Integrating prior knowledge in Automatic Network Reconstruction

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Outline

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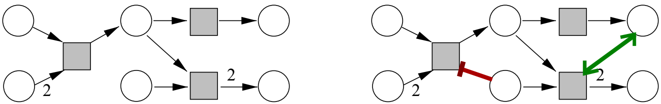
Petri nets: The networks

Standard networks $\mathcal{P} = (P, T, A, w)$

- P set of involved **components** ("places" $\bigcirc$), (molecules, receptors, genes)
- T set of involved **reactions** ("transitions" $\square$), (reactions, activations,...)
- $A \subseteq (P \times T) \cup (T \times P)$ set of directed **links** ("arcs" $\rightarrow$),
- arc weights w as stoichiometric coefficients.



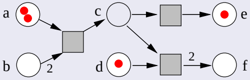
Standard network   Extended network

Extended networks $\mathcal{P} = (P, T, (A \cup A_R \cup A_I), w)$

- $A_R \subset P \times T$ **read-arcs**
- $A_I \subset P \times T$ **inhibitor-arcs**

States

- Each place $p \in P$ can be marked with an integral number $\mathbf{x}_p$ of tokens.
- A **state** can be represented as a vector $\mathbf{x} \in \mathbb{N}^{|P|}$ with entries $\mathbf{x}_p$ for all $p \in P$.



$$x = \begin{pmatrix} 2 \\ 0 \\ 0 \\ 1 \\ 1 \\ 0 \end{pmatrix}$$

Switching transitions

- In a **standard** network, $t \in T$ is **enabled** at a state $\mathbf{x}$ if

  $\mathbf{x}_p \geq w(p,t)$ for all p with $(p,t) \in A$, and

  switching t yiels a new state $\mathbf{x}'$ with $x'_p = x_p + w(p,t)\ \forall (p,t),(t,p) \in A$.
- In an **extended** network, $t \in T$ is **enabled** at a state $\mathbf{x}$ if in addition

  $\mathbf{x}_p \geq w(p,t)$ for all p with $(p,t) \in A_R$, and,
  $\mathbf{x}_p < w(p,t)$ for all p with $(p,t) \in A_I$.

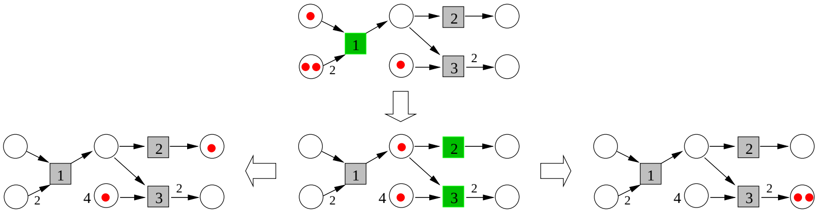
Dynamic processes and reachability

Dynamic processes

Dynamic processes correspond to sequences of system states, obtained by sequences of transition switches.

Starting from an initial state $\mathbf{x}^0$, explore the **dynamic behavior** of the system by

- consecutively switching enabled transitions,
- analyzing the reachability of certain system states.



Can we control transition switches and, thus, the dynamic behavior?

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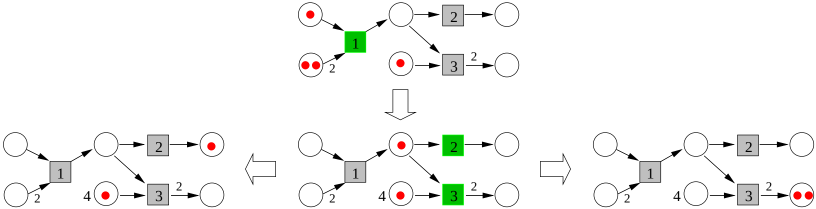

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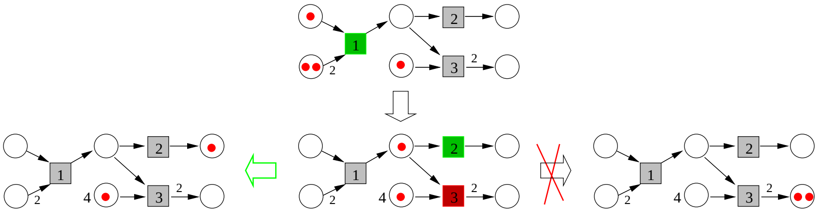
Prediction of the dynamic behavior

Priority relations for transitions (Marwan, W. & Weismantel 2008)

Let G be a network and $\mathcal{O}$ a **priority relation** on its transitions.

- If there are two or more transitions enabled at a state, this transition with **highest priority** will be switched.
- This allows to **predict the dynamic behavior** of the system (instead of listing all potentially possible switching sequences).

Example. Consider the network G with $\mathcal{O} = \{t_2 > t_3\}$.



Outline

The Input

The input $(P, \mathcal{I}_P, \mathcal{X}')$ consists of

- a set P of studied components
- the set $\mathcal{I}_P$ of all known P-invariants
- experimental time-series data $\mathcal{X}' = \{\mathcal{X}'(\mathbf{x}^1, \mathbf{x}^k) : \mathbf{x}^1 \in \mathcal{X}'_{ini}, \mathbf{x}^k \in \mathcal{X}'_{term}\}$ with
  - initial states $\mathcal{X}'_{ini} \subseteq \mathcal{X}'$, terminal states $\mathcal{X}'_{term} \subseteq \mathcal{X}'$
  - time series $\mathcal{X}'(\mathbf{x}^1, \mathbf{x}^k) = (\mathbf{x}^0; \mathbf{x}^1, \ldots, \mathbf{x}^j, \ldots, \mathbf{x}^k)$

Required properties of $\mathcal{X}'$

- **reproducibility:** for each $\mathbf{x}^j \in \mathcal{X}'$ there is a unique observed successor state $\mathrm{succ}_{\mathcal{X}'}(\mathbf{x}^j) = \mathbf{x}^{j+1} \in \mathcal{X}'$
  (can be ensured by pre-processing (W., Wegener 2013))
- **monotonicity:** for each pair $(\mathbf{x}^j, \mathbf{x}^{j+1}) \in \mathcal{X}'$, the values of the elements do not oscillate in the possible intermediate states between $\mathbf{x}^j$ and $\mathbf{x}^{j+1}$
  (depends on the chosen time-points (Durzinsky, W., Weismantel 2008))

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Running example: Input data

Example: Light-induced sporulation of *Physarum polycephalum*

Experimental biological data from Starostzik and Marwan (1995)

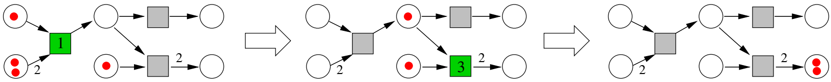
$$
\begin{array}{lll}
P = \{FR, R, P_{FR}, P_R, G, Spo\}, & \mathcal{X}'(\mathbf{x}^1, \mathbf{x}^4) = (\mathbf{x}^0; \mathbf{x}^1, \mathbf{x}^2, \mathbf{x}^3, \mathbf{x}^4), & \mathcal{X}'_{ini} = \{\mathbf{x}^1, \mathbf{x}^5, \mathbf{x}^6\}, \\
\mathcal{I}_P = \{P_{FR}, P_R\}, & \mathcal{X}'(\mathbf{x}^5, \mathbf{x}^0) = (\mathbf{x}^2; \mathbf{x}^5, \mathbf{x}^0), & \mathcal{X}'_{term} = \{\mathbf{x}^4, \mathbf{x}^0, \mathbf{x}^8\} \\
 & \mathcal{X}'(\mathbf{x}^6, \mathbf{x}^8) = (\mathbf{x}^3; \mathbf{x}^6, \mathbf{x}^7, \mathbf{x}^8), &
\end{array}
$$

serve as input for the algorithm, we present all observed states schematically:

$$
\begin{tikzcd}
\overset{\boldsymbol{x}}{\begin{pmatrix} \boldsymbol{x}_{FR} \\ \boldsymbol{x}_{R} \\ \boldsymbol{x}_{P_{FR}} \\ \boldsymbol{x}_{P_R} \\ \boldsymbol{x}_{G} \\ \boldsymbol{x}_{Spo} \end{pmatrix}}
& \overset{\boldsymbol{x}^0}{\begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}} \arrow[r, dashed, "\mathrm{FR}"]
& \overset{\boldsymbol{x}^1}{\begin{pmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}} \arrow[r, "d^1"]
& \overset{\boldsymbol{x}^2}{\begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \end{pmatrix}} \arrow[r, "d^2"] \arrow[d, dashed, "\mathrm{R}"]
& \overset{\boldsymbol{x}^3}{\begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 0 \end{pmatrix}} \arrow[rr, "d^3"] \arrow[d, dashed, "\mathrm{R}"]
& & \overset{\boldsymbol{x}^4}{\begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 1 \end{pmatrix}} \\
& & & \overset{\boldsymbol{x}^5}{\begin{pmatrix} 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \end{pmatrix}} \arrow[ull, bend left, "d^4"]
& \overset{\boldsymbol{x}^6}{\begin{pmatrix} 0 \\ 1 \\ 0 \\ 1 \\ 1 \\ 0 \end{pmatrix}} \arrow[r, "d^5"]
& \overset{\boldsymbol{x}^7}{\begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{pmatrix}} \arrow[r, "d^6"]
& \overset{\boldsymbol{x}^8}{\begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 1 \end{pmatrix}}
\end{tikzcd}
$$

Output: $\mathcal{X}'$-deterministic extended Petri nets with priorities

- Time series $(\mathbf{x}^0, \mathbf{x}^1, \dots, \mathbf{x}^k)$ are sequences of measured system states.
- A network **fits** the given data $\mathcal{X}'$ if it can **reproduce** the observations:



- For given $\mathcal{X}'$, a network $\mathcal{P} = (P, T, (A \cup A_R \cup A_I), w)$ with priorities $\mathcal{O}$ is $\mathcal{X}'$-**deterministic** if it contains and correctly selects transitions to reach, from every observed state $\mathbf{x}^j \in \mathcal{X}'$, its observed successor $\mathbf{x}^{j+1} \in \mathcal{X}'$.

Output

all $\mathcal{X}'$-deterministic extended Petri nets with priorities

Remark: Finding all networks fitting the data means to create all **minimal** ones (that do not reproduce the data anymore after removing any element).

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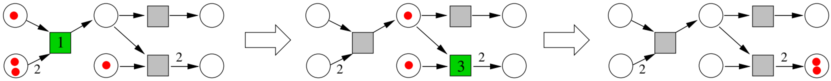

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Step 1: Representation of observed responses

- Time series $(\mathbf{x}^0; \mathbf{x}^1 \ldots, \mathbf{x}^k)$ may not consist of consecutive system states, as between $(\mathbf{x}^j, \mathbf{x}^{j+1}) \in \mathcal{X}'$, there can be **non-observed intermediate states.**
- To reach $\mathbf{x}^{j+1}$ from $\mathbf{x}^j$, we then need a **sequence** of transitions $t_i, \ldots, t_k$ whose update vectors satisfy $\mathbf{x}^{j+1} - \mathbf{x}^j = \mathbf{r}^{t_i} + \ldots + \mathbf{r}^{t_k}$.

Theorem (Durzinsky, W., Weismantel 2008)

To represent the difference $\mathbf{d} = \mathbf{x}^{j+1} - \mathbf{x}^j$, use only sign-compatibel vectors from

$$\text{Box}(\mathbf{d}) = \left\{ \mathbf{r} \in \mathbb{Z}^{|P|} : \begin{array}{rl} 0 \leq r_p \leq d_p & \text{if } d_p > 0 \\ d_p \leq r_p \leq 0 & \text{if } d_p < 0 \\ r_p = 0 & \text{if } d_p = 0 \\ \sum_{p \in P'} r_p = 0 & \forall P' \in \mathcal{I}_P \end{array} \right\} \setminus \{0\}.$$

For each $\mathbf{d} = \mathbf{x}^{j+1} - \mathbf{x}^j$, determine all solutions $\boldsymbol{\lambda} \in \Lambda(\mathbf{d})$ with

$$\mathbf{d} = \sum_{\mathbf{r}^t \in Box(\mathbf{d})} \lambda_t \, \mathbf{r}^t, \ \lambda_t \in \mathbb{Z}_+$$

and let $\mathcal{R}(\mathbf{d}, \boldsymbol{\lambda}) = \{\mathbf{r}^t \in \text{Box}(\mathbf{d}) : \lambda_t \neq 0\}$ be the set of used update vectors.

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Step 1: Representation of observed responses (cont.)

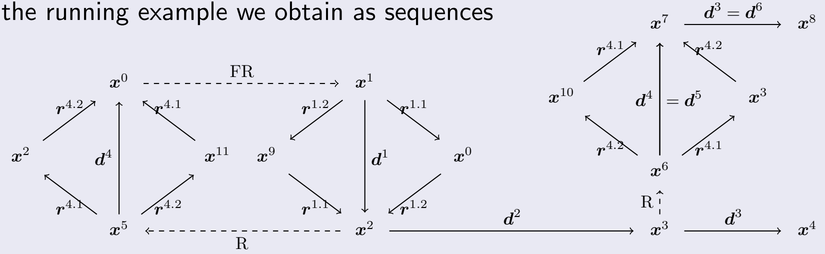
- Every permutation $\pi = (\mathbf{r}^{t_1}, \ldots, \mathbf{r}^{t_m})$ of the elements of a set $\mathcal{R}(\mathbf{d}^j, \boldsymbol{\lambda})$ yields a sequence of intermediate states $\mathbf{x}^j = \mathbf{y}^1, \mathbf{y}^2, ..., \mathbf{y}^m, \mathbf{y}^{m+1} = \mathbf{x}^{j+1}$ with

$$\sigma_{\pi,\boldsymbol{\lambda}}(\mathbf{x}^j, \mathbf{d}^j) = \left((\mathbf{y}^1, \mathbf{r}^{t_1}), (\mathbf{y}^2, \mathbf{r}^{t_2}), \ldots, (\mathbf{y}^m, \mathbf{r}^{t_m})\right).$$

- Every sequence σ respects monotonicity and induces a priority relation $\mathcal{O}_\sigma$.

Example

For the running example we obtain as sequences



with $\mathbf{x}^9 = (1,0,0,1,0,0)^T$, $\mathbf{x}^{10} = (0,1,1,0,1,0)^T$ and $\mathbf{x}^{11} = (0,1,1,0,0,0)^T$.

Step 2: Detecting priority conflicts between sequences

Sequences and their conflicts

Sequences σ and σ' are in **priority conflict** if there are update vectors $\mathbf{r}^t \neq \mathbf{r}^{t'}$ and intermediate states $\mathbf{y}, \mathbf{y}'$ such that both t, t' are enabled at $\mathbf{y}, \mathbf{y}'$ but $(\mathbf{y}, \mathbf{r}^t) \in \sigma$ and $(\mathbf{y}', \mathbf{r}^{t'}) \in \sigma'$ (since this implies $t > t'$ in $\mathcal{O}_\sigma$ but $t' > t$ in $\mathcal{O}_{\sigma'}$).

weak priority conflict (WPC)

if $\mathbf{y} \neq \mathbf{y}'$, the priority conflict **can** be resolved by adding appropriate control-arcs

strong priority conflict (SPC)

if $\mathbf{y} = \mathbf{y}'$, the priority conflict **cannot** be resolved by adding appropriate control-arcs

Note: we have a SPC between the trivial sequence $\sigma(\mathbf{x}^k, \mathbf{0})$ for any terminal state $\mathbf{x}^k$ and any sequence σ containing $\mathbf{x}^k$ as intermediate state.

Example: $\sigma_{\pi_1,\lambda^2}(\mathbf{x}^1, \mathbf{d}^1) = ((\mathbf{x}^1, \mathbf{r}^{1.1}), (\mathbf{x}^0, \mathbf{r}^{1.2}))$ and $\sigma(\mathbf{x}^0, \mathbf{0})$ are in SPC.

Task: select one sequence per $\mathbf{d}^j$ s.t. no SPCs occur between them.

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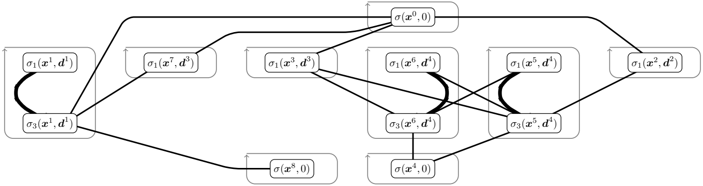
Priority conflict graph $\mathcal{G} = (V_D \cup V_{term}, E_D \cup E_W \cup E_S)$

the nodes correspond to sequences:

- V_D: the sequence $\sigma_{\pi,\boldsymbol{\lambda}}(\mathbf{x}^j, \mathbf{d}^j)$ for all permutations π of $\mathcal{R}(\mathbf{d}^j, \boldsymbol{\lambda})$
- V_{term}: the trivial sequence $\sigma(\mathbf{x}^k, \mathbf{0})$ for all terminal states $\mathbf{x}^k$

the edges correspond to their priority conflicts:

- E_D: all SPCs between two sequences σ, σ' from the same difference vector
- E_S: all SPCs between sequences σ, σ' from distinct difference vectors
- E_W: all WPCs between sequences σ, σ' from distinct difference vectors



In $\mathcal{G}$, there are 8 possible selections S avoiding SPCs.

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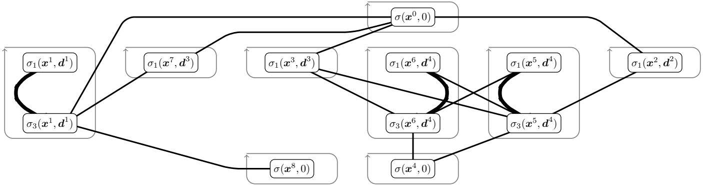

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Step 3: Constructing $\mathcal{X}'$-deterministic Petri nets

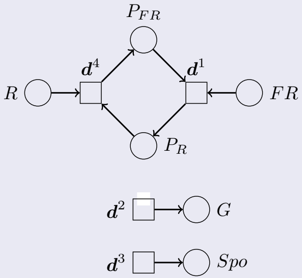
Composition of standard networks

For every selected set S, we obtain a standard network $\mathcal{P}_S$ by deriving transitions from the update vectors in the sets $\mathcal{R}(\mathbf{d}^j, \boldsymbol{\lambda})$ of the selected sequences $\sigma \in S$.

Example

In solution S_1 selecting all canonical sequences $\sigma_1(\mathbf{x}^j, \mathbf{d}^j)$, there are three WPCs:

- between $\sigma_1(\mathbf{x}^2, \mathbf{d}^2)$ and $\sigma(\mathbf{x}^0, \mathbf{0})$ since $\mathbf{d}^2, \mathbf{0}$ are enabled at $\mathbf{x}^2, \mathbf{x}^0$
- between $\sigma_1(\mathbf{x}^3, \mathbf{d}^3)$ and $\sigma(\mathbf{x}^0, \mathbf{0})$ since $\mathbf{d}^3, \mathbf{0}$ are enabled at $\mathbf{x}^3, \mathbf{x}^0$
- between $\sigma_1(\mathbf{x}^7, \mathbf{d}^3)$ and $\sigma(\mathbf{x}^0, \mathbf{0})$ since $\mathbf{d}^3, \mathbf{0}$ are enabled at $\mathbf{x}^7, \mathbf{x}^0$



Step 3: Constructing $\mathcal{X}'$-deterministic Petri nets (cont.)

A WPC(σ, σ') due to $(\mathbf{y}, \mathbf{r}^t) \in \sigma$ and $(\mathbf{y}', \mathbf{r}^{t'}) \in \sigma'$ can be **resolved** by

- either disabling t at state $\mathbf{y}'$ (and adding priority $t > t'$),
- or disabling t' at state $\mathbf{y}$ (and adding priority $t < t'$).

This can be done by inserting control-arcs from CA(σ, σ') which partitions into a subset $\text{CA}_{t>t'}(\sigma, \sigma')$ containing

- a read-arc (p, t) with weight $w(p, t) > y'_p$ for all p with $y_p > y'_p$,
- an inhibitor-arc (p, t) with $w(p, t) < y_p$ for all p with $y_p < y'_p$,

and a subset $\text{CA}_{t<t'}(\sigma, \sigma')$ defined analogously.

Remark: If one of $\mathbf{y}, \mathbf{y}'$ is a terminal state, say $\mathbf{y}'$, one of the alternatives is not possible, then t has to be disabled at $\mathbf{y}'$ and $t > t' = \mathbf{0}$ holds automatically.

- Inserting one control-arc from each CA(σ, σ') resolves all WPCs.
- The obtained extended Petri nets can be made $\mathcal{X}'$-deterministic by adding the requested priorities $t > t'$ or $t < t'$.

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This can be done by inserting control-arcs from CA(σ, σ') which partitions into a subset CA$_{t>t'}(\sigma, \sigma')$ containing

- a read-arc (p, t) with weight $w(p, t) > y'_p$ for all p with $y_p > y'_p$,
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and a subset CA$_{t<t'}(\sigma, \sigma')$ defined analogously.

Remark: If one of $\mathbf{y}, \mathbf{y}'$ is a terminal state, say $\mathbf{y}'$, one of the alternatives is not possible, then t has to be disabled at $\mathbf{y}'$ and $t > t' = \mathbf{0}$ holds automatically.

- Inserting one control-arc from each CA(σ, σ') resolves all WPCs.
- The obtained extended Petri nets can be made $\mathcal{X}'$-deterministic by adding the requested priorities $t > t'$ or $t < t'$.

Step 3: Constructing $\mathcal{X}'$-deterministic Petri nets (cont.)

A WPC(σ, σ') due to $(\mathbf{y}, \mathbf{r}^t) \in \sigma$ and $(\mathbf{y}', \mathbf{r}^{t'}) \in \sigma'$ can be **resolved** by

- either disabling t at state $\mathbf{y}'$ (and adding priority $t > t'$),
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Outline

Inserting minimal sets of control-arcs

In a standard network $\mathcal{P}_S$, we have to add control-arcs that resolve all WPCs:

- Hereby, inserting one control-arc from CA(σ, σ') resolves WPC(σ, σ'), but possibly also another WPC in $\mathcal{P}_S$.
- Let $\mathcal{A}_S$ be the union of all the control-arcs from the sets CA(σ, σ') for all WPC(σ, σ') in $\mathcal{P}_S$.
- To resolve the WPCs in $\mathcal{P}_S$, we have to find subsets A' of $\mathcal{A}_S$ **hitting** each CA(σ, σ').
- Non-minimal hitting sets yield extended Peri nets with unnecessary control-arcs and, thus, being not minimal.

Theorem

All **minimal** extended Petri nets based on $\mathcal{P}_S$ can be obtained by computing all **minimal** hitting sets in $\mathcal{A}_S$.

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All **minimal** extended Petri nets based on $\mathcal{P}_S$ can be obtained by computing all **minimal** hitting sets in $\mathcal{A}_S$.

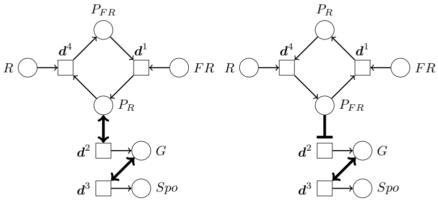
Inserting minimal sets of control-arcs: Example

Example

For the standard network $\mathcal{P}_{S_1}$ with $T_1 = \{\mathbf{d}^1, \mathbf{d}^2, \mathbf{d}^3 = \mathbf{d}^6, \mathbf{d}^4 = \mathbf{d}^5\}$, we have:

	$(P_{FR},\mathbf{d}^2) \in A_I$	$(P_R,\mathbf{d}^2) \in A_R$	$(P_{FR},\mathbf{d}^3) \in A_I$	$(P_R,\mathbf{d}^3) \in A_R$	$(G,\mathbf{d}^3) \in A_R$
WPC1	x	x			
WPC2			x	x	x
WPC3					x

Two minimal hitting sets result in two **minimal** extended Petri nets based on $\mathcal{P}_{S_1}$:



The total number of **minimal** $\mathcal{X}'$-deterministic extended Petri nets is 66.

Outline

Indecomposability of difference vectors

In Step 1 *Representing the observed responses*, the set $\mathrm{Box}(\mathbf{d}^j)$ of update vectors to refine the sequence between $(\mathbf{x}^j, \mathbf{x}^{j+1}) \in \mathcal{X}'$ can be restricted if

- $\mathbf{d}^j$ exactly corresponds to a well-known biochemical reaction (including the correct stoichiometry) or to a well-known mechanism (that a certain trigger is detected by a suitable receptor),
- experiments have shown that subsets of the input components of $\mathbf{d}^j$ do not lead to the observed response,
- $\mathbf{d}^j$ is treated as black box-like reaction where only input and output matter, but not the intermediate mechanism due to the chosen level of detail.

Indecomposability of difference vectors

Exclude the corresponding response $\mathbf{d}^j \in \mathcal{D}$ from decomposition, just define:

$$\mathrm{Box}(\mathbf{d}^j) := \{\mathbf{d}^j\}$$

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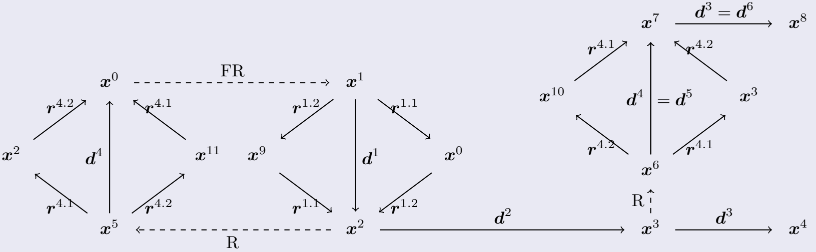
Indecomposability of difference vectors: Example

Example

Since the light-dependent reactions of the photoreceptor are so much faster than the subsequent processes, the difference vectors $\mathbf{d}^1$, $\mathbf{d}^4$ and $\mathbf{d}^5$ describing the photoconversions will not be decomposed due to the chosen level of detail.



Thus, only solutions based on $\mathcal{P}_{S_1}$ with $T_1 = \{\mathbf{d}^1, \mathbf{d}^2, \mathbf{d}^3 = \mathbf{d}^6, \mathbf{d}^4 = \mathbf{d}^5\}$ remain. Accordingly, the total number of solutions reduces from 66 to 2.

Treating equal difference vectors in the same way

If two difference vectors $\mathbf{d}^i, \mathbf{d}^j \in \mathcal{D}$ are equal, we have $\text{Box}(\mathbf{d}^i) = \text{Box}(\mathbf{d}^j)$ and $\Lambda(\mathbf{d}^i) = \Lambda(\mathbf{d}^j)$. In Step 2 *Detecting priority conflicts between sequences*, it is natural to require that $\mathbf{d}^i = \mathbf{d}^j$ are decomposed in the same way: using the same

- $\lambda \in \Lambda(\mathbf{d}^i) = \Lambda(\mathbf{d}^j)$ means that the same subset of molecules involved in a reaction will not interact according to different mechanisms,
- permutation π of the elements in $\mathcal{R}(\mathbf{d}^i, \lambda) = \mathcal{R}(\mathbf{d}^j, \lambda)$ means that the order in which the reactions are applied reflects the relative rates of the reactions in $\mathcal{R}(\mathbf{d}^i, \lambda) = \mathcal{R}(\mathbf{d}^j, \lambda)$, which leads to the same priorities within the resulting sequences.

We call $\sigma_{\pi,\boldsymbol{\lambda}}(\mathbf{x}^i, \mathbf{d}^i)$ and $\sigma'_{\pi,\boldsymbol{\lambda}}(\mathbf{x}^j, \mathbf{d}^j)$ **twin sequences** if $\mathbf{d}^i = \mathbf{d}^j$ and the same $\boldsymbol{\lambda}$, π has been used.

Treating equal difference vectors in the same way

Force that twin sequences are always selected together by adding strong priority conflicts in $\mathcal{G}$ between all other sequences stemming from a pair $\mathbf{d}^i = \mathbf{d}^j \in \mathcal{D}$.

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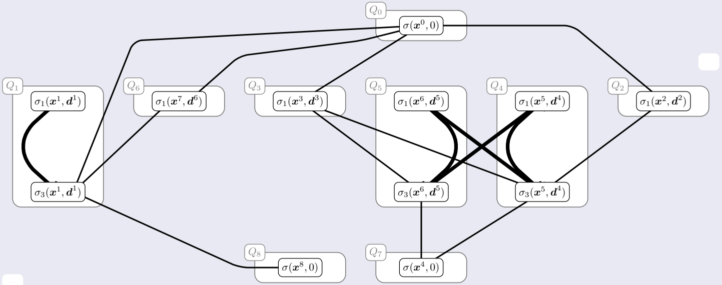
Treating equal difference vectors in the same way: Example

Example

In our running example, we have $\mathbf{d}^3 = \mathbf{d}^6$ and $\mathbf{d}^4 = \mathbf{d}^5$. The latter vectors can be decomposed in different ways, among the resulting sequences we have $\sigma_1(\mathbf{x}^5, \mathbf{d}^4)$, $\sigma_1(\mathbf{x}^6, \mathbf{d}^5)$ and $\sigma_3(\mathbf{x}^5, \mathbf{d}^4)$, $\sigma_3(\mathbf{x}^6, \mathbf{d}^5)$ as pairs of twin sequences.



Forcing to select these pairs together rules out 4 of the previously possible 8 selections. Accordingly, the total number of solutions reduces from 66 to 18.

Integrating knowledge on relative reaction rates

In Step 3 *Constructing $\mathcal{X}'$-deterministic Petri nets*, to resolve a WPC(σ, σ') between σ, σ' involving update vectors $\mathbf{r}^t \neq \mathbf{r}^{t'}$ and intermediate states $\mathbf{y} \neq \mathbf{y}'$, either transition t has to be disabled at $\mathbf{y}'$ or transition t' at $\mathbf{y}$, while the decision between t and t' on the other state can be handled by a priority.

Prior knowledge about the **relative reaction rates** of t and t' can help to decide whether $t > t'$ or $t < t'$ better reflects the reality:

Integrating knowledge on relative reaction rates

- If $\mathbf{y}'$ is a **terminal state** and $\sigma' = \sigma(\mathbf{y}', \mathbf{0})$ its trivial sequence, then $t > \mathbf{0}$ holds automatically at $\mathbf{y}$, but t has to be disabled at $\mathbf{y}'$ using control-arcs from CA$_{t>\mathbf{0}}(\sigma, \sigma')$ whereas CA$_{t<\mathbf{0}}(\sigma, \sigma')$ is empty.
- For a WPC(σ, σ') where the **time-scale** of the corresponding experimental observations clearly differs, deduce the correct priority $t > t'$ or $t < t'$ and reduce CA(σ, σ') accordingly either to CA$_{t>t'}(\sigma, \sigma')$ or to CA$_{t'>t}(\sigma, \sigma')$.

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- For a WPC(σ, σ') where the **time-scale** of the corresponding experimental observations clearly differs, deduce the correct priority $t > t'$ or $t < t'$ and reduce $\mathrm{CA}(\sigma, \sigma')$ accordingly either to $\mathrm{CA}_{t>t'}(\sigma, \sigma')$ or to $\mathrm{CA}_{t'>t}(\sigma, \sigma')$.

Integrating knowledge on relative reaction rates: Example

Example

In our running example, we have different time-scales for the experimental observations as

- $\mathbf{d}^1$ and $\mathbf{d}^4 = \mathbf{d}^5$ need only milliseconds to occur,
- $\mathbf{d}^2$ needs about 1 hour to occur, and
- $\mathbf{d}^3 = \mathbf{d}^6$ need at least 10 hours

which implies $\mathbf{d}^1, \mathbf{d}^4, \mathbf{d}^5 > \mathbf{d}^2 > \mathbf{d}^3, \mathbf{d}^6$.

Consequently, we can reduce the sets $\mathsf{CA}(\sigma, \sigma')$ of four WPCs as follows:

- for WPC4 between $\sigma_3(\mathbf{x}^1, \mathbf{d}^1)$, $\sigma(\mathbf{x}^7, \mathbf{d}^3)$ to $\mathsf{CA}_{\mathbf{r}^{1.2} > \mathbf{d}^3}(\mathsf{WPC4})$;
- for WPC7 between $\sigma_3(\mathbf{x}^5, \mathbf{d}^4)$, $\sigma(\mathbf{x}^2, \mathbf{d}^2)$ to $\mathsf{CA}_{\mathbf{r}^{4.2} > \mathbf{d}^2}(\mathsf{WPC7})$;
- for WPC8 between $\sigma_3(\mathbf{x}^5, \mathbf{d}^4)$, $\sigma(\mathbf{x}^3, \mathbf{d}^3)$ to $\mathsf{CA}_{\mathbf{r}^{4.2} > \mathbf{d}^3}(\mathsf{WPC8})$;
- for WPC9 between $\sigma_3(\mathbf{x}^6, \mathbf{d}^4)$, $\sigma(\mathbf{x}^3, \mathbf{d}^3)$ to $\mathsf{CA}_{\mathbf{r}^{4.2} > \mathbf{d}^3}(\mathsf{WPC9})$.

Accordingly, the number of solutions decreases from 66 to 36.

Outline

Summary and Conclusions

- ANR aims at reconstructing **all** $\mathcal{X}'$-deterministic extended Petri nets that fit given experimental data $\mathcal{X}'$ which typically results in large solution sets.
- To keep this solution set reasonably small while still guaranteeing its completeness, we firstly generate only **minimal** solutions.
- To integrate **prior knowledge** in the reconstruction procedure to make the "right decisions" in some intermediate steps, we extend the input from $(P, I_P, \mathcal{X}')$ to $(P, I_P, \mathcal{X}', \mathcal{D}_{in}, \mathcal{D}_{eq}, \mathcal{O}_D)$ where
  - $\mathcal{D}_{in}$ contains all indecomposable difference vectors;
  - $\mathcal{D}_{eq}$ contains all pairs of equal difference vectors to be treated in the same way;
  - $\mathcal{O}_D$ contains relative reaction rates between difference vectors;

  which results in substantial reductions of solution alternatives.

Impact of ANR

Models computed by an exact reconstruction approach have predictive ability due to the **completeness** of the solution set guaranteed by mathematical **proofs**.

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