Master AIV

Static analysis of protein-protein interactions networks

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March 2012

Joint-work with...

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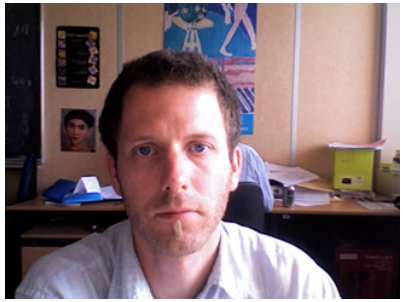
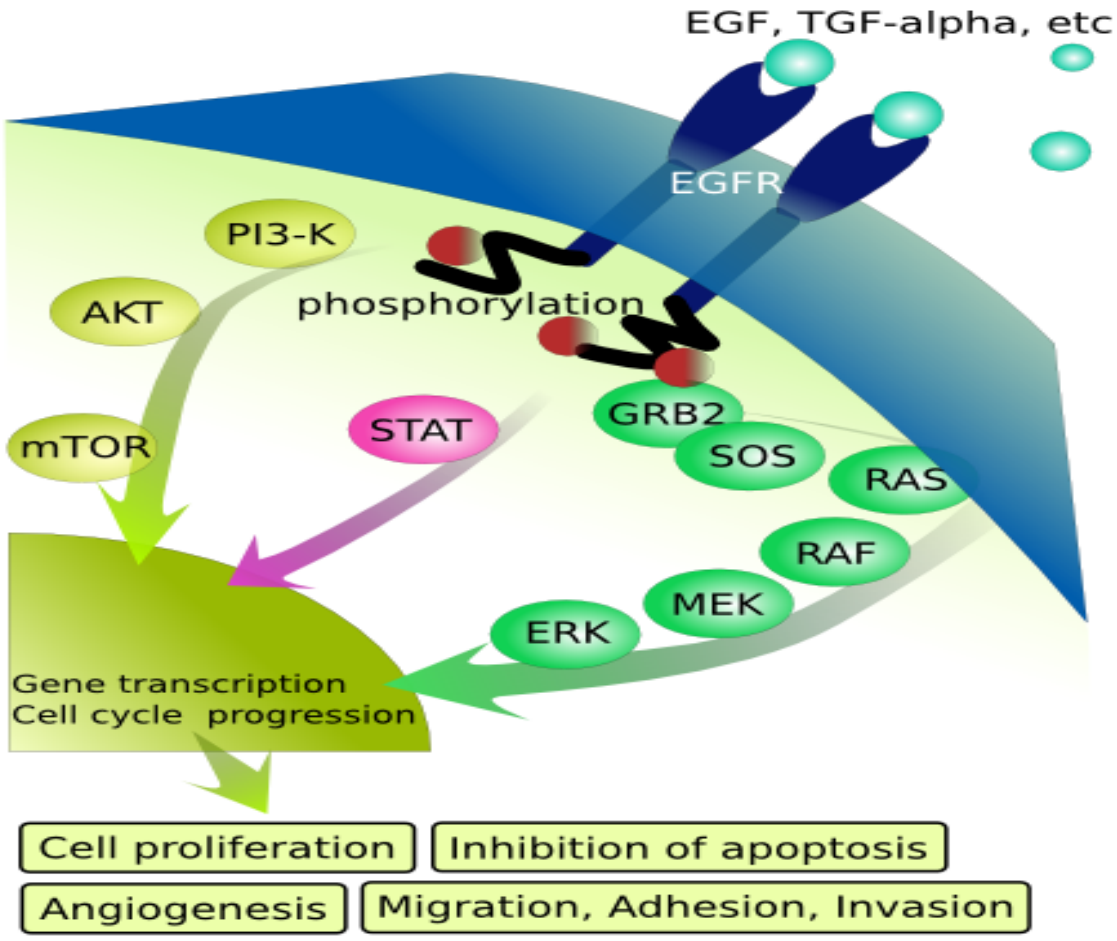


Russ Harmer
Harvard Medical School

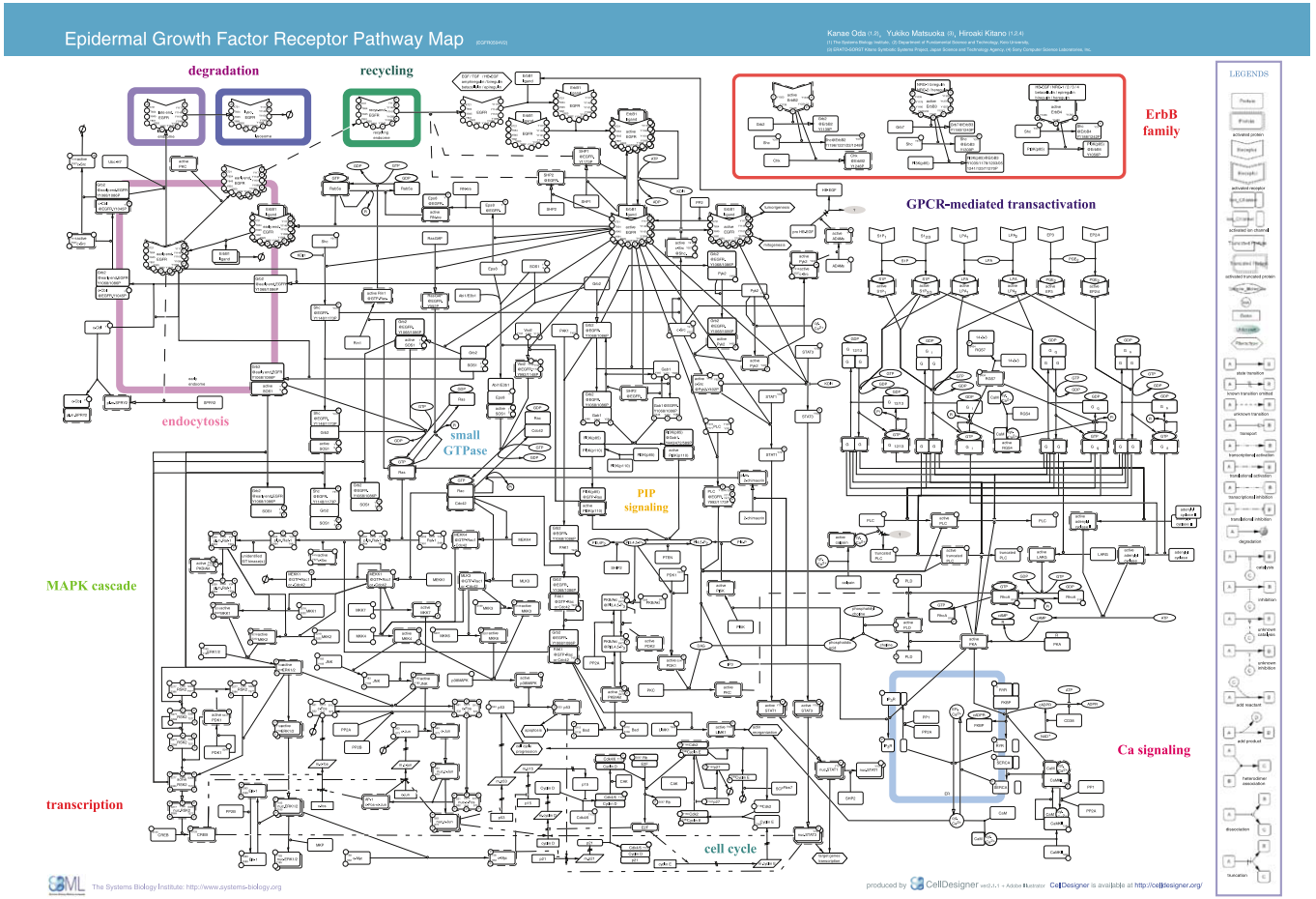
Jean Krivine
Paris VII

Signalling Pathways



Eikuch, 2007

Pathway maps



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

Differential models

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

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

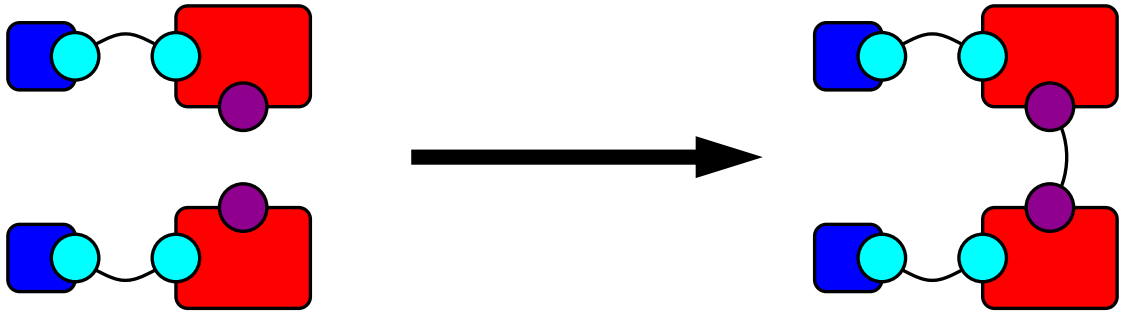
A gap between two worlds

Two levels of description:

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

Rule-based approach

We use site graph rewrite systems

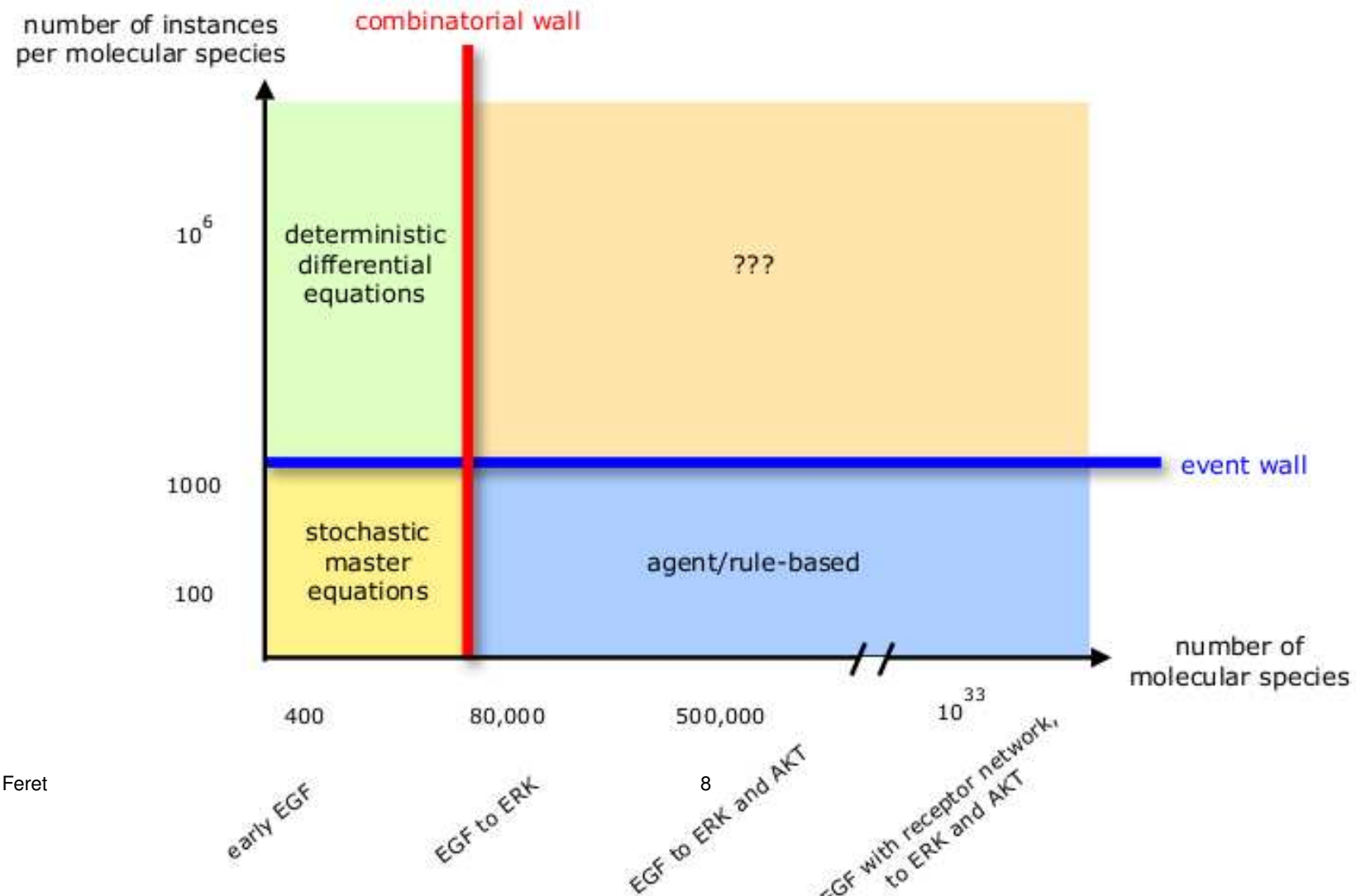


1. The description level matches with both
   - the observation level
   - and the intervention level

   of the biologist.

   We can tune the model easily.
2. Model description is very compact.
3. Quantitative semantics can be defined.

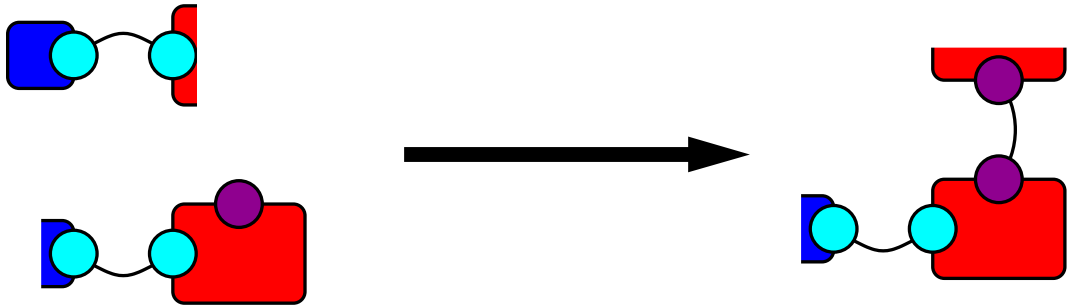
Complexity walls



Static analysis of reachable species (I/II)

Semi-fluid medium: the notion of individual is meaningless.

Design a static analysis to approximate the set of reachable species [VMCAI'08] which focuses on the relationships between the states of the sites of each agent:



This analysis is efficient, suitable to our problem, and accurate.

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]

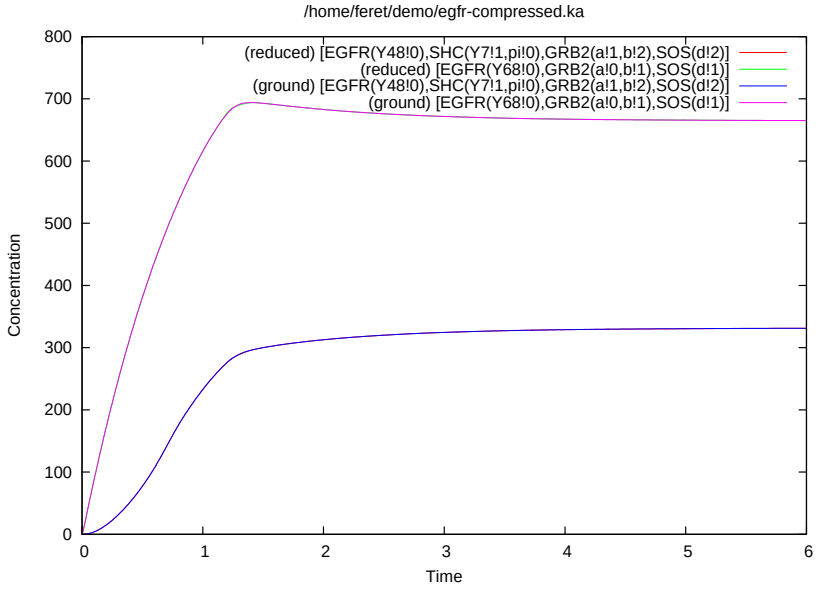
The analysis is complete (no false positif) for a significatif kernel of Kappa [VMCAI'08].

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]

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Reachability Analysis of Rule-based Models

[ICCMSE'07,VMCAI'08]

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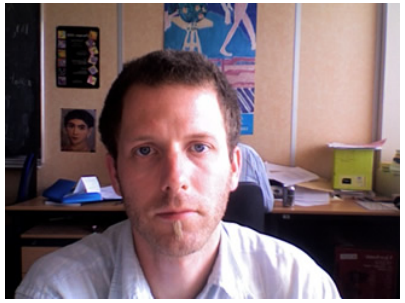

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Overview

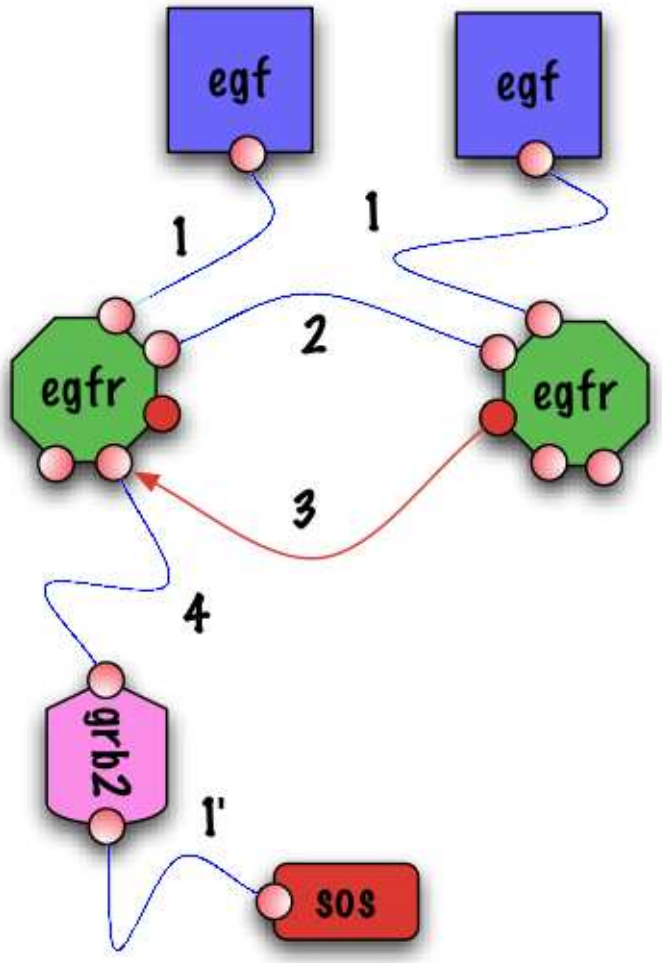
1. Introduction
2. Kappa language
3. Local views
4. Local set of chemical species
5. Local rule systems
6. Decontextualization
7. Conclusion

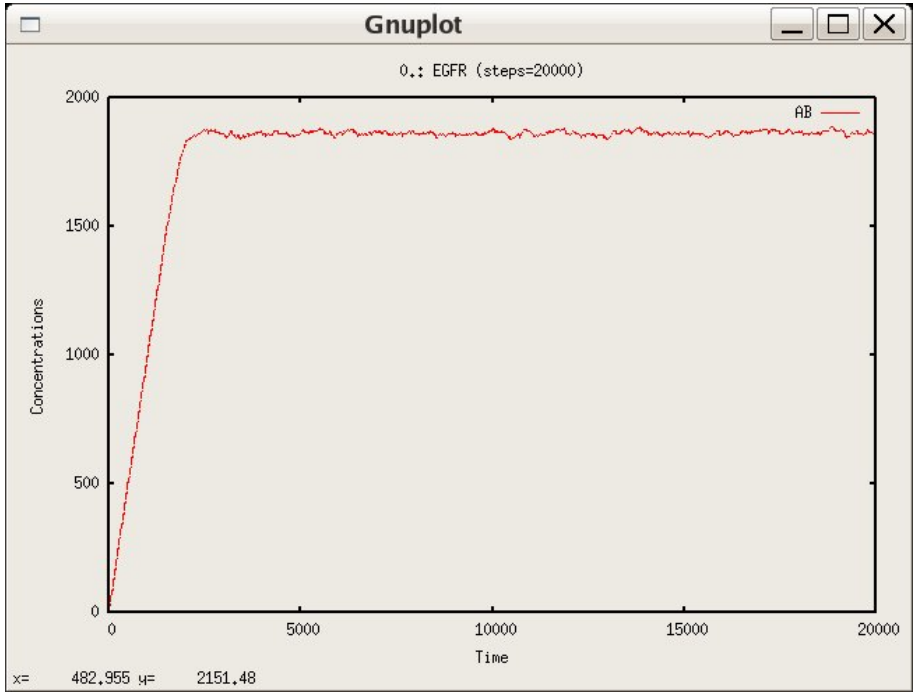
Modeling signaling pathway

- Signaling pathway:
  - A cell measures (i.e. checks thresholds, integrates, compares) the concentration of some proteins in order to make decisions.
  - Many proteins (enzymes, receptors, transport molecules) are involved.
  - They interact by binding with each other and activating each other.
- rule-based models:
  - A site graph-based rewrite language.
  - Description level matches with biologists' observation and manipulation level.
- Static analysis:

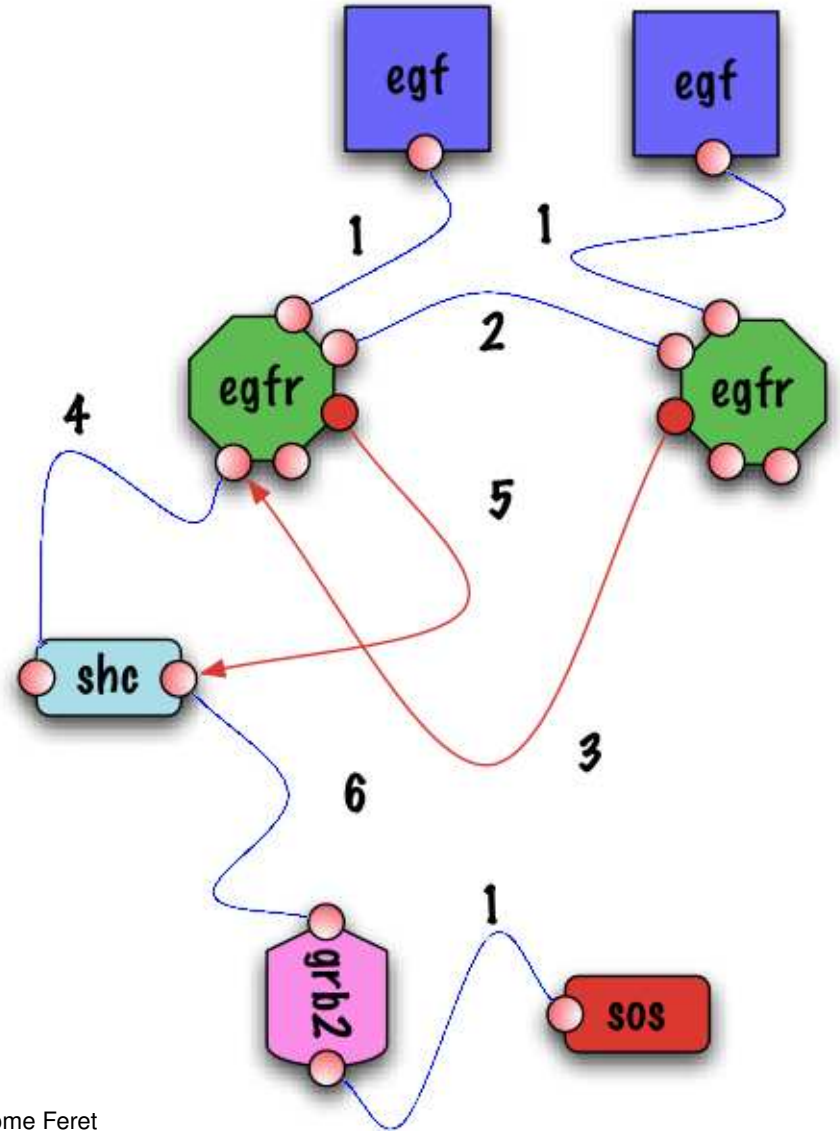
  We propose some static analysis tools in order to:
  - help the design of rule-based models;
  - compute (*abstract*) the properties of rule-based models.

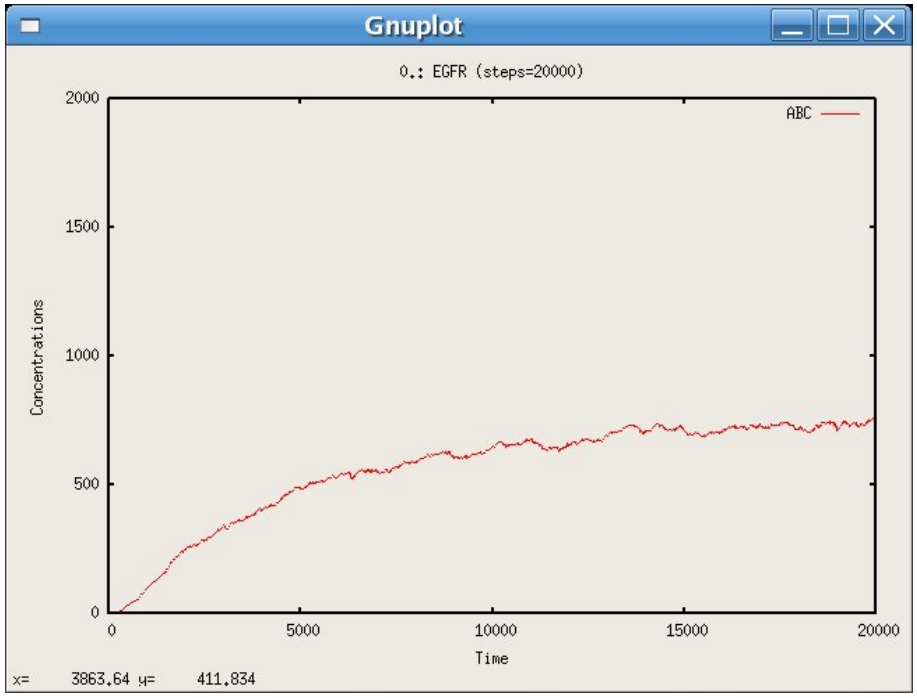
A single story





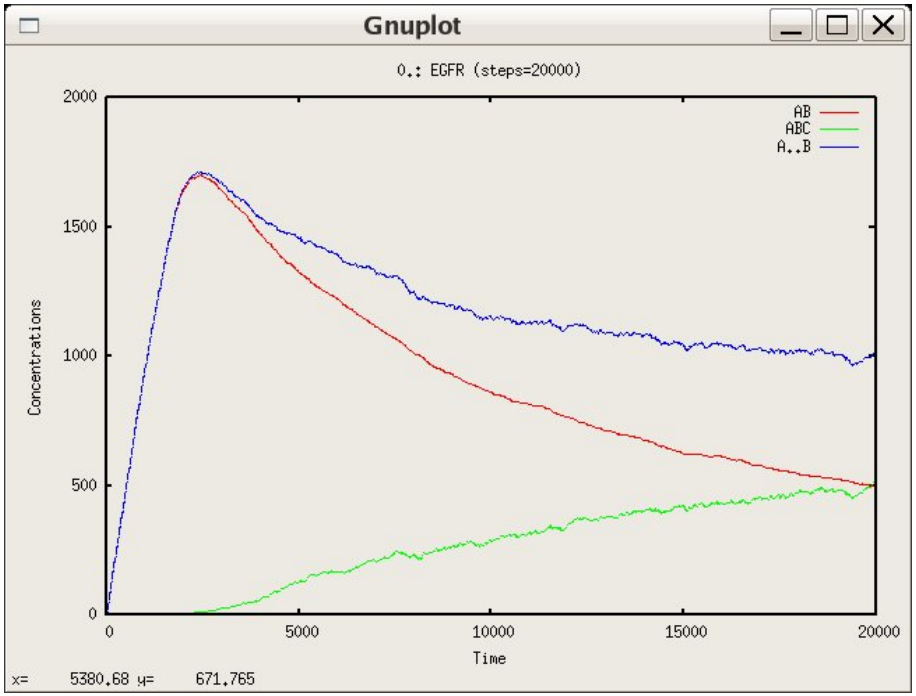
A concurrent story





Overshoot

When we combine the two stories. . .



. . . we get an overshoot.

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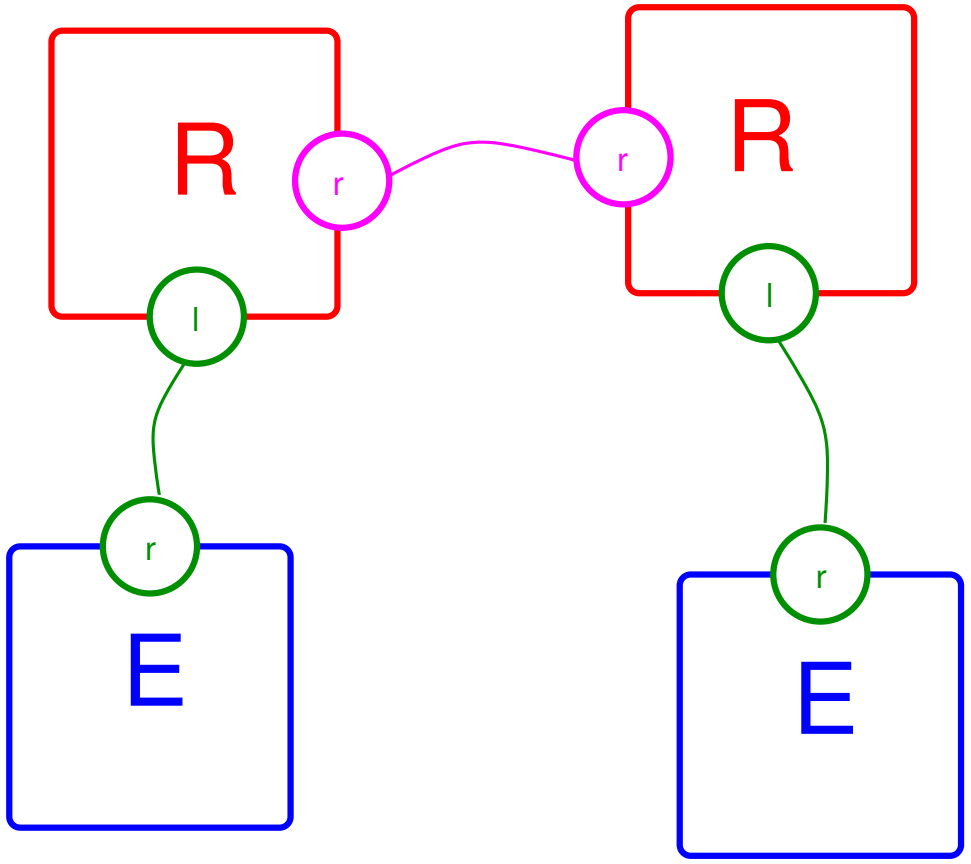
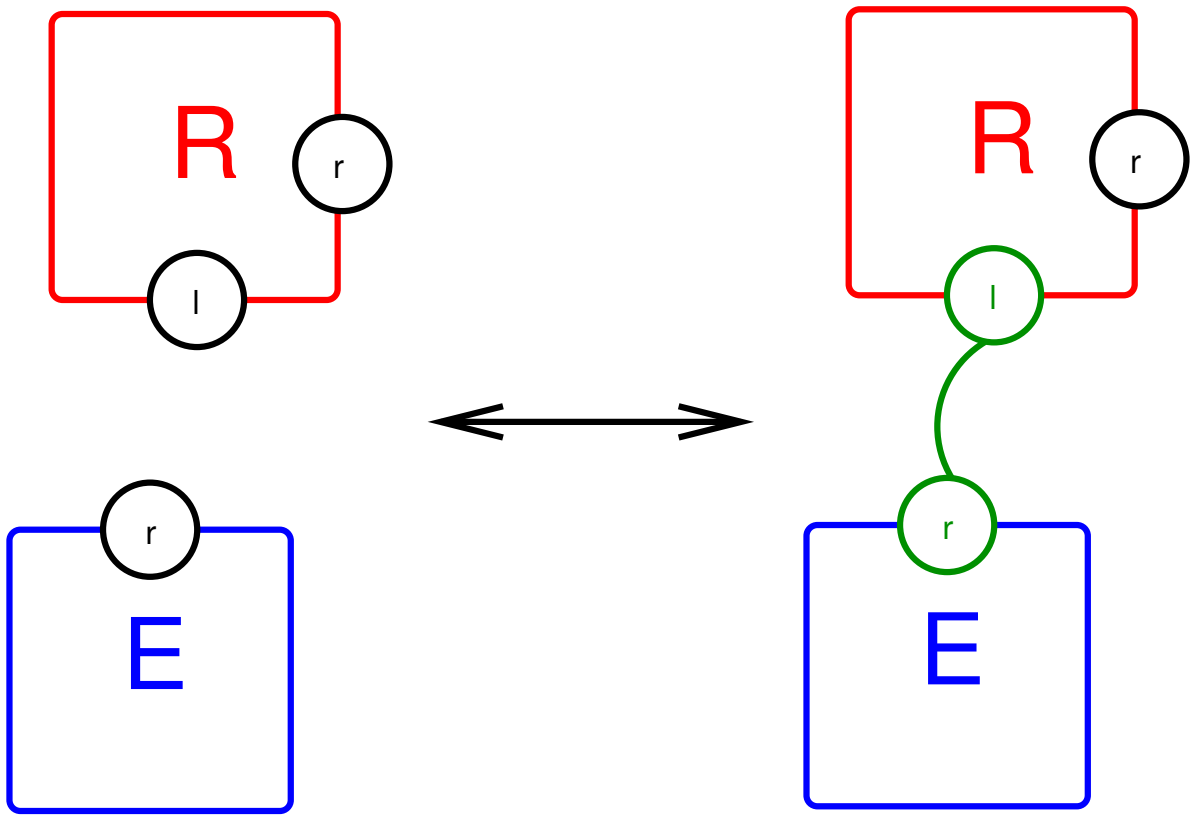
A chemical species



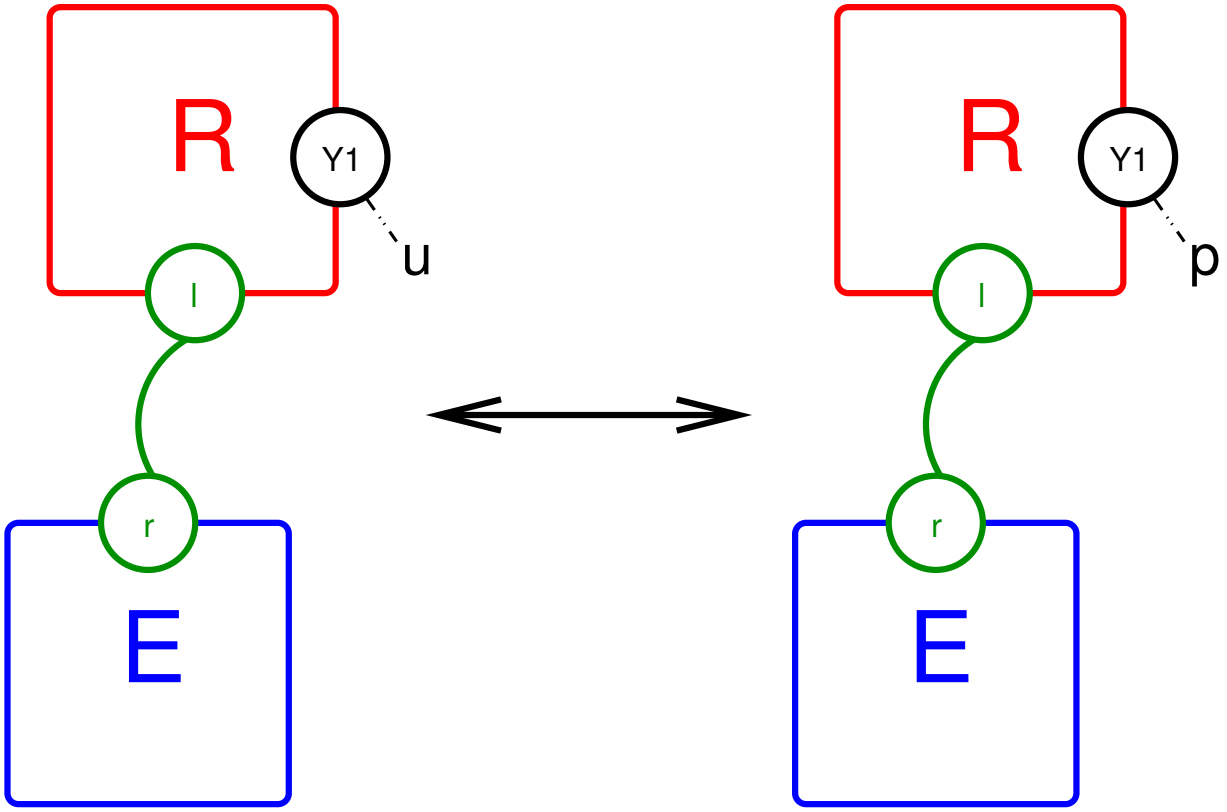
E(r!1), R(l!1,r!2), R(r!2,l!3), E(r!3)

A Unbinding/Binding Rule



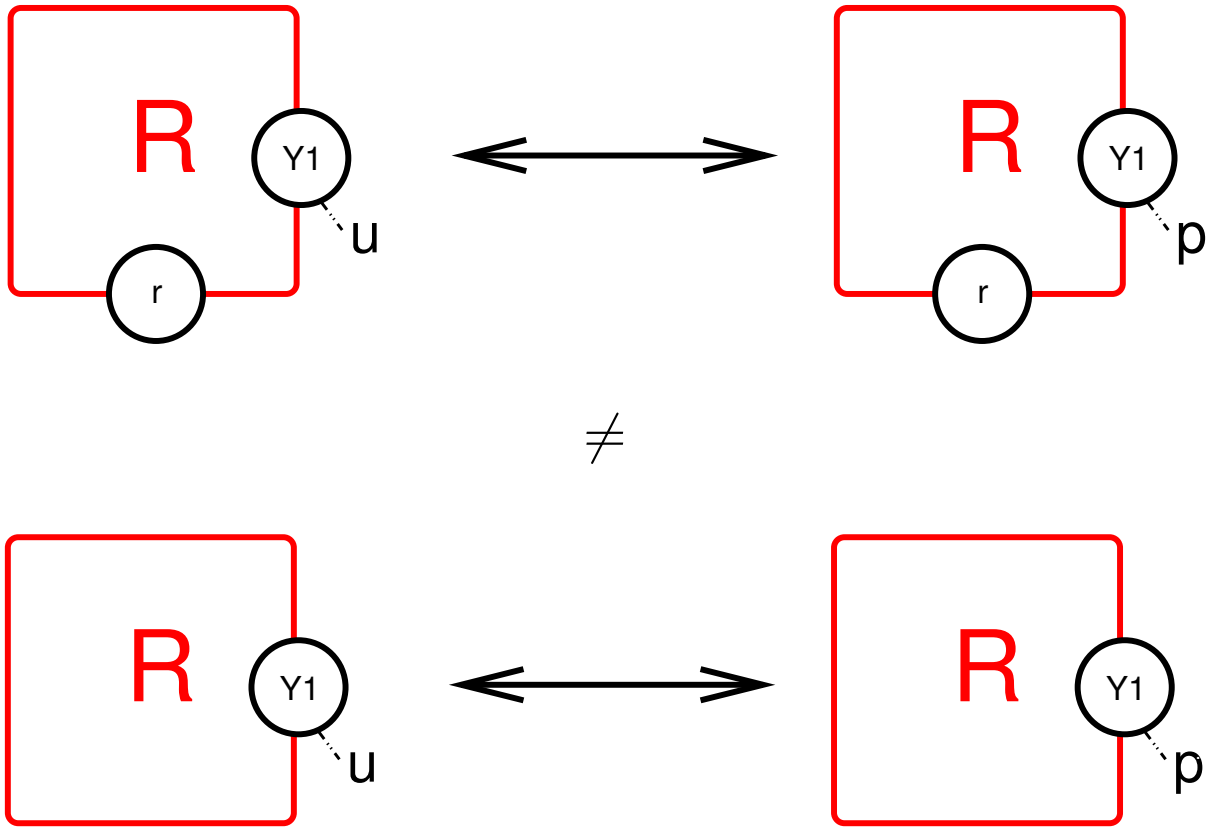
E(r), R(l,r) ⟷ E(r!1), R(l!1,r)

Internal state

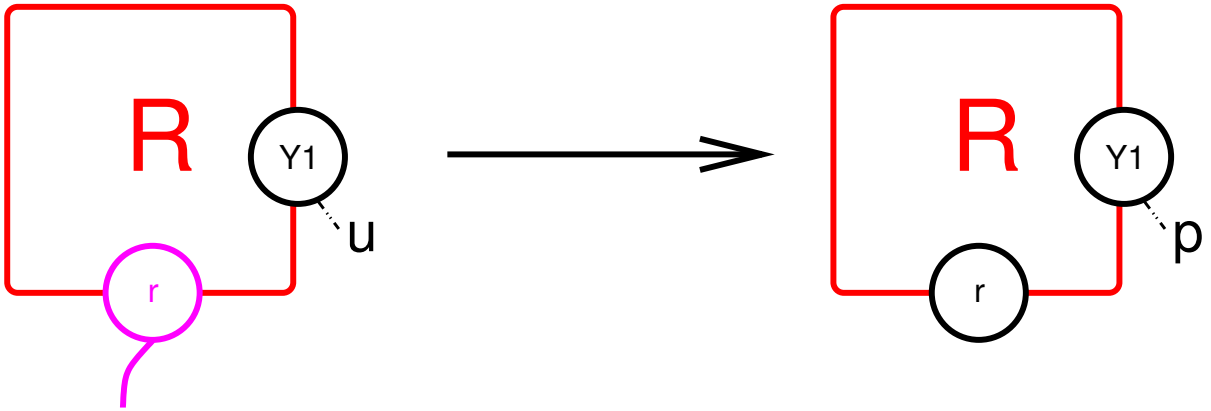


R(Y1~u,l!1), E(r!1) ⟷ R(Y1~p,l!1), E(r!1)

Don’t care, Don’t write

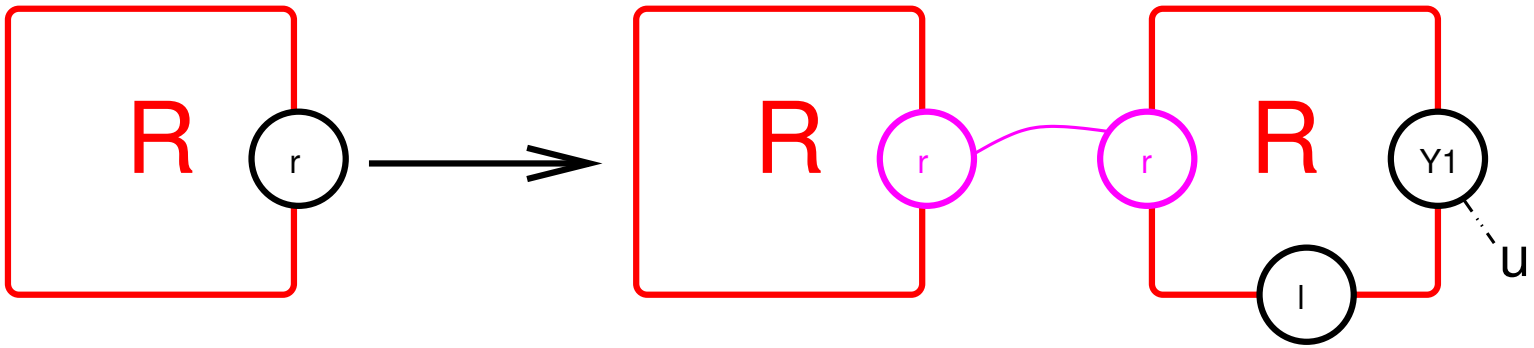


A contextual rule

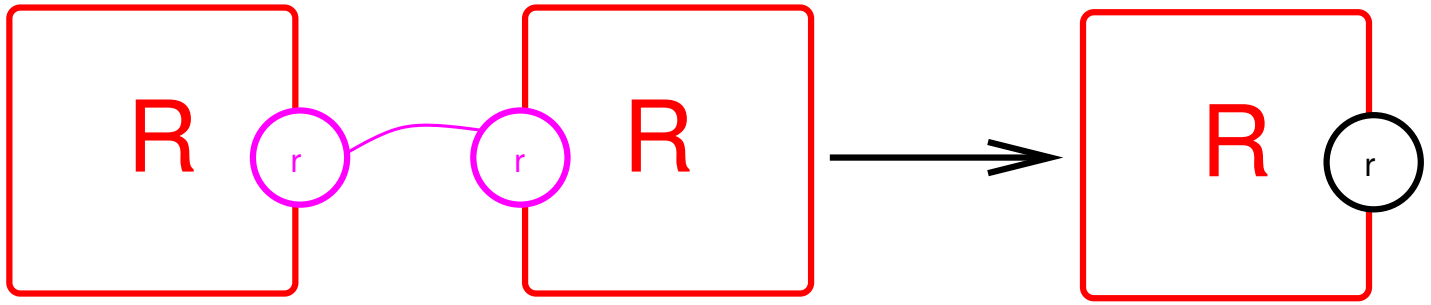


$$R(Y1{\sim}u,r!\_) \rightarrow R(Y1{\sim}p,r)$$

Creation/Suppression



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



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

Early EGF example

egf rules 1

protein shorthands: E:=egf, R:=egfr, So:=Sos,Sh:=Sh,G:=grb2
site abbreviations & fusions: Y68:=Y1068, Y48:=Y1148/73, Y7:=Y317, π:=PTB/SH2

- Ligand-receptor binding, receptor dimerisation, rtk x-phosph, & de-phosph
  - 01: R(l,r), E(r) <-> R(l^1,r), E(r^1)
  - 02: R(l^1,r), R(l^2,r) <-> R(l^1,r^3), R(l^2,r^3)
  - 03: R(r^1,Y68) -> R(r^1,Y68^p)
  - R(Y68^p) -> R(Y68)
  - 04: R(r^1,Y48) -> R(r^1,Y48^p)
  - R(Y48^p) -> R(Y48)

receptor type: R(l,r,Y68,Y48)

- Sh x-phosph & de-phosph
  - 14: R(r^2,Y48^{p1}), Sh(π^1,Y7) -> R(r^2,Y48^{p1}), Sh(π^1,Y7^p)
  - ??: Sh(π^1,Y7^p) -> Sh(π^1,Y7)
  - 16: Sh(π,Y7^p) -> Sh(π,Y7)

refined from Sh(Y7^p)-> Sh(Y7)

- Y68-G binding
  - 09: R(Y68^p), G(a,b) <-> R(Y68^{p1})+G(a^1,b)
  - 11: R(Y68^p), G(a,b^2) <-> R(Y68^{p1})+G(a^1,b^2)

refined from R(Y68^p)+G(a)<->R(Y68^{p1})+G(a^1)

Early EGF example

egf rules 2

refined from
So(d)+G(b)<->So(d¹)+G(b¹)

interface note: highlight the interacting parts

- G-So binding
  - 10: R(Y68^{p1}), G(a¹,b), So(d) <-> R(Y68^{p1}), G(a¹,b²), So(d²)
  - 12: G(a,b), So(d) <-> G(a,b¹), So(d¹)
  - 22: Sh(π,Y7^{p2}), G(a²,b), So(d) <-> Sh(π,Y7^{p2}), G(a²,b¹), S(d¹)
  - 19: Sh(π¹,Y7^{p2}), G(a²,b), So(d) <-> Sh(π¹,Y7^{p2}), G(a²,b¹), S(d¹)
- Y48-Sh binding
  - 13: R(Y48^{p}), Sh(π,Y7) <-> R(Y48^{p1}), Sh(π¹,Y7)
  - 15: R(Y48^{p}), Sh(π,Y7^{p}) <-> R(Y48^{p1}), Sh(π¹,Y7^{p})
  - 18: R(Y48^{p}), Sh(π,Y7^{p1}), G(a¹,b) <-> R(Y48^{p2}), Sh(π²,Y7^{p1}), G(a¹,b)
  - 20: R(Y48^{p}), Sh(π,Y7^{p1}), G(a¹,b³), S(d³) <-> R(Y48^{p2}), Sh(π²,Y7^{p1}), G(a¹,b³), S(d³)
- Sh-G binding
  - 17: R(Y48^{p1}), Sh(π¹,Y7^{p}), G(a,b) <-> R(Y48^{p1}), Sh(π¹,Y7^{p2}), G(a²,b)
  - 21: Sh(π,Y7^{p}), G(a,b) <-> Sh(π,Y7^{p1}), G(a¹,b)
  - 23: Sh(π,Y7^{p}), G(a,b²) <-> Sh(π,Y7^{p1}), G(a¹,b²)
  - 24: R(Y48^{p1}), Sh(π¹,Y7^{p}), G(a,b³), S(d³) <-> R(Y48^{p1}), Sh(π¹,Y7^{p2}), G(a², b³), S(d³)

refined from
R(Y48^{p})+Sh(π)<->R(Y48^{p1})+Sh(π¹)

why not simply G(b³)??

refined from
Sh(π), G(a)<->Sh(π¹), G(a¹)

Properties of interest

1. Show the absence of modelling errors:
   - detect dead rules;
   - detect overlapping rules;
   - detect non exhaustive interactions;
   - detect rules with ambiguous molecularity.
2. Get idiomatic description of the networks:
   - capture causality;
   - capture potential interactions;
   - capture relationships between site states.
     (simplify rules)
3. Allow fast simulation:
   - capture accurate approximation of the wake-up relation.

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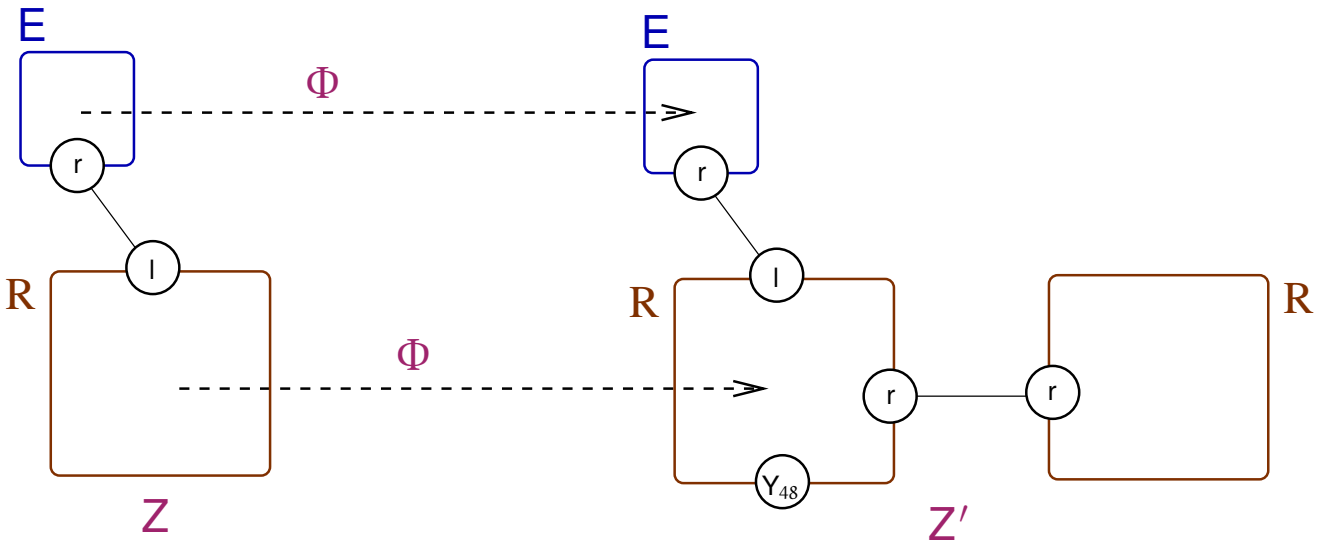
Embedding



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

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

Set of reachable chemical species

Let $\mathcal{R} = \{R_i\}$ be a set of rules.
Let *Species* be the set of all chemical species ($C, c_1, c'_1, \ldots, c_k, c'_k, \ldots \in$ *Species*).
Let $Species_0$ be the set of initial .
We write:

$$c_1, \ldots, c_m \rightarrow_{R_k} c'_1, \ldots, c'_n$$

whenever:

1. there is an embedding of the lhs of R_k in the solution $c_1, \ldots, c_m$;
2. the (embedding/rule) produces the solution $c'_1, \ldots, c'_n$.

We are interested in $Species_\omega$ the set of all chemical species that can be constructed in one or several applications of rules in $\mathcal{R}$ starting from the set $Species_0$ of initial chemical species.

(We do not care about the number of occurrences of each chemical species).

Inductive definition

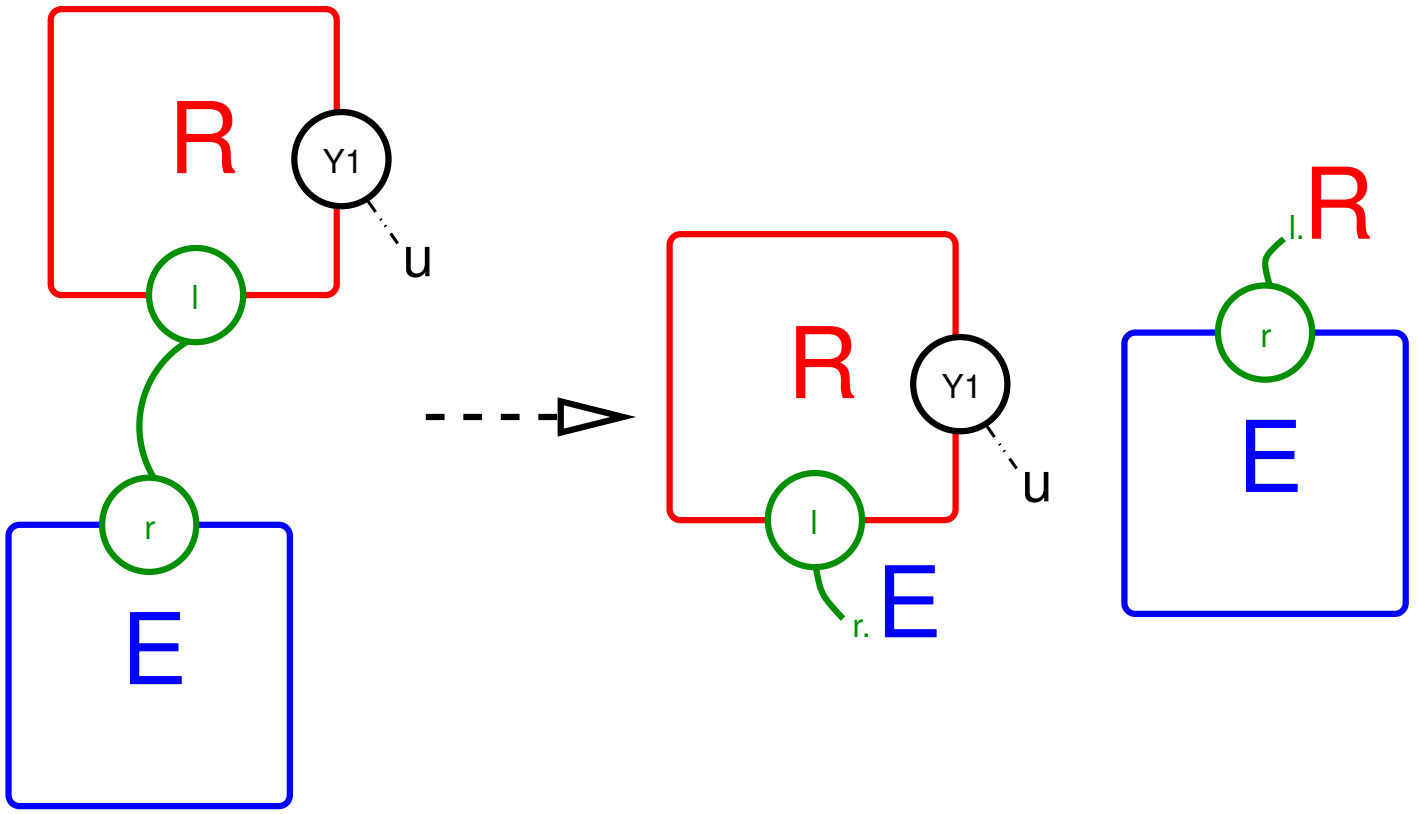
We define the mapping $\mathbb{F}$ as follows:

$$\mathbb{F} : \begin{cases} \wp(\mathit{Species}) & \to \wp(\mathit{Species}) \\ X & \mapsto X \cup \left\{ c'_j \;\middle|\; \begin{array}{l} \exists R_k \in \mathcal{R}, c_1, \ldots, c_m \in X, \\ c_1, \ldots, c_m \to_{R_k} c'_1, \ldots, c'_n \end{array} \right\}. \end{cases}$$

We define the set of reachable chemical species as follows:

$$\mathit{Species}_\omega = \bigcup \left\{ \mathbb{F}^n(\mathit{Species}_0) \;\middle|\; n \in \mathbb{N} \right\}.$$

Local views



$\alpha(\{R(Y1\sim u,l!1), E(r!1)\}) = \{R(Y1\sim u,l!r.E); E(r!l.R)\}.$

Galois connexion

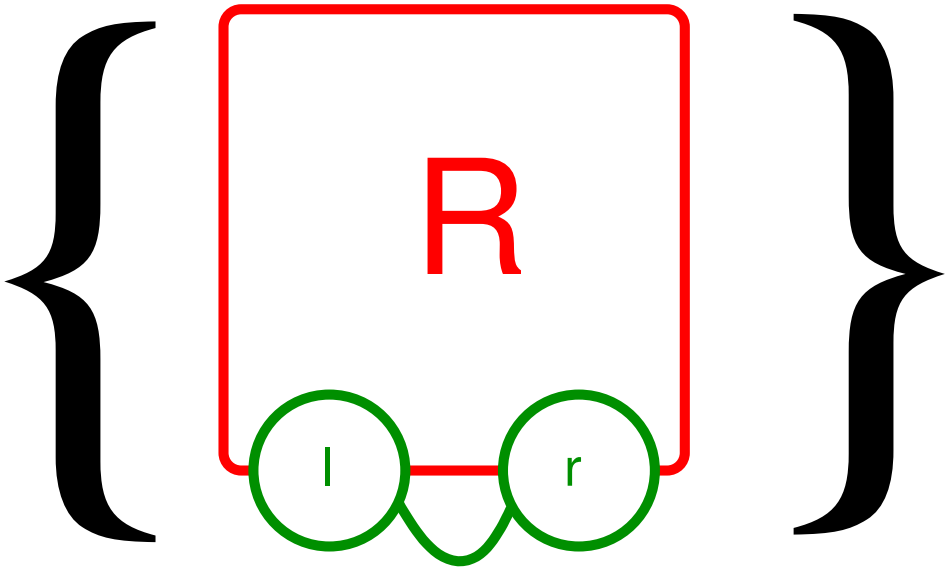
- Let $\mathit{Local\_view}$ be the set of all local views.
- Let $\alpha \in \wp(\mathit{Species}) \rightarrow \wp(\mathit{Local\_view})$ be the function that maps any set of chemical species into the set of their local views.
- Let $\gamma \in \wp(\mathit{Local\_view}) \rightarrow \wp(\mathit{Species})$ be the function that maps any set of local views into the set of chemical species that can be built with these local views.
- The pair (α, γ) forms a Galois connexion:

$$\wp(\mathit{Species}) \underset{\alpha}{\overset{\gamma}{\leftrightarrows}} \wp(\mathit{Local\_view}).$$

$\gamma \circ \alpha$

$\gamma \circ \alpha$ is an upper closure operator: it abstracts away some information.

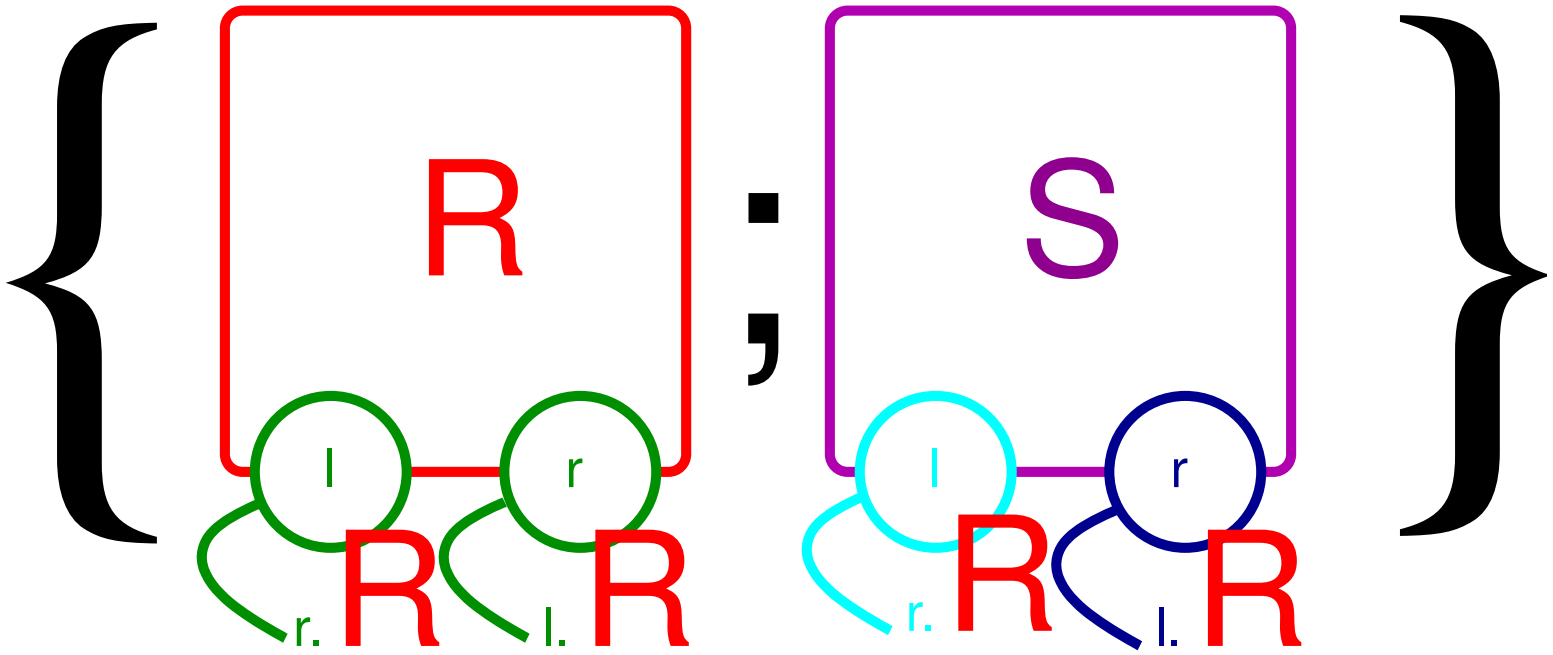
Guess the image of the following set of chemical species ?



$\alpha \circ \gamma$

$\alpha \circ \gamma$ is a lower closure operator: it simplifies (or reduces) constraints.

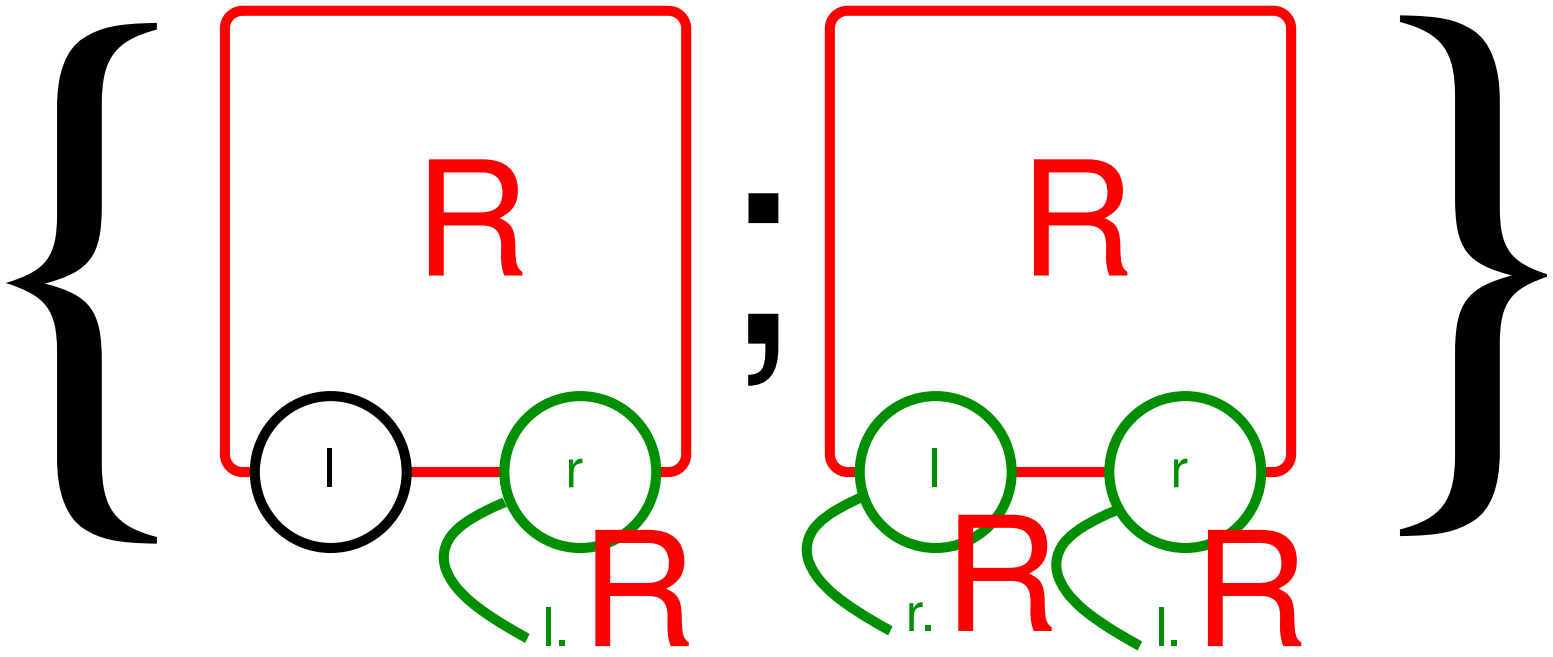
Guess the image of the following set of local views ?



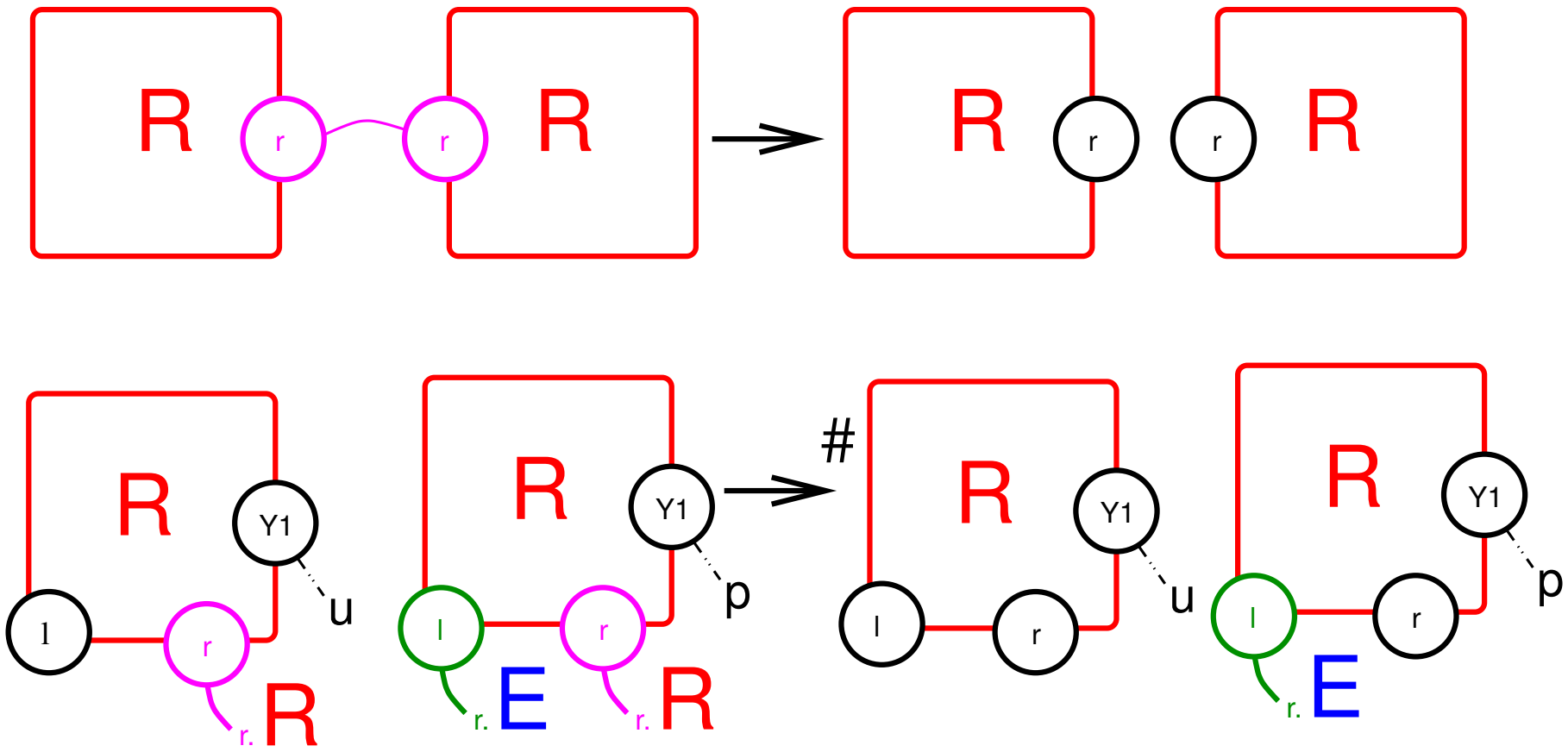
One more question

$\alpha \circ \gamma$ is a lower closure operator: it simplifies (or reduces) constraints.

Guess the image of the following set of local views ?



Abstract rules



Abstract counterpart to $\mathbb{F}$

We define $\mathbb{F}^\sharp$ as:

$$\mathbb{F}^\sharp : \begin{cases} \wp(\mathit{Local\_view}) & \to \wp(\mathit{Local\_view}) \\ X & \mapsto X \cup \left\{ \mathit{lv}'_j \;\middle|\; \begin{array}{l} \exists R_k \in \mathcal{R}, \mathit{lv}_1, \ldots, \mathit{lv}_m \in X, \\ \mathit{lv}_1, \ldots, \mathit{lv}_m \to^\sharp_{R_k} \mathit{lv}'_1, \ldots, \mathit{lv}'_n \end{array} \right\}. \end{cases}$$

Theorem 1 (soundness) It follows that:

1. both $\mathit{lfp}_{x_0}\mathbb{F}$ and $\mathit{lfp}_{\alpha(x_0)}\mathbb{F}^\sharp$ exist,
2. $\mathit{lfp}_{x_0}\mathbb{F} \subseteq \gamma(\mathit{lfp}_{\alpha(x_0)}\mathbb{F}^\sharp)$.

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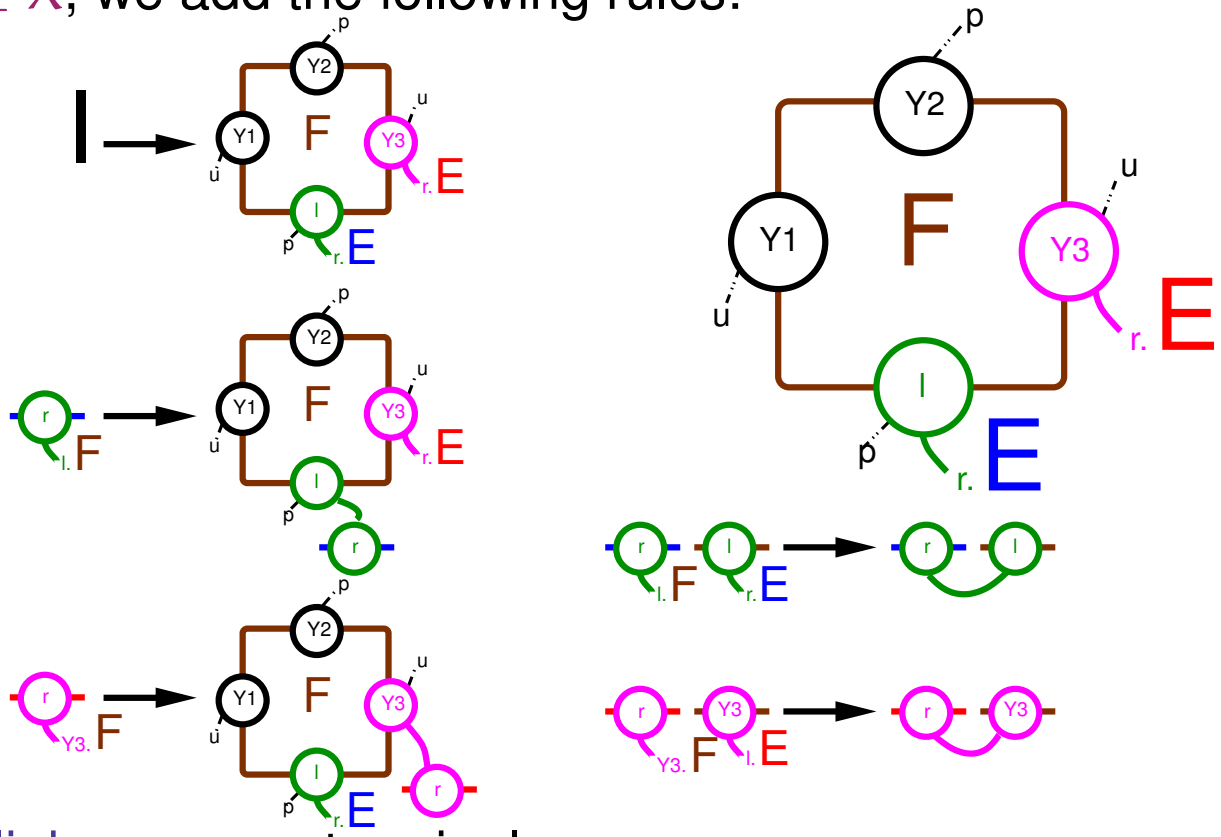
Concretization

For any $X \in \wp(Local\_view)$, $\gamma(X)$ is given by a rewrite system:
For any $lv \in X$, we add the following rules:



I and semi-links are non-terminal.
I is the initial symbol.

Pumping lemma

- We use this rewrite system to enumerate the chemical species of $\gamma(X)$.
- There are two cases:
  1. either there is a finite number of rewrite sequences;
  2. or we encounter cyclic derivations
     i.e. an open chemical species with a cycle of the following form:

     R.l-r.E ... R.l-r.E

     can be built.
- We only enumerate chemical species that are reached through an acyclic rewriting computation.
- It turns out that: if $X \in \alpha(\wp(\mathit{Species}))$ then each rewrite sequence is the prefix of a terminating rewrite sequence.
  (So there is an unbounded number of species if, and only if, there is an unbounded number of rewrite sequences.)

Examples

1. Make the demo for egf
2. Make the demo for fgf
3. Make the demo for Global invariants

Which information is abstracted away ?

Our analysis is exact (no false positive):

- for EGF cascade (356 chemical species);
- for FGF cascade (79080 chemical species);

We know how to build systems with false positives. . .
. . .but they seem to be biologically meaningless.

This raises the following issues:

- Can we characterize which information is abstracted away ?
- Which is the form of the systems, for which we have no false positive ?
- Do we learn something about the biological systems that we describe ?

Local set of chemical species

Definition 1 We say that a set $X \in \wp(Species)$ of chemical species is local if and only if $X \in \gamma(\wp(Local\_view))$.

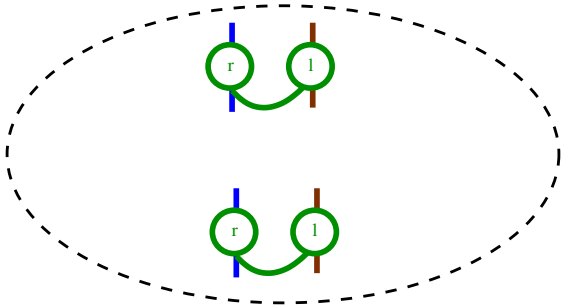
(ie. a set X is local if and only if X is exactly the set of all the species that are generated by a given set of local views.)

Swapping relation

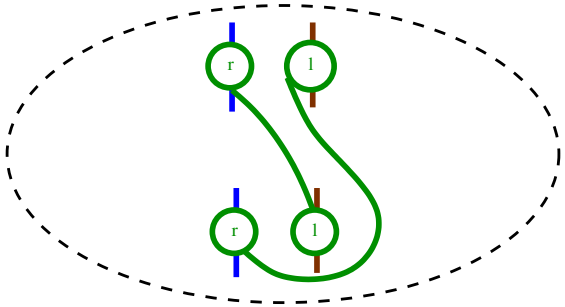
We define the binary relation $\overset{\text{SWAP}}{\sim}$ among tuples *Species** of chemical species.

We say that $(C_1, \ldots, C_m) \overset{\text{SWAP}}{\sim} (D_1, \ldots, D_n)$ if and only if:

$(C_1, \ldots, C_m)$ matches with



while $(D_1, \ldots, D_n)$ matches with



Swapping closure

Theorem 2 Let $X \in \wp(\mathit{Species})$ be a set of chemical species.
The two following assertions are equivalent:

1. the set $X \in \wp(\mathit{Species})$ is local;
2. for any tuples $(C_i), (D_j) \in \mathit{Species}^*$ such that:
   - $(C_i) \in X^*$,
   - and $(C_i) \overset{\text{SWAP}}{\sim} (D_j)$;

   we have $(D_j) \in X^*$.

Consequences

Theorem 3 (completeness) It follows that:

- if the set $\mathit{Species}_\omega$ of reachable chemical species is close with respect swapping $\overset{\text{SWAP}}{\sim}$,
- then the reachability analysis is exact (i.e. $\mathit{Species}_\omega = \gamma(\mathit{lfp}_{\alpha(\mathit{Species}_0)}\mathbb{F}^\sharp)$).

Overview

1. Introduction
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7. Conclusion

Outline

We have proved that:

- if the set $\mathit{Species}_\omega$ of reachable chemical species is close with respect swapping $\overset{\text{SWAP}}{\sim}$,
- then the reachability analysis is exact (i.e. $\mathit{Species}_\omega = \gamma(\mathit{lfp}_{\alpha(\mathit{Species}_0)}\mathbb{F}^\sharp)$).

Now we give some sufficient conditions that ensure this property.

Sufficient conditions

Whenever the following assumptions:

1. initial agents are not bound;
2. rules are atomic;
3. rules are local:
   - only agents that interact are tested,
   - no cyclic patterns (neither in lhs, nor in rhs);
4. binding rules do not interfere i.e. if both:
   - A(a~m,S),B(b~n,T) $\rightarrow$ A(a~m!1,S),B(b~n!1,T)
   - and A(a~m',S'),B(b~n',T') $\rightarrow$ A(a~m'!1,S'),B(b~n'!1,T'),

   then:
   - A(a~m,S),B(b~n',T') $\rightarrow$ A(a~m!1,S),B(b~n'!1,T');
5. chemical species in $\gamma(\alpha(\mathit{Species}_\omega))$ are acyclic,

are satisfied, the set of reachable chemical species is local.

Non local systems

$$Species_0 \triangleq \mathrm{R(a{\sim}u)}$$

$$Rules \triangleq \left\{ \begin{array}{lcl} \mathrm{R(a{\sim}u)} & \leftrightarrow & \mathrm{R(a{\sim}p)} \\ \mathrm{R(a{\sim}u),R(a{\sim}u)} & \rightarrow & \mathrm{R(a{\sim}u!1),R(a{\sim}u!1)} \\ \mathrm{R(a{\sim}p),R(a{\sim}u)} & \rightarrow & \mathrm{R(a{\sim}p!1),R(a{\sim}p!1)} \\ \mathrm{R(a{\sim}p),R(a{\sim}p)} & \rightarrow & \mathrm{R(a{\sim}p!1),R(a{\sim}p!1)} \end{array} \right\}$$

$\mathrm{R(a{\sim}u!1),R(a{\sim}u!1)} \in Species_\omega$

$\mathrm{R(a{\sim}p!1),R(a{\sim}p!1)} \in Species_\omega$

But $\mathrm{R(a{\sim}u!1),R(a{\sim}p!1)} \notin Species_\omega$.

Non local systems

$$Species_0 \triangleq \text{A(a}\sim\text{u),B(a}\sim\text{u)}$$

$$Rules \triangleq \left\{ \begin{array}{l} \text{A(a}\sim\text{u),B(a}\sim\text{u)} \rightarrow \text{A(a}\sim\text{u!1),B(a}\sim\text{u!1)} \\ \text{A(a}\sim\text{u!1),B(a}\sim\text{u!1)} \rightarrow \text{A(a}\sim\text{p!1),B(a}\sim\text{u!1)} \\ \text{A(a}\sim\text{u!1),B(a}\sim\text{u!1)} \rightarrow \text{A(a}\sim\text{u!1),B(a}\sim\text{p!1)} \end{array} \right\}$$

$\text{A(a}\sim\text{u!1),B(a}\sim\text{p!1)} \in Species_\omega$

$\text{A(a}\sim\text{p!1),B(a}\sim\text{u!1)} \in Species_\omega$

But $\text{A(a}\sim\text{p!1),B(a}\sim\text{p!1)} \notin Species_\omega$.

Non local systems

$$Species_0 \triangleq \mathrm{A(a{\sim}u)}$$

$$Rules \triangleq \left\{ \begin{array}{l} \mathrm{A(a{\sim}u)} \leftrightarrow \mathrm{A(a{\sim}p)} \\ \mathrm{A(a{\sim}u),A(a{\sim}p)} \rightarrow \mathrm{A(a{\sim}u!1),A(a{\sim}p!1)} \end{array} \right\}$$

$\mathrm{A(a{\sim}u!1),A(a{\sim}p!1)} \in Species_\omega$
But $\mathrm{A(a{\sim}p!1),A(a{\sim}p!1)} \notin Species_\omega$.

Non local systems

$$\mathit{Species}_0 \triangleq \text{R(a,b)}$$
$$\mathit{Rules} \triangleq \{\ \text{R(a,b),R(a)} \rightarrow \text{R(a,b!1),R(a!1)}\}$$

R(a,b!2),R(a!2,b!1),R(a!1,b)$\in \mathit{Species}_\omega$
But R(a!1,b!1) $\notin \mathit{Species}_\omega$.

Overview

1. Introduction
2. Kappa language
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Outline

- we have a syntactic criterion in order to ensure that the set of reachable chemical species of a kappa system is local ;
- we now design program transformations to help systems satisfying this criterion ;
  1. decontextualization
     - is fully automatic;
     - preserves the transition system;
     - simplifies rules thanks to reachability analysis.
  2. conjugation
     - manual;
     - preserves the set of reachable chemical species;
     - uses backtrack to add new rules.

Example

Initial rule:

R2(l!2,r),R1(l!1,r),E2(r!1),E1(r!2) $\rightarrow$ R2(l!3,r!1),R1(l!2,r!1),E2(r!2),E1(r!3)

Decontextualized rule:

R2(l!_,r),R1(l!_,r) $\rightarrow$ R2(l!_,r!1),R1(l!_,r!1)

We can remove redundant tests.

Example

Initial rules:

$$\begin{aligned}
\text{Sh(Y7}\sim\text{p!2,pi!1),G(a!2,b),R(Y48}\sim\text{p!1)} &\rightarrow \text{Sh(Y7}\sim\text{p,pi!1),G(a,b),R(Y48}\sim\text{p!1)} \\
\text{Sh(Y7}\sim\text{p!3,pi!1),G(a!3,b!2),So(d!2),R(Y48}\sim\text{p!1)} &\rightarrow \text{Sh(Y7}\sim\text{p,pi!1),G(a,b!2),So(d!2),R(Y48}\sim\text{p!1)} \\
\text{Sh(Y7}\sim\text{p!1,pi),G(a!1,b)} &\rightarrow \text{Sh(Y7}\sim\text{p,pi),G(a,b)} \\
\text{Sh(Y7}\sim\text{p!1,pi),G(a!1,b!_)} &\rightarrow \text{Sh(Y7}\sim\text{p,pi),G(a,b!_)}
\end{aligned}$$

Decontextualized rule:

$$\text{Sh(Y7!1),G(a!1)} \rightarrow \text{Sh(Y7),G(a)}$$

We can remove exhaustive enumerations.

An undecontextualizable rule

Initial rule:

Sh(Y7~u,pi!1),R(Y48~p!1,r!_) -> Sh(Y7~p,pi!1),R(Y48~p!1,r!_)

Decontextualized rule:

Sh(Y7~u,pi!1),R(Y48!1,r!_) -> Sh(Y7~p,pi!1),R(Y48!1,r!_)

Conjugation

If a rule $\mathcal{R}'$ is equivalent to a rule in the transitive closure of the system.
Then it may be included in the system without modifying reachable states.
To remove the context $\mathcal{C}$ of a rule, we try to apply it for another context $\mathcal{C}'$ by:

1. removing the context $\mathcal{C}'$ (backtrack) ;
2. building the context $\mathcal{C}$;
3. applying the initial rule ;
4. removing the context $\mathcal{C}$ (backtrack) ;
5. building the context $\mathcal{C}'$.

This is proved manually.

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Conclusion

- A scalable static analysis to abstract the reachable chemical species.
- A class of models for which the abstraction is complete.
- Many applications:
  - idiomatic description of reachable chemical species;
  - dead rule detection;
  - rule decontextualization;
  - computer-driven kinetic refinement.
- It can also help simulation algorithms:
  - wake up/inhibition map (agent-based simulation);
  - flat rule system generation (for bounded set of chemical species);
  - on the fly flat rule generation (for large/unbounded set)

MPRI

Some notions of information flow

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Friday, the 13rd of January, 2012

Syntax

Let $\mathcal{V} \triangleq \{V, V_1, V_2, \ldots\}$ be a finite set of variables.

Let $\mathbb{Z} \triangleq \{z, \ldots\}$ be the set of relative numbers.

Expressions are polynomial of variables $\mathcal{V}$.

$$\mathrm{E} ::= z \mid \mathrm{V} \mid \mathrm{E} + \mathrm{E} \mid \mathrm{E} \times \mathrm{E}$$

Programs are given by the following grammar:

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

Semantics

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

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

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

Flow of information

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

More formally,
$V_1 \Rightarrow_P V_2$ if and only if there exists $\rho \in \mathcal{V} \to \mathbb{R}$, $z, z' \in \mathbb{Z}$ 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 $\rightarrow_{\mathrm{P}}$ among variables in $\mathcal{V}$:
$V_1 \rightarrow_{\mathrm{P}} V_2$ if and only if there is an assignement in P of the form $V_2 := \mathrm{E}$ such that V_1 occurs in E.

Does $V_1 \Rightarrow_{\mathrm{P}} V_2$ imply that $V_1 \rightarrow^*_{\mathrm{P}} V_2$?

Counter-example

We consider the following progrem P:

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

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

Syntactic approximation (tentative)

For each program points p in P,
we denote by *test*(p) the set of variables which occurs in the guard of the test and while loop the scope of which contains the program point p.

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

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

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

Counter-example

We consider the following progrem P:

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

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

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 atacker could observe:

- computation time;
- memory assumption;
- heating.

(attacks cannot be exhaustively specified).

Master AIV

Automatic reduction of differential semantics for protein-protein interaction networks, by abstract interpretation

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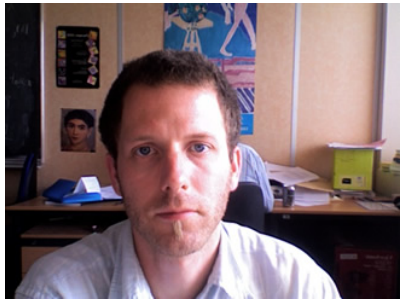

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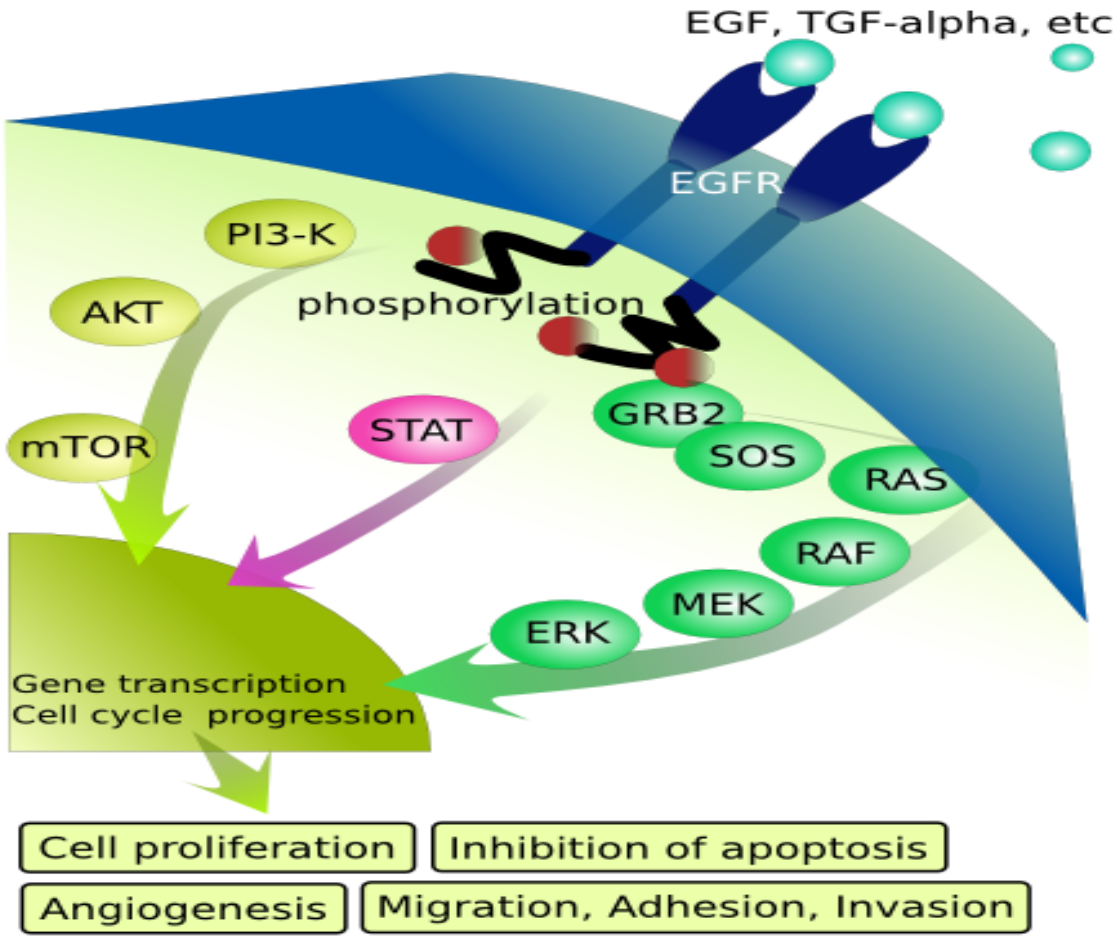
Overview

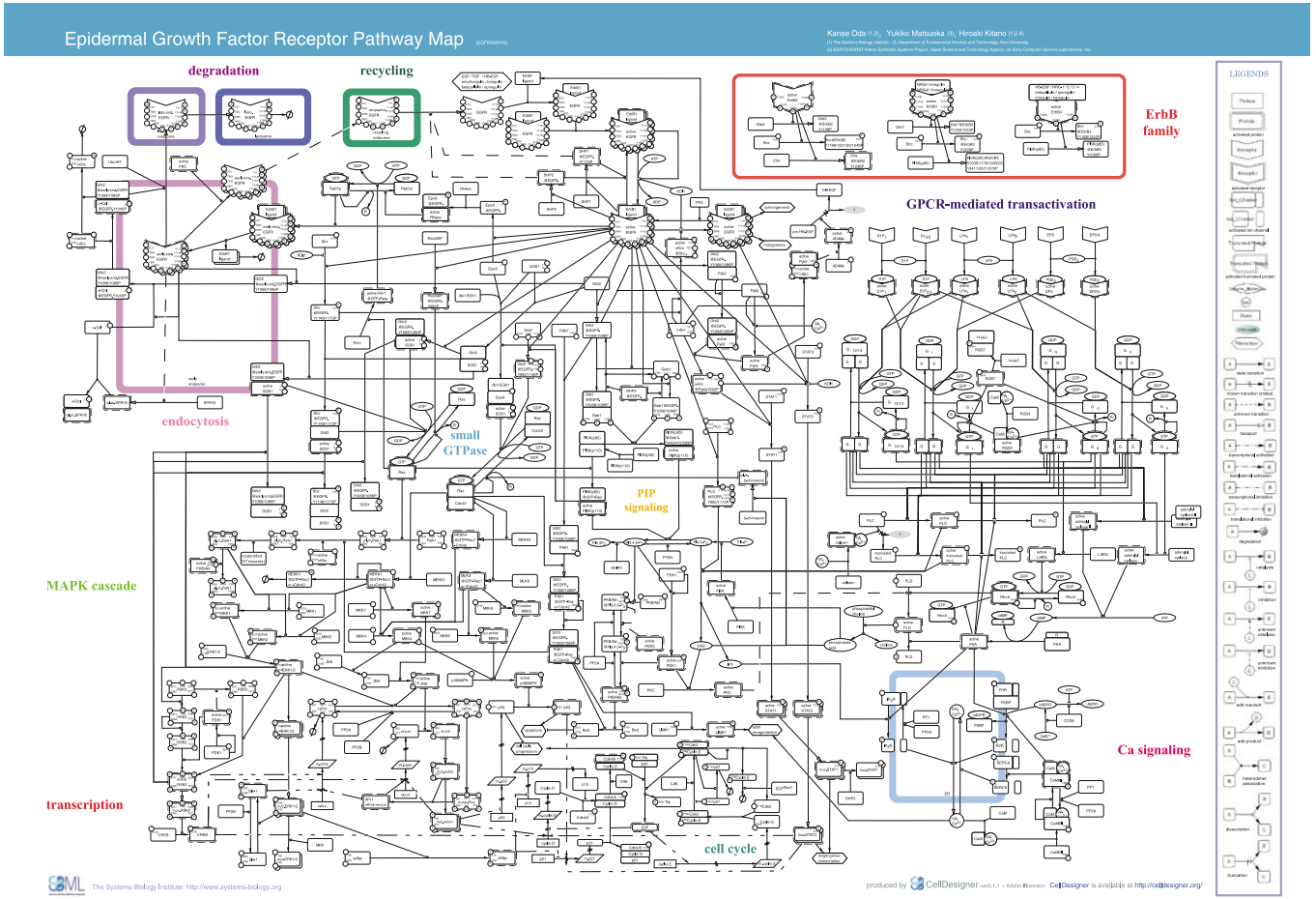
1. Context and motivations
2. Handmade ODEs
3. Abstract interpretation framework
4. Kappa
5. Concrete semantics
6. Abstract semantics
7. Conclusion

Signalling Pathways



Eikuch, 2007

Pathway maps



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

Differential models

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

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

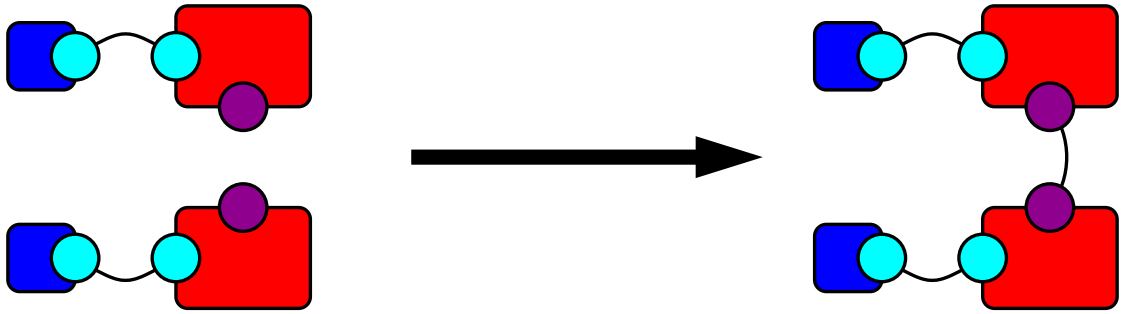
A gap between two worlds

Two levels of description:

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

Rule-based approach

We use site graph rewrite systems



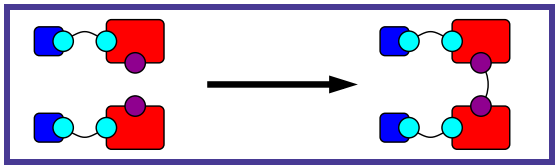
1. The description level matches with both
   - the observation level
   - and the intervention level

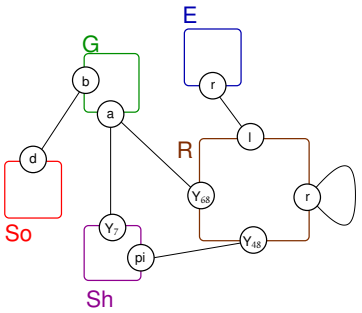
   of the biologist.

   We can tune the model easily.
2. Model description is very compact.
3. Quantitative semantics can be defined.

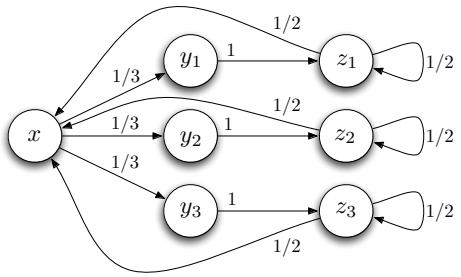
Semantics

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





Interaction map

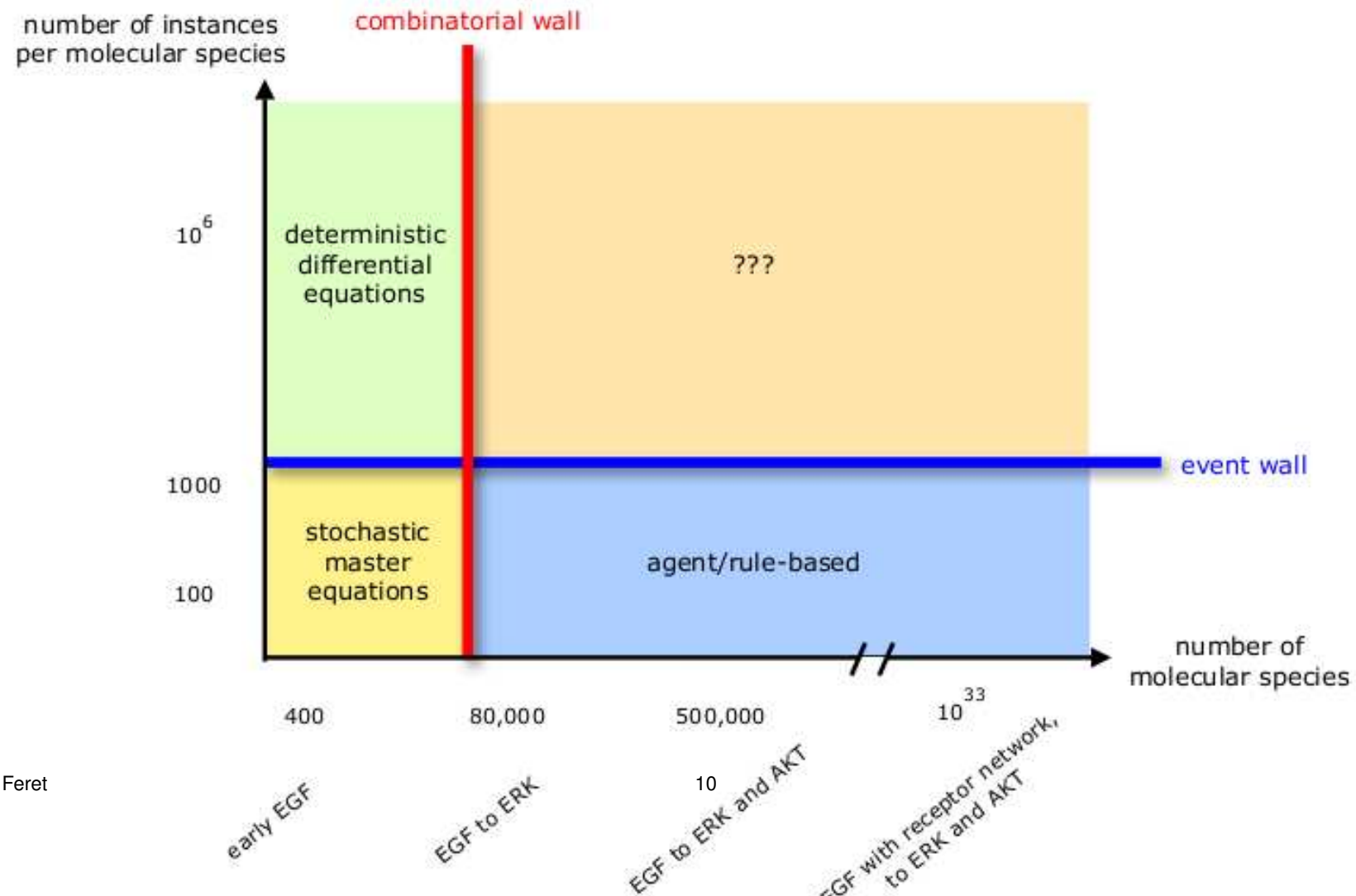


CTMC

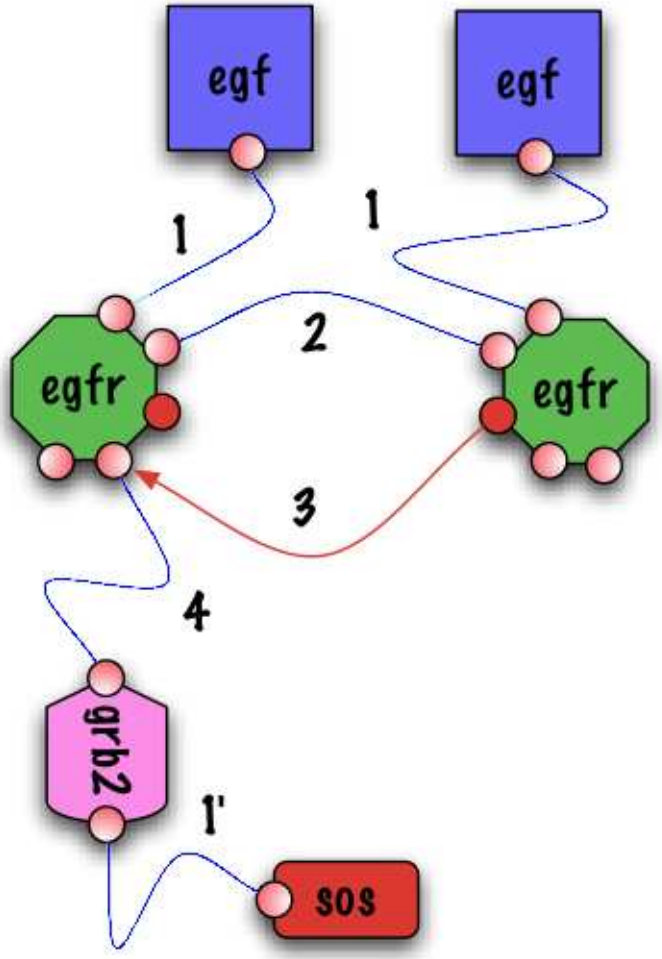
$$\begin{cases} \frac{dx_1}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\ \frac{dx_2}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\ \frac{dx_3}{dt} = k_1 \cdot x_1 \cdot x_2 - k_{-1} \cdot x_3 + 2 \cdot k_2 \cdot x_3 \cdot x_3 - k_{-2} \cdot x_4 \\ \frac{dx_4}{dt} = k_2 \cdot x_3^2 - k_2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

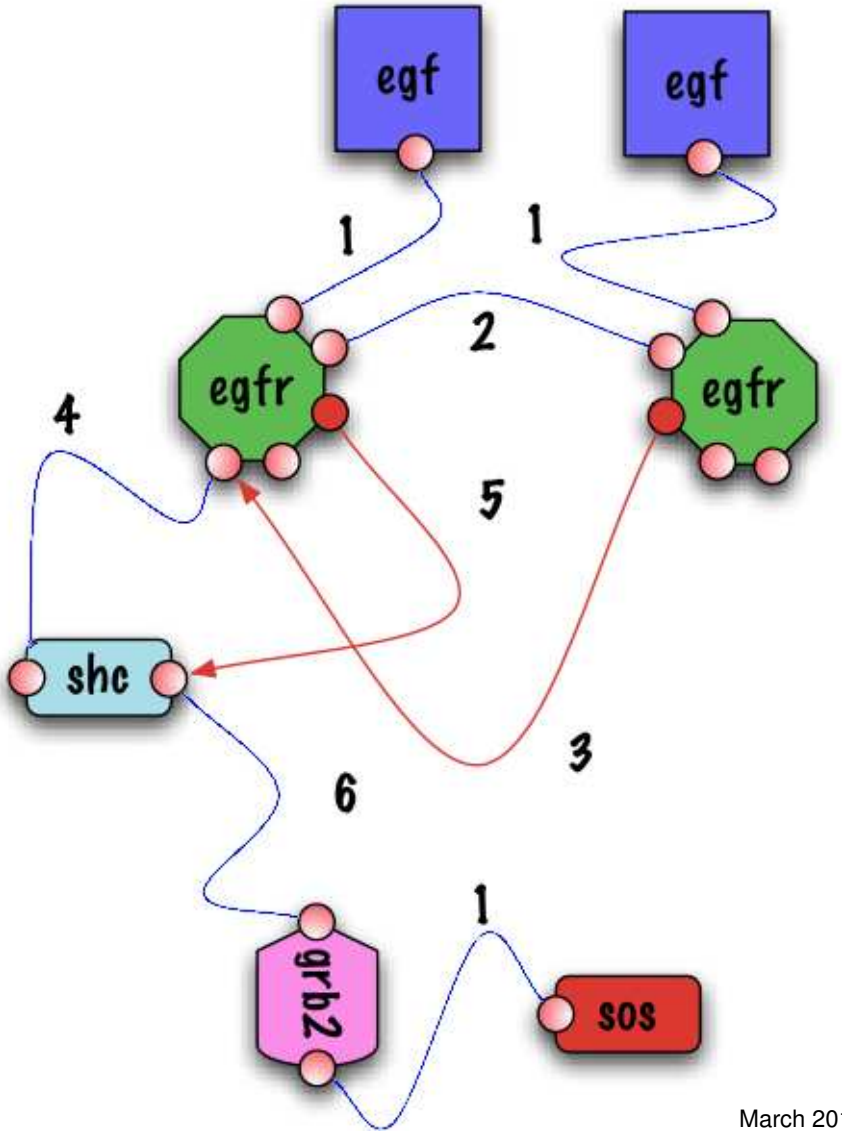
ODEs

Complexity walls



A breach in the wall(s) ?





Overview

1. Context and motivations
2. Handmade ODEs
   (a) Independent subsystems
   (b) Self-consistent subsystems
3. Abstract interpretation framework
4. Kappa
5. Concrete semantics
6. Abstract semantics
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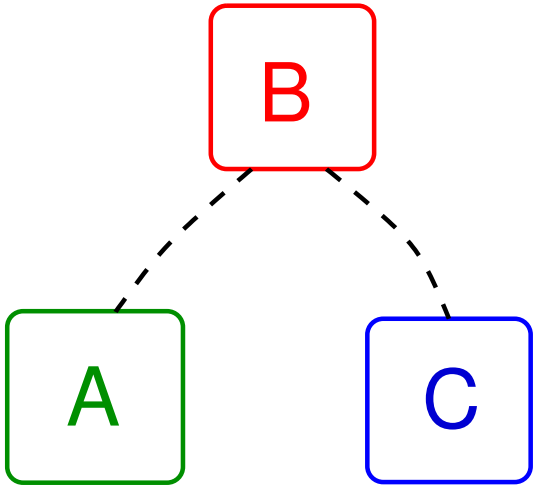
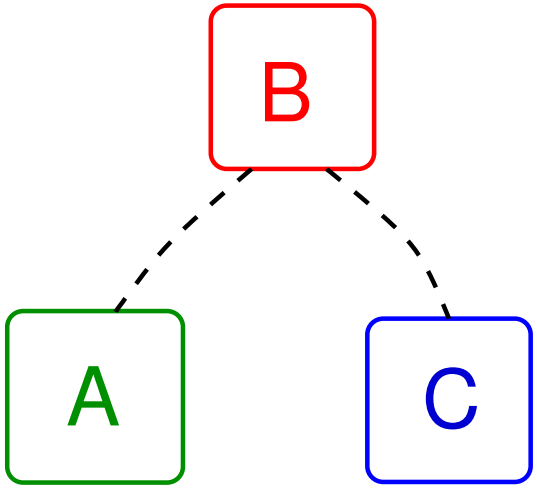
Case study 1: A simple adapter

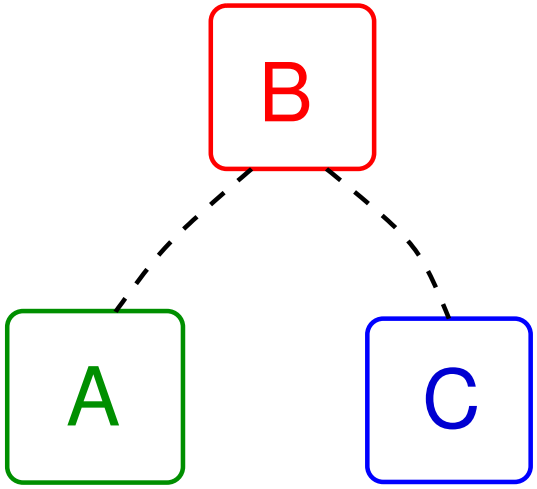


Case study 1: A simple adapter



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

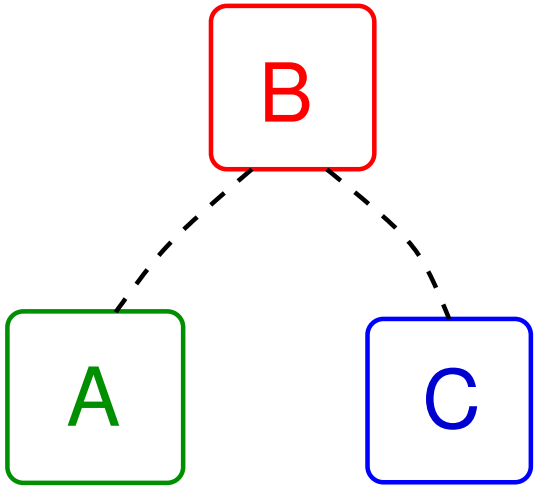
Case study 1: A simple adapter



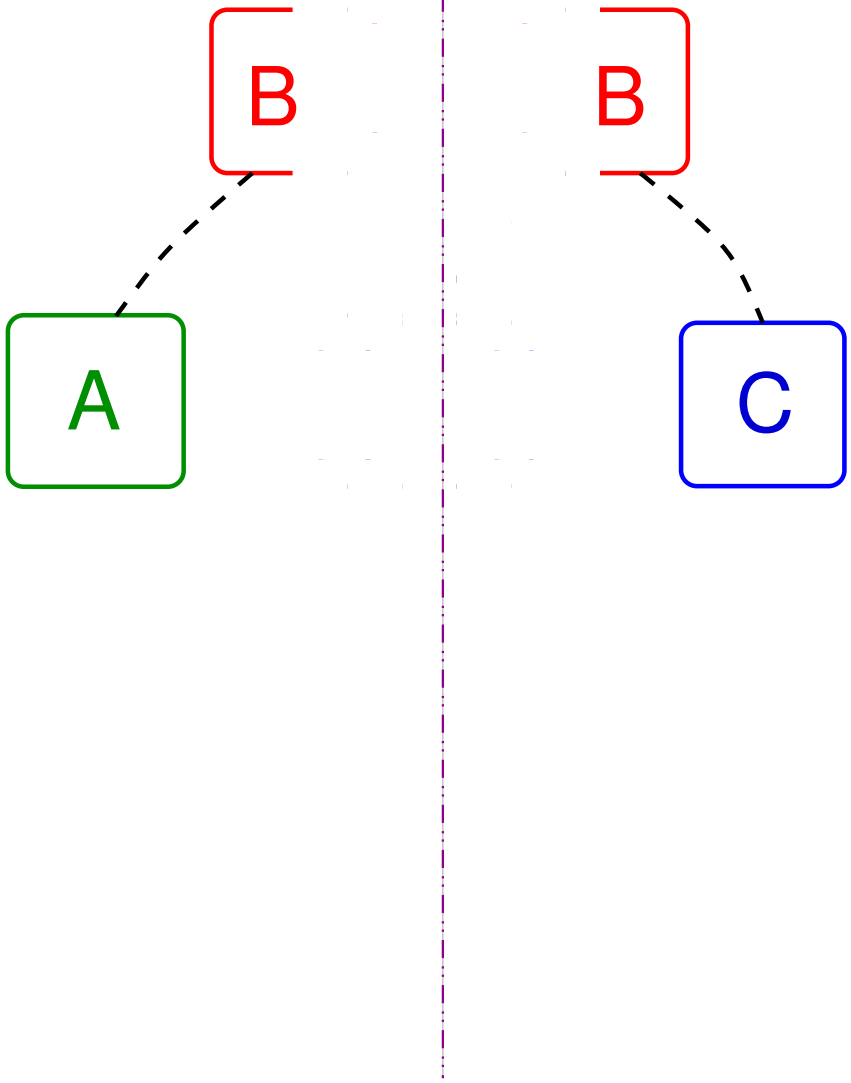
$$
\begin{aligned}
A\,,\,\emptyset B\emptyset &\longleftrightarrow AB\emptyset & k^{AB},k_d^{AB}\\
A\,,\,\emptyset BC &\longleftrightarrow ABC & k^{AB},k_d^{AB}\\
\emptyset B\emptyset\,,\,C &\longleftrightarrow \emptyset BC & k^{BC},k_d^{BC}\\
AB\emptyset\,,\,C &\longleftrightarrow ABC & k^{BC},k_d^{BC}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

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

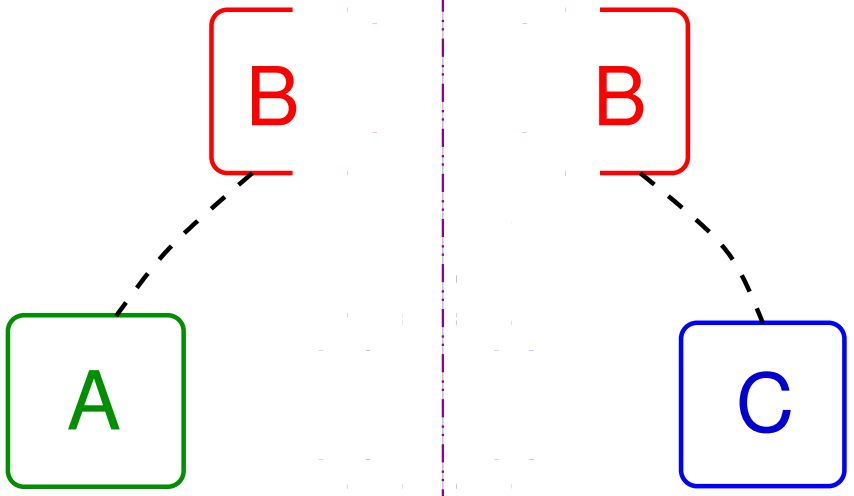
Case study 1: Two subsystems



Case study 1: Two subsystems



Case study 1: Two subsystems



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

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

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

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

Case study 1: Dependence index

We introduce:

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

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

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

Thus we define the dependence index as follows:

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

We have (after a short computation):

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

So the property:

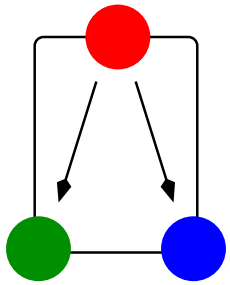
$$[ABC] = \frac{[AB?]\cdot[?BC]}{[?B?]}$$

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

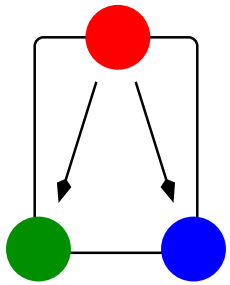
Overview

1. Context and motivations
2. Handmade ODEs
   (a) Independent subsystems
   (b) Self-consistent subsystems
3. Abstract interpretation framework
4. Kappa
5. Concrete semantics
6. Abstract semantics
7. Conclusion

Case study 2: A system with a switch

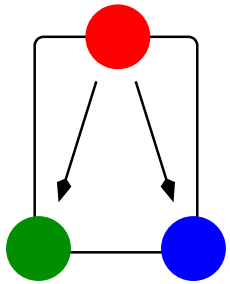


Case study 2: A system with a switch



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

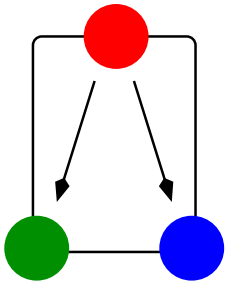
Case study 2: A system with a switch



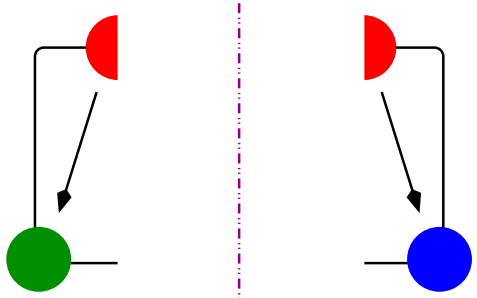
$$
\begin{aligned}
(u,u,u) &\longrightarrow (u,p,u) && k^c \\
(u,p,u) &\longrightarrow (p,p,u) && k^l \\
(u,p,p) &\longrightarrow (p,p,p) && k^l \\
(u,p,u) &\longrightarrow (u,p,p) && k^r \\
(p,p,u) &\longrightarrow (p,p,p) && k^r
\end{aligned}
$$

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

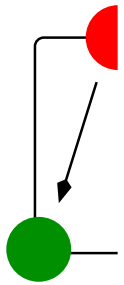
Case study 2: Two subsystems

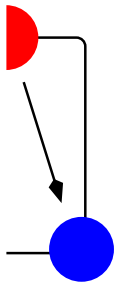


Case study 2: Two subsystems



Case study 2: Two subsystems





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

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

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

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

Case study 2: Dependence index

We introduce:

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

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

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

Thus we define the dependence index as follows:

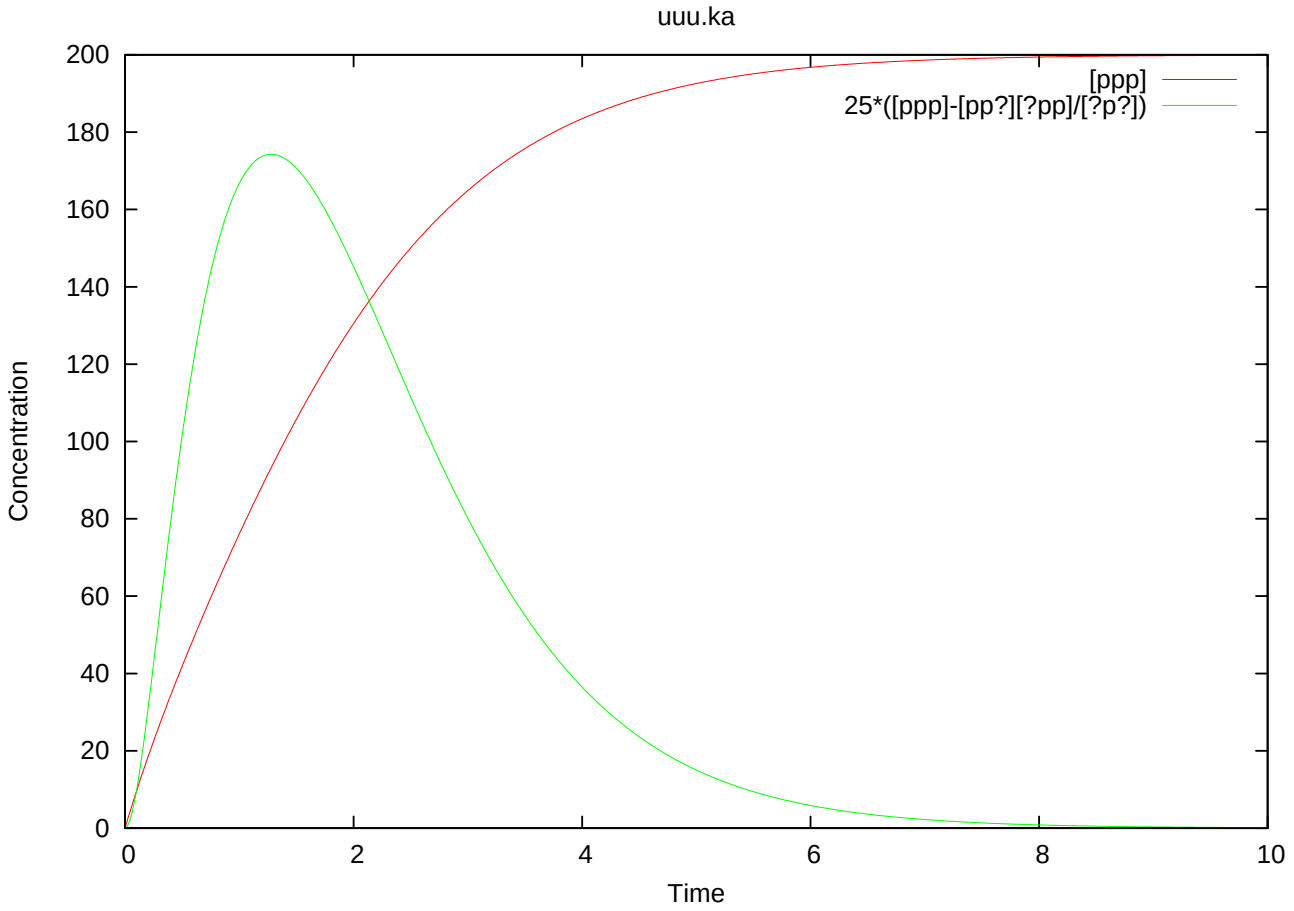
$$X \stackrel{\Delta}{=} [(p,p,p)]\cdot[(?,p,?)] - [(?,p,p)]\cdot[(p,p,?)].$$

We have (after a short computation):

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

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

Case study 2: Erroneous recombination



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

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

Conclusion

1. Independence:
   + the transformation is invertible:
     we can recover the concentration of any species;
   – it is a strong property
     which is hard to prove,
     which is hardly ever satisfied.
2. Self-consistency:
   – some information is abstracted away
     we cannot recover the concentration of any species;
   + it is a weak property
     which is easy to ensure,
     which is easy to propagate;
   + it captures the essence of the kinetics of systems.

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

Overview

1. Context and motivations
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Continuous differential semantics

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

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

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

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

Abstraction

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

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

such that:

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

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

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

Abstraction example

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

(Completeness can be checked analytically.)

Abstract continuous trajectories

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

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

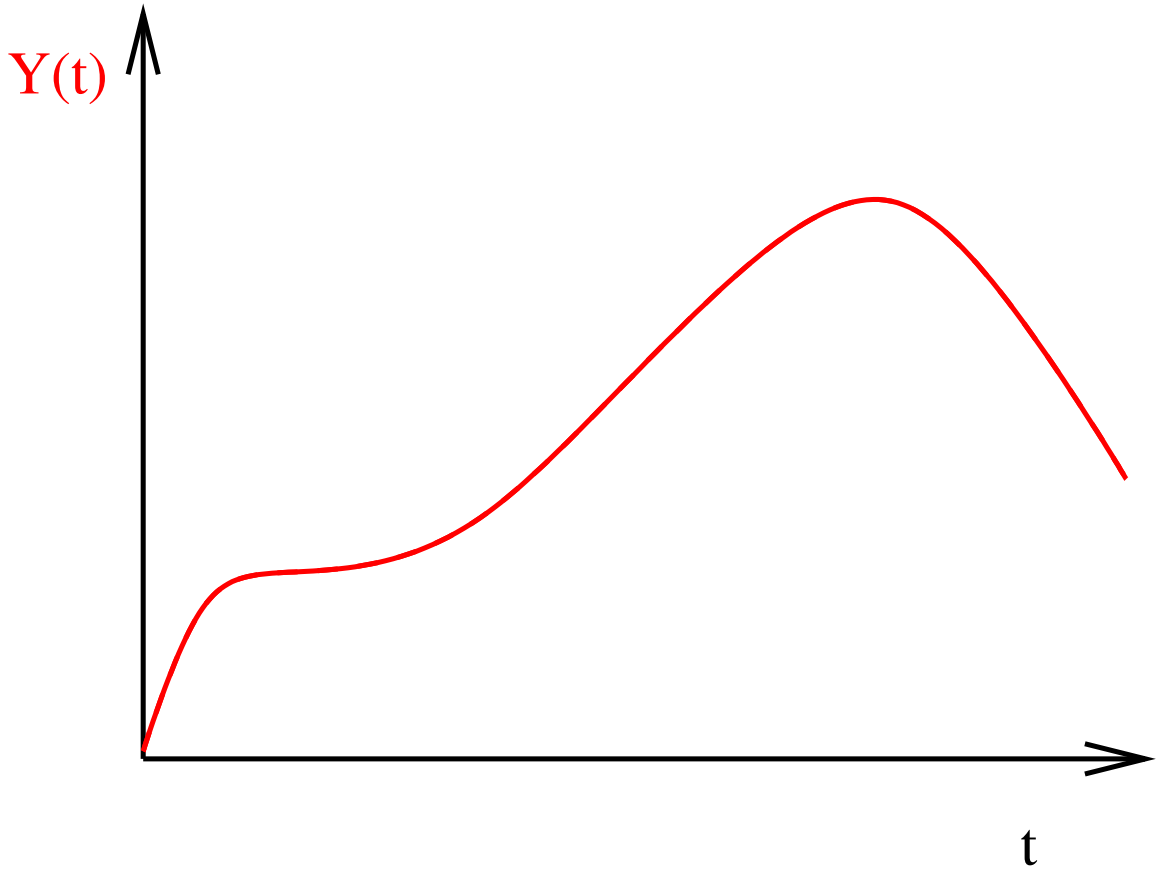
has a unique maximal solution $Y_{\psi(X_0)}$ such that $Y_{\psi(X_0)} = \psi(X_0)$.

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

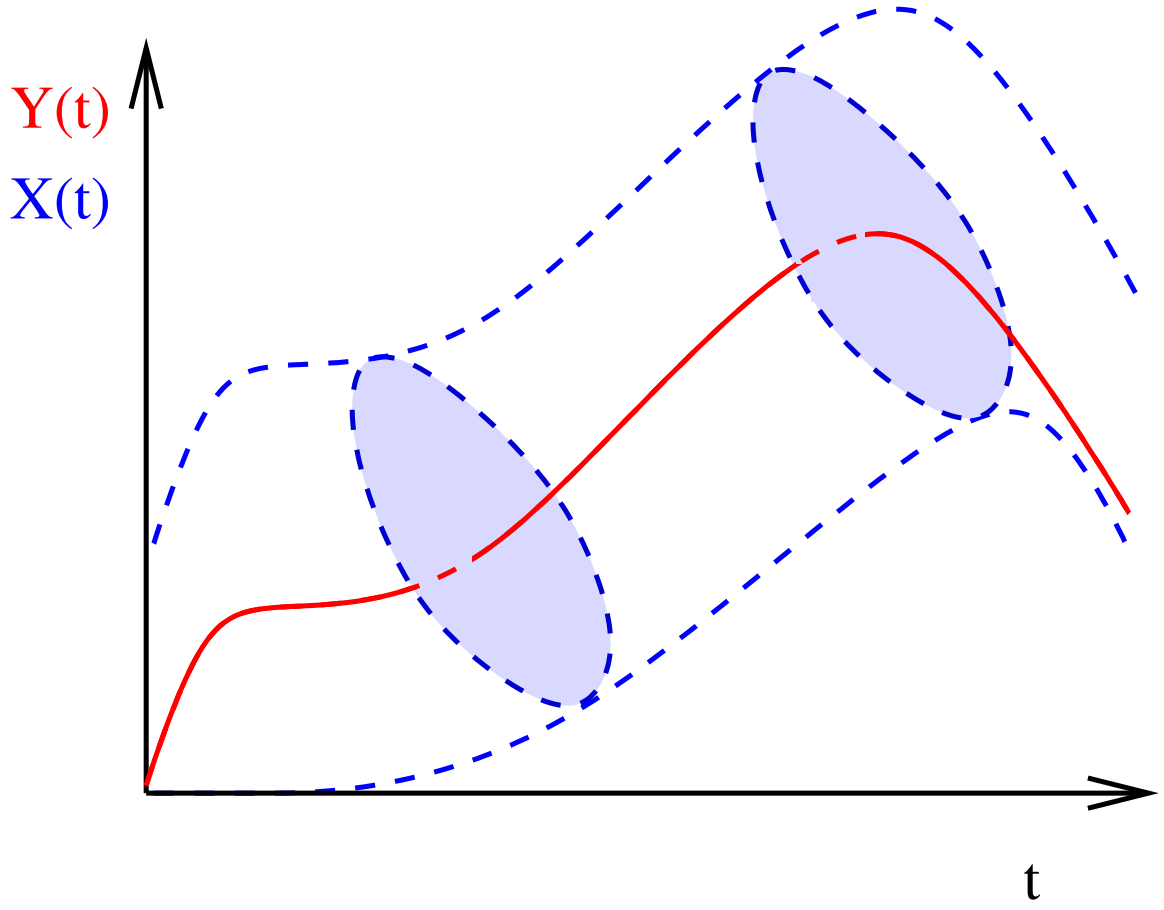
$$X_{X_0}(T) = X_0 + \int_{t=0}^{T} \mathbb{F} \left(X_{X_0}(t) \right) \cdot dt,$$

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

Fluid trajectories



Fluid trajectories



Overview

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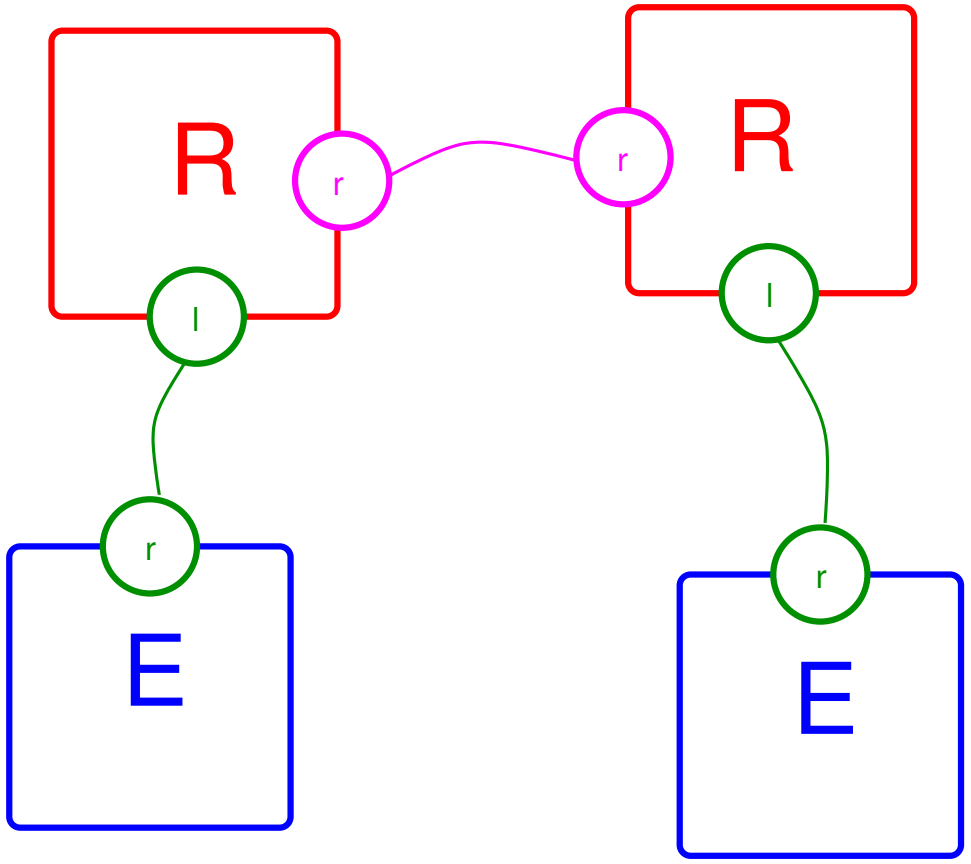
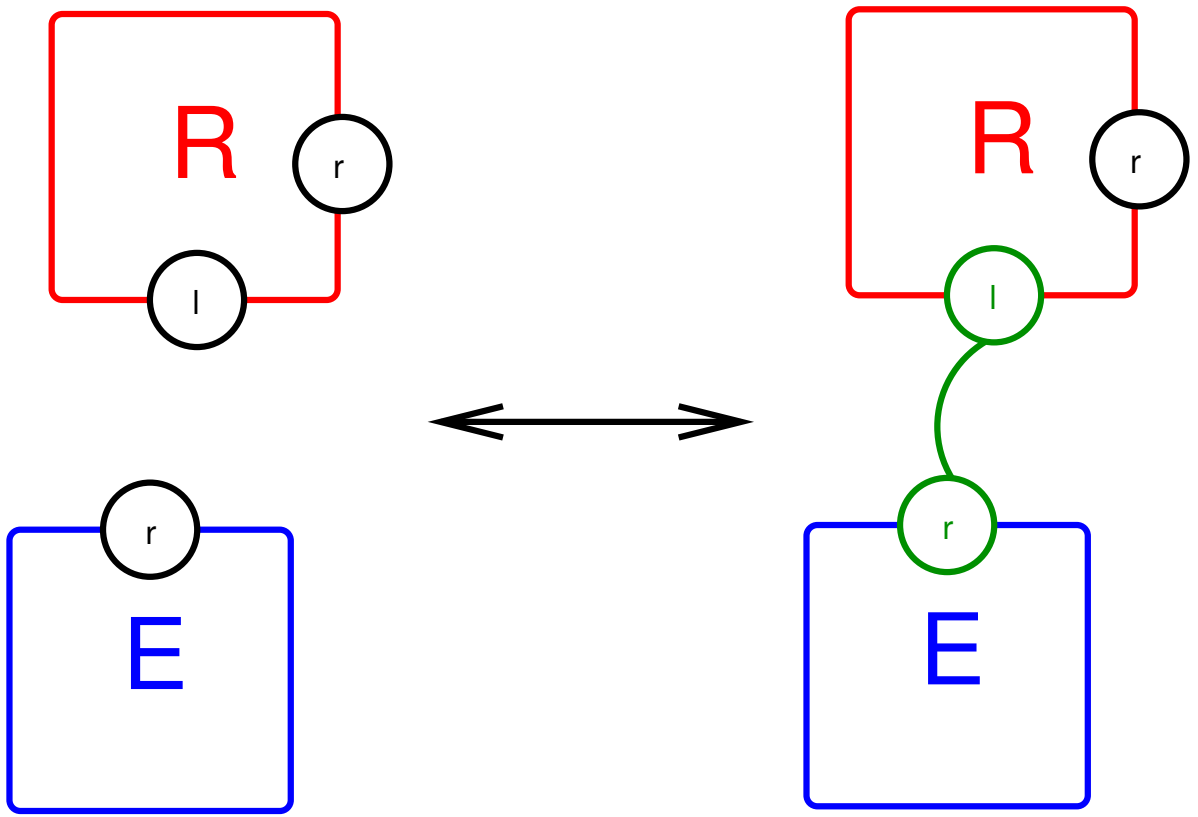
A species



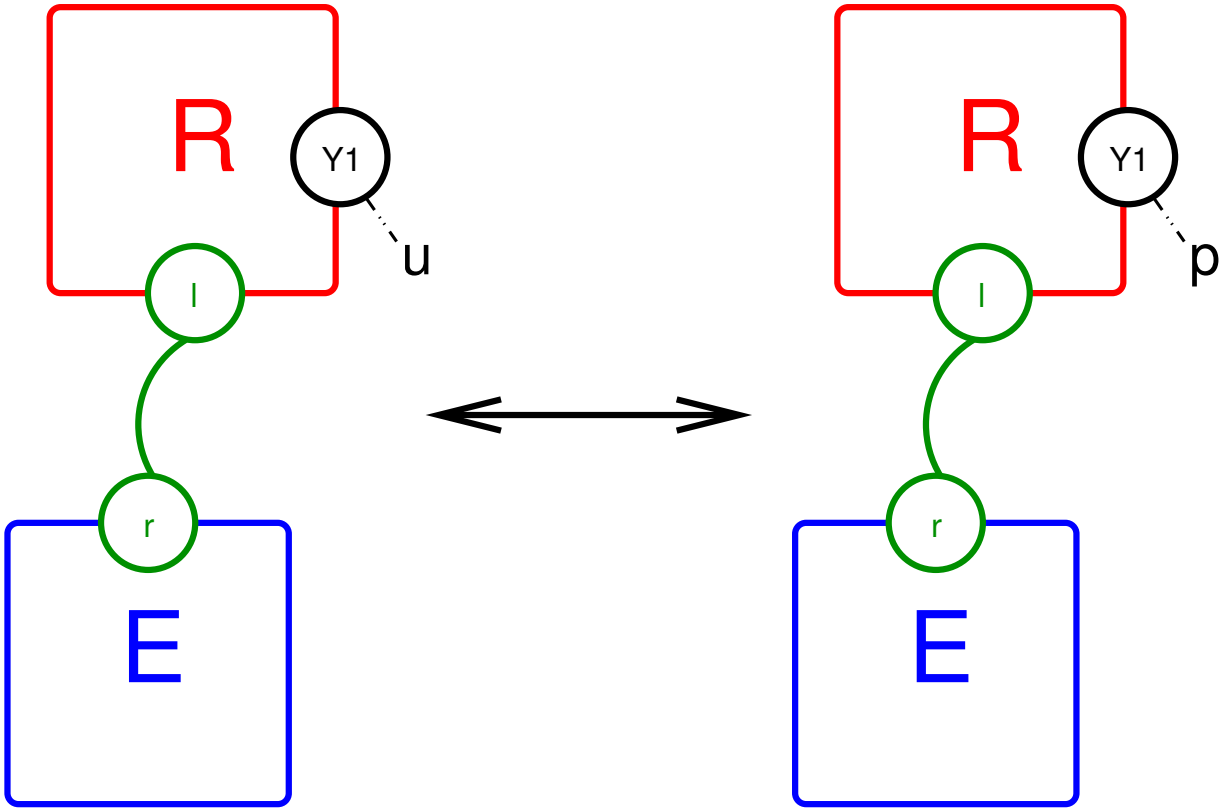
E(r!1), R(l!1,r!2), R(r!2,l!3), E(r!3)

A Unbinding/Binding Rule



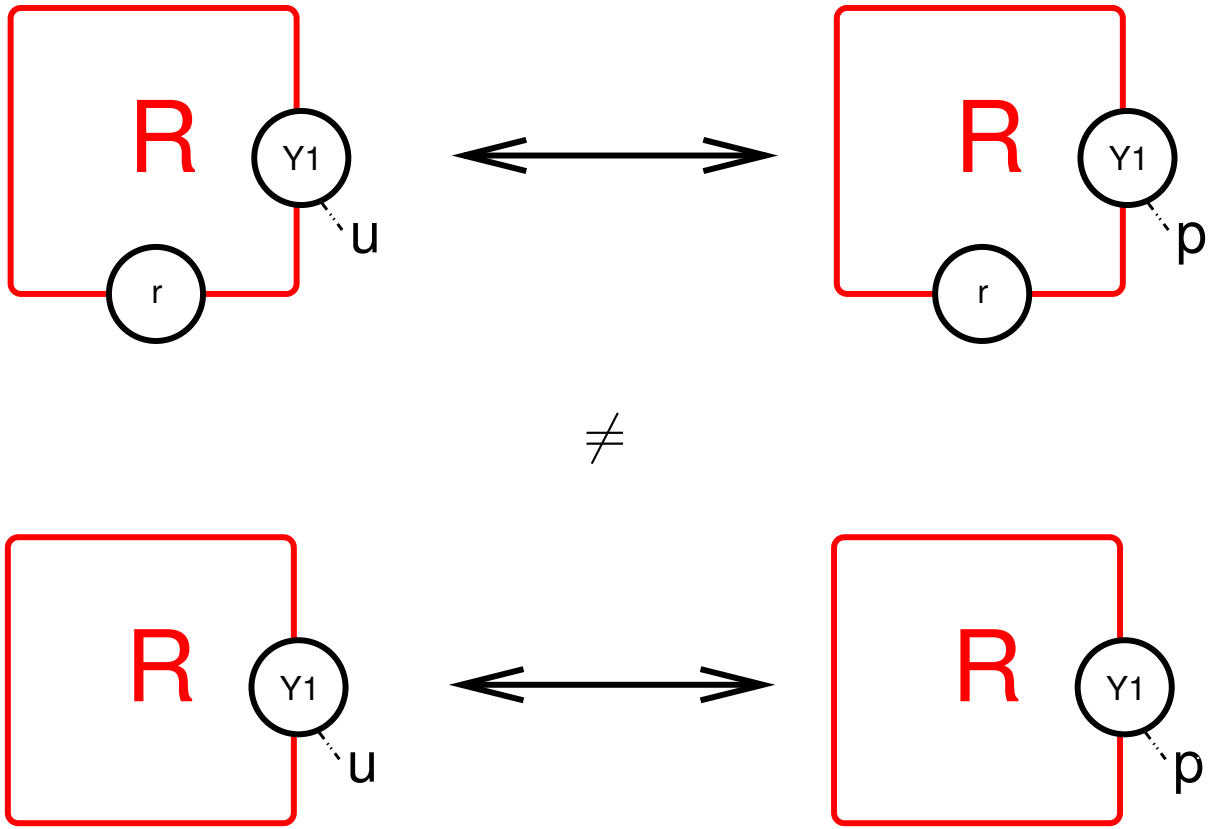
$$E(r),\ R(l,r) \longleftrightarrow E(r!1),\ R(l!1,r)$$

Internal state

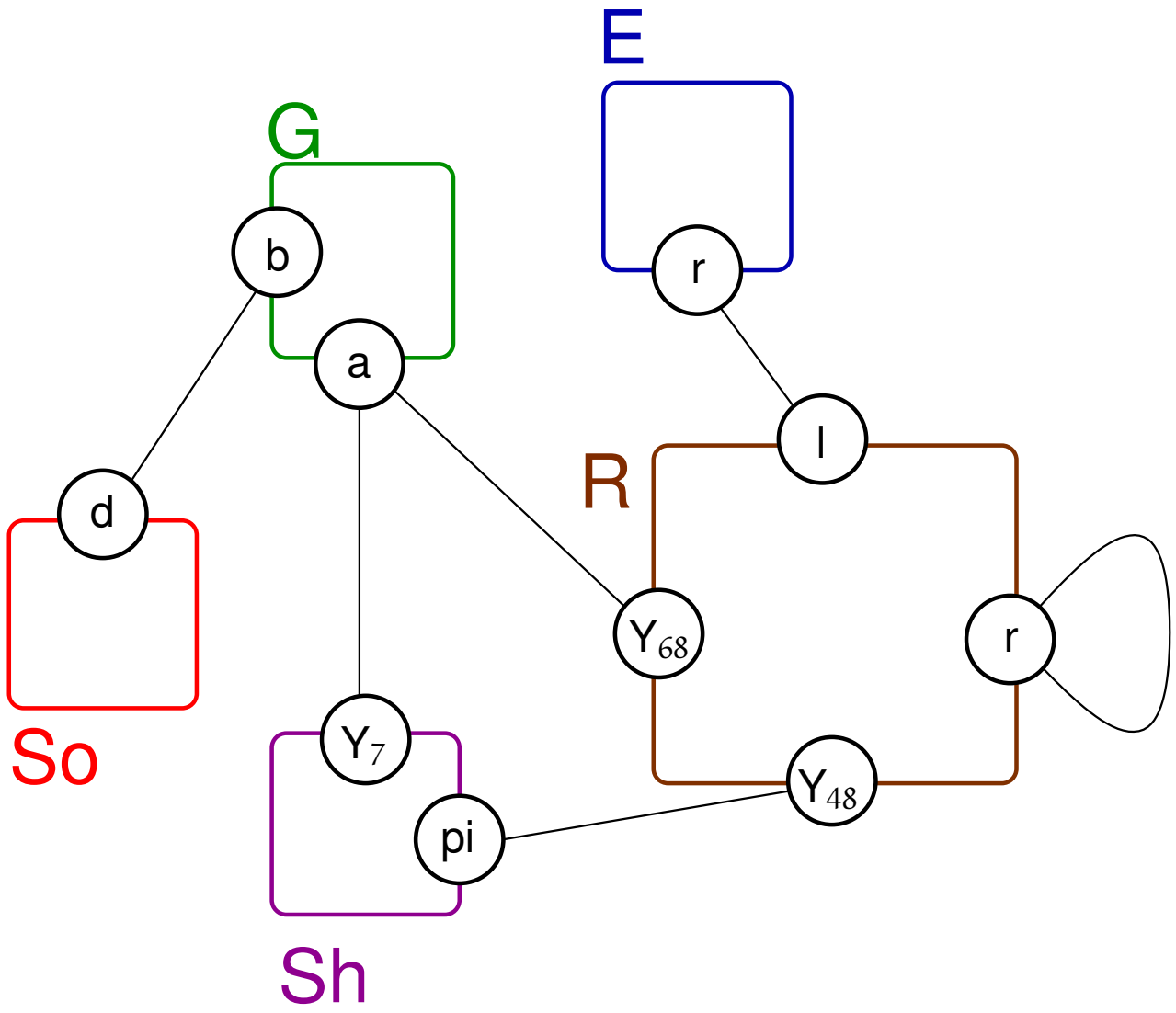


R(Y1~u,l!1), E(r!1) ⟷ R(Y1~p,l!1), E(r!1)

Don’t care, Don’t write



Contact map



Overview

1. Context and motivations
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Requirements

1. Reachable species

   A set $\mathcal{R}$ of connected site-graphs such that:

   - $\mathcal{R}$ is finite;
   - $\mathcal{R}$ is closed with respect to rule application: i.e. applying a rule with a tuple of site-graphs in $\mathcal{R}$ gives a tuple of site-graphs in $\mathcal{R}$;

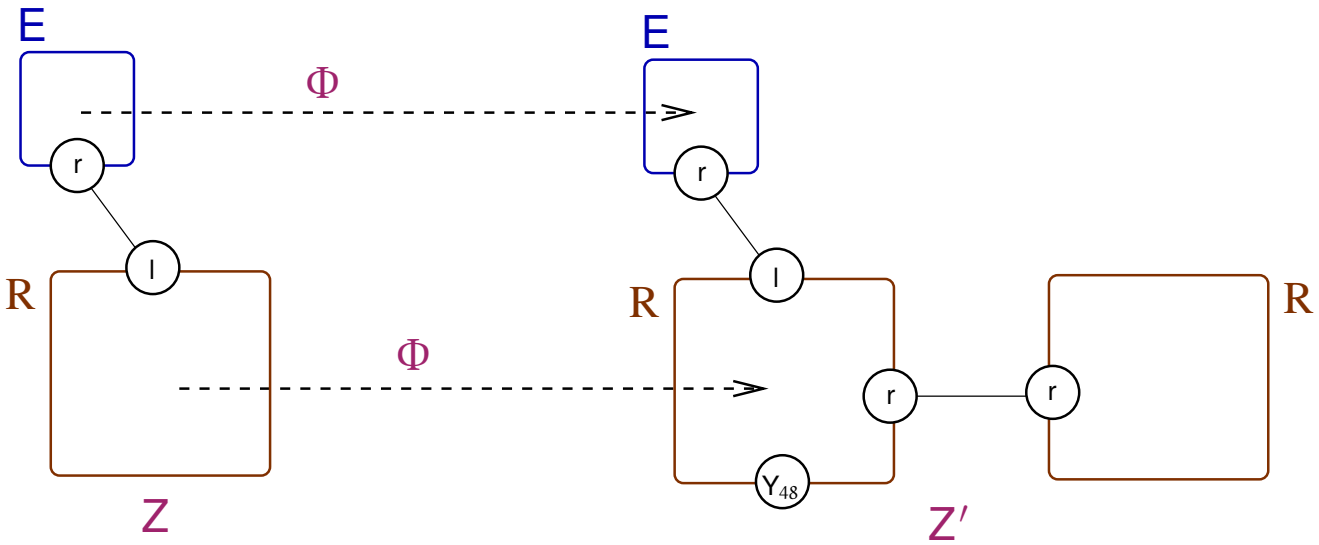
2. Rules are associated with kinetic factors

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

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

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

Embedding



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

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

Differential system

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

A ground instanciation of *rule* is defined by an embedding ϕ between *lhs* into a tuple (r_i) of elements in $\mathcal{R}$ such that:

1. *lhs* and $\mathrm{IM}(\phi)$ have the same number of connected components;
2. ϕ preserves disconnectiveness.

and is written: $r_1, \ldots, r_m \rightarrow p_1, \ldots, p_n \quad k$.

For each such ground instantiation, we get:

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

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

Overview

1. Context and motivations
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6. Abstract semantics
   (a) Fragments
   (b) Soundness criteria
   (c) Abstract counterpart
   (d) Reduction into a network
7. Conclusion

Abstract domain

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

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

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

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

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

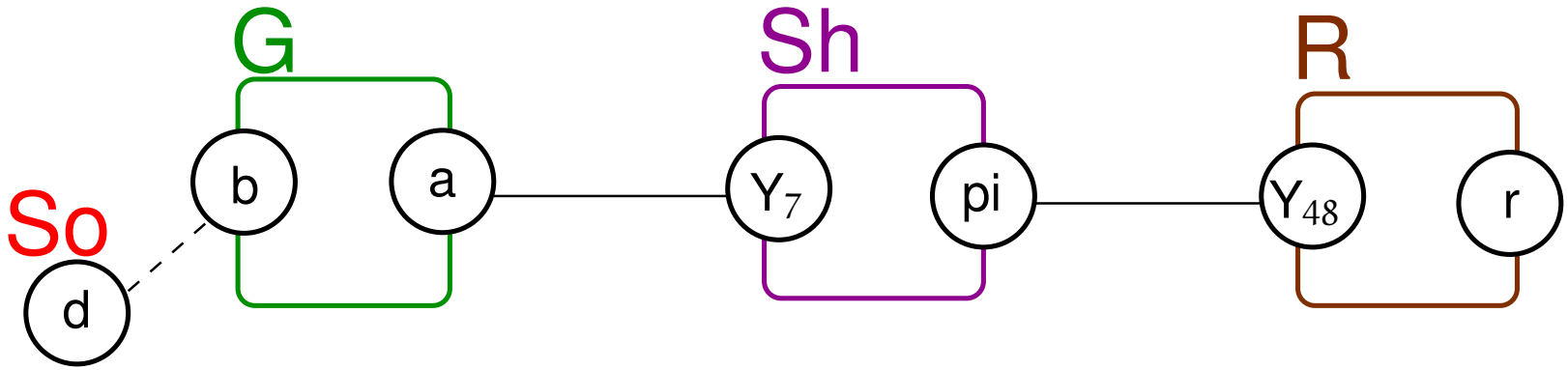
Partial species

Fragments are well-chosen partial species.

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

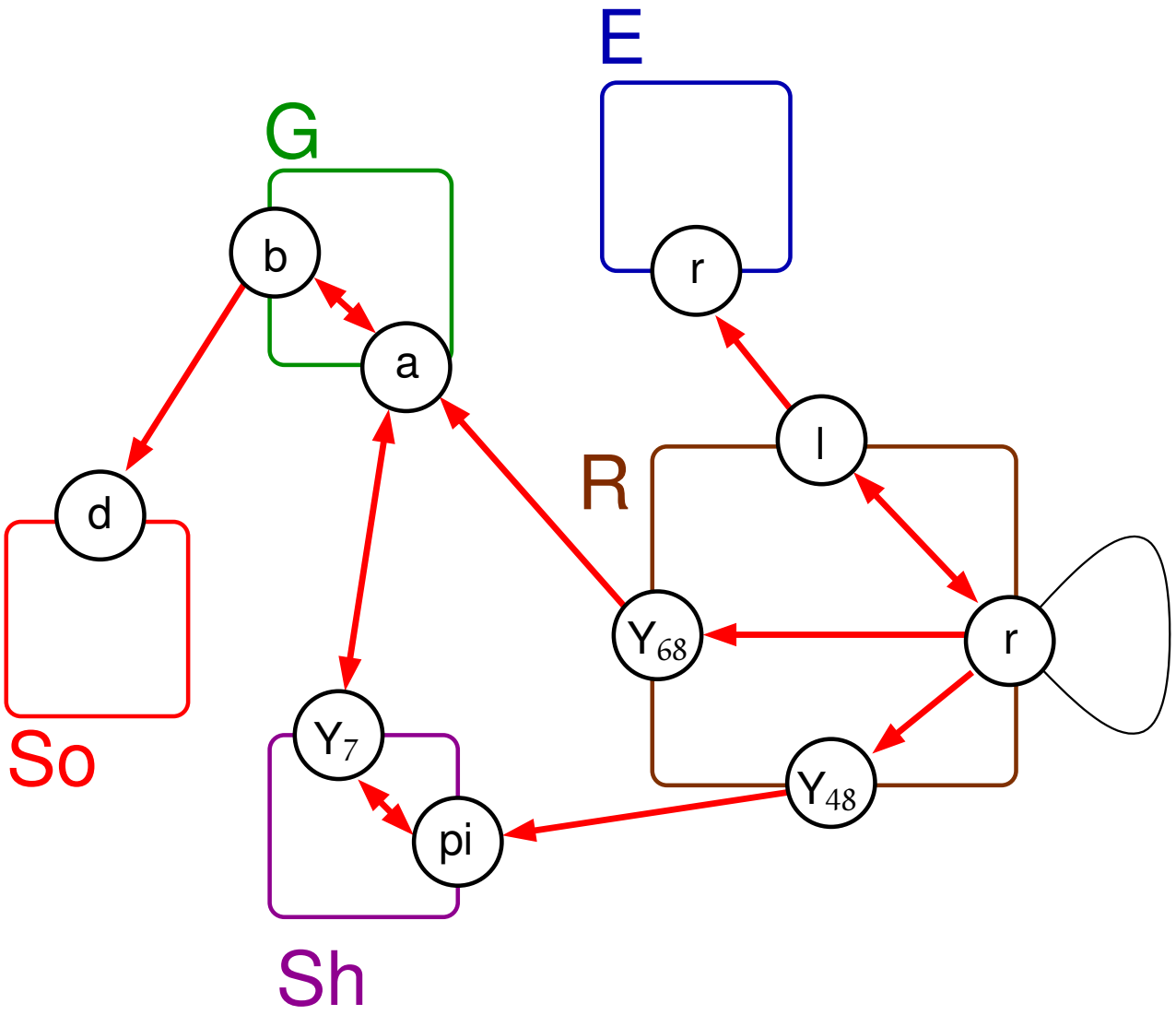
- the set of the sites of each node of type A is a subset of the set of the sites of A;
- sites are free, bound to an other site, or tagged with a binding type.

For instance:



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

Annotated contact map



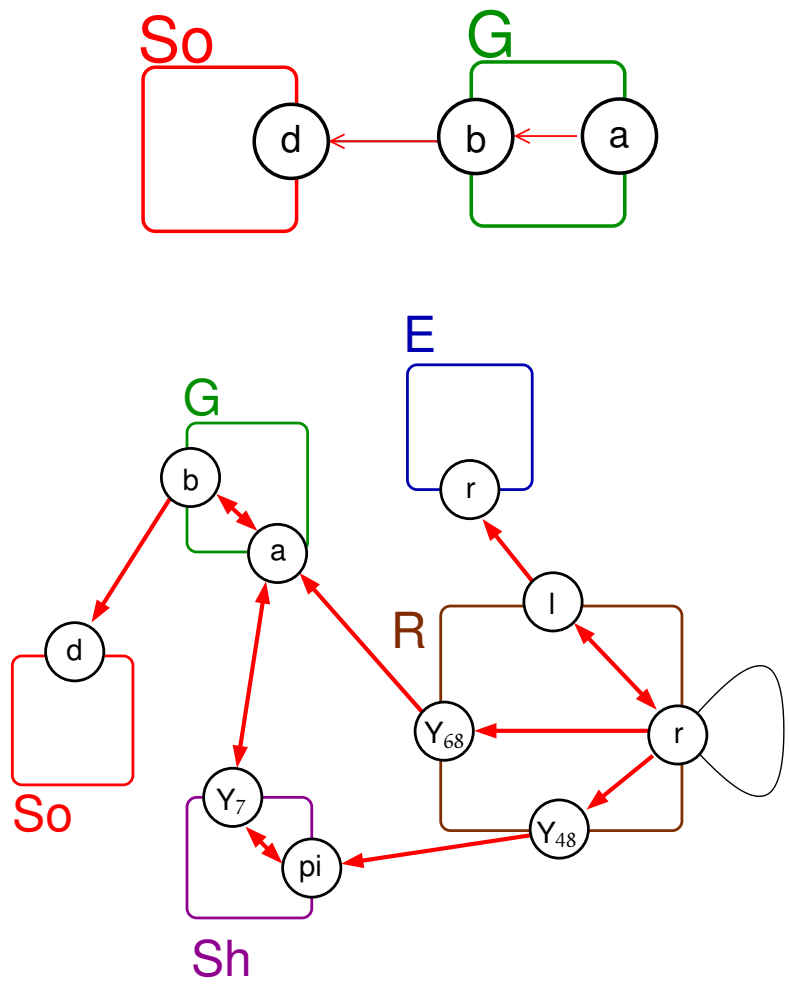
Fragments and prefragments

A prefragment is a partial species for which there exists a binary relations $\rightarrow$ between sites such that:

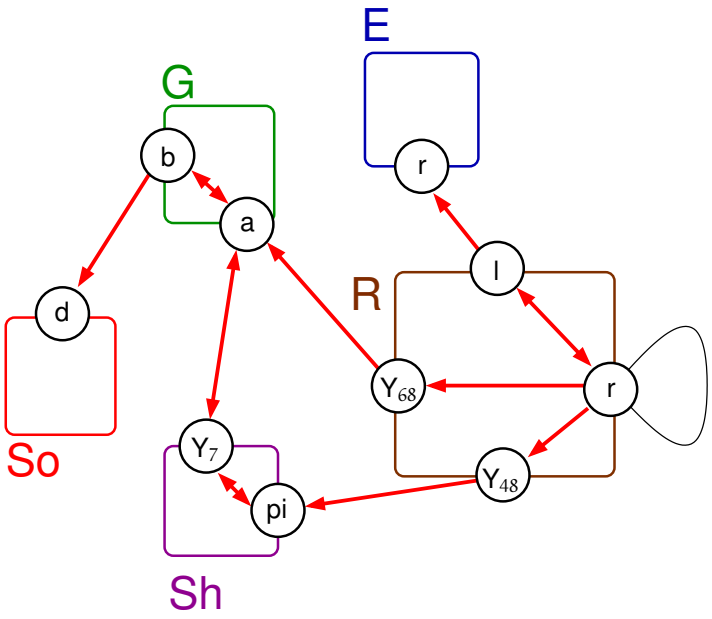
- Directed preorder: for any pair of sites x and y there is a sire z such that: $x \rightarrow^{\star} z$ and $x \rightarrow^{\star} z$.
- Compatibility: any edge $\rightarrow$ can be projected to an edge in the annotated contact map.

A fragment is a prefragment F such that:

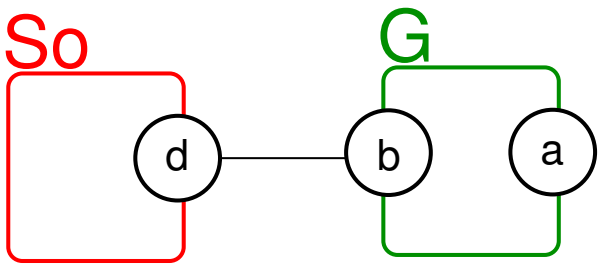
- Parsimoniousness: for any prefragment F' such that $F \lhd F'$, we also have $F' \lhd F$.

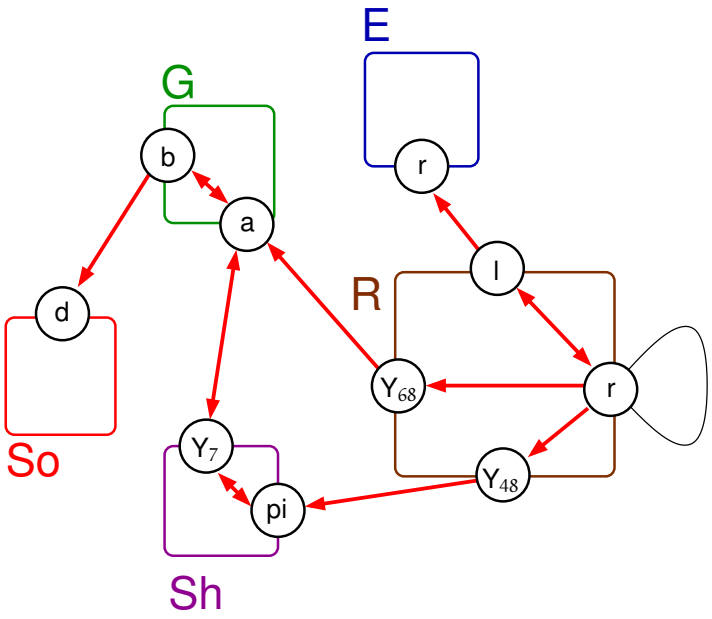


Are they fragments ?

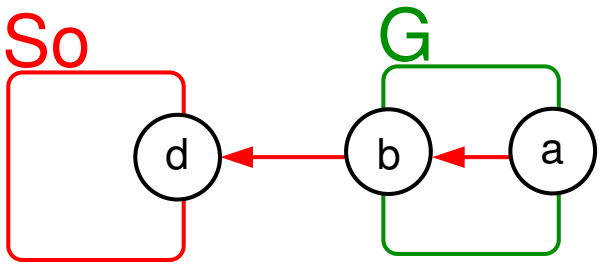


Are they fragments ?

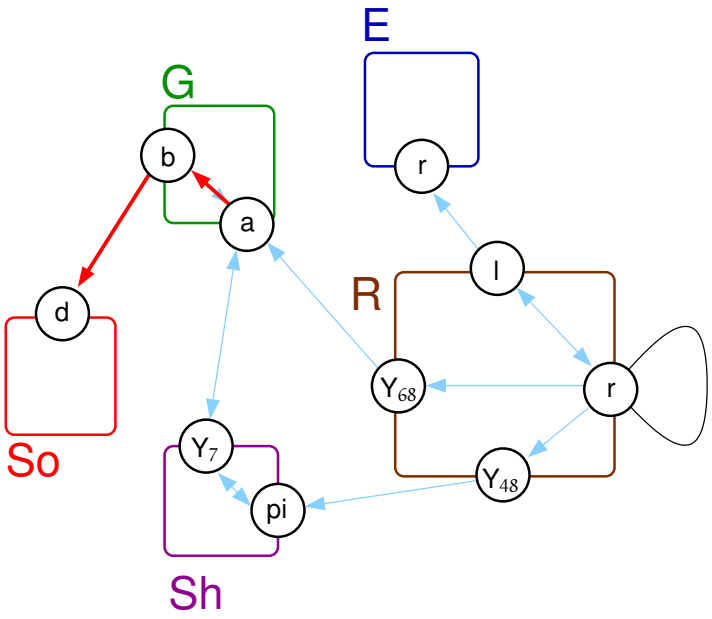




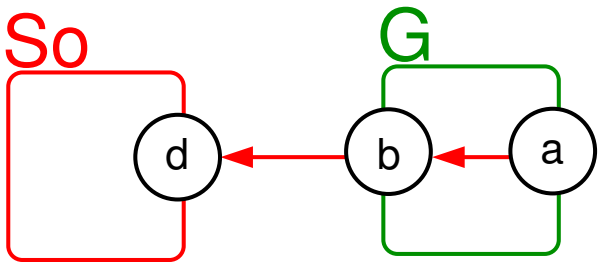
Are they fragments ?



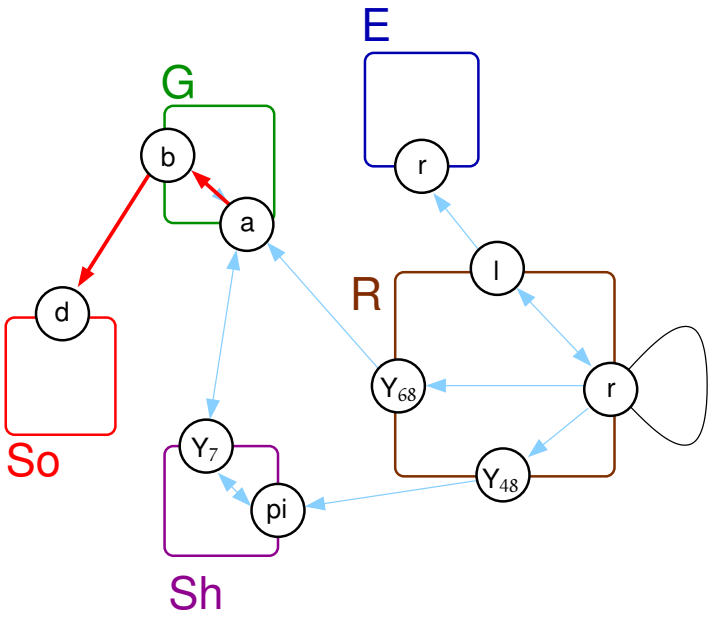
Thus, it is a prefragment.



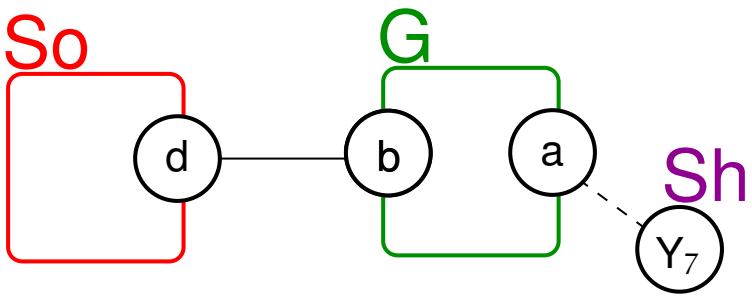
Are they fragments ?

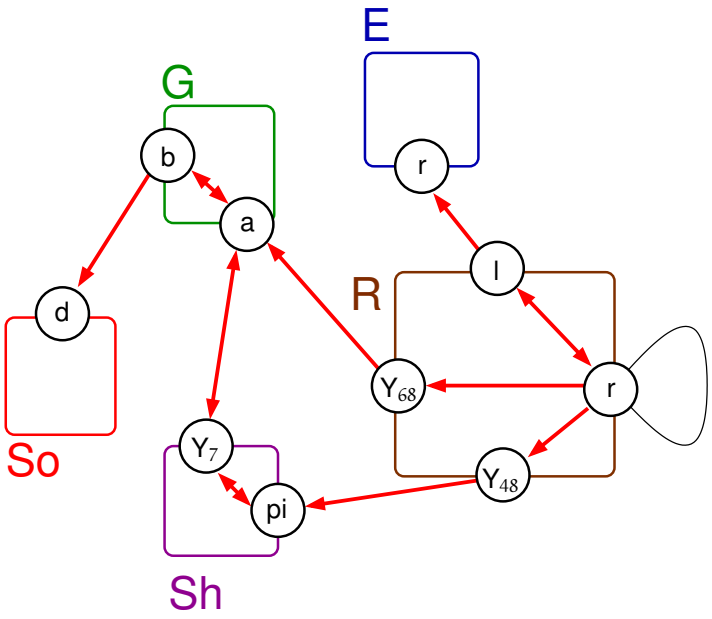


It is maximally specified.
Thus it is a fragment.

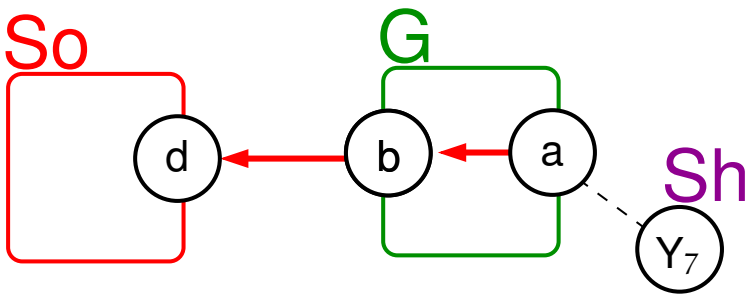


Are they fragments ?

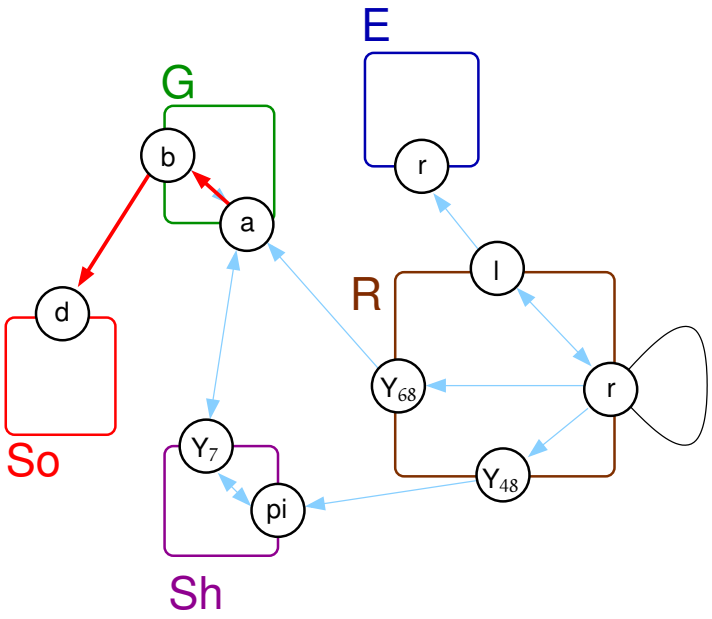




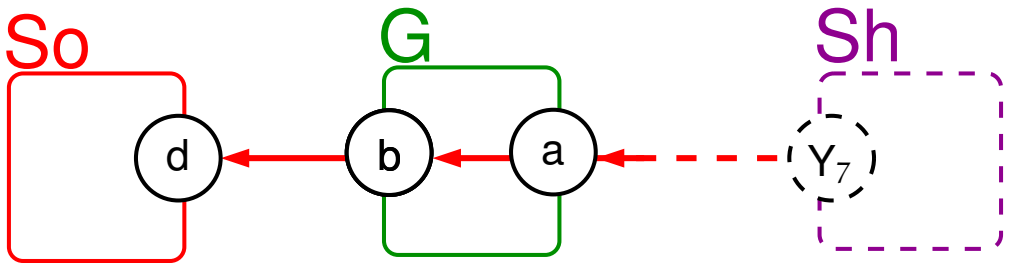
Are they fragments ?



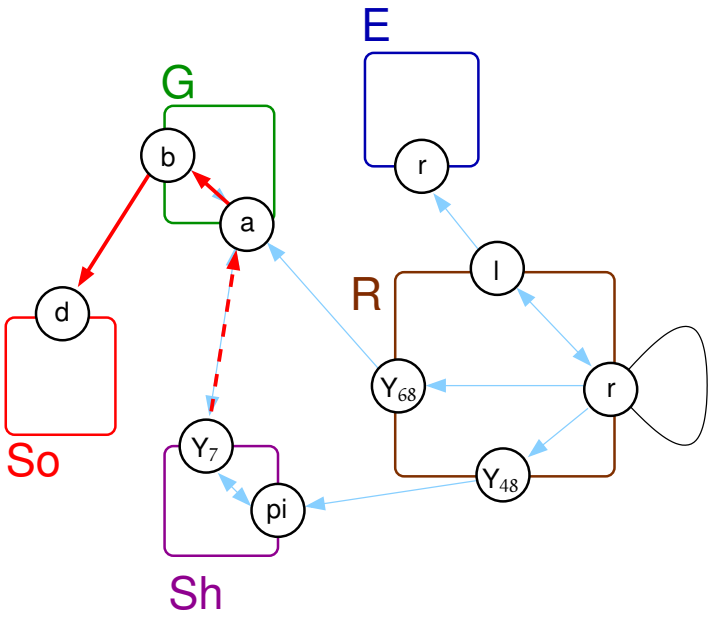
Thus, it is a prefragment.



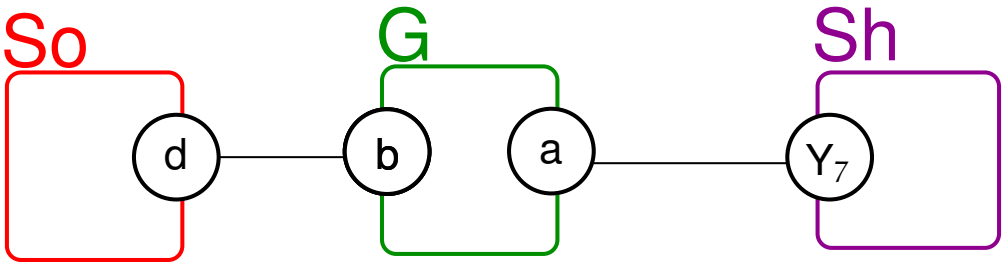
Are they fragments ?

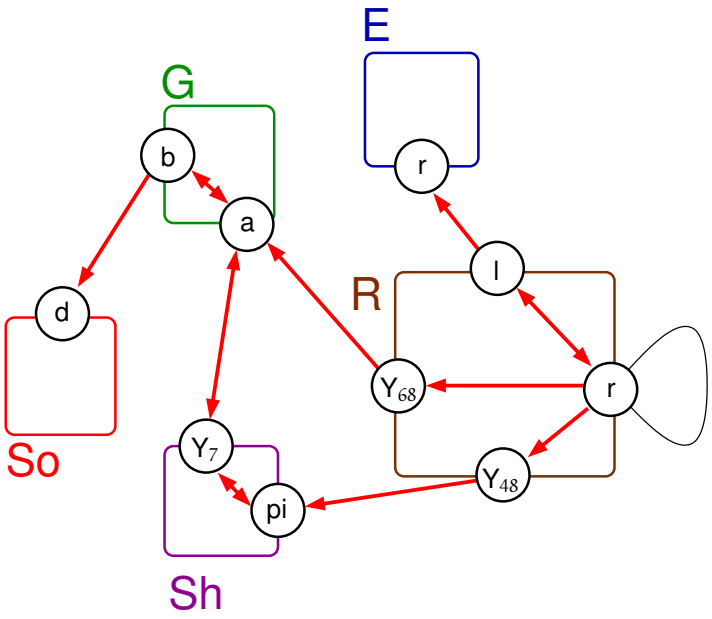


It can be refined into another prefragment.
Thus, it is not a fragment.

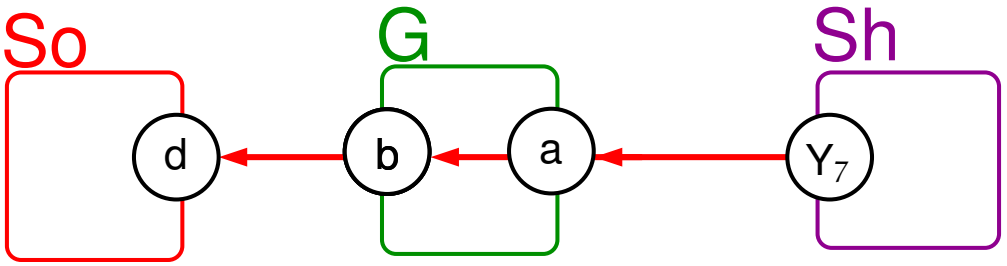


Are they fragments ?

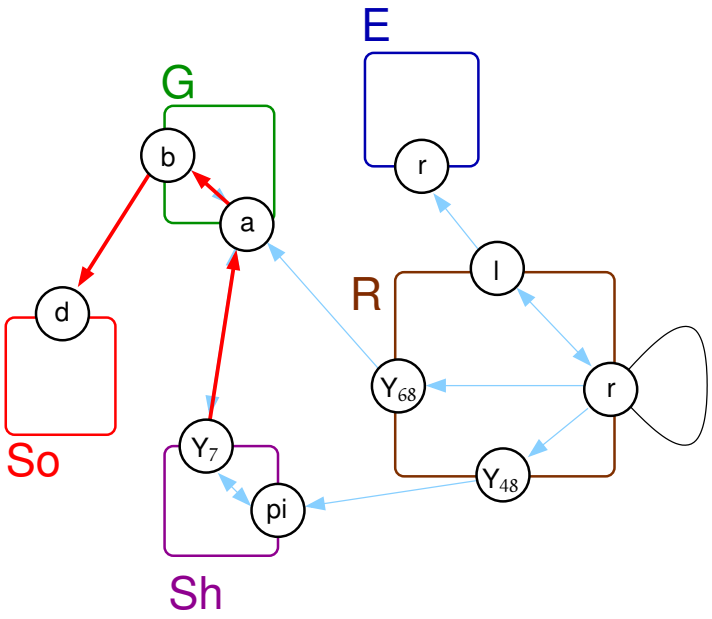




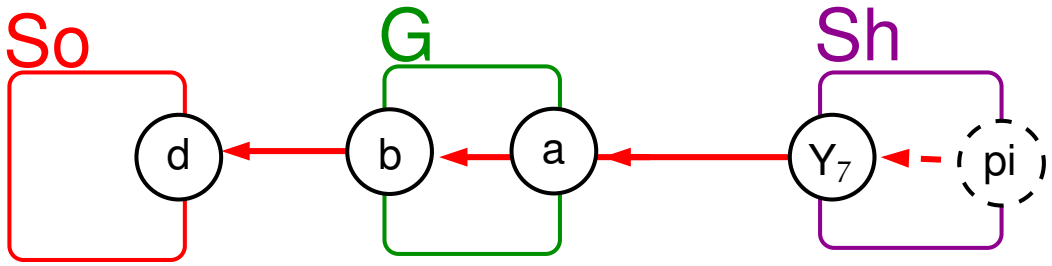
Are they fragments ?



Thus, it is a prefragment.



Are they fragments ?



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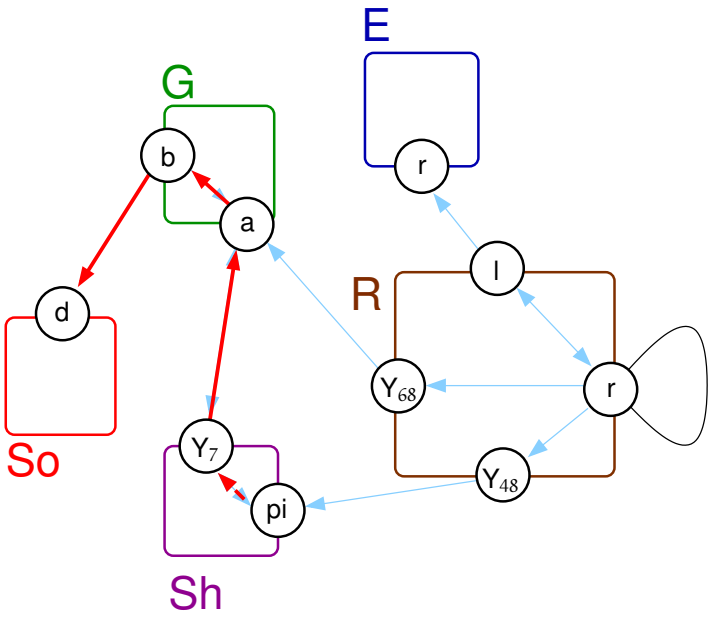
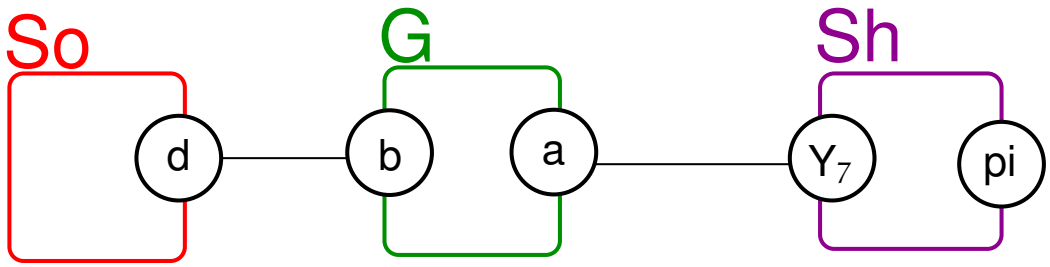
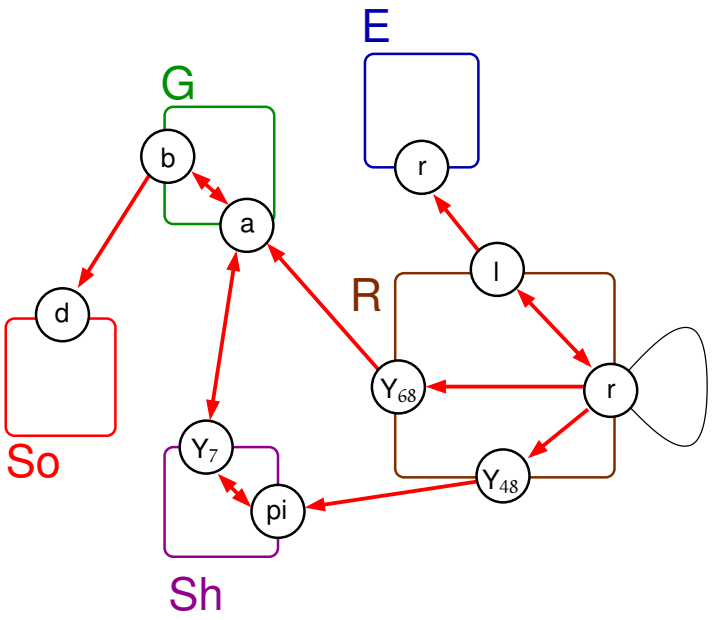
Thus, it is not a fragment.

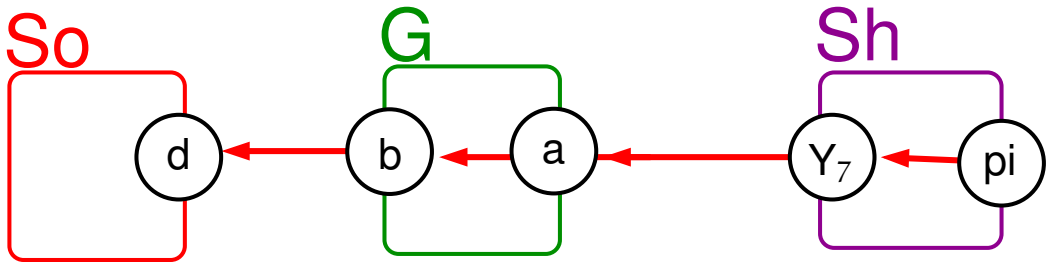


Are they fragments ?

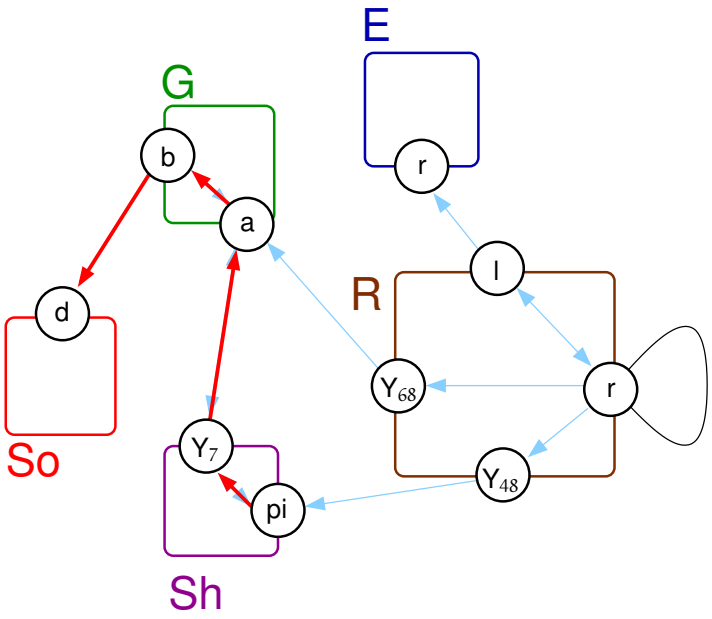




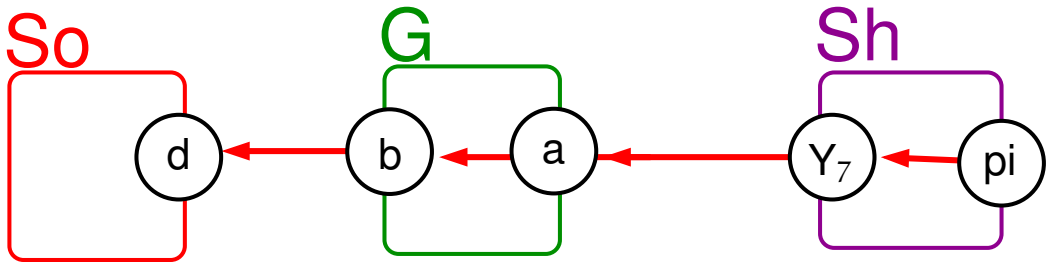
Are they fragments ?



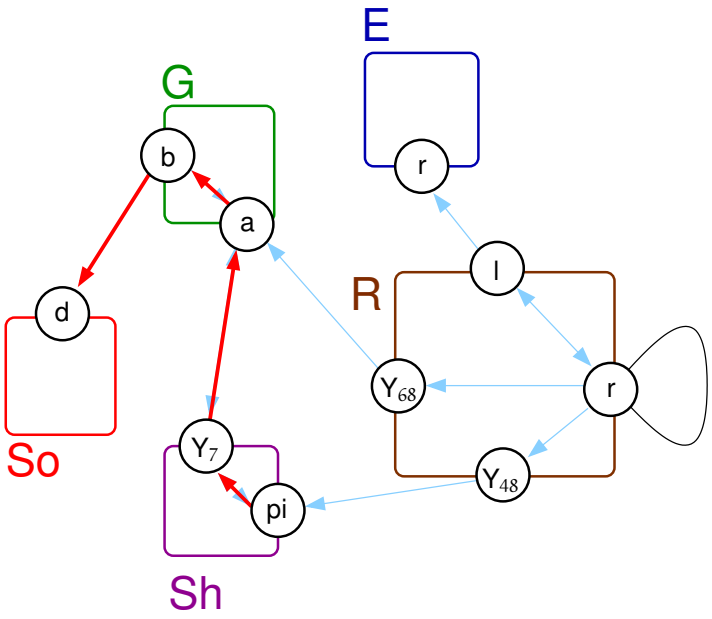
Thus, it is a prefragment.



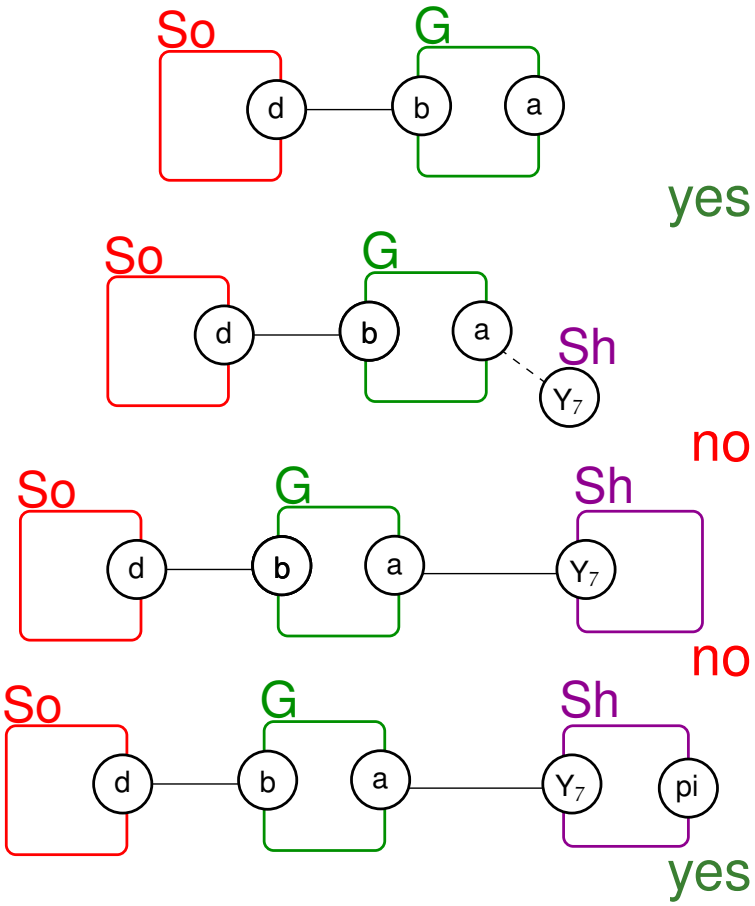
Are they fragments ?

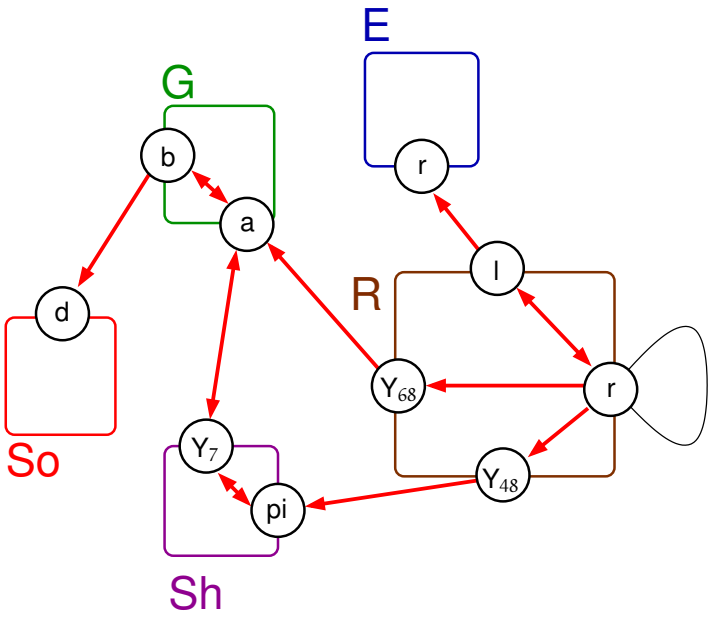


It is maximally specified.
Thus it is a fragment.



Are they fragments ?





Basic properties

1. We call a sub-fragment any partial species which can be embedded into a fragment.

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

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

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

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

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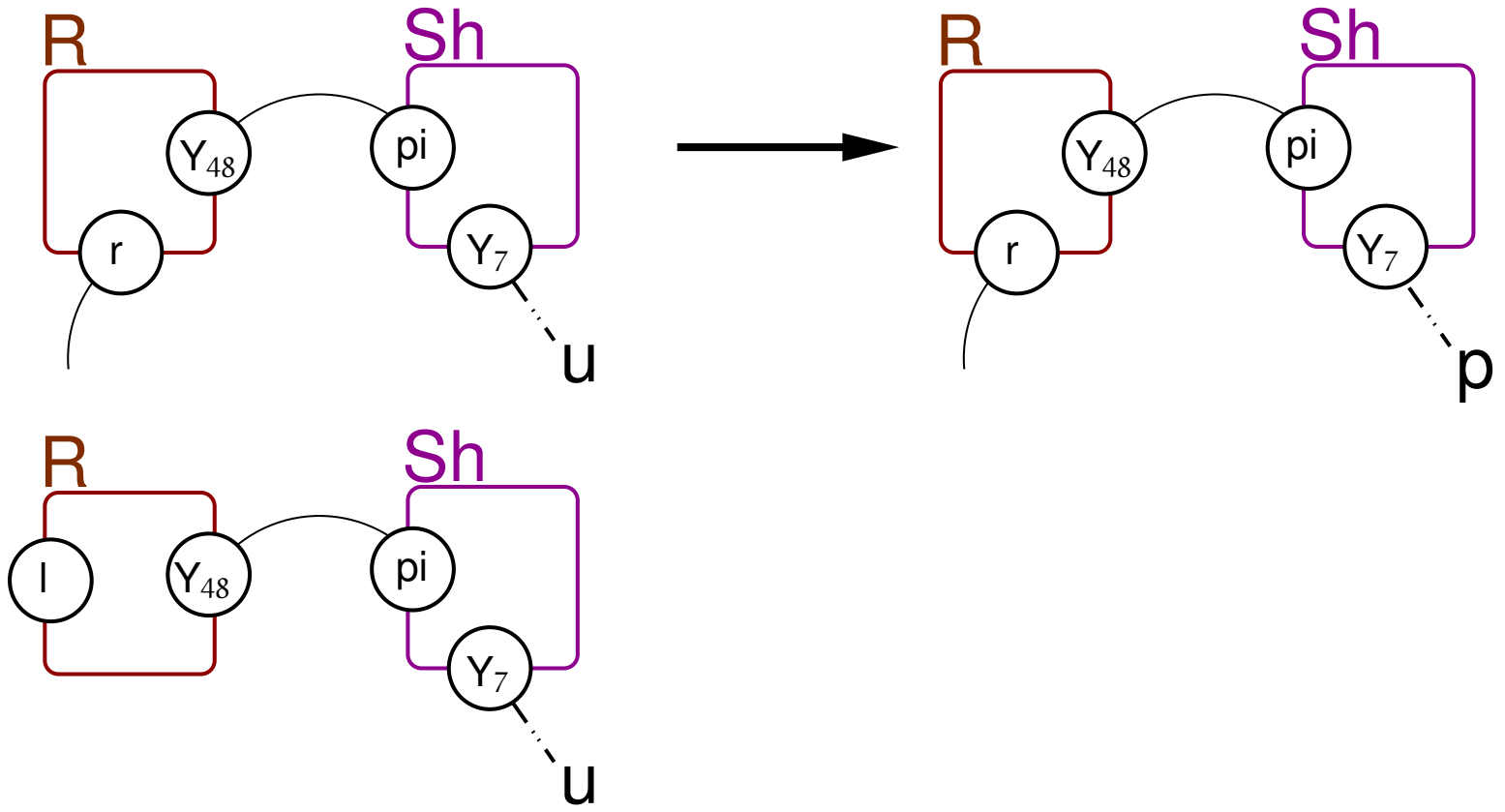
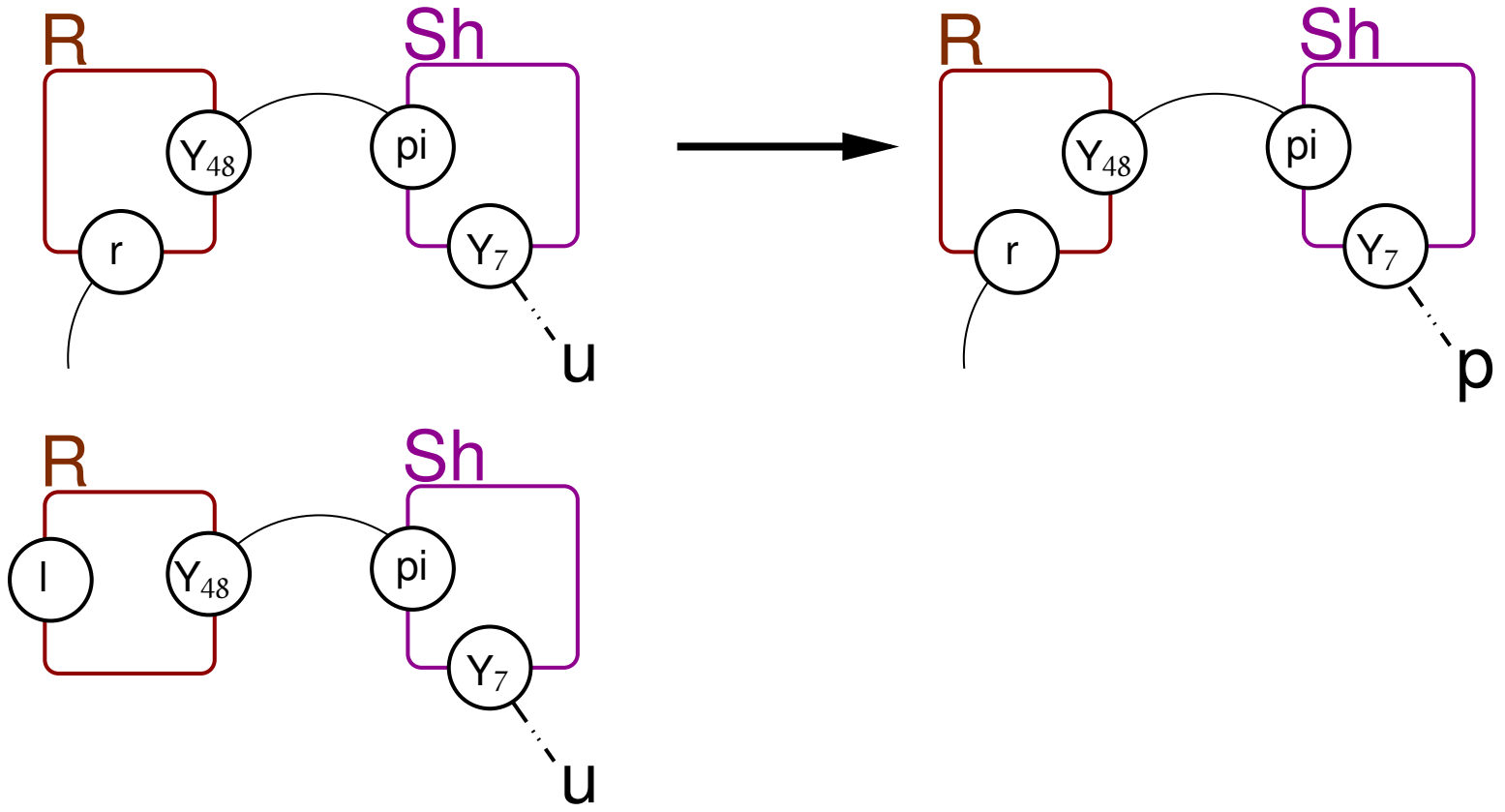
Fragments consumption



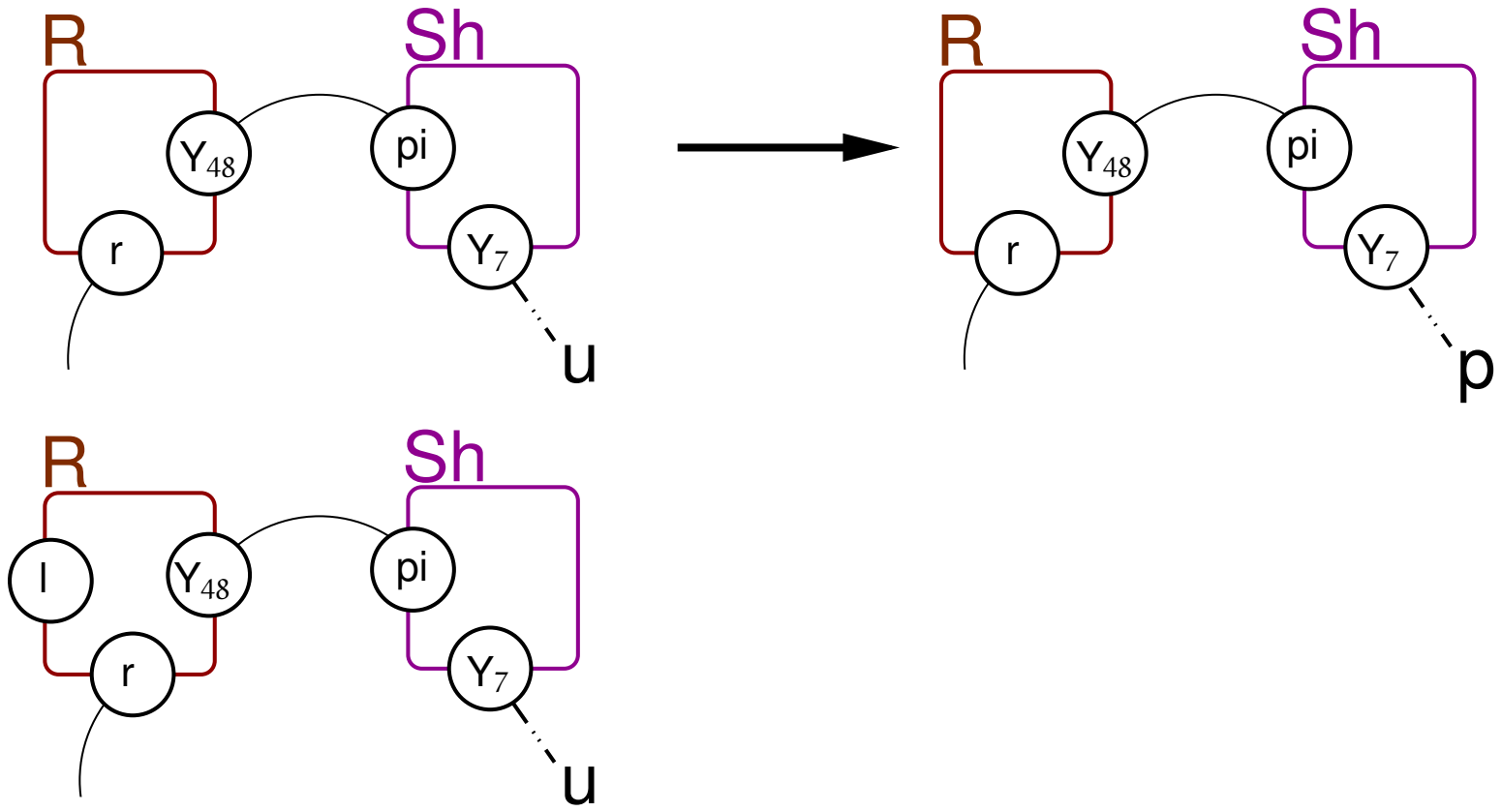
Can we express the amount (per time unit) of this fragment (bellow) concentration that is consumed by this rule (above)?

Fragments consumption



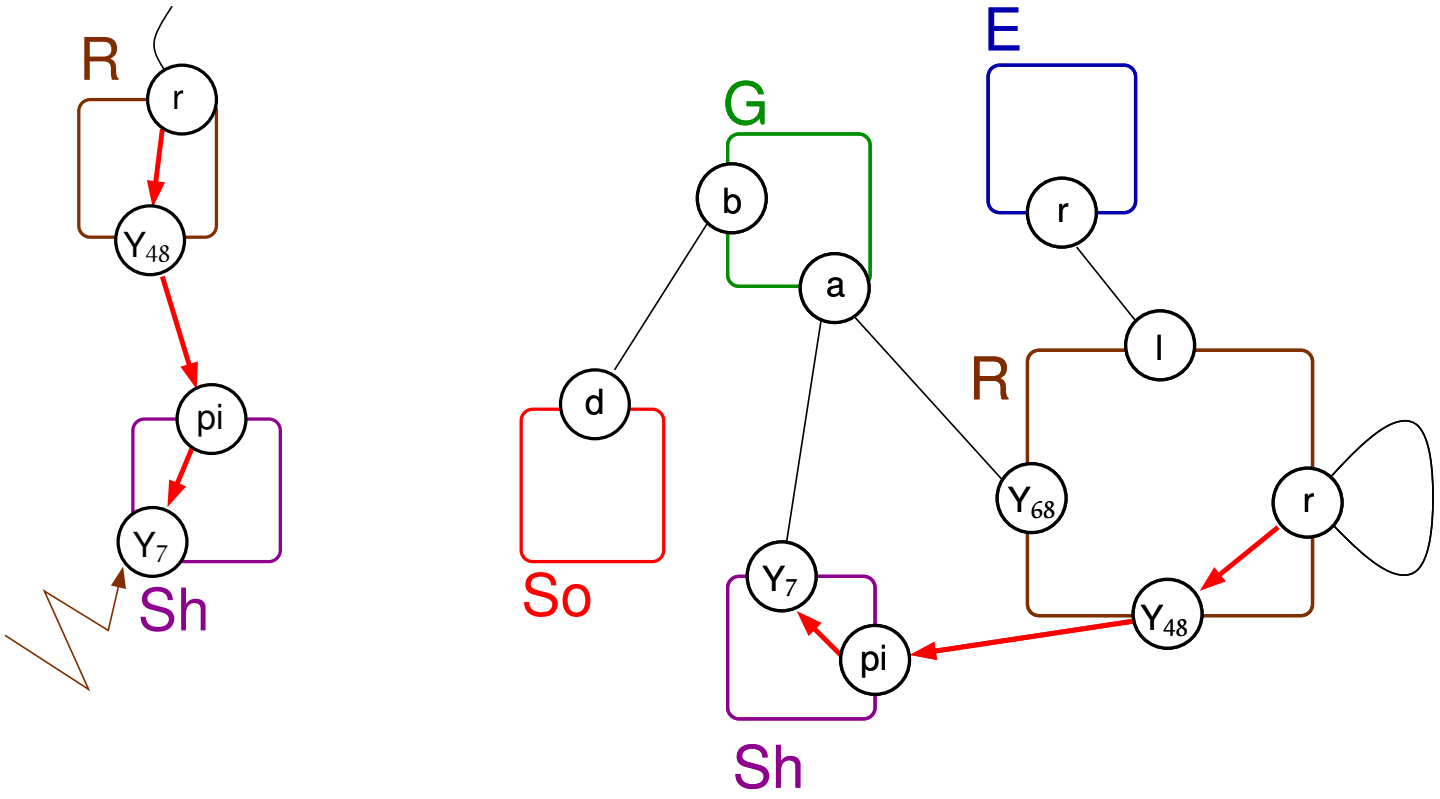
No, because we have abstracted away the correlation between the state of the site `r` and the state of the site `l`.

Fragments consumption
Proper intersection



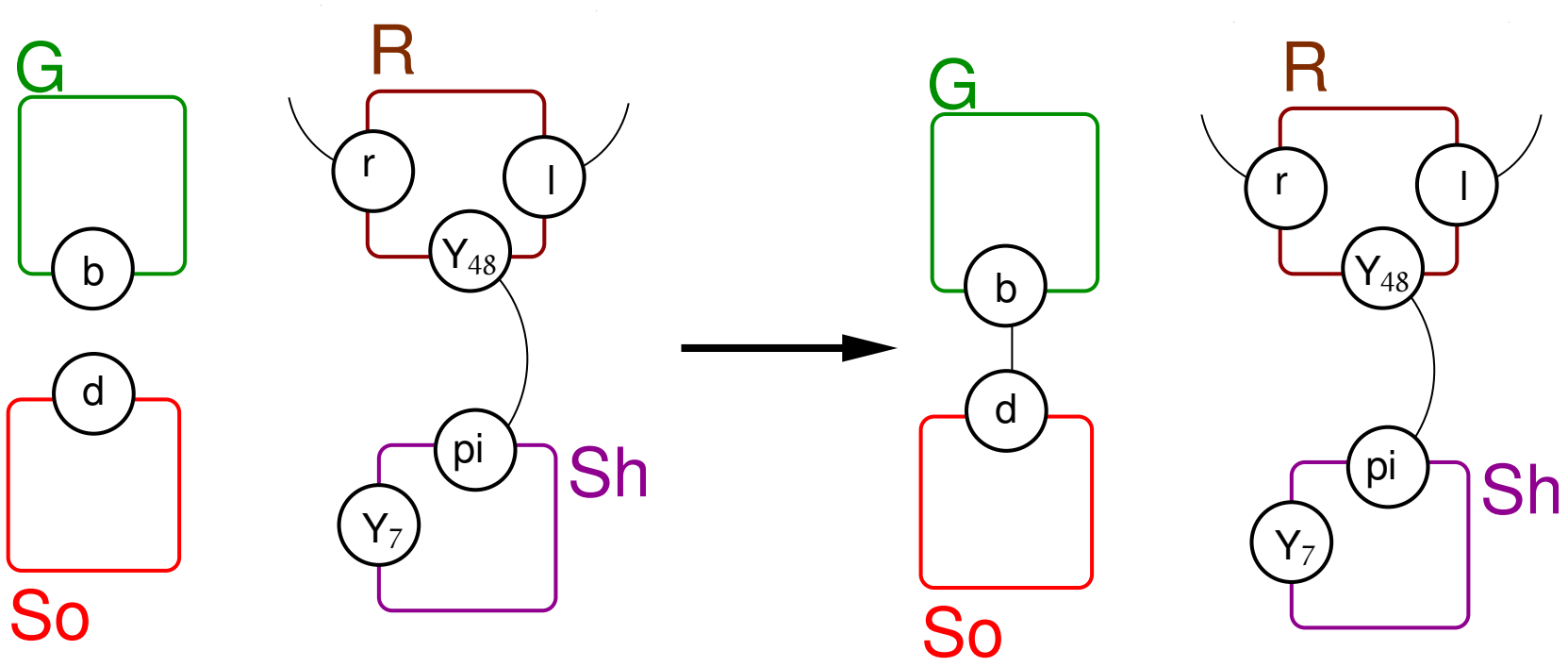
Whenever a fragment intersects a connected component of a lhs on a modified site, then the connected component must be embedded in the fragment!

Fragment consumption
Syntactic criteria



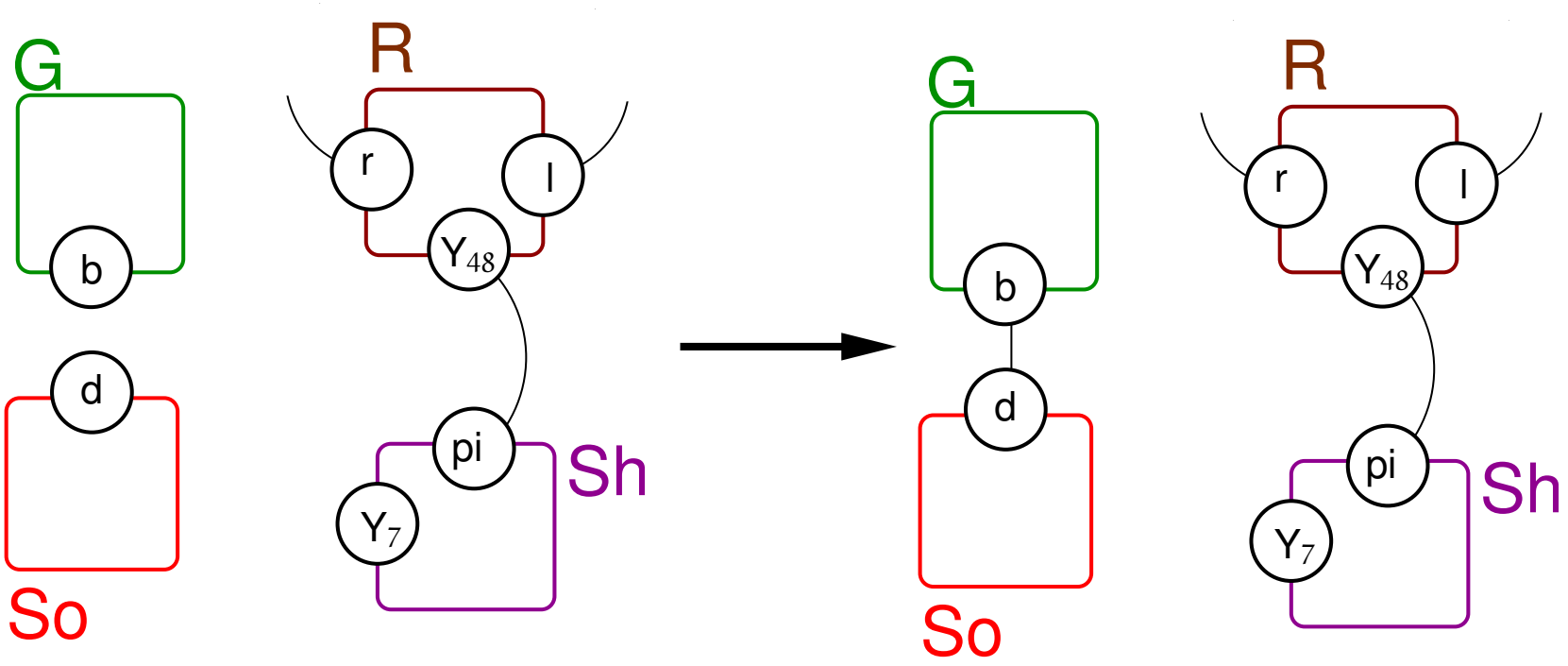
We reflect, in the annotated contact map, each path that stems from a tested site to a modified site (in the lhs of a rule).

Connected components



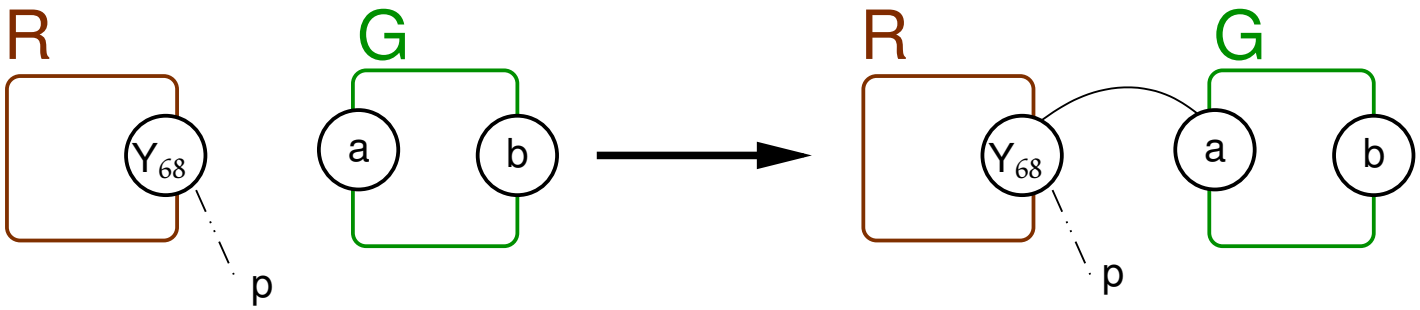
We need to express the “concentration” of any connected component of a lhs with respect to the “concentration” of fragments.

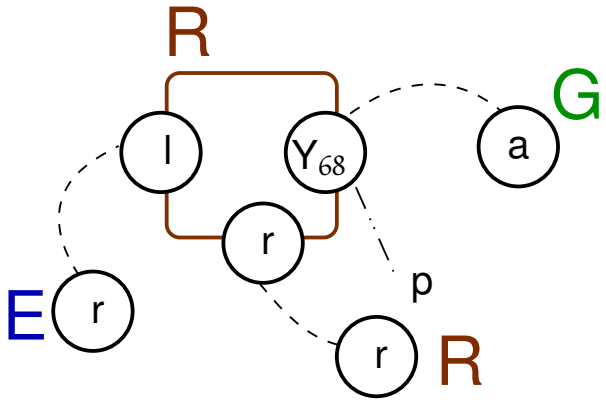
Connected components
Sub-fragment



Each connected component of a lhs must be a sub-fragment.

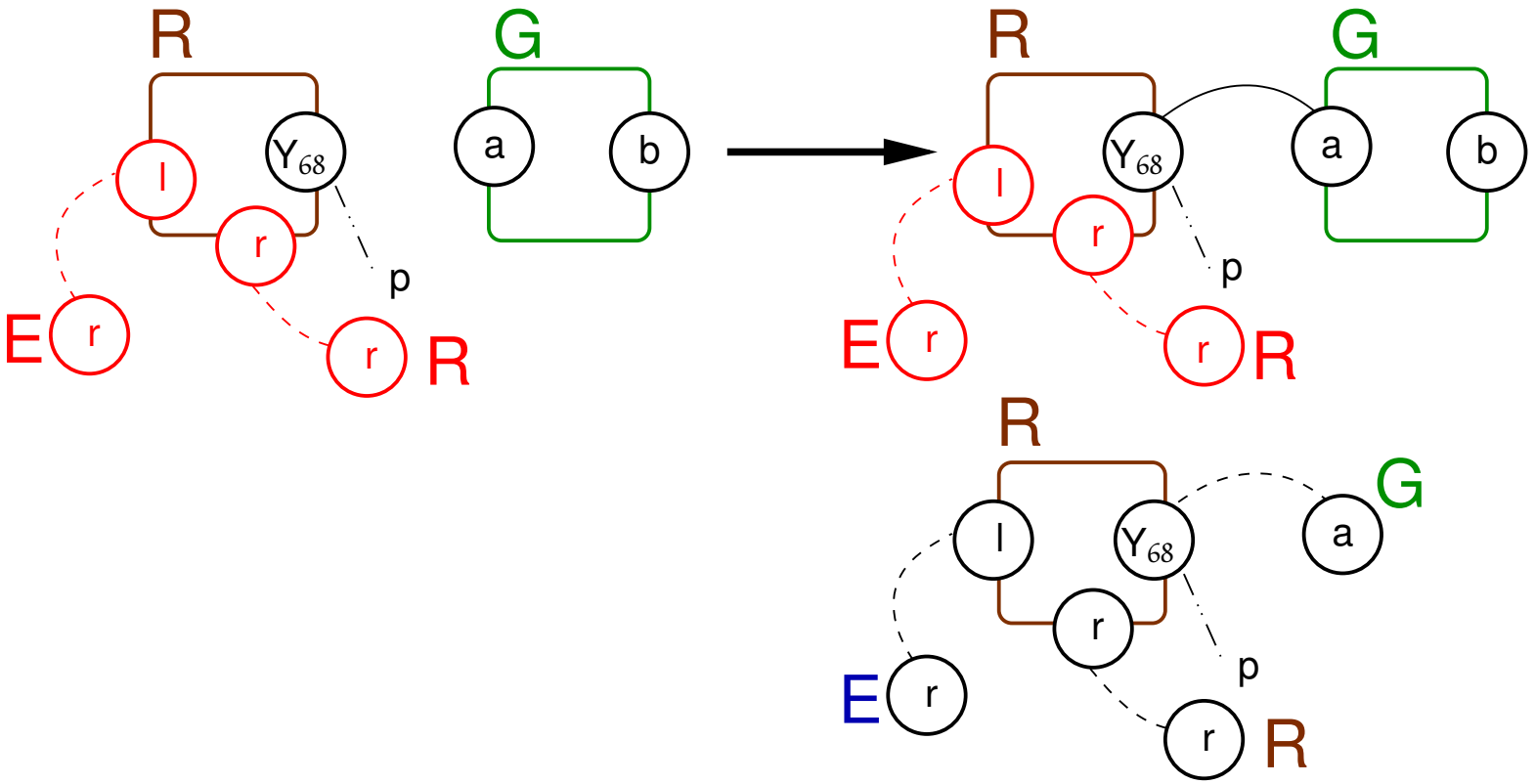
Fragments production





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

Fragments production
Proper intersection (bis)



Yes, if the connected components of the lhs of the refinement are sub-fragments, which is already ensured by previous syntactic criteria.

Fragment properties

If:

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

then:

- we can express the concentration of any connected component occuring in lhss,
- we can express fragment proper consumption,
- we can express fragment proper production (eg. see the LICS'2010 paper),
- WE HAVE A CONSTRUCTIVE DEFINITION FOR $\mathbb{F}^\sharp$.

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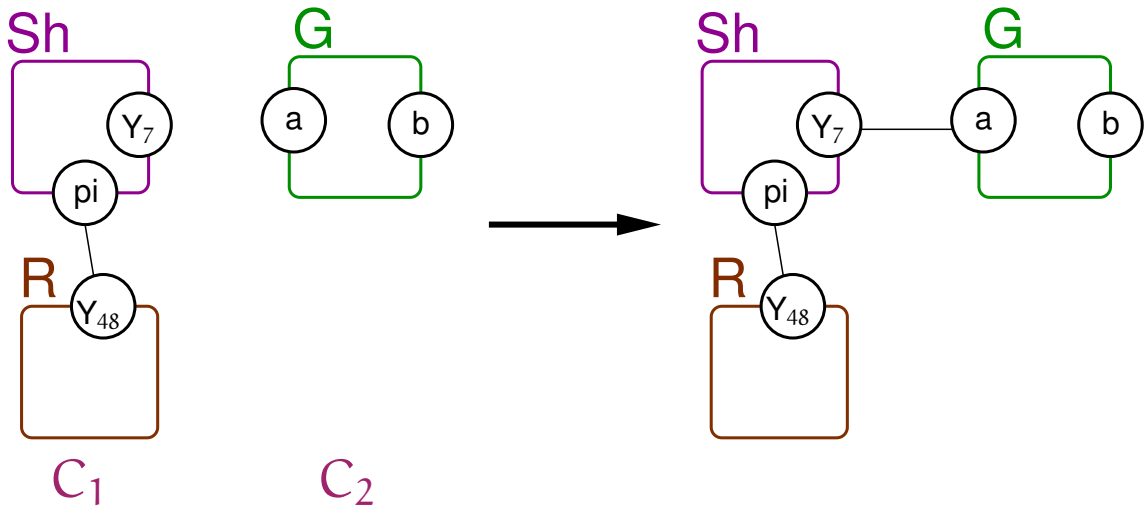
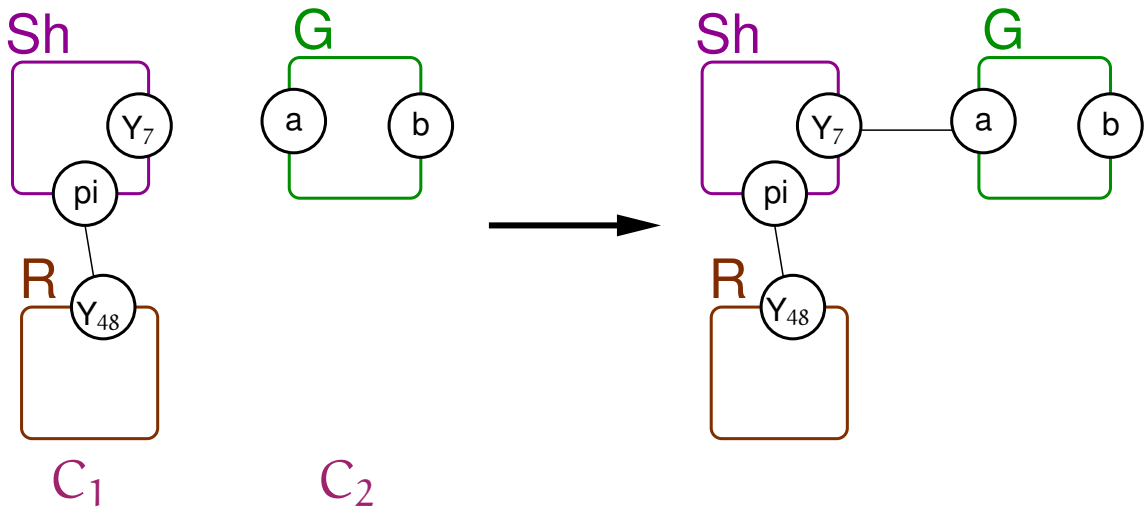
A binding rule

Let us abstract the contribution of a binding rule:



A binding rule: reactants

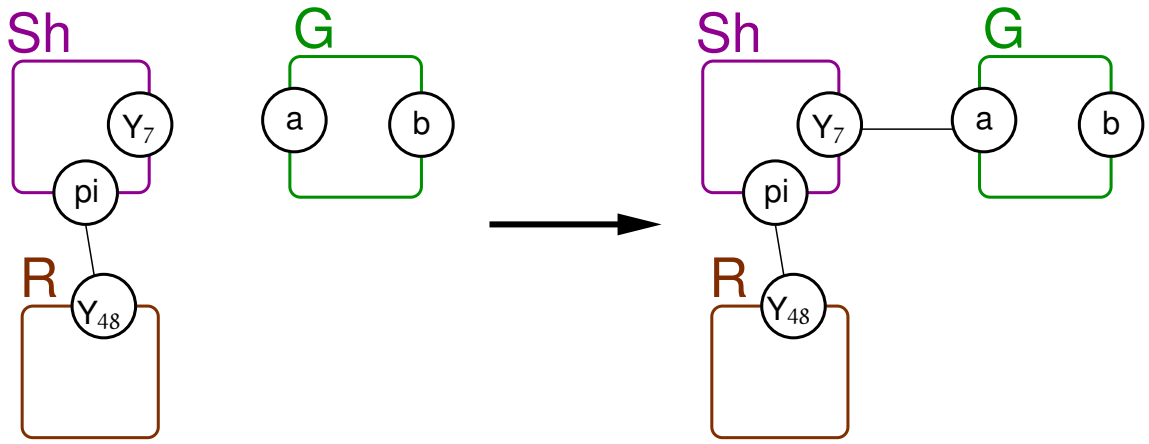


k

For any (F, Φ) such that $C_i \lhd_\Phi F$,

$$\frac{d[F]}{dt} \stackrel{+}{=} -\frac{k \cdot [F] \cdot [C_{3-i}]}{\sharp\{\Phi' \mid C_1, C_2 \lhd_{\Phi'} C_1, C_2\}}.$$

Binding rules: products

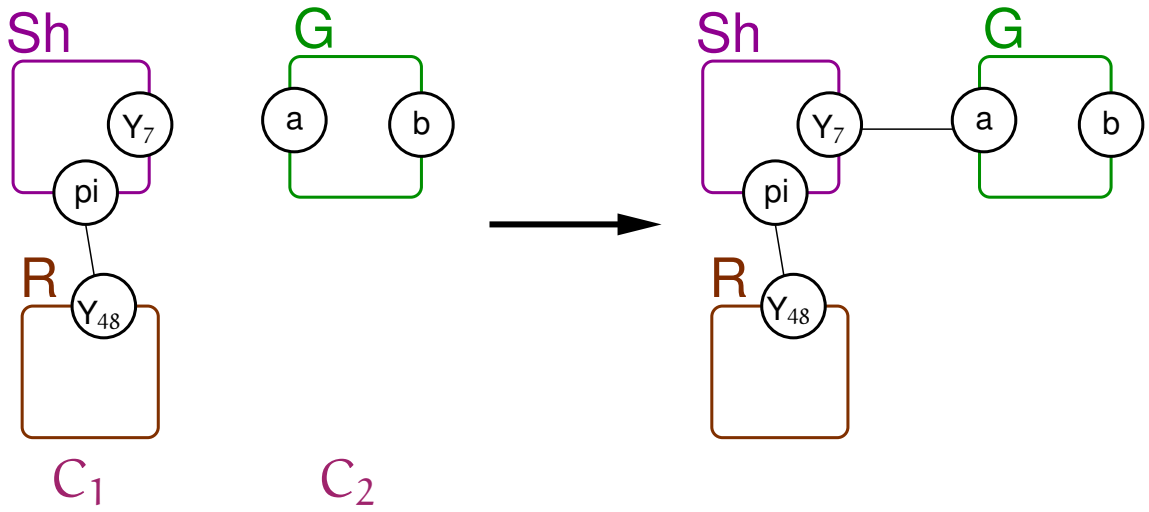


k

If the edge is solid, for any (F_1, Φ_1) and (F_2, Φ_2), such that $C_1 \lhd_{\Phi_1} F_1$ and $C_2 \lhd_{\Phi_2} F_2$,

$$\frac{d[F_1 - F_2]}{dt} = \frac{k \cdot [F_1] \cdot [F_2]}{\sharp\{\Phi' \mid C_1, C_2 \lhd_{\Phi'} C_1, C_2\}}$$

Binding rules: products



k

If the edge is dotted, for any (F, Φ) such that $C_i \lhd_\Phi F$,

$$\frac{d[F\_]}{dt} \stackrel{+}{=} \frac{k \cdot [F] \cdot [C_{3-i}]}{\sharp\{\Phi' \mid C_1, C_2 \lhd_{\Phi'} C_1, C_2\}}.$$

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Curbing the framework

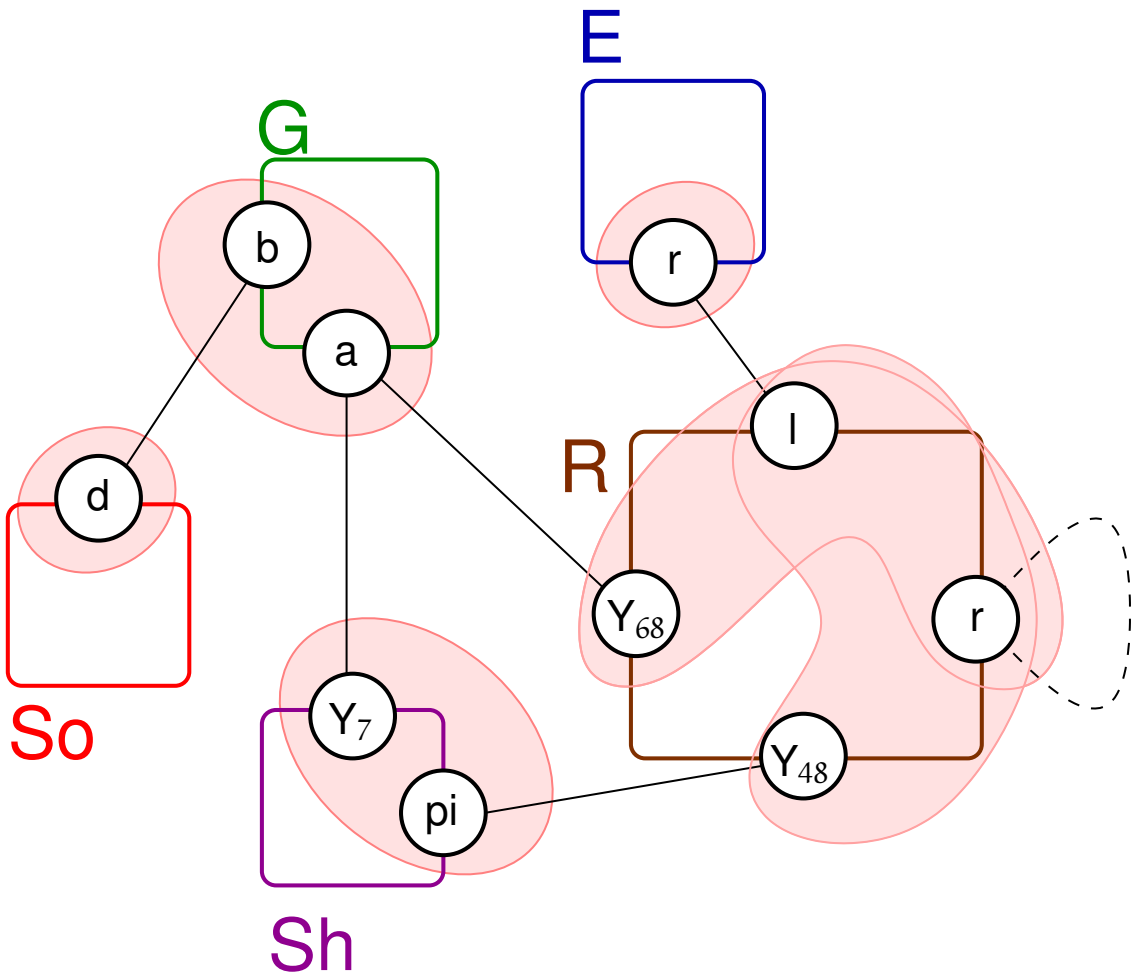
With previous definitions, the differential semantics of a model is reduced into a differential system which might not be the differential semantics of a concrete networks of interactions.

We propose to curb the framework so that the reduced differential semantics matches with the differential semantics of a network of concrete reactions (over fragments).

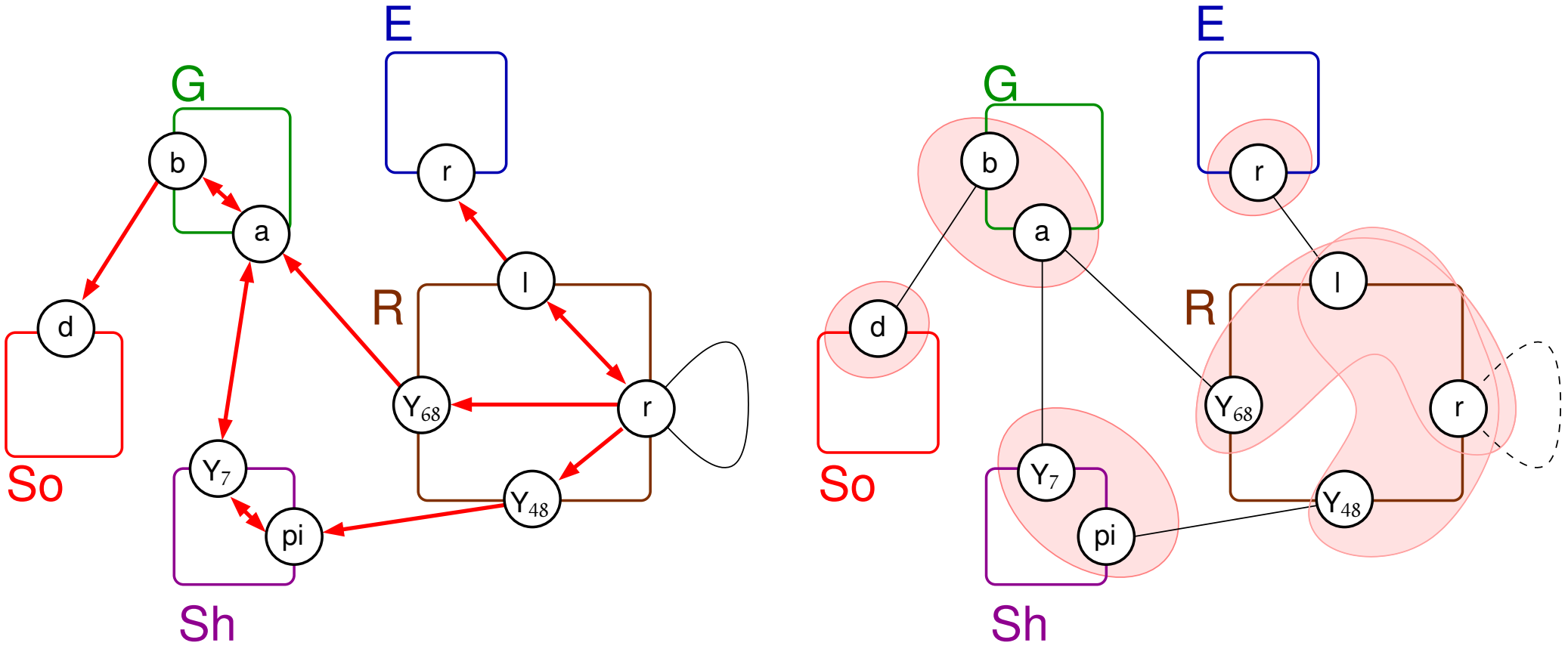
This way, the tools which apply on networks could be applied to the reduced model.

Unoriented annotated contact map

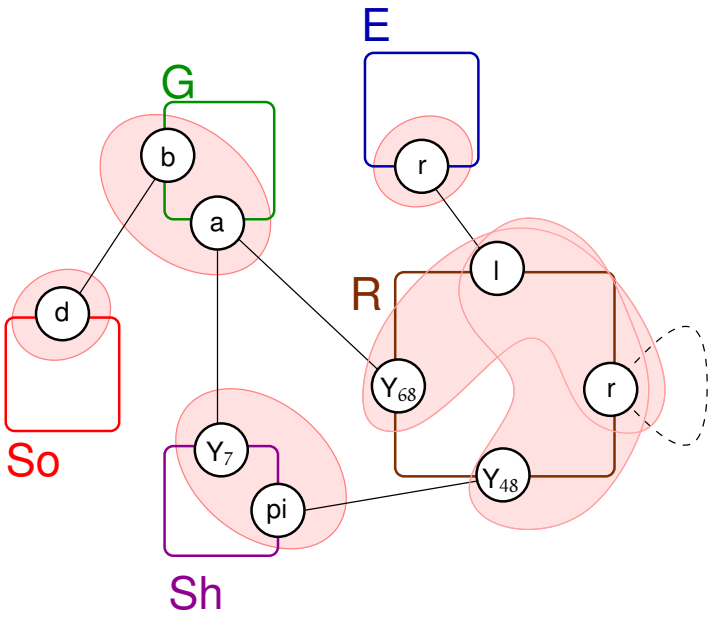
The set of fragments is described by an non oriented annotated contact map.



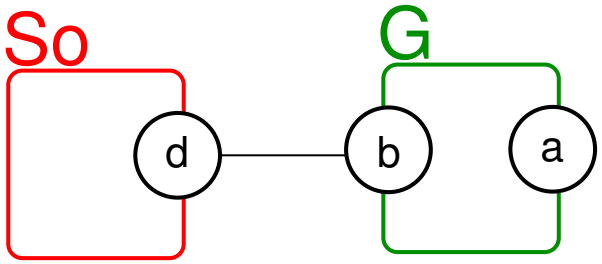
From an oriented contact map to a non oriented contact map

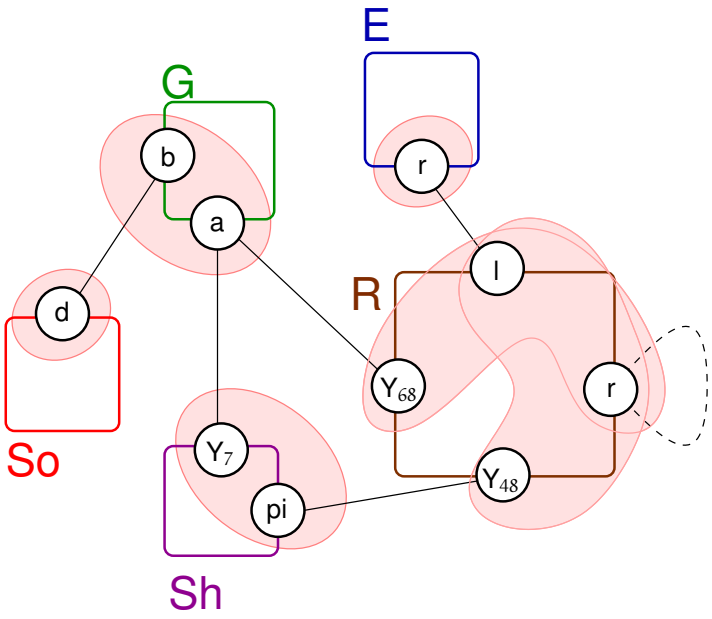


Are they fragments ?

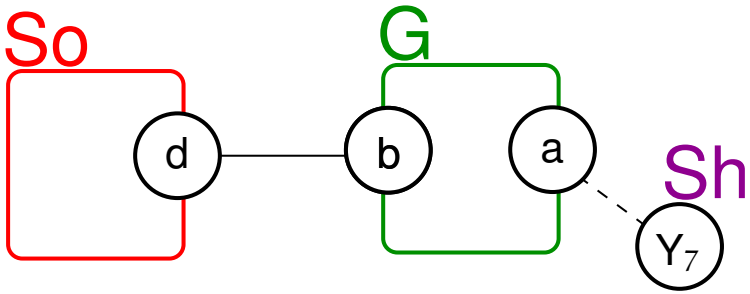


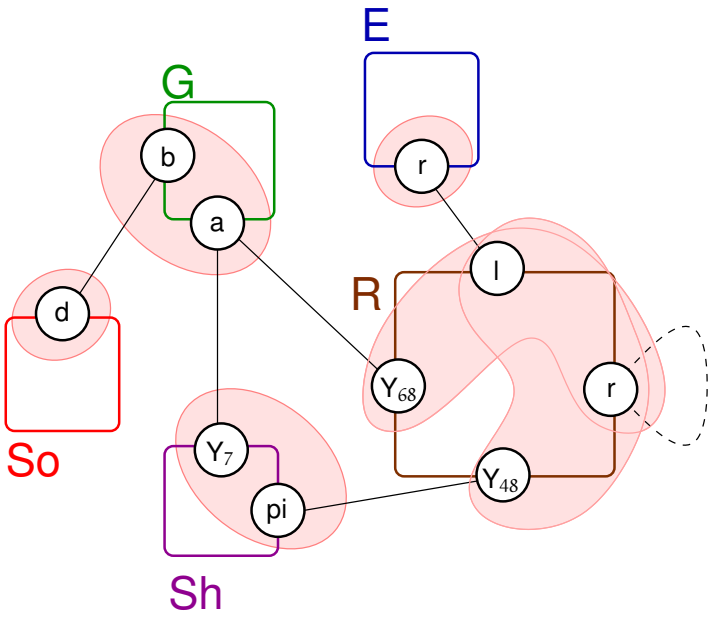
Are they fragments ?



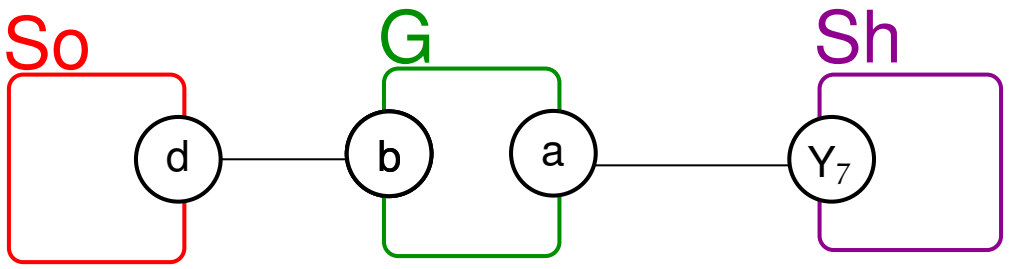


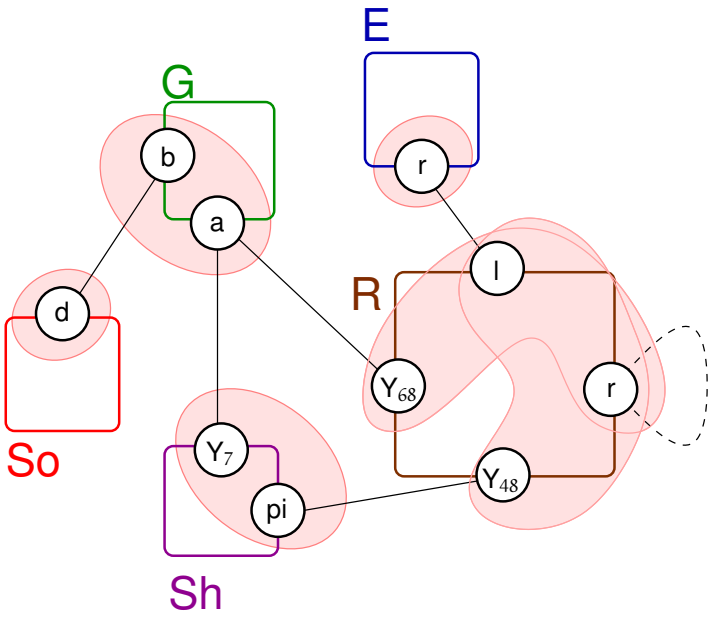
Are they fragments ?



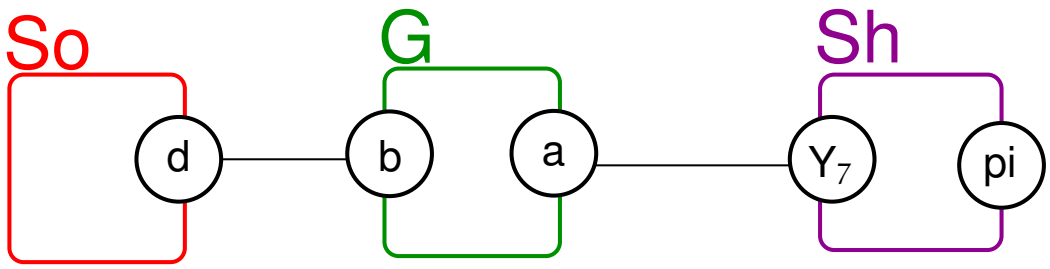


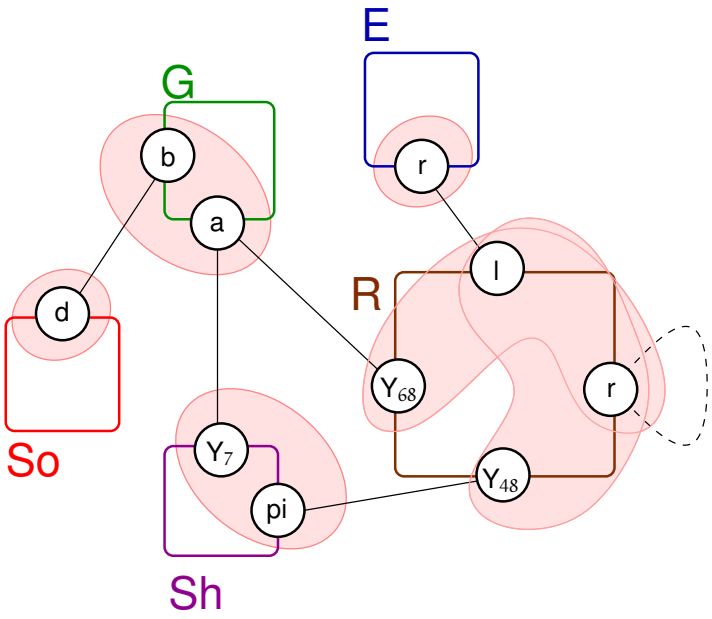
Are they fragments ?



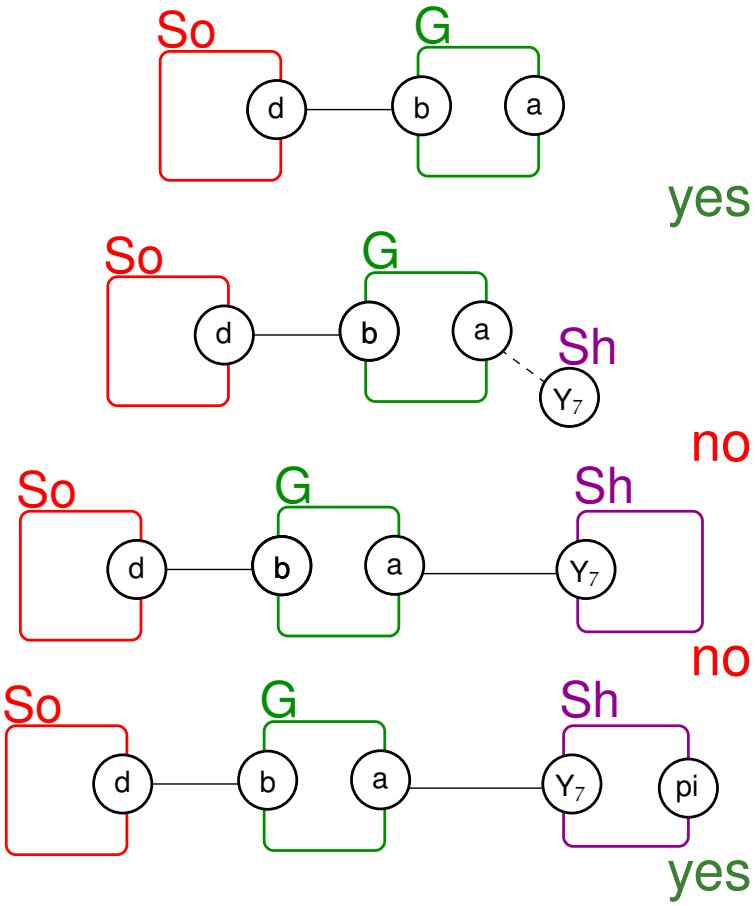


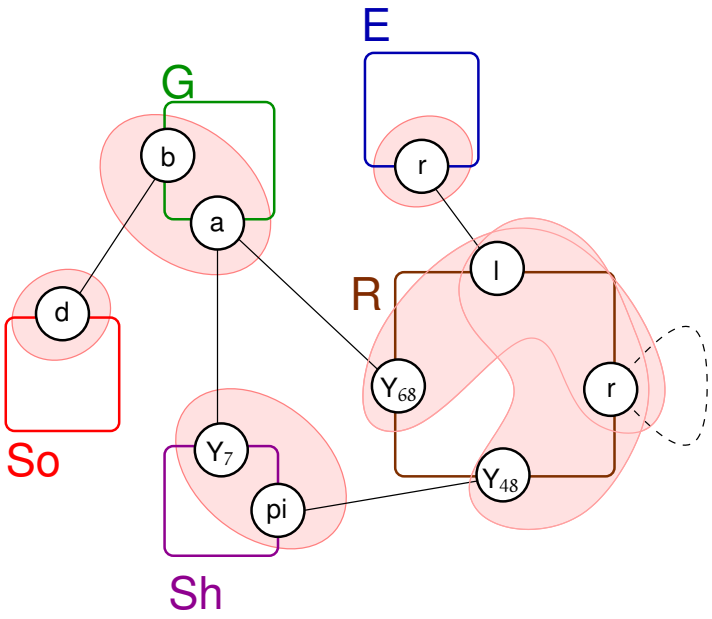
Are they fragments ?





Are they fragments ?





Basic properties

Homogeneous fragments enjoy the sub-fragment and non-degenerescence property.

Additionally:

Property 3 (Closure with respect to the operational semantics)
When we apply a rule with a tuple of fragments, we get a tuple of fragments.

Fragment properties

If:

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

then:

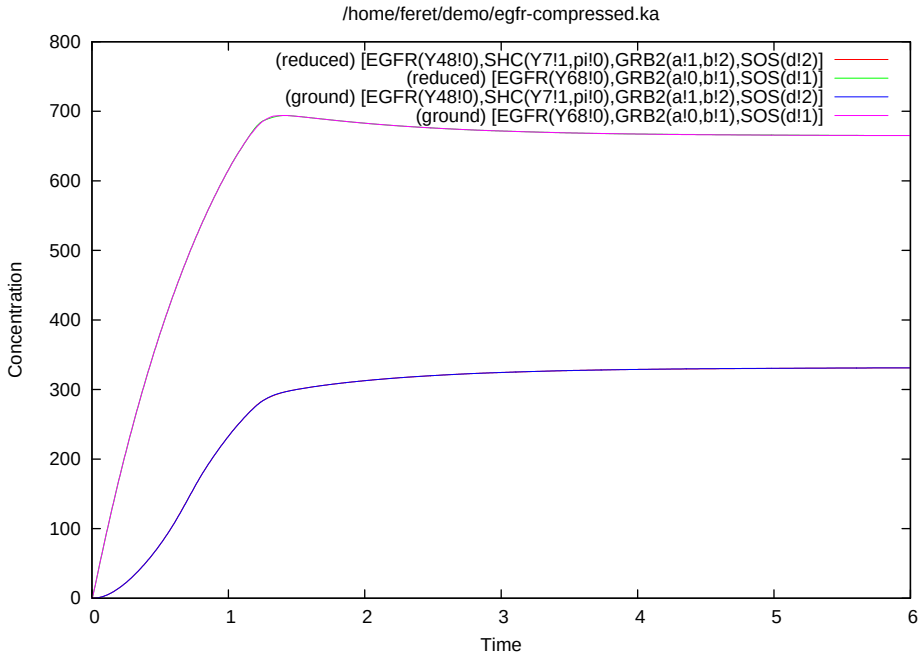
- we can express the concentration of any connected component occurring in lhss,
- we can express fragment proper consumption,
- we can express fragment proper production (eg. see the LICS'2010 paper),
- WE HAVE A CONSTRUCTIVE DEFINITION FOR $\mathbb{F}^\sharp$.

Overview

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

Experimental results

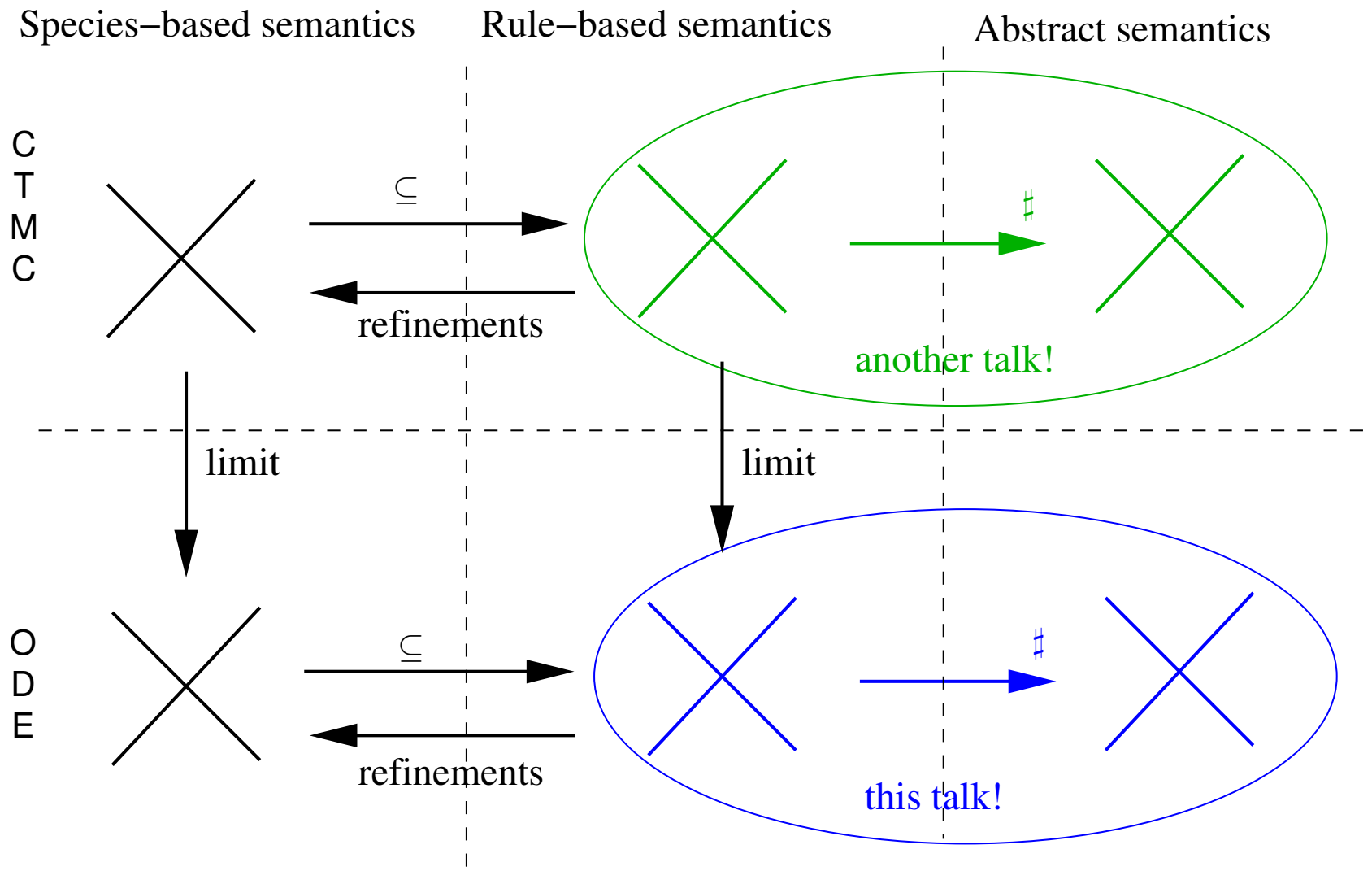
On early egfr, 356 species are simplified into 38 fragments:



Superposition of the ground and the abstract differential semantics.

On a bigger example, $\approx 2 \cdot 10^{19}$ species are simplified into $\approx 2 \cdot 10^{5}$ fragments.

Related issues I: Semantics comparisons



Related issues II:
Semantics approximations

1. ODE approximations:
   - Concrete definition of the control flow and hierarchy of abstractions.

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

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

Master AIV

Model reduction of stochastic rules-based models
Some case studies

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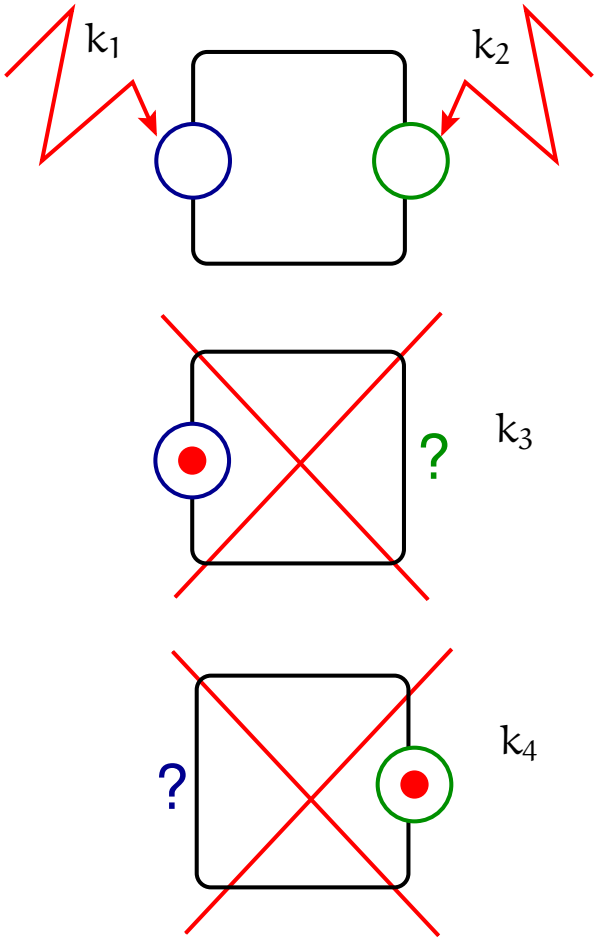
INRIA, ÉNS, CNRS

March 2012

Overview

1. Examples of information flow
2. Symmetric sites
3. Conclusion

A model with ubiquitination



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

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

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

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

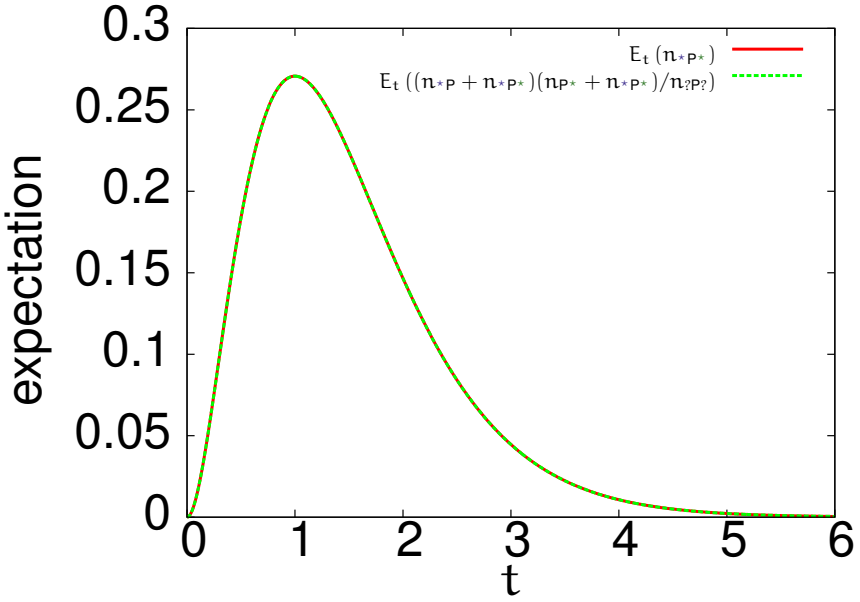
$$P^{\star} \xrightarrow{k_4} \emptyset$$

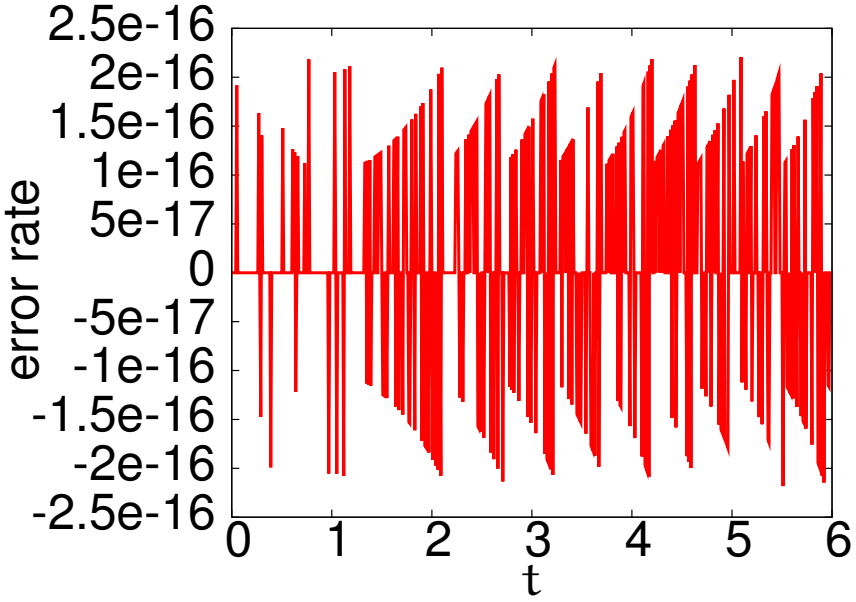
$${}^{\star}P^{\star} \xrightarrow{k_4} \emptyset$$

Statistical independence

We check numerically that:

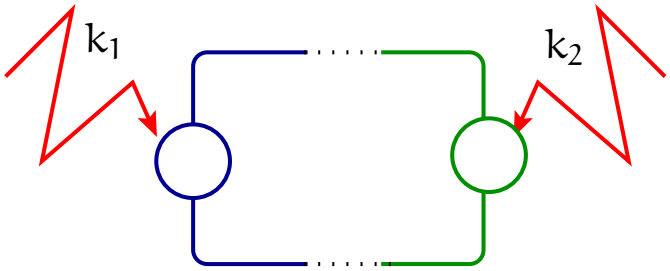
$$E_t\left(n_{\star P^\star}\right) = E_t\left(\frac{(n_{\star P} + n_{\star P^\star})(n_{P^\star} + n_{\star P^\star})}{n_P + n_{P^\star} + n_{\star P} + n_{\star P^\star}}\right).$$





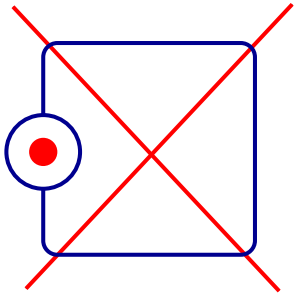
with $k_1 = k_2 = k_3 = k_4 = 1$
and two instances of P at time $t = 0$.

Reduced model



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

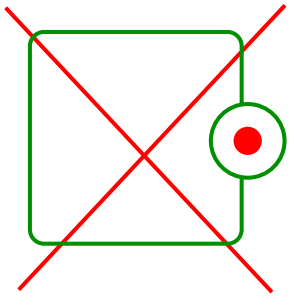
$$P \xrightarrow{k_2} P^{\star}$$



k_3

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

+ side effect: remove one P

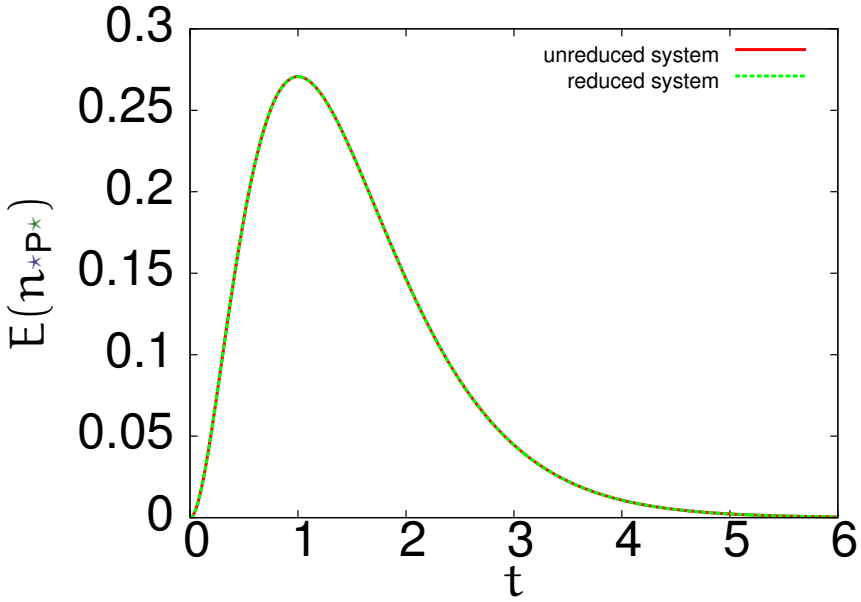


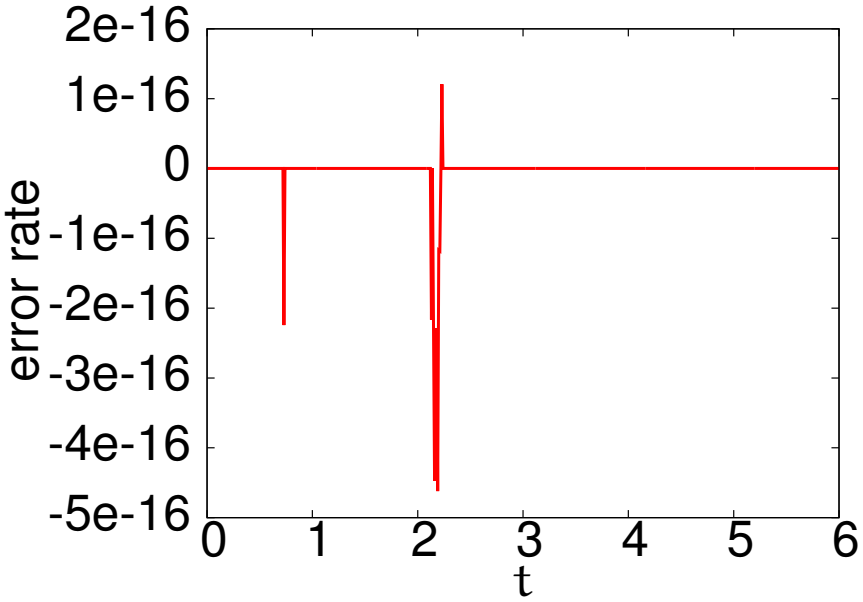
k_4

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

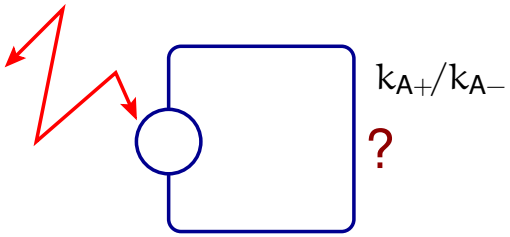
+ side effect: remove one P

Comparison between the two models

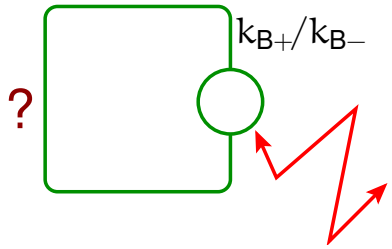




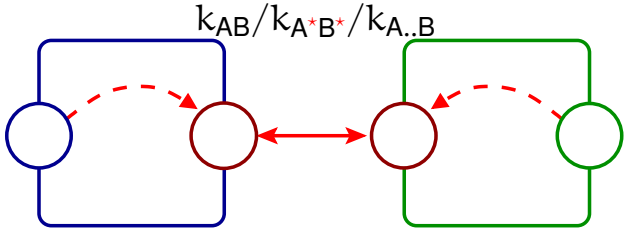
Coupled semi-reactions



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



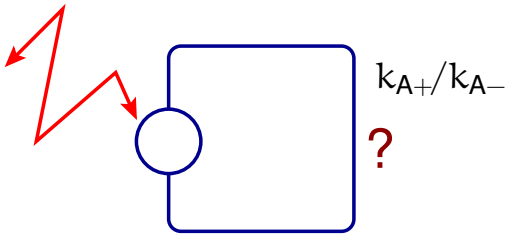
$$B \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} B^\star, \quad AB \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} AB^\star, \quad A^\star B \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} A^\star B^\star$$

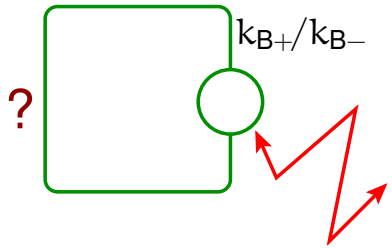


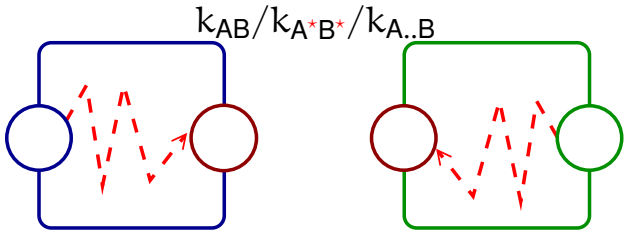
$$A + B \underset{k_{A..B}}{\overset{k_{AB}}{\rightleftharpoons}} AB, \quad A^\star + B \underset{k_{A..B}}{\overset{k_{AB}}{\rightleftharpoons}} A^\star B,$$

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

Reduced model







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

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

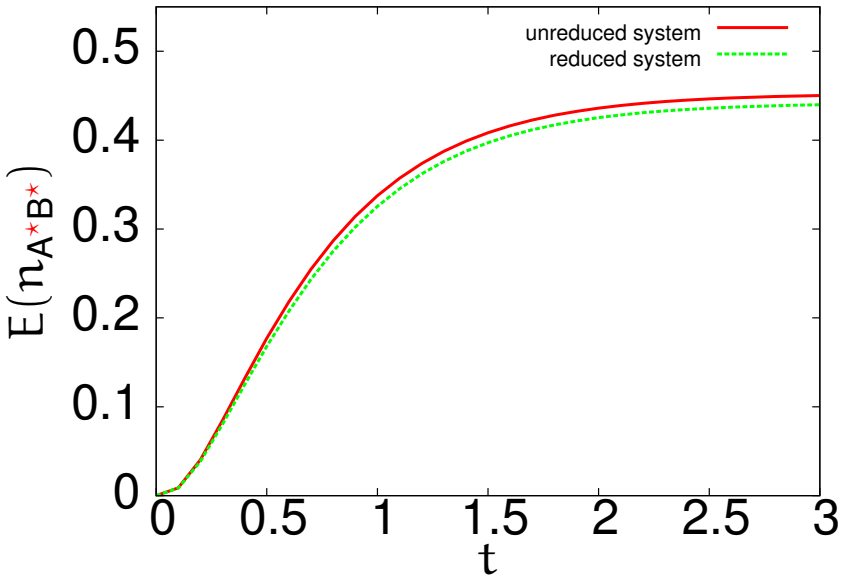
$$A + B \underset{k_{A..B}/(n_{A^\diamond B}+n_{A^\diamond B^\star})}{\overset{k_{AB}}{\rightleftharpoons}} AB^\diamond + A^\diamond B,$$

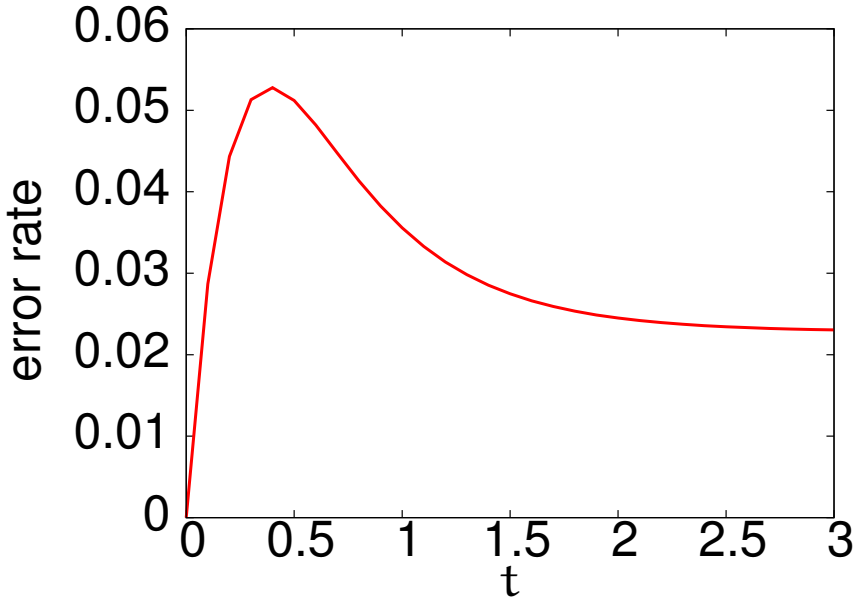
$$A^\star + B \underset{k_{A..B}/(n_{A^\diamond B}+n_{A^\diamond B^\star})}{\overset{k_{AB}}{\rightleftharpoons}} A^\star B^\diamond + A^\diamond B,$$

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

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

Comparison between the two models

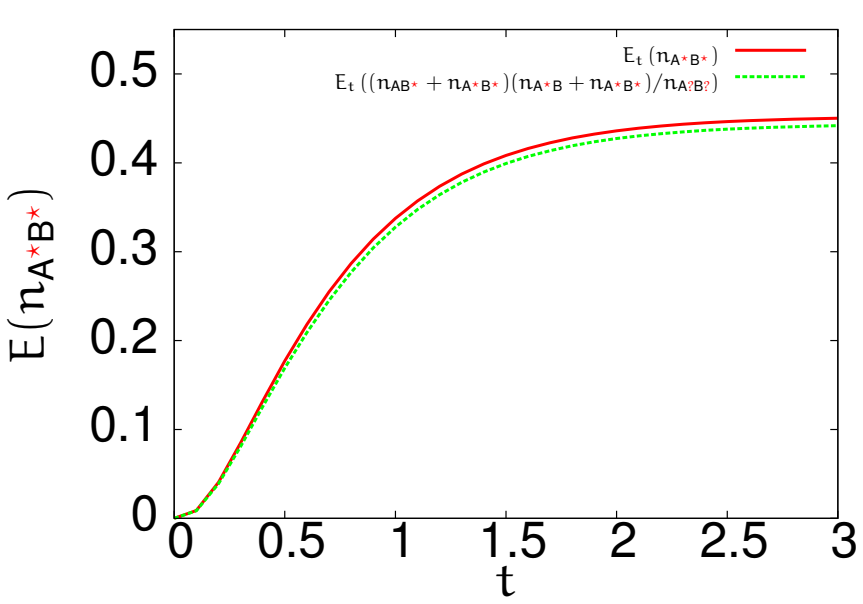


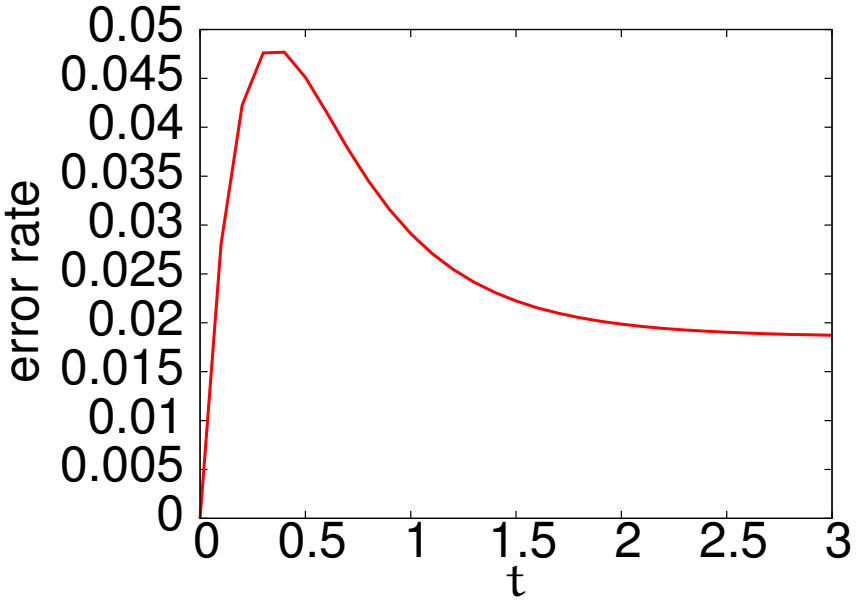


with $k_{A+} = k_{A-} = k_{B+} = k_{B-} = k_{AB} = k_{A..B} = 1$, $k_{A^\star B^\star} = 10$,
and two instances of A and B at time $t = 0$.

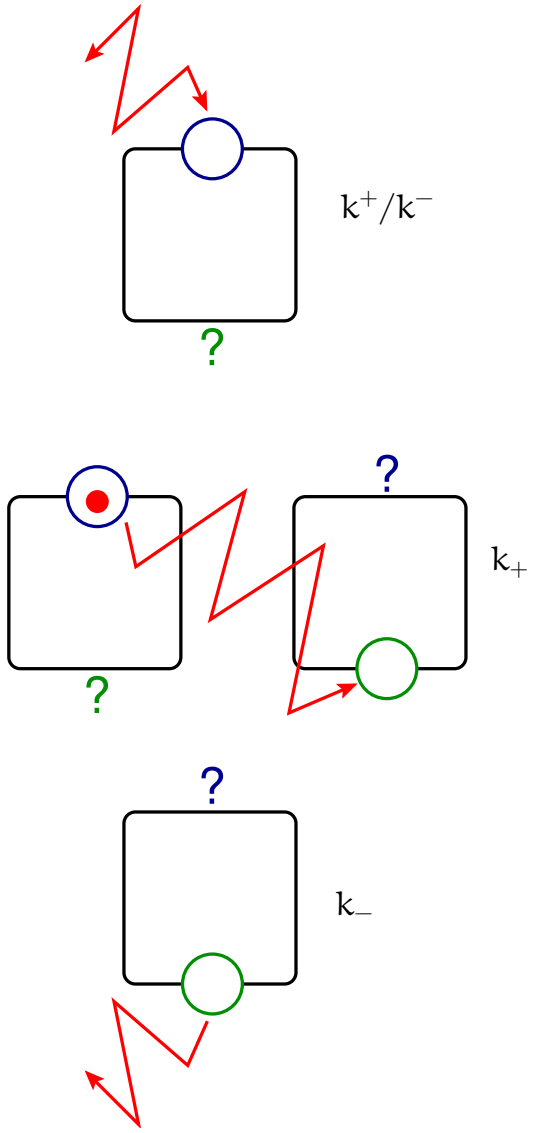
Although the reduction is correct in the ODE semantics.

Degree of correlation (in the unreduced model)





Distant control



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

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

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

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

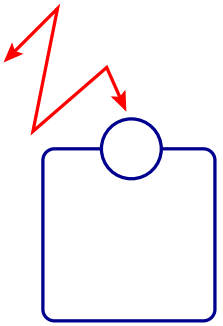
$$A + A^\star_\star \xrightarrow{k_+} A_\star + A^\star_\star$$

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

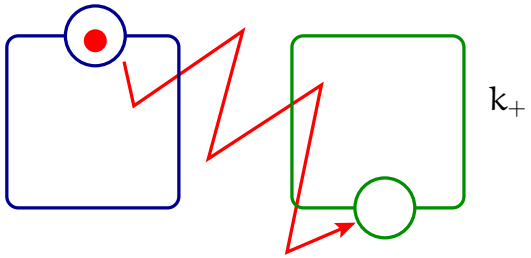
$$A^\star_\star \xrightarrow{k_-} A^\star$$

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

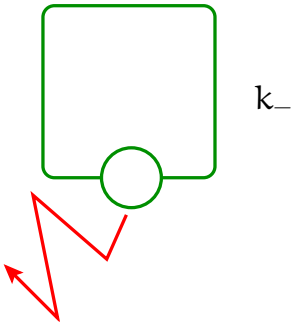
Reduced model



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

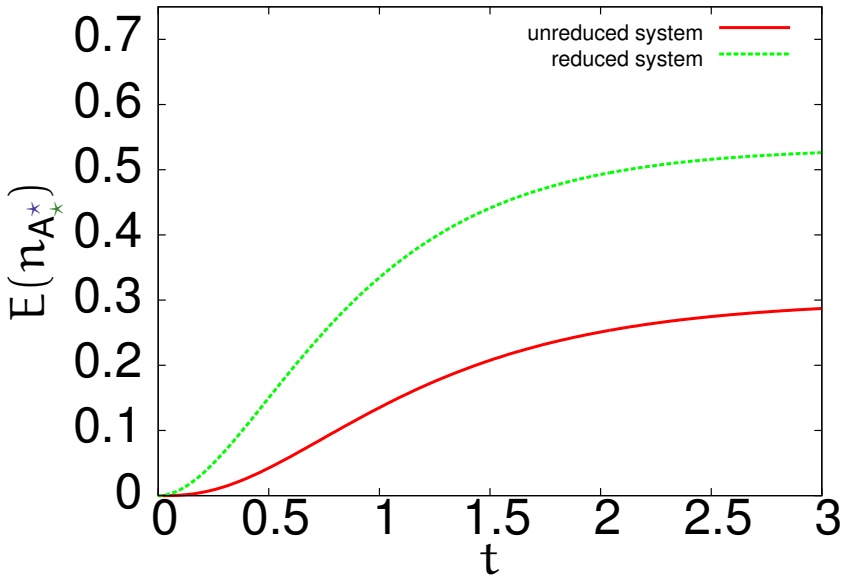


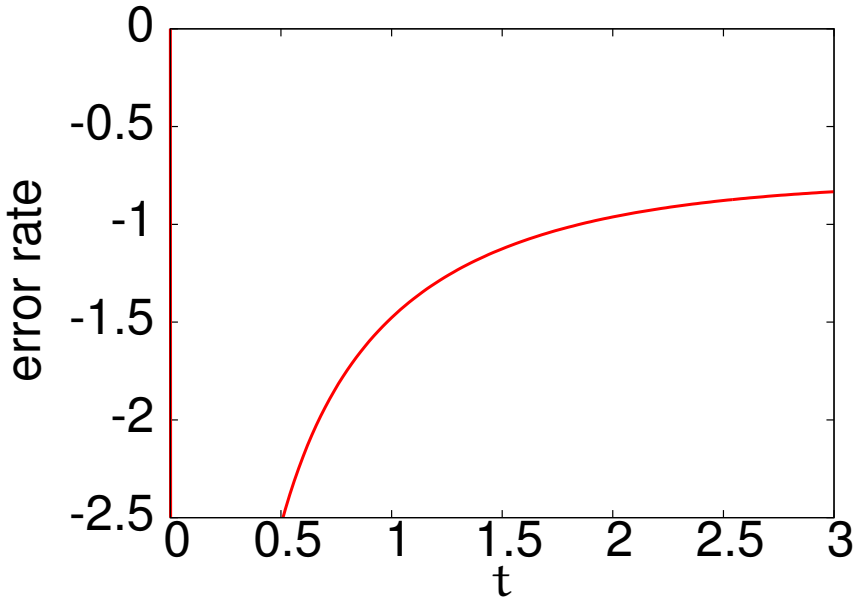
$$A + A^\star \xrightarrow{k_+} A_\star + A^\star$$



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

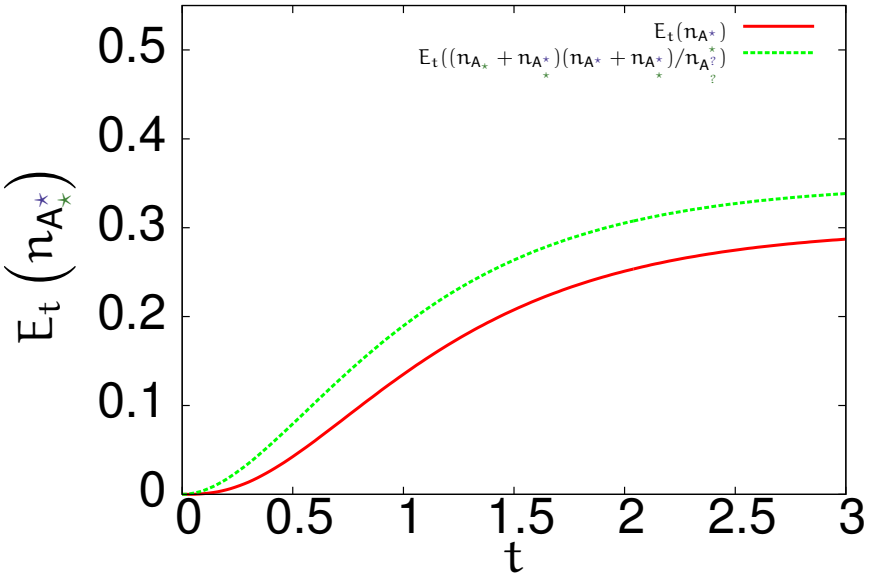
Comparison between the two models

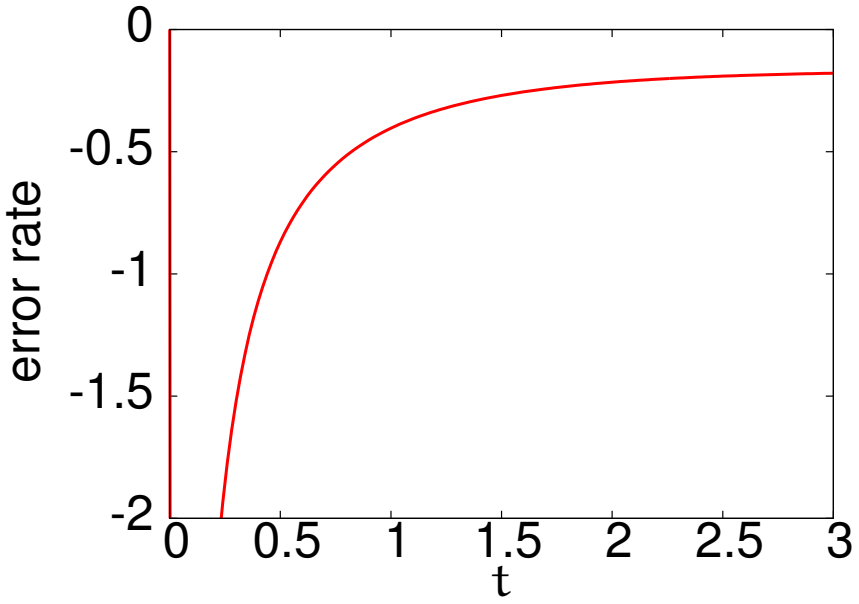




with $k^+ = k^- = k_+ = k_- = 1$,
and two instances of A at time $t = 0$.

Degree of correlation (in the unreduced model)

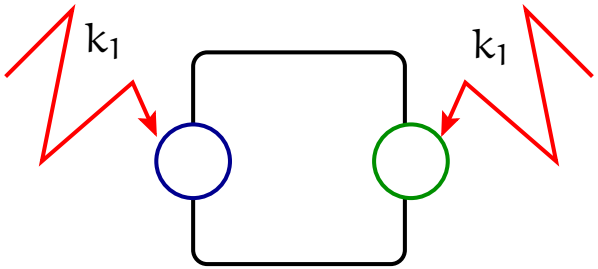




Overview

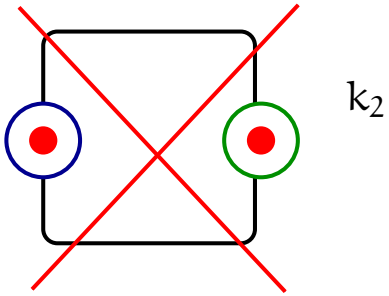
1. Examples of information flow
2. Symmetric sites
3. Conclusion

A model with symmetries



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

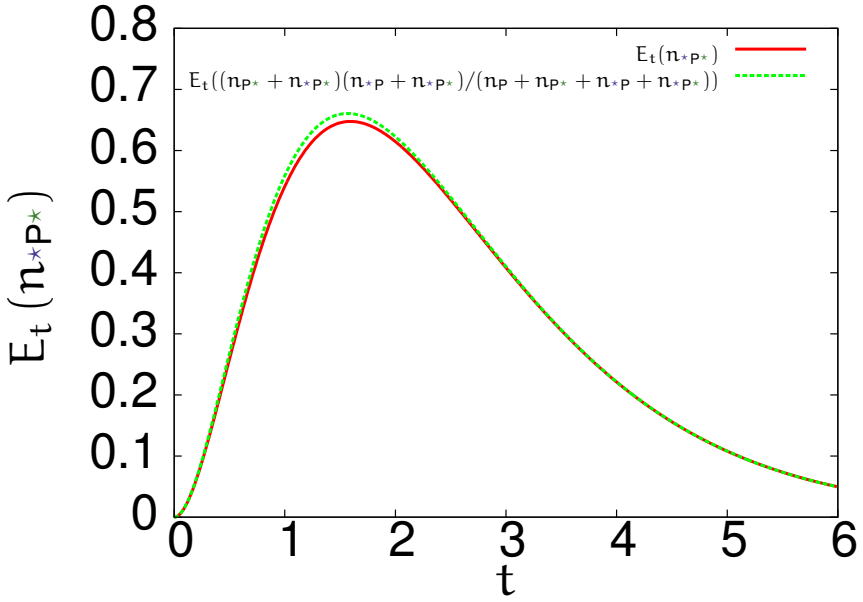
$$P \xrightarrow{k_1} P^\star \qquad {}^\star P \xrightarrow{k_1} {}^\star P^\star$$

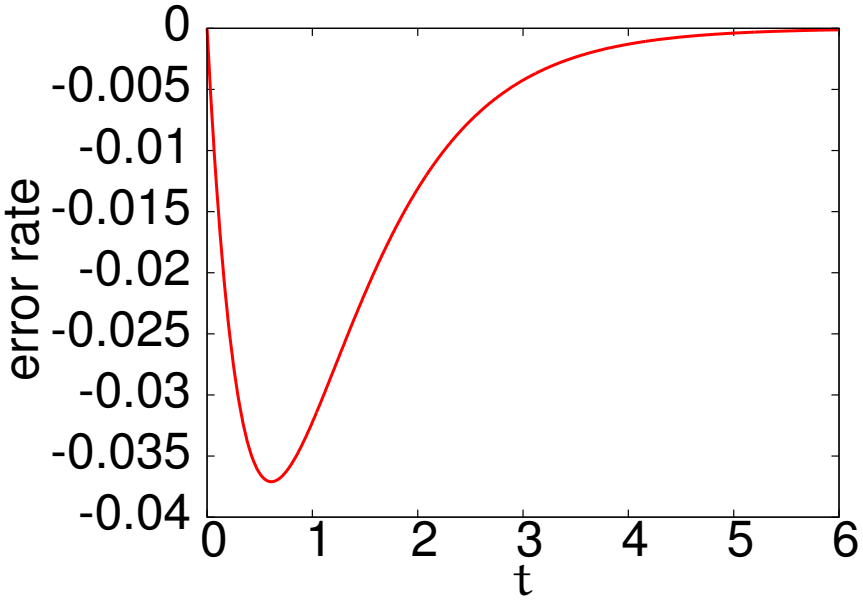


$${}^\star P^\star \xrightarrow{k_2} \emptyset$$

Degree of correlation (in the unreduced model)

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



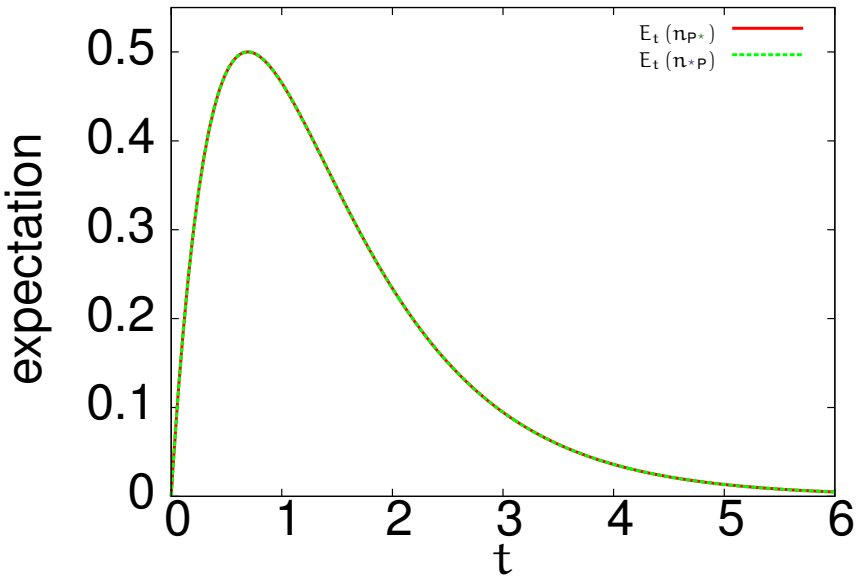


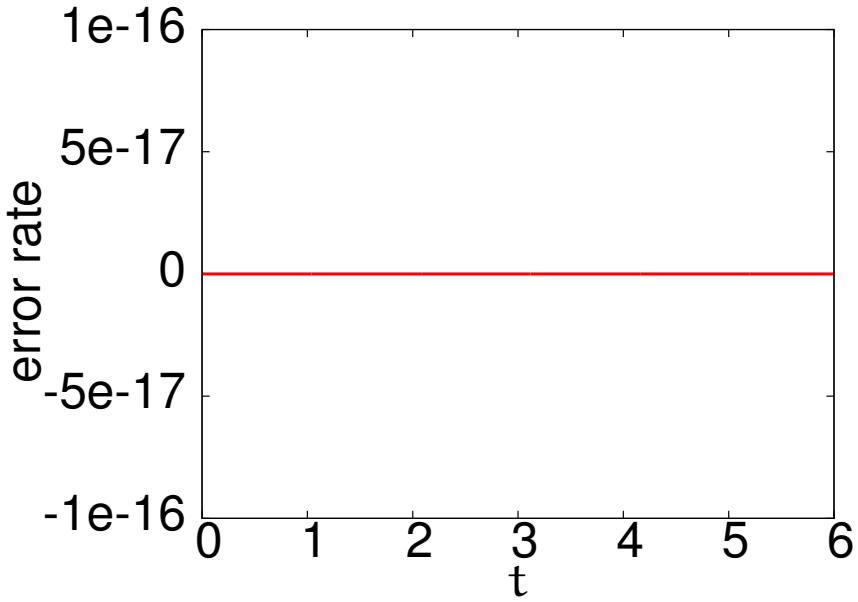
with $k_1 = k_2 = 1$
and two instances of P at time $t = 0$.

Equivalent chemical species

We check numerically that:

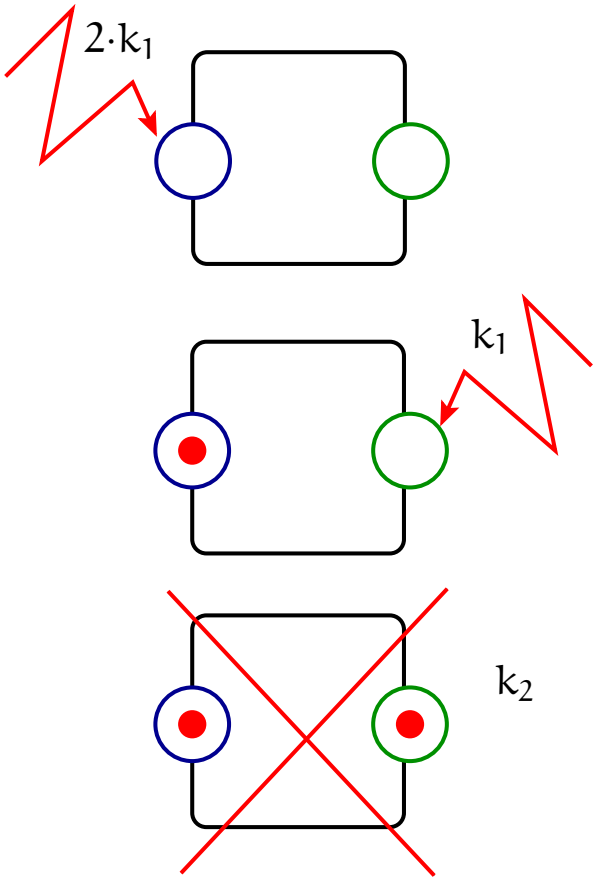
$$E_t\,(n_{P\star}) = E_t\,(n_{\star P}).$$





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

Reduced model



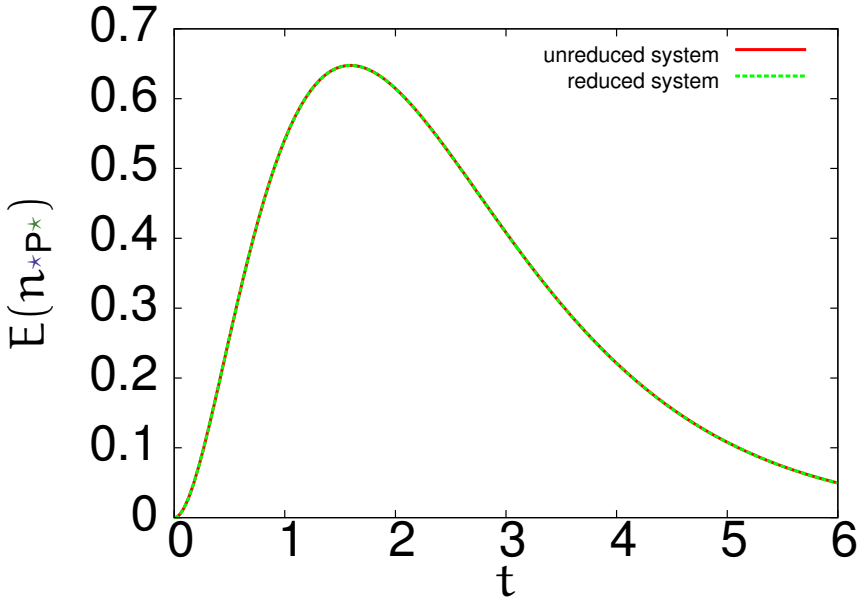
$$P \xrightarrow{2 \cdot k_1} {}^{\star}P$$

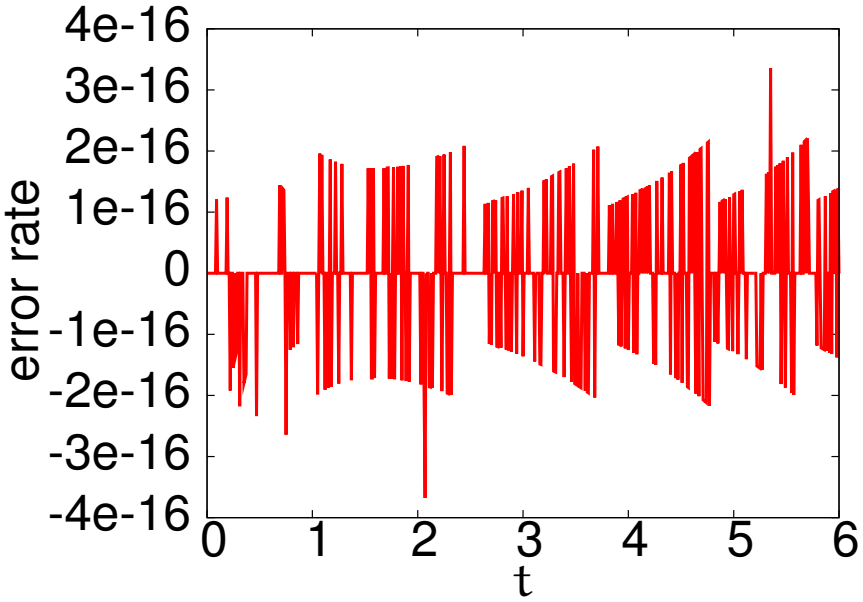
$${}^{\star}P \xrightarrow{k_1} {}^{\star}P^{\star}$$

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

Exponential reduction!!!

Comparison between the two models





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

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

- Forward bisimulations are very convenient to abstract ODE semantics.
  $\Rightarrow$investigate the use of hybrid bisimulation.

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

Announcements

- Implementation is freely distributed on http://www.kappalanguage.org.
- Call for candidates (Internships, Post-doc positions...):

  ANR-Chair of Excellence: AbstractCell
  http://www.di.ens.fr/~feret/abstractcell

- Call for papers/participation:

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