Derivation of dynamical qualitative models from biochemical networks

Wassim Abou-Jaoudé

Institut de Biologie de l’Ecole Normale Supérieure (IBENS)

Département d’Informatique de l’Ecole Normale Supérieure (DIENS)

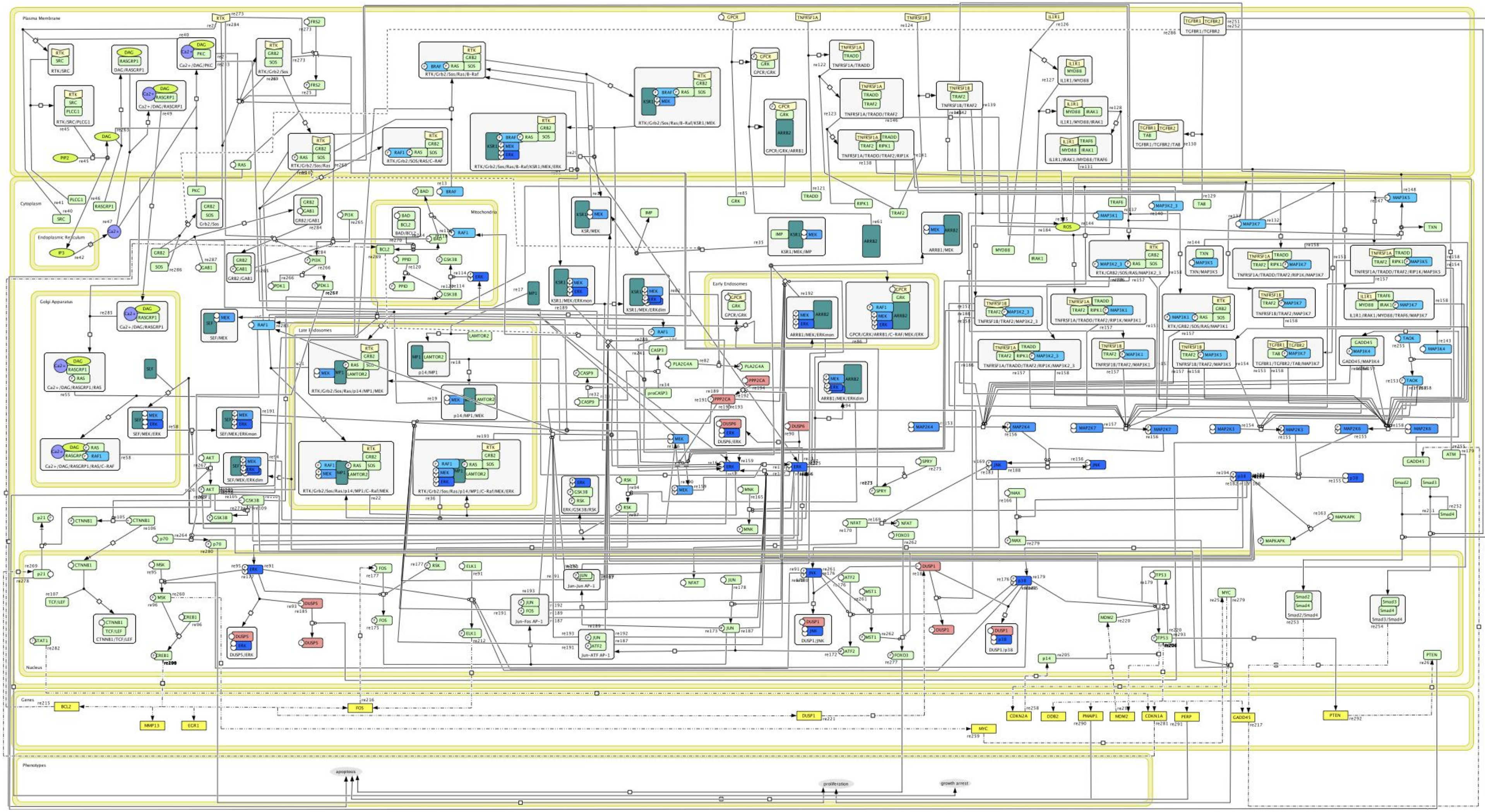
with **Jérôme Feret** (DIENS) and **Denis Thieffry** (IBENS)

Content

1. Aim and motivation
2. Case study
3. Concrete semantics
4. Abstraction to a coarse-grained qualitative semantics
5. Refinements of the abstraction
6. Application to the case study

Aim and motivation

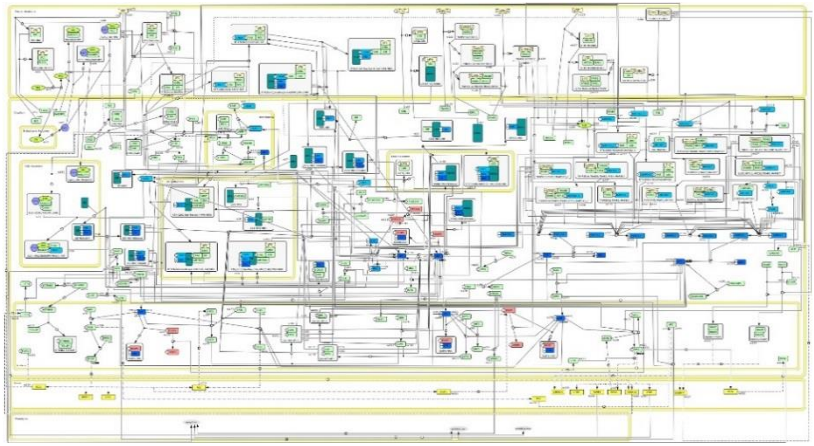
Molecular interaction map representing the MAPK network (involved in cell fate decision)



Grieco et al., *PloS Comp Biol*, 2013

Aim and motivation

Detailed molecular maps



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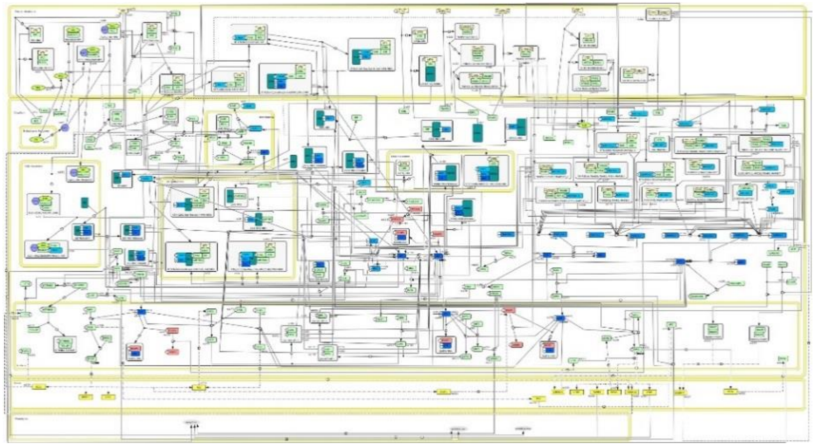
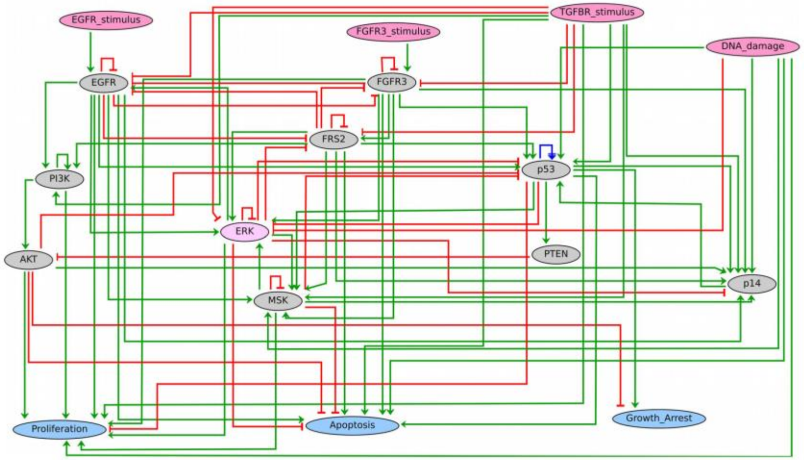


Coarse-grained dynamical models



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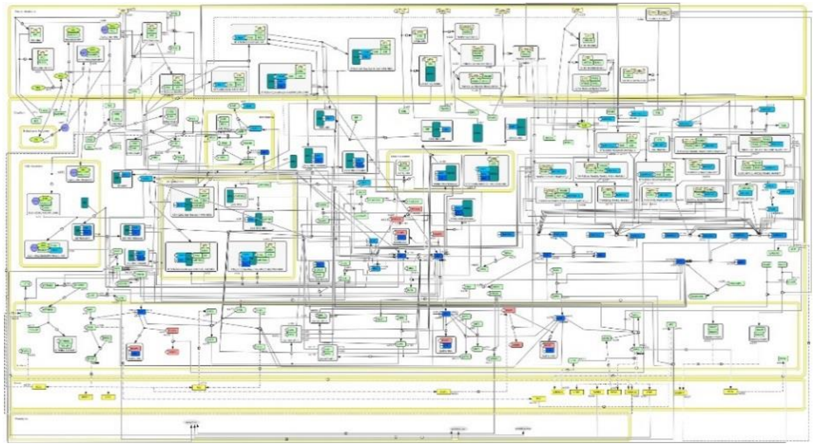
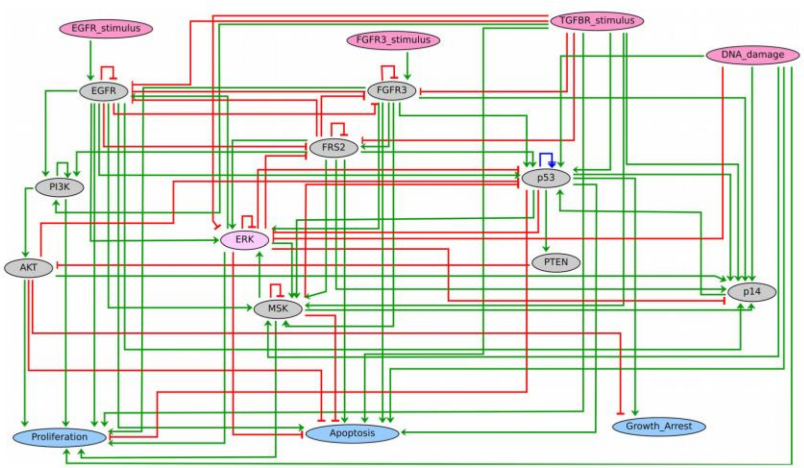


Automatic

Formal

Coarse-grained dynamical models



Grieco et al., *PloS Comp Biol*, 2013

Case study

- A biochemical network showing a sequestration effect of a resource

- Reaction scheme:

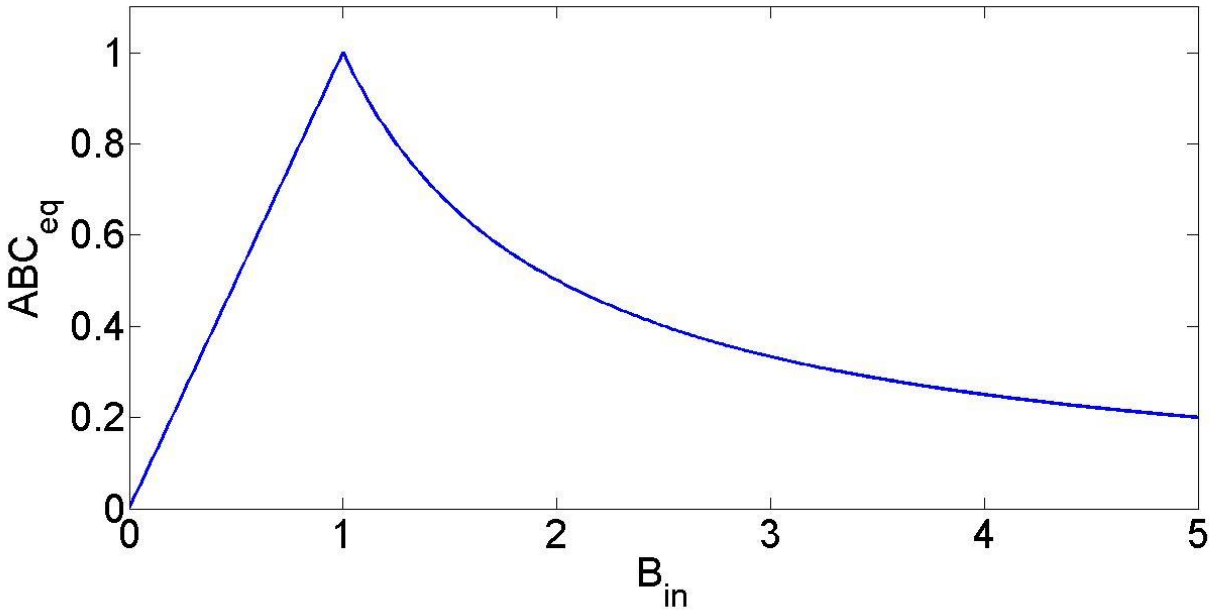
$$
\begin{cases}
A + B \xrightarrow{k_1} AB \\
B + C \xrightarrow{k_2} BC \\
A + BC \xrightarrow{k_1} ABC \\
AB + C \xrightarrow{k_2} ABC
\end{cases}
$$

Case study

- Reaction scheme:

$$\begin{cases} A + B \xrightarrow{k_1} AB \\ B + C \xrightarrow{k_2} BC \\ A + BC \xrightarrow{k_1} ABC \\ AB + C \xrightarrow{k_2} ABC \end{cases}$$

- Analytic solutions (ODE's with mass action laws)



$k_1=k_2=1$

$A_{in}=C_{in}=1$
$AB_{in}=BC_{in}=ABC_{in}=0$

Case study

- Reaction scheme:

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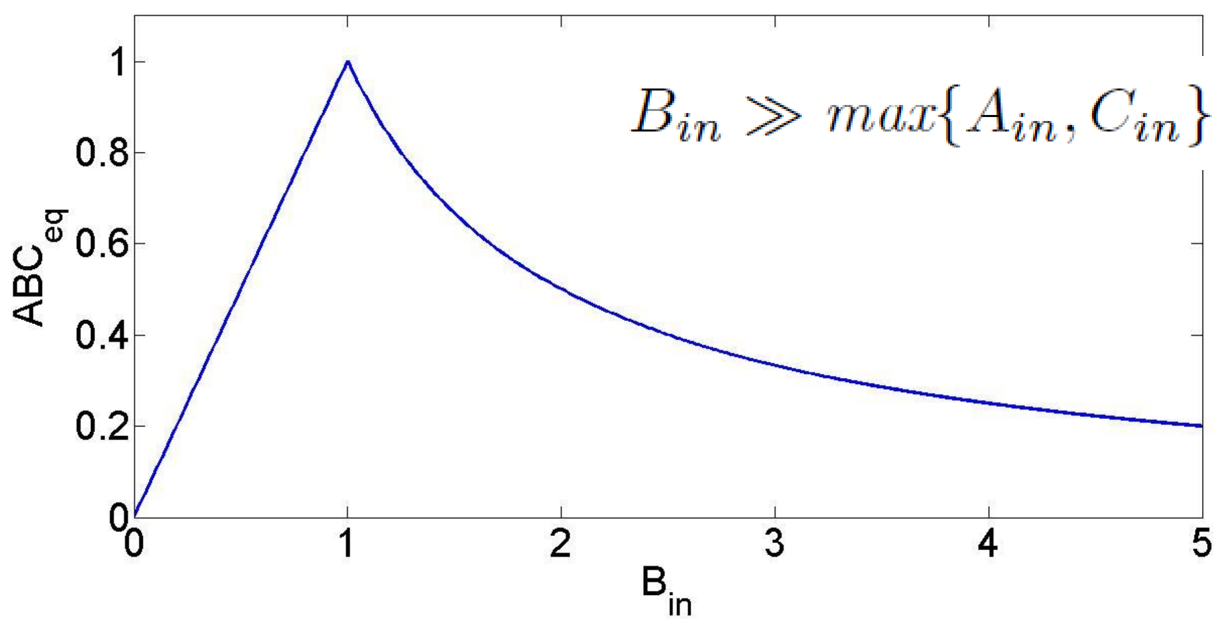

$$B_{in} \gg max\{A_{in}, C_{in}\} \Rightarrow ABC_{eq} \ll 1$$

$k_1=k_2=1$

Ain=Cin=1
ABin=BCin=ABCin=0

Aim and method

- **Aim**

  Setting of an automatic and formal derivation of qualitative dynamical models from reaction networks which capture the salient properties of the case study

  Get insights into the underlying implicit assumptions made in qualitative (e.g. logical) modelling

- **Method**

  Abstract interpretation framework to formally relate models at different levels of description

Reaction network

- **Definition**

A reaction network is defined by:

(1) a set of chemical species ν;

(2) a multi-set of chemical species $M_r : \nu \longrightarrow \mathbb{N}$

(3) a reaction vector $V_r : \nu \longrightarrow \mathbb{Z}$,
such that $M_r(x) + V_r(x) \geq 0$ for any chemical species $x \in \nu$.

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- **An example**

$$\begin{cases} 2A \overset{k_1}{\rightarrow} B \quad (r1) \\ A \overset{k_2}{\rightarrow} C \quad (r2) \end{cases}$$

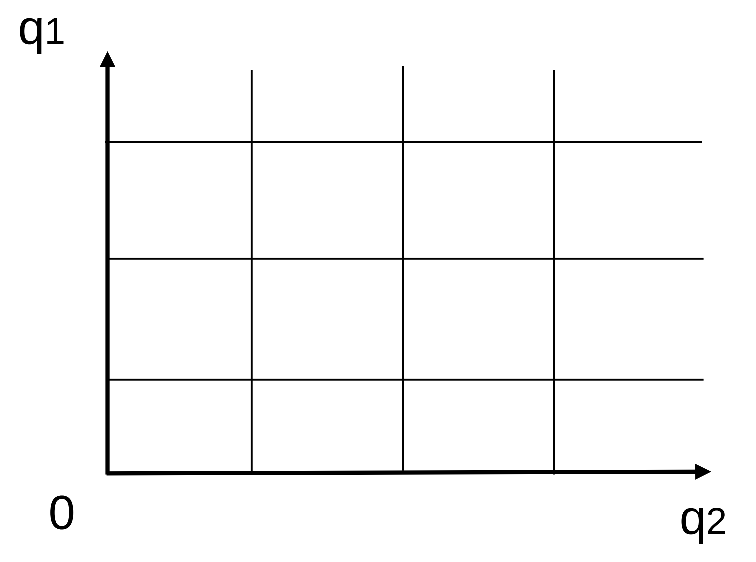
$\nu = \{A, B, C\}$

$M_{r1}(A) = 2, M_{r1}(B) = 0, M_{r1}(C) = 0$ $\qquad$ $M_{r2}(A) = 1, M_{r2}(B) = 0, M_{r2}(C) = 0$

$V_{r1}(A) = -2, V_{r1}(B) = 1, V_{r1}(C) = 0$ $\qquad$ $V_{r2}(A) = -1, V_{r2}(B) = 0, V_{r2}(C) = 1$

Concrete semantics

Transition system



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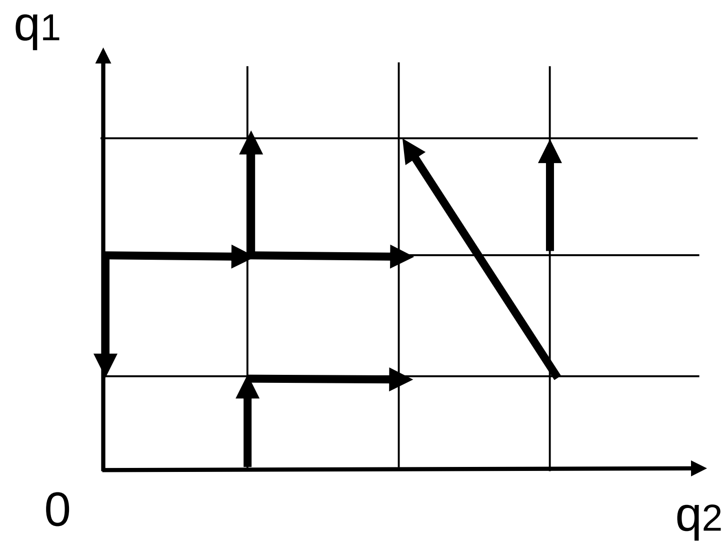
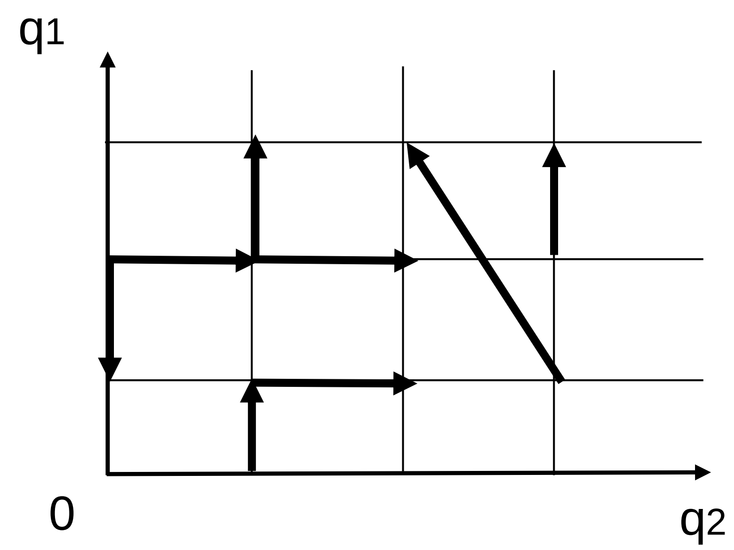
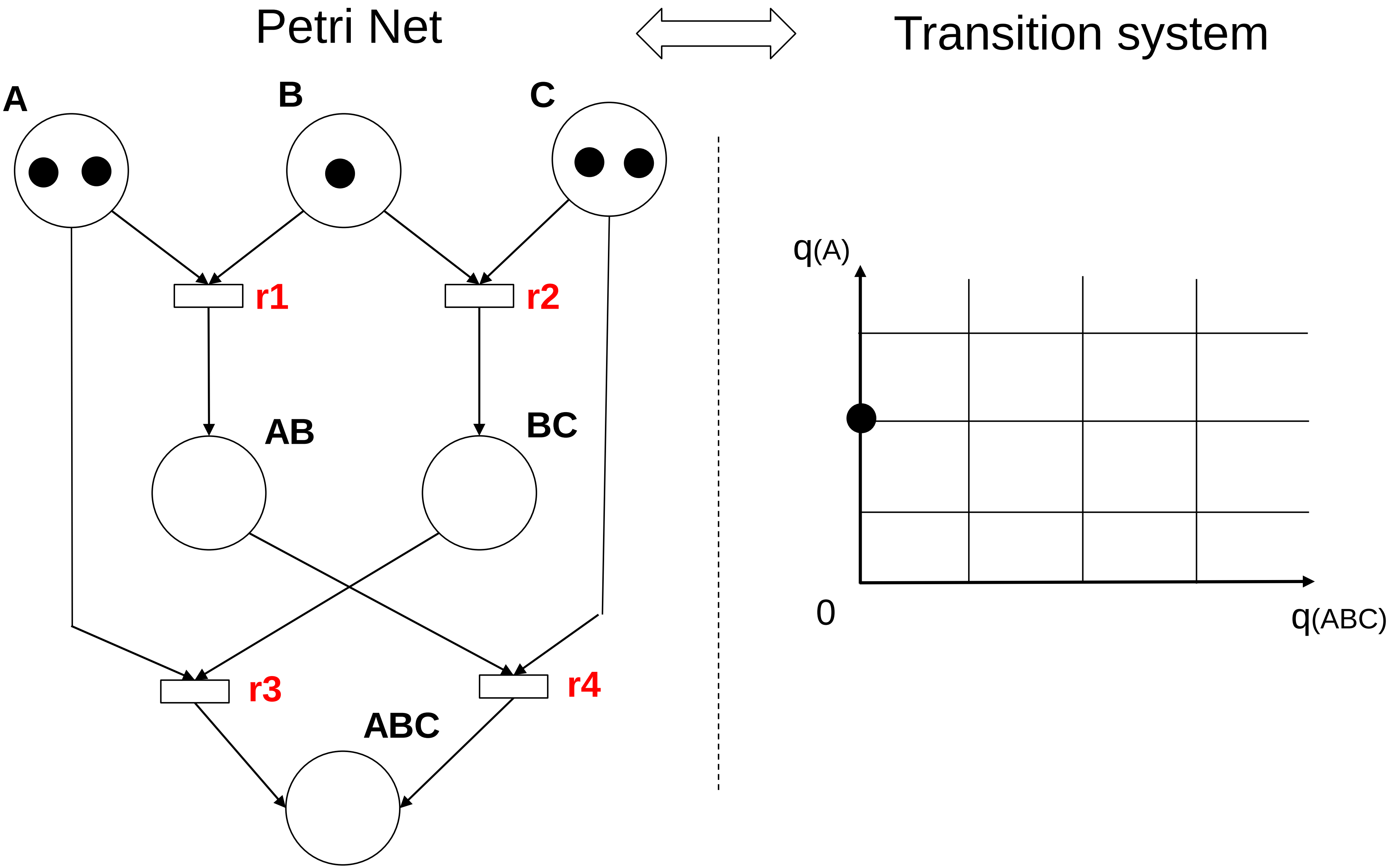


Concrete semantics

Petri Net ⟺ Transition system



Concrete semantics



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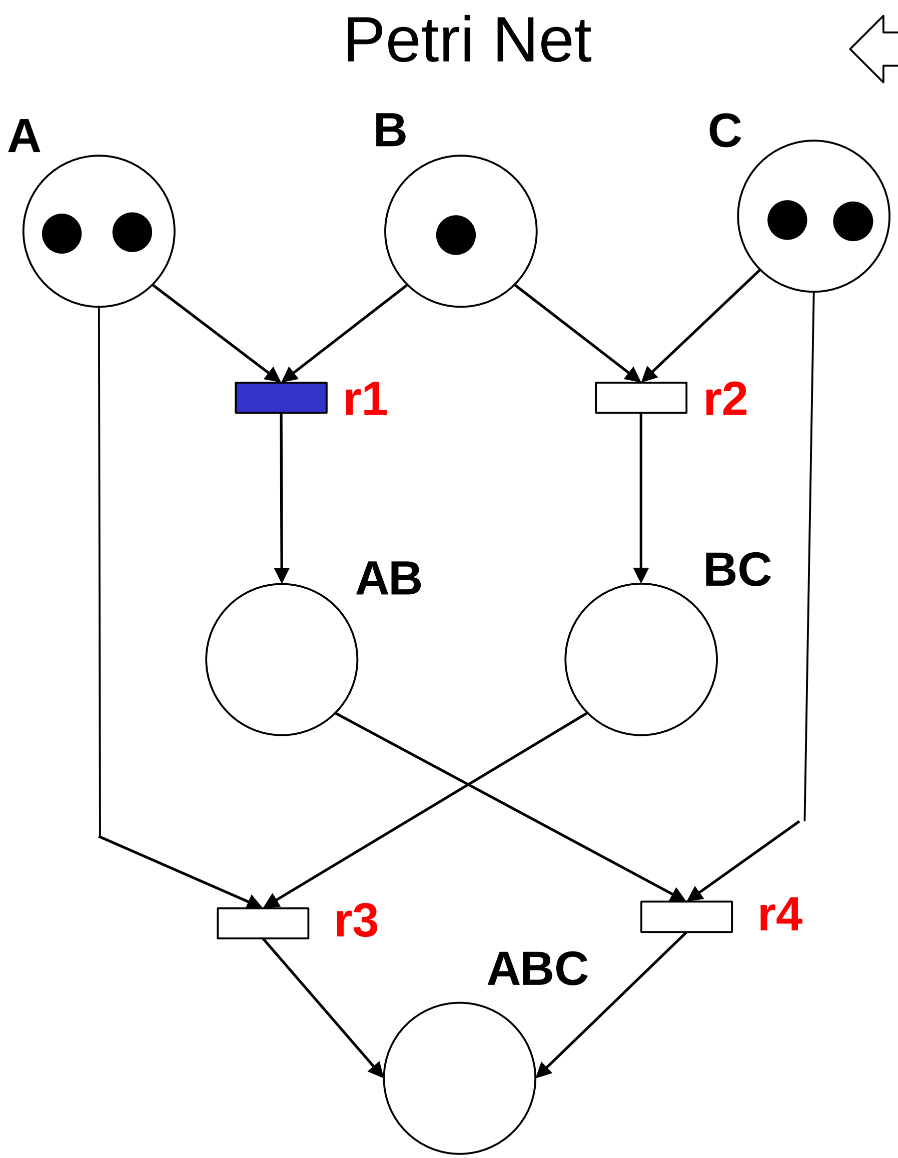

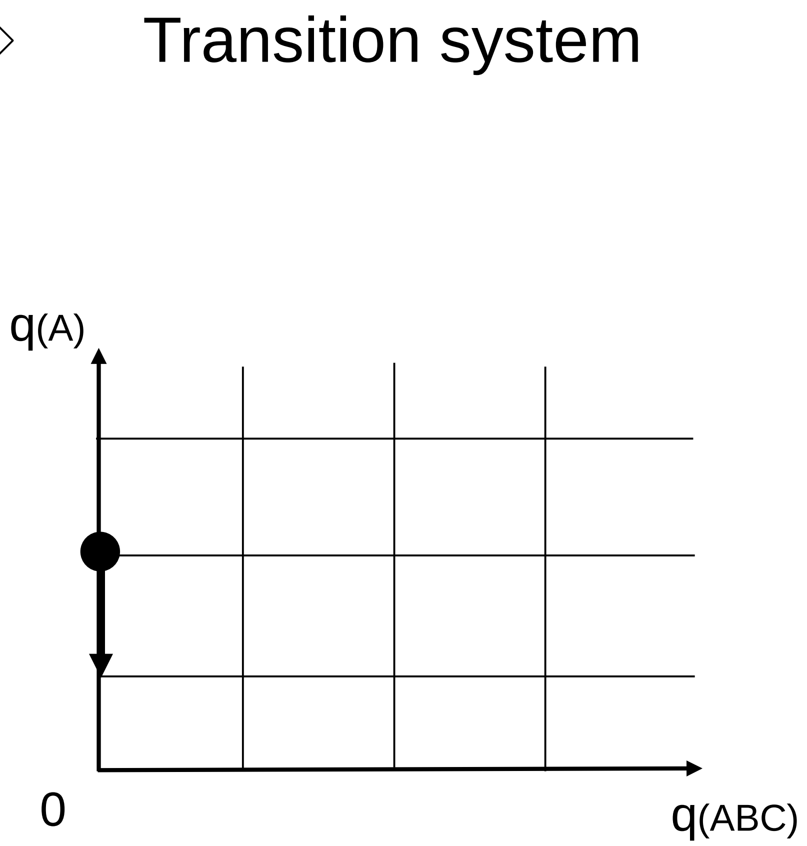

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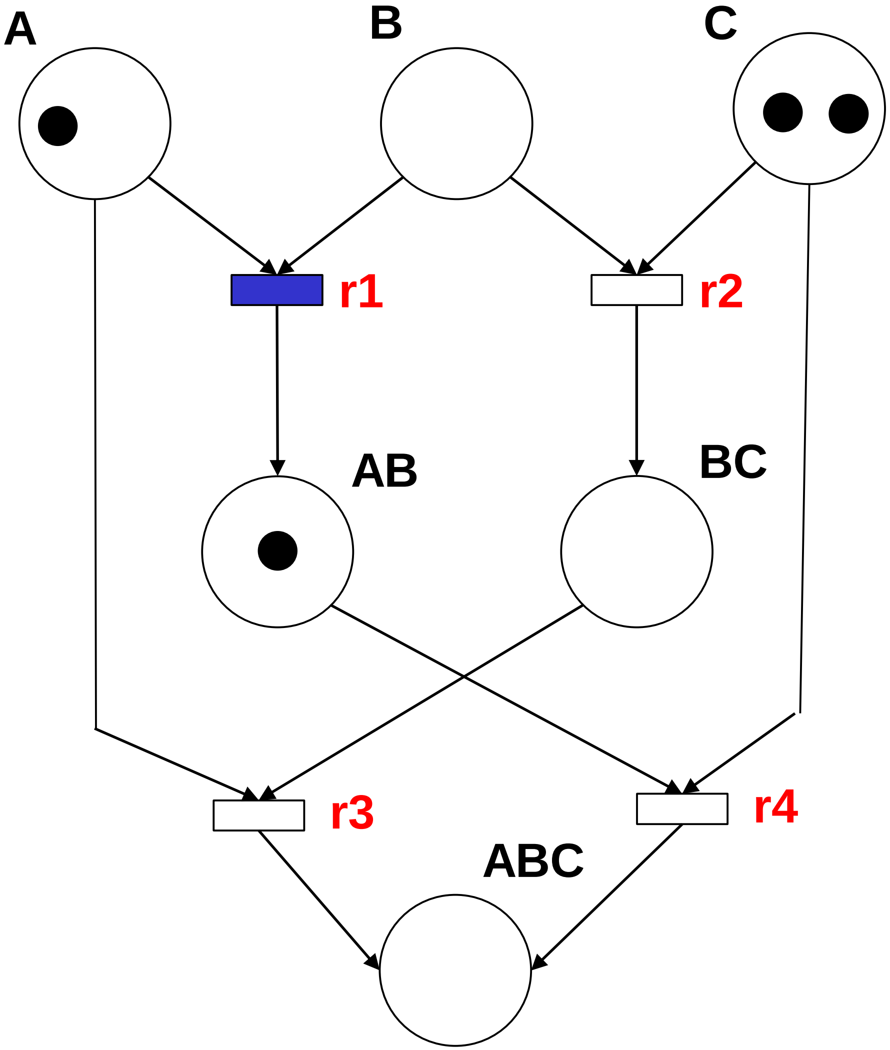

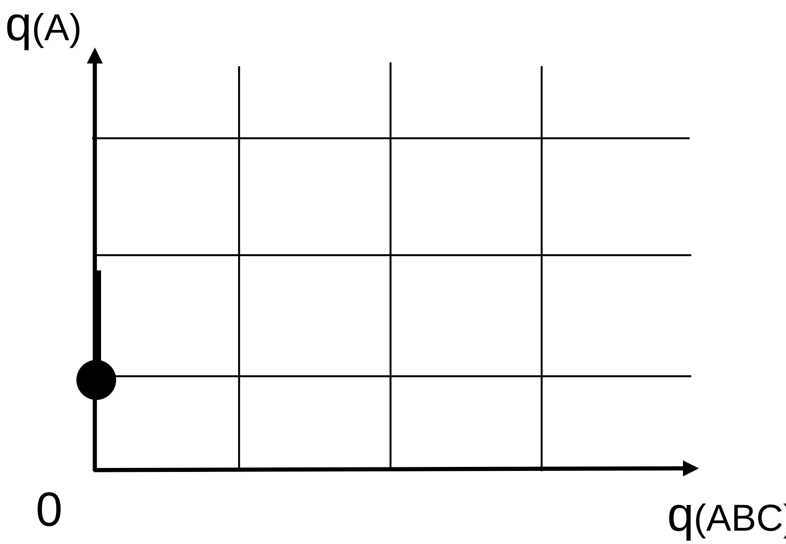

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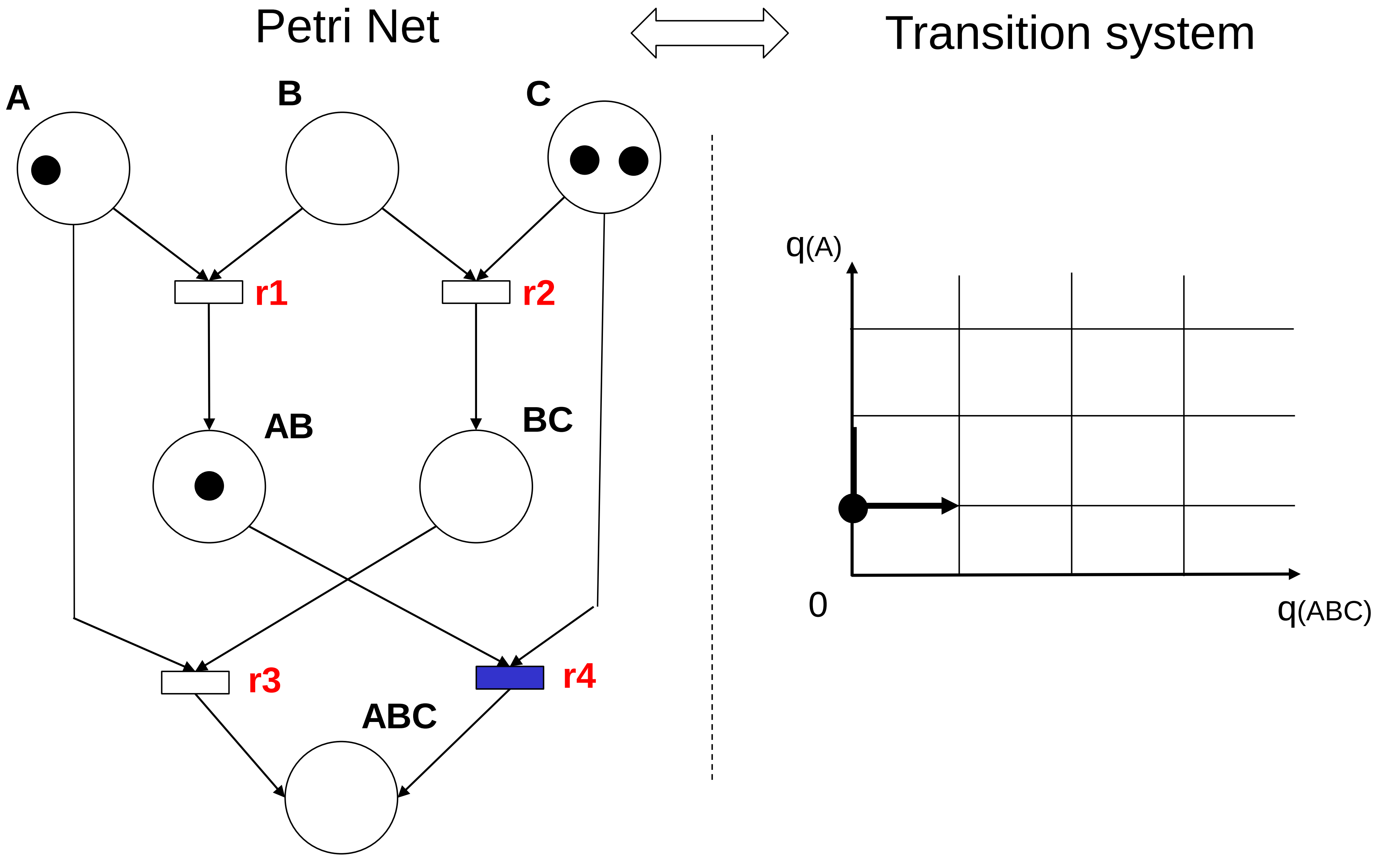

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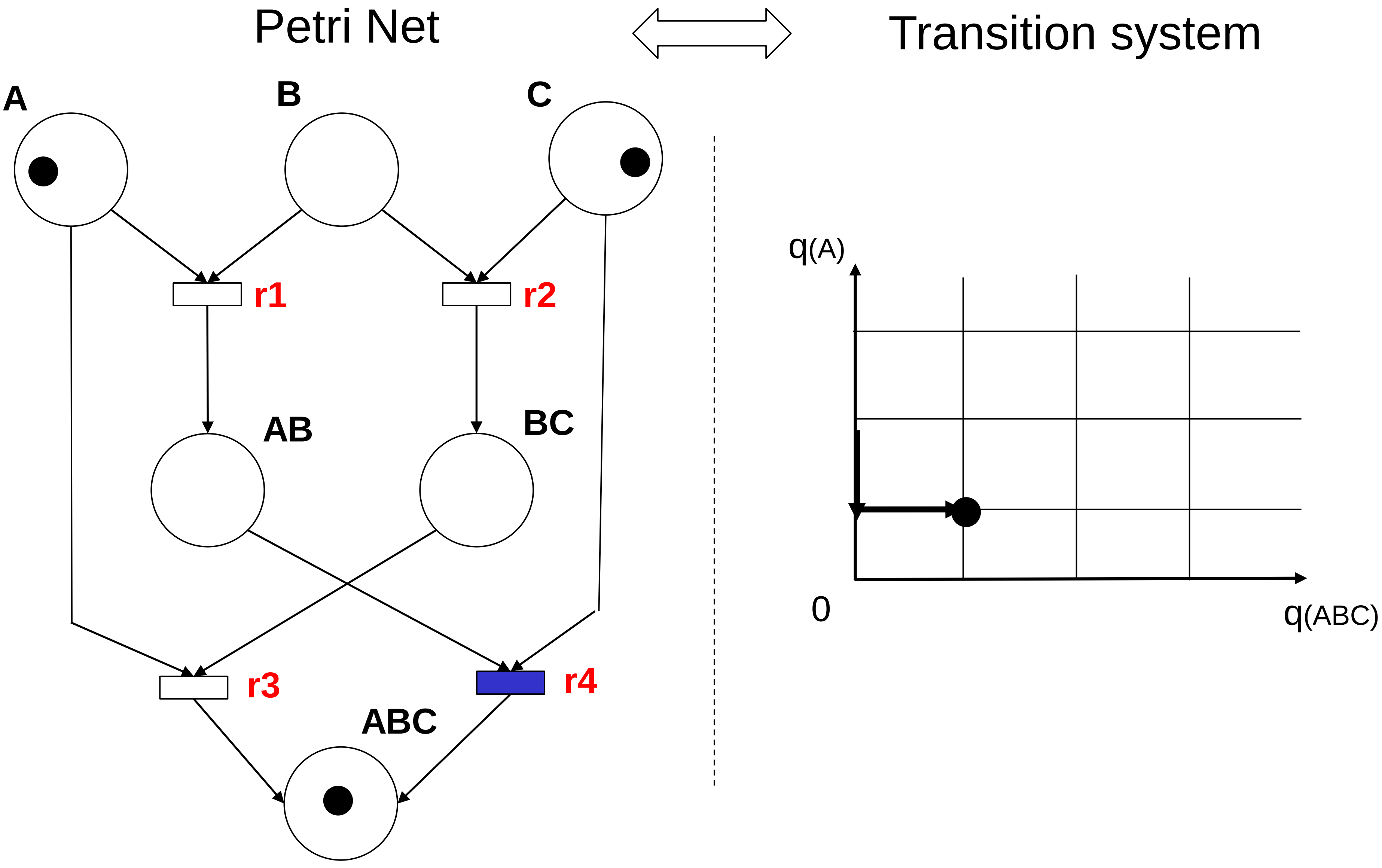

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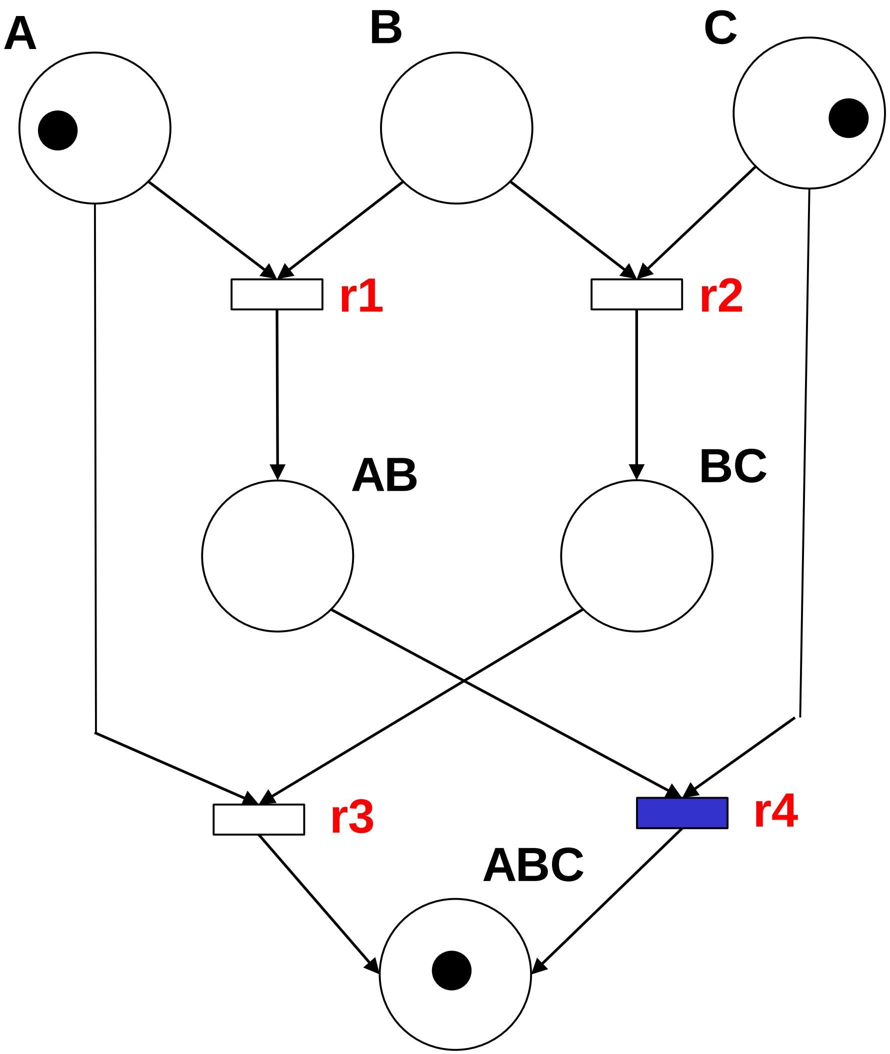
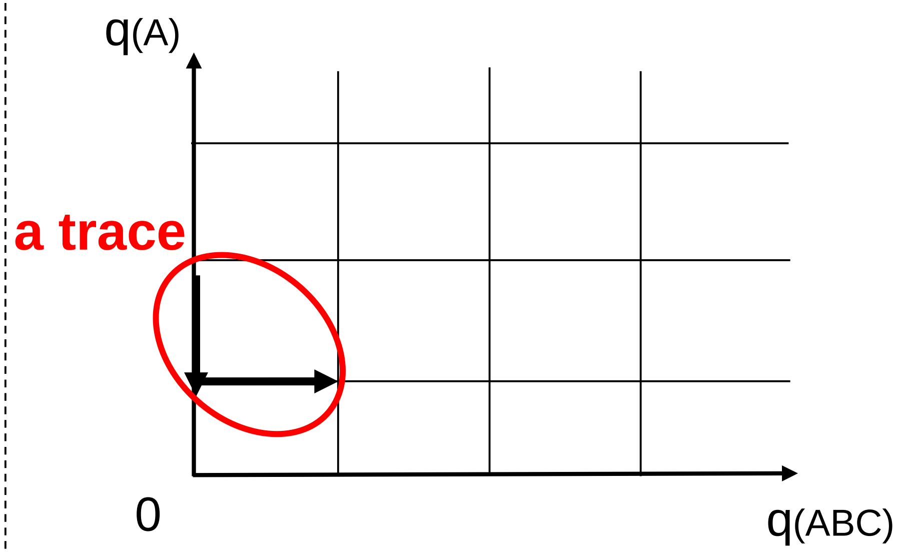




Derivation of a coarse-grained qualitative semantics

- **Automatic** and **formal** derivation of a coarse-grained semantics using abstract interpretation framework

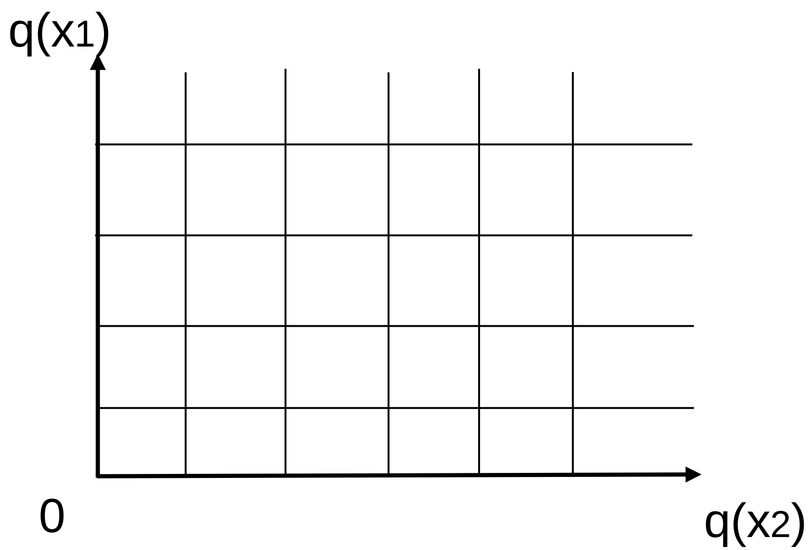
- Abstraction of values: quotienting of the domain of values by intervals

- Abstraction of traces: suppression of the ‘silent’ transitions

Derivation of a coarse-grained qualitative semantics

- **Abstraction of values**

Concrete domain of values



Derivation of a coarse-grained qualitative semantics

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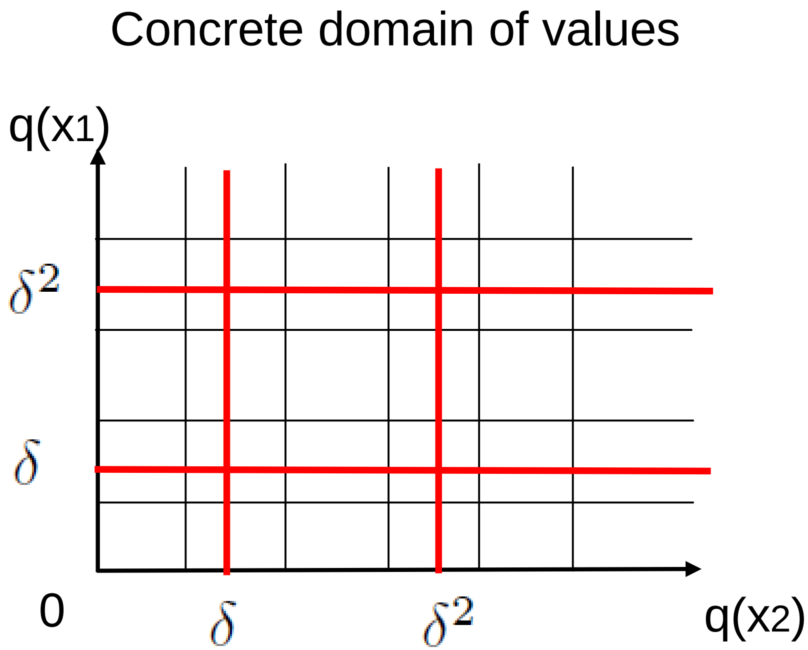

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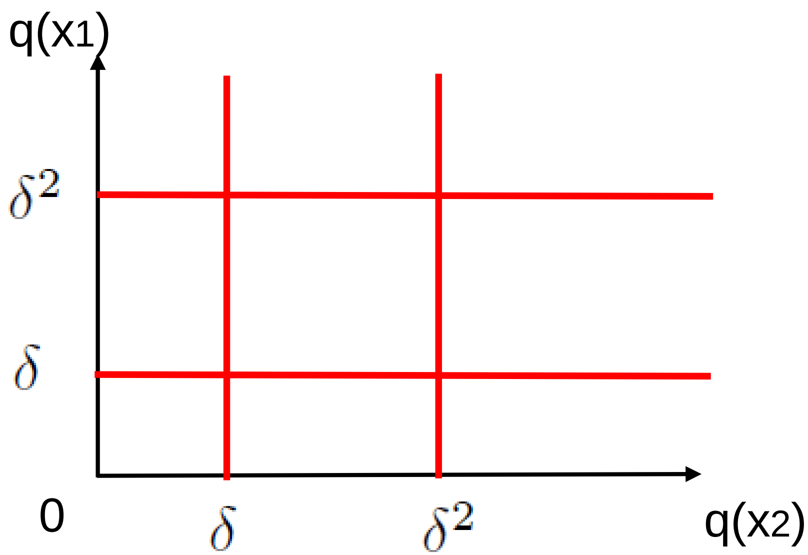

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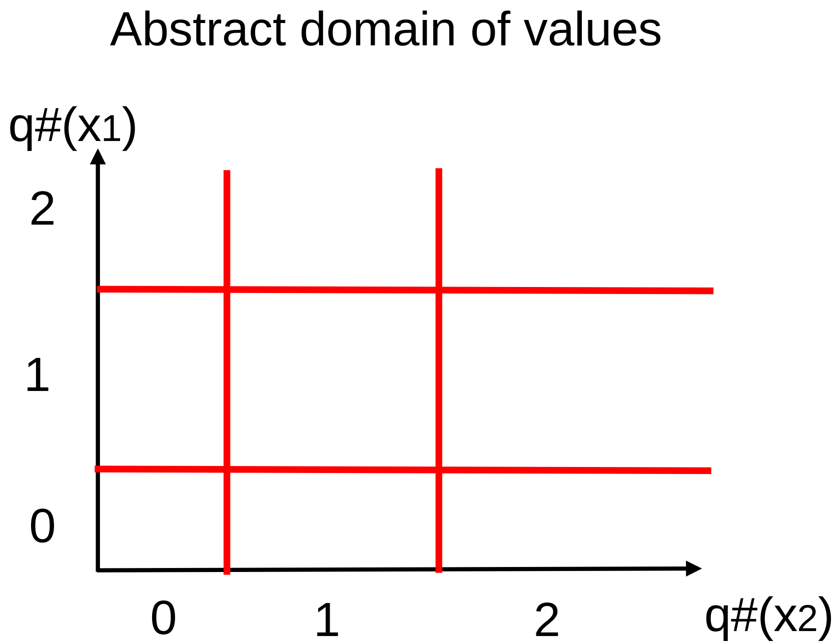
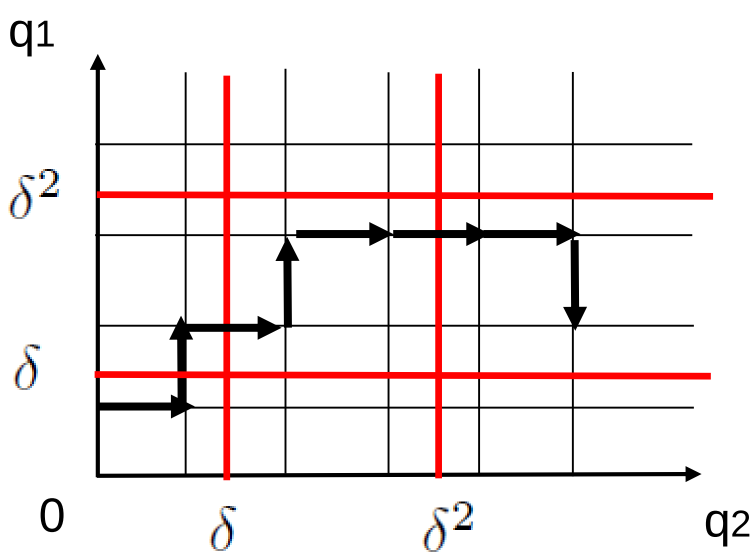


Derivation of a coarse-grained qualitative semantics

- **Abstraction of traces**

Concrete trace



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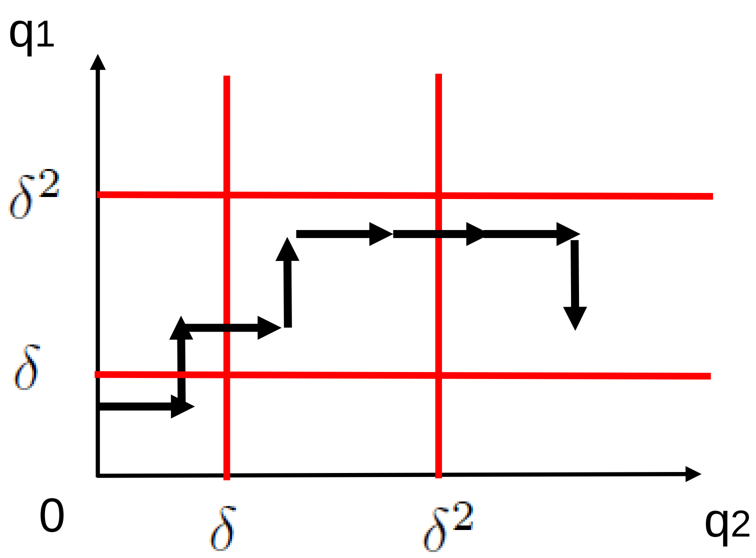

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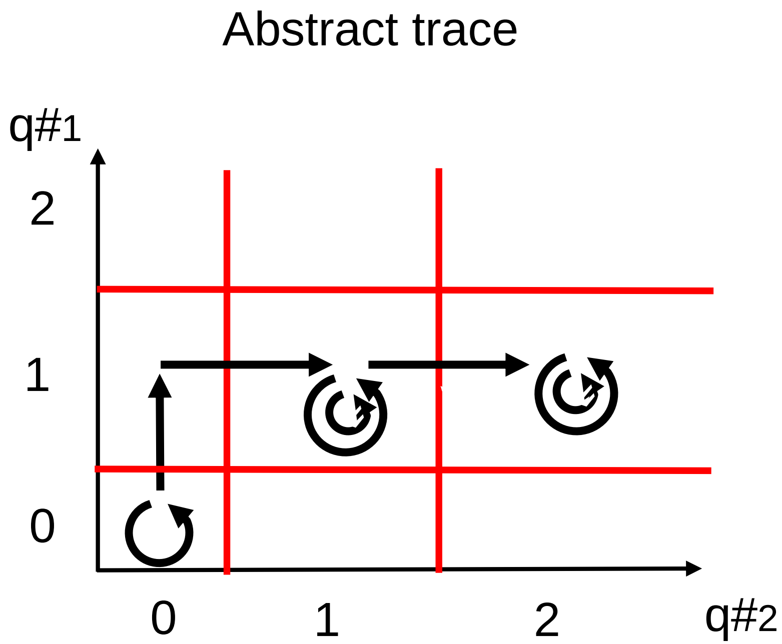

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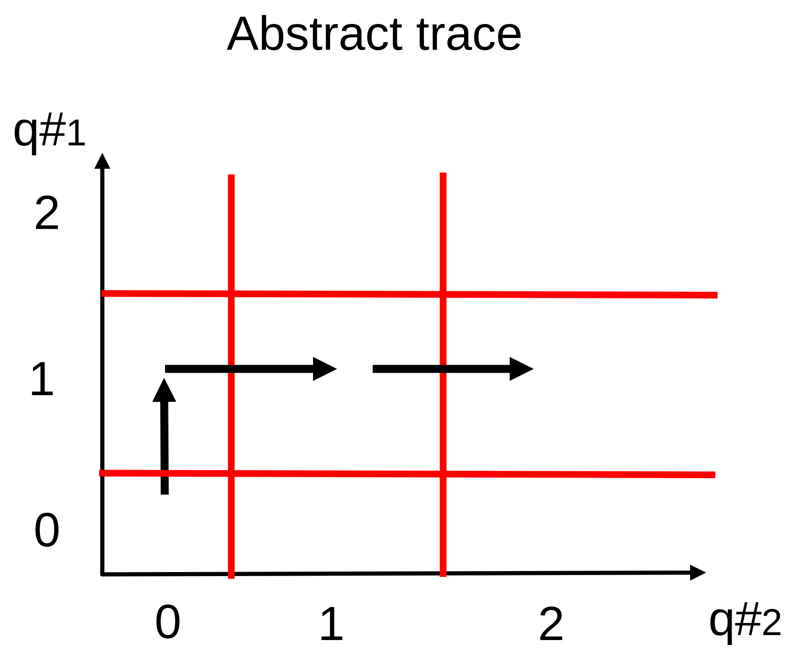

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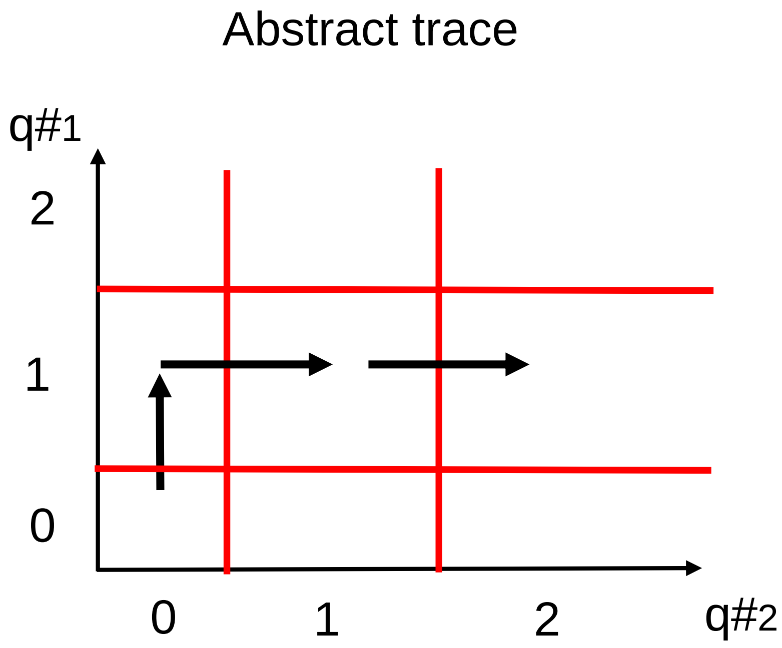

the abstraction is sound, i.e. no behavior of the concrete semantics is lost in the abstract

Derivation of a coarse-grained qualitative semantics

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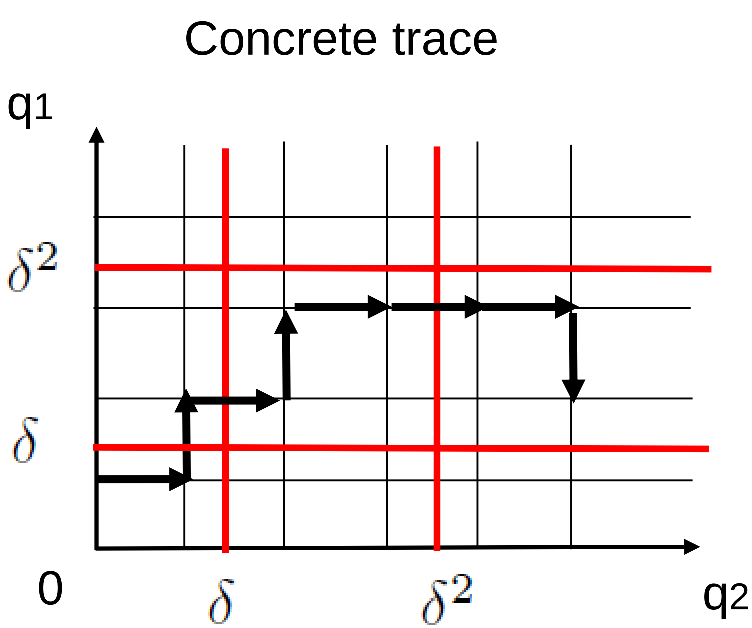

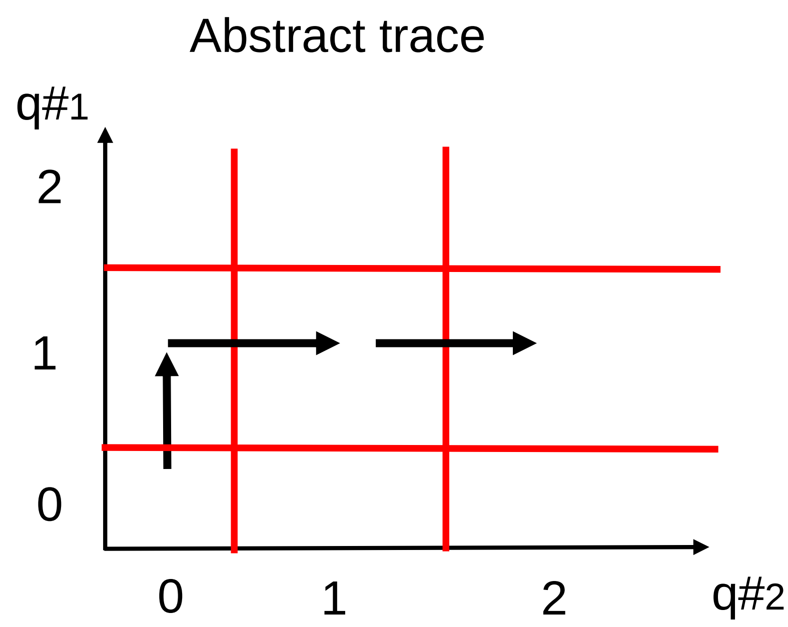

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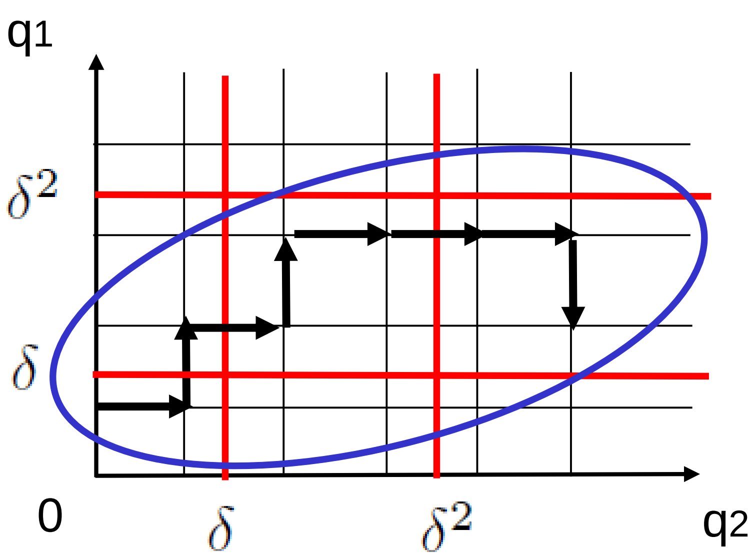
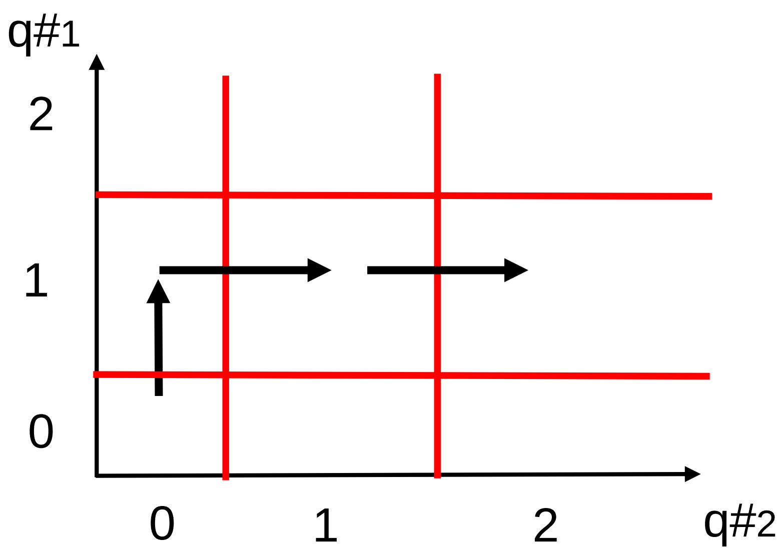


Abstract trace



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Derivation of a coarse-grained qualitative semantics

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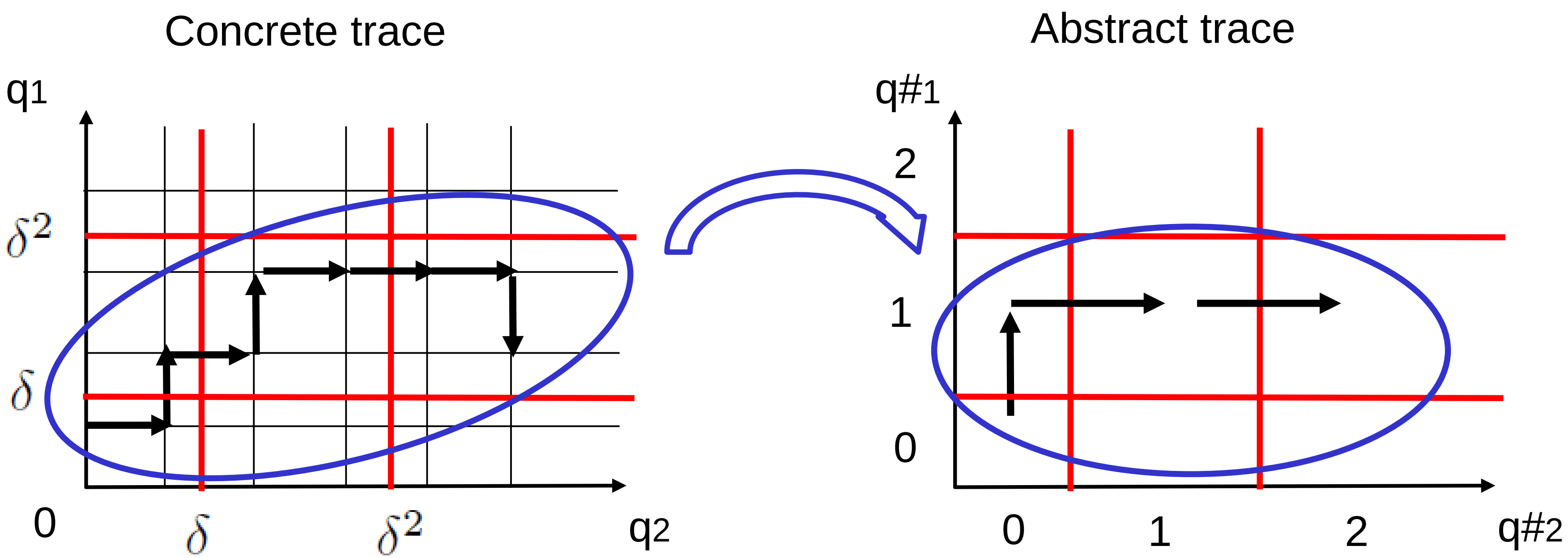

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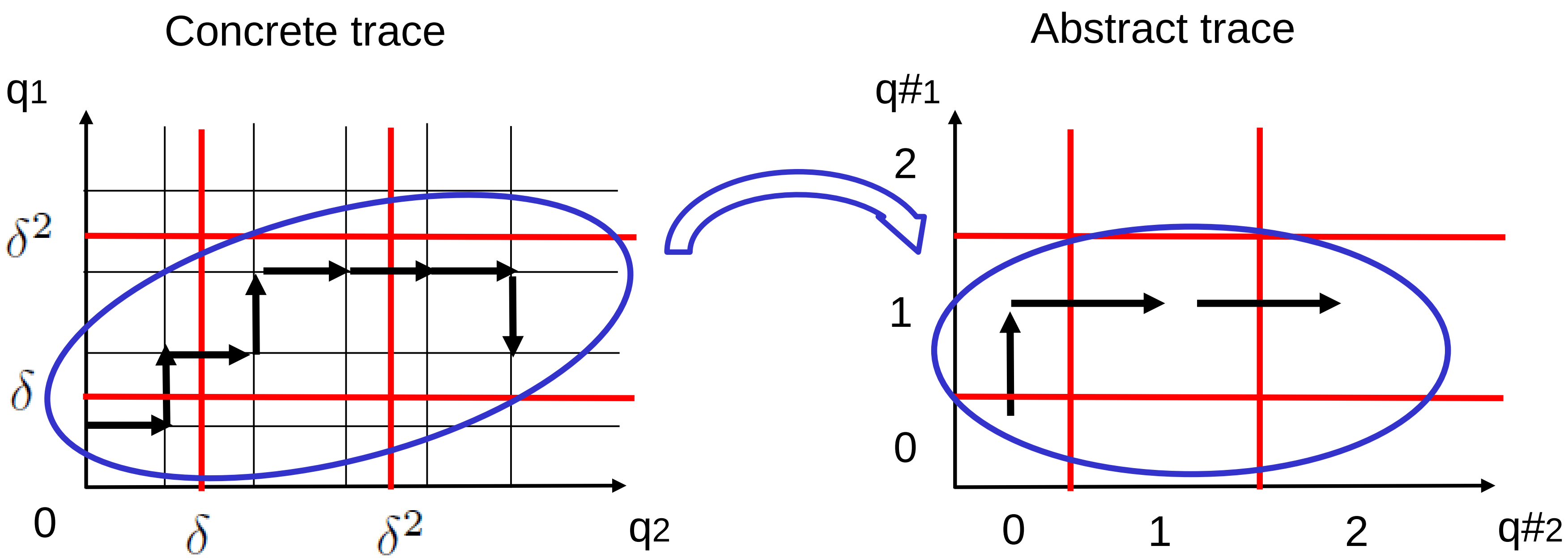
Derivation of a coarse-grained qualitative semantics

- **Abstraction of traces**

Spurious behaviors can be introduced by the abstraction



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Derivation of a coarse-grained qualitative semantics

- **Property**

For any reaction r and any abstract state $q^\sharp$, if $\delta > max(V_\infty, M_\infty)$, then, for any chemical species $y \in \nu$ such that $V_r(y) \neq 0$ and $0 \leq q^\sharp(y) + sign(V_r(y)) \leq p$:

$$(q^\sharp \xrightarrow{r} q^\sharp[y \mapsto q^\sharp(y) + sign(V_r(y))]) \text{ is an abstract transition.}$$

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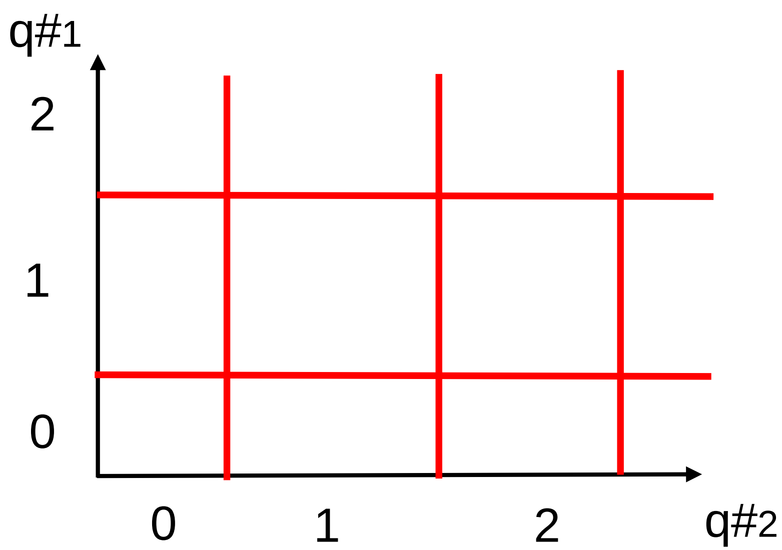

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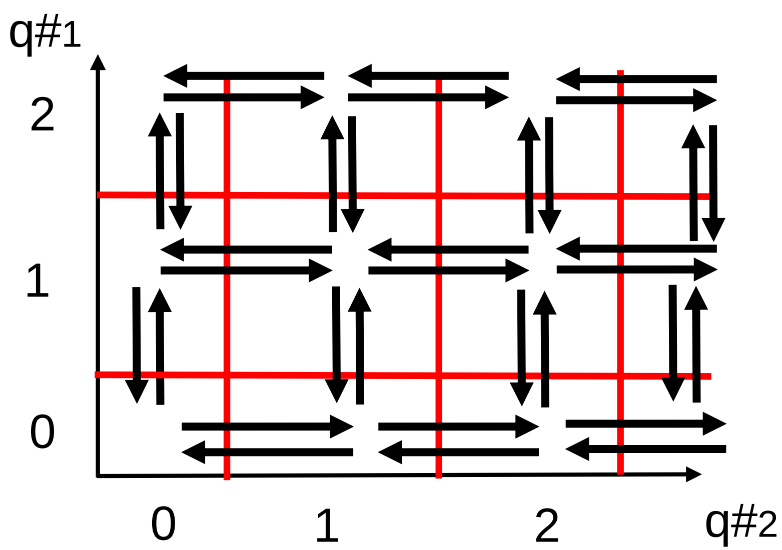

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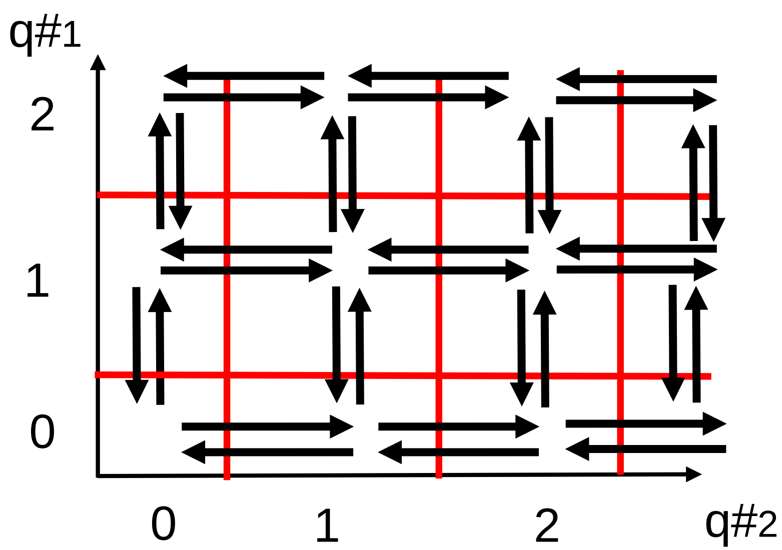

Too coarse abstraction!

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Case study

$$\begin{cases} A + B \overset{k_1}{\rightarrow} AB & (r1) \\ B + C \overset{k_2}{\rightarrow} BC & (r2) \\ A + BC \overset{k_1}{\rightarrow} ABC & (r3) \\ AB + C \overset{k_2}{\rightarrow} ABC & (r4) \end{cases}$$

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$$\begin{array}{c} q^\sharp(ABC) = 0 \\ \downarrow r_3 \\ q^\sharp(ABC) = 1 \\ \vdots \\ \downarrow r_3 \\ q^\sharp(ABC) = p \end{array}$$

Derivation of a coarse-grained qualitative semantics

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This abstract semantics does not capture the sequestration effect of our case study

Refinements of the abstract semantics

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Introduction of three refinements

- Mass invariants

- Limiting resources for the crossing of intervals

- Incorporation of kinetic information

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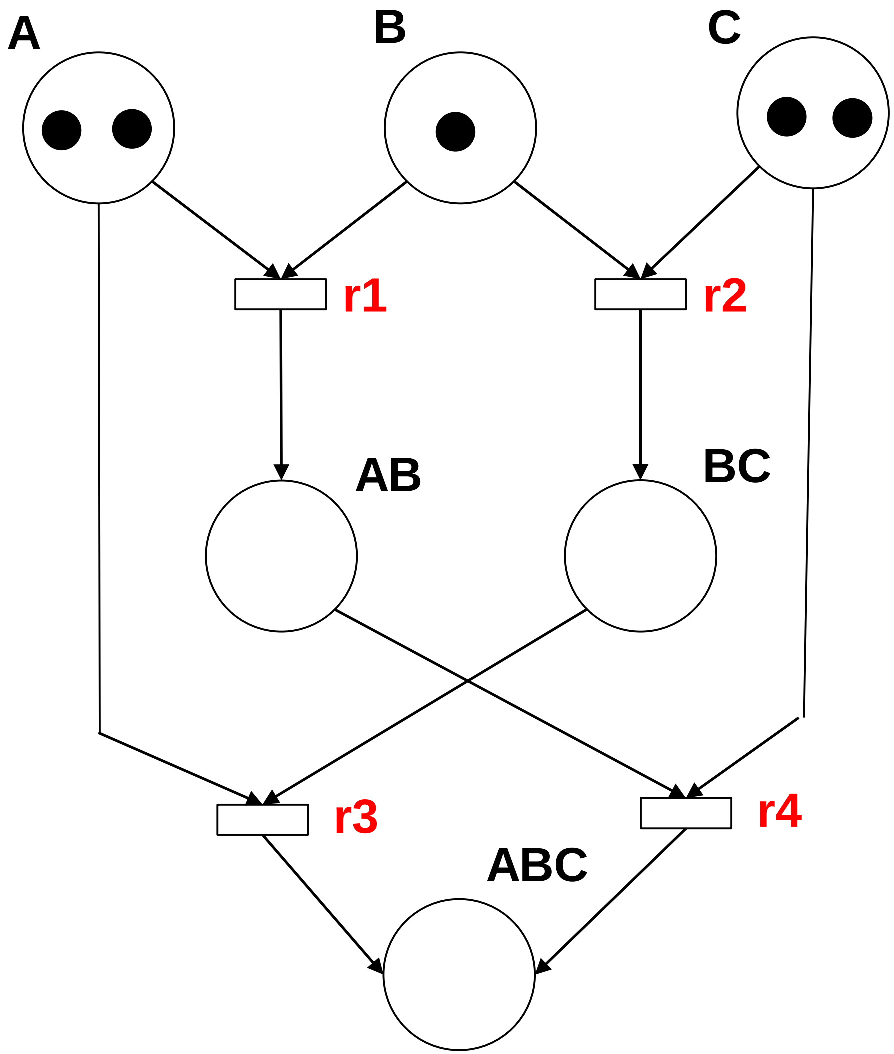
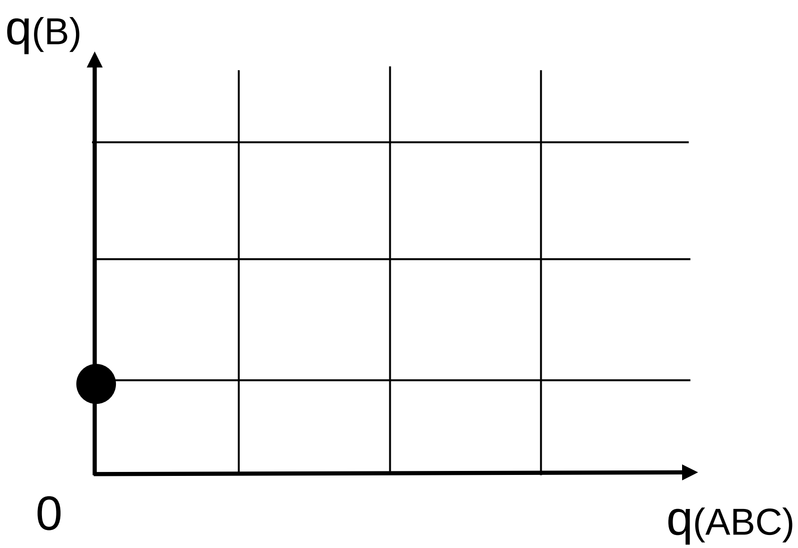
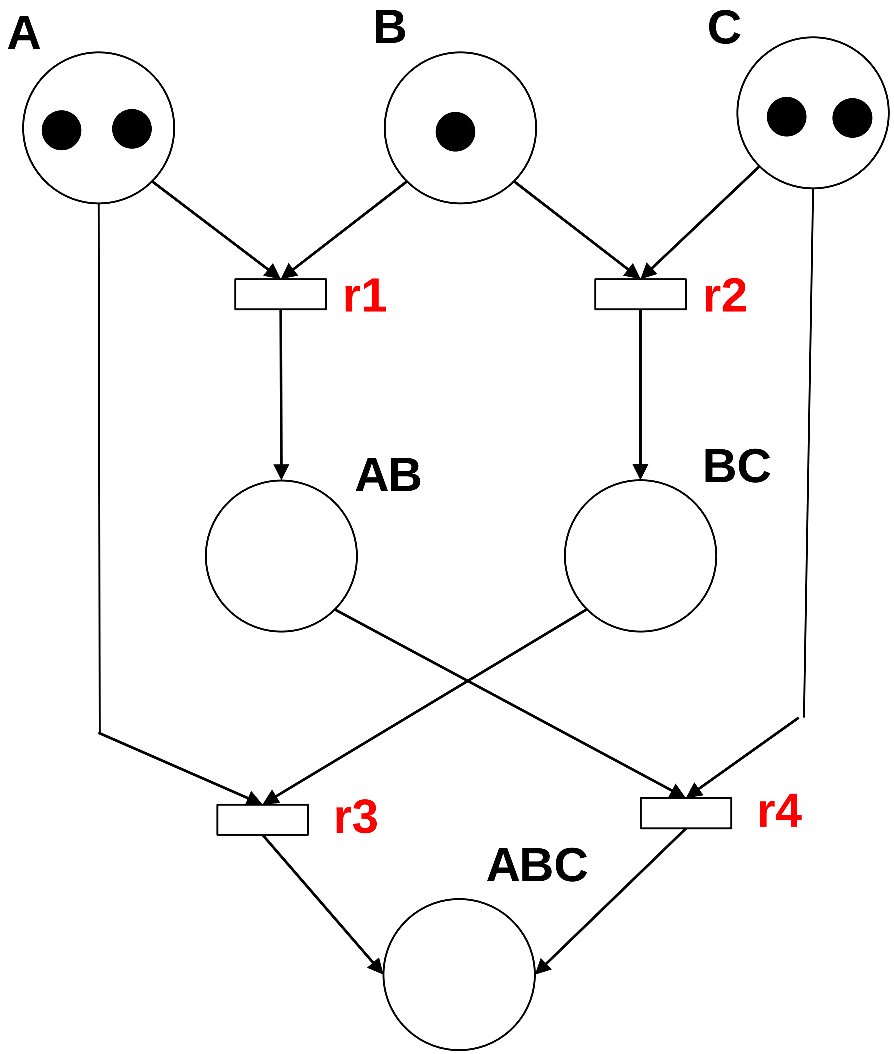
Mass invariants

$B_T = q(B) + q(AB) + q(BC) + q(ABC)$



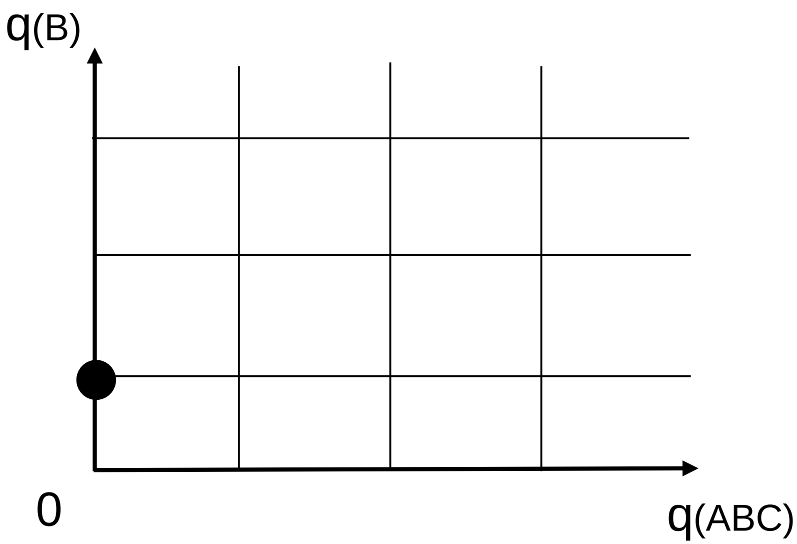


Mass invariants



$$B_T = q(B) + q(AB) + q(BC) + q(ABC)$$

$$1 \quad + \quad 0 \quad + \quad 0 \quad + \quad 0 \quad = \quad 1$$



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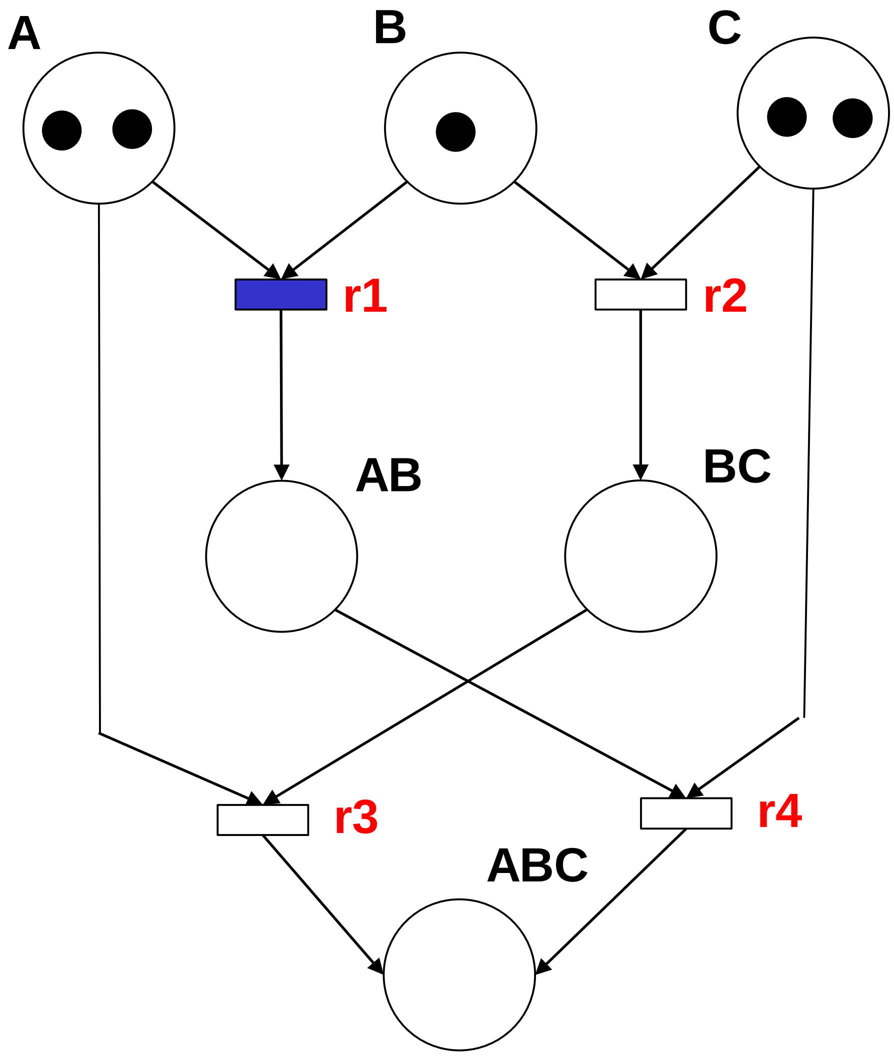
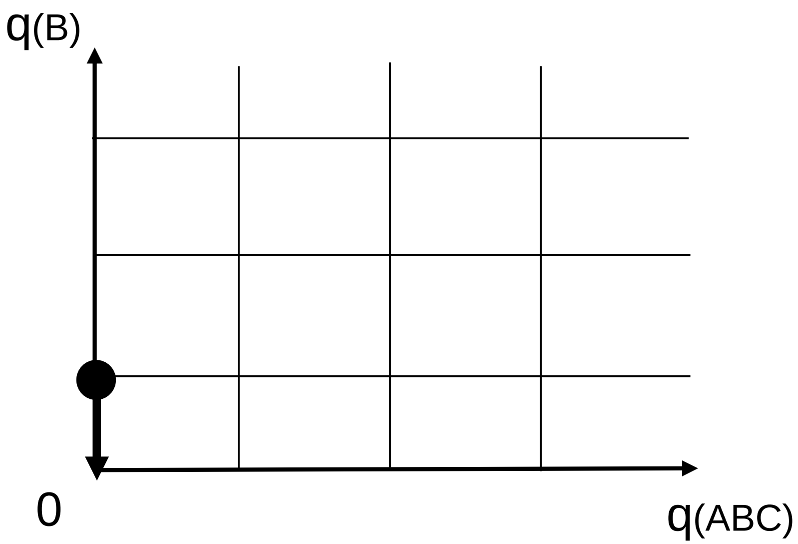


BT = q(B) + q(AB) + q(BC) + q(ABC)

1 + 0 + 0 + 0 = 1



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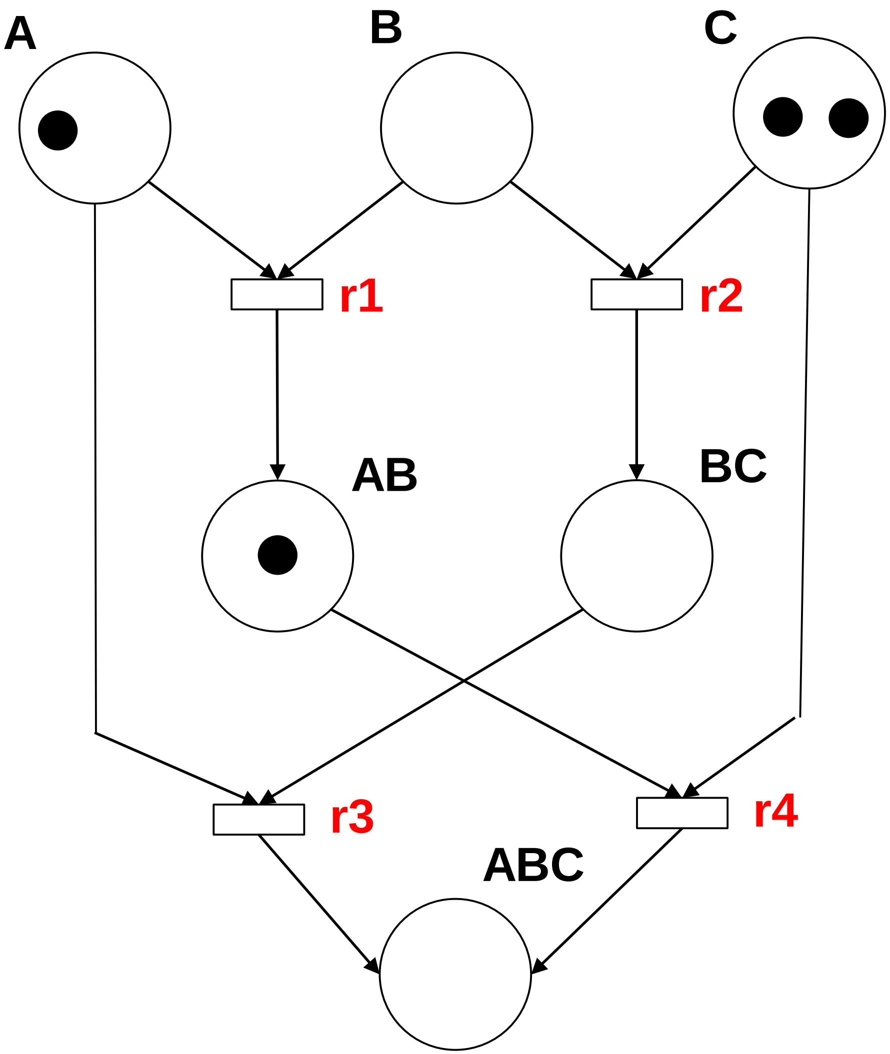
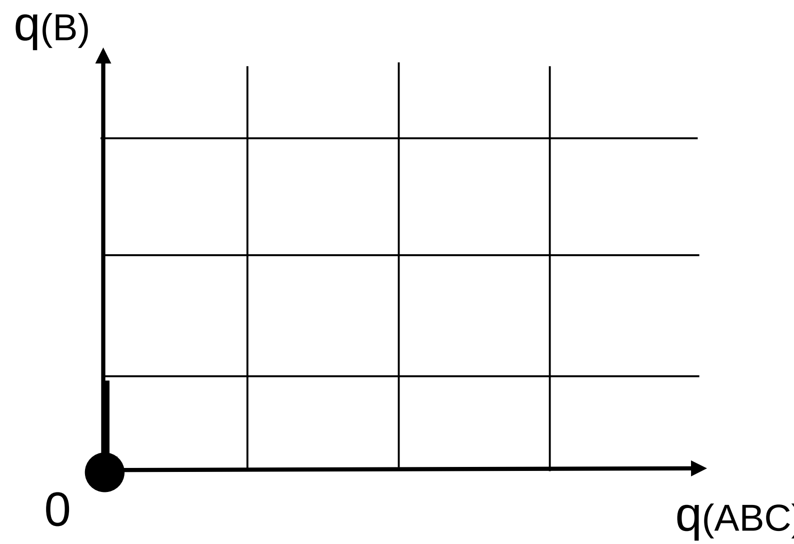


$B_T = q(B) + q(AB) + q(BC) + q(ABC)$

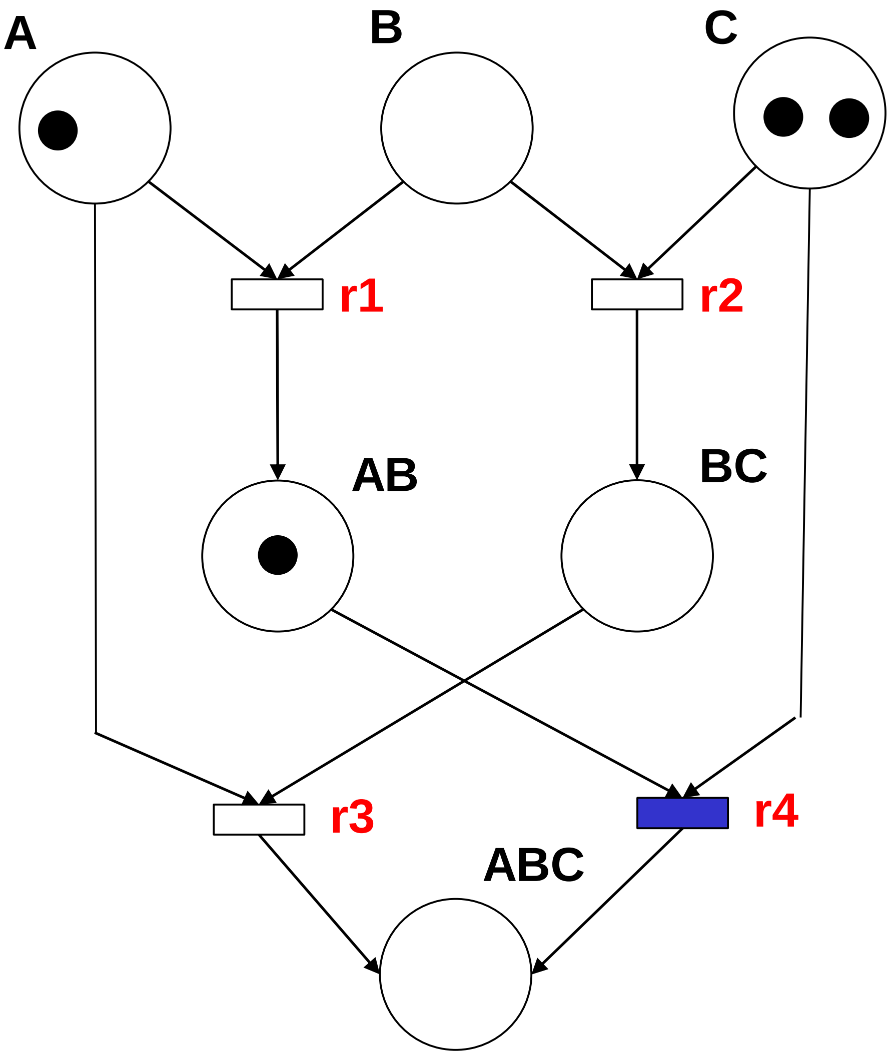
0 + 1 + 0 + 0 = 1

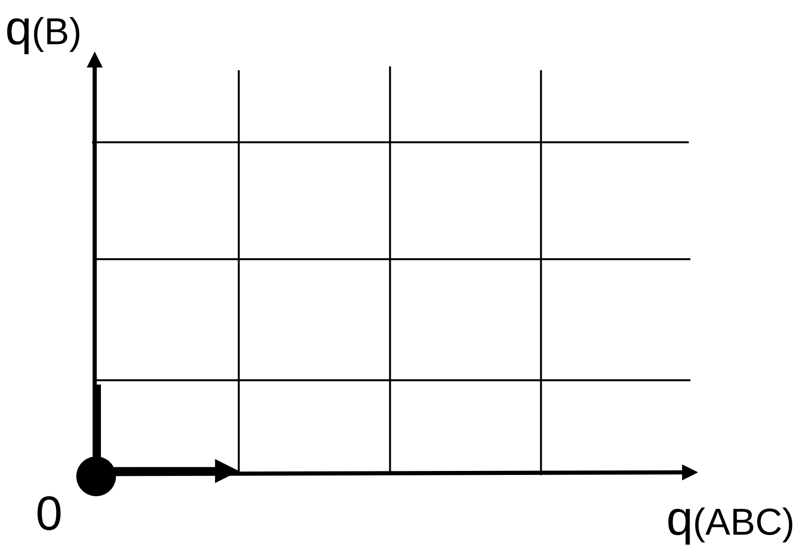


Mass invariants

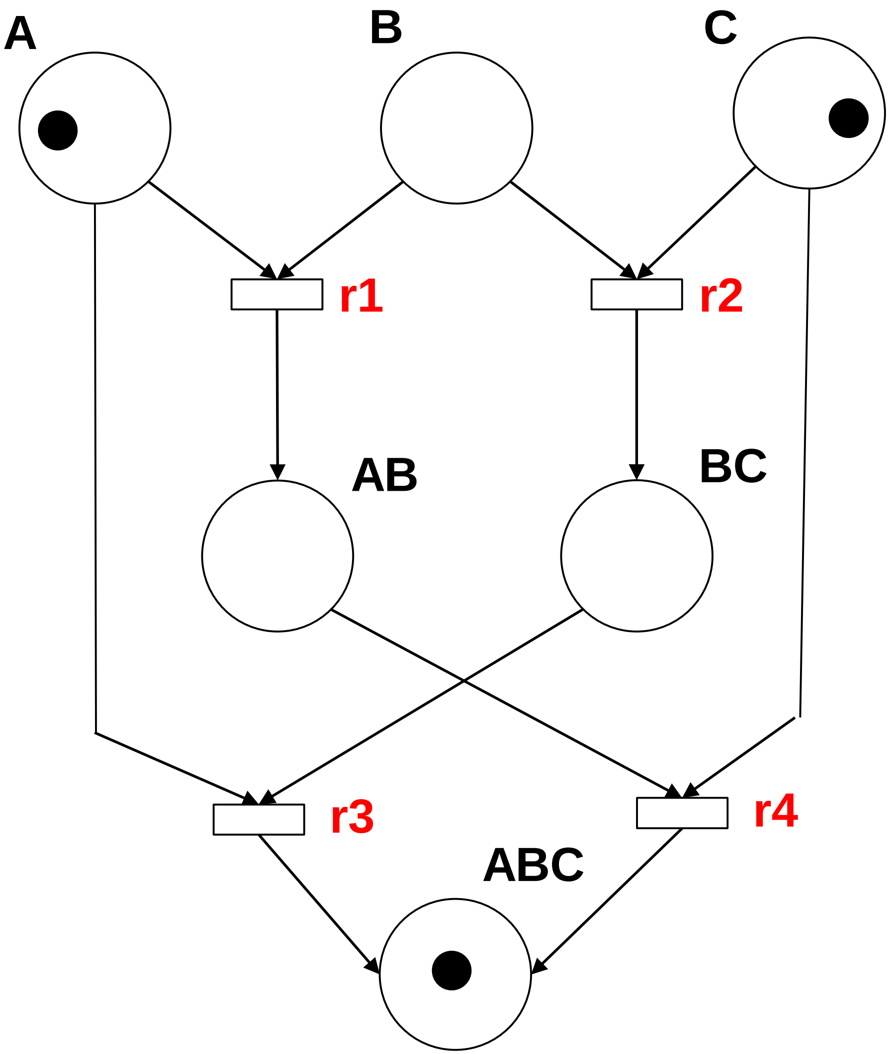
B_T = q(B) + q(AB) + q(BC) + q(ABC)

0 + 1 + 0 + 0 = 1





Mass invariants



Bт = q(B) + q(AB) + q(BC) + q(ABC)

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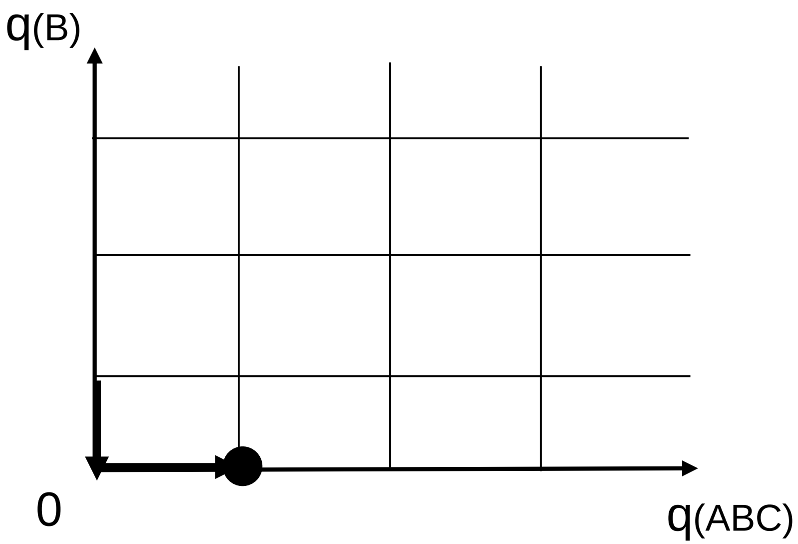
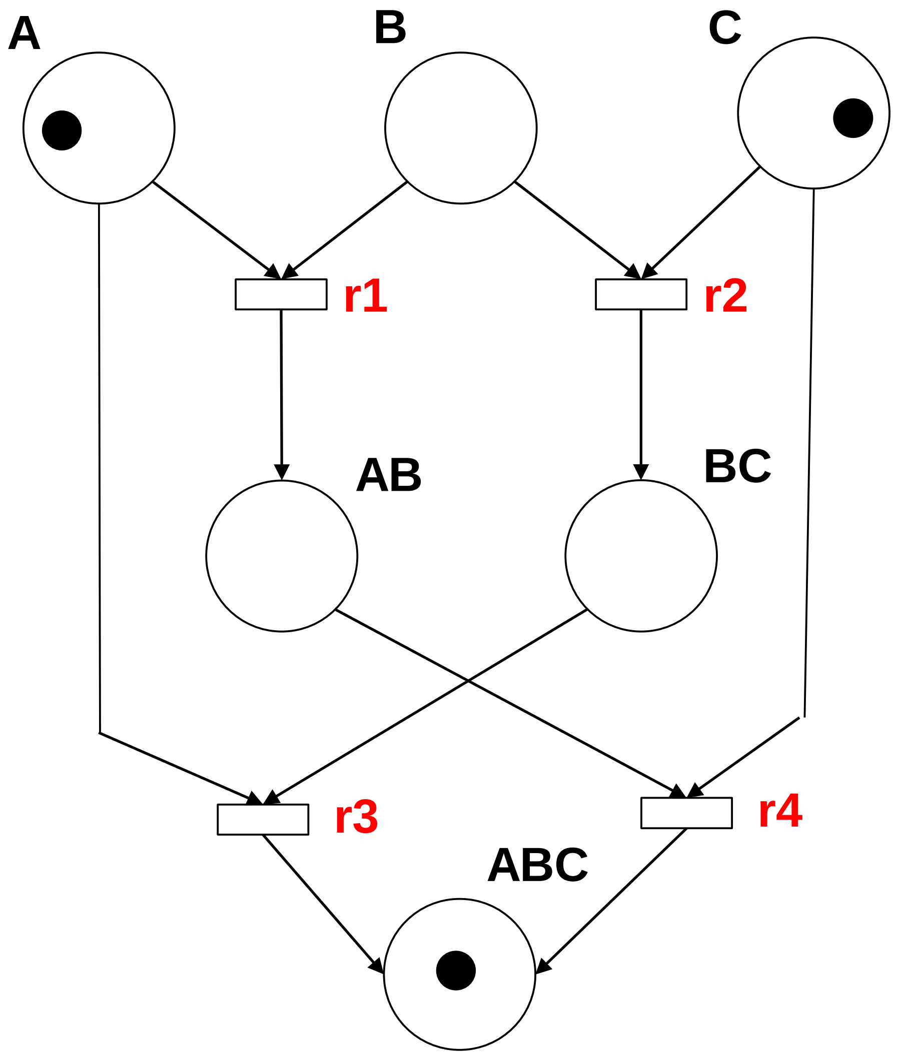
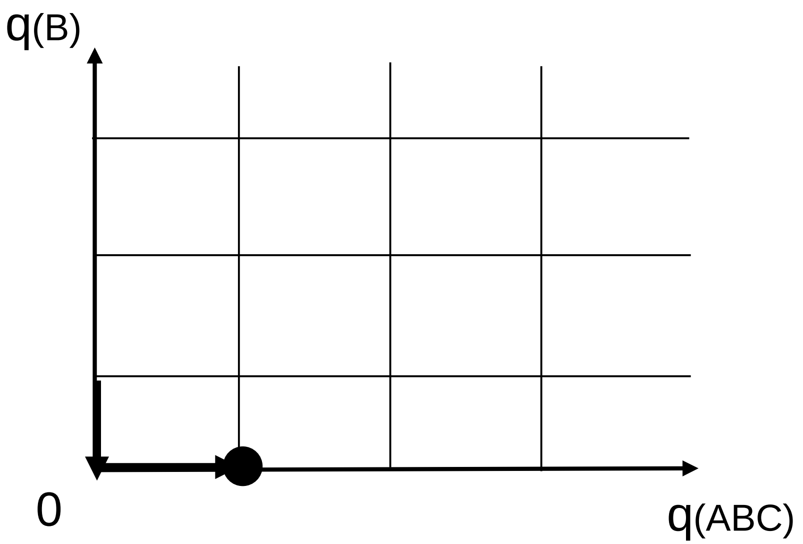


Mass invariants



B_T = q(B) + q(AB) + q(BC) + q(ABC)

B_T is invariant all along a trace



Abstract semantics refined with mass invariants

- Refinement of our abstraction with mass invariants

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⇨ the abstraction is sound (and more precise!)

Abstract semantics refined with mass invariants

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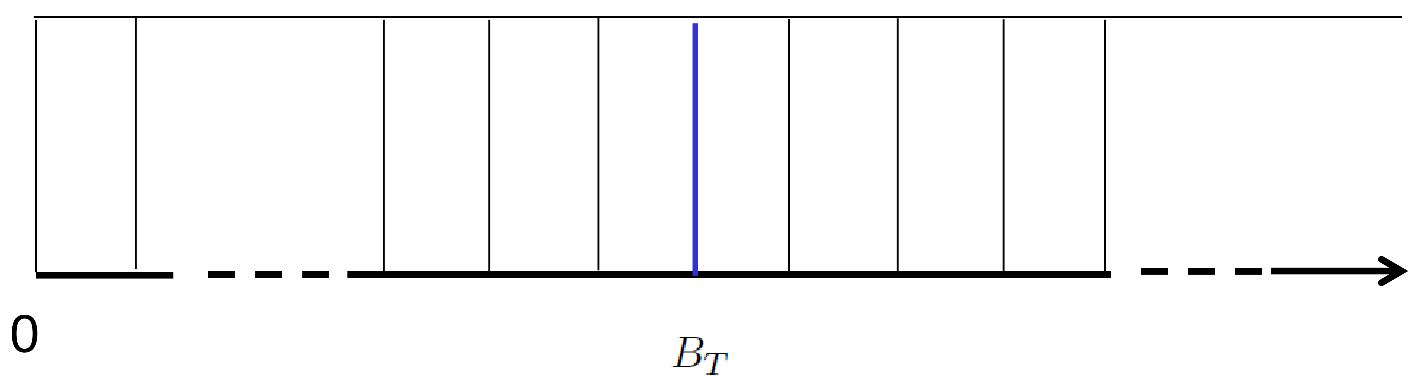
- Computation of the invariant in the abstract

Case study : mass conservation of B



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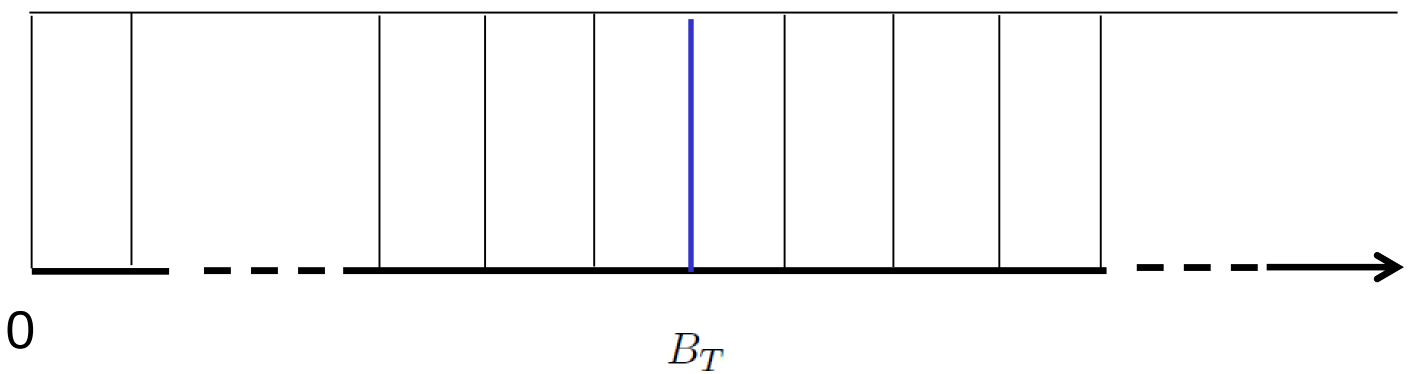

$$max\left(q^\sharp(B), q^\sharp(AB), q^\sharp(BC), q^\sharp(ABC)\right)$$

Abstract semantics refined with mass invariants

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$\Longrightarrow$ the abstraction is sound (and more precise!)

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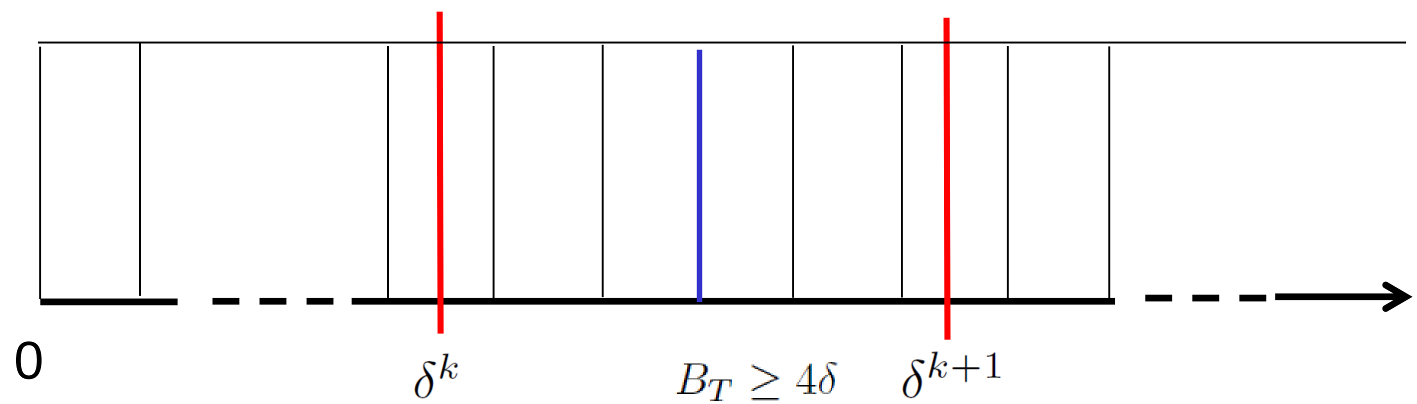
Case study : mass conservation of B

$\delta > 4$



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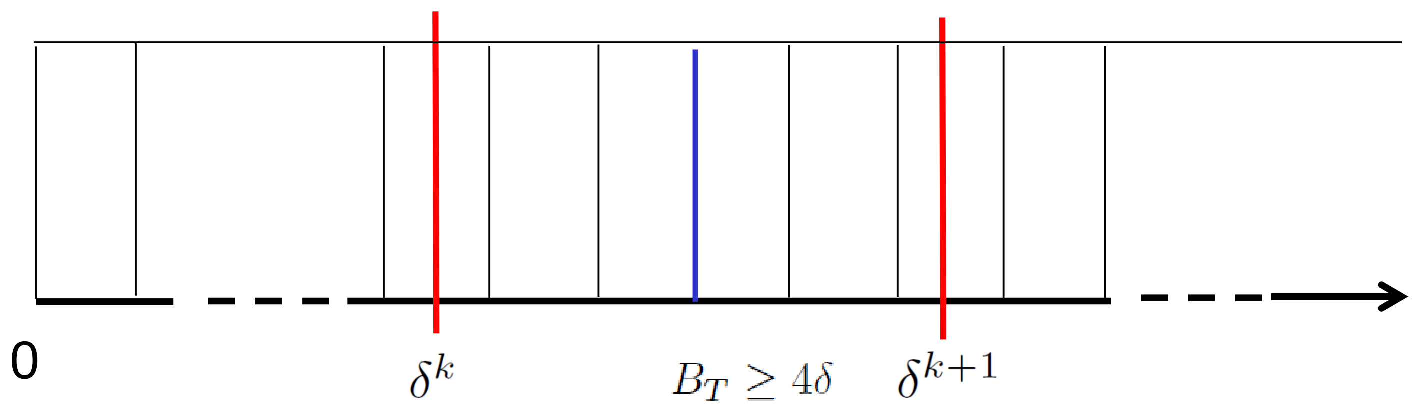


$$max\left(q^\sharp(B), q^\sharp(AB), q^\sharp(BC), q^\sharp(ABC)\right) = k$$

Abstract semantics refined with mass invariants

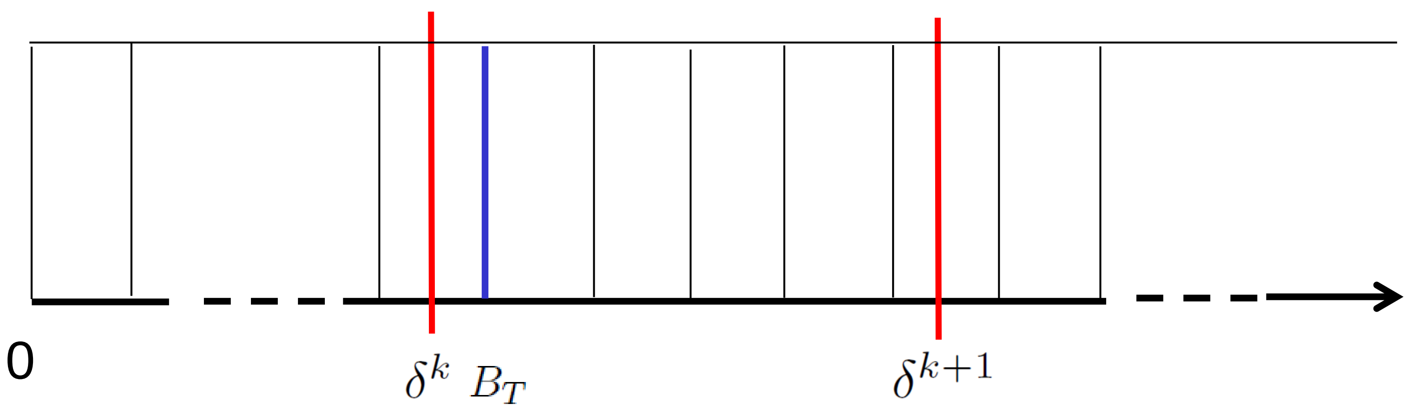
- Refinement of our abstraction with mass invariants

⇨ the abstraction is sound (and more precise!)

- Computation of the invariant in the abstract

Case study : mass conservation of B

$\delta > 4$



$$max\left(q^\sharp(B), q^\sharp(AB), q^\sharp(BC), q^\sharp(ABC)\right)$$

Abstract semantics refined with mass invariants

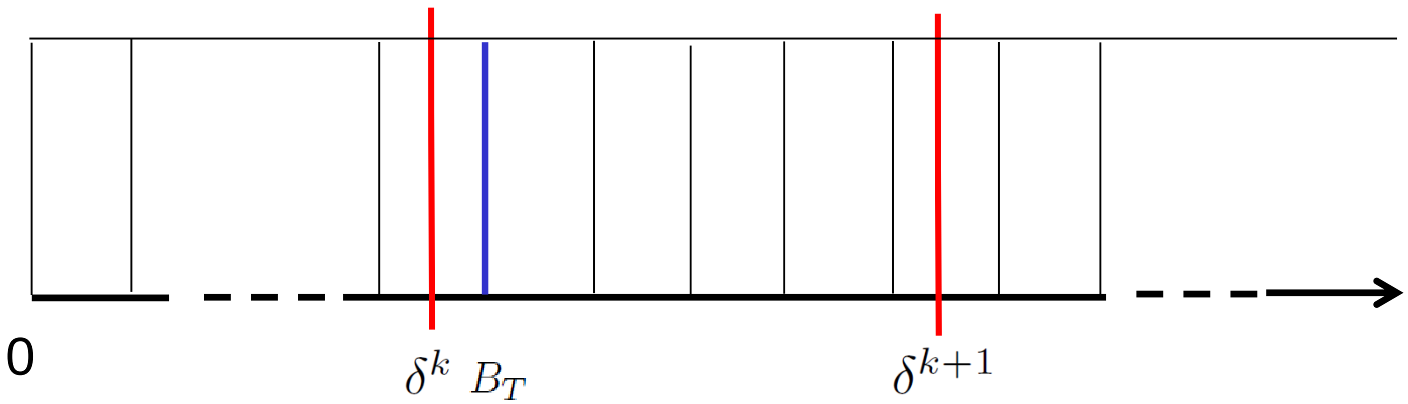
- Refinement of our abstraction with mass invariants

$\Rightarrow$ the abstraction is sound (and more precise!)

- Computation of the invariant in the abstract

Case study : mass conservation of B

$\delta > 4$



$$max\left(q^\sharp(B), q^\sharp(AB), q^\sharp(BC), q^\sharp(ABC)\right) \in \{k, k-1\}$$

Refinements of the abstract semantics

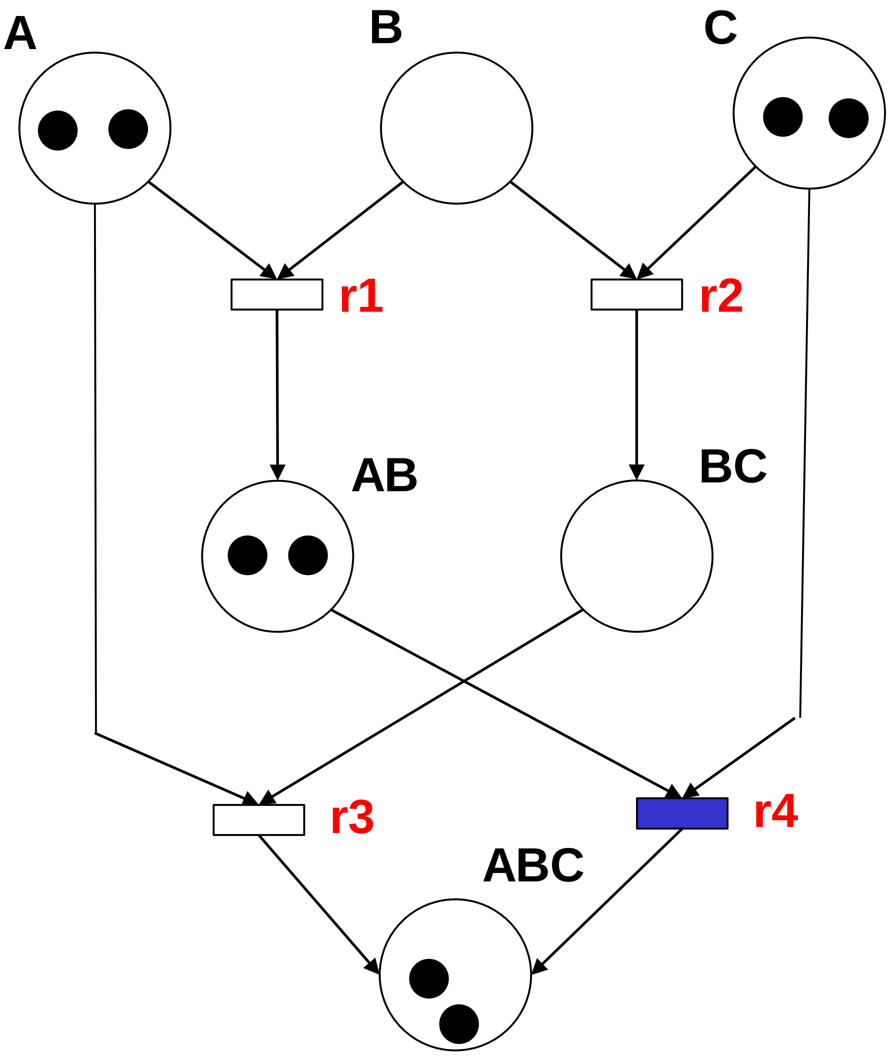
Introduction of three refinements

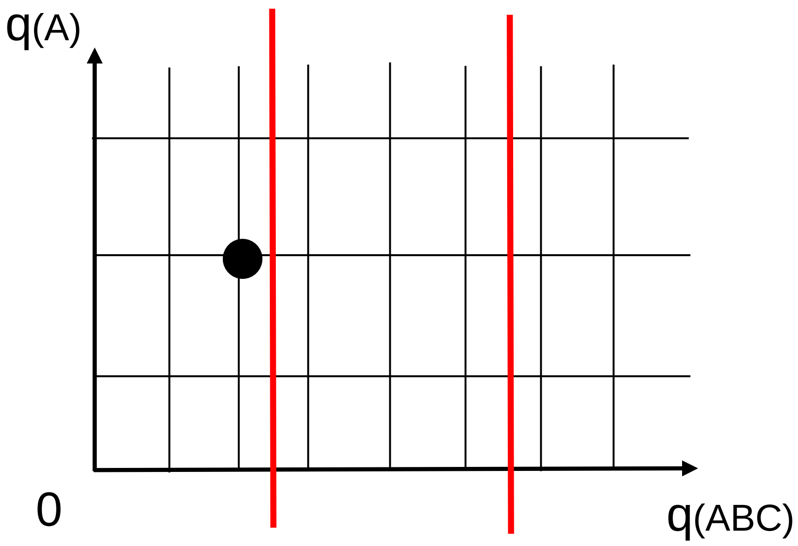
- Mass invariants

- Limiting resources for the crossing of intervals

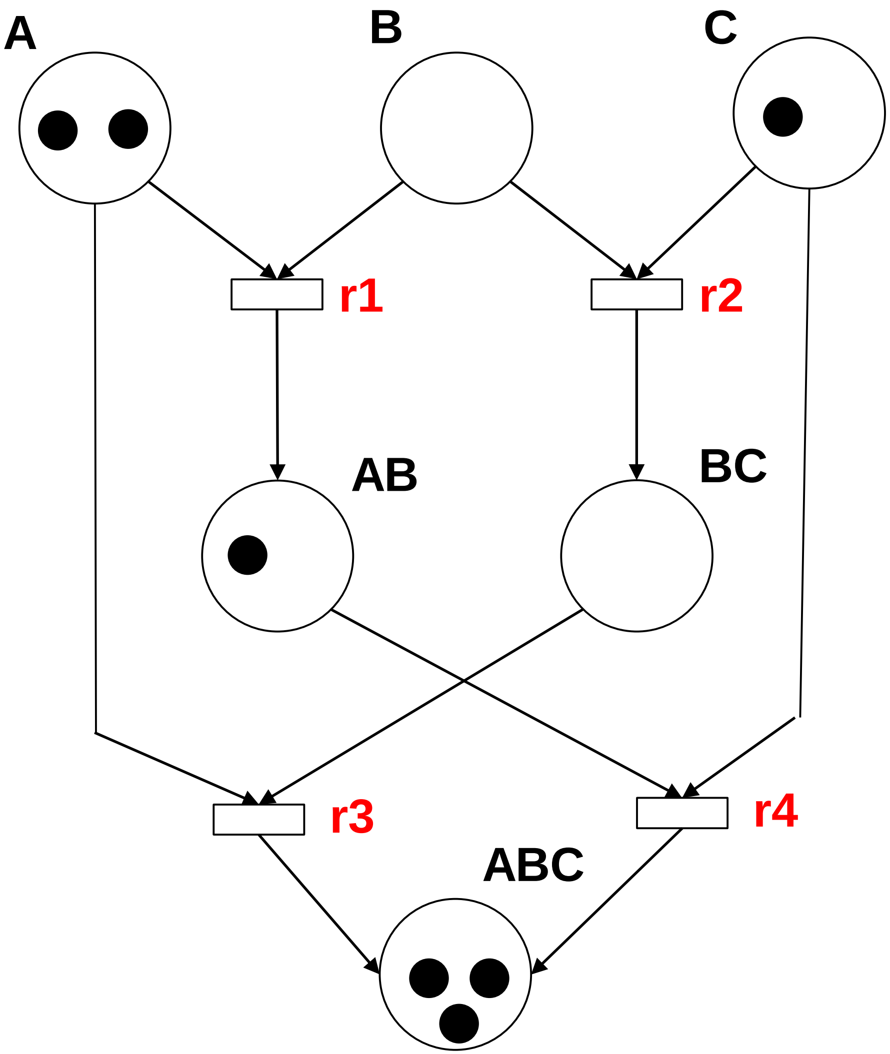
- Time scale separation

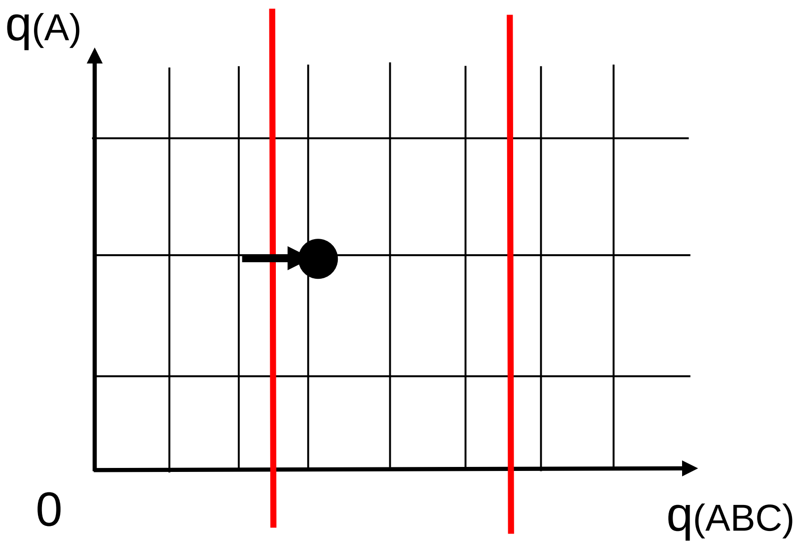
Limiting resources for interval crossing



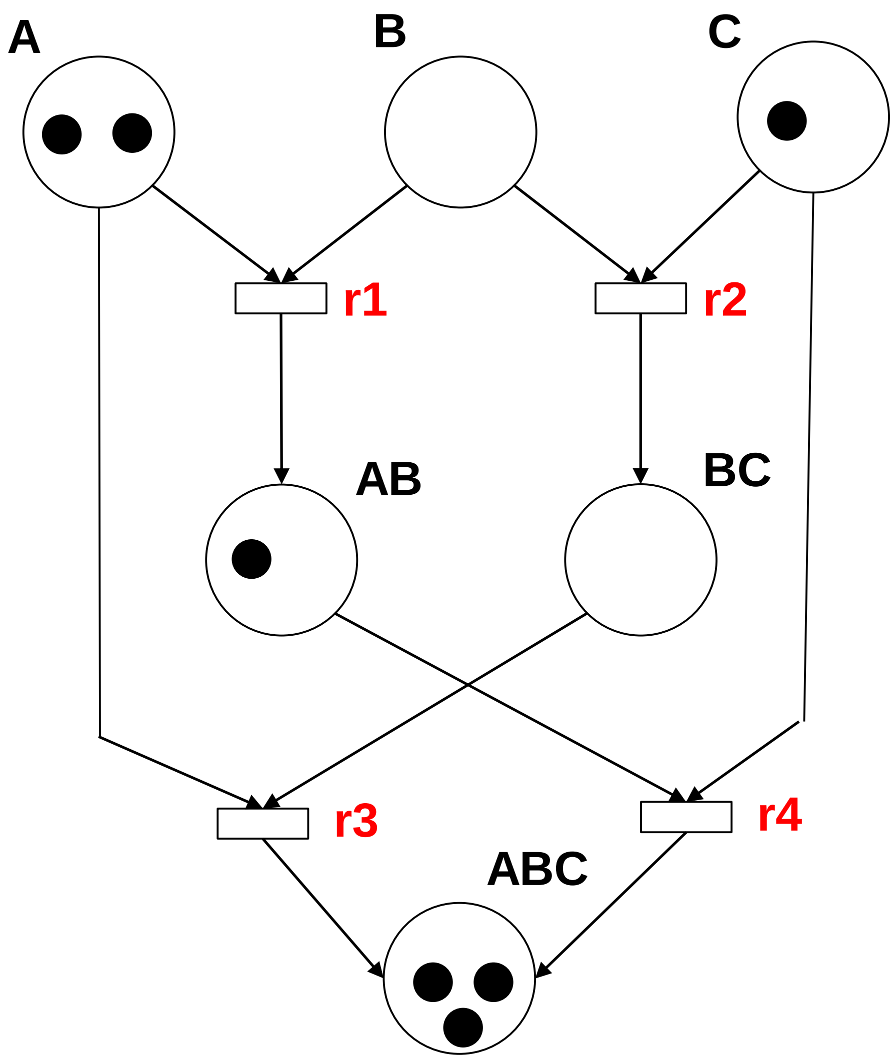


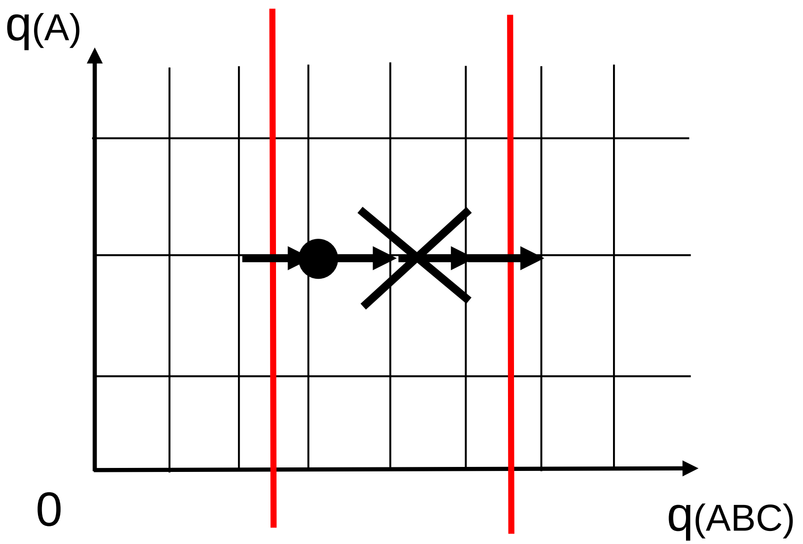
Limiting resources for interval crossing





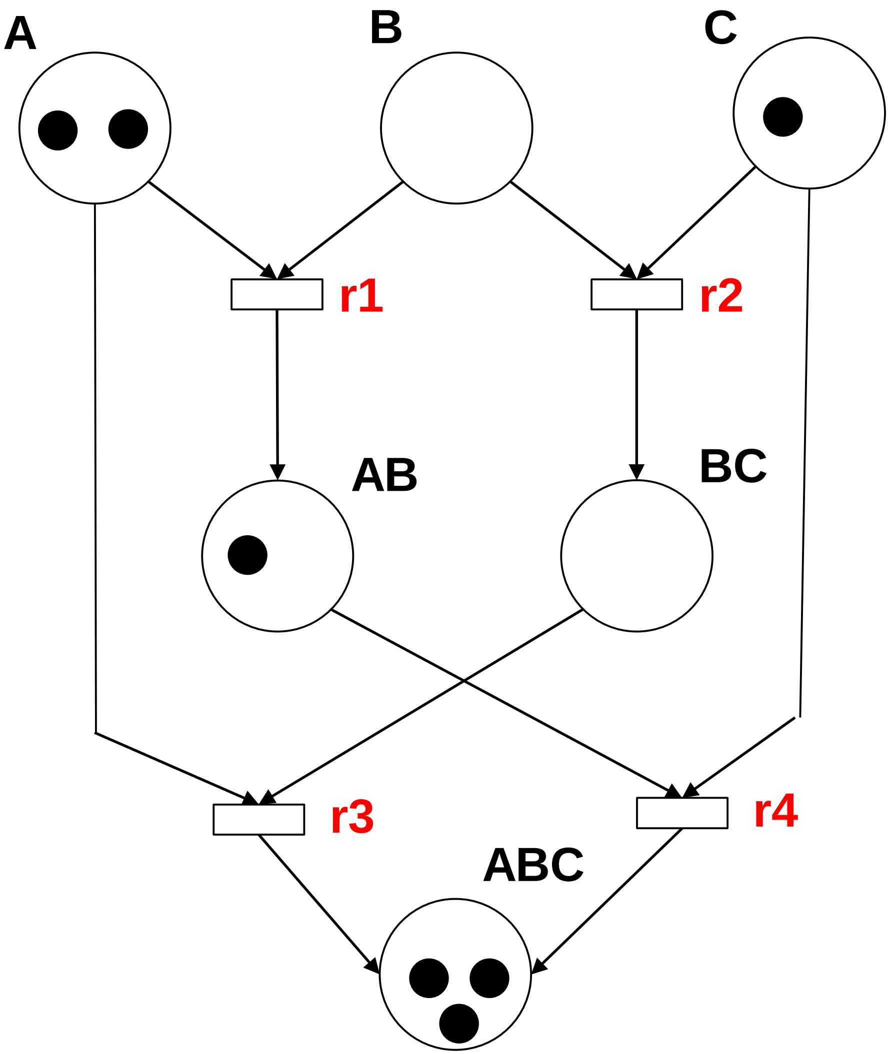
Limiting resources for interval crossing

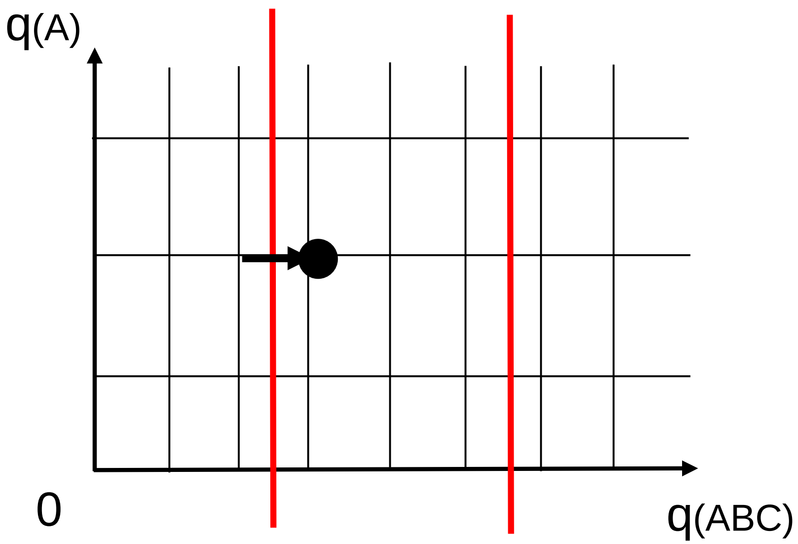




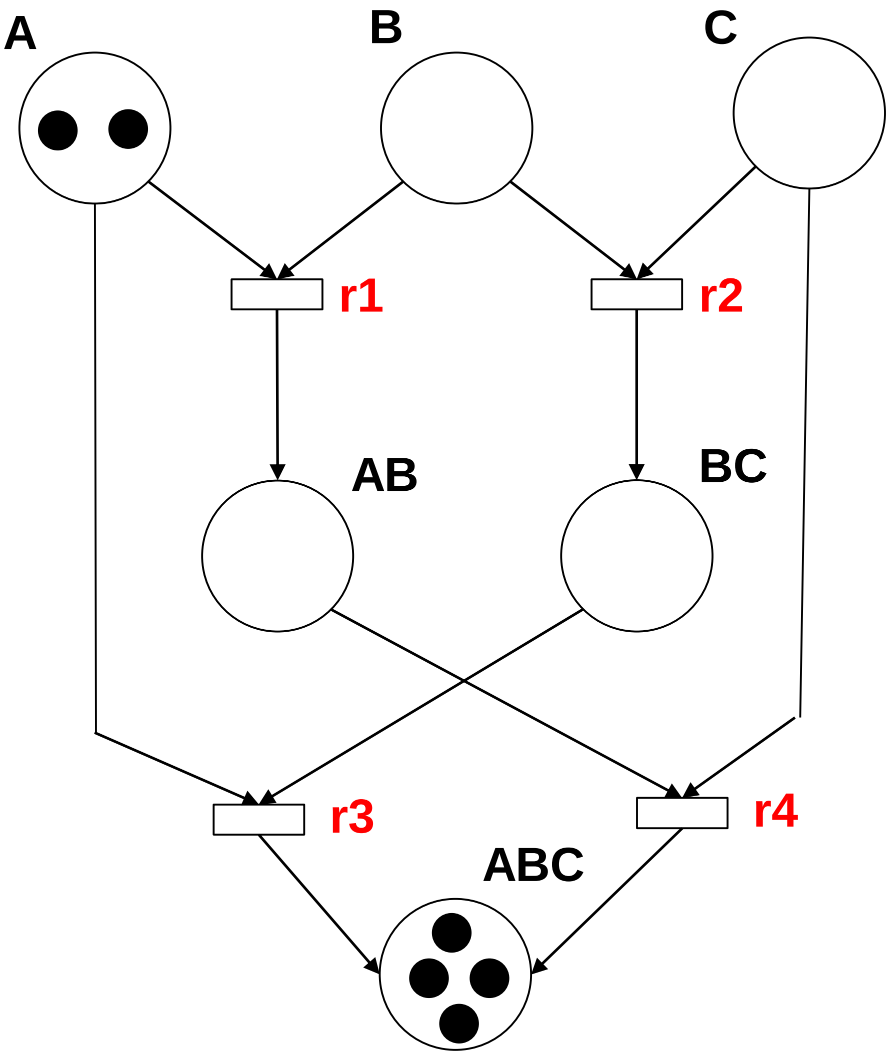
Not enough resources to cross the interval

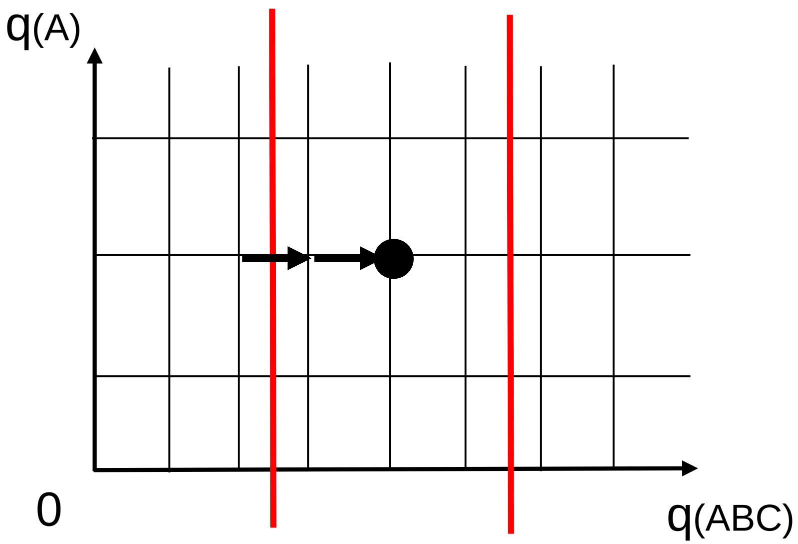
Limiting resources for interval crossing





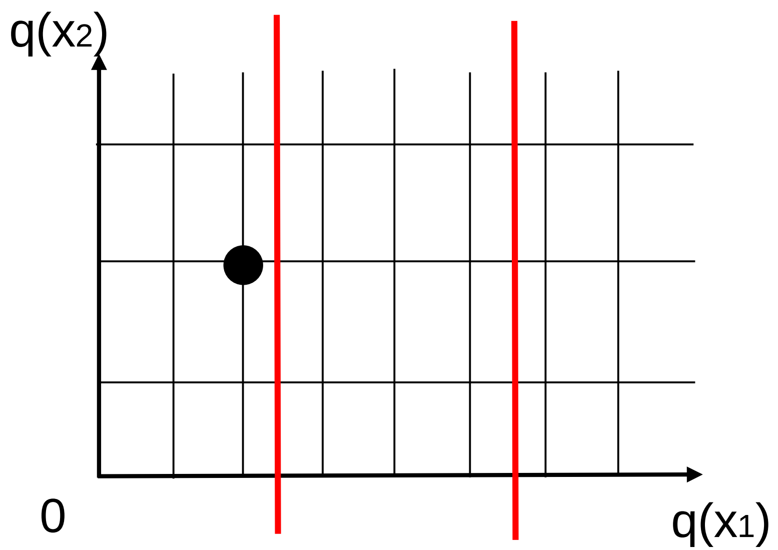
Limiting resources for interval crossing





Limiting resources for interval crossing

- Formalisation of this reasoning: annotation of the chemical species



Limiting resources for interval crossing

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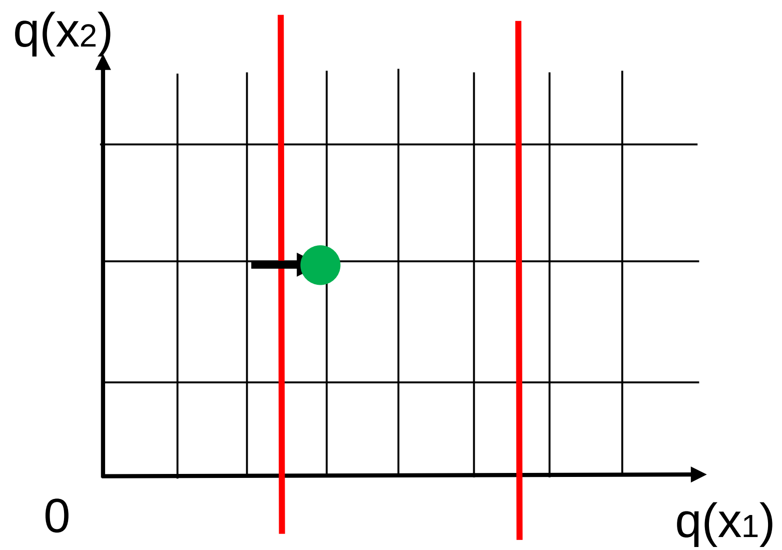
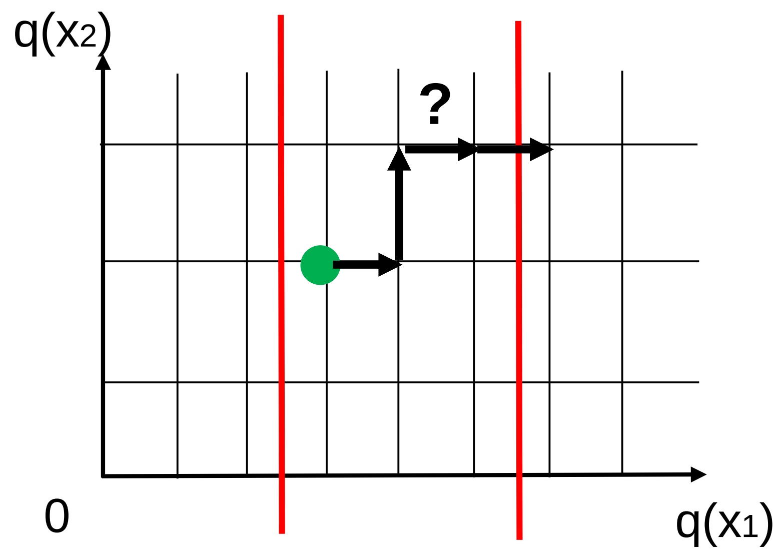


The number of instances of the annotated chemical species is close to the lowest border of its new interval

Limiting resources for interval crossing

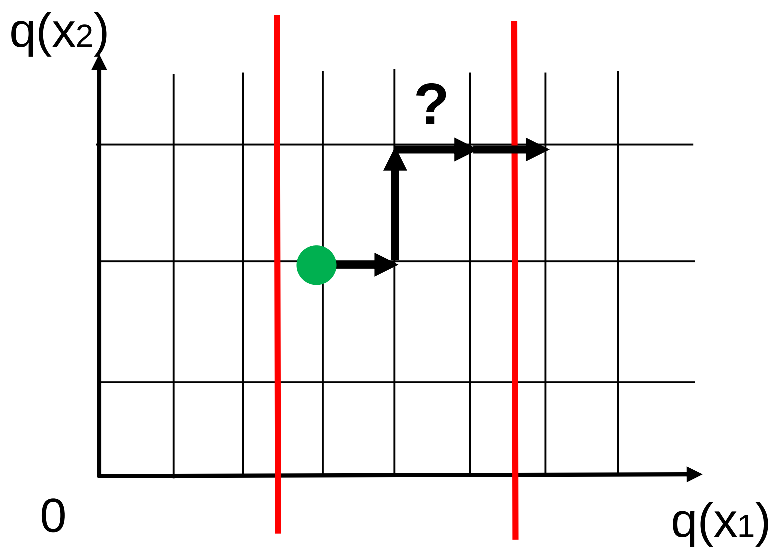
- Formalisation of this reasoning: annotation of the chemical species



Is there a trace which can make x_1 escaping its current interval upwards ?

Limiting resources for interval crossing

- Formalisation of this reasoning: annotation of the chemical species

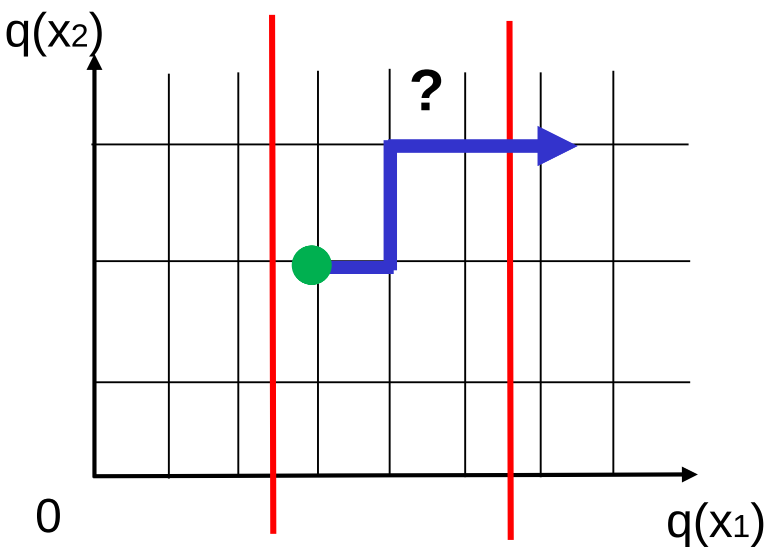


Is there a trace which can make x_1 escaping its current interval upwards ?

⇨ difficult to answer!

Limiting resources for interval crossing

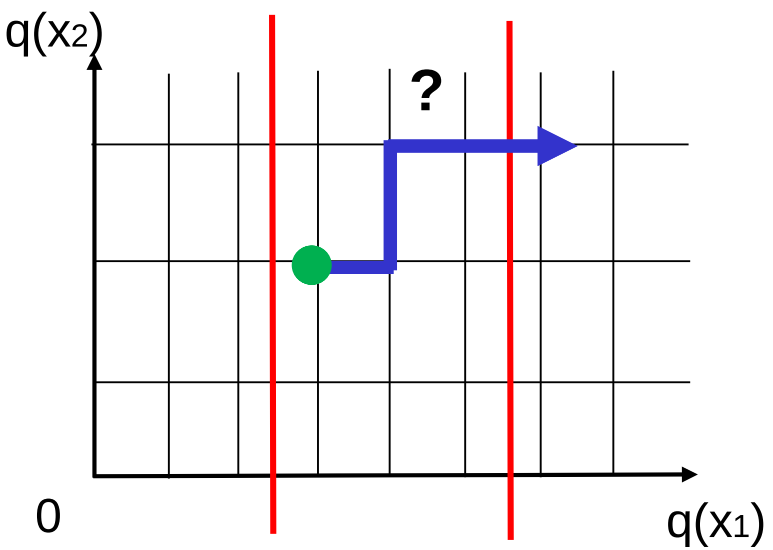
- Formalisation of this reasoning: annotation of the chemical species



Is there a flux vector which can make x_1 escaping its current interval upwards ?

Limiting resources for interval crossing

- Formalisation of this reasoning: annotation of the chemical species



Is there a flux vector which can make x_1 escaping its current interval upwards ?

⇨ linear problem

Limiting resources for interval crossing

- Formalisation of this reasoning: introduction of annotation of the chemical species

- Is there a flux vector which can make a chemical species escaping its current interval upwards ?

⇨ <u>linear decision procedure</u>

Limiting resources for interval crossing

- Formalisation of this reasoning: introduction of annotation of the chemical species

- Is there a flux vector which can make a chemical species escaping its current interval upwards ?

⇨ <u>linear decision procedure</u>: the annotated chemical species can escape its current interval upwards if:

1) there is enough reactant resources

2) enough quantity of the chemical species is produced to escape the interval

Limiting resources for interval crossing

- Formalisation of this reasoning: introduction of annotation of the chemical species

- Is there a flux vector which can make a chemical species escaping its current interval upwards ?

⇨ linear decision procedure: the annotated chemical species can escape its current interval upwards if:

1) there is enough reactant resources

2) enough quantity of the chemical species is produced to escape the interval

- Refinement of the abstraction with the interval crossing constraint

⇨ the abstraction is sound (and more precise!)

Refinements of the abstract semantics

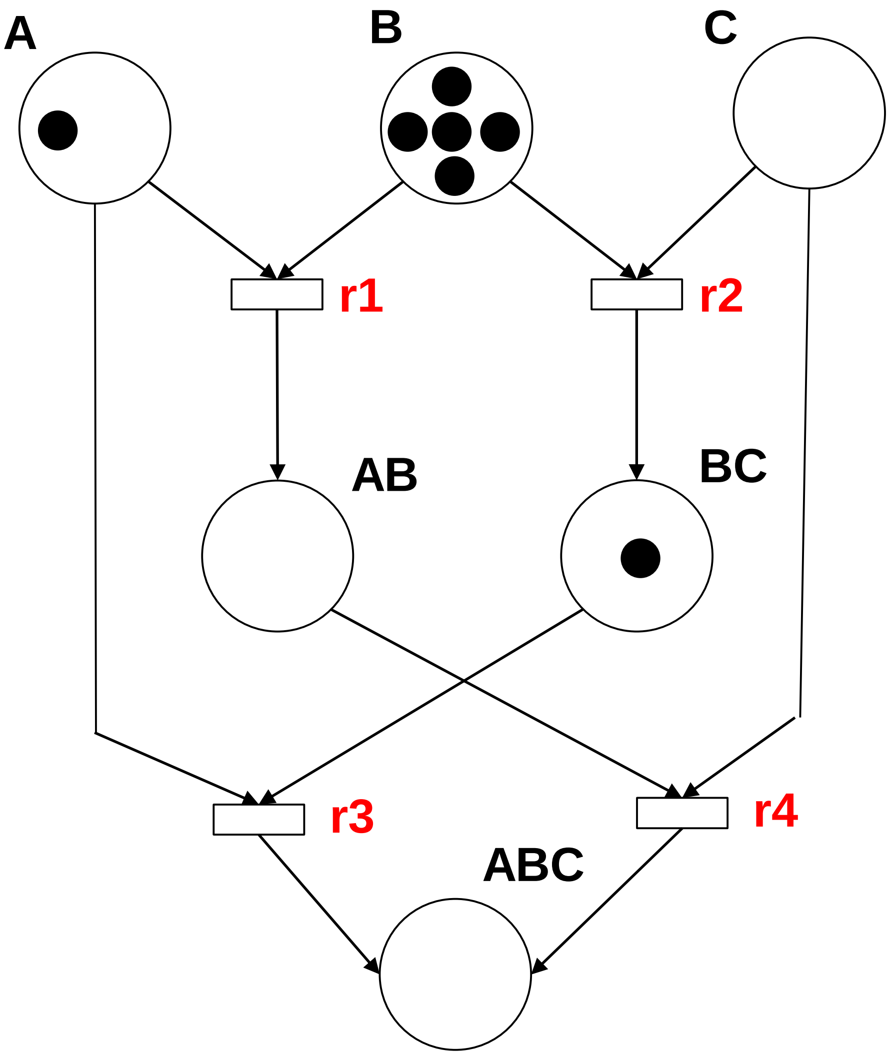
Introduction of three refinements

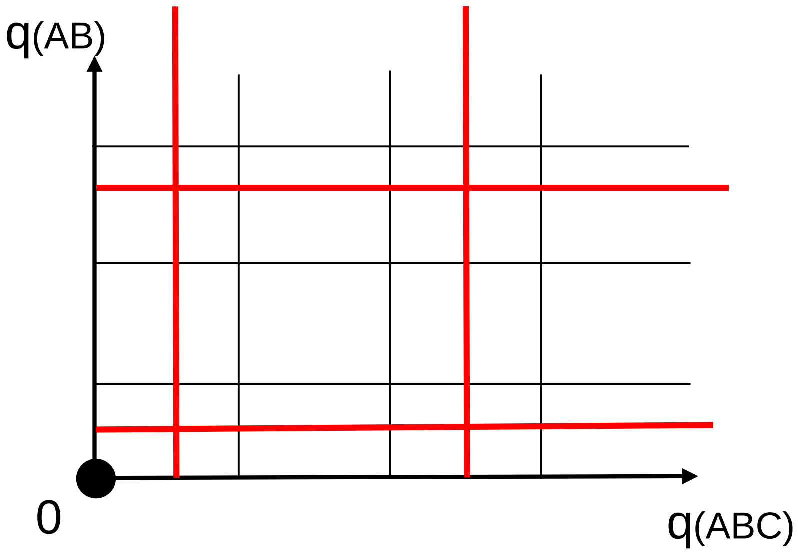
- Mass invariants

- Limiting resources for the crossing of intervals

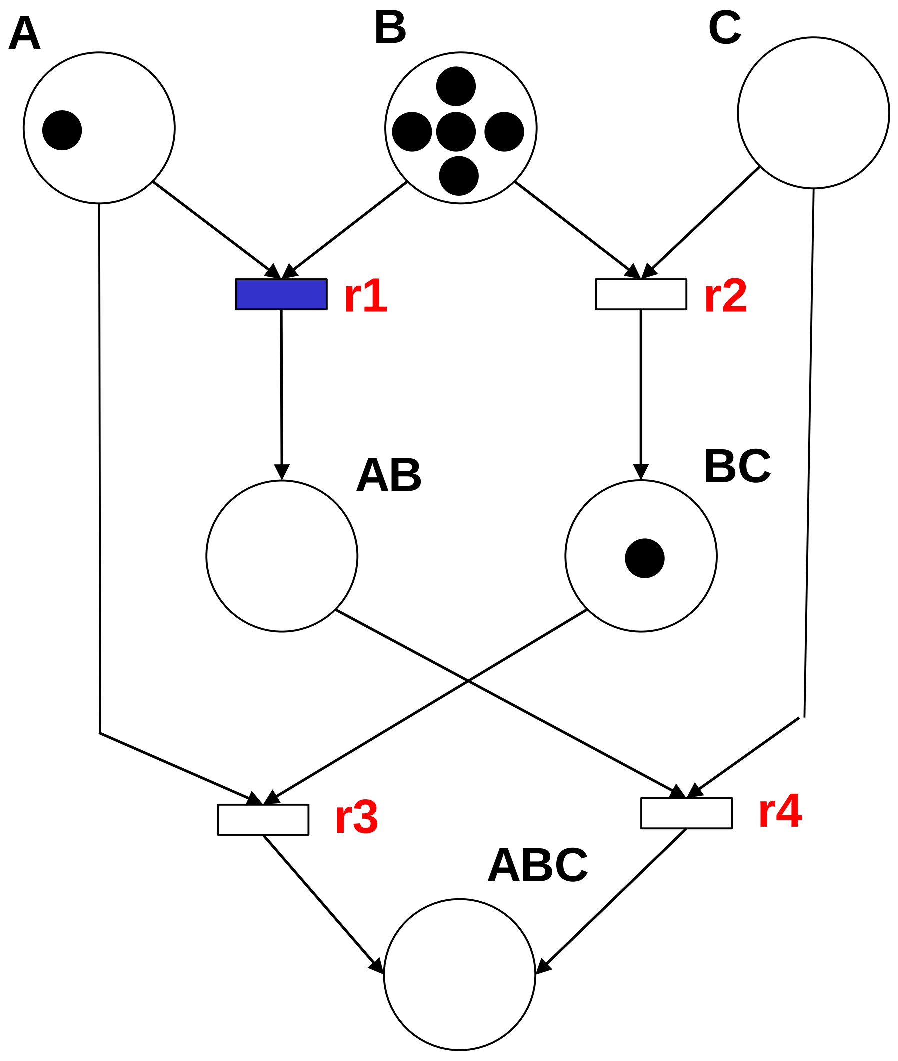
- Time scale separation

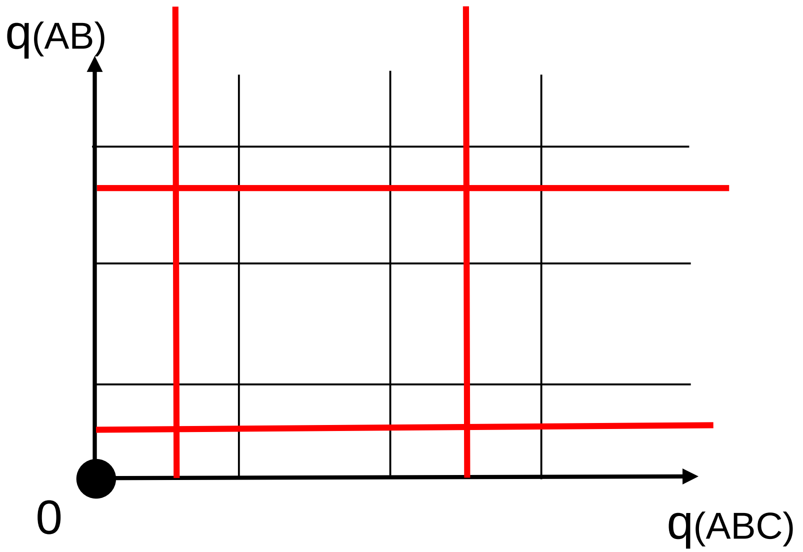
Time scale separation



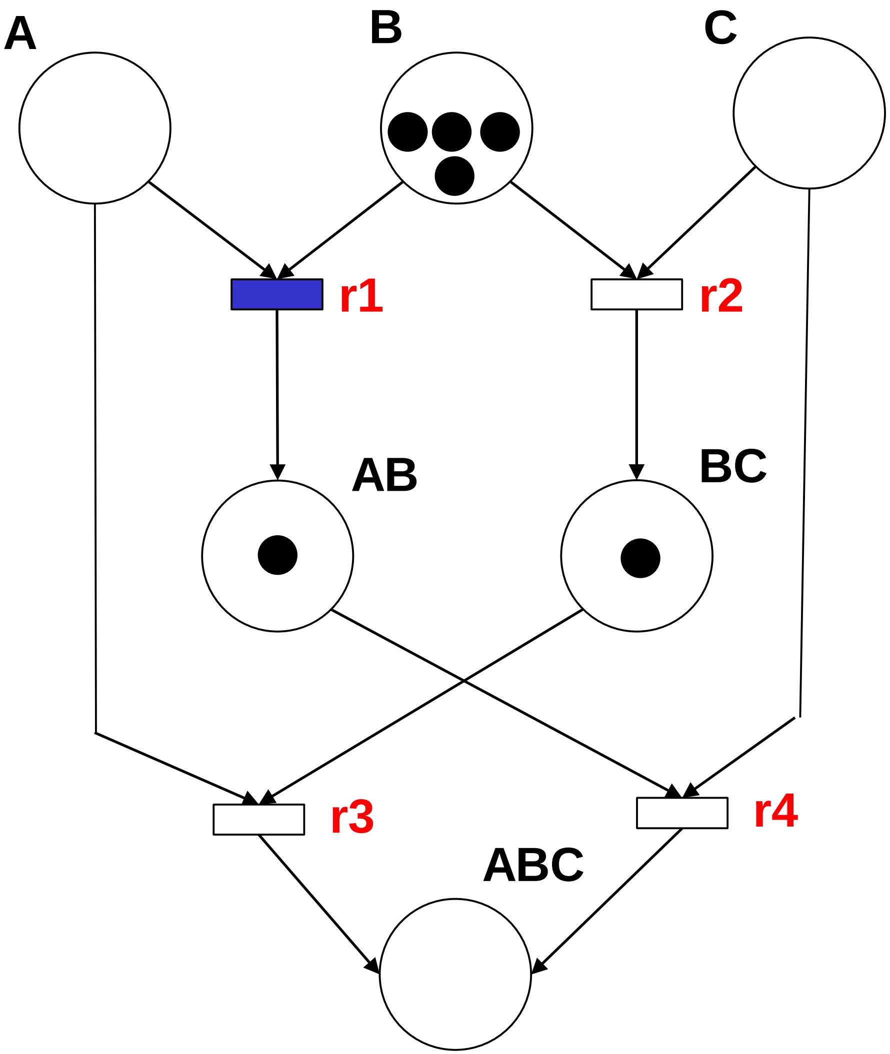


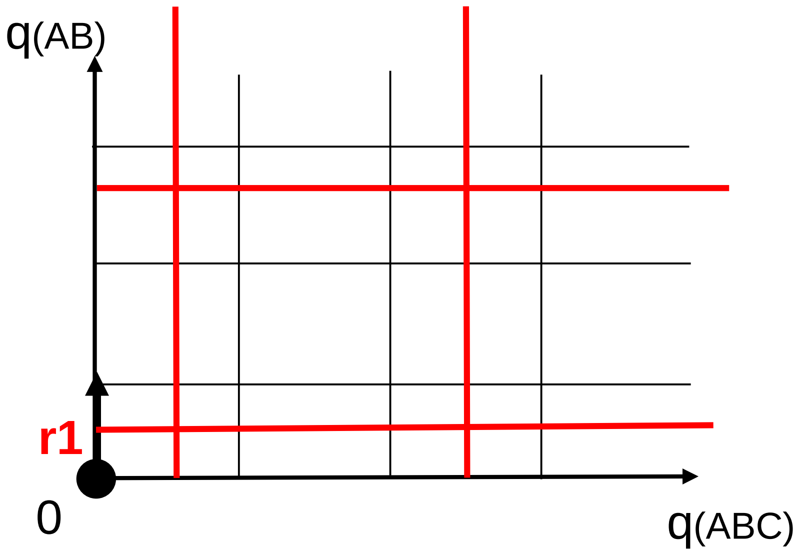
Time scale separation



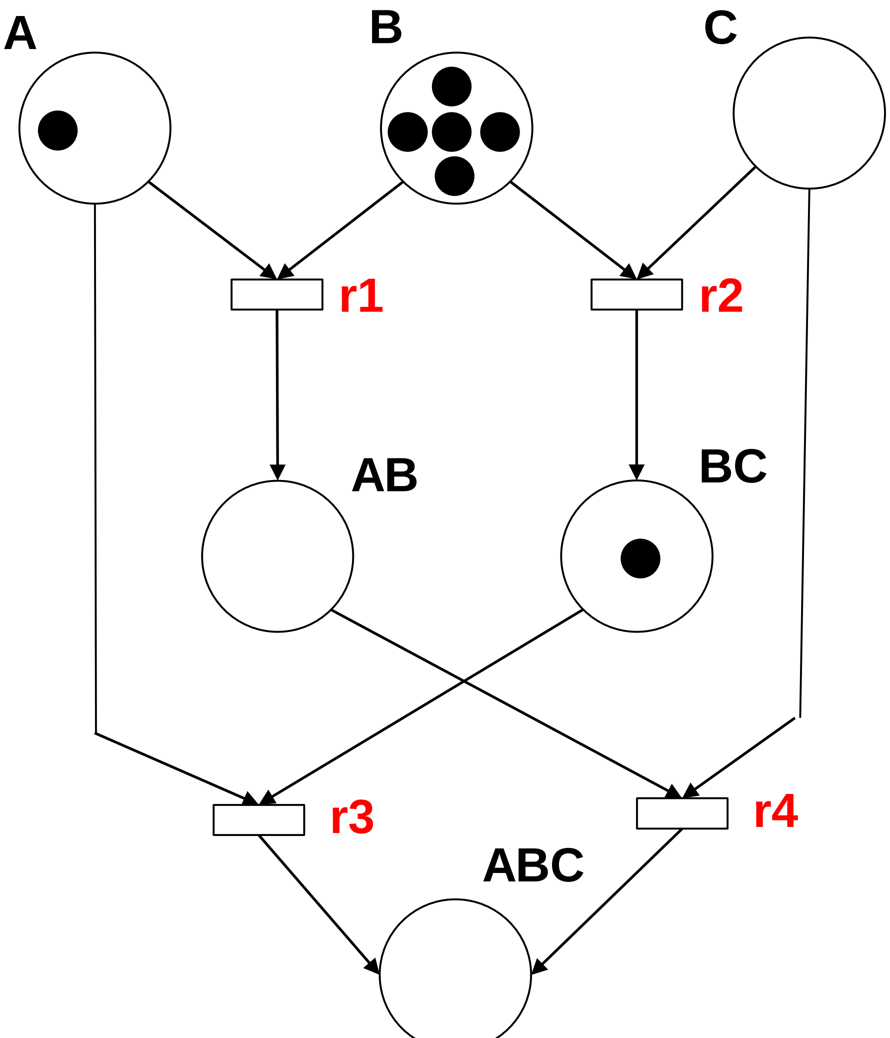


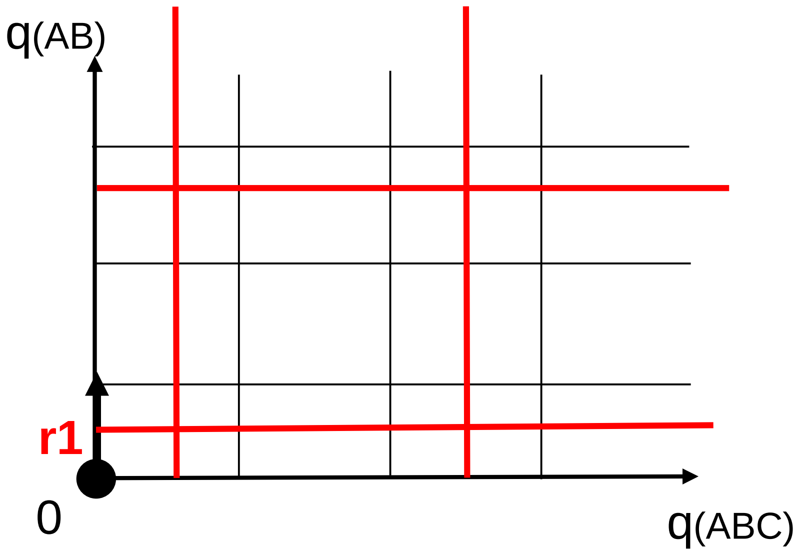
Time scale separation





Time scale separation





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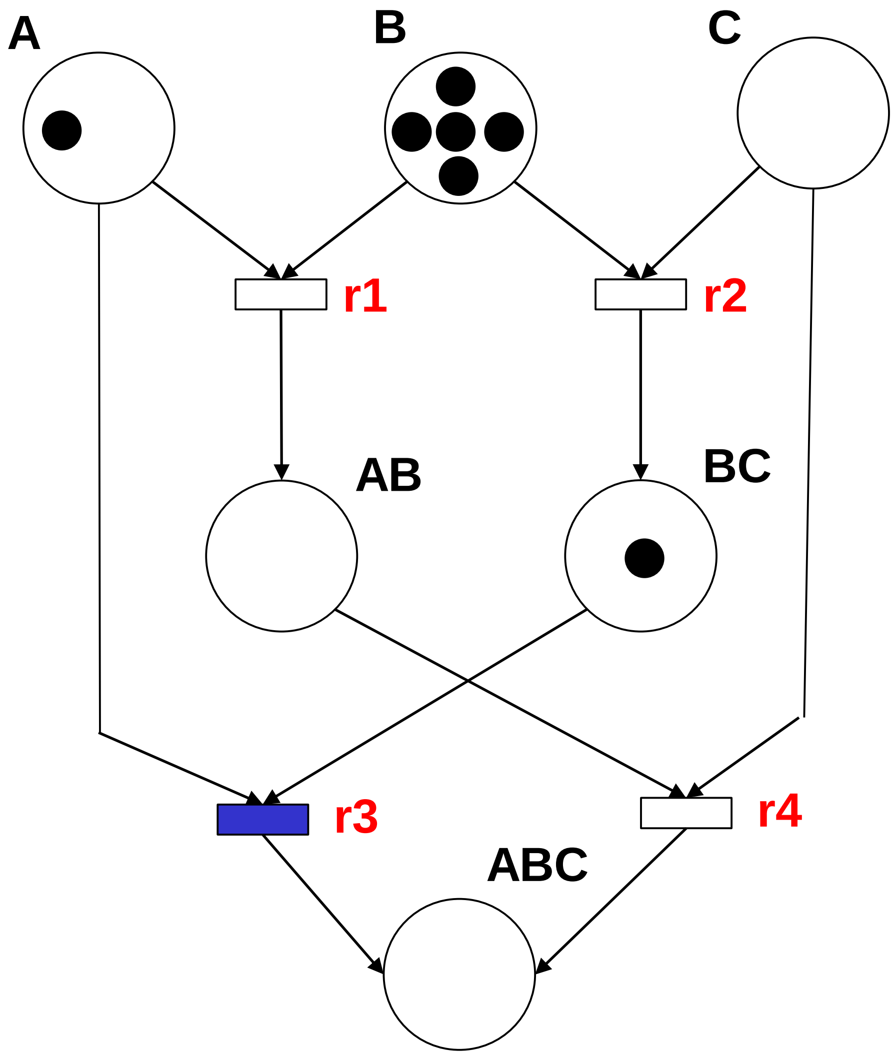
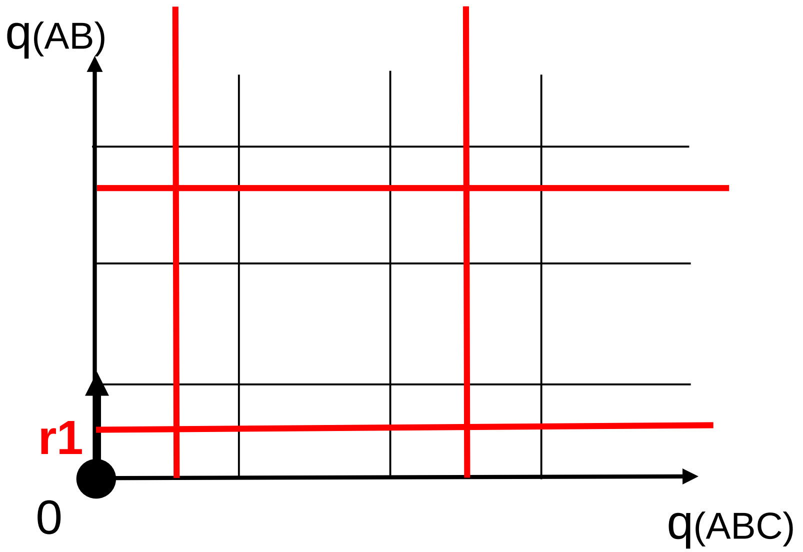
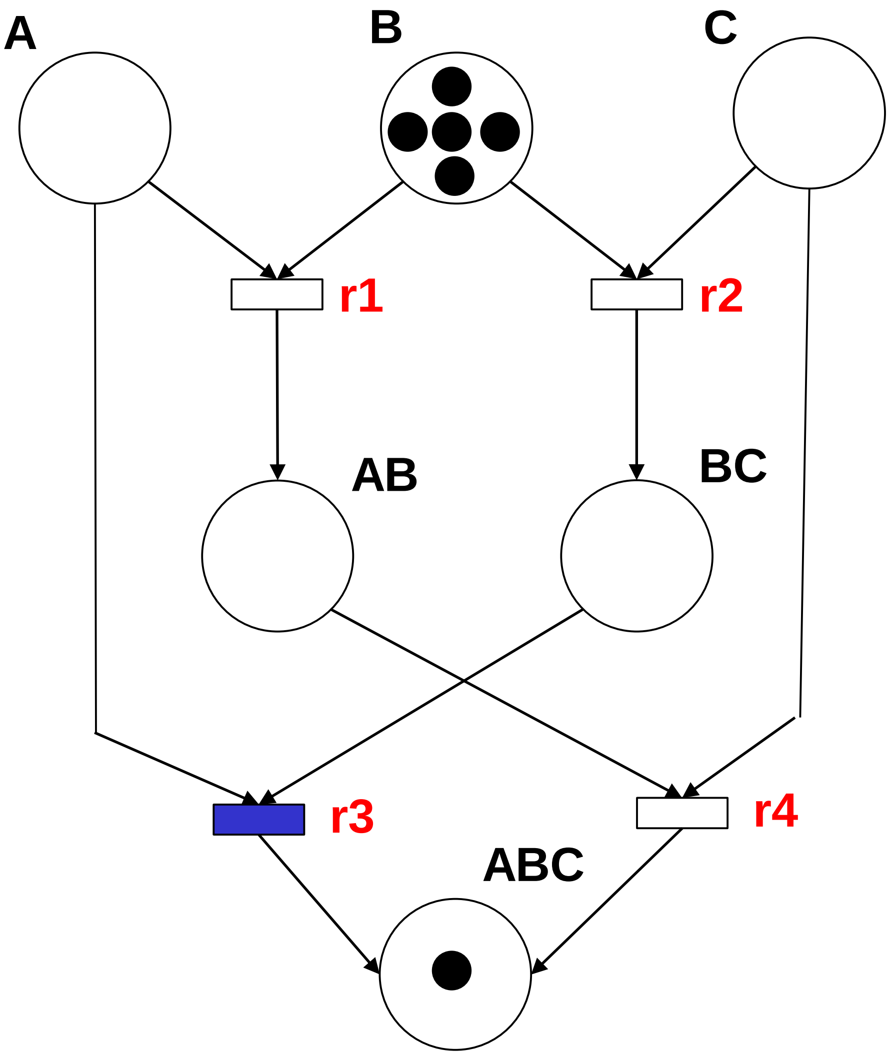
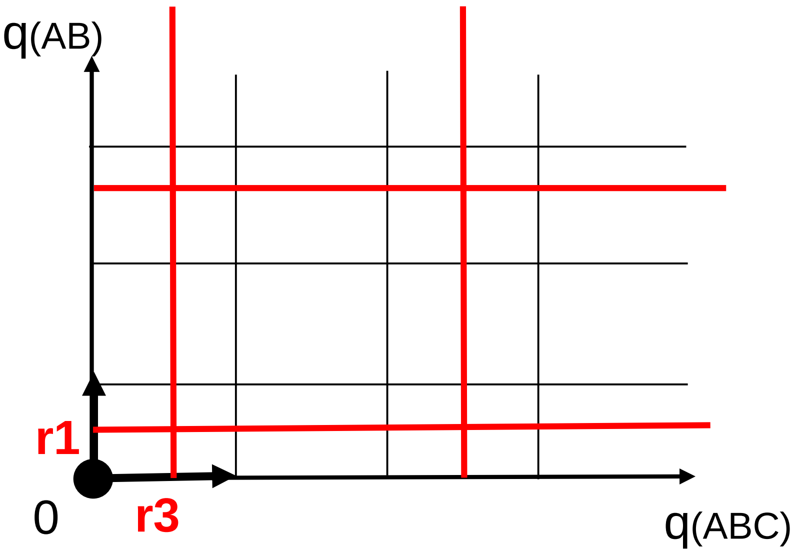




Time scale separation





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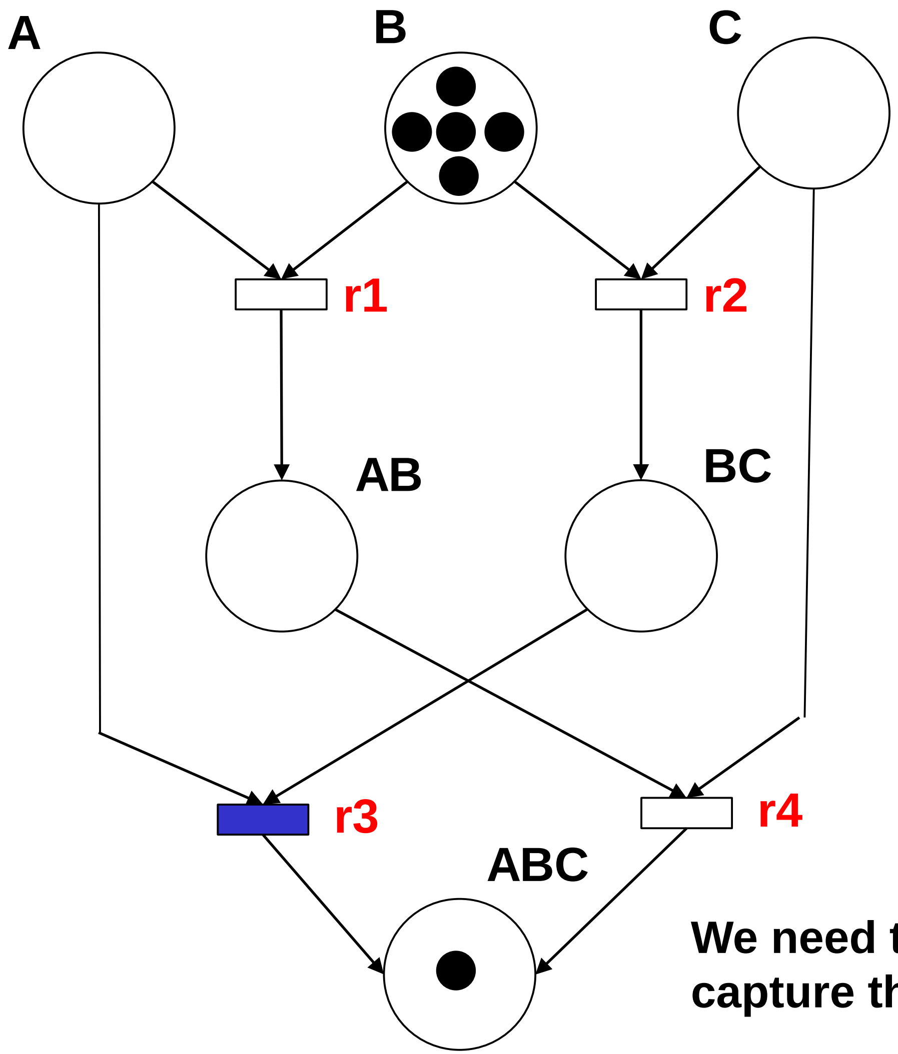
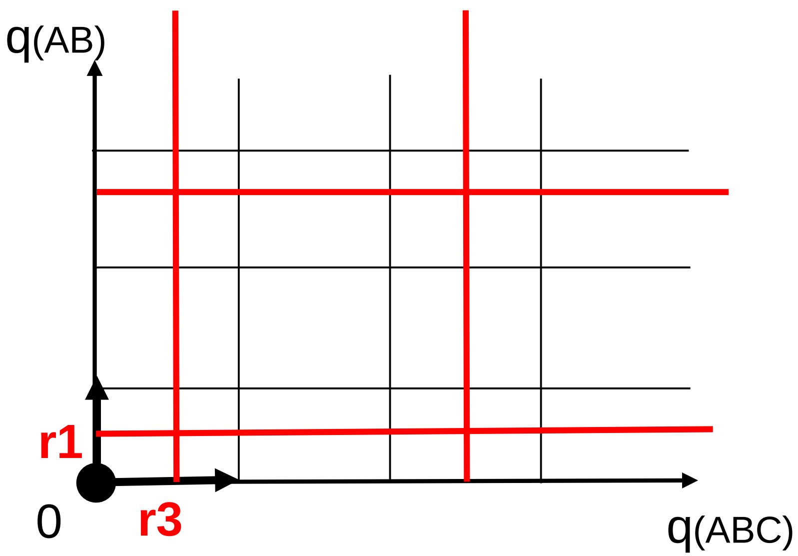
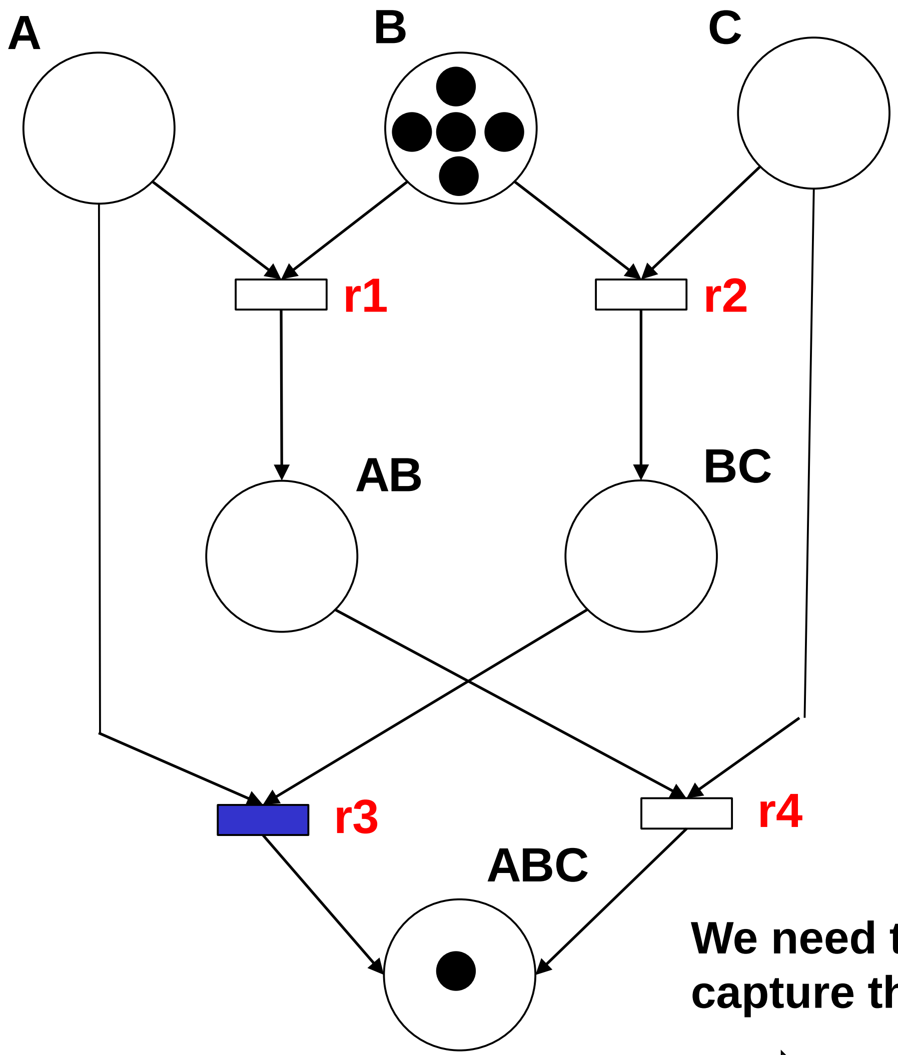
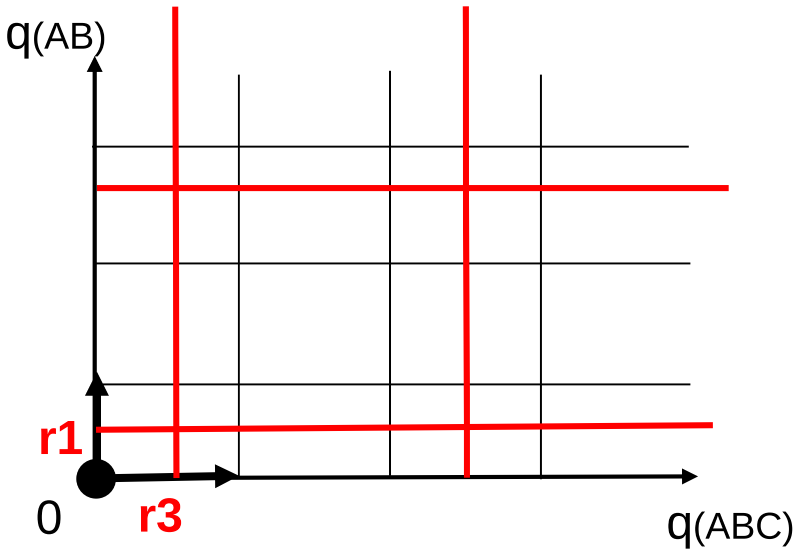




We need to neglect the reaction r3 compared to r1 to capture the sequestration effect in the abstract

Time scale separation





We need to neglect the reaction r3 compared to r1 to capture the sequestration effect in the abstract

Accounting for time scale separation

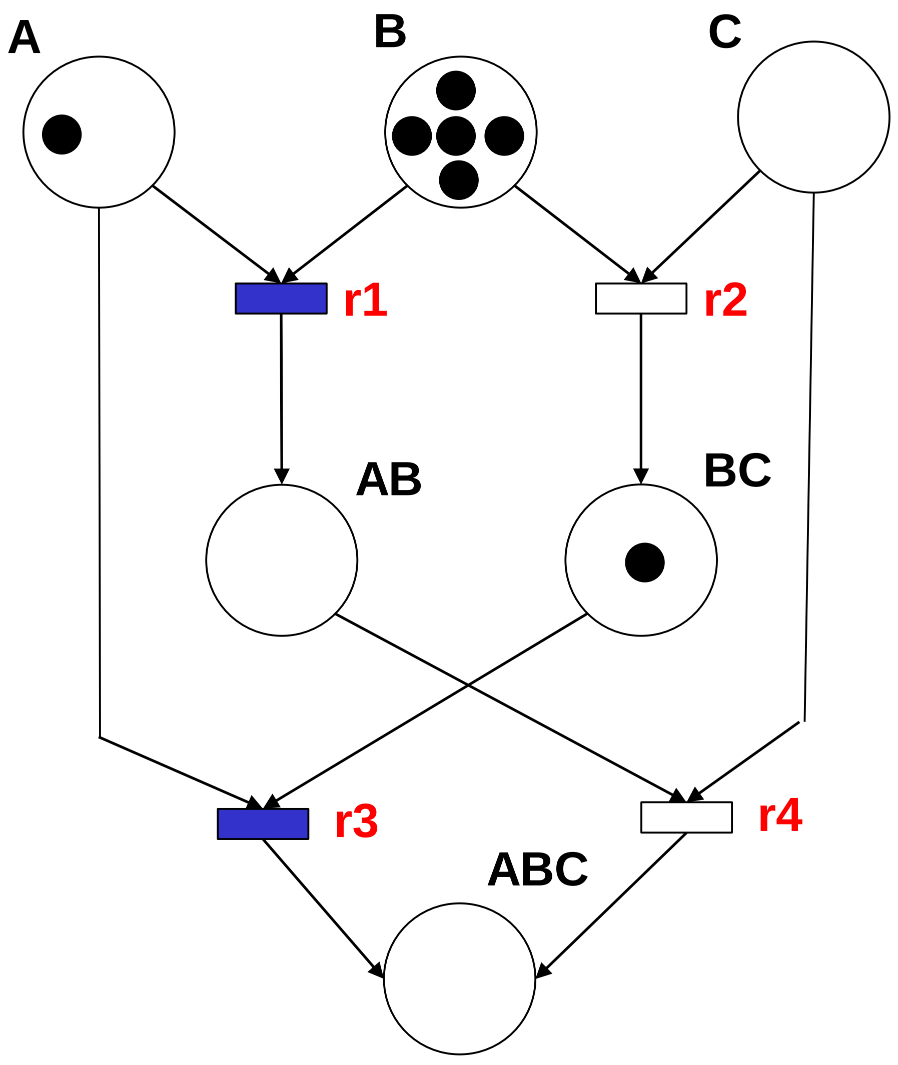
Time scale separation

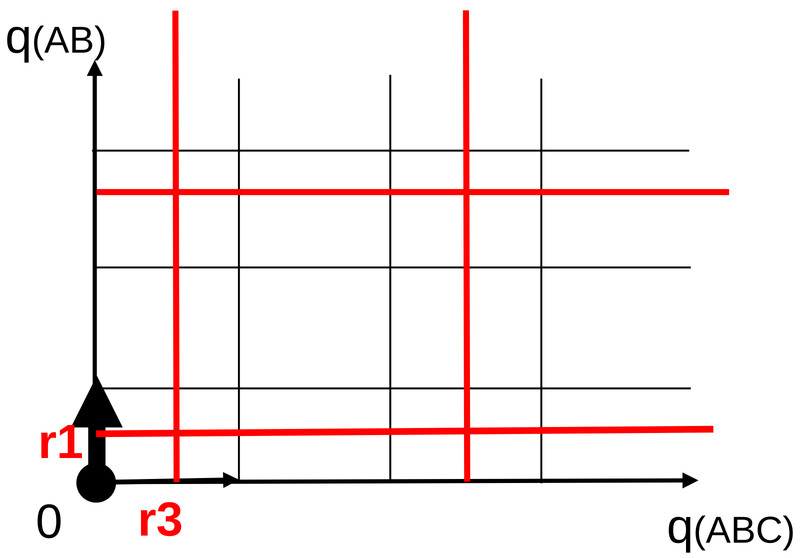
- Refinement of the concrete semantics to take into account time scale separation

  - Kinetic function associated to a reaction

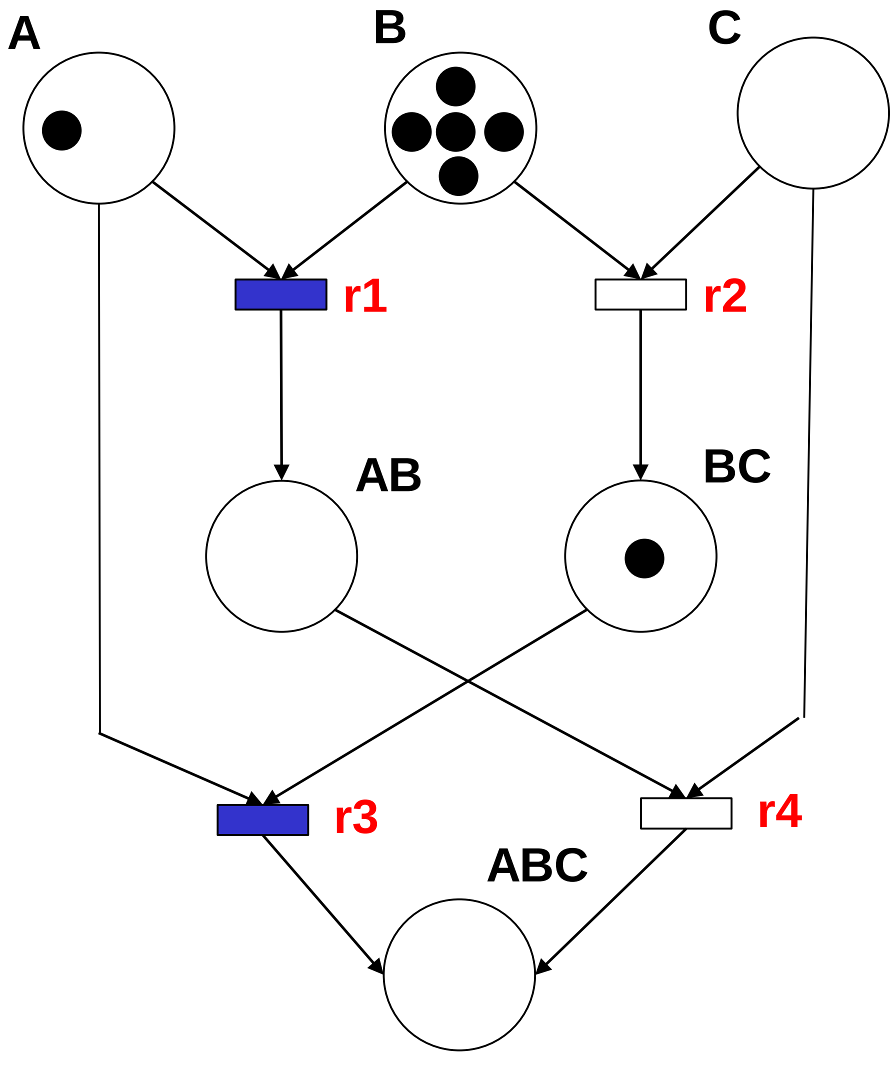
  - Slow reactions are neglected compared to fast reactions

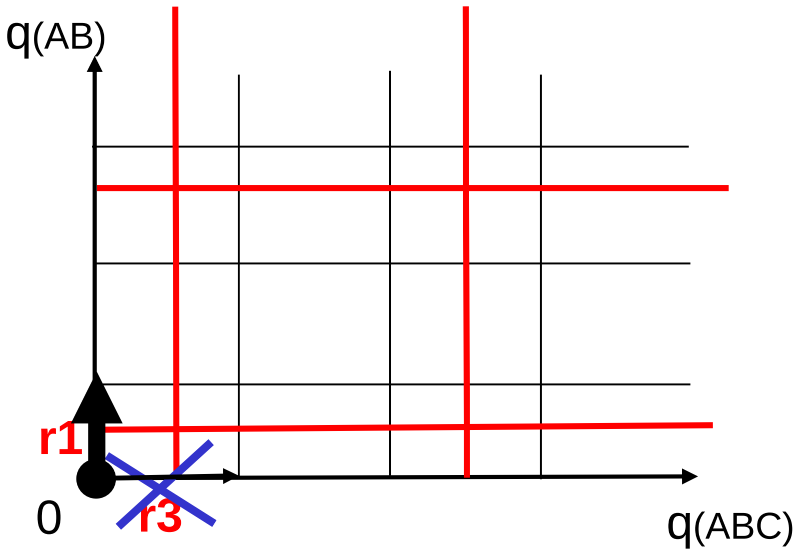
Time scale separation





Time scale separation





Time scale separation

- Refinement of the concrete semantics to take into account time scale separation

  - Kinetic function associated to a reaction

  - Slow reactions are neglected compared to fast reactions

Time scale separation

- Refinement of the concrete semantics to take into account time scale separation

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- Refinement of the abstract semantics with time scale separation

Time scale separation

- Refinement of the concrete semantics to take into account time scale separation

  - Kinetic function associated to a reaction

  - Slow reactions are neglected compared to fast reactions

- Refinement of the abstract semantics with time scale separation

$\Longrightarrow$ the abstraction is sound (with respect to the refined concrete semantics)

Application to our case study

Application to our case study

- **Reaction scheme**

$$\begin{cases} A + B \overset{k_1}{\rightarrow} AB \\ B + C \overset{k_2}{\rightarrow} BC \\ A + BC \overset{k_1}{\rightarrow} ABC \\ AB + C \overset{k_2}{\rightarrow} ABC \end{cases}$$

Application to our case study

- **Reaction scheme**

$$\begin{cases} A + B \xrightarrow{k_1} AB \\ B + C \xrightarrow{k_2} BC \\ A + BC \xrightarrow{k_1} ABC \\ AB + C \xrightarrow{k_2} ABC \end{cases}$$

- **Mass invariants**

$$q(A) + q(AB) + q(ABC) = A_T$$
$$q(B) + q(AB) + q(BC) + q(ABC) = B_T$$
$$q(C) + q(BC) + q(ABC) = C_T$$

Application to our case study

- **Modeling assumptions**

- $\delta > 5$

$\Rightarrow$ All the asynchronous updatings are taken into account

The requirements of the refinements are satisfied

- Mass action stochastic law for the definition of the kinetic function

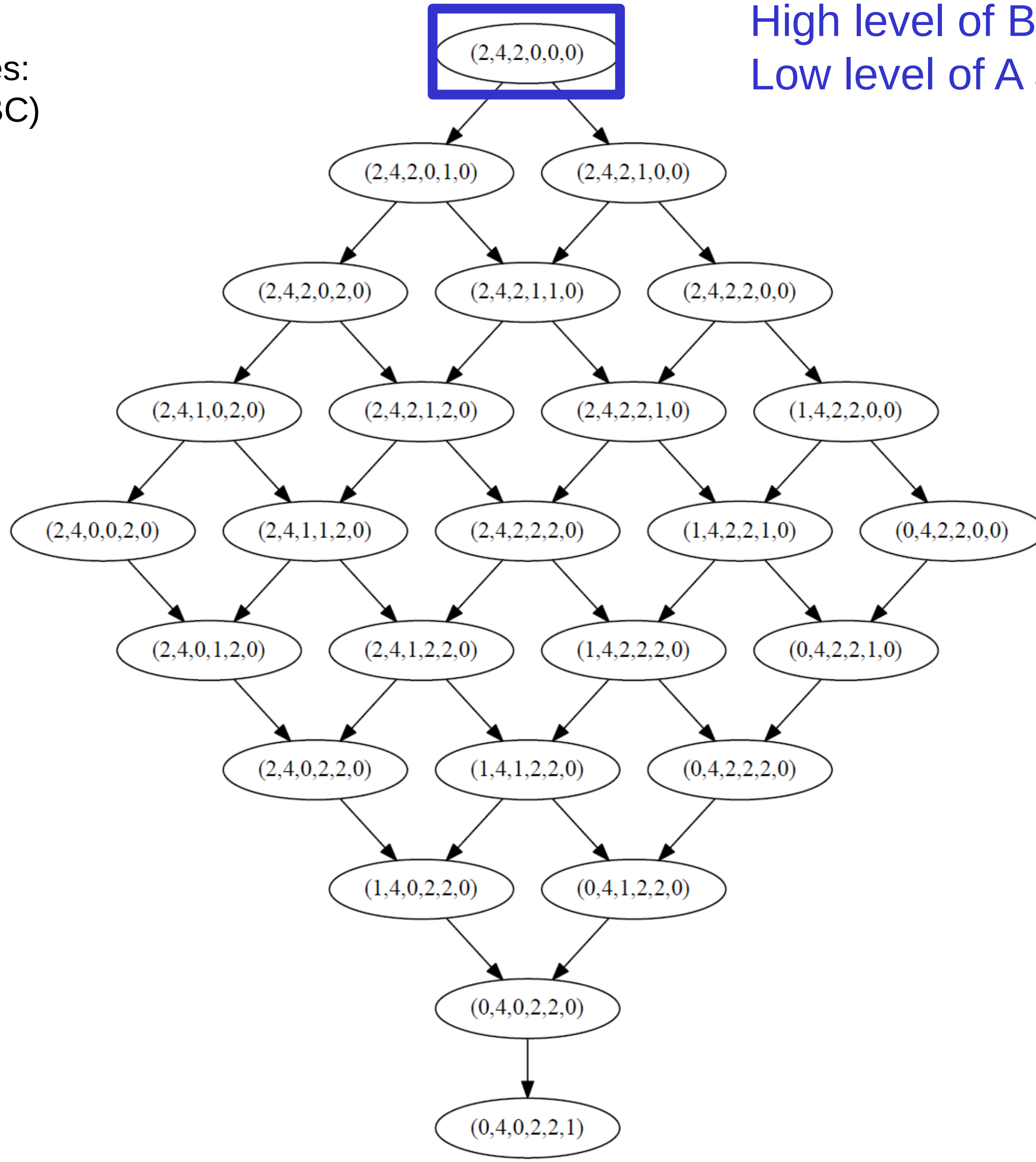
$$k_r(q) = \prod_{x \in \nu} \left(\frac{q(x)!}{(q(x) - M_r(x))!\, M_r(x)!} \;\middle|\; M_r(x) \neq 0 \right)$$

- Asynchronous updating policy

Application to our case study

Order of the variables:
(A, B, C, AB, BC, ABC)

$$A_T = 3\delta^2$$
$$B_T = 4\delta^4$$
$$C_T = 3\delta^2$$



High level of B,
Low level of A and C

Application to our case study

Order of the variables:
(A, B, C, AB, BC, ABC)

$$A_T = 3\delta^2$$
$$B_T = 4\delta^4$$
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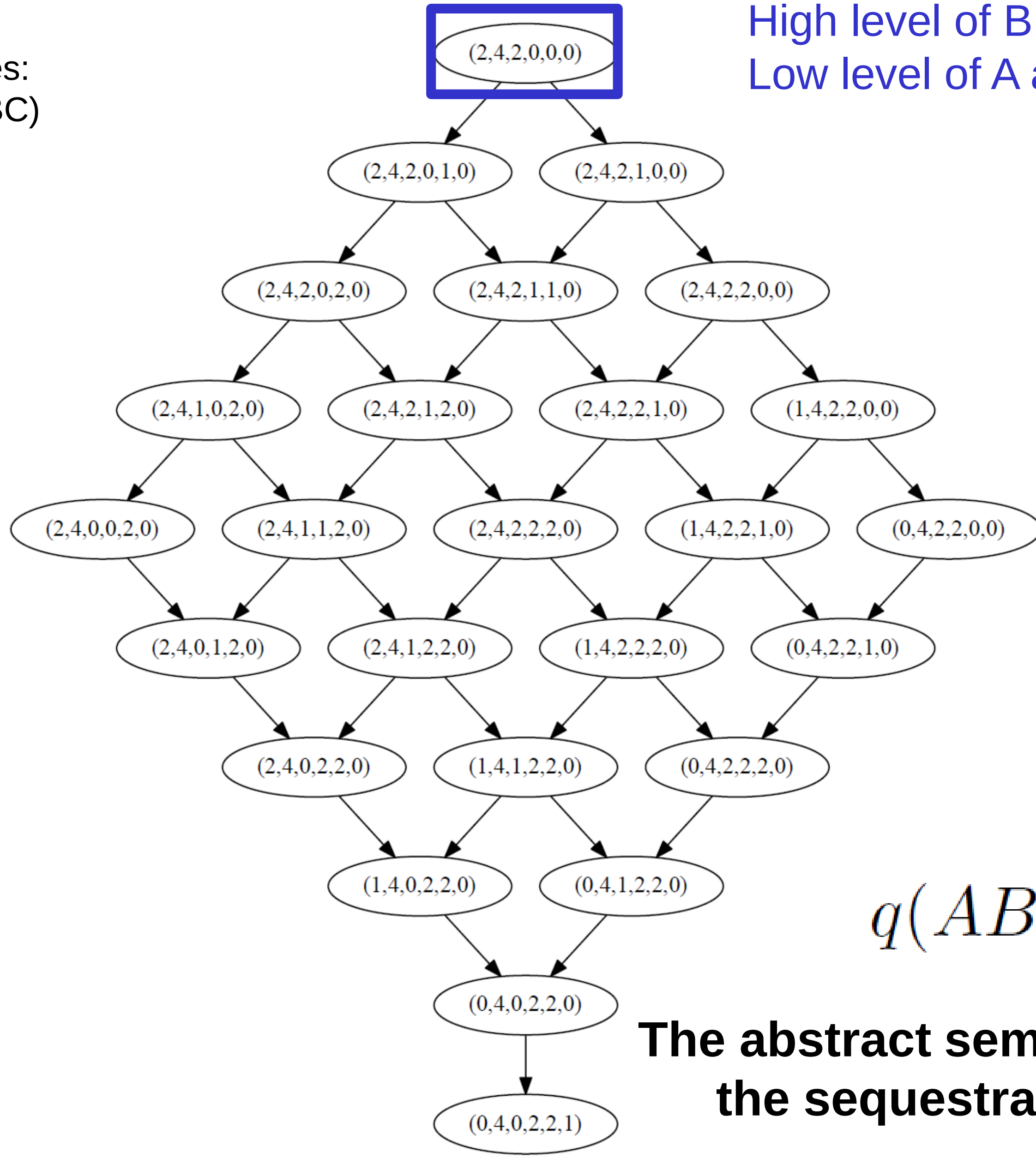


High level of B,
Low level of A and C

$$q(ABC) < \delta^2$$

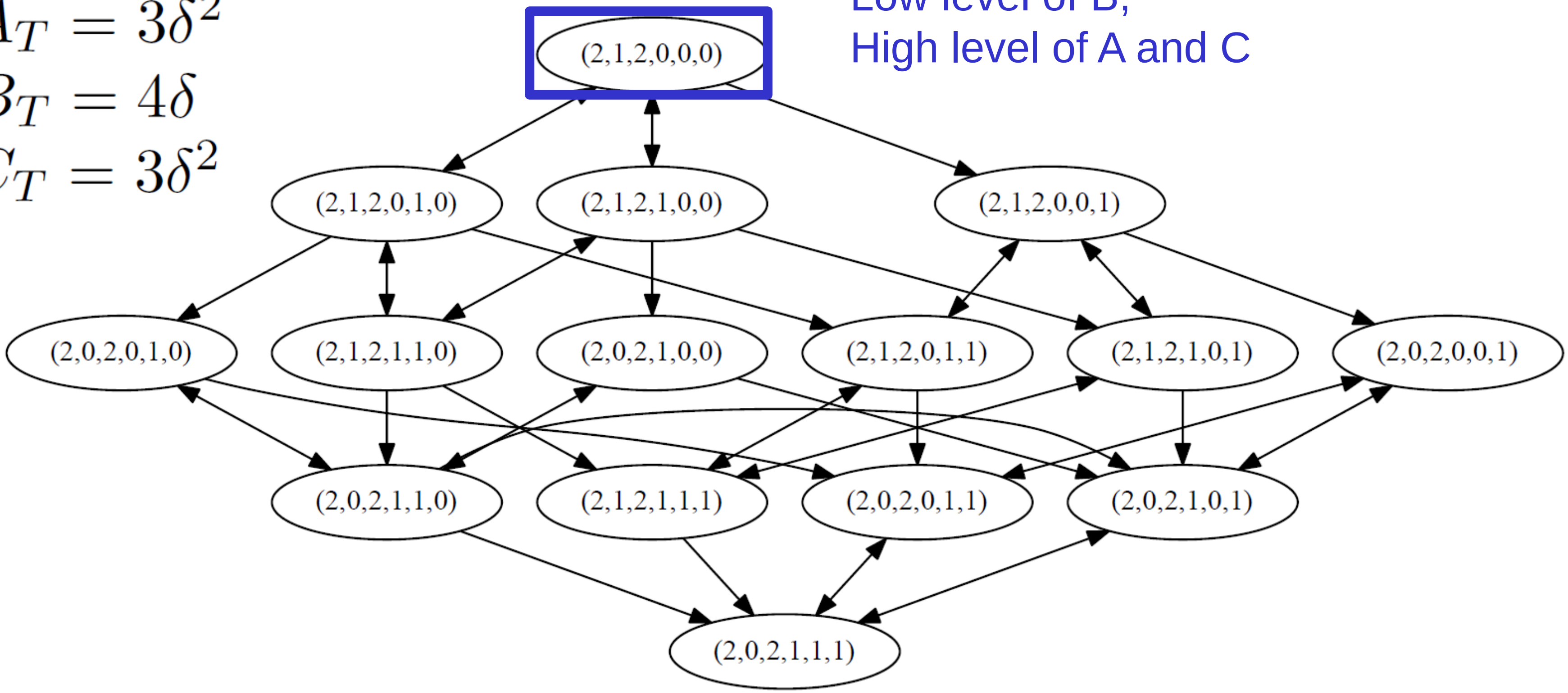
The abstract semantics captures the sequestration property

Application to our case study

Order of the variables:
(A, B, C, AB, BC, ABC)

$$A_T = 3\delta^2$$
$$B_T = 4\delta$$
$$C_T = 3\delta^2$$

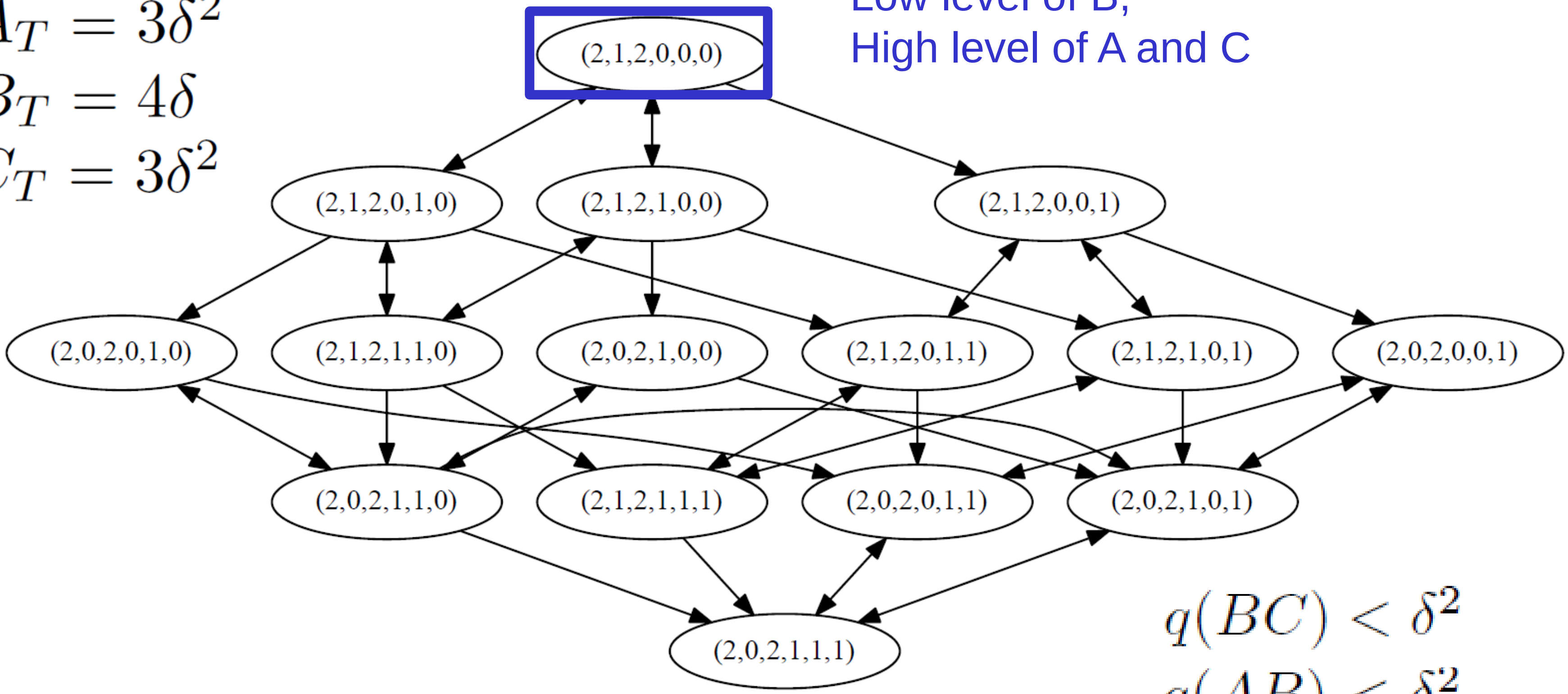
Low level of B,
High level of A and C



Application to our case study

Order of the variables:
(A, B, C, AB, BC, ABC)

$$A_T = 3\delta^2$$
$$B_T = 4\delta$$
$$C_T = 3\delta^2$$



Low level of B,
High level of A and C

$$q(BC) < \delta^2$$
$$q(AB) < \delta^2$$
$$q(ABC) < \delta^2$$

Conclusion and prospects

- Setting of a formal and automatic method for the derivation of an coarse-grained semantics from reaction networks which accounts for the salient properties of our case study

- New trade-off between precision and complexity

- Prospects:
  - Identification of other refinements of the abstraction
  - Test on other case studies showing other properties of interest
  - Scaling up of the method

Thanks!

Limiting resources for interval crossing

Linear decision procedure

The annotated chemical species $x_\ddagger$ can escape its interval at state $q^\sharp$ through the reaction r if there exists a function $w \in \mathbb{N}^{[\![1,n]\!]}$ such that:

(1) $w(r) > 0$,

(2) $\delta^{q^\sharp(x)} + V_\infty + V_w(x) \geq \delta^{q^\sharp(x)+1}$,

(3) $\forall x' \in \nu,\ q^\sharp(x') \neq p \Rightarrow \delta^{q^\sharp(x')+1} + V_w(x) > 0$,

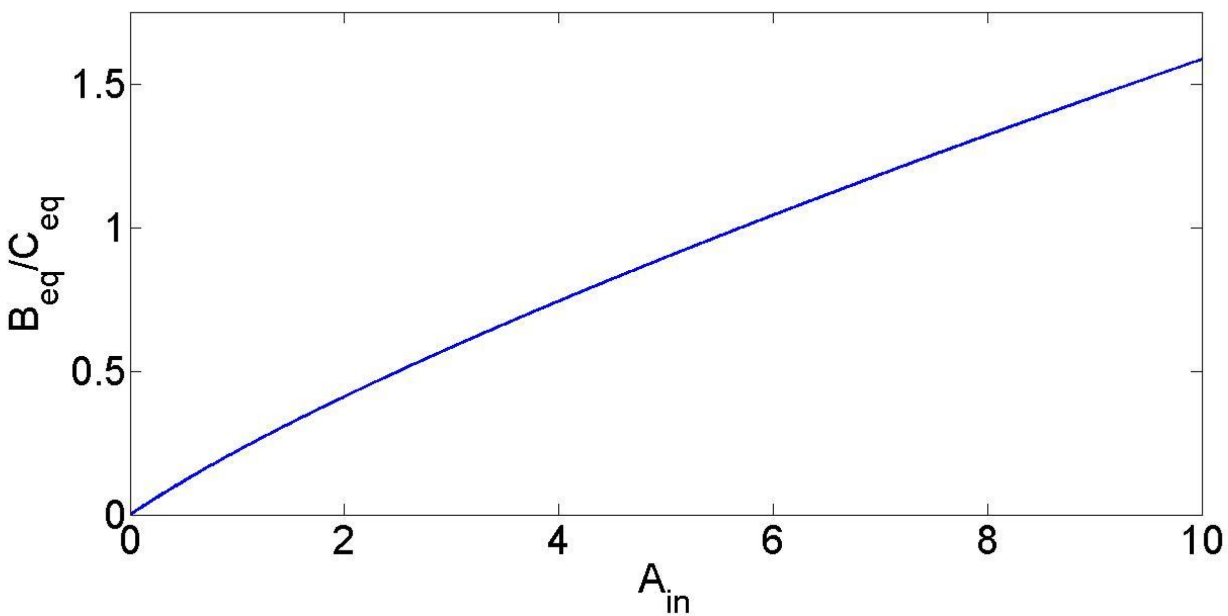
where for any chemical species $x' \in \nu$, $V_w(x)$ denotes the value of the expression $\sum_{1 \leq r' \leq n} w(r')V_{r'}(x')$.

A case showing a race between unary and binary reactions

- Reaction scheme

$$\begin{cases} 2A \xrightarrow{k_1} B \\ A \xrightarrow{k_2} C \end{cases}$$

- Analytic solution (ODE's)



k1=k2=1

Bin=Cin=0

Application to the case study showing a race between unary and binary reactions

- Reaction scheme

$$\begin{cases} 2A \overset{k_1}{\rightarrow} B \\ A \overset{k_2}{\rightarrow} C \end{cases}$$

- Properties

$$k_2 \cdot A_{in} \ll k_1 \Longrightarrow C_{eq} \gg B_{eq}$$

$$k_2 \cdot A_{in} \gg k_1 \Longrightarrow C_{eq} \ll B_{eq}$$

Application to the case study showing a race between unary and binary reactions

- Mass invariant

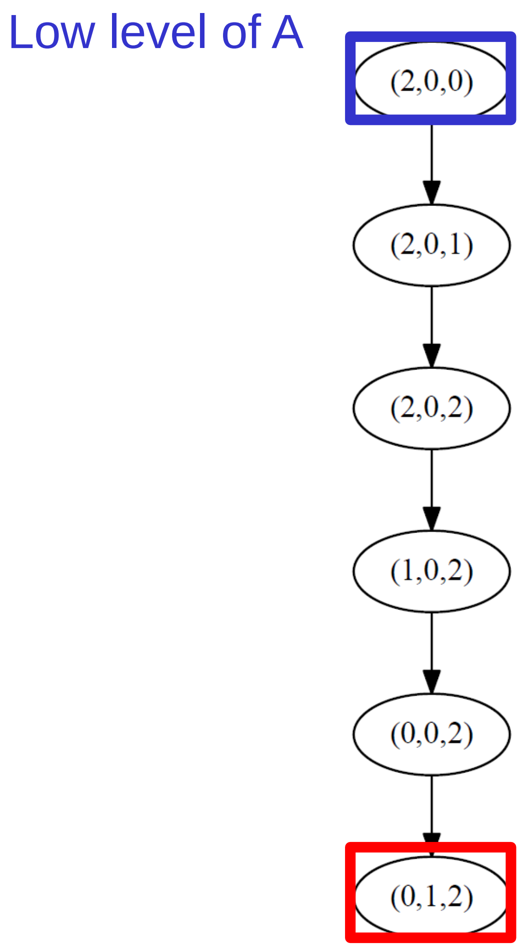
$$q(A) + 2q(B) + q(C) = A_T$$

- Kinetic constant

$$a_{r1} = 1 \quad a_{r2} = \delta^4$$

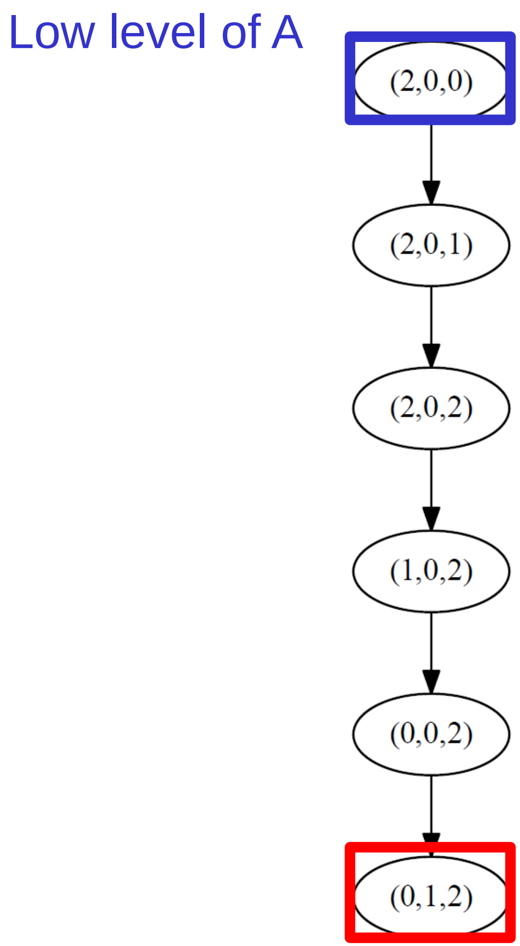
Application to the case study showing a race between unary and binary reactions

$$A_T = 4\delta^2$$



Application to the case study showing a race between unary and binary reactions

$$A_T = 4\delta^2$$

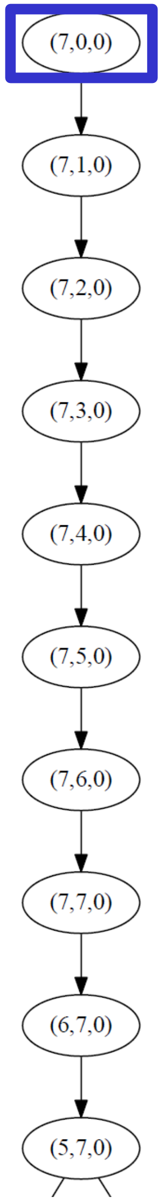


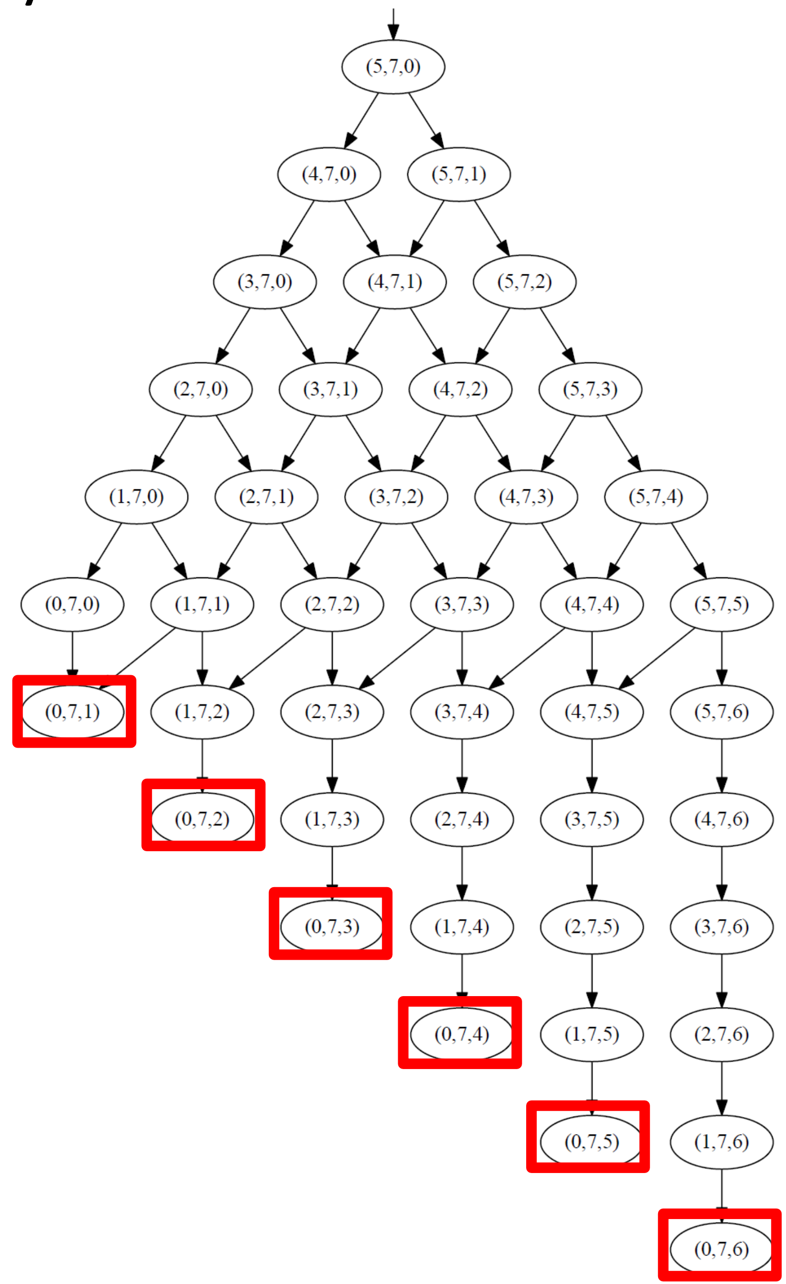
$$q(B) \leq q(C)$$

Application to the case study showing a race between unary and binary reactions

High level of A

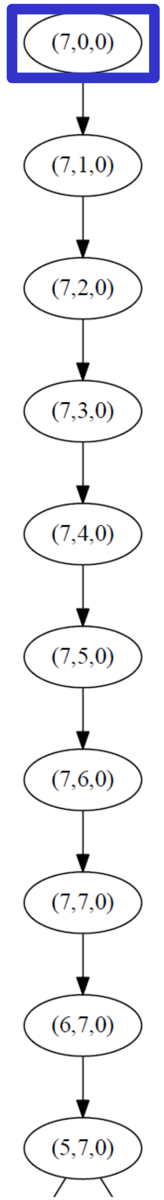
$$A_T = 4\delta^7$$



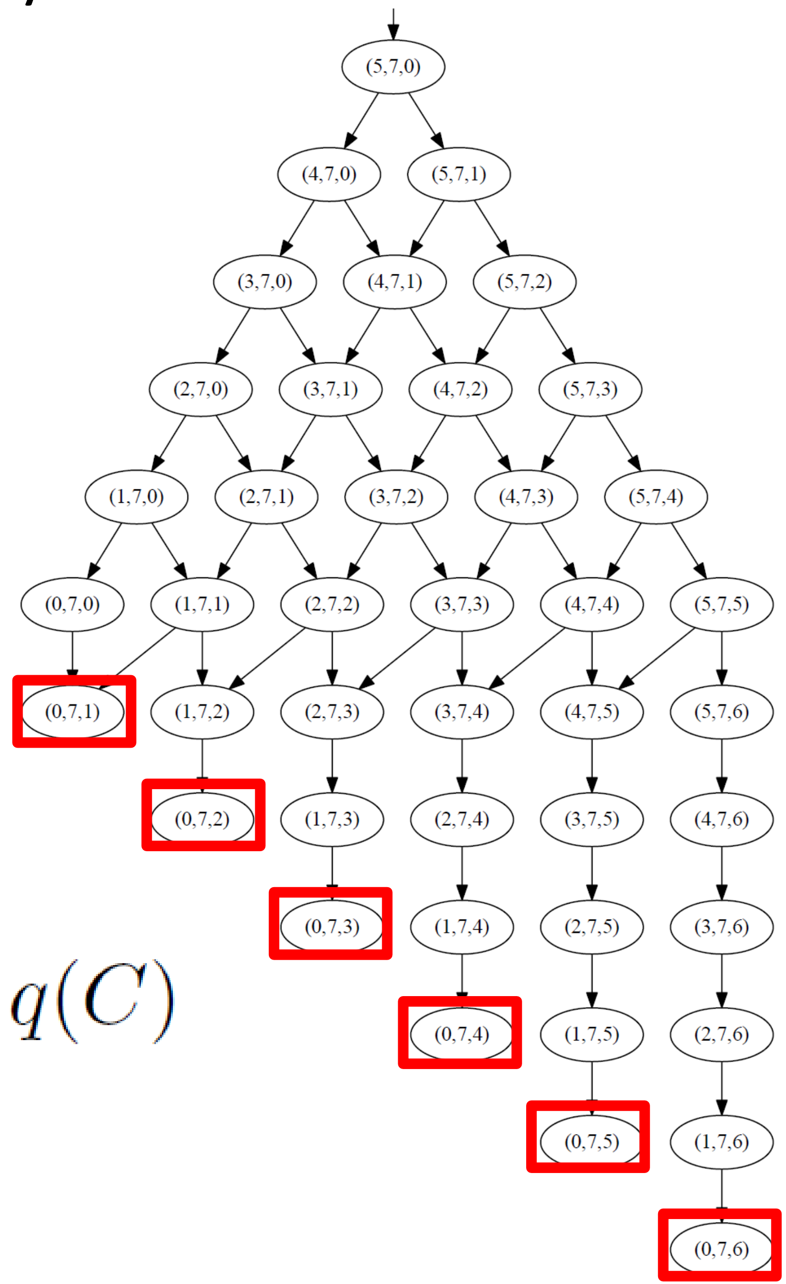


Application to the case study showing a race between unary and binary reactions

High level of A



$$A_T = 4\delta^7$$



$$q(B) \geq q(C)$$