The Effect of Operations on the Deficiency of Chemical Reaction Networks

Awildo Gutierrez, Elijah Starr Leake, and Caelyn Sobie

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Outline

- What is a chemical reaction network?
- What are important properties of a network?
  - rank, deficiency

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- Research question:
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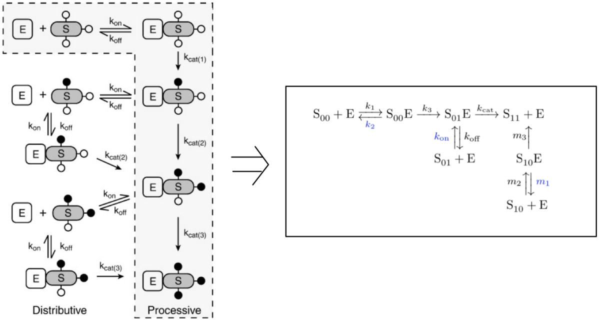
- Results
- Future plans

Motivations: Model for a Phosphorylation Network

- Here we see the construction of a phosphorylation network that shows an enzyme adding a certain number of phosphate groups to a substrate.
- Phosphorylation is a naturally occurring process that involves enzymes adding(or not) a certain number of phosphate groups to a molecule.



Background: What is a chemical reaction network?

- We can use Chemical Reaction Networks to model a phosphorylation network to apply a more mathematical analysis.

Example

$$2A \longrightarrow B+A \longrightarrow 2A + 2B$$

- A chemical reaction network consists of three sets:
  - Species $S = \{X_1, X_2, ..., X_k\}$ (A and B)
  - Complexes $C = \{C_1, C_2, ..., C_l\}$ (2A, B+A, and 2A+2B)
  - Reaction $R = \{C_i \to C_j\}$ ($2A \to B + A$ and $B + A \to 2A + 2B$)

Background: What are important properties of a network?

- The **stoichiometric matrix** $\Gamma_{\mathcal{N}}$ is the matrix where each column is a reaction vector of $\mathcal{N}$.
- **rank**$(\mathcal{N}) = \text{rank}(\Gamma_{\mathcal{N}})$

Example

$$\text{A} \xrightarrow{\begin{bmatrix} 0 \\ 1 \end{bmatrix}} \text{A+B} \xleftarrow{\begin{bmatrix} 1 \\ 0 \end{bmatrix}} \text{B}$$

- For the reaction $A \to A + B$: $\begin{bmatrix} 1 - 1 \\ 1 - 0 \end{bmatrix} = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$
- Here $\Gamma_{\mathcal{N}} = \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix}$, which has rank 2.

Deficiency

Definition

For any network $\mathcal{N}$ on l complexes, s connected components, and rank r, the **deficiency** is

$$\delta(\mathcal{N}) = l - s - r.$$

- When deficiency is low (0 or 1), we are able to predict more about the chemical reaction network (Joshi & Shiu 2014).

Example

$$A+B \rightleftharpoons 3A$$
$$2A + 2B \longrightarrow 0$$

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Example

$$\left.\begin{array}{lcr} A+B & \rightleftharpoons & 3A \\ 2A+2B & \longrightarrow & 0 \end{array}\right\} \delta = 4 - 2 - 2 = 0$$

Deficiency Code

$$2C \longrightarrow A + 3D \rightleftharpoons B + C$$

$$D \longrightarrow 4A$$

Chemical Reaction Network

Connected Component

Complex

Reaction

[[([0,0,2,0], [1,0,0,3]), ([1,0,3,0], [0,1,1,0]), ([0,1,1,0], [1,0,3,0])],
[([0,0,0,1], [4,0,0,0])]]

Operations Overview

Operations were investigated by Banaji, who proved that each of E1-E6 preserve multistationarity of steady states and periodic orbits [1].

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- E6 Splits reactions and adds complexes involving new species (with rank condition)

Research Question

Question

How do these operations affect deficiency?

Summary of Results

Theorem (Gutierrez, Leake, Sobie 2022)

By performing the following operations on a network $\mathcal{N}$ to obtain $\mathcal{N}'$, the deficiencies are:

E1. $\delta(\mathcal{N}') = \delta(\mathcal{N})$ or $\delta(\mathcal{N}') = \delta(\mathcal{N}) + 1$,

E2. $\delta(\mathcal{N}') = \delta(\mathcal{N}) + \text{rank}(\mathcal{N})$, and

E4. $\delta(\mathcal{N}') = \delta(\mathcal{N}) + (\text{genus}(\mathcal{N}) - \text{genus}(\mathcal{N}')) + 1$

Others: (E3, E5, E5′, and E6 Theorems)

$$\delta(\mathcal{N}') = \delta(\mathcal{N}).$$

Results: E3 Theorem 1/2

Definition (E3)

We add a new species Y into the reactions of the original network $\mathcal{N}$, such that the rank of the new network $\mathcal{N}'$ remains the same.

Theorem (Gutierrez, Leake, Sobie)

Let $\mathcal{N}$ be a network. Define a special case of E3 as follows:

- if $C_i \to C_j$ and $C_j \to C_i$ are reactions, then

$$\text{if we change } C_i \to C_j \text{ to } C_i + n_1 Y \to C_j + n_2 Y,$$
$$\text{also change } C_j \to C_i \text{ to } C_j + n_2 Y \to C_i + n_1 Y$$

Results: E3 Theorem 2/2

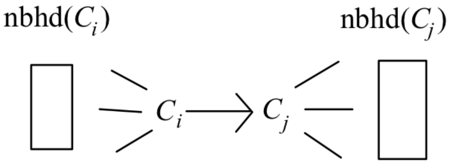
Theorem (Gutierrez, Leake, Sobie)

- if we change $C_i \to C_j$, then

  neighborhood(C_i) is not connected to neighborhood(C_j).

- Then

$$\delta(\mathcal{N}') = \delta(\mathcal{N}).$$



Results: E3 Theorem Example

Example

$$\mathrm{A} \longrightarrow \mathrm{A} + \mathrm{B} \longleftarrow 2\mathrm{A} + \mathrm{B}$$

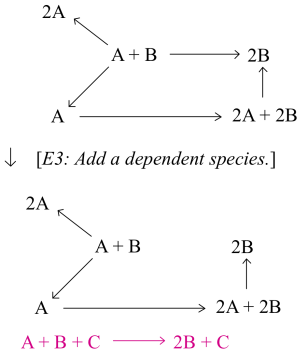
$\downarrow$ [*E3: Add a dependent species.*]

$$\mathrm{A} \longrightarrow \mathrm{A} + \mathrm{B} + \mathrm{C} \longleftarrow 2\mathrm{A} + \mathrm{B}$$

$$\delta(\mathcal{N}) = 3 - 1 - 2 = 0$$

$$\delta(\mathcal{N}') = 3 - 1 - 2 = 0$$

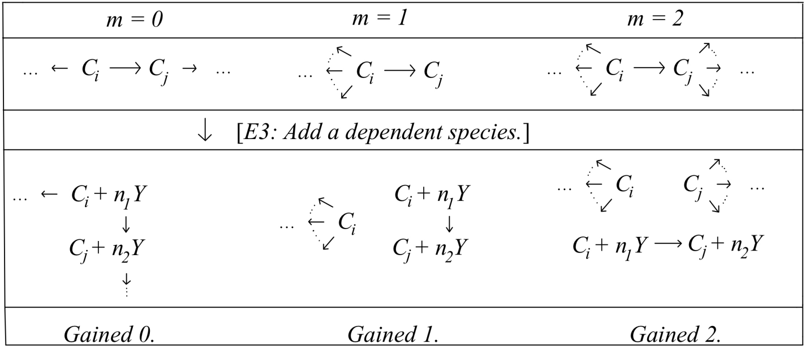
Example



$$l_{\mathcal{N}} = 5, l_{\mathcal{N}'} = 7$$
$$s_{\mathcal{N}} = 1, s_{\mathcal{N}'} = 2$$
$$\delta(\mathcal{N}) = 5 - 1 - 2 = 2, \text{ but}$$
$$\delta(\mathcal{N}') = 7 - 2 - 2 = 3.$$

Proof.

We either add $m = 0$, $m = 1$, or $m = 2$ complexes altering one reaction using E3.



- $l_{\mathcal{N}'} - l_{\mathcal{N}} = s_{\mathcal{N}'} - s_{\mathcal{N}}$

Results: E3 Theorem Proof 2/2

- Since $l_{\mathcal{N}'} - l_{\mathcal{N}} = s_{\mathcal{N}'} - s_{\mathcal{N}}$,

$$\begin{aligned}\delta(\mathcal{N}') - \delta(\mathcal{N}) &= (l_{\mathcal{N}'} - s_{\mathcal{N}'} - r_{\mathcal{N}'}) - (l_{\mathcal{N}} - s_{\mathcal{N}} - r_{\mathcal{N}}) \\ &= ((l_{\mathcal{N}'} - l_{\mathcal{N}}) - (s_{\mathcal{N}'} - s_{\mathcal{N}})) - (r_{\mathcal{N}'} - r_{\mathcal{N}}) \\ &= 0 - 0 = 0.\end{aligned}$$

Genus of a Network

Definition

For any network $\mathcal{N}$ on $n_{\mathcal{N}}$ reactions, the **genus** of $\mathcal{N}$ is

$$g(\mathcal{N}) = n_{\mathcal{N}} - l_{\mathcal{N}} + s_{\mathcal{N}},$$

where $l_{\mathcal{N}}$ is the number of complexes in $\mathcal{N}$ and $s_{\mathcal{N}}$ is the number of connected components in $\mathcal{N}$.

Results: E4 Theorem

Definition (E4)

Add a new species into some or all reactions already present in our network. We also add an inflow and outflow reaction involving the new species and the 0 complex.

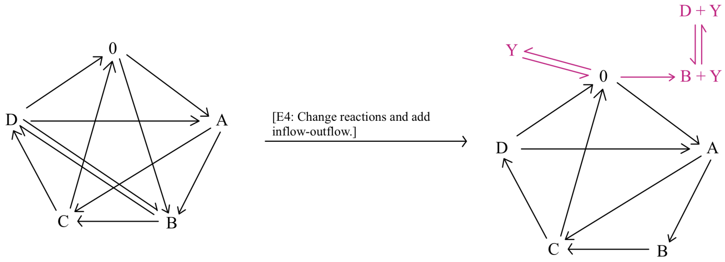
Theorem (Gutierrez, Leake, Sobie 2022)

Let $\mathcal{N}$ be a network and let $\mathcal{N}$' be obtained by applying an E4 operation to add a new species. Then

$$\delta(\mathcal{N}') = \delta(\mathcal{N}) + h + 1,$$

where $h = g(\mathcal{N}) - g(\mathcal{N}')$.

Example



$$\delta(\mathcal{N}) = 5 - 1 - 4 = 0 \qquad \delta(\mathcal{N}') = 8 - 1 - 5 = 2$$

$$g(\mathcal{N}) = 11 - 5 + 1 = 7 \qquad g(\mathcal{N}') = 13 - 8 + 1 = 6$$

Results: E4 Proof

Theorem (Gutierrez, Leake, Sobie 2022)

Let $\mathcal{N}$ be a network and let $\mathcal{N}$' be obtained by applying an E4 operation to add a new species. Then, $\delta(\mathcal{N}') = \delta(\mathcal{N}) + h + 1$.

$$\begin{aligned}
\delta(\mathcal{N}') - \delta(\mathcal{N}) &= (l_{\mathcal{N}'} - s_{\mathcal{N}'} - r_{\mathcal{N}'}) - (l_{\mathcal{N}} - s_{\mathcal{N}} - r_{\mathcal{N}}) \\
&= (l_{\mathcal{N}'} - s_{\mathcal{N}'} - (r_{\mathcal{N}} + 1)) - (l_{\mathcal{N}} - s_{\mathcal{N}} - r_{\mathcal{N}}) \\
&= (l_{\mathcal{N}'} - l_{\mathcal{N}}) + (s_{\mathcal{N}} - s_{\mathcal{N}'}) - 1
\end{aligned}$$

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$$\begin{aligned}h &= g(\mathcal{N}) - g(\mathcal{N}') \\ &= (n_{\mathcal{N}} - l_{\mathcal{N}} + s_{\mathcal{N}}) - (n_{\mathcal{N}'} - l_{\mathcal{N}'} + s_{\mathcal{N}'}) \\ &= (l_{\mathcal{N}'} - l_{\mathcal{N}}) + (s_{\mathcal{N}} - s_{\mathcal{N}'}) - 2\end{aligned}$$

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$$\delta(\mathcal{N}) - \delta(\mathcal{N}') = h + 1$$

Results: E5 Theorem

Definition (E5)

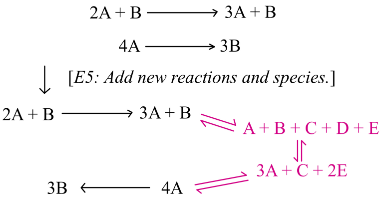
Add m new reversible reactions to $\mathcal{N}$ and $m+i$ new species such that the submatrix of the new **stoichiometric matrix** only containing the new species has rank m.

Theorem (Gutierrez, Leake, Sobie 2022)

Let $\mathcal{N}'$ be obtained from a network $\mathcal{N}$ via an E5 move. Then

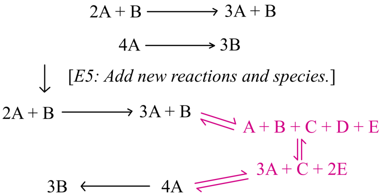
$$\delta(\mathcal{N}') = \delta(\mathcal{N}).$$

Example



$$\Gamma_{\mathcal{N}'} = \begin{bmatrix} 1 & -4 & -1 & -2 & -2 \\ 0 & 3 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 2 & -1 & 1 \end{bmatrix}$$

Results: E5 Theorem Example 2/2



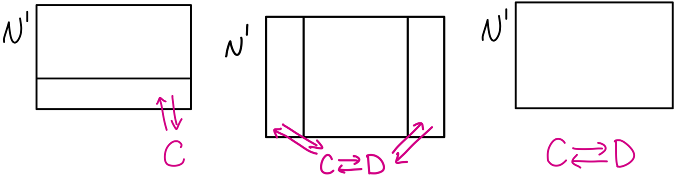
$$\Gamma_{\mathcal{N}'} = \begin{bmatrix} 1 & -4 & -1 & -2 & -2 \\ 0 & 3 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 2 & -1 & 1 \end{bmatrix}$$

- Omit the new reverse reactions
- New species are C, D, and E
- The submatrix of $\Gamma_{\mathcal{N}'}$ consisting of the last three rows must have rank $m = 3$
- $\delta(\mathcal{N}) = 4 - 2 - 2 = 0$ and $\delta(\mathcal{N}') = 6 - 1 - 5 = 0$.

Results: E5 Theorem Proof Idea

Proof.

All E5 operations are combinations of the following cases (A, B, and C):



We know

$$\delta(\mathcal{N}) = l_{\mathcal{N}} - s_{\mathcal{N}} - r_{\mathcal{N}},$$

so $\delta_A(\mathcal{N}') = (l_{\mathcal{N}} + 1) - s_{\mathcal{N}} - (r_{\mathcal{N}} + 1) = \delta(\mathcal{N})$,
$\delta_B(\mathcal{N}') = (l_{\mathcal{N}} + 2) - (s_{\mathcal{N}} - 1) - (r_{\mathcal{N}} + 3) = \delta(\mathcal{N})$, and
$\delta_C(\mathcal{N}') = (l_{\mathcal{N}} + 2) - (s_{\mathcal{N}} + 1) - (r_{\mathcal{N}} + 1) = \delta(\mathcal{N})$. □

Future Work

- Generalize E2 theorem assumptions
- Does E5′ also preserve multistationarity and periodic orbits?
- Is E5′ a sequence of E1-E6 moves?
- How do these operations affect Absolute Concentration Robustness (ACR)?

Conclusion

Thank you!

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