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Abstract Interpretation of Reachable Complexes in Biological Signalling Networks

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Joint work with

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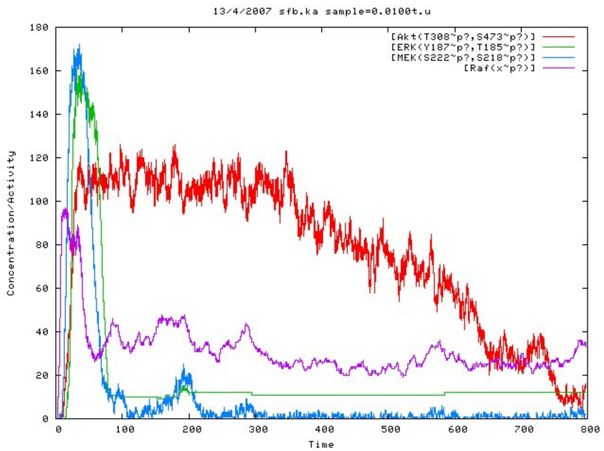
Overview

1. Introduction
2. Kappa language
3. Local views
4. Local set of complexes
5. Local rule systems
6. Conclusion

Modeling 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.
- We want to track the evolution of some species:



- There is a combinatorial blow-up.

Why using modelling tools ?

- Use a concise high-level description of what happens;
- Share parts of models;
- Derive quantitative models automatically:
  - run benchs of simulations,
  - modify initial conditions,
  - update/modify the model at no cost;
- Use static analysis tools in order to check the consistency of a model:
  - dead rules detection,
  - control detection (which site controls which binding),
  - wrong species detection.

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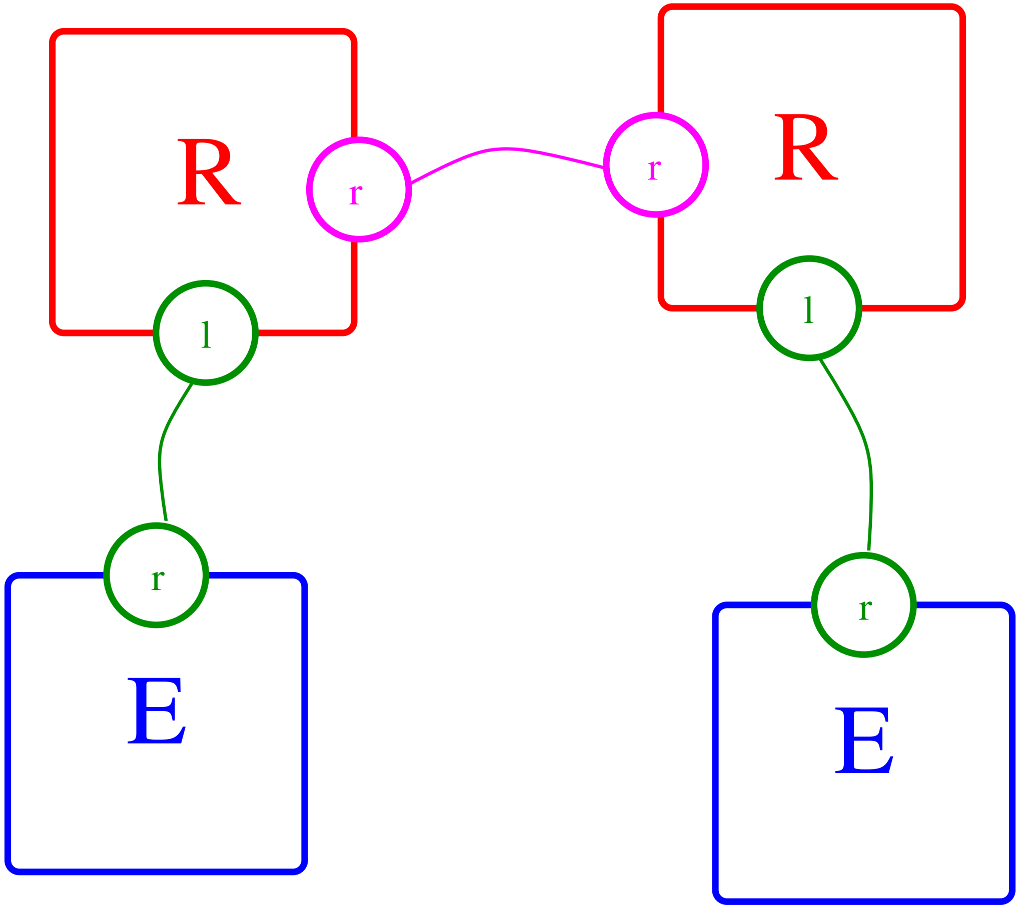
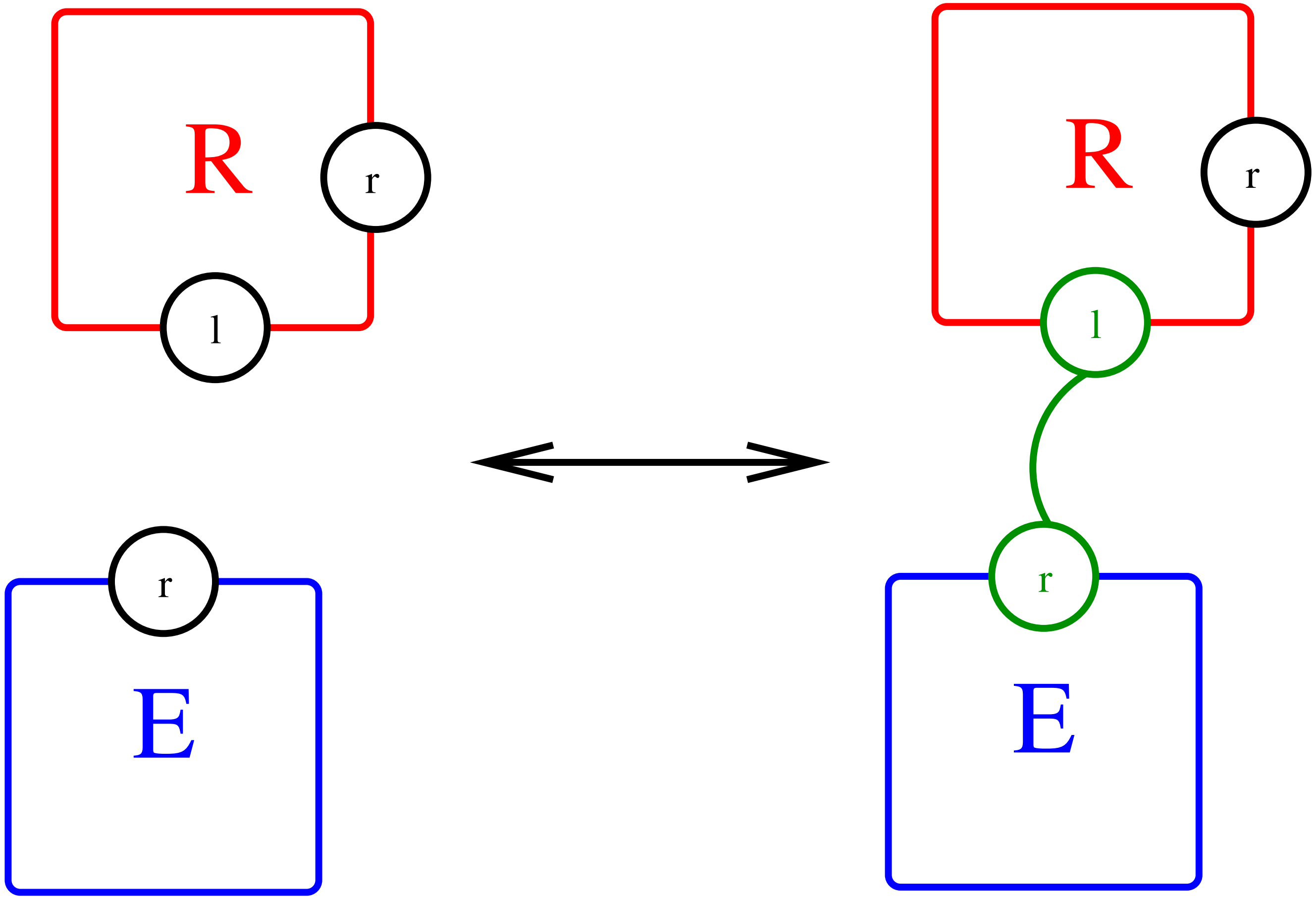
A complex



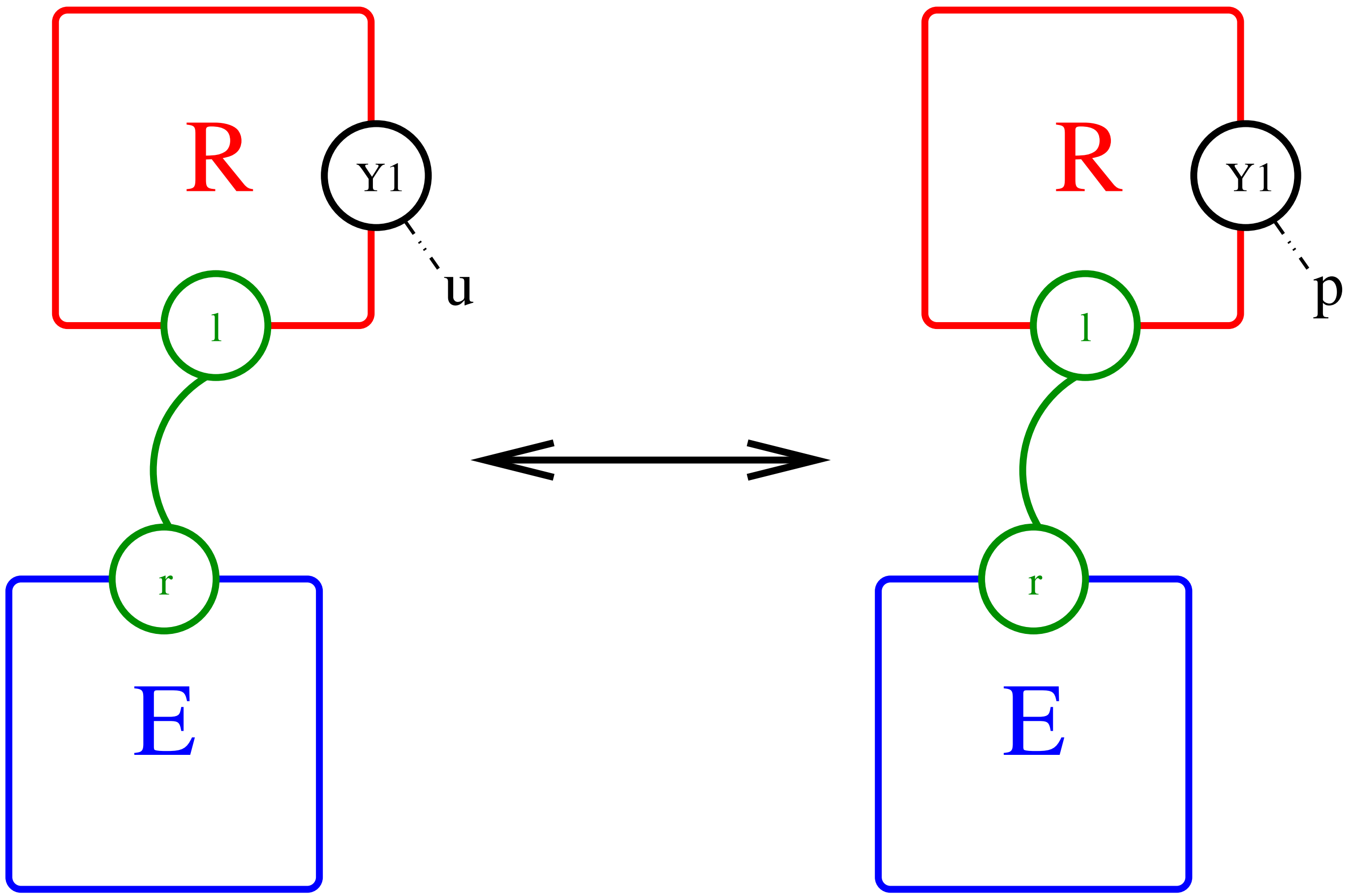
E(r!1), R(l!1,r!2), R(r!2,l!3), E(r!3)

A unbinding/binding Rule



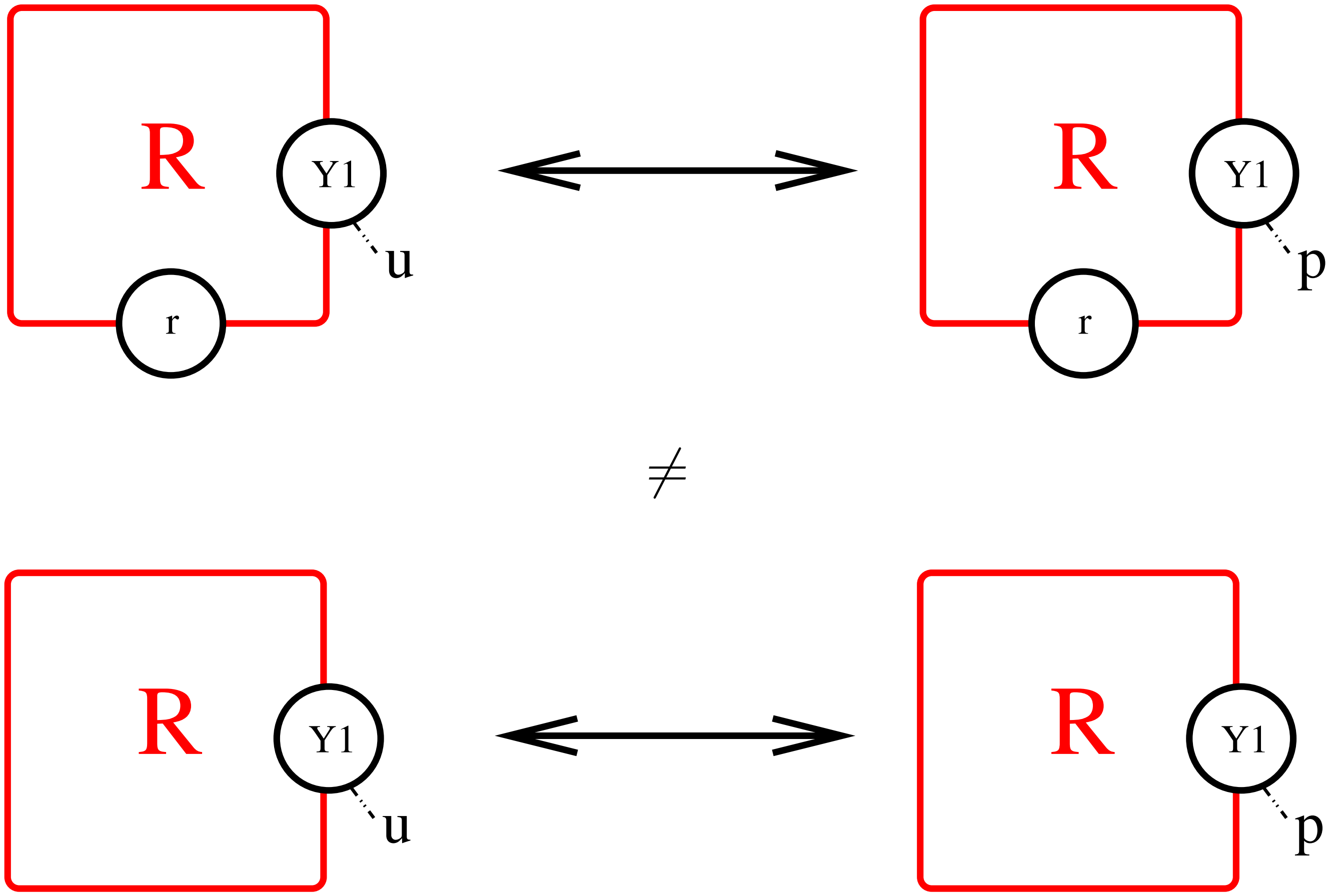
E(r), R(l,r) $\longleftrightarrow$ E(r!1), R(l!1,r)

Internal state

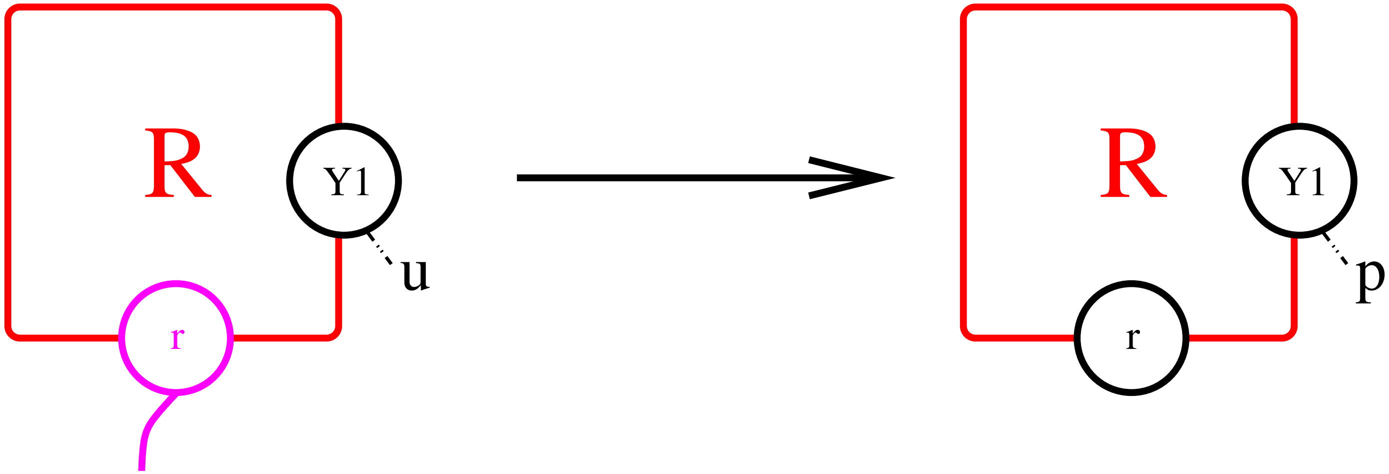


R(Y1~u,l!1), E(r!1) $\longleftrightarrow$ R(Y1~p,l!1), E(r!1)

Don't care, Don't write

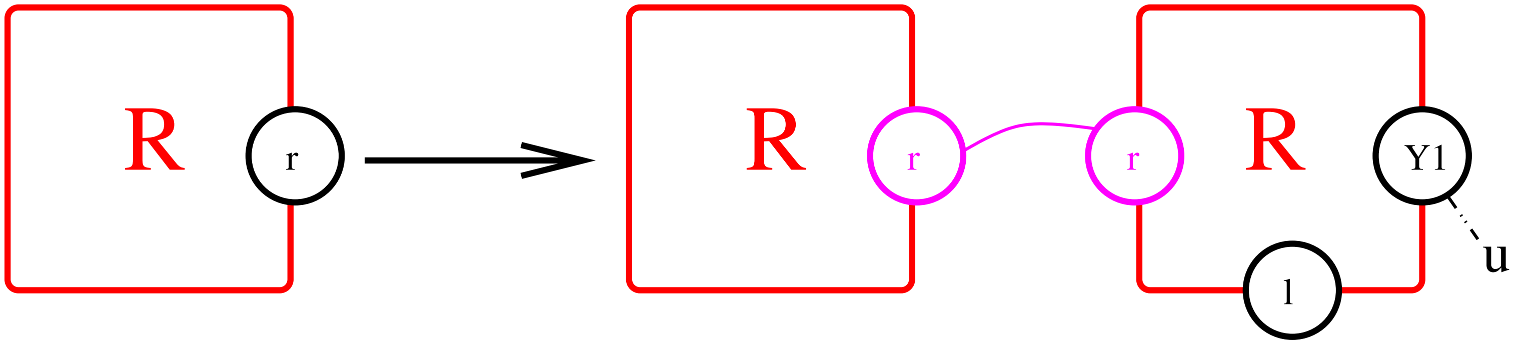


A contextual rule

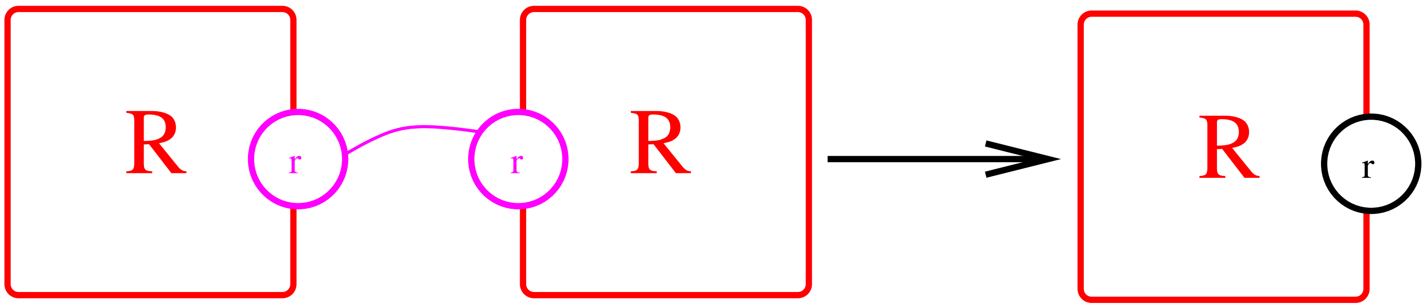


R(Y1~u,r!_) $\rightarrow$ R(Y1~p,r)

Creation/Suppression



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



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

Overview

Set of reachable complexes

Let $\mathcal{R} = \{R_i\}$ be a set of rules.
Let *Complex* be the set of all complexes ($C, c_1, c'_1, \ldots, c_k, c'_k, \ldots \in$ *Complex*).
Let *Complex*$_0$ be the set of initial complexes.
We write:

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

whenever:

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

We are interested in *Complex*$_\omega$ the set of all complexes that can be constructed in one or several applications of rules in $\mathcal{R}$ starting from the set *Complex*$_0$ of initial complexes.

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

Inductive definition

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

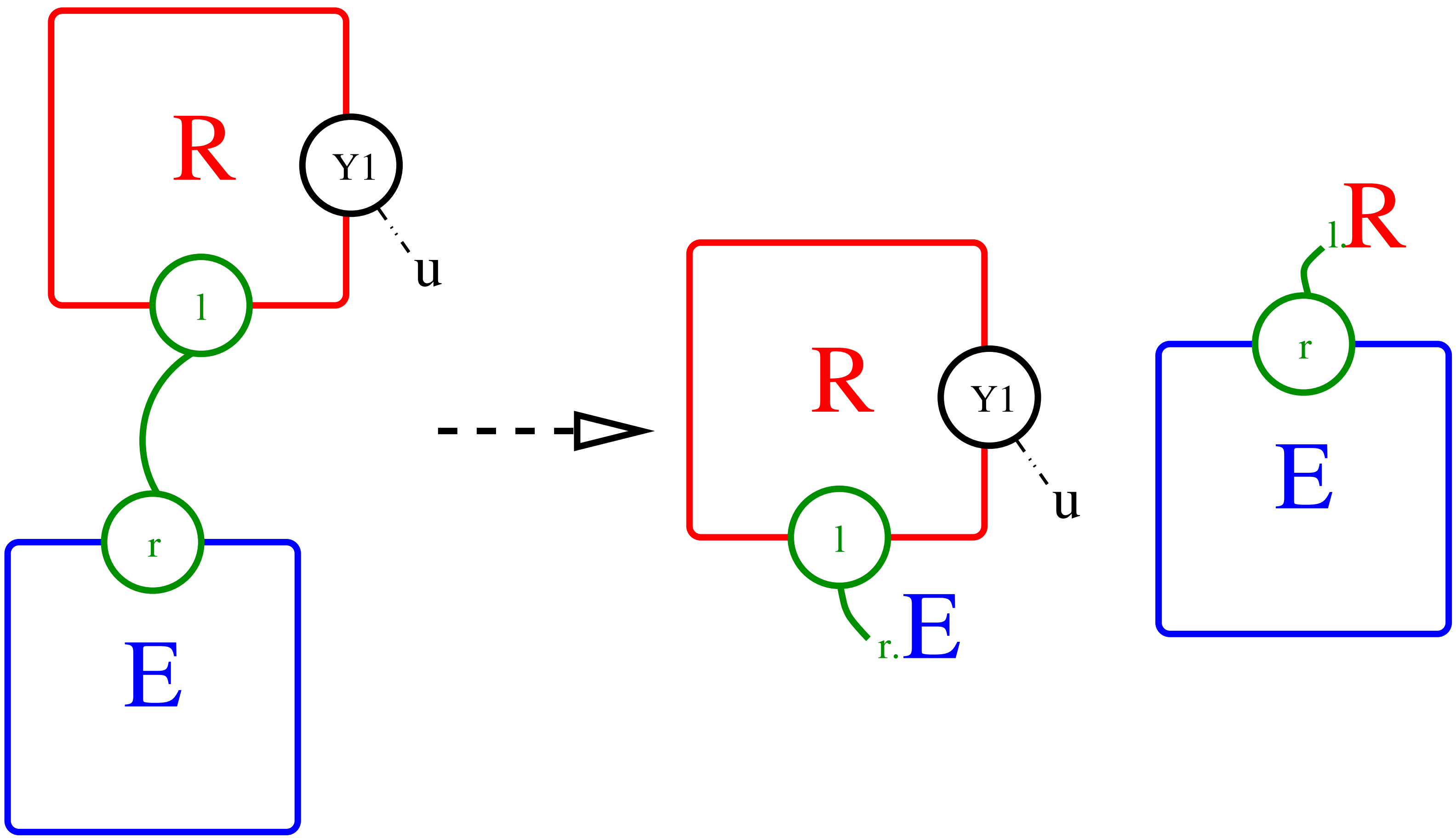
$$\mathbb{F} : \begin{cases} \wp(\mathit{Complex}) & \rightarrow \wp(\mathit{Complex}) \\ X & \mapsto X \cup \left\{ c'_j \;\middle|\; \begin{array}{l} \exists R_k \in \mathcal{R}, c_1, \ldots, c_m \in X, \\ c_1, \ldots, c_m \rightarrow_{R_k} c'_1, \ldots, c'_n \end{array} \right\} \end{cases}.$$

The set $\wp(\mathit{Complex})$ is a complete lattice.
The mapping $\mathbb{F}$ is an extensive $\cup$-complete morphism.

We have:

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

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 *Local_view* be the set of all local views.

Let $\alpha \in \wp(\mathit{Complex}) \rightarrow \wp(\mathit{Local\_view})$ be the function that maps any set of complexes into the set of their local views.

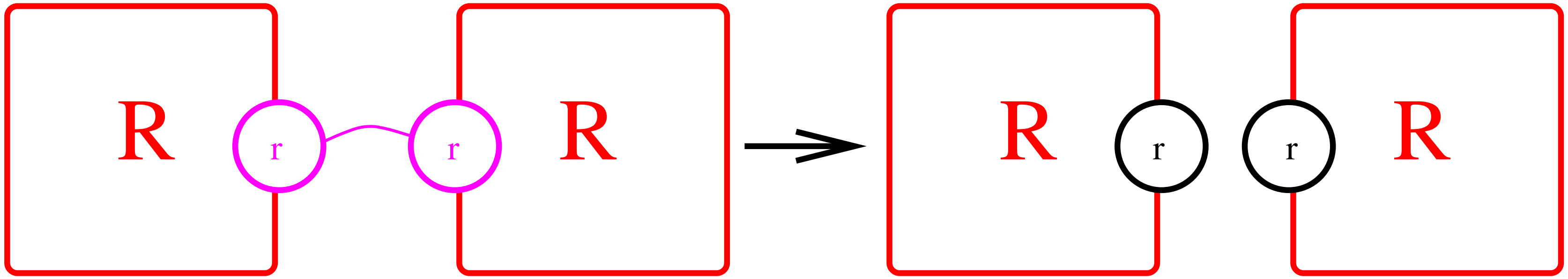
The set $\wp(\mathit{Local\_view})$ is a complete lattice.
The function α is a $\cup$-complete morphism.

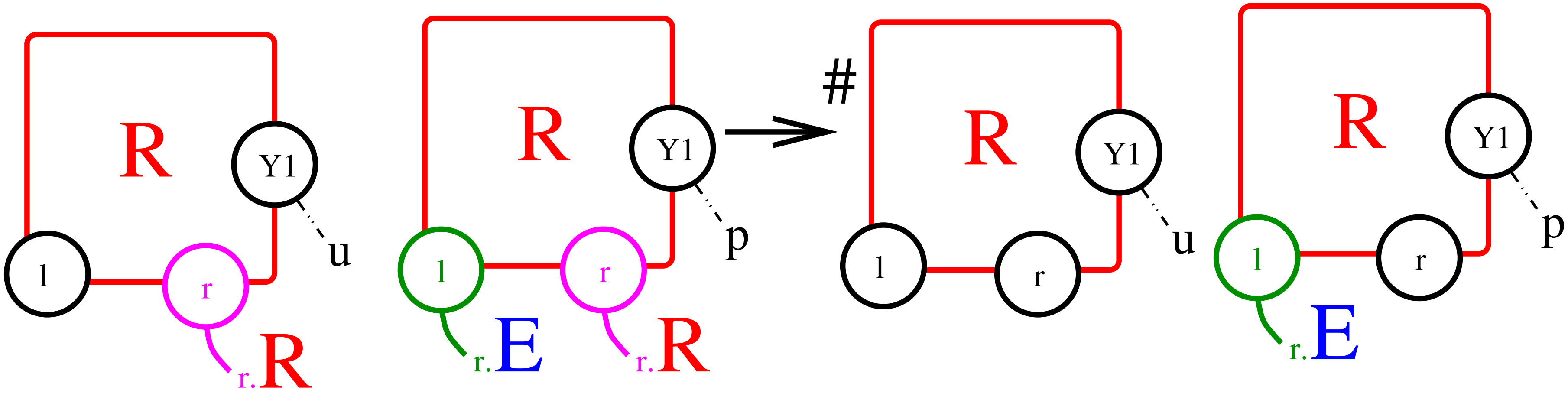
Thus, it defines a Galois connexion:

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

(The function γ maps a set of local views into the set of complexes that can be built with these local views).

Abstract rules





Abstract counterpart to $\mathbb{F}$

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

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

Soundness

We have:

1. $(\wp(\mathit{Complex}), \subseteq, \cup)$ and $(\wp(\mathit{Local\_view}), \subseteq, \cup)$ are chain-complete partial orders;
2. $\wp(\mathit{Complex}) \xrightleftharpoons[\alpha]{\gamma} \wp(\mathit{Local\_view})$ is a Galois connexion;
3. $\mathbb{F} \in \wp(\mathit{Complex}) \to \wp(\mathit{Complex})$ and $\mathbb{F}^\sharp \in \wp(\mathit{Local\_view}) \to \wp(\mathit{Local\_view})$ are extensive and monotonic mappings;
4. $\mathbb{F} \circ \gamma \mathrel{\dot{\subseteq}} \gamma \circ \mathbb{F}^\sharp$;

So:

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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Which information is abstracted away ?

Our analysis is exact (no false positive):

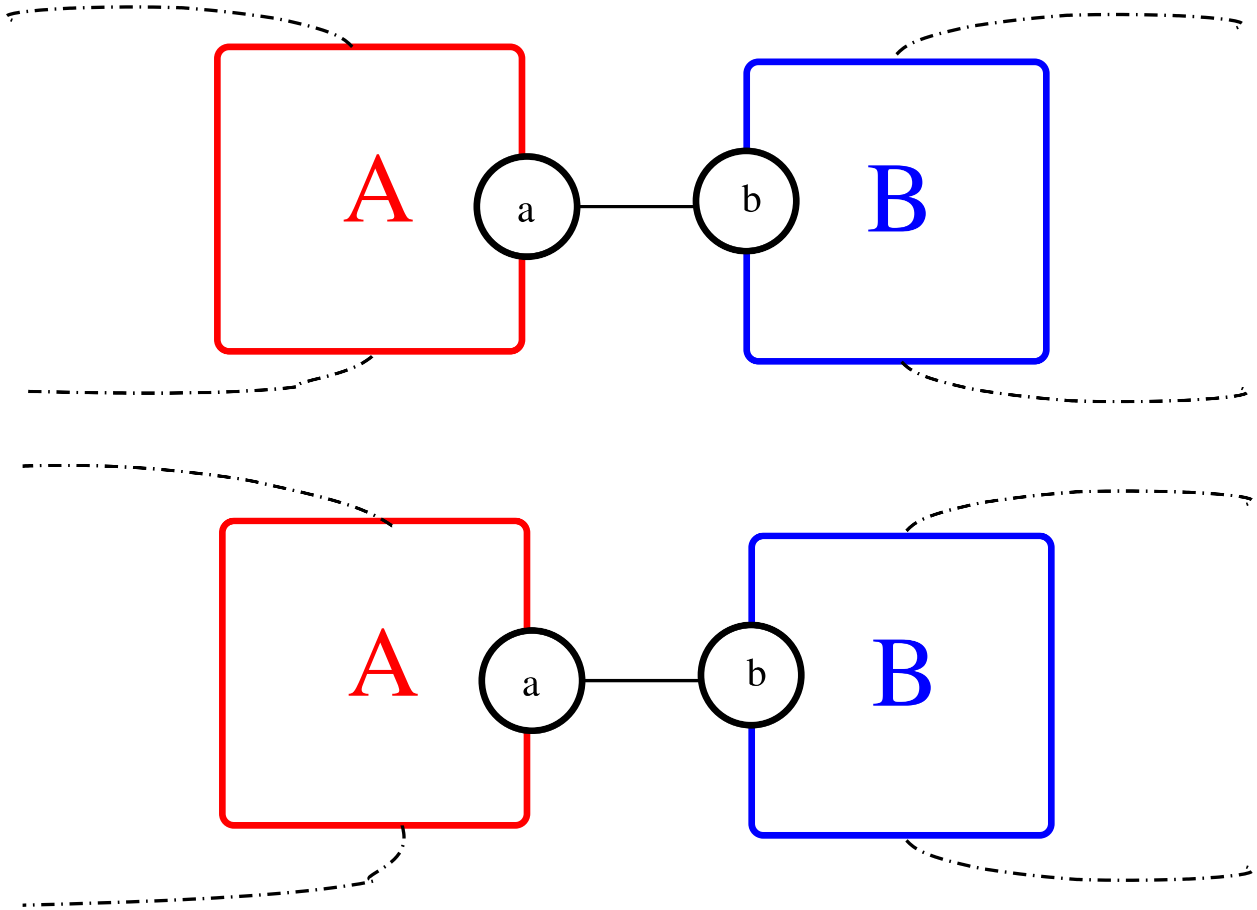
- for the early EGF cascade (356 complexes);
- for the early FGF cascade ($709\,698$ complexes);
- for the EGF cascade with RAS-ERK activation ($\simeq 1.8 * 10^{18}$ complexes);

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

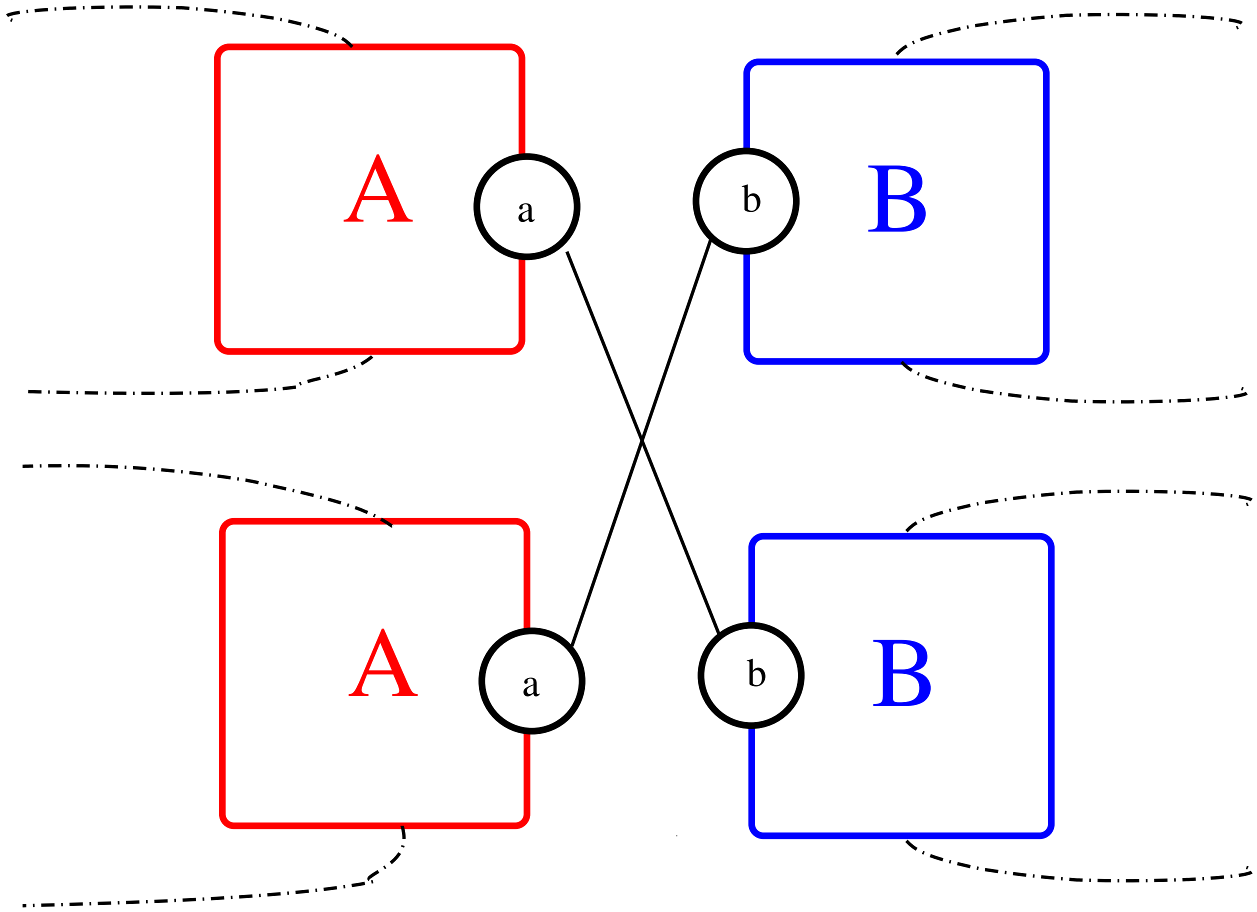
This raises the following issues:

- 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 ?

Swap-closure



Swap-closure



Local set of complexes

Let $X \subseteq$ *Complex* be a set of complexes,

The following assertions are equivalent:

1. $X = \gamma(\alpha(X))$
2. X is closed upon swap.

In such a case, we say that X is local.

As a consequence:

1. Any assembling of views in $\alpha(X)$ can be extended in a close complex in $\gamma(\alpha(X))$;
2. We have $\mathbb{F}^\sharp \circ \alpha = \alpha \circ \mathbb{F} \circ \gamma \circ \alpha$.

When is there no false positive ?

We have:

1. $(\wp(\mathit{Complex}), \subseteq, \cup)$ and $(\wp(\mathit{Local\_view}), \subseteq, \cup)$ are chain-complete partial orders;
2. $(\wp(\mathit{Complex}), \subseteq) \underset{\alpha}{\overset{\gamma}{\leftrightarrows}} (\wp(\mathit{Local\_view}), \subseteq)$ is a Galois connexion;
3. $\mathbb{F} : \wp(\mathit{Complex}) \to \wp(\mathit{Complex})$ is an extensive and monotonic map;
4. $\mathbb{F}^\sharp \circ \alpha = \alpha \circ \mathbb{F} \circ \gamma \circ \alpha$

So:

$$\mathit{lfp}_{x_0}\mathbb{F} \in \gamma(\wp(\mathit{Complex})) \iff \mathit{lfp}_{x_0}\mathbb{F} = \gamma(\mathit{lfp}_{\alpha(x_0)}\mathbb{F}^\sharp).$$

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Local fragment of Kappa

If:

1. initial agents are not bound;
2. rules are atomic;
3. rules are local (only agents that interact are tested);
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. assembled complexes are acyclic;

then:

$$Complex_\omega = \gamma(\alpha(Complex_\omega)).$$

Non local systems

$$Complex_0 \triangleq \text{R(a\textasciitilde u)}$$

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

R(a~u!1),R(a~u!1) $\in$ $Complex_\omega$
R(a~p!1),R(a~p!1) $\in$ $Complex_\omega$
But R(a~u!1),R(a~p!1) $\notin$ $Complex_\omega$.

Non local systems

$$\mathit{Complex}_0 \stackrel{\Delta}{=} \text{A(a\textasciitilde u),B(a\textasciitilde u)}$$

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

A(a~u!1),B(a~p!1) $\in \mathit{Complex}_\omega$

A(a~p!1),B(a~u!1) $\in \mathit{Complex}_\omega$

But A(a~p!1),B(a~p!1) $\notin \mathit{Complex}_\omega$.

Program transformation

- we have a syntactic criterion in order to ensure that the set of reachable complexes of a kappa system is local;
- we use 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 complexes;
     - add some rules that are in the transitive closure of the system.

Example

Initial rule:

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

Decontextualized rule:

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

We can remove redundant tests.

Example

Initial rules:

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

Decontextualized rule:

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

We can remove exhaustive enumerations.

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Conclusion

- A scalable static analysis to abstract the reachable complexes.
- A class of models for which the abstraction is complete.
- Many applications:
  - idiomatic description of reachable complexes;
  - 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 complexes);
  - on the fly flat rule generation (for large/unbounded set).

Future works

- Refine the analysis (and completeness criteria).
  - Deal with locations.
  - Deal with cycles.
  - Shape analysis.
- Quantitative analysis.
  - Can we lift the local-view abstraction to stochastic/differential semantics ?
  - Which information do we obtain ?
- Semi-quantitative abstractions.
  - Can we design abstract domains to discover semi-quantitative properties (i.e. overshoot detection) ?