Finding stationary solutions to the chemical master equation by gluing state spaces at one or two states recursively

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Abstract

Noise is indispensible to key cellular activities, including gene expression coordination and probabilistic differentiation. Stochastic models, such as the chemical master equation (CME), are essential to model noise in the levels of cellular components. In the CME framework, each state is associated with the molecular counts of all component species, and specifies the probability for the system to have that set of molecular counts. Analytic solutions to the CME are rarely known but can bring exciting benefits. For instance, simulations of biochemical reaction networks that are multiscale in time can be sped up tremendously by incorporating analytic solutions of the slow time-scale dynamics. Analytic solutions also enable the design of stationary distributions with properties such as the modality of the distribution, the mean expression level, and the level of noise. One way to derive the analytic steady state response of a biochemical reaction network was recently proposed by (Mélykúti et al. 2014). The paper recursively glues simple state spaces together, for which we have analytic solutions, at one or two states.

In this work, we explore the benefits and limitations of the gluing technique proposed by Mélykúti et al., and introduce recursive algorithms that use the technique to solve for the analytic steady state response of stochastic biochemical reaction networks. We give formal characterizations of the set of reaction networks whose state spaces can be obtained by carrying out single-point gluing of paths, cycles or both sequentially. We find that the dimension of the state space of a reaction network equals the maximum number of linearly independent reactions in the system. We then characterize the complete set of stochastic biochemical reaction networks that have elementary reactions and two-dimensional state spaces. As an example, we propose a recursive algorithm that uses the gluing technique to solve for the steady state response of a mass-conserving system with two connected monomolecular reversible reactions. Even though the gluing technique can only construct finite state spaces, we find that, by taking the size of a finite state space to infinity, the steady state response can converge to the analytic solution on the resulting infinite state space. Finally, we illustrate the aforementioned ideas with the example of two interconnected transcriptional components, which was first studied by (Ghaemi and Del Vecchio 2012).

1 Introduction

There are two approaches to modeling the time evolution of a spatially homogeneous mixture of molecular species that interact through a set of known chemical reactions [1]. The deterministic formulation specifies the time-rates-of-change of the molecular concentrations of component species with a set of coupled ordinary differential equations and assumes continuous variations in the molecular concentrations [2]. The stochastic formulation considers the time evolution as

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a Markovian random walk in the state space of molecular populations, which is governed by a set of differential-difference equations [2]. Although the deterministic approach is adequate in many cases, its assumption that a chemical reaction system evolves deterministically and continuously is invalid because the process is unpredictable in nature and molecular populations are integers [3]. There are a number of biochemical processes for which stochastic models must be used [4]. For instance, many cellular constituents are present in small numbers and stochastic fluctuations in their copy numbers are significant [5, 6]. In addition, stochastic fluctuations in the levels of cellular components are essential to some biological processes, including a variety of probabilistic differentiation strategies [7, 8].

The chemical master equation (CME) is a stochastic model that describes how the probability distribution of the molecular population of a chemically reacting system varies as a function of time and does not require the assumption of large molecular counts [3, 9]. The CME depicts a continuous-time Markov jump process whose state space comprises possible combinations of molecular counts of each component species [10]. However, finding transient and stationary solutions to the CME for general reaction network topologies is still an open question mainly because the number of states increases exponentially with the number of component species [12, 13]. Most commonly, we use Monte Carlo algorithms such as stochastic simulation algorithm (SSA) to approximate the solution to the CME [1, 2]. However, the computational cost of SSA can become enormous when there are numerous reactions present in the system, and the method does not guarantee error bounds on the approximate solution [12]. Analytic solutions to the CME are generally unknown but can bring exciting benefits. For example, simulations of biochemical reaction networks that are multiscale in time can be sped up tremendously by incorporating analytic solutions of the slow time-scale dynamics [11]. Exact stationary solutions also enable accurate analysis of the effect of parameter values on the stationary behavior of a reaction system [11].

The analytic solutions of the stationary distributions of the CME are difficult to find, except for the simplest biochemical reaction networks with particular initial conditions [13]. Examples of biochemical systems with known stationary distributions include closed (i.e. mass-conserving, [14]) linear reaction systems with multinomial initial distributions ([15, 16]) and open linear reaction systems with Poisson initial distributions ([17]).

Mélykúti et al. ([11, 19]) recently proposed a technique to determine stationary distributions of stochastic biochemical reaction networks whose state spaces can be obtained by gluing two finite, irreducible (i.e. any state can be reached from any other state [25]) state spaces at one or two vertices. Given two continuous-time Markov jump processes with finite, irreducible state spaces and known stationary distributions, if exactly one state from each state space is the same, then the resulting state space obtained by gluing the two state spaces at the identical state naturally gives a continuous-time Markov jump process. Reference [11] finds that the stationary distribution on the combined state space is a constant multiple of the equilibria of the single Markov jump processes. When gluing at two vertices, the stationary distribution on the combined state space is hard to obtain in general, but there is a special case when the resulting stationary distribution is a constant multiple of the equilibria of the single Markov jump processes [19].

In principle, the stationary distribution of a continuous-time Markov jump process on a finite, irreducible state space is the left null vector of the transition rate matrix [10]. However, the gluing technique provides an alternative method that solves stationary distributions analytically by constructing more complex state spaces from simple ones [11]. In systems and synthetic biology, it is a central yet generally unsolved problem to predict the dynamic behavior of a biological network from that of its constituent modules [20, 21, 22, 23]. The development of the gluing technique can potentially contribute to solving this problem [19]. In addition, the gluing technique makes it possible to design recursive algorithms that computes the stationary distribution of a continuous-time Markov jump process from the stationary distributions of small components of the state space, which is potentially quicker than pure algebraic manipulations that find the left null vector of the transition rate matrix. To the best of our knowledge, gluing state spaces of Markov processes together is an unusual idea that has been rarely studied

in probability theory.

In this paper, we explore the benefits and limitations of the gluing technique proposed by Mélykúti et al., and introduce recursive algorithms that use the technique to solve for the analytic stationary solution of stochastic biochemical reaction networks. Specifically, we give formal characterizations of the set of reaction networks whose state spaces can be obtained by carrying out single-point gluing of paths, cycles or both sequentially. We find that the dimension of the state space of a reaction network equals the maximum number of linearly independent reactions in the system. We then characterize the complete set of stochastic biochemical reaction networks that have elementary reactions and two-dimensional state spaces. As an example, we propose a recursive algorithm that uses the gluing technique to solve for the stationary solution of a mass-conserving system with two connected monomolecular reversible reactions. Even though the gluing technique can only construct finite state spaces, we find that, by taking the size of a finite state space to infinity, the steady state response can converge to the analytic solution on the resulting infinite state space. Finally, we illustrate the aforementioned ideas with the example of two interconnected transcriptional components, which was first studied by (Ghaemi and Del Vecchio 2012).

The remainder of this paper is organized as follows. In Section 2, we first introduce the CME, the relationship between continuous-time Markov jump processes and graph theory, the gluing techniques proposed in references [11, 19], and relevant notations and definitions in graph theory. Then Section 3 presents three propositions and proofs that characterize graphs which can be obtained by gluing paths, cycles, or both, at one vertex sequentially. In Section 4, we first classify reversible, elementary reactions whose state spaces are in 2-dimensional space and demonstrate the gluing technique with simple chemical reaction systems. We then propose a recursive algorithm that uses the gluing technique to solve the stationary distribution of two interconnected transcriptional components and provide a method that truncates the infinite state space with a certificate of accuracy for an approximate solution. Finally, Section 5 summarizes the main contributions of the paper and points to future work.

2 Background

2.1 The chemical master equation

The CME describes the time evolution of a chemically reacting system as a Markovian random walk in the space of the molecular populations, where each state gives the current number of molecules of every component species [2, 9]. The CME is essentially a set of differential-difference equations which govern how the probability distribution of the molecular population evolves as a function of time in the system [3, 9]. There is one ordinary differential equation per state of the system, which specifies the rate of change of the probability of the state at each instant of time to be equal to the difference between a sum comprising inflow states and a sum comprising outflow states [13].

Consider a system with n chemical species $\mathcal{S}_1, \cdots, \mathcal{S}_n$, which undergo m possible chemical reactions $\mathcal{R}_1, \cdots, \mathcal{R}_m$ in a well-stirred solution of fixed volume and temperature. Let $\Pr(X, t \mid X_0, t_0)$ be the probability of the Markov jump process being in state $X \in \mathbb{Z}_{\geq 0}^n$ at time t given that it was in state $X_0 \in \mathbb{Z}_{\geq 0}^n$ at some time $t_0 \leq t$. The state X gives the number of molecules of each species. For each reaction $\mathcal{R}_j$, denote the propensity function by $a_j(X)$, and the change-of-state vector by ν_j. Then the CME ([9]) is given by

$$\frac{\partial}{\partial t} \Pr(X, t \mid X_0, t_0) = \sum_{j=1}^m a_j(X - \nu_j) \Pr(X - \nu_j, t \mid X_0, t_0) - \sum_{j=1}^m a_j(X) \Pr(X, t \mid X_0, t_0).$$
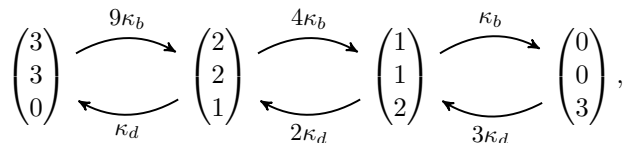
2.2 Relationship between continuous-time Markov jump processes and graph theory

We consider reversible chemical reactions in the rest of the paper. The state space of the continuous-time Markov jump process described by the CME naturally gives an undirected graph: vertices are states, and an edge exists between a pair of vertices if and only if there exists a reversible reaction that allows transition between the two corresponding states.

For instance, a closed system with reaction

$$\mathcal{X}_1 + \mathcal{X}_2 \underset{\kappa_{\mathrm{d}}}{\overset{\kappa_{\mathrm{b}}}{\rightleftharpoons}} \mathcal{X}_3, \tag{1}$$

obeys the conservation relation $X_1 + X_2 + 2X_3 = C$, where C is a constant that is determined by the number of molecules of each species at the initial time [14]. If the initial condition is $(X_1, X_2, X_3)^{\mathrm{T}} = (1, 1, 2)^{\mathrm{T}}$ at time t_0, then the state space is

$$\begin{pmatrix} 3 \\ 3 \\ 0 \end{pmatrix} \underset{\kappa_d}{\overset{9\kappa_b}{\rightleftharpoons}} \begin{pmatrix} 2 \\ 2 \\ 1 \end{pmatrix} \underset{2\kappa_d}{\overset{4\kappa_b}{\rightleftharpoons}} \begin{pmatrix} 1 \\ 1 \\ 2 \end{pmatrix} \underset{3\kappa_d}{\overset{\kappa_b}{\rightleftharpoons}} \begin{pmatrix} 0 \\ 0 \\ 3 \end{pmatrix},$$

and the corresponding graph is a path of length 3 (Figure 1).
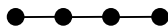
Figure 1: A path of length 3.

If the initial condition is $(X_1, X_2, X_3)^{\mathrm{T}} = (4, 2, 0)^{\mathrm{T}}$, then the state space is

$$\begin{pmatrix} 4 \\ 2 \\ 0 \end{pmatrix} \underset{\kappa_d}{\overset{8\kappa_b}{\rightleftharpoons}} \begin{pmatrix} 3 \\ 1 \\ 1 \end{pmatrix} \underset{2\kappa_d}{\overset{3\kappa_b}{\rightleftharpoons}} \begin{pmatrix} 2 \\ 0 \\ 2 \end{pmatrix},$$
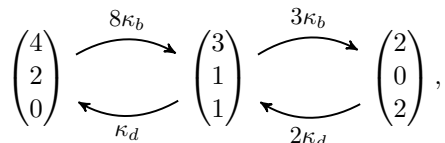
and the corresponding graph is a path of length 2.

2.3 The stationary distribution of a continuous-time Markov jump process glued together from two state spaces at one or two vertices

Reference [11] introduces a technique for solving the stationary distribution of a continuous-time Markov jump process by gluing the state spaces of two finite, irreducible, continuous-time Markov jump processes at exactly one vertex. Reference [19] studies the technique in the case of gluing two such Markov processes at two vertices simultaneously. In both papers, vertices are glued together if and only if they correspond to the same state. No existing literature has studied gluing at more than 2 vertices.

Reference [11] glues the state spaces of two finite, irreducible, continuous-time Markov jump processes at one vertex, while keeping all the other vertices distinct. Without introducing any new jumps or losing any jumps in either Markov process, a new Markov process is naturally identified on the combined state space. Consider two finite, irreducible, continuous-time Markov jump processes A and B. Suppose that process A has known equilibrium ξ^A on states indexed by $\{1, 2, \cdots, r\}$, and process B has known equilibrium distribution ξ^B on states indexed by $\{1, 2, \cdots, s\}$. Without loss of generality, we glue the state spaces of processes A and B at state r of process A and state 1 of process B. Keeping the indices of process A the same and increasing the indices of process B by $r-1$, reference [11] derives the equilibrium distribution of the new Markov process

$$\xi_i = \begin{cases} C\xi_i^A \xi_1^B, & \text{if } i \in \{1, 2, \cdots, r-1\}, \\ C\xi_r^A \xi_1^B, & \text{if } i = r, \\ C\xi_r^A \xi_{i-r+1}^B, & \text{if } i \in \{r+1, r+2, \cdots, r+s-1\}, \end{cases} \tag{2}$$

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where $C = (\xi_r^A + \xi_1^B - \xi_r^A \xi_1^B)^{-1}$ is a normalizing constant.

Reference [19] studies the gluing technique in the case of gluing two finite, irreducible, continuous-time Markov jump processes at two vertices simultaneously. With the same setting as gluing at one vertex, we now glue state $r-1$ of process A and state 1 of process B together, and state r of process A and state 2 of process B together. All the other states in processes A and B are distinct. The labeling of the states does not affect the result, and the glued vertices are not necessarily consecutive in label. In general, deriving the equilibrium distribution of the new Markov process is complicated. However, keeping the indices of process A the same and increasing the indices of process B by $r-2$, reference [19] proves that if the proportionality condition

$$\frac{\xi_{r-1}^A}{\xi_r^A} = \frac{\xi_1^B}{\xi_2^B} \tag{3}$$

is satisfied, then the stationary distribution on the combined state space is

$$\xi_i = \begin{cases} C\xi_i^A \xi_1^B, & \text{if } i \in \{1, 2, \cdots, r-2\}, \\ C\xi_{r-1}^A \xi_1^B, & \text{if } i = r-1, \\ C\xi_r^A \xi_1^B = C\xi_{r-1}^A \xi_2^B, & \text{if } i = r, \\ C\xi_{r-1}^A \xi_{i-r+2}^B, & \text{if } i \in \{r+1, r+2, \cdots, r+s-2\}, \end{cases} \tag{4}$$

where $C = \left[\xi_{r-1}^A + \xi_1^B - \xi_{r-1}^A(\xi_1^B + \xi_2^B)\right]^{-1} = \left[\xi_{r-1}^A + \xi_1^B - \xi_1^B(\xi_{r-1}^A + \xi_r^A)\right]^{-1}$ is a normalizing constant.

2.4 Relevant notations and definitions in graph theory

We introduce some notational conventions and definitions in graph theory based on [26], which will be useful in Section 3. We write $[n]$ to represent the set $\{1, 2, \cdots, n\}$. Let $X^{(k)} = \{A \subseteq X : |A| = k\}$ be the set of k-element subsets of X. For vertices $u \neq v$, let $uv = \{u, v\} = vu$. In other words, we consider undirected graphs. The *endvertices* of an edge uv are u and v.

Definition 1. A *graph* is an ordered pair (V, E) where $V \neq \emptyset$ is a finite set and $E \subseteq V^{(2)}$.

Definition 2. In a graph $G = (V, E)$, the *vertex set* is $V(G)$ and the *edge set* is $E(G)$. Vertices u and v are *adjacent* if $uv \in E(G)$. A vertex v and an edge e are *incident* if v is an endvertex of e. The *degree* of v, $d_G(v)$, is the number of distinct vertices that are adjacent to v. Vertex v is *isolated* if $d_G(v) = 0$.

Definition 3. A graph H is a *subgraph* of a graph G, written $H \subseteq G$, if $V(H) \subseteq V(G)$ and $E(H) \subseteq E(G)$.

Definition 4. A *path of length n*, called an *n-path*, is a graph with vertex set $\{v_i : i \in [n+1]\}$ and edge set $\{v_i v_{i+1} : i \in [n]\}$. By convention, a 0-path is a vertex.

Definition 5. A *cycle of length n*, called an *n-cycle*, is a graph with vertex set $\{v_i : i \in [n]\}$ and edge set $\{v_i v_{i+1} : i \in [n]\}$ with $v_n v_{n+1} = v_n v_1$.

Definition 6. A *walk of length n* in a graph G is a sequence $v_1, v_2, \cdots, v_{n+1}$ of (not necessarily distinct) vertices such that $v_i v_{i+1} \in E(G)$ for each $i \in [n]$. The walk is *closed* if $v_{n+1} = v_1$.

3 Characterizing graphs that can be obtained by gluing paths, cycles, or both, at one vertex sequentially

In this section, we use graph theory to characterize the set of state spaces that can be obtained by gluing paths, cycles, or both, at one vertex sequentially. There are two main reasons why the results are interesting. First, the stationary distribution of a continuous-time Markov jump process on a state space that is obtained by gluing two finite, irreducible state spaces at one state can be easily determined by taking a ratio of the equilibria of the individual Markov

processes. Second, analytic solutions are known for the stationary distributions on path-like and circular state spaces [10, 27, 28].

We find that (i) graphs obtained by gluing paths at one vertex sequentially are trees, (ii) graphs obtained by gluing cycles at one vertex sequentially are "trees of cycles", and (iii) graphs obtained by gluing paths and cycles at one vertex sequentially are "trees of trees and cycles". We give formal propositions and proofs in this section.

We only consider graphs that are undirected and are in 2-dimensional space. A graph is *connected* if any two distinct vertices are joined by a path. Consider a connected graph $G = (V, E)$ and a subgraph $H \subseteq G$. For our purposes, we define the graph $G - H$ as the graph obtained by first deleting edges of H from G and then deleting isolated vertices of the remaining graph $(V, E \setminus E(H))$. Figure 2 gives an example of deleting a subgraph from a graph. Similarly, for a connected graph $G = (V, E)$ on three or more vertices and any of its edges $e = uv$, the graph $G - e$ is obtained by first deleting edge e from G and then removing u (or v) if it becomes an isolated vertex in the remaining graph $(V, E \setminus \{e\})$.
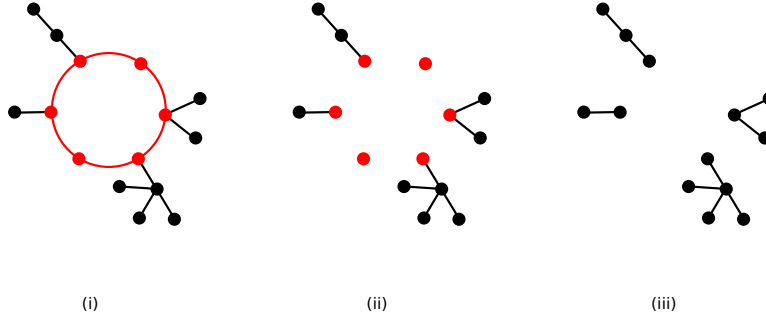

(i)   (ii)   (iii)

Figure 2: Subfigure (i) is an example of a graph G with a subgraph H (in red) being a cycle. To get $G - H$, first delete the edges of H from G (Subfigure (ii)), and then remove the isolated vertices from the remaining graph (Subfigure (iii)).

Definition 7 ([26]). A *tree* is an acyclic connected graph.

Proposition 1. *A graph can be obtained by gluing paths at one vertex sequentially if and only if the graph is a tree.*

Remark. Figure 3 gives an example of a tree and one way to construct the graph by gluing paths at one vertex sequentially.

(ii.a)   (ii.b)   (ii.c)   (ii.d)

(i)

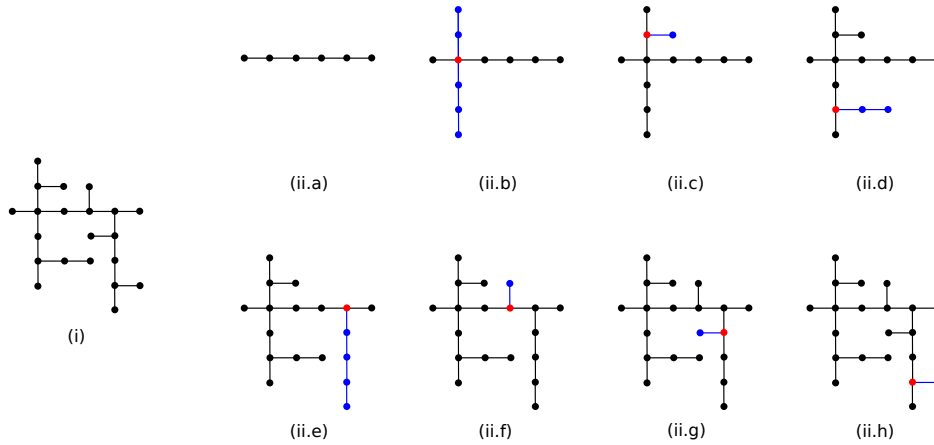(ii.e)   (ii.f)   (ii.g)   (ii.h)

Figure 3: (i) An example of a tree. (ii) One way to construct the tree by gluing paths at one vertex sequentially. Updated graphs are in black. New components are in blue. Red vertices are the vertices at which graphs are glued together.

Proof. We first show that a graph that can be obtained by gluing paths at one vertex sequentially is a tree. It is apparent that any graph that is obtained by gluing paths at one vertex sequentially is connected. This statement follows from a simple inductive proof on the number of paths that we glue together. Hence, we only need to prove that any graph that is obtained by gluing paths at one vertex sequentially is acyclic. We assume by contradiction that gluing paths $P_1, P_2, \cdots, P_k$ at one vertex sequentially gives a graph G that contains a cycle, say C. Then $\{P_1, P_2, \cdots, P_k\} \cap C$ is a set of subpaths and vertices, and cycle C can be obtained by gluing these subpaths at one pair of endvertices (of different subpaths) sequentially. However, this contradicts the fact that gluing two paths at their common endvertex always gives a path. Figure 4 is an example that illustrates the argument.
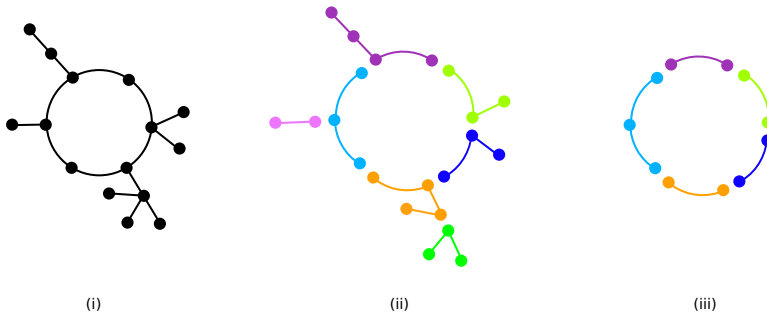

(i) (ii) (iii)

Figure 4: Subfigure (i) is an example of a graph that contains a cycle. If Subfigure (i) could be obtained by gluing paths at one vertex sequentially as shown in Subfigure (ii), then the cycle could be obtained by gluing subpaths at one pair of endvertices (of different subpaths) sequentially. However, this contradicts the fact that gluing two paths at their common endvertex always gives a path.

Conversely, we now show that any tree can be obtained by gluing paths at one vertex sequentially. A tree with one vertex is simply a vertex, and it can be obtained by gluing two 0-paths together. For the inductive step, let n be any positive integer, and suppose that the claim holds for all trees on n or fewer vertices. Consider any tree T with $n + 1 \geq 2$ vertices. Recall that any tree with at least two vertices has at least two leaves [26]. Let vertex v be a *leaf* of T (i.e. $d_T(v) = 1$), and let e be the only edge that is incident on v. By hypothesis, T is connected, so any two distinct vertices $x, y \in V(T - e) \subset V(T)$ are connected by a path in T, say P. The vertex v is not an endvertex of P and $d_T(v) = 1$, so vertex v and edge e cannot be on P. Hence, P is a path in $T - e$. Since $T - e \subset T$ and T is acyclic, it follows that $T - e$ is also acyclic. The graph $T - e$ is also connected, so $T - e$ is a tree. But $|T - e| = n$, so by the induction hypothesis $T - e$ can be obtained by gluing paths at one vertex sequentially. But e is a 1-path, and T can be obtained by gluing e and $T - e$ at the only vertex that is adjacent to v. Hence, T can be obtained by gluing paths at one vertex sequentially. By induction, any tree can be obtained by gluing paths at one vertex sequentially. $\square$

Proposition 2. *A graph can be obtained by gluing cycles at one vertex sequentially if and only if the graph satisfies all of the following conditions:*

   (i) the graph is connected,

   (ii) every vertex has an even degree, and

   (iii) any pair of cycles has at most one common vertex.

Remark. We call such a graph a "tree of cycles". Figure 5 gives an example of a tree of cycles and one way to construct the graph by gluing cycles at one vertex sequentially.

Proof. We first show that a graph that can be obtained by gluing cycles at one vertex sequentially satisfies conditions (i)–(iii) by induction on the number of cycles that we use to construct such a graph.
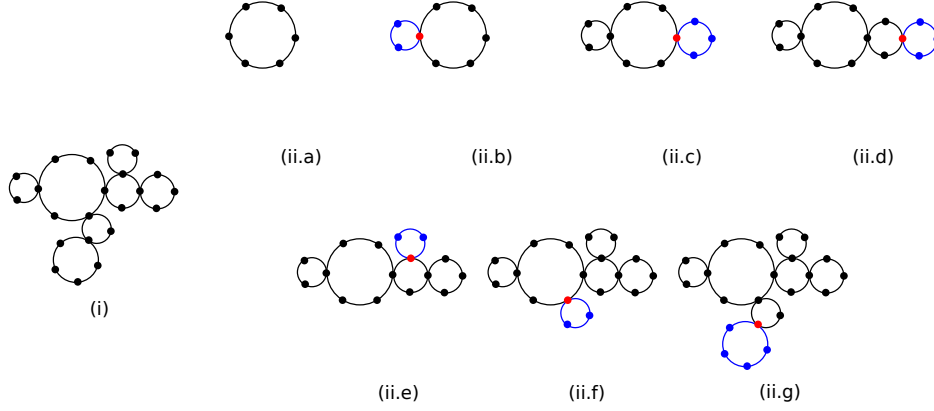
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Figure 5: (i) An example of a tree of cycles. (ii) One way to construct the graph by gluing cycles at one vertex sequentially.

For the base case, consider any cycle. A cycle is connected and every vertex has degree 2. Condition (iii) is trivially true.

For the inductive step, let k be any positive integer and we assume that gluing k or fewer cycles at one vertex sequentially gives a graph that satisfies conditions (i)–(iii). Let G be a graph that is obtained by gluing k cycles at one vertex sequentially. Let C be an arbitrary cycle. Pick any vertex of G and C, say u, and glue G and C at vertex u. We name the new graph $\tilde{G}$. We check that conditions (i)–(iii) hold for $\tilde{G}$.

(i) Since C and G are connected graphs, it follows that $\tilde{G}$ is connected.

(ii) We have $d_{\tilde{G}}(u) = d_G(u) + d_C(u) = d_G(u) + 2$. For all $v \in V(G) \setminus \{u\}$, $d_{\tilde{G}}(u) = d_G(u)$. But every vertex in G has an even degree (in G) and, for all $w \in V(C) \setminus \{u\}$, we have $d_{\tilde{G}}(w) = d_C(w) = 2$. Thus every vertex in $\tilde{G}$ has an even degree (in $\tilde{G}$).

(iii) Consider any two distinct cycles C_1 and C_2 in $\tilde{G}$. If $C_1 = C$ or $C_2 = C$, then C_1 and C_2 have at most one common vertex by construction of $\tilde{G}$. Otherwise, we have $C_1, C_2 \subset G$, and $|V(C_1) \cap V(C_2)| \leq 1$ by hypothesis. Hence, any pair of distinct cycles in $\tilde{G}$ has at most one common vertex.

By induction, any graph that can be obtained by gluing cycles at one vertex sequentially satisfies conditions (i)–(iii).

We now prove the converse by induction on the number of cycles in a graph that satisfies conditions (i)–(iii).

For the base case, we consider a graph H that contains exactly one cycle $\tilde{C}$ and satisfies conditions (i)–(iii). We assume by contradiction that H is not a cycle. Then $H - \tilde{C}$ is a *forest* (i.e. an acyclic graph). Every vertex of $H - \tilde{C}$ has degree of the same parity as it does in H. Every *component* (i.e. maximal connected subgraph) of $H - \tilde{C}$ is a tree on at least two vertices, so every component has two leaves. But every leaf has degree 1 by definition. This contradicts our assumption that every vertex in H has an even degree.

For the inductive step, let k be any positive integer, and suppose that any graph that has exactly k or fewer cycles and satisfies conditions (i)–(iii) can be obtained by gluing cycles at one vertex sequentially. Let $\hat{H}$ be a graph that satisfies conditions (i)–(iii) and contains exactly $k + 1$ cycles. Pick any cycle $\hat{C} \subseteq \hat{H}$. Without loss of generality, suppose that $\hat{H} - \hat{C}$ consists of components $O_1, O_2, \cdots, O_r$ for some positive integer r. We check that each component O_i $(1 \leq i \leq r)$ satisfies conditions (i)–(iii).

(i) Every component O_i is connected by definition.

(ii) For every $x \in V(O_i) \setminus V(\hat{C})$, $d_{O_i}(x) = d_{\hat{H}}(x)$. For every $y \in V(O_i) \cap V(\hat{C})$, $d_{O_i}(y) = d_{\hat{H}}(y) - 2$. But every vertex in $\hat{H}$ has an even degree. Thus every vertex in O_i has an even degree (in O_i).

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(iii) Since $\hat{H}$ satisfies condition (iii) and $O_i \subseteq \hat{H}$, condition (iii) also holds for O_i.

But $O_i \subseteq \hat{H}$ and it has fewer cycles than $\hat{H}$. By hypothesis, O_i can be obtained by gluing cycles at one vertex sequentially.

Since $\hat{H}$ is connected, every component of $\hat{H} - \hat{C}$ shares at least one common vertex with cycle $\hat{C}$. We assume by contradiction that a component O_j $(1 \leq j \leq r)$ has at least two vertices that are also on $\hat{C}$. Suppose that $\hat{C} = z_1 z_2 \cdots z_s$ for some integer $s \geq 3$. Pick $1 \leq p < q \leq s$ such that $z_p, z_q \in O_j$ and $q - p \in \mathbb{Z}_{>0}$ is a minimal number. Since O_j is connected, there exists a z_p–z_q path (i.e. a path with endvertices z_p and z_q) in O_j, say P. Cycle $\hat{C}$ contains two z_p–z_q paths. If the two paths are of different lengths, then let $\hat{P}$ be the shorter one and we have $V(\hat{P}) \cap V(O_j) = \{z_p, z_q\}$. If the two z_p–z_q paths are of the same length, then $V(\hat{C}) \cap V(O_j) = \{z_p, z_q\}$ and pick either of the z_p–z_q paths as $\hat{P}$. In either case, $V(P) \cap V(\hat{P}) = \{z_p, z_q\}$. By our definition of removing subgraphs from a graph, component O_j has at least 3 vertices. Since edge $z_p z_q \notin O_j$, there must exist some $z \in V(O_j) \setminus \{z_p, z_q\}$ such that $z \in V(P)$. Thus P has length at least 2. But $\hat{P}$ has length at least 1, and $E(P) \cap E(\hat{P}) = \emptyset$. Therefore, $P \cup \hat{P}$ has length at least 3. Hence, $P \cup \hat{P}$ is a cycle in $\hat{H}$ that is different from $\hat{C}$ and $\{z_p, z_q\} \subseteq V(P \cup \hat{P}) \cap V(\hat{C})$. This constradicts our assumption that any pair of distinct cycles in $\hat{H}$ has at most one common vertex.

Hence, every component O_i $(1 \leq i \leq r)$ has exactly one common vertex with cycle $\hat{C}$. But every component O_i can be obtained by gluing cycles at one vertex sequentially. Hence, $\hat{H}$ can be obtained by gluing cycles at one vertex sequentially. By induction, any graph that satisfies conditions (i)–(iii) can be obtained by gluing cycles at one vertex sequentially. $\square$

Proposition 3. *A graph can be obtained by gluing paths and cycles at one vertex sequentially if and only if the graph satisfies all of the following conditions:*

(i) the graph is connected, and

(ii) every pair of cycles shares at most one common vertex.

Remark. We call such a graph a "tree of trees and cycles". Figure 6 gives an example of a tree of trees and cycles.
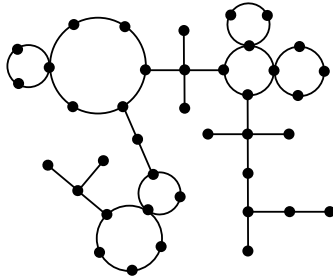

Figure 6: An example of a tree of trees and cycles.

Proof. We first show that a graph that can be obtained by gluing paths and cycles at one vertex sequentially satisfies conditions (i) and (ii) by induction on the number of paths and cycles that we use to construct such a graph.

We have two base cases: a path and a cycle. In both cases, the graph is connected and condition (ii) holds trivially.

For the inductive step, let m and n be any nonnegative integers such that $m + n \geq 1$, and suppose that any graph that is obtained by gluing m or fewer paths and n or fewer cycles satisfies conditions (i) and (ii). Let G be any graph that is constructed by gluing m paths and n cycles at one vertex sequentially. Let P be any path. Glue P and G at any vertex, say u. We name the new graph $\tilde{G}$. Since P and G are connected graphs, it follows that $\tilde{G}$ is also connected. Since $|V(P) \cap V(G)| = 1$ and P is a path, no cycle in $\tilde{G}$ contains any edge on P.

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Thus every cycle in $\tilde{G}$ is a subgraph of G. But any two distinct cycles in G have at most one common vertex (in G). Hence, condition (ii) holds in $\tilde{G}$. Now let C be any cycle. Glue C and G at any vertex, say v. Let $\hat{G}$ be the new graph. Since C and G are connected graphs, it follows that $\hat{G}$ is also connected. Let C_1 and C_2 be any two distinct cycles in $\hat{G}$. If $C_1 = C$ or $C_2 = C$, then $V(C_1) \cap V(C_2) \leq 1$ by construction of $\hat{G}$. Otherwise, since $V(C) \cap V(G) = 1$, we have $E(C) \cap E(G) = \emptyset$, so $\{C_1, C_2\} \subseteq G$. Hence, $V(C_1) \cap V(C_2) \leq 1$ by the induction hypothesis.

By induction, any graph that is obtained by gluing paths and cycles at one vertex sequentially satisfies conditions (i) and (ii).

We now prove the converse by induction on the number of cycles in a graph.

A connected graph that contains no cycles is a tree and satisfies condition (ii) trivially. We have proved in Proposition 1 that any tree can be obtained by gluing paths at one vertex sequentially.

For the inductive step, let k be any nonnegative integer, and suppose that any graph that contains exactly k or fewer cycles and satisfies conditions (i) and (ii) can be obtained by gluing paths and cycles at one vertex sequentially. Let H be a graph that satisfies conditions (i) and (ii) and contains exactly $k+1$ cycles. Let C be any cycle in H. Without loss of generality, suppose that $H - C$ consists of components $O_1, O_2, \cdots, O_r$ for some positive integer r. Components are connected by definition. Every component O_i $(1 \leq i \leq r)$ is a subgraph of $H - C$, so O_i has fewer cycles than H and condition (ii) holds for O_i $(1 \leq i \leq r)$. By hypothesis, O_i can be obtained by gluing paths and cycles at one vertex sequentially. Following a similar argument as in the proof for Proposition 2, we can prove that every component O_i has exactly one common vertex with cycle C. Hence, H can be obtained by gluing paths and cycles at one vertex sequentially. By induction, any graph that satisfies conditions (i) and (ii) can be obtained by gluing paths and cycles at one vertex sequentially. $\square$

4 Demonstration of the gluing technique

4.1 Reversible, elementary reactions with 2-dimensional state spaces

We define an *elementary reaction* in Definition 8 for the purposes of our study. We shall focus on reversible, elementary reactions in closed systems in Section 4. We find that the topology of the undirected graph that corresponds to the state space of such a reaction system is determined by two factors: (i) the number of reversible reactions present, and (ii) the initial molecular population.

Definition 8. Let $\mathcal{S}_1, \mathcal{S}_2, \cdots, \mathcal{S}_n$ be n chemical substances. A reaction of the form

$$\alpha_1 \mathcal{S}_1 + \cdots + \alpha_n \mathcal{S}_n \longrightarrow \beta_1 \mathcal{S}_1 + \cdots + \beta_n \mathcal{S}_n, \tag{5}$$
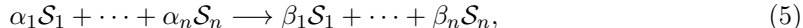
where α_i and β_i $(i \in \{1, \cdots, n\})$ are nonnegative integers, is an *elementary reaction* if all of the following conditions hold

(i) $\sum_i \alpha_i \leq 2$,

(ii) $\sum_i \beta_i \leq 2$, and

(iii) at most one of the sums equals to 2.

Remark. We do not consider reactions whose reactants and products are both second-order. For instance, $\mathcal{X}_1 + \mathcal{X}_2 \rightleftharpoons \mathcal{X}_3 + \mathcal{X}_4$ is not an elementary reaction for our purpose as it should be regarded as an approximation to the reactions $\mathcal{X}_1 + \mathcal{X}_2 \rightleftharpoons \mathrm{C} \rightleftharpoons \mathcal{X}_3 + \mathcal{X}_4$ where $\mathcal{C}$ is a complex species.

4.1.1 One reversible reaction

There are three possible closed systems with exactly one reversible, elementary reaction, which we list in Appendix A. The state spaces of these reactions are simply paths, the lengths of which are determined by the initial molecular population. We first give the known results about the stationary distributions on finite, path-like state spaces, and then discuss the advantages of our recursive algorithm using the gluing technique in this case.

Reference [27] gives the stationary distribution of a continuous-time Markov jump process whose state space is a finite path. Let N be a positive integer and consider a state space indexed by $\{0, 1, \cdots, N\}$ with transition rates p_i from i to $i+1$ ($i \in \{0, 1, \cdots, N-1\}$) and q_i from i to $i-1$ ($i \in \{1, 2, \cdots, N\}$). The stationary distribution $(\pi_0, \pi_1, \cdots, \pi_N)^{\mathrm{T}}$ is given by the relation $\pi_i = \pi_0 \prod_{k=0}^{i-1} \frac{p_k}{q_{k+1}}$ and the normalization equation $\sum_{i=0}^{N} \pi_i = 1$.

However, the gluing technique gives insight into the structure of the stationary distribution, in addition to providing exact solutions. For any positive integer n, an n-path can be obtained by gluing paths of lengths 1, 2, 4, 8, $\cdots$, $2^{\lfloor \log_2 n \rfloor - 1}$ at one vertex sequentially and then gluing a path of length $n - 2^{\lfloor \log_2 n \rfloor}$. A path of length $n - 2^{\lfloor \log_2 n \rfloor}$ can be obtained using a similar gluing strategy. For example, the state space of reaction

$$2\,\mathcal{X}_1 \underset{\kappa_{\mathrm{d}}}{\overset{\kappa_{\mathrm{b}}}{\rightleftharpoons}} \mathcal{X}_2, \tag{6}$$

in a closed system with initial condition $(X_1, X_2)^{\mathrm{T}} = (20, 0)^{\mathrm{T}}$ is a 10-path with states $(20 - 2x, x)^{\mathrm{T}}$ for all $x \in \{1, \cdots, 10\}$. Figure 7 illustrates one way to construct the graph.
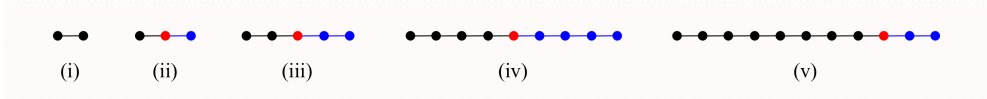

Figure 7: A demonstration of the gluing technique by gluing paths at one vertex sequentially. Updated graphs are in black. New components are in blue. Red vertices are the vertices at which graphs are glued together.

4.1.2 Two reversible reactions

There are eight possible closed systems with exactly two reversible, elementary reactions, which we list in Appendix B. The state spaces of these reactions are symmetrical, triangular grids, which we will illustrate using the example of a mass-conserving system with two connected monomolecular reversible reactions

$$\mathcal{X}_1 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} \mathcal{X}_2 \underset{\kappa_4}{\overset{\kappa_3}{\rightleftharpoons}} \mathcal{X}_3. \tag{7}$$

In addition, we propose a recursive algorithm that constructs symmetrical, triangular grids from such grids of smaller sizes. We also use Reaction System 7 together with the law of conservation of mass ([14]) to illustrate the computation of the stationary distributions on state spaces that are symmetrical, triangular grids.

Consider Reactions 7 in a closed system with the conservation law that the total number of $\mathcal{X}$ molecules, $T \equiv X_1 + X_2 + X_3$, is constant [14]. The corresponding undirected graphs are symmetrical, triangular grids (Figure 8), the sizes of which depend on the initial condition. For ease of representation, we draw graphs using right angles, but all that matters is the connectivity between the vertices. The smallest component of the graph that consists of both of the reversible reactions in Equation 7 has an "L" shape. It turns out that a symmetrical, triangular grid of any size can be constructed by sequential gluing of "L"-shaped components at one or two vertices.

Nevertheless, the computational cost is at least a quadratic function of the number of "L"-shaped components glued together. In addition, we need to check that the proportionality

condition (Equation 3) holds every time we glue graphs at two vertices. In order to improve the computational efficiency of calculating stationary distributions, we propose a recursive algorithm for the cases when T is a power of 2 as shown in Figure 8. In general, for $T = n$ being an arbitrary positive integer, we first use the recursive algorithm to build the state space of the case $T = 2^{\lfloor \log_2 n \rfloor}$ and then glue additional "L"-shaped components at one or two vertices sequentially until we get the complete graph.
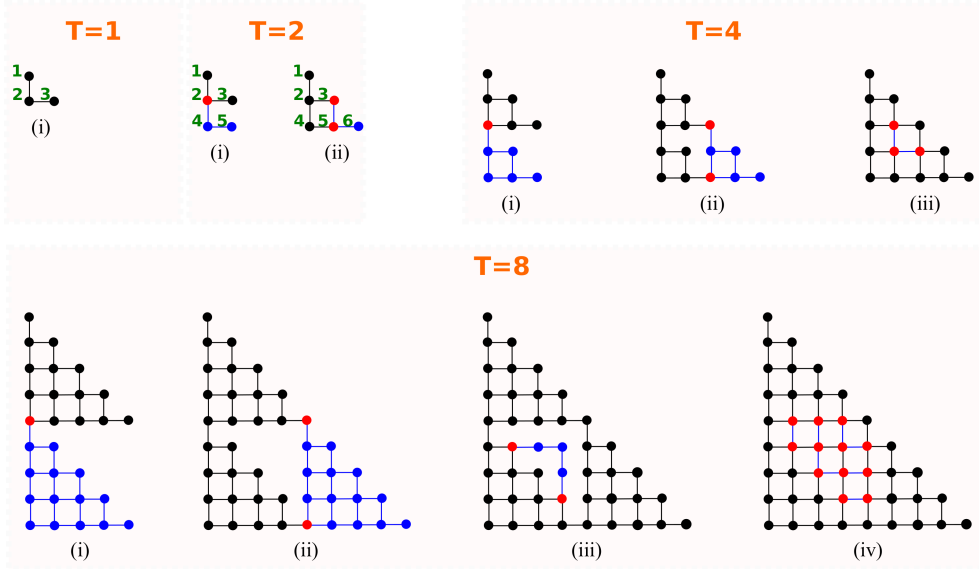

Figure 8: A demonstration of the gluing technique using grids whose smallest components are "L"-shaped. Updated graphs are in black. New components are in blue. Red vertices are the vertices at which graphs are glued together. In Subfigure (i) for $T = 1$ and Subfigure (ii) for $T = 2$, vertices are labeled in green. In Subfigure (iii) for $T = 4$ and Subfigure (iv) for $T = 8$, the blue edges are added one at a time.

We wrote a MAPLE (Waterloo Maple Inc.) code that takes $\log_2 T \in \mathbb{Z}_{\geq 0}$ as an input and gives an output of the corresponding stationary distribution. The computation time of the code is within a few seconds on a standard laptop.

Figure 9 gives an "L"-shaped component of the triangular-grid state space in which a vector $(x_1, x_2, x_3)^{\mathrm{T}}$ indicates that there are x_1 molecules of species $\mathcal{X}_1$, x_2 molecules of species $\mathcal{X}_2$, and $x_3 \equiv T - x_1 - x_2$ molecules of species $\mathcal{X}_3$ in the system. The stationary distribution on such a state space is

$$
\begin{aligned}
\xi_1(x_1, x_2, x_3) \quad &\equiv (\Pr(\text{state 1}), \Pr(\text{state 2}), \Pr(\text{state 3})) \\
&= C_1(x_1, x_2, x_3) \cdot \left[\frac{\kappa_2(x_2+1)}{\kappa_1 x_1}, 1, \frac{\kappa_3(x_2+1)}{\kappa_4(x_3+1)} \right],
\end{aligned}
\tag{8}
$$

where $C_1(x_1, x_2, x_3) = \frac{\kappa_2(x_2+1)}{\kappa_1 x_1} + 1 + \frac{\kappa_3(x_2+1)}{\kappa_4(x_3+1)}$ is a normalizing constant that depends on the values of x_i ($i \in \{1, 2, 3\}$).
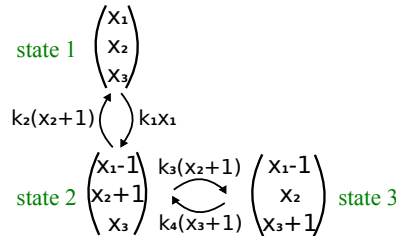

Figure 9: An "L"-shaped component of a triangular-grid state space.

For Reaction System 7 with $T = 1$, we have $(x_1, x_2, x_3) = (1, 0, 0)$. Hence, the stationary

distribution can be obtained by substituting the values of x_i ($i \in \{1, 2, 3\}$) into Equation 8.

To construct the stationary distribution of Reaction System 7 with $T = 2$, we first calculate the result in symbols and then substitute in $(x_1, x_2, x_3) = (2, 0, 0)$. As shown in Subfigure 8(ii), we first glue two "L"-shaped components together at one vertex. The stationary distribution of the new "L"-shaped component is $\xi_1(x_1 - 1, x_2 + 1, x_3)$. According to Equation 2, the stationary distribution of the combined state space keeps the ratios within the single state spaces. The rescaling ratio for adding the new "L"-shaped component is

$$r_1(x_1, x_2, x_3) \equiv \frac{C_1(x_1, x_2, x_3) \cdot 1}{C_1(x_1 - 1, x_2 + 1, x_3) \cdot \frac{\kappa_2(x_2+2)}{\kappa_1(x_1-1)}}. \tag{9}$$

Hence, the stationary distribution of Subfigure 8(ii), $\xi_2(x_1, x_2, x_3)$, is a 5-vector obtained by appending the rescaled probabilities of the two new vertices (i.e. the second and third entries in the vector $\xi_1(x_1 - 1, x_2 + 1, x_3) \cdot r_1(x_1, x_2, x_3)$) to $\xi_1(x_1, x_2, x_3)$ and then multiplying the 5-vector by a normalization constant $C_2(x_1, x_2, x_3)$.

Next, we glue another "L"-shaped component to the updated state space at two vertices simultaneously (Subfigure 8(iii)). The stationary distribution of the new "L"-shaped component is $\xi_1(x_1 - 1, x_2, x_3 + 1)$. The proportionality condition (Equation 3) holds in this case, so Equation 4 applies and the stationary distribution of the combined state space keeps the ratios within the single state spaces. The rescaling ratio for the new "L"-shaped component is

$$r_2(x_1, x_2, x_3) \equiv r_1(x_1, x_2, x_3) \cdot \frac{\kappa_3(x_2 + 2)}{\kappa_4(x_3 + 1)}. \tag{10}$$

Hence, the stationary distribution of Subfigure 8(iii), $\xi_3(x_1, x_2, x_3)$, can be obtained by appending the rescaled probability of the new vertex (i.e. the third entry in the vector $\xi_1(x_1 - 1, x_2, x_3 + 1) \cdot r_2(x_1, x_2, x_3)$) to $\xi_2(x_1, x_2, x_3)$ and then multiplying the 6-vector by a normalization constant $C_3(x_1, x_2, x_3)$. Finally, we compute the stationary distribution on the state space in Subfigure 8(iii) by substituting $(x_1, x_2, x_3) = (3, 0, 0)$ into $\xi_3(x_1, x_2, x_3)$.

The stationary distributions of Reactions 7 in a closed system with $T = 4$ and $T = 8$ can be found in the same recursive fashion. We note that the stationary distribution stays the same if (i) we add a new edge between two existing vertices in a current state space, and (ii) Equation 3 holds. Thus, in step (iii) of the case when $T = 8$, we add a 4-path in order to complete the vertex set. In step (iv), Equation 3 holds for every new edge, so the stationary distribution of Figure 8(iv) is the same as that of Figure 8(iii).

4.1.3 Three reversible reactions

There are three possible closed systems with 2-dimensional state spaces and exactly three reversible, elementary reactions, which we list in Appendix C. For these reaction systems, the smallest components that consist of all reactions are triangles. We note that the three reversible, elementary reactions cannot be independent, and each reaction can be achieved by combining the other two reactions. Otherwise, the stochiometric matrix has rank 3 and the corresponding state space is naturally represented in 3-dimensional space.

Figure 10 gives the state spaces and the recursive gluing algorithm for a mass-conserving system with reactions

$$\mathcal{X}_1 \rightleftharpoons \mathcal{X}_2, \qquad \mathcal{X}_2 \rightleftharpoons \mathcal{X}_3, \qquad \mathcal{X}_3 \rightleftharpoons \mathcal{X}_1, \tag{11}$$
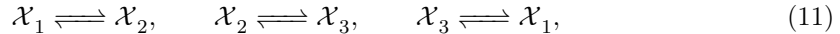
when $T = 1$, 2, 4, and 8 respectively. In general, for $T = n$ being an arbitrary positive integer, we first use the recursive algorithm to build the state space of the case $T = 2^{\lfloor \log_2 n \rfloor}$ and then glue additional triangular components at one or two vertices sequentially until we get the complete graph.
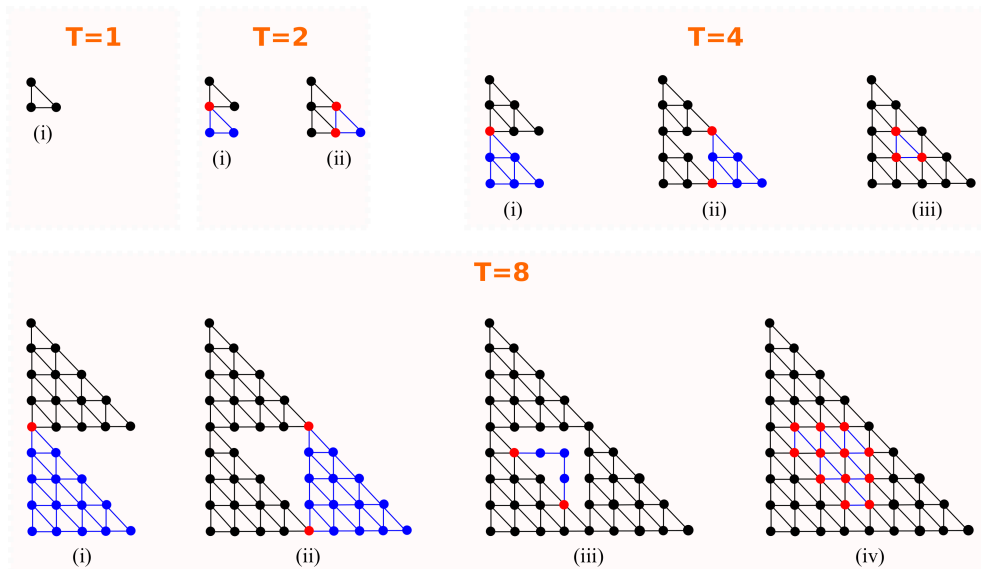
Figure 10: A demonstration of the gluing technique using grids whose smallest components are triangles. Updated graphs are in black. New components are in blue. Red vertices are the vertices at which graphs are glued. In Subgraph (iii) for $T = 4$ and Subgraph (iv) for $T = 8$, the blue edges are added one at a time.

4.2 Stationary distributions of two interconnected transcriptional components

In this subsection, we study the stationary behavior of two interconnected transcriptional components by applying a recursive algorithm that glues state spaces together sequentially at one or two vertices. Specifically, we first model the cascade of two connected transcriptional components by the CME [29]. We then provide a method that truncates the infinite state space to a finite subset with a guarantee of accuracy for how closely the approximation matches the true solution. Finally, we give the exact stationary solution of the CME as a function of the reaction rate constants and the initial molecular population, which confirms the results in [29].

4.2.1 Interconnected transcriptional components and the CME

We first introduce the chemical reactions that are associated with the two interconnected transcriptional components and give the corresponding CME [29].

Figure 11 (reproduced from reference [29]) illustrates a transcriptional component connected to a downstream one. In the upstream component, a protein initiates a cascade which first produces a transcription factor $\mathcal{Z}$ and then activates a reversible binding reaction between $\mathcal{Z}$ and DNA binding sites $\mathcal{P}$ in the downstream component.
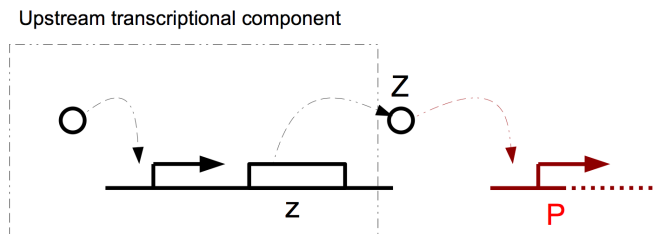

Figure 11: Two interconnected transcriptional components. The figure is reproduced from [29].

Let $\mathcal{C}$ be the complex formed by $\mathcal{Z}$ and $\mathcal{P}$. The chemical reactions described above are given

by

$$\emptyset \xrightleftharpoons[\delta]{\kappa} \mathcal{Z}, \quad \mathcal{Z} + \mathcal{P} \xrightleftharpoons[\kappa_{\text{off}}]{\kappa_{\text{on}}} \mathcal{C}, \tag{12}$$

where κ, δ, κ_{on} and κ_{off} are reaction rates. Let P and C be the numbers of DNA binding sites $\mathcal{P}$ and complexes $\mathcal{C}$ respectively. Since the total amount of DNA is conserved, the equation $P + C = T$ always holds, where T is a constant that is determined by the initial condition.

Assume that the initial condition of the reaction system is $(C(0), Z(0), P(0)) = (c_0, z_0, p_0)$. Then the conservation constant is given by $T = p_0 + c_0$. Let each state in the state space be a 2-vector (C, Z), and the corresponding number of DNA binding sites $\mathcal{P}$ is given by $P = T - C$. Since there can be arbitrarily many transcription factors $\mathcal{Z}$, the reaction system described by Equation 12 has an infinite state space (Figure 12).
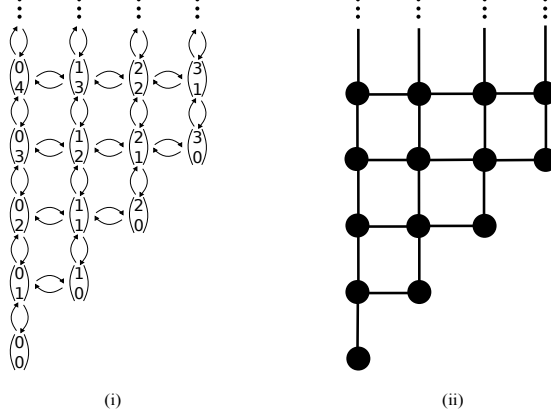

(i)   (ii)

Figure 12: (i) The infinite state space of two interconnected transcriptional components when $T = 3$: expression and degradation of protein $\mathcal{Z}$ corresponds to moving up and down the state space respectively; production and decomposition of complex $\mathcal{C}$ corresponds to moving right and left respectively. (ii) The graph that is given naturally by the state space in (i).

For ease of calculation, we assume that the system has volume $V = 1$. Let $\Pr(c, z)$ be the probability that the stochastic process is in state (c, z) at time t given the initial condition $(C(0), Z(0)) = (c_0, z_0)$ at time $t = 0$. Each state (c, z) in the state space contributes exactly one linear ordinary differential equation to the CME, which is given by

$$\begin{aligned}
\frac{d\Pr(c, z)}{dt} = \ & \kappa \Pr(c, z - 1) + \delta(z + 1) \Pr(c, z + 1) + \kappa_{\text{on}}(z + 1)(T - c + 1) \Pr(c - 1, z + 1) \\
& + \kappa_{\text{off}}(c + 1) \Pr(c + 1, z - 1) - [k + \delta z + \kappa_{\text{on}} z(T - c) + \kappa_{\text{off}} c] \Pr(c, z).
\end{aligned} \tag{13}$$

4.2.2 Truncation of the infinite state space with guaranteed accuracy

We propose a truncation method that is inspired by the finite state projection (FSP) algorithm ([12]). We truncate the infinite space space of two interconnected transcriptional components by imposing a maximum $M \in \mathbb{Z}_{>0}$ on Z, where the value of M is determined by the desired level of accuracy of the approximate solution. Figure 13 gives an example of a truncated graph when $M = 2$.

Suppose that $\epsilon > 0$ is the amount of acceptable error. Let Ω be the infinite state space and $\Omega_{\text{f}} \subset \Omega$ be the finite truncated state space. We can choose the truncation bound $M \in \mathbb{Z}_{>0}$ such that the total probability that the finite state approximation fails to capture (i.e. the total probability accounted by $\Omega_{\text{f}}^{\text{c}} \equiv \Omega \setminus \Omega_{\text{f}}$) is at most ϵ. In order to calculate the missing total probability, we loop the states in Ω_{f} into one single state named ω_{f}, and states in $\Omega_{\text{f}}^{\text{c}}$ into state ω_{c}. The transition rate from ω_{f} to ω_{c} is the sum of the transition rates from Ω_{f} to $\Omega_{\text{f}}^{\text{c}}$. Similarly, the reverse transition rate is the sum of the transition rates from $\Omega_{\text{f}}^{\text{c}}$ to Ω_{f}. Figure 14 illustrates looping the infinite state space into two states when $T = 3$.
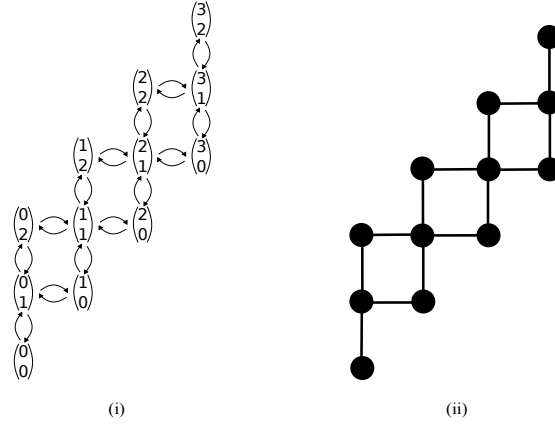
Figure 13: (i) The truncated state space of two interconnected transcriptional components when $M = 2$ and $T = 3$. (ii) The graph that corresponds to the truncated state space in (i).
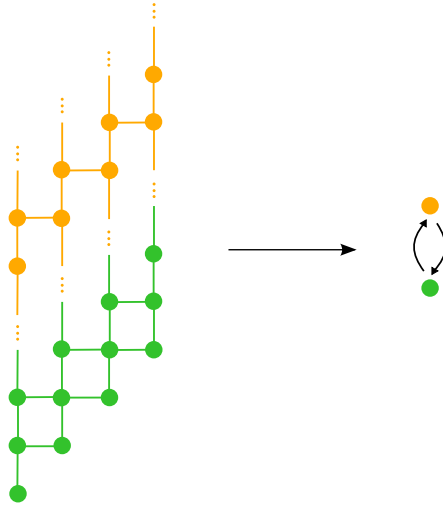

Figure 14: Illustration of looping the infinite state space of two interconnected transcriptional components into two states when $T = 3$. The green component of the graph is the finite subgraph that we want to study. The orange component of the graph accounts for small probability in the stationary distribution and is the part that we want to discard.

For any $T \in \mathbb{Z}_{>0}$, the transition rate from ω_f to ω_c is $\kappa(T+1)$, and the reverse transition rate is $\delta(M+1)(T+1)$. The stationary probabilities of ω_f and ω_c are $\frac{\delta(M+1)}{\delta(M+1)+\kappa}$ and $\frac{\kappa}{\delta(M+1)+\kappa}$ respectively. We choose the the smallest $M \in \mathbb{Z}_{>0}$ such that $\frac{\kappa}{\delta(M+1)+\kappa} \leq \epsilon$. Rearranging terms gives

$$M = \max(1, \left\lceil \frac{\kappa(1-\epsilon)}{\delta\epsilon} \right\rceil - 1). \tag{14}$$

4.2.3 A recursive algorithm for obtaining analytic stationary solutions

We propose a recursive algorithm that calculates the stationary solution to the CME of two interconnected transcriptional components. We provide a MAPLE code in Appendix D that carries out the algorithm automatically. The code takes T, M and the four reaction rate constants (κ, δ, κ_{on}, κ_{off}) as input and gives the stationary distribution on the corresponding truncated finite state space as output. The algorithm constructs the truncated state space recursively by gluing smaller components together sequentially at one or two vertices. We demonstrate the recursive algorithm for the case when $T = 3$ and $M = 2$ but the method is applicable for any positive integers T and M. We construct the truncated state space by

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first gluing lateral-"T" components together sequentially at one vertex and then checking the proportionality condition (Equation 3) for the missing edges. Figure 15 illustrates the method for $T = 3$ and $M = 2$. We label the states in the truncated state space from left to right and from bottom to top so that we get the labeling naturally as we expand the graph.
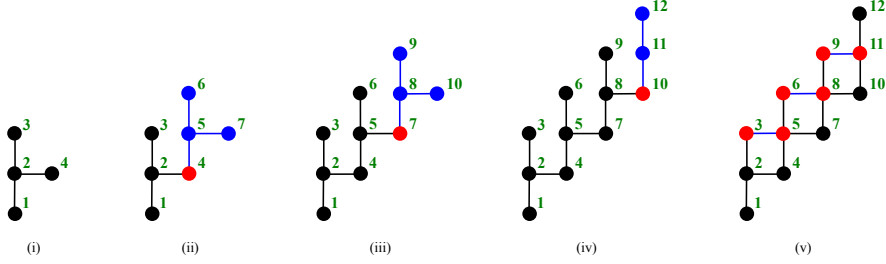

Figure 15: Demonstration of constructing a truncated state space when $M = 2$ and $T = 3$. Updated graphs are in black. New components are in blue. Red vertices are the vertices at which graphs are glued together. In Subfigure (v), the blue edges are added one at a time. Green numbers are labels of vertices.

The stationary distribution of a lateral-"T" component (Figure 16) with the bottom state being $(c, 0)$ ($c \in \{0, 1, 2\}$) has a unique stationary distribution

$$\begin{aligned} \xi_c &\equiv (\Pr(\text{state 1}), \Pr(\text{state 2}), \Pr(\text{state 3}), \Pr(\text{state 4})) \\ &= \psi_c(1, \tfrac{\kappa}{\delta}, \tfrac{\kappa^2}{2\delta^2}, \tfrac{\kappa\kappa_{\text{on}}(3-c)}{\delta\kappa_{\text{off}}(c+1)}), \end{aligned} \tag{15}$$

where ψ_c is a normalization constant. Specifically, the stationary distribution of Subfigure 15(i) is $\xi_0 \equiv \psi_0(1, \tfrac{\kappa}{\delta}, \tfrac{\kappa^2}{2\delta^2}, \tfrac{3\kappa\kappa_{\text{on}}}{\delta\kappa_{\text{off}}})$. The rescaling ratio for adding a second lateral-"T" component to the right of Subfigure 15(i) is

$$r_1 = \frac{3\psi_1\kappa\kappa_{\text{on}}}{\delta\kappa_{\text{off}}}. \tag{16}$$

Hence, the stationary distribution of Subfigure 15(ii) can be obtained by appending the rescaled probabilities of the new states (i.e. the second, third and fourth entries of the vector $\xi_1 \cdot r_1$) to ξ_0 and then normalizing the 7-vector. Similarly, we add a third lateral-"T" component to the right of the existing state space (Subfigure 15(ii)) to obtain the stationary distribution of Subfigure 15(iii). Then we add a path of length 2 (Subfigure 15(iv)) in order to have all the states in the truncated state space. Finally, we check the proportionality condition (Equation 3) for all the missing edges, which always holds in this case.
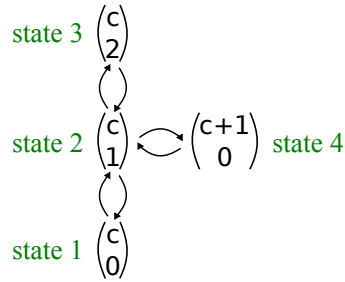
Figure 16: A lateral-"T" component for $T = 3$ and $M = 2$ where $c \in \mathbb{Z}_{\geq 0}$. The first and second entries of each vector gives the number of complexes $\mathcal{C}$ and transcription factors $\mathcal{Z}$ respectively for that particular state.

The above method works for any positive integers T and M in general. A lateral-"T" component consists of $M + 2$ states. We need three steps in order to construct the truncated state space: (i) glue T lateral-"T" components together sequentially at one vertex, (ii) glue a path of length M to the existing state space at one vertex, and (iii) check the proportionality condition (Equation 3) for all missing edges.

For $c \in \{0, 1, 2, \cdots, T-1\}$, the stationary distribution ξ_c on a lateral-"T" component with state 1 (i.e. the bottom vertex) being $(c, 0)$ is given by

$$\text{Pr(state } i) = \begin{cases} \psi_c \frac{(\kappa/\delta)^{i-1}}{(i-1)!}, & \text{if } i \in \{1, 2, 3, \cdots, M+1\}, \\ \psi_c \frac{\kappa \kappa_{\text{on}}(T-c)}{\delta \kappa_{\text{off}}(c+1)}, & \text{if } i = M+2, \end{cases} \tag{17}$$

where ψ_c is a normalization constant. The stationary distribution on the path of length M is given by

$$\text{Pr(state } i) = \psi_T \frac{(\kappa/\delta)^{i-1}}{(i-1)!}, \tag{18}$$

for $i \in \{1, 2, 3, \cdots, M+1\}$, where ψ_T is a normalization constant.

After step (ii), the graph contains all the states from the truncated state space. In order to complete the graph, we need to add $T(M-1)$ edges by gluing at the two endvertices of each edge simultaneously, which requires the proportionality condition (Equation 3) to hold for each missing edge.

Every missing edge is between states (c, z) and $(c+1, z-1)$ for some $c \in \{0, 1, 2, \cdots, \text{T-1}\}$ and $z \in \{2, 3, 4, \cdots, M\}$. The transition rate from (c, z) to $(c+1, z-1)$ is $\kappa_{\text{on}} z(T-c)$ and the reverse transition rate is $\kappa_{\text{off}}(c+1)$. The stationary distribution on the unit-length path is given by

$$\widetilde{\text{Pr}}(\text{state } (c, z)) = \frac{\kappa_{\text{off}}(c+1)}{\kappa_{\text{off}}(c+1) + \kappa_{\text{on}} z(T-c)} \tag{19}$$

and

$$\widetilde{\text{Pr}}(\text{state } (c+1, z-1)) = \frac{\kappa_{\text{on}} z(T-c)}{\kappa_{\text{off}}(c+1) + \kappa_{\text{on}} z(T-c)}. \tag{20}$$

In the graph where the edge is missing, the stationary distribution gives

$$\text{Pr(state } (c, z)) = \psi \binom{T}{c} \left(\frac{\kappa \kappa_{\text{on}}}{\delta \kappa_{\text{off}}} \right)^c \frac{(\kappa/\delta)^z}{z!} \tag{21}$$

and

$$\text{Pr(state } (c+1, z-1)) = \psi \binom{T}{c+1} \left(\frac{\kappa \kappa_{\text{on}}}{\delta \kappa_{\text{off}}} \right)^{c+1} \frac{(\kappa/\delta)^{z-1}}{(z-1)!}, \tag{22}$$

where ψ is a normalization constant. The proportionality condition (Equation 3) holds for every missing edge as

$$\frac{\text{Pr(state } (c, z))}{\text{Pr(state } (c+1, z-1))} = \frac{\widetilde{\text{Pr}}(\text{state } (c, z))}{\widetilde{\text{Pr}}(\text{state } (c+1, z-1))}. \tag{23}$$

Hence, we can add every missing edge to the current graph by gluing at the two endvertices simultaneously. As explained in Subsubsection 4.1.2, the stationary distribution on the truncated state space (e.g. Subfigure 15(v)) is the same as that on the state space before adding the missing edges (e.g. Subfigure 15(iv)).

We note that for, any $c \in \{0, 1, 2, \cdots, T\}$, we have $\text{Pr(state } (c, z)) \to 0$ as $z \to \infty$. This justifies our truncation of the infinite state space to a finite subset by bounding the maximum value of Z. Moreover, the dependence of $\text{Pr(state } (c, z))$ on M is only through the normalization constant ψ. Hence, we can obtain the accurate stationary distribution of the untruncated infinite state space by normalizing over $z \in \mathbb{Z}_{\geq 0}$ and $c \in \{0, 1, 2, \cdots, T\}$, which is

$$\text{Pr(state } (c, z)) = \left(1 + \frac{\kappa \kappa_{\text{on}}}{\delta \kappa_{\text{off}}} \right)^{-T} \binom{T}{c} \left(\frac{\kappa \kappa_{\text{on}}}{\delta \kappa_{\text{off}}} \right)^c e^{-\kappa/\delta} \frac{(\kappa/\delta)^z}{z!}. \tag{24}$$

Equation 24 has a separable product form

$$\text{Pr(state } (c, z)) = \text{Pr(state } c) \, \text{Pr(state } z). \tag{25}$$

This implies the independence between the stationary behavior of the upstream and downstream transcriptional components. In addition, the stationary distribution of random variable C is
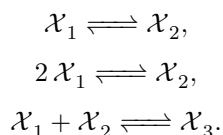
a binomial distribution with parameters $n = T$ and $p = (\frac{\delta \kappa_{\text{off}}}{\kappa \kappa_{\text{on}}} + 1)^{-1}$, and the stationary distribution of random variable Z is a Poisson distribution with parameter κ/δ. Our result of the stationary distribution confirms Theorem 5.1 in [29]. However, reference [29] used Feinberg's deficiency zero theorem ([31]) and the theorem of product-form stationary distributions (Theorem 4.1 of [24]) proposed by Anderson, Craciun and Kurtz.
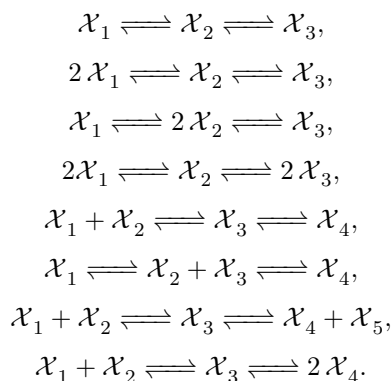
5   Conclusions

In this paper we have explored the benefits and limitations of a technique that was recently proposed by Mélykúti et al. ([11, 19]) to solve stationary distributions of biochemical reaction networks by sequential gluing of finite, irreducible state spaces at one or two vertices. We have explained the relationship between continuous-time Markov jump processes and graph theory, and characterized the set of state spaces that can be obtained by gluing paths, cycles, or both, at one vertex sequentially. In addition, we have classified mass-conserving chemical reaction systems with reversible, elementary reactions and 2-dimensional state spaces according to the topologies of their state spaces. For each category, we have presented a recursive algorithm to solve the stationary distributions and illustrated with the example of a mass-conserving system that has two connected monomolecular reversible reactions. Furthermore, we have showed that an infinite state space can be truncated to a finite subset with a guarantee of accuracy for how closely an approximation solution matches the true solution. Even though the gluing technique can only construct finite state spaces, we find that, by taking the size of a finite state space to infinity, the steady state response can converge to the analytic solution on the resulting infinite state space. Finally, we illustrate the aforementioned ideas with the example of two interconnected transcriptional components.

In future work, we plan to attack the problem of solving the stationary distributions of genetic toggle switches ([30]). We are also interested in trying the gluing technique ([11, 19]) on 3-dimensional state spaces. Another potential direction of future work is to extend the gluing technique to enable the construction of infinite state spaces. As we showed with the example of two interconnected transcriptional components, one possible method is to first solve the stationary distributions on a finite subset of the state space and then analyze the solution in the limit of the size of the state space going to infinity.

A   Systems with one reversible chemical reaction

$$\mathcal{X}_1 \Longleftrightarrow \mathcal{X}_2,$$
$$2\,\mathcal{X}_1 \Longleftrightarrow \mathcal{X}_2,$$
$$\mathcal{X}_1 + \mathcal{X}_2 \Longleftrightarrow \mathcal{X}_3.$$

B   Systems with two reversible chemical reactions

$$\mathcal{X}_1 \Longleftrightarrow \mathcal{X}_2 \Longleftrightarrow \mathcal{X}_3,$$
$$2\,\mathcal{X}_1 \Longleftrightarrow \mathcal{X}_2 \Longleftrightarrow \mathcal{X}_3,$$
$$\mathcal{X}_1 \Longleftrightarrow 2\,\mathcal{X}_2 \Longleftrightarrow \mathcal{X}_3,$$
$$2\mathcal{X}_1 \Longleftrightarrow \mathcal{X}_2 \Longleftrightarrow 2\,\mathcal{X}_3,$$
$$\mathcal{X}_1 + \mathcal{X}_2 \Longleftrightarrow \mathcal{X}_3 \Longleftrightarrow \mathcal{X}_4,$$
$$\mathcal{X}_1 \Longleftrightarrow \mathcal{X}_2 + \mathcal{X}_3 \Longleftrightarrow \mathcal{X}_4,$$
$$\mathcal{X}_1 + \mathcal{X}_2 \Longleftrightarrow \mathcal{X}_3 \Longleftrightarrow \mathcal{X}_4 + \mathcal{X}_5,$$
$$\mathcal{X}_1 + \mathcal{X}_2 \Longleftrightarrow \mathcal{X}_3 \Longleftrightarrow 2\,\mathcal{X}_4.$$

C Systems with three reversible chemical reactions

$$\mathcal{X}_1 \rightleftharpoons \mathcal{X}_2 \qquad \mathcal{X}_2 \rightleftharpoons \mathcal{X}_3 \qquad \mathcal{X}_3 \rightleftharpoons \mathcal{X}_1,$$
$$\mathcal{X}_1 \rightleftharpoons 2\,\mathcal{X}_2 \qquad 2\,\mathcal{X}_2 \rightleftharpoons \mathcal{X}_3 \qquad \mathcal{X}_3 \rightleftharpoons \mathcal{X}_1,$$
$$\mathcal{X}_1 \rightleftharpoons \mathcal{X}_2 + \mathcal{X}_3 \qquad \mathcal{X}_2 + \mathcal{X}_3 \rightleftharpoons \mathcal{X}_4 \qquad \mathcal{X}_4 \rightleftharpoons \mathcal{X}_1.$$
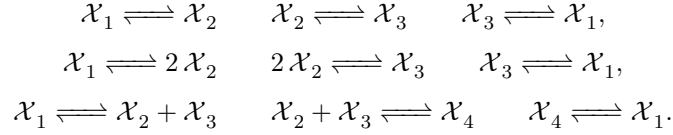
D MAPLE code for solving the stationary distribution of two interconnected transcriptional components

```
ITC_memo := module()
    local memory;
    export ITC;

    memory := table();

    ITC := proc (T::posint, M::posint, a, b, s, t)
        if M=1 then
            statn_distn := Array(1..(2*T+2));
            statn_distn[1] := 1;
            for C from 1 to T do
                statn_distn[2*C] := statn_distn[2*C-1]*a/b;
                statn_distn[2*C+1] := statn_distn[2*C]*(s*(T−C+1)/(t*C));
            end do;
            statn_distn[2*T+2] := statn_distn[2*T+1]*a/b;
            print('The stationary distribution for T=', T, 'and M=1 is ', statn_distn, '.');
        else
            p[0] := Array(1..(M+2));
            p[0][1] := 1;
            for Z from 1 to M do
                p[0][Z+1] := (a/b)^Z/Z!;
            end do;
            p[0][M+2] := a*s*T/(b*t);

            if T=1 then
                statn_distn := ArrayTools[Concatenate](2, p[0], Array(1..M));
                for Z from 1 to M do
                    statn_distn[M+2+Z] := statn_distn[M+1+Z]*a/(Z*b);
                end do;
                for Z from 2 to M do
                    if s*Z*T/t = statn_distn[M+1+Z]/statn_distn[Z+1] then
                        do_nothing := Z;
                    else
                        print('Proportionality condition failed for the edge between (C, Z)=
                            (0, ', Z, ') and (C, Z)=(1, ', Z-1, ') when T=1 and M=', M, '.');
                    end if;
                end do;
            else
                statn_distn := p[0];
                for C from 1 to T−1 do
                    statn_distn := ArrayTools[Concatenate](2, statn_distn, p[0][2..(M+1)]*
                        statn_distn[-1], (a/b)*s*(T−C)/((C+1)*t)*statn_distn[-1]);
                end do;
                statn_distn := ArrayTools[Concatenate](2, statn_distn, Array(1..M));
```

```
        for Z from 1 to M do
            statn_distn[T∗(M+1)+1+Z] := statn_distn[T∗(M+1)+Z]∗a/(Z∗b);
        end do;
        for C from 1 to T do
            for Z from 1 to M−1 do
                if s∗(Z+1)∗(T−C+1)/(t∗C) =
                    statn_distn[C∗(M+1)+Z+1]/statn_distn[C∗(M+1)+Z+1−M] then
                    do_nothing := Z ;
                else
                    print('Proportionality condition failed for the edge between
                        (C, Z)=(', C-1, Z+1, ') and (C, Z)=(', C, Z, ') when
                        T=', T, ' and M=', M, '.')
                end if;
            end do;
        end do;
    end if;
    print('The stationary distribution for T=', T, ' and M=', M, is, statn_distn, '.')
    end if;
  end proc;
end module;
ITC := ITC_memo:-ITC;
```

Acknowledgments

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