

# YOUNG SCIENCE FORUM: IL FUTURO NASCE IN LABORATORIO



**Ricostruzione dei pathway molecolari delle leucemie  
attraverso l'intelligenza artificiale**

*Sara Sommariva*

Dipartimento di Matematica, Università di Genova

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## Outline of the talk

- ▶ Motivation
- ▶ A case study on colon-rectal cancer
- ▶ Towards a model for Leukemia
- ▶ Future directions

## Motivation

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BUT

1 drug  $\rightarrow$  1 possible therapy  
2 drugs  $\rightarrow 2 + 1 = 3$  possible therapies  
3 drugs  $\rightarrow 3 + 3 + 1 = 7$  possible therapies  
 $n$  drugs  $\rightarrow 2^n - 1$  possible therapies

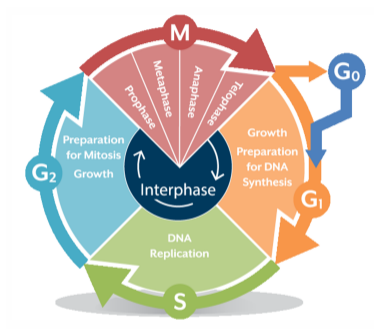
## Motivation

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IDEA: Develop an *in-silico* simulator to preselect the therapies to be tested.

## A case study on colon-rectal cancer

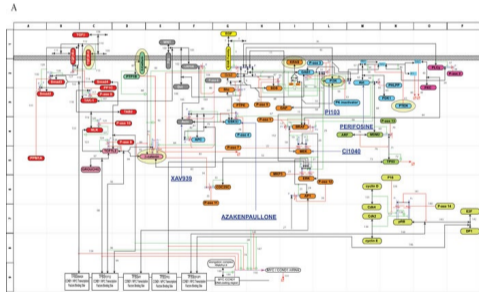
We focus on the G1 – S transition phase of a **single colorectal cell**



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We built a **chemical reaction network** describing the molecular pathway that translates extracellular signals into cellular response.

- ▶ 510 reactions
- ▶ 420 chemical species
- ▶ 10 interacting pathways downstream  $TGF\beta$ , WNT and EGF



Tortolina et al., OncoTarget, 2015

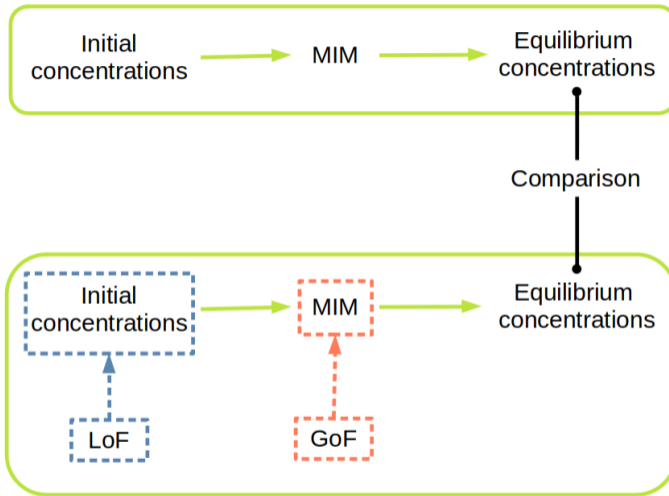
**Objective:** Find the concentration of the chemical species at the equilibrium reached by the cell prior to mitosis.

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Equilibrium = steady state of the dynamical system obtained by interpreting the chemical reactions as components of ODEs:

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

- ▶  $\mathbf{x}(t) = (x_1(t), \dots, x_n(t))$  concentrations of the chemical species
- ▶  $\mathbf{k} = (k_1, \dots, k_p)$  rate constants of the chemical reactions
- ▶  $\mathbf{x}_0$  auxiliary initial condition defining the cell type (physiological vs mutated)
- ▶  $\mathbf{v}(\mathbf{k}, \mathbf{x}(t))$  vector of reaction fluxes
- ▶  $\mathbf{S}$  stoichiometric matrix.



Sommariva et al., Scientific Reports, 2021

We compare the concentration in the *mutated cell* with the concentrations at equilibrium of the *physiological cell*.

$$\delta_i(t) = \frac{x_i^m(t) - x_{e,i}}{x_{e,i}} \quad i = 1, \dots, n$$

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$$\delta_i(t) = \frac{x_i^m(t) - x_{e,i}}{x_{e,i}} \quad i = 1, \dots, n$$

- ▶  $\delta_i(t) = -1$  the mutation cancels the  $i$ -th chemical specie;
- ▶  $\delta_i(t) < 0$  the mutation reduces the  $i$ -th chemical specie;
- ▶  $\delta_i(t) = 0$  the mutation has no effect on the  $i$ -th chemical specie;
- ▶  $\delta_i(t) > 0$  the mutation increases the  $i$ -th chemical specie;

Healthy cell

Healthy cell



Mutated cell

Healthy cell

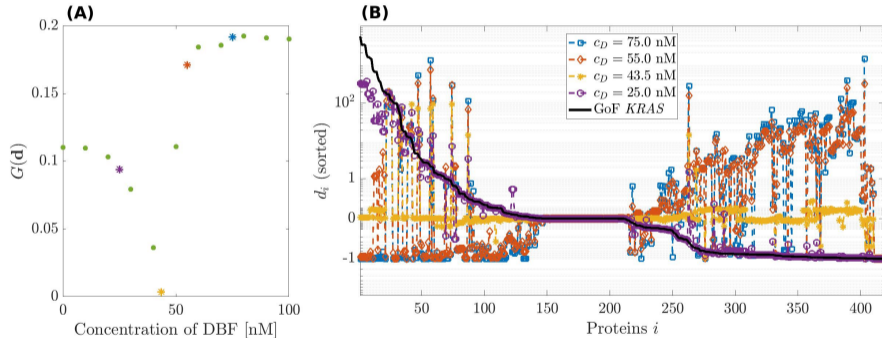


Mutated cell

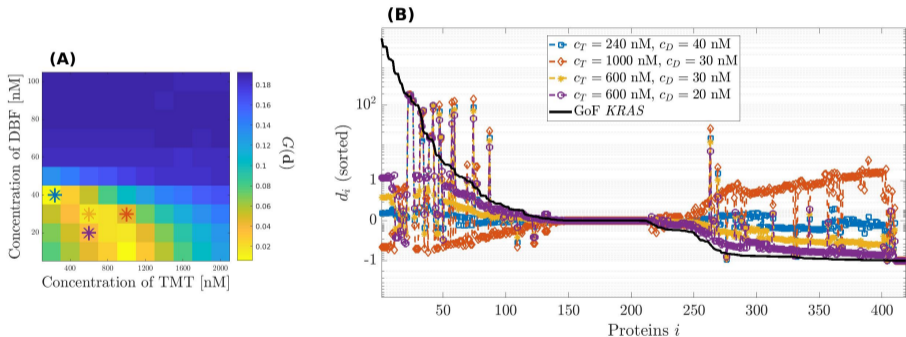


Treated mutated cell

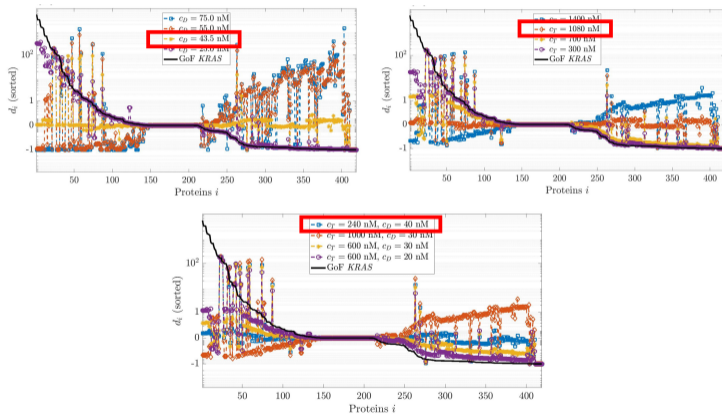
Different **drug dosages** can be tested.



Different combination therapies can be tested.



**Result:** when combined a **small dose** of both drugs produces almost the same effects of either a single infusion of DBF, or TMT, delivered at much higher dose.



Sommariva et al., 2023, Frontiers in system biology.

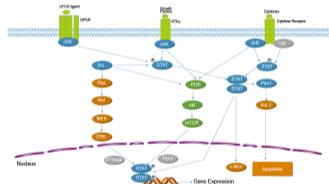
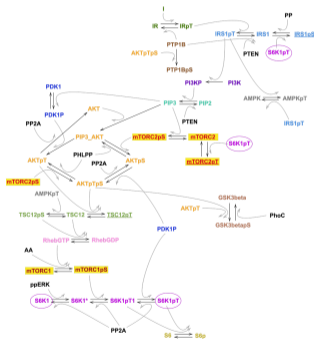
## Towards a model for Leukemia

**Step 1:** Identify pathway to be integrated within our chemical reaction network.

MAPK

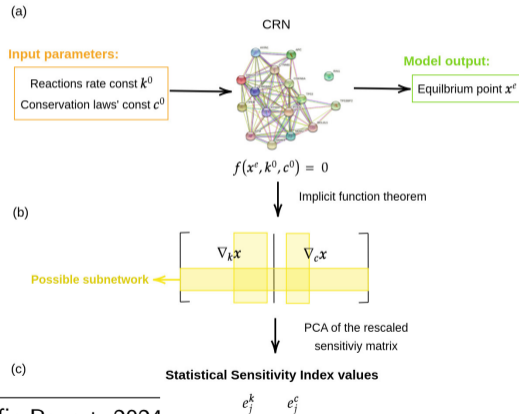
MTOR

JACK-STAT



Berra et al., in preparation

- Step 1:** Identify pathway to be integrated within our chemical reaction network.
- Step 2:** Identify most sensible parameter that need a fine tuning.



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- Step 2: Identify most sensible parameter that need a fine tuning.
- Step 3: Calibrate the most sensible parameters

## Future directions

- ▶ Exploit large language models for automatic pathway identification and implementation.
- ▶ Data acquisition for parameter calibration
- ▶ Further tests of the implemented model

**That's all folks!**