Abstract Interpretation of Chemical Reaction Networks

for the Prediction of Gene Knockouts

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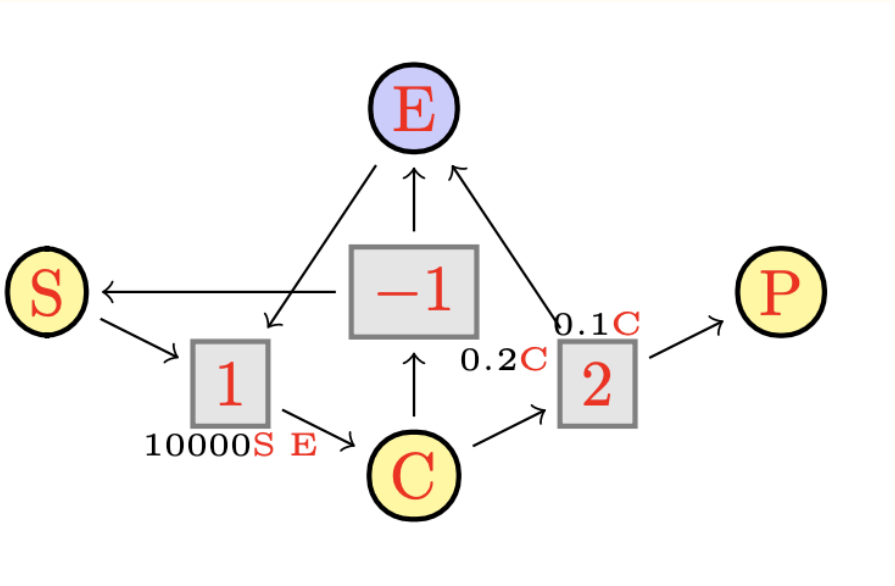
1. Warmup
   - Reaction Networks
   - Steady States
2. Reaction Networks with Complete Kinetic Information
   - From Arithmetic Expressions to ODEs
   - Reaction Networks with Deterministic Semantics
3. Abstract Interpretation of Algebraic Equations
   - Abstract Interpretation over Changes
   - Change Prediction in Steady States
4. Gene Knockout Prediction
   - Reaction Networks with Partial Kinetic Information
   - Application to Metabolic Overproduction
5. Abstract Interpretation of ODEs

Enzymatic Reaction Network

Graph of Species and Reactions



Species

S substrate, P product, C complex S.E, E enzyme

Mass Action Kinetics

the probabilty of reactants to meet in a well-steered solution.

BioCham: Syntax

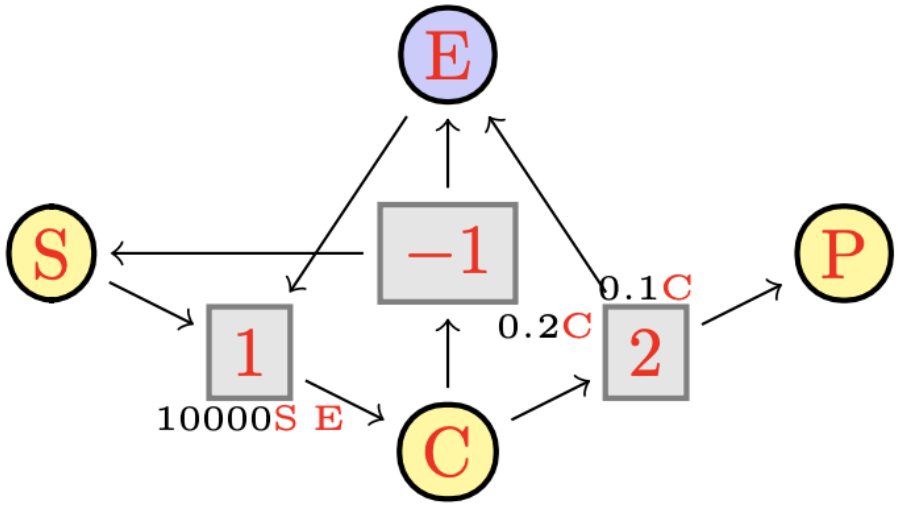
```
Biocham 4.6.19 Copyright (C) 2003-2020 Inria, EPI Lifeware, Sa
```

In [1]:

```
%% reactions %%%%%%%%%%%%%%%%%%%%%%%%

% reaction 1
10000 * S *E for S+E => C.

% reaction -1
0.2 * C for C => S+E.

% reaction 2
0.1 * C for C => P+E.

%%%% initial values %%%%%%%%%%%%%%%%%

present(S,5).
present(E,2).
present(C,0).
```

Ordinary Differential Equations (ODEs)

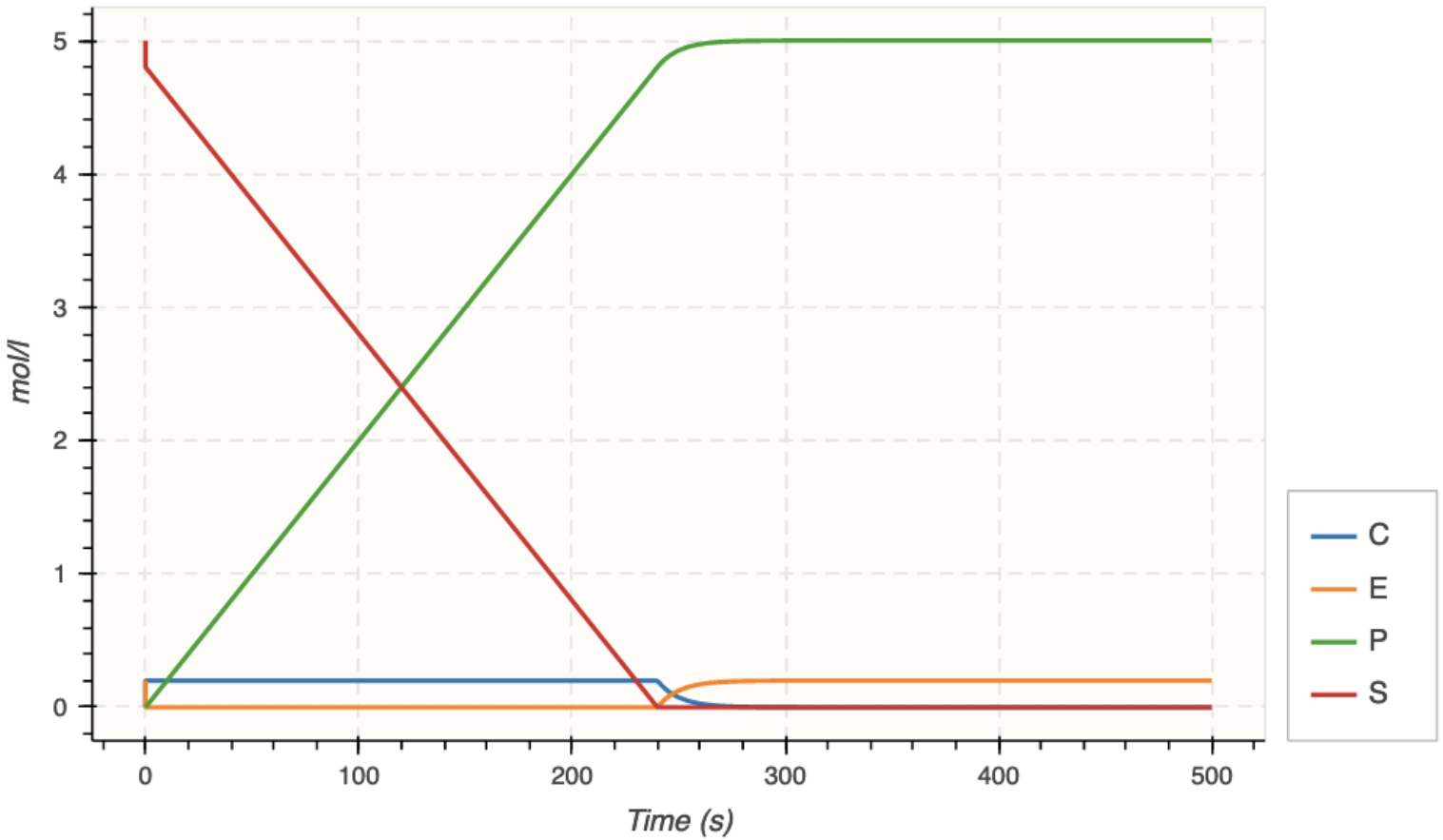
$$\dot{S} = -r_1 + r_{-1}$$
$$\dot{E} = -r_1 + r_{-1} + r_2$$
$$\dot{C} = r_1 - r_{-1} - r_2$$
$$\dot{P} = r_2$$
$$r_1 = 10000 S\, E$$
$$r_{-1} = 0.2C$$
$$r_2 = 0.1C$$



BioCham: numerical_simulation

```
present(S,5).
present(E,0.2).
present(C,0).
```

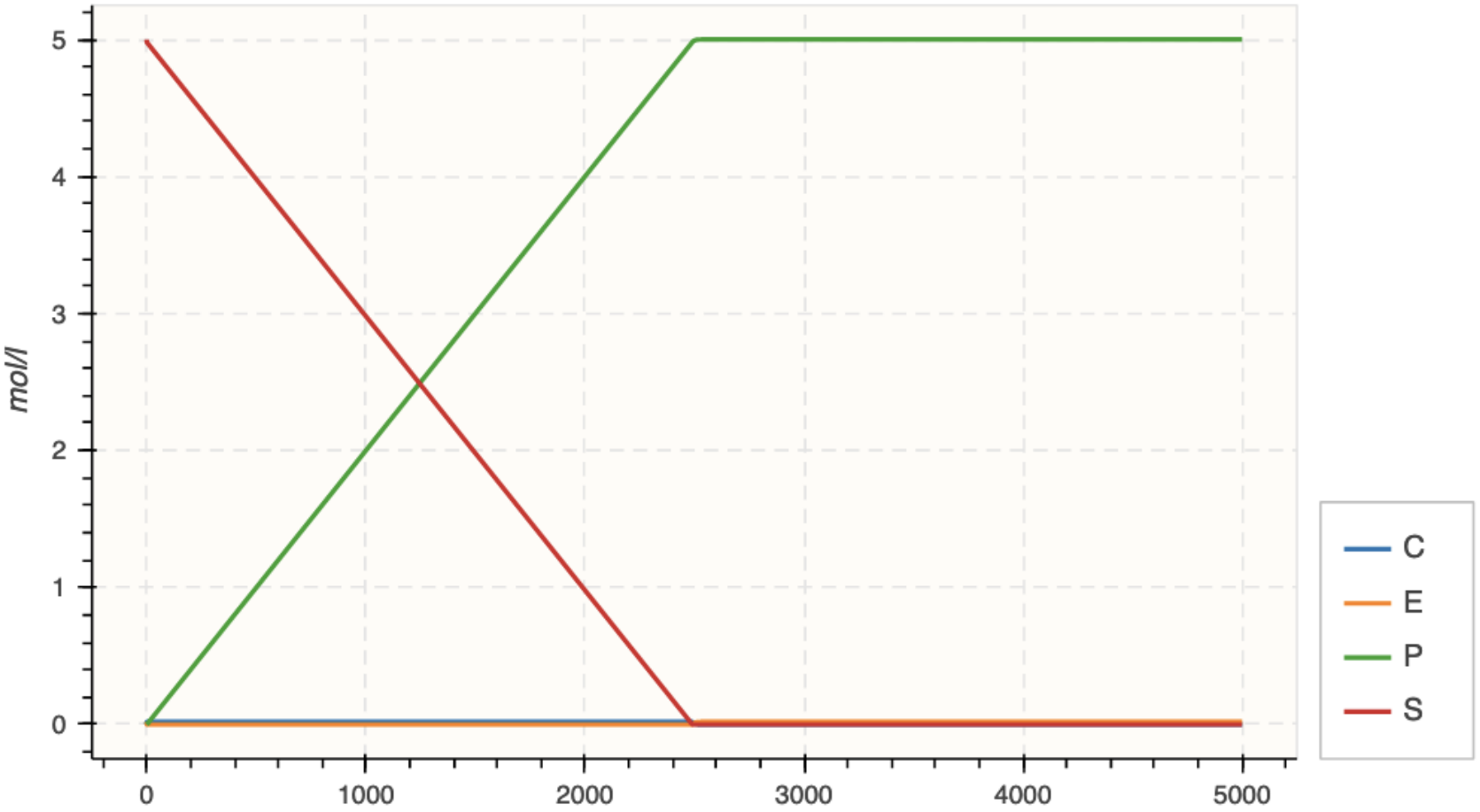
In [5]:
```
numerical_simulation(time:500). plot.
```



What Happens with Less Enzyme?

```
present(S,5).
present(E,0.02).
present(C,0).
```

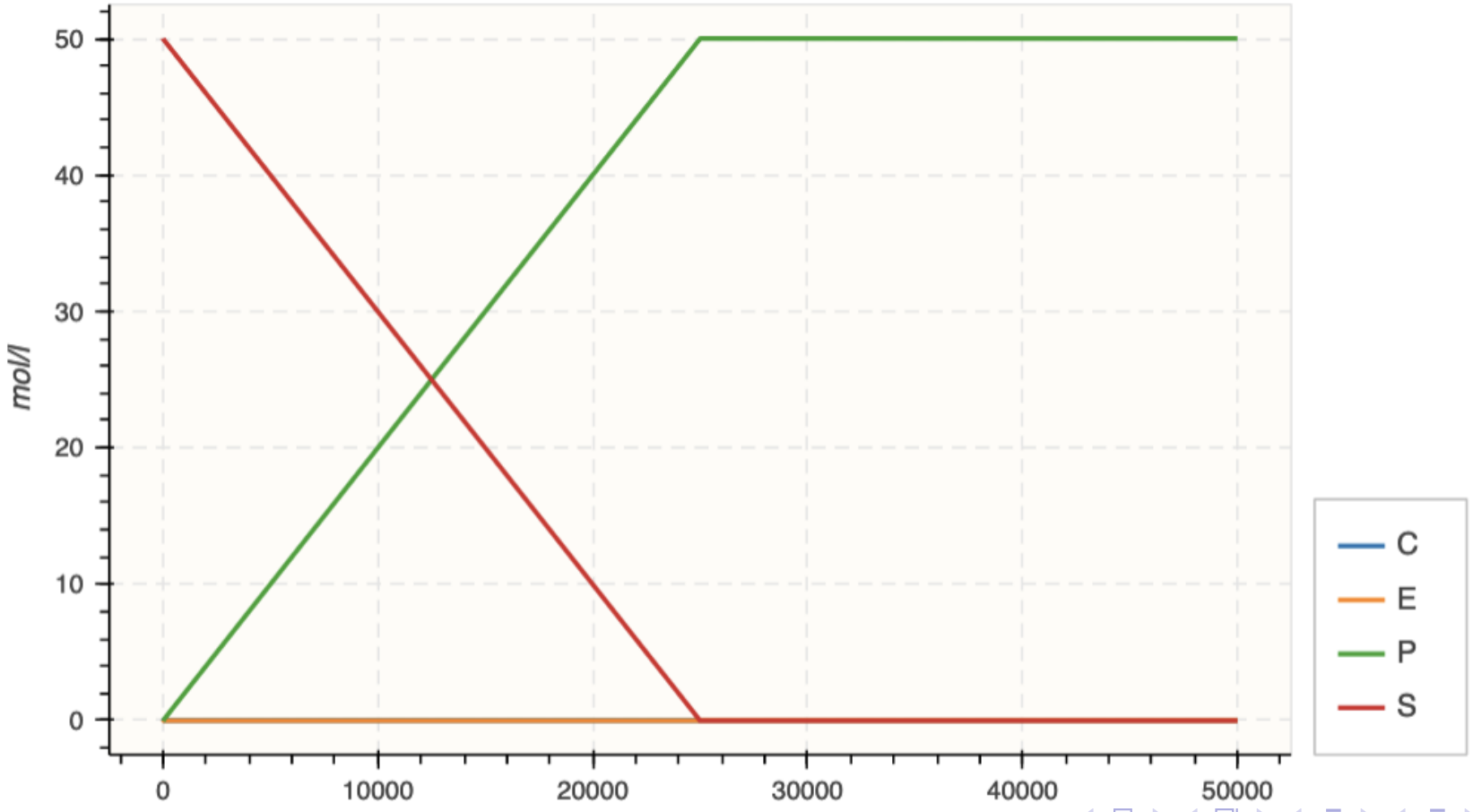
```
numerical_simulation(time:5000). plot.
```



What Happens with More Substrate?

```
present(S,50).
present(E,0.02).
present(C,0).
```

```
numerical_simulation(time:50000). plot.
```

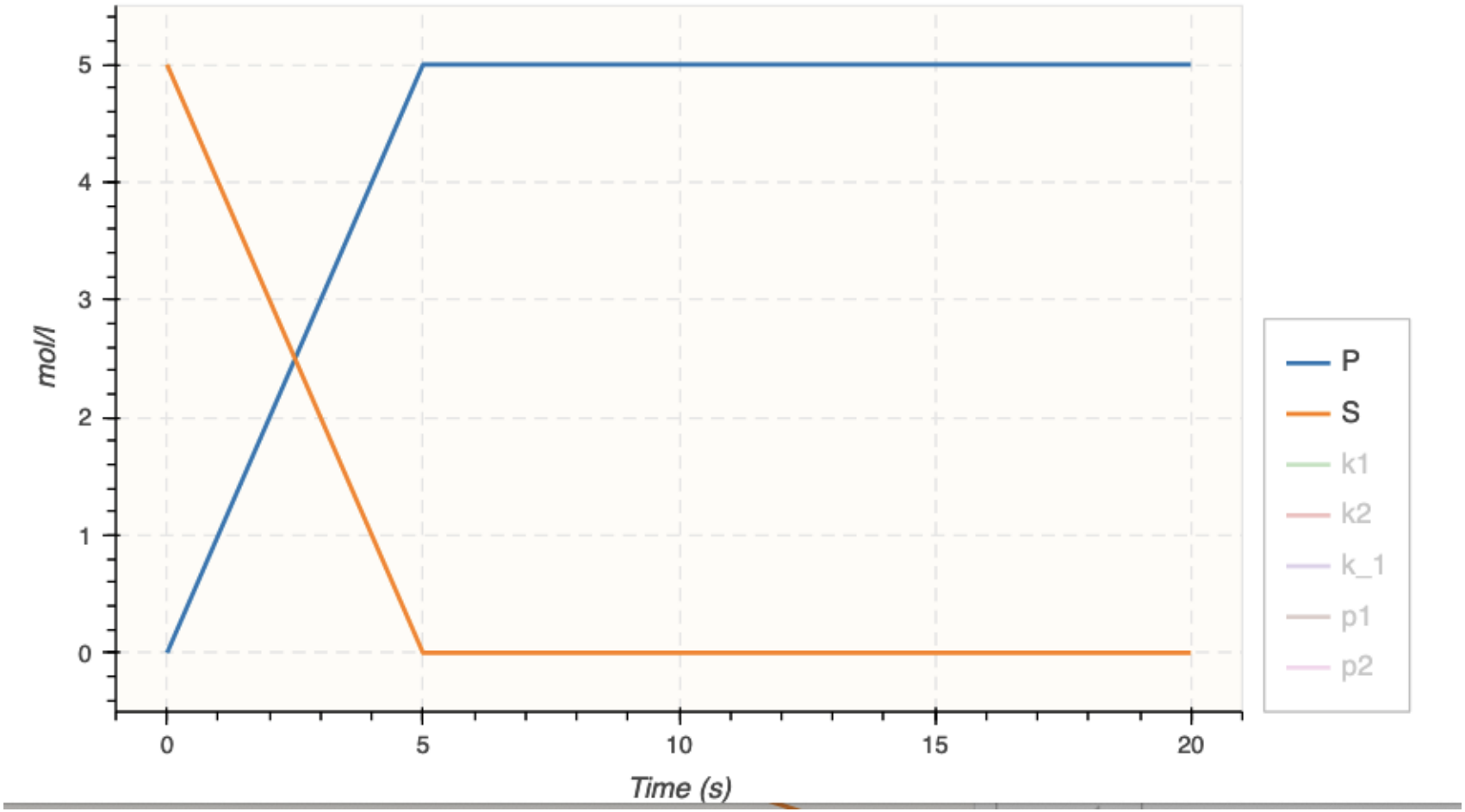


Reaction with Michaelis-Menten Kinetics

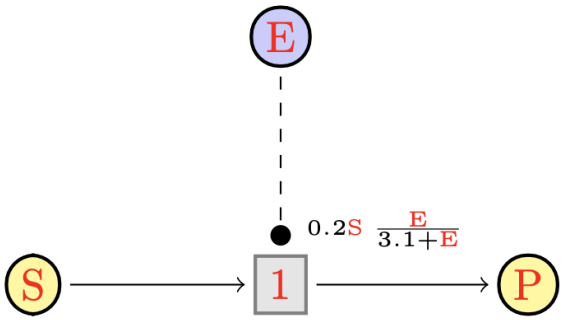
```
p1 * S / (p2 + S)  for S => P.

function(k1  = 10000).
function(k_1 = 0.1).
function(k2  = 0.2).

function(p1 = k2 * 5).
function(p2 = (k_1+k2) /k1).

present(S,5).
present(P,0).
```

Simulation of Reaction with Michaelis-Menten Kinetics

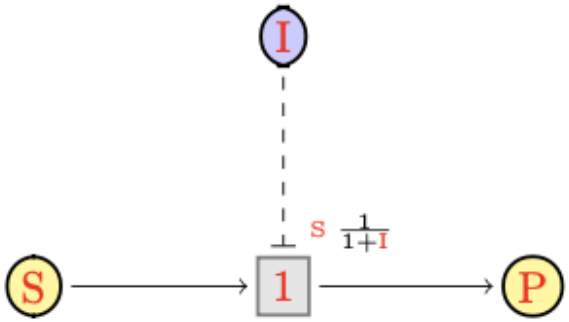
```
numerical_simulation(time:20, method:'rsbk'). plot(show:{S,P}).
```



Representation of Activators of Reactions



Representation of Inhibitors of Reactions



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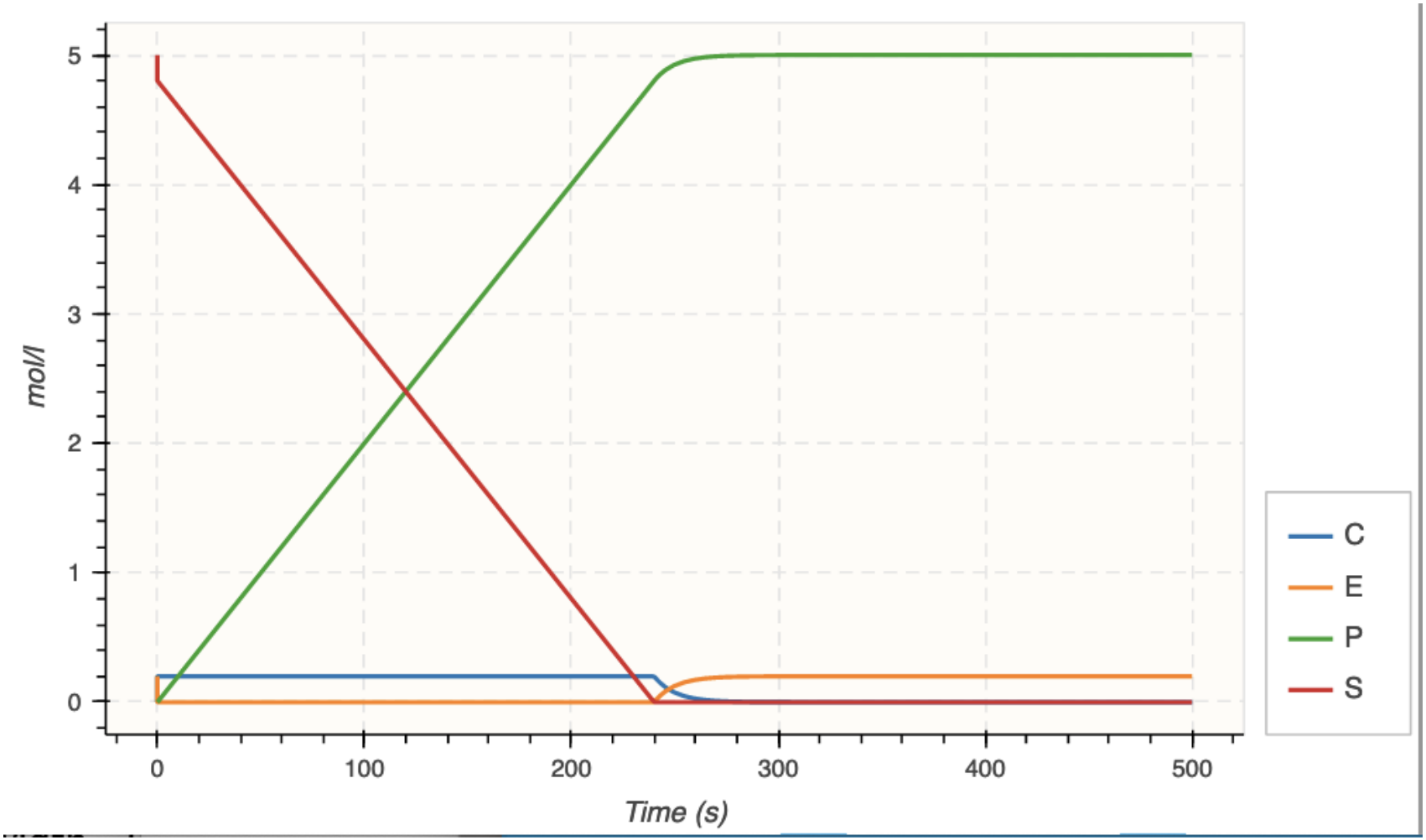
Quasi Steady States

Concentrations will no more change

Quasi Steady States

Concentrations will no more change

May the Enzymatic Network become Steady?



Quasi Steady States

Concentrations will no more change

May the Enzymatic Network become Steady?

No at any real time point

S decreasing but never becomes exactely 0

E+C does not change

P increasing but never become exactely S(0)

Quasi Steady States

Concentrations will no more change

May the Enzymatic Network become Steady?

No at any real time point

S decreasing but never becomes exactely 0

E+C does not change

P increasing but never become exactely S(0)

Yes in the limit: quasi steady state

$S(\infty) = 0$

$P(\infty) = S(0) + C(0)$

$E(\infty) = E(0) + C(0)$

$C(\infty) = 0$

How many Quasi Steady States per Network?

Deterministic Semantics

- at most one state in the limit towards ∞

  for each choice of initial values
  sometimes a signal may fail
  sometimes a signal is periodic, so no limit towards ∞

- though: infinitely many possible choices of initial values

May Networks with Active Reactions become Steady?

Previous enzymatic network

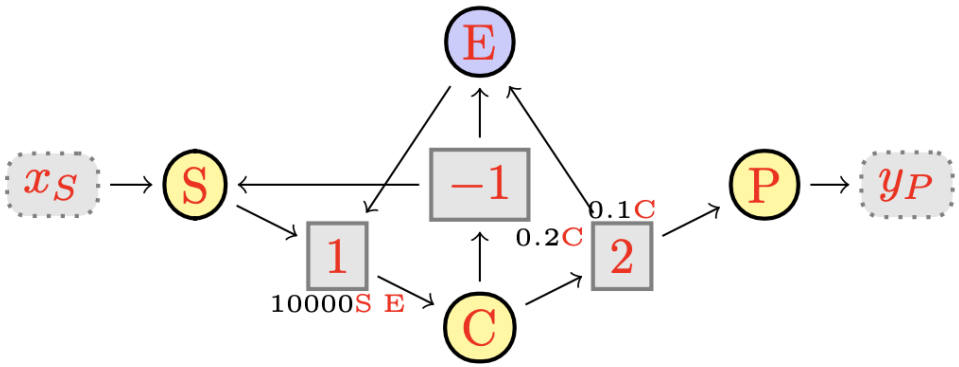
- steady once all substrate has been converted into product
- nothing is produced nor consumed any more

But we can add:

- an inflow producing S, and
- an outflow consuming P

With an Inflow and Outflow

Graph



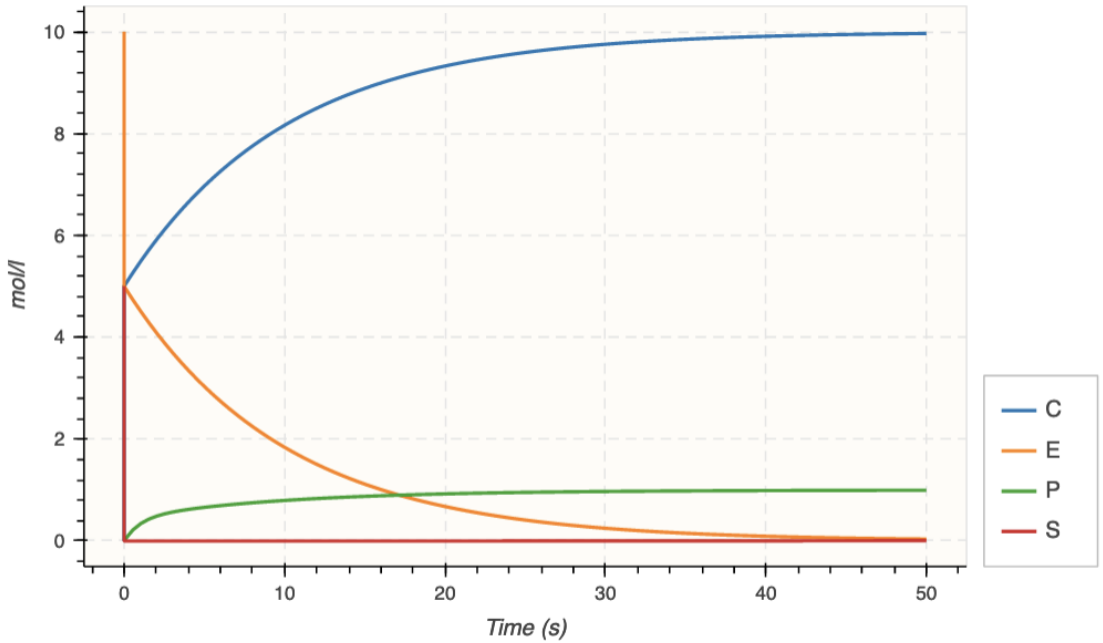
Becomes stable?

???

Enough Enzyme

```
present(S,5).
present(E,10).
present(C,0).
```

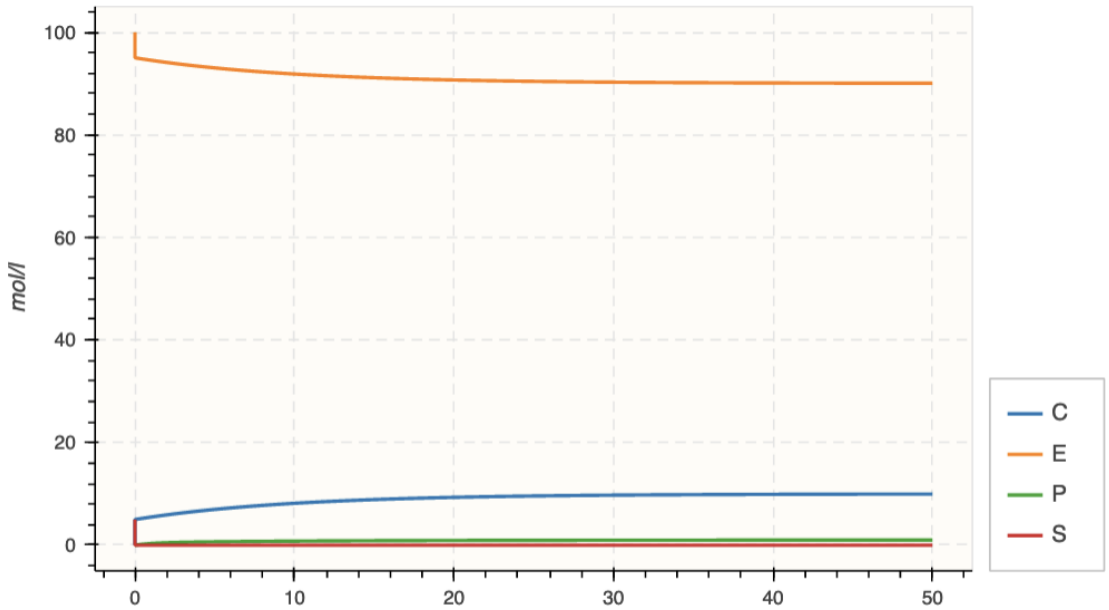
```
numerical_simulation(time:50). plot.
```



More Enzyme

```
present(S,5).
present(E,100).
present(C,0).
```

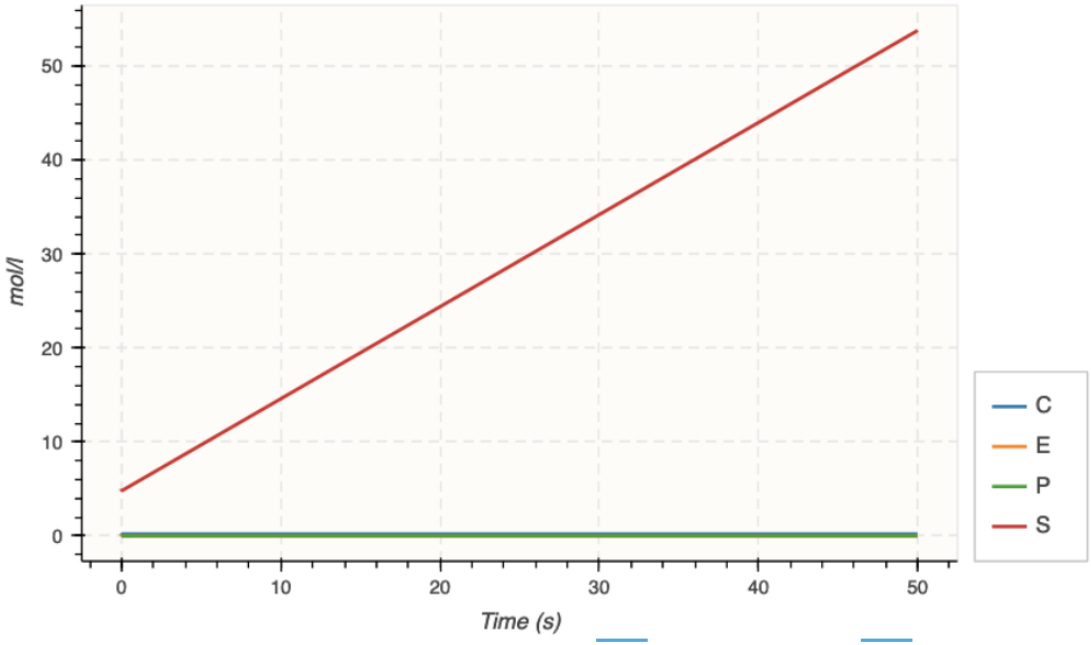
```
numerical_simulation(time:50). plot.
```



Not Enough Enzyme

```
present(S,5).
present(E,0.2).
present(C,0).
```

```
numerical_simulation(time:50). plot.
```



Living Systems in Longer Runs are Active but Steady

Glucose in blood is quasi steady

- eating and dinking all the time
- burning energy all the time

What happens if glucose level increases?

Living Systems in Longer Runs are Active but Steady

Glucose in blood is quasi steady

- eating and dinking all the time
- burning energy all the time

What happens if glucose level increases?

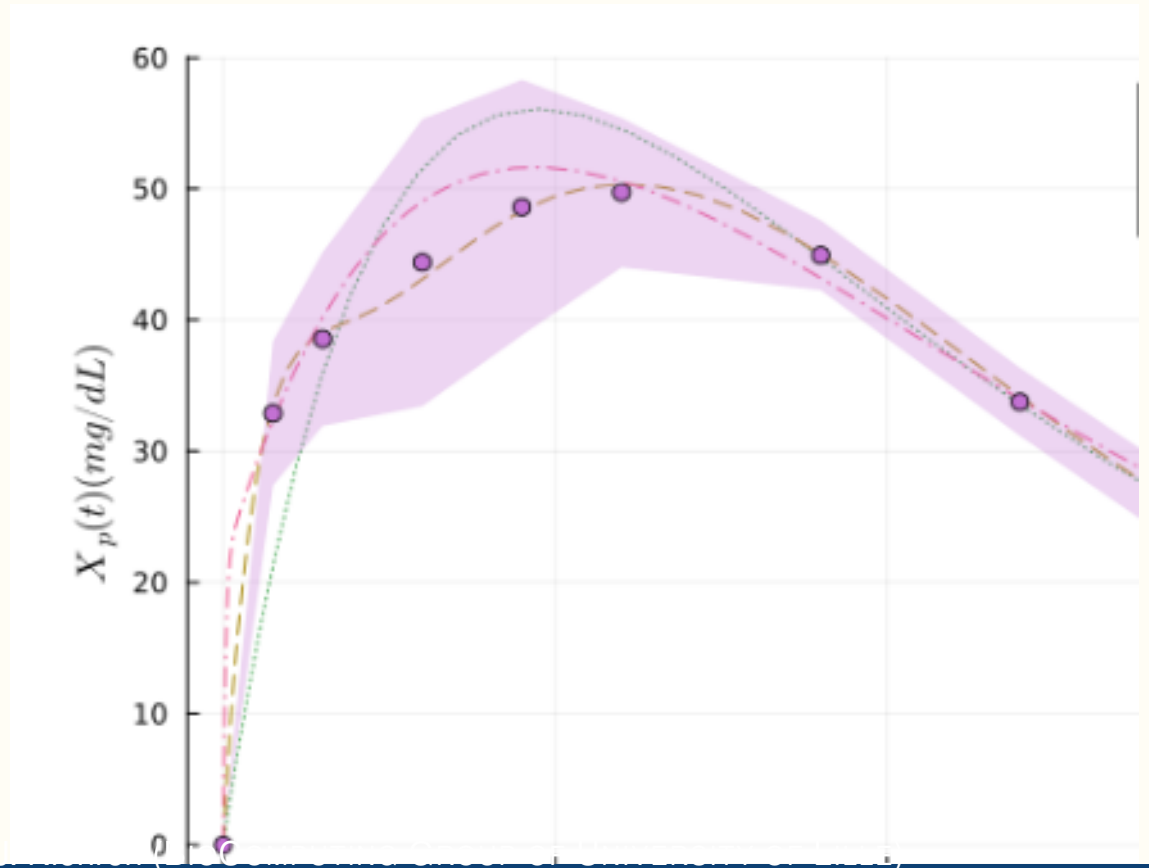
Diabetes!

Living Systems in Shorter Terms are Dynamical

Postprandial glucose regulation

- stabilizes after 4 hours

Typical Dynamics



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Arithmetic and Boolean Expressions

X set of variables.
$F = \sin, \cos, \sqrt{}, \ldots$ predefined arithmetic functions

$$
\begin{array}{rcll}
e, e' \in \mathcal{E}_X & ::= & x \mid k \mid & \text{where} \quad x \in X,\ k \in \mathbb{R}, \\
& \mid & e + e' \mid e - e' \mid e * e' \mid e/e' & \\
& \mid & f(e) & f \in F \\
& \mid & \textbf{if } b \textbf{ then } e \textbf{ else } e' & \\
b, b' & ::= & e \leq e' \mid \neg b \mid b \wedge b' &
\end{array}
$$

Interpretation over the Reals

$$[\![x]\!]^\eta = \eta(x) \qquad [\![k]\!]^\eta = k$$

$$[\![e + e']\!]^\eta = [\![e]\!]^\eta +^{\mathbb{R}} [\![e']\!]^\eta$$
$$[\![e - e']\!]^\eta = [\![e]\!]^\eta -^{\mathbb{R}} [\![e']\!]^\eta$$
$$[\![e * e']\!]^\eta = [\![e]\!]^\eta *^{\mathbb{R}} [\![e']\!]^\eta$$
$$[\![e/e']\!]^\eta = \begin{cases} [\![e]\!]^\eta /^{\mathbb{R}} [\![e']\!]^\eta & \text{if } [\![e']\!]^\eta \neq 0 \\ \mathit{undef} & \text{otherwise} \end{cases}$$

$$[\![f(e)]\!]^\eta = f^{\mathbb{R}\to\mathbb{R}}([\![e]\!]^\eta)$$

$$[\![\textbf{if } b \textbf{ then } e \textbf{ else } e']\!]^\eta = \begin{cases} [\![e]\!]^\eta & \text{if } [\![b]\!]^\eta = 1 \\ [\![e']\!]^\eta & \text{if } [\![b]\!]^\eta = 0 \\ \mathit{undef} & \text{otherwise} \end{cases}$$

$$[\![e \leq e']\!]^\eta = \begin{cases} 1 & \text{if } [\![e]\!]^\eta \leq^{\mathbb{R}} [\![e']\!]^\eta \\ 0 & \text{if } [\![e]\!]^\eta >^{\mathbb{R}} [\![e']\!]^\eta \\ \mathit{undef} & \text{else} \end{cases}$$

$$[\![b \wedge b']\!]^\eta = [\![b]\!]^\eta \wedge^{\mathbb{B}} [\![b']\!]^\eta$$
$$[\![\neg b]\!]^\eta = \neg^{\mathbb{B}}([\![b]\!]^\eta)$$

Interpretation over the Real Functions

let $\alpha(x) : \mathbb{R}_+ \to \mathbb{R}$ for all $x \in X$

Projection of variables assignment

define $\alpha_t(x) \in \mathbb{R}$ for all $x \in X$ and $t \in \mathbb{R}_+$ such that:

$$\alpha_t(x) = \alpha(x)(t)$$

Function interpretation

define $[\![e]\!]^\alpha : \mathbb{R}_+ \to \mathbb{R}$ such that for all $t \in \mathbb{R}_+$:

$$[\![e]\!]^\alpha(t) = [\![e]\!]^{\alpha_t}$$

Piecewise Real Functions

Special variable for identify function

Let $time \in X$ such that $\alpha(time)(t) = t$ for all $t \in \mathbb{R}_+$.

Example of piecewise affine real function

$$\textbf{if } 0 \leq time \wedge time \leq 2.5 \textbf{ then } 1.3 * time \textbf{ else } 0$$

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Reaction Networks

Reactions r with species in X:

$$r = (R, e, P) \text{ where } R, P : X \to \mathbb{N},\ e \in \mathcal{E}_X$$

Written in biocham as:

$$e \text{ for } P \Rightarrow P.$$

Reaction network N is finite set of reactions

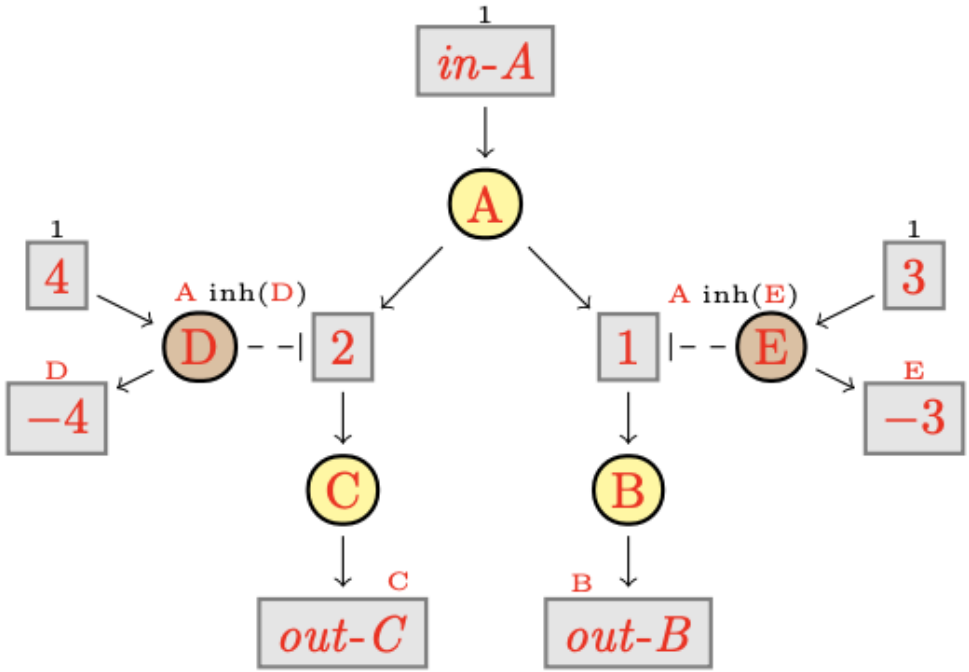
Dynamics by Ordinary Differential Equations (ODEs)

Deterministic semantics of reaction network N.
For each species $x \in X$:

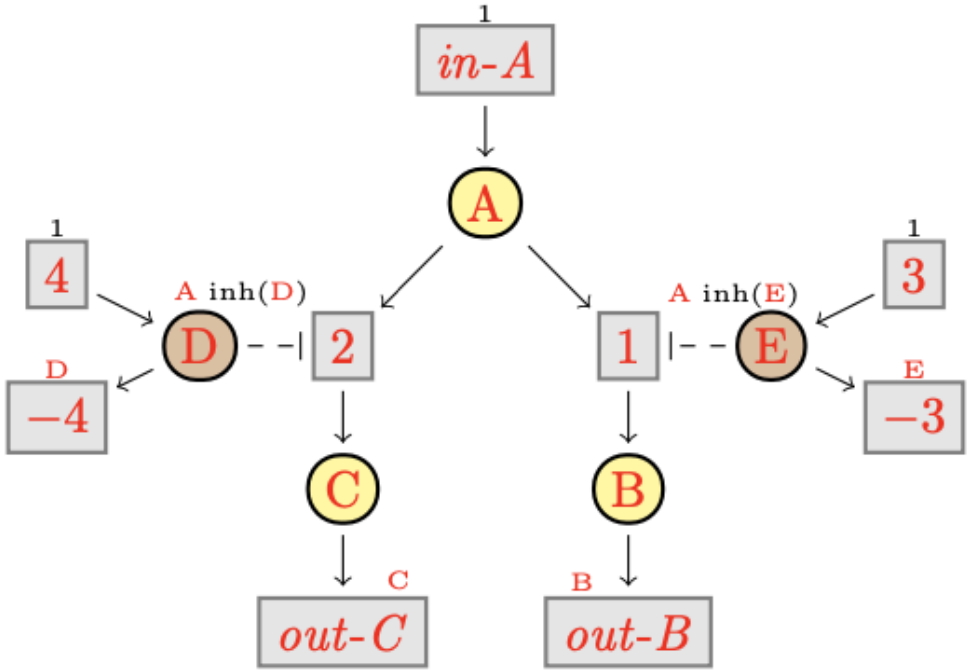
$$\dot{x} = \sum_{(R,e,P) \in N} e * (P(x) - R(x))$$

Equations interpreted over real valued functions.

Example: acyclic network

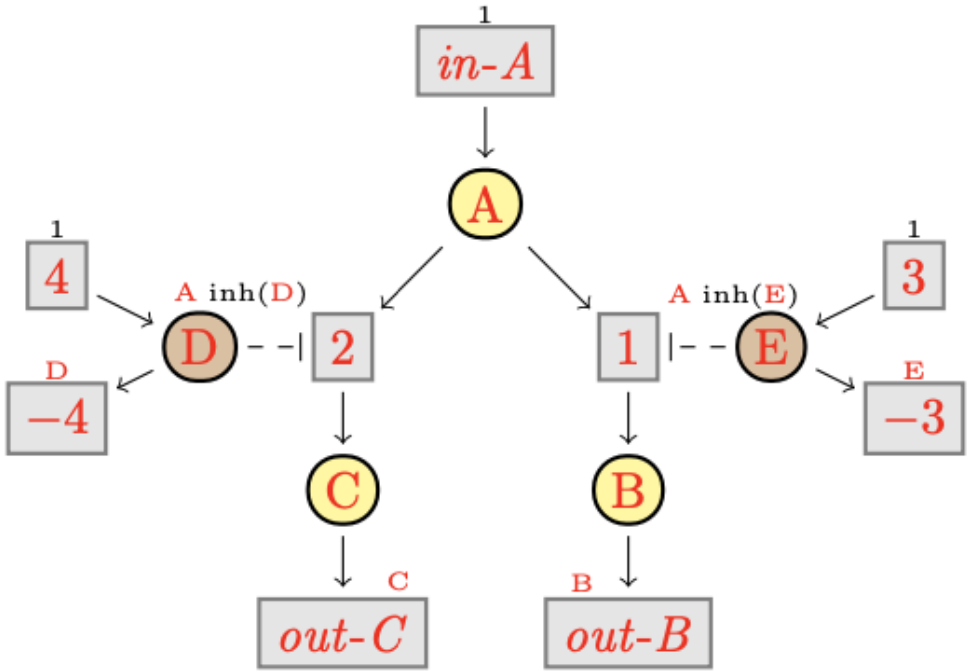


Example: acyclic network



$$\mathring{A} = -r_1 - r_2 + in\text{-}A$$
$$\mathring{B} = r_1 - r_{yB}$$
$$\mathring{C} = r_2 - r_{yC}$$
$$\mathring{D} = -r_{-4} + r_4$$
$$\mathring{E} = -r_{-3} + r_3$$

Example: acyclic network



$$\dot{A} = -r_1 - r_2 + \textit{in-A}$$
$$\dot{B} = r_1 - r_{yB}$$
$$\dot{C} = r_2 - r_{yC}$$
$$\dot{D} = -r_{-4} + r_4$$
$$\dot{E} = -r_{-3} + r_3$$

$$\textit{out-B} = B$$
$$\textit{out-C} = C$$
$$r_1 = A\ inh(E)$$
$$r_2 = A\ inh(D)$$
$$r_{-3} = E$$
$$r_{-4} = D$$

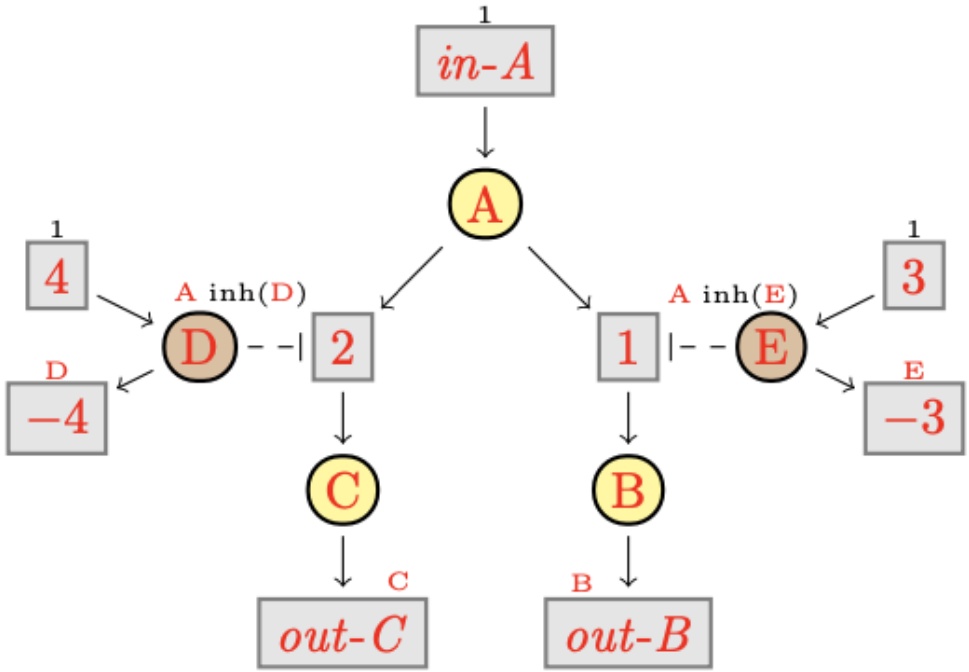
Steady State Equation

For each species $x \in X$:

$$0 = \sum_{(R,e,P) \in N} e * (P(x) - R(x))$$

Equations interpreted over reals.

Example: acyclic network



$$in\text{-}A = r_1 + r_2$$
$$out\text{-}B = r_1$$
$$out\text{-}C = r_2$$
$$r_{-4} = r_4$$
$$r_{-3} = r_3$$

$$out\text{-}B = B$$
$$out\text{-}C = C$$
$$r_1 = A\ inh(E)$$
$$r_2 = A\ inh(D)$$
$$r_{-3} = E$$
$$r_{-4} = D$$

Not only Chemical Reactions

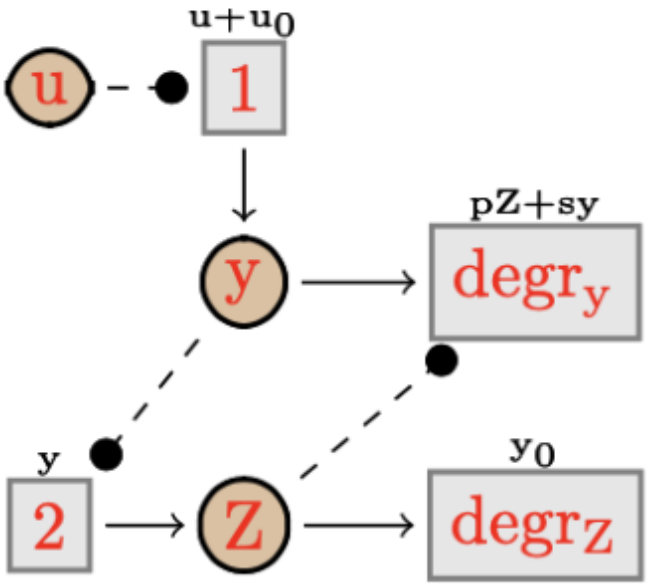
Reactions = Interactions

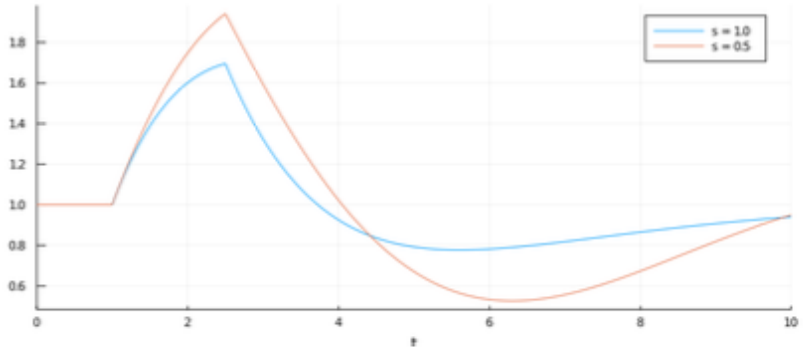
Can represent biological system on all levels

- molecular
- cellular
- tissue
- physiologial
- communities

Not only biological species as variables

Example: Linear Integral Feedback Control





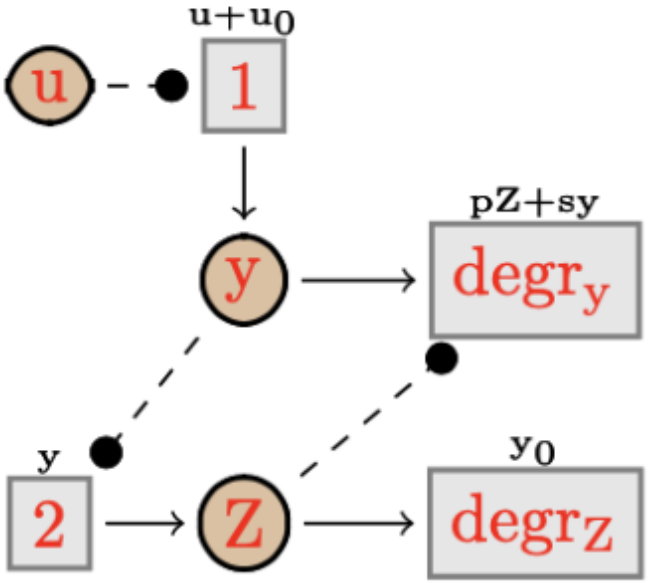
$$\dot{y} = u + u_0 - pZ - sy$$

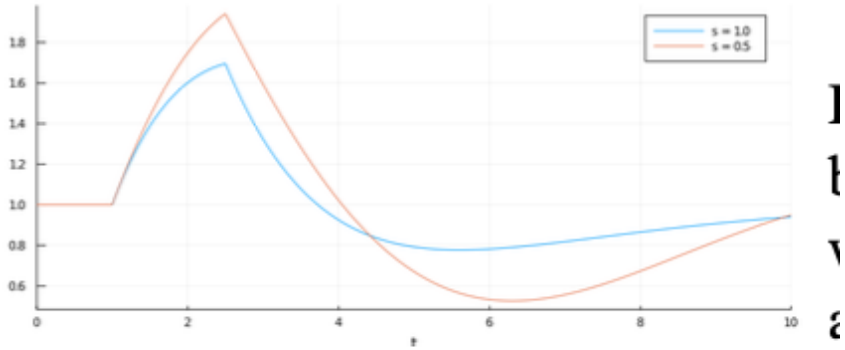
$$\dot{Z} = y - y_0$$

Species as signals: $\mathbb{R}_+ \to \mathbb{R}_+$

u glucose in intestine inflows in reaction 1
y glucose level in blood
s insulin sensiblity in muscles
Z integral error: $Z(t) = \int_0^t y(x) - y(0)dx$

Example: Linear Integral Feedback Control





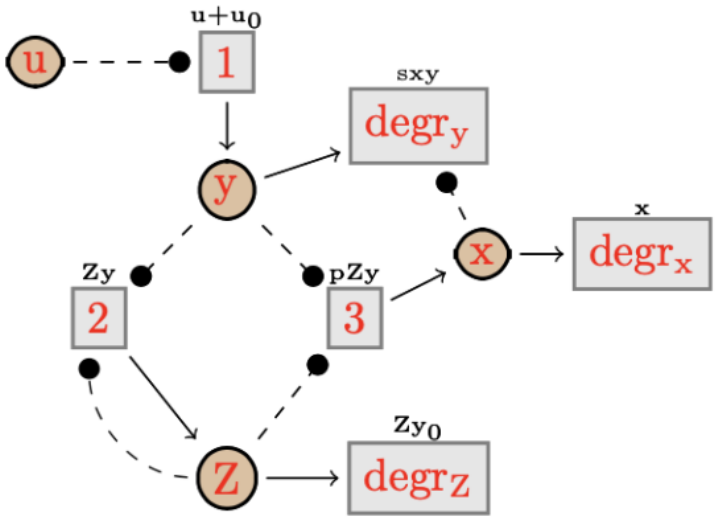
$$\dot{y} = u + u_0 - pZ - sy$$

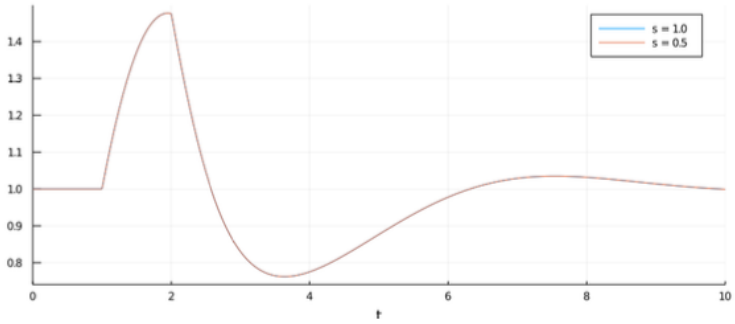
$$\dot{Z} = y - y_0$$

Homeostatis

Constancy for any value of s: $lim_{t\to\infty} y(t) = y(0)$

Example: Dynamical Compensation





$$\dot{y} = u_0 + u - sxy$$
$$\dot{x} = pZy - x$$
$$\dot{Z} = Z(y - y_0)$$

Constancy of the signal

for any value of s, the same signal

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$\{+, *, inh\}$-Structure of Changes

Changes

$\Delta_3 = \{\uparrow, \downarrow, \sim\}$

Operations

$\uparrow +^{\Delta_3} \uparrow = \uparrow$
$\uparrow +^{\Delta_3} \sim = \uparrow$
$\uparrow +^{\Delta_3} \downarrow \in \Delta_3$ everything possible

$\uparrow *^{\Delta_3} \uparrow = \uparrow$
$\uparrow *^{\Delta_3} \sim = \uparrow$
$\ldots$

$$inh^{\Delta_3}(\uparrow) = \downarrow$$
$$inh^{\Delta_3}(\downarrow) = \uparrow$$
$$inh^{\Delta_3}(\sim) = \sim$$

Difference Abstraction

$h_{diff} : \mathbb{R}^2_+ \to \Delta_3$

$$h_{diff}(r, r') = \begin{cases} \uparrow & \text{if } r < r' \quad \textit{increase} \\ \downarrow & \text{if } r > r' \quad \textit{decrease} \\ \sim & \text{if } r = r' \quad \textit{no} - \textit{change} \end{cases}$$

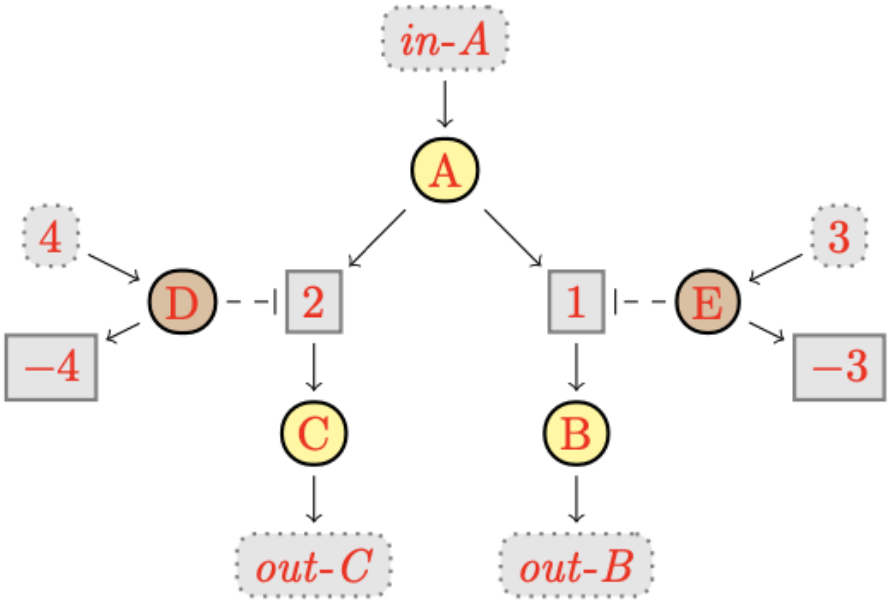
Proposition

$h : \mathbb{R}^2_+ \to \Delta_3$ is a homomorphism between $\{+, *, inh\}$-structures

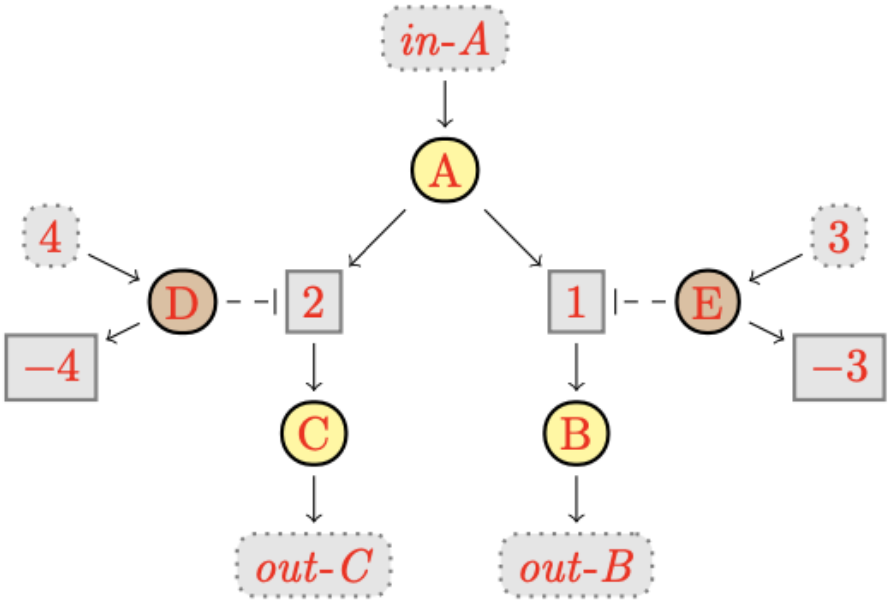
Possible Network Changes

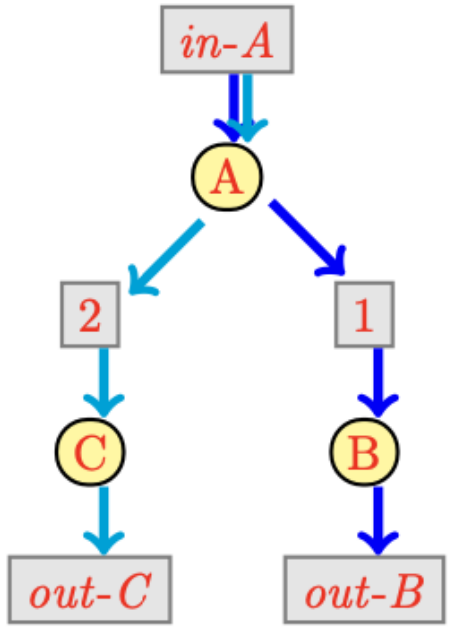
- increase inflow
- decrease inflow
- ...

Which Changes may increase *out-B*

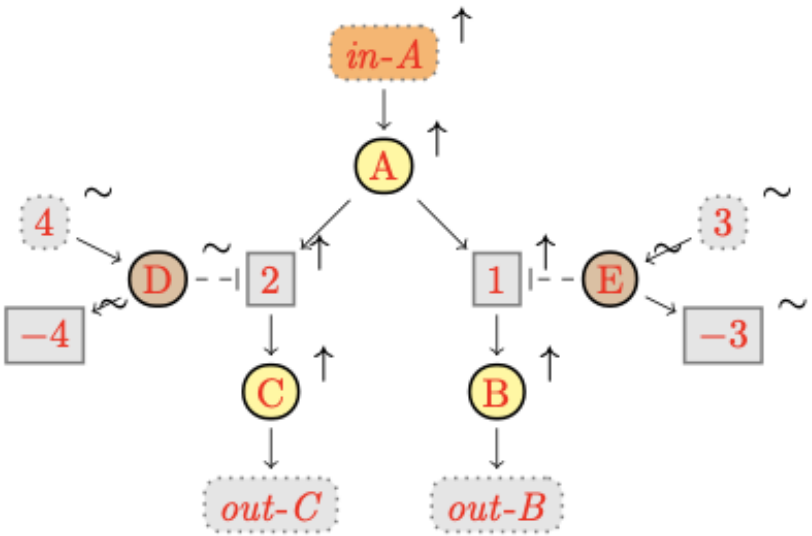


Which Changes may increase *out-B*





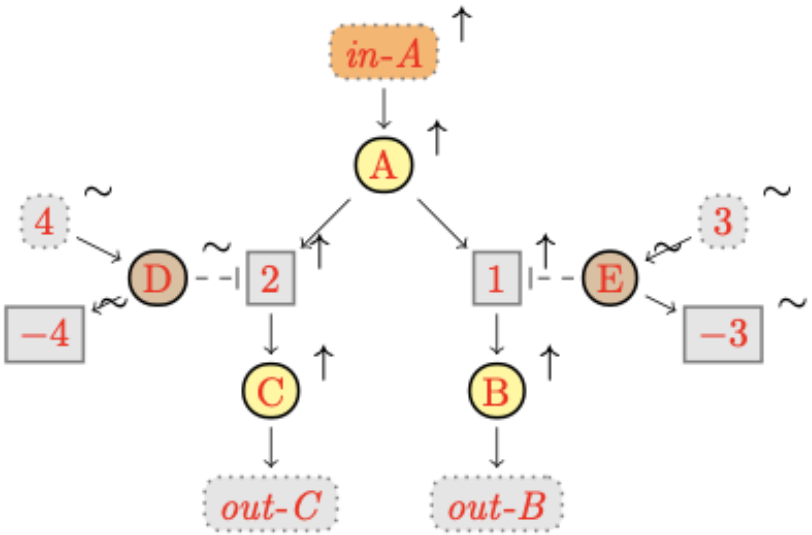
Solutions of Steady State Equations over Changes



$$in\text{-}A = r_1 + r_2$$
$$out\text{-}B = r_1$$
$$out\text{-}C = r_2$$
$$r_{-4} = r_4$$
$$r_{-3} = r_3$$

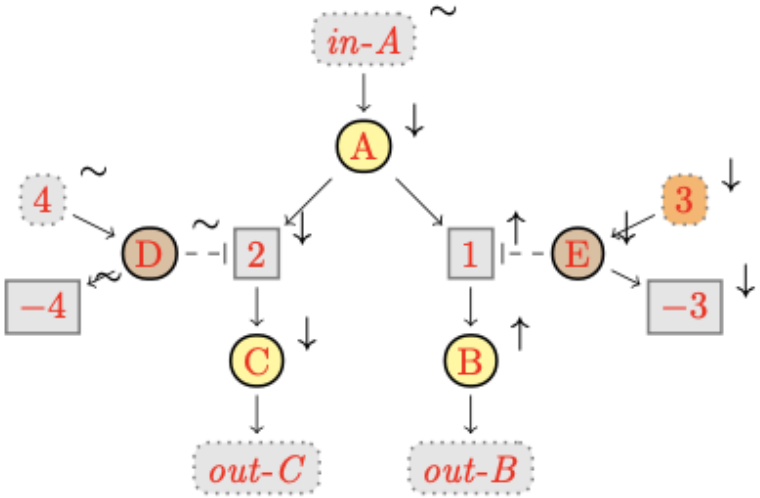
$$out\text{-}B = B$$
$$out\text{-}C = C$$
$$r_1 = A\ inh(E)$$
$$r_2 = A\ inh(D)$$
$$r_{-3} = E$$
$$r_{-4} = D$$

Solutions of Steady State Equations over Changes



$$\begin{aligned} \textit{in-A} &= r_1 + r_2 \\ \textit{out-B} &= r_1 \\ \textit{out-C} &= r_2 \\ r_{-4} &= r_4 \\ r_{-3} &= r_3 \end{aligned}$$

$$\begin{aligned} \textit{out-B} &= B \\ \textit{out-C} &= C \\ r_1 &= A\ \textit{inh}(E) \\ r_2 &= A\ \textit{inh}(D) \\ r_{-3} &= E \\ r_{-4} &= D \end{aligned}$$



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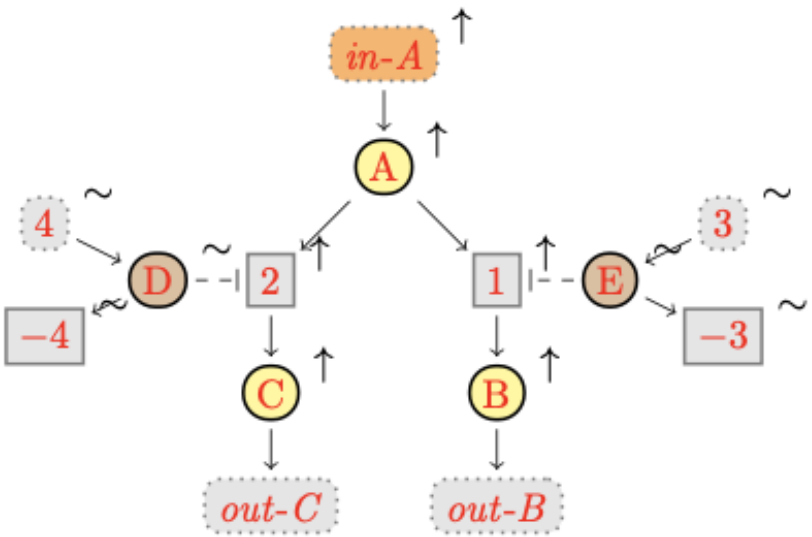

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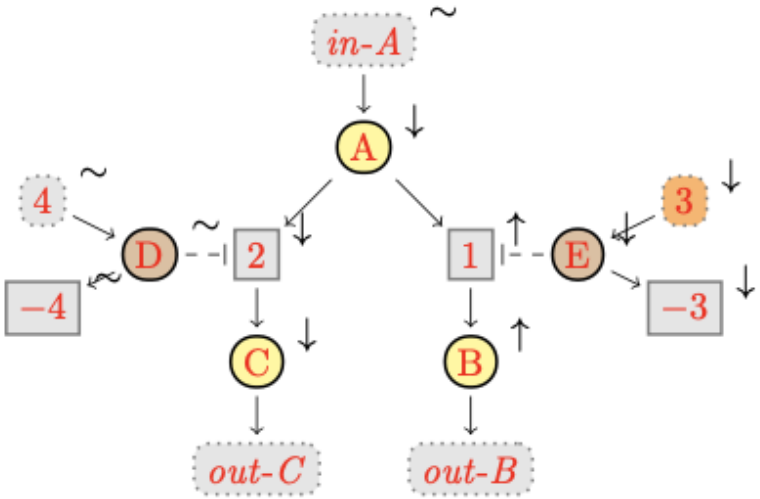

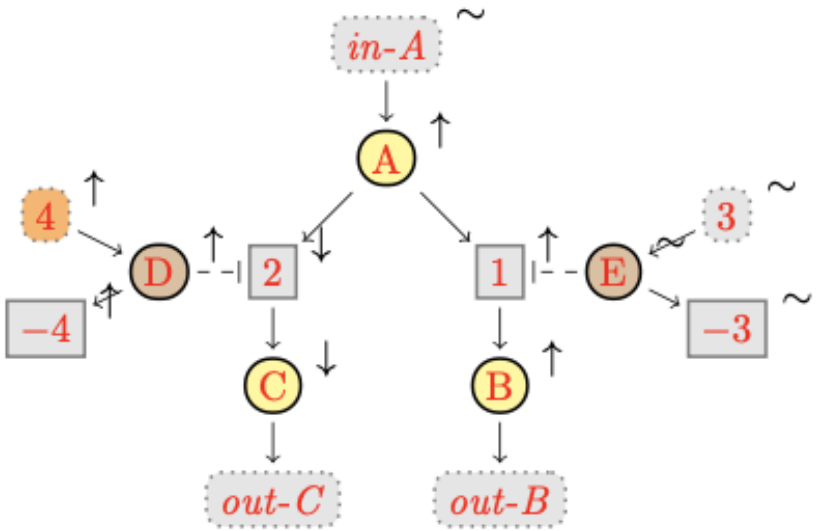

Abstract Interpretation of Algebraic Equations

John's Theorem (2011): Soundness

For each homomorphism $h : A \to B$ between Σ-structures A and B and systems of Σ-equations:

$$h(sol^A(\phi)) \subseteq sol^B(\phi))$$

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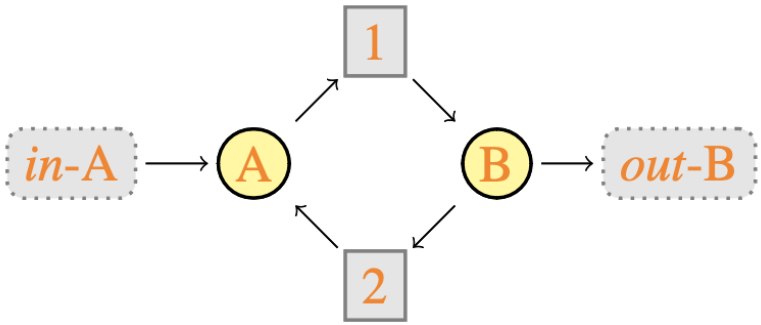
Completeness Conjecture (recent)

Equality holds if ϕ is an acyclic set of equations:

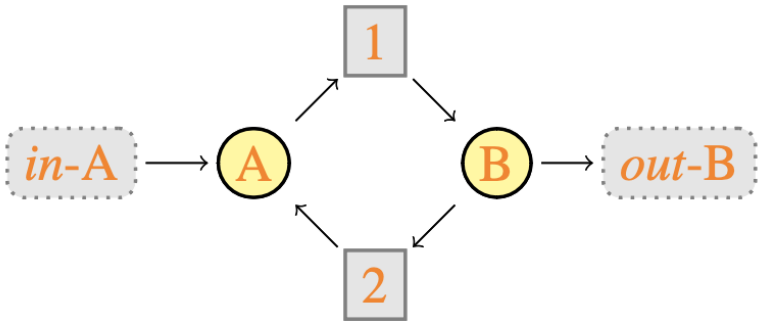
$$h(sol^A(\phi)) = sol^B(\phi))$$

Simple Loop



What happens if one increases *in-A*?

Simple Loop



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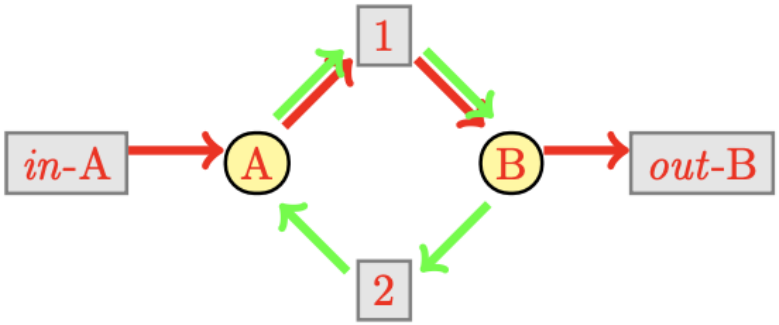
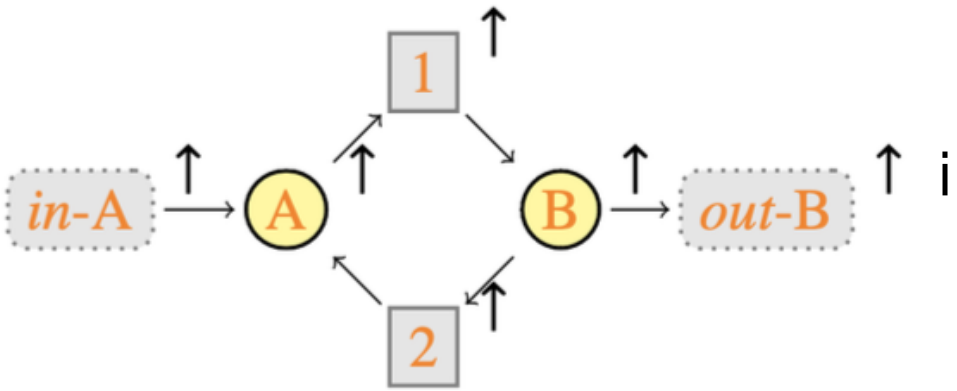
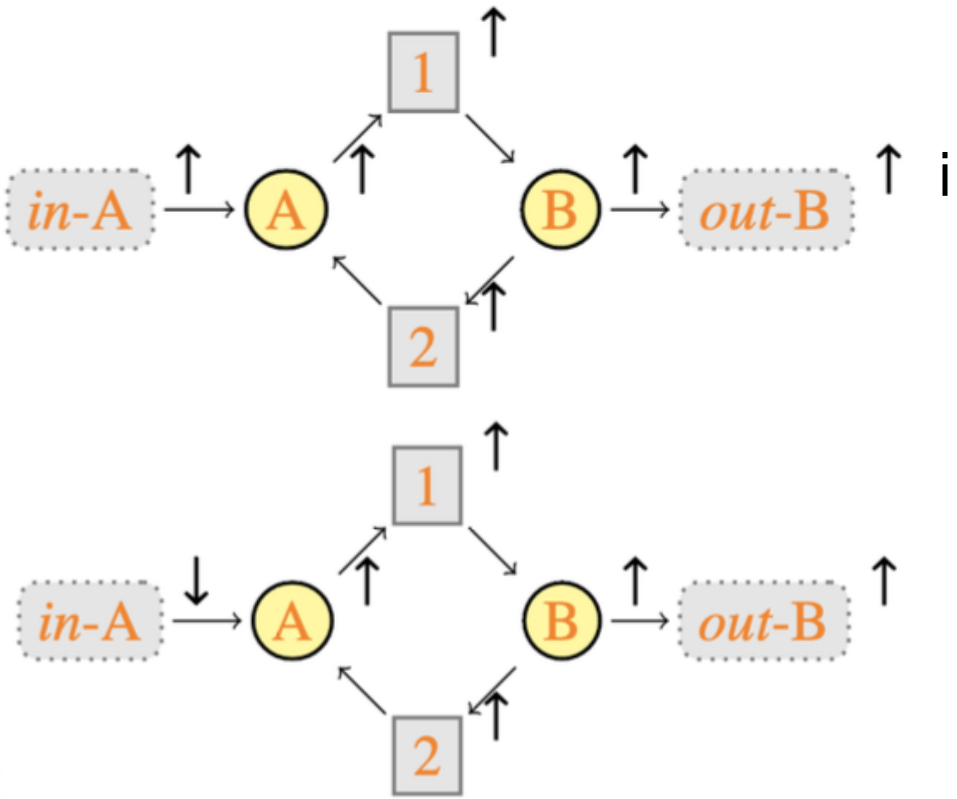


Solutions of Steady State Equations over Δ_3



Abstract interpretation is not complete for the simple loop.

Solutions of Steady State Equations over Δ_3



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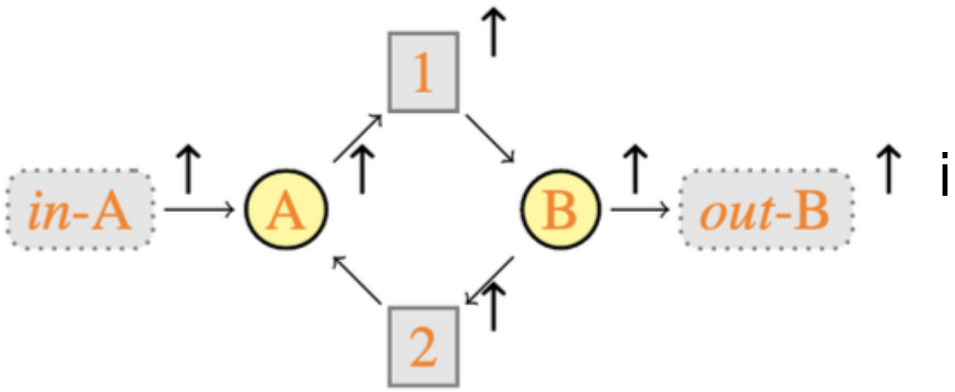
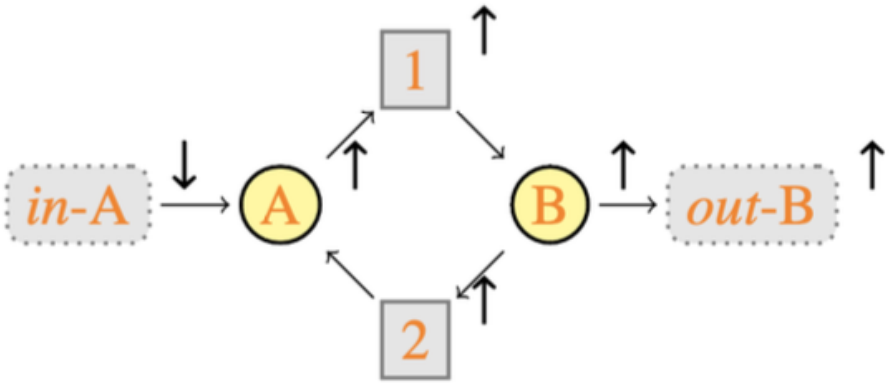
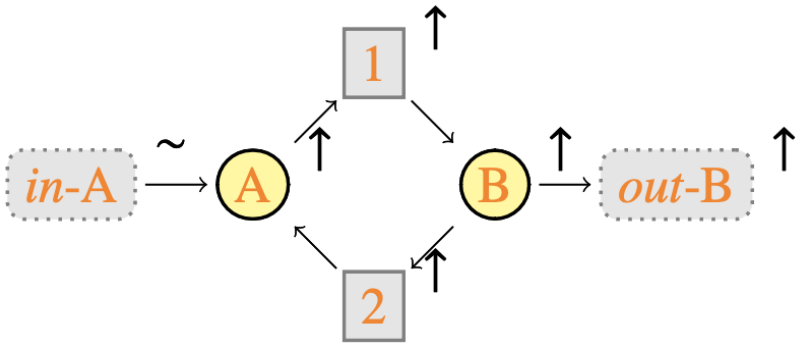
Solutions of Steady State Equations over Δ_3







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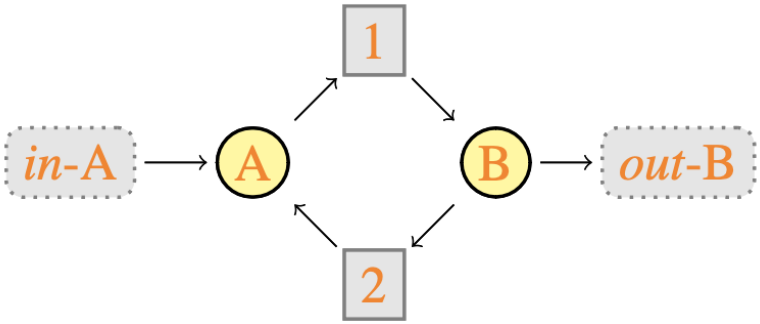
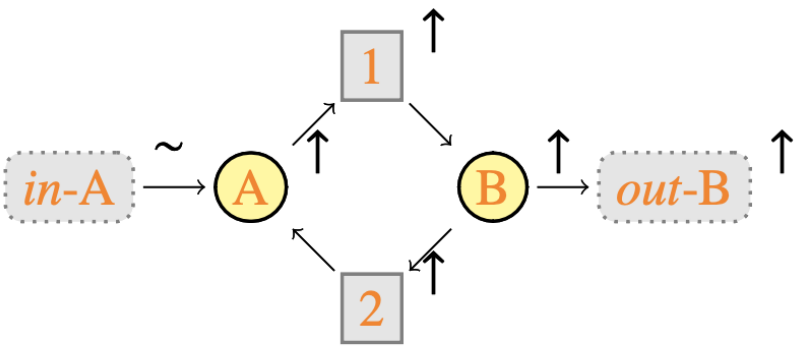


$$in\text{-}A + r_2 = r_1$$
$$r_1 = out\text{-}B + r_2$$
$$\Downarrow$$
$$in\text{-}A = out\text{-}B$$

Logical consequence rules out unjustified abstract solution



How to obtain Completeness

Theorem (Allart, Niehren, Versari 2021)

$h_{diff}(sol^{\mathbb{R}^2_+}(\phi))$ can be computed in at most exponential time for any linear equation system ϕ.

Rewrite linear equation system ϕ based on elementary modes to a linear equation system ϕ' such that:

$$sol^{\Delta_3}(\phi') = h_{diff}(sol^{\mathbb{R}^2_+}(\phi))$$

Then use finite domain constraint programming to compute $sol^{\Delta_3}(\phi')$. In practice based on “libcdd” for elementary modes and “Minizinc” for finite domain constraint programming.

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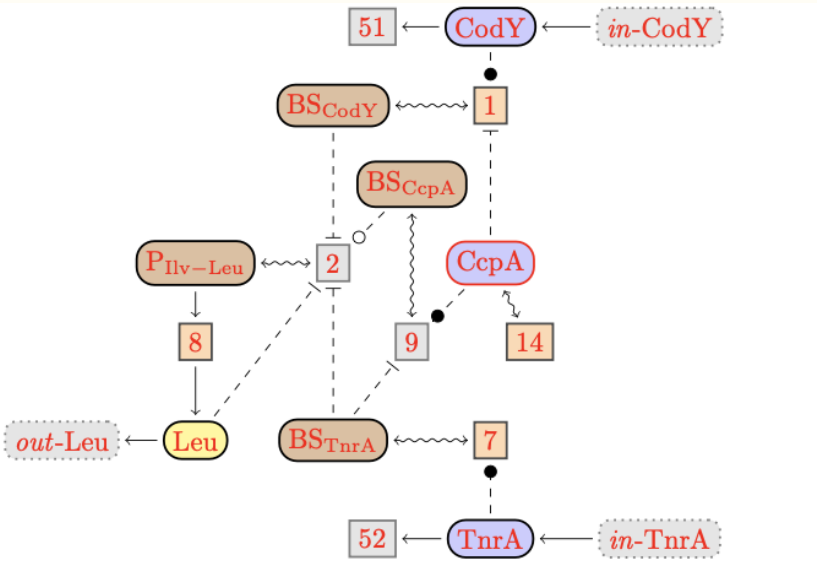
What if we don't know kinetic epxressions?

Partial Kinetic Information

know activator and inhibitor of reactions

Example



Possible Network Changes

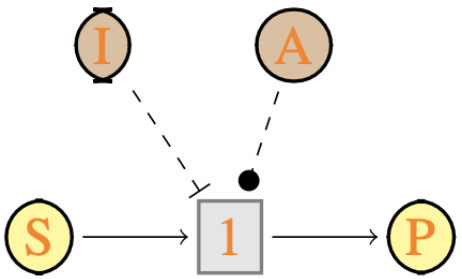
Changes	Application
inflow increase and decreases	change experimental environment or adjacent network
remove reaction	gene knockouts
enhance reaction	gene knockups

Semantics

Idea

Any reaction network with complete kinetic information that justifies inhibors and activators.

Default kinetic expressions



$$e_{default} = S * A * inh(I)$$

where

$$inh(I) = 1/(1 + I)$$

Formally

kinetic expression e of a reaction in completion must be similar to default kinetic expression $e_{default}$ of the reaction in the network with partial kinetic information: $sol^{\Delta_3}(e) = sol^{\Delta_3}(e_{default})$

Change Prediction

Abstract Interpretation

- of steady state equations
- with default kinetic expressions

Algorithmic Techniques

- finite domain constraint programming
- exact rewriting with elementary modes

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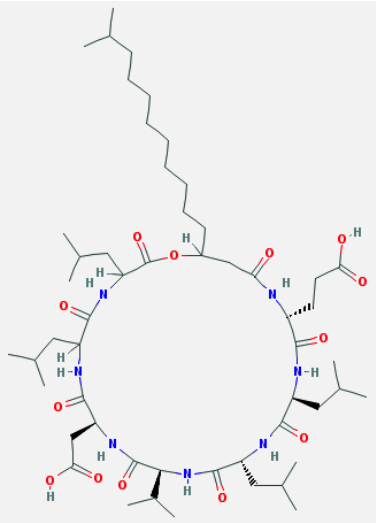
Overproduction of Nonribosomal Peptide by B.Subtilis

Surfactine

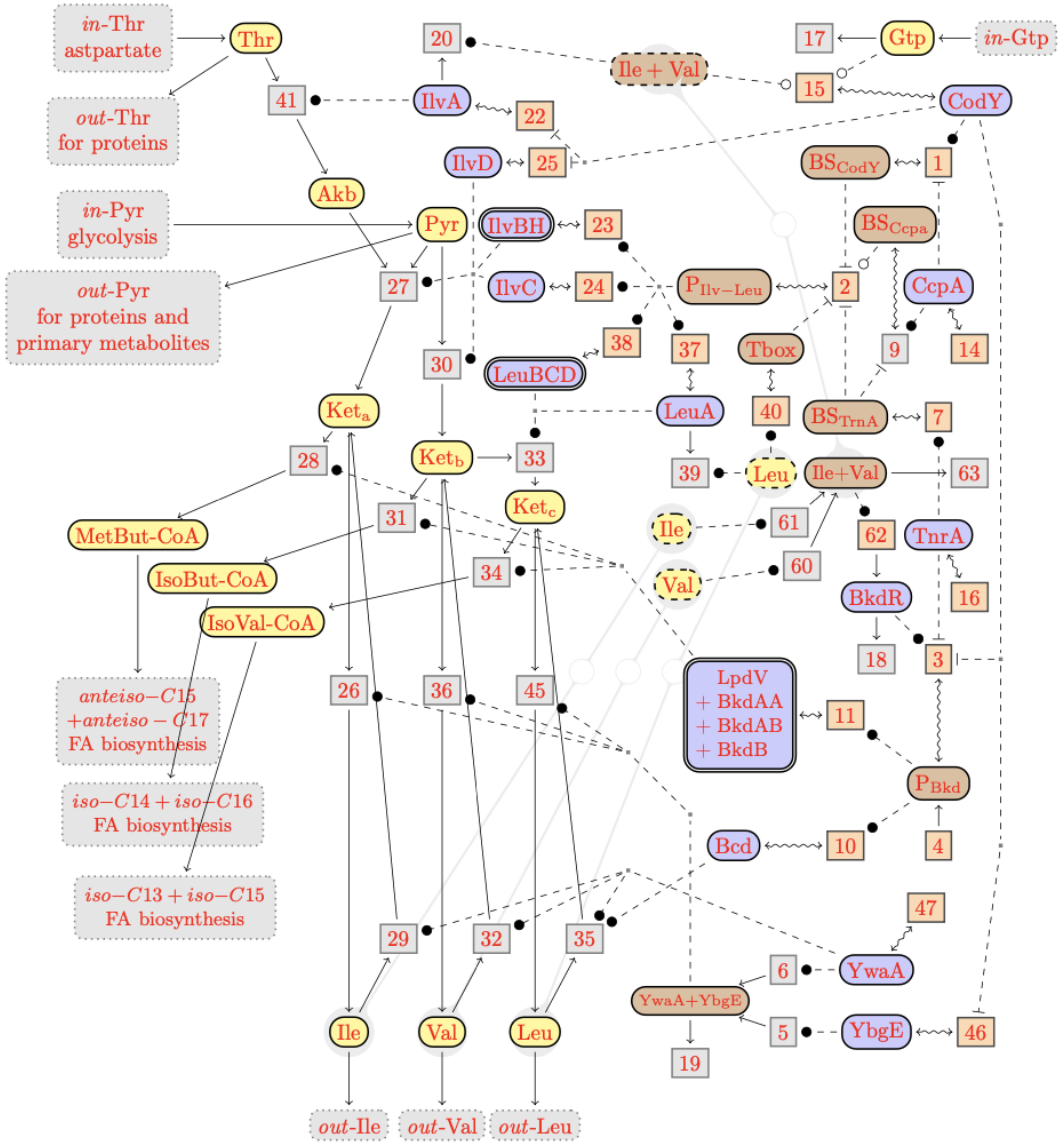
a ring of 7 amino acids of which 4 are leucine



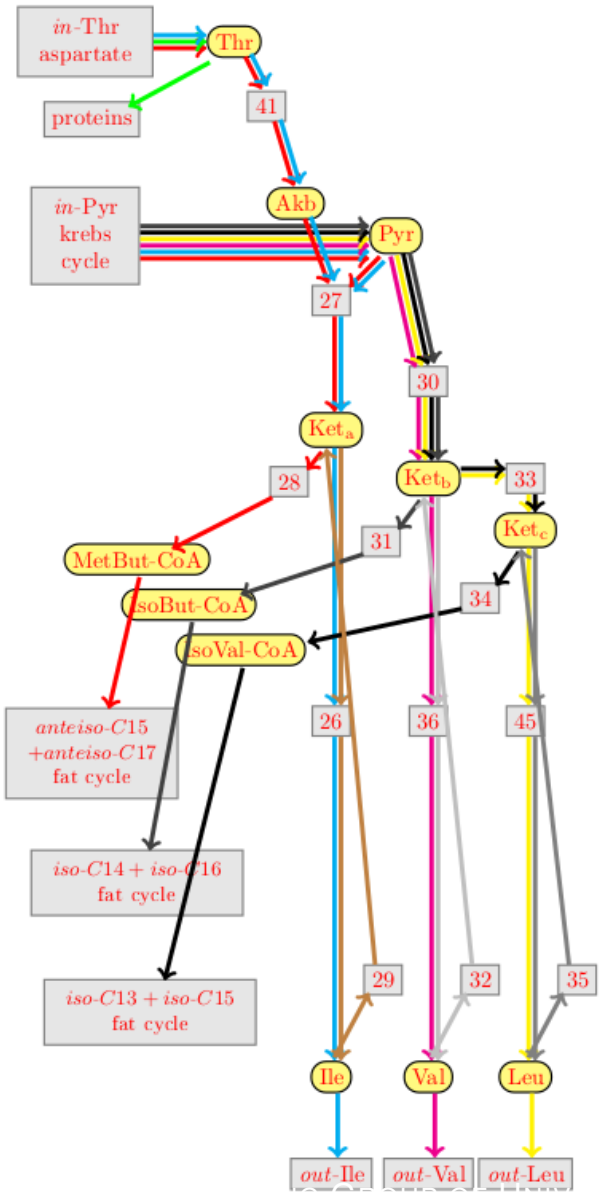
Micosubtilin

same ring of 7 amino acids but with an anteiso-C15 fatty acid chain

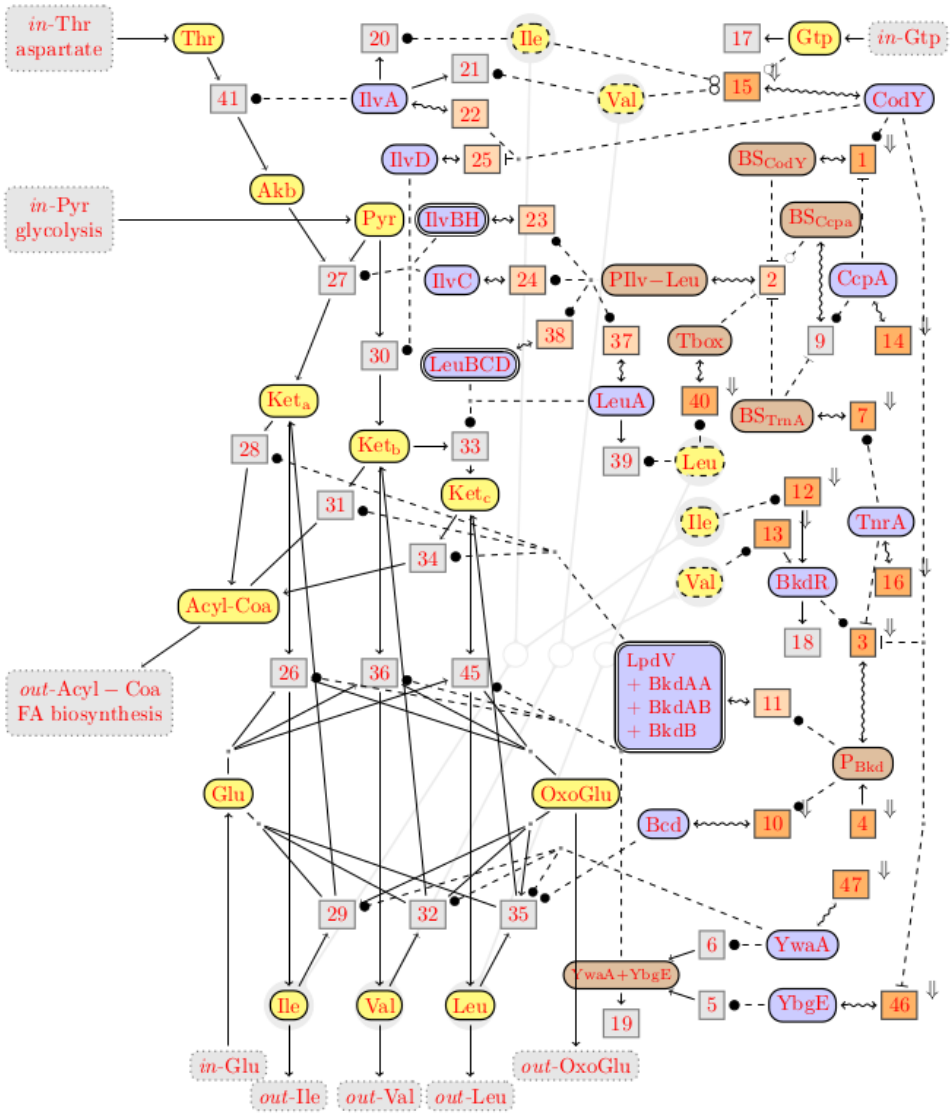
Leucine and Fatty Acids from Threonine and Pyruvate



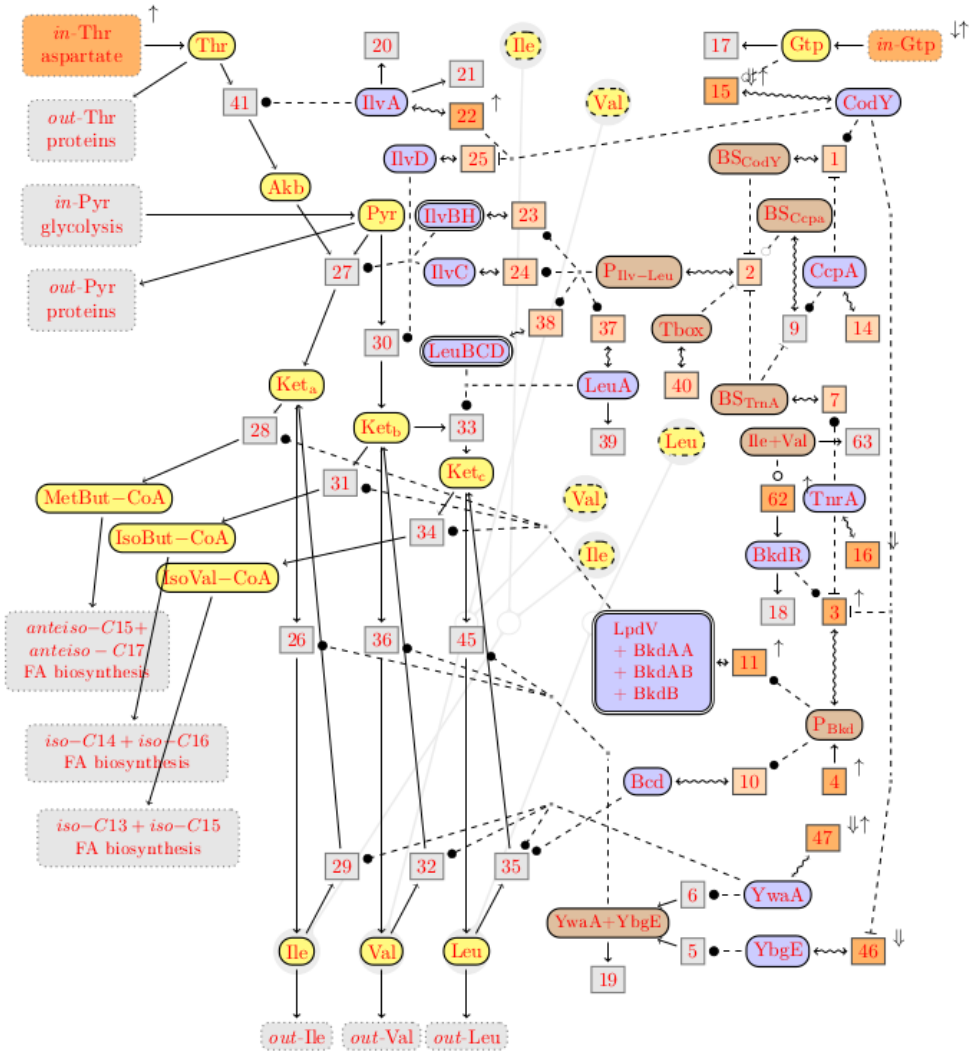
Elementary Flux Modes



Knockout Predictions for Overproducing Leucine



Change Prodictions for Overproducing anteiso-C15



Open Problems

Feedback loops

lead to large overapproximation in case of anteiso-C15
so we removed them even though they are biologically justified
Question: How can we reason properly without changing the model?

Quantitative predictions

How to get to get from qualitative to quantitative predictions?

How to take dynamics into account

not only steady states, but see how the change states the dynamics leading to another steady state.

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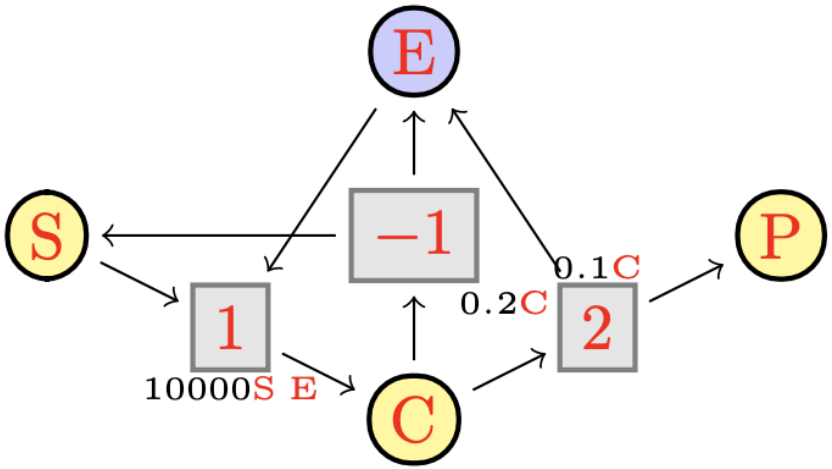
Reconsider Enzymatic Network



Abstract Simulation

Fix threshold $\epsilon > 0$

- X present at time t means: $X(t) > \epsilon$
- X absent at time t means: $X(t) \leq \epsilon$

$\{+, *, \ldots\}$-Structure of Signs $\mathbb{S} = \{0, 1, -1\}$

$-1 *^{\mathbb{S}} -1 = 1, \qquad 1 +^{\mathbb{S}} -1 \in \mathbb{S}$ anything , $\qquad \ldots$

Introduce Booleans and Signs $\mathbb{B} \subseteq \mathbb{S} = \{0, 1, -1\}$

X present $\Rightarrow X = 1$ $\qquad$ X absent $\Rightarrow X = 0$

X increasing $\Rightarrow \mathring{X} = 1$ $\qquad$ X decreasing $\Rightarrow \mathring{X} = -1$

Abstract behavior of $S\mathring{S}ECP\mathring{P}$

$1{-}11001 \rightarrow 1{-}11111 \rightarrow 1{-}10111 \rightarrow 001010$

Abstract Simulation

Does this Depend on Initial Concentrations

No
- only qualitative reasoning
- not quantitative.

How to Compute Abstract Simulation (CMSB 2022)

ideas:
- use abstract interpretation of ODEs over $\mathbb{S}$
- map signs to pairs of booleans
- use exact rewriting of linear equations for boolean abstractions

(Allart, Niehren, Versari 2020)

New Variables for Derivatives + Two Copies of ODEs + Link

$$
\begin{aligned}
&\exists \mathring{\mathrm{S}} \exists \mathring{\mathrm{E}} \exists \mathring{\mathrm{C}} \exists \mathring{\mathrm{P}} \exists \overrightarrow{\mathring{\mathrm{S}}} \exists \overrightarrow{\mathring{\mathrm{E}}} \exists \overrightarrow{\mathring{\mathrm{C}}} \exists \overrightarrow{\mathring{\mathrm{P}}}.\\
&\quad \mathring{\mathrm{S}} \mathrel{\mathring{=}} -r_1 + r_{-1} \qquad \wedge\ \overrightarrow{\mathring{\mathrm{S}}} \mathrel{\mathring{=}} -\overrightarrow{r_1} + \overrightarrow{r_{-1}} \qquad \wedge\ \overrightarrow{\mathrm{S}} \mathrel{\mathring{=}} \mathrm{S} + \mathring{\mathrm{S}} \qquad \wedge\ \mathrm{S} \leq \overrightarrow{\mathrm{S}}\\
&\wedge\ \mathring{\mathrm{E}} \mathrel{\mathring{=}} -r_1 + r_{-1} + r_2 \qquad \wedge\ \overrightarrow{\mathring{\mathrm{E}}} \mathrel{\mathring{=}} -\overrightarrow{r_1} + \overrightarrow{r_{-1}} + \overrightarrow{r_2} \qquad \wedge\ \overrightarrow{\mathrm{E}} \mathrel{\mathring{=}} \mathrm{E} + \mathring{\mathrm{E}} \qquad \wedge\ \mathrm{E} \leq \overrightarrow{\mathrm{E}}\\
&\wedge\ \mathring{\mathrm{C}} \mathrel{\mathring{=}} r_1 - r_{-1} - r_2 \qquad \wedge\ \overrightarrow{\mathring{\mathrm{C}}} \mathrel{\mathring{=}} \overrightarrow{r_1} - \overrightarrow{r_{-1}} - \overrightarrow{r_2} \qquad \wedge\ \overrightarrow{\mathrm{C}} \mathrel{\mathring{=}} \mathrm{C} + \mathring{\mathrm{C}} \qquad \wedge\ \mathrm{C} \leq \overrightarrow{\mathrm{C}}\\
&\wedge\ \mathring{\mathrm{P}} \mathrel{\mathring{=}} r_2 \qquad \wedge\ \overrightarrow{\mathring{\mathrm{P}}} \mathrel{\mathring{=}} \overrightarrow{r_2} \qquad \wedge\ \overrightarrow{\mathrm{P}} \mathrel{\mathring{=}} \mathrm{P} + \mathring{\mathrm{P}} \qquad \wedge\ \mathrm{P} \leq \overrightarrow{\mathrm{P}}\\
&\quad \text{where}\\
&\quad r_1 = 1000000 * \mathrm{S} * \mathrm{E} \qquad r_{-1} = 0.2 * \mathrm{C} \qquad r_2 = 0.1 * \mathrm{C}\\
&\quad \overrightarrow{r_1} = 1000000 * \overrightarrow{\mathrm{S}} * \overrightarrow{\mathrm{E}} \qquad \overrightarrow{r_{-1}} = 0.2 * \overrightarrow{\mathrm{C}} \qquad \overrightarrow{r_2} = 0.1 * \overrightarrow{\mathrm{C}}
\end{aligned}
$$

First-order boolean networks (with nondeterministic updates)

what is relationship to classical boolean networks (with most permissive semantics?)