POLITECNICO DI TORINO

Corso di Laurea Magistrale

in Ingegneria Matematica

Tesi di Laurea Magistrale

New balancing conditions to derive stationary measures for Chemical Reaction Networks

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Anno Accademico 2019-2020

CONTENTS

Page

LIST OF FIGURES

Page

ABSTRACT

The thesis deals, in the context of Chemical Reaction Networks, with the conditions under which the existence of a stationary distribution can be demonstrated, highlighting its connection with the validity of certain balancing conditions.

In this regard, state-of-the-art results and a research study on the existence of new possible conditions are presented.

In particular, the thesis starts from the unpublished draft "Stationary measures for stochastic closed loop networks" by Daniele Cappelletti, Badal Joshi and Enrico Bibbona.

Taking inspiration from it, new balancing conditions on loops of reactions are defined. These conditions are then used in order to demonstrate the existence of a stationary measure and examples are brought in order to corroborate this statement.

In particular, using these new conditions, it is possible to re-prove already known results about the existence of stationary measures for conservative mass-reaction CRNs. On the other hand, even if some interesting results are achieved, it seems impossible to obtain stationary measures for CRNs not included in the state-of-art.

Introduction

The model and study of complex natural systems are typical research topics of the physical and mathematical disciplines. In particular, one of the most recent families of mathematical models that has been studied is that of stochastic Chemical Reaction Networks (CRNs).

These models aim to describe systems whose components interact with each other by exchanging a certain type of "information". Processes of chemical reactions or epidemiological spreads are examples in this regard, in which a set of species or agents interact over time causing mass and energy exchanges in the first case and viral diseases in the second.

CRNs represent these possible interactions using graphs and then associate them a deterministic or stochastic model, in order to describe the evolution of all the species present in the system and their long run behaviour. In addition, CRNs allow to reveal the symmetries of the system, transposing them into the so-called balancing conditions.

CRNs take their foundations in the early 1900 when, after the formulation of the mass action law, the dynamical properties of reaction networks began to be studied by many scientists in chemistry and physics. Among these, Rudolf Wegscheider must be quoted [16] for his definition of detailed balance condition for complex chemical reactions.

However, it was necessary to wait until 1965 to start hearing about CRNs theory, introduced by Rutherfor Aris in [2].

Starting from these basis, in 1972, Fritz Horn, Roy Jackson and Marting Feinberg laid down the first results for deterministic CRNs [12, 11, 7]. In particular they introduced the concepts of complex balanced equilibrium (as generalization of the detailed balanced) and deficiency for a network.

The study of stochastic models dates back more recently, to 2010, in [1] by David F. Anderson, Gheorghe Craciun, and Thomas G. Kurtz, where the authors prove that the existence of a complex balanced equilibrium for the deterministic system implies that of a stationary Poisson-like distribution for the stochastic one. Later the necessary

conditions for the converse to hold were illustrated by Daniele Cappelletti and Carsten Wiuf in [6]. In the same paper, a new stochastic complex balance condition and its equivalence with the deterministic one, were also proved.
Finally only in the last years the way was paved to new balance conditions such as the reaction vector and cycle ones, defined by Daniele Cappelletti and Badal Joshi in [4].

The thesis aims to try to extend the knowledge on CRNs by analyzing balance conditions not yet present in the literature and their implications in terms of stationary distributions.
Starting from the previously mentioned background, a general introduction is given at first, describing how CRNs models are structured, what their properties are, and how their temporal evolution and long run behaviour can be studied. The focus moves then on the latter point, in particular on stochastic models, trying to understand what conditions can guarantee the existence of a stationary measure for the system under consideration.
The state of the art is presented and, in particular, the linkage between the existence of a stationary measure and the fulfillment of certain balancing conditions is highlighted.

Taking inspiration from the draft of an unpublished research article [5], the thesis proceeds then with the definition of a new balancing condition, defined on sets of reaction loops within the network. The properties of this condition are then analyzed, with particular regard on relation to stationarity and to the already existing balance conditions. Finally, the thesis re-proves, under a new perspective, known results regarding the existence of a stationary measure for conservative mass-reaction Chemical Reaction Networks.

Part I

State of the art

1
Chemical Reaction Network

1.1 Definition and General properties

A Chemical Reaction Network is a mathematical model used to describe a biochemical system such as chemical reactions and epidemiological flaws.
Three sets are necessaries in order to define a Chemical Reaction Network:

- *species* $\mathcal{S}$ It is the set of the components that interact in the system and whose distribution we wish to model over time.
- *complexes* C It is the set of the nonnegative linear combinations of species which appear in the system. It represents how the different species can interact with each other.
- *reactions* $\mathcal{R}$ It is the set which describes how each complex converts each one in another.

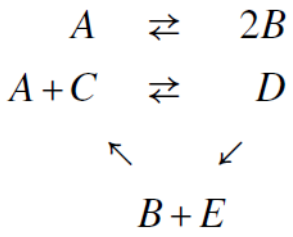

Figure 1.1
Example of Chemical Reaction Network

Example 1.1.1. If we consider the CRN in Figure 1.1 we could easily identify the 3 sets as:
$\mathcal{S} = \{A, B, C, D, E\}, C = \{A, 2B, A + C, D, B + E\}, \mathcal{R} = \{A \overset{k_1}{\leftarrow} 2B, 2B \overset{k_2}{\leftarrow} 2A, A + C \overset{k_3}{\leftarrow} D, D \overset{k_4}{\leftarrow} A + C, D \overset{k_5}{\leftarrow} B + E, B + E \overset{k_6}{\leftarrow} A + C\}$.
Where we have indicated with $\{k_i\}_i$ the reaction rate constants.

In a more formal way we can define a Chemical Reaction Network as follows:

Definition 1.1.2 (Chemical Reaction Network)**.** A Chemical Reaction Network is a triple $\mathcal{G} = \{\mathcal{S}, C, \mathcal{R}\}$, where:

- $\mathcal{S} = \{S_1, S_2, ..., S_n\}$ is the set of species
- $C \subset \{y = \sum_{s=1}^{n} y_s S_s \mid \{y_s\}_{s=1,...,n} \in Z^n_{\geq 0}\}$ is the set of complexes. y_s is called the *stoichiometric coefficient* of species s in the complex y.
- $\mathcal{R} = \{y \to y' | y, y' \in C, y \neq y'\}$ is the set of reactions.

In order to indicate the kth reaction we write:

$$\sum_{s=1}^{n} y_{k,s} S_s \to \sum_{s=1}^{n} y'_{k,s} S_s \tag{1}$$

Now we define two other objects that will be useful later:

Definition 1.1.3 (Reaction vector)**.** For each reaction $y \to y' \in \mathcal{R}$ we define the *reaction vector* ξ as:

$$\xi = y' - y \in Z^n_{\geq 0} \tag{2}$$

Definition 1.1.4 (Stoichiometric subspace)**.** We define the *stoichiometric subspace* of $\mathcal{G}$ the linear subspace of R^n generated by the reaction vectors:

$$S = span\{\xi_i, i = 1, ..., |\mathcal{R}|\}. \tag{3}$$

The sets defined as $(c + S) \cap \mathbb{R}^n_{\geq 0}, \quad \forall c \in \mathbb{R}^n$ are called instead the *stoichiometric compatibility class* of $\mathcal{G}$.
We denote with r the dimension of S and we called it *rank*.

We introduce now a notation that will be useful later in describing the spaces identified by the CRN in a more easy way.
If we consider the set of species $\mathcal{S}$, we can define a new space $\mathbb{R}^{\mathcal{S}}$ as follows: $x \in \mathbb{R}^{\mathcal{S}}$ is a vector which indicates the concentration of the species in the system and

x_s, $s \in \{1, ..., |\mathcal{S}|\}$ is the concentration of the specific species S_s.

In the same way we can define the corresponding space for complexes $\mathbb{R}^C$.

Taking inspiration from [15] we can then define $\{\omega_i\}_{i \in C}$, where:

$$(\omega_i)_j = \begin{cases} 1 & \text{if } j = i \\ 0 & \text{if } j \neq i, \end{cases}$$

this is the *standard basis* for $\mathbb{R}^C$.

So if $x \in \mathbb{R}^C$, we can write:

$$x = \sum_{i \in C} x_i \omega_i.$$

Finally, if we consider a subset $\mathcal{L} \subseteq C$, we can define the indicator function:

$$\omega_{\mathcal{L}} := \sum_{i \in \mathcal{L}} \omega_i = \begin{cases} 1 & \text{if } i \in \mathcal{L} \\ 0 & \text{if } i \in C \setminus \{\mathcal{L}\}. \end{cases}$$

Speaking of subsets of the set $\mathcal{S}$, we can also introduce here the following concepts taken from [8].

Definition 1.1.5. Two complexes $y, y' \in C$ are said to be *linked*, if any of the following conditions is satisfied:

1. $y = y'$
2. $y \to y'$ or $y' \to y$ belongs to $\mathcal{R}$
3. There exists a set of complexes $\{y_1, y_2, ..., y_k\}$ such that:

$$y \leftrightarrow y_1 \leftrightarrow y_2 \leftrightarrow ... \leftrightarrow y_k \leftrightarrow y',$$

where with $' \leftrightarrow'$ we intends that for those complexes condition 2 holds (and we call it *direct link*).

If y and y' are linked we write $y \sim y'$.

This establishes an equivalence relation that induces a partition of C. The equivalences

classes that are created in that way, are called *linkage classes* of the CRN. We denote with l the number of linkage classes in a network.

Definition 1.1.6. We define *cut-link* of a CRN, a direct link $y \leftrightarrow y'$ such that the removal of this link, leaves y and y' unlinked.

Similarly to 1.1.5 we can also define:

Definition 1.1.7. It is said that the complex $y \in C$ *ultimately reacts* to complex $y' \in C$ if any of the following conditions is satisfied:

1. $y = y'$
2. $y \to y' \in \mathcal{R}$
3. There is a path of reactions $y_1, y_2, ..., y_k$ such that

$$\{y \to y_1, y_1 \to y_2, ..., y_{k-1} \to y_k, y_k \to y'\} \in \mathcal{R}.$$

If y ultimately reacts with y' we write $y \Rightarrow y'$.

Lastly we define:

Definition 1.1.8. Two complexes $y, y' \in C$ are *strongly linked* if both $y \Rightarrow y'$ and $y' \Rightarrow y$ hold. In this case we write $y \approx y'$ and this definition establishes an equivalence relation that induces another partition of C in equivalence classes called *strong-linkage classes*. A strong-linkage class $\mathcal{L}$ is in addition called *terminal* if no complex in $\mathcal{L}$ reacts to a complex not in $\mathcal{L}$; that is if $y \in \mathcal{L}$ and $y \to y' \in \mathcal{R}$ then $y' \in \mathcal{L}$. And since $\mathcal{L}$ is also strong-linked,this means that for each path that starts with $y \to y' \in \mathcal{R}_{\mathcal{L}}$, it is contained in a closed directed path. In this case $y \to y'$ is called *terminal reaction*.
We denote with t the number of terminal strong-linkage classes in a CRN.

Definition 1.1.9. A linkage class (strong linkage class) in a reaction network is called *tree like* if every direct link connecting two complex in the class is a cut-link. Moreover if all classes are tree like, the network is said to be *forest like*.

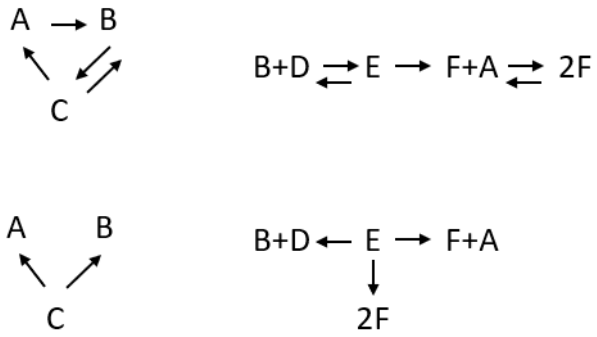

Figure 1.2

Two different CRN with same linkage classes

Remark 1.1.10. Now we give an observation which would be very useful to better understand an important property of CRNs, which we will introduce later. We should notice indeed that, if we consider the two networks described in Figure 1.2 and the definition given in 1.1.5, both of them have same linkage classes $\{A, B, C\}$ and $\{B + D, E, F + A, 2F\}$.

Moreover we observe that if $\xi_1, \xi_2 \in \mathbb{R}^S$ then $span\{\xi_1\} = span\{\xi_2\}$ and $span\{\alpha\xi_1 + \beta\xi_2, \alpha, \beta \in \mathbb{R}\} = span\{\xi_1, \xi_2\}$, then it's easy to see that both networks have also same stoichiometric subspace.

Thus to compute $r = dim(S)$ of a CRN, is easier to calculate that of a simplified network in which for each linkage class we chose one complex and we connect to it each other complex in that class with one link (as the second network in Figure 1.2). We will call this type of network "star-like".

Now, since the "star-like" network has obviously $m - l$ reaction vectors, we have necessarily:

$$r \leq m - l,$$

where m is the number of complexes. The equality holds only when the $m - l$ reaction vectors of the "star-like" network are *linearly independent*.

These considerations naturally lead us to the definition of a characteristic of CRNs, which will have a main role in our text.

Definition 1.1.11 (Deficiency)**.** We define *deficiency* of a CRN with m complexes, l linkage classes and rank s as:

$$\delta = m - l - r. \tag{4}$$

Hence δ is a measure of how independent the reaction vectors are, given the network's linkage class structure, and $\delta = 0$ if these are independent.

Before going ahead in hour study on CRN, we lastly dwell on an other really important property.

Definition 1.1.12 (Weak reversibility)**.** A Chemical Reaction Network is said to be *weak reversible* if $y \Rightarrow y'$ whenever $y' \Rightarrow y$.
If on the other hand we have that $y \to y' \in \mathcal{R}$ implies $y' \to y \in \mathcal{R}$ than we call the CRN *reversible*.

1.2 Kinetic

What we would like to do now that we have a model, is to attach it to a dynamic (so a kinetic model), in order to be able to describe the system evolution over time and to try to find its long run behaviour.
First of all we should ask ourselves how to represent the state of the system whose evolution we would like to study. There are two possibilities:

1. $x(t)$ gives the concentration of each species at instant t (which leads to the *deterministic model*).

2. $X(t)$ gives the number of entities we have for each species at instant t (which is the description at the base of the *stochastic model*)

We will analyze both options, but first we need to give some more definitions (see [4]).

Definition 1.2.1 (Kinetic)**.** Let $\mathcal{G}$ be a CRN and suppose that to each reaction $y \to y' \in \mathcal{R}$, there is associated a non-negative, continuously differentiable *rate function*

$\lambda_{y\to y'} : \mathbb{R}^n \to \mathbb{R}_{\geq 0}$.

By *kinetics* on $\mathcal{G}$ we mean that there is a correspondence between the reactions and the rate functions such:

$$\Lambda : (y \to y' \in \mathcal{R}) \to \lambda_{y\to y'}.$$

We call $(\mathcal{G}, \Lambda)$ a *reaction system*.

Definition 1.2.2. Let $(\mathcal{G}, \Lambda)$ be *reaction system* and let $\Gamma \subseteq \mathbb{R}^{\mathcal{S}}$. Then we define:

- $y \to y' \in \mathcal{R}$ is said to be *active* if $\lambda_{y\to y'}(x) > 0$ for some x. This holds if and only if $supp(y) \subseteq supp(x)$, with $supp(y) = \{s \in \{1, ..., n\} | y_s \neq 0\}$;
- the *active sub network* in Γ is the network determined by the reactions in $\mathcal{R}$ that are active in Γ. We refer to it with $\mathcal{G}_\Gamma$;
- Γ is called *active* if $\mathcal{G}_\Gamma = \mathcal{G}$, that is $\forall\, y \to y' \in \mathcal{R}\ \exists\, x \in \Gamma$ such that $\lambda_{y\to y'} > 0$.

Now we have the basis to analyze the two proposed dynamical system. Notice that if we do not state otherwise, we will refer for the deterministic one to [8] and [4], whereas for the stochastic one to [15] and [1].

Remark 1.2.3. Notice that with the introduction of the state space and looking at Definition 1.1.3, we can give the following interpretation: a reaction vector ξ is the vector that indicates the state transformation that takes place when a reaction occurs.

1.2.1 Deterministic model

Let $x = x(t) \in \mathbb{R}^n_0$ defined as above in the first case. In the deterministic model, given an initial condition $x(0) \in \mathbb{R}^n_0$, we have that the time evolution of the system is expressed by:

$$\frac{dx}{dt} = f(x), \tag{5}$$

with

$$f(x) = \sum_{y\to y' \in \mathcal{R}} \lambda_{y\to y'}(x)\,(y' - y); \tag{6}$$

f is called *species-formation-rate function*.

Hence, for each species s in the network, its evolution is expressed by the sum, over all the reactions in the network that involves s, of the rate at which each reaction occurs times the variation that the reaction causes for species s in the system.

Notice that $f(x) \in S$. That implies that $\forall t > 0\ x(t) \in \mathcal{P}_{x(0)} := (x(0) + S) \cap \mathbb{R}^n_{\geq 0}$. So, given the initial condition, the state of the system remains always in the same stoichiometric compatibility class.

If the compatibility class $\mathcal{P}_x$ is non empty, it is called *positive*.

Definition 1.2.4. $c \in \mathbb{R}^n$ is said to be an *equilibrium* of the deterministic reaction system if:

$$f(x) = \sum_{y \to y' \in \mathcal{R}} \lambda_{y \to y'}(x)(y' - y) = 0. \tag{7}$$

If $x \in \mathbb{R}^n_{>0}$, we say that x is a *positive equilibrium* and we denote it $x > 0$.

An important type of kinetics is the following one:

Definition 1.2.5 (Mass action kinetic)**.** We define *deterministic mass action kinetic* the correspondence $K_D : (y \to y') \to \lambda_{y \to y'}$, where

$$\lambda_{y \to y'}(x) = k_{y \to y'} x^y \mathbb{1}_{x \geq 0}, \tag{8}$$

where $x^y = \prod_{i=1}^n x_i^{y_i}$. The pair $(\mathcal{G}, K_D)$ is called *deterministic mass action system*.

1.2.2 Stochastic model

We will study now the stochastic model. The simplest one considers the state $X(t) \in Z^n_{\geq 0}$ as the number of entities/molecules of each species present at instant t and builds on the reaction network a *Continuous Time Markov Chain* in which $X(t)$ represents the state in t of the chain after all the transitions (in this case the reactions) occurred in $[0, t]$. For simplicity suppose a finite number of transitions.

So for example, if the chain is in state $X(t)$ and in $t + dt$ the reaction $y \to y'$ occurs, we have:

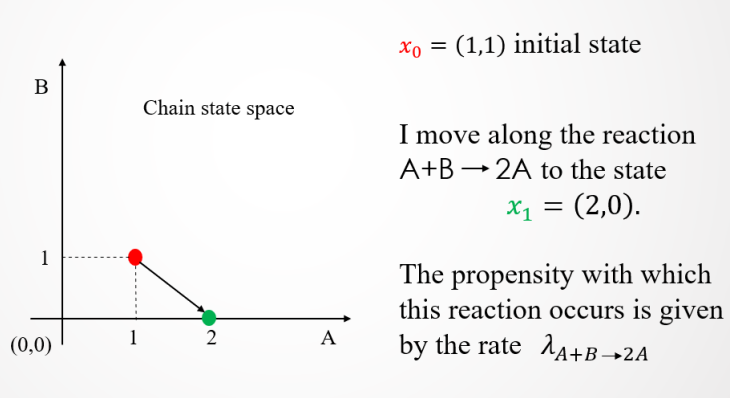

Figure 1.3

Markov chain on a Chemical Reaction Network

$$X(t+dt) = X(t) + y' - y.$$

If we denote with $R_{y\to y'}(t)$ the number of times that reaction $y \to y'$ occurs by time t, then the state of the system at time t can be written as:

$$X(t) = X(0) + \sum_{y\to y'\in\mathcal{R}} R_{y\to y'}(t)(y' - y).$$

Notice that $R_{y\to y'}(t)$ is a *counting process* with the intensity equal to the rate function $\lambda_{y\to y'}(X(t))$. So we can write:

$$R_{y\to y'}(t) = Y_{y\to y'}\left(\int_0^t \lambda_{y\to y'}(X(s))\,ds\right),$$

where $Y_{y\to y'}$ is for each reaction and independent unit-rate Poisson process.

After this premise, we can define:

Proposition 1.2.6. *The generator for the Continuous Markov chain* $(X(t))_t$ *is the operator A defined by:*

$$Af(x) = \sum_{y\to y'\in\mathcal{R}} \lambda_{y\to y'}(x)\big(f(x+y'-y) - f(x)\big), \tag{9}$$

where f is any measurable, bounded function defined on the state space.

So, if we suppose that the initial state of our Markov Chain is $X(0) = x_o$, by generator's properties we have:

$$\frac{d}{dt}\mathbb{E}_{x_0}[f(X(t)] = \mathbb{E}_{x_0}[Af(X(t))]. \tag{10}$$

Recalling that, if π_t is the distribution on $\mathbb{Z}^n$ of $X(t)$, then

$$\mathbb{P}(X(t) = y \mid X_0 = x_0) = \pi_t(y),$$

and we can re-write the previous expression as:

$$\frac{d}{dt}\sum_y f(y)\pi_t(y) = \sum_y Af(y)\pi_t(y). \tag{11}$$

Taking $f(y) = \mathbb{1}_x(y)$ we therefore have that the evolution over time of the CTMC defined on the CRN can be expressed by:

$$\frac{d\pi_t}{dt} = \sum_{y\to y'\in\mathcal{R}} \pi_t(x-y'+y)\lambda_{y\to y'}(x-y'+y) - \sum_{y\to y'\in\mathcal{R}} \pi_t(x)\lambda_{y\to y'}(x). \tag{12}$$

Remark 1.2.7. For a more detailed explanation of (9) and (11) see appendix A.

Similarly to before and as consequence of (12)we can define:

Definition 1.2.8. π measure on $\mathbb{Z}^n$ is said to be a stationary measure of the stochastic reaction system if $\pi_t = \pi,\ t$, that is:

$$\sum_{y\to y'\in\mathcal{R}} \pi(x-y'+y)\lambda_{y\to y'}(x-y'+y) = \sum_{y\to y'\in\mathcal{R}} \pi(x)\lambda_{y\to y'}(x), \quad \forall\, x\in\mathbb{Z}^n. \tag{13}$$

We also define $supp(\pi) = \min\{T \subseteq \mathbb{Z}^n \mid \pi(\mathbb{Z}^n \setminus T) = 0\}$.

Let now $(\mathcal{G}, \Lambda)$ be a stochastic reaction system. As well as for the CRN species space, we can define on the state space $\mathbb{Z}^n$ a concept similar to that of linkage classes.

Definition 1.2.9 (Accessibility)**.** Given $x, x' \in \mathbb{Z}^n$ states of the CTMC, we say that x' is accessible from x if either $x = x'$ or there exists a sequence of states $(x = v_0, v_1, ...v_{k-1}, v_k = x')$, such that $\forall\ (v_i, v_{i+1}), 0 \le i \le k-1$

$$\exists \text{ an active reaction } y \to y' \in \mathcal{R} \text{ at } v_i \text{ with } y' - y = v_{i+1} - v_i$$

Definition 1.2.10 (Irreducible component)**.** Let $\Xi \subseteq \mathbb{Z}^n$ be a nonempty set. Ξ is called *irreducible component* if $\forall\, x \in \Xi$, $\forall\, v \in \mathbb{Z}^n$, v is accessible from x if and only if $v \in \Xi$.

We have then that all stationary distributions of the CTMC describing the system can be expressed as:

$$\pi = \sum_{\Xi} \alpha_{Xi} \pi_{\Xi}, \qquad \alpha_{\Xi} \geq 0, \sum_{\Xi} \alpha_{\Xi} = 1, \tag{14}$$

which is a convex combination of the unique stationary distributions π_{Ξ} such that $\pi_{\Xi}(\Xi) = 1$, for those Ξ, irreducible components, for which a stationary distribution exists.

Lastly, we show also in this case two specific types of kinetics.

Definition 1.2.11 (Mass action kinetics)**.** We define *Stochastic mass action kinetics* the correspondences $K_S : (y \to y') \to \lambda_{y \to y'}$ where

$$\lambda_{y \to y'}(x) = k_{y \to y'} \frac{x!}{(x-y)!} \mathbb{1}_{\{x \geq y\}}, \qquad \forall\, x \in \mathbb{Z}^n. \tag{15}$$

The pair $(\mathcal{G}, K_S)$ is called *stochastic mass action system*.

Definition 1.2.12 (General kinetics)**.** It is possible to define a more general type of kinetics inspired to that of mass action one, with rate function in the form of:

$$\lambda_{y \to y'}(x) = k_{y \to y'} \prod_{s=1}^{n} \prod_{j=0}^{\nu_{s,k}-1} \theta_s(x_s - j), \tag{16}$$

where $\theta_i : \mathbb{Z} \to \mathbb{R}_{\geq 0}$, $\theta_i = 0$ if $x \leq 0$.

1.2.3 Quasi-thermostatic and quasi-thermodynamic kinetic systems

In this subsection we present the definition, from [8], of a different type of reaction systems.

The first type of system we consider is the following one:

Definition 1.2.13 (Quasi-thermostatic kinetic system)**.** Let $(\mathcal{G}, \Lambda)$ be a reaction system. And let $f : \mathbb{R}^{\mathcal{S}} \to S$ be the species-formation-rate function defined above. The system is said to be *quasi-thermostatic* if there exists a $x^* \in R^{\mathcal{S}}$ such that the set of *positive equilibria* is equivalent to the set:

$$E = \{x \in \mathbb{R}^{\mathcal{S}} \mid \ln x - \ln x^* \in S^{\perp}\}.$$

Proposition 1.2.14. *If* $(\mathcal{G}, \Lambda)$ *is a quasi-thermostatic system, then in each stoichiometric compatibility class there is exactly one equilibrium.*

Proof. Let us assume that there exist in one stoichiometric compatibility class two equilibria: x^1, x^2.
For definition of stoichiometric compatibility class we have that $x^2 - x^1 \in S$. Moreover the system is quasi-thermostatic, and so $\ln x^2 - \ln x^1 \in S^\perp$.
The following holds:

$$0 = \langle x^2 - x^1, \ln x^2 - \ln x^1 \rangle = \sum_{s \in \mathcal{S}} (x_s^2 - x_s^1)(\ln x_s^2 - \ln x_s^1).$$

Because the function $ln : \mathbb{R}_+ \to \mathbb{R}$ is strictly increasing, the equality can hold only if $x_s^1 = x_s^2 \; \forall \, s \in \mathcal{S}$. And this obviously concludes the proof. □

Then we define a second type of system as follows:

Definition 1.2.15 (Quasi-thermodynamic kinetic system)**.** A kinetic system $(\mathcal{G}, \Lambda)$ with stoichiometric subspace S and species-formation-rate function f is said to be *quasi-thermodynamic* if there exists a $x^* \in \mathbb{R}_+^{\mathcal{S}}$ such that the system is quasi-thermostatic with respect to x^* and

$$\langle (\ln x - \ln x^*), f(x) \rangle \leq 0, \quad \forall \, x \in \mathbb{R}_+^{\mathcal{S}},$$

with equality holding only if $f(x) = 0$ or if $\ln x - \ln x^* \in S^\perp$.

Proposition 1.2.16. *If* $(\mathcal{G}, \Lambda)$ *is a quasi-thermodynamic kinetic system, the followings hold within each stoichiometric compatibility class:*

1. *there is only one equilibrium*
2. *the equilibrium is asymptotically stable*
3. *there is no nontrivial cyclic trajectory along which all species concentrations are positive*

Proof. 1. The first is simple to prove because is direct consequence of the fact that a quasi-thermodynamic system is also quasi-thermostatic

2. For the second statement consider:

$$h(x) := \sum_{s\in\mathcal{S}} [x_s(\ln x_s - \ln x_s^* - 1) + x_s^*];$$

it's obvious to see that $h(x^*) = 0$.

Moreover, thanks to the concavity property of the logarithmic function it holds that:

$$\ln x_s - \ln x_s^* \geq \frac{1}{x_s}(x_s - x_s^*),$$

with equality holding if and only if $x_s = x_s^*$.

So we have $h(x) > 0, \forall\, x \neq x^*$.

Lastly:

$$\frac{d}{dt}h(x(t)) = \langle \nabla h(x(t)), \dot{x}(t)\rangle = \langle (\ln x - \ln x^*), f(x)\rangle \leq 0, \quad \forall\, x \in (x^* + S) \cap \mathbb{R}_+^{\mathcal{S}},\, x \neq x^*$$

Therefore for each stoichiometric compatibility class S and for the equilibrium x^* contained in it, we have that $h(x)$ restricted to S is a *strict Lyapunov function* for x^* on S. So x^* is asymptotically stable.

3. To show the last sentence, we suppose that there exists a solution $x : [0, T] \to R_+^{\mathcal{S}}$ with $x(t) = x(0)$. Then we can write:

$$h(x(T)) - h(x(0)) = \int_0^T \frac{d}{dt}h(x(t))dt = \int_0^T \langle \nabla h(x(t)), f(x)\rangle\, dt.$$

Because the solution is non constant, using the observation for h made at previous point, we can tell that the integrand is negative. So it holds $h(x(T)) < h(x(0))$, which is clearly a contradiction to the initial hypothesis.

□

2
Balancing

In this chapter we will talk about an important class of properties related to Chemical Reaction Networks and in particular to the graph structure underlying the system and the symmetry that this shows.

We can define a balancing concept both for deterministic and stochastic reaction systems, so we will discuss in detail each case separately.
Unless otherwise specified, the results shown in this section have to be considered taken from [4].

2.1 Balancing for deterministic kinetic systems

For the deterministic case the graph structure underlying the system network could lead to three different types of balancing:

Definition 2.1.1. Let $(\mathcal{G}, \Lambda)$ be a deterministic *reaction system* and let $c \in \mathbb{R}^n$ be a state of the network. Suppose as well that if $y \to y' \neq \mathcal{R}$ we can define $\lambda_{y \to y'} = 0$. Then:

1. c is called *reaction balanced* if $\forall\, y, y' \in C$ we have:

$$\lambda_{y \to y'}(c) = \lambda_{y' \to y}(c) \tag{17}$$

2. c is called *complex balanced* if $\forall\, y \in C$:

$$\sum_{y' \in C} \lambda_{y \to y'}(c) = \sum_{y' \in C} \lambda_{y' \to y}(c) \tag{18}$$

3. c is called *reaction vector balanced* if $\forall\, \xi \in \mathbb{R}^{\mathcal{S}}$:

$$\sum_{y \to y' \in \mathcal{R} | y' - y = \xi} \lambda_{y \to y'}(c) = \sum_{y \to y' \in \mathcal{R} | y' - y = -\xi} \lambda_{y \to y'}(c) \tag{19}$$

4. c is called *cycle balanced* if for every sequence of distinct complexes $(y_1, y_2, ..., y_j \subseteq C,\ j \geq 3)$ we have:

$$\prod_{i=1}^{j} \lambda_{y_i \to y_{i+1}}(c) = \prod_{i=1}^{j} \lambda_{y_{i+1} \to y_i}, \quad \text{with } y_{j+1} := y_1. \tag{20}$$

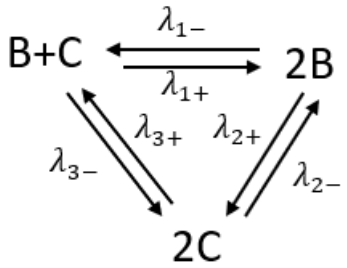

Figure 2.1

Example 2.1.2

Example 2.1.2. Consider the CRN shown in Figure 2.1. If $c \in \mathbb{R}^S$, then:

1. c is reaction balanced if:

$$\begin{cases} \lambda_{1+}(c) = \lambda_{1-}(c) \\ \lambda_{2+}(c) = \lambda_{2-}(c) \\ \lambda_{3+}(c) = \lambda_{3-}(c) \end{cases}$$

2. c is complex balanced if:

$$\begin{cases} \lambda_{1+}(c) + \lambda_{3-}(c) = \lambda_{1-}(c) + \lambda_{3+}(c) \\ \lambda_{2+}(c) + \lambda_{3-}(c) = \lambda_{2-}(c) + \lambda_{3+}(c) \\ \lambda_{1+}(c) + \lambda_{2-}(c) = \lambda_{1-}(c) + \lambda_{2+}(c) \end{cases}$$

3. c is reaction vector balanced if:

$$\begin{cases} \lambda_{2+}(c) = \lambda_{2-}(c) \\ \lambda_{1+}(c) + \lambda_{3+}(c) = \lambda_{1-}(c) + \lambda_{3-}(c) \end{cases}$$

4. c is cycle balanced if:

$$\lambda_{1+}(c)\lambda_{2+}(c)\lambda_{3+}(c) = \lambda_{1-}(c)\lambda_{2-}(c)\lambda_{3-}(c)$$

Definition 2.1.3. Let $(\mathcal{G}, \Lambda)$ be a deterministic reaction system.
Suppose that the system admits at least one equilibrium and that every active equilibrium is reaction balanced (or complex balanced or reaction vector balanced or cycle balanced, respectively). Then $(\mathcal{G}, \Lambda)$ is called *reaction balanced* (or *complex balanced* or *reaction vector balanced* or *cycle balanced*, respectively).

Now we express an important consequence provided by 2.1.1.

Theorem 2.1.4. *Let $(\mathcal{G}, \Lambda)$ be a deterministic reaction system and let $c \in \mathbb{R}^{\mathcal{S}}$. If one of the following holds:*

- *c is a reaction balanced state for the system*
- *c is a complex balanced state for the system*
- *c is a reaction vector balanced state for the system,*

then c is an equilibrium of $(\mathcal{G}, \Lambda)$.

Proof. For simplicity we will prove only that a reaction vector balanced state is an equilibrium. The proof of the other cases is based on reasoning very similar to that proposed.
Let $c \in \mathbb{R}^{\mathcal{S}}$ be a reaction vector balanced state. So it holds:

$$\sum_{y \to y' \in \mathcal{R} | y' - y = \xi} \lambda_{y \to y'}(c) = \sum_{y \to y' \in \mathcal{R} | y' - y = -\xi} \lambda_{y \to y'}(c).$$

If we sum over all $\xi \in \mathbb{R}^{\mathcal{S}}$ and multiply each terms by ξ we have:

$$0 = \sum_{\xi \in \mathbb{R}^{\mathcal{S}}} \left(\sum_{y \to y' \in \mathcal{R} | y' - y = \xi} \lambda_{y \to y'}(c) \right) \xi - \sum_{\xi \in \mathbb{R}^{\mathcal{S}}} \left(\sum_{y \to y' \in \mathcal{R} | y' - y = -\xi} \lambda_{y \to y'}(c) \right) \xi =$$

$$= \sum_{\xi \in \mathbb{R}^{\mathcal{S}}} \left[\sum_{y \to y' \in \mathcal{R} | y' - y = \xi} \lambda_{y \to y'}(c)\, \xi + \sum_{y \to y' \in \mathcal{R} | y' - y = -\xi} \lambda_{y \to y'}(c)\, (-\xi) \right] =$$

$$\sum_{y \to y' \in \mathcal{R}} \lambda_{y \to y'}(y' - y),$$

where the last equality holds if remembering the definition of $\xi = y' - y$.
Notice that this is exactly the expression of $f(c) = 0$ when c is an equilibrium. □

The following express the existing relations between the different types of balancing.

Theorem 2.1.5. *Let $(\mathcal{G}, \Lambda)$ be a deterministic reaction system and let $c \in \mathbb{R}^{\mathcal{S}}$. Then:*

1. *c reaction balanced $\implies$ c complex balanced, reaction vector balanced, cycle balanced*

2. *c complex balanced and cycle balanced $\implies$ c reaction balanced*

Now we report two results (taken from [8]) of fundamental importance for what will come later.

Theorem 2.1.6. *Consider a deterministic mass action system.*
If for a $k \in \mathbb{R}^{\mathcal{R}}$ (where k refers to a set of reaction rate constanst) the system $(\mathcal{G}, K_D)$ admits a positive reaction balanced equilibrium, then the following hold true:

1. *the mass action system is quasi-thermodynamic*

2. *reaction balancing obtains at every positive equilibrium regardless of stoichiometric compatibility class*

Proof. 1. Suppose that there exists a positive reaction balanced equilibrium c^*.
First of all remember, from(6) and (8) that:

$$f(c) = \sum_{y \to y' \in \mathcal{R}} k_{y \to y'} c^y (y' - y).$$

Now, suppose that the CRN is reversible. We can then define the set $\mathcal{R}^{\rightarrow} \subseteq \mathcal{R}$ as the subset containing half of the reactions in $\mathcal{R}$ such that if $y \to y' \in \mathcal{R}^{\rightarrow} \Rightarrow$ $y' \to y \notin \mathcal{R}^{\rightarrow}$.

We can accordingly write:

$$f(c) = \sum_{y \to y' \in \mathcal{R}^{\rightarrow}} \left[k_{y \to y'} c^{y} - k_{y' \to y} c^{y'} \right] (y' - y) = \sum_{y \to y' \in \mathcal{R}^{\rightarrow}} \hat{k}_{y \to y'} \left[\left(\frac{c}{c^*} \right)^{y} - \left(\frac{c}{c^*} \right)^{y'} \right] (y' - y),$$

where $\hat{k}_{y \to y'} = k_{y \to y'} c^{y} = k_{y' \to y} c^{y'}$, considering that $c*$ is reaction balanced.
Define now:

$$\mu(c) := \ln c - \ln c^*.$$

In this case we can write:

$$f(c) = \sum_{y \to y' \in \mathcal{R}^{\rightarrow}} \hat{k}_{y \to y'} \left[e^{\langle y, \mu(c) \rangle} - e^{\langle y', \mu(c) \rangle} \right] (y' - y),$$

and

$$\langle (\ln c - \ln c^*, f(c) \rangle = \sum_{y \to y' \in \mathcal{R}^{\rightarrow}} \hat{k}_{y \to y'} \left[e^{\langle y, \mu(c) \rangle} - e^{\langle y', \mu(c) \rangle} \right] \left[\langle y', \mu(c) \rangle - \langle y, \mu(c) \rangle \right]$$

Since the exponential function is strictly monotonically increasing, we have that:

$$\langle (\ln c - \ln c^*, f(c) \rangle \leq 0, \quad \forall\, c \in \mathbb{R}^{\mathcal{S}}_{+},$$

with the equality holding if and only if $\langle (y' - y), \mu(c) \rangle = 0$, that is when $\ln c - \ln c^* \in S^{\perp}$. Moreover, if c is an equilibrium (meaning that $f(c) = 0$), necessarily (1) must be zero and so $\ln c - \ln c^* \in S^{\perp}$ for what we said before. On the other hand, if c is such that $\ln c - \ln c^* \in S^{\perp}$ we have $\langle y, \mu(c) \rangle = \langle y', \mu(c) \rangle \quad \forall\, y \to y' \in \mathcal{R}^{\rightarrow}$. By placing this equality in (1) we have that c is inevitably an equilibrium.
Hence the system is quasi-thermostatic and (1) holds: by definition the system is quasi-thermodynamic

2. Suppose that c is a generic equilibrium for the system. Because of point 1. we have that $\ln c - \ln c^* \in S^{\perp}$ and so $\langle y, \mu(c) \rangle = \langle y', \mu(c) \rangle \quad \forall\, y \to y' \in \mathcal{R}^{\rightarrow}$. From this it follows that:

$$0 = \hat{k}_{y \to y'} \left[e^{\langle y, \mu(c) \rangle} - e^{\langle y', \mu(c) \rangle} \right] = k_{y \to y'} c^{y} - k_{y' \to y} c^{y'},$$

which is exactly the definition of a reaction balanced state.

□

Theorem 2.1.7. *Consider a deterministic mass action system.*
If the system $(\mathcal{G}, K_D)$ *admits a positive complex balanced equilibrium, then the followings hold true:*

1. *the mass action system is quasi-thermodynamic*
2. *complex balancing obtains at every positive equilibrium regardless of stoichiometric compatibility class*

Proof. 1. Consider as in the previous case the function defined in (6) and define the two subsets $\mathcal{R}_{\to y}, \mathcal{R}_{y\to} \subseteq \mathcal{R}$ as the set of reaction entering and exiting the complex y respectively. Suppose in addition that there exists a complex balanced equilibrium c^*.

We can then write:

$$f(c) = \sum_{y\in\mathcal{C}} \left[\sum_{\mathcal{R}_{\to y}} k_{y'\to y}(c)^{y'} - \sum_{\mathcal{R}_{y\to}} k_{y\to y'}(c)^{y} \right] y. \tag{21}$$

Now consider as before $\mu(c) := \ln c - \ln c^*$, defined $\forall\, c \in \mathbb{R}^{\mathcal{S}}_+$. We have:

$$\langle \mu(c), f(c)\rangle = \sum_{y\to y'\in\mathcal{R}} k_{y\to y'} c^y \langle (y'-y), \mu(c)\rangle =$$
$$\sum_{y\to y'\in\mathcal{R}} k_{y\to y'} (c^*)^y e^{\langle y,\mu(c)\rangle} (\langle y', \mu(c)\rangle - \langle y, \mu(c)\rangle),$$

which for the exponential property $e^x(x'-x) \le e^{x'} - e^x$, is:

$$\langle \mu(c), f(c)\rangle \le \sum_{y\to y'\in\mathcal{R}} k_{y\to y'} (c^*)^y (e^{\langle y',\mu(c)\rangle} - e^{\langle y,\mu(c)\rangle}) =$$
$$\sum_{y\in\mathcal{C}} \left[\sum_{\mathcal{R}_{\to y}} k_{y'\to y}(c^*)^{y'} - \sum_{\mathcal{R}_{y\to}} k_{y\to y'}(c^*)^{y} \right] e^{\langle y,\mu(c)\rangle} = 0,$$

where the last equality holds because c^* is complex balanced.

Notice also that the inequality becomes an equality if and only if $\langle y', \mu(c)\rangle = \langle y, \mu(c)\rangle$ for every $y \to y' \in \mathcal{R}$, which is exactly when $\mu(c) \in S^{\perp}$.

Now to conclude the proof of the first point we must show that the set of positive

equilibria is of the form express by (1.2.13).

We first notice that if $f(c) = 0$ then necessarily $\mu(c) = \ln c - \ln c^* \in S^\perp$. Consider on the other hand $c \in \mathbb{R}^{\mathcal{S}}_+ \mid \ln c - \ln c^* \in S^\perp$. Using (21) we can write:

$$f(c) = \sum_C \left[\sum_{\mathcal{R}_{\to y}} k_{y' \to y} (c^*)^{y'} e^{\langle y', \mu(c) \rangle} - \sum_{\mathcal{R}_{y \to}} k_{y \to y'} (c^*)^y e^{\langle y, \mu(c) \rangle} \right] y =$$

$$\sum_{y \in C} e^{\langle y, \mu(c) \rangle} \left[\sum_{\mathcal{R}_{\to y}} k_{y' \to y} (c^*)^{y'} - \sum_{\mathcal{R}_{y \to}} k_{y \to y'} (c^*)^y \right] y = 0,$$

where the last equality holds because $\mu(c) \in S^\perp \Rightarrow \langle y' - y, \mu(c) \rangle = 0 \; \forall \, y' \mid y \to y' \in \mathcal{R}$ or $y' \to y \in \mathcal{R}$. So c is an equilibrium.

2. Suppose that $\hat{c} \in \mathbb{R}^{\mathcal{S}_+}$ is an other equilibrium different from c^*. Then for what we stated before we have that $\langle y' . y, \mu(\hat{c}) \rangle = 0 \; \forall \, y, y' \mid y \to y' \in \mathcal{R}$ or $y' \to y \in \mathcal{R}$. So we can write:

$$\sum_{\mathcal{R}_{\to y}} k_{y' \to y} (\hat{c})^{y'} - \sum_{\mathcal{R}_{y \to}} k_{y \to y'} (\hat{c})^y =$$

$$\sum_{\mathcal{R}_{\to y}} k_{y' \to y} (c^*)^{y'} e^{\langle y', \mu(\hat{c}) \rangle} - \sum_{\mathcal{R}_{y \to}} k_{y \to y'} (c^*)^y e^{\langle y, \mu(\hat{c}) \rangle} =$$

$$e^{\langle y, \mu(\hat{c}) \rangle} \left[\sum_{\mathcal{R}_{\to y}} k_{y' \to y} (c^*)^{y'} - \sum_{\mathcal{R}_{y \to}} k_{y \to y'} (c^*)^y \right] = 0,$$

where the last it is true because we have initially supposed c^* to be complex balanced. So even $\hat{c}$ satisfies the complex balance condition.

□

Remark 2.1.8. Notice that no theorem such as the ones stated before holds for an equilibrium which is reaction vector balanced. Indeed if we consider the reaction network:

$$\emptyset \leftrightarrows A \qquad 2A \leftrightarrows 3A,$$

we could see that the system admits for $k_{\emptyset \to 2A} = 6$, $k_{A \to \emptyset} = 11$, $k_{2A \to 3A} = 6$, $k_{3A \to 2A} = 1$ three distinct positive reaction vector balanced equilibria $c = 1$, $c = 2$, $c = 3$ within the same positive stoichiometric compatibility class. So the system is neither quasi-thermostatic nor consequently quasi-thermodynamic.

2.2 Balancing for stochastic kinetic systems

Definition 2.2.1. Let $(\mathcal{G}, \Lambda)$ be a stochastic reaction system.
Suppose that π is a measure on $\mathbb{Z}^n$ and that we can take $\lambda_{y\to y'} = 0$ if $y \to y' \notin \mathcal{R}$. Then we can define the following:

- π is called *reaction balanced measure* if $\forall\, y, y' \in C$, $x \in \mathbb{Z}^n$

$$\pi(x)\lambda_{y\to y'}(x) = \pi(x + y' - y)\lambda_{y'\to y}(x + y' - y) \tag{22}$$

- π is called *complex balanced measure* if $\forall\, y \in C$, $x \in \mathbb{Z}^n$

$$\pi(x)\sum_{y'\in C}\lambda_{y\to y'}(x) = \sum_{y'\in C}\pi(x + y' - y)\lambda_{y'\to y}(x + y' - y) \tag{23}$$

- π is called *reaction vector balanced measure* if $\forall\, \xi$, $x \in \mathbb{Z}^n$

$$\pi(x)\sum_{y\to y'\in\mathcal{R}|y'-y=\xi}\lambda_{y\to y'}(x) = \pi(x+\xi)\sum_{y\to y'\in\mathcal{R}|y'-y=-\xi}\lambda_{y\to y'}(x+\xi) \tag{24}$$

- π is said to be *generalized balanced* [9] if there exists a set of tuples of subsets of $\mathcal{R}$, $\{(L_i, R_i)_{i\in A}\}$, with

$$\dot{\bigcup}_{i\in A} L_i = \dot{\bigcup}_{i\in A} R_i = \mathcal{R},$$

  such that $\forall\, i \in A$ and $\forall\, x \in \mathbb{Z}^n$ it holds:

$$\sum_{y\to y'\in L_i}\pi(x + y - y')\lambda_{y\to y'}(x + y - y') = \pi(x)\sum_{y\to y'\in R_i}\lambda_{y\to y'}(x). \tag{25}$$

  Notice that this definition of balancing is a generalization of the previous three defined above.

- π is called *cycle balanced measure* if $\forall\, x \in \mathbb{Z}^n$ and for every sequence of distinct complexes $(y_1, y_2, ..., y_j) \subseteq C$, $j \geq 3$, it holds

$$\prod_{i=1}^{j}\pi(x + y_i)\lambda_{y_i\to y_{i+1}}(x + y_i) = \prod_{i=1}^{j}\pi(x + y_{i+1})\lambda_{y_{i+1}\to y_i}(x + y_{i+1}) \tag{26}$$

Definition 2.2.2. Let $(\mathcal{G}, \Lambda)$ be a stochastic reaction system. If the system has at least one stationary distribution within an active irreducible component and every stationary

distribution within an active irreducible component is reaction balanced (or complex balanced, or reaction vector balanced, or cycle balanced, respectively). Then we say that $(\mathcal{G}, \Lambda)$ is a reaction balanced (or complex balanced, or reaction vector balanced, or cycle balanced, respectively) reaction system.

Just as in the deterministic case, it is also easy to prove that the followings hold:

Theorem 2.2.3. *Let $(\mathcal{G}, \Lambda)$ be a stochastic reaction system. Suppose that π is a measure for the system. If one of the following holds:*

- *π is a reaction balanced measure*
- *π is a complex balanced measure*
- *π is a reaction vector balanced measure,*

then π is a stationary measure of $(\mathcal{G}, \Lambda)$.

We express then the relations existing between different types of stochastic balancing.

Theorem 2.2.4. *Let $(\mathcal{G}, \Lambda)$ be a stochastic reaction system. The followings hold:*

- *π reaction balanced measure $\Longrightarrow$ π reaction vector balanced, complex balanced, cycle balanced measure*
- *π complex balanced and cycle balanced measure $\Longrightarrow$ π reaction balanced measure.*

The other possible implications do not hold.

The theorem that now we will present below is a fundamental connection between the stochastic and deterministic modeling of a Chemical Reaction Network, and in particular it defines a connection between the existence of a complex balanced

equilibrium and of a corresponding complex balanced stationary measure in the reaction system.

Theorem 2.2.5. *Let $\mathcal{G}$ be a Chemical Reaction Network and let $k \in \mathbb{R}^{\mathcal{R}}$ be a choice of rate constant for the mass-action system. Suppose that the system, which such a choice of rates, is complex balanced and so admits a complex balanced equilibrium $c \in \mathbb{R}^n_{>0}$. Then the stochastically model system with rate functions defined as in (15), admits a complex balanced stationary distribution which has the following Poisson form:*

$$\pi(x) = \prod_{s=1}^{n} \frac{c_s^{x_s}}{x_s!} e^{-c_s}, \quad x \in \mathbb{Z}^n_{\geq 0}. \tag{27}$$

Moreover, if $\mathbb{Z}^n_{\geq 0}$ is irreducible, then the one above is the unique stationary distribution of the system, whereas if not we can express π as in (14) *with:*

$$\pi_{\Xi}(x) = \begin{cases} M_{\Xi} \prod_{s=1}^{n} \frac{c_s^{x_s}}{x_s!}, & x \in \Xi \\ 0, & x \notin \Xi, \end{cases} \tag{28}$$

where Ξ is a irreducible component of the system, and M_{Ξ} a normalization constant.

Proof. (by [15]) The measure defined in (27) is a distribution by definition ($\sum_x \pi(x) = 1$). then we have to show that a such defined π satisfies the stationary conditions in (13) only if c is a complex balanced equilibrium for the system.
So, suppose that (13) holds, we write (making easy simplifications):

$$\sum_{y \to y' \in \mathcal{R}} k_{y \to y'} \frac{1}{(x-y)!} \mathbb{1}_{\{x \geq y\}} = \sum_{y \to y' \in \mathcal{R}} k_{y \to y'} c^{y-y'} \frac{1}{(x-y')} \mathbb{1}_{\{x \geq y'\}}$$

$$\sum_{\eta \in C} \sum_{y \to y' \in \mathcal{R} | y = \eta} k_{\eta \to y'} \frac{1}{(x-\eta)!} \mathbb{1}_{\{x \geq \eta\}} = \sum_{\eta \in C} \sum_{y \to y' \in \mathcal{R} | y' = \eta} k_{y \to \eta} c^{y-\eta} \frac{1}{(x-\eta)} \mathbb{1}_{\{x \geq \eta\}}.$$

So for each $x \in \mathbb{Z}^n$ and for each fixed $\eta \in C$, if we multiply by $c^{\eta}(x-\eta)!$ it must hold:

$$\sum_{y \to y' \in \mathcal{R} | y = \eta} k_{\eta \to y'} c^{y} = \sum_{y \to y' \in \mathcal{R} | y = \eta} k_{\eta \to y'} c^{\eta} = \sum_{y \to y' \in \mathcal{R} | y' = \eta} k_{y \to \eta} c^{y},$$

which is the complex balanced equation for c written for a deterministic mass action system with rate function given by (8). □

Remark 2.2.6. It should be noticed that Theorem 2.2.5, when $\mathbb{Z}^n$ is not irreducible, it doesn't require for the equilibrium c used for the construction of the different distribution π_Ξ to be contained within the stoichiometric compatibility class associated with Ξ. On the contrary the Theorem establishes that c can be used to construct a product-form stationary distribution for every closed, irreducible component of the network and viceversa that for a given irreducible component Ξ any positive equilibrium of the system can be used to construct π_Ξ.
The validity of this statement seems to go against the uniqueness of the stationary distribution. However [1] proves this is not true.

Let Ξ be a closed irreducible set associated with the stoichiometric compatibility class $(y+S)\cap\mathbb{Z}^n_{\geq 0}$, and let $c_1, c_2 \in \mathbb{R}^n_{>0}$ be two complex balanced equilibria of the system. Lastly let $x \in \Xi$.
As a consequence of the theorem we can construct two distributions:

$$\pi_i(x) = M_i \frac{c_i^x}{x!},\ i = 1,2.$$

So, for each $x \in \Xi \subset y+S$, we have:

$$\frac{\pi_1(x)}{\pi_2(x)} = \frac{M_1}{M_2}\frac{c_1^x}{c_2^x} = \frac{M_1}{M_2}e^{\langle x,(\ln c_1 - \ln c_2)\rangle} = \frac{M_1}{M_2}e^{\langle y,(\ln c_1 - \ln c_2)\rangle} = \frac{M_1}{M_2}\frac{c_1^y}{c_2^y},$$

where the third equality holds from point 1 in 2.1.7.
In the end we can write:

$$\begin{gathered} 1 = \frac{\left(M_1 \sum_{x\in\Xi}\frac{c_1^x}{x!}\right)}{\left(M_2 \sum_{x\in\Xi}\frac{c_2^x}{x!}\right)} = \\ \frac{M_1}{M_2}\frac{\left(\frac{c_1^y}{c_2^y}\sum_{x\in\Xi}\frac{c_2^x}{x!}\right)}{\left(\sum_{x\in\Xi}\frac{c_2^x}{x!}\right)} = \frac{\pi_1(x)}{\pi_2(x)}. \end{gathered} \tag{29}$$

Then the stationary distribution is independent from c.

Remark 2.2.7. It can be proved (see [1]) that there exists an equivalent theorem as 2.2.5 when we consider a stochastic model of CRNs. defined with rate function as in (16). In this case the stationary distribution take the form:

$$\pi(x) = M\prod_{s=1}^{n}\frac{c_s^{x_s}}{\prod_{j=1}^{x_s}\theta_s(j)},\ x \in \mathbb{Z}^n_{\geq 0}. \tag{30}$$

On completion of this chapter, we present below further results related to the interconnection between the balancing properties in the deterministic and stochastic mass action model of a CRN.

Theorem 2.2.8. *Let $(\mathcal{G}, K_D)$ be a deterministic mass action system and let $(\mathcal{G}, K_S)$ be the corresponding stochastic mass action system. The followings hold:*

- *$(\mathcal{G}, K_D)$ is reaction balanced if and only if $(\mathcal{G}, K_S)$ is reaction balanced.*
- *$(\mathcal{G}, K_D)$ is complex balanced if and only if $(\mathcal{G}, K_S)$ is complex balanced.*
- *$(\mathcal{G}, K_D)$ is cycle balanced if and only if $(\mathcal{G}, K_S)$ is cycle balanced.*
- *if $(\mathcal{G}, K_D)$ is reaction balanced then $(\mathcal{G}, K_S)$ is reaction vector balanced and the converse holds if the function*

  $$y \to y' \longrightarrow y' - y$$

  is a one-to-one correspondence between the reactions in $\mathcal{R}$ and their reaction vectors.
- *if $(\mathcal{G}, K_S)$ is reaction vector balanced and complex balanced, then $(\mathcal{G}, K_D)$ is reaction balanced.*

3
Deficiency Theorem

In this chapter we will state and in some cases prove three main results about the existence of a stationary distribution for a Chemical Reaction Network under specific conditions of the network graph. In particular we aim to highlight the logic path that leads to the definition of the necessary conditions for the existence of a stationary distribution which starts from the properties of a deterministic reaction network, goes through the concept of balancing and then gets to the properties of stochastic reaction networks discussed in the previous chapters. The logical thread that we will follow will be inspired by the one adopted in [8], [15] and [4]. It is therefore recommended to refer to it for any statement that will be presented without proof.

3.1 Deficiency zero Theorem for weak-reversible networks

Theorem 3.1.1. *Let $\mathcal{G} = \{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a Chemical Reaction Network modelled both deterministically and stochastically with a mass-action kinetic. If the network is weak-reversible and has deficiency zero, then for any choice of rate constants $\{k_i\}_i$ there exists in each irreducible set Ξ, associated to a stoichiometric compatibility class, a stationary distribution given by the Poisson product form:*

$$\pi_{\Xi}(x) = \begin{cases} M_{\Xi} \prod_{s=1}^{n} \frac{c_s^{x_s}}{x_s!}, & x \in \Xi \\ 0, & x \notin \Xi. \end{cases} \tag{31}$$

The theorem is extremely important because it guarantees only by the properties of the graph under the CRN, not only the existence of a stationary distribution, but it also gives the form in which such distribution occurs.

We divide the proof into 3 logical steps:

1. Complex balanced equilibria
2. Existence of an equilibrium for the deterministic mass-action system

3. Existence of a Poisson product stationary distribution for the stochastic mass-action system

3.1.1 Complex balanced equilibria

First of all suppose that there exists at least an equilibrium for the deterministic mass action system. We should ask ourselves the following questions: does this equilibrium have any properties? If this is the case does any other equilibrium of the system have the same property? What follows from this?
We will try to answer in this section.

In order to start we introduce the followings

Definition 3.1.2. We define *Stoichiometric map* for a CRN $\mathcal{G}$, the linear transformation $Y : \mathbb{R}^C \longrightarrow \mathbb{R}^S$ such that:

$$Y\omega_y = y, \qquad \forall\, y \in C, \tag{32}$$

where $\{\omega_y\}_y$ are the standard basis for $\mathbb{R}^C$ as defined in 1.1.

Using this mapping we could rewrite the species-formation-rate function defined in (6) as:

$$f(c) = Y \sum_{y \to y' \mathcal{R}} \lambda_{y \to y'}(c)(\omega_{y'} - \omega_y). \tag{33}$$

Definition 3.1.3 (Complex-formation-rate function)**.** We define *complex-formation-rate function* $g : \mathbb{R}^S \longrightarrow \mathbb{R}^C$ for a CRN $\mathcal{G}$, the function:

$$g(c) = \sum_{y \to y' \mathcal{R}} \lambda_{y \to y'}(c)(\omega_{y'} - \omega_y). \tag{34}$$

Notice that if we rewrite g in the form:

$$g(c) = \sum_{y \in C} \left[\sum_{\mathcal{R} \to y} \lambda_{y' \to y}(c) - \sum_{\mathcal{R} y \to} \lambda_{y \to y'}(c) \right] \omega_y,$$

it is obvious to see that if $g(c^*) = 0$, for a $c^* \in \mathbb{R}^S$, then a **complex balancing** occurs at c^*.

Note also that the function g takes values in the span of the set:

$$\Delta_{\rightarrow} := \{\omega_{y'} - \omega_y \in \mathbb{R}^C \mid y \rightarrow y' \in \mathcal{R}\}. \tag{35}$$

Since $y \rightarrow y' \in \mathcal{R}$ implies that y, y' are linked, it follows that if we define:

$$\Delta := \{\omega_{y'} - \omega_y \in \mathbb{R}^C \mid y \sim y'\} \tag{36}$$

we have

$$span(\Delta_{\rightarrow}) \subset span(\Delta). \tag{37}$$

Moreover the following can be proved:

Lemma 3.1.4. *For a CRN $\mathcal{G}$ with n complexes and l linkage classes it holds that*

$$span(\Delta_{\rightarrow}) = span(\Delta), \tag{38}$$

and

$$dim(span(\Delta_{\rightarrow})) = dim(span(\Delta)) = n - l. \tag{39}$$

We now return to the main hypothesis, that is, we assume that there exists for the CRN an equilibrium c^*. Then it must hold:

$$f(c^*) = Y\, g(c^*) = 0,$$

that is $g(c^*) \in \ ker(Y)$.
Recalling from what said before then we must have:

$$g(c^*) \in \ ker(Y) \cap span(\Delta).$$

Proposition 3.1.5. *If $\mathcal{G}$ is a CRN with stoichiometric map Y, deficiency δ and Δ defined as in* (36)*, then:*

$$\delta = dim\left[ker(Y) \cap span(\Delta)\right]. \tag{40}$$

Proof. Let $\hat{Y} : span(\Delta) \longrightarrow \mathbb{R}^{\mathcal{S}}$ be the restriction of Y to $span(\Delta)$. By standard geometry we have:

$$dim(span(\Delta)) = dim(ker(\hat{Y})) + dim(Im(\hat{Y})).$$

Moreover notice that:

- $\hat{Y}(\omega_{y'} - \omega_y) = y' - y$, so $dim(Im(\hat{Y})) = dim(S) = r$.
- $ker(\hat{Y}) = ker(Y) \cap span(\Delta)$.

By 3.1.4 and 1.1.11 we have:

$$dim\big[ker(Y) \cap span(\Delta)\big] = n - l - r = \delta.$$

□

It follows then that if $\mathcal{G}$ has zero deficiency, $dim\big[ker(Y) \cap span(\Delta)\big] = 0$ and so, necessarily, $g(c^*) = 0$.
We can then state:

Theorem 3.1.6. *Complex balancing occurs at every equilibrium of a kinetic system in which the underlying reaction network has a deficiency of zero.*

3.1.2 Existence of an equilibrium for the deterministic mass-action system

In 3.1.1 we showed that if there exists an equilibrium c^* in a CRN with deficiency zero, then complex balancing occurs at that equilibrium. However we have not shown that such an equilibrium exists. This will be the objective of this section.

Let $(\mathcal{G}, \mathcal{K}_D)$ be a deterministic mass-action network. We recall that for such a system, the rate function takes the form:

$$\lambda_{y \to y'}(c) = k_{y \to y'} c^y. \qquad \forall\, c \in \mathbb{R}^S_+,\ \forall\, y \to y' \in \mathcal{R}.$$

In this case we have that the complex-formation-rate function takes the form:

$$g(c) = \sum_{y \to y' \in \mathcal{R}} k_{y \to y'} c^y (\omega_{y'} - \omega_y). \tag{41}$$

Let define the followings linear transformations:

- $A_k : \mathbb{R}^C \longrightarrow \mathbb{R}^C$ such that

$$A_k x := \sum_{y \to y' \in \mathcal{R}} k_{y \to y'} x_y (\omega_{y'} - \omega_y), \tag{42}$$

where x_y is the y^{th} component of x.

- $\Psi : \mathbb{R}_+^{\mathcal{S}} \longrightarrow \mathbb{R}_+^{\mathcal{C}}$ such that

$$\Psi(c) = \sum_{y \in C} c^y \omega_y. \tag{43}$$

With these two new mappings we could rewrite the species-formation-rate and the complex-formation-rate functions as follows:

$$\begin{aligned} f(c) &= Y A_k \Psi(c), \\ g(c) &= A_k \Psi(c). \end{aligned} \tag{44}$$

Then, if we are studying the existence of an equilibrium for the system, we must ask ourselves for which $c \in \mathbb{R}_+^{\mathcal{S}}$ it holds $\Psi(c) \in ker(Y A_k)$.
Notice that if $c \in \mathbb{R}_+^{\mathcal{S}}$ then $\Psi(c) \in \mathbb{R}_+^{\mathcal{C}}$, so we are interested in the study of

$$ker(Y A_k) \cap \mathbb{R}_+^{\mathcal{C}}.$$

We should also observe that if $\Psi(c) \in ker(A_k) \subset ker(Y A_k)$ then $g(c) = 0$ and complex balancing occurs at c, which is an interesting case for our study. However in general for each equilibrium c does not hold $c \in ker(A_k)$. The following statement comes fortunately on our aid.

Lemma 3.1.7. *If a deterministic mass-action network $(\mathcal{G}, \mathcal{K}_D)$ has deficiency zero, then for any $k \in \mathbb{R}^{\mathcal{R}}$ it holds*

$$ker(Y A_k) = ker(A_k). \tag{45}$$

Then under the hypothesis of deficiency zero an equilibrium exists if and only if $\Psi(c) \in ker(A_k)$.

Therefore to conclude we should study the set $ker(A_k) \cap \mathbb{R}_+^{\mathcal{R}}$ and ask ourselves when such set contains at least one point.
The answer is given by the following statement, proved in [8].

Corollary 3.1.8. *Let $(\mathcal{G},\mathcal{K}_D)$ be a deterministic mass-action network. and let $k \in \mathbb{R}^{\mathcal{R}}_+$. Then $ker(A_k) \cap \mathbb{R}^{\mathcal{R}}_+$ is nonempty if and only if the network is* ***weak-reversible****.*

Then by putting together 3.1.8 and 3.1.7 we can state the following:

Proposition 3.1.9. *Let $(\mathcal{G},\mathcal{K}_D)$ be a deterministic mass-action network with deficiency zero. Then there exists a positive equilibrium c^* if and only if the network is weak-reversible.*

3.1.3 Existence of a Poisson product stationary distribution for the stochastic mass-action system

In 3.1.2 we proved that if a deterministic mass action system $(\mathcal{G},\mathcal{K}_D)$ is weak-reversible and has deficiency zero, then there exists at least a positive equilibrium c^*. Moreover in 3.1.1 we proved that such equilibrium is complex balanced.
At this point, recalling 2.1.7 we can state that:

- within each stoichiometric compatibility class there is only one equilibrium which is asymptotically stable;
- complex balancing obtains at every positive equilibrium regardless of stoichiometric compatibility class,

then by definition 2.1.3 **the system is complex balanced**.
Hence the proof simply ends applying Theorem 2.2.5.

3.2 Deficiency zero Theorem for reversible Forest-like networks

Theorem 3.2.1. *Let $\mathcal{G}$ be a reversible forest-like deficiency zero reaction network. Then for any assignment of rate constants $k \in \mathbb{R}^{\mathcal{R}}_+$ the resulting stochastic mass-action*

system admits in each irreducible set Ξ, associated to a stoichiometric compatibility class, a stationary distribution given by the Poisson product form:

$$\pi_{\Xi}(x) = \begin{cases} M_{\Xi} \prod_{s=1}^{n} \frac{c_s^{x_s}}{x_s!}, & x \in \Xi \\ 0, & x \notin \Xi. \end{cases} \tag{46}$$

Proof. Noting the stronger reversibility hypothesis of the network, we concentrate this proof not on complex balancing as before but on reaction balancing instead. We write then the species-formation-rate function as follows:

$$f(c) = \sum_{y \to y' \in \mathcal{R}} \left[\lambda_{y \to y'}(c) - \lambda_{y' \to y}(c) \right] (y' - y). \tag{47}$$

Clearly as stated in 2.1.4 if $c^* \in \mathbb{R}_+^{\mathcal{S}}$ is a state at which reaction balancing occurs, then c^* is an equilibrium. The converse is not necessarily true. However it's easy to see that in the special case in which the set of reaction vectors

$$\{y' - y \in \mathbb{R}^{\mathcal{S}} \mid y \to y' \in \mathcal{R}^{\rightarrow}\} \tag{48}$$

is independent, then **reaction balancing must occur at every equilibrium**.
Since by Definition 1.1.4 the set (48) is a set of generators for the stoichiometric subspace, it will be independent precisely when the number of vectors in (48) is equal to $dim(S) = r$.

Consider now the case in which the network is forest like. By a standard result in graph theory we have that for a forest:

$$e = v + \hat{l},$$

where e is the number of edges, v is the number of vertices and $\hat{l}$ is the number of connected components. It follows that:

$$r = m - l,$$

where r is the rank of the network, m is the number of complexes and l the number of linkage classes.
Then, recalling the definition of deficiency in 1.1.11 the following holds:

Theorem 3.2.2. *Reaction balancing obtains at every equilibrium of a kinetic system in which the underlying reaction network is forest-like and has deficiency zero.*

Now we associate the system with a deterministic mass-action kinetics. The following proposition holds:

Proposition 3.2.3. *Let $\mathcal{G}$ be a reversible forest-like deficiency zero reaction network. Then for any choice of $k \in \mathbb{R}^{\mathcal{R}}_+$, there exists a detailed balanced positive equilibrium.*

Proof. We'd like to prove the existence of $c^* \in \mathbb{R}^{\mathcal{S}}_+$ such that:

$$k_{y\to y'}(c^*)^y = k_{y'\to y}(c^*)^{y'}, \quad \forall\, y \to y' \in \mathcal{R}^{\rightarrow},$$

which is equivalent to prove the existence of a vector $\ln c \in \mathbb{R}^{\mathcal{S}}$ that satisfies:

$$\langle (y' - y), \ln c^* \rangle = \ln \frac{k_{y\to y'}}{k_{y'\to y}}, \quad \forall\, y \to y' \in \mathcal{R}^{\rightarrow}.$$

Because the network is forest-like and has deficiency zero, the set (48) is independent. Then it is a standard result of linear algebra that, in a vector space with scalar product, the set of equations $a_i \cdot x = b_i, \quad i = 1, ..., w$ admits a solution if $\{a_1, .., a_w\}$ is independent and $\{b_1, ..., b_w\}$ is a set of scalars.
Then it is enough to take $c^* = \exp\{\ln c^*\}$. □

Using the results given by 3.2.3 and recalling Theorem 2.1.6 we just proved that for any choice of rate constants $k \in \mathbb{R}^{\mathcal{R}}_+$, if a deterministic mass action system $(\mathcal{G}, \mathcal{K}_D)$ is forest-like and has deficiency zero, then:

- within each stoichiometric compatibility class there is only one equilibrium which is asymptotically stable;
- reaction balancing obtains at every positive equilibrium regardless of stoichiometric compatibility class,

then by definition 2.1.3 **the system is reaction balanced**. Moreover, recalling the relations stated in 2.1.5, the system is also complex balanced.
Hence the proof simply ends applying Theorem 2.2.5. □

3.3 Deficiency One Theorem for weak-reversible networks

Theorem 3.3.1 (Deficiency One Theorem)**.** *Let $\mathcal{G} = \{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a Chemical Reaction Network modelled both deterministically and stochastically with a mass-action kinetics. Suppose that the network is weak-reversible and it has l linkage classes, each containing one terminal strong-linkage class.*
If the following conditions between the deficiency of the network (δ) and the deficiencies of the individual linkage classes (δ_θ, $\theta = 1, ..., l$) hold:

1. $\delta_\theta \leq 1, \qquad \theta = 1, ..., l;$
2. $\sum_{\theta=1}^{l} \delta_\theta = \delta,$

then for any choice of rate constants $\{k_i\}_i$ there exists in each irreducible set Ξ, associated to a stoichiometric compatibility class, a stationary distribution given by the Poisson product form:

$$\pi_\Xi(x) = \begin{cases} M_\Xi \prod_{s=1}^{n} \frac{c_s^{x_s}}{x_s!}, & x \in \Xi \\ 0, & x \notin \Xi. \end{cases}$$

Part II

4
Loops on a Chemical Reaction Network

In this part of the thesis we aim to explore new aspects concerning Chemical Reaction Networks. In particular we will start our dissertation displaying the contents and the results of an unpublished article draft [5], and then we will try to extend this results.

The main innovation brought by the article consists in defining a new notion of balance, defined on loops which could be generated moving from one state to another along reactions. We proceed giving a formal definition of a loop.

4.1 Loop and sets of loops

Definition 4.1.1 (Weighted reaction vector loop)**.** Let $(\mathcal{G}, \Lambda)$ be a stochastic reaction network and let $\Upsilon \subseteq \mathbb{Z}^n_{\geq 0}$ be a closed set.
We define *weighted reaction vector loop* for $\mathcal{S}$ a finite sequence:

$$\gamma = ((\xi_i, p_i))_{i=1}^n, \tag{49}$$

such that the following hold:

1. $\xi_i \in \{y' - y \mid y \to y' \in \mathcal{R}\}$, $\forall\, i$ and:

$$\sum_{i=1}^{n} \xi_i = 0;$$

2. $p_i : \Upsilon \to \mathbb{R}_{\geq 0}$ $\forall\, i$ and:

$$p_i(x) \leq \sum_{y \to y' \in \mathcal{R} | y' - y = \xi_i} \lambda_{y \to y'}(x) \qquad \forall\, x \in \Upsilon; \tag{50}$$

3. $\forall\ 1 \leq i \leq n$, $x \in \Upsilon$ it must hold that $p_1(x) \neq 0$ if and only if $p_{i+1}(x + \xi_i) \neq 0$, with $p_{n+1} = p_1$.

We can observe that Condition 1. is the simply statement that γ is a loop and so the changes caused by the reactions in the system must be zero when we go through the whole loop.

Condition 2. states that we are assigning at each reaction vector in the loop a weight p_i (which more or less denote the propensity with which that state change will occur moving along the loop) but, more important, it states that this weight does not always coincide but it could be smaller than the sum of the rates of all reactions whose reaction vector is ξ_i. The reasons behind this can be explained by the following example.

$$\emptyset \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} A, 2A \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} A+B \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} 2B, B \underset{k_{-4}}{\overset{k_4}{\rightleftarrows}} \emptyset$$

Figure 4.1

Example 4.1.2

Example 4.1.2. Consider the Chemical Reaction Network described in Figure 4.1 with set of species $\mathcal{S} = \{A, B\}$.

First of all if we consider an initial state $x = (a, b)$ it is easy to see that we can define on the network a loop, starting in x, like the one in Figure 4.2 (where on the arrows there are the rates of each reaction). So there exists at least one γ which could be defined on the network.

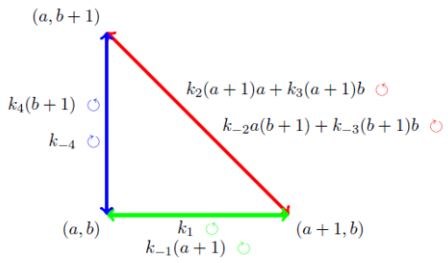

Figure 4.2

Loop Example

Then, due to the presence of reactions $\emptyset \leftrightarrows A$ and $B \leftrightarrows \emptyset$, two possible types of loops can be defined on $\mathcal{S}$ as shown in Figure 4.3. This implies that if we chose as initial state the one indicated by the black dot, we could move along the green reaction which belongs both to the first and second type loop. Defining p_i as in (67) therefore allows to

describe this phenomenon, assigning a propensity both of moving along green reaction on Type 1 loop and on Type 2.

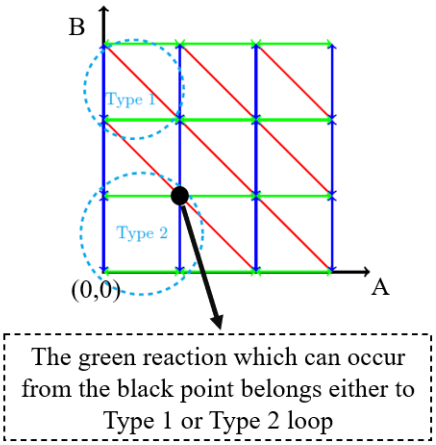

Figure 4.3

Example of reactions belonging to more loops

Last but not least, Condition 3. states that all the propensities p_i of a loop are not zero only if the loop can be entirely covered starting from state x. Here follows an example that shows how this does not always happen.

Example 4.1.3. Consider the CRN in Figure 4.4 and consider as possible reaction vector loop the following:

$$\gamma = \left((\xi_1 = \begin{bmatrix} -1 \\ 1 \\ 0 \end{bmatrix}, p_1); (\xi_2 = \begin{bmatrix} 1 \\ 0 \\ -1 \end{bmatrix}, p_2); (\xi_3 = \begin{bmatrix} 0 \\ -1 \\ 1 \end{bmatrix}, p_3) \right),$$

which in the Figure is referred as Type 2 loop.

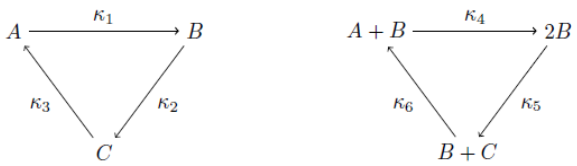

Figure 4.4

Example 4.1.3 (1)

First of all it is obvious to notice that in such network the mass is preserved. So if we define $x_A(t)$, $x_B(t)$, $x_C(c)$ as the number of molecules of each species at time t, it must hold $x_A(t)+x_B(t)+x_C(t)=N$, $\forall\, t \geq 0$ with $x_A(0)+x_B(0)+x_C(0)=N$. So the space of states takes a simplex form, as shown in Figure 4.5.

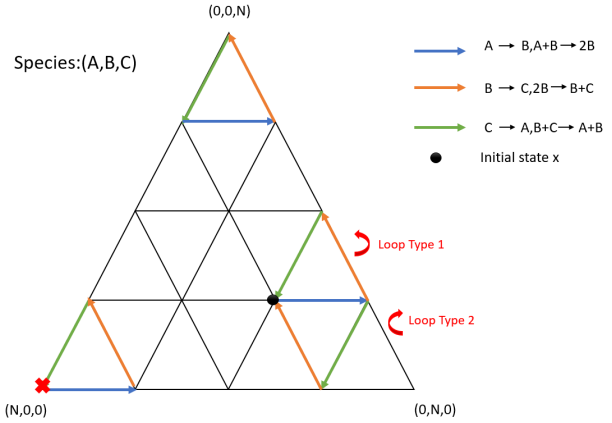

Figure 4.5

Example 4.1.3 (2)

Looking at this representation, we can say that γ can not be considered a loop according to 4.1.1 because it does not satisfy Condition 3. Indeed if we set each p_i as a **proportion of the sum of corresponding rates** $\sum_{y\to y'|y'-y=\xi_i} \lambda_{y\to y'}(x)$ and we consider γ starting from the state $\hat{x}=(N,0,0)$ (identified by the red cross in Figure 4.5), the following hold:

- From this initial state the loop can start but it cannot be fully covered
- The corresponding weights satisfy:
  - $p_1(\hat{x}) \neq 0$ because $\sum_{y\to y'|y'-y=\xi_1} \lambda_{y\to y'}(\hat{x}) \neq 0$
  - $p_2(\hat{x}+\xi_1) = p_3(\hat{x}+\xi_1+\xi_2) = 0$ because the corresponding reactions are not active in these states.

So Condition 3. does not hold.

It is also just as easy to verify that on the contrary the Type 1 loop showed in Figure 4.5 satisfies all the conditions stated in Definition 4.1.1.

4.2 Measures on a set of loops

It makes more sense to define not only one but a set of loops on a network.

Definition 4.2.1 (Complete set of reaction vector loops)**.** Let $(\mathcal{G}, \Lambda)$ be a stochastic reaction network and let $\Upsilon \subseteq \mathbb{Z}^n_{\geq 0}$ be a closed set. We define *complete set of reaction vector loops* for $\mathcal{S}$ on Υ the finite set $\Gamma = \{\gamma_j\}_{j=1}^m$ of weighted reaction vector loops such that:

$$\gamma_j = \left((\xi_i^j, p_i^j)\right)_{i=1}^{n_j},$$

and for each $\xi \in \{y' - y \mid y \to y' \in \mathcal{R}\}$ it holds:

$$\sum_{j=1}^{m} \sum_{i=1 | \xi_i^j = \xi}^{n_j} p_i^j(x) = \sum_{y \to y' \in \mathcal{R} | y' - y = \xi} \lambda_{y \to y'}(x), \qquad \forall\, x \in \Upsilon. \tag{51}$$

Inspired by what was discussed in Chapter 2, we can also define:

Definition 4.2.2 (Γ balancing)**.** Let $(\mathcal{G}, \Lambda)$ be a stochastic reaction network and let $\Upsilon \subseteq \mathbb{Z}^n_{\geq 0}$ be a closed set. Let moreover Γ be a complete set of reaction vector loops on Υ and let μ be a measure with $supp(\mu) = \Upsilon$.
We say that μ is Γ-balanced if:

$$\mu(x) p_i^j(x) = \mu(x + \xi_i^j) p_{i+1}^j(x + \xi_i^j), \qquad \forall\, x \in \Upsilon,\ 1 \leq j \leq m,\ 1 \leq i \leq n_j, \tag{52}$$

where $p_{i+1}^j(x + \xi_i^j) = 0$ *if* $x + \xi_i^j \notin \Upsilon$.

Proposition 4.2.3. *If μ is Γ-balanced on Υ, then μ is a stationary measure for the system.*

Proposition 4.2.4. *Let $(\mathcal{G}, \Lambda)$ be a stochastic reaction network and let $\Upsilon \subseteq \mathbb{Z}^n_{\geq 0}$ be a closed set. Let moreover Γ be a complete set of reaction vector loops on Υ and let μ be a Γ-balanced measure on Υ. Let $\Gamma' = \{\gamma'_j\}_j$ be a complete set of reaction vector loops such that:*

$$\forall\ \gamma'_j = \left((\xi_i'^j, p_i'^j)\right)_{i=1}^{n_j}\ \exists \gamma_j = \left((\xi_i^j, p_i^j)\right)_{i=1}^{n_j} \text{ s.t.}$$

$$\{(\xi_1'^j, p_1'^j), (\xi_2'^j, p_2'^j), ..., (\xi_{n_j}'^j, p_{n_j}'^j)\} = \sigma(\{(\xi_1^j, p_2^j), (\xi_2^j, p_2^j), ..., (\xi_{n_j}^j, p_{n_j}^j)\}),$$

with σ cyclic permutation. Then μ is also Γ'-balanced.

Proof. Let $\gamma'_{j^1} = \left((\xi'^{j^1}_i, p'^{j^1}_i)\right)_{i=1}^{n_{j^1}}$ be a loop in Γ' defined as before. We want to write the balancing conditions for γ'_{j^1}.

From 4.2.4 we know that it exists for sure a γ_{j^2} such that the reaction vectors and the weights in γ'_{j^1} are a cyclic permutation of those in γ_{j^2}. Then for each $(\xi'^{j^1}_i, p'^{j^1}_i)$ it will exist a i^* such that $\xi'^{j^1}_i = \xi^{j^2}_{i^*}$ and $p'^{j^1}_i = p^{j^2}_{i^*}$. Moreover, being γ' a cyclic permutation it will hold $\xi'^{j^1}_{i+1} = \xi'^{j^2}_{i^*+1}$ and $p'^{j^1}_{i+1} = p^{j^2}_{i^*+1}$.

Therefore we can write:

$$\mu(x)p'^{j^1}_i(x) = \mu(x)p^{j^2}_{i^*}(x) = \mu(x+\xi^{j^2}_{i^*})p^{j^2}_{i^*+1}(x+\xi^{j^2}_{i^*}) = \mu(x+\xi^{j^1}_i)p^{j^1}_{i+1}(x+\xi_i j^1), \qquad \forall\, x \in \Upsilon,$$

and so is also Γ'-balanced. □

We go ahead now giving not only a more formal way to verify the existence of a Γ-balanced measure but also a method to directly build it.

We need first some new definitions.

Definition 4.2.5 (Weighted path)**.** Let $(\mathcal{G}, \Lambda)$ be a stochastic reaction network and let $\Upsilon \subseteq \mathbb{Z}^n_{\geq 0}$ be a closed set. Let moreover Γ be a complete set of reaction vector loops on Υ.

Given a feasible path $(x_l)_{l=1}^L$ in Υ such that:

$$x_{l+1} - x_l = \xi^{j_l}_{i_l}, \qquad \forall\, 1 \leq l \leq L-1,\ 1 \leq j_l \leq m,\ 1 \leq i_l \leq n_{j_l},$$

and $p^{i_l}_{j_l} \neq 0$, we define a *weighted path* from x_1 to x_L the sequence:

$$s = ((x_l, i_l, j_l))_{l=1}^{L-1}. \tag{53}$$

If $x_1 = x_L$ the path is called *closed*.

Notice that j_l identifies the loop and i_l the index inside the loop, of the reaction along which the path moves from x_l.

Definition 4.2.6. We define *score* of a weighted path $s = ((x_l, i_l, j_l))_{l=1}^{L-1}$ the quantity defined as:

$$\eta(s(x)) = \prod_{l=1}^{L-1} \frac{p^{j_l}_{i_l}(x_l)}{p^{j_l}_{i_l+1}(x_l + \xi^{j_l}_{i_l})},$$

with $p^{j_l}_{n_{j_l}+1} = p^{j_l}_1$.

Remark 4.2.7. Notice that if we write extensively the product, we find that the score is the product of factors such as:

$$\frac{p^{j_l}_{i_{l+1}}(x_l+\xi^{j_l}_{i_l})}{p^{j_l}_{i_l+1}(x_l+\xi^{j_l}_{i_l})}, \qquad 1\le l\le L-1,$$

in which the numerator is the $(l+1)$th step of the path and the denominator is the step the path should have done after the lth, if it followed the order of reactions imposed by the loop $\left((\xi^j_i, p^j_i)\right)^{n_j}_{i=i}$.

Definition 4.2.8. Let $s=((x_l,i_l,j_l))^{L-1}_{l=1}$ and $s'=\left((x'_l,i'_l,j'_l)\right)^{L'-1}_{l=1}$ be two weighted path in Υ, such that $x_L=x'_1$.
We define *concatenation* of s and s' the weighted path defined as follows:

$$s*s'=\left((\hat{x}_l,\hat{i}_l,\hat{j}_l)\right)^{L+L'-2}_{l=1},$$

with

$$(\hat{x}_l,\hat{i}_l,\hat{j}_l)=\begin{cases}(x_l,i_l,j_l) & \text{if } l\le L-1\\ (x'_{l-L+1},i'_{l-L+1},j'_{l-L+1}) & \text{if } L\le l\le L+L'-2.\end{cases}$$

By definition it also follows that:

$$\eta(s*s')=\eta(s)\cdot\eta(s').$$

Theorem 4.2.9. *Let $(\mathcal{G},\Lambda)$ be a stochastic reaction network and let $\Upsilon\subseteq\mathbb{Z}^n_{\ge 0}$ be a closed and irreducible set. Let moreover Γ be a complete set of reaction vector loops.*
$(\mathcal{G},\Lambda)$ is Γ-balanced om Υ if and only if it holds:

$$\eta(s(x))=1, \qquad \forall \text{ weighted closed path } s \text{ with } x\in\Upsilon. \tag{54}$$

If this is the case, then the score of any weighted path s from $x_1\in\Upsilon$ to $x_L\in\Upsilon$, depends only on the initial and final states x_1, x_L. Moreover for any fixed $x^*\in\Upsilon$ we can build a stationary measure μ on Υ as:

$$\mu(x)=\begin{cases}0 & \text{if } x\notin\Upsilon\\ \eta(s), \text{ with } s \text{ any weighted path from } x^* \text{ to } x & \text{if } x\in\Upsilon\end{cases} \tag{55}$$

Proof. Assume at first that there exists a Γ-balanced measure μ on Υ. Then by Definition 52 we have that:

$$1 = \prod_{l=1}^{L-1} \frac{\mu(x_l) p_{i_l}^{j_l}(x_l)}{\mu(x+\xi_{i_l}^{j_l}) p_{i_l+1}^{j_l}(x_l+\xi_{i_l}^{j_l})} = \eta(s), \qquad \forall \text{ weighted closed paths } s.$$

Notice that the last equality holds because $x_l + \xi_{i_l}^{j_l} = x_{l+1}$, $\forall\, 1 \le l \le L-1$ and $x_L = x_1$. On the other hand suppose that all the scores of weighted closed paths based at a state in Υ are 1. Since Υ is irreducible, for each weighted path $s(x,i,j)$, which is associated with the single transition from state x to state $x+\xi_i^j$, we can define a weighted path $s(x,i,j)$ which goes from $x+\xi_i^J$ to x. Hence $(x,i,j) * s(x,i,j)$ is a weighted closed path and by 4.2.8 we have:

$$1 = \eta\left((x,i,j) * s(x,i,j)\right) = \frac{p_i^j(x)}{p_{i+1}^j(x+\xi_i^j)} \cdot \eta\left(s(x,i,j)\right),$$

and so:

$$\eta\left(s(x,i,j)\right) = \frac{p_{i+1}^j(x+\xi_i^j)}{p_i^j(x)}. \tag{56}$$

Consider also two weighted paths:

$$s = ((x_l, i_l, j_l))_{l=1}^{L-1} \qquad \text{and} \qquad s' = \left((x'_l, i'_l, j'_l)\right)_{l=1}^{L'-1},$$

with $x_1 = x'_1$ and $x_L = x'_L$. And let be:

$$\hat{s} = s * s(x'_{L'-1}, i'_{L'-1}, j'_{L'-1}) * \ldots * s(x'_1, i'_1, j'_1)$$

a closed weighted path. By 4.2.8 and (56) we have:

$$1 = \eta(\hat{s}) = \eta(s) \cdot \prod_{l=1}^{L'-1} \eta\Big(s(x'_l, i'_l, j'_l)\Big)\Big) = \eta(s) \prod_{l=1}^{L'-1} \frac{p_{i'_l+1}^{j'_l}(x'_l + \xi_{i'_l}^{j'_l})}{p_{i'_l}^{j'_l}(x'_l)} = \frac{\eta(s)}{\eta(s')}.$$

Therefore the score of a weighted path only depends on its initial and final states x_1 and x_L and can be denoted by $\eta(x_1, x_L)$. Moreover it follows that for any $x^* \in \Upsilon$ the quantity (55) is well defined.

We last have to prove that (55) is Γ-balanced. This easily follows noting that $\forall\, x \in \Upsilon$ and $\forall\, 1 \le j \le m$, $1 \le i \le n_j$, either $p_i^j = 0$ implying

$$\mu(x) p_i^j(x) = \mu(x+\xi_i^j) p_{i+1}^j(x+\xi_i^j) = 0,$$

or

$$\mu(x)\frac{p_i^j(x)}{p_{i+1}^j(x+\xi_i^j)} = \eta(x^*,x)\frac{p_i^j(x)}{p_{i+1}^j(x+\xi_i^j)} = \eta(x^*,x+\xi_i^j) = \mu(x+\xi_i^j).$$

□

We will report below three examples, two showing the existence and building of a stationary measure for a CRN, and another one showing on the contrary the existence of loops but not of a stationary measure for the CRN under consideration.

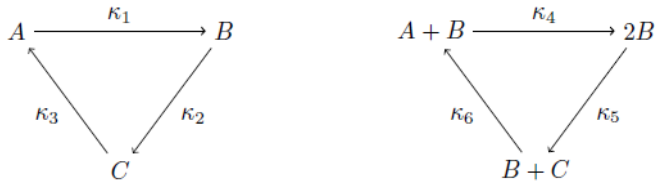

Figure 4.6

Example 4.2.12

Example 4.2.10. Consider the stochastic mass action system given by the CRN in Figure 4.6 and let $\Upsilon = \mathbb{Z}^3_{\geq 0}$. A complete set of reaction loops for the system is given by the single loop:

$$\left(\left(\begin{bmatrix}-1\\1\\0\end{bmatrix}, \lambda_{A\to B}+\lambda_{A+B\to 2B}\right), \left(\begin{bmatrix}0\\-1\\1\end{bmatrix}, \lambda_{B\to C}+\lambda_{2B\to B+C}\right), \left(\begin{bmatrix}1\\0\\-1\end{bmatrix}, \lambda_{C\to A}+\lambda_{B+C\to A+B}\right)\right).$$

We want to verify that the score of all weighted paths on Υ is 1. In order to do so is sufficient to show that the score of all *minimal* weighted closed paths on Υ is equal to 1. Indeed every other path will be a concatenation of minimal paths and so by Definition 4.2.8 its score will be also 1.

In this case the minimal weighted closed paths are:

$$s_1(x) = \left(\left(\begin{bmatrix}x_1\\x_2\\x_3\end{bmatrix}, 1, 1\right), \left(\begin{bmatrix}x_1-1\\x_2+1\\x_3\end{bmatrix}, 2, 1\right), \left(\begin{bmatrix}x_1-1\\x_2\\x_3+1\end{bmatrix}, 3, 1\right)\right),$$

with $x_1 \geq 1$, and

$$s_2(x) = \left(\left(\begin{bmatrix}x_1\\x_2\\x_3\end{bmatrix}, 1, 1\right), \left(\begin{bmatrix}x_1-1\\x_2+1\\x_3\end{bmatrix}, 3, 1\right), \left(\begin{bmatrix}x_1\\x_2+1\\x_3-1\end{bmatrix}, 2, 1\right)\right),$$

with $x_1, x_3 \geq 1$.

Notice that $s_1(x)$ is a *basic path*, that is it follows exactly the order of reactions of (4.2.14), and so by Remark 4.2.7 we obviously have that its score is 1. Therefore we have only to verify that $\eta(s_2(x)) = 1$. Then we have:

$$\eta(s_2(x)) = \frac{(k_1x_1 + k_4x_1x_2)(k_3x_3 + k_6(x_2+1)x_3)(k_2(x_2+1) + k_5(x_2+1)x_2)}{(k_2(x_2+1) + k_5(x_2+1)x_2)(k_1x_1 + k_4x_1(x_2+1))(k_3x_3 + k_6x_2x_3)} =$$

$$\frac{(k_1 + k_4x_2)(k_3 + k_6(x_2+1))}{(k_1 + k_4(x_2+1))(k_3 + k_6x_2)},$$

which is equal to 1 if and only if $\frac{k_4}{k_1} = \frac{k_6}{k_3}$.

If this holds the system is Γ-balanced and we can build a stationary measure as follows.

The closed irreducible set for this model are given by:

$$\Upsilon_N = \{x \in \mathbb{Z}^3_{\geq 0} \mid x_1 + x_2 + x_3 = N, N \in \mathbb{Z}_{\geq 0}\}. \tag{57}$$

For each Υ_N we set $x^* = (N, 0, 0)$. Then if we chose as path from x^* to x the one in which transition $A \to B$ occurs $x_2 + x_3$ times and then transition $B \to C$ occurs x_3 times, by (55) we have:

$$\mu(x) = \eta(x^*, x) = \frac{\prod_{l=0}^{x_2+x_3-1}(x_1 + x_2 + x_3 - l)(k_1 + k_4l)}{\prod_{l=1}^{x_2+x_3} l[k_2 + k_5(l-1)]}$$

$$\frac{\prod_{l=0}^{x_3-1}(x_2 + x_3 - l)[k_2 + k_5(x_2 + x_3 - l - 1)]}{\prod_{l=1}^{x_3} l[k_3 + k_6(x_2 + x_3 - l)]} =$$

$$\frac{(x_1 + x_2 + x_3)!}{x_1!(x_2 + x_3)!}\left(\frac{k_1}{k_3}\right)^{x_3}\prod_{l=0}^{x_2-1}\frac{k_1 + k_4l}{k_2 + k_5l}.$$

Remark 4.2.11. Notice that we proved the existence of a stationary measure for a weak-reversible CRN with deficiency $\delta = |C| - l - s = 6 - 2 - 2 = 2$.

Example 4.2.12. Consider the stochastic mass action system given by the CRN in Figure 4.7 and let $\Upsilon = \mathbb{Z}^3_{\geq 0}$. A complete set of reaction loops for the system is given

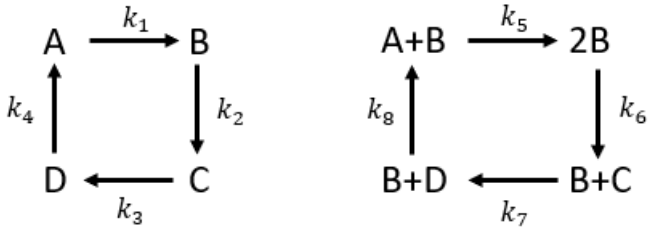

Figure 4.7

Example 4.2

by:

$$\left(\left(\begin{bmatrix}-1\\1\\0\\0\end{bmatrix}, \lambda_{A\to B}+\lambda_{A+B\to 2B}\right), \left(\begin{bmatrix}0\\-1\\1\\0\end{bmatrix}, \lambda_{B\to C}+\lambda_{2B\to B+C}\right), \left(\begin{bmatrix}0\\0\\-1\\1\end{bmatrix}, \lambda_{C\to D}+\lambda_{B+C\to B+D}\right),\right.$$
$$\left.\left(\begin{bmatrix}1\\0\\0\\-1\end{bmatrix}, \lambda_{D\to A}+\lambda_{B+D\to A+B}\right)\right).$$

We want to verify that the score of all weighted paths on Υ is 1.

In this case the minimal and not basic weighted closed paths are:

$$s_1(x)=\left(\left(\begin{bmatrix}x_1\\x_2\\x_3\\x_4\end{bmatrix},1,1\right), \left(\begin{bmatrix}x_1-1\\x_2+1\\x_3\\4\end{bmatrix},2,1\right), \left(\begin{bmatrix}x_1-1\\x_2\\x_3+1\\x_4\end{bmatrix},4,1\right), \left(\begin{bmatrix}x_1\\x_2\\x_3+1\\x_4-1\end{bmatrix},3,1\right)\right),$$

with $x_1 \geq 1$ and $x_4 \geq 1$

$$s_2(x)=\left(\left(\begin{bmatrix}x_1\\x_2\\x_3\\x_4\end{bmatrix},1,1\right), \left(\begin{bmatrix}x_1-1\\x_2+1\\x_3\\4\end{bmatrix},4,1\right), \left(\begin{bmatrix}x_1\\x_2+1\\x_3\\x_4-1\end{bmatrix},2,1\right), \left(\begin{bmatrix}x_1\\x_2\\x_3+1\\x_4-1\end{bmatrix},3,1\right)\right),$$

with $x_1 \geq 1$ and $x_4 \geq 1$.

$$s_3(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 4, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 \\ x_4 - 1 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 \end{bmatrix}, 2, 1\right)\right),$$

with $x_1 \geq 1$, $x_4 \geq 1$ and $x_3 \geq 1$.

$$s_4(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 + 1 \end{bmatrix}, 4, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 \end{bmatrix}, 2, 1\right)\right),$$

with $x_1 \geq 1$ and $x_3 \geq 1$.

$$s_5(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 + 1 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 \\ x_4 + 1 \end{bmatrix}, 4, 1\right)\right),$$

with $x_1 \geq 1$ and $x_3 \geq 1$.

Then we compute the scores:

$$\eta(s_1(x)) = \frac{(k_1 x_1 + k_5 x_1 x_2)(k_2(x_2+1) + k_6(x_2+1)x_2)}{(k_2(x_2+1) + k_6(x_2+1)x_2)(k_3(x_3+1) + k_7(x_3+1)x_2)}$$
$$\frac{(k_4 x_4 + k_8 x_2 x_4)(k_3(x_3+1) + k_7(x_3+1)x_2)}{(k_1 x_1 + k_5 x_1 x_2)(k_4 x_4 + k_8 x_2 x_4)},$$

which is equal to 1.

$$\eta(s_2(x)) = \frac{(k_1 x_1 + k_5 x_1 x_2)(k_4 x_4 + k_8(x_2+1)x_4)}{(k_2(x_2+1) + k_6(x_2+1)x_2)(k_1 x_1 + k_5 x_1(x_2+1))}$$
$$\frac{(k_2(x_2+1) + k_6(x_2+1)x_2)(k_3(x_3+1) + k_7(x_3+1)x_2)}{(k_3(x_3+1) + k_7(x_3+1)x_2)(k_4 x_4 + k_8 x_2 x_4)},$$

which is equal to 1 if and only if $\frac{k_5}{k_1} = \frac{k_8}{k_4}$.

$$\eta(s_3(x)) = \frac{(k_1 x_1 + k_5 x_1 x_2)(k_4 x_4 + k_8(x_2+1)x_4)}{(k_2(x_2+1) + k_6(x_2+1)x_2)(k_1 x_1 + k_5 x_1(x_2+1))}$$
$$\frac{(k_3 x_3 + k_7(x_2+1)x_3)(k_2(x_2+1) + k_6(x_2+1)x_2)}{(k_4 x_4 + k_8(x_2+1)x_4(k_3 x_3 + k_7 x_2 x_3)},$$

which is equal to 1 if and only if $\frac{k_5}{k_1} = \frac{k_7}{k_3}$.

$$\eta(s_4(x)) = \frac{(k_1x_1 + k_5x_1x_2)(k_3x_3 + k_7(x_2+1)x_3)}{(k_2(x_2+1) + k_6(x_2+1)x_2)(k_4(x_4+1) + k_8(x_2+1)(x_4+1))}$$
$$\frac{(k_4(x_4+1) + k_8(x_2+1)(x_4+1))(k_2(x_2+1) + k_6(x_2+1)x_2)}{(k_1x_1 + k_5x_1(x_2+1))(k_3x_3 + k_7x_2x_3)},$$

which is equal to 1 if and only if $\frac{k_5}{k_1} = \frac{k_7}{k_3}$.

$$\eta(s_5(x)) = \frac{(k_1x_1 + k_5x_1x_2)(k_3x_3 + k_7(x_2+1)x_3)}{(k_2(x_2+1) + k_6(x_2+1)x_2)(k_4(x_4+1) + k_8(x_2+1)(x_4+1))}$$
$$\frac{(k_2(x_2+1) + k_6(x_2+1)x_2)(k_4(x_4+1) + k_8x_2(x_4+1))}{(k_3x_3 + k_7x_2x_3)(k_1x_1 + k_5x_1x_2)}$$

which is equal to 1 if and only if $\frac{k_7}{k_3} = \frac{k_8}{k_4}$.

If this holds the system is Γ-balanced and we can build a stationary measure for each closed irreducible set of this model.

Remark 4.2.13. Notice that also in this case we proved the existence of a stationary measure for a weak-reversible CRN with deficiency $\delta = |C| - l - s = 8 - 2 - 3 = 3$. In addition we observe that conditions:

$$\frac{k_5}{k_1} = \frac{k_8}{k_4} \text{ and } \frac{k_5}{k_1} = \frac{k_7}{k_3}$$

are the ones that implies the measure to be complex balanced. Then, in this case, the distribution existence and its form is already known in literature.

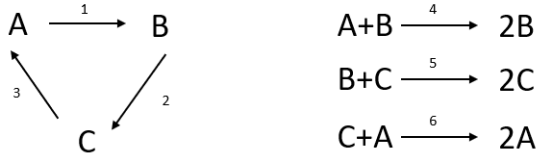

Figure 4.8

Example 4.2.14

Example 4.2.14. Consider the stochastic mass action system given by the CRN in Figure 4.8 and let $\Upsilon = \mathbb{Z}^3_{\geq 0}$. A complete set of reaction loops for the system is given by the single loop:

$$\left(\left(\begin{bmatrix}-1\\1\\0\end{bmatrix}, \lambda_{A\to B} + \lambda_{A+B\to 2B}\right), \left(\begin{bmatrix}0\\-1\\1\end{bmatrix}, \lambda_{B\to C} + \lambda_{B+C\to 2C}\right), \left(\begin{bmatrix}1\\0\\-1\end{bmatrix}, \lambda_{C\to A} + \lambda_{C+A\to 2A}\right)\right).$$

We want to show that in this case the complete set is not Γ-balanced and so no stationary measures could be found on it. To do this we show in this case that, within the minimal weighted paths on Υ there exists at least one which has score different from 1. As shown in previous examples the minimal paths are:

$$s_1(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \end{bmatrix}, 3, 1\right)\right),$$

with $x_1 \geq 1$, and

$$s_2(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \end{bmatrix}, 2, 1\right)\right),$$

with $x_1, x_3 \geq 1$.

Also in this case $s_1(x)$ is a *basic paths*, and so its score is necessarily 1.

Therefore we have only to verify that $\eta(s_2(x)) \neq 1$. We have:

$$\eta(s_2(x)) = \frac{(k_1x_1 + k_4x_1x_2)(k_3x_3 + k_6(x_1 - 1)x_3)(k_2(x_2 + 1) + k_5(x_2 - 1)(x_3 + 1)}{(k_2(x_2 + 1) + k_5(x_2 + 1)x_3)(k_1x_1 + k_4x_1(x_2 + 1))(k_3x_3 + k_6(x_1x_3} \tag{58}$$

Suppose that $\eta(s_2(x)) = 1$ holds, in this case we should have:

$$(k_1x_1 + k_4x_1x_2)(k_3x_3 + k_6(x_1 - 1)x_3)(k_2(x_2 + 1) + k_5(x_2 - 1)(x_3 + 1) =$$
$$(k_2(x_2 + 1) + k_5(x_2 + 1)x_3)(k_1x_1 + k_4x_1(x_2 + 1))(k_3x_3 + k_6(x_1x_3)),$$

for certain values of rate $\{k_i\}_i$.

By carrying out the counts it results:

$$(k_1k_2k_3 - k_1k_3k_5 - k_1k_2k_6 + k_1k_5k_6)x_1x_3 + (k_1k_5k_6 - k_1k_3k_5)x_1x_3^2 - k_1k_5k_6x_1^2x_3^2 +$$

$$(k_1k_2k_3 + k_1k_3k_5 - k_1k_2k_6 - k_1k_5k_6 - k_3k_4k_5 - k_2k_4k_6 + k_4k_5k_6)x_1x_2x_3 +$$

$$k_1k_2k_6x_1^2x_3 + (k_1k_3k_5 - k_1k_5k_6 - k_3k_4k_5 + k_4k_5k_6)x_1x_2x_3^2 +$$

$$(k_1k_2k_6 + k_1k_5k_6 + k_2k_{46} - k_4k_{56})x_1^2x_2x_3 +$$

$$(k_1k_5k_6 - k_4k_5k_6)x_1^2x_2x_3^2 + (k_3k_4k_5 - k_4k_5k_6)x_1x_2^2x_3^2 +$$

$$(k_3k_4k_5 - k_2k_4k_6 - k_4k_5k_6)x_1x_2^2x_3 + (k_2k_4k_6 + k_4k_5k_6)x_1^2x_2^2x_3 + k_4k_5k_6x_1^2x_2^2x_3^2 =$$

$$(k_1k_2k_3 + 2k_2k_3k_4)x_1x_2x_3 + (k_1k_2k_3 + k_2k_3k_4)x_1x_3 + (k_1k_2k_6 + 2k_2k_4k_6)x_1^2x_2x_3$$
$$+(k_1k_2k_6 + k_2k_4k_6)x_1^2x_3 + k_2k_3k_4x_1x_2^2x_3 + k_2k_4k_6x_1^2x_2^2x_3 +$$
$$(k_1k_3k_5 + 2k_3k_4k_5)x_1x_2x_3^2 + (k_1k_3k_5 + k_3k_4k_5)x_1x_3^2 + (k_1k_5k_6 + 2k_4k_5k_6)x_1^2x_2x_3^2 +$$
$$(k_1k_5k_6 + k_4k_5k_6)x_1^2x_3^2 + k_3k_4k_5x_1x_2^2x_3^2 + k_4k_5k_6x_1^2x_2^2x_3^2,$$

from which we obtain the following system of equations having the coefficients as unknowns:

$$\begin{cases} k_1k_2k_3 - k_1k_3k_5 - k_1k_2k_6 + k_1k_5k_6 = k_1k_2k_3 + k_2k_3k_4 \\ k_1k_5k_6 - k_1k_3k_5 = k_1k_3k_5 + k_3k_4k_5 \\ k_1k_2k_3 + k_1k_3k_5 - k_1k_2k_6 - k_1k_5k_6 - k_3k_4k_5 - k_2k_4k_6 + k_4k_5k_6 = k_1k_2k_3 + 2k_2k_3k_4 \\ k_1k_2k_6 = k_1k_2k_6 + k_2k_4k_6 \\ k_1k_3k_5 - k_1k_5k_6 - k_3k_4k_5 + k_4k_5k_6 = k_1k_3k_5 + 2k_3k_4k_5 \\ k_1k_2k_6 + k_1k_5k_6 + k_2k_{46} - k_4k_{56} = k_1k_2k_6 + 2k_2k_4k_6 \\ k_1k_5k_6 - k_4k_5k_6 = k_1k_5k_6 + 2k_4k_5k_6 \\ k_3k_4k_5 - k_4k_5k_6 = k_3k_4k_5 \\ k_3k_4k_5 - k_2k_4k_6 - k_4k_5k_6 = k_2k_3k_4 \\ k_4k_5k_6 = k_4k_5k_6 \\ k_2k_4k_6 + k_4k_5k_6 = k_2k_4k_6 \\ -k_1k_5k_6 = k_1k_5k_6 + k_4k_5k_6 \end{cases} \tag{59}$$

It's easy to notice, by looking at the last two equations, that $k_4k_5k_6 = 0$ and $k_1k_5k_6 = 0$. This is possible if:

- $k_5 = 0$
- $k_6 = 0$
- $k_4 = 0$ and $k_1 = 0$

However all cases are in contradiction with the existence of such a CRN.

Then necessarily $\eta(s_2(x)) \neq 1$ and so the complete set is not Γ-balanced.

4.3 A new and more general form of balancing

Inspired by the definition of a measure Γ-balanced in 52 and by the generalized balancing defined in 25, we'll define in this section a more general type of stochastic balancing.

Definition 4.3.1. Let $(\mathcal{G}, \Lambda)$ be a stochastic reaction system and suppose that π is a measure defined on $\mathbb{Z}^n$. π is said to be *generalized rate balanced* if there exists a set of tuples of subsets of $\mathcal{R}$, $\{(L_i, R_i)_{i\in A}\}$, with

$$\bigcup_{i\in A} L_i = \bigcup_{i\in A} R_i = \mathcal{R}, \tag{60}$$

and can be defined $\forall\, y \to y' \in \mathcal{R}$, and $\forall\, x$ some weights which satisfies:

$$\begin{aligned} &q^{L^i}_{y\to y'}(x) \neq 0 \text{ if and only if } y \to y' \in L_i, \quad \forall\, i \in A \\ &q^{R^i}_{y\to y'}(x) \neq 0 \text{ if and only if } y \to y' \in R_i, \quad \forall\, i \in A \\ &\text{such that } \sum_{i\in A} q^{L^i}_{y\to y'}(x) = \sum_{i\in A} q^{R^i}_{y\to y'}(x) = \lambda_{y\to y'}(x), \end{aligned} \tag{61}$$

and

$$\sum_{y\to y'\in\mathcal{R}} \pi(x+y-y')q^{L^i}_{y\to y'}(x+y-y') = \pi(x) \sum_{y\to y'\in\mathcal{R}} q^{R^i}_{y\to y'}(x). \tag{62}$$

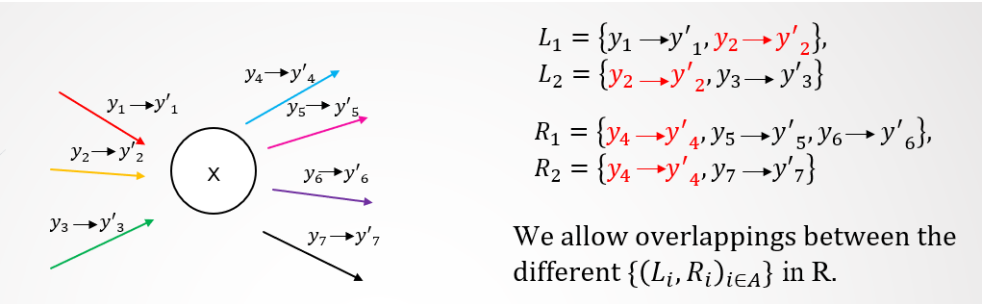

Figure 4.9

Generalized rate balanced

Notice that in (60) it is no longer required for the sets L_i (and respectively R_i) to form a partition of the space of reactions $\mathcal{R}$. In other words we are allowing the same reaction to be present in more than one set and, if this happens, we divide it among the sets in which it is present. An example of this idea is shown in Figure 4.9.

Proposition 4.3.2. *Let $(\mathcal{G}, \Lambda)$ be a stochastic reaction network and let $\Upsilon \subseteq \mathbb{Z}^n_{\geq 0}$ be a closed set. Let moreover Γ be a complete set of reaction vector loops on Υ and let μ be a Γ-balanced measure with $supp(\mu) = \Upsilon$. Then μ is generalized rate balanced.*

Proof. Consider the following set of tuples of subsets of $\mathcal{R}$, $\{(L_i^j, R_i^j)_{1\leq i\leq n_j, 1\leq j\leq m}\}$,such that:

$$L_i^j = \{y \to y' \in \mathcal{R} \mid y' - y = \xi_i^j,\ \forall\, 1 \leq i \leq n_j,\ 1 \leq j \leq m\},$$

and

$$R_i^j = \{y \to y' \in \mathcal{R} \mid y' - y = \xi_{i+1}^j,\ \forall\, 1 \leq i \leq n_j,\ 1 \leq j \leq m\},$$

with $\xi_{n_j+1}^j = \xi_1^j$. It is obvious to see that:

$$\bigcup_{1\leq i\leq n_j,\, 1\leq j\leq m} L_i^j = \bigcup_{1\leq i\leq n_j,\, 1\leq j\leq m} R_i^j = \mathcal{R}.$$

Recall now that we have supposed μ to be Γ-balanced:

$$\mu(x-\xi_i^j)p_i^j(x-\xi_i^j) = \mu(x)p_{i+1}^j(x), \qquad \forall\, x \in \Upsilon,\ 1 \leq j \leq m,\ 1 \leq i \leq n_j.$$

Therefore, if we define $\forall\ y \to y' \in \mathcal{R}$, $\forall\ x$ the following weights:

- If $y \to y' \in L_i^j$ we associate for each $x \in \Upsilon$ a weight $q_{L_i^j}(x) \neq 0$ such that

$$\sum_{y\to y'\in L_i^j} q_{L_i^j}(x) = p_i^j(x),\ \forall\, 1 \leq i \leq n_j,\ 1 \leq j \leq m\}, \tag{63}$$

  otherwise if $y \to y' \notin L_i^j$, $q_{L_i^j} = 0$.

- If $y \to y' \in R_i^j$ we associate for each $x \in \Upsilon$ a weight $q_{R_i^j}(x) \neq 0$ such that

$$\sum_{y\to y'\in R_i^j} q_{R_i^j}(x) = p_{i+1}^j(x),\ \forall\, 1 \leq i \leq n_j,\ 1 \leq j \leq m\}, \tag{64}$$

  otherwise if $y \to y' \notin R_i^j$, $q_{R_i^j} = 0$,

we obtain:

$$\mu(x-\xi_i^j) \sum_{y\to y'\in\mathcal{R}|y'-y=\xi_i^j} q_{L_i^j}(x-\xi_i^j) = \mu(x) \sum_{y\to y'\in\mathcal{R}|y'-y=\xi_{i+1}^j} q_{R_i^j}(x).$$

Summing all over $\xi_i^j \in \mathbb{R}^{\mathcal{S}}$ it results:

$$\sum_{y \to y' \in \mathcal{R}} \mu(x+y-y') q_{L_i^j}(x+y-y') = \sum_{y \to y' \in \mathcal{R}} \mu(x) q_{R_i^j}(x), \qquad \forall\, 1 \le i \le n_j,\, 1 \le j \le m\}, \quad (65)$$

so μ is generalized rate balanced.

Notice that the definition of $q_{L_i^j}$ and $q_{R_i^j}$ is consistent with (61) because Γ is a complete set of reaction vector loops and so (51) holds. □

5

A new perspective: loops defined on reactions

In this chapter we aim to extend the previous results. In particular we will define a different type of loops, based not any more on reaction vectors but on specific reactions and we will give for this loops a new definition of balancing. Then we will try to see the connections between this new balancing form and the Γ-balancing previously introduced, looking for cases for which the new formalization could guarantee, differently than before, the existence of a stationary measure.

5.1 New models

Definition 5.1.1 (Weighted reaction loop)**.** Let $(\mathcal{G}, \Lambda)$ be a stochastic reaction network and let $\Upsilon \subseteq \mathbb{Z}^n_{\geq 0}$ be a closed set. We define *weighted reaction loop*:

$$\delta = \left((y_i \to y_i', q_i)\right)_{i=1}^{n}, \tag{66}$$

such that the following hold:

1. $y_i \to y_i' \in \mathcal{R}$, $\forall\, i$ and
$$\sum_{i=1}^{n} y_i' - y_i = 0;$$
2. $q_i : \Upsilon \to \mathbb{R}_{\geq 0}$, $\forall\, i$ and
$$q_i(x) \leq \lambda_{y_i \to y_i'}(x) \qquad \forall\, x \in \Upsilon; \tag{67}$$
3. $\forall\ 1 \leq i \leq n$, $x \in \Upsilon$ it must hold that $q_i(x) \neq 0$ if and only if $q_{i+1}(x + y_i' - y_i) \neq 0$, with $q_{n+1} = q_1$.

If the CRN is weak-reversible we say that the loop is *graph-related* if it holds:

$$y_i' = y_{i+1}, \quad i = 1, ..., n-1 \text{ and } y_n' = y_1$$

Definition 5.1.2 (Complete set of reaction loops)**.** Let $(\mathcal{G}, \Lambda)$ be a stochastic reaction network and let $\Upsilon \subseteq \mathbb{Z}^n_{\geq 0}$ be a closed set. We define *complete set of reaction loops* for $\mathcal{S}$ on Υ the finite set $\Delta = \{\delta_j\}_{j=1}^m$ of weighted reaction vector loops such that:

$$\delta_j = \left((y_i^j \to y_i'^j, q_i^j)\right)_{i=1}^{n_j},$$

and for each $y \to y' \in \mathcal{R}$ it holds:

$$\sum_{j=1}^{m} \quad \sum_{i=1} q_i^j(x) \mathbb{1}_{(y_i^j = y, y_i'^j = y')} = \lambda_{y \to y'}(x), \qquad \forall\, x \in \Upsilon. \tag{68}$$

The set is called *graph-related* if all the reaction loops in it are graph-related.

Definition 5.1.3 (Δ-reaction balanced)**.** Let $(\mathcal{G}, \Lambda)$ be a stochastic reaction network and let $\Upsilon \subseteq \mathbb{Z}^n_{\geq 0}$ be a closed set. Let moreover Δ be a complete set of reaction loops on Υ and let μ be a measure with $supp(\mu) = \Upsilon$.
We say that μ is Δ- balanced if:

$$\mu(x) q_i^j(x) = \mu(x + y_i'^j - y_i^j) q_{i+1}^j(x + y_i'^j - y_i^j), \qquad \forall\, x \in \Upsilon,\ 1 \leq j \leq m,\ 1 \leq i \leq n_j, \tag{69}$$

where $q_{i+1}^j(x + y_i'^j - y_i^j) = 0$ *if* $x + y_i'^j - y_i^j \notin \Upsilon$.

Proposition 5.1.4. *Let* $(\mathcal{G}, \Lambda)$ *be a stochastic weak-reversible reaction network and let* $\Upsilon \subseteq \mathbb{Z}^n_{\geq 0}$ *be a closed set. Let moreover* Δ *be a complete set of graph-related reaction loops on* Υ *and let* μ *be a* Δ*-balanced measure with* $supp(\mu) = \Upsilon$*. Then* μ *is complex balanced.*

Proof. First of all notice that if the network is weak-reversible, then necessarily each reaction is included in at least one loop and so it is obviously always possible to build a complete set of reaction loops. Secondly fix $x \in \Upsilon$ and $y \in C$.
Then, for each $y' \in C$, if $y' \to y$ is active in $x + y' - y$, then it necessary belongs to a loop of the complete set of graph-related reaction loops by definition of completeness. So using the hypothesis on μ we can write:

$$\mu(x - y_i'^j + y_i^j) q_i^j(x - y_i'^j + y_i^j) = \mu(x) q_{i+1}^j(x),$$

where $y_i'^j = y$ and $y_i^j = y'$.
Notice that if this holds then there necessarily exists a complex $y'' \in C$ such that $y_{i+1}^j = y$

and ${y'_{i+1}}^j = y''$. Moreover the reaction $y \to y''$ is also active by condition 3. in Definition 5.1.1.

Now sum over $y' \in C$ and i, j such that ${y'_i}^j = y$ and $y_i^j = y'$. We have:

$$\sum_{y' \in C} \sum_{i,j} \mu(x - {y'_i}^j + y_i^j) q_i^j (x - {y'_i}^j + y_i^j) \mathbb{1}_{(y_i^j = y, {y'_i}^j = y')} = \sum_{y' \in C} \sum_{i,j} \mu(x) q_{i+1}^j(x) \mathbb{1}_{(y_i^j = y, {y'_i}^j = y')}. \tag{70}$$

Now by definition of q_i^j for a complete set of reaction loops and by renominating the y'' mentioned before as y' (this is possible because we are summing all over y' so we are considering all possible reactions $* \to y$ and so on the other hand all the possible reactions $y \to *$ active in x) we obtain:

$$\sum_{y' \in C} \mu(x + y' - y) \lambda_{y' \to y}(x + y' - y) = \sum_{y' \in C} \mu(x) \lambda_{y \to y'}(x),$$

which is exactly the definition of a complex balanced measure. □

5.2 Reaction loops and Reaction vector loops

We study now the connection between reaction loops and reaction vector loops. Notice first that by Definition 4.2.1 it could happen that in a complete set of reaction vector loops Γ the same cycle appears more than once (that is the same sequence of ξ_i appears in more than one loop, obviously with different weights associated for each loop). Then we could rewrite the set Δ expressed with reactions using reaction vectors as follows:

$$\hat{\gamma}_j = \left((\xi_i^j, q_i^j) \right)_{i=1}^{n_j}, \ \xi_i^j = {y'_i}^j - y_i^j.$$

In addition notice that for each i, j it holds:

$$q_i^j(x) \leq \lambda_{y_i^j \to {y'_i}^j}(x) \leq \sum_{y \to y' \in \mathcal{R} | y' - y = \xi_i^j} \lambda_{y \to y'}(x),$$

and

$$\sum_{j=1}^{m} \sum_{y \to y' \in \mathcal{R} | y' - y = \xi} \sum_{i=1}^{n_j} q_i^j(x) \mathbb{1}_{(y_i^j = y, {y'_i}^j = y')} = \sum_{y \to y' \in \mathcal{R} | y' - y = \xi} \lambda_{y \to y'}(x), \quad \forall \xi \in \mathbb{R}^S \tag{71}$$

So $\Delta = \{\delta_j\}_j$ could be mapped in a complete set of reaction vector loops and definition 5.1.3 corresponds to (52) with weights q_i^j.

Hence, for Δ, Theorem 4.2.9 holds and so we can check the existence of a Δ-balanced measure by computing the score of all minimal paths in Δ. Moreover if this measure exists we know which form it takes.

Notice that when we rewrite the complete set of reaction loops in terms of reaction vectors, we get a complete set of reaction vector loops that contains unnecessary redundancies. Therefore the following definition naturally follows:

Definition 5.2.1. Let $(\mathcal{G}, \Lambda)$ be a stochastic reaction network and let $\Upsilon \subseteq \mathbb{Z}^n_{\geq 0}$ be a closed set. Let also $\Delta = \{\delta_j\}_{j=1}^m$ be a complete set of reaction loops on Υ. We can build what we call a *natural* complete set of reaction vector loops, $\Gamma = \{\gamma_s\}_s$ on Υ, corresponding to Δ in the following way:

Set $s = 1,\ j = 1$
while $(j \leq m)$
if $\exists\ s' \leq s\ |$
$\gamma_{s'} = \left((\xi_t^s, p_t^{s'})\right)_{t=1}^{n_j}$ such that
$\xi_1^{s'} = y'_1{}^j - y_1^j,\ \xi_2^{s'} = y'_2{}^j - y_2^j,\ \ldots,\ \xi_{n_j}^{s'} = y'_{n_j}{}^j - y_{n_j}^j$
$j = j + 1;$
else
set $\gamma_s = \left((\xi_t^s, p_t^s)\right)_t$ such that
$\xi_1^s = y'_1{}^j - y_1^j,\ \xi_2^s = y'_2{}^j - y_2^j,\ \ldots,\ \xi_{n_j}^s = y'_{n_j}{}^j - y_{n_j}^j;$
$s = s + 1;$
$j = j + 1;$
end
end,

with arbitrary weights p_t^s chosen so as to meet the conditions in (4.2.1).
Notice that this is a different type of mapping from that in (5.2), even if it also describes a correspondence between the set of complete set of reaction loops and the set of complete set of reaction vector loops.

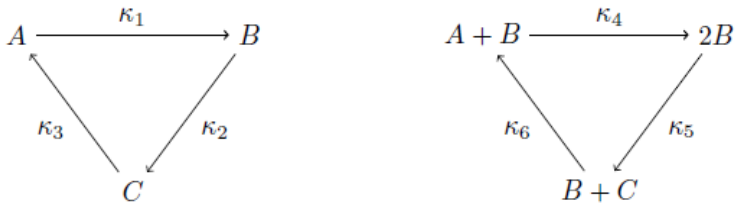

Figure 5.1

Example:5.2.2

After these considerations we would therefore like to study the relations between a complete set of reaction loops Δ and its own arbitrary corresponding natural complete set of reaction vector loops Γ, focusing in particular on the possible relations between the existence of a Δ-reaction balanced measure and that of a Γ-balanced measure.

5.2.1 Γ-balanced does not imply Δ-balanced

In this regard let's consider the following example.

Example 5.2.2. Let $(\mathcal{G}, \Lambda)$ be again the stochastic weak-reversible mass action reaction network based on the CRN in Figure 5.1 and let be Δ^1 a complete set of reaction loops and Δ^2 a graph-related complete set of reaction loops, both with corresponding complete set of reaction vector loops Γ defined as follows:

1.

$$\Delta^1 = \{\delta^1{}_1 = ((r_1{}^{1,1}, q_1{}^{1,1}), (r_2{}^{1,1}, q_2{}^{1,1}), (r_3{}^{1,1}, q_3{}^{1,1}));$$
$$\delta^1{}_2 = ((r_1{}^{1,2}, q_1{}^{1,2}), (r_2{}^{1,2}, q_2{}^{1,2}), (r_3{}^{1,2}, q_3{}^{1,2}))\}$$

$$r_1{}^{1,1} = A + B \to 2B$$
$$r_2{}^{1,1} = B \to C$$
$$r_2{}^{1,1} = C \to A$$
$$r_1{}^{1,2} = A \to B$$
$$r_2{}^{1,2} = 2B \to B + C$$
$$r_3{}^{1,2} = B + C \to A + B$$

$$\begin{cases} {q_1}^{1,1} = \lambda_{A+B\to 2B} \\ {q_2}^{1,1} = \lambda_{B\to C} \\ {q_3}^{1,1} = \lambda_{C\to A} \\ {q_1}^{1,2} = \lambda_{A\to B} \\ {q_2}^{1,2} = \lambda_{2B\to B+C} \\ {q_3}^{1,2} = \lambda_{B+C\to A+B} \end{cases}$$

2.

$$\Delta^2 = \{{\delta^2}_1 = (({r_1}^{1,1}, {q_1}^{2,1}), ({r_2}^{2,1}, {q_2}^{2,1}), ({r_3}^{2,1}, {q_3}^{2,1}));$$

$${\delta^2}_2 = (({r_1}^{2,2}, {q_1}^{2,2}), ({r_2}^{2,2}, {q_2}^{2,2}), ({r_3}^{2,2}, {q_3}^{2,2}))\}$$

$$\begin{aligned} {r_1}^{2,1} &= A \to B \\ {r_2}^{2,1} &= B \to C \\ {r_2}^{2,1} &= C \to A \\ {r_1}^{2,2} &= A + B \to 2B \\ {r_2}^{2,2} &= 2B \to B + C \\ {r_3}^{2,2} &= B + C \to A + B \end{aligned}$$

$$\begin{cases} {q_1}^{2,1} = \lambda_{A\to B} \\ {q_2}^{2,1} = \lambda_{B\to C} \\ {q_3}^{2,1} = \lambda_{C\to A} \\ {q_1}^{2,2} = \lambda_{A+B\to 2B} \\ {q_2}^{2,2} = \lambda_{2B\to B+C} \\ {q_3}^{2,2} = \lambda_{B+C\to A+B} \end{cases}$$

3.

$$\Gamma = \{\gamma = ((\xi_1, p_2), (\xi_2, p_2), (\xi_3, p_3))\},\ with$$

$$\xi_1 = \xi_{A\to B, A+B\to 2B}$$

$$\xi_2 = \xi_{B\to C, 2B\to B+C}$$

$$\xi_3 = \xi_{C\to A, B+C\to A+B}$$

$$\begin{cases} p_1 = \lambda_{A\to B} + \lambda_{A+B\to 2B} \\ p_2 = \lambda_{B\to C} + \lambda_{2B\to B+C} \\ p_3 = \lambda_{C\to A} + \lambda_{B+C\to A+B} \end{cases}$$

Now we want to know if these complete sets are balanced or not. Hence, by 4.2.9, we have to compute the score of all minimal paths for each complete set and check if they are all equal to 1. We have:

1. In this case the corresponding redundant complete set of reaction vector loops to Δ^1 is:

$$\Gamma^1 = \{\hat{\gamma}^1{}_1 = ((\xi_1{}^{1,1}, q_1{}^{1,1}), (\xi_2{}^{1,1}, q_2{}^{1,1}), (\xi_3{}^{1,1}, q_3{}^{1,1}));$$

$$\hat{\gamma}^1{}_2 = ((\xi_1{}^{1,2}, q_1{}^{1,2}), (\xi_2{}^{1,2}, q_2{}^{1,2}), (\xi_3{}^{1,2}, q_3{}^{1,2}))\},\ \textit{with}$$

$$\xi_1{}^{1,1} = \xi_1{}^{1,2} = \xi_{A\to B, A+B\to 2B}$$

$$\xi_2{}^{1,1} = \xi_2{}^{1,2} = \xi_{B\to C, 2B\to B+C}$$

$$\xi_3{}^{1,1} = \xi_3{}^{1,2} = \xi_{C\to A, B+C\to A+B}$$

It is easy to see that the minimal path

$$s^1(x) = \Big((x, 1, 2), (x + \xi_1{}^{1,2}, 2, 1), (x + \xi_1{}^{1,2} + \xi_2{}^{1,1}, 3, 1)\Big)$$

have score different from one. Indeed:

$$s^1(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \end{bmatrix}, 3, 1\right)\right)$$

$$\eta(s^1(x)) = \frac{q_1{}^{1,2}(x)}{q_2{}^{1,2})(x + \xi_1{}^{1,2})} \frac{q_2{}^{1,1}(x + \xi_1{}^{1,2})}{q_3{}^{1,1})(x + \xi_1{}^{1,2} + \xi_2{}^{1,1})} \frac{q_3{}^{1,1})(x + \xi_1{}^{1,2} + \xi_2{}^{1,1})}{q_1{}^{1,1})(x)} =$$

$$\frac{k_{A\to B}x_1}{k_{2B\to B+C}(x_2+1)x_2}\frac{k_{B\to C}(x_2+1)}{k_{C\to A}(x_3+1)}\frac{k_{C\to A}(x_3+1)}{k_{A+B\to 2B}x_1x_2},$$

which is obviously not possible 1 if we look at the first and last denominator. So the complete set of reaction vector loops Δ^1 is not Δ-balanced.

2. In this case the corresponding complete set of reaction vector loops to Δ^2 is:

$$\Gamma^2 = \{\hat{\gamma}^2{}_1 = ((\xi_1{}^{2,1}, q_1{}^{2,1}), (\xi_2{}^{2,1}, q_2{}^{2,1}), (\xi_3{}^{2,1}, q_3{}^{2,1}));$$

$$\hat{\gamma}^2{}_2 = ((\xi_1{}^{2,2}, q_1{}^{2,2}), (\xi_2{}^{2,2}, q_2{}^{2,2}), (\xi_3{}^{2,2}, q_3{}^{2,2}))\},\ with$$

$$\xi_1{}^{2,1} = \xi_1{}^{2,2} = \xi_{A\to B, A+B\to 2B}$$

$$\xi_2{}^{2,1} = \xi_2{}^{2,2} = \xi_{B\to C, 2B\to B+C}$$

$$\xi_3{}^{2,1} = \xi_3{}^{2,2} = \xi_{C\to A, B+C\to A+B}$$

In this case the complete set of graph-related reaction loops Δ^2 is Δ-balanced instead.

We show below the counts for the score of the two more particular minimal paths. The others can be verified in a similar way.

Consider:

$$s^2{}_1(x) = \Big((x,1,2), (x+\xi_1{}^{2,2}, 2, 1), (x+\xi_1{}^{2,2}+\xi_2{}^{2,1}, 3, 1)\Big)$$

$$s^2{}_2(x) = \Big((x,1,1), (x+\xi_1{}^{2,1}, 3, 1), (x+\xi_1{}^{2,1}+\xi_3{}^{2,1}, 2, 1)\Big)$$

We have:

$$s^2{}_1(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1-1 \\ x_2+1 \\ x_3 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1-1 \\ x_2 \\ x_3+1 \end{bmatrix}, 3, 1\right)\right)$$

$$\eta(s^2{}_1(x)) = \frac{q_1{}^{2,2}(x)}{q_2{}^{2,2}(x+\xi_1{}^{2,2})}\frac{q_2{}^{2,1}(x+\xi_1{}^{2,2})}{q_3{}^{2,1}(x+\xi_1{}^{2,2}+\xi_2{}^{2,1})}\frac{q_3{}^{2,1}(x+\xi_1{}^{2,2}+\xi_2{}^{2,1})}{q_1{}^{2,1}(x)} =$$
$$\frac{(k_{A+B\to 2B}x_1x_2}{k_{2B\to B+C}(x_2+1)x_2}\frac{k_{B\to C}(x_2+1)}{k_{C\to A}x_1(x_3+1)}\frac{k_{C\to A}(x_3+1)}{k_{A\to B}x_1},$$

which is obviously equal to 1.

$$s^2{}_2(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1-1 \\ x_2+1 \\ x_3 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2+1 \\ x_3-1 \end{bmatrix}, 2, 1\right)\right)$$

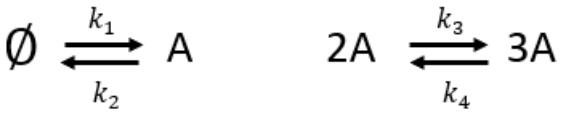

Figure 5.2

Example:5.2.3

$$\eta(s^2{}_2(x)) = \frac{q_1{}^{2,1}(x)}{q_2{}^{2,1}(x+\xi_1{}^{2,1})} \frac{q_3{}^{2,1}(x+\xi_1{}^{2,1})}{q_1{}^{2,1}(x+\xi_1{}^{2,1}+\xi_3{}^{2,1})} \frac{q_2{}^{2,1}(x+\xi_1{}^{2,1}+\xi_3{}^{2,1})}{q_3{}^{2,1}(x)} = \frac{(k_{A\to B}x_1}{k_{B\to C}(x_2+1)} \frac{k_{C\to A}x_3}{k_{A\to B}x_1} \frac{k_{B\to C}(x_2+1)}{k_{C\to A}x_3},$$

which is also obviously equal to 1.

3. In this case the complete set of reaction vector loops is obviously Γ-balanced since we have already proved it in Example 4.2.12.

So if a natural complete set of reaction vector loops is balanced, this does not imply that the corresponding complete set of reaction loop it is. Moreover, it's easy to observe that if the network is weak-reversible, describing it using a complete set of reaction loops is more restrictive then describing it with a complete set of graph-related reaction loops, which in this case is on the contrary balanced as the set of reaction vector loops.
This is because, if loops already naturally exist in the graph structure of the CRN, it's easy to think that as time goes by, reactions will trend to occur following the already defined loops. So, defining a background structure which breaks this intuitive flow, won't fit well with the dynamic model.

Now we can ask ourselves: does natural and Γ-balanced complete set of reaction vector loops imply Δ-balanced corresponding complete set of graph-related reaction loops? Also in this case the answer is no and so the reaction loop model is not equivalent to the reaction vector one. We prove our statement with the following examples.

Example 5.2.3. Consider the weak-reversible CRN in Figure 5.2 and let be Δ and Γ a complete set of graph-related loops and its corresponding natural complete set of

reaction vector loops, defined as follows:

$$\Delta = \{\delta_1 = ((r_1{}^1, q_1{}^1), (r_2{}^1, q_2{}^1));$$

$$\delta_2 = ((r_1{}^2, q_1{}^2), (r_2{}^2, q_2{}^2))\}$$

$$r_1{}^1 = \emptyset \to A$$

$$r_2{}^1 = A \to \emptyset$$

$$r_1{}^2 = 2A \to 3A$$

$$r_2{}^2 = 3A \to 2A$$

$$\begin{cases} q_1{}^1 = \lambda_{\emptyset \to A} \\ q_2{}^1 = \lambda_{A \to \emptyset} \\ q_1{}^2 = \lambda_{2A \to 3A} \\ q_2{}^2 = \lambda_{3A \to 2A} \end{cases}$$

$$\Gamma = \{\gamma = ((\xi_1, p_1), (\xi_2, p_2))\}$$

$$\xi_1 = \xi_{\emptyset \to A, 2A \to 3A}$$

$$\xi_2 = \xi_{A \to \emptyset, 3A \to 2A}$$

$$\begin{cases} p_1 = \lambda_{\emptyset \to A} + \lambda_{2A \to 3A} \\ p_2 = \lambda_{A \to \emptyset} + \lambda_{3A \to 2A} \end{cases}$$

Now we want to verify if these complete sets are balanced.

It is easy to see that the complete set of reaction vector loops is always Γ-balanced. That is because the only minimal not basic path is $s(x) = ((x, 1, 2), (x + \xi_1, 3))$, which is obviously a cyclic permutation of the basic path defined by moving on the loop in Γ. So it is necessarily balanced.

On the other hand we now verify the balancing of Δ.

In this case the corresponding redundant complete set of reaction vector loops to Δ^1 is:

$$\Gamma^d = \{\hat{\gamma^d}_1 = ((\xi_1{}^{d,1}, q_1{}^{d,1}), (\xi_2{}^{d,1}, q_2{}^{d,1}));$$

$$\hat{\gamma^d}_2 = ((\xi_1{}^{d,2}, q_1{}^{d,2}), (\xi_2{}^{d,2}, q_2{}^{d,2}))\}, \ with$$

$$\xi_1{}^{d,1} = \xi_1{}^{d,2} = \xi_{\emptyset \to A, 2A \to 3A}$$

$$\xi_2{}^{d,1} = \xi_2{}^{d,2} = \xi_{A \to \emptyset, 3A \to A}$$

The minimal and not basic paths are:

$$s_1(x) = \Big((x,1,1), (x + \xi_1^{d,1}, 2, 2)\Big),$$

$$s_2(x) = \Big((x,1,2), (x + \xi_1^{d,2}, 2, 1)\Big),$$

and their cyclic permutations. The counts for the scores of these paths are really similar between each other and they all lead to the same results, hence we will show only the first one of them.

$$s_1(x) = ((x,1,1), (x+1,2,2),)$$

$$\eta(s_1(x))) = \frac{q_1{}^{d,1}(x)}{q_2{}^{d,1}(x + \xi_1{}^{d,1})} \frac{q_2{}^{d,2}(x + \xi_1{}^{d,1})}{q_1{}^{d,2}(x)} =$$

$$\frac{k_{\emptyset \to A}}{k_{A \to \emptyset}(x+1)} \frac{k_{3A \to 2A}(x_1+1)x(x-1)}{k_{2A \to 3A} x(x-1)},$$

which is obviously equal to 1 only if $\frac{k_{\emptyset \to A}}{k_{A \to \emptyset}} = \frac{k_{2A \to 3A}}{k_{3A \to 2A}}$.

So it is not true that a natural complete set of reaction vector loops Γ- balanced, implies its corresponding complete set of graph-related reaction loops to be Δ-balanced.

Remark 5.2.4. We should notice two things about the above example:

1. The network has 4 complexes, 2 linkage classes and the rank of the network is obviously 1. So the deficiency is 1.

2. It's easy to see that for the pair of reactions $\emptyset \leftrightarrows A$, the only possible complex balanced measure is $\mu(x) = \frac{(\frac{k_{\emptyset\to A}}{k_{A\to\emptyset}})^x}{x!}$. Moreover this measure is complex balanced for the other pair of reactions if and only if:

$$\frac{(\frac{k_{\emptyset\to A}}{k_{A\to\emptyset}})^{x-1}}{(x-1)!}k_{2A\to 3A}(x-1)(x-2) = \frac{(\frac{k_{\emptyset\to A}}{k_{A\to\emptyset}})^x}{x!}k_{3A\to 2A}x(x-1)(x-2),$$

which holds exactly only if $\frac{k_{\emptyset\to A}}{k_{A\to\emptyset}} = \frac{k_{2A\to 3A}}{k_{3A\to 2A}}$.

This is not only a practical confirmation of the validity of Proposition 5.1.4, but it also means that thanks to reaction vector loops we have found the existence of a stationary measure for cases in which the CRN which has one deficiency but is not complex balanced, which is a case that does not fall under Theorem 3.3.1.Last but not least notice that if we add more reactions of type $\alpha A \to (\alpha+1)A$, with $\alpha > 2$, we found CRN with deficiency greater then 1, for which is always possible to find a stationary measure describing the network with a complete set of reaction vector loops, even in not complex balanced cases.

In other words, with these examples we have shown that Γ-balanced does not necessary imply Δ-balance. Then for sure the two balancing conditions are not equivalent. We should however ask ourselves what happens about the other implication, that is does Δ-balanced imply Γ-balanced?
We will show that in this case the answer depends on the definition of the complete set of reaction loops.

5.2.2 When Δ-balanced implies Γ-balanced

Proposition 5.2.5. *Let $(\mathcal{G}, \Lambda)$ be a generic stochastic reaction network and let $\Upsilon \subseteq \mathbb{Z}^n_{\geq 0}$ be a closed set.*
Let moreover $\Delta = \{\delta_j\}_{j=1}^{m_1}$:

$$\delta_j = \left((y_i^j \to y_i'^j, q_i^j)\right)_{i=1}^{n_j}$$

be a complete set of reaction loops containing all possible loops in Υ and let μ be a Δ-balanced measure on Υ.

Moreover let be:

$$\Gamma = \{\gamma_s\}_{s=1}^{m_2},$$

$$\gamma_s = ((\xi_t^s, p_t^s))_{t=1}^{n_s},$$

one natural complete set of reaction vector loops in Υ *corresponding to* Δ*, with weights defined as follows for each* s *and* t^* *fixed:*

$$p_{t^*}^s(x) = \frac{1}{M} \sum_{\hat{\gamma}_j | \{y_i'^j - y_i^j\}_i = \sigma(\{\xi_t^s\}_t)} \quad \sum_{y_i'^j - y_i^j = \xi_{t^*}^s} q_i^j(x),$$

where M *is the number of all reactions in* $\{\gamma_s\}_s \in \Gamma$ *which have reaction vector* $\xi = \xi_s^{t^*}$*, and* σ *is a cyclic permutation.*
Then μ *is also* Γ*-balanced.*

Proof. We have to show that the Γ-balanced equation holds for μ for each γ_s. So we write:

$$\mu(x) p_{t^*}^s(x) \; =$$

$$\sum_{\hat{\gamma}_j | \{y_i'^j - y_i^j\}_i = \sigma(\{\xi_t^s\}_t)} \quad \frac{1}{M} \sum_{y_i'^j - y_i^j = \xi_{t^*}^s} \mu(x) q_i^j(x) =$$

$$\sum_{\hat{\gamma}_j | \{y_i'^j - y_i^j\}_i = \sigma(\{\xi_t^s\}_t)} \quad \frac{1}{M} \sum_{y_i'^j - y_i^j = \xi_{t^*+1}^s} \mu(x + y_i'^j - y_i^j) q_{i+1}^j(x + y_i'^j - y_i^j) =$$

where the last equality derives from writing the first summation extensively, applying the definition of Δ- balanced, from the type of set we chose for pick up the q_i^j in the definition of p_t^s and from Proposition 4.2.4.
This is equal to:

$$\mu(x + \xi_{t^*+1}^s) \frac{1}{M} \sum_{\hat{\gamma}_j | \{y_i'^j - y_i^j\}_i = \sigma(\{\xi_t^s\}_t)} \quad \sum_{y_i'^j - y_i^j = \xi_{t^*+1}^s} q_{i+1}^j(x + \xi_{t^*}^s) =$$

$$\mu(x + \xi_{t^*+1}^s) p_{t^*}^s(x + \xi_{t^*+1}^s)$$

The same reasoning holds $\forall\, s, t$. So the natural complete set of reaction vector loops is Γ-balanced with respect to measure μ. □

Notice that if we have a Δ-balance CRN, with Δ complete set of reaction loops, not graph related and which does not contain all possible closed paths in the network, then

Δ-balance does not necessary imply Γ-balance.

Suppose indeed that:

$$\Delta = \{l\delta_1 = \{(r_1^1, q_1^1), (r_2^1, q_2^1), (r_3^1, q_3^1)\},$$

$$\delta_2 = \{(r_1^2, q_1^2), (r_2^2, q_2^2), (r_3^2, q_3^2)\}\},$$

where

$$\begin{aligned} q_1^1(x) &= a_1 \lambda_{r_1^1}(x), \\ q_2^1(x) &= a_2 \lambda_{r_2^1}(x), \\ q_3^1(x) &= a_3 \lambda_{r_3^1}(x), \\ q_1^2(x) &= b \lambda_{r_1^2}(x), \\ q_2^2(x) &= \lambda_{r_2^2}(x), \\ q_3^2(x) &= \lambda_{r_3^2}(x), \end{aligned} \tag{72}$$

with $a_i, b \in [0, 1]$. Suppose now that r_1^1 and r_1^2 lead to the same state change, that is they have same reaction vector ξ. Moreover suppose that $\xi_i^1 \neq \xi_j^2,\ i, j \in \{2, 3\}$ instead. Consider now the corresponding complete set of reaction vector loops:

$$\Gamma = \{\gamma_1 = \{(\xi_1^1, p_1^1), (\xi_2^1, p_2^1), (\xi_3^1, p_3^1)\},$$

$$\gamma 2 = \{(\xi_1^2, p_1^2), (\xi_2^2, p_2^2), (\xi_3^2, p_3^2)\}\},$$

where:

$$\begin{aligned} \xi_1^1 = \xi_1^2 = \xi_{r_1^1, r_1^2} &= \xi, \\ \xi_2^1 &= \xi_{r_2^1}, \\ \xi_3^1 &= \xi_{r_3^1}, \\ \xi_2^2 &= \xi_{r_2^2}, \\ \xi_3^2 &= \xi_{r_3^2}. \end{aligned}$$

$$p_1^1(x) = \lambda_{r_1^1}(x) + \lambda_{r_1^2}(x),$$
$$p_2^1(x) = \lambda_{r_2^1}(x),$$
$$p_3^1(x) = \lambda_{r_3^1}(x),$$
$$p_1^2(x) = \lambda_{r_1^1}(x) + \lambda_{r_1^2}(x),$$
$$p_2^2(x) = \lambda_{r_2^2}(x),$$
$$p_3^1(x) = \lambda_{r_3^2}(x).$$

Notice that the network could be Γ-balanced, only if, for the following closed path

$$s^*(x) = \left((x,1,1), \left(x+\xi_1^1, 3, 1\right), \left(x+\xi_1^1+\xi_3^1), 2, 1\right)\right),$$

it also holds:

$$\eta(s^*(x)) = \frac{p_1^1(x)}{p_2^1(x+\xi_1^1)} \frac{p_3^1(x+\xi_1^1)}{p_1^1(x+\xi_1^1+\xi_3^1))} \frac{p_2^1(x+\xi_1^1+\xi_3^1)}{p_3^1(x)} =,$$

$$\frac{\lambda_{r_1^1}(x) + \lambda_{r_1^2}(x)}{\lambda_{r_2^1}(x+\xi_1^1)} \frac{\lambda_{r_3^1}(x+\xi_1^1)}{\lambda_{r_1^1}(x+\xi_1^1+\xi_3^1)) + \lambda_{r_1^2}(x+\xi_1^1+\xi_3^1))} \frac{\lambda_{r_2^1}(x+\xi_1^1+\xi_3^1))}{\lambda_{r_3^1}(x)} = 1.$$

Now came back to the complete set of reaction loops. We supposed that Δ is balanced and so the score of all closed paths on the network is necessarily 1. Then, if we take the paths:

$$s_1(x) = \left((x,1,1), \left(x+{y'_1}^1 - y_1^1, 3, 1\right), \left(x+{y'_1}^1 - y_1^1 + {y'_3}^1 - y_3^1), 2, 1\right)\right),$$

$$s_2(x) = \left((x,1,2), \left(x+{y'_1}^2 - y_1^2, 3, 1\right), \left(x+{y'_1}^2 - y_1^2 + {y'_3}^1 - y_3^1), 2, 1\right)\right),$$

the following must hold:

$$\eta(s_1(x)) = \frac{a_1\lambda_{r_1^1}(x)}{a_2\lambda_{r_2^1}(x+{y'_1}^1 - y_1^1)} \frac{a_3\lambda_{r_3^1}(x+{y'_1}^1 - y_1^1)}{a_1\lambda_{r_1^1}(x+{y'_1}^1 - y_1^1 + {y'_3}^1 - y_3^1)} \frac{a_2\lambda_{r_2^1}(x+{y'_1}^1 - y_1^1 + {y'_3}^1 - y_3^1)}{a_3\lambda_{r_3^1}(x)} = 1.$$

$$\eta(s_2(x)) = \frac{b\lambda_{r_1^2}(x)}{a_2\lambda_{r_2^1}(x+{y'_1}^2 - y_1^2)} \frac{a_3\lambda_{r_3^1}(x+{y'_1}^2 - y_1^2)}{a_1\lambda_{r_1^1}(x+{y'_1}^2 - y_1^2 + {y'_3}^1 - y_3^1)} \frac{a_2\lambda_{r_2^1}(x+{y'_1}^1 - y_1^1 + {y'_3}^1 - y_3^1)}{a_3\lambda_{r_3^1}(x)} = 1.$$

It is easy to see, recalling

$${y'_1}^1 - y_1^1 = {y'_1}^2 - y_1^2 = \xi = \xi_1^1 = \xi_1^2$$

$${y'_2}^1 - y_2^1 = \xi_2^1$$

$$y_3'^1 - y_3^1 = \xi_3^1$$

that $\eta(s_1(x)) = \eta(s_2(x)) = 1$ does not imply $\eta(s^*(x)) = 1$. And so we can state that Δ-balanced does not imply Γ-balanced.

In addition it is possible to show that this depends on how the complete set of reaction loops is defined. Indeed suppose to take $\Delta = \{\delta_1, \delta_2, \delta_3\}$ with δ_1, δ_2 defined as before and

$$\delta_3 = \{(r_1^3, q_1^3), (r_2^3, q_2^3), (r_3^3, q_3^3)\}$$

$$r_1^3 = r_1^2$$

$$r_2^3 = r_2^1$$

$$r_3^3 = r_3^1$$

$$q_1^3(x) = c_1 \lambda_{r_1^2}(x),$$

$$q_2^3(x) = c_2 \lambda_{r_2^1}(x),$$

$$q_3^3(x) = c_3 \lambda_{r_3^1}(x),$$

with $c_i \in [0, 1]$.

Then it is possible to take the following closed path:

$$s_3(x) = \left((x, 1, 3), \left(x + y_1'^3 - y_1^3, 3, 3\right), \left(x + y_1'^3 - y_1^3 + y_3'^3 - y_3^3), 2, 3\right)\right),$$

with score

$$\eta(s_3(x)) = \frac{c_1 \lambda_{r_1^2}(x)}{\lambda_{r_2^1}(x + y_1'^2 - y_1^2)} \frac{\lambda_{r_3^1}(x + y_1'^2 - y_1^2)}{c_1 \lambda_{r_1^2}(x + y_1'^2 - y_1^2 + y_3'^1 - y_3^1)} \frac{\lambda_{r_2^1}(x + y_1'^1 - y_1^1 + y_3'^1 - y_3^1)}{\lambda_{r_3^1}(x)} = 1,$$

because we have supposed Δ to be balanced.

It is easy to see that, under specific rate coefficient conditions, in this case Δ-balanced implies Γ-balanced. Notice in particular that we are exactly in the case presented in Proposition 5.2.5.

5.2.3 Δ-balanced with graph-related reaction loops does not imply Γ-balanced

Notice that in Proposition 5.2.5 we have considered a generic Chemical Reaction Network. In addition, the hypothesis which leads to the validity of the proposition

itself, implies that the chosen complete set of reaction loops it is necessarily not graph related.

We would like then to know what happens in the case the CRN is weak-reversible and so when a graph-related complete set of reaction loops could be defined.

We provide in this regard the following examples.

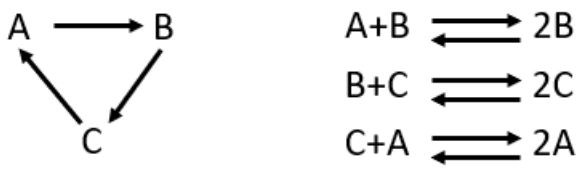

Figure 5.3

Example:5.2.6

Example 5.2.6. Consider the CRN in Figure 5.3. Remembering Example 4.2.14 it is obvious to see that the network is not Γ-balanced. We will show on the contrary that it is Δ-balanced on a graph-related complete set of reaction loops.

We define:

$$\Delta = \{\delta_1 = ((r_1{}^1, q_1{}^1), (r_2{}^1, q_2{}^1), (r_3{}^1, q_3{}^1));$$

$$\delta_2 = ((r_1{}^2, q_1{}^2), (r_2{}^2, q_2{}^2));$$

$$\delta_3 = ((r_1{}^3, q_1{}^3), (r_2{}^3, q_2{}^3));$$

$$\delta_4 = ((r_1{}^4, q_1{}^4), (r_2{}^4, q_2{}^4))\}$$

$$
\begin{aligned}
r_1{}^1 &= A \to B \\
r_2{}^1 &= B \to C \\
r_3{}^1 &= C \to A \\
r_1{}^2 &= A + B \to 2B \\
r_2{}^2 &= 2B \to A + B \\
r_1{}^3 &= B + C \to 2C \\
r_2{}^3 &= 2C \to B + C \\
r_1{}^4 &= C + A \to 2A \\
r_2{}^4 &= 2A \to C + A
\end{aligned}
$$

$$
\begin{cases}
q_1{}^1 = \lambda_{A\to B} \\
q_2{}^1 = \lambda_{B\to C} \\
q_3{}^1 = \lambda_{C\to A} \\
q_1{}^2 = \lambda_{A+B\to 2B} \\
q_2{}^2 = \lambda_{2B\to A+B} \\
q_1{}^3 = \lambda_{B+C\to 2C} \\
q_2{}^3 = \lambda_{2C\to B+C} \\
q_1{}^4 = \lambda_{C+A\to 2A} \\
q_2{}^4 = \lambda_{2A\to C+A}
\end{cases}
$$

The minimal, not basic closed paths are:

$$
s_1(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \end{bmatrix}, 2, 1\right)\right)
$$

$$
s_2(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \end{bmatrix}, 3, 1\right)\right)
$$

$$s_3(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \end{bmatrix}, 2, 1\right)\right)$$

$$s_4(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 1, 3\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \end{bmatrix}, 3, 1\right)\right)$$

$$s_5(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \end{bmatrix}, 1, 3\right)\right)$$

$$s_6(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \end{bmatrix}, 1, 4\right)\right)$$

$$s_7(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 1, 4\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \end{bmatrix}, 2, 1\right)\right)$$

$$s_8(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 1, 3\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \end{bmatrix}, 3, 1\right)\right)$$

$$s_9(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \end{bmatrix}, 1, 3\right)\right)$$

$$s_{10}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \end{bmatrix}, 1, 4\right)\right)$$

$$s_{11}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 1, 4\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \end{bmatrix}, 2, 1\right)\right)$$

$$s_{12}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 1, 3\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \end{bmatrix}, 1, 4\right)\right)$$

$$s_{13}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 1, 4\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \end{bmatrix}, 1, 3\right)\right)$$

$$s_{14}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 1, 3\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \end{bmatrix}, 1, 4\right)\right)$$

$$s_{15}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 1, 4\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \end{bmatrix}, 1, 3\right)\right)$$

$$s_{16}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 2\right)\right)$$

$$s_{17}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 - 1 \\ x_3 + 1 \end{bmatrix}, 2, 3\right)\right)$$

$$s_{18}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 + 1 \\ x_2 \\ x_3 - 1 \end{bmatrix}, 2, 4\right)\right)$$

Below we compute the score for the most identifying paths. The other ones have similar structure and so the counts are almost the same and lead to similar results and same conditions.

$$\eta(s_2(x)) = \frac{k_{A+B\to 2B} x_1 x_2}{k_{2B\to A+B}(x_2+1)x_2} \frac{k_{B\to C}(x_2+1)}{k_{C\to A}(x_3+1)} \frac{k_{C\to A}(x_3+1)}{k_{A\to B} x_1},$$

which is equal to 1 if and only if $\frac{k_{A+B\to 2B}}{k_{2B\to A+B}} = \frac{k_{A\to B}}{k_{B\to C}}$.

$$\eta(s_3(x)) = \frac{k_{A+B\to 2B} x_1 x_2}{k_{2B\to A+B}(x_2+1)x_2} \frac{k_{C\to A} x_3}{k_{A\to B} x_1} \frac{k_{B\to C}(x_2+1)}{k_{C\to A} x_3},$$

which is equal to 1 if and only if $\frac{k_{A+B\to 2B}}{k_{2B\to A+B}} = \frac{k_{A\to B}}{k_{B\to C}}$.

$$\eta(s_8(x)) = \frac{k_{A+B\to 2B}x_1x_2}{k_{2B\to A+B}(x_2+1)x_2}\frac{k_{B+C\to 2C}(x_2+1)x_3}{k_{2C\to B+C}(x_3+1)x_3}\frac{k_{C\to A}(x_3+1)}{k_{A\to B}x_1},$$

which is equal to 1 if and only if $\frac{k_{A+B\to 2B}}{k_{2B\to A+B}}\frac{k_{B+C\to 2C}}{k_{2C\to B+C}}\frac{k_{C\to A}}{k_{A\to B}} = 1$.

$$\eta(s_9(x)) = \frac{k_{A+B\to 2B}x_1x_2}{k_{2B\to A+B}(x_2+1)x_2}\frac{k_{C\to A}x_3}{k_{A\to B}x_1}\frac{k_{B+C\to 2C}(x_2+1)(x_3-1)}{k_{2C\to B+C}x_3(x_3-1)},$$

which is equal to 1 if and only if $\frac{k_{A+B\to 2B}}{k_{2B\to A+B}}\frac{k_{B+C\to 2C}}{k_{2C\to B+C}}\frac{k_{C\to A}}{k_{A\to B}} = 1$.

$$\eta(s_{14}(x)) = \frac{k_{A+B\to 2B}x_1x_2}{k_{2B\to A+B}(x_2+1)x_2}\frac{k_{B+C\to 2C}(x_2+1)x_3}{k_{2C\to B+C}(x_3+1)x_3}\frac{k_{C+A\to 2A}(x_3+1)(x_1-1)}{k_{2A\to C+A}x_1(x_1-1)},$$

which is equal to 1 if and only if $\frac{k_{A+B\to 2B}}{k_{2B\to A+B}}\frac{k_{B+C\to 2C}}{k_{2C\to B+C}}\frac{k_{C+A\to 2A}}{k_{2A\to C+A}} = 1$.

$$\eta(s_{15}(x)) = \frac{k_{A+B\to 2B}x_1x_2}{k_{2B\to A+B}(x_2+1)x_2}\frac{k_{C+A\to 2A}x_3(x_1-1)}{k_{2A\to C+A}x_1(x_1-1)}\frac{k_{B+C\to 2C}(x_2+1)(x_3-1)}{k_{2C\to B+C}x_3(x_3-1)},$$

which is equal to 1 if and only if $\frac{k_{A+B\to 2B}}{k_{2B\to A+B}}\frac{k_{B+C\to 2C}}{k_{2C\to B+C}}\frac{k_{C+A\to 2A}}{k_{2A\to C+A}} = 1$.

$$\eta(s_{16}(x)) = \frac{k_{A\to B}x_1}{k_{B\to C}(x_2+1)}\frac{k_{2B\to A+B}(x_2+1)x_2}{k_{A+B\to 2B}x_1x_2},$$

which is equal to 1 if and only if $\frac{k_{A+B\to 2B}}{k_{2B\to A+B}} = \frac{k_{A\to B}}{k_{B\to C}}$.

$$\eta(s_{17}(x)) = \frac{k_{B\to C}x_2}{k_{C\to A}(x_3+1)}\frac{k_{2C\to B+C}(x_3+1)x_3}{k_{B+C\to 2C}x_2x_3},$$

which is equal to 1 if and only if $\frac{k_{B+C\to 2C}}{k_{2C\to B+C}} = \frac{k_{B\to C}}{k_{C\to A}}$.

$$\eta(s_{18}(x)) = \frac{k_{C\to A}x_3}{k_{A\to B}(x_1+1)}\frac{k_{2A\to C+A}(x_1+1)x_1}{k_{C+A\to 2A}x_1x_3},$$

which is equal to 1 if and only if $\frac{k_{C+A\to 2A}}{k_{2A\to C+A}} = \frac{k_{C\to A}}{k_{A\to B}}$.

Then **if the conditions hold** the score of all minimal closed paths is 1 and the network is Δ-balanced. Hence we can build a stationary complex balanced (remember Proposition 5.1.4) measure for the system in the following way.

The closed irreducible sets for this model are given by:

$$\Upsilon_N = \{x \in \mathbb{Z}^3_{\geq 0} \mid x_1 + x_2 + x_3 = N, N \in \mathbb{Z}_{\geq 0}\}. \tag{73}$$

For each Υ_N we set $x^* = (N, 0, 0)$. Then if we chose as path from x^* to x the one in which transition $A \to B$ occurs $x_2 + x_3$ times and then transition $B \to C$ occurs x_3 times, by (55) we have:

$$\mu(x) = \eta(x^*, x) = \frac{\prod_{l=0}^{x_2+x_3-1} k_{A\to B}(x_1+x_2+x_3-l)}{\prod_{l=1}^{x_2+x_3} k_{B\to C}l}\frac{\prod_{l=0}^{x_3-1} k_{B\to C}(x_2+x_3-l)}{\prod_{l=1}^{x_3} k_{C\to A}l} =$$

$$\frac{k_{A\to B}^{x_2+x_3}}{k_{B\to C}^{x_2}k_{C\to A}^{x_3}}\frac{(x_1+x_2+x_3)!}{x_1!x_2!x_3!}.$$

Remark 5.2.7. Notice that we prove the existence of a stationary measure for a complex-balanced, weak-reversible and conservative CRN with deficiency $\delta = |C| - l - s = 9 - 4 - 2 = 3$.

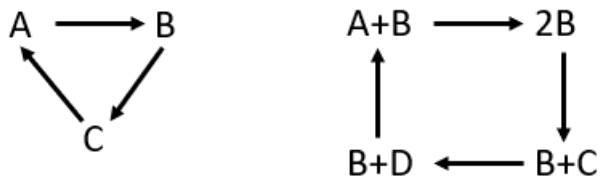

Figure 5.4

Example:5.2.8

Example 5.2.8. Consider the CRN in Figure 5.4. Also in this case it is obvious to see that the network is not Γ-balanced. Indeed if we consider the complete set of reaction vector loops:

$$\Gamma = \{\gamma_1 = ((\xi_1{}^1, p_1{}^1), (\xi_2{}^1, p_2{}^1), (\xi_3{}^1, p_3{}^1));$$

$$\gamma_2 = ((\xi_1{}^2, p_2{}^2), (\xi_2{}^2, p_2{}^2), (\xi_3{}^2, p_3{}^2), (\xi_4{}^2, p_4{}^2))\},$$

with:

$$\xi_1{}^1 = \xi_1{}^2 = \xi_{A\to B, A+B\to 2B}$$

$$\xi_2{}^1 = \xi_2{}^2 = \xi_{B\to C, 2B\to B+C}$$

$$\xi_3{}^1 = \xi_{C\to A}$$

$$\xi_3{}^2 = \xi_{B+C\to B+D}$$

$$\xi_4{}^2 = \xi_{B+D\to A+B},$$

and

$$
\begin{aligned}
{p_1}^1 &= \alpha(\lambda_{A\to B} + \lambda_{A+B\to 2B}) \\
{p_1}^2 &= (1-\alpha)(\lambda_{A\to B} + \lambda_{A+B\to 2B}) \\
{p_2}^1 &= \beta(\lambda_{B\to C} + \lambda_{2B\to B+C}) \\
{p_2}^2 &= (1-\beta)(\lambda_{B\to C} + \lambda_{2B\to B+C}) \\
{p_3}^1 &= \lambda_{C\to A} \\
{p_3}^2 &= \lambda_{B+C\to B+D} \\
{p_4}^2 &= \lambda_{B+D\to A+B},
\end{aligned}
$$

with $\alpha, \beta \geq 0$. And if we compute the score of the closed path:

$$
s(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \end{bmatrix}, 2, 1\right)\right),
$$

we have:

$$
\eta(s(x)) = \frac{k_{A\to B}x_1 + k_{A+B\to 2B}x_1x_2}{k_{B\to C}(x_2+1) + k_{2B\to B+C}(x_2+1)x_2} \frac{k_{C\to A}x_3}{k_{A\to B}x_1 + k_{A+B\to 2B}x_1(x_2+1)}
$$
$$
\frac{k_{B\to C}(x_2+1) + k_{2B\to B+C}(x_2+1)x_2}{k_{C\to A}x_3},
$$

which is obviously different from 1.

On the other hand we want to verify if the network is Δ-balanced on a graph-related complete set of reaction loops.

We define:

$$
\Delta = \{\delta_1 = (({r_1}^1, {q_1}^1), ({r_2}^1, {q_2}^1), ({r_3}^1, {q_3}^1));
$$
$$
\delta_2 = (({r_1}^2, {q_1}^2), ({r_2}^2, {q_2}^2), ({r_3}^2, {q_3}^2), ({r_4}^2, {q_4}^2))\}
$$

$$
\begin{aligned}
{r_1}^1 &= A \to B \\
{r_2}^1 &= B \to C \\
{r_3}^1 &= C \to A \\
{r_1}^2 &= A + B \to 2B \\
{r_2}^2 &= 2B \to B + C \\
{r_3}^2 &= B + C \to B + D \\
{r_4}^2 &= B + D \to A + B
\end{aligned}
$$

$$
\begin{cases}
{q_1}^1 = \lambda_{A \to B} \\
{q_2}^1 = \lambda_{B \to C} \\
{q_3}^1 = \lambda_{C \to A} \\
{q_1}^2 = \lambda_{A+B \to 2B} \\
{q_2}^2 = \lambda_{2B \to B+C} \\
{q_3}^2 = \lambda_{B+C \to B+D} \\
{q_4}^2 = \lambda_{B+D \to A+B}
\end{cases}
$$

The minimal, not basic closed paths are:

$$
s_1(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1 \right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ x_4 \end{bmatrix}, 3, 1 \right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 \end{bmatrix}, 2, 1 \right) \right)
$$

$$
s_2(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 2 \right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ x_4 \end{bmatrix}, 2, 1 \right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \\ x_4 \end{bmatrix}, 3, 1 \right) \right)
$$

$$s_3(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ x_4 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 \end{bmatrix}, 2, 1\right)\right)$$

$$s_4(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ x_4 \end{bmatrix}, 2, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \\ x_4 \end{bmatrix}, 3, 1\right)\right)$$

$$s_5(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ x_4 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 \end{bmatrix}, 2, 2\right)\right)$$

$$s_6(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ x_4 \end{bmatrix}, 2, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \\ x_4 \end{bmatrix}, 3, 1\right)\right)$$

$$s_7(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ x_4 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 \end{bmatrix}, 2, 2\right)\right)$$

$$s_7(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ x_4 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 \end{bmatrix}, 2, 2\right)\right)$$

$$s_8(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 2, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \\ x_4 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 + 1 \\ x_4 - 1 \end{bmatrix}, 3, 2\right)\right),$$

$$s_9(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 \\ x_4 - 1 \end{bmatrix}, 2, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 + 1 \\ x_4 - 1 \end{bmatrix}, 3, 2\right)\right),$$

$$s_{10}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 \\ x_4 - 1 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 \end{bmatrix}, 2, 2\right)\right),$$

$$s_{11}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 + 1 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 \end{bmatrix}, 2, 2\right)\right),$$

$$s_{12}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 + 1 \end{bmatrix}, 2, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 \\ x_4 + 1 \end{bmatrix}, 4, 2\right)\right),$$

$$s_{13}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 2, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \\ x_4 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 + 1 \\ x_4 - 1 \end{bmatrix}, 3, 2\right)\right),$$

$$s_{14}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 \\ x_4 - 1 \end{bmatrix}, 2, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 + 1 \\ x_4 - 1 \end{bmatrix}, 3, 2\right)\right),$$

$$s_{15}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 \\ x_4 - 1 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 \end{bmatrix}, 2, 2\right)\right),$$

$$s_{15}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 + 1 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 \end{bmatrix}, 2, 2\right)\right),$$

$$s_{17}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 + 1 \end{bmatrix}, 2, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 \\ x_4 + 1 \end{bmatrix}, 4, 2\right)\right),$$

$$s_{18}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \\ x_4 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 + 1 \\ x_4 - 1 \end{bmatrix}, 3, 2\right)\right),$$

$$s_{19}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 \\ x_4 - 1 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 + 1 \\ x_4 - 1 \end{bmatrix}, 3, 2\right)\right),$$

$$s_{20}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 \\ x_4 - 1 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 \end{bmatrix}, 2, 1\right)\right),$$

$$s_{21}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 + 1 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 \end{bmatrix}, 2, 1\right)\right),$$

$$s_{22}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 + 1 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 \\ x_4 + 1 \end{bmatrix}, 4, 2\right)\right),$$

$$s_{23}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 1 \\ x_4 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 + 1 \\ x_4 - 1 \end{bmatrix}, 3, 2\right)\right),$$

$$s_{24}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 \\ x_4 - 1 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 + 1 \\ x_4 - 1 \end{bmatrix}, 3, 2\right)\right),$$

$$s_{25}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 \\ x_4 - 1 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 \end{bmatrix}, 2, 1\right)\right),$$

$$s_{26}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 + 1 \end{bmatrix}, 4, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 \end{bmatrix}, 2, 1\right)\right),$$

$$s_{27}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \\ 4 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 - 1 \\ x_4 + 1 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 \\ x_4 + 1 \end{bmatrix}, 4, 2\right)\right),$$

Below we compute the score for the most identifying paths. The other ones derive from similar counts or were already computed in previous examples.

$$\eta(s_{23}(x)) = \frac{k_{A\to B}x_1}{k_{B\to C}(x_2+1)} \frac{k_{B\to C}(x_2+1)}{k_{C\to A}(x_3+1)} \frac{k_{B+D\to A+B}x_2x_4}{k_{A+B\to 2B}x_1x_2} \frac{k_{B+C\to B+D}x_2(x_3+1)}{k_{B+D\to A+B}x_2x_4},$$

which is equal to 1 if and only if $\frac{k_{A+B\to 2B}}{k_{B+C\to B+D}} = \frac{k_{A\to B}}{k_{C\to A}}$.

$$\eta(s_{24}(x)) = \frac{k_{A\to B}x_1}{k_{B\to C}(x_2+1)} \frac{k_{B+C\to B+D}(x_2+1)x_3}{k_{B+D\to A+B}(x_2+1)(x_4+1)} \frac{k_{B\to C}(x_2+1)}{k_{C\to A}x_3} \frac{k_{B+D\to A+B}x_2(x_4+1)}{k_{A+B\to 2B}x_1x_2},$$

which is equal to 1 if and only if $\frac{k_{A+B\to 2B}}{k_{B+C\to B+D}} = \frac{k_{A\to B}}{k_{C\to A}}$.

$$\eta(s_{25}(x)) = \frac{k_{A\to B}x_1}{k_{B\to C}(x_2+1)} \frac{k_{B+C\to B+D}(x_2+1)x_3}{k_{B+D\to A+B}(x_2+1)(x_4+1)} \frac{k_{B+D\to A+B}(x_2+1)(x_4+1)}{k_{A+B\to 2B}x_1(x_2+1)} \frac{k_{B\to C}(x_2+1)}{k_{C\to A}x_3},$$

which is equal to 1 if and only if $\frac{k_{A+B\to 2B}}{k_{B+C\to B+D}} = \frac{k_{A\to B}}{k_{C\to A}}$.

$$\eta(s_{26}(x)) = \frac{k_{A\to B}x_1}{k_{B\to C}(x_2+1)}\frac{k_{B+D\to A+B}(x_2+1)x_4}{k_{A+B\to 2B}x_1(x_2+1)}\frac{k_{B+C\to B+D}(x_2+1)x_3}{k_{B+D\to A+B}(x_2+1)x_4}\frac{k_{B\to C}(x_2+1)}{k_{C\to A}x_3},$$

which is equal to 1 if and only if $\frac{k_{A+B\to 2B}}{k_{B+C\to B+D}} = \frac{k_{A\to B}}{k_{C\to A}}$.

$$\eta(s_{27}(x)) = \frac{k_{A\to B}x_1}{k_{B\to C}(x_2+1)}\frac{k_{B+D\to A+B}(x_2+1)x_4}{k_{A+B\to 2B}x_1(x_2+1)}\frac{k_{B\to C}(x_2+1)}{k_{C\to A}(x_3+1)}\frac{k_{B+C\to B+D}x_2(x_3+1)}{k_{B+D\to A+B}x_2x_4},$$

which is equal to 1 if and only if $\frac{k_{A+B\to 2B}}{k_{B+C\to B+D}} = \frac{k_{A\to B}}{k_{C\to A}}$.

Then carrying out the counts, if the conditions $\frac{k_{A+B\to 2B}}{k_{2B\to B+C}} = \frac{k_{A\to B}}{k_{B\to C}}$, $\frac{k_{2B\to B+C}}{k_{B+C\to B+D}} = \frac{k_{B\to C}}{k_{C\to A}}$, $\frac{k_{A+B\to 2B}}{k_{B+C\to B+D}} = \frac{k_{A\to B}}{k_{C\to A}}$ hold, the score of all minimal closed paths is 1 and the network is Δ-balanced. Hence we can build a stationary complex balanced (remember Proposition 5.1.4) measure for the system in the following way.

The closed irreducible sets for this model are given by:

$$\Upsilon_N = \{x \in \mathbb{Z}^3_{\geq 0} \mid x_1 + x_2 + x_3 + x_4 = N, N \in \mathbb{Z}_{\geq 0}\}. \tag{74}$$

For each Υ_N we set $x^* = (N, 0, 0, 0)$. Then if chose as path from x^* to x the one in which transition $A \to B$ occurs $x_2 + x_3 + x_4$ times, then transition $2B \to B + C$ occurs $x_3 + x_4$ times and then transition $B + C \to B + D$ occurs x_4 times, by (55) we have:

$$\mu(x) = \eta(x^*, x) = \frac{\prod_{l=0}^{x_2+x_3+x_4-1} k_{A\to B}(x_1+x_2+x_3+x_4-l)}{\prod_{l=1}^{x_2+x_3+x_4} k_{B\to C}l}$$

$$\frac{\prod_{l=0}^{x_3+x_4-1} k_{2B\to B+C}(x_2+x_3+x_4-l)(x_2+x_3+x_4-l-1)}{\prod_{l=1}^{x_3+x_4} k_{B+C\to B+D}l(x_2+x_3+x_4-l))}$$

$$\frac{\prod_{l=0}^{x_4-1} k_{B+C\to B+D}(x_3+x_4-l)x_2}{\prod_{l=1}^{x_4} k_{B+D\to A+B}lx_2} =$$

$$\frac{k_{A\to B}^{x_2+x_3+x_4}k_{2B\to B+C}^{x_3+x_4}}{k_{B\to C}^{x_2+x_3+x_4}k_{B+C\to B+D}^{x_3}k_{B+D\to A+B}^{x_4}}\frac{(x_1+x_2+x_3+x_4)!}{x_1!x_2!x_3!x_4!}.$$

Remark 5.2.9. Notice that we prove the existence of a complex-balanced stationary measure for a complex-balanced, weak-reversible and conservative CRN with deficiency $\delta = |C| - l - s = 7 - 2 - 3 = 2$.

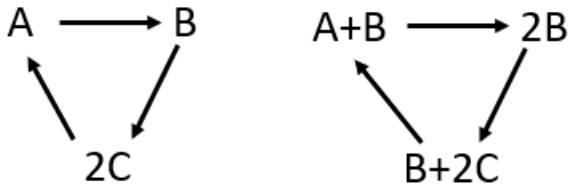

Figure 5.5

Example:5.2.10

Example 5.2.10. Consider the CRN in Figure 5.5. We would like to know if we can find and build a stationary measure for the system.

Let's consider the following graph-related complete set of reaction loops:

$$\Delta = \{\delta_1 = ((r_1{}^1, q_1{}^1), (r_2{}^1, q_2{}^1), (r_3{}^1, q_3{}^1));$$

$$\delta_2 = ((r_1{}^2, q_1{}^2), (r_2{}^2, q_2{}^2), (r_3{}^2, q_3{}^2))\}$$

$$r_1{}^1 = A \to B$$

$$r_2{}^1 = B \to 2C$$

$$r_3{}^1 = 2C \to A$$

$$r_1{}^2 = A + B \to 2B$$

$$r_2{}^2 = 2B \to B + 2C$$

$$r_3{}^2 = B + 2C \to A + B$$

$$\begin{cases} {q_1}^1 = \lambda_{A\to B} \\ {q_2}^1 = \lambda_{B\to 2C} \\ {q_3}^1 = \lambda_{2C\to A} \\ {q_1}^2 = \lambda_{A+B\to 2B} \\ {q_2}^2 = \lambda_{2B\to B+2C} \\ {q_3}^2 = \lambda_{B+2C\to A+B} \end{cases}$$

The minimal, not basic closed paths are:

$$s_1(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 2 \end{bmatrix}, 2, 1\right)\right)$$

$$s_2(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 2 \end{bmatrix}, 3, 1\right)\right)$$

$$s_3(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 2 \end{bmatrix}, 2, 1\right)\right)$$

$$s_4(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 2 \end{bmatrix}, 3, 1\right)\right)$$

$$s_5(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 2 \end{bmatrix}, 2, 2\right)\right)$$

$$s_6(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 2 \end{bmatrix}, 3, 2\right)\right)$$

$$s_7(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 2 \end{bmatrix}, 2, 1\right)\right)$$

$$s_8(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 2 \end{bmatrix}, 3, 1\right)\right)$$

$$s_9(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 2 \end{bmatrix}, 2, 2\right)\right)$$

$$s_{10}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 2 \end{bmatrix}, 3, 2\right)\right)$$

$$s_{11}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 2 \end{bmatrix}, 2, 1\right)\right)$$

$$s_{12}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 2 \end{bmatrix}, 3, 2\right)\right)$$

$$s_{13}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 2 \end{bmatrix}, 2, 2\right)\right)$$

$$s_{14}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 2 \end{bmatrix}, 2, 2\right)\right)$$

$$s_{15}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 2 \end{bmatrix}, 3, 2\right)\right)$$

$$s_{16}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 2 \end{bmatrix}, 2, 2\right)\right)$$

$$s_{17}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 2 \end{bmatrix}, 3, 2\right)\right)$$

$$s_{18}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 2 \end{bmatrix}, 2, 1\right)\right)$$

$$s_{19}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 2 \end{bmatrix}, 3, 1\right)\right)$$

$$s_{20}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 2 \end{bmatrix}, 2, 2\right)\right)$$

$$s_{21}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 2 \end{bmatrix}, 3, 2\right)\right)$$

$$s_{22}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 2\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 2 \end{bmatrix}, 2, 1\right)\right)$$

$$s_{23}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 2 \end{bmatrix}, 3, 1\right)\right)$$

$$s_{24}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 2 \end{bmatrix}, 2, 2\right)\right)$$

$$s_{25}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 2, 1\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 \\ x_3 + 2 \end{bmatrix}, 3, 1\right)\right)$$

$$s_{26}(x) = \left(\left(\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, 1, 2\right), \left(\begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ x_3 \end{bmatrix}, 3, 1\right), \left(\begin{bmatrix} x_1 \\ x_2 + 1 \\ x_3 - 2 \end{bmatrix}, 2, 1\right)\right)$$

Below we compute the score for the most identifying paths.

$$\eta(s_1(x)) = \frac{k_{A\to B}x_1}{k_{B\to 2C}(x_2+1)}\frac{k_{2C\to A}x_3(x_3-1)}{k_{A\to B}x_1}\frac{k_{B\to 2C}(x_2+1)}{k_{2C\to A}x_3(x_3-1)}\frac{k_{B+C\to B+D}x_2(x_3+1)}{k_{B+D\to A+B}x_2x_4},$$

which is equal to 1.

$$\eta(s_8(x)) = \frac{k_{A+B\to 2B}x_1x_2}{k_{2B\to B+2C}(x_2+1)x_2}\frac{k_{2B\to B+2C}(x_2+1)x_2}{k_{B+2C\to A+B}x_2(x_3+2)(x_3+1)}\frac{k_{2C\to A}(x_3+2)(x_3+1)}{k_{A\to B}x_1},$$

which is equal to 1 if and only if $\frac{k_{A+B\to 2B}}{k_{B+2C\to A+B}} = \frac{k_{A\to B}}{k_{2C\to A}}$.

$$\eta(s_{14}(x)) = \frac{k_{A+B\to 2B}x_1x_2}{k_{2B\to B+2C}(x_2+1)x_2}\frac{k_{B+2C\to A+B}(x_2+1)x_3(x_3-1)}{k_{A+B\to 2B}x_1(x_2+1)}\frac{k_{2B\to B+2C}(x_2+1)x_2}{k_{B+2C\to A+B}x_2x_3(x_3-1)},$$

which is equal to 1.

Then carrying out the counts, if the conditions $\frac{k_{A+B\to 2B}}{k_{2B\to B+2C}} = \frac{k_{A\to B}}{k_{B\to 2C}}$, $\frac{k_{2B\to B+2C}}{k_{B+2C\to A+B}} = \frac{k_{B\to 2C}}{k_{2C\to A}}$ hold, the score of all minimal closed paths is 1 and the network is Δ-balanced. Hence we can build a stationary complex balanced measure for the system in the following way.

The closed irreducible sets for this model are given by:

$$\Upsilon_N = \{x \in \mathbb{Z}^3_{\geq 0} \mid 2x_1 + 2x_2 + x_3 = N, N \in \mathbb{Z}_{\geq 0}\}. \tag{75}$$

For each Υ_N we set $x^* = (0, 0, N)$. Then if chose as path from x^* to x the one in which transition $2C \to A$ occurs $x_1 + x_1$ times, then transition $A \to B$ occurs x_2 times, by (55) we have:

$$\mu(x) = \eta(x^*, x) = \frac{\prod_{l=0}^{x_1+x_2-1} k_{2C\to A}(2x_1 + 2x_2 + x_3 - 2l)(2x_1 + 2x_2 + x_3 - 2l - 1)}{\prod_{l=1}^{x_1+x_1} k_{A\to B} l}$$

$$\frac{\prod_{l=0}^{x_2-1} k_{A\to B}(x_1 + x_1 - l)}{\prod_{l=1}^{x_2} k_{B\to 2C} l}$$

$$\frac{k_{2C\to A}^{x_1+x_1}}{k_{A\to B}^{x_1} k_{B\to 2C}^{x_2}} \frac{(2x_1 + 2x_2 + x_3)!}{x_1!x_2!x_3!}.$$

Remark 5.2.11. Notice that we prove the existence of a complex-balanced stationary measure for a complex-balanced, weak-reversible and conservative CRN with deficiency $\delta = |C| - l - s = 6 - 2 - 2 = 2$.

Then we proved that Δ-balancing on a graph-related complete set of reaction loops does not imply Γ-balancing for the corresponding natural complete set of reaction vector loops.
Moreover we found that Δ-balancing on graph-related complete set of reaction vector loops makes it possible to find complex-balanced (then stationary) measures, for Chemical Reaction Networks with deficiency greater then 1.

Remark 5.2.12. Notice that there is a specific reason because of which the previous balance conditions are verified, that is the score of all closed paths are ones.

Let $(\mathcal{G}, \Lambda)$ be a stochastic weak-reversible mass-action reaction network and let $\Upsilon \subseteq \mathbb{Z}^n_{\geq 0}$ be a closed set. Let moreover Δ be a graph-related complete set of reaction loops on Υ.
Let's take $\delta_1 = \left((y^1_i \to y'^1_i, q^1_i)\right)_{i=1}^{n_1}$, $\delta_2 = \left((y^2_j \to y'^2_j, q^2_j)\right)_{j=1}^{n_2} \in \Delta$ and suppose that:

- the CRN restricted to δ_1 is balanced
- there exist $k \in \{1, ..., n_1\}$ and $h \in \{1, ..., n_2\}$ such that $y'^1_k - y^1_k = y'^2_h - y^2_h = \xi$, with:

$$y^1_k \to y'^1_k \text{ equal to } \sum_{s\in\mathcal{S}} y^1_{k,s} S_s \to \sum_{s\in\mathcal{S}} (y^1_{k,s} + \xi_s) S_s \tag{76}$$

  and

$$y^2_h \to y'^2_h \text{ equal to } \sum_{s\in\mathcal{S}} y^2_{h,s} S_s \to \sum_{s\in\mathcal{S}} (y^2_{h,s} + \xi_s) S_s. \tag{77}$$

- $q^1_i(x) = a_i \lambda_{y^1_i \to y'^1_i}(x)$, $i = 1, ..., n_1$ and $q^2_j(x) = b_j \lambda_{y^2_j \to y'^2_j}(x)$, $j = 1, ..., n_2$, with $a_i, b_j \in [0, 1]$, $\forall\, i, j$

Now fix $x \in \Upsilon$ and consider a generic closed path build on γ_1:

$$s(x) = \{(x_l, i_l, 1)\}_{l=1}^{n_1 - 1}, \text{ with } x_1 = x.$$

We have that, by hypothesis:

$$\eta(s(x)) = \prod_{l=1}^{n_1-1} \frac{q^1_{i_l}(x_l)}{q^1_{i_l+1}(x_l + y'^1_{i_l} - y^1_{i_l})} = 1.$$

Now we know that necessarily there exists $l^* \in \{1, ..., n_1 - 1\} \mid i_{l^*} = k$, with corresponding factor:

$$\frac{q^1_k(x_{l^*})}{q^1_{k+1}(x_{l^*} + y'^1_k - y^1_k)} =$$

$$\prod_{s\in\mathcal{S}} a_k k_{y^1_k \to y'^1_k} \frac{x_s!}{(x_s - y^1_{k,s})!} \frac{1}{a_{k+1} k_{y'^1_k \to y'^1_{k+1}}} \frac{(x_s + \xi_s - (y^1_{k,s} + \xi_s))!}{(x_s + \xi_s)!} =$$

$$\prod_{s\in\mathcal{S}} \frac{a_k k_{y^1_k \to y'^1_k}}{a_{k+1} k_{y'^1_k \to y'^1_{k+1}}} \frac{x_s!}{(x_s + \xi_s)!},$$

with this holding because of the definition of graph-related complete set and of rate coefficients for a stochastic mass-action network.

Now, since $y^2_h \to y'^2_h$ leads to the same system change ξ, we can build a new path as follows:

$$\hat{s}(x) = \{(x_1, i_1, 1), (x_2, i_2, 1), ..., (x_{l^*-1}, i_{l^*-1}, 1), (x_{l^*}, h, 22), (x_{l^*+1}, i_{l^*+1}, 1), ..., (x_{n_1-1}, i_{n_1-1}, 1)\},$$

with $x_1 = x$.

We want to prove that also $\eta(\hat{s}) = 1$.

If we consider the definition of $\eta(\hat{s})$ and the more general definition of score for a path, it's easy to see that $\eta(\hat{s})$ differs from $\eta(s)$ only for the l^*th factor, which in this case is:

$$\frac{q^2_h(x_{l^*})}{q^2_{h+1}(x_{l^*} + y'^2_h - y^2_h))}. \tag{78}$$

Notice that we haven't changed x_{l^*} because the two reactions lead to the same state change, and so the state succession remains the same.

Then exactly as before (78) is equal to:

$$\prod_{s\in\mathcal{S}} b_h k_{y^2_h \to y'^2_h} \frac{x_s!}{(x_s - y^2_{h,s})!} \frac{1}{b_{h+1} k_{y'^2_h \to y'^2_{h+1}}} \frac{(x_s + \xi_s - (y^2_{h,s} + \xi_s))!}{(x_s + \xi_s)!} =$$

$$\prod_{s\in\mathcal{S}} \frac{b_h k_{y^2_h \to y'^2_h}}{b_{h+1} k_{y'^2_h \to y'^2_{h+1}}} \frac{x_s!}{(x_s + \xi_s)!}.$$

Then, under the condition

$$\frac{a_k k_{y^1_k \to y'^1_k}}{a_{k+1} k_{y'^1_k \to y'^1_{k+1}}} = \frac{b_h k_{y^2_h \to y'^2_h}}{b_{h+1} k_{y'^2_h \to y'^2_{h+1}}}, \tag{79}$$

the factor has the same value of the one before, and then $\eta(\hat{s}) = \eta(s) = 1$.

In the end notice that the same reasoning could be used when more then one reaction in one loop could be replaced with reactions belonging to other loops in the set. This because as we have just proved, each reaction will lead to a different factor in the score which however will have same value of the previous one. Hence, the total score will remain unchanged.

Conclusion

We showed that, for some Chemical Reaction Networks, it is possible to build a set of loops defined on the network reactions and, through them, characterize the state space of the corresponding Continuous Time Markov Chain. Starting from such a set of loops, a new balance condition has been defined for a system measure under which the measure has been proven to be both stationary and complex balanced.
Finally the thesis analyzed different CRNs, focusing in particular on conservative mass-action networks with deficiency greater than one. For these networks the existence and analytic form of a stationary measure, even if already known, were obtained again through the previous results, offering a new point of view from which to observe the problem. Examples were also provided as support.

Appendix A: On a generator of a Continuous time Markov chain

In this appendix we want to clarify the definition of generator for the CTMC modelling the underling network.
Consider a CTMC with rate matrix Λ and transition matrix of the underling DTMC Π. Firstly we introduce the following tools:

Definition 6.0.1 (Transition operator)**.** Let $f : E \to \mathbb{R}$ be a measurable function, with $f \in B(E)$ Banach space.
We define the **transition operator** P_t of f as:

$$(P_t f)(i) = \mathbb{E}[f(X_t)_0 = 0] = \mathbb{E}_i[f(X_t)] = \sum_{j \in E} f(j)\Pi_{ij}(t).$$

Definition 6.0.2 (Generator)**.** We call *generator* of the Markov chain, the operator A defined as follows:

$$Af(i) = \lim_{t \to 0} \frac{P_t f - f}{t}(i). \tag{80}$$

Proposition 6.0.3. *The following properties hold:*

1. $(P_s \circ P_t) = P_{s+t}$
2. $P_0 = I$
3. $(P_t)_t$ *is strongly continuous*
4. $Af(i) = \sum_j \Lambda_{ij}[f(j) - f(i)]$
5. *since* P_t *is strongly continuous we have*

$$\frac{d}{dt} P_t f = A(P_t f) = P_t(Af)$$

Proof. 1.

$$((P_s \circ P_t)f)(i) = (P_s(P_t f))(i) =$$

$$\mathbb{E}_i[P_t f(X_s)] = \sum_{k \in E} P_t f(k)\Pi_{ik}(s) =$$

$$\sum_{k\in E}\left[\sum_{j\in E} f(j)\Pi_{kj}(t)\right]\Pi_{ik}(s) =$$
$$\sum_{j\in E} f(j)\sum_{k\in E}\Pi_{ik}(s)\Pi_{kj}(t) =$$
$$\sum_{j\in E} f(j)\Pi_{ij}(s+t) =$$
$$\mathbb{E}_i\left[f(X_{t+s})\right] = P_{s+t}f(i),$$

where we have used the Chapman-Kolmogorov equation on the transition matrix of the underling DTMC.

2.

$$P_0 f(i) = \mathbb{E}\left[f(X_0)\dim X_0 = i\right] = f(i)$$

Notice that 1.+2. implies that the set of P_t is a semi-group.

3.

$$\lim_{t\to 0}(P_t f)(i) = \lim_{t\to 0}\mathbb{E}_i\left[f(X_t)\right] =$$
$$\lim_{t\to 0}\sum_{j\in E} f(j)\Pi_{ij}(t) =$$
$$\sum_{j\in E} f(j)\lim_{t\to 0}\Pi_{ij}(t) =$$
$$\sum_{j\in E} f(j)\delta_{ij} = f(i).$$

So $(P_t)_t$ is strongly continuous.

4.

$$Af(i) = \lim_{t\to 0}\frac{P_t f - f}{t}(i) =$$
$$\left(\frac{d}{dt}P_t f\right)|_{t=0}(i) =$$
$$\lim_{t\to 0}\sum_{j\in E} f(j)\frac{\Pi_{ij}(t)-\delta_{ij}}{t} =$$
$$\sum_{j\neq i}\left(f(j)\lim_{t\to 0}\frac{\Pi_{ij}(t)}{t}\right) - f(i)\lim_{t\to 0}\frac{\Pi_{ii}(t)-1}{t} =$$
$$\sum_{j\neq i} f(j)\Lambda_{ij} - f(i)\left(-\sum_{i\neq j}\Lambda_{ij}\right) =$$

$$\sum_j \Lambda_{ij} [f(j) - f(i)] .$$

□

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