ROSAEC workshop

First session

Reachability Analysis of Kappa Models

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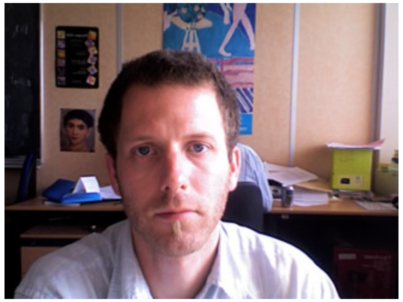

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Overview

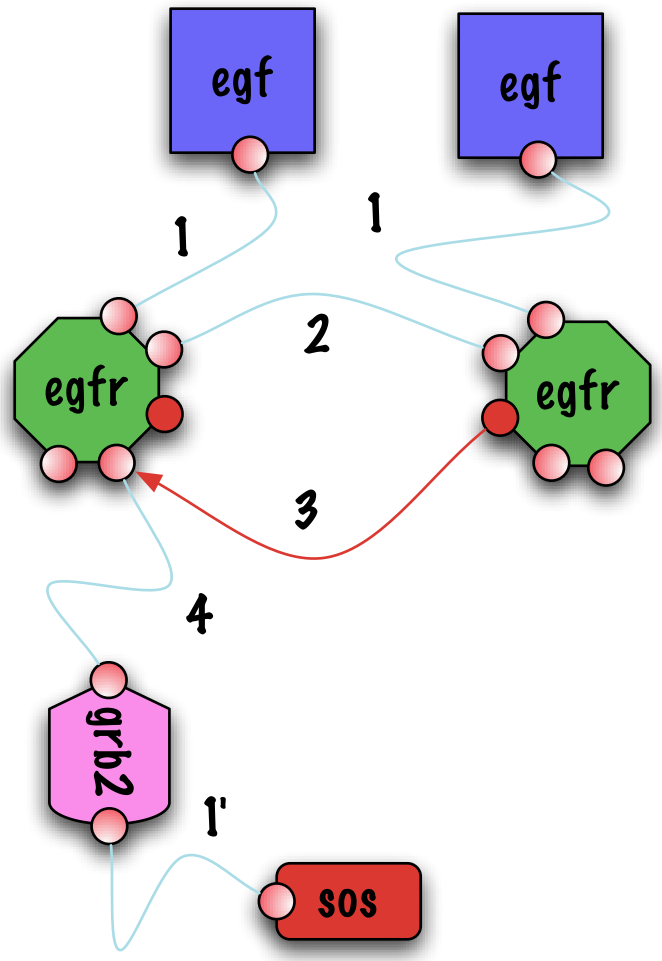
1. Introduction
2. Outline
3. Kappa language
4. Local views
5. Local set of complexes
6. Local rule systems
7. Decontextualization
8. Conclusion

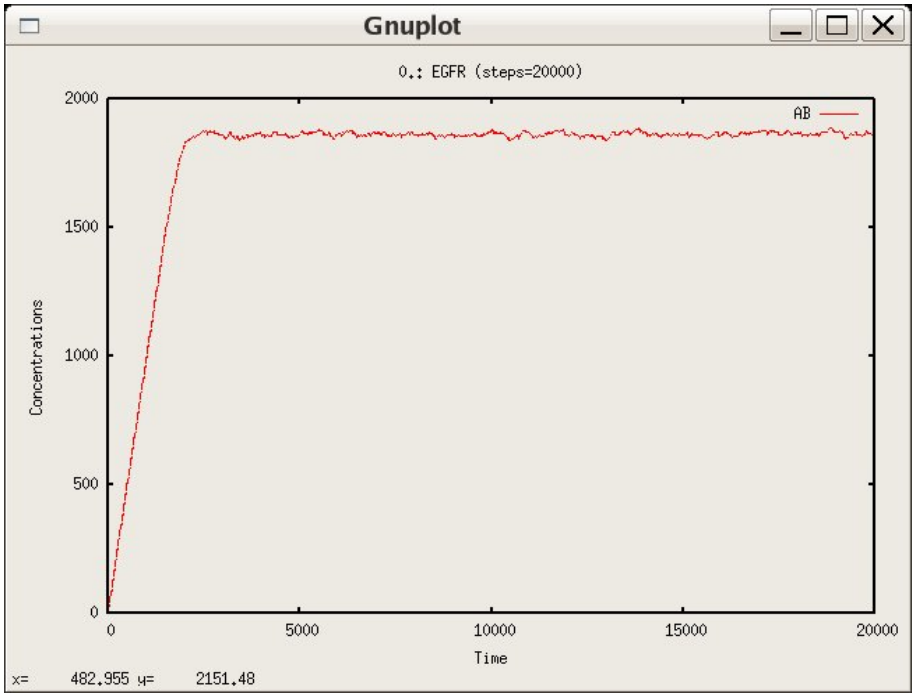
Modeling signaling pathway

- 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.
- Kappa calculus:
  - A site graph-based rewrite language.
  - Description level matches with biologists' observation and manipulation level.
- Static analysis:

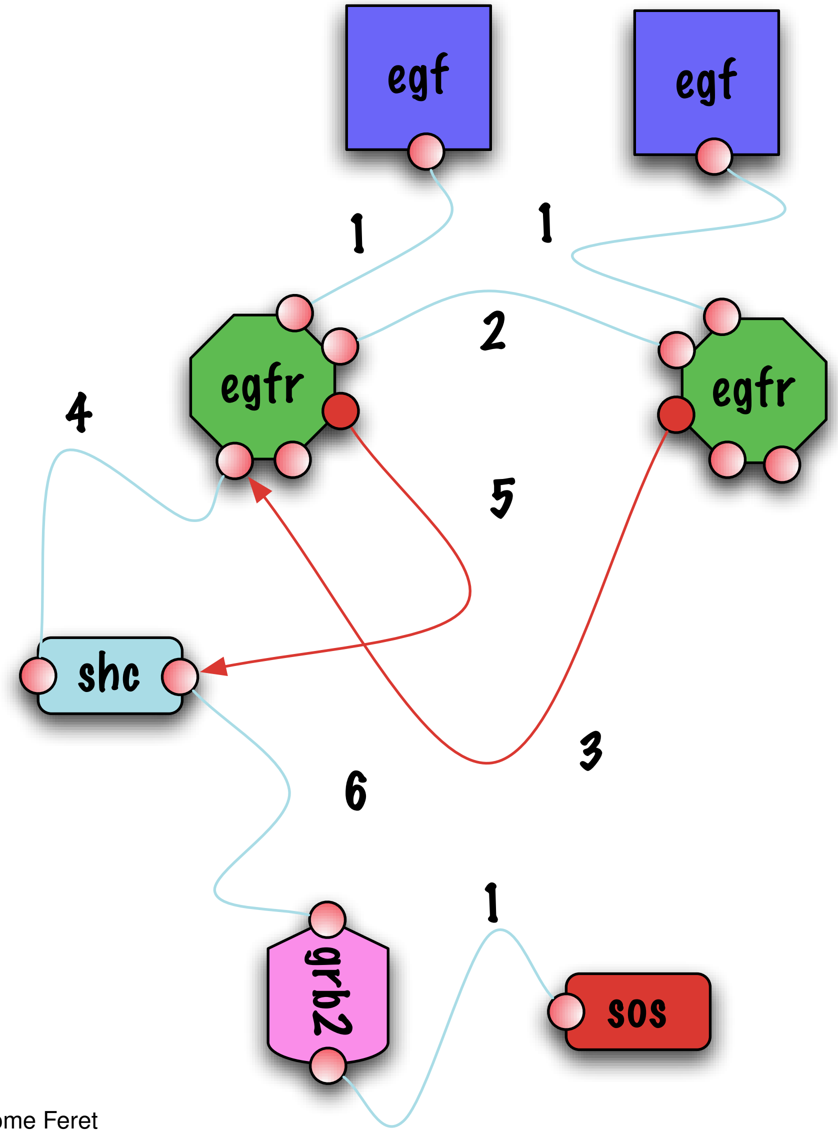
  We propose some static analysis tools in order to:
  - help the design of Kappa models;
  - compute (*abstract*) the properties of Kappa models.

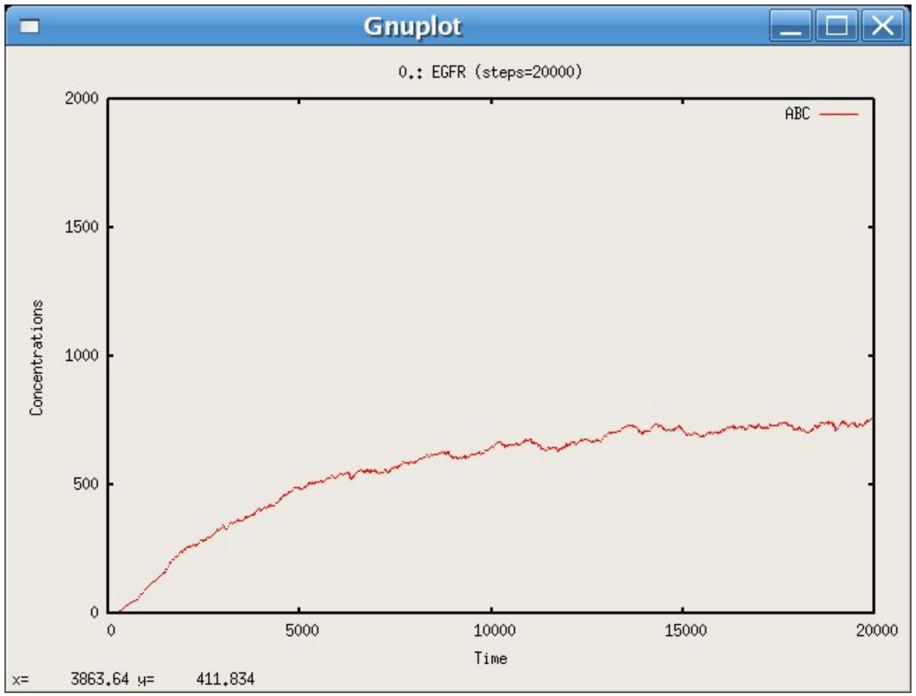
A single story





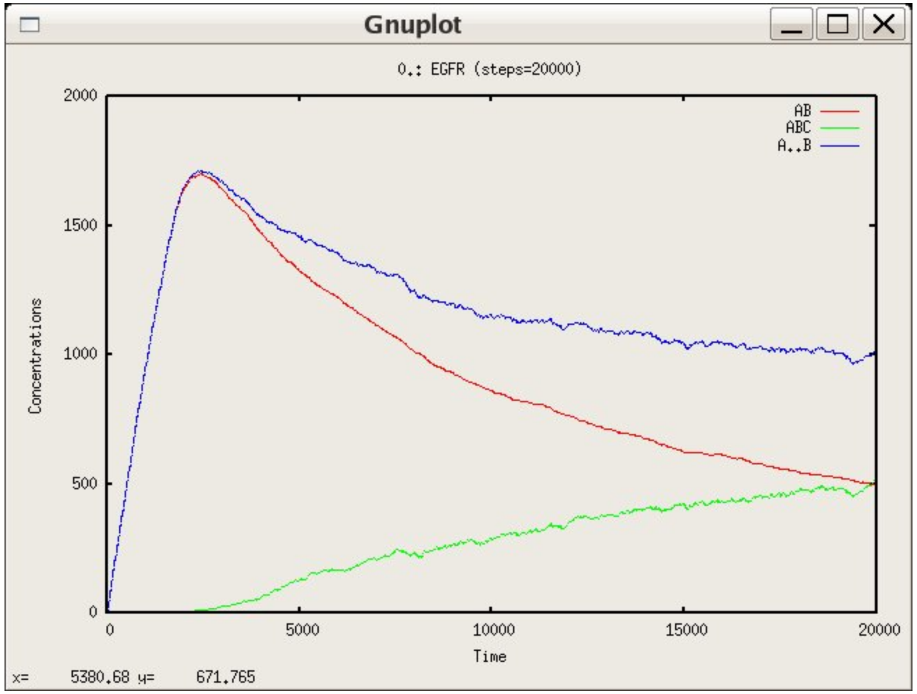
Another concurrent story





Overshoot

When we combine the two stories. . .



. . . we get an overshoot.

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Outline

- Language: $\mathcal{L}$
- Semantics domains: $D \underset{\alpha}{\overset{\gamma}{\leftrightarrows}} D^\sharp$
- Semantics functions: $[\![p]\!] \subseteq \gamma([\![p]\!]^\sharp)$
- (*Strong*) completeness ?
  for which $p \in \mathcal{L}$ do we have $[\![p]\!] = \gamma([\![p]\!]^\sharp)$?
  - Semantics characterization:
    $A \subseteq D$ such that: if $[\![p]\!] \in A$ then $[\![p]\!] = \gamma([\![p]\!]^\sharp)$;
  - Syntactic characterization:
    $\mathcal{K} \subseteq \mathcal{L}$ such that: if $p \in \mathcal{K}$ then $[\![p]\!] \in A$;
  - Driven program transformation:
    $T : D^\sharp \times \mathcal{L} \to \mathcal{L}$ such that: if $[\![p]\!] \subseteq \gamma(A^\sharp)$ then $\begin{cases} [\![p]\!] = [\![T(A^\sharp, p)]\!], \\ p \in \mathcal{K} \Rightarrow T(A^\sharp, p) \in \mathcal{K}. \end{cases}$

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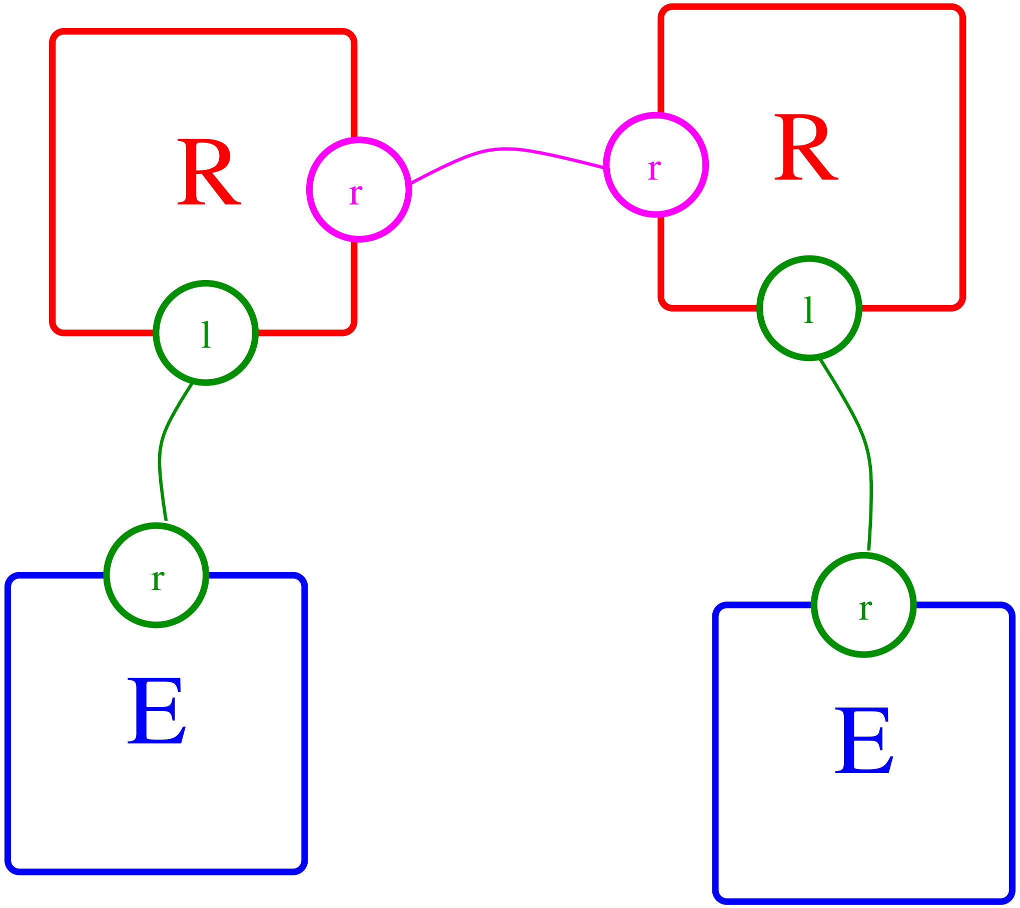
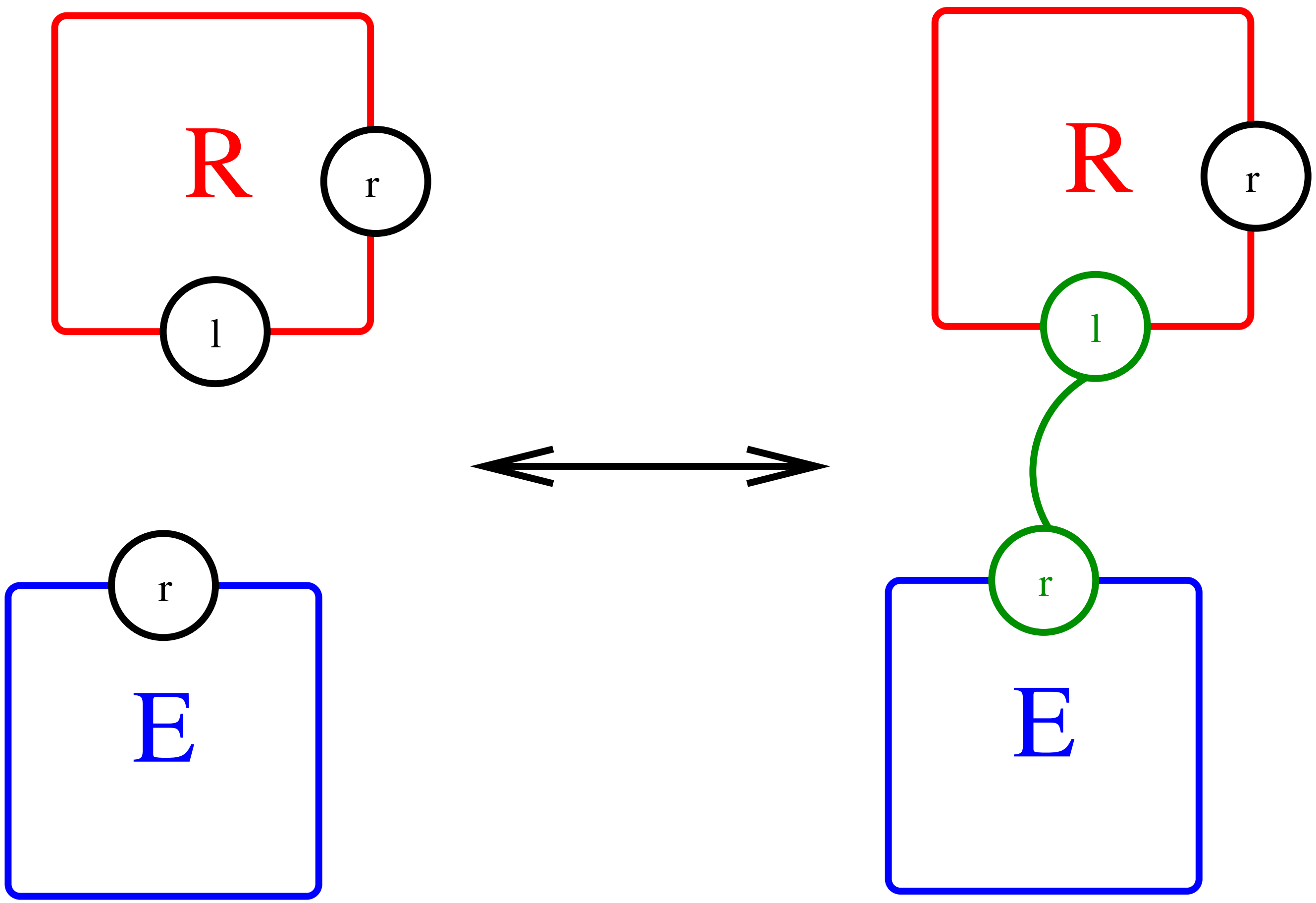
A complex



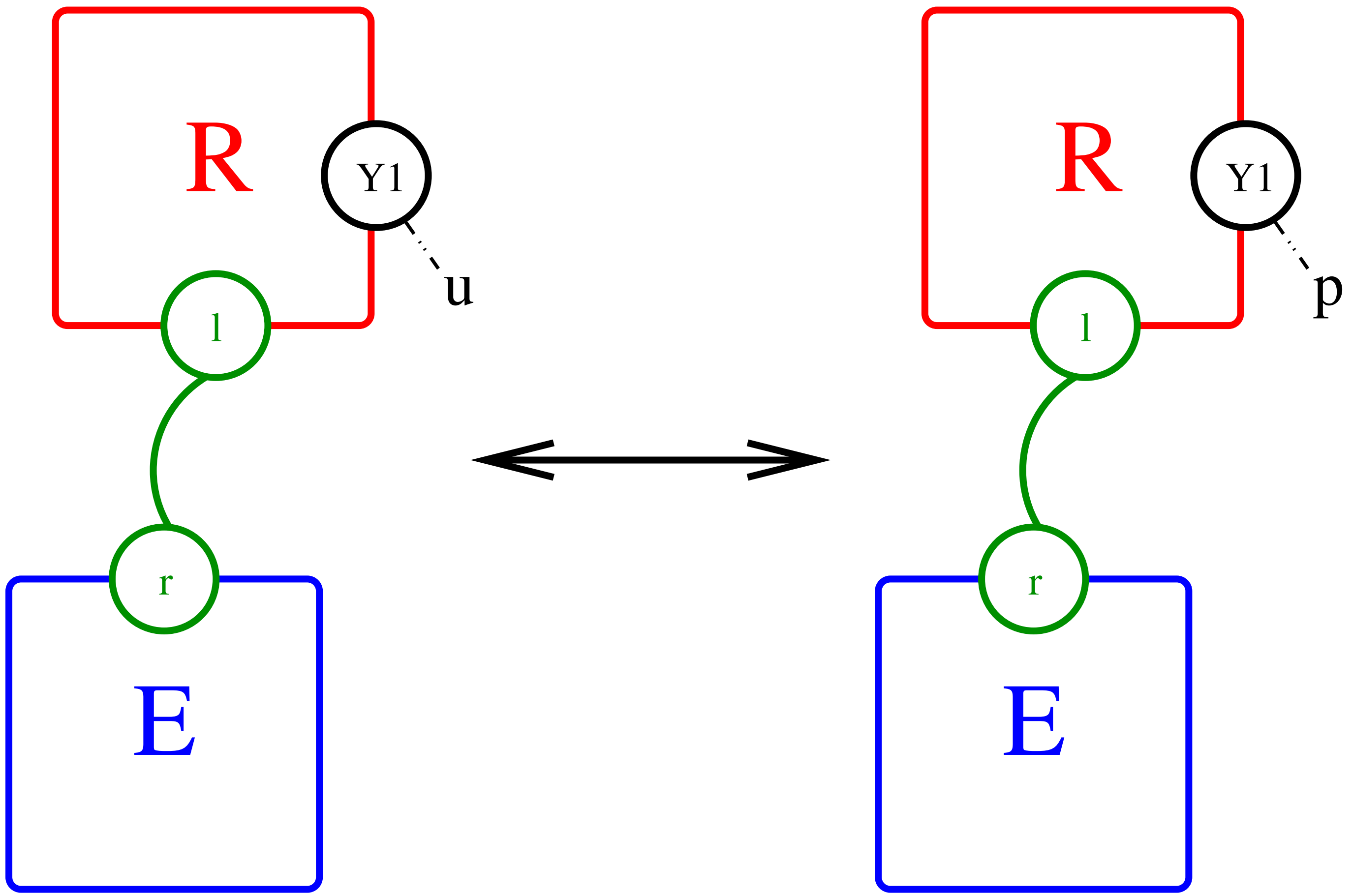
E(r!1), R(l!1,r!2), R(r!2,l!3), E(r!3)

A Unbinding/Binding Rule



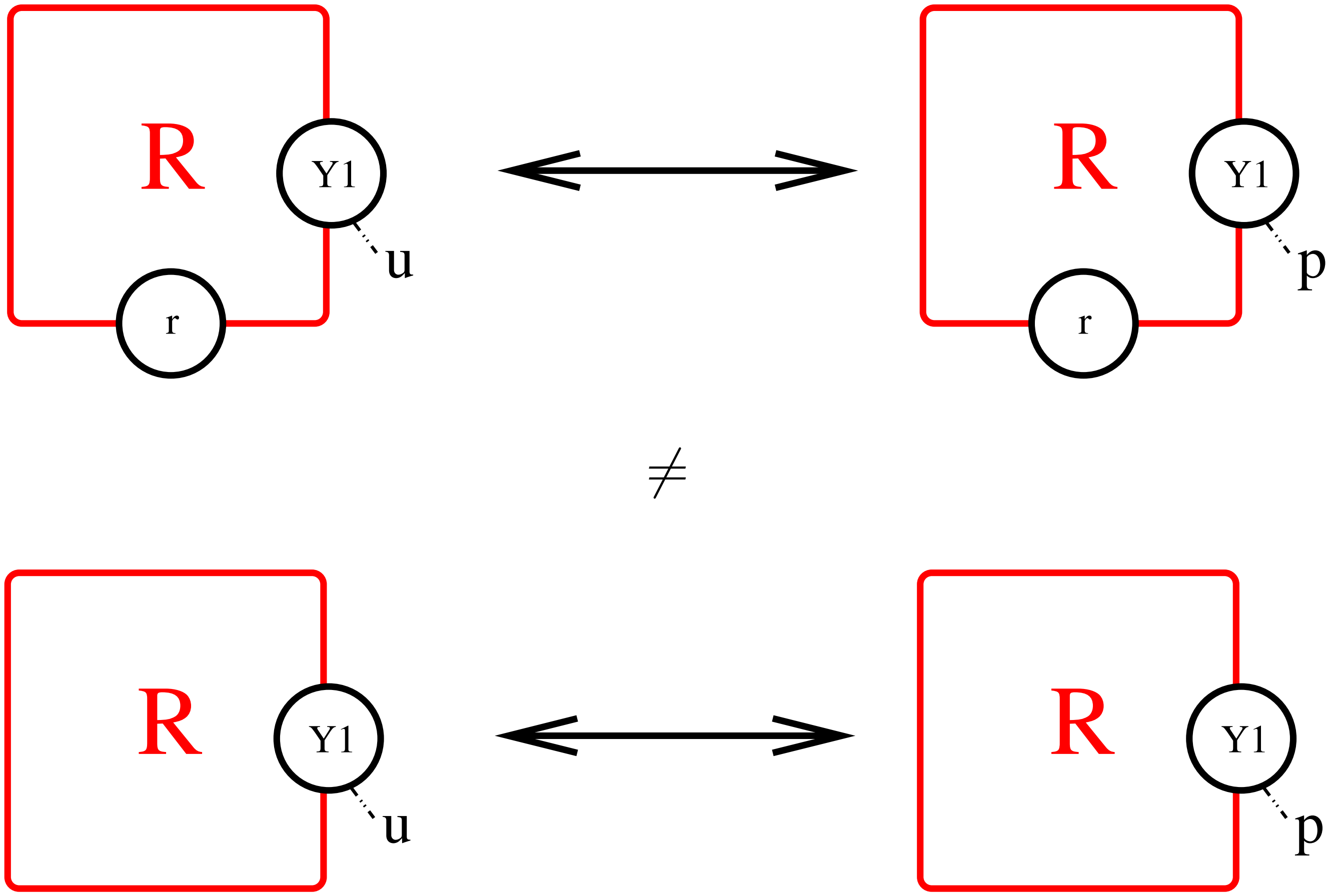
E(r), R(l,r) $\longleftrightarrow$ E(r!1), R(l!1,r)

Internal state

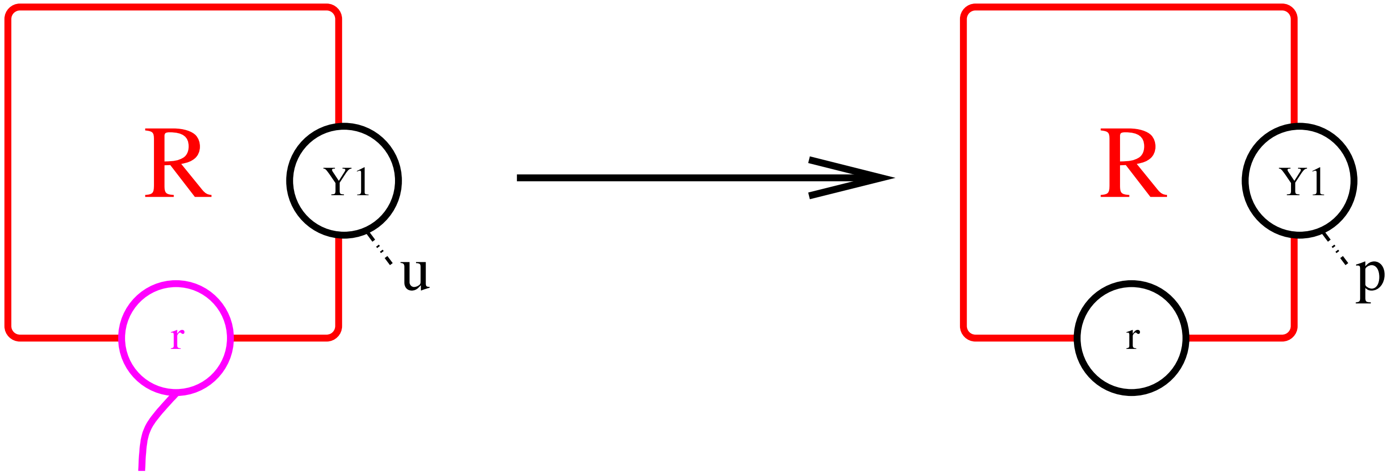


R(Y1~u,l!1), E(r!1) $\longleftrightarrow$ R(Y1~p,l!1), E(r!1)

Don’t care, Don’t write

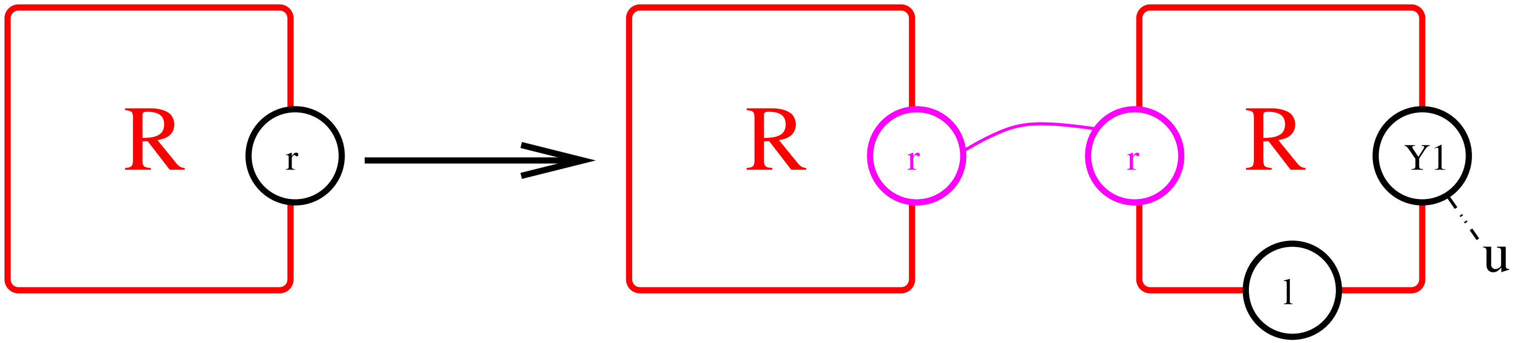


A contextual rule

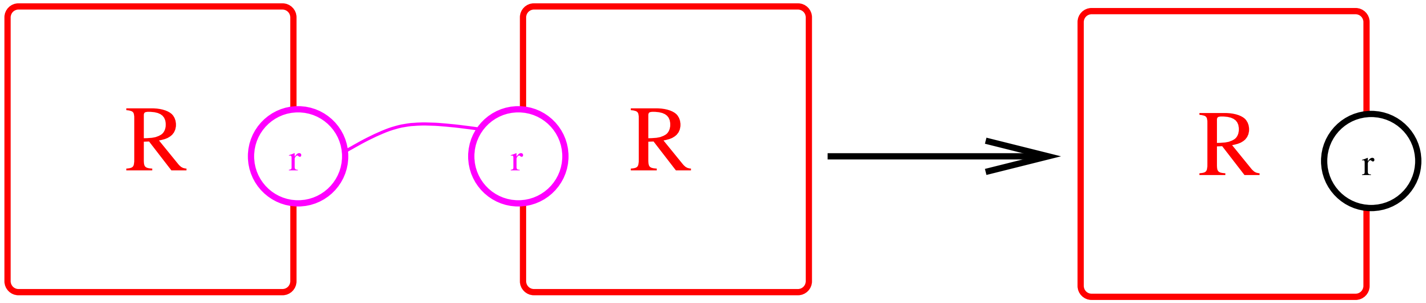


R(Y1~u,r!_) $\rightarrow$ R(Y1~p,r)

Creation/Suppression



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



R(r!1), R(r!1) $\longrightarrow$ 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: $R(l,r), E(r) \leftrightarrow R(l^1,r), E(r^1)$
  - 02: $R(l^1,r), R(l^2,r) \leftrightarrow R(l^1,r^3), R(l^2,r^3)$
  - 03: $R(r^1,Y68) \rightarrow R(r^1,Y68^p)$
  - $R(Y68^p) \rightarrow R(Y68)$
  - 04: $R(r^1,Y48) \rightarrow R(r^1,Y48^p)$
  - $R(Y48^p) \rightarrow R(Y48)$

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

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

refined from
$Sh(Y7^p) \rightarrow Sh(Y7)$

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

refined from
$R(Y68^p)+G(a) \leftrightarrow R(Y68^{p1})+G(a^1)$

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: $R(Y68^{p1}), G(a^1,b), So(d)$ <-> $R(Y68^{p1}), G(a^1,b^2), So(d^2)$
  - 12: $G(a,b), So(d)$ <-> $G(a,b^1), So(d^1)$
  - 22: $Sh(\pi,Y7^{p2}), G(a^2,b), So(d)$ <-> $Sh(\pi,Y7^{p2}), G(a^2,b^1), S(d^1)$
  - 19: $Sh(\pi^1,Y7^{p2}), G(a^2,b), So(d)$ <-> $Sh(\pi^1,Y7^{p2}), G(a^2,b^1), S(d^1)$
- Y48-Sh binding
  - 13: $R(Y48^p), Sh(\pi,Y7)$ <-> $R(Y48^{p1}), Sh(\pi^1,Y7)$
  - 15: $R(Y48^p), Sh(\pi,Y7^p)$ <-> $R(Y48^{p1}), Sh(\pi^1,Y7^p)$
  - 18: $R(Y48^p), Sh(\pi,Y7^{p1}), G(a^1,b)$ <-> $R(Y48^{p2}), Sh(\pi^2,Y7^{p1}), G(a^1,b)$
  - 20: $R(Y48^p), Sh(\pi,Y7^{p1}), G(a^1,b^3), S(d^3)$ <-> $R(Y48^{p2}), Sh(\pi^2,Y7^{p1}), G(a^1,b^3), S(d^3)$

refined from
$R(Y48^p)+Sh(\pi)$<->$R(Y48^{p1})+Sh(\pi^1)$

why not simply $G(b^3)$??

- Sh-G binding
  - 17: $R(Y48^{p1}), Sh(\pi^1,Y7^p), G(a,b)$ <-> $R(Y48^{p1}), Sh(\pi^1,Y7^{p2}), G(a^2,b)$
  - 21: $Sh(\pi,Y7^p), G(a,b)$ <-> $Sh(\pi,Y7^{p1}), G(a^1,b)$
  - 23: $Sh(\pi,Y7^p), G(a,b^2)$ <-> $Sh(\pi,Y7^{p1}), G(a^1,b^2)$
  - 24: $R(Y48^{p1}), Sh(\pi^1,Y7^p), G(a,b^3), S(d^3)$ <-> $R(Y48^{p1}), Sh(\pi^1,Y7^{p2}), G(a^2, b^3), S(d^3)$

refined from
$Sh(\pi), G(a)$<->$Sh(\pi^1), G(a^1)$

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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:

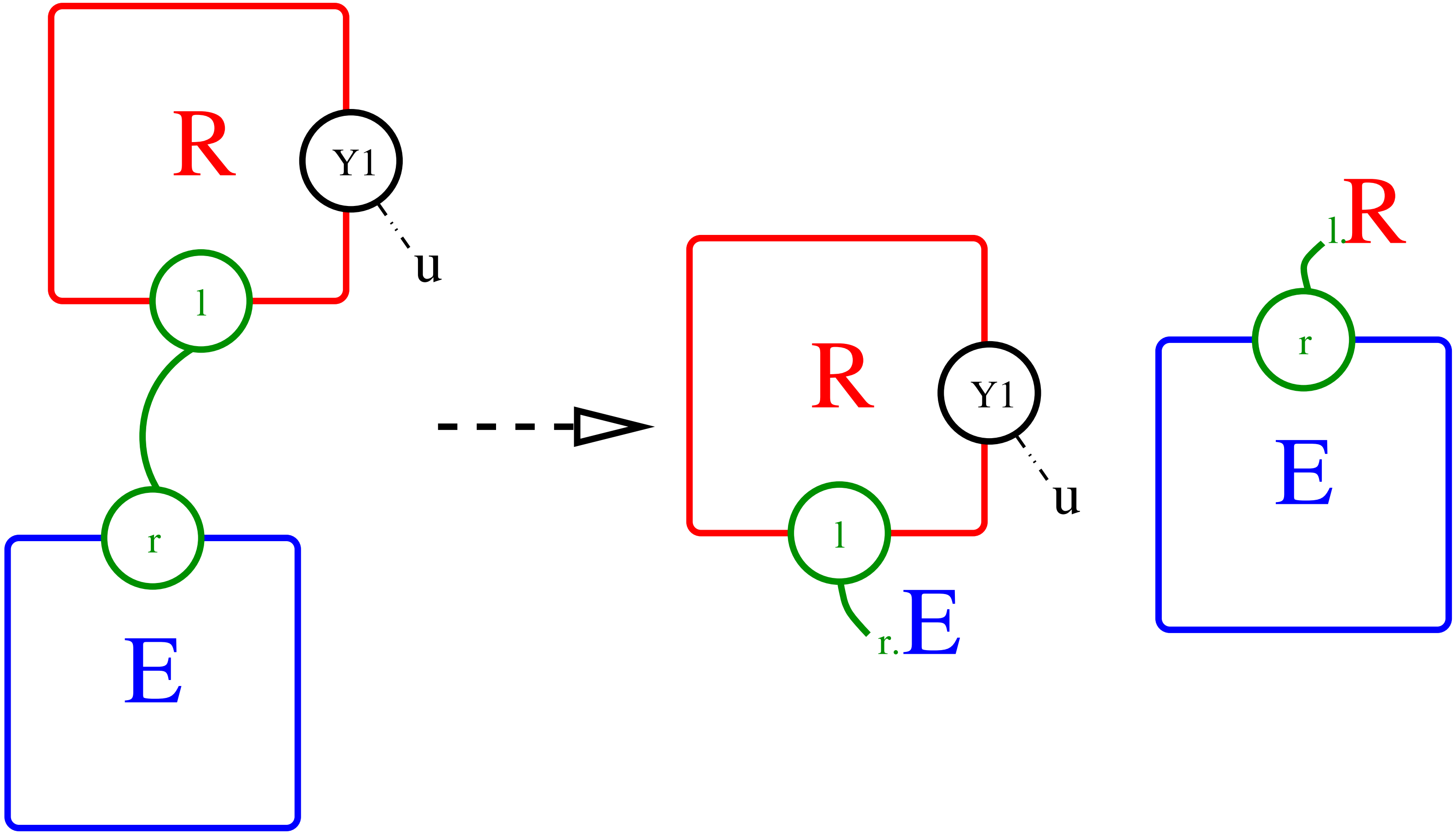
$$\mathbb{F} : \begin{cases} \wp(\mathit{Complex}) & \to \wp(\mathit{Complex}) \\ X & \mapsto X \cup \left\{ c'_j \;\middle|\; \begin{array}{l} \exists R_k \in \mathcal{R}, c_1, \ldots, c_m \in X, \\ c_1, \ldots, c_m \to_{R_k} c'_1, \ldots, c'_n \end{array} \right\} \end{cases}.$$

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 $\alpha \in \wp(\mathit{Complex}) \to \wp(\mathit{local\_view})$ 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:

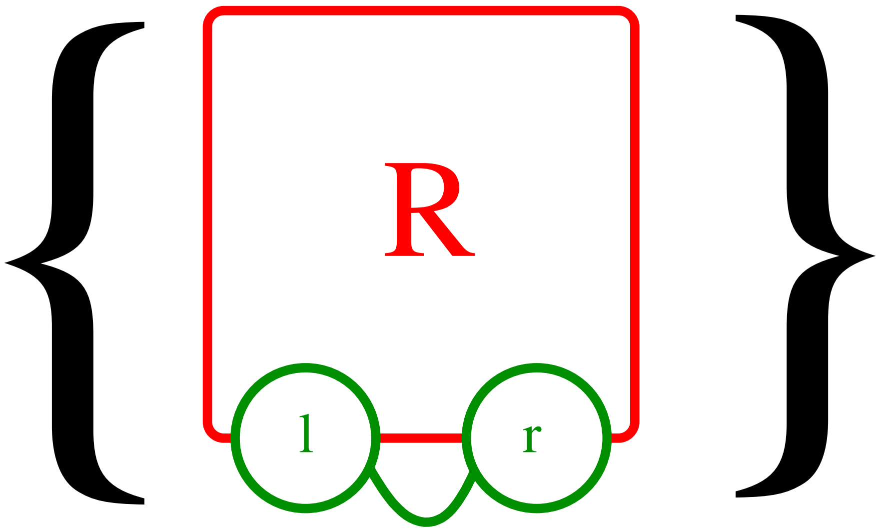
$$\wp(\mathit{Complex}) \underset{\alpha}{\overset{\gamma}{\leftrightarrows}} \wp(\mathit{local\_view}).$$

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

$\gamma \circ \alpha$

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

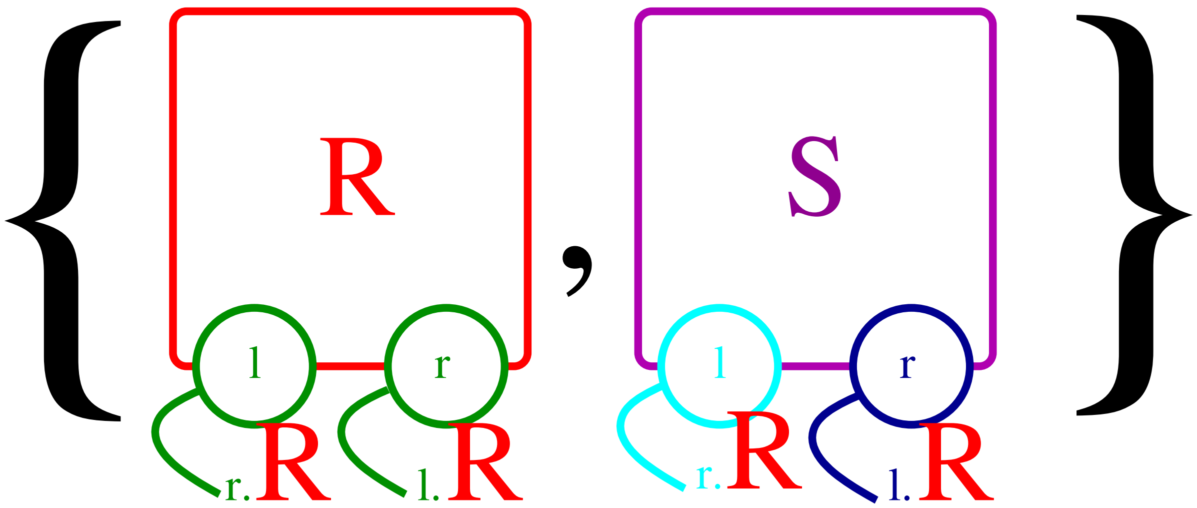
Guess the image of the following set of complexes ?



$\alpha \circ \gamma$

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

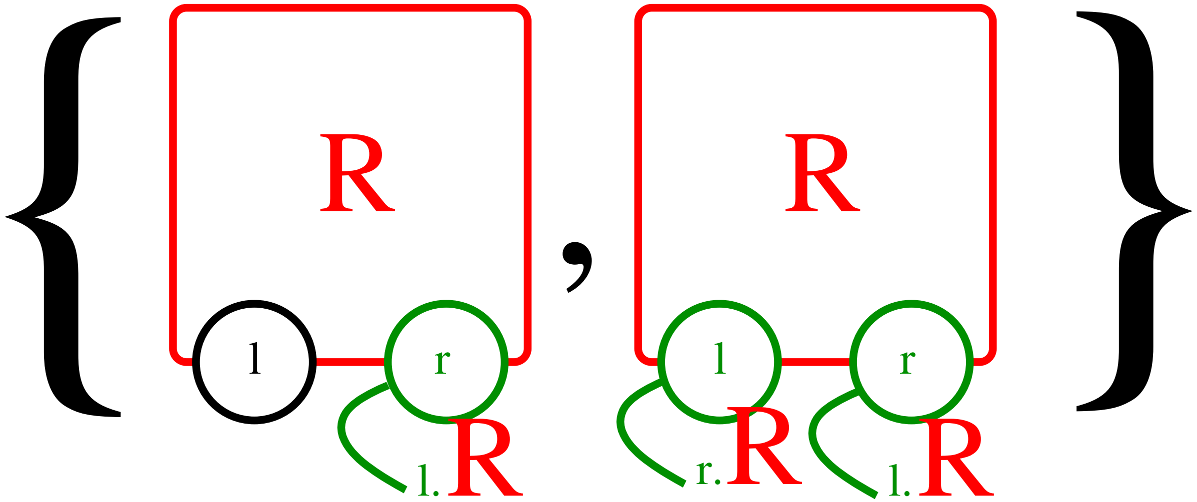
Guess the image of the following set of local views ?



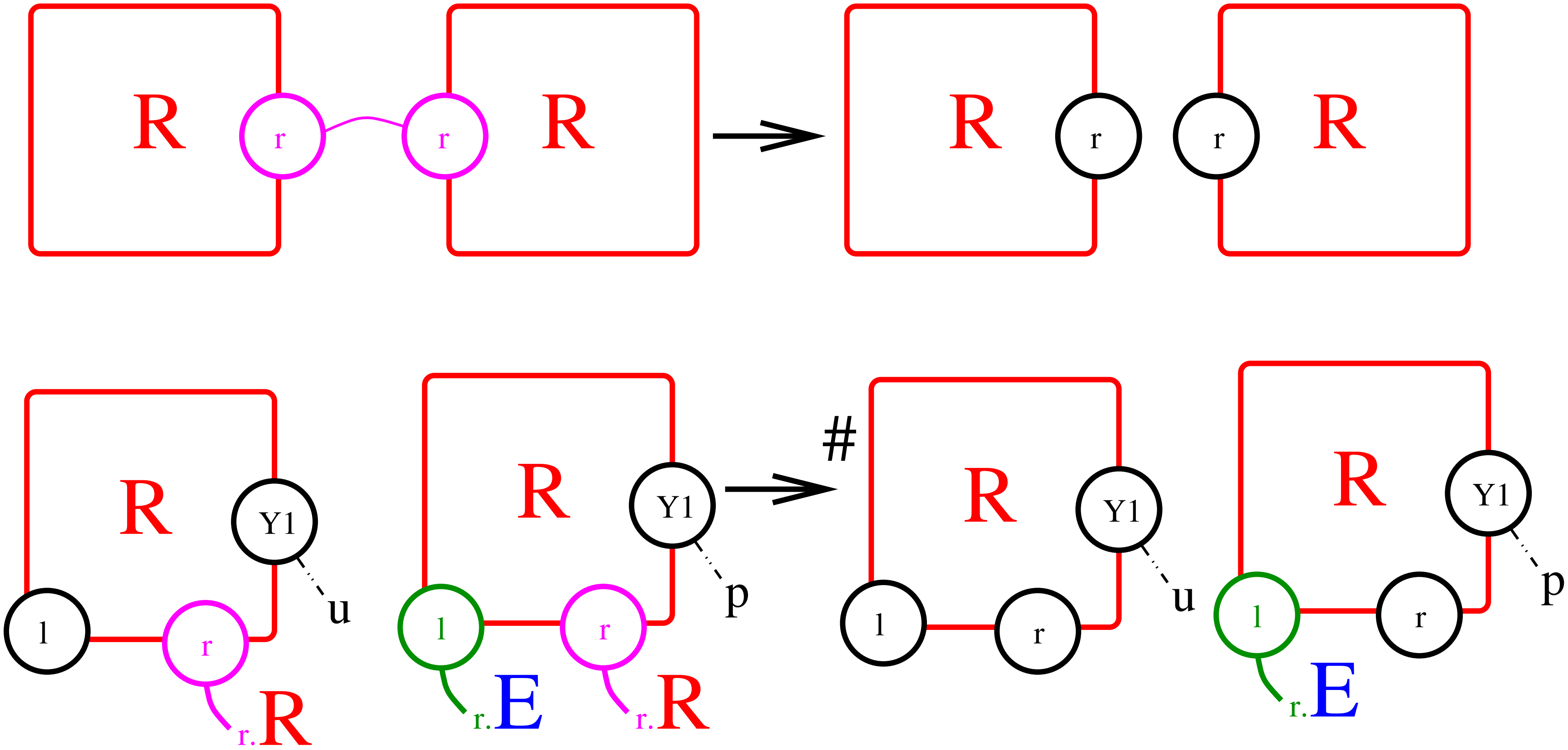
One more question

$\alpha \circ \gamma$ 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:

$$\mathbb{F}^\sharp : \begin{cases} \wp(\mathit{local\_view}) & \rightarrow \wp(\mathit{local\_view}) \\ X & \mapsto X \cup \left\{ lv'_j \;\middle|\; \begin{array}{l} \exists R_k \in \mathcal{R}, lv_1, \ldots, lv_m \in X, \\ lv_1, \ldots, lv_m \rightarrow^\sharp_{R_k} lv'_1, \ldots, lv'_n \end{array} \right\}. \end{cases}$$

We have:

- $\mathbb{F}^\sharp$ is extensive;
- $\mathbb{F}^\sharp$ is monotonic;
- $\mathbb{F} \circ \gamma \mathrel{\dot{\subseteq}} \gamma \circ \mathbb{F}^\sharp$;
- $\mathbb{F}^\sharp \circ \alpha = \alpha \circ \mathbb{F} \circ \gamma \circ \alpha$.

Soundness

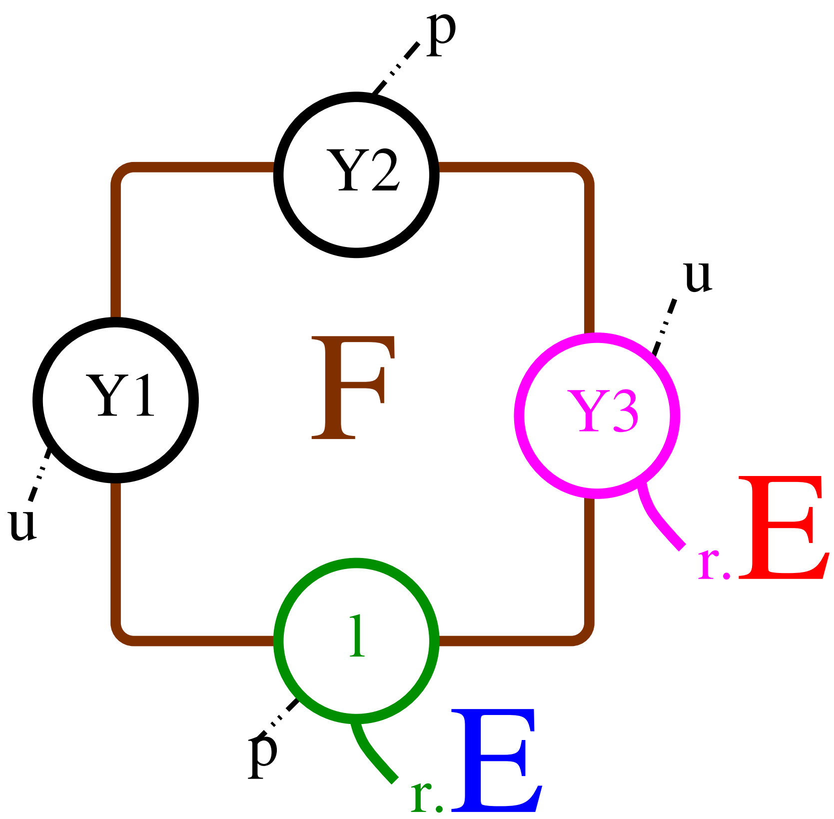
Theorem 1 Let:

1. $(D, \subseteq, \cup)$ and $(D^\sharp, \sqsubseteq, \sqcup)$ be chain-complete partial orders;
2. $D \underset{\alpha}{\overset{\gamma}{\leftrightarrows}} D^\sharp$ be a Galois connexion;
3. $\mathbb{F} \in D \rightarrow D$ and $\mathbb{F}^\sharp \in D^\sharp \rightarrow D^\sharp$ be monotonic mappings such that: $\mathbb{F} \circ \gamma \ \dot{\subseteq}\ \gamma \circ \mathbb{F}^\sharp$;
4. $x_0 \in D$ be an element such that: $x_0 \subseteq \mathbb{F}(x_0)$;

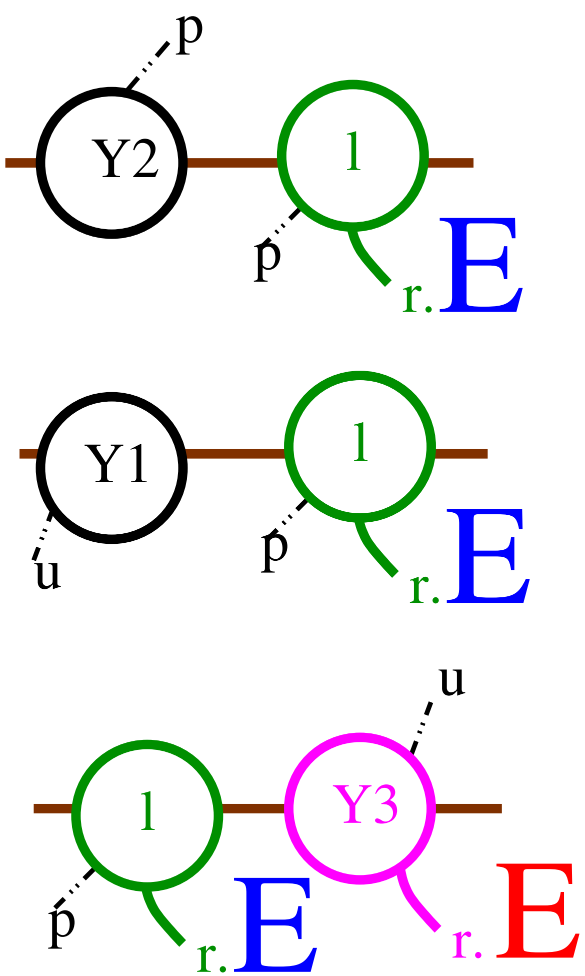
Then:

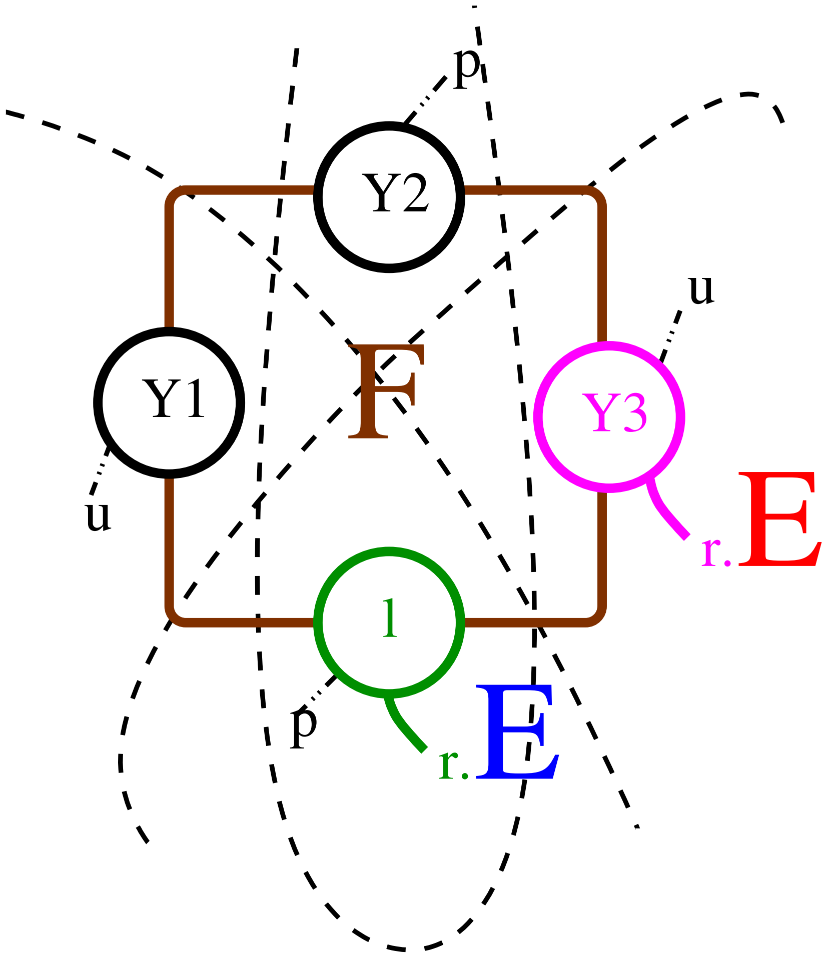
1. both $\mathit{lfp}_{x_0}\mathbb{F}$ and $\mathit{lfp}_{\alpha(x_0)}\mathbb{F}^\sharp$ exist,
2. $\mathit{lfp}_{x_0}\mathbb{F} \subseteq \gamma(\mathit{lfp}_{\alpha(x_0)}\mathbb{F}^\sharp)$.

Combinatorial blow up



Avoiding combinatorial blow up





Packing

- packing strategy: a covering $\mathcal{P}$ of the set of sites.
- template: a class $p \in \mathcal{P}$ in the covering.
- projection: for any $p \in \mathcal{P}$, the function Π_p restricts a local view to p.
- sub-local-view: $\textit{sub\_local\_view} = \{\Pi_p(\textit{lv}) \mid \textit{lv} \in \textit{local\_view},\ p \in \mathcal{P}\}$.
- abstraction: the following function

$$\alpha_{\text{PACKS}} : \begin{cases} \wp(\textit{local\_view}) & \rightarrow \wp(\textit{sub\_local\_view}) \\ X & \mapsto \{\Pi_p(\textit{lv}) \mid \textit{lv} \in X,\ p \in \mathcal{P}\}. \end{cases}$$

  is a $\cup$-complete morphism.
  It defines a Galois connexion $\wp(\textit{local\_view}) \underset{\alpha_{\text{PACK}}}{\overset{\gamma_{\text{PACK}}}{\leftrightarrows}} \wp(\textit{sub\_local\_view})$.
- counterpart: $\mathbb{F}^\sharp_{\text{PACK}} = \alpha_{\text{PACK}} \circ \mathbb{F}^\sharp \circ \gamma_{\text{PACK}}$.

Automatic packing

Let P be a covering such that:

1. each site is at least in one class of P;
2. whenever a rule modifies two sites a and b, then, for any $p \in P$, $a \in p \iff b \in p$;
3. whenever a rule modifies a site a and tests a site b, then for any $p \in P$, $a \in p \implies b \in p$;
4. $\mathit{Complex}_0 \in \gamma_{\mathsf{PACKS}}(\wp(\mathit{sub\_local\_view}))$.

Then, for any $n \in \mathbb{N}$,

$$\gamma_{\mathsf{PACKS}}(\mathbb{F}^{\sharp\, n}_{\mathsf{PACKS}}(\alpha_{\mathsf{PACKS}}(\mathit{Complex}_0))) = \mathbb{F}^{\sharp n}(\mathit{Complex}_0).$$

So, automatic packing never changes analysis results !!!

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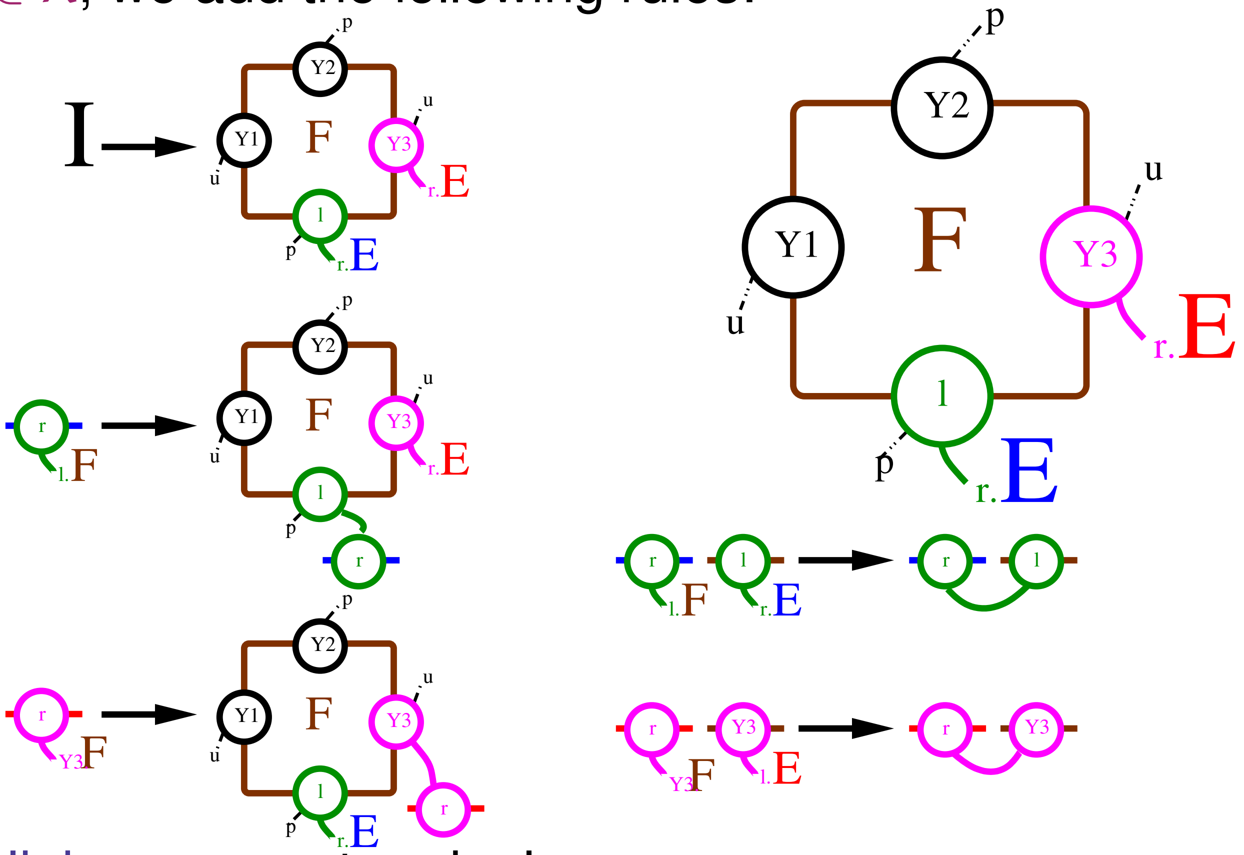
Concretization

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



I and semi-links are non-terminal.

Pumping lemma

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

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

     can be built.
- We only enumerate complexes that are reached through an acyclic rewriting computation.
- We prove later that: if $X \in \alpha(\wp(\mathit{Complex}))$ then each partial rewrite sequence is the prefix of a terminating rewrite sequence.

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 complexes);
- for FGF cascade (79080 complexes);

We know how to build systems with false positives. . .

. . .but they seem to be biologically meaningless.

This raises the following issues:

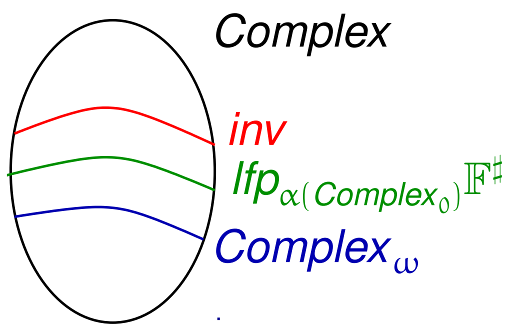
- Can we characterize which information is abstracted away ?
- Which is the form of the systems, for which we have no false positive ?
- Do we learn something about the biological systems that we describe ?

Which information is abstracted away ?

Theorem 2 We suppose that:

1. $(\mathcal{D}, \subseteq)$ be a partial order;
2. $(\mathcal{D}^\sharp, \sqsubseteq, \sqcup)$ be chain-complete partial order;
3. $\mathcal{D} \underset{\alpha}{\overset{\gamma}{\leftrightarrows}} \mathcal{D}^\sharp$ be a Galois connexion;
4. $\mathbb{F} \in \mathcal{D} \to \mathcal{D}$ and $\mathbb{F}^\sharp \in \mathcal{D}^\sharp \to \mathcal{D}^\sharp$ are monotonic;
5. $\mathbb{F} \circ \gamma \,\dot{\subseteq}\, \gamma \circ \mathbb{F}^\sharp$;
6. $x_0, \mathit{inv} \in \mathcal{D}$ such that:
    - $x_0 \subseteq \mathbb{F}(x_0) \subseteq \mathbb{F}(\mathit{inv}) \subseteq \mathit{inv}$,
    - $\mathit{inv} = \gamma(\alpha(\mathit{inv}))$,
    - and $\alpha(\mathbb{F}(\gamma(\alpha(\mathit{inv})))) = \mathbb{F}^\sharp(\alpha(\mathit{inv}))$;

Then, $\mathit{lfp}_{\alpha(x_0)}\mathbb{F}^\sharp$ exists and $\gamma(\mathit{lfp}_{\alpha(x_0)}\mathbb{F}^\sharp) \subseteq \mathit{inv}$.



When is there no false positive ?

Theorem 3 We suppose that:

1. $(\mathcal{D}, \subseteq, \cup)$ and $(\mathcal{D}^\sharp, \sqsubseteq, \sqcup)$ are chain-complete partial orders;
2. $(\mathcal{D}, \subseteq) \xleftarrow[\alpha]{\gamma} \xrightarrow{} (\mathcal{D}^\sharp, \sqsubseteq)$ is a Galois connexion;
3. $\mathbb{F} : \mathcal{D} \to \mathcal{D}$ is a monotonic map;
4. x_0 is a concrete element such that $x_0 \subseteq \mathbb{F}(x_0)$;
5. $\mathbb{F}^\sharp \circ \alpha = \alpha \circ \mathbb{F} \circ \gamma \circ \alpha$

Then:

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

Local set of complexes

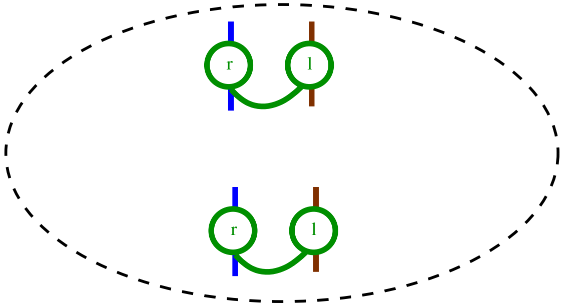
Definition 1 We say that a set $X \in \wp(\mathit{Complex})$ of complexes is local if and only if it satisfies $X = \gamma(\alpha(X))$.

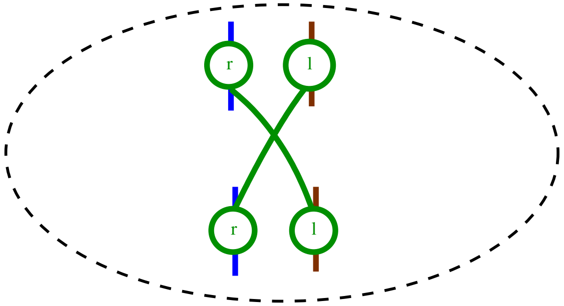
Remark 1 *A set* $X \in \wp(\mathit{Complex})$ *is local if and only if* $X \in \gamma(\wp(\mathit{local\_view}))$*.*

Swapping relation

We define the binary relation $\overset{\text{SWAP}}{\sim}$ among tuples *Complex** of complexes.

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 4 Let $X \in \wp(\textit{Complex})$ be a set of complexes.
The two following assertions are equivalent:

1. the set $X \in \wp(\textit{Complex})$ is local (i.e. $\gamma(\alpha(X)) = X$);
2. for any tuples $(C_i), (D_j) \in \textit{Complex}^*$ such that:
   - $(C_i) \in X^*$,
   - and $(C_i) \overset{\text{SWAP}}{\sim} (D_j)$;

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

Proof (easier implication way)

If:

- $X = \gamma(\alpha(X))$,
- $(C_i) \in X^*$,
- and $(C_i) \overset{\text{SWAP}}{\sim} (D_j)$;

Then:

we have $\alpha(\{C_i\}) = \alpha(\{D_j\})$ (because $(C_i) \overset{\text{SWAP}}{\sim} (D_j)$)
and $\alpha(\{C_i\}) \subseteq \alpha(X)$ (because $(C_i) \in X^*$ and by monotonicity);
so $\alpha(\{D_j\}) \subseteq \alpha(X)$;
so $\{D_j\} \subseteq \gamma(\alpha(X))$ (by def. of Galois connexions);
so $\{D_j\} \subseteq X$ (since $X = \gamma(\alpha(X))$);
so $(D_j) \in X^*$.

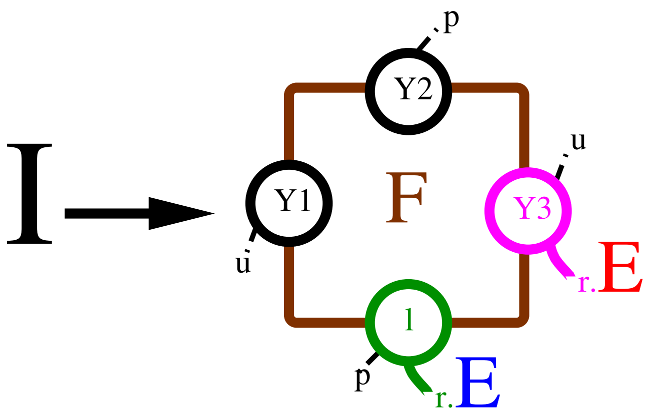
Proof (more difficult implication way)

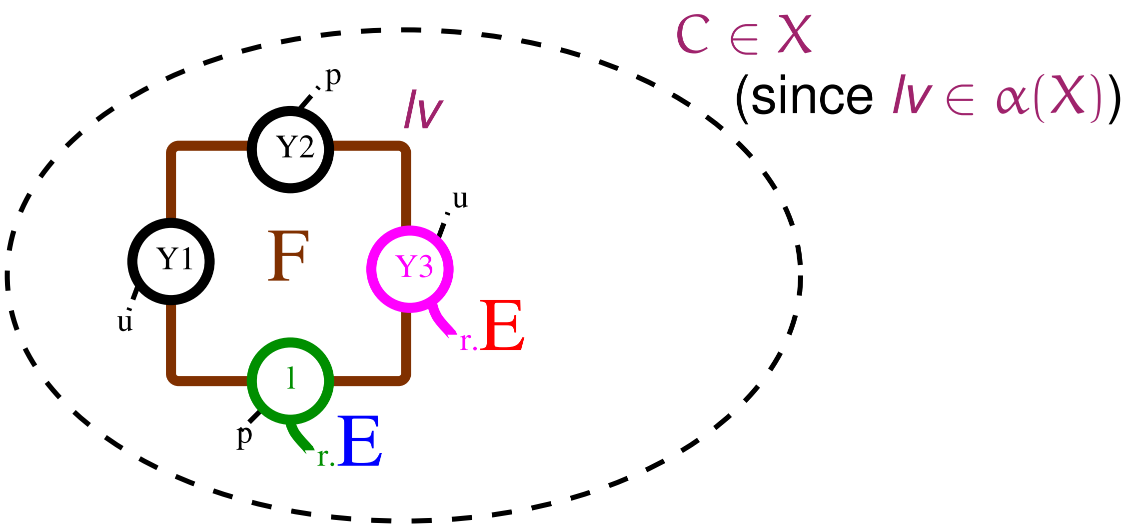
We suppose that X is close with respect to $\overset{\text{SWAP}}{\sim}$.
We want to prove that $\gamma(\alpha(X)) \subseteq X$.

We prove, by induction, that any open complex that can be built using the rewrite system (associated with $\alpha(X)$) can be embedded in a complex in X:

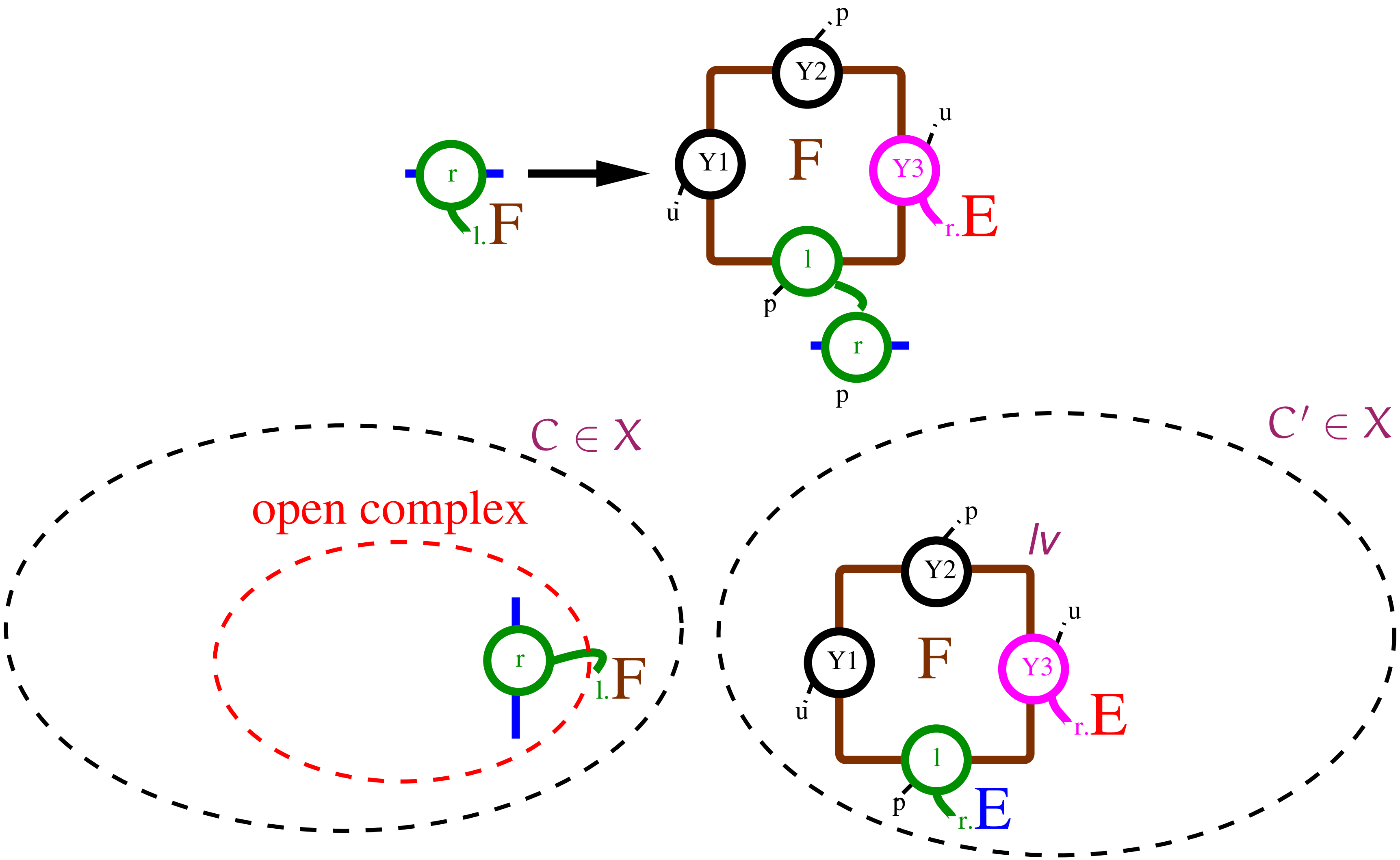
- By def. of α, this is satisfied for any local view in $\alpha(X)$;
- This remains satisfied after unfolding a semi-link with a local view;
- This remains satisfied after binding two semi-links.

Initialization

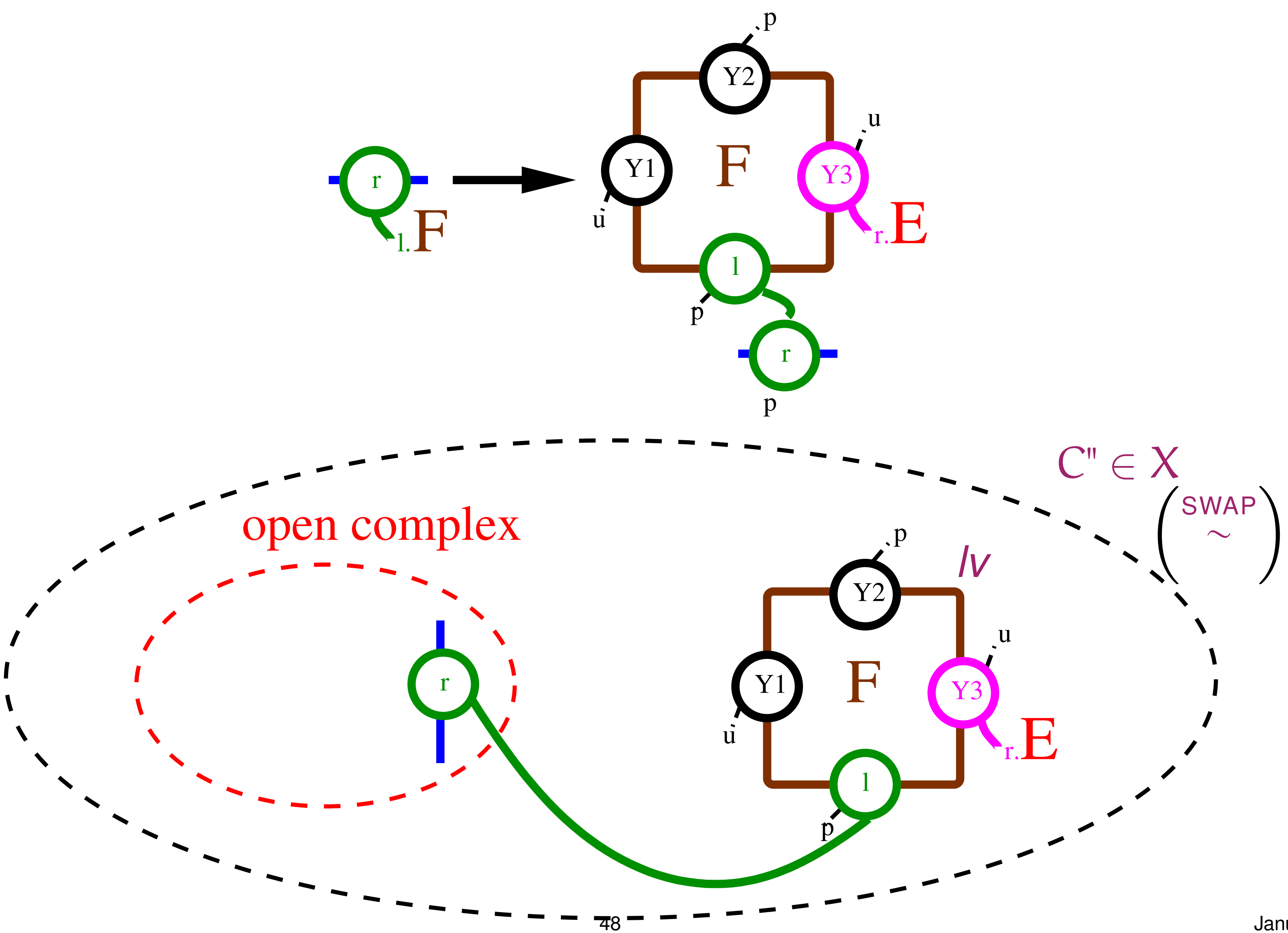




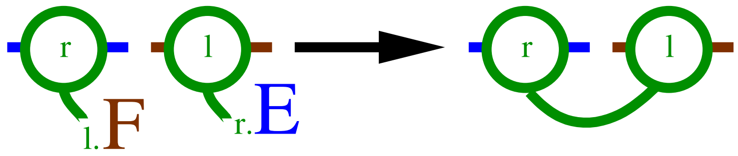
Unfolding a semi-link

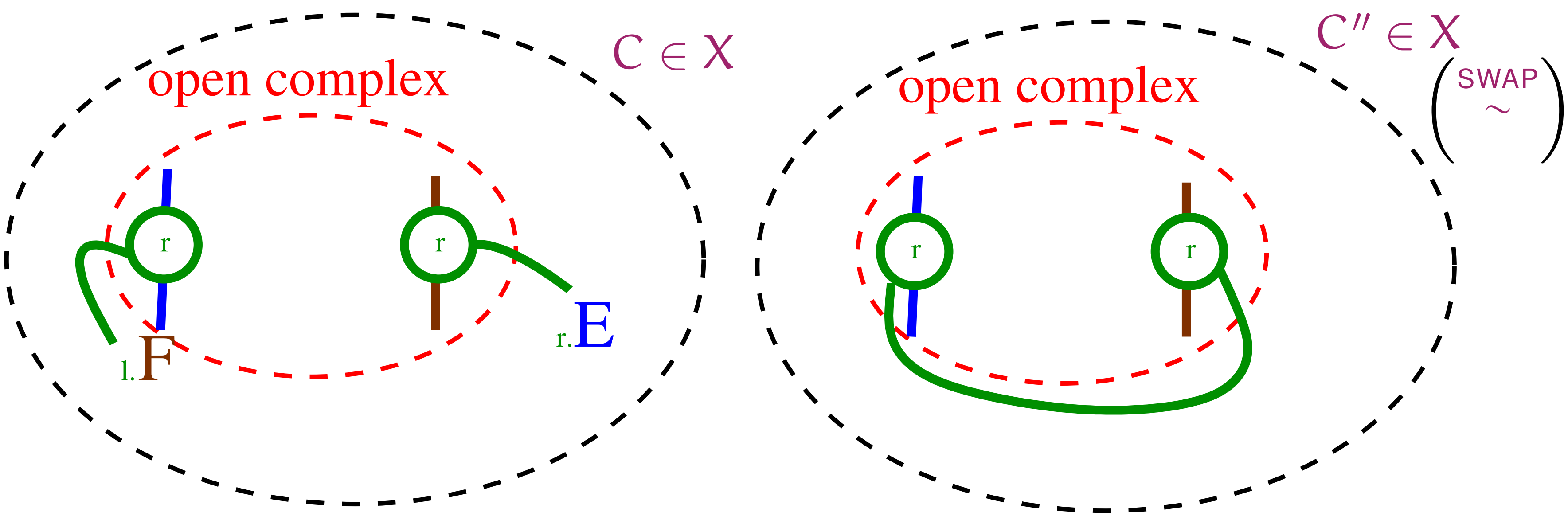


Unfolding a semi-link



Binding two semi-links





Consequences

Let $X \in \alpha(\wp(\mathit{Complex}))$ be a set of complexes.

1. Each open complex C built with the local views in X is a sub-complex of a close complex C' in $\gamma(X)$.

2. When considering the rewrite system that computes $\gamma(X)$, any partial rewriting sequence can be completed in a successful one.

3. We have $\mathbb{F}^\sharp \circ \alpha = \alpha \circ \mathbb{F} \circ \gamma \circ \alpha$.

4. We have $\mathit{lfp}_{\alpha(x_0)}\mathbb{F}^\sharp \in \alpha(\wp(\mathit{Complex}))$.

Overview

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Outline

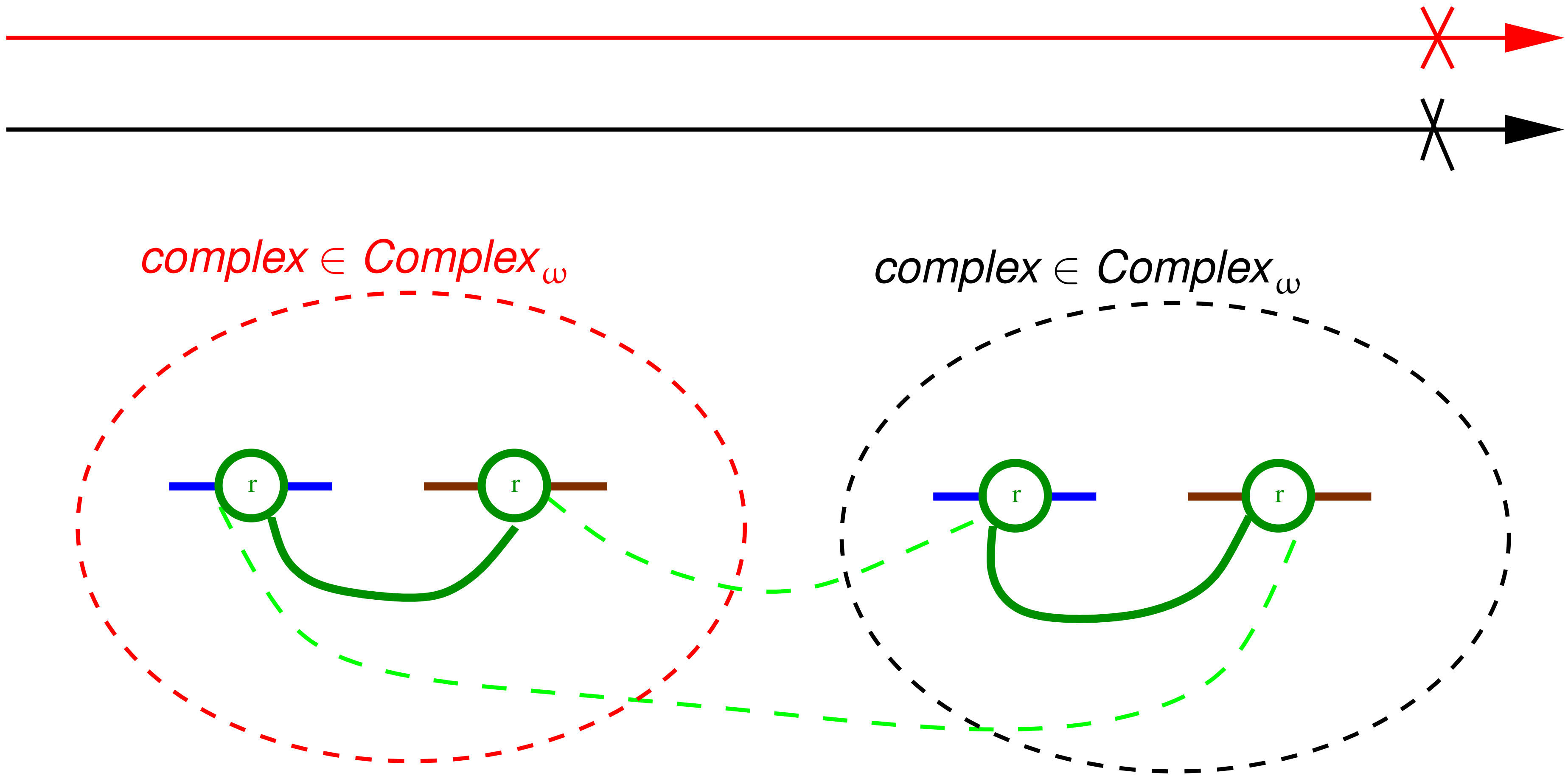
We have proved that:

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

We sketch a proof in order to discover sufficient conditions that ensure this property:

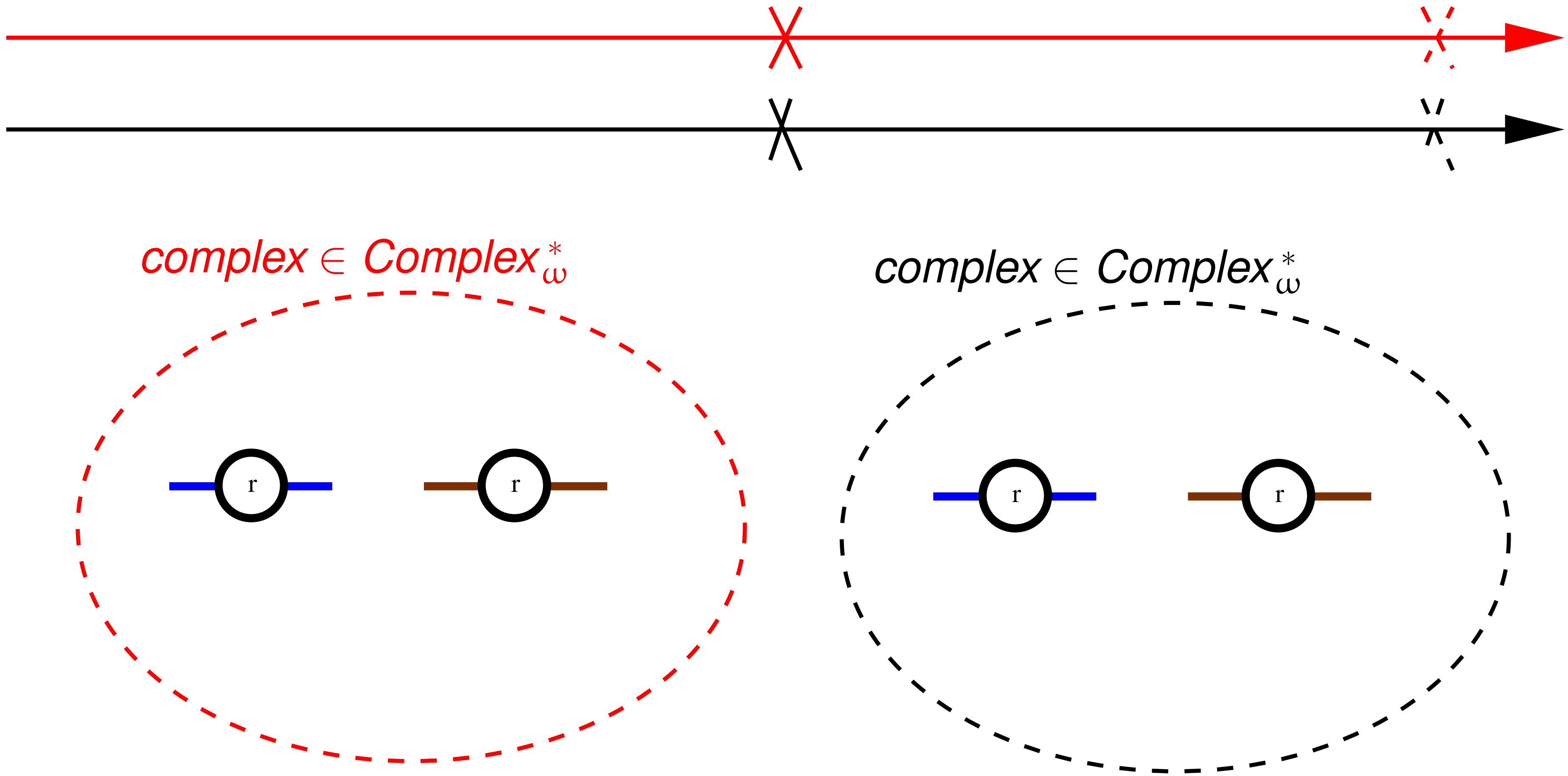
- We consider tuples of complexes in which the same kind of links occur twice.
- We want to swap these links.
- We introduce the history of their computation.
- There are several cases. . .

First case (I/V)



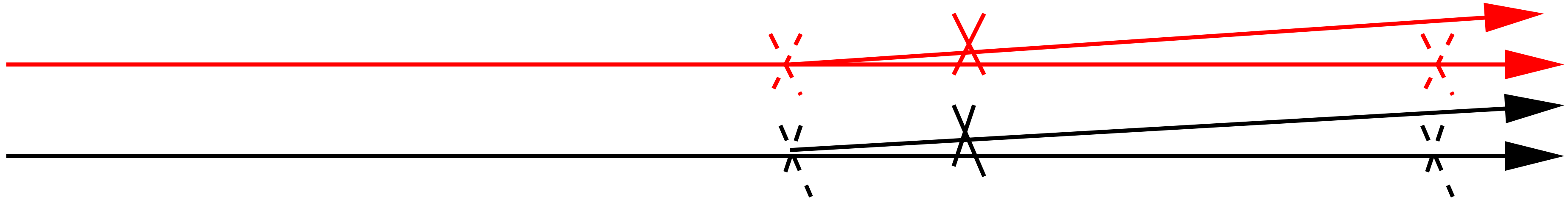
First case (II/V)

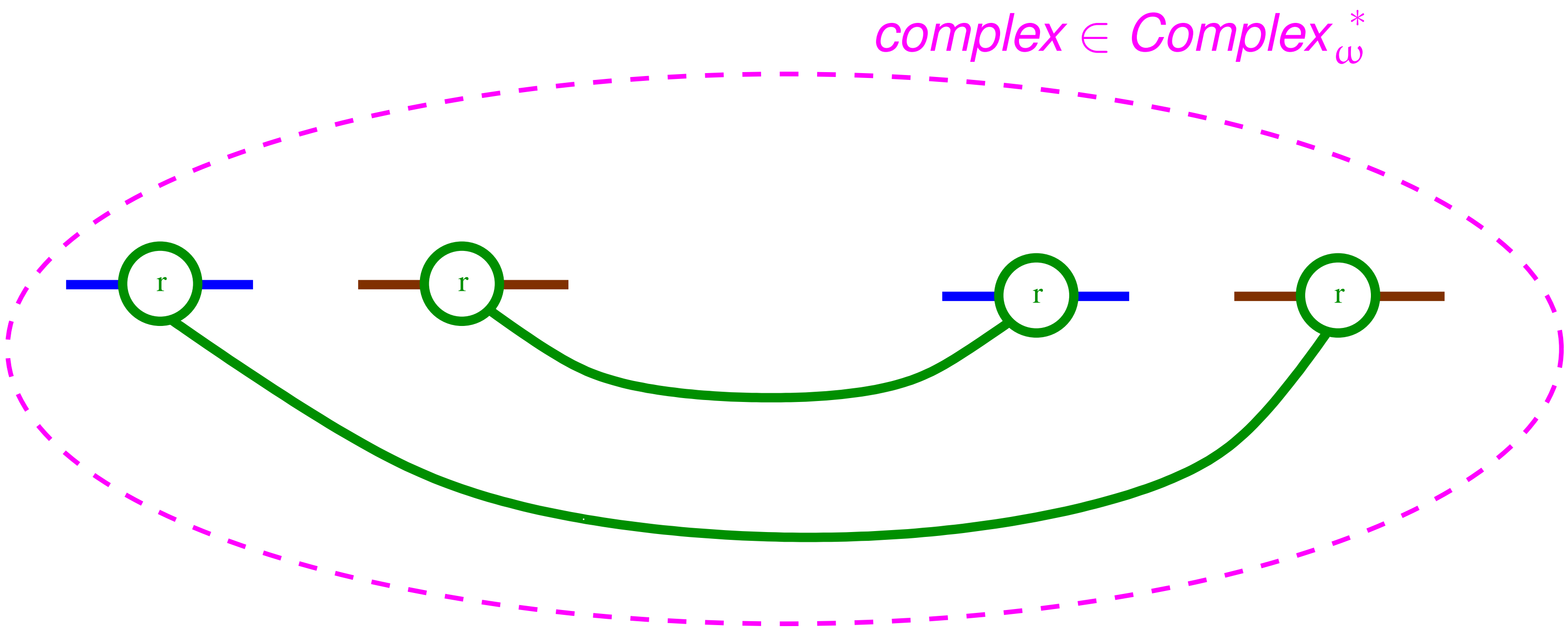
just before the links are made



First case (III/V)

we suppose we can swap the links





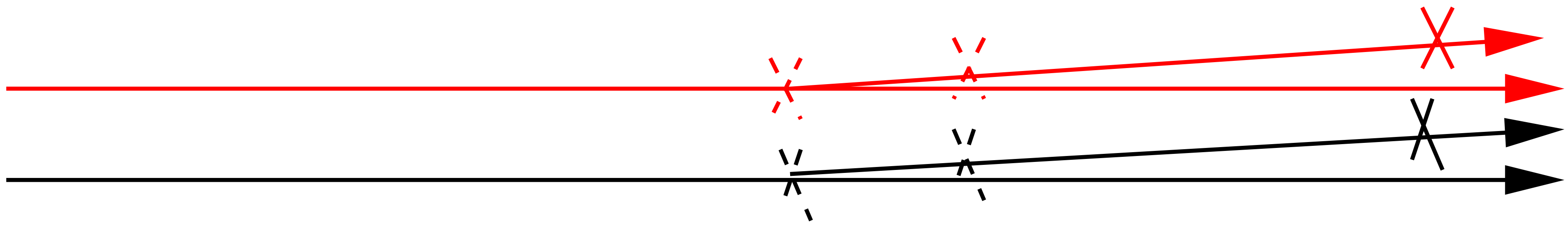
First case (IV/V)

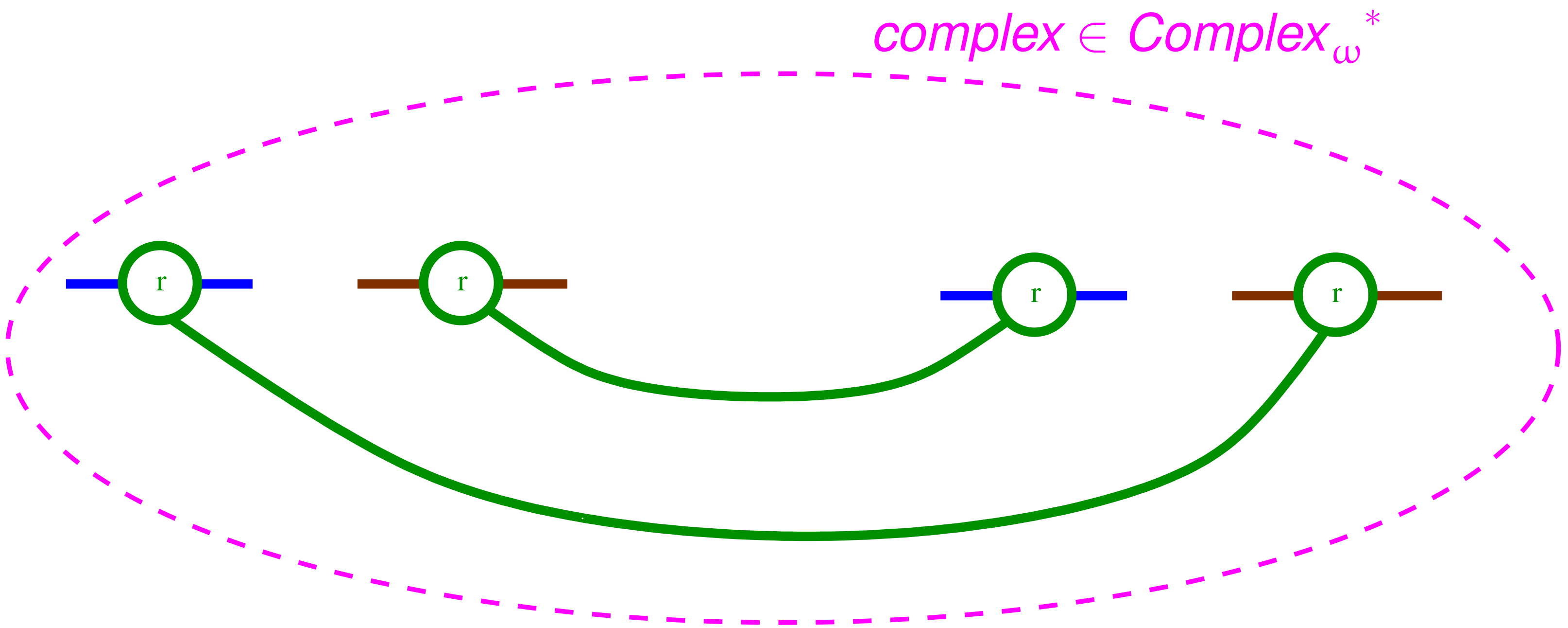
Then, we ensure that further computation steps:

- are always possible;
- have the same effect on local views;
- commute with the swapping relation $\overset{\text{SWAP}}{\sim}$.

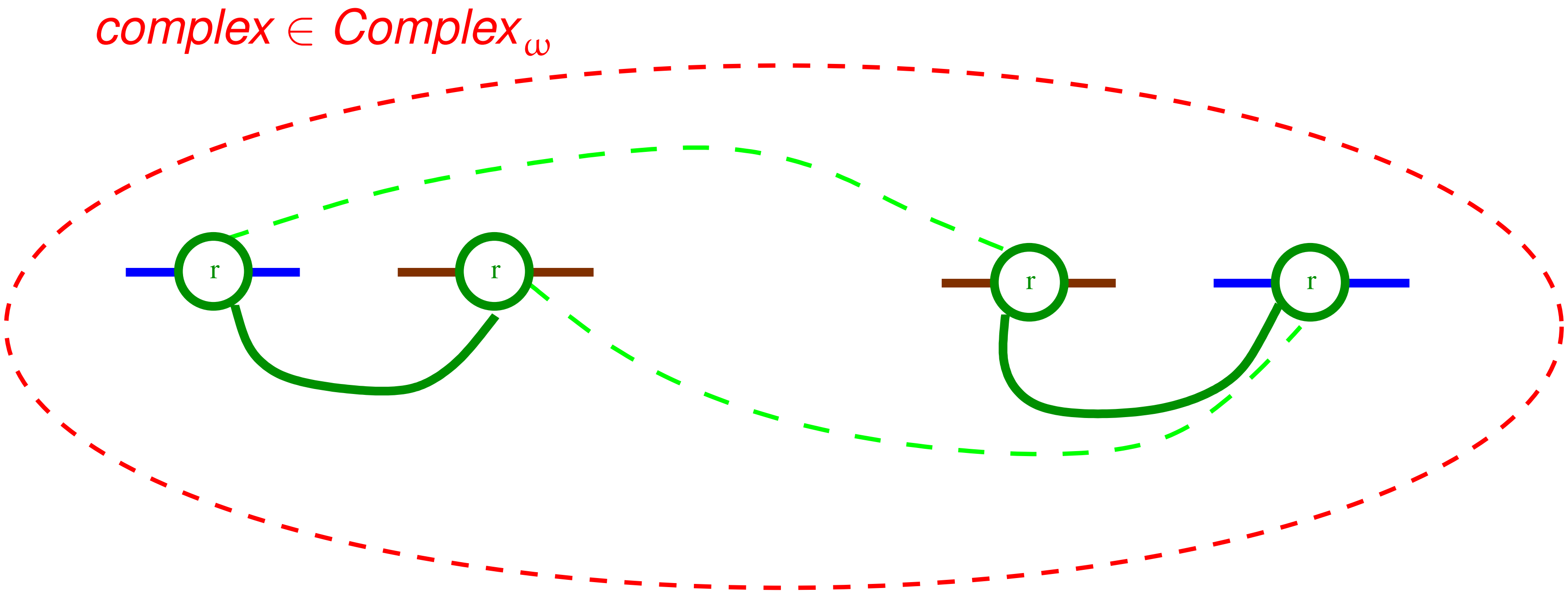
$$
\begin{tikzcd}
C_n \arrow[r, "\overset{\text{SWAP}}{\sim}{,}\sigma"] \arrow[d, "R{,}\phi"] & C'_n \arrow[d, "R{,}\phi"] \\
C_{n+1} \arrow[r, dotted, "\overset{\text{SWAP}}{\sim}{,}\sigma"] & C'_{n+1}
\end{tikzcd}
$$

First case (V/V)



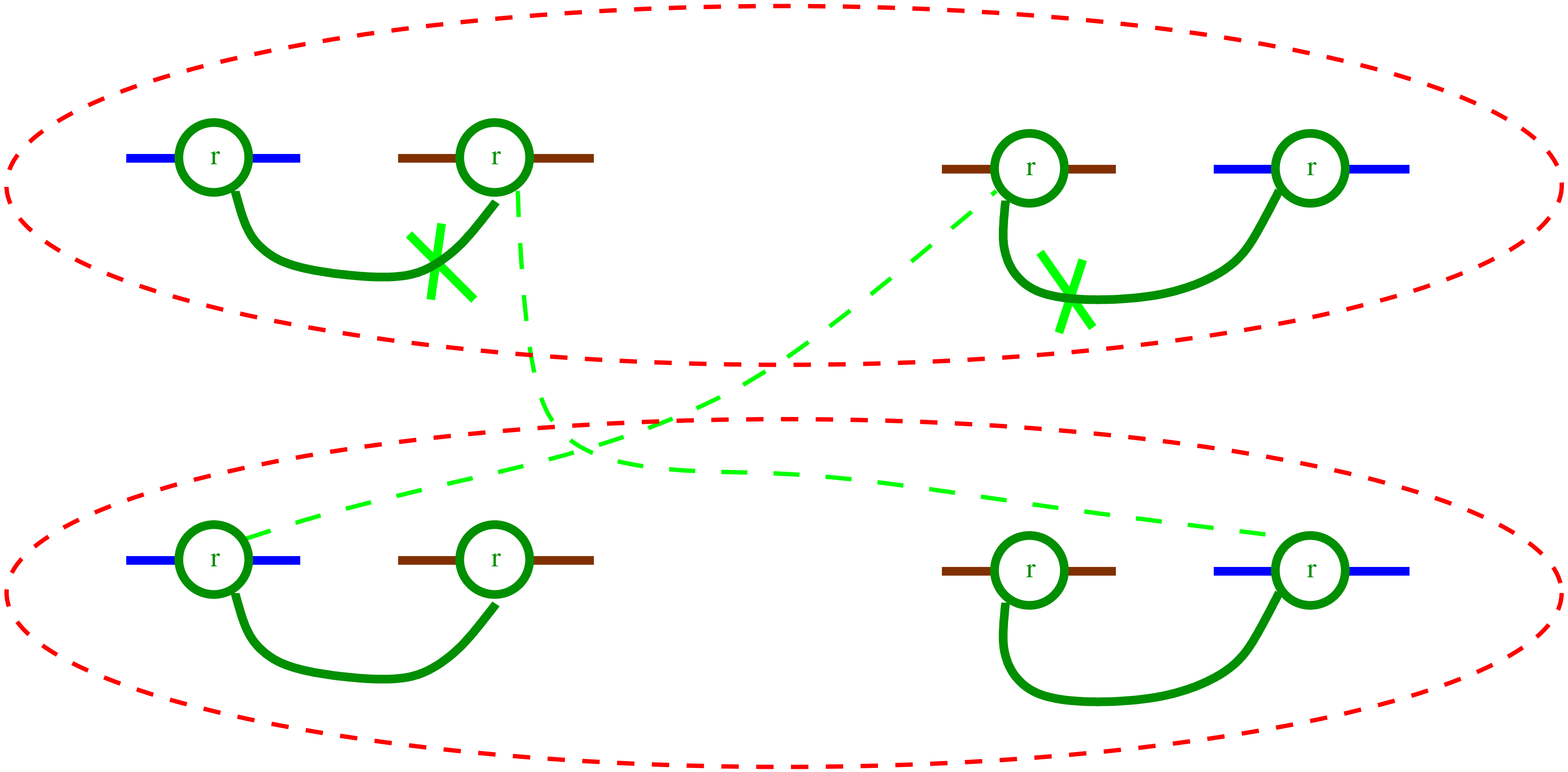


Second case (I/II)



we assume that the complex *complex* is acyclic

Second case (II/II)



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$\sim$m,S),B(b$\sim$n,T) $\rightarrow$ A(a$\sim$m!1,S),B(b$\sim$n!1,T)
   - and A(a$\sim$m',S'),B(b$\sim$n',T') $\rightarrow$ A(a$\sim$m'!1,S'),B(b$\sim$n'!1,T'),

   then:

   - A(a$\sim$m,S),B(b$\sim$n',T') $\rightarrow$ A(a$\sim$m!1,S),B(b$\sim$n'!1,T');
5. ...

are satisfied, the set of reachable complexes is local.

Non local systems

$$\mathit{Complex}_0 \triangleq \mathrm{R(a{\sim}u)}$$

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

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

$$Complex_0 \stackrel{\Delta}{=} \text{A(a$\sim$u),B(a$\sim$u)}$$

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

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

Non local systems

$$\mathit{Complex}_0 \triangleq \text{A(a}{\sim}\text{u)}$$

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

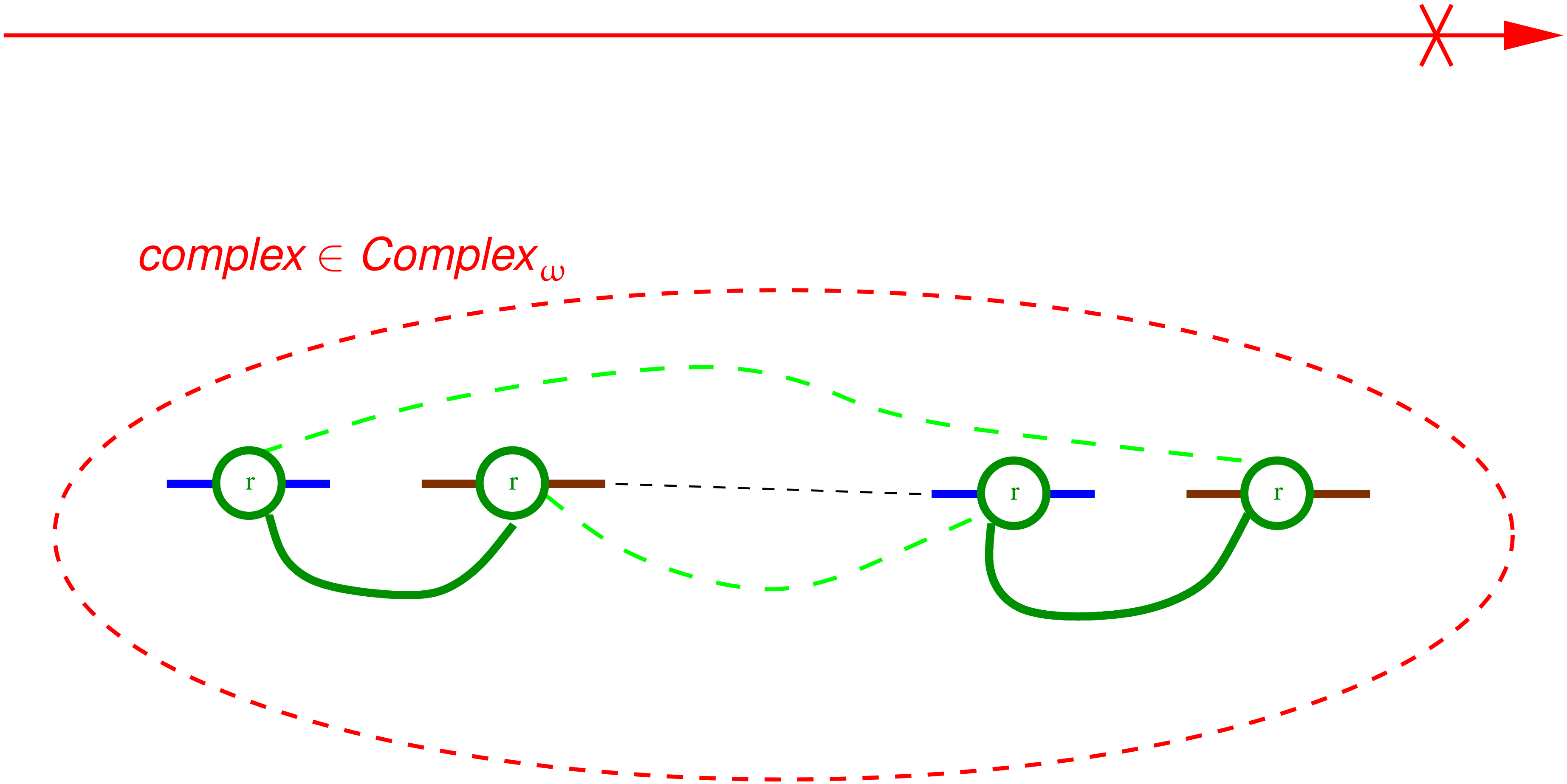
A(a~u!1),A(a~p!1) $\in$ *Complex*$_\omega$
But A(a~p!1),A(a~p!1) $\notin$ *Complex*$_\omega$.

Non local systems

$$
\begin{array}{lcl}
\textit{Complex}_0 & \triangleq & \mathrm{R(a,b)} \\
\textit{Rules} & \triangleq & \{\ \mathrm{R(a,b),R(a)} \rightarrow \mathrm{R(a,b!1),R(a!1)}\}
\end{array}
$$

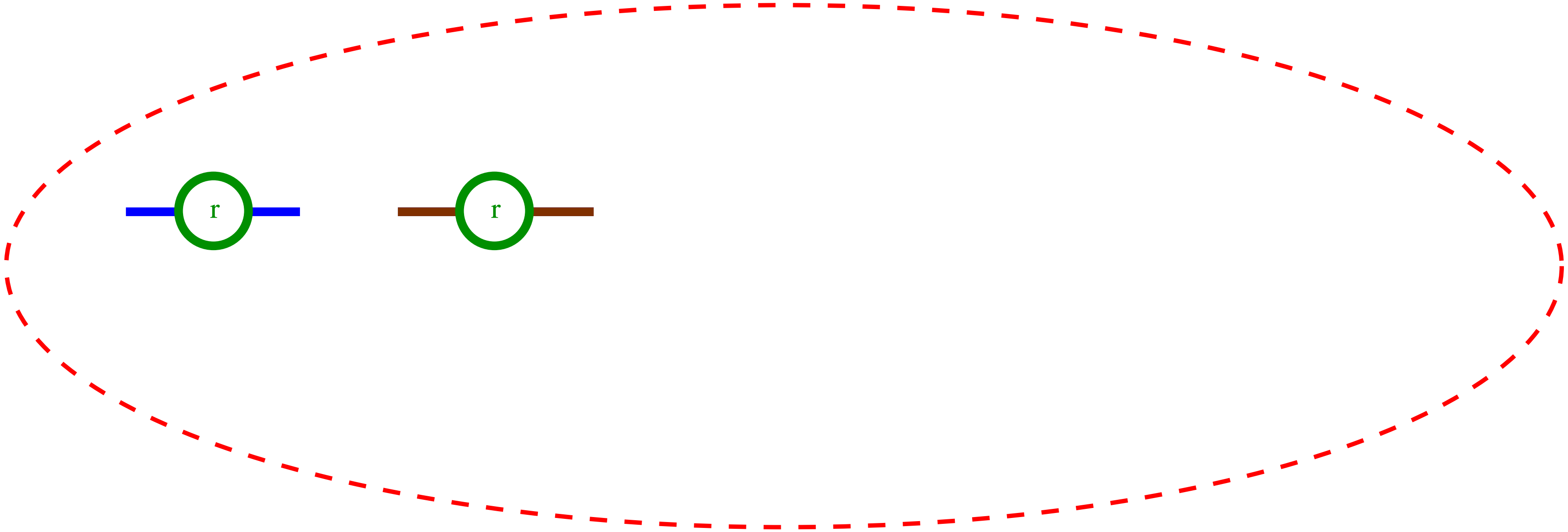
R(a,b!2),R(a!2,b!1),R(a!1,b)$\in$ *Complex*$_\omega$
But R(a!1,b!1) $\notin$ *Complex*$_\omega$.

Third case (I/III)

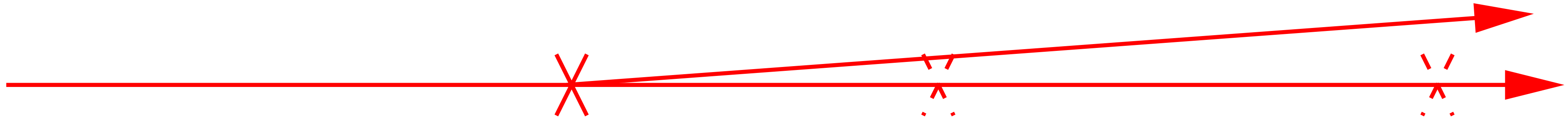


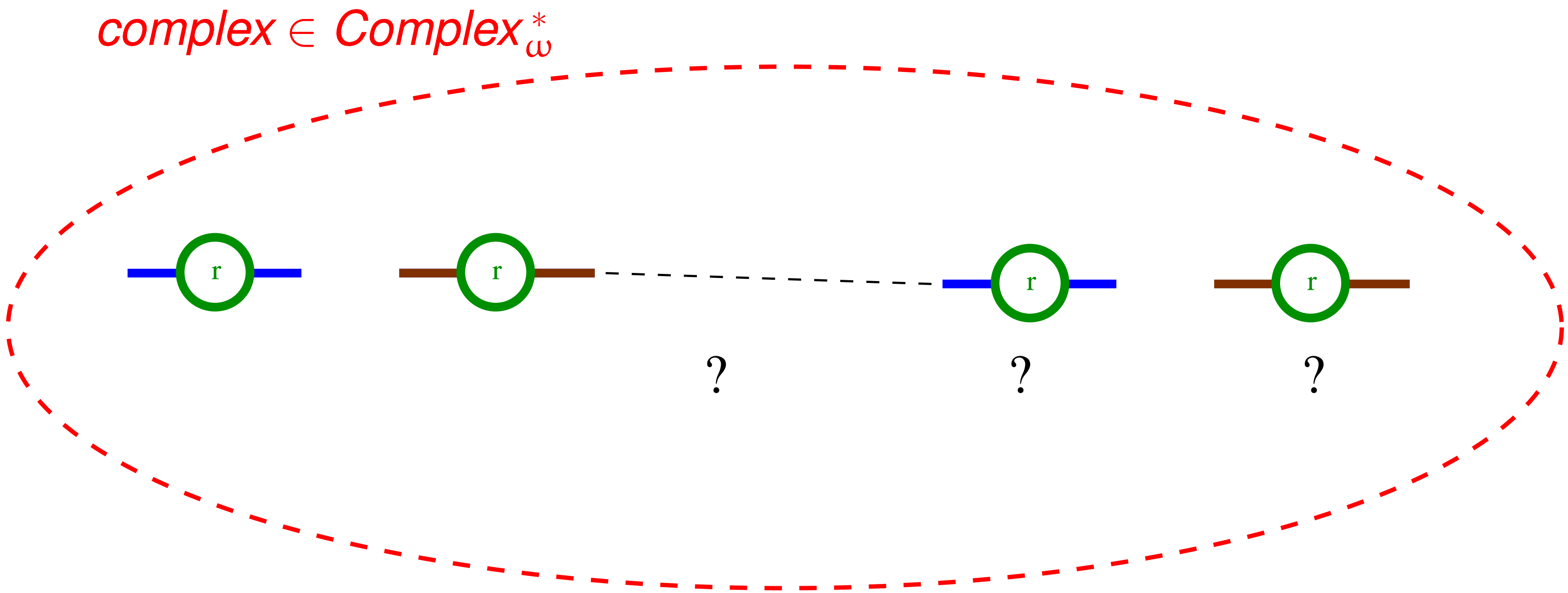
Third case (II/III)

complex $\in$ *Complex*$_{\omega}^{*}$



Third case (II/III)





Dangerous sites

A site is dangerous if it may occur in a cycle within a complex ($\in \gamma(\alpha(\mathit{Complex}_{\omega}))$).

To ensure that the set of reachable complexes is local, we also require that:

- The binding state of a dangerous site is never tested, unless for binding or unbinding this site.
- When we bind dangerous sites, we only test that these sites are free.

Then, we prove that:

1. we can build any complex with free dangerous sites,
2. then, we can bind them as much as we like.

Overview

Outline

- we have a syntactic criterion in order to ensure that the set of reachable complexes 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 complexes;
     - 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:

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

Decontextualized rule:

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

We can remove exhaustive enumerations.

How does it work ?

To remove a test, we prove that:

- this test is satisfied whenever the other tests are satisfied;
- or each complex that passes all tests but this one also matches with the left hand side of another rule that performs the same action.

More formally

More formally:

- Each rule R is associated with the set $S(R)$ of open complexes that can match its lhs;
- Rules are gathered in equivalence classes according to the actions they perform;
- For each class $[R]$, we compute:

$$\mathcal{G}([R]) = \cup\{S(R') \mid R' \in [R]\}.$$

- For each class $[R]$, $\mathit{Reach}([R])$ is an over approximation of the set of open complexes that may match the lhs of a rule $R' \in [R]$.

A rule R may be decontextualized in a rule R' if:

$$S(R') \cap \mathit{Reach}([R]) \subseteq \mathcal{G}([R]).$$

Decontextualization is more efficient, if the reachability analysis is accurate.

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 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 C of a rule, we try to apply it for another context C' by:

1. removing the context C' (backtrack) ;
2. building the context C ;
3. applying the initial rule ;
4. removing the context C (backtrack) ;
5. building the context C'.

This is proved manually.

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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

- Reachability analysis.
  - Shape analysis: three valued logic, Mauborgne's graph abstract domains.
- Trace abstraction.
  - Can we lift the local-view abstraction to trace semantics ?
  - Which information do we obtain ?
- Quantitative/Semi-quantitative abstractions.
  - Can we design abstract domains to discover semi-quantitative properties (i.e. overshoot detection) ?