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A Computational Tool For Sensitivity Analysis in Chemical Reaction Networks Modeling Cancer Cell Signaling

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Introduction and Goal

Biological Background

Chemical Reaction Networks (CRNs)

- are a biological model capable of describing phenomena that happen inside a cell;
- model the flow of a collection of reactions;
- describe the interaction between many different cellular pathways.

Realistic CRNs consist of a huge number of chemical reactions r that involve a large number n of chemical species. In general,

- CRNs translate extracellular **signals** into intracellular responses;
- CRNs can be altered by the presence of different types of **mutations**, causing diseases like cancer [2];
- Targeted **drugs** can restore CRNs' physiological behavior.

Mathematical Background

A CRN can be modeled through a **system of ODE**:

$$\begin{cases} \dot{\mathrm{x}}(t) = \mathrm{S}\mathrm{v}(\mathrm{x}(t), \mathrm{k}^0) \\ \mathrm{x}(0) = \mathrm{x}_0 \end{cases}$$

where

- $\mathrm{x}(t) = (x_1(t), \dots, x_n(t))^T$: chemical species concentrations
- $\mathrm{k}^0 = (k_1^0, \dots, k_r^0)^T$: reaction rate constants
- $\mathrm{v}(\mathrm{x}(t), \mathrm{k}^0)$: reaction fluxes
- S: stoichiometric matrix
- x_0: initial condition

By defining $\mathrm{N} \in \mathbb{R}^{p \times n}$ such that $\mathrm{NS} = 0$ and $\mathrm{c}^0 := \mathrm{N}\mathrm{x}_0$, the CRN's conservation laws are $\mathrm{N}\mathrm{x}(t) = \mathrm{c}^0$ [1].

Our Goal: Local Sensitivity Analysis

It can be shown [5] that the equilibrium point $\mathrm{x}^e = \lim_{t\to\infty} \mathrm{x}(t)$ is the solution of

$$\begin{cases} \mathrm{S}_2\mathrm{v}(\mathrm{x}, \mathrm{k}^0) = 0 \\ \mathrm{N}\mathrm{x} - \mathrm{c}^0 = 0 \end{cases}$$

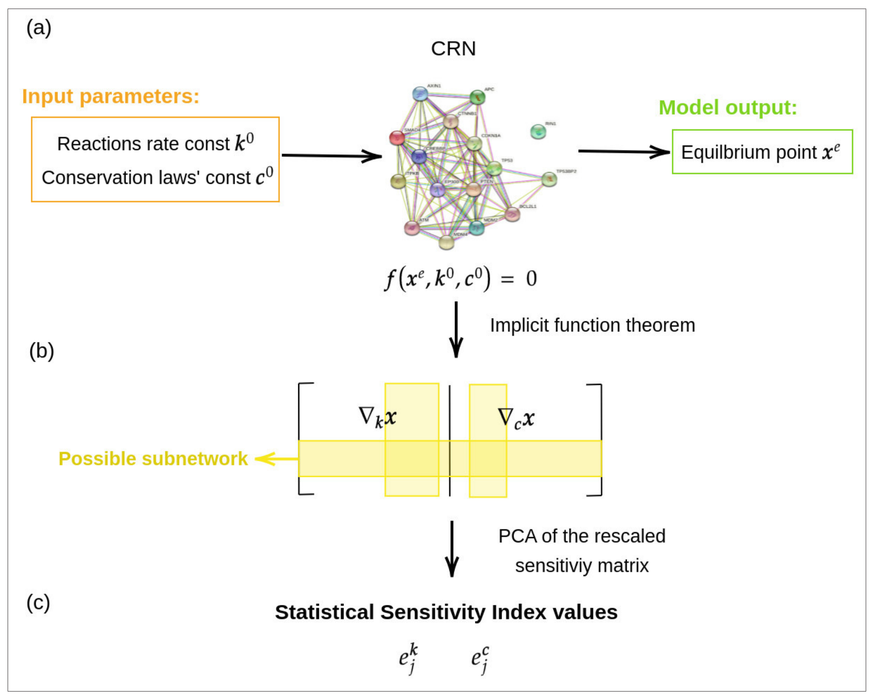
with S_2 submatrix of S. Defined $\mathrm{h}^0 = (\mathrm{k}^0, \mathrm{c}^0)$

$$\begin{array}{ccc} \mathrm{h}^0 & \longrightarrow & \mathrm{h} = \mathrm{h}^0 + \Delta\mathrm{h} \\ \downarrow & & \downarrow \\ \mathrm{x}^e & & \mathrm{x}^e(\mathrm{h}) \end{array}$$

Motivation:

- model reduction
- drug repurposing and the search for new therapeutic targets in cancer

Methods



(a) Visualization of the model.

(b) By applying the Implicit Function Theorem to $f : \mathbb{R}^n \times \mathbb{R}^{r+p} \to \mathbb{R}^n$

$$f(\mathrm{x}, \mathrm{h}) = \begin{bmatrix} \mathrm{S}_2\mathrm{v}(\mathrm{x}, \mathrm{k}) \\ \mathrm{N}\mathrm{x} - \mathrm{c} \end{bmatrix},$$

it follows that there exists one and only one $\mathrm{x} = \mathrm{x}(\mathrm{h})$ such that for h in a neighborhood of h^0

$$f(\mathrm{x}(\mathrm{h}), \mathrm{h}) = \mathbf{0}.$$

The **local sensitivity matrix** of equilibrium with respect to parameters is obtained by computing

$$\nabla_{\mathrm{h}}\mathrm{x}(\mathrm{h}^0) = -\left[\nabla_{\mathrm{x}} f(\mathrm{x}(\mathrm{h}^0), \mathrm{h}^0)\right]^{-1} \nabla_{\mathrm{h}} f(\mathrm{x}(\mathrm{h}^0), \mathrm{h}^0)\,.$$

(c) The first order Taylor expansion of $\mathrm{x}(\mathrm{h})$ leads to

$$\hat{\Delta}\mathrm{x} = \boldsymbol{\mathcal{S}}\,\hat{\Delta}\mathrm{h}\ ,$$

with

$$\hat{\Delta}\mathrm{x} = \left[\frac{x_1(\mathrm{h}) - x_1^e}{x_1^e}, \dots, \frac{x_n(\mathrm{h}) - x_n^e}{x_n^e}\right]^T, \qquad \hat{\Delta}\mathrm{h} = \left[\frac{h_1 - h_1^0}{h_1^0}, \dots, \frac{h_{r+p} - h_{r+p}^0}{h_{r+p}^0}\right]^T,$$

$$\boldsymbol{\mathcal{S}}_{ij} = \frac{h_j^0}{x_i^e}(\nabla_{\mathrm{x}}\mathrm{x}(\mathrm{h}^0))_{ij}$$

From the definition of the semi-positive quadratic form [4]

$$Q = \hat{\Delta}\mathrm{x}^T\hat{\Delta}\mathrm{x} = \hat{\Delta}\mathrm{h}^T\boldsymbol{\mathcal{S}}^T\boldsymbol{\mathcal{S}}\hat{\Delta}\mathrm{h}$$

a Principal Component Analysis of $\boldsymbol{\mathcal{S}}^T\boldsymbol{\mathcal{S}}$ can be computed to find the **Statistical Sensitivity Indexes** (SSI)

$$e_j^{\mathrm{h}} = \frac{\sum_{a=1}^{r+p} \lambda_a\, u_{ja}^2}{\sum_{a=1}^{r+p} \lambda_a},$$

where $\lambda_1, \dots, \lambda_{r+p}$, with $\lambda_1 \geq \lambda_2 \geq \dots \geq \lambda_{r+p} \geq 0$, and $\mathrm{u}_1, \dots, \mathrm{u}_{r+p}$ are the eigenvalues and the corresponding normalized eigenvectors of $\boldsymbol{\mathcal{S}}^T\boldsymbol{\mathcal{S}}$, respectively.

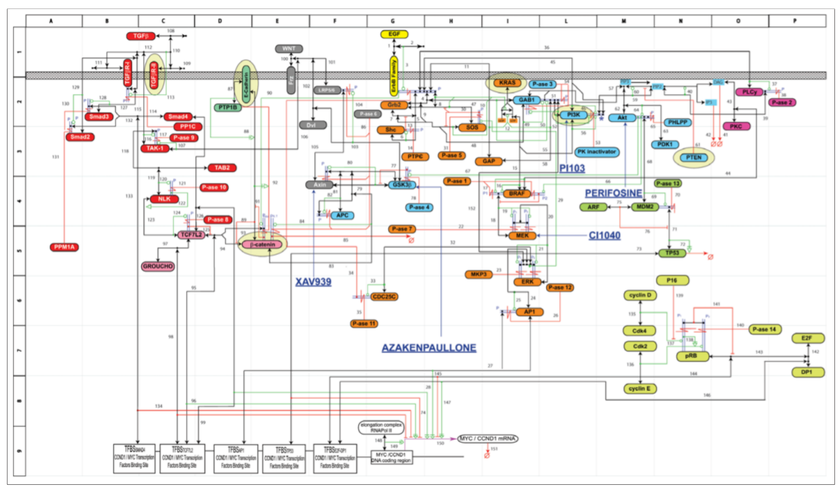
Mutated CRN

- A Loss of Function mutation (LoF) nullifies the concentration of a chemical species [1].
  - remove from S, x and N the entries referred to the chemical species that don't appear in the network anymore;
  - remove from S and v the entries referred to the reactions that don't happen in the network anymore.
- A Gain of Function mutation (GoF) increases the concentration of a chemical species [1].
  - remove from S and v the entries referred to the reactions that don't happen in the network anymore.

Data: Colorectal cell CRN

Colorectal cell CRN (CRC-CRN) [3]:

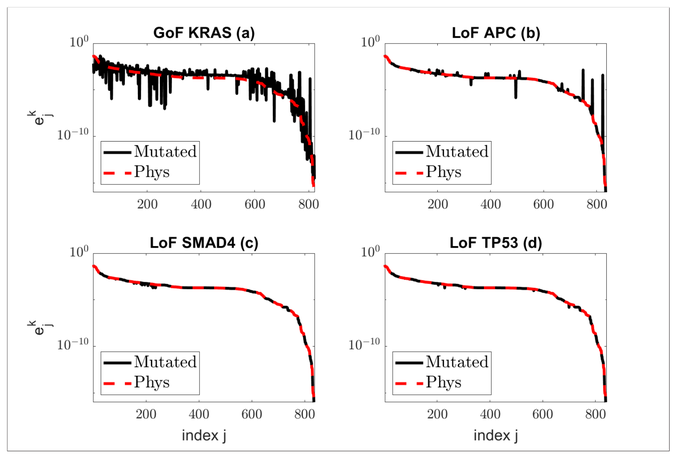
- $n = 419$ chemical species
- $r = 850$ chemical reactions
- $p = 81$ conservation laws



Results: a mutated CRC-CRN

Considered mutations:

(a) GoF of KRAS;
(b) LoF of APC;
(c) LoF of SMAD4;
(d) LoF of TP53.



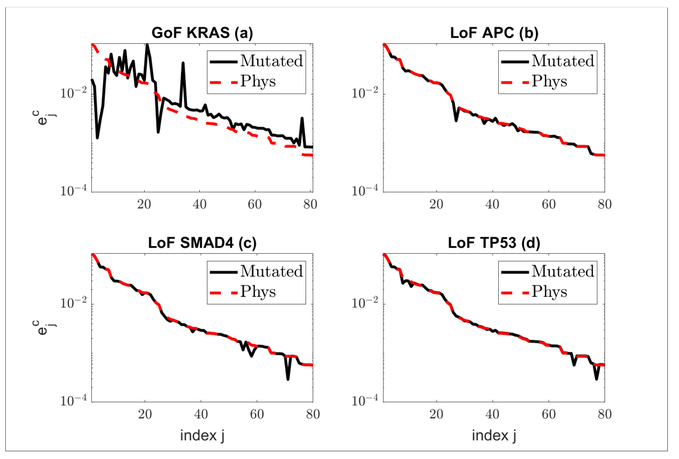


Figure SSI values for all rate constants (left panel) and for all conservation laws' constants (right panel) in the case of four mutated networks (black solid line) with respect to the SSI values of the physiological CRN (red dashed line).

Reference #	Reaction	δe_j^{k}
R41	Ras + GDP → Ras_GDP	1.91e+07
R294	ERBP_ShP_G_S → ERBP_ShP_G + SOS	2.91e+04
R49	RP_ShP_G_S_Ras + GTP → RP_ShP_G_S_Ras_GTP	2.88e+04
R412	ERB3P_Sh → ERB3P + Shc	2.86e+04
R415	ShP + ERB3P → ERB3P_ShP	1.23e+04
R297	ERBP_ShP + G_S → ERBP_ShP_G_S	8.64e+03
R302	ERBP_ShP_G_S_Ras + GDP → ERBP_ShP_G_S_Ras_GDP	5.78e+02
R57	RP_G_S_Ras_GDP → RP_G_S_Ras + GDP	5.78e+02
R420	ERB3P_ShP_G + SOS → ERB3P_ShP_G_S	5.78e+02
R52	RP_ShP_G_S + Ras_GTP → RP_ShP_G_S_Ras_GTP	4.95e+02

Table Reactions whose sensitivity indexes are mostly effected by the GoF mutation of KRAS.
The third column contains the relative differences of e_j^{k} between the mutated and the physiological CRC-CRN.

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