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Identifying transition rates of ionic channels via observations at a *single* state

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Abstract
We consider how to determine all transition rates of an ion channel when it can be described by a birth–death chain or a Markov chain on a star-graph with continuous time. It is found that all transition rates are uniquely determined by the distribution of its lifetime and death-time histograms at a *single* state. An algorithm to calculate the transition rates exactly, based on the statistics of the lifetime and death-time of the Markov chain at the state, is provided. Examples to illustrate how an ion channel activity is fully determined by the observation of a single state of the ion channel are included.

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1. Introduction

The study of ionic channel activity plays an important role in biophysics and neuroscience [4, 17, 1, 16, 19]. It serves as a bridge to connect molecular biology and physiology: neuron spikes are generated due to the opening (ions can pass through) and closing of many ionic channels. Calcium channel activity is of vital importance to the survival of the cell, to the long-term potentiation and depression and intra-cellular, extra-cellular signalling [5]. For an ionic channel, let σ be its open time and τ be its close time. The observations of σ and τ are denoted by $\sigma_1, \sigma_2, \ldots$ and $\tau_1, \tau_2, \ldots$ etc. The histogram of σ is the open lifetime histogram and the histogram of τ is the close lifetime histogram. Unfortunately, in experiments the ionic channel activity is usually partly observable: it is relatively easy to determine the open and close lifetime histograms (see, for example, figures 3.18 and 3.19 in [1]) of a single state. It is usually difficult to tell apart conformational states (more than one close or open state). It is stated in [1], p 165, that the time constants (transition rates) of these conformational states cannot be determined directly from the lifetime histograms of close and open states.

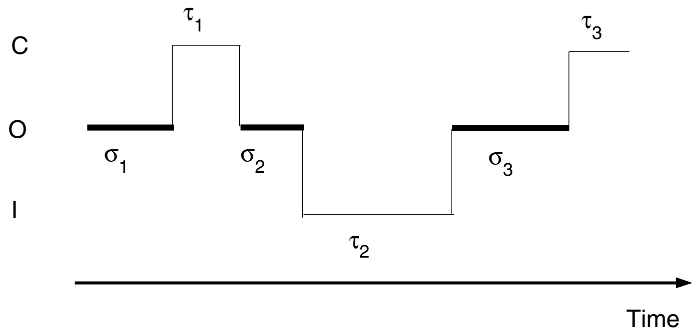

Figure 1. Schematic plot of the trajectory of the Markov chain on a star-graph of case I. The histogram of $\sigma_1, \sigma_2, \sigma_3, \ldots$ gives the open lifetime histogram and $\tau_1, \tau_2, \tau_3, \cdots$ give the close lifetime histogram.

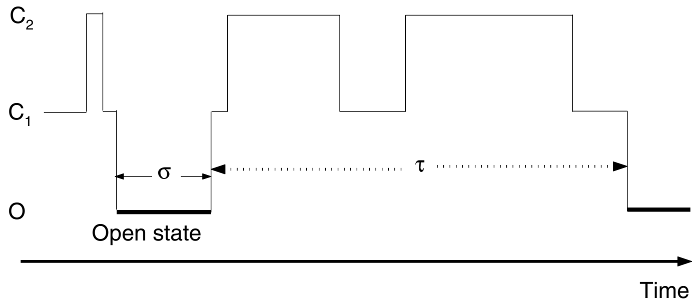

Figure 2. Illustrated lifetime σ and death-time τ of the open state (observable state) of case II.

As an example let us consider two cases.

Case I (Markov chain on a star graph, see figure 1):

$$C \underset{\lambda_1}{\overset{\alpha_1}{\rightleftharpoons}} O \underset{\alpha_2}{\overset{\lambda_2}{\rightleftharpoons}} I \tag{1.1}$$

where O is the open state, C is one close state, I is another close (inactive) state, $\alpha_1, \alpha_2, \lambda_1$ and λ_2 are transition rates from one state to another, i.e. they measure the 'speed' to jump from one state to another (see equation (2.2) in section 2 for an exact definition). In matrix term, we can define a matrix (transition rate matrix)

$$Q = \begin{pmatrix} -\lambda_1 - \lambda_2 & \lambda_1 & \lambda_2 \\ \alpha_1 & -\alpha_1 & 0 \\ \alpha_2 & 0 & -\alpha_2 \end{pmatrix}$$

which contains all information of the Markov chain.

Case II (a birth–death chain with a two-side reflecting, see figure 2):

$$C_2 \underset{\lambda_1}{\overset{\mu_2}{\rightleftharpoons}} C_1 \underset{\lambda_0}{\overset{\mu_1}{\rightleftharpoons}} O \tag{1.2}$$

where O is open state, C_1, C_2 are two close states, μ_1, μ_2, λ_1 and λ_0 are transition rates from one state to another. Again the information of the Markov chain is completely described by the matrix Q

$$Q = \begin{pmatrix} -\lambda_0 & \lambda_0 & 0 \\ \mu_1 & -\mu_1 - \lambda_1 & \lambda_1 \\ 0 & \mu_2 & -\mu_2 \end{pmatrix}.$$

Suppose we have detailed information about the one state, for example we know exactly the lifetime histogram of the open state and lifetime histogram of the close state (death-time histogram of the open state). Can we uniquely determine the full channel activity in terms of the data from an observation of the open state alone? By this, we mean to obtain the transition rate from one (any) state to another state. For example, in case I, we have the distribution density of τ and σ, we intend to find out constants $\alpha_1, \alpha_2, \lambda_1$ and λ_2.

When a channel activity can be described by a two-side reflecting birth–death chain with continuous time parameter, there are two cases: we can observe the lifetime and death-time of one of the reflecting barriers, i.e. edge states (O and C_2 in case II above) and that of the non-reflecting states (C_1 in case II above).

- We conclude that statistically the whole birth–death chain is uniquely determined by the probability density functions (p.d.fs) of the lifetime σ and death-time τ at one of the reflecting barriers. In other words, the observed sequences $\{\sigma_n\}$ and $\{\tau_n\}$ are sufficient statistics of the transition rate matrix Q. This seems a quite surprising result: *the whole Markov chain is fully determined by an observation at a single state of the chain*. The underlying mechanism is that the death-time p.d.fs can be written as a linear summation of N different exponential functions, where N is the total states of the Markov chain (see [1] at page 165). The decay rates of the exponential functions are the eigenvalues of the matrix Q. The coefficients of the linear summation are functions of the eigenvectors of the matrix Q. In the case of a two-side reflecting birth–death chain, in terms of the p.d.fs of the lifetime and death-time, we can fully recover the matrix Q. In section 2, we first present the simplest case of a Markov chain on a star-graph to explain the idea.
- If one can only observe the lifetime σ and the death-time τ of a state of non-reflecting barriers, then the p.d.fs of σ and τ are not sufficient for determining Q. In this case, if we establish an equivalent relation (see below) among the transition matrix Q and obtain the quotient set (the set of equivalent classes) of all Q-matrices under the equivalent relation, then the p.d.fs of the lifetime and the death-time of non-reflecting barrier are sufficient for determining which equivalent class this chain belongs to. This means that we do not have enough information to determine the transition rate matrix completely from the observation data described above, but enough information to determine a part of transitions in Q (see theorem 4).

In sections 2 and 3, we address the above issues. In section 4, we include some applications of our theory to single-ion channels in biology and two examples which illustrate the algorithm and statistical significance of our results.

The issue that how to determine the transition matrix in terms of a partial observation of the whole channel activity, as one might expect, has been addressed early in the literature [13]. However our approach is totally different from their approach. In [13], they estimated the matrix Q, directly using the maximum likelihood estimate, and the estimation could be very rough (see page 1983 in [13]). Here we develop our algorithms employing the intrinsic properties of the Markov process and all calculations are simply reduced to the fitting of lifetime and death-time histograms. Once we have them, all subsequent calculations are then

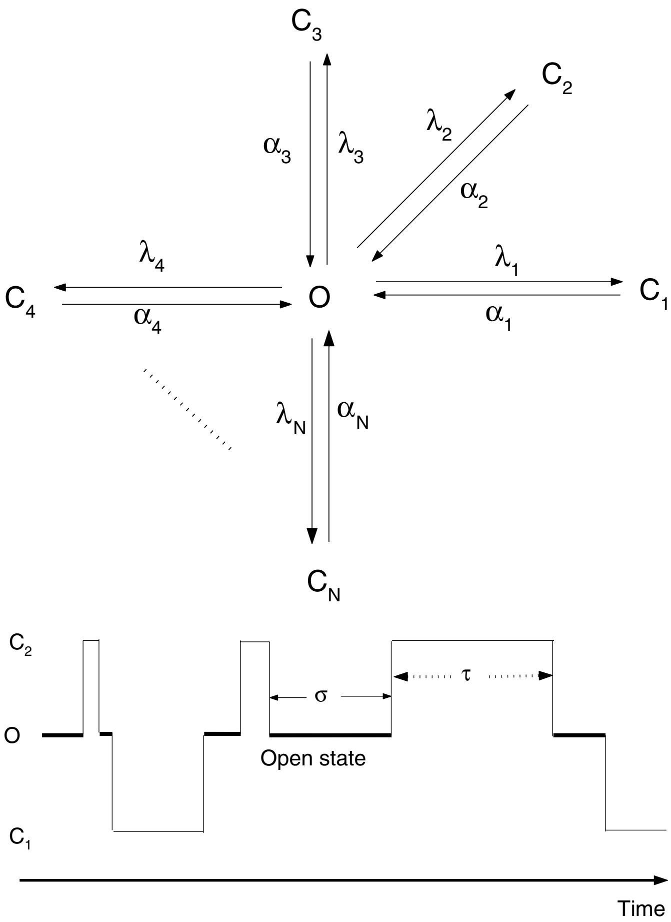

Figure 3. Schematic plot of a Markov chain on a star-graph (upper panel) and its trajectory (bottom panel), with two close states only.

rigorous and exact. Hence we expect that our approach provides us with a more powerful and natural way to estimate transition rates.

2. Statistics of Markov chains on star-graphs

We first consider an easy case to illustrate the general idea behind our approach. Let $\{X_t : t \geqslant 0\}$ be a Markov chain on a star-graph with state space $S = \{O, C_1, C_2, \ldots, C_N\}$. For the concise of notation, from now on, we denote $i = C_i$ and $O = 0$. Suppose that the state $O = 0$ is the *centre state* (see figure 3) and the transition rate matrix $Q = (q_{i,j})$ has the following form

$$Q = \begin{pmatrix} -\lambda_0 & \lambda_1 & \lambda_2 & \cdots & \lambda_N \\ \alpha_1 & -\alpha_1 & 0 & \cdots & 0 \\ \alpha_2 & 0 & -\alpha_2 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ \alpha_N & 0 & 0 & \cdots & -\alpha_N \end{pmatrix}$$

where $\lambda_i > 0, \alpha_i > 0$ ($i = 1, 2, \ldots, N$) and $\lambda_0 = \lambda_1 + \cdots + \lambda_N$. Set

$$\pi_0 = \left(1 + \sum_{i=1}^{N} \frac{\lambda_i}{\alpha_i}\right)^{-1} \qquad \pi_i = \frac{\lambda_i}{\alpha_i}\pi_0 \qquad 1 \leqslant i \leqslant N. \tag{2.1}$$

Then $\{\pi_0, \pi_1, \ldots, \pi_N\}$ is the unique initial invariant probability measure of Q and satisfies

$$\pi_i q_{ij} = \pi_j q_{ji} \ (\forall i, j \in S).$$

Let $\sigma = \inf\{t > 0 : X_t \neq 0\}$ and $\tau = \inf\{t > 0 : X_t = 0\}$ (the lifetime and the death-time of the centre state O, respectively). Define $S_0 = \{1, 2, \ldots, N\}$, $\hat{Q} = (q_{i,j})_{i,j \in S_0}$, which is the matrix by deleting the 0th row and the 0th column from Q.

In the sequel, we always use P to denote the probability distribution measure on a probability space $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geqslant 0})$ such that the initial distribution is the invariant measure $\{\pi_i\}$ and P_{S_0} denotes the probability measure of the process starting in S_0, where $\mathcal{F}_t$ is the sub-sigma algebra of $\mathcal{F}$ generated by $\{X_s, 0 \leqslant s \leqslant t\}$. We know that

$$q_{ij} = \lim_{t\to 0} \frac{P(X_t = j|X_0 = i) - \delta_{ij}}{t} \tag{2.2}$$

for $i, j \in S$ and delta function δ_{ij}. Then, for $t \geqslant 0$, it is easily seen that

$$\begin{aligned} P(\tau > t) &= \sum_{i=0}^{N} P(\tau > t|X_0 = i) P_{S_0}(X_0 = i) \\ &= \sum_{i=1}^{N} \pi_i{}^* \sum_{j=1}^{N} \hat{p}_{ij}(t) \\ &= \frac{1}{1-\pi_0} \sum_{i=1}^{N} \pi_i \,\mathrm{e}^{-\alpha_i t} \end{aligned} \tag{2.3}$$

where $\pi_i^* = \pi_i/(1 - \pi_0)$, $(\hat{p}_{ij}(t)) = \hat{P}(t) = \mathrm{e}^{\hat{Q}t}$.

We can easily get the following result.

Lemma 1. *The p.d.fs of σ and τ are*

$$f_\sigma(t) = \begin{cases} \lambda_0 \,\mathrm{e}^{-\lambda_0 t} & \text{if} \quad t > 0 \\ 0 & \text{if} \quad t \leqslant 0 \end{cases} \tag{2.4}$$

and

$$f_\tau(t) = \begin{cases} \sum_{i=1}^{N} \gamma_i \,\mathrm{e}^{-\alpha_i t} & \text{if} \quad t > 0 \\ 0 & \text{if} \quad t \leqslant 0 \end{cases} \tag{2.5}$$

where $\gamma_i = \dfrac{\pi_0}{1-\pi_0}\lambda_i$.

Proof. Equation (2.4) is obvious. Equation (2.5) is a direct consequence of equations (2.1) and (2.3). □

Lemma 2. *Let* $d = \sum_{i=1}^{N} \gamma_i$. *Then*

$$\pi_0 = \frac{d}{\lambda_0 + d} \qquad \lambda_i = \frac{\lambda_0}{d}\gamma_i \qquad (1 \leqslant i \leqslant N).$$

Proof. Since

$$d = \sum_{i=1}^{N} \gamma_i = \frac{\pi_0}{1-\pi_0} \sum_{i=1}^{N} \lambda_i = \frac{\pi_0}{1-\pi_0}\lambda_0$$

and

$$\lambda_i = \frac{1-\pi_0}{\pi_0}\gamma_i$$

thus the conclusions hold. □

From lemmas 1 and 2, we can immediately obtain the following theorem.

Theorem 1. *For a Markov chain on a star-graph, if the initial measure is the invariant measure* $\{\pi_i\}$*, then the transition rates of the Markov chain on the star-graph* $\{X_t; t \geqslant 0\}$ *can be fully determined by the p.d.fs of* $f_\sigma(t)$ *and* $f_\tau(t)$*.*

For Markov chains on a star-graph, we can easily see that it is not possible to uniquely assign α_i, λ_i to a single state. When $N = 2$, the situation considered here is a special case of subsection 3.2. We refer the reader to subsection 3.2 for more details on the issue about the uniqueness.

In practical applications, if we suppose that an ionic channel activity is described as a Markov chain on a star-graph of N states, we can measure a sequence of death-time τ_i and lifetime σ_i, $i = 1, \ldots, n$ for the open state. We can then fit the histogram of τ_i by

$$\sum_{i=1}^{N} \hat{\gamma}_i \exp(-\hat{\alpha}_i t)$$

(see, for example, [13–15] on exactly fitting methods) and the histogram of σ_i by

$$\hat{\lambda}_0 \exp(-\hat{\lambda}_0 t).$$

According to lemma 2, we can easily obtain the transition matrix Q. More exactly, we have $\hat{\alpha}_i, \hat{\gamma}_i$ available for $i = 0, \ldots, N$, and $\hat{\lambda}_i$ are obtained via

$$\hat{d} = \sum_{i=1}^{N} \hat{\gamma}_i \qquad \hat{\pi}_0 = \frac{\hat{d}}{\hat{\lambda}_0 + \hat{d}} \qquad \hat{\lambda}_i = \frac{\hat{\lambda}_0}{\hat{d}}\hat{\gamma}_i \qquad i = 1, \ldots, N.$$

Hence once we have the fitting of the death-time histogram, all subsequent calculations are rigorous and exact. In other words, we can determine the transition rates directly from the histogram of τ and σ, in contrast with the claim mentioned above [1].

In summary, the basic idea of our approach is that from the p.d.fs of the lifetime and death-time, we have enough information to recover the whole transition matrix Q.

3. Statistics of finite birth–death chains

In this section, we turn our attention to the case of a birth–death chain (see figure 4), which is a proper model for many ionic channels.

Let $\{X_t : t \geqslant 0\}$ be a birth–death chain with state space $S = \{0, 1, \ldots, N\}$ and transition rate matrix $Q = (q_{i,j})$ which satisfies

$$q_{i,j} = \begin{cases} -(\lambda_i + \mu_i) & \text{if} \quad j = i \\ \mu_i & \text{if} \quad j = i - 1 \\ \lambda_i & \text{if} \quad j = i + 1 \\ 0 & \text{if} \quad |j - i| > 1 \end{cases} \tag{3.1}$$

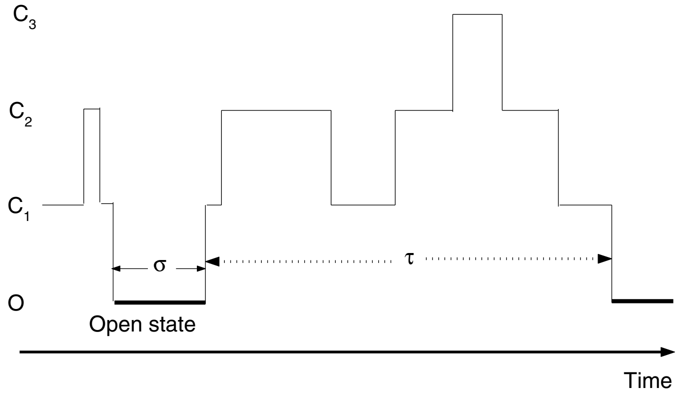

Figure 4. Trajectories of a birth–death chain with four states.

where $\mu_0 = 0, \lambda_N = 0, \lambda_i > 0\ (0 \leqslant i \leqslant N-1), \mu_i > 0\ (1 \leqslant i \leqslant N)$, i.e.

$$Q = \begin{pmatrix} -\lambda_0 & \lambda_0 & 0 & 0 & \cdots & 0 & 0 \\ \mu_1 & -\mu_1 - \lambda_1 & \lambda_1 & 0 & \cdots & 0 & 0 \\ 0 & \mu_2 & -\mu_2 - \lambda_2 & \lambda_2 & \cdots & 0 & 0 \\ & & \vdots & & & & \\ 0 & 0 & 0 & 0 & \cdots & \mu_N & -\mu_N \end{pmatrix}.$$

Hence $\{0, N\}$ are two reflecting barriers. Set

$$\pi_0 = \left(1 + \sum_{i=1}^{N} \frac{\lambda_0 \lambda_1 \cdots \lambda_{i-1}}{\mu_1 \mu_2 \cdots \mu_i}\right)^{-1} \qquad \pi_i = \frac{\lambda_0 \lambda_1 \cdots \lambda_{i-1}}{\mu_1 \mu_2 \cdots \mu_i} \pi_0 \qquad 1 \leqslant i \leqslant N. \tag{3.2}$$

Then $\{\pi_0, \pi_1, \ldots, \pi_N\}$ is the unique invariant probability measure of Q and satisfies $\pi_i q_{ij} = \pi_j q_{ji}\ (i, j \in S)$.

3.1. *Reflecting barriers*

For the concreteness of further development, we concentrate on state 0. As before, define $\tau = \inf\{t > 0 : X_t = 0\}$ and $\sigma = \inf\{t > 0 : X_t \neq 0\}$ (the death-time and lifetime of reflecting barrier 0, respectively). Here let us always employ the standard convention that the infimum of an empty set is infinity. Set $\hat{Q} = (q_{i,j})_{i,j \in S_0}$, where $S_0 = \{1, 2, \ldots, N\}$, which is the matrix by deleting the 0th row and the 0th column from Q. Let P be a probability measure such that $\{X_t; t \geqslant 0\}$ with the initial distribution $\{\pi_0, \ldots, \pi_N\}$ and the transition rate matrix Q. P_{S_0} denotes the probability measure such that $\{X_t; t \geqslant 0\}$ starts in S_0. Define

$$\hat{P}(t) = (\hat{p}_{ij}(t)) \equiv \mathrm{e}^{\hat{Q}t} \equiv \sum_{n=0}^{\infty} \frac{t^n}{n!} \hat{Q}^n \qquad t \geqslant 0.$$

Thus

$$\begin{aligned} P(\tau > t) &= \sum_{i=1}^{N} P(\tau > t | X_0 = i) P_{S_0}(X_0 = i) \\ &= \sum_{i=1}^{N} \pi_i{}^* \sum_{j=1}^{N} \hat{p}_{ij}(t) \end{aligned} \tag{3.3}$$

where

$$P_{S_0}(X_0 = i) = \pi_i{}^* = \frac{\pi_i}{1 - \pi_0}.$$

For convenience, we always use $\langle \cdots \rangle$ denoting a column vector, $(\cdots)$ a row vector, $\mathrm{diag}(\cdots)$ a diagonal matrix, and A^T the transpose of A. Write $\Pi = \mathrm{diag}(\pi_1, \pi_2, \ldots, \pi_N)$.

On the real vector space $\mathbf{R}^\mathbf{N}$, we define inner product

$$(X, Y)_\Pi = \sum_{i=1}^{N} \pi_i x_i y_i \qquad \text{for any} \quad X, Y \in \mathbf{R}^N.$$

It is easy to verify that $\hat{P}$ and $\hat{Q}$ are symmetric linear transition matrices with respect to the inner product $(\cdot, \cdot)_\Pi$. Thus $\hat{Q}$ has N real eigenvalues $-\alpha_1, -\alpha_2, \ldots, -\alpha_N$ such that $\alpha_i > 0$ (see [6, 24]) and N orthogonal unit eigenvectors $\epsilon_1, \epsilon_2, \ldots, \epsilon_N$ with respect to $(\cdot, \cdot)_\Pi$, where $\epsilon_i = \langle \epsilon_{1i}, \ldots, \epsilon_{Ni} \rangle$ $(i = 1, 2, \ldots, N)$, that is to say, for any $i, j \in S$,

$$\hat{Q}\epsilon_i = -\alpha_i \epsilon_i \tag{3.4}$$

$$(\epsilon_i, \epsilon_j)_\Pi = \sum_{k=1}^{N} \epsilon_{ki}\epsilon_{kj}\pi_k = \delta_{ij}. \tag{3.5}$$

Set $E = (\epsilon_1, \ldots, \epsilon_N) = (\epsilon_{ij})$, $W = (\omega_{ij}) = E^{-1}$. Write $A = \mathrm{diag}(\alpha_1, \alpha_2, \ldots, \alpha_N)$. By (3.4) and (3.5), we get

$$\begin{aligned} &\hat{Q} = -W^{-1}AW \qquad && W^T W = \Pi \\ &W\hat{Q} = -AW \qquad && \Pi\hat{Q} = -W^T AW. \end{aligned} \tag{3.6}$$

Let $\beta = \langle \beta_1, \beta_2, \ldots, \beta_N \rangle \equiv W\mathbf{I}$, where $\mathbf{I} = \langle 1, 1, \ldots, 1 \rangle$. Then, by (3.3) and (3.6), for $t \geqslant 0$

$$\begin{aligned} P(\tau > t) &= \frac{1}{1 - \pi_0} \sum_{i=1}^{N} \pi_i \sum_{j=1}^{N} \hat{p}_{ij}(t) \\ &= \frac{1}{1 - \pi_0} \sum_{i=1}^{N} \pi_i (\hat{P}(t)\mathbf{I})_i \\ &= \frac{1}{1 - \pi_0} \mathbf{I}^T \Pi W^{-1} \,\mathrm{e}^{-At} W\mathbf{I} \\ &= \frac{1}{1 - \pi_0} \beta^T \,\mathrm{e}^{-At} \beta \\ &= \frac{1}{1 - \pi_0} \sum_{i=1}^{N} \beta_i{}^2 \,\mathrm{e}^{-\alpha_i t}. \end{aligned} \tag{3.7}$$

If we define

$$\begin{cases} \gamma_i = \dfrac{\beta_i^2 \alpha_i}{1 - \pi_0} & 1 \leqslant i \leqslant N \\ c_n = \sum_{i=1}^{N} \beta_i{}^2 \alpha_i{}^n = \beta^T A^n \beta & n \geqslant 0 \\ d_n = \sum_{i=1}^{N} \gamma_i \alpha_i^{n-1} & n \geqslant 0 \end{cases} \tag{3.8}$$

then we have

$$c_n = (1 - \pi_0) d_n. \tag{3.9}$$

Lemma 3. *The p.d.f. of* τ *is*

$$f_\tau(t) = \begin{cases} \sum_{i=1}^{N} \gamma_i\, \mathrm{e}^{-\alpha_i t} & \text{if} \quad t > 0 \\ 0 & \text{if} \quad t \leqslant 0. \end{cases} \tag{3.10}$$

For $n \geqslant 1$,

$$d_n = (-1)^n \frac{\mathrm{d}^n}{\mathrm{d}t^n} P(\tau > t)|_{t=0} \qquad (n \geqslant 1). \tag{3.11}$$

Proof. It follows directly from (3.7) and (3.8). □

For the p.d.f. of the lifetime σ, it is easy to check that (see [22, 23])

$$f_\sigma(t) = \begin{cases} \lambda_0\, \mathrm{e}^{-\lambda_0 t} & \text{if} \quad t > 0 \\ 0 & \text{if} \quad t \leqslant 0. \end{cases} \tag{3.12}$$

Thus $\lambda_0 = 1/E\sigma$. Therefore, λ_0 can be simply estimated by the p.d.f. of σ.

Lemma 4. *We have the following conclusions*

(i)

$$\pi_0 = \frac{d_1}{\lambda_0 + d_1}. \tag{3.13}$$

(ii) For $1 \leqslant n \leqslant N-1$, λ_n *can be expressed in terms of rational functions of* $\{\lambda_0, d_1, d_2, \ldots, d_{2n+1}\}$.

(iii) For $1 \leqslant n \leqslant N$, μ_n *can be expressed in terms of rational functions of* $\{\lambda_0, d_1, d_2, \ldots, d_{2n}\}$.

Proof. Since $\hat{Q}\mathbf{I} = \langle -q_{1,0}, 0, \ldots, 0\rangle$, by (3.6), we have

$$\pi_1 q_{1,0} = -\mathbf{I}^T \Pi \hat{Q}\mathbf{I} = \mathbf{I}^T W^T A W \mathbf{I} = \beta^T A \beta = c_1. \tag{3.14}$$

By (2), $\pi_0\lambda_0 = \pi_1 q_{1,0}$, then $\pi_0\lambda_0 = c_1 = (1-\pi_0)d_1$. Thus (i) holds.

Now let us prove (ii) and (iii). Let $q_i = -q_{i,i}$, $W_i = \langle \omega_{1i}, \omega_{2i}, \ldots, \omega_{Ni}\rangle$ is the ith column vector of W.

According to

$$\pi_0 = \frac{d_1}{\lambda_0 + d_1} \qquad c_n = \frac{\lambda_0 d_n}{\lambda_0 + d_1}$$

and $\lambda_N = 0$, we only need to prove the following facts: for $1 \leqslant n \leqslant N$,

(H1) $\mu_n = q_{n,n-1}$, $\lambda_n + \mu_n = -q_{n,n} = q_n$, $\lambda_n = q_{n,n+1}$ and π_n all are rational functions of $\{c_1, c_2, \ldots, c_{2n+1}\}$;

(H2) $W_n = g_n(A)A\beta$, where $g_n(A)$ is a polynomial of A with $\deg(g_n) = n-1$ (here $\deg(g)$ denoting the degree of g) and its coefficients are rational functions of $\{c_1, c_2, \ldots, c_{2n}\}$.

Now let us use mathematical induction to prove these facts as follows.

When $n = 1$, since

$$W\hat{Q}\mathbf{I} = W\langle -q_{1,0}, 0, \ldots, 0\rangle = -q_{1,0}W_1$$

then by (3.6), we get

$$q_{1,0}W_1 = A\beta. \tag{3.15}$$

Thus

$$\pi_1 q_{1,0}^2 = W_1^T W_1 q_{1,0}^2 = (A\beta)^T(A\beta) = \beta^T A^2 \beta = c_2. \tag{3.16}$$

By (3.14)–(3.16), we obtain

$$\begin{aligned} \mu_1 &= q_{1,0} = \frac{\pi_1 q_{1,0}^2}{\pi_1 q_{1,0}} = \frac{c_2}{c_1} \\ \pi_1 &= \frac{(\pi_1 q_{1,0})^2}{\pi_1 q_{1,0}^2} = \frac{c_1^2}{c_2} \\ W_1 &= \frac{c_1}{c_2} A\beta \equiv g_1(A) A\beta \end{aligned} \tag{3.17}$$

where $g_1(A) = \dfrac{c_1}{c_2} I$.

Again by (3.6), $\Pi \hat{Q} = -W^T A W$, that is to say

$$\pi_i q_{ij} = -W_i^T A W_j \qquad i, j \in S_0 \tag{3.18}$$

and again by (3.15),

$$\begin{aligned} \pi_1 q_1 &= W_1^T A W_1 = \frac{1}{q_{1,0}^2} (q_{1,0} W_1)^T A (q_{1,0} W_1) \\ &= \frac{1}{q_{1,0}^2} (A\beta)^T A (A\beta) = \frac{c_3}{q_{1,0}^2}. \end{aligned}$$

Thus by (3.16)

$$\begin{aligned} \lambda_1 + \mu_1 &= -q_{1,1} = q_1 = \frac{c_3}{\pi_1 q_{1,0}^2} = \frac{c_3}{c_2} \\ q_{1,2} &= \lambda_1 = q_1 - q_{1,0} = \frac{c_3}{c_2} - \frac{c_2}{c_1}. \end{aligned} \tag{3.19}$$

Therefore, according to (3.17) and (3.19), for $n = 1$ the inductive assumptions hold.

Now we suppose that for all $1 \leqslant n \leqslant k$, these results hold. Then, when $n = k+1$ (setting $W_0 = 0$), by (3.6), we have

$$q_{k+1,k} W_{k+1} = (q_k I - A) W_k - q_{k-1,k} W_{k-1}. \tag{3.20}$$

By (3.18), we get

$$\pi_{k+1} q_{k+1,k} = \pi_k q_{k,k+1} = -W_k^T A W_{k+1}. \tag{3.21}$$

Hence

$$\begin{aligned} q_{k+1,k} &= \frac{q_{k+1,k}}{\pi_k q_{k,k+1}} \left(-W_k^T A W_{k+1} \right) \text{ (by (3.21))} \\ &= \frac{1}{\pi_k q_{k,k+1}} \left[W_k^T A (A - q_k I) W_k + q_{k-1,k} W_k^T A W_{k-1} \right] \text{ (by (3.20))} \\ &\equiv \beta^T A h(A) A \beta \end{aligned} \tag{3.22}$$

where

$$h(A) = \frac{1}{\pi_k q_{k,k+1}} \left[(A^2 - q_k A) g_k^2(A) + q_{k-1,k} g_{k-1}(A) g_k(A) \right].$$

Thus, by the inductive assumptions (H1), π_k, $q_{k,k+1}$ are rational functions of $\{c_1, c_2, \ldots, c_{2k}\}$. Furthermore, we have $W_{k-1} = g_{k-1}(A) A\beta$ and $W_k = g_k(A) A\beta$ from (H2). Then we have that $h(A)$ is a polynomial of A of $\deg(h) = 2k$, and so $q_{k+1,k}$ is a linear combination of $\beta^T A^{i+2} \beta$ $(i = 0, 1, \ldots, 2k)$, with coefficients of rational functions of $\{c_1, c_2, \ldots, c_{2k}\}$. Therefore, by

(3.8) (i.e. $\beta^T A^n \beta = c_n$) and (3.22), $q_{k+1,k}$ is a rational function of $\{c_1, c_2, \ldots, c_{2k+1}, c_{2k+2}\}$ and so do

$$\pi_{k+1} = \frac{\pi_k q_{k,k+1}}{q_{k+1,k}}.$$

Now let us prove that W_{k+1} has the properties of the inductive assumption in (H2). Again using (3.20) we know that $W_{k+1} = g_{k+1}(A)A\beta$, where

$$g_{k+1}(A) = \frac{1}{q_{k+1,k}}[(q_k I - A)g_k(A) - q_{k-1,k}g_{k-1}(A)]$$

and from the result about $q_{k+1,k}$, we have that $\deg(g_{k+1}) = k$ and its coefficients are rational functions of $\{c_1, c_2, \ldots, c_{2k+2}\}$.

About $q_{k+1,k+2}$ and q_{k+1}, by (17), we get

$$\pi_{k+1}q_{k+1} = W_{k+1}^T A W_{k+1} = \beta^T g_{k+1}(A)A^3 g_{k+1}(A)\beta.$$

Hence, using the results about $g_{k+1}(A)$ and (3.8), q_{k+1} and $q_{k+1,k+2} = q_{k+1} - q_{k+1,k}$ are rational functions of $\{c_1, \ldots, c_{2k+2}, c_{2k+3}\}$.

These have proved that the conclusions of induction are true for $n = k + 1$ $(1 \leqslant n \leqslant N)$. □

From lemmas 3 and 4, we can easily obtain the following main theorem in this section.

Theorem 2. *If the initial measure is the invariant measure $\{\pi_i\}$, then the probability measure of birth–death process $\{X_t; t \geqslant 0\}$ can be uniquely determined by the p.d.fs $f_\sigma(t)$ and $f_\tau(t)$. And every element of its birth–death matrix $Q = (q_{i,j})$ can be expressed in terms of rational functions of $d_1, d_2, \ldots, d_{2N}, \lambda_0$ in (3.11) and (3.12).*

Remark. Obviously the result also holds for the reflecting barrier *N*.

Let

$$\mathbf{X} = S^{[0,+\infty)} = \{X = (x_t : t \geqslant 0) : x_t \in S \text{ for any } t \geqslant 0\}$$

be the path space of the birth–death chain $\{X_t; t \geqslant 0\}$. We define two i.i.d. sample sequences on $\mathbf{X}$, the lifetime sample sequence $\{\sigma_n : n \geqslant 0\}$ and the death-time sample sequence $\{\tau_n : n \geqslant 0\}$ as follows:

$$\tau_k = t_{2k} - t_{2k-1} \qquad (k \geqslant 0)$$
$$\sigma_k = t_{2k+1} - t_{2k} \qquad (k \geqslant 0)$$

and

$$t_{-1} \equiv 0$$
$$t_0 = \inf\{t > 0 : X_t = 0\}$$
$$t_1 = \inf\{t > t_0 : X_t \neq 0\}$$

for any $k \geqslant 1$,

$$t_{2k} = \inf\{t > t_{2k-1} : X_t = 0\}$$
$$t_{2k+1} = \inf\{t > t_{2k} : X_t \neq 0\}.$$

In theorem 3, we will give a new statistics for Markov chains by utilizing the lifetime sequence $\{\sigma_n\}$ and the death-time sequence $\{\tau_n\}$.

Theorem 3. *Every element $q_{i,j}(i, j \in S)$ of the transition rate matrix can be estimated sufficiently by the i.i.d. sample sequences $\{\sigma_k\}$ and $\{\tau_k\}$.*

Proof. First, by the law of large number, we note that the p.d.fs $f_\sigma(t)$ and $f_\tau(t)$ of σ and τ, i.e. λ_0 and coefficients $\left(\alpha_i, \beta_i^2\right)$ $(i = 1, 2, \ldots, N)$ of $f_\sigma(t)$ and $f_\tau(t)$, can be estimated sufficiently by the i.i.d. sample sequences $\{\sigma_n\}$ and $\{\tau_n\}$. Next, by lemmas 3 and 4, $q_{i,j}$ $(i, j \in S)$ is a fractional function of λ_0 and d_n $(n = 1, 2, \ldots, 2N)$, which is the rational function of $\left(\alpha_i, \beta_i^2\right)$ $(i = 1, 2, \ldots, N)$. Therefore the results of the theorem hold. □

Algorithm of calculating Q

Suppose that we have distribution functions as defined by equations (3.10) and (3.12).

Step 1. Calculate $\gamma_i, i = 1, \ldots, N, c_k, d_k, k \geqslant 0$ according to equation (3.8).

Step 2. Calculate $\pi_1, q_{1,1}, q_{1,2}, q_{1,0}$ according to equations (3.17) and (3.19), and

$$g_1(A) = \frac{c_1}{c_2} I.$$

Step 3. Suppose that we have $\pi_k, q_{k,k-1}, q_{k,k}$ and $q_{k,k+1}$ for $k = 1, 2, \ldots, n$, then

$$q_{n+1,n} = \beta^T A h(A) \beta$$

where

$$h(A) = \frac{1}{\pi_n q_{n,n+1}} \left[(A^2 - q_n A) g_n^2(A) + q_{n-1,n} g_{n-1}(A) g_n(A) \right]$$

with $g_0 = 0$

$$g_{n+1}(A) = \frac{1}{q_{n+1,n}} [(q_n I - A) g_n(A) - q_{n-1,n} g_{n-1}(A)]$$

$$q_{n+1,n+1} = \beta^T g_{n+1}(A) A^3 g_{n+1}(A) \beta$$

and then finally

$$q_{n+1,n+2} = q_{n+1,n+1} - q_{n+1,n}$$

$$\pi_{n+1} = \frac{\pi_n q_{n,n+1}}{q_{n+1,n}}.$$

Step 4. For $n = N$, we have simply $q_{N,N} = -q_{N,N-1}$.

3.2. Non-reflecting barriers

In the case of observing at a state of non-reflecting barriers, we cannot obtain the results in theorem 2, because the information obtained from observation cannot distinguish which side it comes from (left or the right). We can tackle the problem via two different approaches. One is to establish an equivalent relationship among $Q = (q_{i,j})$ such that from the observed data, one can uniquely determine an equivalent class. The other way is to increase the number of observable states. In fact, the observation of the lifetime and the death-time of two neighbouring states of birth–death chains can determine the whole chain. If the two observable states are not neighbouring, from the observation of their states, it cannot be sufficient for estimating the whole birth–death chain, because there is the same problem as the case of non-reflecting barriers.

Now we follow the first approach to deal with the case when Q is not uniquely determined by the observed data. Set

$$\Theta = \{\theta = (\lambda_0, \lambda_1, \ldots, \lambda_{N-1}; \mu_1, \ldots, \mu_N); \lambda_i > 0, \mu_i > 0\}. \tag{3.23}$$

For each $\theta \in \Theta$, let P^θ be a probability measure with the transition rate matrix Q corresponding to θ in (1). Let k_0 be a non-reflecting barrier in S, $1 \leqslant k_0 \leqslant N - 1$. Set $\sigma_{k_0} = \inf\{t > 0 : X_t \neq k_0\}$ and $\tau_{k_0} = \inf\{t > 0 : X_t = k_0\}$. Since there is one-to-one corresponding relation in θ, Q^θ and P^θ (under initial invariant measure), we can define an equivalent relation on Θ as follows: $\theta_1, \theta_2 \in \Theta$ are called *equivalent*, if τ_{k_0} has the same probability distribution under P^{θ_1} and P^{θ_2}. We denote the quotient space of Θ under this equivalent relation as $\tilde{\Theta}$.

Let Q^θ and $\{\pi_i(\theta)\}$ correspond to θ in terms of the way of equations (3.23), (3.1) and (3.2). Let $\hat{Q}^\theta$ be the matrix by deleting the k_0th row and the k_0th column from Q^θ. Then we have the following result as the ways in (3.3)–(3.7).

Lemma 5. *For any $\theta \in \Theta$, the probability distribution of τ_{k_0} under P^θ has the following form*

$$P^\theta\big(\tau_{k_0} > t\big) = \frac{1}{1-\pi_{k_0}(\theta)} \sum_{i=0, i\neq k_0}^{N} \beta_i^2(\theta)\, \mathrm{e}^{-\alpha_i(\theta)t} \qquad (t \geqslant 0) \tag{3.24}$$

where $\alpha_i(\theta) > 0$, $\beta_i^2(\theta) > 0$ $(i = 1, 2, \ldots, N)$, $\sum_{i=0,i\neq k_0}^{N} \beta_i^2(\theta) = 1 - \pi_{k_0}(\theta)$, and $-\alpha_i(\theta)$ $(i = 1, 2, k_0 - 1, k_0 + 1, \ldots, N)$ is the eigenvalues of $\hat{Q}^\theta$.

Theorem 4. *Let $q_{k_0} > 0$, and $\alpha_0, \ldots, \alpha_{k_0-1}, \alpha_{k_0+1}, \ldots, \alpha_N$, $\gamma_0, \gamma_2, \ldots, \gamma_{k_0-1}, \gamma_{k_0+1}, \ldots, \gamma_N$ be positive numbers such that $\sum_{i=0,i\neq k_0}^{N} \gamma_i {\alpha_i}^{-1} = 1$. Then there exists an unique element $\tilde{\theta}$ in $\tilde{\Theta}$ such that for $\forall\ \theta \in \tilde{\theta}$, τ_{k_0} under P^θ has the p.d.f.*

$$f_{\tau_{k_0}}(t) = \sum_{i=0,i\neq k_0}^{N} \gamma_i\, \mathrm{e}^{-\alpha_i t} \qquad (t > 0) \tag{3.25}$$

and σ_{k_0} under P^θ has the p.d.f.

$$f_{\sigma_{k_0}}(t) = q_{k_0}\, \mathrm{e}^{-q_{k_0} t} \qquad (t > 0).$$

Furthermore, if $\alpha_0, \alpha_1, \ldots, \alpha_N$ are different from each other, then there are $C_N^{k_0}$ different elements θ for each $\tilde{\theta}$, and each entry of $\theta \in \tilde{\theta}$ can be expressed by a rational function of $\alpha_0, \alpha_1, \ldots, \alpha_N$; $\gamma_0, \gamma_1, \ldots, \gamma_N$ and q_{k_0}.

Proof. The existence and (3.25) come from the following construction proof. The uniqueness follows from theorem 2 and the definition of equivalent relation. Now we prove the remaining parts of the theorem.

Selecting k_0 numbers from N different positive numbers $\alpha_0, \alpha_1, \ldots, \alpha_{k_0-1}, \alpha_{k_0+1}, \ldots, \alpha_N$, there are $C_N^{k_0}$ different ways. Once some k_0 positive numbers have been selected, such as $\alpha_0, \alpha_1, \ldots, \alpha_{k_0}$; then the corresponding coefficients γ_i of exponential function $\mathrm{e}^{-\alpha_i t}$ have also been selected. According to theorem 2, the k_0 pairs of number (α_i, γ_i) $(i = 0, 1, 2, \ldots, k_0)$ and q_{k_0} can uniquely determine a matrix $\hat{Q}_{S_1}$ (where $S_1 = \{0, 1, 2, \ldots, k_0\}$), and the other $N - k_0$ pairs of number (α_i, γ_i) $(i = k_0 + 1, \ldots, N)$ and q_{k_0} can uniquely determine a matrix $\hat{Q}_{S_2}$ (where $S_2 = \{k_0 + 1, \ldots, N\}$). By (3.2), $\pi_{k_0}\lambda_{k_0} = \pi_{k_0+1}\mu_{k_0+1}, \pi_{k_0}\mu_{k_0} = \pi_{k_0-1}\lambda_{k_0-1}$, we know that λ_{k_0} and μ_{k_0} can be uniquely determined by α_i, γ_i $(i = 0, 1, 2, \ldots, N)$ and q_{k_0}. Hence, if some k_0 pairs of numbers (α_i, γ_i) $(i = 0, 1, 2, \ldots, k_0)$ are selected, then they can uniquely determine a matrix Q with the form (3.1), and by lemma 5, the p.d.f. of τ_{k_0} is defined by (3.25) under P^θ, where θ corresponds to Q. The other conclusions simply follow from theorem 2. □

Remark 1. We can extend the results of theorem 2 to infinite countable birth–death chains under some mild conditions, such as uniqueness of Q-processes. The method mainly follows from the spectral methods of the transition probability and the death-time distribution in the same ways in this section.

Remark 2. For Markov chains on star-graphs, theorem 3 also holds.

4. Numerical examples

In this section, we present some applications of our theory to kinetic analysis of single-ion channels and two examples, which show how our general method works in calculation of transition rate matrix from the p.d.fs of lifetime and death-time.

There are different opening levels in ion channels, on which many interesting characteristics of behaviour of single-ion channels depend. The behaviour of ion channels has been analysed by Colquhoun and Hawkes [6–8] in terms of a Markov chain with the states which are the different opening levels. In most cases of practical interest, there are two kinds of mechanisms which are commonly considered for single-ion channels: birth–death chains and Markov chains on star-graphs. In these mechanisms, there are likely to be only one observable state, called open state, which means that the channel is fully open (say highest opening level), and several experimentally non-observable shut states, which indicate different opening levels. Then the experimental record can provide two sequences, one is the lifetime sequence and the other is the death-time sequence. Both of them are i.i.d. sequences from the observation of the Markov chain staying or not staying at the state 0 (see figure 2).

(a) *The mechanism of chains on star-graphs.* One sort of mechanism to consider for single-ion channel has N shut states (say state $1, 2, \ldots, N$) and only one open state (say state 0). In this kind of systems, any transition cannot directly happen between the shut states, that is to say, the transition rate from one state to another is zero; while each shut state can transit to the open state. Therefore, the shut states cannot intercommunicate directly but only by going through the open state. Thus this is the case of Markov chains on star-graphs, considered in section 2 with the centre state 0 (see figure 1).

(b) *The mechanism of birth–death chains.* Another sort of mechanism for single-ion channel mechanism also has N shut states (say state $1, 2, \ldots, N$), which are the different levels of openings, and one open state (say state 0). However, in this case, the shut states can only intercommunicate directly with their neighbouring level of shut states, i.e. $1 \rightleftharpoons 2 \rightleftharpoons \cdots \rightleftharpoons N$, and the open state 0 can only transit to the first level of shut state (state 1). This is the case of birth–death chains that we consider in section 2 with a reflecting barrier 0 .

In the following, we give two examples to illustrate the algorithm and statistical significance of our results.

Example 1. Let $\{X_t; t \geqslant 0\}$ be a birth–death chain with state space $S = \{0, 1, 2\}$ and transition rate matrix

$$Q = (q_{i,j})_{S\times S} = \begin{pmatrix} -1 & 1 & 0 \\ 0.5 & -1 & 0.5 \\ 0 & 1 & -1 \end{pmatrix}. \tag{4.1}$$

Then it is easy to know that the invariant measure of Q is

$$(\pi_0, \pi_1, \pi_2) = (0.25, 0.5, 0.25)$$

and the eigenvalues of $\hat{Q}$ are $-\alpha_1 = -1 + \frac{\sqrt{2}}{2}$, $-\alpha_2 = -1 - \frac{\sqrt{2}}{2}$, and

$$P(\tau > t) = \frac{3 + 2\sqrt{2}}{6}\,\mathrm{e}^{-\alpha_1 t} + \frac{3 - 2\sqrt{2}}{6}\,\mathrm{e}^{-\alpha_2 t} \qquad (t \geqslant 0)$$

$$f_\tau(t) = \frac{2 + \sqrt{2}}{12}\,\mathrm{e}^{-\alpha_1 t} + \frac{2 - \sqrt{2}}{12}\,\mathrm{e}^{-\alpha_2 t} \qquad (t > 0)$$

$$f_\sigma(t) = \mathrm{e}^{-t} \qquad (t > 0).$$

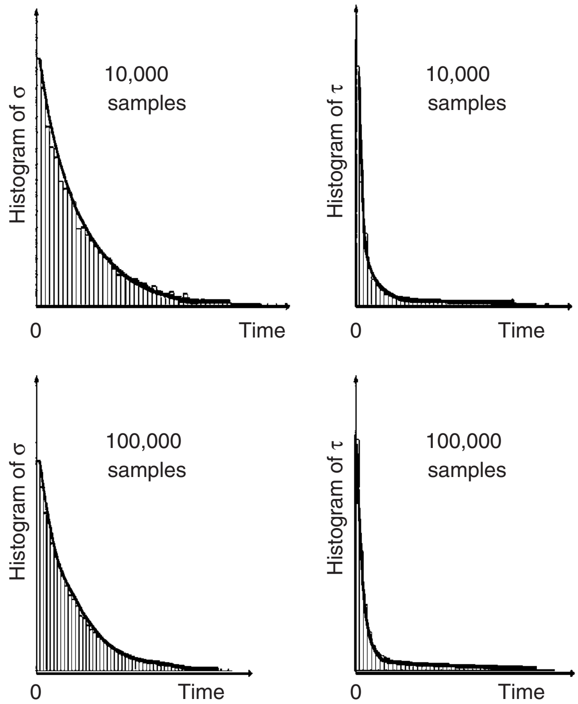

Figure 5. Lifetime and death-time histograms of example 1 with 10 000 samples (upper panel), with 100 000 samples (bottome panel).

We can calculate the transition rate matrix Q from $f_\sigma(t)$ and $f_\tau(t)$ by using the method of lemma 4. We omit the details to avoid repeating similar thing in example 2.

In the following we first get the i.i.d. sample sequences of σ and τ, by simulating the sample path of this Q-process, and then we obtain the estimates of the p.d.fs of σ and τ, and finally we calculate the corresponding transition rate matrix in (4.3) and (4.2) (see figure 5). From figure 3 for 10 000 and 100 000 σ and τ respectively, we can see that the accuracies of such estimates for the p.d.fs of σ and τ are very good.

(1) *10 000 samples.* The estimating p.d.fs of σ and τ are (see figure 5)

$$f_\sigma(t) = 1.000\,970\,\mathrm{e}^{-1.000\,970t}$$

$$f_\tau(t) = 3.279\,642\,\mathrm{e}^{-0.293\,548t} + 0.024\,288\,\mathrm{e}^{-1.534\,449t}.$$

The transition matrix obtained from $f_\sigma(t)$ and $f_\tau(t)$ is

$$Q = \begin{pmatrix} -1.000\,970 & 1.000\,970 & 0 \\ 0.502\,388 & -0.931\,411 & 0.429\,023 \\ 0 & 0.896\,586 & -0.896\,586 \end{pmatrix}. \qquad (4.2)$$

(2) *100 000 samples.* The estimating p.d.fs of σ and τ are (see figure 5)

$$f_\sigma(t) = 1.000\,802\,\mathrm{e}^{-1.000\,802t}$$

$$f_\tau(t) = 3.324\,511\,\mathrm{e}^{-0.292\,942t} + 0.015\,630\,\mathrm{e}^{-1.676\,964t}.$$

The transition matrix obtained from $f_\sigma(t)$ and $f_\tau(t)$ is

$$Q = \begin{pmatrix} -1.000\,802 & 1.000\,802 & 0 \\ 0.477\,728 & -0.941\,594 & 0.463\,866 \\ 0 & 1.028\,313 & -1.028\,313 \end{pmatrix}. \qquad (4.3)$$

Comparing the matrices (4.3) and (4.2) with the original Q-matrix in (4.1), it illustrates that the statistics is very efficient.

Example 2 (estimation of single-ion channel)**.** From the experiment records in brain neurilemma of newborn mouse (see [21]), we obtain the estimation of p.d.fs of open time σ and shut time τ as follows

$$f_\sigma(t) = 0.1960\,\mathrm{e}^{-0.1960t}$$
$$f_\tau(t) = 0.006\,15\,\mathrm{e}^{-0.0504t} + 0.007\,25\,\mathrm{e}^{-0.0219t} + 0.209\,00\,\mathrm{e}^{-0.3840t}$$

where $N = 3$ is the total number of kinetically distinguishable shut states that the system can adopt. Using the method in section 3, we have

$$q_0 = -q_{0,0} = q_{0,1} = \lambda_0 = 0.1960. \tag{4.4}$$

Let

$$\alpha_1 = 0.0504 \qquad \alpha_2 = 0.0219 \qquad \alpha_3 = 0.3840$$
$$\gamma_1 = 0.006\,15 \qquad \gamma_2 = 0.007\,25 \qquad \gamma_3 = 0.209\,00.$$

Because $d_1 = \gamma_1 + \gamma_2 + \gamma_3 = 0.222\,40$, hence $\pi_0 = \frac{d_1}{\lambda_0 + d_1} = 0.531\,55$, $1 - \pi_0 = 0.468\,45$. Since

$$d_n = \gamma_1\alpha_1^{n-1} + \gamma_2\alpha_2^{n-1} + \gamma_3\alpha_3^{n-1} \qquad c_n = (1 - \pi_0)d_n = 0.468\,45 d_n$$

using the induction process in the proof of theorem 2, we can obtain that

$$\begin{aligned} q_{1,0} &= \mu_1 = \frac{c_2}{c_1} = 0.362\,971 \\ q_{1,2} &= \lambda_1 = \frac{c_3}{c_2} - \frac{c_2}{c_1} = 0.019\,036 \\ q_1 &= q_{1,0} + q_{1,2} = 0.382\,007 \end{aligned} \tag{4.5}$$

and

$$\begin{aligned} q_{2,1} &= \mu_2 = \frac{c_1(c_4 - q_1 c_3)}{c_1 c_3 - c_2^2} = 0.035\,693 \\ q_2 &= \lambda_2 + \mu_2 = \frac{c_5 - 2q_1 c_4 + q_1^2 c_3}{c_4 - q_1 c_3} = 0.040\,073 \\ q_{2,3} &= \lambda_2 = q_2 - \mu_2 = 0.004\,380 \end{aligned} \tag{4.6}$$

and

$$\begin{aligned} \mu_3 &= q_{3,2} \\ &= \frac{1}{\lambda_2(c_4 - q_1 c_3)}\big[c_6 - (2q_1 + q_2)c_5 + \big(q_1^2 + 2q_1 q_2 - \lambda_1\mu_2\big)c_4 - \big(q_1^2 q_2 - q_1\lambda_1\mu_2\big)c_3\big] \\ &= 0.031\,720. \end{aligned} \tag{4.7}$$

By (4.4)–(4.7),

$$Q = (q_{i,j}) = \begin{pmatrix} -0.196\,000 & 0.196\,000 & 0 & 0 \\ 0.362\,971 & -0.382\,007 & 0.019\,036 & 0 \\ 0 & 0.035\,693 & -0.040\,073 & 0.004\,380 \\ 0 & 0 & 0.031\,720 & -0.031\,720 \end{pmatrix}.$$

If we use O denoting the open state 0 and C_1, C_2, C_3 denoting the first, second, third shut states 1, 2, 3, respectively, then the transition rate between one state and another has the following form:

$$O \underset{0.362971}{\overset{0.196000}{\rightleftharpoons}} C_1 \underset{0.035693}{\overset{0.019036}{\rightleftharpoons}} C_2 \underset{0.031720}{\overset{0.004380}{\rightleftharpoons}} C_3.$$

From the results above, we know that the occupation time at the second and third shut states is usually longer than at the open state because their occupation times obey exponential distributions with smaller exponents. And if the ion channel is at the first shut state, it mostly goes to the open state, and rarely goes to the second and third shut states. Thus the observation record of conductance of ion channel tends to a kind of cluster phenomena. Here our results are consistent with the experimental results and biological intuitive view (see [21]).

5. Discussion

In the research of single-ion channel, there are many other sorts of mechanisms as proposed in [6–8], such as circle-form chains, etc. Thus there is the same problem to be considered, but it is seemly impossible to solve this problem by observing the lifetime and death-time at a single state. Let us look into the issues we discussed in the paper. Basically we intend to estimate $2N$ independent parameters in the Q matrix. What we have from experiments is a set of $2N + 1$ independent parameters in the distribution density function of the lifetime and death-time. Therefore the results: to recover the full matrix Q or characterize the full Markov chain in terms of the observation at a single state, might not be so surprising. For general case, it is certainly not possible.

Generally for Markov chains, we can propose the following open problems: if one can observe the lifetime and death-time of a subset of the whole state space, under what conditions of this subset, we can sufficiently determine the statistical characteristics of the whole Markov chain? In fact, the results in the present paper also suggest a new kind of statistics for Markov chains: to estimate the whole chain exclusively in terms of the observation of a part of states. We will apply our results to more biological data and report them in further publications in statistics journals.

Our ultimate purpose is to build a theory to bridge the single-channel activity and the single-cell activity, which lacks in the current literature despite many years research (for example, see [11, 12] for reviews).

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