VERIFICATION OF ROBUSTNESS PROPERTY IN CHEMICAL REACTION NETWORKS

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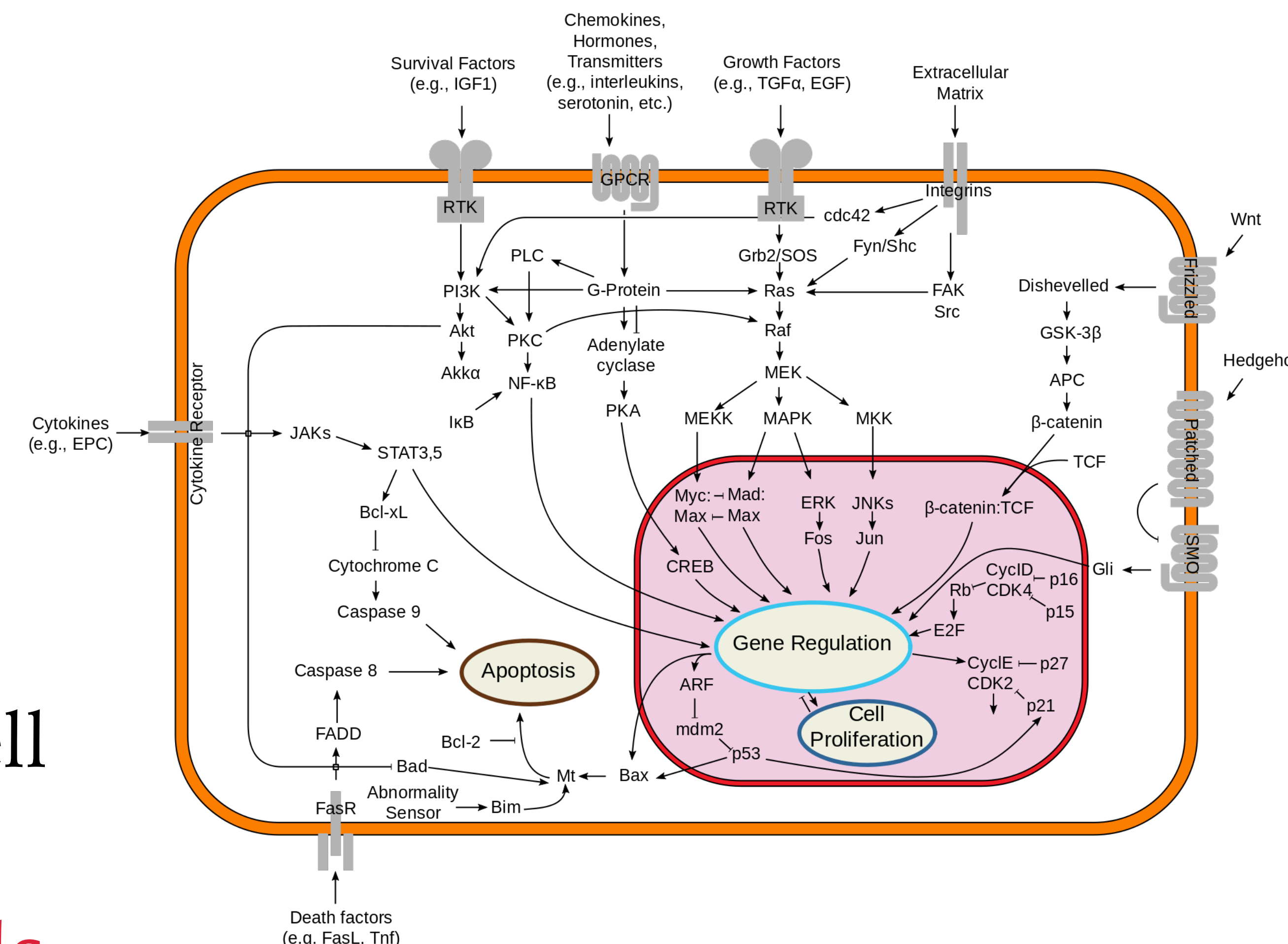
OUTLINE

- What is **robustness**?
- Formalisation problem: **CRN** and **Petri Nets**
- Why and how to study **monotonicity** in CRN?
- Results: **Sufficient conditions** and **Tool**
- Application: **Becker-Döring equations**
- Future work

BACKGROUND

- A cell is a **very complex system**
- Chemical reaction networks (*pathways*) govern the basic cell's activities
- To examine the structure of the cell as a whole, we can design **multiscale and predictive models**



ROBUSTNESS PROPERTY

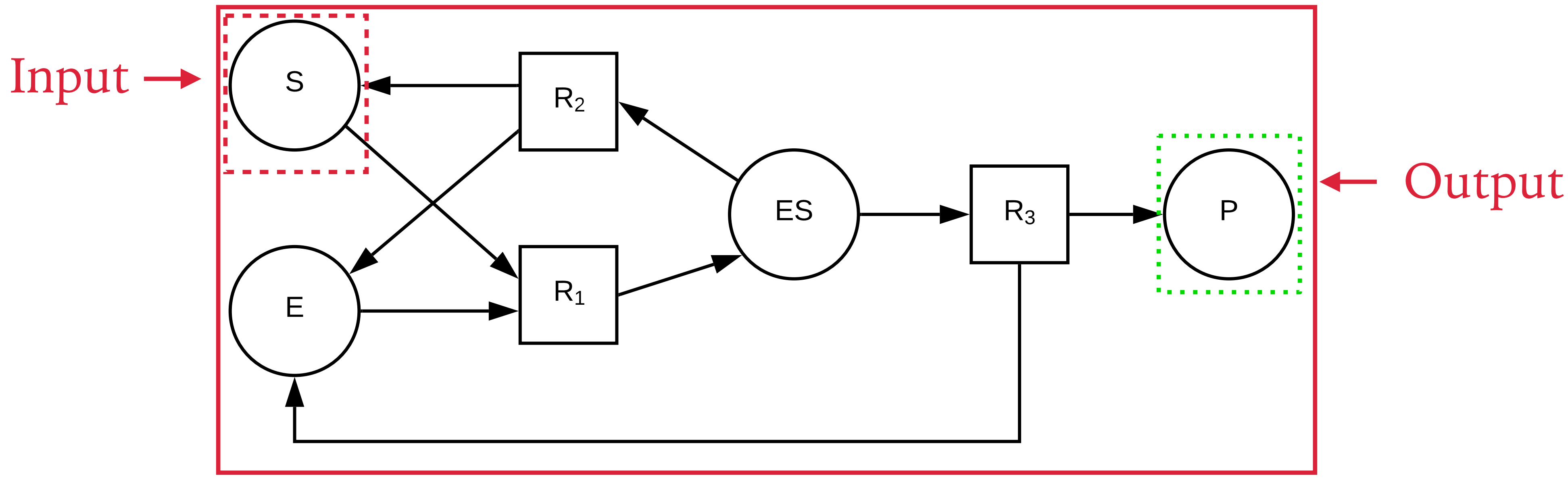
- **Robustness:** A fundamental feature of complex evolving systems, for which the behaviour of the system remain essentially constant, despite the presence of internal and external perturbations.

In nature, there are **different mechanisms** ensuring this property:

- **Modularity:** many components
- **System control:** amplification of the input signal
- **Redundancy:** many structures for the same function
- **Structural stability:** adaptation to external input

OUR NEW DEFINITION OF INITIAL CONCENTRATION ROBUSTNESS

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$$



$$\begin{cases} \frac{d[E]}{dt} = -k_1[E][S] + k_2[ES] + k_3[ES] \\ \frac{d[S]}{dt} = -k_1[E][S] + k_2[ES] \\ \frac{d[ES]}{dt} = +k_1[E][S] - k_2[ES] - k_3[ES] \\ \frac{d[P]}{dt} = +k_3[ES] \end{cases}$$

- Using Petri net → Formal definition of **α-Robustness** and **β-Robustness**

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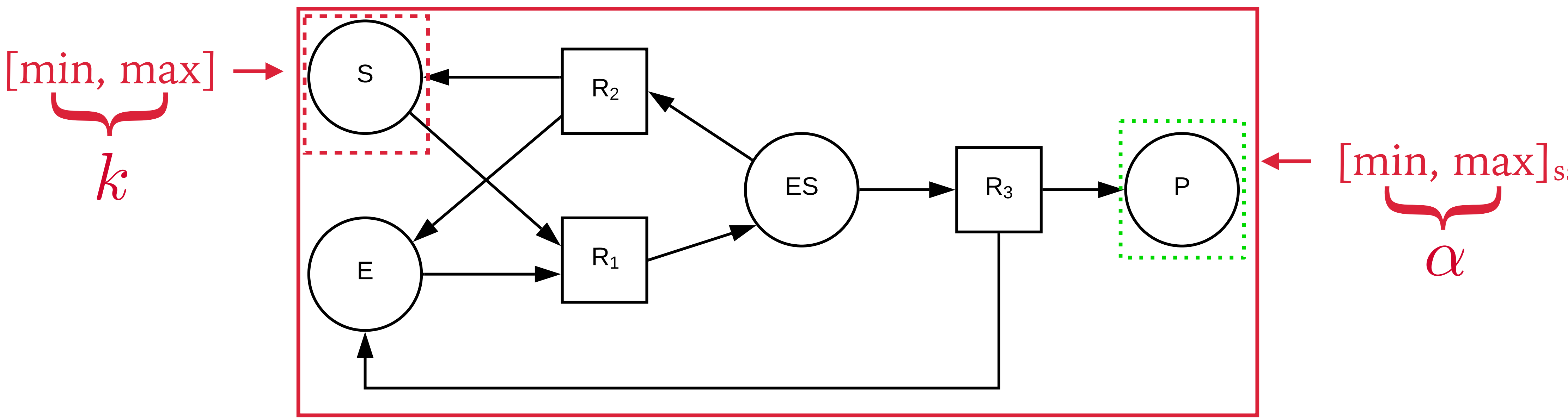

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$$\approx \frac{\alpha}{k}$$

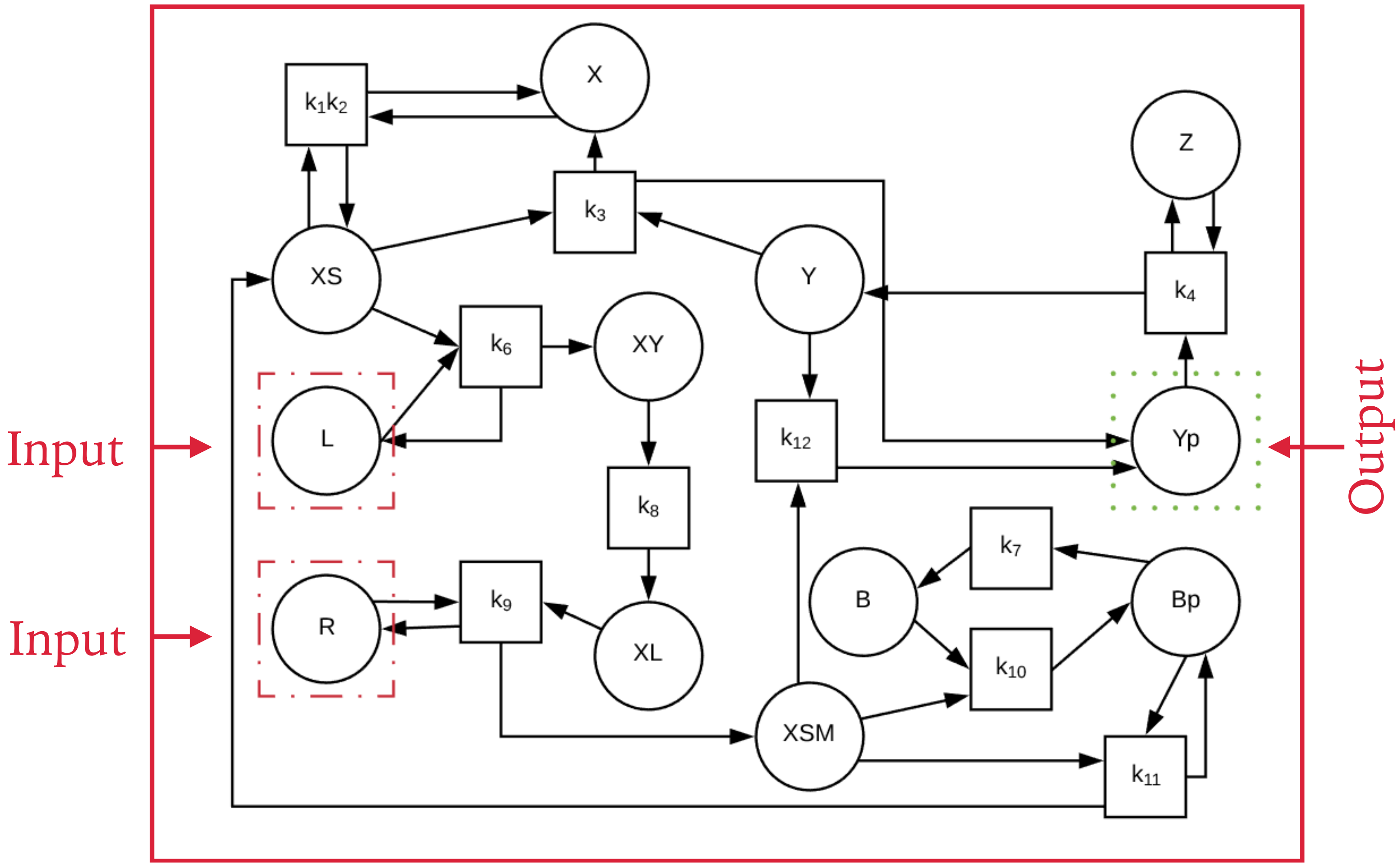
- Using Petri net → Formal definition of α-**Robustness** and β-**Robustness**

EXAMPLE OF APPLICATION OF OUR DEFINITION: CHEMOTAXIS OF E. COLI

- Given a set of reactions:

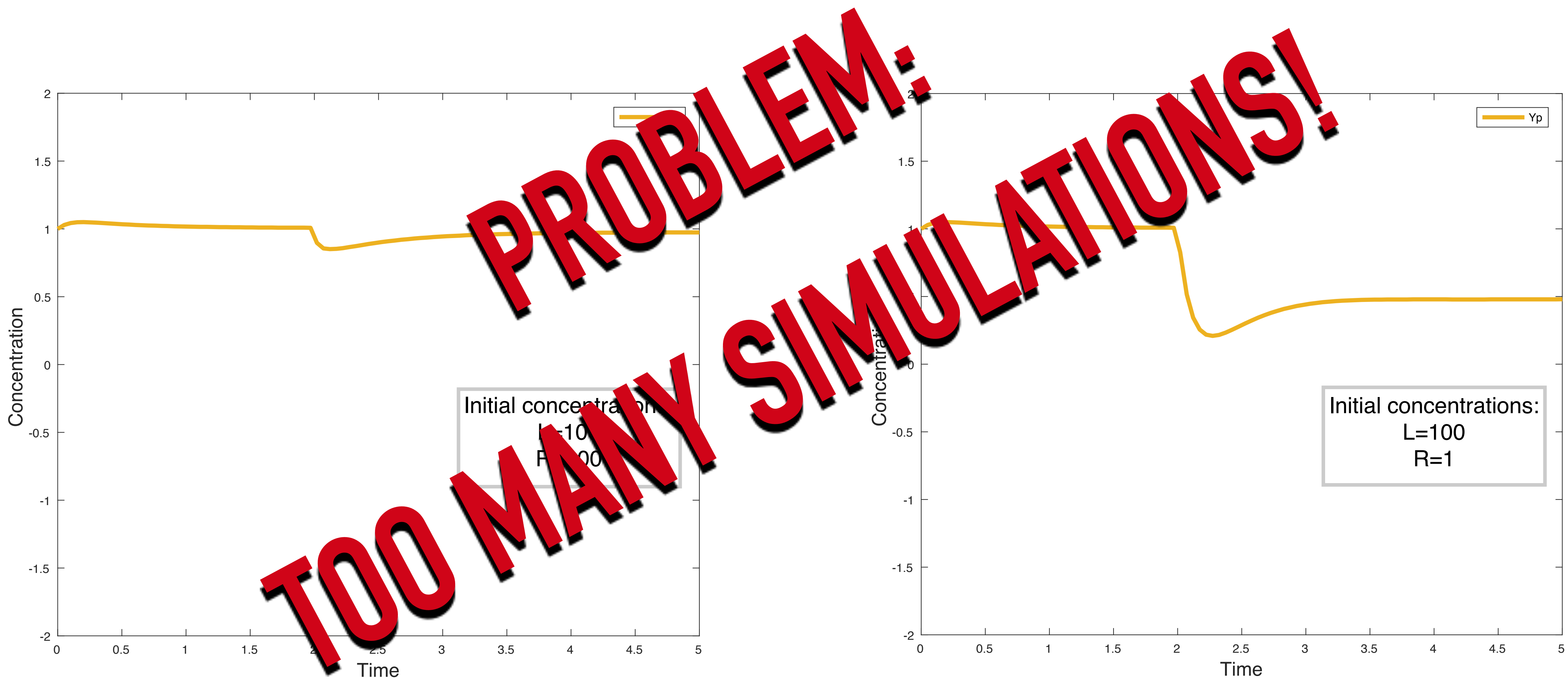
$$X \underset{k_2}{\overset{k_1}{\rightleftharpoons}} XS$$
$$XS + Y \xrightarrow{k_3} Yp + X$$
$$Yp + Z \xrightarrow{k_4} Y + Z$$
$$Yp \xrightarrow{k_5} Y$$
$$L + XS \xrightarrow{k_6} L + XY$$
$$BP \xrightarrow{k_7} B$$
$$XY \xrightarrow{k_8} XL$$
$$R + XL \xrightarrow{k_9} XSM + R$$
$$XSM + B \xrightarrow{k_{11}} Bp + XSM$$
$$XSM + Bp \xrightarrow{k_{12}} XS + Bp$$
$$XSM + Y \xrightarrow{k_{13}} Yp + X$$

- We build the Petri net:



CHEMOTAXIS OF E.COLI: SIMULATION RESULTS

We vary the **initial concentration of the inputs** ([R]) and we obtain these concentrations for the species [Yp]. Hence, we obtain α=0.5 and β=0.35.



HOW TO LIMIT THE COMPUTATIONAL EFFORT OF SIMULATIONS?

MONOTONICITY

MONOTONICITY IN CRN

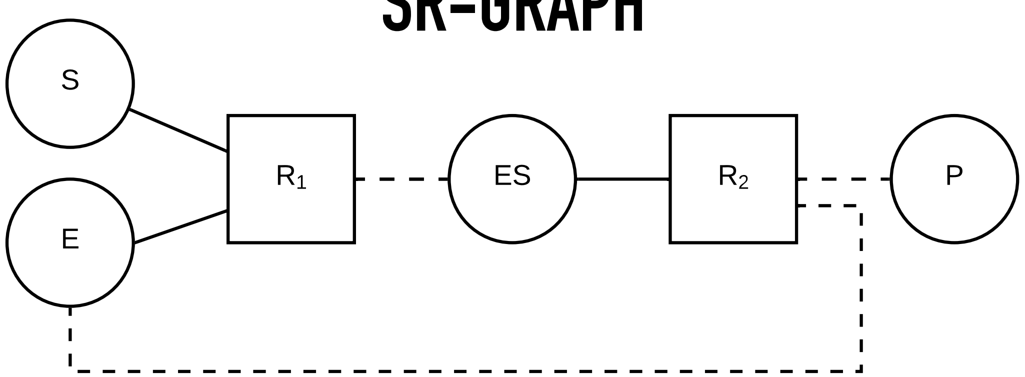
$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$$

➤ In [Angeli *et al.*, 2008]:

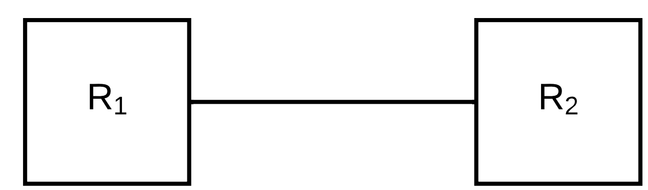
1. Very **strong notion of monotonicity**: each species have to increase or decrease continually
2. This notion of monotonicity work on **particular chemical reaction networks**
3. To provide graphical conditions to check **global monotonicity:**

The system is **orthant-monotone** if the associated R-graph is **sign consistent**, hence when any loop has an even number of negative edges.

SR-GRAPH



R-GRAPH



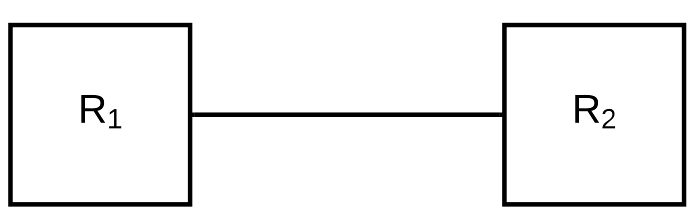
INPUT-OUTPUT MONOTONICITY

- **Positive Input-Output Monotonicity.** Given a set of reactions R, species O is positively monotonic w.r.t $I \in R$ iff, $\forall\ \bar{I} \geq I$, $\bar{O} \geq O$, for every time $t \in \mathbb{R}_{\geq 0}$.

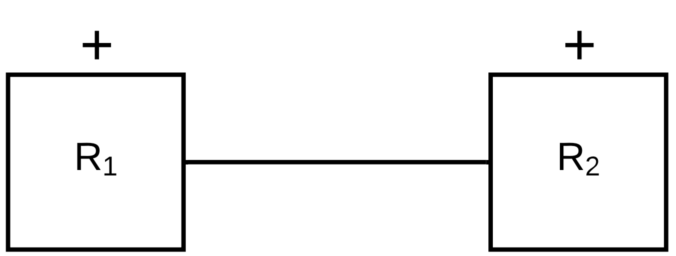
- **Negative Input-Output Monotonicity.** Given a set of reactions R, species O is negatively monotonic w.r.t $I \in R$ iff, $\forall\ \bar{I} \geq I$, $\bar{O} \leq O$, for every time $t \in \mathbb{R}_{\geq 0}$.

- A **consistent labelling of a signed graph** (V_R, E_+, E_-) is a labelling $s: V \rightarrow \{+,-\}$ in which vertices $R_i, R_j \in V_R$ have the same label if $R_i, R_j \in E_+$, and opposite labels if $R_i, R_j \in E_-$

R-GRAPH



LR-GRAPH



OUR RESULT: INPUT-OUTPUT MONOTONICITY THEOREM

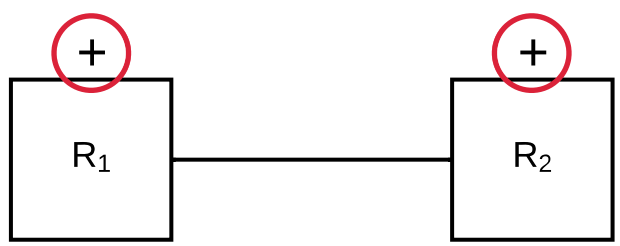
- **Theorem.** Let a set of chemical reactions G be given, with I and O as input and output species. If the following three conditions hold:

  1. the R-graph of G has the **positive loop property** and hence admits a **consistent labelling s;**
  2. The species I participates in **only one reaction** R_I;
  3. The species O participates in **only one reaction** $R_{O.}$

INPUT-OUTPUT MONOTONICITY: MICHAELIS MENTEN KINETICS

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$$

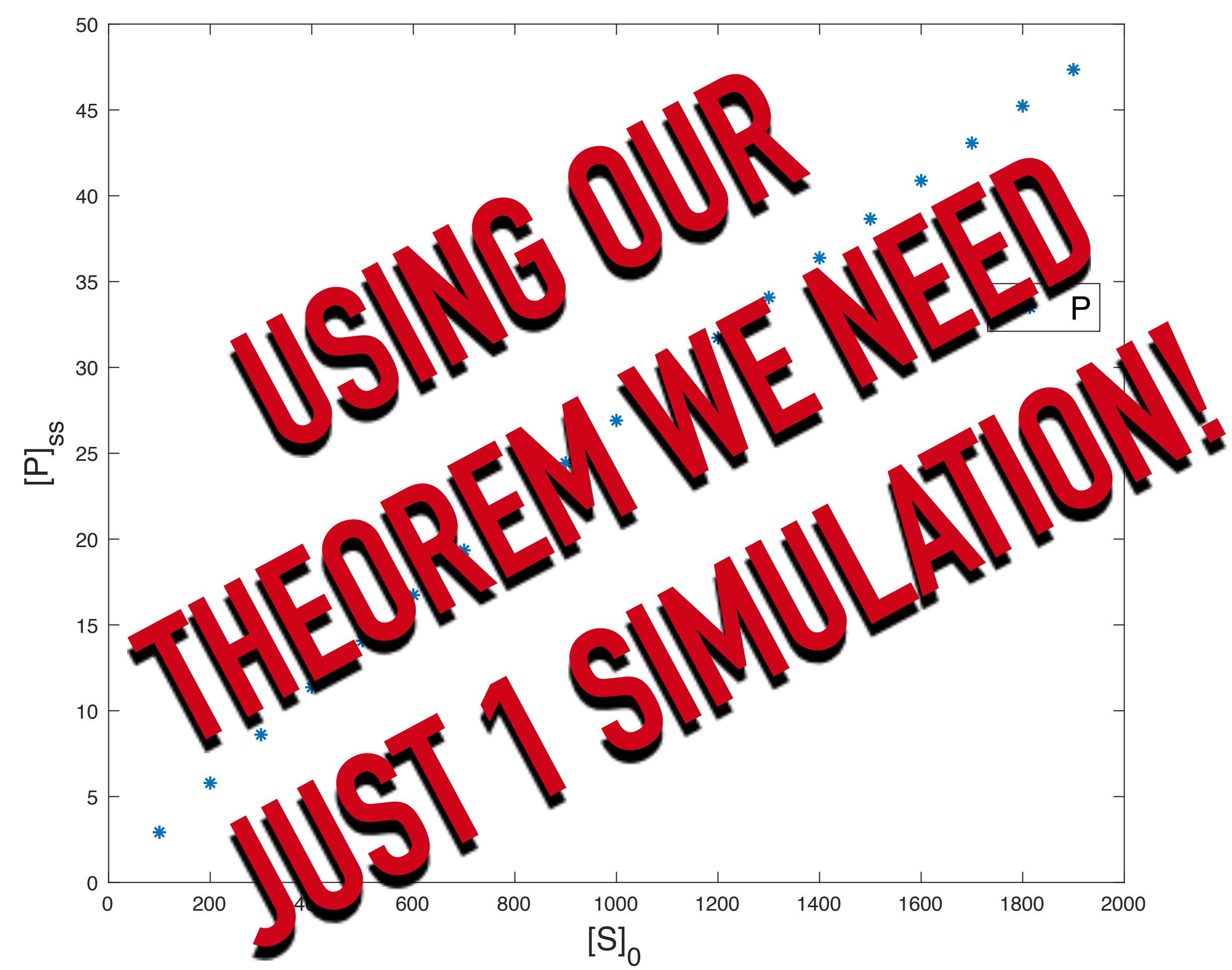
LR-GRAPH



STOICHIOMETRIC MATRIX

$$\Gamma = \begin{array}{c} \\ E \\ S \\ ES \\ P \end{array} \begin{array}{c} \begin{array}{cc} R_1 & R_2 \end{array} \\ \begin{pmatrix} -1 & +1 \\ -1 & 0 \\ +1 & -1 \\ 0 & +1 \end{pmatrix} \end{array}$$

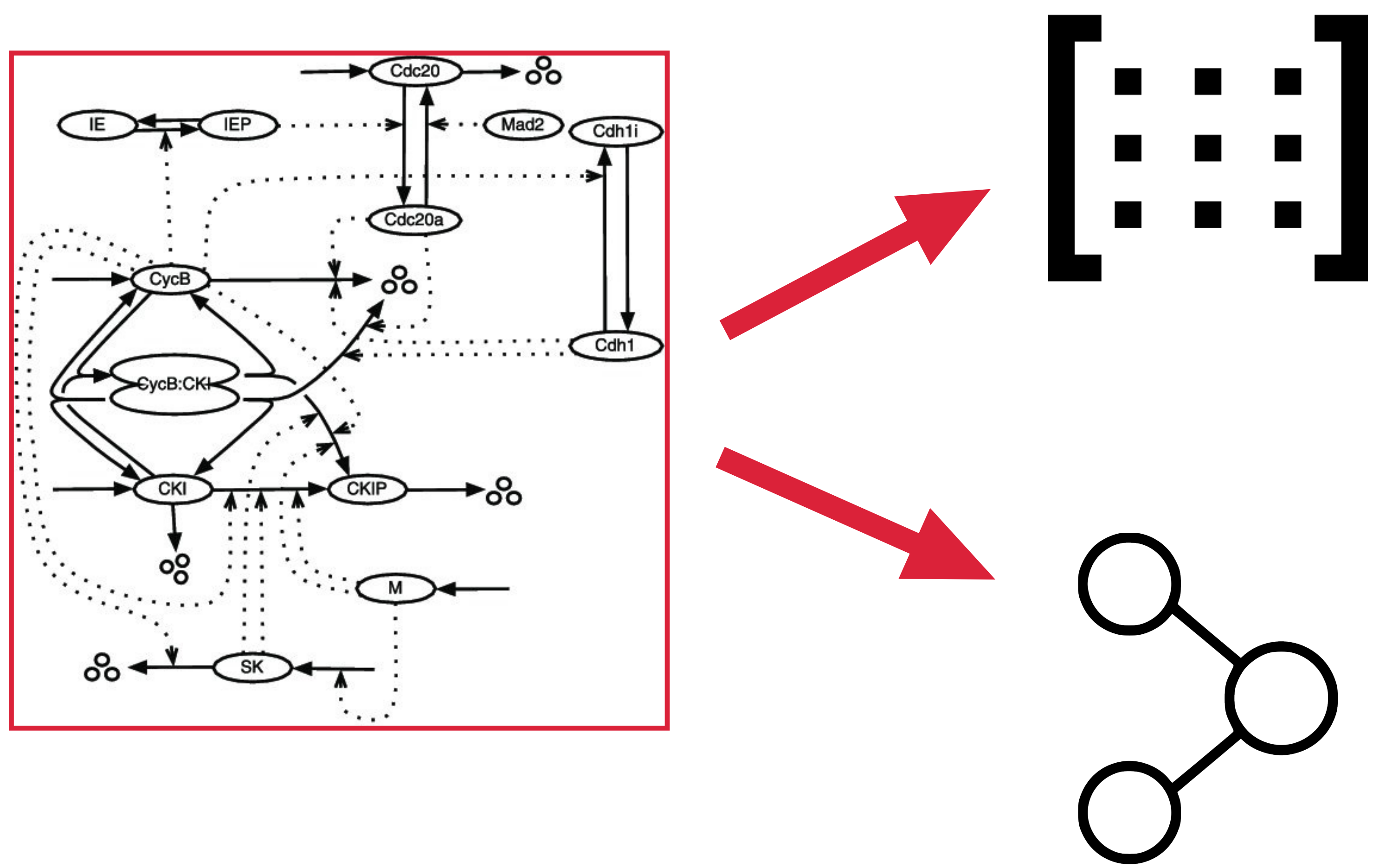
SIMULATION RESULT



➤ P is positively monotonic w.r.t S

INPUT-OUTPUT GRAPHTOOL

- Tool (in Python) to verify our sufficient conditions on big graphs



BECKER-DÖRING MODEL

- It is a model that describes **condensations phenomena** at different pressures
- The clusters give rise to two types of reactions:

$$C_1 + C_i \underset{b_{i+1}}{\overset{a_i}{\rightleftharpoons}} C_{i+1}$$

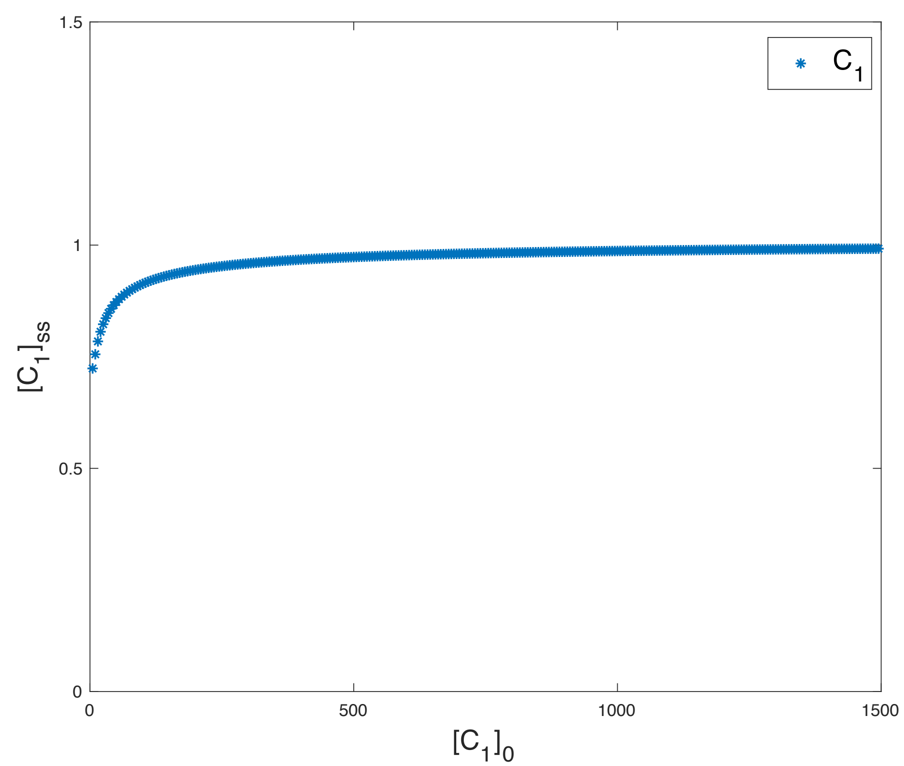
where:

- C_i denotes clusters consisting of i particles
- Coefficients a_i and b_{i+1} stand, respectively, for the rate of **aggregation** and **fragmentation**
- Rates may depend on the size of clusters involved in the reactions
- The mass is **constant** and it depends on the initial condition of the system

STEADY STATE ANALYSIS

- **Theorem 3.** Let a and b be the coefficient rates of coagulation and fragmentation process in the Becker-Döring system, ρ the mass of the system and $[C_1]_{ss}$ the concentration of monomers at the steady state. Then, as $\rho \to \infty$, $[C_1]_{ss} \to \frac{b}{a}$.

- With rates a=b, changing the initial concentration of C_1, the monomer concentration at the steady state tends to 1



RESULTS

- **Formal definition** of absolute and relative concentration robustness
- Analysis of the systems by **simulations**
- **Sufficient conditions** to study monotonicity between Input and Output species
- Implementation of **Input-Output GraphTool**
- Verification of Robustness of **Becker-Döring equations**

PROPOSED RESEARCH PROJECT

1. Stochasticity
2. Investigation of other topological features
3. Applicability to new specific problems
4. Interdisciplinary studies

PROPOSED RESEARCH PROJECT

Stochasticity

- Avoid approximations
- Perturbations don't affect the system uniformly

PROPOSED RESEARCH PROJECT

1. Investigation of other **topological features**
    - Persistence
    - Stability
    - Activity
    - Reversibility
    - …
2. To use ML methods to automatically infer topological properties

PROPOSED RESEARCH PROJECT

Applicability to **new specific problems**

- Different robustness notions (Modularity, Redundancy, System control…)
- Verification of robustness in different biological systems

PROPOSED RESEARCH PROJECT

Interdisciplinary studies:

- Comparing the model expectations with real experiments
- Apply theoretical background to new issues

QUESTIONS?

thank you!