t} e^\top_{i'} e e^{Q_m (u-t)} e_i dt du \right], \]

where we have denoted by \( e_i = (0, \cdots, 1, \cdots, 0) \) a \((w \times 1)\) unit vector with value one on the \( i\)th element and zero otherwise.

**Proof of the first statement**

**Proof.** The proofs are based on adapting similar arguments to that of Theorem 5.1 in Albert (1962) by dividing the interval \([0,T]\) into \( n \) equal parts of length \( h = T/n \). Then, by dominated convergence theorem, \( N^k_{ij} = \sum_{\ell=0}^{n-1} X^k_\ell (i, j) \) with \( X^k_\ell (i, j) = I(X^k_\ell h = i, X^k_{(\ell+1)h} = j), (i, j) \in S \). Thus,

\[ E_\theta (\Phi_{k,m} B^k_i N^k_{ij}) = E_\theta \left( \sum_{\ell=0}^{n-1} \Phi_{k,m} B^k_i X^k_\ell (i, j) \right) \]

\[ = \sum_{\ell=0}^{n-1} \mathbb{P}_\theta (X^k_\ell h = i, X^k_{(\ell+1)h} = j, X^k_0 = i', \Phi_{k,m} = 1) \]

\[ = \sum_{\ell=0}^{n-1} \mathbb{P}_\theta (X^k_\ell = i') \mathbb{P}_\theta (\Phi_{k,m} = 1 | X^k_0 = i') \mathbb{P}_\theta (X^k_\ell h = i | \Phi_{k,m} = 1, X^k_0 = i') \]

\[ \times \mathbb{P}_\theta (X^k_{(\ell+1)h} = j | \Phi_{k,m} = 1, X^k_\ell h = i, X^k_0 = i') \]

\[ = \sum_{\ell=0}^{n-1} \pi_{i'i'} e^\top_{i'} e^{Q_m \ell h} e_i q_{ij,n} h, \]

which converges by dominated convergence to the one claimed. ■

**Proof of the second statement**

**Proof.** By Fubini’s theorem, Bayes’ formula, and Markov property of \( X_m \),

\[ E_\theta (\Phi_{k,m} B^k_i T^k_i) = E_\theta (\Phi_{k,m} B^k_i \int_0^T 1_{(X^k_u = i)} du) \]

\[ = \int_0^T \mathbb{P}_\theta (X^k_u = i, X^k_0 = i', \Phi_{k,m} = 1) du \]

\[ = \int_0^T \mathbb{P}_\theta (X^k_0 = i') \mathbb{P}_\theta (\Phi_{k,m} = 1 | X^k_0 = i') \mathbb{P}_\theta (X^k_u = i | \Phi_{k,m} = 1, X^k_0 = i') du, \]

which indeed gives the second statement. ■
Proof of the third statement

Proof. Using representation $N^k_{ij} = \sum_{\ell=0}^{n-1} X^k_\ell(i, j)$, one can write

$$
\Phi_{k,m}N^k_{ij}N^k_{i'j'} = \sum_{\ell=0}^{n-1} \Phi_{k,m}X^k_\ell(i, j)X^k_\ell(i', j') + \sum_{\ell=1}^{n-1} \sum_{r<\ell} \Phi_{k,m}X^k_\ell(i, j)X^k_r(i', j') + \sum_{\ell=0}^{n-2} \sum_{r>\ell} \Phi_{k,m}X^k_\ell(i, j)X^k_r(i', j')
$$

$$
= \sum_{\ell=0}^{n-1} \Phi_{k,m}X^k_\ell(i, j)X^k_\ell(i', j') + \sum_{\ell=1}^{n-1} \sum_{r=0}^{\ell-1} \Phi_{k,m}X^k_\ell(i, j)X^k_r(i', j') + \sum_{r=1}^{n-1} \sum_{\ell=0}^{r-1} \Phi_{k,m}X^k_\ell(i, j)X^k_r(i', j').
$$

Therefore,

$$
\mathbb{E}_\theta(\Phi_{k,m}N^k_{ij}N^k_{i'j'}) = \mathbb{E}_\theta\left(\sum_{\ell=0}^{n-1} \Phi_{k,m}X^k_\ell(i, j)X^k_\ell(i', j')\right) + \mathbb{E}_\theta\left(\sum_{\ell=1}^{n-1} \sum_{r=0}^{\ell-1} \Phi_{k,m}X^k_\ell(i, j)X^k_r(i', j')\right) + \mathbb{E}_\theta\left(\sum_{r=1}^{n-1} \sum_{\ell=0}^{r-1} \Phi_{k,m}X^k_\ell(i, j)X^k_r(i', j')\right).
$$

Since an initial state is chosen randomly at probability $\pi$, the first expectation can be worked out using Bayes' formula and the law of total probability,

$$
\mathbb{E}_\theta\left(\sum_{\ell=0}^{n-1} \Phi_{k,m}X^k_\ell(i, j)X^k_\ell(i', j')\right) = \sum_{\ell=0}^{n-1} \mathbb{E}_\theta\left(\Phi_{k,m}X^k_\ell(i, j)X^k_\ell(i', j')\right)
$$

$$
= \sum_{\ell=0}^{n-1} \mathbb{P}_\theta\{X^k_\ell = i, X^k_{\ell+1} = j, X^k_{\ell+1} = i', \Phi_{k,m} = 1\}
$$

$$
= \delta_i(i')\delta_j(j') \sum_{\ell=0}^{n-1} \mathbb{P}_\theta\{X^k_\ell = i', X^k_{\ell+1} = j', \Phi_{k,m} = 1\}
$$

$$
= \delta_i(i')\delta_j(j') \sum_{\ell=0}^{n-1} \mathbb{P}_\theta\{X^k_\ell = i', X^k_{\ell+1} = j', \Phi_{k,m} = 1, X^k_0 = v\}
$$

$$
= \delta_i(i')\delta_j(j') \sum_{\ell=0}^{n-1} \sum_{v\in S} \mathbb{P}_\theta\{X^k_\ell = i', X^k_{\ell+1} = j', \Phi_{k,m} = 1, X^k_0 = v\}
$$

$$
	imes \mathbb{P}_\theta\{X^k_{\ell+1} = i'|\Phi_{k,m} = 1, X^k_0 = v\}
$$

$$
	imes \mathbb{P}_\theta\{X^k_{\ell+1} = j'|\Phi_{k,m} = 1, X^k_{\ell+1} = i', X^k_0 = v\}
$$

$$
= \delta_i(i')\delta_j(j') \sum_{\ell=0}^{n-1} \sum_{v\in S} \pi_v \phi_{v,m} e_v^T e_{Q_{m\ell} h} e_{v_q} q_{i'j',m} h
$$
\[ q_{i'i',m} \delta_i(i') \delta_j(j') \sum_{\ell=0}^{n-1} \pi^\top D_m e^{Q_m \ell h} e_{i'} h, \]

which by dominated convergence theorem the last sum converges:

\[ q_{i'i',m} \delta_i(i') \delta_j(j') \sum_{\ell=0}^{n-1} \pi^\top D_m e^{Q_m \ell h} e_{i'} h \xrightarrow{h \to 0} q_{i'i',m} \delta_i(i') \delta_j(j') \int_0^T \pi^\top D_m e^{Q_m u} e_{i'} du. \]

The second sum in (4) can be worked out as follows.

\[
\mathbb{E}_\theta \left( \sum_{\ell=1}^{n-1} \sum_{r=0}^{\ell-1} \Phi_{k,m} X_i^k(i,j) X_j^k(i',j') \right) = \sum_{\ell=1}^{n-1} \sum_{r=0}^{\ell-1} \mathbb{E}_\theta \left( \Phi_{k,m} X_i^k(i,j) X_j^k(i',j') \right)
\]

\[
= \sum_{\ell=1}^{n-1} \sum_{r=0}^{\ell-1} \mathbb{P}_\theta \{ X_i^k = i, X_j^k = j, X_r^k = i', X_{(r+1)}^k = j', \Phi_{k,m} = 1 \}
\]

\[
= \sum_{\ell=1}^{n-1} \sum_{r=0}^{\ell-1} \mathbb{P}_\theta \{ X_i^k = i, X_j^k = j, X_r^k = i', X_{(r+1)}^k = j', \Phi_{k,m} = 1 \}
\]

\[
= \sum_{\ell=1}^{n-1} \sum_{r=0}^{\ell-1} \mathbb{P}_\theta \{ X_i^k = i, X_j^k = j, X_r^k = i', X_{(r+1)}^k = j', \Phi_{k,m} = 1 \}
\]

\[
= \sum_{\ell=1}^{n-1} \sum_{r=0}^{\ell-1} \mathbb{P}_\theta \{ X_i^k = i, X_j^k = j, X_r^k = i', X_{(r+1)}^k = j', \Phi_{k,m} = 1 \}
\]

\[
= \sum_{\ell=1}^{n-1} \sum_{r=0}^{\ell-1} \sum_{v \in S} \pi_{\ell,v} \phi_{v,m} e_{i} e_{Q_m \ell h} e_{i'} e_{Q_m (h-(r+1))} e_{i'} q_{ij,m} h
\]

\[
= q_{ij,m} q_{i'i',m} \sum_{\ell=1}^{n-1} \sum_{r=0}^{\ell-1} \pi^\top D_m e^{Q_m \ell h} e_{i'} e_{Q_m (h-(r+1))} e_{i'} h
\]

which by dominated convergence theorem the last sum converges:

\[
q_{ij,m} q_{i'i',m} \sum_{\ell=1}^{n-1} \sum_{r=0}^{\ell-1} \pi^\top D_m e^{Q_m \ell h} e_{i'} e_{Q_m (h-(r+1))} e_{i'} h \xrightarrow{h \to 0} q_{ij,m} q_{i'i',m} \int_0^T \int_0^u \pi^\top D_m e^{Q_m t} e_{i'} e_{Q_m (u-t)} e_{i'} dt du.
\]

Similarly, following the same arguments, one can show that the third sum in (4)

\[
\mathbb{E}_\theta \left( \sum_{\ell=0}^{n-1} \sum_{r=1}^{\ell-1} \Phi_{k,m} X_i^k(i,j) X_j^k(i',j') \right)
\]

\[
= q_{ij,m} q_{i'i',m} \sum_{\ell=0}^{n-1} \sum_{r=1}^{\ell-1} \pi^\top D_m e^{Q_m \ell h} e_{i'} e_{Q_m (h-(r+1))} e_{i'} h \xrightarrow{h \to 0} q_{ij,m} q_{i'i',m} \int_0^T \int_0^u \pi^\top D_m e^{Q_m t} e_{i'} e_{Q_m (u-t)} e_{i'} dt du.
\]

Putting the three limiting integrals together yields the third statement.
Proof of the fourth statement

Proof. Applying Fubini’s theorem we get
\[
E_\theta(\Phi_{k,m}^{T_k}T_i^{kT_i}) = \int_0^T \int_0^T \mathbb{P}_\theta\{X_t^k = i, X_u^k = i', \Phi_{k,m} = 1\}dtdu
\]
\[
= \int_0^T \int_0^u \mathbb{P}_\theta\{X_t^k = i, X_u^k = i', \Phi_{k,m} = 1\}dtdu
\]
\[
+ \int_0^T \int_u^T \mathbb{P}_\theta\{X_t^k = i, X_u^k = i', \Phi_{k,m} = 1\}dtdu.
\]
The first double integral can be worked out as follows
\[
\int_0^T \int_0^u \mathbb{P}_\theta\{X_t^k = i, X_u^k = i', \Phi_{k,m} = 1\}dtdu
\]
\[
= \int_0^T \int_0^u \sum_{v \in \mathcal{S}} \mathbb{P}_\theta\{X_0^k = v\} \mathbb{P}_\theta\{\Phi_{k,m} = 1|X_0^k = v\} \mathbb{P}_\theta\{X_t^k = i|\Phi_{k,m} = 1, X_0^k = v\} \mathbb{P}_\theta\{X_u^k = i'|\Phi_{k,m} = 1, X_0^k = v\}dtdu
\]
\[
= \int_0^T \int_0^u \sum_{v \in \mathcal{S}} \pi_v e_i^\top e_Q e_i^\top e_Q(u-t)e_{i'}dtdu
\]
By the same lines of arguments, we get
\[
\int_0^T \int_u^T \mathbb{P}_\theta\{X_t^k = i, X_u^k = i', \Phi_{k,m} = 1\}dtdu
\]
\[
= \int_0^T \int_u^T \pi_i^\top D_me_i^\top e_Q e_i^\top e_Q(u-t)e_{i'}dtdu
\]
where the last integral was due to using change of variable. Thus, the claim on the fourth statement is established. ■

Proof of the fifth statement

Proof. For notational convenience, define for \( j \in \mathcal{S}, u > 0, Y^k_{j}(u) = \mathbf{1}_{\{X_u^k = j\}}. \)
\[
E_\theta(\Phi_{k,m}N^{k}T_i^{kT_i}) = E_\theta\left(\sum_{\ell=0}^{n-1} \int_0^T \Phi_{k,m}Y^k_{\ell}(u)X^k_{\ell}(i,j)du\right)
\]
where the convergence is due to dominated convergence theorem. Furthermore, We evaluate each term in the last equality one by one. For the first term,

\[ \sum_{\ell=0}^{n-1} \int_{0}^{T} \mathbb{P}_{\theta}\{X^k_{\ell+1} = i, X^k_{(\ell+1)h} = j, X^k_u = i', \Phi_{k,m} = 1, X^k_0 = v\} \, du \]

\[ = \sum_{\ell=0}^{n-1} \int_{0}^{T} \sum_{v \in S} \mathbb{P}_{\theta}\{X^k_{\ell+1} = i, X^k_{(\ell+1)h} = j, X^k_u = i', \Phi_{k,m} = 1, X^k_0 = v\} \, du \]

\[ = \sum_{\ell=0}^{n-1} \int_{0}^{(\ell+1)h} \sum_{v \in S} \mathbb{P}_{\theta}\{X^k_{(\ell+1)h} = i, X^k_{(\ell+1)h} = j, X^k_u = i', \Phi_{k,m} = 1, X^k_0 = v\} \, du \]

\[ + \sum_{\ell=0}^{n-1} \int_{(\ell+1)h}^{T} \sum_{v \in S} \mathbb{P}_{\theta}\{X^k_{(\ell+1)h} = i, X^k_{(\ell+1)h} = j, X^k_u = i', \Phi_{k,m} = 1, X^k_0 = v\} \, du \]

We evaluate each term in the last equality one by one. For the first term,

\[ \sum_{\ell=0}^{n-1} \int_{0}^{(\ell+1)h} \sum_{v \in S} \mathbb{P}_{\theta}\{X^k_{(\ell+1)h} = i, X^k_{(\ell+1)h} = j, X^k_u = i', \Phi_{k,m} = 1, X^k_0 = v\} \, du \]

\[ = \sum_{\ell=0}^{n-1} \int_{0}^{(\ell+1)h} \sum_{v \in S} \mathbb{P}_{\theta}\{X^k_0 = v\} \, \mathbb{P}_{\theta}(\Phi_{k,m} = 1|X^k_0 = v) \, \mathbb{P}_{\theta}(X^k_u = i'|\Phi_{k,m} = 1, X^k_0 = v) \]

\[ \times \mathbb{P}_{\theta}(X^k_{(\ell+1)h} = i|\Phi_{k,m} = 1, X^k_u = i', X^k_0 = v) \]

\[ \times \mathbb{P}_{\theta}(X^k_{(\ell+1)h} = j|\Phi_{k,m} = 1, X^k_u = i', X^k_0 = v) \]

\[ = \sum_{\ell=0}^{n-1} \int_{0}^{(\ell+1)h} \sum_{v \in S} \mathbb{P}_{\theta}\{X^k_0 = v\} \, \mathbb{P}_{\theta}(\Phi_{k,m} = 1|X^k_0 = v) \, \mathbb{P}_{\theta}(X^k_u = i'|\Phi_{k,m} = 1, X^k_0 = v) \]

\[ \times \mathbb{P}_{\theta}(X^k_{(\ell+1)h} = i|\Phi_{k,m} = 1, X^k_u = i', X^k_0 = v) \]

\[ \times \mathbb{P}_{\theta}(X^k_{(\ell+1)h} = j|\Phi_{k,m} = 1, X^k_u = i', X^k_0 = v) \]

\[ \overset{h \to 0}{\longrightarrow} q_{ij,m} \int_{0}^{T} \int_{0}^{t} \pi^\top D_m Q_m u e_{ij} e_{ij}^\top e_{ij} Q_m (t-u) e_{ij} q_{ij,m} du dt, \]

where the convergence is due to dominated convergence theorem. Furthermore,
The absorption probabilities

\[ D_{\text{Absorption probabilities for the two-regime g-mixture}} \]

derive the asymptotic distribution based on the same arguments for fixed

similar ideas to those in Lemma B2. Then use the Central Limit Theorem to

results corresponding to those in Proposition C1 for absorption time

The proof for absorption time follows similar arguments by first obtaining the

which in turn establishes the claim for the fifth statement.

The last equality is due to fact that for \( \ell h \leq u < (\ell + 1)h \),

Similarly, \( e_j^T e Q_m((\ell + 1)h - u) e_j \approx q_{j,j'} h \). Thus, the

contribution of the second term in the decomposition of \( \mathbb{E}_\theta(\Phi_{k,m} X_{ij}^k T_{ij}^k) \) is negligible.

Finally, the third term is evaluated as follows.

\[
\sum_{\ell=0}^{n-1} \int_{(\ell+1)h}^{T} \sum_{v \in S} \mathbb{P}_\theta\{X_{\ell,h}^k = i, X_{(\ell+1)h}^k = j, X_u^k = i', \Phi_{k,m} = 1, X_0^k = v\} du
\]

\[
= \sum_{\ell=0}^{n-1} \int_{(\ell+1)h}^{T} \sum_{v \in S} \mathbb{P}_\theta\{X_0^k = v\} \mathbb{P}_\theta\{\Phi_{k,m} = 1 | X_0^k = v\}
\]

\[
\times \mathbb{P}_\theta\{X_{\ell,h}^k = i | \Phi_{k,m} = 1, X_0^k = v\}
\]

\[
\times \mathbb{P}_\theta\{X_{(\ell+1)h}^k = j | \Phi_{k,m} = 1, X_{\ell,h}^k = i, X_0^k = v\}
\]

\[
\times \mathbb{P}_\theta\{X_u^k = i' | \Phi_{k,m} = 1, X_{(\ell+1)h}^k = j, X_{\ell,h}^k = i, X_0^k = v\}
\]

\[
= \sum_{\ell=0}^{n-1} \int_{(\ell+1)h}^{T} \sum_{v \in S} \pi_v \phi_v \mathbb{E}_v (e_j^T e Q_m(t) e_{i'|m} h e_{j'}^T e Q_m(u-(\ell+1)h) e_j) du
\]

\[
= q_{ij,m} \sum_{\ell=0}^{n-1} \int_{(\ell+1)h}^{T} \pi^T D_m e Q_m(t) e_{i'|m} h e_{j'}^T e Q_m(u-(\ell+1)h) e_j du
\]

\[
\xrightarrow{h \rightarrow 0} q_{ij,m} \int_{0}^{T} \int_{0}^{u} \pi^T D_m e Q_m(t) e_{i'|m} h e_{j'}^T e Q_m(u-t) e_j dt du
\]

which in turn establishes the claim for the fifth statement.

The proof for absorption time follows similar arguments by first obtaining the

results corresponding to those in Proposition C1 for absorption time \( T \) using

similar ideas to those in Lemma B2. Then use the Central Limit Theorem to
derive the asymptotic distribution based on the same arguments for fixed \( T \).

D Absorption probabilities for the two-regime g-mixture

The absorption probabilities \( f_{ij,m} = 1, 2 \), from state \( i \in E = \{1, 2\} \) into absorbing states

\( j \in \Delta = \{3, 4\} \), are computed using the transition matrices of the discrete Markov chains
embedded in continuous time Markov chains, see Theorem 11.6 in Ch.11 of Grinstead and
Snell (1997). Such embedded transition matrix of the \( m \)-th discrete-time Markov chain,
denoted by $P_m$, is obtained from the m-th intensity matrix of a continuous-time Markov chain by
\[ p_{ij,m} = \frac{q_{ij,m}}{|q_{ii,m}|}, \quad i \in E, j \in S, j \neq i, \]
where $q_{ij,m}$ is an (i,j)th entry in the intensity matrix $Q_m$. For the purpose of estimating $f_{ij,m}$, $m = 1, 2$, for the g-mixture, we use $\hat{Q}_m$ from Section 6.3 to obtain the estimates $\hat{P}_m$ of $P_m$:
\[
\hat{P}_1 = \frac{1}{2} \begin{pmatrix} 0 & 0.10283 & 0.89717 & 0.00000 \\ 0.87269 & 0 & 0.10155 & 0.02576 \end{pmatrix},
\]
and
\[
\hat{P}_2 = \frac{1}{2} \begin{pmatrix} 0 & 0.12431 & 0.78503 & 0.09066 \\ 0.50746 & 0 & 0.24046 & 0.25208 \end{pmatrix},
\]
where for notational convenience, the last two rows of zero were deleted. We then use $\hat{P}_m$, $m = 1, 2$, to obtain the equations for the estimated absorption probabilities, $\hat{f}_{ij,m}$, for $(i = 1, 2)$ and $(j = 3, 4)$, see Exercise 34 in Ch.11 of Grinstead and Snell (1997).
\[
\hat{f}_{13,m} = \hat{p}_{13,m} + \hat{p}_{12,m}\hat{f}_{23,m},
\]
\[
\hat{f}_{14,m} = \hat{p}_{14,m} + \hat{p}_{12,m}\hat{f}_{24,m},
\]
and
\[
\hat{f}_{23,m} = \hat{p}_{23,m} + \hat{p}_{21,m}\hat{f}_{13,m},
\]
\[
\hat{f}_{24,m} = \hat{p}_{24,m} + \hat{p}_{21,m}\hat{f}_{14,m},
\]
from which we obtain $\hat{f}_{ij,m}$, $m = 1, 2$, explicitly as
\[
\hat{f}_{13,m} = \frac{\hat{p}_{13,m} + \hat{p}_{12,m}\hat{f}_{23,m}}{1 - \hat{p}_{12,m}\hat{p}_{21,m}},
\]
\[
\hat{f}_{14,m} = \frac{\hat{p}_{14,m} + \hat{p}_{12,m}\hat{f}_{24,m}}{1 - \hat{p}_{12,m}\hat{p}_{21,m}},
\]
and
\[
\hat{f}_{23,m} = \frac{\hat{p}_{23,m} + \hat{p}_{21,m}\hat{f}_{13,m}}{1 - \hat{p}_{12,m}\hat{p}_{21,m}},
\]
\[
\hat{f}_{24,m} = \frac{\hat{p}_{24,m} + \hat{p}_{21,m}\hat{f}_{14,m}}{1 - \hat{p}_{12,m}\hat{p}_{21,m}}.
\]

### E Comparison between c-mixture and g-mixture

The EM algorithm provided the following mles of the c-mixture’s parameters. The mles of the regime 1 and 2 probabilities are given in $\hat{D}_c^{\phi} = \text{diag}(\hat{\phi}_{1,1}, \hat{\phi}_{2,1}) = (0.0015, 0.1515)$.
and \( \hat{D}_2 = \text{diag}(\hat{\phi}_{1,2}, \hat{\phi}_{2,2}) = \text{diag}(0.9985, 0.8485) \), respectively. The estimated total number of \( X_1 \) patients is obtained by summing the elements of the vector \( \hat{C}_1 = (367, 380) \hat{D}_1 = [0.5505, 57.57] \) to be approximately 58. Similarly summing the elements of \( \hat{C}_2 = (367, 380) \hat{D}_2 = [366.4495, 322.43] \) we get the estimated total number of \( X_2 \) patients to be approximately 689. The mle of the intensity matrix for \( X^c_1 \) patients is

\[
\hat{Q}_1^c = \hat{\Gamma} \hat{Q}_2^c = \frac{1}{2} \begin{pmatrix}
-0.06734 & 0.00742 & 0.05784 & 0.00208 \\
0.01983 & -0.02772 & 0.00448 & 0.00342
\end{pmatrix},
\]

and for \( X^c_2 \) patients is

\[
\hat{Q}_2^c = \frac{1}{2} \begin{pmatrix}
-0.15093 & 0.01662 & 0.12966 & 0.00465 \\
0.06917 & -0.09671 & 0.01561 & 0.01193
\end{pmatrix},
\]

where

\[
\hat{\Gamma} = \frac{1}{2} \begin{pmatrix}
0.44614 & 0 \\
0 & 0.28665
\end{pmatrix}.
\]

We observe that regime 2 is a fast regime compared to regime 1; it has much higher exit rates from states 1 and 2 and also higher discharge and death rates from states 1 and 2 than regime 1. This is in contrast to regime 2 in the g-mixture which has higher death rates but lower discharge rates compared to the g-mixture regime 1. The awkward split in the c-mixture into 689 fast regime patients and 58 slow regime patients is caused by the constraint \( \hat{Q}_1^c = \hat{\Gamma} \hat{Q}_2^c \), which does not allow for mixing on the direction of movement. It also implies that the fast and slow regime have the same absorption probabilities. In the g-mixture, the two regimes have different absorption probabilities. Thus, the results from the application of the c-mixture and g-mixture to ventICU data, show that the g-mixture provides a much more informative split of the patients into two regimes. This is confirmed by the likelihood ratio test rejecting the c-mixture in favor of the g-mixture.