MPRI

Some notions of information flow

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Wednesday, the 18th of February, 2015

Syntax

Let $\mathcal{V} \stackrel{\Delta}{=} \{V, V_1, V_2, \ldots\}$ be a finite set of variables.
Let $\mathbb{Z} \stackrel{\Delta}{=} \{z, \ldots\}$ be the set of relative numbers.
Expressions are polynomial of variables $\mathcal{V}$.

$$E ::= z \mid V \mid E + E \mid E \times E$$

Programs are given by the following grammar:

$$\begin{array}{lll} P & :== & \text{skip} \\ & \mid & P;P \\ & \mid & V := E \\ & \mid & \text{if } (V \geq 0)\ \{P\} \text{ else } \{P\} \\ & \mid & \text{while } (V \geq 0)\ \{P\} \end{array}$$

Semantics

We define the semantics $[\![P]\!] \in \mathcal{F}((\mathcal{V} \to \mathbb{Z}) \cup \Omega)$ of a program P:

- $[\![\text{skip}]\!](\rho) = \rho$,
- $[\![P_1;P_2]\!](\rho) = \begin{cases} \Omega & \text{if } [\![P_1]\!](\rho) = \Omega \\ [\![P_2]\!]([\![P_1]\!](\rho)) & \text{otherwise} \end{cases}$
- $[\![V := E]\!](\rho) = \begin{cases} \Omega & \text{if } \rho = \Omega \\ \rho\,[V \mapsto \overline{\rho}(E)] & \text{otherwise} \end{cases}$
- $[\![\text{if } (V \geq 0)\ \{P_1\} \text{ else } \{P_2\}]\!](\rho) = \begin{cases} \Omega & \text{if } \rho = \Omega \\ [\![P_1]\!](\rho) & \text{if } \rho(V) \geq 0 \\ [\![P_2]\!](\rho) & \text{otherwise} \end{cases}$
- $[\![\text{while } (V \geq 0)\ \{P\}]\!](\rho) = \begin{cases} \Omega & \text{if } \rho = \Omega \\ \rho' & \text{if } \{\rho'\} = \{\rho' \in \mathit{Inv} \mid \rho'(V) < 0\} \\ \Omega & \text{otherwise} \end{cases}$

  where $\mathit{Inv} = \mathit{lfp}\,(X \mapsto \{\rho\} \cup \{\rho'' \mid \exists \rho' \in X,\ \rho'(V) \geq 0 \text{ and } \rho'' \in [\![P]\!](\rho')\})$.

Flow of information

Given a program P, we say that the variable V_1 flows into the variable V_2 if, and only if, the final value of V_2 depends on the initial value of V_1, which is written $V_1 \Rightarrow_P V_2$.

More formally,
$V_1 \Rightarrow_P V_2$ if and only if there exists $\rho \in \mathcal{V} \rightarrow \mathbb{Z}$, $z, z' \in \mathbb{Z}$ such that one of the following three assertions is satisfied:

1. $[\![P]\!](\rho[V_1 \mapsto z]) \neq \Omega$, $[\![P]\!](\rho[V_1 \mapsto z']) \neq \Omega$, and $[\![P]\!](\rho[V_1 \mapsto z])(V_2) \neq [\![P]\!](\rho[V_1 \mapsto z'])(V_2)$;
2. $[\![P]\!](\rho[V_1 \mapsto z]) = \Omega$ and $[\![P]\!](\rho[V_1 \mapsto z']) \neq \Omega$;
3. $[\![P]\!](\rho[V_1 \mapsto z]) \neq \Omega$ and $[\![P]\!](\rho[V_1 \mapsto z']) = \Omega$.

Syntactic approximation (tentative)

Let P be a program.

We define the following binary relation $\rightarrow_P$ among variables in $\mathcal{V}$:
$V_1 \rightarrow_P V_2$ if and only if there is an assignement in P of the form $V_2 := E$ such that V_1 occurs in E.

Does $V_1 \Rightarrow_P V_2$ imply that $V_1 \rightarrow_P^* V_2$?

Counter-example

We consider the following progrem P:

$$
\begin{array}{rl}
P ::= & \text{if } (V_1 \geq 0) \\
& \quad \{V_2 := 0\} \\
& \text{else} \\
& \quad \{V_2 := 1\}
\end{array}
$$

For any $\rho \in \mathcal{V} \to \mathbb{Z}$,
we have $[\![P]\!](\rho[V_1 \mapsto 0])(V_2) = 0$;
but, $[\![P]\!](\rho[V_1 \mapsto 1])(V_2) = 1$;
so $V_1 \Rightarrow_P V_2$;
But $V_1 \not\twoheadrightarrow^*{}_P V_2$.

Syntactic approximation (tentative)

For each program point p in P,
we denote by *test*(p) the set of variables which occur in the guards of tests and while loops the scope of which contains the program point p.

We define the following binary relation $\rightarrow$ among variables in $\mathcal{V}$:
$V_1 \rightarrow_P V_2$ if and only if there is an assignement in P of the form $V_2 := E$ at program point p such that:

1. either V_1 occurs in E;
2. or $V_1 \in$ *test*(p).

Does $V_1 \Rightarrow_P V_2$ imply that $V_1 \rightarrow_P^* V_2$?

Counter-example

We consider the following progrem P:

$$P ::= \quad \text{while } (V_1 \geq 0) \ \{\text{skip}\}$$

For any $\rho \in \mathcal{V} \rightarrow \mathbb{Z}$,
we have $[\![P]\!](\rho[V_1 \mapsto -1]) \neq \Omega$;
but, $[\![P]\!](\rho[V_1 \mapsto 0]) = \Omega$;
so $V_1 \Rightarrow_P V_2$;
But $V_1 \not\rightarrow_P^* V_2$.

Approximation of the information flow

So as to get a sound approximation of the information flow,
we have to consider that a variable that is tested in the guard of a loop may flow in any variable.

We define the following binary relation $\rightarrow_P$ among variables in $\mathcal{V}$:
$V_1 \rightarrow V_2$ if and only if there is an assignement in P of the form $V_2 := E$ at program point p such that:

1. either V_1 occurs in E;
2. or V_1 is tested in the guard of a loop;
3. or $V_1 \in$ *test*(p).

Theorem 1 If $V_1 \Rightarrow_P V_2$, then $V_1 \rightarrow_P^* V_2$!

Limitations

The approximation is highly syntax-oriented.

- It is context-insensitive;
- It is very rough in the case of while loop,

  $\Longrightarrow$ we could show statically that some loops always terminate to avoid fictitious dependencies;
- we could detect some invariants to avoid fictitious dependencies.

Other forms of attacks could be modeled in the semantics: an attacker could observe:

- computation time;
- memory assumption;
- heating.

(attacks cannot be exhaustively specified).

Cours MPRI

Internal coarse-graining of molecular systems

[PNAS'09,LICS'10,MFPS'11]

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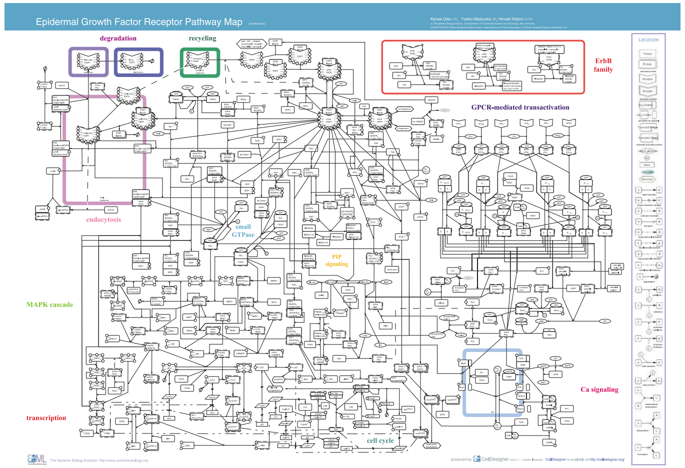
Overview

1. Context and motivations
2. Handmade ODEs
3. Abstract interpretation framework
4. Kappa
5. Concrete semantics
6. Abstract semantics
7. Conclusion

Bridging the gap between...

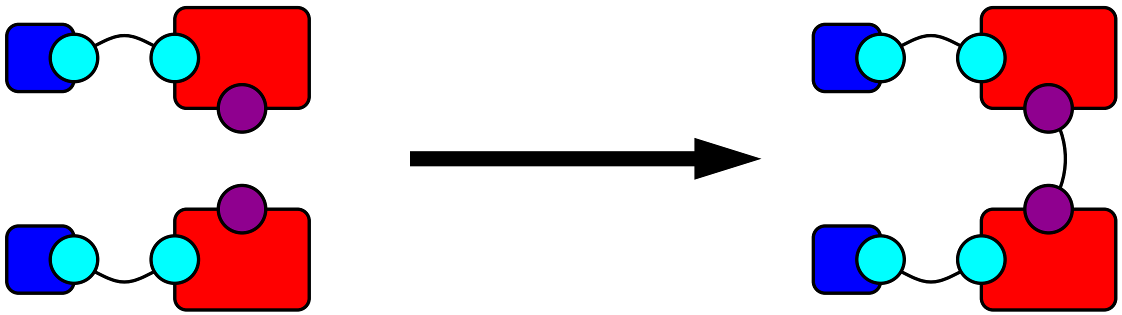


$$\begin{cases} \frac{dx_1}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\ \frac{dx_2}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\ \frac{dx_3}{dt} = k_1 \cdot x_1 \cdot x_2 - k_{-1} \cdot x_3 + 2 \cdot k_2 \cdot x_3 \cdot x_3 - k_{-2} \cdot x_4 \\ \frac{dx_4}{dt} = k_2 \cdot x_3^2 - k_2 \cdot x_4 + \frac{v_4 \cdot x_5}{p_4 + x_5} - k_3 \cdot x_4 - k_{-3} \cdot x_5 \\ \frac{dx_5}{dt} = \cdots \\ \vdots \\ \frac{dx_n}{dt} = -k_1 \cdot x_1 \cdot c_2 + k_{-1} \cdot x_3 \end{cases}$$

knowledge representation **and** **models of dynamical systems**

Rule-based approach

We use site graph rewrite systems

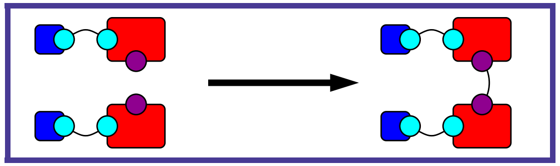


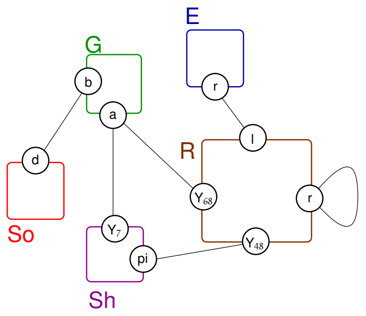
1. The description level matches with both
   - the observation level
   - and the intervention level

   of the biologist.

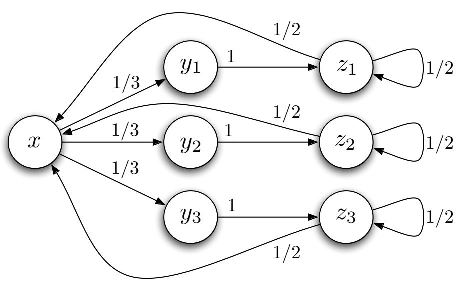
   We can tune the model easily.
2. Model description is very compact.

Rule-based models





Interaction map

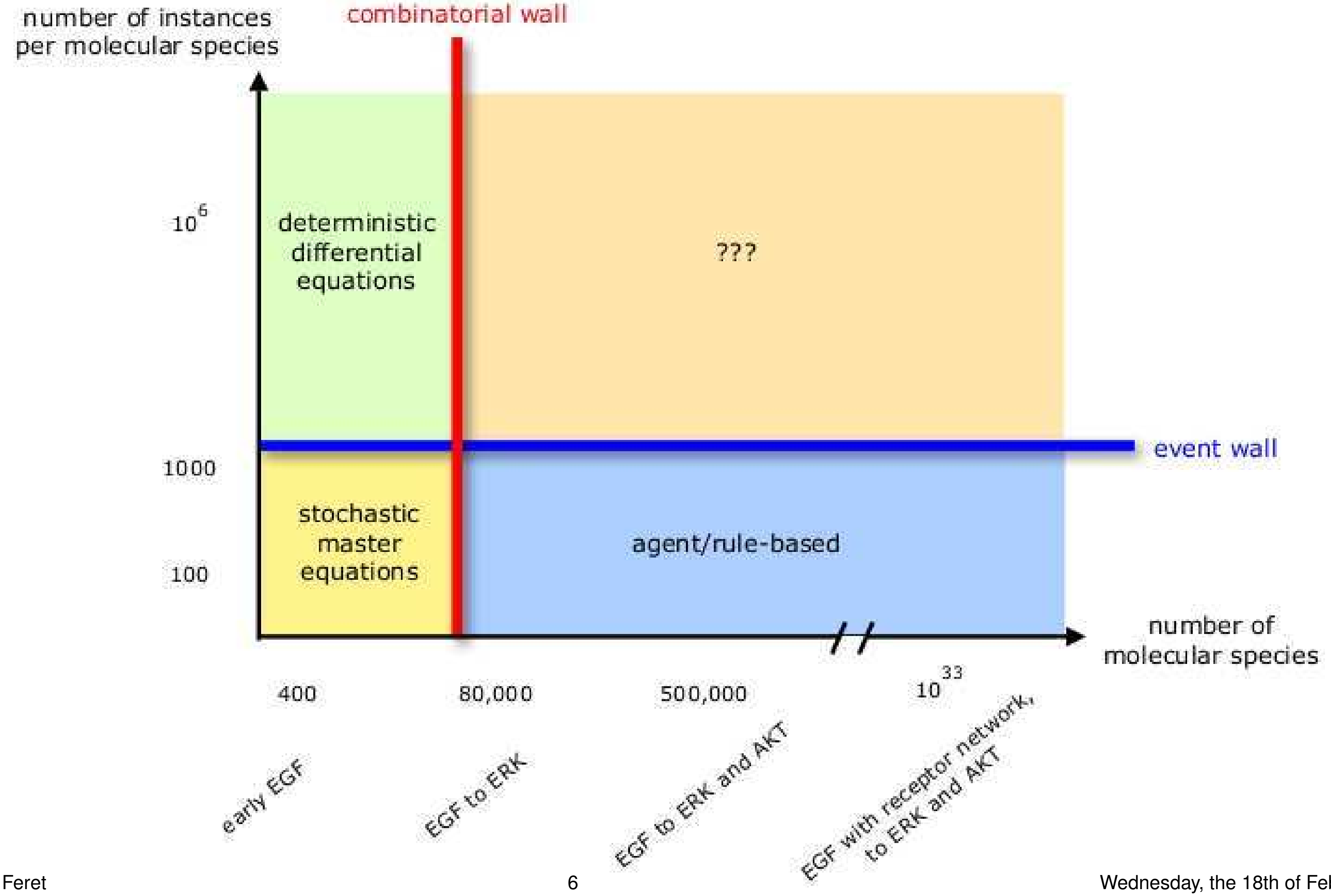


CTMC

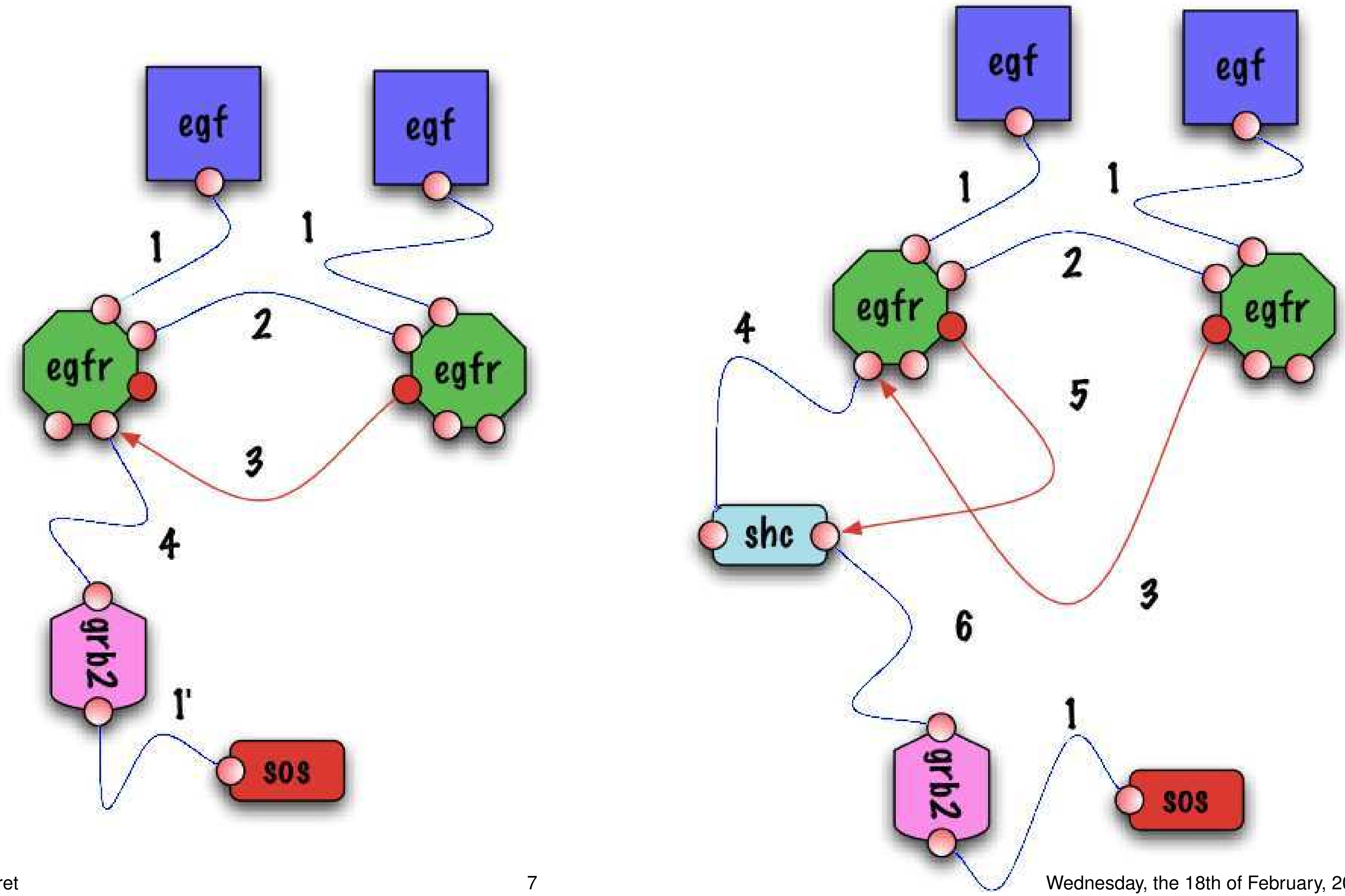
$$
\begin{cases}
\frac{dx_1}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
\frac{dx_2}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
\frac{dx_3}{dt} = k_1 \cdot x_1 \cdot x_2 - k_{-1} \cdot x_3 + 2 \cdot k_2 \cdot x_3 \cdot x_3 - k_{-2} \cdot x_4 \\
\frac{dx_4}{dt} = k_2 \cdot x_3^2 - k_2 \cdot x_4 + \frac{v_4 \cdot x_5}{p_4 + x_5} - k_3 \cdot x_4 - k_{-3} \cdot x_5 \\
\frac{dx_5}{dt} = \cdots \\
\vdots \\
\frac{dx_n}{dt} = -k_1 \cdot x_1 \cdot c_2 + k_{-1} \cdot x_3
\end{cases}
$$

ODEs

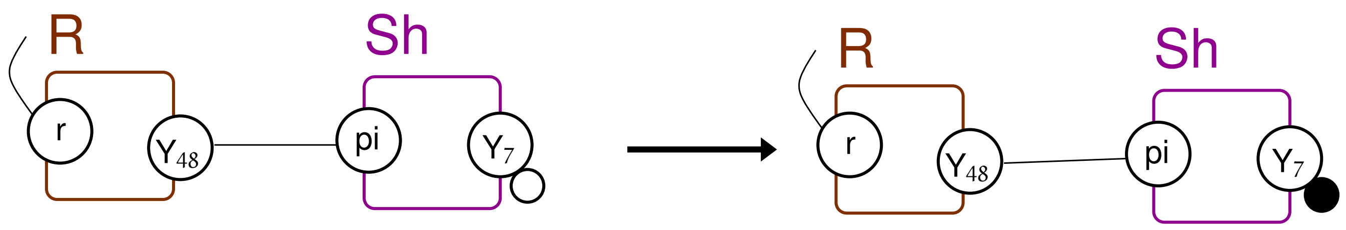
Complexity walls



A breach in the wall(s) ?



Summarising the flow of information



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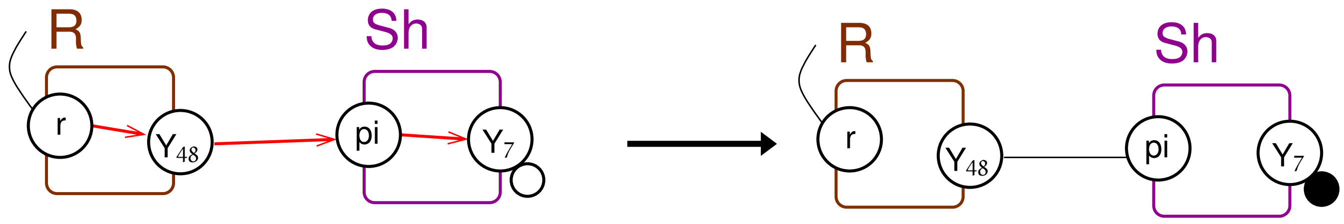
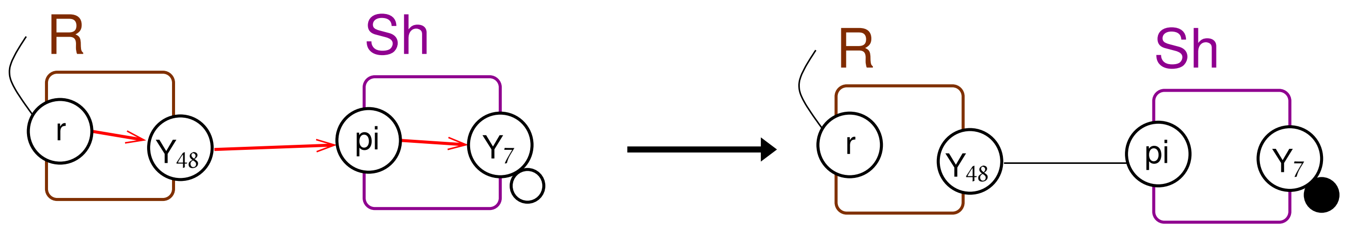
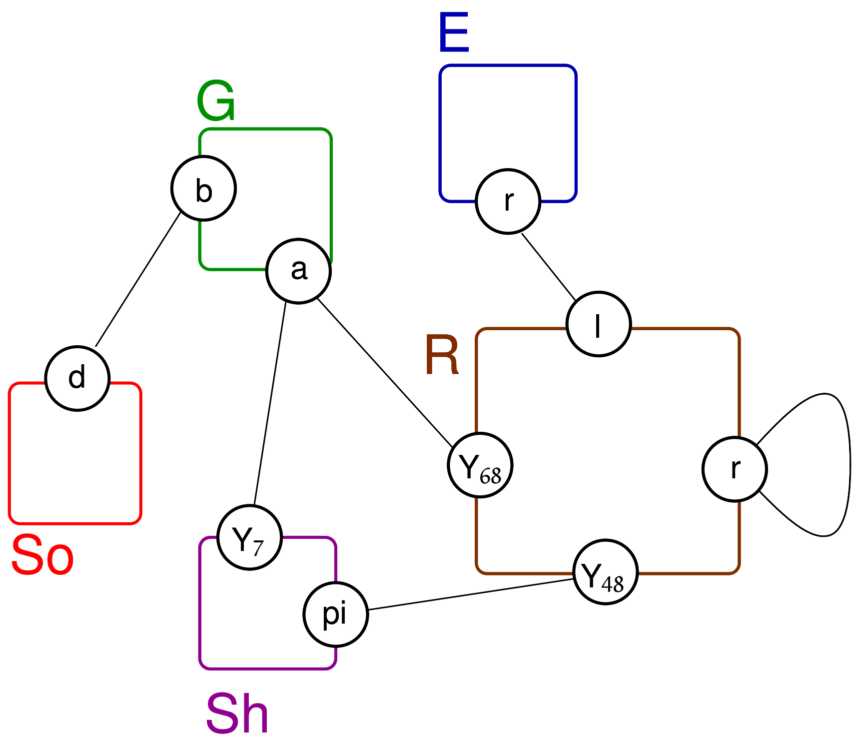
Summarising the flow of information



Summarising the flow of information





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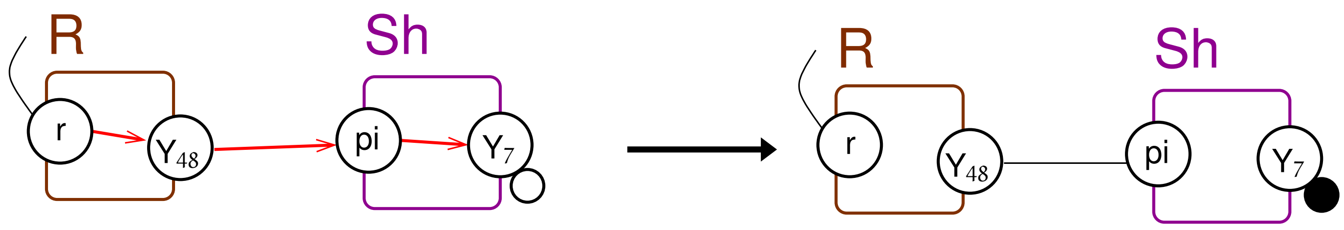
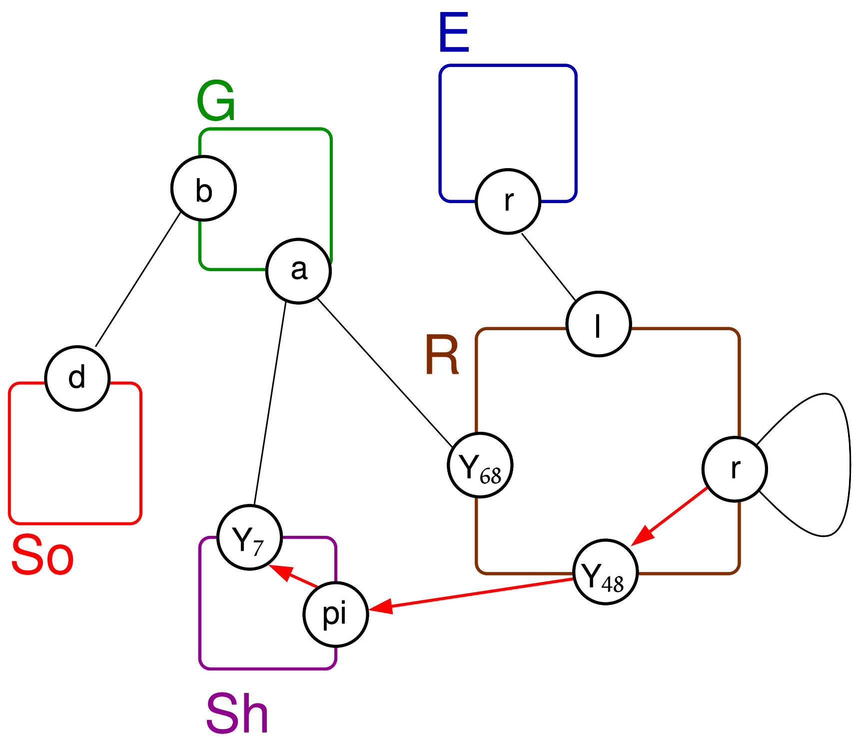
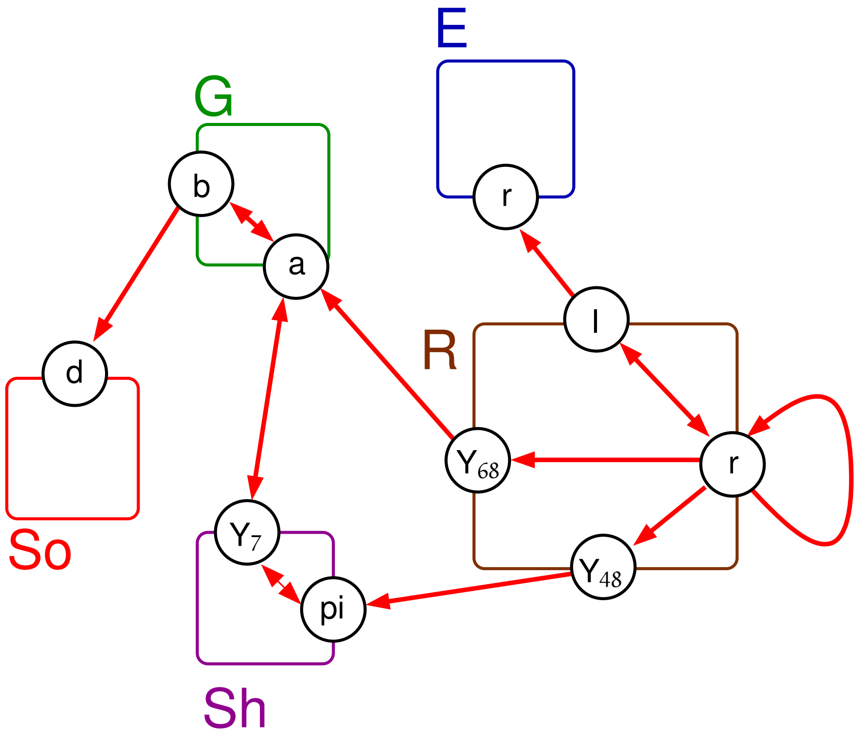
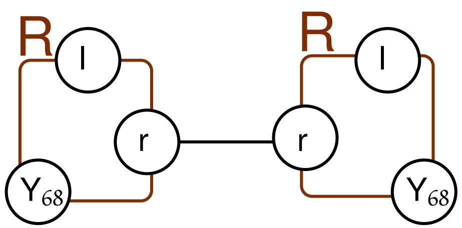
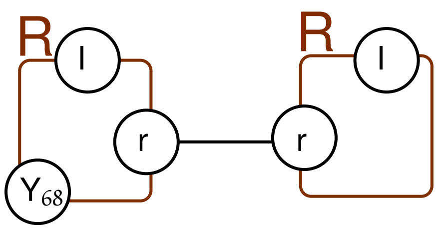




Deducing patterns of interest







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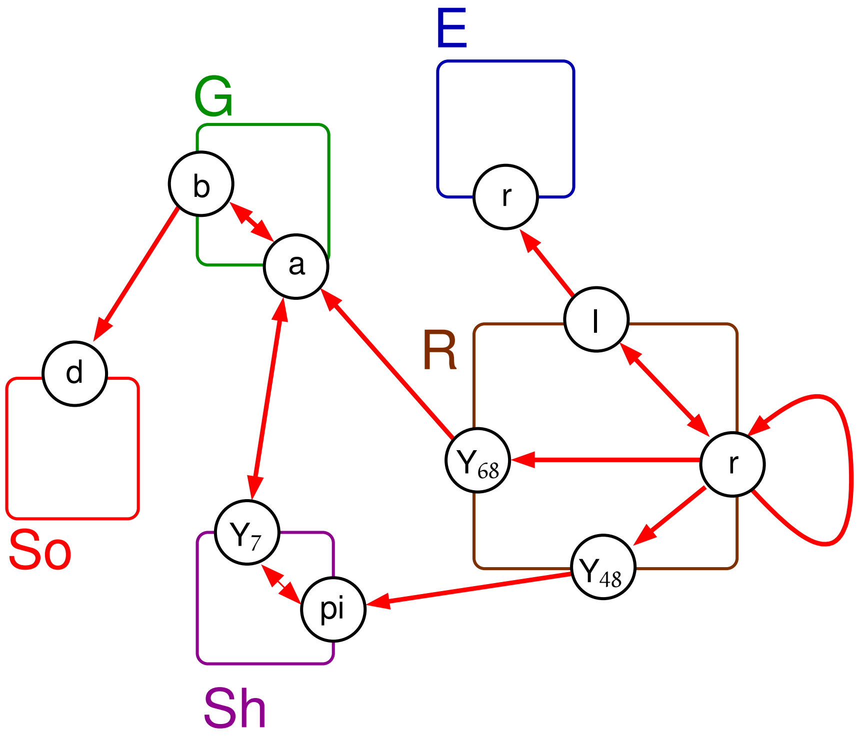
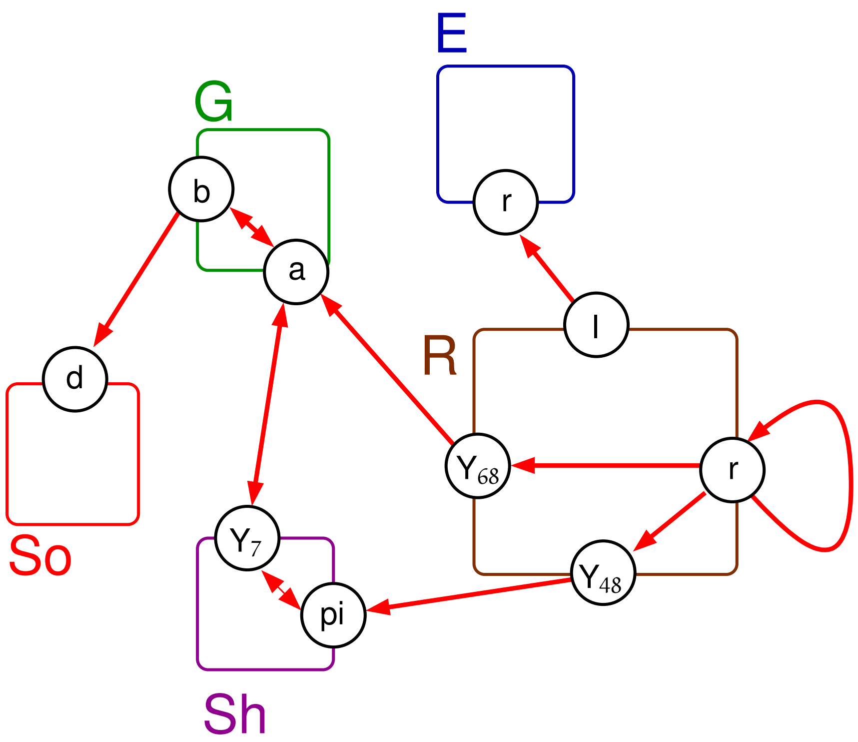
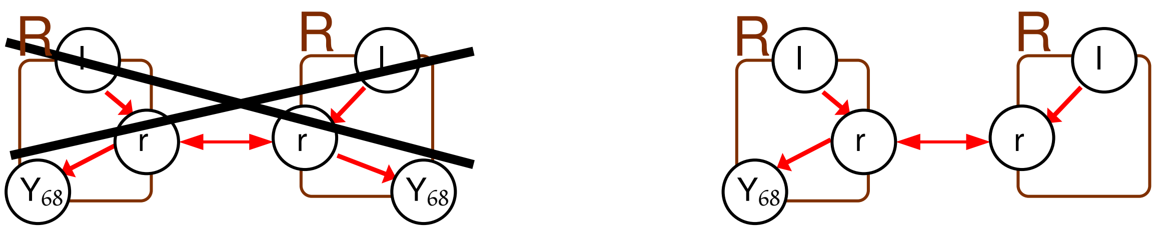


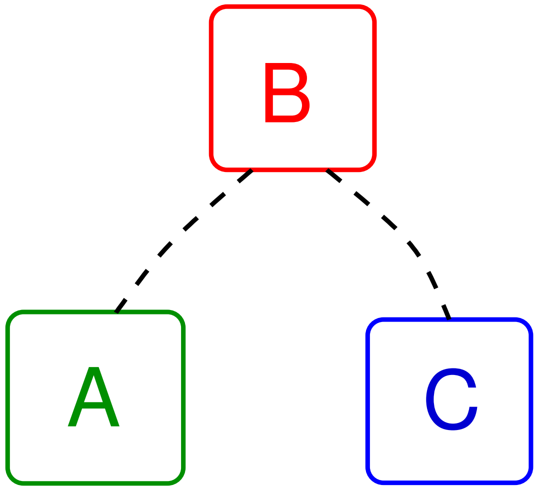
Deducing patterns of interest



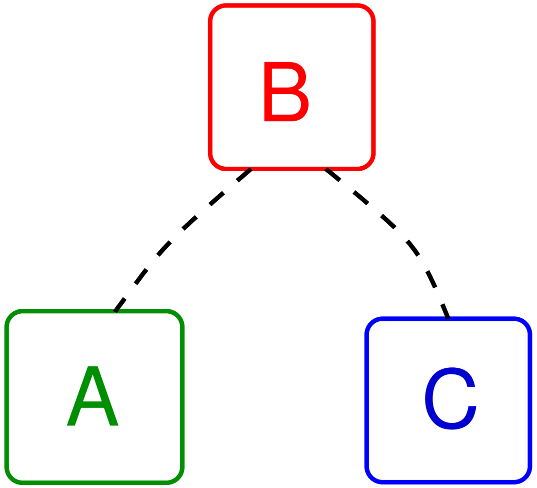


Overview

A simple adapter

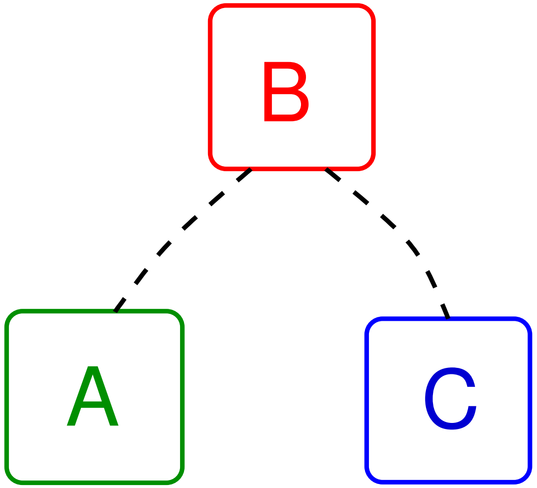


A simple adapter



A , ∅B∅	$\longleftrightarrow$	AB∅	k^{AB}, k_d^{AB}
A , ∅BC	$\longleftrightarrow$	ABC	k^{AB}, k_d^{AB}
∅B∅ , C	$\longleftrightarrow$	∅BC	k^{BC}, k_d^{BC}
AB∅ , C	$\longleftrightarrow$	ABC	k^{BC}, k_d^{BC}

A simple adapter



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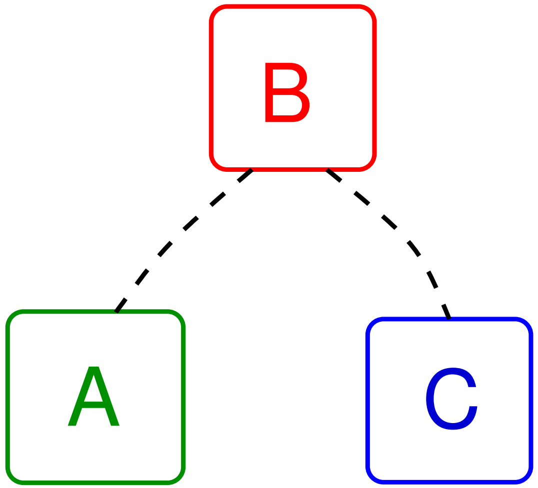
∅B∅ , C	$\longleftrightarrow$	∅BC	k^{BC}, k_d^{BC}
AB∅ , C	$\longleftrightarrow$	ABC	k^{BC}, k_d^{BC}

$$
\begin{cases}
\frac{d[A]}{dt} = k_d^{AB}\cdot[AB\emptyset] + k_d^{AB}\cdot[ABC] - k^{AB}\cdot[A]\cdot\emptyset B\emptyset - k^{AB}\cdot A\cdot\emptyset BC \\
\frac{d[C]}{dt} = k_d^{BC}\cdot\left([\emptyset BC] + [ABC]\right) - [C]\cdot k^{BC}\cdot\left([\emptyset B\emptyset] + [AB\emptyset]\right) \\
\frac{d[\emptyset B\emptyset]}{dt} = k_d^{AB}\cdot[AB\emptyset] + k_d^{BC}\cdot[\emptyset BC] - k^{AB}\cdot[A]\cdot[\emptyset B\emptyset] - k^{BC}\cdot[\emptyset B\emptyset]\cdot[C] \\
\frac{d[AB\emptyset]}{dt} = k^{AB}\cdot[A]\cdot[\emptyset B\emptyset] + k_d^{BC}\cdot[ABC] - k_d^{AB}\cdot[AB\emptyset] - k^{BC}\cdot[AB\emptyset]\cdot[C] \\
\frac{d[\emptyset BC]}{dt} = k_d^{AB}\cdot[ABC] + k^{BC}\cdot[C]\cdot[\emptyset B\emptyset] - [\emptyset BC]\cdot\left(k_d^{BC} + [A]\cdot k^{AB}\right) \\
\frac{d[ABC]}{dt} = k^{AB}\cdot[A]\cdot[\emptyset BC] + k^{BC}\cdot[C]\cdot[AB\emptyset] - [ABC]\cdot\left(k_d^{AB} + k_d^{BC}\right)
\end{cases}
$$

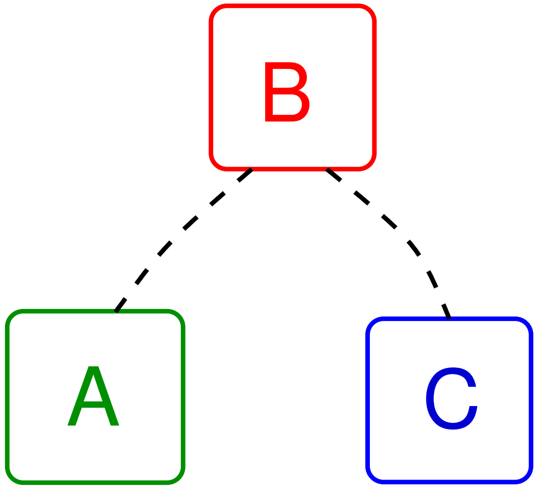
A simple adapter



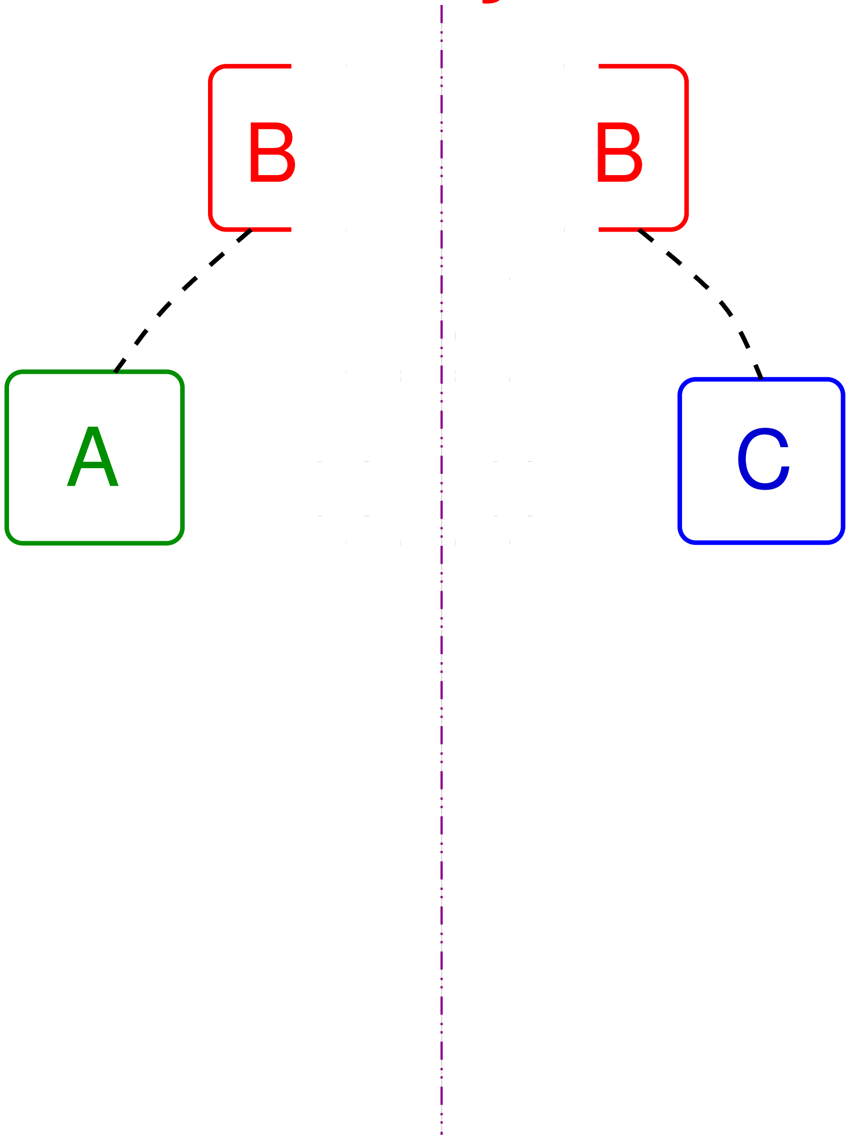
$A\ ,\ \emptyset B\emptyset$	$\longleftrightarrow$	$AB\emptyset$	k^{AB},k_d^{AB}
$A\ ,\ \emptyset BC$	$\longleftrightarrow$	ABC	k^{AB},k_d^{AB}
$\emptyset B\emptyset\ ,\ C$	$\longleftrightarrow$	$\emptyset BC$	k^{BC},k_d^{BC}
$AB\emptyset\ ,\ C$	$\longleftrightarrow$	ABC	k^{BC},k_d^{BC}

$$\begin{cases}
\frac{d[A]}{dt} = \boxed{k_d^{AB}\cdot[AB\emptyset]} + k_d^{AB}\cdot[ABC] - \boxed{k^{AB}\cdot[A]\cdot\emptyset B\emptyset} - k^{AB}\cdot A\cdot\emptyset BC \\
\frac{d[C]}{dt} = k_d^{BC}\cdot([\emptyset BC]+[ABC]) - [C]\cdot k^{BC}\cdot([\emptyset B\emptyset]+[AB\emptyset]) \\
\frac{d[\emptyset B\emptyset]}{dt} = \boxed{k_d^{AB}\cdot[AB\emptyset]} + k_d^{BC}\cdot[\emptyset BC] - \boxed{k^{AB}\cdot[A]\cdot[\emptyset B\emptyset]} - k^{BC}\cdot[\emptyset B\emptyset]\cdot[C] \\
\frac{d[AB\emptyset]}{dt} = \boxed{k^{AB}\cdot[A]\cdot[\emptyset B\emptyset]} + k_d^{BC}\cdot[ABC] - \boxed{k_d^{AB}\cdot[AB\emptyset]} - k^{BC}\cdot[AB\emptyset]\cdot[C] \\
\frac{d[\emptyset BC]}{dt} = k_d^{AB}\cdot[ABC] + k^{BC}\cdot[C]\cdot[\emptyset B\emptyset] - [\emptyset BC]\cdot(k_d^{BC}+[A]\cdot k^{AB}) \\
\frac{d[ABC]}{dt} = k^{AB}\cdot[A]\cdot[\emptyset BC] + k^{BC}\cdot[C]\cdot[AB\emptyset] - [ABC]\cdot(k_d^{AB}+k_d^{BC})
\end{cases}$$

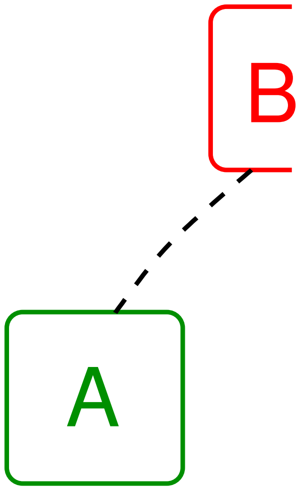
Two subsystems



Two subsystems



Two subsystems

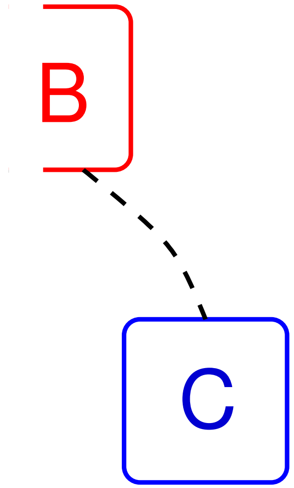


$$[\mathsf{A}] = [\mathsf{A}]$$

$$[\mathsf{AB?}] \triangleq [\mathsf{AB}\emptyset] + [\mathsf{ABC}]$$

$$[\emptyset\mathsf{B?}] \triangleq [\emptyset\mathsf{B}\emptyset] + [\emptyset\mathsf{BC}]$$

$$\begin{cases} \frac{d[\mathsf{A}]}{dt} = k_d^{\mathsf{AB}} \cdot [\mathsf{AB?}] - [\mathsf{A}] \cdot k^{\mathsf{AB}} \cdot [\emptyset\mathsf{B?}] \\ \frac{d[\mathsf{AB?}]}{dt} = [\mathsf{A}] \cdot k^{\mathsf{AB}} \cdot [\emptyset\mathsf{B?}] - k_d^{\mathsf{AB}} \cdot [\mathsf{AB?}] \\ \frac{d[\emptyset\mathsf{B?}]}{dt} = k_d^{\mathsf{AB}} \cdot [\mathsf{AB?}] - [\mathsf{A}] \cdot k^{\mathsf{AB}} \cdot [\emptyset\mathsf{B?}] \end{cases}$$



$$[\mathsf{C}] = [\mathsf{C}]$$

$$[\mathsf{?BC}] \triangleq [\emptyset\mathsf{BC}] + [\mathsf{ABC}]$$

$$[\mathsf{?B}\emptyset] \triangleq [\emptyset\mathsf{B}\emptyset] + [\mathsf{AB}\emptyset]$$

$$\begin{cases} \frac{d[\mathsf{C}]}{dt} = k_d^{\mathsf{BC}} \cdot [\mathsf{?BC}] - [\mathsf{C}] \cdot k^{\mathsf{BC}} \cdot [\mathsf{?B}\emptyset] \\ \frac{d[\mathsf{?BC}]}{dt} = [\mathsf{C}] \cdot k^{\mathsf{BC}} \cdot [\mathsf{?B}\emptyset] - k_d^{\mathsf{BC}} \cdot [\mathsf{?BC}] \\ \frac{d[\mathsf{?B}\emptyset]}{dt} = k_d^{\mathsf{BC}} \cdot [\mathsf{?BC}] - [\mathsf{C}] \cdot k^{\mathsf{BC}} \cdot [\mathsf{?B}\emptyset] \end{cases}$$

Dependence index

The binding with A and with C would be independent if, and only if:

$$\frac{[ABC]}{[?BC]} = \frac{[AB?]}{[\emptyset B?] + [AB?]}.$$

Thus we define the dependence index as follows:

$$X \triangleq [ABC]\cdot([\emptyset B?] + [AB?]) - [AB?]\cdot[?BC].$$

We have (after a short computation):

$$\frac{dX}{dt} = -X\cdot\left([A]\cdot k^{AB} + k_d^{AB} + [C]\cdot k^{BC} + k_d^{BC}\right).$$

So the property:

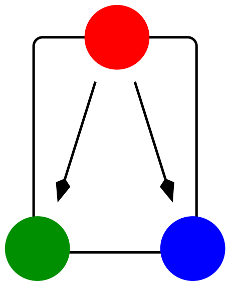
$$\frac{[ABC]}{[?BC]} = \frac{[AB?]}{[\emptyset B?] + [AB?]}.$$

is an invariant (i.e. if it holds at time t, it holds at any time $t' \geq t$).

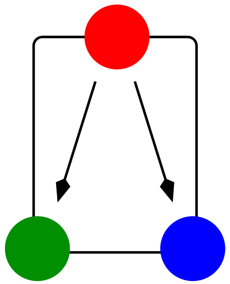
Overview

1. Context and motivations
2. Handmade ODEs
    (a) a simple adapter
    (b) a system with a switch
    (c) a system with symmetries
3. Abstract interpretation framework
4. Kappa
5. Concrete semantics
6. Abstract semantics
7. Conclusion

A system with a switch

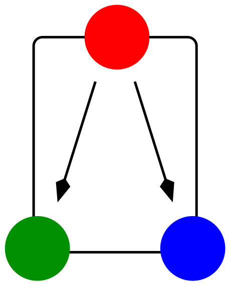


A system with a switch



(u,u,u)	$\longrightarrow$	(u,p,u)	k^c
(u,p,u)	$\longrightarrow$	(p,p,u)	k^l
(u,p,p)	$\longrightarrow$	(p,p,p)	k^l
(u,p,u)	$\longrightarrow$	(u,p,p)	k^r
(p,p,u)	$\longrightarrow$	(p,p,p)	k^r

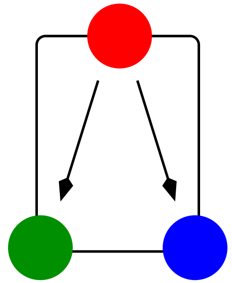
A system with a switch



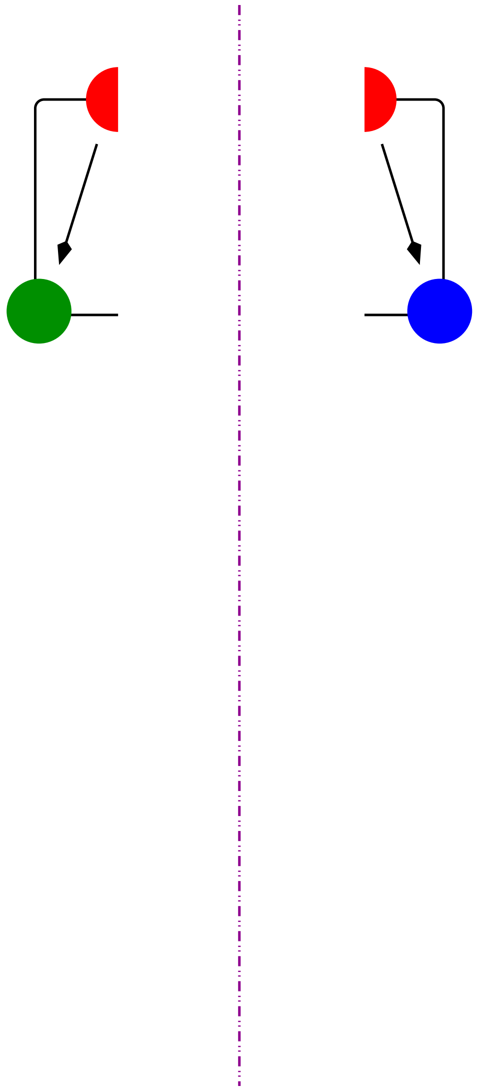
$$
\begin{array}{lcll}
(u,u,u) & \longrightarrow & (u,p,u) & k^c \\
(u,p,u) & \longrightarrow & (p,p,u) & k^l \\
(u,p,p) & \longrightarrow & (p,p,p) & k^l \\
(u,p,u) & \longrightarrow & (u,p,p) & k^r \\
(p,p,u) & \longrightarrow & (p,p,p) & k^r
\end{array}
$$

$$
\begin{cases}
\frac{d[(u,u,u)]}{dt} = -k^c \cdot [(u,u,u)] \\
\frac{d[(u,p,u)]}{dt} = -k^l \cdot [(u,p,u)] + k^c \cdot [(u,u,u)] - k^r \cdot [(u,p,u)] \\
\frac{d[(u,p,p)]}{dt} = -k^l \cdot [(u,p,p)] + k^r \cdot [(u,p,u)] \\
\frac{d[(p,p,u)]}{dt} = k^l \cdot [(u,p,u)] - k^r \cdot [(p,p,u)] \\
\frac{d[(p,p,p)]}{dt} = k^l \cdot [(u,p,p)] + k^r \cdot [(p,p,u)]
\end{cases}
$$

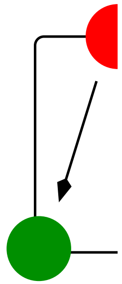
Two subsystems

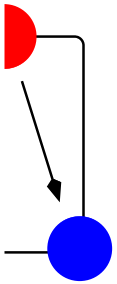


Two subsystems



Two subsystems





$[(u,u,u)] = [(u,u,u)]$

$[(u,p,?)] \triangleq [(u,p,u)] + [(u,p,p)]$

$[(p,p,?)] \triangleq [(p,p,u)] + [(p,p,p)]$

$$\begin{cases} \frac{d[(u,u,u)]}{dt} = -k^c \cdot [(u,u,u)] \\ \frac{d[(u,p,?)]}{dt} = -k^l \cdot [(u,p,?)] + k^c \cdot [(u,u,u)] \\ \frac{d[(p,p,?)]}{dt} = k^l \cdot [(u,p,?)] \end{cases}$$

$[(u,u,u)] = [(u,u,u)]$

$[(?,p,u)] \triangleq [(u,p,u)] + [(p,p,u)]$

$[(?,p,p)] \triangleq [(u,p,p)] + [(p,p,p)]$

$$\begin{cases} \frac{d[(u,u,u)]}{dt} = -k^c \cdot [(u,u,u)] \\ \frac{d[(?,p,u)]}{dt} = -k^r \cdot [(?,p,u)] + k^c \cdot [(u,u,u)] \\ \frac{d[(?,p,p)]}{dt} = k^r \cdot [(?,p,u)] \end{cases}$$

Dependence index

The states of left site and right site would be independent if, and only if:

$$\frac{[(?,p,p)]}{[(?,p,u)]+[(?,p,p)]}=\frac{[(p,p,p)]}{[(p,p,?)]}.$$

Thus we define the dependence index as follows:

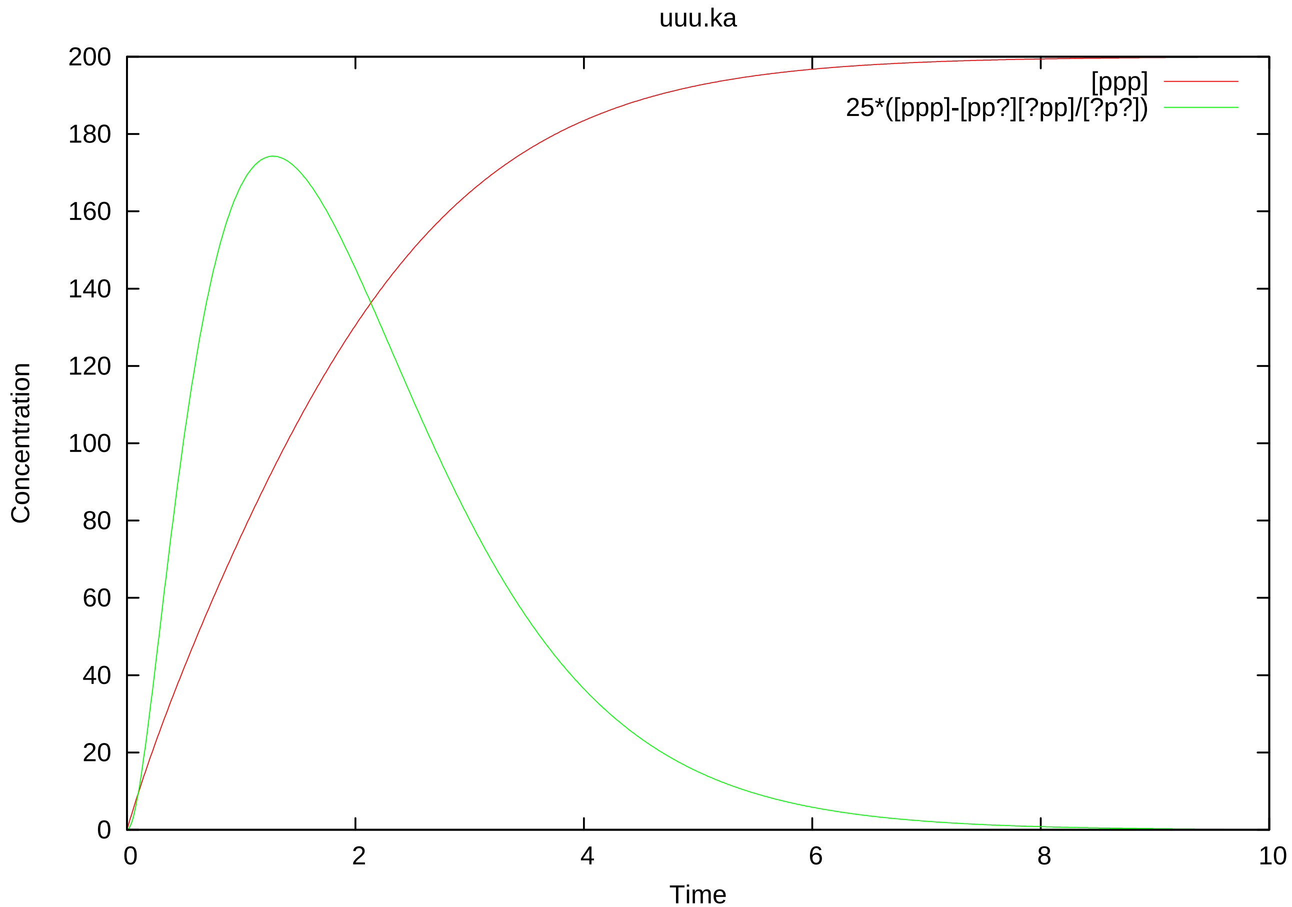
$$X \stackrel{\Delta}{=} [(p,p,p)]\cdot([(?,p,u)]+[(?,p,p)])-[(?,p,p)]\cdot[(p,p,?)].$$

We have:

$$\frac{dX}{dt}=-X\cdot\left(k^{l}+k^{r}\right)+k^{c}\cdot[(p,p,p)]\cdot[(u,u,u)].$$

So the property $(X=0)$ is not an invariant.

Erroneous recombination



Concentrations evolution with respect to time ($[(\mathrm{u},\mathrm{u},\mathrm{u})](0) = 200$).

$[(\mathrm{p},\mathrm{p},\mathrm{p})]$ and $25 \cdot \left([(\mathrm{p},\mathrm{p},\mathrm{p})] - \frac{[(\mathrm{p},\mathrm{p},?)] \cdot [(?,\mathrm{p},\mathrm{p})]}{[(?,\mathrm{p},?)]}\right)$

Conclusion

We can use the absence of flow of information to cut chemical species into self-consistent fragments of chemical species:

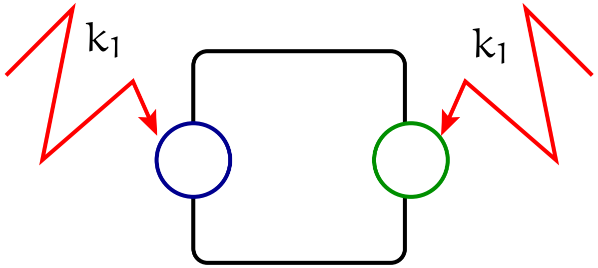
– some information is abstracted away:
  we cannot recover the concentration of any species;

+ flow of information is easy to abstract;

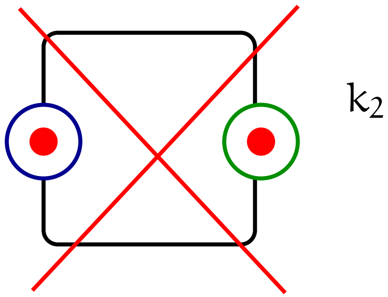
We are going to track the correlations that are read by the system.

Overview

A model with symmetries

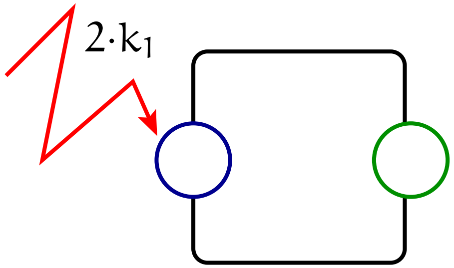


$$P \longrightarrow {}^{\star}P \quad k_1 \qquad P^{\star} \longrightarrow {}^{\star}P^{\star} \quad k_1$$
$$P \longrightarrow P^{\star} \quad k_1 \qquad {}^{\star}P \longrightarrow {}^{\star}P^{\star} \quad k_1$$

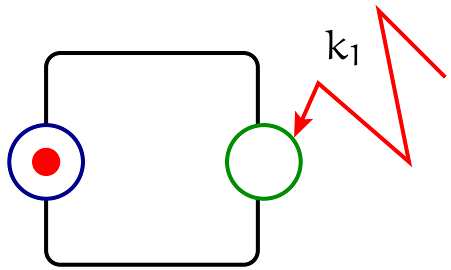


$${}^{\star}P^{\star} \longrightarrow \emptyset \quad k_2$$

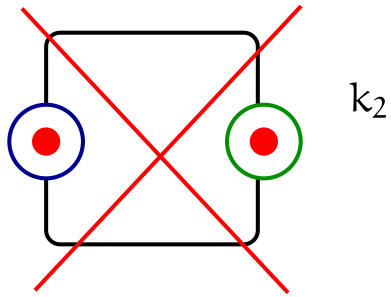
Reduced model



$$P \longrightarrow {}^{\star}P \quad 2\cdot k_1$$



$${}^{\star}P \longrightarrow {}^{\star}P^{\star} \quad k_1$$



$${}^{\star}P^{\star} \longrightarrow \emptyset \quad k_2$$

Differential equations

- Initial system:

$$\frac{d}{dt}\begin{bmatrix} P \\ {}^{\star}P \\ P^{\star} \\ {}^{\star}P^{\star} \end{bmatrix} = \begin{bmatrix} -2\cdot k_1 & 0 & 0 & 0 \\ k_1 & -k_1 & 0 & 0 \\ k_1 & 0 & -k_1 & 0 \\ 0 & k_1 & k_1 & -k_2 \end{bmatrix} \cdot \begin{bmatrix} P \\ {}^{\star}P \\ P^{\star} \\ {}^{\star}P^{\star} \end{bmatrix}$$

- Reduced system:

$$\frac{d}{dt}\begin{bmatrix} P \\ {}^{\star}P + P^{\star} \\ 0 \\ {}^{\star}P^{\star} \end{bmatrix} = \begin{bmatrix} -2\cdot k_1 & 0 & 0 & 0 \\ 2\cdot k_1 & -k_1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & k_1 & 0 & -k_2 \end{bmatrix} \cdot \begin{bmatrix} P \\ {}^{\star}P + P^{\star} \\ 0 \\ {}^{\star}P^{\star} \end{bmatrix}$$

Invariant

We wonder whether or not:

$$[{}^{\star}P] = [P^{\star}],$$

Thus we define the difference X as follows:

$$X \stackrel{\Delta}{=} [{}^{\star}P] - [P^{\star}].$$

We have:

$$\frac{dX}{dt} = -k_1 \cdot X.$$

So the property $(X = 0)$ is an invariant.

Thus, if $[{}^{\star}P] = [P^{\star}]$ at time $t = 0$, then $[{}^{\star}P] = [P^{\star}]$ forever.

Conclusion

We can abstract away the distinction between chemical species which are equivalent up to symmetries (with respect to the reactions).

1. If the symmetries are satisfied in the initial state:

   $+$ the abstraction is invertible:

   we can recover the concentration of any species,

   (thanks to the invariants).

2. Otherwise:

   $-$ some information is abstracted away:

   we cannot recover the concentration of any species;

   $+$ the system converges to a state which satisfies the symmetries.

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6. Abstract semantics
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Differential semantics

Let $\mathcal{V}$, be a finite set of variables ;
and $\mathbb{F}$, be a $\mathcal{C}^\infty$ mapping from $\mathcal{V} \rightarrow \mathbb{R}^+$ into $\mathcal{V} \rightarrow \mathbb{R}$,
as for instance,

- $\mathcal{V} \stackrel{\Delta}{=} \{[(u,u,u)], [(u,p,u)], [(p,p,u)], [(u,p,p)], [(p,p,p)]\}$,
- $\mathbb{F}(\rho) \stackrel{\Delta}{=} \begin{cases} [(u,u,u)] \mapsto -k^c \cdot \rho([(u,u,u)]) \\ [(u,p,u)] \mapsto -k^l \cdot \rho([(u,p,u)]) + k^c \cdot \rho([(u,u,u)]) - k^r \cdot \rho([(u,p,u)]) \\ [(u,p,p)] \mapsto -k^l \cdot \rho([(u,p,p)]) + k^r \cdot \rho([(u,p,u)]) \\ [(p,p,u)] \mapsto k^l \cdot \rho([(u,p,u)]) - k^r \cdot \rho([(p,p,u)]) \\ [(p,p,p)] \mapsto k^l \cdot \rho([(u,p,p)]) + k^r \cdot \rho([(p,p,u)]). \end{cases}$

The differential semantics maps each initial state $X_0 \in \mathcal{V} \rightarrow \mathbb{R}^+$ to the maximal solution $X_{X_0} \in [0, T^{max}_{X_0}[\rightarrow (\mathcal{V} \rightarrow \mathbb{R}^+)$ which satisfies:

$$X_{X_0}(T) = X_0 + \int_{t=0}^{T} \mathbb{F}(X_{X_0}(t)) \cdot dt.$$

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Abstraction

An abstraction $(\mathcal{V}^\sharp, \psi, \mathbb{F}^\sharp)$ is given by:

- $\mathcal{V}^\sharp$: a finite set of observables,
- ψ: a mapping from $\mathcal{V} \rightarrow \mathbb{R}$ into $\mathcal{V}^\sharp \rightarrow \mathbb{R}$,
- $\mathbb{F}^\sharp$: a $\mathcal{C}^\infty$ mapping from $\mathcal{V}^\sharp \rightarrow \mathbb{R}^+$ into $\mathcal{V}^\sharp \rightarrow \mathbb{R}$;

such that:

- ψ is linear with positive coefficients,
- the following diagram commutes:

$$\begin{array}{ccc}
(\mathcal{V} \rightarrow \mathbb{R}^+) & \xrightarrow{\mathbb{F}} & (\mathcal{V} \rightarrow \mathbb{R}) \\
\psi \big\downarrow \ell^* & & \big\downarrow \ell^* \psi \\
(\mathcal{V}^\sharp \rightarrow \mathbb{R}^+) & \xrightarrow{\mathbb{F}^\sharp} & (\mathcal{V}^\sharp \rightarrow \mathbb{R})
\end{array}$$

  i.e. $\psi \circ \mathbb{F} = \mathbb{F}^\sharp \circ \psi$.

- for any sequence $(x_n) \in (\mathcal{V} \rightarrow \mathbb{R}^+)^{\mathbb{N}}$ such that $(||x_n||)$ diverges towards $+\infty$, then $(||\psi(x_n)||^\sharp)$ diverges as well (for arbitrary norms $|| \cdot ||$ and $|| \cdot ||^\sharp$).

Abstraction example

- $\mathcal{V} \triangleq \{[(u,u,u)], [(u,p,u)], [(p,p,u)], [(u,p,p)], [(p,p,p)]\}$
- $\mathbb{F}(\rho) \triangleq \begin{cases} [(u,u,u)] \mapsto -k^c \cdot \rho([(u,u,u)]) \\ [(u,p,u)] \mapsto -k^l \cdot \rho([(u,p,u)]) + k^c \cdot \rho([(u,u,u)]) - k^r \cdot \rho([(u,p,u)]) \\ [(u,p,p)] \mapsto -k^l \cdot \rho([(u,p,p)]) + k^r \cdot \rho([(u,p,u)]) \\ \ldots \end{cases}$
- $\mathcal{V}^\sharp \triangleq \{[(u,u,u)], [(?,p,u)], [(?,p,p)], [(u,p,?)], [(p,p,?)]\}$
- $\psi(\rho) \triangleq \begin{cases} [(u,u,u)] \mapsto \rho([(u,u,u)]) \\ [(?,p,u)] \mapsto \rho([(u,p,u)]) + \rho([(p,p,u)]) \\ [(?,p,p)] \mapsto \rho([(u,p,p)]) + \rho([(p,p,p)]) \\ \ldots \end{cases}$
- $\mathbb{F}^\sharp(\rho^\sharp) \triangleq \begin{cases} [(u,u,u)] \mapsto -k^c \cdot \rho^\sharp([(u,u,u)]) \\ [(?,p,u)] \mapsto -k^r \cdot \rho^\sharp([(?,p,u)]) + k^c \cdot \rho^\sharp([(u,u,u)]) \\ [(?,p,p)] \mapsto k^r \cdot \rho^\sharp([(?,p,u)]) \\ \ldots \end{cases}$

(Completeness can be checked analytically.)

Abstract differential semantics

Let $(\mathcal{V}, \mathbb{F})$ be a concrete system.
Let $(\mathcal{V}^\sharp, \psi, \mathbb{F}^\sharp)$ be an abstraction of the concrete system $(\mathcal{V}, \mathbb{F})$.
Let $X_0 \in \mathcal{V} \to \mathbb{R}^+$ be an initial (concrete) state.

We know that the following system:

$$Y_{\psi(X_0)}(T) = \psi(X_0) + \int_{t=0}^{T} \mathbb{F}^\sharp \left(Y_{\psi(X_0)}(t)\right) \cdot dt$$

has a unique maximal solution $Y_{\psi(X_0)}$ such that $Y_{\psi(X_0)} = \psi(X_0)$.

Theorem 1 Moreover, this solution is the projection of the maximal solution X_{X_0} of the system

$$X_{X_0}(T) = X_0 + \int_{t=0}^{T} \mathbb{F} \left(X_{X_0}(t)\right) \cdot dt.$$

(i.e. $Y_{\psi(X_0)} = \psi(X_{X_0})$)

Abstract differential semantics
Proof sketch

Given an abstraction $(\mathcal{V}^\sharp, \psi, \mathbb{F}^\sharp)$, we have:

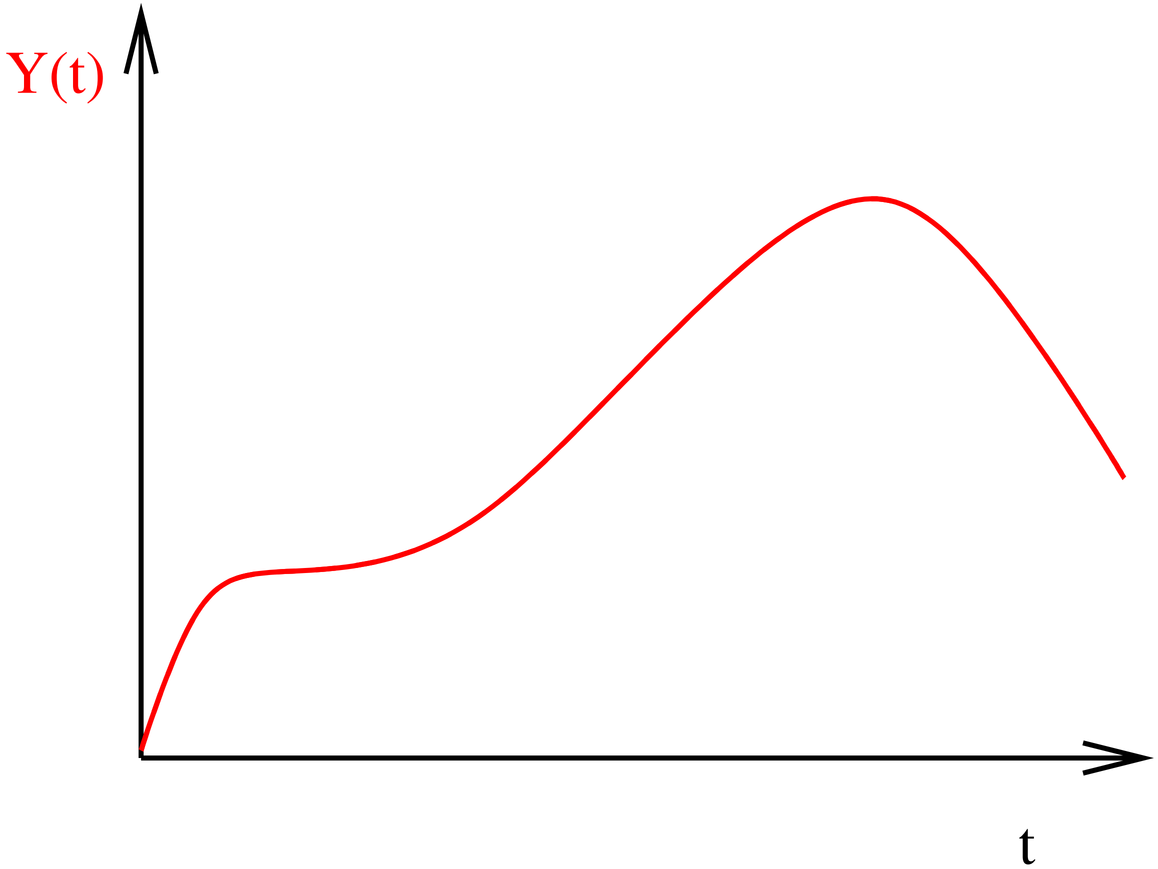
$$\begin{aligned}
X_{X_0}(T) &= X_0 + \int_{t=0}^{T} \mathbb{F}\left(X_{X_0}(t)\right) \cdot dt \\
\psi\left(X_{X_0}(T)\right) &= \psi\left(X_0 + \int_{t=0}^{T} \mathbb{F}\left(X_{X_0}(t)\right) \cdot dt\right) \\
\psi\left(X_{X_0}(T)\right) &= \psi(X_0) + \int_{t=0}^{T} [\psi \circ \mathbb{F}]\left(X_{X_0}(t)\right) \cdot dt \quad (\psi \text{ is linear}) \\
\psi\left(X_{X_0}(T)\right) &= \psi(X_0) + \int_{t=0}^{T} \mathbb{F}^\sharp\left(\psi\left(X_{X_0}(t)\right)\right) \cdot dt \quad (\mathbb{F}^\sharp \text{ is } \psi\text{-complete})
\end{aligned}$$

We set $Y_0 \triangleq \psi(X_0)$ and $Y_{Y_0} \triangleq \psi \circ X_{X_0}$.
Then we have:

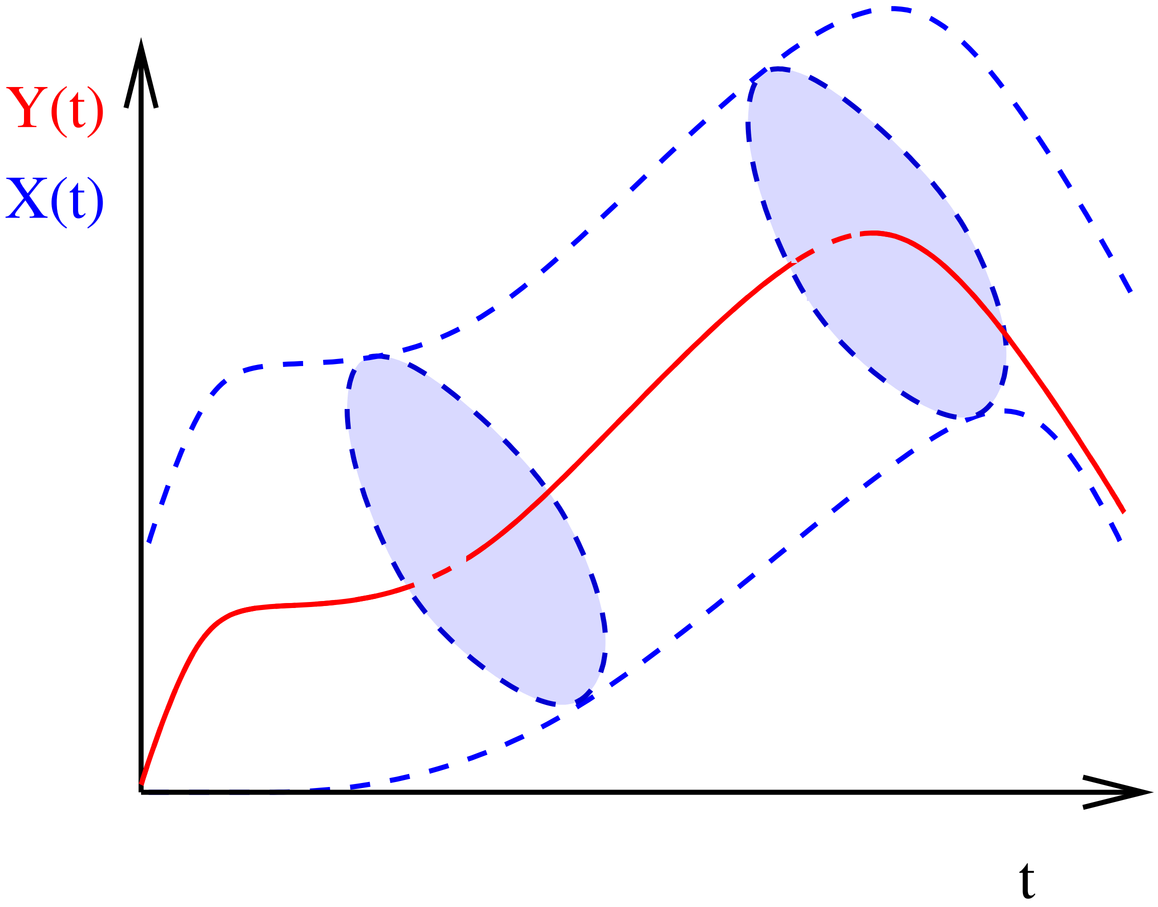
$$\boxed{Y_{Y_0}(T) = Y_0 + \int_{t=0}^{T} \mathbb{F}^\sharp\left(Y_{Y_0}(t)\right) \cdot dt}$$

The assumption about $\|\cdot\|$, $\|\cdot\|^\sharp$, and ψ ensures that $\psi \circ X_{X_0}$ is a maximal solution.

Fluid trajectories



Fluid trajectories



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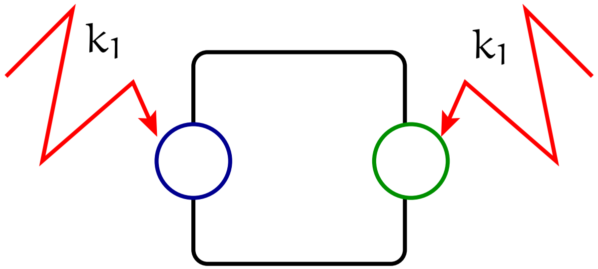
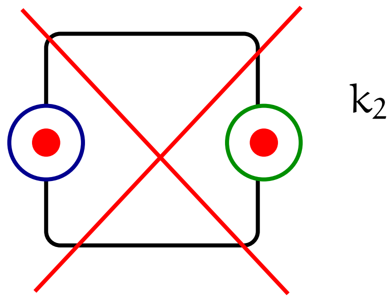
A model with symmetries



$$P \longrightarrow {}^{\star}P \quad k_1 \qquad\qquad P^{\star} \longrightarrow {}^{\star}P^{\star} \quad k_1$$

$$P \longrightarrow P^{\star} \quad k_1 \qquad\qquad {}^{\star}P \longrightarrow {}^{\star}P^{\star} \quad k_1$$



$${}^{\star}P^{\star} \longrightarrow \emptyset \quad k_2$$

Differential equations

- Initial system:

$$\frac{d}{dt}\begin{bmatrix} P \\ {}^{\star}P \\ P^{\star} \\ {}^{\star}P^{\star} \end{bmatrix} = \begin{bmatrix} -2\cdot k_1 & 0 & 0 & 0 \\ k_1 & -k_1 & 0 & 0 \\ k_1 & 0 & -k_1 & 0 \\ 0 & k_1 & k_1 & -k_2 \end{bmatrix} \cdot \begin{bmatrix} P \\ {}^{\star}P \\ P^{\star} \\ {}^{\star}P^{\star} \end{bmatrix}$$

- Reduced system:

$$\frac{d}{dt}\begin{bmatrix} P \\ {}^{\star}P + P^{\star} \\ 0 \\ {}^{\star}P^{\star} \end{bmatrix} = \begin{bmatrix} -2\cdot k_1 & 0 & 0 & 0 \\ 2\cdot k_1 & -k_1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & k_1 & 0 & -k_2 \end{bmatrix} \cdot \begin{bmatrix} P \\ {}^{\star}P + P^{\star} \\ 0 \\ {}^{\star}P^{\star} \end{bmatrix}$$

Differential equations

- Initial system:

$$\frac{d}{dt}\begin{bmatrix} P \\ {}^{\star}P \\ P^{\star} \\ {}^{\star}P^{\star} \end{bmatrix} = \begin{bmatrix} -2\cdot k_1 & 0 & 0 & 0 \\ k_1 & -k_1 & 0 & 0 \\ k_1 & 0 & -k_1 & 0 \\ 0 & k_1 & k_1 & -k_2 \end{bmatrix} \cdot \begin{bmatrix} P \\ {}^{\star}P \\ P^{\star} \\ {}^{\star}P^{\star} \end{bmatrix}$$

- Reduced system:

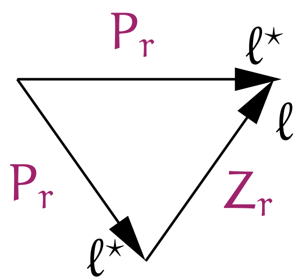
$$\frac{d}{dt}\begin{bmatrix} P \\ {}^{\star}P + P^{\star} \\ 0 \\ {}^{\star}P^{\star} \end{bmatrix} = \underbrace{\begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}}_{P} \cdot \begin{bmatrix} -2\cdot k_1 & 0 & 0 & 0 \\ k_1 & -k_1 & 0 & 0 \\ k_1 & 0 & -k_1 & 0 \\ 0 & k_1 & k_1 & -k_2 \end{bmatrix} \cdot \underbrace{\begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}}_{Z} \cdot \begin{bmatrix} P \\ {}^{\star}P + P^{\star} \\ 0 \\ {}^{\star}P^{\star} \end{bmatrix}$$

Pair of projections induced by an equivalence relation among variables

Let r be an idempotent mapping from $\mathcal{V}$ to $\mathcal{V}$.
We define two linear projections $P_r, Z_r \in (\mathcal{V} \to \mathbb{R}^+) \to (\mathcal{V} \to \mathbb{R}^+)$ by:

- $P_r(\rho)(V) = \begin{cases} \sum\{\rho(V') \mid r(V') = r(V)\} & \text{when } V = r(V) \\ 0 & \text{when } V \neq r(V); \end{cases}$
- $Z_r(\rho) = \begin{cases} V \mapsto \rho(V) & \text{when } V = r(V) \\ V \mapsto 0 & \text{when } V \neq r(V). \end{cases}$

We notice that the following diagram commutes:



Induced bisimulation

The mapping r induces a bisimulation,

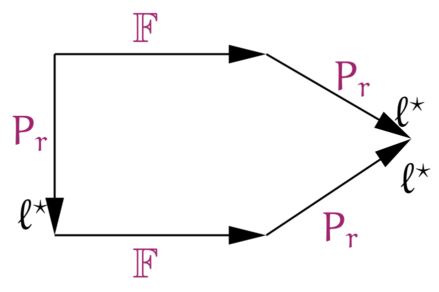
$\stackrel{\Delta}{\Longleftrightarrow}$

for any $\sigma, \sigma' \in \mathcal{V} \rightarrow \mathbb{R}^{+}$, $P_r(\sigma) = P_r(\sigma') \implies P_r(\mathbb{F}(\sigma)) = P_r(\mathbb{F}(\sigma'))$.

Indeed the mapping r induces a bisimulation,

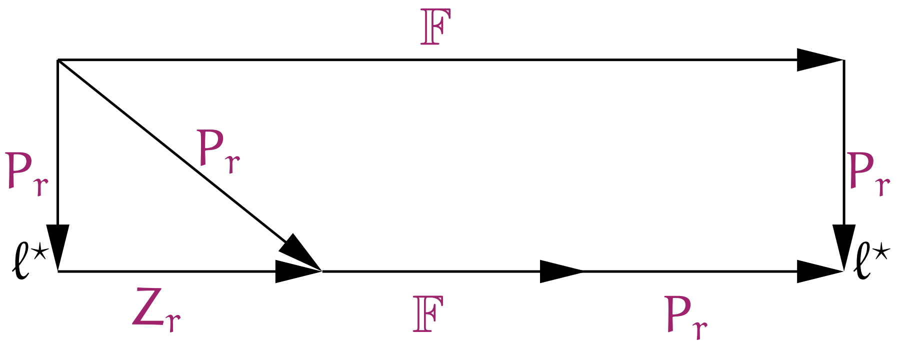
$\Longleftrightarrow$

for any $\sigma \in \mathcal{V} \rightarrow \mathbb{R}^{+}$, $P_r(\mathbb{F}(\sigma)) = P_r(\mathbb{F}(P_r(\sigma)))$.



Induced abstraction

Under these assumptions $(r(\mathcal{V}), P_r, P_r \circ \mathbb{F} \circ Z_r)$ is an abstraction of $(\mathcal{V}, \mathbb{F})$, as proved in the following commutative diagram:



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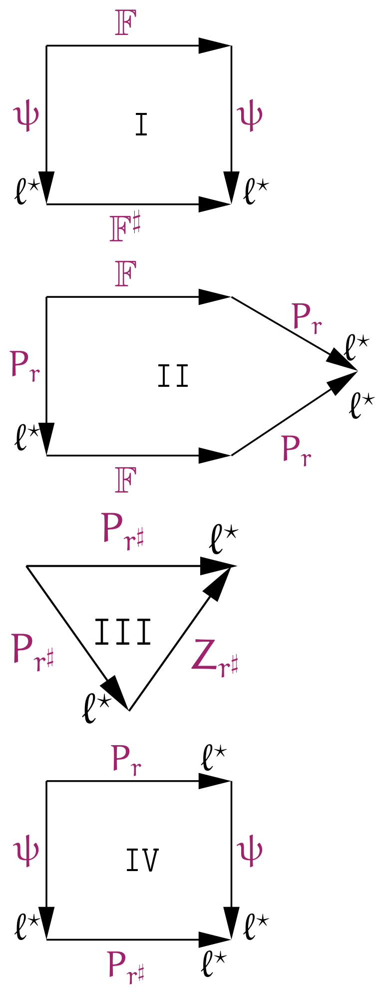
Abstract projection

We assume that we are given:

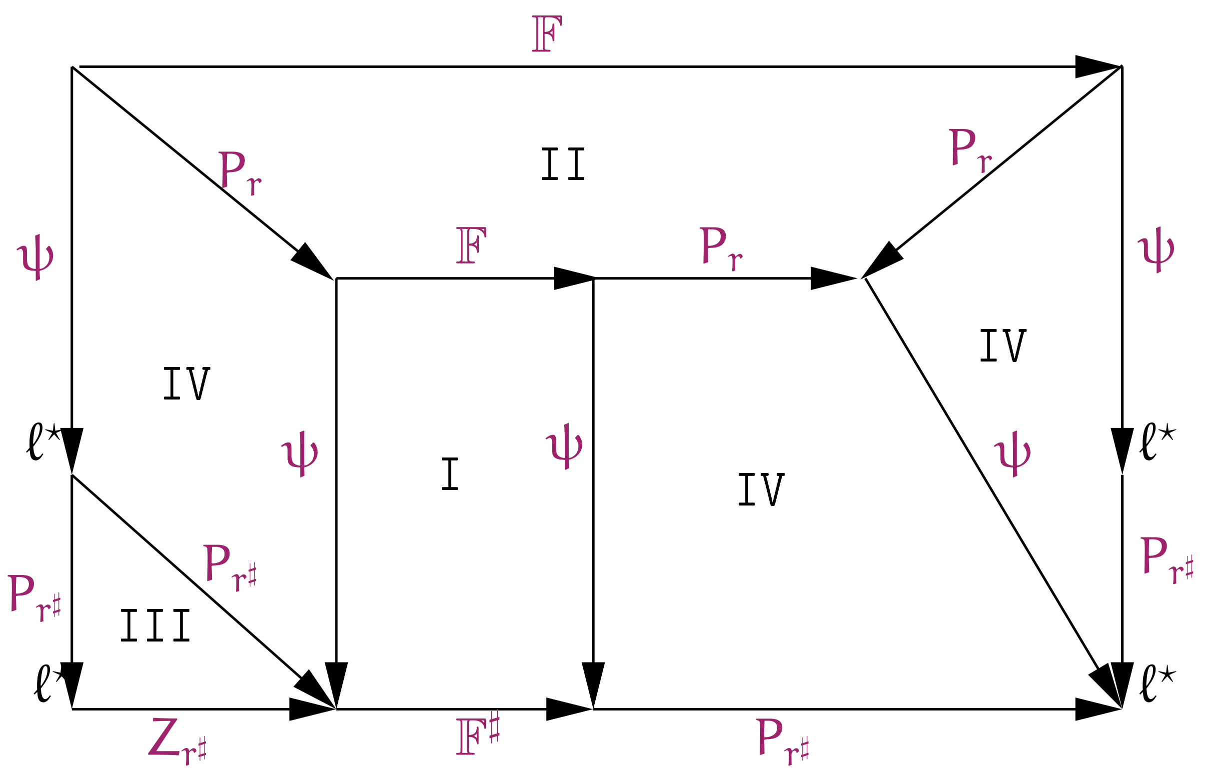
- a concrete system $(\mathcal{V}, \mathbb{F})$;
- an abstraction $(\mathcal{V}^\sharp, \psi, \mathbb{F}^\sharp)$ of $(\mathcal{V}, \mathbb{F})$ (I);
- an idempotent mapping r over $\mathcal{V}$ which induces a bisimulation (II);
- an idempotent mapping $r^\sharp$ over $\mathcal{V}^\sharp$ (III);

such that: $\psi \circ P_r = P_{r^\sharp} \circ \psi$ (IV).



Combination of abstractions

Under these assumptions, $(r^\sharp(\mathcal{V}^\sharp), P_{r^\sharp} \circ \psi, P_{r^\sharp} \circ \mathbb{F}^\sharp \circ Z_{r^\sharp})$ is an abstraction of $(\mathcal{V}, \mathbb{F})$, as proved in the following commutative diagram:



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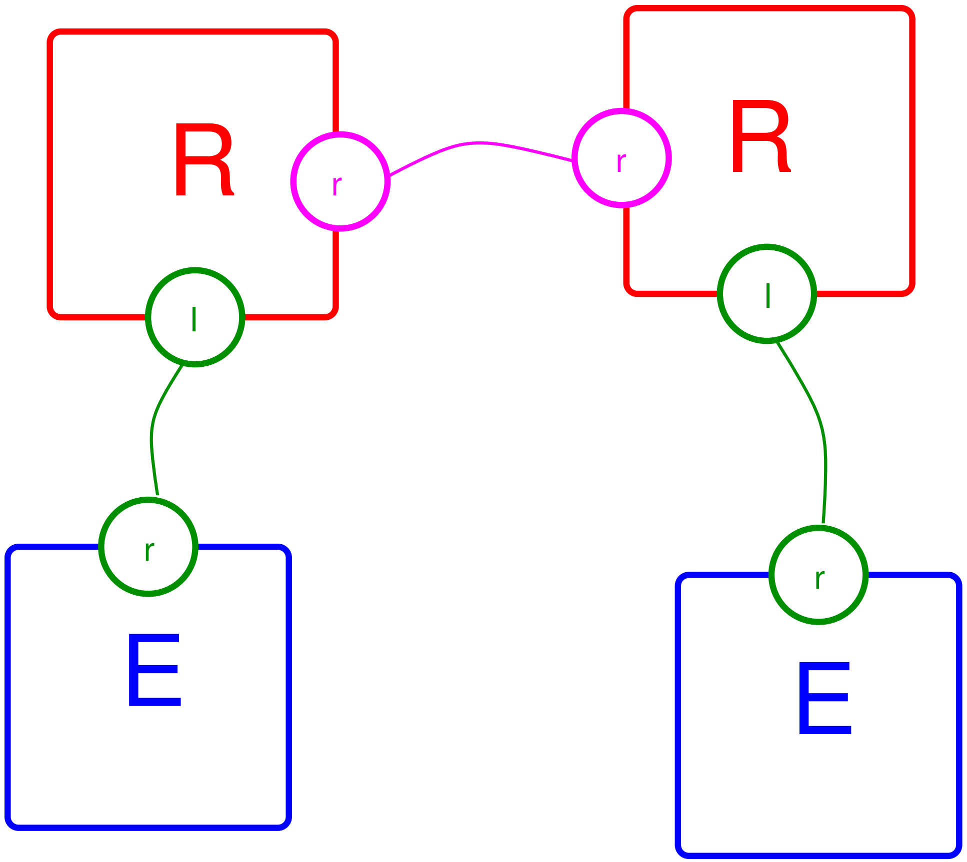
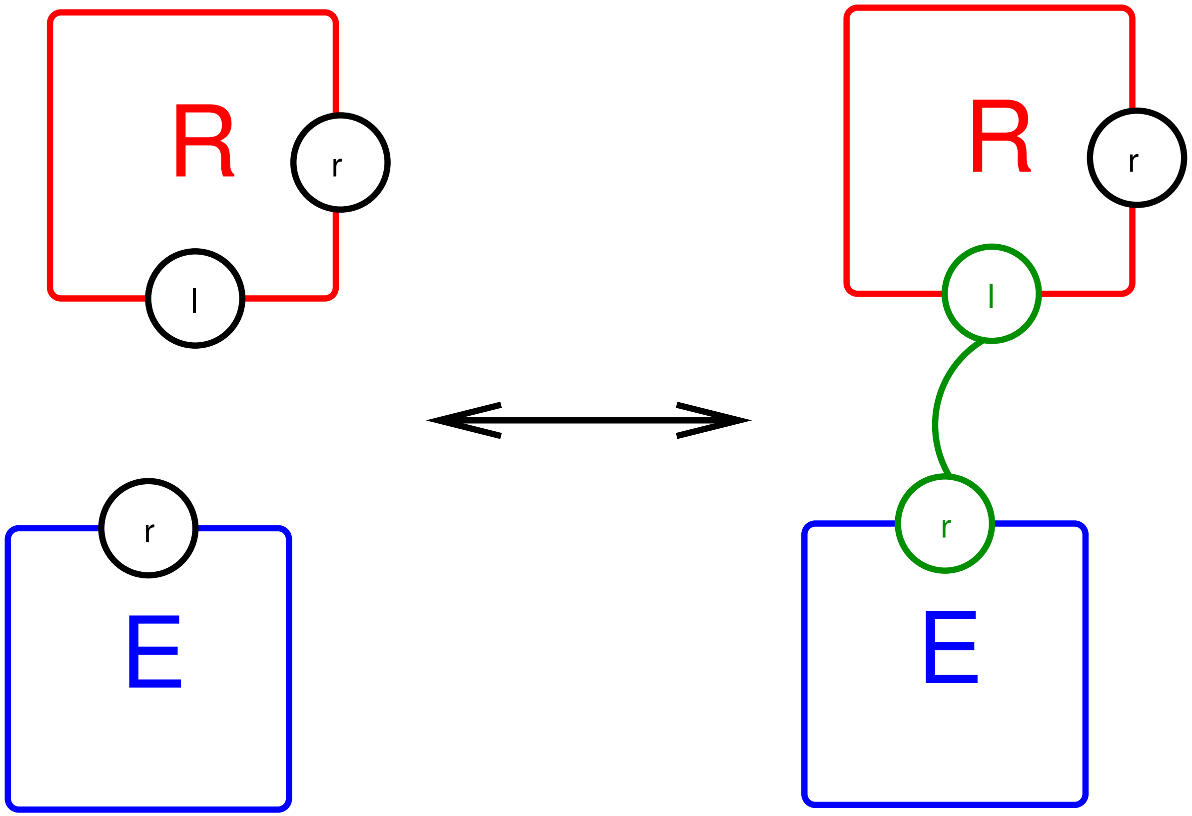
A species



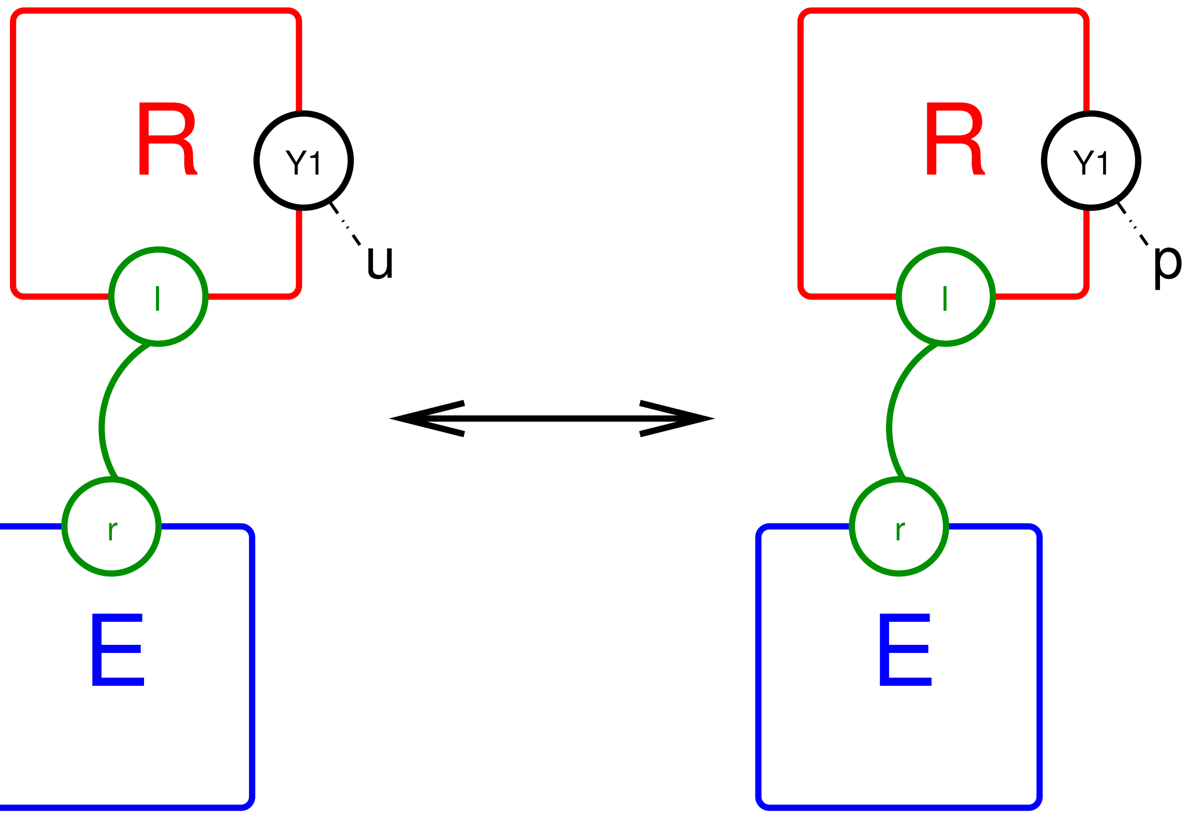
E(r!1), R(l!1,r!2), R(r!2,l!3), E(r!3)

A Unbinding/Binding Rule



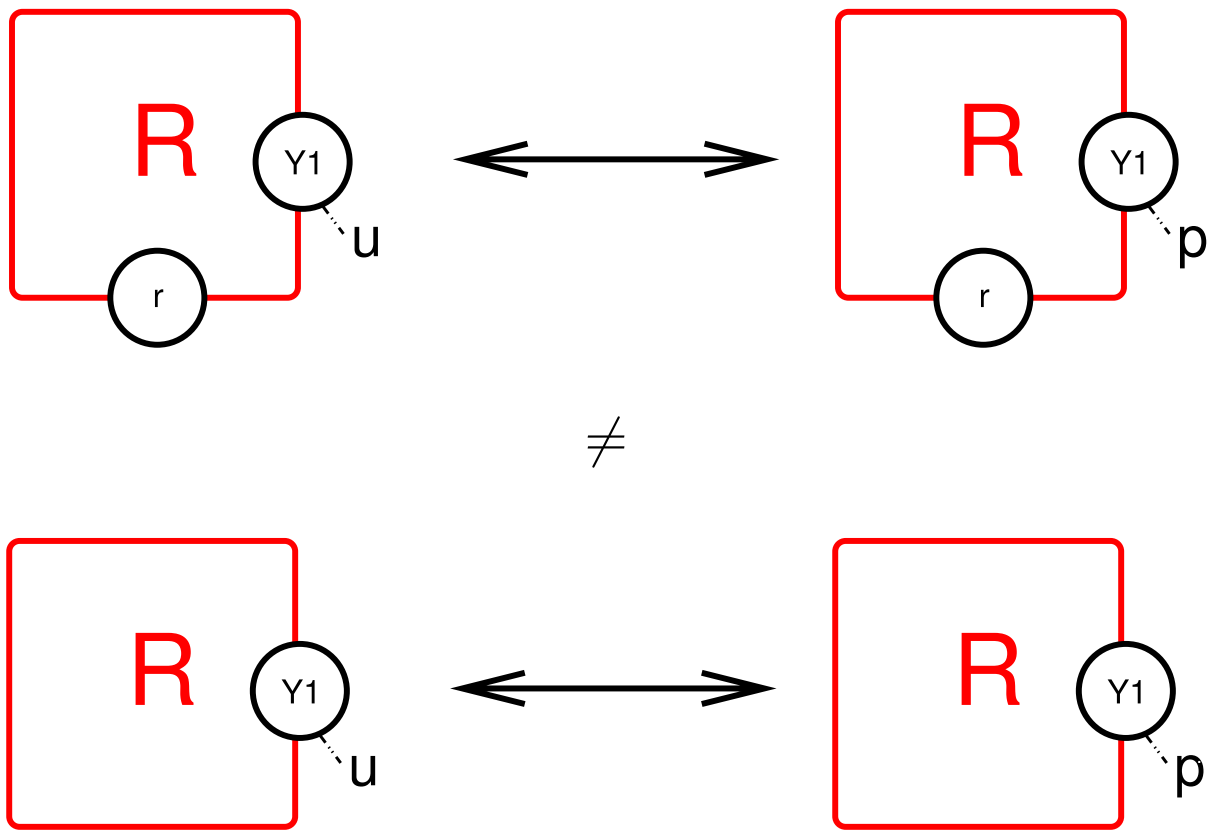
E(r), R(l,r) $\longleftrightarrow$ E(r!1), R(l!1,r)

Internal state

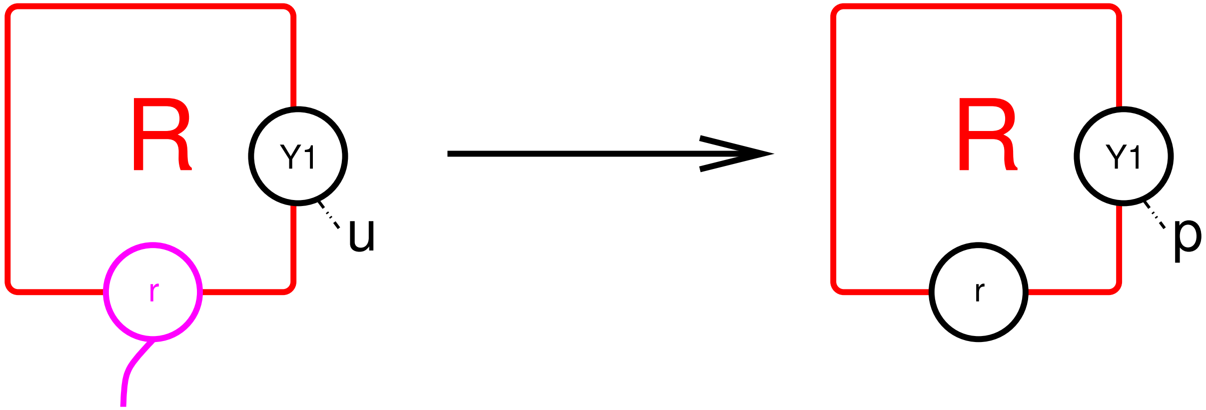


R(Y1∼u,l!1), E(r!1) ⟷ R(Y1∼p,l!1), E(r!1)

Don’t care, Don’t write

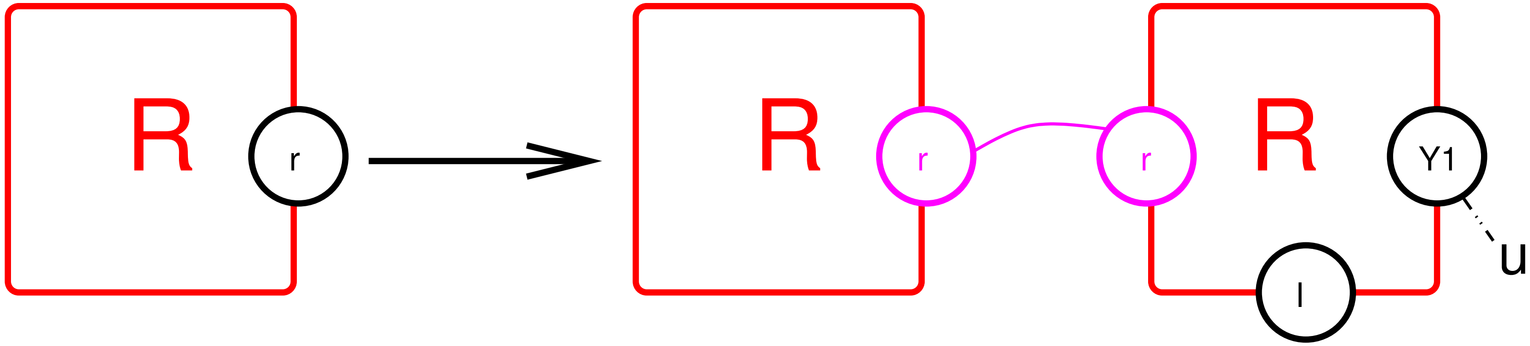


A contextual rule

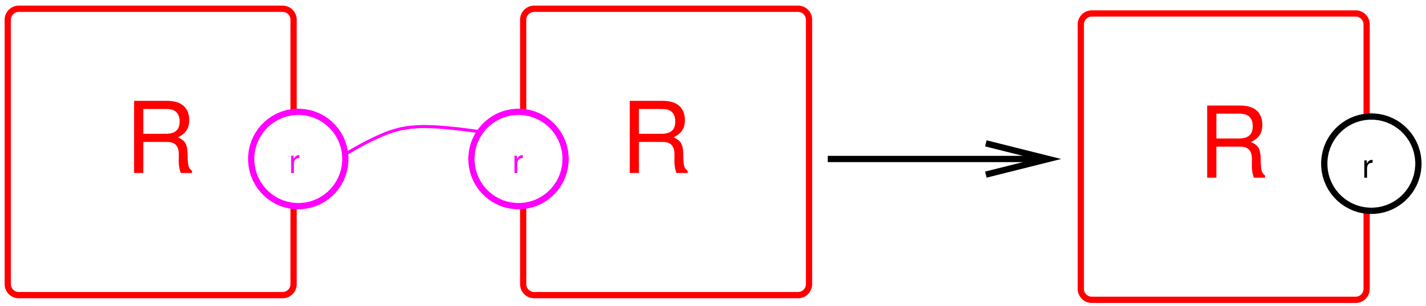


R(Y1~u,r!_) $\longrightarrow$ R(Y1~p,r)

Creation/Suppression



R(r) $\longrightarrow$ R(r!1), R(r!1,l,Y1)



R(r!1), R(r!1) $\longrightarrow$ R(r)

Overview

Differential system

Each rule *rule*: *lhs* $\rightarrow$ *rhs* is associated with a rate constant k.

Such a rule is seen as a symbolic representation of a set of chemical reactions:

$$r_1, \ldots, r_m \rightarrow p_1, \ldots, p_n \quad k.$$

For each such reaction, we get the following contribution:

$$\frac{d[r_i]}{dt} \stackrel{-}{=} \frac{k \cdot \prod [r_i]}{\mathrm{SYM}(lhs)} \qquad \text{and} \qquad \frac{d[p_i]}{dt} \stackrel{+}{=} \frac{k \cdot \prod [r_i]}{\mathrm{SYM}(lhs)}.$$

where $\mathrm{SYM}(E)$ is the number of automorphisms in E.

Overview

Abstract domain

We are looking for suitable pair $(\mathcal{V}^\sharp, \psi)$ (such that $\mathbb{F}^\sharp$ exists).

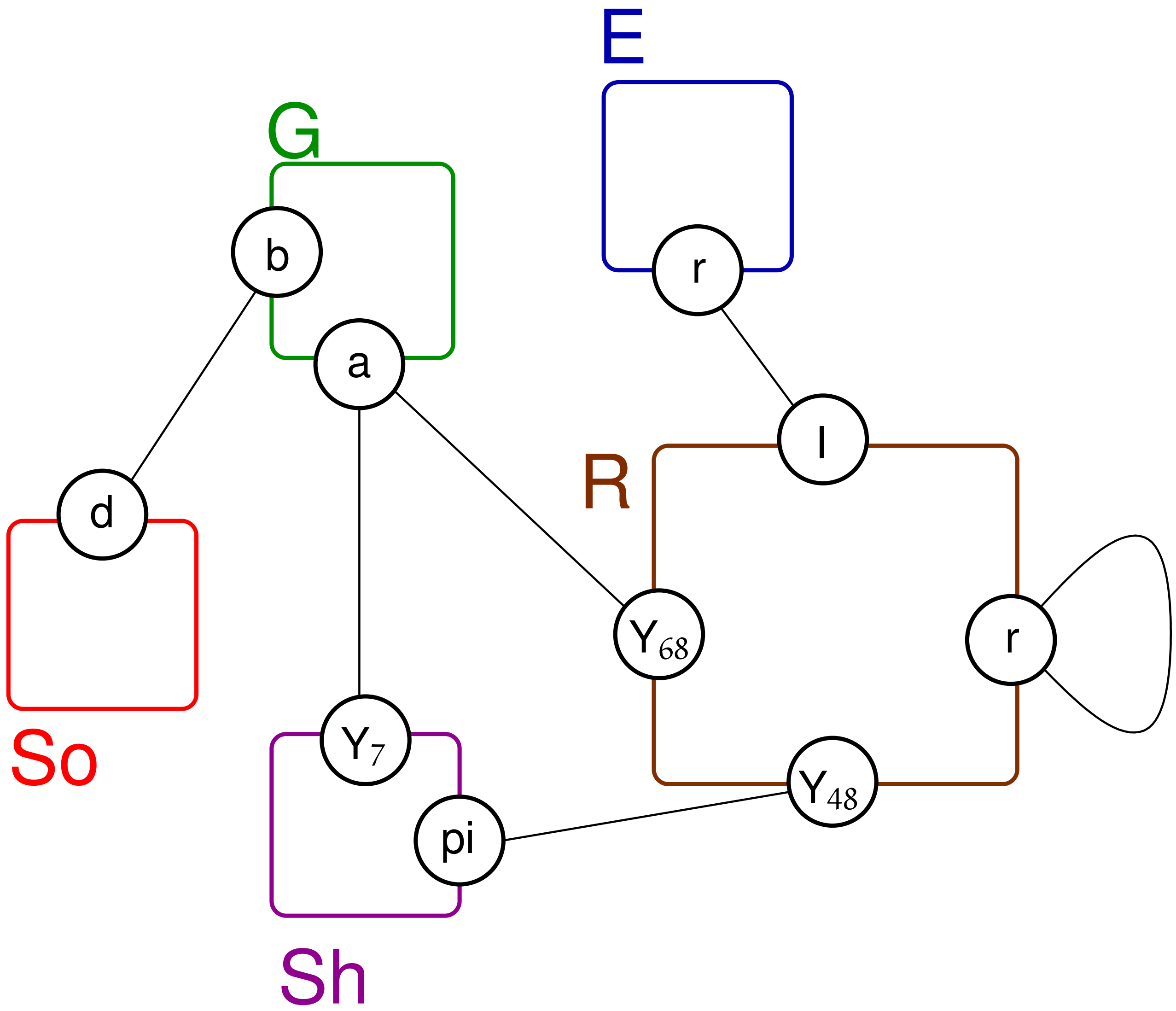
The set of linear variable replacements is too big to be explored.

We introduce a specific shape on $(\mathcal{V}^\sharp, \psi)$ so as:

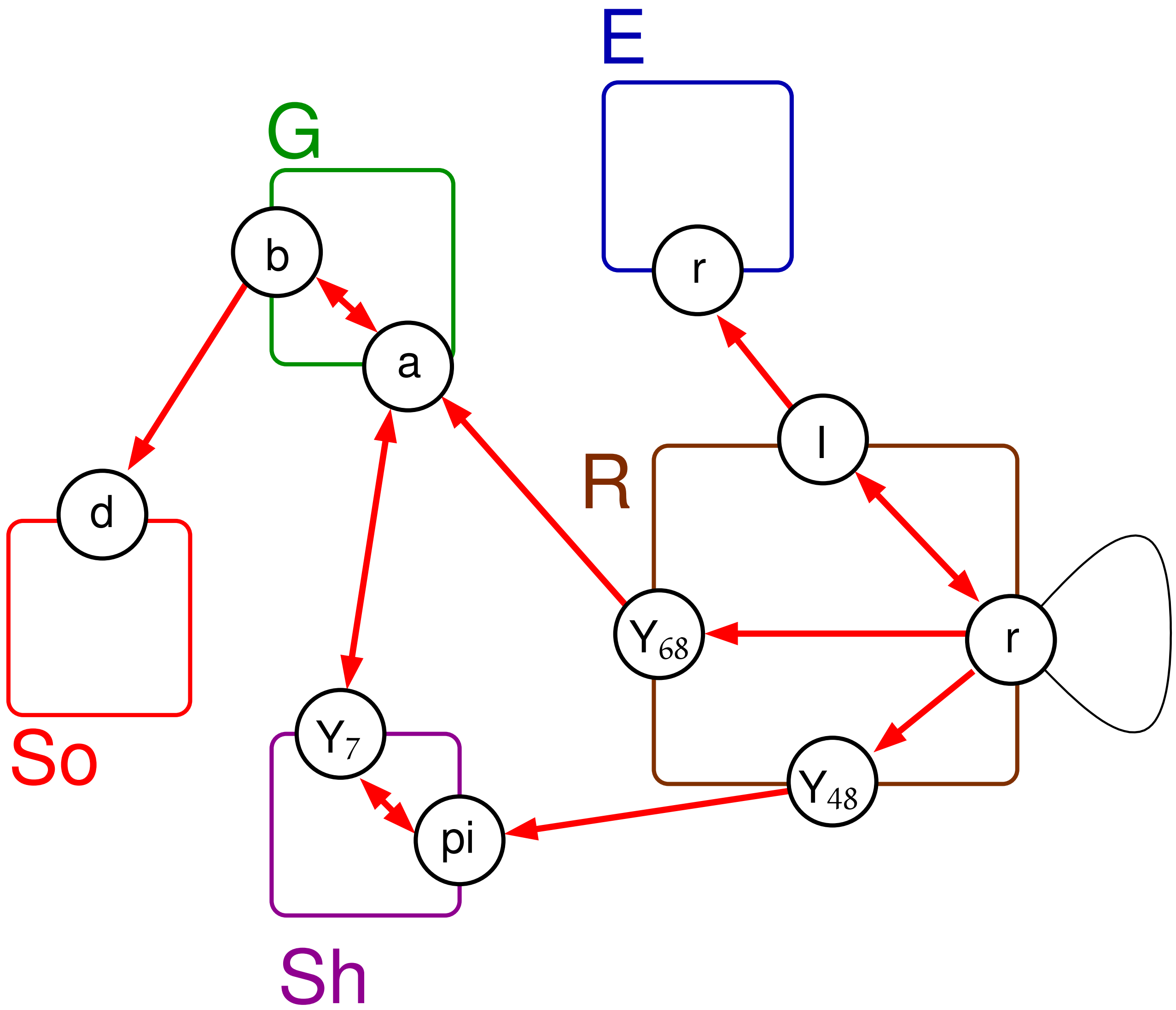
- restrict the exploration;
- drive the intuition (by using the flow of information);
- having efficient way to find suitable abstractions $(\mathcal{V}^\sharp, \psi)$ and to compute $\mathbb{F}^\sharp$.

Our choice might be not optimal, but we can live with that.

Contact map



Annotated contact map



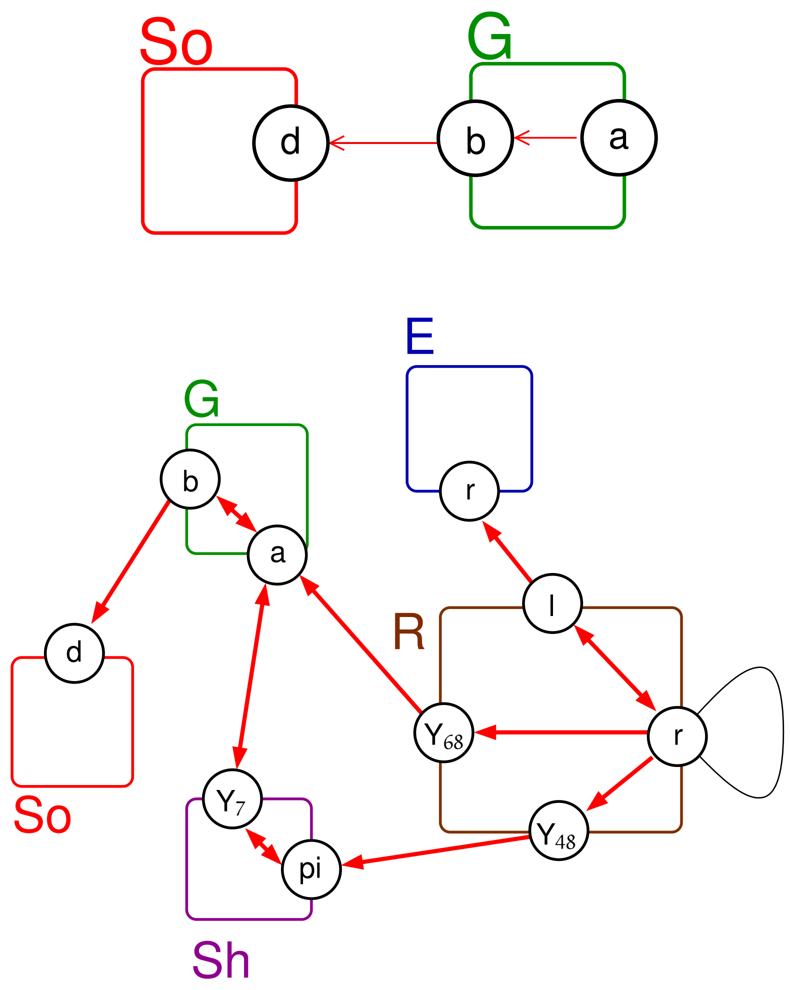
Fragments and prefragments

A prefragment is a connected site graph for which there exists a binary relations $\rightarrow$ between sites such that:

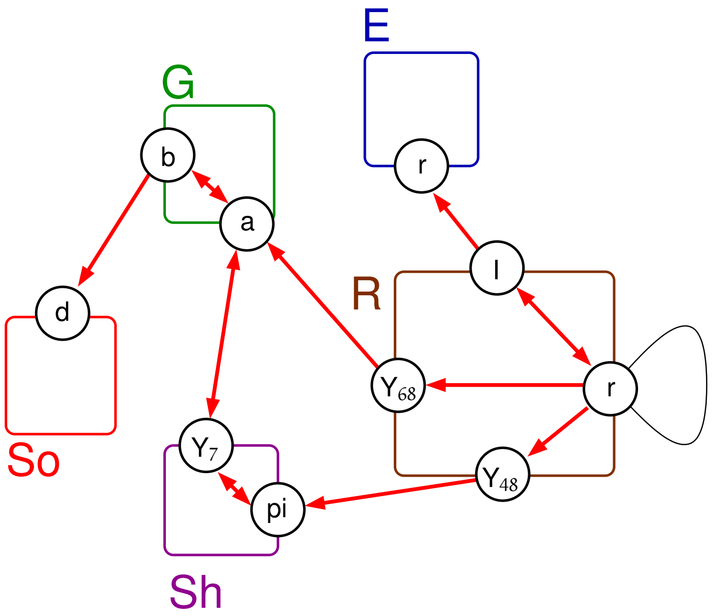
- Compatibility: any edge $\rightarrow$ matches with an edge in the annotated contact map.
- Directed preorder: for any pair of sites x and y there is a site z such that: $x {\rightarrow}^{\star} z$ and $y {\rightarrow}^{\star} z$.

A fragment is a prefragment F such that:

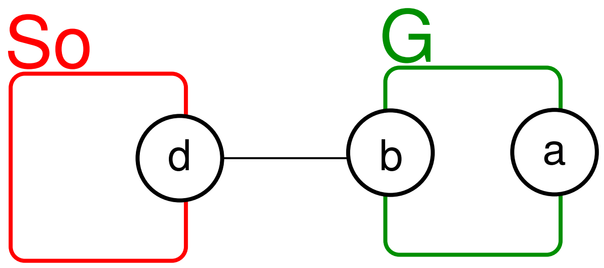
- Parsimoniousness: for any prefragment F' such that F embeds in F', F' also embeds into F.

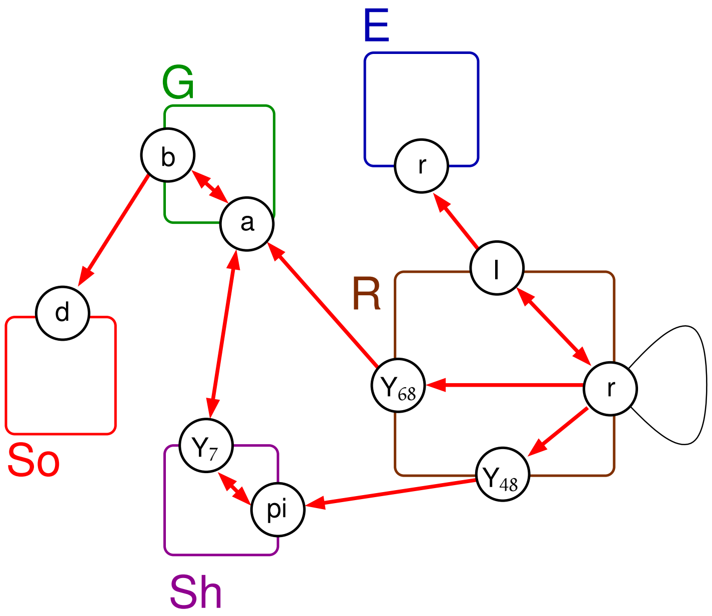


Are they fragments ?

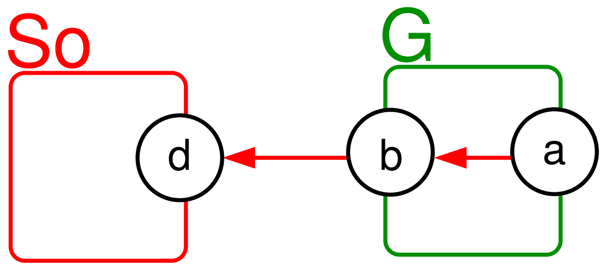


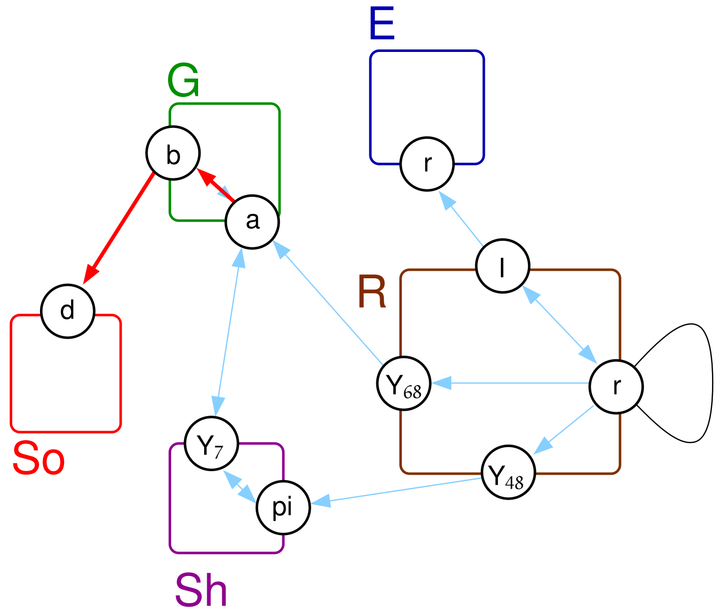
Are they fragments ?





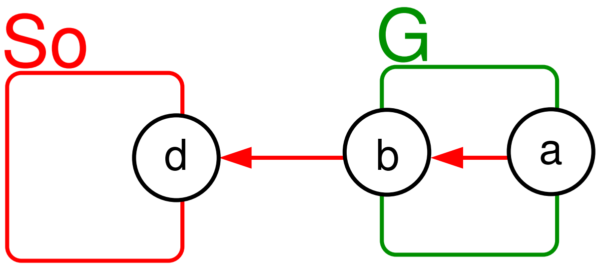
Are they fragments ?

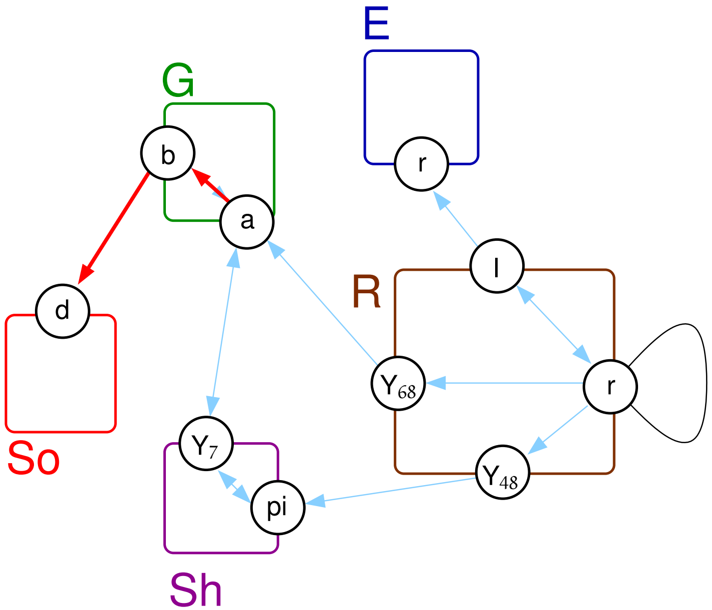




Thus, it is a prefragment.

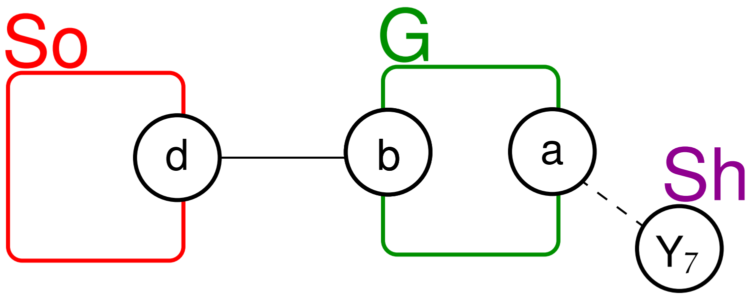
Are they fragments ?

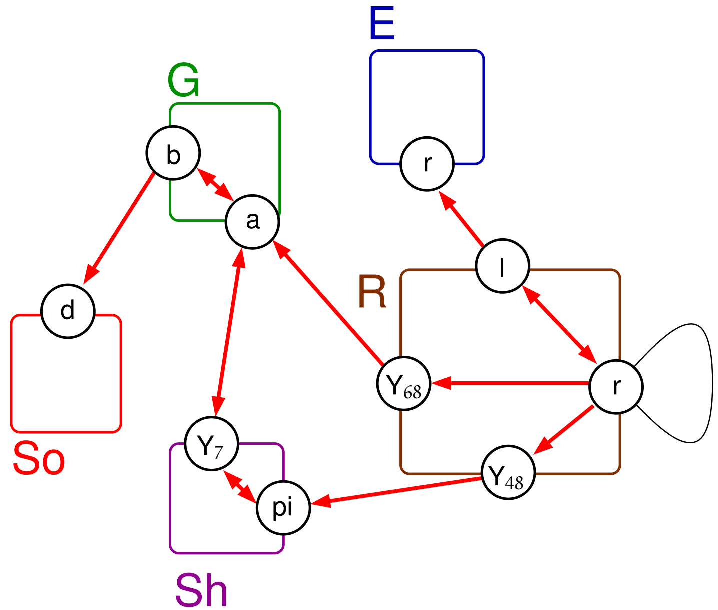




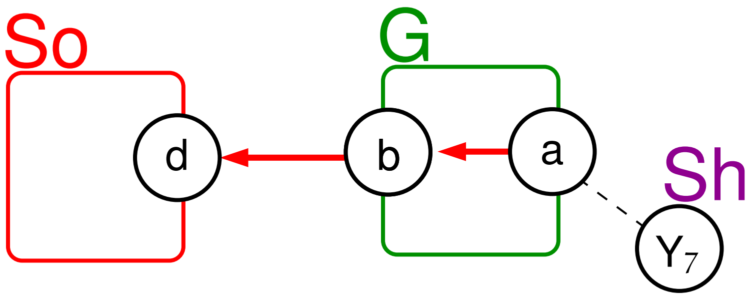
It is maximally specified.
Thus it is a fragment.

Are they fragments ?

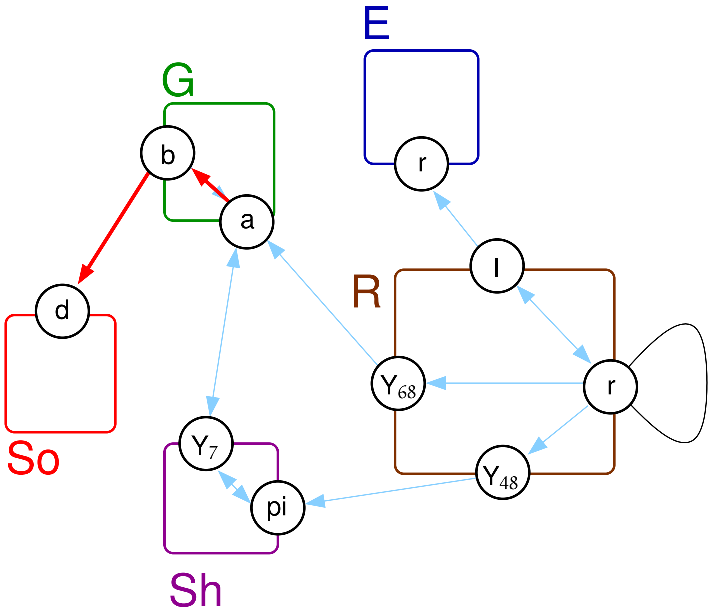




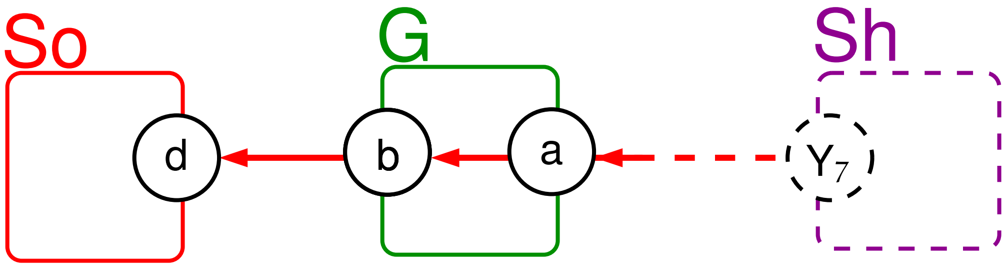
Are they fragments ?



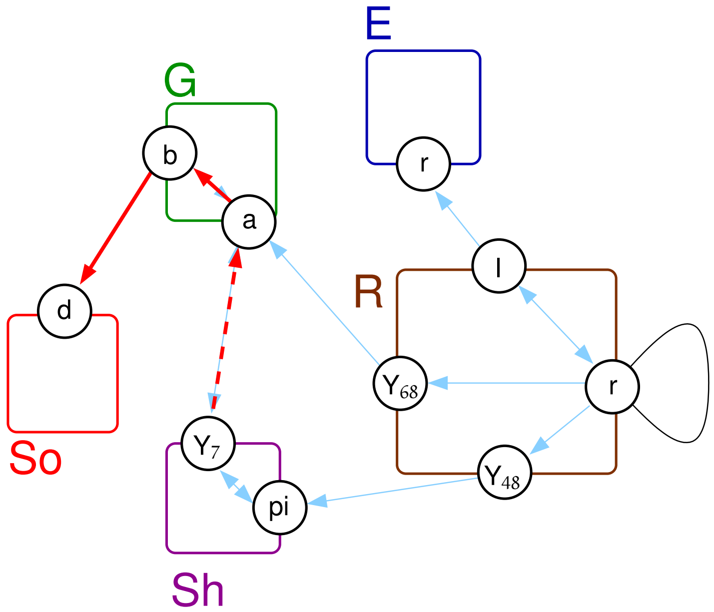
Thus, it is a prefragment.



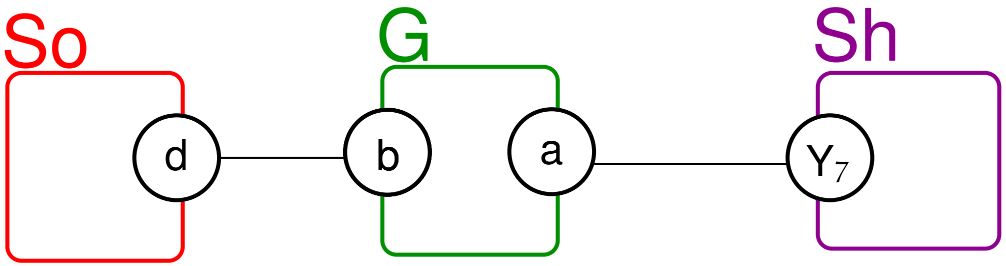
Are they fragments ?

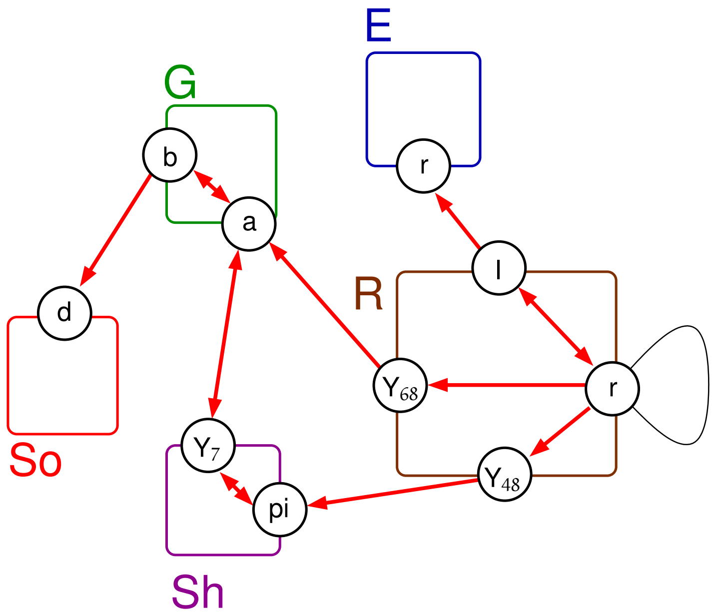


It can be refined into another prefragment.
Thus, it is not a fragment.

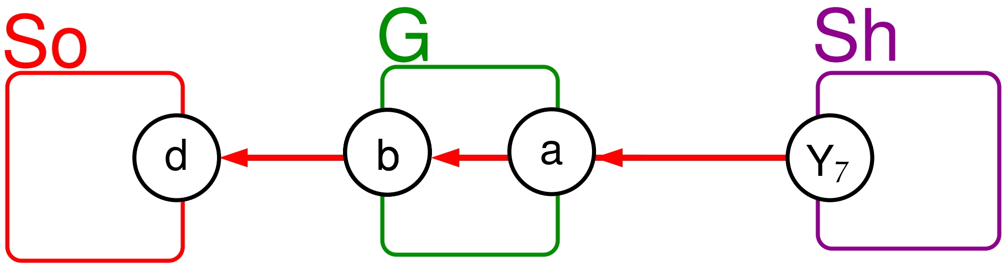


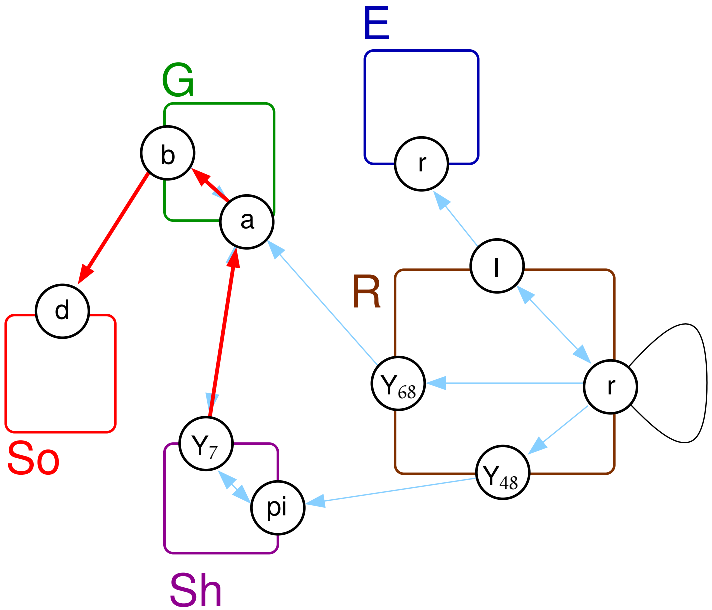
Are they fragments ?





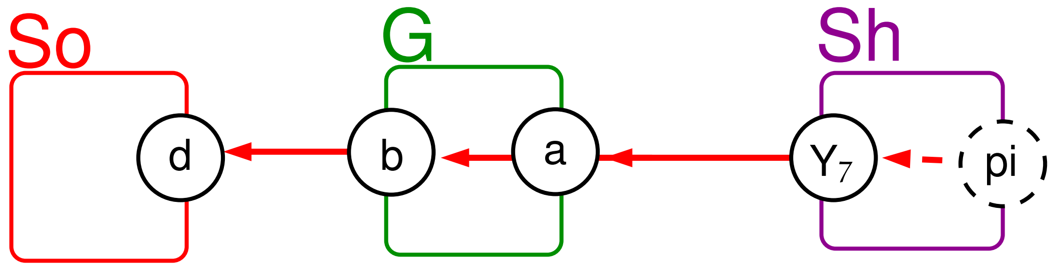
Are they fragments ?

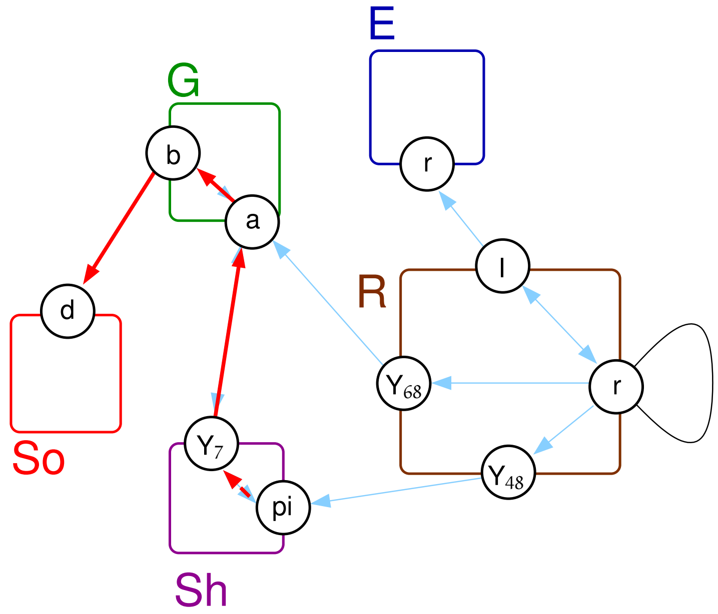




Thus, it is a prefragment.

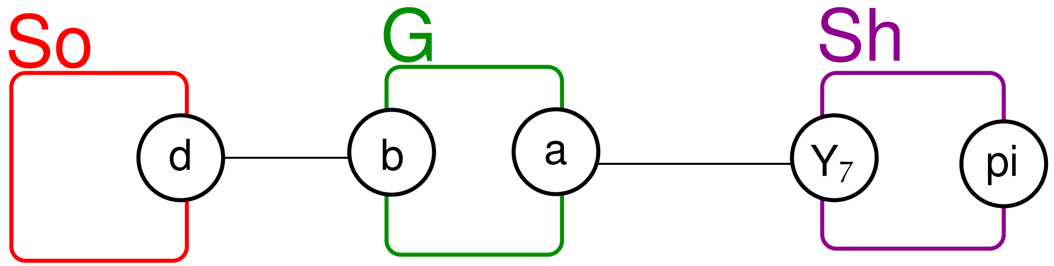
Are they fragments ?

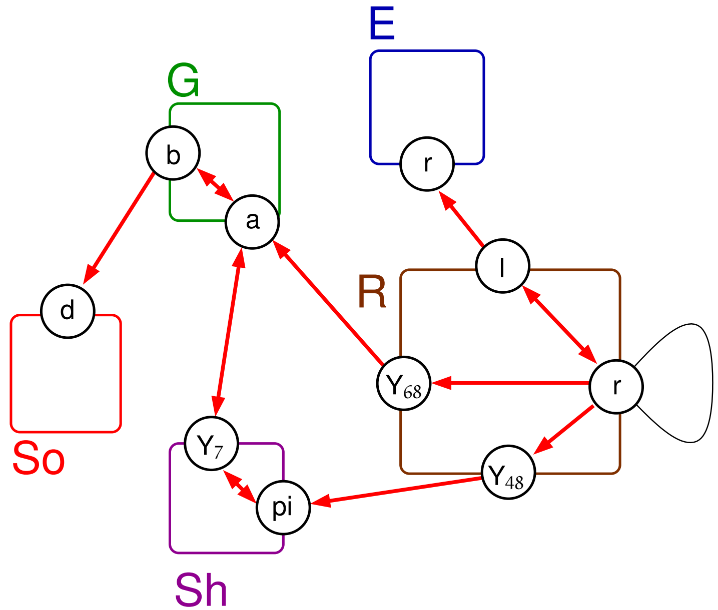




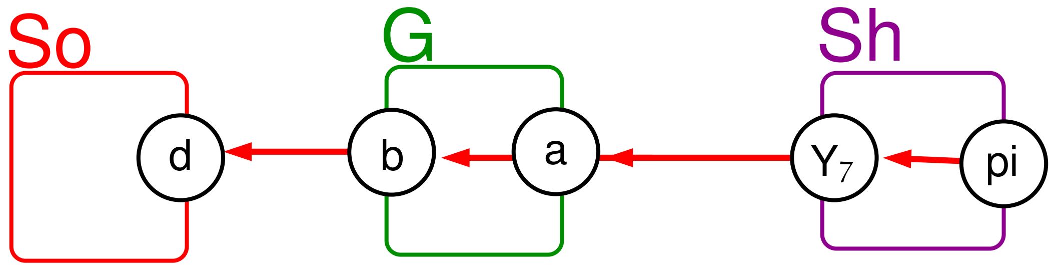
It can be refined into another prefragment.
Thus, it is not a fragment.

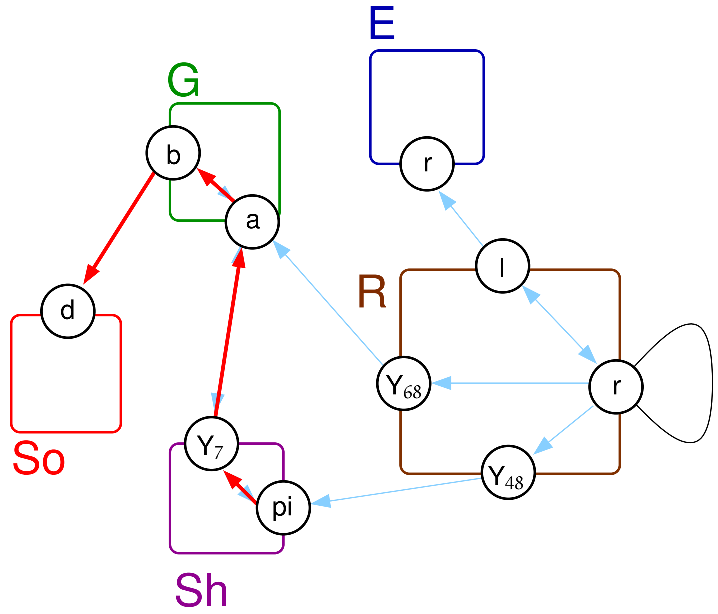
Are they fragments ?





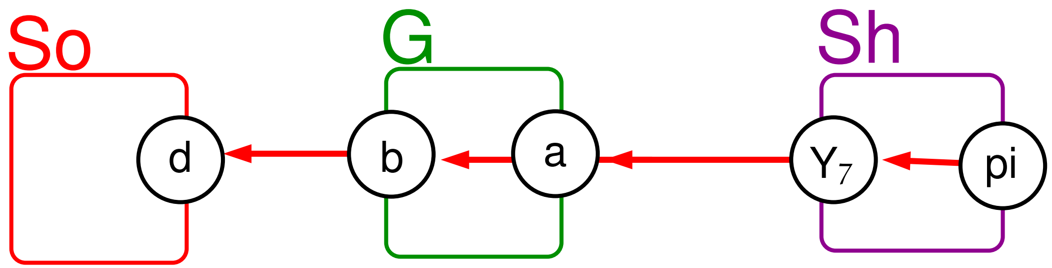
Are they fragments ?



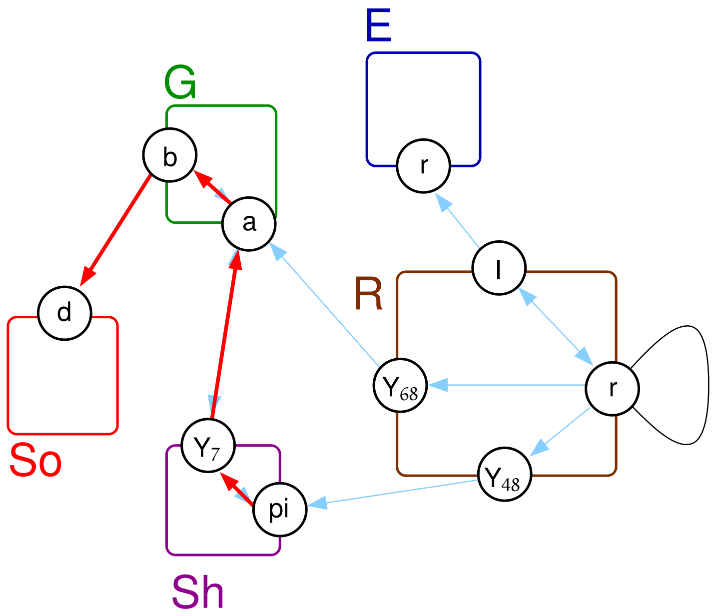


Thus, it is a prefragment.

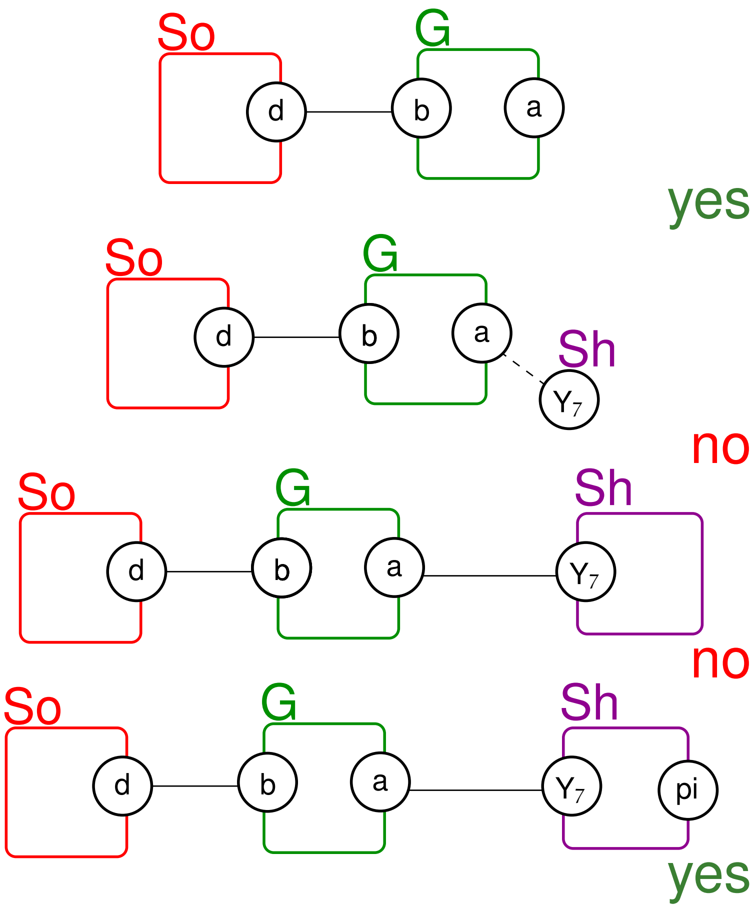
Are they fragments ?

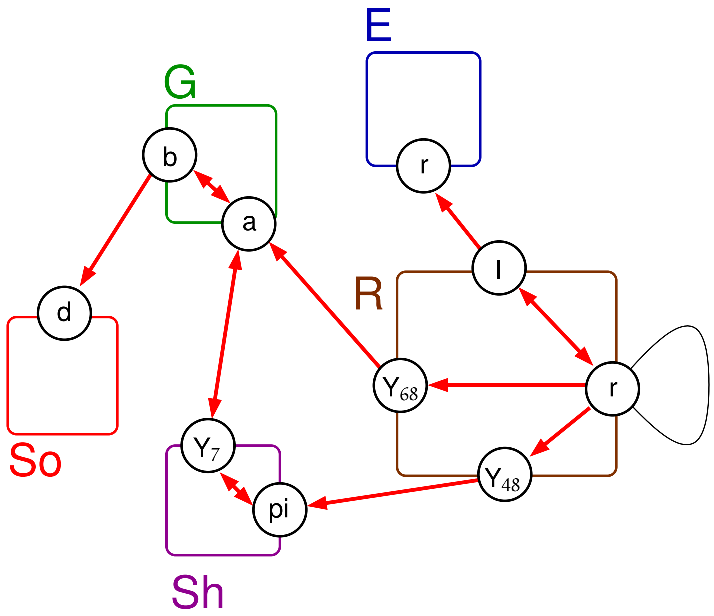


It is maximally specified.
Thus it is a fragment.

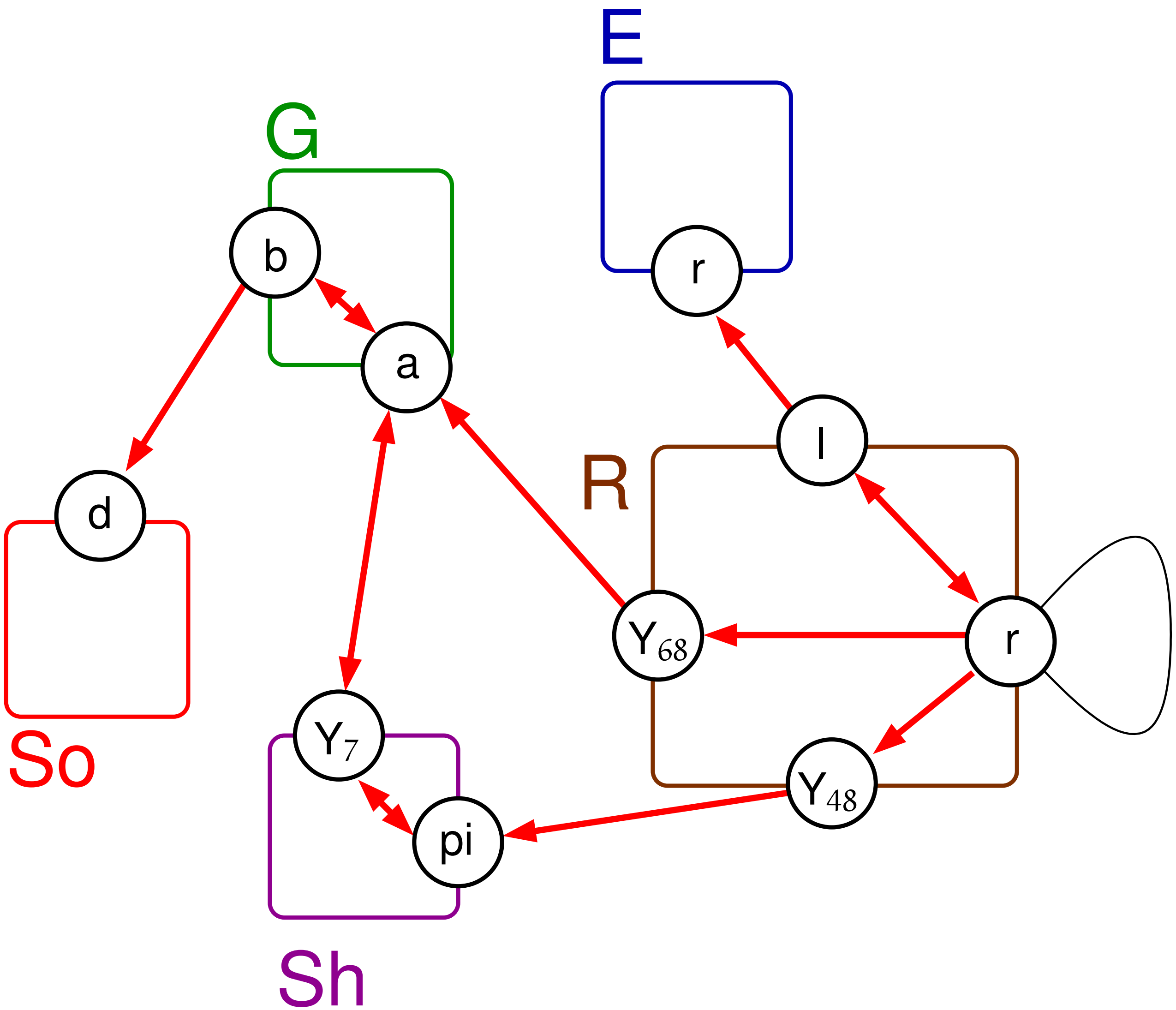


Are they fragments ?

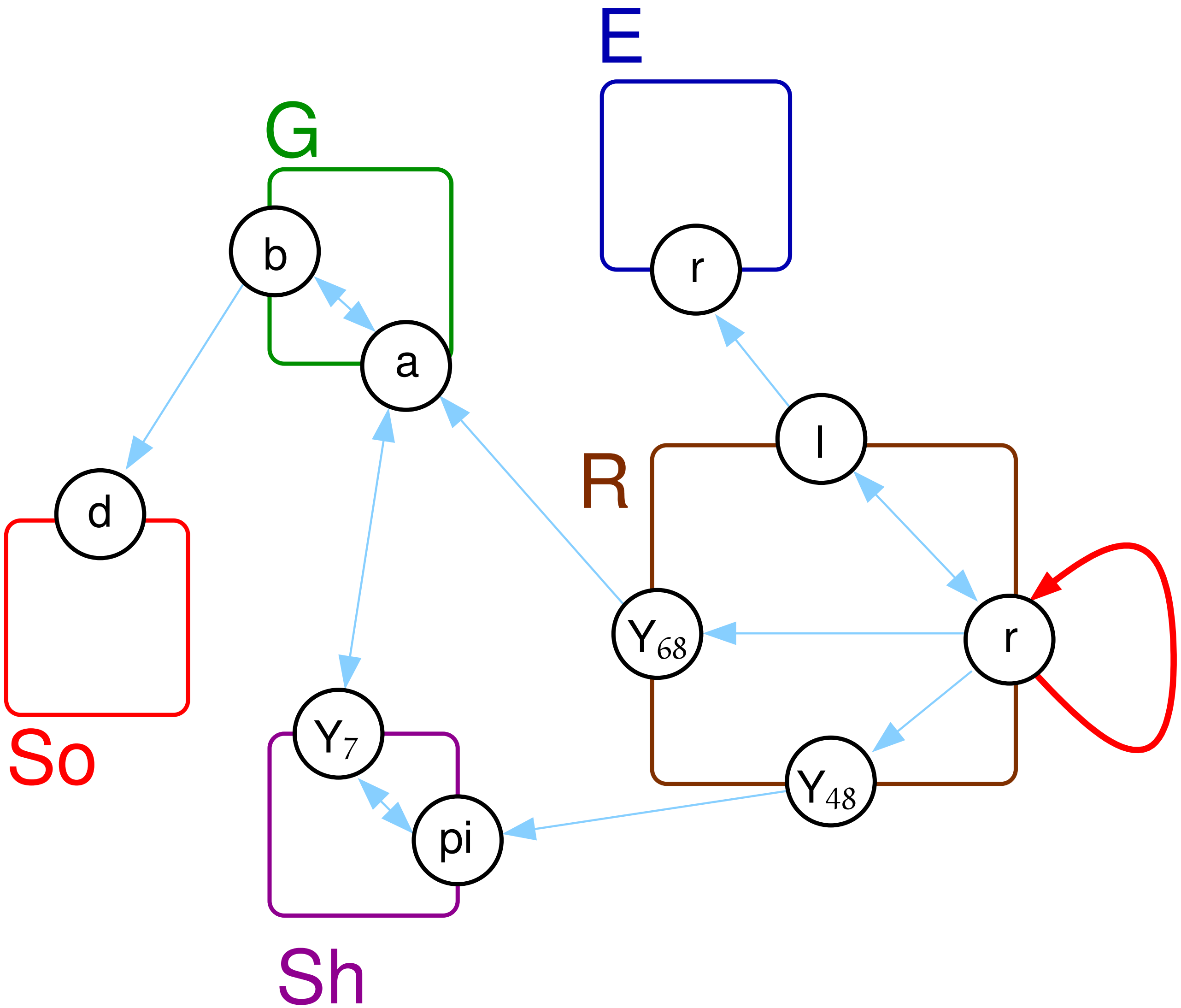




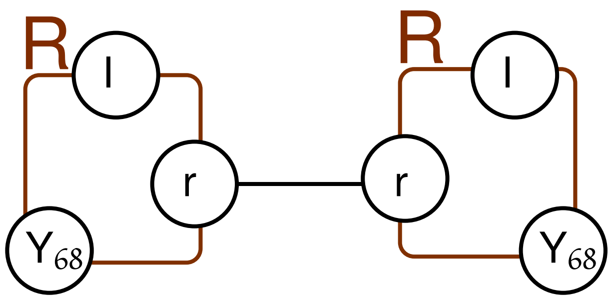
Annotated contact map

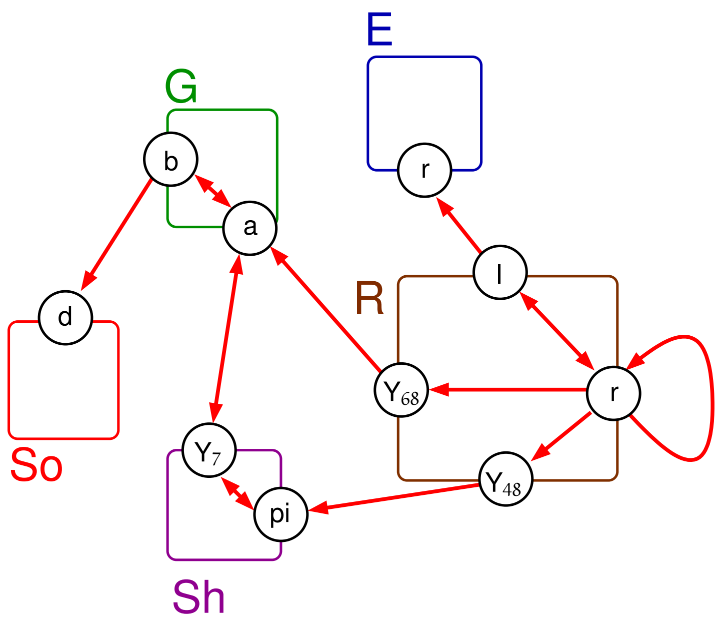


What if we were adding this flow ?

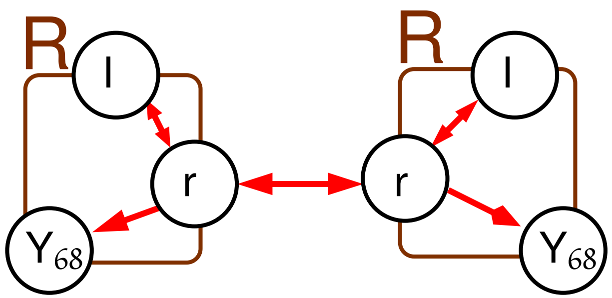


Are they fragments ?
stage 2



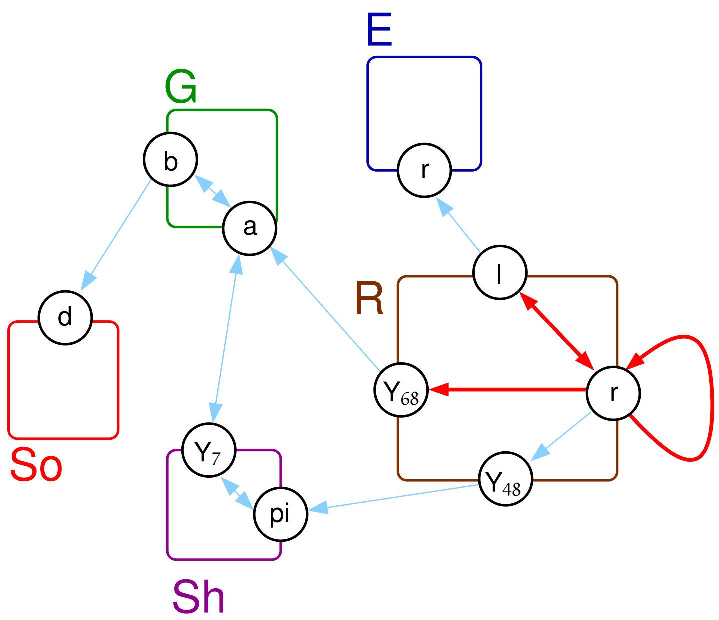


Are they fragments ?
stage 2

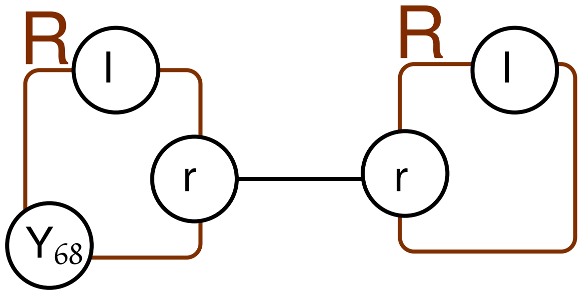


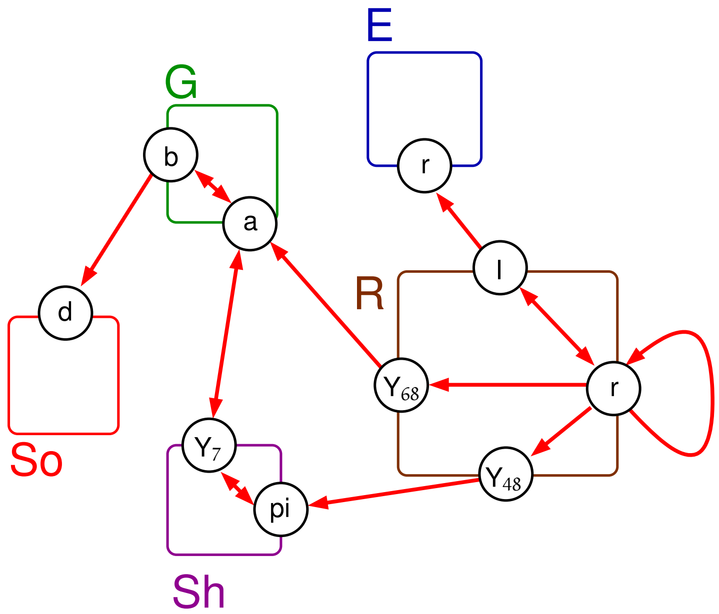
There is no way to make a path from the first Y_{68} and the second one or to make a path from the second one to the first one.

Thus it is not even a prefragment.

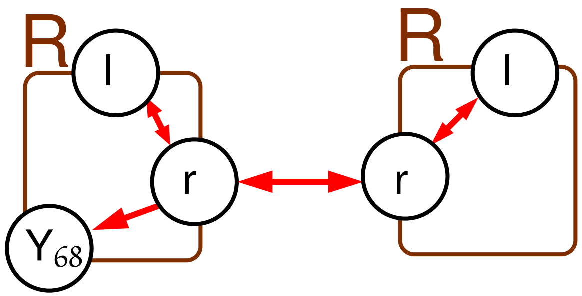


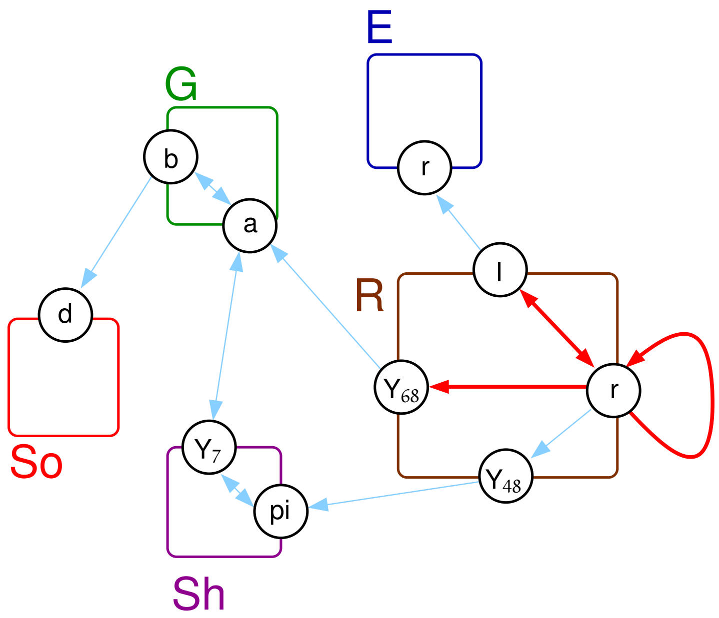
Are they fragments ?
stage 2





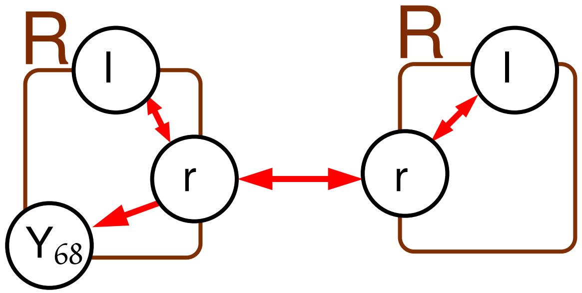
Are they fragments ?
stage 2

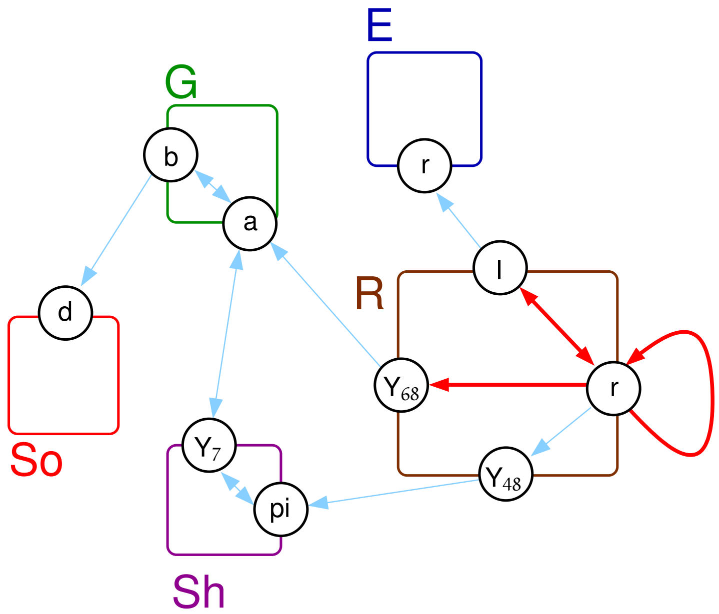




Thus it is a prefragment.

Are they fragments ?
stage 2





There is no way to refine it, while preserving the directedness.

Thus it is a fragment.

Basic properties

Property 1 (prefragment) The concentration of any prefragment can be expressed as a linear combination of the concentration of some fragments.

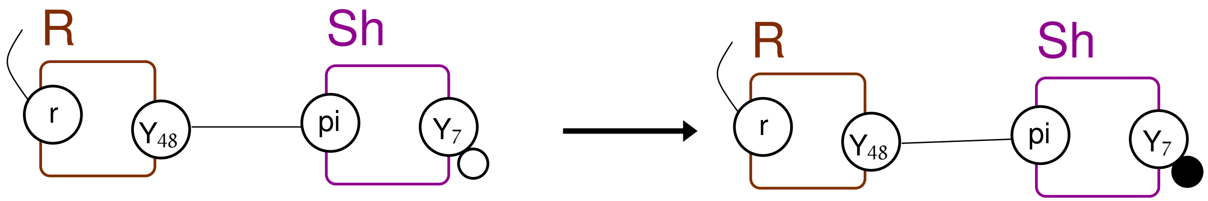
We consider two norms $||\cdot||$ on $\mathcal{V} \longrightarrow \mathbb{R}^+$ and $||\cdot||^\sharp$ on $\mathcal{V}^\sharp \longrightarrow \mathbb{R}^+$.

Property 2 (non-degenerescence) Given a sequence of valuations $(x_n)_{n\in\mathbb{N}} \in (\mathcal{V} \rightarrow \mathbb{R}^+)^{\mathbb{N}}$ such that $||x_n||$ diverges toward $+\infty$, then $||\phi(x_n)||^\sharp$ diverges toward $+\infty$ as well.

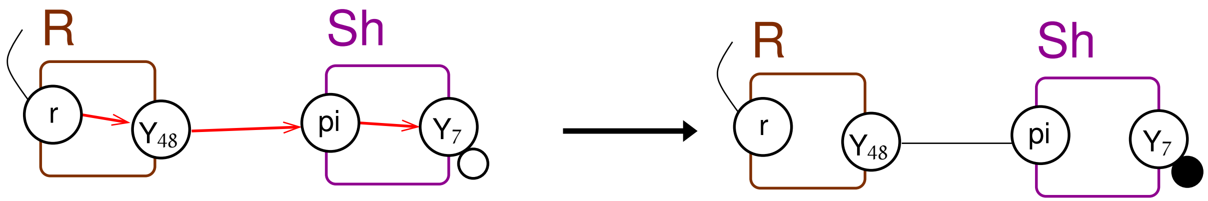
Which other properties do we need so that the function $\mathbb{F}^\sharp$ can be defined ?

Overview

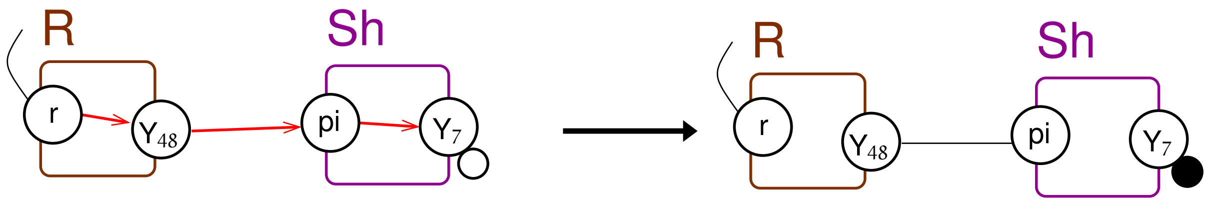
Flow of information

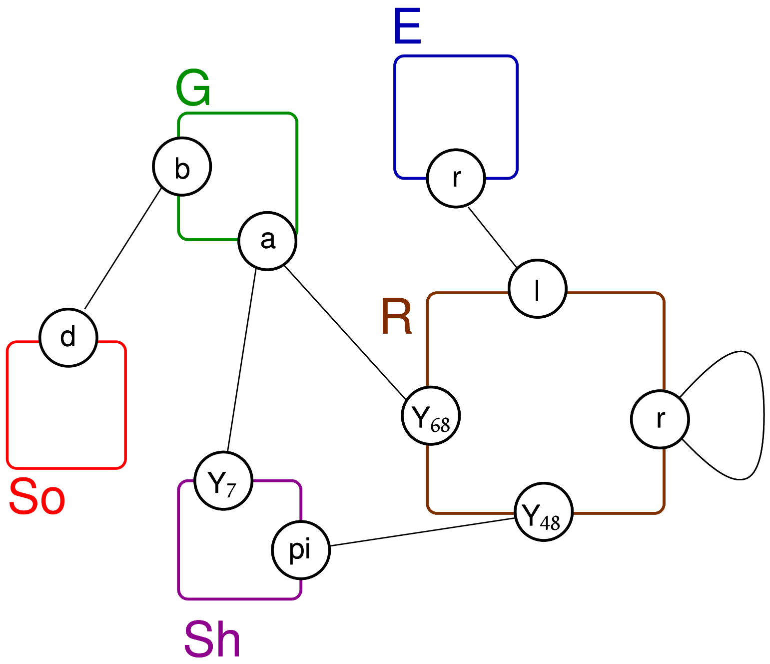


Flow of information

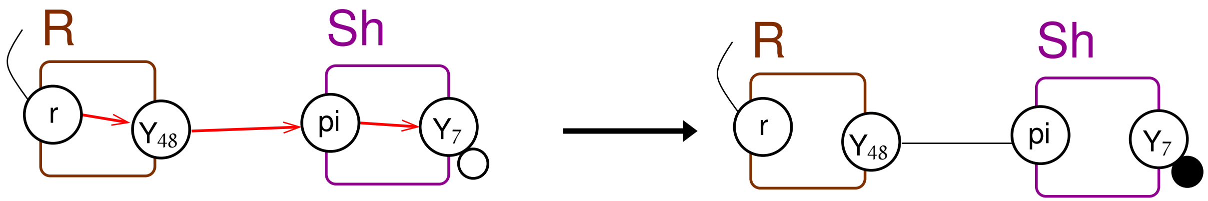


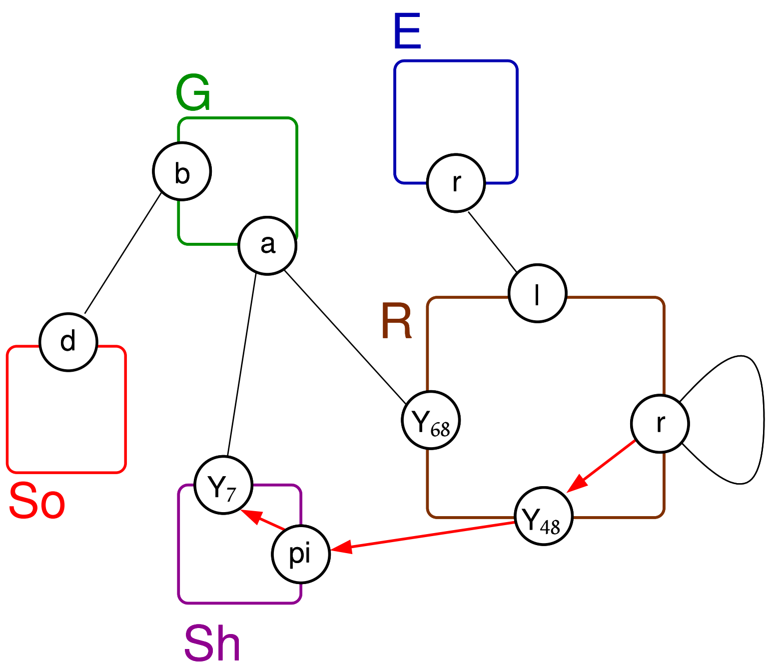
Flow of information





Flow of information

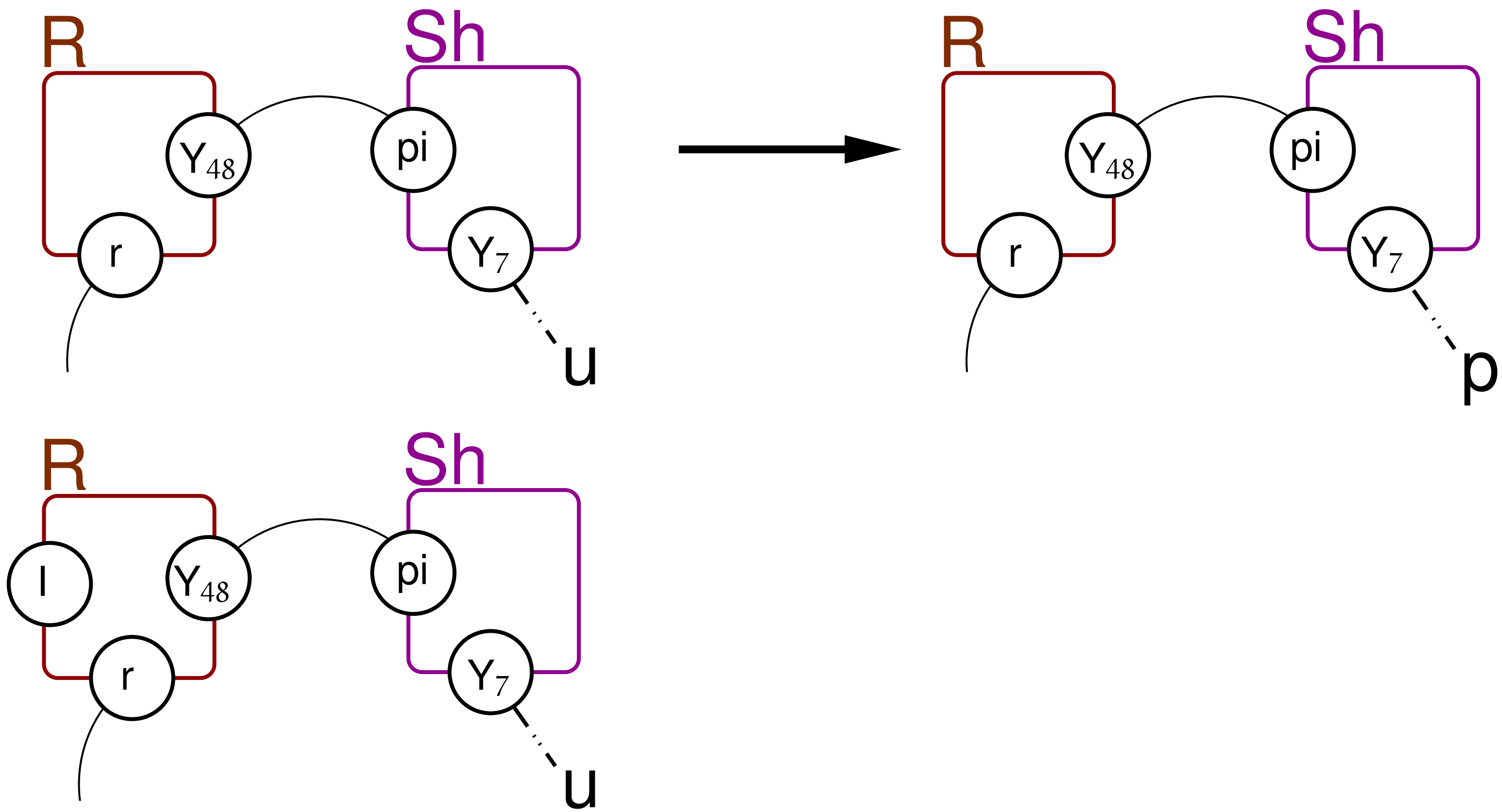




We reflect, in the annotated contact map, each path that stems from a site that is tested to a site that is modified.

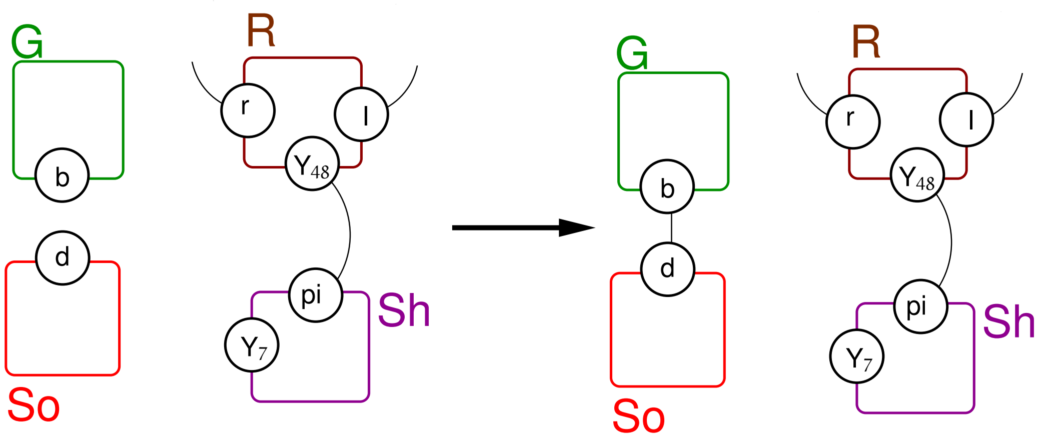
Overview

Fragments consumption
Proper intersection



Whenever a fragment intersects a connected component of a lhs on a modified site, then the connected component must be embedded in the fragment!

Fragment consumption



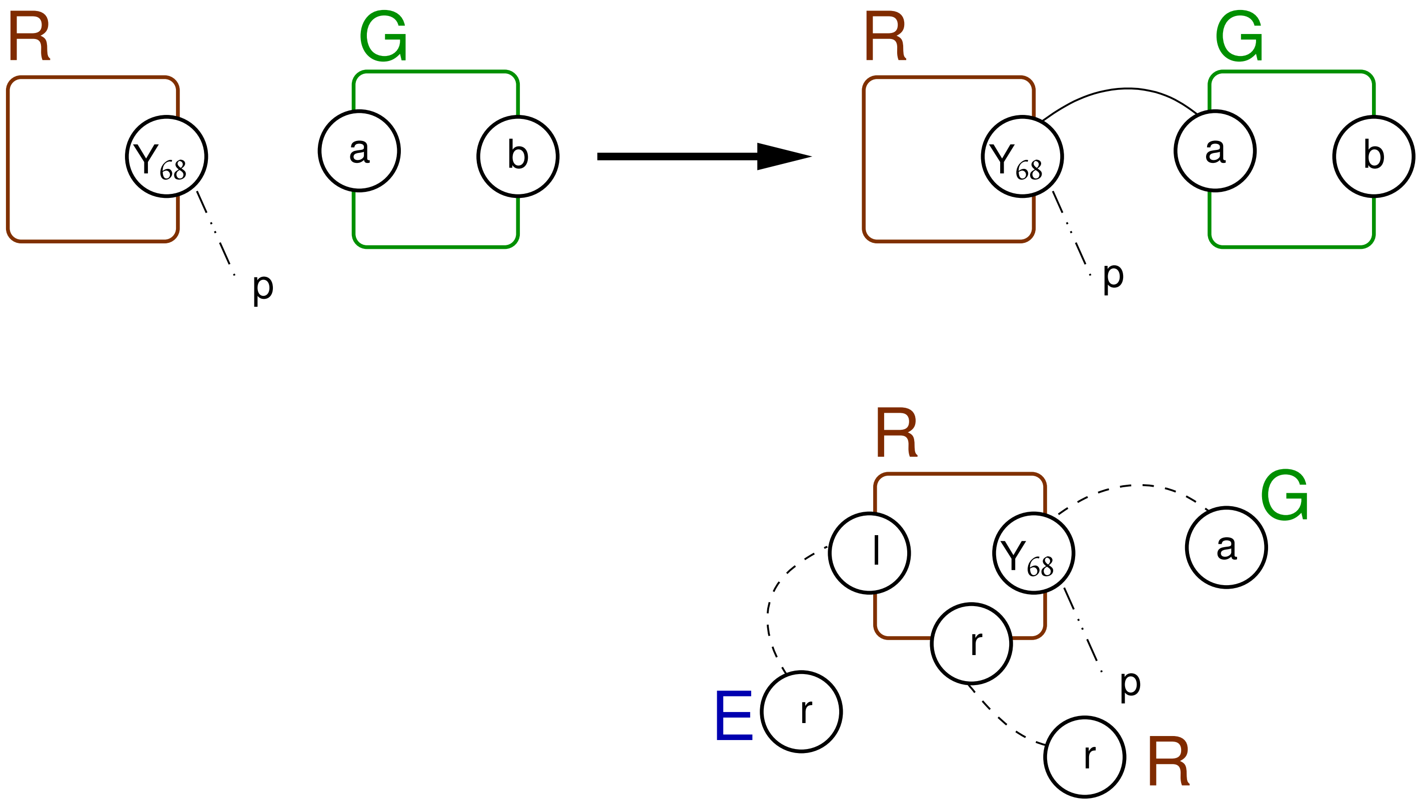
For any rule:

$$\textit{rule}: C_1, \ldots, C_n \to \textit{rhs} \quad k$$

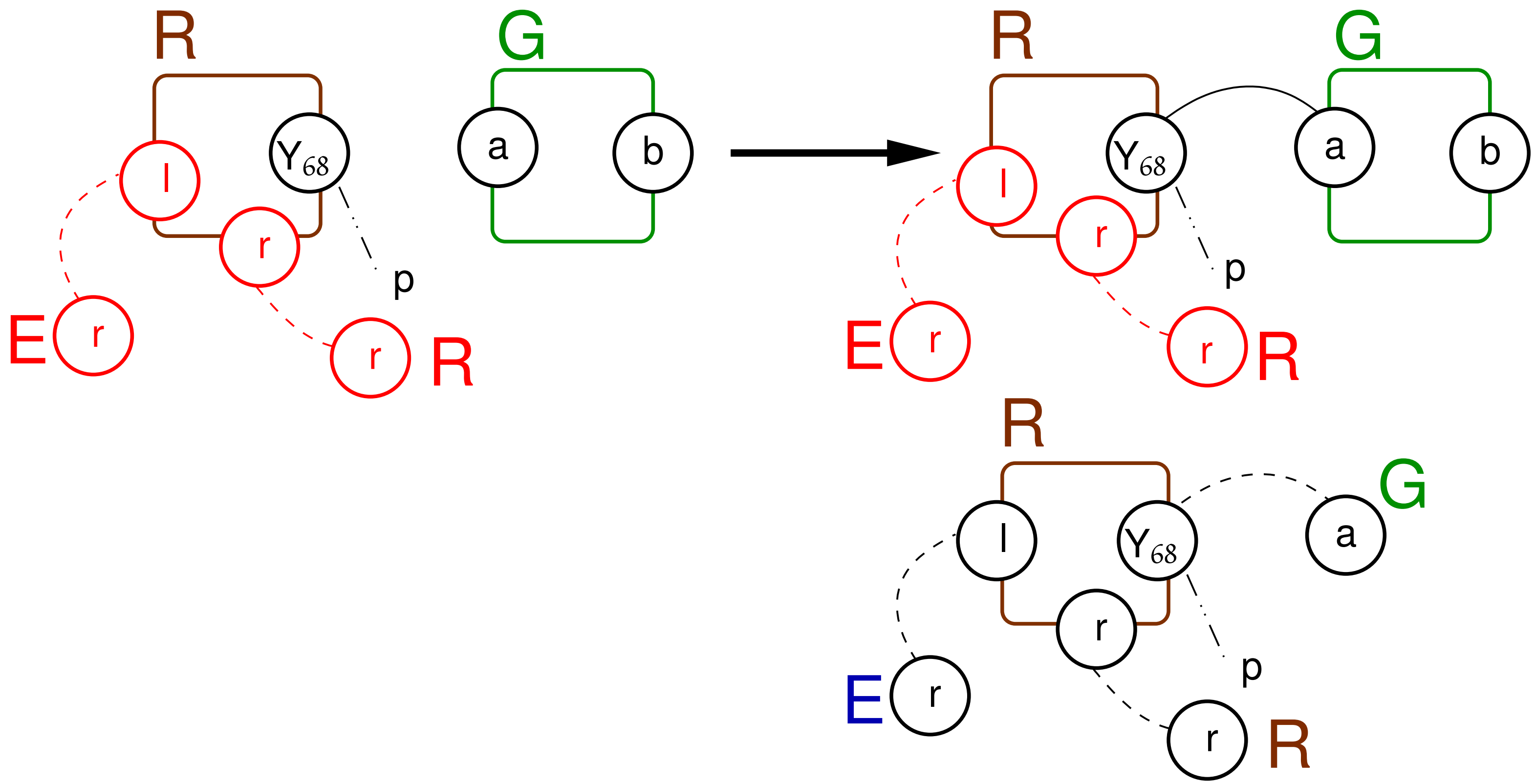
and any embedding between a modified connected component C_k and a fragment F, we get:

$$\frac{d[F]}{dt} \stackrel{-}{=} \frac{k \cdot [F] \cdot \prod_{i \neq k} [C_i]}{\mathsf{SYM}(C_1, \ldots, C_n) \cdot \mathsf{SYM}(F)}.$$

Fragment production

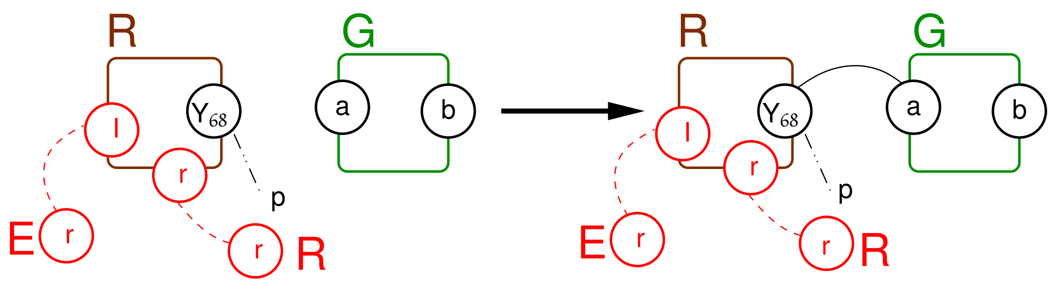


Fragment production
Proper intersection (bis)



Any connected component of the lhs of the refinement is prefragments.

Fragment production



For any rule:

$$\textit{rule} : C_1, \ldots, C_m \rightarrow \textit{rhs} \quad k$$

and any overlap between a fragment F and *rhs* on a modified site, we write $C'_1, \ldots, C'_n$ the lhs of the refined rule.

We get:

$$\frac{d[F]}{dt} \stackrel{+}{=} \frac{k \cdot \prod_i \left[C'_i\right]}{\mathsf{SYM}(C_1, \ldots, C_m) \cdot \mathsf{SYM}(F)}.$$

Overview

1. Context and motivations
2. Handmade ODEs
3. Abstract interpretation framework
4. Kappa
5. Concrete semantics
6. Abstract semantics
    (a) Fragments
    (b) Flow of information
    (c) Abstract counterpart
    (d) Symmetries between sites
7. Conclusion

Symmetries among sites

Let $\mathcal{R}$ be a set of rules.

Two sites x_1 and x_2 are symmetric in the agent A in the set of rules $\mathcal{R}$,
$\stackrel{\Delta}{\Longleftrightarrow}$

1. for each rule of the model, if we swap the site x_1 and the site x_2 in one instance of A in a rule of $\mathcal{R}$, we get a rule that is isomorphic to a rule in $\mathcal{R}$. (this rule may be the same, or a different one)
2. given two such symmetric rules, the quotient between the sum of the rates of the isomorphic rules and the product between the number of automorphisms in the left hand side, and the number of symmetric isomorphic rules, is the same.

Example I

$$\begin{array}{lcll} A(x_u) & \longrightarrow & A(x_p) & k_1 \\ A(y_u) & \longrightarrow & A(y_p) & k_1 \\ A(x_p, y_p) & \longrightarrow & & k_2 \end{array}$$

Are x and y symmetric in A?

Example I

$$\begin{array}{lcll} A(x_u) & \longrightarrow & A(x_p) & k_1 \\ A(y_u) & \longrightarrow & A(y_p) & k_1 \\ A(x_p,y_p) & \longrightarrow & & k_2 \end{array}$$

We get:

$$\frac{k_1}{1 \cdot 1} = \frac{k_1}{1 \cdot 1}.$$

So x and y are symmetric in A.

Example II

$$
\begin{array}{llll}
A(x_u) & \longrightarrow & A(x_p) & k_1 \\
A(y_u) & \longrightarrow & A(y_p) & k_2 \\
A(x_p,y_p) & \longrightarrow & & k_3
\end{array}
$$

Are x and y symmetric in A?

Example II

$$\begin{array}{lcll} A(x_u) & \longrightarrow & A(x_p) & k_1 \\ A(y_u) & \longrightarrow & A(y_p) & k_2 \\ A(x_p,y_p) & \longrightarrow & & k_3 \end{array}$$

The sites are symmetric if and only if $\frac{k_1}{1 \cdot 1} = \frac{k_2}{1 \cdot 1}$.

So, x and y are symmetric in A, if and only if $k_1 = k_2$!

Example III

$$A(x), A(x) \longrightarrow A(x^1), A(x^1) \quad k$$
$$A(y), A(y) \longrightarrow A(y^1), A(y^1) \quad k$$

Are x and y symmetric in A?

Example III

$$A(x) \ , A(x) \ \longrightarrow \ A(x^1) \ , A(x^1) \quad k$$

$$A(y) \ , A(y) \ \longrightarrow \ A(y^1) \ , A(y^1) \quad k$$

The sites are symmetric if and only if $\frac{k}{2 \cdot 1} = \frac{k}{2 \cdot 1} = \frac{0}{1 \cdot 2}$.

So, x and y are symmetric in A, if and only if $k = 0$!

Example IV

$$\begin{array}{lllll} A(x)\ , A(x) & \longrightarrow & A(x^1)\ , A(x^1) & k_1 \\ A(y)\ , A(y) & \longrightarrow & A(y^1)\ , A(y^1) & k_2 \\ A(x)\ , A(y) & \longrightarrow & A(x^1)\ , A(y^1) & k_3 \end{array}$$

Are x and y symmetric in A?

Example IV

$$
\begin{array}{llll}
A(x), A(x) & \longrightarrow & A(x^1), A(x^1) & k_1 \\
A(y), A(y) & \longrightarrow & A(y^1), A(y^1) & k_2 \\
A(x), A(y) & \longrightarrow & A(x^1), A(y^1) & k_3
\end{array}
$$

The sites are symmetric if and only if $\frac{k_1}{2\cdot 1} = \frac{k_2}{2\cdot 1} = \frac{k_3}{1\cdot 2}$.

So, x and y are symmetric in A, if and only if $k_1 = k_2 = k_3$!

Symmetries among sites

- We consider a family of triples $(x_i, y_i, A_i)_{i \in I}$ such that, for each $i \in I$:
  - x_i and y_i are symmetric in the agent A_i;
  - x_i and y_i are connected in both directions in the annotated contact map;
- We define $\sim_{\text{ag}}$ over agents (with interfaces) by $A_i(\sigma[x_i, y_i]) \sim_{\text{ag}} A_i(\sigma[y_i, x_i])$.
- We define $\sim_{\text{pattern}}$ over expressions by:

$$\frac{A_i \sim_{\text{ag}} A'_i, 1 \leq i \leq k}{A_1, \ldots, A_k \sim_{\text{pattern}} A'_1, \ldots, A'_k}.$$

- Then, it is (quite) easy to build $r \in \mathcal{V} \to \mathcal{V}$ and $r^\sharp \in \mathcal{V}^\sharp \to \mathcal{V}^\sharp$, such that:
  1. for any $X \in \mathcal{V}$, $r(X) \sim_{\text{pattern}} X$,
  2. for any $F \in \mathcal{V}^\sharp$, $r^\sharp(F) \sim_{\text{pattern}} F$,
  3. and $\psi \circ P_r = P_{r^\sharp} \circ \psi$.

Overview

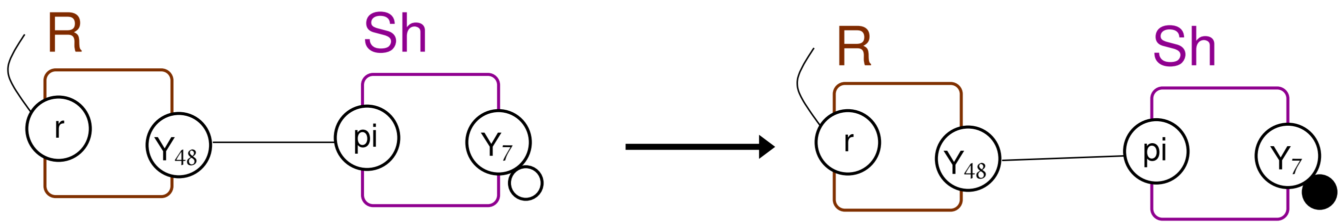
1. Context and motivations
2. Handmade ODEs
3. Abstract interpretation framework
4. Kappa
5. Concrete semantics
6. Abstract semantics
7. Conclusion

Experimental results

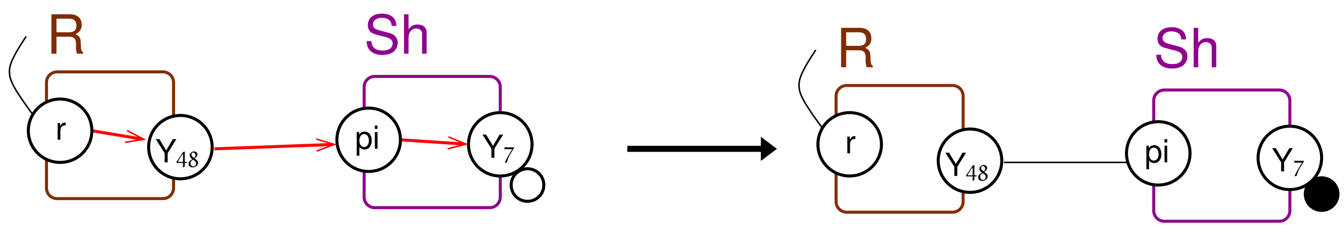
Model	early EGF	EGF/Insulin	SFB
#species	356	2899	$\sim 2.10^{19}$
#fragments (ODEs)	38	208	$\sim 2.10^{5}$
#fragments (CTMC)	356	618	$\sim 2.10^{19}$

Summary

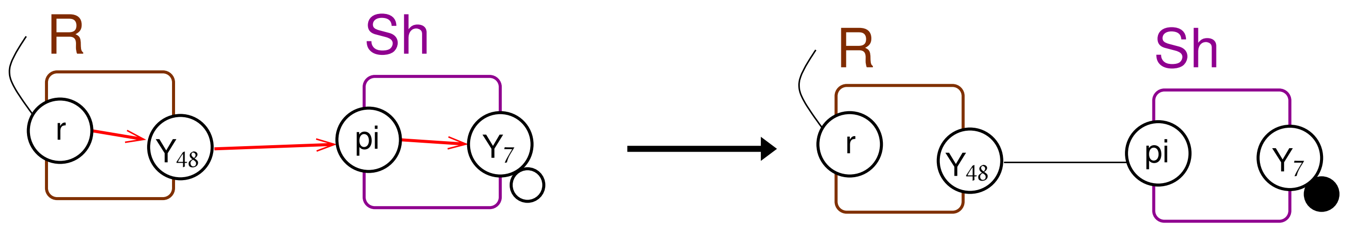
Summarising the flow of information

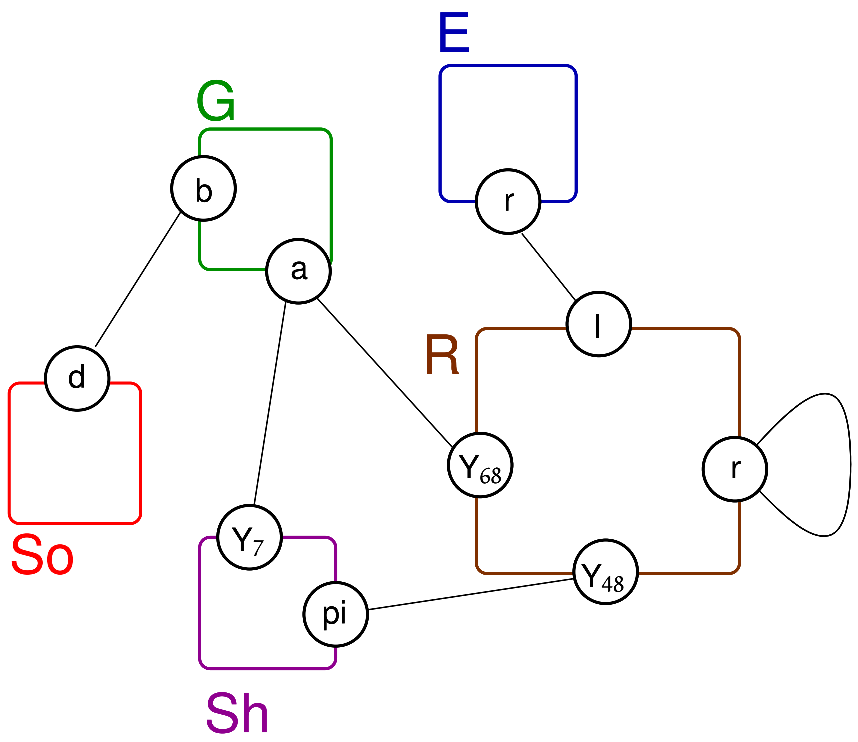


Summarising the flow of information

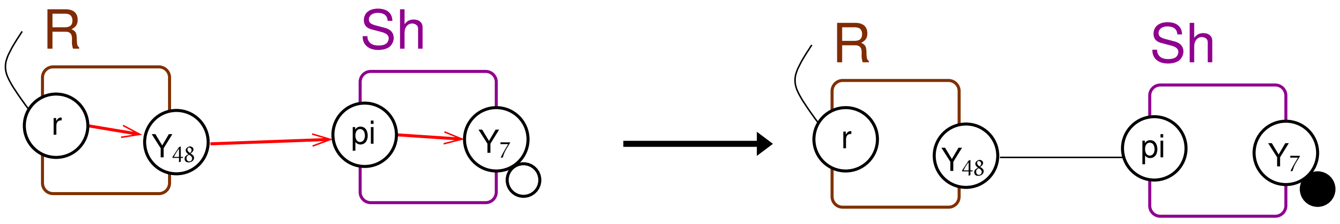


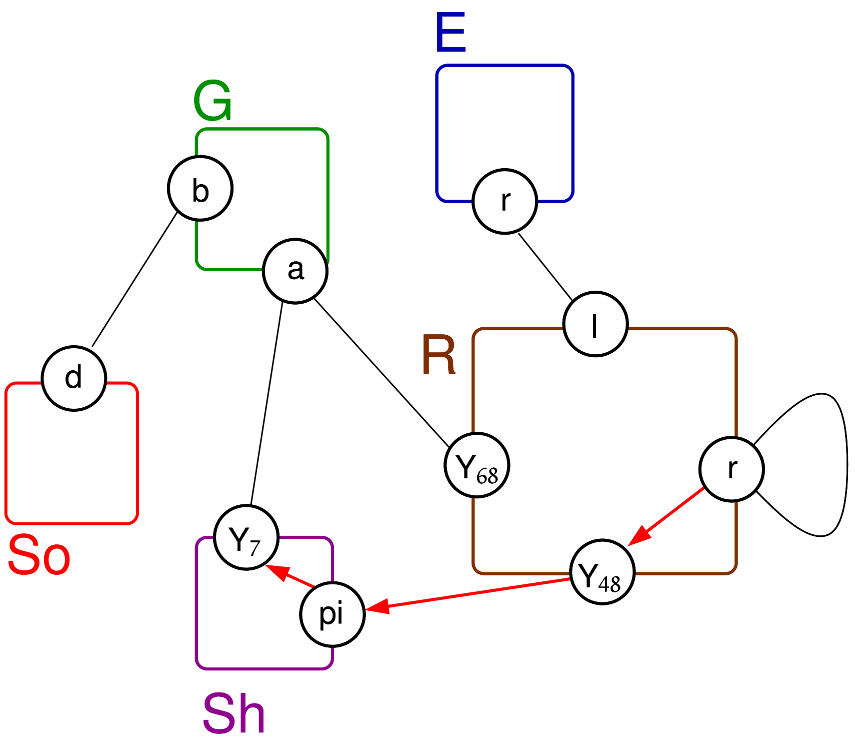
Summarising the flow of information



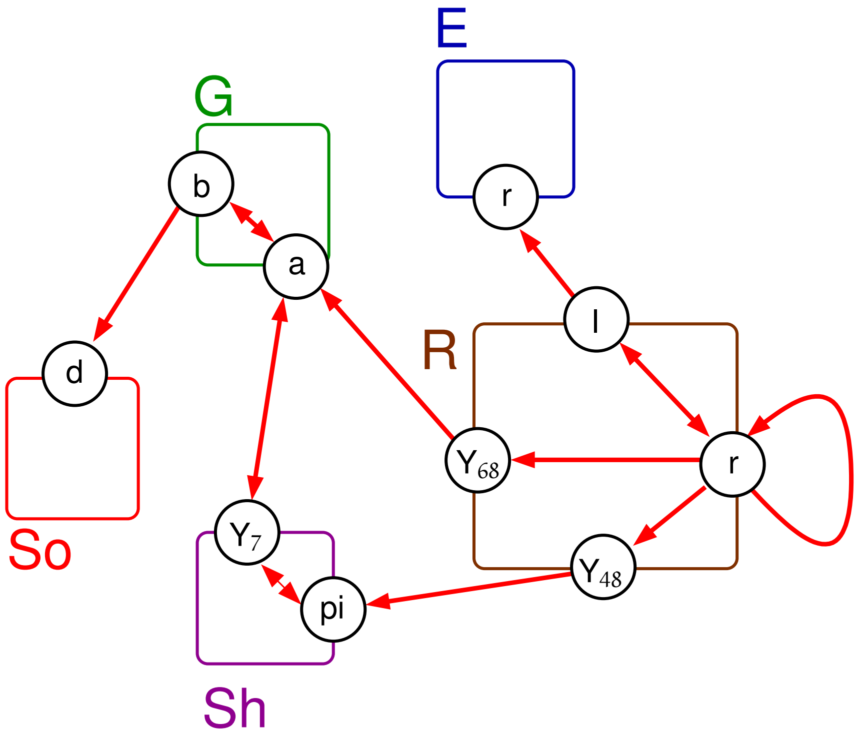


Summarising the flow of information

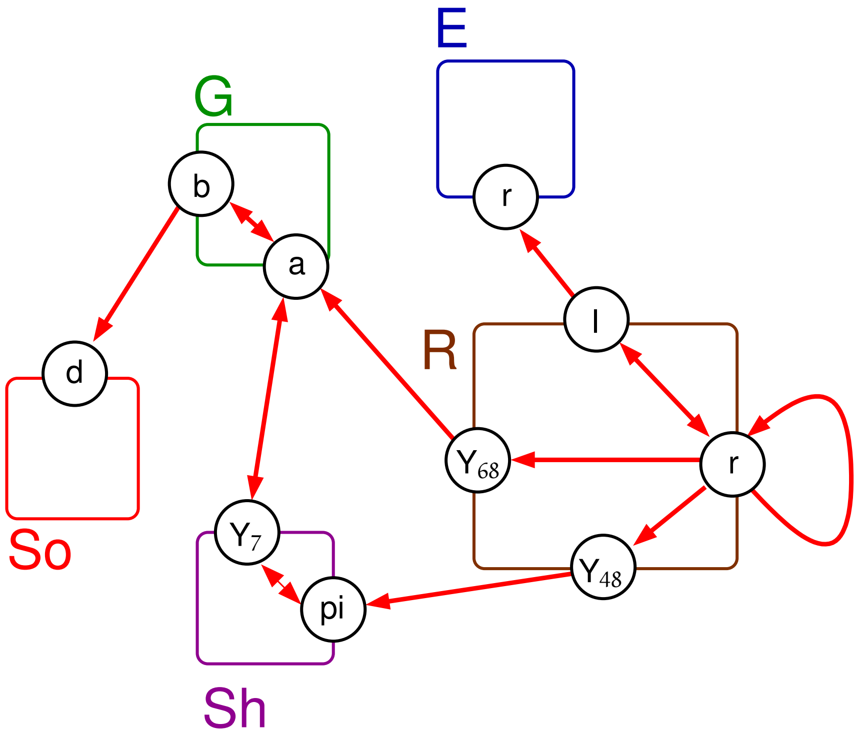


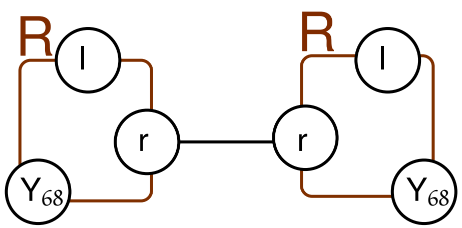


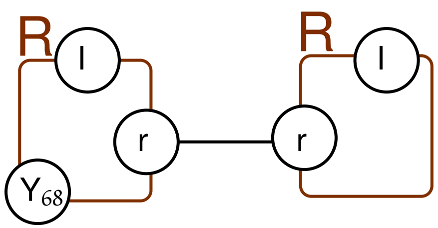
Deducing patterns of interest



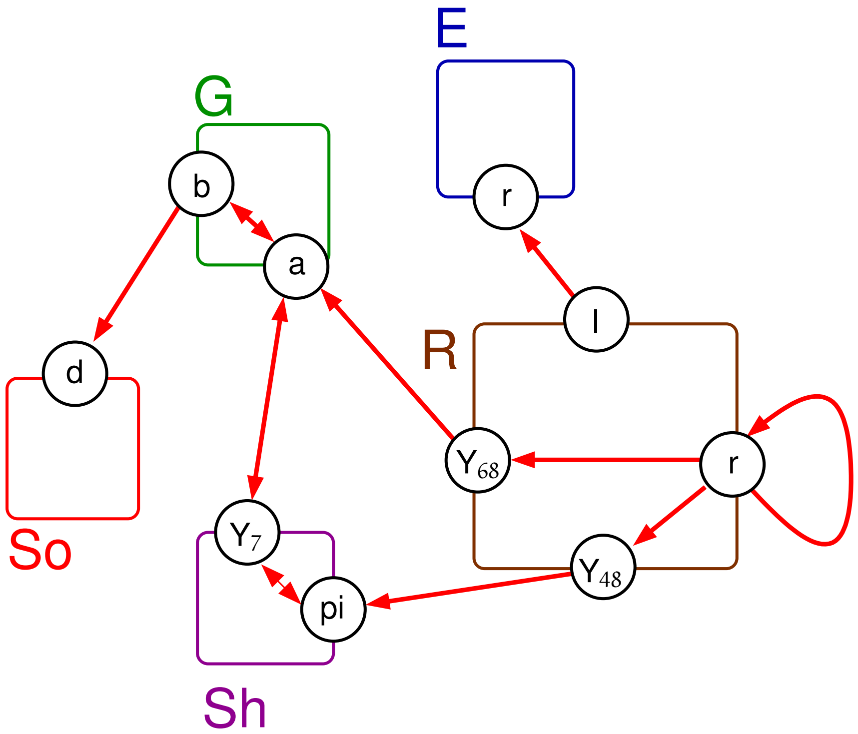
Deducing patterns of interest

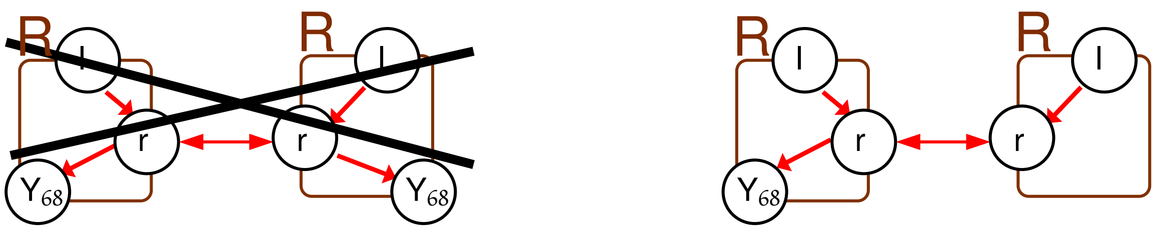






Deducing patterns of interest





Related issues and acknowledgements

- Coarse-graining of the differential semantics
  Vincent Danos, Walter Fontana, Russ Harmer, Jean Krivine
- Context-sensitive coarse-graining of the differential semantics
  Ferdinanda Camporesi
- Coarse-graining of the stochastic semantics
  Tatjana Petrov, Heinz Koeppl, Tom Henzinger
- Bisimulation metrics
  Norm Ferns.

ANR-Chair of Excellence
“AbstractCell”
(2009-2013)

DARPA programme
“Big Mechanism”
(2014-2017)

Cours MPRI

Model reduction of stochastic rules-based models

[CS2Bio'10,MFPS'10,MeCBIC'10,ICNAAM'10]

Jérôme Feret
Laboratoire d'Informatique de l'École Normale Supérieure
INRIA, ÉNS, CNRS

Wednesday, the 18th of February, 2015

Joint-work with...

Ferdinanda Camporesi
Bologna / ÉNS

Thomas Henzinger
IST Austria

Heinz Koeppl
ETH Zürich

Tatjana Petrov
EPFL

Overview

1. Introduction
2. Examples of information flow
3. Symmetric sites
4. Stochastic semantics
5. Lumpability
6. Bisimulations
7. Hierarchy of semantics
8. Conclusion

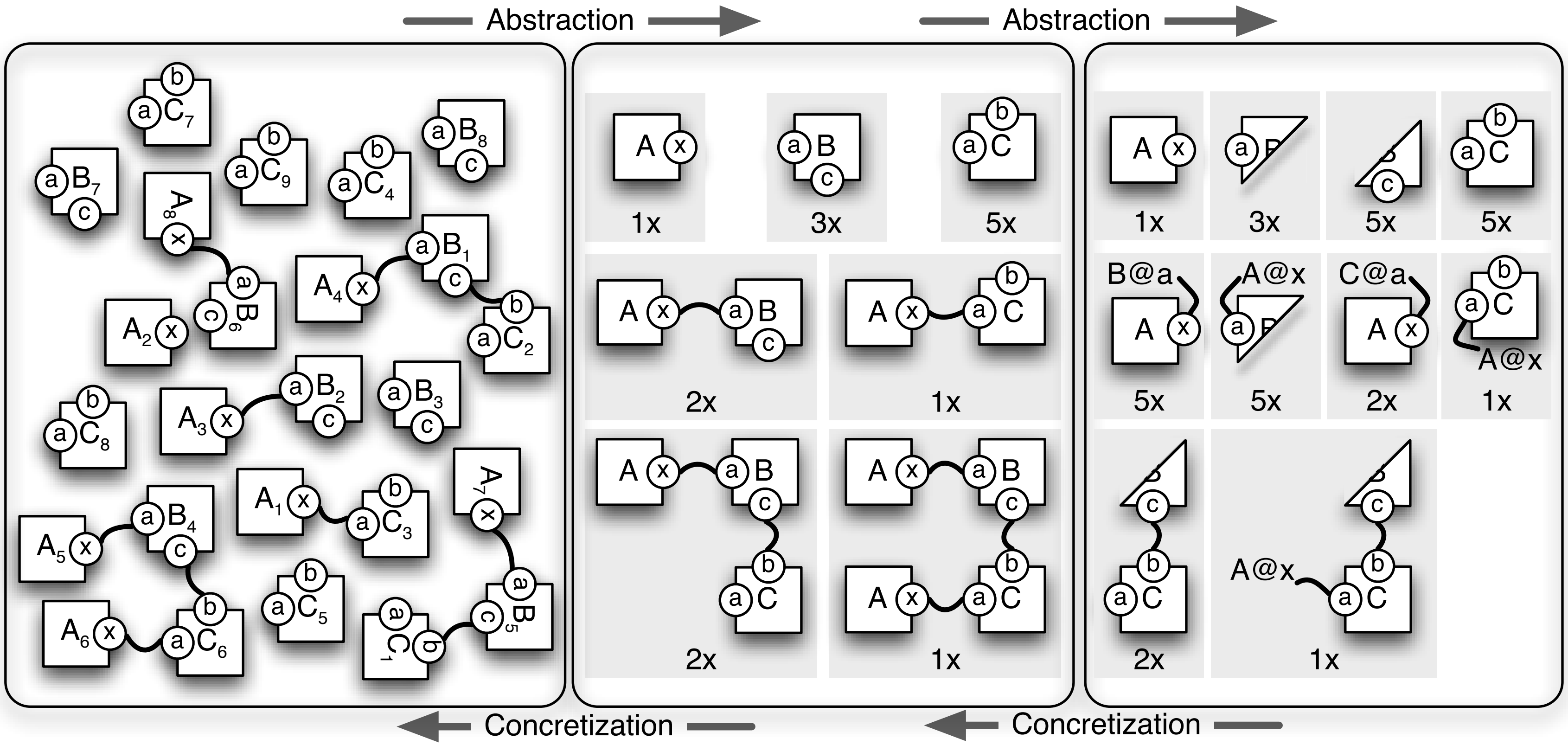
ODE fragments

In the ODE semantics, using the flow of information backward, we can detect which correlations are not relevant for the system, and deduce a small set of portions of chemical species (called fragments) the behavior of the concentration of which can be described in a self-consistent way.

(ie. the trajectory of the reduced model are the exact projection of the trajectory of the initial model).

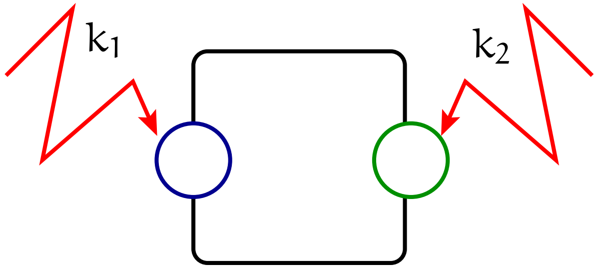
Can we do the same for the stochastic semantics?

Stochastic fragments ?



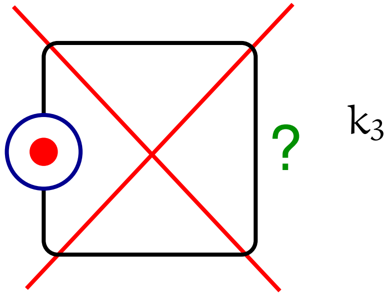
Overview

A model with ubiquitination



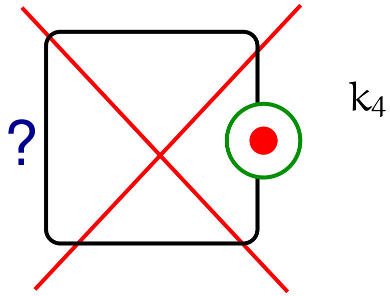
$$P \xrightarrow{k_1} {}^{\star}P \qquad P^{\star} \xrightarrow{k_1} {}^{\star}P^{\star}$$

$$P \xrightarrow{k_2} P^{\star} \qquad {}^{\star}P \xrightarrow{k_2} {}^{\star}P^{\star}$$



$${}^{\star}P \xrightarrow{k_3} \emptyset$$

$${}^{\star}P^{\star} \xrightarrow{k_3} \emptyset$$



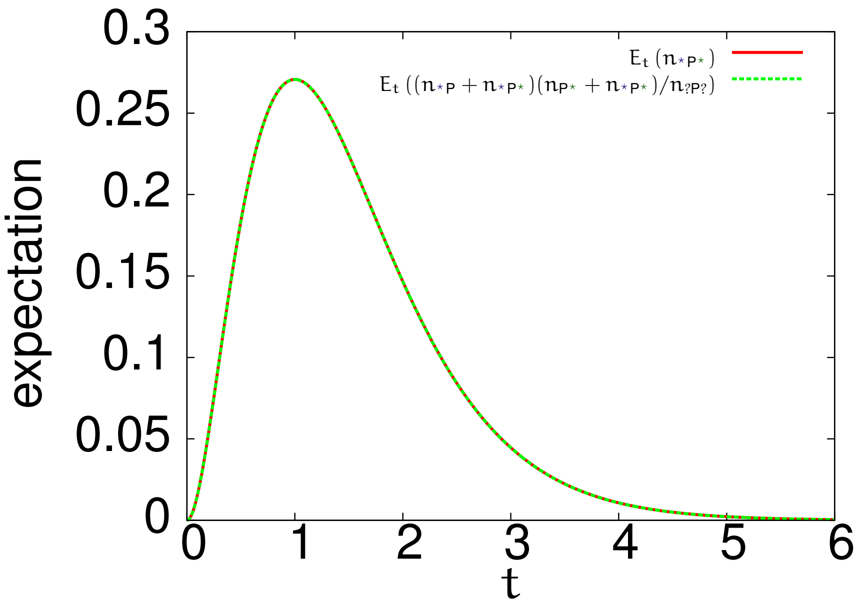
$$P^{\star} \xrightarrow{k_4} \emptyset$$

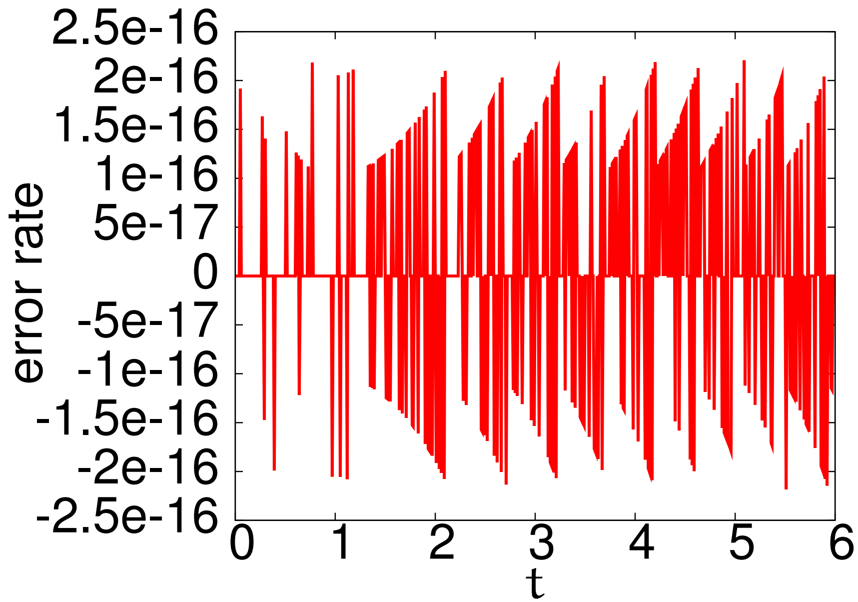
$${}^{\star}P^{\star} \xrightarrow{k_4} \emptyset$$

Statistical independence

We check numerically that:

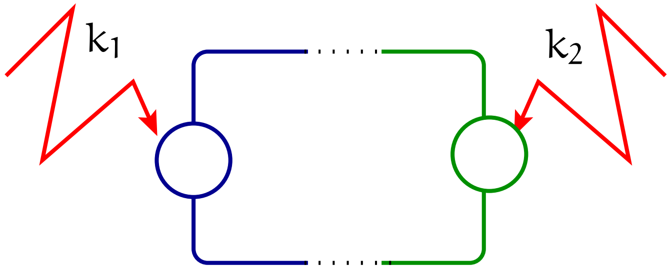
$$E_t\left(n_{\star P\star}\right) = E_t\left(\frac{(n_{\star P} + n_{\star P\star})(n_{P\star} + n_{\star P\star})}{n_P + n_{P\star} + n_{\star P} + n_{\star P\star}}\right).$$



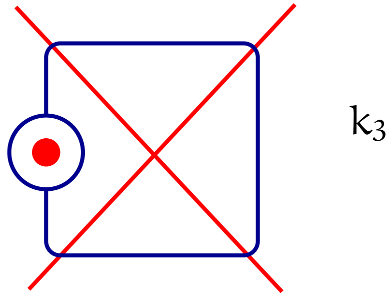


with $k_1 = k_2 = k_3 = k_4 = 1$
and two instances of P at time $t = 0$.

Reduced model

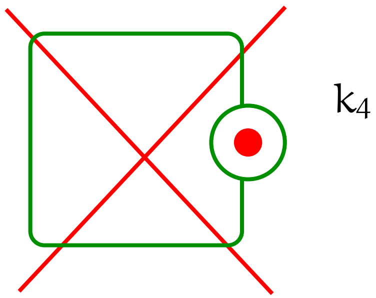


$$P \xrightarrow{k_1} {}^{\star}P$$
$$P \xrightarrow{k_2} P^{\star}$$



$${}^{\star}P \xrightarrow{k_3} \emptyset$$

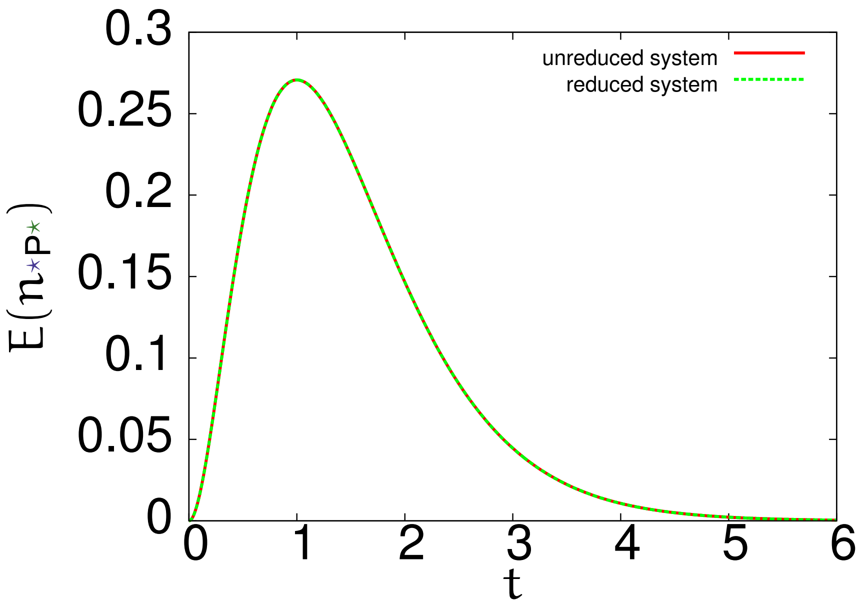
+ side effect: remove one P

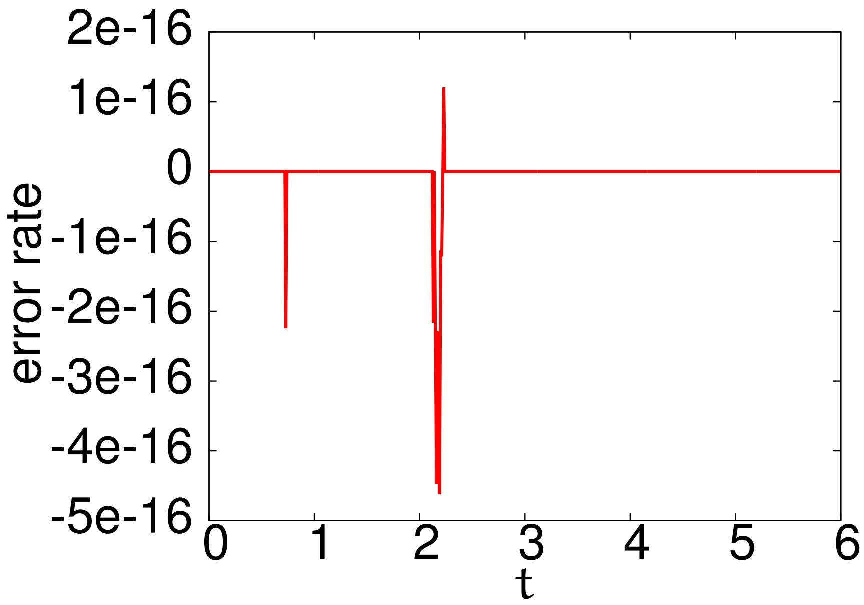


$$P^{\star} \xrightarrow{k_4} \emptyset$$

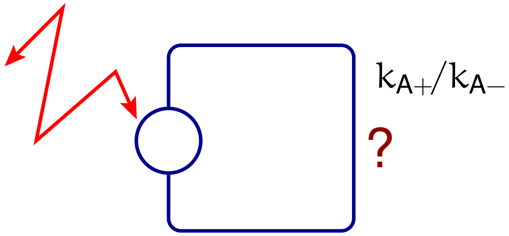
+ side effect: remove one P

Comparison between the two models

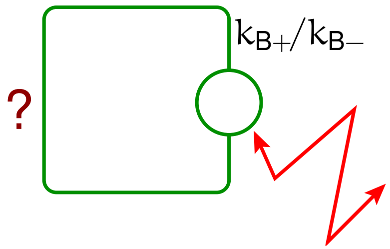




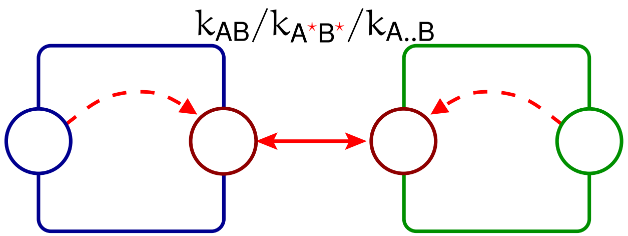
Coupled semi-reactions



$$A \underset{k_{A-}}{\overset{k_{A+}}{\rightleftharpoons}} A^{\star}, \quad AB \underset{k_{A-}}{\overset{k_{A+}}{\rightleftharpoons}} A^{\star}B, \quad AB^{\star} \underset{k_{A-}}{\overset{k_{A+}}{\rightleftharpoons}} A^{\star}B^{\star}$$



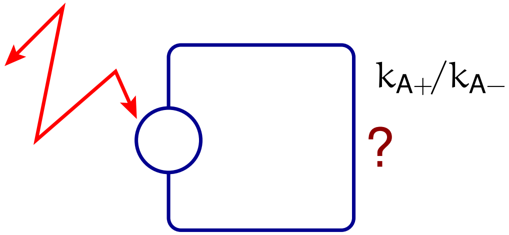
$$B \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} B^{\star}, \quad AB \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} AB^{\star}, \quad A^{\star}B \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} A^{\star}B^{\star}$$



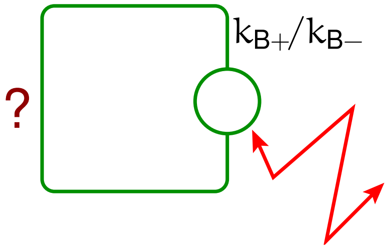
$$A + B \underset{k_{A..B}}{\overset{k_{AB}}{\rightleftharpoons}} AB, \quad A^{\star} + B \underset{k_{A..B}}{\overset{k_{AB}}{\rightleftharpoons}} A^{\star}B,$$

$$A + B^{\star} \underset{k_{A..B}}{\overset{k_{AB}}{\rightleftharpoons}} AB^{\star}, \quad A^{\star} + B^{\star} \underset{k_{A..B}}{\overset{k_{A^{\star}B^{\star}}}{\rightleftharpoons}} A^{\star}B^{\star}$$

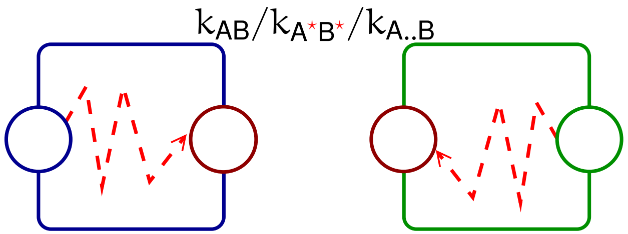
Reduced model



$$A \underset{k_{A-}}{\overset{k_{A+}}{\rightleftharpoons}} A^{\star}, \quad AB^{\diamond} \underset{k_{A-}}{\overset{k_{A+}}{\rightleftharpoons}} A^{\star}B^{\diamond},$$



$$B \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} B^{\star}, \quad A^{\diamond}B \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} A^{\diamond}B^{\star},$$



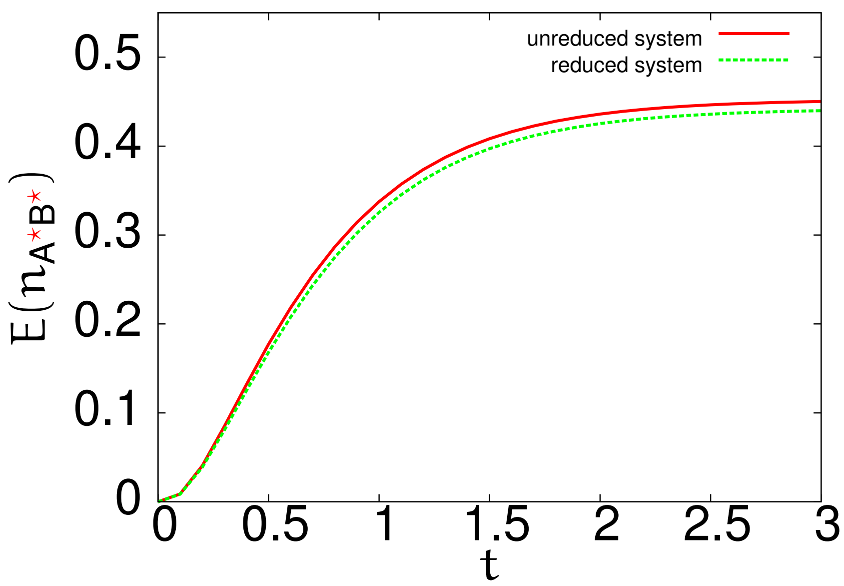
$$A + B \underset{k_{A..B}/(n_{A^{\diamond}B}+n_{A^{\diamond}B^{\star}})}{\overset{k_{AB}}{\rightleftharpoons}} AB^{\diamond} + A^{\diamond}B,$$

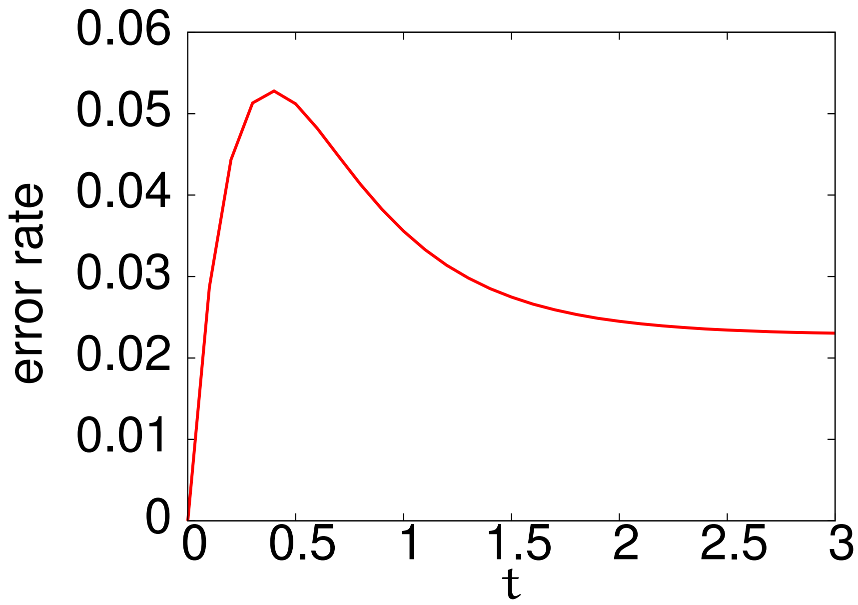
$$A^{\star} + B \underset{k_{A..B}/(n_{A^{\diamond}B}+n_{A^{\diamond}B^{\star}})}{\overset{k_{AB}}{\rightleftharpoons}} A^{\star}B^{\diamond} + A^{\diamond}B,$$

$$A + B^{\star} \underset{k_{A..B}/(n_{A^{\diamond}B}+n_{A^{\diamond}B^{\star}})}{\overset{k_{AB}}{\rightleftharpoons}} AB^{\diamond} + A^{\diamond}B^{\star},$$

$$A^{\star} + B^{\star} \underset{k_{A..B}/(n_{A^{\diamond}B}+n_{A^{\diamond}B^{\star}})}{\overset{k_{A^{\star}B^{\star}}}{\rightleftharpoons}} A^{\star}B^{\diamond} + A^{\diamond}B^{\star}$$

Comparison between the two models

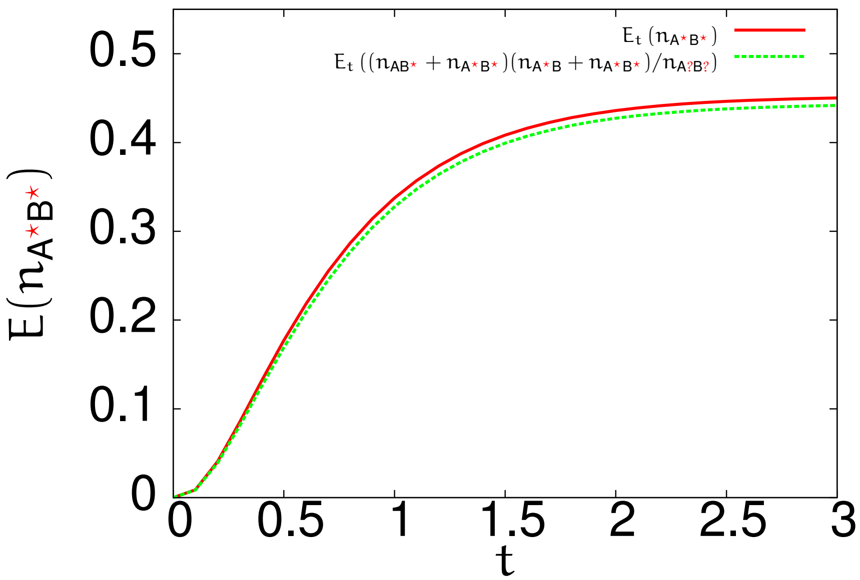


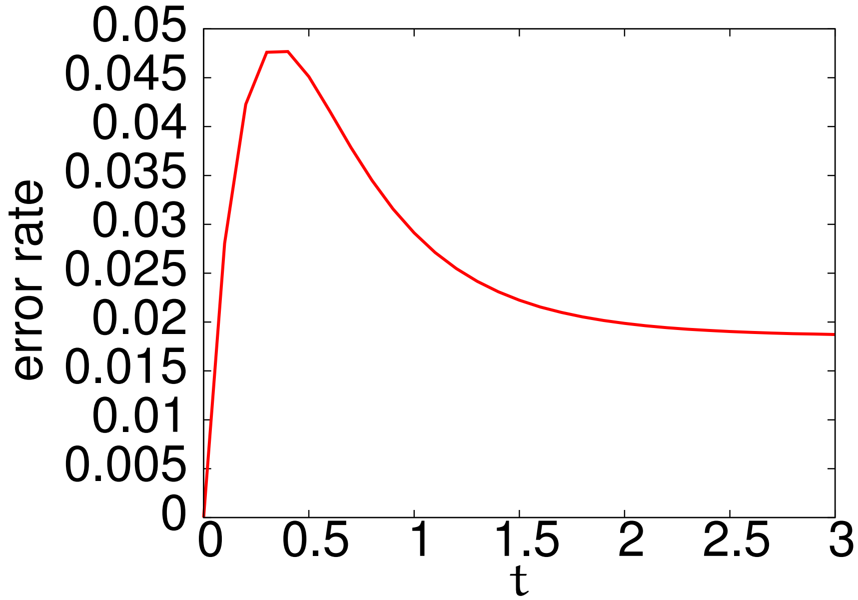


with $k_{A+} = k_{A-} = k_{B+} = k_{B-} = k_{AB} = k_{A..B} = 1$, $k_{A^\star B^\star} = 10$,
and two instances of A and B at time $t = 0$.

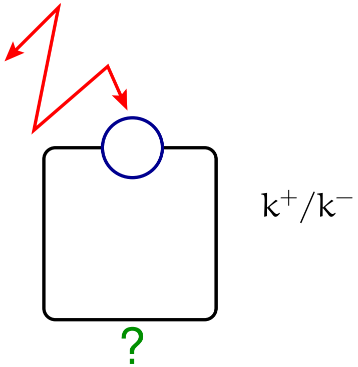
Although the reduction is correct in the ODE semantics.

Degree of correlation
(in the unreduced model)



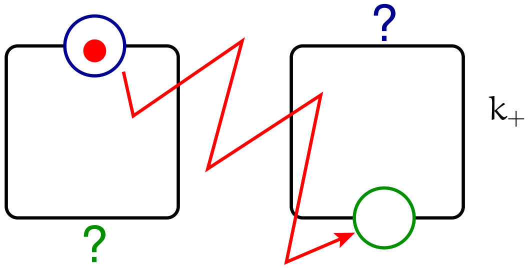


Distant control



$$A \underset{k^-}{\overset{k^+}{\rightleftharpoons}} A^{\star}$$

$$A_{\star} \underset{k^-}{\overset{k^+}{\rightleftharpoons}} A^{\star}_{\star}$$

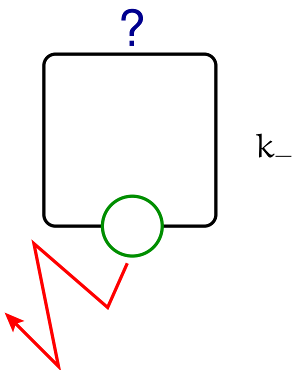


$$A + A^{\star} \xrightarrow{k_+} A_{\star} + A^{\star}$$

$$A^{\star} + A^{\star} \xrightarrow{k_+} A^{\star}_{\star} + A^{\star}$$

$$A + A^{\star}_{\star} \xrightarrow{k_+} A_{\star} + A^{\star}_{\star}$$

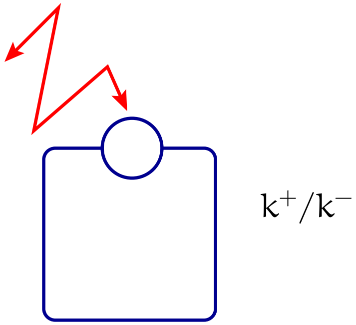
$$A^{\star} + A^{\star}_{\star} \xrightarrow{k_+} A^{\star}_{\star} + A^{\star}_{\star}$$



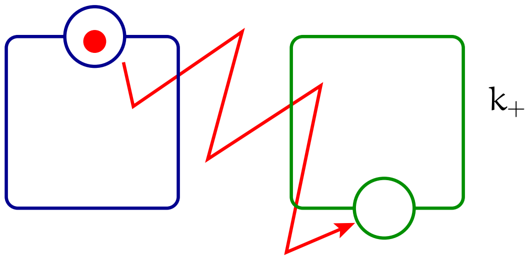
$$A^{\star}_{\star} \xrightarrow{k_-} A^{\star}$$

$$A_{\star} \xrightarrow{k_-} A$$

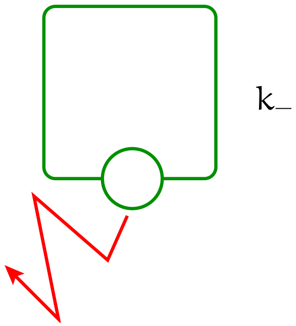
Reduced model



$$A \underset{k^-}{\overset{k^+}{\rightleftharpoons}} A^\star$$

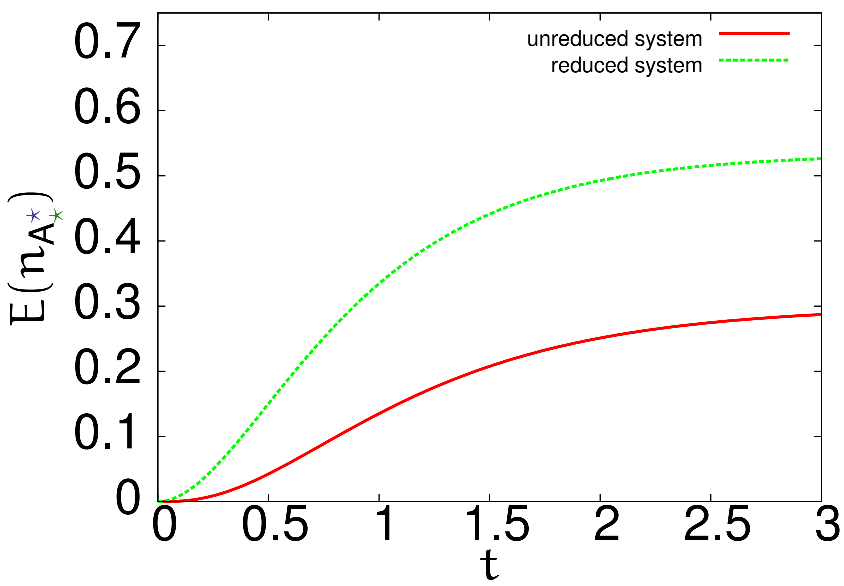


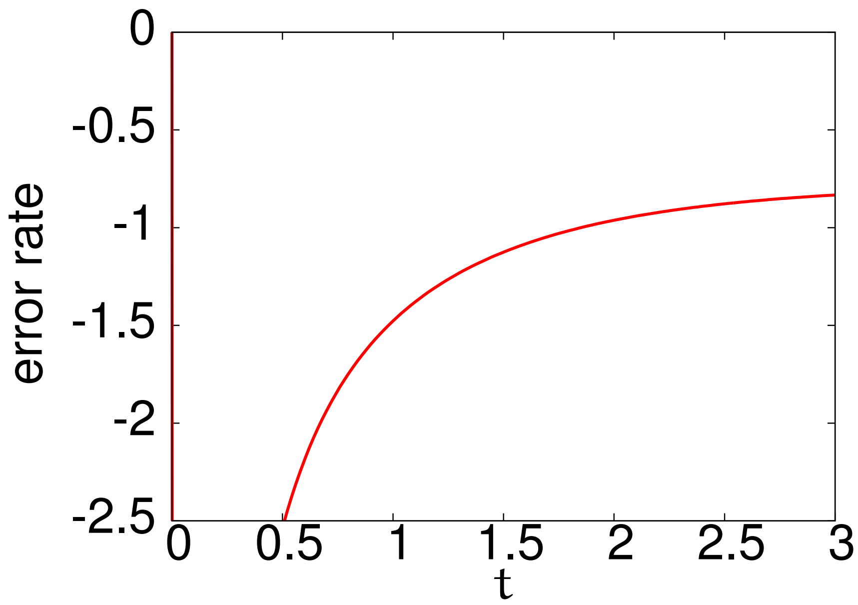
$$A + A^\star \xrightarrow{k_+} A_\star + A^\star$$



$$A_\star \xrightarrow{k_-} A$$

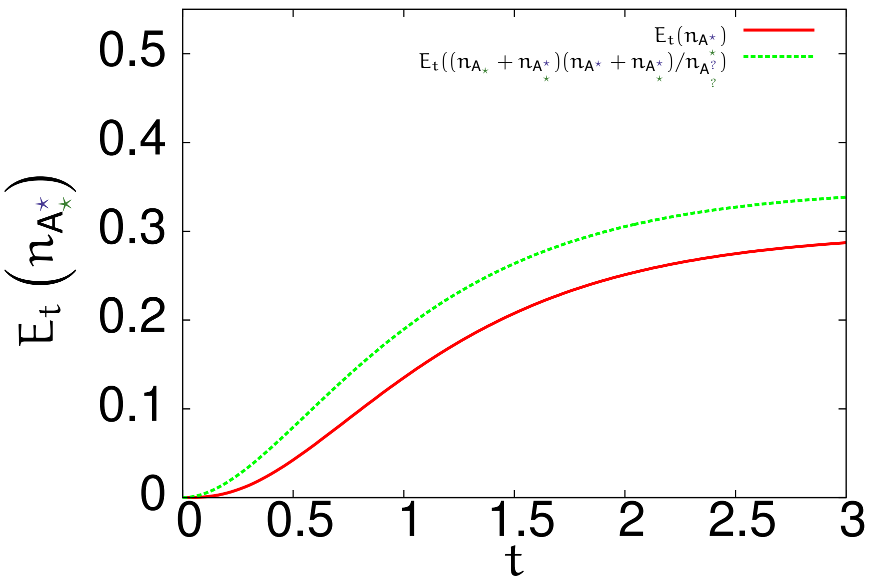
Comparison between the two models

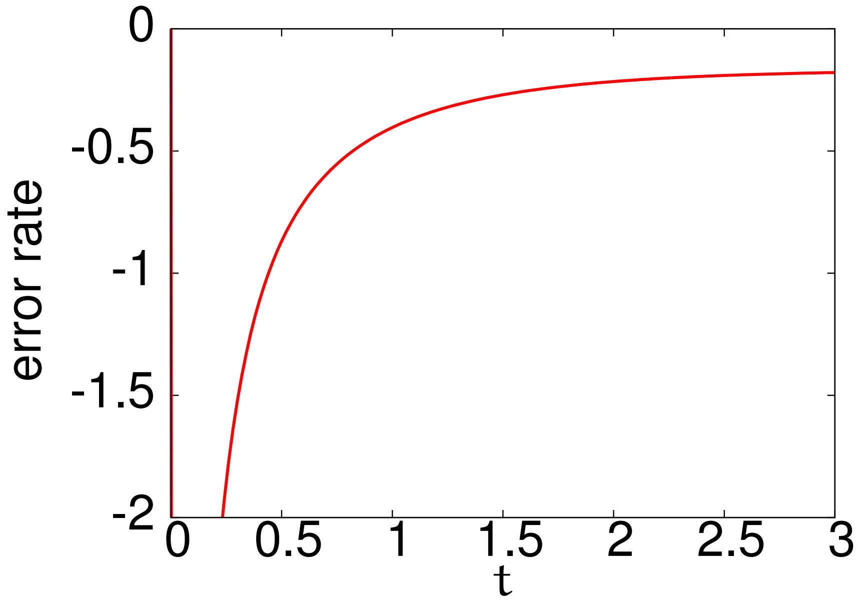




with $k^+ = k^- = k_+ = k_- = 1$,
and two instances of A at time $t = 0$.

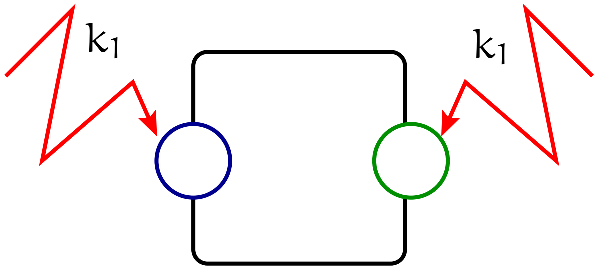
Degree of correlation
(in the unreduced model)





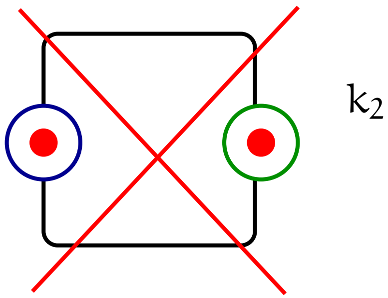
Overview

A model with symmetries



$$P \xrightarrow{k_1} {}^{\star}P \qquad P^{\star} \xrightarrow{k_1} {}^{\star}P^{\star}$$

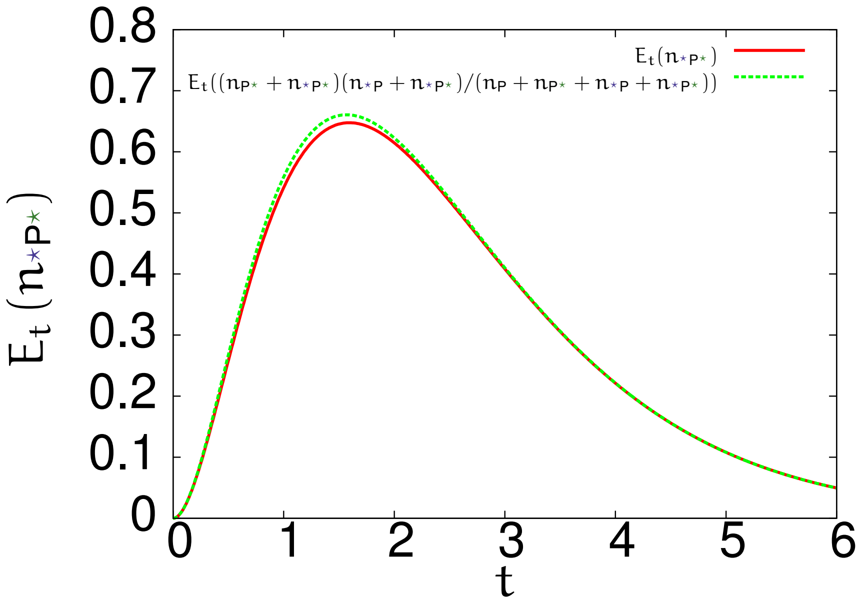
$$P \xrightarrow{k_1} P^{\star} \qquad {}^{\star}P \xrightarrow{k_1} {}^{\star}P^{\star}$$

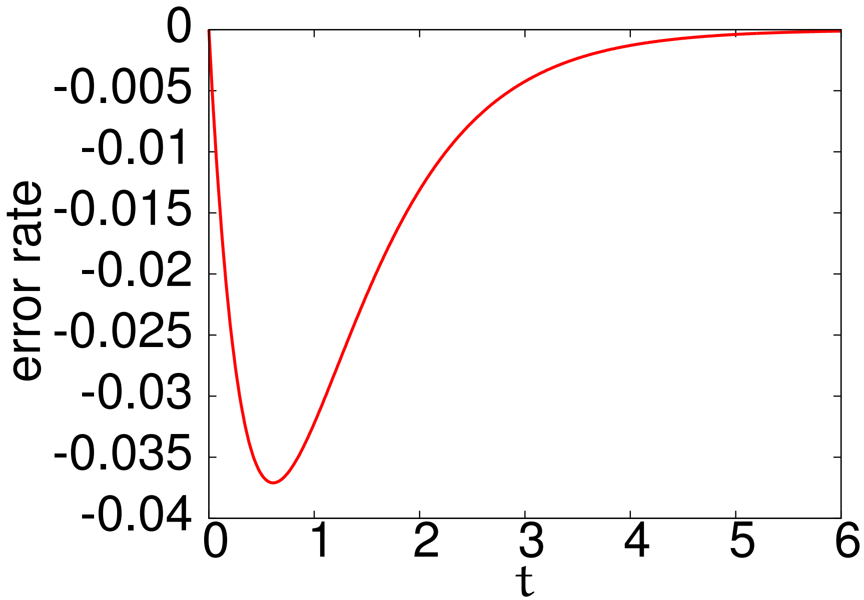


$${}^{\star}P^{\star} \xrightarrow{k_2} \emptyset$$

Degree of correlation (in the unreduced model)

$$E_t\,(n_{\star P\star}) = E_t\left(\frac{(n_{\star P} + n_{\star P\star})(n_{P\star} + n_{\star P\star})}{n_P + n_{P\star} + n_{\star P} + n_{\star P\star}}\right).$$



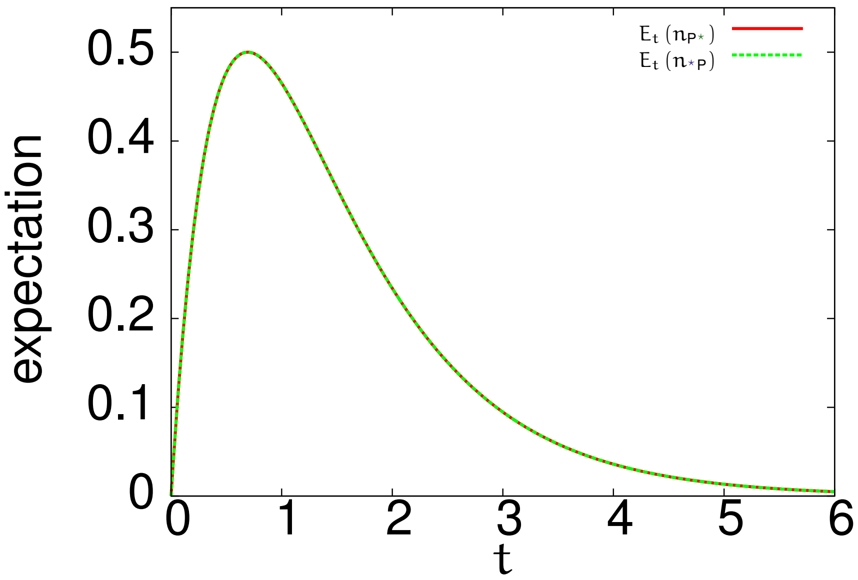


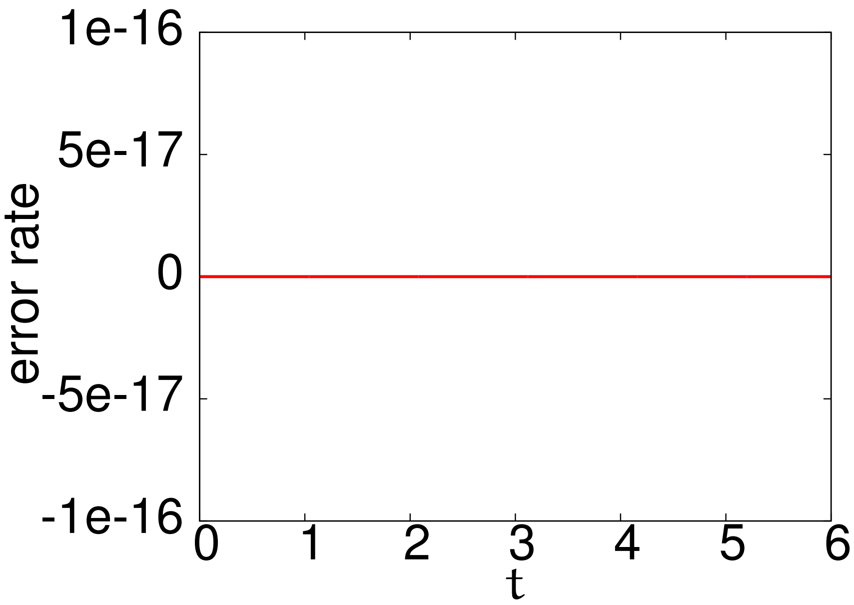
with $k_1 = k_2 = 1$
and two instances of P at time $t = 0$.

Equivalent chemical species

We check numerically that:

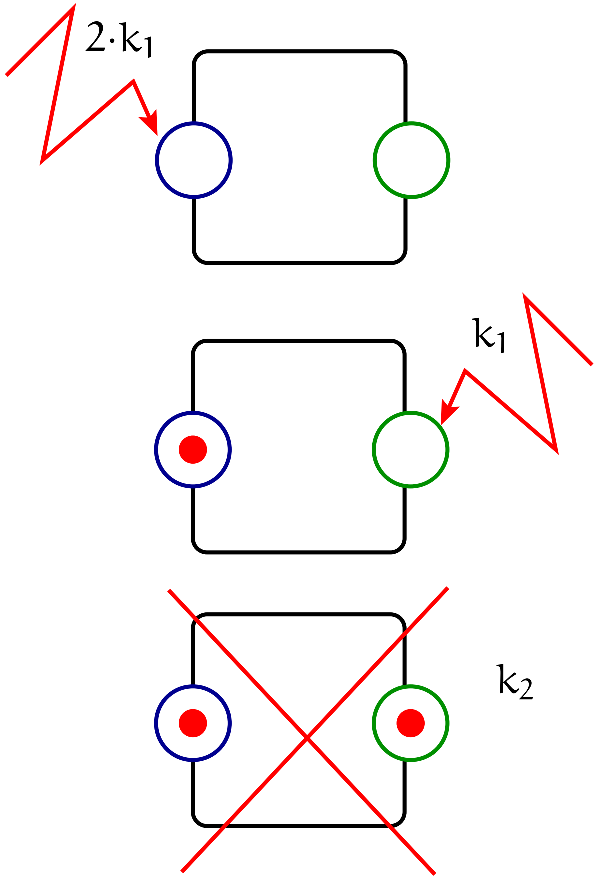
$$E_t(n_{P\star}) = E_t(n_{\star P}).$$





with $k_1 = k_2 = 1$
and two instances of P at time $t = 0$.

Reduced model



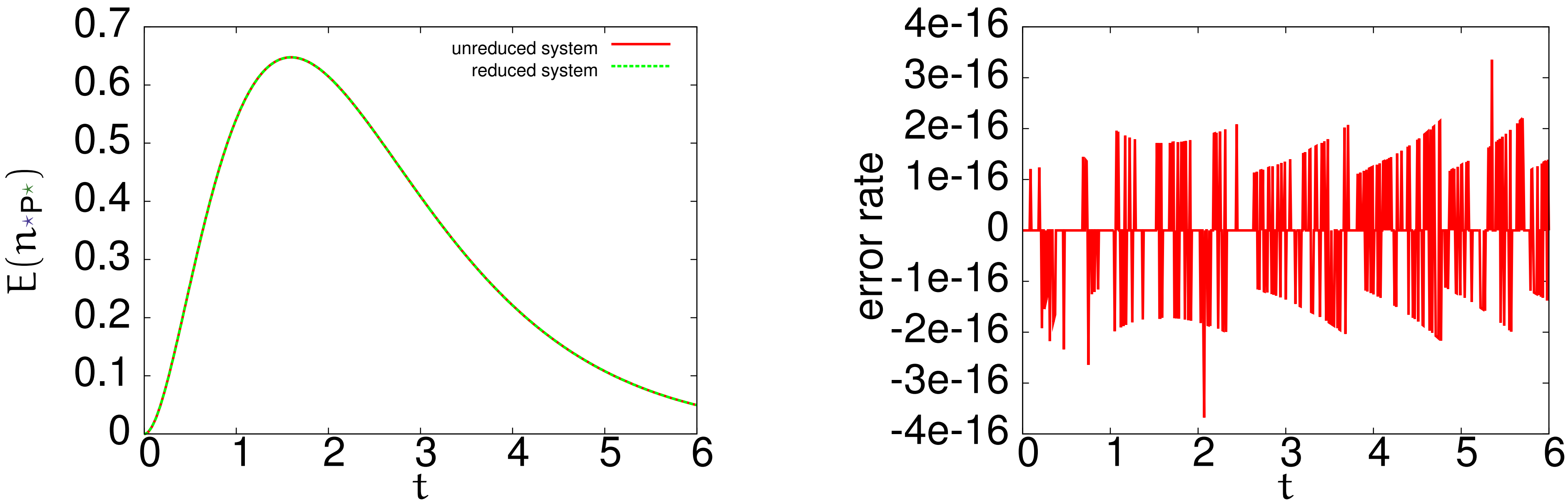
$$P \xrightarrow{2\cdot k_1} {}^{\star}P$$

$$^{\star}P \xrightarrow{k_1} {}^{\star}P^{\star}$$

$$^{\star}P^{\star} \xrightarrow{k_2} \emptyset$$

Exponential reduction!!!

Comparison between the two models



with $k_1 = k_2 = 1$
and two instances of P at time $t = 0$.

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Weighted Labelled Transition Systems

A weighted-labelled transition system $\mathcal{W}$ is given by:

- $\mathcal{Q}$, a countable set of states;
- $\mathcal{L}$, a set of labels;
- $w : \mathcal{Q} \times \mathcal{L} \times \mathcal{Q} \to \mathbb{R}_0^+$, a weight function;
- $\pi_0 : \mathcal{Q} \to [0, 1]$, an initial probability distribution.

We also assume that:

- the system is finitely branching, i.e.:
  - the set $\{q \in \mathcal{Q} \mid \pi_0(q) > 0\}$ is finite
  - and, for any $q \in \mathcal{Q}$, the set $\{l, q' \in \mathcal{L} \times \mathcal{Q} \mid w(q, l, q') > 0\}$ is finite.
- the system is deterministic:
  if $w(q, \lambda, q_1) > 0$ and $w(q, \lambda, q_2) > 0$, then: $q_1 = q_2$.

Trace distribution

A cylinder set of traces is defined as:

$$\tau \stackrel{\Delta}{=} q_0 \stackrel{\lambda_1,I_1}{\longrightarrow} q_1 \ldots q_{k-1} \stackrel{\lambda_k,I_k}{\longrightarrow} q_k$$

where:

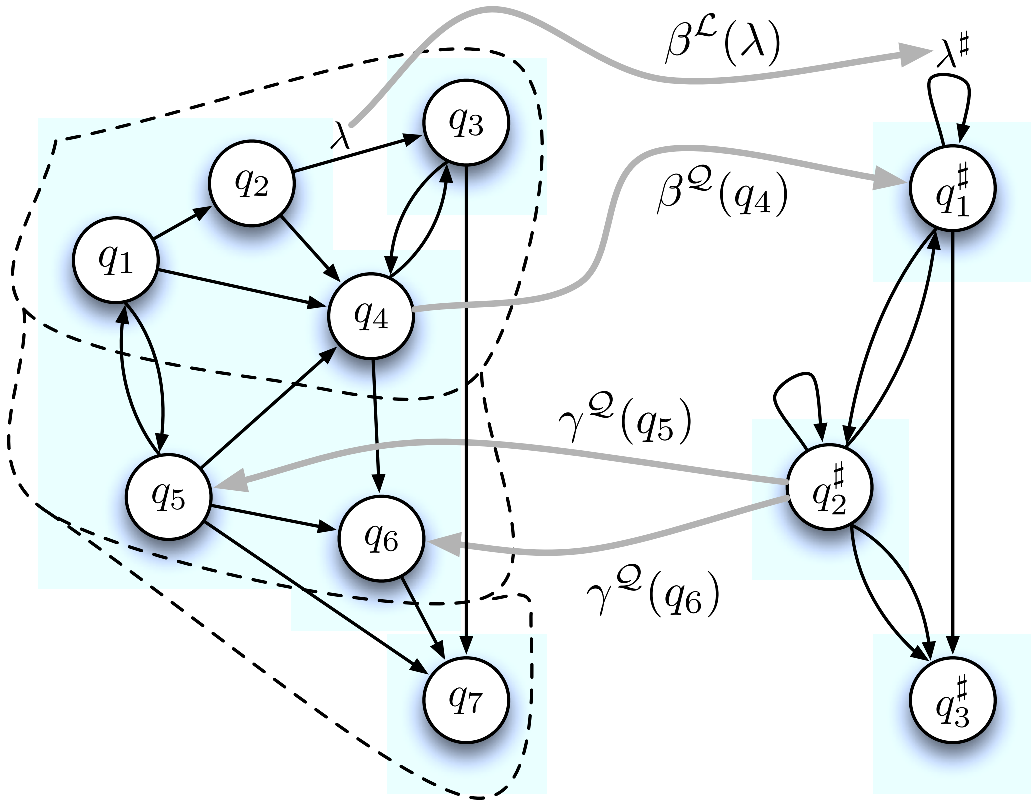
- $(q_i)_{0\leq i\leq k} \in \mathcal{Q}^{k+1}$ and $(\lambda_i)_{1\leq i\leq k} \in \mathcal{L}^k$,
- $(I_i)_{1\leq i\leq k}$ is a family of open intervals in $\mathbb{R}_0^+$.

The probability of a cylinder set of traces is defined as follows:

$$\mathcal{P}r(\tau) \stackrel{\Delta}{=} \pi_0(q_0) \prod_{i=1}^{k} \frac{w(q_{i-1}, l_i, q_i)}{a(q_{i-1})} \left(e^{-a(q_{i-1})\cdot\mathsf{inf}(I_i)} - e^{-a(q_{i-1})\cdot\mathsf{sup}(I_i)}\right),$$

where $a(q) \stackrel{\Delta}{=} \sum_{\lambda,q'} w(q,\lambda,q')$.

Abstraction between WLTS



Soundness

Given:

- two WLTS $\mathcal{S} \stackrel{\Delta}{=} (\mathcal{Q}, \mathcal{L}, \rightarrow, w, \mathcal{I}, \pi_0)$ and $\mathcal{S}^\sharp \stackrel{\Delta}{=} (\mathcal{Q}^\sharp, \mathcal{L}^\sharp, \rightsquigarrow, w^\sharp, \mathcal{I}^\sharp, \pi_0^\sharp)$,
- two abstraction functions $\beta^{\mathcal{Q}} : \mathcal{Q} \rightarrow \mathcal{Q}^\sharp$ and $\beta^{\mathcal{L}} : \mathcal{L} \rightarrow \mathcal{L}^\sharp$,

$\mathcal{S}^\sharp$ is a sound abstraction of $\mathcal{S}$, if and only if, for any cylinder set τ of traces of $\mathcal{S}$, we have:

$$\mathcal{P}r(\beta^{\mathbb{T}}(\tau)) = \sum_{\tau'} (\mathcal{P}r(\tau') \mid \beta^{\mathbb{T}}(\tau) = \beta^{\mathbb{T}}(\tau')),$$

where,

$$\beta^{\mathbb{T}}(q_0 \stackrel{\lambda_1, I_1}{\longrightarrow} q_1 \ldots q_{k-1} \stackrel{\lambda_k, I_k}{\longrightarrow} q_k)$$
$$\stackrel{\Delta}{=} \beta^{\mathcal{Q}}(q_0) \stackrel{\beta^{\mathcal{L}}(\lambda_1), I_1}{\longrightarrow} \beta^{\mathcal{Q}}(q_1) \ldots \beta^{\mathcal{Q}}(q_{k-1}) \stackrel{\beta^{\mathcal{L}}(\lambda_k), I_k}{\longrightarrow} \beta^{\mathcal{Q}}(q_k).$$

Completeness

Given:

- two WLTS $\mathcal{S} \triangleq (\mathcal{Q}, \mathcal{L}, \rightarrow, w, \mathcal{I}, \pi_0)$ and $\mathcal{S}^\sharp \triangleq (\mathcal{Q}^\sharp, \mathcal{L}^\sharp, \rightsquigarrow, w^\sharp, \mathcal{I}^\sharp, \pi_0^\sharp)$,
- two abstraction functions $\beta^{\mathcal{Q}} : \mathcal{Q} \rightarrow \mathcal{Q}^\sharp$ and $\beta^{\mathcal{L}} : \mathcal{L} \rightarrow \mathcal{L}^\sharp$,
- a concretization function $\gamma^{\mathcal{Q}} : \mathcal{Q} \rightarrow \mathbb{R}^+$,

$\mathcal{S}^\sharp$ is a sound and complete abstraction of $\mathcal{S}$, if and only if,

1. it is a sound abstraction;
2. for any cylinder set $\tau^\sharp$ of abstract traces of $\mathcal{S}^\sharp$ which ends in the abstract state $q_k^\sharp$, we have:

$$\gamma^{\mathcal{Q}}(s) = \mathcal{P}r(q_k = s \mid \tau \text{ such that } \beta^{\mathbb{T}}(\tau) \in \tau^\sharp) \times \sum \{\gamma^{\mathcal{Q}}(s') \mid \beta^{\mathcal{Q}}(s') = q_k^\sharp\}.$$

Overview

Markovian Property

We consider a stochastic process:

- $\mathbb{T} = \mathbb{R}_0^+$: time range;
- $\mathcal{Q}$: a countable set of states;
- $(\mathcal{X}_t)_{t\in\mathbb{T}}$: a family of random variables over $\mathcal{Q}$;

We say that $(\mathcal{X}_t)$ satisfies the Markovian property,
if, for any family $(s_t)_{t\in\mathbb{T}}$ of states indexed over $\mathbb{T}$, and any time $t_1 < t_2$,
we have:

$$\mathcal{P}r(X_{t_2} = s_{t_2} \mid X_{t_1} = s_{t_1}) = \mathcal{P}r(X_{t_2} = s_{t_2} \mid X_t = s_t, \forall t < t_1).$$

Lumpability property

Given:

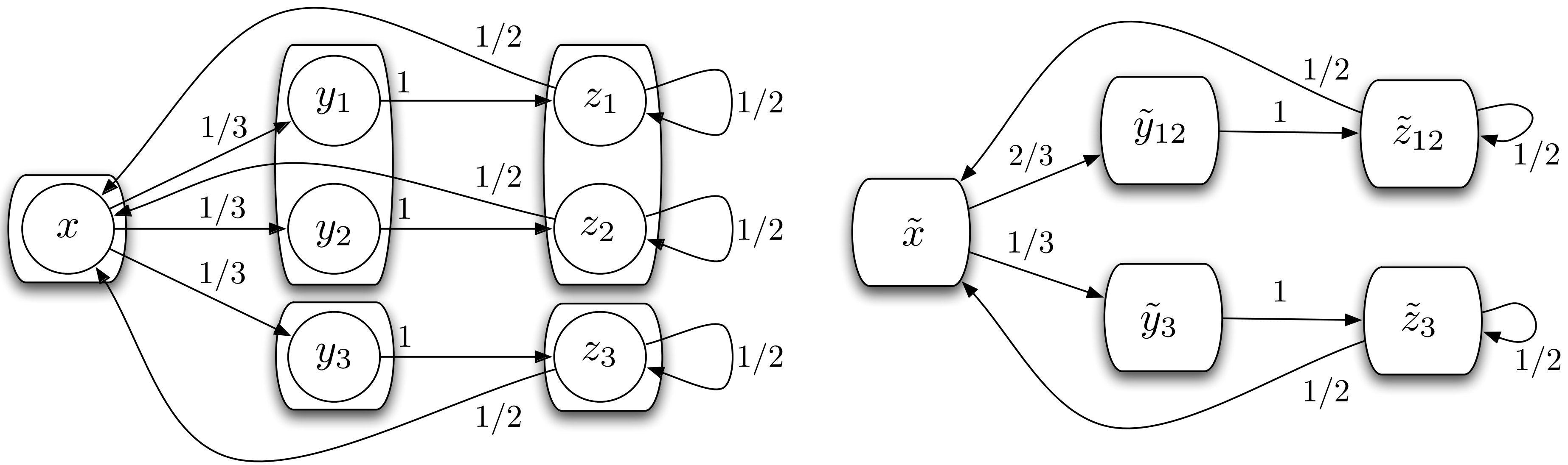
- a stochastic process $(\mathcal{X}_t)$ which satisfies the Markovian property,
- an initial distribution $\pi_0 \; : \; \mathcal{Q} \to [0, 1]$,
- an equivalence relation $\sim$ over $\mathcal{Q}$,

we define the lumped process $(\mathcal{Y}_t)$ on the state space $\mathcal{Q}_{/\sim}$ as:

$$\mathcal{P}r(\mathcal{Y}_t = [x_t]_{/\sim} \mid \mathcal{Y}_0 = [s_0]_{/\sim}) \stackrel{\Delta}{=} \mathcal{P}r(\mathcal{X}_t \in [s_t]_{/\sim} \mid \mathcal{X}_0 \in [s_0]_{/\sim}).$$

We say that $(\mathcal{X})_t$ is $\sim$-lumpable with respect to π_0 if and only if, the stochastic process $(\mathcal{Y}_t)$ satisfies the Markovian property as well.

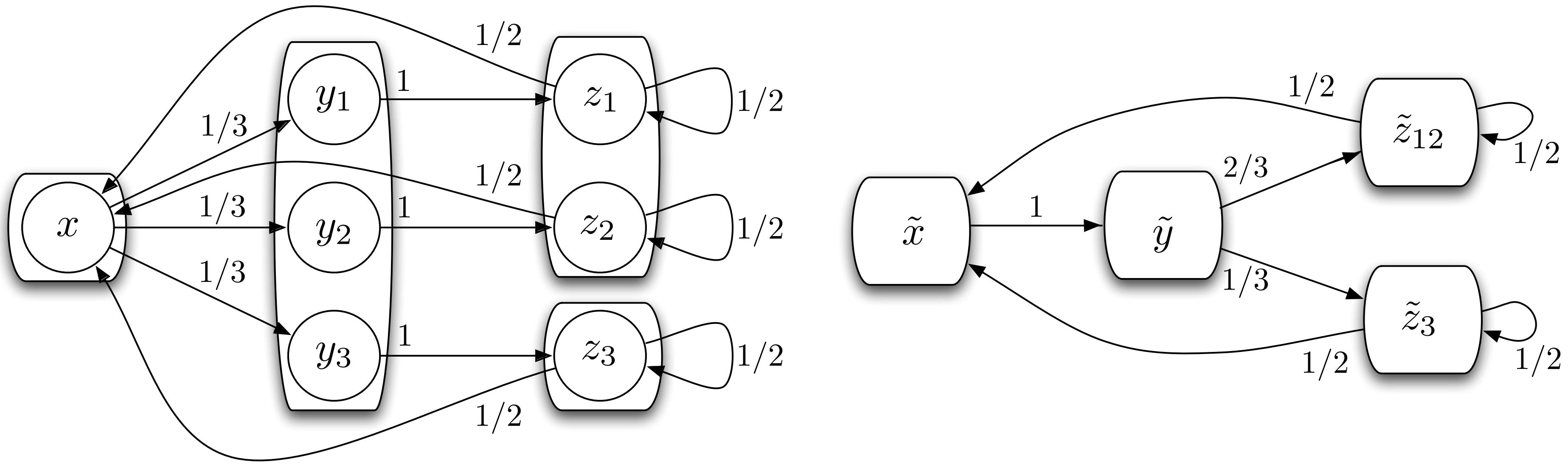
Strong lumpability



A stochastic process is $\sim$-strongly lumpable, if:

it is $\sim$-lumpable with respect to any initial distribution.

Weak lumpability



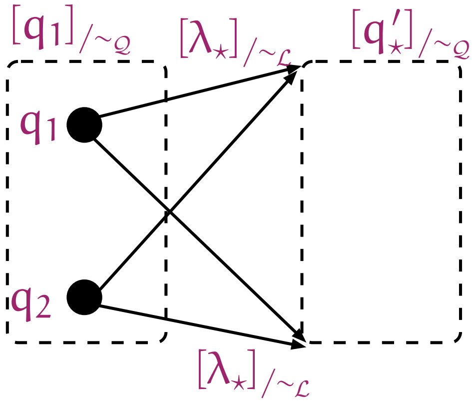
A stochastic process $(\mathcal{X}_t)$ is $\sim$-weakly lumpable, if:
there exists an initial distribution with respect to which $(\mathcal{X}_t)$ is $\sim$-lumpable.

Overview

Forward bisimulation

Let $\sim_{\mathcal{Q}}$ be an equivalence relation over $\mathcal{Q}$ and $\sim_{\mathcal{L}}$ be an equivalence relation over $\mathcal{L}$.

We say that $(\sim_{\mathcal{Q}}, \sim_{\mathcal{L}})$ is a forward bisimulation, if and only if, for any $q_1, q_2 \in \mathcal{Q}$ such that $q_1 \sim_{\mathcal{Q}} q_2$:

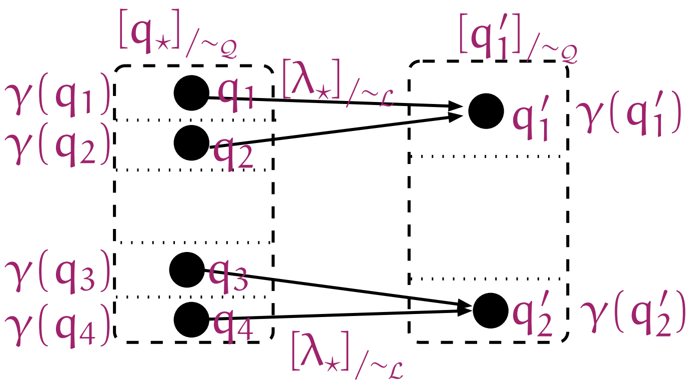


- $a(q_1) = a(q_2)$;
- and for any $\lambda_\star \in \mathcal{L}$, $q'_\star \in \mathcal{Q}$, $\mathsf{fwd}(q_1, [\lambda_\star]_{/\sim_{\mathcal{L}}}, [q'_\star]_{/\sim_{\mathcal{Q}}}) = \mathsf{fwd}(q_2, [\lambda_\star]_{/\sim_{\mathcal{L}}}, [q'_\star]_{/\sim_{\mathcal{Q}}})$

where: $\mathsf{fwd}(q, [\lambda_\star]_{/\sim_{\mathcal{L}}}, [q'_\star]_{/\sim_{\mathcal{Q}}}) = \sum_{\lambda', q'} (w(q, \lambda', q') \mid \lambda' \sim_{\mathcal{L}} \lambda_\star,\ q' \sim_{\mathcal{Q}} q'_\star)$.

Backward bisimulation

Let $\sim_{\mathcal{Q}}$ be an equivalence relation over $\mathcal{Q}$ and $\sim_{\mathcal{L}}$ be an equivalence relation over $\mathcal{L}$.



We say that $(\sim_{\mathcal{Q}}, \sim_{\mathcal{L}})$ is a backward bisimulation, if and only if, there exists $\gamma : \mathcal{Q} \to \mathbb{R}^+$, such that: for any $q'_1, q'_2 \in \mathcal{Q}$ which satisfies $q'_1 \sim_{\mathcal{Q}} q'_2$:

- $a(q'_1) = a(q'_2)$;
- and for any $\lambda_\star \in \mathcal{L}$, $q_\star \in \mathcal{Q}$,
  $\text{bwd}([q_\star]_{/\sim_{\mathcal{Q}}}, [\lambda_\star]_{\sim/\mathcal{L}}, q'_1) = \text{bwd}([q_\star]_{/\sim_{\mathcal{Q}}}, [\lambda_\star]_{\sim/\mathcal{L}}, q'_2)$

where: $\text{bwd}([q_\star]_{/\sim_{\mathcal{Q}}}, [\lambda_\star]_{\sim/\mathcal{L}}, q') = \sum_{q,\lambda'} \left(\frac{\gamma(q)}{\gamma(q')} w(q, \lambda', q') \,|\, q \sim_{\mathcal{Q}} q_\star, \lambda' \sim_{\mathcal{L}} \lambda_\star \right)$.

Logical implications

- if $(\sim_{\mathcal{Q}}, \sim_{\mathcal{L}})$ is a forward bisimulation, then the process is $\sim_{\mathcal{Q}}$-strongly lumpable,

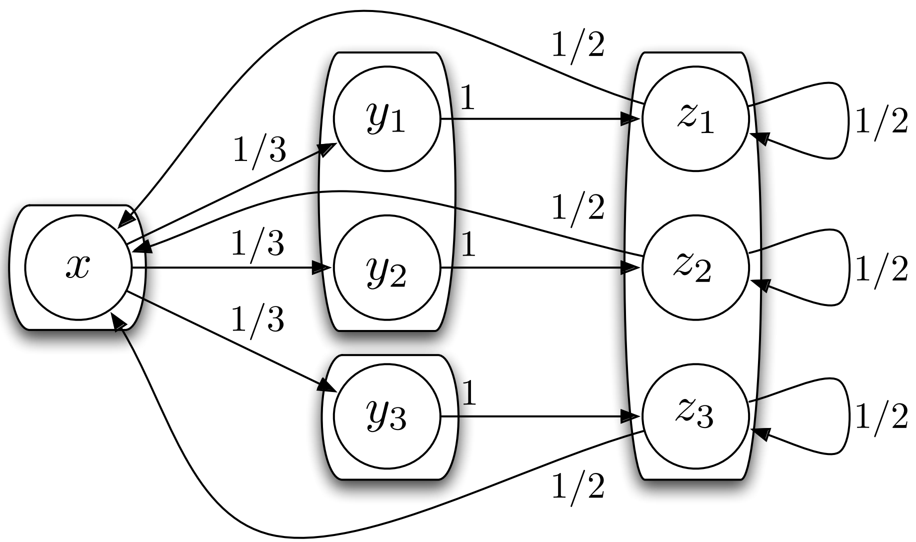
  moreover, it induces a sound abstraction;
- if $(\sim_{\mathcal{Q}}, \sim_{\mathcal{L}})$ is a backward bisimulation, then the process is $\sim_{\mathcal{Q}}$-weakly lumpable, for the initial distributions which satisfy:

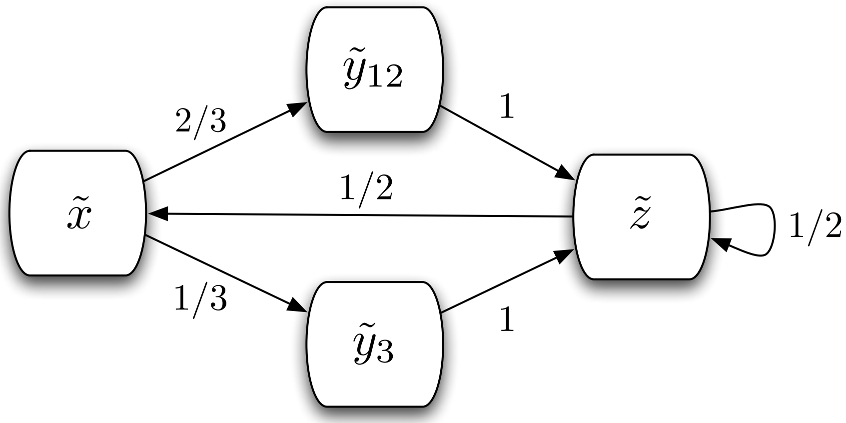
  $$q \sim_{\mathcal{Q}} q' \Rightarrow [\pi_0(q) \cdot \gamma(q') = \pi_0(q') \cdot \gamma(q)];$$

  it induces a sound and complete abstraction for these initial distributions;
- there exist forward bisimulations which are not backward bisimulations;
- there exist backward bisimulations which are not forward bisimulations.

Counter-example I

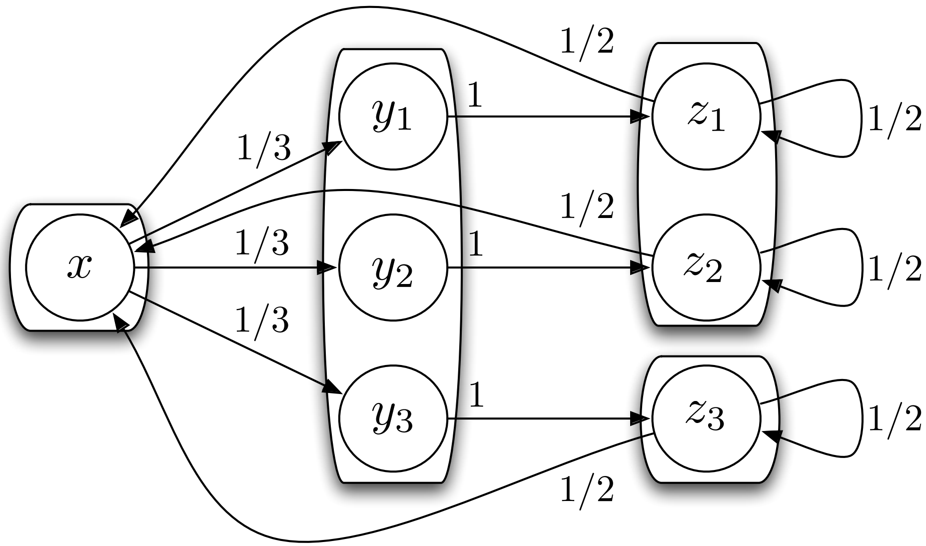
A forward bisimulation which is not a backward bisimulation:

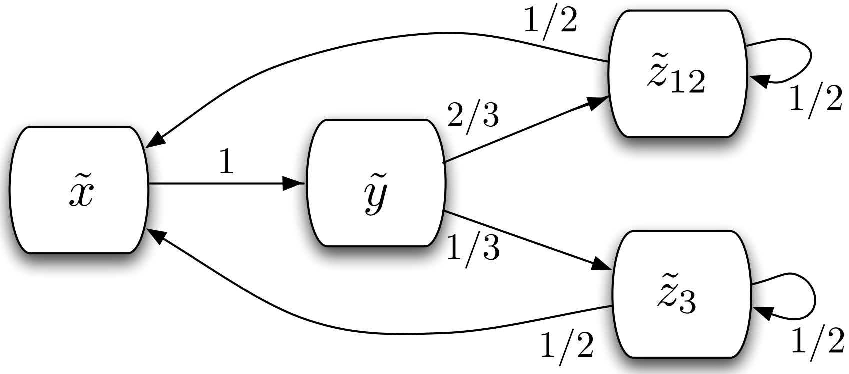




Counter-example II

A backward bisimulation which is not a forward bisimulation:





Uniform backward bisimulation

Given $q_\star, q' \in \mathcal{Q}$ and $\lambda_\star \in \mathcal{L}$, we denote:

$$\mathsf{pred}([q_\star]_{/\sim_{\mathcal{Q}}}, [\lambda_\star]_{\sim_{/\mathcal{L}}}, q') \stackrel{\Delta}{=} \{(q,\lambda) \mid w(q,\lambda,q') > 0, q \sim_{\mathcal{Q}} q_\star,\ \lambda \sim_{\mathcal{L}} \lambda_\star\}.$$

If,

- $q_1 \sim_{\mathcal{Q}} q_2 \implies a(q_1) = a(q_2)$;
- for any $q_1', q_2' \in \mathcal{Q}$, such that $q_1' \sim_{\mathcal{Q}} q_2'$, and any $q_\star \in \mathcal{Q}$ and $\lambda_\star \in \mathcal{L}$, there is a 1-to-1 mapping between $\mathsf{pred}([q_\star]_{/\sim_{\mathcal{Q}}}, [\lambda_\star]_{\sim_{/\mathcal{L}}}, q_1')$ and $\mathsf{pred}([q_\star]_{/\sim_{\mathcal{Q}}}, [\lambda_\star]_{\sim_{/\mathcal{L}}}, q_2')$ which is compatible with w,

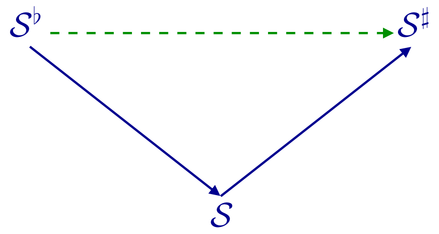
then:

- $(\sim_{\mathcal{Q}}, \sim_{\mathcal{L}})$ is a backward bisimulation (with $\gamma(q) = 1,\ \forall q \in \mathcal{Q}$).

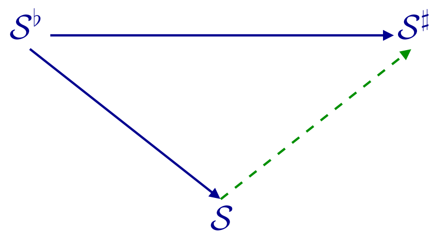
Abstraction algebra

(Sound/Complete) abstractions can be:

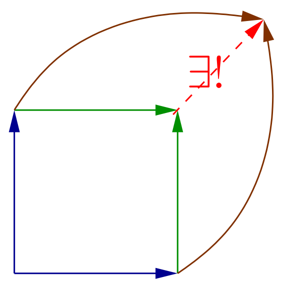
- composed:



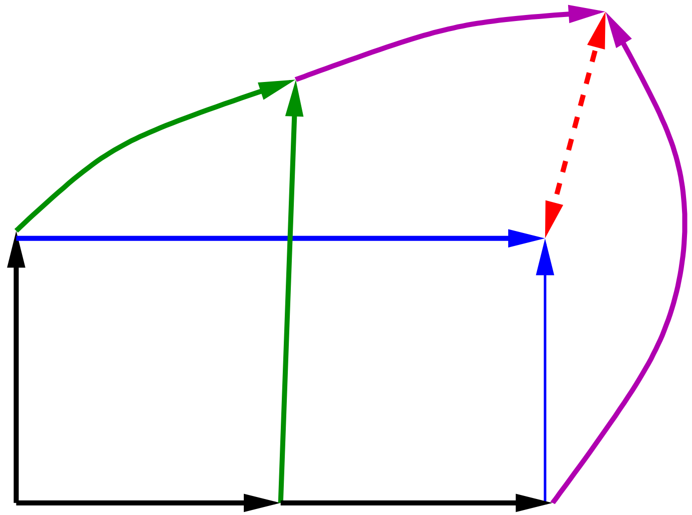
- factored:



- combined with a symmetric product (c.f. lub or pushout):



Compatibility between composition and pushout



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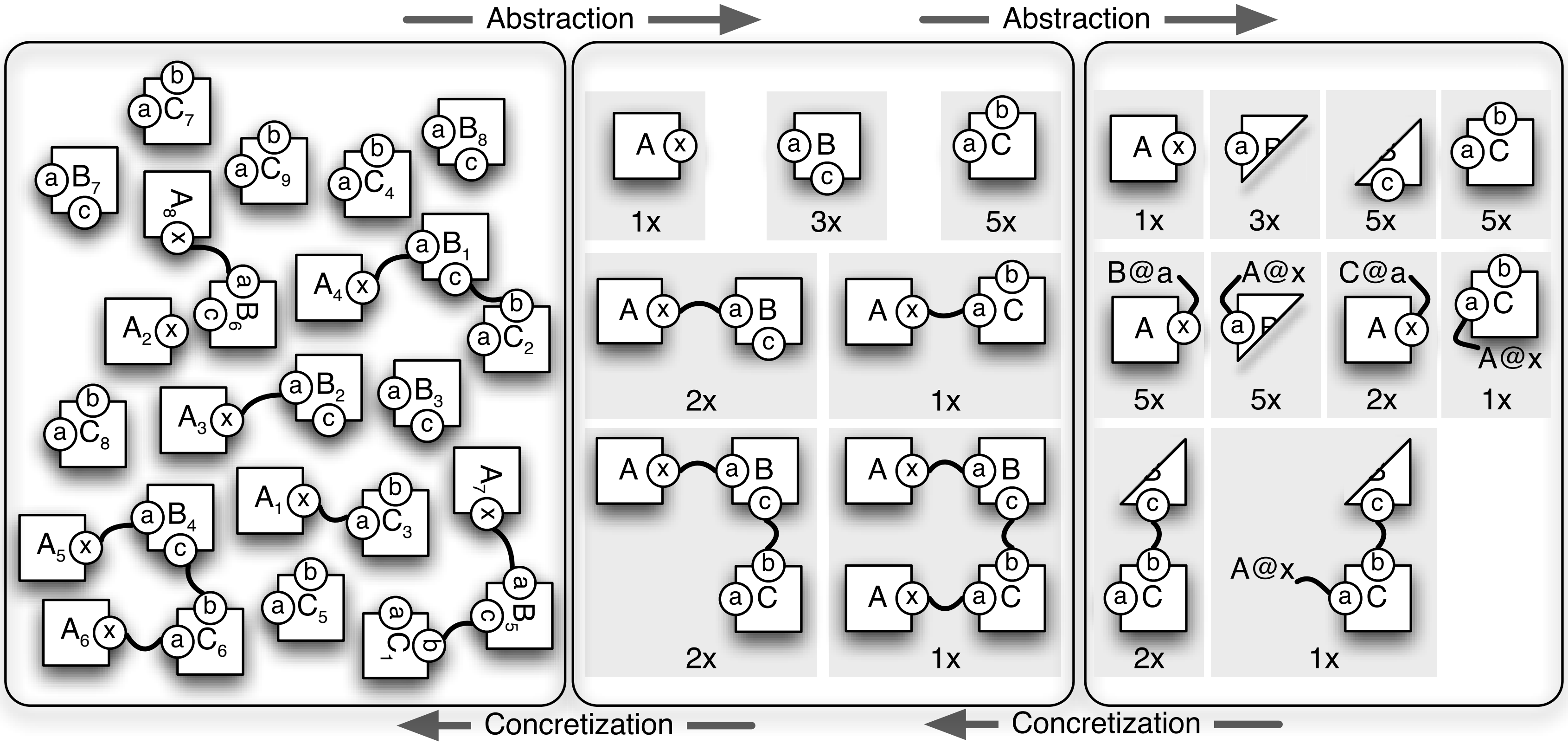

Abstraction
Abstraction
Concretization
Concretization
1x
3x
5x
2x
1x
2x
1x
1x
3x
5x
5x
B@a
A@x
C@a
A@x
5x
5x
2x
1x
A@x
2x
1x

From individuals to population

- Individual semantics:

  In the individual semantics, each agent is tagged with a unique identifier which can be tracked along the trace;

- Population semantics:

  In the population semantics, the state of the system is seen up to injective substitution of agent identifier;

  equivalently, the state of the system is a multi-set of chemical species.

Fragments

An annotated contact map is valid with respect to the stochastic semantics, if:

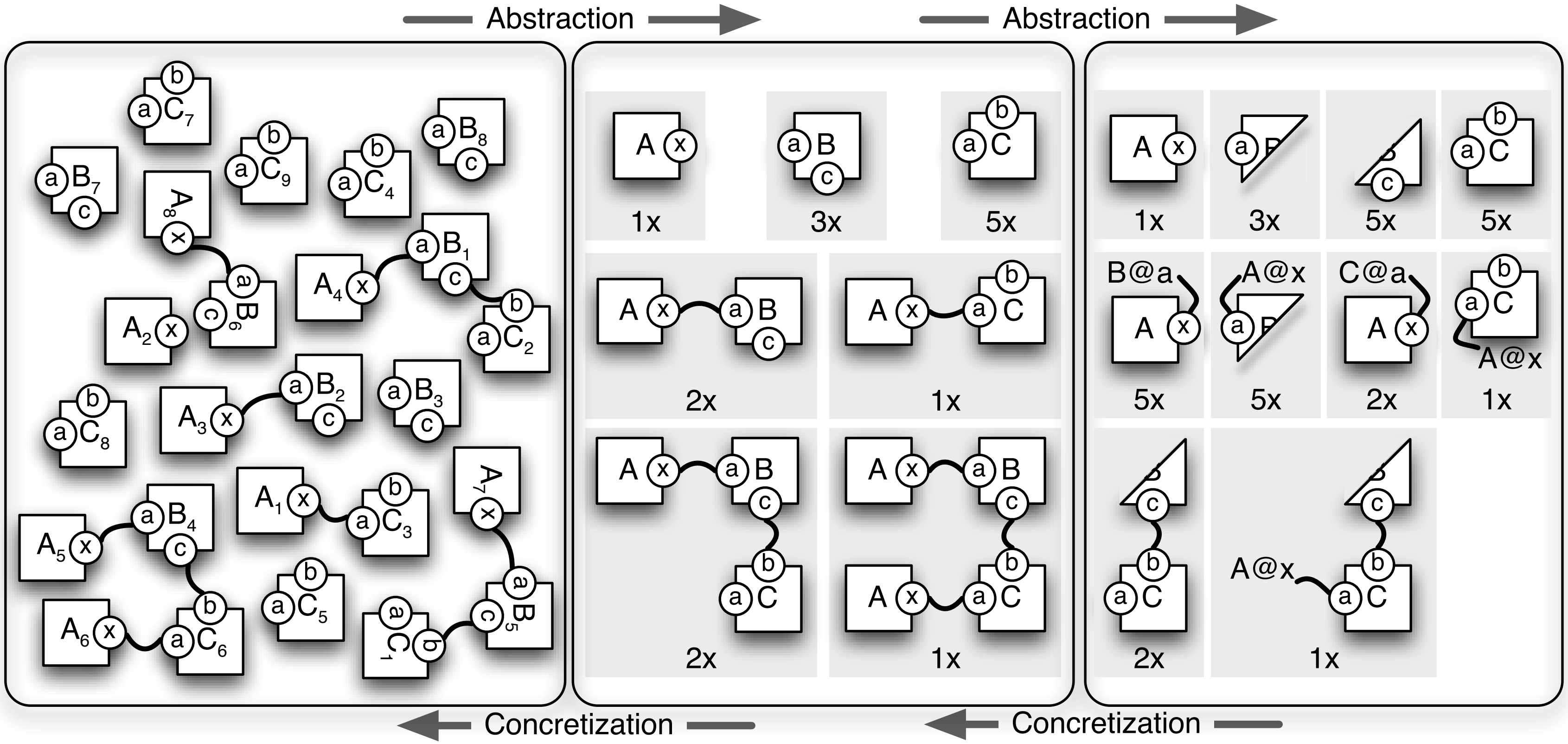
- Whenever the site *x* and *y* both occurs in the same or in distinct agent of type *A* in a rule, then, there should be a bidirectional edge between the site *x* and the *y* of *A*.
- Whenever there is a bond between two sites, each of which either carries an internal state of, is connected to some other sites of its agent, then the bond if oriented in both directions.

From population to fragments

- Population of fragments:

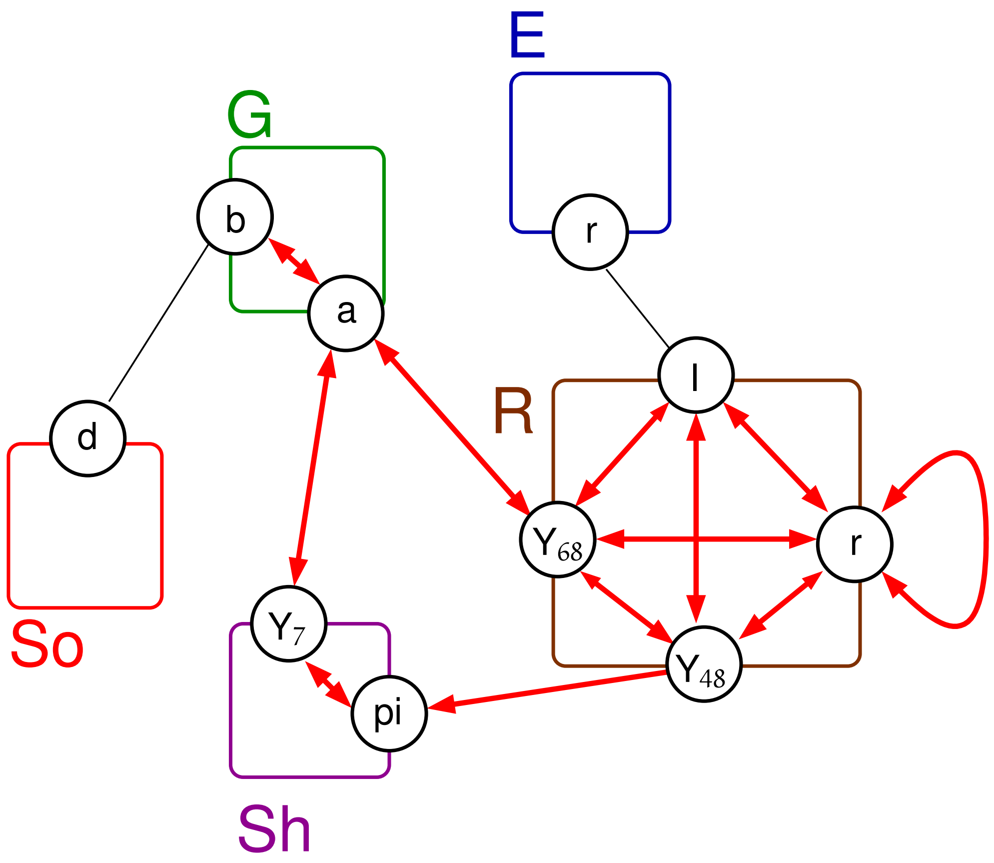
  1. In the annotated contact, each agent is fitted with a binary equivalence over its sites. We split the interface of agents into equivalence classes of sites. Then we abstract away which subagents belong to the same agent.

  2. Whenever an edge is not oriented in the annotated contact map, we cut each instance of this bond into two half bonds, and abstract away which partners are bond together.



Abstraction
Abstraction
1x
3x
5x
2x
1x
2x
1x
1x
3x
5x
5x
B@a
A@x
C@a
A@x
5x
5x
2x
1x
A@x
2x
1x
Concretization
Concretization

Example



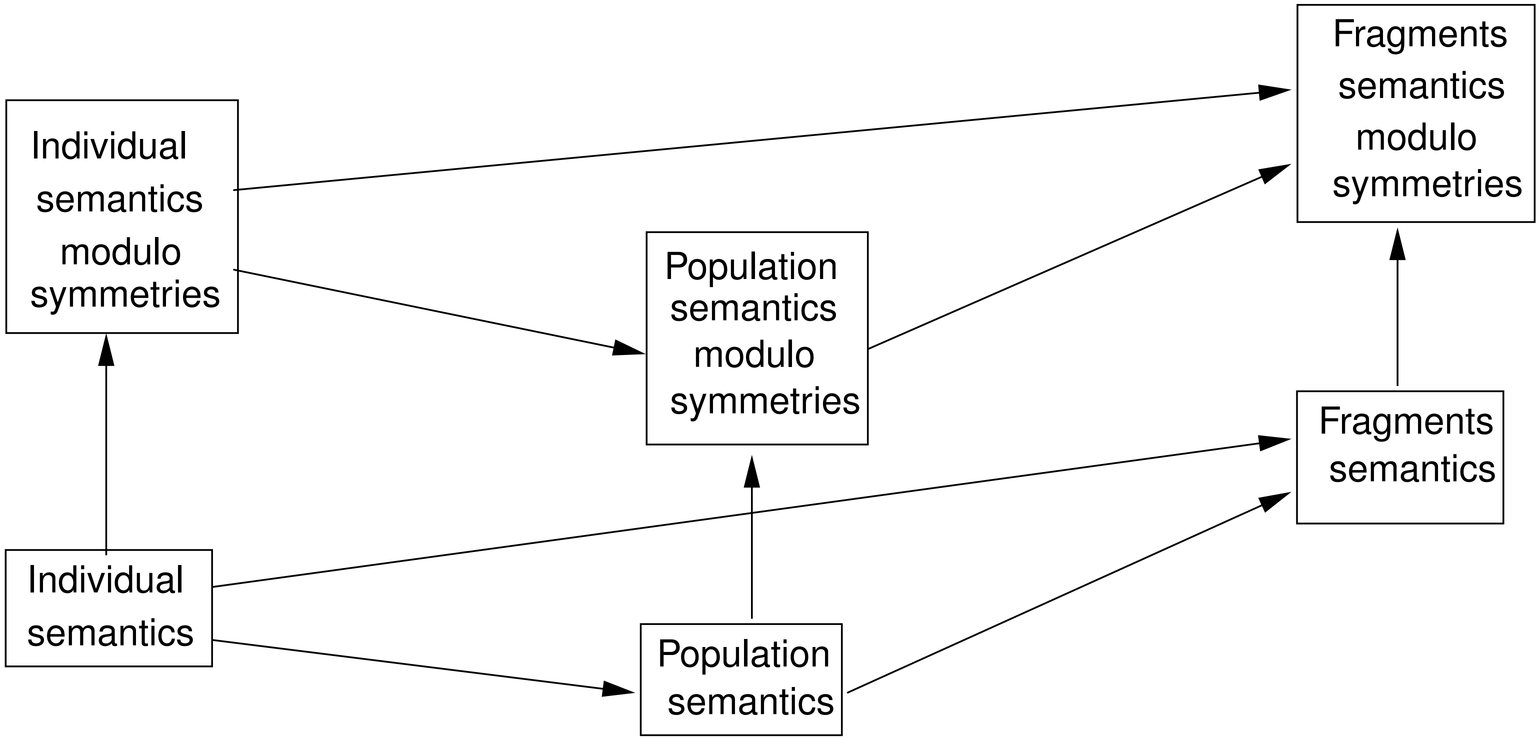
Symmetries among sites

Let $\mathcal{R}$ be a set of rules and $\mathcal{M}_0$ be an initial mixture.

Two sites x_1 and x_2 are symmetric in the agent A in the set of rules $\mathcal{R}$ and the initial mixture $\mathcal{M}_0$ whenever the following three properties are satisfied:

1. for each rule of the model, if we swap the site x_1 and the site x_2 in one instance of A in a rule of $\mathcal{R}$, we get a rule that is isomorphic to a rule in $\mathcal{R}$. (this rule may be the same, or a different one)
2. given two such symmetric rules, the quotient between the sum of the rates of the isomorphic rules and the product between the number of automorphisms in the left hand side, and the number of symmetric isomorphic rules, is the same.
3. each agent A in $\mathcal{M}_0$ has their sites x_1 and x_2 free, with the same internal state.

Hierarchy of semantics



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Conclusion

- A framework for reducing stochastic rule-based models.
  - We use:
    - the sites the state of which are uncorrelated;
    - the sites having the same capabilities of interactions.
  - Algebraic operators combine these abstractions.

- We use backward bisimulations in order to prove statistical invariants, we use them to reduce the dimension of the continuous-time Markov chains.

Future works

- Investigate the use of hybrid bisimulation.

- Propose approximated simulation algorithms to approximate different scale rate reactions.
  - hybrid systems,
  - tau-leaping,
  - …