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A novel approach to identify the rate constants of ion channel of four-state-loop via partially observable information

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Abstract

Among the equations between rate constants and the derivatives, the novel equations between rate constants and the moments of open and shut lifetime distribution for a given state set of Markov Chain are applied to identify the rate constants of ion channels. For gating scheme of ion channels of four-state-loop, it is derived by the underlying information that rate constants can be identified by their open lifetime and shut lifetime distributions at any two states.

Keywords: Ion channel; four-state-loop; rate constants; open litetime; shut lifetime.

1. Introduction

The gating scheme of ion channels can be modeled kinetically as a time-homogeneous Markov chain [1-4]. The transition rates with the underlying Markov chain indicate the kinetic properties of ion channel. In experiment, the transition between the various states cannot be directly observable and only a few open states are observable. The issue that how to determine all transition rates or rates constants in terms of the partially observable information has been addressed directly by using the maximum likelihood estimate [5-6]. Although this approach is powerful, it leads to the non-identifiability and the subsequent problems.

Therefore we develop a different approach by employing the intrinsic properties of the Markov

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process. The study is to derive the necessary constrained equations between the transition rates and the PDFs (probability density functions) of open lifetime and shut lifetime of observable states. The rate constants are then obtained as roots to this system of equations. Then all calculations are simply reduced to the estimation of PDFs of open lifetime and shut lifetime of observable states. As a result, we have addressed the ion channels with such as line, star-graph, star-graph branch, loop and hierarchical scheme [7-12]. It is shown that the rate constants of ion channel of loop (at most five states) can be identified by the PDFS of open lifetime and shut lifetime of two adjacent states [12], in which the constrained equations between the rate constants and the derivatives of PDFs of open lifetime and shut lifetime of observable states are used to solve the constants. That two adjacent states are observable, however, is a strict condition in realistic channels. Therefore a natural question is arises as to whether it is possible to identify the constants by the observable information of arbitrary two states. In this letter, we will demonstrate that it is indeed possible for the loop ion channel with four states at most.

Here a four-state-loop ion channel is addressed. The novel system of equations between the constants and the moments of PDFs of open and shut lifetime of observable states are used to obtain the constants. Then it is found that the rate constants can be determined by observation at arbitrary two states.

This paper is set out as follows. Section 2 will introduce the general theorems that give the system of equations between the constants and the PDFs of open and shut lifetime of observable states. The solution and algorithm is derived in section 3.

2. General theorem

For convenience, we always use <…> denoting a column vector, (…) a row vector, *diag*(…) a diagonal matrix, A^T the transpose of *A*, and. A_{ij} the *i*th row and *j*th column element from the matrix A. And let us always employ the standard convention that the infimum of an empty set is infinity.

2.1. Distribution of open lifetime and shut lifetime

Let $\{X_t : t \geq 0\}$ be a reversible Markov chain with the state space $S = \{0,1,\cdots,N\}$, which has the transition rate matrix *Q* such that $Q = (q_{ij})_{i,j\in S}\ (q_{ij} > 0, q_i \equiv -q_{ii} = \sum_{j=1}^{M} q_{ij})$, and $\{\pi_0, \pi_1, \cdots, \pi_N\}$ be the unique invariant probability measure of Q and satisfies $\pi_i q_{ij} = \pi_j q_{ij} (i, j \in s), \sum_{i=0}^{N} \pi_i = 1$.

Assume S_O is a subset of the state space S. Let $S_C = S - S_O$. The open lifetime and shut lifetime of S_O can be defined as $\sigma = \inf\{t > 0 : X_t \notin S_O\}$ and $\tau = \inf\{t > 0 : X_t \in S_O\}$, respectively.

Rewrite the matrix *Q* in a partitioned matrix term with four sub-matrixes Q_{OO}, Q_{OC}, Q_{CO} and Q_{CC}. Set $N = \|S_C\|$ and $S_O = \{1,2,\cdots,N\}, \Pi = diag(\pi_1,\pi_2,\cdots,\pi_N) \equiv diag(\pi_i, i \in S_C)$. Thus Q_{CC} has *N* real eigenvalues $-\alpha_1, -\alpha_2, \cdots, -\alpha_N$ such that $\alpha_i > 0$ and *N* orthogonal unit eigenvectors $\varepsilon_1, \varepsilon_2, \cdots, \varepsilon_N$ with respect to $(.,.)_\Pi$, where $\varepsilon_i = \langle \varepsilon_{1i}, \cdots, \varepsilon_{Ni} \rangle$. Set $E = (\varepsilon_1, \cdots, \varepsilon_N) = (\varepsilon_{ij})$, $W = (\omega_{ij}) = E^{-1}$, $A = diag(\alpha_1, \alpha_2, \cdots, \alpha_N)$. We get (see [10])

$$Q_{CC} = -W^{-1}AW, W^T W = \Pi, WQ_{CC} = -AW, \Pi Q_{CC} = -W^T AW \quad (1)$$

Let $\beta = <\beta_1, \cdots, \beta_N> \equiv WI$, where $I = <1, \cdots, 1>$, $\gamma_i = \beta_i^2 \alpha_i (1 \leq i \leq N)$, $d_n = \sum_{i=1}^{N} \gamma_i \alpha_i^{n-1}$, $c_n = \beta^T A^n \beta = \sum_{i=1}^{N} \gamma_i \alpha_i^{n-1}$ .Then we have $c_n = \sum_{i\in S_C} \pi_i d_n = (1 - \sum_{i\in S_O} \pi_i) d_n = (1 - \pi^*) d_n$. Thus we can obtain the theorem as follows [10-11].

Theorem 1 The shut lifetime has a $\|S_C\|$-mixed exponential density $f_\tau(t) = \sum_{i=1}^{\|S_C\|} \gamma_i e^{-\alpha_i t}, t > 0$. Here $(\gamma_i, \alpha_i)_{i=1,\cdots,\|S_C\|}$ say their parameters. In particular, if $S_O = \{i\}$, the open lifetime σ of a single state *i* has an exponential form $f_\sigma(t) = q_i e^{-q_i t}, t > 0$. And $q_i = 1/E\sigma, \pi_i = d_1/(q_i + d_1) = c_1 E\sigma$.

It shows, based on the PDF of a single state *i*, we can obtain q_i, π_i, d_n and $c_n (n \geq 1)$. Generally speaking, if we observe a subset S_O, we can obtain the corresponding $\pi_i (i \in S_O)$ and $c_n (n \geq 1)$. In realistic ion channel, the required mixed exponential density can be fitted by the corresponding open lifetime and shut lifetime sequences at given state set (cf. see [12-13]).

2.2. The constrained equations between the rate constants and the lifetime distributions

Let $\{X_t : t \geq 0\}$ be a reversible Markov chain with the state space $S = \{0,1,\cdots,N\}$, which has the transition rate matrix *Q* such that $Q = (q_{ij})_{i,j\in S} (q_{ij} > 0, q_i \equiv -q_{ii} = \sum_{j=1}^{M} q_{ij})$, and $\{\pi_0, \pi_1, \cdots, \pi_N\}$ be the unique invariant probability measure of Q and satisfies $\pi_i q_{ij} = \pi_j q_{ij} (i, j \in s), \sum_{i=0}^{N} \pi_i = 1$.

On one hand, for the *n*th derivatives of the shut lifetime distribution of S_O at *t=0*, we have $d_n = \beta^T A^n \beta / (1 - \pi^*)$. On the other hand, Eq. 1 yields $\beta^T A^n \beta = (-1)^n I^T \prod Q_{CC}^n I$, we get.

Theorem 2 The derivatives of the shut lifetime distribution of S_O at *t=0* are related to the transition rates with a formula

$$c_n = (-1)^n I^T \prod Q_{CC}^n I = \sum_{i \in S_C} \pi_i \sum_{j=1}^{\|S_C\|} (Q_{CC}^n)_{ij}, n \geq 1 \tag{2}$$

where the derivative d_n is replaced with the quantity c_n by multiplied a known constant.

Likewise, if we put $e_n = (1-\pi^*) \sum_{i=1}^{N} \gamma_i \alpha_i^{-(n+1)} = \sum_{i=1}^{N} \beta_i^2 \alpha_i^{-n}$, we can give the constrained equations between the transition rates and the moments of lifetime distributions.

Theorem 3 The moments of the shut lifetime distribution of S_O at *t=0* are related to the transition rates by the expression

$$e_n = (-1)^n I^T \prod Q_{CC}^{-n} I = \sum_{i \in S_C} \pi_i \sum_{j=1}^{\|S_C\|} (Q_{CC}^{-n})_{ij}, n \geq 1 \tag{3}$$

where the moment is replaced with the quantity e_n by multiplied a known constant. Most of uses of this constraint in the present study will be with n=1 to give the mean lifetime.

3. Solution and algorithm for four-state-loop type

Here one sort of scheme to consider for single ion channel has 4 states (say state 0, 1, 2, 3), which indicate 4 different opening levels. In this case, all states can only transit to their adjacent states. Furthermore, the reaction step in such mechanism is reversible, and the mechanism obeys principle of microscopic reversibility or detailed balance. Thus it can be modeled as a reversible Markov chain with a state space $S = \{0,1,2,3\}$, which has the transition rate matrix $Q = (q_{ij})$ such that

$$Q = \begin{pmatrix} -(\lambda_0 + \mu_0) & \lambda_0 & 0 & \mu_0 \\ \mu_1 & -(\lambda_1 + \mu_1) & \lambda_1 & 0 \\ 0 & \mu_2 & -(\lambda_2 + \mu_2) & \lambda_2 \\ \lambda_3 & 0 & \mu_3 & -(\lambda_3 + \mu_3) \end{pmatrix}.$$

Where $\lambda_i > 0, \mu_i > 0 (0 \leq i \leq 3)$ and $\lambda_0 \lambda_1 \lambda_2 \lambda_3 = \mu_0 \mu_1 \mu_2 \mu_3$ (for reversibility, i.e. the principle of microscopic reversibility or detailed balance in channels).

Set $\pi_0 = \left(1 + \sum_{i=1}^{3} \frac{\lambda_0 \lambda_1 \cdots \lambda_{i-1}}{\mu_1 \mu_2 \cdots \mu_i} \right)^{-1}$, $\pi_i = \frac{\lambda_0 \lambda_1 \cdots \lambda_{i-1}}{\mu_1 \mu_2 \cdots \mu_i} \pi_0, 1 \leq i \leq 3$. Then $\{\pi_0, \pi_1, \pi_2, \pi_3\}$ be the unique invariant probability measure of Q and satisfy Eq. 1. As discussed in [12], we have given an approach to identify the rate constants as the following theorem.

Theorem 4 For an ion channel with underlying Markov chain of four-state-loop, all transition rates can be determined by the PDFs of open lifetime and shut lifetime at *any two adjacent states*.

Due to the strict condition of observation at two adjacent states in realistic channels, we develop a novel approach by using the conclusions in theorem 2 and 3 to solve the current issue. A direct conclusion is that observation at any two states can be applied to identify the rate constants for current model.

3.1. Observation at state 0

Set $S_O = \{0\}$. Let $\sigma^{(0)}$ and $\tau^{(0)}$ be the open lifetime and shut lifetime of state *0*, respectively. It is known by Theorem 1 that the open lifetime $\sigma^{(0)}$ has an exponential density with a parameter q_0, and the shut lifetime $\tau^{(0)}$ has the 3-mixed exponential density with the parameters $\left(\gamma_i^{(0)}, \alpha_i^{(0)}\right)_{i=1,2,3}$. Set $d_n^{(0)} = \sum_{i=1}^{3} \gamma_i^{(0)} \left(\alpha_i^{(0)}\right)^{n-1}$, $c_n^{(0)} = (1-\pi_0) d_n^{(0)}, n \geq 1$. From Theorem 2, it follows Lemma 1 which depicts the relationship between $E\sigma^{(0)}, c_n^{(0)}$ and q_{ij}.

Lemma 1 The following equations hold.

$$\frac{1}{E\sigma^{(0)}} = q_0 = q_{01} + q_{03} \tag{4}$$

$$c_1^{(0)} = \pi_1 q_{10} + \pi_3 q_{30} \tag{5}$$

3.2. Observation at state 2

Here $S_O = \{2\}$. Now the open lifetime $\sigma^{(2)}$ is an exponential density with a parameter q_2, and the shut lifetime $\tau^{(2)}$ has the 3-mixed exponential density with the parameters $\left(\gamma_i^{(2)}, \alpha_i^{(2)}\right)_{i=1,2,3}$. Set $d_n^{(2)} = \sum_{i=1}^{3} \gamma_i^{(2)} \left(\alpha_i^{(2)}\right)^{n-1}$, $c_n^{(2)} = (1-\pi_0) d_n^{(2)}, n \geq 1$.

Lemma 2 The following equations hold.

$$\frac{1}{E\sigma^{(2)}} = q_2 = q_{21} + q_{23} \tag{6}$$

$$c_1^{(2)} = \pi_1 q_{12} + \pi_3 q_{32} \tag{7}$$

3.3. Observation at state set {0, 2}

Here $S_O = \{0,2\}$. It is obvious that the shut lifetime $\tau^{(0,2)}$ has the 2-mixed exponential density with the parameters $(\gamma_i, \alpha_i)_{i=1,2}$. From theorem 3, it is easy to derive the following lemma.

Lemma 3 The following system of equations hold for n=1,2,3,4.

$$\frac{\pi_1}{q_1^n} + \frac{\pi_3}{q_3^n} = \frac{\gamma_1}{\alpha_1^{n+1}} + \frac{\gamma_2}{\alpha_2^{n+1}} \tag{8}$$

3.4. Main conclusion and algorithm

Theorem 5 Let $\{X_t : t \geq 0\}$ is a four-state-loop Markov chain with a state space $S = \{0,1,2,3\}$. If the initial measure is the invariant measure $\{\pi_i, i \in S\}$, then every element of its transition rates matrix $Q = (q_{ij})$ and $\{\pi_i\}$ can be determined by the PDFs of open lifetime and shut lifetime at state 0 and 2.

Proof: Suppose that we have obtained the corresponding PDFs as defined in above section. First, according to observation at state 0 and 2, together with equation (4) and (6), we can obtain π_0, π_2, q_0, q_2. Second, by the system of equations (8), we can get π_1, π_3, q_1, q_3. Subsequently, by equation (5) and (7), we yield q_{10}, q_{30}. Thus we get $q_{12} = q_1 - q_{10}, q_{32} = q_3 - q_{30}$. Finally, we can obtain the rest of rate constants as follows.

$$q_{01} = \frac{\pi_1 q_{10}}{\pi_0}, q_{03} = \frac{\pi_3 q_{30}}{\pi_0}, q_{21} = \frac{\pi_1 q_{12}}{\pi_2}, q_{23} = \frac{\pi_3 q_{32}}{\pi_2} \tag{9}$$

It is mentioned that the course of proof indicates the corresponding algorithm. Together with conclusion in theorem 4, we provide a more general theorem.

Theorem 6 For an ion channel with underlying Markov chain of four-state-loop, all transition rates can be determined by the PDFs of open lifetime and shut lifetime at *any two states*.

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