MPRI

Abstract interpretation of protein-protein interactions networks

Jérôme Feret
Laboratoire d'Informatique de l'École Normale Supérieure
INRIA, ÉNS, CNRS
http://www.di.ens.fr/∼feret

Friday, the 18th of January, 2013

Joint-work with...

Walter Fontana
Harvard Medical School

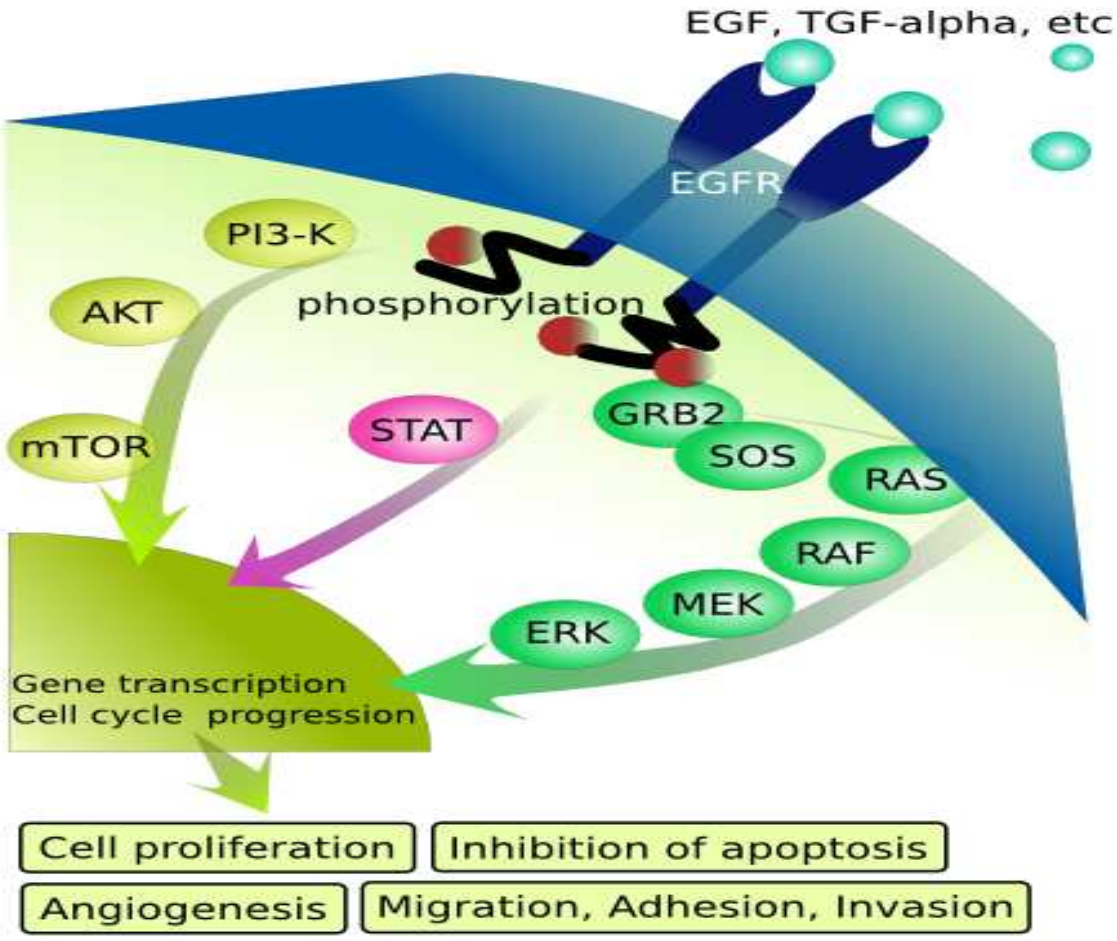
Vincent Danos
Edinburgh

Ferdinanda Camporesi
Bologna / ÉNS

Russ Harmer
Paris VII

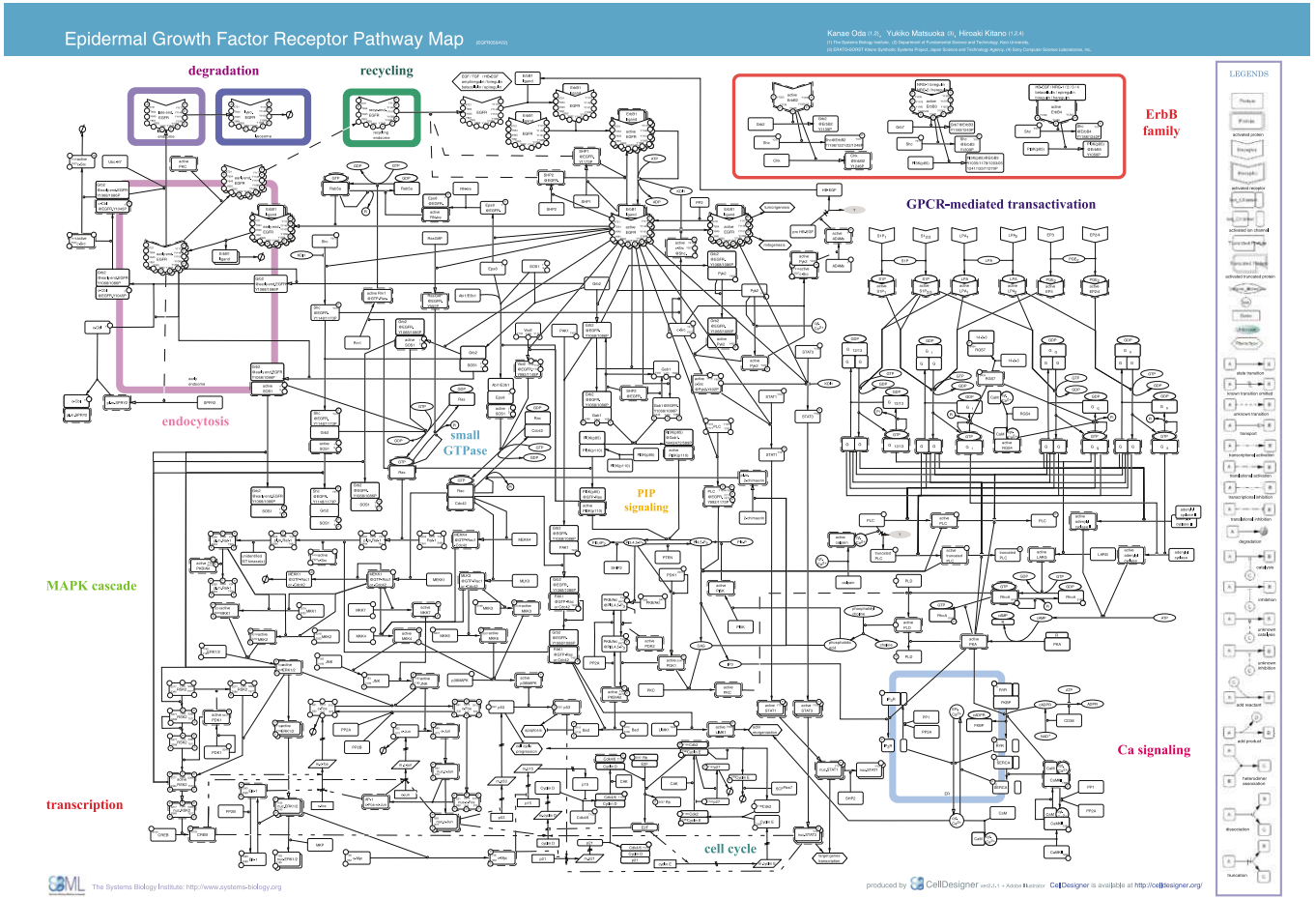
Jean Krivine
Paris VII

Signalling Pathways



Eikuch, 2007

Pathway maps



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

Differential models

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

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

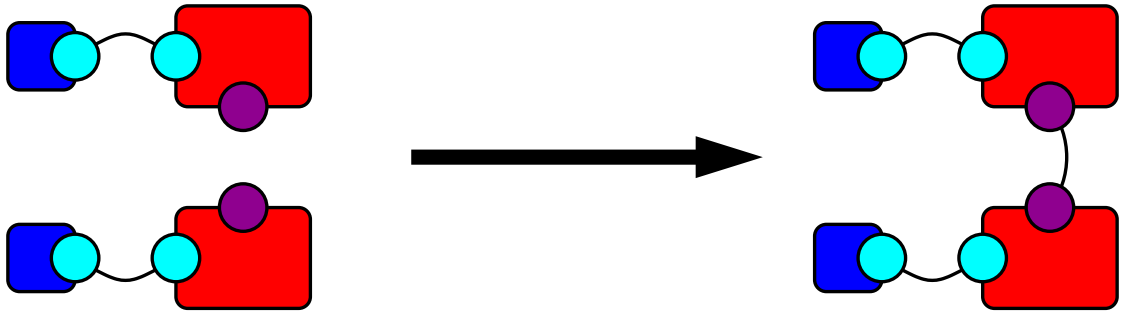
A gap between two worlds

Two levels of description:

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

Rule-based approach

We use site graph rewrite systems

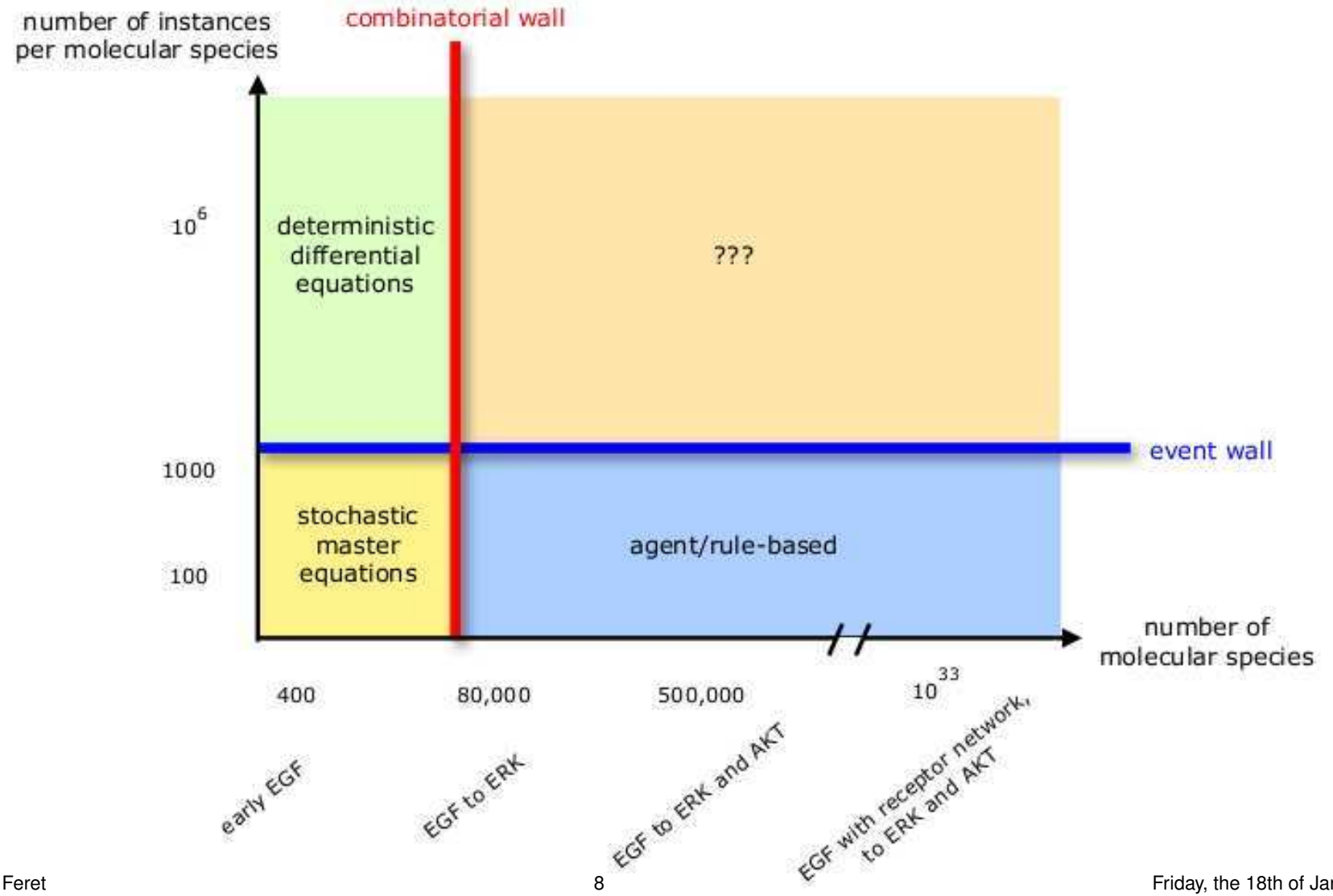


1. The description level matches with both
   - the observation level
   - and the intervention level

   of the biologist.

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

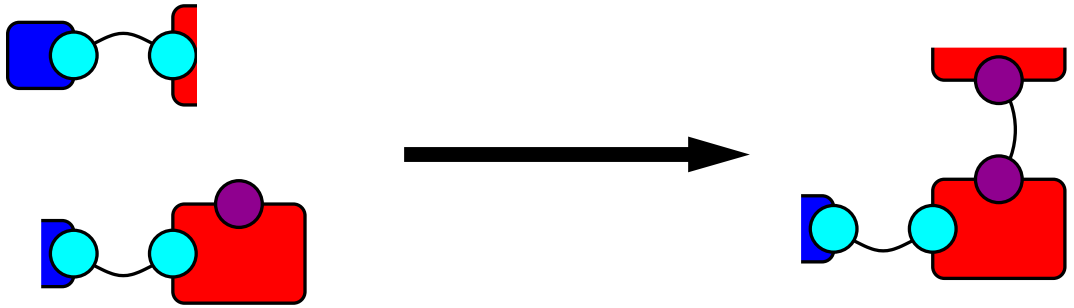
Complexity walls



Static analysis of reachable species (I/II)

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

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



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

Static analysis of reachable species (II/II)

Applications:

1. check the consistency of a model [ICCMSE'07]
2. compute the properties to allow fast simulation [APLAS'07]
3. simplify models,
4. compute independent fragments of chemical species [PNAS'09, LICS'10,Chaos'10]

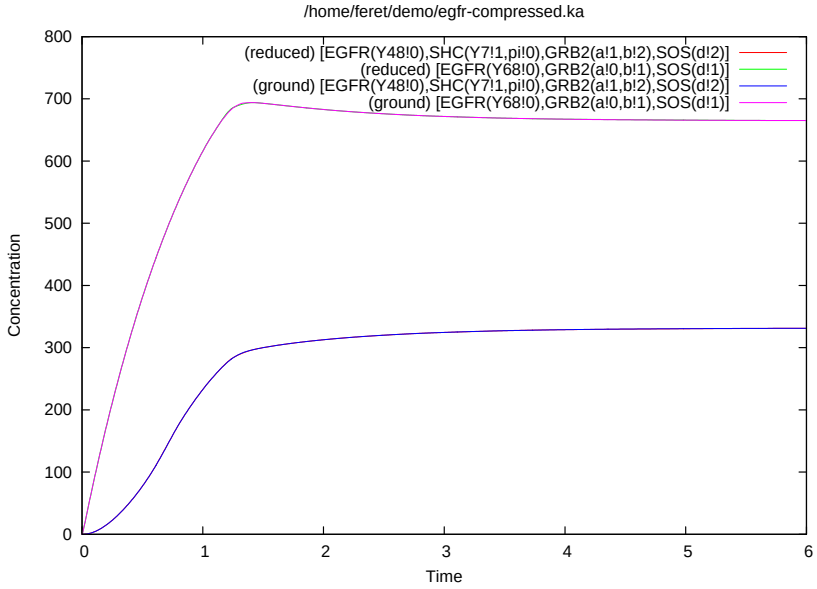
The analysis is complete (no false positif) for a significatif kernel of Kappa [VMCAI'08].

Model reduction

The ground differential system uses one variable per chemical species;

We directly compute its exact projection over independent fragments of chemical species.

With a small model, 356 chemical species are reduced into 38 fragments:



On a bigger model, 10^{19} chemical species are reduced into 180 000 fragments. [PNAS'09,LICS'10,Chaos'10]

MPRI

Reachability Analysis of Rule-based Models

[ICCMSE'07,VMCAI'08]

Jérôme Feret
Laboratoire d'Informatique de l'École Normale Supérieure
INRIA, ÉNS, CNRS
http://www.di.ens.fr/~feret

Friday, the 18th of January, 2013

Joint-work with...

Walter Fontana
Harvard Medical School

Vincent Danos
Edinburgh

Russ Harmer
Paris VII

Jean Krivine
Paris VII

Overview

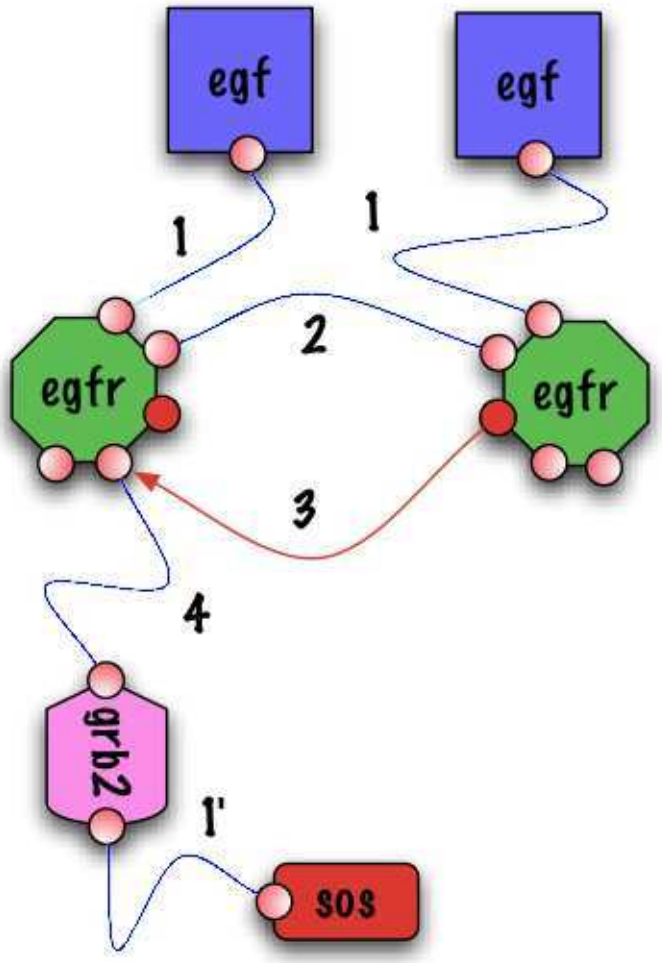
1. Introduction
2. Kappa language
3. Local views
4. Local set of chemical species
5. Local rule systems
6. Decontextualization
7. Conclusion

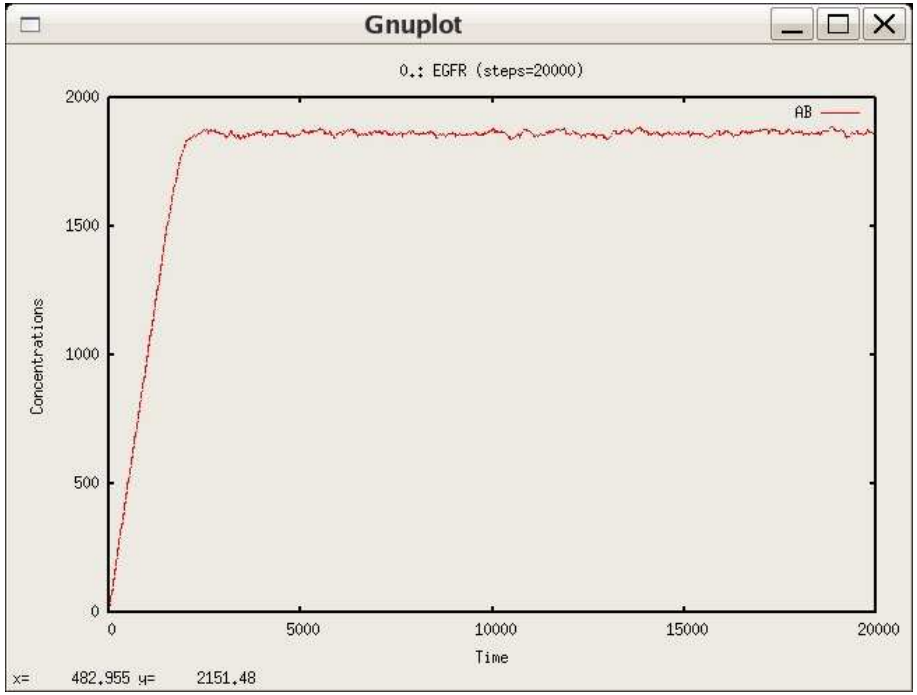
Modeling signaling pathway

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

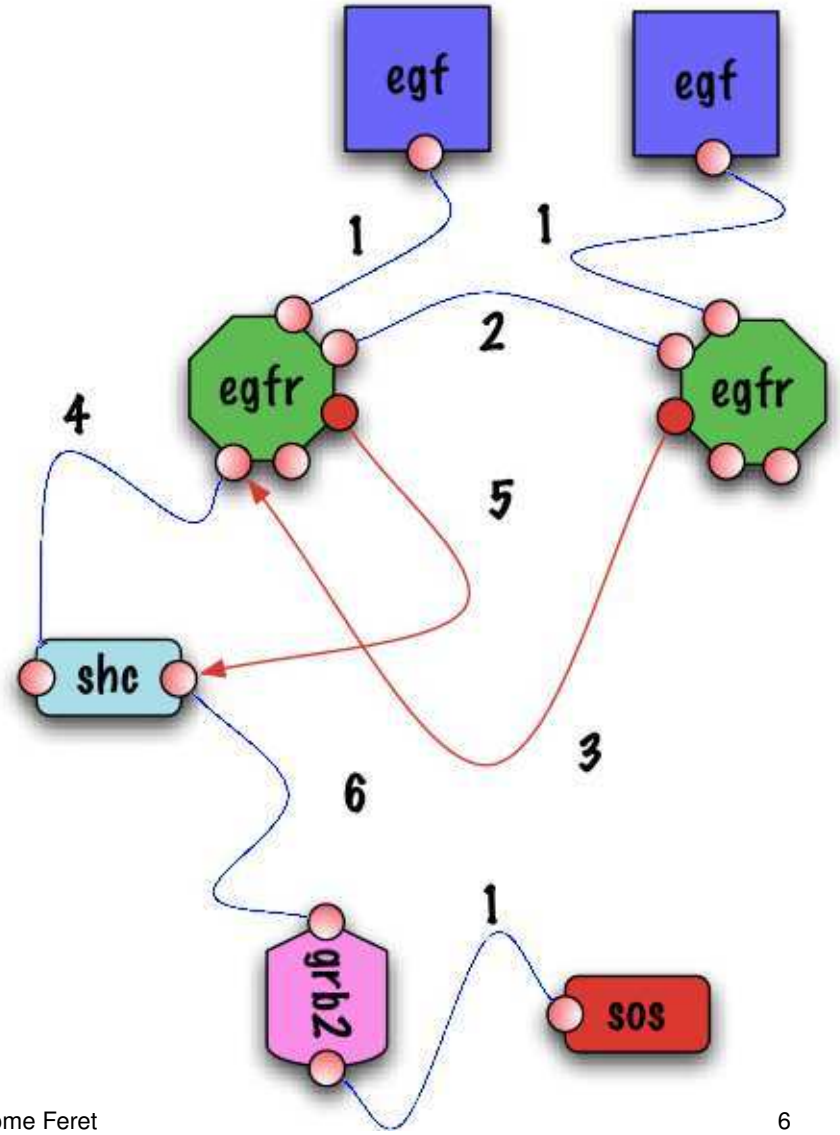
  We propose some static analysis tools in order to:
  - help the design of rule-based models;
  - compute (*abstract*) the properties of rule-based models.

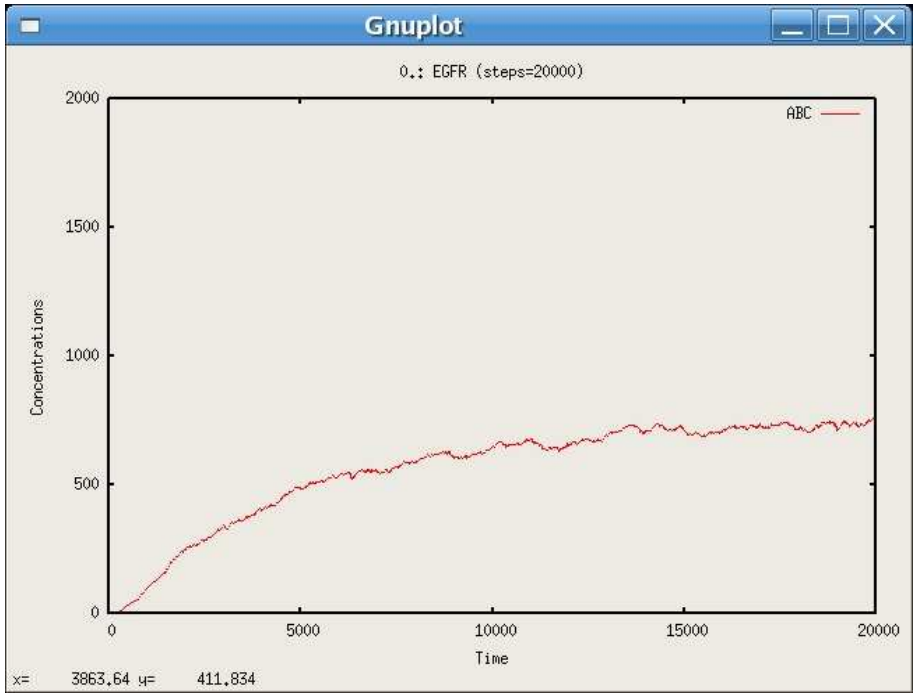
A single story





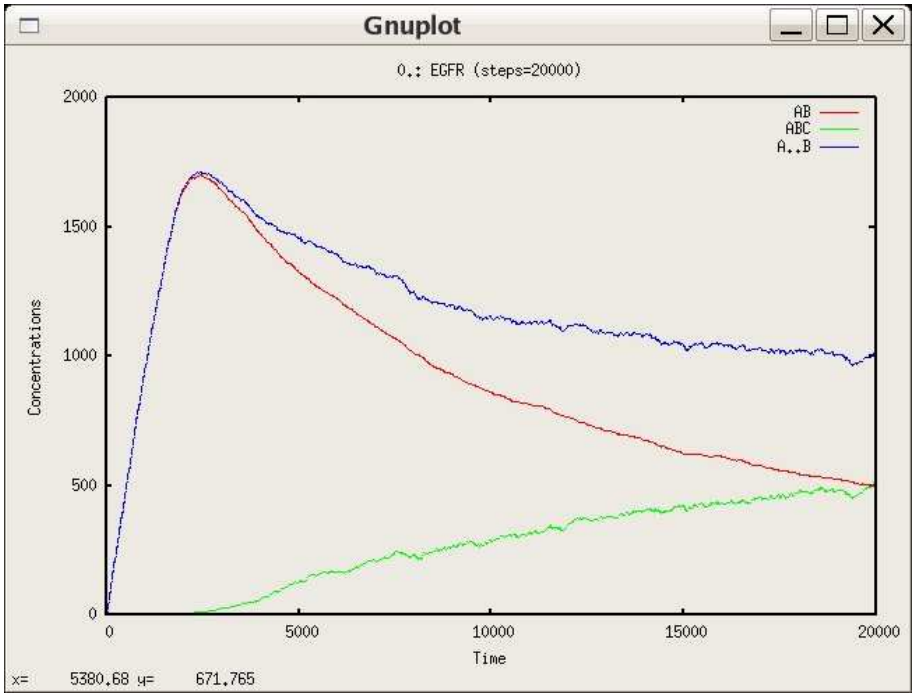
A concurrent story





Overshoot

When we combine the two stories. . .

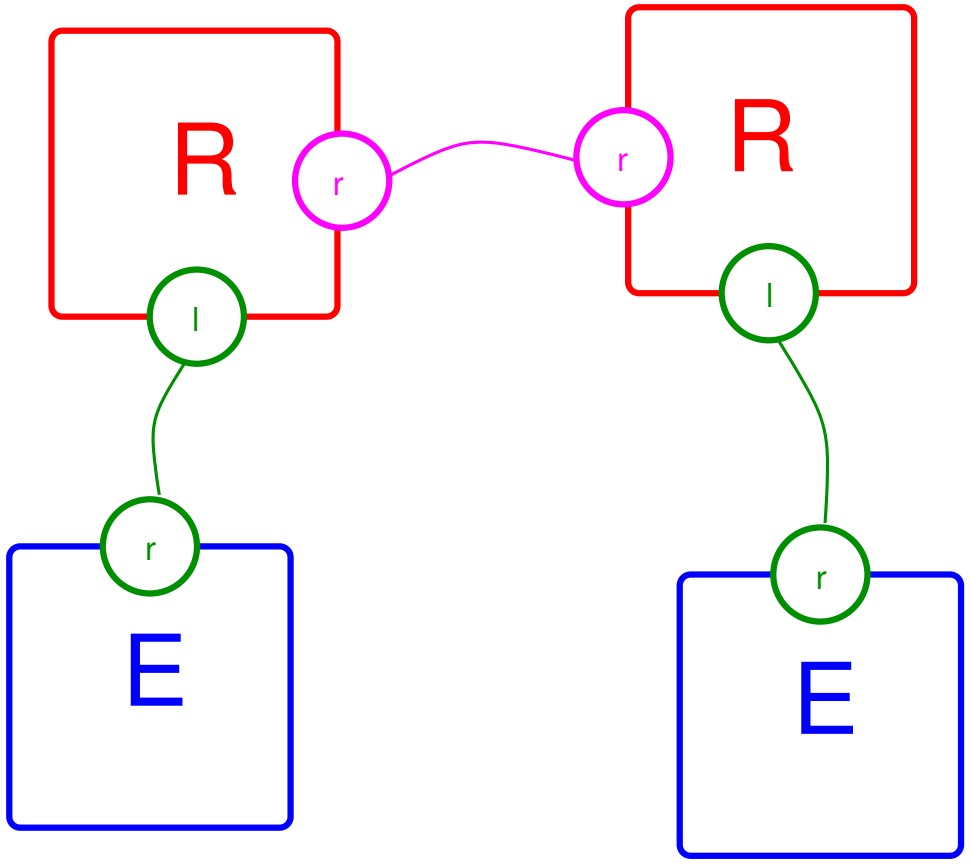


. . . we get an overshoot.

Overview

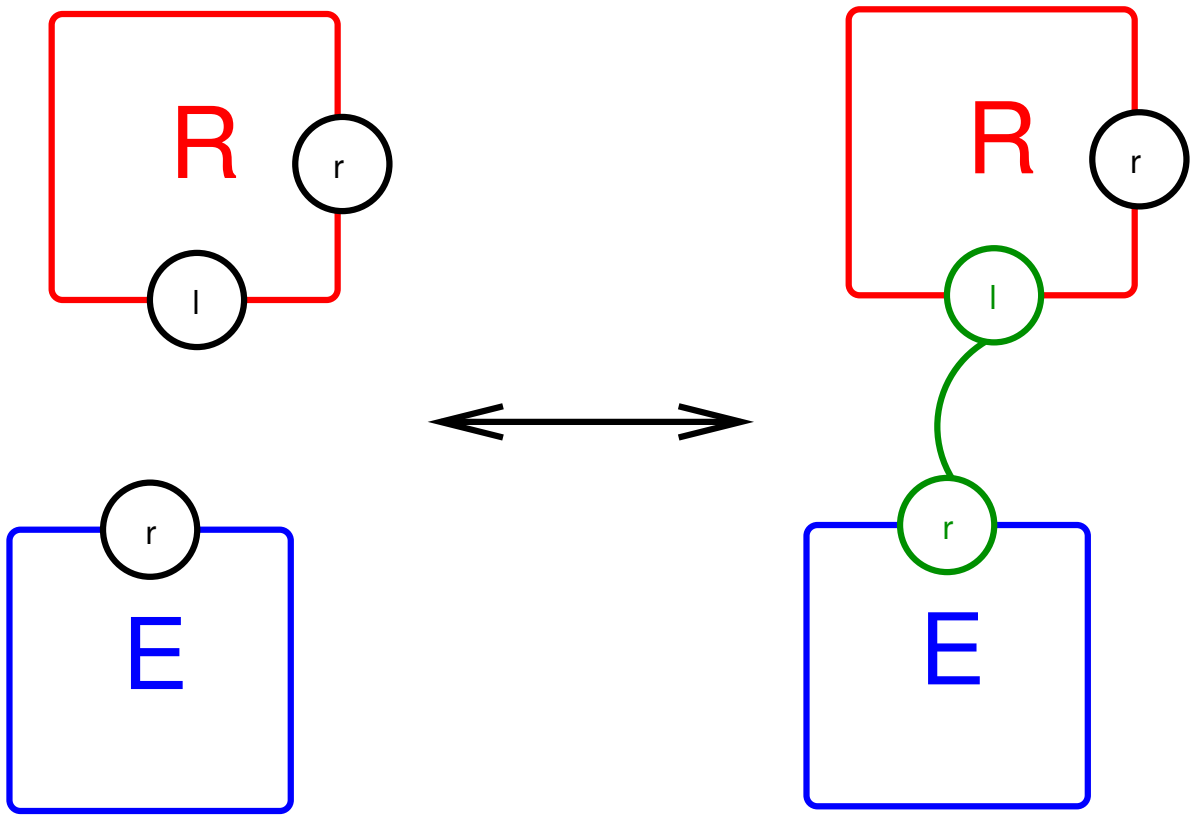
1. Introduction
2. Kappa language
3. Local views
4. Local set of chemical species
5. Local rule systems
6. Decontextualization
7. Conclusion

A chemical species



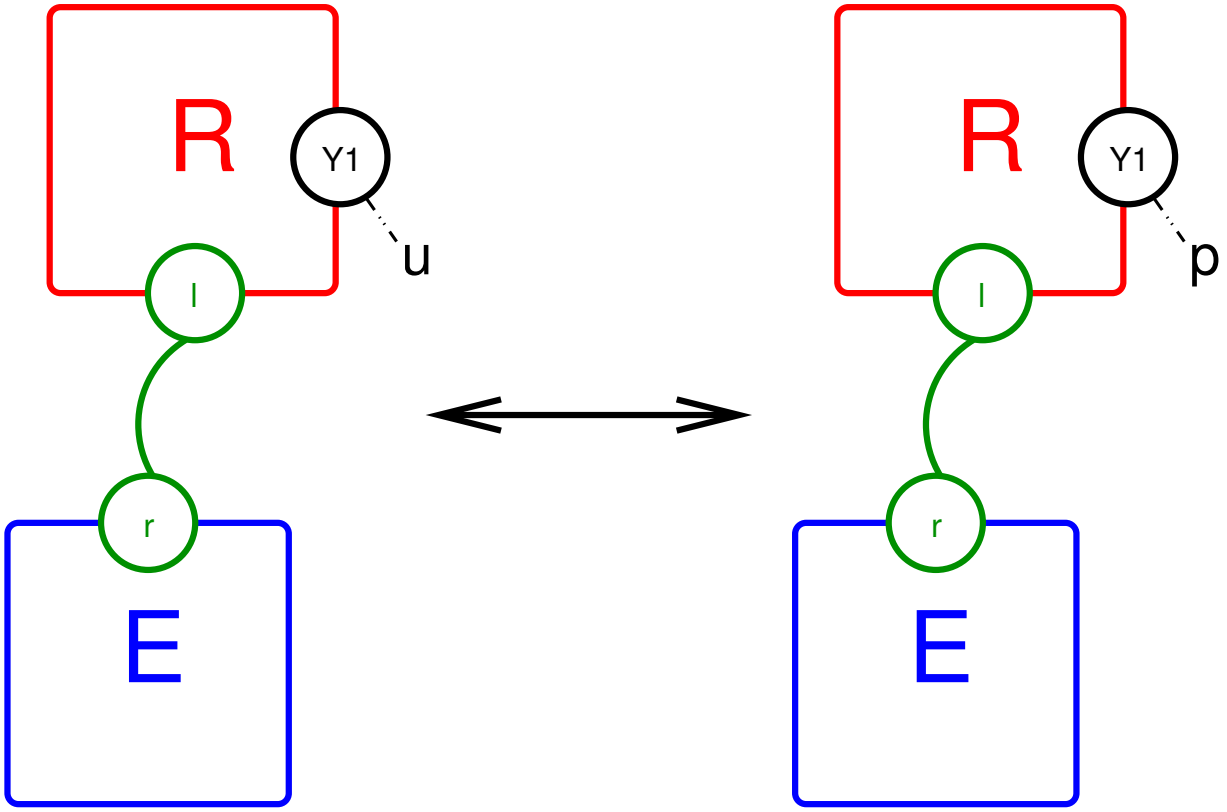
E(r!1), R(l!1,r!2), R(r!2,l!3), E(r!3)

A Unbinding/Binding Rule



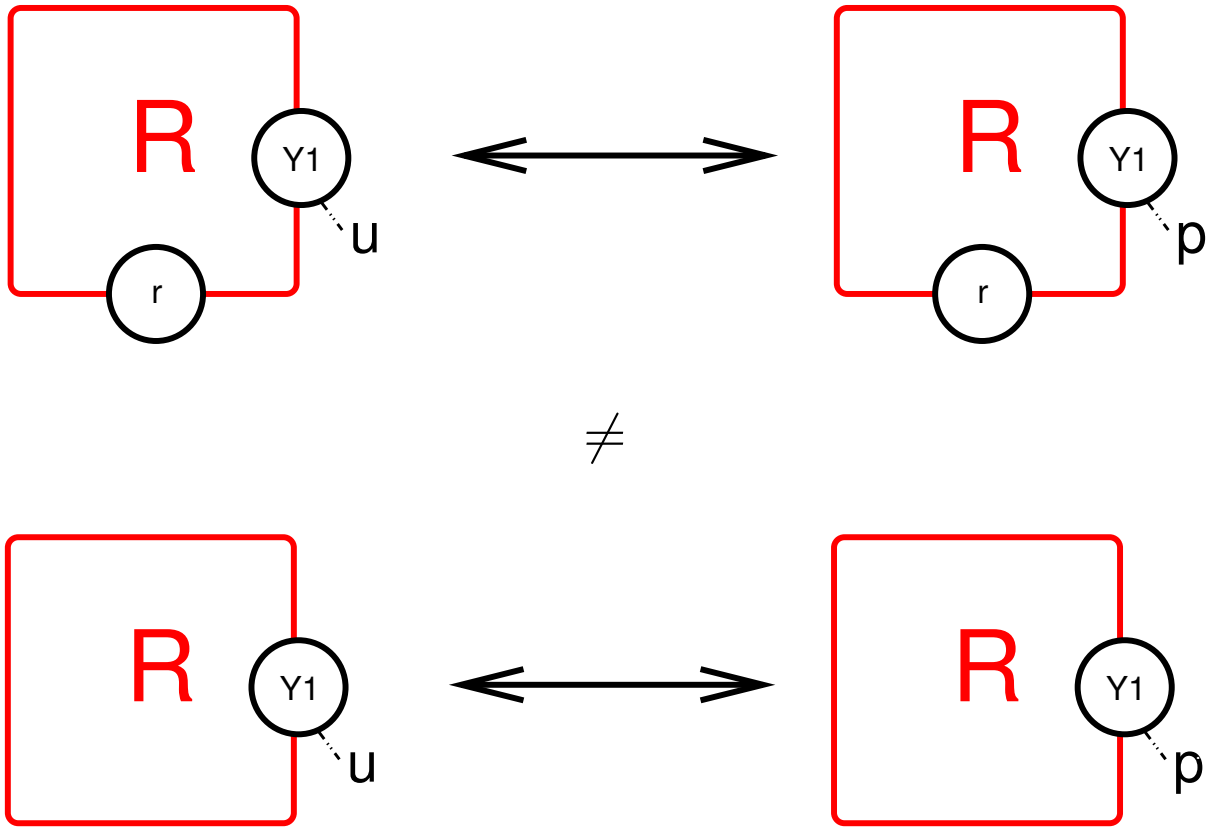
$$E(r),\ R(l,r) \longleftrightarrow E(r!1),\ R(l!1,r)$$

Internal state

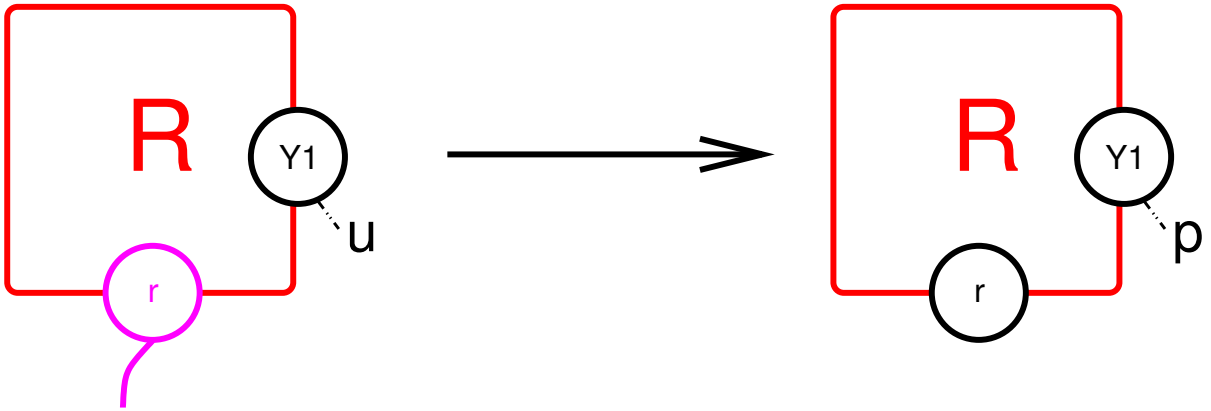


R(Y1~u,l!1), E(r!1) ⟷ R(Y1~p,l!1), E(r!1)

Don’t care, Don’t write

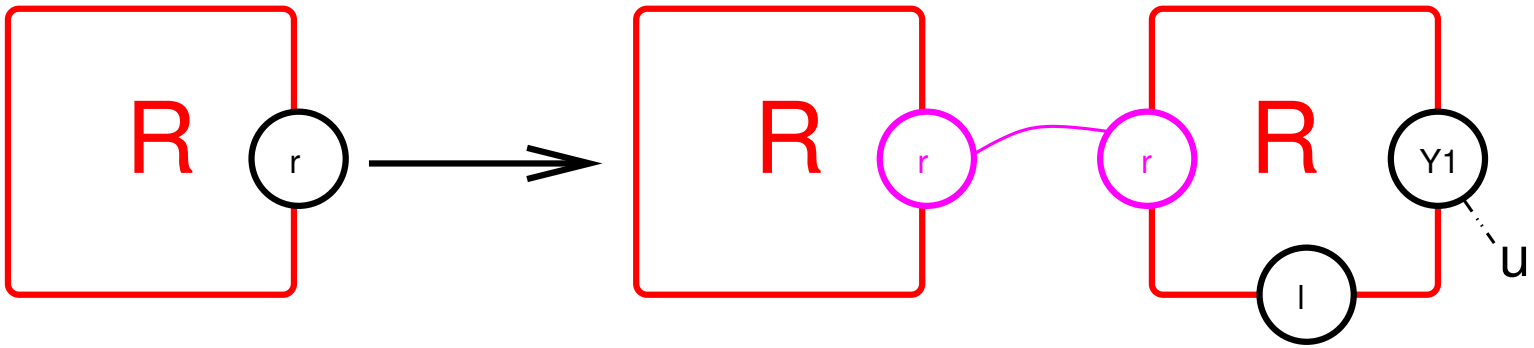


A contextual rule

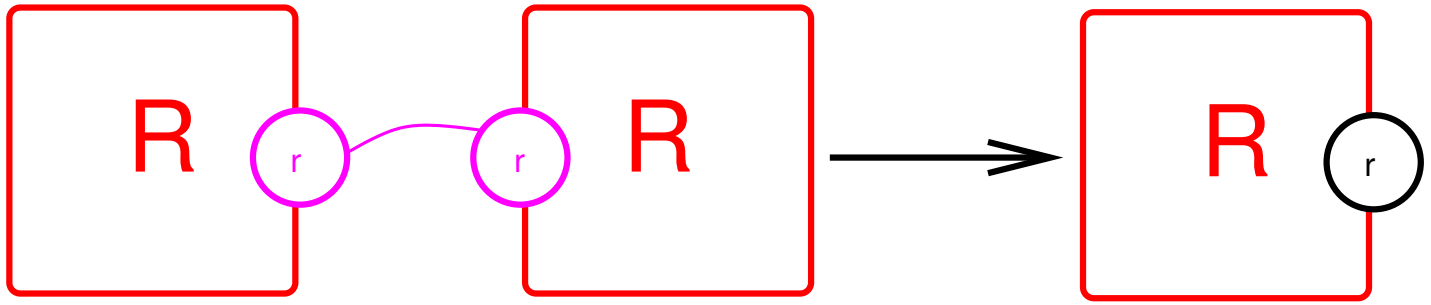


$$R(Y1{\sim}u,r!\_) \rightarrow R(Y1{\sim}p,r)$$

Creation/Suppression



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



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

Early EGF example

egf rules 1

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

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

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

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

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

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

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

Early EGF example

egf rules 2

refined from
So(d)+G(b)<->So(d^1)+G(b^1)

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

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

why not simply G(b^3)??

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

refined from
Sh(π), G(a)<->Sh(π^1), G(a^1)

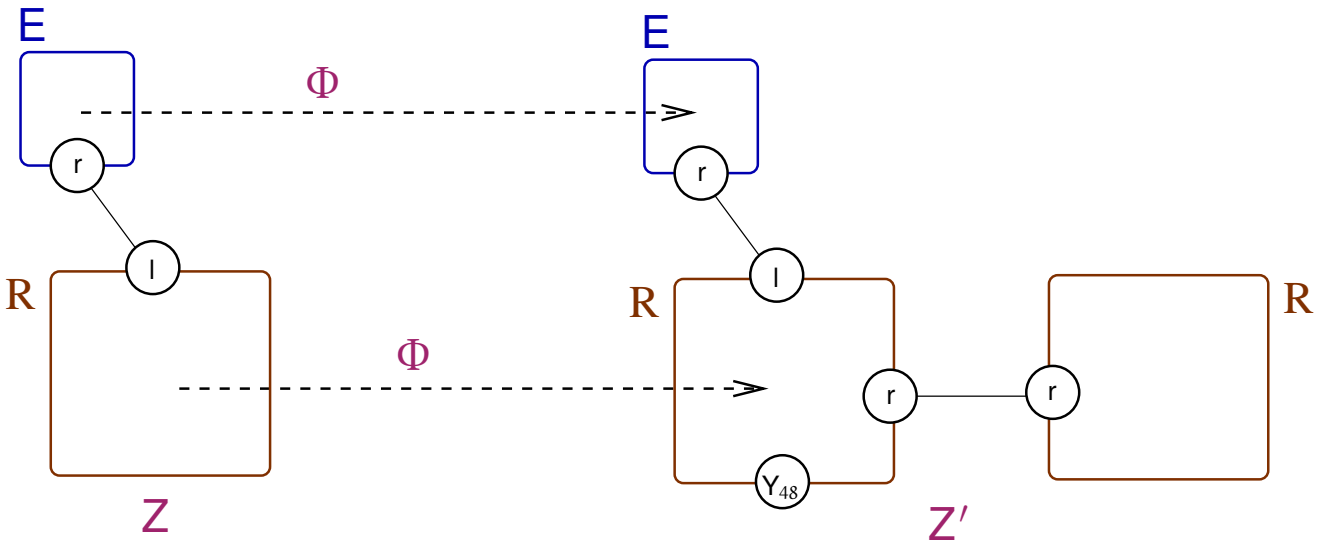
Properties of interest

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

Overview

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

Embedding



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

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

Set of reachable chemical species

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

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

whenever:

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

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

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

Inductive definition

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

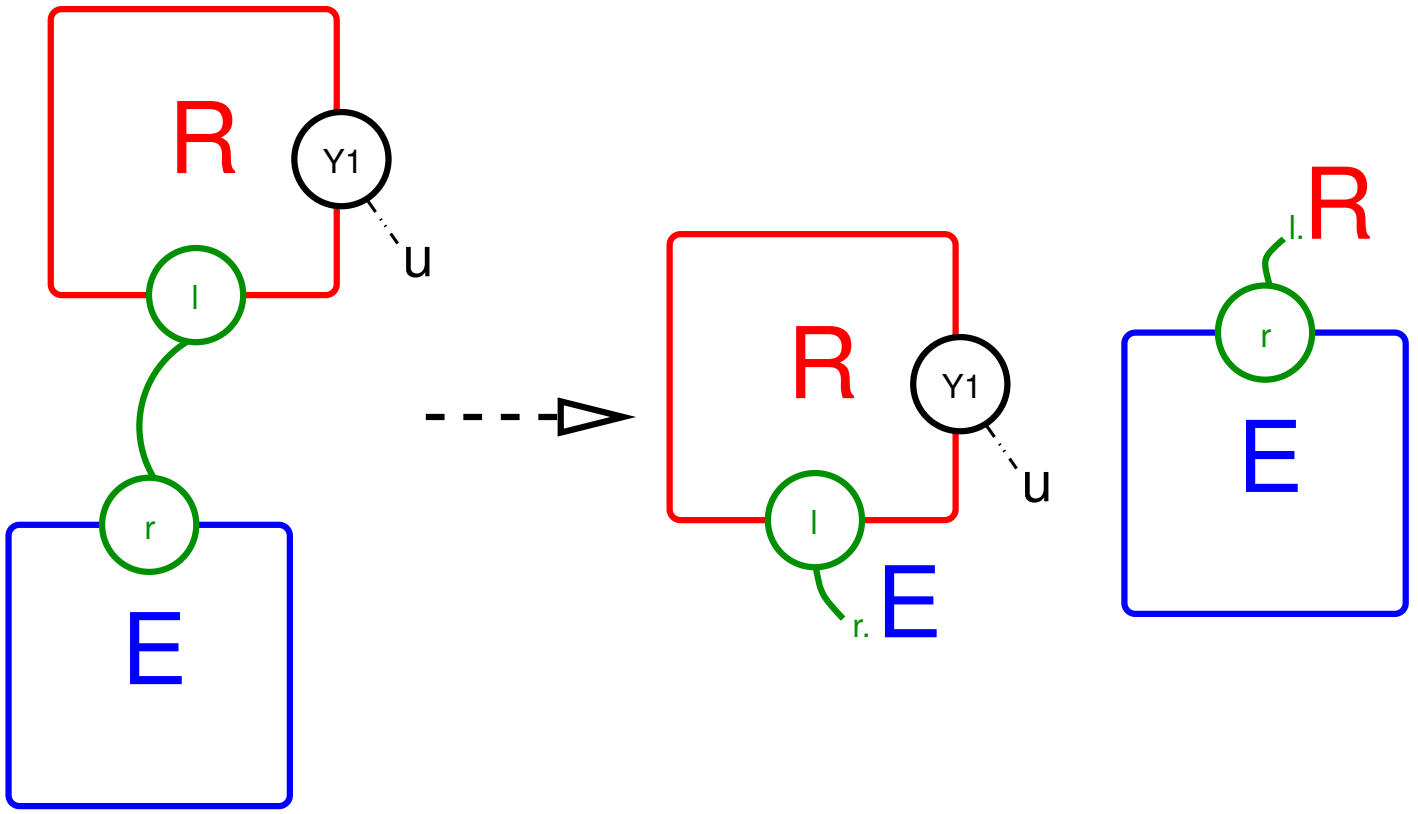
$$\mathbb{F} : \begin{cases} \wp(\mathit{Species}) & \to \wp(\mathit{Species}) \\ X & \mapsto X \cup \left\{ c'_j \;\middle|\; \begin{array}{l} \exists R_k \in \mathcal{R}, c_1, \ldots, c_m \in X, \\ c_1, \ldots, c_m \to_{R_k} c'_1, \ldots, c'_n \end{array} \right\}. \end{cases}$$

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

We define the set of reachable chemical species as follows:

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

Local views



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

Galois connexion

Let $\mathit{Local\_view}$ be the set of all local views.

Let $\alpha \in \wp(\mathit{Species}) \to \wp(\mathit{Local\_view})$ 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:

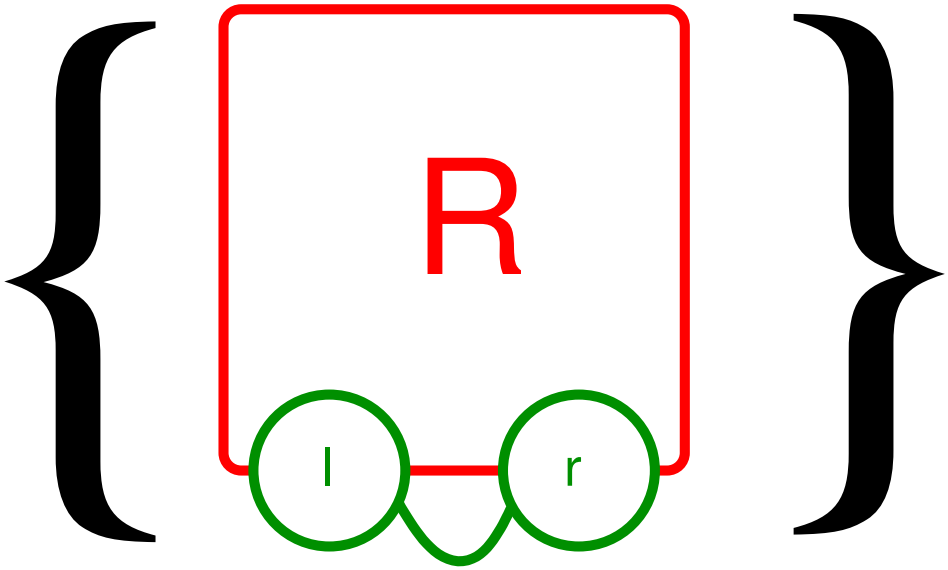
$$\wp(\mathit{Species}) \underset{\alpha}{\overset{\gamma}{\leftrightarrows}} \wp(\mathit{Local\_view}).$$

(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.

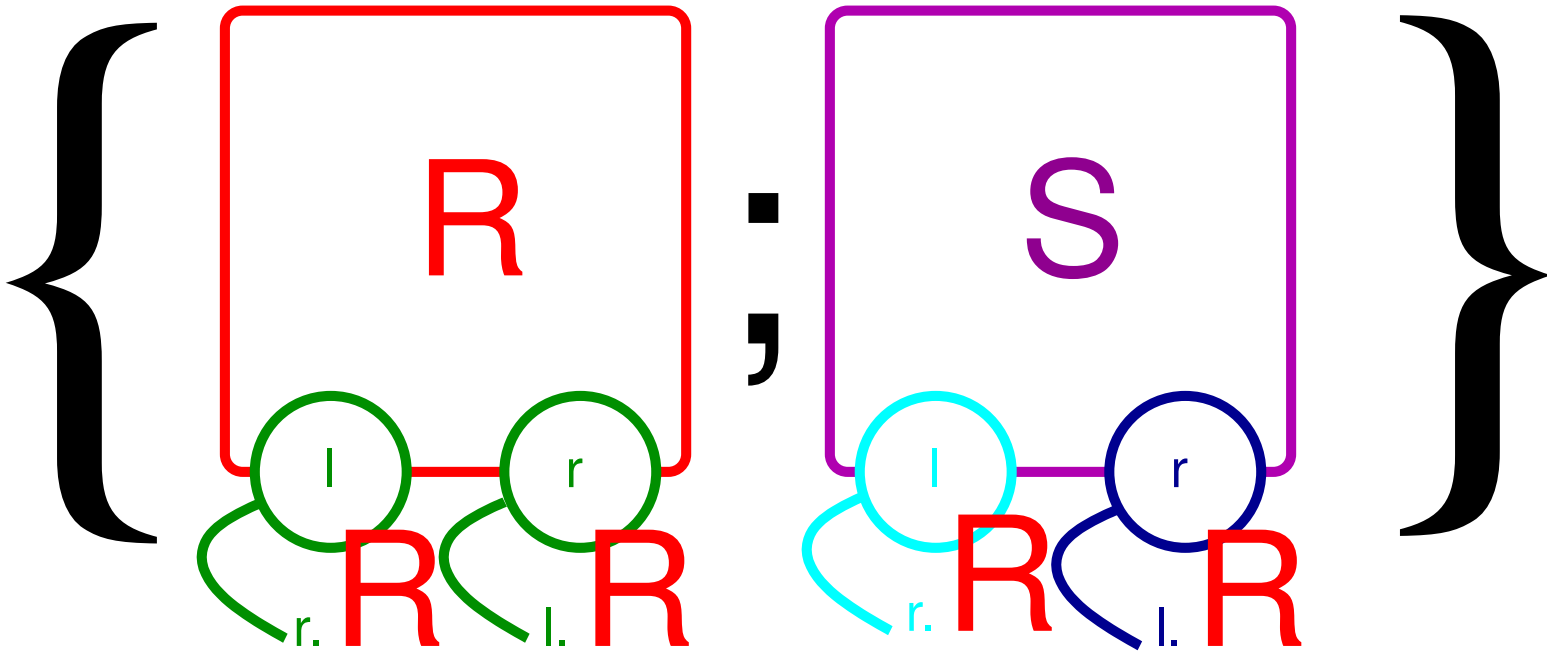
Guess the image of the following set of chemical species ?



$\alpha \circ \gamma$

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

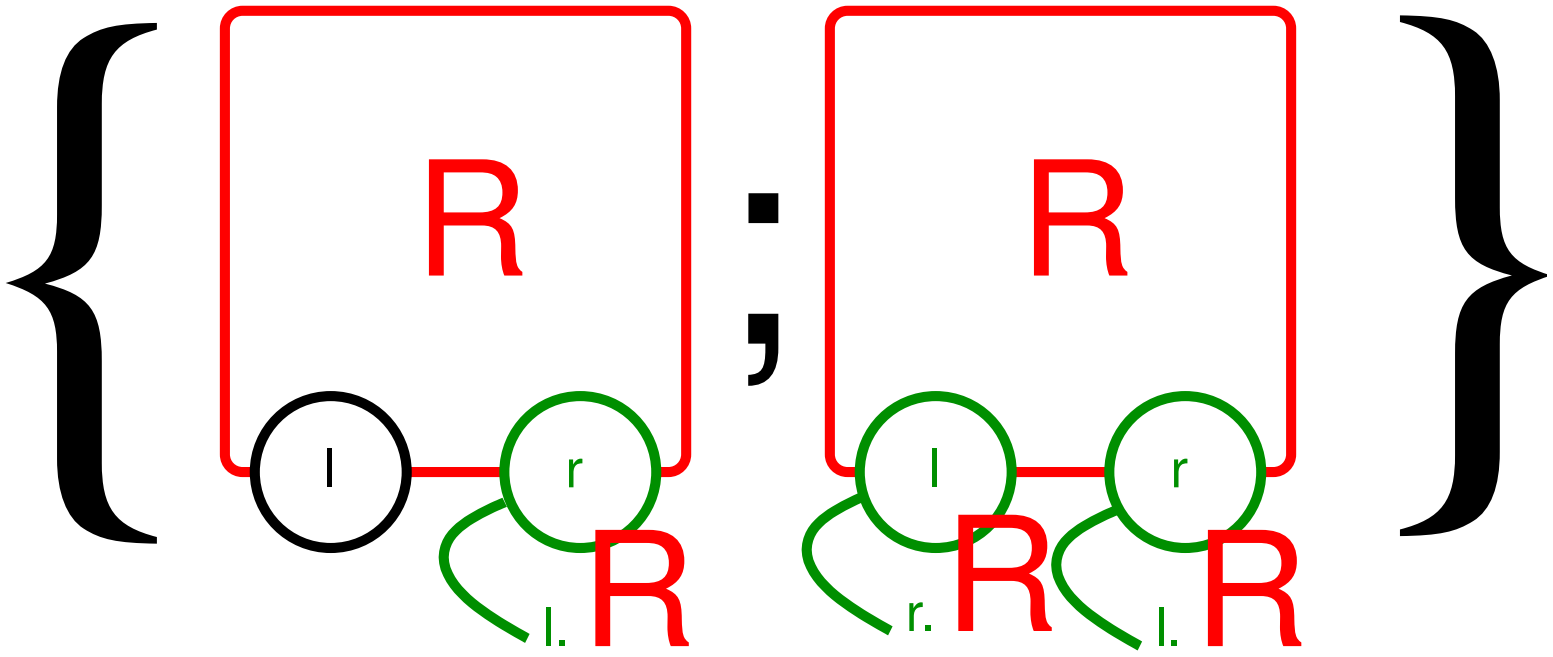
Guess the image of the following set of local views ?



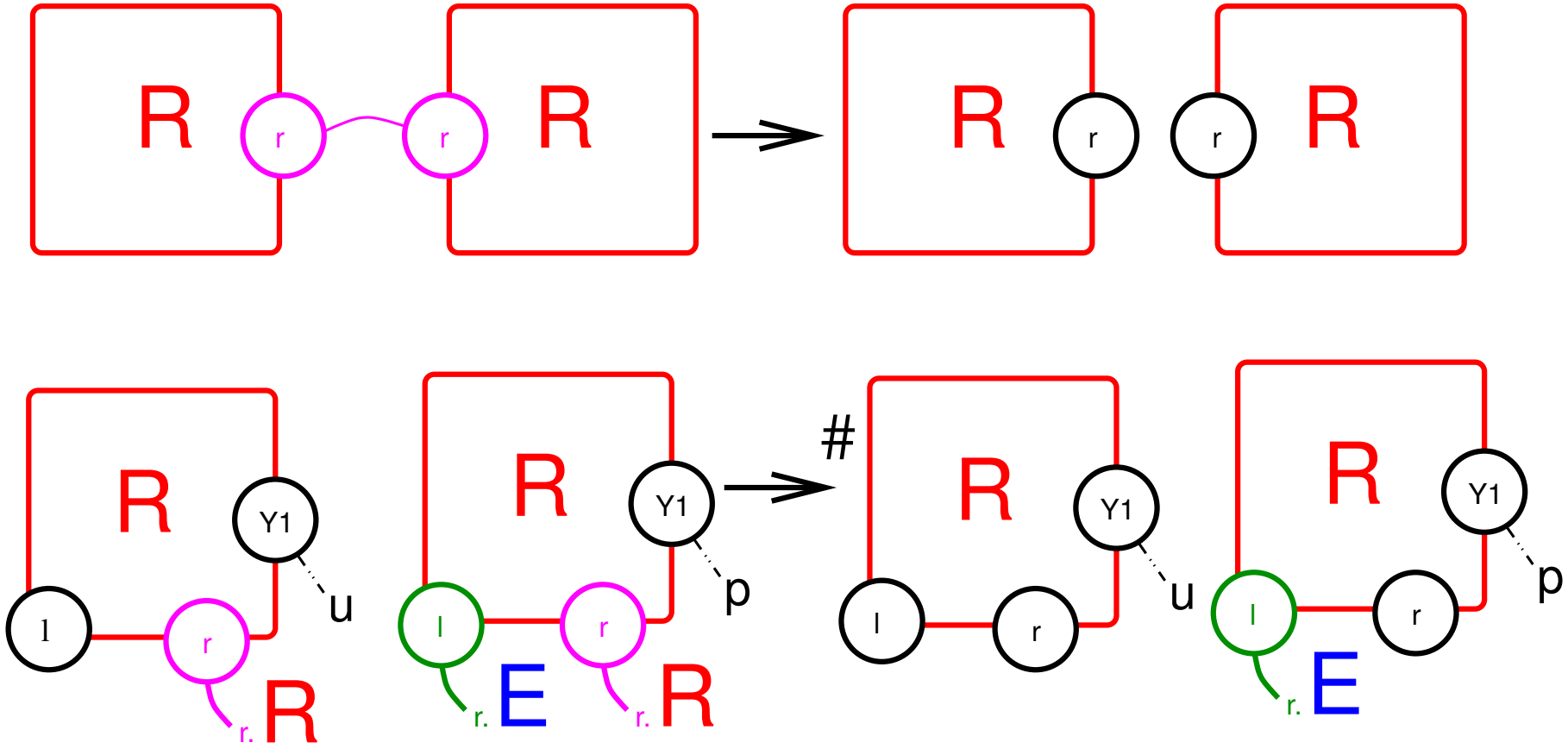
One more question

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

Guess the image of the following set of local views ?



Abstract rules



Abstract counterpart to $\mathbb{F}$

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

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

We have:

- $\mathbb{F}^\sharp$ is extensive;
- $\mathbb{F}^\sharp$ is monotonic;
- $\mathbb{F} \circ \gamma \mathrel{\dot\subseteq} \gamma \circ \mathbb{F}^\sharp$;
- $\mathbb{F}^\sharp \circ \alpha = \alpha \circ \mathbb{F} \circ \gamma \circ \alpha$ (we will see later why).

Soundness

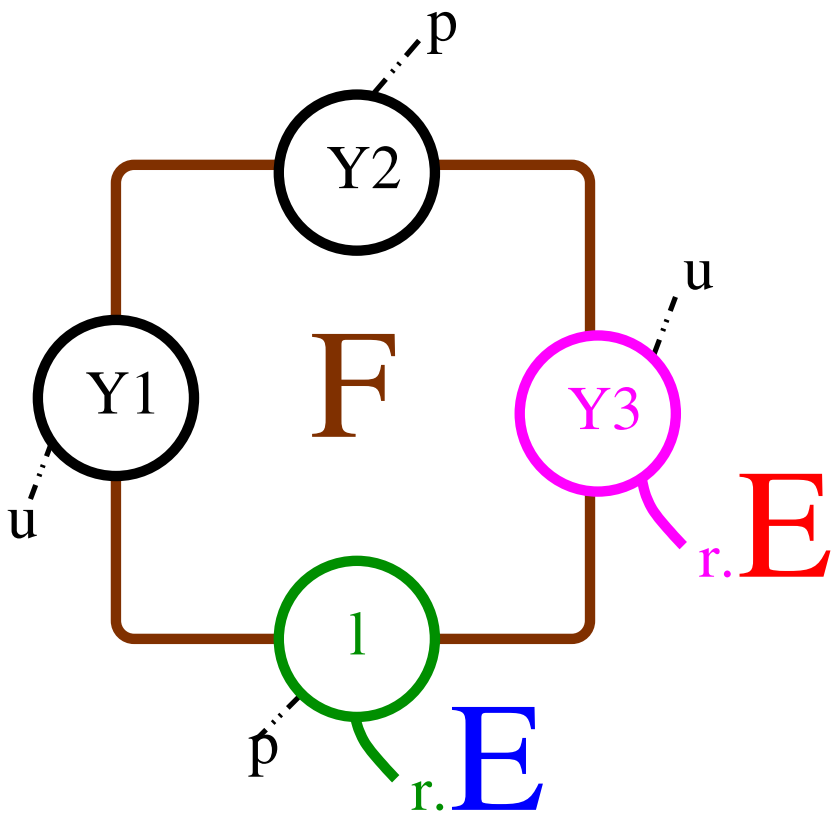
Theorem 1 Let:

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. $\mathbb{F} \in D \to D$ and $\mathbb{F}^\sharp \in D^\sharp \to D^\sharp$ 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: $x_0 \subseteq \mathbb{F}(x_0)$;

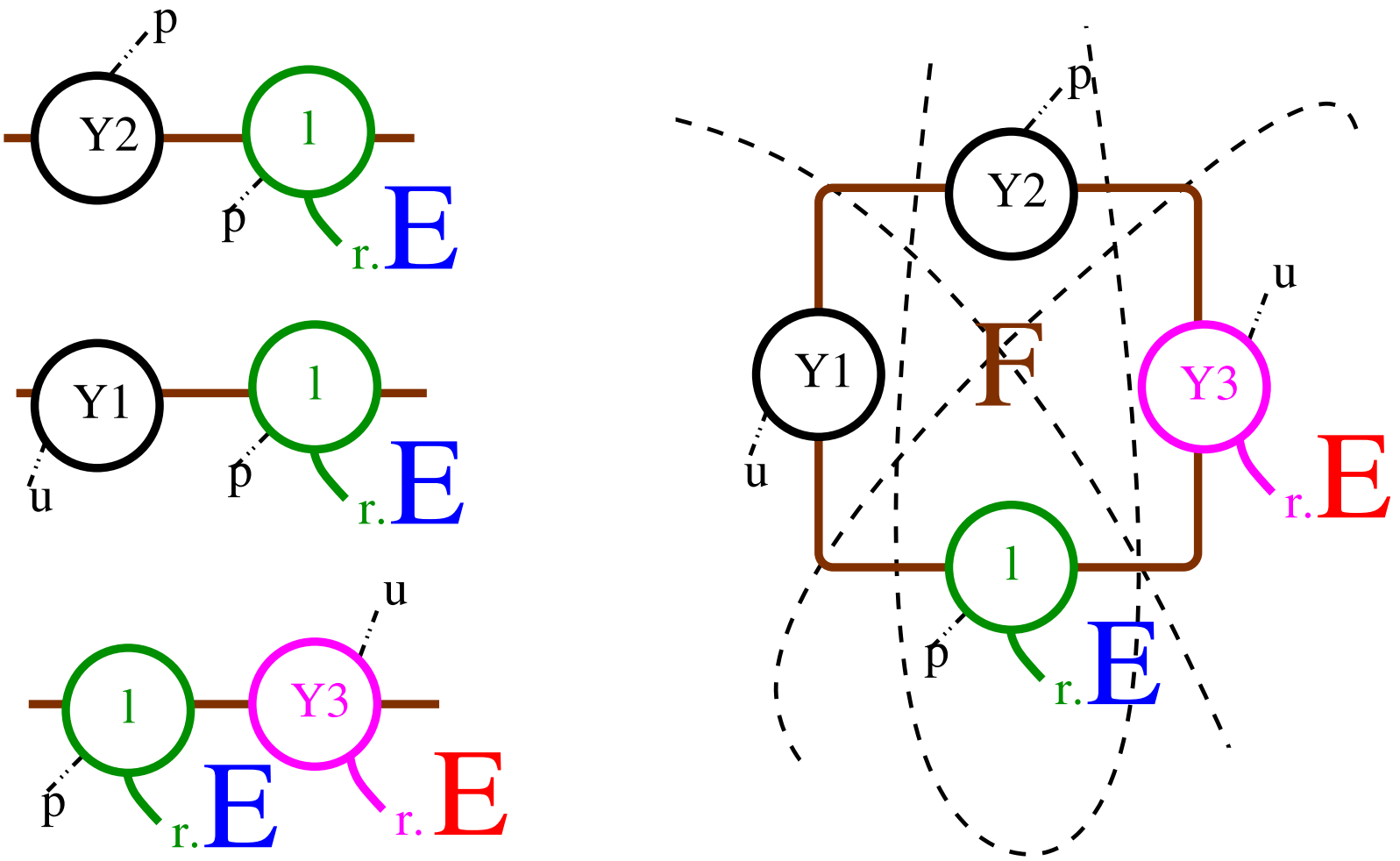
Then:

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 P of the set of sites.
- template: a class $\mathrm{p} \in \mathrm{P}$ in the covering.
- projection: for any $\mathrm{p} \in \mathrm{P}$, the function Π_{p} restricts a local view to p.
- sub-local-view: $\mathit{sub\_local\_view}_{\mathrm{P}} = \{\Pi_{\mathrm{p}}(\mathit{lv}) \mid \mathit{lv} \in \mathit{Local\_view},\ \mathrm{p} \in \mathrm{P}\}$.
- abstraction: the following function

$$\alpha_{\mathrm{P}} : \begin{cases} \wp(\mathit{Local\_view}) & \to \wp(\mathit{sub\_local\_view}_{\mathrm{P}}) \\ \mathrm{X} & \mapsto \{\Pi_{\mathrm{p}}(\mathit{lv}) \mid \mathit{lv} \in \mathrm{X},\ \mathrm{p} \in \mathrm{P}\}. \end{cases}$$

  is a $\cup$-complete morphism.

  It defines a Galois connexion $\wp(\mathit{Local\_view}) \underset{\alpha_{\mathrm{P}}}{\overset{\gamma_{\mathrm{P}}}{\leftrightarrows}} \wp(\mathit{sub\_local\_view}_{\mathrm{P}})$.

- counterpart: $\mathbb{F}^{\sharp}_{\mathrm{P}} = \alpha_{\mathrm{P}} \circ \mathbb{F}^{\sharp} \circ \gamma_{\mathrm{P}}$.

Automatic packing

Let P be a covering such that:

1. each site is at least in one class of P;
2. whenever a rule tests two sites a and b,
   then, for any $\mathrm{p} \in \mathrm{P}$, $\mathrm{a} \in \mathrm{p} \iff \mathrm{b} \in \mathrm{p}$;
3. whenever a rule modifies two sites a and b,
   then, for any $\mathrm{p} \in \mathrm{P}$, $\mathrm{a} \in \mathrm{p} \iff \mathrm{b} \in \mathrm{p}$;
4. whenever a rule modifies a site a and tests a site b,
   then for any $\mathrm{p} \in \mathrm{P}$, $\mathrm{a} \in \mathrm{p} \implies \mathrm{b} \in \mathrm{p}$;

Then:

$$\mathbb{F}(\gamma_{\mathrm{P}}(\wp(\mathit{sub\_local\_view}_{\mathrm{P}}))) \subseteq \gamma_{\mathrm{P}}(\wp(\mathit{sub\_local\_view}_{\mathrm{P}}))$$

Relative completeness

Theorem 2 We suppose that:

1. $(\mathrm{D}, \subseteq, \cup)$ and $(\mathrm{D}^\sharp, \sqsubseteq, \sqcup)$ are chain-complete partial orders;
2. $(\mathrm{D}, \subseteq) \underset{\alpha}{\overset{\gamma}{\leftrightarrows}} (\mathrm{D}^\sharp, \sqsubseteq)$ is a Galois connexion;
3. $\gamma(\mathrm{D}^\sharp)$ is closed by $\cup$;
4. $\mathbb{F} : \mathrm{D} \to \mathrm{D}$ is a monotonic map;
5. x_0 is a concrete element such that $\mathrm{x}_0 \subseteq \mathbb{F}(\mathrm{x}_0)$;
6. $\alpha \circ \mathbb{F} \circ \gamma = \mathbb{F}^\sharp$;
7. $\mathrm{x}_0 \in \gamma(\mathrm{D}^\sharp)$;
8. $\mathbb{F}(\gamma(\mathrm{D}^\sharp)) \subseteq \gamma(\mathrm{D}^\sharp)$.

Then:

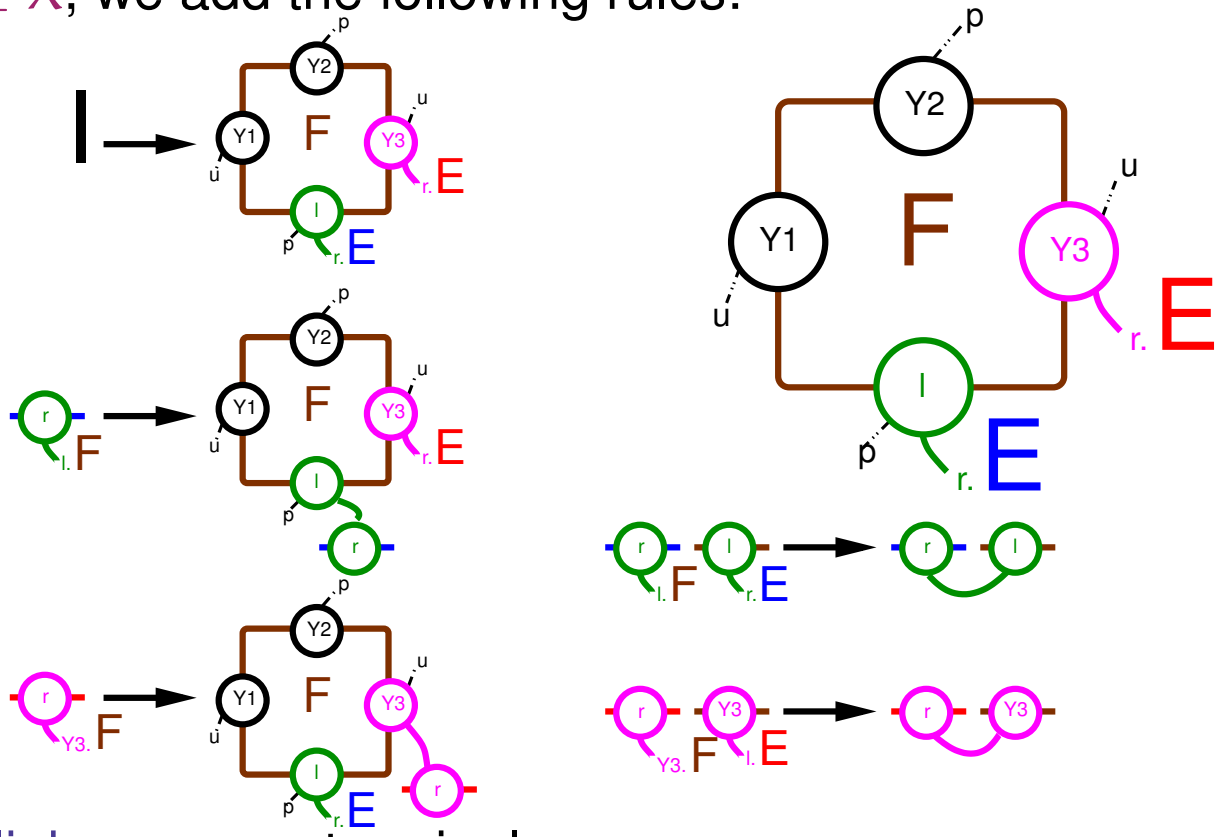
- $\mathit{lfp}_{\mathrm{x}_0}\mathbb{F}$ and $\mathit{lfp}_{\alpha(\mathrm{x}_0)}\mathbb{F}^\sharp$ exist;
- $\mathit{lfp}_{\mathrm{x}_0}\mathbb{F} = \gamma(\mathit{lfp}_{\alpha(\mathrm{x}_0)}\mathbb{F}^\sharp)$.

Overview

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

Concretization

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



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

Pumping lemma

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

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

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

Examples

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

Counting chemical species

Given a set of local views X, we can easily count the number of species in $\gamma(X)$ by using the following lemmas:

Lemma 1 (rigidity) An embedding between two connected components is fully characterized by the image of one agent.

Lemma 2 (automorphism) If $\gamma(X)$ is finite, then for any $C \in \gamma(X)$:

- C has at most two automorphisms;
- if C has two automorphisms, then C has a bond of the form $R.r - r.R$. Moreover one automorphism swaps the two R of this bond.

Lemma 3 (Euler) If a chemical species has no cycle, then it has an agent with only one site.

sketch the algorithm

Which information is abstracted away ?

Our analysis is exact (no false positive):

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

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

This raises the following issues:

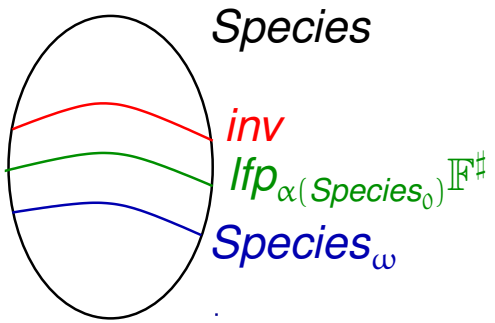
- Can we characterize which information is abstracted away ?
- Which is the form of the systems, for which we have no false positive ?
- Do we learn something about the biological systems that we describe ?

Which information is abstracted away ?

Theorem 3 We suppose that:

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

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 4 We suppose that:

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

Then:

- $\mathit{lfp}_{x_0}\mathbb{F}$ and $\mathit{lfp}_{\alpha(x_0)}\mathbb{F}^\sharp$ exist;
- $\mathit{lfp}_{x_0}\mathbb{F} \in \gamma(\mathrm{D}^\sharp) \iff \mathit{lfp}_{x_0}\mathbb{F} = \gamma(\mathit{lfp}_{\alpha(x_0)}\mathbb{F}^\sharp)$.

Local set of chemical species

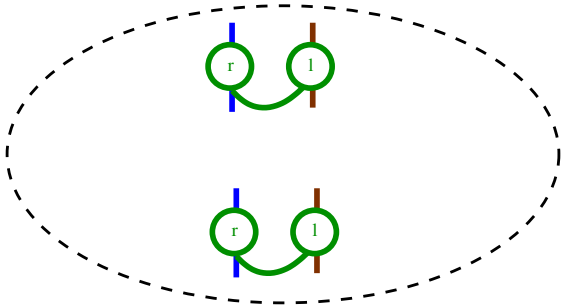
Definition 1 We say that a set $X \in \wp(Species)$ of chemical species is local if and only if $X \in \gamma(\wp(Local\_view))$.

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

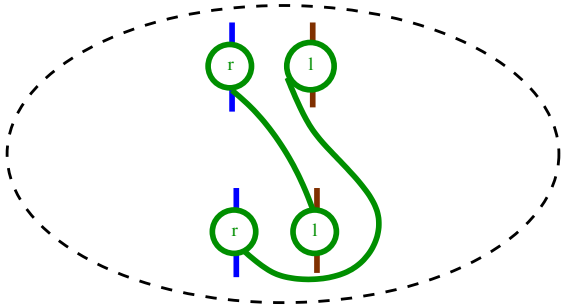
Swapping relation

We define the binary relation $\overset{\text{SWAP}}{\sim}$ among tuples *Species** of chemical species.
We say that $(C_1, \ldots, C_m) \overset{\text{SWAP}}{\sim} (D_1, \ldots, D_n)$ if and only if:

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



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



Swapping closure

Theorem 5 Let $X \in \wp(\mathit{Species})$ be a set of chemical species.
The two following assertions are equivalent:

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

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

Consequences

Let $X \in \alpha(\wp(\mathit{Species}))$ be a set of local views.

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

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 $(D_j) \in X^*$.	

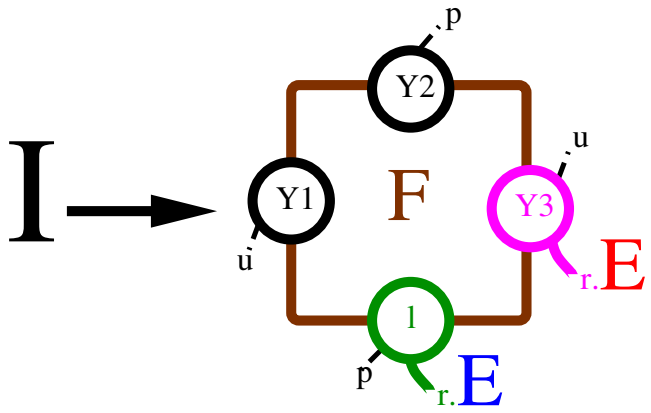
Proof (more difficult implication way)

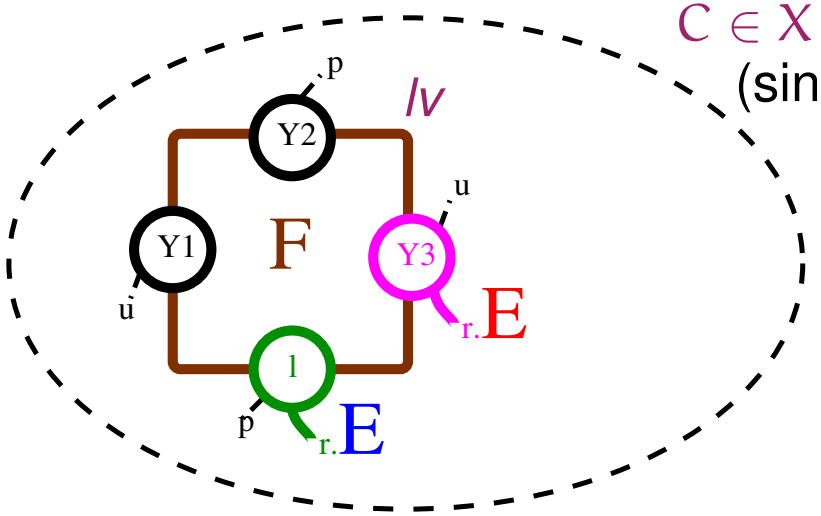
We suppose that X is close with respect to $\overset{\text{SWAP}}{\sim}$.
We want to prove that $\gamma(\alpha(X)) \subseteq X$.

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.

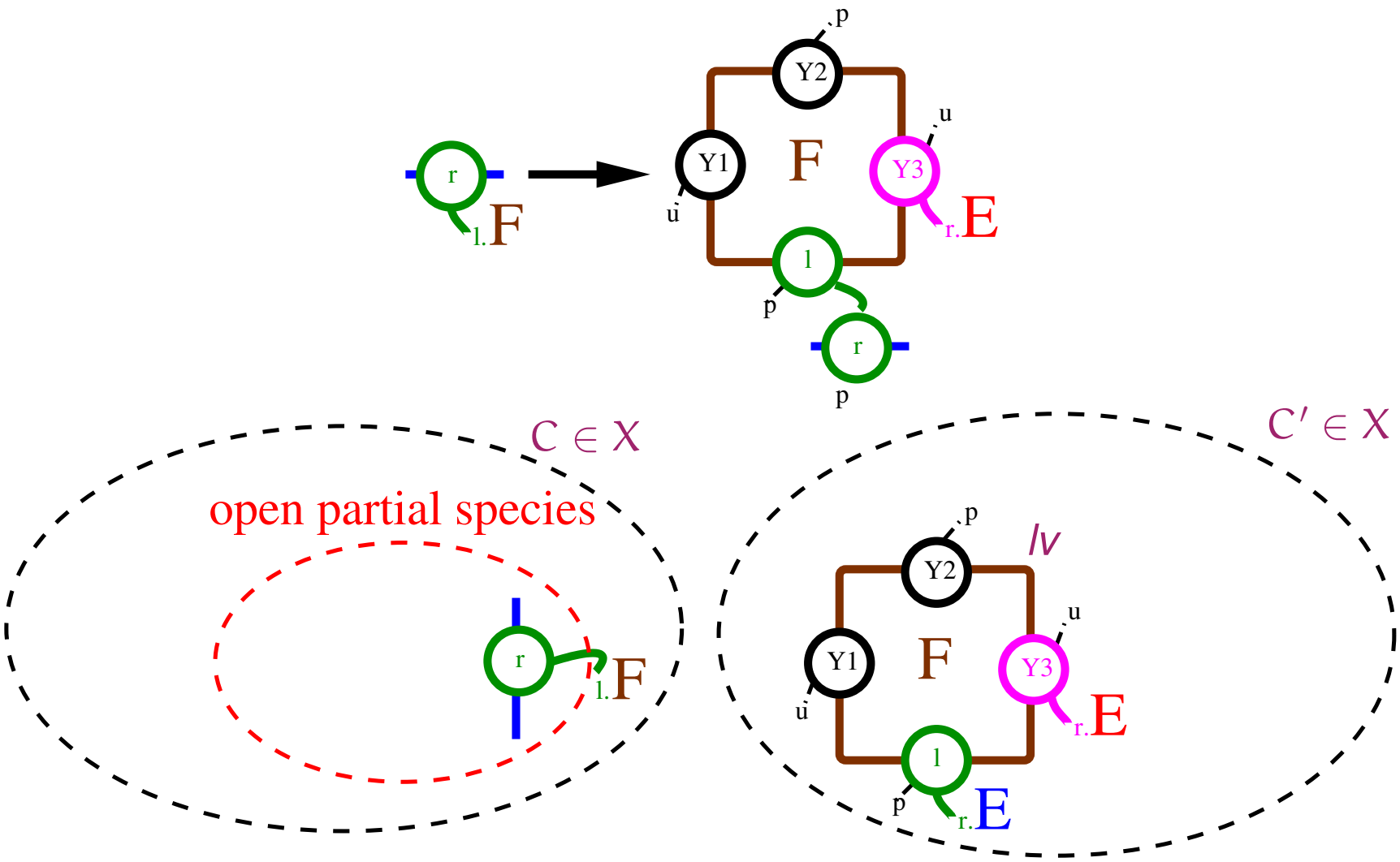
Initialization



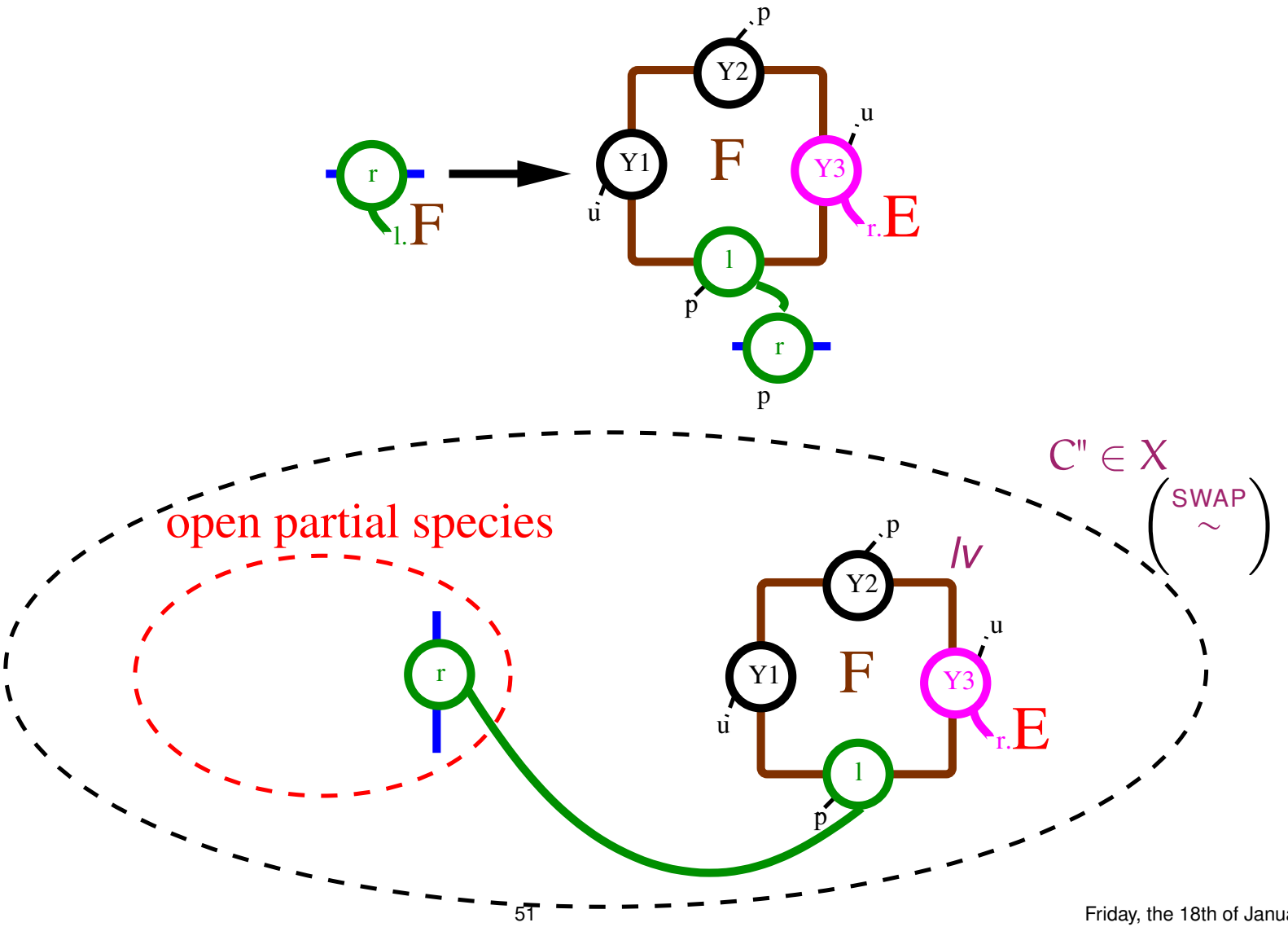


$C \in X$
(since $lv \in \alpha(X)$)

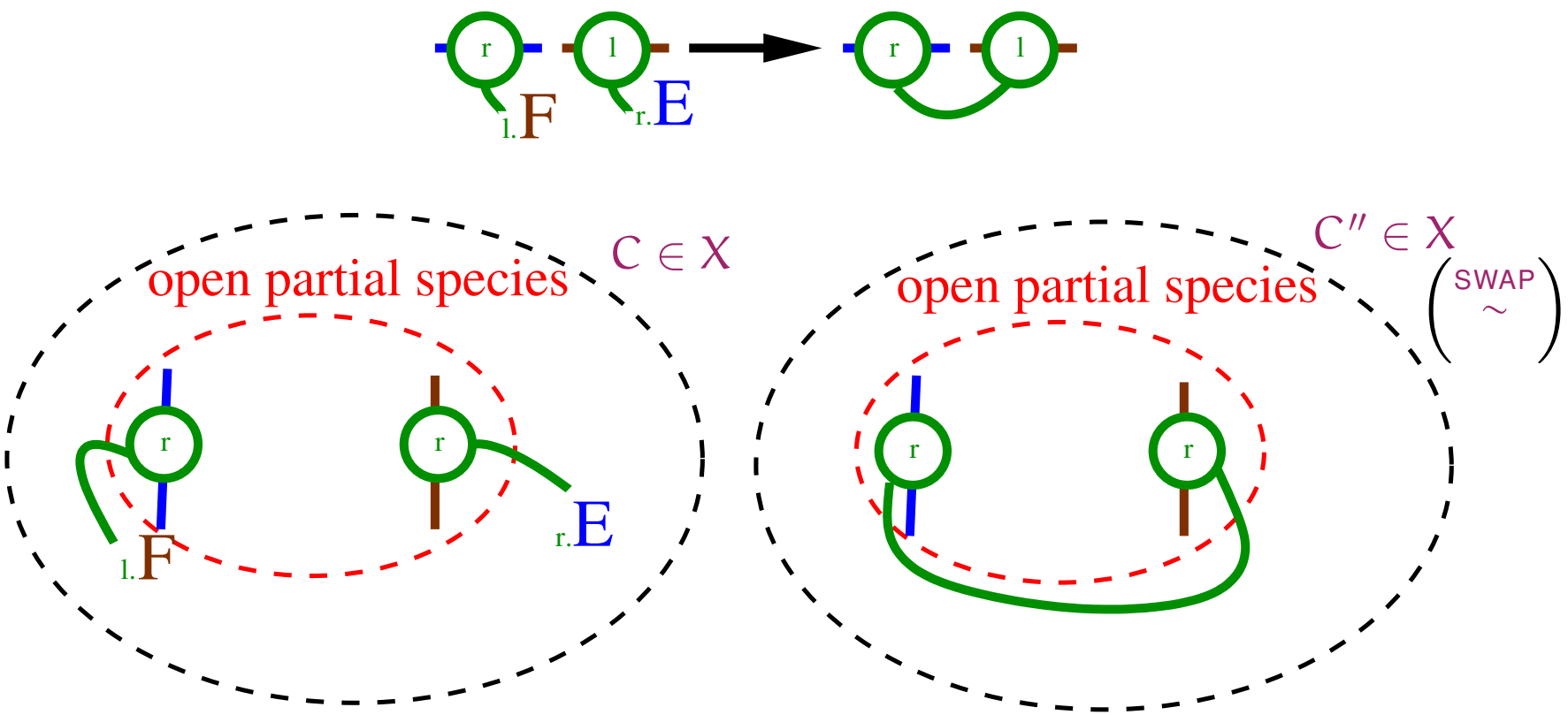
Unfolding a semi-link



Unfolding a semi-link



Binding two semi-links



Consequences

Let $X \in \alpha(\wp(\mathit{Species}))$ be a set of local views.

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

Overview

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

Outline

We have proved that:

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

Now we give some sufficient conditions that ensure this property.

Sufficient conditions

Whenever the following assumptions:

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

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

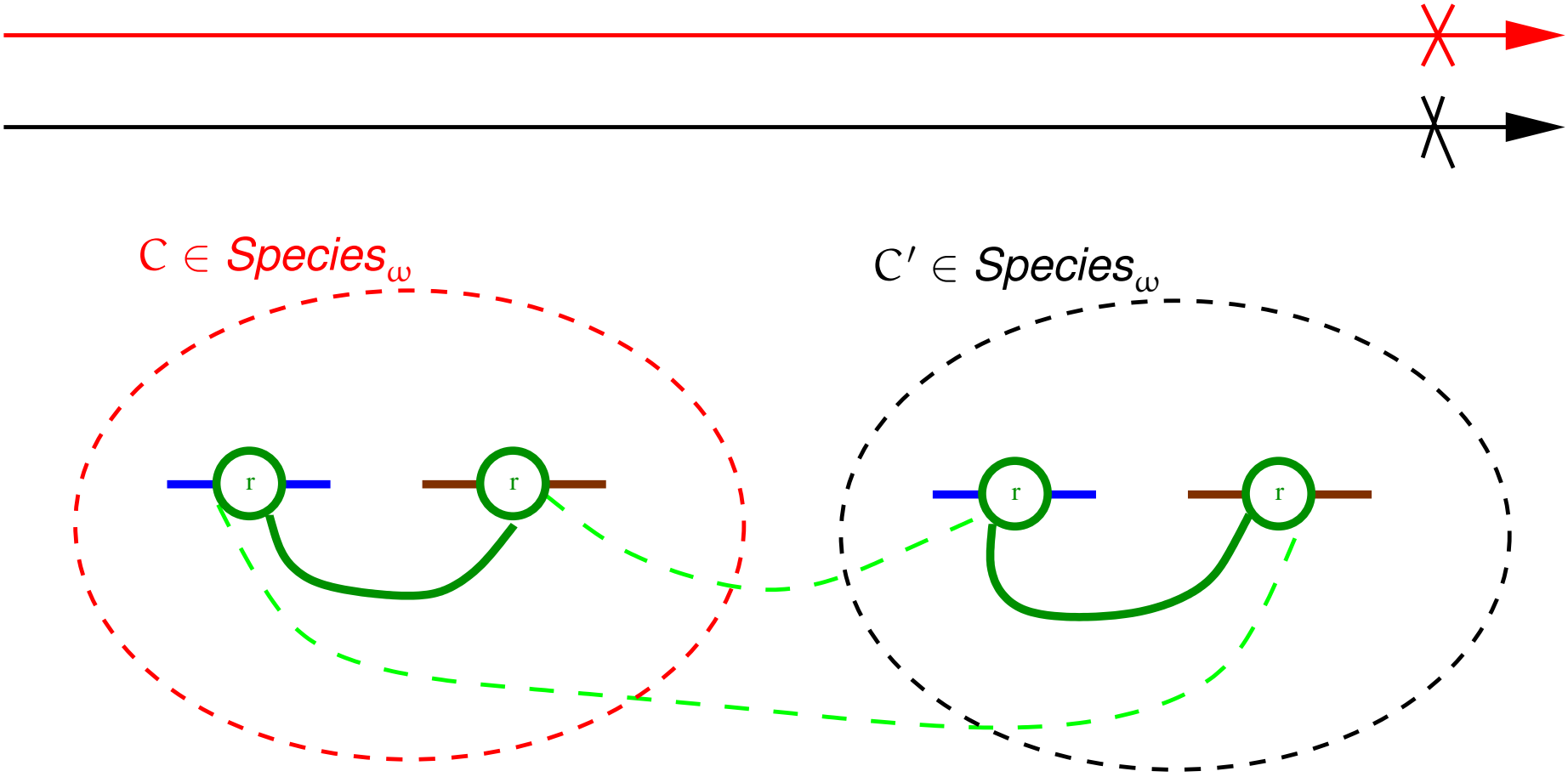
are satisfied, the set of reachable chemical species is local.

Proof outline

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

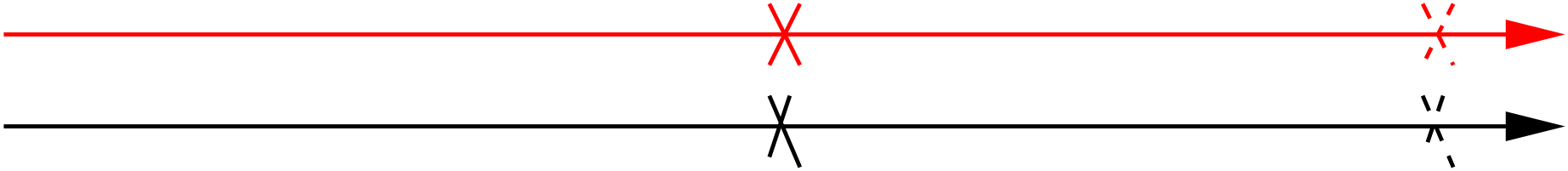
- We consider tuples of complexes in which the same kind of links occur twice.
- We want to swap these links.
- We introduce the history of their computation.
- There are several cases. . .

First case (I/V)

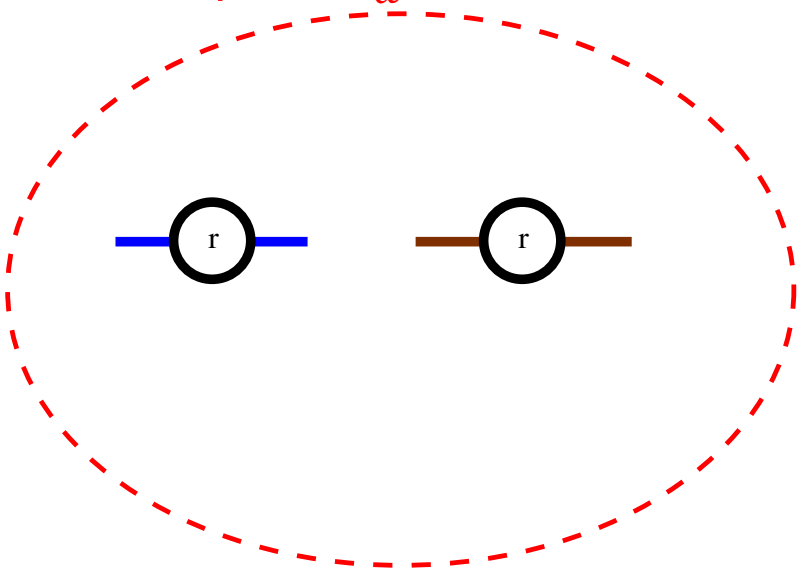


First case (II/V)

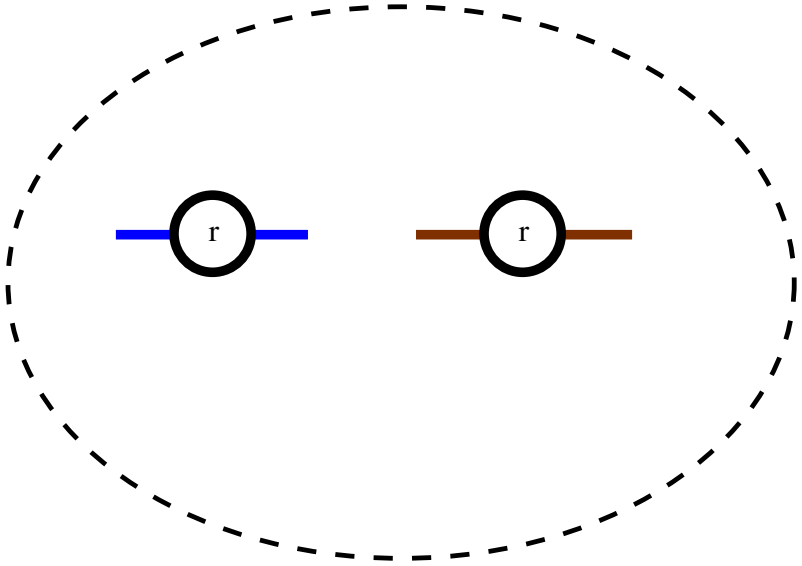
just before the links are made



$\mathcal{C} \in Species^*_\omega$

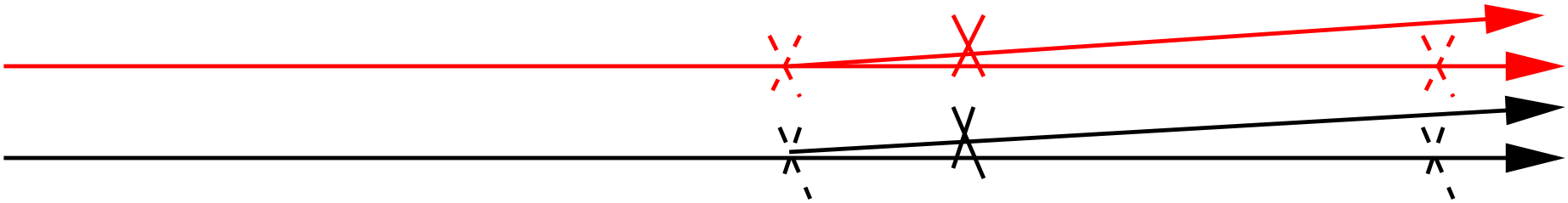


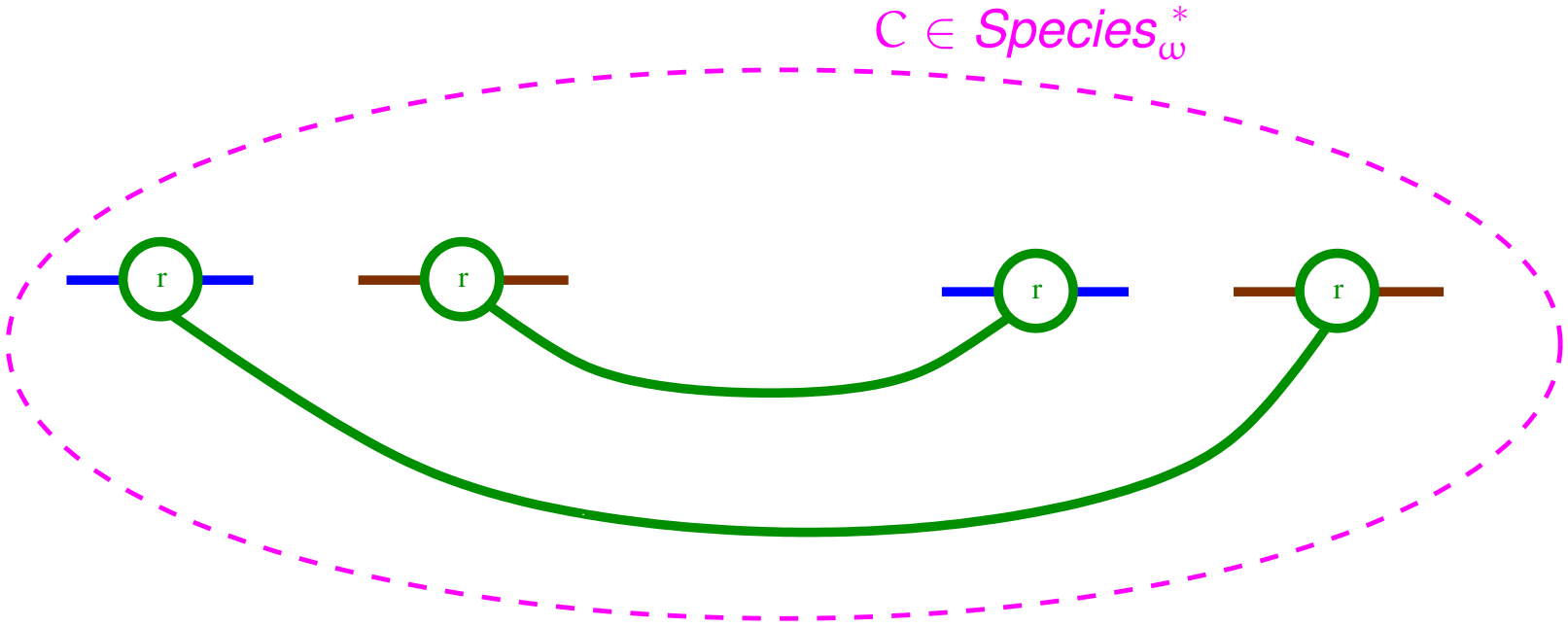
$\mathcal{C}' \in Species^*_\omega$



First case (III/V)

we suppose we can swap the links

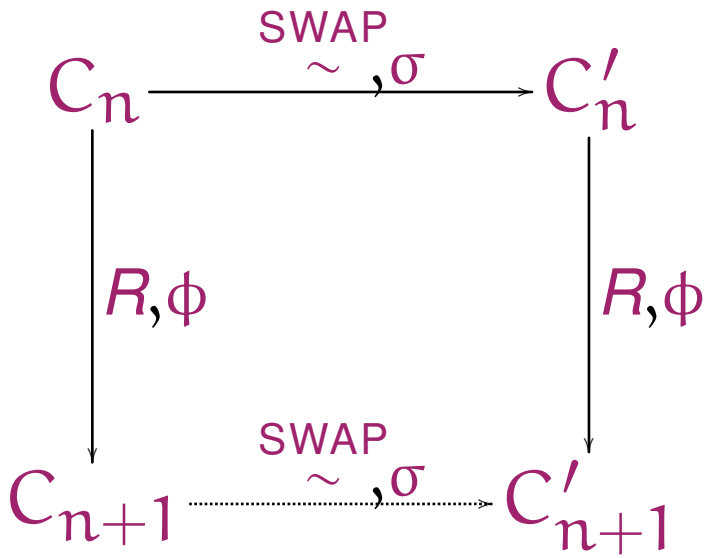




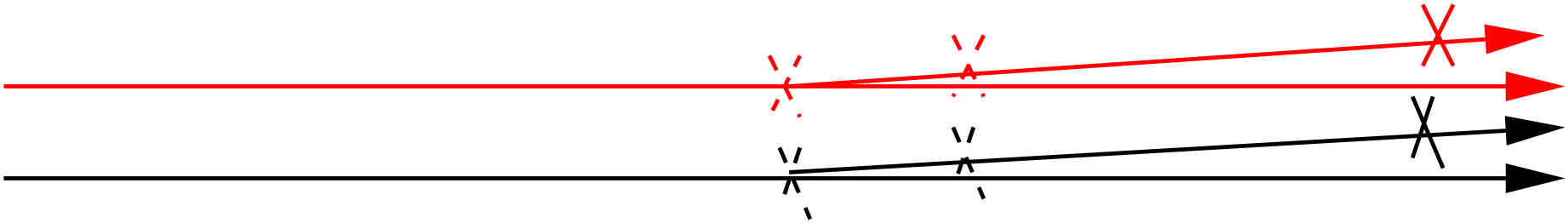
First case (IV/V)

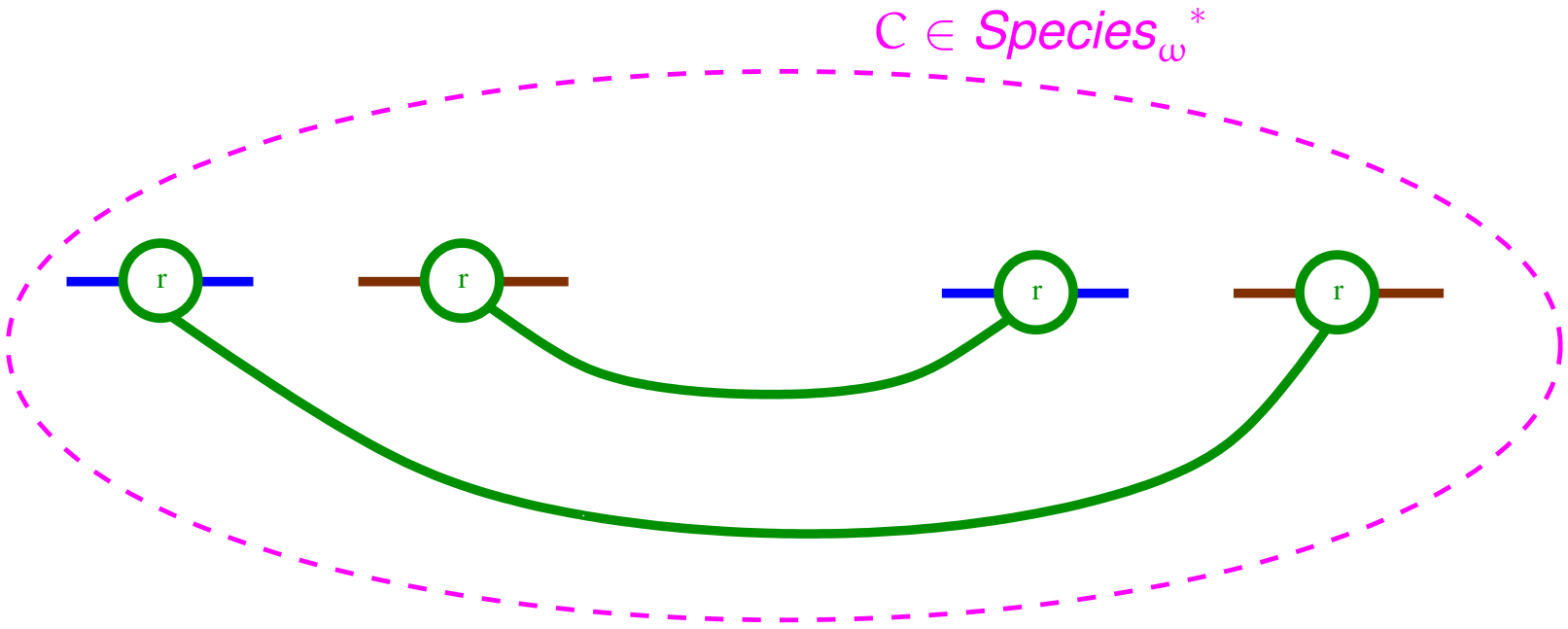
Then, we ensure that further computation steps:

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

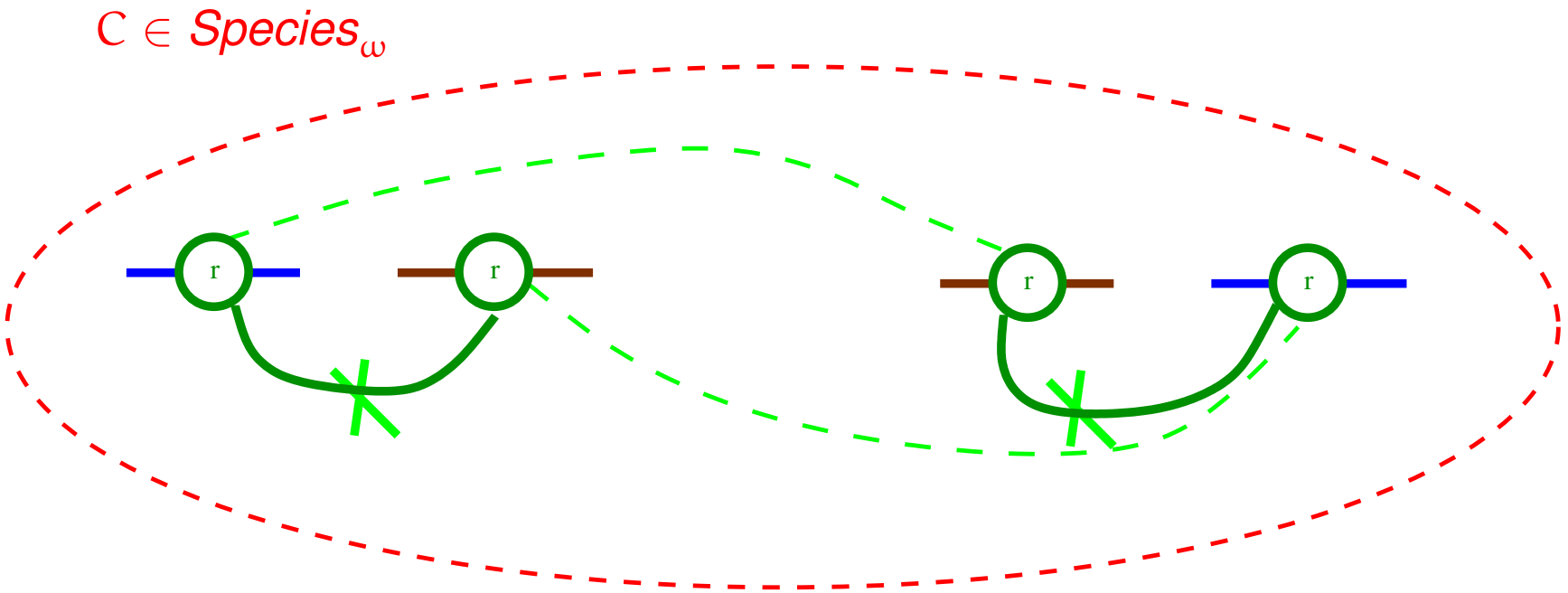


First case (V/V)



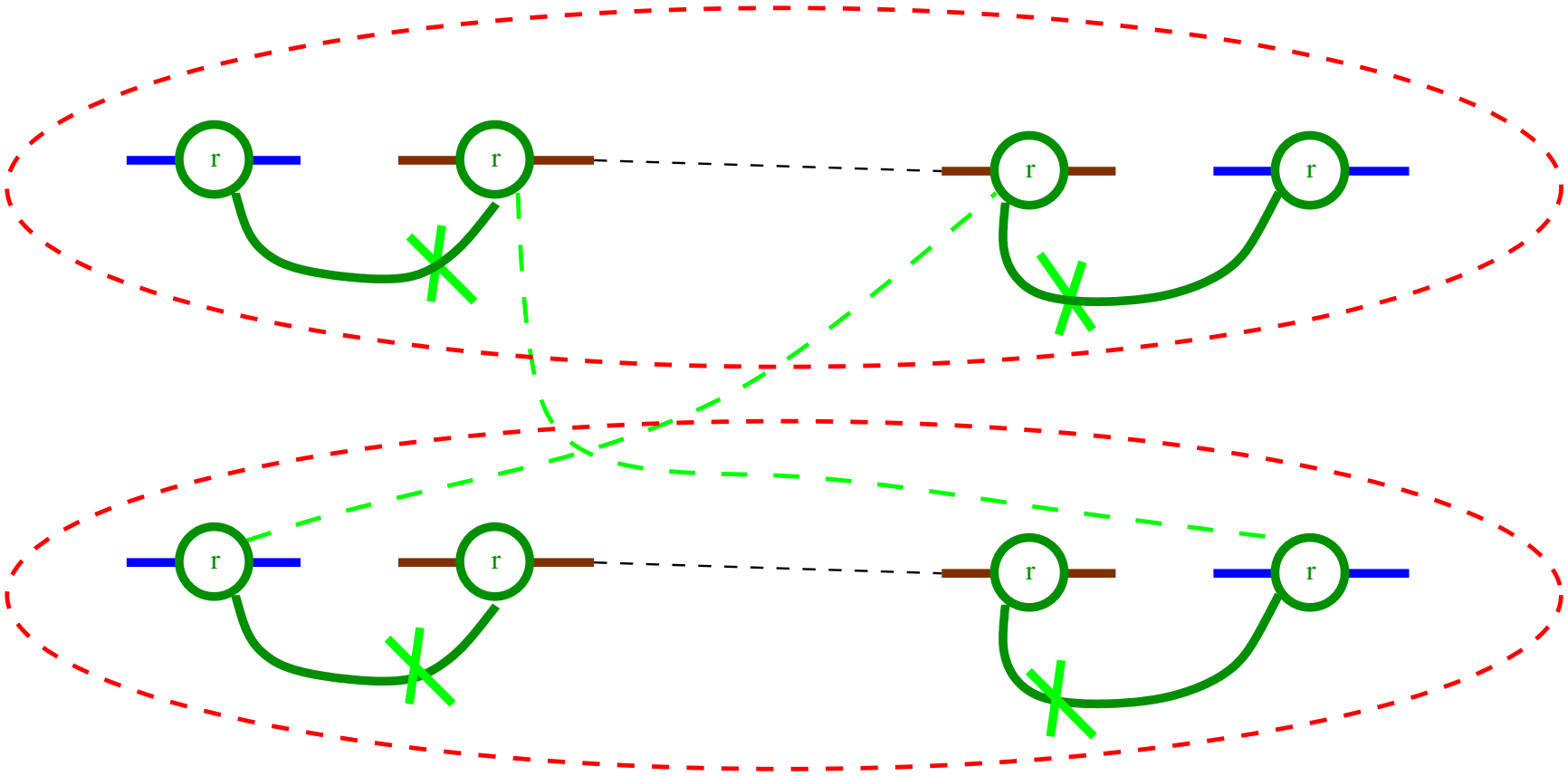


Second case (I/II)



we assume that the chemical species C is acyclic

Second case (II/II)



Sufficient conditions

Whenever the following assumptions:

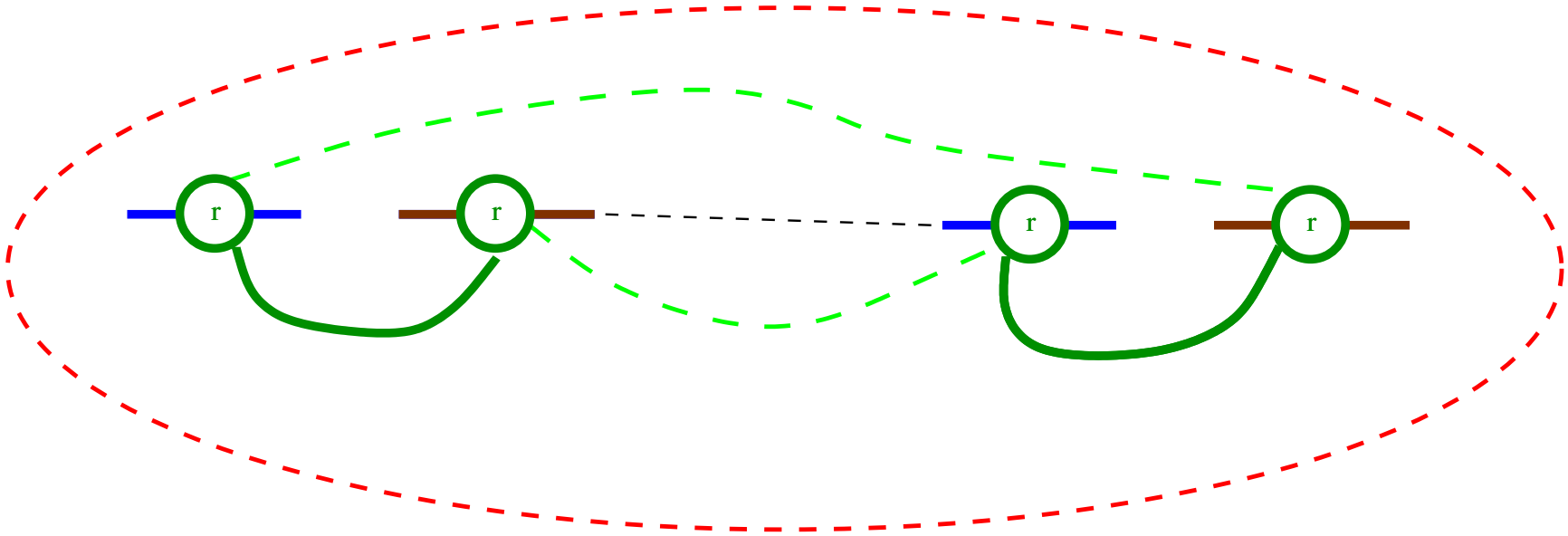
1. initial agents are not bound;
2. rules are atomic;
3. rules are local:
   - only agents that interact are tested,
   - no cyclic patterns (neither in lhs, nor in rhs);
4. binding rules do not interfere i.e. if both:
   - A(a~m,S),B(b~n,T) $\rightarrow$ A(a~m!1,S),B(b~n!1,T)
   - and A(a~m',S'),B(b~n',T')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

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

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

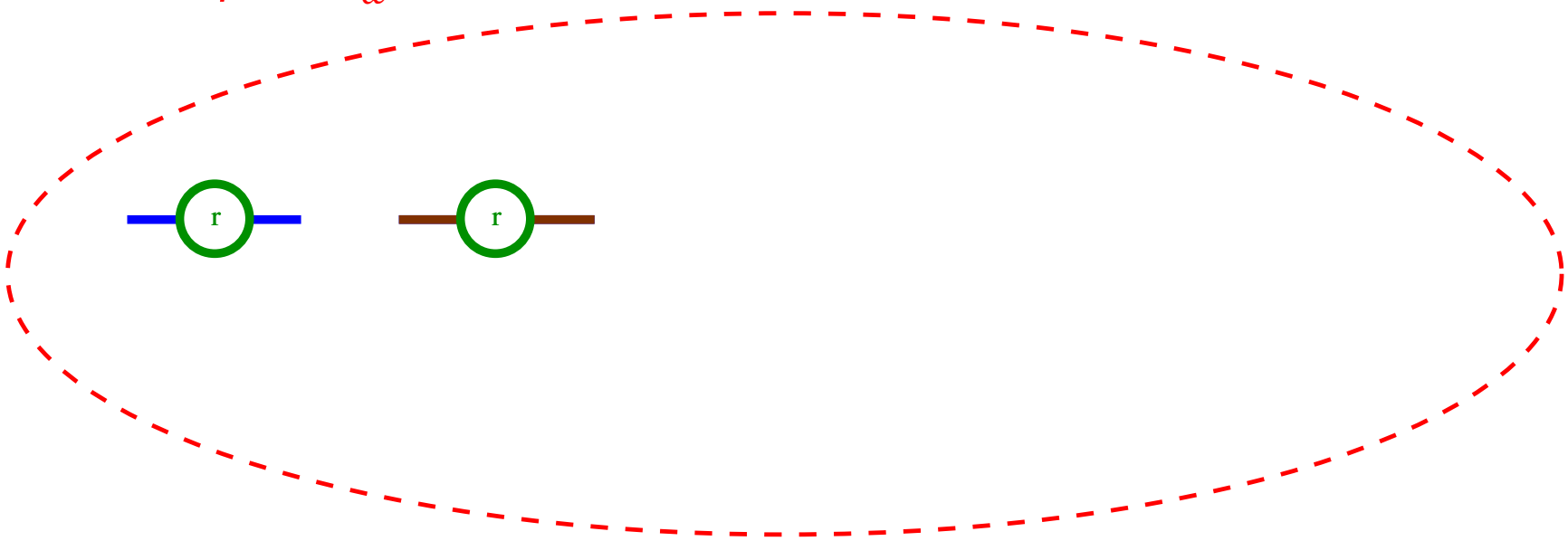
Third case (I/III)

$\mathcal{C} \in Species_{\omega}$

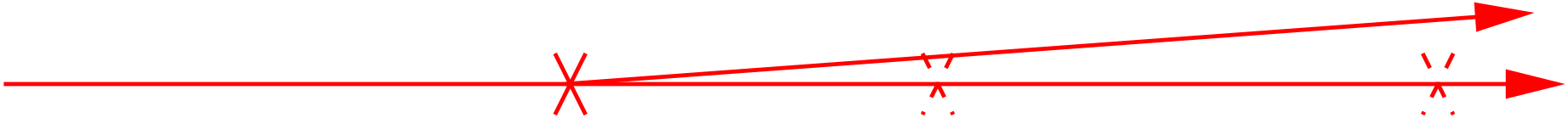


Third case (II/III)

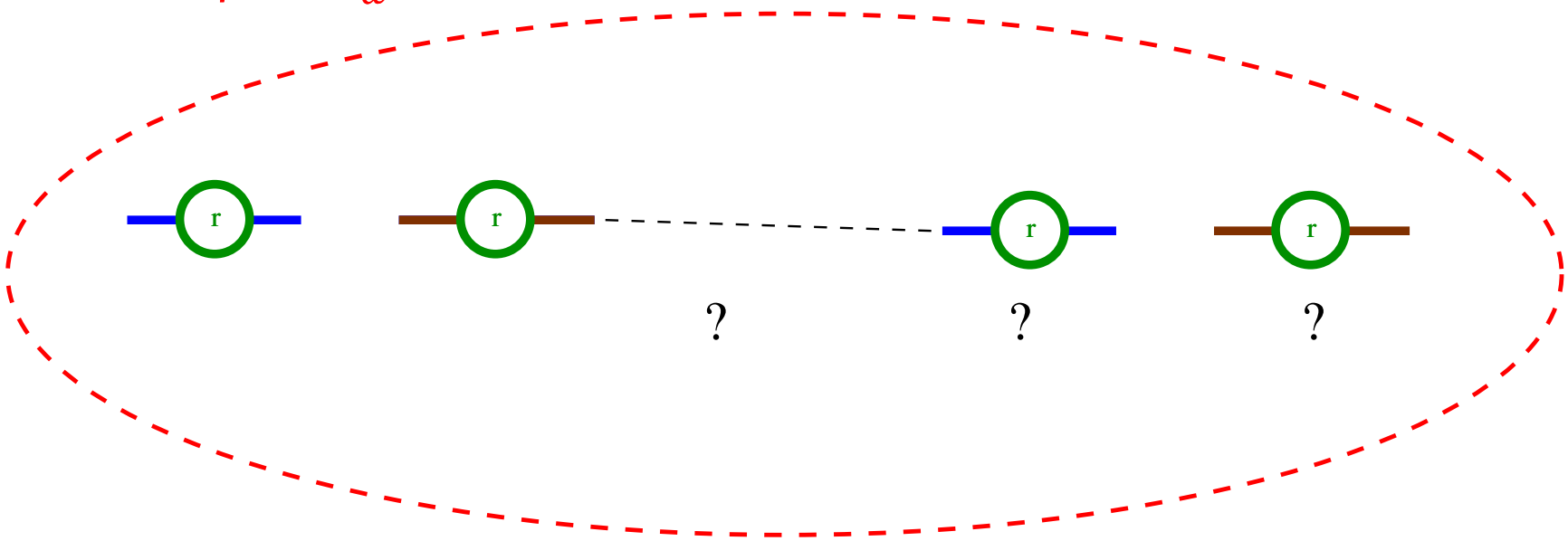
$\mathcal{C} \in Species^*_\omega$



Third case (II/III)



$\mathbb{C} \in Species_{\omega}^{*}$



Dangerous sites

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

We would weaken the fifth requirement into:

- 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.

Non local systems

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

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

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

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

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

Non local systems

$$\mathit{Species}_0 \triangleq \text{A(a}\sim\text{u),B(a}\sim\text{u)}$$

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

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

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

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

Non local systems

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

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

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

Non local systems

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

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

Overview

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

Outline

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

Example

Initial rule:

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

Decontextualized rule:

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

We can remove redundant tests.

Example

Initial rules:

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

Decontextualized rule:

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

We can remove exhaustive enumerations.

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 $S(\mathrm{R})$ of open chemical species that can match its lhs;
- Rules are gathered in equivalence classes according to the actions they perform;
- For each class $[\mathrm{R}]$, we compute:

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

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

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

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

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.

Overview

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

Conclusion

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