TOWARDS AN EFFICIENT VERIFICATION METHOD FOR MONOTONICITY PROPERTIES OF CHEMICAL REACTION NETWORKS

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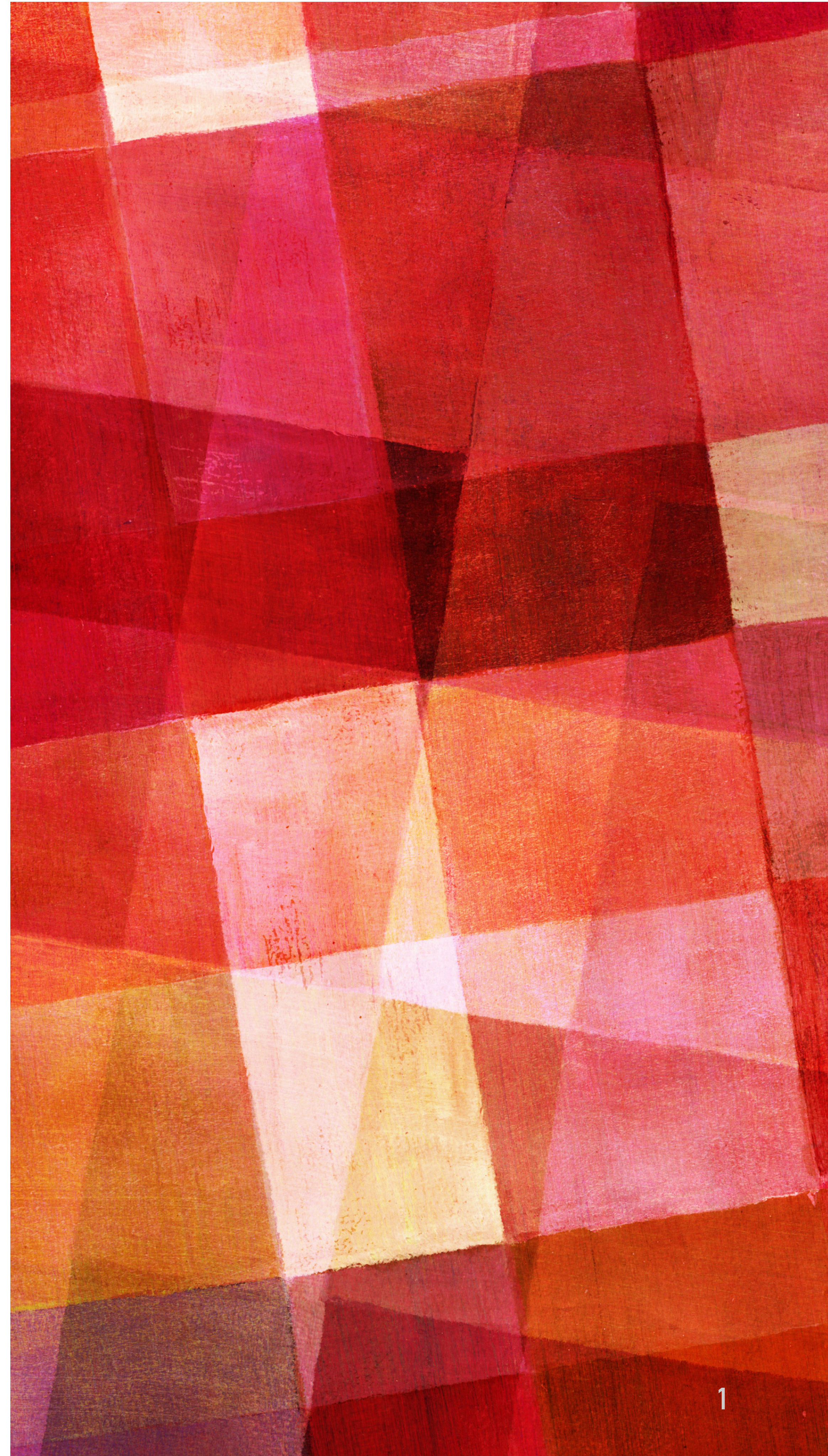
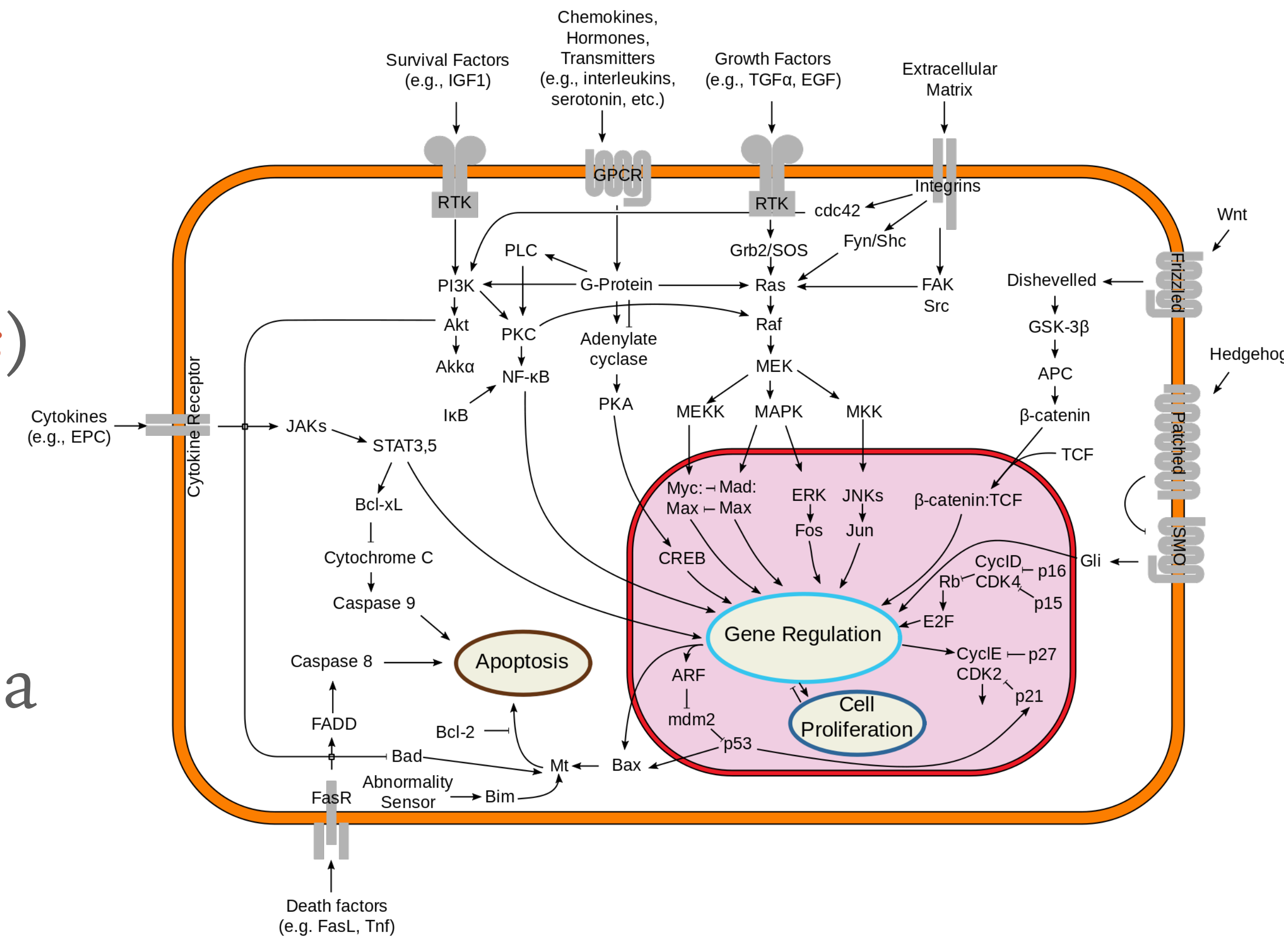


BACKGROUND

- 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**



Experiments *in vitro* ⟷ Experiments *in silico*

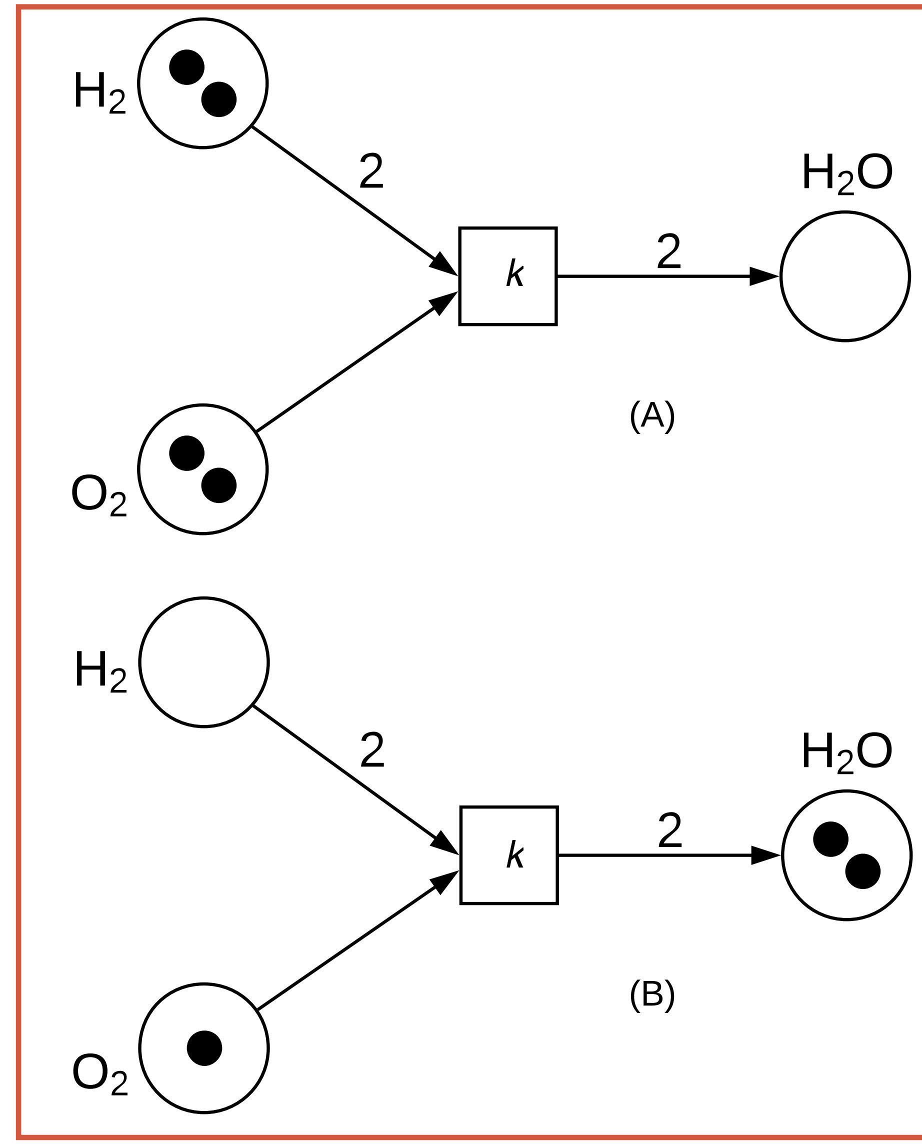
CHEMICAL REACTIONS

Stoichiometric coefficient

$$aA + bB \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} cC + dD$$

Reactants | Rate | Products

- **Kinetic rate:** rate of a reaction
- **Reactant:** chemical species that is consumed
- **Product:** chemical species that is created
- **Stoichiometric coefficient:** the number of species involved in the reaction
- **Concentrations:** [A], [B], [C], [D]



$$2\,H_2 + O_2 \xrightarrow{k} 2\,H_2O$$

CHEMICAL KINETICS

$$aA + bB \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} cC + dD$$

- **Law of mass action:** reaction rate is proportional to the reactants product

$$r \propto [reactants] \longrightarrow r = k_1[A]^a[B]^b$$

$$r_{direct} = r_{inverse}$$

$$\frac{d[A]}{dt} = \overbrace{-ak_1[A]^a[B]^b}^{\text{direct reaction term}} \overbrace{+ak_{-1}[C]^c[D]^d}^{\text{inverse reaction term}}$$

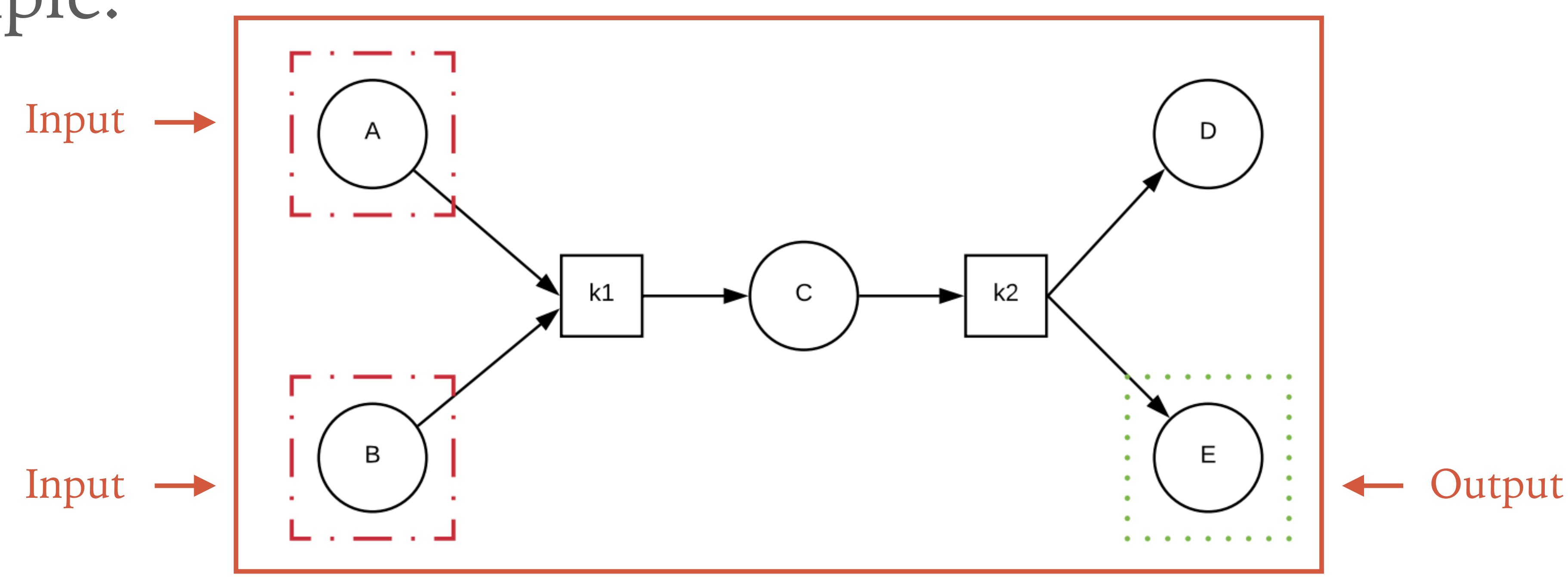
$$\frac{d[B]}{dt} = -bk_1[A]^a[B]^b + bk_{-1}[C]^c[D]^d$$

$$\frac{d[C]}{dt} = +ck_1[A]^a[B]^b - ck_{-1}[C]^c[D]^d$$

$$\frac{d[D]}{dt} = +dk_1[A]^a[B]^b - dk_{-1}[C]^c[D]^d$$

OUR GOAL

- Our goal: to study **dynamical behaviour** of biological system:
- **Robustness** allows the system to preserve its functions despite internal and external perturbations
- How: experiments by **simulations**
- Example:



$$A + B \xrightarrow{k_1} C \xrightarrow{k_2} D + E$$

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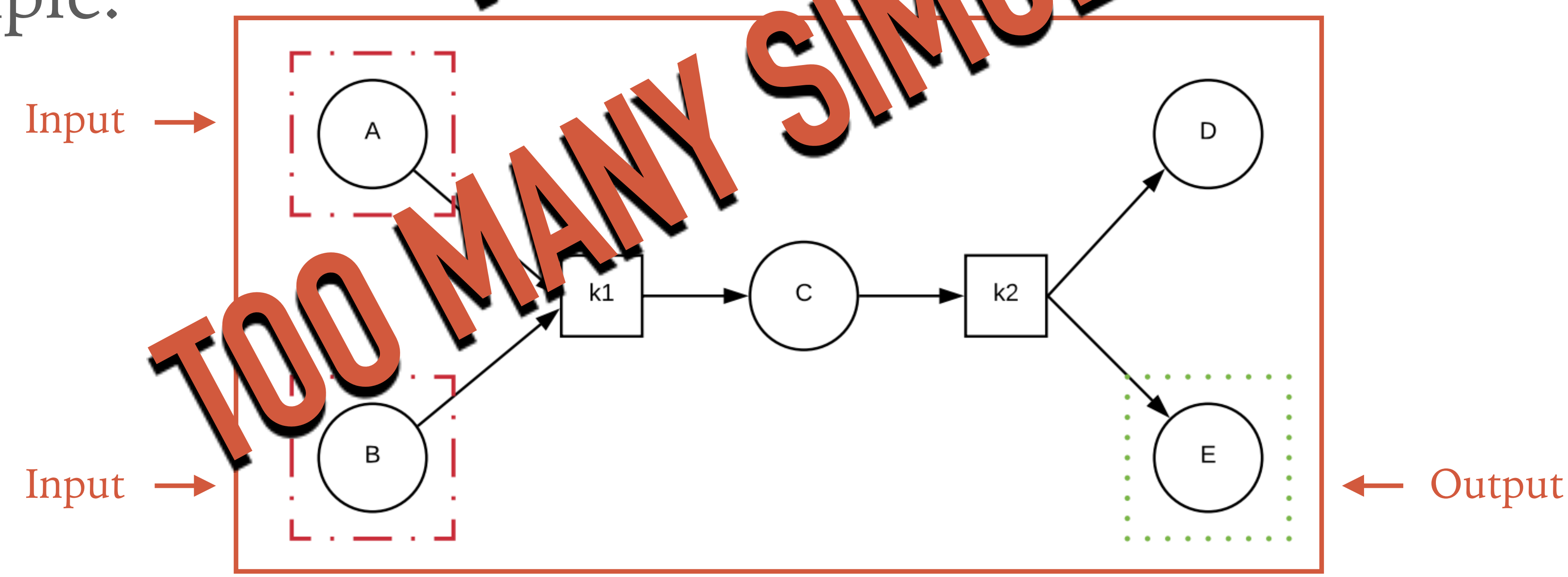
PROBLEM: TOO MANY SIMULATIONS!



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HOW TO LIMIT THE COMPUTATIONAL EFFORT OF SIMULATIONS?

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MONOTONICITY

MONOTONICITY OF CHEMICAL REACTION NETWORKS IN LITERATURE

➤ 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.

DEFINITION OF MONOTONICITY BETWEEN INPUT AND OUTPUT SPECIES

Definition 1 (Reaction). *Given a set of species* S*, a reaction is a tuple (u,v,k) denoted* $u \xrightarrow{k} v$*, where* $u, v \in S^*$ *and* $k \in \mathbb{R}^+$.

Definition 2 (Positive Monotonicity). *We say that* S_O *in* R *is* positively monotonic *with respect to* S_I *if and only if:*

$$S_I^0 < S_I'^0 \Longrightarrow F_{S_O}(t, S_1^0, ..., S_I^0, ...S_n^0) \leq F_{S_O}(t, S_1^0, ..., S_I'^0, ...S_n^0)$$

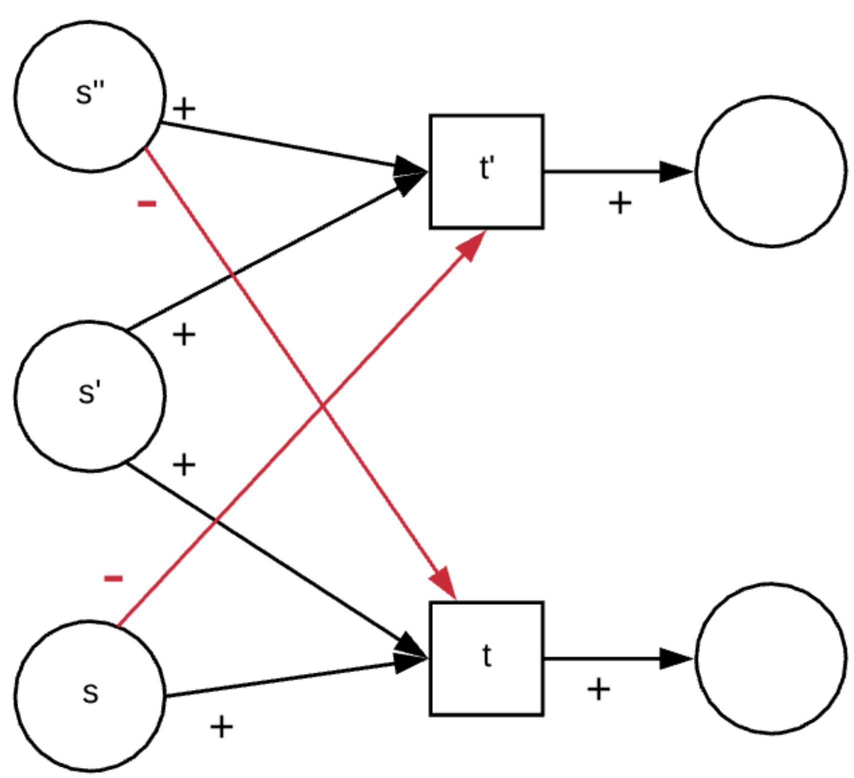
Definition 3 (Negative Monotonicity). *We say that* S_O *in* R *is* negatively monotonic *with respect to* S_I *if and only if:*

$$S_I^0 < S_I'^0 \Longrightarrow F_{S_O}(t, S_1^0, ..., S_I^0, ...S_n^0) \geq F_{S_O}(t, S_1^0, ..., S_I'^0, ...S_n^0)$$

DEPENDENCY GRAPH

Definition 4 (Dependency graph). *Given a finite set of reactions R over a set of species S, the dependency graph G of R is the tuple $< S, R, E_+, E_- >$, where $E_+ \subseteq (S \times R) \cup (R \times S)$ and $E_- \subseteq (S \times R)$, are such that given $s \in S$, $u \xrightarrow{k} v \in R$:*

- $(s, u \xrightarrow{k} v) \in E_+ \iff s \in u$
- $(u \xrightarrow{k} v, s) \in E_+ \iff s \in v \wedge |v|a > |u|a$
- $(s, u \xrightarrow{k} v) \in E_- \iff s \notin u \wedge \exists\ u' \xrightarrow{k'} v' \in R\ (u \cap u' \neq \emptyset \wedge s \in u')$

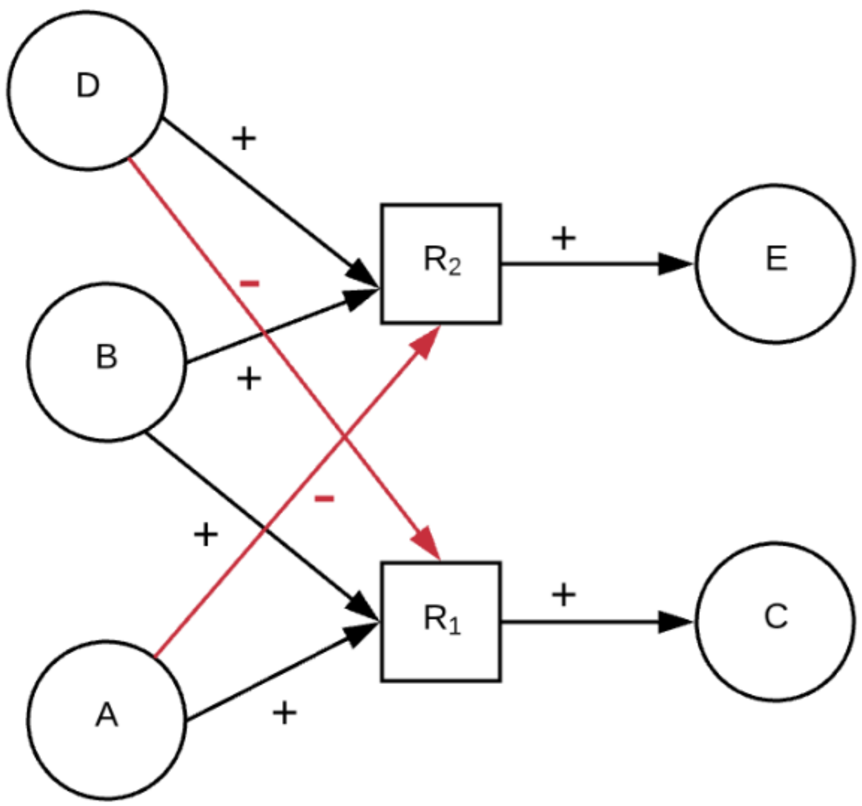


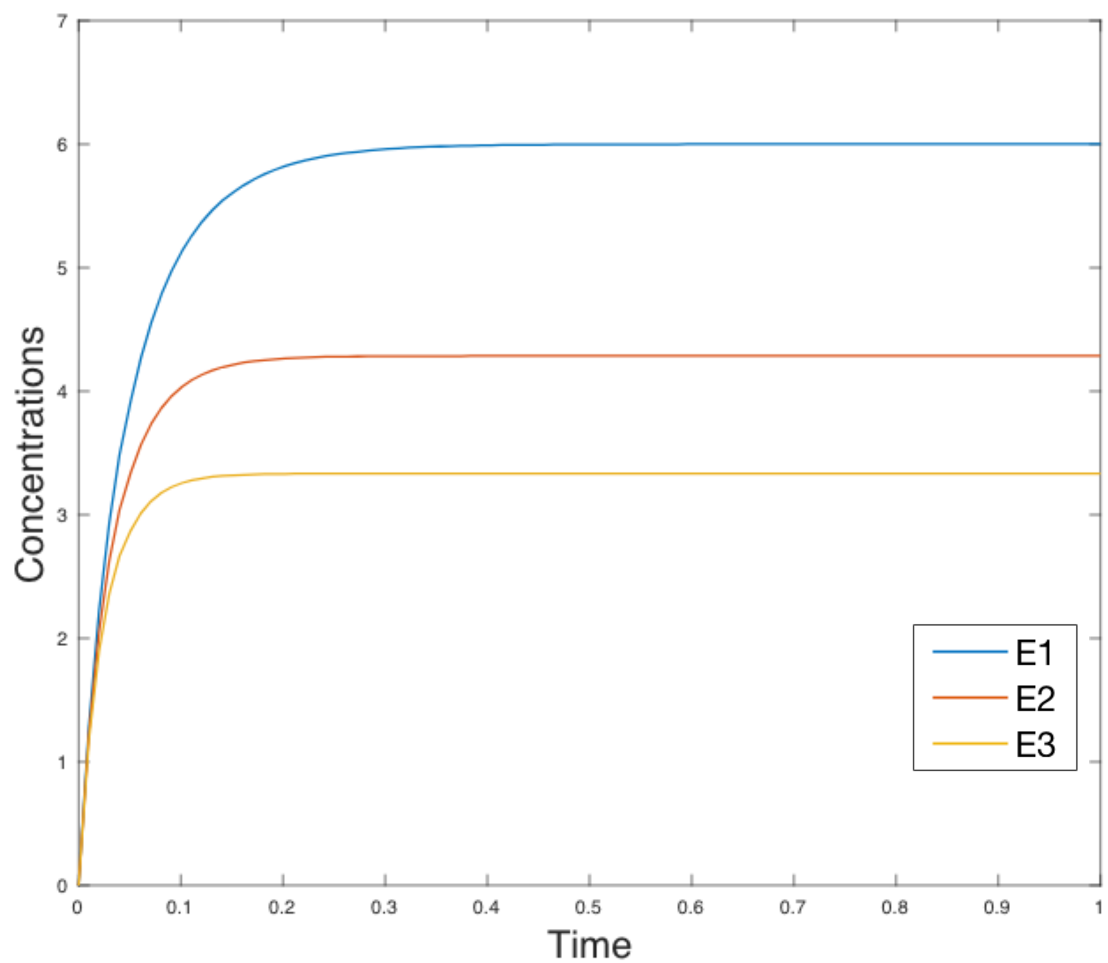
MONOTONE EXAMPLE

$$A + B \xrightarrow{k_1} C$$

$$B + D \xrightarrow{k_2} E$$

- E1 with A(0)=20
- E2 with A(0)=25
- E3 with A(0)=1000



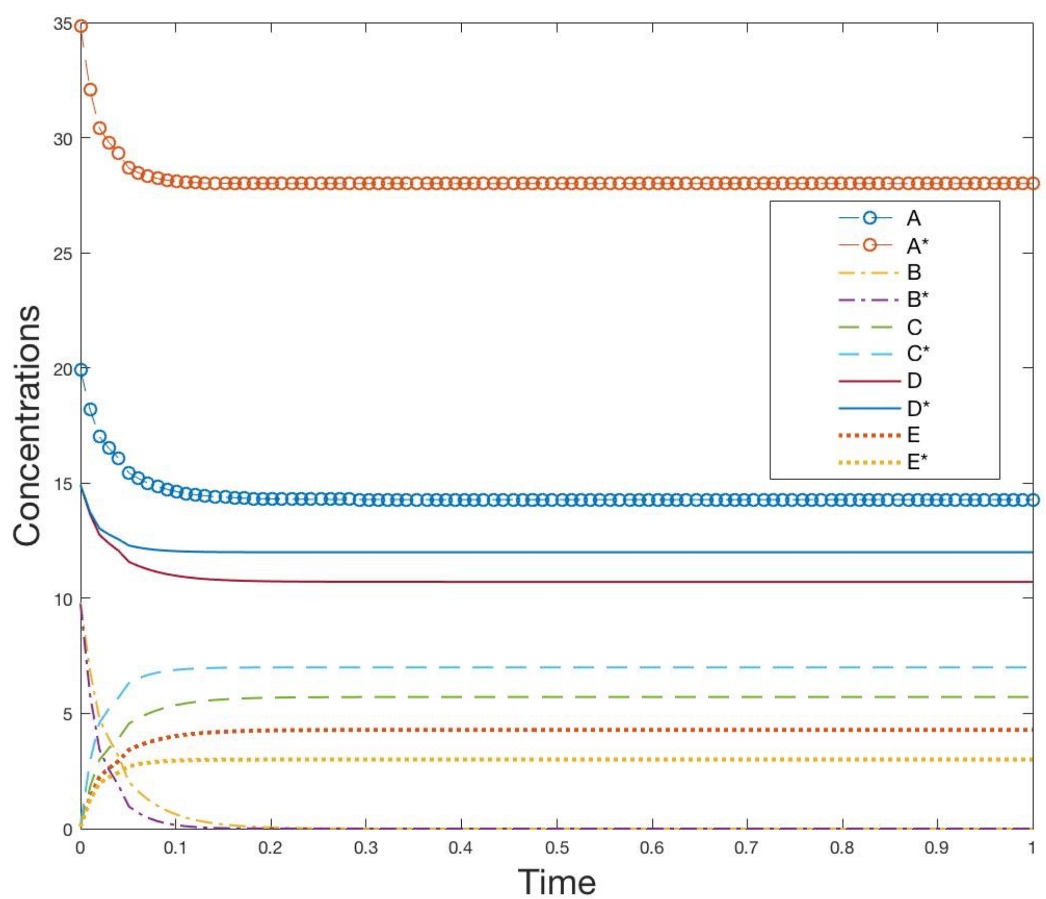


MONOTONE EXAMPLE: EXPERIMENTALLY PROVED

$$\boxed{A} + B \xrightarrow{k_1} C$$

$$B + D \xrightarrow{k_2} \boxed{E}$$

- Given the concentrations A_i, B_i, C_i, D_i, E_i, at the *i-th* temporal step, and A'_i, B'_i, C'_i, D'_i, E'_i, with $A_0 < A'_0$, we prove that $A_i < A'_i$, $B_i > B'_i$, $C_i < C'_i$, $D_i < D'_i$, $E_i > E'_i$ $\forall$ *i*.



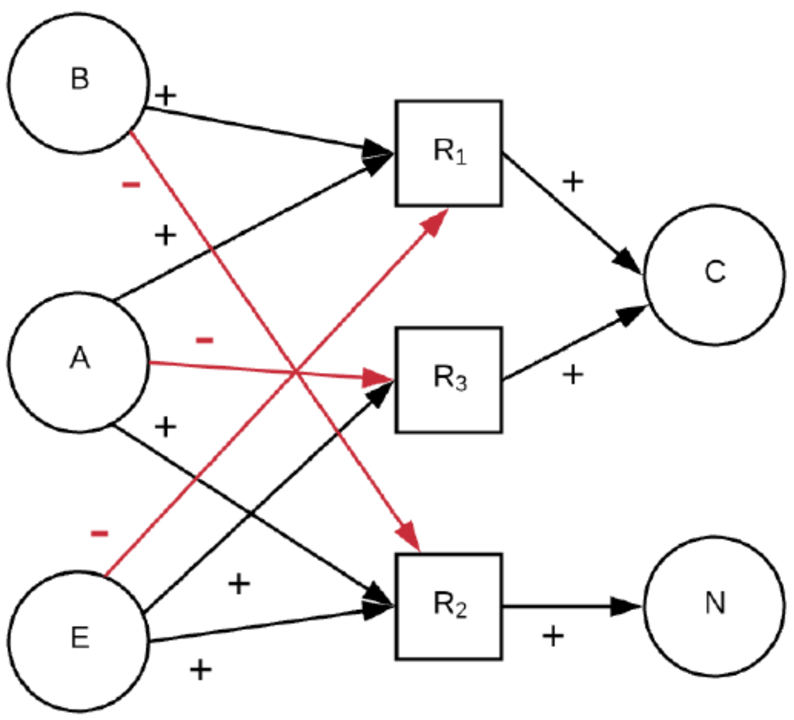
EXAMPLE OF NON-MONOTONICITY

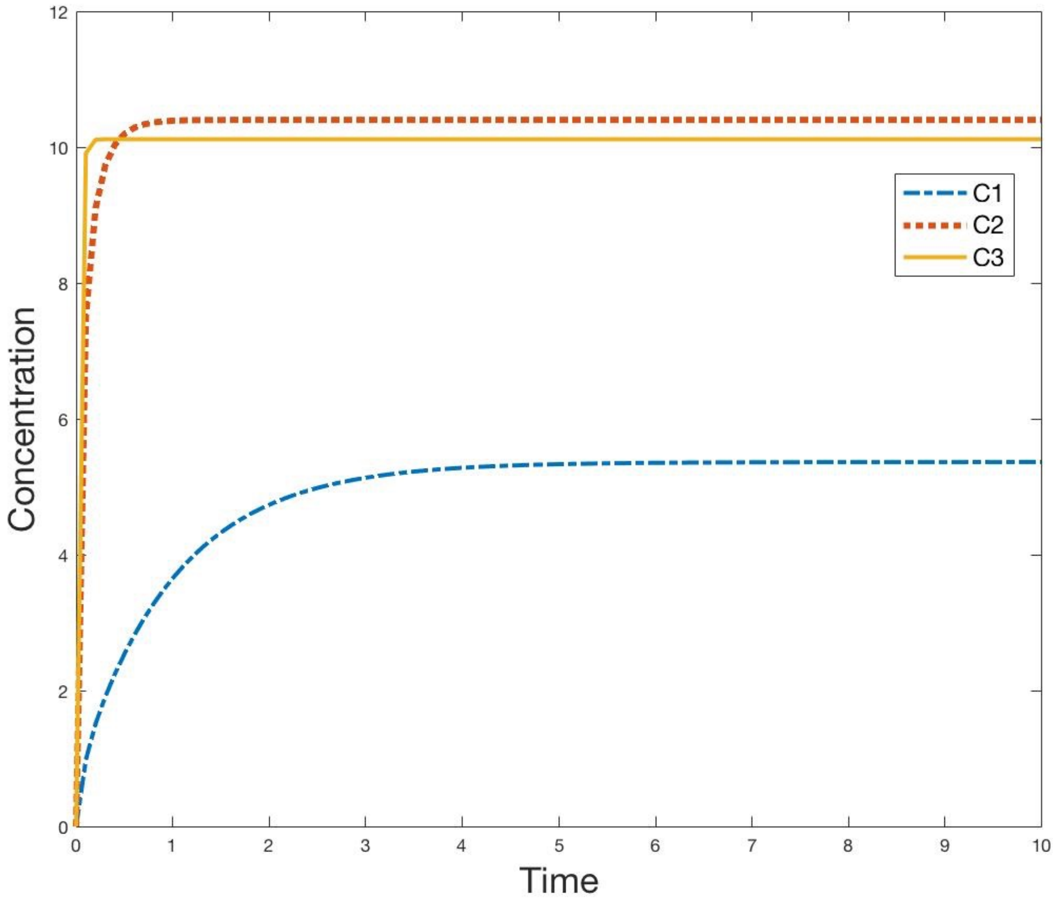
$$\boxed{A} + B \xrightarrow{k_1} C \quad (R_i)$$

$$A + E \xrightarrow{k_2} N$$

$$E \xrightarrow{k_3} \boxed{C} \quad (R_j)$$

- C1 with A(0)=1
- C2 with A(0)=20
- C3 with A(0)=50





- Proved by simulations
- The input A produces C and - at the same time - consumes E (which produces C)

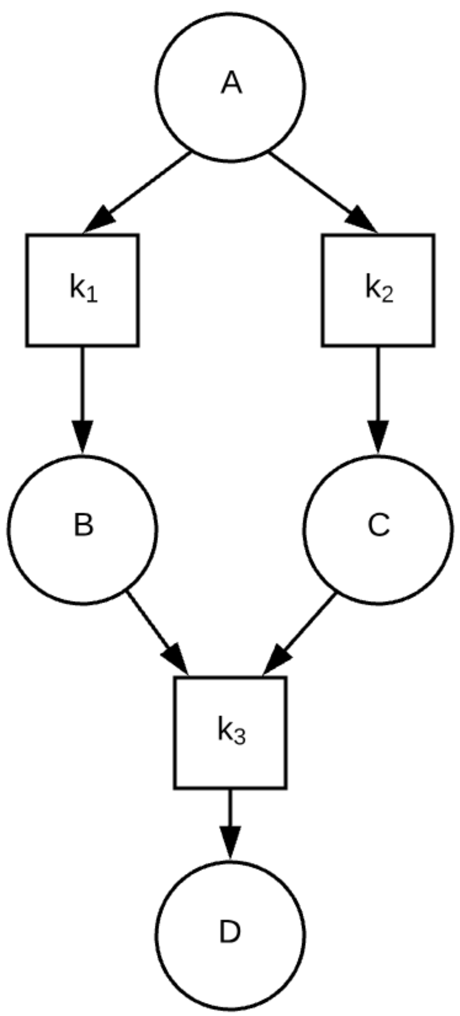
PROBLEM: COUNTEREXAMPLE

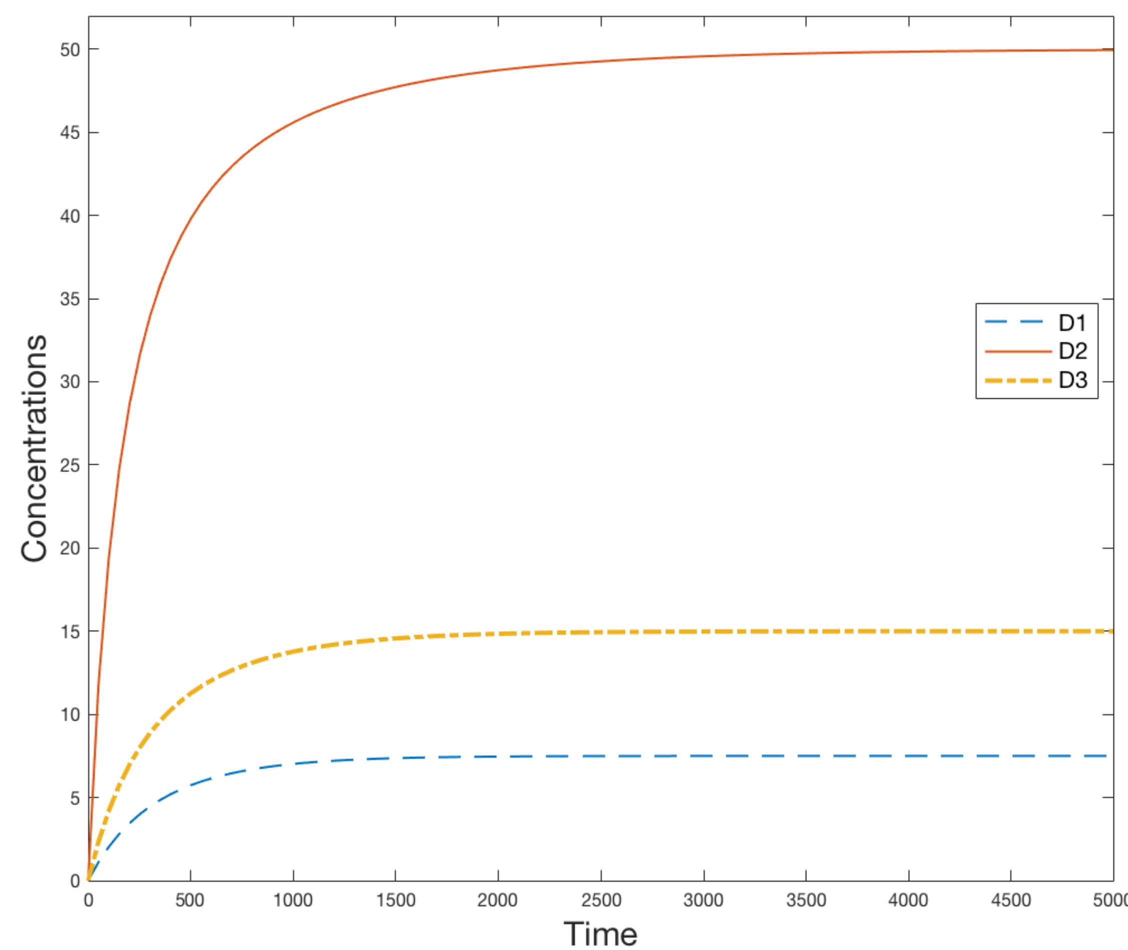
$$\boxed{A} \xrightarrow{k_1} B$$

$$A \xrightarrow{k_2} C$$

$$B + C \xrightarrow{k_3} \boxed{D}$$

- D1 with A(0)=10
- D2 with A(0)=20
- D3 with A(0)=80



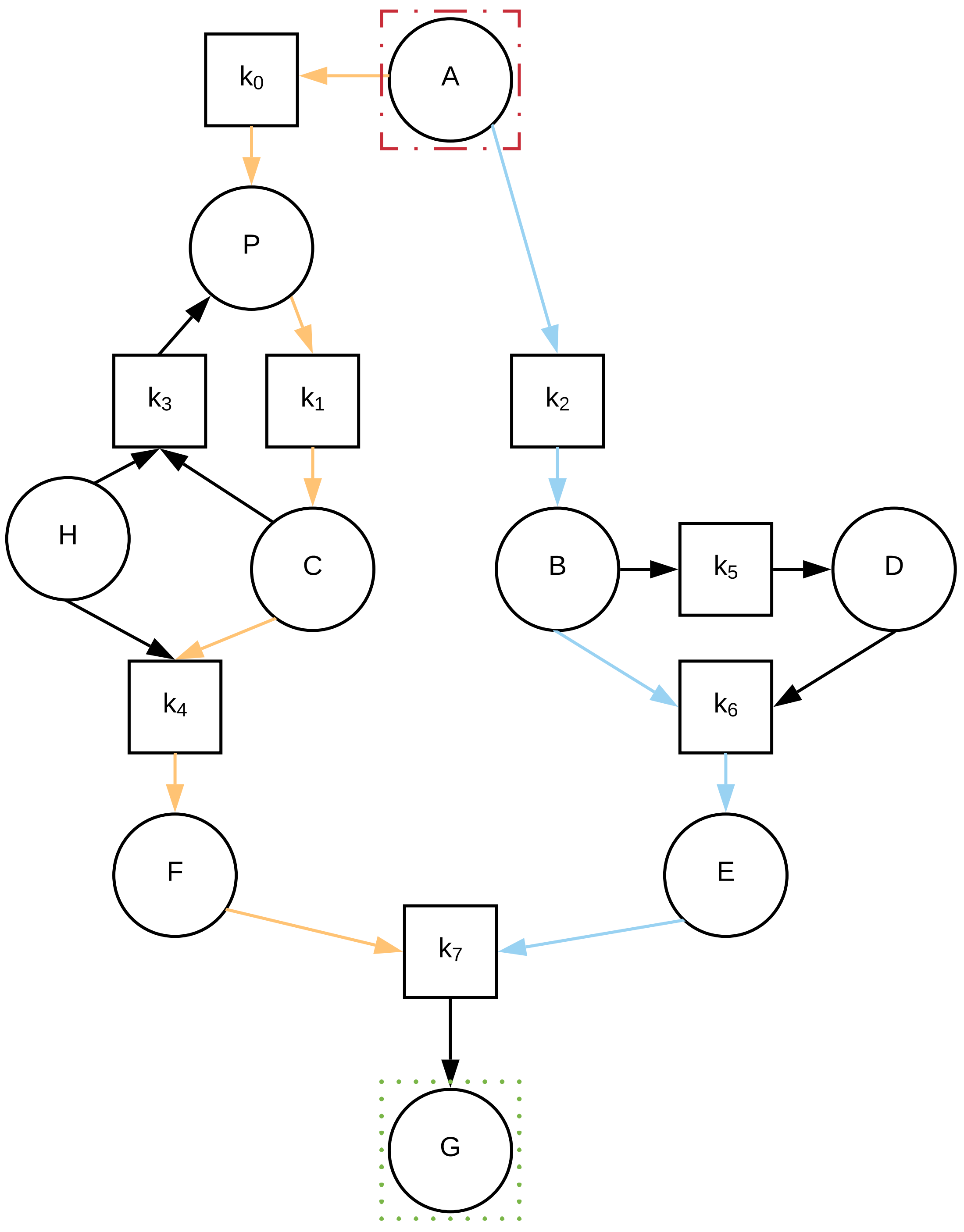


STEP FORWARD

- Restriction on the type of graphs:

Given an input and an output, there must not be two different paths, between the input and the output, with a reaction in common, whose having two reactants influenced by the input.

- The graph becomes more complex



COMPARATIVE EXAMPLE

- Given this chemical reaction network:

$$A \xrightarrow{k_0} P$$

$$P \xrightarrow{k_1} C$$

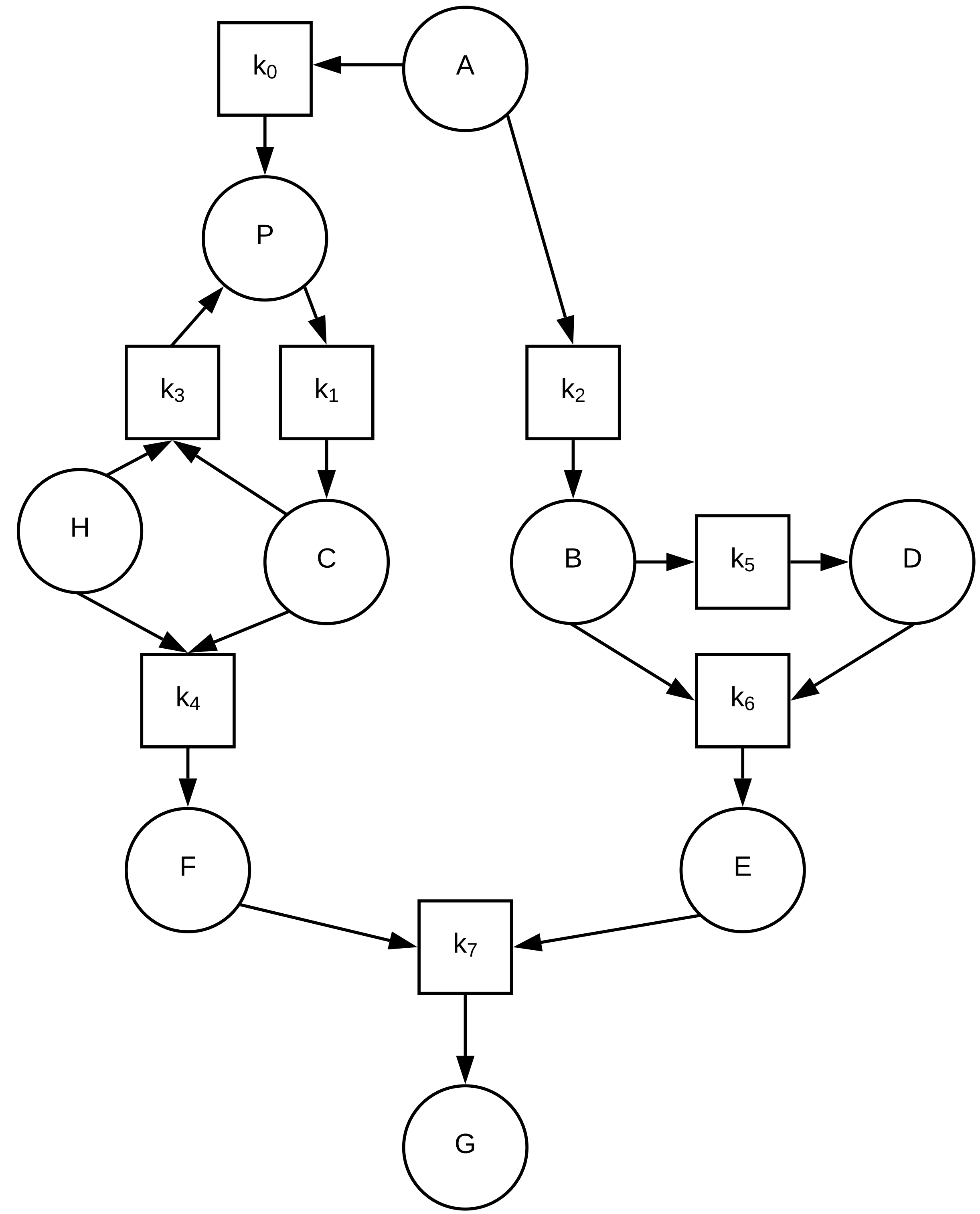
$$A \xrightarrow{k_2} B$$

$$H + C \xrightarrow{k_3} P$$

$$H + C \xrightarrow{k_4} F$$

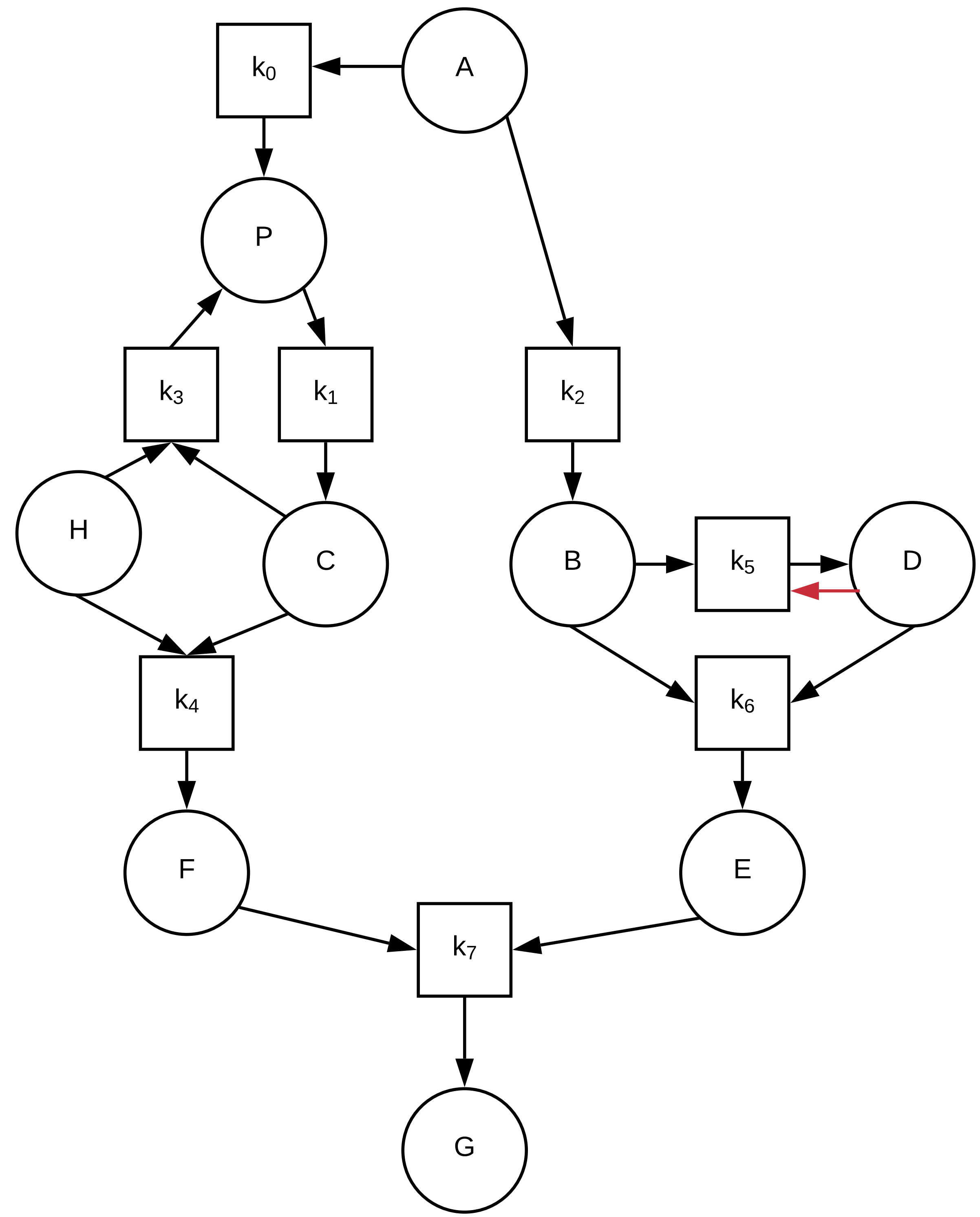
$$B \xrightarrow{k_5} D$$

$$E + F \xrightarrow{k_7} G$$



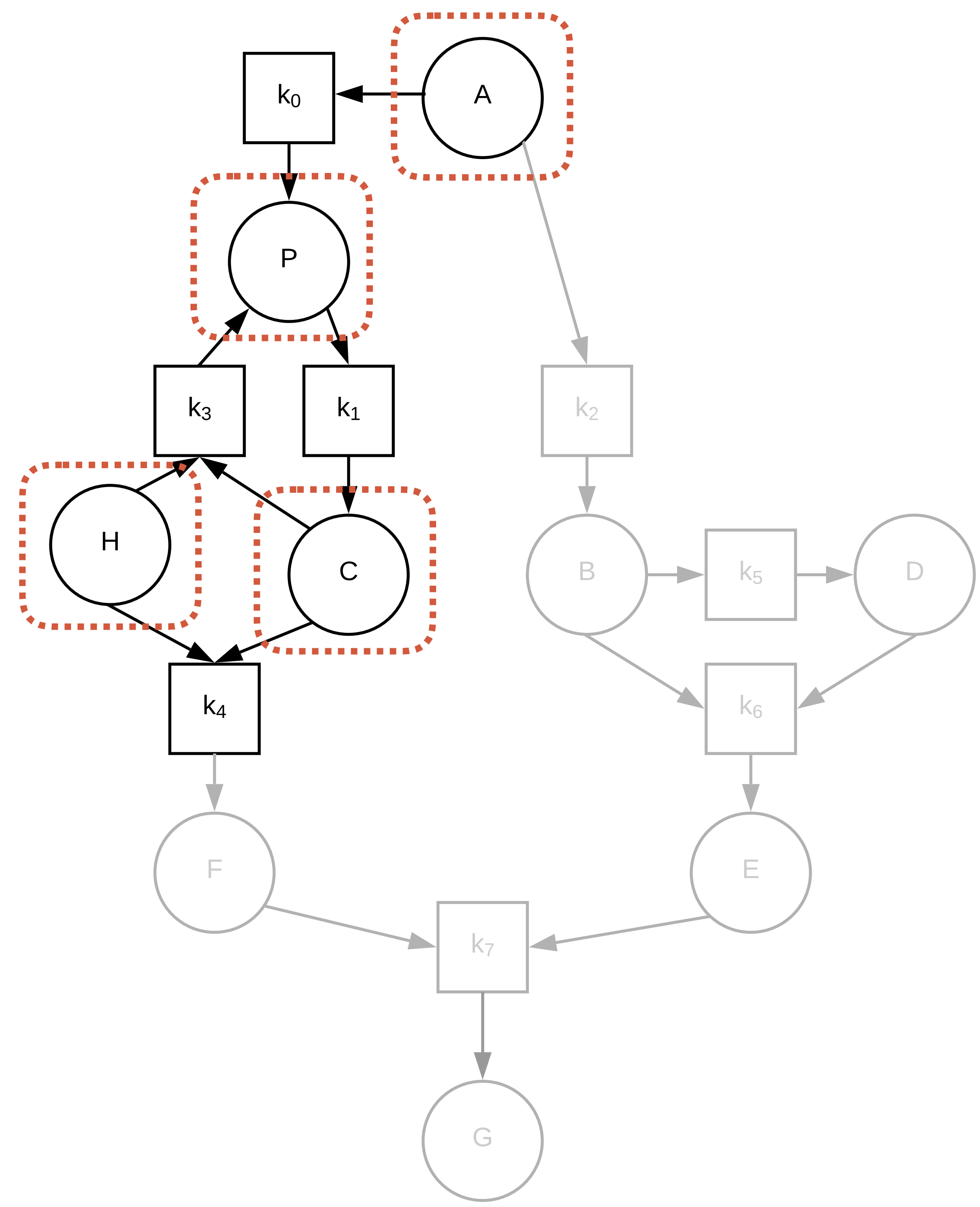
COMPARATIVE EXAMPLE: D. ANGELI APPROACH

- According to D. Angeli: this network is **not sign consistent**, because there are not an even number of negative edges.



COMPARATIVE EXAMPLE: OUR APPROACH

- Following the restriction on the graph, we cannot study all the paths
- We can study if there are monotonicity relations among A, C, P and H
- With the DependencyGraph we can say: P and C are monotone w.r.t to A
- With a new method (future work!) we can say more also on H



FUTURE WORK

- To improve the algorithm
- Extension of the method to investigate other relations between the species
- To validate our method on the Dataset BioModels

QUESTIONS?

thank you!