ROSAEC workshop

Second session

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

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

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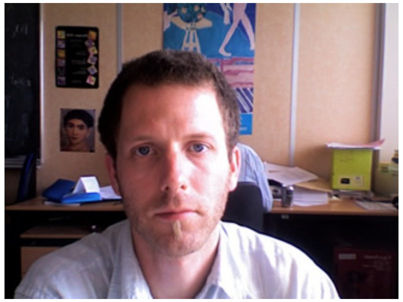
# Joint-work with...

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

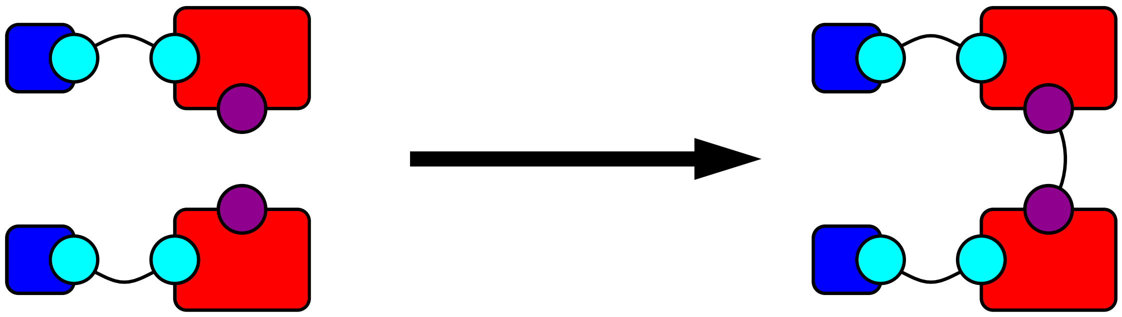
   + can be integrated

   – opaque modelling process, models cannot be modified

There are also some scalability issues.

# Agent-based approach

We use site graph rewrite systems

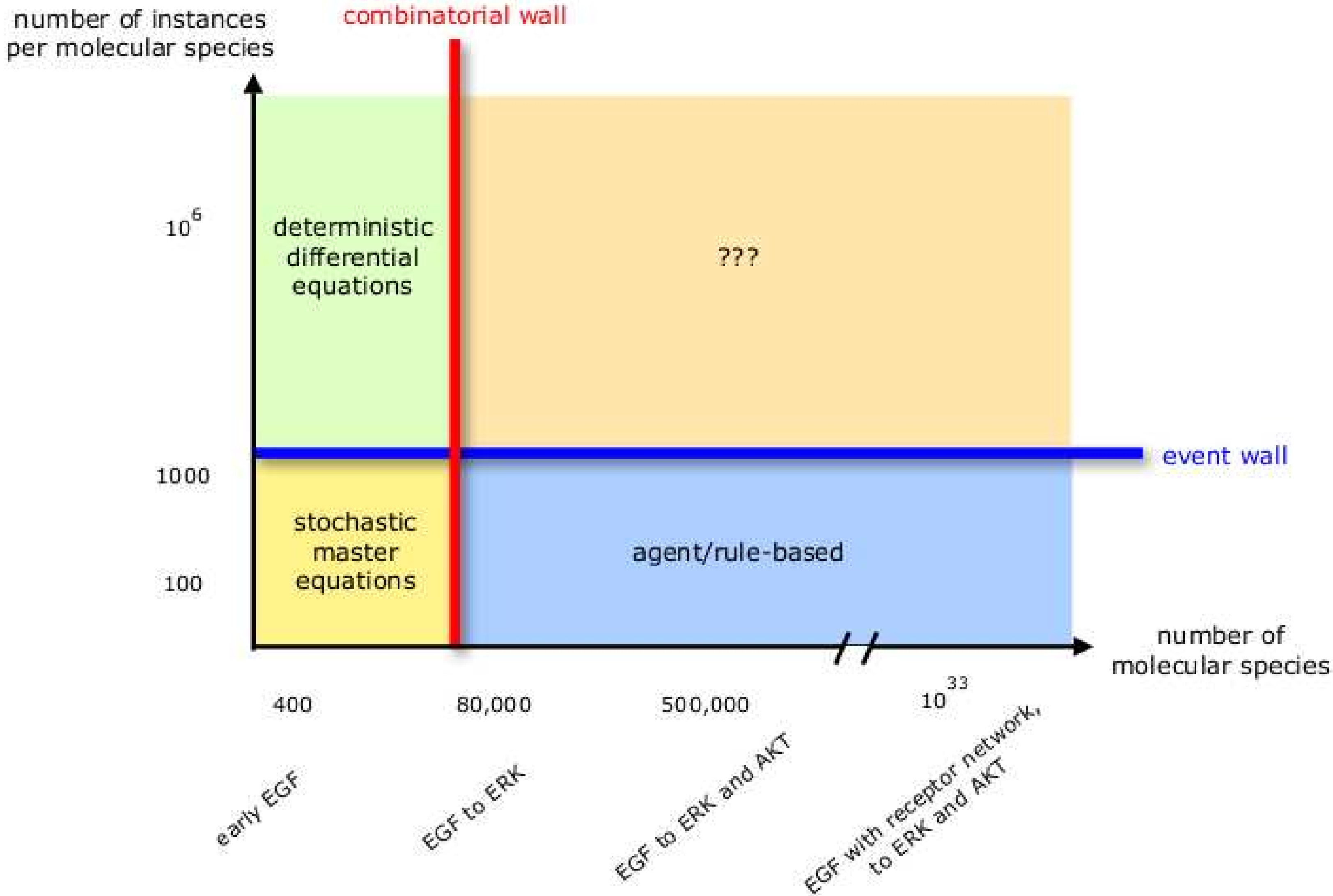


1. The description level matches with both
    - the observation level
    - and the intervention level

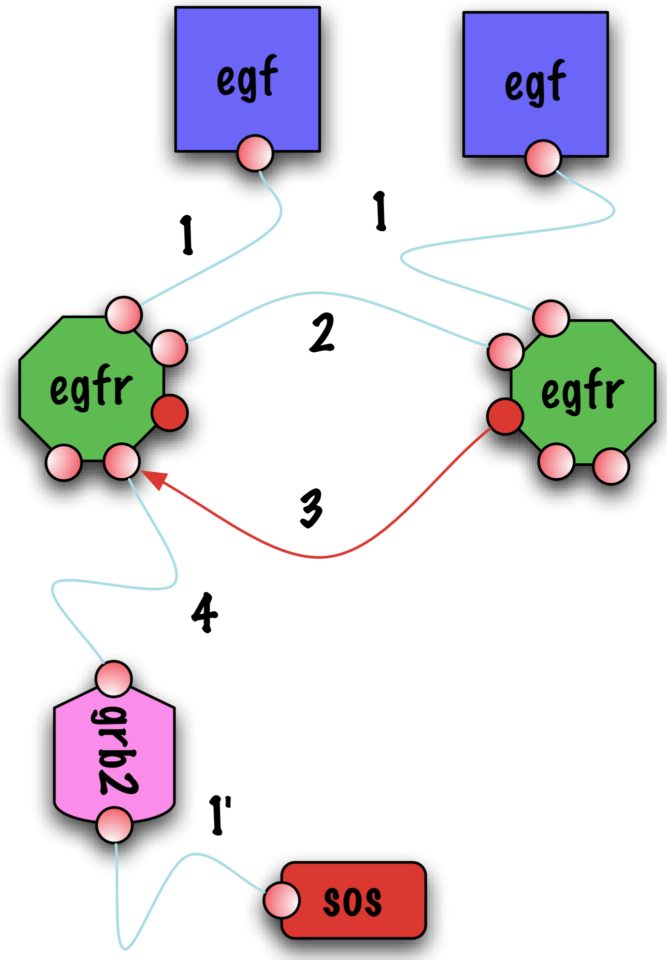
   of the biologist.

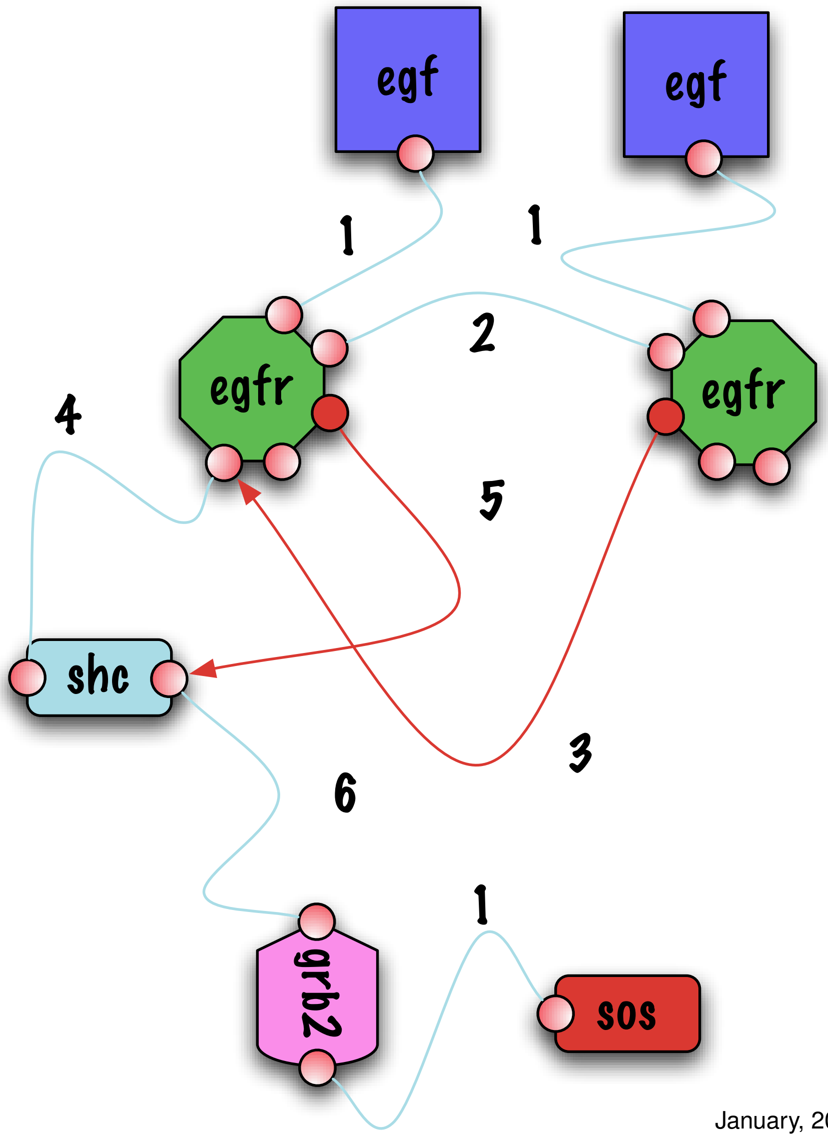
   We can tune the model easily.
2. Model description is very compact.
3. Quantitative semantics can be defined.

# Complexity walls



# A breach in the wall(s) ?



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   (b) Self-consistent subsystems
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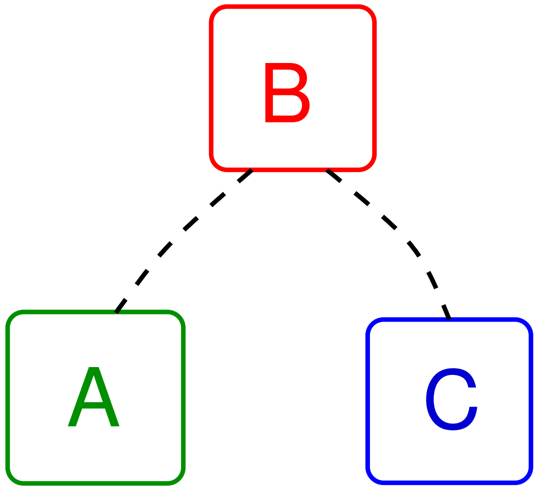
# Case study 1: A simple scaffold



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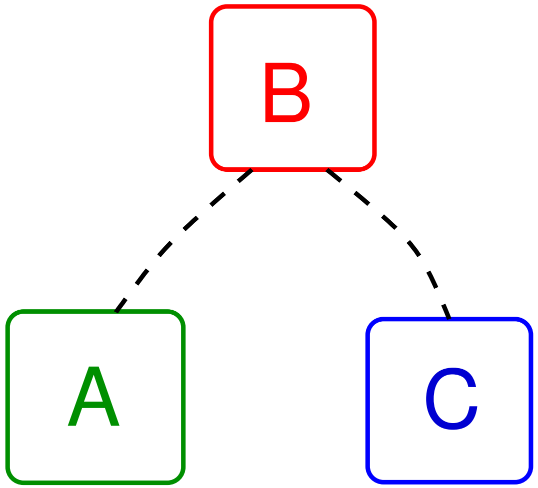
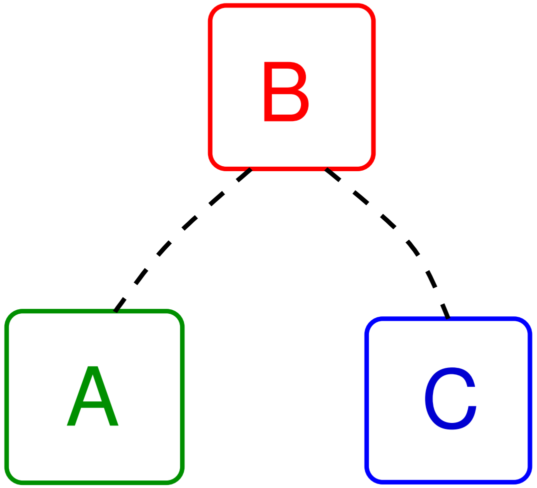



| | | | |
|---|---|---|---|
| A , ∅B∅ | $\longleftrightarrow$ | AB∅ | $k^{AB}, k_d^{AB}$ |
| A , ∅BC | $\longleftrightarrow$ | ABC | $k^{AB}, k_d^{AB}$ |
| ∅B∅ , C | $\longleftrightarrow$ | ∅BC | $k^{BC}, k_d^{BC}$ |
| AB∅ , C | $\longleftrightarrow$ | ABC | $k^{BC}, k_d^{BC}$ |

# Case study 1: A simple scaffold




| | | | |
|---|---|---|---|
| A , ∅B∅ | ⟷ | AB∅ | $k^{AB}, k_d^{AB}$ |
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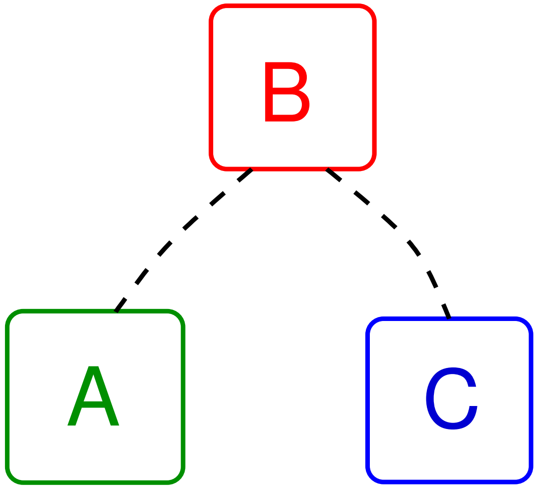
| ∅B∅ , C | ⟷ | ∅BC | $k^{BC}, k_d^{BC}$ |
| AB∅ , C | ⟷ | ABC | $k^{BC}, k_d^{BC}$ |

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

# Case study 1: Two subsystems



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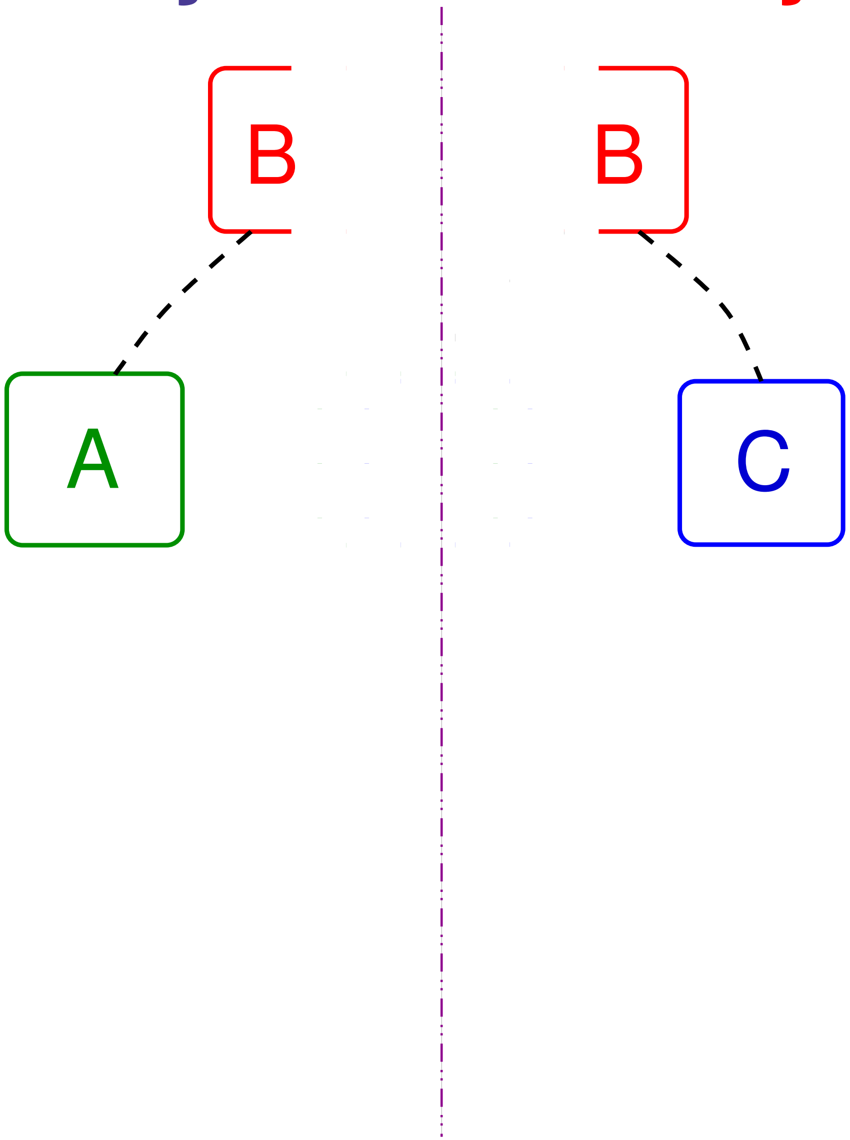
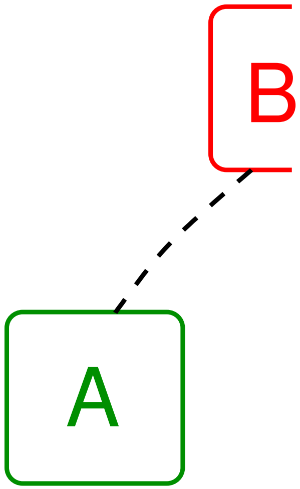


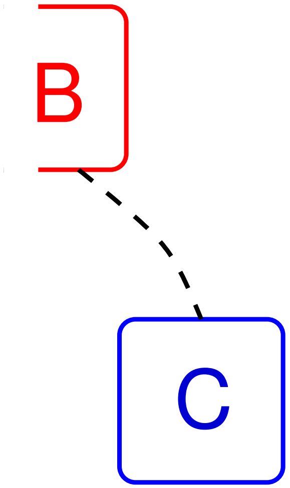
# Case study 1: Two subsystems




$$[AB?] \triangleq [AB\emptyset] + [ABC]$$

$$[\emptyset B?] \triangleq [\emptyset B\emptyset] + [\emptyset BC]$$

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




$$[?BC] \triangleq [\emptyset BC] + [ABC]$$

$$[?B\emptyset] \triangleq [\emptyset B\emptyset] + [AB\emptyset]$$

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

# 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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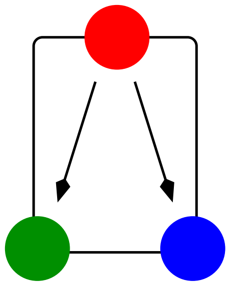
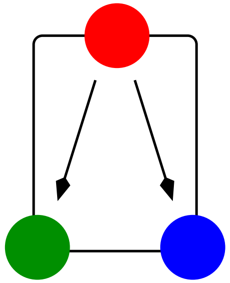
# Case study 2: A system with a switch

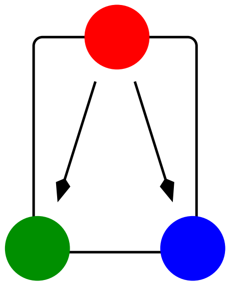


# Case study 2: A system with a switch



| | | | |
|---|---|---|---|
| (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) | $k^r$ |

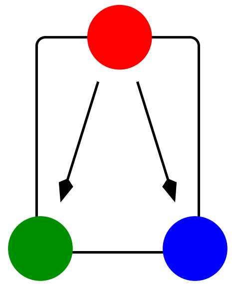
# Case study 2: A system with a switch



| | | | |
|---|---|---|---|
| (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) | $k^r$ |

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

# Case study 2: Two subsystems



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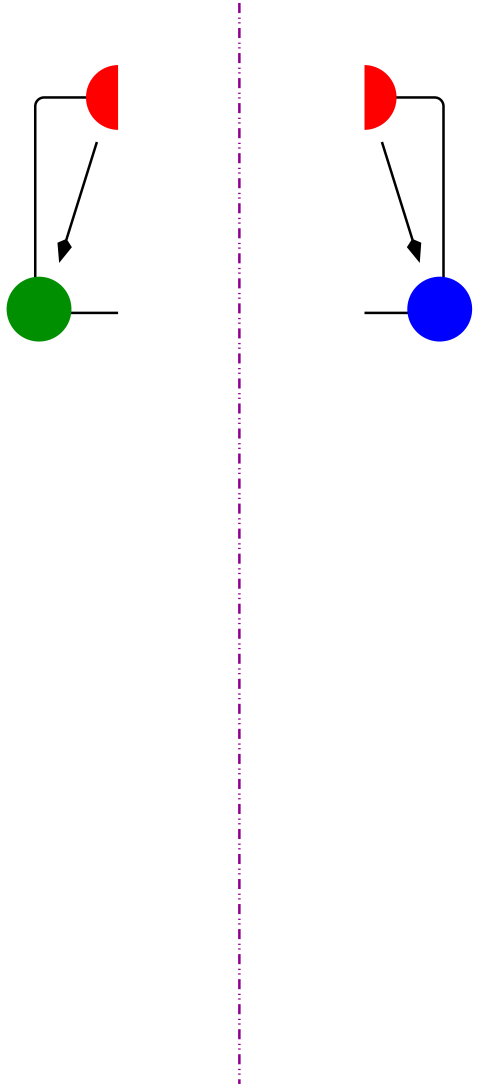

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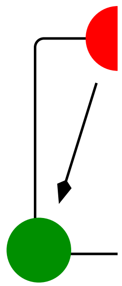
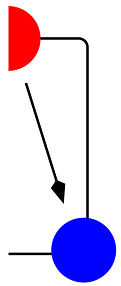


$$[(u,p,?)] \triangleq [(u,p,u)] + [(u,p,p)]$$

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

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



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

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

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

# 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:

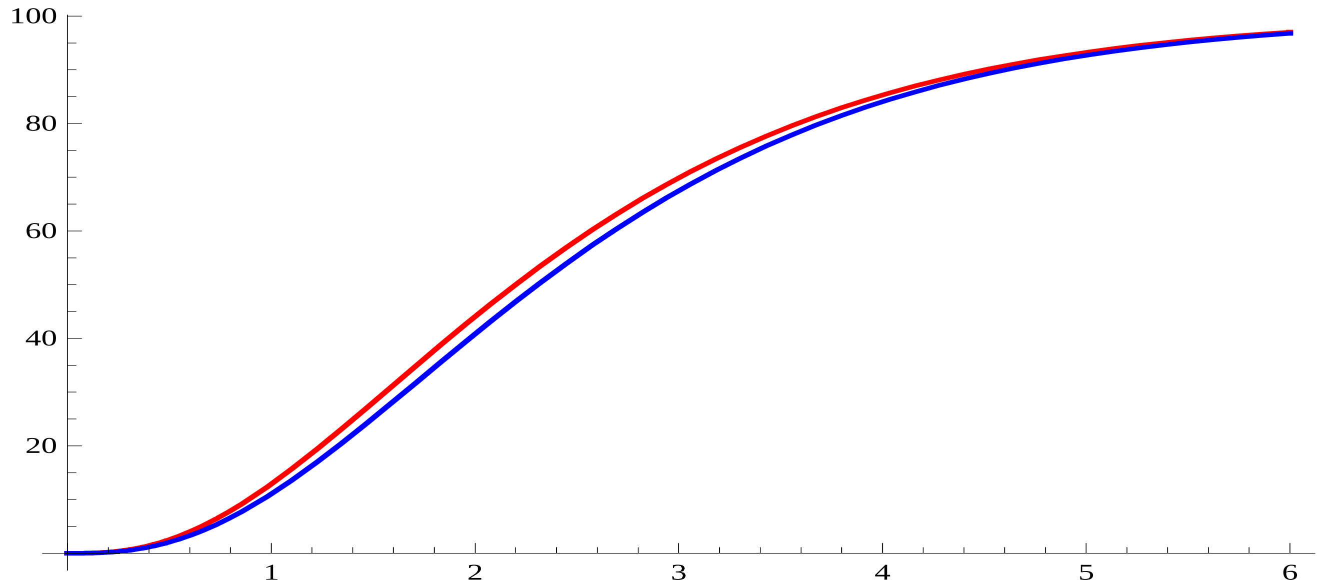
$$X \stackrel{\Delta}{=} [(p,p,p)]\cdot[(?,p,?)] - [(?,p,p)]\cdot[(p,p,?)].$$

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 ($[(u,u,u)](0) = 100$).

$[(p,p,p)]$ 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 $\mathcal{C}^\infty$ mapping from $\mathcal{V} \rightarrow \mathbb{R}^+$ into $\mathcal{V} \rightarrow \mathbb{R}$.

as for instance,

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

we can define the continuous differential semantics as follows:

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

# Abstraction

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

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

such that:

- $\psi$ is linear with positive coefficients,
- $\mathbb{F}^\sharp$ is $\psi$forward-complete
  i.e. the following diagram commutes:

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

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

# Abstraction example

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

(Forward completeness can be checked analytically.)

# Abstract continuous trajectories

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

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

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

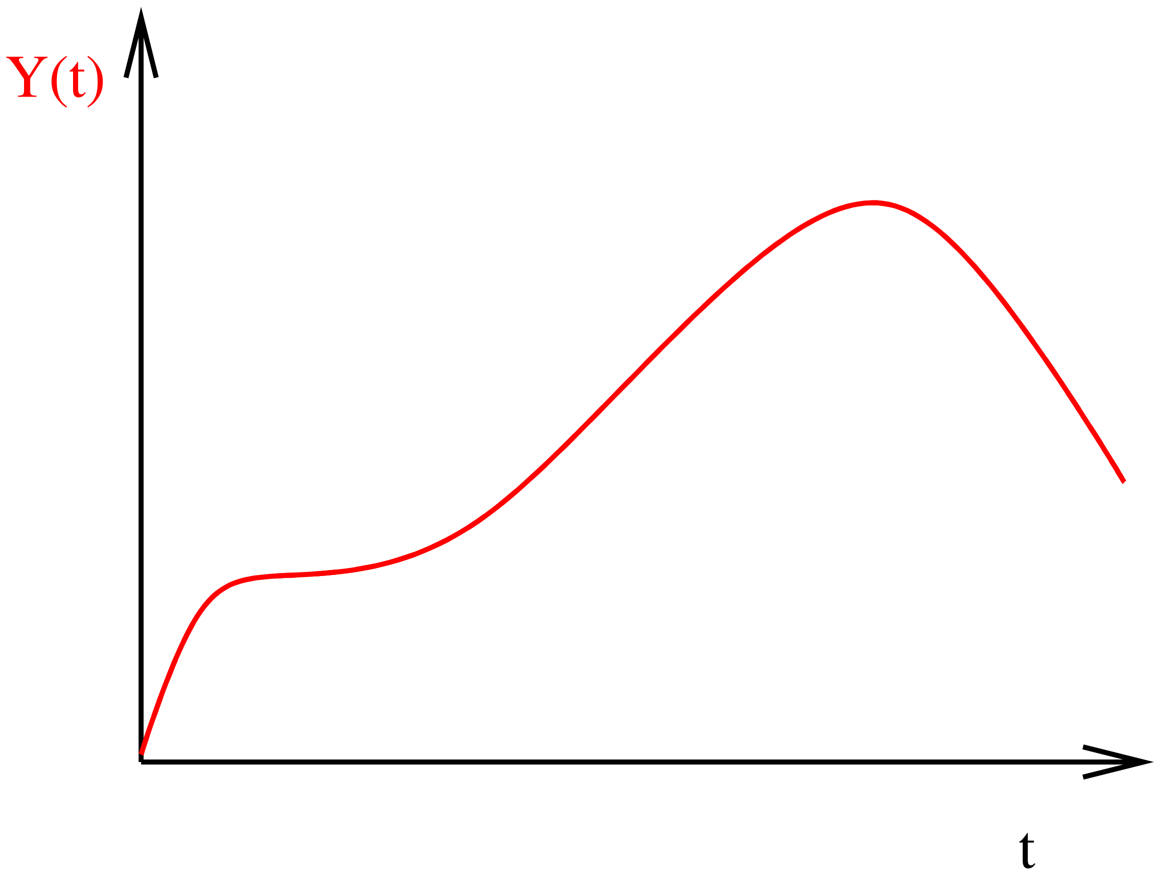
$$\psi\left(X_c(X_0, T)\right) = \psi(X_0) + \int_{t=0}^{T} \mathbb{F}^\sharp\left(\psi\left(X_c(X_0, t)\right)\right) \cdot dt \quad (\mathbb{F}^\sharp \text{ is } \psi \text{forward-complete})$$

We set $Y_0 \stackrel{\Delta}{=} \psi(X_0)$ and $Y_c \stackrel{\Delta}{=} \psi \circ X_c$.

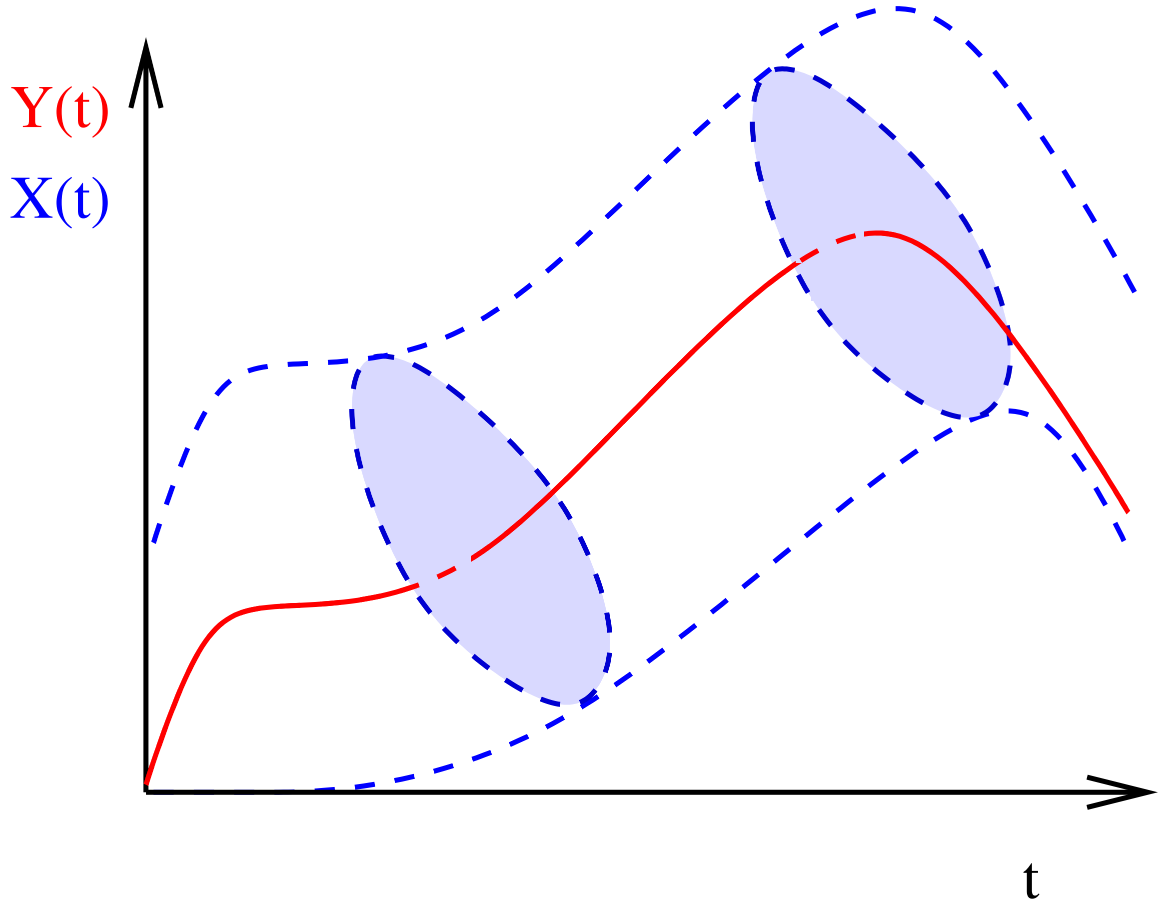
Then we have:

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

# Fluid trajectories

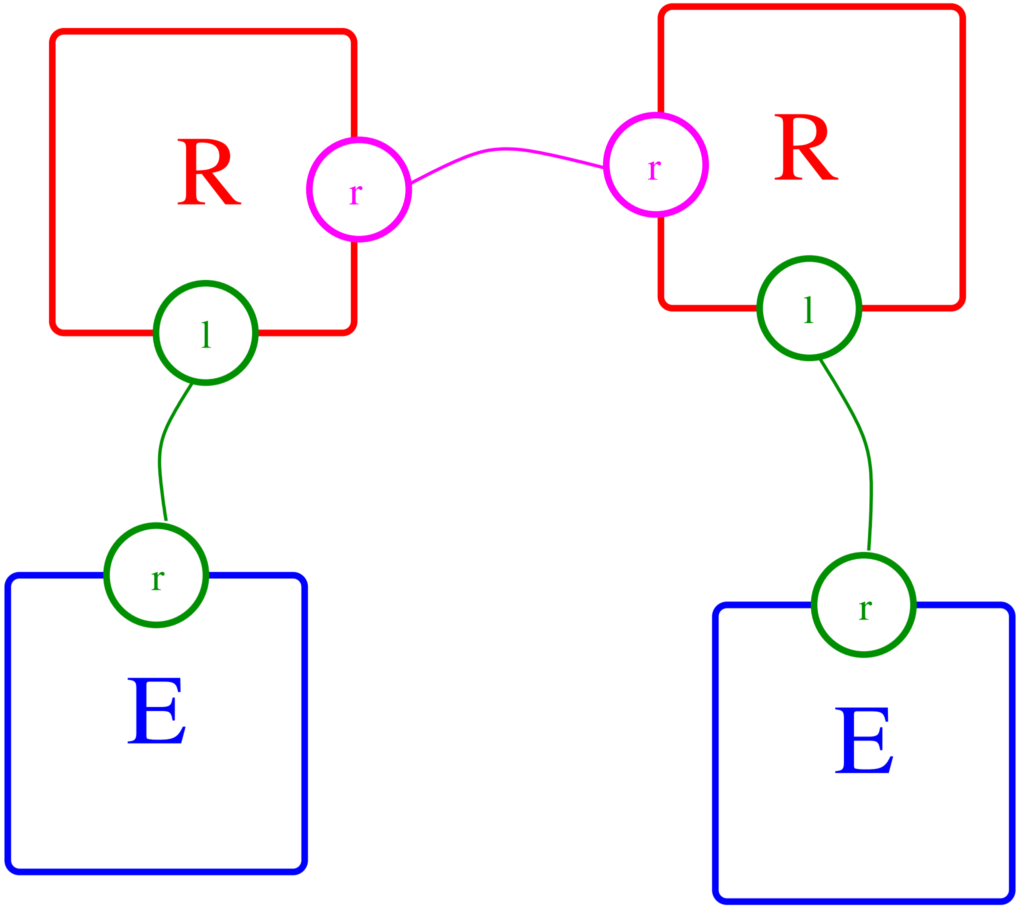


# Fluid trajectories



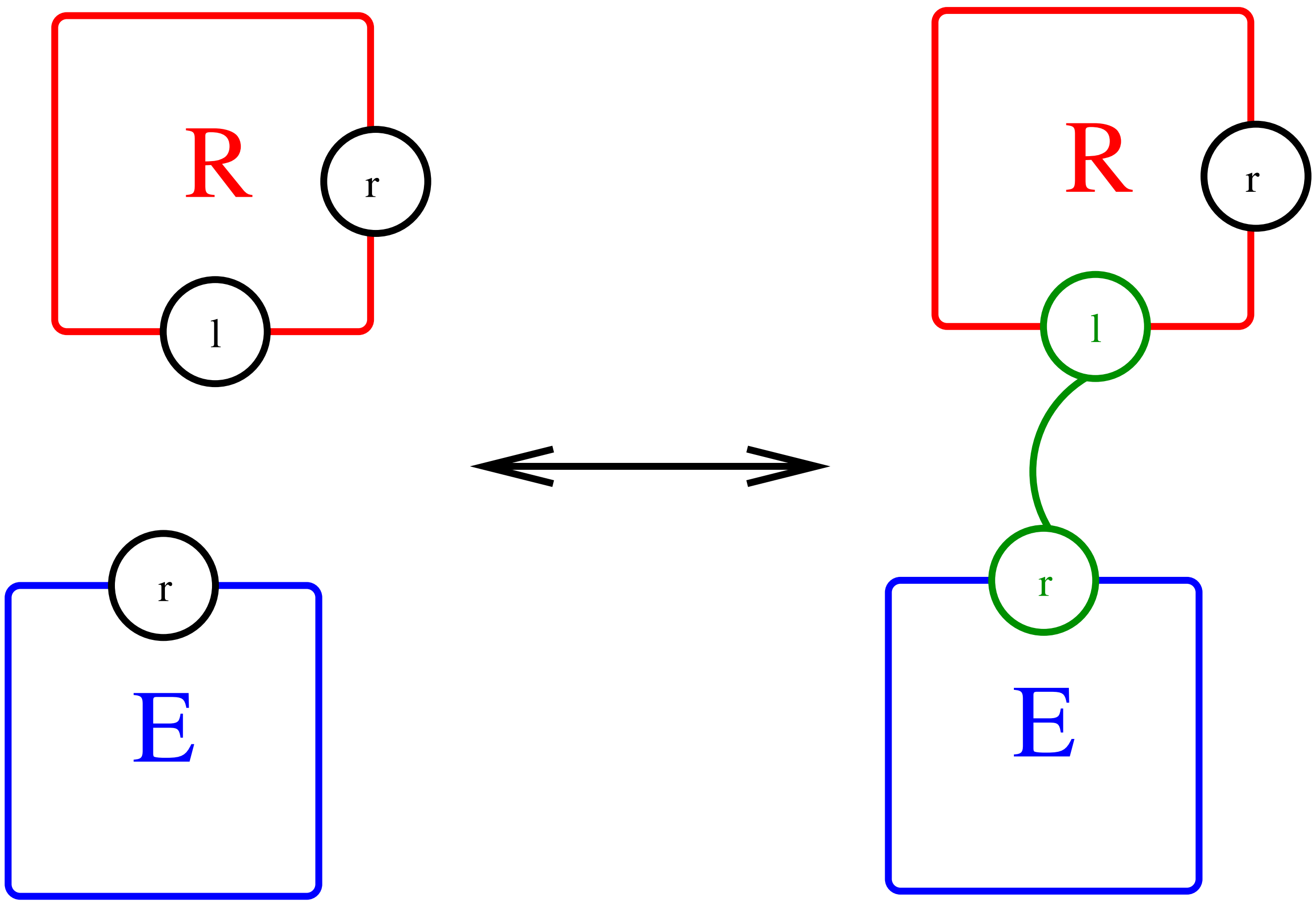
# Overview

# A species



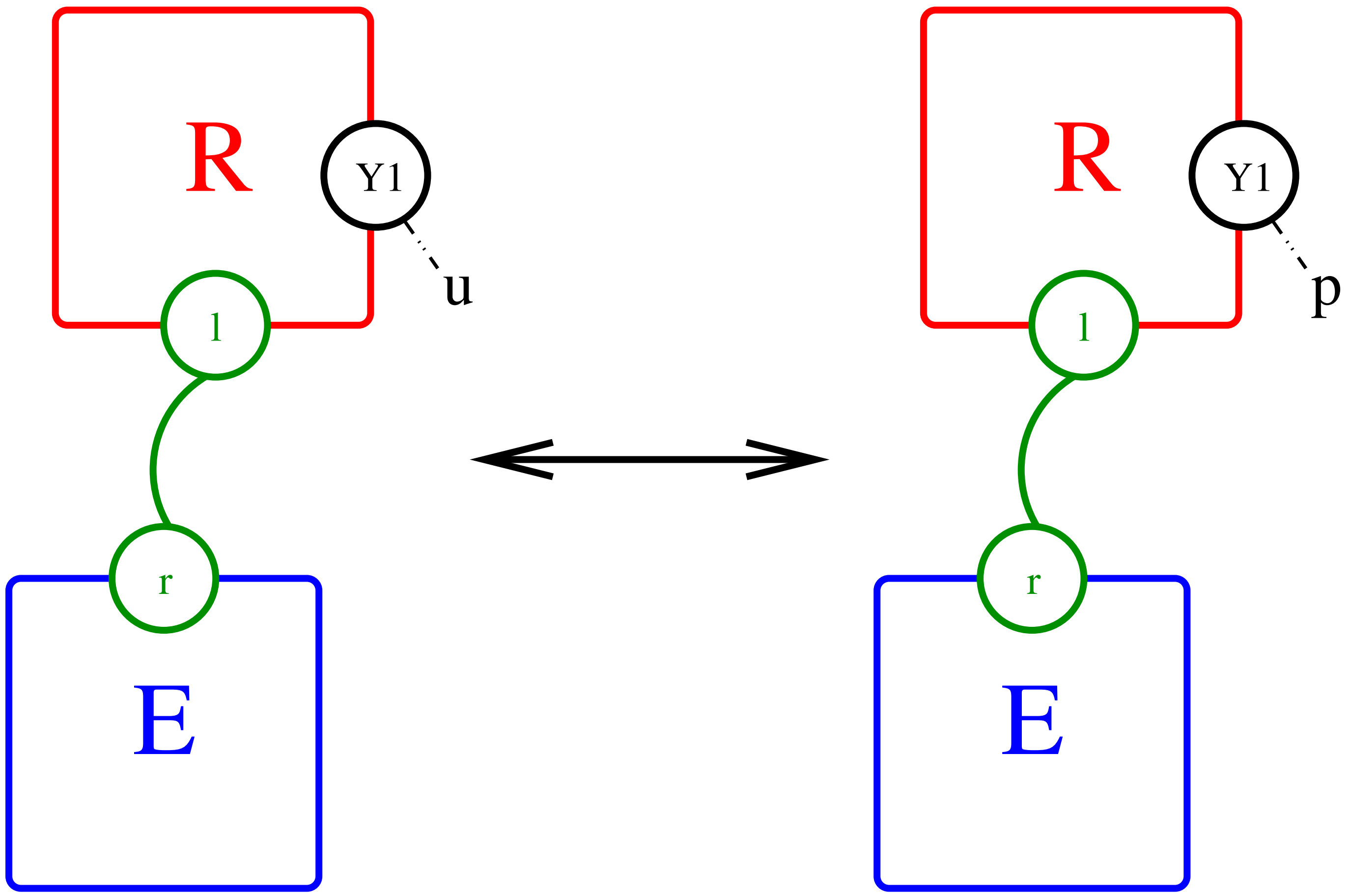

E(r!1), R(l!1,r!2), R(r!2,l!3), E(r!3)

# A unbinding/binding Rule



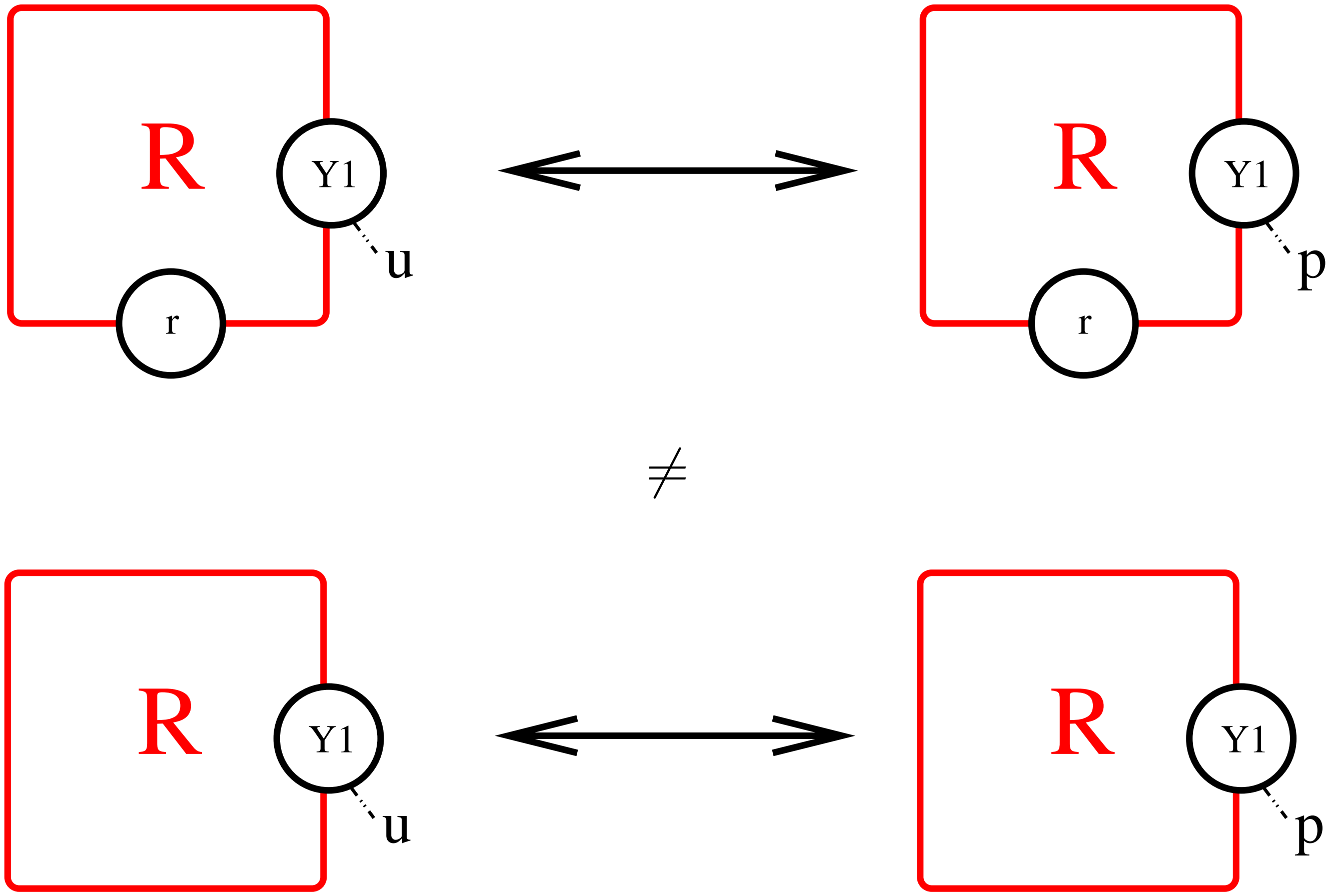

E(r), R(l,r) $\longleftrightarrow$ E(r!1), R(l!1,r)

# Internal state

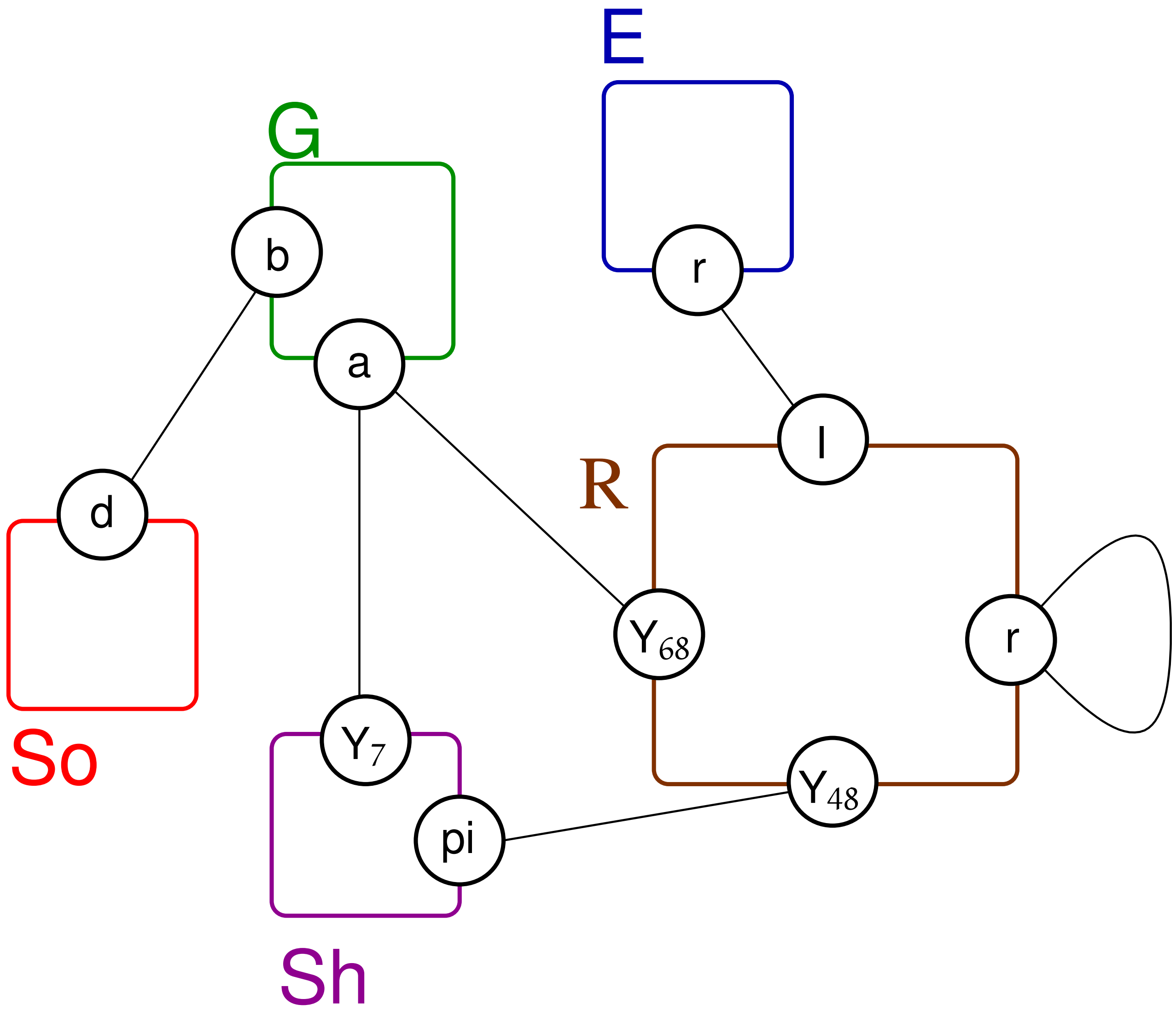



R(Y1~u,l!1), E(r!1) $\longleftrightarrow$ R(Y1~p,l!1), E(r!1)

# Don’t care, Don’t write



# Contact map



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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 $\mathcal{R}$;

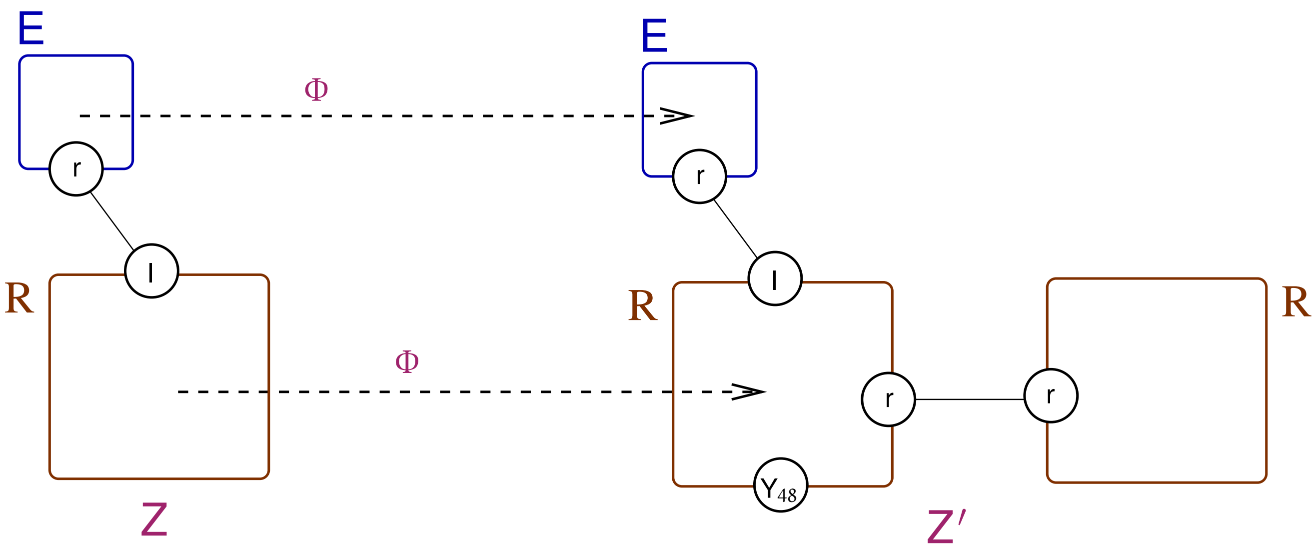
2. Rules are associated with kinetic factors

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

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

     where *arity* is the number of connected components in the lhs;
   - we assume that there are no arity mismatch.

# Embedding




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

- $\Phi$ 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 $(\Phi(i'), s')$.
- $\Phi$ is an into map (injective):
  - $\Phi(i) = \Phi(i')$ implies that $i = i'$.

# Differential system

Let us consider a rule *rule*:

$$\textit{lhs} \rightarrow \textit{rhs} \quad k.$$

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 $(r_i, \Phi i)$ such that $\forall i, r_i \in \mathcal{R}$ and $C_i \lhd_{\Phi i} r_i$.
3. The ground instantiation can be written as follows:

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

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

$$\textit{act}_{(r_i,\Phi i)} = \frac{k \cdot \prod [r_i]}{\sharp\{\Phi \mid \textit{lhs} \lhd_\Phi \textit{lhs}\}}.$$

5. Each ground instantiation induces the following contributions:

$$\frac{d[r_i]}{dt} \stackrel{+}{=} -\textit{act}_{(r_i,\Phi i)}, \qquad \frac{d[p_i]}{dt} \stackrel{+}{=} \textit{act}_{(r_i,\Phi i)}.$$

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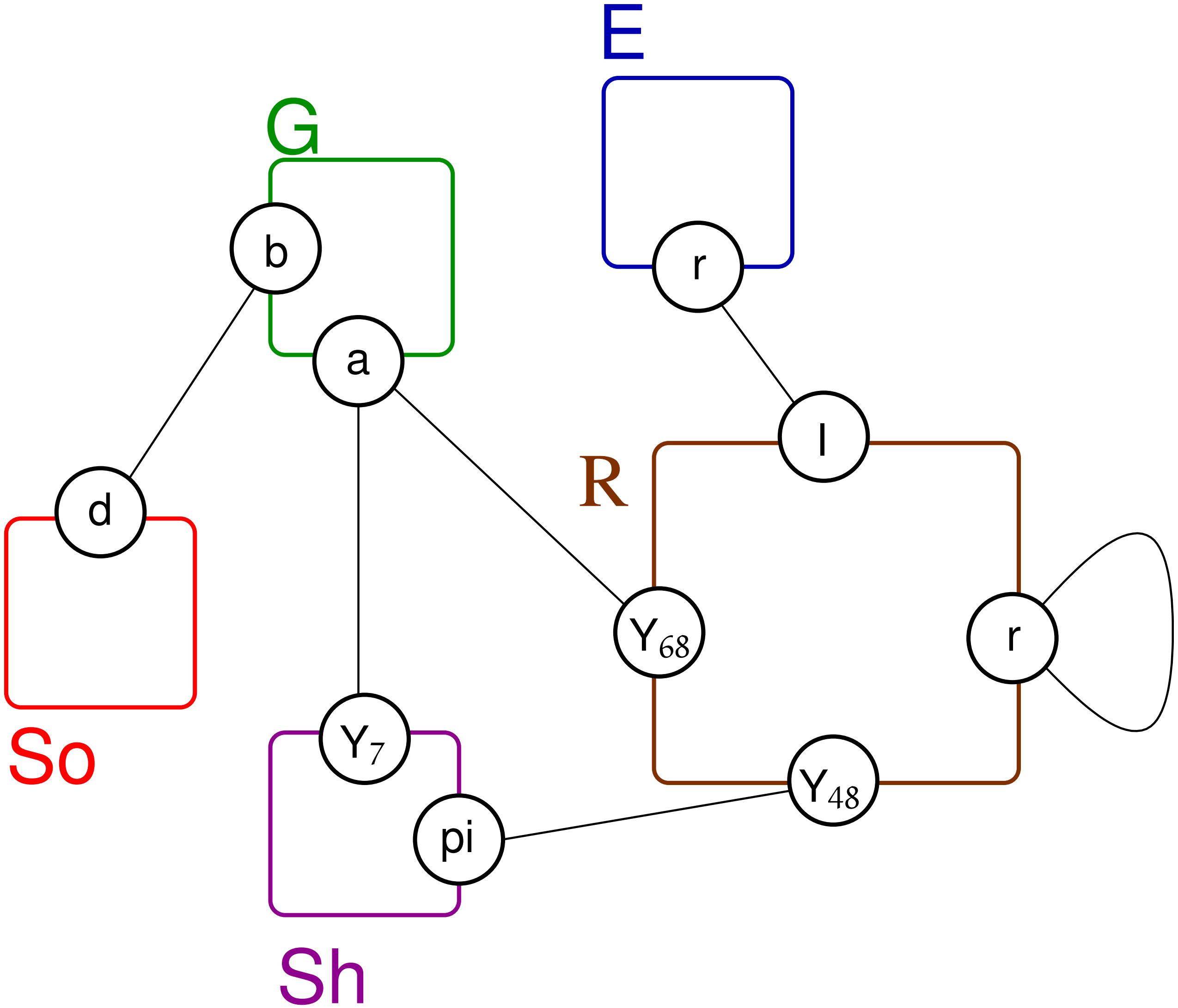
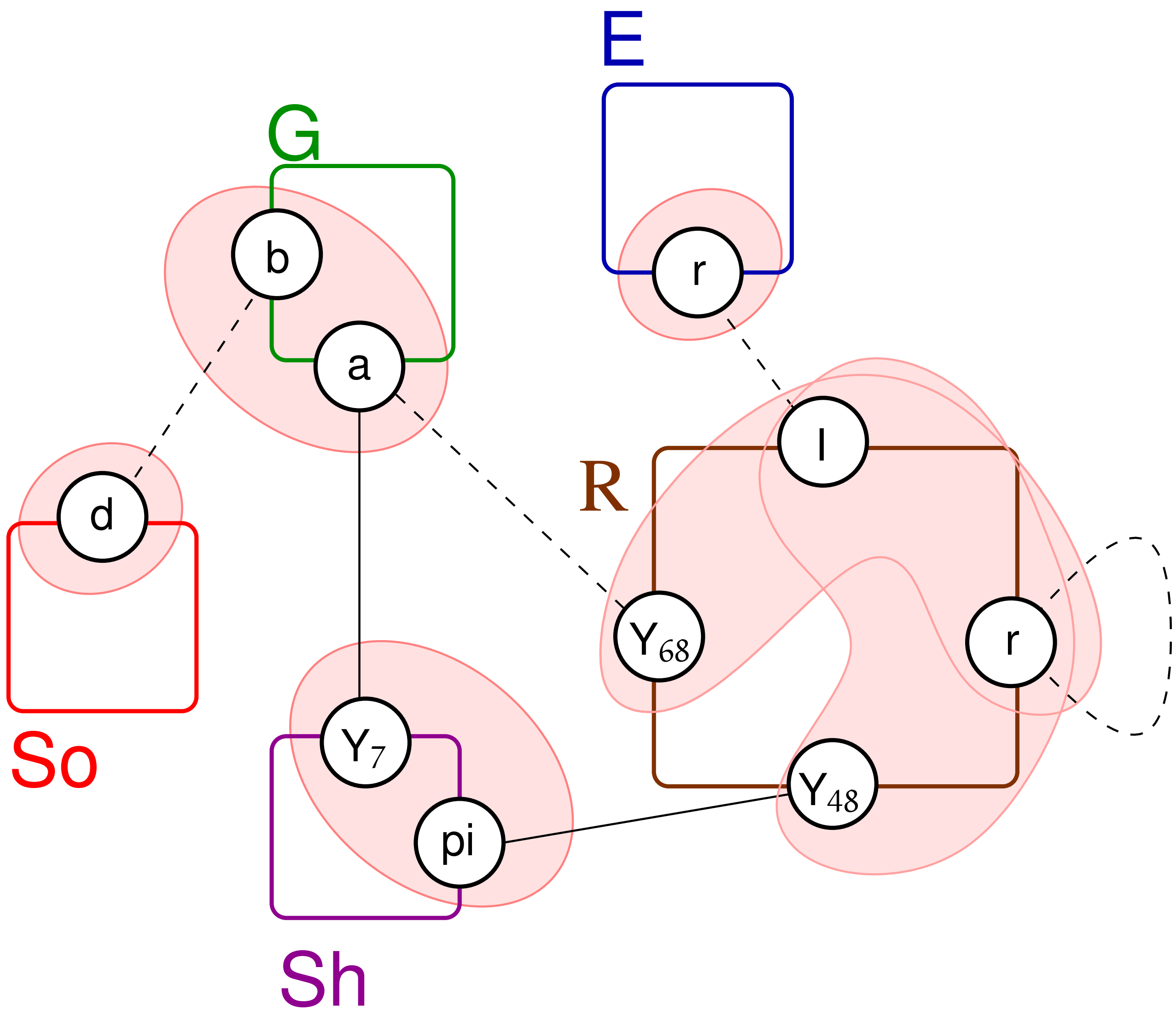
# Contact map



# Annotated contact map



# Annotated contact map

An annotation of the contact map is given by:

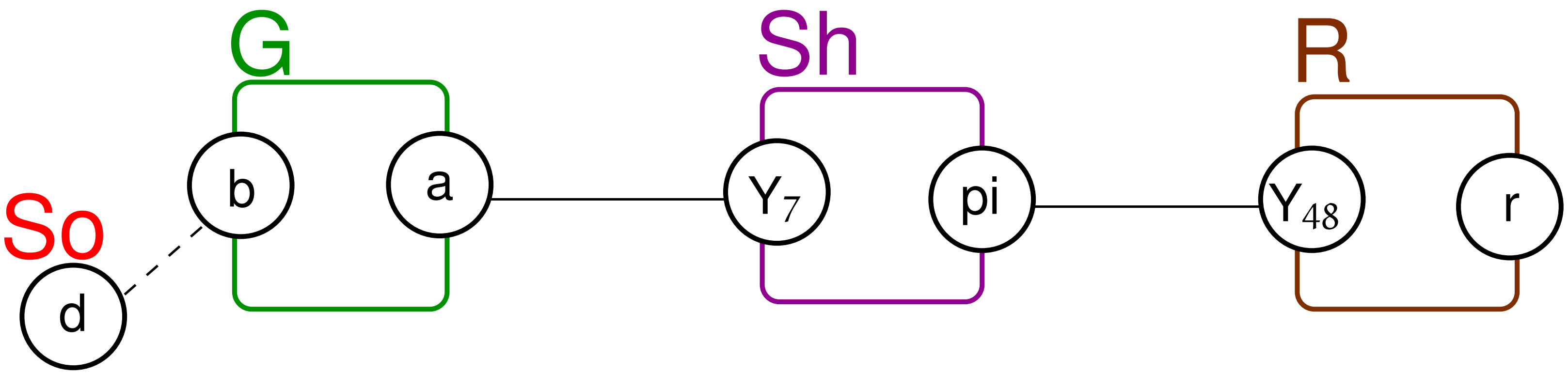
1. a set of dotted edges (other edges are solid),
2. and, for each agent type $A$, a parsimonious covering $C(A) \in \wp(\Sigma(A))$ of the set of sites of $A$, i.e. :
   (a) $\emptyset \notin C(A)$,
   (b) $\bigcup C(A) = S$,
   (c) for all $c_1, c_2 \in C(A)$, $c_1 \neq c_2$ implies that $c_1 \not\subseteq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



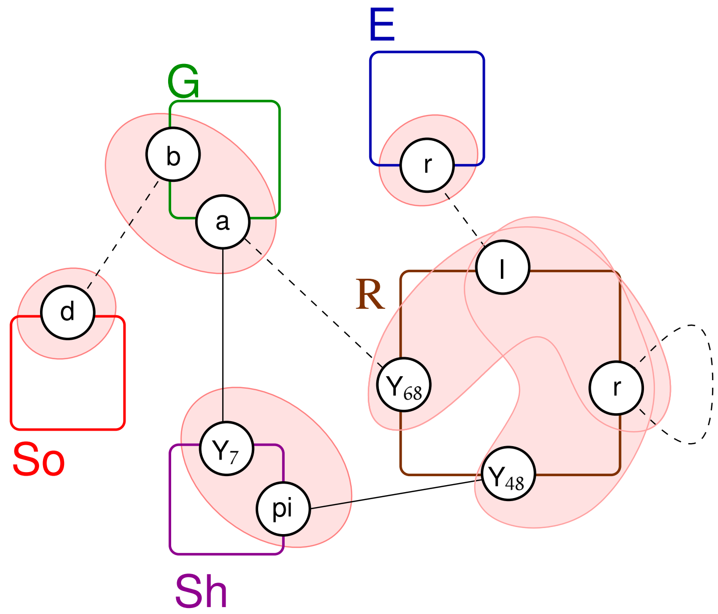

G(b!d.So,a!1),Sh($Y_7$!1,pi!2),R($Y_{48}$!2,r)

# Fragment definition

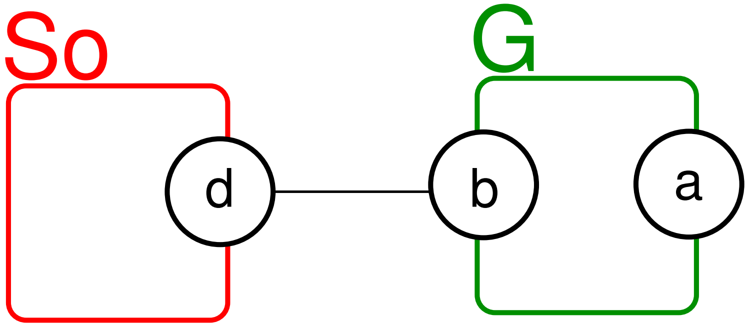
A fragment is a partial species such that:

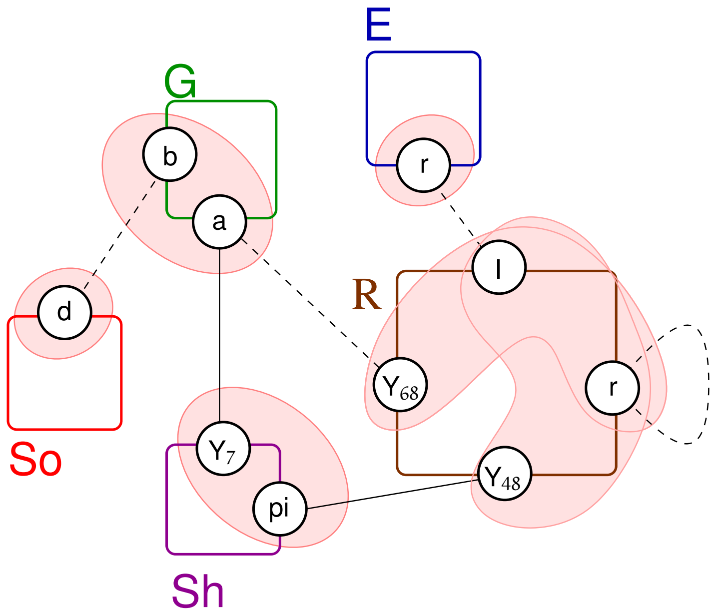
1. for any agent of type $A$, the set of sites is a class in $\mathcal{C}(A)$;
2. for any binding type $A(x!y.B)$, the edge between the site $x$ of $A$ and the site $y$ and $B$ in the contact map is dotted;
3. for any bond $A(x!1), B(y!1)$, the edge between the site $x$ of $A$ and the site $y$ and $B$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

# Are they fragments ?

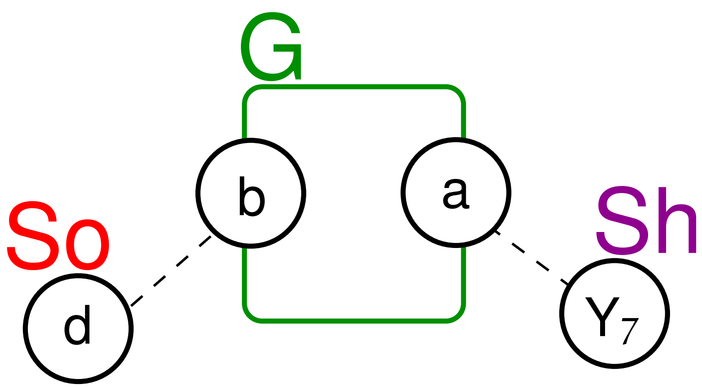


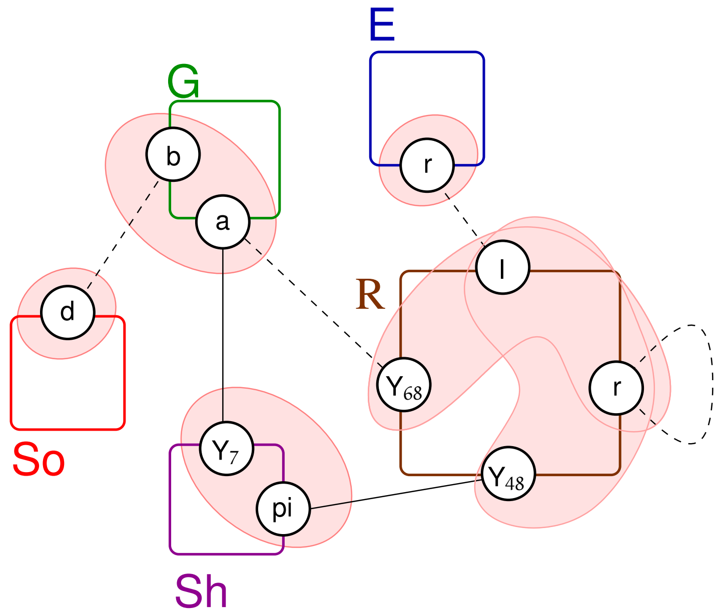
# Are they fragments ?



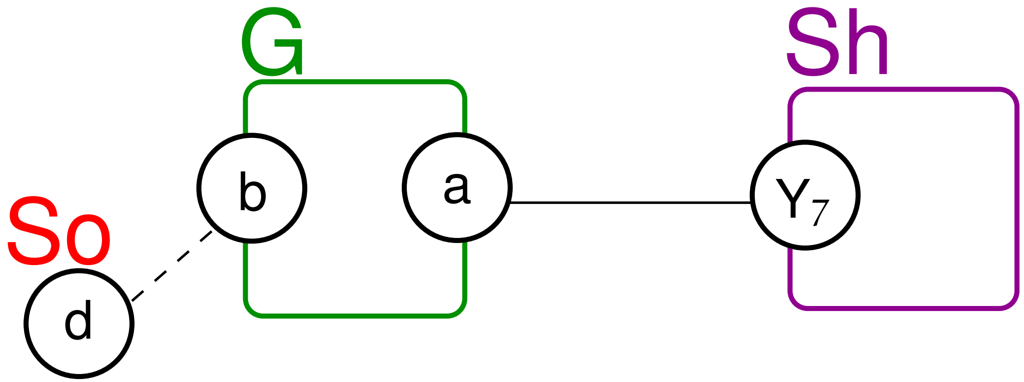



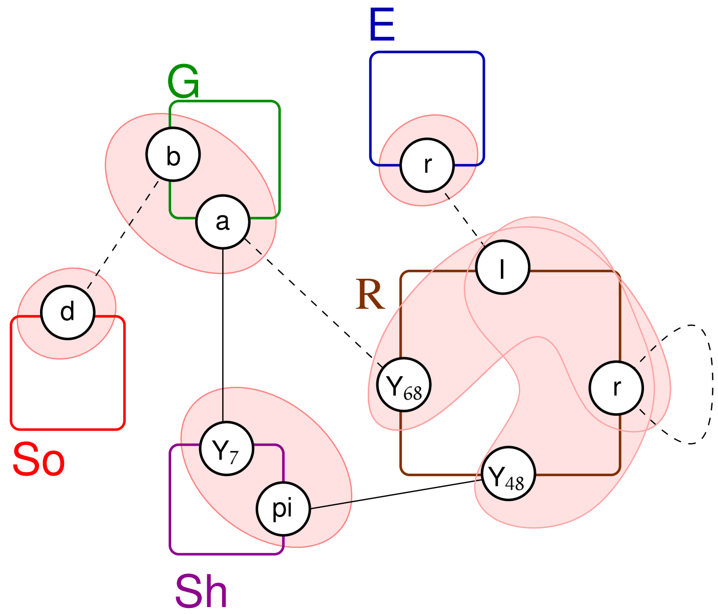
# Are they fragments ?



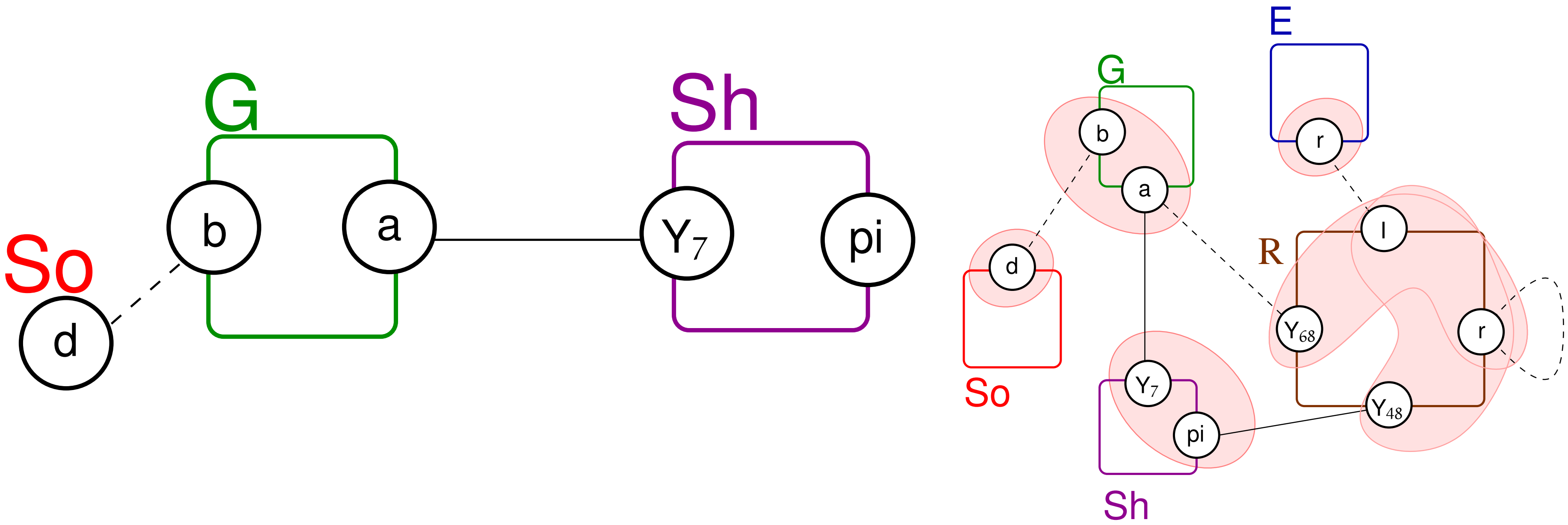



# Are they fragments ?

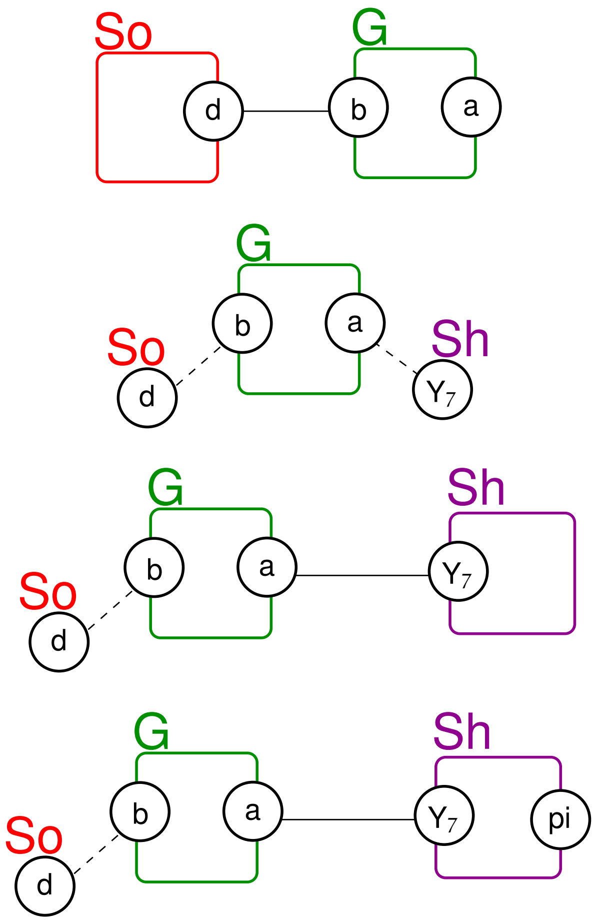


# Are they fragments ?



# Are they fragments ?

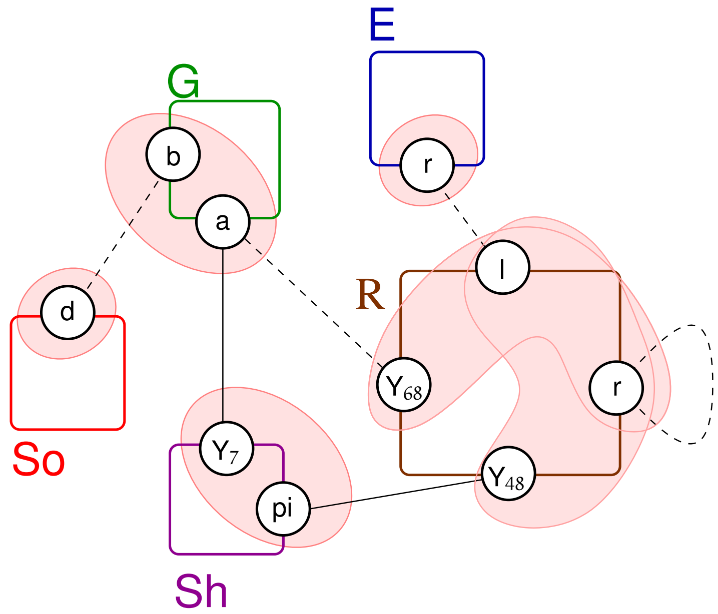



no

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 $\mathbb{F}^\sharp$ can be defined ?

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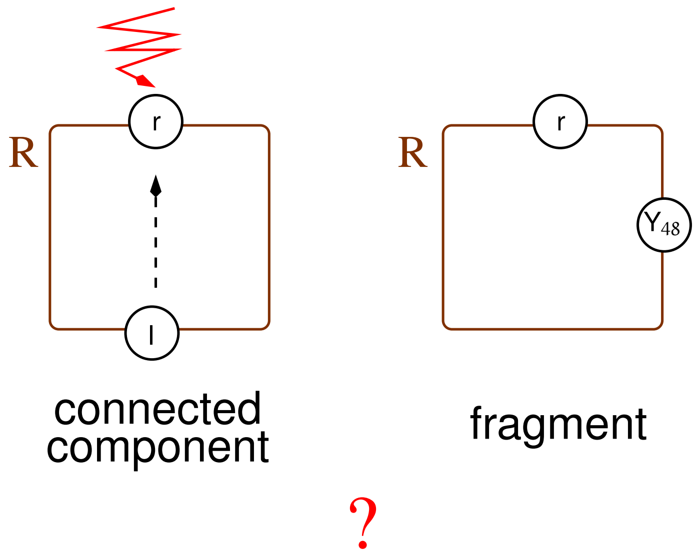
# Two more requirements

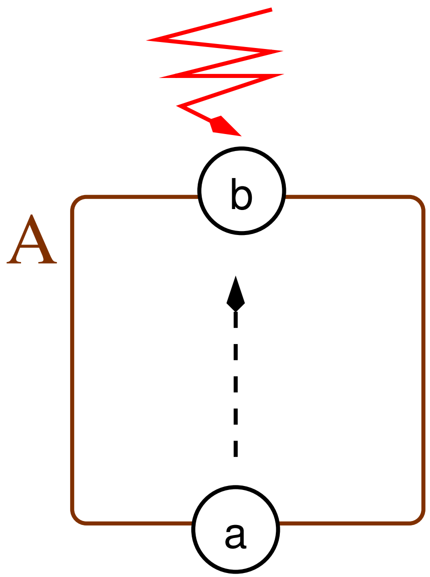
1. We must compute the concentration of any lhs connected component:
   Any connected component of a lhs must be embedded in a fragment.
2. When a fragment is modified, we need to compute how the activity of the rule is distributed between this fragment and the others.




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

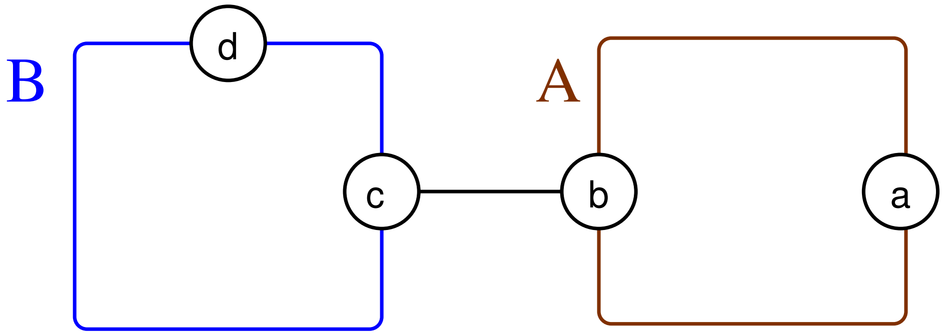
Let us give sufficient syntactic criteria that ensure these last two properties. . . .

# Syntactic criteria: backward closure



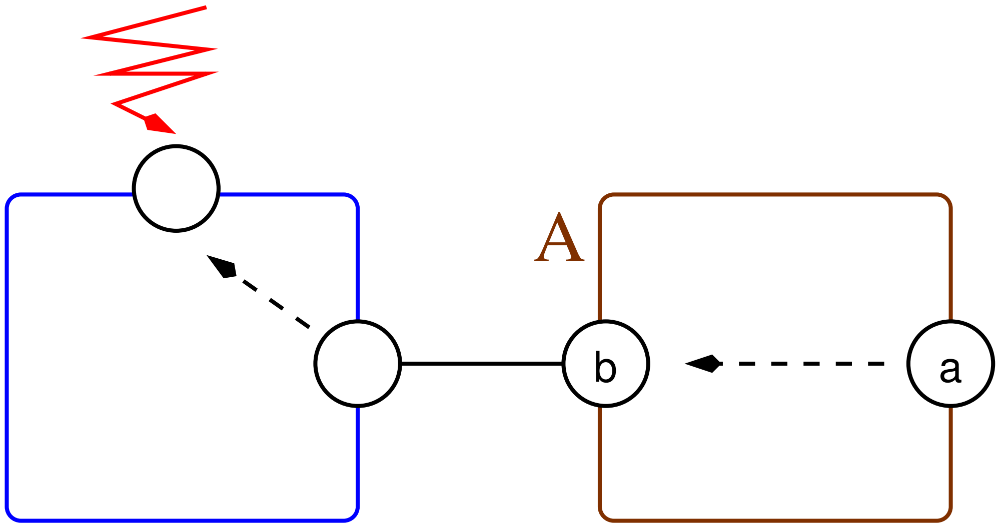

If a rule tests a site $a$ in an agent $A$ and modifies a site $b$ in the same agent $A$, then any class in $C(A)$ that contains $b$ also contains $a$.

# Syntactic criteria: control pipe



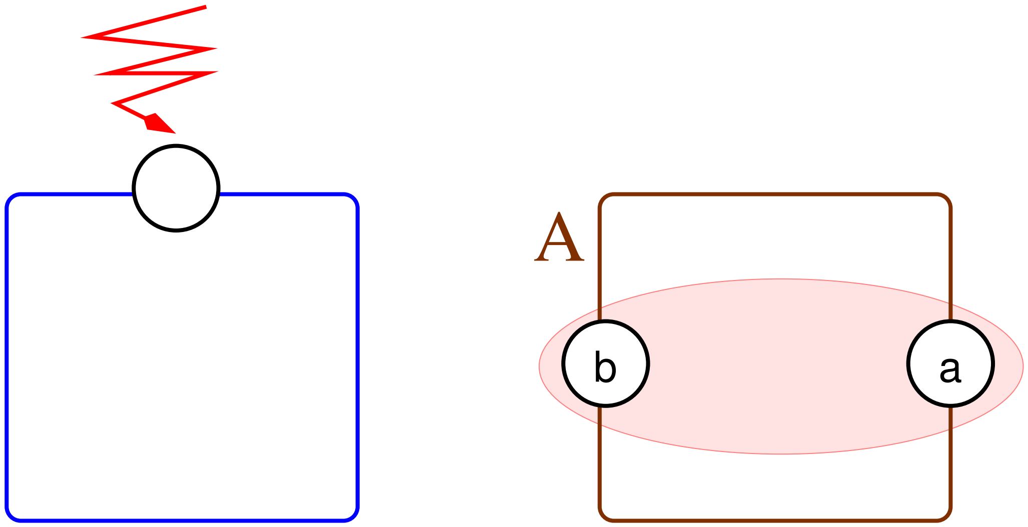

If the left hand side of a rule contains a bond and any other test (either on internal states, or on binding states), then this bond must be solid.

# 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.

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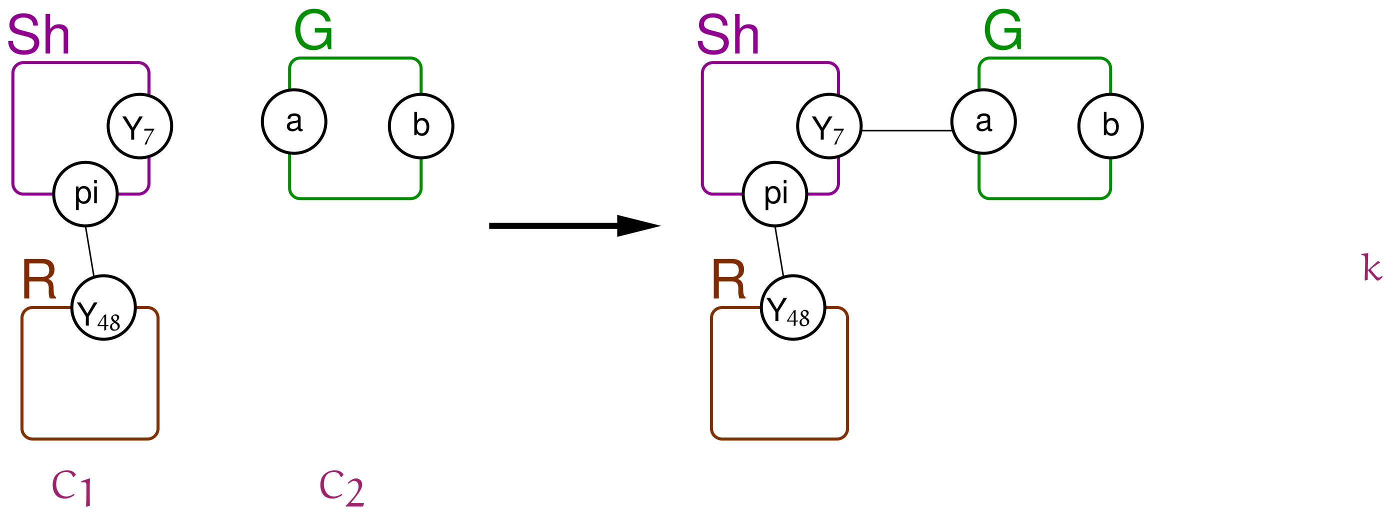
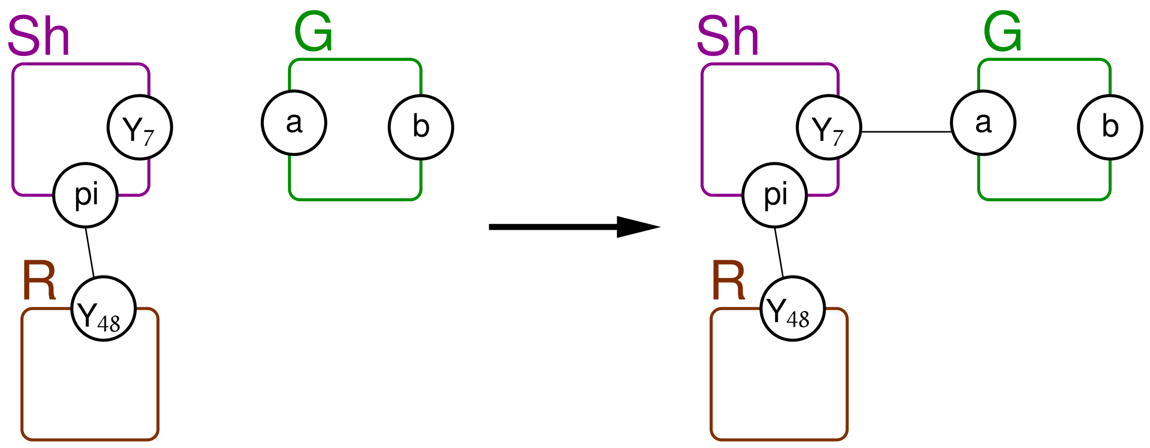
# A binding rule

Let us abstract the contribution of a binding rule:



# A binding rule: reactants

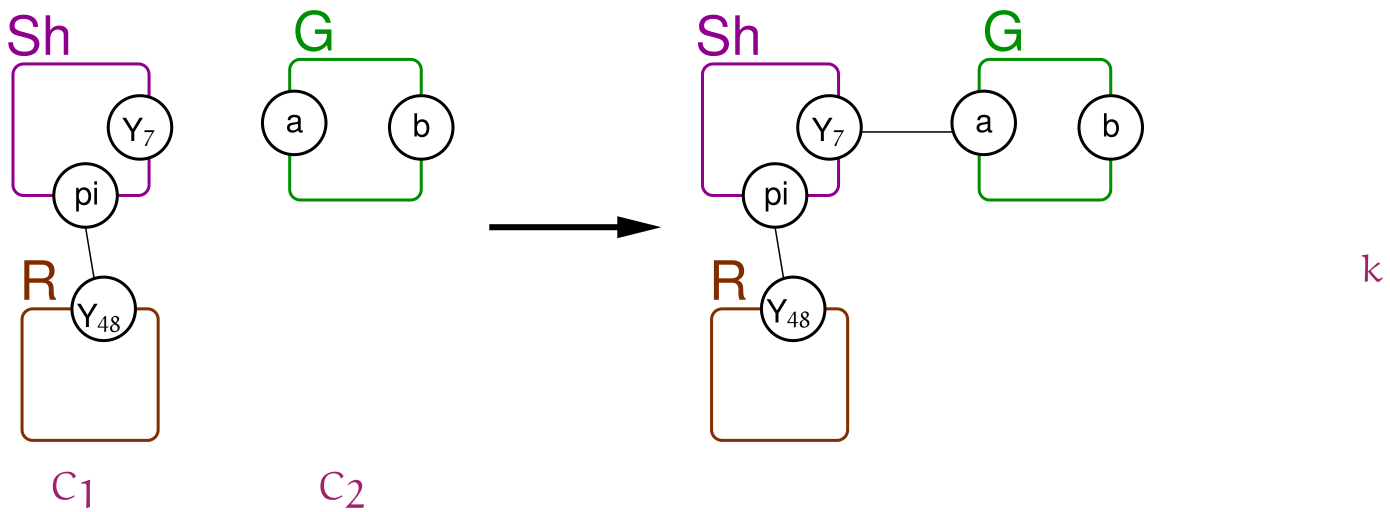



$C_1$ $C_2$ $k$

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

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

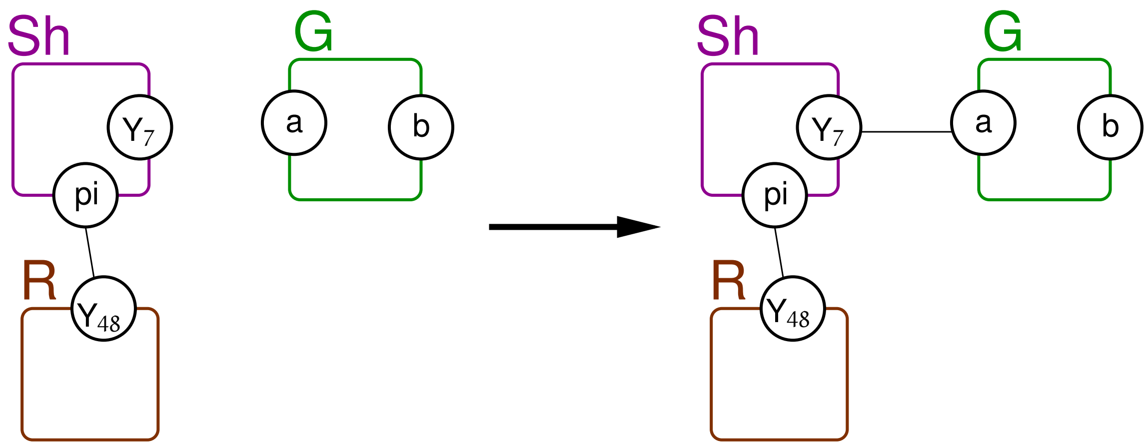
# Binding rules: products




If the edge is solid, for any $(F_1, \Phi_1)$ and $(F_2, \Phi_2)$, 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




$C_1$ $C_2$

$k$

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

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

# Soundness

If:

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

Then, the abstract dynamic $\mathbb{F}^\sharp$ is $\psi$forward-complete.

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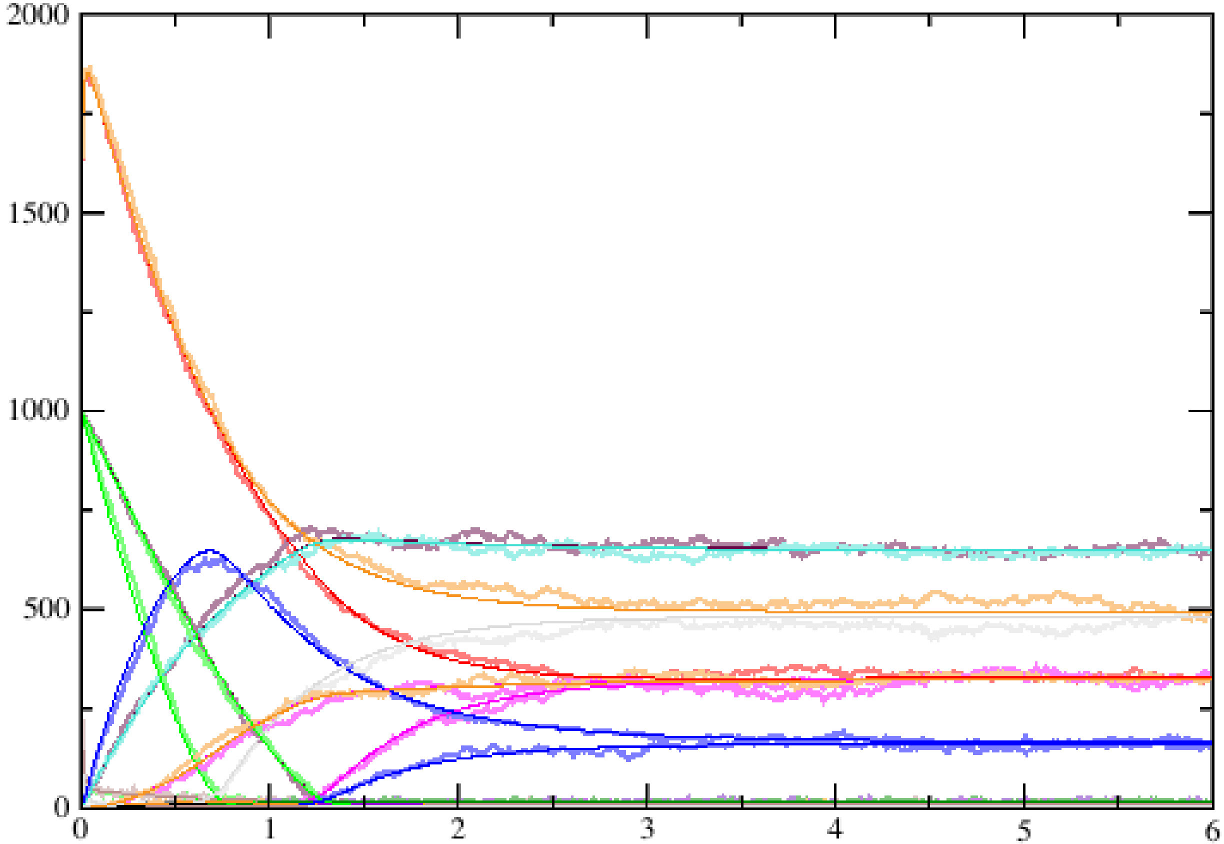
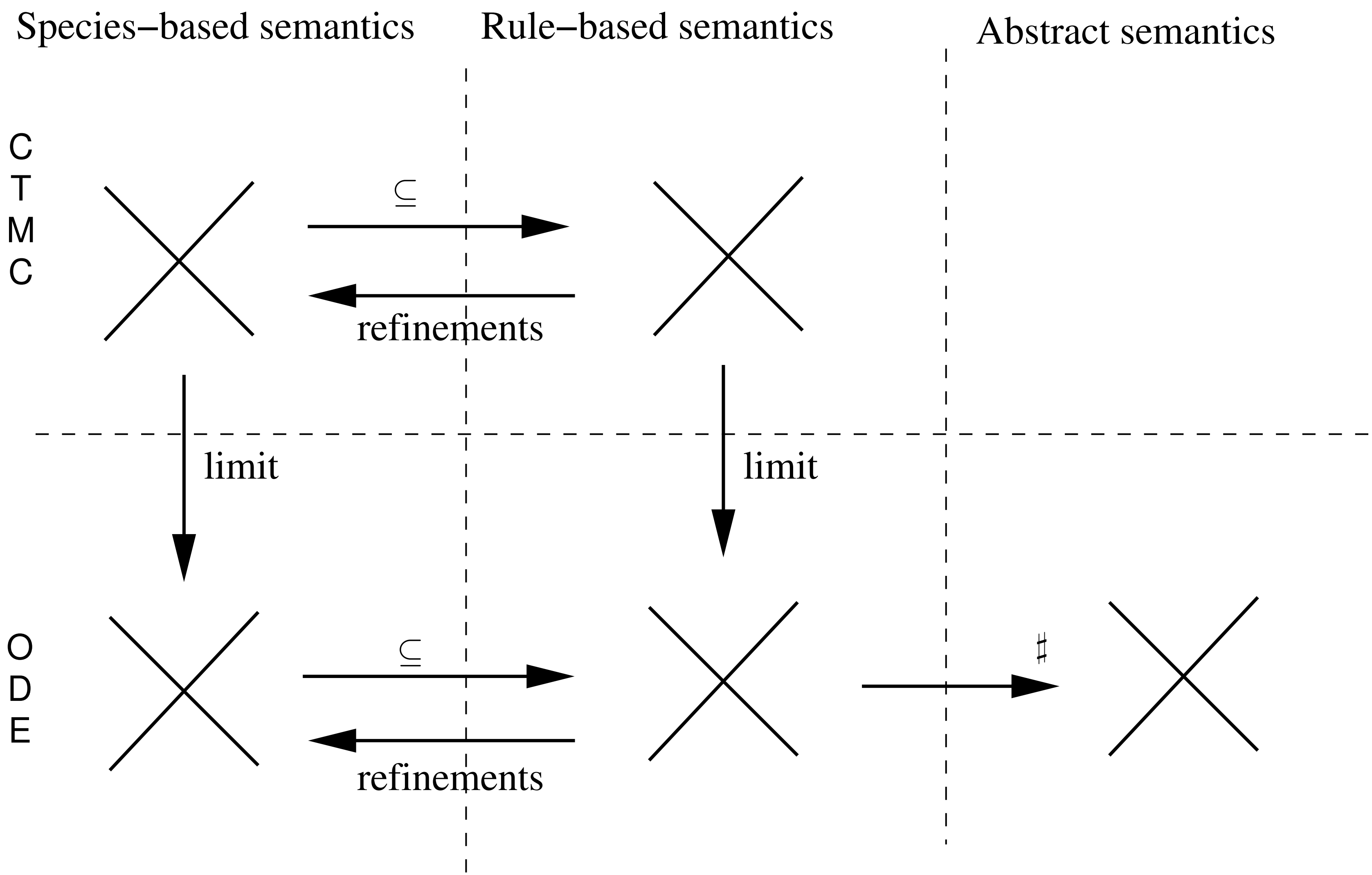
# Experimental results

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:
   - Independency 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.