Modelling Reaction Systems with Petri nets

Jetty Kleijn & Grzegorz Rozenberg
Leiden University
The Netherlands

Maciej Koutny
Newcastle University
United Kingdom

Universiteit Leiden

Newcastle University

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Computational systems biology

Key features of the computational (algorithmic) approach to systems biology:

- computations (operational description) rather than equations (denotational description)
- discrete state spaces (precise description of changes) rather than continuous state spaces (average behaviour)

C.Priami [Communication of the ACM, May 2009]:

- "... causality between events, the temporal ordering of interactions and the spatial distribution of components are becoming essential to addressing questions at system level ..."
- "... design principles of large software systems can help in developing an algorithmic discipline not only for systems biology but also for synthetic biology ..."
- "... the convergence of CS and biology will serve both disciplines, providing each with greater power and relevance ..."

Motivation

- Computational *understanding* of the functioning of living cells
- Formal framework of *reaction systems* (investigation of processes carried out by biochemical reactions in living cells)
- Functioning of living cell is based on interactions between individual reactions regulated by two mechanisms:

  facilitation

  inhibition
- Interactions determine *dynamic processes*
- Two axioms:

  non-permanency (cell is an open system)

  non-counting (high level of abstraction)
- Stochasticity / time / counting etc can be introduced later through *contexts* (not included in the basic model) in order not to preclude other explanations

Motivation

- This paper aims [CfP: ... standard Petri nets for qualitative modelling, if kinetics are unknown or deliberately abstracted ...] :

  faithful Petri net model of reaction systems

  qualitative approach to biological processes using Petri nets

- Long term aim:

  establishing whether Petri net based concepts (such as causal processes) and methods (such as synthesis of nets) could be transferred to reaction systems

- Not in this paper:

  direct feedback to the area of biological applications

Outline

- Basic reaction systems
- Reaction systems and low-level Petri nets
- Reaction systems and high-level Petri nets
- Set-nets
- Reaction systems and set-nets
- Concluding remarks

Reaction systems

- Reaction system $\mathcal{A}$ = (S,A) where:

  S finite background set comprising entities
  A set of reactions

- Reaction a=(R,I,P) of sets of entities:

  R reactants
  I inhibitors
  P products

- Initialised reaction system A=(S,A,C) where C is an initial state (a set of entities)

- Example: $\mathcal{A}$ =({w,x,y,z},{a,b,c},{x,z}) where:

  a = ({x},{y},{y,z})
  b = ({y},{x},{x,z})
  c = ({z},{w},{z})

Reaction systems

- Reaction $a = (R,I,P)$ is enabled at a state C if
  R is included in C
  I and C are disjoint
- The result $res_a(C)$ of a on C is P if a is enabled, and the empty set otherwise
- The result $res_A(C)$ of A on C is the union of all the reactions' results and we denote:
  $C \rightarrow res_A(C)$
- Example: $\mathcal{A} = (\{w,x,y,z\},\{a,b,c\},\{x,z\})$ where:
  $a = (\{x\},\{y\},\{y,z\})$
  $b = (\{y\},\{x\},\{x,z\})$
  $c = (\{z\},\{w\},\{z\})$
-

  $\{x,z\} \rightarrow \{y,z\}$
  $\{y,z\} \rightarrow \{x,z\}$
- *Note:* all entities present in C which are not produced disappear
  Note: there is no conflict between reactions in the "classic" sense
  Note: reactions systems are qualitative rather than quantitative

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Reaction system example

Context independent

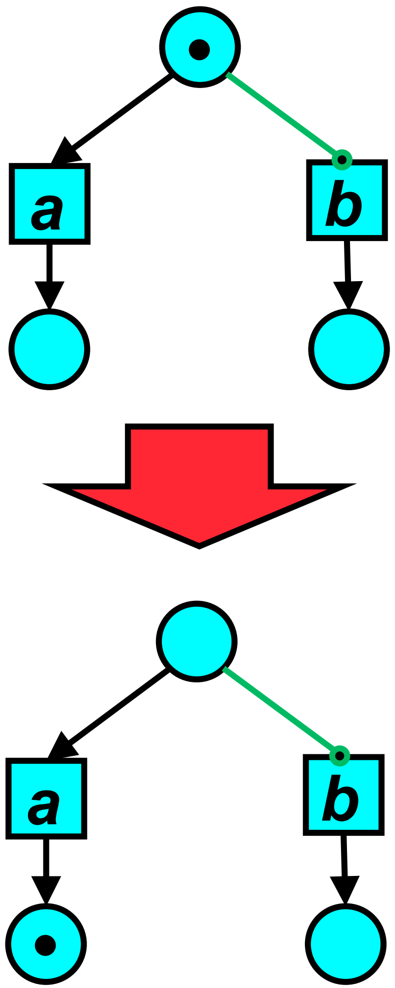
$\mathcal{A}$ = ({x,y,z}, {a,b,c})

a = ({x},{y},{y,z})
b = ({y},{x},{x,z})
c = ({z},{ },{z})

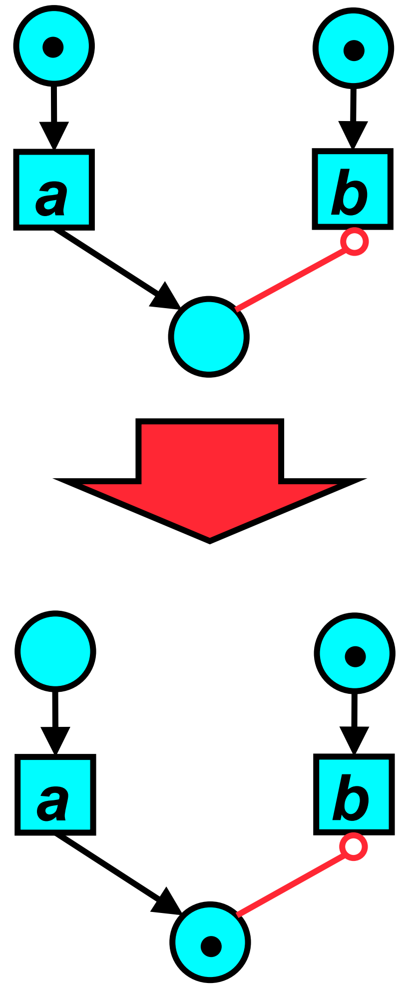
{x,z} *is our initial state*

entities	⇒	*places*
reactions		*transitions*
state		*marking*

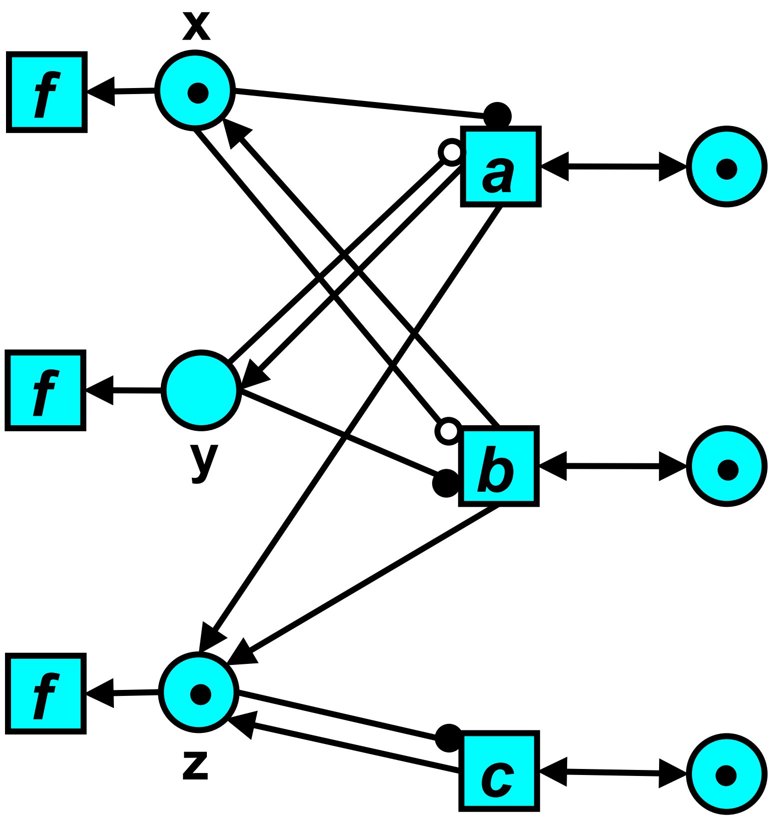
Activator / inhibitor arc



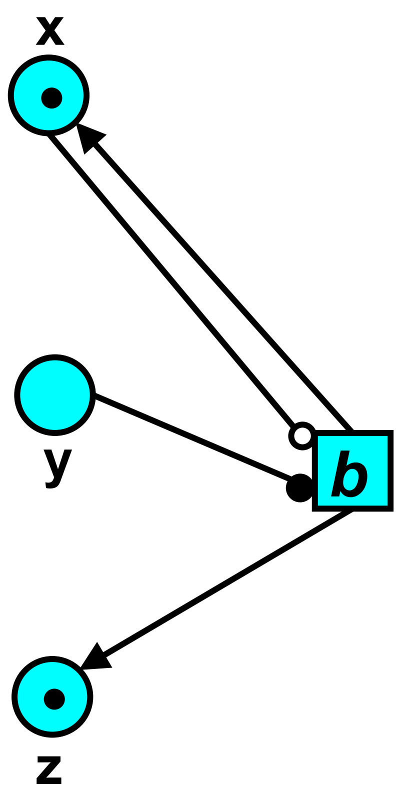
testing for
presence / absence
of tokens



Method I



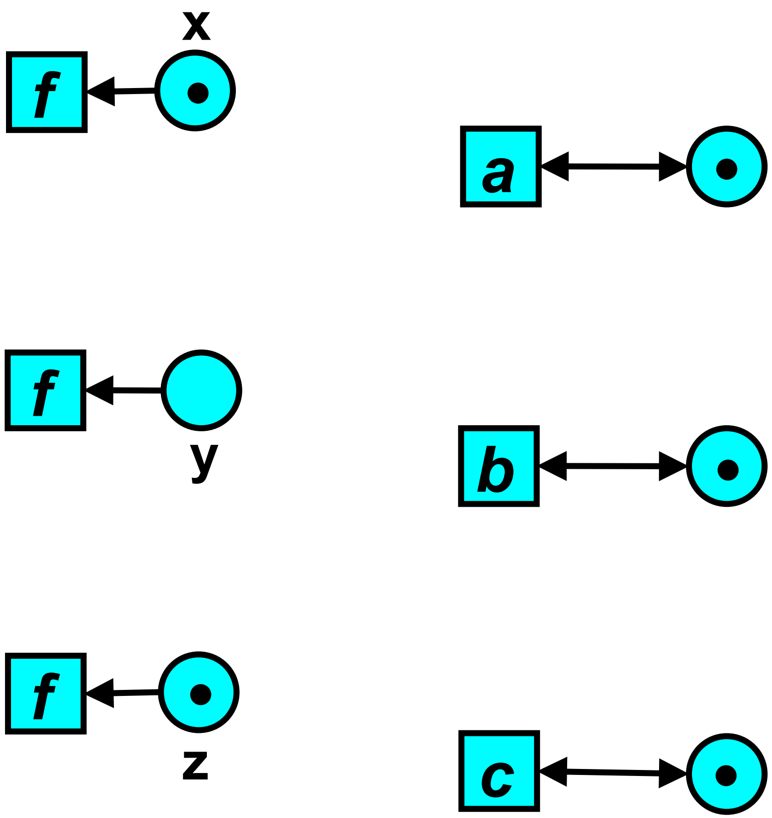
Method I (details)



b = ({y},{x},{x,z})

{x,z} is initial configuration

Method I (details)

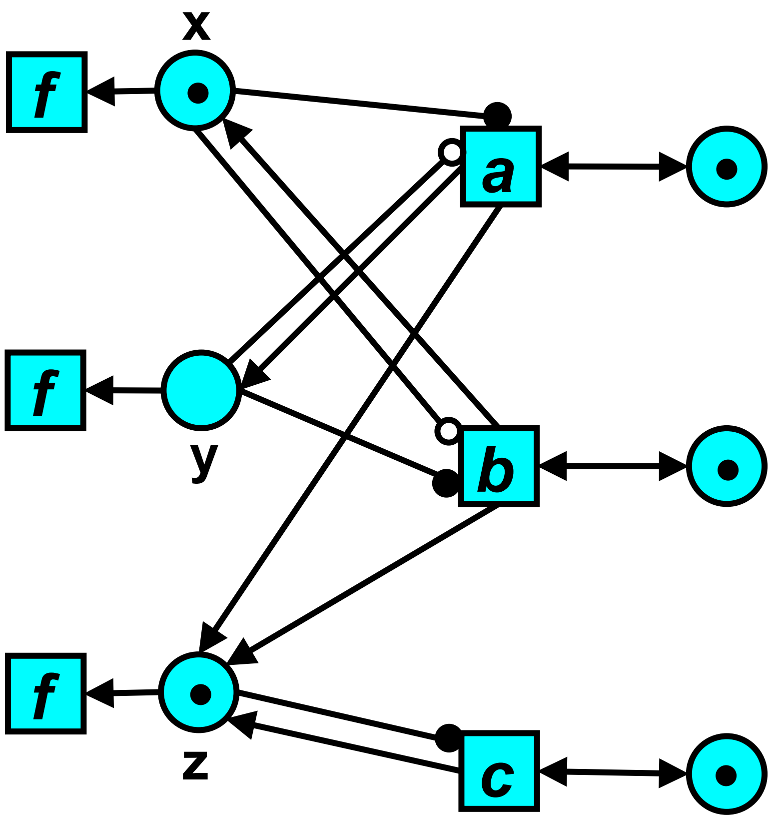


maximal concurrency

implies

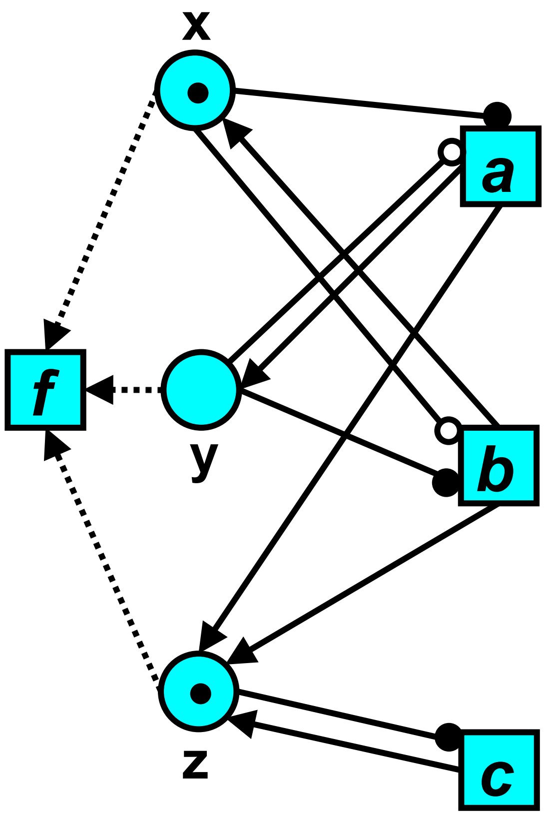
tokens in x y z are "flushed"

Method I (results)



- *the net simulates $\mathcal{A}$*
- *one execution in $\mathcal{A}$ may correspond to many executions in the net*
- *steps of transitions are multisets*

Method II



- *the net simulates $\mathcal{A}$*
- *steps are sets*
- *one execution in $\mathcal{A}$ may correspond to many executions in the net*

reset arcs empty x y z

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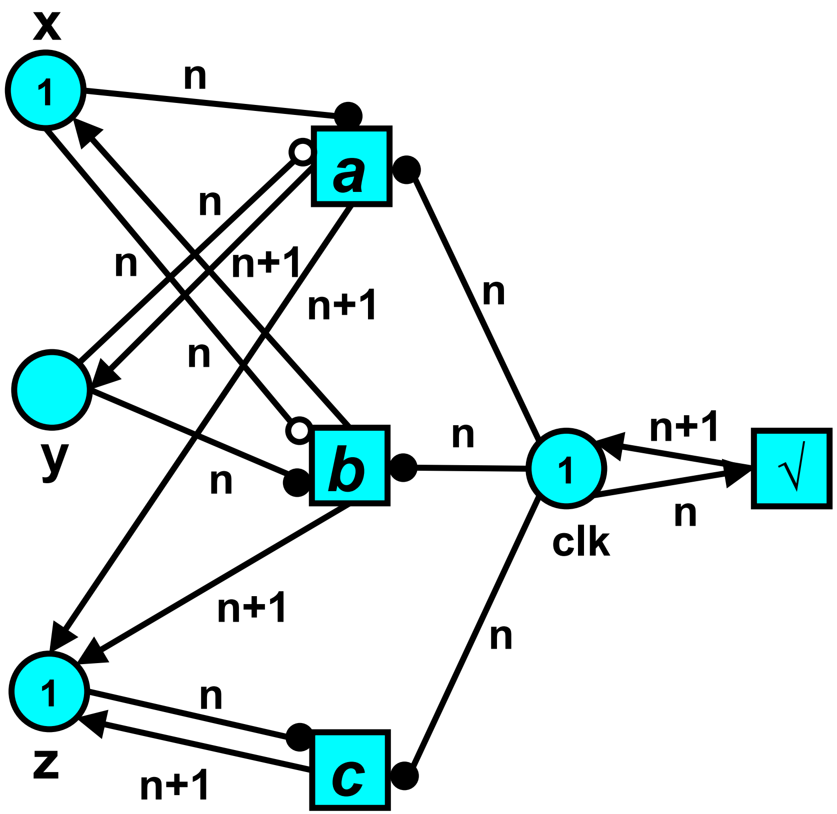
Method III

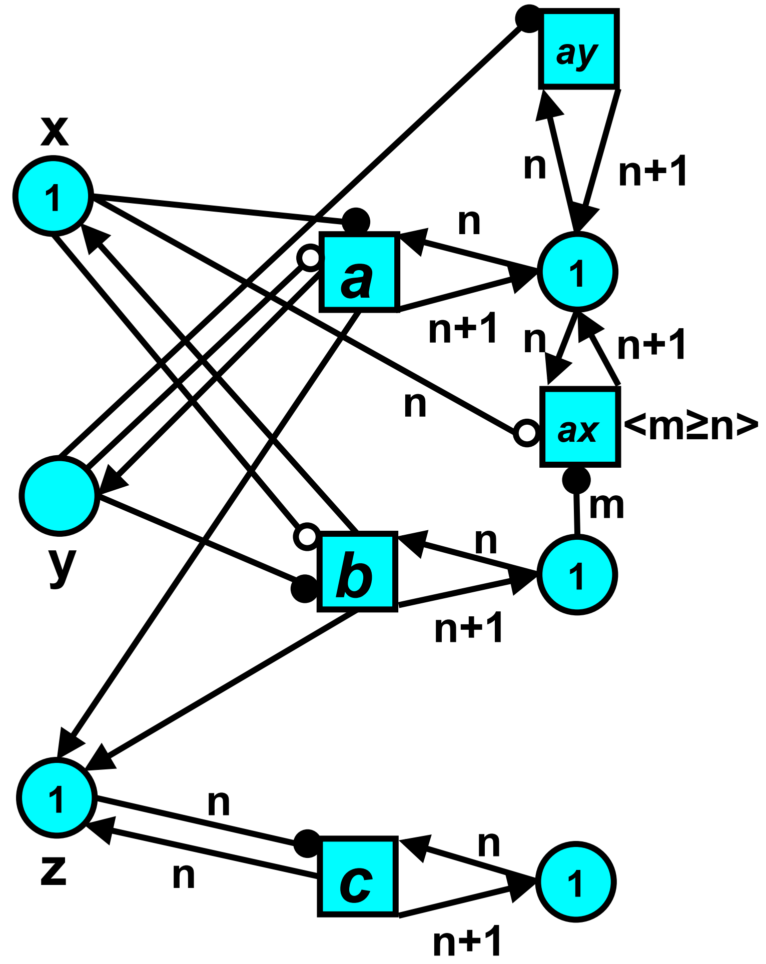


- *the net simulates $\mathcal{A}$*
- *steps are sets*
- *no "flushing"*
- *unboundedness*

tokens are time points

clock values are increased at each step

Method IV



- *the net simulates $\mathcal{A}$*
- *steps are sets*
- *no "flushing"*
- *interleaving executions can simulate maximally concurrent executions*
- *unboundedness*

individual clocks
auxiliary transitions update local clocks

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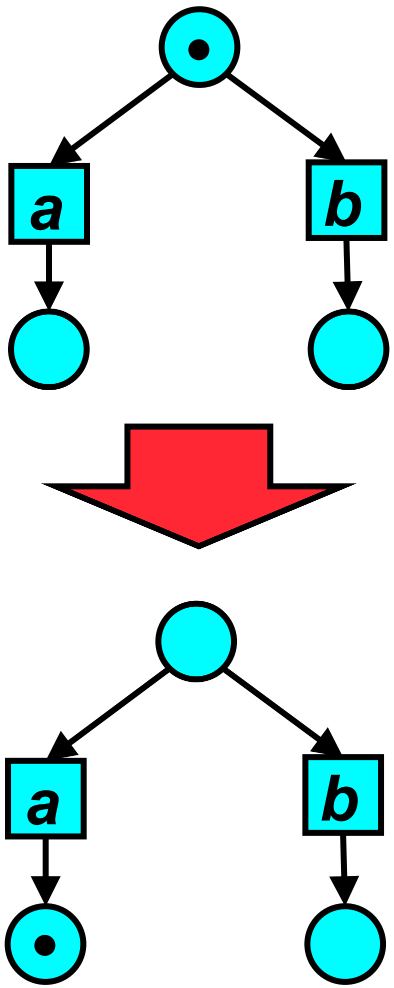
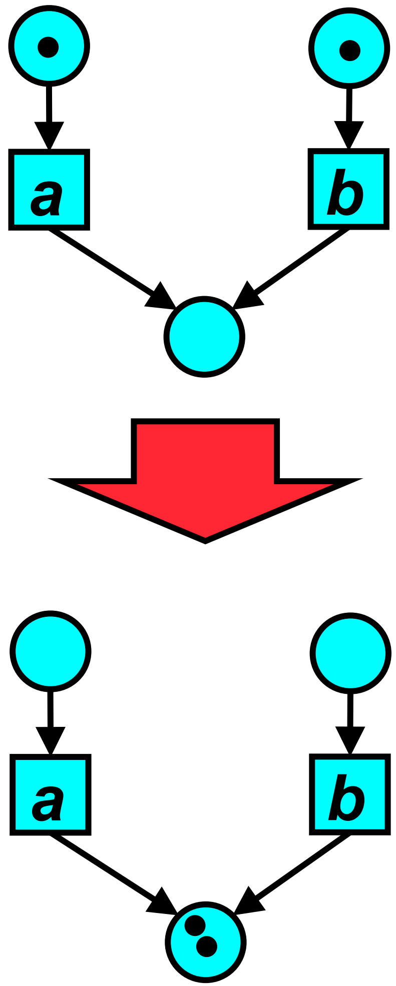
Discussion

- No method provides a direct and/or elegant representation of the behaviour of the reaction system
- No counting, just “presence” or “absence” (also in production), is difficult to manage in the standard models of Petri nets (even the most fundamental ones, including Elementary Net systems)
- Hence we propose a NEW class of nets based on set arithmetic

P/T-nets

conflict

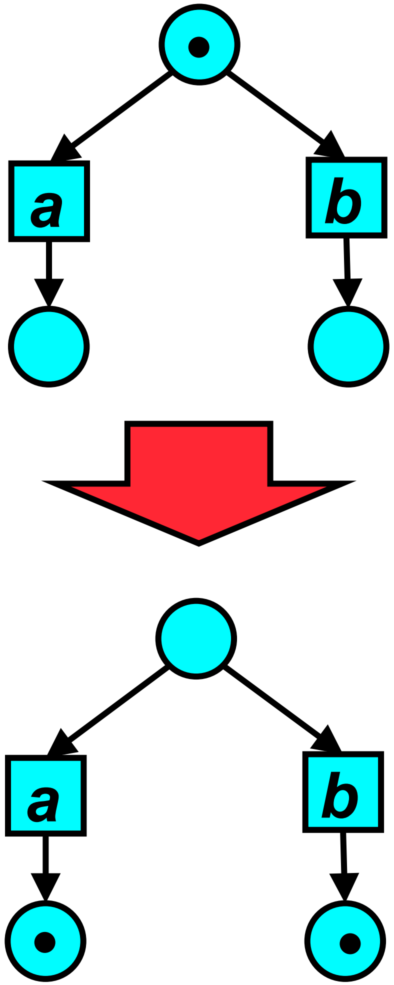


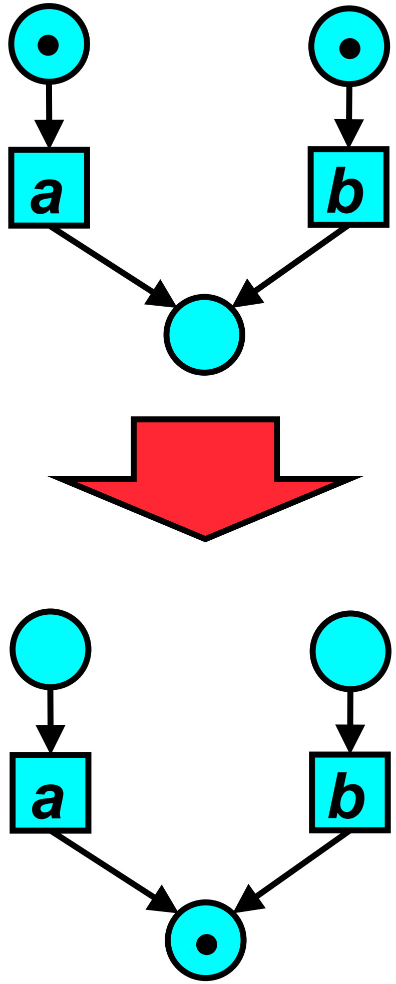


counting

Set-nets

no conflict





no counting

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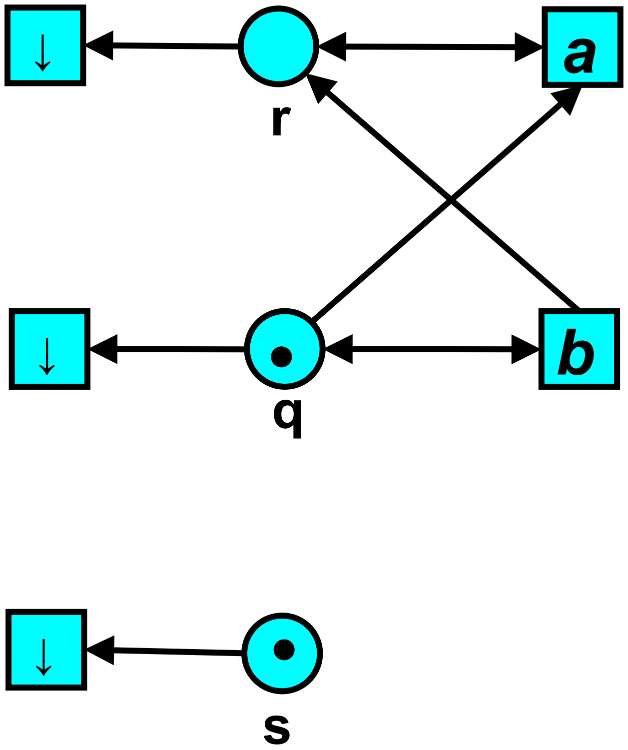
Method V



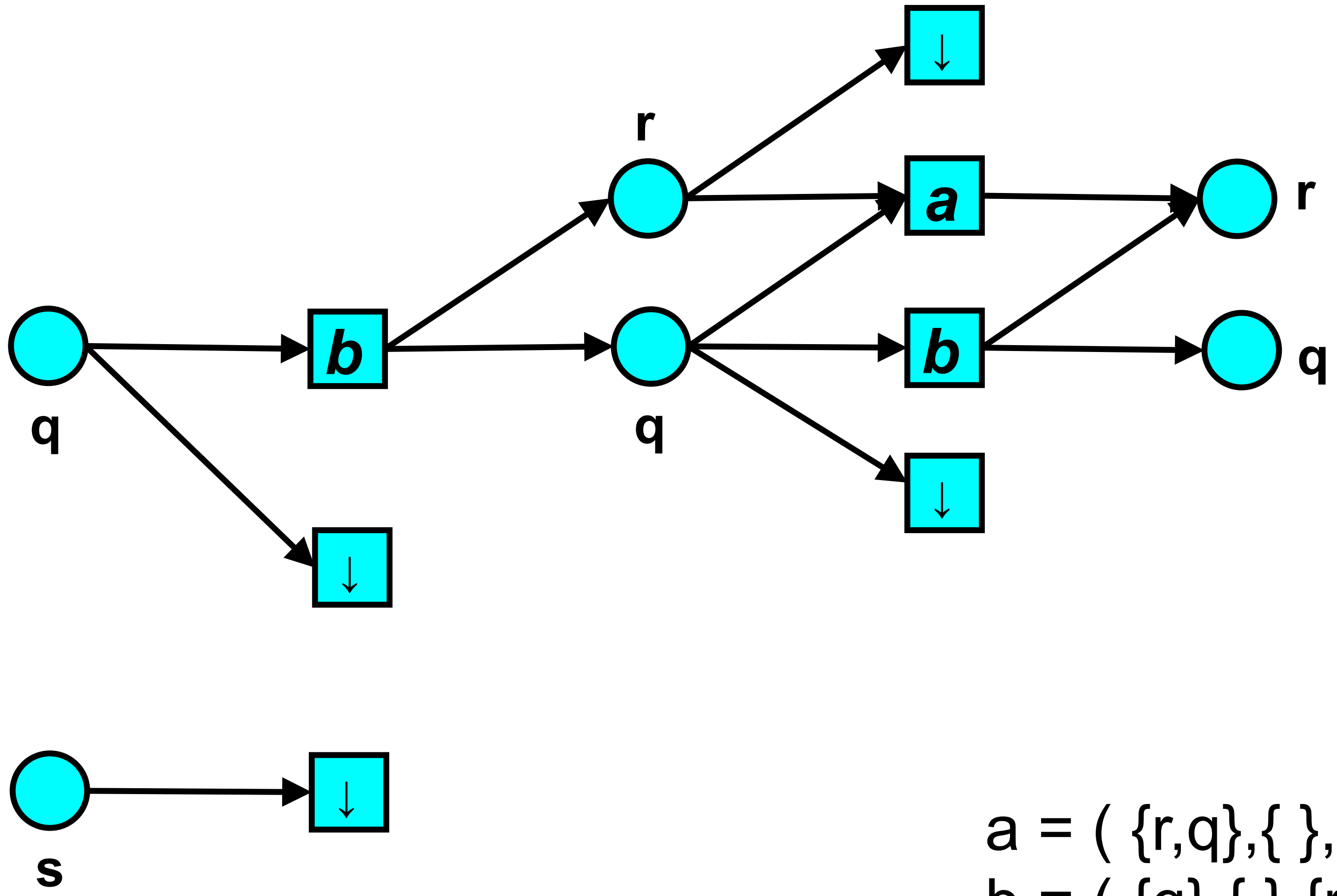
•*the net simulates $\mathcal{A}_1$*

•*one-to-one correspondence of the dynamic behaviours*

•*steps of transitions are sets*

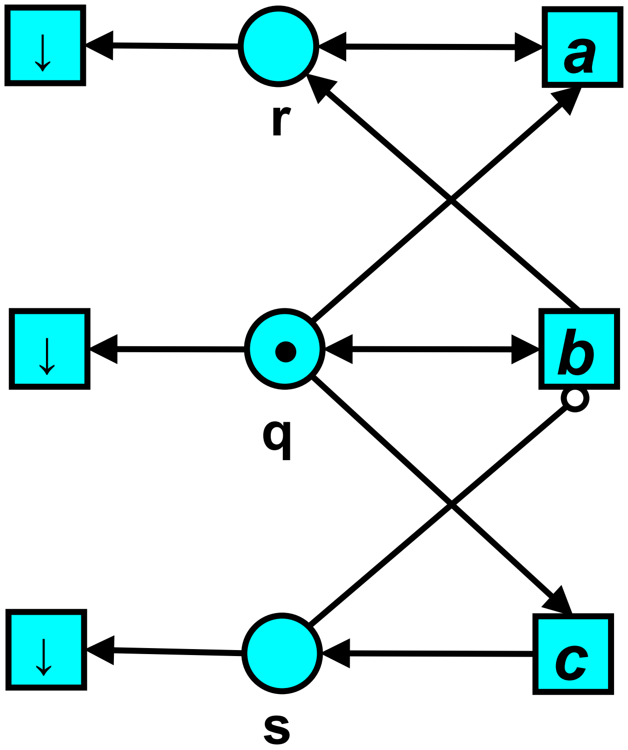
$\mathcal{A}_1$: a = ({r,q},{ },{r})
b = ({q},{ },{r,q})

Set-net processes of $\mathcal{A}_1$



a = ({r,q},{ },{r})
b = ({q},{ },{r,q})

Method V (extended)



$\mathcal{A}2$: a = ({r,q},{ },{r})
b = ({q},{s},{r,q})
c = ({q},{ },{s})

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- Reaction systems *inspired* new class of Petri nets
- Set-nets are a *fundamental* Petri net model
- Set-nets can bring Petri net *analytical methods* to reaction systems

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Concluding remarks

- Reaction systems *inspired* new class of Petri nets
- Set-nets are a *fundamental* Petri net model
- Set-nets can bring Petri net *analytical methods* to reaction systems
- BUT one first needs to *re-cast* Petri net methods in terms of set-nets

... for example ...

Concluding remarks

- Two types of subnets:

  siphon - once empty remains empty
  trap – once marked remains marked

- *"A Structural Theorem [Hack 1970s]"*

  If every siphon contains a marked trap then a P/T-net is deadlock-free

  Numerous applications/extensions/structure theory

- *"Another Structural Theorem"*

  If every siphon contains a marked trap then a set-net is deadlock-free

Concluding remarks

Future work:

process semantics (causality)

analytical techniques

synthesis (initially, region based as in ART'11)

...

Thank you!