MPRI

Abstract interpretation of protein-protein interactions networks

Jérôme Feret

DI - ÉNS

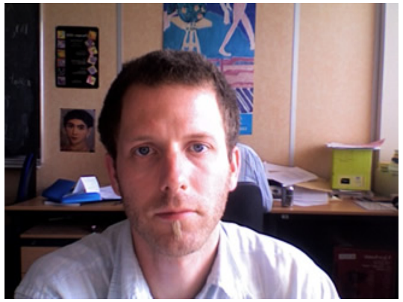
Wednesday, the 14th of December, 2016

Joint-work with...

Walter Fontana
Harvard Medical School

Vincent Danos
ÉNS

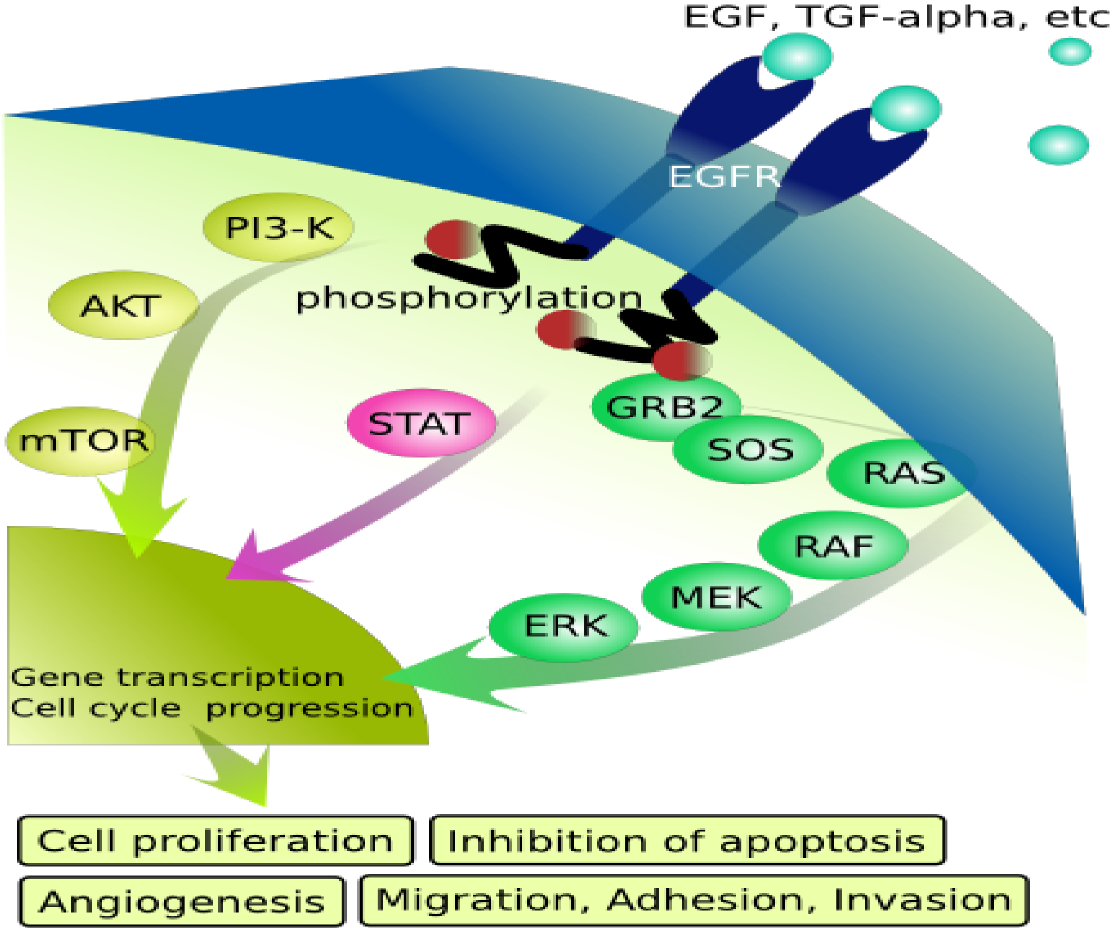
Ferdinanda Camporesi
Bologna / ÉNS



Russ Harmer
ÉNS Lyon

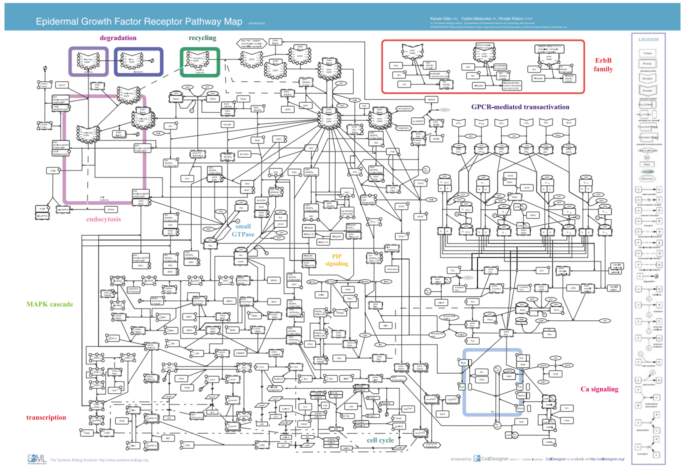
Jean Krivine
Paris VII

Signalling Pathways



Eikuch, 2007

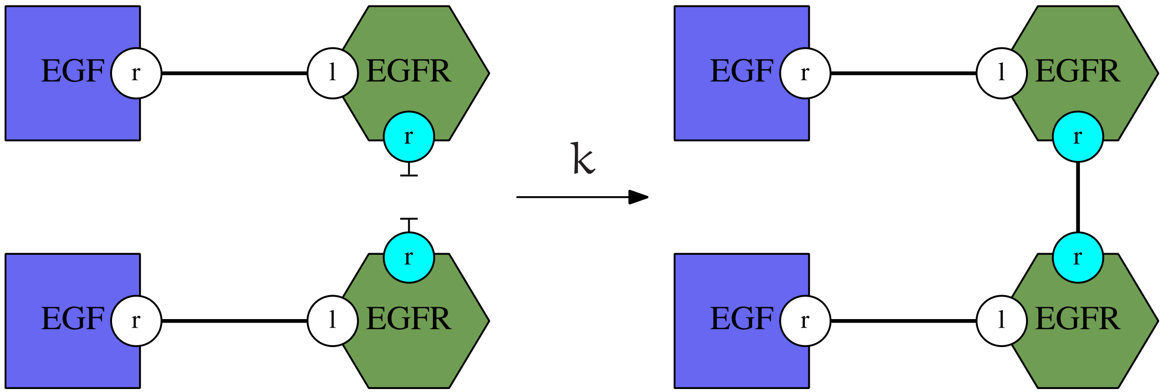
Bridging the gap between. . .



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

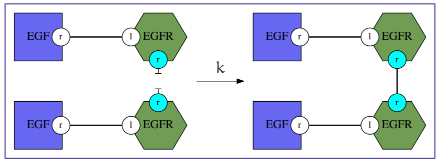
knowledge representation **and** **models of the behaviour of systems**

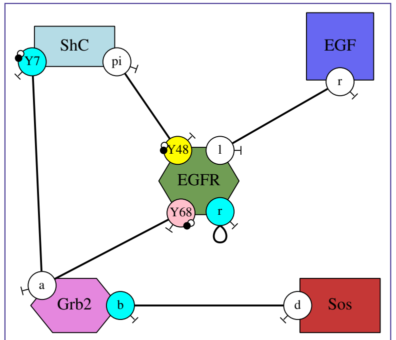
Site-graphs rewriting



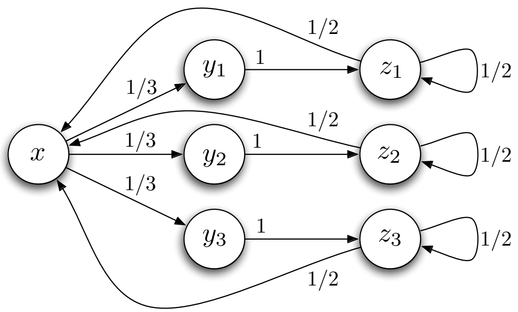
- a language close to knowledge representation;
- rules are easy to update;
- a compact description of models.

Choices of semantics





interaction map

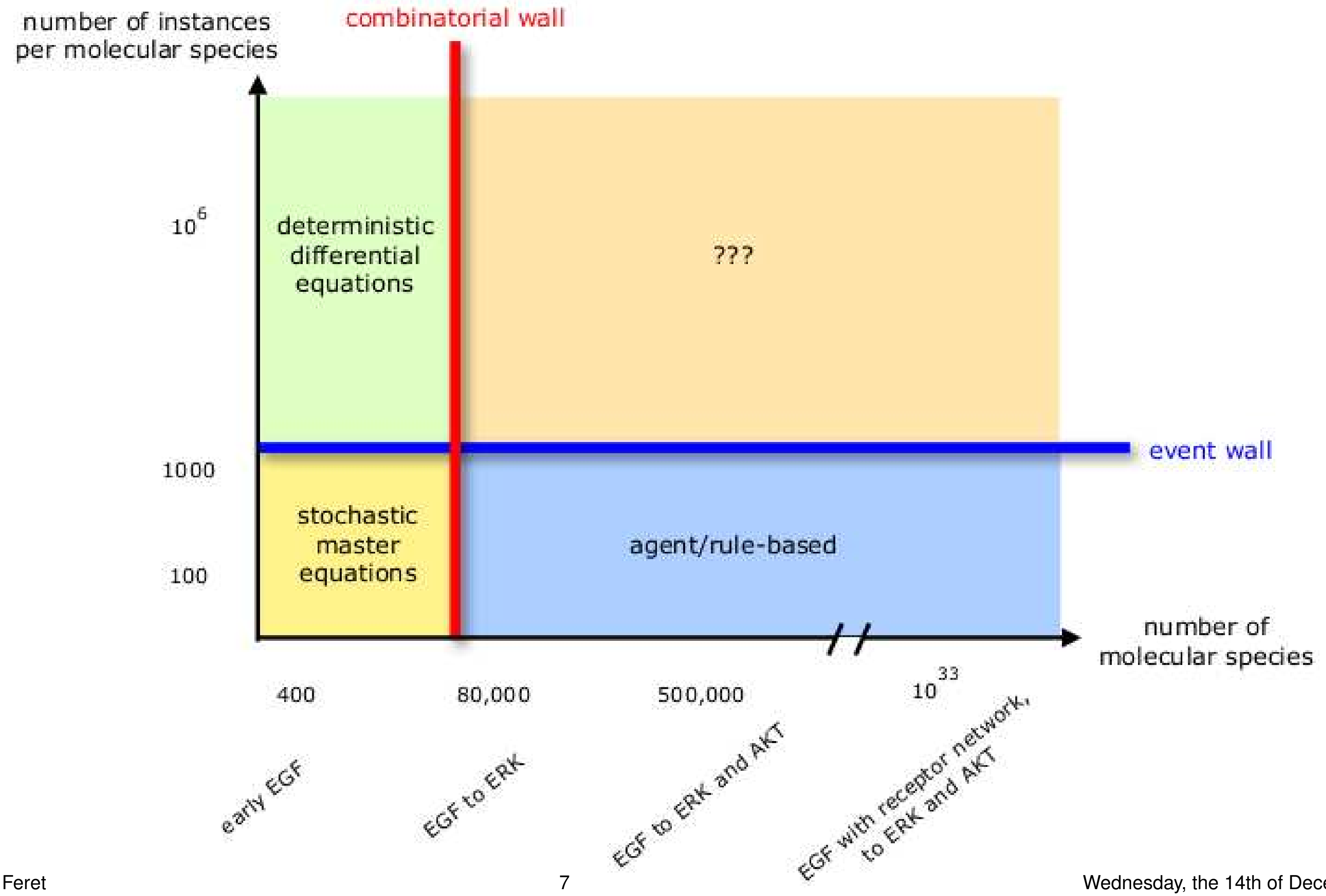


Markov chain

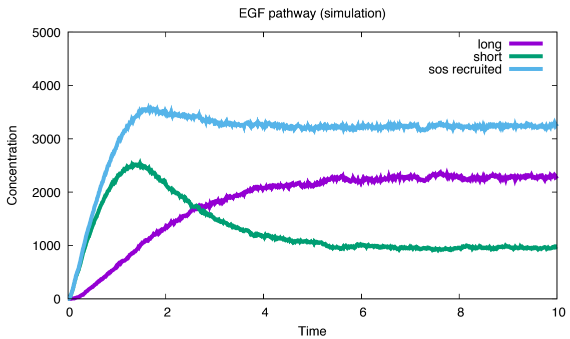
$$\begin{cases} \frac{dx_1}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\ \frac{dx_2}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\ \frac{dx_3}{dt} = k_1 \cdot x_1 \cdot x_2 - k_{-1} \cdot x_3 + 2 \cdot k_2 \cdot x_3 \cdot x_3 - k_{-2} \cdot x_4 \\ \frac{dx_4}{dt} = k_2 \cdot x_3^2 - k_2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

ordinary differential equations

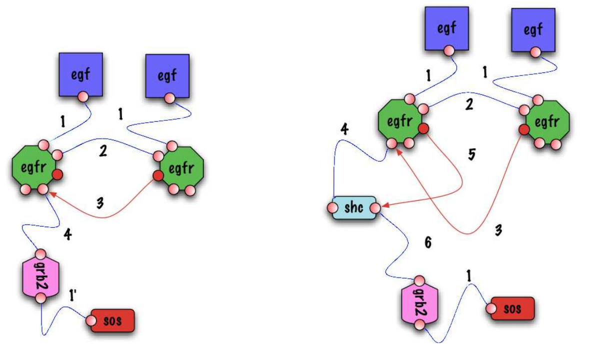
Complexity walls



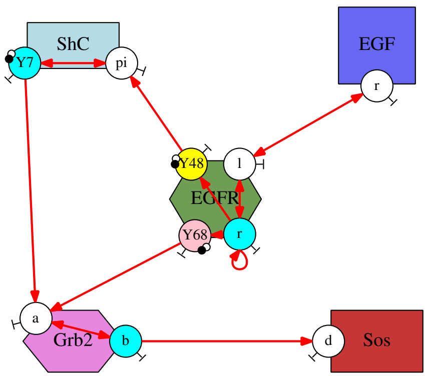
Abstractions offer different perspectives on models



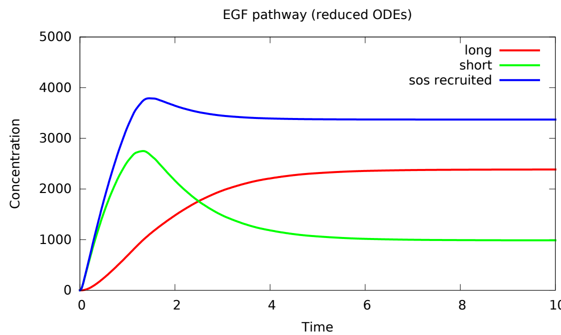
concrete semantics



causal traces



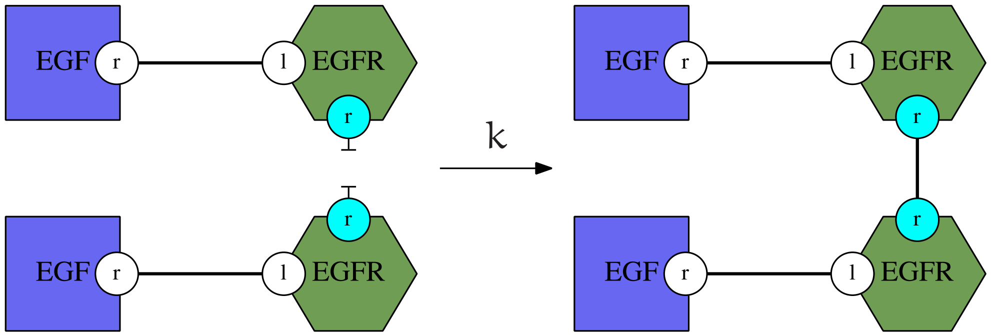
information flow



exact projection
of the ODE semantics

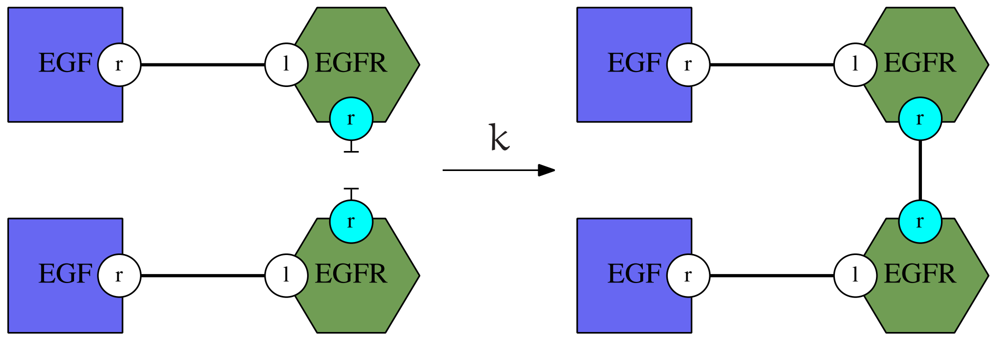
Static analysis of reachable species (I/II)

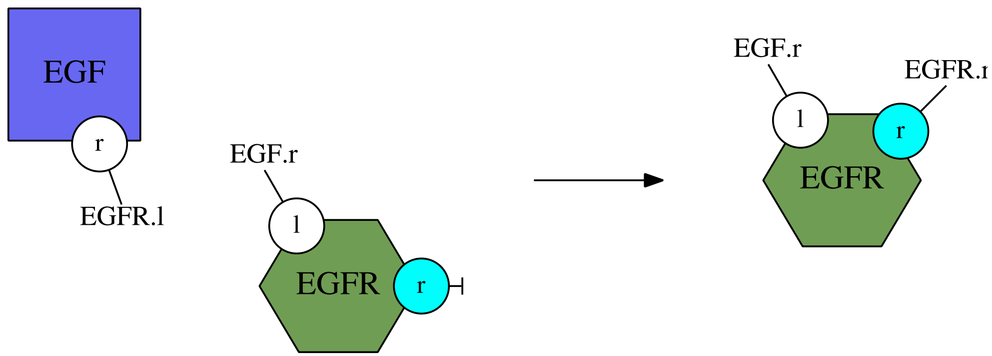
We capture the relationships between the states of the sites of each agent.



Static analysis of reachable species (I/II)

We capture the relationships between the states of the sites of each agent.





Static analysis of reachable species (II/II)

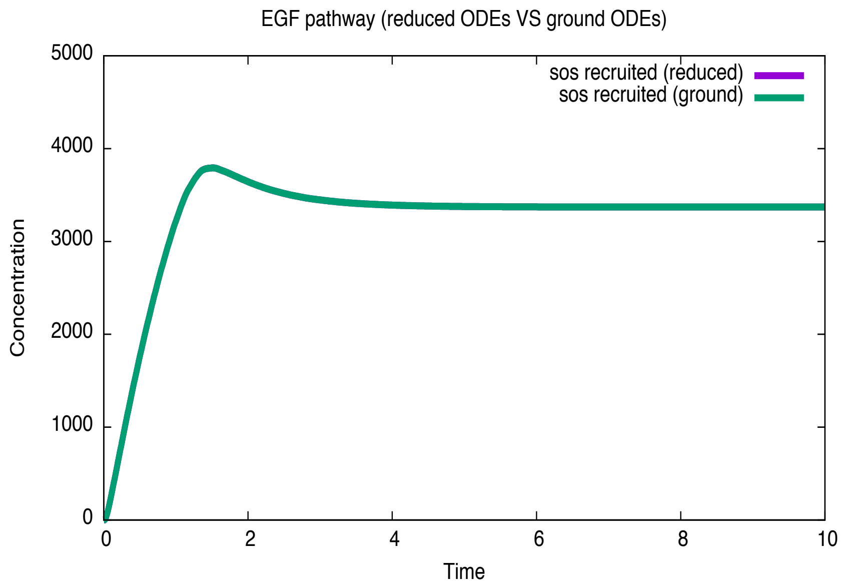
Applications:

1. check the consistency of a model [ICCMSE'07]
2. compute the properties to allow fast simulation [APLAS'07]
3. simplify models,
4. compute independent fragments of chemical species [PNAS'09, LICS'10,Chaos'10]

The analysis is complete (no false positif) for a significatif kernel of Kappa [VMCAI'08].

Model reduction

The ground differential system uses one variable per chemical species;
We directly compute its exact projection over independent fragments of chemical species.
With a small model, 356 chemical species are reduced into 38 fragments:



On a bigger model, 10^{19} chemical species are reduced into 180 000 fragments. [PNAS'09,LICS'10,Chaos'10]

MPRI

Some notions of information flow

Jérôme Feret
Laboratoire d'Informatique de l'École Normale Supérieure
INRIA, ÉNS, CNRS
http://www.di.ens.fr/~feret

Wednesday, the 4th of January, 2017

Syntax

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

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

Programs are given by the following grammar:

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

Semantics

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

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

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

Flow of information

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

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

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

For any $\rho \in \mathcal{V} \rightarrow \mathbb{Z}$,
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 $V_1 \not\rightarrow^*{}_P V_2$.

Syntactic approximation (tentative)

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

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

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

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

Counter-example

We consider the following progrem P:

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

For any $\rho \in \mathcal{V} \to \mathbb{Z}$,
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 $V_1 \not\rightarrow^*_P V_2$.

Approximation of the information flow

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

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

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

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

Limitations

The approximation is highly syntax-oriented.

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

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

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

- computation time;
- memory assumption;
- heating.

(attacks cannot be exhaustively specified).

MPRI

Reduction of models of intra-cellular signalling pathways

Jérôme Feret
DI - ÉNS

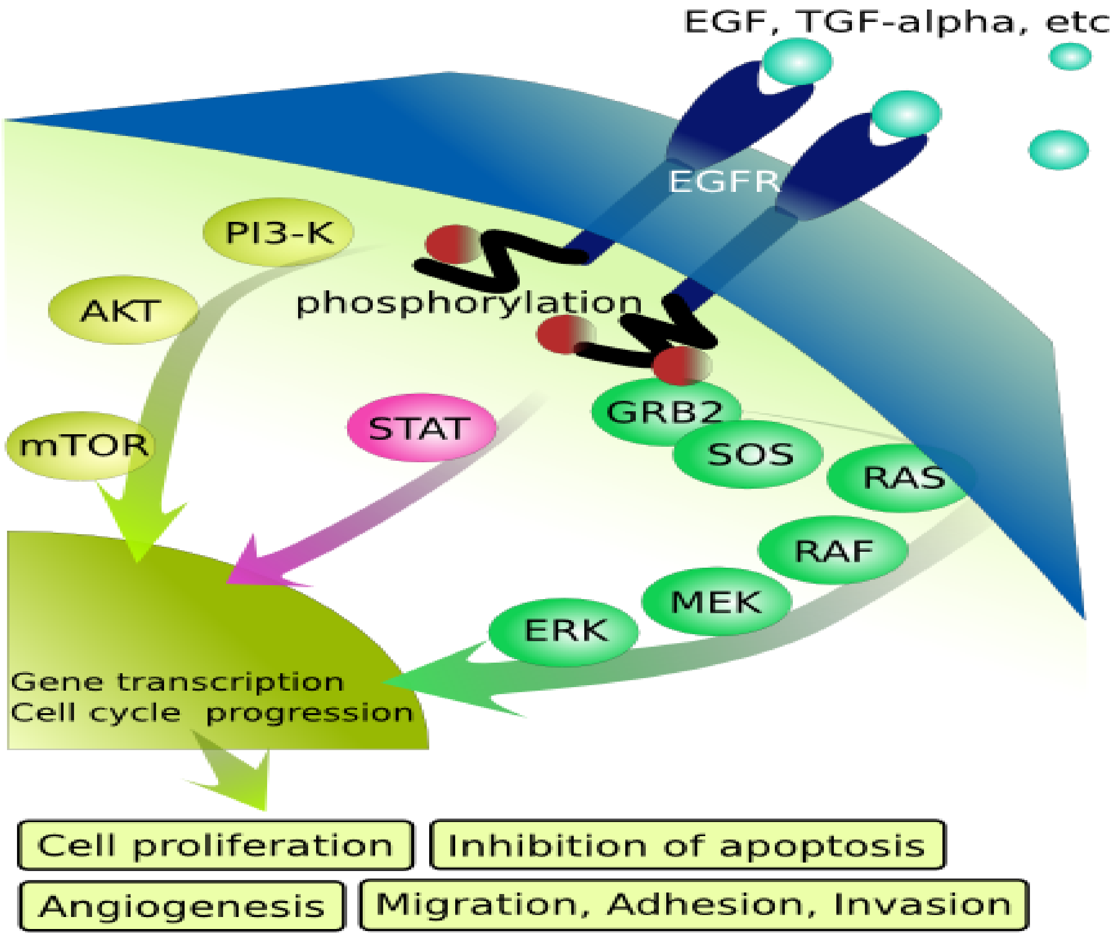
http://www.di.ens.fr/~feret

Wednesday, the 4th of January, 2017

On the menu today

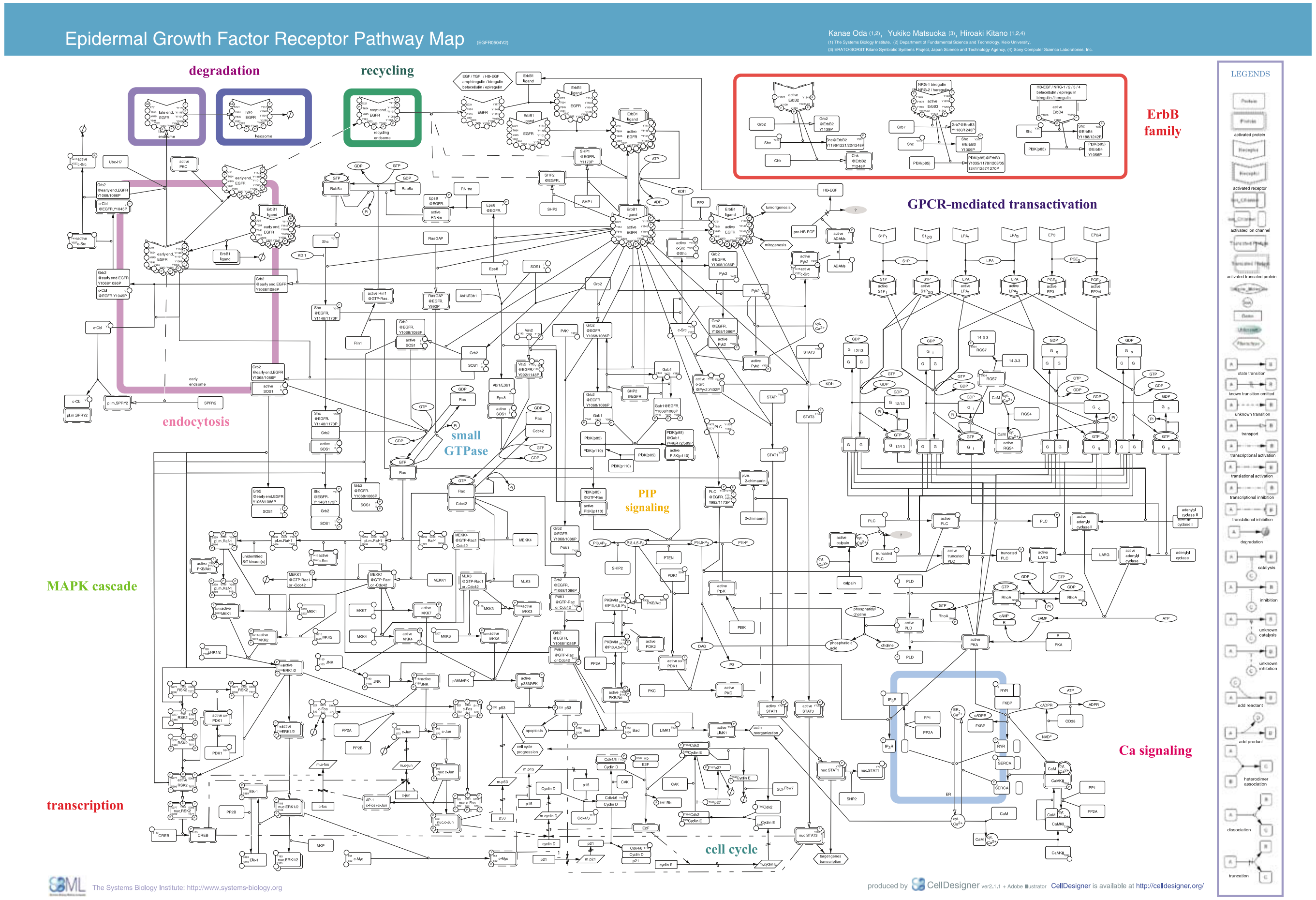
1. Context and motivations
2. Case studies
3. Reduction of ordinary differential equations
4. Abstraction of the information flow
5. Model reduction
6. Conclusion

Intra-cellular signalling pathways



Eikuch, 2007

Interaction maps

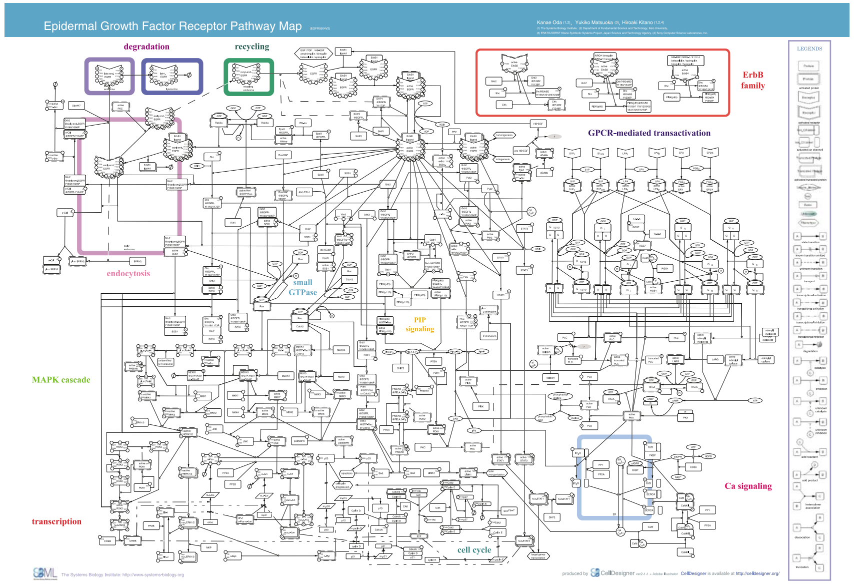


Oda et al, 2005

Models of the behaviour of the system

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

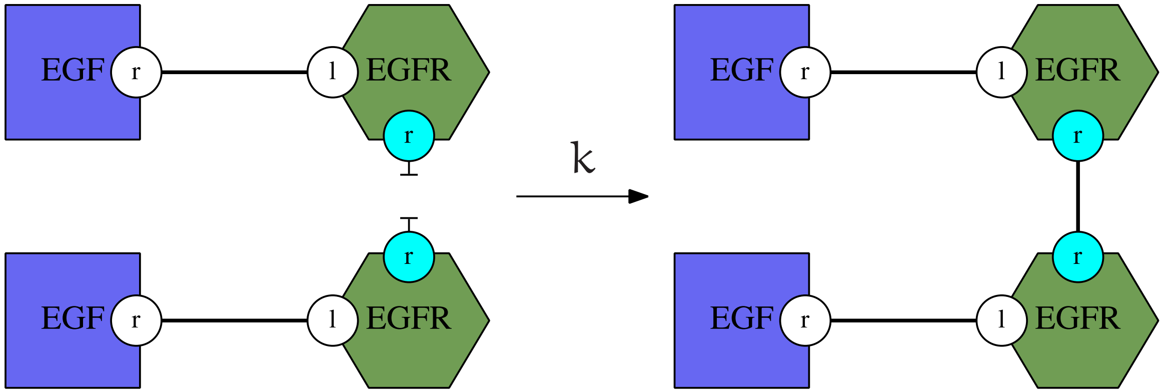
Bridge the gap between...



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

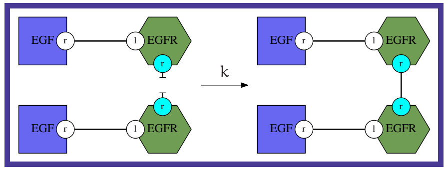
knowledge representation **and** **models of the behaviour of systems**

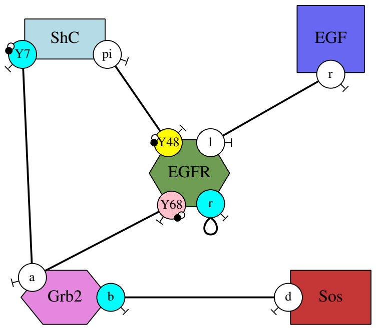
Site-graphs rewriting



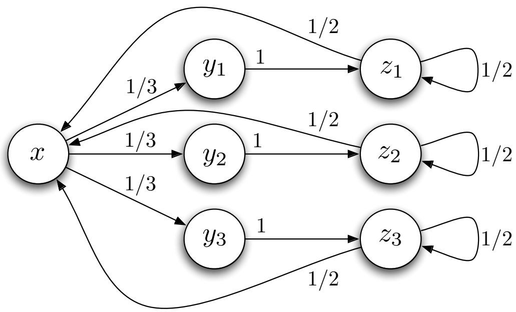
- a language close to knowledge representation;
- rules are easy to update;
- a compact description of models.

Choices of semantics





interaction map

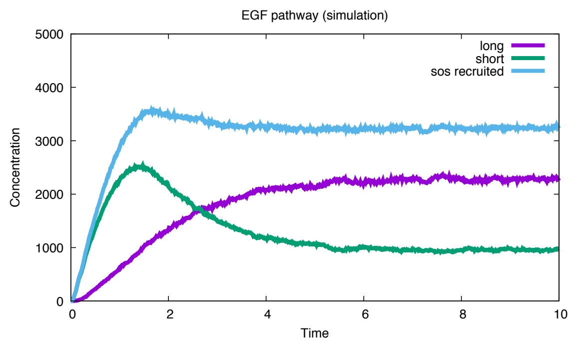


Markov chain

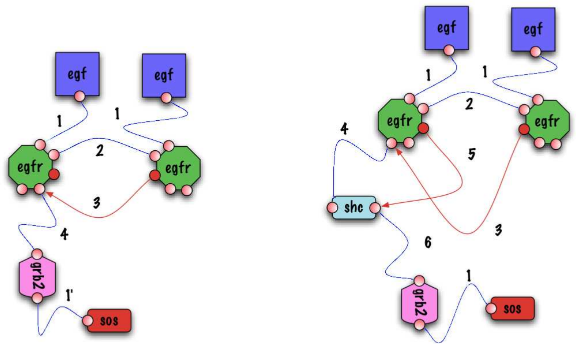
$$
\begin{cases}
\frac{dx_1}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
\frac{dx_2}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
\frac{dx_3}{dt} = k_1 \cdot x_1 \cdot x_2 - k_{-1} \cdot x_3 + 2 \cdot k_2 \cdot x_3 \cdot x_3 - k_{-2} \cdot x_4 \\
\frac{dx_4}{dt} = k_2 \cdot x_3^2 - k_2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

ordinary differential equations

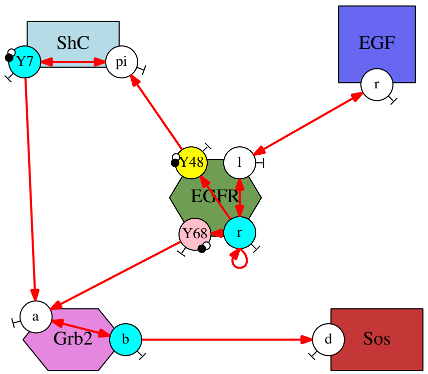
Abstractions offer different perspectives on models



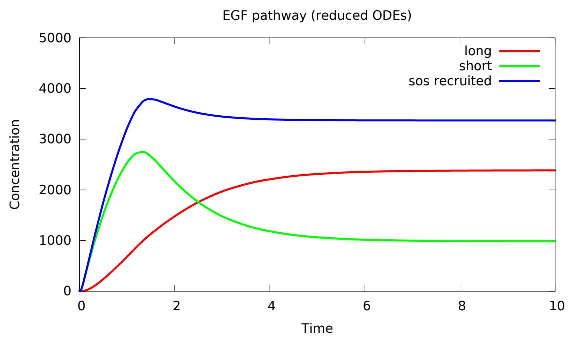
concrete semantics



causal traces

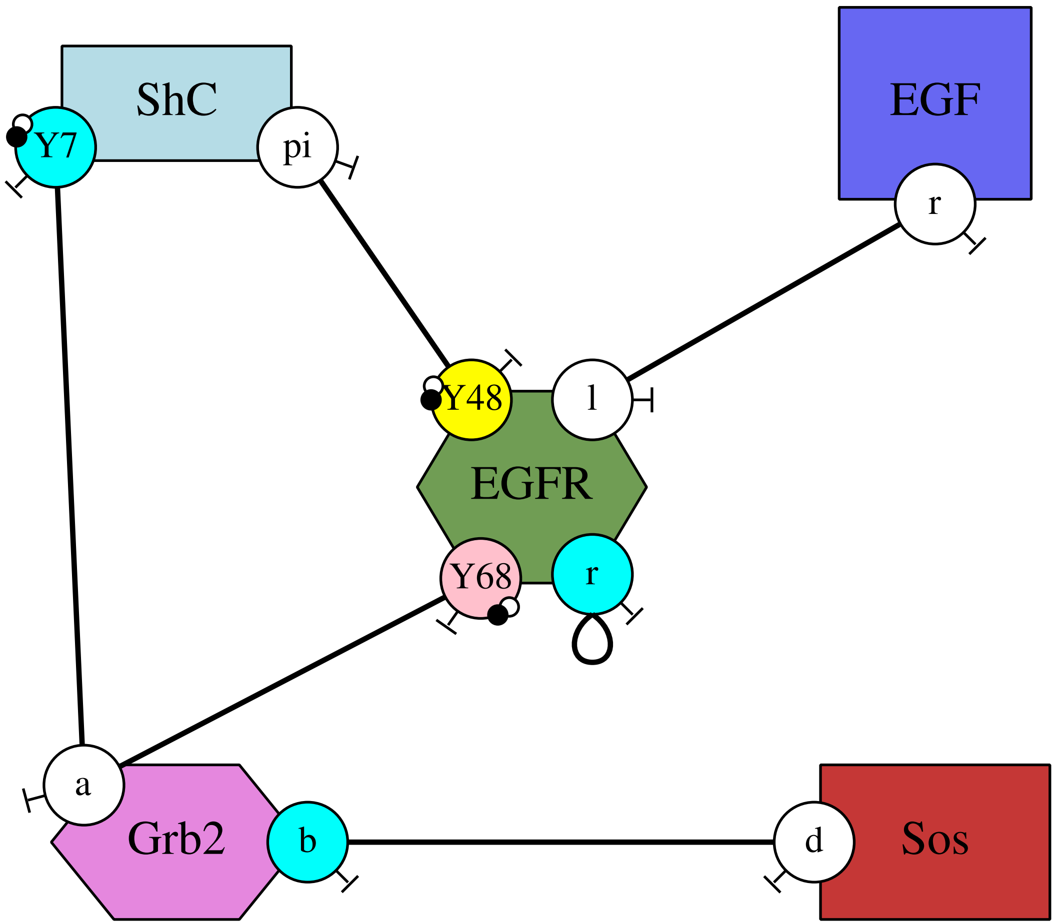


information flow

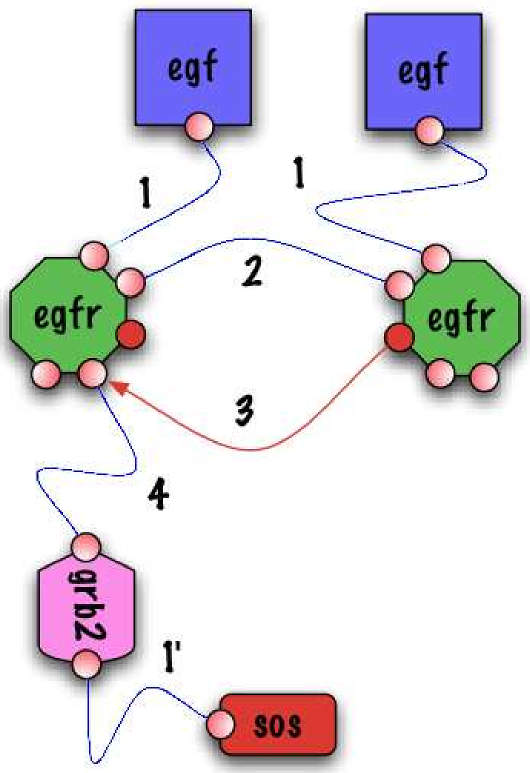


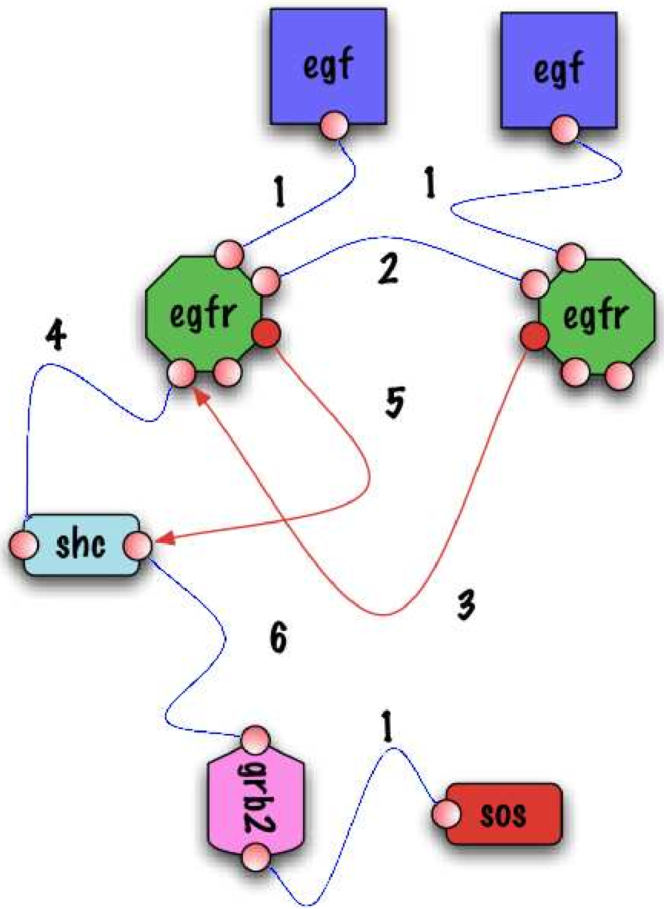
exact projection
of the ODE semantics

Contact map

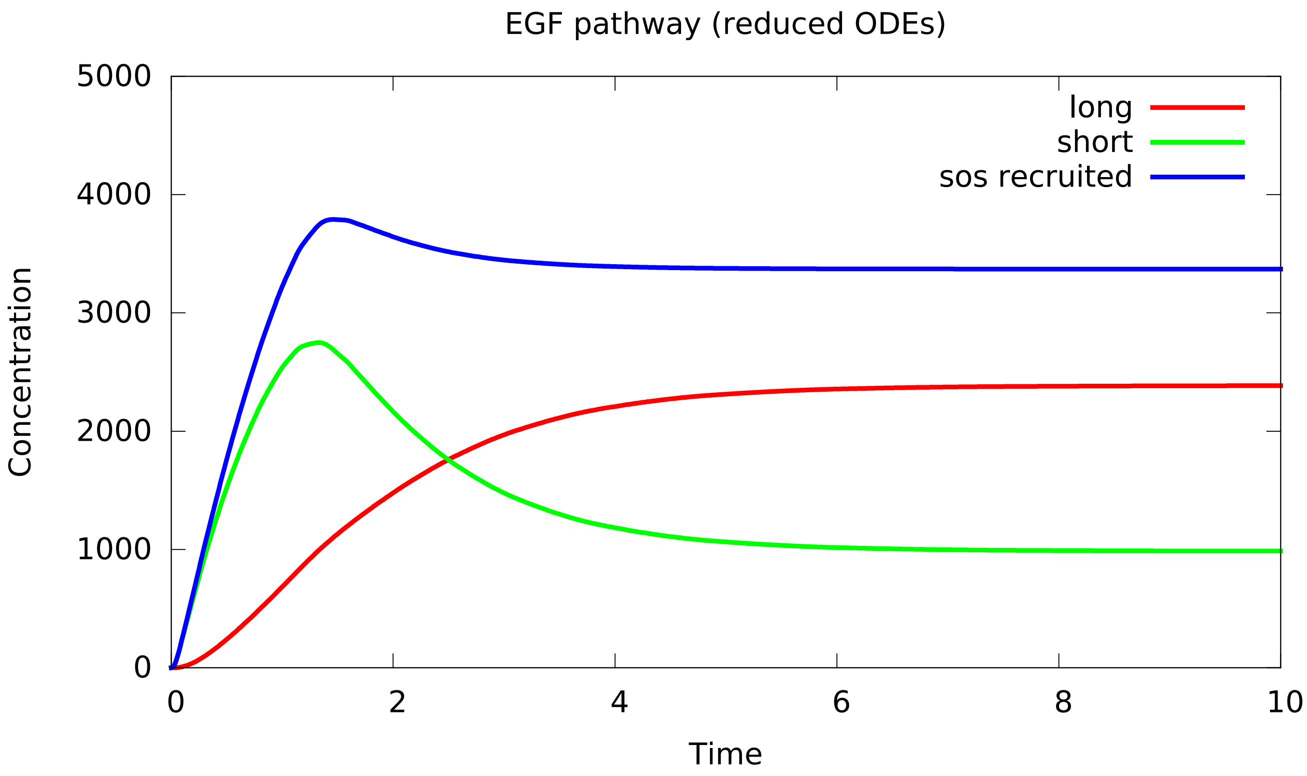


Causal traces

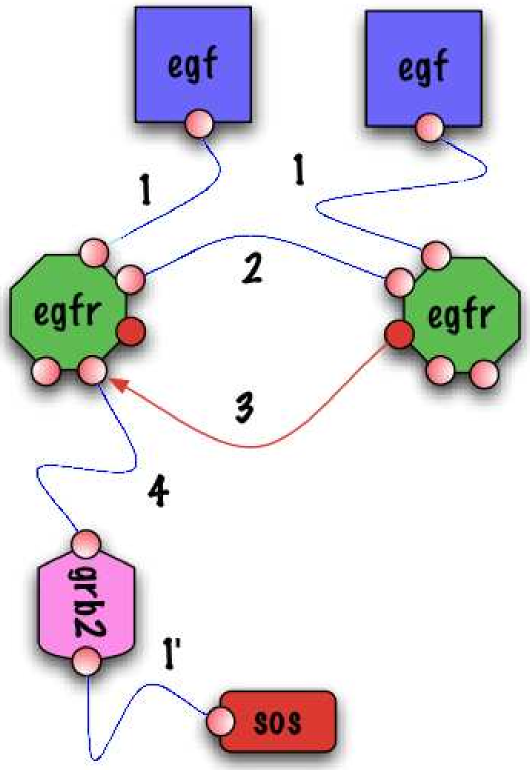


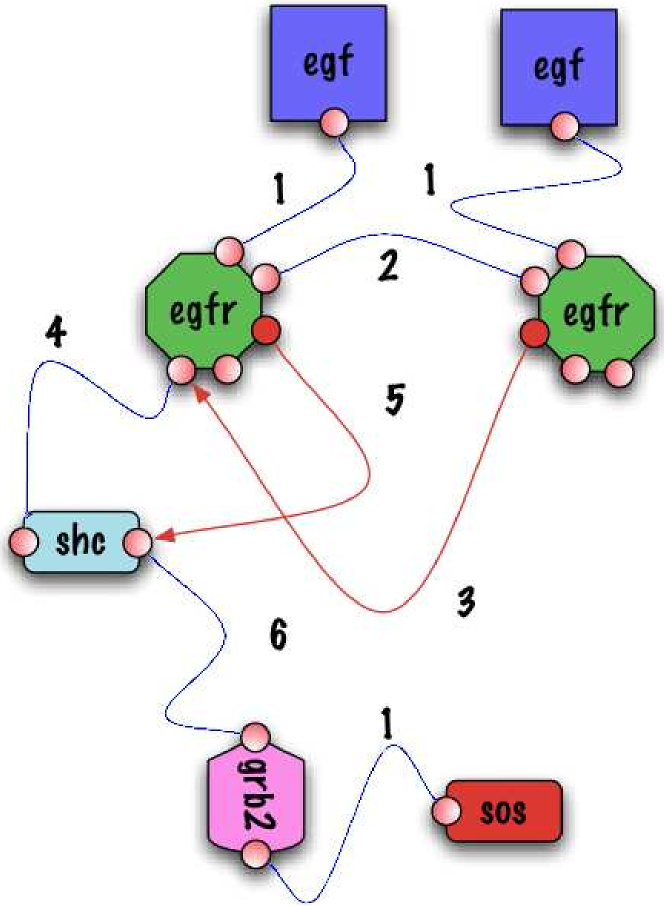


ODE semantics

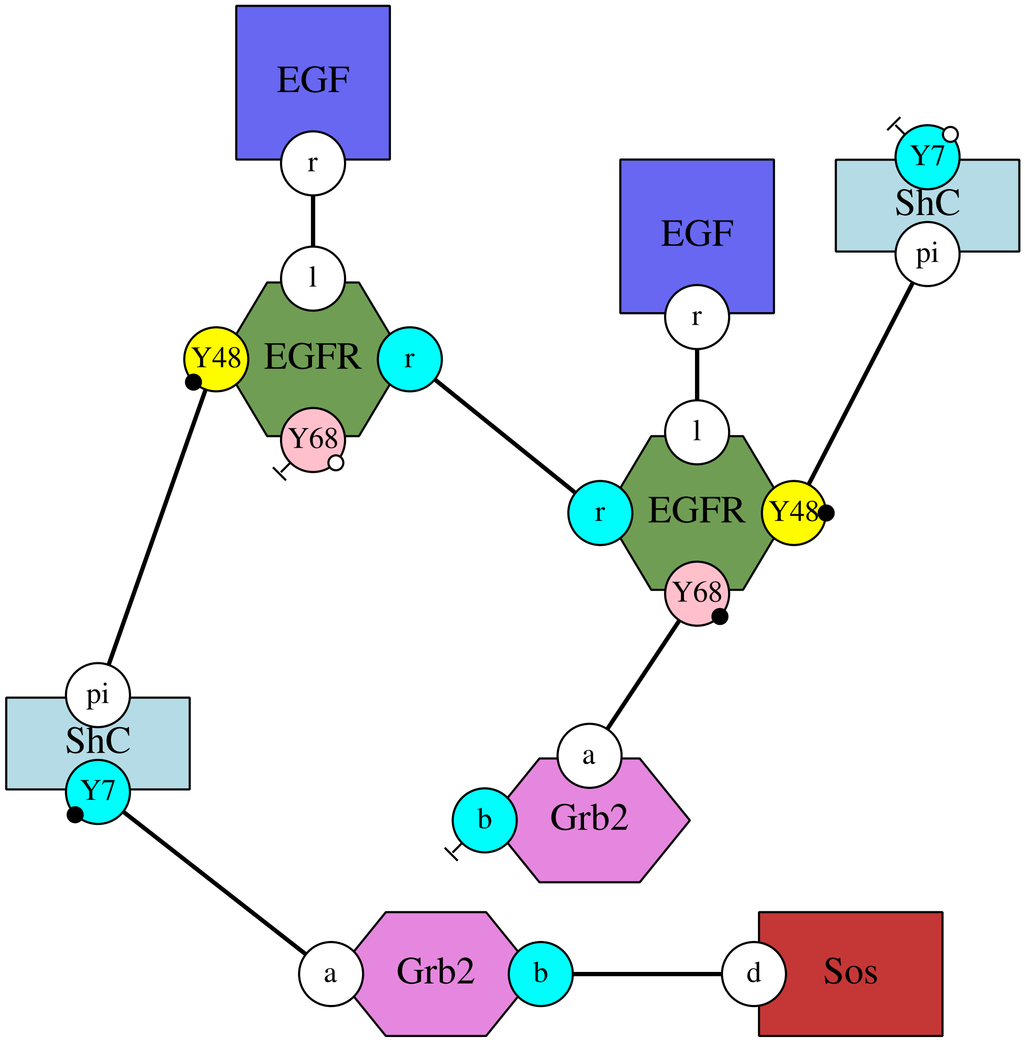


Causal traces

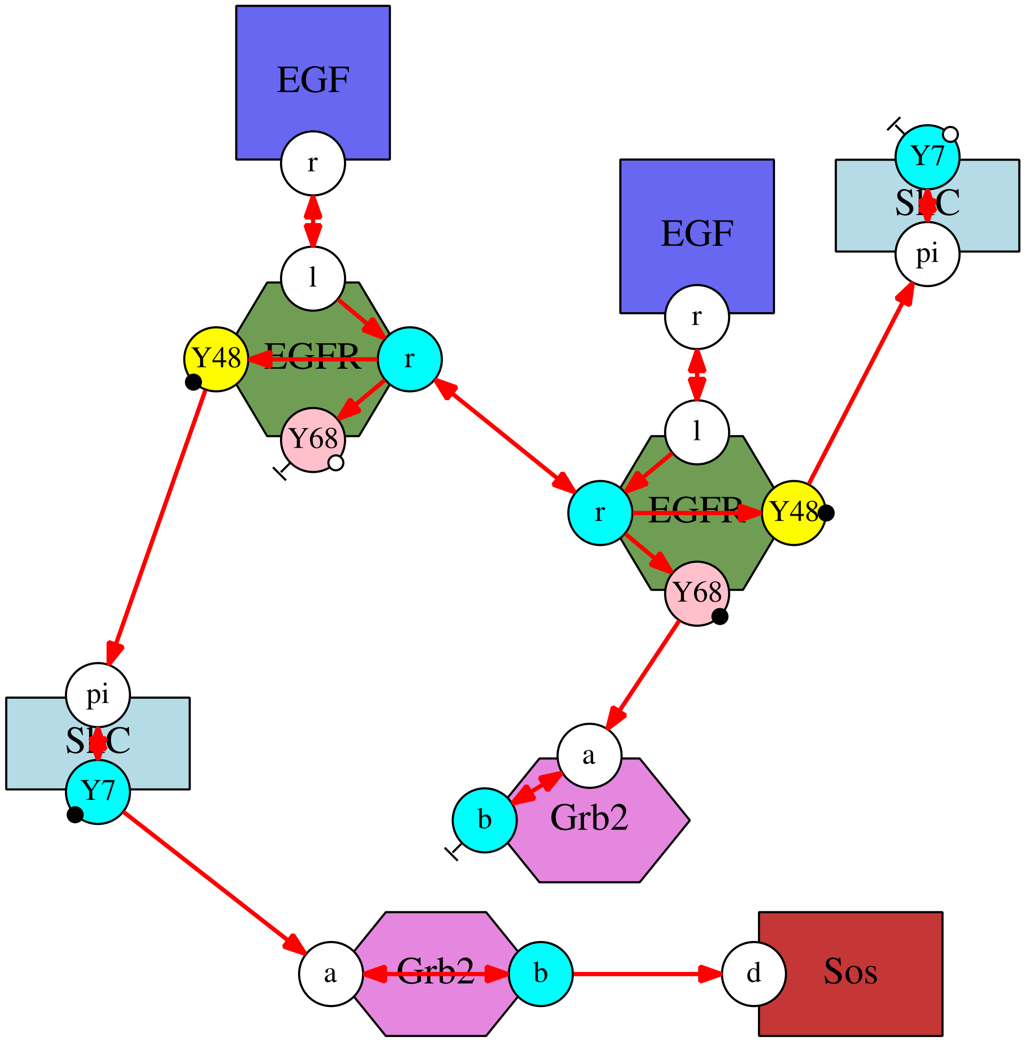




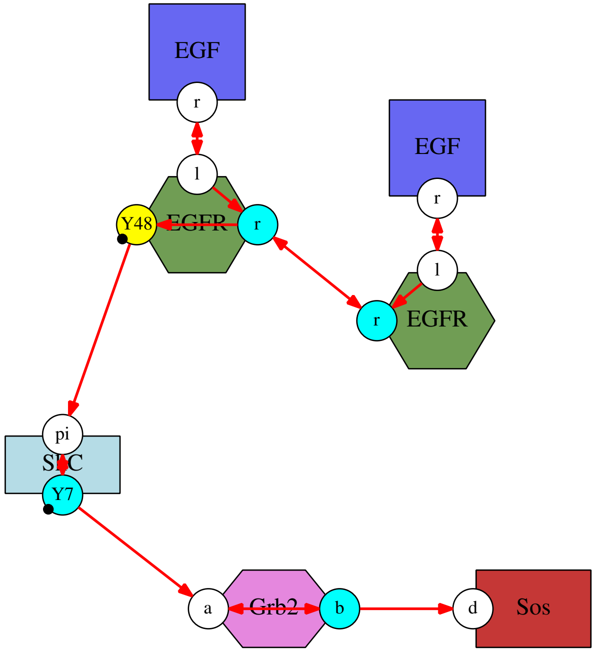
Combinatorial wall

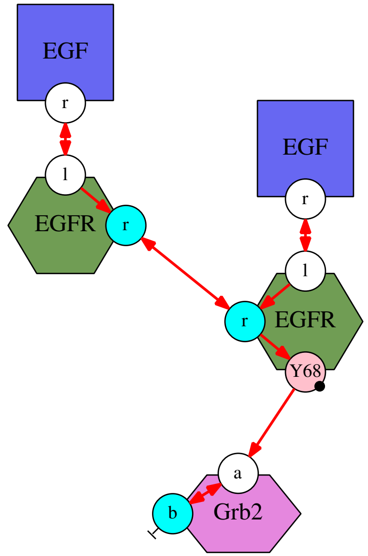


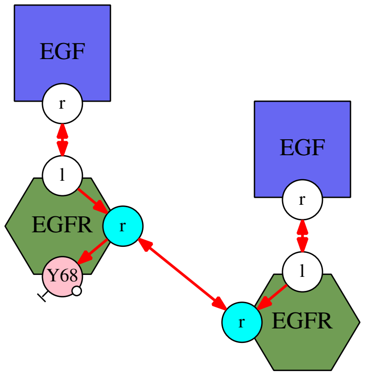
Information flow

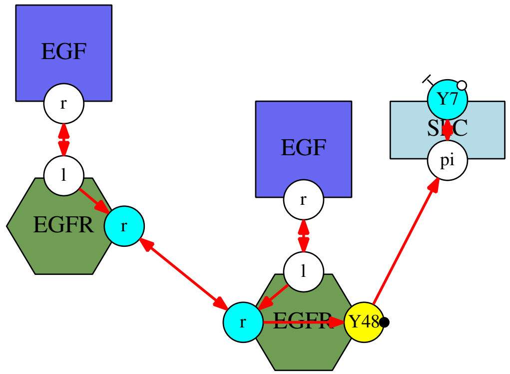


A potential breach

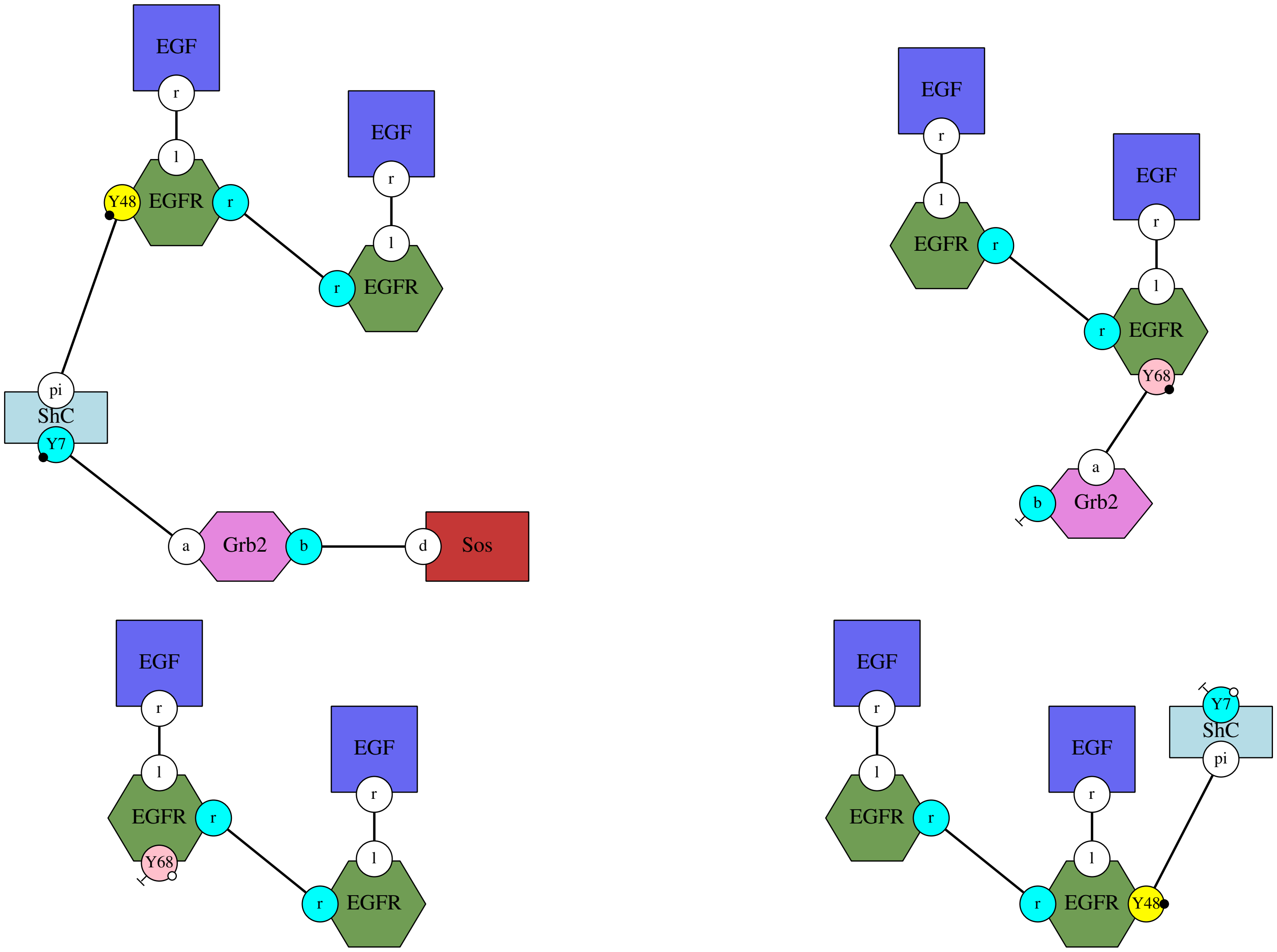








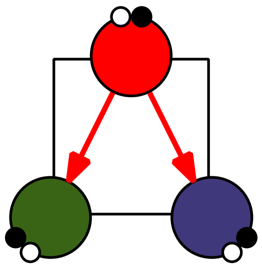
A potential breach



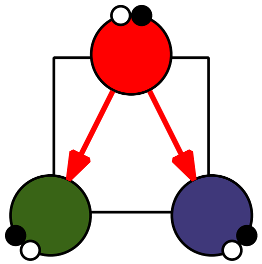
On the menu today

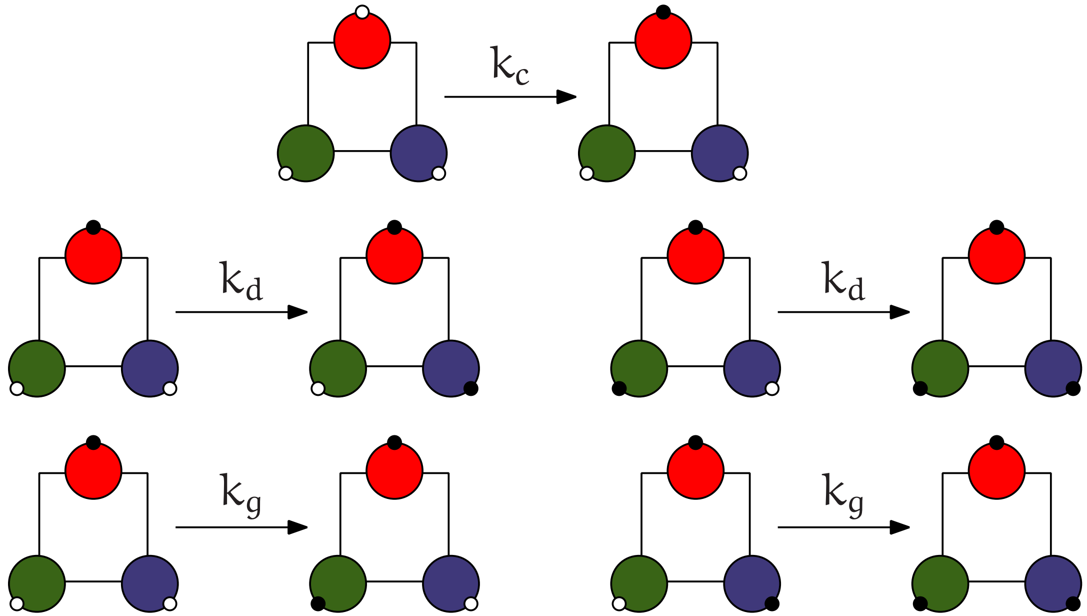
1. Context and motivations
2. Case studies
3. Reduction of ordinary differential equations
4. Abstraction of the information flow
5. Model reduction
6. Conclusion

Case study



Case study





Law of mass action

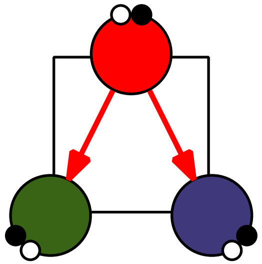
We consider that chemical species are elementary particles without any volume, and that they are diffusing in an infinite, perfectly fluid and homogeneous medium without borders.
Let $\mathcal{X}$ be a set of chemical species.
A reaction network is a set of reactions $\mathcal{R}$.
Each reaction r is defined by:

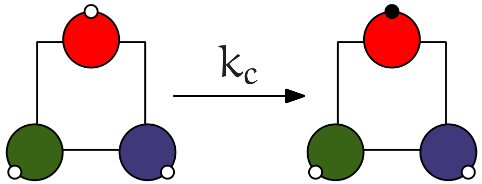
1. α_r, a function from X to $\mathbb{N}$ (the reactants);
2. β_r, a function from X to $\mathbb{N}$ (the products);
3. k_r, a non negative real number (the kinetic rate).

With these notations, the law of mass action defines the behaviour of the concentration $[X]$ of each chemical species X:

$$\frac{d[X]}{dt} = \sum_{r \in \mathcal{R}} k_r \cdot (\beta_r(X) - \alpha_r(X)) \cdot \prod_{X' \in \mathcal{X}} [X']^{\alpha_r(X')}.$$

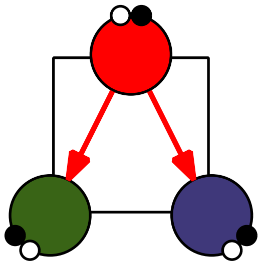
Case study

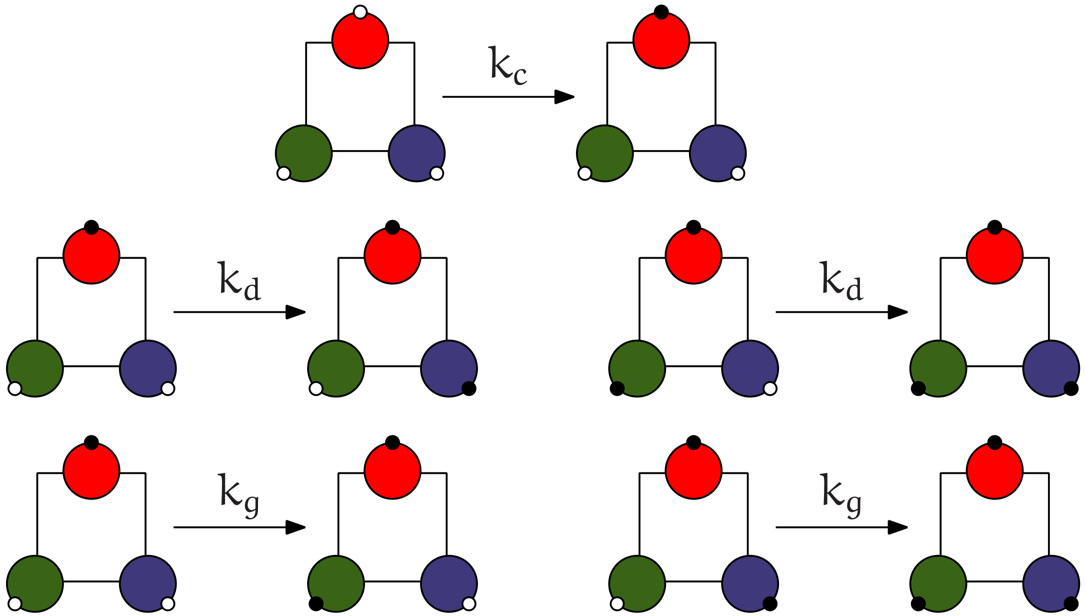




$$\begin{cases} \frac{d[(u,u,u)]}{dt} = -k_c \cdot [(u,u,u)] \\ \frac{d[(u,{\color{red}p},u)]}{dt} = k_c \cdot [(u,u,u)] \end{cases}$$

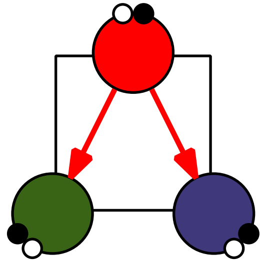
Case study





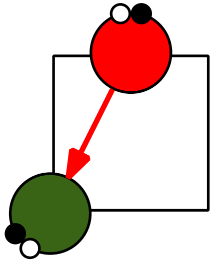
$$\begin{cases} \frac{d[(u,u,u)]}{dt} = -k_c \cdot [(u,u,u)] \\ \frac{d[(u,p,u)]}{dt} = -k_g \cdot [(u,p,u)] + k_c \cdot [(u,u,u)] - k_d \cdot [(u,p,u)] \\ \frac{d[(u,p,p)]}{dt} = -k_g \cdot [(u,p,p)] + k_d \cdot [(u,p,u)] \\ \frac{d[(p,p,u)]}{dt} = k_g \cdot [(u,p,u)] - k_d \cdot [(p,p,u)] \\ \frac{d[(p,p,p)]}{dt} = k_g \cdot [(u,p,p)] + k_d \cdot [(p,p,u)] \end{cases}$$

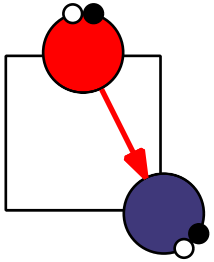
Case study



Case study

Case study





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

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

$$\begin{cases} \frac{d[(u,u,u)]}{dt} = -k_c \cdot [(u,u,u)] \\ \frac{d[(u,p,?)]}{dt} = -k_g \cdot [(u,p,?)] + k_c \cdot [(u,u,u)] \\ \frac{d[(p,p,?)]}{dt} = k_g \cdot [(u,p,?)] \end{cases}$$

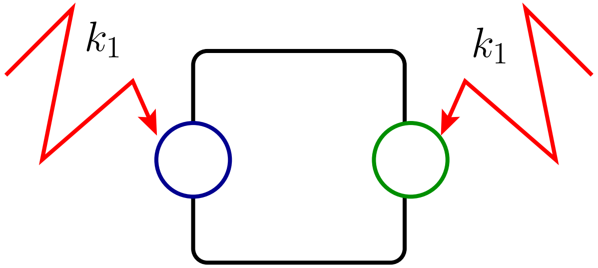
$$\begin{cases} \frac{d[(u,u,u)]}{dt} = -k_c \cdot [(u,u,u)] \\ \frac{d[(?,p,u)]}{dt} = -k_d \cdot [(?,p,u)] + k_c \cdot [(u,u,u)] \\ \frac{d[(?,p,p)]}{dt} = k_d \cdot [(?,p,u)] \end{cases}$$

What we have learned so far:

We can use the absence of information flow to detect useless correlations between the states of sites in chemical species. We can use this to cut chemical species into fragments.

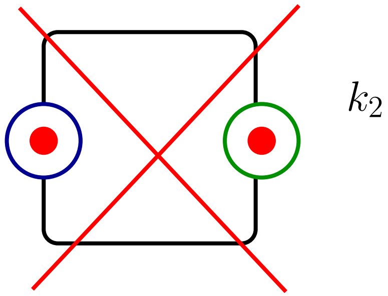
This transformation loses some information: we cannot compute the concentration of each chemical species anymore.

A model with symmetries



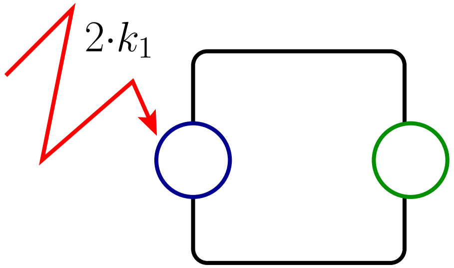
$$\mathrm{P} \longrightarrow {}^{\star}\mathrm{P} \quad k_1 \qquad \mathrm{P}^{\star} \longrightarrow {}^{\star}\mathrm{P}^{\star} \quad k_1$$

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

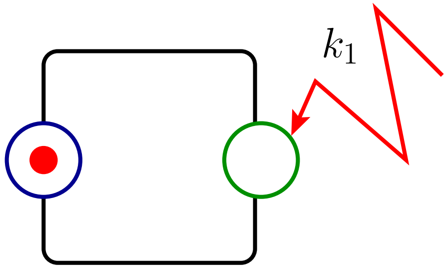


$$ {}^{\star}\mathrm{P}^{\star} \longrightarrow \emptyset \quad k_2$$

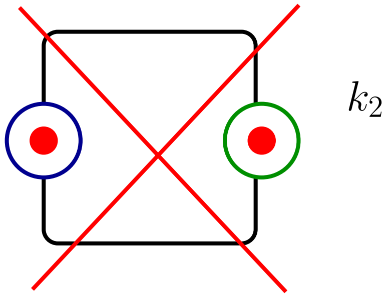
Reduced model



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



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



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

Differential equations

- Initial system:

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

- Reduced system:

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

Invariant

We wonder whether or not:

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

Thus we define the difference X as follows:

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

We have:

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

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

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

On the menu today

1. Context and motivations
2. Case studies
3. Reduction of ordinary differential equations
4. Abstraction of the information flow
5. Model reduction
6. Conclusion

Differential semantics

A system of ordinary differential equations is a pair $(\mathcal{V}, \mathbb{F})$ where:

- $\mathcal{V}$ is a finite set of variables,
- $\mathbb{F}$ is a continuous function from $\mathcal{V} \to \mathbb{R}^+$ to $\mathcal{V} \to \mathbb{R}$.

Elements of $\mathcal{V} \to \mathbb{R}^+$ are called states.

The differential semantics maps each initial state $X_0 \in \mathcal{V} \to \mathbb{R}^+$ to the solution $X_{X_0} \in [0, T_{X_0}^{\max}[\to (\mathcal{V} \to \mathbb{R}^+)$ of the following equation:

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

that is defined over the widest time interval as possible.

Back to the case study

1. $\mathcal{V} \triangleq \{[(u,u,u)], [(u,p,u)], [(p,p,u)], [(u,p,p)], [(p,p,p)]\}$,

2. $$\mathbb{F}(\rho) \triangleq \begin{cases} [(u,u,u)] \mapsto -k_c \cdot \rho([(u,u,u)]) \\ [(u,p,u)] \mapsto -k_g \cdot \rho([(u,p,u)]) + k_c \cdot \rho([(u,u,u)]) - k_d \cdot \rho([(u,p,u)]) \\ [(u,p,p)] \mapsto -k_g \cdot \rho([(u,p,p)]) + k_d \cdot \rho([(u,p,u)]) \\ [(p,p,u)] \mapsto k_g \cdot \rho([(u,p,u)]) - k_d \cdot \rho([(p,p,u)]) \\ [(p,p,p)] \mapsto k_g \cdot \rho([(u,p,p)]) + k_d \cdot \rho([(p,p,u)]). \end{cases}$$

Abstraction

An abstraction is a 5-uple $(\mathcal{V}, \mathbb{F}, \mathcal{V}^\sharp, \psi, \mathbb{F}^\sharp)$, where:

- $(\mathcal{V}, \mathbb{F})$ is a system of ordinary equations,
- $\mathcal{V}^\sharp$ is a finite set of observables,
- ψ is a function from the set $\mathcal{V} \rightarrow \mathbb{R}$ into the set $\mathcal{V}^\sharp \rightarrow \mathbb{R}$,
- $\mathbb{F}^\sharp$ is a function $\mathcal{C}^\infty$ from the set $\mathcal{V}^\sharp \rightarrow \mathbb{R}^+$ into the set $\mathcal{V}^\sharp \rightarrow \mathbb{R}$;

such that:

- ψ is linear with positive coefficients only and such that each variable $v \in \mathcal{V}$ occurs in the image of at least one observable $v^\sharp \in \mathcal{V}^\sharp$ with a non-zero coefficient;
- the following diagram commutes:

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

  that is to say that $\psi \circ \mathbb{F} = \mathbb{F}^\sharp \circ \psi$.

Back to the case study

1. $\mathcal{V} \triangleq \{[(u,u,u)], [(u,p,u)], [(p,p,u)], [(u,p,p)], [(p,p,p)]\}$
2. $\mathbb{F}(\rho) \triangleq \begin{cases} [(u,u,u)] \mapsto -k_c{\cdot}\rho([(u,u,u)]) \\ [(u,p,u)] \mapsto -k_g{\cdot}\rho([(u,p,u)]) + k_c{\cdot}\rho([(u,u,u)]) - k_d{\cdot}\rho([(u,p,u)]) \\ [(u,p,p)] \mapsto -k_g{\cdot}\rho([(u,p,p)]) + k_d{\cdot}\rho([(u,p,u)]) \\ \ldots \end{cases}$
3. $\mathcal{V}^\sharp \triangleq \{[(u,u,u)], [(?,p,u)], [(?,p,p)], [(u,p,?)], [(p,p,?)]\}$
4. $\psi(\rho) \triangleq \begin{cases} [(u,u,u)] \mapsto \rho([(u,u,u)]) \\ [(?,p,u)] \mapsto \rho([(u,p,u)]) + \rho([(p,p,u)]) \\ [(?,p,p)] \mapsto \rho([(u,p,p)]) + \rho([(p,p,p)]) \\ \ldots \end{cases}$
5. $\mathbb{F}^\sharp(\rho^\sharp) \triangleq \begin{cases} [(u,u,u)] \mapsto -k_c{\cdot}\rho^\sharp([(u,u,u)]) \\ [(?,p,u)] \mapsto -k_d{\cdot}\rho^\sharp([(?,p,u)]) + k_c{\cdot}\rho^\sharp([(u,u,u)]) \\ [(?,p,p)] \mapsto k_d{\cdot}\rho^\sharp([(?,p,u)]) \\ \ldots \end{cases}$

Let us apply the abstraction function

Let:

1. $(\mathcal{V}, \mathbb{F}, \mathcal{V}^{\sharp}, \psi, \mathbb{F}^{\sharp})$ be an abstraction,
2. and $X_0 \in \mathcal{V} \to \mathbb{R}^+$ be an initial state.

We have, at any time T within the time interval $[0, T_{X_0}^{\max}[$:

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

So:

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

Let us push ψ towards the right

Let:

1. $(\mathcal{V}, \mathbb{F}, \mathcal{V}^\sharp, \psi, \mathbb{F}^\sharp)$ be an abstraction,
2. and $X_0 \in \mathcal{V} \to \mathbb{R}^+$ be an initial state.

We have, at any time T within the time interval $[0, T^{\max}_{X_0}[$:

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

So:

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

Let us push ψ towards the right

Let:

1. $(\mathcal{V}, \mathbb{F}, \mathcal{V}^\sharp, \psi, \mathbb{F}^\sharp)$ be an abstraction,
2. and $X_0 \in \mathcal{V} \rightarrow \mathbb{R}^+$ be an initial state.

We have, at any time T within the time interval $[0, T_{X_0}^{\max}[$:

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

So:

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

Let us push ψ towards the right

Let:

1. $(\mathcal{V}, \mathbb{F}, \mathcal{V}^\sharp, \psi, \mathbb{F}^\sharp)$ be an abstraction,
2. and $X_0 \in \mathcal{V} \to \mathbb{R}^+$ be an initial state.

We have, at any time T within the time interval $[0, T_{X_0}^{\max}[$:

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

So:

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

Let us push ψ towards the right

Let:

1. $(\mathcal{V}, \mathbb{F}, \mathcal{V}^\sharp, \psi, \mathbb{F}^\sharp)$ be an abstraction,
2. and $X_0 \in \mathcal{V} \rightarrow \mathbb{R}^+$ be an initial state.

We have, at any time T within the time interval $[0, T^{\max}_{X_0}[$:

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

So:

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

Abstract semantics

Let $(\mathcal{V}, \mathbb{F}, \mathcal{V}^\sharp, \psi, \mathbb{F}^\sharp)$ be an abstraction.
The couple $(\mathcal{V}^\sharp, \mathbb{F}^\sharp)$ is a system of differential equations.
Let us denote by Y its semantics.
For each state $Y_0 \in \mathcal{V}^\sharp \to \mathbb{R}^+$, we denote by $[0, T^{\sharp\max}_{Y_0}[$ the domain of the function Y_{Y_0}. We have, at any time $T^\sharp \in [0, T^{\sharp\max}_{X_0}[$,

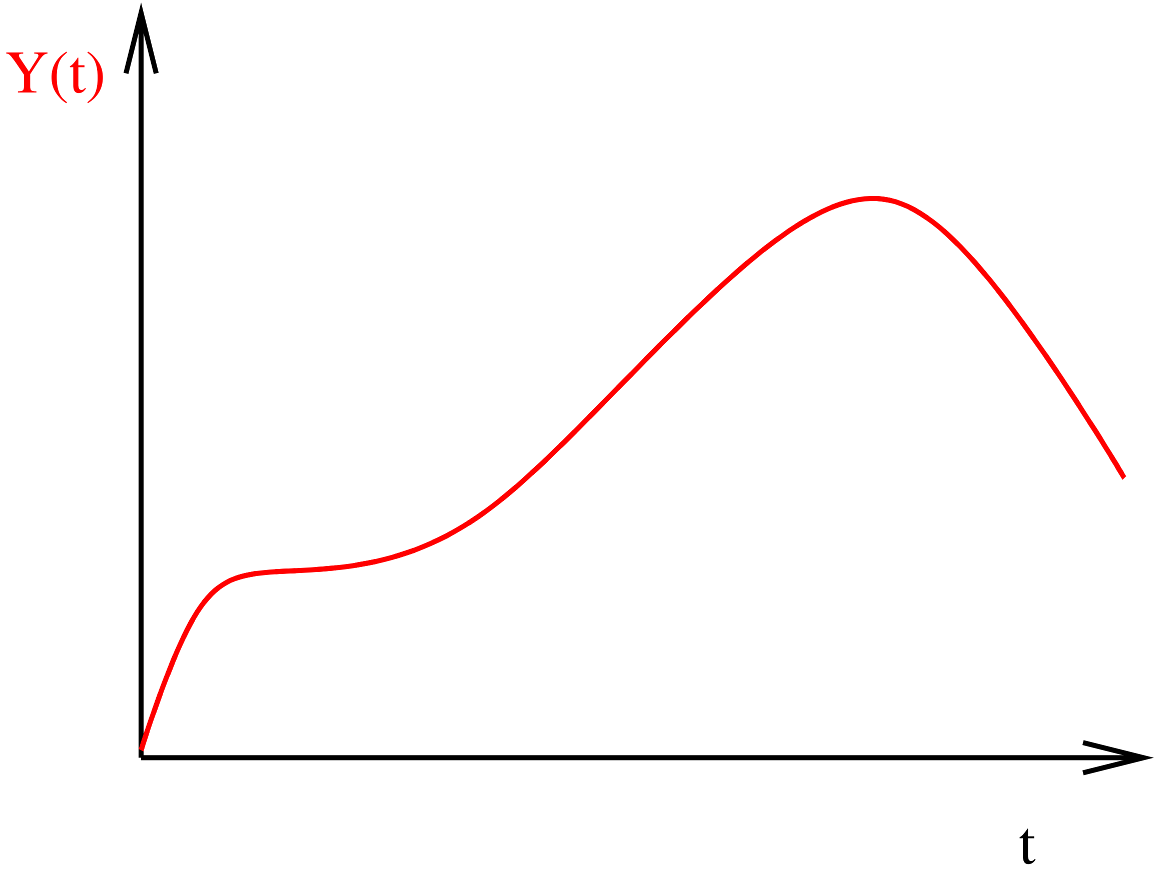
$$Y_{Y_0}(T^\sharp) = Y_0 + \int_{t=0}^{T^\sharp} \mathbb{F}^\sharp(Y_{Y_0}(t)) \cdot dt.$$

ThÃl'orÃÍme 1 For each initial state $X_0 \in \mathcal{V} \to \mathbb{R}^+$, we have:

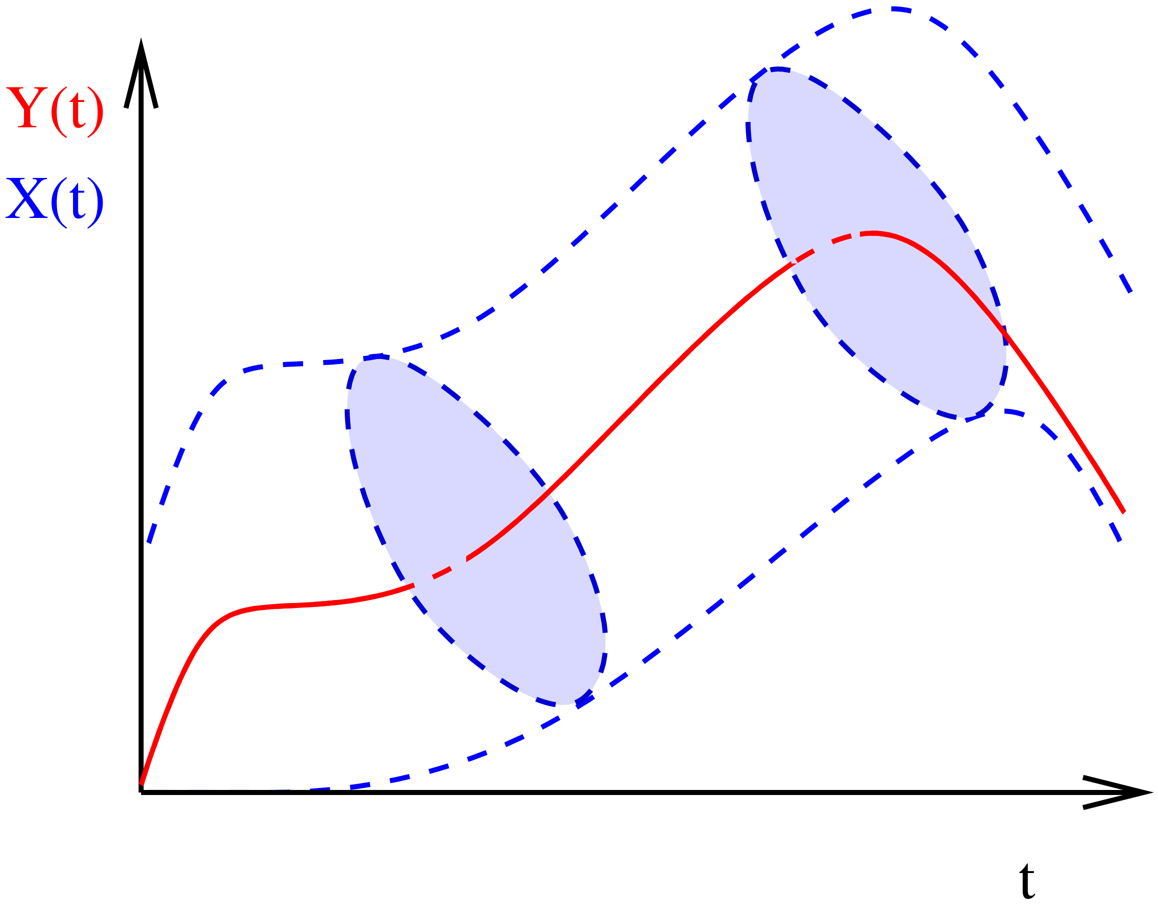
1. $T^{\sharp\max}_{\psi(X_0)} = T^{\max}_{X_0}$;
2. at any time $T \in [0, T^{\max}_{X_0}[$, $\psi(X_{X_0}(T)) = Y_{\psi(X_0)}(T)$.

That is to say that the abstract semantics is the image of the concrete semantics by the abstraction function.

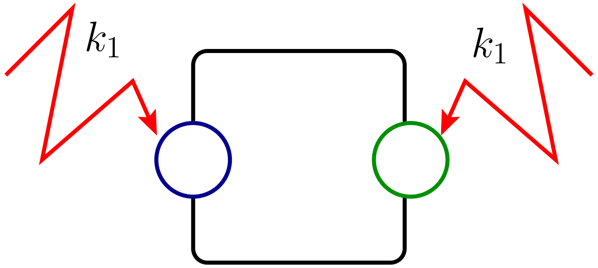
Abstract trajectories



Concrete trajectories

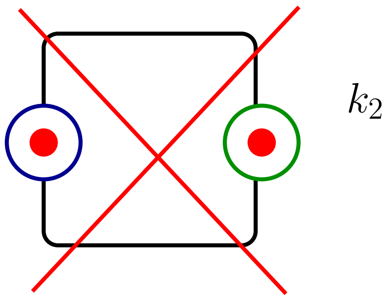


A model with symmetries



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

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



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

Differential equations

- Initial system:

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

- Reduced system:

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

Differential equations

- Initial system:

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

- Reduced system:

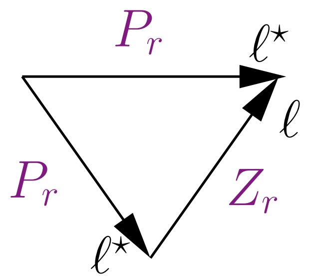
$$\frac{d}{dt}\begin{bmatrix} \mathrm{P} \\ {}^{\star}\mathrm{P}+\mathrm{P}^{\star} \\ 0 \\ {}^{\star}\mathrm{P}^{\star} \end{bmatrix} = \underbrace{\begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}}_{P} \cdot \begin{bmatrix} -2{\cdot}k_1 & 0 & 0 & 0 \\ k_1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

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 $P_r, Z_r \in (\mathcal{V} \rightarrow \mathbb{R}^+) \rightarrow (\mathcal{V} \rightarrow \mathbb{R}^+)$ 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,

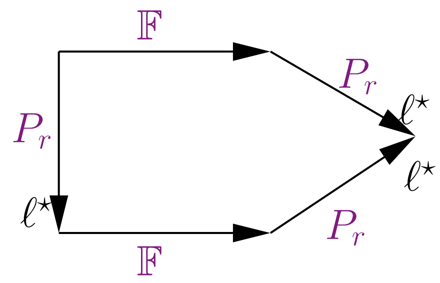
$\stackrel{\Delta}{\Longleftrightarrow}$

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,

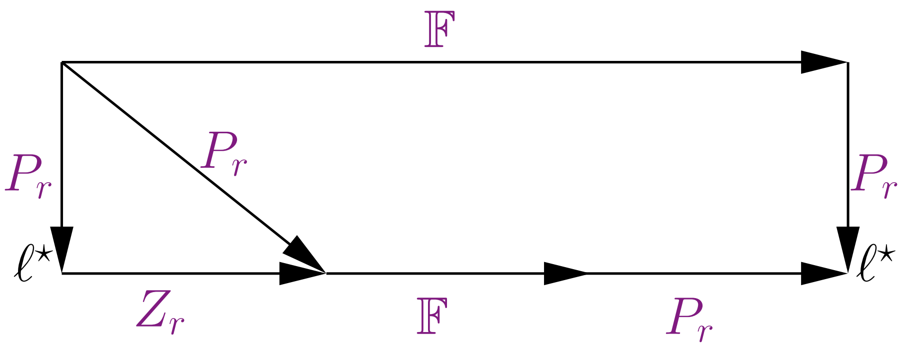
$\Longleftrightarrow$

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:

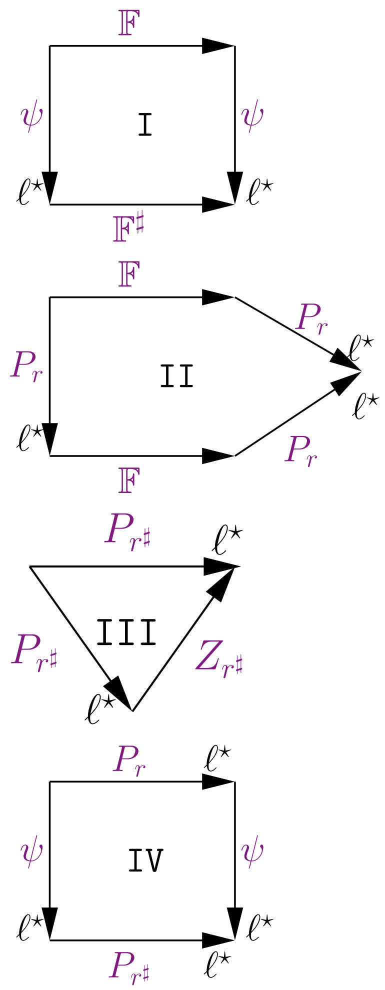


Abstract projection

We assume that we are given:

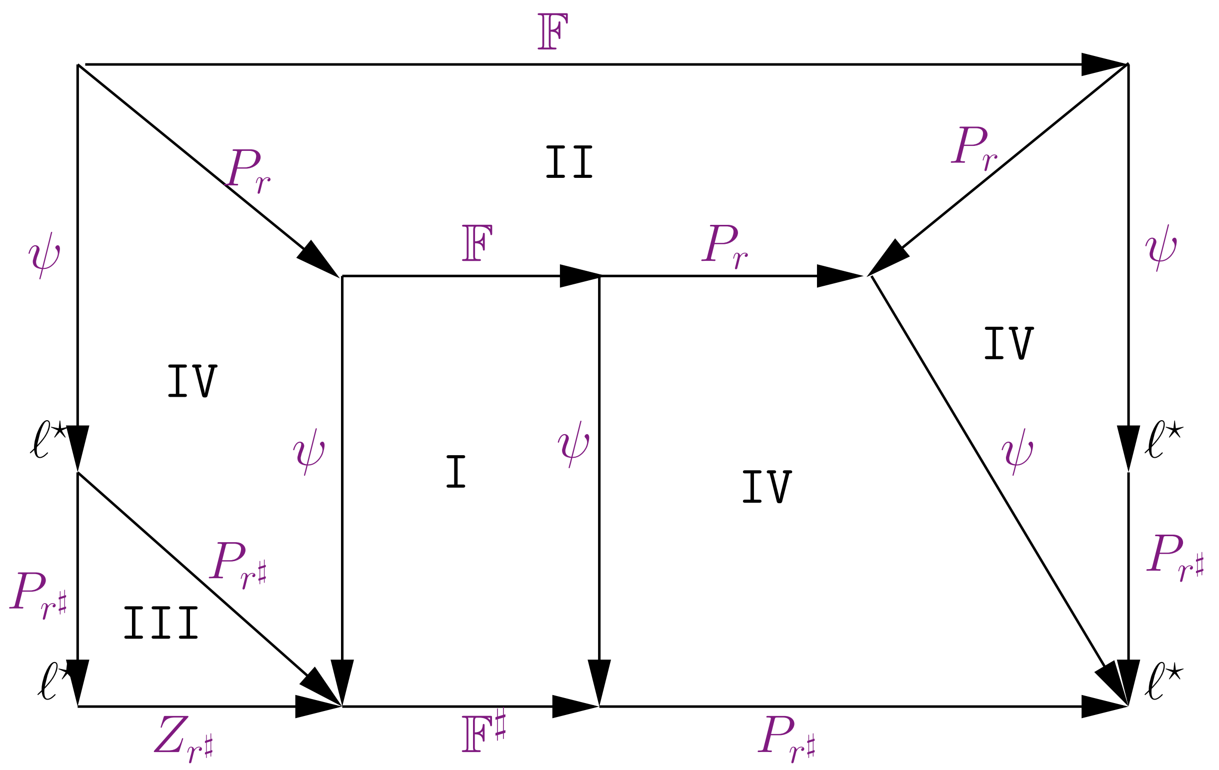
- a concrete system $(\mathcal{V}, \mathbb{F})$;
- an abstraction $(\mathcal{V}^\sharp, \psi, \mathbb{F}^\sharp)$ of $(\mathcal{V}, \mathbb{F})$ (`I`);
- an idempotent mapping r over $\mathcal{V}$ which induces a bisimulation (`II`);
- an idempotent mapping $r^\sharp$ over $\mathcal{V}^\sharp$ (`III`);

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:



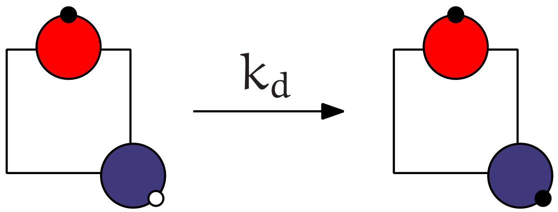
On the menu today

1. Context and motivations
2. Case studies
3. Reduction of ordinary differential equations
4. Abstraction of the information flow
5. Model reduction
6. Conclusion

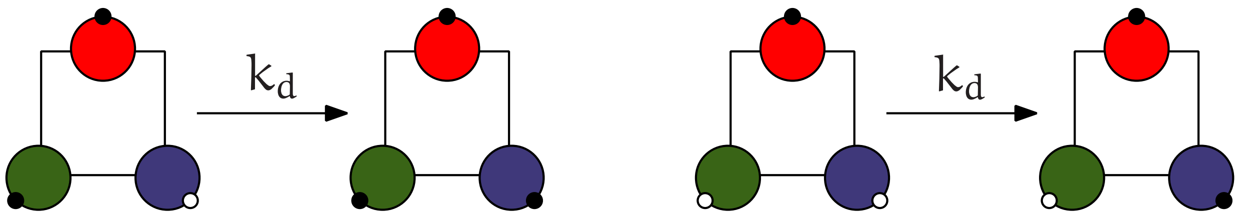
Concrete semantics

A rule is a symbolic representation of a multi-set of reactions.

For instance, the rule:



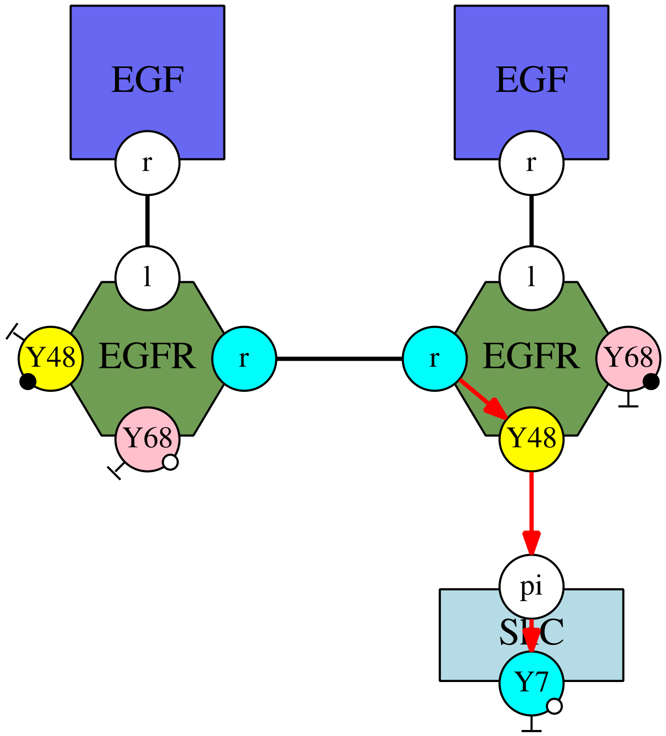
denotes the following two rules:



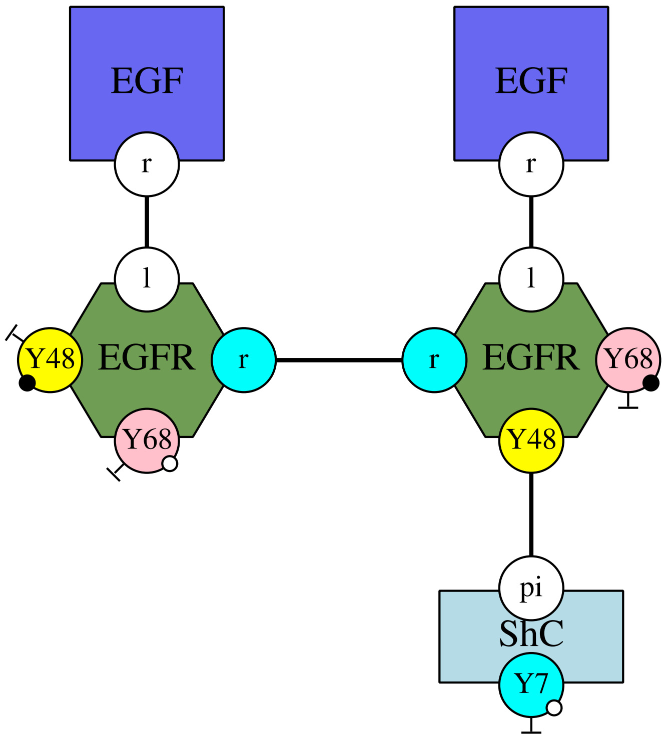
The semantics of a set of rules is the semantics of the underlying multi-set of reactions.

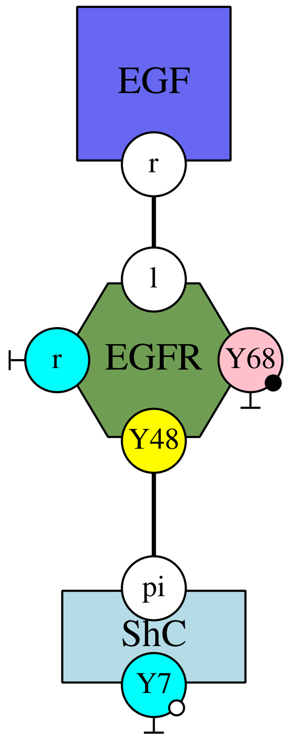
Flow of information (in the concrete)

Does the state of a given site influence the capability to modify another site?



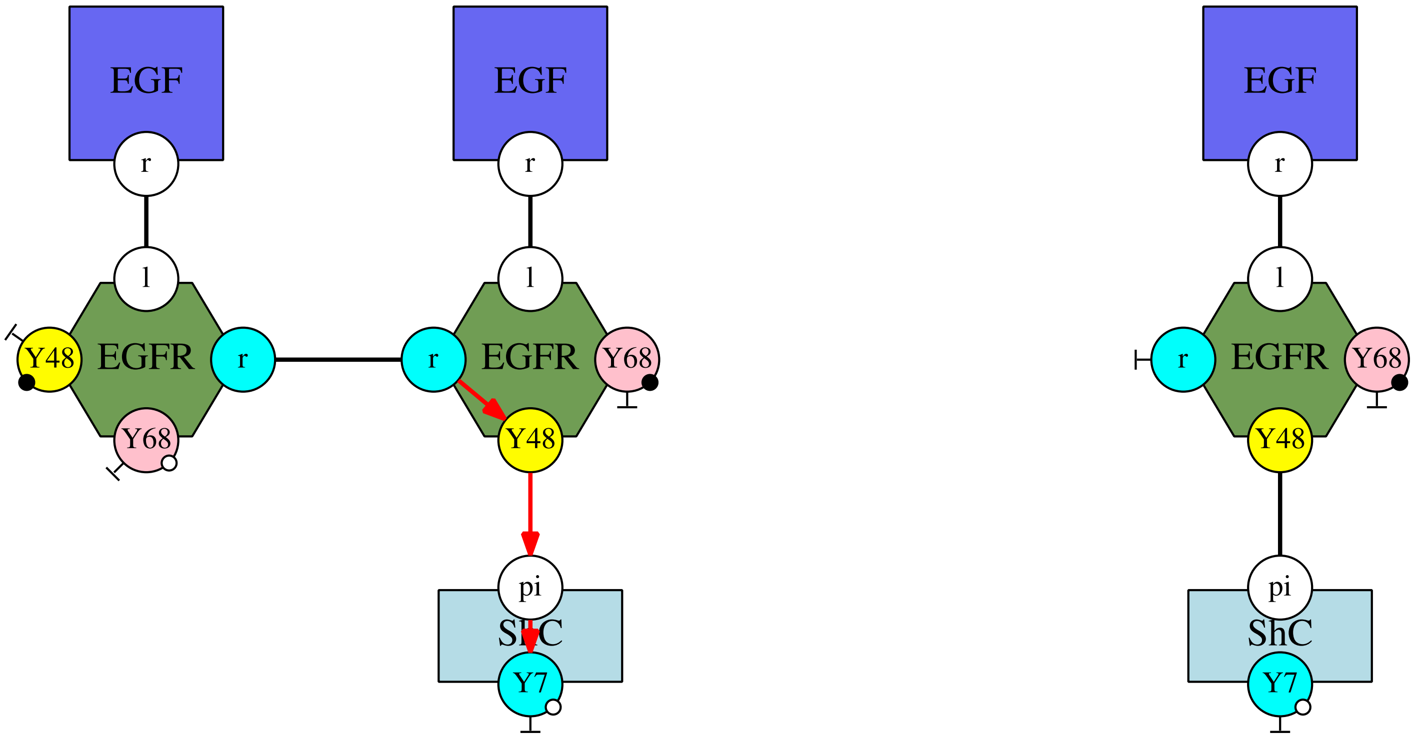
Flow of information (in the concrete)



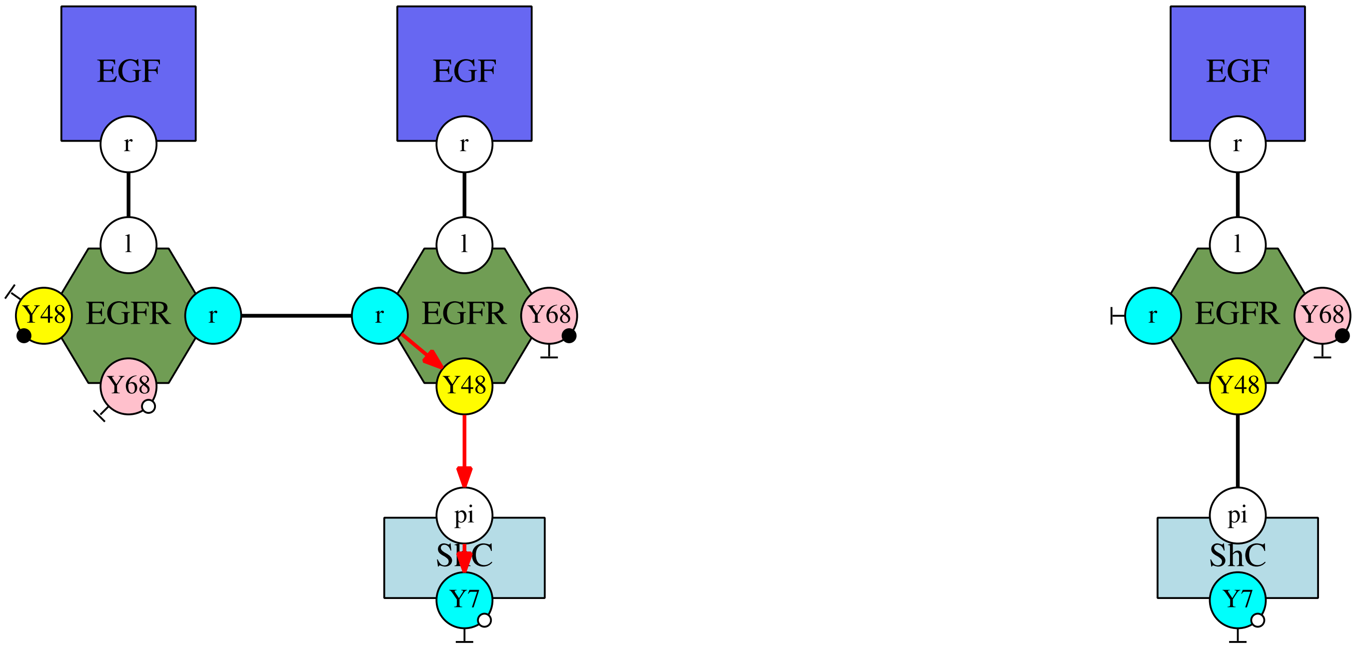


Flow of information (in the concrete)

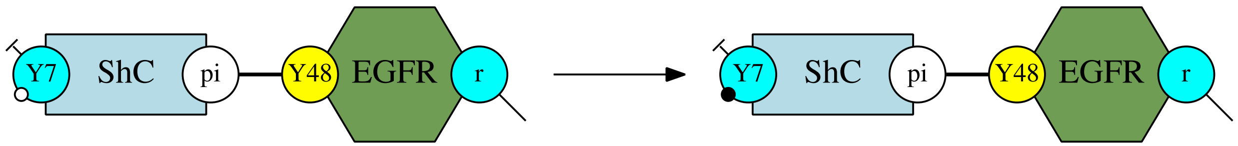
If there exists a soup of chemical species in which the activation rate of the site of *ShC* is different in these two contexts, then there may be a flow of information.



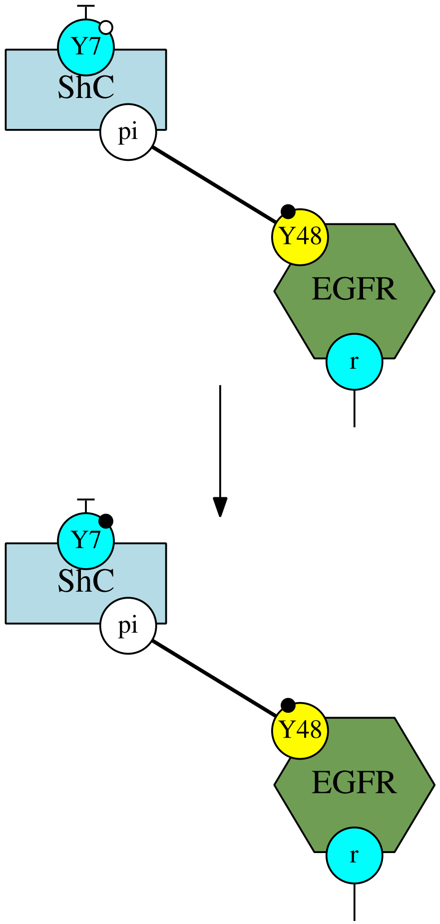
Discrimination by a rule

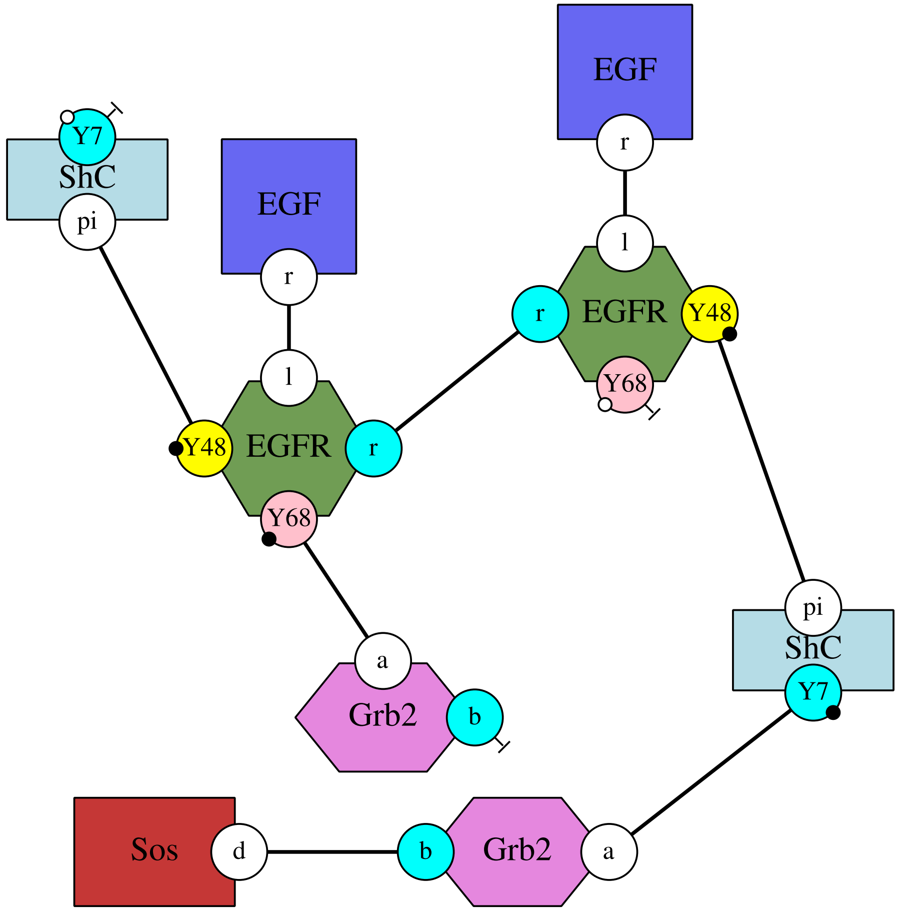


In this case, there exists a rule which makes a difference between these two contexts, for instance the following one:

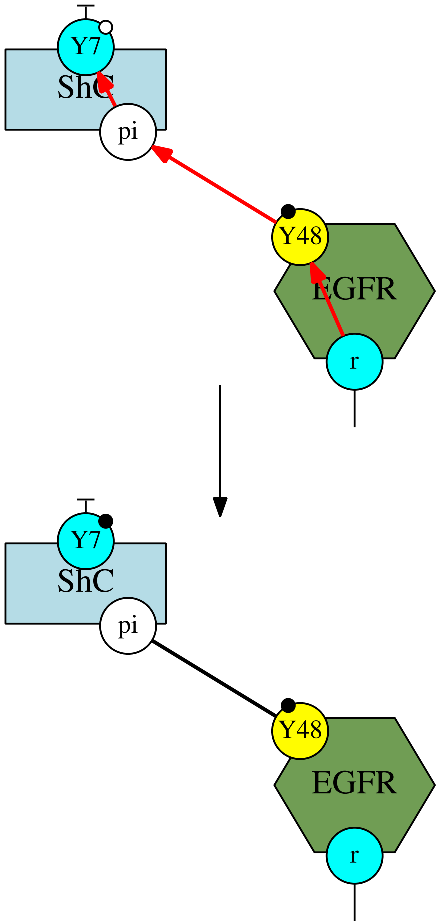


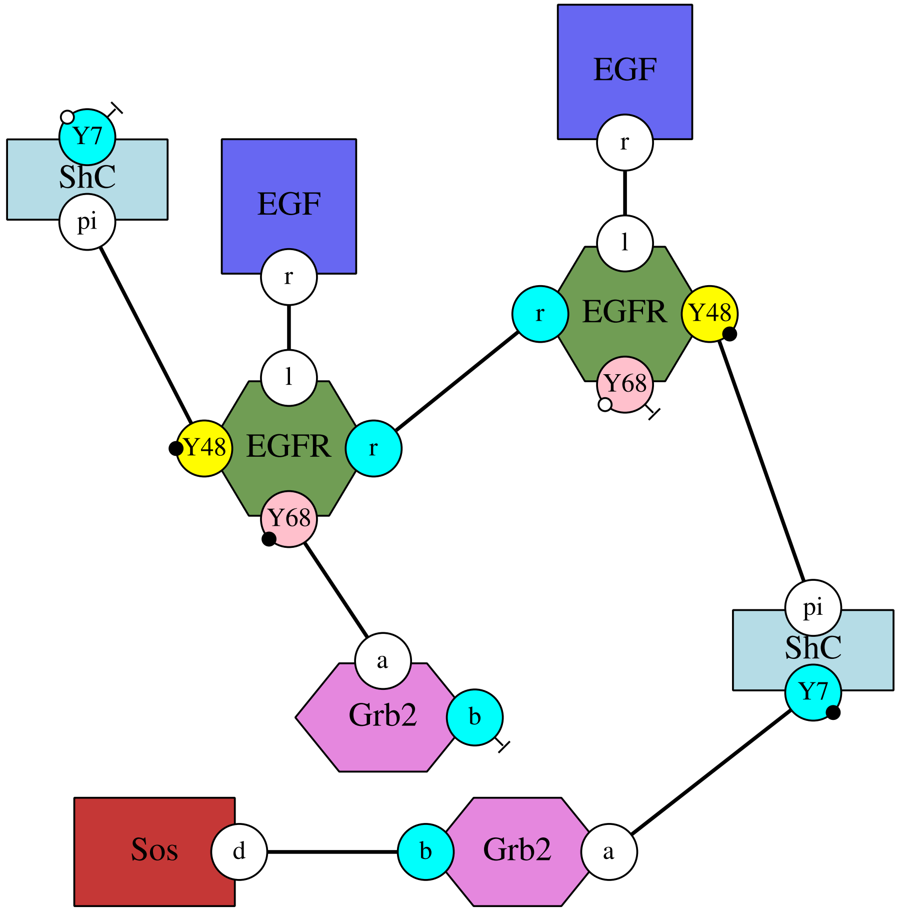
Flow of information due to a rule



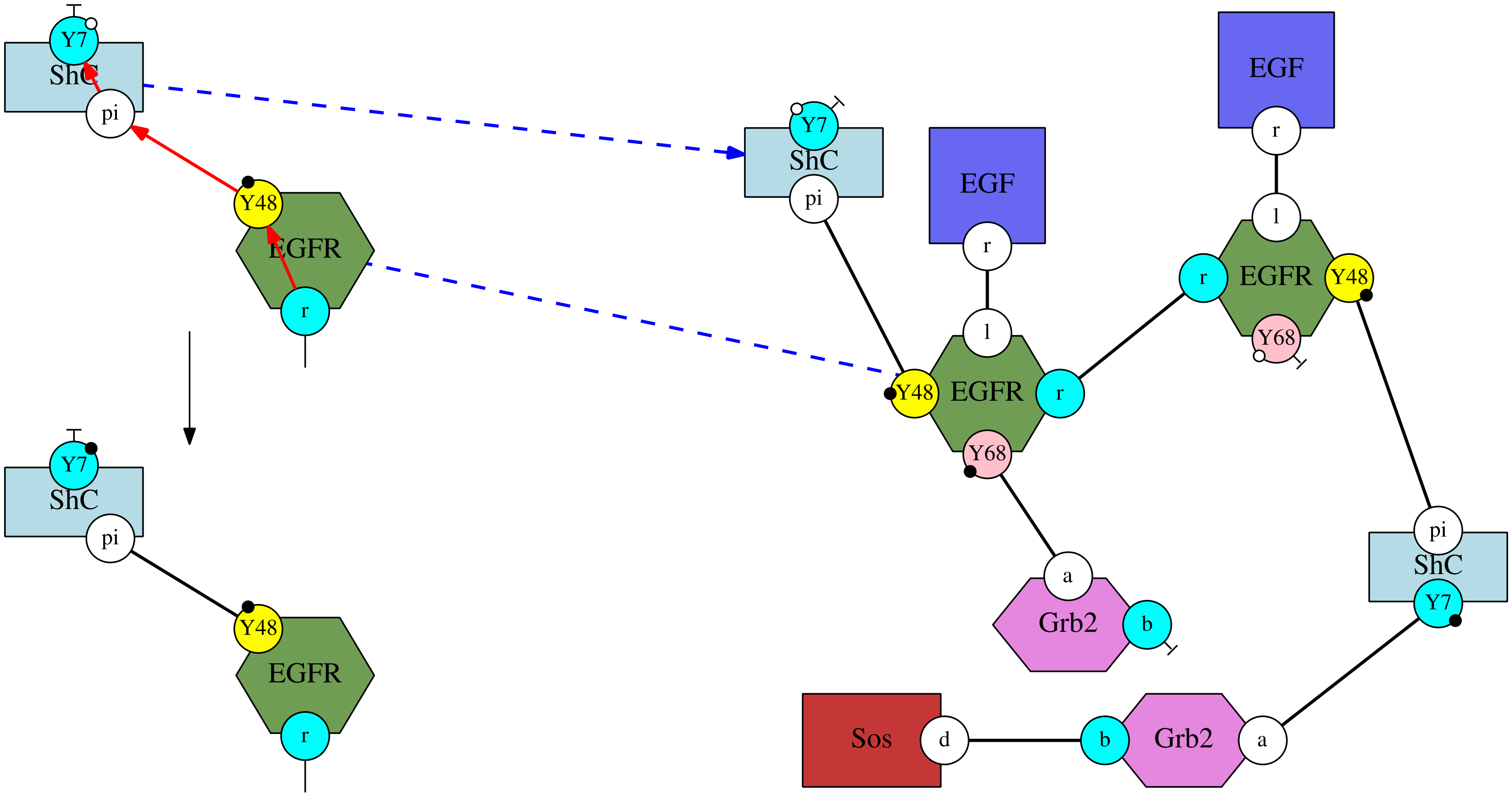


Flow of information due to a rule

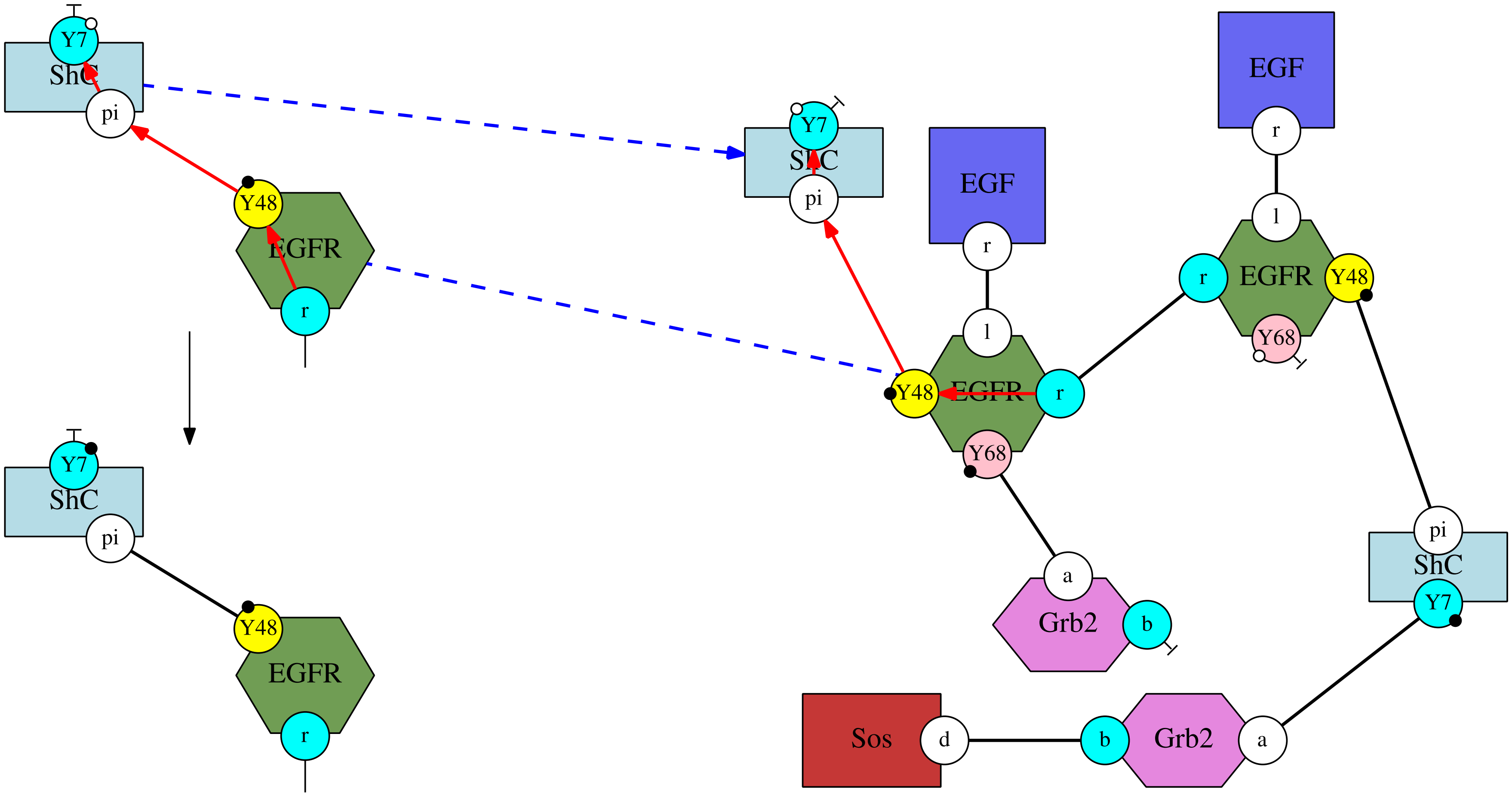




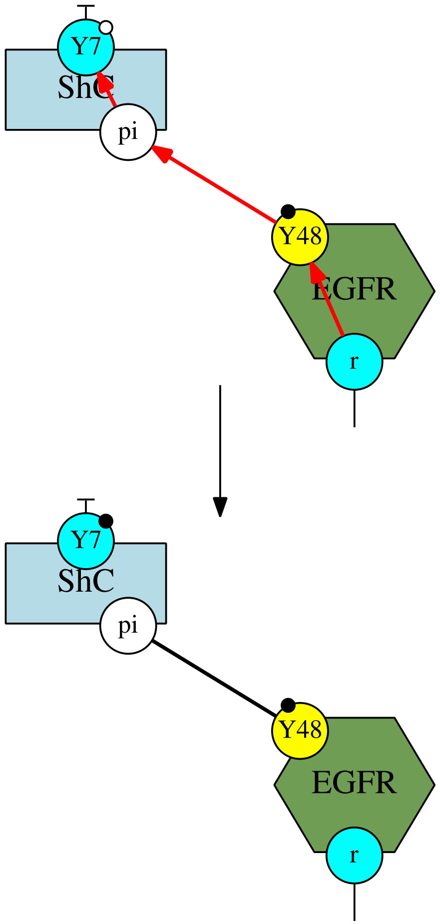
Flow of information due to a rule

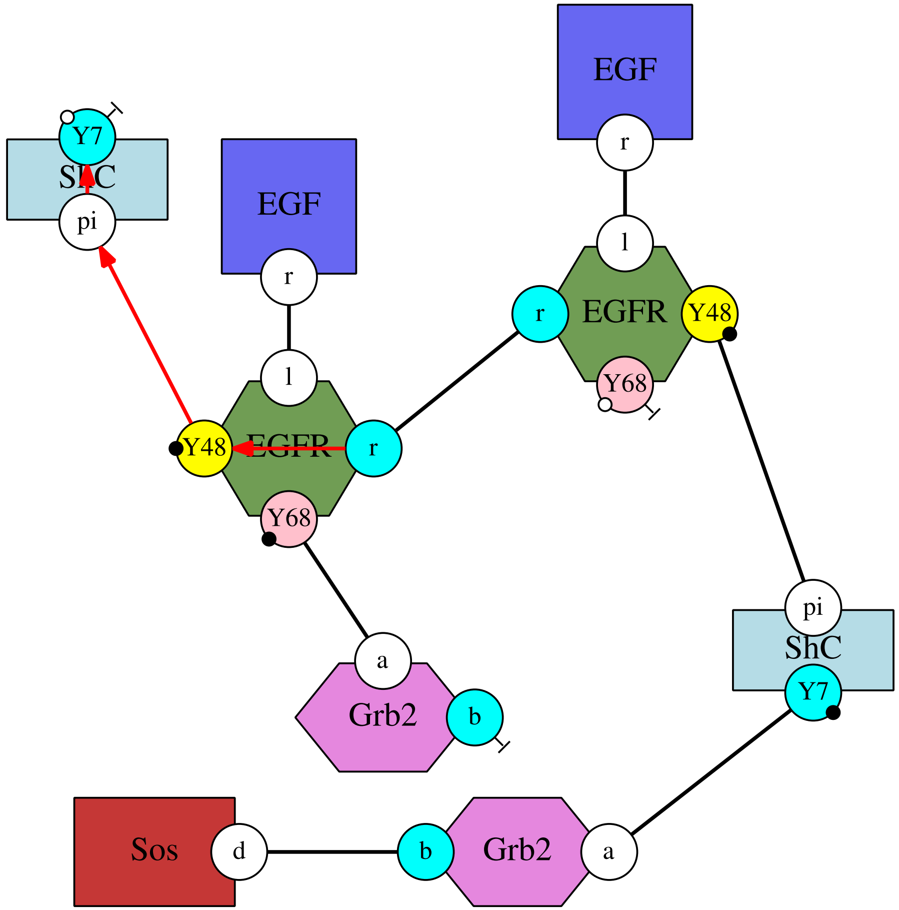


Flow of information due to a rule

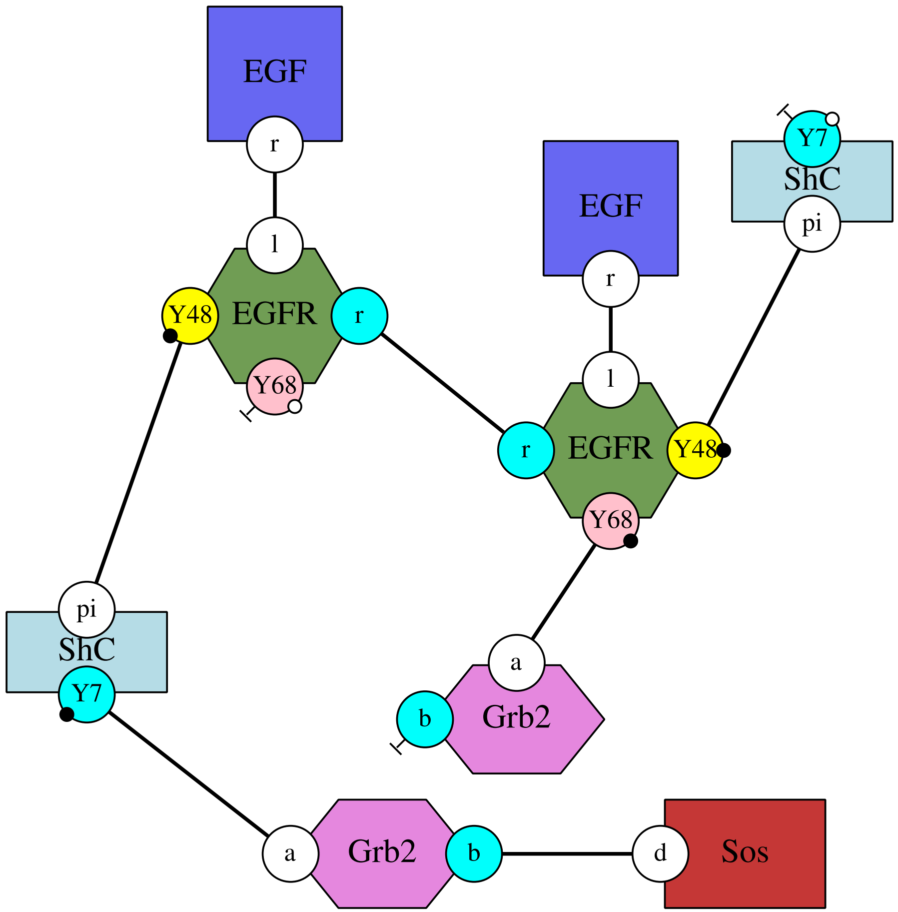


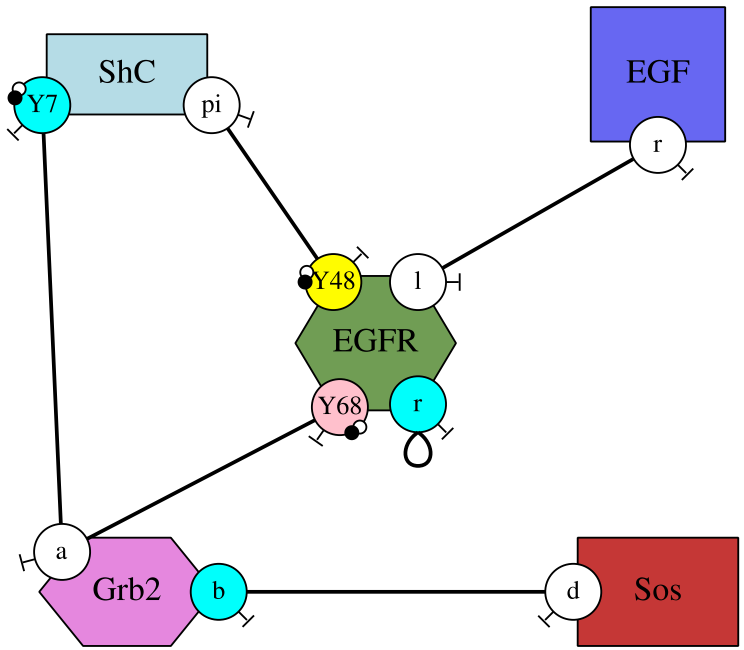
Flow of information due to a rule



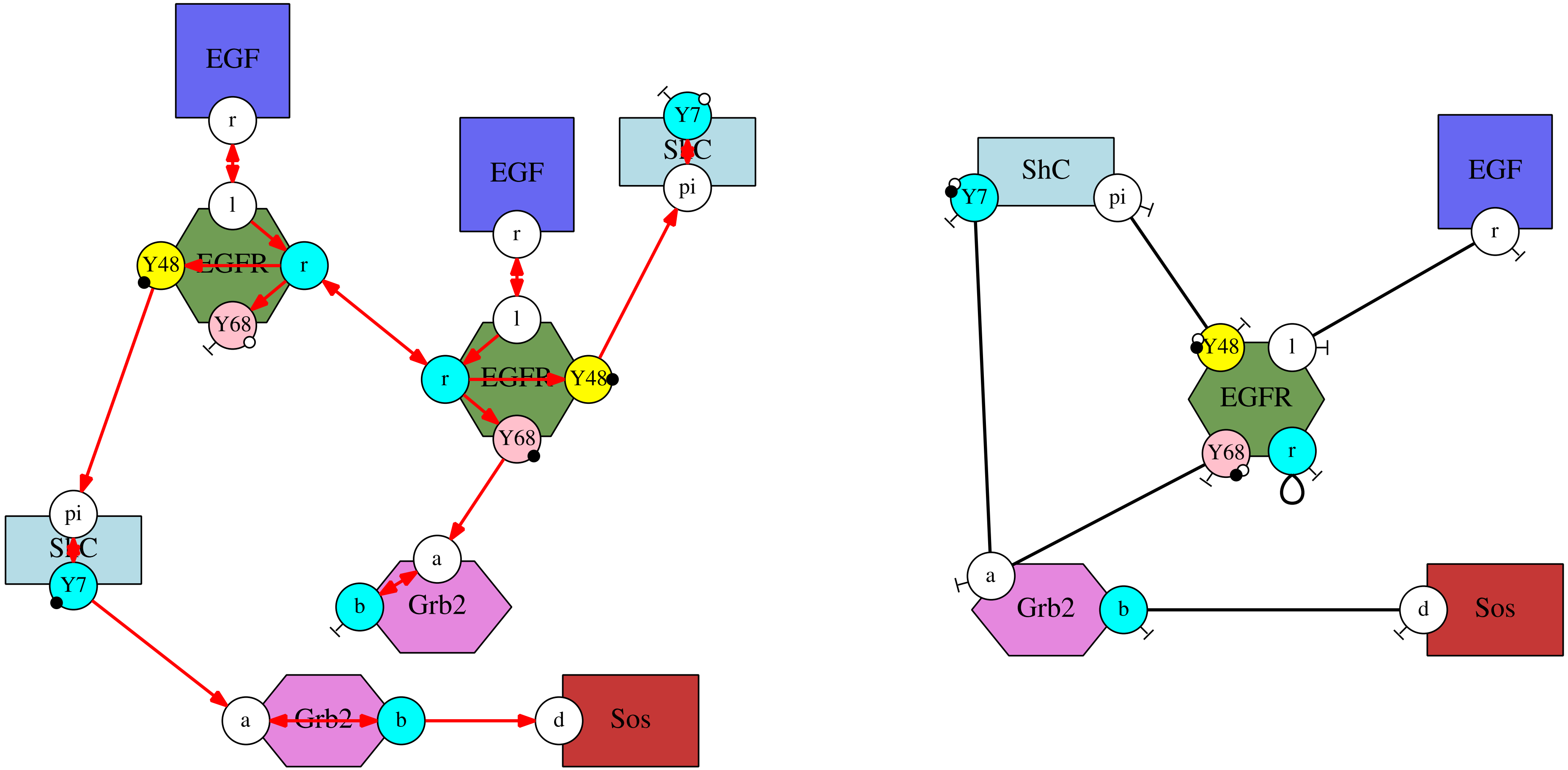


Projection on the contact map

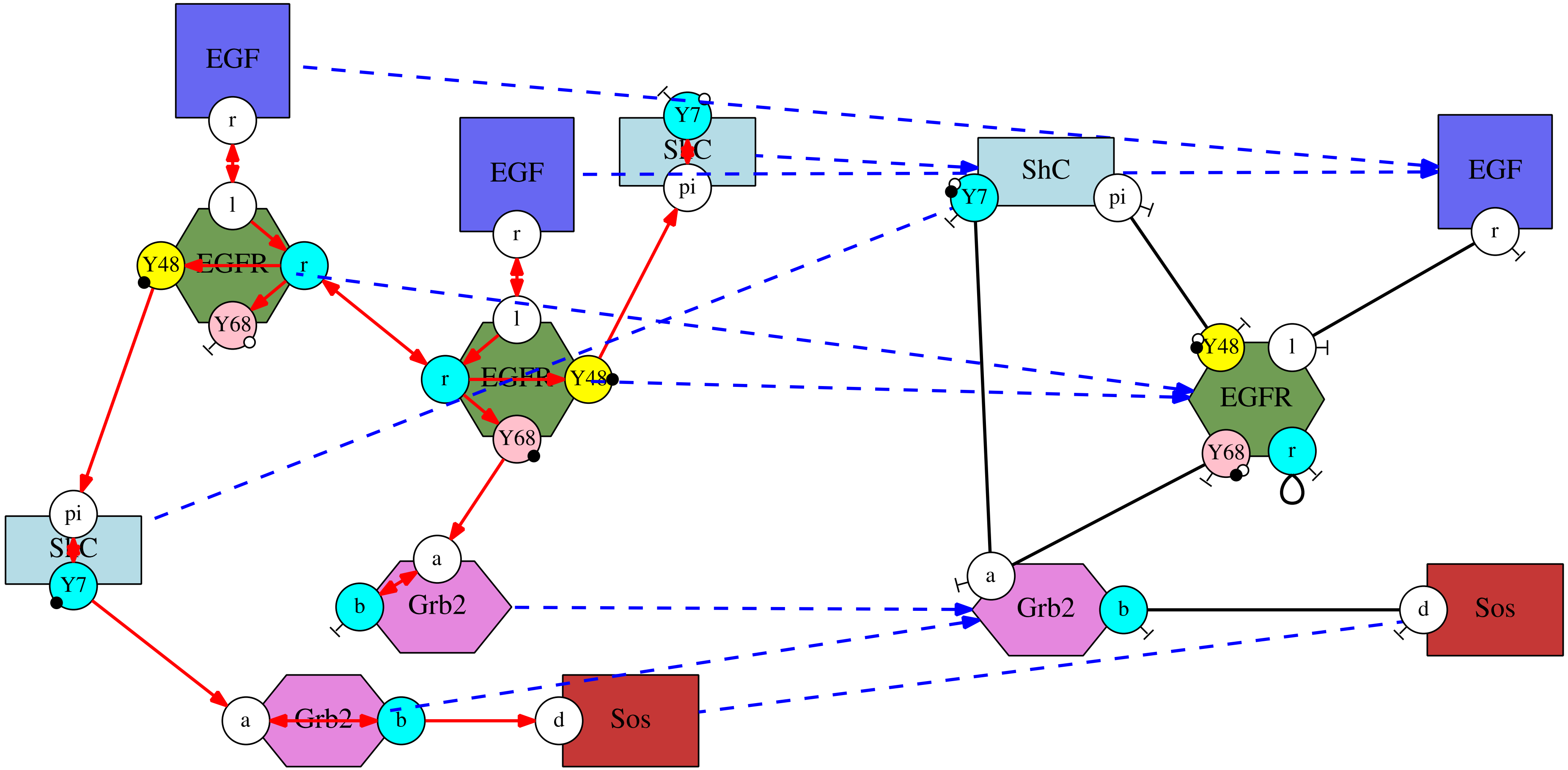




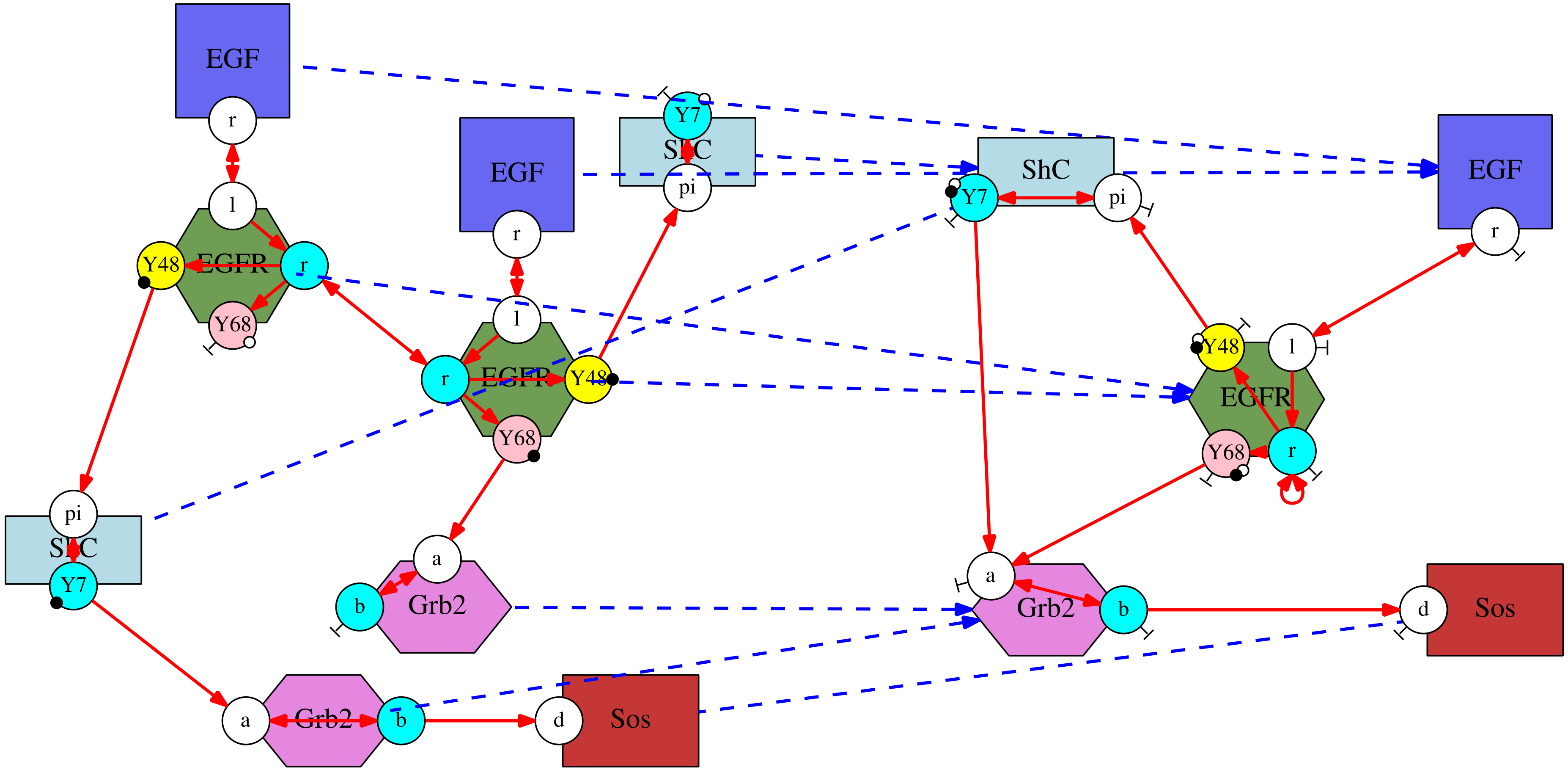
Projection on the contact map



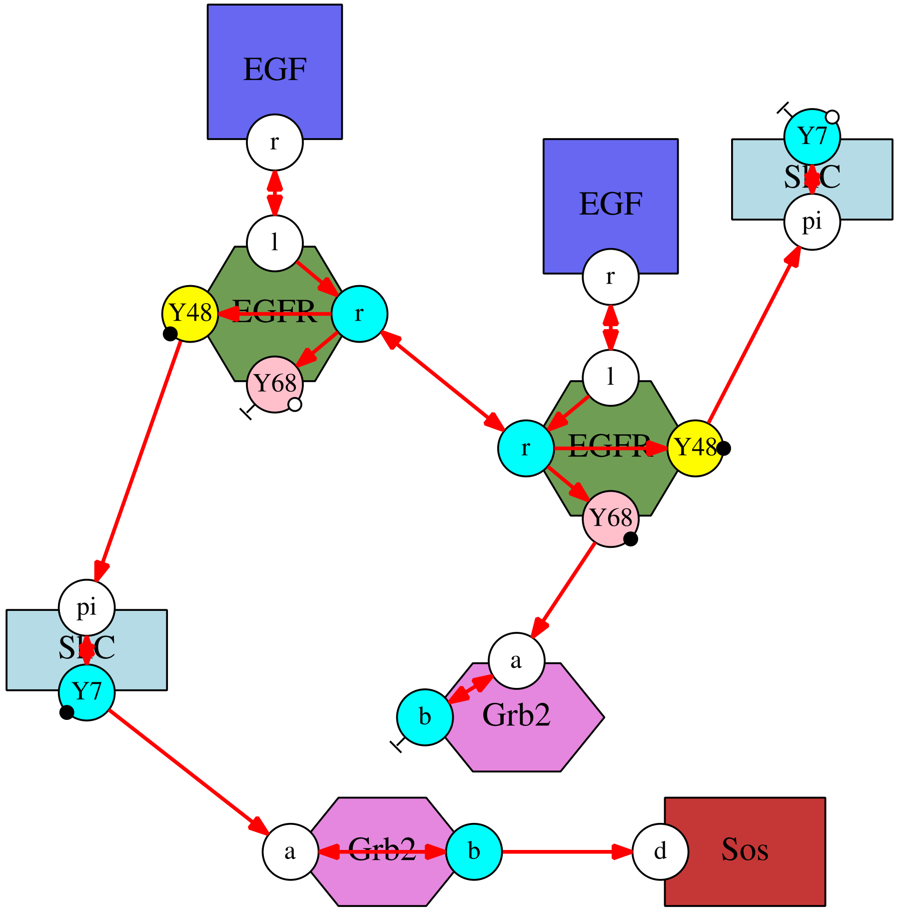
Projection on the contact map

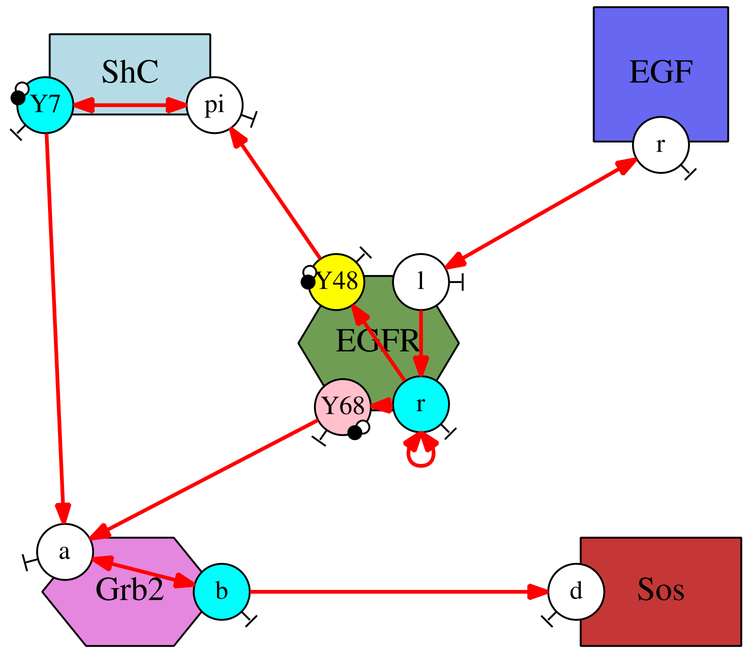


Projection on the contact map

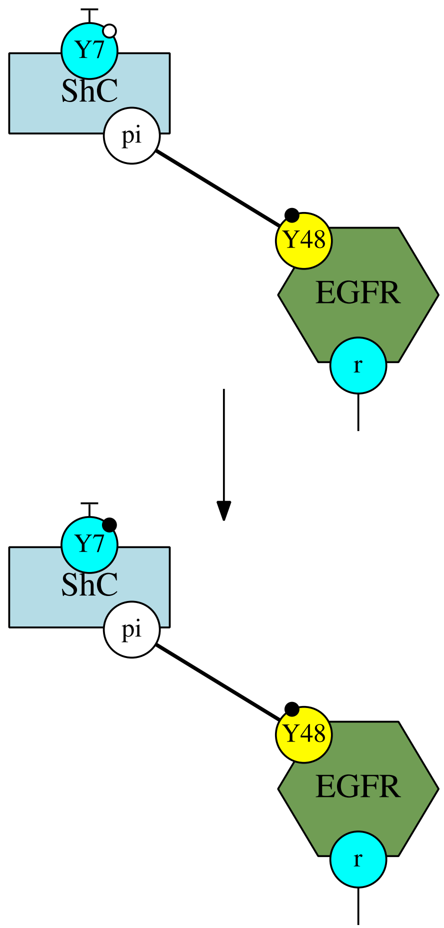


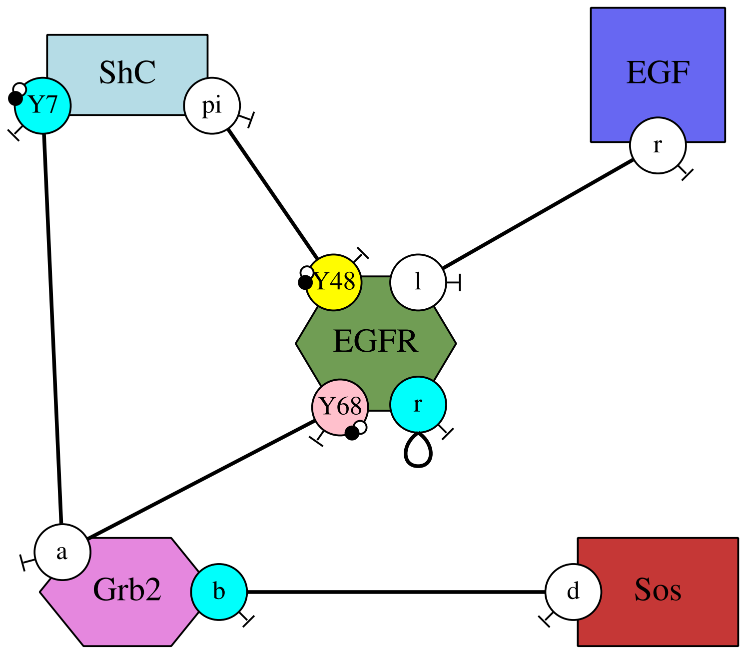
Projection on the contact map



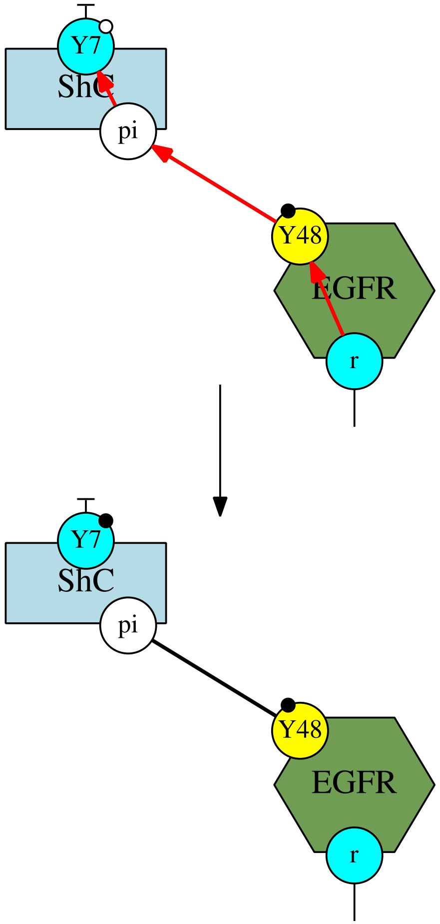


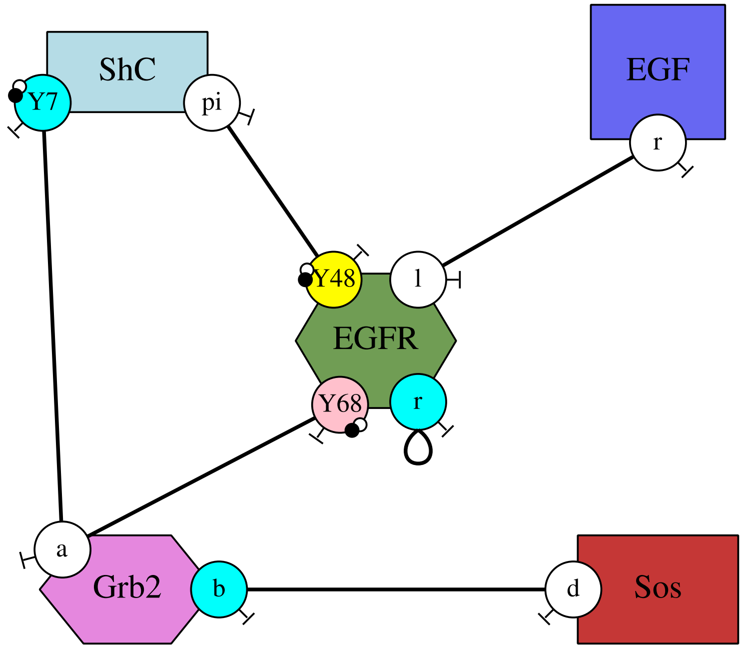
Direct computation



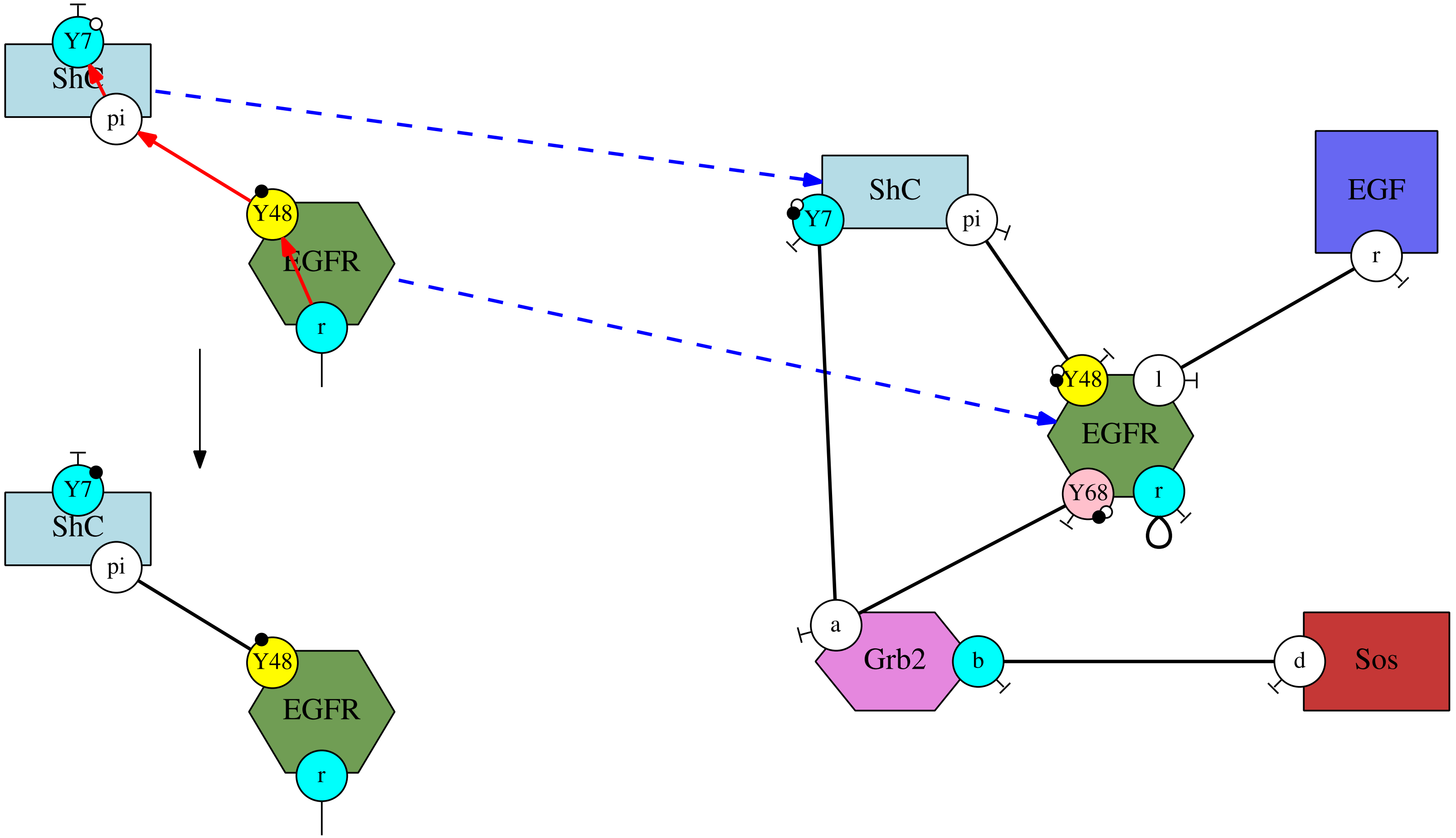


Direct computation

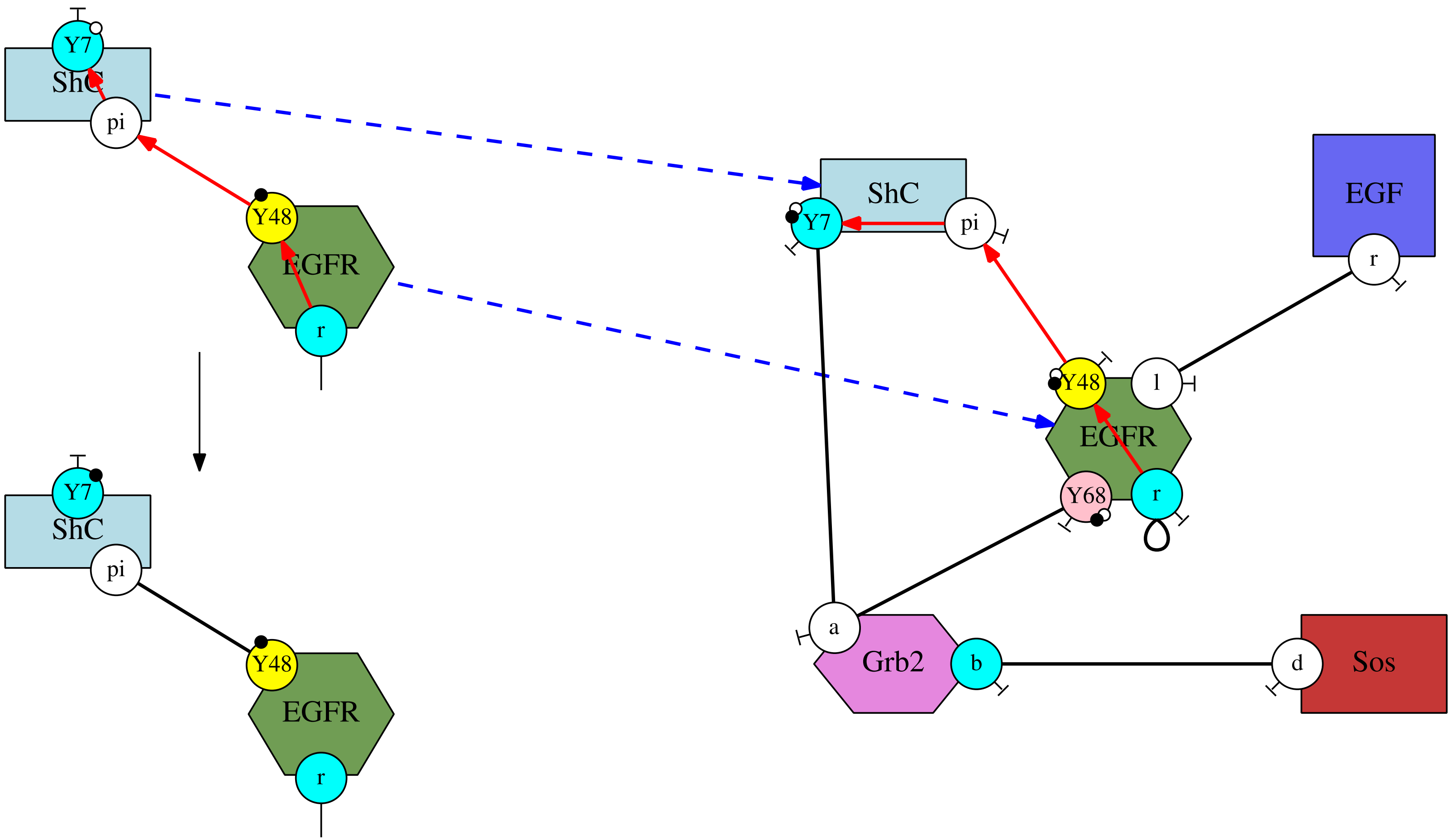




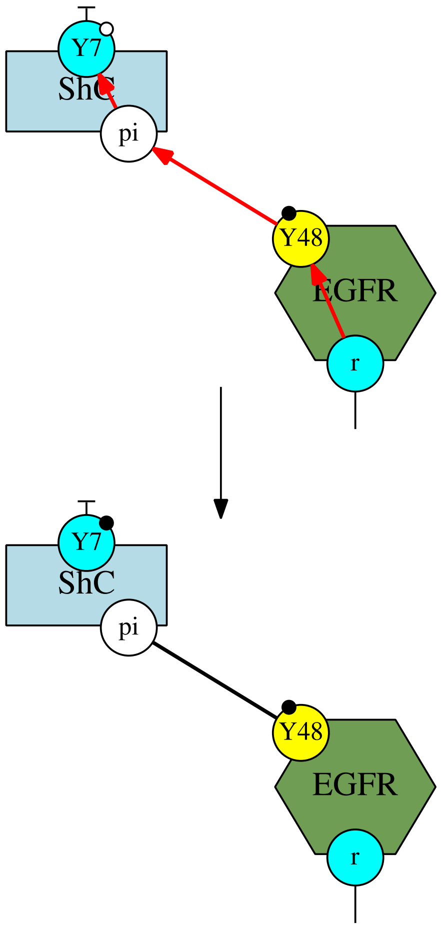
Direct computation

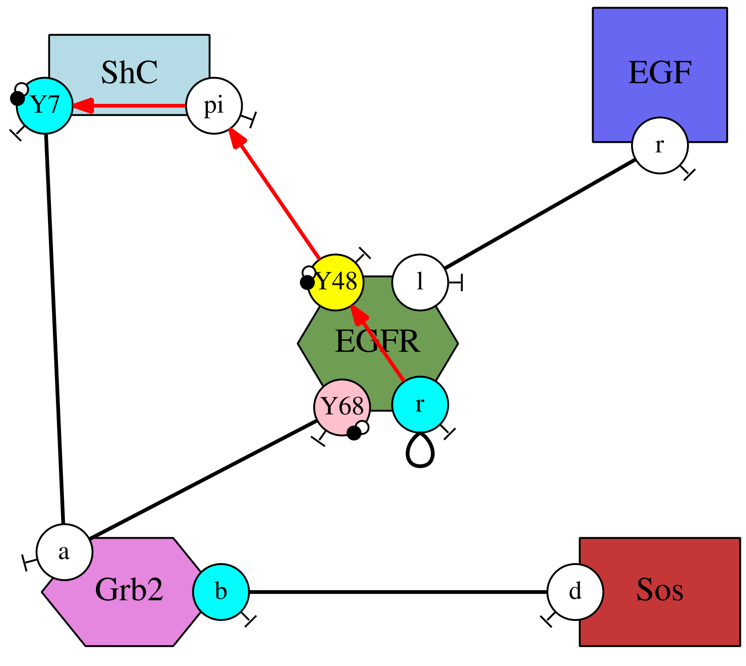


Direct computation



Direct computation

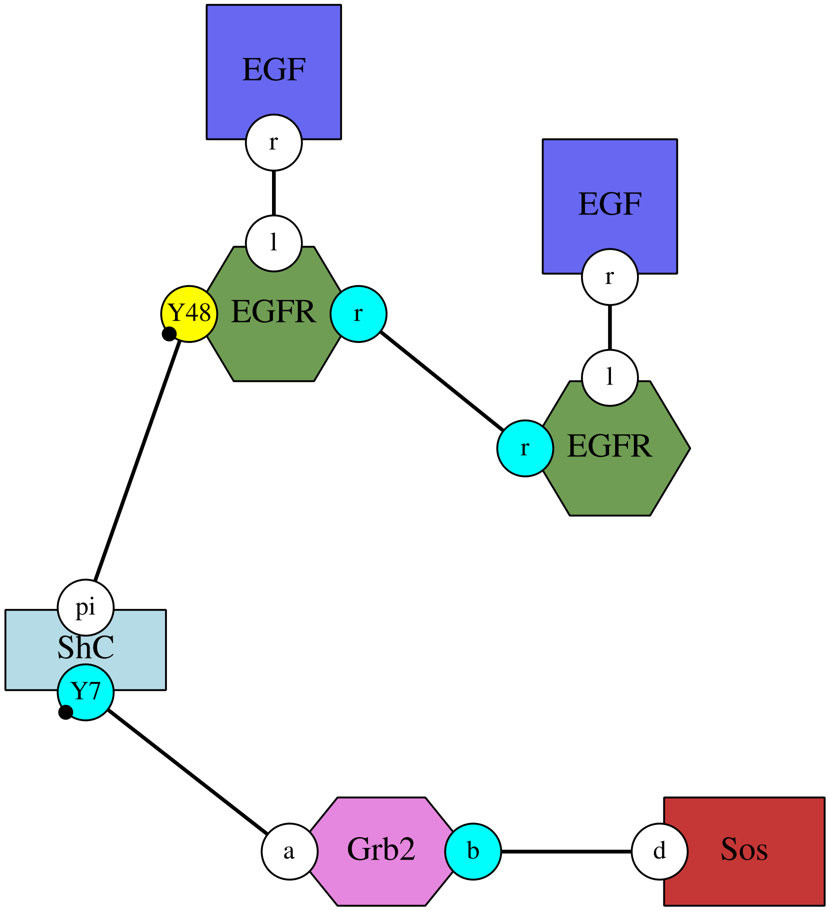




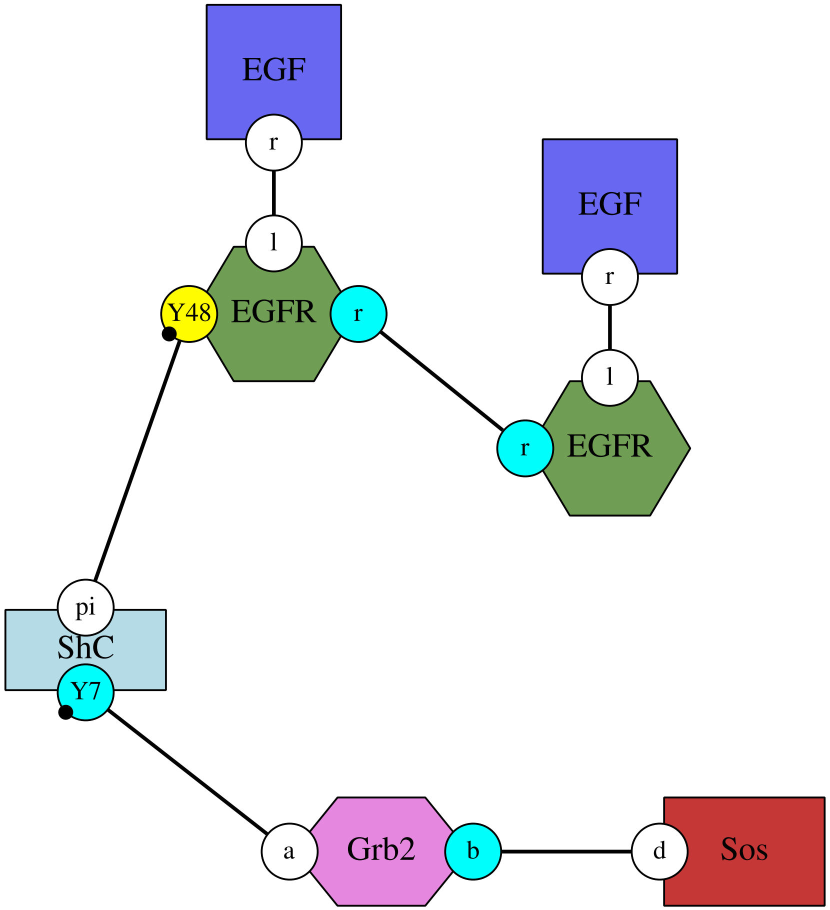
On the menu today

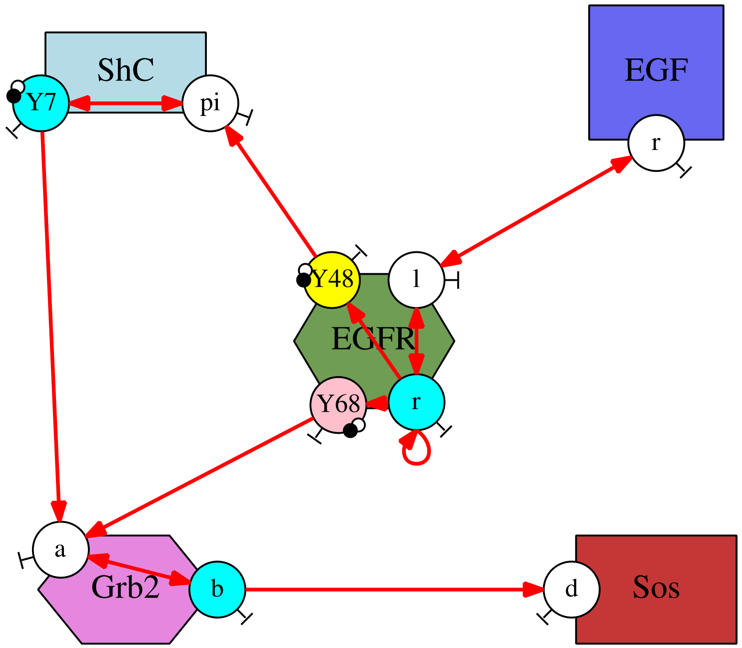
1. Context and motivations
2. Case studies
3. Reduction of ordinary differential equations
4. Abstraction of the information flow
5. Model reduction
6. Conclusion

Which patterns shall we keep?

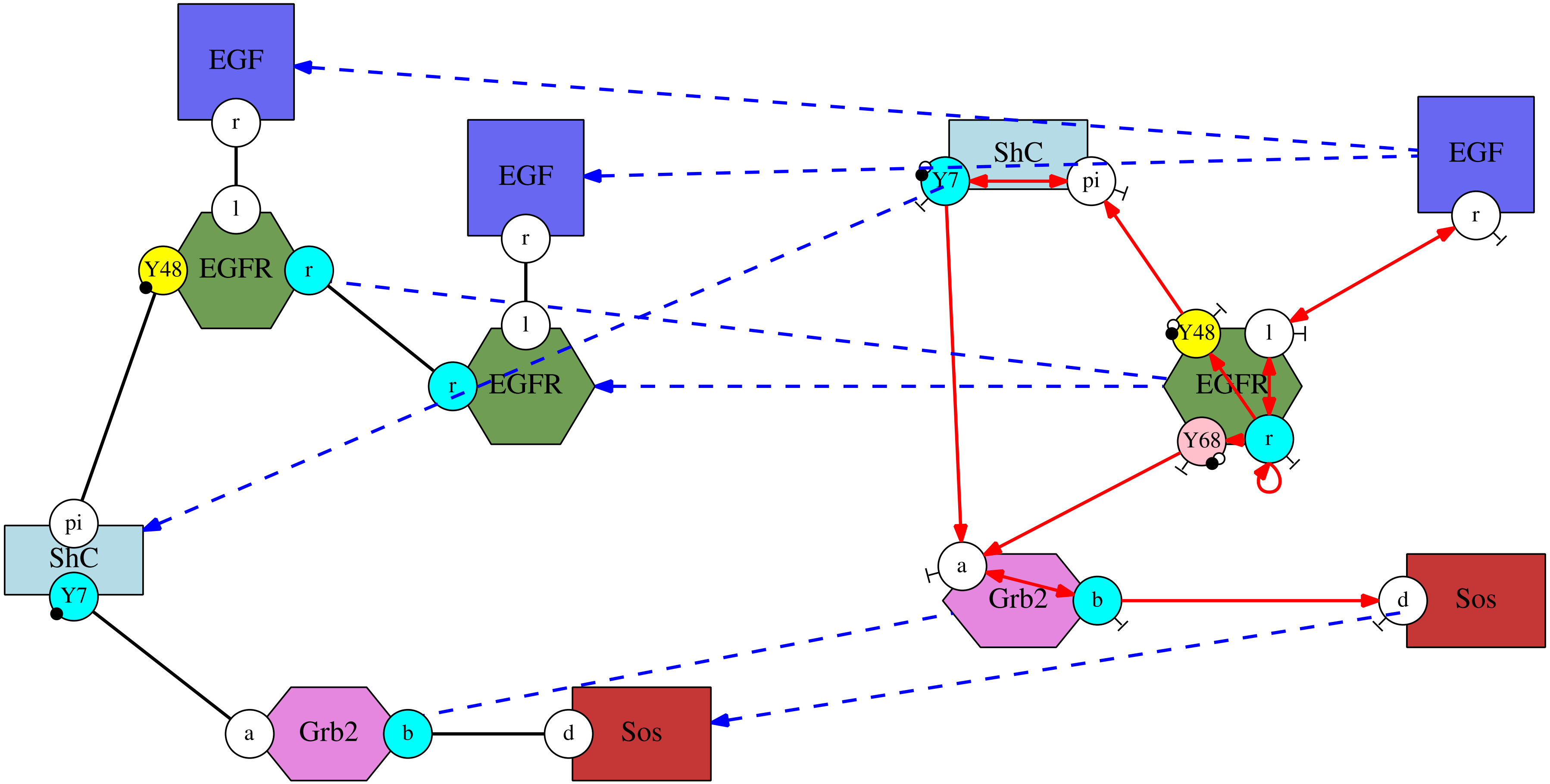


Which patterns shall we keep?

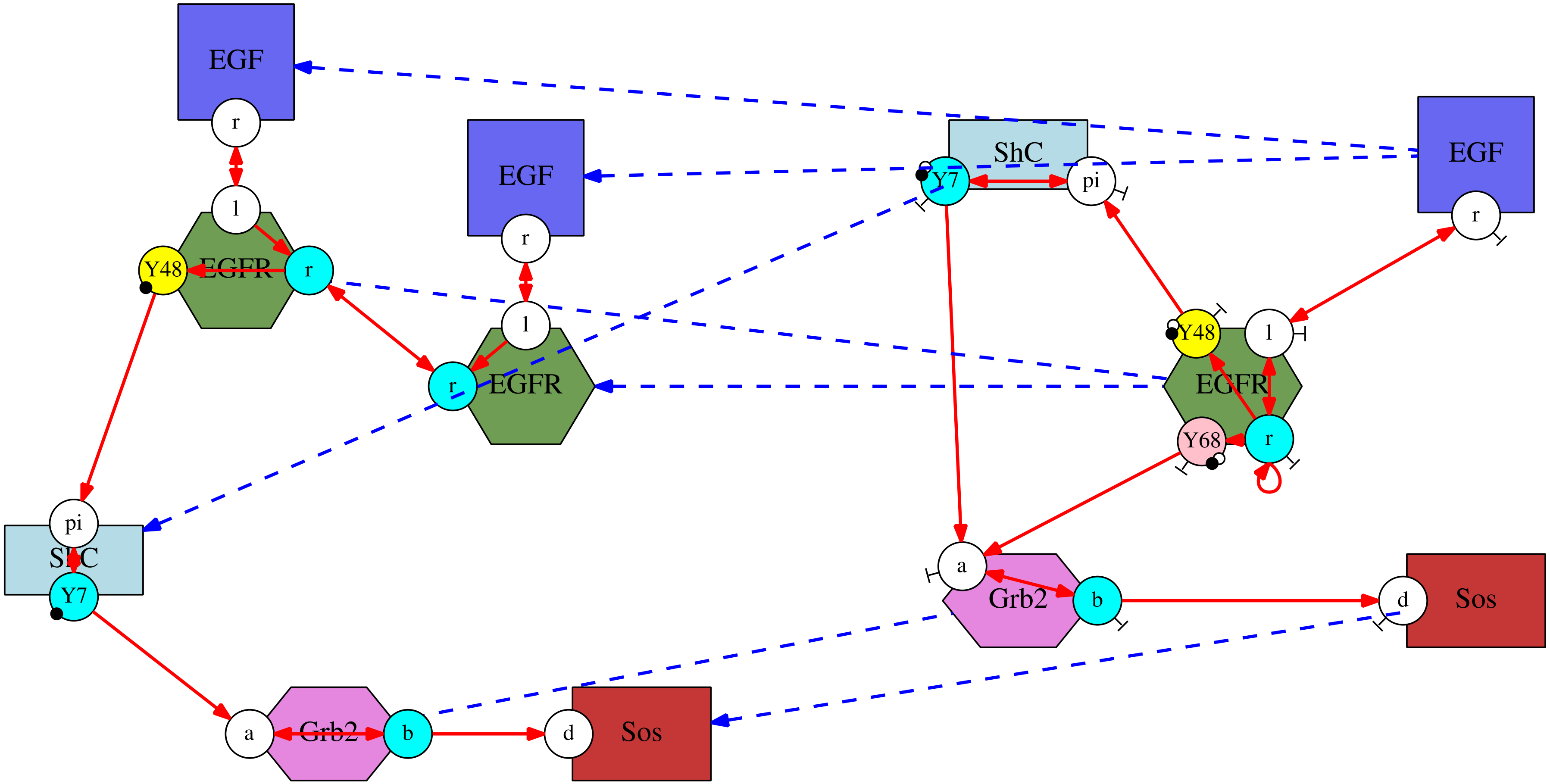




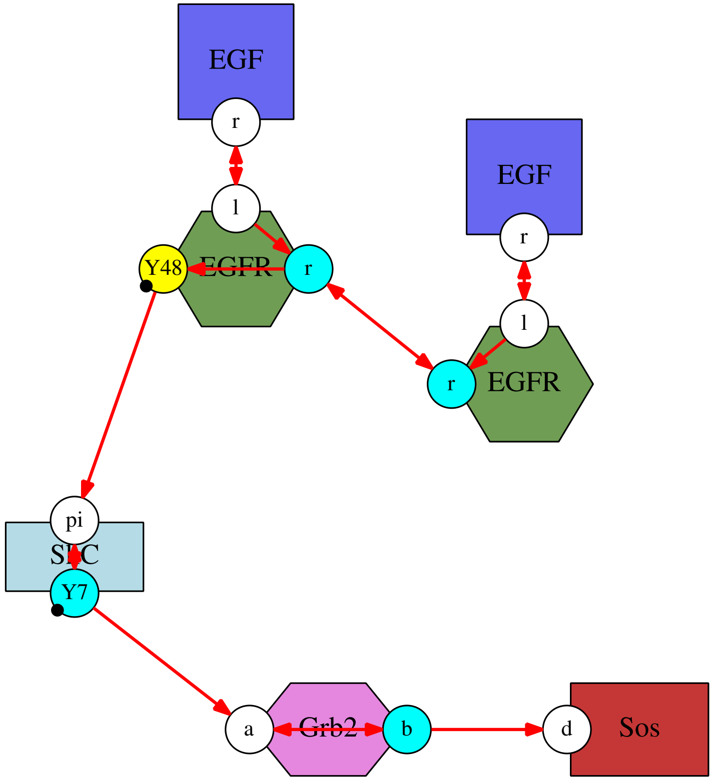
Pattern annotation



Pattern annotation

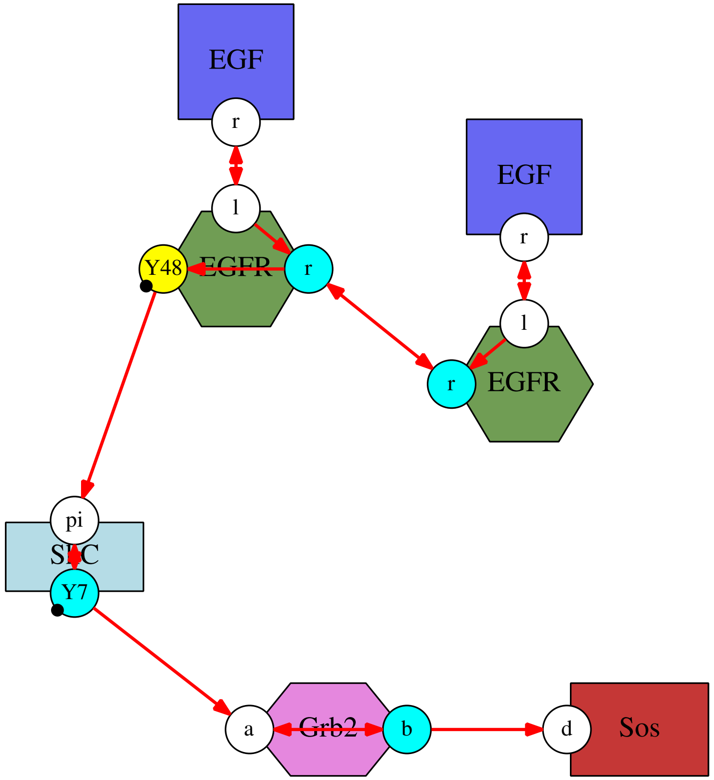


Prefragment



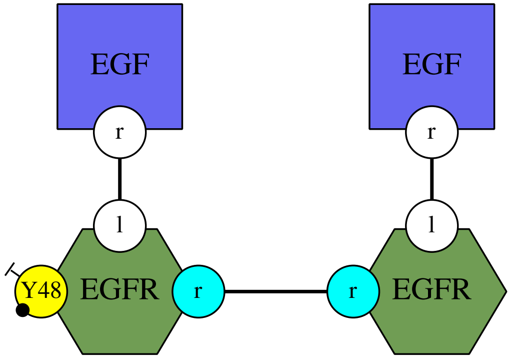
DÃl'finition 1 (prefragment) A pattern is a prefragment if, in its annotated form, there exists a site that it is reachable from every site (following the flow of information).

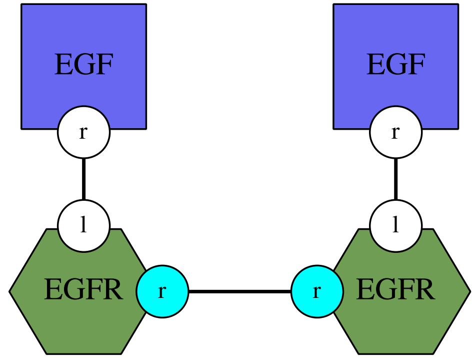
Fragments

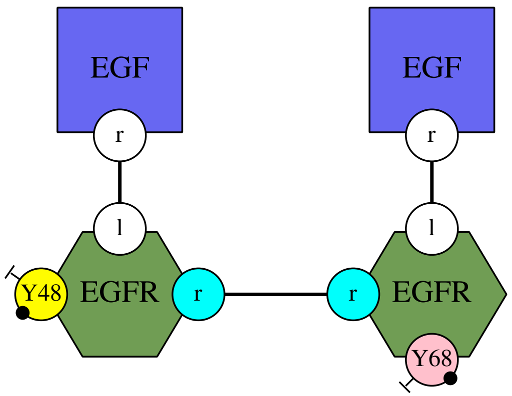


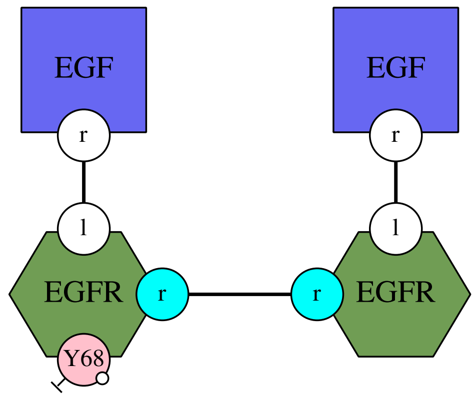
DÃl'finition 2 (fragment) A fragment is a prefragment that cannot be embedded in any bigger prefragment.

Examples
Which patterns are fragments?

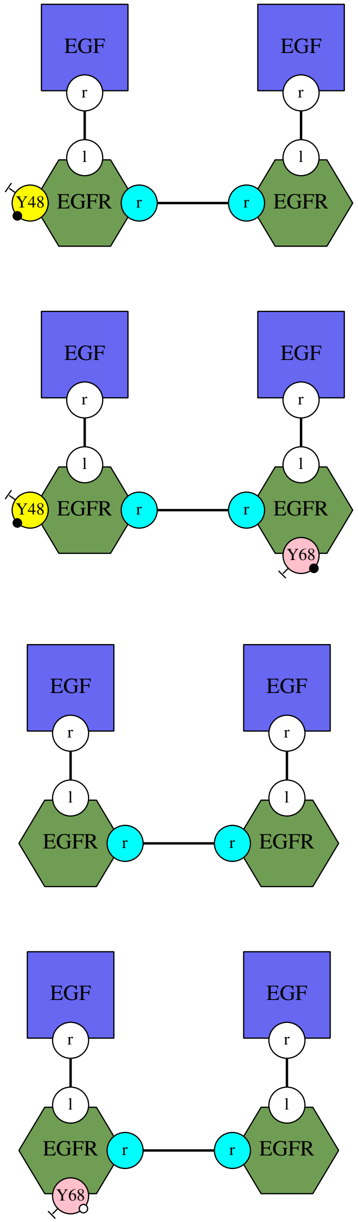


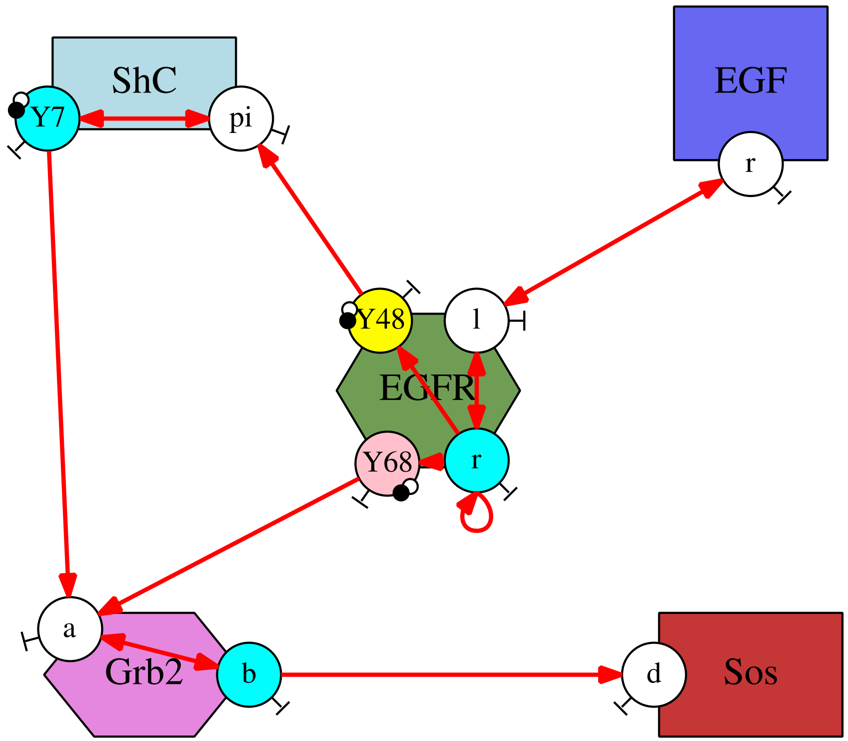




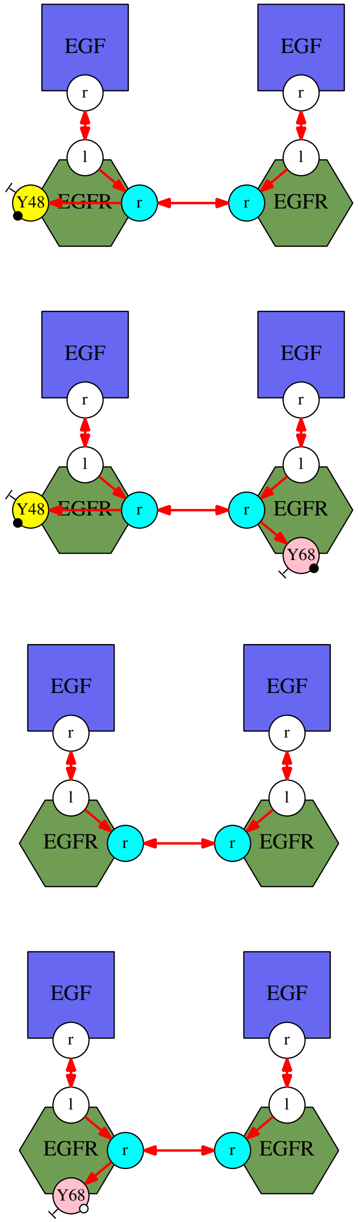


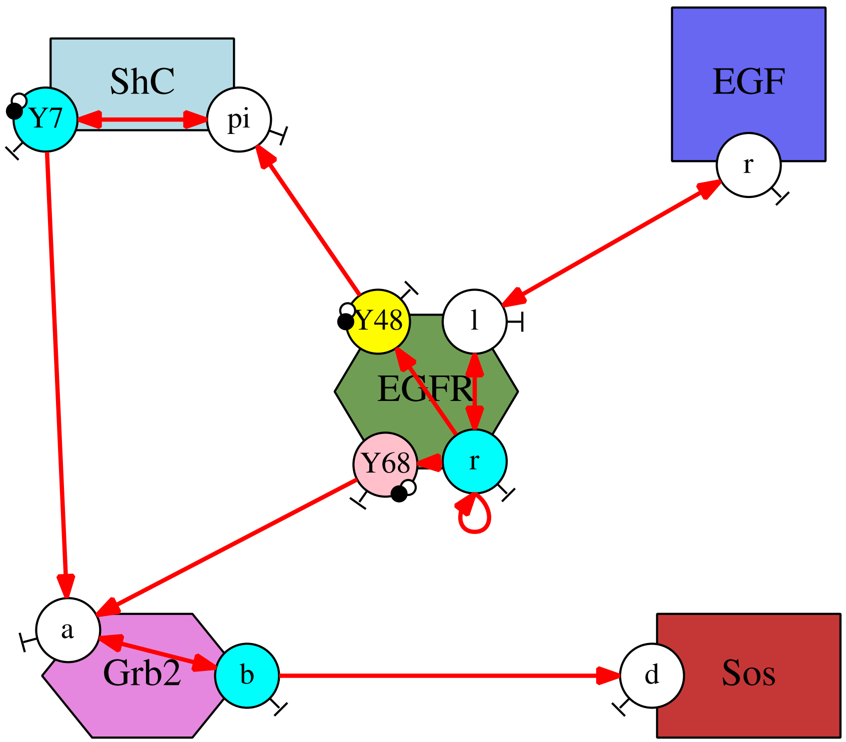
Examples : annotated map



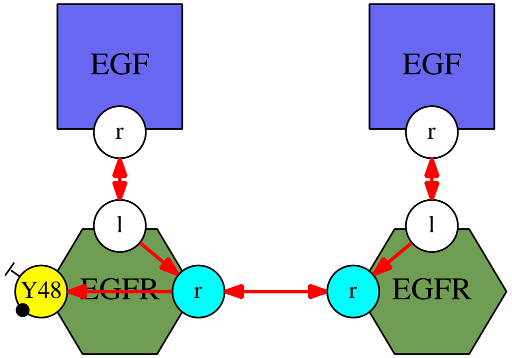


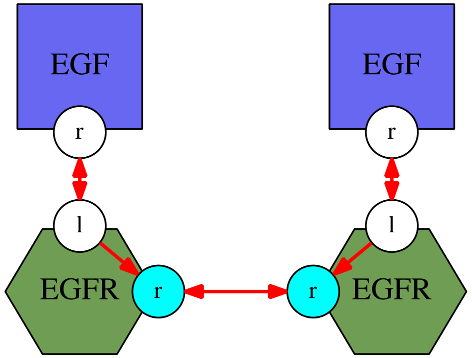
Examples : pattern annotation

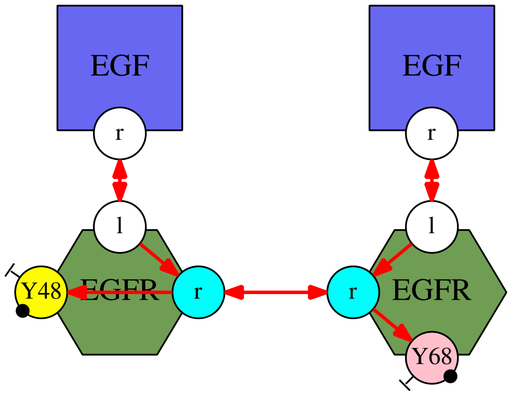


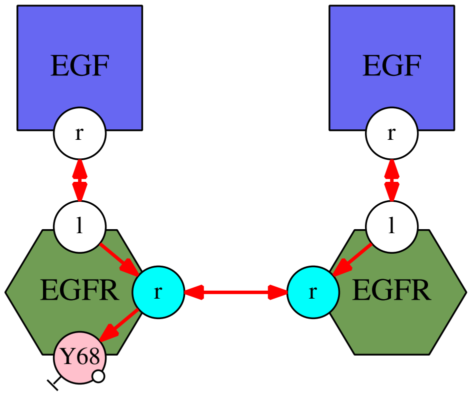


Examples
Which patterns are prefragments?

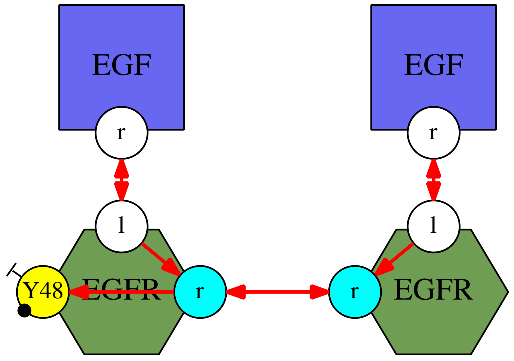


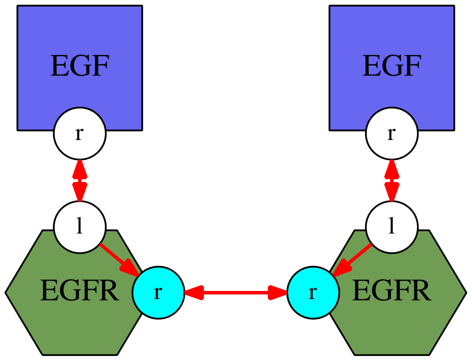


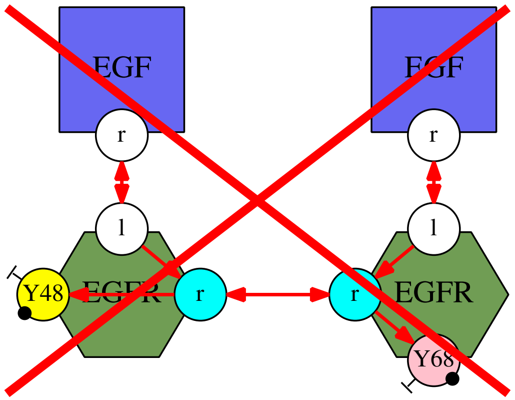


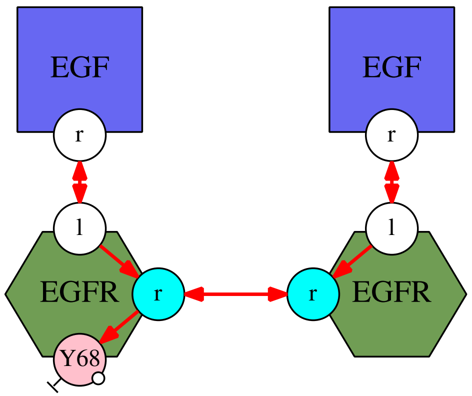


Examples
Prefragments

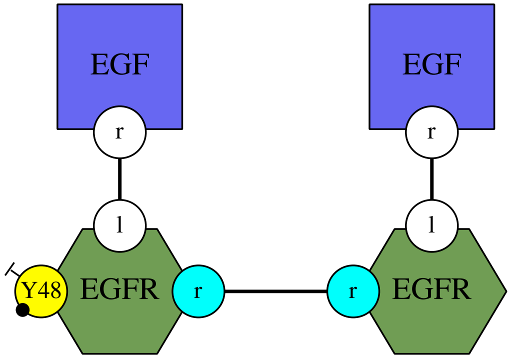


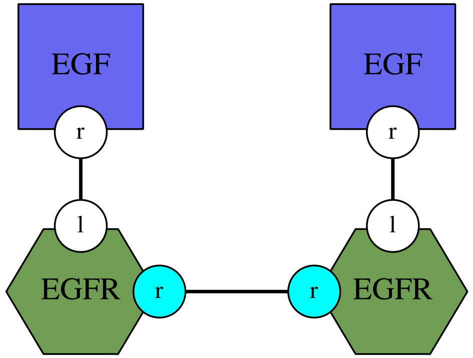


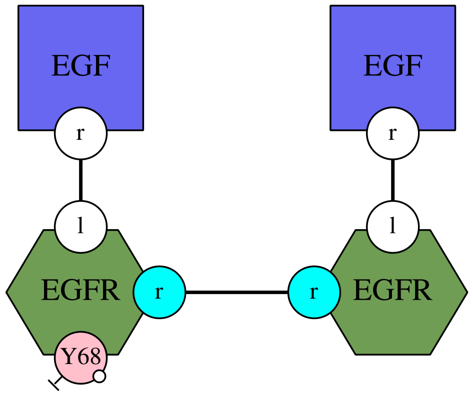




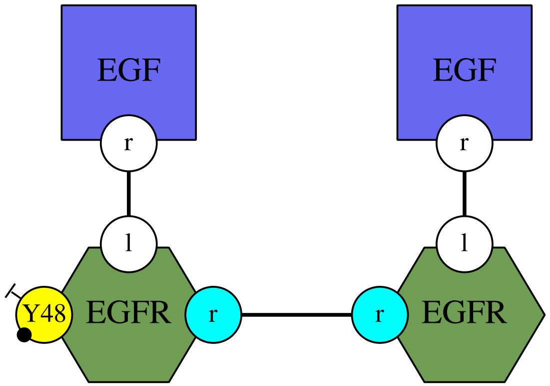
Examples
Which patterns are fragments?

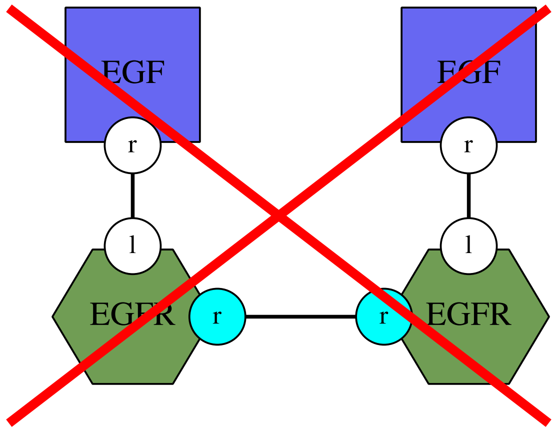


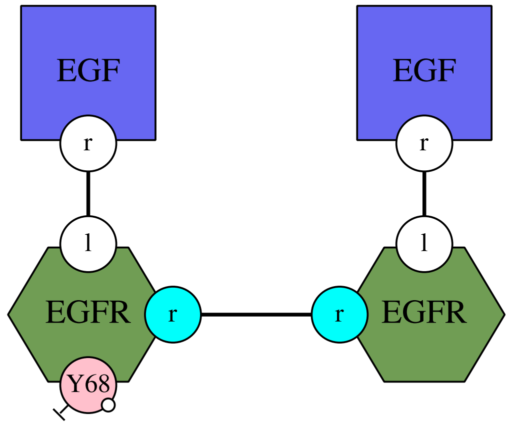




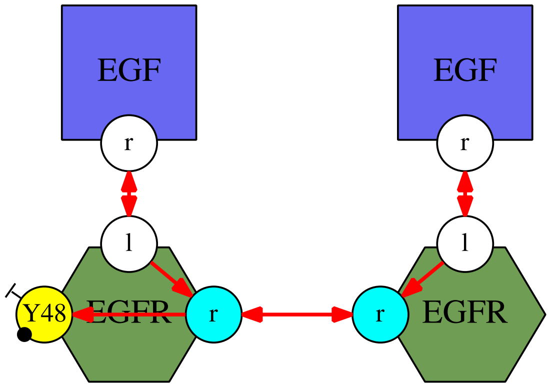
Examples
Fragments

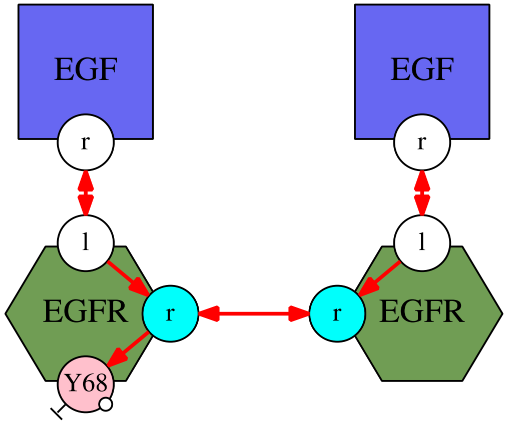






Examples : fragments



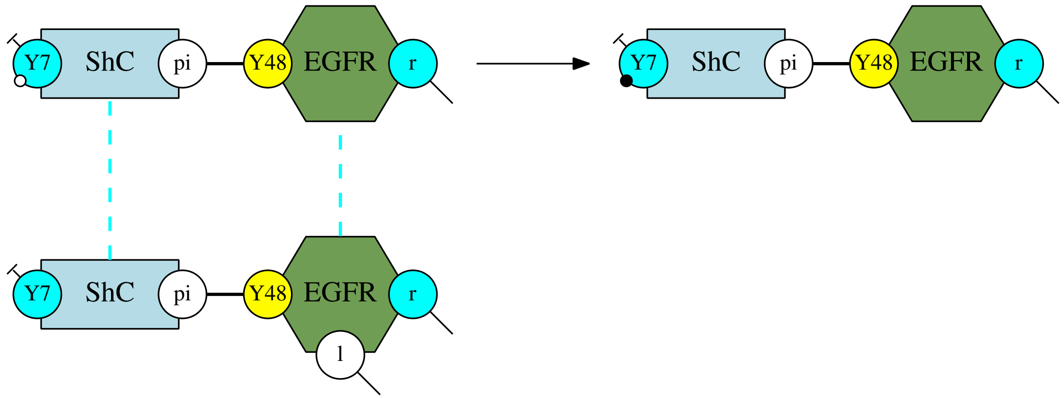


Almost done...

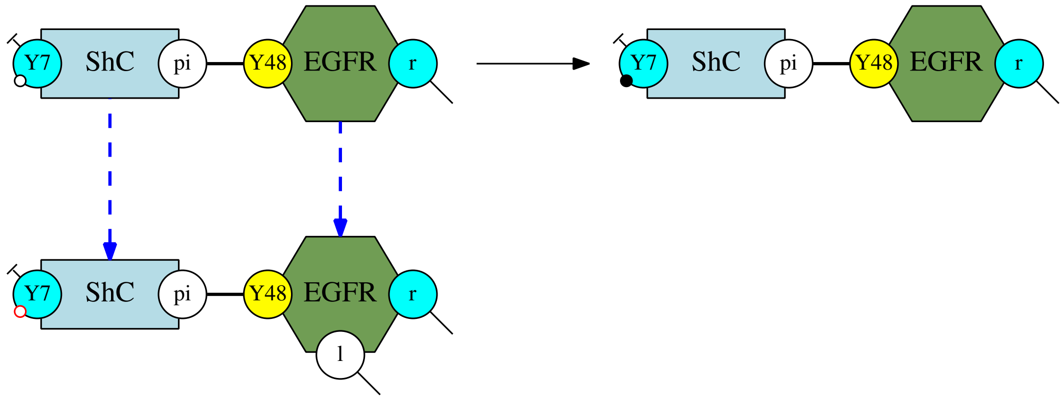
We are left to express the consumption and the production (in concentration) of each fragment as expressions of the concentration of fragments.

Firstly, we notice that the concentration of each prefragment can be expressed as a linear combination of the concentration of the fragments.

Fragments consumption

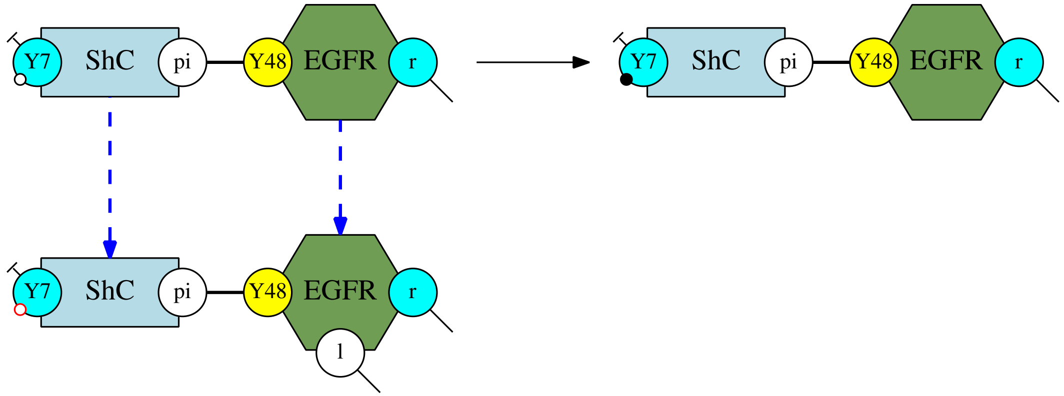


Fragments consumption



Whenever there is an overlap between a fragment and a connected component in the left hand side of a rule such that the common region contains a site that is modified by the rule, then the connected component embeds in the fragement.

Fragments consumption



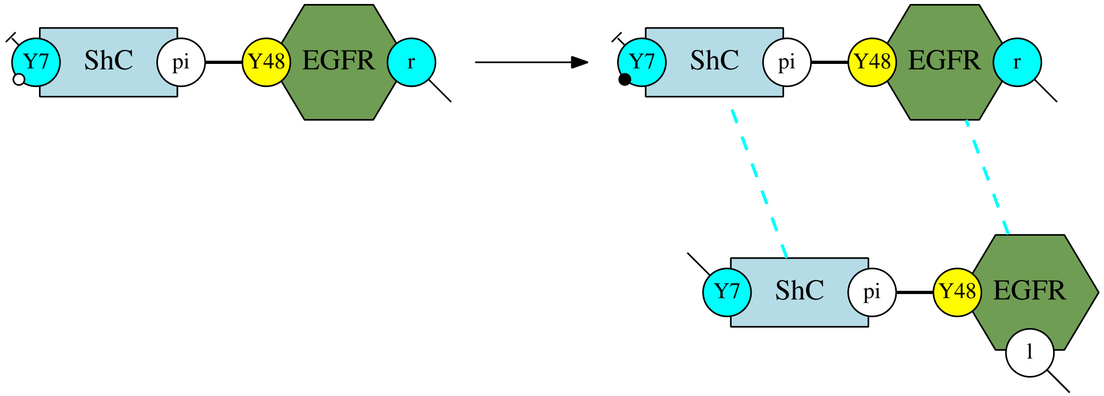
For each fragment F, for each rule:

$$r: \; C_1, \ldots, C_n \rightarrow rhs \quad k$$

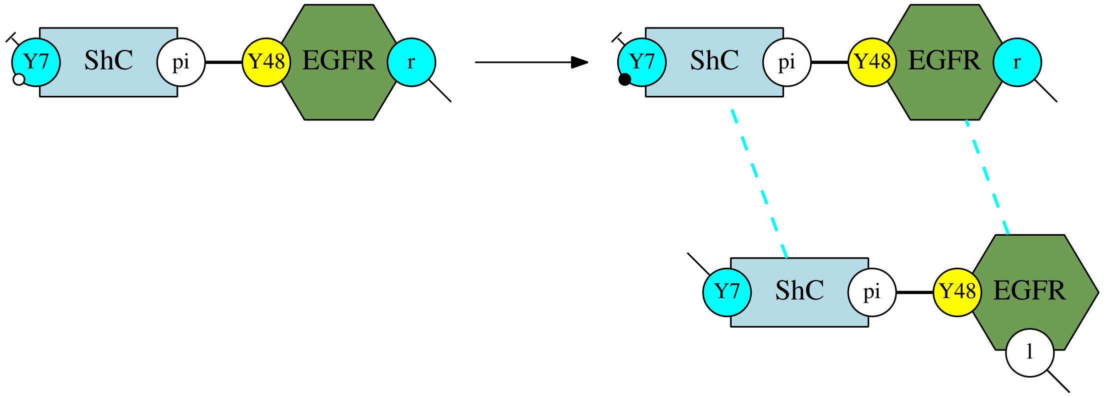
and for each occurrence of a connected component C_j that is modified by the rule, in a the fragment F, we have the following contribution:

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

Fragments production

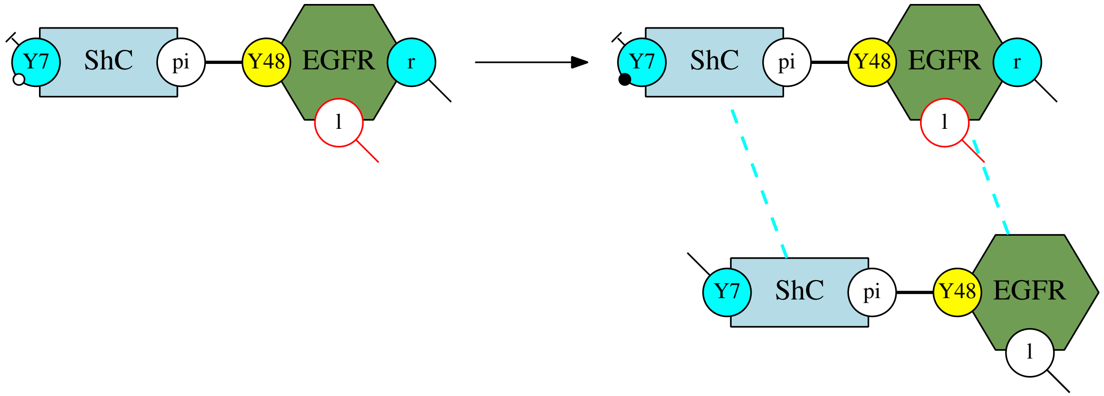


Fragments production



Whenever there is an overlap between a fragment and the right hand side of a rule, such that the common region contains a site that is modified by the rule. . .

Fragments production



Whenever there is an overlap between a fragment and the right hand side of a rule such that the common region contains a site that is modified by the rule, each connected component in the left hand side of the refined rule, is a prefragment.

Fragment production

For each overlap ch between a fragment and the right hand side of a rule, such that the common region contains a site that is modified by the rule:

$$r \ : C_1, \ldots, C_m \rightarrow \textit{rigth hand side} \quad k,$$

we have the following contribution:

$$\frac{d[F]}{dt} \stackrel{+}{=} \frac{k \cdot \prod_i [C'_i]}{\textsc{sym}[C_1, \ldots, C_m] \cdot \textsc{sym}[F]}.$$

where $C'_1, \ldots, C'_n$ is the left hand side of the refined rule.

On the menu today

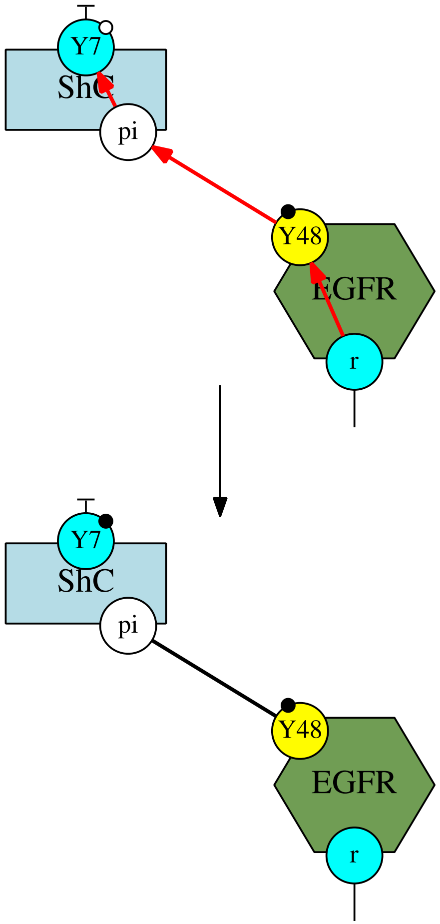
1. Context and motivations
2. Case studies
3. Reduction of ordinary differential equations
4. Abstraction of the information flow
5. Model reduction
6. Conclusion

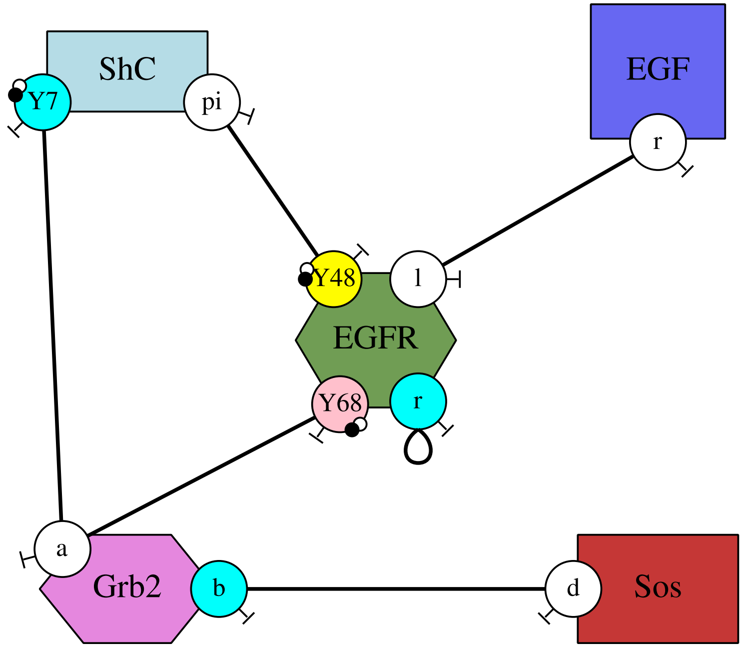
Benchmark

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

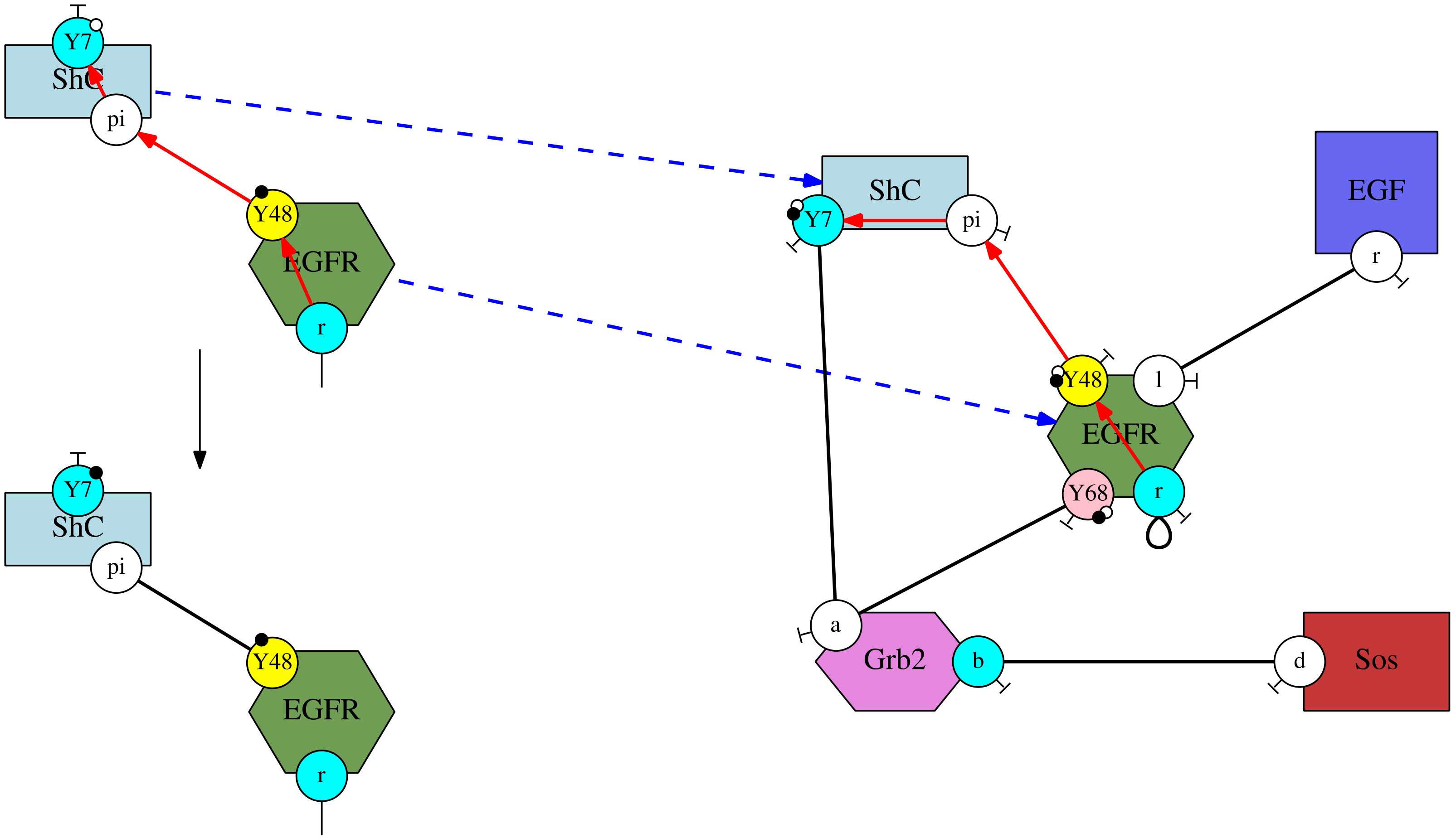
In short

Abstraction of the information flow

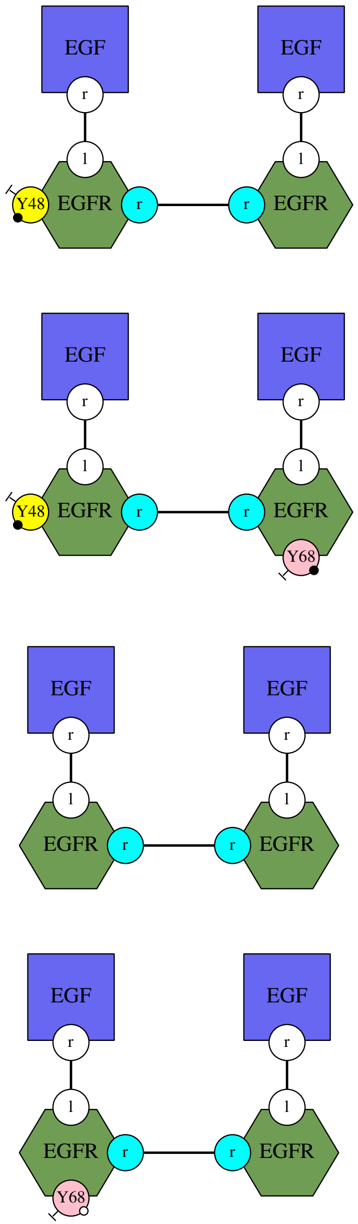


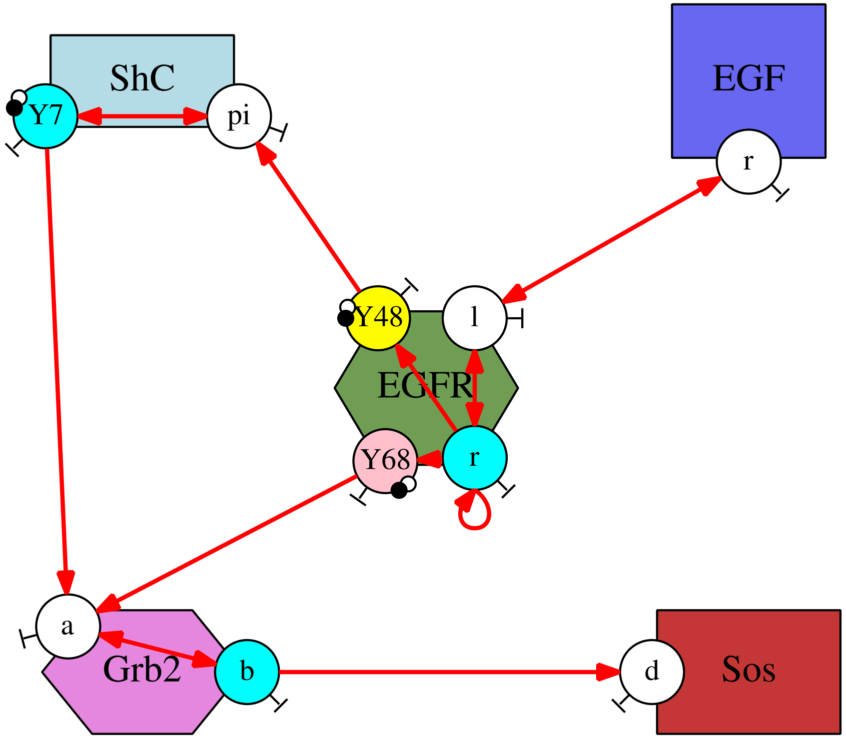


Abstraction of the information flow

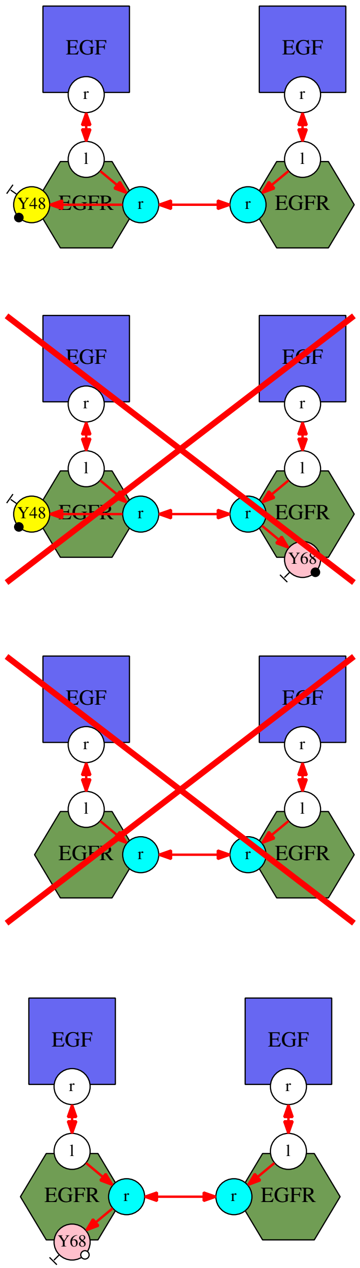


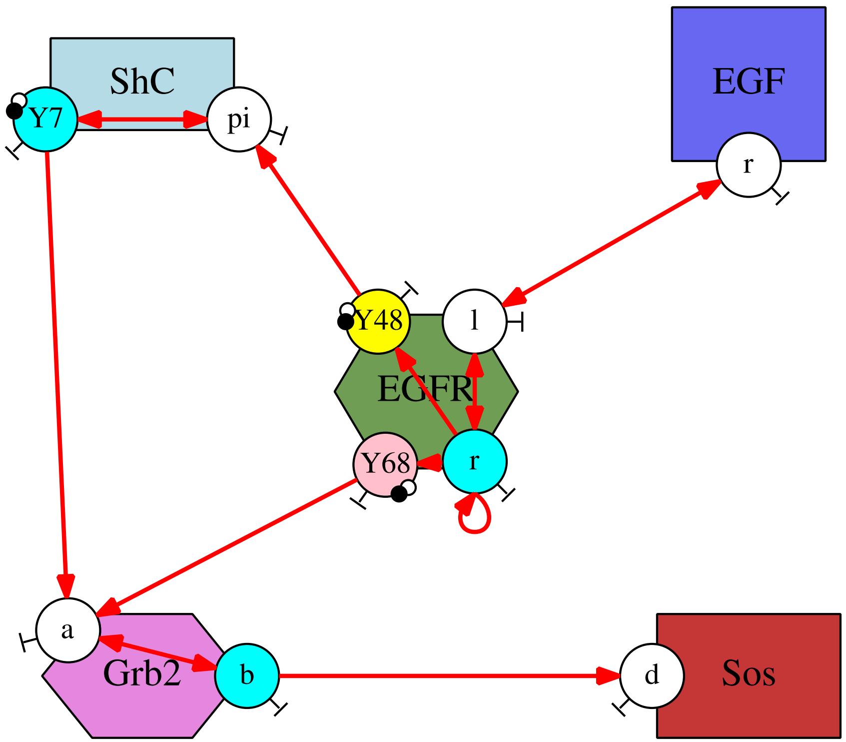
Patterns of interest





Patterns of interest





Related topics and acknowledgements

- Model reduction (ODEs semantics)
  Vincent Danos, Walter Fontana, Russ Harmer, Jean Krivine
- Context-sensitive abstraction of information flow
  Ferdinanda Camporesi
- Model reduction (CTMC semantics)
  Tatjana Petrov, Heinz Koeppl, Tom Henzinger
- Bisimulations metrics
  Norm Ferns.

"AbstractCell" (2009-2013)

"Big Mechanism" (2014-2017)
"CwC" (2015-2018)

"TGFβSysBio" (2015-2018)

MPRI

An algebraic approach for inferring and using symmetries in rule-based models

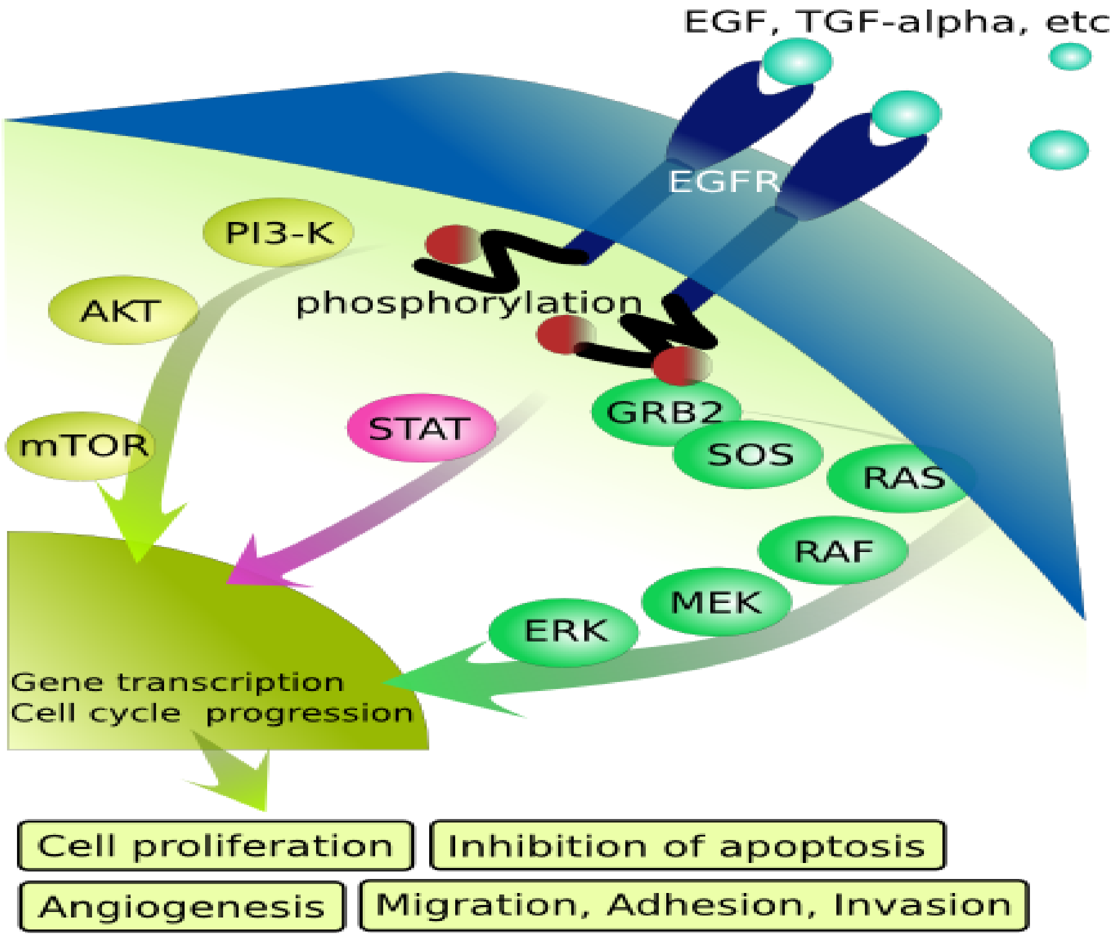
Jérôme Feret
DI - ÉNS

Wednesday, the 4th of January, 2017

Overview

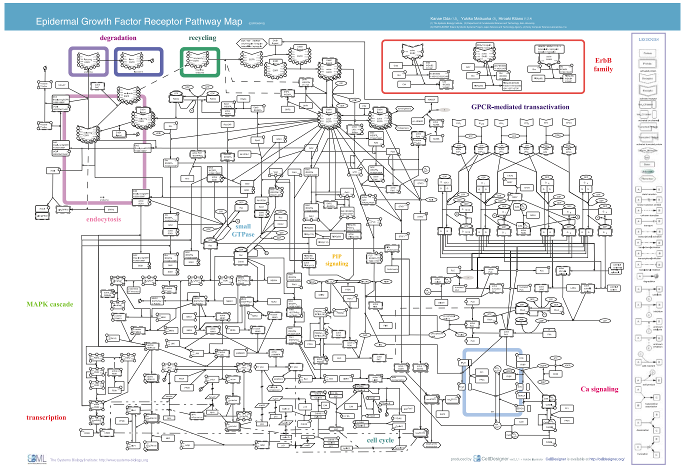
1. Context and motivations
2. Case study
3. Kappa semantics
4. Symmetries in site-graphs
5. Symmetric models
6. Conclusion

Signalling Pathways



Eikuch, 2007

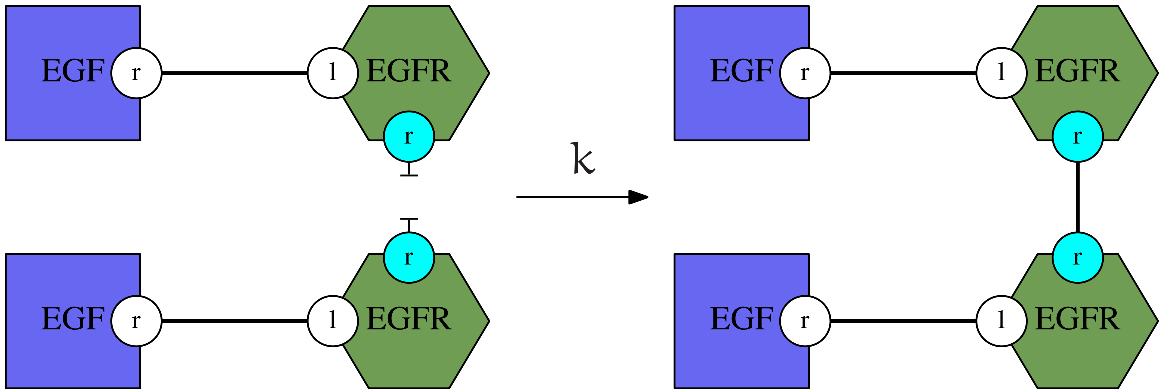
Bridging the gap between...



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

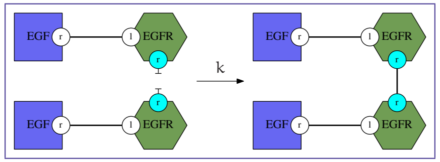
knowledge representation **and** **models of the behaviour of systems**

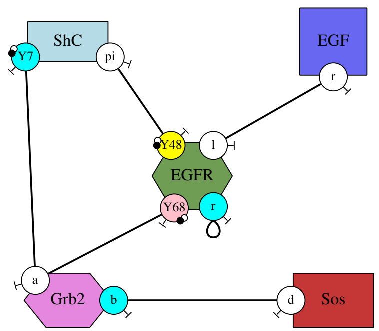
Site-graphs rewriting



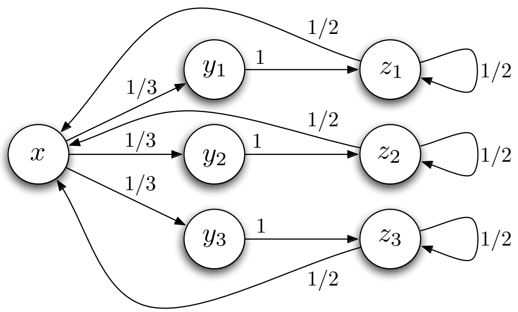
- a language close to knowledge representation;
- rules are easy to update;
- a compact description of models.

Choices of semantics





interaction map

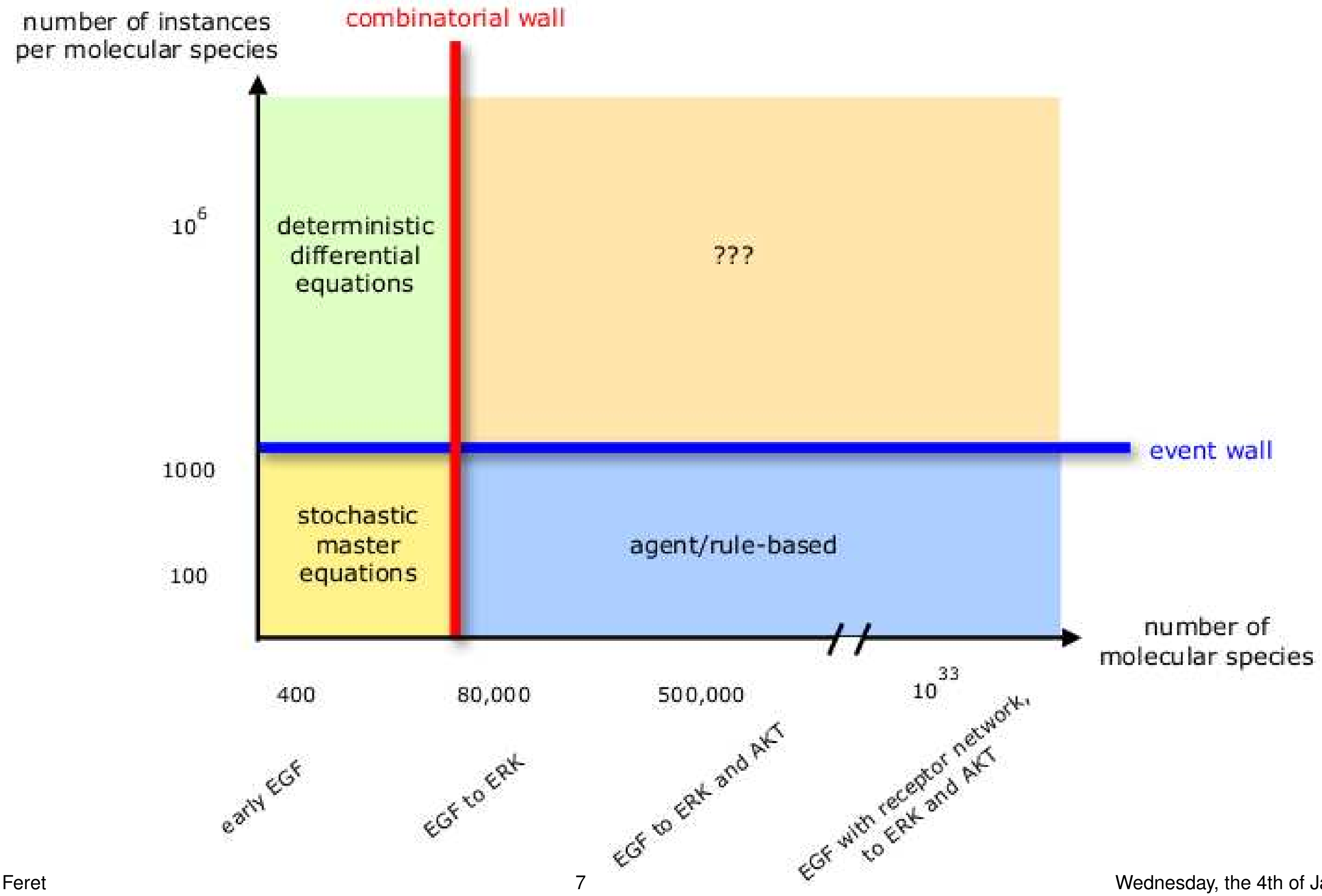


Markov chain

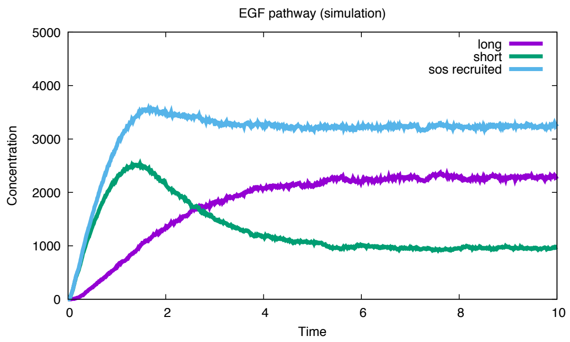
$$
\begin{cases}
\frac{dx_1}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
\frac{dx_2}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
\frac{dx_3}{dt} = k_1 \cdot x_1 \cdot x_2 - k_{-1} \cdot x_3 + 2 \cdot k_2 \cdot x_3 \cdot x_3 - k_{-2} \cdot x_4 \\
\frac{dx_4}{dt} = k_2 \cdot x_3^2 - k_2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

ordinary differential equations

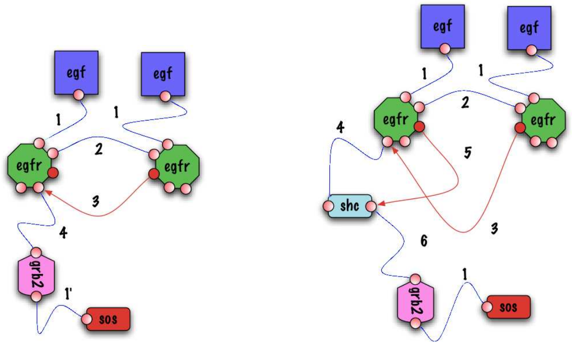
Complexity walls



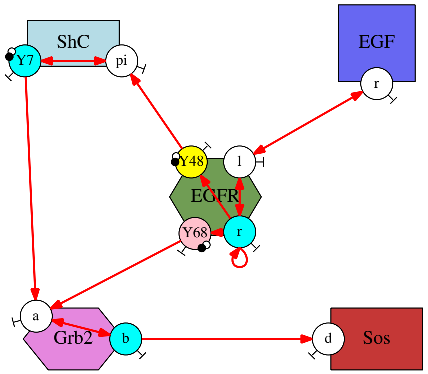
Abstractions offer different perspectives on models



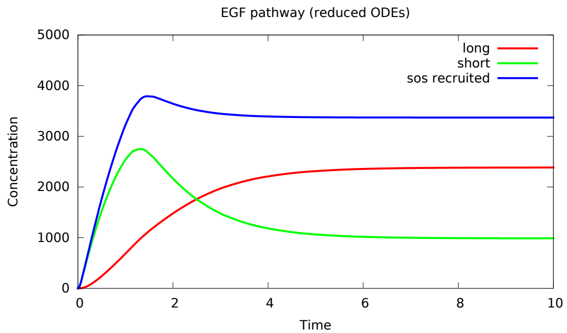
concrete semantics



causal traces



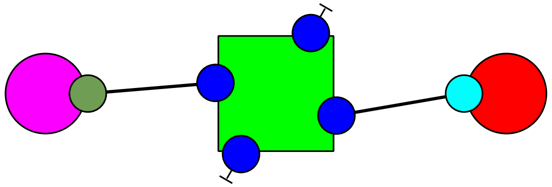
information flow



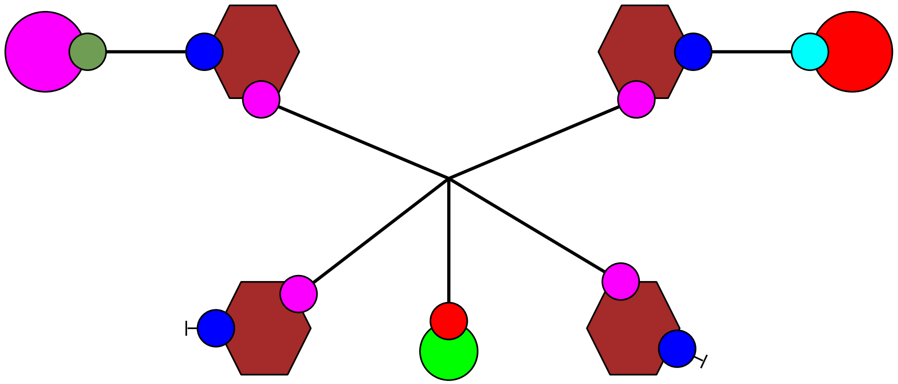
exact projection
of the ODE semantics

Symmetric sites

- in BNGL or MetaKappa (multiple-occurrences of sites):

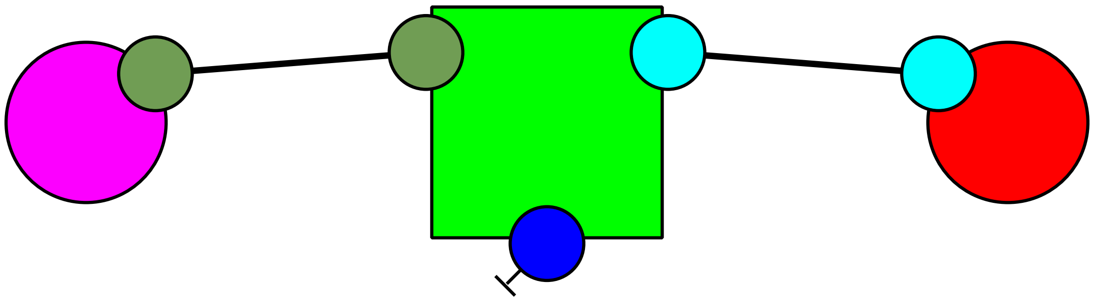


- in Formal Cellular Machinery or React(C) (hyper-edges):

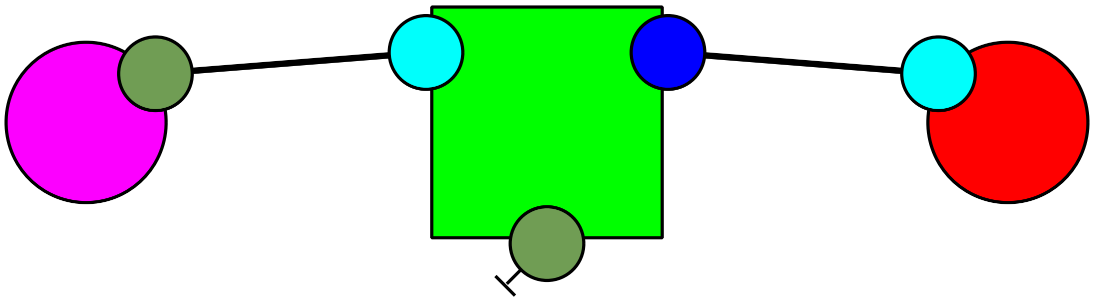


Blinov et al., BioNetGen: software for rule-based modeling of signal transduction based on the interactions of molecular domains, Bioinformatics 2004
Danos et al., Rule-Based Modelling and Model Perturbation, TCSB 2009
Damgaard et al., Formal cellular machinery, Damgaard et al., SASB 2011
John et al., Biochemical Reaction Rules with Constraints, ESOP 2011

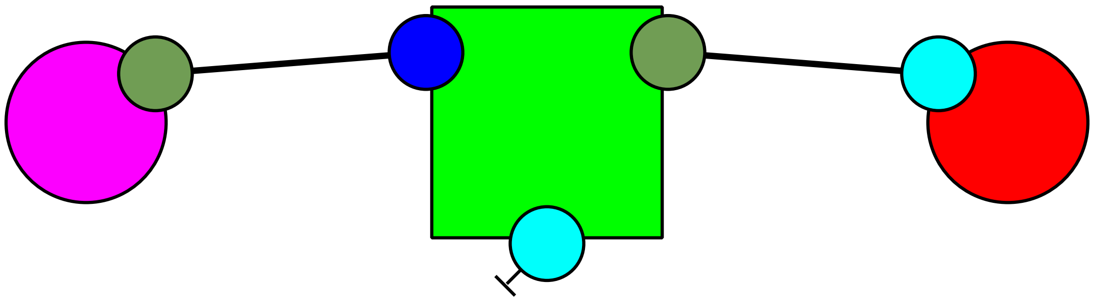
Other kinds of symmetries:
Circular permutations



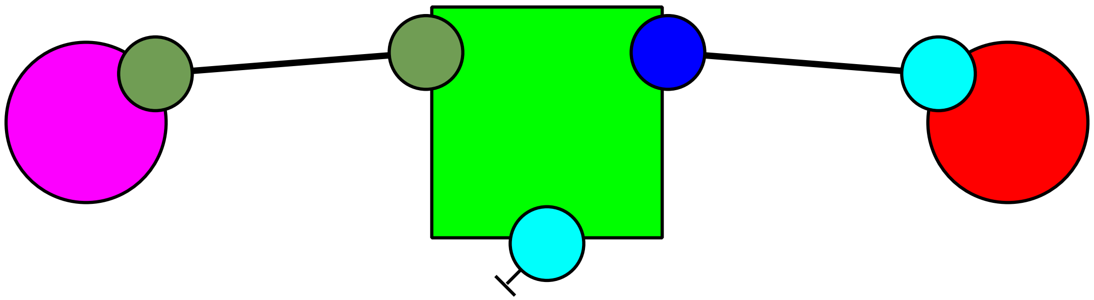
Other kinds of symmetries:
Circular permutations



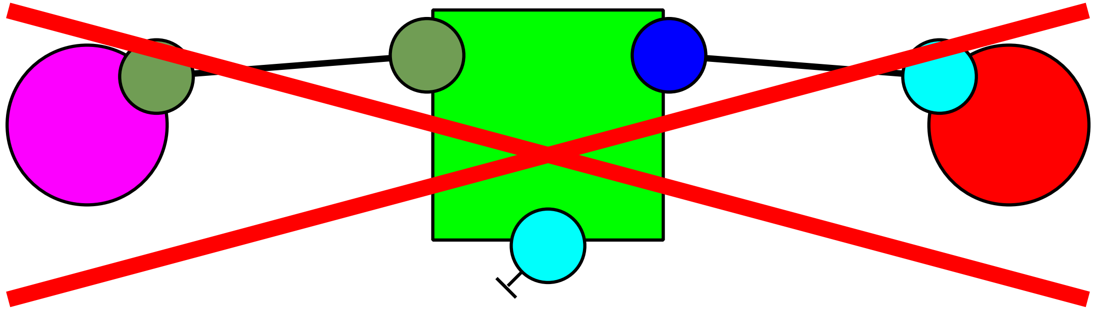
Other kinds of symmetries:
Circular permutations



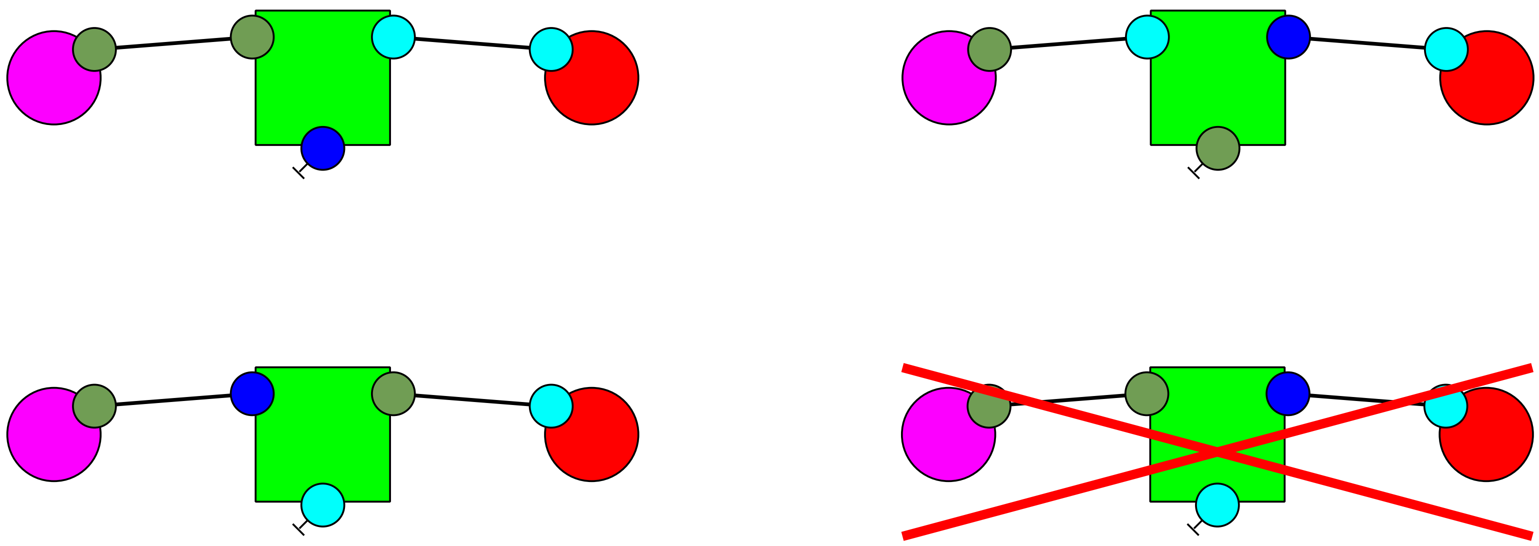
Other kinds of symmetries:
Circular permutations



Other kinds of symmetries:
Circular permutations

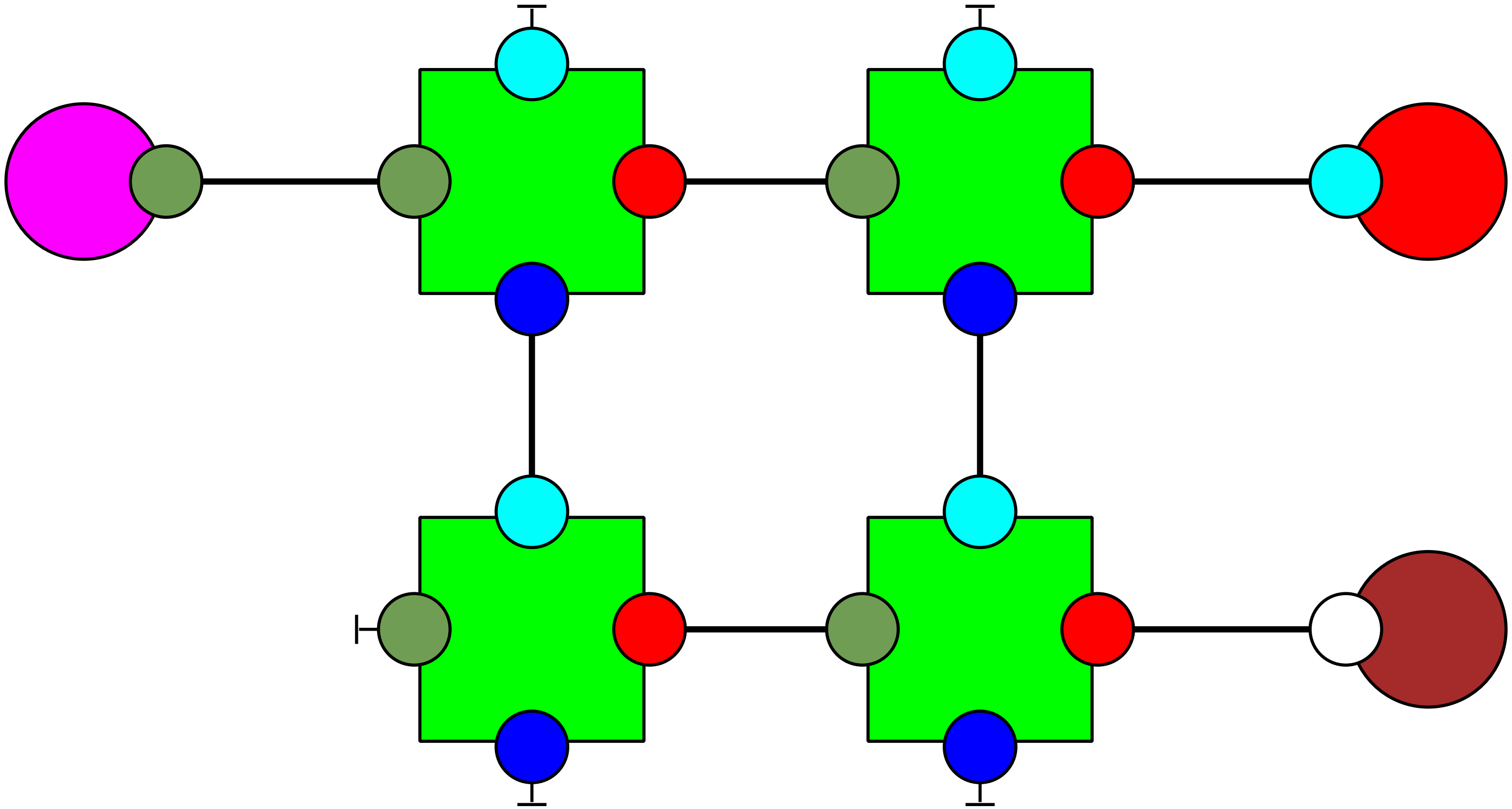


Other kinds of symmetries:
Circular permutations



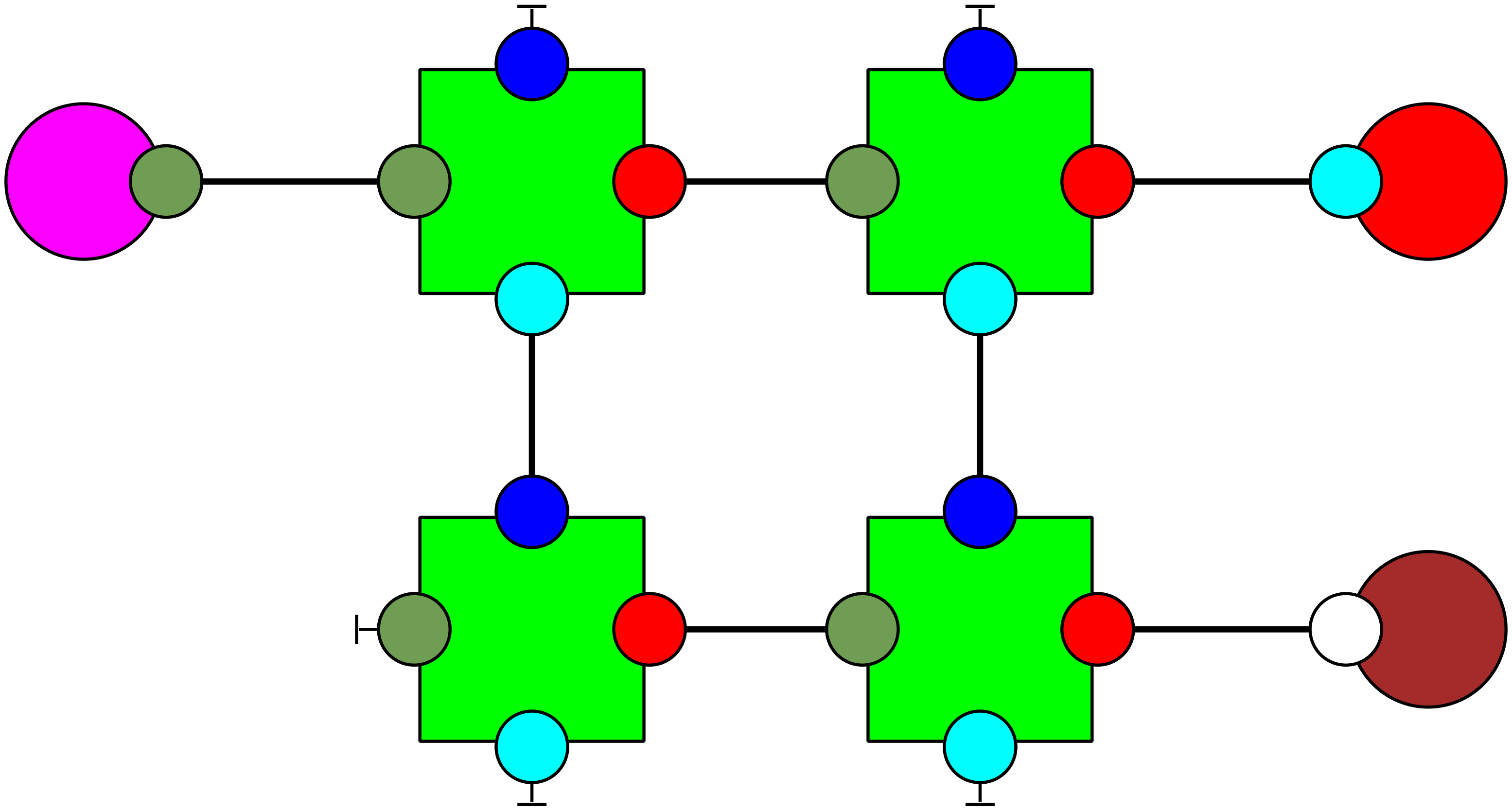
Other kinds of symmetries: Homogeneous symmetries

We can compute a horizontal reflection.



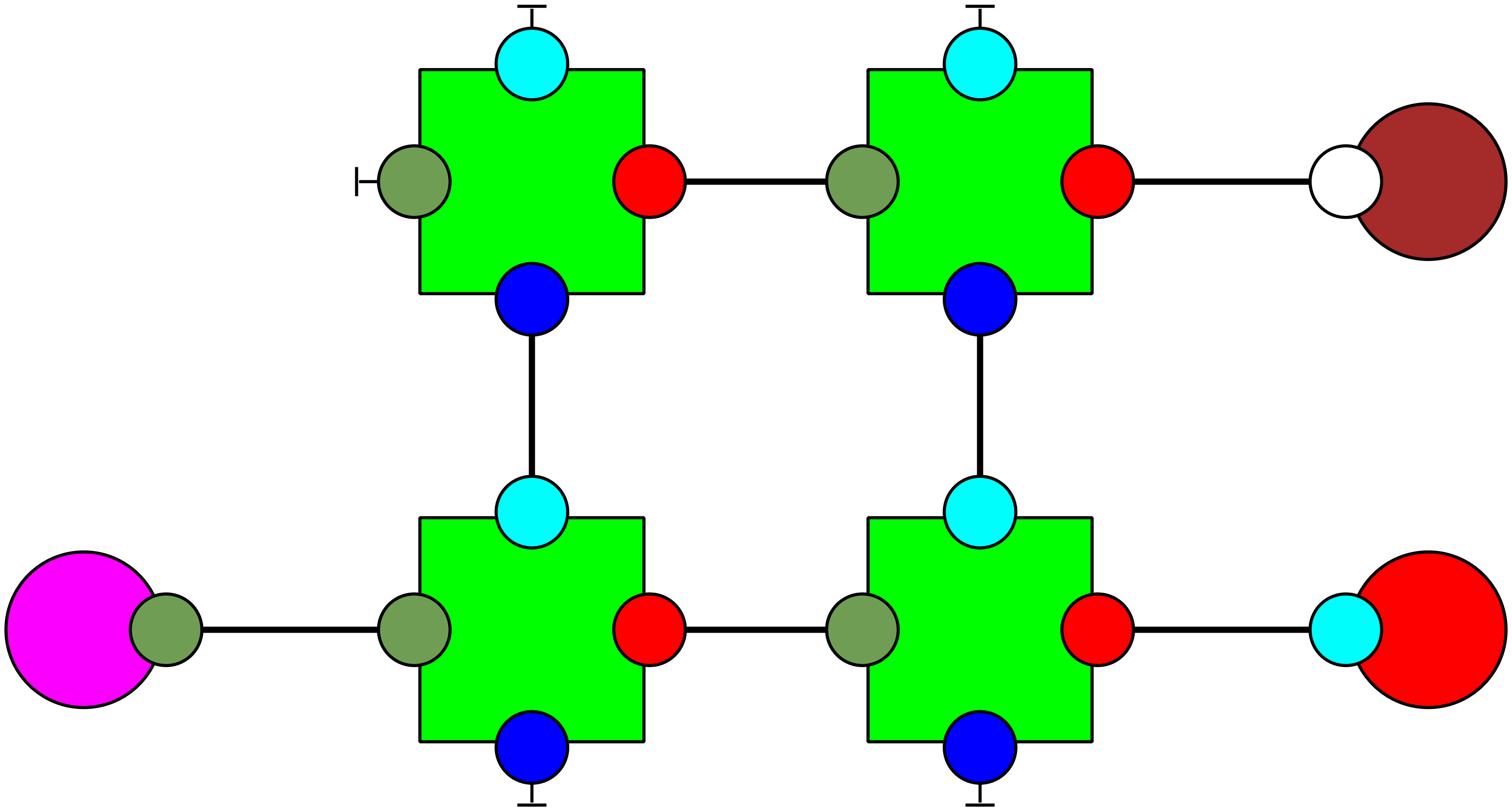
Other kinds of symmetries: Homogeneous symmetries

We can compute a horizontal reflection.



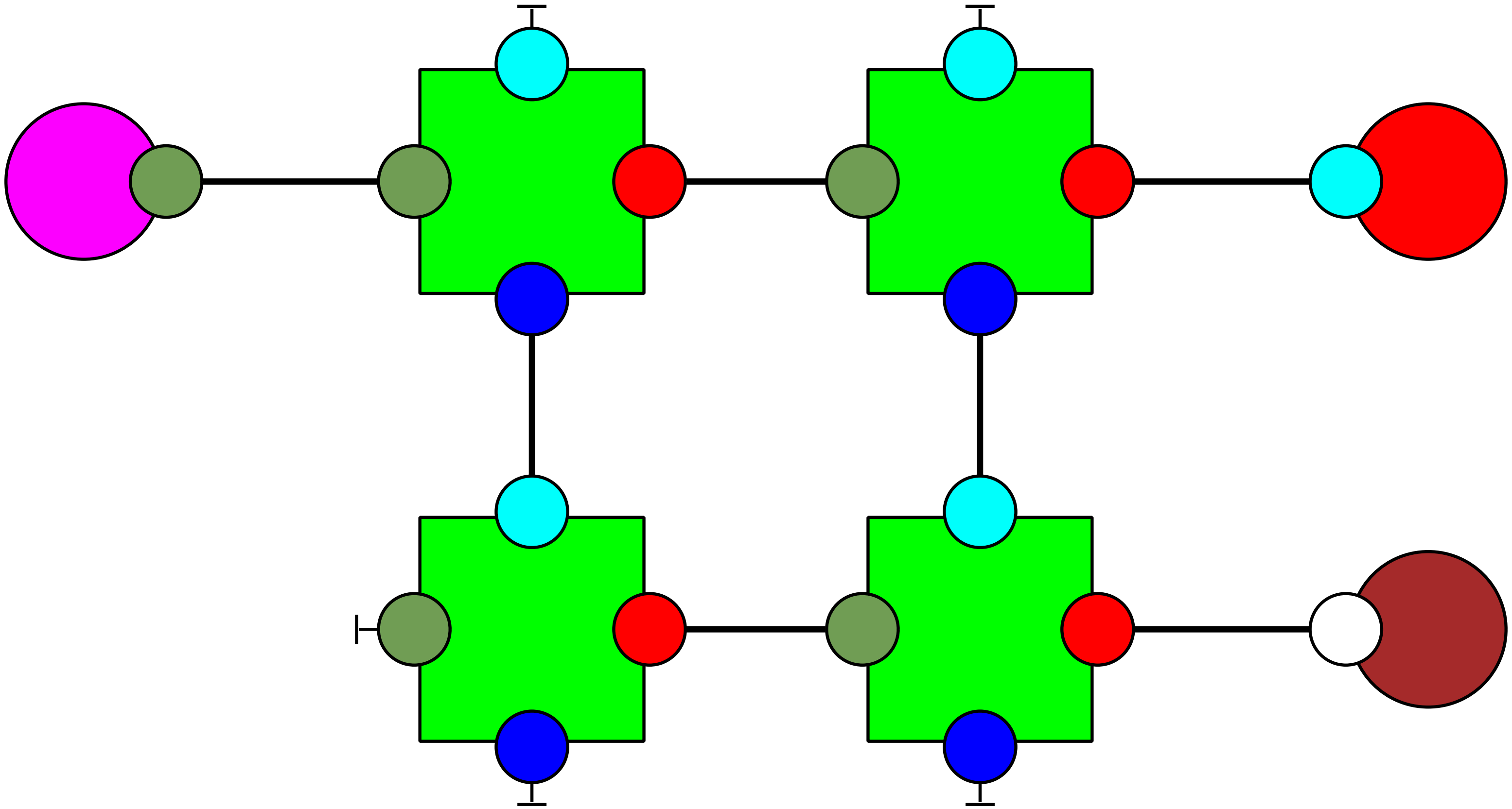
Other kinds of symmetries: Homogeneous symmetries

We can compute a horizontal reflection.



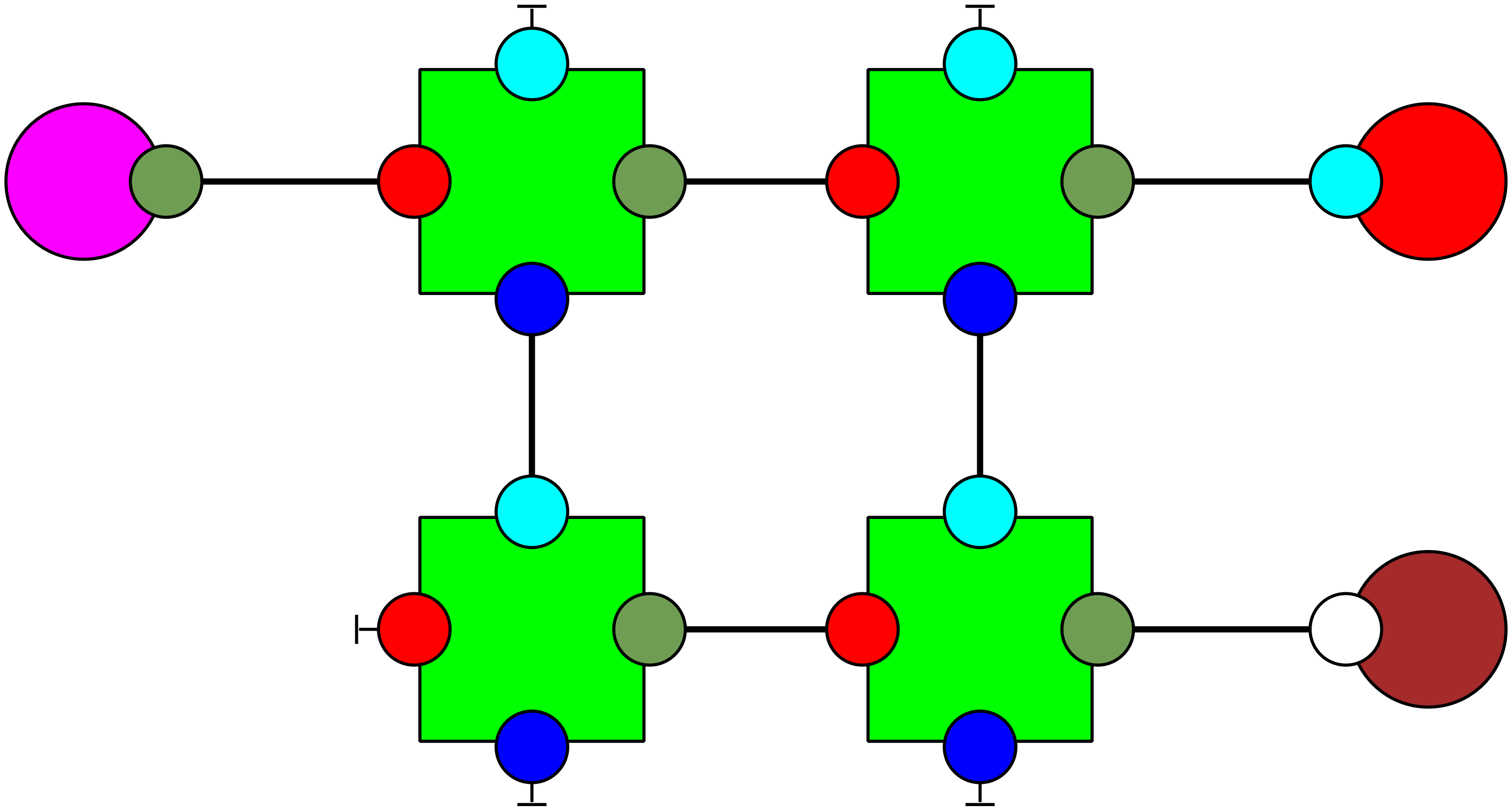
Other kinds of symmetries: Homogeneous symmetries

We can compute a vertical reflection.



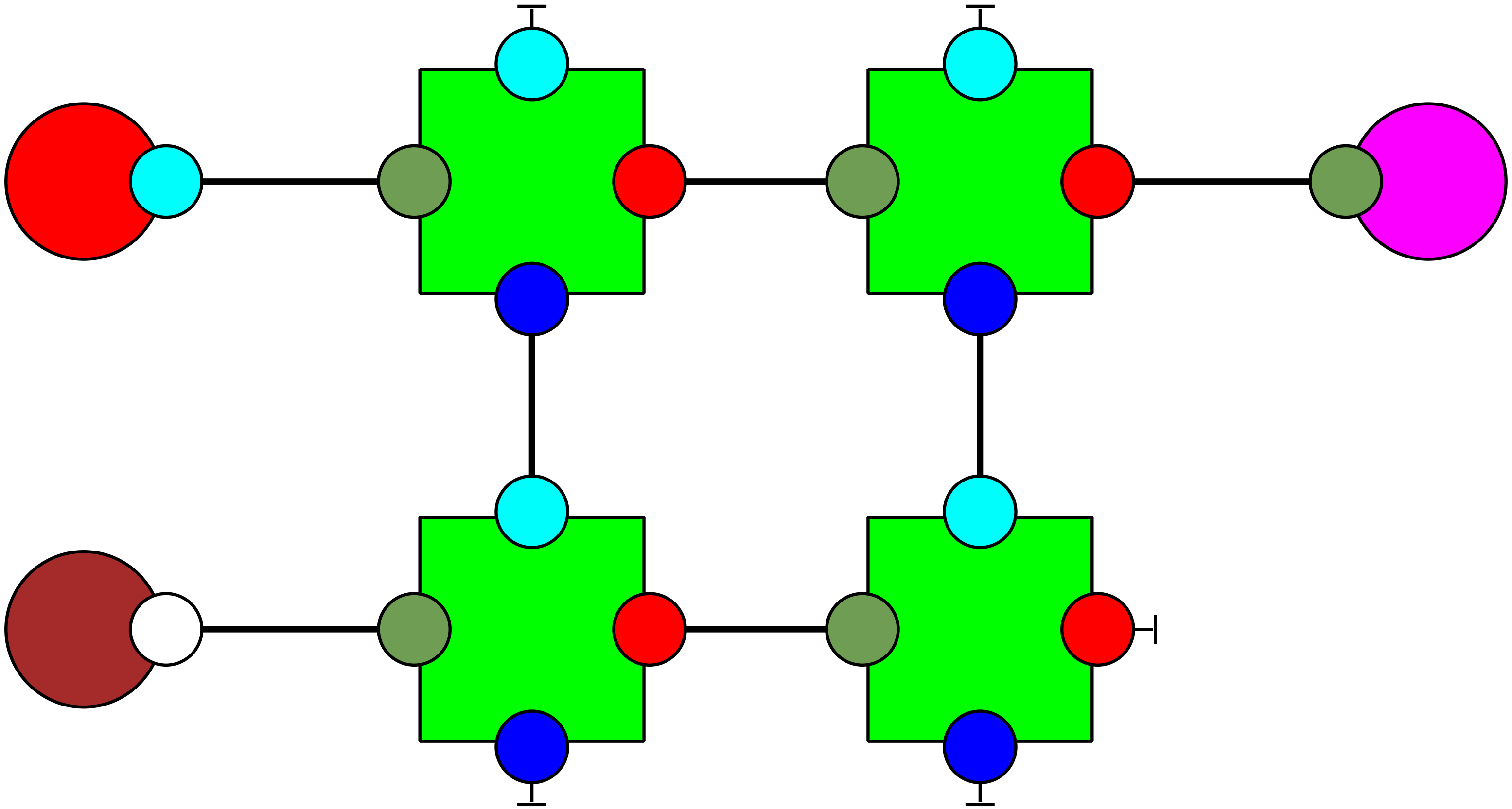
Other kinds of symmetries: Homogeneous symmetries

We can compute a vertical reflection.



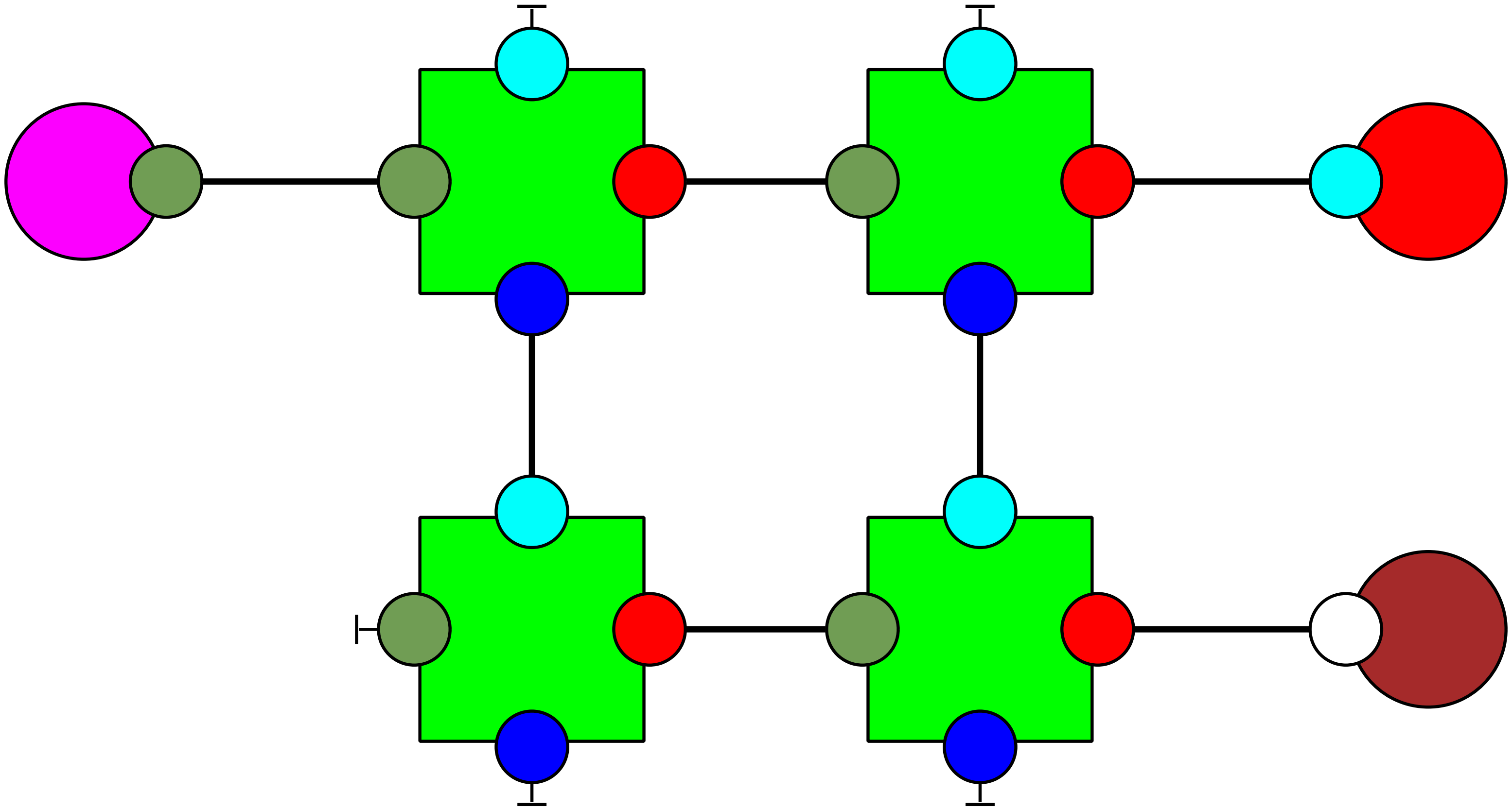
Other kinds of symmetries:
Homogeneous symmetries

We can compute a vertical reflection.



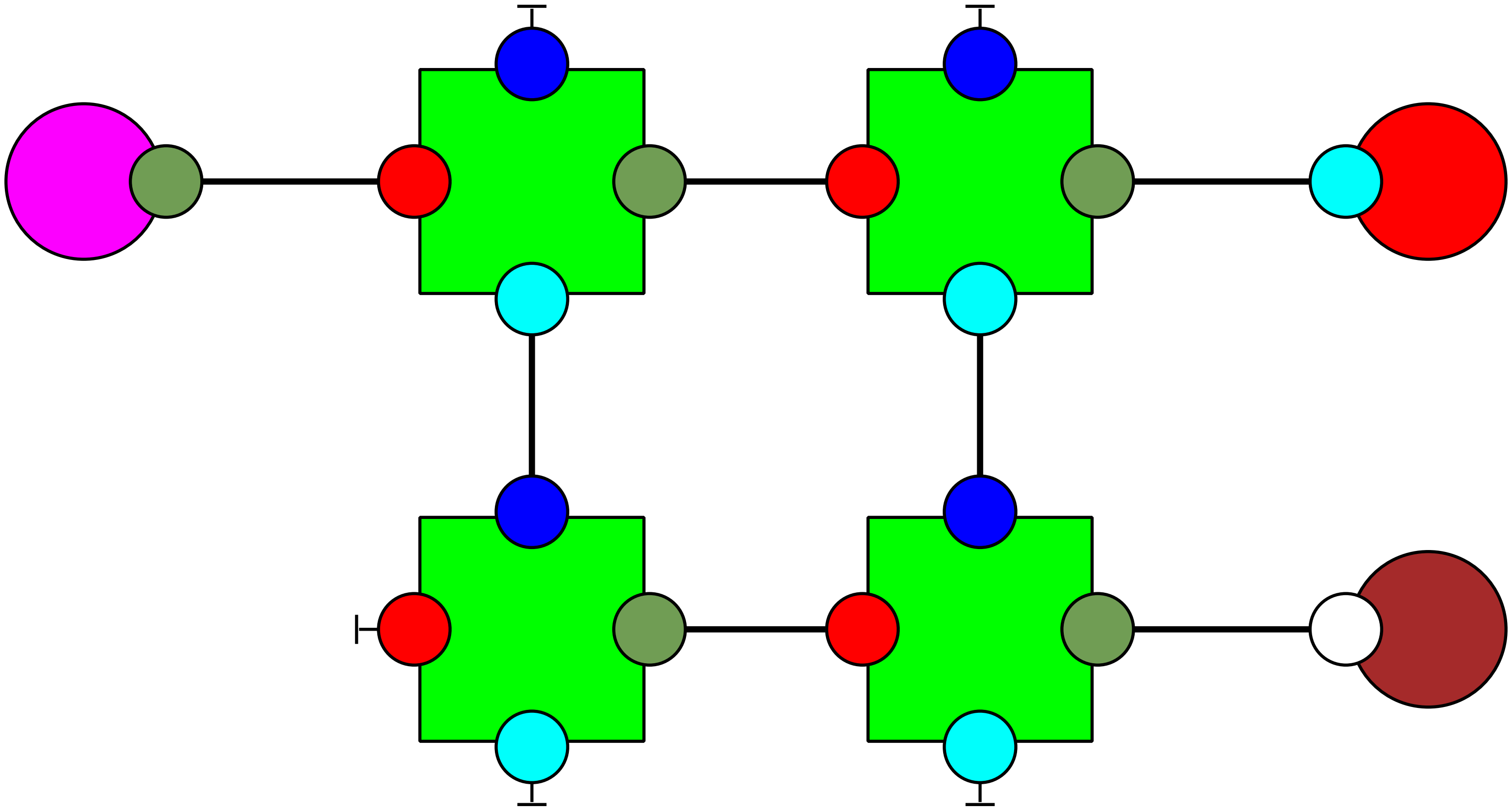
Other kinds of symmetries: Homogeneous symmetries

We can compute both reflections.



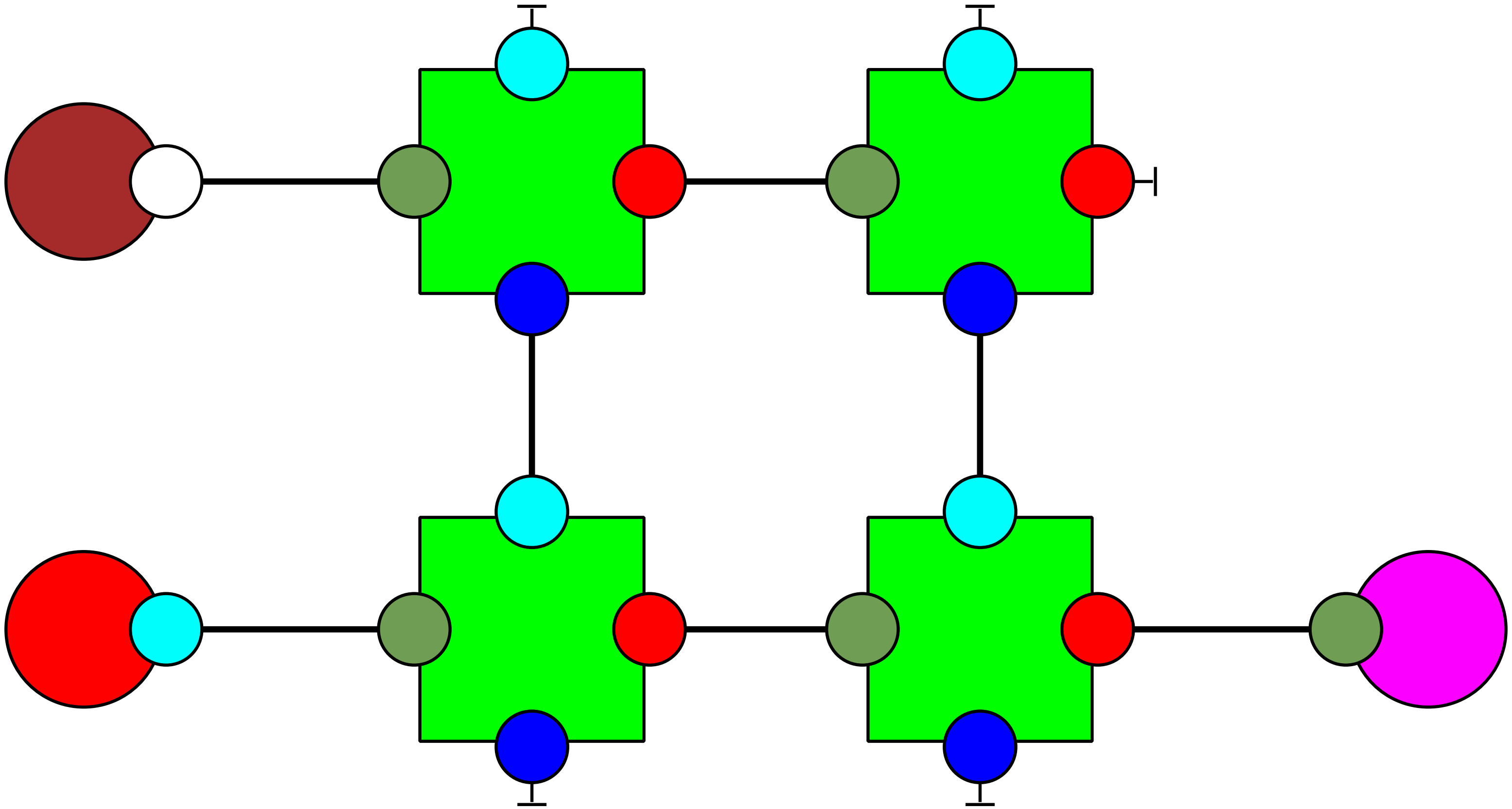
Other kinds of symmetries:
Homogeneous symmetries

We can compute both reflections.



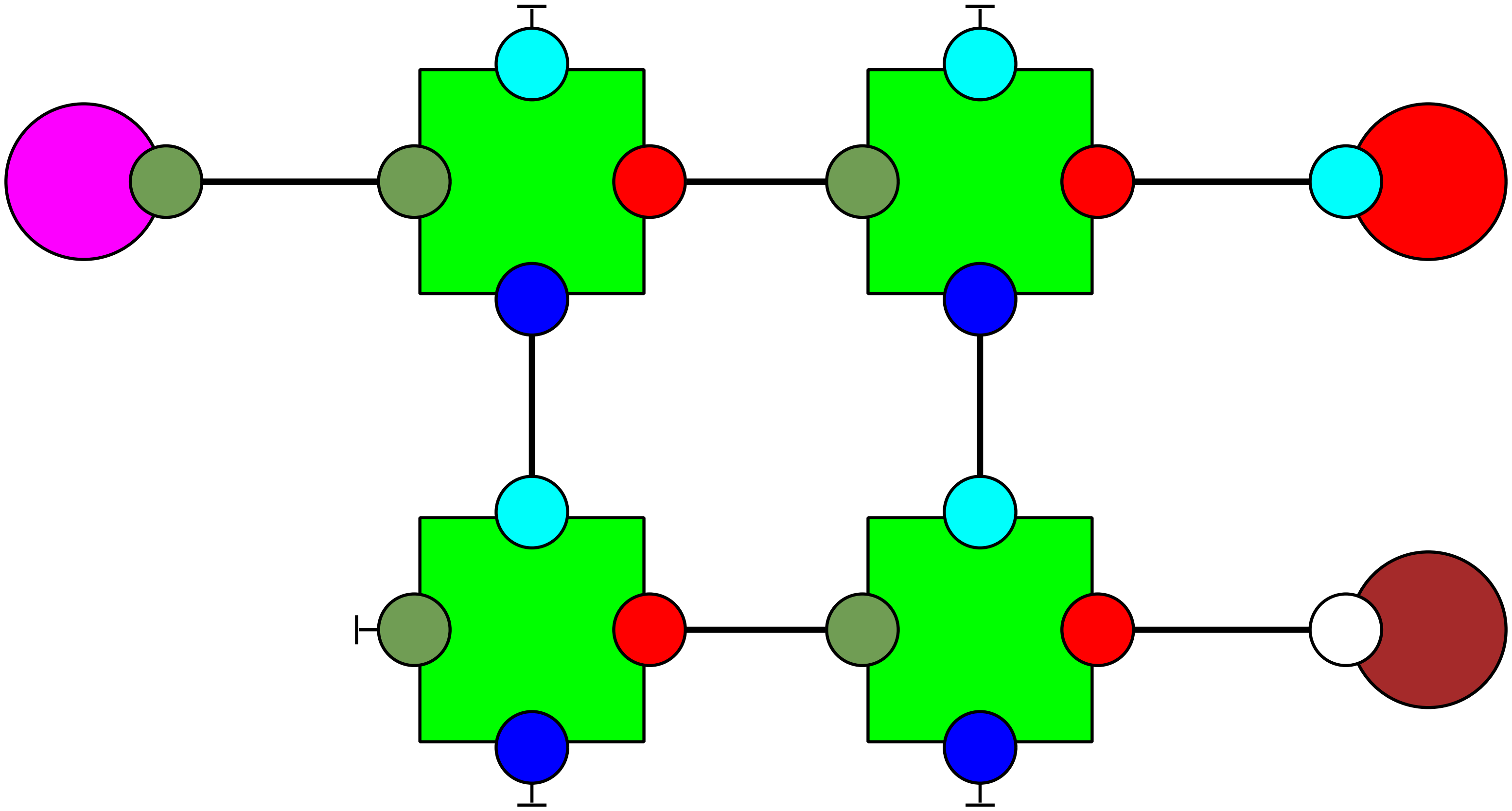
Other kinds of symmetries: Homogeneous symmetries

We can compute both reflections.



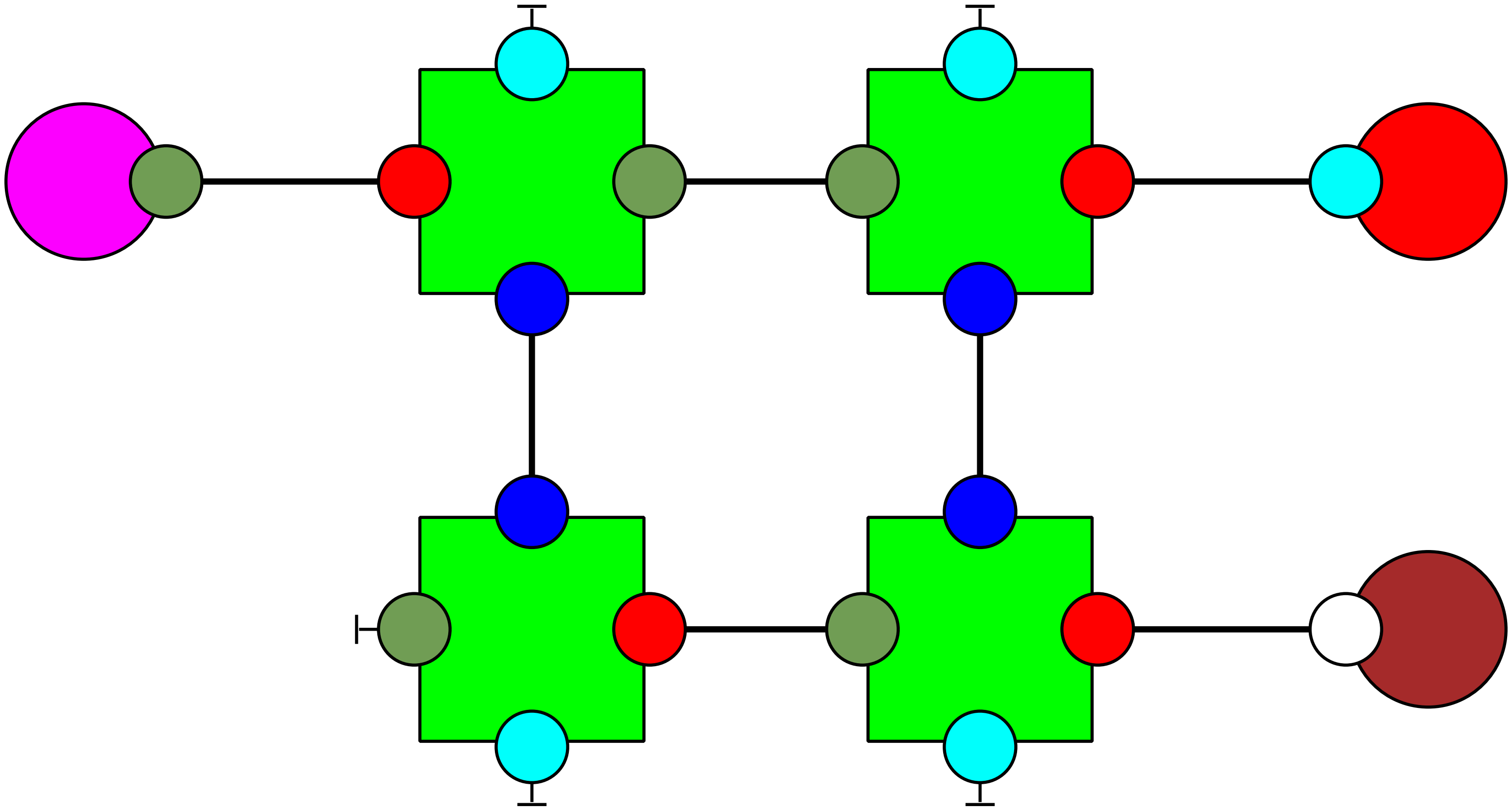
Other kinds of symmetries:
Homogeneous symmetries

But we cannot apply different permutations!!!.



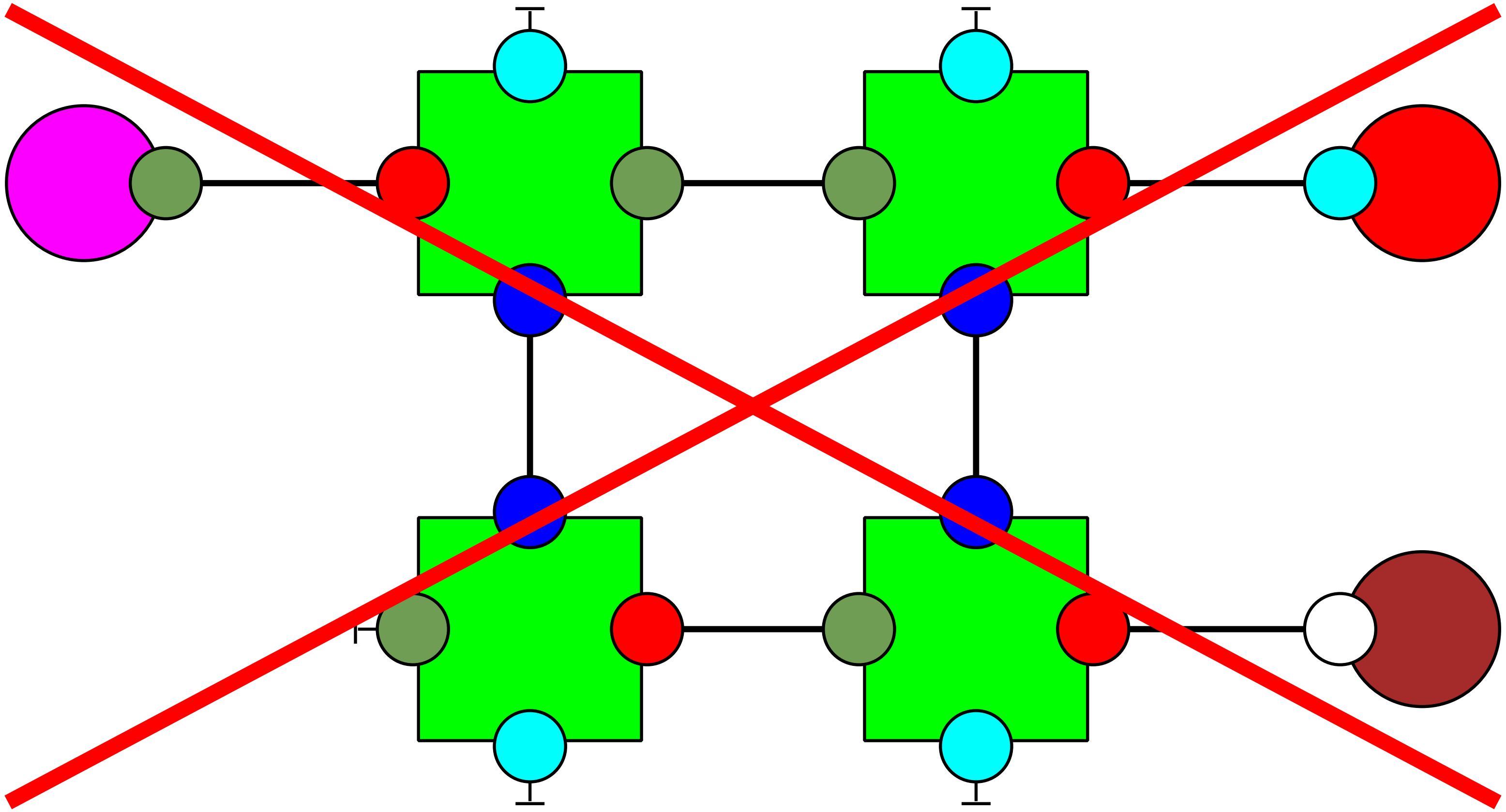
Other kinds of symmetries: Homogeneous symmetries

But we cannot apply different permutations!!!.

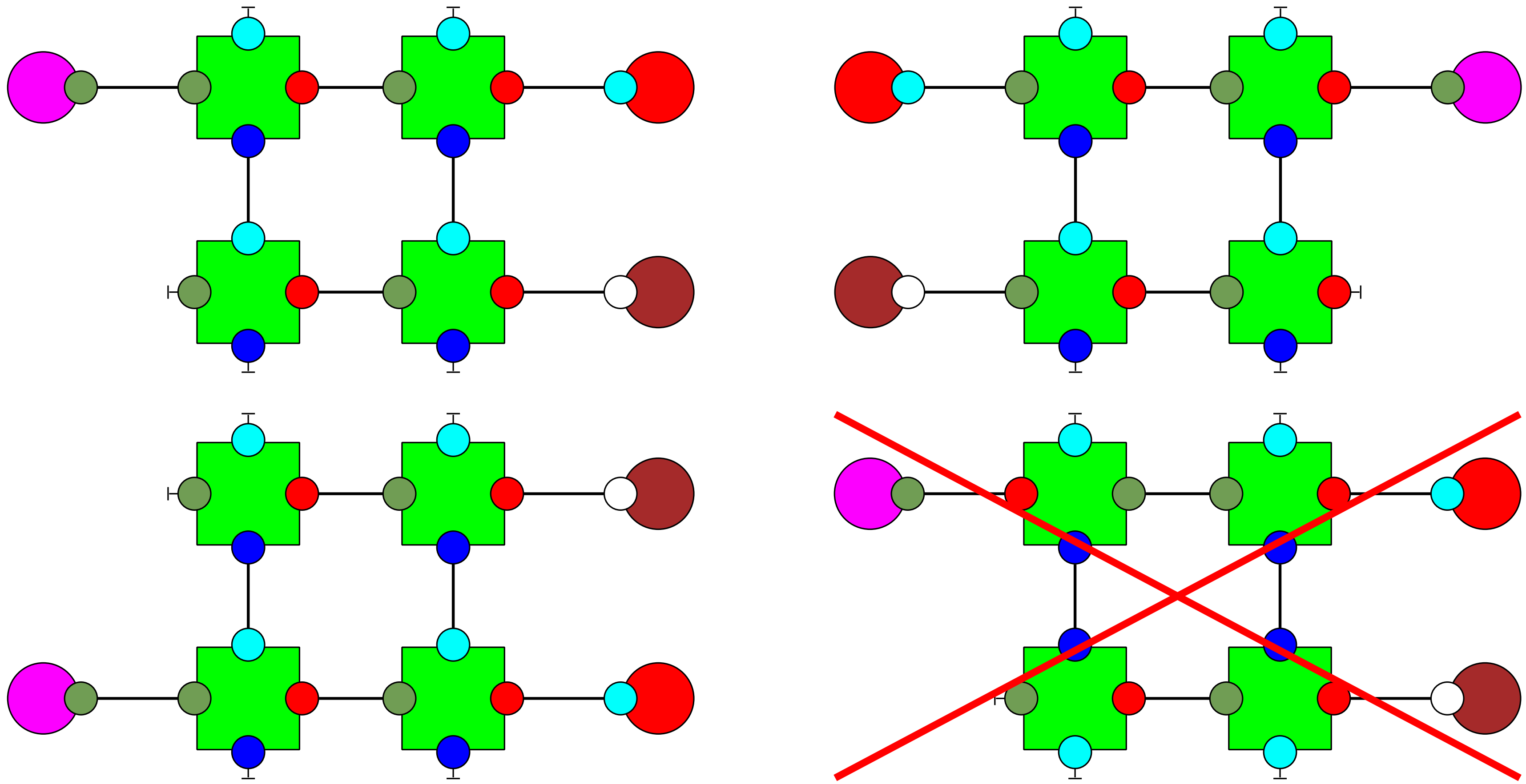


Other kinds of symmetries: Homogeneous symmetries

But we cannot apply different permutations!!!.



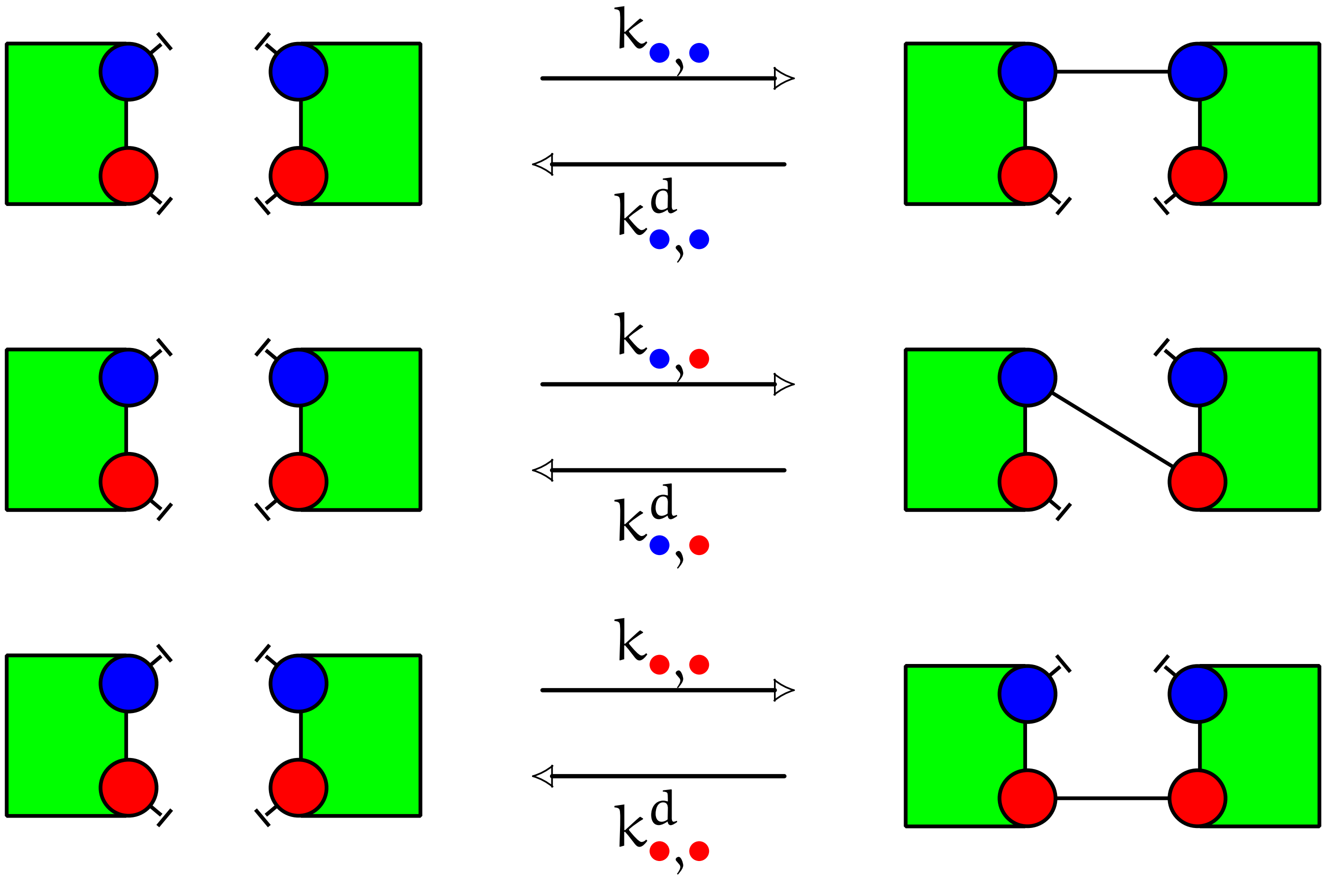
Other kinds of symmetries:
Homogeneous symmetries



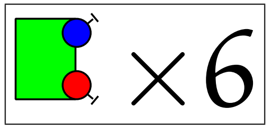
Overview

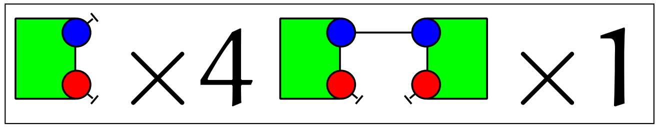
1. Context and motivations
2. Case study
   (a) Symetric model with symmetric initial state
   (b) Symmetric model with non-symmetric initial state
   (c) Non-symmetric model
3. Kappa semantics
4. Symmetries in site-graphs
5. Symmetric models
6. Conclusion

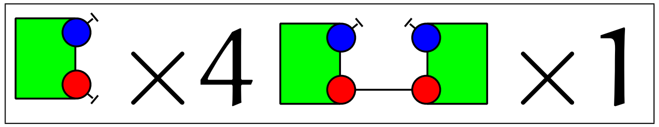
Case study

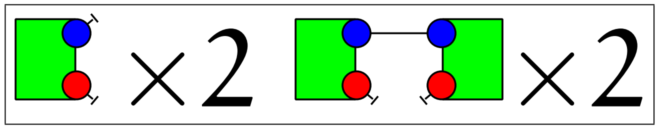


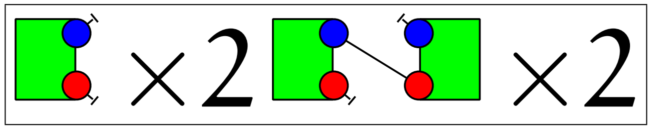
State distribution

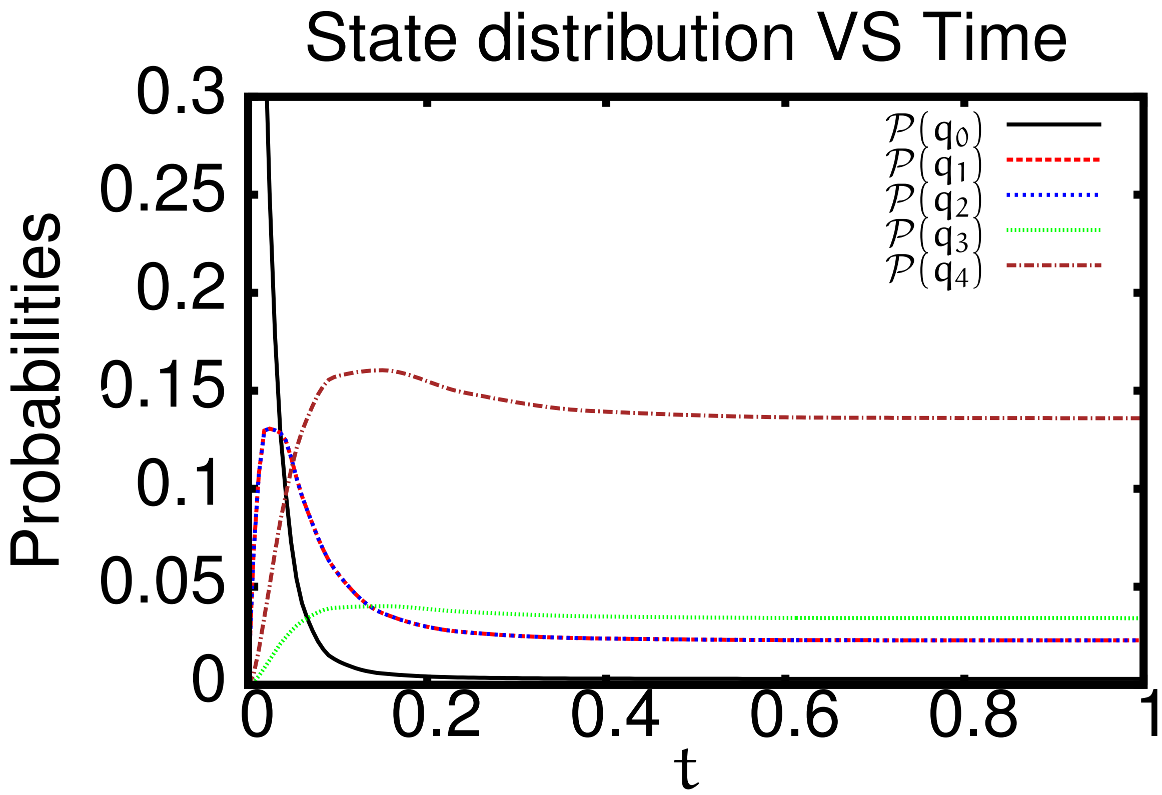
q_0 : 

q_1 : 

q_2 : 

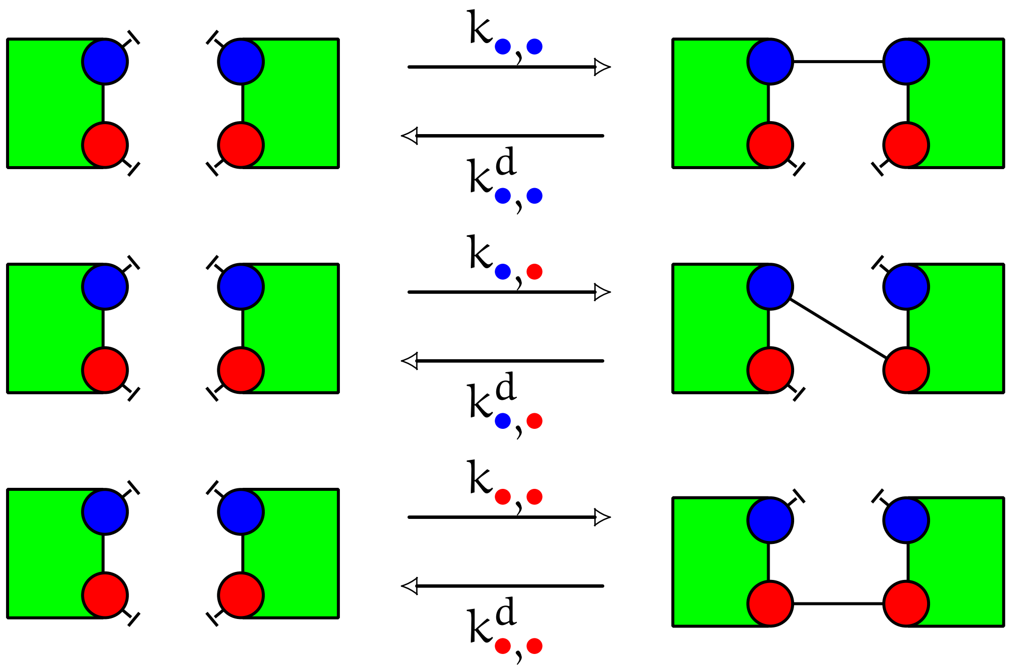
q_3 : 

q_4 : 



with: $$\begin{cases} k_{{\color{blue}\bullet},{\color{blue}\bullet}} = k_{{\color{red}\bullet},{\color{red}\bullet}} = 1 \\ k_{{\color{blue}\bullet},{\color{red}\bullet}} = k^d_{{\color{blue}\bullet},{\color{blue}\bullet}} = k^d_{{\color{red}\bullet},{\color{red}\bullet}} = k^d_{{\color{blue}\bullet},{\color{red}\bullet}} = 2 \\ P(q_0 \mid t = 0) = 1 \end{cases}$$

Lumpability

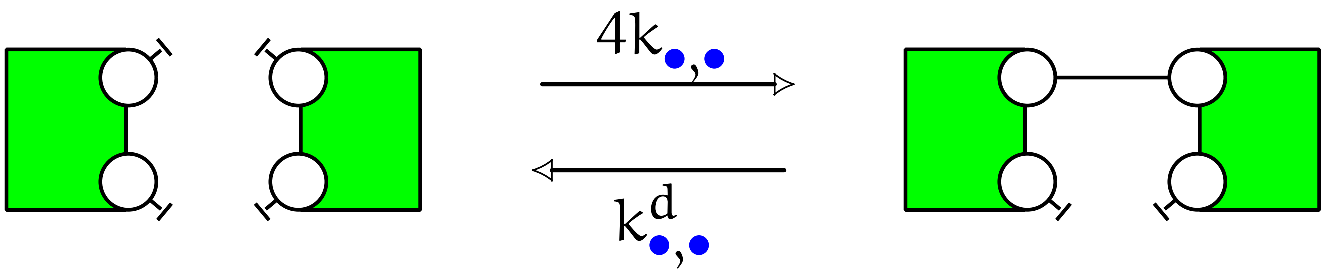


Whenever:

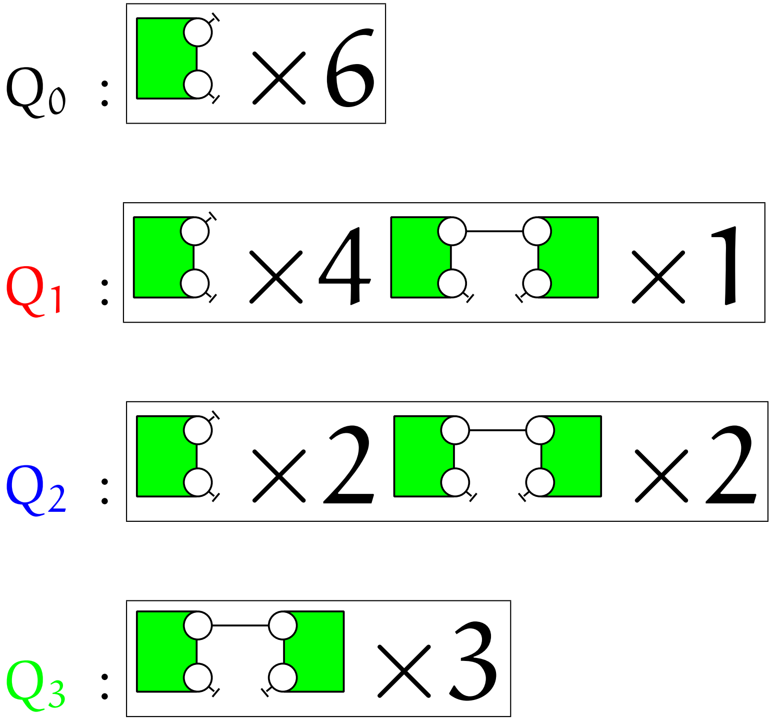
$$\begin{cases} 2k_{\textcolor{blue}{\bullet},\textcolor{blue}{\bullet}} = 2k_{\textcolor{red}{\bullet},\textcolor{red}{\bullet}} = k_{\textcolor{blue}{\bullet},\textcolor{red}{\bullet}} \\ k^{d}_{\textcolor{blue}{\bullet},\textcolor{blue}{\bullet}} = k^{d}_{\textcolor{blue}{\bullet},\textcolor{red}{\bullet}} = k^{d}_{\textcolor{red}{\bullet},\textcolor{red}{\bullet}} \end{cases}$$

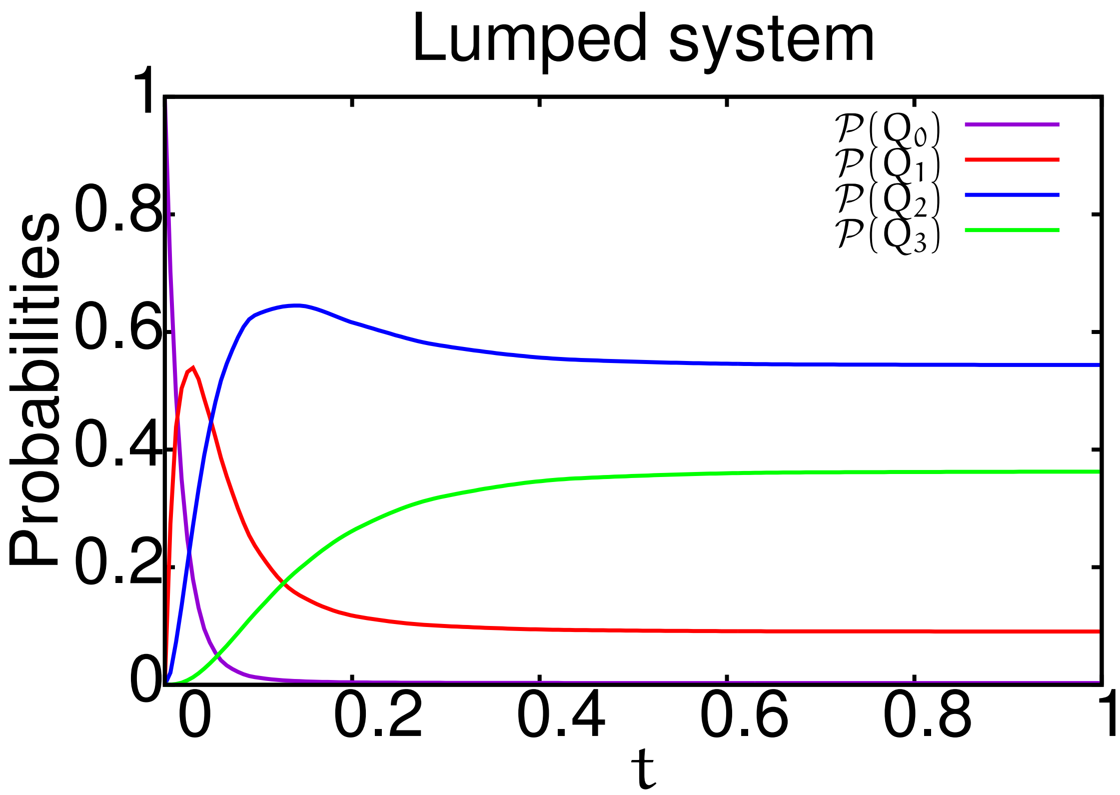
We can lump the system.

Lumped system



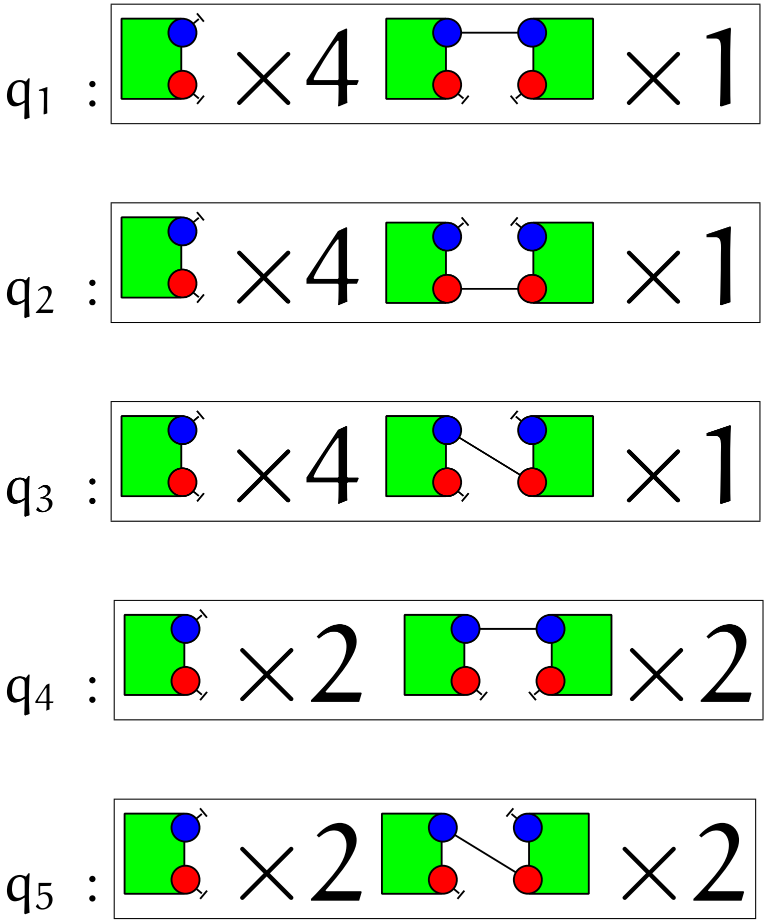
Macrostate distribution

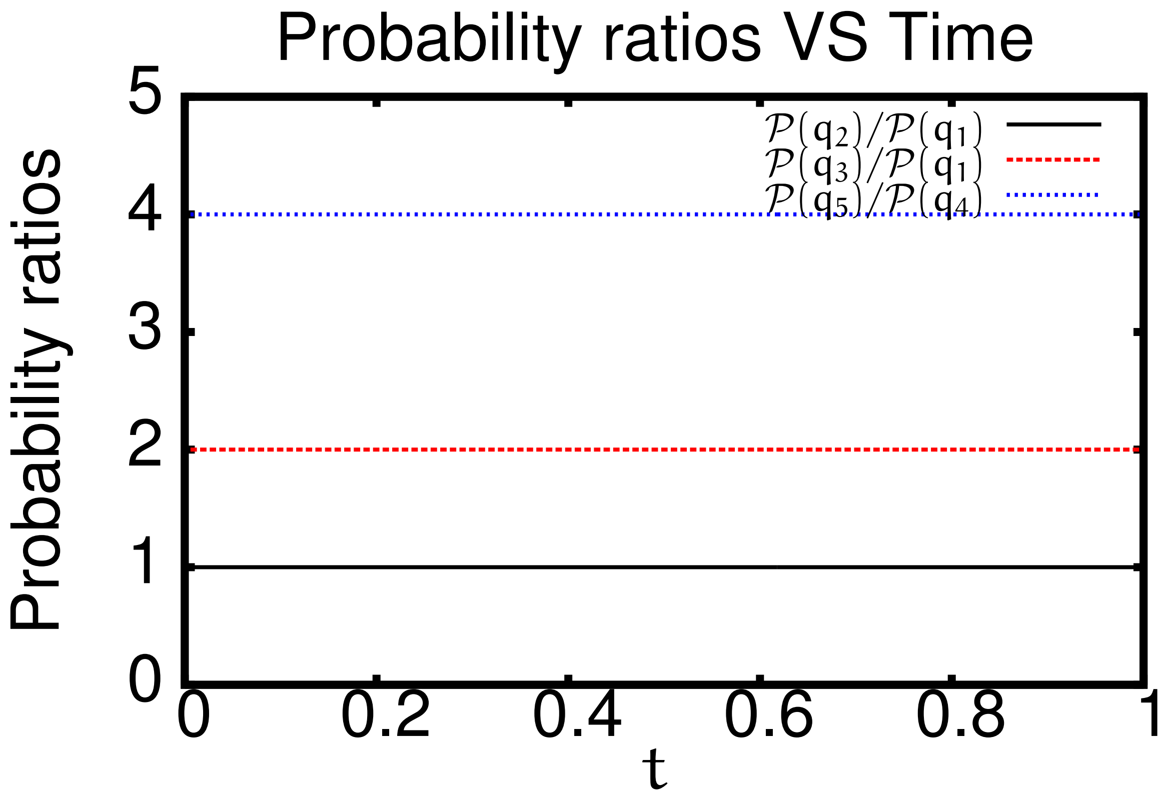




with: $\begin{cases} k_{\bullet,\bullet} = 1 \\ k^{d}_{\bullet,\bullet} = 2 \\ P(q_0 \mid t = 0) = 1 \end{cases}$

Probability ratios



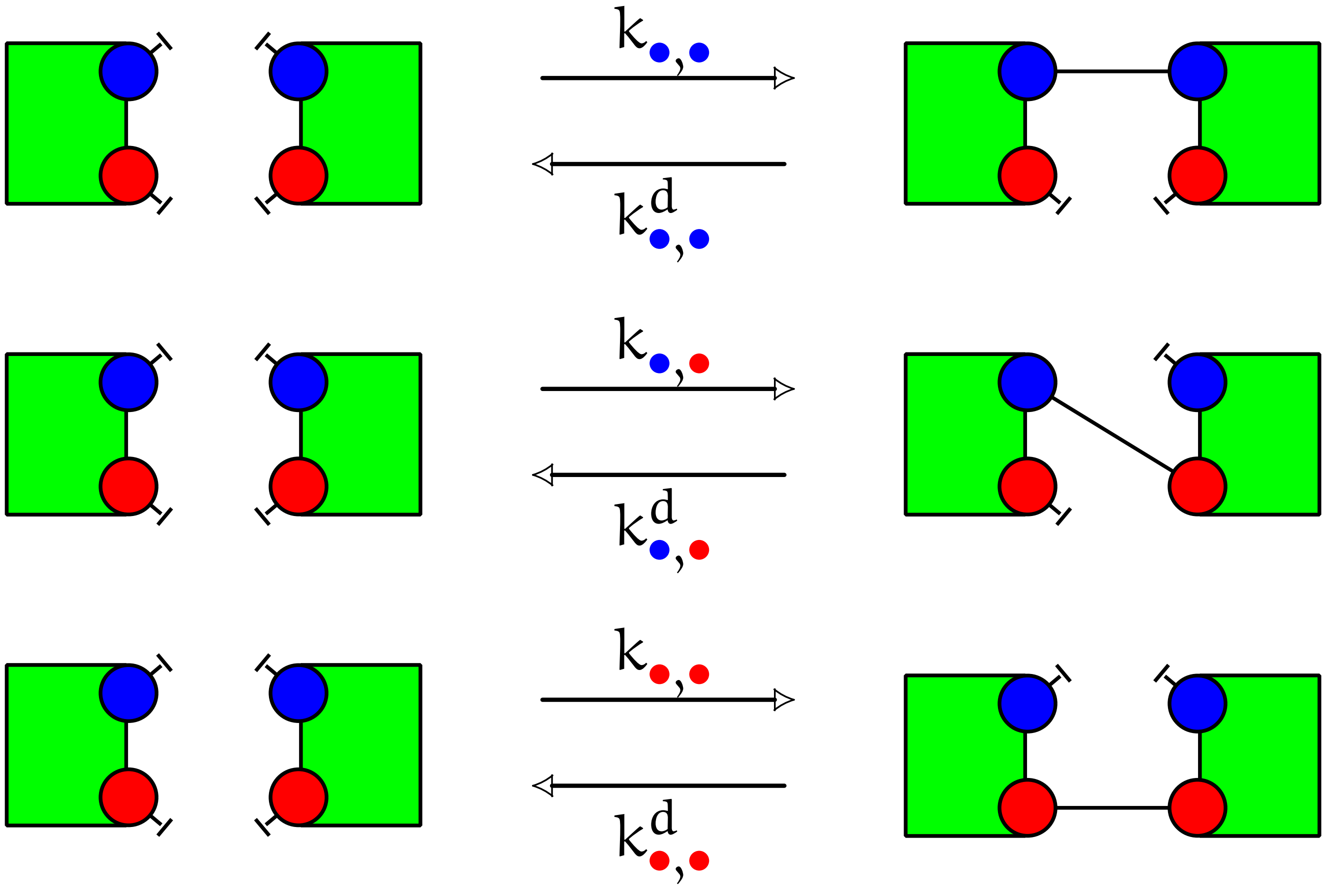


with: $\begin{cases} k_{{\color{blue}\bullet},{\color{blue}\bullet}} = k_{{\color{red}\bullet},{\color{red}\bullet}} = 1 \\ k_{{\color{blue}\bullet},{\color{red}\bullet}} = k^{d}_{{\color{blue}\bullet},{\color{blue}\bullet}} = k^{d}_{{\color{red}\bullet},{\color{red}\bullet}} = k^{d}_{{\color{blue}\bullet},{\color{red}\bullet}} = 2 \\ P(q_0 \mid t = 0) = 1 \end{cases}$

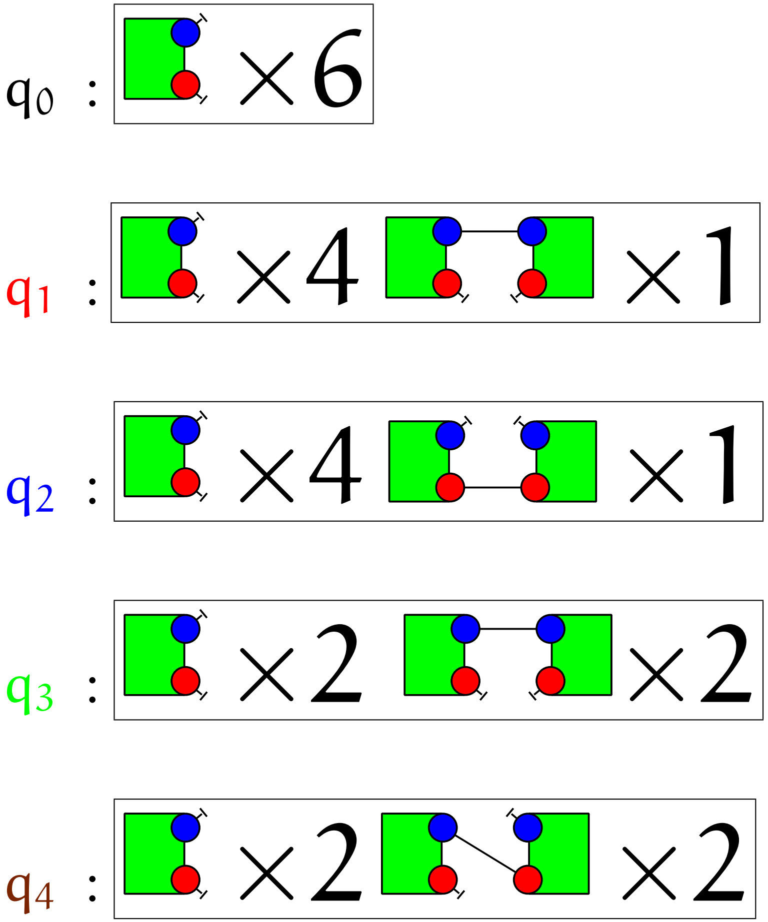
Overview

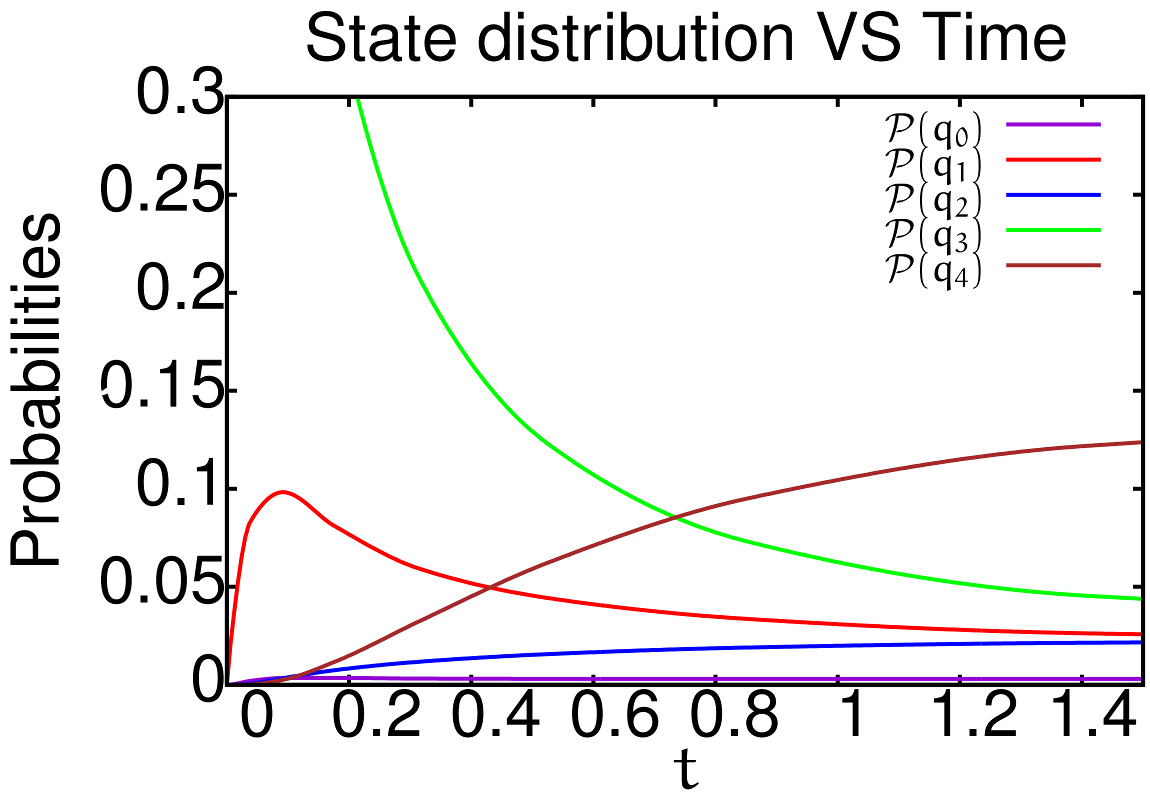
1. Context and motivations
2. Case study
   (a) Symetric model with symmetric initial state
   (b) Symmetric model with non-symmetric initial state
   (c) Non-symmetric model
3. Kappa semantics
4. Symmetries in site-graphs
5. Symmetric models
6. Conclusion

Model



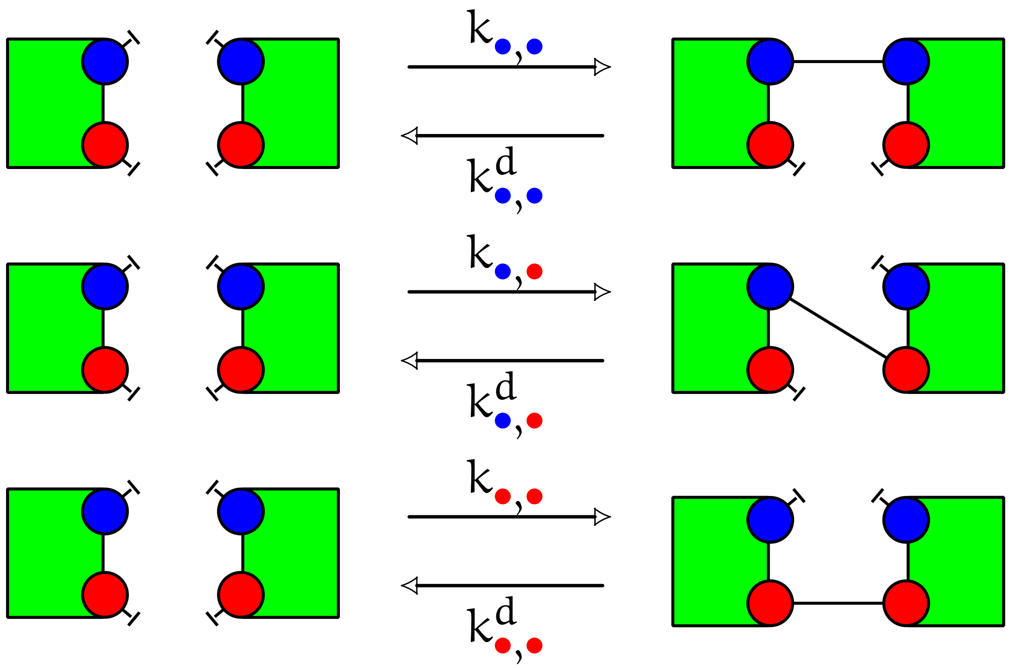
State distribution





with: $\begin{cases} k_{\bullet,\bullet} = k_{\bullet,\bullet} = 1 \\ k_{\bullet,\bullet} = k^{d}_{\bullet,\bullet} = k^{d}_{\bullet,\bullet} = k^{d}_{\bullet,\bullet} = 2 \\ P(q_3 \mid t = 0) = 1 \end{cases}$

Lumpability

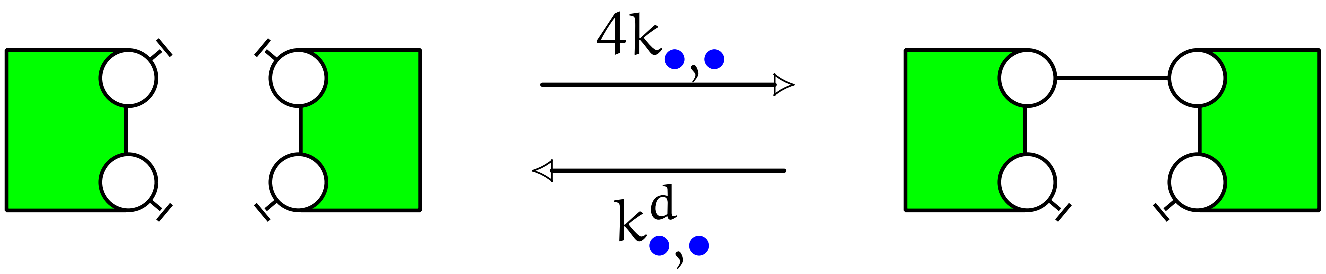


Whenever:

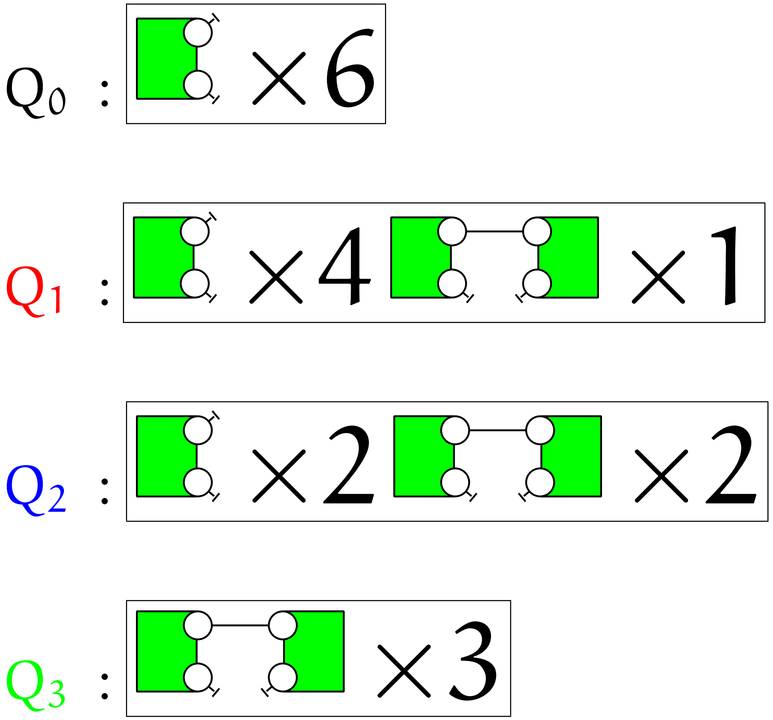
$$\begin{cases} 2k_{{\color{blue}\bullet},{\color{blue}\bullet}} = 2k_{{\color{red}\bullet},{\color{red}\bullet}} = k_{{\color{blue}\bullet},{\color{red}\bullet}} \\ k^{d}_{{\color{blue}\bullet},{\color{blue}\bullet}} = k^{d}_{{\color{blue}\bullet},{\color{red}\bullet}} = k^{d}_{{\color{red}\bullet},{\color{red}\bullet}} \end{cases}$$

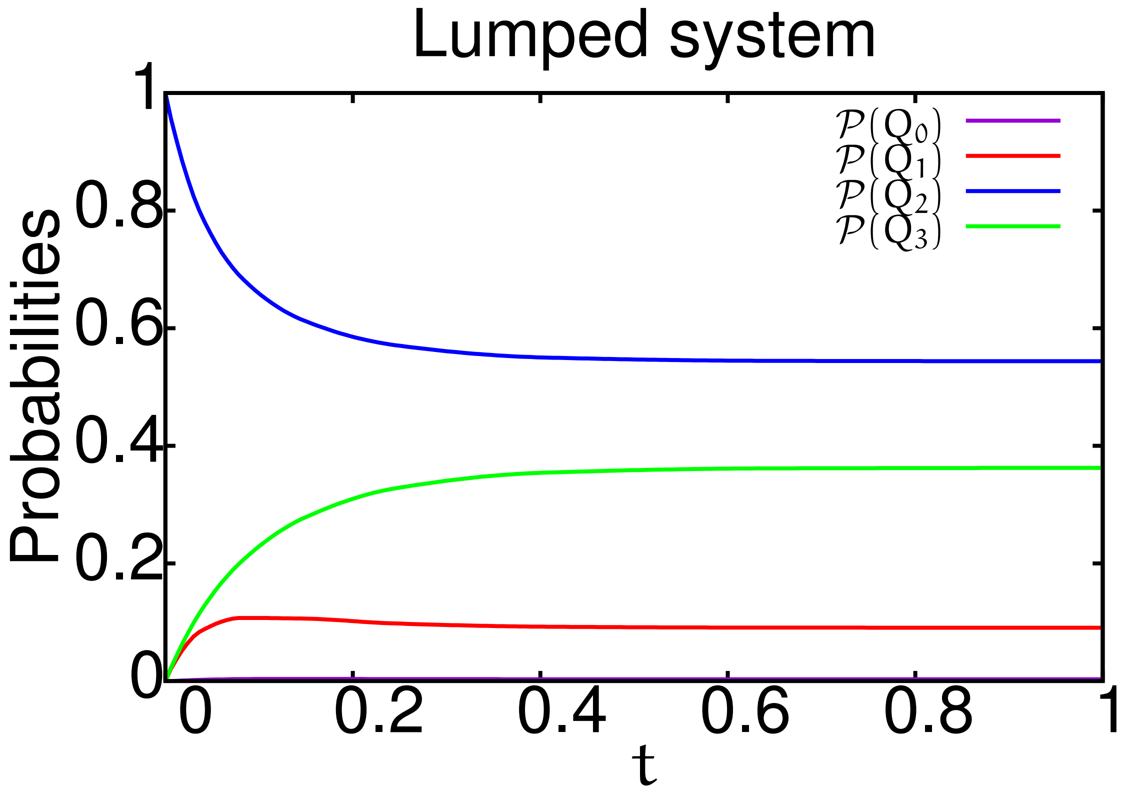
We can lump the system.

Lumped system

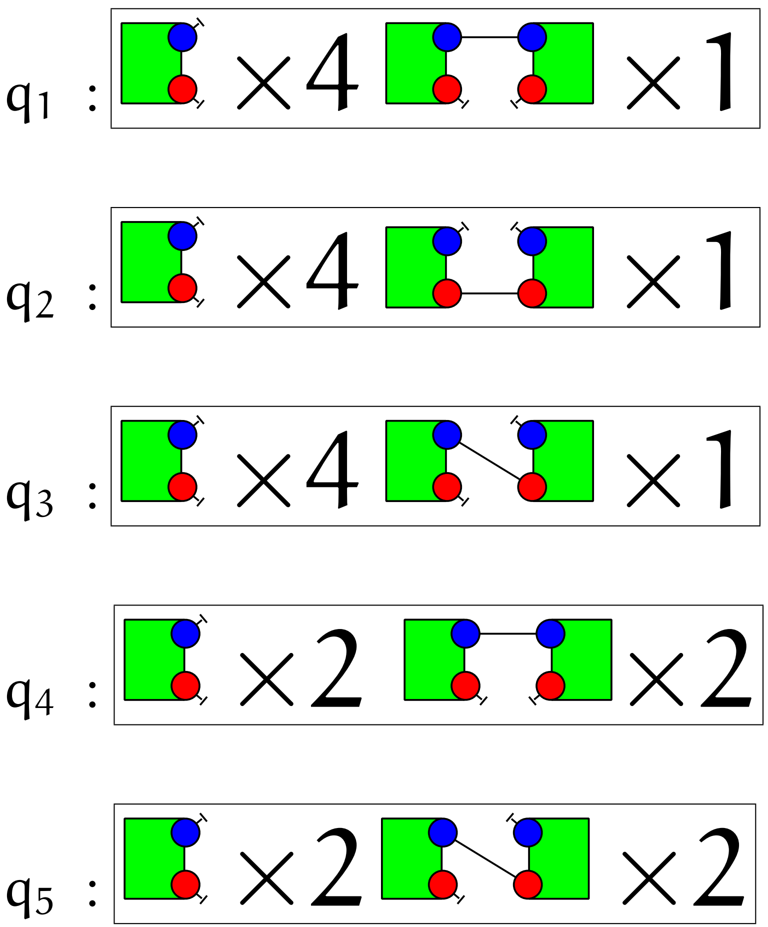


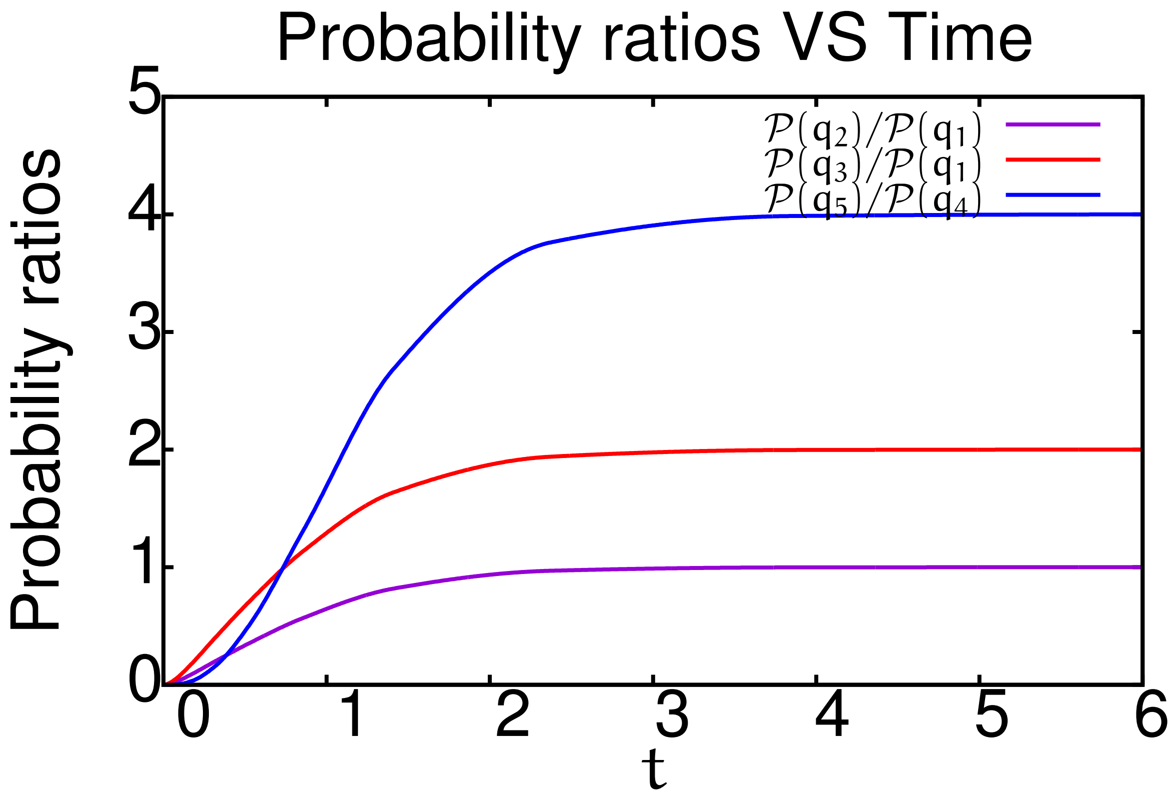
Macrostate distribution





Probability ratios (wrong initial condition)



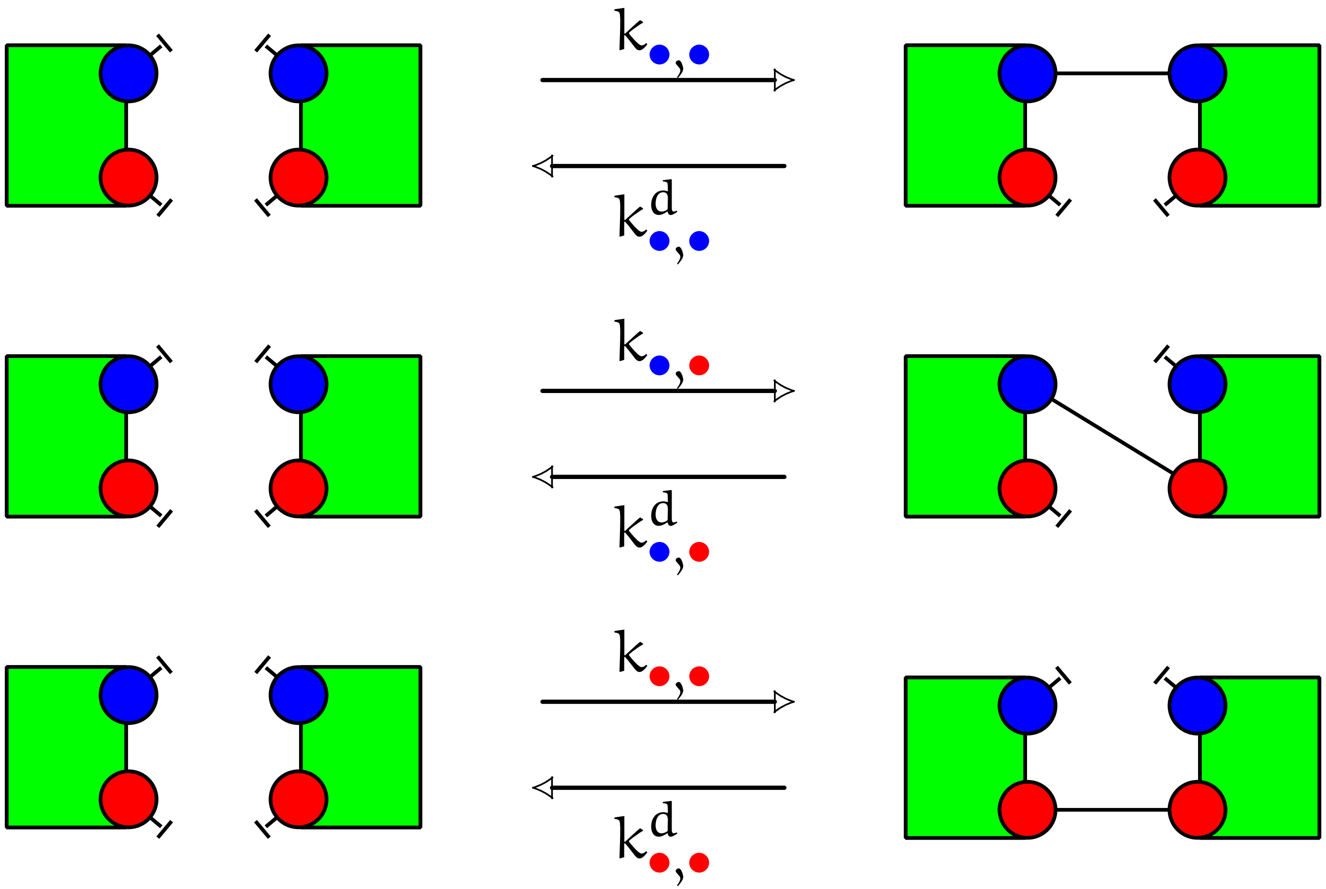


with: $\begin{cases} k_{{\color{blue}\bullet},{\color{blue}\bullet}} = k_{{\color{red}\bullet},{\color{red}\bullet}} = 1 \\ k_{{\color{blue}\bullet},{\color{red}\bullet}} = k^{d}_{{\color{blue}\bullet},{\color{blue}\bullet}} = k^{d}_{{\color{red}\bullet},{\color{red}\bullet}} = k^{d}_{{\color{blue}\bullet},{\color{red}\bullet}} = 2 \\ P(q_4 \mid t = 0) = 1 \end{cases}$

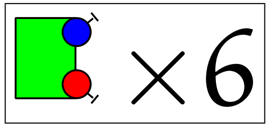
Overview

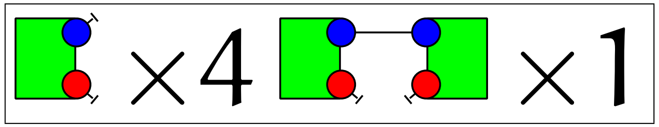
1. Context and motivations
2. Case study
   (a) Symetric model with symmetric initial state
   (b) Symmetric model with non-symmetric initial state
   (c) Non-symmetric model
3. Kappa semantics
4. Symmetries in site-graphs
5. Symmetric models
6. Conclusion

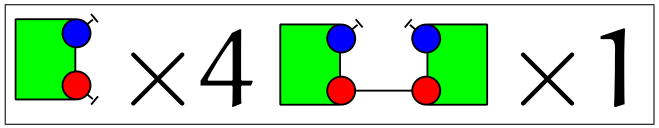
Model

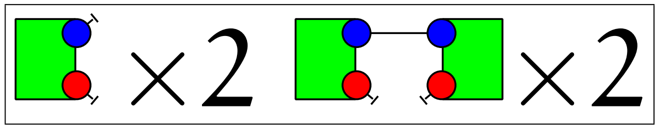


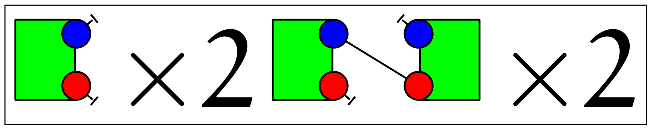
State distribution

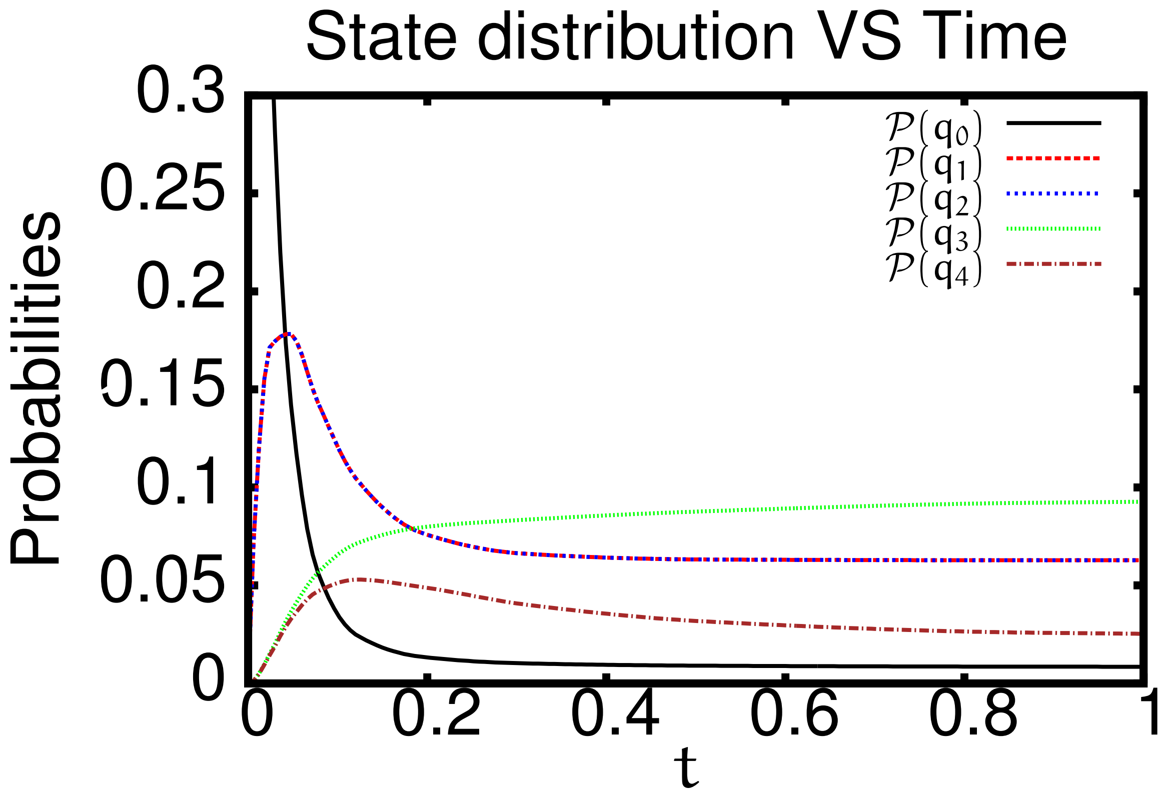
q_0 : 

q_1 : 

q_2 : 

q_3 : 

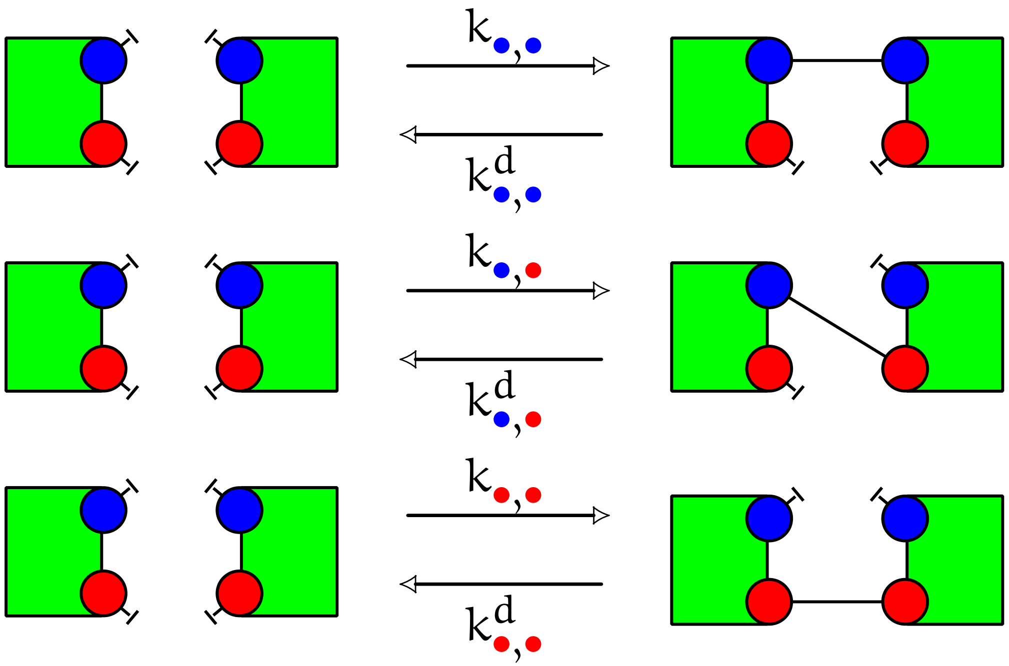
q_4 : 



with:

$$\begin{cases} k_{{\color{blue}\bullet},{\color{blue}\bullet}} = k_{{\color{red}\bullet},{\color{red}\bullet}} = k_{{\color{blue}\bullet},{\color{red}\bullet}} = 1 \\ k^d_{{\color{blue}\bullet},{\color{blue}\bullet}} = k^d_{{\color{red}\bullet},{\color{red}\bullet}} = 2 \\ k^d_{{\color{blue}\bullet},{\color{red}\bullet}} = 4 \\ P(q_0 \mid t = 0)) = 1 \end{cases}$$

Lumpability



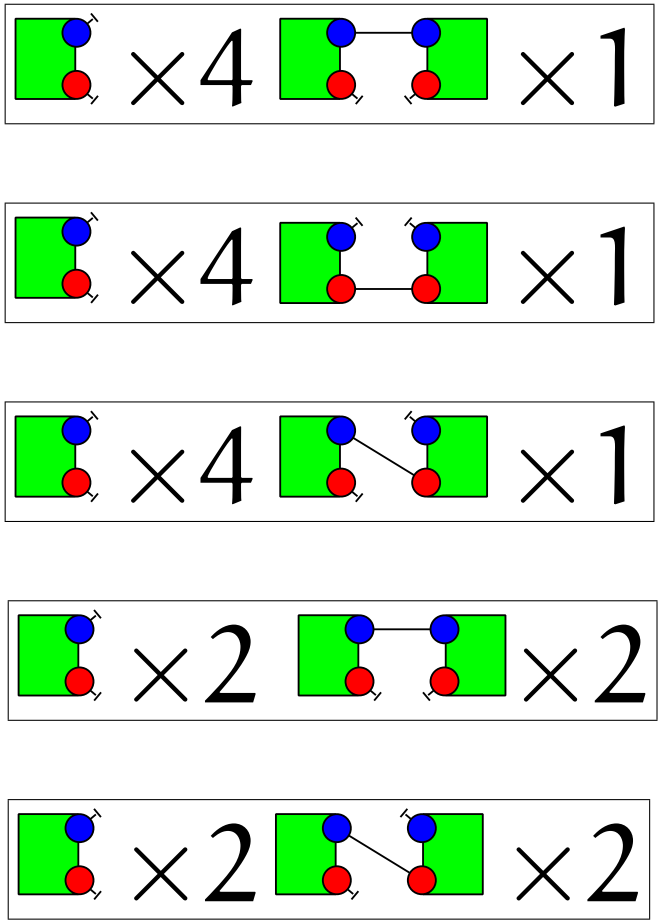
In general, when the following system:

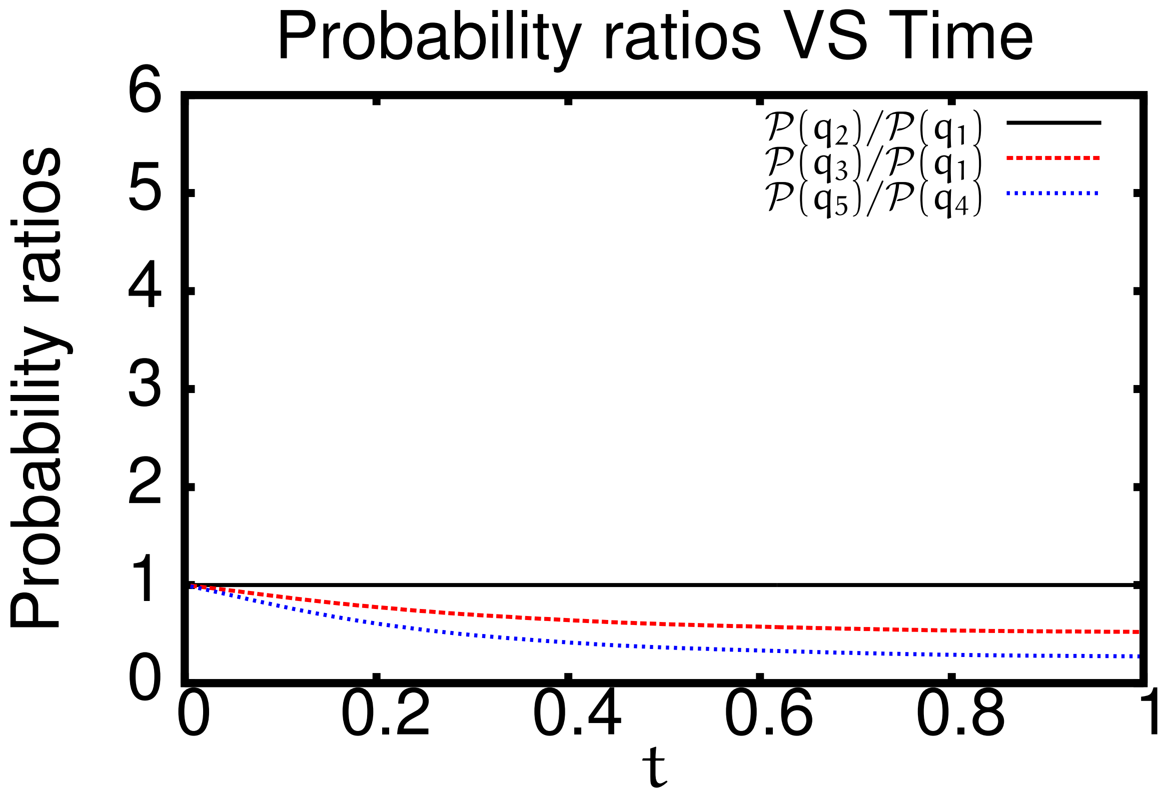
$$\begin{cases} 2k_{{\color{blue}\bullet},{\color{blue}\bullet}} = 2k_{{\color{red}\bullet},{\color{red}\bullet}} = k_{{\color{blue}\bullet},{\color{red}\bullet}} \\ k^{d}_{{\color{blue}\bullet},{\color{blue}\bullet}} = k^{d}_{{\color{blue}\bullet},{\color{red}\bullet}} = k^{d}_{{\color{red}\bullet},{\color{red}\bullet}} \end{cases}$$

is not satisfied, we cannot lump the system.

Probability ratios (wrong coefficients)

q_1 :
q_2 :
q_3 :
q_4 :
q_5 :





with:

$$\begin{cases} k_{\bullet,\bullet} = k_{\bullet,\bullet} = k_{\bullet,\bullet} = 1 \\ k^d_{\bullet,\bullet} = k^d_{\bullet,\bullet} = 2 \\ k^d_{\bullet,\bullet} = 4 \\ P(q_0 \mid t = 0)) = 1 \end{cases}$$

In this talk

An algebraic notion of symmetries over site graphs:

- compatible with the SPO (Single Push-Out) semantics of Kappa;
- with a notion of subgroups of symmetries;
- with a notion of symmetric models.

Some conditions so that symmetries over a model induce

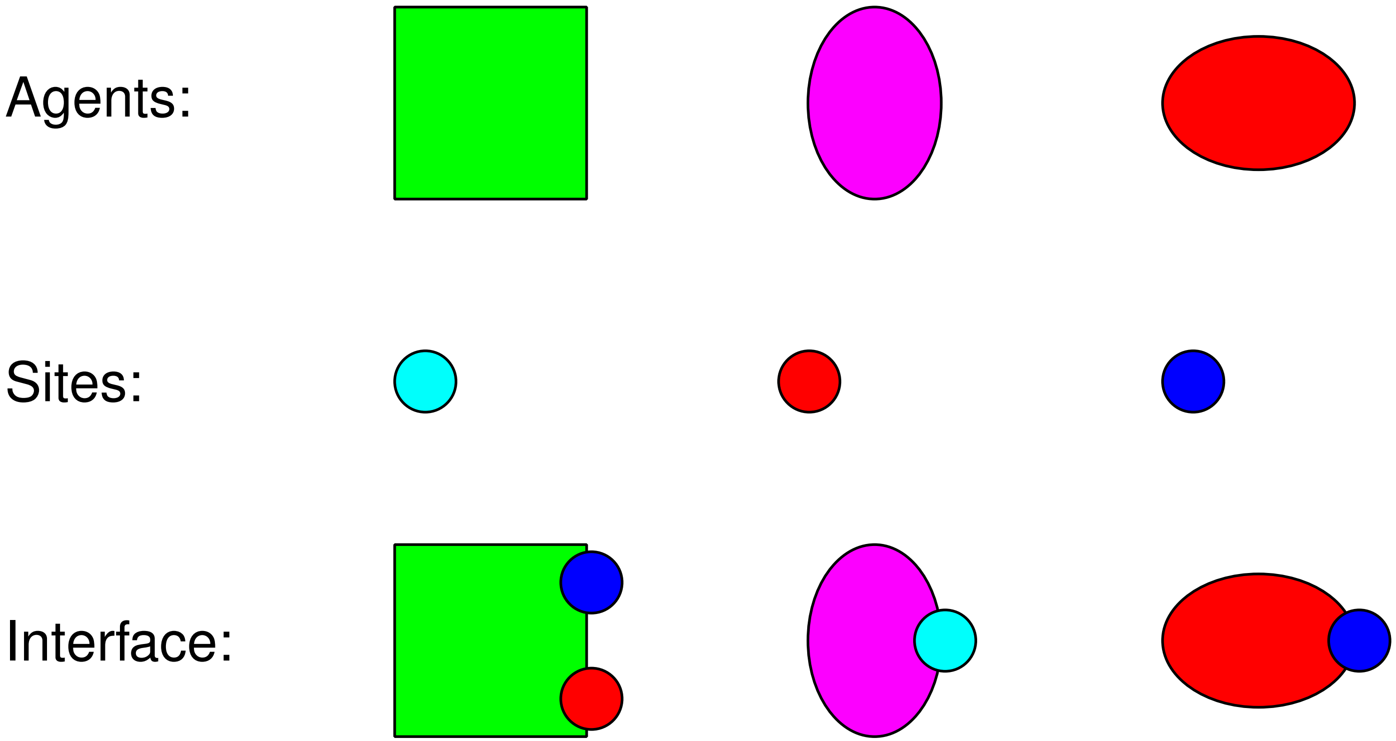
- a forward bisimulation;
- a backward bisimulation.

In this talk, we consider only a side-effect free fragment of Kappa.
The full language is handled with in, the paper.

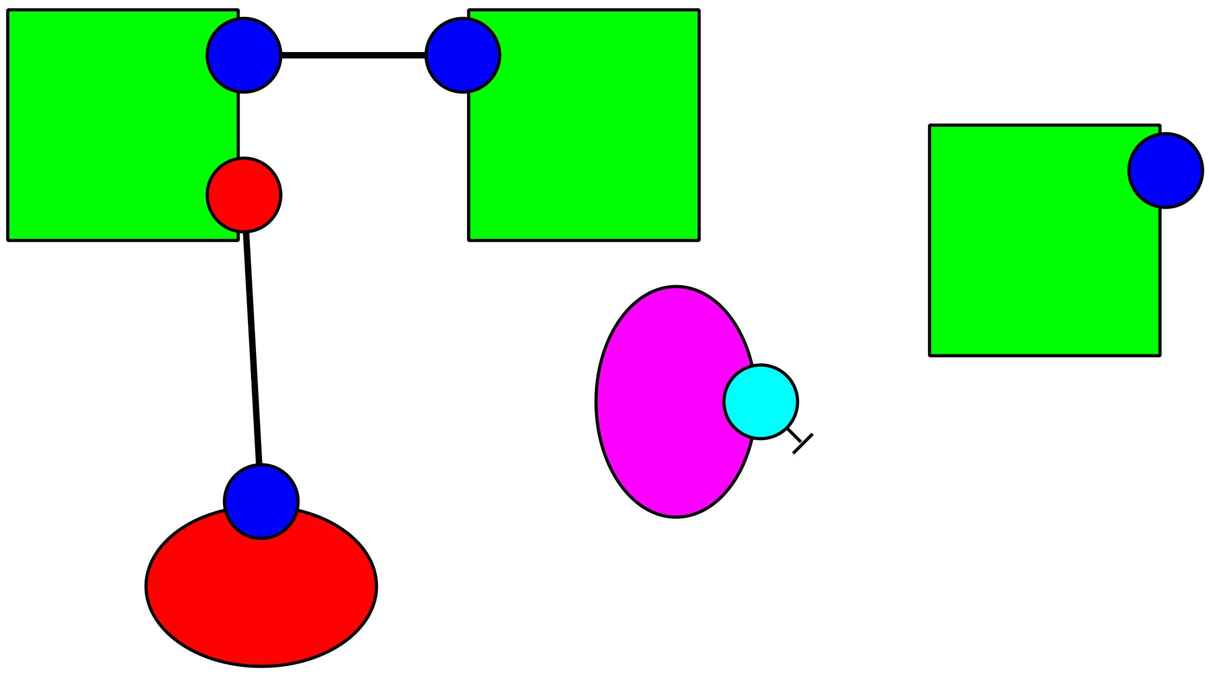
Overview

1. Context and motivations
2. Case study
3. Kappa semantics
4. Symmetries in site-graphs
5. Symmetric models
6. Conclusion

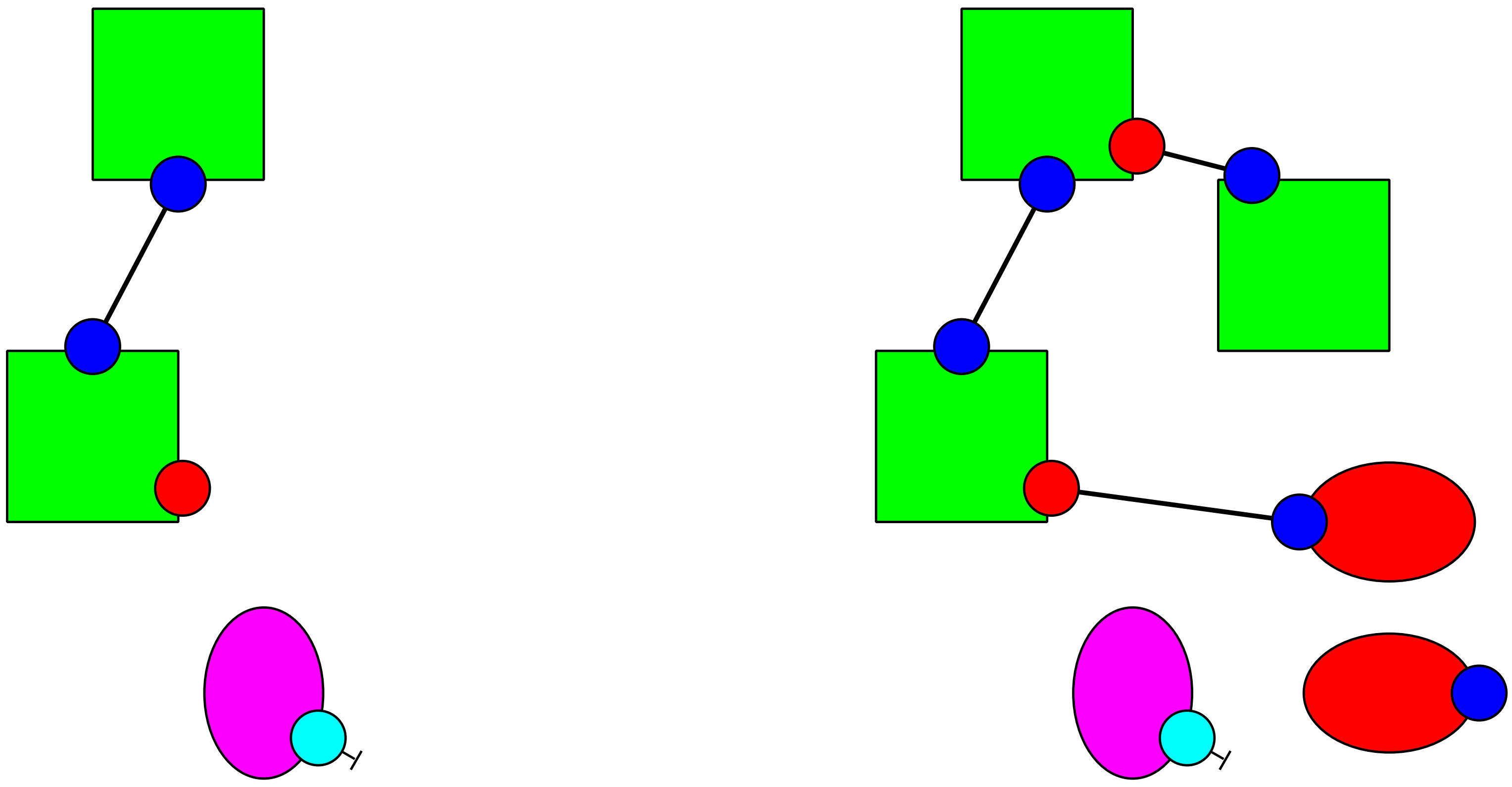
Signature



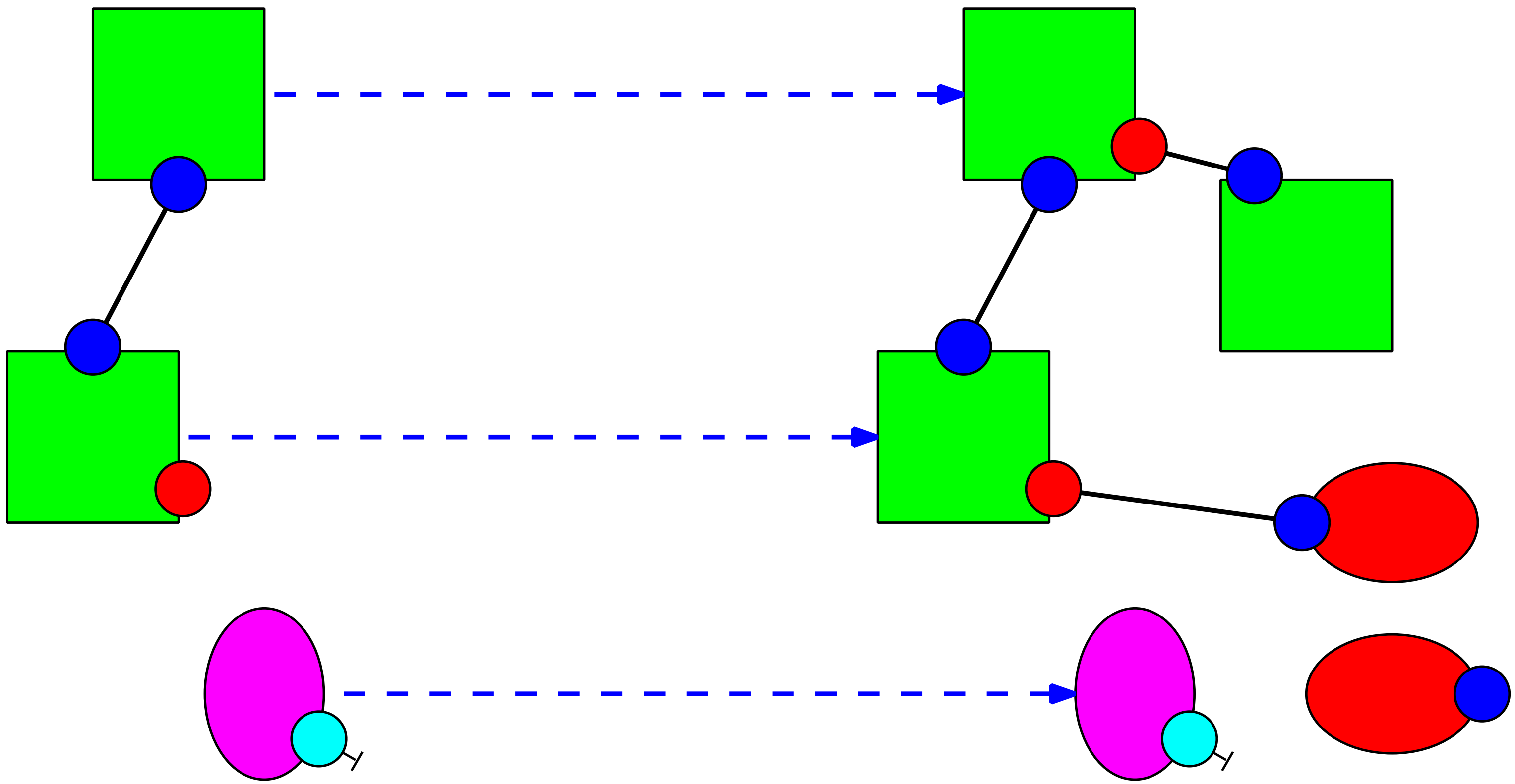
Site graphs



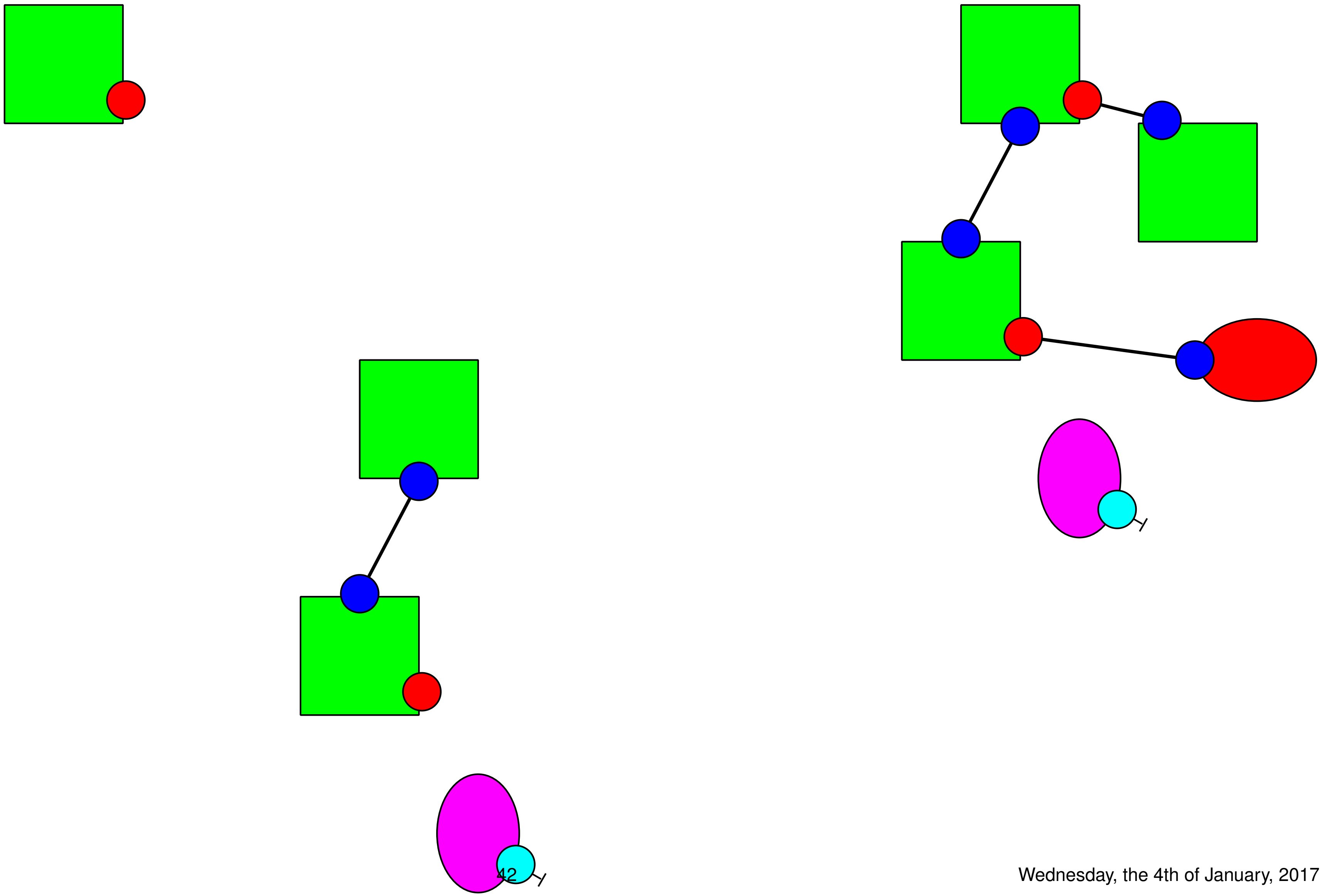
Embeddings



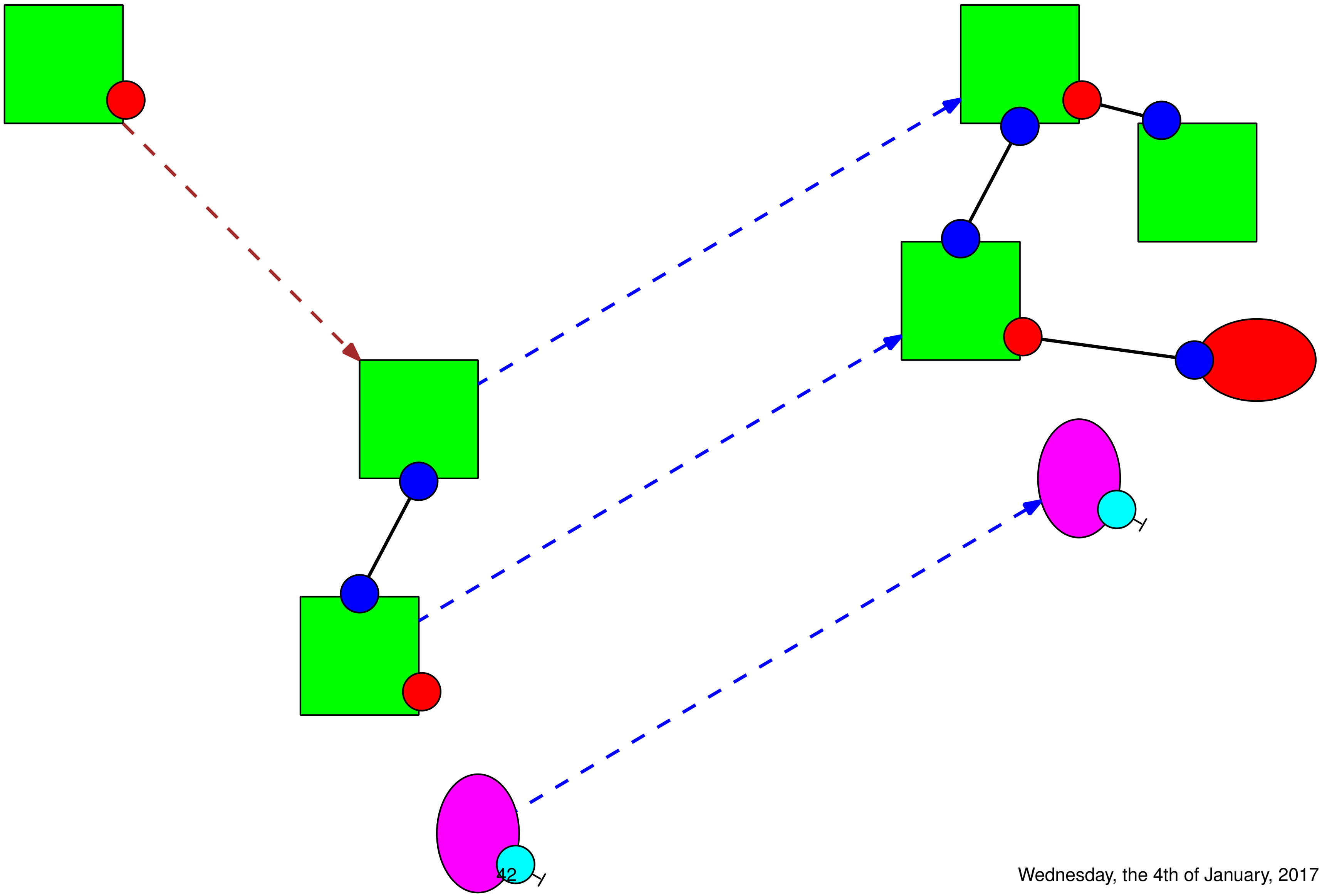
Embeddings



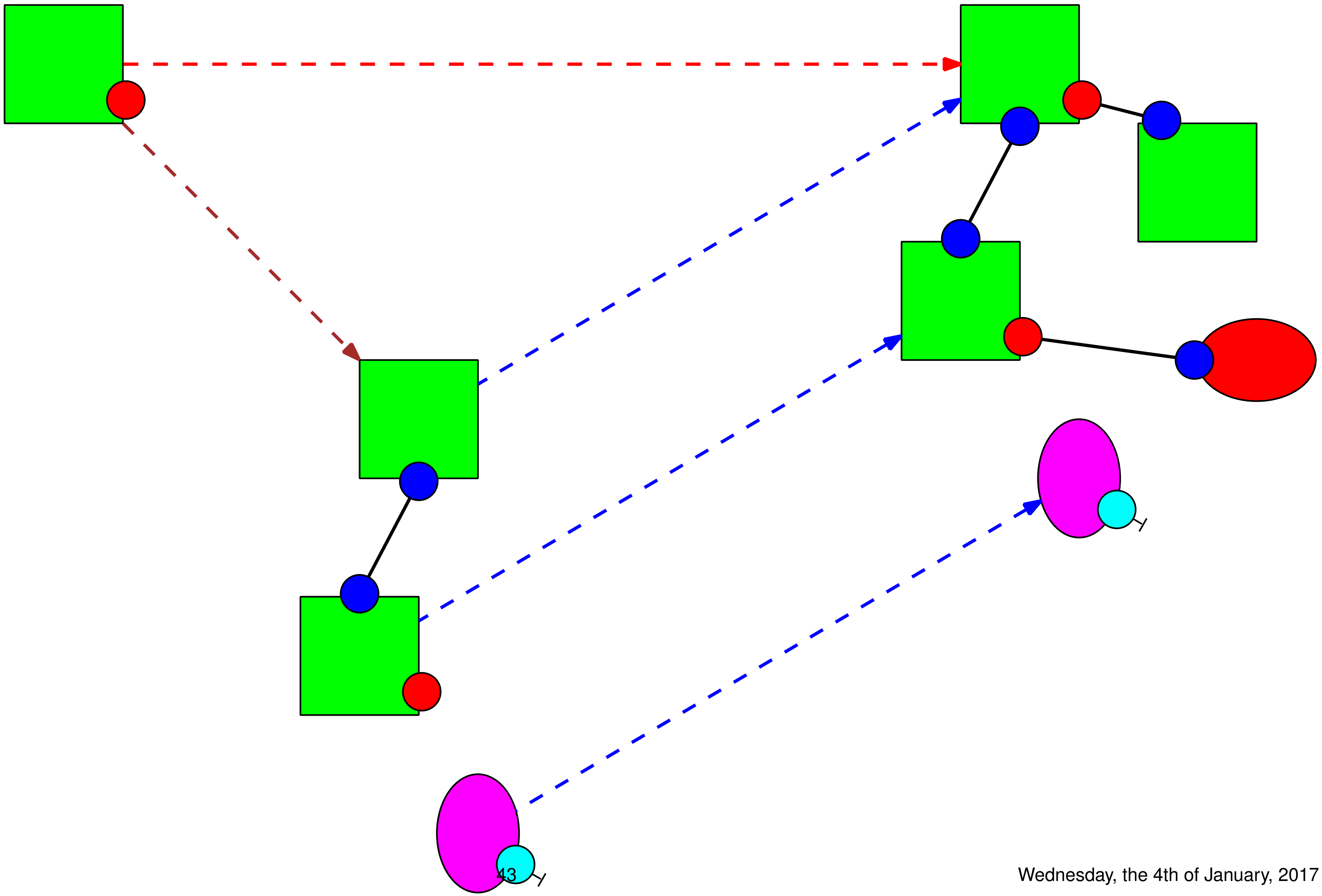
Composition of embeddings



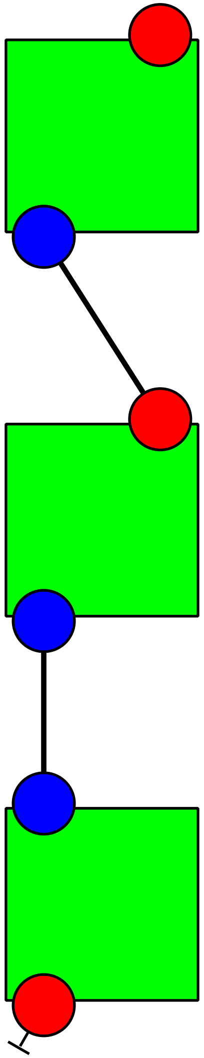
Composition of embeddings

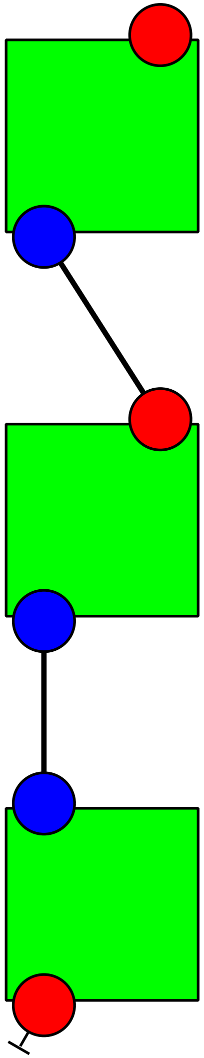


Composition of embeddings

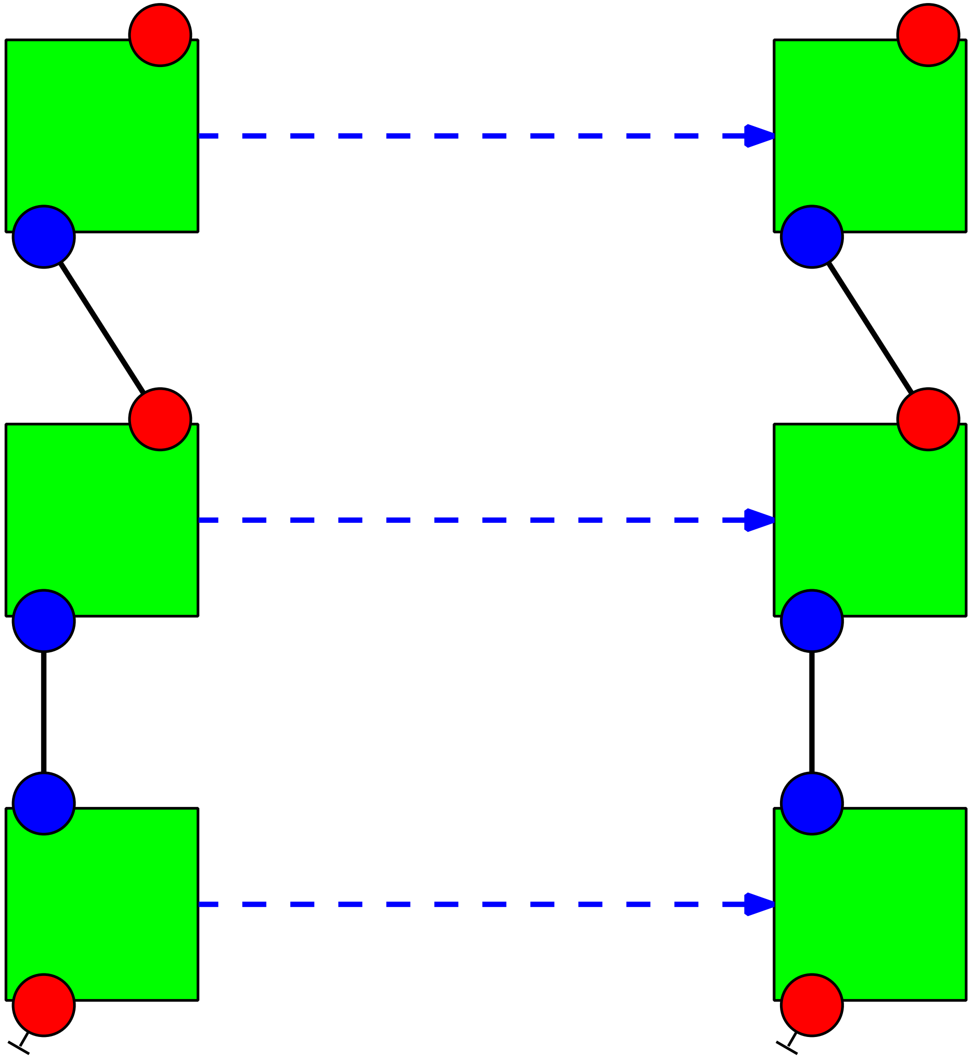


Identity embeddings

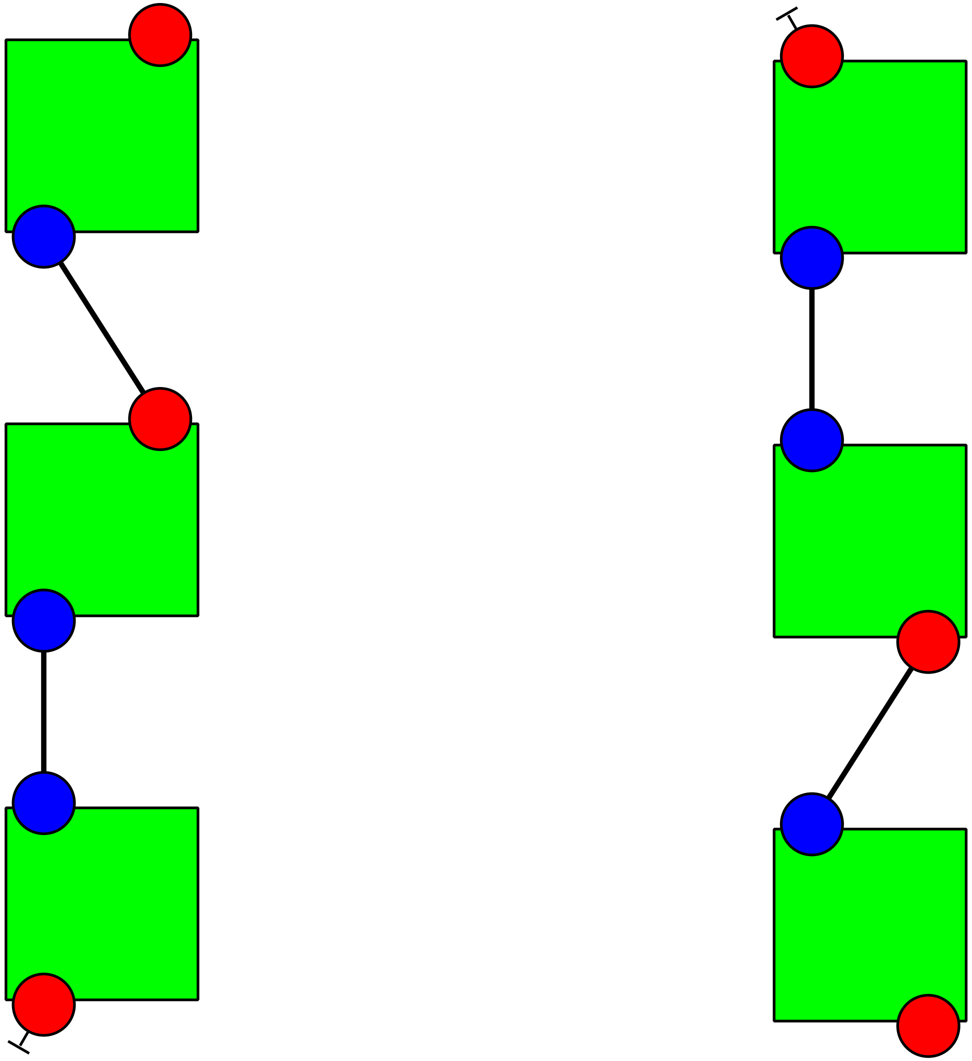




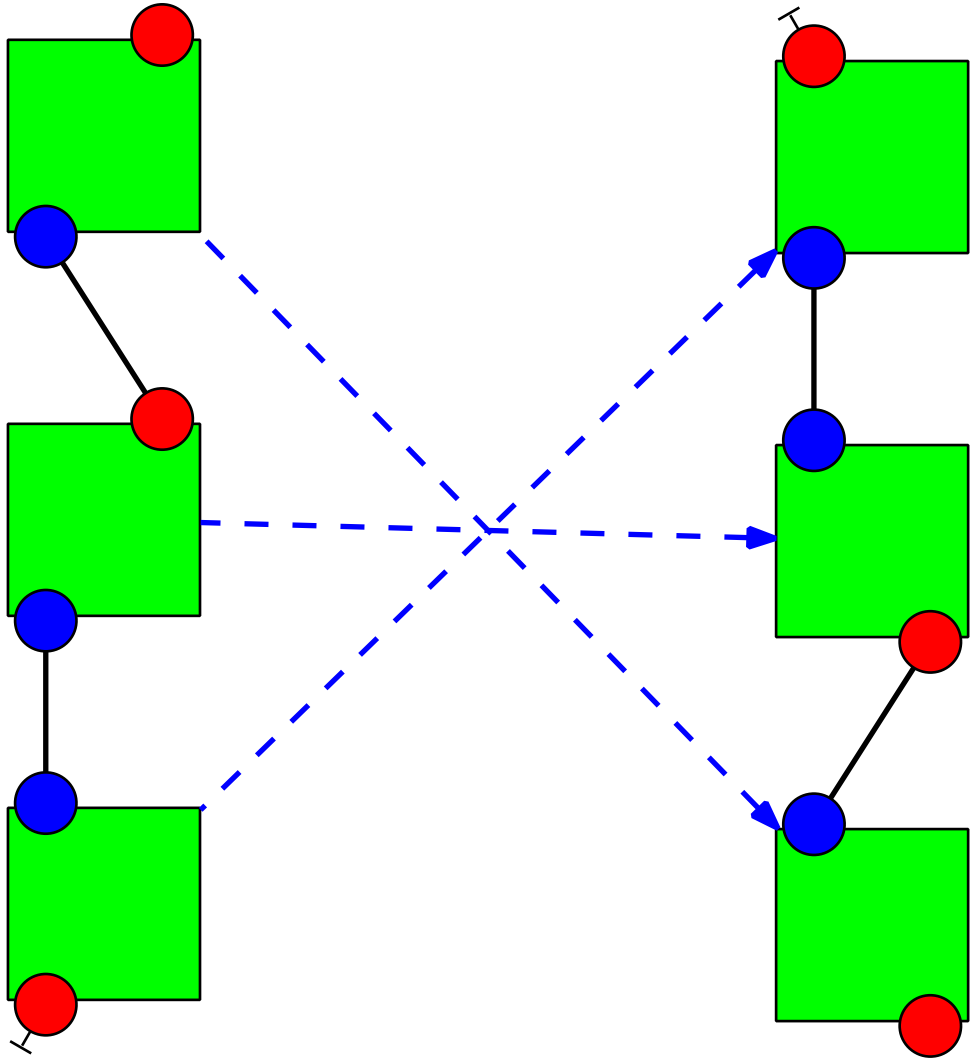
Identity embeddings



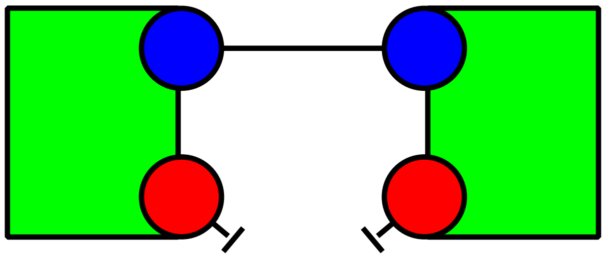
Isomorphisms



Isomorphisms

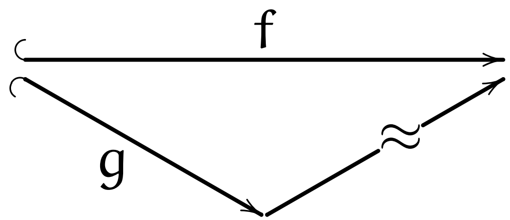


Fully specified site graphs



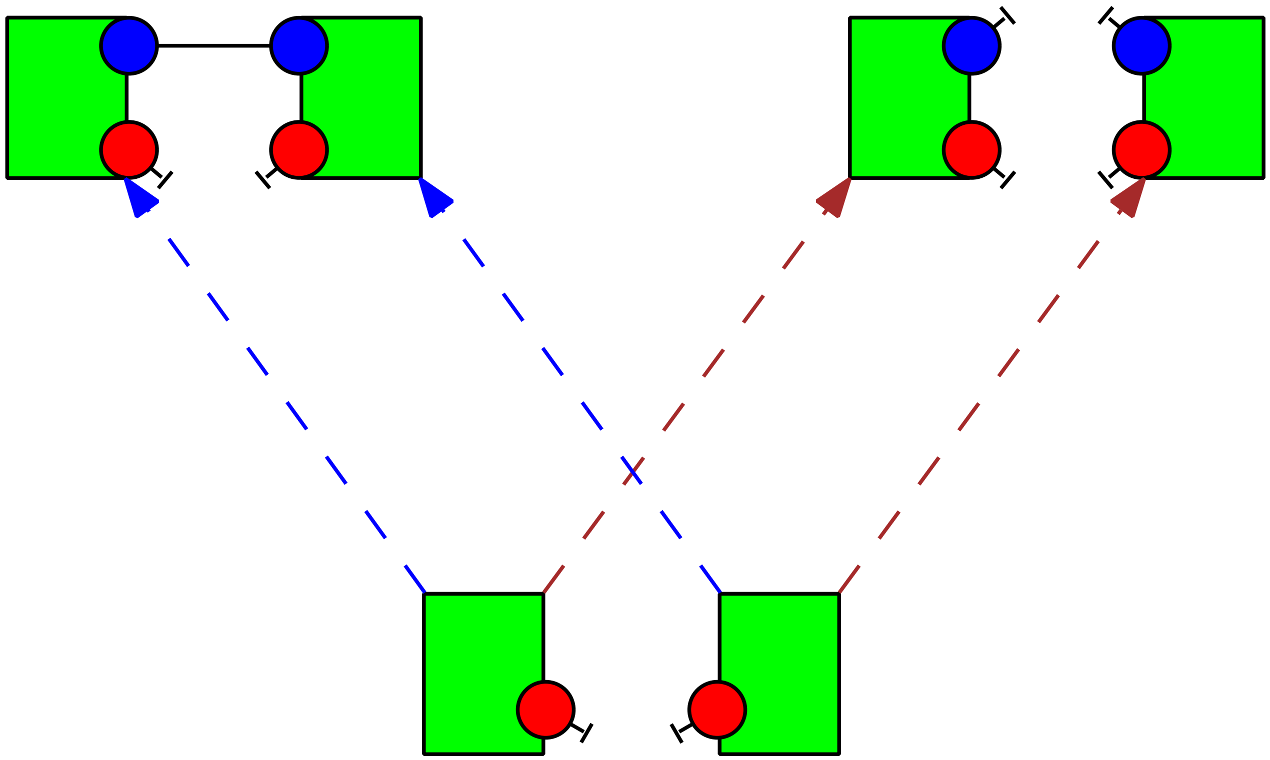
Isomorphic embeddings

When the following diagram:

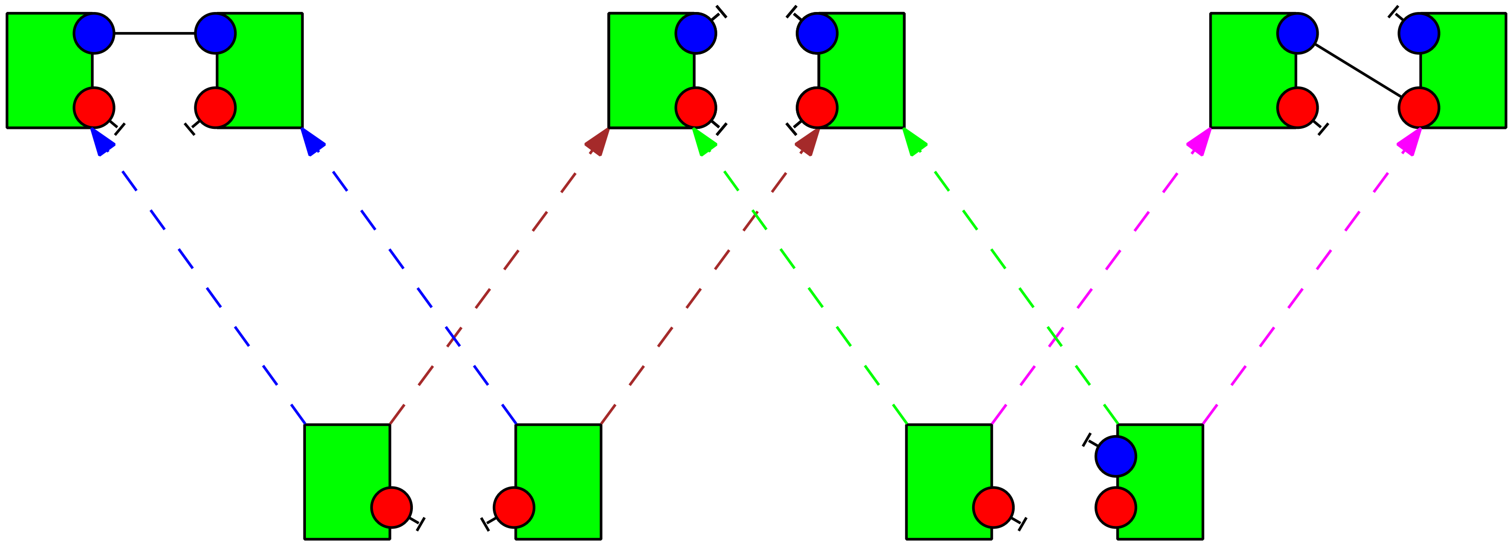


commutes, we say that the embeddings f and g are isomorphic, and we write $f \approx g$.

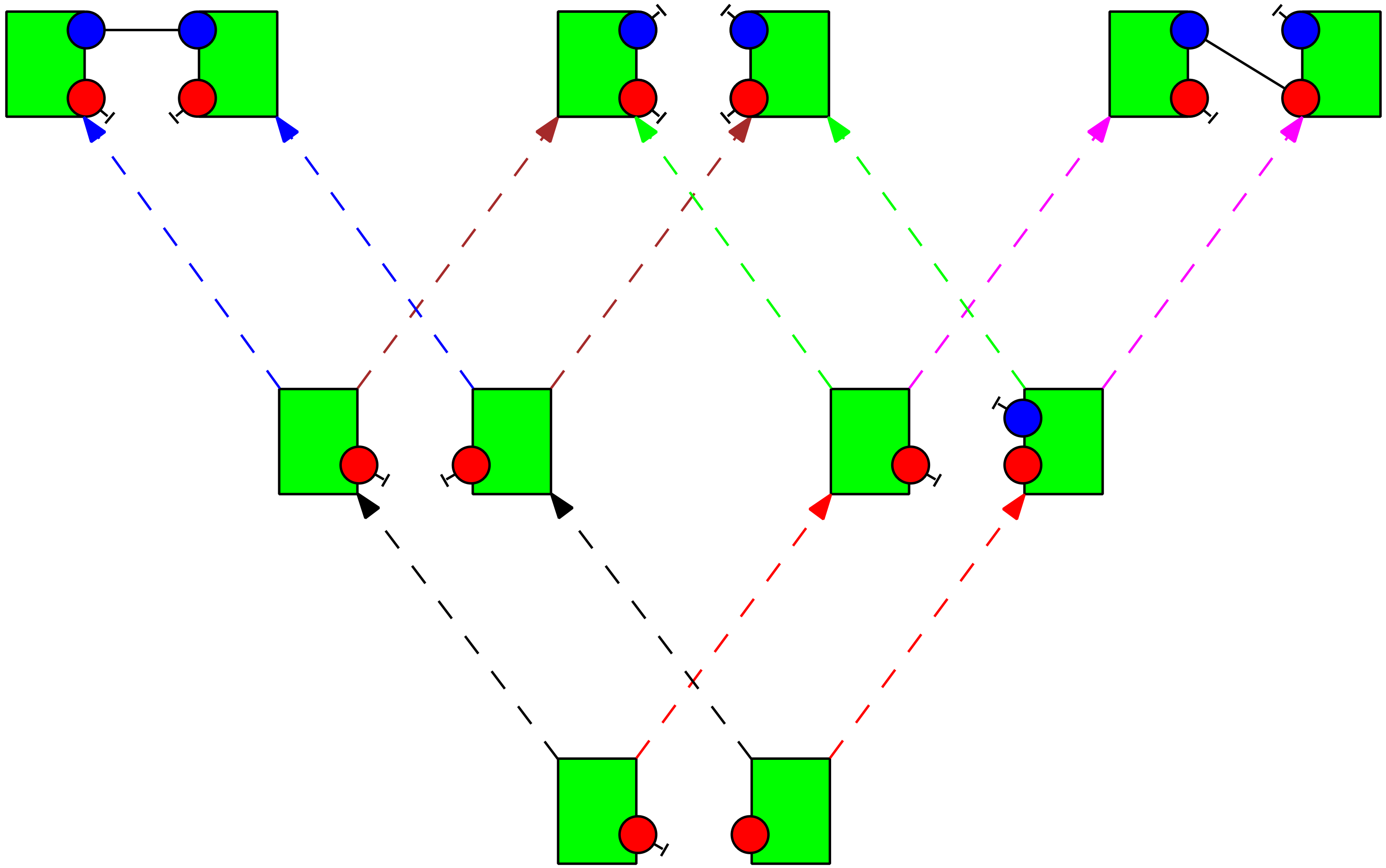
Partial embeddings



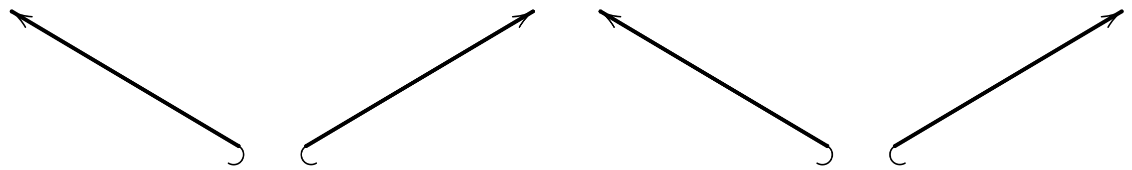
Composition of partial embeddings



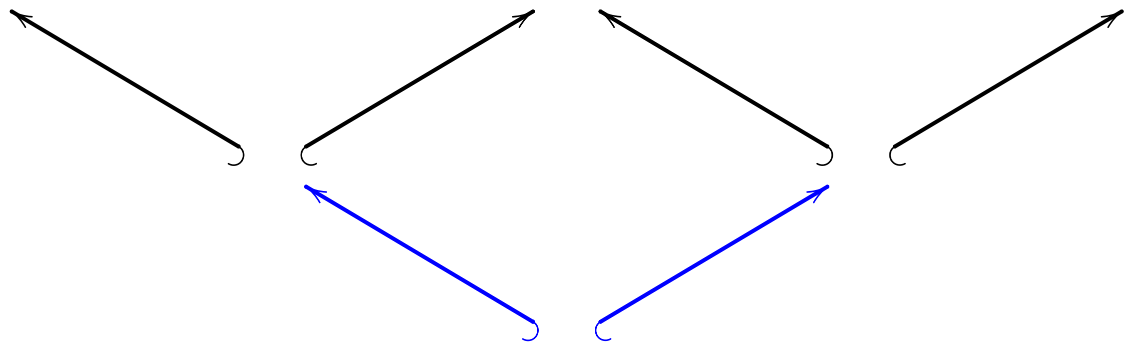
Composition of partial embeddings



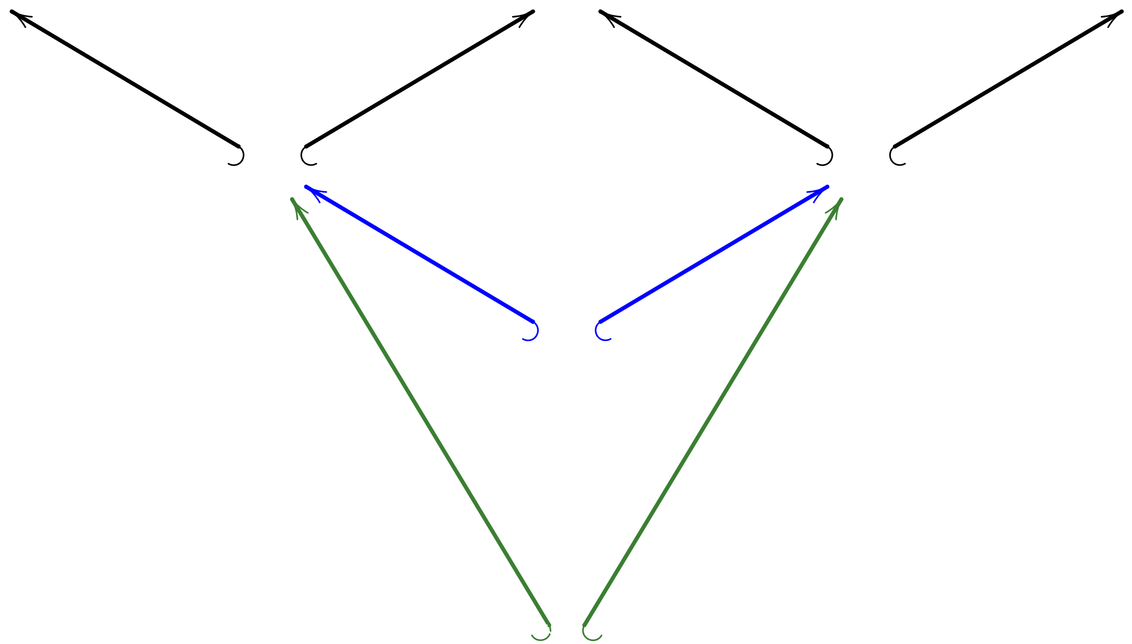
Composition of partial embeddings



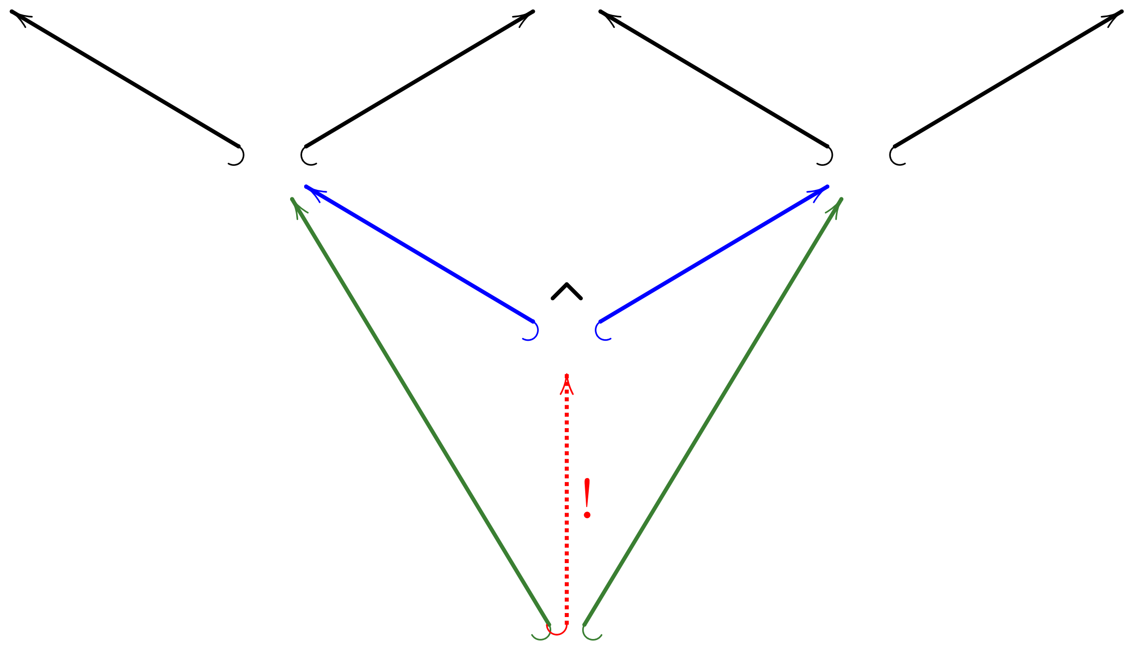
Composition of partial embeddings



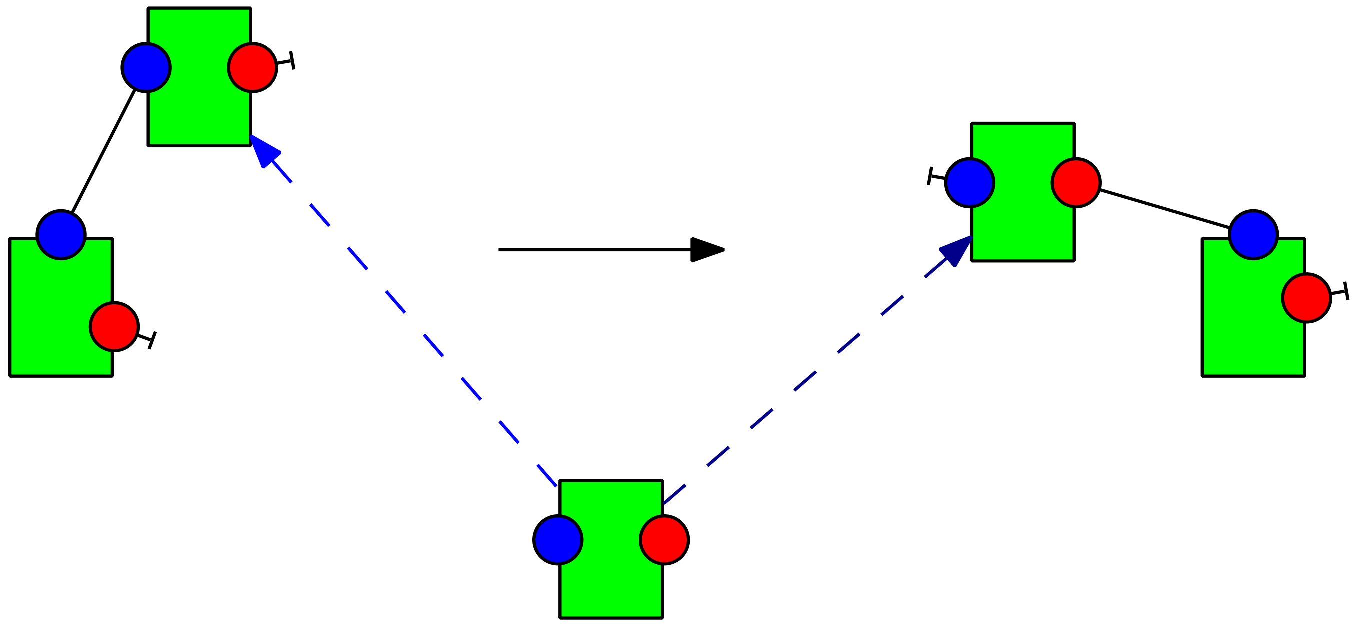
Composition of partial embeddings



Composition of partial embeddings



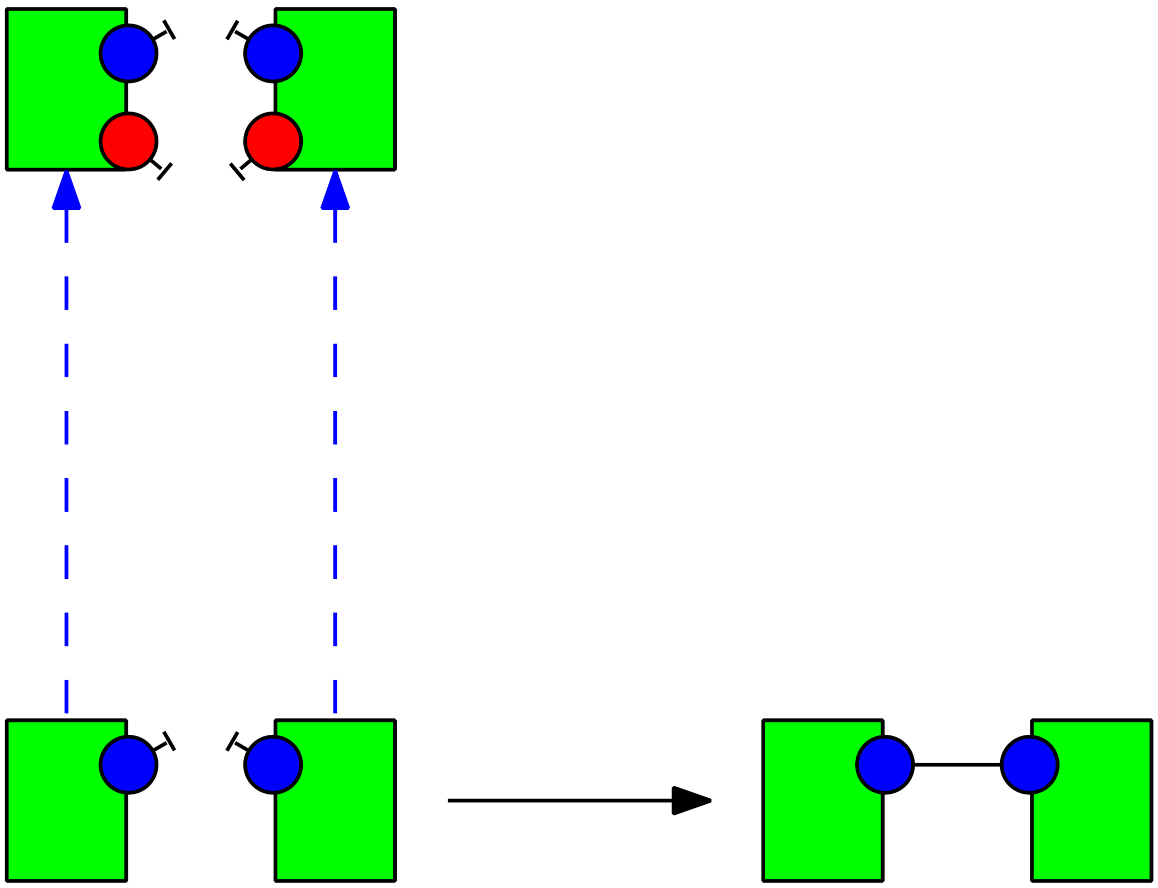
Rules



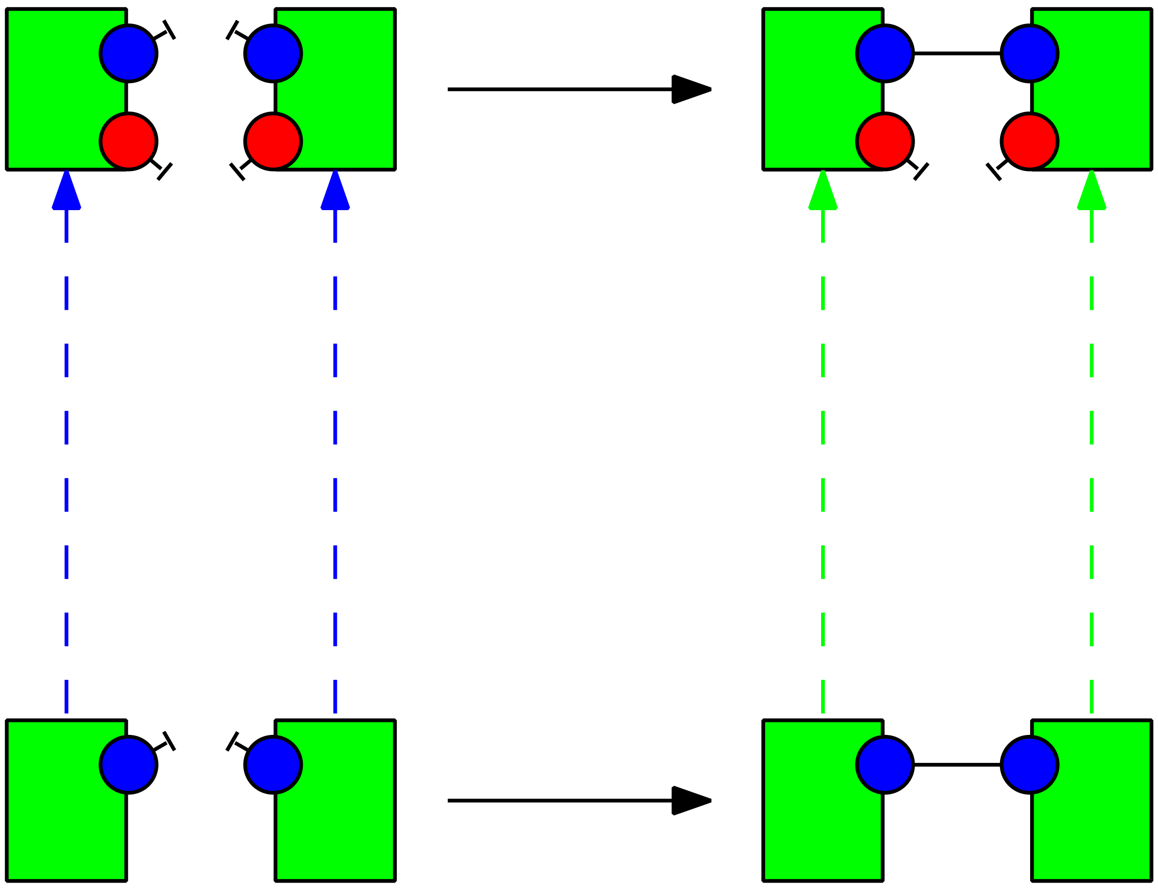
A rule is a partial embedding such that:

- the domain (D) is maximal;
- some constraints that we omit here are satisfied.

Rule application

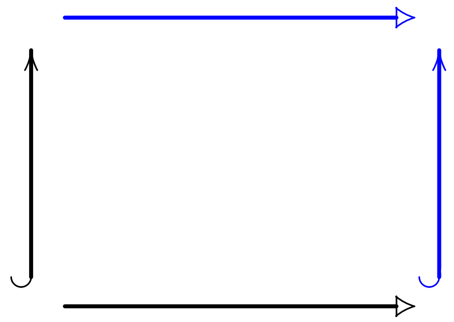


Rule applications

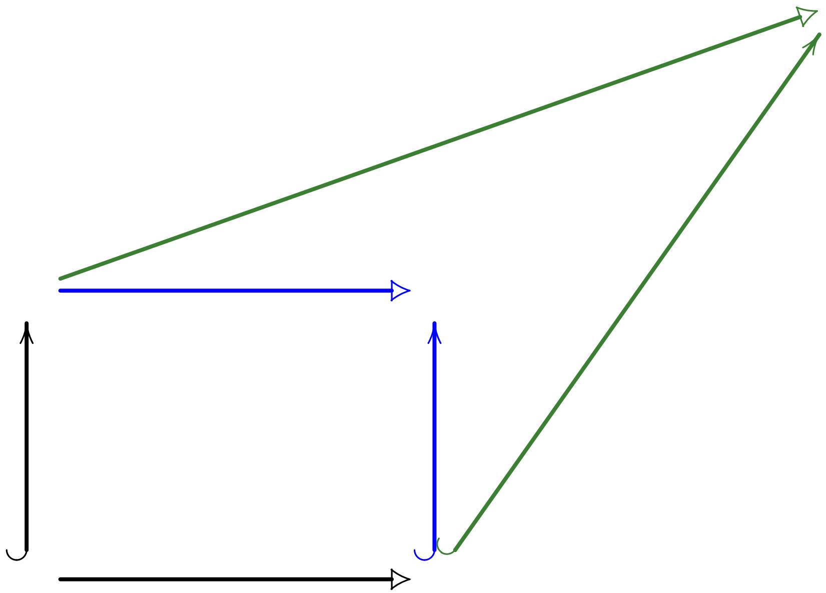


Refinement

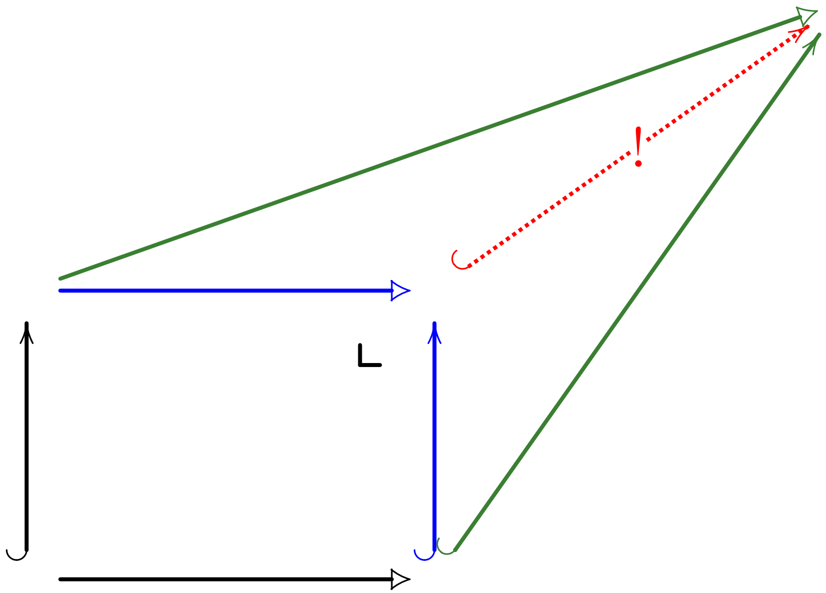
Refinement



Refinement

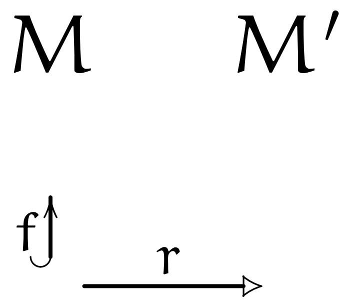


Refinement



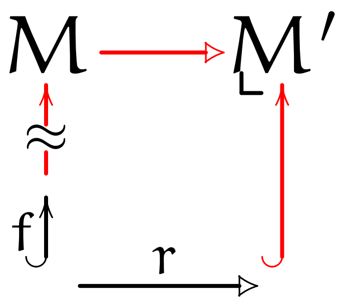
Semantics

1. A model is a map k from rules to non negative real numbers;
2. $\mathcal{Q} \stackrel{\Delta}{=} \{[G]_{\approx} \mid G$ fully specified site graph$\}$;
3. $\mathcal{L} \stackrel{\Delta}{=} \left\{ (r, [f]_{\approx}) \;\middle|\; \begin{array}{l} r \text{ a rule , } f \text{ an embedding from } \textit{lhs}(r) \\ \text{to a fully specified site graph} \end{array} \right\}$;
4. $[M]_{\approx} \xrightarrow{(r,[\phi]_{\approx})} [M']_{\approx}$ if and only if:



Semantics

1. A model is a map k from rules to non negative real numbers;
2. $\mathcal{Q} \stackrel{\Delta}{=} \{[G]_{\approx} \mid G$ fully specified site graph$\}$;
3. $\mathcal{L} \stackrel{\Delta}{=} \left\{ (r, [f]_{\approx}) \;\middle|\; \begin{array}{l} r \text{ a rule }, f \text{ an embedding from } \textit{lhs}(r) \\ \text{to a fully specified site graph} \end{array} \right\}$;
4. $[M]_{\approx} \xrightarrow{(r,[f]_{\approx})} [M']_{\approx}$ if and only if:

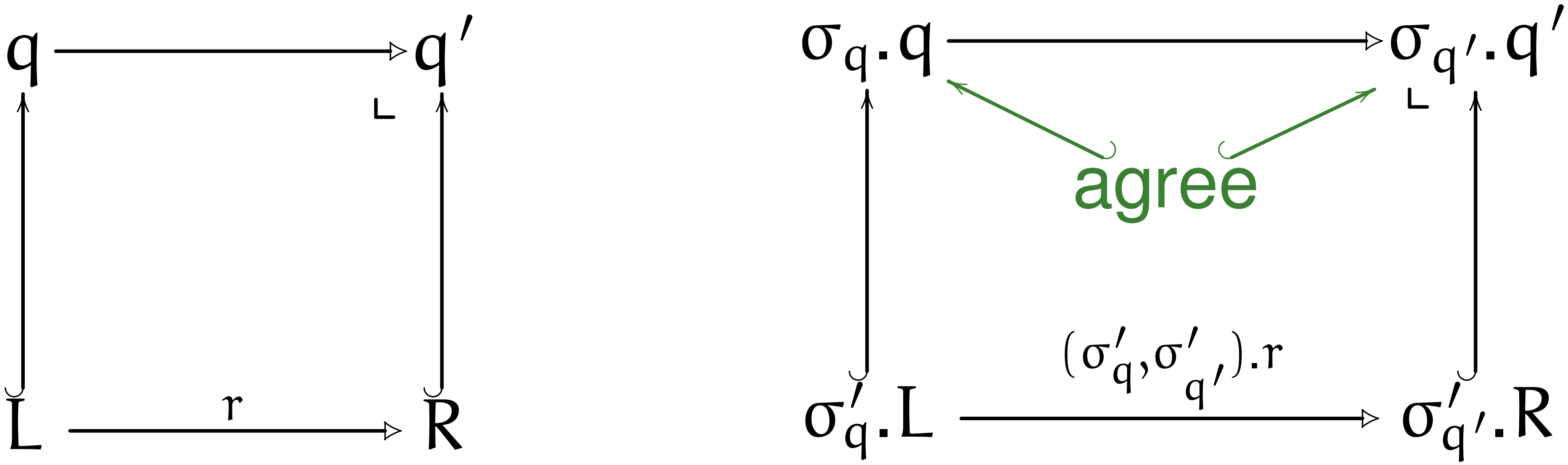


The rate of such a transition is defined as:

$$\frac{\gamma(r)\textit{card}(\{\phi f \mid \phi \in \textit{Aut}(\textit{im}(f))\})}{\textit{card}(\textit{Aut}(\textit{lhs}(r)))}.$$

Applying transformations over push-outs

We would like to make pairs of transformations act over push-outs,



whenever they act the same way on preserved agents.

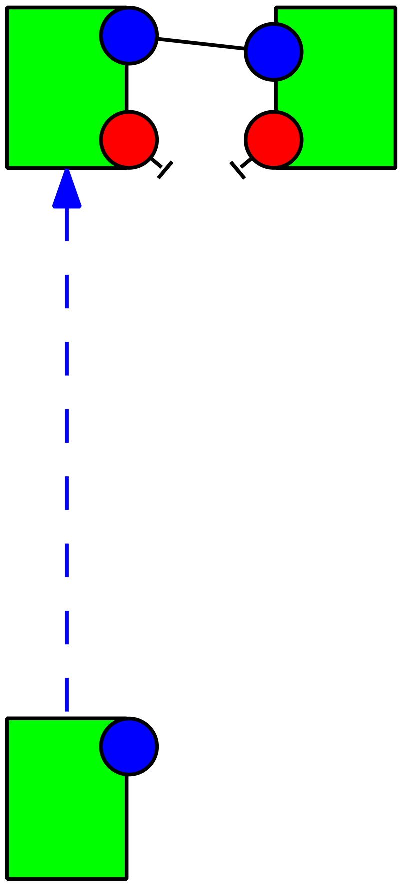
Overview

Transformations over site graphs

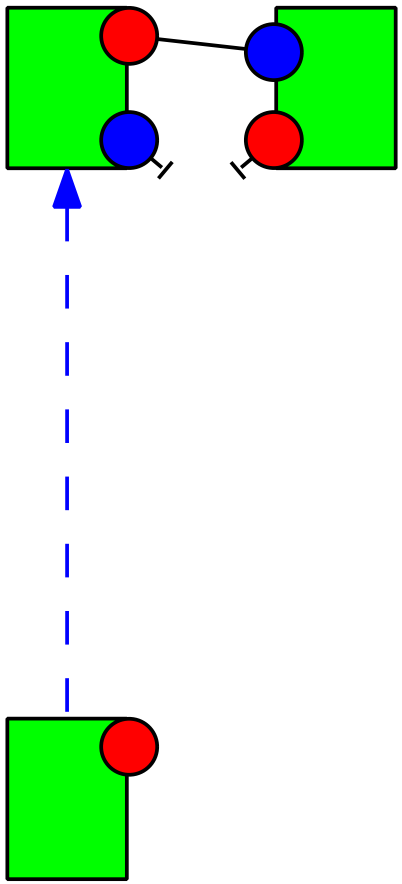
- For any site graph G, we introduce a finite group of transformations $\mathbb{G}_G$.

- For any site graph G and any transformation $\sigma \in \mathbb{G}_G$, we introduce the site graph $\sigma.G$ and we call it the image of G by σ.
- We assume that $\mathbb{G}_G$ and $\mathbb{G}_{(\sigma.G)}$ are the same group.

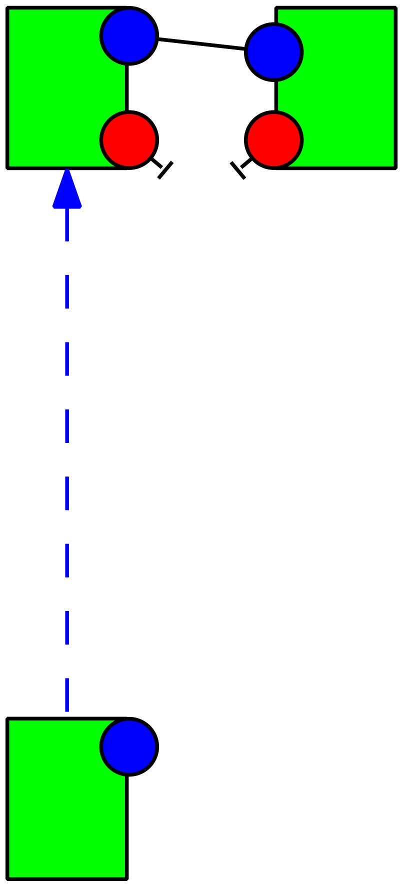
Restricting a transformation to the domain of an embedding



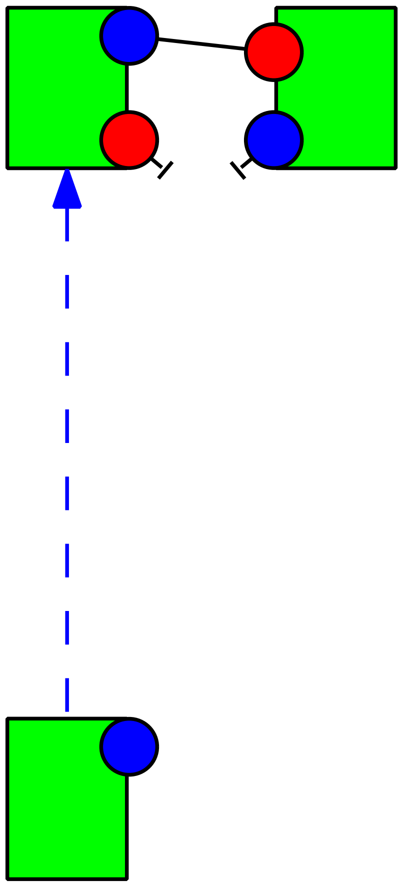
Restricting a transformation to the domain of an embedding



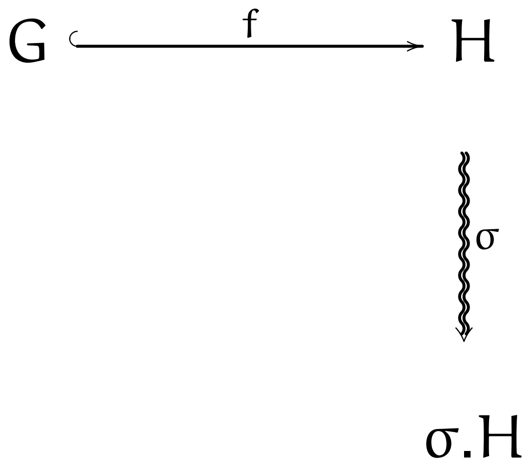
Restricting a transformation to the domain of an embedding



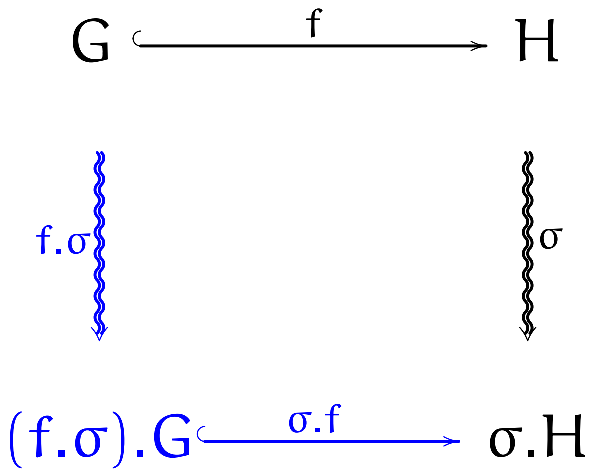
Restricting a transformation to the domain of an embedding



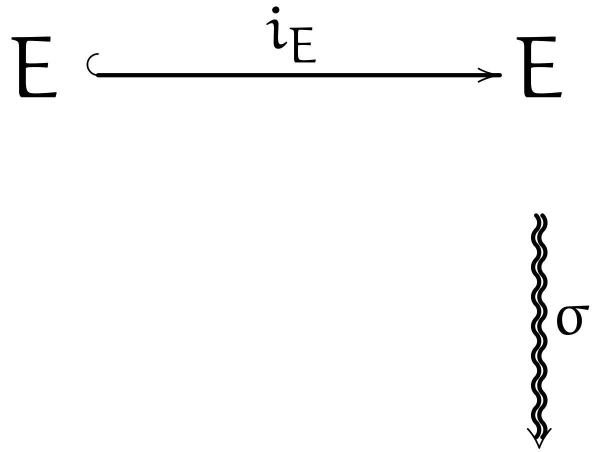
Restriction of symmetry to the domain of an embedding



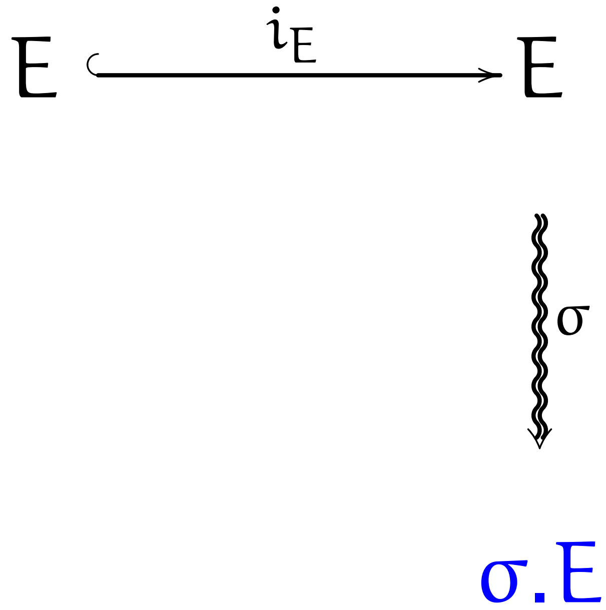
Restriction of symmetry
to the domain of an embedding



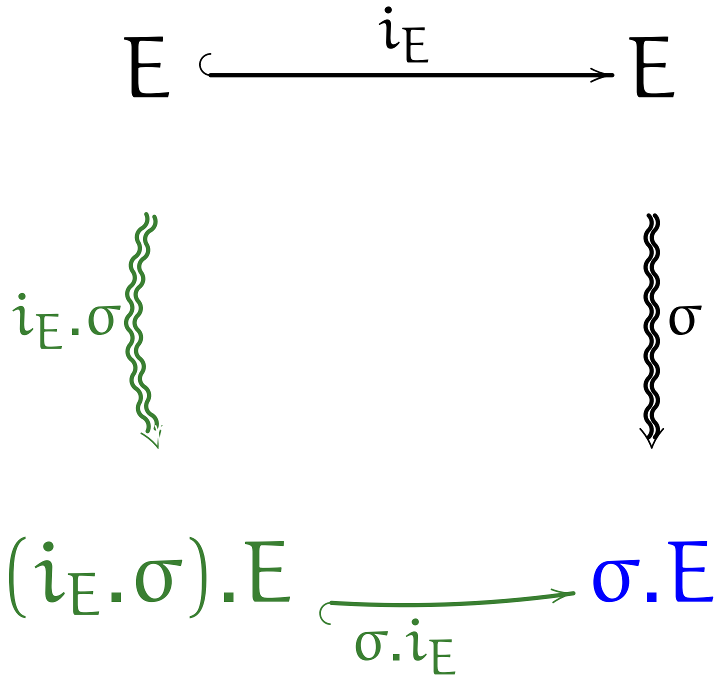
Identity function



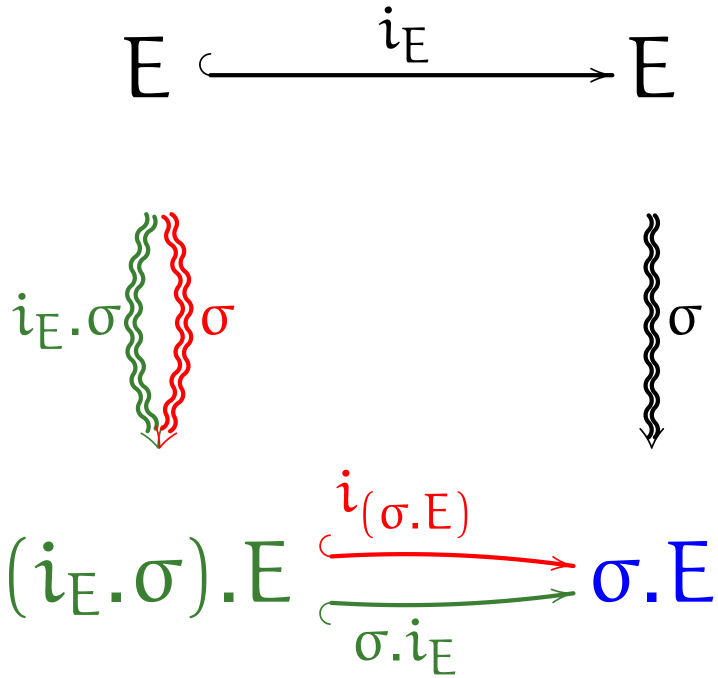
Identity function



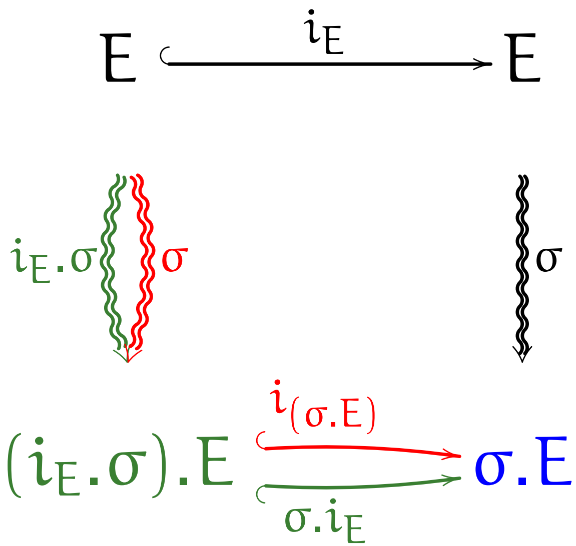
Identity function



Identity function



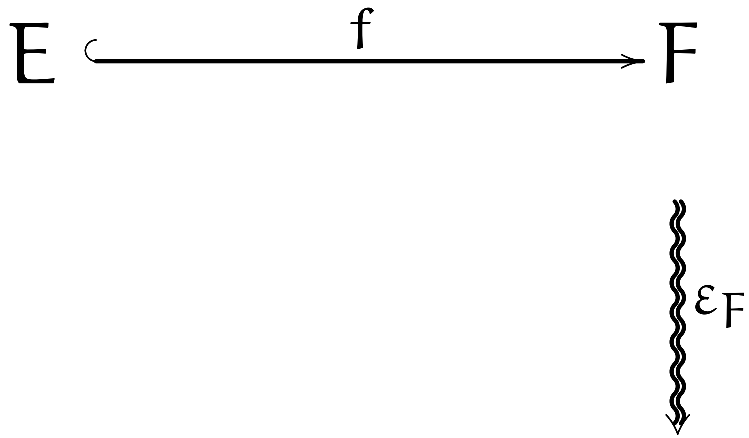
Identity function



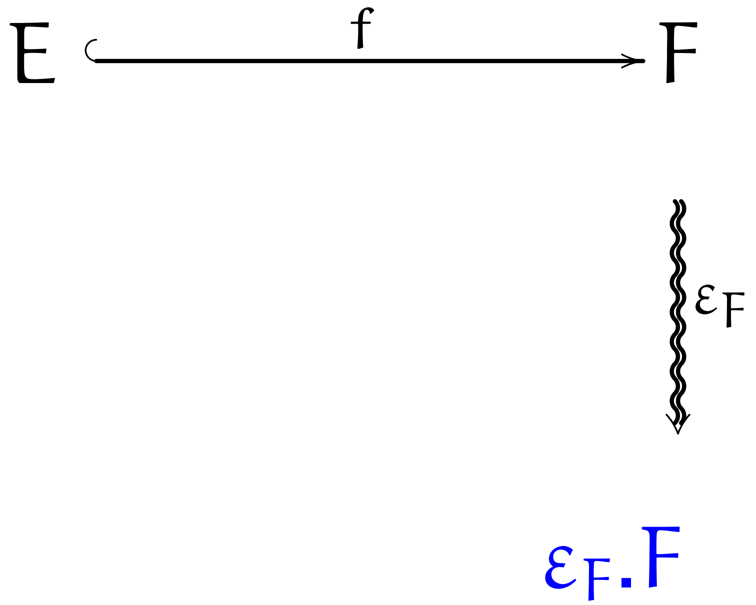
We assume that:

- $i_E.\sigma = \sigma$
- $\sigma.i_E = i_{(\sigma.E)}$

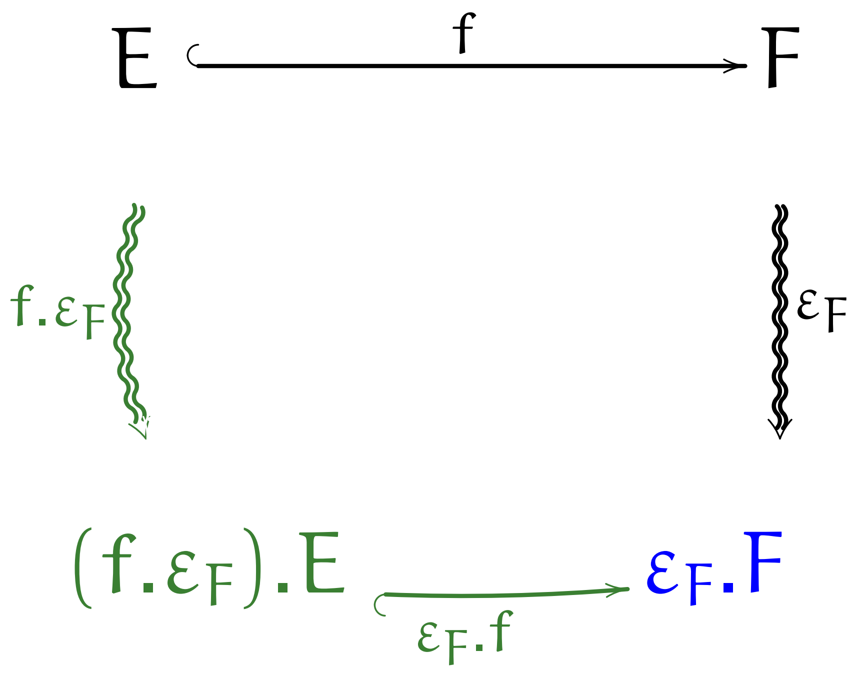
Identity symmetry



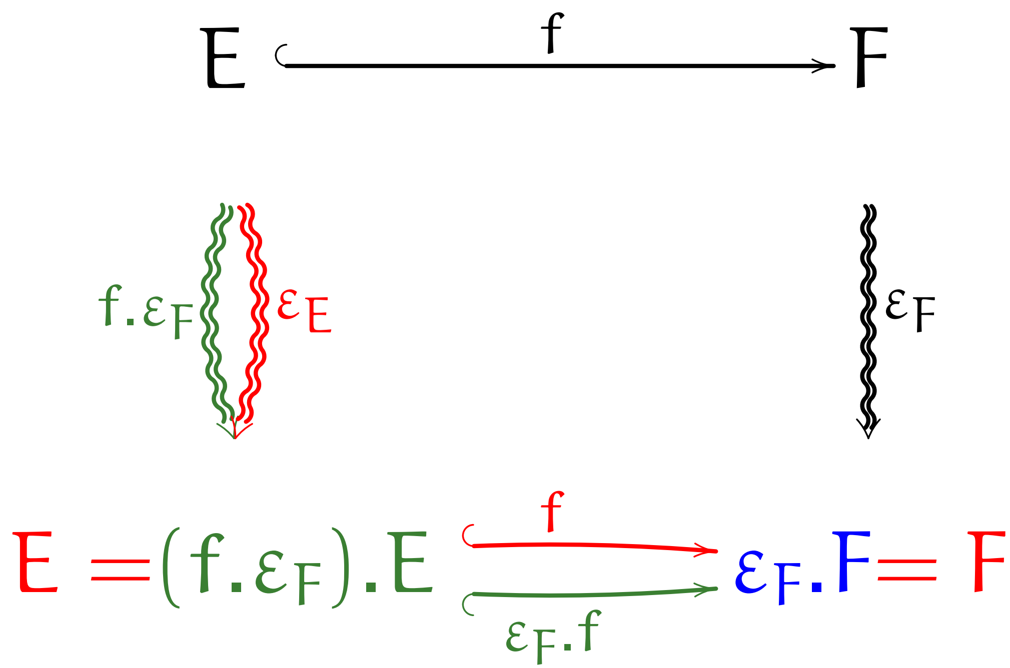
Identity symmetry



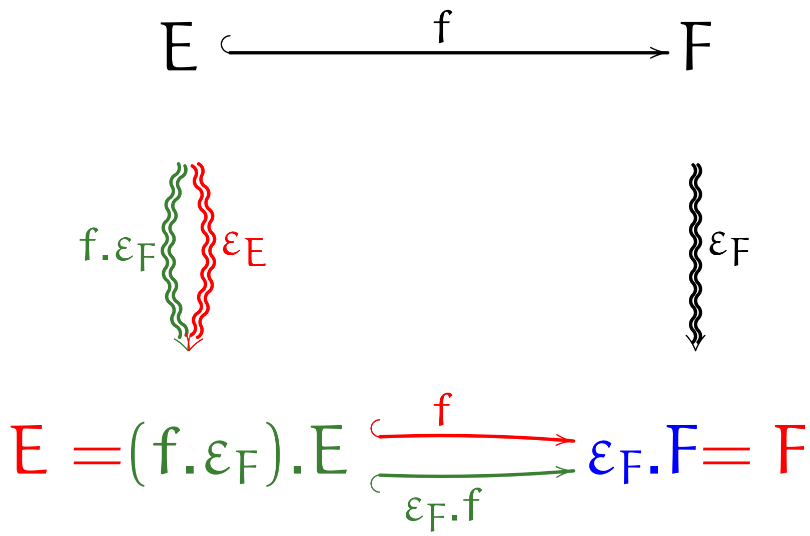
Identity symmetry



Identity symmetry



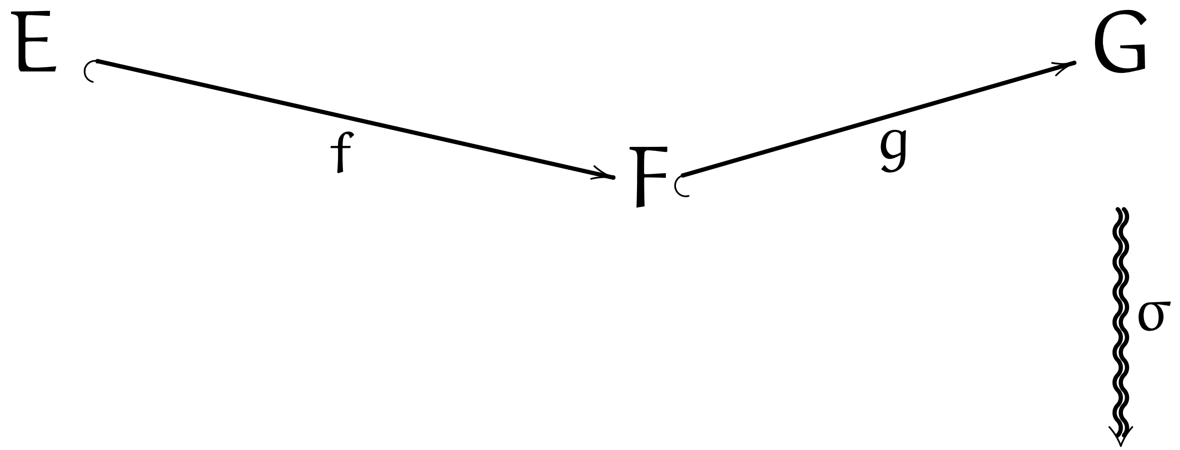
Identity symmetry



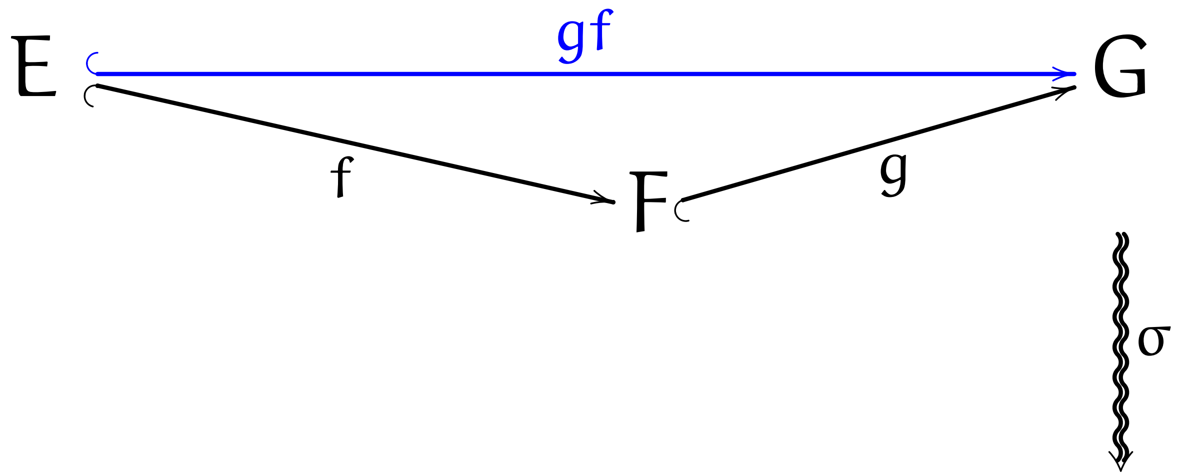
We assume that:

- $\varepsilon_F.F = F$
- $f.\varepsilon_F = \varepsilon_E$
- $\varepsilon_F.f = f$

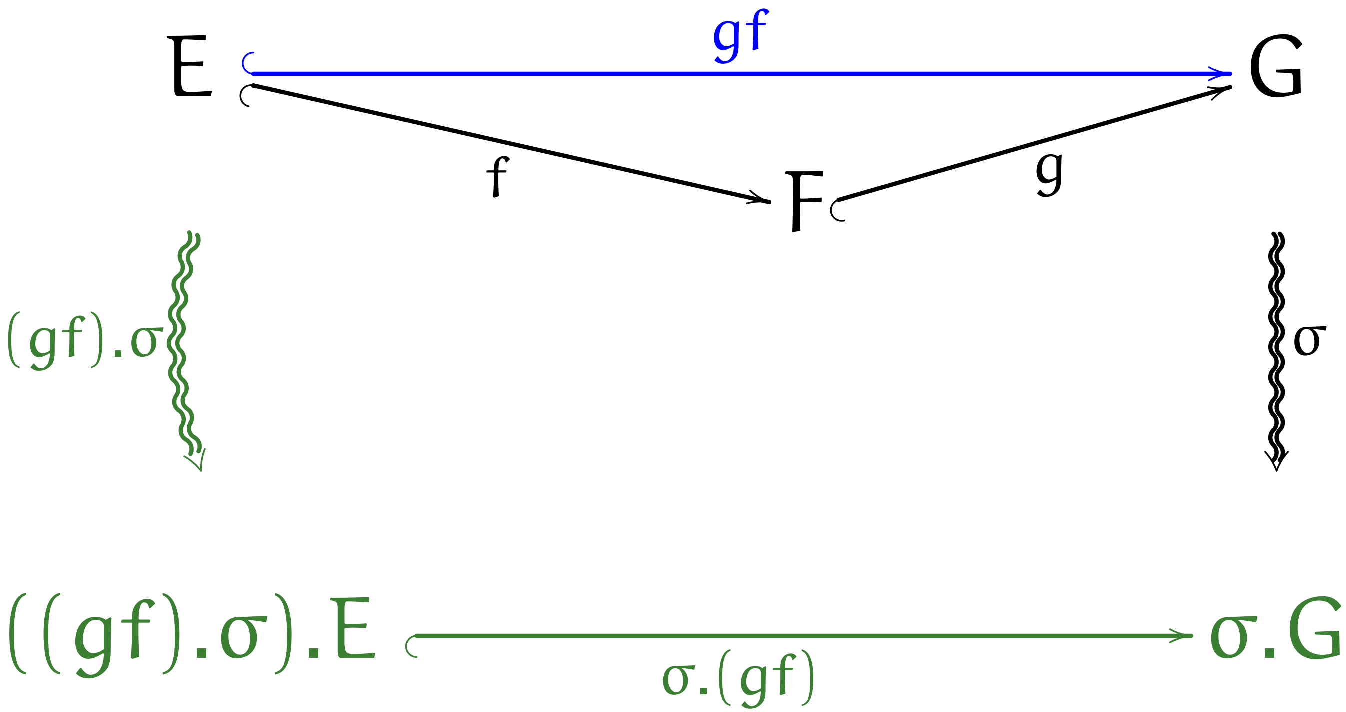
Composition of embeddings



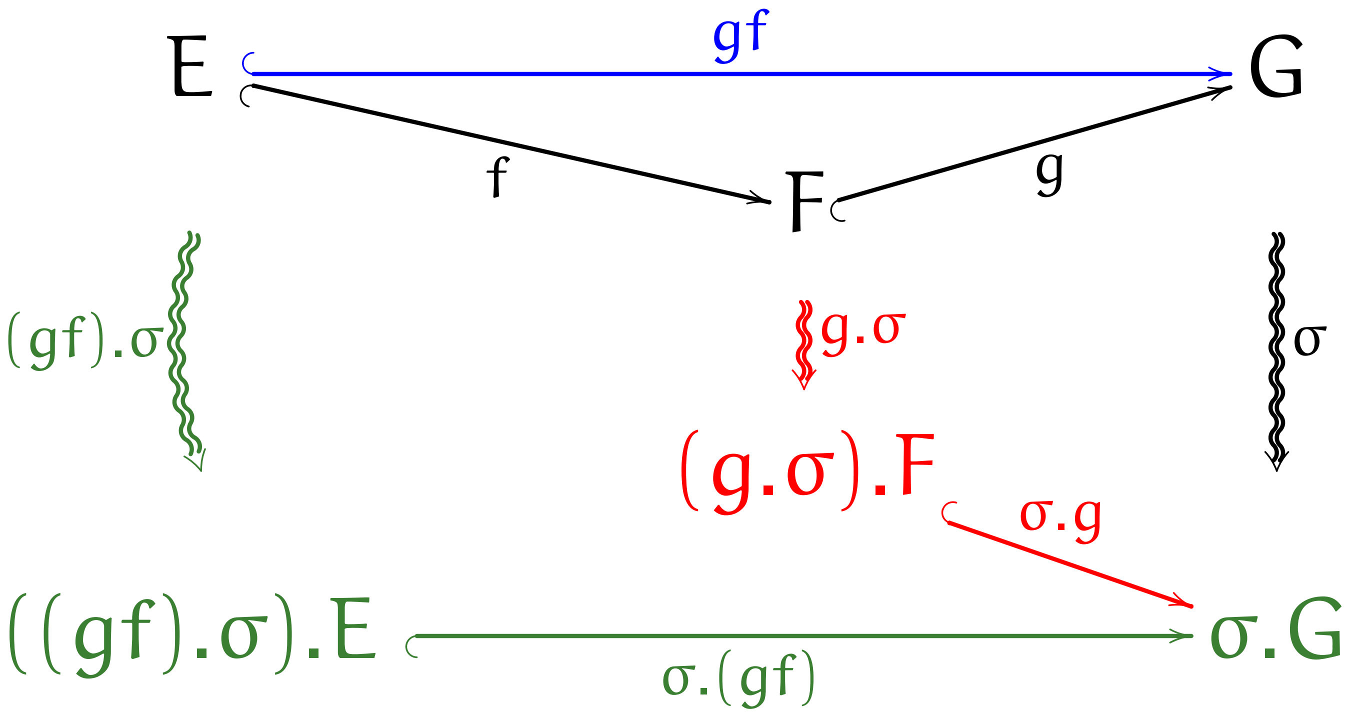
Composition of embeddings



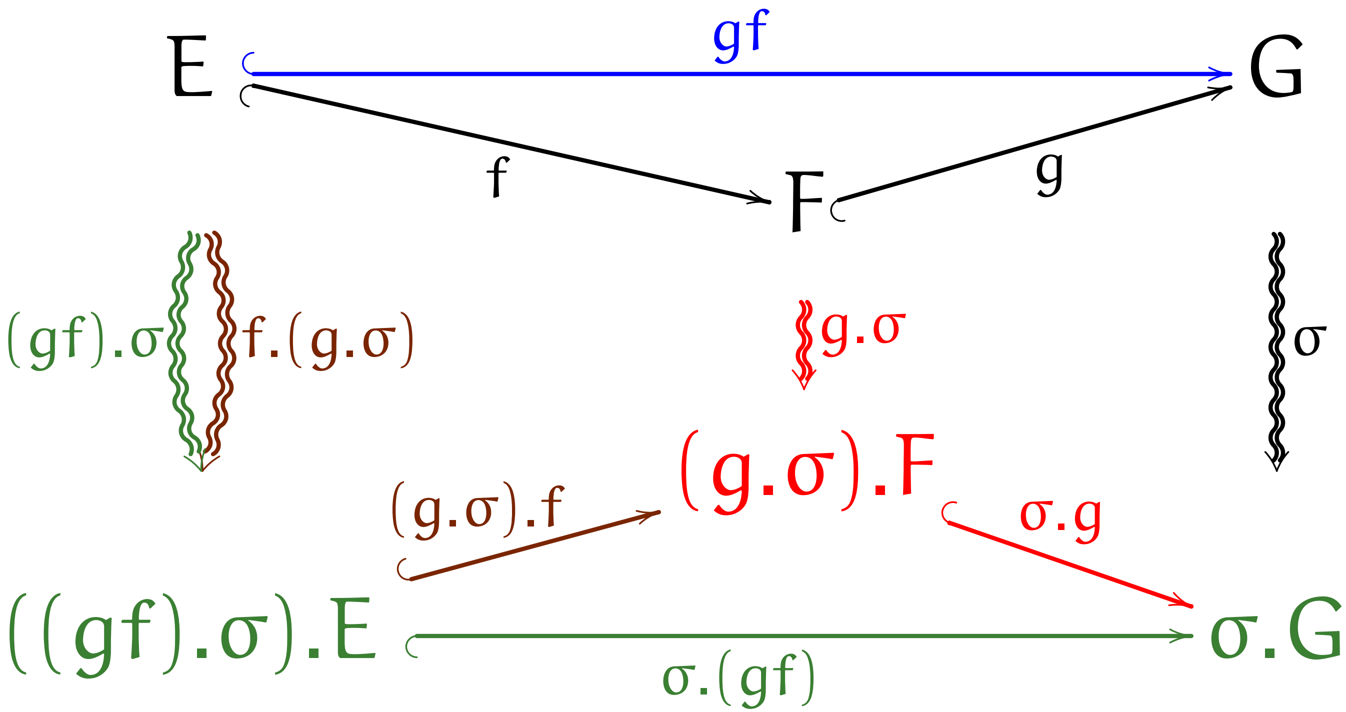
Composition of embeddings



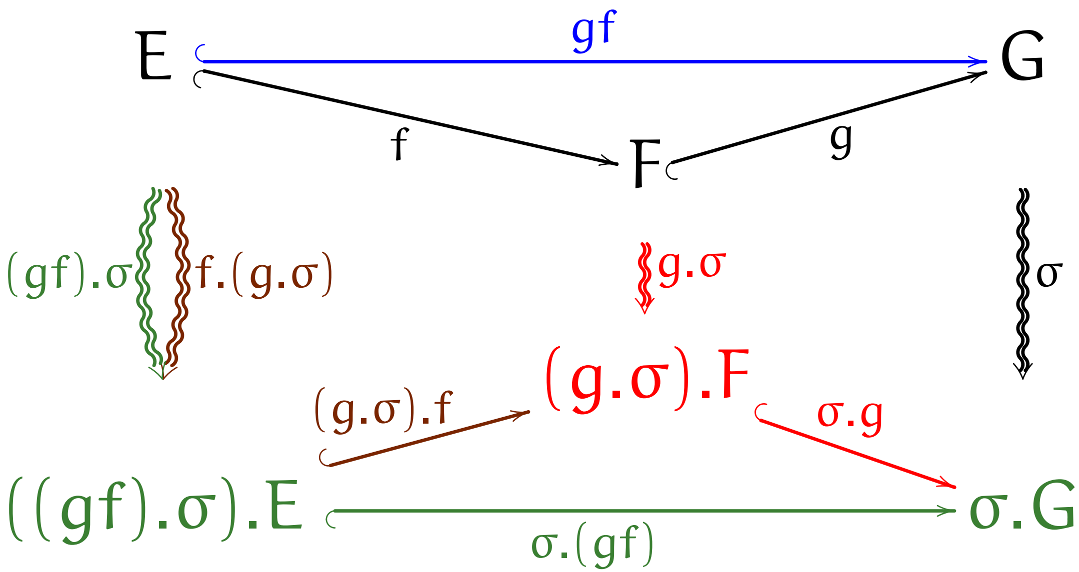
Composition of embeddings



Composition of embeddings



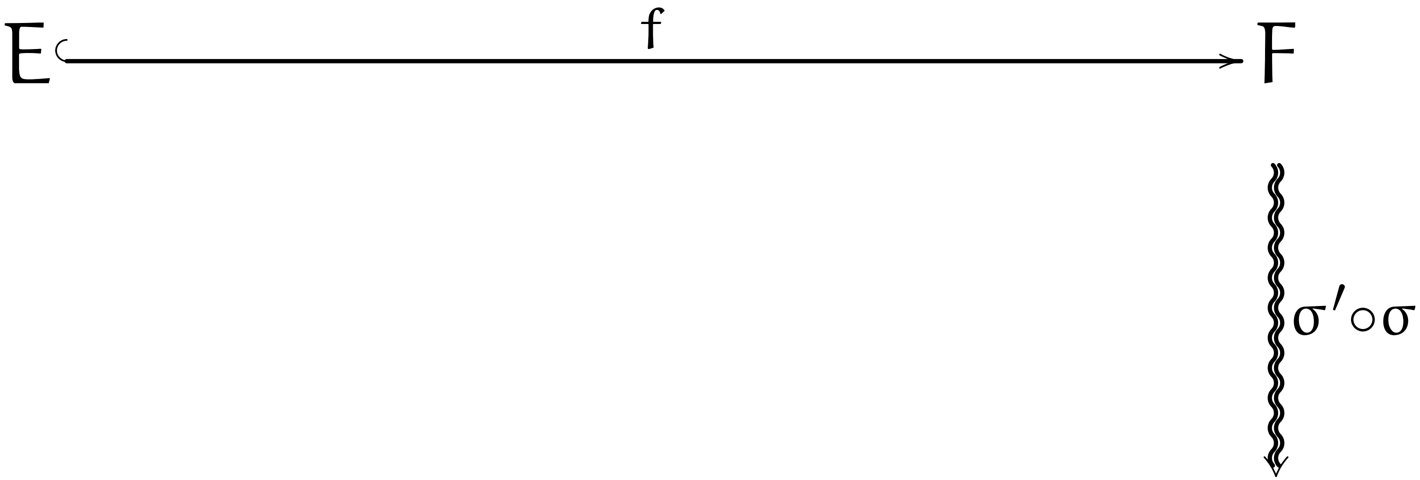
Composition of embeddings



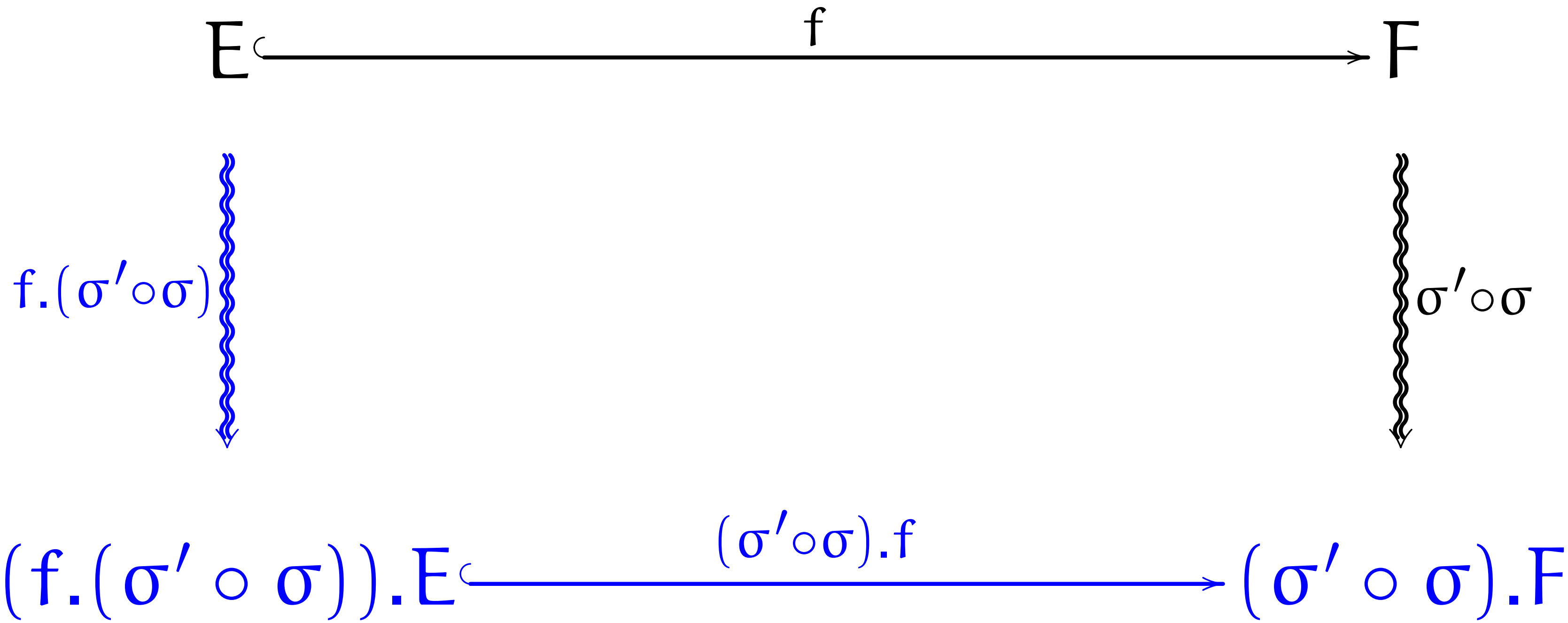
We assume that:

- $(gf).\sigma = f.(g.\sigma)$
- $\sigma.(gf) = (\sigma.g)((g.\sigma).f)$

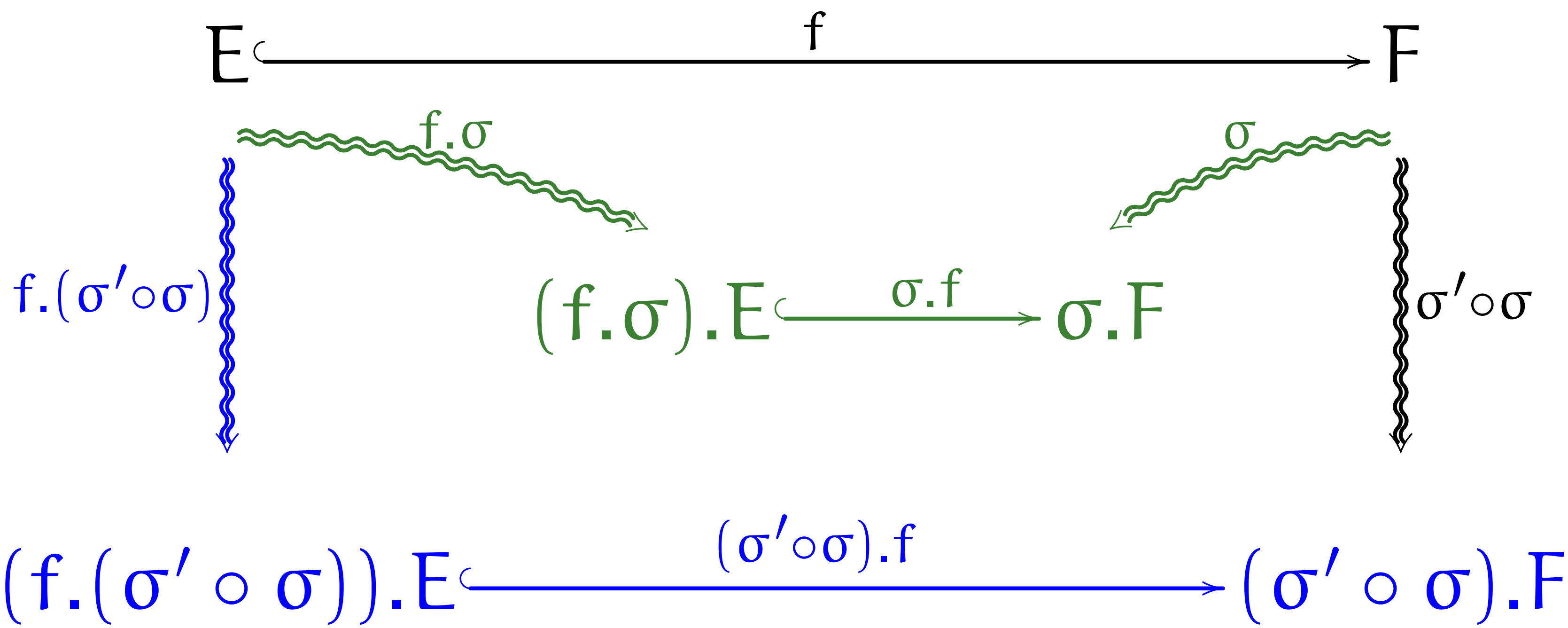
Product of transformations



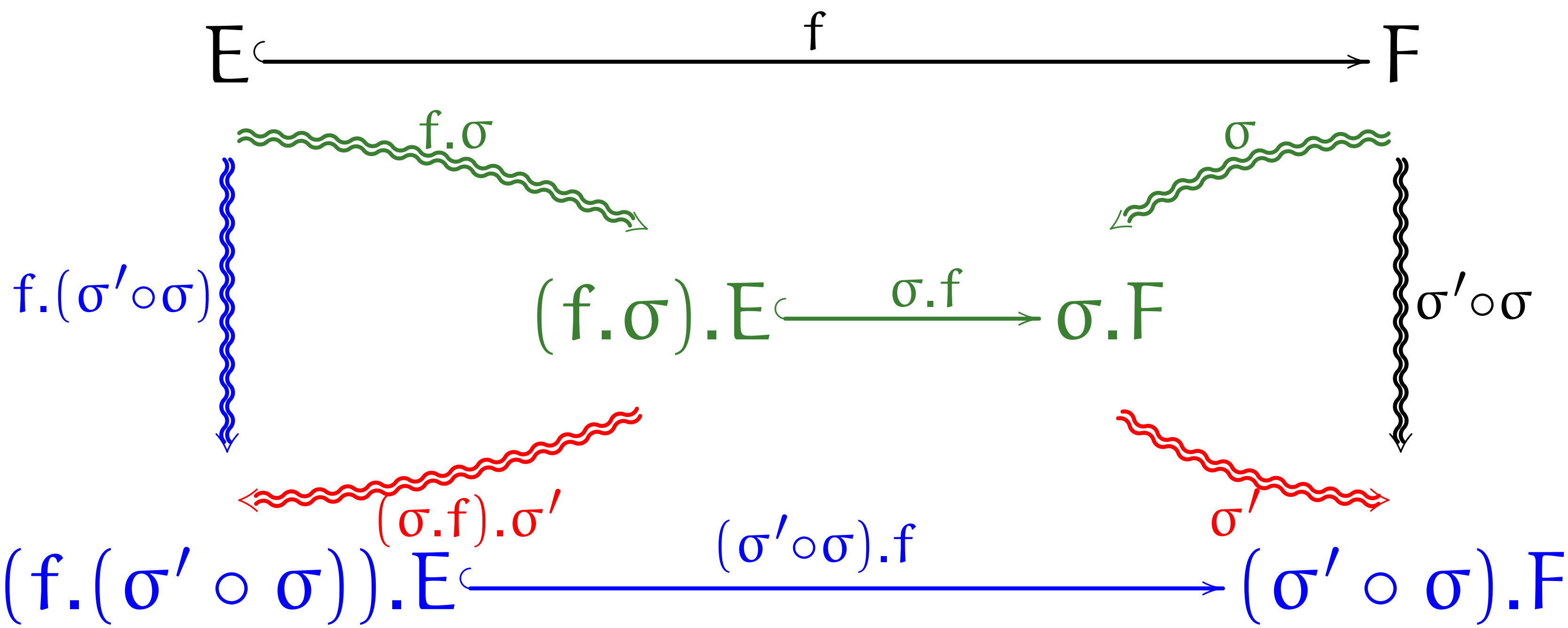
Product of transformations



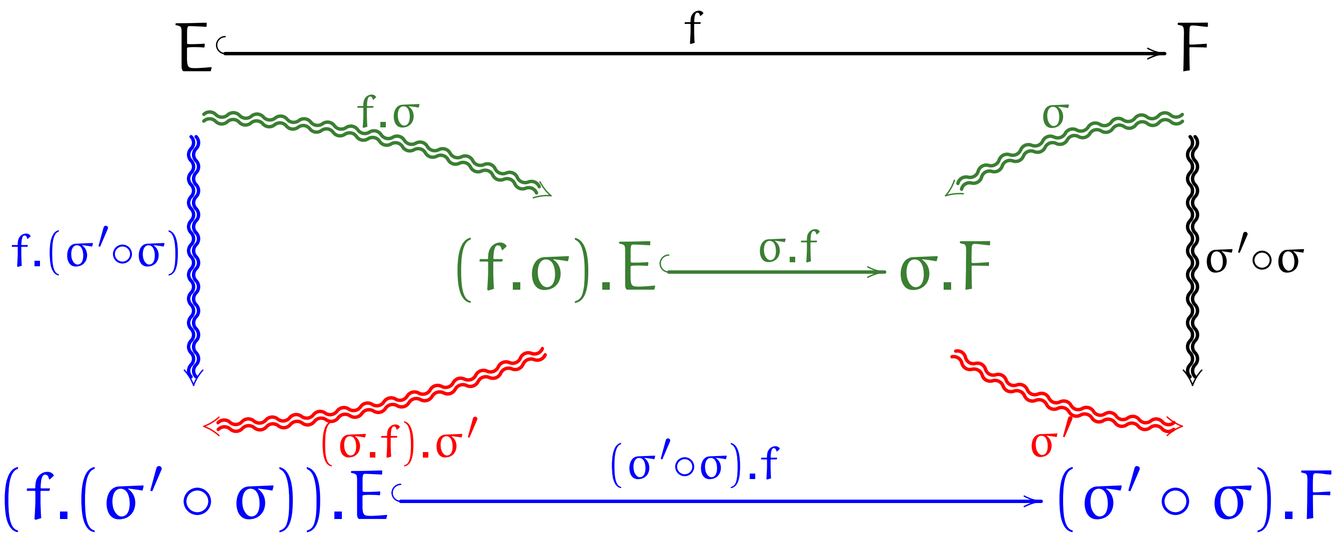
Product of transformations



Product of transformations



Product of transformations



We assume that:

- $(\sigma' \circ \sigma).F = \sigma'.(\sigma.F)$
- $f.(\sigma' \circ \sigma) = ((f.\sigma).\sigma') \circ (f.\sigma)$
- $(\sigma' \circ \sigma).f = \sigma'.(\sigma.f)$

Images of fully specified site graphs

We assume that for any site graph G and any transformation $\sigma \in \mathbb{G}_G$ the two following assertions are equivalent:

1. G is fully specified;
2. $\sigma.G$ is fully specified.

Images of partial embeddings

For any partial embedding $\phi : L \stackrel{f}{\hookleftarrow} D \stackrel{g}{\hookrightarrow} R$,
We assume that:

- if
$$\begin{cases} f.\sigma_L = g.\sigma_R \\ f.\sigma'_L = g.\sigma'_R \end{cases}$$
- then
$$f.(\sigma_L \circ \sigma'_L) = g.(\sigma_R \circ \sigma'_R),$$

for any $\sigma_L, \sigma'_L \in \mathbb{G}_L$, $\sigma_R, \sigma'_R \in \mathbb{G}_R$,

We consider:
$$\mathbb{G}_\phi \stackrel{\Delta}{=} \{(\sigma_L, \sigma_R) \in \mathbb{G}_L \times \mathbb{G}_R \mid f.\sigma_L = g.\sigma_R\}.$$

Images of rules

We assume that for any partial embedding $\phi : L \overset{f}{\hookleftarrow} D \overset{g}{\hookrightarrow} R$ and any (pair of) transformation(s) $(\sigma_L, \sigma_R) \in \mathbb{G}_\phi$ the two following assertions are equivalent:

1. ϕ is a rule;
2. $\sigma_L.L \overset{\sigma_L.f}{\hookleftarrow} (f.\sigma_L).D \overset{\sigma_R.g}{\hookrightarrow} \sigma_R.R$ is a rule.

Images of push-outs

Theorem 1 Let r be a rule, and $(\sigma_L, \sigma_R) \in \mathbb{G}_r$ be a pair of transformations. If the following diagram:

$$
\begin{array}{ccc}
L' & \xrightarrow{\quad r \quad} & R' \\
{\scriptstyle h_L}\big\uparrow & & \big\uparrow{\scriptstyle h_R} \\
L & \xrightarrow[\quad r' \quad]{} & R
\end{array}
$$

is a push-out, then the following diagram:

$$
\begin{array}{ccc}
\sigma_L.L' & \xrightarrow{\quad (\sigma_L,\sigma_R).r \quad} & \sigma_R.R' \\
{\scriptstyle \sigma_L.h_L}\big\uparrow & & \big\uparrow{\scriptstyle \sigma_R.h_R} \\
(h_L.\sigma_L).L & \xrightarrow[\quad (h_L.\sigma_L,h_R.\sigma_R).r' \quad]{} & (h_R.\sigma_R).R
\end{array}
$$

is a push-out as well.

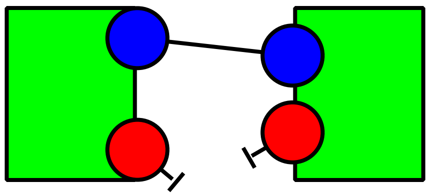
Subgroups of transformations

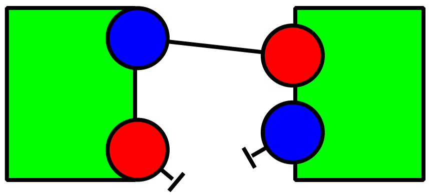
Theorem 2
If, for any embedding h between two site graphs G and H:

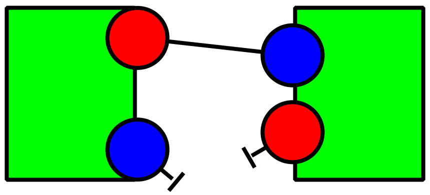
- we have a subset $\mathbb{G}_G^{'}$ of $\mathbb{G}_G$;
- for any transformation $\sigma \in \mathbb{G}_G^{'}$, $\mathbb{G}_G^{'} = \mathbb{G}_{(\sigma.G)}^{'}$;
- for any two σ, σ' transformations in $\mathbb{G}_G^{'}$, $\sigma \circ \sigma' \in \mathbb{G}_G^{'}$;
- for any transformation $\sigma \in \mathbb{G}_H^{'}$, $h.\sigma \in \mathbb{G}_G^{'}$;

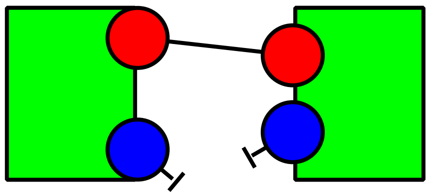
then the groups $(\mathbb{G}_G^{'})$ define a set of transformations.

Example:
Heterogeneous site permutations

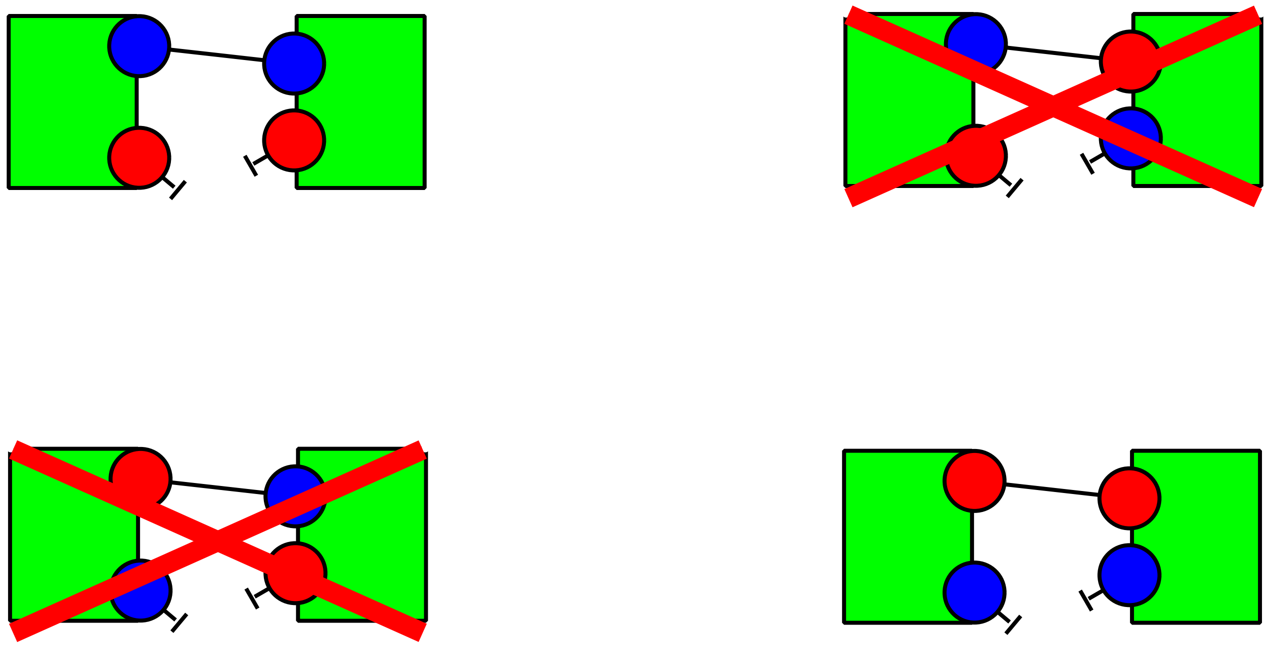








Example:
Homogeneous site permutations



Overview

1. Context and motivations
2. Case study
3. Kappa semantics
4. Symmetries in site-graphs
   (a) Groups of transformations
   (b) Action of the transformations
5. Symmetric models
6. Conclusion

Group actions over site graphs

Let G, G' be two site graphs.

We write $G \approx_{\mathbb{G}} G'$ if and only if there exists $\sigma \in \mathbb{G}_G$ such that $G' = \sigma.G$.

The function:

$$\begin{cases} \mathbb{G}_G \times [G]_{\approx_{\mathbb{G}}} & \rightarrow & [G]_{\approx_{\mathbb{G}}} \\ (\sigma, G) & \mapsto & \sigma.G \end{cases}$$

is a group action.

That is to say:

- $\varepsilon.G = G$;
- $\sigma'.(\sigma.G) = (\sigma' \circ \sigma).G$.

Group actions over embeddings

Let f, f' be two embeddings.

We write $f \approx_{\mathbb{G}} f'$ if and only if there exists $\sigma \in \mathbb{G}_{\mathsf{IM}(f)}$ such that $f' = \sigma.f$.

The function:

$$\begin{cases} \mathbb{G}_{\mathsf{IM}(f)} \times [f]_{\approx_{\mathbb{G}}} & \rightarrow & [f]_{\approx_{\mathbb{G}}} \\ (\sigma, f) & \mapsto & \sigma.f \end{cases}$$

is a group action.

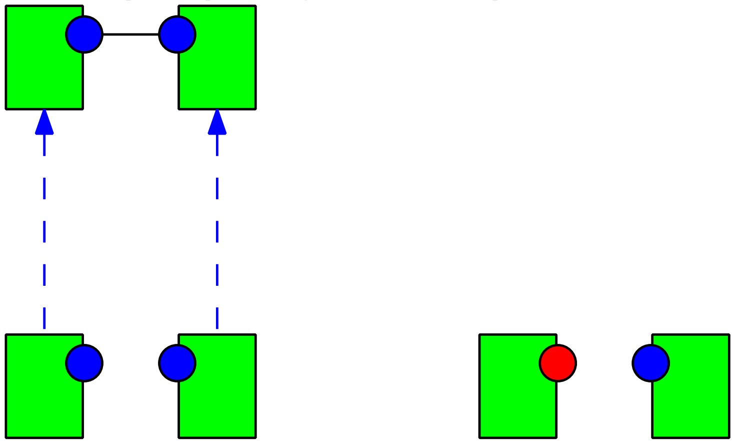
Compatible embeddings

An embedding f between two site graphs G and H is said compatible if and only if:

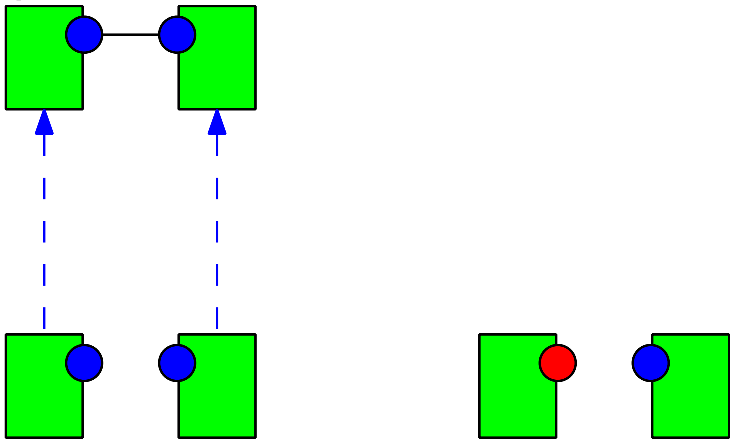
$$\mathbb{G}_G = \{f.\sigma \mid \sigma \in \mathbb{G}_H\}$$

(that is to say that any transformation that can be applied to the domain of f can be extended to the image of f).

This property is not preserved by subgroups of transformations:



Heterogeneous permutations



Homogeneous permutations

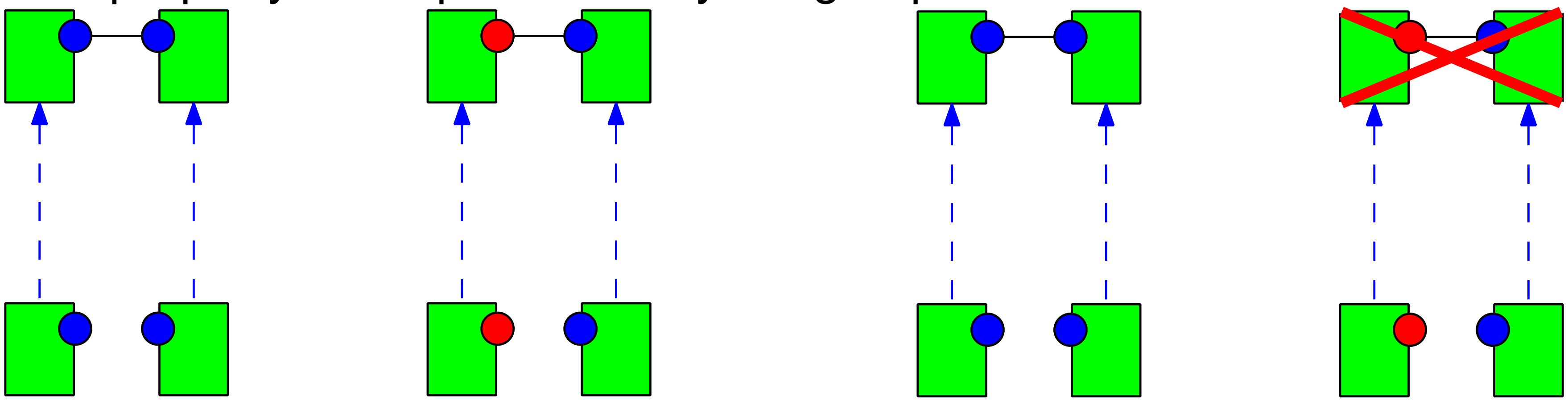
Compatible embeddings

An embedding f between two site graphs G and H is said compatible if and only if:

$$\mathbb{G}_G = \{f.\sigma \mid \sigma \in \mathbb{G}_H\}$$

(that is to say that any transformation that can be applied to the domain of f can be extended to the image of f).

This property is not preserved by subgroups of transformations:



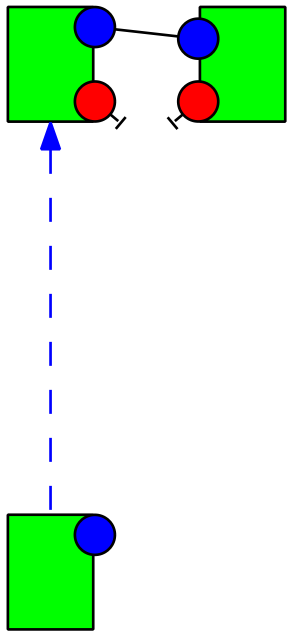
Heterogeneous permutations

Homogeneous permutations

Decomposition of transformations along an embedding

When f is an embedding between two site graphs G and H, we have:

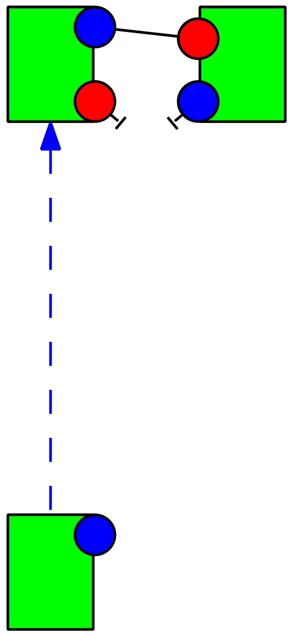
$$\mathbb{G}_H \approx \{\sigma \in \mathbb{G}_H \mid f.\sigma = \varepsilon_G\} \times \{h.\sigma \mid \sigma \in \mathbb{G}_H\}.$$



Decomposition of transformations along an embedding

When f is an embedding between two site graphs G and H, we have:

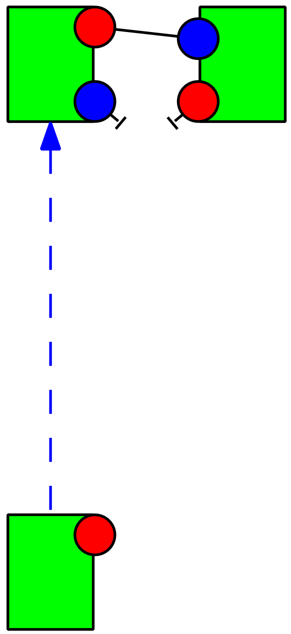
$$\mathbb{G}_{\mathrm{H}} \approx \{\sigma \in \mathbb{G}_{\mathrm{H}} \mid \mathrm{f}.\sigma = \varepsilon_{\mathrm{G}}\} \times \{\mathrm{h}.\sigma \mid \sigma \in \mathbb{G}_{\mathrm{H}}\}.$$



Decomposition of transformations along an embedding

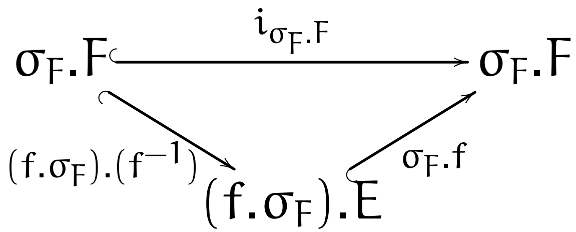
When f is an embedding between two site graphs G and H, we have:

$$\mathbb{G}_H \approx \{\sigma \in \mathbb{G}_H \mid f.\sigma = \varepsilon_G\} \times \{h.\sigma \mid \sigma \in \mathbb{G}_H\}.$$



Images of isomorphisms

The image of an isomorphism is an isomorphism.



The image of an automorphism may be not an automorphism.

Yet, for any site graph G, we have:

$$\textit{Card}(G) = \textit{Card}(\{\phi \mid \phi \in \textit{Aut}(G)\}) \times \textit{Card}(\{G' \mid G' \approx G \textit{ and } G' \approx_{\mathbb{G}} G\}).$$

Group actions over rules

Let $r : L \overset{f}{\hookleftarrow} D \overset{g}{\hookrightarrow} R$ be a rule.

We define the symmetric of r by a symmetry $(\sigma_L, \sigma_R) \in \mathbb{G}_r$ as follows:

$$(\sigma_L, \sigma_R).r \triangleq \sigma_L.L \overset{\sigma_L.f}{\hookleftarrow} (f.\sigma_L).D \overset{\sigma_R.g}{\hookrightarrow} \sigma_R.R$$

We write $r \approx_{\mathbb{G}} r'$ if and only if there exists $\sigma \in \mathbb{G}_r$ such that $r' = \sigma.r$.

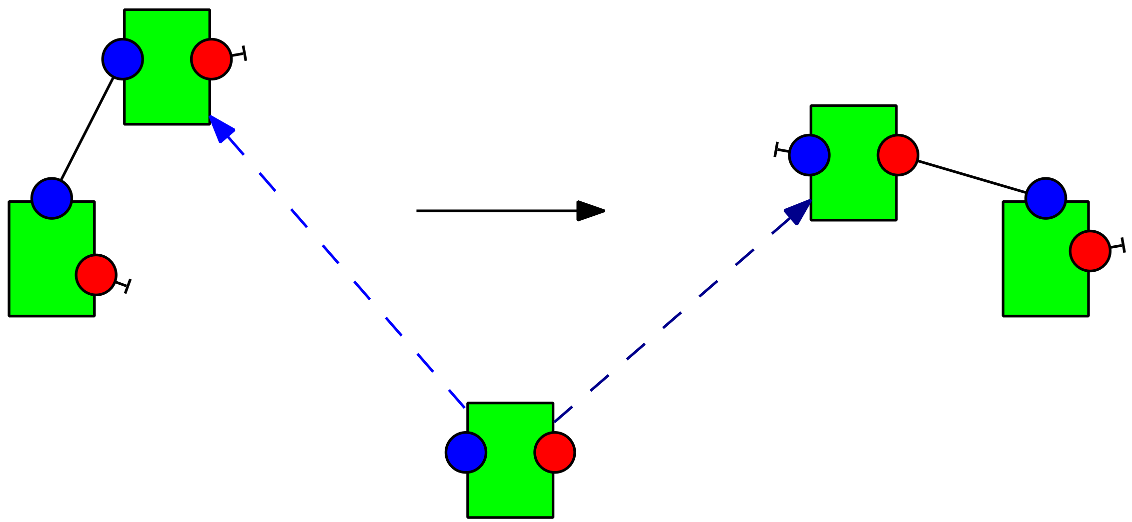
Then:

- $\mathbb{G}_r$ is a group.
- the groups $\mathbb{G}_r$ and $\mathbb{G}_{\sigma.r}$ are the same, for any symmetry $\sigma \in \mathbb{G}_r$.
- The function:

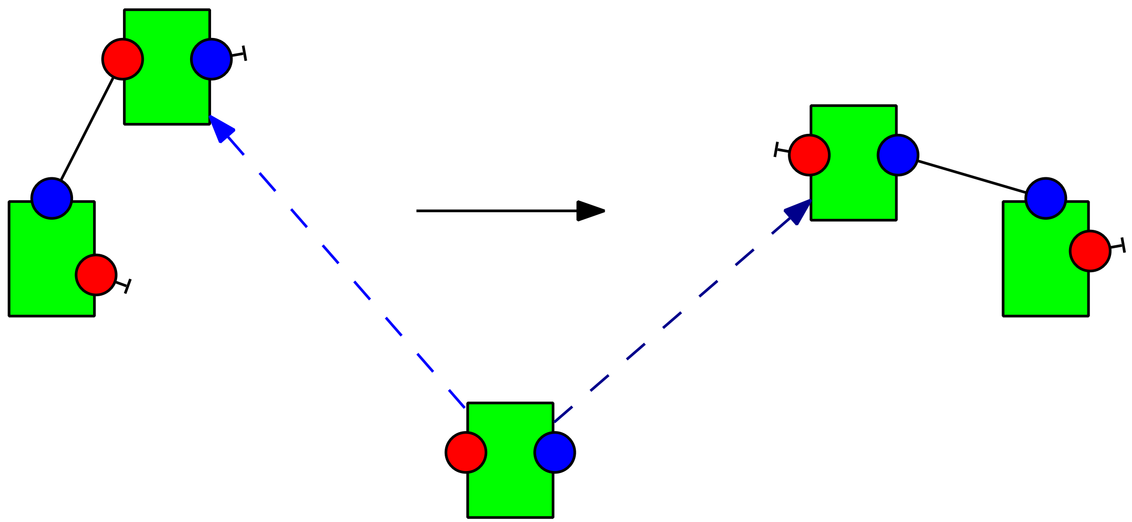
$$\begin{cases} \mathbb{G}_r \times [r]_{\approx_{\mathbb{G}}} & \rightarrow & [r]_{\approx_{\mathbb{G}}} \\ (\sigma, r) & \mapsto & \sigma.r. \end{cases}$$

  is a group action.

Decomposition of the group of transformations over a rule

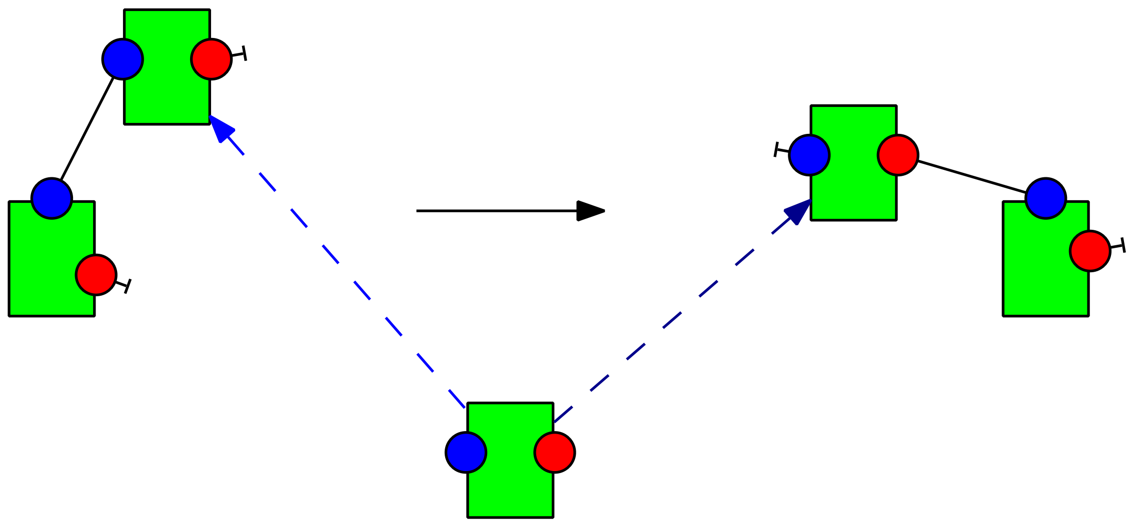


Decomposition of the group of transformations over a rule

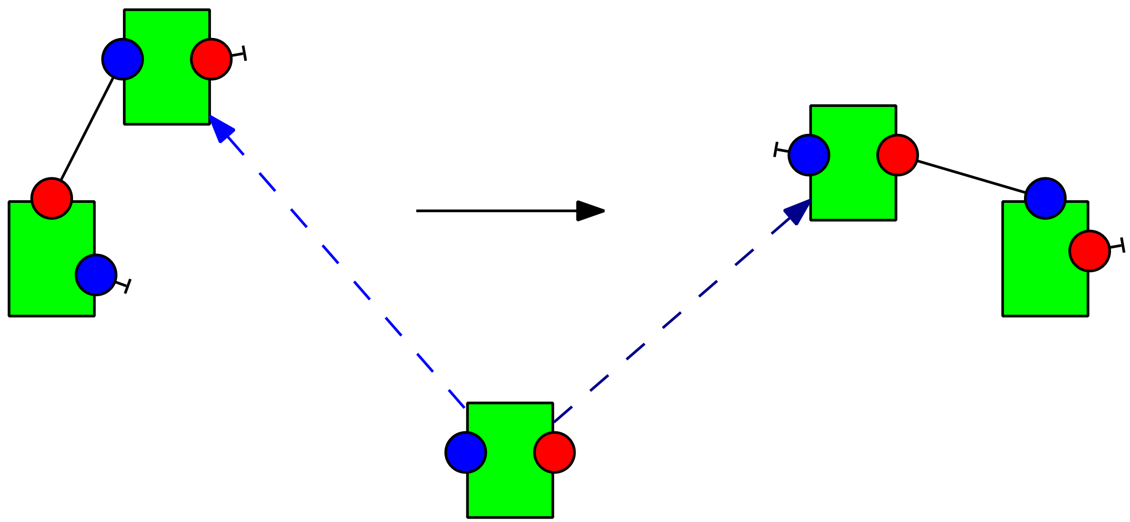


Some transformations operate on the domain of the rule.

Decomposition of the group of transformations over a rule

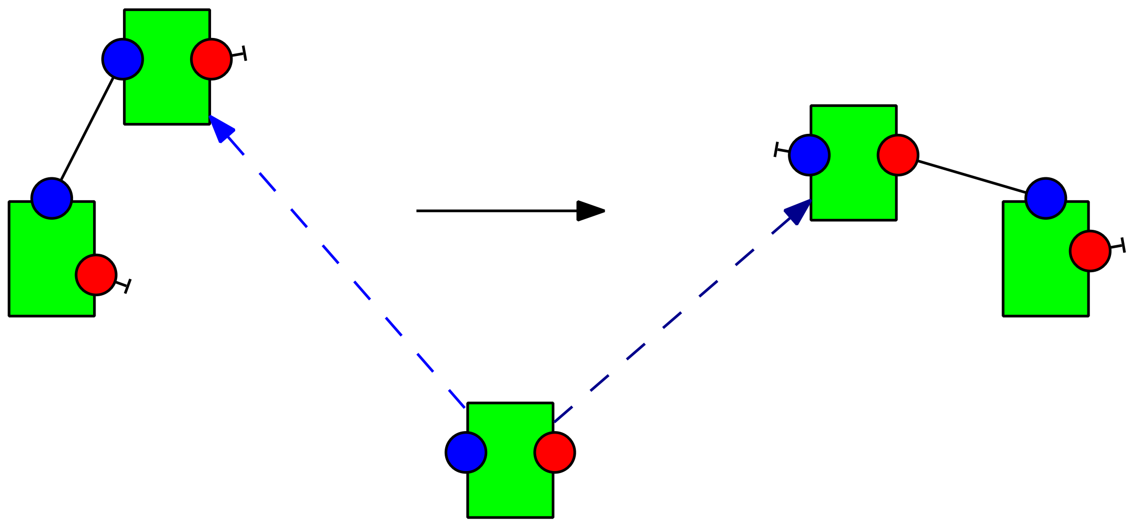


Decomposition of the group of transformations over a rule

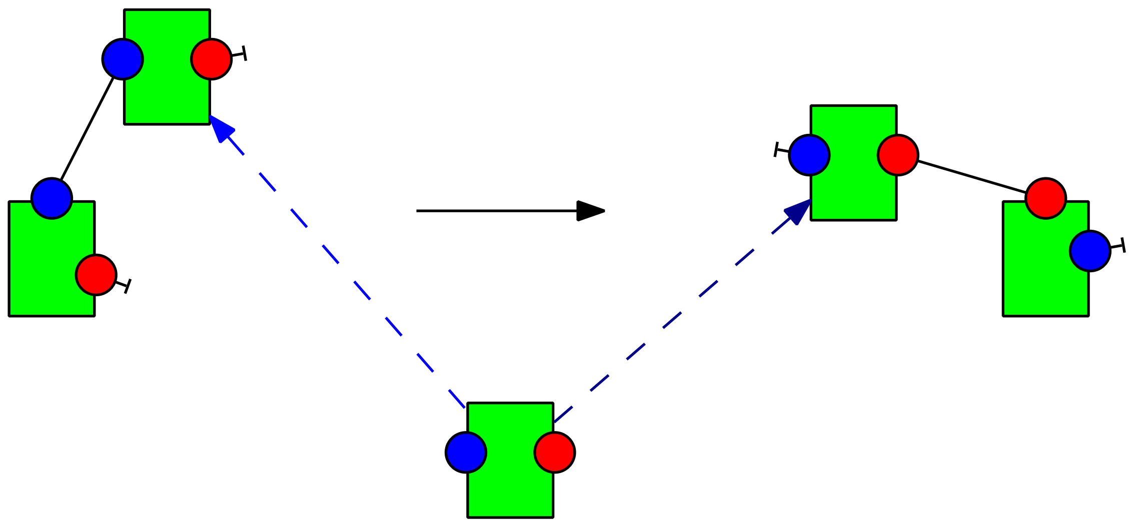


Some transformations operate on degraded agents.

Decomposition of the group of transformations over a rule



Decomposition of the group of transformations over a rule



Some transformations operate on created agents.

Decomposition of the group of transformations over a rule

When $r : L \overset{f}{\hookleftarrow} D \overset{g}{\hookrightarrow} R$ is a rule,
we have:

$$\mathbb{G}_r \approx \{\sigma \in \mathbb{G}_L \mid f.\sigma = \varepsilon_D\} \times \{\sigma \mid \exists(\sigma_L, \sigma_R) \in \mathbb{G}_r,\ \sigma = f.\sigma_L = f.\sigma_R\} \times \{\sigma \in \mathbb{G}_R \mid g.\sigma = \varepsilon_D\}.$$

Symmetries distribute over:

1. the ones on removed agents;
2. the ones on new agents;
3. the ones on the domain which are compatible with rule.

Group actions over push-out

Theorem 3 Let r be a rule. The function which maps each pair of transformations $(\sigma_L, \sigma_R) \in \mathbb{G}_r$ and each push-out of the form:

$$\begin{array}{ccc} L' & \xrightarrow{\quad r' \quad} & R' \\ h_L \uparrow & \lrcorner & \uparrow h_R \\ L & \xrightarrow[\quad r'' \quad]{} & R \end{array}$$

with $r' \approx_{\mathbb{G}} r$, to the push-out:

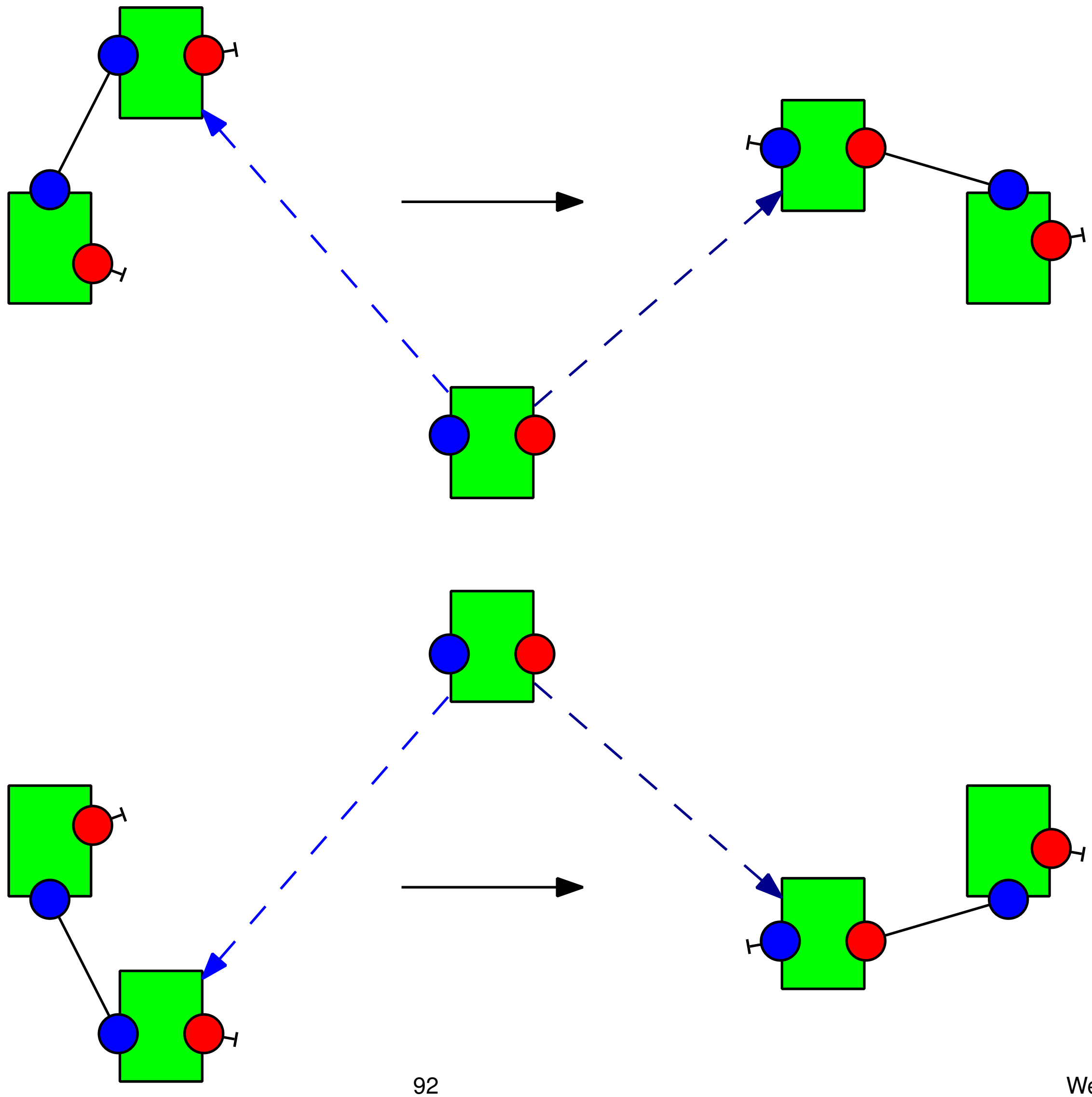
$$\begin{array}{ccc} \sigma_L.L' & \xrightarrow{\quad (\sigma_L,\sigma_R).r' \quad} & \sigma_R.R' \\ \sigma_L.h_L \uparrow & \lrcorner & \uparrow \sigma_R.h_R \\ (h_L.\sigma_L).L & \xrightarrow[\quad (h_L.\sigma_L, h_R.\sigma_R).r'' \quad]{} & (h_R.\sigma_R).R \end{array}$$

is a group action.

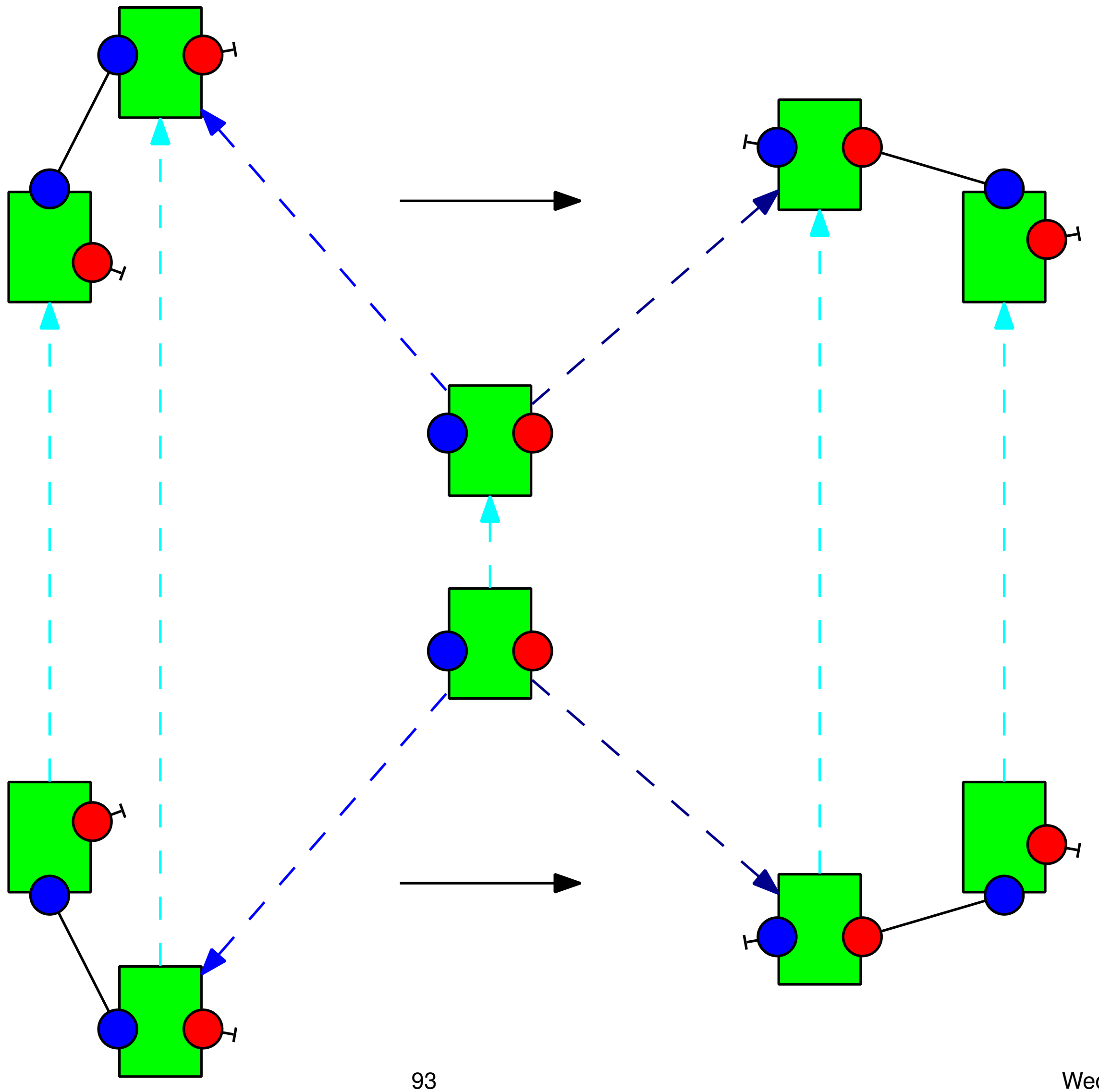
Overview

1. Context and motivations
2. Case study
3. Kappa semantics
4. Symmetries in site-graphs
5. Symmetric models
    (a) Symmetries among set of rules
    (b) Induced bisimulations
6. Conclusion

Isomorphic rules



Isomorphic rules



Symmetric model

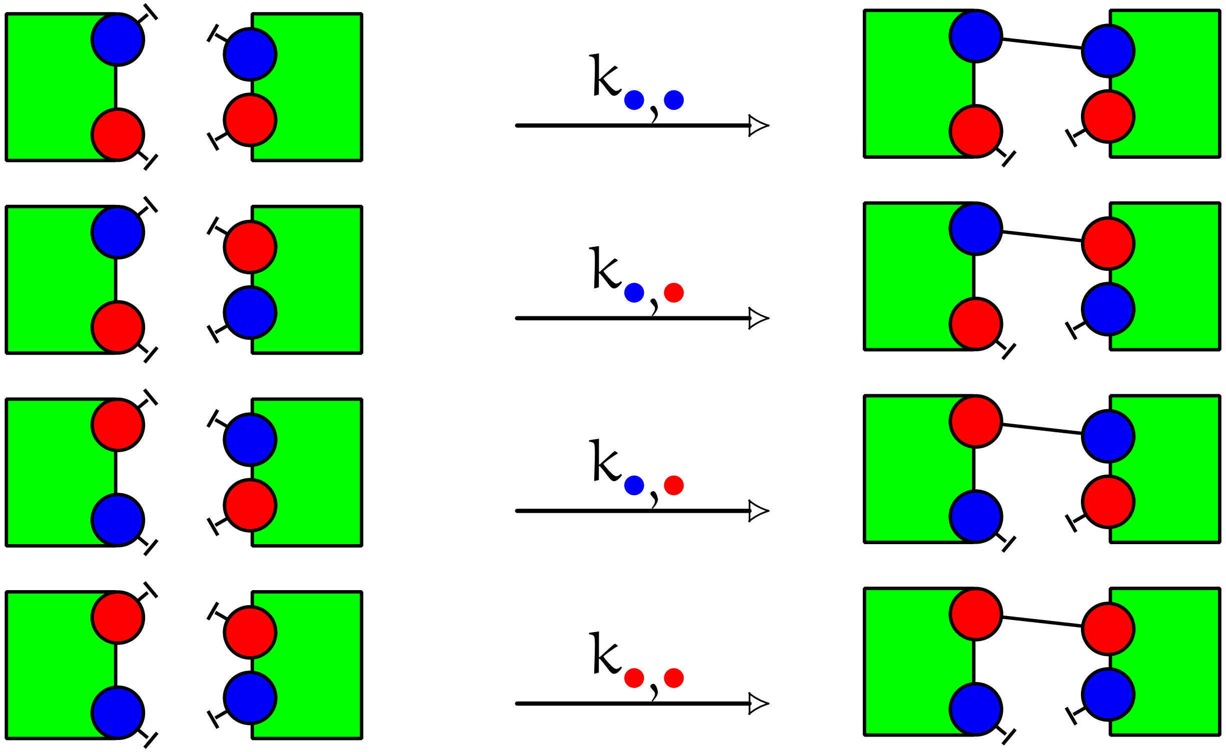
We assume that the model contains atmost one rule per isomorphism class.

A model is $\mathbb{G}$-symmetric if and only if:

- for any rule r in the model and any pair of symmetries $\sigma \in \mathbb{G}_r$, there is (unique) a rule r' in the model that is isomorphic to the rule $\sigma.r$.
- and, with the same notations, we have $g(r) = g(r')$ where:

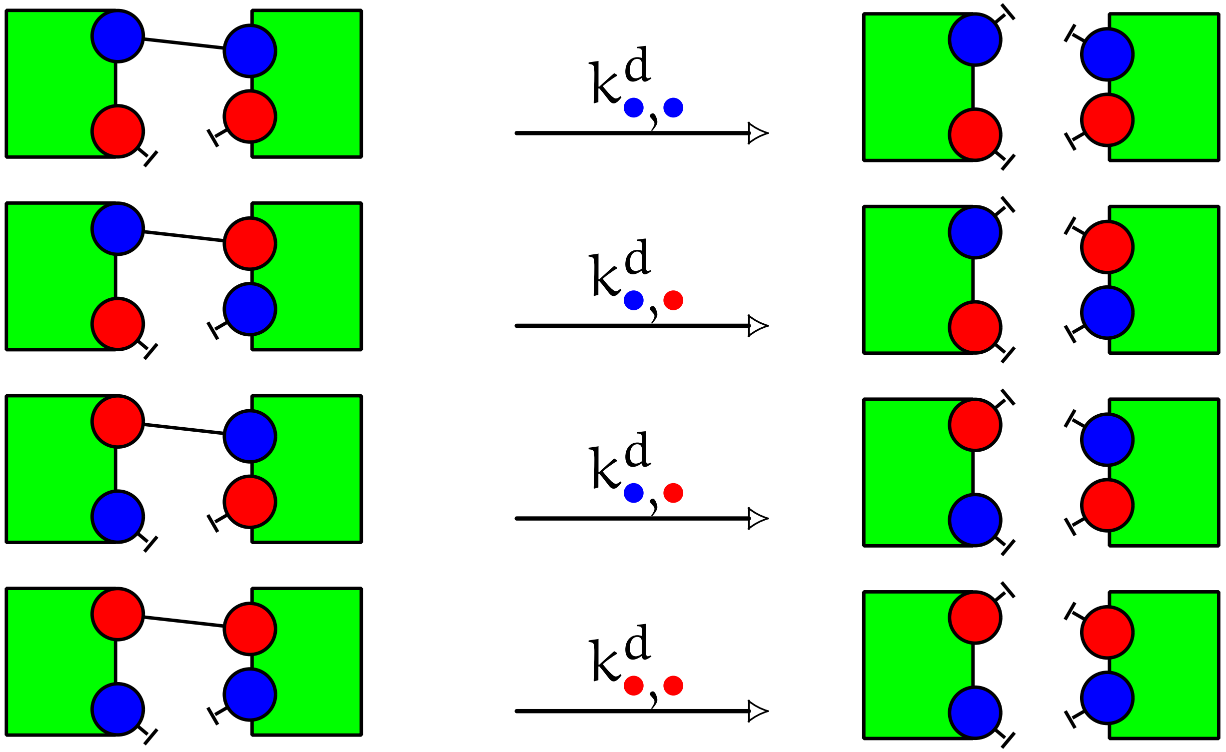
$$g(r) \stackrel{\Delta}{=} \frac{k(r)}{\textit{card}(\{\sigma \in \mathbb{G}_r \mid \sigma.r \approx r\})\textit{card}(\textit{Aut}(\textit{lhs}(r)))}.$$

Binding rules



$$\frac{k_{{\color{blue}\bullet},{\color{blue}\bullet}}}{1\cdot 2} = \frac{k_{{\color{red}\bullet},{\color{red}\bullet}}}{1\cdot 2} = \frac{k_{{\color{blue}\bullet},{\color{red}\bullet}}}{2\cdot 2}$$

Unbinding rules



$$\frac{k^d_{{\color{blue}\bullet},{\color{blue}\bullet}}}{1 \cdot 2} = \frac{k^d_{{\color{red}\bullet},{\color{red}\bullet}}}{1 \cdot 2} = \frac{k^d_{{\color{blue}\bullet},{\color{red}\bullet}}}{2 \cdot 1}$$

Overview

1. Context and motivations
2. Case study
3. Kappa semantics
4. Symmetries in site-graphs
5. Symmetric models
    (a) Symmetries among set of rules
    (b) Induced bisimulations
6. Conclusion

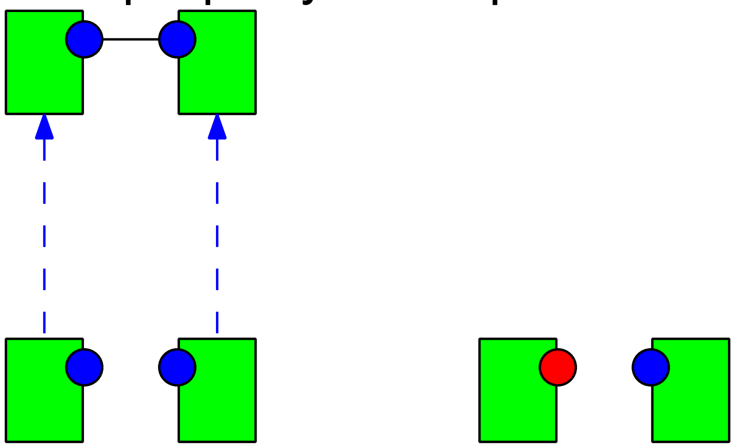
Compatible embeddings (reminders)

An embedding f between two site graphs G and H is said compatible if and only if:

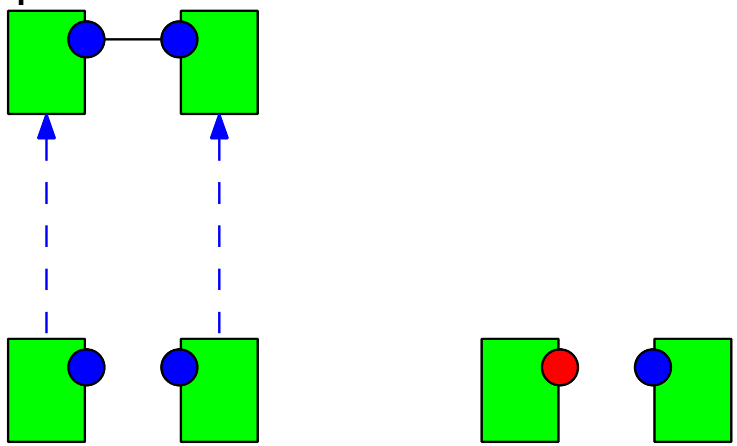
$$\mathbb{G}_G = \{f.\sigma \mid \sigma \in \mathbb{G}_H\}$$

(that is to say that any transformation that can be applied to the domain of f can be extended to the image of f).

This property is not preserved by subgroups of transformations:



Heterogeneous permutations



Homogeneous permutations

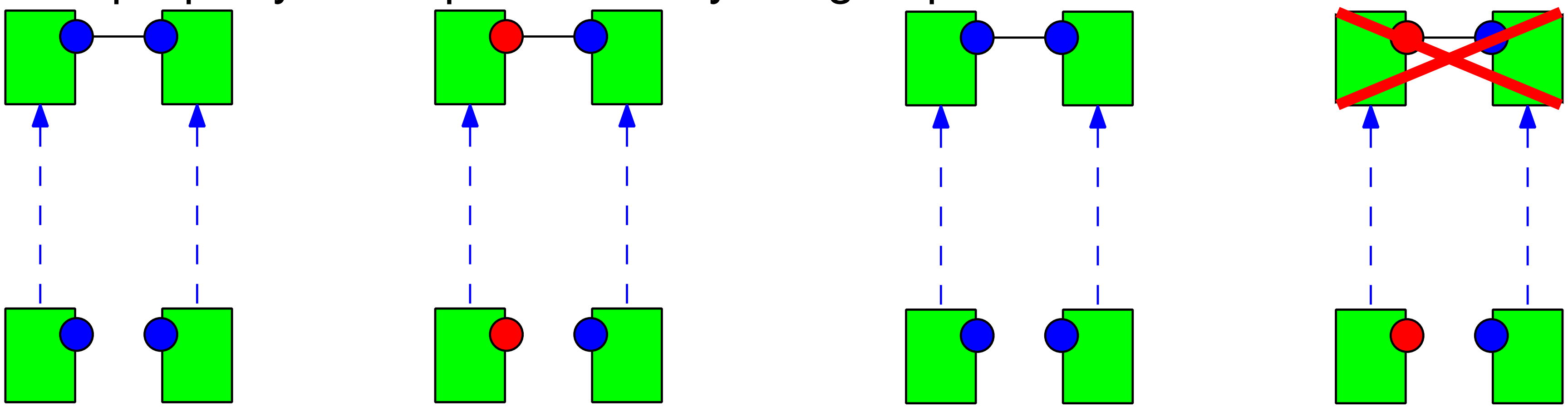
Compatible embeddings (reminders)

An embedding f between two site graphs G and H is said compatible if and only if:

$$\mathbb{G}_G = \{f.\sigma \mid \sigma \in \mathbb{G}_H\}$$

(that is to say that any transformation that can be applied to the domain of f can be extended to the image of f).

This property is not preserved by subgroups of transformations:

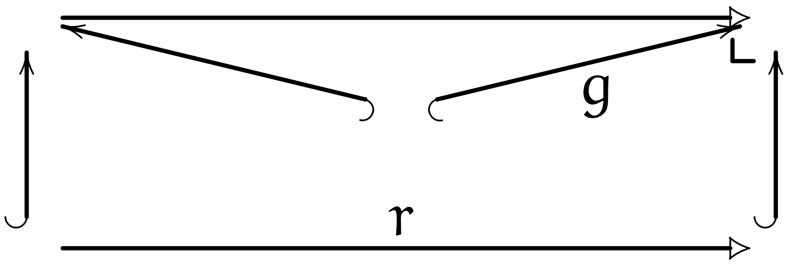


Heterogeneous permutations

Homogeneous permutations

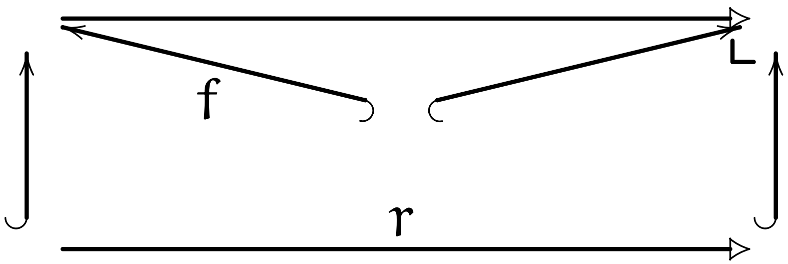
Compatible rules

We say that a rule r is forward-compatible if and only if, for any push-out of the following form:



the embedding g is compatible.

We say that a rule r is backward-compatible if and only if, for any push-out of the following form:



the embedding f is compatible.

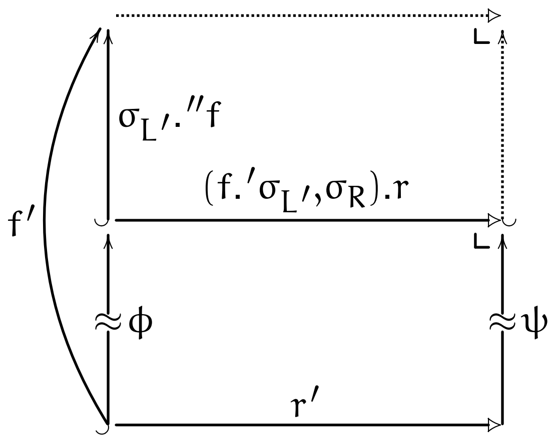
Lumping states

We say that two states $q, q' \in \mathcal{Q}$ are isomorphic if and only if there exist $M \in q$ and $M' \in q'$ such that $M \approx_{\mathbb{G}} M'$.

In such a case, we write $q \approx_{\mathbb{G}} q'$.
$\approx_{\mathbb{G}}$ is an equivalence relation.

Lumping the transtion labels

We say that two labels $(r, C) \in \mathcal{L}$ and $(r', C') \in \mathcal{L}$ are isomorphic if and only if there exist an embedding $f \in C$, an embedding $f' \in C'$, a pair of symmetries $(\sigma_{L'}, \sigma_R) \in \mathbb{G}_{\mathsf{IM}(f)} \times \mathbb{G}_{\mathsf{rhs}(r)}$ such that $(f.'\sigma_{L'}, \sigma_R) \in \mathbb{G}_r$ and two isomorphisms ϕ and ψ such that the following diagram commutes:



In such a case, we write $(r, C) \approx_{\mathbb{G}} (r', C')$ (this is also an equivalence relation).

Weighted flow

Let $X, X' \subseteq \mathcal{Q}$ and $Y \subseteq \mathcal{L}$.
Let ω be a function from $\mathcal{Q}$ to $\mathbb{R}^+$.

We define the flow from X to X' via Y, weighted by the reward function ω by:

$$\mathsf{FLOW}_{\omega}\left(X, Y, X'\right) \stackrel{\Delta}{=} \sum_{q \in X, q' \in X', \lambda \in Y,\ q \xrightarrow{\lambda} q'} \omega(q)\mathsf{RATE}(\lambda)$$

Forward bisimulation

Theorem 4 Let $q, q', q'' \in \mathcal{Q}$ such that $q \approx_{\mathbb{G}} q'$. Let $\lambda \in \mathcal{L}$.
If the model is symmetric and if the rules of the models are forward-compatible, then the following equality holds:

$$\mathsf{FLOW}_{\omega}\left(\{q\}, [\lambda]_{\approx_{\mathbb{G}}}, [q'']_{\approx_{\mathbb{G}}}\right) = \mathsf{FLOW}_{\omega}\left(\{q'\}, [\lambda]_{\approx_{\mathbb{G}}}, [q'']_{\approx_{\mathbb{G}}}\right),$$

with $\omega(q_1) = 1$ for any $q_1 \in \mathcal{Q}$.

Backward bisimulation (DTMC)

Theorem 5 Let $q, q', q'' \in \mathcal{Q}$ such that $q' \approx_{\mathbb{G}} q''$. Let $\lambda \in \mathcal{L}$.
If the model is symmetric and if the rules of the models are backward-compatible, then the following equality holds:

$$\omega(q'')\mathsf{FLOW}_{\omega}\left([q]_{\approx_{\mathbb{G}}}, [\lambda]_{\approx_{\mathbb{G}}}, \{q'\}\right) = \omega(q')\mathsf{FLOW}_{\omega}\left([q]_{\approx_{\mathbb{G}}}, [\lambda]_{\approx_{\mathbb{G}}}, \{q''\}\right),$$

with $\omega(q_1) \stackrel{\Delta}{=} \dfrac{1}{\mathit{card}(\mathit{Aut}(q))}$, for any $q_1 \in \mathcal{Q}$.

Backward bisimulation (CTMC)

Theorem 6 Let $q, q', q'' \in \mathcal{Q}$ such that $q' \approx_{\mathbb{G}} q''$. Let $\lambda \in \mathcal{L}$.
If the model is symmetric and if the rules of the models are both forward- and backward-compatible,
then the following equalities holds:

1. $\mathsf{FLOW}_{\omega}(\{q'\}, \mathcal{Q}, \mathcal{L}) = \mathsf{FLOW}_{\omega}(\{q''\}, \mathcal{Q}, \mathcal{L})$,
   with $\omega(q_1) = 1$ for any $q_1 \in \mathcal{Q}$;
2. $\omega(q'')\mathsf{FLOW}_{\omega}\left([q]_{\approx_{\mathbb{G}}}, [\lambda]_{\approx_{\mathbb{G}}}, \{q'\}\right) = \omega(q')\mathsf{FLOW}_{\omega}\left([q]_{\approx_{\mathbb{G}}}, [\lambda]_{\approx_{\mathbb{G}}}, \{q''\}\right)$,
   with $\omega(q_1) \triangleq \dfrac{1}{\mathit{card}(\mathit{Aut}(q))}$, for any $q_1 \in \mathcal{Q}$.

Overview

1. Context and motivations
2. Case study
3. Kappa semantics
4. Symmetries in site-graphs
5. Symmetric models
6. Conclusion

Conclusion

A fully algebraic framework to infer and use symmetries in Kappa;

- Compatible with the SPO semantics (see [FSTTCS'2012]);
- Can handle side-effects (see the paper);
- Induces forward and/or back and forth bisimulations;
- Can be applied to discover model reductions for the qualitative semantics, the ODEs semantics, and the stochastic semantics [MFPSXXVII];
- Can be combined with other exact model reductions [MFPSXXVI].

This framework is cleaner and more general that the process algebra based one [MFPSXXVII].

Camporesi et al., Combining model reductions. MFPS XXVI (2010)
Camporesi et al., Formal reduction of rule-based models, MFPS XXVII (2011)
Danos et al., Rewriting and Pathway Reconstruction for Rule-Based Models, FSTTCS 2012

Future work

- Investigate which specific classes of symmetries and which specific classes of rules ensure that rules are forward and/or backward compatible with the symmetries;
- Check the compatibility with the DPO (Double Push-Out) semantics;
- Design approximate symmetries using bisimulation metrics
  (ask Norman Ferns).

“AbstractCell” (2009-2013)

“Big Mechanism” (2014-2017)
“CwC” (2015-2018)

“TGFβSysBio" (2015-2018)

MPRI

Model reduction of stochastic rules-based models

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

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

Wednesday, the 4th of January, 2017

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

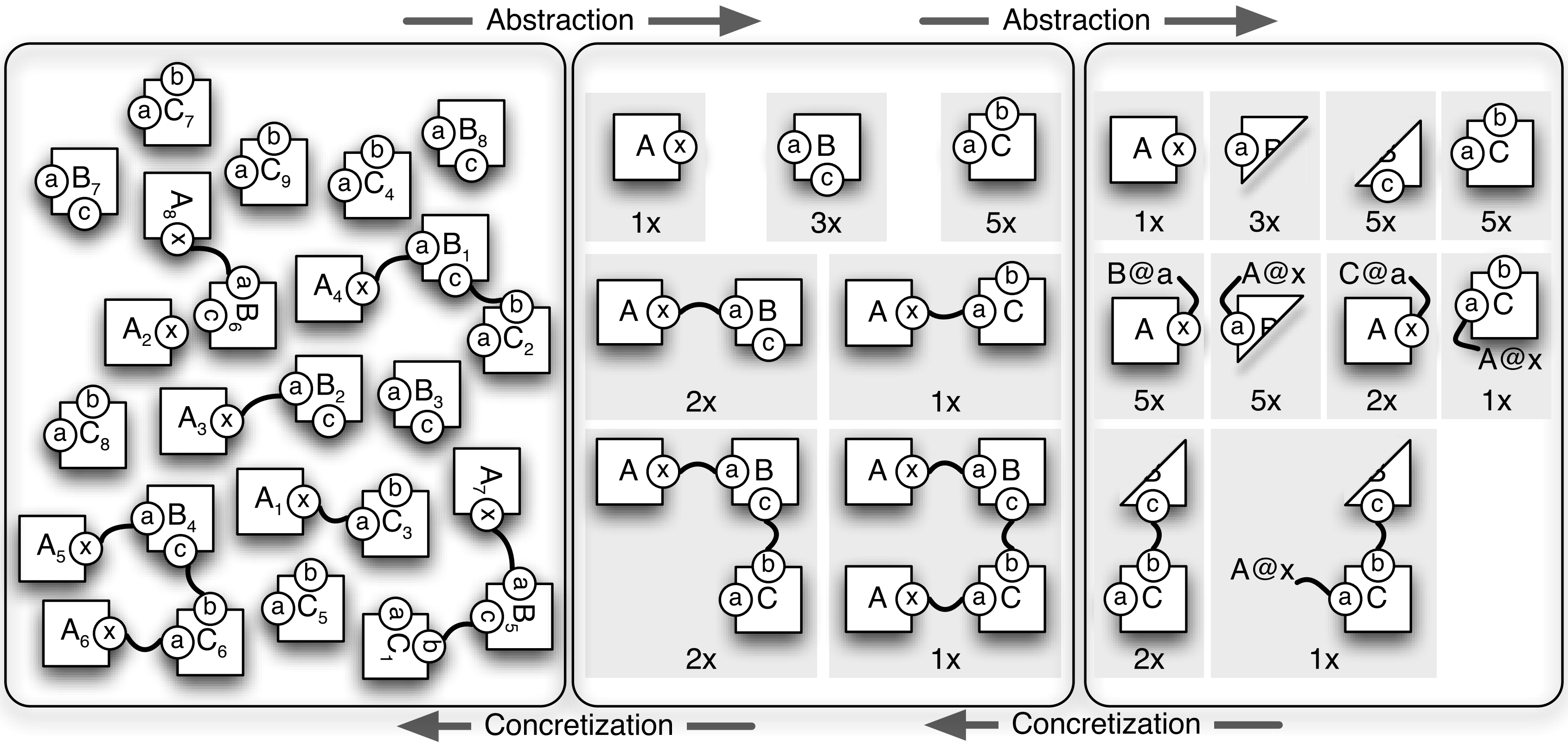
ODE fragments

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?

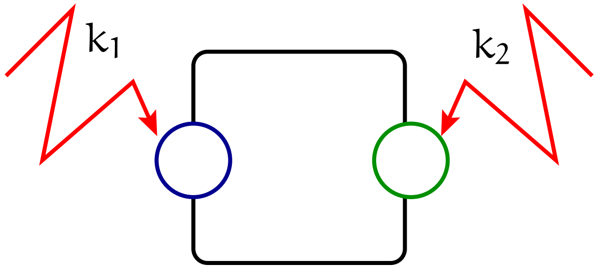
Stochastic fragments ?



Overview

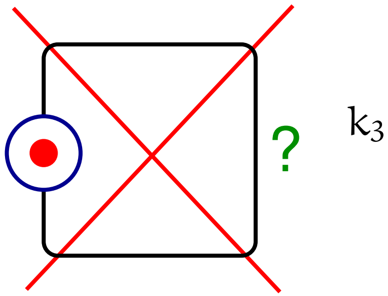
1. Introduction
2. Examples of information flow
3. Symmetric sites
4. Stochastic semantics
5. Lumpability
6. Bisimulations
7. Hierarchy of semantics
8. Conclusion

A model with ubiquitination



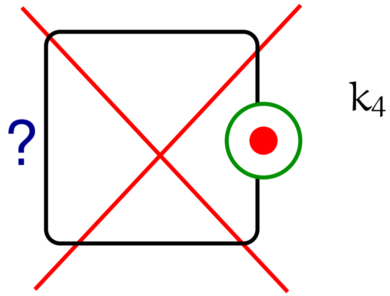
$$P \xrightarrow{k_1} {}^{\star}P \qquad P^{\star} \xrightarrow{k_1} {}^{\star}P^{\star}$$

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



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

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



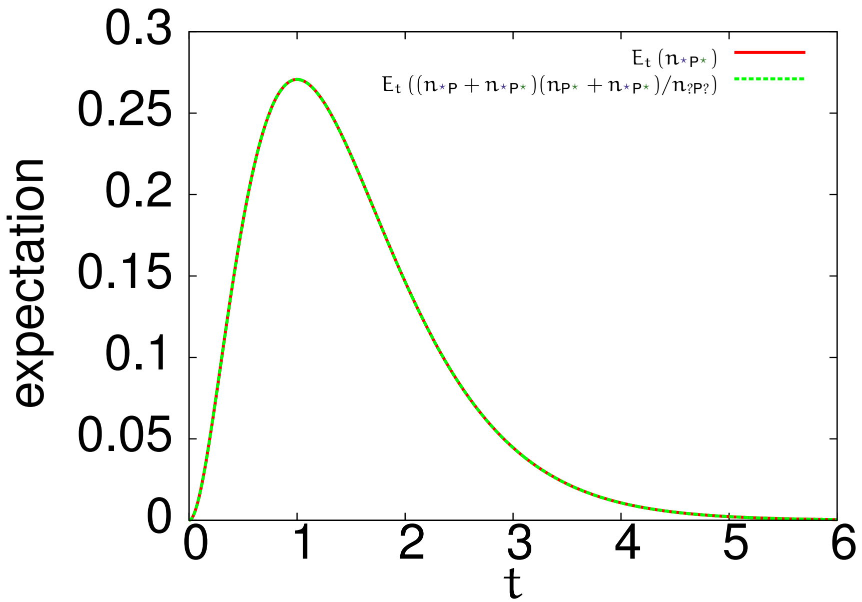
$$P^{\star} \xrightarrow{k_4} \emptyset$$

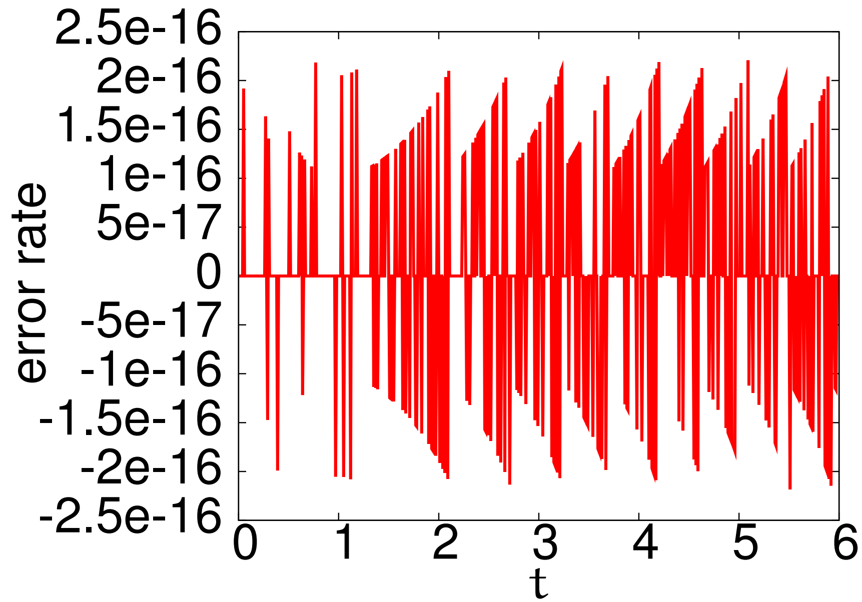
$${}^{\star}P^{\star} \xrightarrow{k_4} \emptyset$$

Statistical independence

We check numerically that:

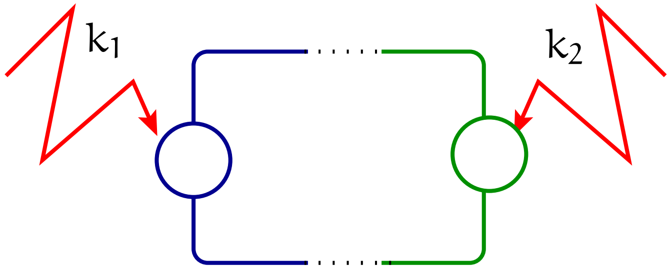
$$E_t\left(n_{\star P\star}\right) = E_t\left(\frac{(n_{\star P} + n_{\star P\star})(n_{P\star} + n_{\star P\star})}{n_P + n_{P\star} + n_{\star P} + n_{\star P\star}}\right).$$





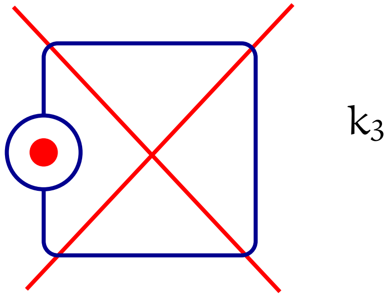
with $k_1 = k_2 = k_3 = k_4 = 1$
and two instances of P at time $t = 0$.

Reduced model



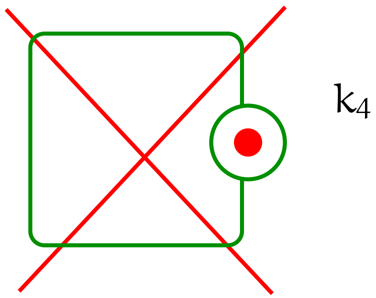
$P \xrightarrow{k_1} {}^{\star}P$

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



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

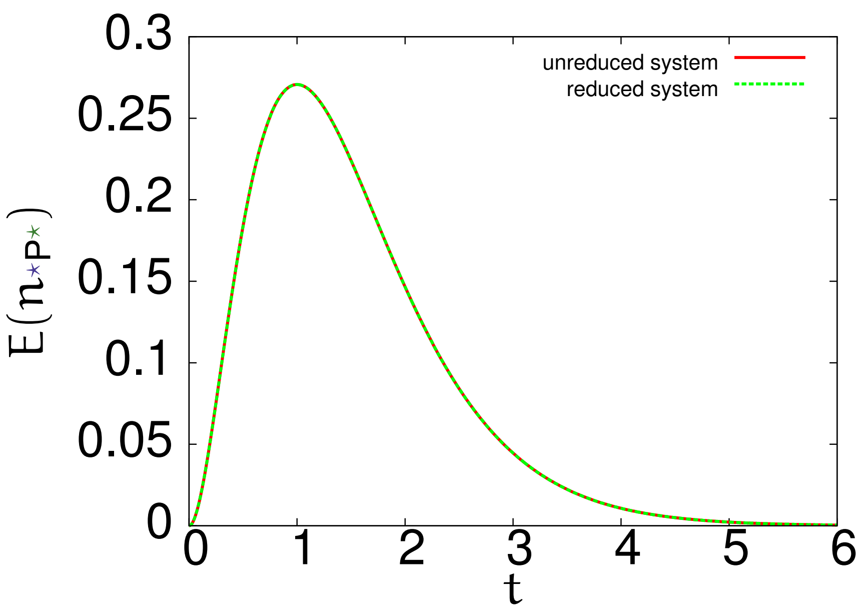
+ side effect: remove one P

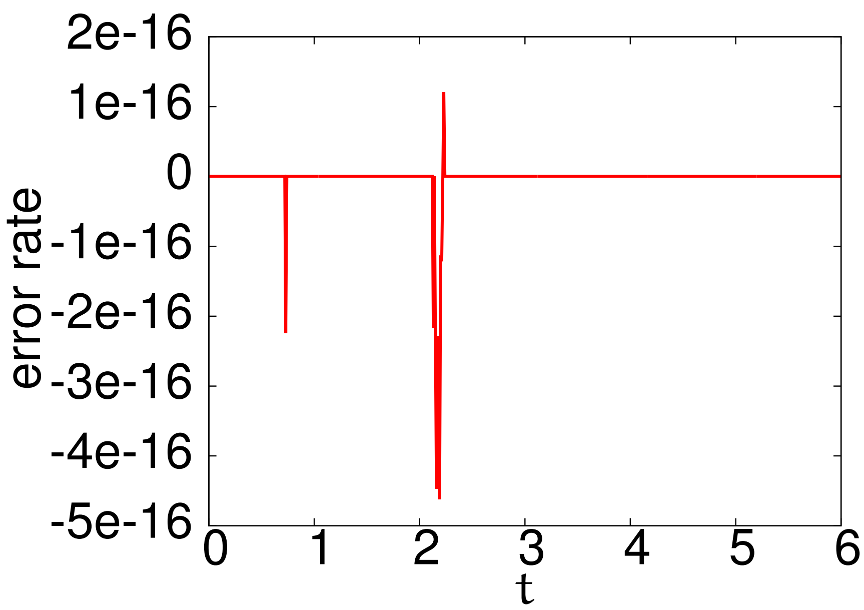


$P^{\star} \xrightarrow{k_4} \emptyset$

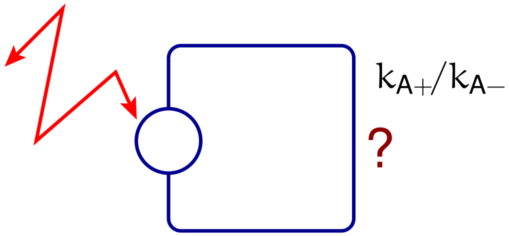
+ side effect: remove one P

Comparison between the two models

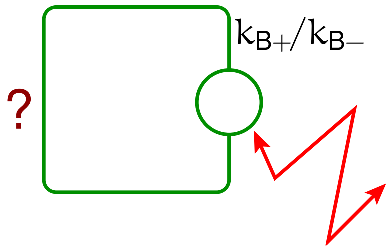




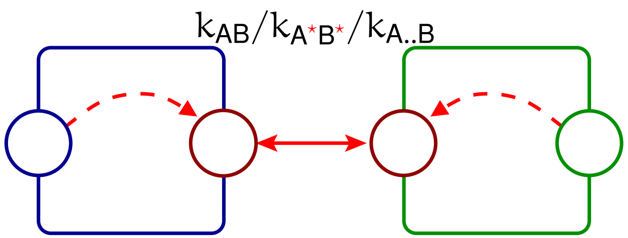
Coupled semi-reactions



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



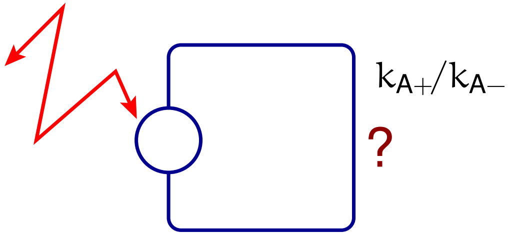
$$B \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} B^{\star}, \quad AB \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} AB^{\star}, \quad A^{\star}B \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} A^{\star}B^{\star}$$



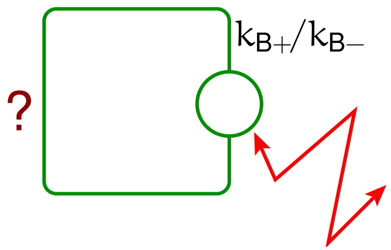
$$A + B \underset{k_{A..B}}{\overset{k_{AB}}{\rightleftharpoons}} AB, \quad A^{\star} + B \underset{k_{A..B}}{\overset{k_{AB}}{\rightleftharpoons}} A^{\star}B,$$

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

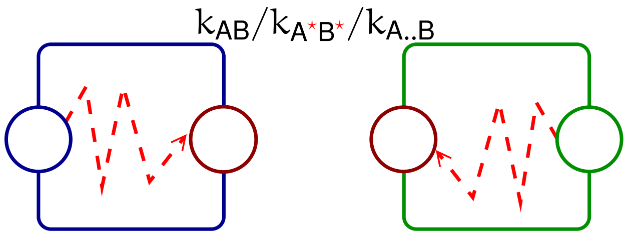
Reduced model



$$A \xrightleftharpoons[k_{A-}]{k_{A+}} A^{\star}, \quad AB^{\diamond} \xrightleftharpoons[k_{A-}]{k_{A+}} A^{\star}B^{\diamond},$$



$$B \xrightleftharpoons[k_{B-}]{k_{B+}} B^{\star}, \quad A^{\diamond}B \xrightleftharpoons[k_{B-}]{k_{B+}} A^{\diamond}B^{\star},$$



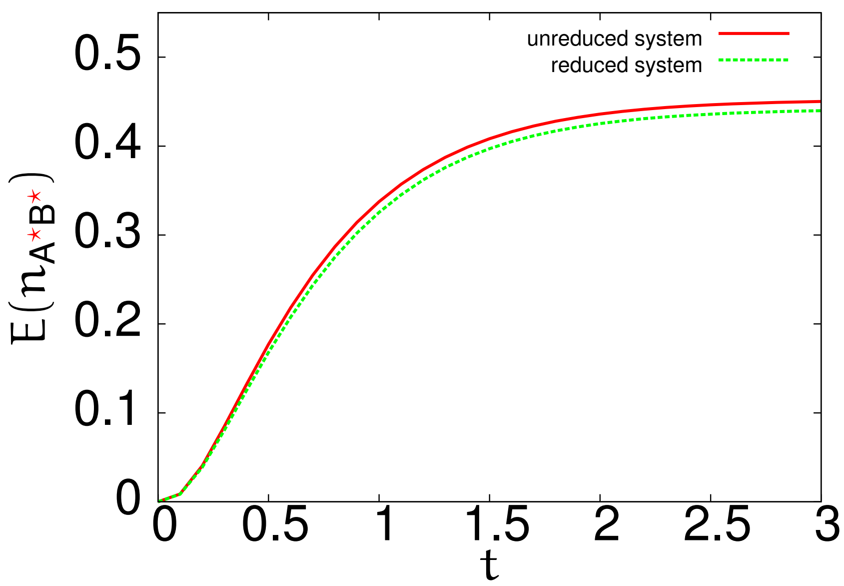
$$A + B \xrightleftharpoons[k_{A..B}/(n_{A^{\diamond}B}+n_{A^{\diamond}B^{\star}})]{k_{AB}} AB^{\diamond} + A^{\diamond}B,$$

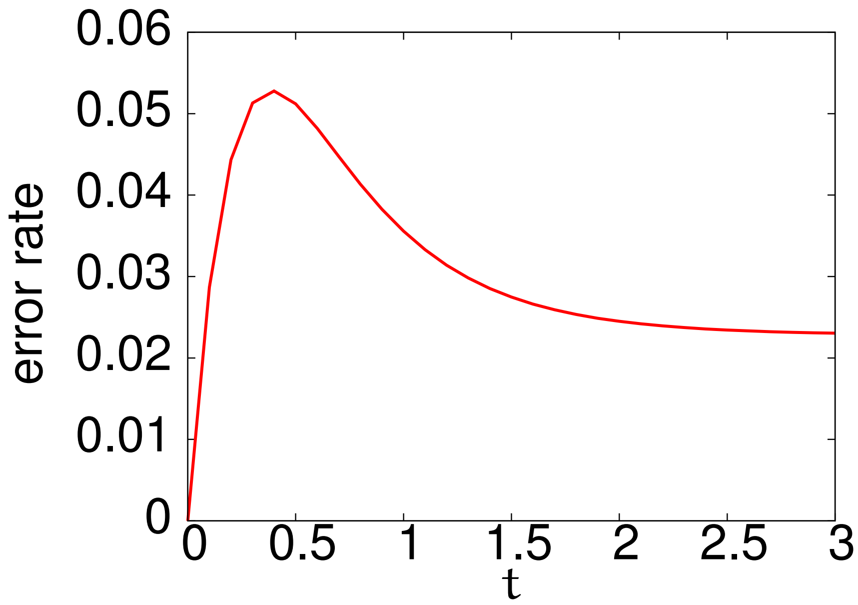
$$A^{\star} + B \xrightleftharpoons[k_{A..B}/(n_{A^{\diamond}B}+n_{A^{\diamond}B^{\star}})]{k_{AB}} A^{\star}B^{\diamond} + A^{\diamond}B,$$

$$A + B^{\star} \xrightleftharpoons[k_{A..B}/(n_{A^{\diamond}B}+n_{A^{\diamond}B^{\star}})]{k_{AB}} AB^{\diamond} + A^{\diamond}B^{\star},$$

$$A^{\star} + B^{\star} \xrightleftharpoons[k_{A..B}/(n_{A^{\diamond}B}+n_{A^{\diamond}B^{\star}})]{k_{A^{\star}B^{\star}}} A^{\star}B^{\diamond} + A^{\diamond}B^{\star}$$

Comparison between the two models

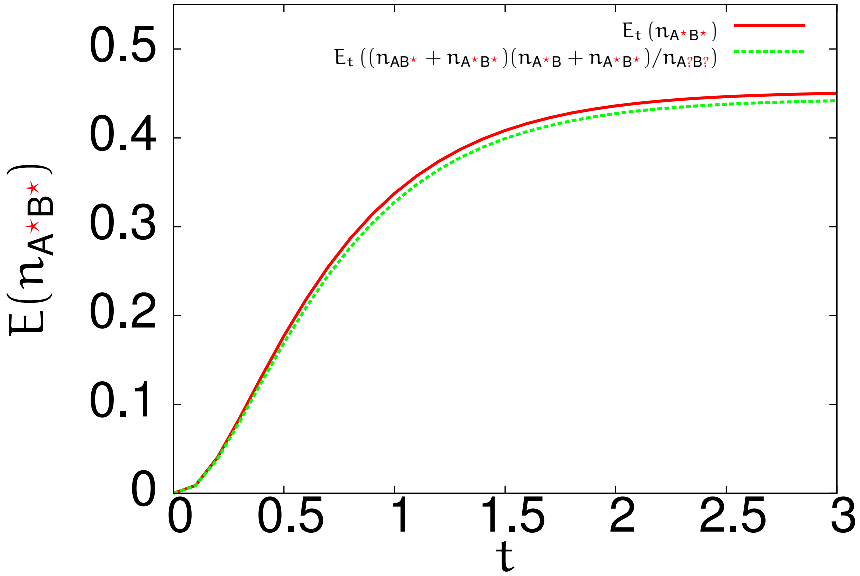


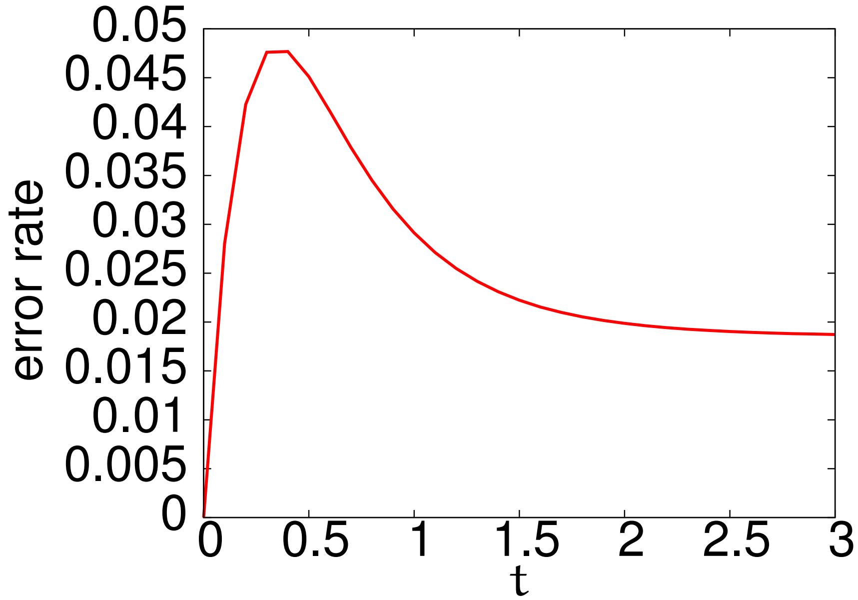


with $k_{A+} = k_{A-} = k_{B+} = k_{B-} = k_{AB} = k_{A..B} = 1$, $k_{A^\star B^\star} = 10$,
and two instances of A and B at time $t = 0$.

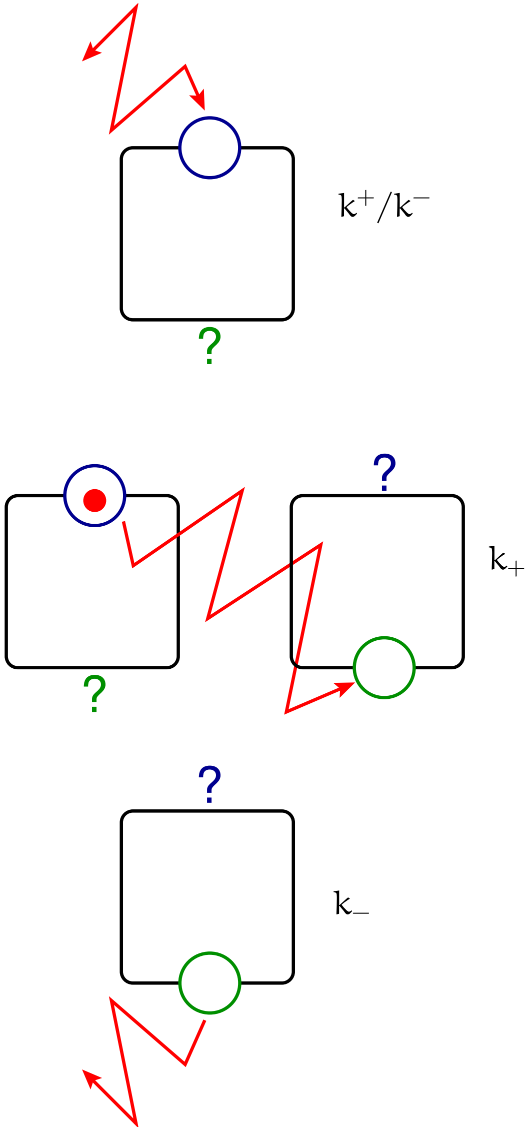
Although the reduction is correct in the ODE semantics.

Degree of correlation (in the unreduced model)





Distant control



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

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

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

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

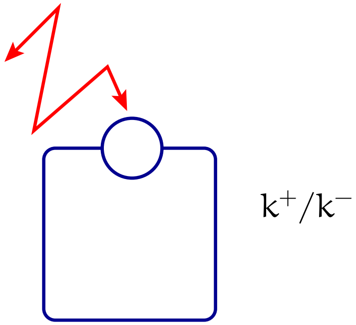
$$A + A_{\star}^{\star} \xrightarrow{k_+} A_{\star} + A_{\star}^{\star}$$

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

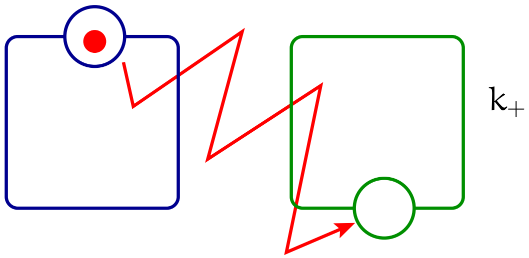
$$A_{\star}^{\star} \xrightarrow{k_-} A^{\star}$$

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

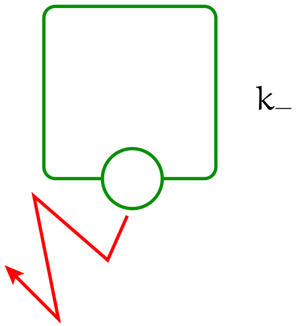
Reduced model



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

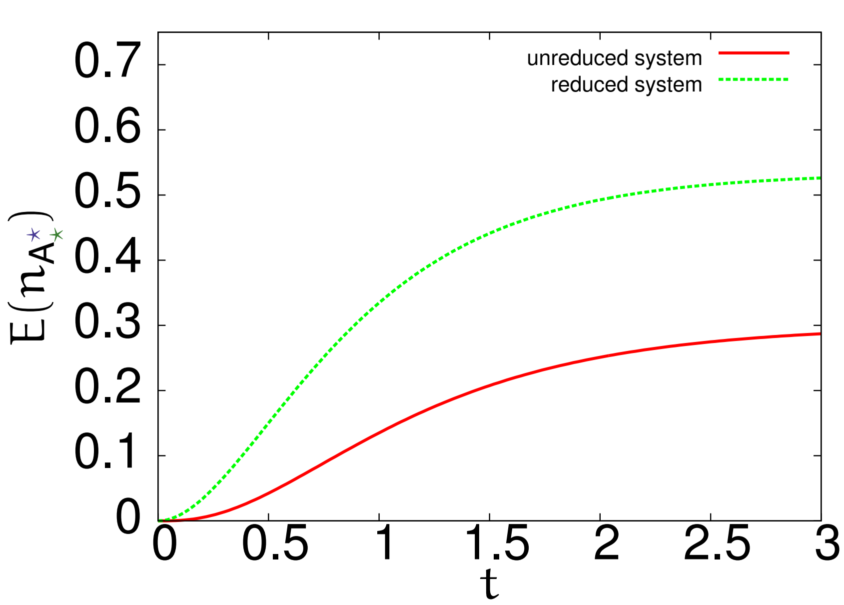


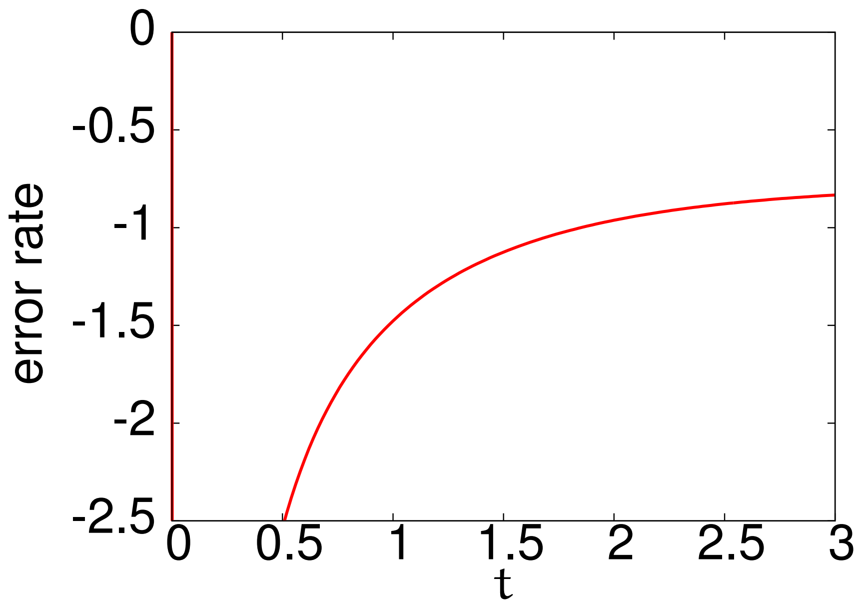
$$A + A^\star \xrightarrow{k_+} A_\star + A^\star$$



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

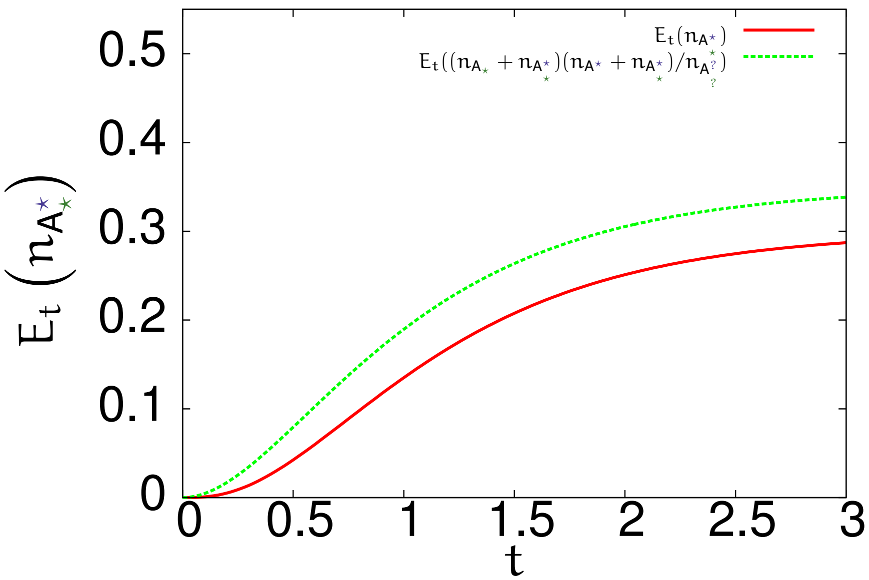
Comparison between the two models

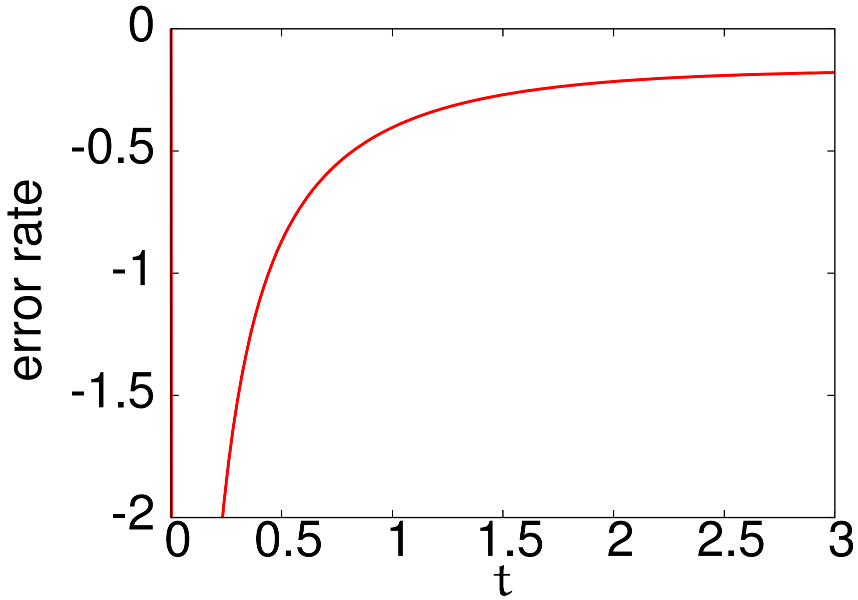




with $k^+ = k^- = k_+ = k_- = 1$,
and two instances of A at time $t = 0$.

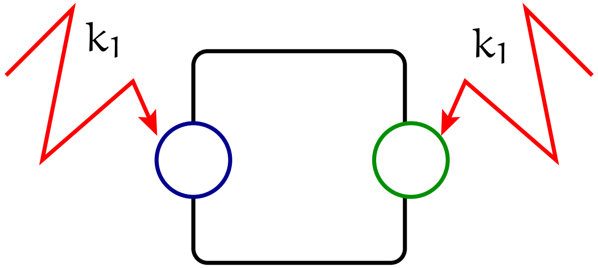
Degree of correlation (in the unreduced model)





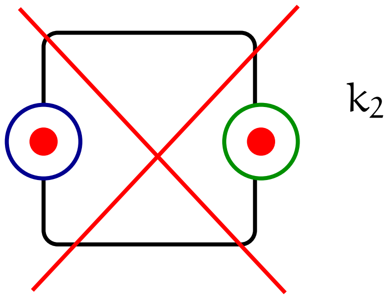
Overview

A model with symmetries



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

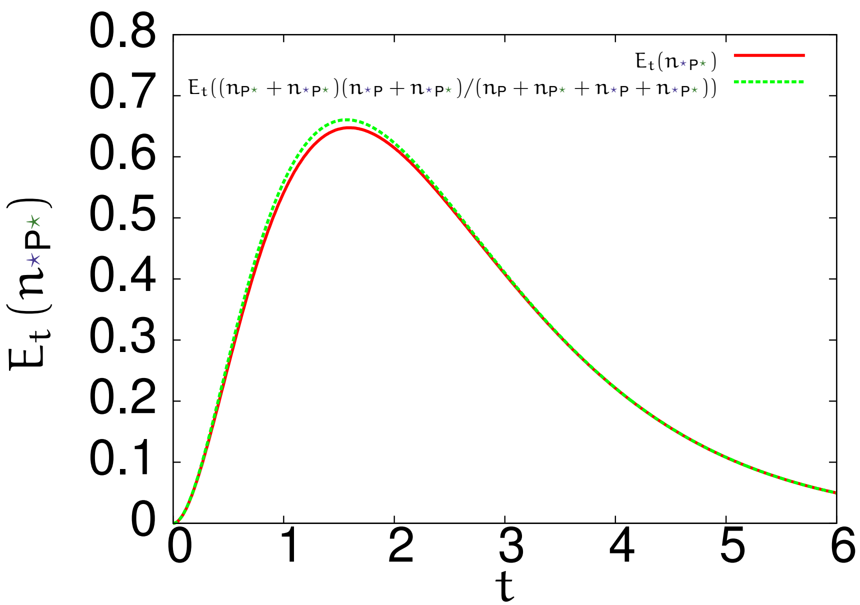
$$P \xrightarrow{k_1} P^{\star} \qquad {}^{\star}P \xrightarrow{k_1} {}^{\star}P^{\star}$$

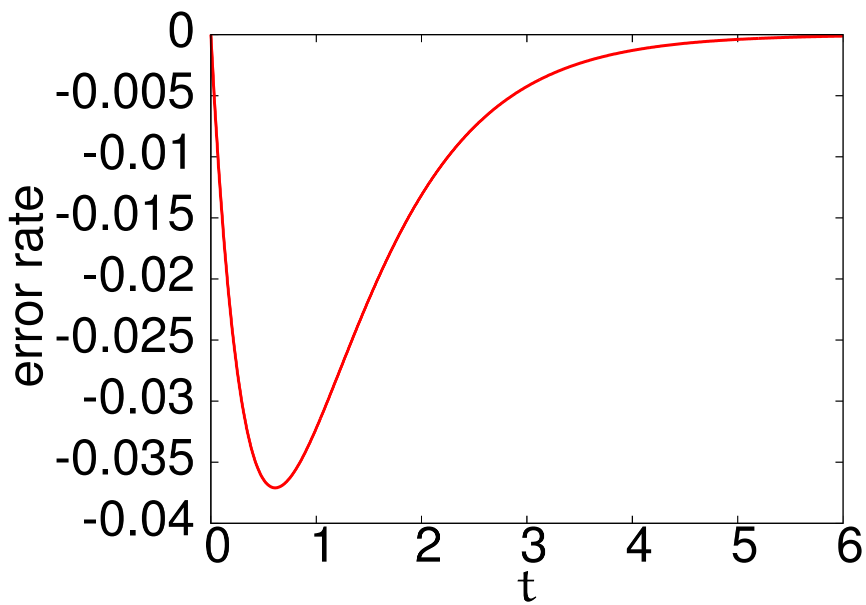


$${}^{\star}P^{\star} \xrightarrow{k_2} \emptyset$$

Degree of correlation
(in the unreduced model)

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



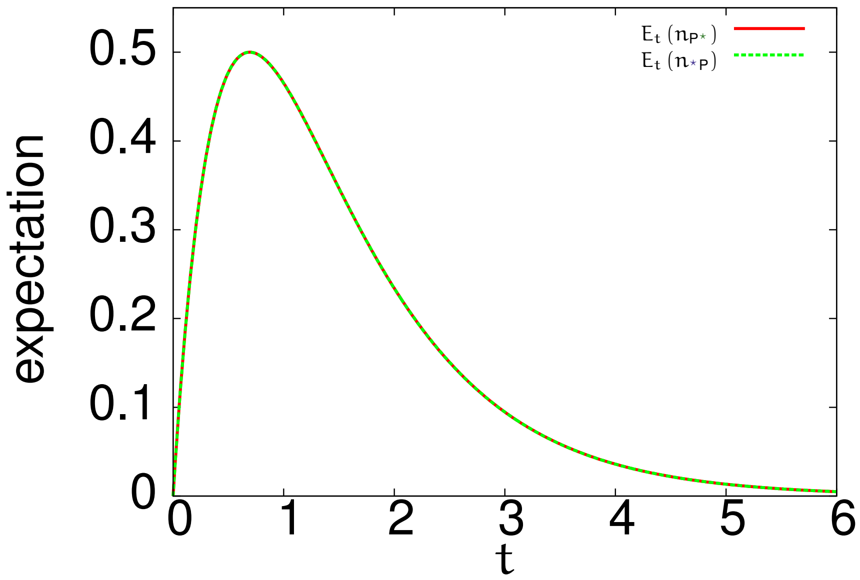


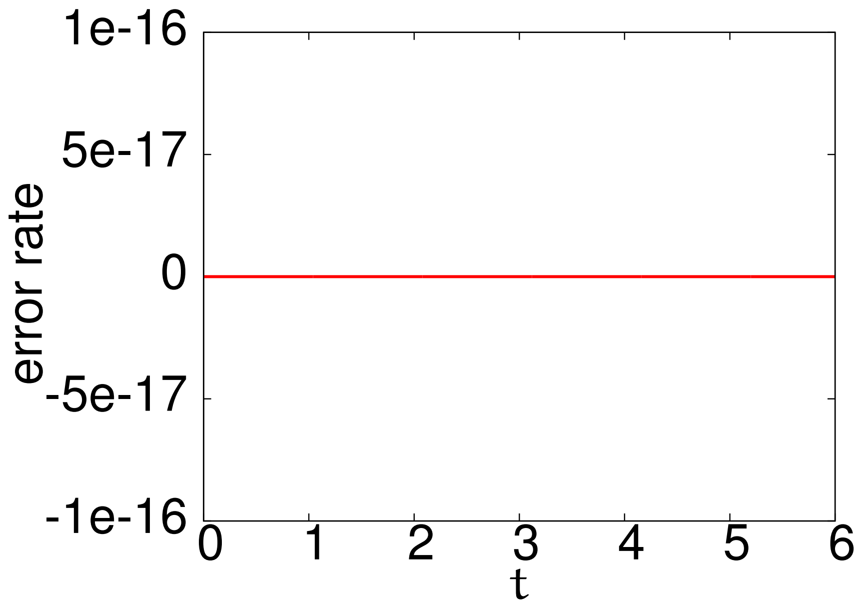
with $k_1 = k_2 = 1$
and two instances of P at time $t = 0$.

Equivalent chemical species

We check numerically that:

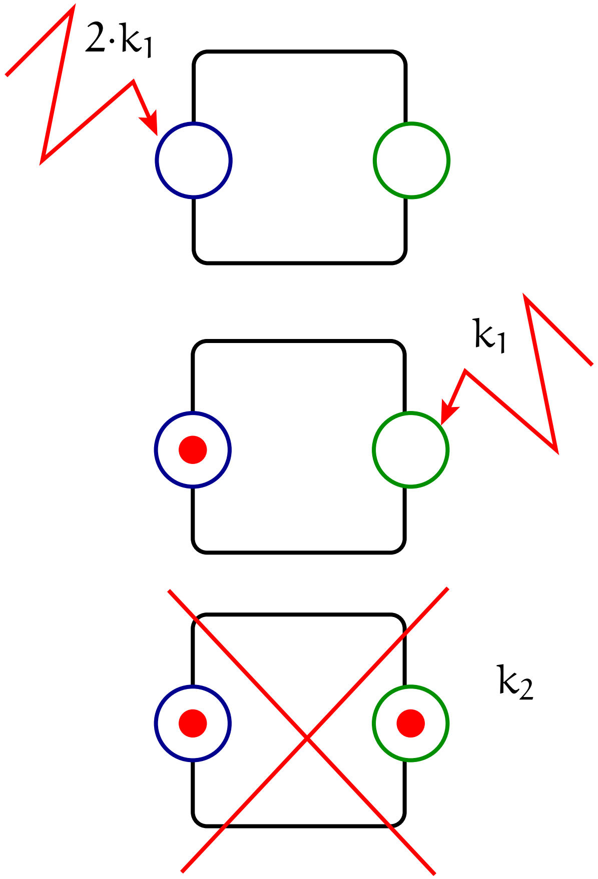
$$E_t(n_{P\star}) = E_t(n_{\star P}).$$





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

Reduced model



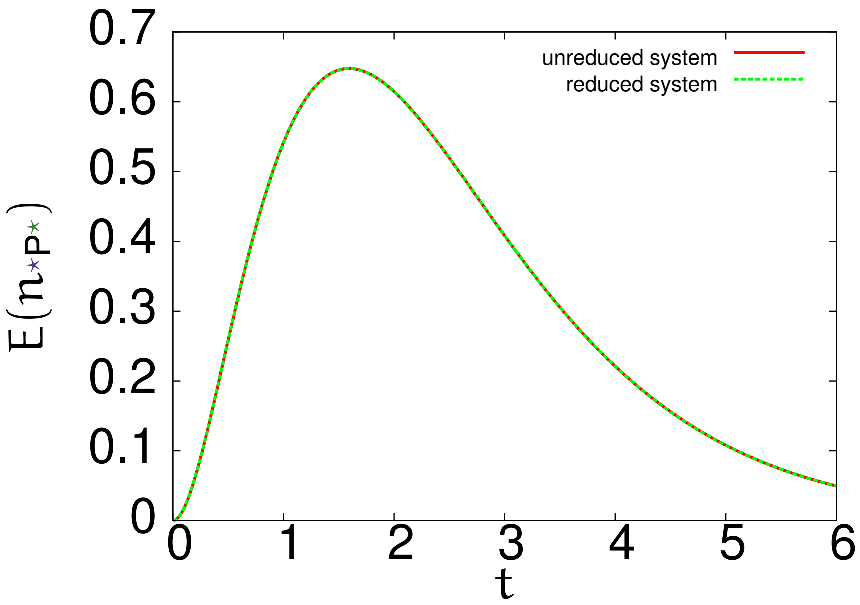
$$P \xrightarrow{2\cdot k_1} {}^{\star}P$$

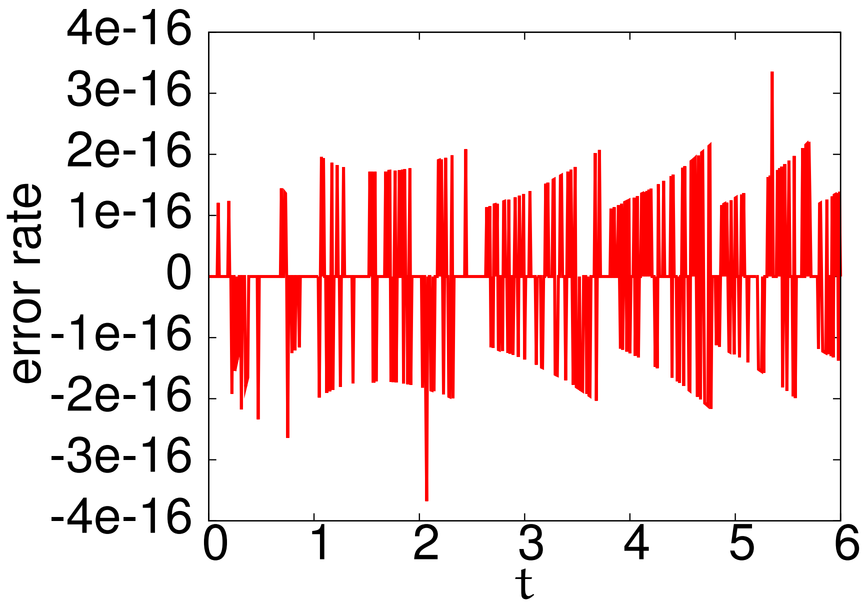
$$^{\star}P \xrightarrow{k_1} {}^{\star}P^{\star}$$

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

Exponential reduction!!!

Comparison between the two models





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

Overview

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:

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

where:

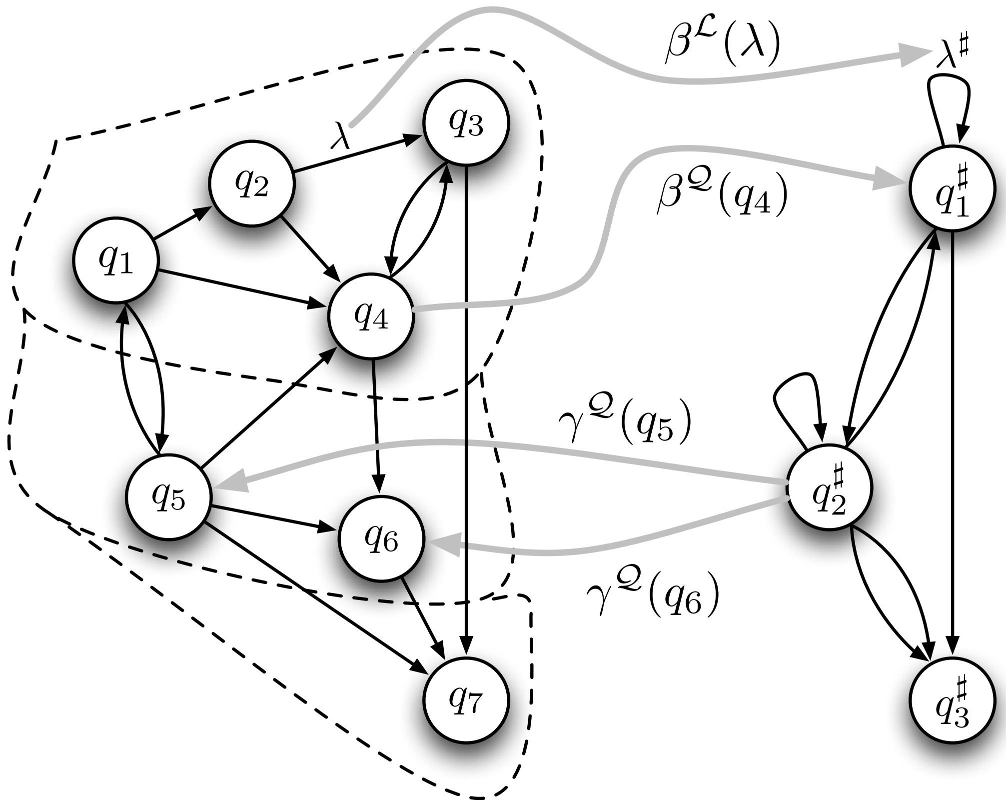
- $(q_i)_{0 \le i \le k} \in \mathcal{Q}^{k+1}$ and $(\lambda_i)_{1 \le i \le k} \in \mathcal{L}^k$,
- $(I_i)_{1 \le i \le k}$ is a family of open intervals in $\mathbb{R}_0^+$.

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

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

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 τ of traces of $\mathcal{S}$, we have:

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

where,

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

Completeness

Given:

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

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

Markovian Property

We consider a stochastic process:

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

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

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

Lumpability property

Given:

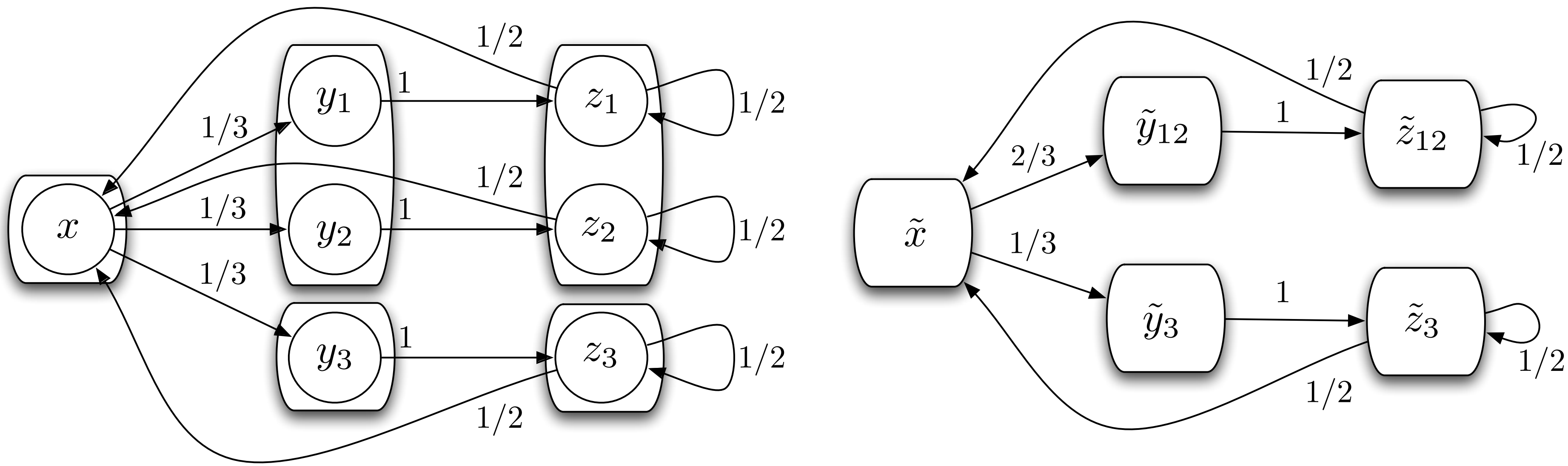
- a stochastic process $(\mathcal{X}_t)$ which satisfies the Markovian property,
- an initial distribution $\pi_0 \ : \ \mathcal{Q} \to [0, 1]$,
- an equivalence relation $\sim$ over $\mathcal{Q}$,

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

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

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

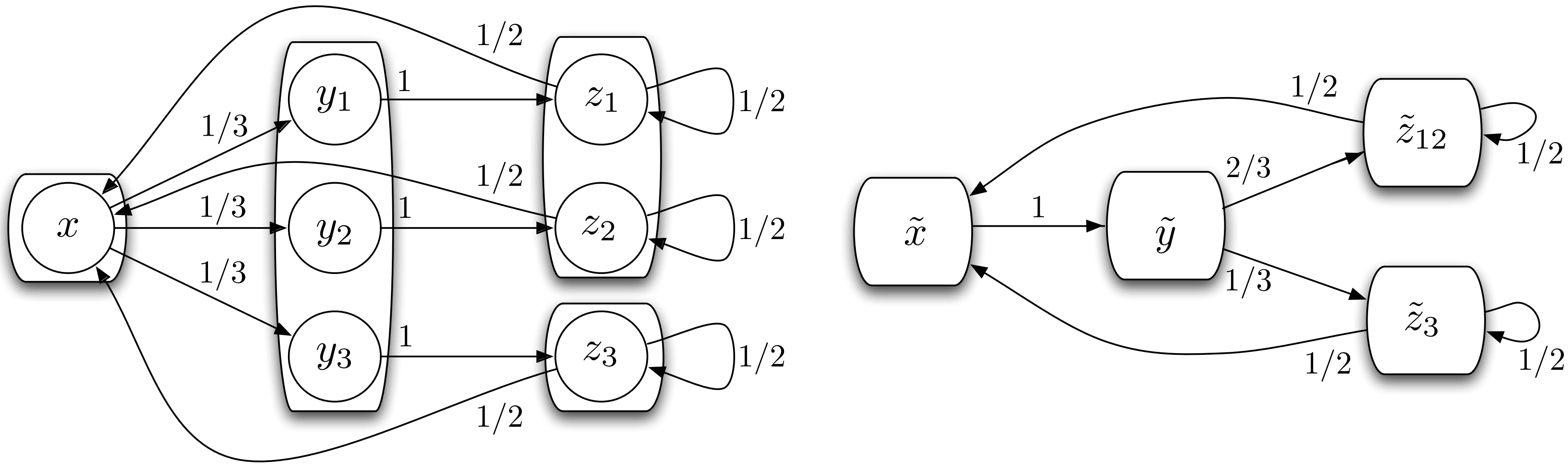
Strong lumpability



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

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

Weak lumpability



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

Overview

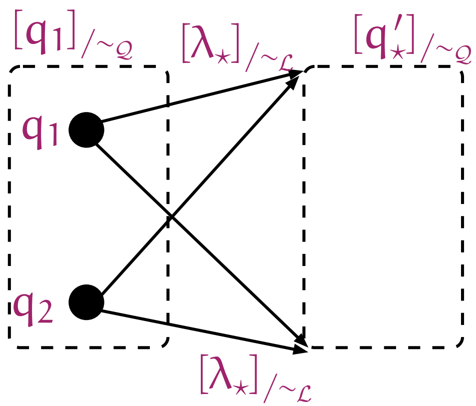
1. Introduction
2. Examples of information flow
3. Symmetric sites
4. Stochastic semantics
5. Lumpability
6. Bisimulations
7. Hierarchy of semantics
8. Conclusion

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

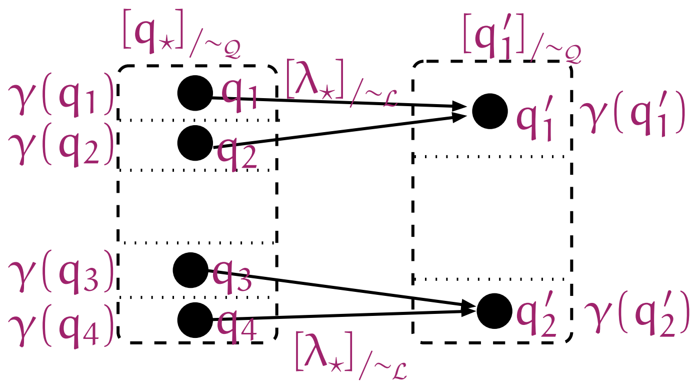
- $a(q_1) = a(q_2)$;
- and for any $\lambda_\star \in \mathcal{L}$, $q'_\star \in \mathcal{Q}$,
  $\mathsf{fwd}(q_1, [\lambda_\star]_{/\sim_{\mathcal{L}}}, [q'_\star]_{/\sim_{\mathcal{Q}}}) = \mathsf{fwd}(q_2, [\lambda_\star]_{/\sim_{\mathcal{L}}}, [q'_\star]_{/\sim_{\mathcal{Q}}})$



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 $\gamma : \mathcal{Q} \to \mathbb{R}^+$, such that: for any $q'_1, q'_2 \in \mathcal{Q}$ which satisfies $q'_1 \sim_{\mathcal{Q}} q'_2$:

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

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,

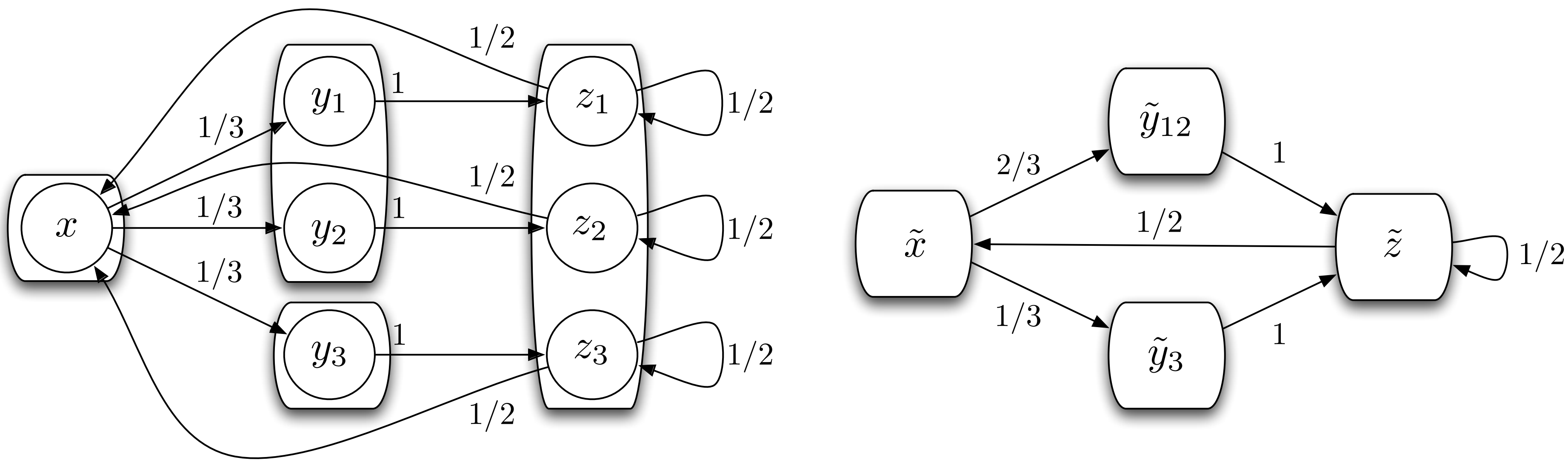
  moreover, it induces a sound abstraction;
- if $(\sim_{\mathcal{Q}}, \sim_{\mathcal{L}})$ is a backward bisimulation, then the process is $\sim_{\mathcal{Q}}$-weakly lumpable, for the initial distributions which satisfy:

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

  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.

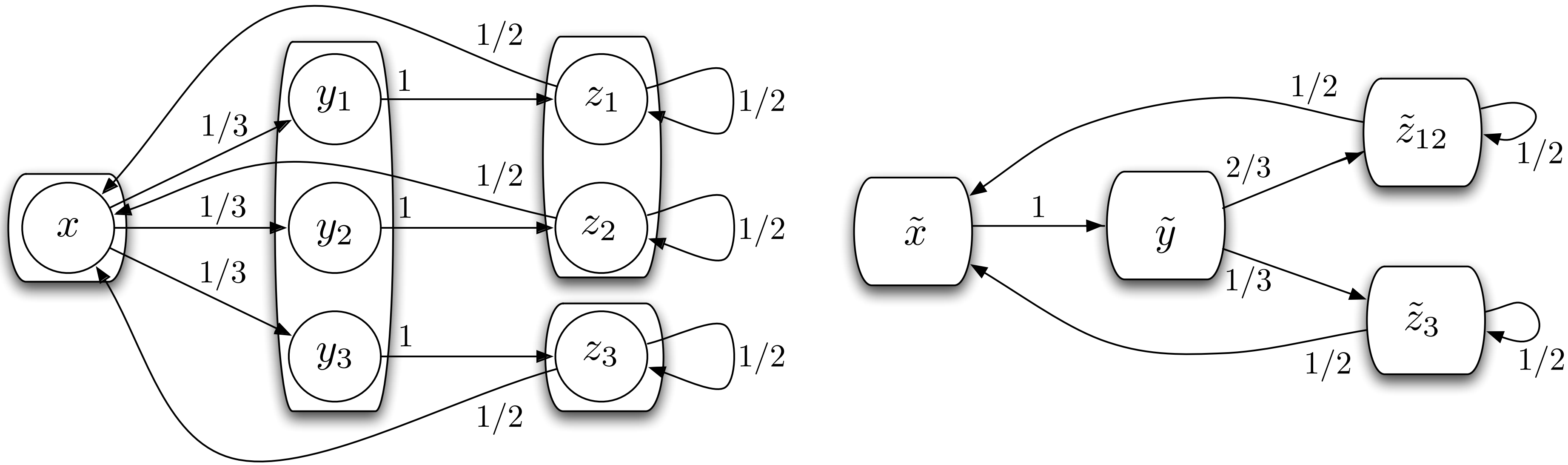
Counter-example I

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:

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

If,

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

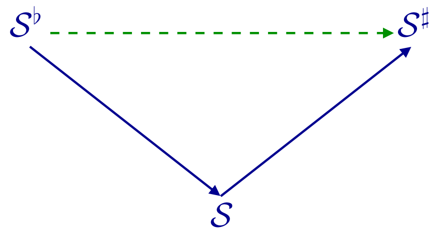
then:

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

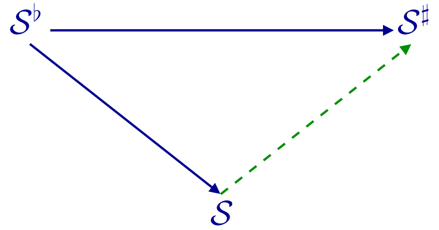
Abstraction algebra

(Sound/Complete) abstractions can be:

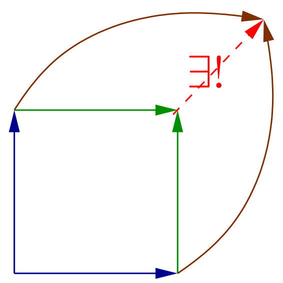
- composed:



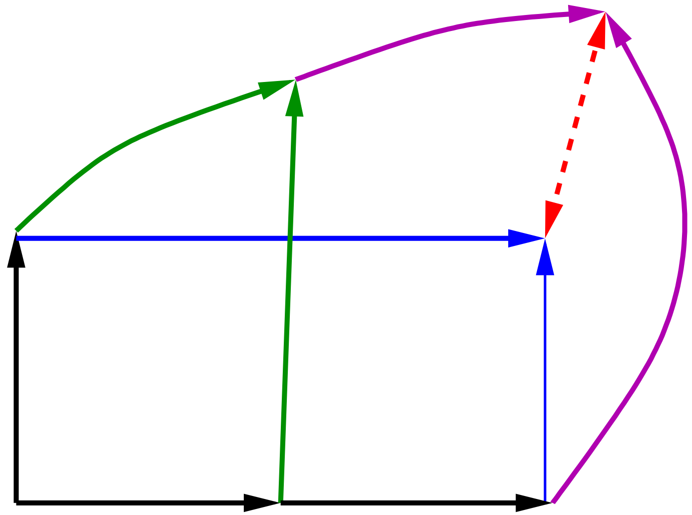
- factored:



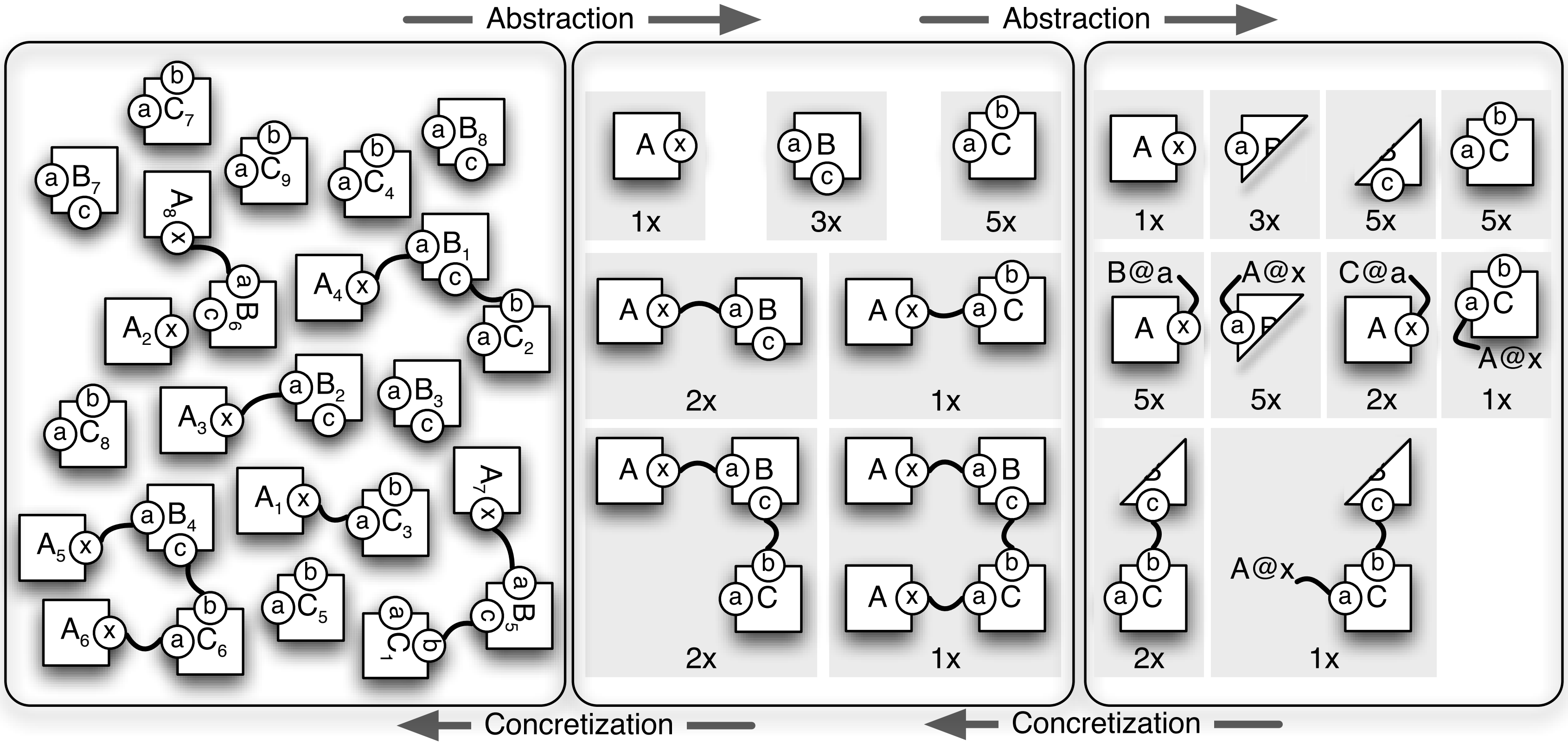
- combined with a symmetric product (c.f. lub or pushout):



Compatibility between composition and pushout



Overview



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

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:

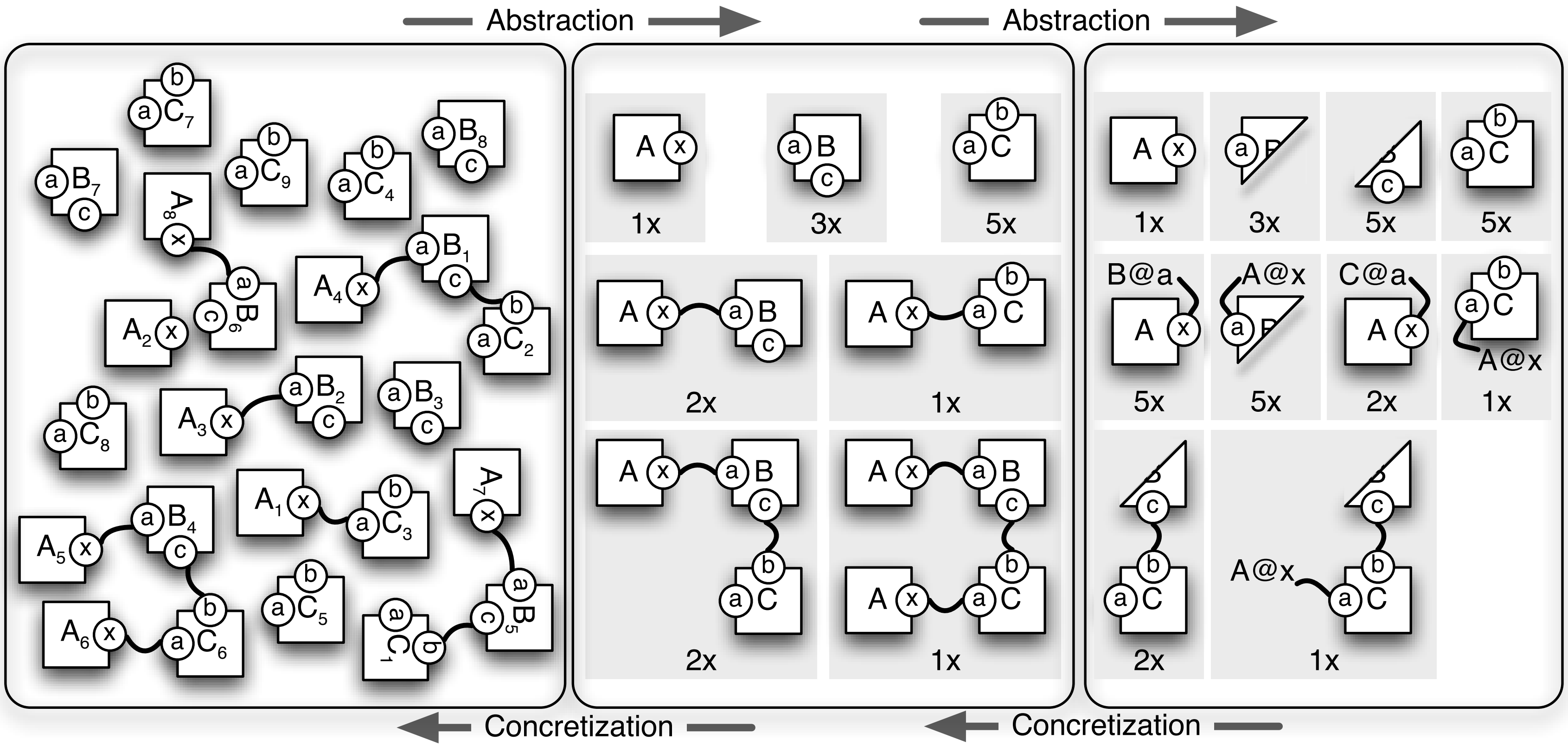
- Whenever the site x and y both occurs in the same or in distinct agent of type A in a rule, then, there should be a bidirectional edge between the site x and the y of A.
- Whenever there is a bond between two sites, each of which either carries an internal state of, is connected to some other sites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

From population to fragments

- Population of fragments:

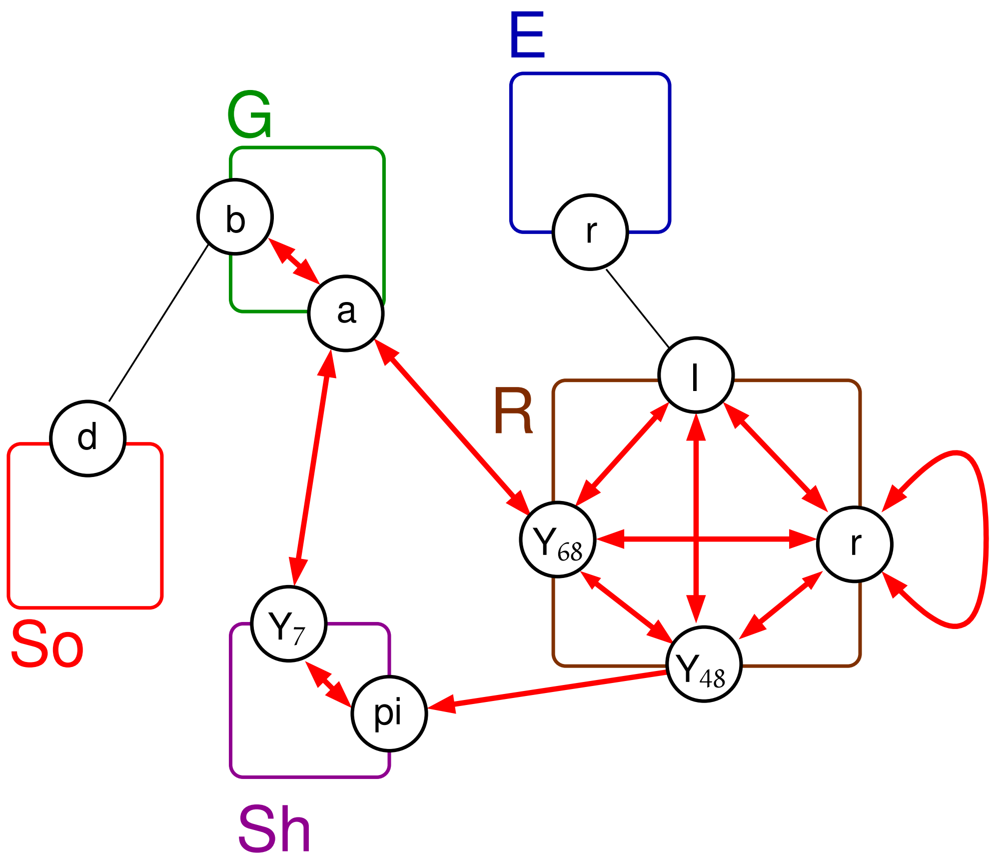
  1. In the annotated contact, each agent is fitted with a binary equivalence over its sites. We split the interface of agents into equivalence classes of sites. Then we abstract away which subagents belong to the same agent.

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

Example



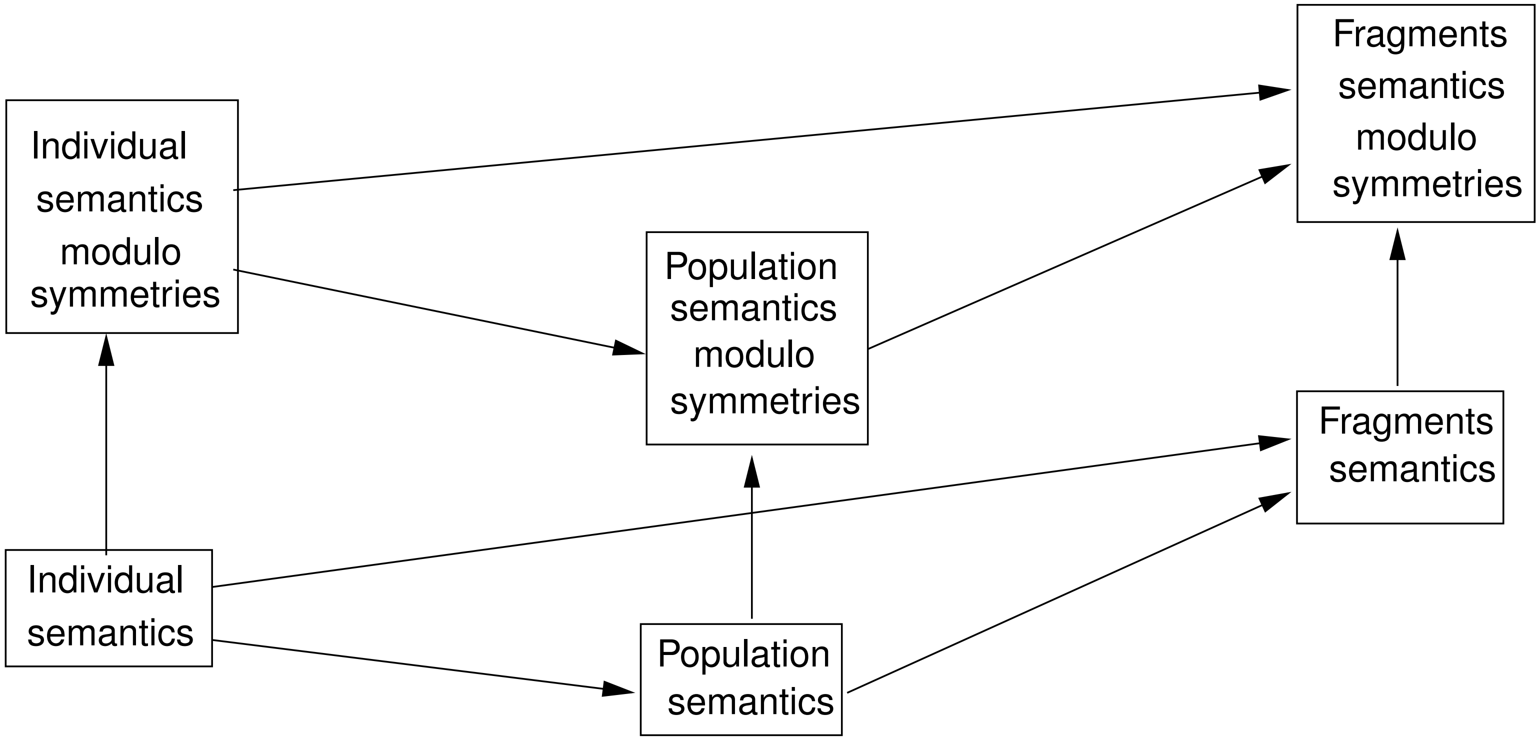
Symmetries among sites

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

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

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

Hierarchy of semantics



Overview

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

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,
  - …