SYNBIOTIC 4th meeting

Formal reduction for rule-based models

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Joint-work with...

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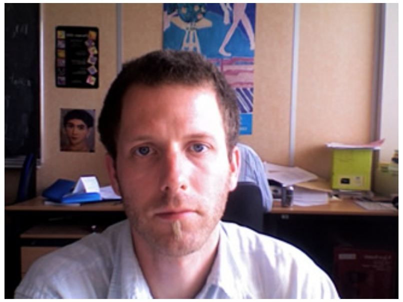


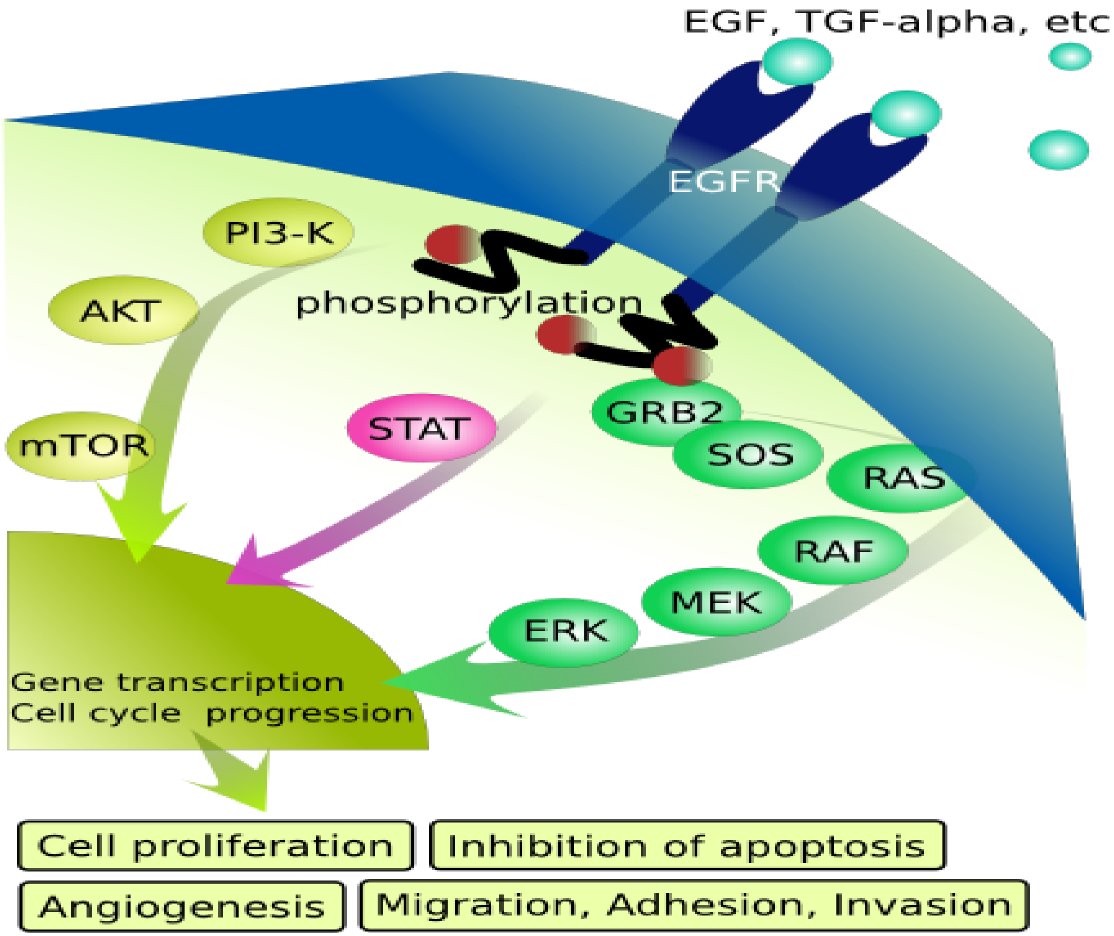
Russ Harmer
Harvard Medical School

Jean Krivine
Paris VII

Overview

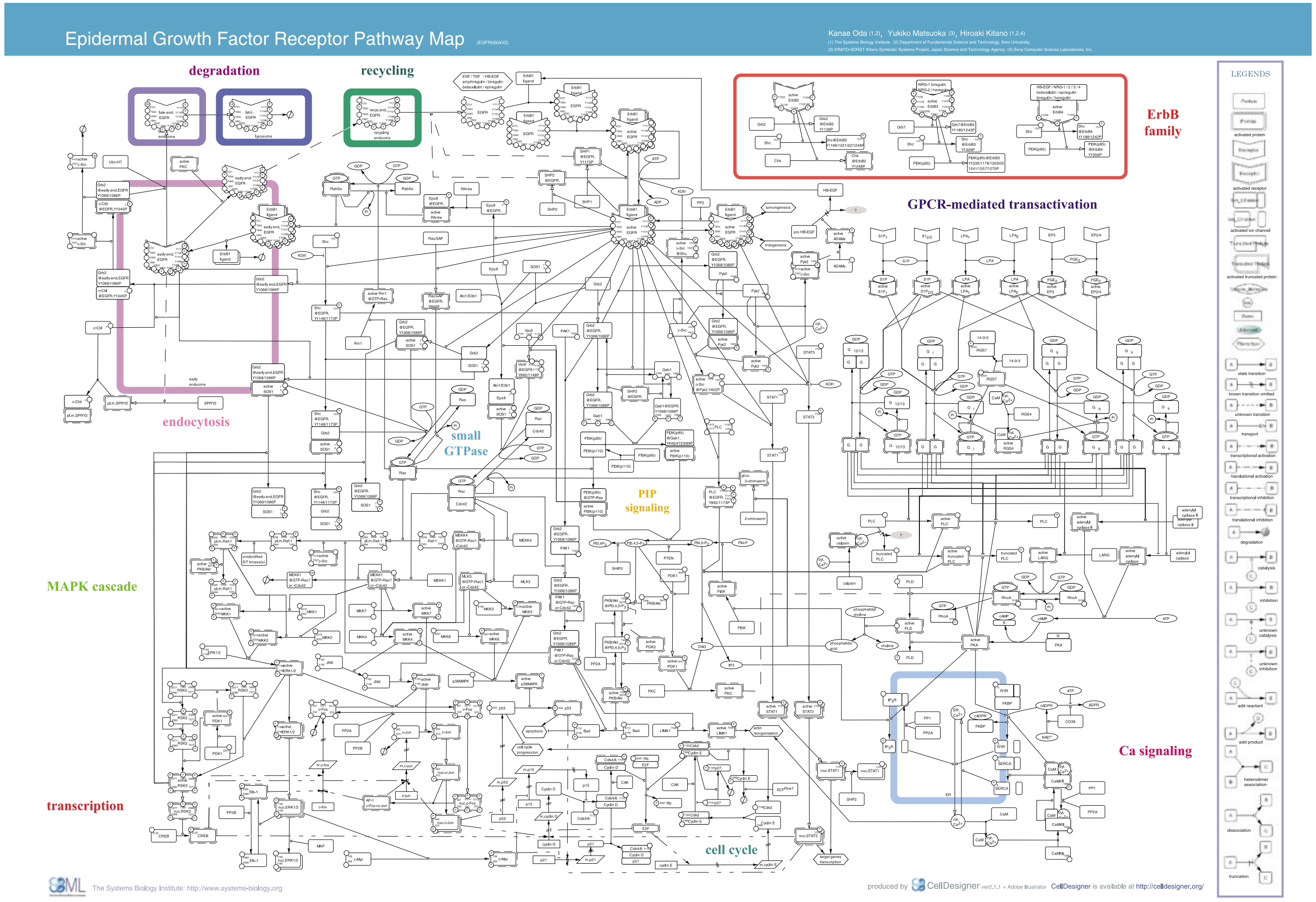
1. Context and motivations
2. Handmade ODEs
3. Abstract interpretation framework
4. Kappa
5. Concrete semantics
6. Abstract semantics
7. Conclusion

Signalling Pathways



Eikuch, 2007

Pathway maps



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

Differential models

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

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

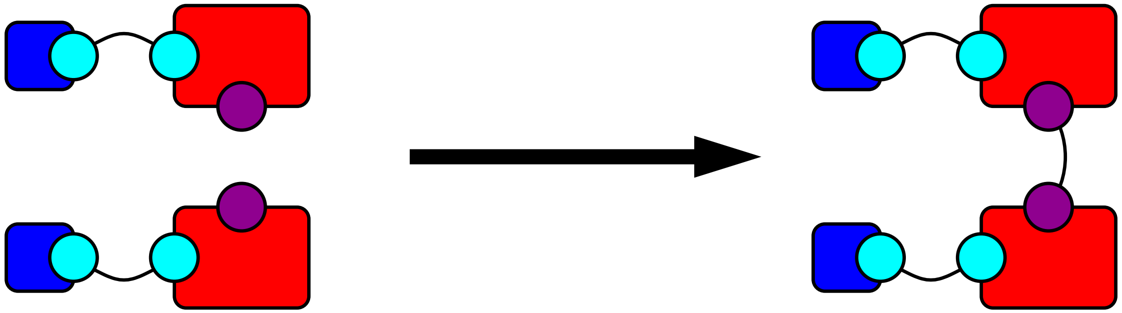
A gap between two worlds

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



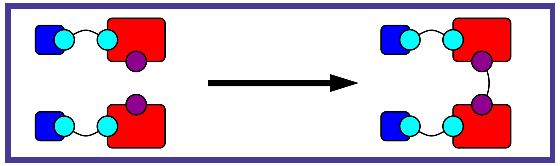
1. The description level matches with both
   - the observation level
   - and the intervention level

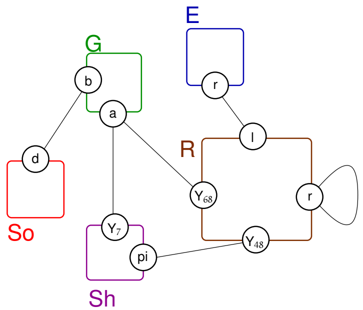
   of the biologist.

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

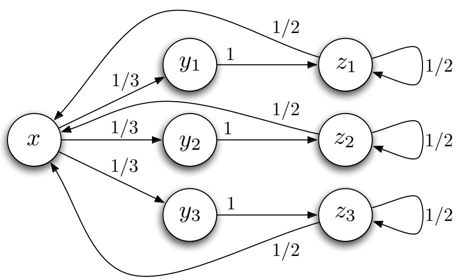
Semantics

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





Interaction map



CTMC

$$
\begin{cases}
\frac{dx_1}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
\frac{dx_2}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
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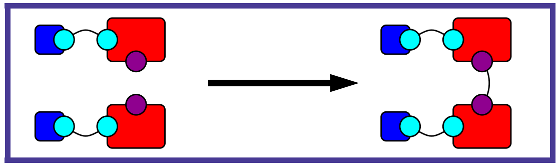
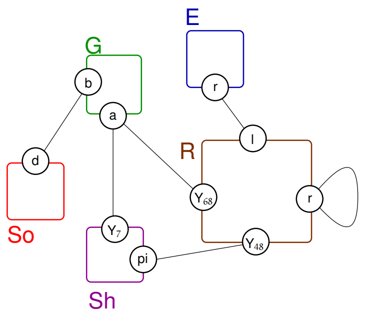
\frac{dx_5}{dt} = \cdots \\
\vdots \\
\frac{dx_n}{dt} = -k_1 \cdot x_1 \cdot c_2 + k_{-1} \cdot x_3
\end{cases}
$$

ODEs

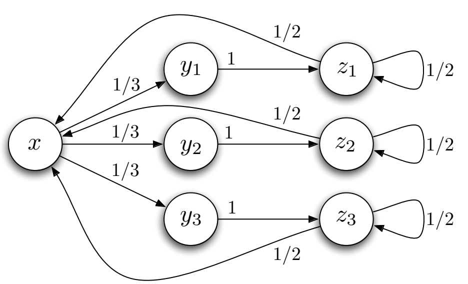
Semantics

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





Interaction map



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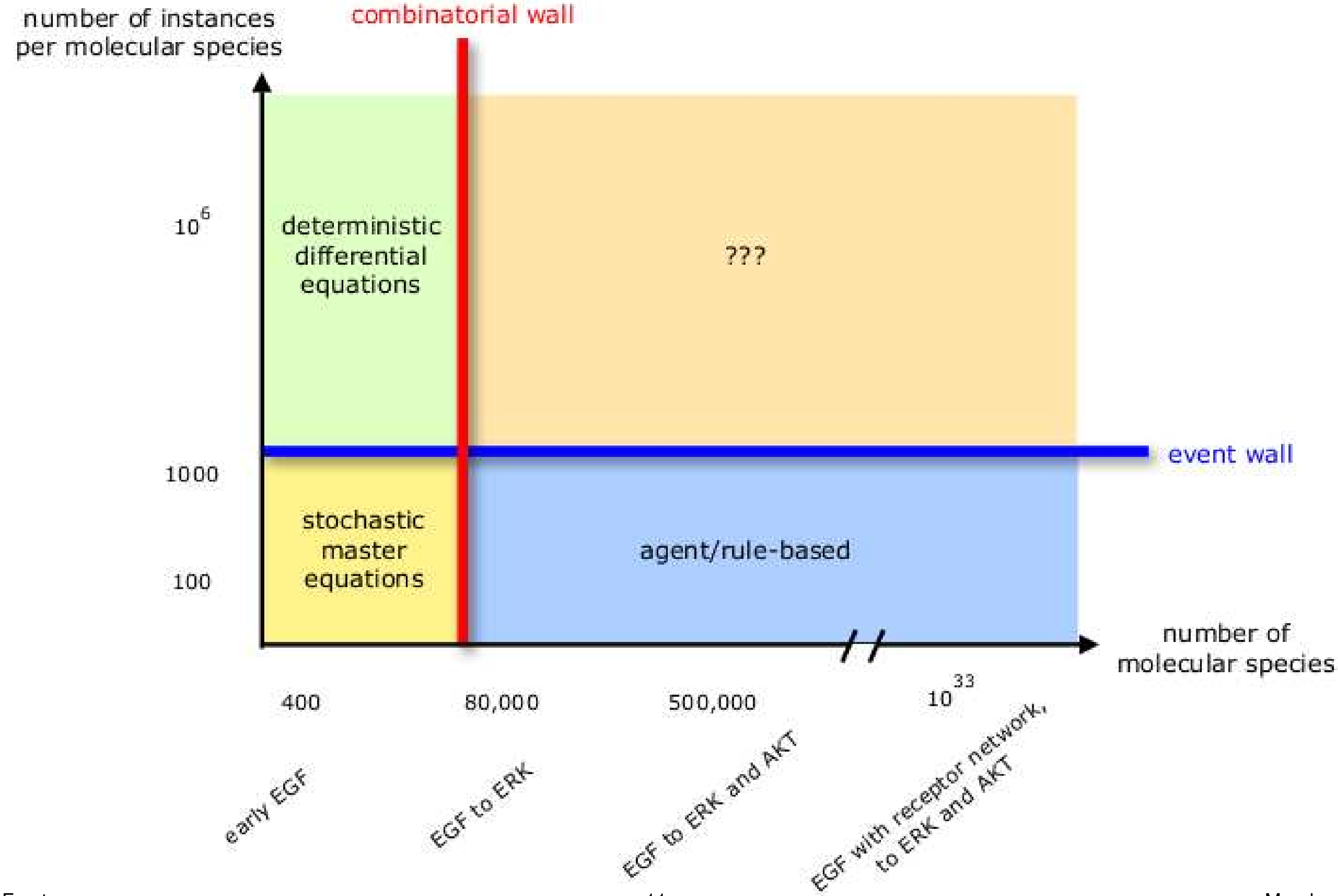
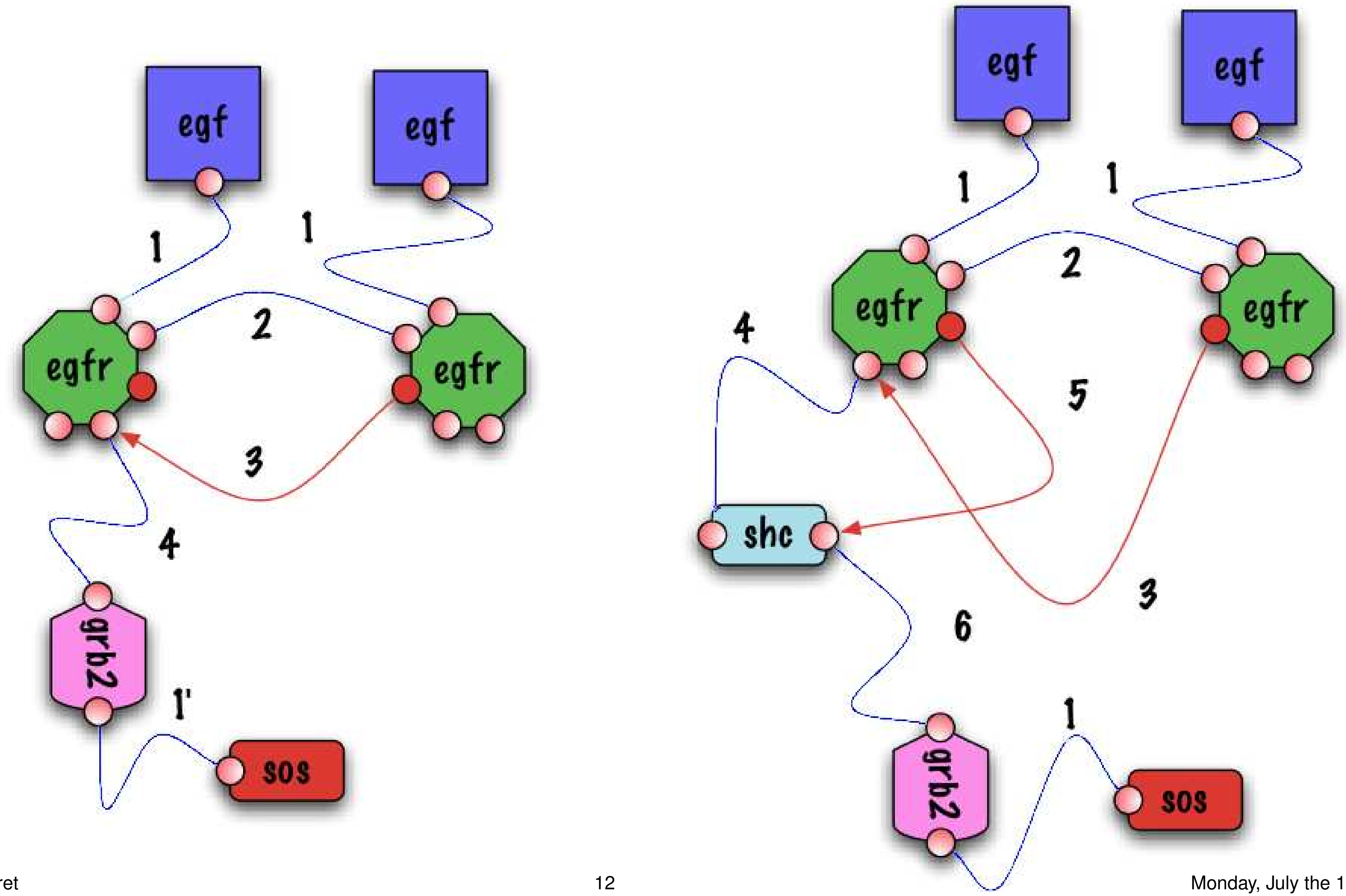
\frac{dx_5}{dt} = \cdots \\
\vdots \\
\frac{dx_n}{dt} = -k_1 \cdot x_1 \cdot c_2 + k_{-1} \cdot x_3
\end{cases}
$$

ODEs

Complexity walls



A breach in the wall(s) ?



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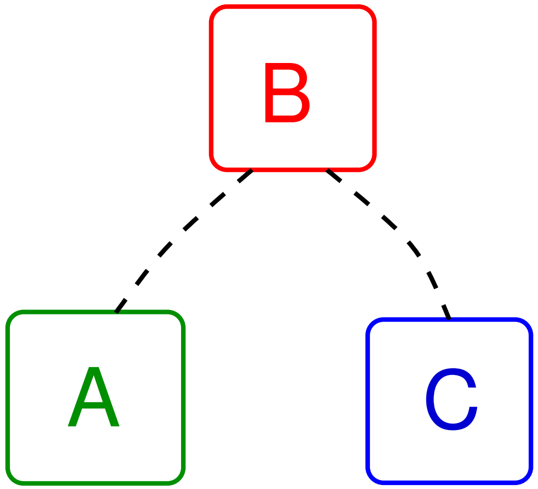
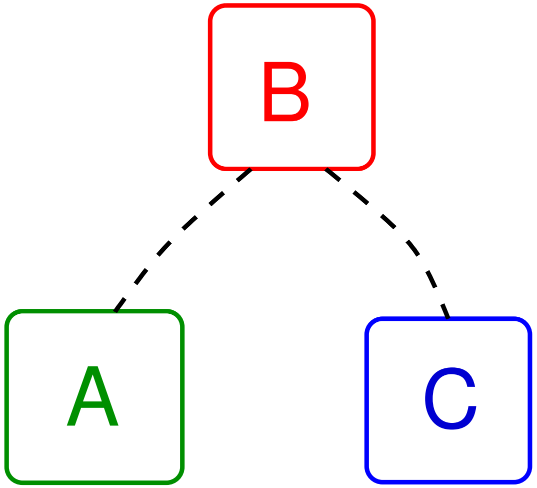
A simple adapter



A simple adapter



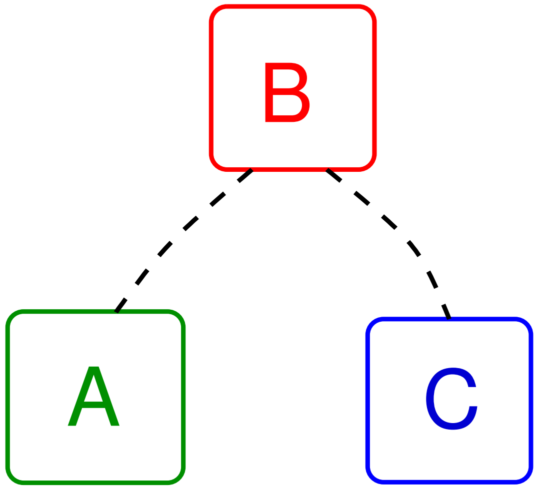
$$\mathsf{A}\ ,\ \emptyset\mathsf{B}\emptyset \longleftrightarrow \mathsf{AB}\emptyset \qquad k^{AB}, k_d^{AB}$$

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

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

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

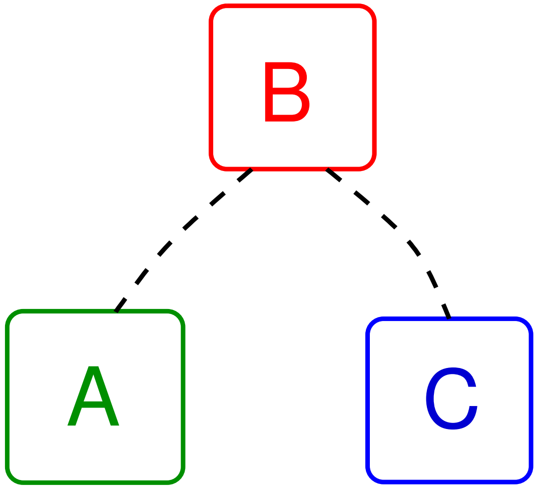
A simple adapter



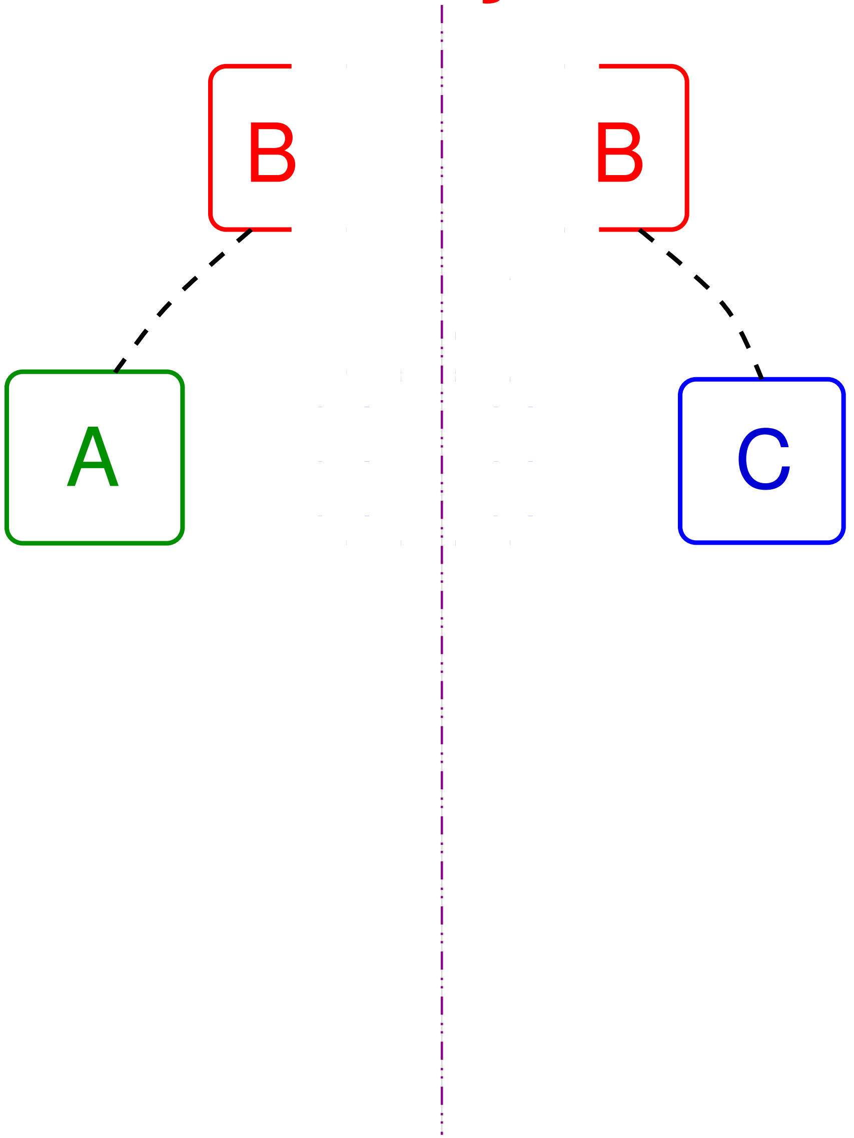
$$\begin{array}{lcll}
A\ ,\ \emptyset B\emptyset & \longleftrightarrow & AB\emptyset & k^{AB}, k_d^{AB} \\
A\ ,\ \emptyset BC & \longleftrightarrow & ABC & k^{AB}, k_d^{AB} \\
\emptyset B\emptyset\ ,\ C & \longleftrightarrow & \emptyset BC & k^{BC}, k_d^{BC} \\
AB\emptyset\ ,\ C & \longleftrightarrow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

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

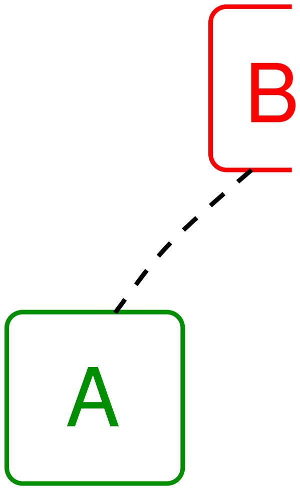
Two subsystems



Two subsystems



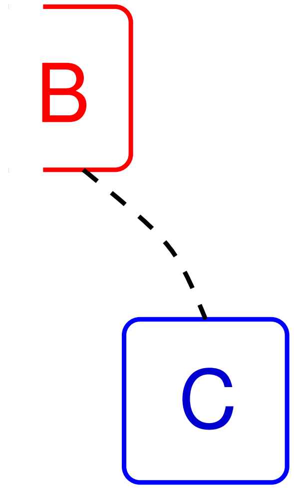
Two subsystems



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

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

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



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

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

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

Dependence index

We introduce:

$$[?B?] \stackrel{\Delta}{=} [?B\emptyset] + [?BC].$$

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

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

Thus we define the dependence index as follows:

$$X \stackrel{\Delta}{=} [ABC]{\cdot}[?B?] - [AB?]{\cdot}[?BC].$$

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:

$$[ABC] = \frac{[AB?]{\cdot}[?BC]}{[?B?]}$$

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

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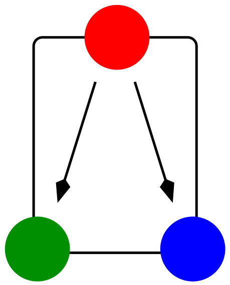
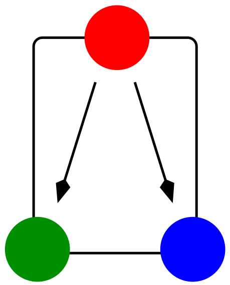
A system with a switch

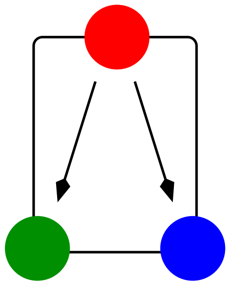


A system with a switch



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

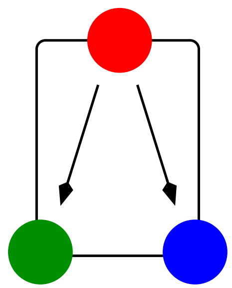
A system with a switch



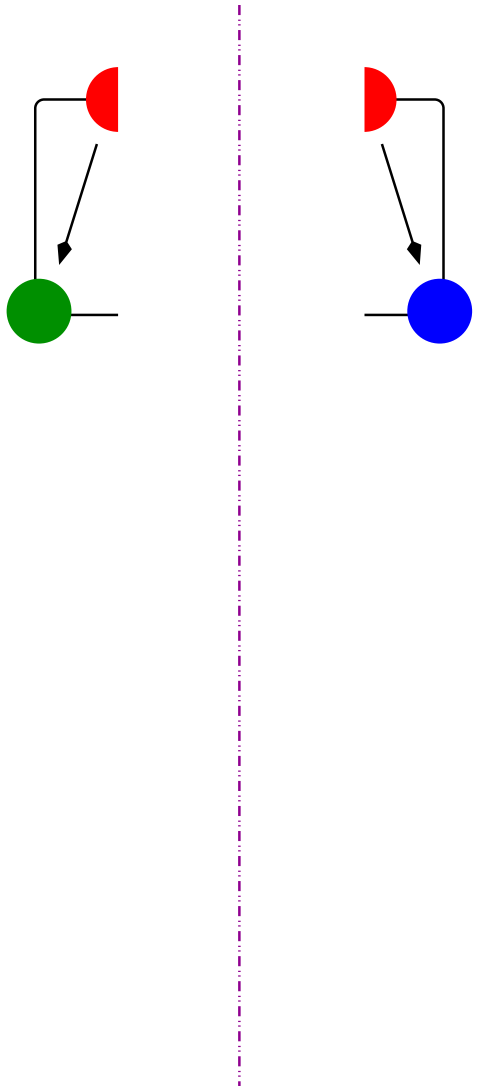
$$
\begin{array}{lcll}
(u,u,u) & \longrightarrow & (u,p,u) & k^c \\
(u,p,u) & \longrightarrow & (p,p,u) & k^l \\
(u,p,p) & \longrightarrow & (p,p,p) & k^l \\
(u,p,u) & \longrightarrow & (u,p,p) & k^r \\
(p,p,u) & \longrightarrow & (p,p,p) & k^r
\end{array}
$$

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

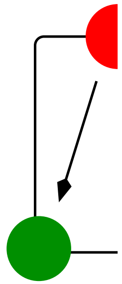
Two subsystems



Two subsystems

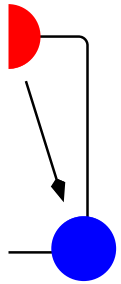


Two subsystems



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

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



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

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

Dependence index

We introduce:

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

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

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

Thus we define the dependence index as follows:

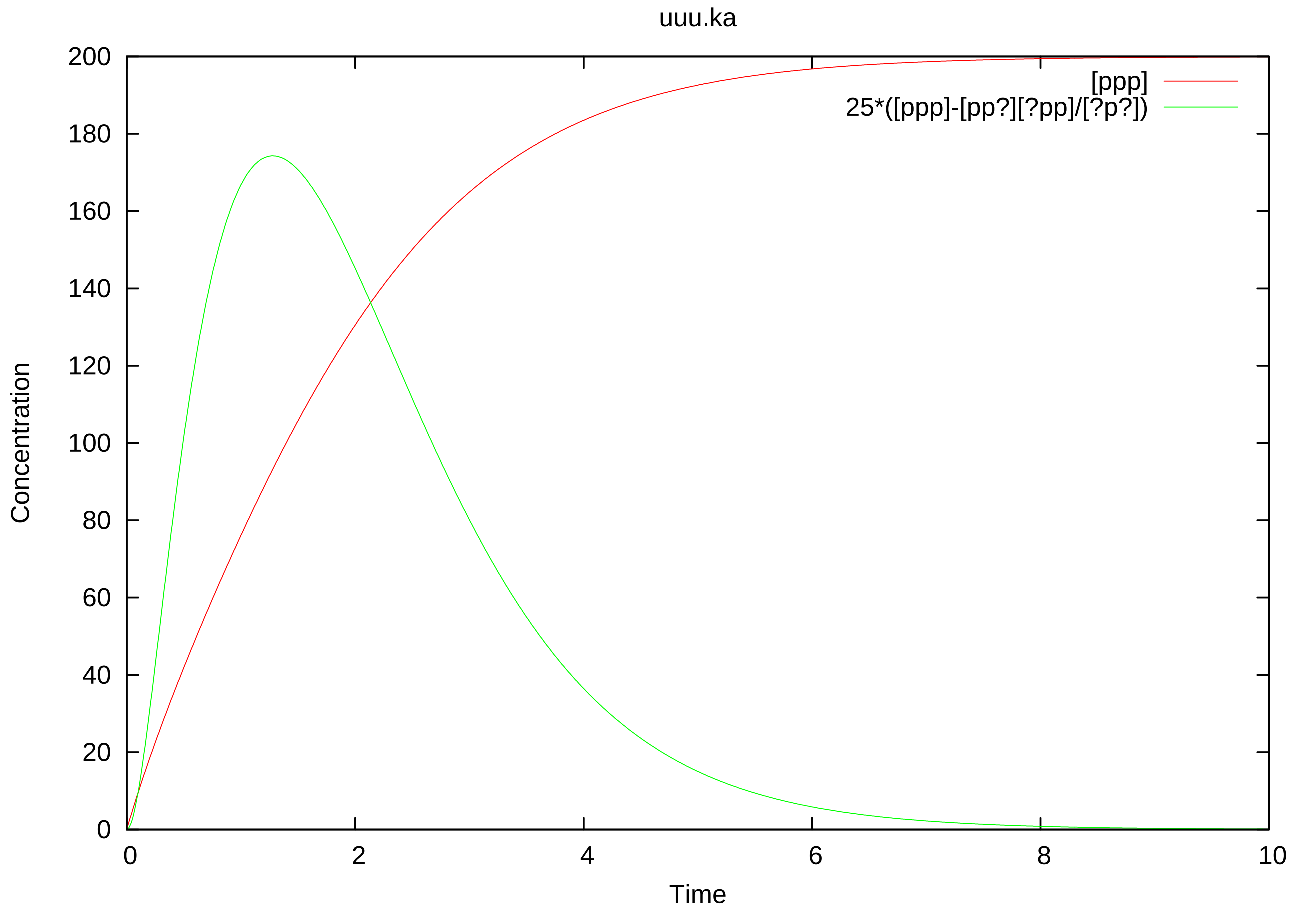
$$X \stackrel{\Delta}{=} [(p,p,p)] \cdot [(?,p,?)] - [(?,p,p)] \cdot [(p,p,?)].$$

We have (after a short computation):

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

As a consequence, the property $X = 0$ is not an invariant.
We can split the system into two subsystems,
but we cannot recombine both subsystems without errors.

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

- Independence:

  + the transformation is invertible:

    we can recover the concentration of any species;

  – it is a strong property

    which is hard to prove,

    which is hardly ever satisfied.

- Self-consistency:

  – some information is abstracted away

    we cannot recover the concentration of any species;

  + it is a weak property

    which is easy to ensure,

    which is easy to propagate;

  + it captures the essence of the kinetics of systems.

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

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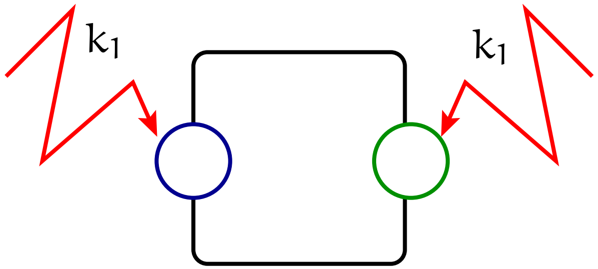
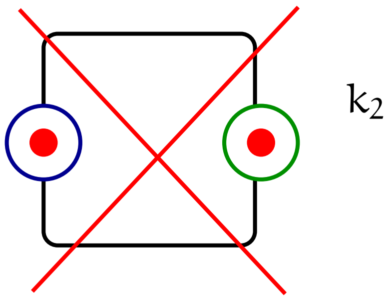
A model with symmetries

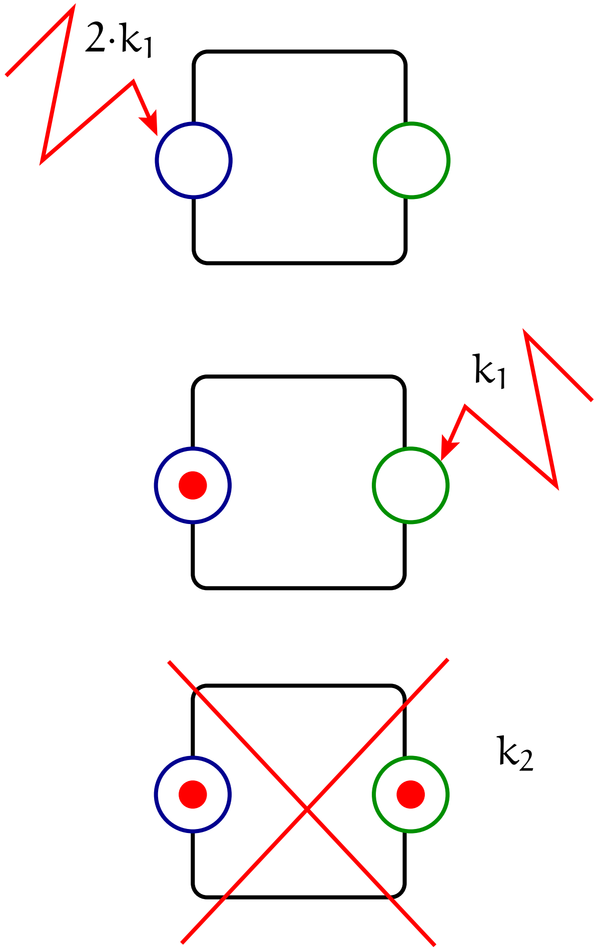


$$P \longrightarrow {}^{\star}P \quad k_1 \qquad P^{\star} \longrightarrow {}^{\star}P^{\star} \quad k_1$$
$$P \longrightarrow P^{\star} \quad k_1 \qquad {}^{\star}P \longrightarrow {}^{\star}P^{\star} \quad k_1$$



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

Reduced model



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

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

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

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    (a) Concrete semantics
    (b) Abstraction
    (c) Bisimulation
    (d) Combination
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Continuous differential semantics

Let $\mathcal{V}$, be a finite set of variables;
and $\mathbb{F}$, be a $\mathcal{C}^\infty$ mapping from $\mathcal{V} \to \mathbb{R}^+$ into $\mathcal{V} \to \mathbb{R}$,
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 continuous semantics maps each initial state $X_0 \in \mathcal{V} \to \mathbb{R}^+$ to the maximal solution $X_{X_0} \in [0, T^{max}_{X_0}[\to (\mathcal{V} \to \mathbb{R}^+)$ 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 $\mathcal{V} \to \mathbb{R}$ into $\mathcal{V}^\sharp \to \mathbb{R}$,
- $\mathbb{F}^\sharp$: a $\mathcal{C}^\infty$ mapping from $\mathcal{V}^\sharp \to \mathbb{R}^+$ into $\mathcal{V}^\sharp \to \mathbb{R}$;

such that:

- ψ is linear with positive coefficients,
  and for any sequence $(x_n) \in (\mathcal{V} \to \mathbb{R}^+)^{\mathbb{N}}$ such that $(||x_n||)$ diverges towards $+\infty$, then $(||\psi(x_n)||^\sharp)$ diverges as well
  (for arbitrary norms $||\cdot||$ and $||\cdot||^\sharp$),
- $\mathbb{F}^\sharp$ is ψ-complete, i.e. the following diagram commutes:

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

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

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 continuous trajectories

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

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

which satisfies $X_{X_0}(0) = X_0$.
(ie $Y_{\psi(X_0)} = \psi(X_{X_0})$)

Abstract continuous trajectories
Proof sketch

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

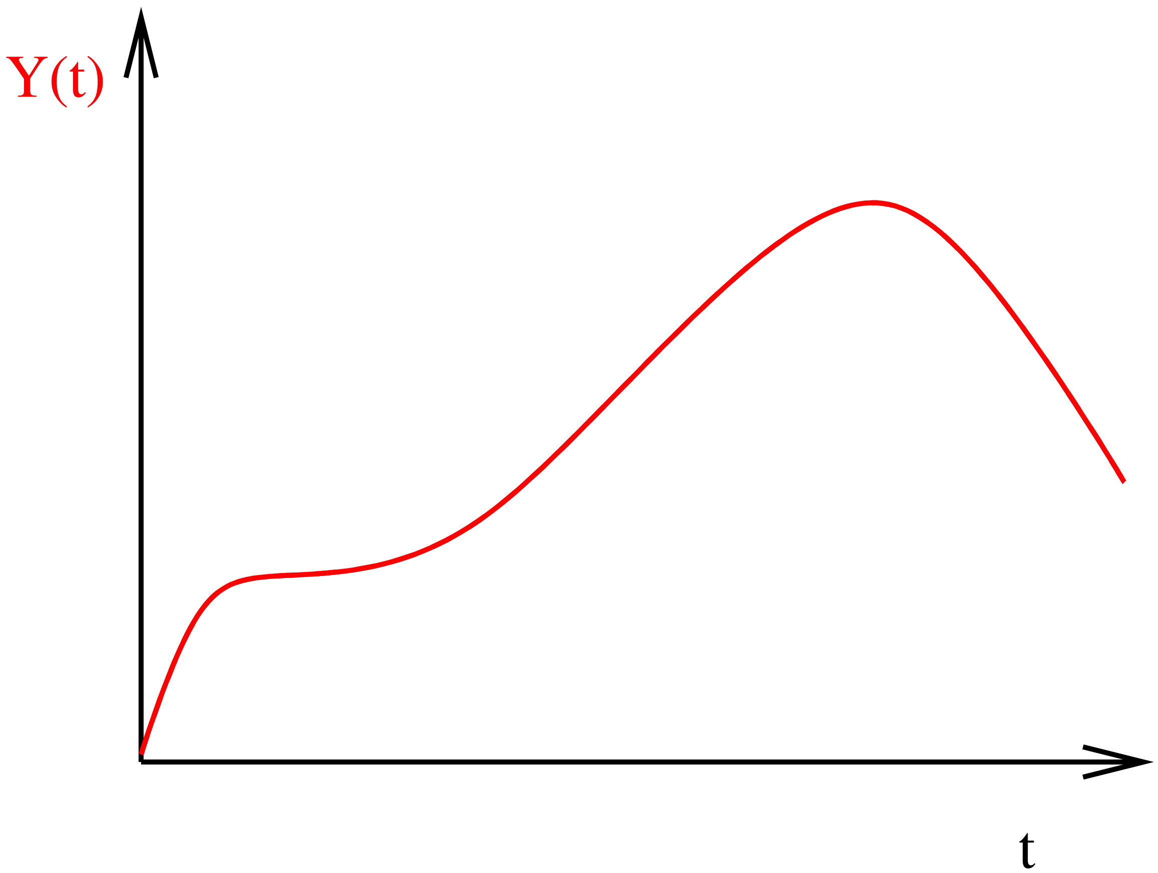
$$\begin{array}{rcl} X_{X_0}(T) & = & X_0 + \int_{t=0}^{T} \mathbb{F}\left(X_{X_0}(t)\right) \cdot dt \\ \psi\left(X_{X_0}(T)\right) & = & \psi\left(X_0 + \int_{t=0}^{T} \mathbb{F}\left(X_{X_0}(t)\right) \cdot dt\right) \\ \psi\left(X_{X_0}(T)\right) & = & \psi(X_0) + \int_{t=0}^{T} [\psi \circ \mathbb{F}]\left(X_{X_0}(t)\right)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

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

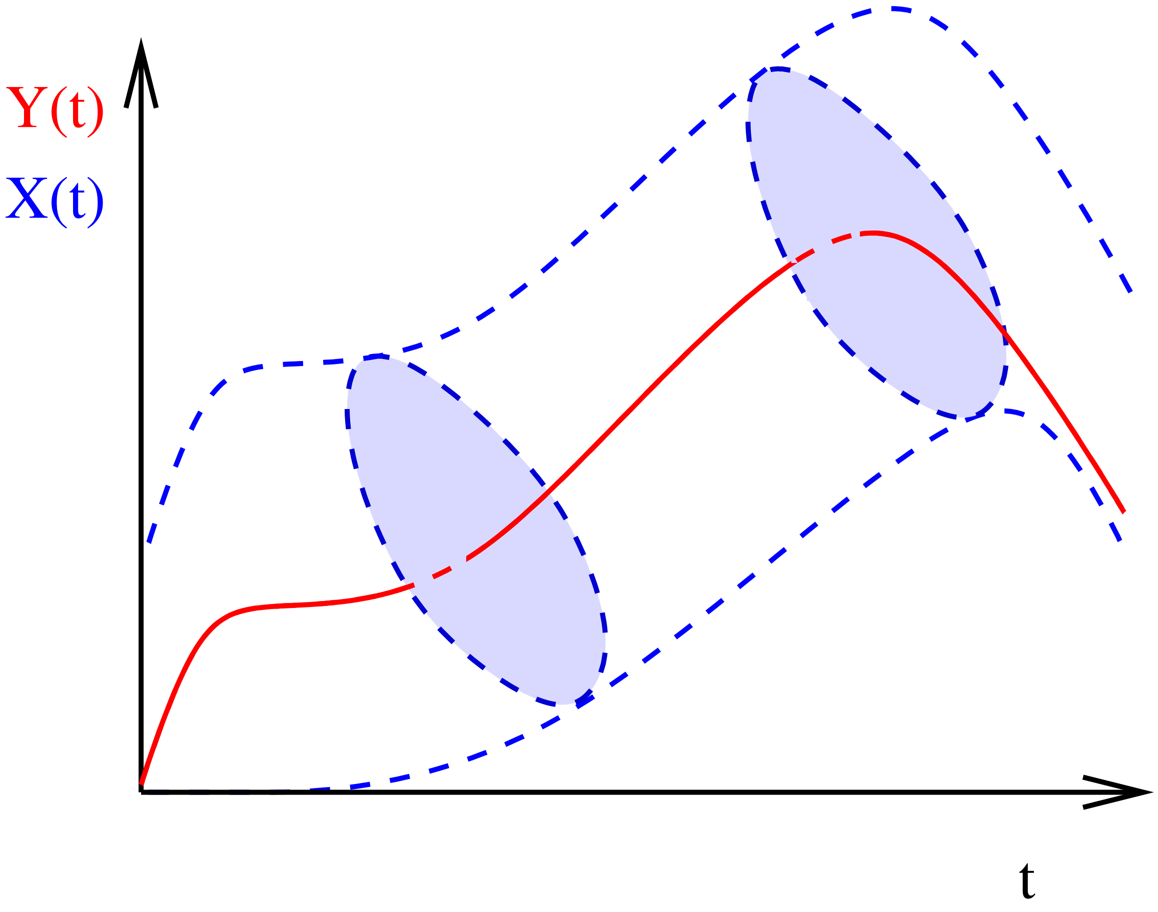
$$\boxed{Y_{Y_0}(T) = Y_0 + \int_{t=0}^{T} \mathbb{F}^\sharp\left(Y_{Y_0}(t)\right) \cdot dt}$$

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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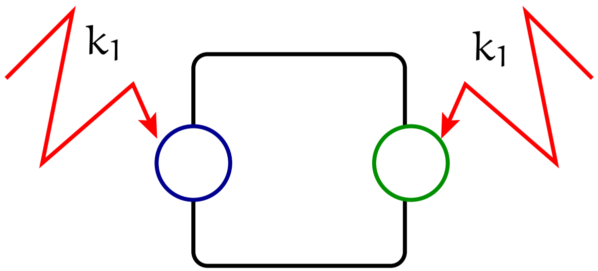
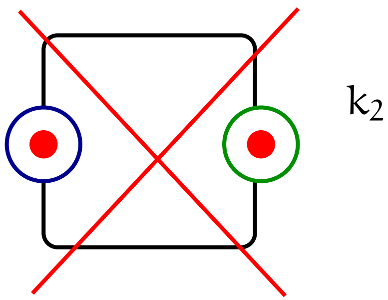
A model with symmetries



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

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



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

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:

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

- Reduced system:

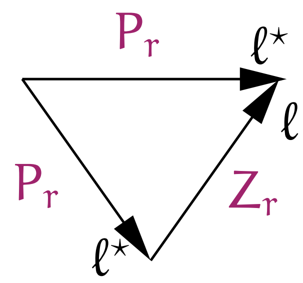
$$\frac{d}{dt}\begin{bmatrix} \mathsf{P} \\ {}^{\star}\mathsf{P} + \mathsf{P}^{\star} \\ 0 \\ {}^{\star}\mathsf{P}^{\star} \end{bmatrix} = \underbrace{\begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}}_{P} \cdot \begin{bmatrix} -2\cdot k_1 & 0 & 0 & 0 \\ k_1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

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,

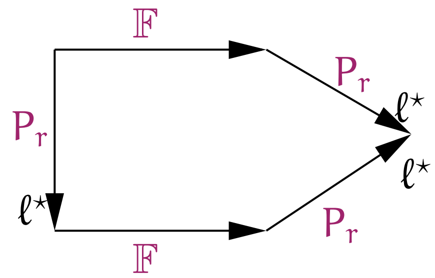
$\overset{\Delta}{\Longleftrightarrow}$

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,

$\Longleftrightarrow$

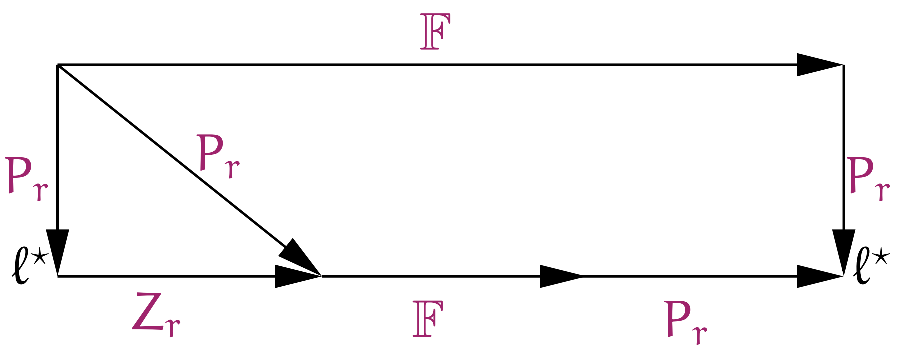
for any $\sigma \in \mathcal{V} \rightarrow \mathbb{R}^+$, $P_r(\mathbb{F}(\sigma)) = P_r(\mathbb{F}(P_r(\sigma)))$.



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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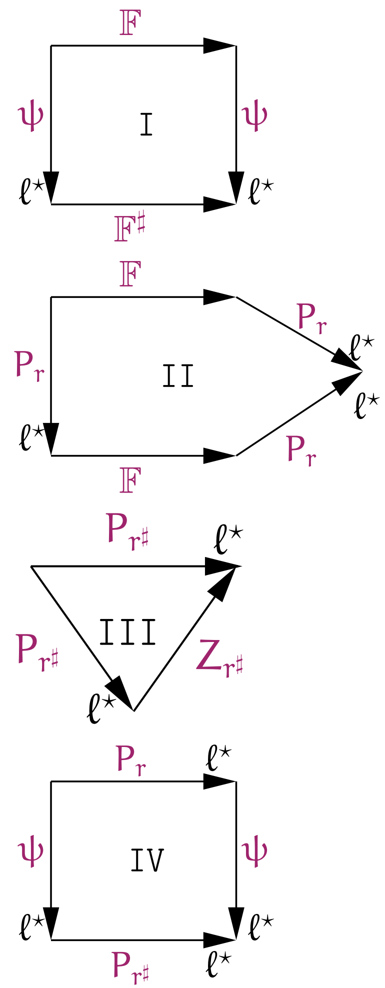
Abstract projection

We assume that we are given:

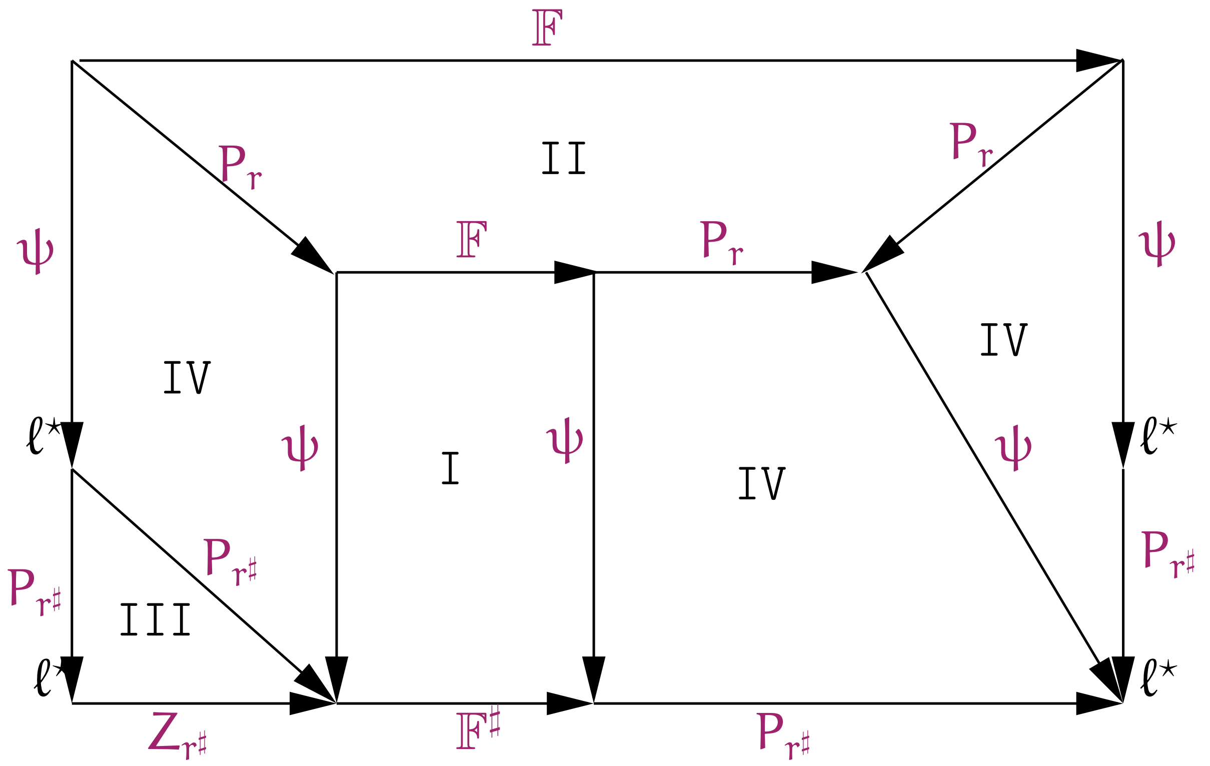
- a concrete system $(\mathcal{V}, \mathbb{F})$;
- an abstraction $(\mathcal{V}^\sharp, \psi, \mathbb{F}^\sharp)$ of $(\mathcal{V}, \mathbb{F})$ $(\mathtt{I})$;
- an idempotent mapping r over $\mathcal{V}$ which induces a bisimulation $(\mathtt{II})$;
- an idempotent mapping $r^\sharp$ over $\mathcal{V}^\sharp$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

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



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:



Overview

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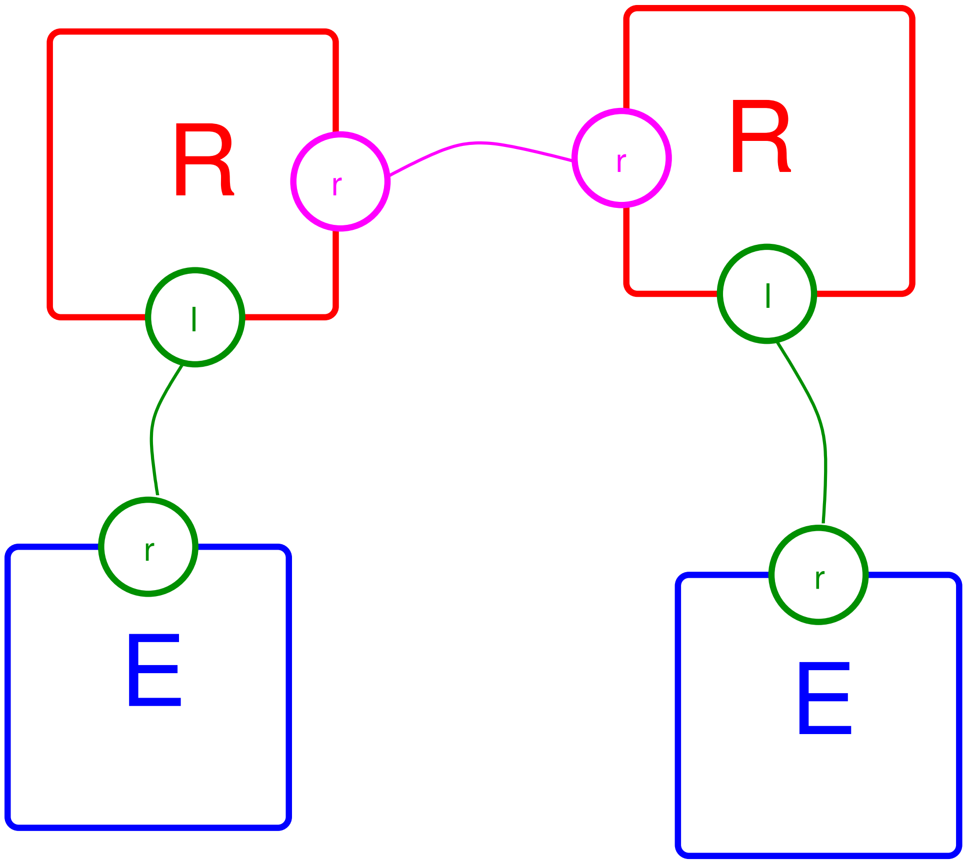
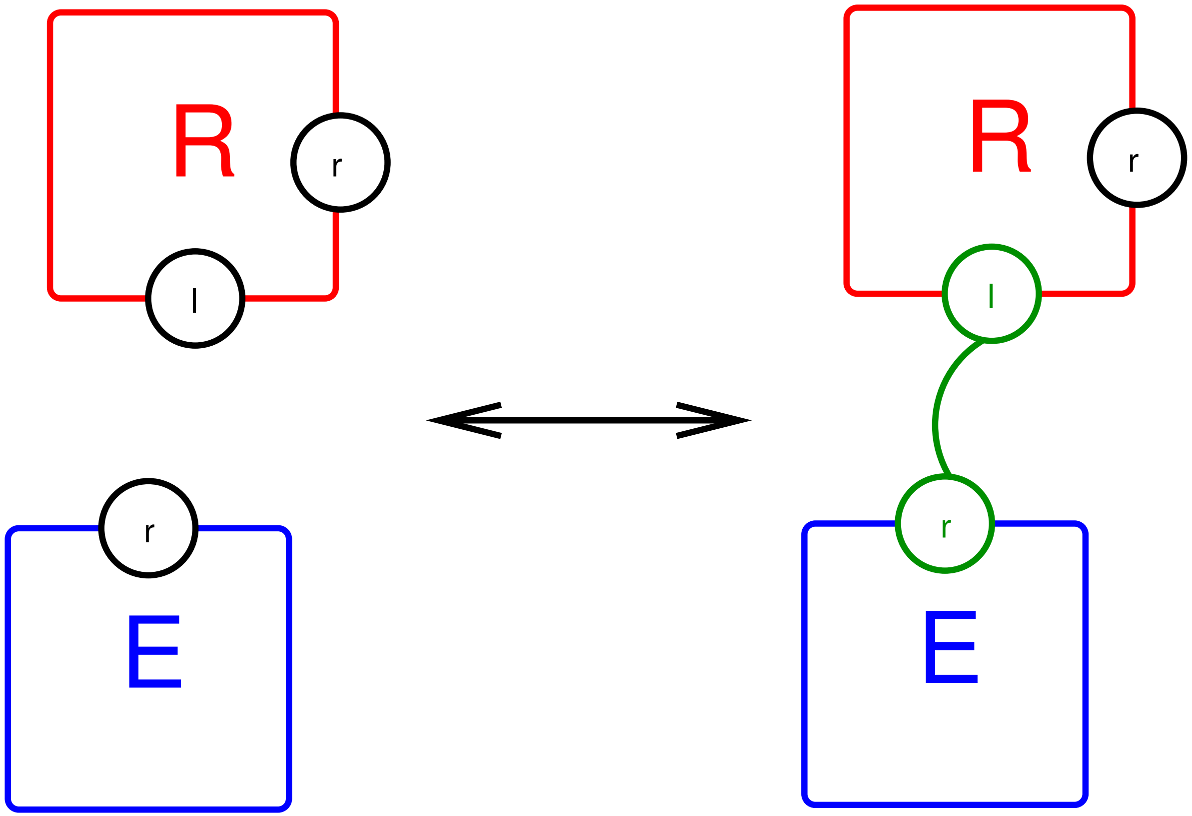
A species



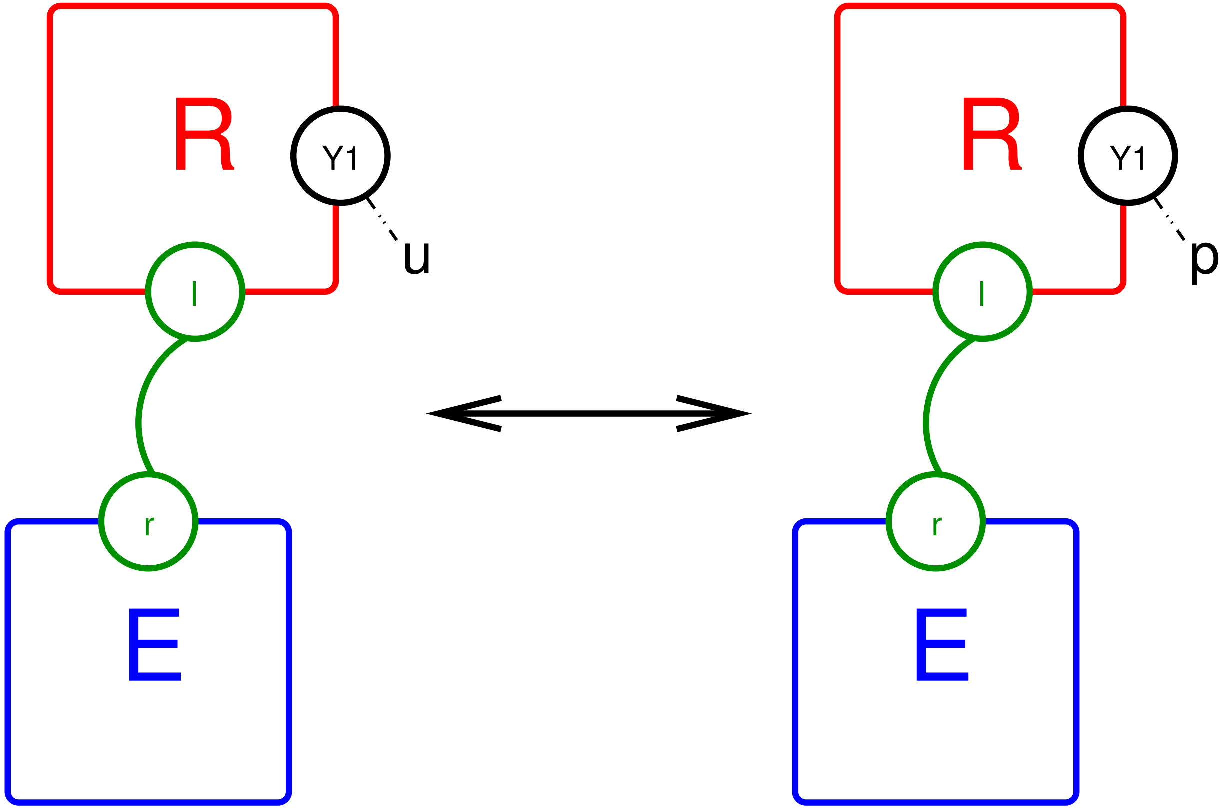
E(r!1), R(l!1,r!2), R(r!2,l!3), E(r!3)

A Unbinding/Binding Rule



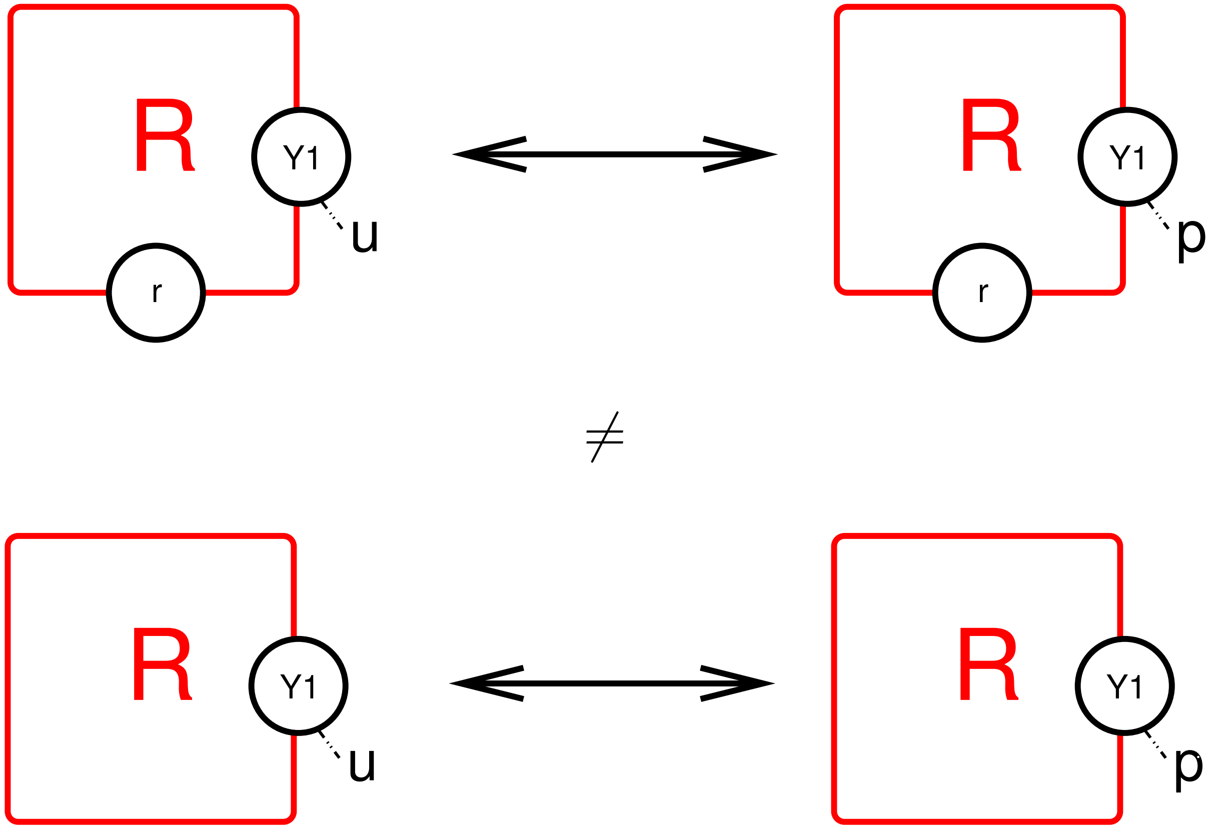
E(r), R(l,r) $\longleftrightarrow$ E(r!1), R(l!1,r)

Internal state



R(Y1~u,l!1), E(r!1) $\longleftrightarrow$ R(Y1~p,l!1), E(r!1)

Don’t care, Don’t write



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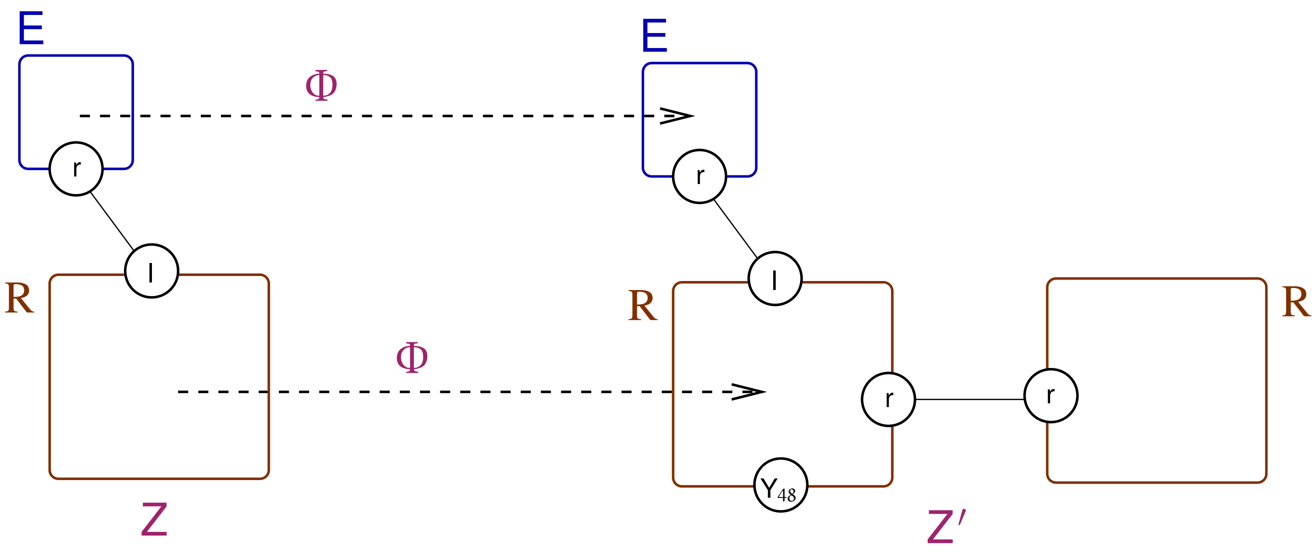
Embedding



We write $Z \lhd_{\Phi} Z'$ iff:

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

Requirements

1. Reachable species

   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: i.e. applying a rule with a tuple of site-graphs in $\mathcal{R}$ gives a tuple of site-graphs in $\mathcal{R}$;

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 ϕ between *lhs* into a tuple (r_i) of elements in $\mathcal{R}$ such that:

1. ϕ is mono;
2. ϕ 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:

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

where $\mathsf{SYM}(E) = \sharp\{\Phi \mid E \lhd_{\Phi} E\}$.

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   (b) Soundness criteria
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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;
- 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.

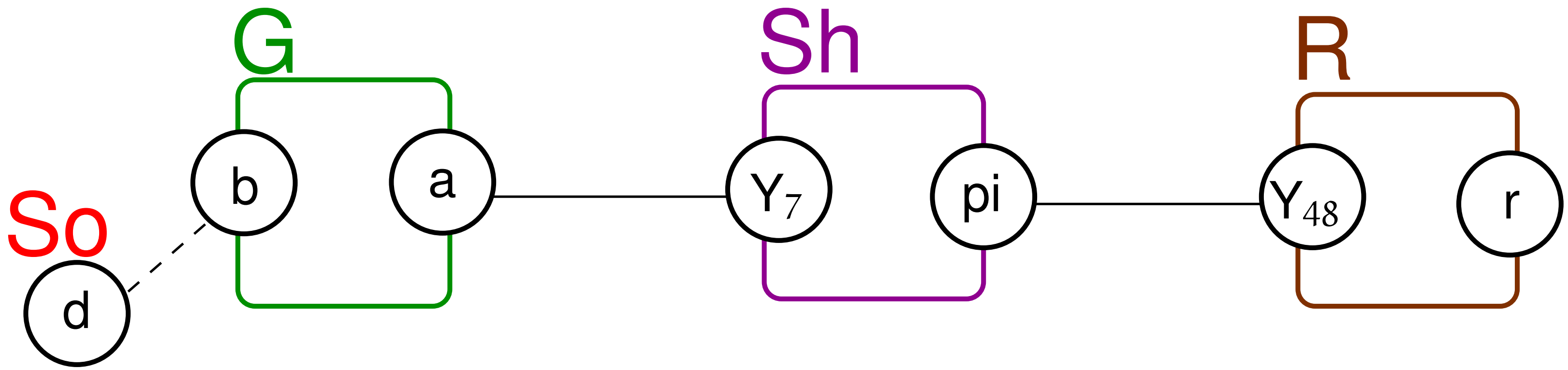
Partial species

Fragments are well-chosen partial species.

A partial species $X \in \mathcal{P}$ is a connected site-graph such that:

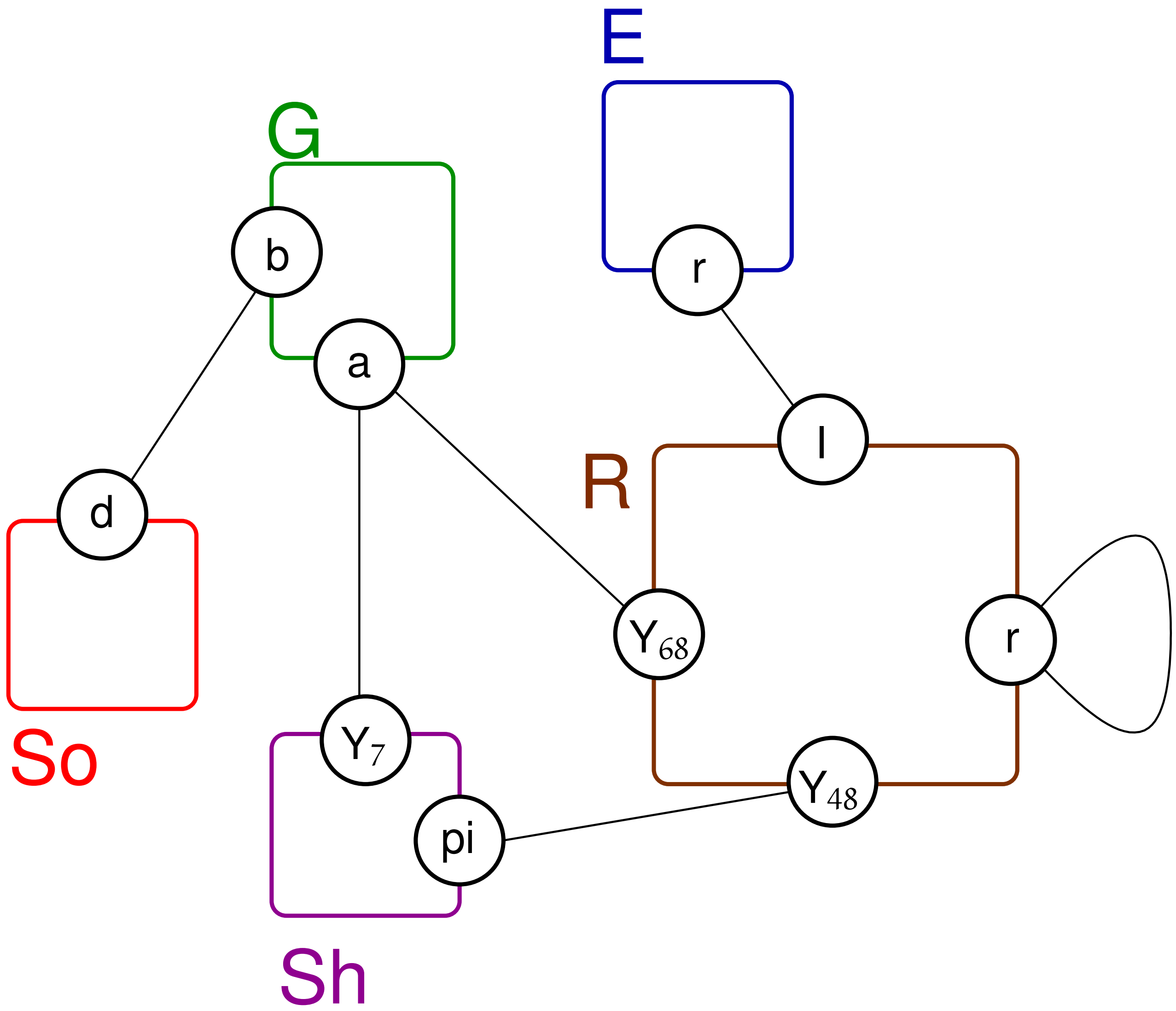
- the set of the sites of each node of type A is a subset of the set of the sites of A;
- sites are free, bound to an other site, or tagged with a binding type.

For instance:

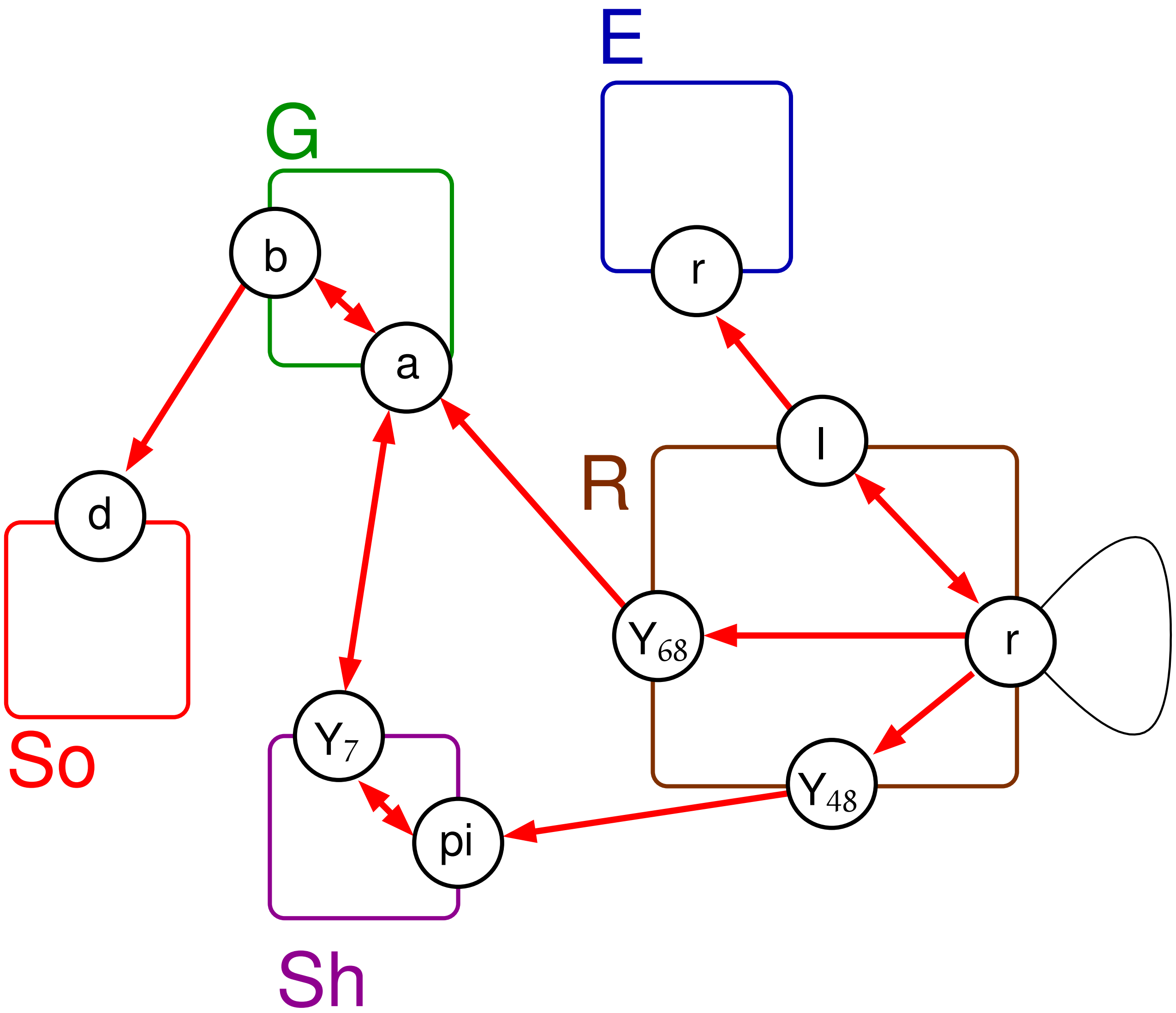


G(b!d.So,a!1),Sh(Y_7!1,pi!2),R(Y_{48}!2,r)

Contact map



Annotated contact map

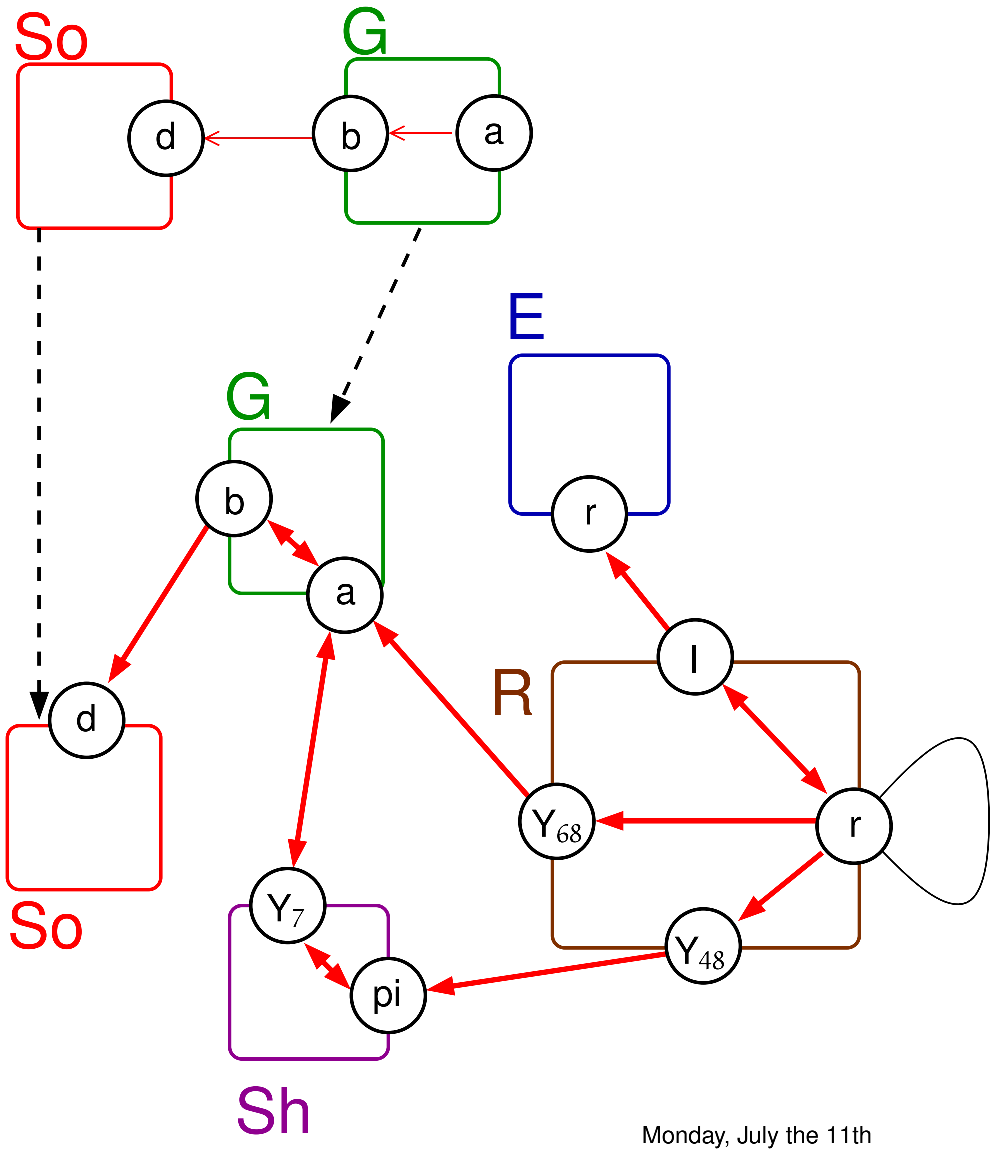


Fragments and prefragments

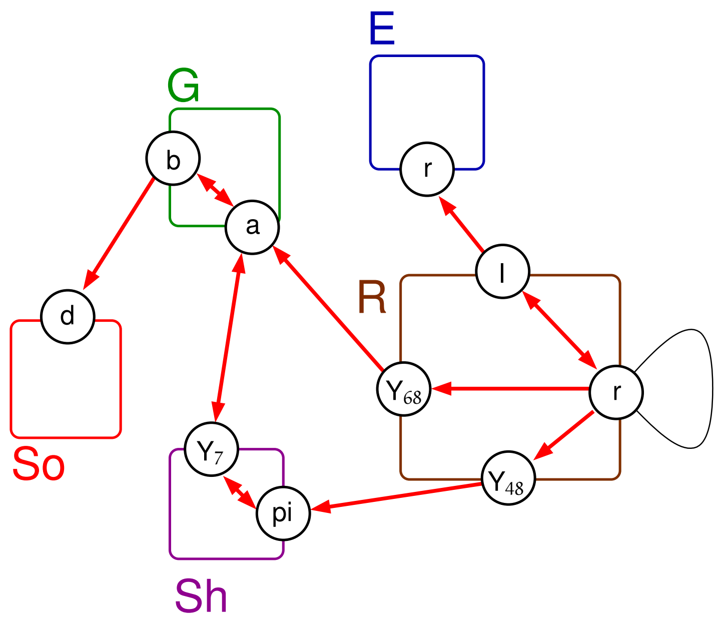
A prefragment is a connected site-graph which can be annotated with a binary relation $\longrightarrow$ over the sites, such that:

1. There would be a site which is reachable from each other sites, via the reflexive and transitive closure of $\longrightarrow$;
2. Any relation over sites can be projected over a relation on the annotated interaction map.

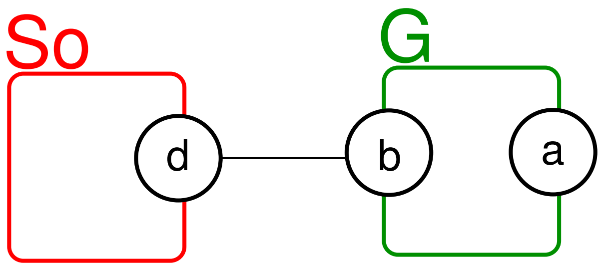
A fragment is a maximal prefragment (for the embedding order).

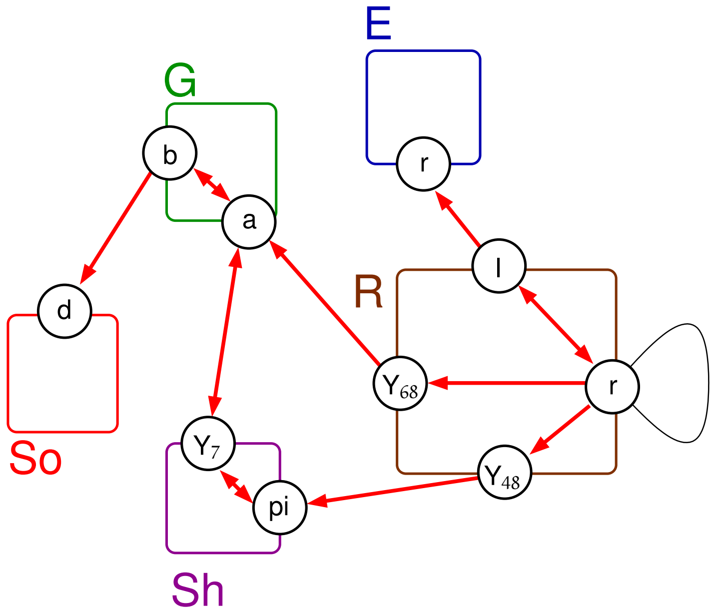


Are they fragments ?

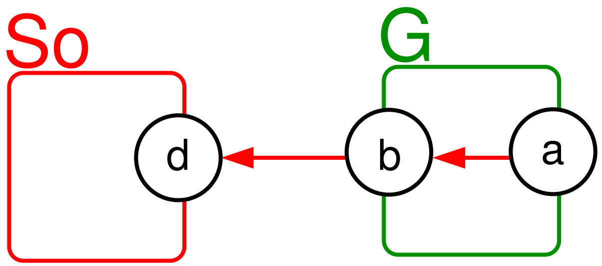


Are they fragments ?

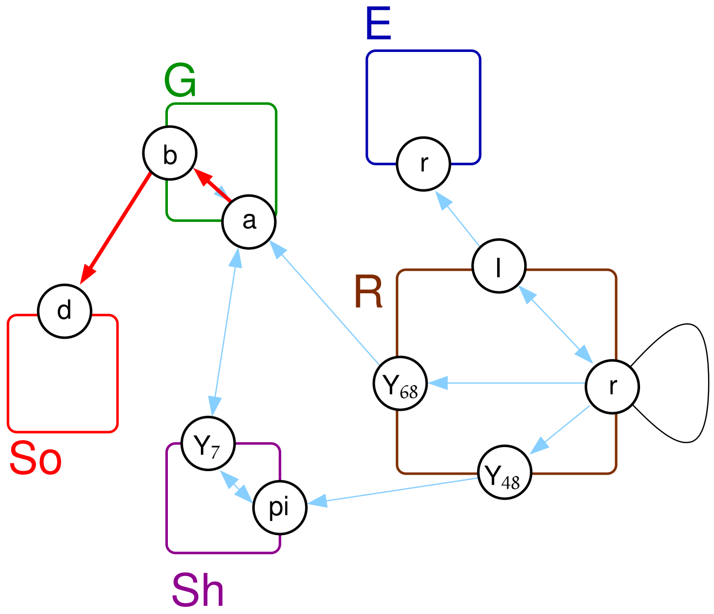




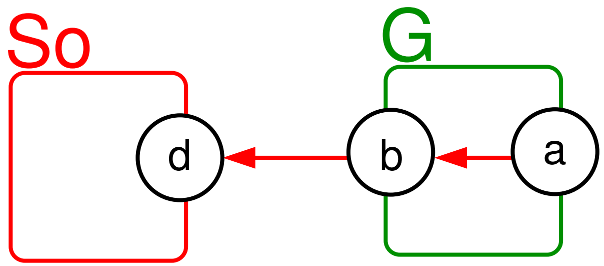
Are they fragments ?

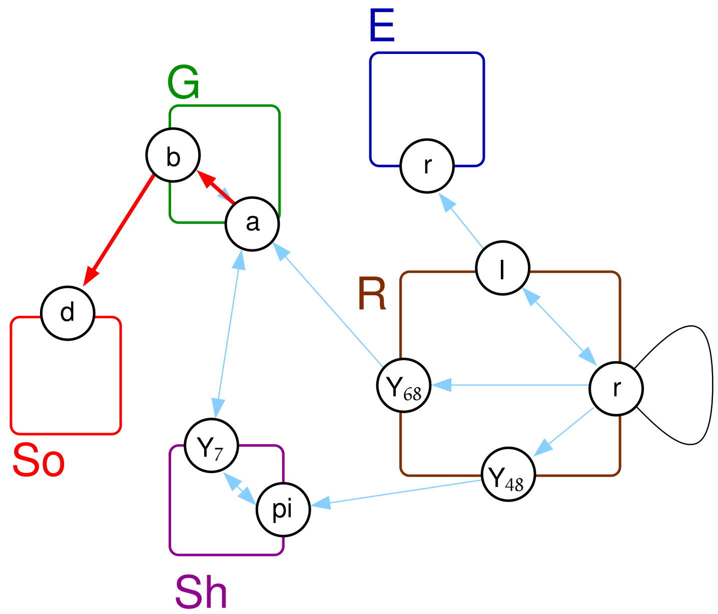


Thus, it is a prefragment.



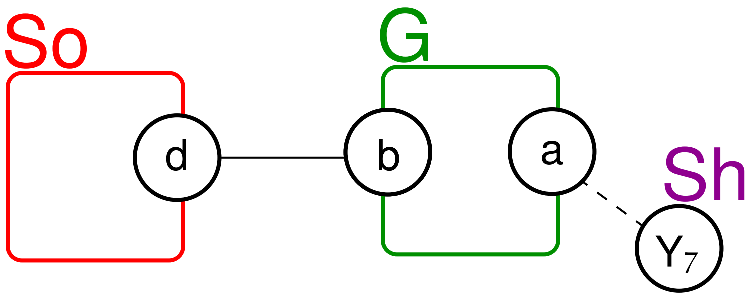
Are they fragments ?

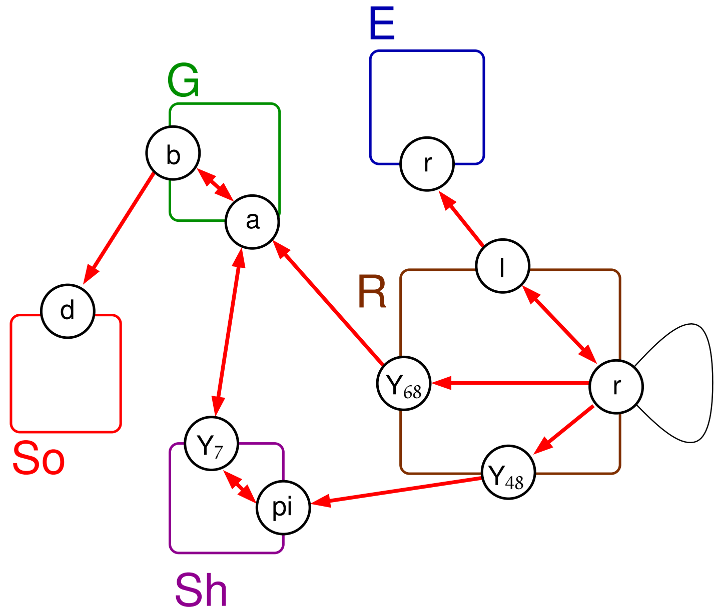




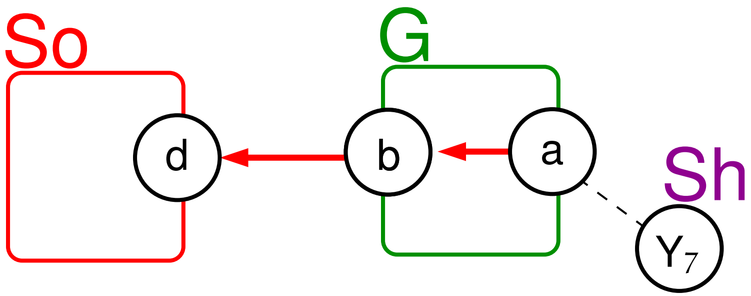
It is maximally specified.
Thus it is a fragment.

Are they fragments ?

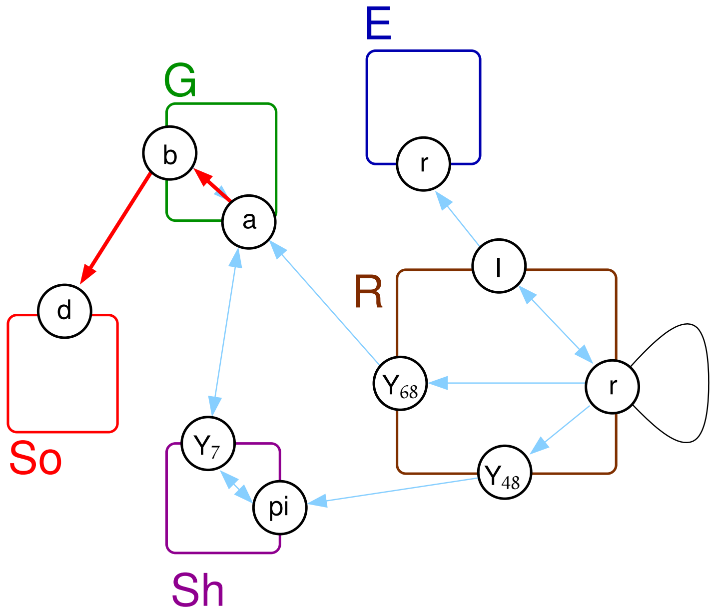




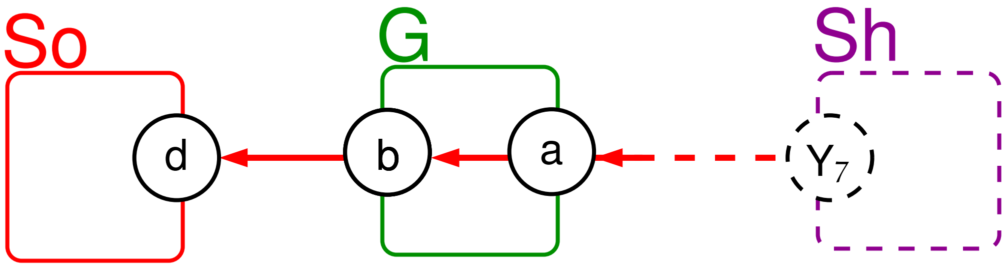
Are they fragments ?

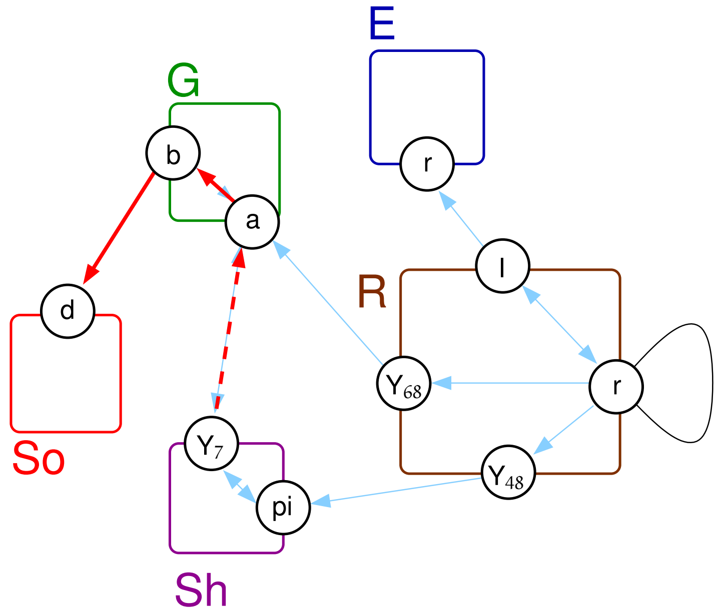


Thus, it is a prefragment.



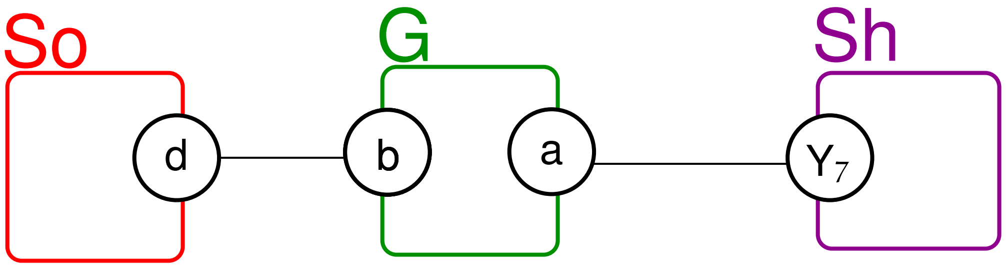
Are they fragments ?

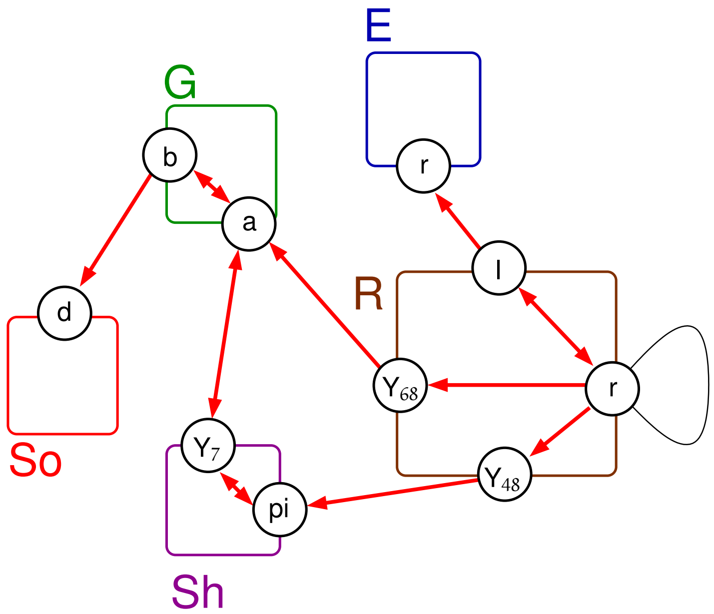




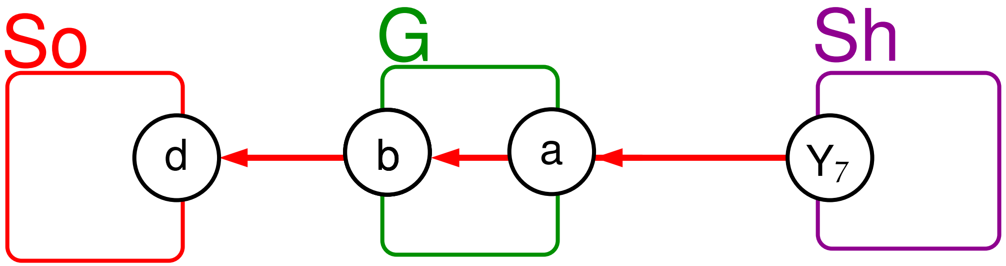
It can be refined into another prefragment.
Thus, it is not a fragment.

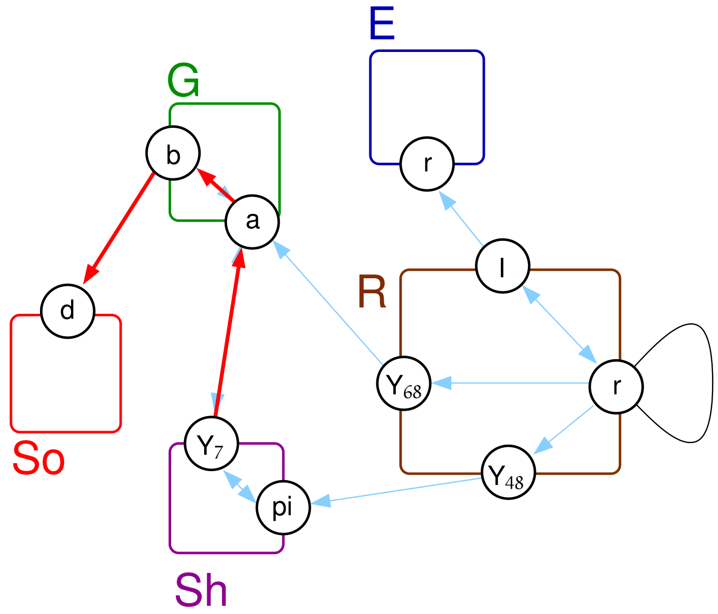
Are they fragments ?





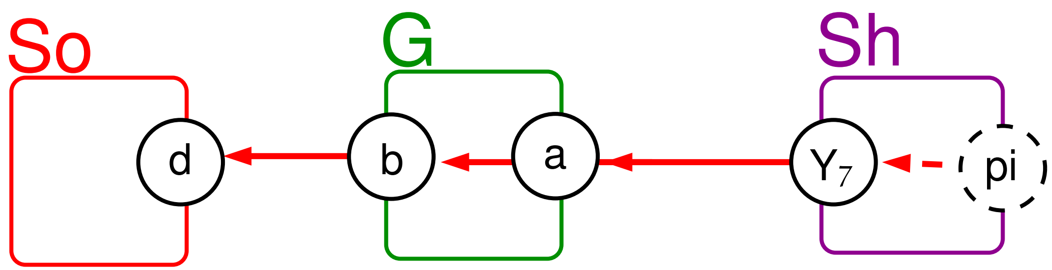
Are they fragments ?



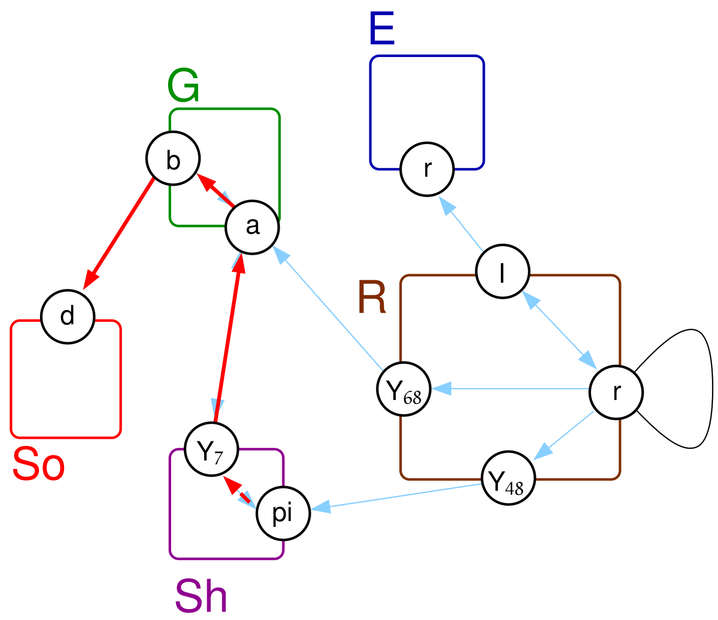


Thus, it is a prefragment.

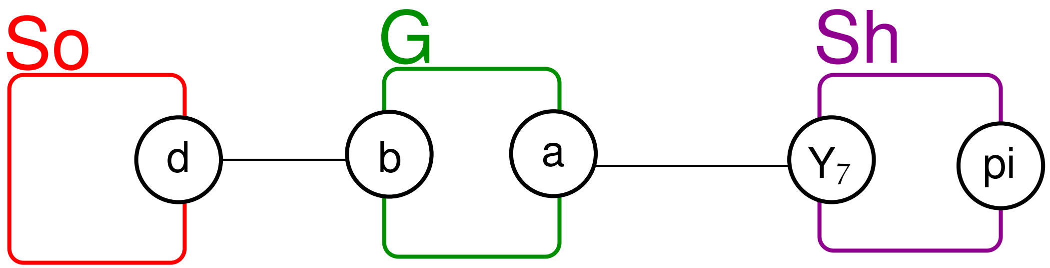
Are they fragments ?

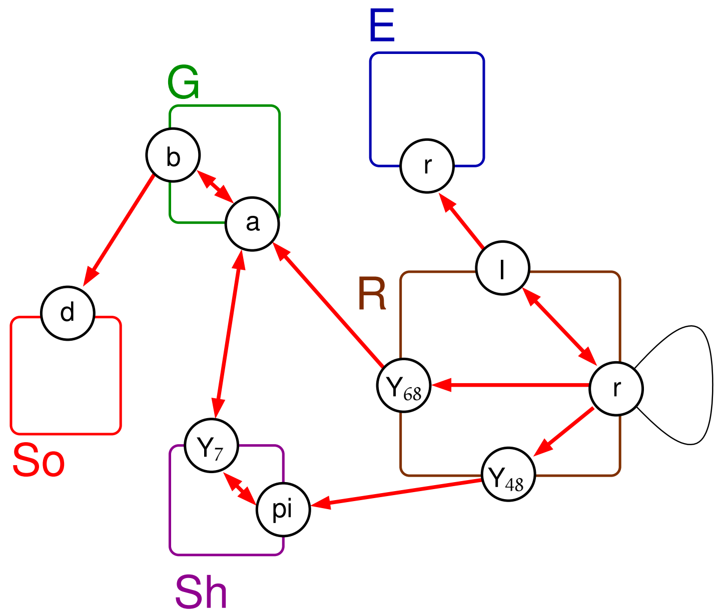


It can be refined into another prefragment.
Thus, it is not a fragment.

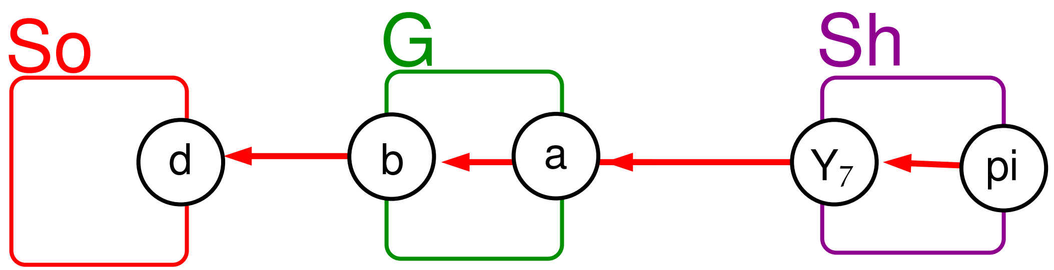


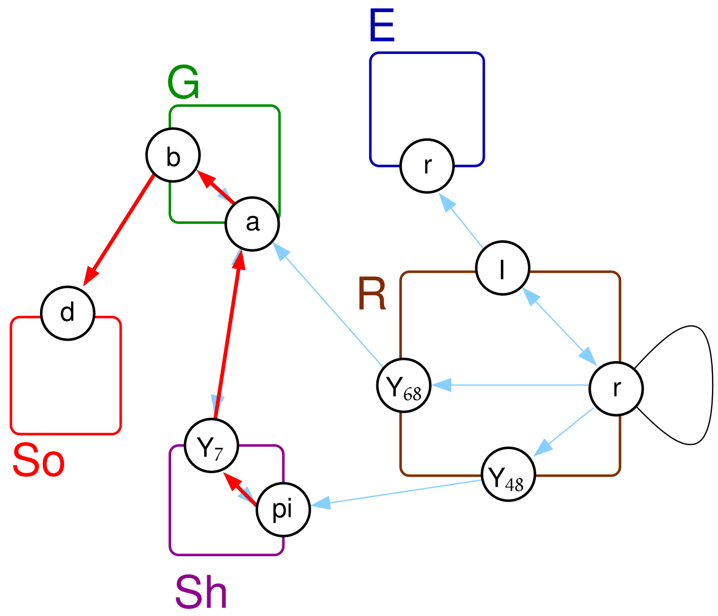
Are they fragments ?





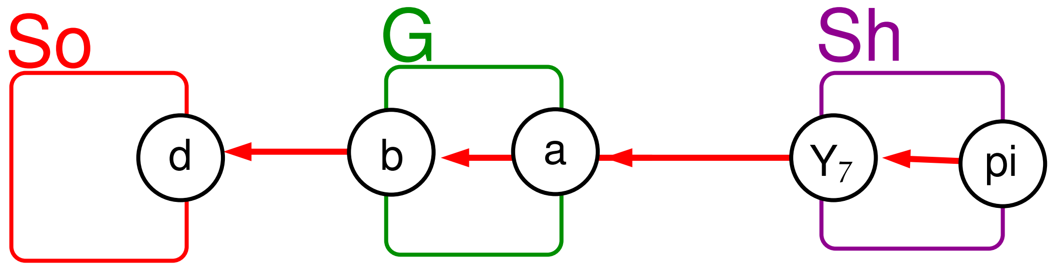
Are they fragments ?

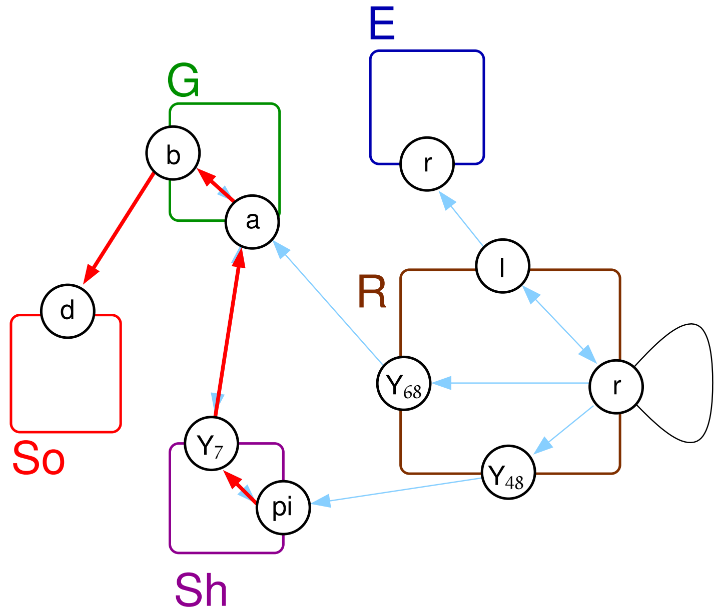




Thus, it is a prefragment.

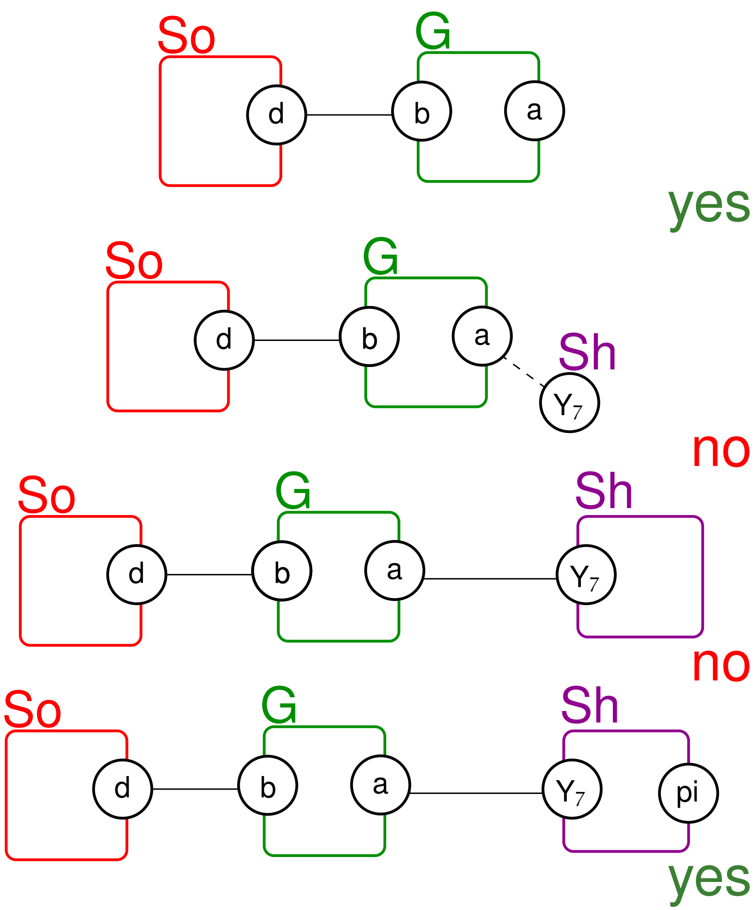
Are they fragments ?

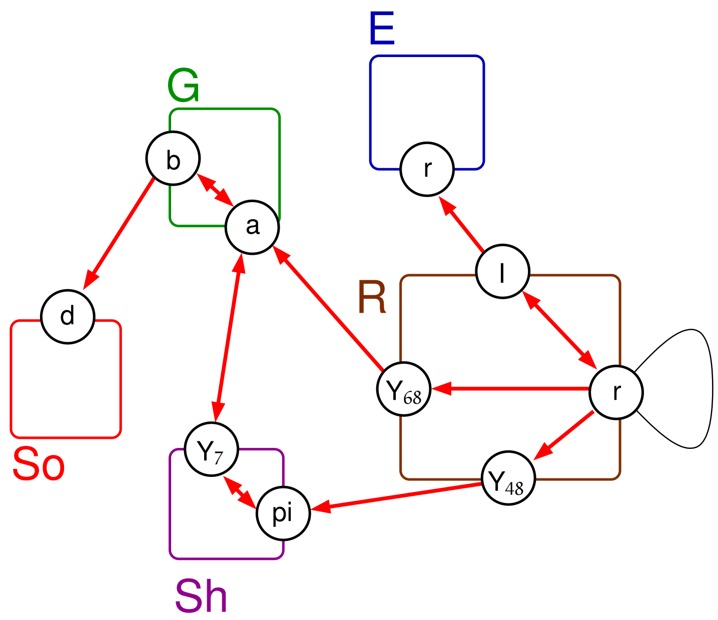




It is maximally specified.
Thus it is a fragment.

Are they fragments ?





Basic properties

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

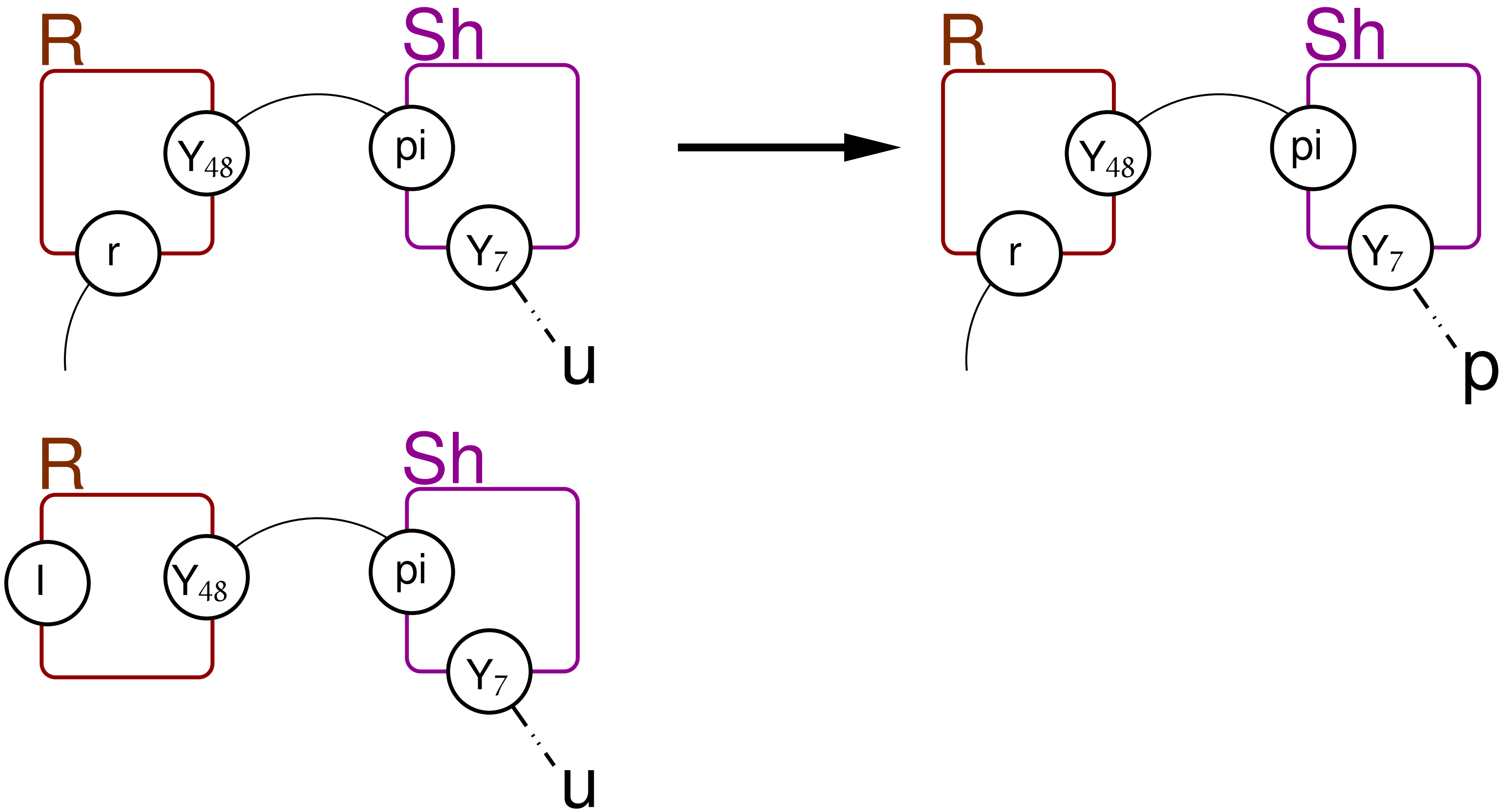
We consider two norms $||\cdot||$ on $\mathcal{V} \rightarrow \mathbb{R}^+$ and $||\cdot||^\sharp$ on $\mathcal{V}^\sharp \rightarrow \mathbb{R}^+$.

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 ?

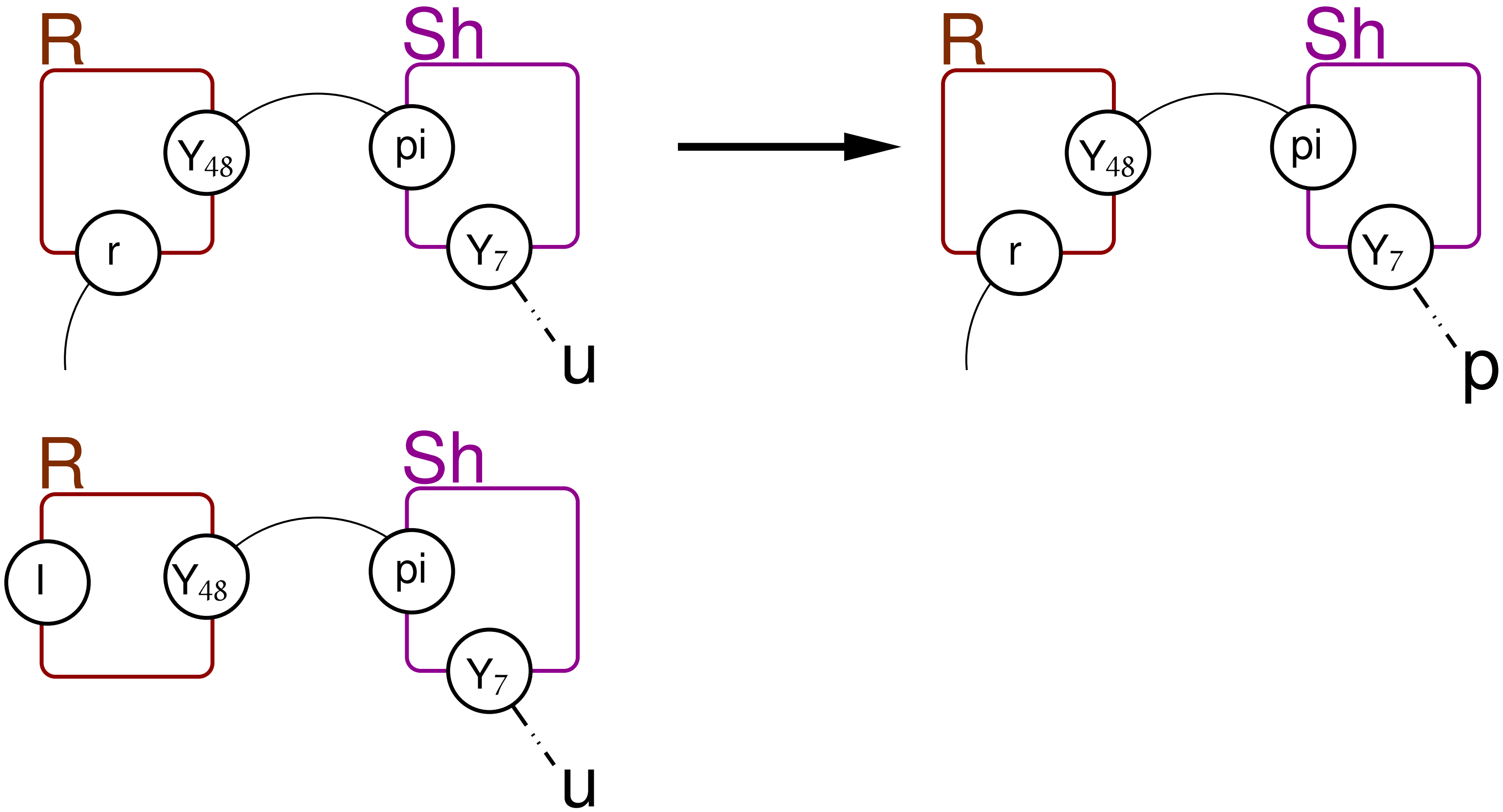
Overview

Fragments consumption



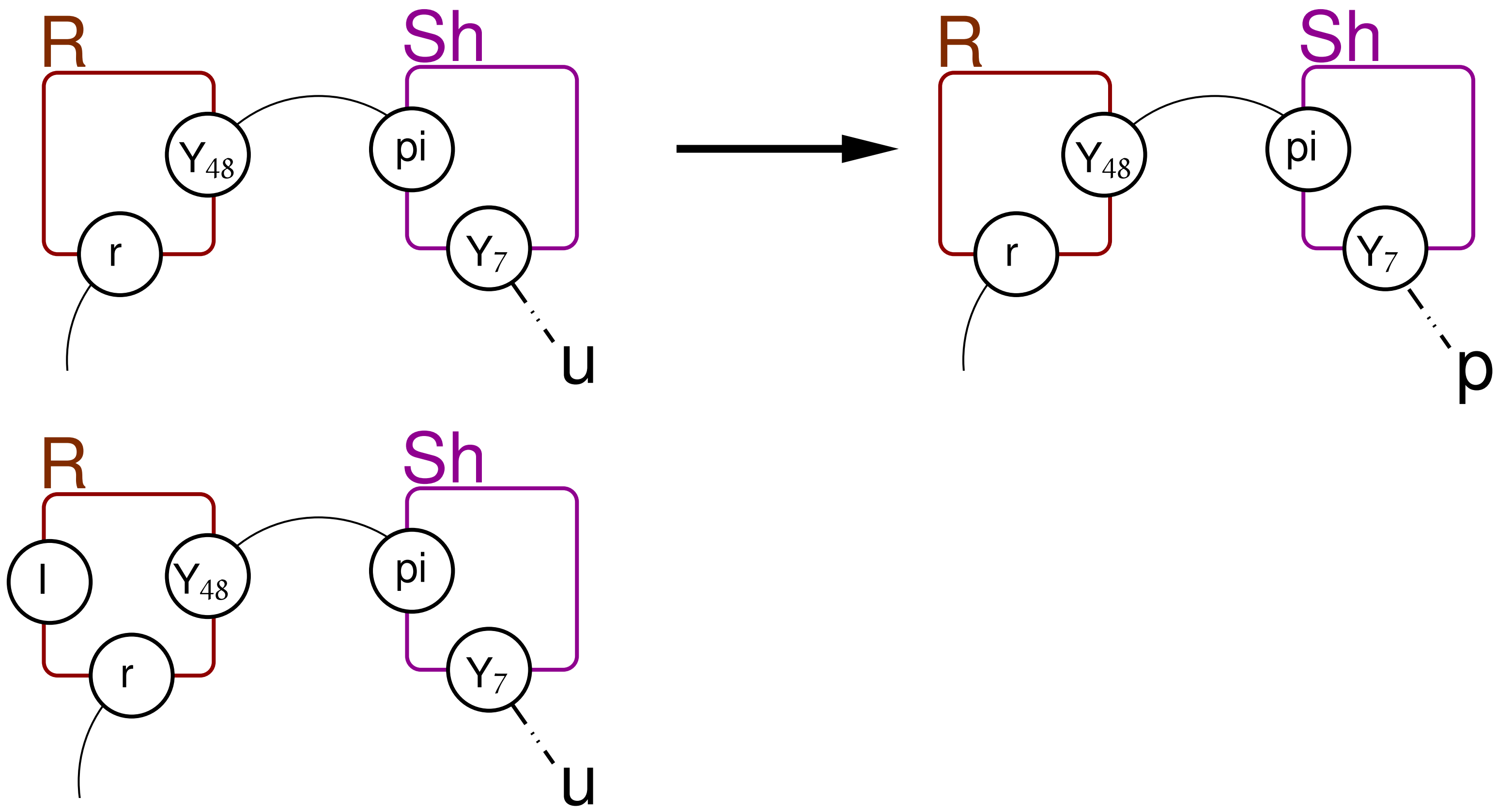
Can we express the amount (per time unit) of this fragment (bellow) concentration that is consumed by this rule (above)?

Fragments consumption



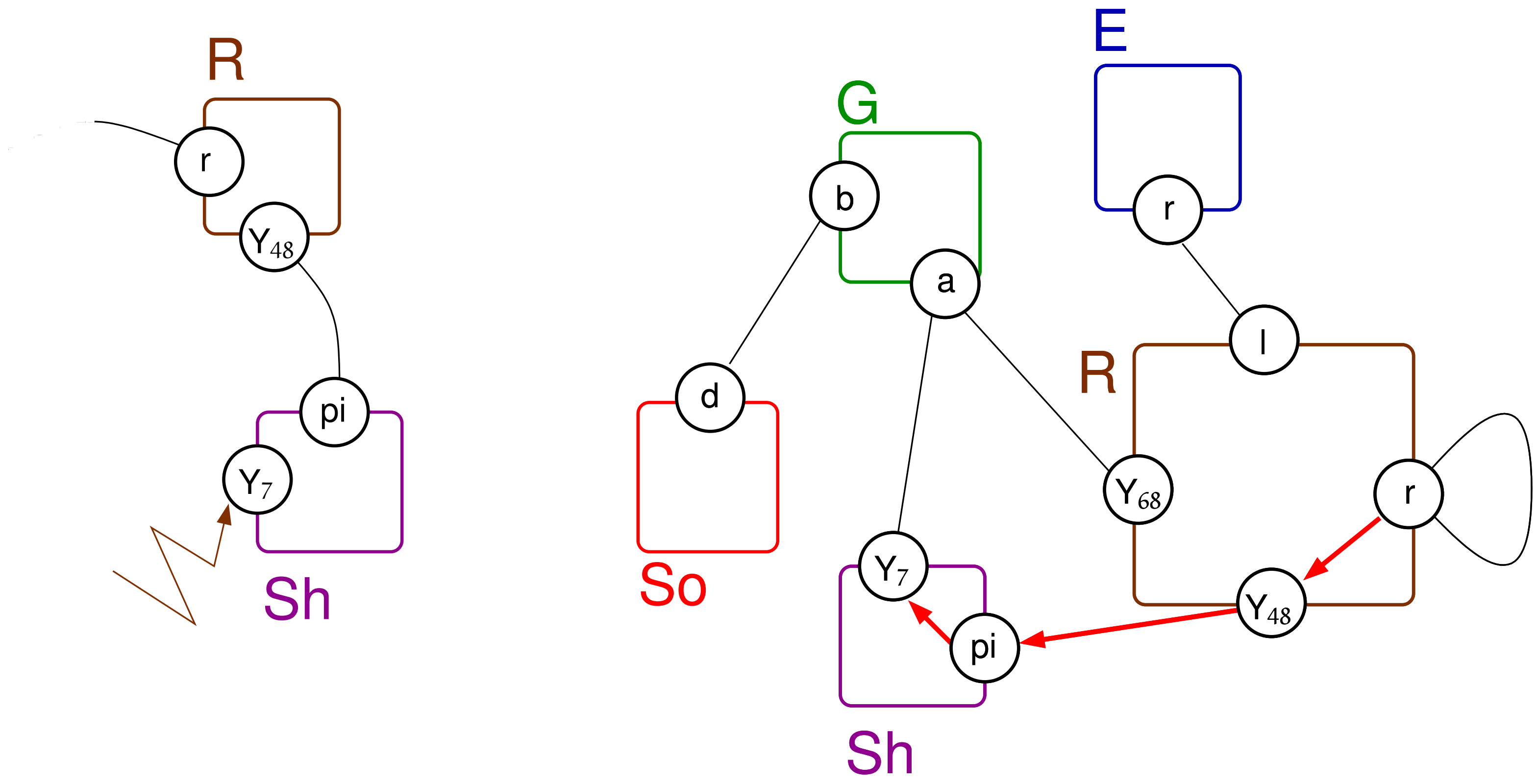
No, because we have abstracted away the correlation between the state of the site $\mathtt{r}$ and the state of the site $\mathtt{l}$.

Fragments consumption
Proper intersection



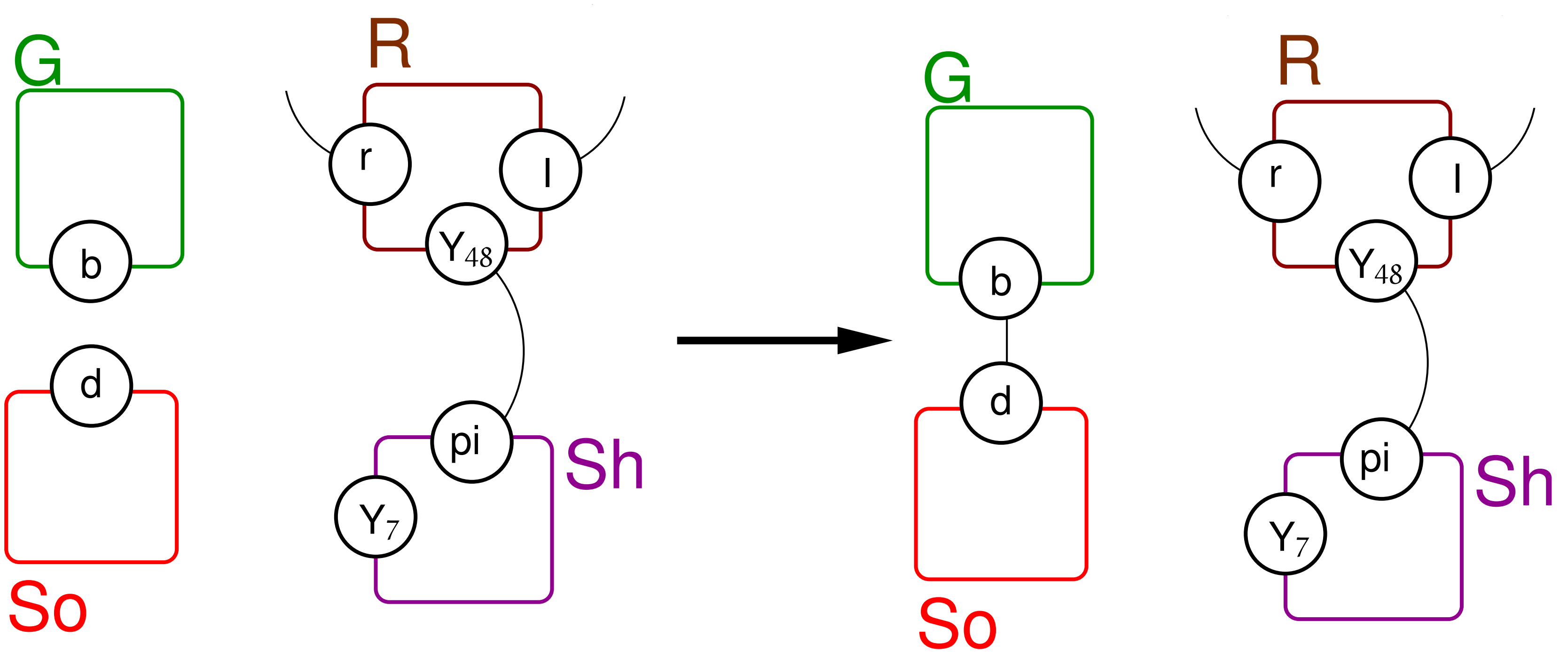
Whenever a fragment intersects a connected component of a lhs on a modified site, then the connected component must be embedded in the fragment!

Fragment consumption
Syntactic criteria



We reflect, in the annotated contact map, each path that stems from a tested site to a modified site (in the lhs of a rule).

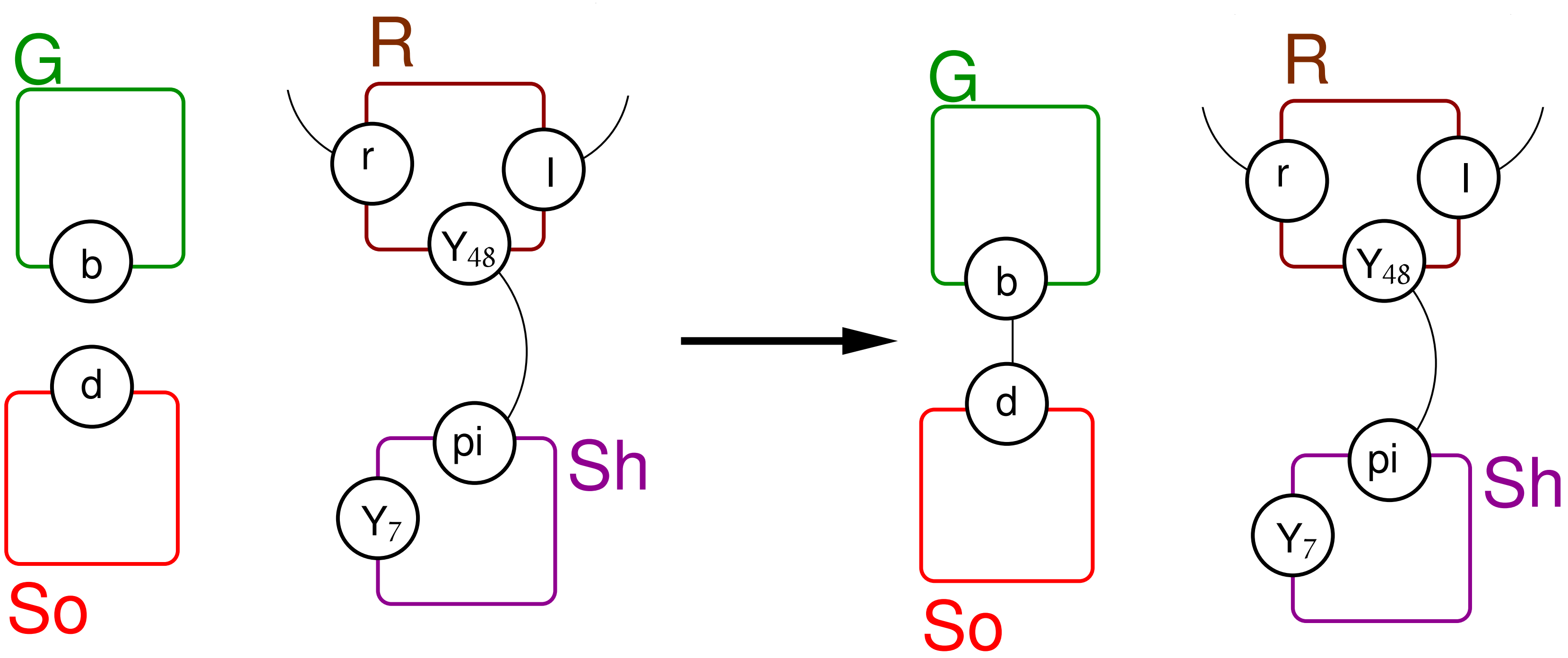
Connected components



We need to express the “concentration” of any connected component of a lhs with respect to the “concentration” of fragments.

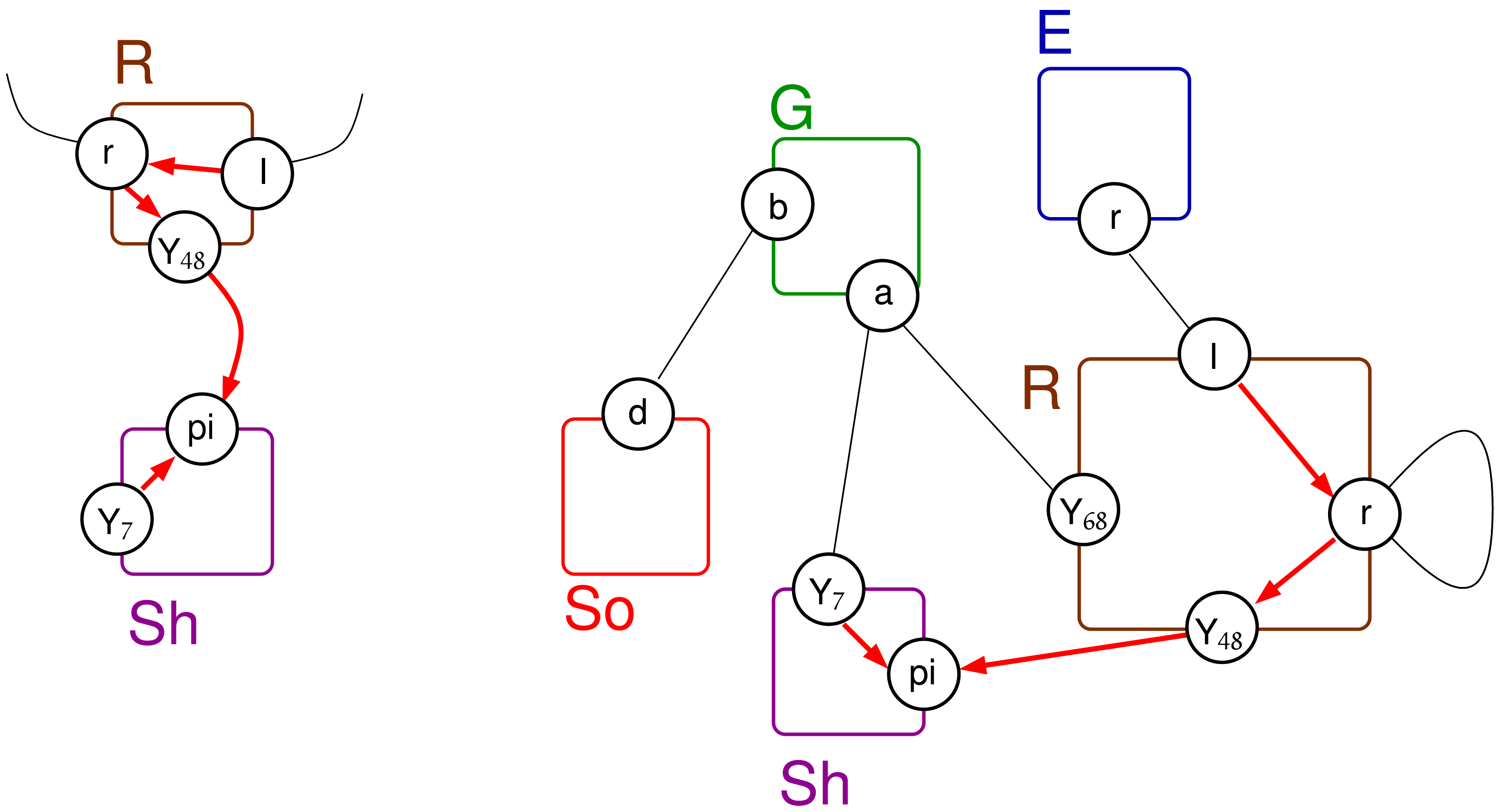
Connected components

Prefragment



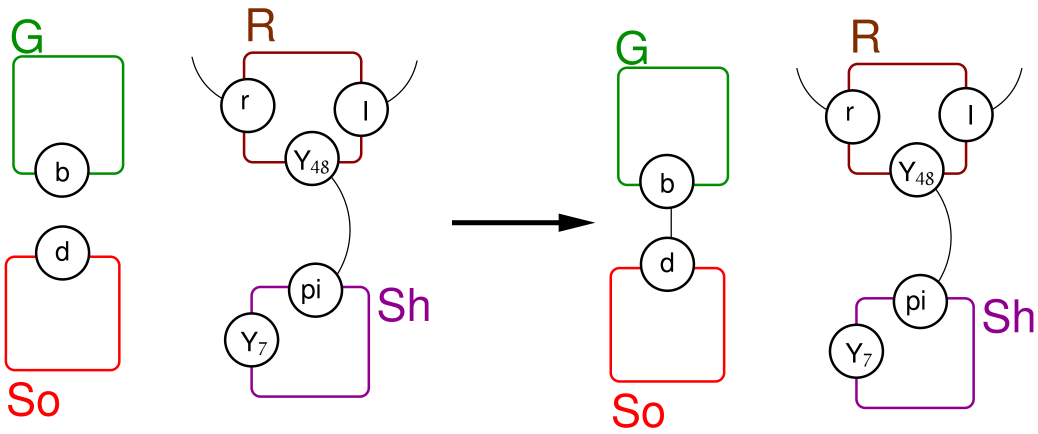
Each connected component of a lhs must be a prefragment.

Connected components
Syntactic criteria



For each connected component of a lhs, there must exists a site which is reachable from all the other ones.

Fragment consumption



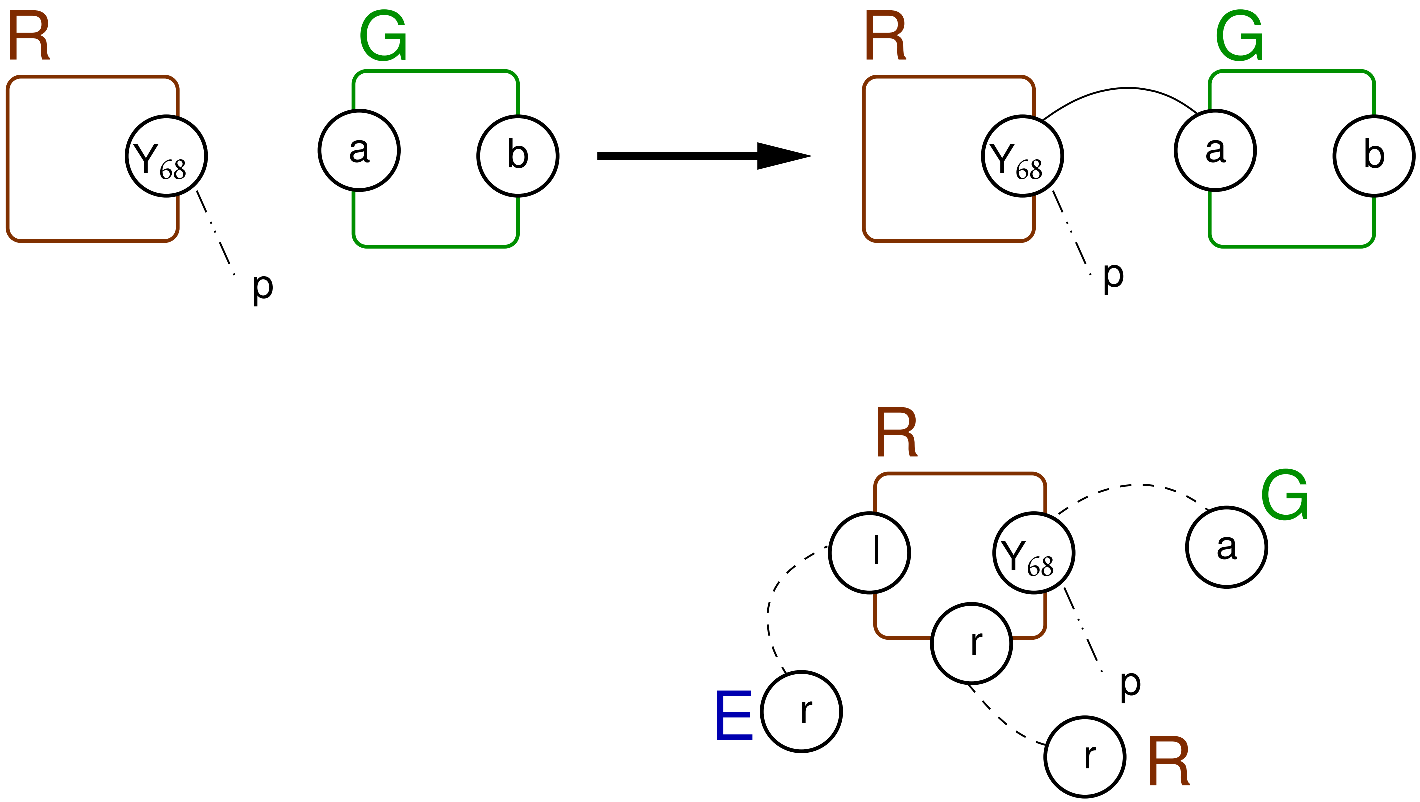
For any rule:

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

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

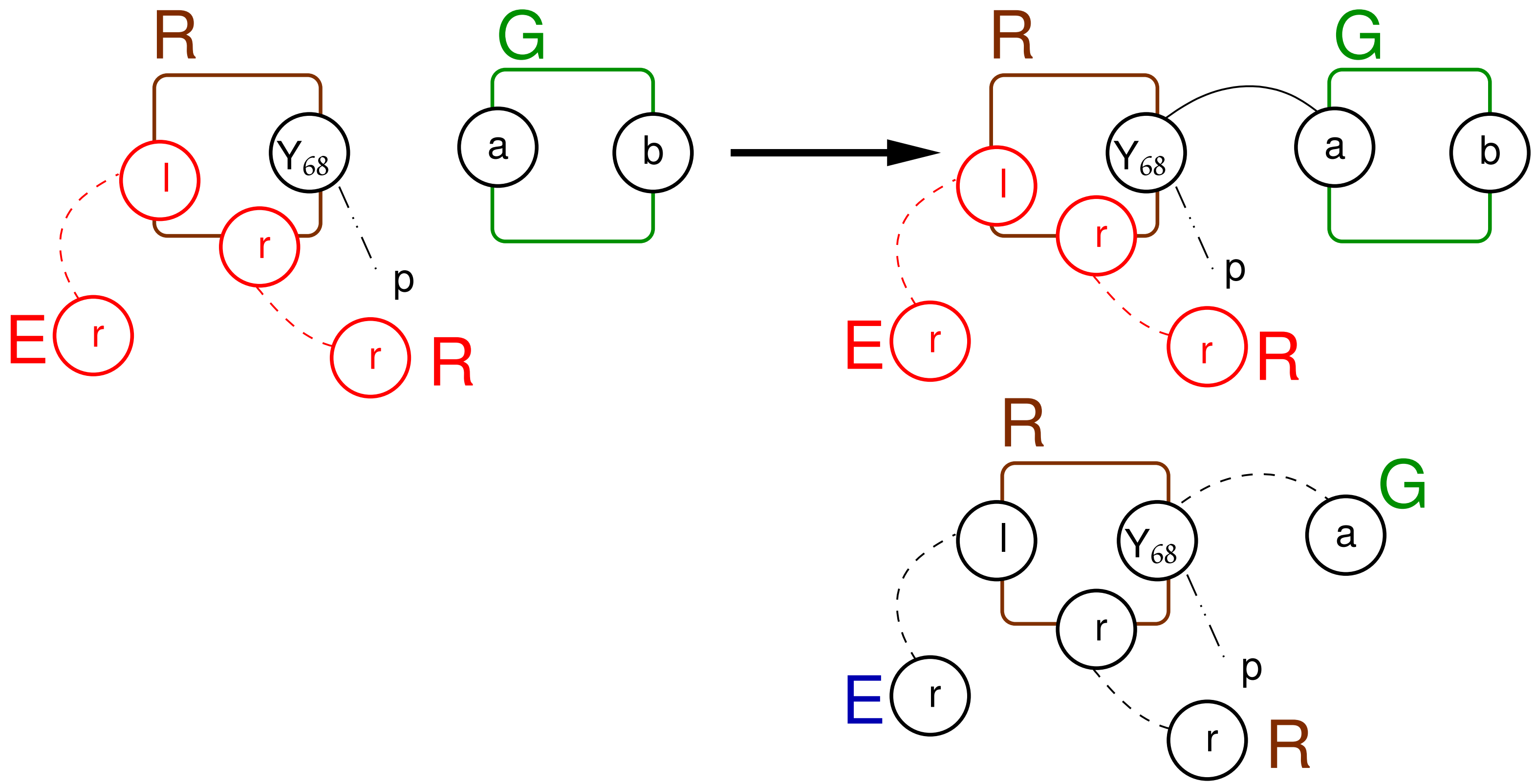
$$\frac{d[F]}{dt} \stackrel{-}{=} \frac{k \cdot [F] \cdot \prod_{i \neq k} [C_i]}{\mathsf{SYM}(C_1, \ldots, C_n) \cdot \mathsf{SYM}(F)}.$$

Fragment production



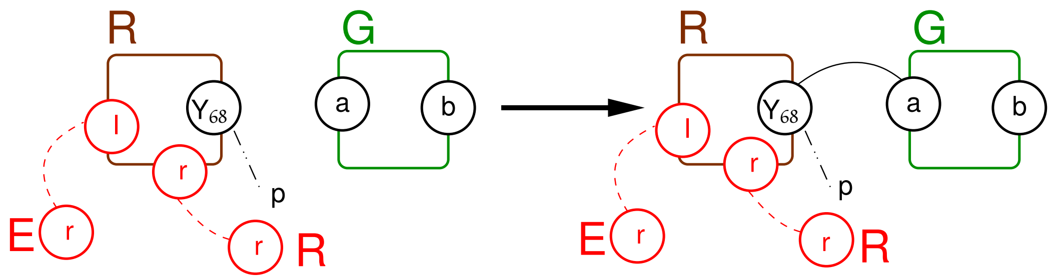
Can we express the amount (per time unit) of this fragment (bellow) concentration that is produced by the rule (above)?

Fragment production
Proper intersection (bis)



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

Fragment production
Proper intersection (bis)



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:

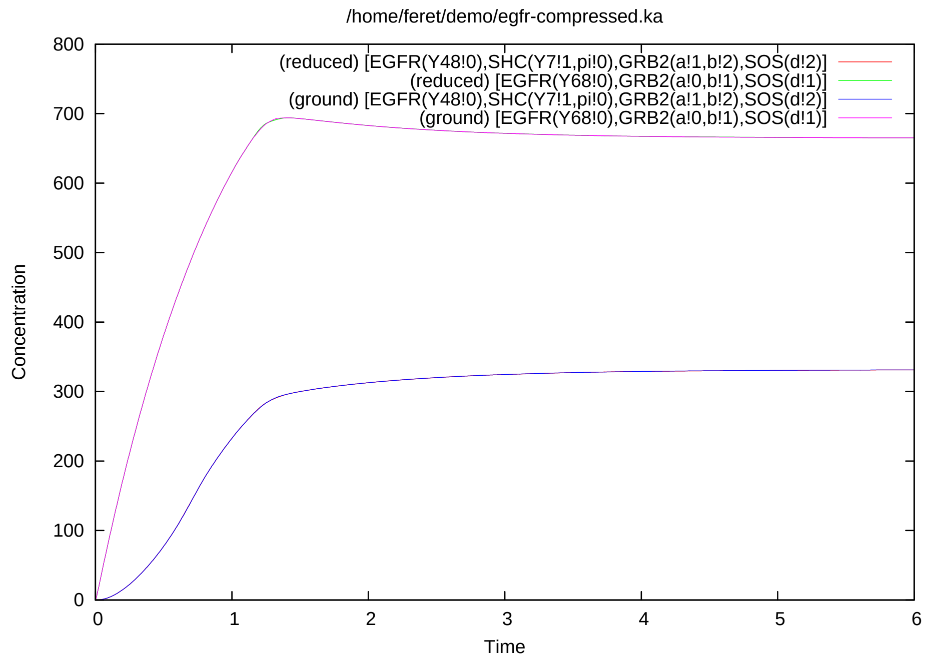
- we can express the concentration of any connected component occuring in lhss,
- we can express fragment proper consumption,
- we can express fragment proper production,
- WE HAVE A CONSTRUCTIVE DEFINITION FOR $\mathbb{F}^\sharp$.

Overview

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

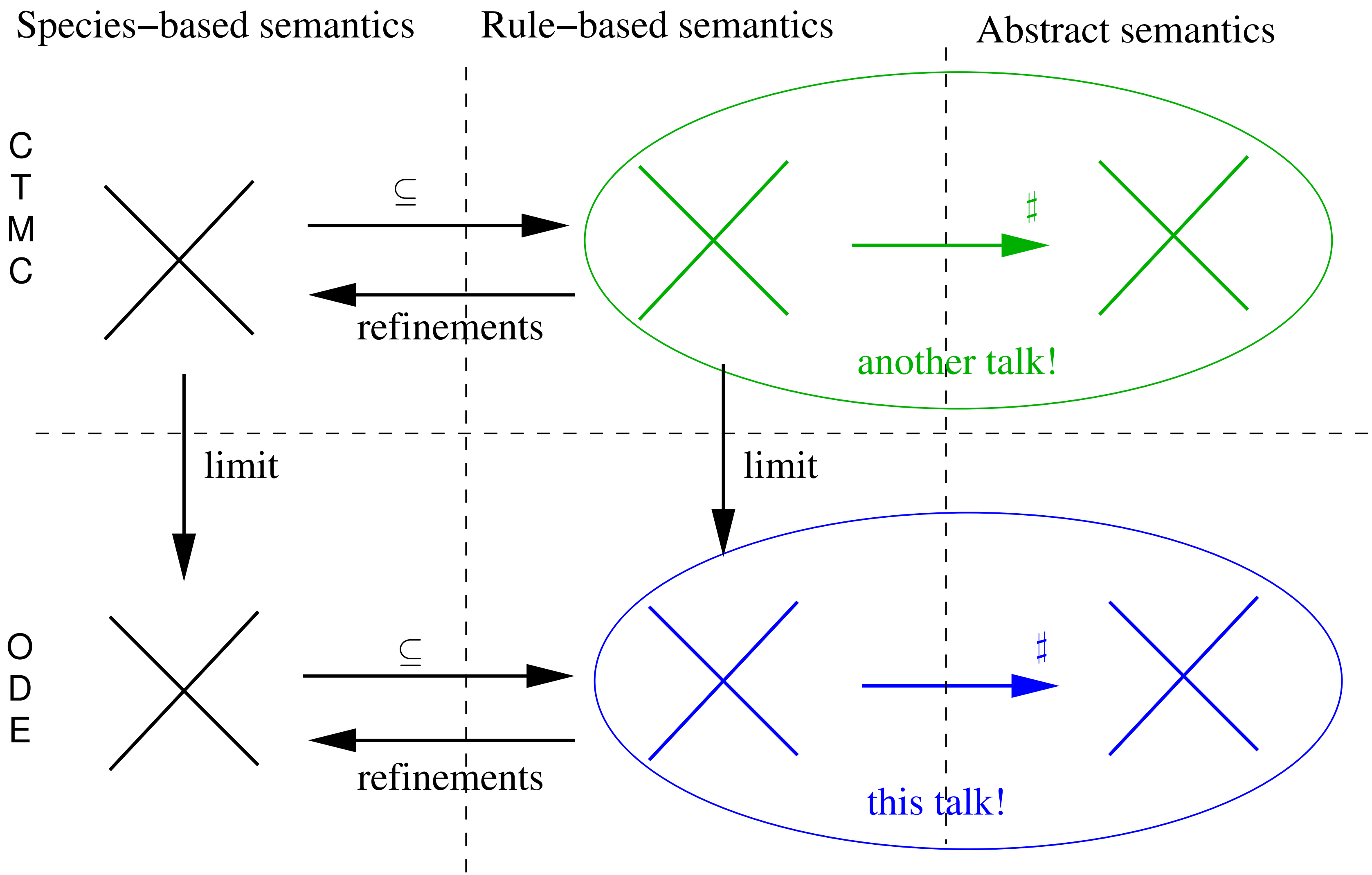
Experimental results

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	$\sim 2.10^{19}$



Both differential semantics
(4 curves with match pairwise)

Related issues I: Semantics comparisons



Related issues II:
Semantics approximations

1. ODE approximations:
   - Concrete definition of the control flow and hierarchy of abstractions. A notion of control flow which would be invariant by:
     - neutral rule refinement;
     - compilation of a Kappa system into a Kappa system with only one agent type.

   Joint work with Ferdinanda Camporesi (Bologna)
2. Stochastic semantics approximations:
   - Can we design abstraction ?
   - Find the adequate soundness criteria.

   Joint work with Thomas Henzinger (IST-Vienna), Heinz Koeppl (ETH-Zurich), Tatjana Petrov (EPFL)

Call for participation

Second Workshop on Static Analysis and Systems Biology
(SASB 2011)
(co-chaired with Andre Levchenko)
13th Sept 2011, Venice
http://www.di.ens.fr/sasb2011

Invited speakers:

- Boris Kholodenko
- Edda Klipp
- Jean Krivine