The reversibility of stochastic reaction model and its relationship with multistability

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Abstract In this paper, we study the reversibility of the chemical master equation model. We will give an easily verifiable necessary and sufficient condition for the chemical master equation model to satisfy the Kolmogorov’s cycle criterion. Next we prove that the quasi-potential, which plays a key role in the problem of exit from a domain, can be expressed by the potential function of some vector field in a line integral provided its existence. We then explore the relationship among the path independence of the line integral, the reversibility of the chemical master equation model and the reversibility of the deterministic model. As an application of our results, we find a non-trivial class of chemical systems that may exhibit multistability, and the transitions between steady states can be explicitly described.

Keywords Reversibility · Large deviations · Line integral · Multistability

1 Introduction

Chemical master equation model is a relatively accurate description for biochemical kinetics, especially for systems that can exhibit multistability, which has been widely detected in biological systems (see (Amiranashvili et al., 2016) for an example). However, chemical master equation model can be difficult to analyse (Vellela and Qian, 2008), and its corresponding diffusion approximation may be inaccurate in some sense (Qian, 2011). So most papers investigating multistability in chemical systems merely study simple systems such as the...
Schlögl model (Qian, 2011), which is essentially a one-dimensional birth-death process.

Transitions between steady states have been understood as rare events (Qian, 2011), which are exactly what large deviations theory concerns about. (Kurtz, 1972) proved that the stochastic trajectories of the chemical master equation model will converge to the trajectory of the deterministic model in finite time when taking thermodynamic limit. This result indicates that it is possible to establish large deviations results for the chemical master equation model. To the best of the authors’ knowledge, the first concrete step towards this direction is made by (Shwartz and Weiss, 1995), who have established the large deviations estimates and Freidlin-Wentzell theory for general density dependent Markov chains (Kurtz et al., 1978). To be specific, they defined “quasi-potential” and proved that it plays a key role in the problem of exit from a domain (Freidlin and Wentzell, 1998). After that, (Agazzi, 2017) derived large deviations results specifically for the chemical master equation model, but the existence of stationary distribution and its exponential estimates was not presented.

However, the definition of the quasi-potential is rather abstract. It is not likely to obtain an explicit expression of it in general situations, except for the situation when $b = -\nabla U$ (Jia et al., 2014), since everything can be explicitly calculated in this case. Moreover, It is noteworthy that $X^\epsilon$, which is the main object in (Freidlin and Wentzell, 1998), is reversible with respect to its stationary distribution when $b = -\nabla U$. This fact reveals the underlying relationship between the quasi-potential and the reversibility of the stochastic model.

The relationship between the reversibility of the stochastic reaction model and the reversibility of the deterministic reaction model (existence of the detailed balanced equilibrium) has been explored by (Whittle, 1986), but miscited by (Anderson et al., 2010), and corrected by (Joshi, 2013). The correct result is that the reversibility of the deterministic reaction model is stronger than the reversibility of the stochastic reaction model in general situations. Moreover, (Malyshev and Pirogov, 2008) showed that if the equilibrium of the deterministic model is detailed balanced, then the stochastic chemical reaction model is reversible with respect to its Poisson-like product form stationary distribution, which is unimodal and can not exhibit multistability.

The aims of this paper are to thoroughly discuss the reversibility of the chemical master equation model and discuss the relationship between the reversibility of the chemical master equation model and the large deviations related to this stochastic model. The paper is organized as follows. In Section 2, we briefly review the stochastic model and the deterministic model for chemical reaction networks. In Section 3, we will provide a new method to verify that whether a Markov chain satisfies the Kolmogorov’s cycle criterion (Jiang et al., 2003). In Section 4, we use the results in Section 3 to study the reversibility of chemical master equation model, and we find a specific class of chemical systems whose corresponding stochastic models satisfy the Kolmogorov’s cycle criterion, which contains a trivial subclass and a non-trivial subclass of
chemical systems. In Section 5, we introduce previous results about the trivial subclass of chemical systems. Those results show that the trivial subclass of chemical systems cannot exhibit multistability because of the existence of the detailed balanced equilibrium for the deterministic model. In Section 6, at first we briefly introduce the large deviations and Freidlin-Wentzell theory for the chemical master equation model. Then we will introduce a line integral for the chemical reaction network, and prove that the quasi-potential can be explicitly expressed by the potential function of the vector field in the line integral provided its existence. In Section 7, we discuss the relationship between the reversibility of the stochastic model and the path independence of the line integral. In Section 8, we establish the existence and asymptotic exponential estimate of the stationary distribution when the stochastic model satisfies the Kolmogorov’s cycle criterion. In Section 9, we will provide a method for constructing multistable chemical systems. For these systems, the transitions between steady states can be explicitly described.

2 Preliminaries

The following notations will be used throughout the paper.

Let $x = (x_1, \ldots, x_m) \in \mathbb{R}^m_+$, $y = (y_1, \ldots, y_m) \in \mathbb{Z}^m$, $z = (z_1, \ldots, z_m) \in \mathbb{N}^m$, denote $x^y = \prod_{j=1}^{m} x_j^{y_j}$, $z! = \prod_{j=1}^{m} z_j!$, $|x| = \sum_{j=1}^{m} x_j$, $\|x\| = \sqrt{\sum_{j=1}^{m} x_j^2}$.

$\forall \alpha, \beta \in \mathbb{R}^m$, we say $\alpha < \beta$ if $\alpha_i < \beta_i$ for the first $i$ where $\alpha_i$ and $\beta_i$ differ.

2.1 chemical reaction network

A chemical reaction network comprises a family of reactions involving a set of chemical species $\{S_1, \ldots, S_m\}$,

$$R_i : \sum_{j=1}^{m} \nu_{ij} S_j \rightarrow \sum_{j=1}^{m} \nu'_{ij} S_j, i = 1, \ldots, r,$$

where $\nu_{ij}, \nu'_{ij} \in \mathbb{N}$. We denote $\nu_i = (\nu_{i1}, \ldots, \nu_{im}), \nu'_i = (\nu'_{i1}, \ldots, \nu'_{im})$ and sometimes abbreviate $R_i$ to $\nu_i \rightarrow \nu'_i$.

Definition 1 Let $S = \{S_1, \ldots, S_m\}, C = \{\nu_i, \nu'_i|i = 1, \ldots, r\}, R = \{R_i|i = 1, \ldots, r\}$ denote the sets of species, complexes, and reactions respectively. The triple $\{S, C, R\}$ is called a chemical reaction network.

For each chemical reaction network, there is a unique corresponding directed graph. We construct it in the following manner.

Definition 2 The nodes of the graph are the complexes, and a directed edge is drawn from complex $\nu_i$ to complex $\nu'_i$ if and only if there is a reaction $R_i : \nu_i \rightarrow \nu'_i$. Each connected component of the resulting graph is termed a linkage class of the graph.
A chemical reaction network is called weakly reversible, if for any reaction \( \nu_i \rightarrow \nu'_i \), there exist \( \nu_1, \ldots, \nu_k \in \mathcal{C} \) such that \( \nu'_i \rightarrow \nu_1, \nu_1 \rightarrow \nu_2, \ldots, \nu_k \rightarrow \nu_i \).

A chemical reaction network is called strongly reversible, if for any reaction \( R_i : \nu_i \rightarrow \nu'_i \), there exists a reaction \( \nu'_i \rightarrow \nu_i \), and we denote it by \( R_i^{-1} \).

For strongly reversible chemical reaction network, let \( \nu_i \leftrightarrow \nu'_i \) be a pair of reversible reactions, we say \( \nu_i \rightarrow \nu'_i \) is a forward reaction if \( \nu_i < \nu'_i \). Otherwise we say it is a backward reaction.

**Remark 1** The reason why we use strongly reversible instead of reversible is to avoid confusion with the reversibility of Markov chain.

Throughout the paper, we assume that all chemical reaction networks are strongly reversible.

We call \( \nu'_i - \nu_i \) the reaction vector of reaction \( R_i \). Notice that different reactions may have the same reaction vector, it will be shown that this situation is very important throughout the paper, so we give the following definition.

**Definition 3** Let \( V(\mathcal{R}) = \{ \nu'_i - \nu_i | \nu_i < \nu'_i \} \), and denote the elements in \( V(\mathcal{R}) \) by \( v_p = (v_{p1}, \ldots, v_{pm}), \forall 1 \leq p \leq \#V(\mathcal{R}) \). Let \( \mathcal{R}_{p} = \{ R_i | \nu_i < \nu'_i, \nu'_i - \nu_i = v_p \} \), \( \mathcal{R}^{-}_{p} = \{ R^{-}_i | \nu_i < \nu'_i, \nu'_i - \nu_i = v_p \} \), and relabel the elements in \( \mathcal{R}_{p} \) and \( \mathcal{R}^{-}_{p} \) as

\[
R_{pl} : \sum_{j=1}^{m} v_{plj} S_j \rightarrow \sum_{j=1}^{m} v'_{plj} S_j, 1 \leq l \leq r_p,
\]

\[
R^{-}_{pl} : \sum_{j=1}^{m} v'_{plj} S_j \rightarrow \sum_{j=1}^{m} v_{plj} S_j, 1 \leq l \leq r_p,
\]

where \( r_p = \#\mathcal{R}_{p} \), and we denote \( v_{pl} = (v_{pl1}, \ldots, v_{plm}), v'_{pl} = (v'_{pl1}, \ldots, v'_{plm}) \).

### 2.2 Mathematical models

We firstly introduce the chemical master equation model with mass action kinetics. Let \( X^V(t) = (X_1^V(t), \ldots, X_m^V(t)) \), where \( X_j^V(t) \) denotes the concentration of \( S_j \) at time \( t \) and volume \( V \), i.e. the number of \( S_j \) at time \( t \) divided by \( V \). We assume that \( X^V(t) \) is a continuous-time Markov chain with state space \( S^V = \{ (z_1/V, \ldots, z_m/V) | z_p \in \mathbb{N}, p \leq m \} \) and transition rate matrix defined as follows: \( \forall p \leq \#V(\mathcal{R}) \),

\[
q^V_{x \xrightarrow{+} x+v_p} = \sum_{l=1}^{r_p} k_{pl} \frac{1}{V|v_p|} \prod_{j=1}^{m} \left( x_j \right)^{x_j} \mathcal{I}((x_j \geq v_{plj}), \forall x = (x_1, \ldots, x_m) \in \mathbb{N}^m),
\]

\[
q^V_{x \xrightarrow{-} x-v_p} = \sum_{l=1}^{r_p} k_{pl} \frac{1}{V|v_p|} \prod_{j=1}^{m} \left( x_j \right)^{x_j} \mathcal{I}((x_j \geq v'_{plj}), \forall x = (x_1, \ldots, x_m) \in \mathbb{N}^m),
\]

\[
q^V_{x \xrightarrow{=}} = -\sum_{p=1}^{\#V(\mathcal{R})} (q^V_{x \xrightarrow{+} v_p} + q^V_{x \xrightarrow{-} v_p}), \forall x = (x_1, \ldots, x_m) \in \mathbb{N}^m,
\]
where $|v_{jd}| = \sum_{j=1}^{m} v_{jd}$.

Remark 2 Many papers neglected the possibility that different reactions may have the same reaction vector.

On the macroscopic level, the same chemical reaction system can be described by the **deterministic model** with mass action kinetics: Let $x(t) = (x_1(t), \ldots, x_n(t))$, where $x_i(t)$ denotes the macroscopic concentration of $S_j$ at time $t$, then $x(t)$ satisfies the following ordinary differential equations:

$$
\begin{align*}
\dot{x}(t) &= \sum_{p=1}^{#V(R)} (\sum_{i=1}^{r_p} k_{pi} x(t)^{v_{pi}} - \sum_{i=1}^{r_q} k_{qi} x(t)^{v_{qi}}) v_{ip}, \\
x(0) &= x_0.
\end{align*}
$$

(1)

3 the reversibility of Markov chain

A Markov chain is said to be reversible if it is stochastically identical to its time-reversed version, the classical results about the reversibility of Markov chains can be summarized as follows.

**Lemma 1** Suppose that $\{X(t) | t \geq 0\}$ is an irreducible, positive recurrent and stationary Markov chain with countable state space $S$, then the following statements are equivalent:

(1.1) The chain is time reversible.

(1.2) The transition rate matrix $Q$ satisfies the Kolmogorov’s cycle criterion:

$$
q(i_1,i_2)q(i_2,i_3) \cdots q(i_{p-1},i_p)q(i_p,i_1) = q(i_1,i_p)q(i_p,i_{p-1}) \cdots q(i_3,i_2)q(i_2,p_1)
$$

for any $i_1, i_2, \ldots, i_p \in S$.

(1.3) There exist a potential function $\phi$ on $S$, such that $q(i,j)/q(j,i) = \exp\{\phi(i) - \phi(j)\}$.

For any $i_1, i_2 \in S$ such that $q_{i_1,i_2} > 0, q_{i_2,i_1} > 0$, we define $g(i_1,i_2) = \log \frac{q_{i_1,i_2}}{q_{i_2,i_1}}$.

Let $c : i_1 \to i_2 \to \cdots \to i_p \to i_1$ be a closed path, define $G(c) = g(i_1,i_2) + \cdots + g(i_p,i_1)$, then the transition rate matrix $Q$ satisfies the Kolmogorov’s cycle criterion if and only if $G(c) = 0$ for any closed path.

Inspired by the above discussion, we would like to compare the reversibility of Markov chain with the path independence of line integral.

**Lemma 2** Suppose that $f_i : \mathbb{R}^m \to \mathbb{R}$ is continuously differentiable, then the following statements are equivalent:

(2.1) $\int (f_1, \ldots, f_m) \cdot ds$ is independent of path.

(2.2) $\int (f_1, \ldots, f_m) \cdot ds = 0$ for each closed path $r$.

(2.3) There exist a potential function $\phi$ such that $\nabla \phi = (f_1, \ldots, f_m)$.

(2.4) The Jacobian matrix of $(f_1, \ldots, f_m)$ is symmetric at any $x \in \mathbb{R}^m$, i.e.

$$
\frac{\partial f_i}{\partial x_j} = \frac{\partial f_j}{\partial x_i}, \forall x \in \mathbb{R}^m, \forall i, j \leq m.
$$
In most cases, the Kolmogorov's cycle criterion is regarded as the main tool to verify that whether a stationary Markov chain is reversible, which is the counterpart of (2.2) in Theorem 2. However, we all use (2.4), instead of (2.2), to verify that whether a line integral is independent of path. In this paper, we will give the counterpart of (2.4) in the setting of Markov chain.

The following definitions are mostly taken from (Jiang et al., 2003).

**Definition 4** Suppose \( \{X(t)| t \geq 0\} \) is a Markov chain with countable state space \( S \), we say that \((i_1, i_2, \ldots, i_p, i_1)\) is a directed circuit if \( q_{i_j, i_{j+1}} > 0, \forall 1 \leq j \leq p \), here we regard \( i_{p+1} \) as \( i_1 \). We do not distinguish between a directed circuit with its shift, i.e. we assume that \((i_1, i_2, \ldots, i_p, i_1) = (i_2, \ldots, i_p, i_1, i_2)\).

For any directed circuit \( c = (i_1, i_2, \ldots, i_p, i_1) \), we write \( V(c) = \{i_1, \ldots, i_p\} \) and \( E(c) = \{ [i_1, i_2], [i_2, i_3], \ldots, [i_p, i_1] \} \).

The reverse of a directed circuit \( c = (i_1, i_2, \ldots, i_p, i_1) \), \( p > 1 \), is the directed circuit \( c^{-} = (i_1, i_p, i_{p-1}, \ldots, i_2, i_1) \).

**Definition 5** Let \( c_1, c_2 \) be two directed circuits, we say that they are summable if \( V(c_1) \cap V(c_2) \neq \emptyset \) and \( E(c_1) \cap E(c_2) = \emptyset \).

We are now in a position to define the sum of two summable directed circuits. If \( E(c_1) \cap E(c_2) = \emptyset \) and \( V(c_1) \cap V(c_2) = i_0 = i_{n_1} = i_{n_2} \), we say \( i_0 \) is a simple intersection, we define \( c_1 \oplus c_2 = (i_1^1, \ldots, i_{n_1}, i_1^2, i_{n_2+1}, \ldots, i_{n_2}, i_{n_1+1}, i_1^3) \)

Similarly, we can define the sum of two directed circuits if they have two or more simple intersections.

We now consider the case when \( E(c_1^{-}) \cap E(c_2) \neq \emptyset \), we assume for simplicity that \( c_1, c_2 \) have no simple intersection. Suppose that \( E(c_1^{-}) \cap E(c_2) = [i_0, i_1] \) with \( i_0 = i_d^1 = i^2_d, i_1 = i^1_d = i^2_{n+1} \), then we define \( c_1 \oplus c_2 = (i_1^1, \ldots, i_{d-1}, i_{n+2}, \ldots, i^2_n, i^1_{d+1}, i^1_1) \)

Similarly, we can define the sum of two directed circuits if \( E(c_1^{-}) \cap E(c_2) \) has two or more elements.
The reason why we introduce the sum of directed circuits can be seen by the following result.

**Lemma 3** Suppose that \( c = c_1 \oplus c_2 \oplus \cdots \oplus c_K \), then

\[
G(c) = \sum_{k=1}^{K} G(c_k)
\]

**Proof**: The proof follows directly from the definition of \( \oplus \) and the fact that \( g(i_1, i_2) + g(i_2, i_1) = 0 \).

**Definition 6** We say a directed circuit \( c \) is irreducible, if there does not exist two directed circuits \( c_1, c_2 \) such that \( c = c_1 \oplus c_2 \).

Intuitively speaking, irreducible directed circuits are the smallest and the simplest directed circuits. Thereom 3 shows that in order to prove that \( G(c) = 0 \) for any directed circuit \( c \), we only need to prove that \( G(c) = 0 \) for any irreducible directed circuits!

**Example 1** Random jump model on \( \mathbb{Z}^m \) and let \( \{v_1, \ldots, v_m \mid v_p \in \mathbb{Z}^m, \forall 1 \leq p \leq m \} \) be a basis of \( \mathbb{R}^m \), and we write \( v_{-p} = -v_p, \forall p \). Suppose that \( \{X(t) \mid t \geq 0\} \) is a continuous time Markov chain with irreducible state space \( S \subset \mathbb{Z}^m \) and transition rate matrix defined as follow: For any \( x \in S \), \( q(x, x + v_p) > 0, \forall p \in \{\pm 1, \ldots, \pm m\} \).

Then the corresponding irreducible directed circuits are \( \{(x, x + v_{p_1}, x + v_{p_2}, x) \mid \forall x \in \mathbb{Z}^m, p_1 \neq p_2, p_1, p_2 \in \{\pm 1, \ldots, \pm m\} \} \).

We define \( c_{p_1, p_2}(x) = (x, x + v_{p_1}, x + v_{p_2}, x) \), then we have

\[
F(c_{p_1, p_2}(x)) = \log \frac{q(x + v_{p_1}, x)}{q(x, x + v_{p_1})} + \log \frac{q(x + v_{p_1}, x + v_{p_2}, x + v_{p_1})}{q(x + v_{p_1}, x + v_{p_2})}
+ \log \frac{q(x + v_{p_2}, x + v_{p_1} + v_{p_2})}{q(x + v_{p_2}, x)} + \log \frac{q(x, x + v_{p_2})}{q(x + v_{p_2}, x)}
\]

\[
= \log \frac{q(x + v_{p_2}, x + v_{p_1} + v_{p_2})}{q(x + v_{p_2}, x + v_{p_1})} + \log \frac{q(x, x + v_{p_2})}{q(x + v_{p_2}, x)}
+ \log \frac{q(x + v_{p_1}, x + v_{p_2})}{q(x + v_{p_1}, x + v_{p_2}, x + v_{p_1})} + \log \frac{q(x, x + v_{p_1})}{q(x + v_{p_1}, x)}
\]

If we write

\[
F_{p_1}(x) = \log \frac{q(x, x + v_{p_1})}{q(x + v_{p_1}, x)}, \forall p_1 \in \{\pm 1, \ldots, \pm m\}.
\]

Then

\[
F(c_{p_1, p_2}(x)) = F_{p_1}(x + v_{p_2}) - F_{p_1}(x) - [F_{p_2}(x + v_{p_1}) - F_{p_2}(x)].
\]

Therefore, satisfies the Kolmogorov’s criterion if and only if \( F(c_{p_1, p_2}(x)) = 0, \forall p_1, p_2 \in \{\pm 1, \ldots, \pm m\}, \forall x \in S \), i.e

\[
F_{p_1}(x + v_{p_2}) - F_{p_1}(x) = F_{p_2}(x + v_{p_1}) - F_{p_2}(x), \forall p_1, p_2 \in \{\pm 1, \ldots, \pm m\}, \forall x \in S.
\]
Here we suggest readers to compare (2) with (2.4) in Theorem 2. Furthermore, recall that \( g \) involve both the forward reactions and backward reactions, one can verify that if (2) holds for some \(-p_1 < 0, p_2 > 0\), then it will also holds for \( p_1, p_2 \).

**Theorem 1** [Parallelogram Condition] The transition rate matrix of random jump model satisfies the Kolmogorov’s cycle criterion if and only if (2) hold for any \( x \in S \) and any \( p_1, p_2 \in \{1, \ldots, m\} \).

4 The reversibility of the chemical master equation model

**Assumption 1** The elements in \( V(\mathcal{R}) \) are linearly independent.

Suppose that a chemical reaction network is strongly reversible and satisfies Assumption 1, we now want to use Theorem 1 to study the reversibility of the chemical master equation model.

**Definition 7** We say that \( p_1 \leq m \) satisfies Condition 1, if \( r_{p_1} > 1 \) and \((v_{p_1, i} - v_{p_1, l_2})v_{p_2}^j = 0, \forall l_1, l_2 \leq r_{p_1}, \forall p_2 \neq p_1, \forall j \).

**Theorem 2** Consider a chemical reaction network \((S, C, \mathcal{R})\) that is strongly reversible and satisfies Assumption 1. If for any \( p_1 \leq m \) which does not satisfy Condition 1, we have the following equality

\[
\frac{k_{p_1, 1}}{k_{p_1, j}} = \frac{k_{p_1, 2}}{k_{p_1, 1}} = \cdots = \frac{k_{p_1, r_{p_1}}}{k_{p_1, 1}} \tag{3}
\]

then \( X^V \) satisfies the Kolmogorov’s Criterion for any \( V \).

**Proof** For the sake of brevity, we assume \( V = 1 \), and write \( q_{x,x+v_p} = q^1_{x,x+v_p} \).

For \( x \) which is away from the boundary, the Parallelogram Condition (2) is equivalent to

\[
\log \frac{\sum_{l=1}^{r_{p_1}} k_{p_1, l} \frac{(x+v_p, x+v_p)\!}{(x+v_p, x+v_p)} - \sum_{l=1}^{r_{p_1}} k_{p_1, l} \frac{(x+v_p, x+v_p)\!}{(x+v_p, x+v_p)}}{\sum_{l=1}^{r_{p_2}} k_{p_2, l} \frac{(x+v_p, x+v_p)\!}{(x+v_p, x+v_p)}} = \log \frac{\sum_{l=1}^{r_{p_1}} k_{p_1, l} \frac{(x+v_p, x+v_p)\!}{(x+v_p, x+v_p)} - \sum_{l=1}^{r_{p_1}} k_{p_1, l} \frac{(x+v_p, x+v_p)\!}{(x+v_p, x+v_p)}}{\sum_{l=1}^{r_{p_2}} k_{p_2, l} \frac{(x+v_p, x+v_p)\!}{(x+v_p, x+v_p)}}.
\]

It is further equivalent to

\[
\log \frac{\sum_{l=1}^{r_{p_1}} k_{p_1, l} \frac{(x+v_p, x+v_p)\!}{(x+v_p, x+v_p)} - \sum_{l=1}^{r_{p_1}} k_{p_1, l} \frac{(x+v_p, x+v_p)\!}{(x+v_p, x+v_p)}}{\sum_{l=1}^{r_{p_2}} k_{p_2, l} \frac{(x+v_p, x+v_p)\!}{(x+v_p, x+v_p)}} = \log \frac{\sum_{l=1}^{r_{p_1}} k_{p_1, l} \frac{(x+v_p, x+v_p)\!}{(x+v_p, x+v_p)} - \sum_{l=1}^{r_{p_1}} k_{p_1, l} \frac{(x+v_p, x+v_p)\!}{(x+v_p, x+v_p)}}{\sum_{l=1}^{r_{p_2}} k_{p_2, l} \frac{(x+v_p, x+v_p)\!}{(x+v_p, x+v_p)}}.
\]
We now prove that both sides of the above equation equal to zero. 

If \( r_{p_1} = 1 \), then

\[
\log \frac{\sum_{l=1}^{r_{p_1}} k_{p_1,l}(v_{x+p_2} - v_{x-p_1,l})}{\sum_{l=1}^{r_{p_1}} k_{p_1,l}(v_{x+p_2} - v_{x-p_1,l})} \rightarrow \log \frac{\sum_{l=1}^{r_{p_1}} k_{p_1,l}v_{x+p_2}}{\sum_{l=1}^{r_{p_1}} k_{p_1,l}v_{x-p_1,l}} = \log \frac{k_{p_1,1}}{k_{p_1,1}} = 0.
\]

If \( r_{p_1} > 1 \) but does not satisfies Condition 1 (see Definition 7), then (3) holds, one can verify that this case is identical to the first case.

If \( r_{p_1} > 1 \) and satisfies Condition 1, for any \( p_2 \) we denote \( J_{p_2} = \{1 \leq j \leq m|v_{p_2}^j \neq 0\} \), then according to Condition 1 we have that \( v_{p_1,l,j} = v_{p_1,l,j}, \forall l, j \leq r_{p_1}, j \in J_{p_2} \).

Now we back to our problem. We have that

\[
\sum_{l=1}^{r_{p_1}} \frac{k_{p_1,l}^{-1}}{1} \frac{1}{\sum_{l=1}^{r_{p_1}} k_{p_1,l}^{-1}} = \sum_{l=1}^{r_{p_1}} \frac{k_{p_1,l}^{-1}}{1} \frac{1}{\sum_{l=1}^{r_{p_1}} k_{p_1,l}^{-1}} = \sum_{l=1}^{r_{p_1}} \frac{k_{p_1,l}^{-1}}{1} \frac{1}{\sum_{l=1}^{r_{p_1}} k_{p_1,l}^{-1}},
\]

where the second equality follows from \( v_{p_1,l,j} = v_{p_1,l,j}, \forall l, j \leq r_{p_1}, j \in J_{p_2} \), and \( v_{p_2}^j = 0, \forall j \notin J_{p_2} \), and the third equality follows from \( v_{p_1,l,j} = v_{p_1,l,j}, \forall l, j \leq r_{p_1}, j \in J_{p_2} \) again.

However, we have to point out that some irreducible directed circuits near the boundary may still be complicated, for example

\[
\begin{array}{c}
\text{i-1} \\
/ \\
| \\
\text{i-2} \\
/ \\
| \\
\text{i-3} \\
/ \\
\text{i-4} \\
/ \\
\text{i-5} \\
/ \\
\text{i-6}
\end{array}
\]

If \( q_{i_3,i_6} = 0 \) because of the lack of chemical species, then \( c = (i_1, i_2, \ldots, i_6, i_4) \) is irreducible. But if we can prove that

\[
g(i_1, i_2) + g(i_2, i_3) = g(i_1, i_6) + C,
\]

and

\[
g(i_1, i_6) + C = g(i_6, i_5) + g(i_5, i_4),
\]
with a same constant $C$, then we can still prove that $G(c) = 0$. Therefore we can still use the Parallelogram condition to prove the desired result if we can properly define $g(i_3, i_6)$ when $q_{i_3, i_6} = 0$, and we omit the details for the sake of brevity.

Obviously, we have proved the following corollary through the proof of Theorem 2.

**Corollary 1** Suppose that $(S, C, R)$ is strongly reversible and satisfies Assumption 1. If for any $p \leq \#V(R)$ we have

$$\frac{k_{p,1}}{k_{p,l}} = \frac{k_{p,2}}{k_{p,2}} = \cdots = \frac{k_{p,r_p}}{k_{p,r_p}},$$

then the transition rate matrix of the corresponding chemical master equation model satisfies the Kolmogorov’s cycle criterion.

We will discuss the difference between Theorem 2 and Corollary 1 in the following sections.

We now give an example which satisfies the condition of Theorem 2, but does not satisfies the condition of Corollary 1.

**Example 2** Consider the following chemical reaction network.

\[
\begin{align*}
\emptyset & \xrightleftharpoons[k_1]{k_{21}} S_1 \xrightleftharpoons[k_{22}]{k_{21}} S_2, \quad S_1 + 2S_2 & \xrightleftharpoons[k_{22}]{k_{22}} 3S_2.
\end{align*}
\]

Notice that $V(R) = \{v_1 = (1, 0), v_2 = (-1, 1)\}, r_1 = 1, r_2 = 2$, and $(v_{22j} - v_{21j})v_1^l = 0, j = 1, 2$, therefore *Condition 1* holds for $v_2$. Then by Theorem 2, we know that the corresponding chemical master equation model satisfies the Kolmogorov’s cycle criterion for any given chemical reaction rate constants!

We will discuss this model in more detail in the final of this paper.

5 Detailed balanced equilibrium and product form stationary distribution

In this section, we will show that under the condition of Corollary 1, the stationary distribution of the chemical master equation model is of Poisson-like. Such Poisson-like product form stationary distribution has been studied in (Anderson et al., 2010) under weaker conditions, but in our case, the Markov chain is reversible with respect to its stationary distribution.

**Assumption 2** $\#V(R) = m$.

If both assumption 1 and assumption 2 hold, then matrix $(v_1^T, \ldots, v_m^T)$ is invertible. Let $(e_1^T, \ldots, e_m^T) = (v_1^T, \ldots, v_m^T)A$ for some invertible matrix $A$, where $e_i$ denotes the $i$-th unit row vector.

The following theorem is taken from (Joshi, 2013), and we will give a concise proof of it. To avoid notation abuse, we assume Assumption 2 holds.
**Lemma 4** Let \((S,C,R)\) be a strongly reversible chemical reaction network. If (4) is satisfied for any \(p \leq \#V(R)\), then the transition rate matrix of \(X^V\) satisfies the kolmogorov’s cycle criterion for any volume if and only if the deterministic model (1) has an equilibrium \(c \in \mathbb{R}^m_{>0}\), such that \(k_{pl}c^{v_p} = k_{pl}^{-1}c^{v_p}, \forall p \leq m, l \leq r_p\).

**Remark 3** The principle of detailed balance (Lewis, 1925) (Beard and Qian, 2008) states that when the strongly reversible reaction system is at chemical equilibrium, the reaction rate of each elementary reaction is equal to the reaction rate of its reverse reaction, therefore \(c\) is also called the chemical equilibrium (point), and this theorem actually states that the deterministic detailed balance is equivalent to the stochastic detailed balance in some cases. For more relevant results we refer readers to (Ge and Qian, 2017).

**Proof** If \(c \in \mathbb{R}^m_{>0}\) satisfies \(k_{pl}c^{v_p} = k_{pl}^{-1}c^{v_p}, \forall p \leq m, l \leq r_p\), then

\[
\frac{k_{pl}}{k_{pl}} = c^{v_p}, \forall l \leq r_p, p \leq m,
\]

which is equivalent to that

\[
\sum_{j=1}^{m} v_p^j \log c_j = \log \frac{k_{pl}}{k_{pl}}, \forall l \leq r_p, \forall p \leq m.
\]  

(5)

It can be seen that, in order for (5) to be valid when \(r_p > 1\), (4) must be satisfied.

Expressing (5) by matrix we have the following system of linear equations

\[
\begin{pmatrix}
v_1^1 & v_2^1 & \ldots & v_m^1 \\
v_1^2 & \ldots & \\
v_1^m & \ldots & v_m^m
\end{pmatrix}
\begin{pmatrix}
\log c_1 \\
\vdots \\
\log c_m
\end{pmatrix}
= \begin{pmatrix}
\log \frac{k_{11}}{k_{11}} \\
\vdots \\
\log \frac{k_{m1}}{k_{m1}}
\end{pmatrix}.
\]

So the detailed balance equilibrium exists when the rank of the augmented matrix and that of the coefficient matrix are equal.

If the coefficient matrix is row full rank, then the detailed balance equilibrium always exists. If the rank of the coefficient matrix is \(s < m\), we assume without loss of generality that the first \(s\) row vectors are linearly independent over rational number field \(\mathbb{Q}\), then there exist \(z_{p} \in \mathbb{Z}, p \leq s + 1\) such that

\[
\sum_{p=1}^{s+1} z_p v_p = 0.
\]  

(6)

Here we used the fact that since \(v_p^j \in \mathbb{Q}\), therefore \(\{v_1, \ldots, v_s\}\) is linearly independent over \(\mathbb{Q}\) if and only if \(\{v_1, \ldots, v_s\}\) is linearly independent over any extension field of \(\mathbb{Q}\). To see this, we point out that the rank of a matrix can also be characterized by minor determinants, which are independent of fields.
The equation (6) says that for any \( p \leq m \), if \( R_p \) occurs \( z_p \) times (By \( z_p < 0 \) we mean that the reverse reaction of \( R_p \) occurs \(-z_p\) times. This will be used frequently in the rest of the paper), then the trajectory will return to its initial point. Therefore we can induce closed paths in \( S^V \) from (6), and we plan to apply the Kolmogorov’s cycle criterion to these paths.

Fortunately, Corollary 1 tells us that if one of these paths satisfies the Kolmogorov’s cycle criterion, then others will also satisfy the Kolmogorov’s cycle criterion. Therefore for any \( V > 0 \), if the transition rate matrix of \( X^V \) satisfies the kolmogorov’s cycle criterion, then for any induced closed path, we have that

\[
1 = \prod_{n=0}^{N-1} \frac{q_{V, n+1}^V}{q_{V, n}^V} = \prod_{n=0}^{N-1} \frac{1}{\sum_{l=1}^{r_{p(n)}} k_{p(n)}^V V^{-v_{p(n)}^V l} (V^V_{n+1} - v_{p(n)}^V)!} = \prod_{n=0}^{N-1} \frac{1}{k_{p(n)}^V V^V_{n+1} - v_{p(n)}^V!} = \prod_{n=0}^{N-1} \frac{1}{k_{p(n)}^V V^V_{n+1} - v_{p(n)}^V!}
\]

where \( N = \sum_{p=1}^{s+1} |z_p| \). Taking logarithm on both sides yields

\[
\sum_{p=1}^{s+1} z_p \log \frac{k_p^-}{k_p^+} = 0.
\]

Combine the above equation and (6), then we know that the \( s + 1 \)-th row vector of the augmented matrix can also be linearly expressed by the first \( s \) row vectors of the augmented matrix, therefore the existence of detailed balanced equilibrium follows.

The converse follows directly from the following lemma.

\[\text{Lemma 5 (Malyshev and Pirogov, 2008)}\] Suppose that the chemical reaction network \( (S, C, R) \) is strongly reversible. If there exists a \( c \in \mathbb{R}^m_{>0} \) such that \( k_p^c c^p = k_p^c c^p, \forall p \leq m, l \leq r_p \), then \( \pi^V(x) \equiv \frac{V^V_{n+1}}{V^V_{n+1} - v_{p(n)}^V} x, x \in S^V \) satisfies the detailed balance condition: \( \pi^V(x) q_{x,y}^V = \pi^V(y) q_{y,x}^V, \forall x, y \in S^V, \forall V \).

The above results shows that, the transition rate matrix of \( X^V \) satisfies the Kolmogorov’s cycle criterion when the deterministic equilibrium is detailed balanced, furthermore, the stationary distribution will be unimodal. Therefore in order for the chemical master equation to exhibit multistability, the equilibrium of the deterministic model must not be detailed balanced.

6 Explicit expression of the quasi-potential

Those systems with multistability receive more concerns in biophysics, and how to describe the transitions between different steady states is the core issues for multistable systems. In the past decades, many physicists (Qian, 2011)
have noticed that the Freidlin-Wentzell theory (Freidlin and Wentzell, 1998)
can be used to analyse the transitions between steady states. In this section,
we will prove that the quasi-potential, which plays a key role in the Freidlin-
Wentzell theory related to the chemical master equation (Agazzi, 2017),
can be explicitly expressed in some cases.

In the rest of the paper, unless otherwise stated we always assume that
Assumption 1 and Assumption 2 are satisfies.

Denote by $D_{0,T}[\mathbb{R}_+^m]$ the space containing all the functions of $t \in [0,T]$ 
with values in $\mathbb{R}_+^m$ that are right continuous with left limits.

For any $x \in \mathbb{R}_+^m, y \in \mathbb{R}_+^m, \theta \in \mathbb{R}_+^m$, denote
\[
g(x, \theta) = \sum_{p=1}^m \left[ F_p^+(x)(e^{vp\theta} - 1) + F_p^-(x)(e^{-vp\theta} - 1) \right],
\]
with $F_p^+(x) = \sum_{l=1}^{r_p} k_{pl}x_{vl}$, $F_p^-(x) = \sum_{l=1}^{r_p} k_{pl}^{-}x_{vl}$. Define the local rate function
\[
l(x, y) = \sup_{\theta \in \mathbb{R}_+^m} (\theta \cdot y - g(x, \theta)), \forall x \in \mathbb{R}_+^m, y \in \mathbb{R}_+^m.
\]

For any $\phi \in D_{0,T}[\mathbb{R}_+^m]$, define the rate function
\[
I_0^T(\phi) = \begin{cases} 
\int_0^T l(\phi(s), \dot{\phi}(s)) ds & \text{if } \phi \text{ is absolutely continuous,} \\
+\infty & \text{otherwise.}
\end{cases}
\]

(Agazzi, 2017) proved that $X^V$ satisfies the large deviation principle with the
good rate function $I_0^T$ in $D_{0,T}[\mathbb{R}_+^m]$ under some weak conditions. (Agazzi,
2017) also studied the problem of exit from a domain related to the chemical
master equation model. Suppose that $O \subset D$ is an asymptotic stable equilib-
rium of the deterministic model (1), (Agazzi, 2017) proved that the asymptotic
estimation of the exit time from $D$ is determined by the following quantity:
\[
I(O, x) \triangleq \inf_{T \geq 0} \{ \inf_{\phi \in D_{0,T}[\mathbb{R}_+^m] \{ \phi(0) = O, \phi(T) = x \}} I_0^T(\phi),
\]
where $x \in D$. $I(O, x)$ is usually called the quasi-potential.

**Lemma 6** For any given $x, y \in \mathbb{R}_+^m$, and any absolutely continuous path
\{r(t), t \in [0, T]\} with $r(0) = x, r(T) = y$, define its reverse path $\bar{r}(t) = r(T - t), \forall t$,
we have
\[
I_0^T(r) - I_0^T(\bar{r}) = S(r),
\]
where
\[
S(r) \triangleq \int_r \left( \log \sum_{l=1}^{r_1} k_{1l}x_{l1}^{r_1} \ldots \log \sum_{l=1}^{r_m} k_{ml}x_{ml}^{r_m} \right) A.(dx_1, \ldots, dx_m).
\]

In this paper, we call (8) the line integral of the chemical reaction network.
Expressing this by matrix we have the following system of linear equations

\[
\begin{pmatrix}
  v_1^1 & v_2^1 & \cdots & v_m^1 \\
v_1^2 & v_2^2 & \cdots & v_m^2 \\
  \vdots & \vdots & \ddots & \vdots \\
v_1^m & v_2^m & \cdots & v_m^m \\
\end{pmatrix}
\begin{pmatrix}
  F_1^+(r(t))e^{v_1 \cdot \phi_1(t)} - F_1^-(r(t))e^{-v_1 \cdot \phi_2(t)} \\
  \vdots \\
  F_m^+(r(t))e^{v_m \cdot \phi_1(t)} - F_m^-(r(t))e^{-v_m \cdot \phi_2(t)} \\
\end{pmatrix}
= \begin{pmatrix}
  \dot{r}_1(t) \\
  \vdots \\
  \dot{r}_m(t) \\
\end{pmatrix}.
\]

(9)

Notice that the coefficient matrix is invertible, so the above system of linear equations has a unique solution \((b_1, \ldots, b_m) \in \mathbb{R}^m\). Then we consider

\[
F_p^+(r(t))e^{v_p \cdot \phi_1(t)} - F_p^-(r(t))e^{-v_p \cdot \phi_2(t)} = b_p, \forall p \leq m,
\]

this is equivalent to

\[
F_p^+(r(t))e^{v_p \cdot \phi_1(t)} - F_p^-(r(t))e^{-v_p \cdot \phi_2(t)} = 0, \forall p \leq m.
\]

Regarding the above equation as a quadratic equation of \(x = \exp\{v_p \phi_1(t)\}\), we will get two solutions, one is negative, and the other is positive. Since the exponential function is always positive, there exist a unique number \(c_p \in \mathbb{R}\) such that \(v_p \phi_1(t) = c_p, \forall p \leq m\).

We now have \(\theta_1(t) = (c_1, \ldots, c_m)^T\), therefore \(\theta_1(t)\) is unique, and it can be expressed by basic elementary functions, therefore \(l(x, y)\) is continuous with respect to \(x\) and \(y\).

As for the reverse path

\[
l(\bar{r}(T - t), \dot{\bar{r}}(T - t)) = \sup_\theta (\theta \cdot \dot{\bar{r}}(T - t) - g(\bar{r}(T - t), \theta))
\]

\[
= \sup_\theta (\theta \cdot (-\dot{r}(t)) - g(r(t), \theta)) = l(r(t), -\dot{r}(t)),
\]

so let \(\theta_2(t)\) be the vector such that \(l(r(t), -\dot{r}(t)) = \theta_2(t) \cdot (-\dot{r}(t)) - g(r(t), \theta_2(t))\).

Similarly, \(\theta_2(t)\) we have

\[
\begin{pmatrix}
  v_1^1 & v_2^1 & \cdots & v_m^1 \\
v_1^2 & v_2^2 & \cdots & v_m^2 \\
  \vdots & \vdots & \ddots & \vdots \\
v_1^m & v_2^m & \cdots & v_m^m \\
\end{pmatrix}
\begin{pmatrix}
  F_1^+(r(t))e^{v_1 \cdot \phi_1(t)} - F_1^-(r(t))e^{-v_1 \cdot \phi_2(t)} \\
  \vdots \\
  F_m^+(r(t))e^{v_m \cdot \phi_1(t)} - F_m^-(r(t))e^{-v_m \cdot \phi_2(t)} \\
\end{pmatrix}
= \begin{pmatrix}
  -\dot{r}_1(t) \\
  \vdots \\
  -\dot{r}_m(t) \\
\end{pmatrix}.
\]

(10)

Combine (9) with (10) we obtain

\[
\begin{pmatrix}
  v_1^1 & v_2^1 & \cdots & v_m^1 \\
v_1^2 & v_2^2 & \cdots & v_m^2 \\
  \vdots & \vdots & \ddots & \vdots \\
v_1^m & v_2^m & \cdots & v_m^m \\
\end{pmatrix}
\begin{pmatrix}
  \sum_{i=1}^2 (F_1^+(r(t))e^{v_i \cdot \phi_1(t)} - F_1^-(r(t))e^{-v_i \cdot \phi_2(t)}) \\
  \vdots \\
  \sum_{i=1}^2 (F_m^+(r(t))e^{v_i \cdot \phi_1(t)} - F_m^-(r(t))e^{-v_i \cdot \phi_2(t)}) \\
\end{pmatrix}
= \begin{pmatrix}
  0 \\
  \vdots \\
  0 \\
\end{pmatrix}.
\]
Recall that $A$ is invertible, hence

$$F_p^+ (r(t)) e^{v_p \cdot \theta_1(t)} - F_p^- (r(t)) e^{-v_p \cdot \theta_1(t)} + F_p^+ (r(t)) e^{v_p \cdot \theta_2(t)} - F_p^- (r(t)) e^{-v_p \cdot \theta_2(t)} = 0, \forall p \leq m.$$ 

Equivalently, $\forall p \leq m$

$$F_p^+(r(t)) e^{v_p \cdot \theta_1(t)} + F_p^+(r(t)) e^{v_p \cdot \theta_2(t)} = F_p^-(r(t)) e^{-v_p \cdot \theta_1(t)} + F_p^-(r(t)) e^{-v_p \cdot \theta_2(t)},$$

$$F_p^+(r(t)) e^{v_p \cdot (\theta_1(t) + \theta_2(t))} = F_p^-(r(t)) e^{v_p \cdot \theta_1(t)} + F_p^-(r(t)) e^{-v_p \cdot \theta_2(t)};$$

$$v_p \cdot (\theta_1(t) + \theta_2(t)) = \log \frac{F_p^+(r(t))}{F_p^+(r(t))}.$$ 

So we get the following system of linear equations

$$(\theta_1(t) + \theta_2(t))(v_1^T, \ldots, v_m^T) = (\log \frac{F_1^-(r(t))}{F_1^+(r(t))}, \ldots, \log \frac{F_m^-(r(t))}{F_m^+(r(t))});$$

from which follows that

$$(\theta_1(t) + \theta_2(t)) = (\log \frac{F_1^-(r(t))}{F_1^+(r(t))}, \ldots, \log \frac{F_m^-(r(t))}{F_m^+(r(t))}) A.$$ 

Since

$$l(r(t), \dot{r}(t)) - l(\hat{r}(T-t), \dot{\hat{r}}(T-t))$$

$$= \theta_1(t) \cdot \dot{r}(t) - g(r(t), \theta_1(t)) - \theta_2(t) \cdot (\dot{\hat{r}}(t) - g(r(t), \theta_2(t)))$$

$$= (\theta_1(t) + \theta_2(t)) \cdot \dot{r}(t) - (g(r(t), \theta_1(t)) - g(r(t), \theta_2(t)))$$

$$= (\theta_1(t) + \theta_2(t)) \cdot \dot{r}(t) - \left( \sum_{p=1}^{m} F_p^+(r(t)) (e^{v_p \cdot \theta_1(t)} - e^{v_p \cdot \theta_2(t)}) + F_p^-(r(t)) (e^{-v_p \cdot \theta_2(t)} - e^{-v_p \cdot \theta_1(t)}) \right)$$

$$= (\theta_1(t) + \theta_2(t)) \cdot \dot{r}(t) - \left( \sum_{p=1}^{m} (F_p^+(r(t)) e^{v_p \cdot (\theta_1(t) + \theta_2(t))} - F_p^-(r(t)) (e^{-v_p \cdot \theta_2(t)} - e^{-v_p \cdot \theta_1(t)}) \right)$$

$$= (\theta_1(t) + \theta_2(t)) \cdot \dot{r}(t) = (\log \frac{F_1^-(r(t))}{F_1^+(r(t))}, \ldots, \log \frac{F_m^-(r(t))}{F_m^+(r(t))}) A \cdot \dot{r}(t).$$ 

Finally, apply the above results we conclude

$$I_T^0 (r(t)) - I_0^T (\hat{r}(t)) = \int_0^T l(r(t), \dot{r}(t)) dt - \int_0^T l(\hat{r}(t), \dot{\hat{r}}(t)) dt$$

$$= \int_0^T l(r(t), \dot{r}(t)) dt - \int_0^T l(\hat{r}(T-t), \dot{\hat{r}}(T-t)) dt$$

$$= \int_0^T (l(r(t), \dot{r}(t)) - l(\hat{r}(T-t), \dot{\hat{r}}(T-t))) dt$$

$$= \int_0^T \left( \log \frac{F_1^-(r(t))}{F_1^+(r(t))}, \ldots, \log \frac{F_m^-(r(t))}{F_m^+(r(t))} \right) A \cdot \dot{r}(t) dt = S(r).$$
(8) is essentially a line integral of a vector field. If the vector field has a potential, then (8) is independent of path when the initial point and the end point are fixed. We will show that, when (8) is independent of path, the quasi-potential can be explicitly expressed by the potential function of the vector field.

Firstly, we need the following lemmas.

**Lemma 7** *(Shwartz and Weiss, 1995)* If \( \{r(t)| t \in [0, T]\} \) is the trajectory of the deterministic model (1), then \( I_0^T(r) = 0 \).

This result agrees with Kurtz’s result *(Kurtz, 1972)*.

**Lemma 8** *(Logemann and Ryan, 2014)* [Lyapunov asymptotic stability] Consider the following ordinary differential equation

\[
\dot{x} = f(x),
\]

where \( f : \mathbb{R}^m \to \mathbb{R}^m \) is continuous, and there is a point \( O \) such that \( f(O) = 0 \). If there is a continuously differentiable function \( V \) and a bounded domain \( D \) such that:

1. \( O \in D, V(O) = 0 \);
2. \( \forall x \in D \setminus \{O\}, V(x) > V(O) \), and
3. \[
\frac{dV(\phi_x(t))}{dt} \bigg|_{t=0} < 0,
\]

where \( \phi_x(t) \) denotes the trajectory of the differential equation started at \( x \). Then \( O \) is an asymptotic stable equilibrium, and \( D \) is attracted to \( O \).

Now we state our second main result.

**Theorem 3** Let \( D \subset \mathbb{R}_{>0}^m \) be a bounded domain with smooth boundary. Suppose that (8) is independent of path and denote the potential function of the vector field in (8) by \( F \). If \( F(x) > F(O), \nabla F(x) \neq 0, \forall x \in D \setminus \{O\} \), then \( \forall x \in D \), we have that

\[
I(O, x) = F(x) - F(O).
\]

**Proof:** Firstly, we will show that \( F \) is the strict Lyapunov function of (1). Let \( \phi(t) \) be a trajectory of (1) started in \( D \),

\[
\frac{dF(\phi(t))}{dt} = \nabla F \cdot \frac{d\phi(t)}{dt} = \left( \log \frac{F_1^+}{F_1^-}, \ldots, \log \frac{F_m^+}{F_m^-} \right) A \cdot \sum_{p=1}^m (F_p^+ - F_p^-) v_p
\]

\[
= \left( \log \frac{F_1^+}{F_1^-}, \ldots, \log \frac{F_m^+}{F_m^-} \right) A \begin{pmatrix} F_1^- - F_1^+ & \vdots & F_m^- - F_m^+ \end{pmatrix} \begin{pmatrix} v_1^T \vdots v_m^T \end{pmatrix}
\]

\[
= \sum_{p=1}^m \left( \log \frac{F_p^+}{F_p^-} \right) (F_p^+ - F_p^-) = \sum_{p=1}^m (\log F_p^+ - \log F_p^-)(F_p^+ - F_p^-) \leq 0.
\]
Recall the condition that $\nabla F(x) \neq 0, \forall x \in D \setminus \{O\}$, then the strict inequality holds for all $x \in D \setminus \{O\}$, and $\nabla F(O) = (\log \frac{F_{x_1}}{F_{x_1}}, \ldots, \log \frac{F_{x_n}}{F_{x_n}})A = 0$ implies that $O$ is an equilibrium of (1). By Lemma 8 we conclude that $O$ is an asymptotic stable equilibrium, and $D$ is attracted to $O$.

For any $x \in D$, let $\{r(t) | t \in [0, T]\}$ be any given absolutely continuous path from $O$ to $x$. Since (8) is independent of path, by Theorem 6 we have $I_O^T(r) = F(x) - F(O) + I_O^T(\tilde{r}) \geq F(x) - F(O)$, and therefore $I(O, x) \geq F(x) - F(O)$.

Notice that $D$ is attracted to $O$, denote by $\phi_x(t)$ the trajectory of (1) starting at $x \in D$, then we have $\lim_{t \to \infty} \phi_x(t) = O$. Denote $x_T = \phi_x(T)$, let $r_1(t) = \phi_x(T - t), \forall t \in [0, T]$, this is the reverse path of the deterministic path $\{\phi_x(t) | t \in [0, T]\}$. Apply Theorem 6 again, we get $I_O^T(r_1) = F(x) - F(x_T) + I_O^T(\phi_x) = F(x) - F(x_T)$, where the last equality follows from Lemma 7.

Define $\zeta_T(t) = O + (x_T - O)t/\|x_T - O\|, 0 \leq t \leq \|x_T - O\|$, it is an absolutely continuously path from $O$ to $x_T$. By the continuity of $l$ (recall the proof the Theorem 6), there exist constant $C$ such that

$$F_{\|x_T - O\|}(\zeta_T) \leq C\|x_T - O\|.$$  

Combine the two paths $\zeta_T$ and $r_1$ together, we get an absolutely continuous path from $O$ to $x$, so $I(O, x) \leq C\|x_T - O\| + F(x) - F(x_T)$. Let $T \to \infty$ then we have $I(O, x) \leq F(x) - F(O)$, and finally $I(O, x) = F(x) - F(O)$.  

The following theorem is the direct result of Theorem 3 and Agazzi’s result (Agazzi, 2017).

**Corollary 2** Let $D \subset \mathbb{R}^n_{>0}$ be a bounded domain with smooth boundary, suppose that (8) is independent of path, and denote the potential function of the vector field in (8) by $F$. If there exists an $O \in D^p$ such that $F(x) > F(O), \nabla F(x) \neq 0, \forall x \in D \setminus \{O\}$; and there exists a unique point $y_0 \in \partial D$ such that $F(x) > F(y_0), \forall x \in \partial D$, then for any $x_0 \in D^p$, and any $x_0^V \to x_0, x_0^V \in S^V$, we have

$$\lim_{V \to \infty} \frac{1}{V} \log E_{x_0^V}(\tau(D)) = F(y_0) - F(O),$$

$$\lim_{\delta \to 0} \lim_{V \to \infty} P_{x_0^V}^V(||X^V(\tau(D^V)) - y_0|| < \delta) = 1.$$  

This result generalizes the calculation of the Schlögl model (Qian, 2011), and more importantly, demonstrates that if the line integral is independent of path, then the attractors of the deterministic model and their attraction basins can be described clearly, as well as the large deviations behaviour of the corresponding chemical master equation model.

### 7 The reversibility of the stochastic model and path independence of the line integral

In the last section, we introduced the line integral of $(\mathcal{S}, \mathcal{C}, \mathcal{R})$, and explained the importance of its path independence. In this section, we will prove that
if $X^V$ satisfies the Kolmogorov’s cycle criterion at any $V > 0$, then the line integral of $(S,C,R)$ is independent of path.

The motivation comes from the fact that, $X^\epsilon$, which is the main object in the classic Freidlin-Wentzell theory (Freidlin and Wentzell, 1998), is reversible with respect to its stationary distribution when $b = -\nabla U$. We refer readers who are not familiar with the reversibility of diffusion process to Chapter 3 of (Jiang et al., 2003).

**Lemma 9** Let $D$ be a bounded convex closed domain in $\mathbb{R}_0^m$, then there exists a constant $C$ which depends only on $D$ such that for any $V$ and any $x^V \in D^V \triangleq D \bigcap S^V$, if $y^V \in D$ and $y^V = x^V + v_p/V$ for some $p \leq m$, then we have

$$|\log \frac{q_{x^V,x^V}}{q_{x^V,y^V}} - f_p(x^V)| \leq \frac{C}{V},$$

where $f_p(x) \triangleq \log \frac{\sum_{l=1}^{r_p} k_{pl} \prod_{j=1}^{m} V y^V_j V y^V_{j-1} - 1}{\sum_{l=1}^{r_p} k_{pl} \prod_{j=1}^{m} V x^V_j V x^V_{j-1} - 1}.$

**Proof**: Notice that

$$\log \frac{q_{x^V,x^V}}{q_{x^V,y^V}} = \log \frac{\sum_{l=1}^{r_p} k_{pl} \prod_{j=1}^{m} V y^V_j V y^V_{j-1} - 1}{\sum_{l=1}^{r_p} k_{pl} \prod_{j=1}^{m} V x^V_j V x^V_{j-1} - 1}.$$

The right-hand side of the above equation is slightly different from the function $f_p(x^V)$. We will define a new function to bridge the gap between the right-hand side of the above equation and $f_p(x^V)$.

For any $\tilde{x} = (x_{11}, \ldots, x_{1m}, x_{r_p1}, \ldots, x_{r_pm}, x_{11}', \ldots, x_{1m}', x_{r_p1}', \ldots, x_{r_pm}'),$ where $x_{lj} = (x_{lj})_{k=1}^{r_{plj}} \in \mathbb{R}_{>0}^{r_{plj}}$, $x_{lj}' = (x_{lj}')_{k=1}^{r_{plj}} \in \mathbb{R}_{>0}^{r_{plj}}$. If $v_{plj} = 0$ or $v_{plj}' = 0$, then we remove $x_{lj}$ or $x_{lj}'$ from $\tilde{x}$ respectively. Define $h_{plj} : \mathbb{R}_{>0}^{r_{plj}} \to \mathbb{R}_{>0}$, $h_{plj}(x_{lj}) = \prod_{k=1}^{r_{plj}} x_{lj}$. Then we can define a function of the variable $\tilde{x}$

$$h_p(\tilde{x}) = \log \frac{\sum_{l=1}^{r_p} k_{pl} \prod_{j=1}^{m} h_{plj}(x_{lj})}{\sum_{l=1}^{r_p} k_{pl} \prod_{j=1}^{m} h_{plj}(x_{lj})}.$$

If we set $x_{lj} = \left(\frac{V y^V_1}{V x^V_1}, \ldots, \frac{V y^V_{j-1}}{V x^V_{j-1}}, \frac{V y^V_j - v_{plj}}{V x^V_j}, \ldots, \frac{V y^V_{m} - v_{plj}'}{V x^V_{m}}\right)$, and $x_{lj}' = \left(\frac{V y^V_1'}{V x^V_1'}, \ldots, \frac{V y^V_{j-1}'}{V x^V_{j-1}'}, \frac{V y^V_j - v_{plj}'}{V x^V_j'}, \ldots, \frac{V y^V_{m} - v_{plj}'}{V x^V_{m}'}\right)$, for all $l, j$, then the corresponding $\tilde{x}_1$ satisfies

$$h_p(\tilde{x}_1) = \log \frac{q_{x^V,x^V}}{q_{x^V,y^V}}.$$

If we set $x_{lj} = \left(x_{lj}', \ldots, x_{lj}^{'}\right)$ for all $l, j$, then the corresponding $\tilde{x}_2$ satisfies

$$h_p(\tilde{x}_2) = f_p(x^V).$$
Notice that the euclidean distance between $\tilde{x}_1$ and $\tilde{x}_2$ can be bounded by $C_1/V$ for some constant $C_1$. Therefore by the differential mean value theorem, we can find a constant $C$ which depends only on the domain $D$ such that

$$|\log \frac{q_{V,xV}}{q_{V,yV}} - f_p(x^V)| \leq \frac{C}{V}. \quad (11)$$

**Remark 4** If $y^V = x^V - v_p/V$, the result can be similarly obtained if we notice that $\log \frac{q_{V,yV}}{q_{V,xV}}$ and $f_p(x)$ involve both the forward reaction and the backward reaction.

By Lemma 9, we can prove the following result.

**Corollary 3** Let $D \subset \mathbb{R}^m_{>0}$ be a bounded closed convex domain, and let $\{\phi(t)|t \in [0,T]\} \subset D$ be a piecewise smooth path from $\alpha$ to $\beta$, then there exists a constant $C_{\phi}$ which depends only on $\phi$ such that for any $\delta$ sufficiently small, there exists $V_0$ such that $\forall V \geq V_0$, there exists a path $\alpha^V = \xi_0^V \to \xi_1^V \to \cdots \to \xi_{N^V}^V = \beta^V$ with $\xi_n^V \in D^V$ satisfies

$$\left| \frac{1}{V} \sum_{n=0}^{N^V-1} \log \frac{q_{V_1}^{\xi_{n+1}^V,\xi_n^V}}{q_{V_2}^{\xi_{n}^V,\xi_{n+1}^V}} - S(\phi) \right| \leq C_{\phi}\delta, \quad (12)$$

where $\alpha^V$ denotes the best approximation point of $\alpha$ in $S^V$, and $\beta^V$ denotes the best approximation point of $\beta$ in $S_{\alpha^V}^V \triangleq \{\eta^V \in S^V|\eta^V$ is accessible from $\alpha^V\}$.

**Proof**: We only give the sketch of the proof.

The proof strategy is, $\delta > 0$, we construct a partition $\{t_h\}_{h=0}^H$ of $[0,T]$ such that the length of the largest sub-interval is bounded by $\delta$. Denote $\phi_h^V$ by the best approximation point of $\phi(t_h)$ in $S_{\alpha^V}^V$. We construct the shortest path (By shortest we mean the number of needed reactions is minimal) from $\phi_h^V$ to the next one, and meanwhile guarantee that the whole paths stay in the ball centered at $\phi(t_h)$ with radius $2(\phi(t_{n+1}) - \phi(t_n))$. The whole paths compose a path from $\alpha^V$ to $\beta^V$, and they do exist when $V$ is sufficiently large, since we will have enough chemical species at this time.

From this construction, if $\xi_h^V \to \xi_{n+1}^V$ occurs in the $h(n)$-th path and $\xi_{n+1}^V - \xi_n^V = v_{p(n)}/V$, then $\log \frac{q_{V_{n+1}}^{\xi_{n+1}^V,\xi_n^V}}{q_{V_{n}}^{\xi_{n}^V,\xi_{n+1}^V}}$ can be estimated by $\log \frac{f_{p(n)(\phi(t_{h(n)}))}}{f_{p(n)(\phi(t_{h(n)}))}}$ by using (11), and the error term is $O(\delta)$ when $V$ is sufficiently large.

Then the remaining task is to estimate the number of occurrence of each reaction in each path. Notice that

$$(V\phi^V_{h-1} - V\phi^V_{h-1})A^T \begin{pmatrix} v_{h-1} \\ \vdots \\ v_0 \end{pmatrix} = \phi^V_h - \phi^V_{h-1}.$$
This equation shows that, for any \( p \leq m \), the number of occurrence of \( R_p \) which is needed in the \( h \)-th path approximately equals to the \( p \)-th coefficient of \( (V\phi(t_{h+1}) - V\phi(t_h))A^T \in \mathbb{R}^m \). Furthermore, \( (\phi(t_{h+1}) - \phi(t_h))A^T(t_{h+1} - t_h) \). Combine with the estimates of the reactions occur in each path, we can obtain the desired result.

**Theorem 4** If the transition rate matrix of \( X^V \) satisfies the Kolmogorov’s cycle criterion for any \( V \), then the line integral is independent of path.

**Proof** Suppose that the line integral is not independent of path, then there exist two piecewise smooth paths \( \phi_1, \phi_2 \) from \( \alpha \) to \( \beta \) such that \( S(\phi_1) \neq S(\phi_2) \). Choose a bounded closed convex domain \( D \) such that \( \alpha, \beta \in D \). We can choose proper \( \delta > 0 \) such that the two paths from \( \alpha^V \) to \( \beta^V \) constructed in Corollary 3, satisfy that the loop constructed from this two paths does not satisfies the Kolmogorov’s cycle criterion when \( V \) is sufficiently large. \( \square \)

**8 Mathematical aspects of the stationary distribution**

In this section, we always assume that \( X^V \) satisfies the Kolmogorov’s cycle criterion at any \( V \). By Theorem 4, the line integral (8) is independent of path, and we denote the potential function of the vector field in (8) by \( F \).

Given \( \xi^V \in S^V \), let \( \mu(\xi^V) = 1 \), for any \( \eta^V \in S^V \) accessible from \( \xi^V \) and any path \( \xi^V_0 \to \xi^V_1 \to \cdots \to \xi^V_N \) with \( \xi^V_0 = \xi^V \to \xi^V_N = \eta^V \), define

\[
\mu(\eta^V) = \prod_{n=0}^{N-1} \frac{q_{\xi^V_n, \xi^V_{n+1}}}{q_{\xi^V_{n+1}, \xi^V_n}} \mu(\xi^V).
\]

The above definition is well-defined due to the Kolmogorov’s cycle criterion.

For \( \eta^V \in S^V \) which is not accessible from \( \xi^V \), we define \( \mu(\eta^V) = 0 \).

Obviously, \( \{\mu(\eta^V)|\eta^V \in S^V\} \) are in detailed balance

\[
\mu(\xi^V)q_{\xi^V, \eta^V} = \mu(\eta^V)q_{\eta^V, \xi^V}, \forall \eta^V, \xi^V \in S^V.
\]

So if \( \sum_{\eta^V \in S^V} \mu(\eta^V) \leq \mu^V < \infty \), then \( \{\mu(\eta^V)|\eta^V \in S^V\} \) is the stationary distribution of the chemical master equation model \( X^V \).

**Lemma 10** \( X^V \) has a unique stationary distribution \( \nu^V \) for any \( V > 0 \).

**Proof** Fix \( V \), choose the shortest path from \( \xi^V \) to \( \eta^V \), \( \xi^V = \xi^V_0 \to \xi^V_1 \to \cdots \to \xi^V_N = \eta^V \). It is easy to see that there exists a constant \( C \), which is independent of volume \( V \) and endpoints \( \xi^V \) and \( \eta^V \), such that \( N \leq C\|\xi^V - \eta^V\|V \). Let
Denote the first term by $g(\xi_0, \xi_{n+1}),$ and for it we have 
\[
0 < \min_{l=1} r_{p(n)} \{ \frac{k_{p(n)}}{k_{p(n)_l}} \} \leq g(\xi_0, \xi_{n+1}) \leq \max_{l=1} \{ \frac{k_{p(n)}}{k_{p(n)_l}} \},
\]
so $g(\xi_0, \xi_{n+1})$ is bounded. For the whole paths from $\xi$ to $\eta$ we have 
\[
\prod_{n=0}^{N-1} \frac{q_{\xi_0, \xi_{n+1}}}{q_{\xi_0, \xi_{n+1}}^}\frac{V_{\eta V}^N!}{V_{\xi V}^N!} \times \prod_{n=0}^{N-1} g(\xi_0, \xi_{n+1}) \times V_{\xi V}^N \frac{V_{\eta V}^N - V_{\xi V}^N}{V_{\eta V}^N - V_{\xi V}^N},
\]
so 
\[
\mu(\eta V) = \mu(\xi V) \prod_{n=0}^{N-1} \frac{q_{\xi_0, \xi_{n+1}}}{q_{\xi_0, \xi_{n+1}}^}\frac{V_{\xi V}^N!}{V_{\eta V}^N!} \times V_{\xi V}^N \frac{V_{\eta V}^N - V_{\xi V}^N}{V_{\eta V}^N - V_{\xi V}^N} \times \prod_{n=0}^{N-1} \frac{1}{g(\xi_0, \xi_{n+1}).}
\]
By Stirling’s formula, we know that when $V$ is fixed, $V_{\eta V}^N!$ increases much faster than $V_{\xi V}^N \frac{V_{\eta V}^N - V_{\xi V}^N}{V_{\eta V}^N - V_{\xi V}^N}$ as $V V$ goes to infinity, meanwhile notice that $\sum_{n=1}^{\infty} \frac{1}{V V} \leq \infty,$ so we can conclude that $\sum_{\eta V \in S^V} \mu(\eta V) < \infty.$ Therefore the stationary distribution exists.

Having established the existence of stationary distribution, we next study the asymptotic exponential estimate of the stationary distribution.

**Corollary 4** For any $\xi, \eta \in \mathbb{R}_{\geq 0}^m,$ denote $\xi V, \eta V$ by the best approximation points of $\xi, \eta$ in $S^V,$ then we have 
\[
\lim_{V \to \infty} \frac{1}{V} \log \frac{\nu^V(\xi V)}{\nu^V(\eta V)} = F(\eta) - F(\xi).
\]

*Proof:* Choose the shortest path from $\xi$ to $\eta,$ $\xi \to \xi_1 \to \cdots \to \xi_N = \eta,$ and denote the directed line from $\xi_0$ to $\xi_{n+1}$ by $L_{\xi V}^N.$ The proof is straightforward by considering $S(L_{\eta V}^N)$ and exploiting Lemma 9.

Moreover, by Stirling’s formula, it is easy to see that the stationary distribution $\nu^V$ outside some bounded set will exponentially decay, hence we can finally get the following Freidlin-Wentzell type result.
Corollary 5 If there exists $O \in \mathbb{R}^m_{\geq 0}$ such that $F(x) > F(O), \forall x \in \mathbb{R}^m_{> 0} \setminus \{O\}$, then for any bounded domain $D$ we have

$$\lim_{V \to \infty} \frac{1}{V} \log \nu^V(D^V) = F(O) - \inf_{x \in D} F(x),$$

where $D^V \triangleq D \cap S^V$.

9 Discussion about multistability

In the final section of the paper, we will provide a method for constructing multistable chemical systems. Different from previous results, the transitions between different steady states of these systems can be explicitly described.

If there exists a $p_0$ such that $r_{p_0} > 1, r_{p_0} \neq p_0, \forall l \leq r_{p_0}$, and $v_{lp} = 0, \forall p \neq p_0$, one can verify that $p_0$ satisfies Condition 1 (recall Definition 7). At this time, $(v^1_1, \ldots, v^l_m)$ is of the following form

$$
\begin{pmatrix}
\vdots & \vdots \\
0 & 0 & v^m_p \\
0 & 0 & \vdots \\
\vdots & \vdots 
\end{pmatrix}.
$$

One can verify, by considering the adjugate matrix, that the matrix $A$ is also of the same form.

For other $p \neq p_0$, we set $k^+_{p1}/k_{p1} = k^+_{p2}/k_{p2} = \cdots = k^+_{p_p}/k_{p_p}$, then

$$\sum_{l=1}^{r_p} \frac{k^+_{p_l} x^{p_l}}{k_{p_l}} = \frac{k^+_{p1}}{k_{p1}}.$$

By Theorem 2 and Theorem 4, the line integral is independent of path. For the potential function, we have that

$$\left(\frac{\partial F}{\partial x_1}, \ldots, \frac{\partial F}{\partial x_m}\right) = f A = \left(\log \sum_{l=1}^{r_1} k^+_{1l} x^{p_l}, \ldots, \log \sum_{l=1}^{r_m} k^+_{ml} x^{p_l}\right) A$$

$$= \left(\log \sum_{l=1}^{r_1} k_{1l} x^{p_l}, \ldots, \log \sum_{l=1}^{r_m} k_{ml} x^{p_l}\right) A + (\log x_1, \ldots, \log x_m).$$

We assert that, $\frac{\partial F}{\partial x_j}$ is simply a function of the variable $x_j, \forall j$. In fact, we only need to consider the case when $j = p_0$. For $p_0$, notice that $v_{p_0} = 0, \forall l \neq p_0, \forall l \leq r_{p_0}$, then $\sum_{l=1}^{r_0} \frac{k^-_{p0} x^{p_0}}{k_{p0} x^{p_0}}$ is a function of the variable of $x_{p_0}$. After that, the proof is straightforward because of the special form of matrix $A$.

In order to find the steady points of $F$, we need to solve the equation $\nabla F(x) = 0$, i.e. $\frac{\partial F}{\partial x_j} = 0, \forall j$. However, if $\frac{\partial F}{\partial x_j}$ is only a function of variable $x_j, \forall j$, we only need to solve those equations separately.
Notice that $\frac{\partial F}{\partial p_0}$ may have multiple local minimum points just like the Schögl model (Qian, 2011) because of the particularity of $p_0$. In this case, the potential function will also have multiple local minimum points.

Now we back to Example 2. Theorem 2 and Theorem 4 tells us that the line integral of this chemical reaction model is independent of path, and the potential function satisfies

$$
\left( \frac{\partial F}{\partial x_1}, \frac{\partial F}{\partial x_2} \right) = \begin{pmatrix} \log k_1^{-1} x_1 & \log \frac{k_21 x_2 + k_22 x_2^2}{k_{21} x_1 + k_{22} x_1 x_2^2} \end{pmatrix} \begin{pmatrix} 1 & 1 \\ 0 & 1 \end{pmatrix} = \begin{pmatrix} \log k_1^{-1} x_1 & \log \frac{k_1^{-1} x_2 + k_22 x_2^3}{k_1 k_{21} + k_{22} x_2^2} \end{pmatrix}.
$$

If $c = (c_1, c_2) \in \mathbb{R}_+^2$ satisfies $\nabla F(c) = 0$, then

$$
c_1 = \frac{k_1}{k_1^{-1} k_{22} c_2^3 - k_1 k_{22} c_2^2 + k_1^{-1} k_{21} c_2 - k_1 k_{21} = 0}.
$$

It can be obviously seen that it is possible for the above cubic function to have three distinct positive roots, two local minimum points $c_A, c_C$ and one saddle point $c_B$ (see figure 1). For any $\delta > 0$, we have that
\[
\lim_{V \to \infty} \frac{1}{V} \log E_{\epsilon^V_A} \sigma(\{B(c_C, \delta)\}) = F(c_B) - F(c_A),
\]

where \(\sigma\) denotes the first hitting time, \(\epsilon^V_A\) denotes the best approximation point of \(c_A\) in \(S^V\), and \(B(c_C, \delta)\) denotes the open ball centered at \(c_C\) with radius \(\delta\).

Moreover, the stationary distribution exists and it is multimodal when \(V\) is sufficiently large.

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