A compact modeling approach for deterministic biological systems

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Brussels, June 22nd

Modeling phenomena in cellular networks

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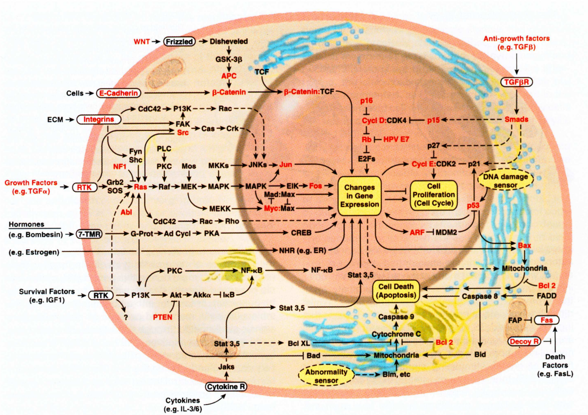

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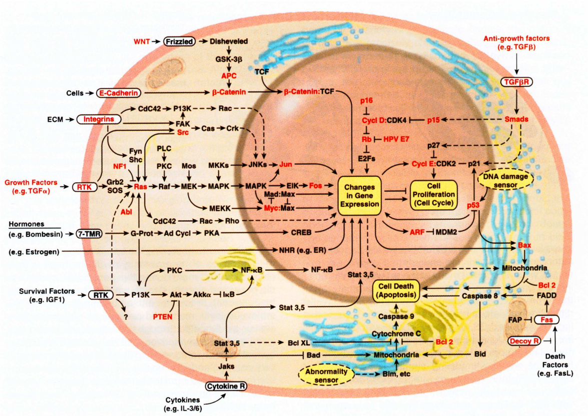

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Adequate models for the structure and dynamics of biological systems?

Modeling phenomena in cellular networks

Systems biology aims at the integrated experimental and theoretical analysis of cellular networks

- network inference
  reconstructing interaction networks of biological entities
- network analysis
  mining the information content of the network
- dynamic modeling
  connecting interaction network and dynamic behaviour

Application areas

- study biological processes "in silico"
  - response of cells/organs/organisms to environmental changes
  - immune responses to virus infection
  - effects of gene defects
  - internal activities of a cell: proliferation, differentiation, motility
- identify good conditions for growth
- design intervention strategies (pharmaceutical)

Outline

- Introduction
  - Petri Nets
  - Applications and limitations
- Modeling deterministic systems
  - The transition conflict graph
  - Valid orientations
- Model reconstruction from experimental data
  - Partial orientations and the MVTP
  - The Optimal Test Set Extension Problem
- Summary

Outline

Petri nets

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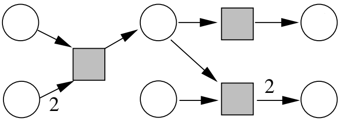
The network is modeled as a weighted bipartite digraph $G = (N \cup T, A, w)$ with

- $N = \{1, \ldots, n\}$ places (e.g. metabolites ◯)
- $T = \{1, \ldots, \tau\}$ transitions (e.g. reactions □)
- arc weights $\rightsquigarrow$ stoichiometric coefficients

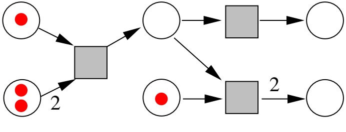
The network can be represented through its incidence matrix $M \in \mathbb{Z}^{n \times \tau}$:



$$M = \begin{pmatrix} -1 & 0 & 0 \\ -2 & 0 & 0 \\ 1 & -1 & -1 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \\ 0 & 0 & 2 \end{pmatrix}$$

Petri nets: dynamics

- states of the system are modeled through assignments of tokens to places [“markings”]
- some places may have bounded capacities



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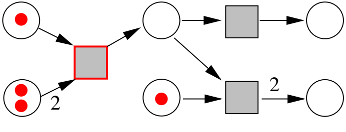

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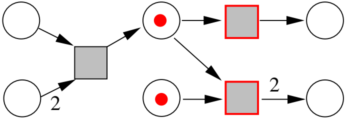

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The state digraph

- the potential space state is given by:

$$\mathcal{X} := \{x \in \mathbb{Z}^n : 0 \leq x_p \leq u_p, \forall p \in N_B\}$$

- the state digraph $\mathcal{G} = (\mathcal{X}, \mathcal{A})$ contains arcs $(x, y) \in \mathcal{A}$ for all y obtained from x by firing one single transition

- dynamic processes are modeled as sequences of transition fires starting from an initial state x^0:
  - movement of tokens in G
  - paths in reachability (marking) digraph $\mathcal{G}(x^0)$

Some central problems

- Reachability:
  Can the system reach one of a set of target states starting from an initial state x^0?
- Boundedness:
  Are there sequences of transition fires that lead to unlimited token accumulation at some place?
- Existence of deadlocks:
  Can the system reach a state at which no transitions are enabled?
- Liveness:
  Is it (im)possible to reach a state where some transition is permanently disabled?

Outline

Application fields

Petri nets have been widely used to model several kinds of dynamic systems

- asynchronous hardware circuits
  [Yakovlev, Koelmans, Semenov & Kinniment 1996]
- production and workflow systems
  [Adam, Atluri & Huang 1998]
- batch processes
  [Gu & Bahri 2002]
- distributed algorithms
  [Reisig 1998]
- biological networks
  [Hardy & Robillard 2004; Chaouiya, Remy & Thieffry 2008]

Petri Nets for cellular networks

Some (non-exhaustive) references:

- Blätke MA, Heiner M, Marwan W (2015) *BioModel Engineering with Petri Nets.* In: Algebraic and Discrete Mathematical Methods for Modern Biology. Elsevier
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Limitations

- Petri Nets are well-suited for studying concurrent systems
- reachability graph $\mathcal{G}(x^0)$ provides local point of view

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- for biological systems a model aiming at a global understanding of the (inferred) network is pursued
- $\mathcal{G}$ is not adequate for encoding dynamic behaviors: exponential on the size of the Petri Net
- some biological systems are deterministic:
  each state x has a unique successor x^+, even if several transitions are enabled

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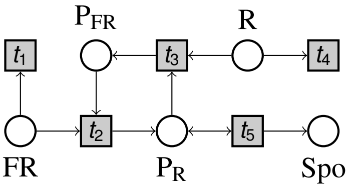
Challenge:

Find a compact adequate way to encode system dynamics!!

Example

Light-induced sporulation of *Physarum polycephalum*

- entering the sporulation pathway is controlled by environmental factors like visible light
- a photoreversible photoreceptor occurs in two conformational states P_{FR} and P_R
- P_{FR} + far-red light $FR \rightsquigarrow$ converted into P_R, causes sporulation
- P_R + red light $R \rightsquigarrow$ converted back to P_{FR}, prevents sporulation



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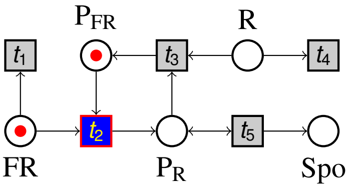

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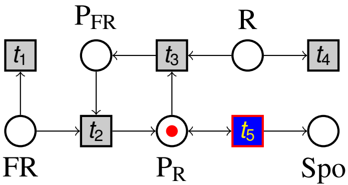

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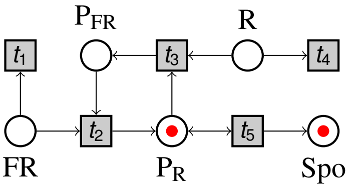

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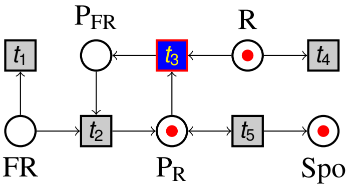

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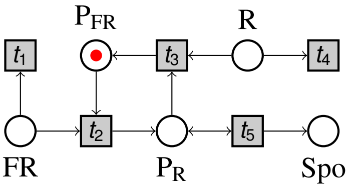
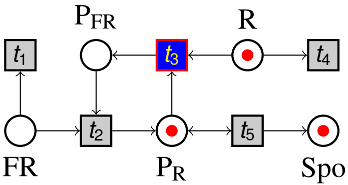


Example

Potential system states $\mathcal{X}$:

FR	0	0	0	0	0	0	0	0	1	1	1	1
R	0	0	0	0	1	1	1	1	0	0	0	0
P_{FR}	1	0	1	0	1	0	1	0	1	0	1	0
P_R	0	1	0	1	0	1	0	1	0	1	0	1
Spo	0	0	1	1	0	0	1	1	0	0	1	1
	x^1	x^2	x^3	x^4	x^5	x^6	x^7	x^8	x^9	x^{10}	x^{11}	x^{12}



Outline

Modeling determinism via transition priorities

Deterministic systems can be modeled via a successor oracle:

$$x \in \mathcal{X} \mapsto x^+ \qquad \text{(successor state)}$$

We consider those systems where the oracle can be implemented through a transition selection function:

$$\mathcal{X} \to T$$
$$x \mapsto t^*(x) \in T(x),$$

where $T(x)$ is the set of enabled transitions at state x, so that...

- firing $t^*(x)$ puts the system in state x^+
- $t^*(x)$ is called the highest-priority transition at x

Modeling determinism via transition priorities

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$$\begin{aligned} \mathcal{X} &\to T \\ x &\mapsto t^*(x) \in T(x), \end{aligned}$$

Idea:

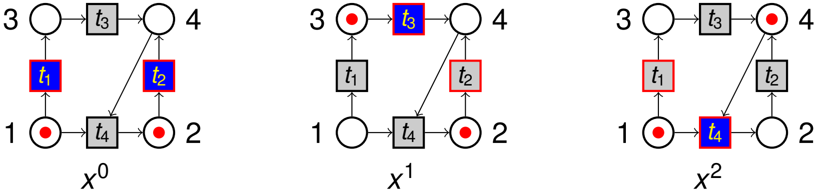
Find a compact encoding for t^*.

Modeling determinism via transition priorities

Can all deterministic systems be modelled in this way?

Modeling determinism via transition priorities

Can all deterministic systems be modelled in this way?
No!



j	branching state x^j	$T(x^j)$	x^{j+}
0	$(1,1,0,0)^T$	$\{\mathbf{t_1}, \mathbf{t_2}\}$	$(0,0,1,1)^T$
1	$(0,1,1,0)^T$	$\{t_2, \mathbf{t_3}\}$	$(0,1,0,1)^T$
2	$(1,0,0,1)^T$	$\{t_1, \mathbf{t_4}\}$	$(0,1,0,0)^T$
3	$(1,1,1,0)^T$	$\{t_2, \mathbf{t_3}\}$	$(1,1,0,1)^T$

The transition conflict graph

- two transitions are in conflict if they are both enabled at some state
- they are in dynamic conflict if firing one disables the other

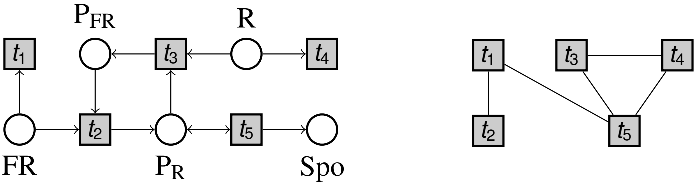
Lemma (TW 2011)

Transitions $t, t' \in T$ are in conflict if and only if

$$\begin{aligned} w_{pt} &\leq u_p - w_{t'p} && \forall p \in \mathrm{P}^-(t) \cap \mathrm{P}^+(t') \cap B, \text{ and} \\ w_{pt'} &\leq u_p - w_{tp} && \forall p \in \mathrm{P}^-(t') \cap \mathrm{P}^+(t) \cap B. \end{aligned}$$

The transition conflict graph

Transition conflicts can be represented by a graph $\mathbb{K} := (T, \mathbb{E})$



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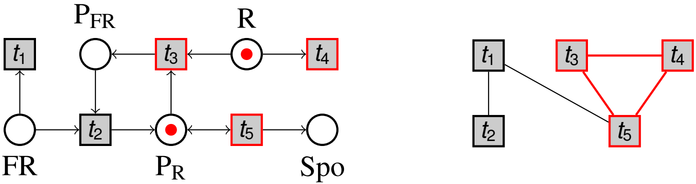

- for every $x \in STS$, $T(x)$ induces a clique in $\mathbb{K}$

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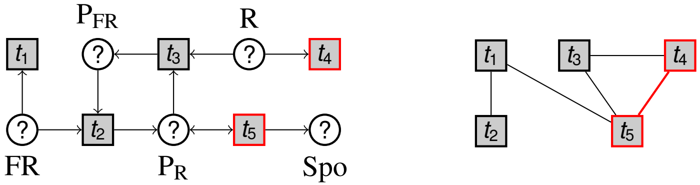

- for every $x \in STS$, $T(x)$ induces a clique in $\mathbb{K}$
- not all cliques correspond to states

The transition conflict graph

The structure of $\mathbb{K}$ is very difficult to characterize from a graph theoretical point of view!

Theorem (TW 2011)

Let $H = (V, E)$ be an (arbitrary) undirected graph and $\mathcal{Q}$ the family containing all cliques in H. Then there exists a network $G = (N \cup T, A, w)$ that satisfies

- $H = \mathbb{K}$
- $\mathcal{Q} := \{T(x) : x \in \mathcal{X}\}$

Outline

Valid orientations

Idea

Encode transition priorities by orienting the edges of $\mathbb{K}$

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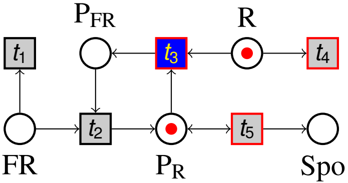
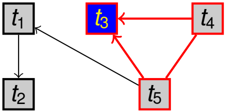




Definition (Valid orientation)

An orientation $\mathbb{D}$ of the edges of $\mathbb{K}$ is valid if

- $\forall x \in \mathcal{X},\ T(x)$ induces a clique with a unique sink

Valid orientations

Theorem (TW 2009)

There is a valid orientation of $\mathbb{K}$ iff for any pair of states $x, x' \in \mathcal{X}$ with $t^*(x) \in T(x) \cap T(x')$,

- *either $t^*(x') = t^*(x)$ or $t^*(x') \in T(x') \setminus T(x)$*

- in this case $\mathbb{D}$ encodes the dynamics of the system.
- the successor oracle can be implemented as
  - select $t^*(x)$ as unique sink in clique in $\mathbb{K}$ induced by x
  - obtain x^+ by swtiching $t^*(x)$

Successor oracle

Input: $(G, u, \mathbb{D})$, $x \in \mathcal{X}$
Output: x^+
Construct the set $T(x)$ of enabled transitions
if $T(x) = \emptyset$ **then**
  return x
end if
{Compute out-degree of transitions in the subgraph of $\mathbb{D}$ induced by $T(x)$}
for $t \in T(x)$ **do**
  $\delta^-(t) := |\{tt' \in \mathbb{A} : t' \in T(x)\}|$
end for
{Return successor state}
$t^* \leftarrow t \in T(x)$ with $\delta^-(t) = 0$
return $x + M_{\cdot t^*}$

Predecesor oracle

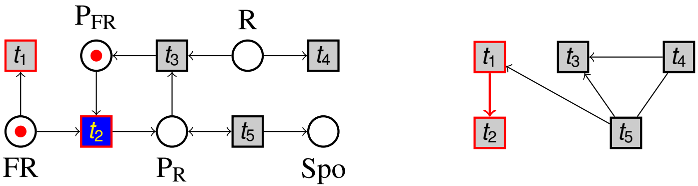
Input: $(G, u, \mathbb{D})$, $x \in \mathcal{X}$
Output: pred(x)
{Construct set of transition candidates}

$$\text{cand}(x) \leftarrow \{t \in T \;:\; x_p + w_{pt} \leq u_p, \forall p \in \mathrm{P}^-(t) \cap B; \\ x_p - w_{tp} \geq 0, \forall p \in \mathrm{P}^+(t)\}$$

{Call successor-oracle to construct sets of predecessors}
pred$(x) \leftarrow \emptyset$
for $t \in \text{cand}(x)$ **do**
  $y \leftarrow x - M_{\cdot t}$
  if $t^*(y) = t$ **then**
    pred$(x) \leftarrow$ pred$(x) \cup \{y\}$
  end if
end for
{Return set of possible predecessors}
return pred(x)

Example

Light-induced sporulation of *Physarum polycephalum*



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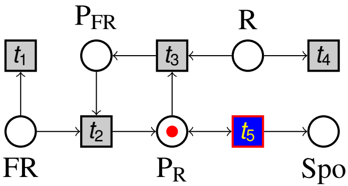

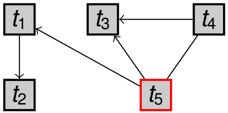

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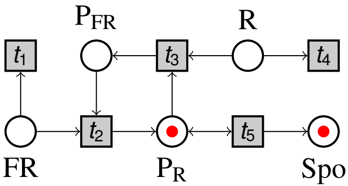

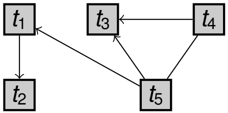

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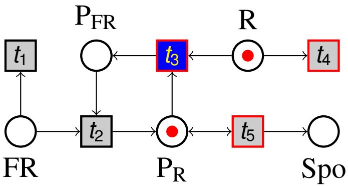

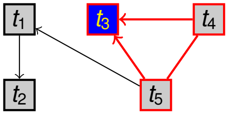

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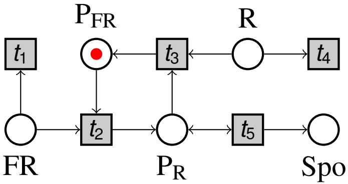

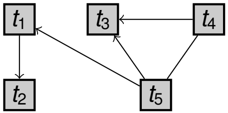

Strongly valid orientations

- in general, valid orientations are difficult to characterize
- an orientation is strongly valid, if it is valid for all Petri Nets sharing the same conflict graph
- strongly valid orientations have a unique sink for each clique

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Theorem (TW 2009)

- *$\mathbb{D}$ is strongly valid if it does not contain a directed cycle of length 3*
- *in particular, acyclic orientations are strongly valid*

Outline

The Minimum Valid Test Set Problem

Problem

For a deterministic system whose dynamic behavior is prescribed by an unknown valid orientation $\mathbb{D}$,

- determine $\mathbb{D}$ by observing some pairs (x, x^+)
- use as few observations as possible

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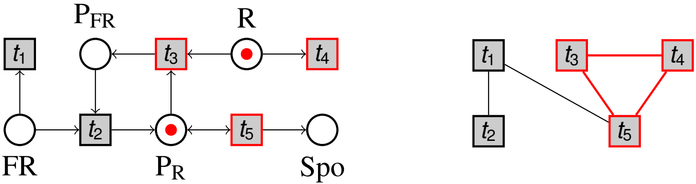

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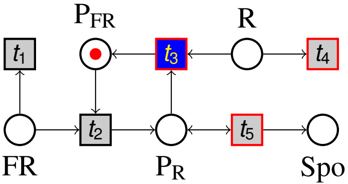

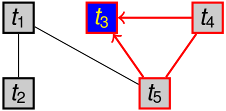

The Minimum Valid Test Set Problem

Problem

For a deterministic system whose dynamic behavior is prescribed by an unknown valid orientation $\mathbb{D}$,

- determine $\mathbb{D}$ by observing some pairs (x, x^+)
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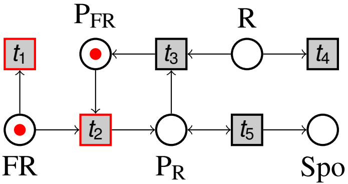

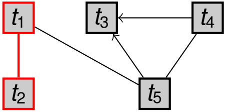

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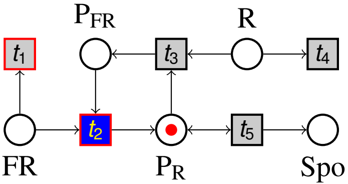

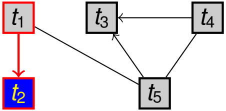

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ModeMat

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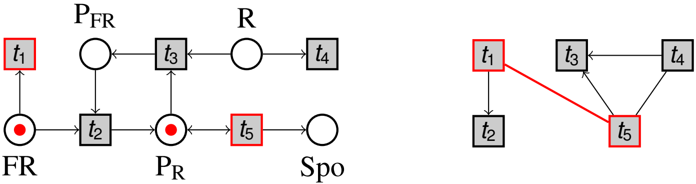

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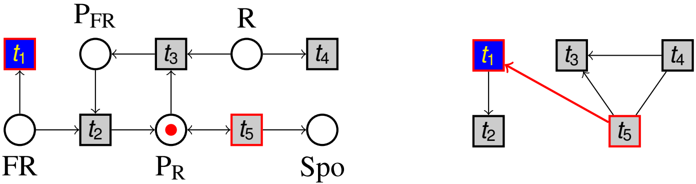

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A set $\mathcal{X}' \subset \mathcal{X}$ is a valid test set if knowledge about

$$\{(x, x^+) : x \in \mathcal{X}'\}$$

is sufficient for determining $\mathbb{D}$.

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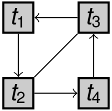
Minimum Valid Test Set Problem (MVTP)

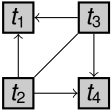
Determine a valid test set of minimum cardinality.

Partial orientations

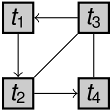
- a partial orientation $\mathbb{D}' := (T, \mathbb{A}', \mathbb{E}')$ is a mixed graph obtained by fixing directions of some edges of $\mathbb{K}$
- $\mathbb{D}'$ is extendible if it is possible to choose directions for the edges in $\mathbb{E}'$ to obtain a valid orientation



non-extendible



extendible



sufficient

Inferable, dominated, and essential arcs

- an edge $tt' \in \mathbb{E}'$ is inferable as (t, t') if the digraph $(T, \mathbb{A}' \cup \{(t', t)\}, \mathbb{E}' \setminus \{tt'\})$ is not extendible
- an edge $tt' \in \mathbb{E}'$ is dominated if

$$\forall x \in \mathcal{X} \text{ with } t, t' \in T(x), t^*(x) \notin \{t, t'\}$$

- $\mathbb{D}'$ is sufficient if all edges in $\mathbb{E}'$ are either inferable or dominated
- an arc (t, t') of $\mathbb{D}$ is essential if
  - tt' is not dominated
  - the orientation $\mathbb{D}_2 := (T, \mathbb{A} \setminus \{(t, t')\} \cup \{(t', t)\})$ is valid

Characterizing optimal solutions for MVTP

Theorem (TW 2009)

Let $\mathbb{A}^*$ be the set of all essential arcs. Then,

- *the partial orientation $\mathbb{D}^* := (T, \mathbb{A}^*, \mathbb{E}^*)$ is sufficient*
- *for any $x \in \mathcal{X}$, knowledge about (x, x^+) allows orientation of at most one essential arc*
- *$\mathcal{X}' \subset \mathcal{X}$ is an optimal solution for MVTP iff for every $x \in \mathcal{X}'$*

$$\{(t, t^*(x)) : t \in T(x),\, t \neq t^*(x)\} \cap \mathbb{A}^* \neq \emptyset$$

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We consider in the following the special case when $\mathbb{D}$ is acyclic...

Acyclic graphs

Lemma (TW 2015)

If $\mathbb{D}$ is acyclic, then every clique Q has a unique sink, and a directed hamiltonian path P_Q through its nodes.

Lemma (TW 2015)

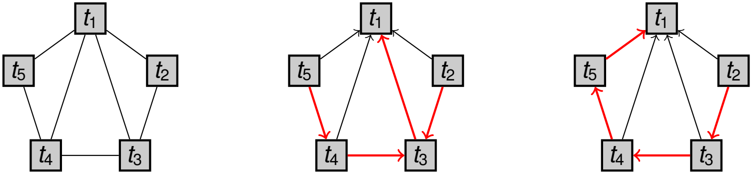
If $\mathbb{D}$ is acyclic, the essential arcs of a clique are exactly the arcs corresponding to P_Q.

Algorithm

Input: (G, u, t^*) {deterministic system with oracle for computing t^*}
Output: $\mathbb{D}$ {valid orientation}

```
initialize 𝒬 as the set of all inclusion-wise maximal cliques in 𝕂
while 𝒬 ≠ ∅ do
    retrieve a clique Q from 𝒬
    while |Q| > 1 and ∃x ∈ 𝒳 with T(x) = Q do
        call the oracle and determine t* := t*(x)
        orient the arcs {(t, t*) : t ∈ T(x), t ≠ t*}
        deduce orientations for inferable edges
        remove t* from Q
    end while
    if Q contains more than one node then
        compute 𝒬′ := {T(x) ⊂ Q : x ∈ 𝒳}
        remove from 𝒬′ cliques that are not inclusion-wise maximal
        𝒬 := 𝒬 ∪ 𝒬′
    end if
end while
while there are yet unoriented edges do
    deduce an orientation for all yet unoriented inferable edges
    choose an arbitrary orientation for a yet unoriented dominated edge
end while
```

What about the “online” problem?



- states induce either edges or cliques of size 3 (triangles)
- for every $e \in \mathbb{K}$, there is an acyclic orientation where e is not essential
- the figures show that the same holds for every triangle

$\rightsquigarrow$ for every $x \in \mathcal{X}$, there is at least one valid orientation for which (x, x^+) does not provide the direction of any essential arc
$\rightsquigarrow$ no “winning strategy”

Outline

Experiment design for model verification

In practice...

- network G is not known a priori
- both G and $\mathbb{D}$ have to be reconstructed simultaneously from experimental observations
- it is not always possible to observe pairs (x, x^+)
- instead...
  - system is set to an initial state x^0
  - sequence $\text{sequ}(x^0) = (x^1, \ldots, x^k)$ of state changes in response to initial trigger is observed
  - there might be intermediate non-observed states

Experiment design for model verification

Let $\mathcal{X}'$ be a collection of states observed in some experiments

- $(G, \mathbb{D}')$ is $\mathcal{X}'$-deterministic if it fits the experimental data
- $P(\mathcal{X}')$ is the set of all $\mathcal{X}'$-deterministic models $(G, \mathbb{D}')$
- $P(\mathcal{X}')$ can be computed with an exhaustive reconstruction approach [1]

[1] M. Favre, A. Wagler. *Reconstructing $\mathcal{X}'$-deterministic extended Petri nets from experimental time-series data $\mathcal{X}'$*. CEUR Workshop Proceedings 988:45–59, 2013. (Special Issue BioPPN 2013)

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Optimal Test Set Extension Problem

Given $\mathcal{X}' \subseteq \mathcal{X}$ and $P(\mathcal{X}')$, find an optimal extension $\overline{\mathcal{X}'}$ of $\mathcal{X}'$ such that

- each network in $P(\mathcal{X}')$ can be either completed to an $\overline{\mathcal{X}'}$-deterministic network or ruled out as "false positive",
- all networks in $P(\overline{\mathcal{X}'})$ are either equivalent or not further distinguishable

Example

Light-induced sporulation of *Physarum polycephalum*.

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Perform two experiments:

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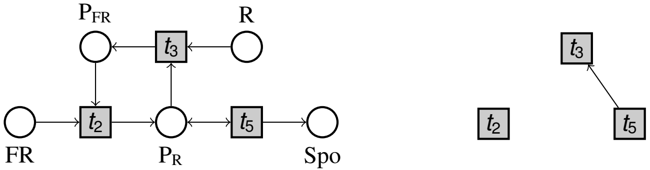

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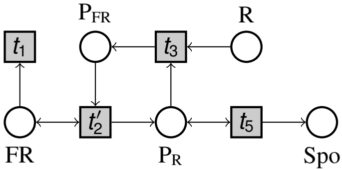

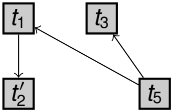

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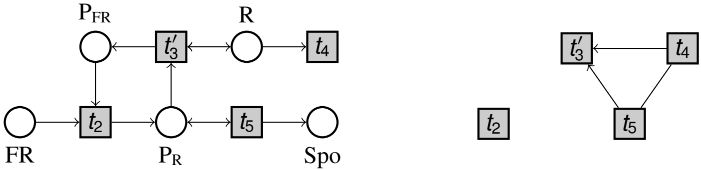

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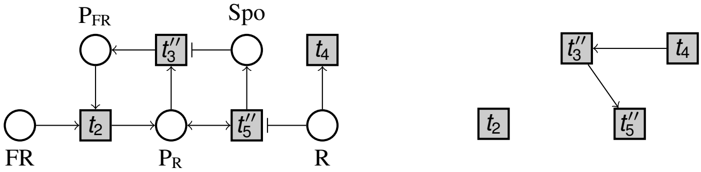

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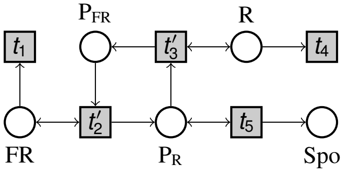

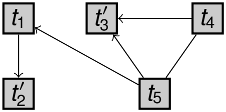

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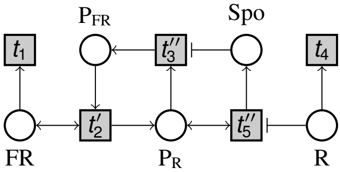
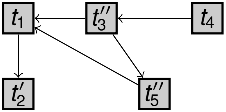
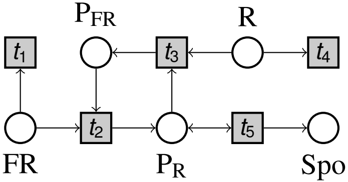




Example

Potential system states $\mathcal{X}$:

FR	0	0	0	0	0	0	0	0	1	1	1	1
R	0	0	0	0	1	1	1	1	0	0	0	0
P_{FR}	1	0	1	0	1	0	1	0	1	0	1	0
P_R	0	1	0	1	0	1	0	1	0	1	0	1
Spo	0	0	1	1	0	0	1	1	0	0	1	1
	x^1	x^2	x^3	x^4	x^5	x^6	x^7	x^8	x^9	x^{10}	x^{11}	x^{12}



Example

Possible successors $\mathcal{X}$:

	x^{3+}	x^{5+}	x^{7+}	x^{8+}	x^{10+}	x^{11+}	x^{12+}
P_1	x^3	x^5	x^7	x^3	x^{12}	x^4	x^{12}
P_2	x^3	x^5	x^7	x^3	x^2	x^{12}	x^4
P_{3a}	x^3	x^1	x^3	x^7	x^{12}	x^4	x^{12}
P_{3b}	x^3	x^1	x^3	x^4	x^{12}	x^4	x^{12}
P_{4a}	x^3	x^1	x^3	x^7	x^2	x^{12}	x^4
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- a test $\text{sequ}(x^{12}) = (x^4)$ discards P_1, P_{3a} and P_{3b}

Outline

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- Petri Nets are a well-established framework for modeling and analyzing several processes in Systems Biology
  - interrelations of components in complex systems
  - concurrency

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  - interrelations of components in complex systems
  - concurrency
- we presented an extension for encoding the dynamics of certain deterministic systems in a compact manner
  - global point of view
  - reconstructing model structure from experimental data
- we assume successor oracle can be represented via priorities among transitions
  (not all deterministic systems can be modeled in this way)

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  - acyclic orientations are always (strongly) valid
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  - an "optimal offline" strategy in terms of essential edges
  - reconstruction algorithm
  - no (online) "winning strategy"
- experiment design (OTSEP)
  - reconstruct both network and valid orientation
  - extend or rule out models that do not fit the data
  - assist in the choice of new experiments

Future work

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- integration in available software tools for Petri Nets (Snoopy, CHARLIE, ...)

For Further Reading

- Marwan, W., Sujatha, A., Starostzik, C.: Reconstructing the regulatory network controlling commitment and sporulation in physarum polycephalum based on hierarchical Petri net modeling and simulation.
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Thank you!!!