Using ML tools to predict number of solutions of parametric system of polynomial equations with the help of CRNs

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Introduction

- Main question of interest
- A quick look at CRN theory
- Hungarian Lemma
- Can ML be used in CRN?
- Plan for the next steps

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2 solutions, $x = 2$ and $x = 3$.

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where b and c are two fixed positive real numbers, but not given, i.e. two parameters over $\mathbb{R}_{>0}$.

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It has 0 solutions.

What is the question we are trying to answer?

How many non-negative real solutions does the following equation have?

$$\begin{cases} -k_1x_1x_2 - k_2x_1x_2^2 - k_3x_1x_2^3 + k_5 - k_6x_1 & = 0 \\ -k_4x_2 + k_7 - k_8x_2 & = 0 \\ k_1x_1x_2 + k_2x_1x_2^2 + k_3x_1x_2^3 + k_9 - k_{10}x_3 & = 0 \\ k_4x_2 + k_{11} - k_{12}x_4 & = 0 \end{cases}$$

where $k_1, \ldots, k_{12}$ are positive real valued parameters?

What is the question we are trying to answer?

The target question

Given a system of parametric equations with some constraints on values of the variables and parameters, how many solutions can this system obtain?

A chemical reaction

$$2\,O_2{}^{-} + 2\,H^{+} \longrightarrow O_2 + H_2O_2$$

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The nodes are linear combinations of some things X_1, X_2, X_3 and X_4.

What is a Chemical Reaction Network?

A reaction network $\mathcal{N}$ consists of three finite sets:

- $\mathcal{S}$ Species.

- $\mathcal{C}$ Complexes: Linear combinations of species with non-negative integer coefficients.

- $\mathcal{R}$ Reactions: Ordered pairs of complexes.

$$X_0 + E \rightleftharpoons Y_1 \longrightarrow Y_2 \rightleftharpoons X_1 + E$$
$$2X_1 + X_2 \longrightarrow 2X_2$$

We call this graph representation, CR-graph of the CRN.

Steady states

Reaction network

$$X_0 + E \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Y_1 \xrightarrow{k_3} Y_2 \underset{k_5}{\overset{k_4}{\rightleftharpoons}} X_1 + E$$

$$2X_1 + X_2 \xrightarrow{k_6} 2X_2$$

ODE system

$$\begin{cases} \dot{x}_0 = -k_1 x_0 e + k_2 y_1 \\ \dot{x}_1 = k_4 y_2 - k_5 x_1 e - 2k_6 x_1^2 x_2 \\ \dot{x}_2 = k_6 x_1^2 x_2 \\ \dot{e} = -k_1 x_0 e + k_2 y_1 + k_4 y_2 - k_5 x_1 e \\ \dot{y}_1 = k_1 x_0 e - k_2 y_1 - k_3 y_1 \\ \dot{y}_2 = k_3 y_1 - k_4 y_2 + k_5 x_1 e \end{cases}$$

To study steady states of a reaction network, solve the system after replacing 0 for $\dot{x}_i$s.

A CRN is multistationary if there exists a choice of parameter values such that the system has more than one steady states in the same stoichiometric compatibility class.

Detecting multistationarity

There are different approaches to detect multistationarity of a given CRN.

- CRNToolbox: using deficiency theorems and algorithms.
- Atoms of multistationarity: simplifying the network and using results on inheritance of properties.
- Algebraic approach: using discriminant variety and cylindrical algebraic decomposition ... (expensive tool).
- Injectivity criteria: capable of only precluding multistationarity.
- ... .

Hungarian Lemma

Realizations of kinetic differential equations

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Elisa Tonello § János Tóth ¶ Polly Y. Yu ‖

Abstract

The induced kinetic differential equations of a reaction network endowed with mass action type kinetics is a system of polynomial differential equations. The problem studied here is: Given a system of polynomial differential equations, is it possible to find a network which induces these equations; in other words: is it possible to find a *kinetic realization* of this system of differential equations? If yes, can we find a network with some chemically relevant properties (implying also important dynamic consequences), such as reversibility, weak reversibility, zero deficiency, detailed balancing, complex balancing, mass conservation, etc.? The constructive answers presented to a series of questions of the above type are useful when fitting differential equations to datasets, or when trying to find out the dynamic behavior of the solutions of differential equations. It turns out that some of these results can be applied when trying to solve seemingly unrelated mathematical problems, like the existence of positive solutions to algebraic equations.

Keywords: kinetic equations, reversibility, weak reversibility, mass action kinetics, reaction networks, realizations

“*It turns out that some of these results can be applied when trying to solve seemingly unrelated mathematical problems, like the existence of positive solutions to algebraic equations.*” [Craciun et al. 2020]

Hungarian Lemma

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Example

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$$X_1 + X_2 \xrightarrow{k_1} X_2 + X_3$$

$$X_1 + 2X_2 \xrightarrow{k_2} 2X_2 + X_3$$

$$X_1 + 3X_2 \xrightarrow{k_3} 3X_2 + X_3$$

$$X_2 \xrightarrow{k_4} X_4$$

$$X_i \underset{k_{2i+3}}{\overset{k_{2i+4}}{\rightleftharpoons}} 0, i = 1, 2, 3, 4$$

Hungarian Lemma

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Non-example

$$\begin{cases} x_2 - x_1 & = 0 \\ x_1 - x_1 x_3 - x_2 & = 0 \\ x_1 x_2 - x_3 & = 0 \end{cases}$$

Limitations of deterministic approaches

$$X_1 + X_2 \longrightarrow X_3$$
$$X_2 + X_3 \rightleftharpoons X_1 + X_4$$
$$X_3 + X_5 \longrightarrow 2X_6$$
$$X_4 \longrightarrow X_5$$
$$X_1 + 2X_5 \longrightarrow X_1$$
$$X_i \rightleftharpoons 0, i = 1, \ldots, 6$$

All 4 approaches to decide multistationarity of the above CRN fails to answer it (on a normal computer).

Let's use ML

What algorithm and how to feed CRNs into it?

$$X_1 + 2X_2 \rightleftharpoons 3X_1 + X_2$$
$$X_i \rightleftharpoons 0, i = 1, 2$$

Everyone first thinks of using SVM and RF. These algorithms receive the input data as vectors. Can a CRN be written as a vector?

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$$\begin{bmatrix} 1 & 2 & 3 & 1 \\ 3 & 1 & 1 & 2 \\ 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

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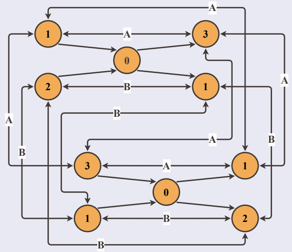
Everyone first thinks of using SVM and RF. These algorithms receive the input data as vectors of the same length. Can a CRN be written as a vector?

$$\begin{bmatrix} 1 & 2 & 3 & 1 \\ 3 & 1 & 1 & 2 \\ 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

But the size of this matrix changes when the number of species and reactions change.

why not using graph learning algorithms?

There are many graph representations of CRNs, in [Yao et al. 2024] the following graph representation is used together with graph attntion networks (GAT) for fully open CRNs.



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

Need to a large dataset

How to create a large dataset?

Using [Joshi 2013] and [Joshi-Shiu 2013], i.e. atoms of multistationarity, many CRNs with the multistationary label can be generated. But without generating same amount of non-multistationary networks, the training dataset will be unbalanced.

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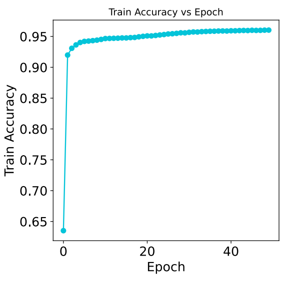
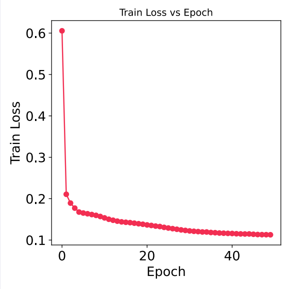
In [Yao et al. 2024] we extended results of [Feliu-Wiuf 2015] about using the theory of positive feedback loops to preclude multistationarity. It helped us to create enough many non-multistationary fully open CRNs.

Results of the model

The training loss and accuracy of the GAT model [Yao et al. 2024]





Test on differently generated CRNs

Actual	Predicted	
	Multi	Non-Multi
Multi	**8**	3
Non-Multi	6	**15**

Future work

- Experimenting with different representations of CRNs and learning algorithms.
- Creating more diverse dataset.
- Trying to find new mathematical conjectures and theorems with the help of trained ML models.
- Going beyond the limits of Hungarian lemma.

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Thank you for listening.