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Identifying transition rates of ionic channels of star-graph branch type

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Abstract
We consider how to determine all transition rates of an ionic channel when it can be conformationally described by a star-graph branch Markov chain with continuous time. It is found that all transition rates are uniquely determined by the distributions of their lifetime and death-time at the end state of each branch. An algorithm to exactly calculate all transition rates is developed. Numerical examples are included to demonstrate the application of our approach to data.

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1. Introduction

The study of ionic channel activity plays an important role in biophysics and neuroscience [1, 10, 12, 29]. It serves as a bridge to connect molecular biology with cellular physiology: neuron spikes are generated due to the opening and closing of many ionic channels. Calcium channel is vital to the survival of the cell, to the long-term potentiation and depression and intra-cellular, extra-cellular signalling [6]. There are many different opening levels for an ionic channel. In general, an ionic channel can be conformationally described by a Markov chain with continuous time (there are different opinions, see for example [14, 15, 19, 21, 22, 24, 25, 27, 30, 31], whether it can be conformationally described by a Markov or non-Markov chain). The behaviour of ionic channels has been analysed in detail in the literature [7, 8, 29] in terms of a Markov chain with states at different opening levels. As an example let us consider the following case.

The ionic channel of star-graph chain. A single ionic channel has only one observable state, called open state (say state O), and N experimentally non-observable closed states (say state $C_1, C_2, \ldots, C_N$), which indicate different opening levels. For the channel, transition

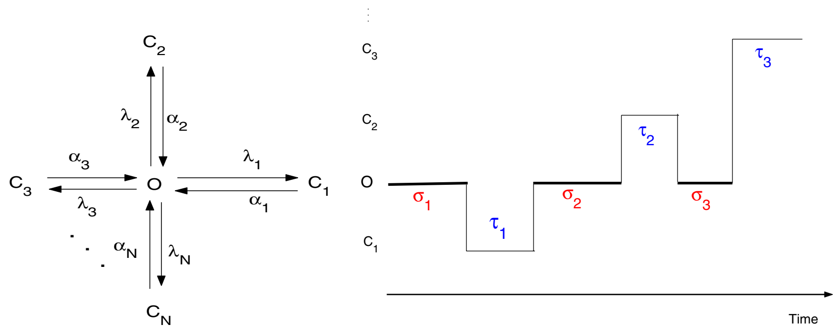

Figure 1. Left panel: schematic plot of a star-graph chain. Right panel: schematic plot of the trajectory of the star-graph chain activity. $\sigma_1, \sigma_2, \ldots$ are the lifetime sequences, and $\tau_1, \tau_2, \ldots$ are the death-time sequences.

cannot directly happen between the closed states; while each closed state can transit to the open state. Therefore, the closed states cannot intercommunicate directly but can only by going through the open state. The channel activity can be conformationally described by a star-graph chain with continuous time (see figure 1, left panel). Let us denote α_i and λ_i $(i = 1, \ldots, N)$ as transition rates from one state to another, i.e., they measure the 'speed' to jump from one to another. In the matrix term, we can define a matrix (transition rates matrix or Q matrix)

$$Q = \begin{pmatrix} -\sum_{i=1}^{N} \lambda_i & \lambda_1 & \lambda_2 & \cdots & \lambda_N \\ \alpha_1 & -\alpha_1 & 0 & \cdots & 0 \\ \alpha_2 & 0 & -\alpha_2 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \alpha_N & 0 & 0 & \cdots & -\alpha_N \end{pmatrix},$$

which contains all information of the activity of the chain.

In a biological experiment, the ionic channel activity is usually only partly observable [9, 10, 12, 29]. For example, only the open state is observable in the star-graph chain depicted in figure 1. For the open state of the ionic channel, let σ be its open time (lifetime) and τ its closed time (death-time). The observations of σ and τ are denoted by $\sigma_1, \sigma_2, \ldots$ and $\tau_1, \tau_2, \ldots$ as in figure 1 (right panel). The histogram of σ is called the lifetime histogram and the histogram of τ is the death-time histogram.

It is always relatively easy to determine the lifetime and death-time histograms of a single state. Suppose we know exactly the lifetime histogram and death-time histogram of every open state. Can we uniquely determine the full-channel activity in terms of the data from the observation of these open states? By this, we mean to obtain the transition rates from one state to another state. For example, in the star-graph chain as in figure 1, we have the distribution density of τ and σ, we intend to find out constants α_i and $\lambda_i (i = 1, \ldots, N)$.

The issue that how to determine all transition rates in terms of the partial observation of the whole-channel activity, as one might expect, has been addressed early in the literature [16]. In [16], they estimated the matrix Q, directly using the maximum likelihood estimate. However, the estimation could be very rough since it involves the estimating of some latent variables. In the current paper, we develop a totally different approach. Our algorithms employ the intrinsic

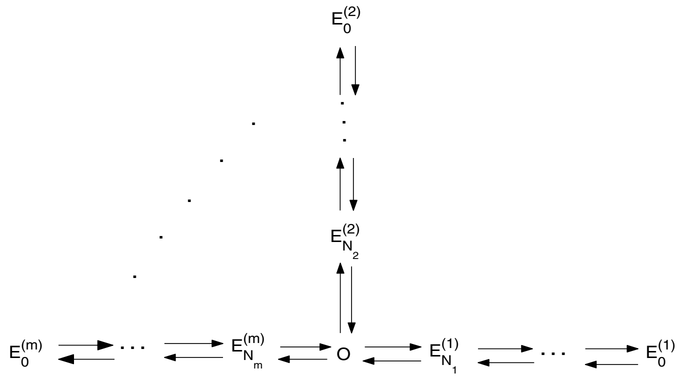

Figure 2. Schematic plot of a star-graph branch Markov chain.

properties of the Markov process and all calculations are simply reduced to the estimation of PDFs (probability density functions) of lifetime and death-time of observable states. Once we have them, all subsequent calculations are then automatic and exact. Hence we expect that our approach provides us with a more powerful and natural way to estimate transition rates. The star-graph chain, birth–death chain, cyclic chain and hierarchical chain are reported in our series of publications [11, 34, 35]. Here we take into account the star-graph branch Markov chain ionic channel. It is found that all transition rates are uniquely determined by the PDFs of the lifetime and death-time at the end state of each branch.

In section 2, we address the issues mentioned above, including all theoretical conclusions, proofs and algorithms. In section 3, we present a numerical example to illustrate the applications of our algorithm to data.

2. Statistics of star-graph branch Markov chain

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 matrix A. We adopt the standard convention that the infimum of an empty set is infinity.

Consider an ionic channel which can be described by a star-graph branch Markov chain $\{X_t; t \geqslant 0\}$ (see figure 2) with a state space

$$S = \left\{E_0^{(1)}, E_1^{(1)}, \ldots, E_{N_1}^{(1)}, E_0^{(2)}, E_1^{(2)}, \ldots, E_{N_2}^{(2)}, \ldots\ldots, E_0^{(m)}, E_1^{(m)}, \ldots, E_{N_m}^{(m)}, O\right\}.$$

and the transition rate matrix $Q = (q_{ij})$ satisfies

$$Q = (q_{ij})_{S\times S} = \begin{pmatrix} H_1 & O & O & \cdots & O & A_1 \\ O & H_2 & O & \cdots & O & A_2 \\ O & O & H_3 & \cdots & O & A_3 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ O & O & O & \cdots & H_m & A_m \\ B_1 & B_2 & B_3 & \cdots & B_m & -q \end{pmatrix}$$

where

$$S_k = \left\{E_0^{(k)}, E_1^{(k)}, \ldots, E_{N_k}^{(k)}\right\}, \qquad 1 \leqslant k \leqslant m,$$

and

$$H_k = \left(q_{ij}^{(k)}\right)_{S_k \times S_k} = \begin{pmatrix} -\lambda_0^{(k)} & \lambda_0^{(k)} & 0 & \cdots & 0 & 0 \\ \mu_1^{(k)} & -\left(\lambda_1^{(k)} + \mu_1^{(k)}\right) & \lambda_1^{(k)} & \cdots & 0 & 0 \\ 0 & \mu_2^{(k)} & -\left(\lambda_2^{(k)} + \mu_2^{(k)}\right) & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & \mu_{N_k}^{(k)} & -\left(\mu_{N_k}^{(k)} + a_k\right) \end{pmatrix},$$

with

$$\begin{aligned} &A_k = \left(q_{ij}^{(k)}\right)_{S_k \times 1} = \langle 0, 0, \ldots, a_k \rangle, && a_k > 0, 1 \leqslant k \leqslant m, \\ &B_k = \left(q_{ij}^{(k)}\right)_{1 \times S_k} = (0, 0, \ldots, b_k), && b_k > 0, 1 \leqslant k \leqslant m, \\ &\lambda_i^{(k)} > 0 (0 \leqslant i \leqslant N_k - 1), && 1 \leqslant k \leqslant m, \\ &\mu_i^{(k)} > 0 (1 \leqslant i \leqslant N_k), && 1 \leqslant k \leqslant m, \\ &q = \sum_{k=1}^{m} b_k. \end{aligned}$$

It is easy to know that the chain $\{X_t : t \geqslant 0\}$ is reversible. Thus there exists an invariant probability measure

$$\widehat{\pi} = \left\{\pi_0^{(1)}, \ldots, \pi_{N_1}^{(1)}, \pi_0^{(2)}, \ldots, \pi_{N_2}^{(2)}, \ldots\ldots, \pi_0^{(m)}, \ldots, \pi_{N_m}^{(m)}, \pi\right\}$$

such that

$$\operatorname{diag}(\widehat{\pi}) * Q = (\operatorname{diag}(\widehat{\pi}) * Q)^T = Q^T * \operatorname{diag}(\widehat{\pi}), \tag{1}$$

and

$$\sum_{k=1}^{m} \sum_{i=0}^{N_k} \pi_i^{(k)} + \pi = 1. \tag{2}$$

In the following sections, we first work out how to estimate all transition rates along the branch of $E_0^{(1)}$, and the conclusions are generalized to the general case.

2.1. Observation at the end state $E_0^{(1)}$

Define $\tau = \inf\left\{t > 0, X_t = E_0^{(1)}\right\}$ and $\sigma = \inf\left\{t > 0, X_t \neq E_0^{(1)}\right\}$ (the death-time and lifetime at the end state $E_0^{(1)}$, respectively). In the following, we will prove that every element of H_1 and A_1 can be uniquely determined by the PDFs of the lifetime and death-time at the end state $E_0^{(1)}$.

For the concise of notation, we rewrite the state space S as

$$S = \{0, 1, 2, \ldots, M, M+1, \ldots\ldots, N\}$$

with $M = N_1, N = \sum_{k=1}^{m}(N_k + 1)$.

Simply to write $Q = (q_{ij})_{S \times S}$ and $\widehat{\pi} = \{\pi_0, \pi_1, \ldots, \pi_M, \pi_{M+1}, \ldots, \pi_N\}$. Then

$$H_1 = (q_{ij})_{S_1 \times S_1} = \begin{pmatrix} -\lambda_0 & \lambda_0 & 0 & \cdots & 0 & 0 \\ \mu_1 & -(\lambda_1 + \mu_1) & \lambda_1 & \cdots & 0 & 0 \\ 0 & \mu_2 & -(\lambda_2 + \mu_2) & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & \mu_M & -(\mu_M + a_1) \end{pmatrix},$$

where $\lambda_i > 0 (0 \leqslant i \leqslant M - 1)$, $\mu_i > 0 (1 \leqslant i \leqslant M)$, $S_1 = \{0, 1, 2, \ldots, M\}$.

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 $(S_0 = \{1, 2, \ldots, N\})$. Define

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

Thus

$$P(\tau > t) = \sum_{i=1}^{N} P(\tau > t | X_0 = i) P_{S_0}(X_0 = i) = \sum_{i=1}^{N} \pi_i{}^* \sum_{j=1}^{N} \widehat{p}_{ij}(t), \tag{3}$$

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

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

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

where $\Pi = \mathrm{diag}(\pi_1, \pi_2, \ldots, \pi_N)$.

It is easy to verify that $\widehat{P}$ and $\widehat{Q}$ are symmetric linear transition matrices with respect to the inner product $(\cdot, \cdot)_\Pi$. Thus $\widehat{Q}$ has N real eigenvalues $-\alpha_1, -\alpha_2, \ldots, -\alpha_N$ such that $\alpha_i > 0$ (see [3, 36]) 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 $i, j \in S$,

$$\widehat{Q}\epsilon_i = -\alpha_i \epsilon_i, \tag{4}$$

$$(\epsilon_i, \epsilon_j)_\Pi = \sum_{k=1}^{N} \epsilon_{ki} \epsilon_{kj} \pi_k = \delta_{ij}. \tag{5}$$

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 (4) and (5), we get

$$\begin{aligned} \widehat{Q} &= -W^{-1} A W, \qquad & W^T W &= \Pi, \\ W\widehat{Q} &= -AW, \qquad & \Pi \widehat{Q} &= -W^T A W. \end{aligned} \tag{6}$$

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) and (6), for $t \geqslant 0$

$$\begin{aligned} P(\tau > t) &= \frac{1}{1-\pi_0} \sum_{i=1}^{N} \pi_i \sum_{j=1}^{N} \widehat{p}_{ij}(t) \\ &= \frac{1}{1-\pi_0} \sum_{i=1}^{N} \pi_i (\widehat{P}(t)\mathbf{I})_i \\ &= \frac{1}{1-\pi_0} \mathbf{I}^T \Pi W^{-1} \mathrm{e}^{-At} W\mathbf{I} \\ &= \frac{1}{1-\pi_0} \beta^T \mathrm{e}^{-At} \beta \\ &= \frac{1}{1-\pi_0} \sum_{i=1}^{N} \beta_i{}^2 \mathrm{e}^{-\alpha_i t}. \end{aligned} \tag{7}$$

If we put

$$\begin{aligned}
\gamma_i &= \frac{\beta_i^2\alpha_i}{1-\pi_0}, && 1 \leqslant i \leqslant N, \\
c_n &= \sum_{i=1}^{N} {\beta_i}^2 {\alpha_i}^n = \beta^T A^n \beta, && n \geqslant 0, \\
d_n &= \sum_{i=1}^{N} \gamma_i \alpha_i^{n-1}, && n \geqslant 0,
\end{aligned} \tag{8}$$

then we have

$$c_n = (1-\pi_0)d_n. \tag{9}$$

Lemma 2.1.1.

(i) The PDF of the lifetime σ is

$$f_\sigma(t) = \begin{cases} \lambda_0\,\mathrm{e}^{-\lambda_0 t} & \text{if } t > 0, \\ 0 & \text{if } t \leqslant 0. \end{cases} \tag{10}$$

Thus $\lambda_0 = \frac{1}{E\sigma}$. Therefore, λ_0 can be estimated by the PDF of σ.

(ii) The PDF of the death-time τ is

$$f_\tau(t) = \begin{cases} \sum_{i=1}^{N} \gamma_i\,\mathrm{e}^{-\alpha_i t} & \text{if } t > 0, \\ 0 & \text{if } t \leqslant 0. \end{cases} \tag{11}$$

Lemma 2.1.2. *The following conclusions hold.*

(i)

$$\pi_0 = \frac{d_1}{\lambda_0 + d_1}. \tag{12}$$

(ii) For $1 \leqslant n \leqslant M-1$, a_1 and λ_n can be expressed in terms of rational functions of $\{\lambda_0, d_1, d_2, \ldots, d_{2n+1}\}$.

(iii) For $1 \leqslant n \leqslant M$, μ_n can be expressed in terms of rational functions of $\{\lambda_0, d_1, d_2, \ldots, d_{2n}\}$, where $d_n = \sum_{i=1}^{N} \gamma_i \alpha_i^{n-1}$, $n \geqslant 1$.

Proof. Since $\widehat{Q}\mathbf{I} = \langle -q_{10}, 0, \ldots, 0\rangle$, by (6), we have

$$\pi_1 q_{10} = -\mathbf{I}^T \Pi \widehat{Q}\mathbf{I} = \mathbf{I}^T W^T A W \mathbf{I} = \beta^T A \beta = c_1. \tag{13}$$

By (1), $\pi_0\lambda_0 = \pi_1 q_{10}$, then $\pi_0\lambda_0 = c_1 = (1-\pi_0)d_1$. Thus (i) holds true.

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

According to $\pi_0 = \frac{d_1}{\lambda_0+d_1}$, $c_n = \frac{\lambda_0 d_n}{\lambda_0+d_1}$ and $a_1 = q_M - q_{M,M-1}$, we only need to prove the following facts: for $1 \leqslant n \leqslant M$,

(H1) $\mu_n = q_{n,n-1}$, $\lambda_n + \mu_n = -q_{nn} = q_n$, $\lambda_n = q_{n,n+1}$ 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

$$W\widehat{Q}\mathbf{I} = W\langle -q_{10}, 0, \ldots, 0\rangle = -q_{10}W_1,$$

then by (6), we get

$$q_{10}W_1 = A\beta. \tag{14}$$

Thus

$$\pi_1 q_{10}^2 = W_1^T W_1 q_{10}^2 = (A\beta)^T(A\beta) = \beta^T A^2 \beta = c_2. \tag{15}$$

By (13)–(15), we obtain

$$\begin{aligned} \mu_1 &= q_{10} = \frac{\pi_1 q_{10}^2}{\pi_1 q_{10}} = \frac{c_2}{c_1}, \\ \pi_1 &= \frac{(\pi_1 q_{10})^2}{\pi_1 q_{10}^2} = \frac{c_1^2}{c_2}, \\ W_1 &= \frac{c_1}{c_2} A\beta \equiv g_1(A)A\beta, \end{aligned} \tag{16}$$

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

Again by (6), $\Pi\widehat{Q} = -W^T A W$, that is to say

$$\pi_i q_{ij} = -W_i^T A W_j, \qquad i, j \in S_0, \tag{17}$$

and again by (14),

$$\pi_1 q_1 = W_1^T A W_1 = \frac{1}{q_{10}^2}(q_{10}W_1)^T A(q_{10}W_1) = \frac{1}{q_{10}^2}(A\beta)^T A(A\beta) = \frac{c_3}{q_{10}^2}.$$

Thus by (15)

$$\lambda_1 + \mu_1 = -q_{11} = q_1 = \frac{c_3}{\pi_1 q_{10}^2} = \frac{c_3}{c_2}, \qquad q_{12} = \lambda_1 = q_1 - q_{10} = \frac{c_3}{c_2} - \frac{c_2}{c_1}. \tag{18}$$

Therefore, according to (16) and (18), 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 (6), we have

$$q_{k+1,k}W_{k+1} = (q_k I - A)W_k - q_{k-1,k}W_{k-1}. \tag{19}$$

By (17), we get

$$\pi_{k+1}q_{k+1,k} = \pi_k q_{k,k+1} = -W_k^T A W_{k+1}. \tag{20}$$

Hence

$$\begin{aligned} q_{k+1,k} &= \frac{q_{k+1,k}}{\pi_k q_{k,k+1}}\left(-W_k^T A W_{k+1}\right) \text{ (by (20))} \\ &= \frac{1}{\pi_k q_{k,k+1}}\left[W_k^T A(A - q_k I)W_k + q_{k-1,k}W_k^T A W_{k-1}\right] \text{ (by (19))} \\ &\equiv \beta^T A h(A) A\beta, \end{aligned} \tag{21}$$

where

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

By the inductive assumptions (H1), $\pi_k, q_{k,k+1}$ are rational functions of $\{c_1, c_2, \ldots, c_{2k+1}\}$. 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 (8) (i.e. $\beta^T A^n \beta = c_n$) and (23), $q_{k+1,k}$ is a rational function of $\{c_1, c_2, \ldots, c_{2k+1}, c_{2k+2}\}$ and so is $\pi_{k+1} = \frac{\pi_k q_{k,k+1}}{q_{k+1,k}}$.

Now let us prove that W_{k+1} has the properties of the inductive assumption in (H2). Again using (19) 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 (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 $n = k + 1 (1 \leqslant n \leqslant M)$. $\square$

From lemmas 2.1.1 and 2.1.2, we can easily obtain the following theorem.

Theorem 2.1.3. *If $\{\pi_i, i \in S\}$ is the invariant probability measure of star-graph branch Markov chain $\{X_t; t \geqslant 0\}$, then $\{\pi_i, i \in S_1\}$ and every element of H_1 and A_1 can be determined by the PDFs of the lifetime and death-time at the end state $E_0^{(k)}$.*

Algorithm 2.1.4 (algorithm of calculating H_1 and A_1)**.** *Suppose that we have the corresponding PDFs as defined by lemma 2.1.1.*

Step 1. Calculate $\gamma_i, \alpha_i (i = 1, 2, \ldots, N), d_1$ and $c_j (j = 1, 2, \ldots, 2M + 1)$ according to equations (11), (8) and (9).

Step 2. Calculate $\pi_0, q_{10}, \pi_1, q_{11}, q_{12}$, according to (12), (16) and (18), and

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

Step 3. Suppose that we have $\pi_j, q_{j,j-1}, q_{jj}$ and $q_{j,j+1}$ for $j = 1, 2, \ldots, n$, then we calculate

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

where

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

with $g_0(A) = 0$,

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

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

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

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

Step 4. For $n = M$, we have simply $q_{M,M+1} = 0, a_1 = -q_{MM} - q_{M,M-1}$.

2.2. Observation at the end state $E_0^{(k)}$

Let

$$S = \left\{E_0^{(k)}, E_1^{(k)}, \ldots, E_{N_k}^{(k)}, \ldots\ldots, O\right\}, \qquad Q = (q_{ij})_{S\times S} = \begin{pmatrix} H_k & \cdots & A_k \\ \vdots & \ddots & \vdots \\ B_k & \cdots & -q \end{pmatrix}.$$

Define $\tau^{(k)} = \inf\left\{t > 0, X_t = E_0^{(k)}\right\}$ and $\sigma^{(k)} = \inf\left\{t > 0, X_t \neq E_0^{(k)}\right\}$ (the death-time and lifetime at the end state $E_0^{(k)}$, respectively). According to discussions in section 2.1.1, we have

Theorem 2.2.1. *If $\{\pi_i, i \in S\}$ is the invariant probability measure of star-graph branch Markov chain $\{X_t; t \geqslant 0\}$, then $\{\pi_i, i \in S_k\}$ and every element of H_k and A_k can be determined by the PDFs of the lifetime and death-time for the end state $E_0^{(k)} (k = 1, \ldots, m)$.*

2.3. Main theorem and algorithm

Theorem 2.3.1. *If $\{\pi_i, i \in S\}$ is the invariant probability measure of a star-graph branch Markov chain $\{X_t; t \geqslant 0\}$, then all transition rates of $\{X_t; t \geqslant 0\}$ can be determined by the PDFs of lifetime and death-time at the end state of each branch (i.e., $E_0^{(1)}, E_0^{(2)}, \ldots, E_0^{(m)}$).*

Proof. By theorem 2.2.1, a_k in A_k and every element $q_{ij}^{(k)} (i, j \in S_k)$ of H_k can be determined by the PDFs of the lifetime and death-time for the end state $E_0^{(k)} (k = 1, \ldots, m)$.

Again by (1) and (2), we have

$$\pi = 1 - \sum_{k=1}^{m}\sum_{i=0}^{N_k} \pi_i^{(k)}, \qquad b_k = \frac{\pi_{N_k}^{(k)} a_k}{\pi}, \quad k = 1, \ldots, m.$$

Therefore

$$q = \sum_{k=1}^{m} b_k.$$

It can be seen from above that all conclusions of the theorem follow. □

Algorithm 2.3.2 (algorithm of calculating Q)**.** *Suppose that we have H_k, A_k and $\pi_i^{(k)} (k = 1, 2, \ldots, m)$ according to algorithm 2.1.4}, then*

Step 1. Calculate $\pi = 1 - \sum_{k=1}^{m}\sum_{i=0}^{N_k}\pi_i^{(k)}$ according to equation (2).

Step 2. Calculate b_k in $B_k (1 \leqslant k \leqslant m)$ as follows:

$$b_k = \frac{\pi_{N_k}^{(k)} a_k}{\pi}.$$

Step 3. We have simply $q = \sum_{k=1}^{m} b_k$.

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 star-graph branch chain $\{X_t : t \geqslant 0\}$. We define two i.i.d. sample sequences on $\mathbf{X}$, the lifetime sample sequence $\left\{\sigma_n^{(k)} : n \geqslant 0\right\}$ and the death-time sample sequence $\left\{\tau_n^{(k)} : n \geqslant 0\right\}$ of the state $E_0^{(k)}$ $(k = 1, \ldots, m)$ as follows:

$$\tau_n^{(k)} = t_{2n} - t_{2n-1} \quad (n \geqslant 0),$$
$$\sigma_n^{(k)} = t_{2n+1} - t_{2n} \quad (n \geqslant 0),$$

and

$$t_{-1}^{(k)} \equiv 0,$$
$$t_0^{(k)} = \inf\left\{t > 0 : X_t = E_0^{(k)}\right\},$$
$$t_1^{(k)} = \inf\left\{t > t_0 : X_t \neq E_0^{(k)}\right\},$$

for any $n \geqslant 1$,

$$t_{2n}^{(k)} = \inf\left\{t > t_{2n-1} : X_t = E_0^{(k)}\right\}, \qquad t_{2n+1}^{(k)} = \inf\left\{t > t_{2n} : X_t \neq E_0^{(k)}\right\}.$$

In theorem 2.3.4, we will present a new approach to estimate the transition rates for the star-graph-type Markov chain in terms of the lifetime sequence $\left\{\sigma_n^{(k)} : n \geqslant 0\right\}$ and the death-time sequence $\left\{\tau_n^{(k)} : n \geqslant 0\right\}$. To this end, we first prove the following lemma.

Lemma 2.3.3. *If* $\{\pi_i, i \in S\}$ *is the invariant probability measure of star-graph branch Markov chain* $\{X_t; t \geqslant 0\}$*, then* a_k *in* A_k *and every element* q_{ij} $(i, j \in S_k)$ *of* H_k *can be estimated in terms of the i.i.d. sample sequences* $\left\{\sigma_n^{(k)} : n \geqslant 0\right\}$ *and* $\left\{\tau_n^{(k)} : n \geqslant 0\right\}$ $(k = 1, \ldots, m)$.

Proof. Without loss of generality, we only prove the conclusion with $k = 1$. First, by the law of large number, we note that the PDFs $f_\sigma(t)$ and $f_\tau(t)$ of σ and τ, i.e. λ_0, α_i and γ_i $(i = 1, 2, \ldots, N)$ can be estimated by the i.i.d. sample sequences $\{\sigma_n\}$ and $\{\tau_n\}$. Next, by lemmas 1 and 2, a_1 and q_{ij} $(i, j \in S_1)$ are fractional functions of λ_0 and d_n $(n = 1, 2, \ldots, 2M + 1)$, which is the rational function of α_i and γ_i $(i = 1, 2, \ldots, N)$. Therefore the conclusions of the theorem hold true. □

In summary, we arrive at the following conclusions.

Theorem 2.3.4. *For a star-graph branch Markov chain* $\{X_t; t \geqslant 0\}$*, all transition rates of* $\{X_t; t \geqslant 0\}$ *can be exactly estimated based upon the i.i.d. sample sequences* $\left\{\sigma_n^{(k)} : n \geqslant 0\right\}$ *and* $\left\{\tau_n^{(k)} : n \geqslant 0\right\}$ $(1 \leqslant k \leqslant m)$.

3. Numerical examples

To demonstrate how to apply our algorithms to real data, we present a numerical example here. As we mentioned before, the data we have are the observed PDFs of lifetime and death-time at the end state of each branch. Based upon these data, we could find all the transition rates of an ionic channel.

Example. An ionic channel can be conformationally described by a star-graph branch Markov chain (see figure 3) with state space $S = \{0, 1, 2, 3, 4, 5, 6, 7, 8, 9\}$ (states 0, 3 and 6 are three end and therefore open states) and the true transition rates matrix $Q = (q_{ij})_{S\times S}$ is given by

$$Q = \begin{pmatrix} -10 & 10 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 20 & -70 & 50 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 25 & -75 & 0 & 0 & 0 & 0 & 0 & 0 & 50 \\ 0 & 0 & 0 & -100 & 100 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 200 & -350 & 200 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 300 & -450 & 0 & 0 & 0 & 150 \\ 0 & 0 & 0 & 0 & 0 & 0 & -25 & 25 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 50 & -250 & 200 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 100 & -300 & 200 \\ 0 & 0 & 100 & 0 & 0 & 50 & 0 & 0 & 50 & -200 \end{pmatrix}. \tag{22}$$

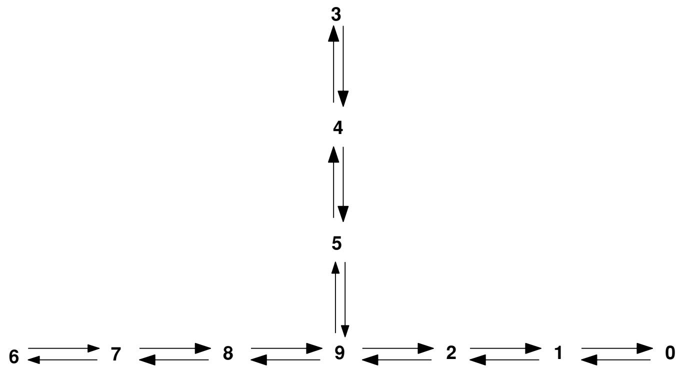

Figure 3. Schematic plot of a star-graph branch Markov chain with three branches.

We can divide the calculation into two steps: fitting lifetime and death-time histogram and transition rates estimation.

Step 1 (lifetime and death-time histogram estimate). Suppose that we have obtained the PDFs of lifetime and death-time by observation and their histograms can be fitted (see Discussion) as follows:

$$\begin{aligned} f_\tau(t) &= 0.000\,0001\mathrm{e}^{-643.796\,756t} + 0.000\,004\mathrm{e}^{-445.713\,365t} \\ &\quad + 0.000\,149\mathrm{e}^{-285.848\,968t} + 0.001\,718\mathrm{e}^{-205.873\,825t} + 0.068\,305\mathrm{e}^{-121.755\,971t} \\ &\quad + 0.464\,591\mathrm{e}^{-76.342\,605t} + 1.901\,507\mathrm{e}^{-1.953\,757t} + 0.416\,733\mathrm{e}^{-22.161\,497t} \\ &\quad + 0.021\,244\mathrm{e}^{-16.553\,257t} \qquad (t \geqslant 0), \\ f_\sigma(t) &= 10\mathrm{e}^{-10t} \qquad (t > 0). \end{aligned} \tag{23}$$

$$\begin{aligned} f_{\tau'}(t) &= 1.949\,789\mathrm{e}^{-630.123\,531t} + 0.120\,315\mathrm{e}^{-444.791\,002t} \\ &\quad + 2.895\,117\mathrm{e}^{-255.440\,780t} + 8.128\,486\mathrm{e}^{-167.600\,852t} + 0.310\,173\mathrm{e}^{-121.094\,790t} \\ &\quad + 0.706\,960\mathrm{e}^{-75.276\,457t} + 0.333\,774\mathrm{e}^{-20.585\,844t} + 2.274\,442\mathrm{e}^{-2.686\,048t} \\ &\quad + 0.767\,283\mathrm{e}^{-12.400\,696t} \qquad (t \geqslant 0), \\ f_{\sigma'}(t) &= 100\mathrm{e}^{-100t} \qquad (t > 0). \end{aligned} \tag{24}$$

$$\begin{aligned} f_{\tau''}(t) &= 0.000\,022\mathrm{e}^{-643.796\,957t} + 0.024\,344\mathrm{e}^{-444.809\,621t} \\ &\quad + 0.013\,629\mathrm{e}^{-285.322\,792t} + 0.040\,708\mathrm{e}^{-204.266\,920t} + 0.078\,292\mathrm{e}^{-118.785\,191t} \\ &\quad + 0.038\,611\mathrm{e}^{-76.566\,327t} + 0.011\,004\mathrm{e}^{-22.910\,254t} + 0.501\,357\mathrm{e}^{-0.502\,944t} \\ &\quad + 0.009\,738\mathrm{e}^{-8.039\,996t} \qquad (t \geqslant 0), \\ f_{\sigma''}(t) &= 25\mathrm{e}^{-25t} \qquad (t > 0). \end{aligned} \tag{25}$$

where

$f_\sigma(t)$ ($f_\tau(t)$) is the PDF of lifetime (death-time) at the state 0;
$f_{\sigma'}(t)$ ($f_{\tau'}(t)$) is the PDF of lifetime (death-time) at the state 3;
$f_{\sigma''}(t)$ ($f_{\tau''}(t)$) is the PDF of lifetime (death-time) at the state 6.

Step 2 (transition rate calculations). Firstly, by (23) and according to algorithm 2.3.2, we have

$$q_0 = -q_{00} = q_{01} = 10.$$

Let

$$\begin{array}{lll}
\alpha_1 = 643.796\,756, & \alpha_2 = 445.713\,365, & \alpha_3 = 285.848\,968,\\
\alpha_4 = 205.873\,825, & \alpha_5 = 121.755\,971, & \alpha_6 = 76.342\,605,\\
\alpha_7 = 1.953\,757, & \alpha_8 = 22.161\,497, & \alpha_9 = 16.553\,257;\\
\gamma_1 = 0.000\,0001, & \gamma_2 = 0.000\,004, & \gamma_3 = 0.000\,149,\\
\gamma_4 = 0.001\,718, & \gamma_5 = 0.068\,305, & \gamma_6 = 0.464\,591,\\
\gamma_7 = 1.901\,507, & \gamma_8 = 0.416\,733, & \gamma_9 = 0.021\,244.
\end{array}$$

Because $d_1 = \sum_{i=1}^{9} \gamma_i = 2.874\,251$, hence $\pi_0 = \frac{d_1}{q_{01}+d_1} = 0.223\,256$, $1 - \pi_0 = 0.776\,744$. Since

$$d_n = \sum_{i=1}^{9} \gamma_i \alpha_i^{n-1},\ c_n = (1-\pi_0) d_n = 0.776\,744 d_n,$$

we have

$$\begin{array}{lll}
c_1 = 2.232\,558, & c_2 = 44.651\,163, & c_3 = 3125.581\,395,\\
c_4 = 274\,604.651\,163, & c_5 = 27\,315\,348.837\,209. &
\end{array}$$

Thus, we can obtain that

$$\begin{array}{ll}
q_{10} = \dfrac{c_2}{c_1} = 20.000\,001, & q_1 = \dfrac{c_3}{c_2} = 69.999\,999,\\
\pi_1 = \dfrac{c_1^2}{c_2} = 0.111\,628, & q_{12} = q_1 - q_{10} = 49.999\,998,\\
q_{21} = \dfrac{c_1 * (c_4 - q_1 * c_3)}{(c_1 * c_3 - c_2^2)} = 25.000\,001, & \pi_2 = \dfrac{\pi_1 q_{12}}{q_{21}} = 0.223\,256,\\
q_2 = \dfrac{c_5 - 2 * q_1 * c_4 + q_1^2 * c_3}{c_4 - q_1 * c_3} = 74.999\,999, & q_{29} = q_2 - q_{21} = 49.999\,998.
\end{array}$$

Therefore

$$H_1 = \begin{pmatrix} -10 & 10 & 0 \\ 20.000\,001 & -69.999\,999 & 49.999\,998 \\ 0 & 25.000\,001 & -74.999\,999 \end{pmatrix}, \qquad A_1 = \begin{pmatrix} 0 \\ 0 \\ 49.999\,998 \end{pmatrix}. \tag{26}$$

Secondly, by (24) and (25), using the same method as above, we have

$$H_2 = \begin{pmatrix} -100 & 100 & 0 \\ 199.999\,999 & -350.000\,000 & 150.000\,001 \\ 0 & 299.999\,998 & -450.000\,000 \end{pmatrix}, \qquad A_2 = \begin{pmatrix} 0 \\ 0 \\ 150.000\,002 \end{pmatrix}. \tag{27}$$

$$H_3 = \begin{pmatrix} -25 & 25 & 0 \\ 50.000\,030 & -249.999\,999 & 199.999\,969 \\ 0 & 100.000\,016 & -299.999\,999 \end{pmatrix}, \qquad A_3 = \begin{pmatrix} 0 \\ 0 \\ 199.999\,983 \end{pmatrix}. \tag{28}$$

Finally, according to algorithm 2.3.2, we can obtain that

$$\pi_9 = 1 - \sum_{i=0}^{8} \pi_i = 0.111\,626,$$
$$q_{92} = \frac{\pi_2 q_{29}}{\pi_9} = \frac{0.223\,256 * 49.999\,998}{0.111\,626} = 100.000\,179,$$
$$q_{95} = \frac{\pi_5 q_{59}}{\pi_9} = \frac{0.037\,209 * 150.000\,002}{0.111\,626} = 50.000\,449,$$
$$q_{98} = \frac{\pi_8 q_{89}}{\pi_9} = \frac{0.027\,907 * 199.999\,983}{0.111\,626} = 50.000\,892,$$
$$q_9 = q_{92} + q_{95} + q_{98} = 200.001\,520.$$

Thus, we have

$$B_1 = (0\ 0\ 100.000\,179), \qquad B_2 = (0\ 0\ 50.000\,449), \qquad B_3 = (0\ 0\ 50.000\,892) \tag{29}$$

and the transition rate matrix of $\{X_t : t \geqslant 0\}$ is given by

$$Q = \begin{pmatrix} H_1 & O & O & A_1 \\ O & H_2 & O & A_2 \\ O & O & H_3 & A_3 \\ B_1 & B_2 & B_3 & -200.001\,520 \end{pmatrix}. \tag{30}$$

where H_k, A_k and $B_k (k = 1, 2, 3)$ are given in (26), (27), (28) and (29).

Comparing the matrix (30) with the original Q matrix (22), it is not difficult to find that our approach is very efficient under the condition that we obtain an accurate PDF of their death-time and lifetime at the end state of each branch.

4. Discussion

Algorithms, based upon rigorous results, have been presented to estimate all transition rates of a star-graph branch type Markov chain, with observations at the end state of each branch. In comparison with maximum likelihood approaches in the literature, our approach has explored the intrinsic mechanisms of the Markov chain and has obvious advantages as we have discussed in previous sections.

As pointed out in the introduction, in experiments we are not able to access data of all states of an ionic channel. The key issue is then how many states are necessary to be observed to figure out all details of an ionic channel. We answer the question in our paper and it should be helpful for colleagues working on experiments when they design their experimental set-up, and finally leads to a better understanding on how an ionic channel functions. However, our approach has pros and cons. The main issue is related to the estimation of the histogram of the lifetime and death-time.

- *Structure issue*. For a single-ionic channel, there are many possible and different ways of open and closed states [4, 26]. The consideration in our current papers is a special case: the star-graph branch type. We have to resort to experimentlists to decide whether a channel behaves as a star-graph branch type or not.
- *Number of states in a single branch*. After we confirm that the channel behaves as a star-graph branch type of Markov chain, we are in the position to assess the possible state of each branch. Fortunately, many existing approaches have been reported in the literature; see for example [4, 18] for reviews. Actually similar issues have been

extensively discussed in the literature as well, for example, to determine the order of an ARMA sequence and the number of hidden units in a neural network. In time series, AIC is usually applied to fit an ARMA model to data. In neural networks, the number of hidden units is decided using the learning errors and generalization errors. We can, of course, use a similar approach here, to best fit the data with a trade-off between the fitting accuracy and the number of states. This would be one of the key issues when we deal with experimental data and we will explore it in our further publications.

Finally, from theoretical point of view, for a Markov chain, we face the following open problem: 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, these results in the present paper also suggest a new kind of statistics for Markov chain: to estimate the whole chain exclusively in terms of the observation of a part of states. 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 [12, 13] for reviews).

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