MPRI

# Some notions of information flow

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# 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:

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

# Semantics

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

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

  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 pf $V_1$, which is written $V_1 \Rightarrow_P V_2$.

More formally,
$V_1 \Rightarrow_P V_2$ if and only if there exists $\rho \in \mathcal{V} \to \mathbb{Z}$, $z, z' \in \mathbb{Z}$ 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 $P$:

$$P ::= \text{if } (V_1 \geq 0) \; \{V_2 := 0\} \; \text{else} \; \{V_2 := 1\}$$

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 $V_1 \not\to^*{}_P V_2$.

# Syntactic approximation (tentative)

For each program points $p$ in $P$,
we denote by *test*$(p)$ the set of variables which occurs in the guard of the test and while loop 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 $\rho \in \mathcal{V} \to \mathbb{Z}$,
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 $V_1 \not\to_P^* V_2$.

# 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 atacker could observe:

- computation time;
- memory assumption;
- heating.

(attacks cannot be exhaustively specified).

Cours MPRI

# Formal model reduction

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# Joint-work with...

Walter Fontana
Harvard Medical School

Vincent Danos
Edinburgh

Ferdinanda Camporesi
Bologna / ÉNS

Russ Harmer
Paris VII

Jean Krivine
Paris VII

# Overview

1. Context and motivations
2. Handmade ODEs
3. Abstract interpretation framework
4. Kappa
5. Concrete semantics
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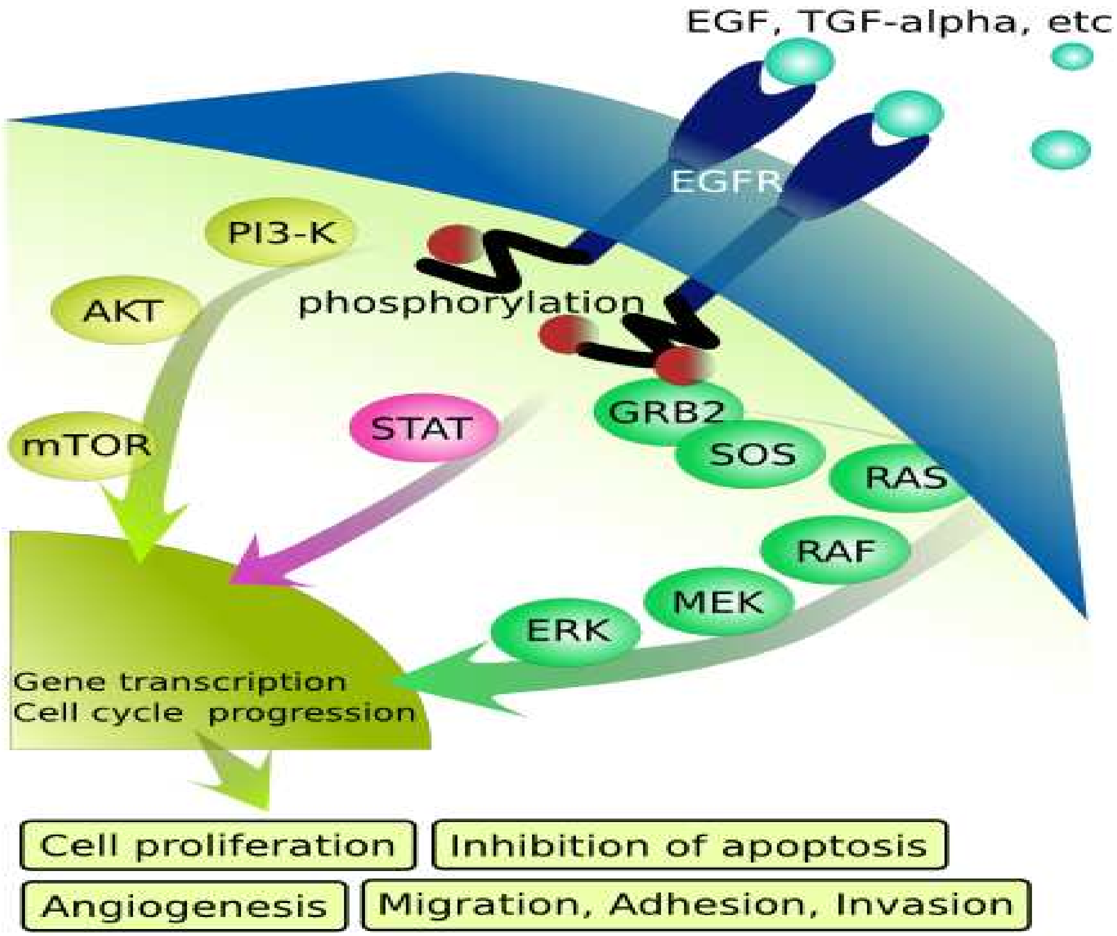
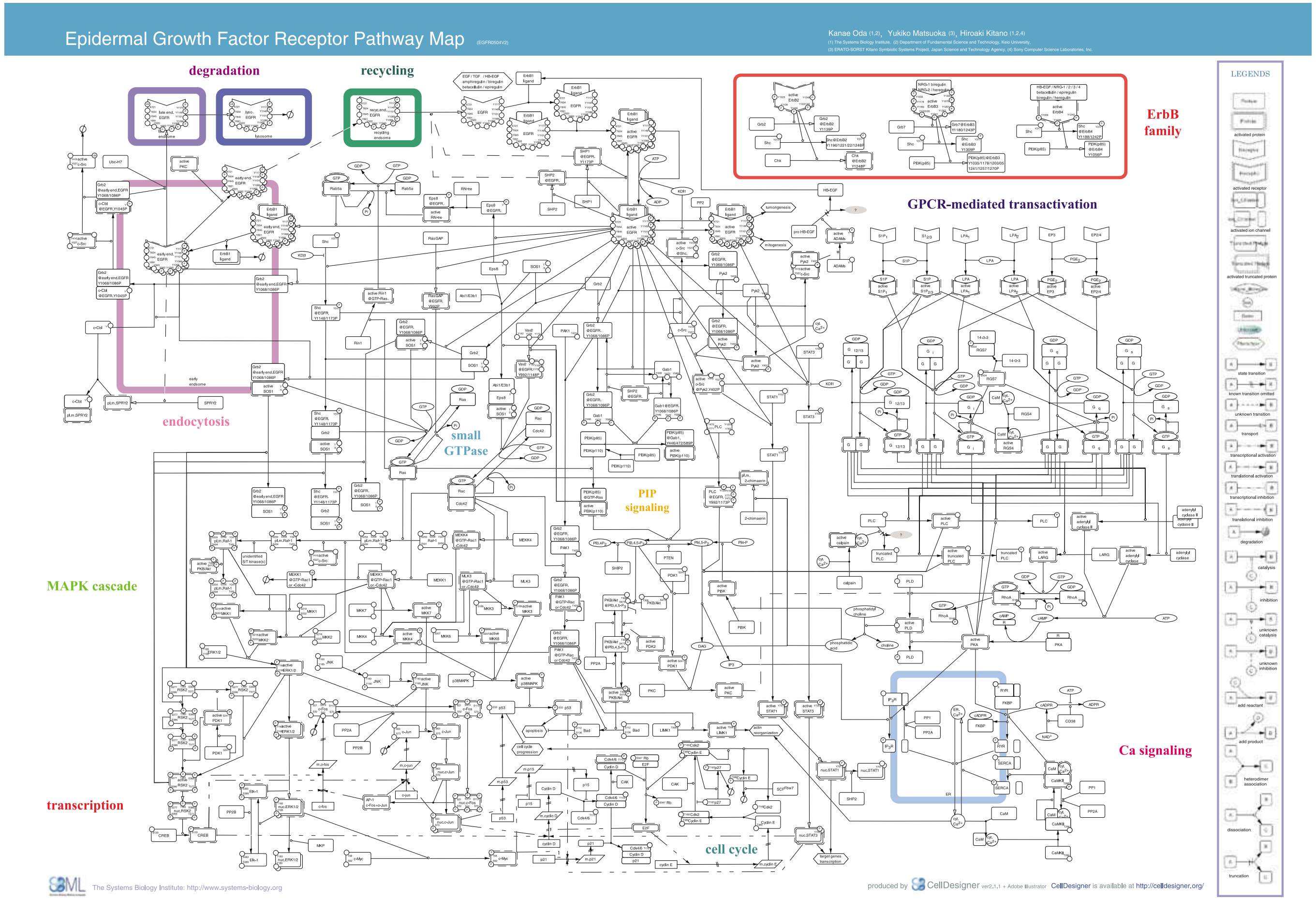
# Signalling Pathways




Eikuch, 2007

# Pathway maps




Oda, Matsuoka, Funahashi, Kitano, Molecular Systems Biology, 2005

# Differential models

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

– do not describe the structure of molecules;
– combinatorial explosion: forces choices that are not principled;
– a nightmare to modify.

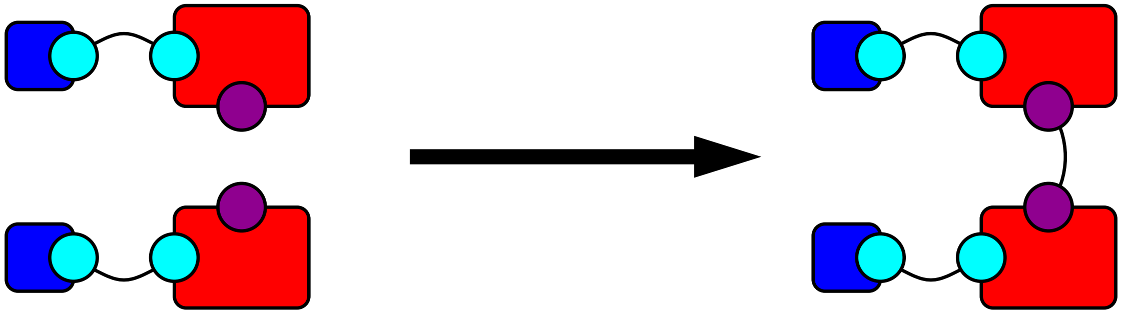
# A gap between two worlds

Two levels of description:

1. Databases of proteins interactions in natural language
   + documented and detailed description
   + transparent description
   – cannot be interpreted
2. ODE-based models
   + can be integrated
   – opaque modelling process, models can hardly be modified
   – there are also some scalability issues.

# Rule-based approach

We use site graph rewrite systems



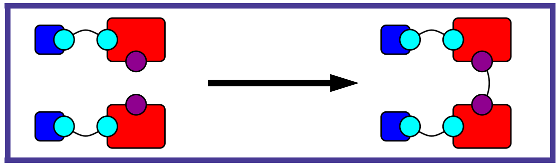
1. The description level matches with both
   - the observation level
   - and the intervention level

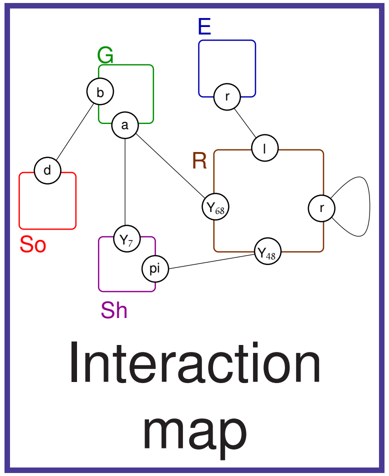
   of the biologist.

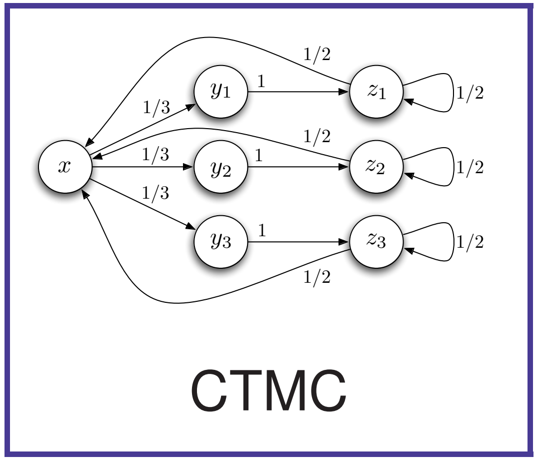
   We can tune the model easily.
2. Model description is very compact.

# Semantics

Several semantics (qualititative and/or quantitative) can be defined.



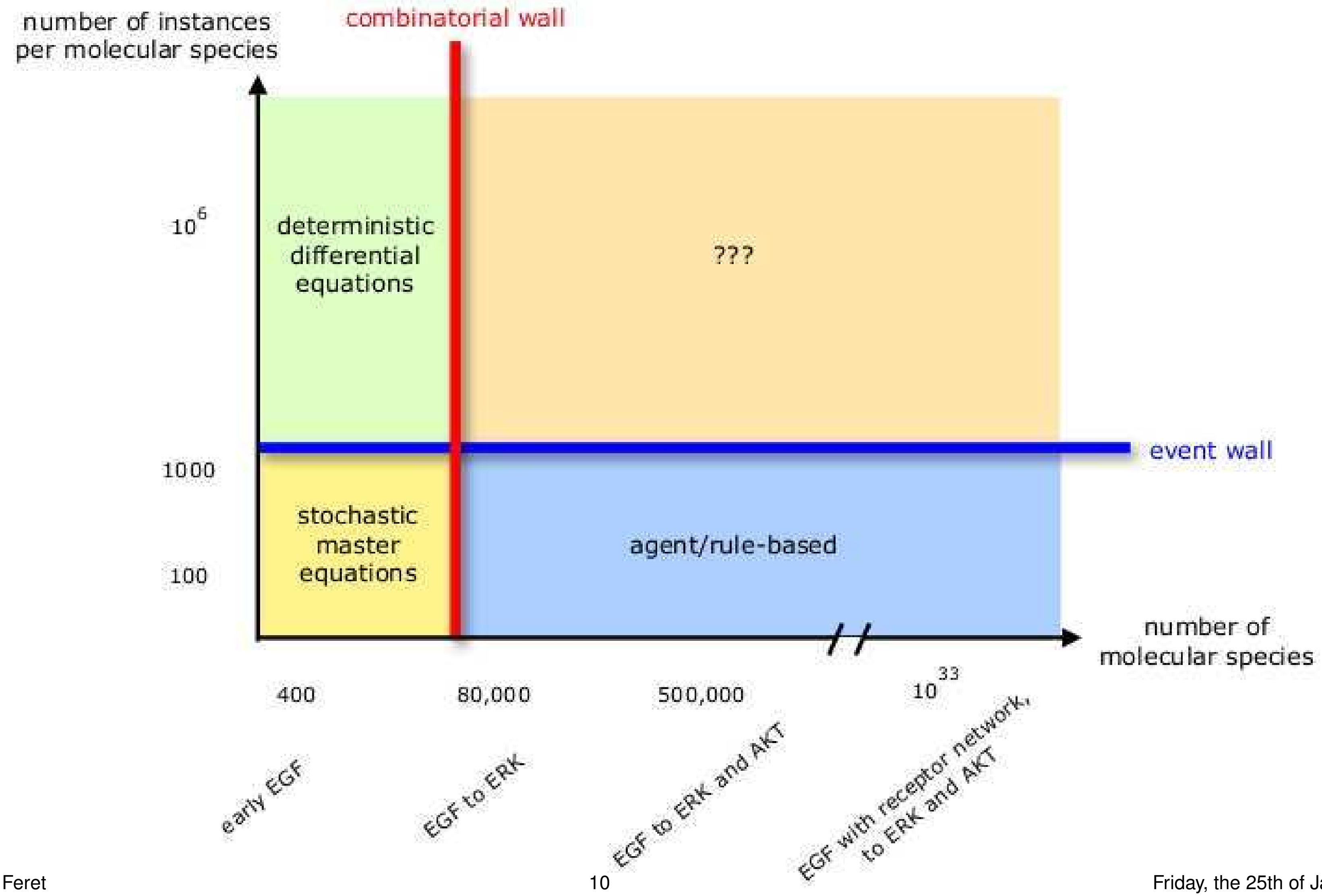


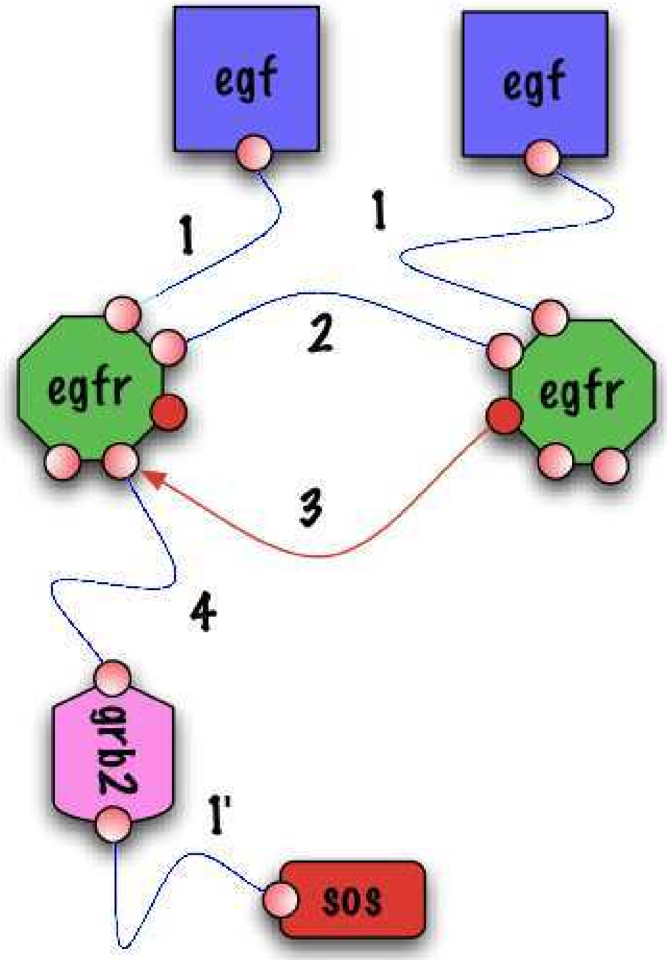

$$
\begin{cases}
\frac{dx_1}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
\frac{dx_2}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
\frac{dx_3}{dt} = k_1 \cdot x_1 \cdot x_2 - k_{-1} \cdot x_3 + 2 \cdot k_2 \cdot x_3 \cdot x_3 - k_{-2} \cdot x_4 \\
\frac{dx_4}{dt} = k_2 \cdot x_3^2 - k_2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

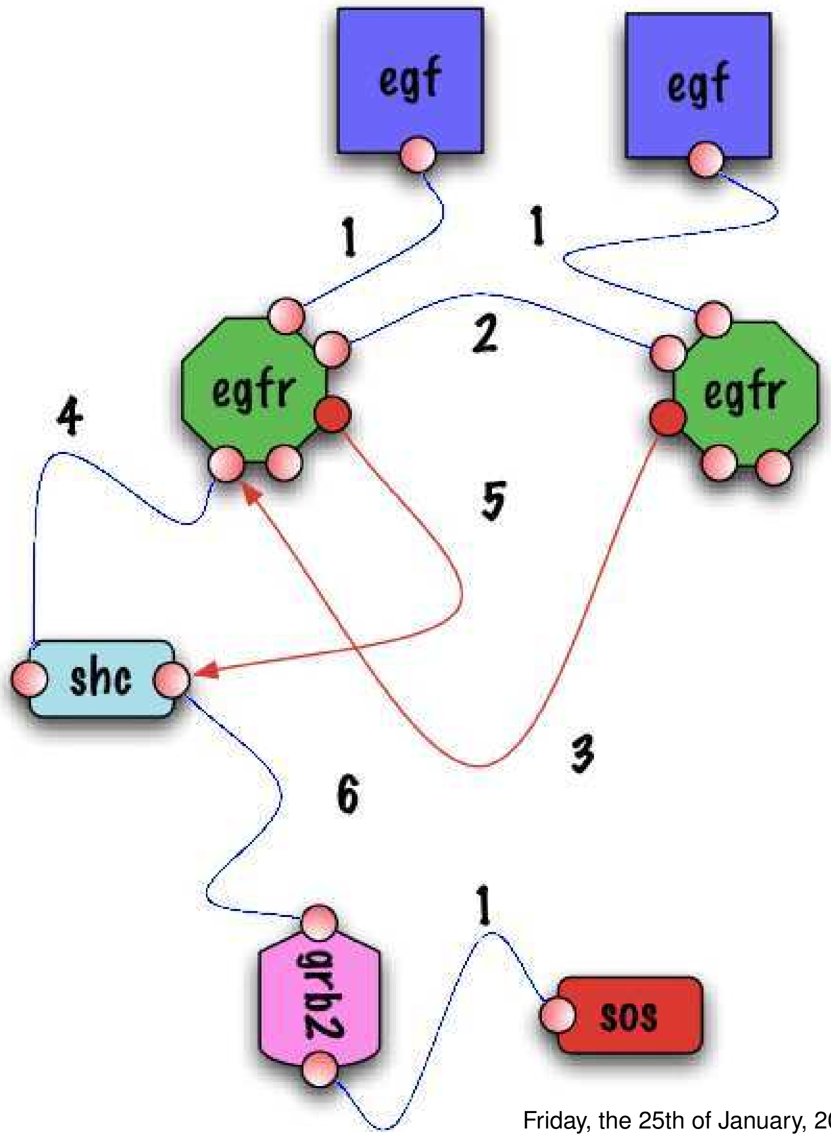
ODEs

# Complexity walls



# A breach in the wall(s) ?



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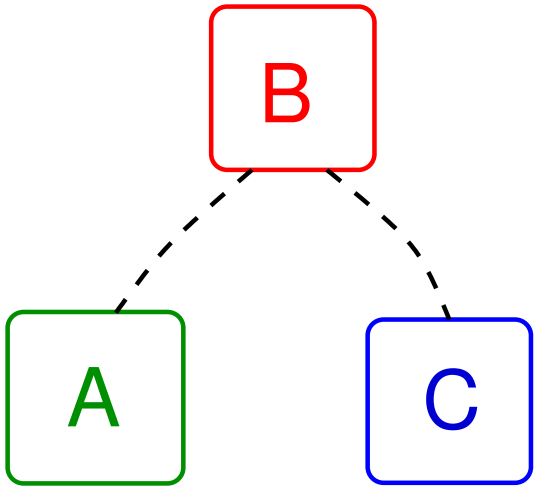
# A simple adapter



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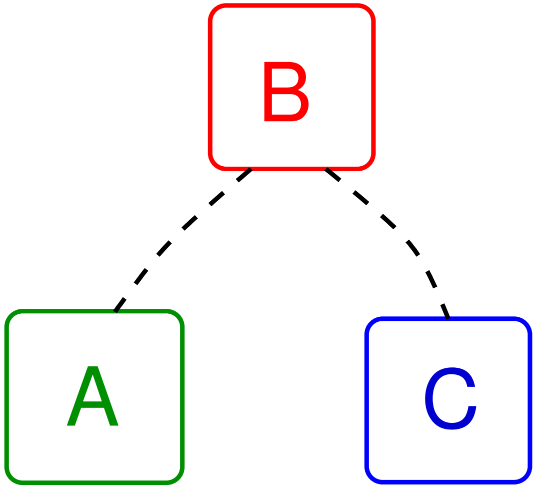


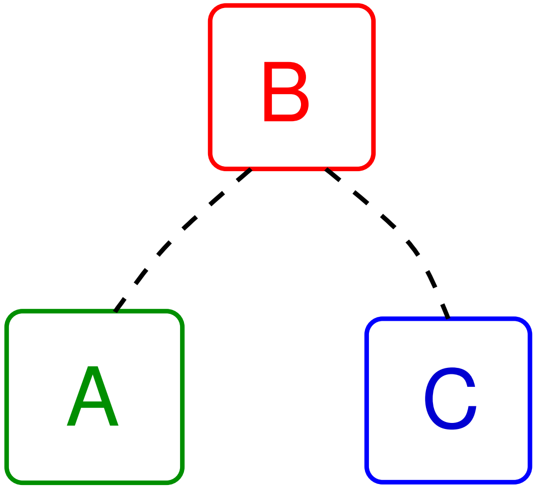

$$A\ ,\ \emptyset B \emptyset \longleftrightarrow AB\emptyset \qquad k^{AB}, k_d^{AB}$$

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

$$\emptyset B \emptyset\ ,\ C \longleftrightarrow \emptyset BC \qquad k^{BC}, k_d^{BC}$$

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

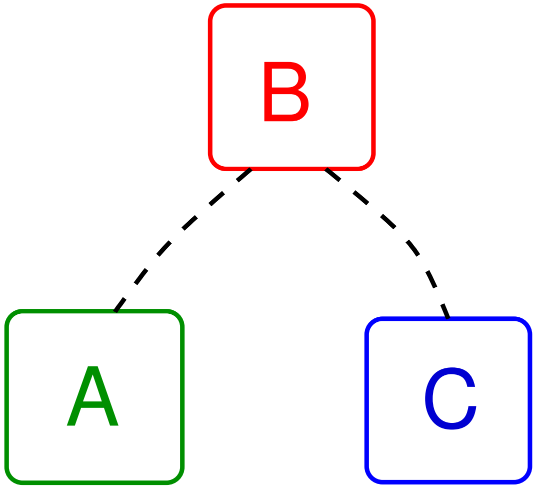
# A simple adapter




$$
\begin{array}{lcll}
A\ ,\ \emptyset B\emptyset & \longleftrightarrow & AB\emptyset & k^{AB},k_d^{AB} \\
A\ ,\ \emptyset BC & \longleftrightarrow & ABC & k^{AB},k_d^{AB} \\
\emptyset B\emptyset\ ,\ C & \longleftrightarrow & \emptyset BC & k^{BC},k_d^{BC} \\
AB\emptyset\ ,\ C & \longleftrightarrow & ABC & k^{BC},k_d^{BC}
\end{array}
$$

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

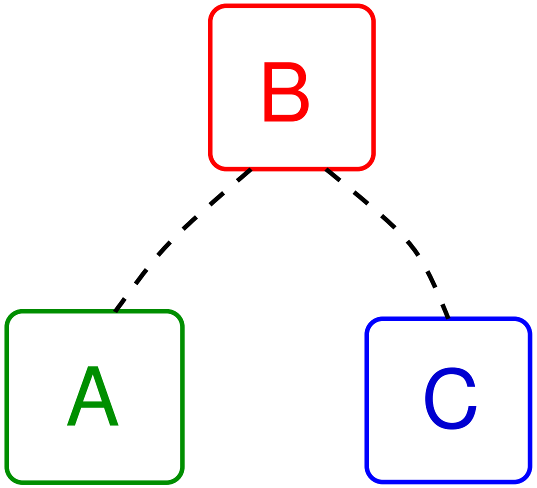
# A simple adapter




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

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

# Two subsystems



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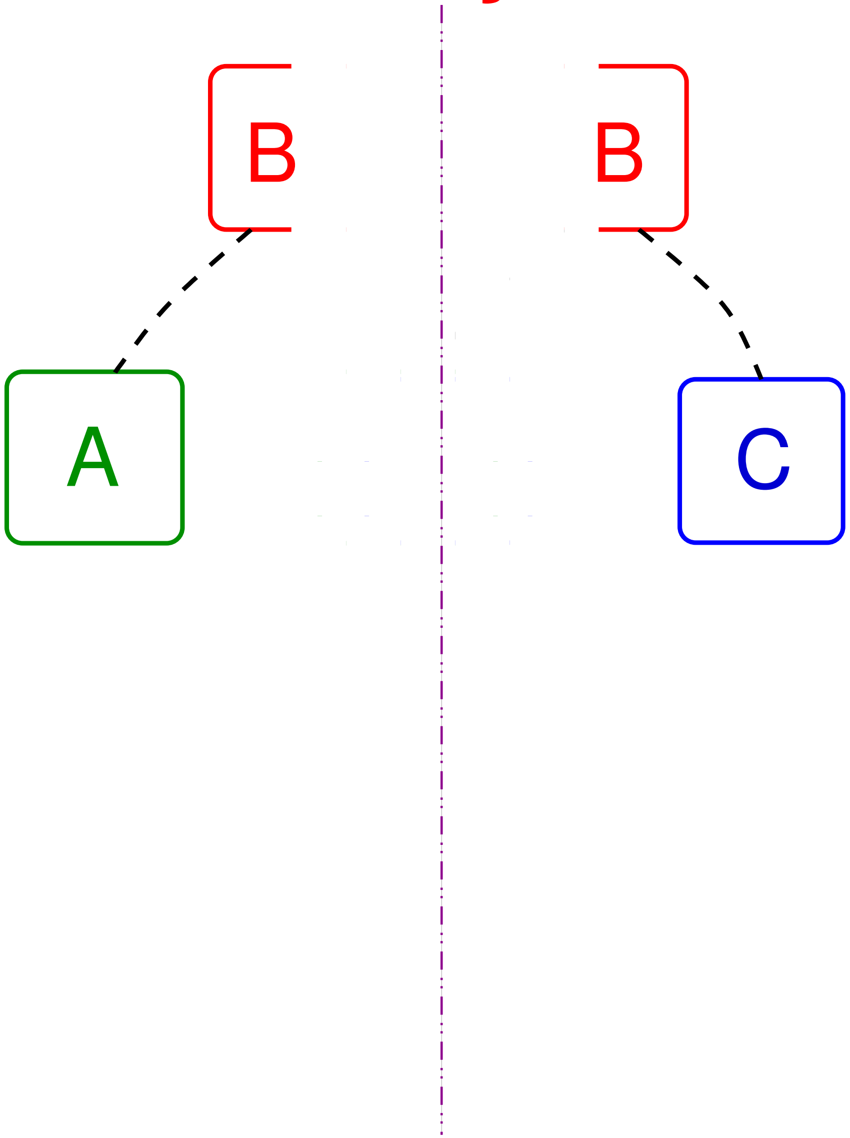

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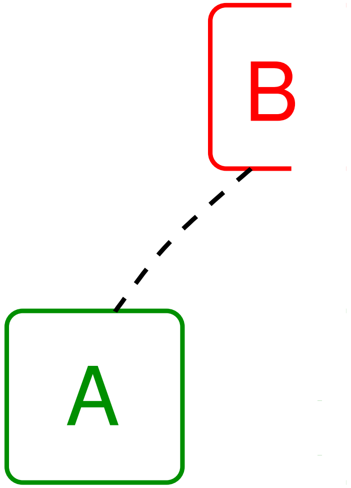


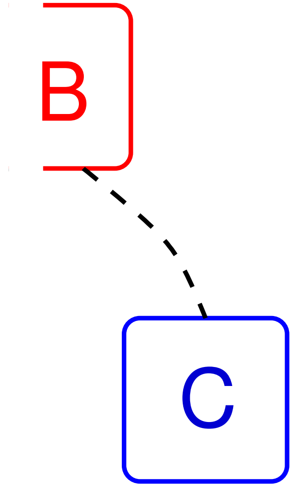


$$[A] = [A]$$
$$[AB?] \stackrel{\Delta}{=} [AB\emptyset] + [ABC]$$
$$[\emptyset B?] \stackrel{\Delta}{=} [\emptyset B\emptyset] + [\emptyset BC]$$

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

$$[C] = [C]$$
$$[?BC] \stackrel{\Delta}{=} [\emptyset BC] + [ABC]$$
$$[?B\emptyset] \stackrel{\Delta}{=} [\emptyset B\emptyset] + [AB\emptyset]$$

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

# 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 $t' \geq t$).

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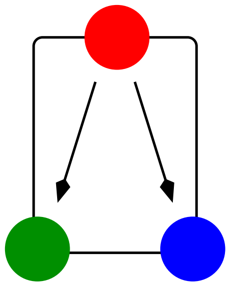
# A system with a switch



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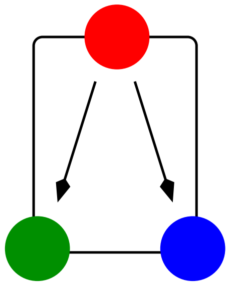
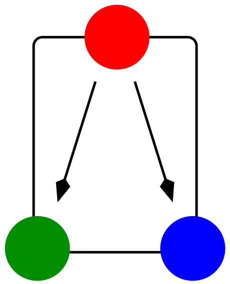


| | | | |
|---|---|---|---|
| (u,u,u) | $\longrightarrow$ | (u,p,u) | $k^c$ |
| (u,p,u) | $\longrightarrow$ | (p,p,u) | $k^l$ |
| (u,p,p) | $\longrightarrow$ | (p,p,p) | $k^l$ |
| (u,p,u) | $\longrightarrow$ | (u,p,p) | $k^r$ |
| (p,p,u) | $\longrightarrow$ | (p,p,p) | $k^r$ |

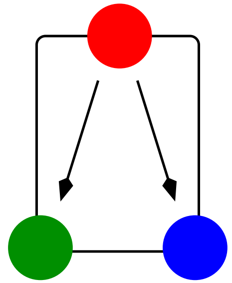
# A system with a switch



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

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

# Two subsystems



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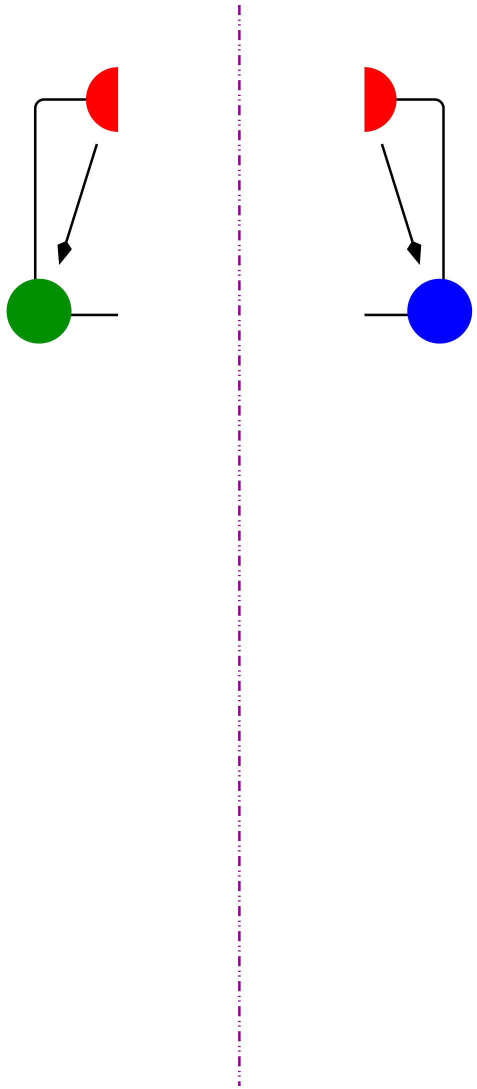

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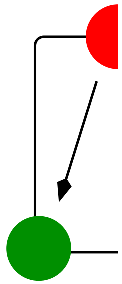
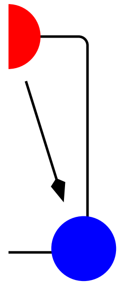




$$[(u,u,u)] = [(u,u,u)]$$

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

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

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

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

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

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

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

# 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:

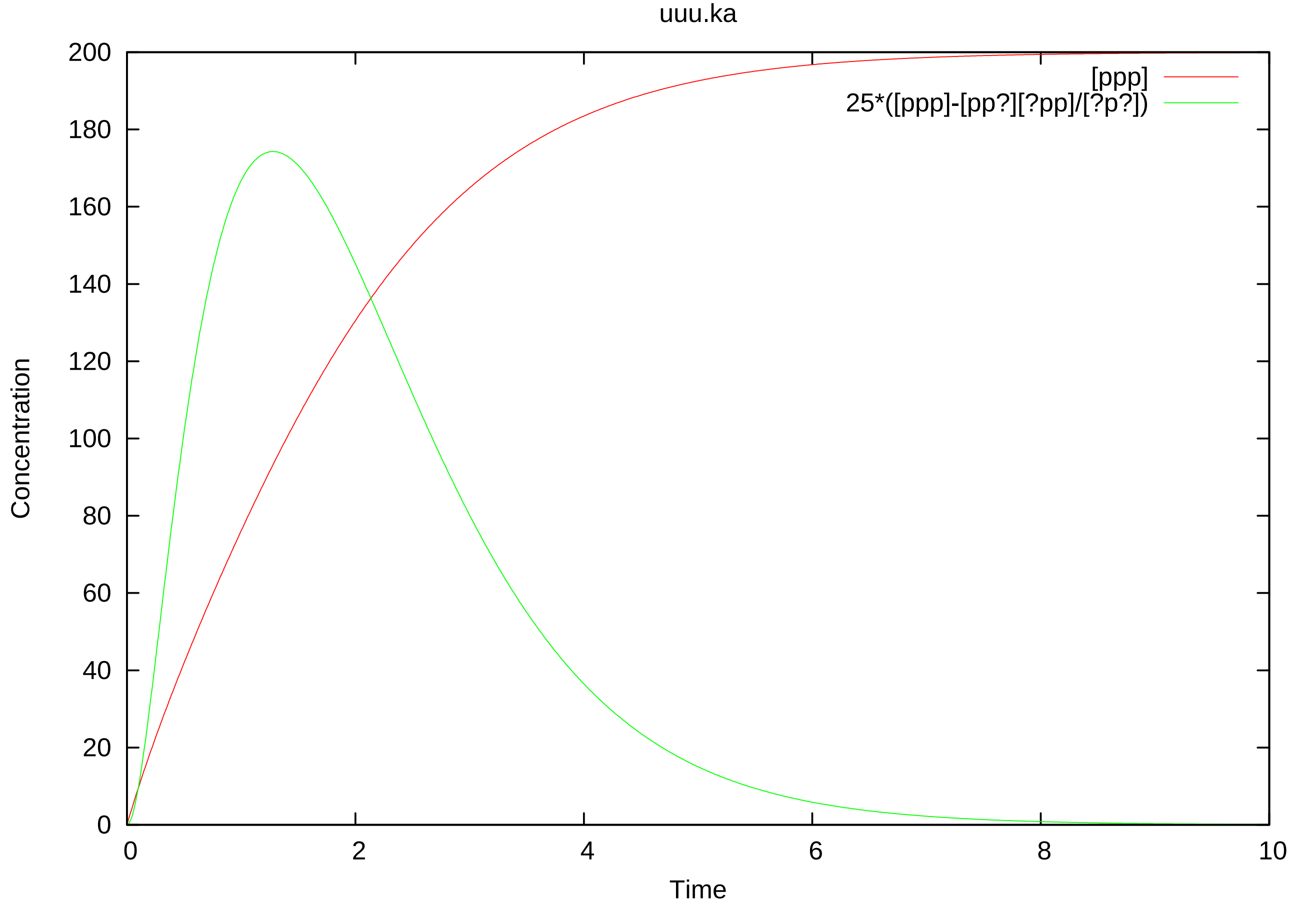
$$X \triangleq [(p,p,p)]\cdot([(?,p,u)] + [(?,p,p)]) - [(?,p,p)]\cdot[(p,p,?)].$$

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 ($[(u,u,u)](0) = 200$).

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

# 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.

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   (b) a system with a switch
   (c) a system with symmetries
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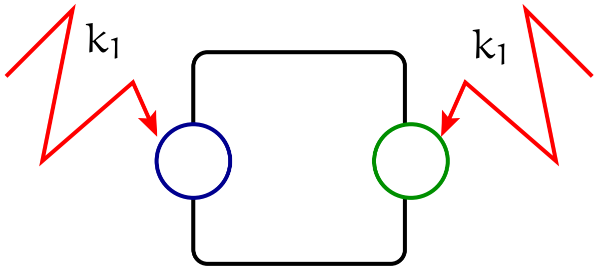
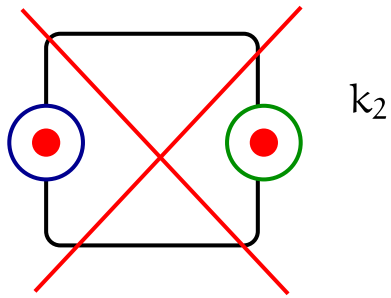
# A model with symmetries



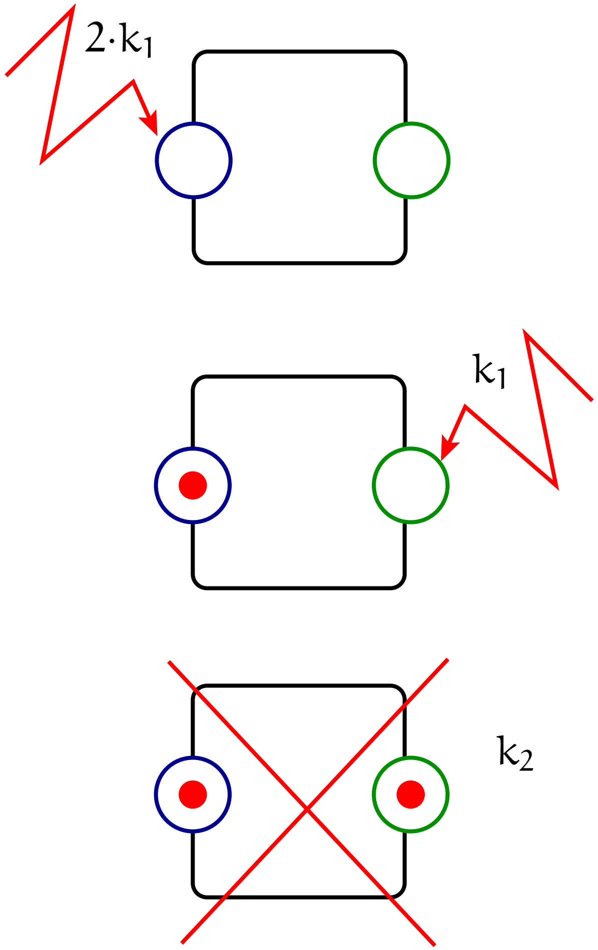

$$P \longrightarrow {}^{\star}P \quad k_1$$
$$P \longrightarrow P^{\star} \quad k_1$$

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




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

# 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:

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

Thus we define the difference $X$ as follows:

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

We have:

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

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

Thus, if $[{}^{\star}\mathsf{P}] = [\mathsf{P}^{\star}]$ at time $t = 0$, then $[{}^{\star}\mathsf{P}] = [\mathsf{P}^{\star}]$ 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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# 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,
- $\psi$: 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:

- $\psi$ 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

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

(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 $X_0 \in \mathcal{V} \rightarrow \mathbb{R}^+$ 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:

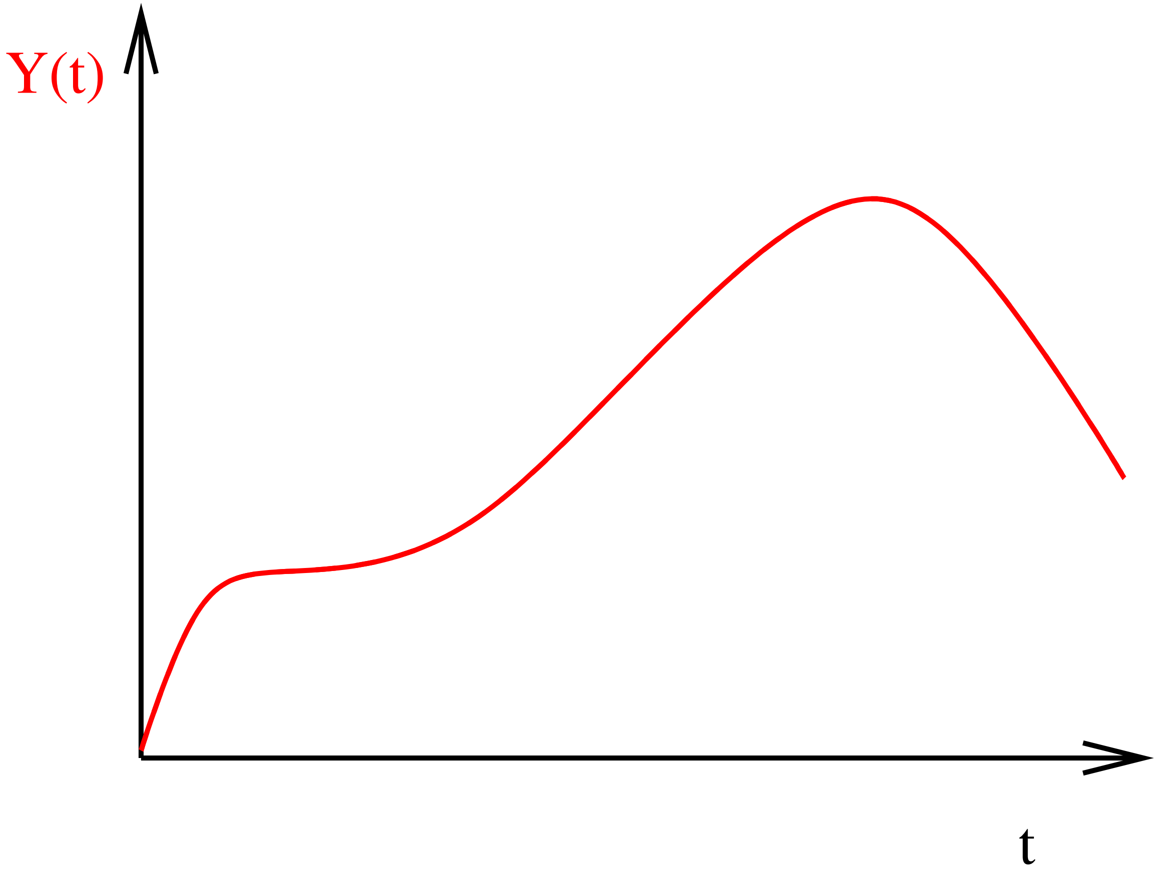
$$
\begin{aligned}
X_{X_0}(T) &= X_0 + \int_{t=0}^{T} \mathbb{F}\left(X_{X_0}(t)\right) \cdot dt \\
\psi\left(X_{X_0}(T)\right) &= \psi\left(X_0 + \int_{t=0}^{T} \mathbb{F}\left(X_{X_0}(t)\right) \cdot dt\right) \\
\psi\left(X_{X_0}(T)\right) &= \psi(X_0) + \int_{t=0}^{T} [\psi \circ \mathbb{F}]\left(X_{X_0}(t)\right)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

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

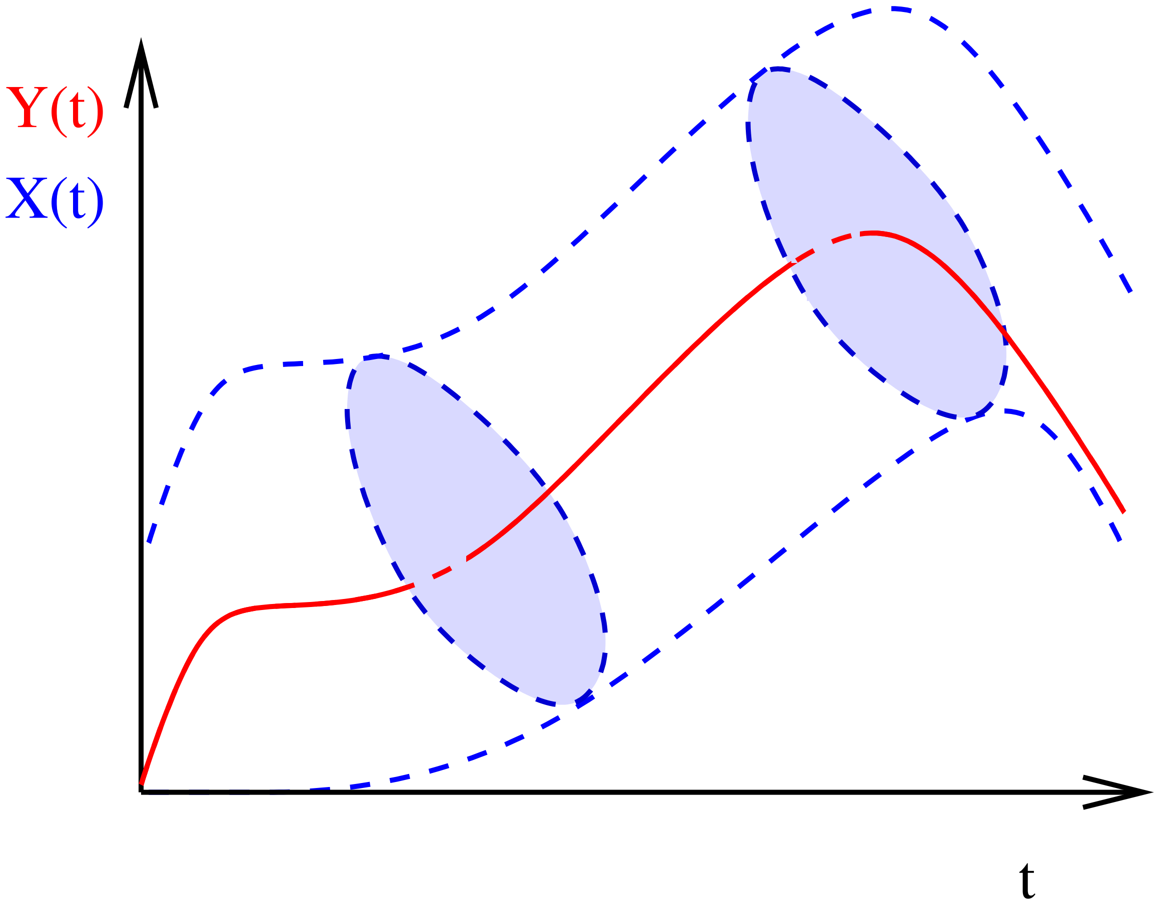
$$
\boxed{Y_{Y_0}(T) = Y_0 + \int_{t=0}^{T} \mathbb{F}^\sharp\left(Y_{Y_0}(t)\right) \cdot dt}
$$

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

# Fluid trajectories



# Fluid trajectories



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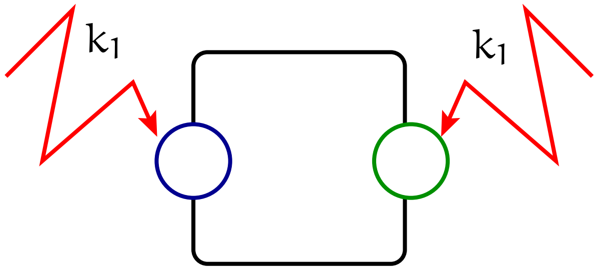
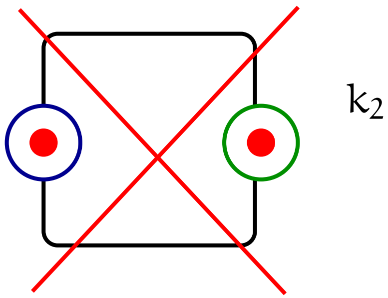
# A model with symmetries




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

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




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

# 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:

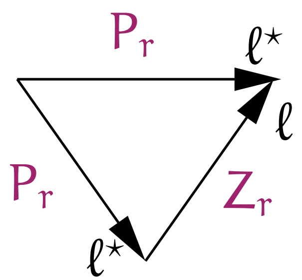
$$\frac{d}{dt}\begin{bmatrix} P \\ {}^{\star}P + P^{\star} \\ 0 \\ {}^{\star}P^{\star} \end{bmatrix} = \underbrace{\begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}}_{P} \cdot \begin{bmatrix} -2\cdot k_1 & 0 & 0 & 0 \\ k_1 & -k_1 & 0 & 0 \\ k_1 & 0 & -k_1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

# 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,

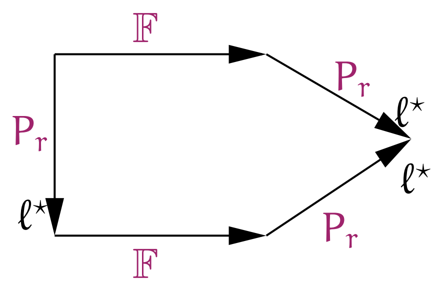
$\stackrel{\Delta}{\Longleftrightarrow}$

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,

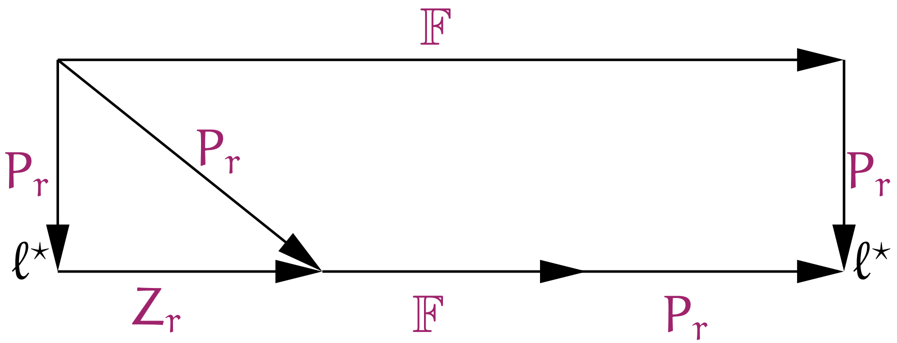
$\Longleftrightarrow$

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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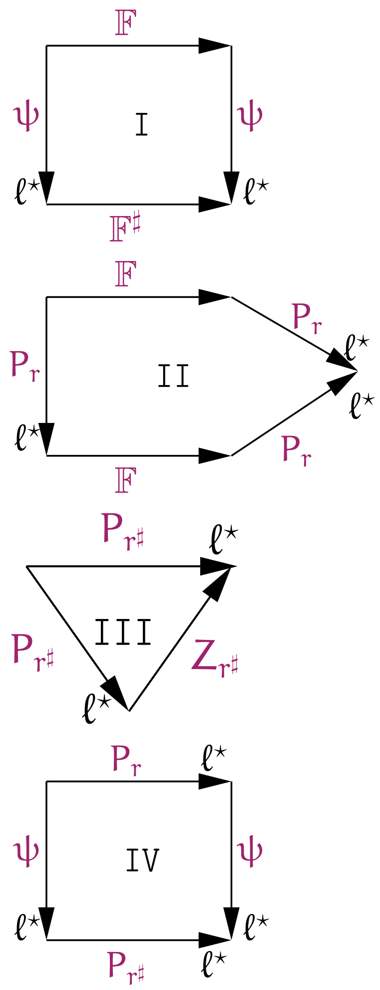
# Abstract projection



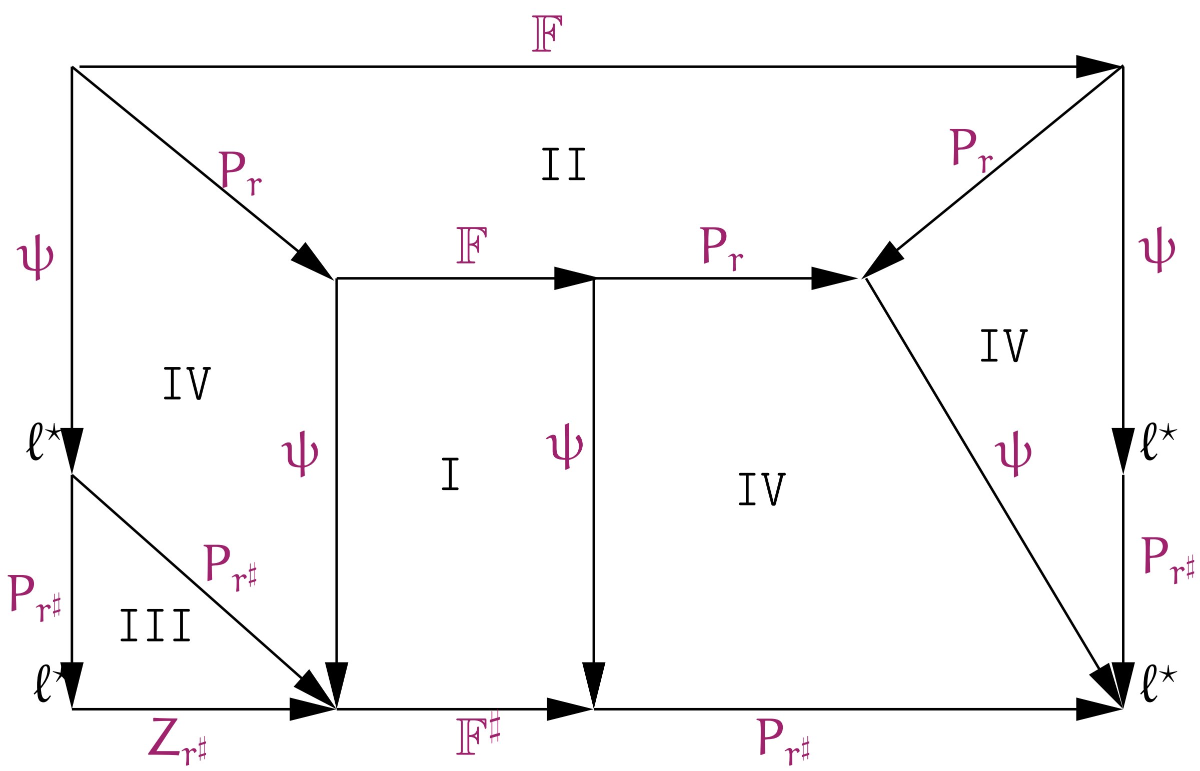

We assume that we are given:

- 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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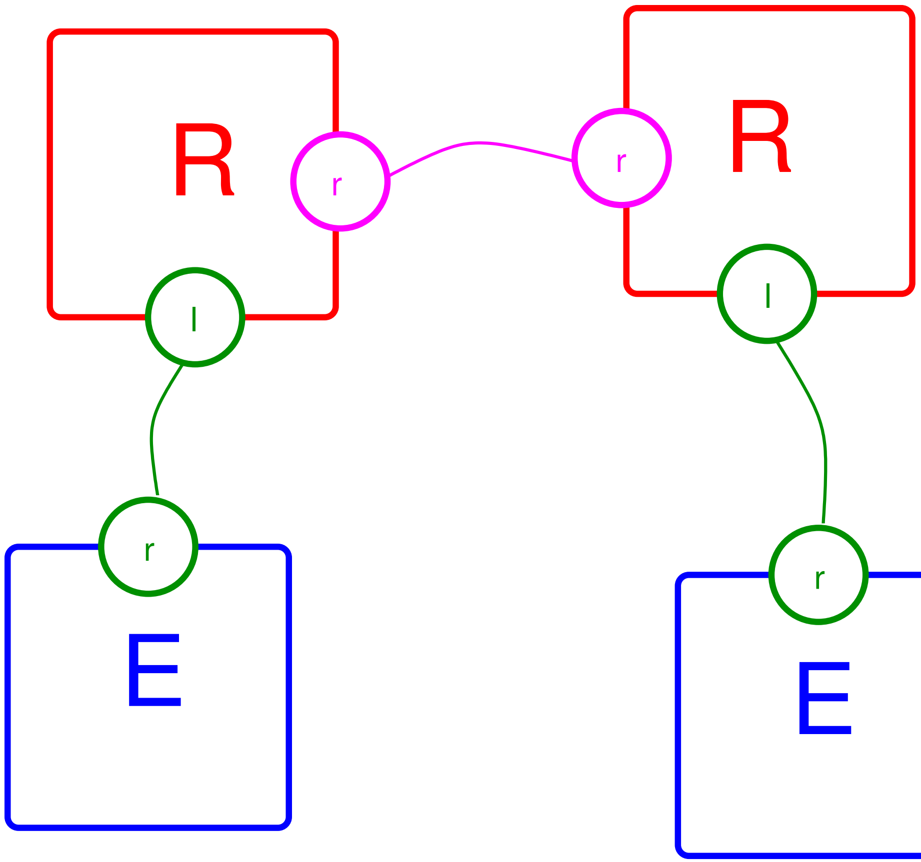
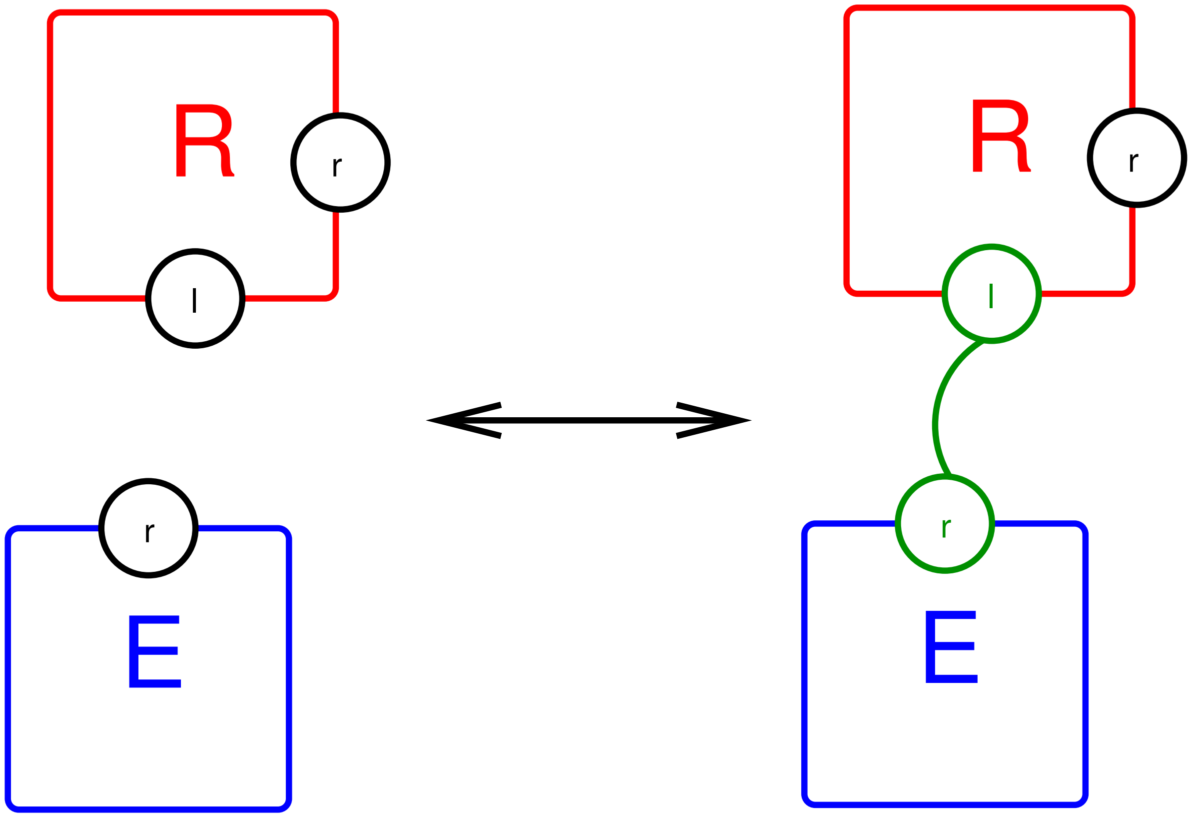
# A species



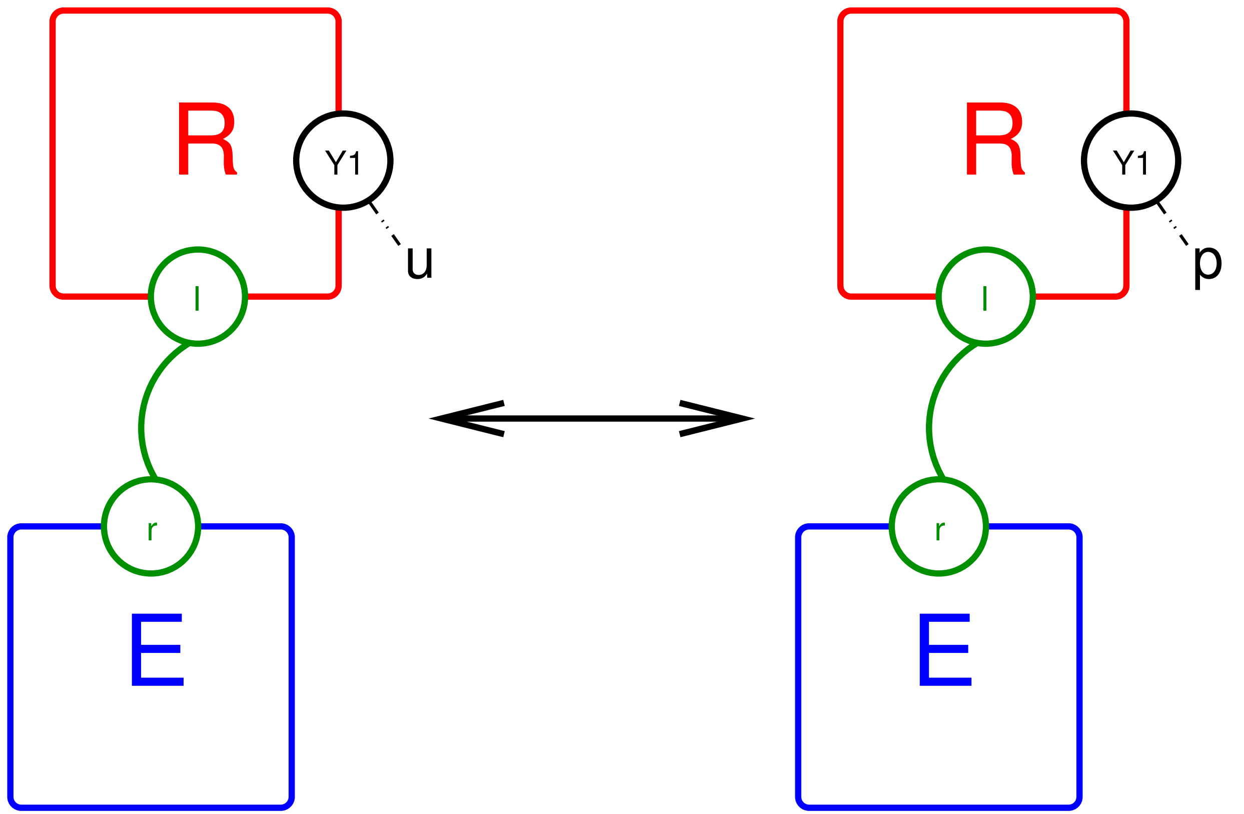

E(r!1), R(l!1,r!2), R(r!2,l!3), E(r!3)

# A Unbinding/Binding Rule



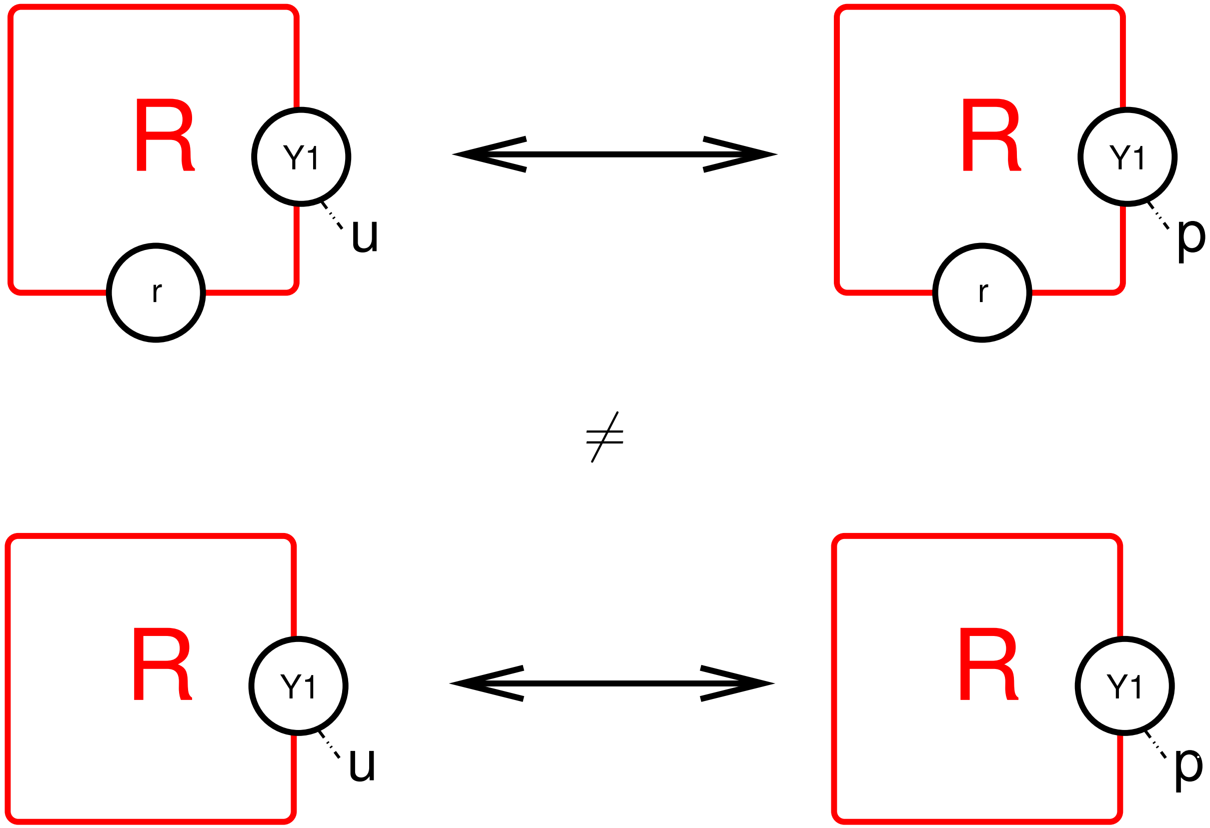

E(r), R(l,r) $\longleftrightarrow$ E(r!1), R(l!1,r)

# Internal state

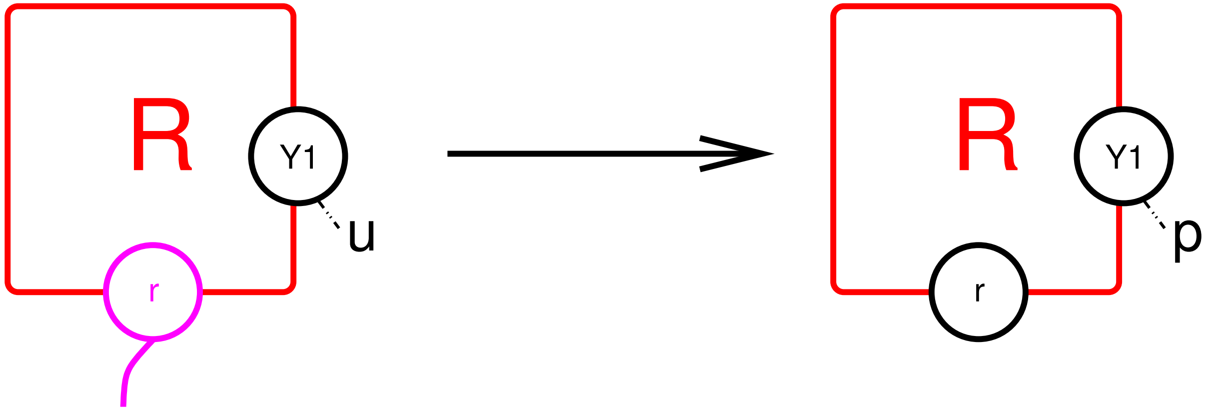



$R(Y1{\sim}u, l!1), E(r!1) \longleftrightarrow R(Y1{\sim}p, l!1), E(r!1)$

# Don't care, Don't write

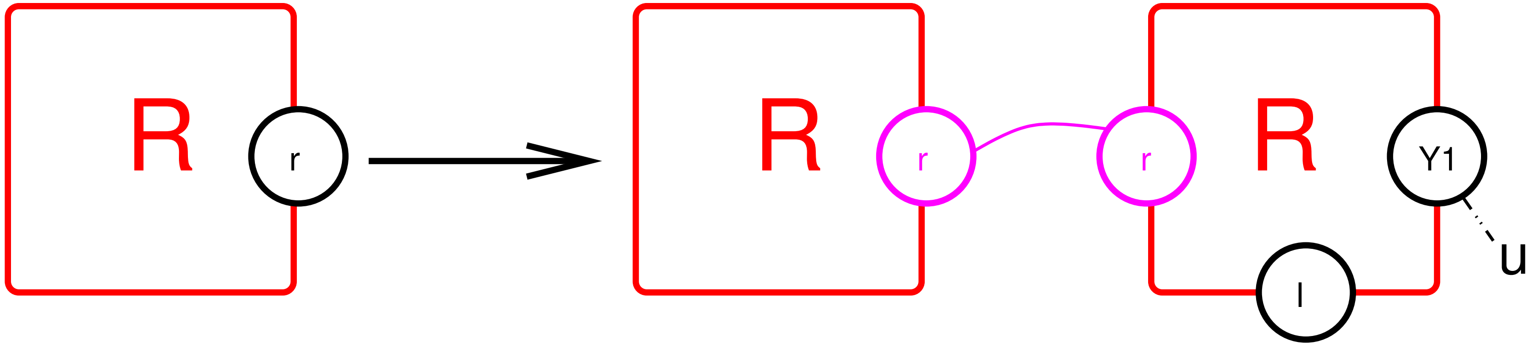


# A contextual rule

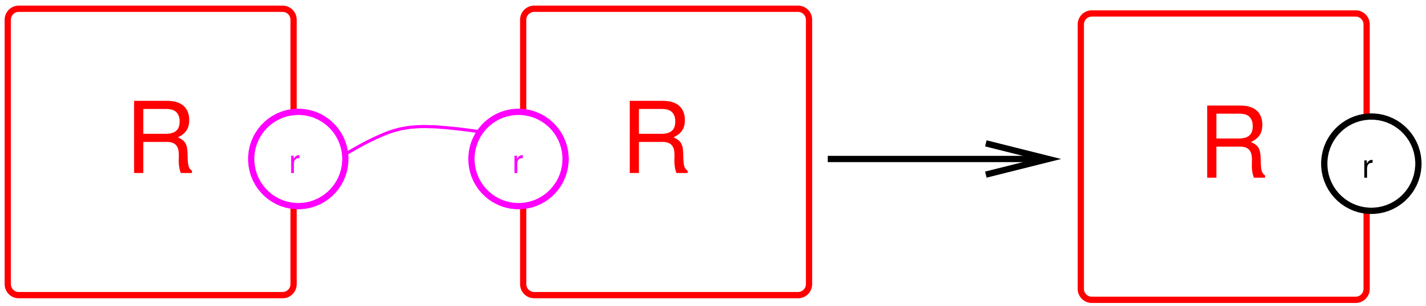



R(Y1~u,r!_) → R(Y1~p,r)

# Creation/Suppression




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




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

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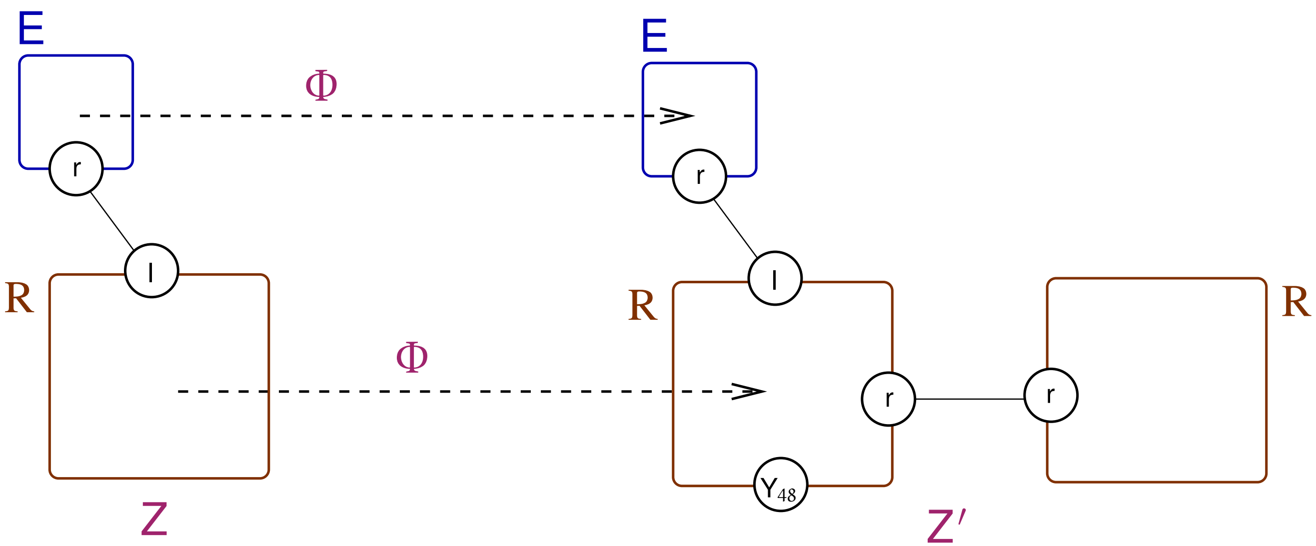
# Embedding




We say that $\Phi$ is an embedding between $Z$ and $Z'$ iff:

- $\Phi$ is a site-graph morphism:
  - $i$ is less specific than $\Phi(i)$,
  - there is a link between $(i, s)$ and $(i', s')$, if and only if there is a link between $(\Phi(i), s)$ and $(\Phi(i'), s')$.
- $\Phi$ is an into map (injective):
  - $\Phi(i) = \Phi(i')$ implies that $i = i'$.

# Requirements

1. Reachable species

   We are given a set $\mathcal{R}$ of connected site-graphs such that:

   - $\mathcal{R}$ is finite;
   - $\mathcal{R}$ contains at most one site-graph per isomorphism class;
   - $\mathcal{R}$ is closed with respect to rule application;

2. Rules are associated with kinetic factors.

   - the unit depends on the arity of the rule as follows:

$$\left(\frac{L}{mol}\right)^{arity-1} \cdot s^{-1}$$

   where *arity* is the number of connected components in the lhs.

# Differential system

Let us consider a rule *rule*: *lhs* $\rightarrow$ *rhs* $\quad k$.

A ground instanciation of *rule* is defined by an embedding $\phi$ between *lhs* into a tuple $(r_i)$ of elements in $\mathcal{R}$ which preserves disconnectiveness,
and is written: $r_1, \ldots, r_m \rightarrow p_1, \ldots, p_n \quad k$.

For each such ground instantiation, we get the following contribution:

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

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

# Overview

1. Context and motivations
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4. Kappa
5. Concrete semantics
6. Abstract semantics
    (a) Fragments
    (b) Soundness criteria
    (c) Symmetries between sites
7. Conclusion

# Abstract domain

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

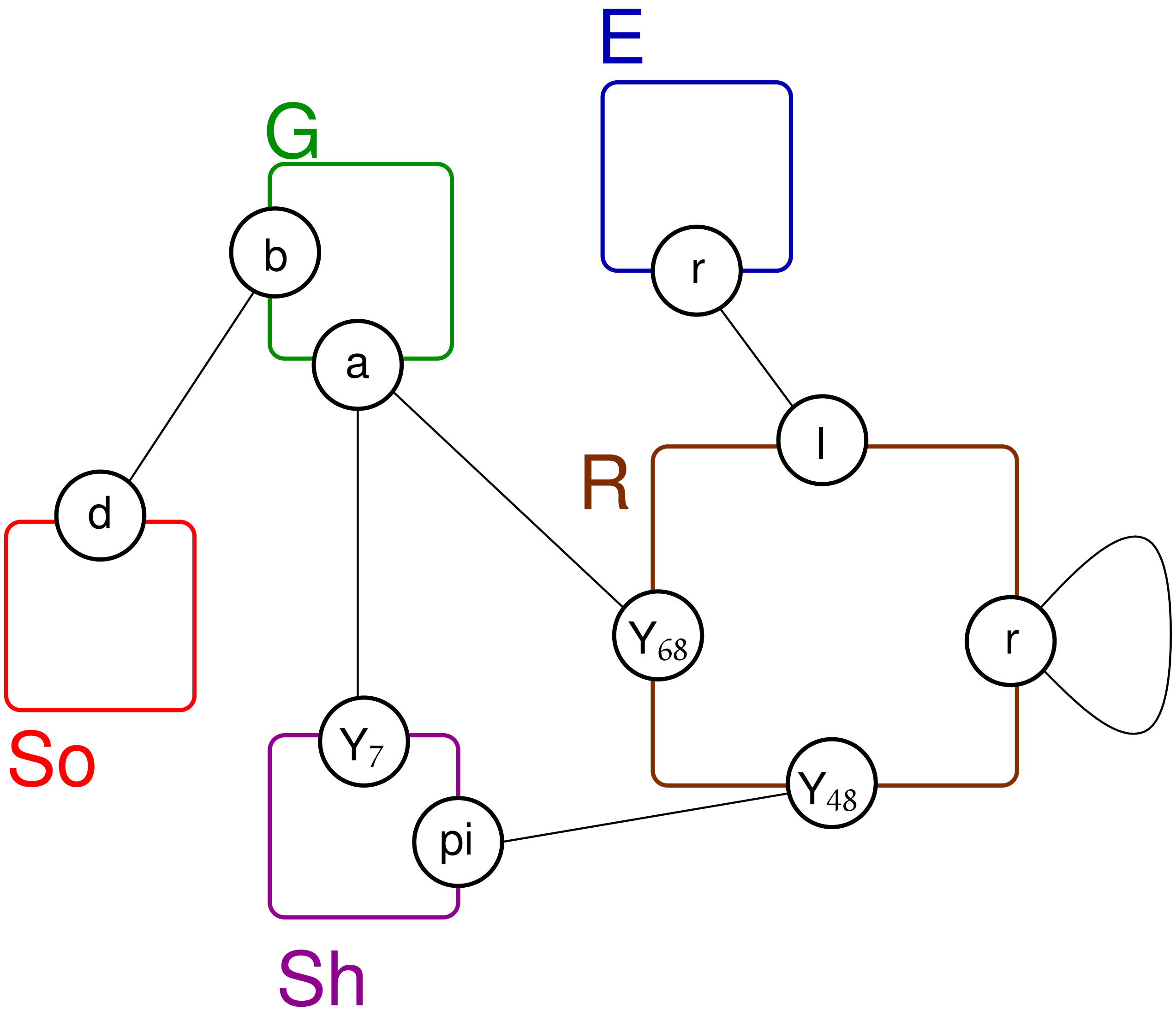
The set of linear variable replacements is too big to be explored.

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

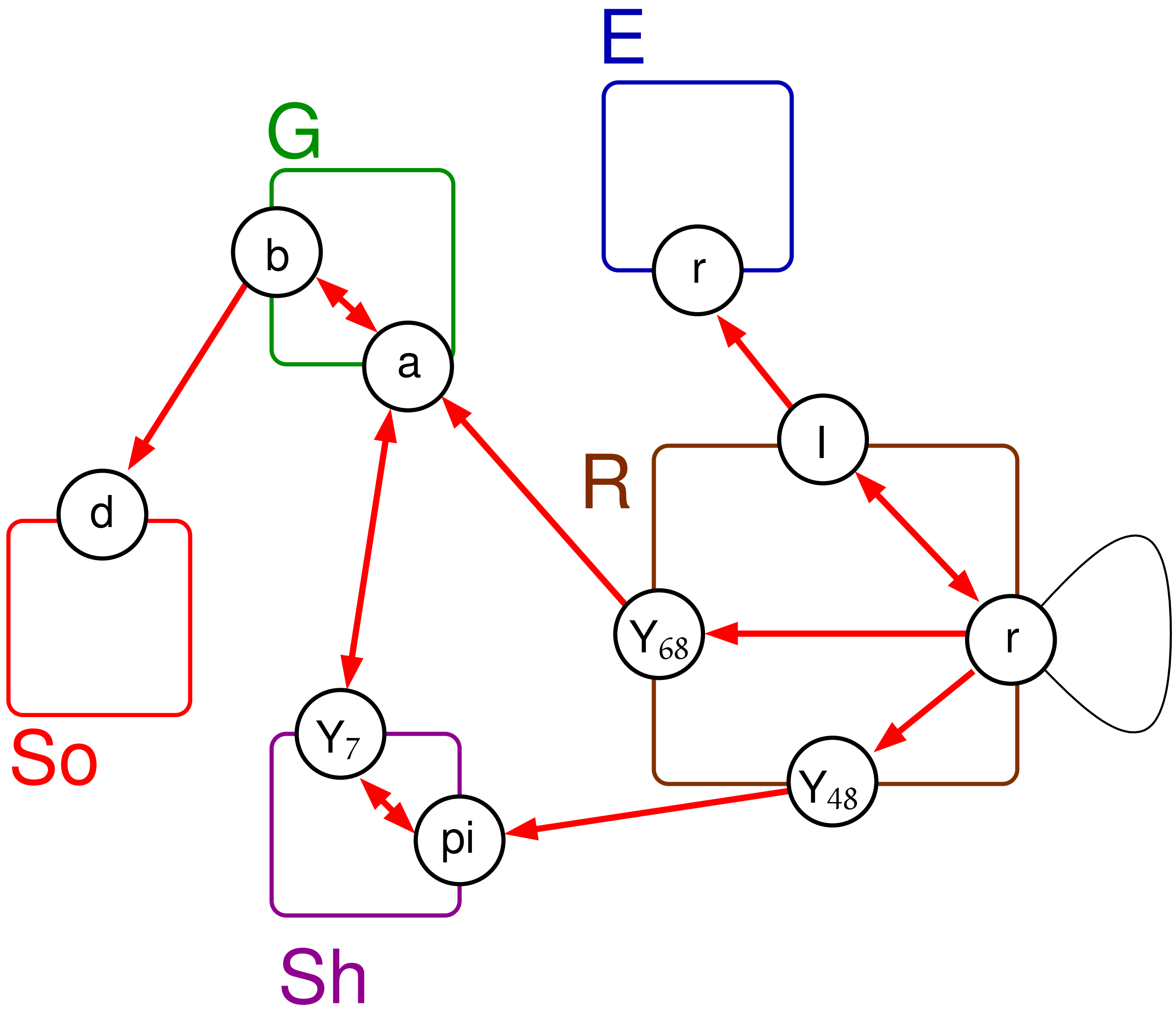
- restrict the exploration;
- drive the intuition (by using the flow of information);
- having efficient way to find suitable abstractions $(\mathcal{V}^\sharp, \psi)$ and to compute $\mathbb{F}^\sharp$.

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

# Contact map



# Annotated contact map



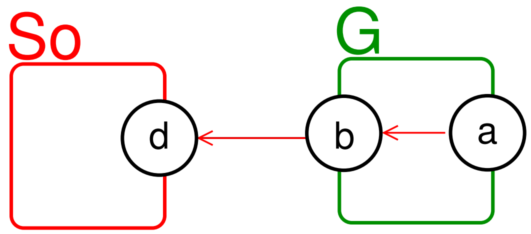
# Fragments and prefragments

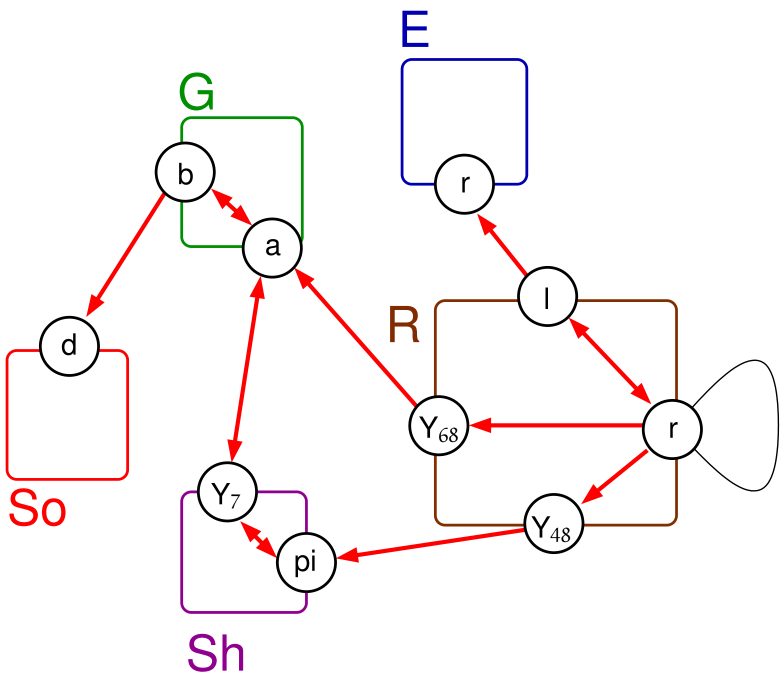
A prefragment is a connected site graph for which there exists a binary relations $\rightarrow$ between sites such that:

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

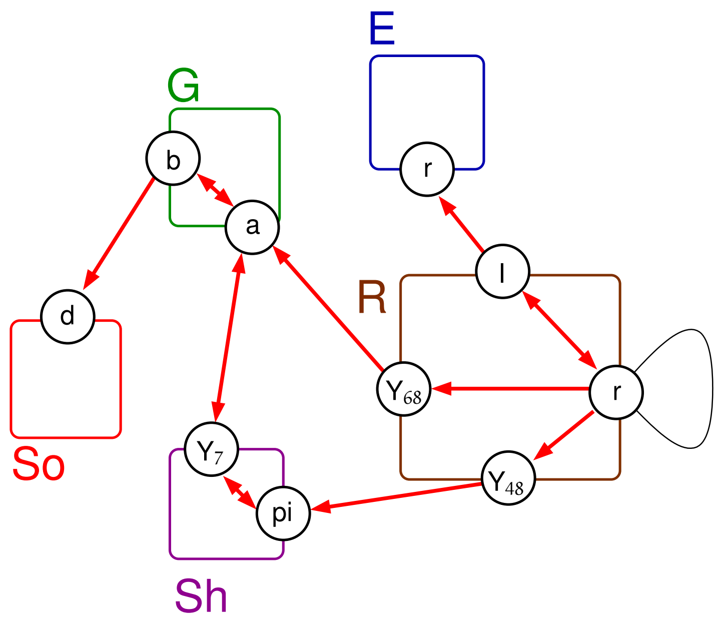
A fragment is a prefragment $F$ such that:

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

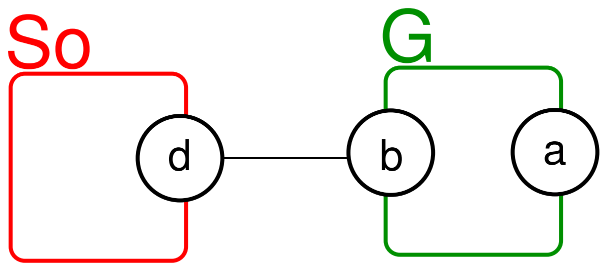


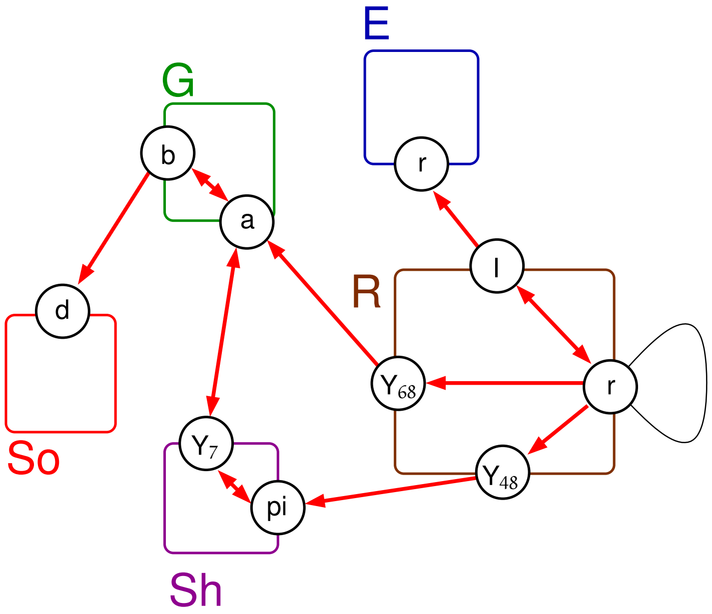



# Are they fragments ?

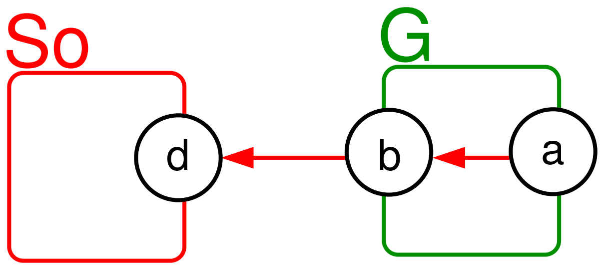


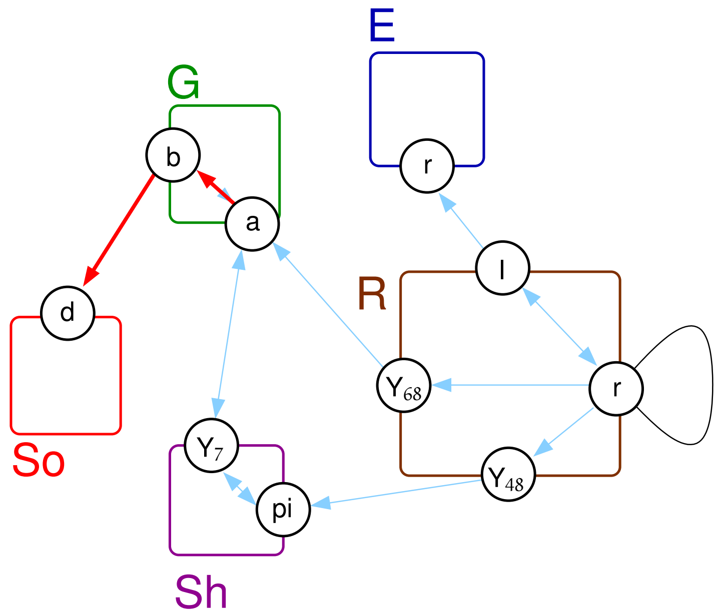
# Are they fragments ?



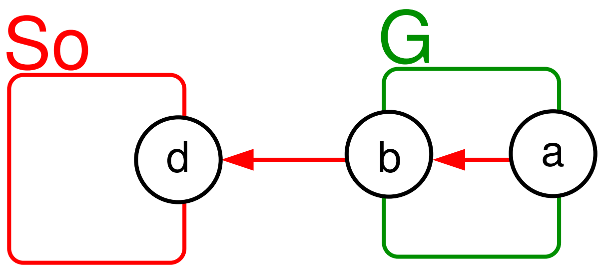
# Are they fragments ?



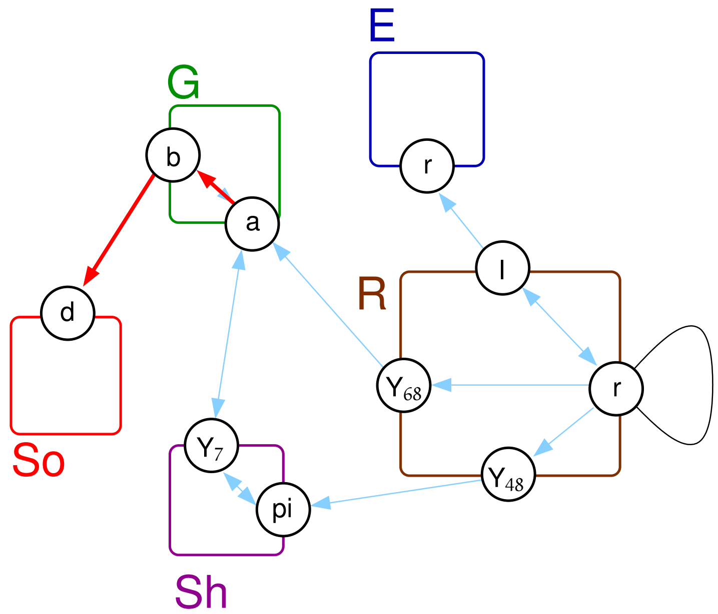




Thus, it is a prefragment.

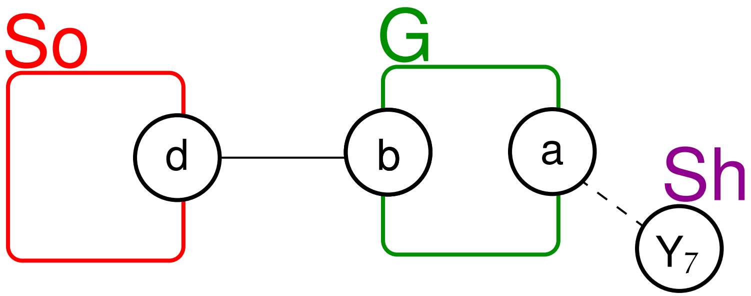
# Are they fragments ?

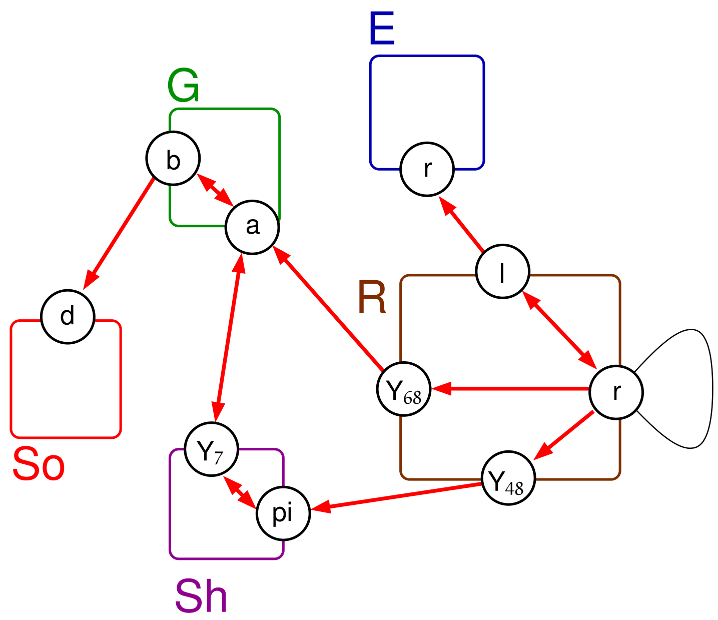



It is maximally specified.
Thus it is a fragment.

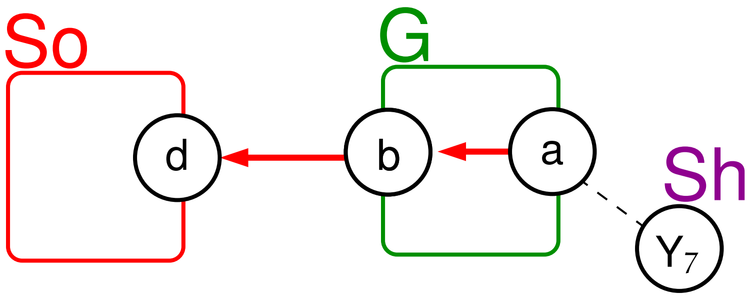


# Are they fragments ?

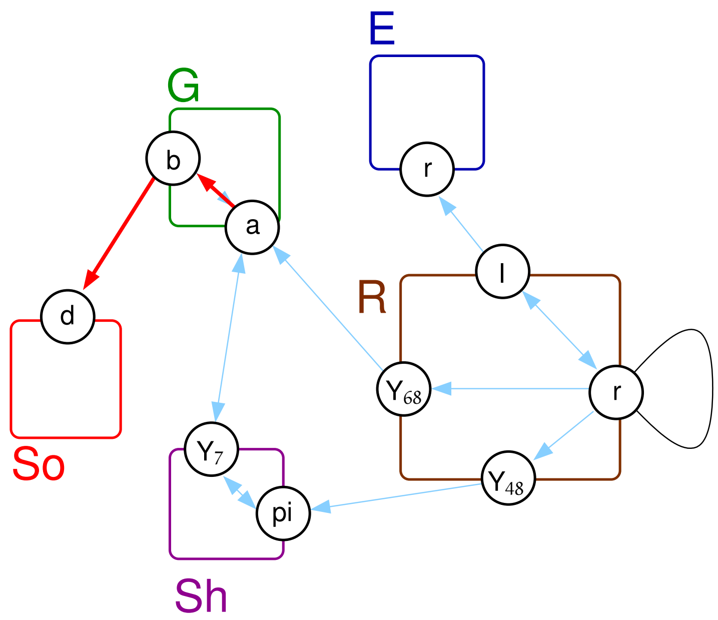


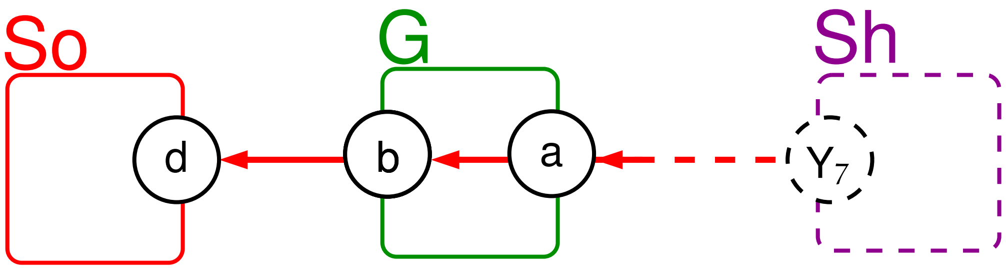
# Are they fragments ?



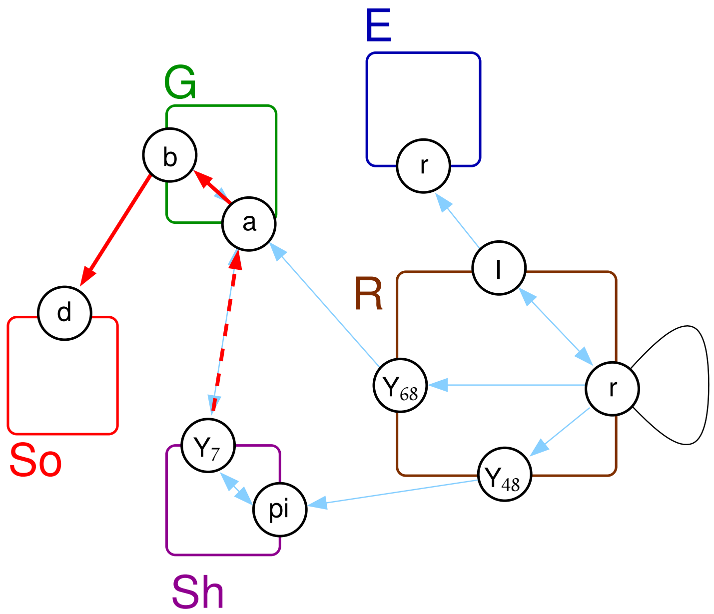

Thus, it is a prefragment.



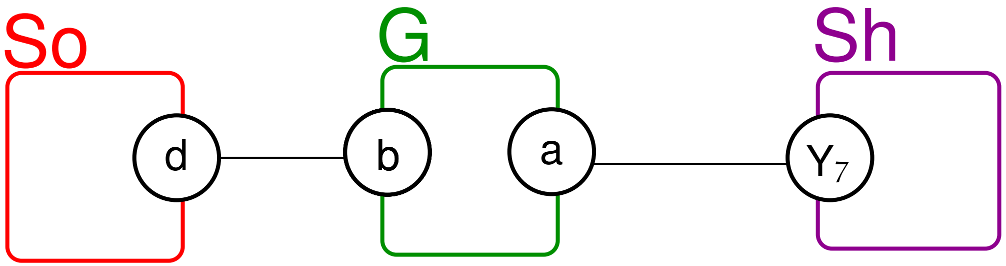
# Are they fragments ?

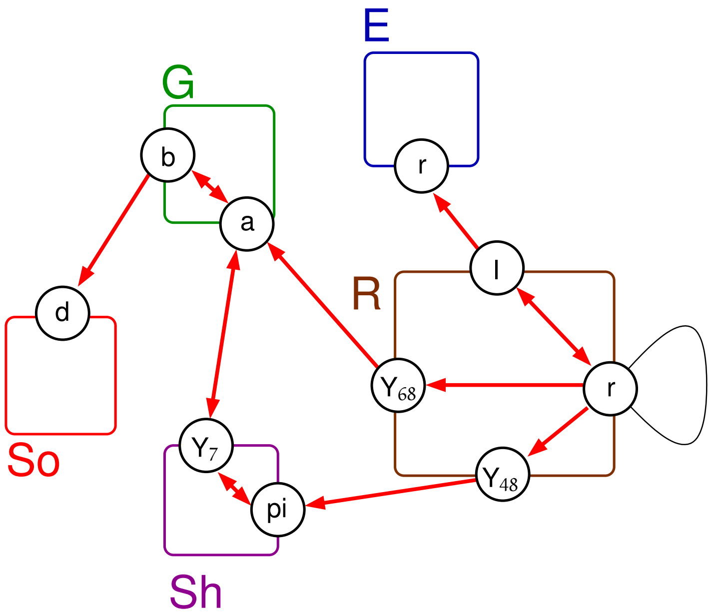



It can be refined into another prefragment.
Thus, it is not a fragment.

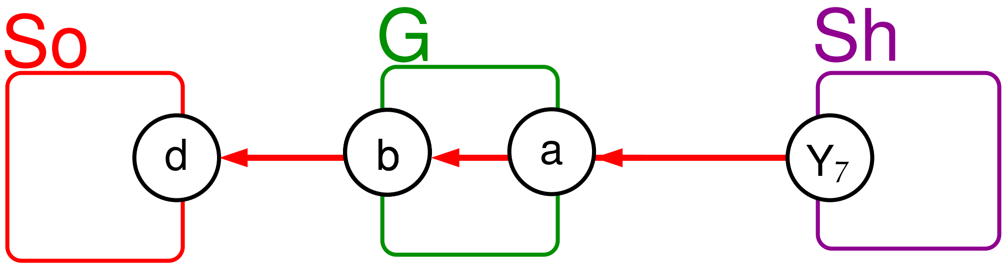


# Are they fragments ?

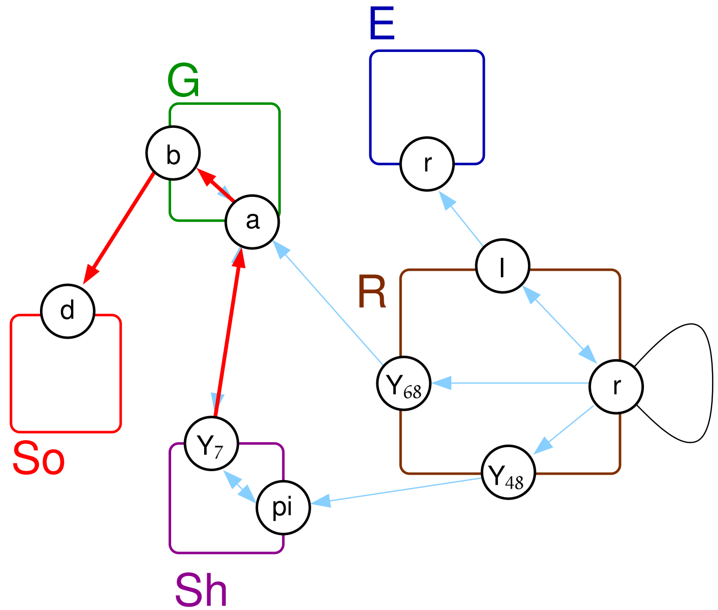


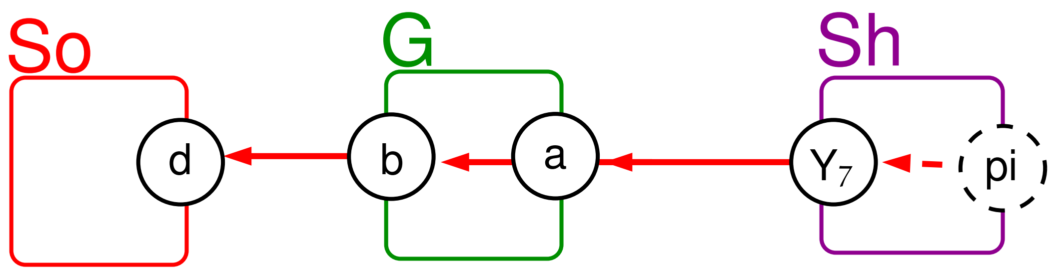
# Are they fragments ?




Thus, it is a prefragment.



# Are they fragments ?




It can be refined into another prefragment.
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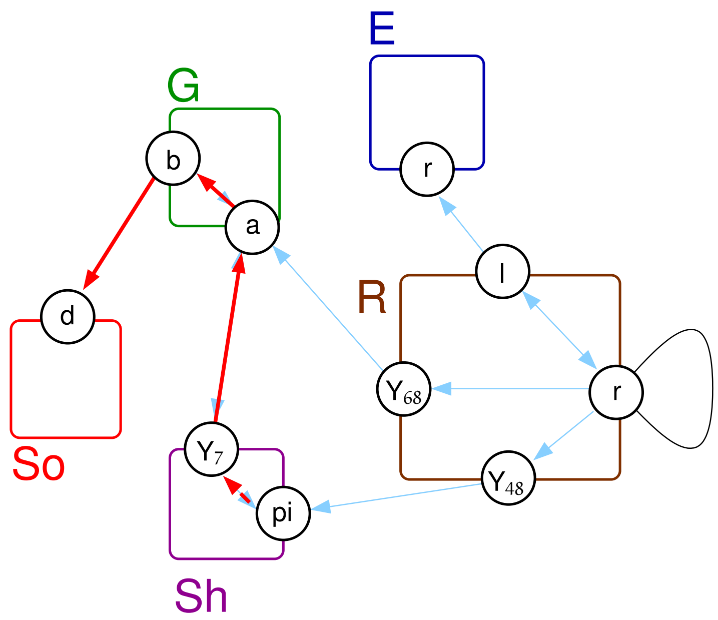
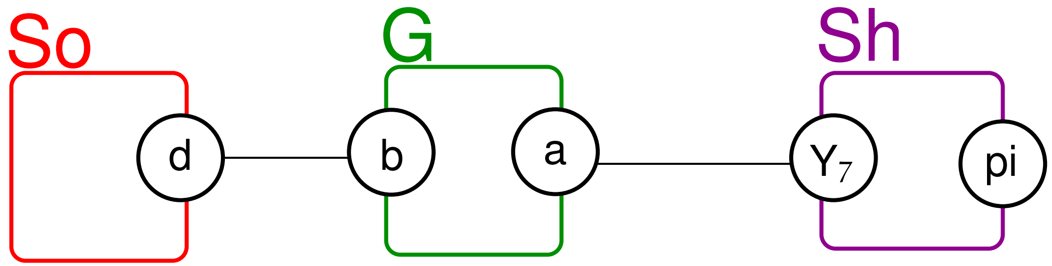
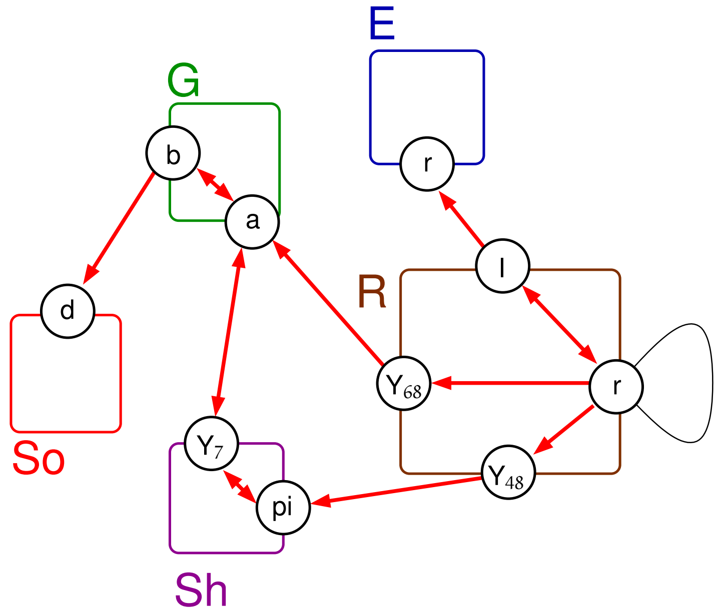
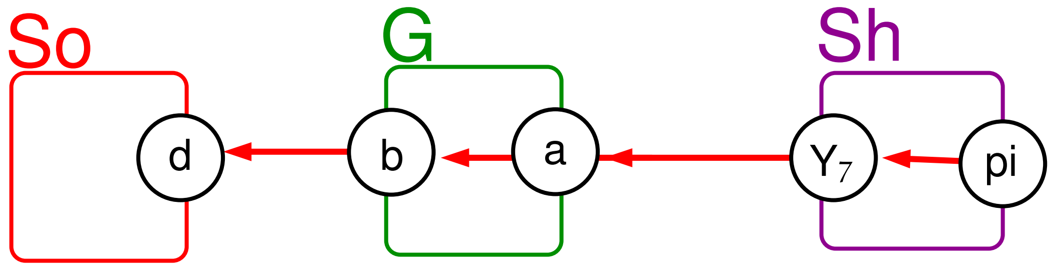


# Are they fragments ?

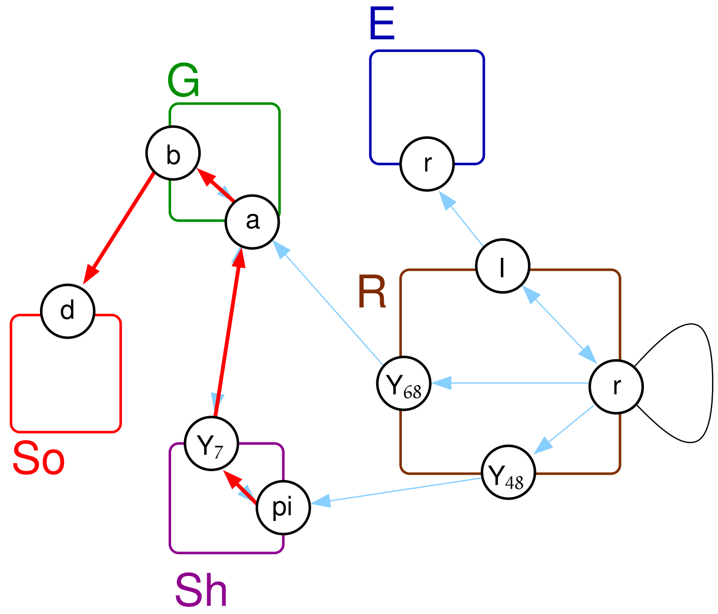


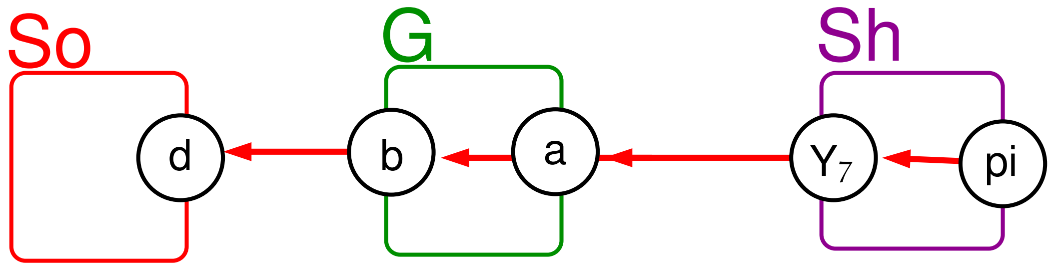
# Are they fragments ?

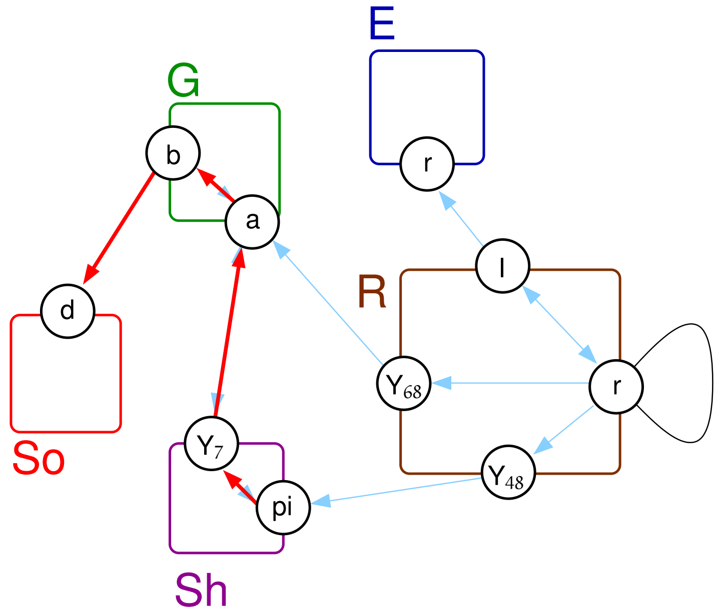



Thus, it is a prefragment.



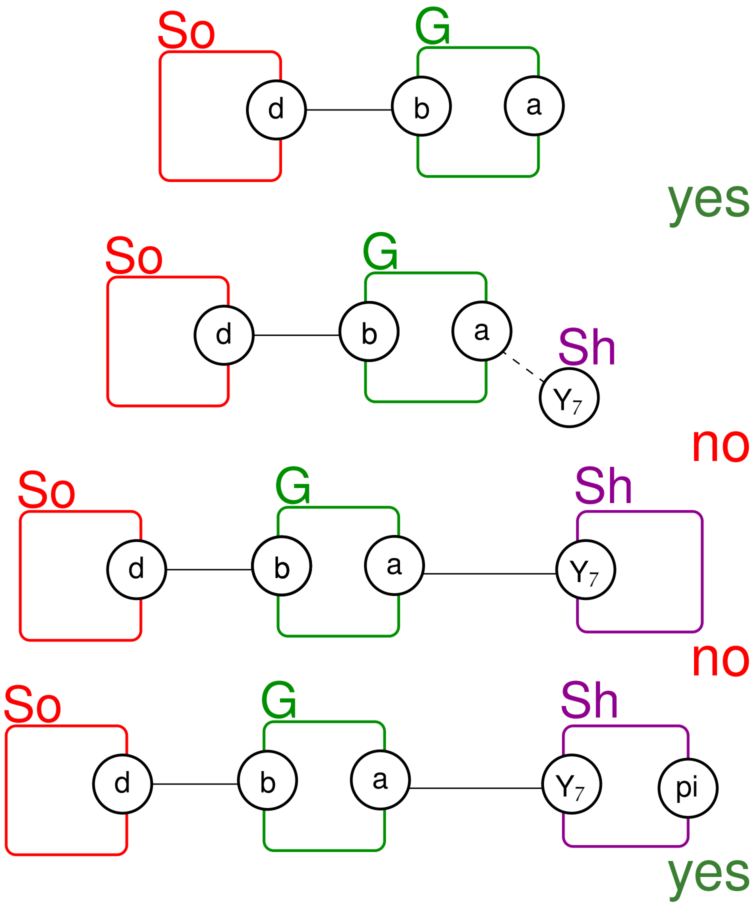
# Are they fragments ?

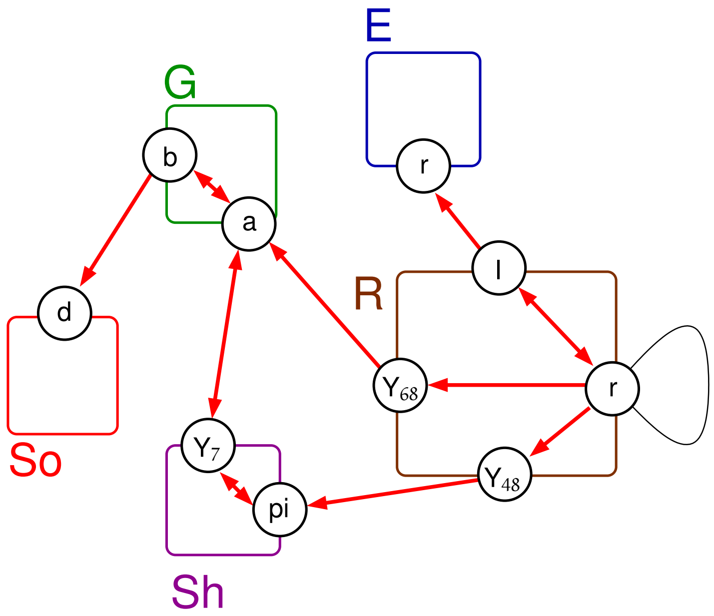


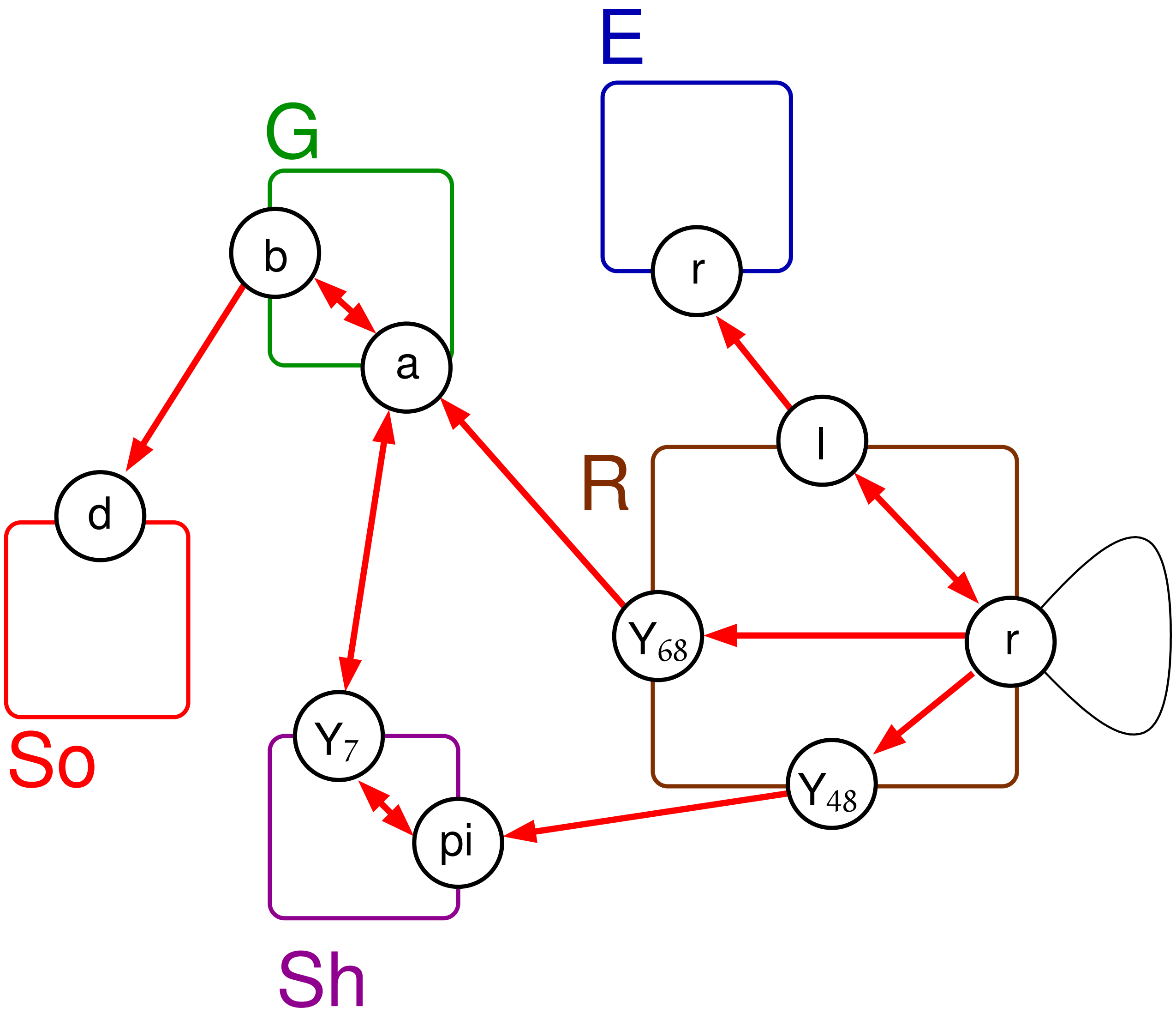

It is maximally specified.
Thus it is a fragment.

# Are they fragments ?

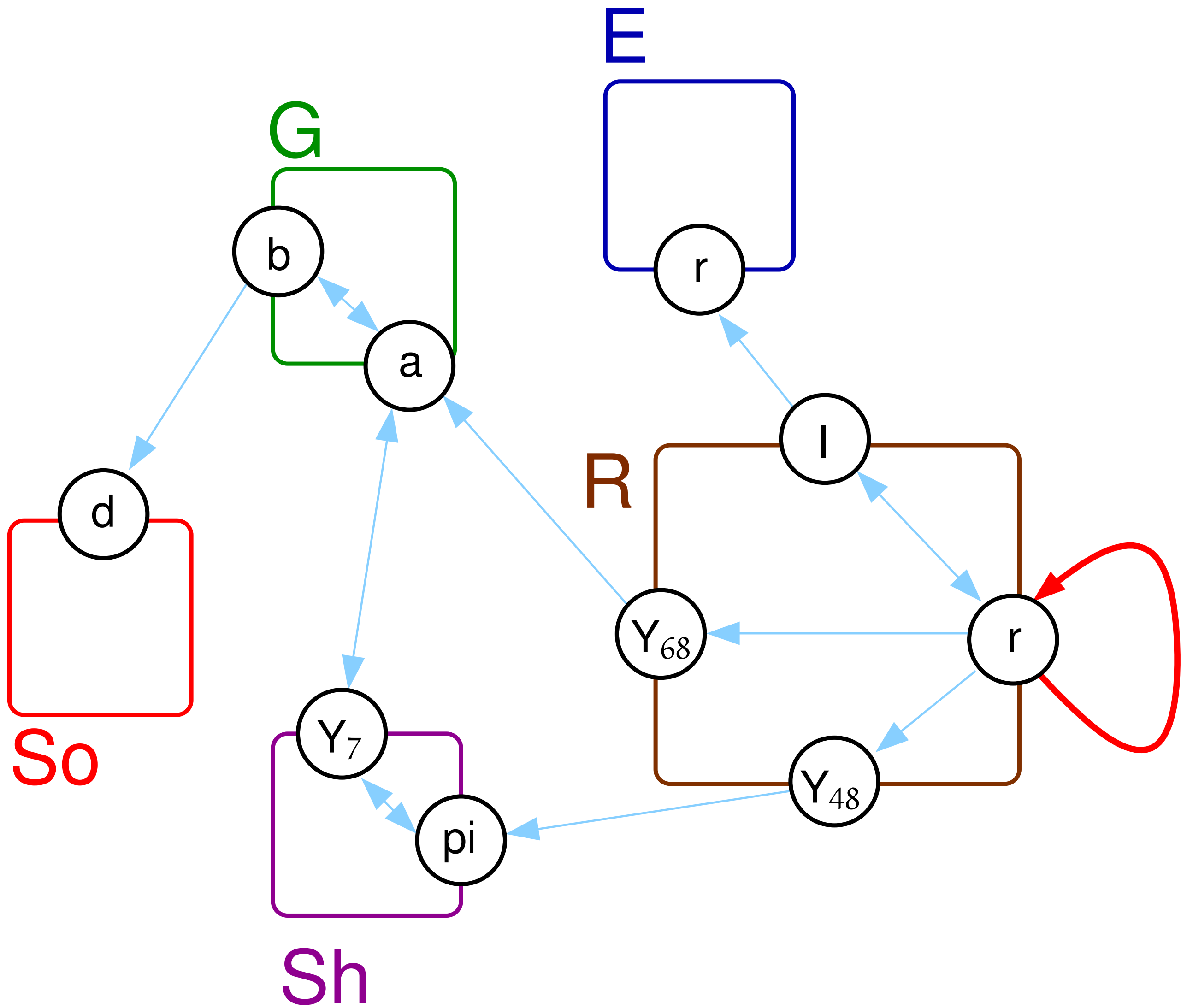


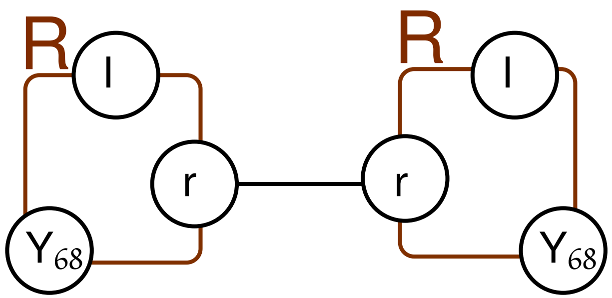
# Annotated contact map

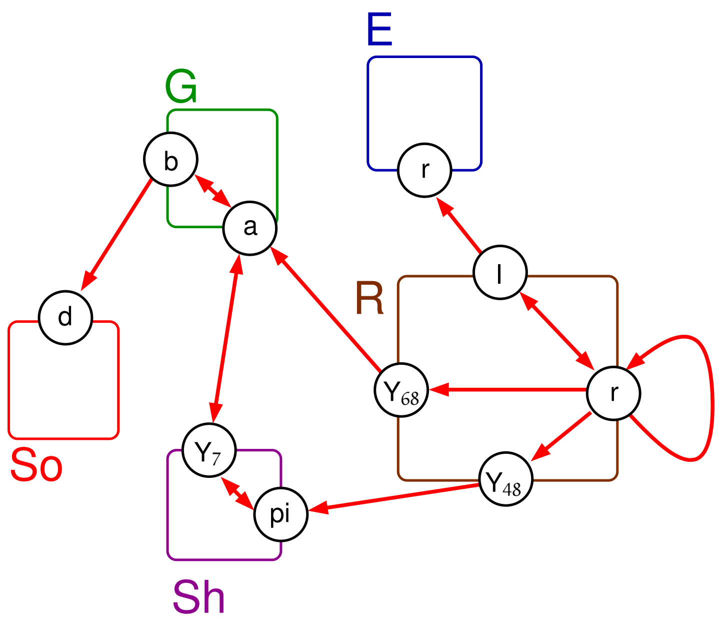


# What if we were adding this flow ?

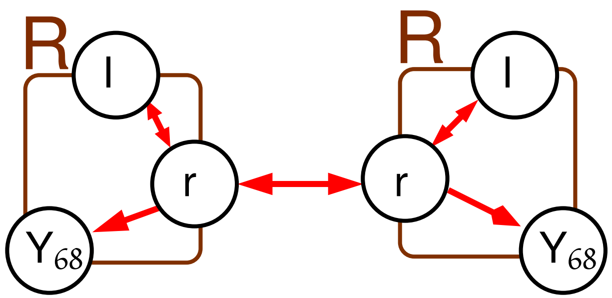


# Are they fragments ?
## stage 2



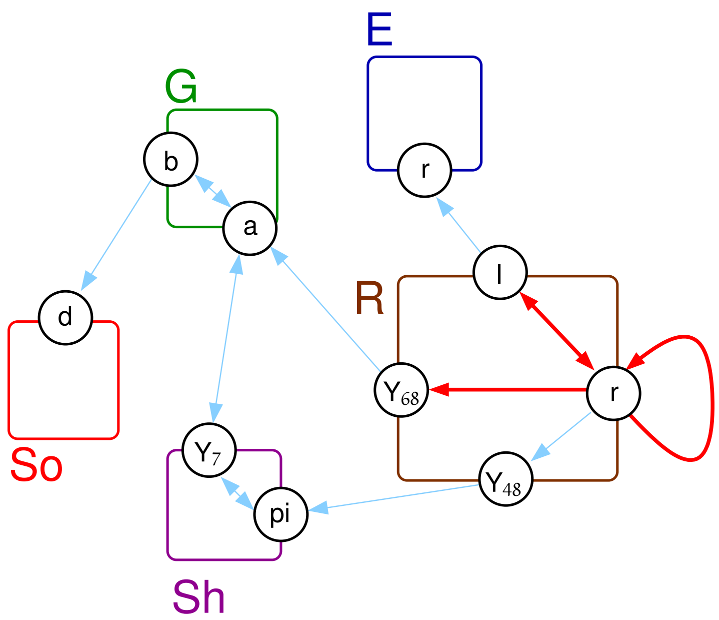



# Are they fragments ?
## stage 2

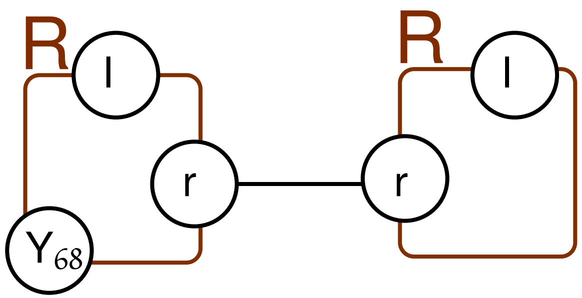


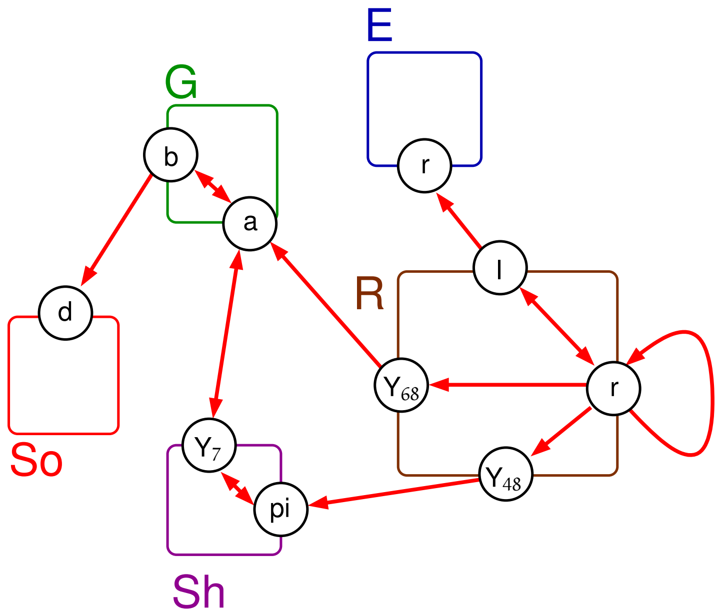

There is no way to make a path from the first $Y_{68}$ and the second one or to make a path from the second one to the first one.

Thus it is not even a prefragment.

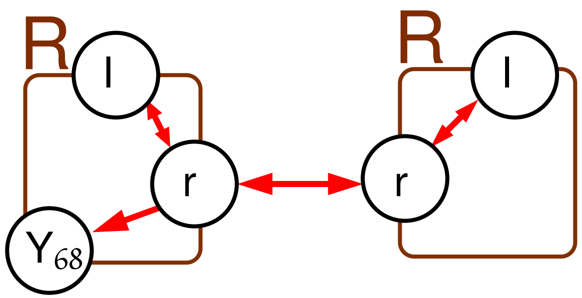


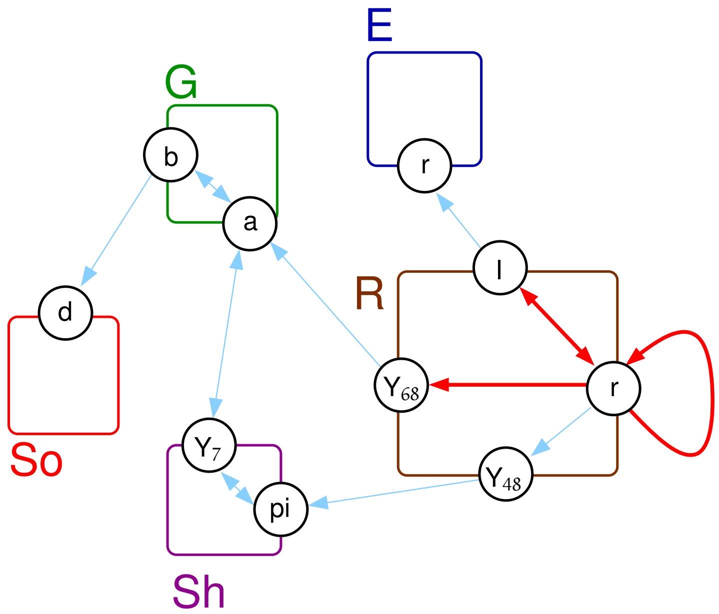
# Are they fragments ?
## stage 2



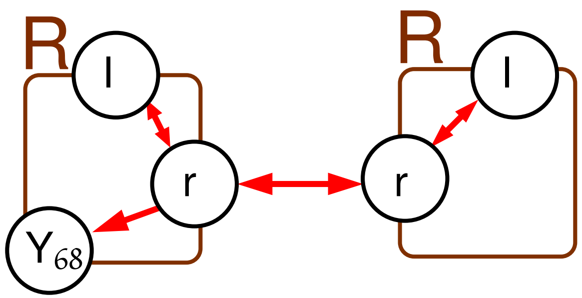
# Are they fragments ?
## stage 2



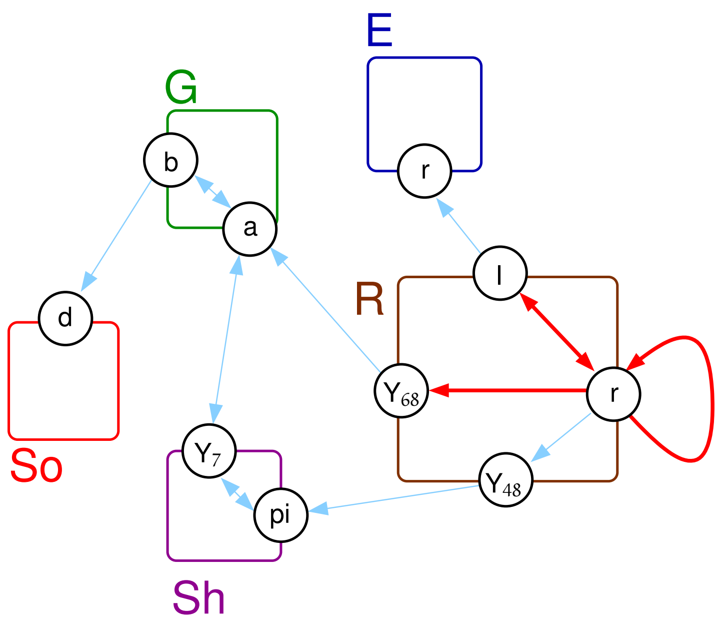

Thus it is a prefragment.

# 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 $\mathcal{V} \rightarrow \mathbb{R}^+$ and $||\cdot||^\sharp$ on $\mathcal{V}^\sharp \rightarrow \mathbb{R}^+$.

**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 ?

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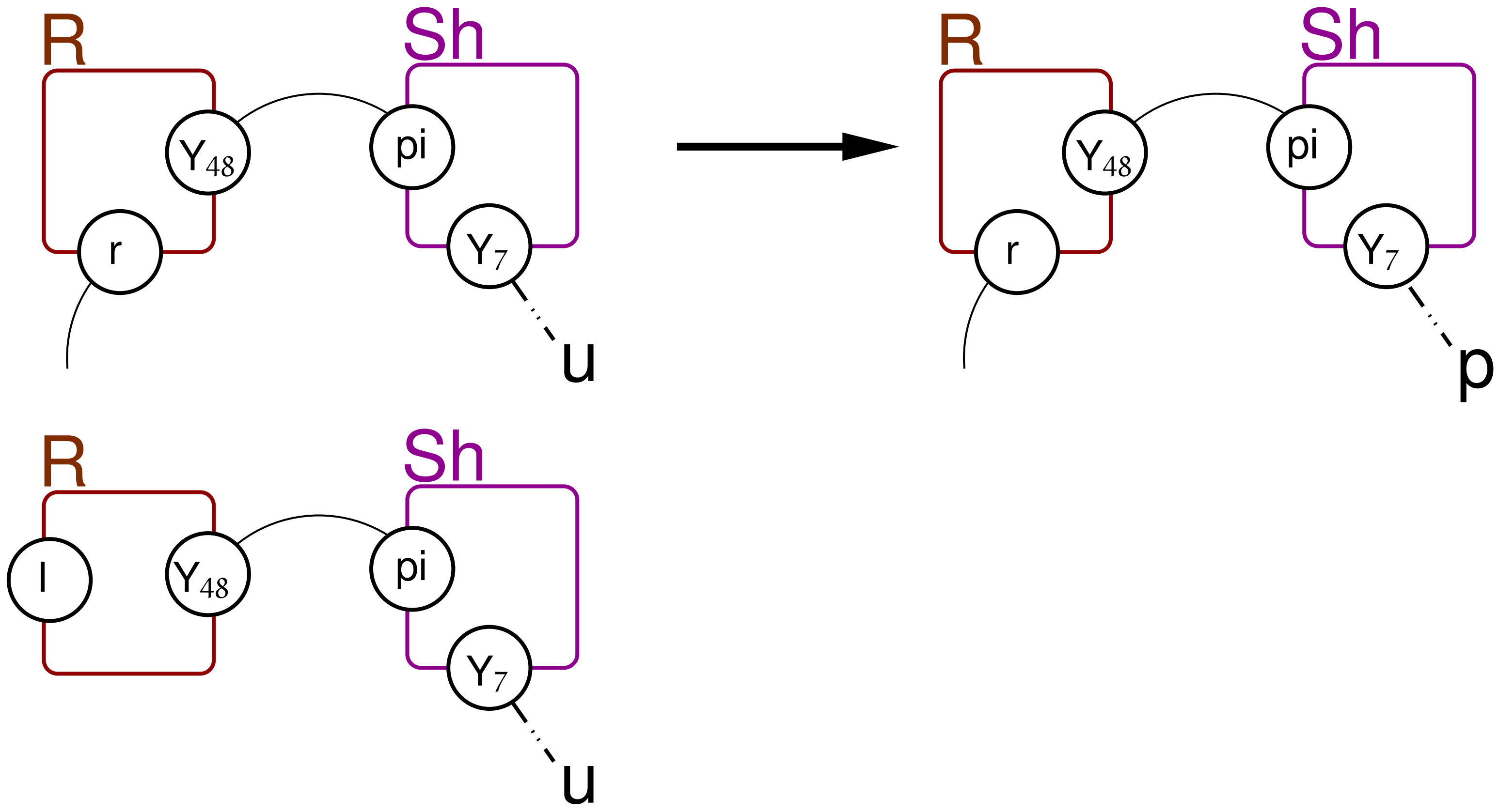
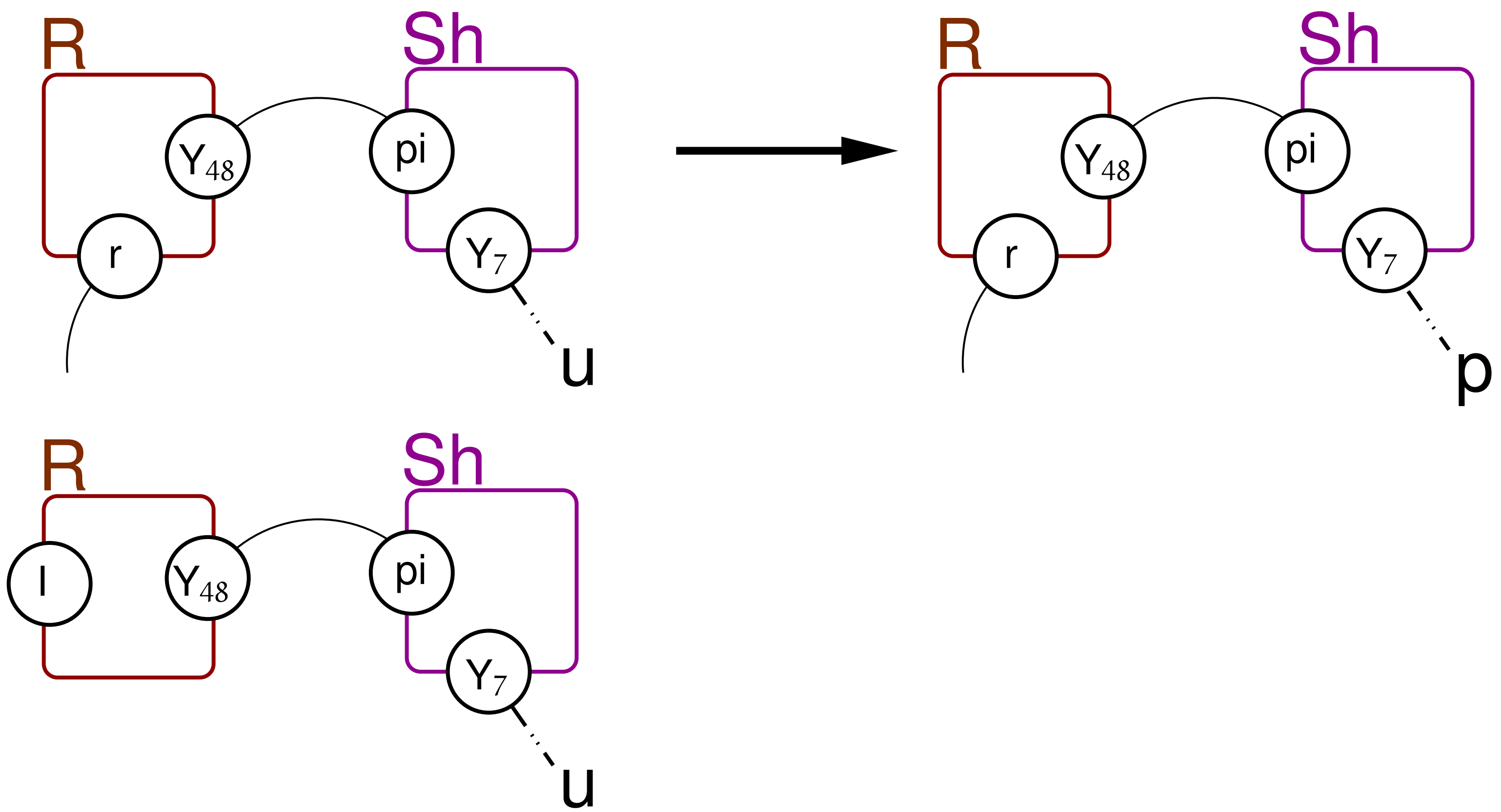
# Fragments consumption



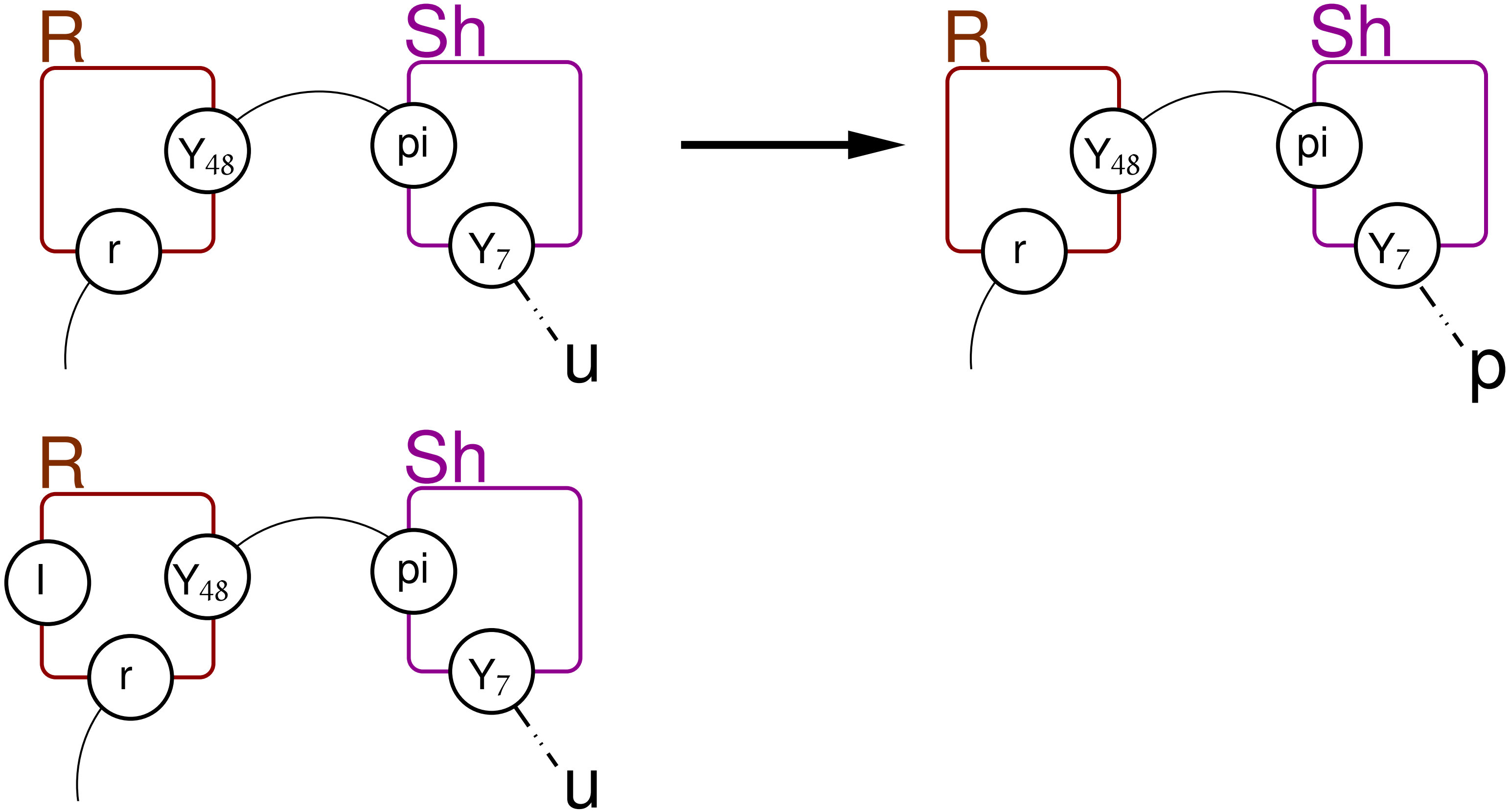

Can we express the amount (per time unit) of this fragment (bellow) concentration that is consumed by this rule (above)?

# Fragments consumption



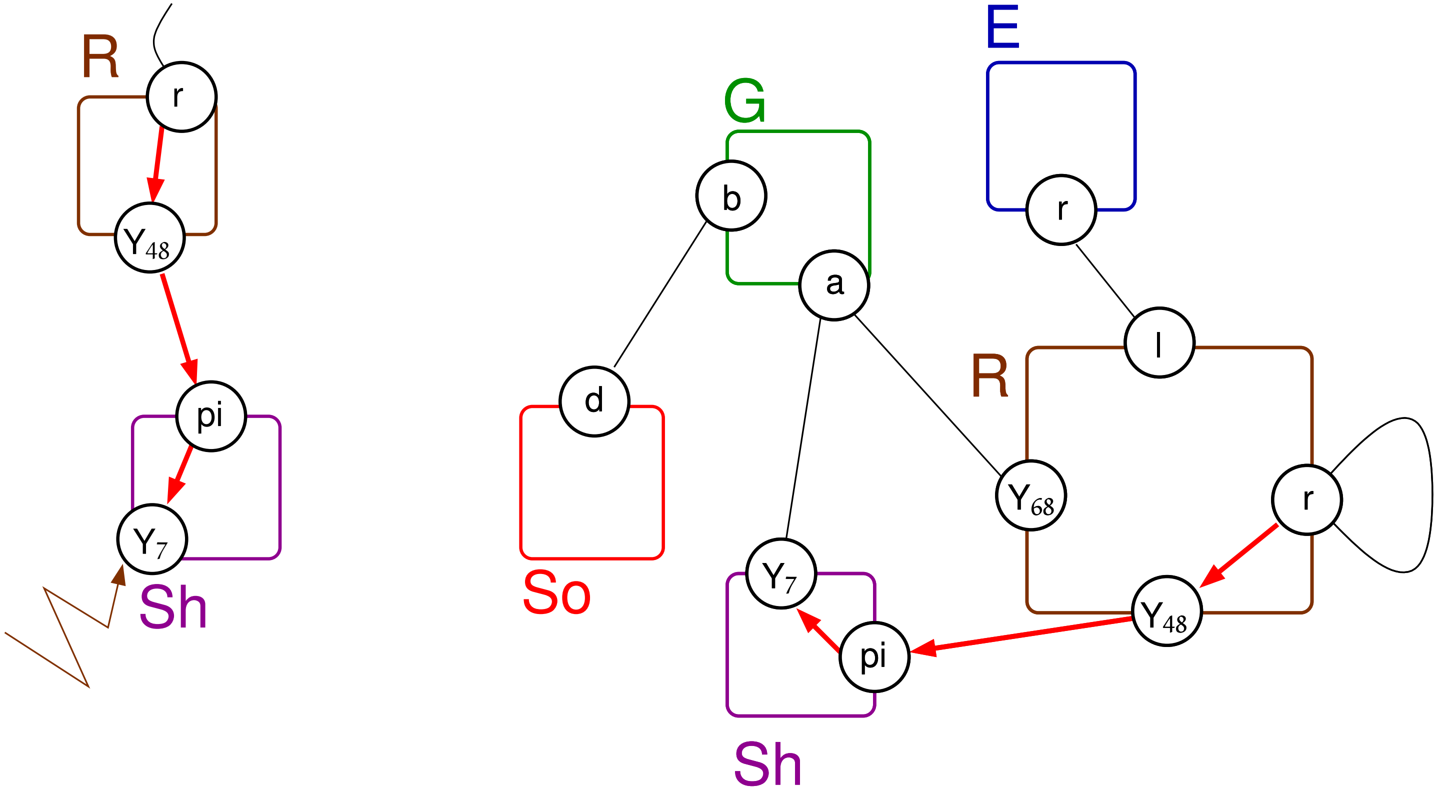

No, because we have abstracted away the correlation between the state of the site $\mathtt{r}$ and the state of the site $\mathtt{l}$.

# Fragments consumption
## Proper intersection



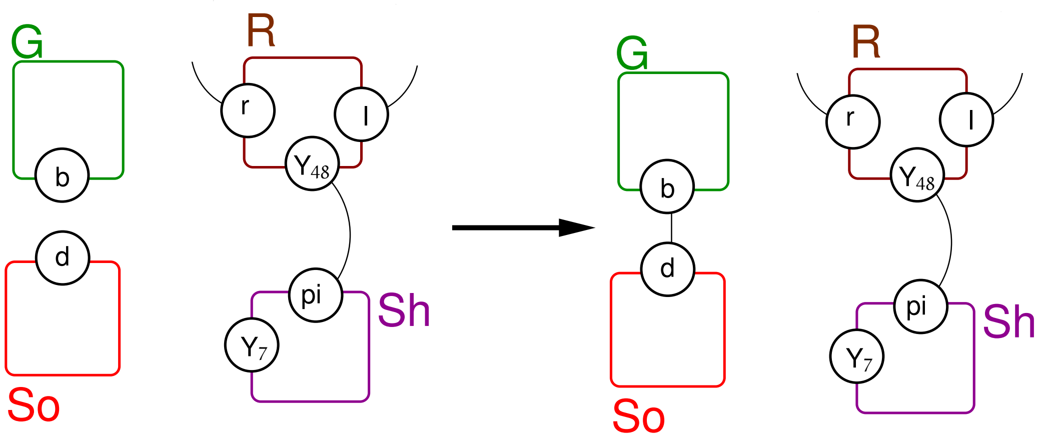

Whenever a fragment intersects a connected component of a lhs on a modified site, then the connected component is indeed embedded in the fragment!

# Fragment consumption
# Syntactic criteria




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

# Fragment consumption



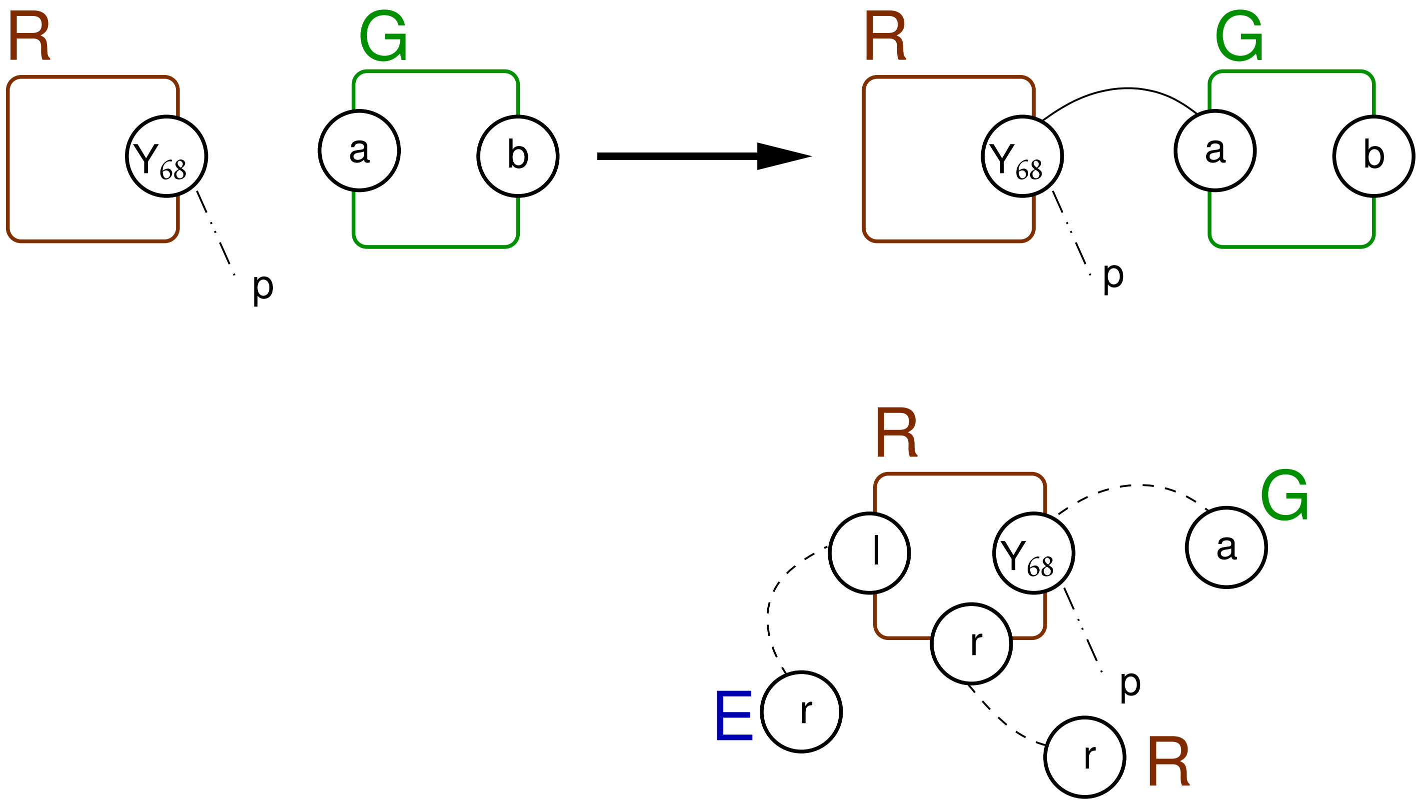

For any rule:

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

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

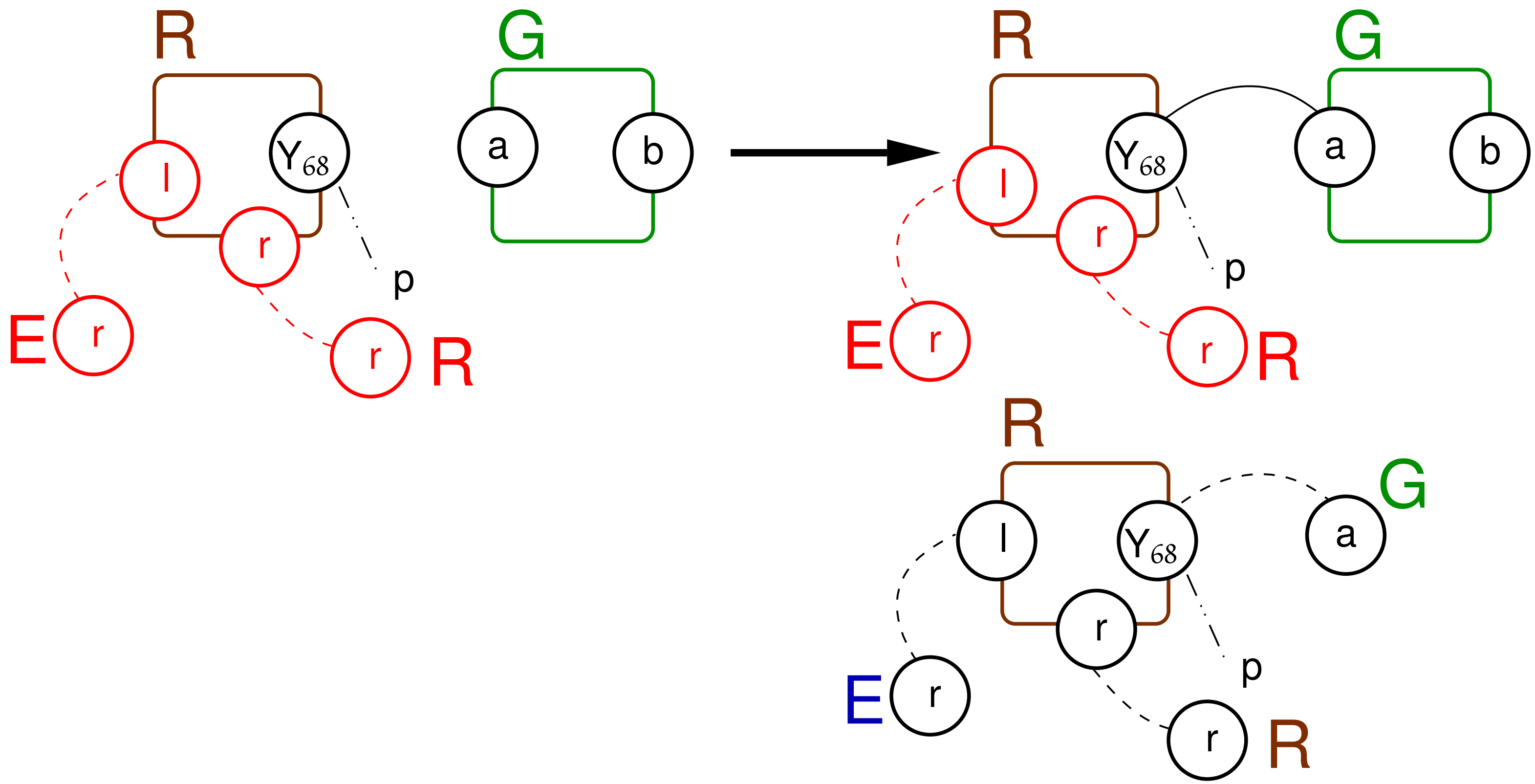
$$\frac{d[F]}{dt} \stackrel{-}{=} \frac{k \cdot [F] \cdot \prod_{i \neq k} [C_i]}{\mathsf{SYM}(C_1, \ldots, C_n) \cdot \mathsf{SYM}(F)}.$$

# Fragment production



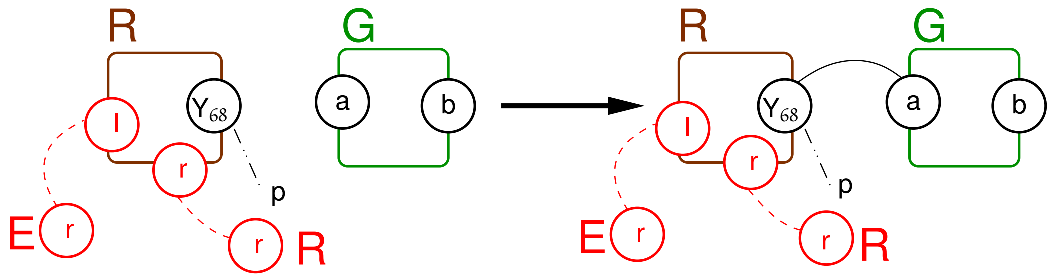

Can we express the amount (per time unit) of this fragment (bellow) concentration that is produced by the rule (above)?

# Fragment production
## Proper intersection (bis)




Yes, if the connected components of the lhs of the refinement are prefragments. This is already satisfied thanks to the previous syntactic criteria.

# Fragment production




For any rule:

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

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;
if $m = n$, then we get:

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

otherwise, we get no contribution.

# Fragment properties

If:

- an annotated contact map satisfies the syntactic criteria,
- fragments are defined by this annotated contact map,
- we know the concentration of fragments;

then:

- we can express the concentration of any connected component occuring in lhss,
- we can express fragment proper consumption,
- we can express fragment proper production,
- WE HAVE A CONSTRUCTIVE DEFINITION FOR $\mathbb{F}^\sharp$.

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# 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 $\mathcal{R}$,
$\stackrel{\Delta}{\iff}$
$\mathcal{R}$ is preserved (modulo $\equiv$) if we replace each rule with all the combinations of rules which can be obtained by replacing (independently) each occurrence of $x_1$ and $x_2$ with $x_1$ or $x_2$ (and dividing kinetic rate by the number of combinations, and taking care of gain/loss of automorphisms).

# Example I

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

# 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:

$$
\begin{array}{lcll}
A(x_u) & \longrightarrow & A(x_p) & \frac{k_1}{2} + \frac{k_1}{2} \\
A(y_u) & \longrightarrow & A(y_p) & \frac{k_1}{2} + \frac{k_1}{2} \\
A(x_p,y_p) & \longrightarrow & & \frac{k_2}{2} + \frac{k_2}{2}
\end{array}
$$

So, x and y are symmetric in A!

# Example II

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

# Example II

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

We get:

$$\begin{array}{llll} A(x_u) & \longrightarrow & A(x_p) & \frac{k_1}{2} + \frac{k_2}{2} \\ A(y_u) & \longrightarrow & A(y_p) & \frac{k_1}{2} + \frac{k_2}{2} \\ A(x_p,y_p) & \longrightarrow & & \frac{k_3}{2} + \frac{k_3}{2} \end{array}$$

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

# Example III

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

# Example III

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

We get:

$$A(x),\ A(x) \longrightarrow A(x^1),\ A(x^1) \quad \frac{k}{2}$$
$$A(y),\ A(y) \longrightarrow A(y^1),\ A(y^1) \quad \frac{k}{2}$$
$$A(x),\ A(y) \longrightarrow A(x^1),\ A(y^1) \quad \frac{k}{2}$$

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

# Example IV

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

# Example IV

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

We get:

$$
\begin{array}{lllll}
A(x), A(x) & \longrightarrow & A(x^1), A(x^1) & \frac{k_1}{4} + \frac{k_2}{4} + \frac{k_3}{2} \\
A(y), A(y) & \longrightarrow & A(y^1), A(y^1) & \frac{k_1}{4} + \frac{k_2}{4} + \frac{k_3}{2} \\
A(x), A(y) & \longrightarrow & A(x^1), A(y^1) & \frac{k_1}{4} + \frac{k_2}{4} + \frac{k_3}{2}
\end{array}
$$

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:

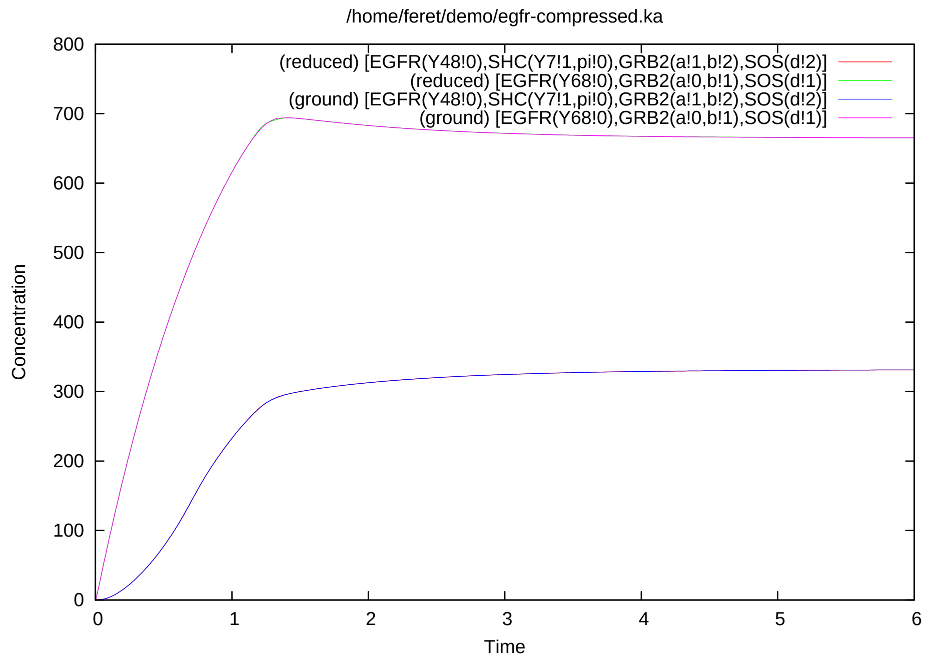
$$\frac{A_i \sim_{\text{ag}} A'_i, 1 \leq i \leq k}{A_1, \ldots, A_k \sim_{\text{pattern}} A'_1, \ldots, A'_k}.$$

- 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

# 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 | $\sim 2.10^{19}$ |




Both differential semantics
(4 curves with match pairwise)

# Related issues

1. Model reduction of the ODE semantics:
   Joint work with Ferdinanda Camporesi
   - Less syntactic approximation of the flow of information
   - A hierarchy of abstractions tuned by the level of context-sensitivity

2. Model reduction of the stochastic semantics:
   Joint work with Thomas Henzinger, Heinz Koeppl, Tatjana Petrov
   - a framework that preserves the trace distribution
     (lumpability, backward bisimulation, equiprobability of equivalent concrete configurations)
   - Compositionality of the framework
   - Symmetry reduction

# SASB 2013

Fourth International Workshop
on Static Analysis and Systems Biology
http://www.di.ens.fr/sasb2013/

June, 19th, 2013,
Seattle, USA

Co-chaired by:

- Jérôme Feret
- Andre Levchenko.

Keynote speakers:

- Eric Deeds,
- ...

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

Friday, the 25th of January, 2013

# 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

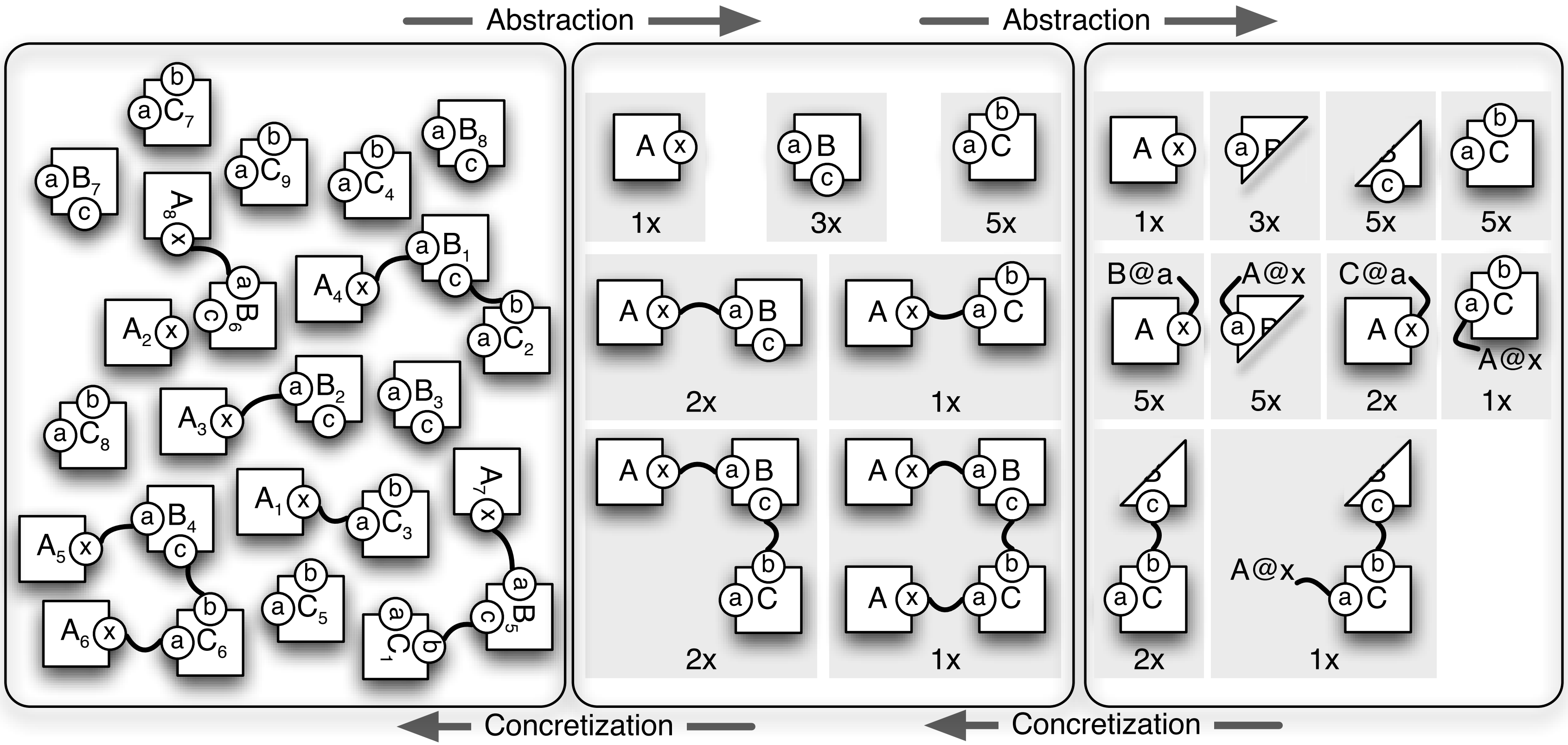
# ODE fragments

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

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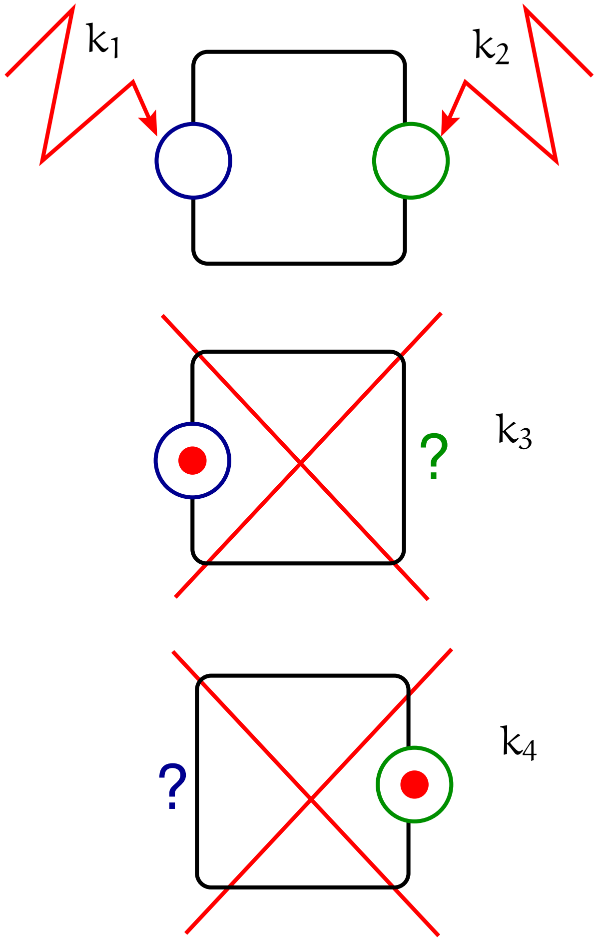
# A model with ubiquitination




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

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

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

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

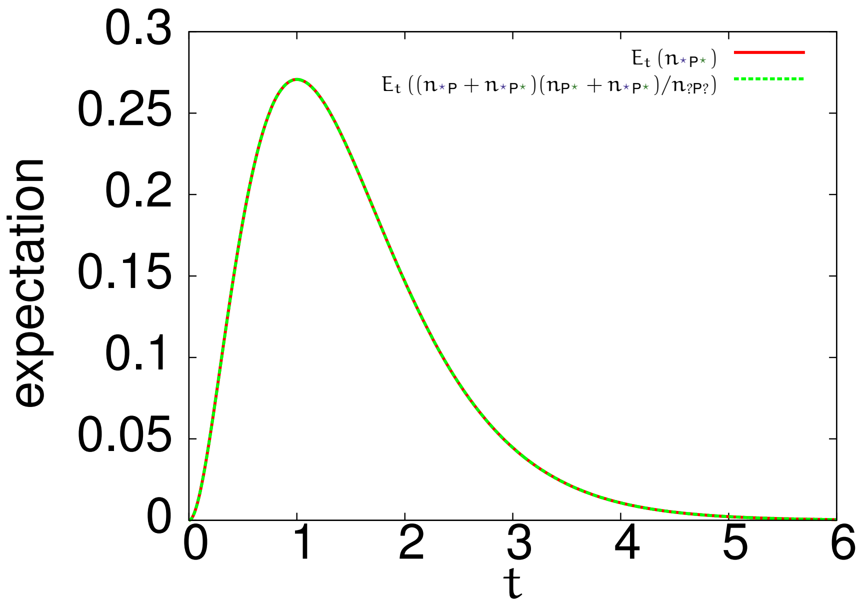
$$P^{\star} \xrightarrow{k_4} \emptyset$$

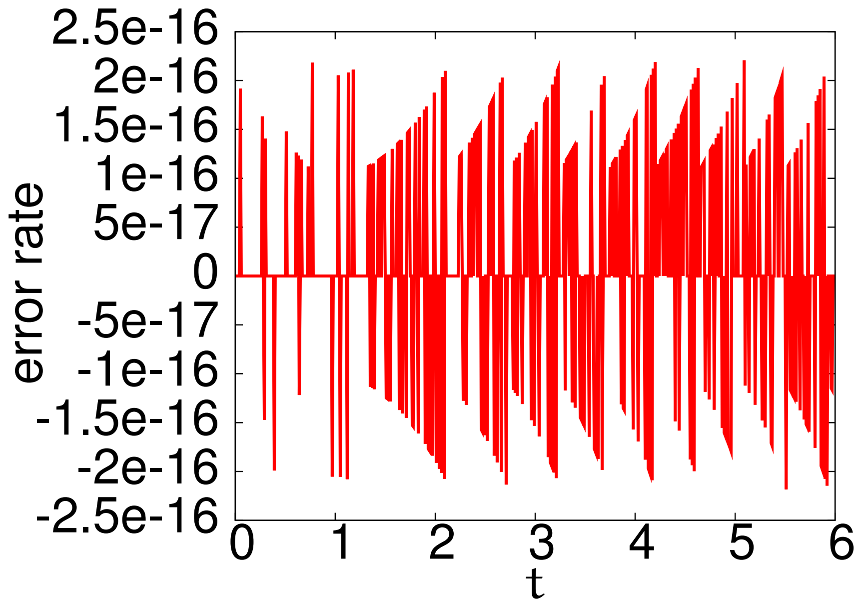
$$ {}^{\star}P^{\star} \xrightarrow{k_4} \emptyset$$

# Statistical independence

We check numerically that:

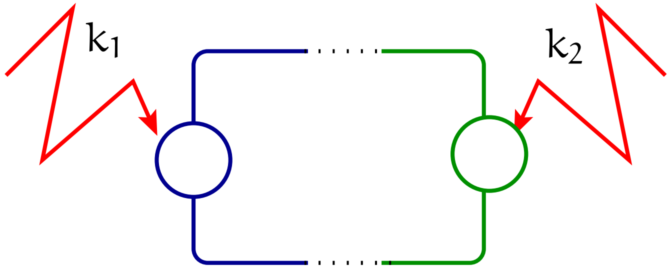
$$E_t\left(n_{\star P \star}\right) = E_t\left(\frac{(n_{\star P} + n_{\star P \star})(n_{P \star} + n_{\star P \star})}{n_P + n_{P \star} + n_{\star P} + n_{\star P \star}}\right).$$



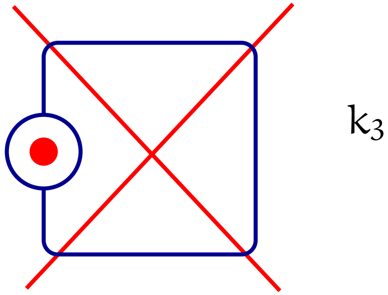




with $k_1 = k_2 = k_3 = k_4 = 1$
and two instances of P at time $t = 0$.

# Reduced model

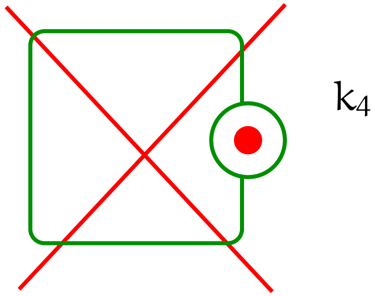



$$P \xrightarrow{k_1} {}^{\star}P$$
$$P \xrightarrow{k_2} P^{\star}$$




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

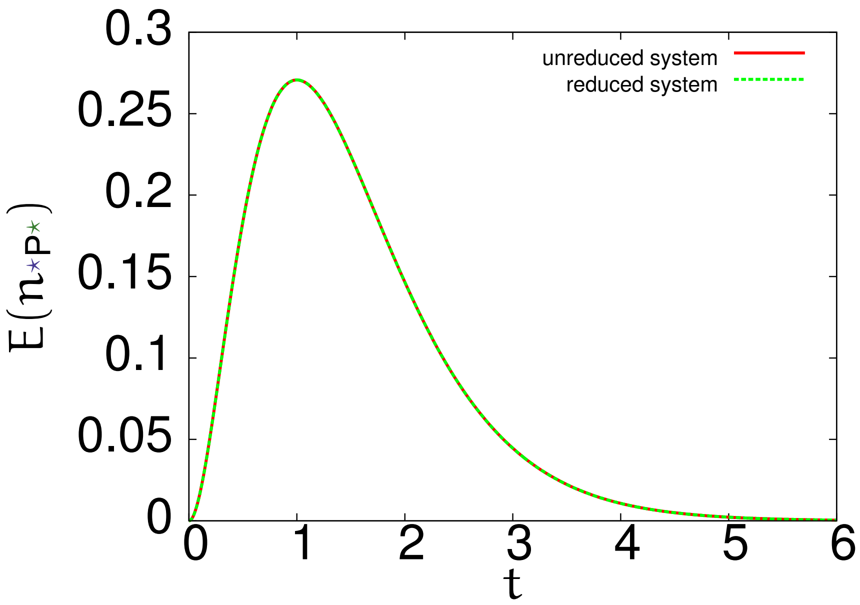
+ side effect: remove one P

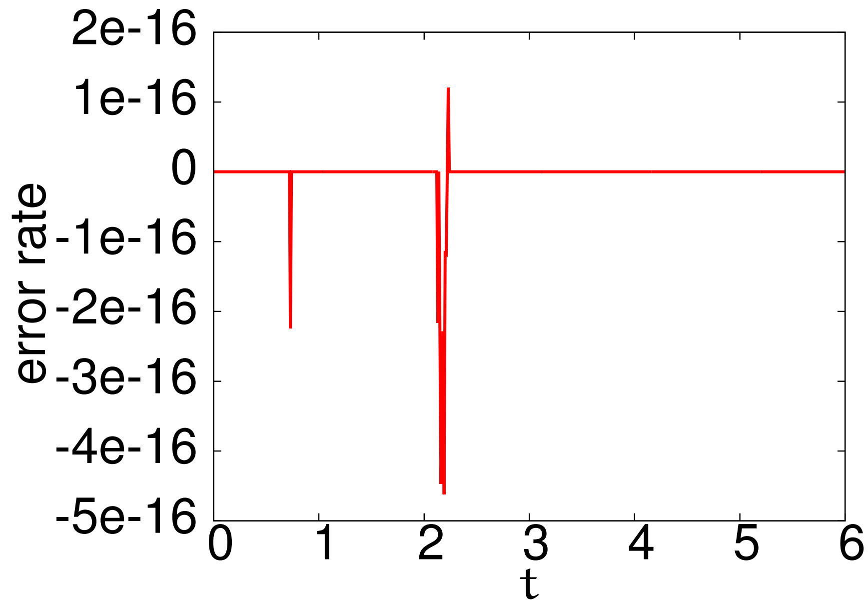



$$P^{\star} \xrightarrow{k_4} \emptyset$$

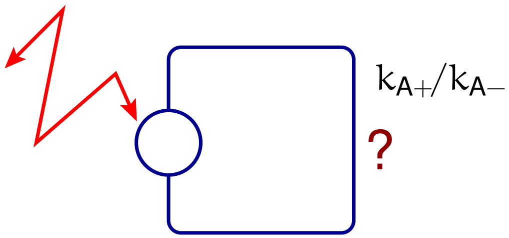
+ side effect: remove one P

# Comparison between the two models

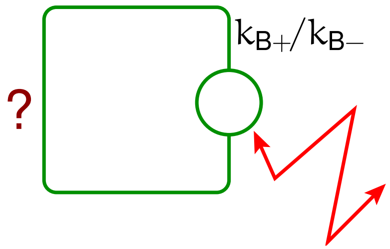


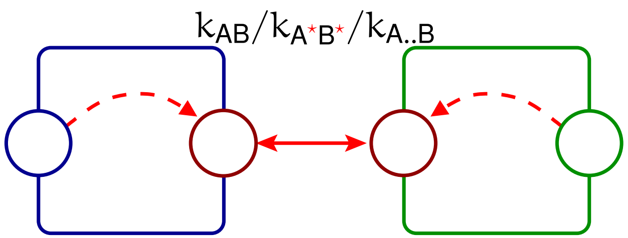
# Coupled semi-reactions




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



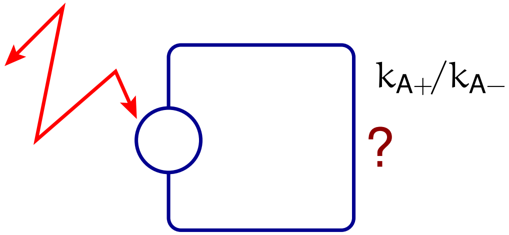

$$B \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} B^{\star},\quad AB \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} AB^{\star},\quad A^{\star}B \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} A^{\star}B^{\star}$$



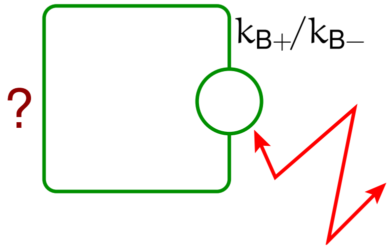

$$A + B \underset{k_{A..B}}{\overset{k_{AB}}{\rightleftharpoons}} AB,\quad A^{\star} + B \underset{k_{A..B}}{\overset{k_{AB}}{\rightleftharpoons}} A^{\star}B,$$

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

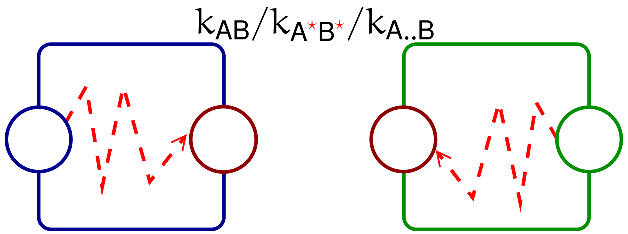
# Reduced model




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




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



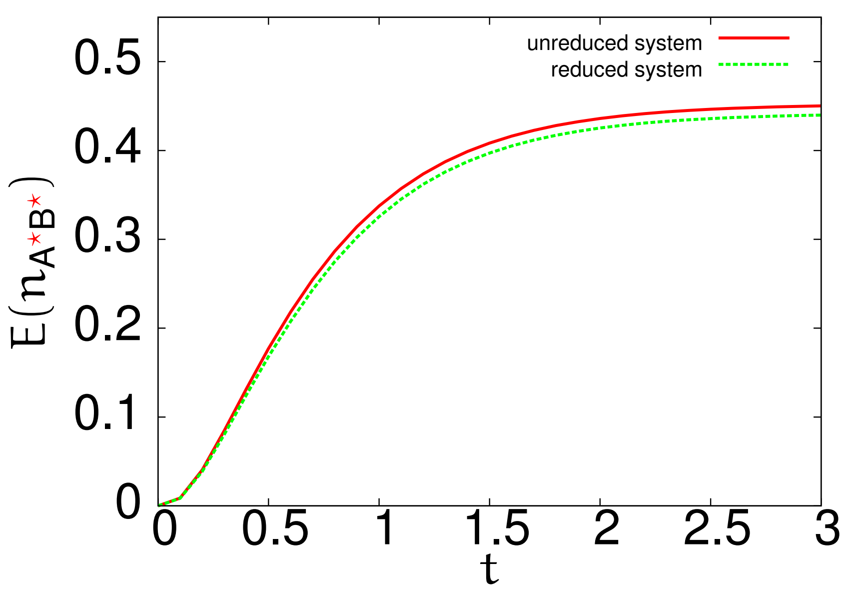

$$A + B \underset{k_{A..B}/(n_{A^{\diamond}B}+n_{A^{\diamond}B^{\star}})}{\overset{k_{AB}}{\rightleftharpoons}} AB^{\diamond} + A^{\diamond}B,$$

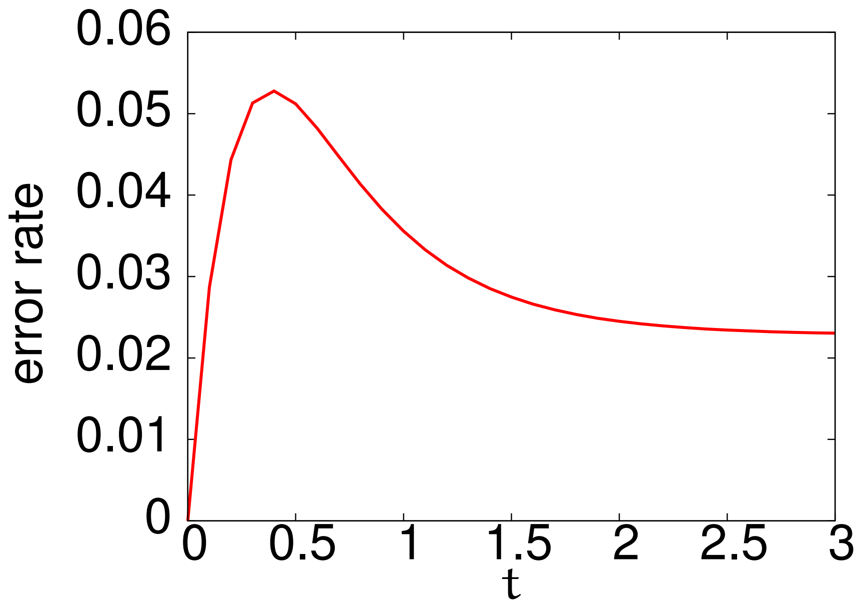
$$A^{\star} + B \underset{k_{A..B}/(n_{A^{\diamond}B}+n_{A^{\diamond}B^{\star}})}{\overset{k_{AB}}{\rightleftharpoons}} A^{\star}B^{\diamond} + A^{\diamond}B,$$

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

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

# Comparison between the two models

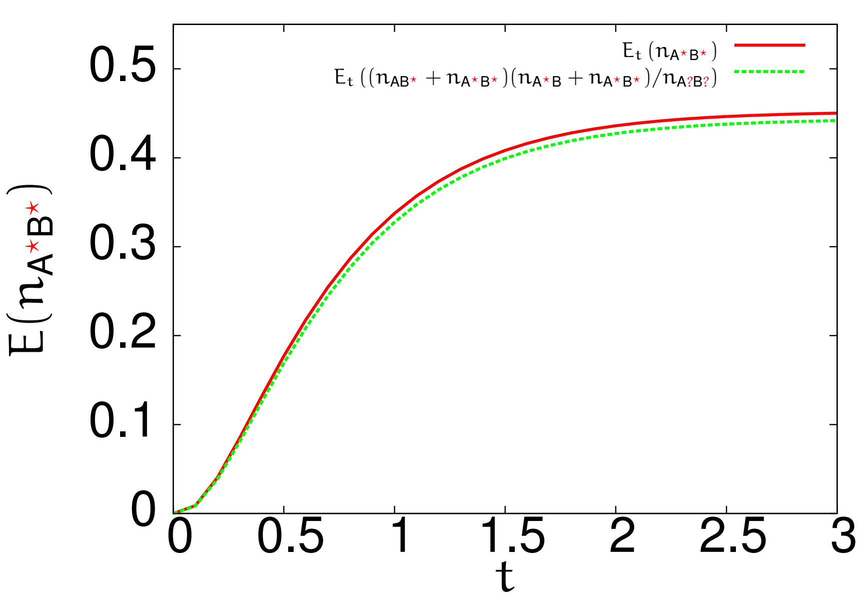


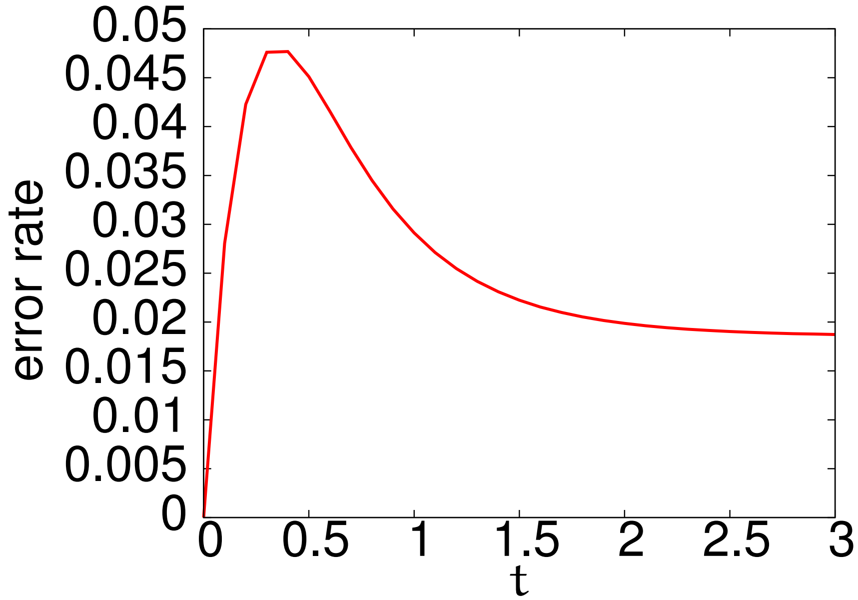




with $k_{A+} = k_{A-} = k_{B+} = k_{B-} = k_{AB} = k_{A..B} = 1$, $k_{A^\star B^\star} = 10$,
and two instances of A and B at time $t = 0$.

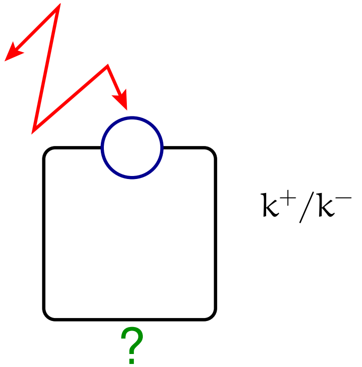
Although the reduction is correct in the ODE semantics.

# Degree of correlation (in the unreduced model)



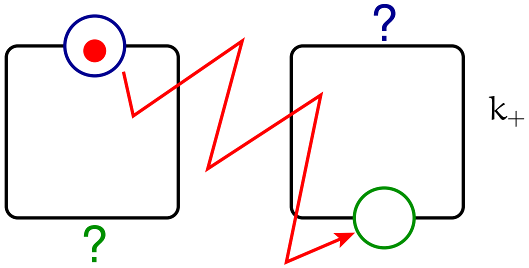



# Distant control




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

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

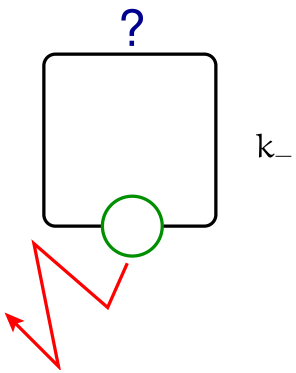



$$A + A^{\star} \xrightarrow{k_+} A_{\star} + A^{\star}$$

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

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

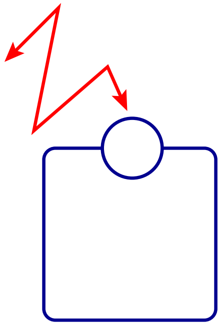
$$A^{\star} + A^{\star}_{\star} \xrightarrow{k_+} A^{\star}_{\star} + A^{\star}_{\star}$$




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

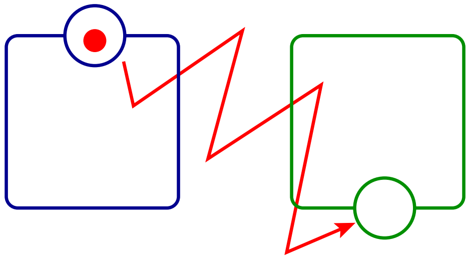
$$A_{\star} \xrightarrow{k_-} A$$

# Reduced model



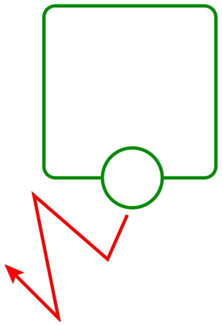
$k^+/k^-$

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



$k_+$

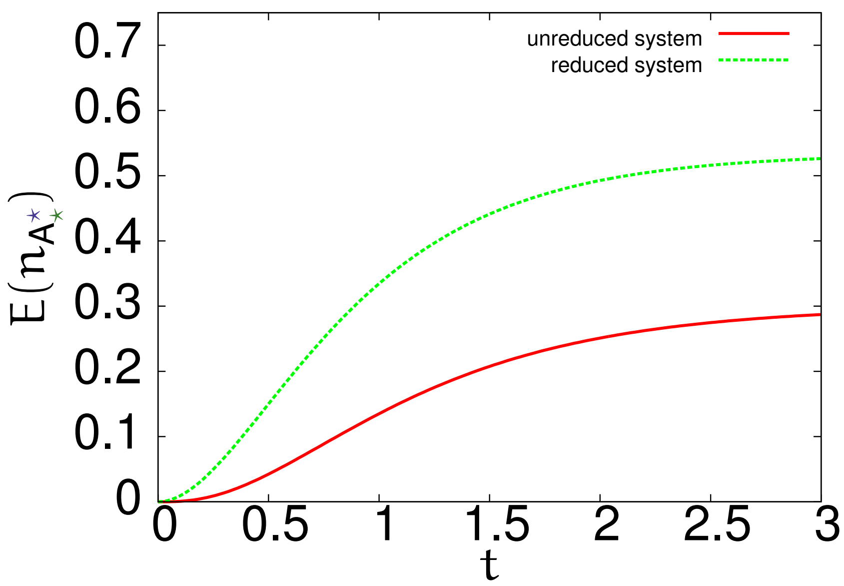
$$A + A^\star \xrightarrow{k_+} A_\star + A^\star$$

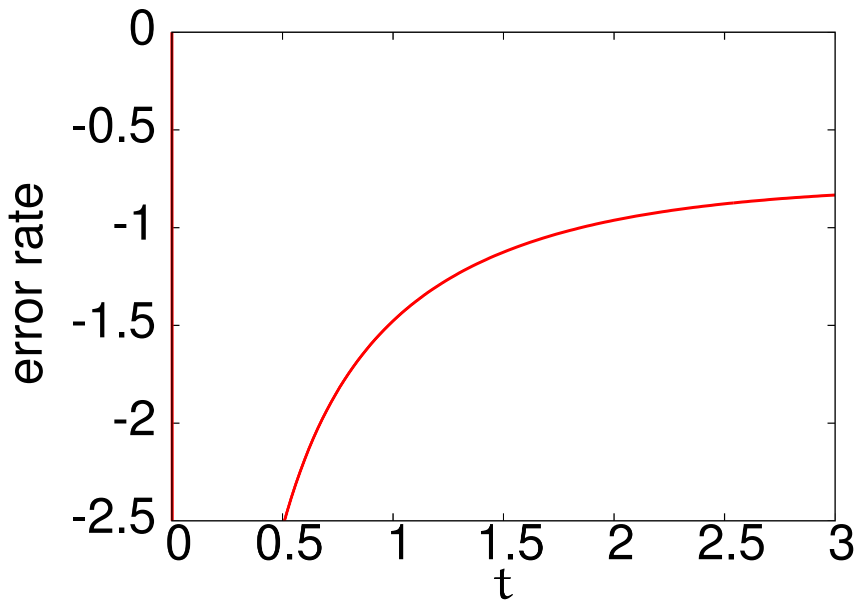


$k_-$

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

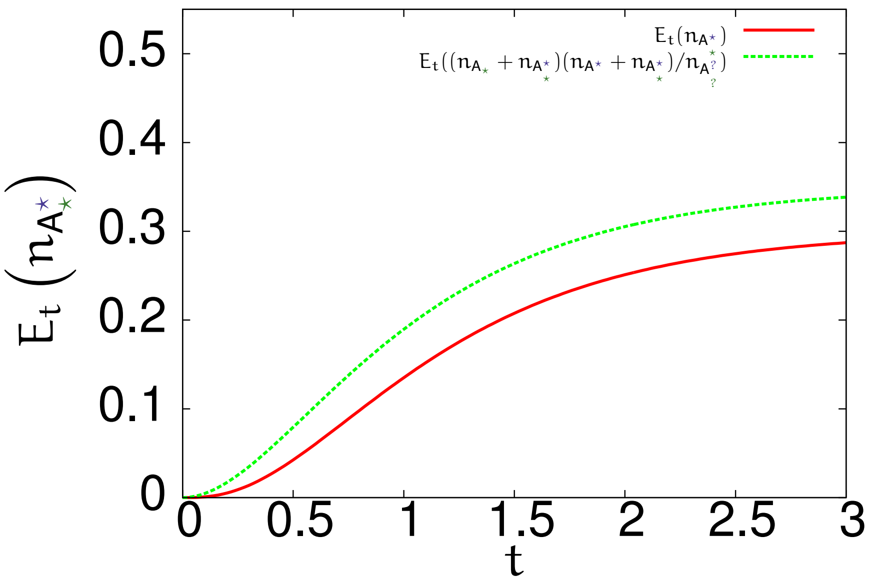
# Comparison between the two models

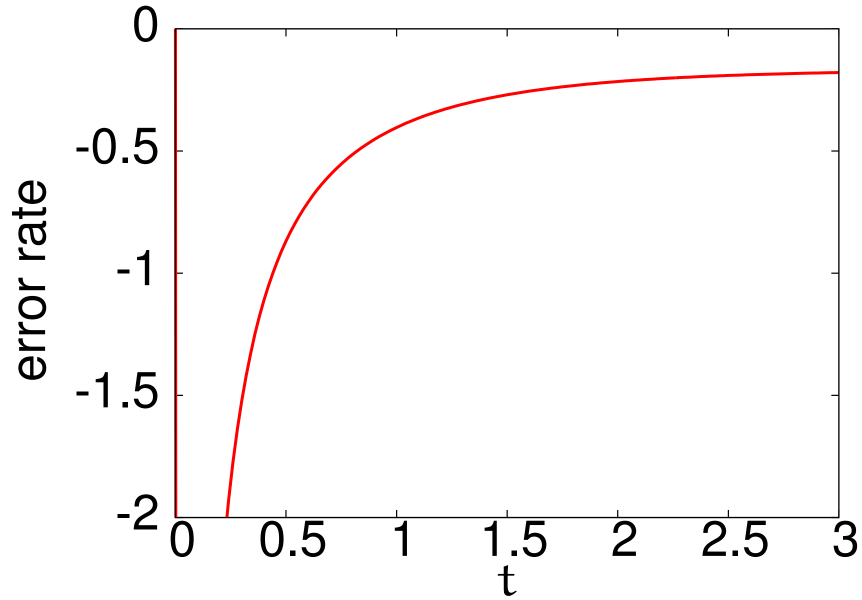



with $k^+ = k^- = k_+ = k_- = 1$,
and two instances of A at time $t = 0$.

# Degree of correlation
# (in the unreduced model)



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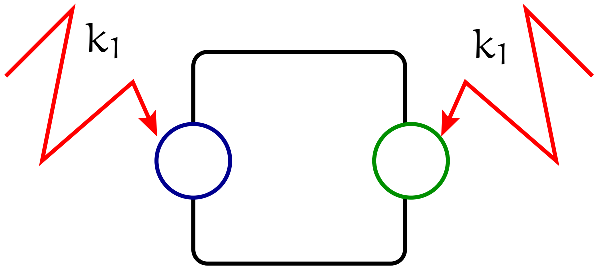
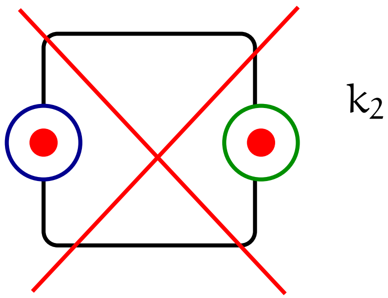
# A model with symmetries




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

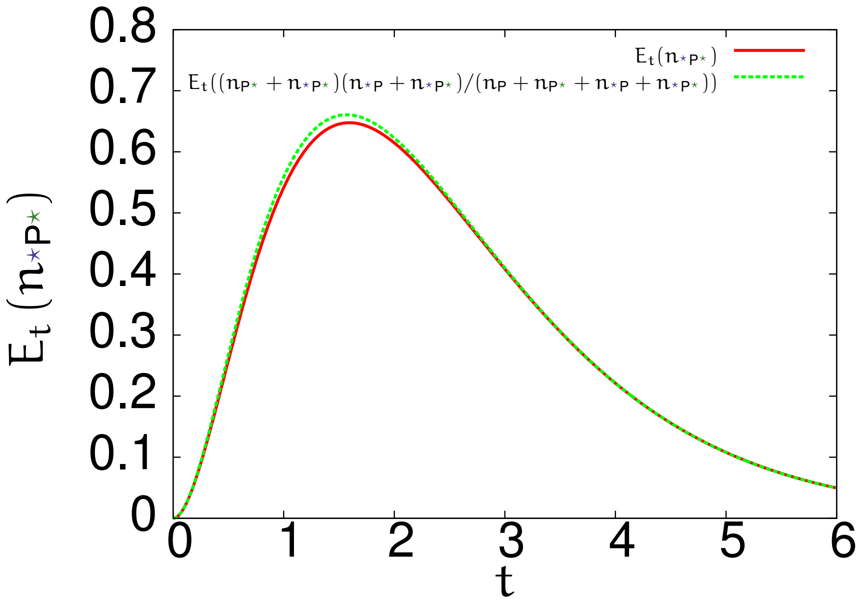
$$P \xrightarrow{k_1} P^{\star} \qquad {}^{\star}P \xrightarrow{k_1} {}^{\star}P^{\star}$$

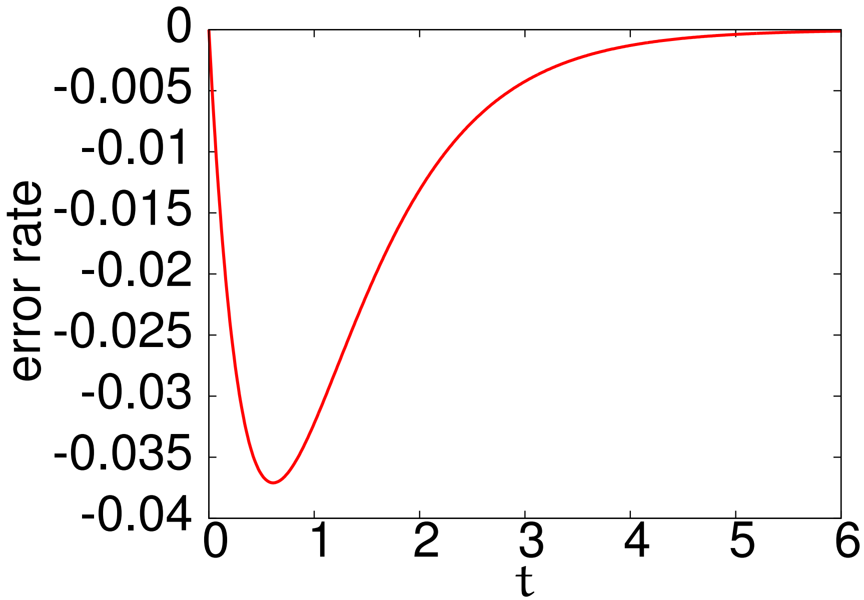



$${}^{\star}P^{\star} \xrightarrow{k_2} \emptyset$$

# Degree of correlation (in the unreduced model)

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



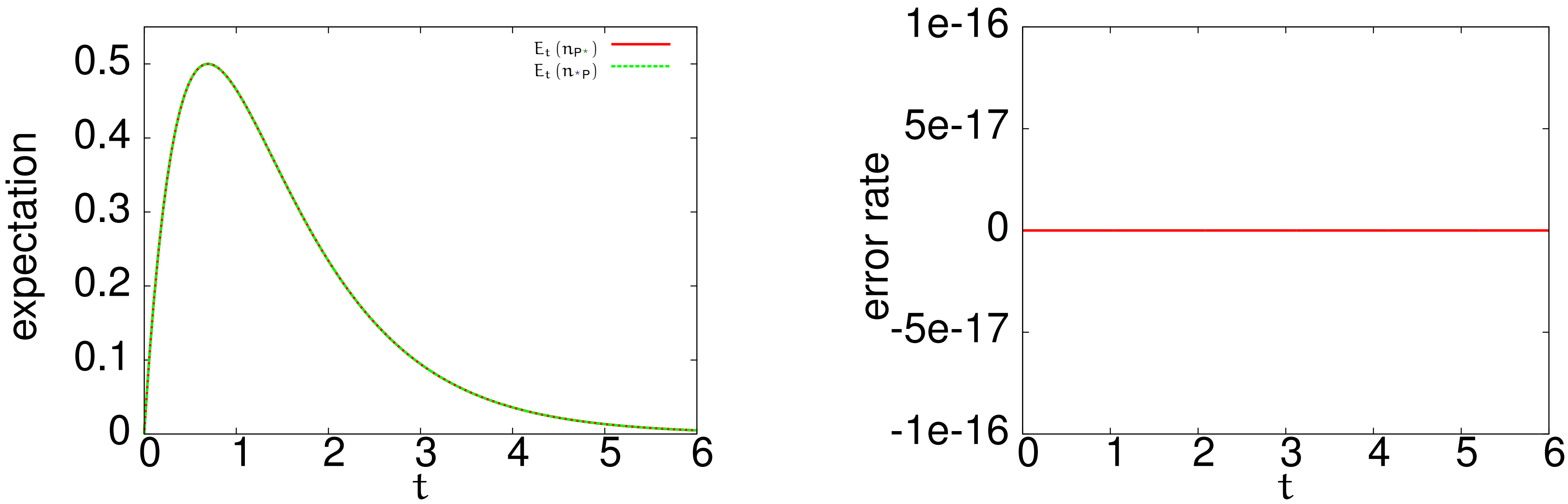

with $k_1 = k_2 = 1$

and two instances of P at time $t = 0$.

# Equivalent chemical species

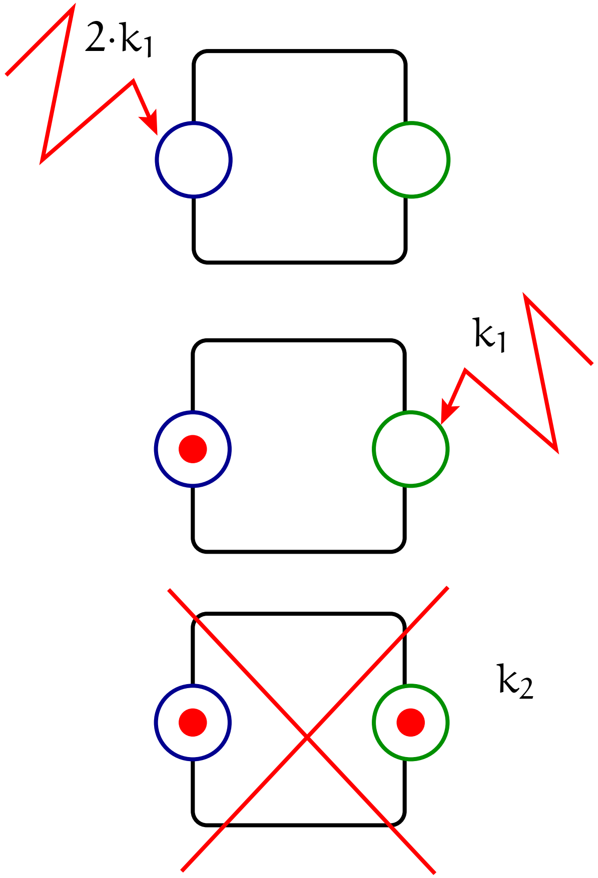
We check numerically that:

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




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

# Reduced model



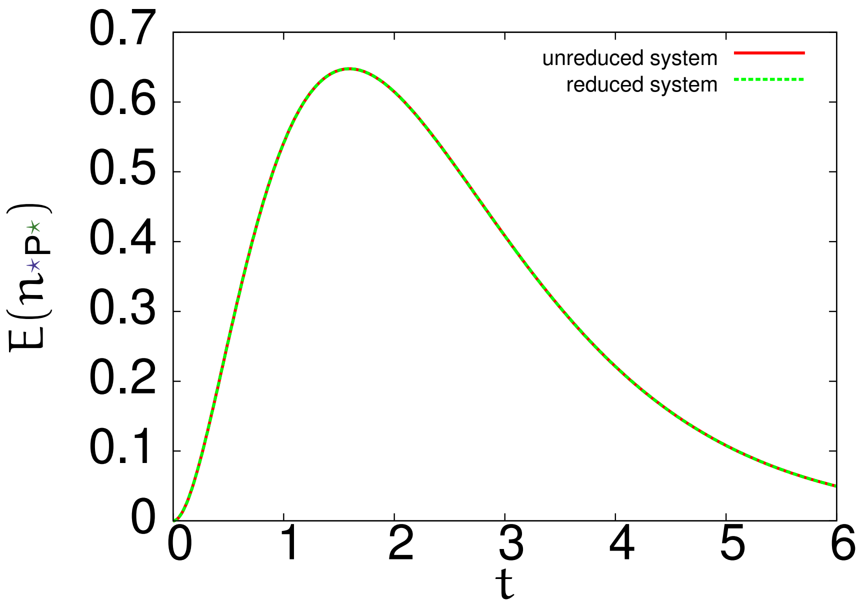

$$P \xrightarrow{2\cdot k_1} {}^{\star}P$$

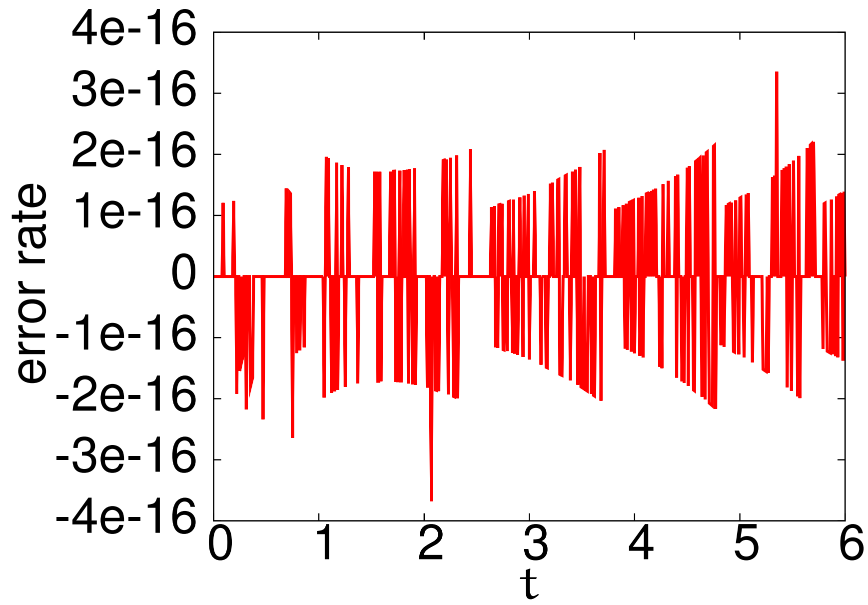
$$^{\star}P \xrightarrow{k_1} {}^{\star}P^{\star}$$

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

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:

$$\tau \triangleq q_0 \overset{\lambda_1, I_1}{\rightarrow} q_1 \ldots q_{k-1} \overset{\lambda_k, I_k}{\rightarrow} q_k$$

where:

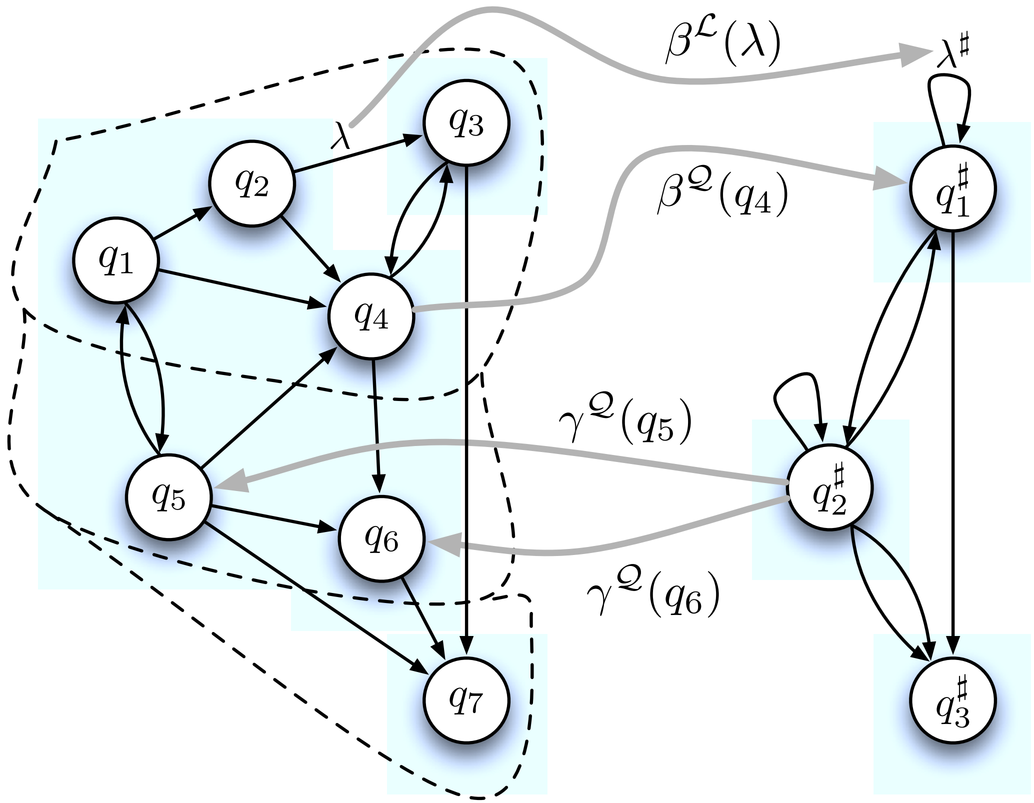
- $(q_i)_{0 \leq i \leq k} \in \mathcal{Q}^{k+1}$ and $(\lambda_i)_{1 \leq i \leq k} \in \mathcal{L}^k$,
- $(I_i)_{1 \leq i \leq k}$ is a family of open intervals in $\mathbb{R}_0^+$.

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

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

where $a(q) \triangleq \sum_{\lambda, q'} w(q, \lambda, q')$.

# 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 $\tau$ 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 $\mathcal{S} \stackrel{\Delta}{=} (\mathcal{Q}, \mathcal{L}, \rightarrow, w, \mathcal{I}, \pi_0)$ 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 $\beta^{\mathcal{L}} : \mathcal{L} \rightarrow \mathcal{L}^\sharp$,
- 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:

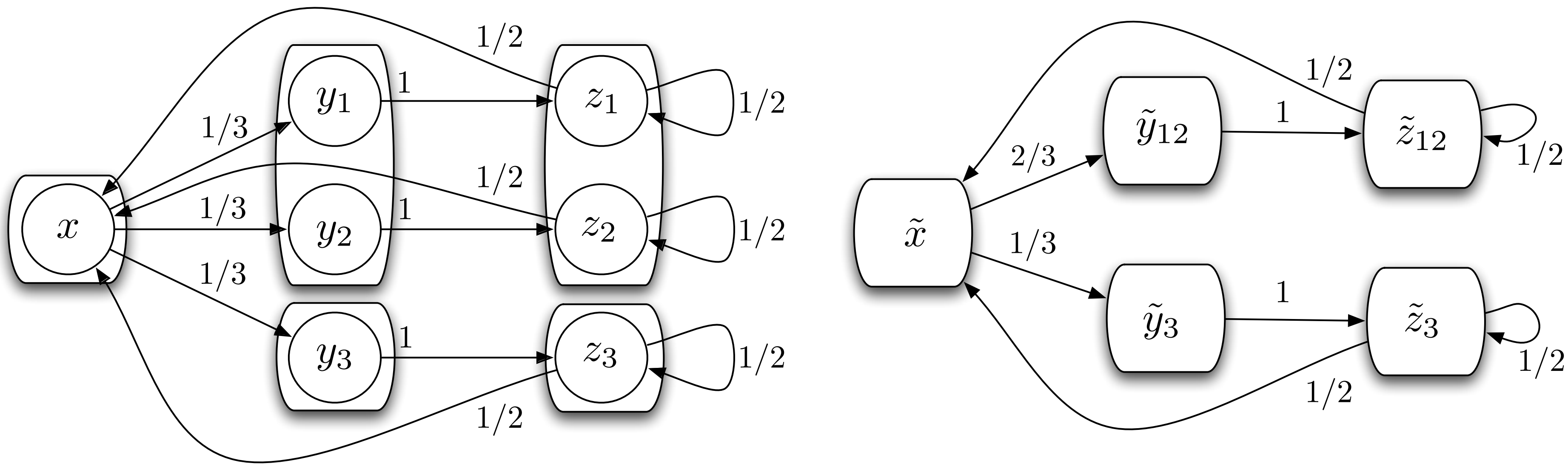
- a stochastic process $(\mathcal{X}_t)$ which satisfies the Markovian property,
- an initial distribution $\pi_0 \; : \; \mathcal{Q} \to [0,1]$,
- an equivalence relation $\sim$ over $\mathcal{Q}$,

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

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

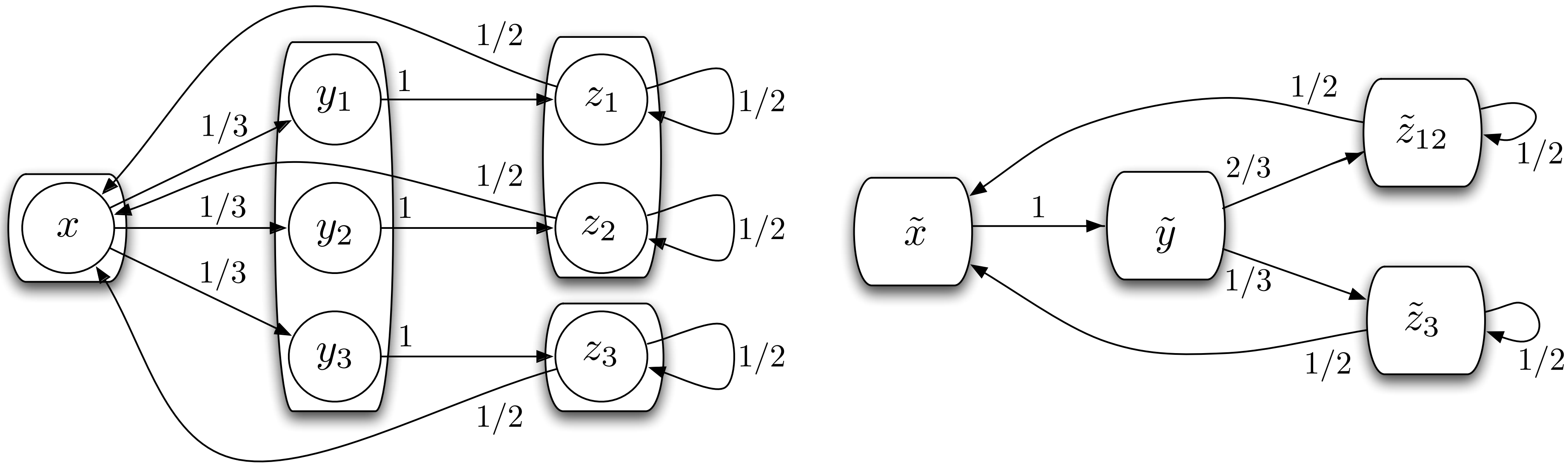
We say that $(\mathcal{X})_t$ is $\sim$-lumpable with respect to $\pi_0$ if and only if, the stochastic process $(\mathcal{Y}_t)$ satisfies the Markovian property as well.

# Strong lumpability




A stochastic process is ~-strongly lumpable, if:
it is ~-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

1. Introduction
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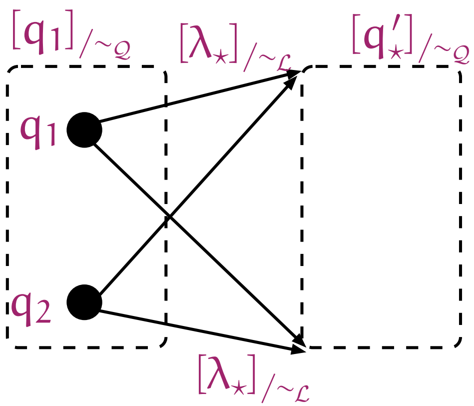
8. Conclusion

# 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 $q_1 \sim_{\mathcal{Q}} q_2$:

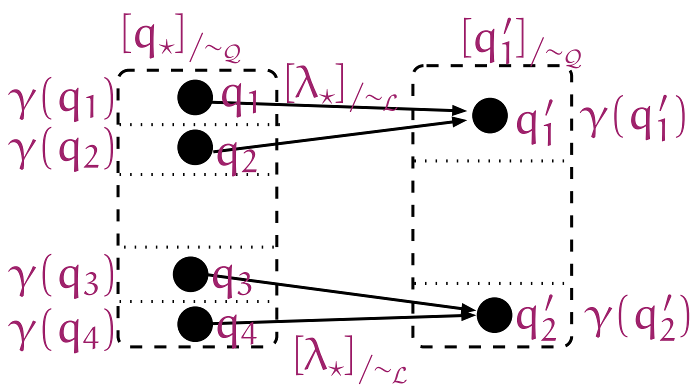
- $a(q_1) = a(q_2)$;
- and for any $\lambda_\star \in \mathcal{L}$, $q'_\star \in \mathcal{Q}$,
  $\mathsf{fwd}(q_1, [\lambda_\star]_{/\sim_{\mathcal{L}}}, [q'_\star]_{/\sim_{\mathcal{Q}}}) = \mathsf{fwd}(q_2, [\lambda_\star]_{/\sim_{\mathcal{L}}}, [q'_\star]_{/\sim_{\mathcal{Q}}})$




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 $\gamma : \mathcal{Q} \rightarrow \mathbb{R}^+$, 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 $\lambda_\star \in \mathcal{L}$, $q_\star \in \mathcal{Q}$,
  $\mathsf{bwd}([q_\star]_{/\sim_{\mathcal{Q}}}, [\lambda_\star]_{\sim_{/\mathcal{L}}}, q'_1) = \mathsf{bwd}([q_\star]_{/\sim_{\mathcal{Q}}}, [\lambda_\star]_{\sim_{/\mathcal{L}}}, q'_2)$

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

# Logical implications

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

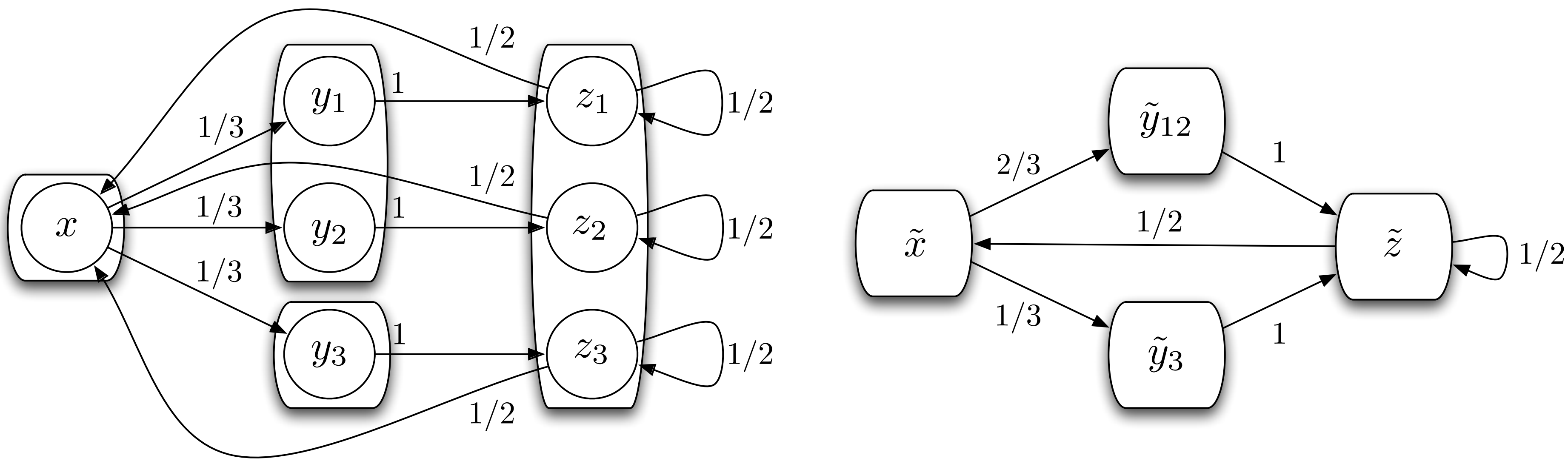
  moreover, it induces a sound abstraction;
- if $(\sim_{\mathcal{Q}}, \sim_{\mathcal{L}})$ is a backward bisimulation, then the process is $\sim_{\mathcal{Q}}$-weakly lumpable, for the initial distributions which satisfy:

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

  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.

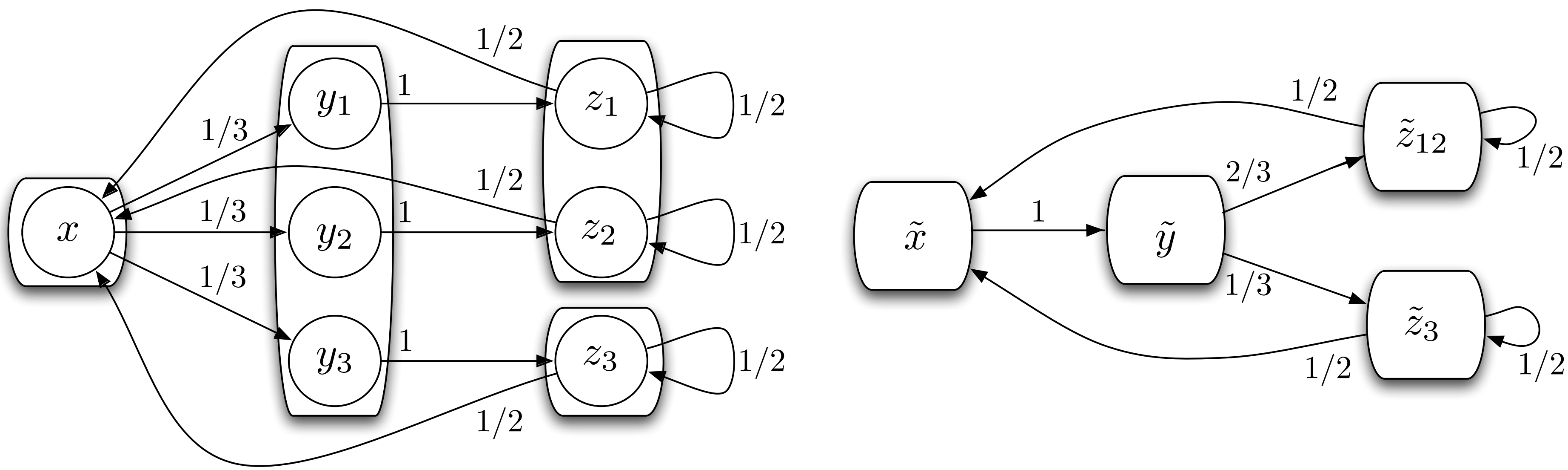
# Counter-example I

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:

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

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 $\text{pred}([q_\star]_{/\sim_\mathcal{Q}}, [\lambda_\star]_{\sim_{/\mathcal{L}}}, q_1')$ and $\text{pred}([q_\star]_{/\sim_\mathcal{Q}}, [\lambda_\star]_{\sim_{/\mathcal{L}}}, q_2')$ which is compatible with $w$,

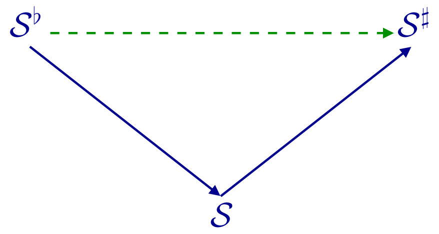
then:

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

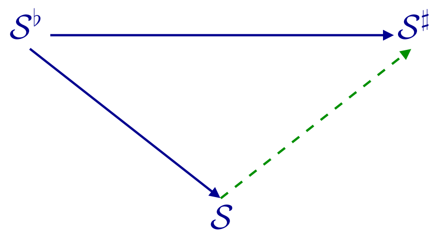
# Abstraction algebra

(Sound) abstractions can be:

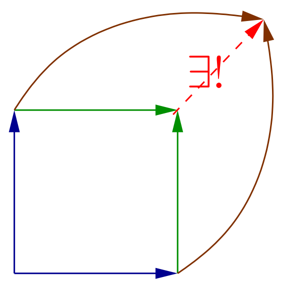
- composed:



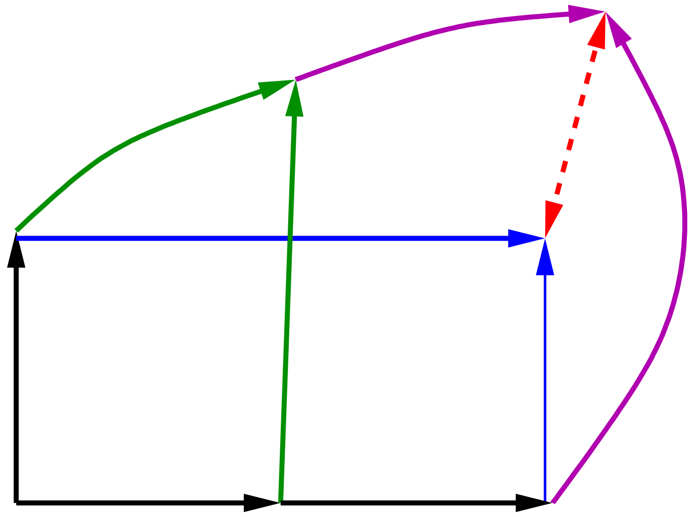

- factored:




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



# Compatibility between composition and pushout



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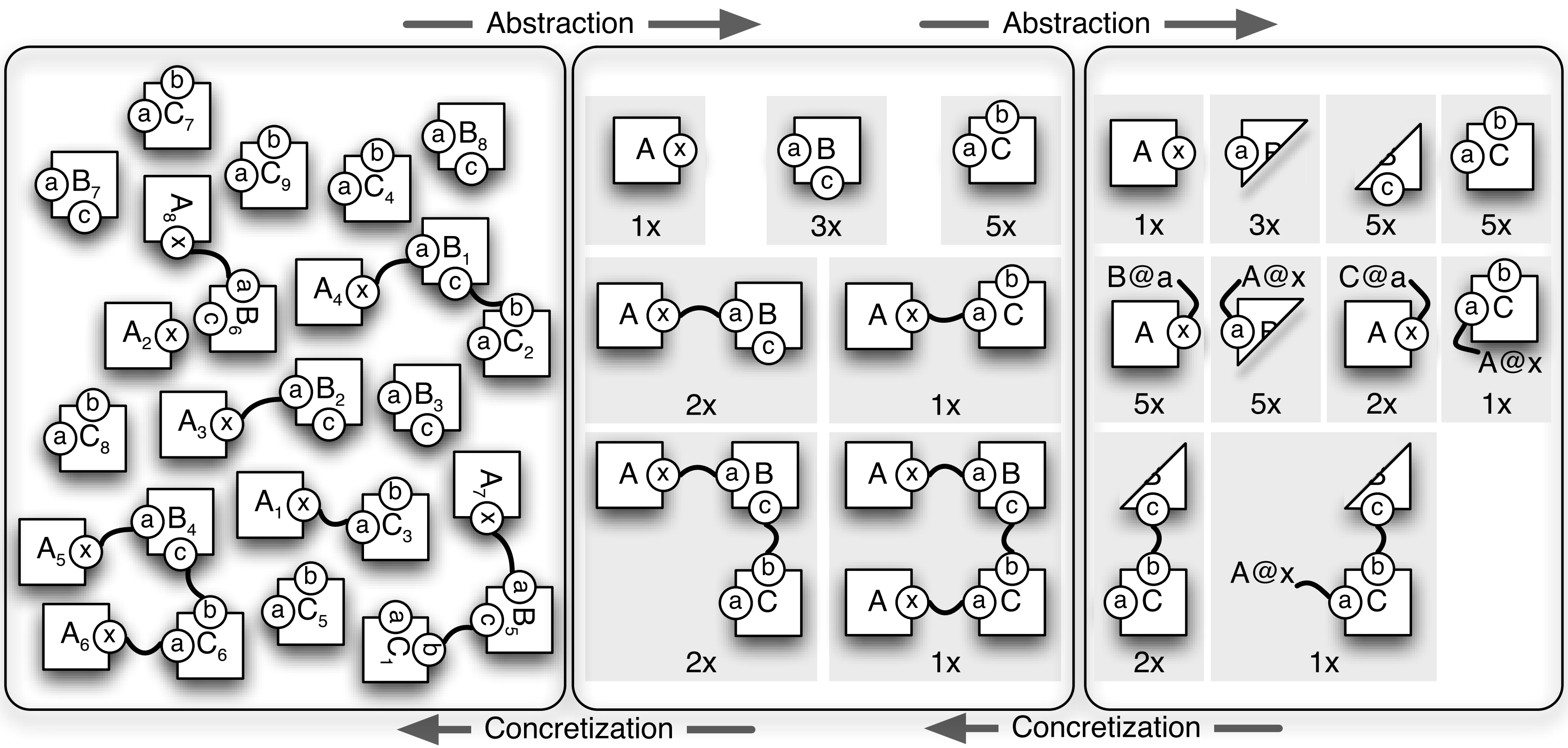


Abstraction
Abstraction
Concretization
Concretization
1x
3x
5x
2x
1x
2x
1x
B@a
A@x
C@a
A@x

# 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:

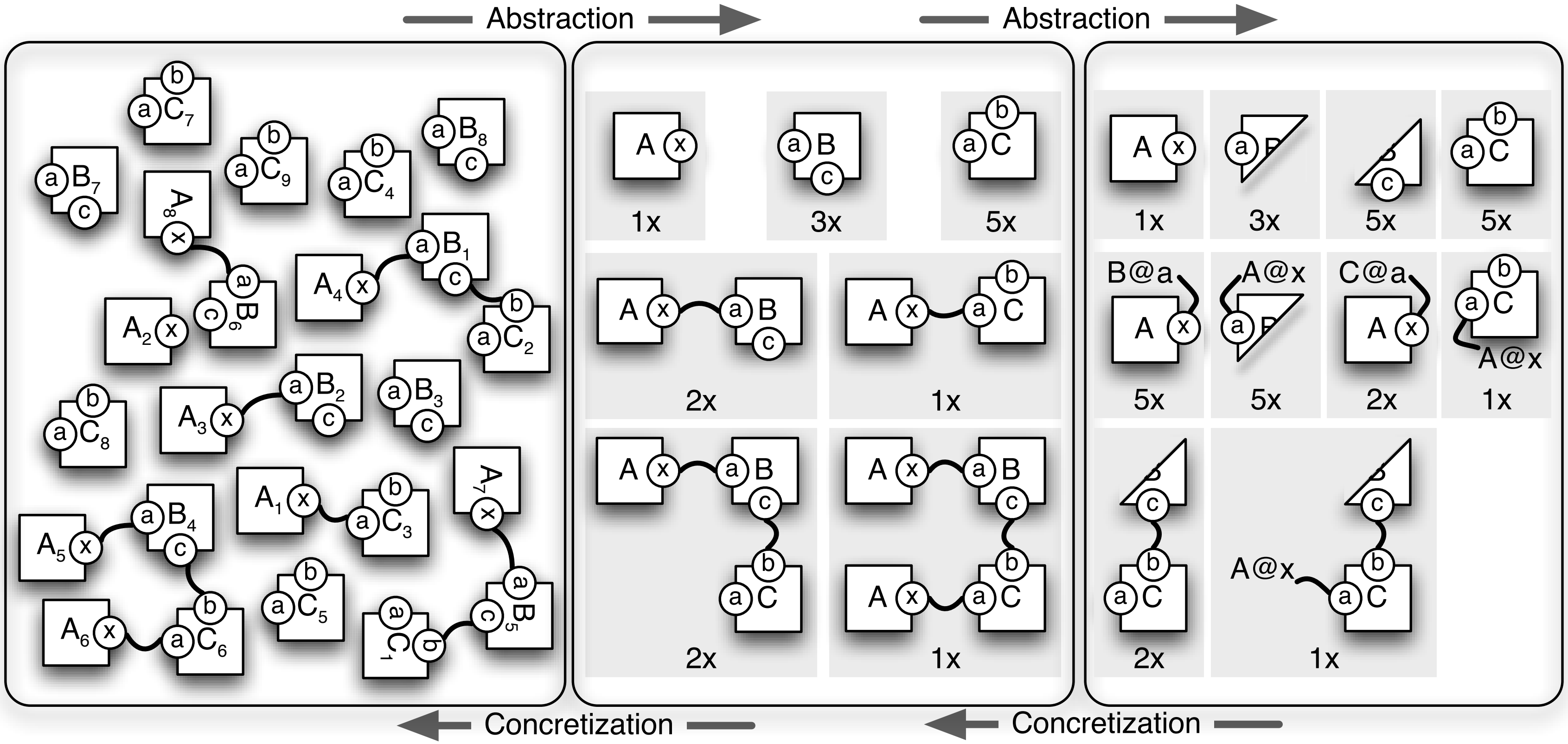
- Whenever the site $x$ and $y$ both occurs in the same or in distinct agent of type $A$ in a rule, then, there should be a bidirectional edge between the site $x$ and the $y$ of $A$.
- Whenever there is a bond between two sites, each of which either carries an internal state of, is connected to some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

# From population to fragments

- Population of fragments:

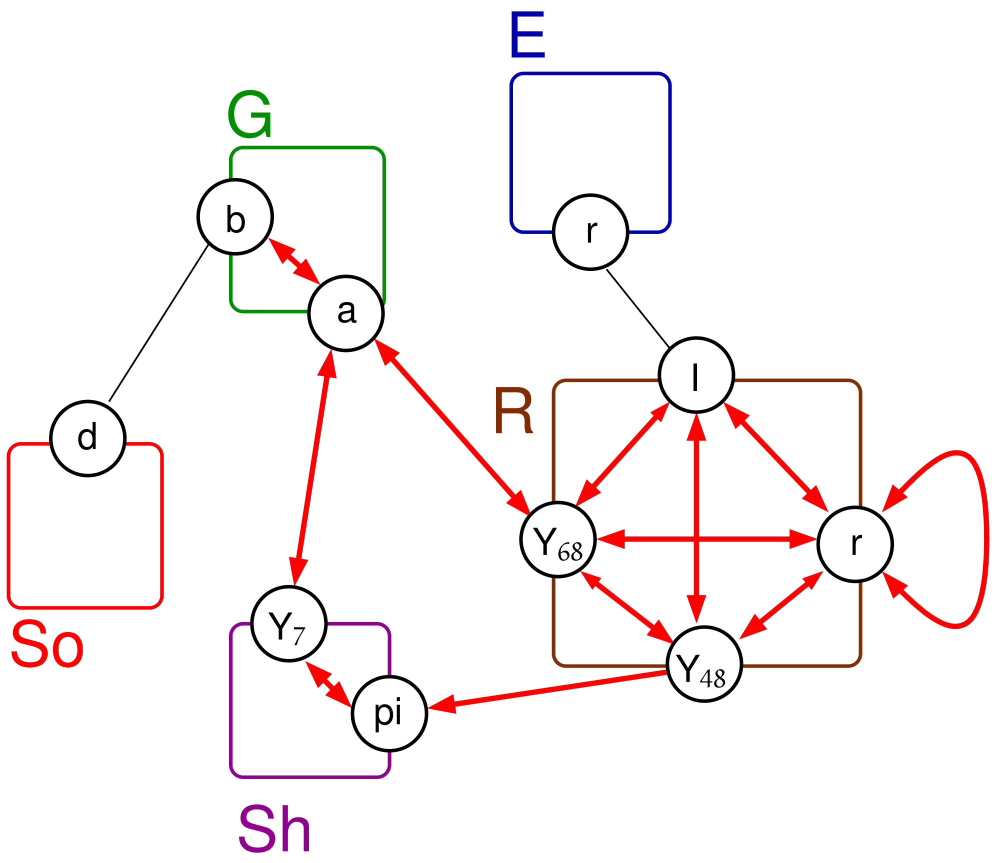
1. In the annotated contact, each agent is fitted with a binary equivalence over its sites. We split the interface of agents into equivalence classes of sites. Then we abstract away which subagents belong to the same agent.

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

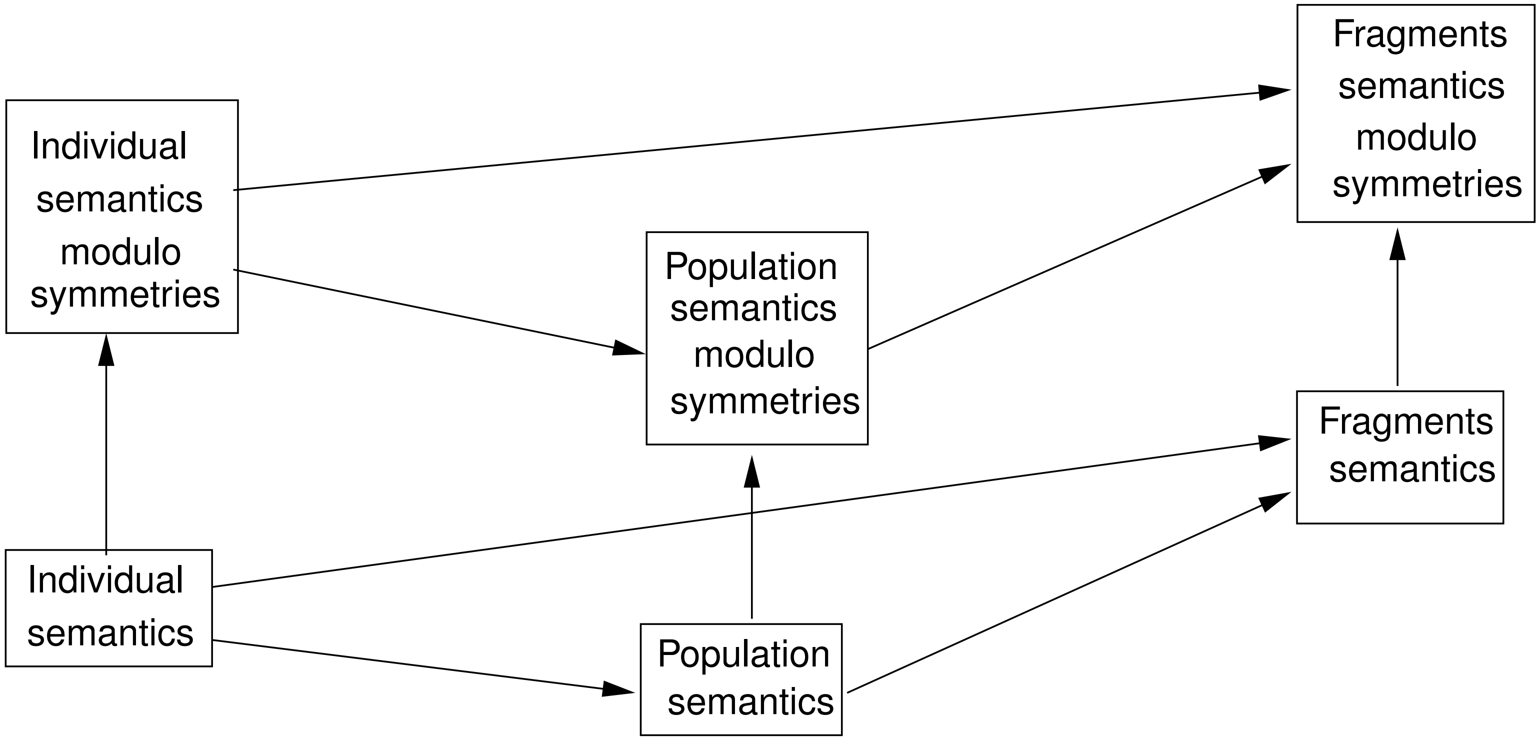
Let $\mathcal{R}$ be a set of rules and $\mathcal{M}_0$ be an initial mixture.

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

$\overset{\Delta}{\Longleftrightarrow}$

- $\mathcal{R}$ is preserved (modulo $\equiv$) if we replace each rule with all the combinations of rules which can be obtained by replacing (independently) each occurrence of $x_1$ and $x_2$ with $x_1$ or $x_2$ (and dividing the kinetic rate by the number of combinations, and taking care of gain/loss of automorphisms).
- each agent of type $A_i$ in $\mathcal{M}_0$ has their sites $x_1$ and $x_2$ free, with the same internal state.

# Hierarchy of semantics



# Overview

# 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,
  - ...

# SASB 2012

Fourth Workshop on Static Analysis and Systems Biology
(co-chaired with Andre Levchenko)
19th June 2013, Seattle
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