

ROSAEC workshop

Second session

Automatic Reduction of ODE Semantics for Protein-Protein Interaction Networks*

Jérôme Feret

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

* This research has been done during my Post-Doc at Harvard Medical School

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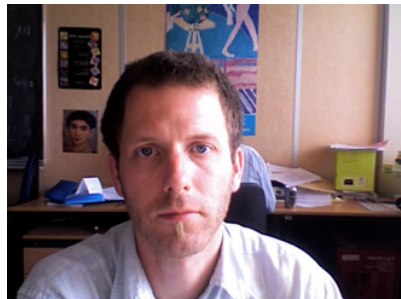
Joint-work with...



Walter Fontana
Harvard Medical School



Vincent Danos
Edinburgh



Russ Harmer
Paris VII



Jean Krivine
Harvard Medical School

Overview

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

Modelling

A cell measures (i.e. checks thresholds, integrates, compares) the concentration of some proteins in order to make decisions.

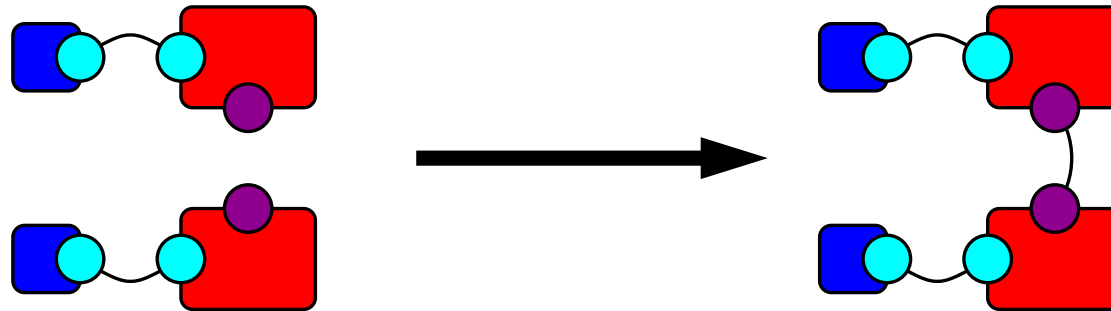
Two approaches:

1. Description 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 cannot be modified

There are also some scalability issues.

Agent-based approach

We use site graph rewrite systems



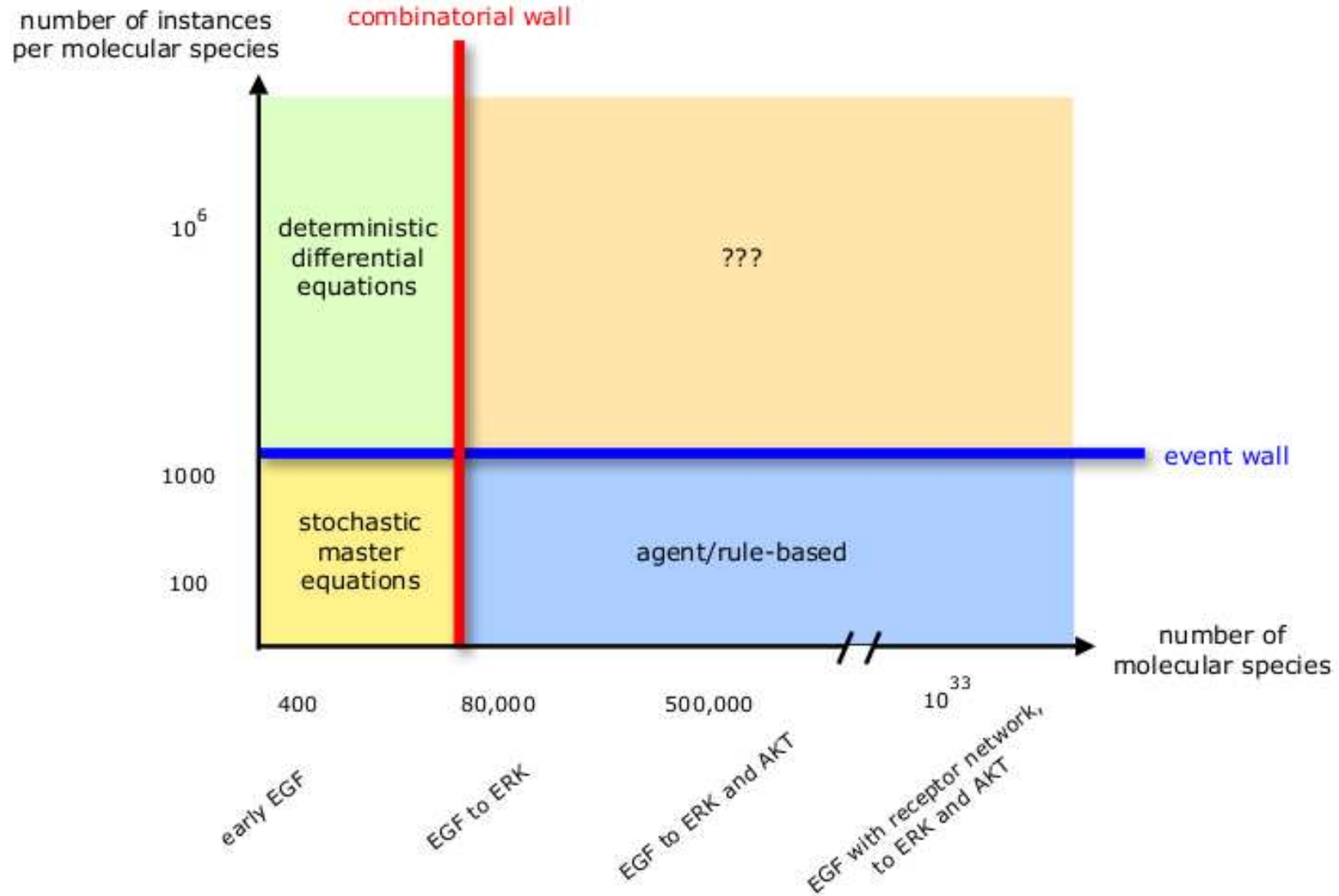
1. The description level matches with both
 - the observation level
 - and the intervention level

of the biologist.

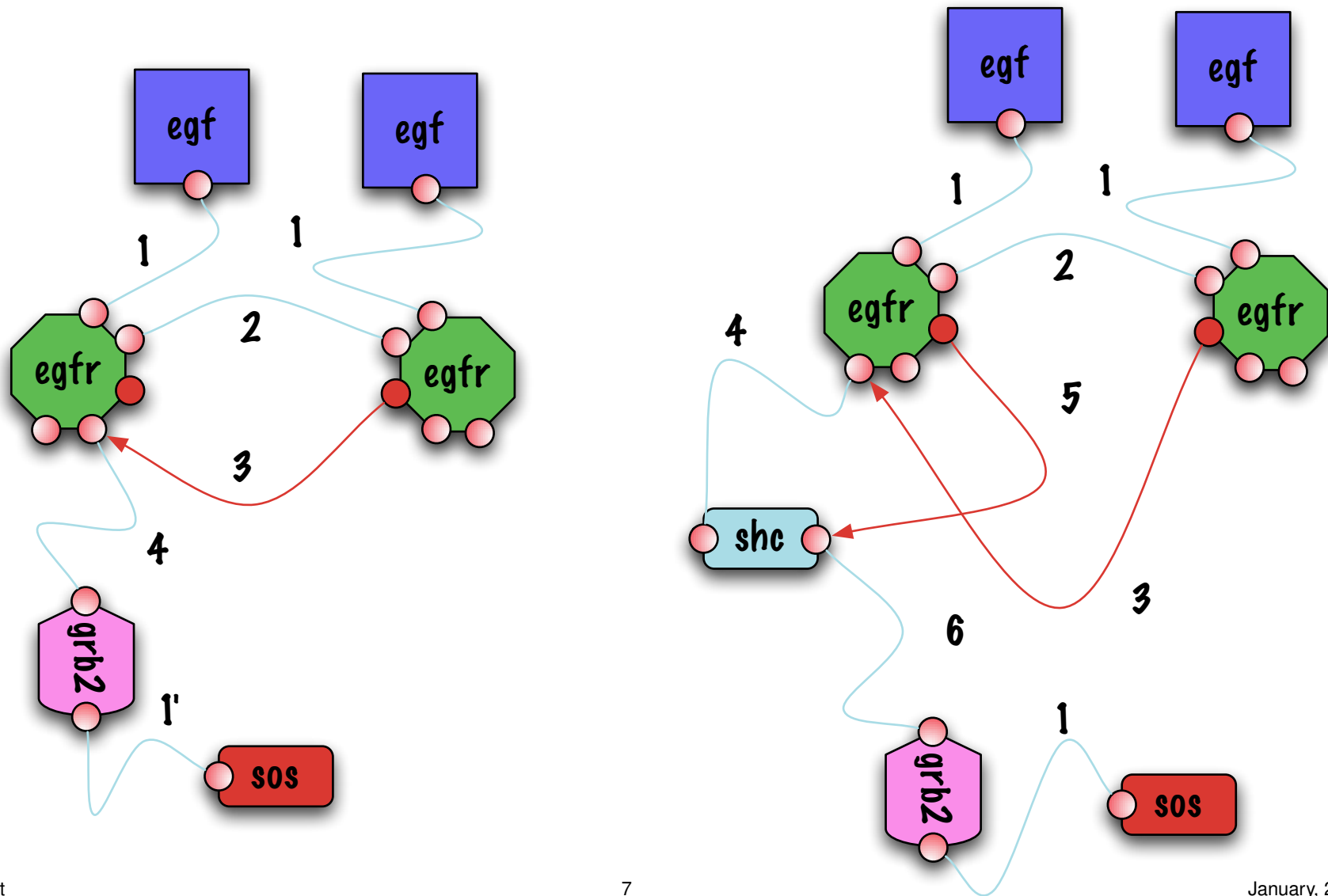
We can tune the model easily.

2. Model description is very compact.
3. Quantitative semantics can be defined.

Complexity walls



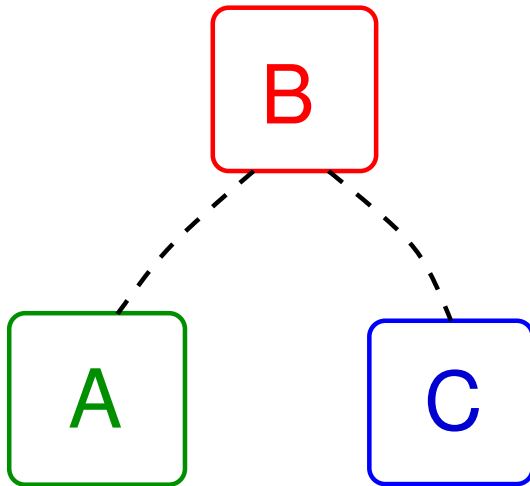
A breach in the wall(s) ?



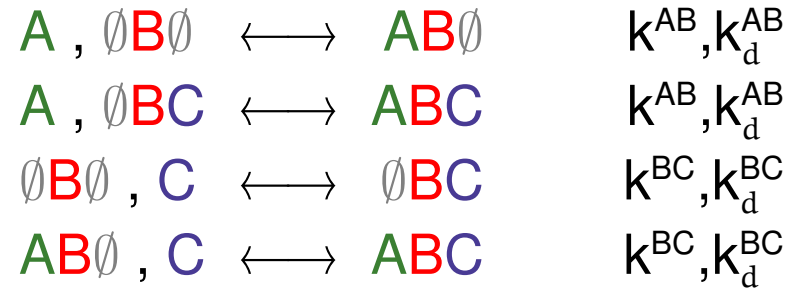
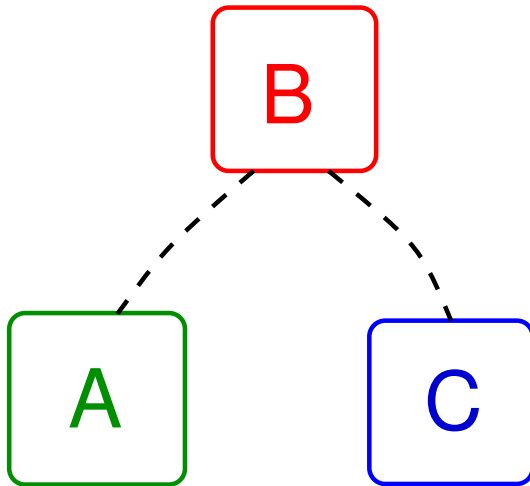
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 - (a) Independent subsystems
 - (b) Self-consistent subsystems
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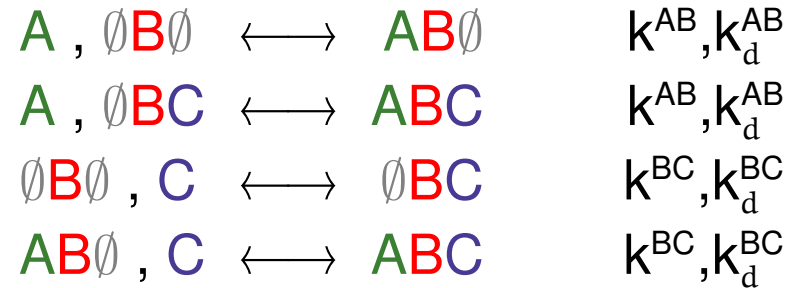
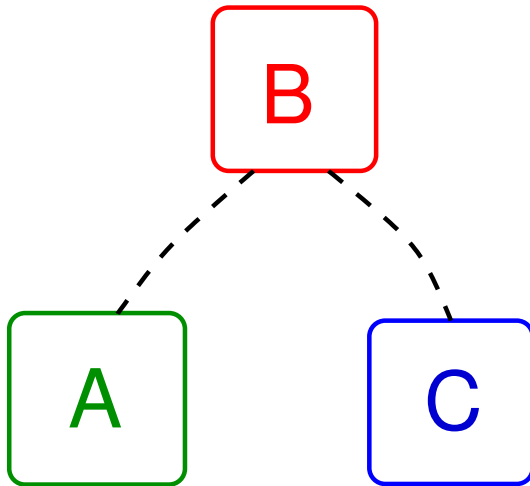
Case study 1: **A simple scaffold**



Case study 1: A simple scaffold

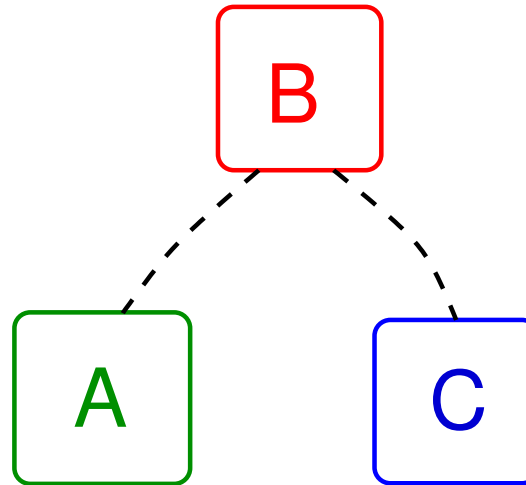


Case study 1: A simple scaffold

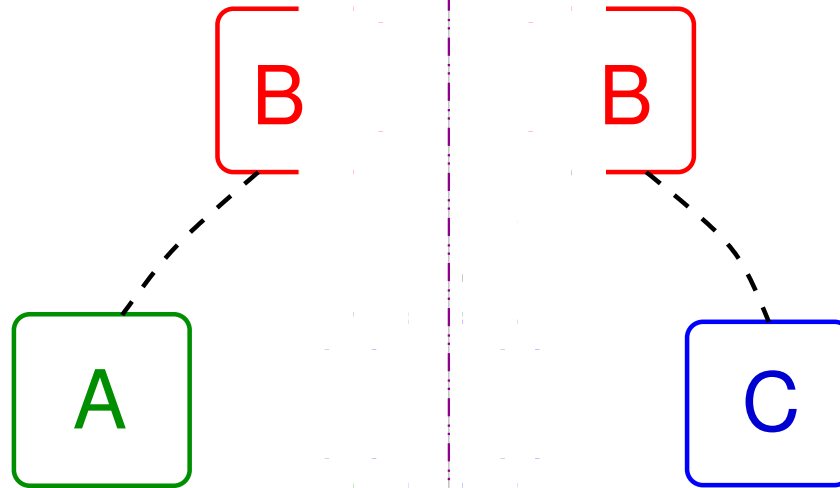


$$\left\{ \begin{array}{l}
 \frac{d[A]}{dt} = k_d^{AB} \cdot ([AB \emptyset] + [ABC]) - [A] \cdot k_d^{AB} \cdot ([\emptyset B \emptyset] + [\emptyset BC]) \\
 \frac{d[C]}{dt} = k_d^{BC} \cdot ([\emptyset BC] + [ABC]) - [C] \cdot k_d^{BC} \cdot ([\emptyset B \emptyset] + [AB \emptyset]) \\
 \frac{d[\emptyset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

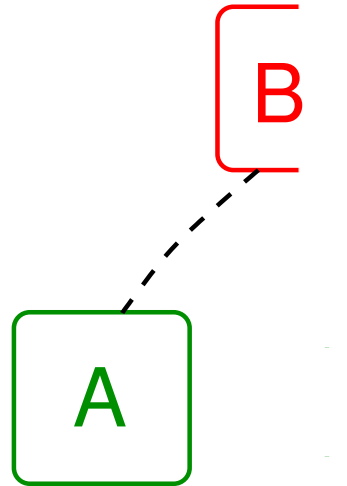
Case study 1: **Two subsystems**



Case study 1: **Two subsystems**



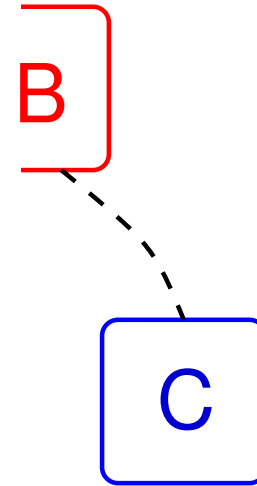
Case study 1: Two subsystems



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

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

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



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

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

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

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:

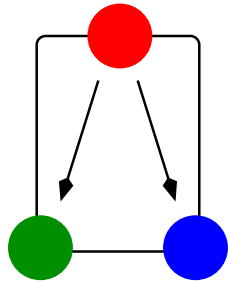
$$[ABC] = \frac{[AB?] \cdot [?BC]}{[?B?]}$$

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

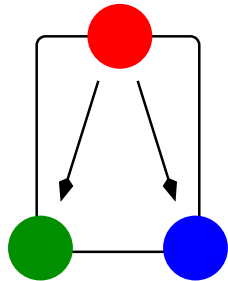
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Case study 2: **A system with a switch**

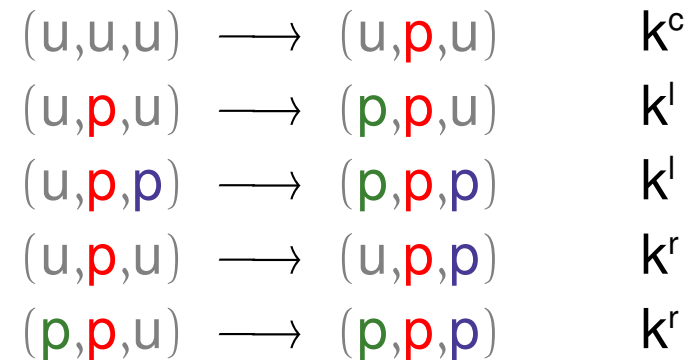
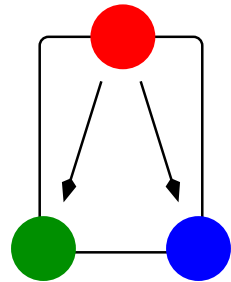


Case study 2: **A system with a switch**



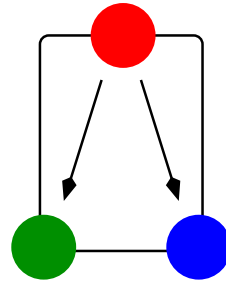
(u, u, u)	\longrightarrow	(u, p, u)	k^c
(u, p, u)	\longrightarrow	(p, p, u)	k^l
(u, p, p)	\longrightarrow	(p, p, p)	k^l
(u, p, u)	\longrightarrow	(u, p, p)	k^r
(p, p, u)	\longrightarrow	(p, p, p)	k^r

Case study 2: A system with a switch

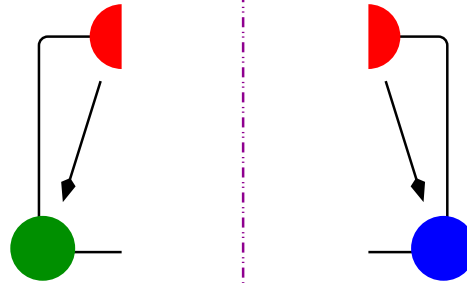


$$\left\{ \begin{array}{l} \frac{d[(u, u, u)]}{dt} = -k^c \cdot [(u, u, u)] \\ \frac{d[(u, p, u)]}{dt} = -k^l \cdot [(u, p, u)] + k^c \cdot [(u, u, u)] - k^r \cdot [(u, p, u)] \\ \frac{d[(u, p, p)]}{dt} = -k^l \cdot [(u, p, p)] + k^r \cdot [(u, p, u)] \\ \frac{d[(p, p, u)]}{dt} = k^l \cdot [(u, p, u)]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

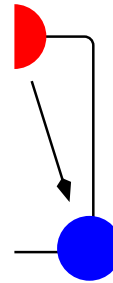
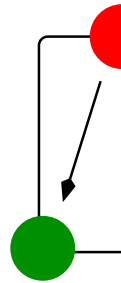
Case study 2: **Two subsystems**



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:

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

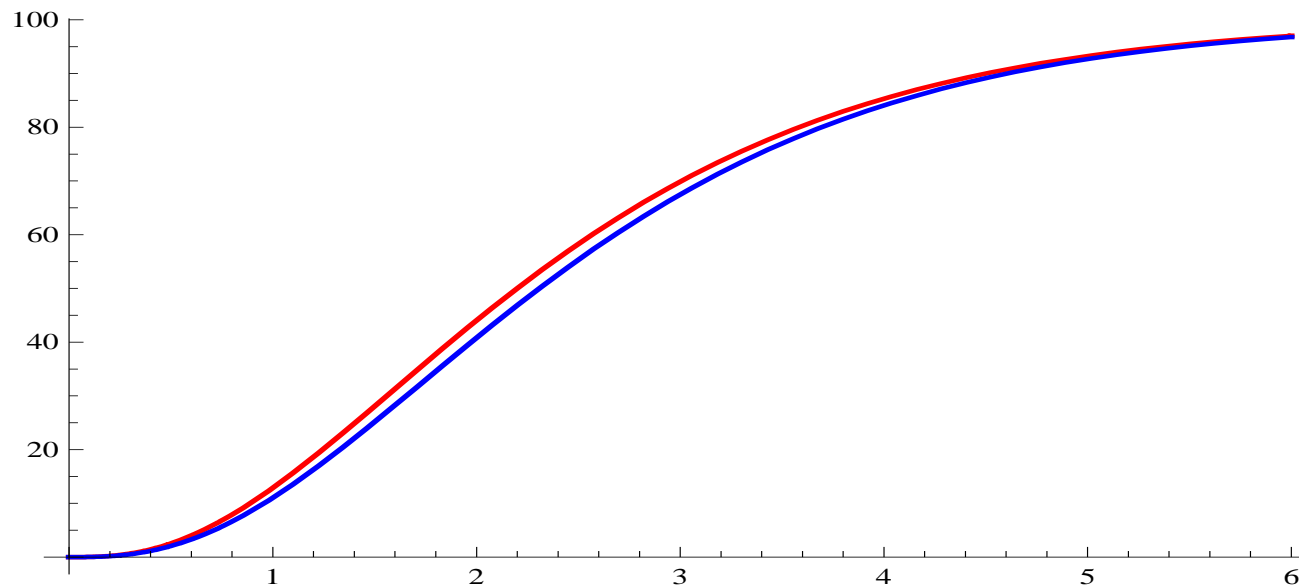
We have (after a short computation):

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

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 ($[(u,u,u)](0) = 100$).
 $[(p,p,p)]$ and $\frac{[(p,p,?)]\cdot[(?,p,p)]}{[(?,p,?)]}$

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 read by the system.

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Continuous differential semantics

Given \mathcal{V} , a finite set of variables;

and \mathbb{F} , a \mathcal{C}^∞ mapping from $\mathcal{V} \rightarrow \mathbb{R}^+$ into $\mathcal{V} \rightarrow \mathbb{R}$.

as for instance,

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

we can define the continuous differential semantics as follows:

$$\mathcal{X}_c : \begin{cases} (\mathcal{V} \rightarrow \mathbb{R}^+) \times \mathbb{R}^+ \rightarrow (\mathcal{V} \rightarrow \mathbb{R}^+) \\ (X_0, T) \mapsto X_0 + \int_{t=0}^T \mathbb{F}(X_c(X_0, t)) \cdot dt. \end{cases}$$

Abstraction

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

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

such that:

- ψ is linear with positive coefficients,
- $\mathbb{F}^\#$ is ψ forward-complete

i.e. the following diagram commutes:

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

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

Abstraction example

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

(Forward completeness can be checked analytically.)

Abstract continuous trajectories

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

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

$$\psi(X_c(X_0, T)) = \psi(X_0) + \int_{t=0}^T [\psi \circ \mathbb{F}](X_c(X_0, t)) \cdot dt \quad (\psi \text{ is linear})$$

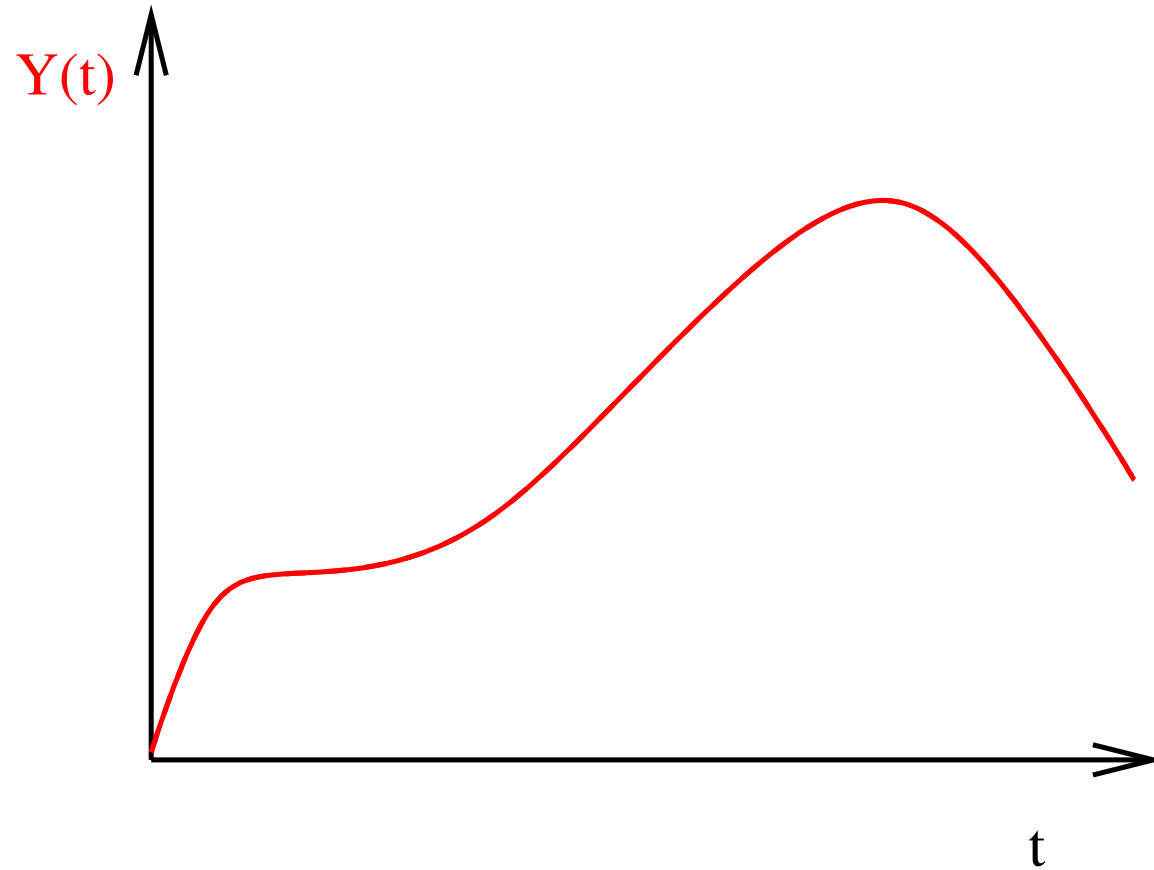
$$\psi(X_c(X_0, T)) = \psi(X_0) + \int_{t=0}^T \mathbb{F}^\#(\psi(X_c(X_0, t))) \cdot dt \quad (\mathbb{F}^\# \text{ is } \psi \text{ forward-complete})$$

We set $Y_0 \triangleq \psi(X_0)$ and $Y_c \triangleq \psi \circ X_c$.

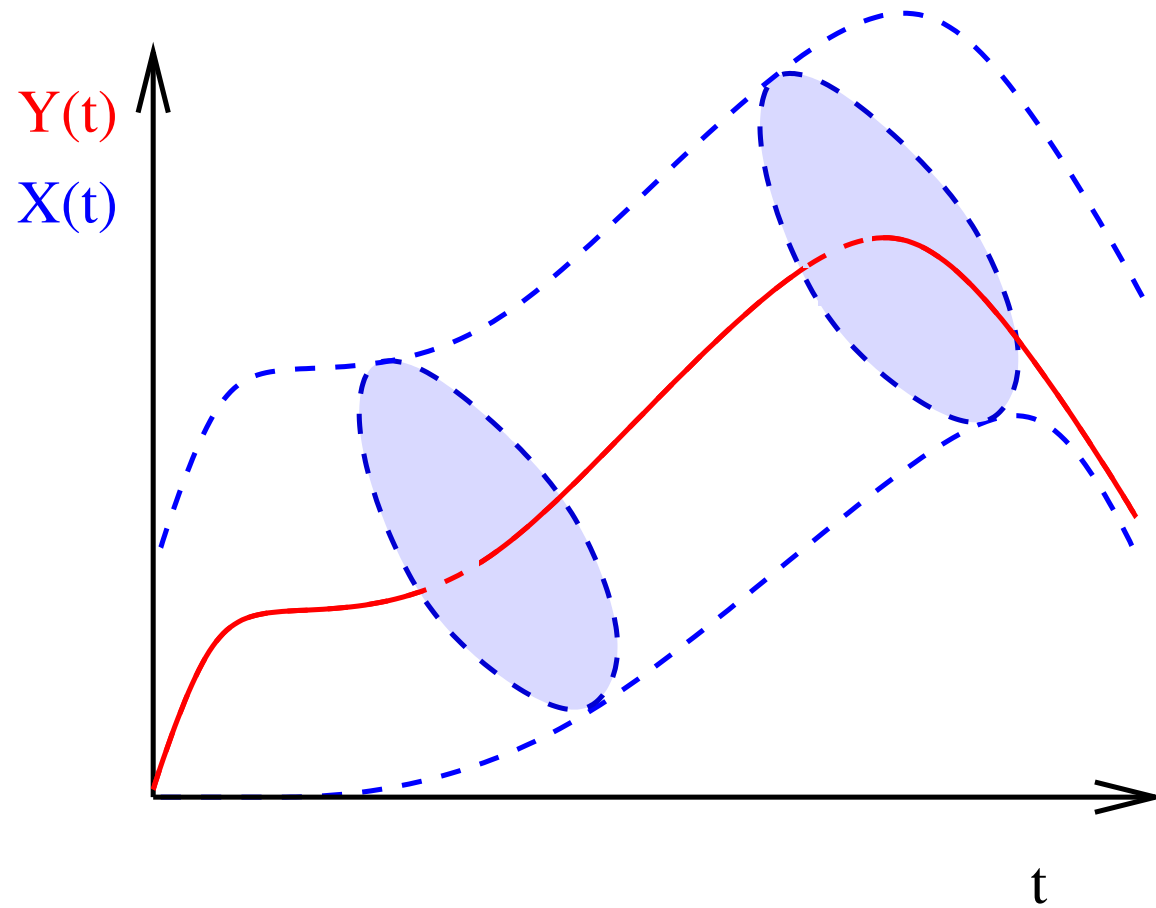
Then we have:

$$Y_c(X_0, T) = Y_0 + \int_{t=0}^T \mathbb{F}^\#(Y_c(X_0, t)) \cdot dt$$

Fluid trajectories



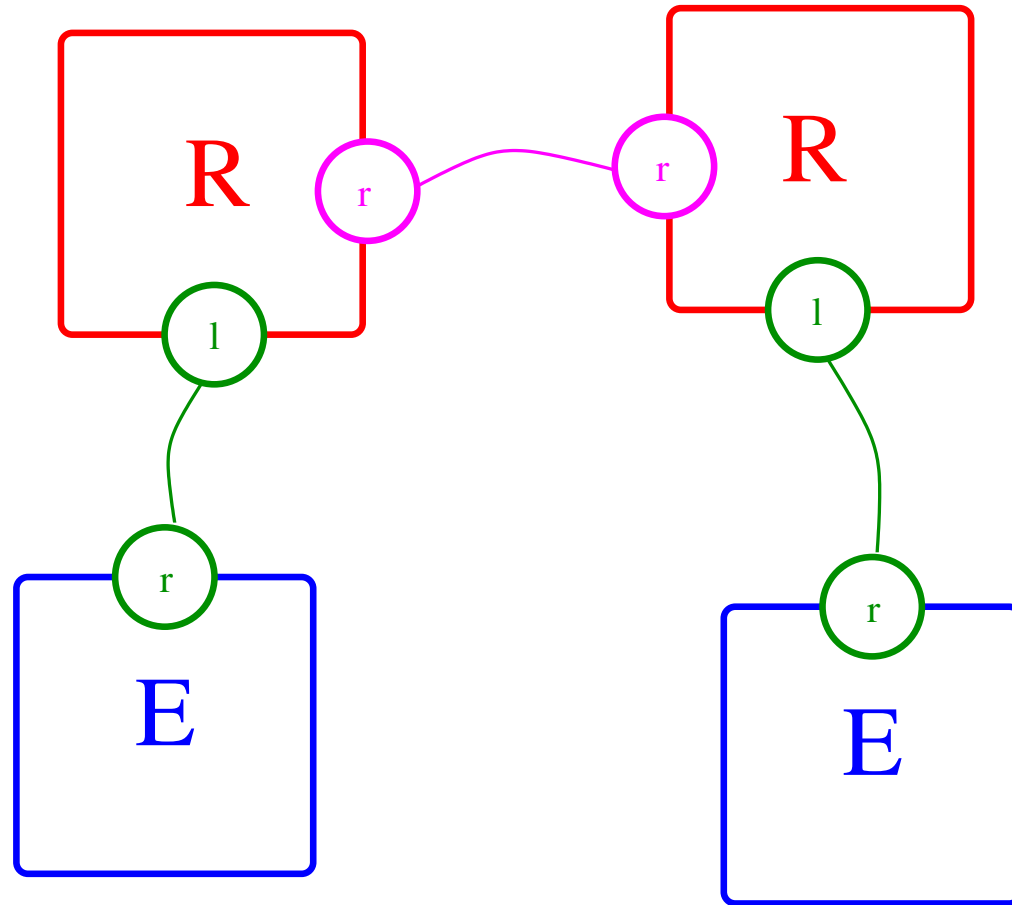
Fluid trajectories



Overview

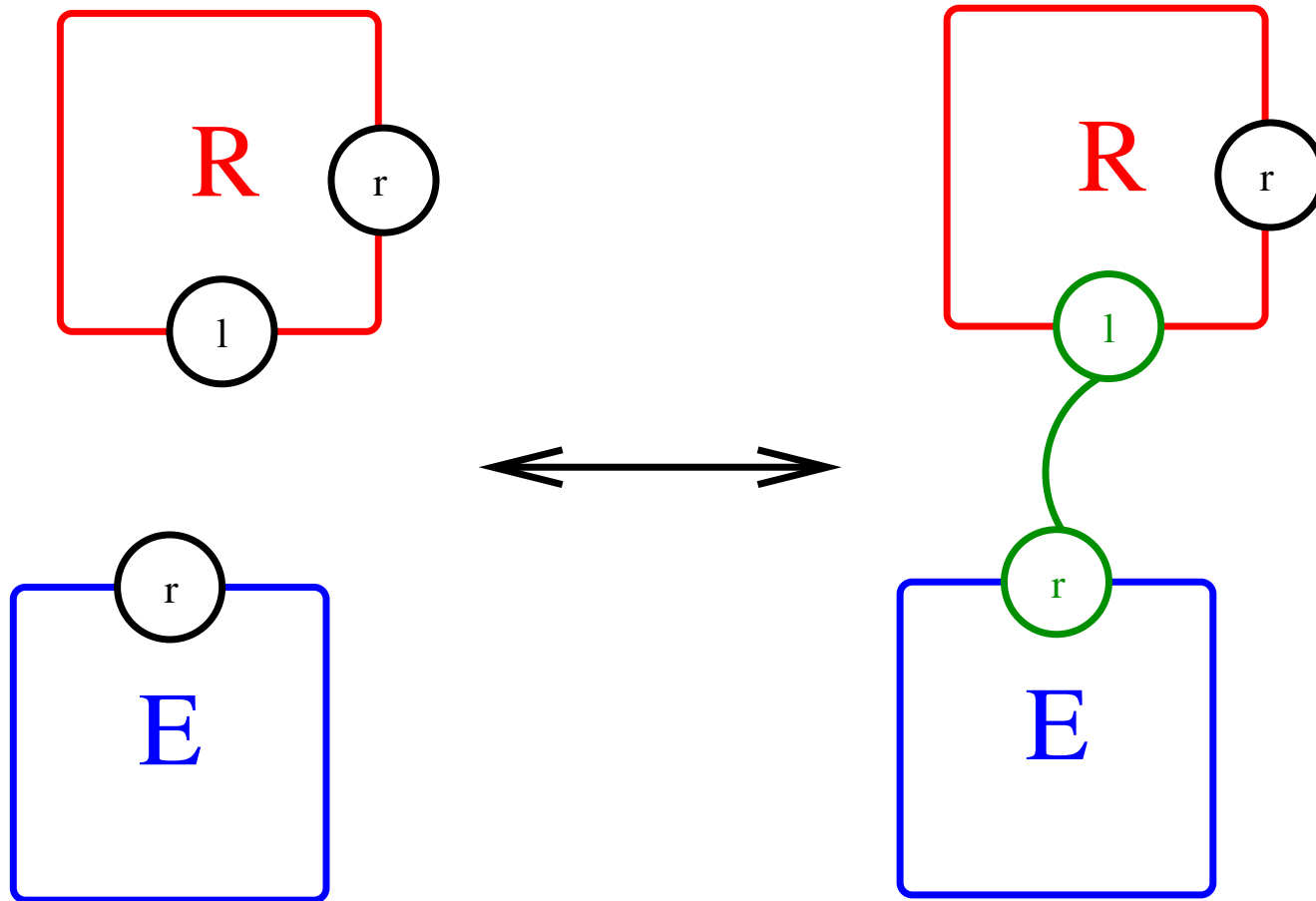
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A species



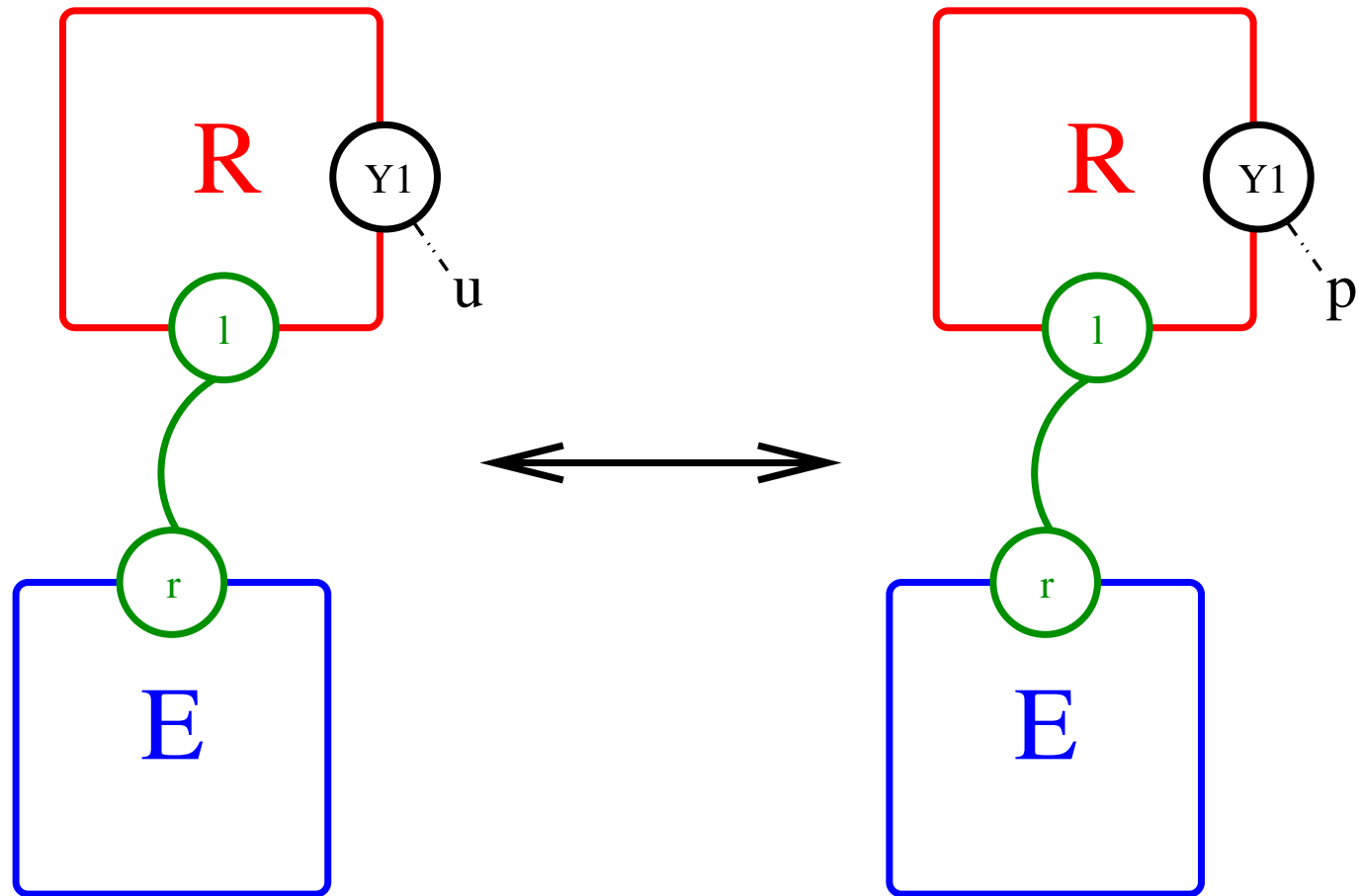
$E(r!1), R(l!1, r!2), R(r!2, l!3), E(r!3)$

A unbinding/binding Rule



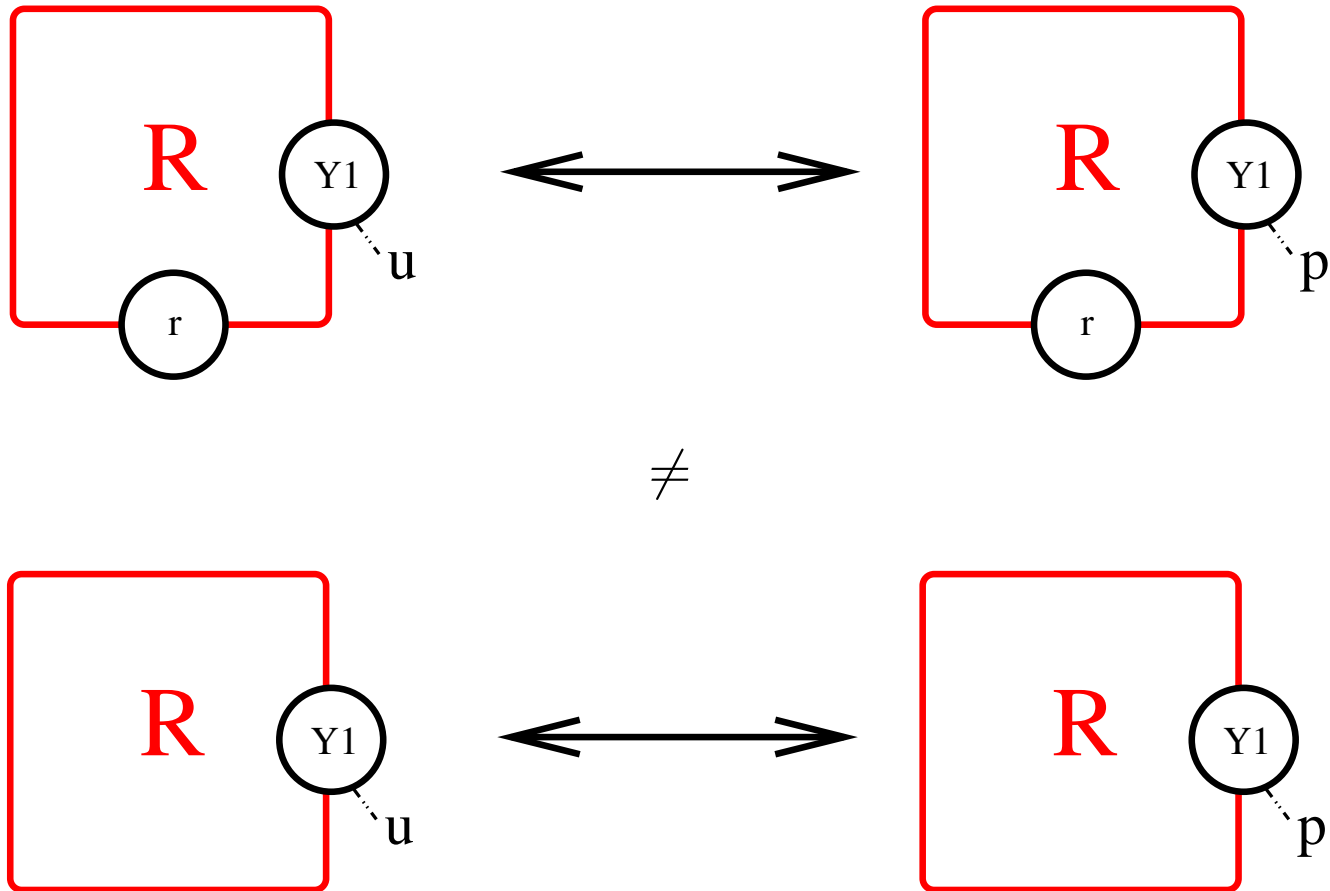
$$E(r), R(l,r) \longleftrightarrow E(r!1), R(l!1,r)$$

Internal state

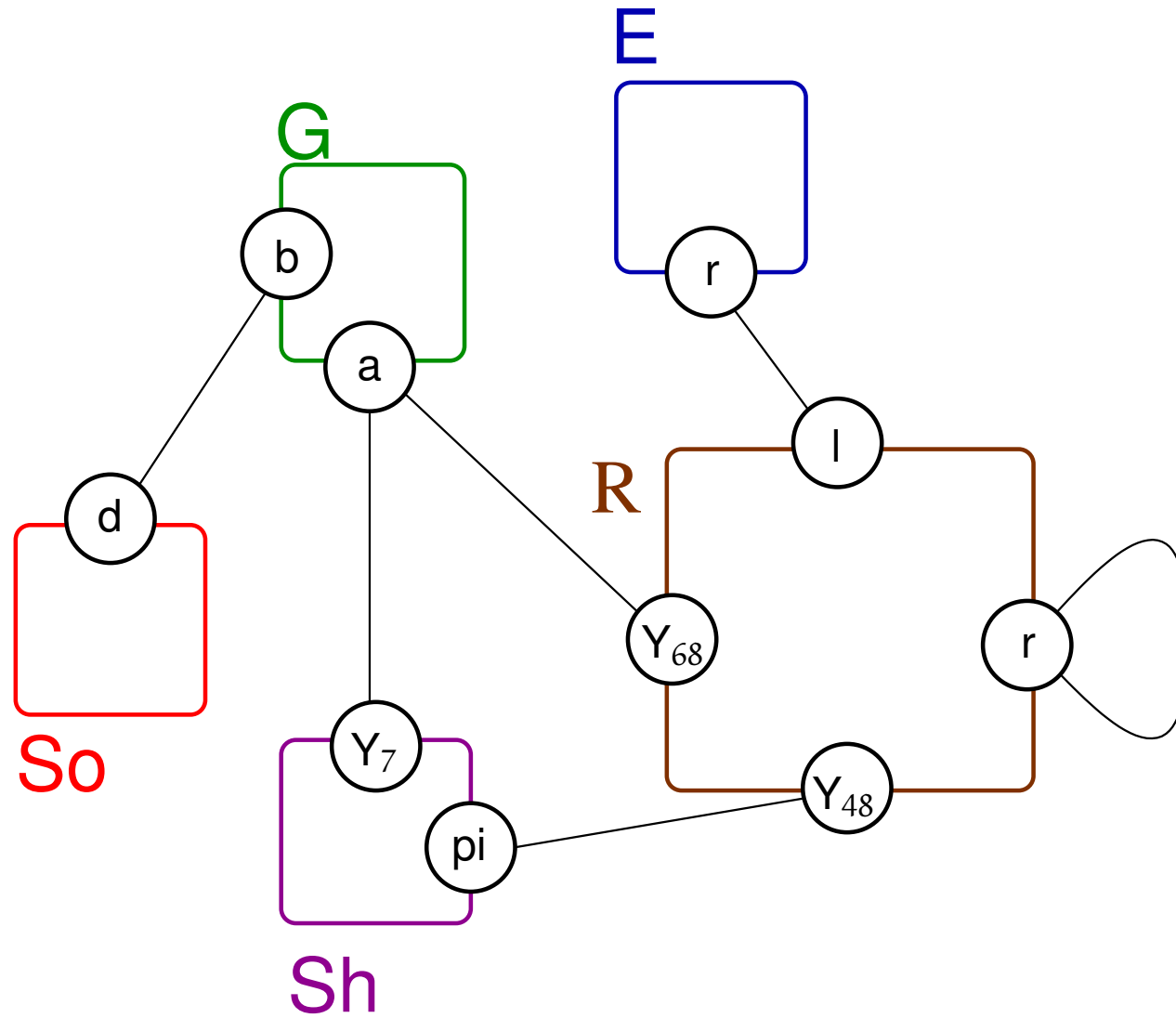


$$R(Y1 \sim u, l!1), E(r!1) \longleftrightarrow R(Y1 \sim p, l!1), E(r!1)$$

Don't care, Don't write



Contact map



Overview

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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

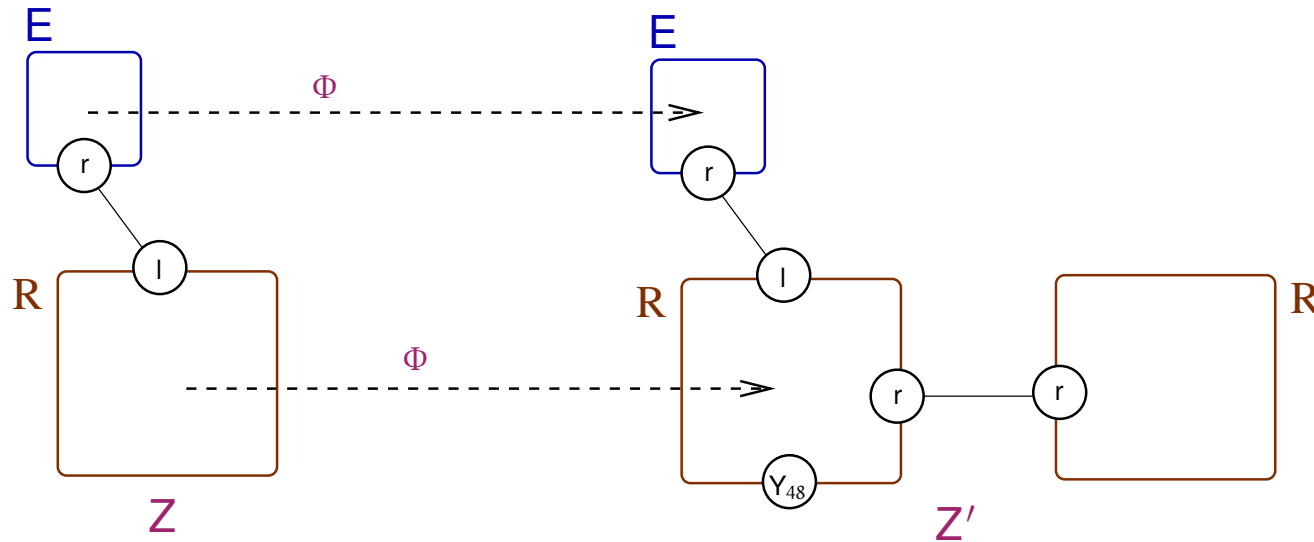
- the unit depends on the arity of the rule as follows:

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

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

- we assume that there are no arity mismatch.

Embedding



We write $Z \triangleleft_{\Phi} Z'$ 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*:

$$lhs \rightarrow rhs \quad k.$$

1. We write *lhs* as a multi-set $\{C_i\}$ of non empty connected components.
2. A ground instantiation of the rule *rule* is defined by a tuple (r_i, Φ_i) such that $\forall i, r_i \in \mathcal{R}$ and $C_i \triangleleft_{\Phi_i} r_i$.
3. The ground instantiation can be written as follows:

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

4. The activity of a ground instantiation is defined as:

$$act_{(r_i, \Phi_i)} = \frac{k \cdot \prod [r_i]}{\#\{\Phi \mid lhs \triangleleft_{\Phi} lhs\}}.$$

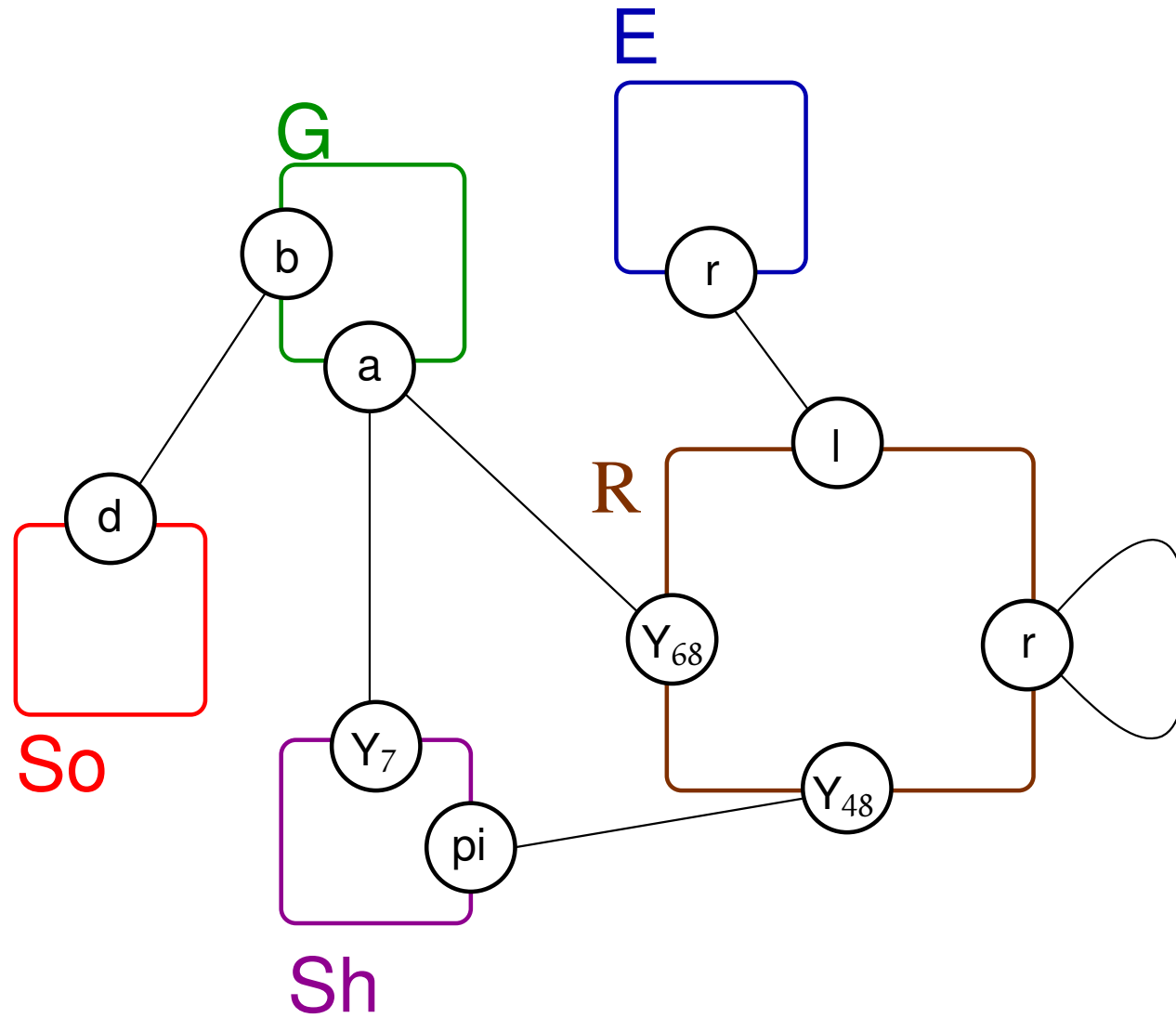
5. Each ground instantiation induces the following contributions:

$$\frac{d[r_i]}{dt} \stackrel{+}{=} -act_{(r_i, \Phi_i)}, \quad \frac{d[p_i]}{dt} \stackrel{+}{=} act_{(r_i, \Phi_i)}.$$

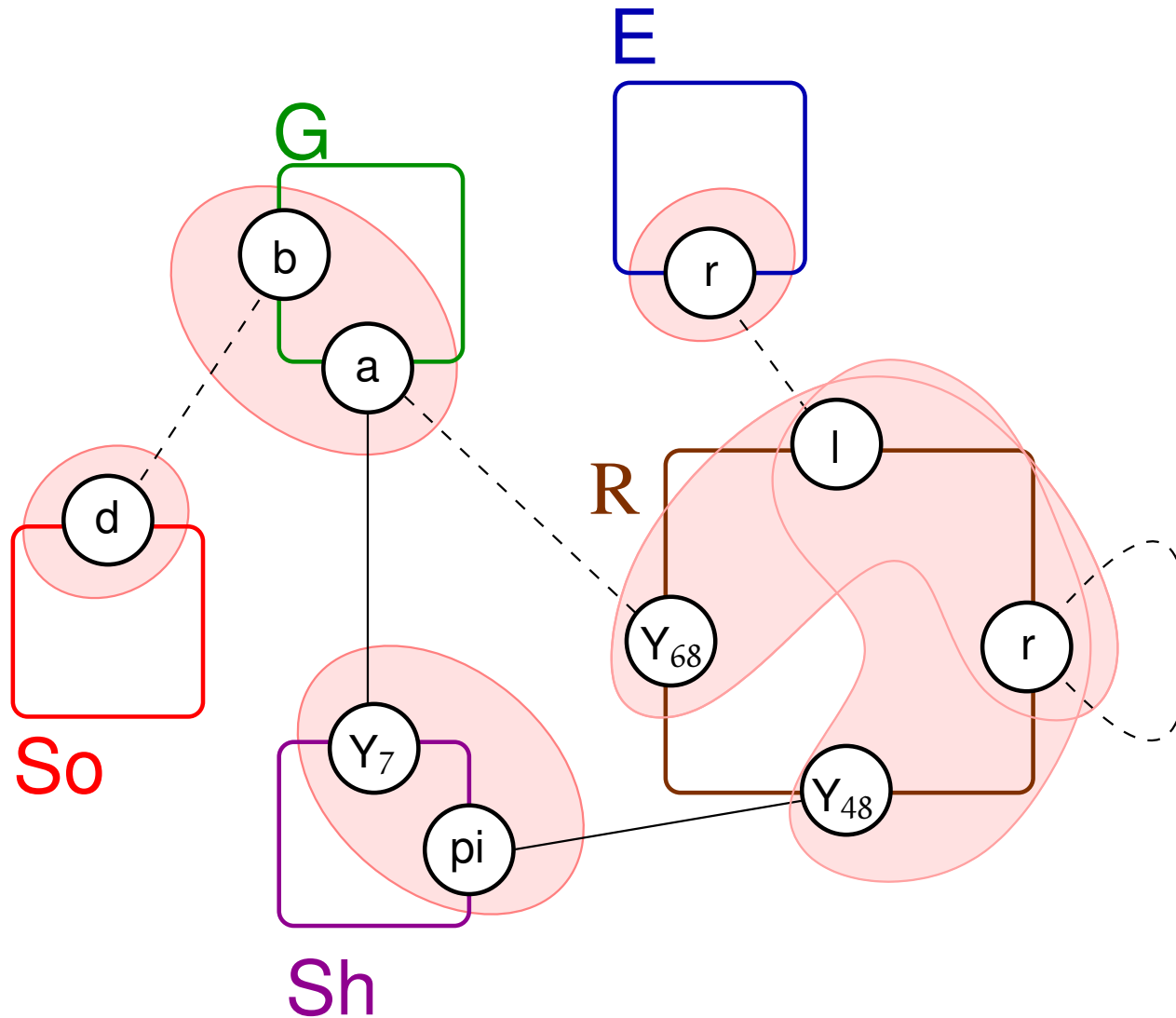
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 - (a) **Fragments**
 - (b) Soundness criteria
 - (c) Abstract counterpart
7. Conclusion

Contact map



Annotated contact map



Annotated contact map

An annotation of the contact map is given by:

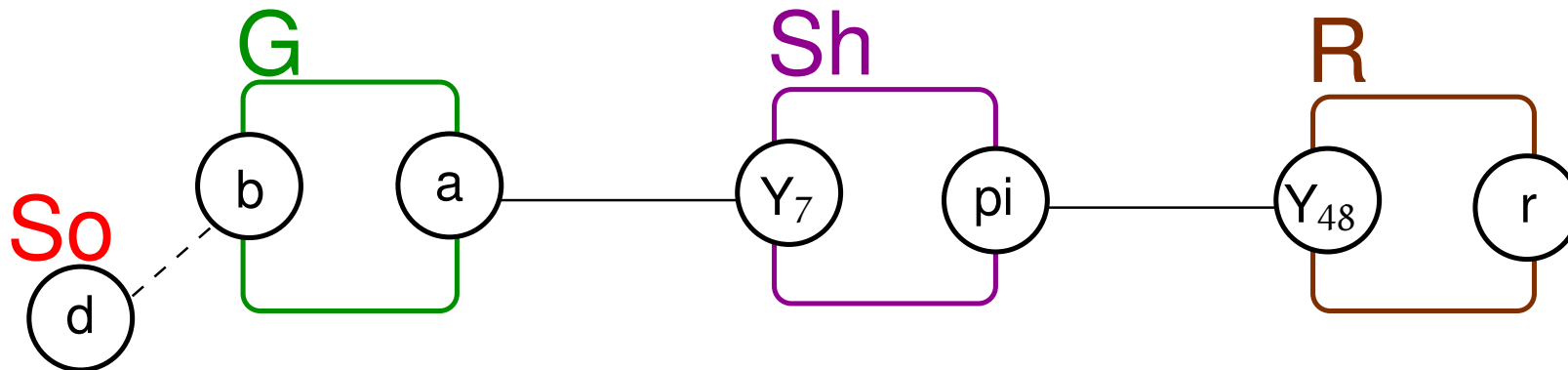
1. a set of dotted edges (other edges are solid),
2. and, for each agent type A , a parsimonious covering $C(A) \in \wp(\Sigma(A))$ of the set of sites of A , i.e. :
 - (a) $\emptyset \notin C(A)$,
 - (b) $\bigcup C(A) = S$,
 - (c) for all $c_1, c_2 \in C(A)$, $c_1 \neq c_2$ implies that $c_1 \not\subseteq c_2$,
 - (d) $C(A)$ is not necessarily a partition
(i.e. there may exist $c_1, c_2 \in C(A)$ such that $c_1 \neq c_2$ and $c_1 \cap c_2 \neq \emptyset$).

Partial species

A partial species 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:



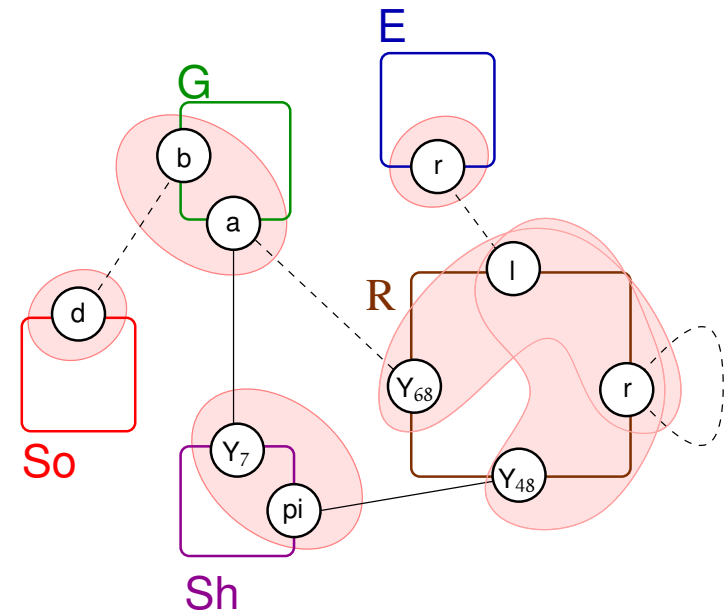
$G(b!d.S_o, a!1), Sh(Y_7!1, pi!2), R(Y_{48}!2, r)$

Fragment definition

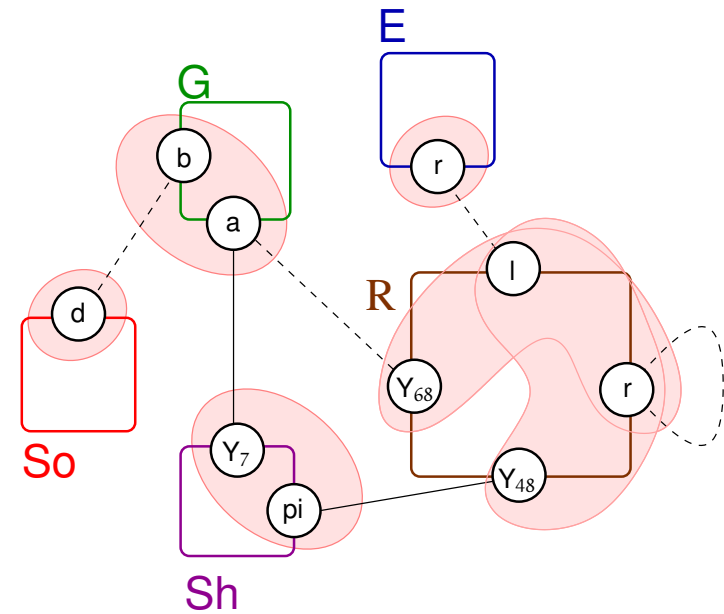
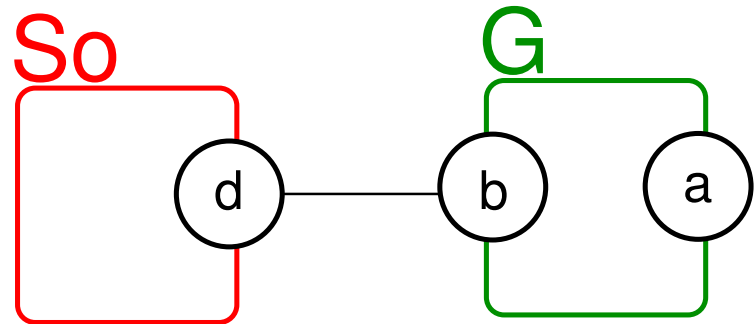
A fragment is a partial species such that:

1. for any agent of type A , the set of sites is a class in $C(A)$;
2. for any binding type $A(x!y.B)$, the edge between the site x of A and the site y and B in the contact map is dotted;
3. for any bond $A(x!1), B(y!1)$, the edge between the site x of A and the site y and B is solid.

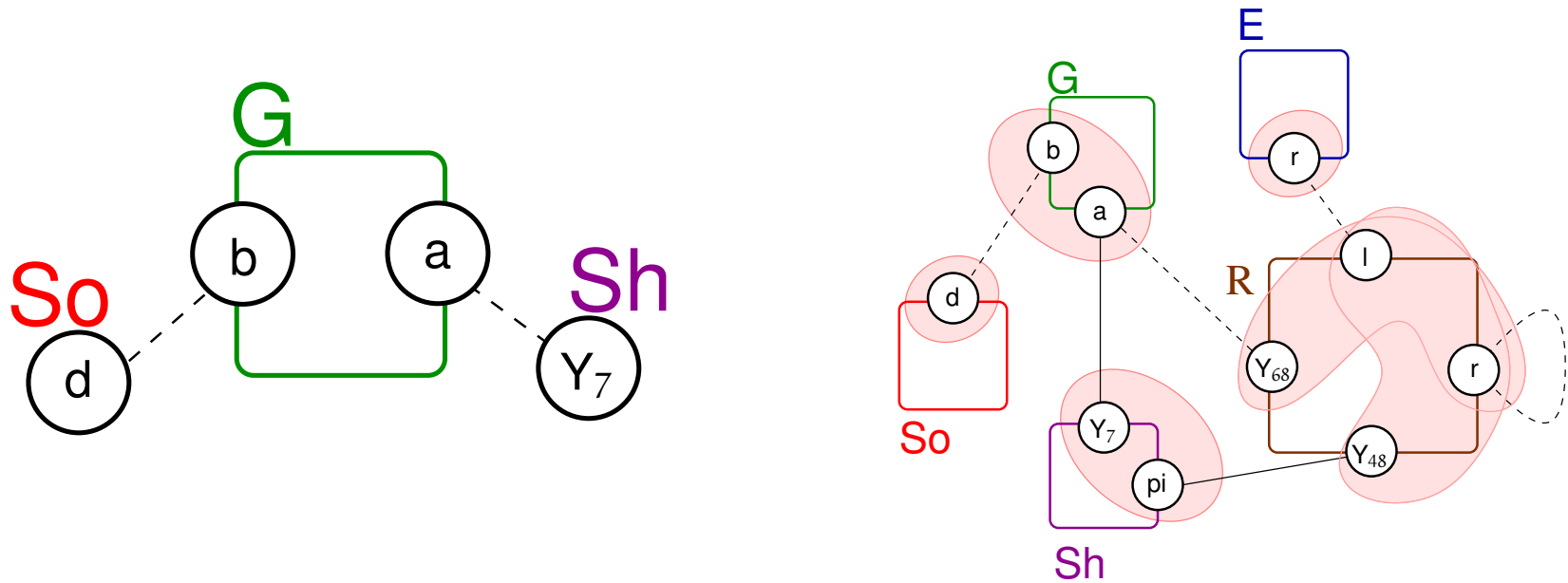
Are they fragments ?



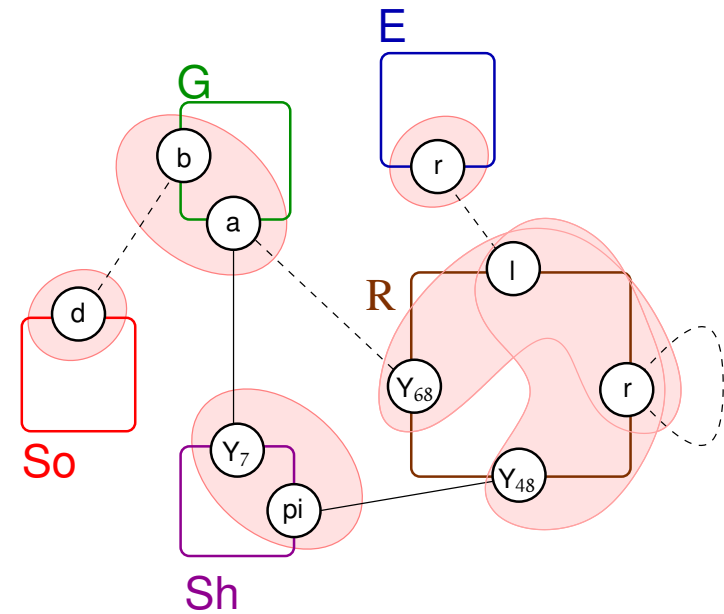
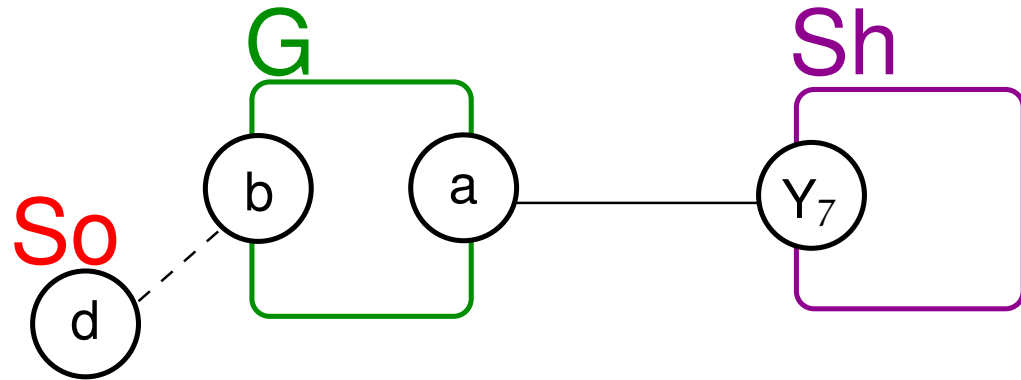
Are they fragments ?



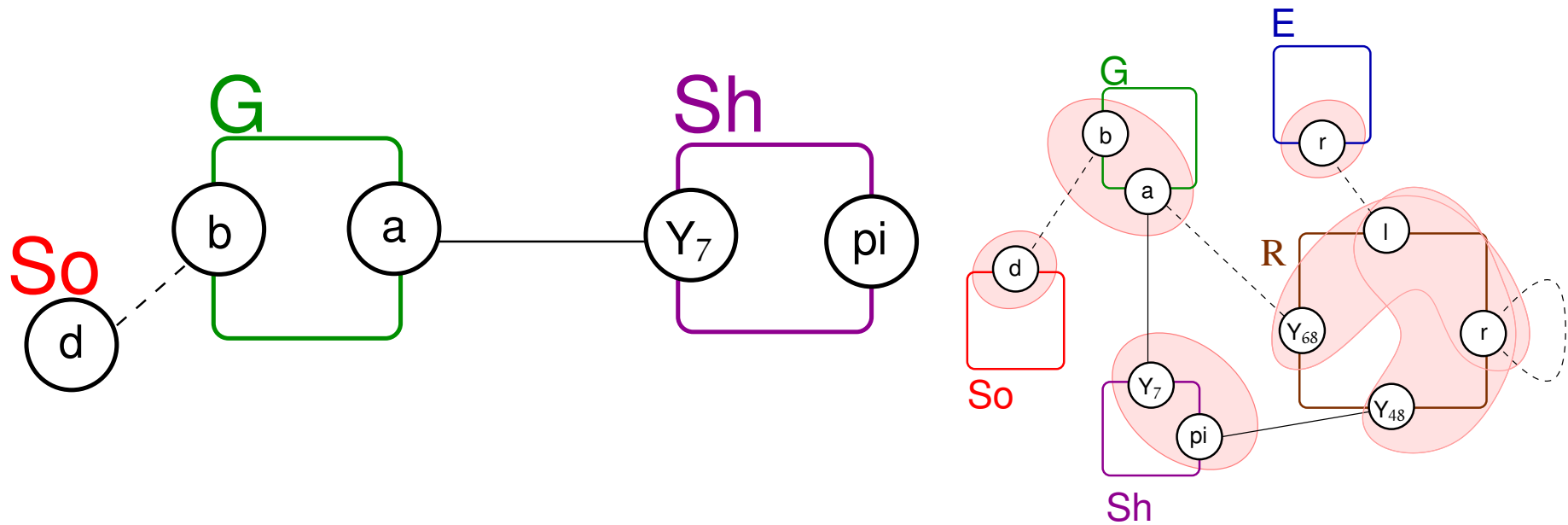
Are they fragments ?



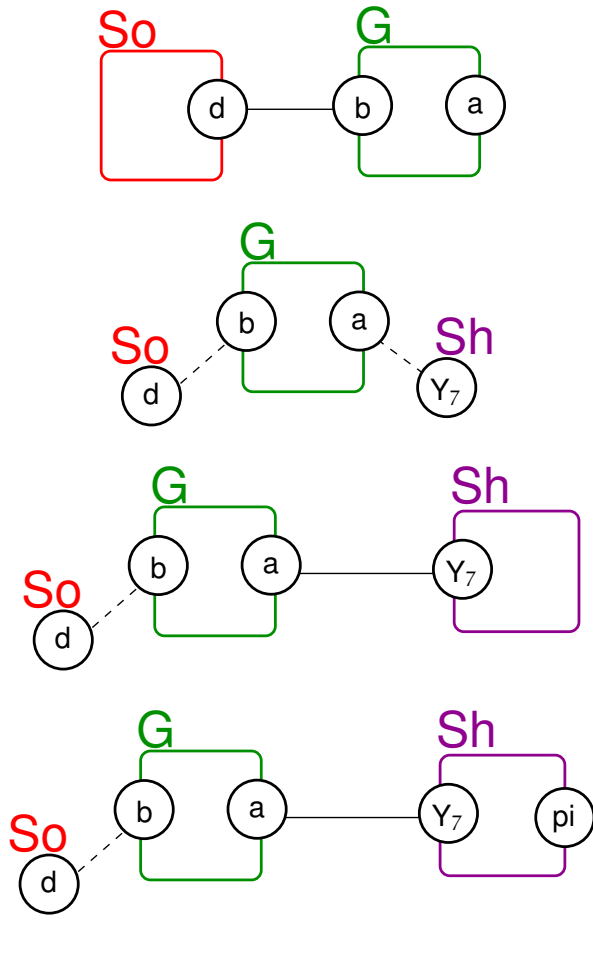
Are they fragments ?



Are they fragments ?



Are they fragments ?

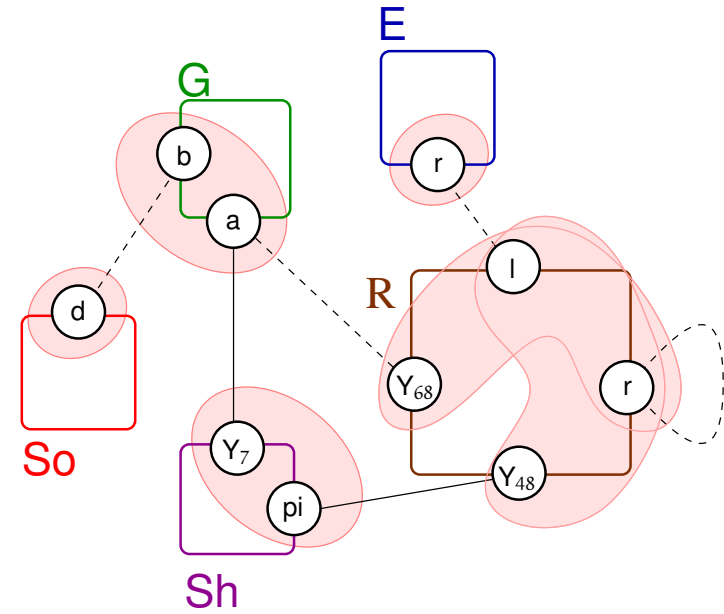


no

no

no

yes



Basic properties

The set of fragments enjoys two convenient properties:

1. Closure with respect to the operational semantics:

When we apply a rule with a tuple of fragments, we get a tuple of fragments.

2. Subfragments:

We can express the concentration of any sub-fragment as a linear combination of the concentration of some fragments.

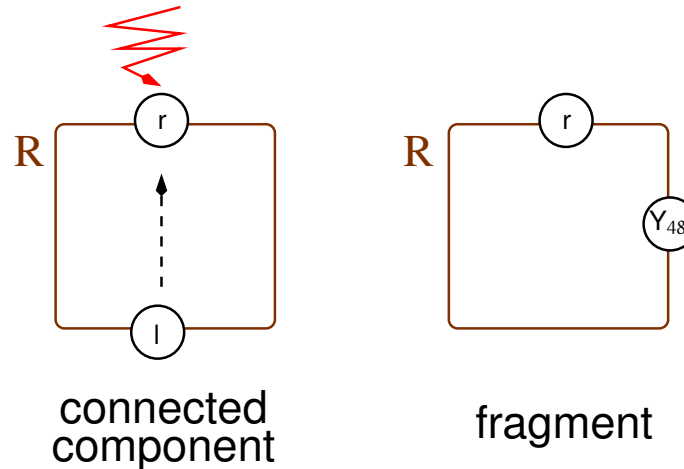
Which other properties do we need so that the function $\mathbb{F}^\#$ can be defined ?

Overview

1. Motivations
2. Handmade ODEs
3. Abstract interpretation framework
4. Kappa
5. Concrete semantics
6. **Abstract semantics**
 - (a) Fragments
 - (b) **Soundness criteria**
 - (c) Abstract counterpart
7. Conclusion

Two more requirements

1. We must compute the concentration of any lhs connected component:
Any connected component of a lhs must be embedded in a fragment.
2. When a fragment is modified, we need to compute how the activity of the rule is distributed between this fragment and the others.

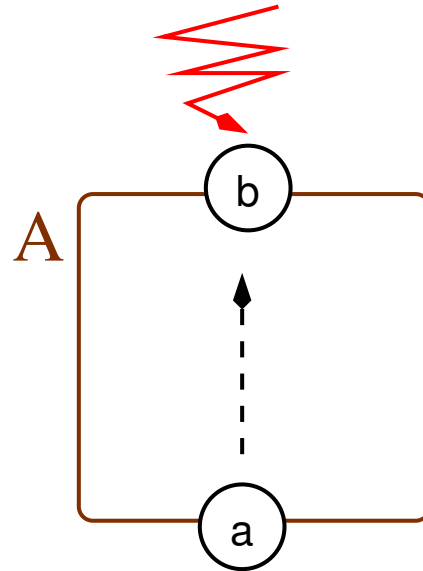


?

Whenever a fragment intersects a lhs on a modified site, the left hand side must be embedded in the fragment.

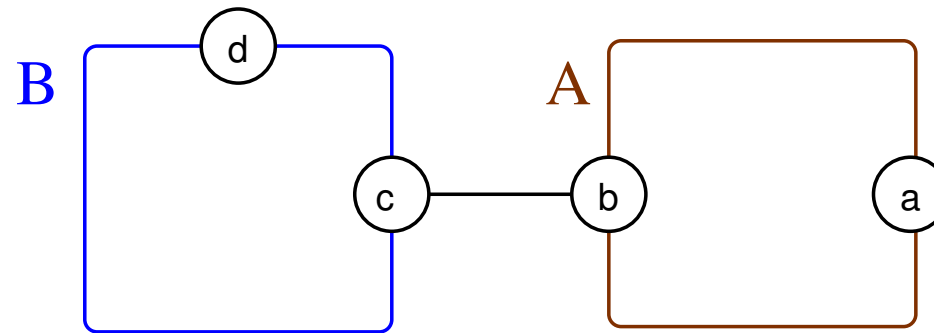
Let us give sufficient syntactic criteria that ensure these last two properties....

Syntactic criteria: backward closure



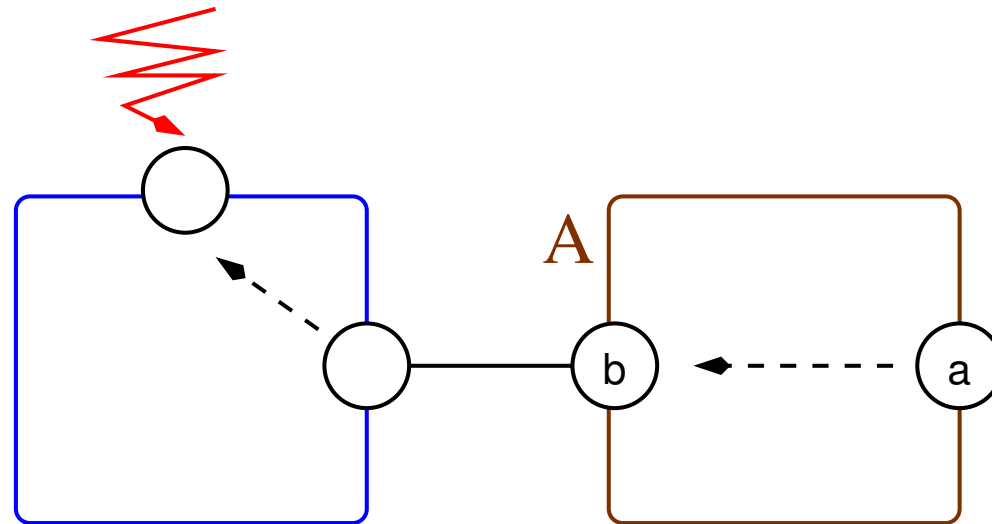
If a rule tests a site a in an agent A and modifies a site b in the same agent A , then any class in $C(A)$ that contains b also contains a .

Syntactic criteria: control pipe



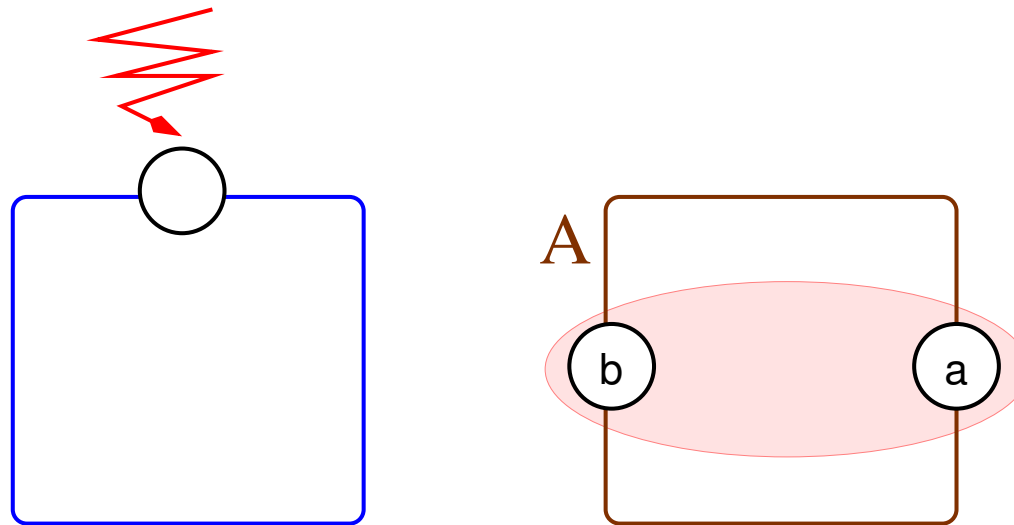
If the left hand side of a rule contains a bond and any other test (either on internal states, or on binding states), then this bond must be solid.

Syntactic criteria: control portal



If a rule tests a site a in an agent A , and A is connected through a site b to an agent that is modified, then any class in $C(A)$ that contains b must also contain a .

Syntactic criteria: remote test



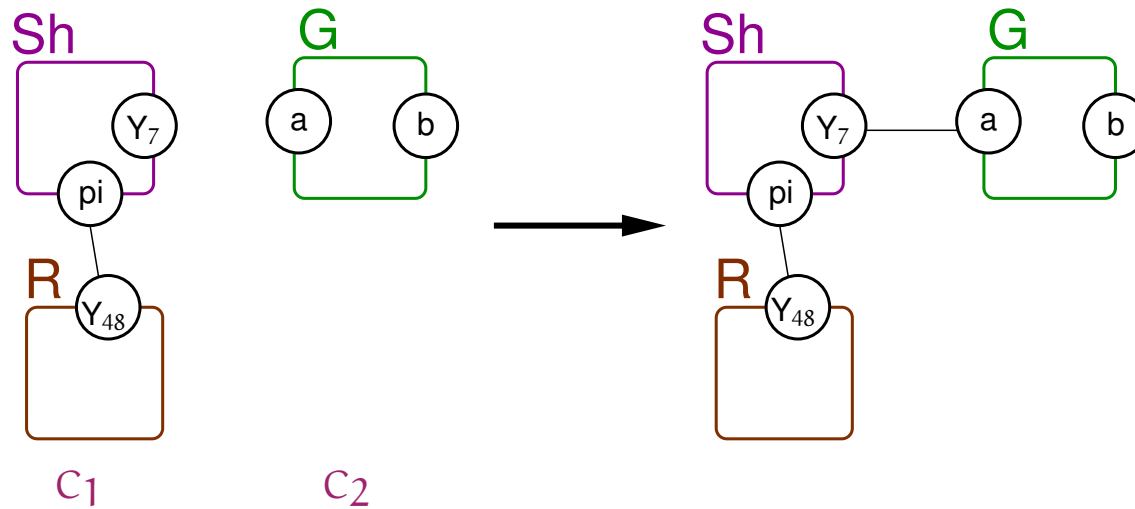
For each agent A in an unmodified pattern component on the lhs of a rule, there must be a class in $C(A)$ that contains the sites tested by the rule.

Overview

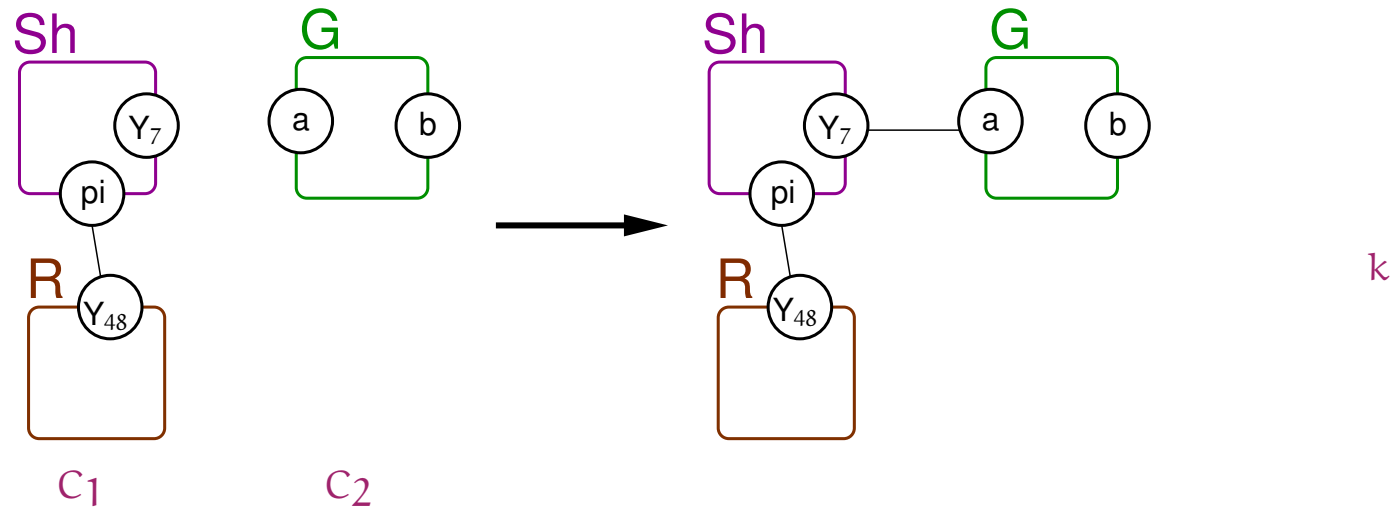
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A binding rule

Let us abstract the contribution of a binding rule:



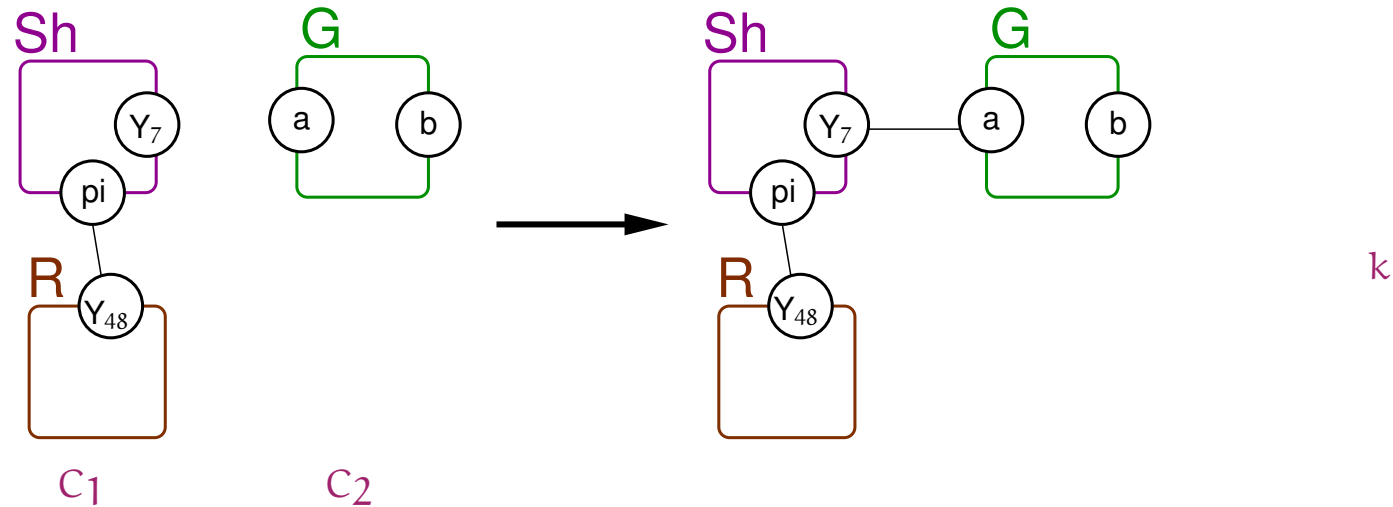
A binding rule: reactants



For any (F, Φ) such that $C_i \triangleleft_{\Phi} F$,

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

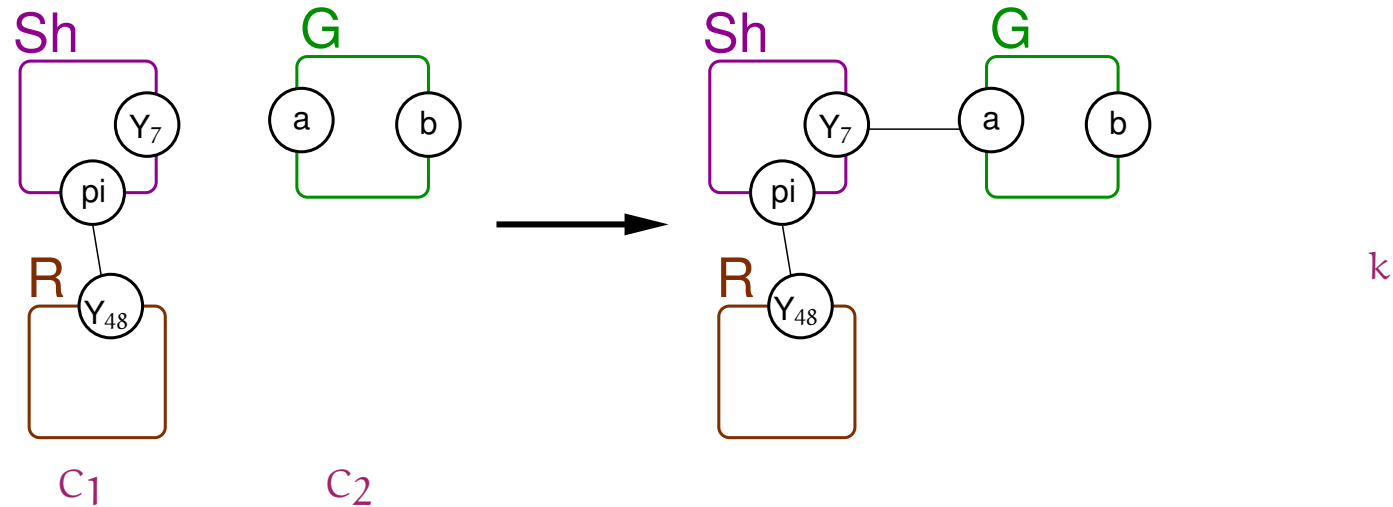
Binding rules: products



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

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

Binding rules: products



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

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

Soundness

If:

1. the annotated contact map satisfies the criteria on slides 50 to 53;
2. the abstraction ψ gives the concentration of fragments, knowing the concentration of species;
3. the abstract dynamic $F^\#$ is defined as in slides 56 to 58.

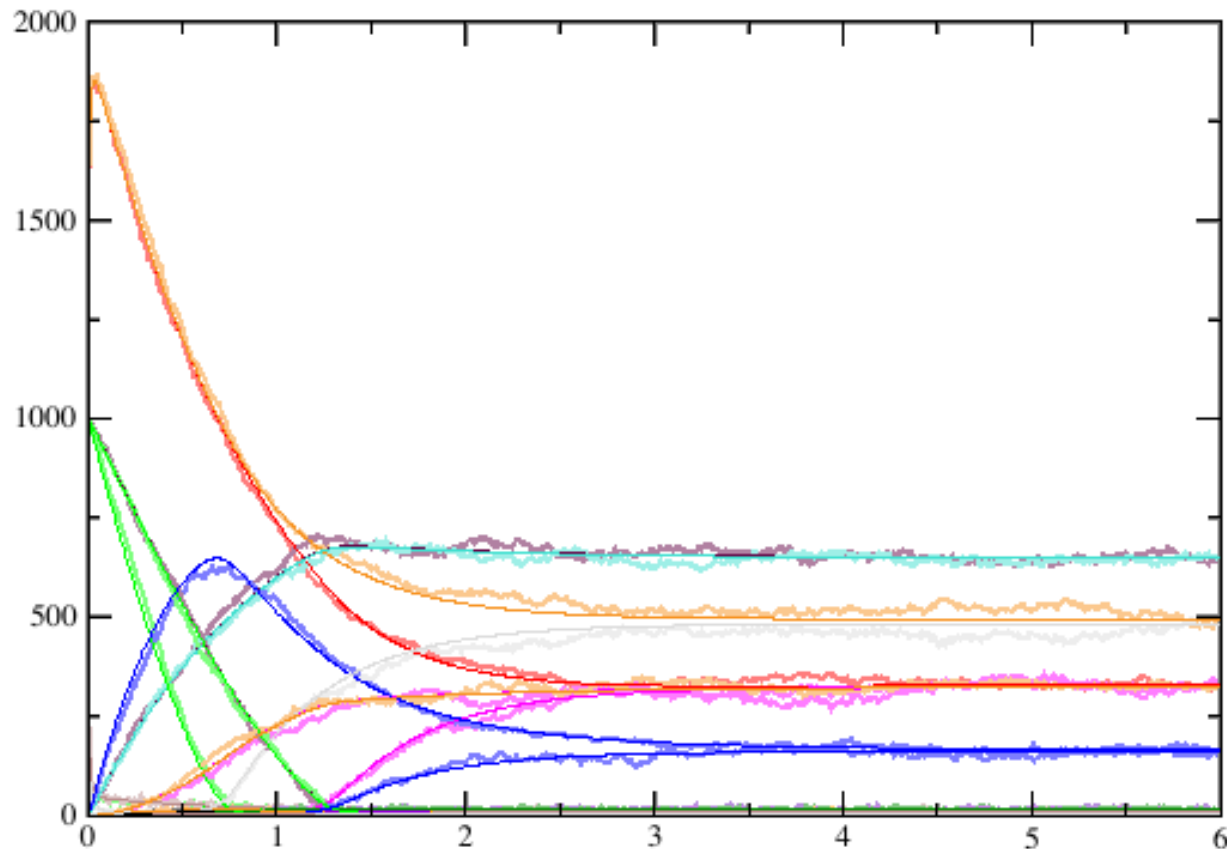
Then, the abstract dynamic $F^\#$ is ψ forward-complete.

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Experimental results

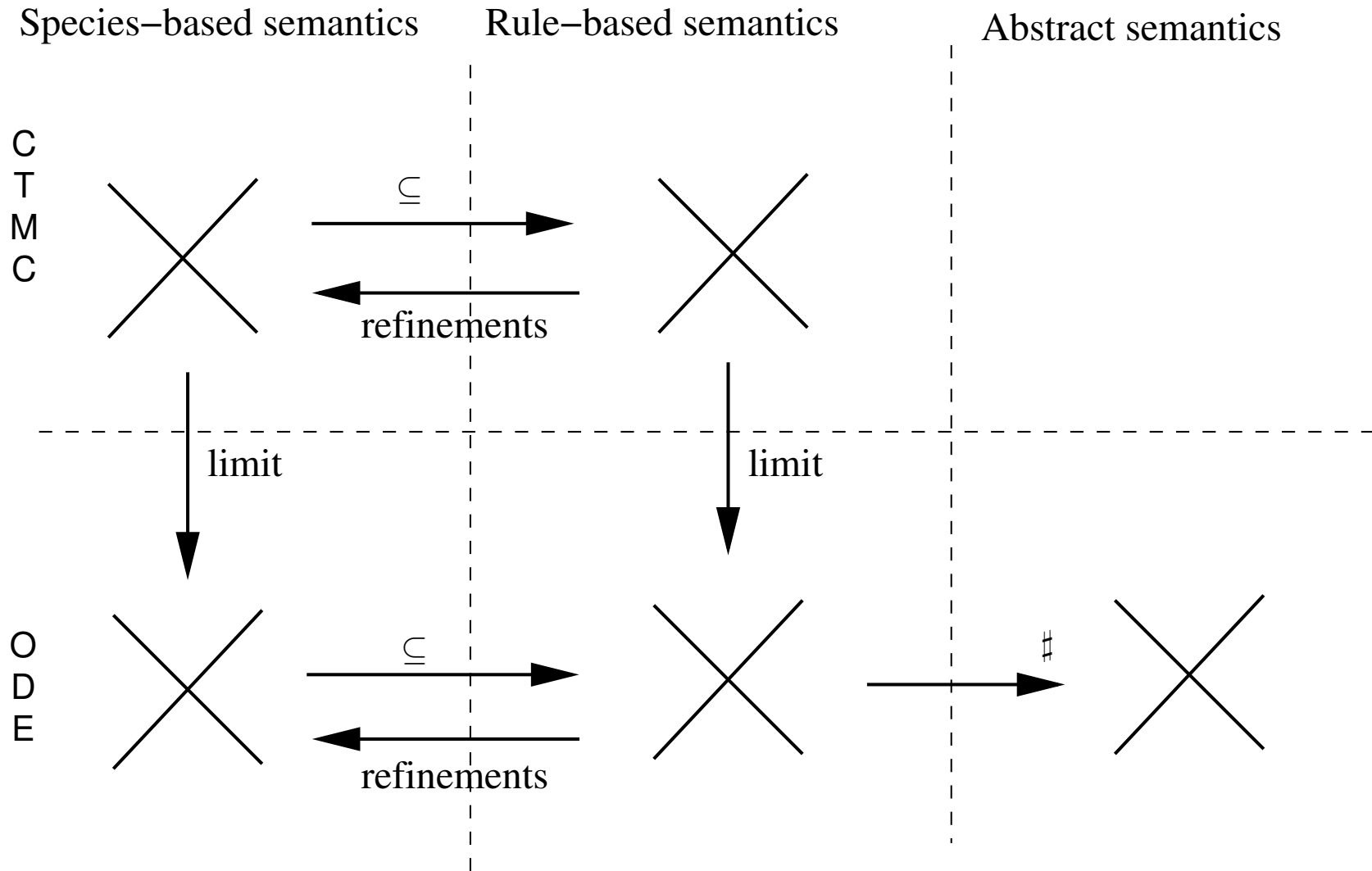
On early egfr, 356 species are simplified into 38 fragments:



Wiggly curves: stochastic semantics.

Steady curves: abstract differential semantics.

Future works I: Semantics comparisons



Future works II: Semantics approximations

1. ODE approximations:

- Independence invariants can be used to relax syntactic criteria.
Can we design hybrid method ?
- Because of the use of annotated contact map, fragments have a homogeneous structure (or signature).
Can we design and use heterogeneous fragments ?

2. Stochastic semantics approximations:

- Can we design abstraction ?
- Find the adequate soundness criteria.