Duality-based calculations for transition probabilities in stochastic chemical reactions

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An idea for evaluating transition probabilities in chemical reaction systems is proposed, which is efficient for repeated calculations with various rate constants. The idea is based on duality relations; instead of direct time-evolutions of the original reaction system, the dual process is dealt with. Usually, if one changes rate constants of the original reaction system, the direct time-evolutions should be performed again, using the new rate constants. On the other hand, only one solution of an extended dual process can be re-used to calculate the transition probabilities for various rate constant cases. The idea is demonstrated in a parameter estimation problem for the Lotka-Volterra system.

I. INTRODUCTION

Recent developments of experimental techniques enable us to obtain detailed data for bio-chemical reactions within cells, and the importance of the role of data analysis has been increased. In small systems such as cells, it has been shown that discrete characteristics could play important roles and, hence chemical reactions in such small systems should be treated as chemical master equations. That is, conventional rate equations are not adequate, in which the noise effects are neglected and numbers of chemical substances are approximated as continuous variables. Hence, it would be necessary to treat discrete variables directly. The time-evolution of the discrete variables is directly expressed via the chemical master equations. In the past, various analytical and numerical methods for the chemical master equations have been developed (for example, see [2].)

Transition probabilities in the chemical master equations are one of the important quantities, especially in time-series data analysis. For example, consider an estimation problem for rate constants from time-series data of chemical reactions. When all time-series data for numbers of chemical substances and chemical reactions are available, the Bayesian statistics gives easily the estimation of the rate constants. However, it is in general difficult to obtain such detailed time-series data, and partial observations with discrete time steps should be considered in realistic experiments. In general, the partial observation cases need many numerical time-evolutions for different rate constants, and large computational costs are needed. For example, in [3], an estimation method based on gradient descent techniques has been proposed, and the method needs many iterated calculations to seek rate constants with the largest likelihood value. Although sometimes the estimation problems have been performed via approximations, these approximations treat discrete variables as continuous ones, and then the approximations could be inadequate for small systems such as cells. Hence, it is useful to develop more rapid and direct evaluation methods for transition probabilities for different rate constant cases.

In the present paper, an idea to evaluate transition probabilities in chemical master equations is proposed. The idea is based on duality concepts; instead of direct time-evolutions for the original chemical master equations, the corresponding dual processes are evaluated. Employing extensions of states, it is possible to construct an extended dual process which does not explicitly include some rate constants of the original processes. Furthermore, it will be shown that only a time-evolution for the extended dual process enables us to evaluate transition probabilities for the original chemical master equations with various rate constants. This characteristics of the extended dual processes could reduce largely the computational costs for the calculations of the transition probabilities for various rate constants.

This paper is organized as follows. In Sec. II the basic idea for the usage of the dual process is explained. Section III gives a demonstration for the derivation of the dual processes using the Lotka-Volterra system. Concluding remarks are given in Sec. IV.

II. DUALITY RELATIONS FOR TRANSITION PROBABILITIES

In this section, the idea based on the duality relations is explained. A concrete example for the derivations of the dual process will be given in Sec. III.

A. Stochastic chemical reaction systems

Consider a stochastic chemical reaction system with \( M \) chemical substances, \( X_1, \ldots, X_M \). Denote \( \mathbf{n} = (n_1, \ldots, n_M) \) as the state of the reaction systems, where \( n_m \) denotes the number of chemical substance \( X_m \). Note that \( n_m \) takes any positive integer or zero \( (n_m \in \{0, 1, 2, \cdots\}) \). Assume that there are \( R \) chemical reac-
tions, which take the form
\[
\begin{align*}
\{ u_{11}X_1 + \cdots u_{1M}X_M \rightarrow v_{11}X_1 + \cdots v_{1M}X_M, \\
u_{21}X_1 + \cdots u_{2M}X_M \rightarrow v_{21}X_1 + \cdots v_{2M}X_M, \\
\vdots \\
u_{R1}X_1 + \cdots u_{RM}X_M \rightarrow v_{R1}X_1 + \cdots v_{RM}X_M,
\end{align*}
\]
where \( u_{rm} \) and \( v_{rm} \) correspond to the stoichiometries associated with the \( m \)-th reactant and product of the \( r \)-th reaction, respectively. The \( r \)-th chemical reaction has a rate constant \( c_r \). The actual rate for the \( r \)-th reaction depends on the number of chemical substances, and a rate law or hazard, \( h_r(n, c_r) \), is introduced \cite{8}. For example, for \( 2X_j + X_k \rightarrow X_l \), the hazard should be defined as \( h(n, c) = c \frac{n_j(n_j - 1)}{2} n_k \), and so on. In the present paper, the following redefined hazard, \( h'_r(n) \), is introduced:
\[
h'_r(n) = \tilde{c}_r h'_r(n),
\]
where
\[
\tilde{c}_r = c_r \prod_{m=1}^{M} \frac{1}{u_{rm}!},
\]
and
\[
h'_r(n) \equiv \prod_{m=1}^{M} \frac{n_m!}{(n_m - u_{rm})!}.
\]
These notations are convenient to describe the extension of the dual process later. In addition, using the quantities \( \{u_{rm}\} \) and \( \{v_{rm}\} \), the net effect reaction matrix \( A \) is defined \cite{8}; the components of \( A \), \( \{a_{rm}\} \), are defined as
\[
a_{rm} = v_{rm} - u_{rm}.
\]
Using the above notations, the chemical master equations are written as follows:
\[
\frac{\partial}{\partial t} P(n, t) = \sum_{r=1}^{R} \left[ \tilde{c}_r h'_r(n - A_r) P(n - A_r, t) - \tilde{c}_r h'_r(n) P(n, t) \right],
\]
where \( A_r \) is the \( r \)-th row of the matrix \( A \). For details of the master equations, see, for example, \cite{2, 3}.

When one employs the direct numerical time-integration for the original chemical master equations in Eq. (5) (with a suitable truncation for finite numbers of equations), the transition probability for a certain initial state \( n \) to final state \( m \) with fixed rate constants \( \{c_1, \ldots, c_R\} \) can be evaluated. If one wants to know the transition probabilities for different rate constant cases, the numerical time-integrations must be performed again with the new rate constants; these repeated time-integrations are time-consuming when one wants to know transition probabilities for various rate constant cases. Hence, in the following discussions, the chemical master equations are investigated from the viewpoint of bosonic operators, which enables us to obtain an idea to avoid the repeated time-integrations.

### B. Doi-Peliti formalism

The chemical master equations in Eq. (5) are essentially the infinite number of coupled ordinary differential equations. There are some analytical methods to rewrite the chemical master equations, and one of the methods is the so-called Doi-Peliti formalism \cite{8, 10}. The Doi-Peliti formalism has been widely used, ranging from the research fields of reaction-diffusion systems \cite{11} to genetic switches \cite{12, 13}. The method is based on the algebraic probability theory \cite{14, 15}, and the following bosonic creation and annihilation operators for the \( m \)-th chemical substance, \( a_m^\dagger \), and annihilation operators, \( a_m \), are used:
\[
\begin{align*}
[a_m, a_m^\dagger] & = a_m^\dagger a_m - a_m a_m^\dagger = 1, \\
[a_m^\dagger, a_m] & = [a_m, a_m^\dagger] = 0, \\
[a_m, a_m'] & = [a_m^\dagger, a_m'] = 0, \quad \text{for } m \neq m'.
\end{align*}
\]
That is, the creation and annihilation operators for the same chemical substance \( X_m \) do not commute with each other; for different chemical substances, these operators can commute.

The actions of the creation and annihilation operators on state \( |n\rangle = |n_1, \ldots, n_M\rangle \) in a Fock space are defined as
\[
\begin{align*}
a_m^\dagger |n_1, \ldots, n_m, \ldots, n_M\rangle & = |n_1, \ldots, n_m + 1, \ldots, n_M\rangle, \\
a_m |n_1, \ldots, n_m, \ldots, n_M\rangle & = n_m |n_1, \ldots, n_m - 1, \ldots, n_M\rangle.
\end{align*}
\]
The corresponding dual (bra) states \( \langle m | = \langle m_1, \ldots, m_M | \) are introduced as satisfying the following inner product:
\[
\langle m | n \rangle = \delta(n_1, m_1) \cdots \delta(n_M, m_M) n!,
\]
where \( \delta(n_m, m_m) \) is the Kronecker delta, and
\[
n! \equiv n_1! \cdots n_M!.
\]
It is easy to confirm that the actions of the creation and annihilation operators to the bra states become as follows:
\[
\begin{align*}
\langle n_1, \ldots, n_m, \ldots, n_M | a_m^\dagger & = n_m \langle n_1, \ldots, n_m - 1, \ldots, n_M |, \\
\langle n_1, \ldots, n_m, \ldots, n_M | a_m & = \langle n_1, \ldots, n_m + 1, \ldots, n_M |.
\end{align*}
\]
Using the above notations, the state $|P(t)\rangle$ is defined as

$$|P(t)\rangle = \sum_{n_1=0}^{\infty} \cdots \sum_{n_M=0}^{\infty} P(n,t) |n\rangle. \quad (15)$$

In order to derive the time-evolution equation for the state $|P(t)\rangle$, the following quantities are introduced, which correspond to the redefined hazards in the original chemical master equations:

$$\mathcal{H}_r = \prod_{m=1}^{M} (a_m^\dagger \upsilon_{rm} a_m)^{u_{rm}}, \quad (16)$$

$$\mathcal{H}_r^{\text{diag}} = \prod_{m=1}^{M} (a_m^\dagger \upsilon_{rm} a_m)^{u_{rm}}. \quad (17)$$

Then, the original chemical master equations in Eq. (5) are rewritten as follows:

$$\frac{d}{dt} |P(t)\rangle = \mathcal{L} |P(t)\rangle, \quad (18)$$

where

$$\mathcal{L} = \sum_{r=1}^{R} \mathcal{L}_r, \quad (19)$$

and

$$\mathcal{L}_r = \tilde{c}_r (\mathcal{H}_r - \mathcal{H}_r^{\text{diag}}). \quad (20)$$

Finally, the transition probability $P_{n\rightarrow m}(t)$ is written in terms of the Doi-Peliti formalism as

$$P_{n\rightarrow m}(t) = \frac{1}{m!} \langle m|P(t)\rangle = \frac{1}{m!} \langle m|e^{\mathcal{L}t}|n\rangle, \quad (21)$$

where $e^{\mathcal{L}t}|n\rangle$ corresponds to a solution of the time-evolution starting from state $n$. Note that we need the factor $1/m!$ because of the characteristics of the inner product in Eq. (14).

**C. Extended dual process**

Here, additional bosonic operators are introduced to obtain an extended dual process, in which some rate constants are vanished and additional states emerge. For simplicity, here only one rate constant $c_1$ will be replaced with the additional bosonic operator; extensions for multiple cases are straightforward.

First, additional bosonic operators, $a_{c_1}^\dagger$ and $a_{c_1}$, are introduced. Here, the following property of the coherent states is important:

$$a_{c_1}|z_1\rangle = z_1|z_1\rangle, \quad (22)$$

where $|z_1\rangle$ is the coherent state with parameter $z_1 \in \mathbb{R}$, which is defined as

$$|z_1\rangle = e^{z_1 a_{c_1}^\dagger}|0\rangle. \quad (23)$$

In addition, noting $\langle n_{c_1}| = \langle 0|a_{c_1}^{n_{c_1}}$, we have

$$\langle n_{c_1}|z_1\rangle = z_1^{n_{c_1}}. \quad (24)$$

Second, the following time-evolution operator $\mathcal{L}^{\text{ex}}$ is introduced instead of the original $\mathcal{L}$:

$$\mathcal{L}^{\text{ex}} = \mathcal{L}_1^{\text{ex}} + \sum_{r=2}^{R} \mathcal{L}_r, \quad (25)$$

where

$$\mathcal{L}_1^{\text{ex}} = a_{c_1}(H_1 - H_1^{\text{diag}}). \quad (26)$$

Furthermore, the state $|P(t)\rangle$ is extended as

$$|P^{\text{ex}}(t)\rangle = \sum_{n_1=0}^{\infty} \cdots \sum_{n_M=0}^{\infty} P(n,t) |n\rangle |z_1\rangle, \quad (27)$$

and the time-evolution for the extended state $|P^{\text{ex}}(t)\rangle$ obeys

$$\frac{\partial}{\partial t} |P^{\text{ex}}(t)\rangle = \mathcal{L}^{\text{ex}} |P^{\text{ex}}(t)\rangle. \quad (28)$$

Note that $\mathcal{L}^{\text{ex}}$ in Eq. (28) gives the same quantity with $\mathcal{L}$ in Eq. (18) when $z_1 = c_1$, because of the characteristics of the coherent state in Eq. (22).

Third, the following bra state is defined:

$$\langle \phi(t)| = \sum_{n_{c_1}=0}^{\infty} \sum_{n_M=0}^{\infty} \sum_{n_1=0}^{\infty} \langle \phi(n, n_{c_1}, t) | n_{c_1} | n \rangle | n \rangle, \quad (29)$$

where $|n\rangle = |n_1, \ldots, n_M\rangle$, and $|n_{c_1}\rangle$ corresponds to the state related to the additional bosonic creation and annihilation operators $a_{c_1}^{\dagger}$ and $a_{c_1}$.

Fourth, instead of the time-evolution for $|P^{\text{ex}}(t)\rangle$, the following time-evolution for the bra state is considered:

$$\frac{\partial}{\partial t} \langle \phi(t)| = \langle \phi(t)| \mathcal{L}^{\text{ex}}, \quad (30)$$

that is,

$$\frac{\partial}{\partial t} |\phi(t)\rangle = (\mathcal{L}^{\text{ex}})^\dagger |\phi(t)\rangle, \quad (31)$$

where $(\mathcal{L}^{\text{ex}})^\dagger$ is the conjugate of $\mathcal{L}^{\text{ex}}$. Equation (31) is written in terms of the Doi-Peliti formalism, and it is possible to derive the corresponding infinite coupled ordinary differential equations for $\{\phi(n, n_{c_1}, t)\}$. That is, introducing the following ‘hazard’:

$$\tilde{h}_r^{\prime}(n) = \prod_{m=1}^{M} \frac{n_m!}{(n_m - \nu_{rm})!}, \quad (32)$$

we have

$$\frac{\partial}{\partial t} \phi(n, n_{c_1}, t) = \tilde{h}_r^{\prime}(n + A_r) \phi(n + A_r, n_{c_1} - 1, t) - \tilde{h}_r^{\prime}(n) \phi(n, n_{c_1} - 1, t)$$

$$+ \sum_{r=2}^{R} \tilde{c}_r \tilde{h}_r^{\prime}(n + A_r) \phi(n + A_r, n_{c_1}, t) - \tilde{c}_r \tilde{h}_r^{\prime}(n) \phi(n, n_{c_1}, t). \quad (33)$$
Here, note that the time-evolution equations for \(\{\phi(n, n_{c_1}, t)\}\) are not the chemical master equations in general; the equations do not satisfy the probability conservation law, and then \(\{\phi(n, n_{c_1}, t)\}\) cannot be interpreted as a probability distribution. Although it is possible to recover the probabilistic nature by using similar discussions used in \([10]\), it is enough to use \(\{\phi(n, n_{c_1}, t)\}\) to calculate the transition probabilities here.

The main idea in the present paper is the replacement of the time-evolution for \(|P(t)|\) with \(|\phi(t)|\). Hence,

\[
P_{n \rightarrow m}(t) = \frac{1}{m!} \langle m | e^{Lt} | n \rangle
\]

\[
= \frac{1}{m!} \langle n_{c_1} = 0 | (m | e^{L^{ex}t} | n) \rangle |z_1 = c_1 \rangle
\]

\[
= \frac{1}{m!} \sum_{n_{c_1}=0}^{\infty} \sum_{n_1=0}^{\infty} \cdots \sum_{n_M=0}^{\infty} \phi(n', n_{c_1}, t) \langle n_{c_1} | (n' | n) \rangle |z_1 = c_1 \rangle
\]

\[
= \frac{n!}{m!} \sum_{n_{c_1}=0}^{\infty} c_1^{n_{c_1}} \phi(n, n_{c_1}, t),
\]

where the initial condition for the bra state is

\[
\phi(n_1', \ldots, n_M', n_{c_1}, t = 0) = \begin{cases} 
1 & \text{for } n_1' = m_1, \ldots, n_M' = m_M, n_{c_1} = 0, \\
0 & \text{otherwise}.
\end{cases}
\]

The above discussions imply the following fact: The transition probabilities with the rate constant \(c_1\) can be evaluated from Eq. (33) using the solutions of the extended dual process. Note that the solutions for the extended dual process, \(\{\phi(n, n_{c_1}, t)\}\), does not include the rate constant \(c_1\) explicitly. Hence, only one numerical time-integration for the extended dual process is necessary to evaluate the transition probabilities \(n \rightarrow m\) for various \(c_1\) cases.

III. DEMONSTRATION OF THE DERIVATION AND APPLICATIONS OF DUAL PROCESSES

Here, a demonstration for the derivation of the extended dual process is shown by using the famous Lotka-Volterra system, which has been already used for parameter estimation problem in \([8]\):

\[
\begin{aligned}
X_1 & \xrightarrow{\alpha} 2X_1, \\
X_1 + X_2 & \xrightarrow{\beta} X_2, \\
X_1 + X_2 & \xrightarrow{\delta} X_1 + 2X_2, \\
X_2 & \xrightarrow{\gamma} 0.
\end{aligned}
\]

The chemical master equation for the Lotka-Volterra system is written as

\[
\frac{dP(n_1, n_2, t)}{dt} = \alpha [(n_1 - 1)P(n_1 - 1, n_2, t) - n_1 P(n_1, n_2, t)]
\]

\[
+ \beta [(n_1 + 1)n_2 P(n_1 + 1, n_2, t) - n_1 n_2 P(n_1, n_2, t)]
\]

\[
+ \delta [n_1 (n_2 - 1)P(n_1, n_2 - 1, t) - n_1 n_2 P(n_1, n_2, t)]
\]

\[
+ \gamma [(n_2 + 1)P(n_1, n_2 + 1, t) - n_2 P(n_1, n_2, t)].
\]

(37)

where \(n_1)\) and \(n_2)\) are the numbers of particles \(X_1)\) and \(X_2)\), respectively. The time-evolution operator in the Doi-Peliti formalism is defined as

\[
L = \alpha (a^1_1 a^1_1 - a^1_1 a_1) + \beta (a_1 a^1_1 a_2 - a^1_1 a^1_1 a_2)
\]

\[
+ \delta (a_1 a^1_1 a_2 - a^1_1 a^1_1 a_2) + \gamma (a_2 - a^1_1 a_2).
\]

(38)

We assume that precise values for the rate constants \(\alpha)\) and \(\beta)\) are unknown. Therefore, the two bosonic operators \(a_\alpha)\) and \(a_\beta)\) and their adjoint operators \(a^\dagger_\alpha)\) and \(a^\dagger_\beta)\) are introduced. Using certain constants \(\alpha)\) and \(\beta)\) in Eq. (38) are replaced as \(\alpha)\) and \(\beta)\), respectively, and then the following extended time-evolution operator is derived:

\[
\mathcal{L}^{ex} = \alpha (a^\dagger_1 a^1_1 a_1 - a^1_1 a_1) + \beta (a_1 a^1_1 a_2 - a^1_1 a^1_1 a_2)
\]

\[
+ \delta (a_1 a^1_1 a_2 - a^1_1 a^1_1 a_2) + \gamma (a_2 - a^1_1 a_2).
\]

(39)

Note that the replacement \(\alpha) \rightarrow \alpha)\) is used here, instead of \(\alpha) \rightarrow a_\alpha)\) (and the same as \(\beta)\). These replacements do not mean approximations; they correspond to simple variable transformations. The reasons to introduce the replacements are as follows:

- Sometimes we know the rough values (or only the orders) of unknown rate constants; these additional information can be embedded into the extended dual process with small modifications of the discussions in Sec. II, as we will see here.

- As we will see below (Eq. (40)), the final expression corresponds to the Taylor-type (Maclaurin-type) expansion. Hence, in practical, it is important to use small \(\alpha/\alpha)\) and \(\beta/\beta)\) to confirm the rapid convergence of the summation in Eq. (40). Hence, sometimes the replacements reduce the practical computational issues.

The adjoint operator for \(\mathcal{L}^{ex})\) is

\[
(\mathcal{L}^{ex})^\dagger = \alpha^\dagger a^\dagger_1 a^1_1 a_1 - a^1_1 a_1) + \beta^\dagger a^\dagger_1 a^1_1 a_2 - a^1_1 a^1_1 a_2)
\]

\[
+ \delta (a_1 a_1 a^1_1 a_2 - a^1_1 a^1_1 a_2) + \gamma (a_2 - a^1_1 a_2).
\]

(40)

and using the discussions in Sec. III, the extended dual process obeys the following time-evolution equation:

\[
\frac{\partial}{\partial t} |\phi(t)\rangle = (\mathcal{L}^{ex})^\dagger |\phi(t)\rangle.
\]
The solutions of Eq. (43) are used to evaluate a transition probability from state 1 to state 2. Then, the following coupled ordinary differential equations are derived:

\[
\frac{\partial}{\partial t} \phi(n_1, n_2, n_\alpha, n_\beta, t) = \alpha'[n_1 + 1] \phi(n_1 + 1, n_2, n_\alpha, n_\beta, t) - n_1 \phi(n_1, n_2, n_\alpha, n_\beta, t) + \beta'[n_2 \phi(n_1 - 1, n_2, n_\alpha, n_\beta - 1, t) - n_1 n_2 \phi(n_1, n_2, n_\alpha, n_\beta - 1, t)] + \delta[n_1(n_2 + 1) \phi(n_1, n_2 + 1, n_\alpha, n_\beta, t) - n_1 n_2 \phi(n_1, n_2, n_\alpha, n_\beta, t)] + \gamma[\phi(n_1, n_2 - 1, n_\alpha, n_\beta, t) - n_2 \phi(n_1, n_2, n_\alpha, n_\beta, t)].
\]

Finally, the solutions of Eq. (43) are used to evaluate a transition probability from state 1 to state 2 as follows:

\[
P_{n_1, n_2 \rightarrow m_1, m_2}(t) = \frac{n_1! n_2!}{m_1! m_2!} \sum_{n_\alpha = 0}^{\infty} \sum_{n_\beta = 0}^{\infty} \left( \frac{\alpha'}{\alpha} \right)^{n_\alpha} \left( \frac{\beta'}{\beta} \right)^{n_\beta} \phi(n_1, n_2, n_\alpha, n_\beta, t).
\]

Notice that Eq. (44) has a form of the Taylor-type expansion around the origin. Hence, the usage of the dual process corresponds to calculations of the expansion coefficients. In addition, it is easy to calculate the derivatives with respect to the parameters from the same \(\phi(n_1, n_2, n_\alpha, n_\beta, t)\); there is no need to perform additional time-evolution.

The derived formula for the transition probabilities in Eq. (44) can be, for example, used in parameter estimation problems. Assume that we have discrete-time observations of time-series data, which are depicted in Fig. 1. The observation-time interval is \(\Delta_{t, \text{obs}} = 0.3\), and the full time-series data are not available. That is, only the observation values \(n_1(i)\) and \(n_2(i)\) at discrete time \(t(i)\) are available, where \(t(i+1) - t(i) = \Delta_{t, \text{obs}} = 0.3\), and \(N = 31\) in Fig. 1.

Assume that two parameters \(\delta\) and \(\gamma\) are known. The other two parameters, \(\alpha\) and \(\beta\), should be estimated from the time-series data. In order to seek the parameters, the following likelihood function is calculated;

\[
\mathcal{L}(\alpha, \beta) = \prod_{i=1}^{N-1} \text{Prob}(n_1(i+1), n_2(i+1) | n_1(i), n_2(i); \alpha, \beta),
\]

where \(\text{Prob}(n_1(i+1), n_2(i+1) | n_1(i), n_2(i); \alpha, \beta)\) is the probability of the state change with parameters \(\alpha\) and \(\beta\). Additionally, it is usual to calculate the following log-likelihood function,

\[
\ell(\alpha, \beta) = \log \mathcal{L}(\alpha, \beta),
\]

instead of the original likelihood function.

In general, the log-likelihood function in Eq. (46) should be re-calculated for various values of \(\alpha\) and \(\beta\), and the tasks need high computational costs. In contrast, the formula in Eq. (44) is suitable to depict the contour or heatmap for the log-likelihood function. That is, values of the log-likelihood function can be evaluated only from a time-integration of the extended dual process. Hence, there is no need to repeat the time-integration for different parameters. (Here, assume that the orders of scales of \(\alpha\) and \(\beta\) are previously known, and the settings \(\alpha' = 1.0\) and \(\beta' = 0.1\) are used in Eq. (43).) Additionally, the information of the derivatives of the log-likelihood functions is easily obtained from Eq. (44); there is no need to perform additional time-integrations.

In order to demonstrate the usage of the duality relations, the numerical calculations for heatmaps and nullclines for the log-likelihood functions are performed as follows. Both Eqs. (44) and (45) are coupled ordinary differential equations, and the numbers of the equations are, in principle, infinite. Usually, the time-integration needs a finite cut-off for states; here, only states with \(0 \sim 69\) are considered for each particle. I checked that the finite cut-off is enough for the truncation of the summation in Eq. (43). For the time-integration for the dual processes, the usual 4th-order Runge-Kutta method is employed. Figures (a) and (b) are the results for the heatmap; Fig. (b) is the enlarged one of Fig. (a). Figure (c) shows the directions of derivatives of the log-likelihood.
functions, and nullclines. Again, note that there is no need to perform additional time-integrations here; only the same solutions for the extended dual process are repeatedly re-used to depict all Figs. 2(a), (b), and (c).

Finally, I give some comments for the radius of convergence of the power series in Eq. 51. Equation 51 has two variables, and we here introduce the following

coefficients:

\[ c_n^{(\alpha)} = \frac{n_1!n_2!}{m_1!m_2!} \sum_{n_\beta=0}^{\infty} \left( \frac{\beta}{\alpha} \right)^{n_\beta} \phi(n_1, n_2, n_\beta, t), \]

(47)

\[ c_n^{(\beta)} = \frac{n_1!n_2!}{m_1!m_2!} \sum_{n_\alpha=0}^{\infty} \left( \frac{\alpha}{\beta} \right)^{n_\alpha} \phi(n_1, n_2, n_\alpha, t). \]

(48)

Note that \( c_n^{(\alpha)} \) and \( c_n^{(\beta)} \) depend on \( n_1, n_2, m_1, m_2, \beta, \beta' \) and \( t \); the dependencies are not explicitly shown in \( c_n^{(\alpha)} \) and \( c_n^{(\beta)} \) for notational simplicity. Then, the transition probability is written in the following power-series with one variable:

\[ P_{n_1, n_2 \rightarrow m_1, m_2}(t) = \sum_{n=0}^{\infty} c_n^{(\alpha)} \left( \frac{\alpha}{\alpha'} \right)^n \]

(49)

\[ = \sum_{n=0}^{\infty} c_n^{(\beta)} \left( \frac{\beta}{\beta'} \right)^n. \]

(50)

In order to discuss the radius of convergence of the power-series, one may use the so-called Domb–Sykes plot 13. Here, we use the method introduced by Mercer and Roberts 19 because complicated patterns appear in \( \{ c_n^{(\alpha)} \} \) and \( \{ c_n^{(\beta)} \} \). In the Mercer–Roberts method, the following quantities are calculated:

\[ (B_n^{(\alpha)})^2 = \frac{c_n^{(\alpha)} + c_{n-1}^{(\alpha)} - (c_n^{(\alpha)})^2}{c_n^{(\alpha)} c_{n-2}^{(\alpha)} - (c_n^{(\alpha)})^2}, \]

(51)

\[ (B_n^{(\beta)})^2 = \frac{c_n^{(\beta)} + c_{n-1}^{(\beta)} - (c_n^{(\beta)})^2}{c_n^{(\beta)} c_{n-2}^{(\beta)} - (c_n^{(\beta)})^2}, \]

(52)

for \( n = 2, 3, 4, \ldots \). As discussed in 19, for example, the reciprocal of the radius of convergence, \( 1/r \), for Eq. 49...
IV. CONCLUDING REMARKS

As shown in the present paper, the duality relations enable us to reduce the repeated time-integrations for various rate constants. This feature is applicable, for example, to obtain heatmaps for the log-likelihood functions; compared to the direct time-integrations for the original system, only one time-integration for the extended dual process is enough, as demonstrated in the present paper. In addition, the derivatives of the log-likelihood functions can also be obtained easily by using the same numerical solutions for the extended dual process. Of course, it is also possible to calculate the Jacobian matrix, the Hessian matrix, and so on.

It should be noted here that the number of random variables in the extended dual processes is larger than the original one. Hence, the computational cost for one time-integration becomes larger than the original one. However, if we can perform the time-integration for the extended dual process with reasonable computational costs, the numerical results can be repeatedly re-used, which will finally reduce the whole computational costs.

Here, the current limitations of the usage of the duality relations should be stated.

1. As discussed above, the usage of the duality relations corresponds to the Taylor-type expansion. Hence, we must pay attention to the convergence. In practice, it is preferable that the expanded variables take values smaller than 1. In order to avoid this convergence issue, it is useful to use the replacements (variable transformations) in Sec. III.

2. In the demonstration, the coupled ordinary differential equations for the dual process should be solved numerically. When the numbers of parameters in the expansion are large, it becomes impossible to solve the coupled ordinary differential equations (the curse of dimensionality.) Hence, at this stage, the current approach is suitable to see the behavior of the log-likelihood functions with a few varying variables.

3. In order to treat many variable cases, one may wonder if the Monte Carlo approach is available. It is, in principle, true; although the time-evolution equation for the dual process does not correspond to a stochastic process in general, the stochastic nature can be recovered by using more extensions (see [10].) Actually, as for the duality between the stochastic differential equations and the birth-death processes, the Monte Carlo approach has already been employed [17]. However, the Taylor-type expansion needs sometimes solutions with high precisions, and the Monte Carlo approach is still time-consuming. The usage of the importance sampling may avoid this problem; this is beyond the scope of the present paper, and under investigation.

At the present moment, the duality relations are useful to investigate cases with a few varying variables. In future works, it is important to develop approximation methods or efficient numerical methods for the extended dual processes.

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