Linear Conjugacy of Chemical Reaction Networks

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1 Background

- Chemical Reaction Networks
- Mass-Action Kinetics
- Reaction Graphs
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2 Linearly Conjugate Networks
   - Realizations
   - Linearly Conjugate Networks
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3 Computation Approach
   - Sparse and Dense Realizations
   - Linear Conjugacy
   - Weak Reversibility as a Linear Constraint
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A **chemical reaction network** consists of a set of reactants which turn into a set of products, e.g.

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\[ 2\text{H}_2 + \text{O}_2 \xrightarrow{k} 2\text{H}_2\text{O} \]

Species/Reactants
A chemical reaction network consists of a set of reactants which turn into a set of products, e.g.

$$2H_2 + O_2 \xrightarrow{k} 2H_2O$$

Reactant Complex
A chemical reaction network consists of a set of reactants which turn into a set of products, e.g.

\[ 2\text{H}_2 + \text{O}_2 \xrightarrow{k} 2\text{H}_2\text{O} \]

Product Complex
A chemical reaction network consists of a set of reactants which turn into a set of products, e.g.

\[ 2\text{H}_2 + \text{O}_2 \xrightarrow{k} 2\text{H}_2\text{O} \]

Reaction Constant
A chemical reaction network consists of a set of reactants which turn into a set of products, e.g.

$$2\text{H}_2 + \text{O}_2 \xrightarrow{k} 2\text{H}_2\text{O}$$

Chemical kinetics is the study of the rates/dynamics resulting from systems of such reactions.
A **chemical reaction network** consists of a set of reactants which turn into a set of products, e.g.

$$2\text{H}_2 + \text{O}_2 \xrightarrow{k} 2\text{H}_2\text{O}$$

**Chemical kinetics** is the study of the **rates/dynamics** resulting from systems of such reactions.

Applications in industrial chemistry, pharmaceutics, systems biology, gene regulation, and many other areas.
Significant recent work has been done on the connection between network structure and dynamical behaviour.
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CRN with "good" graph $\Rightarrow$ Understood dynamical behaviour!
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![Diagram](attachment:diagram.png)

CRN with "good" graph \rightarrow \text{Understood dynamical behaviour!}

CRN with "bad" graph
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We can say something about the dynamics without having to analyse the governing set of differential equations!
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QUESTION #1:

Can we find more general conditions under which two networks have the same qualitative dynamics?
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Current results require the governing differential equations to be identical.

This could be used to widen the umbrella of classes of networks with understood dynamics (e.g. weakly reversible networks).
QUESTION #2:

Given a network with “bad” structure, can we find a network with “good” structure with related dynamics?
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Given a network with “bad” structure, can we find a network with “good” structure with related dynamics?

We are typically given a single network and the related network may not be apparent.

The development of computer algorithms is essential.
Consider the general network $\mathcal{N}$ given by

$$
\mathcal{N} : \quad C_i \xrightarrow{k(i,j)} C_j, \quad (i,j) \in \mathcal{R}.
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$$\mathcal{N} : \quad \mathcal{C}_i \xrightarrow{k(i,j)} \mathcal{C}_j, \quad (i,j) \in \mathcal{R}.$$ 

Under **mass-action kinetics**, this network is governed by

$$\frac{d\mathbf{x}}{dt} = Y A_k \Psi(\mathbf{x}). \quad (1)$$
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We have the following important components:

- $Y$ is the stoichiometric matrix,
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We have the following important components:

- $Y$ is the stoichiometric matrix,
- $A_k$ is the kinetics matrix (keeps track of connections),
- $\Psi(\mathbf{x})$ is the mass-action vector (with entries $\Psi_i(\mathbf{x}) = \prod_{j=1}^{m}(x_j)^{z_{ij}}$).
Consider the reversible network

\[ A_1 \xrightleftharpoons[k(2,1)]{k(1,2)} 2A_2. \]
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This has the governing dynamics

\[
\begin{bmatrix}
\frac{dx_1}{dt} \\
\frac{dx_2}{dt}
\end{bmatrix} = \begin{bmatrix}
1 & 0 \\
0 & 2
\end{bmatrix} \begin{bmatrix}
-k(1,2) & k(2,1) \\
k(1,2) & -k(2,1)
\end{bmatrix} \begin{bmatrix}
x_1 \\
x_2
\end{bmatrix}
\]

\[
= k(1,2) \begin{bmatrix}
-1 \\
2
\end{bmatrix} x_1 + k(2,1) \begin{bmatrix}
1 \\
-2
\end{bmatrix} x_2^2
\]

where \( x_1 \) and \( x_2 \) are the concentrations of \( A_1 \) and \( A_2 \) respectively.
Consider the reversible network

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\end{bmatrix} \begin{bmatrix}
x_1 \\
x_2
\end{bmatrix}
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\]

where \( x_1 \) and \( x_2 \) are the concentrations of \( \mathcal{A}_1 \) and \( \mathcal{A}_2 \) respectively.
Figure: Previous system with $k_1 = k_2 = 1$. 
Figure: Previous system with $k_1 = k_2 = 1$. 
Figure: Previous system with $k_1 = k_2 = 1$. 
Chemical reaction networks can be treated as weighted directed graphs $G(V, E)$:
Chemical reaction networks can be treated as weighted \textbf{directed graphs} $G(V,E)$:

\[
\begin{align*}
C_1 & \xrightarrow{k(1,2)} C_2 \\
& \xleftarrow{k(3,1)} \sqrt{\downarrow k(2,3)} \\
C_3 & \xrightarrow{k(4,5)} C_4 \iff C_5 \\
& \xleftarrow{k(5,4)}
\end{align*}
\]
Chemical reaction networks can be treated as weighted **directed graphs** $\mathcal{G}(V, E)$:

\[
\begin{align*}
    C_1 & \xrightarrow{k(1,2)} C_2 \\
    C_3 & \xleftarrow{k(3,1)} \sqrt[k(2,3)]{C_2} \\
    C_4 & \xleftrightarrow{k(4,5)} C_5 \\
    C_3 & \xrightarrow{k(5,4)} \sqrt[k(2,3)]{C_5}
\end{align*}
\]

- The vertexes are the distinct complexes
Chemical reaction networks can be treated as weighted directed graphs $G(V, E)$:

$$
\begin{align*}
C_1 \xrightarrow{k(1,2)} & C_2 \\
\text{k(3,1)} \quad \text{k(2,3)} \quad \text{k(5,4)} & \quad \text{k(4,5)} \\
\text{C}_3 & \quad \text{C}_4 \leftrightarrow \text{C}_5
\end{align*}
$$

- The vertexes are the distinct complexes, $V = C$. 
Chemical reaction networks can be treated as weighted **directed graphs** $G(V, E)$:

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C_1 \xrightarrow{k(1,2)} C_2 \\
\xleftarrow{k(3,1)} \quad \checkmark \quad \checkmark \quad \xrightarrow{k(2,3)} \quad \xleftarrow{k(4,5)} C_4 \leftrightarrow C_5 \\
\xleftarrow{k(5,4)} C_3
$$

- The vertexes are the distinct complexes, $V = C$.
- The edges are the reactions
Chemical reaction networks can be treated as weighted **directed graphs** $G(V, E)$:

- The vertexes are the distinct complexes, $V = C$.
- The edges are the reactions, $E = R$.

\[
\begin{align*}
C_1 & \xrightarrow{k(1,2)} C_2 \\
& \xleftarrow{k(3,1)} \quad \uparrow \quad \xleftarrow{k(2,3)} \quad \downarrow \quad \xrightarrow{k(4,5)} C_4 \\
& \xleftarrow{k(5,4)} C_5
\end{align*}
\]
Chemical reaction networks can be treated as weighted **directed graphs** $G(V, E)$:

$$
\begin{align*}
& C_1 \xrightarrow{k(1,2)} C_2 \\
& k(3,1) \leftarrow C_3 \xrightarrow{k(2,3)} C_2 \\
& C_4 \leftrightarrow C_5 \\
& k(4,5) \\
& k(5,4)
\end{align*}
$$

- The vertexes are the distinct complexes, $V = C$.
- The edges are the reactions, $E = R$.
- We are interested in all the standard components of graphs, e.g. paths, cycles, connected components, trees, etc.
The particular class of networks I have been interested in are weakly reversible networks.
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\[ C_1 \xrightarrow{k(1,2)} C_2 \]
\[ k(3,1) \quad \xleftarrow{k(2,3)} \quad k(5,4) \]
\[ C_3 \quad \xleftrightarrow{k(4,5)} \quad C_4 \quad C_5 \]
The particular class of networks I have been interested in are weakly reversible networks.

\[
\begin{align*}
C_1 & \xrightarrow{k(1,2)} C_2 \\
C_3 & \xleftarrow{k(2,3)} C_2 \\
C_4 & \xleftrightarrow{k(4,5),k(5,4)} C_5 \\
\end{align*}
\]

A network is weakly reversible if a path from one another complex to another implies a path back.
The particular class of networks I have been interested in are weakly reversible networks.

\[
\begin{array}{ccc}
C_1 & \xrightarrow{k(1,2)} & C_2 \\
\llcorner & k(3,1) & \llcorner \\
C_3 & \llcorner \iff \llcorner & C_3 \\
\iff & k(2,3) & \iff \\
C_4 & \xleftrightarrow{k(4,5)} & C_5 \\
\llcorner & k(5,4) & \llcorner \\
\end{array}
\]

A network is weakly reversible if a path from one another complex to another implies a path back, e.g.

\[
C_1 \rightarrow C_2
\]
The particular class of networks I have been interested in are **weakly reversible networks**.

\[ C_1 \xrightarrow{k(1,2)} C_2 \]
\[ k(3,1) \]
\[ \xleftarrow{k(2,3)} C_3 \]

A network is weakly reversible if a path from one another complex to another implies a path back, e.g.

\[ C_1 \rightarrow C_2 \rightarrow C_3 \rightarrow C_1 \]
The particular class of networks I have been interested in are weakly reversible networks.

\[
C_1 \xrightarrow{k(1,2)} C_2 \\
\leftarrow k(3,1) \quad \leftarrow k(2,3) \\
C_3 \\
\xleftarrow{k(4,5)} C_4 \leftrightarrow C_5 \xleftarrow{k(5,4)} C_5
\]

A network is weakly reversible if a path from one another complex to another implies a path back, e.g.

\[
C_1 \rightarrow C_2 \rightarrow C_3 \rightarrow C_1, \quad C_4 \rightarrow C_5 \rightarrow C_4.
\]
The particular class of networks I have been interested in are weakly reversible networks.

\[ C_1 \xrightarrow{k(1,2)} C_2 \quad k(3,1) \xleftarrow{k(2,3)} \]

\[ C_4 \xleftrightarrow{k(4,5)} C_5 \quad k(5,4) \]

A network is weakly reversible if a path from one another complex to another implies a path back, e.g.

\[ C_1 \rightarrow C_2 \rightarrow C_3 \rightarrow C_1, \quad C_4 \rightarrow C_5 \rightarrow C_4. \]

Strong dynamical properties follow from weak reversibility!
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Under the assumption of mass-action kinetics, it is possible for two chemical reaction networks to be \textit{dynamically equivalent} \cite{1, 2}.
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**Definition**

In the case that two networks $\mathcal{N}$ and $\mathcal{N}'$ give rise to the same mass-action kinetics (1) we will say that $\mathcal{N}'$ is an alternative **realization** of $\mathcal{N}$ and vice-versa.
Under the assumption of mass-action kinetics, it is possible for two chemical reaction networks to be dynamically equivalent [1, 2].

**Definition**

In the case that two networks $\mathcal{N}$ and $\mathcal{N}'$ give rise to the same mass-action kinetics (1) we will say that $\mathcal{N}'$ is an alternative realization of $\mathcal{N}$ and vice-versa.

If one realization has known dynamics while another does not, the dynamics are transferred to the unknown network!
Consider the set of polynomial differential equations

\[
\begin{align*}
\dot{x}_1 &= -2x_1^2 + x_2^2 \\
\dot{x}_2 &= 2x_1^2 - x_2^2.
\end{align*}
\]
Consider the set of polynomial differential equations

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\begin{align*}
\dot{x}_1 &= -2x_1^2 + x_2^2 \\
\dot{x}_2 &= 2x_1^2 - x_2^2.
\end{align*}
\]

This governs the dynamics of \textbf{both of the networks}

\[
\mathcal{N} : \quad 2A_1 \xrightarrow{1} 2A_2 \xrightarrow{1} A_1 + A_2
\]

\[
\mathcal{N}' : \quad 2A_1 \xleftrightarrow{0.5} 2A_2.
\]
Consider the set of polynomial differential equations
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\end{align*}
\]
This governs the dynamics of both of the networks
\[
\mathcal{N}: \quad 2\mathcal{A}_1 \xrightarrow{1} 2\mathcal{A}_2 \xrightarrow{1} \mathcal{A}_1 + \mathcal{A}_2
\]
\[
\mathcal{N}': \quad 2\mathcal{A}_1 \xleftrightarrow{0.5} 2\mathcal{A}_2.
\]
\mathcal{N}' has “good” structure...
Consider the set of polynomial differential equations

\[
\begin{align*}
\dot{x}_1 &= -2x_1^2 + x_2^2 \\
\dot{x}_2 &= 2x_1^2 - x_2^2.
\end{align*}
\]

This governs the dynamics of \textbf{both of the networks}

\[
\mathcal{N} : \quad 2A_1 \xrightarrow{1} 2A_2 \xrightarrow{1} A_1 + A_2
\]

\[
\mathcal{N'} : \quad 2A_1 \xrightarrow{1} \text{ or } \xleftarrow{0.5} 2A_2.
\]

\(\mathcal{N}'\) has “good” structure...
...we know its dynamics...
Consider the set of polynomial differential equations

\[
\begin{align*}
\dot{x}_1 &= -2x_1^2 + x_2^2 \\
\dot{x}_2 &= 2x_1^2 - x_2^2.
\end{align*}
\]

This governs the dynamics of both of the networks

\[
\mathcal{N} : \quad 2A_1 \xrightarrow{1} 2A_2 \xrightarrow{1} A_1 + A_2
\]

\[
\mathcal{N}' : \quad 2A_1 \xrightleftharpoons{1\ \text{or}\ 0.5} 2A_2.
\]

\(\mathcal{N}'\) has “good” structure...

... we know its dynamics...

... so we know the dynamics of \(\mathcal{N}'\) as well.
Consider the networks

\[ \mathcal{N} : \]
\[ A_1 \xrightarrow{k_1} A_2 \]
\[ 2A_2 \xrightarrow{k_2} 2A_1 \]

\[ \mathcal{N}' : \]
\[ A_1 \xleftrightarrow{\tilde{k}_1} 2A_2 \]
\[ 2A_2 \xleftrightarrow{\tilde{k}_2} 2A_1 \]

These networks look very similar (but not identical).
Consider the networks

\( \mathcal{N} : \)

\[
A_1 \xrightarrow{k_1} A_2 \\
2A_2 \xrightarrow{k_2} 2A_1
\]

\[
\frac{dx_1}{dt} = -k_1 x_1 + 2k_2 x_2^2 \\
\frac{dx_2}{dt} = k_1 x_1 - 2k_2 x_2^2.
\]

\( \mathcal{N}' : \)

\[
A_1 \xleftrightarrow{\tilde{k}_1} 2A_2 \\
\tilde{k}_2
\]
Consider the networks

\[ \mathcal{N} : \]
\[
\begin{align*}
A_1 & \xrightarrow{k_1} A_2 \\
2A_2 & \xrightarrow{k_2} 2A_1
\end{align*}
\]
\[
\begin{align*}
\frac{dx_1}{dt} &= -k_1 x_1 + 2k_2 x_2^2 \\
\frac{dx_2}{dt} &= k_1 x_1 - 2k_2 x_2^2.
\end{align*}
\]

\[ \mathcal{N}' : \]
\[
\begin{align*}
\bar{A}_1 & \xleftrightarrow{\tilde{k}_1} 2\bar{A}_2 \\
\bar{A}_2 & \xleftrightarrow{\tilde{k}_2} 2\bar{A}_1
\end{align*}
\]
\[
\begin{align*}
\frac{dy_1}{dt} &= -\tilde{k}_1 y_1 + \tilde{k}_2 y_2^2 \\
\frac{dy_2}{dt} &= 2\tilde{k}_1 y_1 - 2\tilde{k}_2 y_2^2.
\end{align*}
\]
Consider the networks

\[ \mathcal{N} : \begin{array}{c}
A_1 \xrightarrow{k_1} A_2 \\
2A_2 \xrightarrow{k_2} 2A_1
\end{array} \implies \begin{array}{c}
\frac{dx_1}{dt} = -k_1x_1 + 2k_2x_2^2 \\
\frac{dx_2}{dt} = k_1x_1 - 2k_2x_2^2.
\end{array} \]

\[ \mathcal{N}' : \begin{array}{c}
A_1 \xleftrightarrow{\tilde{k}_1 \ \tilde{k}_2} 2A_2
\end{array} \implies \begin{array}{c}
\frac{dy_1}{dt} = -\tilde{k}_1y_1 + \tilde{k}_2y_2^2 \\
\frac{dy_2}{dt} = 2\tilde{k}_1y_1 - 2\tilde{k}_2y_2^2.
\end{array} \]

These networks look very similar (but not identical).
Consider the networks

\[ \mathcal{N} : \quad A_1 \xrightarrow{k_1} A_2 \quad 2A_2 \xrightarrow{k_2} 2A_1 \quad \implies \quad \begin{align*}
\frac{dx_1}{dt} &= -k_1x_1 + 2k_2x_2^2 \\
\frac{dx_2}{dt} &= k_1x_1 - 2k_2x_2^2.
\end{align*} \]

\[ \mathcal{N}' : \quad A_1 \xleftrightarrow{\tilde{k}_1} 2A_2 \quad \implies \quad \begin{align*}
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These networks look **very similar** (but not identical).
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$\mathcal{N}: \begin{align*}
A_1 & \xrightarrow{k_1} A_2 \\
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\end{align*} \implies \begin{align*}
\frac{dx_1}{dt} &= -k_1x_1 + 2k_2x_2^2 \\
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\end{align*}$

$\mathcal{N}': \begin{align*}
A_1 & \xleftrightarrow{\tilde{k}_1} 2A_2 \\
2A_2 & \xleftrightarrow{\tilde{k}_2} A_1
\end{align*} \implies \begin{align*}
\frac{dy_1}{dt} &= -\tilde{k}_1y_1 + \tilde{k}_2y_2^2 \\
\frac{dy_2}{dt} &= 2\tilde{k}_1y_1 - 2\tilde{k}_2y_2^2.
\end{align*}$

These networks look very similar (but not identical).
Is there a way we can relate the dynamics of $N$ to $N'$?

**YES!** These networks are related by the transformation

\[
\begin{align*}
x_1 &= 2y_1 \\
x_2 &= y_2
\end{align*}
\] (a linear transformation)!
QUESTION:

Is there a way we can relate the dynamics of $\mathcal{N}$ to $\mathcal{N}'$?
QUESTION:
Is there a way we can relate the dynamics of $\mathcal{N}$ to $\mathcal{N}'$?

YES! These networks are related by the transformation $x_1 = 2y_1$, $x_2 = y_2$ (a linear transformation)!
Definition

We will say $\mathcal{N}$ and $\mathcal{N}'$ are **linearly conjugate** if their flows under mass-action kinetics are related by a linear transformation.
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We will say $\mathcal{N}$ and $\mathcal{N}'$ are **linearly conjugate** if their flows under mass-action kinetics are related by a linear transformation.

The qualitative dynamics (e.g. number and stability of equilibria, persistence, boundedness, etc.) of linearly conjugate networks are identical!
Definition

We will say $\mathcal{N}$ and $\mathcal{N}'$ are **linearly conjugate** if their flows under mass-action kinetics are related by a linear transformation.

The qualitative dynamics (e.g. number and stability of equilibria, persistence, boundedness, etc.) of linearly conjugate networks are identical!

**Linear conjugacy includes dynamical equivalence** as a special case (identity transformation).
Linearly conjugate networks were the central focus of study in the paper of M. D. Johnston and D. Siegel [3].
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**Theorem (Theorem 3.2 of [3] and Theorem 2 of [4])**

Consider the kinetics matrix $A_k$ corresponding to $\mathcal{N}$ and suppose that there is a kinetics matrix $A_b$ with the same structure as $\mathcal{N}'$ and a vector $\mathbf{c} \in \mathbb{R}^n_{>0}$ such that

$$Y \cdot A_k = T \cdot Y \cdot A_b$$

where $T = \text{diag}\{\mathbf{c}\}$. Then $\mathcal{N}$ is linearly conjugate to $\mathcal{N}'$ with kinetics matrix

$$A_k' = A_b \cdot \text{diag}\{\Psi(\mathbf{c})\}.$$
1 Background
   ■ Chemical Reaction Networks
   ■ Mass-Action Kinetics
   ■ Reaction Graphs

2 Linearly Conjugate Networks
   ■ Realizations
   ■ Linearly Conjugate Networks

3 Computation Approach
   ■ Sparse and Dense Realizations
   ■ Linear Conjugacy
   ■ Weak Reversibility as a Linear Constraint
**PROBLEM:**

If we are just given a single network $\mathcal{N}$, e.g.,

$$\mathcal{N} : 2A_1 \xrightarrow{1} 2A_2 \xrightarrow{1} A_1 + A_2,$$

how do we find a linearly conjugate network $\mathcal{N}'$ with known dynamics?
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The development of computer algorithms is vital to making this theory applicable.
For dynamical equivalence, G. Szederkényi placed this problem within a linear programming optimization framework [5].
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### Dynamical Equivalence

\[
\begin{align*}
Y A_k &= M \quad (= Y A'_k) \\
\sum_{i=1}^{m} [A_k]_{ij} &= 0, \quad j = 1, \ldots, m \\
[A_k]_{ij} &\geq 0, \quad i, j = 1, \ldots, m, \quad i \neq j \\
[A_k]_{ii} &\leq 0, \quad i = 1, \ldots, m.
\end{align*}
\]
Consider the binary variables $\delta_{ij} \in \{0, 1\}$, let $u_{ij}, \epsilon > 0$ be constants, and consider the constraints

$$0 \leq \epsilon \delta_{ij} \leq [A_k]_{ij} \leq u_{ij} \delta_{ij}, \quad i, j = 1, \ldots, m, \ i \neq j.$$
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$$0 \leq \epsilon \delta_{ij} \leq [A_k]_{ij} \leq u_{ij} \delta_{ij}, \quad i, j = 1, \ldots, m, i \neq j.$$ 

1. For $\delta_{ij} = 0$ we have $[A_k]_{ij} = 0$
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1. For $\delta_{ij} = 0$ we have $[A_k]_{ij} = 0 \implies$ reaction is ‘off’.

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Consider the binary variables $\delta_{ij} \in \{0, 1\}$, let $u_{ij}, \epsilon > 0$ be constants, and consider the constraints

$$0 \leq \epsilon \delta_{ij} \leq [A_k]_{ij} \leq u_{ij} \delta_{ij}, \quad i, j = 1, \ldots, m, i \neq j.$$

1. For $\delta_{ij} = 0$ we have $[A_k]_{ij} = 0 \implies$ reaction is ‘off’.

2. For $\delta_{ij} = 1$ we have $0 < \epsilon \leq [A_k]_{ij} \leq u_{ij} \implies$ reaction is ‘on’.
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1. For $\delta_{ij} = 0$ we have $[A_k]_{ij} = 0 \Rightarrow$ reaction is ‘off’.

2. For $\delta_{ij} = 1$ we have $0 < \epsilon \leq [A_k]_{ij} \leq u_{ij} \Rightarrow$ reaction is ‘on’.

The $\delta_{ij}$’s tell us whether the reaction $C_j \longrightarrow C_i$ is in the network or not.
Summing over $\delta_{ij}, \ i, j = 1, \ldots, m, i \neq j$, tells us how many reactions there are in the network!
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**Sparse/Dense Realizations**

\[
\begin{align*}
\text{minimize} & \quad \sum_{i,j=1, i \neq j}^{m} \delta_{ij} \quad \text{or} \quad \text{minimize} & \quad \sum_{i,j=1, i \neq j}^{m} -\delta_{ij} \\
0 & \leq [A_k]_{ij} - \epsilon \delta_{ij} \\
0 & \leq -[A_k]_{ij} + u_{ij} \delta_{ij} \\
\delta_{ij} & \in \{0, 1\} \\
i, j &= 1, \ldots, m, i \neq j
\end{align*}
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Summing over $\delta_{ij}$, $i, j = 1, \ldots, m, i \neq j$, tells us how many reactions there are in the network!

Sparse/Dense Realizations

minimize $\sum_{i,j=1,i\neq j}^{m} \delta_{ij}$ or minimize $\sum_{i,j=1,i\neq j}^{m} -\delta_{ij}$

$0 \leq [A_k]_{ij} - \epsilon \delta_{ij}$

$0 \leq -[A_k]_{ij} + u_{ij}\delta_{ij}$

$\delta_{ij} \in \{0, 1\}$

$i, j = 1, \ldots, m, i \neq j$
Reconsider the network

\[ \mathcal{N} : \quad 2A_1 \overset{1}{\rightarrow} 2A_2 \overset{1}{\rightarrow} A_1 + A_2. \]
Reconsider the network

\[ \mathcal{N} : 2A_1 \xrightarrow{1} 2A_2 \xrightarrow{1} A_1 + A_2. \]

Running the optimization procedure in GLPK gives the following realizations:

(a) \[
\begin{array}{c}
2A_1 \\
\downarrow 0.5 \\
2A_2
\end{array}
\]

(b) \[
\begin{array}{c}
2A_1 \\
\xleftrightarrow{0.1} \ 0.45 \\
2A_2 \\
\xleftrightarrow{1.8 \ 0.1 \ 0.1} \\
A_1 + A_2
\end{array}
\]

Figure: Sparse (a) and dense (b) networks which generate the same kinetics as \(\mathcal{N}\).
This is a mixed integer linear programming (MILP) problem which is known to be NP-hard.
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1. Can we adapt this to linearly conjugate networks?
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In subsequent papers, further conditions have been imposed on the networks (detailed and complex balancing, weak and full reversibility) [6, 7].

There are still several remaining questions:

1. Can we adapt this to linearly conjugate networks?

2. Can we simplify the requirement for weak reversibility?
In order to incorporate linear conjugacy, we need to satisfy

\[ M = Y \cdot A_k = T \cdot Y \cdot A_b. \]
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\[ M = Y \cdot A_k = T \cdot Y \cdot A_b. \]

### Linear Conjugacy

\[ Y \cdot A_b = T^{-1} \cdot M \]

\[
\sum_{i=1}^{m} [A_b]_{ij} = 0, \quad j = 1, \ldots, m
\]

\[ [A_b]_{ij} \geq 0, \quad i, j = 1, \ldots, m, \quad i \neq j \]

\[ [A_b]_{ii} \leq 0, \quad i = 1, \ldots, m \]

\[ \epsilon \leq c_j \leq 1/\epsilon, \quad j = 1, \ldots, n \]

\[ T = \text{diag}\{c\} \]
Reconsider the network

\[ N : \]

\[ \begin{align*}
A_1 & \xrightarrow{1} A_2 \\
2A_2 & \xrightarrow{1} 2A_1.
\end{align*} \]
Reconsider the network

\[ N : \begin{align*}
A_1 & \xrightarrow{1} A_2 \\
2A_2 & \xrightarrow{1} 2A_1.
\end{align*} \]

Running this in GLPK for both a **sparse and dense linearly conjugate network** gives

\[ N' : \begin{align*}
A_1 & \Leftrightarrow 2A_2 \\
1/2 & \\
\end{align*} \]

with conjugacy constants \(c_1 = 1\), \(c_2 = 1/2\).
QUESTION:

Can we incorporate weak reversibility as a linear constraint in the MILP procedure?
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Existing method requires checking for weak reversibility as a separate step and requires (potentially) multiple MILP optimizations [7].
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It can also only handle dense networks not sparse.
ANSWER:

Yes we can!... But we have to be sneaky...
The kinetics matrix $A_k$ of a weakly reversible network has a positive vector in its kernel, i.e.

$$A_k \, b = 0, \quad b \in \mathbb{R}^m_{>0}.$$
ANSWER:

Yes we can!... But we have to be sneaky...

The kinetics matrix $A_k$ of a weakly reversible network has a positive vector in its kernel, i.e.

$$A_k \ b = 0, \quad b \in \mathbb{R}^m_{>0}.$$

We can introduce $b_j, j = 1, \ldots, m$ as decision variables and impose that $b_j > 0$, but the constraint is non-linear...
Define the matrix $\tilde{A}_k$ with entries $[\tilde{A}_k]_{ij} = [A_k]_{ij} \cdot b_j$ (i.e. multiply $b$ through $A_k$).
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The constraints are **linear** in these new variables!
Define the matrix \( \tilde{A}_k \) with entries \( [\tilde{A}_k]_{ij} = [A_k]_{ij} \cdot b_j \) (i.e. multiply \( b \) through \( A_k \)).

The constraints are \textit{linear} in these new variables!

### Weak Reversibility

\[
\sum_{i=1,i\neq j}^{m} [\tilde{A}_k]_{ij} = \sum_{i=1,i\neq j}^{m} [\tilde{A}_k]_{ji}, \quad j = 1, \ldots , m
\]

\[
[\tilde{A}_k]_{ij} \geq 0, \quad i, j = 1, \ldots , m, \quad i \neq j.
\]
Example 1: Consider the reaction network $\mathcal{N}$ given by

$$\begin{align*}
A_1 + 2A_2 & \xrightleftharpoons{1} 2A_1 + 2A_2 & \xrightarrow{1} 2A_1 + A_2 \\
A_1 & \xleftarrow{2} 2A_1 & \xrightarrow{1} 2A_1 + A_3 \\
2A_1 + 2A_3 & \xleftarrow{1} A_1 + 2A_3 & \xrightarrow{1} A_1 + A_2 + 2A_3 \\
& \downarrow 3 & \\
& A_1 + A_3.
\end{align*}$$
Example 1: Consider the reaction network $\mathcal{N}$ given by

\[
\begin{align*}
\mathcal{A}_1 + 2\mathcal{A}_2 & \xrightarrow{1} 2\mathcal{A}_1 + 2\mathcal{A}_2 \quad 2\mathcal{A}_1 + 2\mathcal{A}_2 & \xrightarrow{1} 2\mathcal{A}_1 + \mathcal{A}_2 \\
\mathcal{A}_1 & \xleftarrow{2} \mathcal{A}_1 + 2\mathcal{A}_2 & \mathcal{A}_1 + 2\mathcal{A}_2 & \xrightarrow{1} 2\mathcal{A}_1 + \mathcal{A}_3 \\
2\mathcal{A}_1 + 2\mathcal{A}_3 & \xleftarrow{1} \mathcal{A}_1 + 2\mathcal{A}_3 & \mathcal{A}_1 + 2\mathcal{A}_3 & \xrightarrow{1} \mathcal{A}_1 + \mathcal{A}_2 + 2\mathcal{A}_3 \\
& & \downarrow{3} \quad \mathcal{A}_1 + \mathcal{A}_3.
\end{align*}
\]

In terms of network structure, this is a mess!
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2A_1 + 2A_3 & \xleftarrow{1} A_1 + 2A_3 \quad A_1 + 2A_3 & \xrightarrow{1} A_1 + A_2 + 2A_3 \\
& \quad \downarrow 3 \quad A_1 + A_3.
\end{align*}
\]

In terms of network structure, this is a mess!

We can say very little about the dynamics of the mass-action system without directly analysing it.
There are weakly reversible networks which are linearly conjugate to $\mathcal{N}$ (found very quickly with GLPK)!
There are weakly reversible networks which are linearly conjugate to $\mathcal{N}^\prime$ (found very quickly with GLPK)!

**Figure:** Weakly reversible networks which are linearly conjugate to $\mathcal{N}^\prime$. The network in (a) is sparse while the network in (b) is dense.
Example 2: Consider the chemical reaction network $\mathcal{N}$ given by

$$
\begin{align*}
X_1 + 2X_2 & \xrightarrow{1.5} X_1 \\
\mathcal{N}: \quad 2X_1 + X_2 & \xrightarrow{1} 3X_2 \\
X_1 + 3X_2 & \xrightarrow{1} X_1 + X_2 \xrightarrow{1} 3X_1 + X_2.
\end{align*}
$$
Example 2: Consider the chemical reaction network $\mathcal{N}$ given by

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X_1 + 2X_2 & \xrightarrow{1.5} X_1 \\
\mathcal{N} : & \\
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X_1 + 3X_2 & \xrightarrow{1} X_1 + X_2 \xrightarrow{1} 3X_1 + X_2.
\end{align*}
$$

Again, the network structure does not tell us anything about the dynamics.
Running the optimization problem in GLPK very quickly produces weakly reversible realizations.
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![Chemical Reaction Network Diagram]

**Figure:** Weakly reversible networks which are linearly conjugate to $\mathcal{N}$. The network in (a) is dense while the network in (b) is sparse. The dense realizations has a trivial linear conjugacy while the sparse realization does not.
**SUMMARY:**

We can find sparse and dense weakly reversible networks which are linearly conjugate to a given network in a single MILP step.
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1. Extend linear conjugacy to non-linear cases and alternate dynamics.
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We can find sparse and dense weakly reversible networks which are linearly conjugate to a given network in a single MILP step.

Areas of future work include:

1. Extend linear conjugacy to non-linear cases and alternate dynamics.

2. Search for applied systems where these results are applicable.
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Gheorghe Craciun and Casian Pantea.
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