Signed sensitivity of Markov chains and application to chemical reaction networks

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July 2022

Abstract

We consider continuous-time Markov chains on a finite state space that admit a unique stationary distribution. The state space together with the set of possible transitions form a directed graph that defines the structure of the Markov chain. We study how the stationary distribution responds to small changes in the transition rates and how this sensitivity is connected to the underlying graph structure. We provide a full qualitative description of the signs of the response, independent of the specific transition rates but purely dependent on the network structure. We show that these results can be extended to the more general setting of allowing negative rates in the Laplacian matrix. In the second part, these results are applied to study the sensitivity of chemical reaction networks. It is shown that the sensitivity of equilibria in reaction networks can be computed using the sensitivity of Laplacians containing potentially negative off-diagonal entries. This results in a new description of the sensitivity of general chemical reaction networks in terms of their underlying network structure.

1 Introduction

Markov chains are among the most common tools in mathematical modelling. They can be applied to create simplified models for population dynamics (including chemical reaction networks), molecular systems or coarse-grained random walks [1, 2]. Due to their simplicity, Markov chains can be studied both analytically and numerically, oftentimes with little effort. In this work we will only consider continuous-time Markov chains, for short CTMCs, on a finite state space that admit a stationary distribution.

We study the sensitivity of this equilibrium, i.e. how it responds to small perturbations in the transition rates. This analysis can be carried out in two different ways. There is the numerical viewpoint, which answers the question of how large these responses in the equilibrium can get, and there is the analytical view-point which analyses how exactly the response looks like. The latter case, which is the one we will focus on, is one of the key steps in the control problem, i.e. in order to achieve a desired response in the equilibrium one needs to understand how each possible perturbation of the system parameters influences the equilibrium. We present two main results on the sensitivity of CTMCs:

- **Theorem 3.1** An explicit formula of the sensitivity of the stationary distribution of an irreducible CTMC on a finite state space in terms of its underlying graph structure;

- **Corollary 3.2** A complete description of the algebraic signs of the sensitivity based on the underlying network structure, which can be determined efficiently.
These results motivate an extension to more complex dynamics. We show that such an extension is possible after generalizing the results for CTMCs to the abstract setting of Markov chains with negative transition rates. Clearly, negative transition rates cannot be interpreted in a stochastic setting anymore, however many concepts of Markov chains like stationary distributions and their sensitivity generalize.

We apply these generalized results to the equilibrium of chemical reaction networks. Chemical reaction networks mathematically model the evolution of chemicals components in a simplified model. These models may admit an equilibrium in which the concentrations of the components no longer fluctuate. Once again, it is possible to study the response of these equilibria to small perturbations in the system parameters. We consider the sensitivity analysis in an algebraic way, as it has been done by [3, 4]. While it is a common approach to model chemical reaction networks as a Markov chain [1], we will only use the sensitivity results of generalized CTMCs to obtain sensitivity results for reaction networks. In particular, we describe the sensitivity in terms of the network structure, i.e. the way that the chemical components are linked to one another by the reactions.

Section 2 introduces the necessary definitions on Markov chains and graph theory that will be needed for the following sections. Section 3 contains the main results on the sensitivity of CTMCs. In Section 3.1 we consider the generalized setting in which negative rates are allowed and show how the key concepts of stationary distributions and their sensitivity generalize. Section 3.2 contains the proofs of all results in Section 3. In Section 4 we briefly introduce chemical reaction networks and their sensitivity. In Section 4.1 we then show how the sensitivity results of generalized CTMCs can be applied to the sensitivity of chemical reaction networks and present a description of the sensitivity in terms of the structure of the reaction network. We conclude with an outlook on open problems in Section 5.

2 Preliminaries

2.1 Continuous-time Markov chains

Continuous-time Markov chains, short CTMCs, are one of the most basic types of stochastic processes. We will briefly describe a CTMC in stochastic terminology before switching to a purely deterministic characterisation. A CTMC on a finite state space can be described as a random walker \((X_t)_{t\in\mathbb{R}_+}\) on a directed graph \(\mathcal{G} = (\mathcal{V}, \mathcal{E})\), where \(\mathcal{V}\) is a finite set of nodes and \(\mathcal{E} \subset \mathcal{V} \times \mathcal{V}\) is a set of directed edges. In the following, we will not allow self-loops, i.e. edges of the form \((vv)\). We typically use letters \(u, v, w\) for nodes while edges are denoted with the letter \(j\).

At each point in time, the position of the random walker is given by a node in \(\mathcal{V}\), i.e. \(X_t \in \mathcal{V}\). The trajectory of \(X\) is assumed to be càdlàg. Hence, the process \(X\) jumps between the discrete states at discrete points in time. The edges \(\mathcal{E}\) indicate which transitions between the states are possible. To each edge \((uv) \in \mathcal{E}\) we associate a positive rate at which the walker is transitioning to \(v\) when in node \(u\). For an explicit formulation of continuous-time Markov chains, we refer to [5]. We denote the transition rate of an edge \((uv) \in \mathcal{E}\) by \(\ell_{uv}\) or simply \(\ell_j\) for \(j \in \mathcal{E}\). Hence, the rates \(\ell_j\) can be understood as weights of the edges in the graph. For \((uv) \notin \mathcal{E}\) we set \(\ell_{uv} = 0\). We define the Laplacian \(\mathcal{L} \in \mathbb{R}^{\mathcal{V} \times \mathcal{V}}\) of the CTMC as

\[
\mathcal{L}_{uv} = \begin{cases} 
\ell_{uv}, & u \neq v \\
-\sum_{w \neq v} \ell_{wv}, & u = v.
\end{cases} \tag{2.1}
\]

The diagonal entries \(\mathcal{L}_{vv}\) contain the total outgoing transition rates from a node \(v\). This matrix is
oftentimes referred to as the *generator* of the CTMC.

We shall study the probability distribution \( p(t) \in \mathbb{R}^V \) of the process \((X_t)_{t \in \mathbb{R}_+}\), which is defined as

\[
p(t)_v = P(X_t = v), \quad \forall v \in V.
\]

The Laplacian provides a purely deterministic representations of the Markov chain as a linear differential equation. Given an initial distribution \( p_0 \in \mathbb{R}^V \) of \( X_0 \), the probability vector \( p(t) \) satisfies

\[
\dot{p}(t) = L p(t),
\]

\[p(0) = p_0. \tag{2.2}\]

We will usually only characterize a CTMC by its Laplacian \( L \). The underlying graph structure can be derived from the positive values in \( L \). We call \( \mathcal{G} = (V, E) \) the *underlying graph* of the CTMC. We also write \( \mathcal{G} = (V, E, \ell) \) for the weighted graph whose edge weights are given by \((\ell_{ij})_{i,j \in E}\).

A probability vector \( \mu \in \mathbb{R}^V \) which is in the right kernel of \( L \) is called a *stationary distribution*, short stat. dist. A well-known result is that under suitable conditions a stationary distribution exists and is unique.

**Theorem 2.1.** Consider a CTMC with Laplacian \( L \) and let \( \mathcal{G} = (V, E) \) be the underlying graph. If \( \mathcal{G} \) is strongly connected, i.e. for any two nodes \( u, v \in V \) there is a directed path from \( u \) to \( v \), then a stat. dist. exists and is unique. In formula, there exists a unique vector \( \mu \in \mathbb{R}^V \) such that

\[
L \mu = 0, \quad \sum_{v \in V} \mu_v = 1.
\]

Additionally it holds that \( \mu_v > 0 \) for any \( v \in V \).

For a proof of the theorem, we refer to [6, Chapter 3], in which much more general results are stated. A CTMC whose underlying graph is strongly connected is called *irreducible*.

### 2.2 Rooted trees

Rooted trees are a common structure in graph theory, usually when working with determinants of graph-related matrices like in the matrix tree theorem [7].

**Definition 2.2.** Given a directed graph \( \mathcal{G} = (V, E) \) and a root node \( v_0 \in V \), we call a subgraph \( \mathcal{T} = (V', E') \) a *tree rooted in \( v_0 *\) if \( \mathcal{T} \) is a tree and every edge is directed towards \( v_0 \).

For a more detailed description of (rooted) trees, we refer to [8]. A rooted tree is also often referred to as an *arborescence* in the literature. Note that a rooted tree does not need to contain all vertices. In the case \( V' = V \), we call \( \mathcal{T} \) a *rooted spanning tree*. For any root node \( v_0 \in V \) we denote the set of all spanning trees rooted in \( v_0 \) by

\[
\mathcal{A}^{v_0} := \{ \mathcal{T} \subset \mathcal{G}, \mathcal{T} \text{ spanning tree rooted in } v_0 \}.
\]

The set of all rooted trees in \( \mathcal{G} \) is then defined as

\[
\mathcal{A} := \bigcup_{v_0 \in V} \mathcal{A}^{v_0}.
\]
If the graph is equipped with weights \((w_j)_{j \in E}\) (in general, we may allow negative weights) we can define the weight of a rooted tree \(T\) (not necessarily spanning) by

\[
\|T\| := \prod_{j \in T} w_j.
\]

Consequently, we define the quantities

\[
\|A^v_0\| := \sum_{T \in A^v_0} \|T\|, \\
\|A\| := \sum_{v_0 \in V} \|A^v_0\|.
\]  

(2.3)

In [9], these quantities are referred to as the focus of \(v_0\), respectively the total focus of the weighted graph \(G\). We include a remark about the extension of rooted trees, which will be a useful tool in some of the proofs later. It comes in the form of the following lemma.

**Lemma 2.3.** Let \(G = (V, E)\) be a directed graph and consider \(T' = (V', E')\) a tree rooted in some \(v_0 \in V'\) with \(V' \neq V\), i.e. \(T'\) is not spanning. Under the assumption that \(v_0\) is reachable from any \(v \in V\) by a directed path in \(G\), there exists a spanning tree \(T\) which is rooted in \(v_0\) such that \(T'\) is a subgraph of \(T\).

**Proof:** We provide an explicit construction of \(T\). We start with \(T = T'\). Consider any node \(u \notin T\). Since \(G\) is strongly connected, there exists a directed path \(\gamma\) from \(u\) to \(v_0\). Starting at \(u\), we add the edges of \(\gamma\) to \(T\) until we arrive at a node that is already in \(T\) (at the latest, this happens at \(v_0\)). The resulting \(T\) is still a tree, since we could not have added a loop. Additionally, \(T\) is still rooted in \(v_0\) since all edges that were added are directed towards \(v_0\). This procedure can be repeated until all nodes are part of \(T\). By construction \(T\) is a spanning tree rooted in \(v_0\) such that \(T'\) is a subgraph of \(T\).

\(\square\)

**Remark:** A special case of this Lemma states that in a strongly connected graph \(G\) there exists at least one spanning tree rooted in \(v_0\) for any \(v_0 \in V\). If all edge-weights of the graph are positive, this implies that \(\|A^v_0\| > 0\) and thereby \(\|A\| > 0\).

Finally, we define divided tree pairs, also known in the literature as 2-trees [10], which are a substructure of directed graphs. These structures will be the central object in the results of the following sections.

**Definition 2.4.** Let \(G = (V, E)\) be a directed graph. For \(w_1, w_2 \in V\), we call \((T_{w_1}, T_{w_2})\) a ’divided tree pair’, short dTp, if

(i) \(T_{w_i} \subset G\) is a tree rooted in \(w_i\), for \(i = 1, 2\);

(ii) \(\forall u \in V\) either \(u \in T_{w_1}\) (exclusive) or \(u \in T_{w_2}\).

For an edge \(j \in E\), we call a dTp \((T_{w_1}, T_{w_2})\) a \(j\)-divided tree pair, short \(j\)-dTp, if additionally

(iii) \(T_{w_1} \cup T_{w_2} \cup j\) is weakly connected.
There are a few observations to point out in this definition. The trees are allowed to consist of a single node. Condition (ii) forbids \( w_1 = w_2 \). Condition (iii) implies that the edge \( j \) has to connect the two tree and hence is part of neither of them. Additionally, for an edge \( j = (uv) \) and any \( j \)-divided tree pair \((T_{w_1}, T_{w_2})\) we find that either \( u \in T_{w_1}, v \in T_{w_2} \) or \( v \in T_{w_1}, u \in T_{w_2} \). To distinguish these cases in formula, we use square brackets to interpret a Boolean term as a numerical value of 0 or 1.

We write \( [u \in T_{w_1}] := \begin{cases} 1, & u \in T_{w_1} \\ 0, & u \notin T_{w_1} \end{cases} \). (2.4)

3 Markov chain sensitivity

In this section we will study how the stat. dist. \( \mu \) of an irreducible Markov chain changes when slightly perturbing the transition rates. For simplicity, we study the effect of perturbing only one selected transition rate at a time. Our aim is to study how the structure of the underlying graph dictates the changes in the stat. dist. under such perturbations.

Consider an irreducible CTMC with Laplacian \( \mathcal{L} \) and let \( \mathcal{G} = (\mathcal{V}, \mathcal{E}) \) be the underlying graph. Let \( j^* = (u^*v^*) \in \mathcal{E} \) with rate \( \ell_{u^*u^*} > 0 \) be the transition we want to perturb, i.e. replace \( \ell_{u^*u^*} \) by \( \ell_{u^*u^*} + \epsilon \). It is important to notice that increasing \( \ell_{u^*u^*} \) by \( \epsilon \) requires us to decrease the leaving rate \( \ell_{u^*u^*} \) by \( \epsilon \) to preserve the Laplacian property. We define the perturbed Laplacian

\[
\mathcal{L}(\epsilon) := \mathcal{L} + \epsilon \left( E_{u^*u^*} - E_{u^*u^*} \right),
\]

where \( E_{vu} \) is the matrix with only 0’s and one 1 in row \( v \) and column \( u \). For sufficiently small \( \epsilon \) (to be precise \( |\epsilon| < \ell_{v^*u^*} \)) the Laplacian \( \mathcal{L}(\epsilon) \) corresponds to an irreducible CTMC, which has a unique stat. dist. \( \mu(\epsilon) \). Naturally, the underlying graph structure does not change under these perturbations. We are interested in the quantity

\[
\delta^*: = \frac{\partial \mu(\epsilon)}{\partial \epsilon} \bigg|_{\epsilon=0},
\]

which we call the response vector to a perturbation of \( j^* \). Equivalently, we may understand \( \mu \) as a function of the transition rates \( (\ell_j)_{j \in \mathcal{E}} \) and define the response as \( \frac{\partial \mu(\ell)}{\partial \ell_j} \). Our aim is derive a description of the response vector \( \delta^* \) in which the transition rates \( (\ell_j)_{j \in \mathcal{E}} \) are left as variables. Hence, the response vector is a function \( \delta^*: \mathbb{R}^\mathcal{E}_+ \rightarrow \mathbb{R}^\mathcal{V} \) which only depends on the underlying graph \( \mathcal{G} = (\mathcal{V}, \mathcal{E}) \). In particular, we study the signed response, i.e. whether the entries of \( \delta^* \) are always positive / always negative / always zero or may change signs. Formally we define the algebraic sign of an entry \( \delta^*_{u^*} \) as

\[
\text{sign}(\delta^*_{u^*}) = \begin{cases} +, & \forall \ell \in \mathbb{R}^\mathcal{E}_+: \delta^*_{u^*}(\ell) > 0 \\ -, & \forall \ell \in \mathbb{R}^\mathcal{E}_+: \delta^*_{u^*}(\ell) < 0 \\ 0, & \forall \ell \in \mathbb{R}^\mathcal{E}_+: \delta^*_{u^*}(\ell) = 0 \\ \pm, & \text{else.} \end{cases}
\]

We stress again that the algebraic sign of the entries of \( \delta^* \) only depends on the graph structure of \( \mathcal{G} \). The main results on the response vector comes in form of the following Theorem providing a formula of the response vector and a Corollary which characterizes the algebraic signs of the entries.
Theorem 3.1. Consider an irreducible CTMC with Laplacian \(L\) and let \(G = (\mathcal{V}, \mathcal{E}, \mathcal{L})\) be the underlying weighted graph. When perturbing \(j^* = (u^*v^*) \in \mathcal{E}\), the response of the stat. dist. in a node \(u' \in \mathcal{V}\) like defined in (3.2) is given by

\[
\delta_{u'}^{j^*} = \mu_{u^*} \frac{1}{\|A\|} \sum_{w \neq u'} \sum_{(T_{u',T_w}) \in j^*-dTP} (-1)^{[w^* \in T_w]} \|T_w\| \|T_{u'}\|.
\]  

Corollary 3.2. Consider an irreducible CTMC with Laplacian \(L\) and let \(G = (\mathcal{V}, \mathcal{E})\) be the associated graph. When perturbing \(j^* = (u^*v^*) \in \mathcal{E}\), the sign of \(\delta_{u'}^{j^*}\) for \(u' \in \mathcal{V}\) is

(i) \(+\), if and only if any path from \(u^*\) to \(u'\) contains \(v^*\).

(ii) \(-\), if and only if there is no path from \(u^*\) to \(u'\) containing \(v^*\).

(iii) \(\pm\), if and only if there are paths \(\gamma_1, \gamma_2\) from \(u^*\) to \(u'\) such that \(\gamma_1 \ni v^* \notin \gamma_2\).

In particular, the sign of \(\delta_{u^*}^{j^*}\) is always \(-\), while the sign of \(\delta_{v^*}^{j^*}\) is always \(+\). An entry which has sign \(0\) cannot occur.

The proof of the Theorem and its Corollary can be found in Section 3.2.

Remark: The existence of paths like described in Corollary 3.2 can be checked algorithmically with a complexity of \(O(|\mathcal{V}| \cdot |\mathcal{E}|)\). Hence, the algebraic sign of the response to a perturbation can be computed efficiently.

Theorem 3.1 does not provide an efficient way to compute the entries of \(\delta^j\) yet, as determining \(j^*\)-divided tree pairs is a computationally expensive task. However, the formula of the theorem provides deep insight into the relation of the graph structure of \(G\) and the responses \(\delta_{u^*}^{j^*}\). Additionally, this formula will be the central tool in the study of the sensitivity in chemical reaction networks in Section 4.

3.1 Laplacians with negative rates

In this section, we will abstract the concept of the Laplacian of a continuous-time Markov chain to support negative rates \(\ell_j\). In the stochastic interpretation this makes little sense but the definition of a stationary distribution \(\mu\) and its sensitivity can be defined almost analogously. In particular, we will show that the sensitivity results are identical. This generalized framework will be necessary when applying our results to chemical reaction networks where negative rates will come up.

Consider a Laplacian matrix \(L\) as described by (2.1) with an underlying graph \(G = (\mathcal{V}, \mathcal{E})\), i.e. \(\ell_{uv} \neq 0\) if and only if \((uv) \in \mathcal{E}\) for any \(u \neq v\). However, we do no longer require \(\ell_j \in \mathbb{R}_+\). Instead, we allow \(\ell_j \in \mathbb{R}_x\), the reals without 0. In this setting we call such a matrix a generalized Laplacian. The weighted graph \(G = (\mathcal{V}, \mathcal{E}, \mathcal{L})\) may therefore now include negative edge-weights. Hence, the quantities \(\|A^{uv}\|\) and \(\|A\|\) are not guaranteed to be non-negative anymore.

Remark: In general, a generalized Laplacian \(L\) is simply a matrix whose columns sum to 0. However, the sparsity structure of \(L\) is of utmost importance for our purposes as it defines the underlying graph \(G\).

We extends the definition of a stationary distribution to generalized Laplacians.
**Definition 3.3.** Given a generalized Laplacian \( \mathcal{L} \), we call a vector \( \mu \in \mathbb{R}^V \) a stat. dist. of \( \mathcal{L} \) if it holds
\[
\mathcal{L}\mu = 0, \quad \sum_{v \in V} \mu_v = 1.
\]

However, existence and positivity of \( \mu \) can no longer be guaranteed. Note that any stat. dist. \( \mu \) is a solution to
\[
\mathcal{L}^{(v)} \mu = e_v,
\]
for any \( v \in V \), where \( \mathcal{L}^{(v)} \in \mathbb{R}^{V \times V} \) is the matrix \( \mathcal{L} \) with its \( v \)-row replaced by a row of 1’s.

**Proposition 3.4.** For a generalized Laplacian \( \mathcal{L} \) it holds that
\[
\text{det}(\mathcal{L}^{(v)}) = (-1)^{|V|-1} \|A\|, \quad \forall v \in V.
\]
Assuming that \( \|A\| \neq 0 \), there exists a unique stat. dist. \( \mu \) which is the unique solution to
\[
\mathcal{L}^{(v)} \mu = e_v, \tag{3.5}
\]
for any \( v \in V \).

**Remark:** This shows that if \( \text{det}(\mathcal{L}^{(v)}) \neq 0 \) for some \( v \in V \) the same holds true for any other choice of \( v \) as well. For the Laplacian of an irreducible CTMC it holds that \( \|A\| > 0 \) since all weights are positive and the underlying graph is strongly connected. Hence, (3.5) is an alternative characterization of the stat. dist. of an irreducible CTMC.

We proceed to studying the sensitivity of the stat. dist. of generalized Laplacians. Let \( \mathcal{L} \) be a generalized Laplacian and \( \mathcal{G} = (V, \mathcal{E}) \) its underlying graph. We assume \( \|A\| \neq 0 \) such that we find a unique stat. dist. \( \mu \). In this generalized setting, we may study the response to perturbation of arbitrary edges, not only those of \( \mathcal{E} \). For \( j^* = (u^* v^*) \), not necessarily in \( \mathcal{E} \), we define the perturbed Laplacian as
\[
\mathcal{L}(\epsilon) := \mathcal{L} + \epsilon \left( E_{v^* u^*} - E_{u^* v^*} \right). \tag{3.6}
\]
For sufficiently small \( \epsilon \), we still find \( \|A(\epsilon)\| \neq 0 \) and we may define \( \mu(\epsilon) \) as the unique solution to
\[
\mathcal{L}^{(v)}(\epsilon) \mu(\epsilon) = e_v. \tag{3.7}
\]

It should be noted that \( \mathcal{L}^{(v)}(\epsilon) \) is the matrix obtained by first adding the \( \epsilon \) terms and then replacing the \( v \)-row by 1’s. This may overwrite one of the \( \epsilon \)-terms if \( v \in \{u^*, v^*\} \). The response vector \( \delta^{j^*} \) to a perturbation of \( j^* \) is defined as
\[
\delta^{j^*} := \frac{\partial \mu(\epsilon)}{\partial \epsilon} \bigg|_{\epsilon=0}. \tag{3.8}
\]
The sensitivity result of Theorem 3.1 extends to this generalized setting.

**Theorem 3.5.** Consider an generalized Laplacian \( \mathcal{L} \) with rates \( \ell_j \in \mathbb{R}_x \) and let \( \mathcal{G} = (V, \mathcal{E}, \mathcal{L}) \) be the underlying weighted graph. We assume \( \|A\| \neq 0 \). When perturbing an edge \( j^* = (u^* v^*) \), not necessarily in \( \mathcal{E} \), the response of the stat. dist. in a node \( u' \in V \) is given by
\[
\delta^{j^*}_{u'} = \mu_{u'} \frac{1}{\|A\|} \sum_{w \neq u'} \sum_{(T_{w'}, T_w)} (-1)^{|w^* \in T_w|} \|T_{w'}\| \|T_w\|. \tag{3.9}
\]
In this generalized setting the quantities $\|A\|, \mu_r, \|T_w\|$ and $\|T_w\|$ do not need to be positive anymore and might even be zero, with the exception of $\|A\|$ which is non-zero by assumption. Hence, a description of the sign of the responses like Corollary 3.2 is not derivable anymore. Instead, one can verify that by inverting the sign of each transition rate, i.e. considering $-L$, the response vector equals $-\delta^*$. Hence, in the generalized setting, the algebraic signs of the entries may only be 0 or ±, such that no interesting characterization of the signs is possible anymore.

It would be an interesting topic to study the algebraic sign of the responses in a signed Laplacian where each transition rate is fixed to be either positive or negative. In that setting, a characterization of the algebraic sign of the entries as in Corollary 3.2 should be possible, even though the conditions might be much more complex.

### 3.2 Proofs

This section contains the proofs to Theorem 3.1, Corollary 3.2, Proposition 3.4 and Theorem 3.5. Note that Theorem 3.1, the sensitivity of CTMCs, is in fact only a special case of the analogous Theorem 3.2 on generalized Laplacians. Hence, it suffices to prove the latter.

The central tool of the proofs is the ’All Minors Matrix Tree Theorem’ [11]. It provides a formula for the determinants of a generalized Laplacian when deleting rows/columns from the matrix. Let us consider a generalized Laplacian $L$ with underlying weighted graph $G = (V, E, L)$. Additionally we fix an ordering of the vertices, i.e. a bijection $\sigma : V \rightarrow \{1, \ldots, |V|\}$. For two sets of vertices $U, W \subset V$, not necessarily disjoint, we denote by $L(W \setminus U)$ the submatrix of $L$ obtained from deleting the rows indexed by $W$ and the columns indexed by $U$. For $U = \{u_1, \ldots, u_n\}$ and $W = \{w_1, \ldots, w_m\}$ we may also write $L(u_1, \ldots, u_n | w_1 \ldots w_m)$. The theorem can be stated as follows

**Theorem 3.6.** [11] For $U, W \subset V$ with $|U| = |W|$ it holds that

$$
\det(L(U \setminus W)) = (-1)^{|V| - |U|} (-1)^{\sum_{u \in U} \sigma(u) + \sum_{w \in W} \sigma(w)} \sum_{\pi} \text{sgn}(\pi_F) \|F\|,
$$

where the sum is over all spanning forests $F$ of $G$ such that

(i) $F$ contains exactly $|W| = |U|$ trees;

(ii) Each tree in $F$ contains exactly one node in $U$ and exactly one node in $W$;

(iii) Each tree in $F$ is rooted in its node of $W$.

$F$ defines a bijection $\pi_F : U \rightarrow W$ such that $\pi(u) = w$ if and only if $u$ is in the tree of $F$ which is rooted in $w$. The product of the edge weights in $F$ is denoted by $\|F\|$.

We will only apply this theorem in the cases $|W| = |U| = 1$ and $|W| = |U| = 2$. In the first case, the forests $F$ are simply spanning trees rooted in the node of $W$. In the latter case, the forests are divided tree pairs. More precisely, for $U = \{u_1, u_2\}$ and $W = \{w_1, w_2\}$ a forest $F$ as in the theorem is a $(u_1 u_2)$-divided tree pair ($T_{w_1}, T_{w_2}$).

**Proof of Proposition 3.4.** Let $L$ be a generalized Laplacian and fix any $v \in V$. We compute the determinant of $L(v)$ via the Laplace-expansion in the $v$-row (whose entries are only 1’s)

$$
\det(L(v)) = \sum_{w \in V} (-1)^{\sigma(v) + \sigma(w)} \det(L(v \upharpoonright w)).
$$

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1 We will only ever consider sets with $|U| = |W|$.  

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Theorem 3.6 yields
\[
\det(L(v \mid w)) = (-1)^{|V|-1}(-1)^{\sigma(v)+\sigma(w)} \sum_{\mathcal{F}} \text{sgn}(\pi_{\mathcal{F}}) \|\mathcal{F}\|.
\]
The sum runs over all spanning trees rooted in \(w\). The bijection \(\pi_{\mathcal{F}}\) maps between singleton sets and thus trivially has \(\text{sgn}(\pi_{\mathcal{F}}) = +1\). We conclude
\[
\det(L(v)) = (-1)^{|V|-1} \sum_{w \in V} A^w
\]
\[
= (-1)^{|V|-1} \|A\|.
\]
Now let us assume \(\|A\| \neq 0\). By construction any stat. dist. \(\mu\) of \(L\) satisfies
\[
L^{(v)} \mu = e_v, \tag{3.10}
\]
for any \(v \in V\). Hence, invertibility of the \(L^{(v)}\) already implies that there is at most one stat. dist. To obtain existence, fix any \(v \in V\) and let \(\mu\) be the unique solution to (3.10). To show that \(\mu\) is a stat. dist. of \(L\), we need to compute the product of \(\mu\) with the \(v\)-row of \(L\), which we denote by \(L_v\).
\[
L_v \cdot \mu = -\sum_{w \neq v} L_w \cdot \mu
\]
\[
= 0,
\]
where we used the fact that all columns of \(L\) sum to 0. Hence \(\mu\) is the unique stat. dist. of \(L\).

\[
\square
\]

**Proof of Theorem 3.5**: Let \(L\) be a generalized Laplacian with underlying weighted graph \(G = (V, E, L)\) such that \(\|A\| \neq 0\). Let \(j^* = (u^*v^*)\) be the edge we are perturbing. The stat. dist. \(\mu(\epsilon)\) of the perturbed Laplacian \(L(\epsilon)\) is the unique solution to
\[
L^{(v)}(\epsilon) \mu(\epsilon) = e_v,
\]
for any \(v \in V\) (compare (3.7)). We choose \(v = u^*\), the source node of \(j^*\). This choice simplifies the matrix \(L^{(u^*)}(\epsilon)\), since one of the two \(\epsilon\) terms is replaced by a 1 (compare (3.6)). We find
\[
L^{(u^*)}(\epsilon) = L^{(u^*)} + \epsilon E_{v^*u^*}.
\]
Hence, all \(\mu(\epsilon)\) satisfy \(f(\epsilon, \mu(\epsilon)) = 0\), where
\[
f : \mathbb{R} \times \mathbb{R}^V \rightarrow \mathbb{R}^V
\]
\[
(\epsilon, x) \mapsto L^{(u^*)}x + \epsilon x_{u^*} e_{v^*} - e_{u^*}.
\]
To apply the implicit function theorem, we verify that
\[
\frac{\partial f}{\partial x}(0, \mu) = L^{(u^*)},
\]
is invertible. By implicit differentiation we obtain

$$\frac{\partial \mu(\epsilon)}{\partial \epsilon} \bigg|_{\epsilon=0} = - \left( \frac{\partial f}{\partial x}(0, \mu) \right)^{-1} \frac{\partial f}{\partial \epsilon}(0, \mu) = - (\mathcal{L}^{(u^*)})^{-1}(\mu_{u^*} e_{v^*}).$$  \hfill (3.11)

The left-hand-side of the equation is exactly the response vector $\delta^{i^*}$ whose entries we aim to compute. We can rewrite (3.11) as

$$\mathcal{L}^{(u^*)} \delta^{i^*} = - \mu_{u^*} e_{v^*}.$$  

Now let us fix a target node $u' \in \mathcal{V}$ in which we compute the response $\delta^{i^*}_{u'}$. Using Cramer’s rule

$$\delta^{i^*}_{u'} = \frac{\det(A(u'))}{\det(\mathcal{L}^{(u^*)})},$$

where $A(u')$ is the matrix obtained from replacing the $u'$-column of $\mathcal{L}^{(u^*)}$ by $-\mu_{u^*} e_{v^*}$. The determinant of $\mathcal{L}^{(u^*)}$ in the denominator was already computed in Proposition 3.4. We obtain

$$\delta^{i^*}_{u'} = (-1)^{|\mathcal{V}|-1} \frac{1}{\|A\|} \det(A(u')).$$

The determinant of $A(u')$ can be described using the Laplace-expansion in the $u'$-column. Since the $u'$-column is $-\mu_{u^*} e_{v^*}$ by construction, there is only one non-zero entry. The Laplace-expansion reads

$$\det(A(u')) = -\mu_{u^*} (-1)^{|\mathcal{V}|} \sigma(u^*) \det \left( \mathcal{L}^{(u^*)}(v^* | u') \right). \hfill (3.12)$$

However, $\mathcal{L}^{(u^*)}$ is not a matrix we may apply Theorem 3.6 to, as it is not a generalized Laplacian. Therefore, we need to use yet another Laplace-expansion, this time in the $u^*$-row (which only contains 1’s)

$$\det \left( \mathcal{L}^{(u^*)}(v^* | u') \right) = \sum_{w \in \mathcal{V}} (-1)^{\sigma_{v^*}(u^*) + \sigma_{v^*}(w)} \det \left( \mathcal{L}(u^*, v^* | u', w) \right).$$

The terms of the form $\sigma_{v^*}(b)$ denote the order of $b$ in $\sigma$ after deleting $a$. The order of $b$ only changes if $a$ came before $b$, i.e. $\sigma(a) < \sigma(b)$ in which case it is reduced by one. We can rewrite the term as

$$\sigma_{v^*}(b) = \sigma(b) - [\sigma(a) < \sigma(b)],$$

using the Boolean square bracket notation analogous to (2.4). We summarize

$$\delta^{i^*}_{u'} = \mu_{u^*} \frac{1}{\|A\|} \sum_{w \in \mathcal{V}} \sum_{u \neq u'} \text{sign}(u^*, v^*, u', w) \det(\mathcal{L}(u^*, v^* | u', w)), \hfill (3.13)$$

where, for spatial reasons, we abbreviated the signs of the summands as

$$\text{sign}(u^*, v^*, u', w) = (-1)(-1)^{|\mathcal{V}|-1}(-1)^{\sigma(u^*)+\sigma(v^*)+\sigma(u')+\sigma(w)} (-1)^{\sigma(v^*)<\sigma(u^*)} + [\sigma(u')<\sigma(w)].$$

Now we apply Theorem 3.6 to compute the determinant of $\mathcal{L}(u^*, v^* | u', w)$

$$\det(\mathcal{L}(u^*, v^* | u', w)) = (-1)^{|\mathcal{V}|-2}(-1)^{\sigma(u^*)+\sigma(v^*)+\sigma(u')+\sigma(w)} \sum_{\mathcal{F}} \text{sgn}(\pi_{\mathcal{F}}) \|\mathcal{F}\|. \hfill (3.14)$$
As mentioned before, the sum runs over divided tree pairs \((T_u', T_w)\) such that \(u^*\) is in one and \(v^*\) is in the other tree. Hence, the \(\mathcal{F}\) are exactly the \(j^*-dTp\) of \(\mathcal{G}\). To compute the sign of the bijection \(\pi_{\mathcal{F}}\), we consider the two cases individually

**Case** \(u^* \in T_{u'}\): The bijection \(\pi_{\mathcal{F}}\) is given by

\[
\pi_{\mathcal{F}}(u^*) = u' \quad \pi_{\mathcal{F}}(v^*) = w.
\]

One can check that the sign of this permutation is given by

\[
\text{sgn}(\pi_{\mathcal{F}}) = (-1)^{\sigma(v^*)<\sigma(u^*)+\sigma(u')<\sigma(w)}.
\]

**Case** \(u^* \notin T_{u'}\): The bijection \(\pi_{\mathcal{F}}\) is given by

\[
\pi_{\mathcal{F}}(u^*) = w \quad \pi_{\mathcal{F}}(v^*) = u'.
\]

One can check that the sign of this permutation is given by

\[
\text{sgn}(\pi_{\mathcal{F}}) = (-1)^{\sigma(v^*)<\sigma(u^*)+\sigma(u')<\sigma(w)}.
\]

The two cases are summarized by

\[
\text{sgn}(\pi_{\mathcal{F}}) = (-1)^{|u^* \in T_{u'}|} \left( -1 \right)^{\sigma(v^*)<\sigma(u^*)+\sigma(u')<\sigma(w)}.
\]

Inserting this computation into (3.14) and again using the abbreviation of \(\text{sign}(u^*, v^*, u', w)\), we arrive at

\[
\det(\mathcal{L}(u^*, v^* \mid u', w)) = \text{sign}(u^*, v^*, u', w) \sum_{(T_{u'}, T_w) \atop j^*-dTp} \left( -1 \right)^{|u^* \in T_{u'}|} \| T_{u'} \| \| T_w \| . \tag{3.15}
\]

Inserting (3.15) into (3.13), we get

\[
\delta_{u'}^{j^*} = \frac{1}{\|A\|} \sum_{w \in V} (T_{u'}, T_w) \sum_{j^*-dTp} \left( -1 \right)^{|u^* \in T_{u'}|} \| T_{u'} \| \| T_w \| .
\]

This completes the proof.

As stated before, Theorem 3.1 is just a special case of Theorem 3.5 and does not need to be proven separately. We conclude this section with the proof of the corollary of Theorem 3.1.

**Proof of Corollary 3.2**: We consider the formula of the response in \(u' \in V\) to the perturbation of an edge \(j^* = (u^*v^*) \in E\)

\[
\delta_{u'}^{j^*} = \frac{1}{\|A\|} \sum_{w \neq \neq u'} (T_{u'}, T_w) \sum_{j^*-dTp} \left( -1 \right)^{|u^* \in T_{u'}|} \| T_{u'} \| \| T_w \| .
\]

Since all the transition rates \((\ell_{j})_{j \in E}\) are positive, both \(\mu_{u^*}\) and \(\frac{1}{\|A\|}\) are strictly positive and do not influence the sign of \(\delta_{u'}^{j^*}\). The products \(\| T_{u'} \| \| T_w \|\) are monomials of degree \(|V| - 2\) of the positive
transition rates. Note that no monomial can appear twice and each monomial has a coefficient of either +1 or −1. Hence, the sign of \( \delta_{uv}^* \) is determined by the existence of monomials with positive, respectively negative coefficient. This corresponds to the existence of a \( j^* \)-divided tree pair such that \( u^* \in T_w, \) respectively \( u^* \in T_u' \). Indeed, if both types of \( j^* \)-dTp exists, the sign of \( \delta_{uv}^* \) is ± while if only one type exist, the sign is +, respectively −. This requires the existence of at least one \( j^* \)-divided tree pair. As we will see, this can be guaranteed.

To prove the corollary, it suffices to prove the following claim.

Claim:

(i) There exists a \( w \in \mathcal{V} \) and a \( j^* \)-dTp \( (\mathcal{T}_{u'}, \mathcal{T}_w) \) with \( u^* \in \mathcal{T}_w \) if and only if there is a directed path \( \gamma \) from \( u^* \) to \( u' \) that contains \( v^* \).

(ii) There exists a \( w \in \mathcal{V} \) and a \( j^* \)-dTp \( (\mathcal{T}_{u'}, \mathcal{T}_w) \) with \( u^* \in \mathcal{T}_{u'} \) if and only if there is a directed path \( \gamma \) from \( u^* \) to \( u' \) that does not contain \( v^* \).

Proving (i): Consider a \( j^* \)-dTp \( (\mathcal{T}_{u'}, \mathcal{T}_w) \) with \( u^* \in \mathcal{T}_w \). This implies \( v^* \in \mathcal{T}_{u'} \), and hence there is a directed path from \( v^* \) to \( u' \). Adding \( j^* \) to the beginning of the path yields a directed path \( \gamma \) from \( u^* \) to \( u' \) that contains \( v^* \).

Consider a directed path \( \gamma \) from \( u^* \) to \( u' \) that contains \( v^* \) (This rules out \( u' = u^* \)). This path can be interpreted as a tree \( \mathcal{T}' \) rooted in \( u' \). By the extension Lemma 2.3, we can find a spanning tree \( \mathcal{T} \) rooted in \( u' \) that contains \( \mathcal{T}' \). Deleting the outgoing edge of \( u^* \) splits \( \mathcal{T} \) into a tree rooted in \( u' \) and one rooted in \( u^* \). Hence, it becomes a \( j^* \)-dTp \( (\mathcal{T}_{u'}, \mathcal{T}_w) \) for which it clearly holds that \( u^* \in \mathcal{T}_{u'} \) (in this case we have \( w = u^* \)).

Proving (ii): Consider a \( j^* \)-dTp \( (\mathcal{T}_{u'}, \mathcal{T}_w) \) with \( u^* \in \mathcal{T}_{u'} \). Hence, there is a directed path \( \gamma \) from \( u^* \) to \( u' \) in \( \mathcal{T}_{u'} \). Since \( v^* \in \mathcal{T}_w \), this path does not contain \( v^* \).

Consider a directed path \( \gamma \) from \( u^* \) to \( u' \) that does not contain \( v^* \) (This rules out \( u' = v^* \)). This path can be interpreted as a tree \( \mathcal{T}' \) rooted in \( u' \). By the extension Lemma 2.3, we can find a spanning tree \( \mathcal{T} \) rooted in \( u' \) that contains \( \mathcal{T}' \). Deleting the outgoing edge of \( v^* \) splits \( \mathcal{T} \) into a tree rooted in \( u' \) and one rooted in \( v^* \). Hence, it becomes a \( j^* \)-dTp \( (\mathcal{T}_{u'}, \mathcal{T}_w) \) for which it holds that \( u^* \in \mathcal{T}_{u'} \) since \( \gamma \) is still part of \( \mathcal{T}_{u'} \) (in this case we have \( w = v^* \)).

This proves the claim. Since \( \mathcal{G} \) is strongly connected, there exists at least one directed path from \( u^* \) to \( u' \) and therefore at least one \( j^* \)-dTp exists. Note that the second part of the claim covers the case \( u^* = u' \).

\( \Box \)

4 Chemical reaction networks

In this section we present one application of the sensitivity results for Markov chains and generalized Laplacians from the previous section. Since CTMCs are one of the most basic types of time-continuous dynamics on networks, they can be used to model a variety of more complex processes on networks.

For chemical reaction networks it is a common approach to model the system as a Markov chain population dynamic \([1]\). However, this is not the type of application we are aiming for in this section. Instead, we construct a generalized Laplacian to imitate the linearization of a reaction network in a given equilibrium. As it turns out, the sensitivity of the chemical reaction network can be derived
from the sensitivity of the constructed Laplacian and computed using the results from the previous section.

In this brief introduction to chemical reaction networks, we closely follow the work of Vassena [12], which summarizes the framework of Mochizuki, Fiedler and Brehm [3, 13, 14]. Following their vocabulary, we refer to reaction networks as metabolic networks.

A metabolic network consist of a set of metabolites $\mathcal{M}$ and set of reactions $\mathcal{R}$ between them. A typical reaction $j \in \mathcal{R}$ might look like

$$j : A + 2B \rightarrow 2C + D,$$

where $A, B, C, D \in \mathcal{M}$ are metabolites. We call the metabolites on the left side of the reaction the inputs and those on the right side the outputs. A metabolite can be both input and output of one and the same reaction. In the general form, a reaction $j$ can be represented as

$$j : \sum_{m \in \mathcal{M}} s^j_m m \rightarrow \sum_{m \in \mathcal{M}} \bar{s}^j_m m,$$

where $s^j_m, \bar{s}^j_m$ are non-negative values. We call them the stoichiometric coefficients. Most of the times, the stoichiometric coefficients are integer-valued, however this is not required. In this general definition a metabolite $m$ is an input if $s^j_m \neq 0$ and an output if $\bar{s}^j_m \neq 0$. There are two special types of reactions that we address explicitly. Those without inputs, which we call feed-reactions and those without output, which we call exit-reactions. We write these using the notation of the zero-complex $0$ [15], i.e. $j : 0 \rightarrow \cdot$, respectively $j : \cdot \rightarrow 0$. Feed reactions can be understood as a constant inflow of certain metabolites into the system, while exit reactions can indicate the production of a substance which is not part of the system, e.g. biomass or energy.

Writing $s^j$ and $\bar{s}^j$ as vectors in $\mathbb{R}^\mathcal{M}$ we can define the stoichiometric matrix $S \in \mathbb{R}^{\mathcal{M} \times \mathcal{R}}$, whose $j$-column is given by

$$S^j = \bar{s}^j - s^j.$$

With this definition, we can describe the metabolic network as a differential equation. The quantities we consider are the concentrations $x_m$ of the individual metabolites $m \in \mathcal{M}$. The values of the concentrations are not normalized, i.e. they are not required to sum to 1 (or even be less than 1). The temporal evolution of the concentration vector $x \in \mathbb{R}^\mathcal{M}$ is described by the potentially non-linear differential equation

$$\dot{x} = Sr(x),$$

where $r : \mathbb{R}^\mathcal{M} \rightarrow \mathbb{R}^\mathcal{R}$ are the reaction rates. We impose a few constraints on the reaction rates $r$. The rate $r_j(x)$ of a reaction $j$ is assumed to be differentiable, non-negative and only dependent on the input metabolites of $j$. Additionally, the rate of $j$ increases monotonically with the concentration of the inputs. We can specify these constraint via the derivatives of $r$. Namely, we require that for any non-negative concentration vector $x \in \mathbb{R}^\mathcal{M}_{\geq 0}$ it holds

$$\frac{\partial r_j}{\partial x_m}(x) > 0 \iff m \text{ is an input of } j.$$ (4.2)

In particular, this implies that feed reactions are indeed constant, since their rate does not depend on the concentration of the metabolites. Common choices of the reaction rate function are defined by the
mass-action kinetics or Michaelis-Menten kinetics, both of which satisfy the condition posed in (4.2). However, we do not focus on any specific choice of the reaction rate function but aim to study the sensitivity of equilibria for arbitrary reaction rate functions.

An equilibrium of the system is a vector \( x^* \in \mathbb{R}^M_{\geq 0} \) for which it holds
\[
Sr(x^*) = 0. \tag{4.3}
\]
Existence and uniqueness of equilibria is a topic that can be studied on its own. Here, we assume the existence of an equilibrium \( x^* \) and study its sensitivity as introduced by Mochizuki and Fiedler in [3]. In particular, we describe the changes in the equilibrium when increasing the rate of a particular reaction \( j^* \). In practice, this can be achieved by adding a catalyst of the reaction to the system. Mathematically, we make the reaction rate \( r_j^*(x) \) depend additionally on a formal reaction parameter \( \epsilon \). We write \( r_j^*(\epsilon, x) \) and assume that \( \epsilon = 0 \) corresponds to the unperturbed reaction rate function. The parameter \( \epsilon \) models the added catalyst for reaction \( j^* \) such that \( \frac{\partial r_j^*}{\partial \epsilon}(\epsilon, x) > 0 \).

All other reactions are assumed to be unaffected by \( \epsilon \). Still, we write \( r(\epsilon, x) \) for the reaction rate vector, even though only the \( j^* \)-entry actually depends on \( \epsilon \). We denote the equilibrium corresponding to \( r(\epsilon, \cdot) \) by \( x^*(\epsilon) \), i.e.
\[
0 = Sr(\epsilon, x^*(\epsilon)).
\]
In [3] the metabolite response vector \( \Delta j^* \in \mathbb{R}^M \) was introduced which is the change in the equilibrium concentrations due to the perturbation of the reaction \( j^* \)
\[
\Delta j^* := \left. \frac{\partial x^*(\epsilon)}{\partial \epsilon} \right|_{\epsilon = 0}
\]
It was shown that \( x^*(\epsilon) \), and thereby the metabolite response \( \Delta j^* \), are well-defined under non-degeneracy of the Jacobian of (4.1) in the equilibrium \( x^* \). To compute this Jacobian we define
\[
R_{jm} := \frac{\partial r_j}{\partial x_m}(x^*), \tag{4.4}
\]
the derivatives of the reaction rates in the equilibrium. Writing these values as a matrix \( R \in \mathbb{R}^{\mathcal{R} \times \mathcal{M}} \), the Jacobian of the system is then given by \( SR \). Hence, we require
\[
\det(SR) \neq 0. \tag{4.5}
\]
By implicit differentiation of the function
\[
f : \mathbb{R} \times \mathbb{R}^\mathcal{M} \rightarrow \mathbb{R}^\mathcal{M}
\]
\[
(\epsilon, x) \rightarrow Sr(\epsilon, x)
\]
in the point \((0, x^*)\), we get
\[
\left. \frac{\partial x^*(\epsilon)}{\partial \epsilon} \right|_{\epsilon = 0} = -\left( \frac{\partial f}{\partial x}(0, x^*) \right)^{-1} \left( \frac{\partial f}{\partial \epsilon}(0, x^*) \right)
= -(SR)^{-1} \left( S \left( \frac{\partial r_j}{\partial \epsilon}(0, x^*) e_{j^*} \right) \right)
= -\frac{\partial r_j^*}{\partial \epsilon}(0, x^*)(SR)^{-1} Se_{j^*}. \tag{4.6}
\]
The first factor of the final term indicates how strongly the reaction rate of $j^*$ is influenced by the parameter $\epsilon$. Since we are more interested in the qualitative behavior of the sensitivity and $\epsilon$ is an abstract parameter that was introduced by us, we can simply assume this factor to be 1. We arrive at the formula

$$\Delta j^* = -(SR)^{-1} S j^*.$$  (4.7)

Note that the response vector does not depend on the actual values of the reaction rate $r(x^*)$, but only on the derivatives $R_{jm}$ in the equilibrium. Similar to the CTMC setting in which we considered arbitrary positive transition rates $(\ell_j)_{j \in E}$, we leave the non-zero values $R_{jm}$ as positive parameters and aim to describe the response vector as a function of these values symbolically. By (4.2), an entry $R_{jm}$ is a non-zero variable if and only if $m$ is an input to reaction $j$. The non-degeneracy condition (4.5) can be understood as the determinant being non-zero as a function of the values in $R_{jm}$. In [14] Theorem 2.1 an analysis of this condition is provided. In [3,14] it is described under what condition $\Delta j^* \neq 0$ holds algebraically, i.e. as functions. A function is considered algebraically non-zero if there is at least one valid input that yields a non-zero output. The work of Vassena [12] then addressed the question of signed sensitivity, i.e. determining the algebraic sign (compare (3.3)) of $\Delta j^*$.

It should be mentioned that in a system with, for example the mass-action kinetic, the derivatives $R_{jm}$ can not be chosen arbitrarily, since they are tied to the particular equilibrium $x^*$. This does not make any of the algebraic statements about $\Delta$ wrong, but makes them vastly over-generalized.

### 4.1 Sensitivity using generalized Laplacians

As seen in the previous section, the sensitivity of a metabolic network depends solely on the linearization $SR$ in a given equilibrium. In this section, we will interpret $SR$ as part of a generalized Laplacian $L$ and obtain sensitivity results similar to Theorem 3.5.

Consider a metabolic network with set of metabolites $\mathcal{M}$ and set of reactions $\mathcal{R}$. Let $x^*$ be a given equilibrium of the differential equation (4.1) and let $SR$ be the linearization in $x^*$. We assume $\det(SR) \neq 0$. We construct a generalized Laplacian $L$ on the set $\mathcal{M} \cup \{0\}$ in the following way

$$L = \begin{pmatrix} 0 & -1SR \\ 0 & SR \end{pmatrix},$$  (4.8)

where the first row/column corresponds to the state 0. The symbol $1$ is used to denote the vector of appropriate shape that consists only of 1’s. Hence, $1SR$ is a row vector containing the column sums of $SR$. Indeed, $1SR$ is a generalized Laplacian, i.e. all columns sum to 0. We call $\mathcal{G} = (\mathcal{M} \cup \{0\}, \mathcal{E})$, the underlying graph of $L$, the influence graph of the reaction network in an equilibrium. Let us stress that the graph structure of $\mathcal{G}$ depends neither on the chosen equilibrium $x^*$ nor on the values $R_{jm}$, but purely on the set of metabolites $\mathcal{M}$ and set of reactions $\mathcal{R}$. However, given an equilibrium $x^*$ and choice of values $R_{jm}$, we can equip $\mathcal{G}$ with weights using the generalized Laplacian constructed in (4.8). We write $\mathcal{G} = (\mathcal{M} \cup \{0\}, \mathcal{E}, L)$ for the weighted influence graph. Before we continue, let us provide some intuition for the generalized Laplacian (4.8) and the influence graph. We consider a example reaction network in Figure 1.
The stoichiometric matrix \( S \) and the derivative matrix \( R \) are given by
\[
S = \begin{pmatrix}
0 & 1 & 2 & 3 \\
A & 1 & -1 & -1 & 0 \\
B & 0 & 1 & -1 & 0 \\
C & 0 & 0 & 1 & -1
\end{pmatrix}, \quad R = \begin{pmatrix}
A & B & C \\
0 & 0 & 0 \\
1 & R_{1A} & 0 & 0 \\
2 & R_{2A} & R_{2B} & 0 \\
3 & 0 & 0 & R_{3C}
\end{pmatrix},
\]

The generalized Laplacian \( L \) is given by
\[
L = \begin{pmatrix}
0 & R_{2A} & R_{2B} & R_{3C} \\
0 & -R_{1A} - R_{2A} & -R_{2B} & 0 \\
0 & R_{1A} - R_{2A} & -R_{2B} & 0 \\
0 & R_{2A} & R_{2B} & -R_{3C}
\end{pmatrix}.
\] (4.9)

Note that the edge from \( A \) to \( B \) has the weight \( R_{1A} - R_{2A} \) and hence does not only consist of one variable. Also the variables \( R_{jm} \) no longer appear only once, but in multiple edges. This makes analyzing these graphs much harder.

Remark: It is convenient to model edges with more than one variable in their weight as multiedges, i.e. multiple edges with the same start and target node. This turns the influence graph \( G \) into a multigraph. The entire theory of this article can be directly extended to the multigraph setting. However, this is not necessary for the results we present, so for simplicity multigraphs are not considered.

In a general chemical reaction network, the structure of the influence graph \( G = (\mathcal{M} \cup \{0\}, \mathcal{E}) \) can be characterized in the following way

- For metabolites \( m_1, m_2 \), there is an edge \( (m_1m_2) \in \mathcal{E} \) if and only if there is a reaction \( j \in \mathcal{R} \) in which \( m_1 \) is an input and \( m_2 \) is either an input or an output;

- For \( m \in \mathcal{M} \) there is an edge \( (m0) \in \mathcal{E} \) if and only if \( m \) is the input of a reaction \( j \in \mathcal{R} \) that has an unequal number of inputs and outputs, i.e. \( \mathbf{1} S^j \neq 0 \). In particular, this is the case for exit-reaction \( m \to 0 \).

Note that feed-reactions do not affect this graph in any way as they have no metabolite-input. We obtain the following result which describes the response of \( x^* \) to a reaction perturbation in terms of the influence graph.
Theorem 4.1. When perturbing a reaction \( j^* \in \mathcal{R} \) the response of the equilibrium \( x^* \) in a metabolite \( m' \) is given by

\[
\Delta_{m'}^{j^*} = \frac{1}{\|A^0\|} \sum_{T_{m'}:T_0} \left( \sum_{m \in \mathcal{M}} S_{mj^*} [m \in T_{m'}] \right) \|T_{m'}\| \|T_0\|.
\]

The graph-related terms of the formula refer to the weighted influence graph \( G = (\mathcal{M} \cup \{0\}, \mathcal{E}, \mathcal{L}) \). It holds \( \|A^0\| = \det(SR) \neq 0 \).

Corollary 4.2. When perturbing a monomolecular reaction \( j^* \in \mathcal{R} \) of the form \( j^*: m^* \rightarrow m \) for \( m^*, m \in \mathcal{M} \cup \{0\} \), the response of the equilibrium \( x^* \) in a metabolite \( m' \) is given by

\[
\Delta_{m'}^{j^*} = \frac{1}{\|A^0\|} \sum_{j^*-dTp} (-1)^{[m^* \in T_{m'}]} \|T_{m'}\| \|T_0\|,
\]

where we may interpret \( j^* \) as the edge \((m^*m)\) in \( \mathcal{E} \).

Remark: From \( \|A^0\| \neq 0 \) we can derive that there is at least one tree rooted in \( 0 \) and hence there are directed path in the influence graph from any metabolite to \( 0 \).

Proof of Theorem 4.1: To prove this theorem, we build a connection between the sensitivity of metabolic networks and the sensitivity of generalized Laplacians. First, we find that \( \mathcal{L} \) has a stat. dist. which is given by \( \mu = e_0 \) (compare (4.8)). One can check that it holds \( \det(\mathcal{L}(0)) = \det(SR) \neq 0 \) such that \( \mu \) is in fact the unique stat. dist. by Proposition 3.4. We show that the response \( \delta \) of \( \mu \) to certain perturbations in \( \mathcal{L} \) has the same form as the responses \( \Delta \) of the reaction network. We start by considering the case of perturbing an edge \( j_m \) of the form \((0m)\) in \( \mathcal{L} \) and studying the response vector \( \delta^{jm} \in \mathbb{R}^{\mathcal{M} \cup \{0\}} \). We obtain from (3.11), the implicit differentiation of \( \mu(e) \)

\[
\delta^{jm} = -\left(\mathcal{L}(0)\right)^{-1}(\mu_0e_m).
\]

Since \( \mu_0 = 1 \), the factor can be omitted. The inverse of \( \mathcal{L}(0) \) is easily verified to be given by

\[
\left(\mathcal{L}(0)\right)^{-1} = \begin{pmatrix}
1 & -1(SR)^{-1} \\
0 & (SR)^{-1}
\end{pmatrix}.
\]

It follows that the response vector \( \delta^{jm} \) restricted to the set of metabolites \( \mathcal{M} \) has a similar form as the metabolite response vectors in the reaction network (compare (4.7))

\[
\delta^{jm}|_\mathcal{M} = -(SR)^{-1}e_m.
\]

We observe from (4.7) that the metabolite response to the perturbation of a reaction \( j^* \in \mathcal{R} \) can be decomposed into summands of this form

\[
\Delta j^* = -(SR)^{-1}Sj^* = \sum_{m \in \mathcal{M}} S_{mj^*} \left(-(SR)^{-1}e_m\right).
\]
Using the formula of Theorem 3.5 to describe the entries of $\delta^{jm}$, we compute for $m' \in M$

$$\Delta^{j*}_{m'} = \sum_{m \in M} S_{mj*} \left( - (SR)^{-1} e_m \right)_{m'}$$

$$= \sum_{m \in M} S_{mj*} \delta^{jm}_{m'}$$

$$= \sum_{m \in M} S_{mj*} \left( \frac{1}{\|A^0\|} \sum_{(T_{m'}, T_0)}^{(T_{m'}, T_0)} \|T_{m'}\| \|T_0\| \right)$$

$$= \frac{1}{\|A^0\|} \sum_{(T_{m'}, T_0)}^{(T_{m'}, T_0)} \left( \sum_{m \in M} S_{mj*} \left[ m \in T_{m'} \right] \right) \|T_{m'}\| \|T_0\| .$$

This completes the proof of Theorem 4.1.

□

5 Outlook

Analyzing the sensitivity of an equilibrium is one of the key steps in approaching the control problem, i.e. achieving a desired response equilibrium by perturbing particular system parameters. In the case of CTMCs on finite state spaces that admit a unique stationary distribution Theorem 3.1 provides a solid basis for this setting. However, to achieve a desired response in the stat. dist. it is oftentimes
necessary to perturb more than one transition rate. This may result in cancellation when the sign of two responses differ. Understanding these cancellations is crucial in order to effectively apply the results we presented to the control problem.

The final goal of the sensitivity study of chemical reaction networks as we carried it out is to precisely link the algebraic sign of the response to the network underlying structure, similar to Corollary 3.2. The formula of theorem 4.1 reduced this problem to determining whether positive/negative summands occur. However, determining the sign of a summand is non-trivial for general networks. The difficulty does not necessarily lie in the existence of both positive and negative rates, but rather in the fact that the same variable may occur multiple times in the generalized Laplacian (compare (4.9)). For monomolecular networks, this is not an issue and the algebraic sign of the sensitivity can be characterized precisely from the network structure. Such a result for monomolecular networks can be found in [16]. It is not ruled out that for general reaction networks determining the algebraic signs of the sensitivity based on the graph structure is in NP (assuming P不是NP) such that a simple characterization is impossible. In that case, further assumptions on the network, e.g. ruling out catalytic reactions (reaction in which a metabolite is both input and output), could make a 'simple' characterization possible. In order to find these suitable assumptions, one needs to study which conditions the influence graph of a reaction network needs to satisfy such that determining the signs in Theorem 4.1 becomes easier.

6 Acknowledgements

I thank Bernold Fiedler and Nicola Vassena for introducing me to the presented topic as well as motivating many of the results and methods used. Special thanks go to Maximilian Engel and Dennis Chemnitz for their support by reading through the manuscript and refining its structure. My work on this topic has been funded by the Berlin Mathematical School.

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