Unveiling the hidden structure of complex stochastic biochemical networks

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Complex Markov models are widely used and powerful predictive tools to analyze stochastic biochemical processes. However, when the network of states is unknown, it is necessary to extract information from the data to partially build the network and estimate the values of the rates. The short-time behavior of the first-passage time distributions between two states in linear chains has been shown recently to behave as a power of time with an exponent equal to the number of intermediate states. For a general Markov model we derive the complete Taylor expansion of the first-passage time distribution between two arbitrary states. By combining algebraic methods and graph theory approaches it is shown that the first term of the Taylor expansion is determined by the shortest path from the initial state to the final state. When this path is unique, we prove that the coefficient of the first term can be written in terms of the product of the transition rates along the path. It is argued that the application of our results to first-return times may be used to estimate the dependence of rates on external parameters in experimentally measured time distributions.

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I. INTRODUCTION

Many processes in stochastic chemical kinetics are modeled in terms of Markov chains, i.e., by chemical transitions on a network of discrete states representing biochemical states of a complex process.1 Prominent examples are given by enzymatic reactions leading to the movement of motor proteins2–4 or properties of single molecule reactions on complex substrates.5–7 This is especially important for understanding dynamics of biological molecular motors since there are many problems associated with the determination of the time distributions until certain states have been reached by the process. These problems are closely connected with first-passage events and their distributions can be obtained in terms of Markov chains, i.e., by chemical transitions rather restrictive and the question arises as to whether this restriction on the rates, by solving the forward Master equation in terms of phase-type distributions.14 Being the exponential of the infinitesimal generator of the Markov chain, the phase type distribution allows us to explicitly write the entire Taylor series of the first-passage time probability density and thus to identify both the power of the first term and its coefficient, which are expressed in terms of the product of rates. It is found that the coefficients of the expansion are associated to walks and paths on the network of states. The first term of the expansion corresponds to the shortest path from the initial to the chosen absorbing state.

II. RESULTS

There is one important observation, which will be used throughout this manuscript, that the first-passage times can be very efficiently computed as absorption times. For the purpose of simplifying calculations, the network of states that we consider is modified in such a way that the state to be visited becomes an absorbing state of the process. While this trick does not change anything on the nature of the first-passage times it allows us to use a set of very powerful tools aimed at computing the absorption times. The first part of this section, therefore, is devoted to the derivation of the full Taylor series

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of the absorption time probability density into one specific absorbing state. The applications of the general result to some typical cases arising in the modeling of stochastic biochemical processes is presented in the second part.

A. Absorption time for a process starting in \( i \) and absorbing in one of several absorbing states

We consider a Markov chain \( X(t) \) on the state space \( \sigma = \sigma_0 \cup \sigma_A \), composed of a subset \( \sigma_0 = \{0, 1, \ldots, n-1\} \) of transient states, and a subset \( \sigma_A = \{n, n+1, \ldots, N\} \) of absorbing states. The infinitesimal generator of the process is a block matrix

\[
Q = \begin{pmatrix} \mathbf{S}_0 & \mathbf{S}_A \\ \mathbf{0}_{n \times n} & \mathbf{0}_{a \times a} \end{pmatrix},
\]

where \( a = N - n + 1 \) is the number of absorbing states, the off-diagonal elements of the \( n \times n \) matrix \( \mathbf{S}_0 \) are the transition rates between the transient states, and the \( n \times a \) matrix \( \mathbf{S}_A \) contains the transition rates from the transient to the absorbing states. Therefore, the element \((i, k)\) of the matrix \( Q \), denoted as \( q_{ik} \), governs the infinitesimal transitions

\[
\Pr\{X(t + \tau) = k \mid X(t) = i\} = q_{ik} \tau + o(\tau),
\]

for \( \tau \) infinitesimal. The diagonal elements of \( Q \) are negative or zero and are fixed to satisfy the usual summation property \( \sum_{k \in \sigma} q_{ik} = 0 \) for any \( i \).

Hereafter, we consider processes that start in the state \( i \), i.e., \( X(0) = i \), and we look for the probabilities

\[
P_{ik}(t) = \Pr\{X(t) = k \mid X(0) = i\},
\]

for any \( i, k \in \sigma \), by solving the corresponding forward Master equation:

\[
\frac{d \mathbf{P}}{dt} = \mathbf{P} \cdot \mathbf{Q}.
\]

This equation is supplemented with the initial condition that \( \mathbf{P}(0) \) is a row vector of length \( N + 1 \) defined on \( \sigma \) with all zeros except at the element corresponding to the state \( i \). In terms of phase-type distributions \(^9,10,14\), the general solution of the Master equation is thus given by

\[
\mathbf{P}(t) = \mathbf{P}(0) \sum_{\ell = 1}^\infty \frac{t^\ell}{\ell!} \mathbf{Q}^\ell \equiv \mathbf{P}(0) \exp(\mathbf{Q}t).
\]

It can be split into the solution for the transient states \( \sigma_0 \) and the solution for the absorbing states \( \sigma_A \) due to the block form of the infinitesimal generator \( Q \).

Together with the initial condition \( X(0) = i \in \sigma_0 \) we consider an absorbing state \( j \in \sigma_A \) (see Fig. 1 for an illustration). The probability \( P_{ij}(t) \) to find the process in the absorbing state \( j \) at time \( t \) is given by the corresponding component of the solution vector computed in Eq. (5). By exploiting the block form of the matrix \( Q \) in Eq. (5), we obtain

\[
P_{ij}(t) = \tilde{e}_i^T [\mathbf{S}_0^{-1} \exp(\mathbf{S}_0t) - \mathbf{1d}_a] \mathbf{e}_j^T,
\]

where \( \tilde{e}_i \) is a \( n \)-dimensional row unit vector defined on \( \sigma_0 \) with all zeros except at element \( i \), whereas \( \mathbf{e}_j \) is a column unit vector defined in \( \sigma_A \) with all zeros except at the element corresponding to state \( j \). The matrix \( \mathbf{1d} \) is a \( n \times n \) unit matrix (all zeros except in the diagonal, where it has all ones).

1. **Exact full Taylor series of the absorption time**

The limit for \( t \to \infty \) of \( P_{ij}(t) \) gives the probability \( u_{ij} \) that a process starting in \( i \) is absorbed in \( j \). By taking the limit \( t \to \infty \) of the matrix in the square brackets of (6), one obtains the matrix

\[
\mathbf{U} = -\mathbf{S}_0^{-1} \mathbf{S}_A,
\]

of all absorption probabilities from any transient state to any absorbing state. Therefore, we obtain

\[
u_{ij} = \lim_{t \to \infty} P_{ij}(t) = \tilde{e}_i^T \mathbf{U} \mathbf{e}_j^T,
\]

as the element of the matrix \( \mathbf{U} \) corresponding to the absorption probability from the transient state \( i \) to the absorbing state \( j \). This indicates that the probability of absorption in \( j \) must be taken properly into account, in order to define the probability density \( \rho_{ij} \) of the random time \( T_{ij} \) that the process starting in \( i \) is conditioned to be absorbed in \( j \). It can be shown\(^8\) that the probability density must be normalized by the probability of absorption \( u_{ij} \) given in (8), namely,

\[
\rho_{ij}(t) = \frac{1}{u_{ij}} \tilde{e}_i^T [\exp(\mathbf{S}_0t) \mathbf{S}_A] \mathbf{e}_j^T,
\]

where we recall that \( \tilde{e}_i \) is a \( n \)-dimensional row vector, \( \mathbf{e}_j^T \) is a column vector of length equal to the rank of \( \sigma_A \) with a one corresponding to the state \( j \), \( \mathbf{S}_0 \) is a \( n \times n \) matrix, and \( \mathbf{S}_A \) is a \( n \times a \) dimensional matrix. In addition, we obtain also the average absorption time from \( i \) to \( j \) as

\[
E[T_{ij}] = -\frac{1}{u_{ij}} \tilde{e}_i^T [\mathbf{S}_0^{-1} \mathbf{U}] \mathbf{e}_j^T,
\]

FIG. 1. A generic network with absorbing states. The green vertices represent absorbing states. The arrows pointing towards them from the transient states indicate that these transitions are irreversible. The initial state, in red, is one of the transient states, which are otherwise yellow. The transitions between the transient states are bi-directional. In this network there are several paths from the state \( i \) to the state \( j \), but one path that has only one intermediate state is the shortest one. According to our theory, therefore, here the short-time behavior of the probability density function of the absorption time is linear.
which is a simple result based only on the matrix algebra not requiring any integration.

The Taylor series of $\rho_{ij}(t)$ is given by expanding Eq. (9) as

$$
\rho_{ij}(t) = \frac{1}{u_{ij}} \sum_{m=0}^{\infty} \frac{t^m}{m!} [S^0_{ij} \cdot S_A] \tilde{e}^T_j,
$$

where the explicit form of the generic terms is

$$
\rho_{ij}(t) = \frac{q_{ij}}{u_{ij}} + \frac{t}{u_{ij}} \sum_{k_1=0}^{n-1} q_{ik_1} q_{k_1 j} + \ldots + \frac{t^\ell}{u_{ij} \ell!} \sum_{k_0=0}^{n-1} \sum_{k_1=0}^{n-1} q_{ik_0} q_{ik_1 k_2} \cdots q_{k_\ell j} + \ldots
$$

In this equation, the terms have a graph theoretical interpretation, which is an extremely valuable observation. It is important to stress that the expression (12) shows that each coefficient of the Taylor series can be written explicitly as a sum of the products of the transition rates.

2. Graph theoretical interpretation of the coefficients in the Taylor series

The graph $G$ associated with the Markov chain $X$ has the states $\sigma$ of the process as vertices. The elements $a_{ik}$ of the adjacency matrix $A$ are defined as

$$
a_{ik} = \begin{cases} 
1 & \text{if } q_{ik} \neq 0 \\
0 & \text{otherwise}
\end{cases}
$$

for any $i, k \in \sigma$. We will say that the vertex $k$ is a neighbor of the vertex $i$ if there is a directed edge that connects $i$ to $k$, namely, if $a_{ik} = 1$. Herewith we do not impose any restriction on the neighborhood relationship, but it must be noticed that by the definition of the absorbing state if $j \in \sigma_A$ then $a_{ik} = 0$ for any $i \in \sigma$. Therefore, the vertices associated to states in $\sigma_A$ have only incoming edges. A walk on $G$ starting in $i$ and ending in $j$ is an alternating sequence of edges and vertices, where the same vertex and the same edge may be visited once or more times. On the network $G$, a walk can contain self-loops as well. A path from $i$ to $j$ is instead a special walk without loops where each state visited on the path is visited only once time.

The generic term of the expansion (12),

$$
q_{ik_1} q_{k_1 k_2} \cdots q_{k_\ell j},
$$

for $k_1, \ldots, k_\ell \in \sigma_0$ is different from zero only if each term in the product is different from zero. If $t = 0$ is different from zero, then there exists a walk made of $\ell + 1$ steps from state $i$ to state $j$ through the states $k_1, \ldots, k_\ell$. If instead the generic term (14) is zero, it means that at least one of the rates in the product is zero. In this case, that precise walk through the states $k_1, \ldots, k_\ell$ does not exist. In summary, each single term in each of the coefficients of the expansion (12) corresponds to a walk on the state space. In particular, the generic term (14) describes a walk through $\ell$ states, which may include cycles and self loops and is directly associated to the power $\ell$ of the Taylor series. As a consequence, the coefficient of each $\ell$th power of the Taylor series is the sum of all contributions from walks through exactly $\ell$ states, some of which possibly visited more than one time.

3. The shortest path contributes to the coefficient of the first term in the Taylor expansion

If the process $X$ could transit directly from state $i$ to state $j$, i.e., if $q_{ij} > 0$, then the states $i$ and $j$ would be directly connected, i.e., $a_{ij} = 1$, and the first contribution to the Taylor series (12) of $\rho_{ij}$ would be the zero order term. If the states $i$ and $j$ are not directly connected, i.e., $a_{ij} = 0$, the zeroth-order term is absent and the first order term might give the first contribution. The first-order term in the expansion of $\rho_{ij}$ will contribute only if the state $j$ is a neighbor of at least one state $k$ that is a neighbor of state $i$, i.e., if there is at least one state $k$ directly connected to state $j$ and which can be reached from state $i$ in one step. If there is no such intermediate state, the first-order term will be zero as well.

By direct inspection of the expansion (12) we notice that the first contribution to the Taylor series of $\rho_{ij}$ must come from a path and in particular it will be the shortest path that connects the state $i$ with the state $j$. If the shortest path consists of $m + 1$ steps, it involves $m$ intermediate states and contributes with the power $t^m$ to the Taylor expansion. If the shortest path is unique, the coefficient of the $n$th term gives the product of the rates along this path divided by the absorption probability $u_{ij}$, as in (12), thus indicating that at short times we have the asymptotic behavior

$$
\rho_{ij}(t) \sim \left( \frac{q_{ik_1} q_{k_1 k_2} \cdots q_{k_\ell j}}{u_{ij}} \right) t^m \frac{1}{m!} + \ldots,
$$

by neglecting higher order terms for small $t$.

If the shortest path is not unique, the coefficient is a sum of the product of the rates along several distinct paths, which may share some sub-paths. If the term $t^m$ is the first contribution to the Taylor series of $\rho_{ij}$ then all other higher order terms $t^r$, for $r > m$, do also contribute. Notice that apart from the absorption probability $u_{ij}$, the first term as in (15) is the product of the forward transition rates along the path from $i$ to $j$. This result is very general, because it holds regardless of the values of the backward rates.

To illustrate that Eq. (15) describes the short-time behavior of the probability density of the absorption time correctly, a generic network with three absorbing states as shown in Fig. 2 is discussed as a simple example. Different numbers of intermediate states are chosen for the shortest pathway of reaching the absorbing states $j_0$, $j_1$, and $j_2$ starting from the initial state $i$ which are 0, 1, and 2, respectively. We simply choose 0.5/s for the forward rates from the initial state to the absorbing states and 0.1/s for the backward rates. The probability densities of the absorption time for these three absorbing states can be calculated exactly from Eq. (9) which are shown in Fig. 3 as solid lines. The probabilities $u_{ij}$ of absorption are equal to $0.486829$, $0.402722$, and $0.110449$, for the absorbing states $j_0$, $j_1$, and $j_2$, respectively. According to Eq. (15), the asymptotic behavior at short times for the probability densities of the three absorption times will be described...
by expressions $0.5/u_{ij}$, $0.25t/u_{ij}$, and $0.125t^2/(2u_{ij})$, respectively, shown as dotted lines in Fig. 3. The dotted and solid lines agree perfectly with each other for the three cases thus indicating that Eq. (15) correctly predicts the asymptotic behavior of the probability density of the absorption time.

B. First-passage and first-return times

In Sec. II A we have derived the general theory concerning the absorption times. In this section we argue instead that the technique with absorbing states is useful to compute several important properties such as the distributions of the first-passage times and of the first-return times. The starting point here is a Markov chain $Y$ without absorbing states, which has a regular behavior including a well-defined steady state. Let $Q$ be the infinitesimal generator of $Y$ and let $\sigma_0 = \{0, 1, \ldots, n-1\}$ be the state space of the process. All processes considered here will start from the initial state $i \in \sigma_0$. Furthermore, in our derivations we will make no restrictions on the transition rates. In particular, we will in general assume that all transitions are reversible.

1. First passage time to $j \neq i$

Let $j \neq i$ be another state for which we would like to know the distribution of the first passage time starting from $i$.

To study this problem, we enlarge the state space of the process by adding one absorbing state $j'$ and by redirecting all rates intended to $j$ towards $j'$, instead. An illustration of this procedure is shown in Fig. 4. This defines a new Markov chain $X$, whose infinitesimal generator $Q'$ has the same form as (1) with $\sigma_X = \{j'\}$ and $a = 1$. The probability density $f_{ij}(t)$ of the first passage time is thus given by the probability density $\rho'_{ij}$ of the absorption time in $j'$ starting from $i$. Given that $q'_{kj} = q_{kj}$ and using the results obtained above we therefore have

$$f_{ij}(t) = q_{ij} + t \sum_{k_1=0}^{n-1} q_{ik_1} q_{k_1j} + \ldots$$

$$+ \frac{t}{\ell!} \sum_{k_1=0}^{n-1} \cdots \sum_{k_{\ell}=0}^{n-1} q_{ik_1} q_{k_1k_2} \cdots q_{k_{\ell}j} + \ldots,$$

which is almost identical to (12) with the difference that the probability of absorption in $j'$ is one. If the shortest path from $i$ to $j'$ is unique and has length $m$, then the first term of the expansion of $f_{ij}$ is given by

$$f_{ij}(t) \sim (q_{ik_1} q_{k_1k_2} \cdots q_{k_{m}j}) \frac{t^m}{m!} + \ldots,$$

by neglecting higher order terms for small $t$. Thus, it indicates that the first coefficient is strictly proportional to the product of the intermediate rates.

![Figure 2](image2.png)

**FIG. 2.** A generic network with three absorbing states. The number of intermediate states from initial state $i$ to absorbing states $j_0$, $j_1$, and $j_2$ for the shortest pathway is 0, 1, and 2, respectively. According to our theory, therefore, the leading term of the probability density function of the absorption time is constant, linear, and quadratic for these three cases at short time scales.

![Figure 3](image3.png)

**FIG. 3.** The probability density functions of the absorption time for the three absorbing states as shown in Fig. 2. The probability density at short times is shown in the main figure and the full probability density is indicated in the inset. The solid lines are from exact analytical solutions described by Eq. (9) and the dotted lines are just given by the leading term of the probability density functions as described by Eq. (15). The blue, red, and green curves correspond to the absorbing states $j_0$, $j_1$, and $j_2$, respectively.

![Figure 4](image4.png)

**FIG. 4.** A network transformation to compute the first-passage times as absorption times. In panel (a) we have a regular network of states without the absorbing states. To compute the distribution of the first-passage times from $i$ to $j$, the incoming transitions into the state $j$ are redirected towards a new state $j'$, thus leading to the network in panel (b). The first-passage time from $i$ to $j$ on the network in panel (a) has the same distribution as the absorption time from $i$ to $j'$ in the network (b).
2. First passage time to $j$ without returns to $i$

One could notice that the expansion (16) includes all terms that start in $i$ and finish in $j'$. So it includes also those walks on the network of states which visit state $i$ once or more times before arriving at the state $j'$. Although these walks are not involved in the shortest path from $i$ to $j'$, their weight in the normalization has an influence on the coefficient of the first term (17) of the expansion.

To consider only those realizations of the process that visit state $j'$ before returning to state $i$, we need to proceed as follows. We create a second absorbing state $i'$ towards which we redirect all transitions that are originally directed towards state $i$ and we consider a process $X$ with two absorbing states $\sigma_A = \{j', i'\}$, with initial condition in $i$ (see Fig. 5 for an illustration). At this point, the first-passage time in $j$ conditioned that the process is not allowed to return to $i$ has a probability density function $\tilde{f}_{ij|j}$ with a simple application of Eq. (12),

$$\tilde{f}_{ij|j} = \frac{q_{ij}}{u_{ij'}} + \frac{t}{u_{ij'}} \sum_{k_1=0}^{n-1} q_{ik_1} q_{kj} + \ldots$$

$$+ \frac{t^t}{u_{ij'} t!} \sum_{k_1=0}^{n-1} \sum_{k_2=0}^{n-1} \cdots \sum_{k_t=0}^{n-1} q_{ik_1} q_{k_2} \cdots q_{k_t} + \ldots$$

(18)

where all intermediate states are different from $i$, i.e., $k_\ell \neq i$, and $u_{ij'}$ is the absorption probability in $j'$, which is the same as the probability to visit the state $j$ before returning to the state $i$.

3. First-return times in $i$

We consider here again the condition discussed at the beginning of Sec. II B for the Markov chain $Y$ without absorbing states with the infinitesimal generator $Q$ on the state space $\sigma_0 = \{0, 1, \ldots, n - 1\}$. We let $i \in \sigma_0$ be the initial condition of the process and we are interested in the computation of the probability density of the first-return times in $i$. This is accomplished by considering the arguments from Sec. II B by setting $j = i$. The absorbing state $i'$ receives the edges that are otherwise directed towards $i$ (see Fig. 6 for the illustration).

Therefore, the first-return time probability density $r_i$ is equal to the absorption time probability density $\rho_{ii'}$ according to Eq. (12) by setting $u_{ij'} = 1$ and $q_{ii'} = q_{ii'}$.

Under the physically relevant assumption that there are no irreversible transitions, however, the first term of the expansion of $r_i$ is certainly linear. Indeed, a transition back to $i$ from any neighbor of $i$ must be possible. This gives the first term of the expansion

$$r_i(t) \sim \left( \sum_k q_{ik} q_{ki} \right) t + \ldots$$

(19)

where non-zero contributions to the sum come exclusively from those states that are neighbors of $i$. If the state $i$ is accessible experimentally under a variety of external conditions, the short-time behavior of the return time probability density may reveal important dependencies of the rates on the varying parameters.

III. SUMMARY AND CONCLUSIONS

It is shown that for a general Markov chain the distribution of the first-passage times from a state $i$ to any other state $j$ can be computed as the distribution of absorption times after a suitable modification of the state space. We therefore focused our attention on the absorption time distribution from an initial state to a chosen absorbing state in the presence of other absorbing states. There, by using exact methods, we have been able to analytically compute the complete Taylor series of the absorption time distribution. It has been found that each coefficient of the series can be written explicitly as a sum of the products of the transition rates.
By employing graph theory methods, we also determined that each term in the coefficients of the expansion corresponds to a walk that includes cycles and self-loops in the state space. This allowed us to show that the number of states visited during each walk corresponds exactly to the power of the corresponding term of the Taylor series. Furthermore, it was argued that the first term of the Taylor series must correspond to a specific path. In particular, since the first term of the Taylor series corresponds to the smallest power of the series, the coefficient corresponds to the shortest path on the network between the initial and the absorbing state. If the shortest path is unique, we have shown that the coefficient of the first term of the Taylor series can be written in terms of the product of the rates along this path. In addition, it was found that this general framework can be easily adapted to several other situations. It includes the first-passage time from a recurrent to another recurrent state, with or without visiting the initial state, and the return time to any given experimentally accessible state.

It is important to note that our results are independent on the network’s topology. We believe that the explicit expression of the coefficients in terms of the rates could be practically used to selectively determine the functional dependency of the rates on the external parameters from the experimental data. In this respect, a particularly useful result concerns the return time to a fixed initial condition. In this case, indeed, there is always only one intermediate state and the short-time expansion of the probability density must be linear so that the only unknown is the coefficient. It will be very valuable if these theoretical predictions could be tested in single-molecule experimental measurements for complex biochemical systems. From the practical point of view, however, the determination of the number of states along the shortest path may require highly resolved data at small times.

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