

Systems Biology: Dynamical features of metabolic networks

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Systems Biology

Focus on interactions between entities

Goal: Understand dynamic and emergent properties of complex biological systems

Applications:

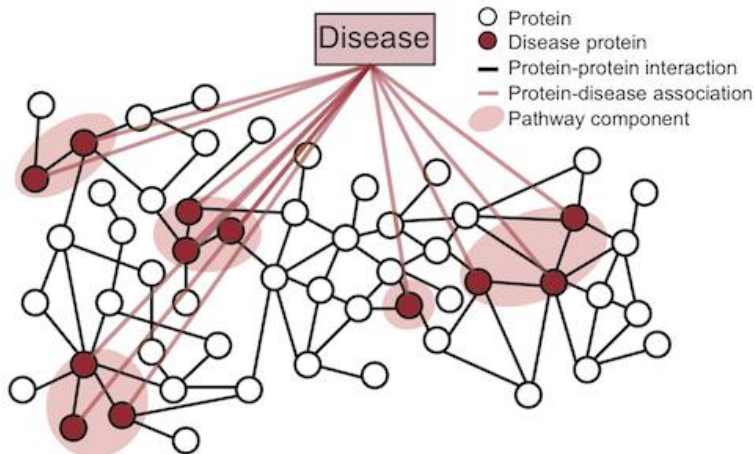
- Drug discovery and analysis
- Synthetic Biology
- Predictive understanding

Systems Biology

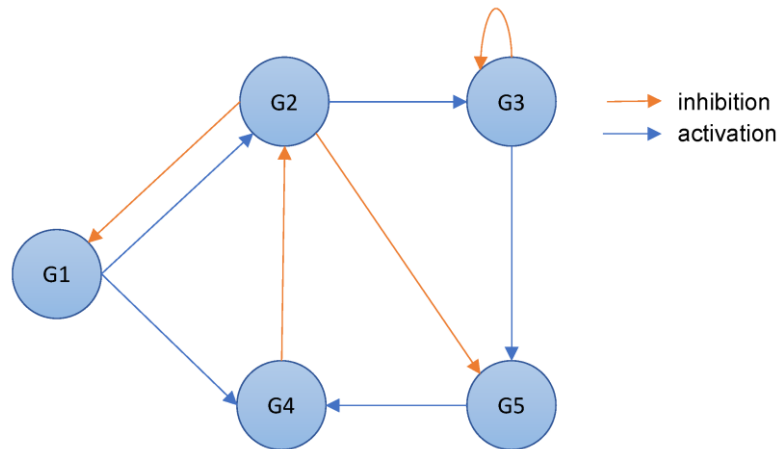
Focus on interactions between entities

Vast use of networks

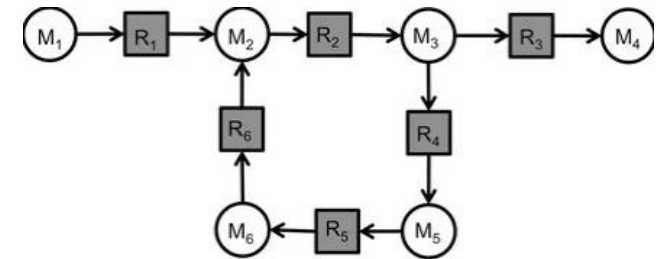
PPI networks



GRnetworks



Metabolic pathways





Metabolism

Reactions in the cell that maintain organism functioning

Entities: Metabolites

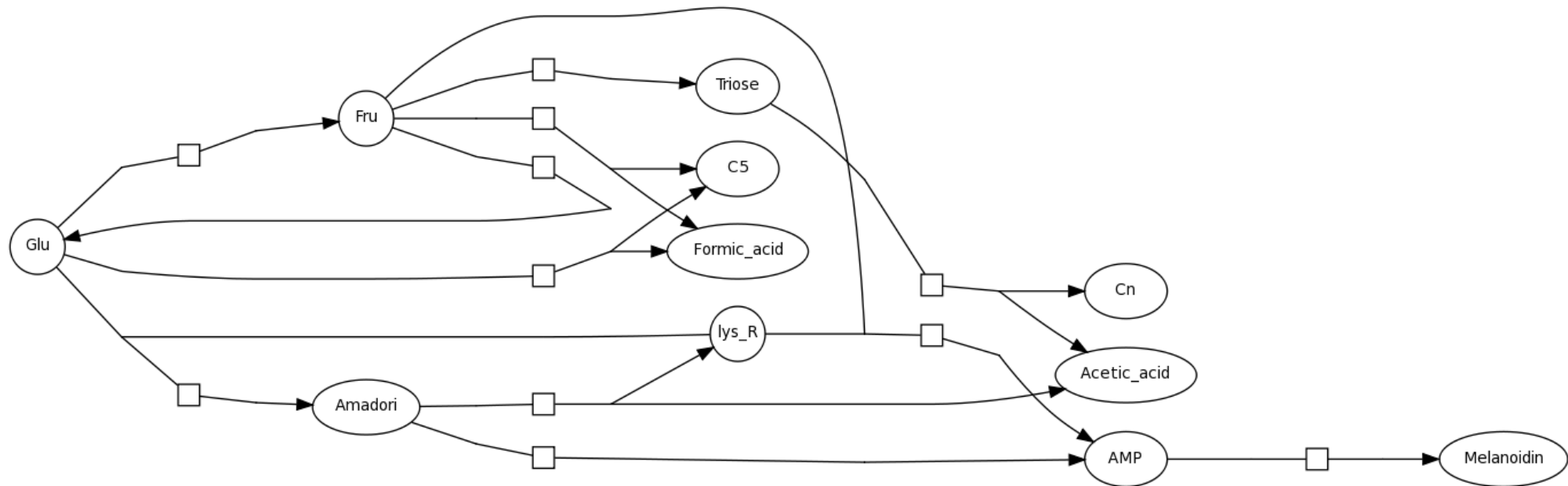
Interactions: Chemical reactions

Organized in pathways

Circuits associated to specific functions

Pathways as networks

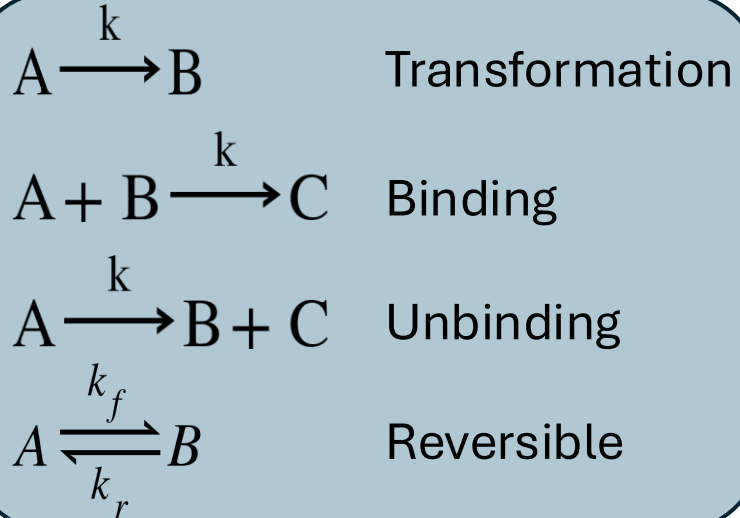
Bipartite graph representation





Pathways as Chemical Reaction Networks

Types of reactions



Parameters

- $[A]$, $[B]$, $[C]$: concentrations of metabolites
- k : kinetic constant of the reactions

Determine reactions rate

$$rate(j) = \prod_{R \in Reactants(j)} [R] k$$

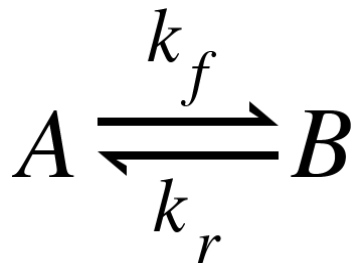
Basic terminology

Species: reactants and products

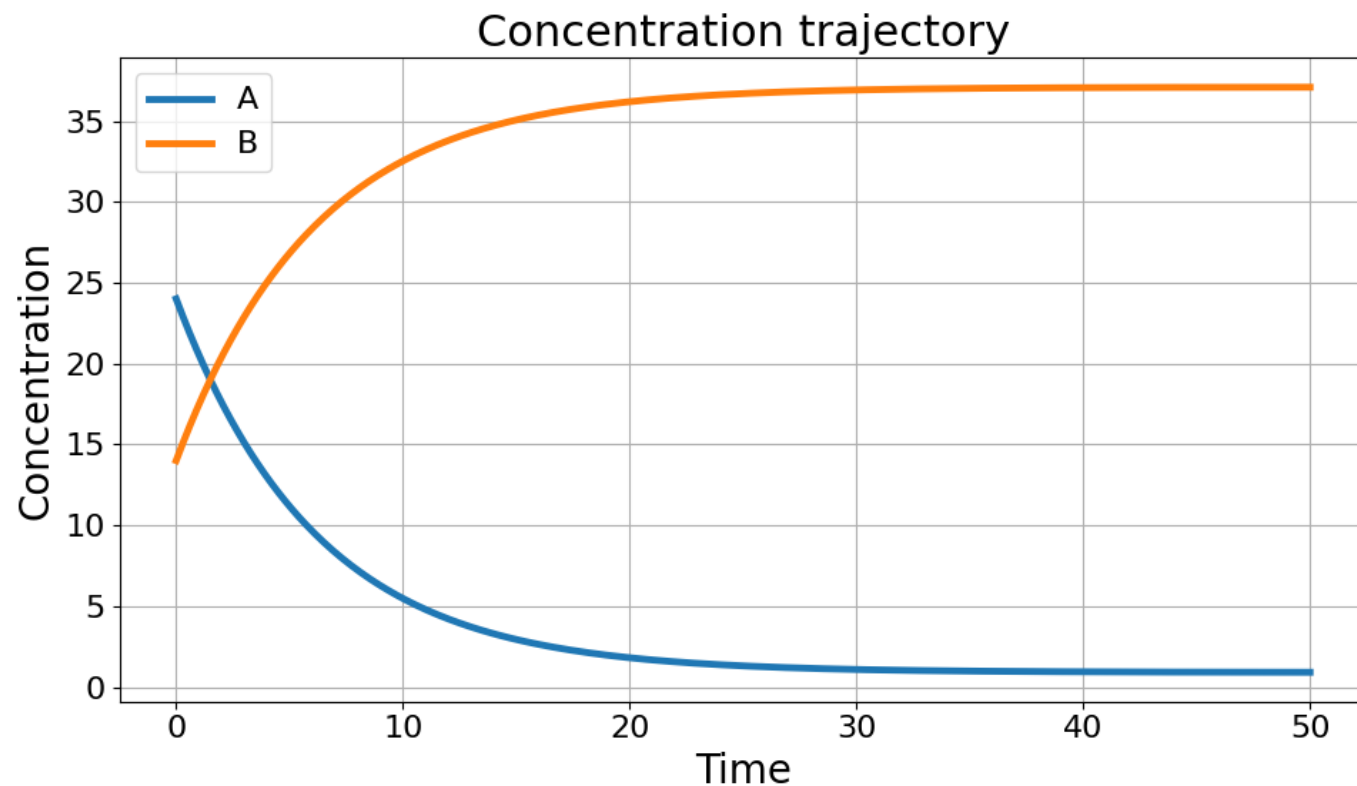
Dynamic equilibrium: Forward and reverse processes have the same rate



Pathways as dynamical system



$$\begin{cases} \frac{d[A]}{dt} = -k_f [A] + k_r [B] \\ \frac{d[B]}{dt} = -k_r [B] + k_f [A] \end{cases}$$





Dynamical properties

Stability: Small changes in parameters leave the reached steady state unchanged

Robustness: Ability of a system to maintain its function under wide variety of perturbations (functional resilience)

Applications

- Identify critical metabolites/reactions
- Predict drugs/mutation resistance



Perturbation analysis

How changes in parameters affect system behavior

Typical perturbations: Changes in kinetic constants,
enzyme concentrations

Why do they happen?

Biological variability

Mutation-induced changes

Experimental interventions

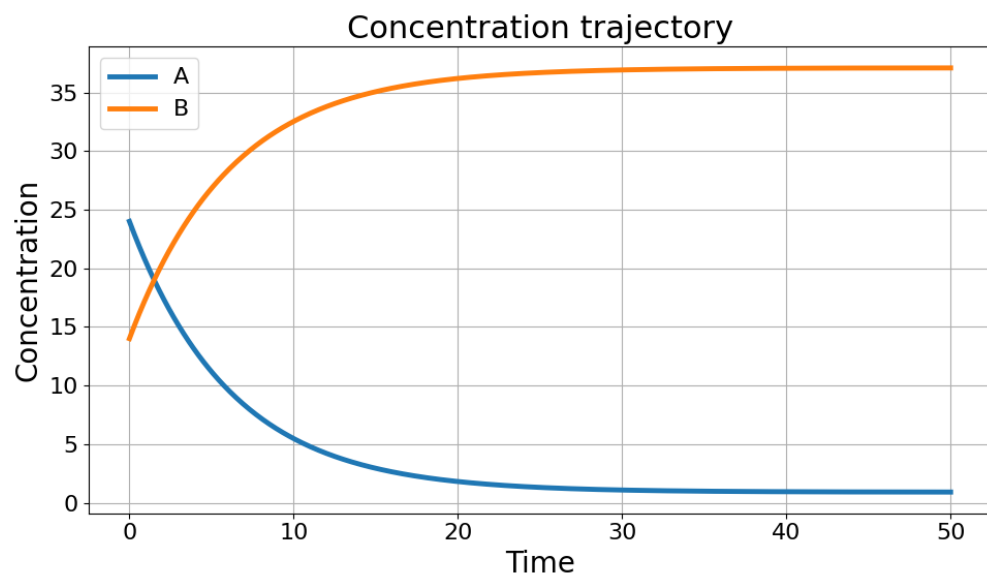
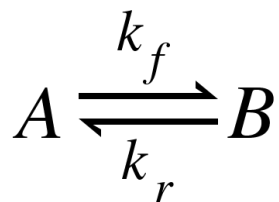
Gene knockout,
Drug inhibition



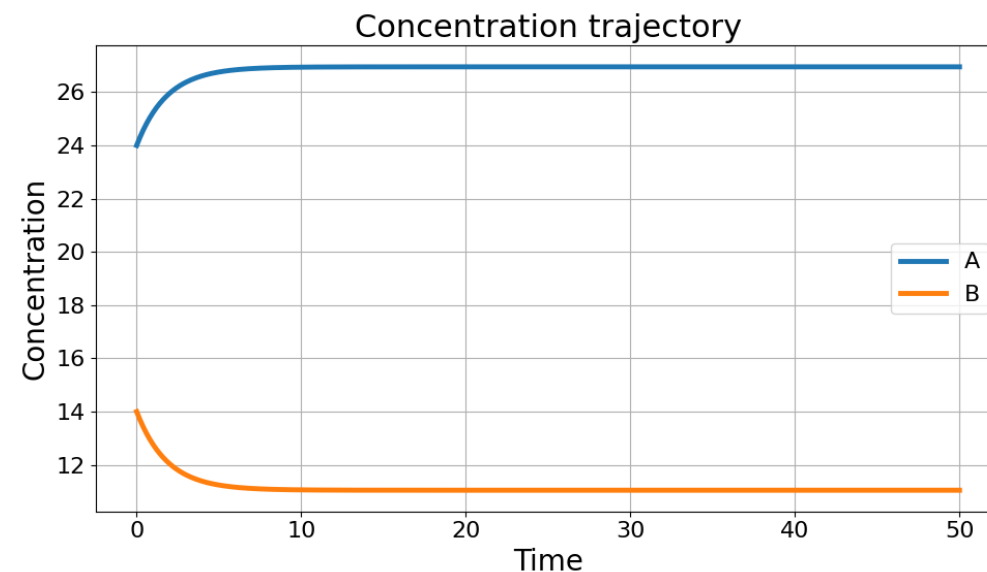
Perturbation analysis-Simulation approaches

Pipeline

Simulate → Alter parameter → Simulate → Compare



Base case



Altered k_r



Perturbation analysis-Simulation approaches

Limitation

Need to know every parameter

Desiderata

Approximate, qualitative methods



Network propagation approach

Main idea

Network topology linked to perturbation patterns

Approach

- 1) Mark a node with a positive label
- 2) Spread the signal according to a specific rule
- 3) Repeat 1,2 until no changes



Network propagation approach

Marked node: Perturbed reaction

Update policy: Abstraction of chemical kinetics

Chemical kinetics

- Species concentrations
- Reaction rates



Real physical quantities

Network propagation

- Species shifts
- Reaction potentials



Abstract numbers,
related to spreading dynamics

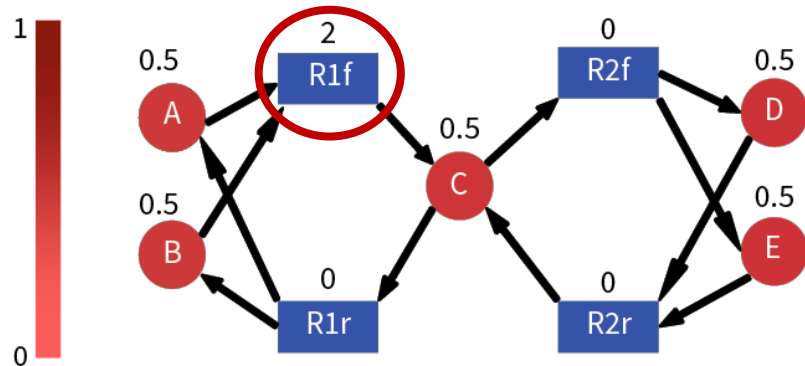
How represented a species is

How strong a reaction is

Network propagation approach

t_0 :

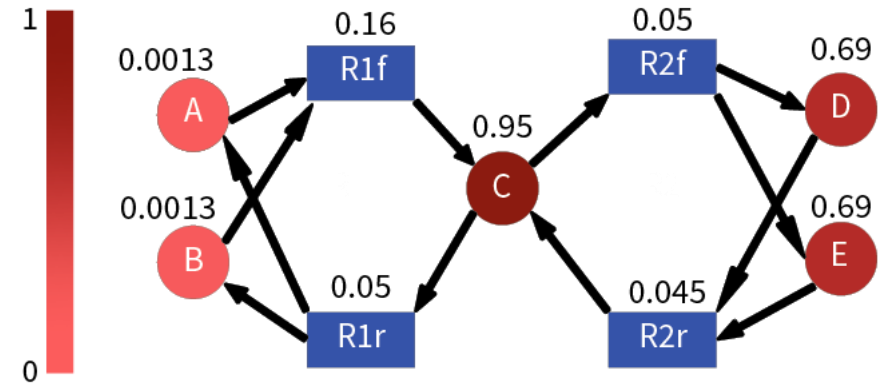
- Every species at 0.5
- Every reaction at 0 but the altered one



...

t_{final} :

Potentials and shifts are updated



$C, D, E > 0.5$: they increase
 $A, B < 0.5$: they decrease



Network propagation approach

Strength

Good performances when the system reaches dynamic equilibrium

Weakness

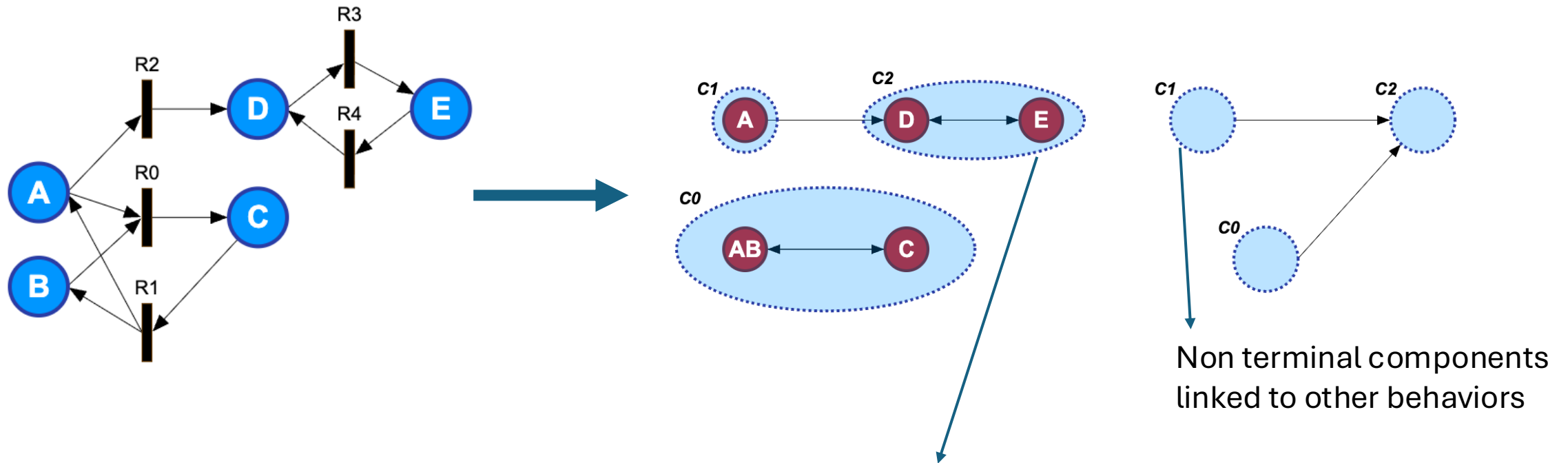
Does not capture some features

- Is every reaction critical?
- Are there species that are not affected by a perturbation?

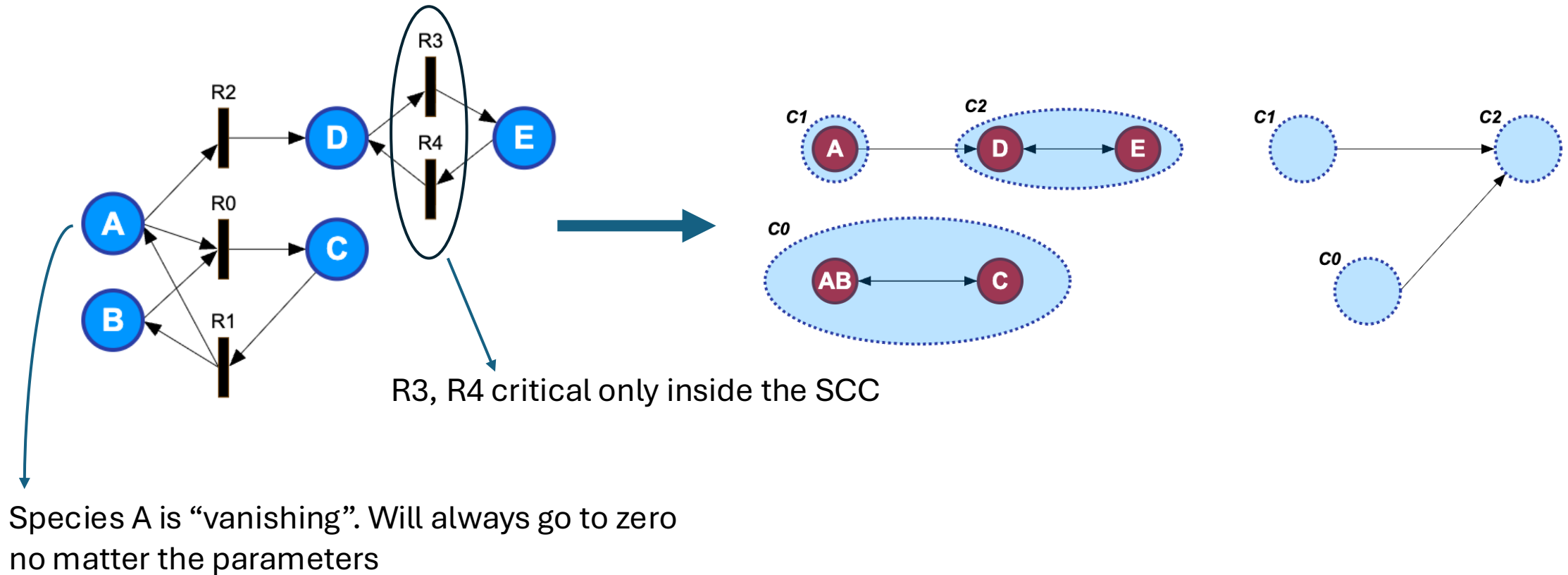
Structural approach

Question

Can we relate structure to dynamical features?



Structural approach





Approximate approaches

Stoichiometry matrix analysis

Strength

Can deal with vanishing species and non critical reactions

Limitation

Requires specific properties of the stoichiometry matrix, computationally demanding

Structural analysis + network propagation

Strength

No assumptions on the structure

Limitation

Not fully developed yet



Open questions

Structure-dynamics link:

To which extent can we relate structural and dynamical features?

Controllability:

How can we control a pathway to achieve a desired outcome?

What is the minimal intervention needed?



Thank you