École Jeunes Chercheuses et Jeunes Chercheurs en Informatique Mathématiques

Rule-based Modeling

Static analysis

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In this talk...

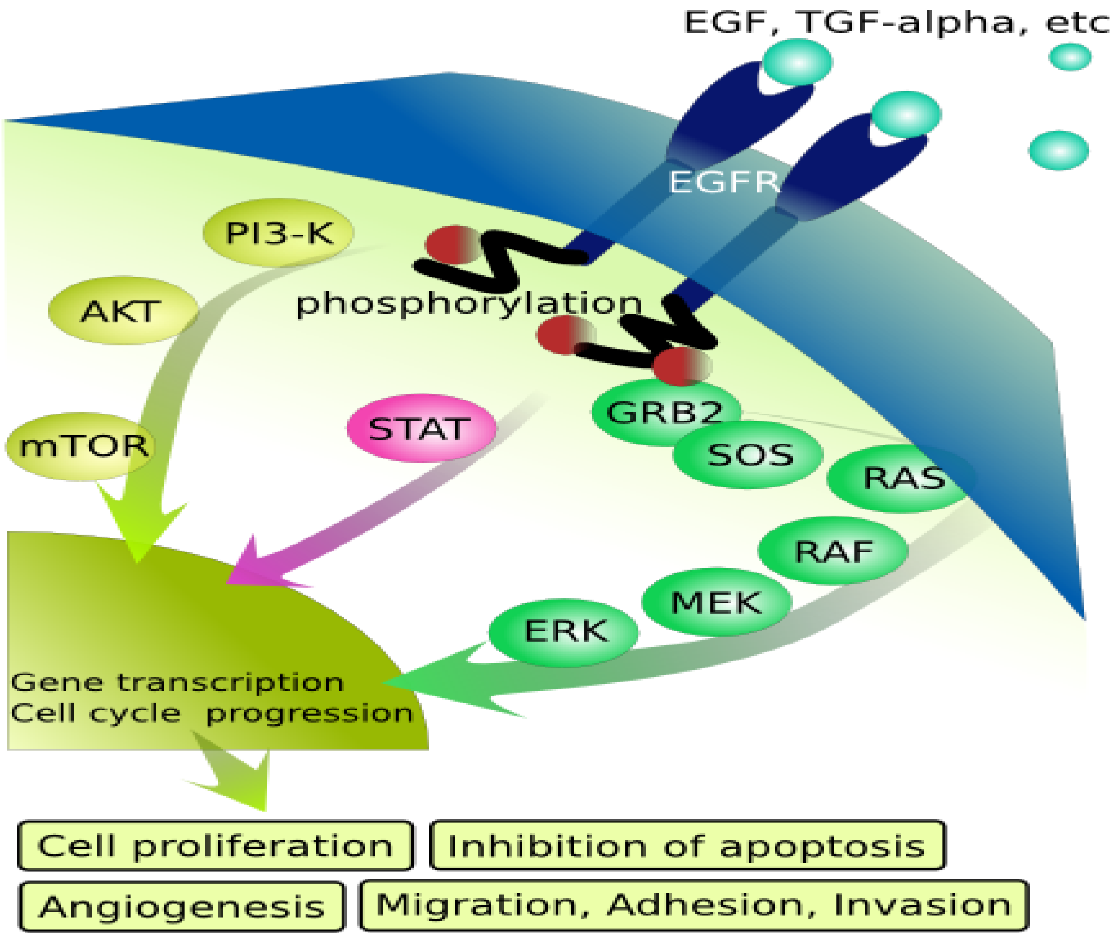
We illustrate the following concepts:

- Galois connections:
  - the upper closure operator $\gamma \circ \alpha$,
  - the lower closure operator $\alpha \circ \gamma$;
- soundness:
  - the abstraction forgets no behavior;
- completeness:
  - sufficient conditions that ensure the absence of false positive;

on an abstraction of the reachable connected components in a site-graph rewriting language.

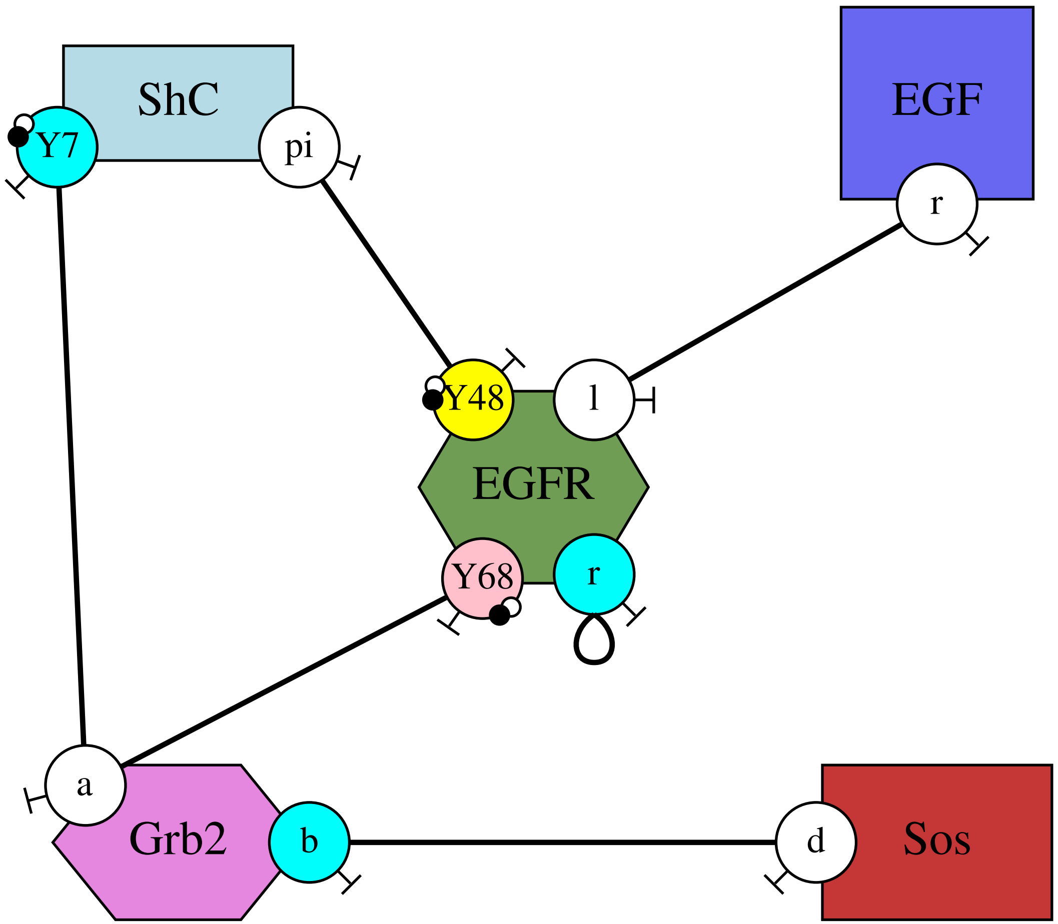
Overview

Signaling Pathways

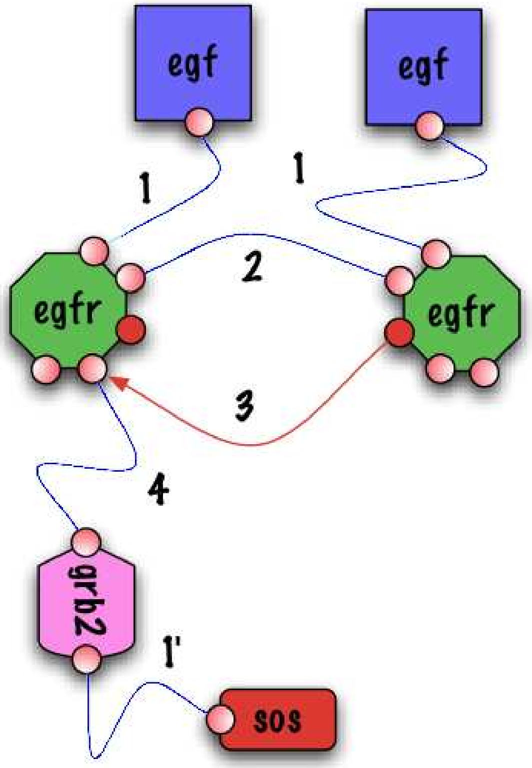


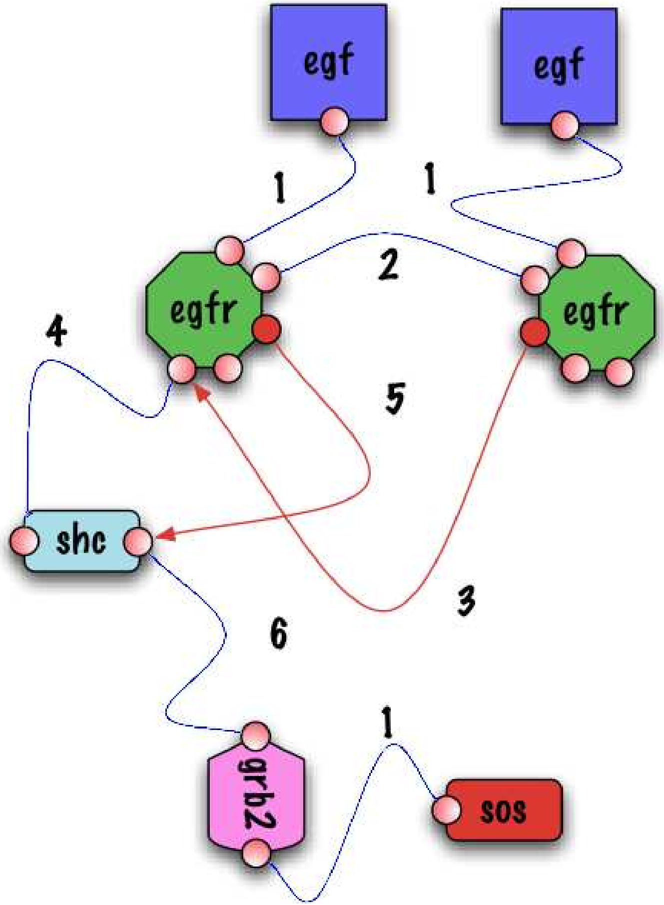
Eikuch, 2007

Contact map

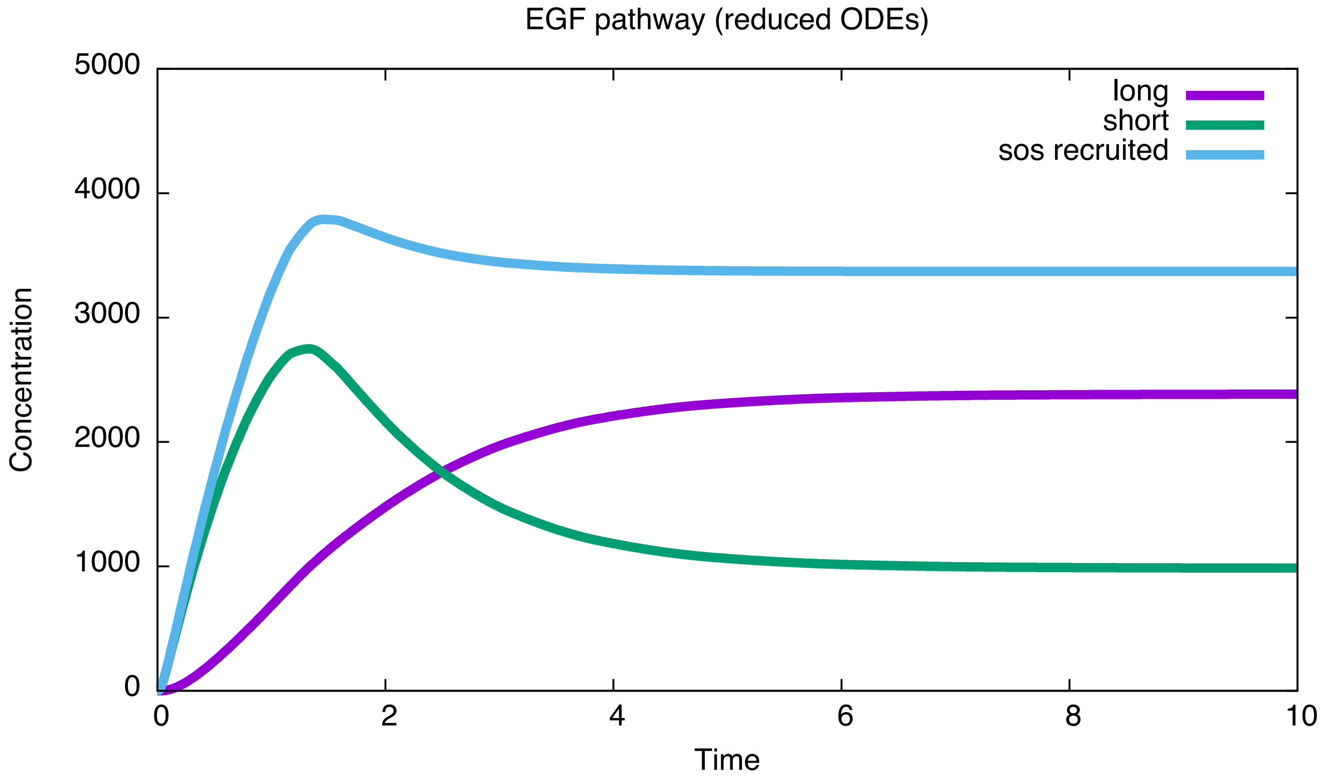


Causal traces

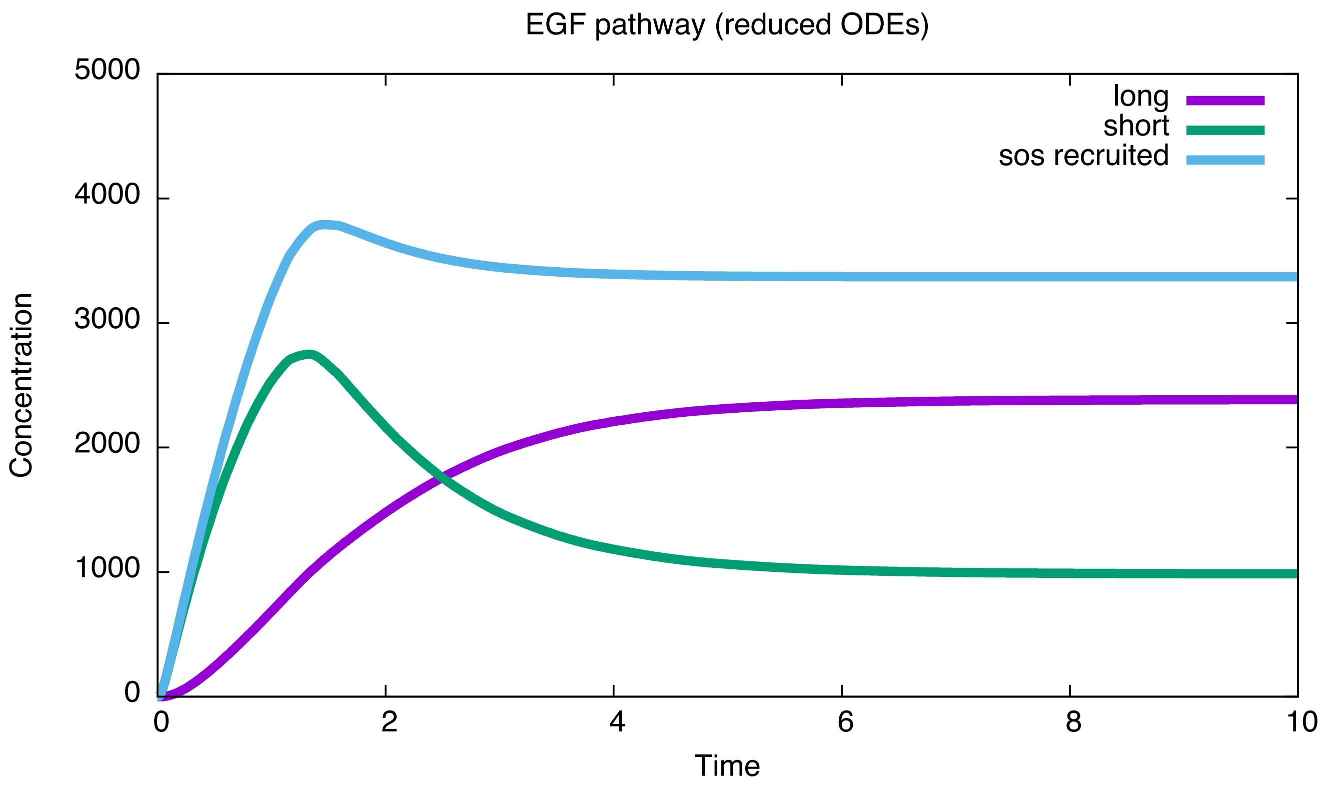




ODE semantics

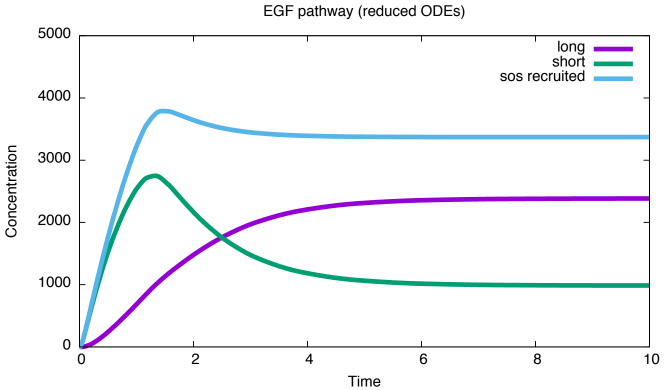


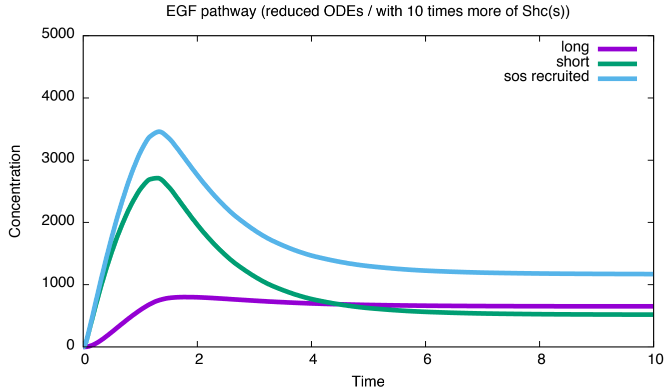
ODE semantics



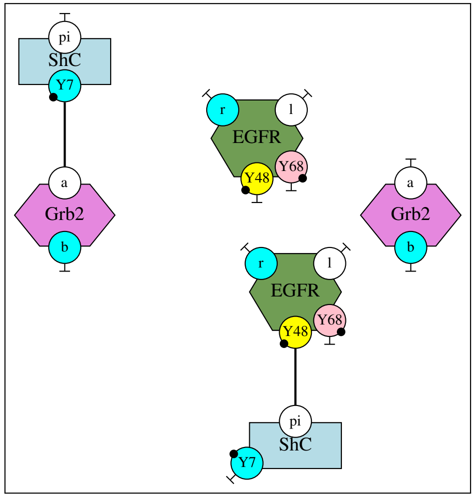
What will happen if more Shc(s) is put in the system?

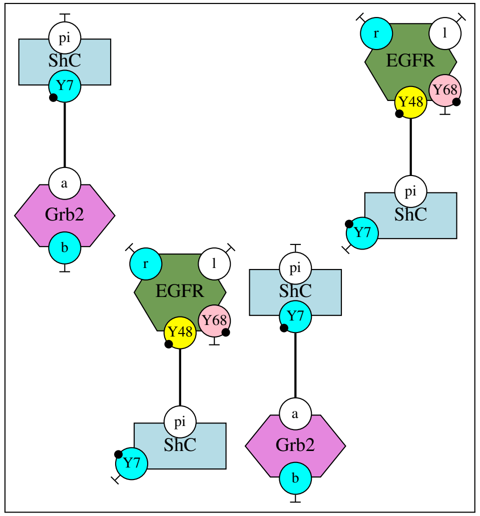
ODE semantics

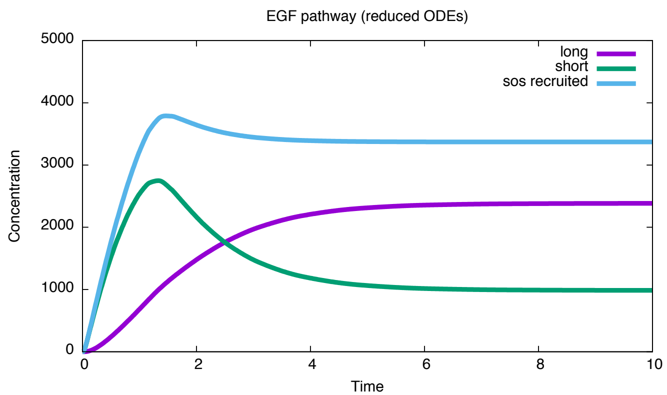


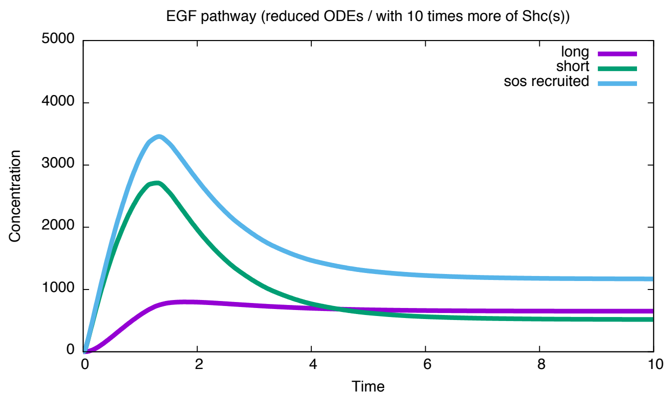


Crowding effect









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: $R(r^2,Y48^{p1}), Sh(\pi^1,Y7) -> R(r^2,Y48^{p1}), Sh(\pi^1,Y7^p)$
  - ??: $Sh(\pi^1,Y7^p) -> Sh(\pi^1,Y7)$
  - 16: $Sh(\pi,Y7^p) -> Sh(\pi,Y7)$

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 modeling 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.

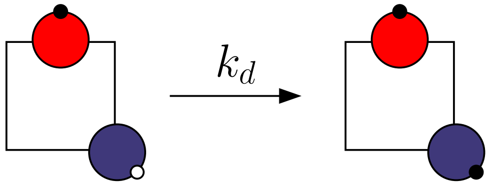
Overview

1. Introduction
2. Abstraction: Local views
3. Completeness: false positives?
4. Local fragment of Kappa
5. Conclusion

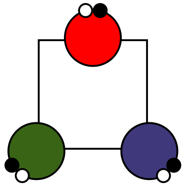
Concrete semantics

A rule is a symbolic representation of a multi-set of reactions.

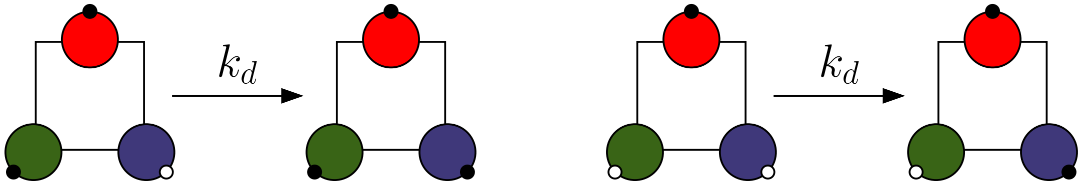
For instance, the rule:



within a model with the following signature:



denotes the following two reactions:



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 chemical species.

We are interested in $Species_\omega$ the set of all chemical species that can be constructed in one or several applications of the reactions induced by the 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:

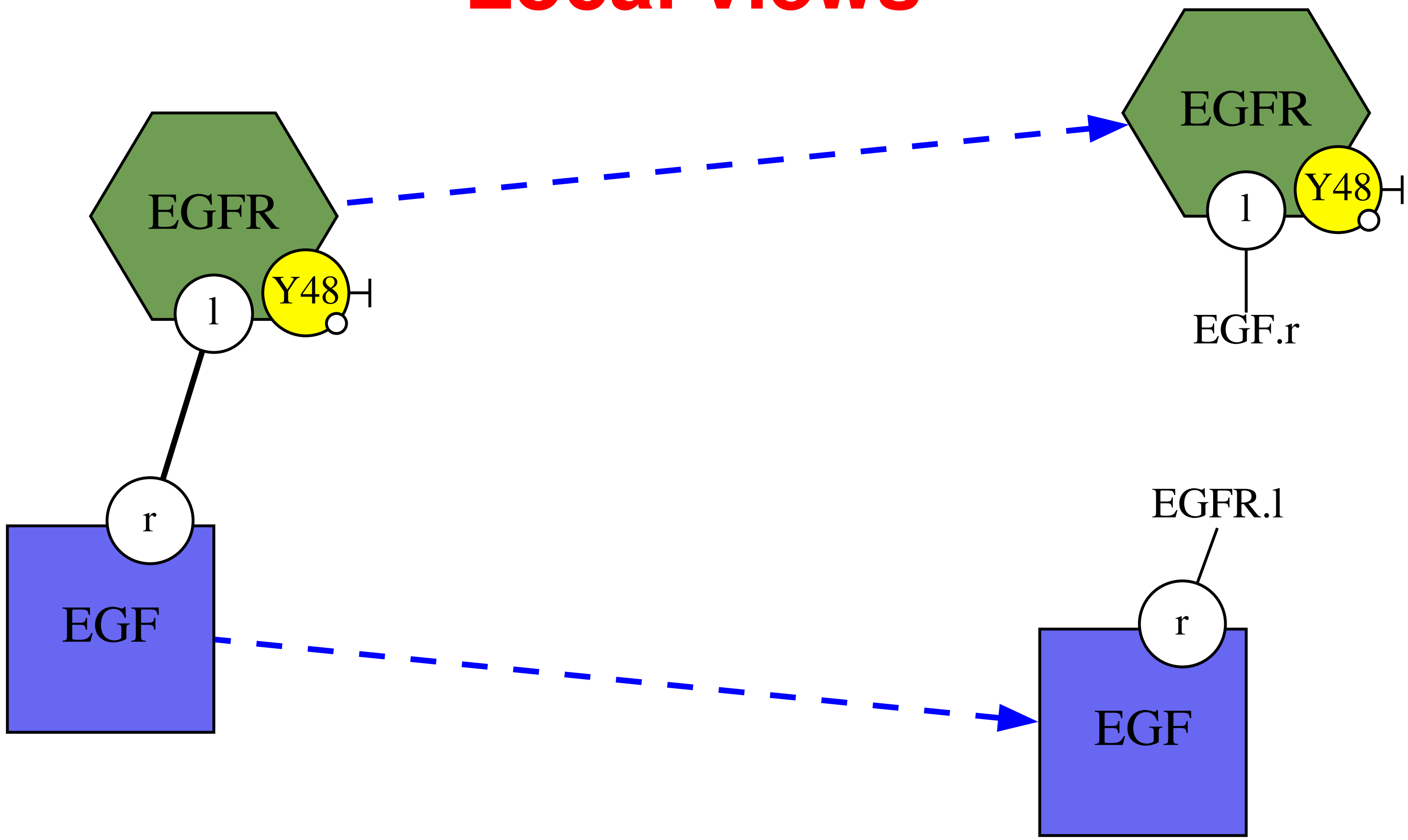
$$\mathbb{F} : \begin{cases} \wp(Species) & \rightarrow \wp(Species) \\ X & \mapsto X \cup \left\{ c'_j \;\middle|\; \begin{array}{l} \exists R_k \in \mathcal{R}, c_1, \ldots, c_m \in X, \\ c_1, \ldots, c_m \rightarrow_{R_k} c'_1, \ldots, c'_n \end{array} \right\} \end{cases}.$$

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

We define the set of reachable chemical species as follows:

$$Species_\omega = \bigcup \left\{ \mathbb{F}^n(Species_0) \;\middle|\; n \in \mathbb{N} \right\}.$$

Local views



α({EGFR(Y48{u}[.] l[1]) EGF(r[1])}) =
{EGFR(Y48{u}[.] l[r.EGF]); EGF(r[l.EGFR])}.

Galois connection

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

Let $\alpha \in \wp(Species) \rightarrow \wp(Local\_view)$ be the function that maps any set of chemical species into the set of their local views.

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

Thus, it defines a Galois connection:

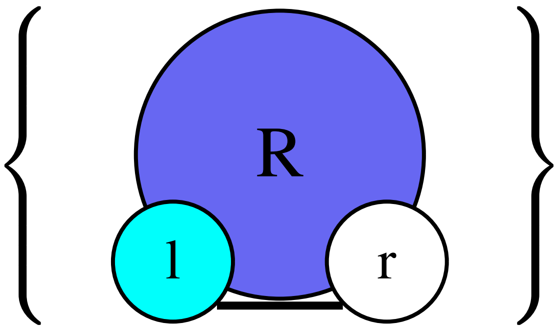
$$\wp(Species) \xleftarrow[\alpha]{\gamma} \wp(Local\_view).$$

(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.

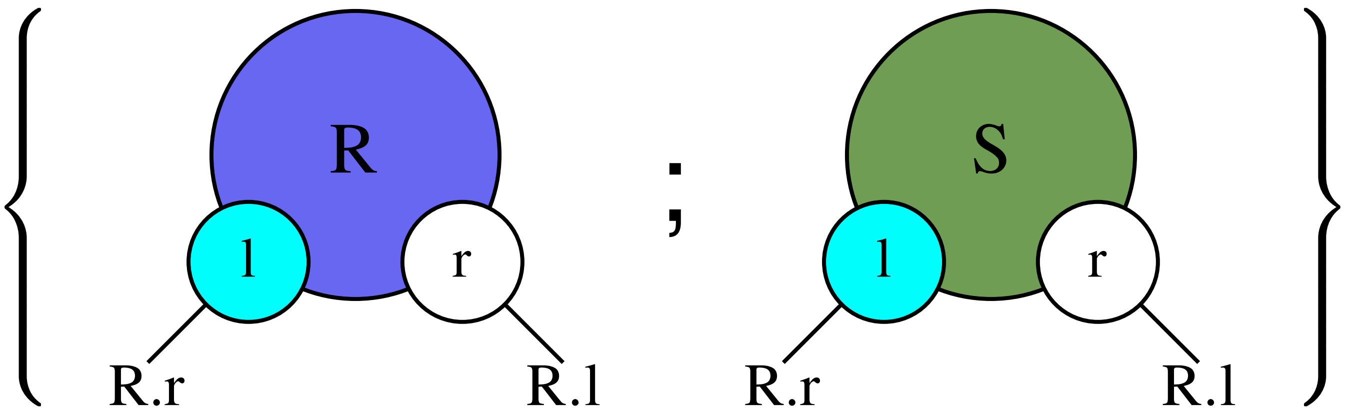
Guess the image of the following set of chemical species ?



$\alpha \circ \gamma$

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

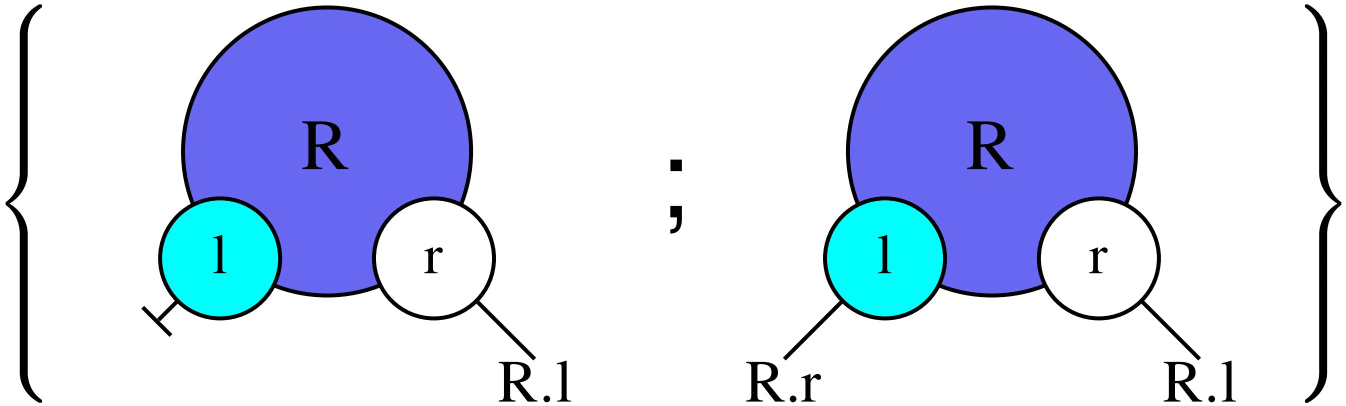
Guess the image of the following set of local views ?



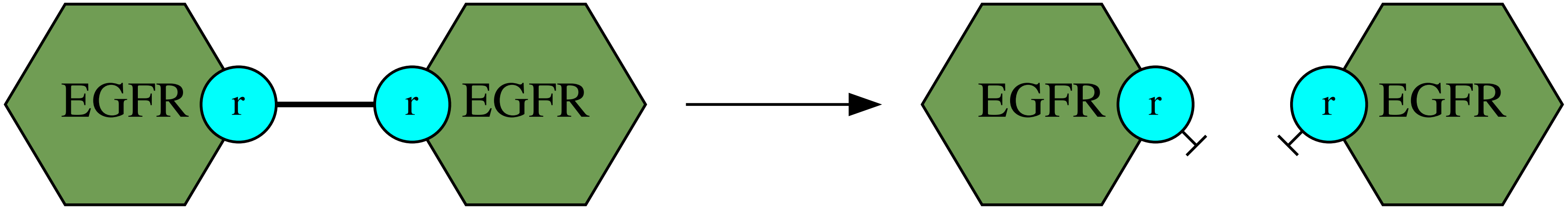
One more question

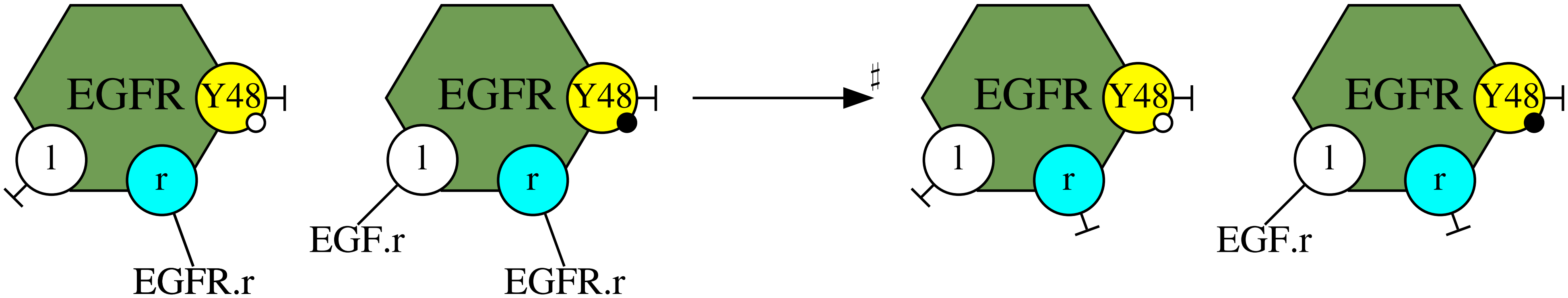
$\alpha \circ \gamma$ is a lower closure operator: it simplifies (or reduces) constraints.

Guess the image of the following set of local views ?



Abstract reactions





Abstract counterpart to $\mathbb{F}$

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

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

We have:

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

Soundness

Theorem 1 Let:

1. $(D, \subseteq, \cup)$ and $(D^\sharp, \sqsubseteq, \sqcup)$ be chain-complete partial orders;
2. $D \xleftarrow[\alpha]{\gamma} D^\sharp$ be a Galois connection;
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. $\mathit{lfp}_{X_0}\mathbb{F} \subseteq \gamma(\mathit{lfp}_{\alpha(X_0)}\mathbb{F}^\sharp)$.

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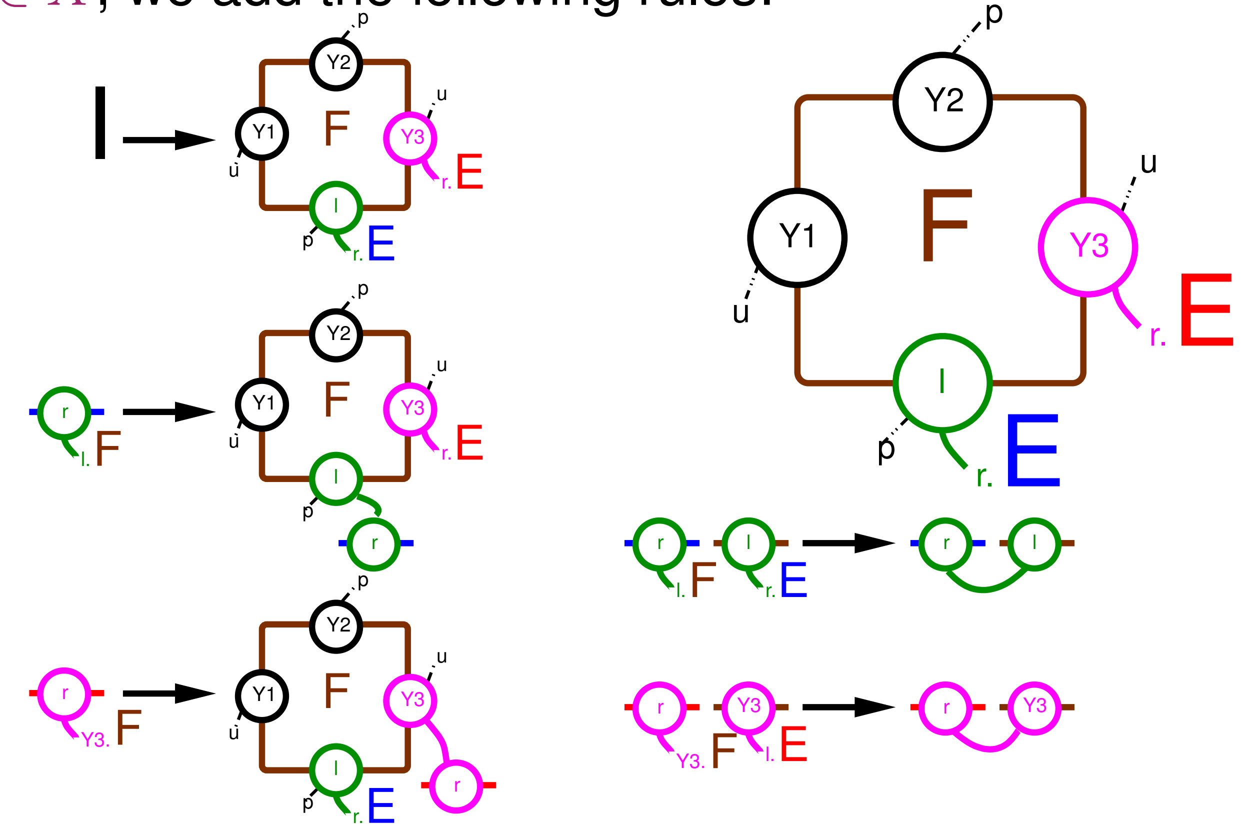
From views to species

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.

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 chemical species);
- for FGF cascade (79080 chemical species);
- for SBF cascade (around 10^{19} chemical species).

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

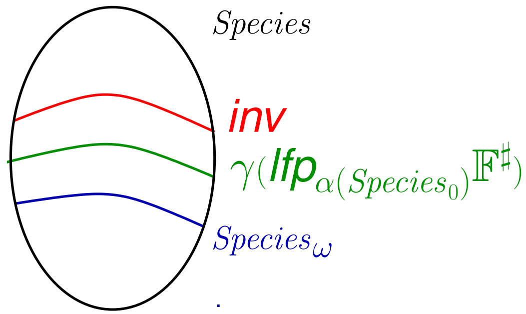
This raises the following issues:

- 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 2 We suppose that:

1. $(D, \subseteq)$ be a partial order;
2. $(D^\sharp, \sqsubseteq, \sqcup)$ be chain-complete partial order;
3. $D \xleftrightarrow[\alpha]{\gamma} D^\sharp$ be a Galois connection;
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 $\gamma(\mathit{lfp}_{\alpha(X_0)}\mathbb{F}^\sharp) \subseteq \mathit{inv}$.

Proof I/III

We know (eg. see transfinite itterations) that:

1. *lfp*$_{\alpha(X_0)}\mathbb{F}^\sharp$ exists;
2. there exists an ordinal δ such that *lfp*$_{\alpha(X_0)}\mathbb{F}^\sharp = {\mathbb{F}^\sharp}^\delta(\alpha(X_0))$.

Proof II/III

Let us show that $\gamma(\textit{lfp}_{\alpha(X_0)}\mathbb{F}^\sharp) \subseteq \textit{inv}$.

Let us prove instead by induction over δ that $\mathbb{F}^{\sharp\delta}(\alpha(X_0)) \sqsubseteq \alpha(\textit{inv})$.

- If $Y \in D^\sharp$ is an element such that $Y \sqsubseteq \alpha(\textit{inv})$,
  $\mathbb{F}^\sharp(Y) \sqsubseteq \mathbb{F}^\sharp(\alpha(\textit{inv}))$ ($\mathbb{F}^\sharp$ is mon)
  $\mathbb{F}^\sharp(\alpha(\textit{inv})) = \alpha(\mathbb{F}(\textit{inv}))$ (assumption)
  $\alpha(\mathbb{F}(\textit{inv})) \sqsubseteq \alpha(\textit{inv})$. ($\alpha$ is mon and *inv* is a post)

  Thus: $\mathbb{F}^\sharp(Y) \sqsubseteq \alpha(\textit{inv})$
- If $Y_i \in D^{\sharp I}$ is a chain of elements such that $Y_i \sqsubseteq \alpha(\textit{inv})$ for any $i \in I$, then, $\sqcup Y_i \sqsubseteq \alpha(\textit{inv})$ (lub).

So: $\mathbb{F}^{\sharp\delta}(\alpha(X_0)) \sqsubseteq \alpha(\textit{inv})$.

Proof III/III

We have:

$$\mathbb{F}^{\sharp\delta}(\alpha(X_0)) \sqsubseteq \alpha(\textit{inv}).$$

Since γ is monotonic:

$$\gamma(\mathbb{F}^{\sharp\delta}(\alpha(X_0))) \subseteq \gamma(\alpha(\textit{inv})).$$

But, by assumption, $\gamma(\alpha(\textit{inv})) = \textit{inv}$.
Thus,

$$\gamma(\mathbb{F}^{\sharp\delta}(\alpha(X_0))) \subseteq \textit{inv}.$$

When is there no false positive ?

Theorem 3 We suppose that:

1. $(D, \subseteq, \cup)$ and $(D^\sharp, \sqsubseteq, \sqcup)$ are chain-complete partial orders;
2. $(D, \subseteq) \xleftarrow[\alpha]{\gamma} (D^\sharp, \sqsubseteq)$ is a Galois connection;
3. $\mathbb{F} : D \rightarrow D$ 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;
- $\mathit{lfp}_{X_0}\mathbb{F} = \gamma(\alpha(\mathit{lfp}_{X_0}\mathbb{F})) \iff \mathit{lfp}_{X_0}\mathbb{F} = \gamma(\mathit{lfp}_{\alpha(X_0)}\mathbb{F}^\sharp)$.

We need to understand under which assumptions $\mathit{lfp}_{X_0}\mathbb{F} = \gamma(\alpha(\mathit{lfp}_{X_0}\mathbb{F}))$.

Local set of chemical species

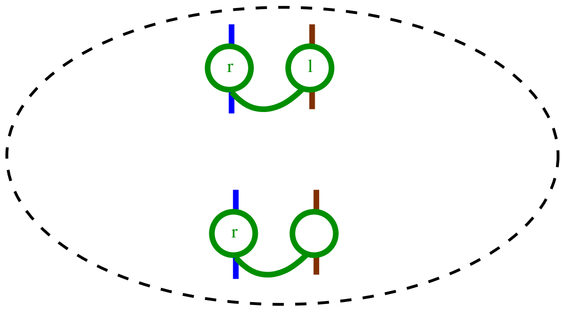
Definition 1 We say that a set $X \in \wp(Species)$ of chemical species is local if and only if $X \in \gamma(\wp(Local\_view))$.

(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.)

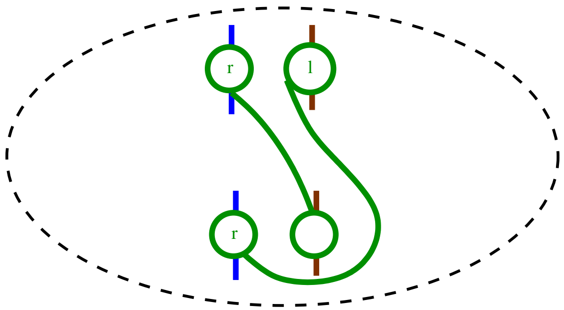
Swapping relation

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 4 Let $X \in \wp(Species)$ be a set of chemical species.

The two following assertions are equivalent:

1. $X = \gamma(\alpha(X))$;
2. for any tuples $(C_i), (D_j) \in Species^*$ 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:

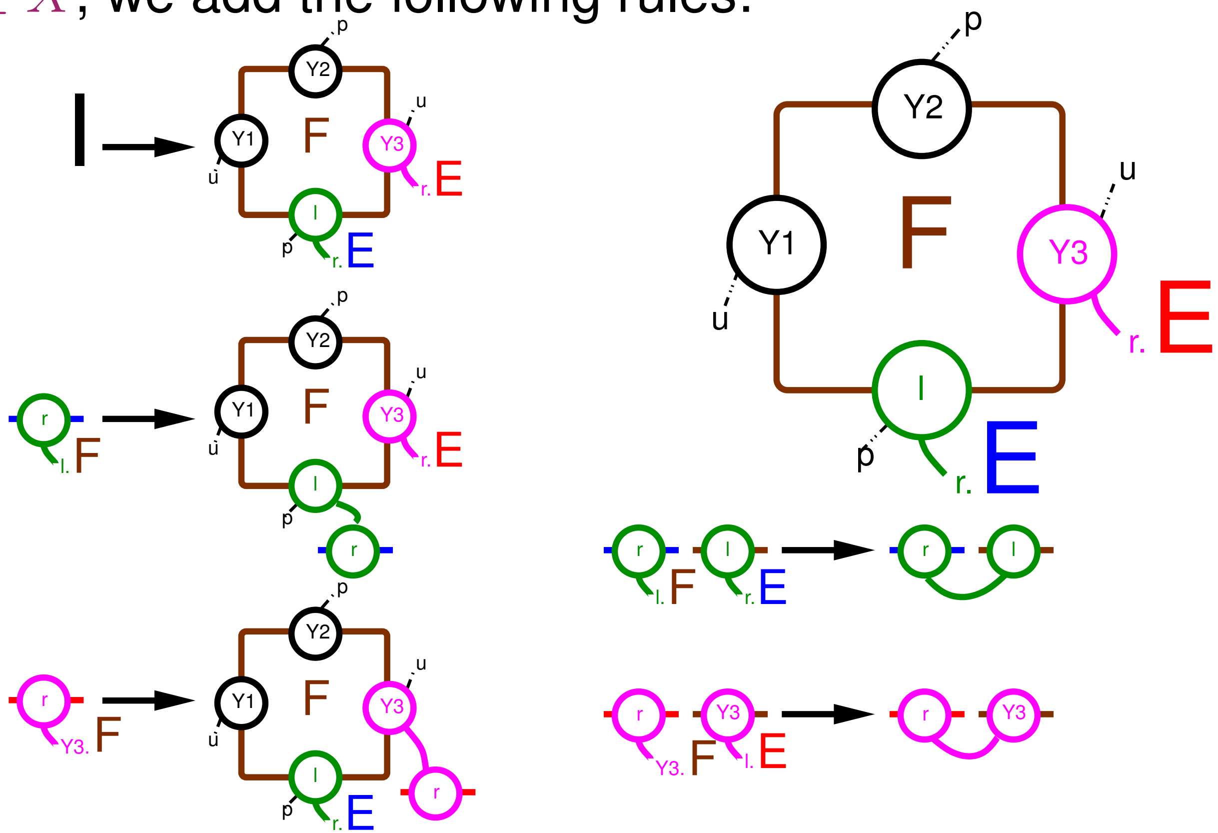
- $X = \gamma(\alpha(X))$,
- $(C_i)_{i \in I} \in X^*$,
- and $(C_i)_{i \in I} \overset{\text{SWAP}}{\sim} (D_j)_{j \in J}$;

Then:

we have $\alpha(\{C_i \mid i \in I\}) = \alpha(\{D_j \mid j \in J\})$ (because $(C_i) \overset{\text{SWAP}}{\sim} (D_j)$)
and $\alpha(\{C_i \mid i \in I\}) \subseteq \alpha(X)$ (because $(C_i) \in X^*$ and α mon);
so $\alpha(\{D_j \mid j \in J\}) \subseteq \alpha(X)$;
so $\{D_j \mid j \in J\} \subseteq \gamma(\alpha(X))$ (by def. of Galois connections);
so $\{D_j \mid j \in J\} \subseteq X$ (since $X = \gamma(\alpha(X))$);
so $(D_j)_{j \in J} \in X^*$.

Proof: more difficult implication way

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.

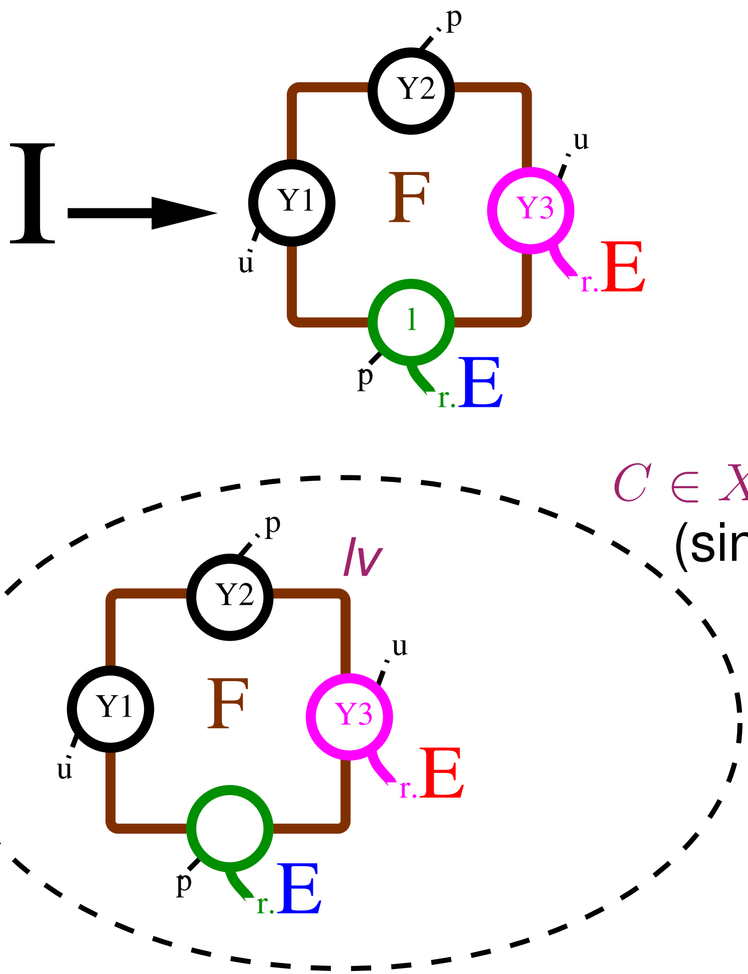
Proof (more difficult implication way)

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 by gathering the views of $\alpha(X)$, can be embedded in a complex in X:

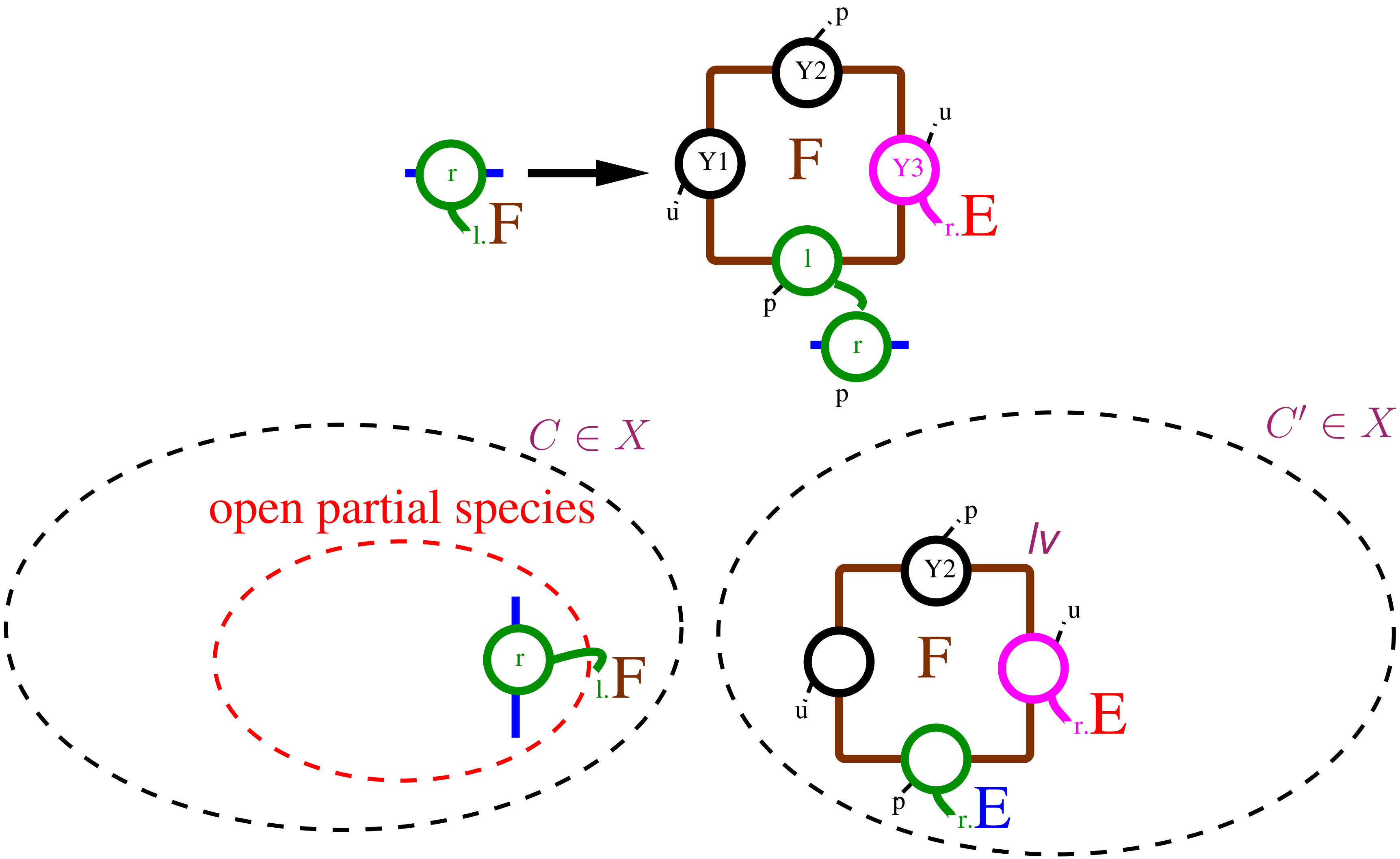
- By def. of α, this is satisfied for any local view in $\alpha(X)$;
- This remains satisfied after unfolding a semi-link with a local view;
- This remains satisfied after binding two semi-links.

Initialization

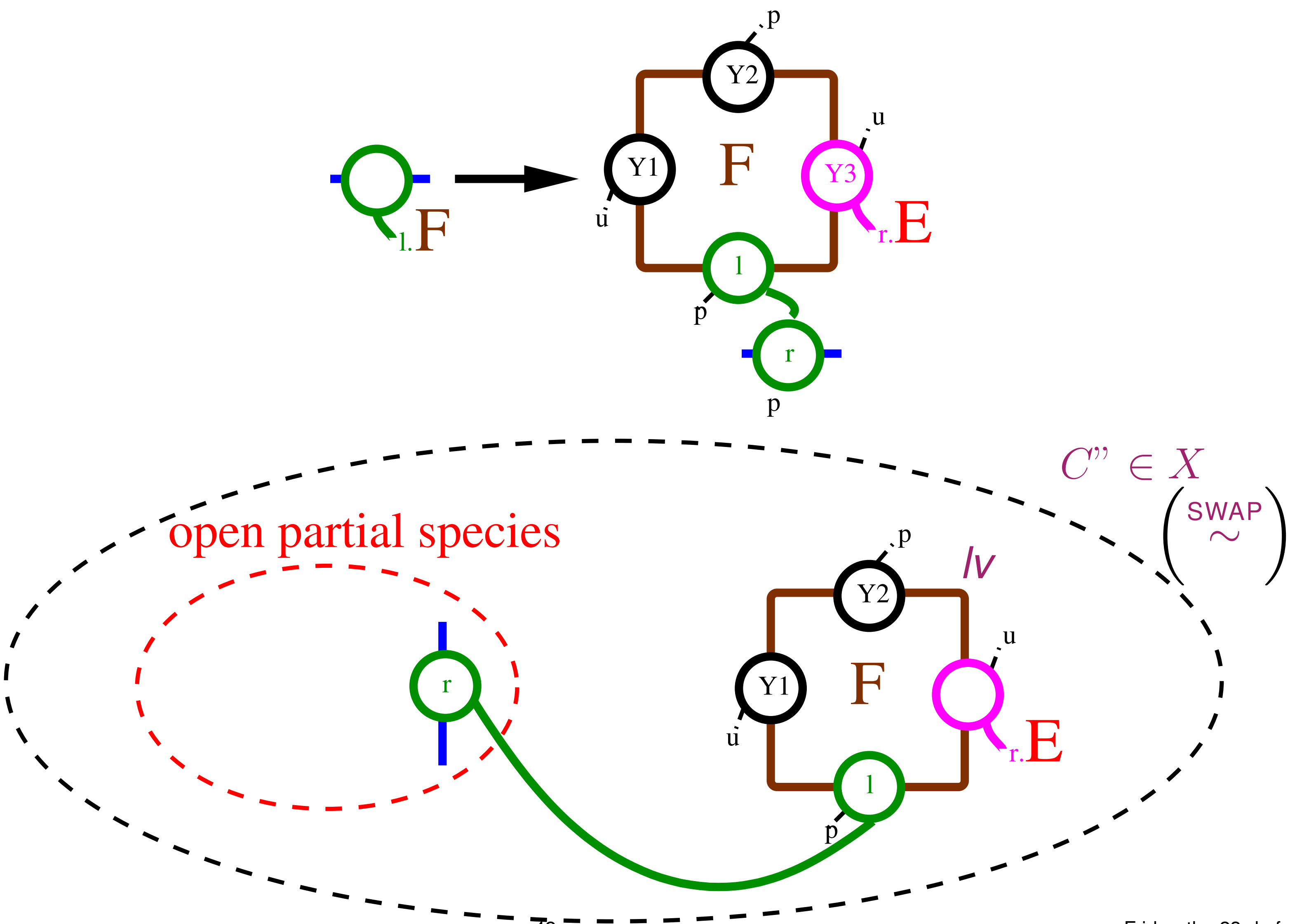


$C \in X$
(since *lv* $\in \alpha(X)$)

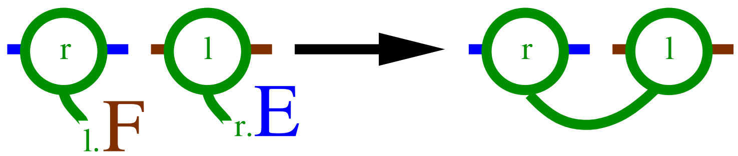
Unfolding a semi-link

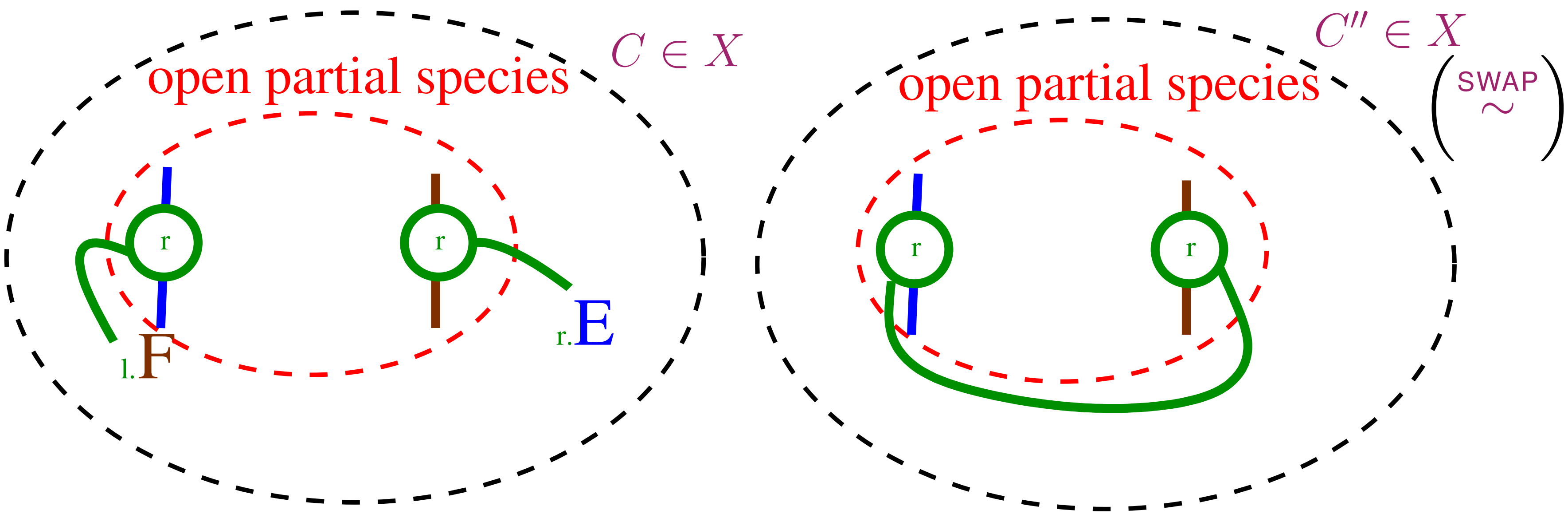


Unfolding a semi-link



Binding two semi-links





Consequences

Let $Y \in \wp(Local\_view))$ be a set of local views such that $\alpha(\gamma(Y)) = Y$.

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

   (by replacing X by $\gamma(Y)$ in the previous proof)

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

   Thus:

   (a) $\gamma(Y)$ is finite if and only if the grammar has a finite set of prefixes (and the latter is decidable);

   (b) We have $\mathbb{F}^\sharp \circ \alpha = \alpha \circ \mathbb{F} \circ \gamma \circ \alpha$.

Overview

Outline

We have proved that:

- if the set $Species_{\omega}$ of reachable chemical species is close with respect swapping $\overset{\text{SWAP}}{\sim}$,
- then the reachability analysis is exact (i.e. $Species_{\omega} = \gamma(\textit{lfp}_{\alpha(Species_0)}\mathbb{F}^{\sharp})$).

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,

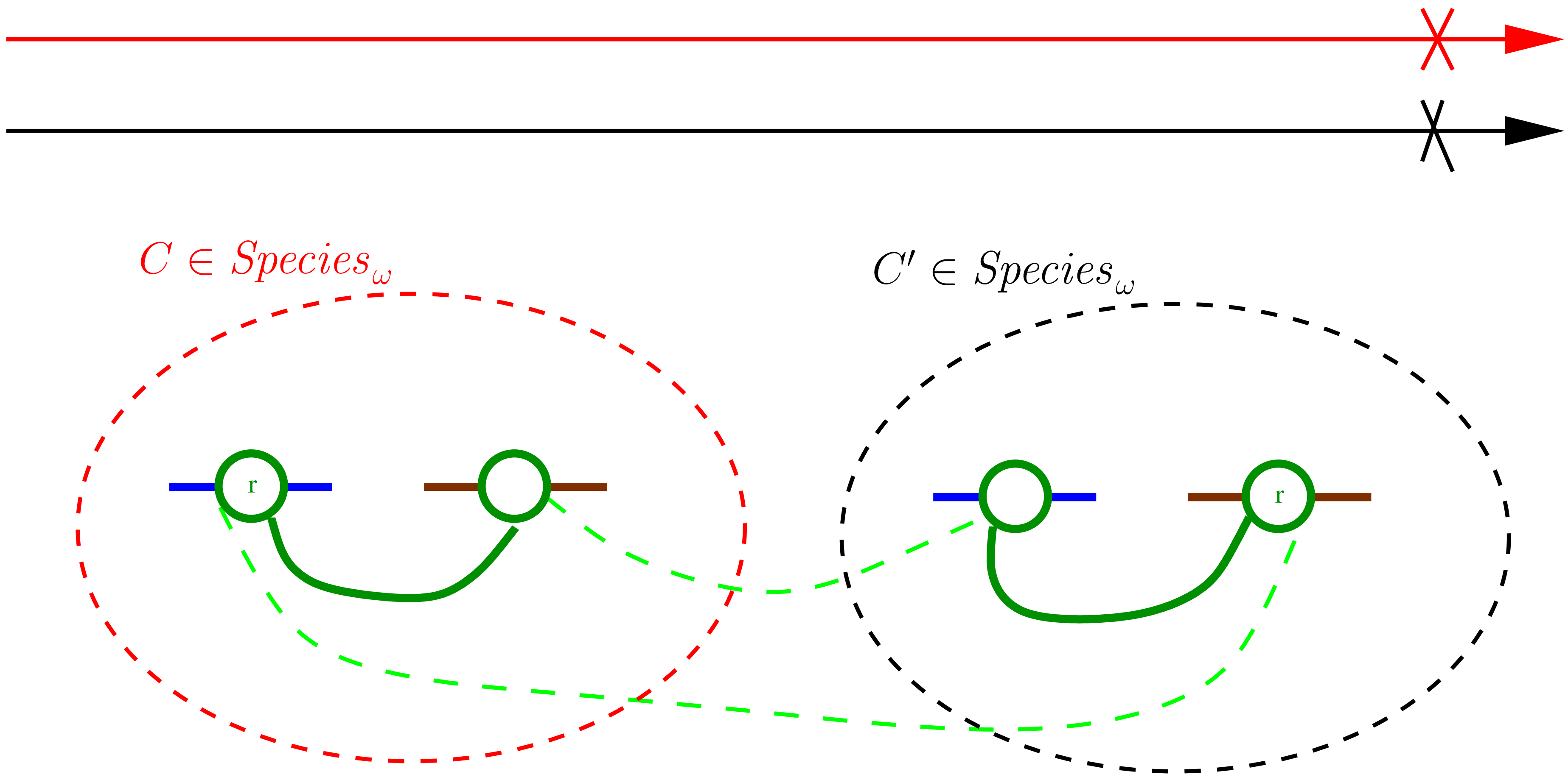
are satisfied, the set of reachable chemical species is local.

Proof outline

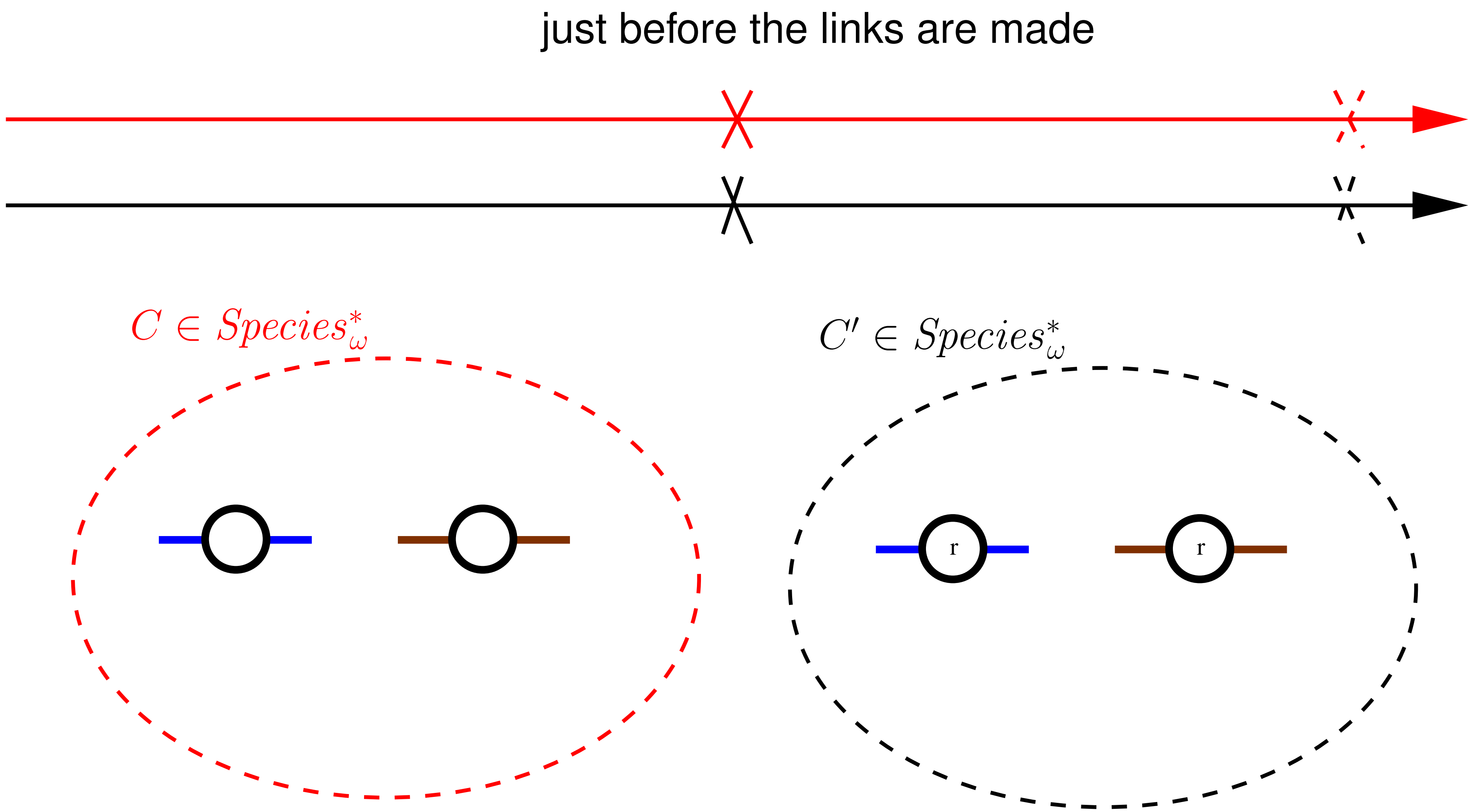
We sketch a proof in order to discover sufficient conditions that ensure this property:

- 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)

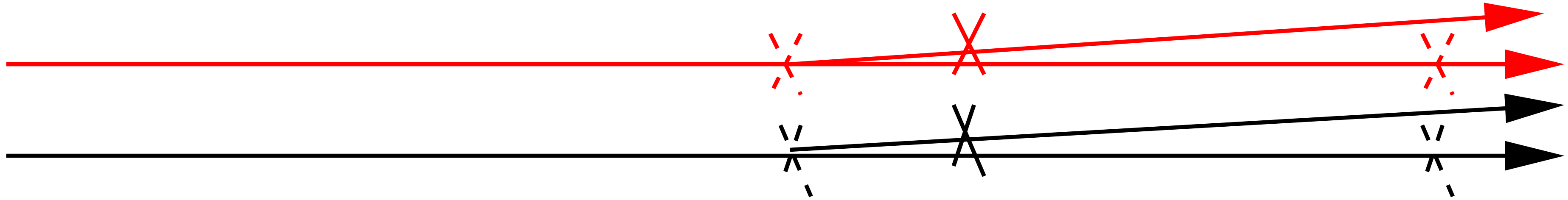


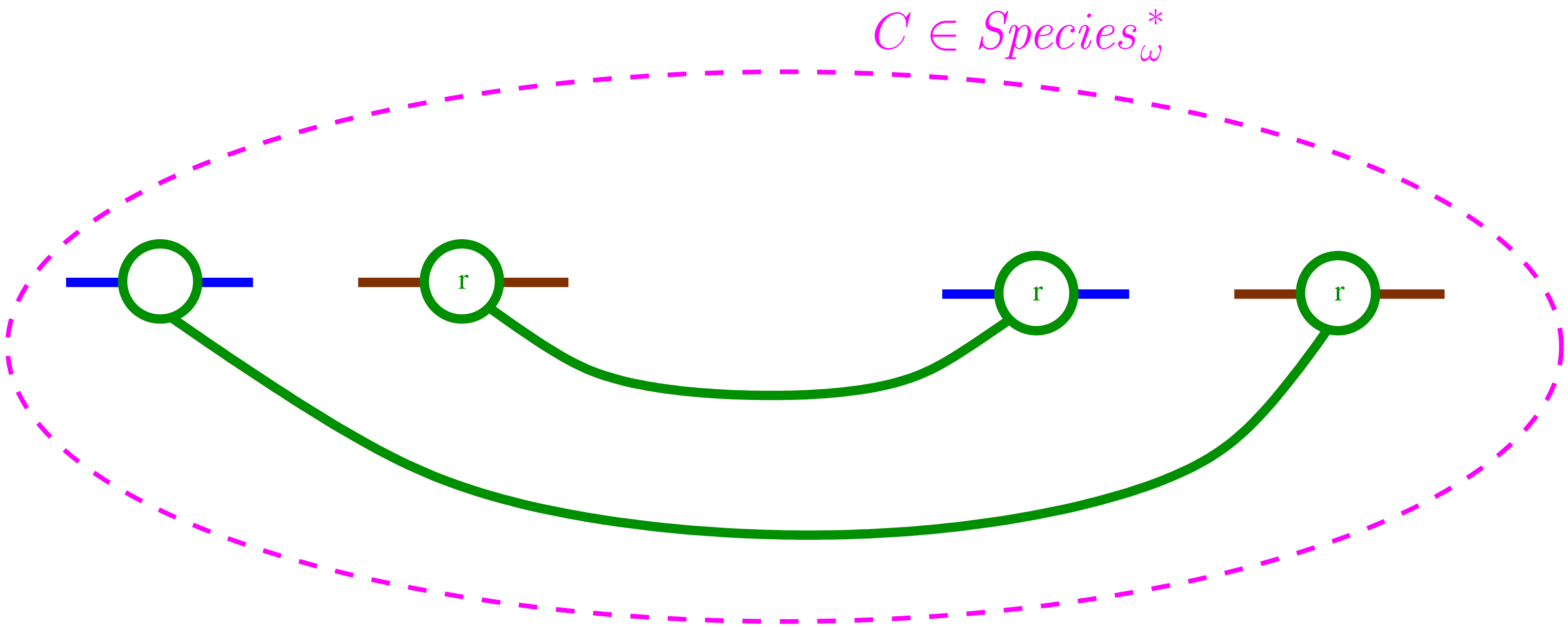
First case (II/V)



First case (III/V)

we suppose we can swap the links

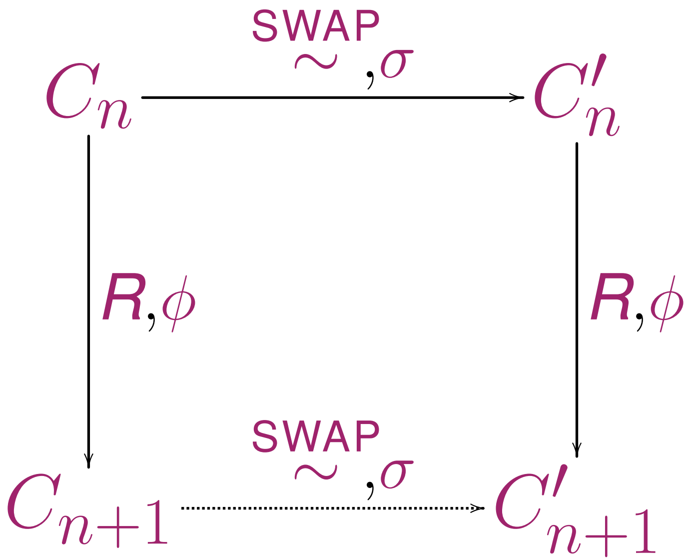




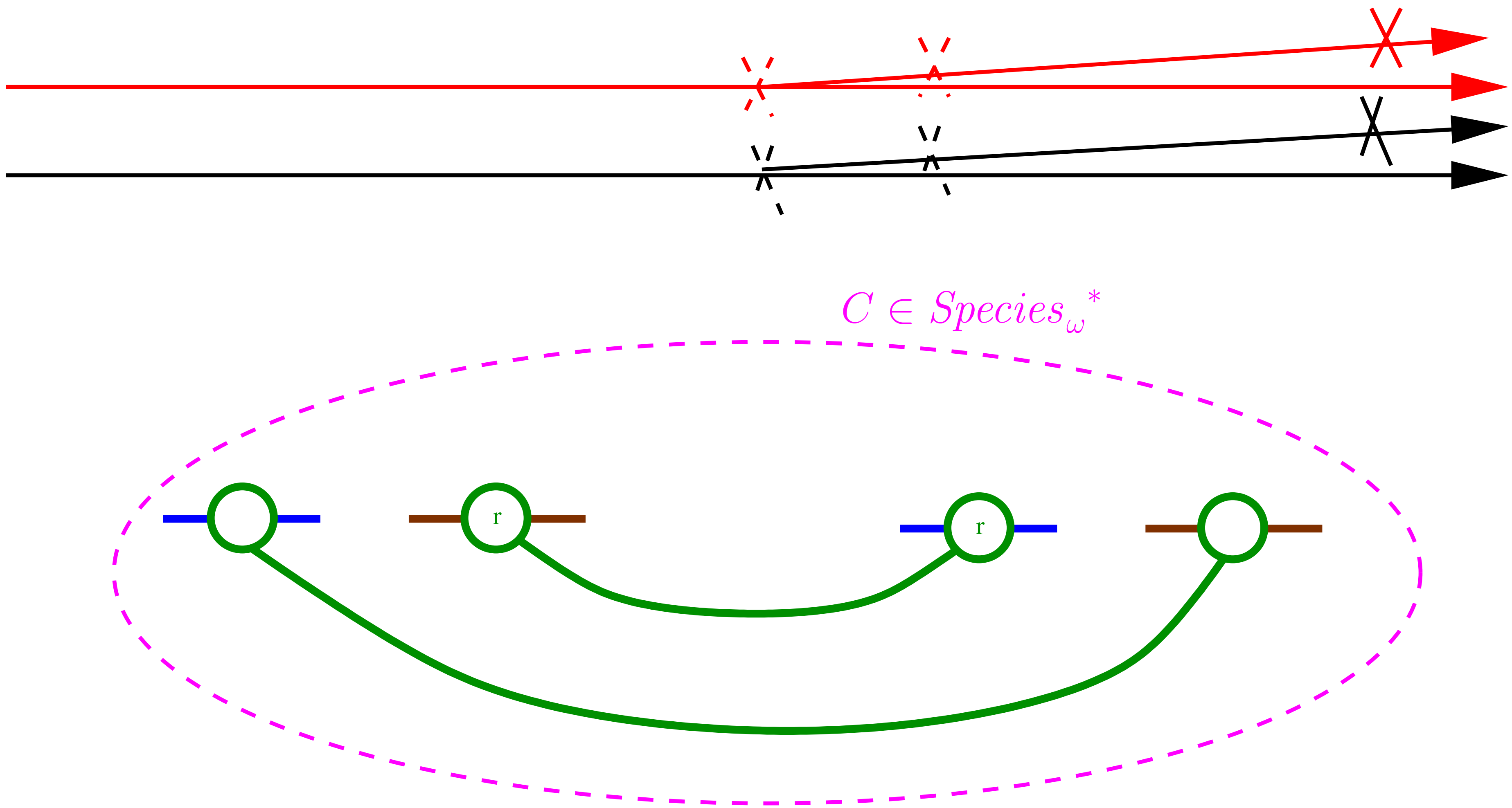
First case (IV/V)

Then, we ensure that further computation steps:

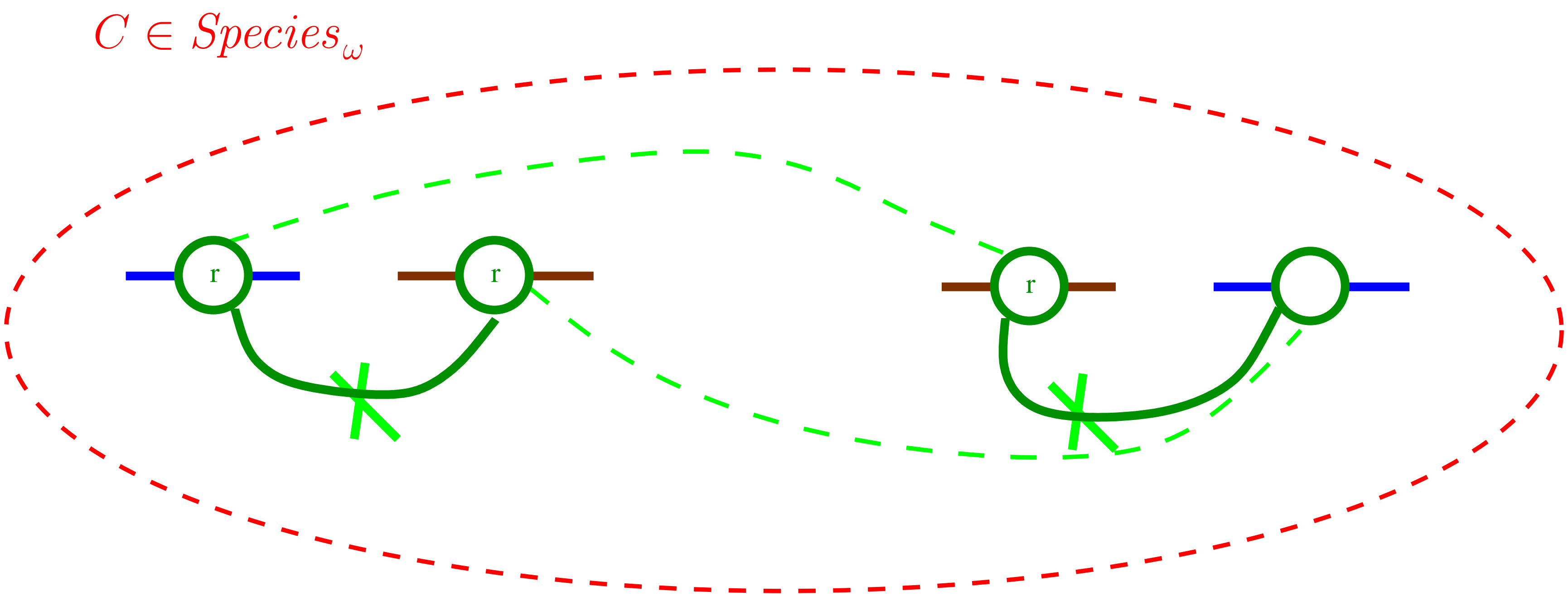
- are always possible;
- have the same effect on local views;
- commute with the swapping relation $\overset{\text{SWAP}}{\sim}$.



First case (V/V)

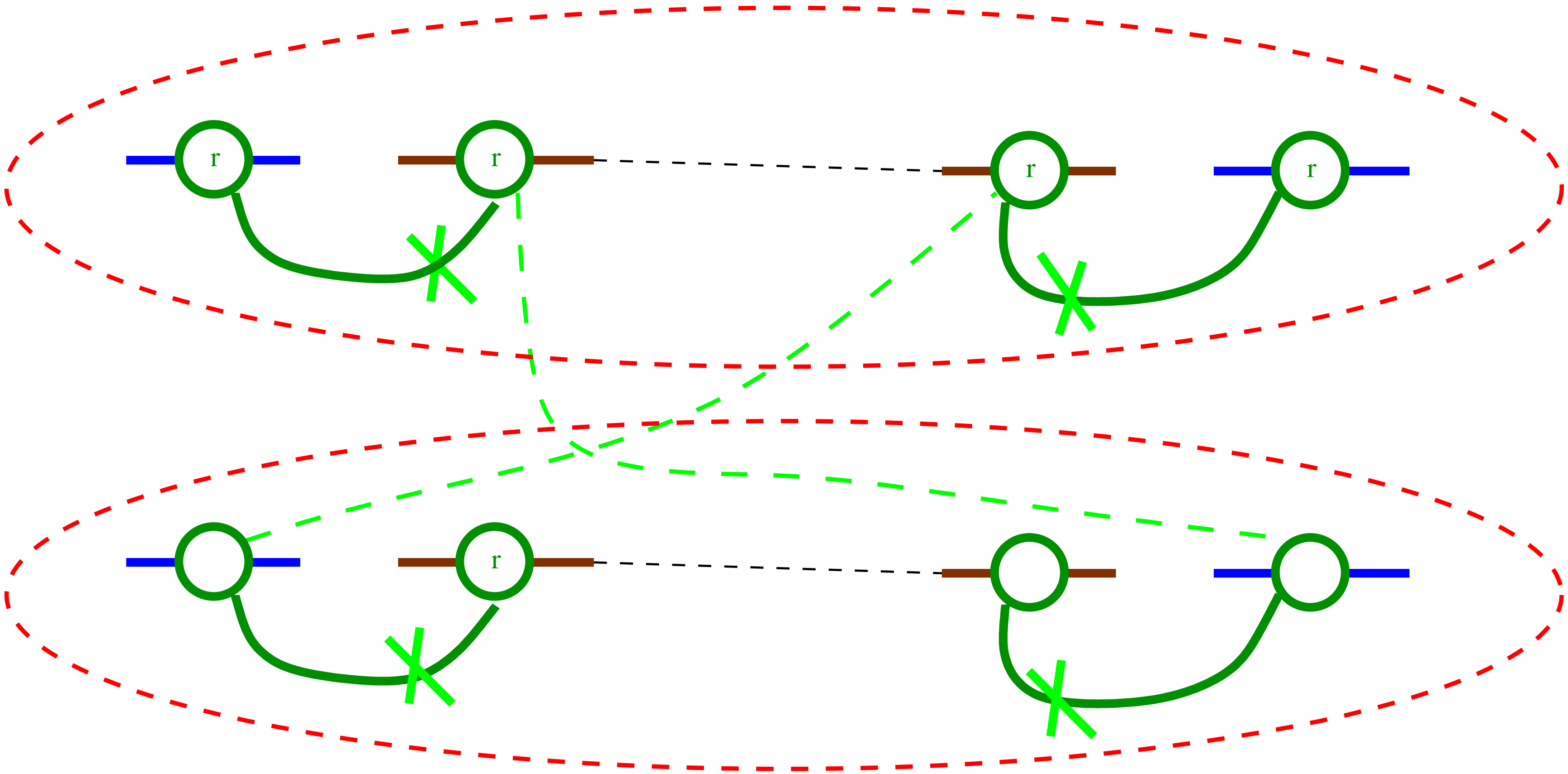


Second case (I/II)



we assume that the chemical species C is acyclic

Second case (II/II)



Sufficient conditions

Whenever the following assumptions:

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   then:
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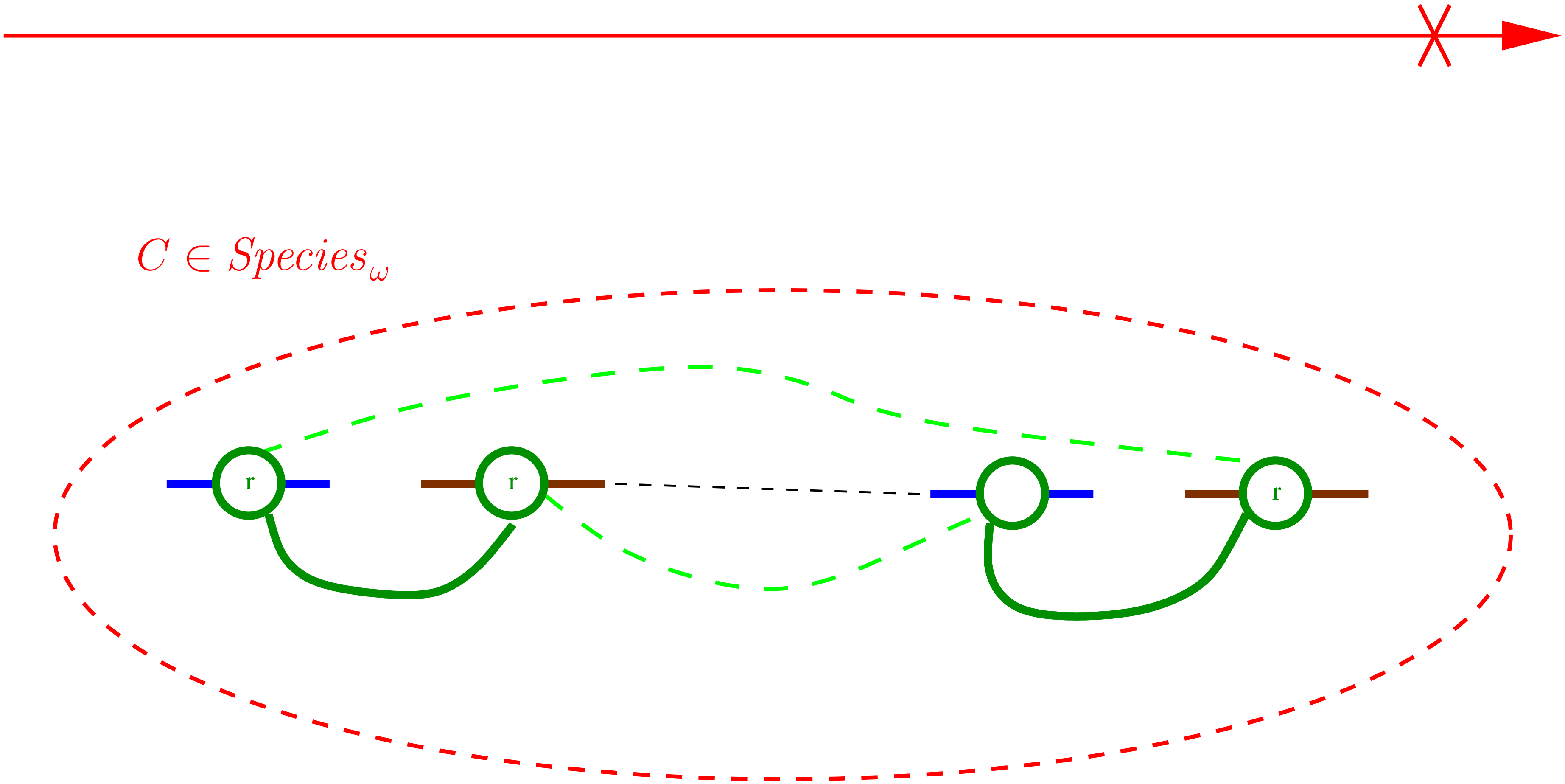
5. chemical species in $\gamma(\alpha(Species_{\omega}))$ are acyclic,

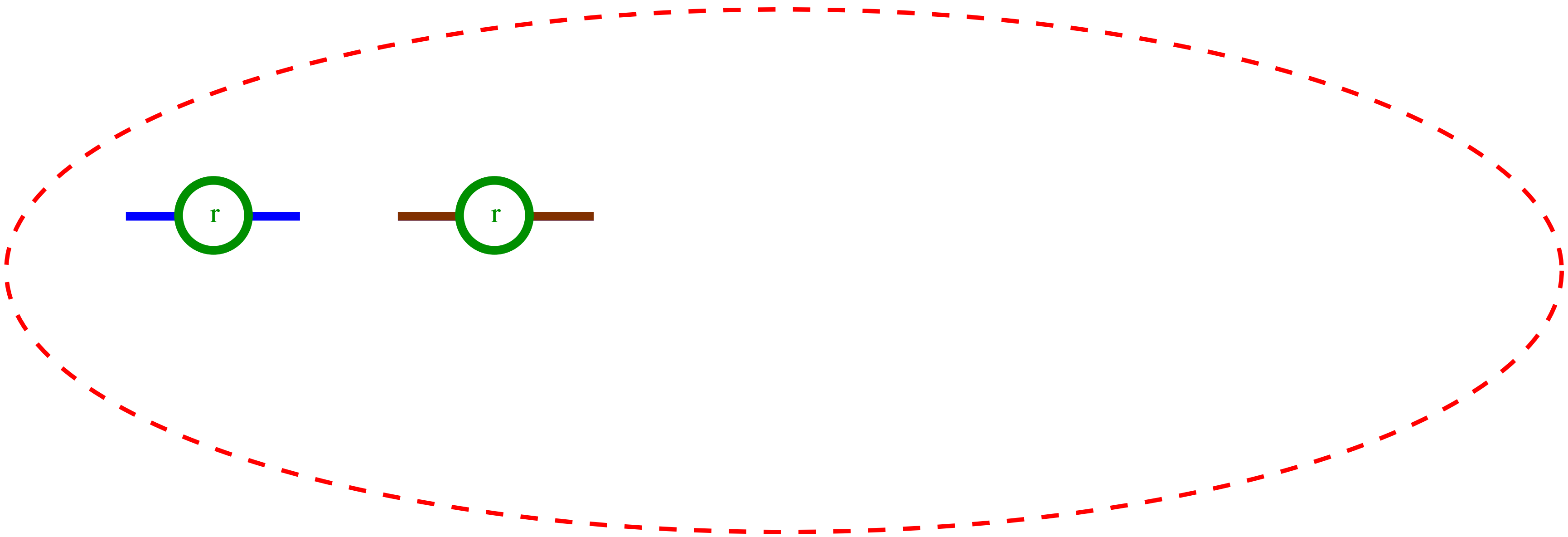
are satisfied, the set of reachable chemical species is local.

Third case (I/III)

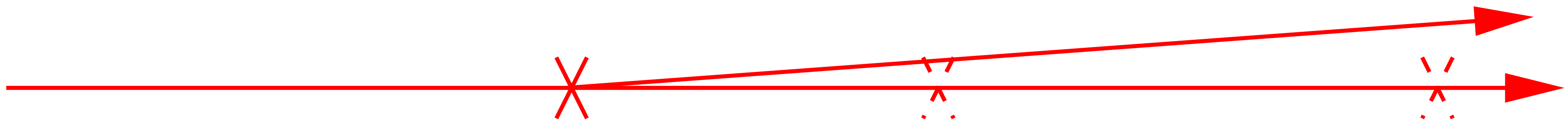


Third case (II/III)

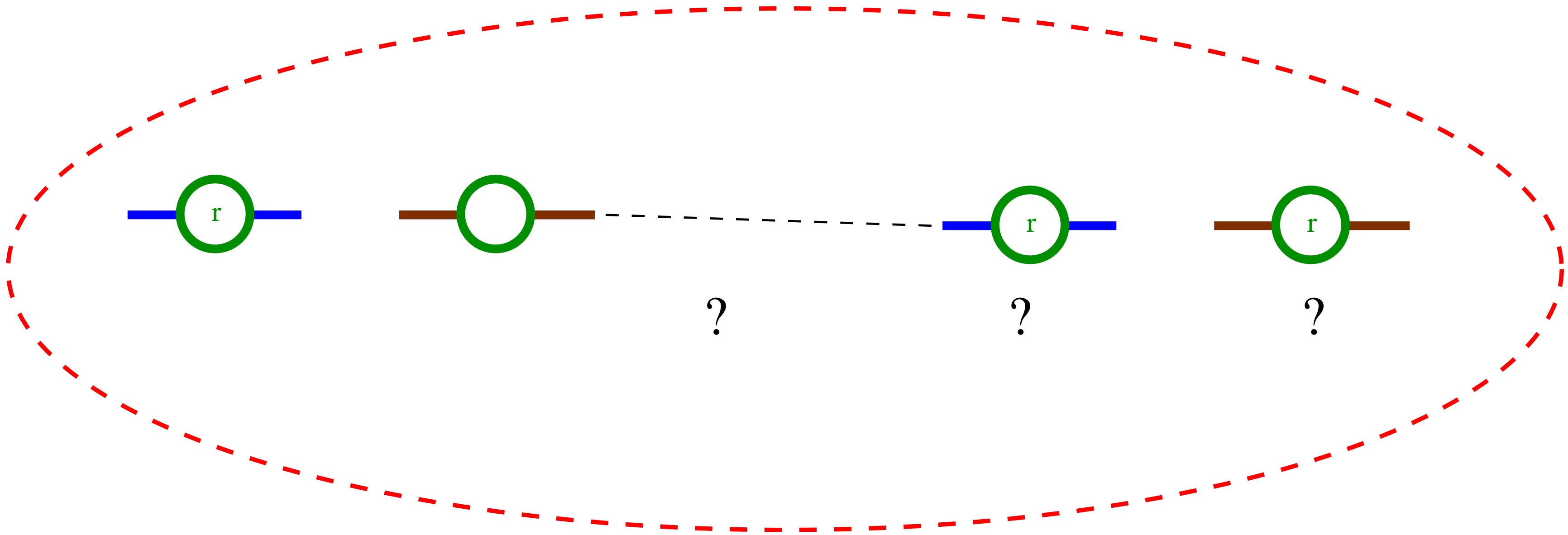
$C \in Species_{\omega}^{*}$



Third case (II/III)



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



Non local systems

$$\mathcal{Species}_0 \triangleq \text{R(a\{u\}[.])}$$

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

R(a{u}[1]),R(a{u}[1]) $\in \mathcal{Species}_\omega$

R(a{p}[1]),R(a{p}[1]) $\in \mathcal{Species}_\omega$

But R(a{u}[1]),R(a{p}[1]) $\notin \mathcal{Species}_\omega$.

Non local systems

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

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

A(a{u}[1]),B(a{p}[1]) $\in \mathit{Species}_\omega$

A(a{p}[1]),B(a{u}[1]) $\in \mathit{Species}_\omega$

But A(a{p}[1]),B(a{p}[1]) $\notin \mathit{Species}_\omega$.

Non local systems

$$\mathit{Species}_0 \triangleq \text{A(a\{u\}[.])}$$

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A(a{u}[1]),A(a{p}[1]) $\in \mathit{Species}_\omega$
But A(a{p}[1]),A(a{p}[1]) $\notin \mathit{Species}_\omega$.

Non local systems

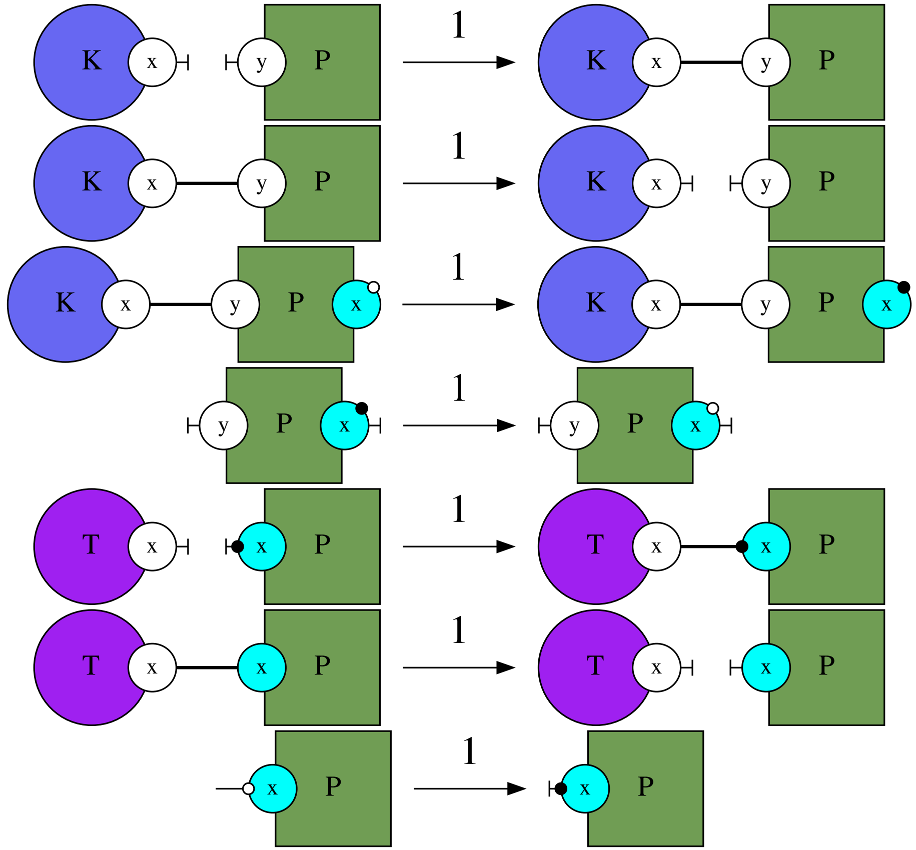
$Species_0 \triangleq$ R(a[.],b[.])

Rules $\triangleq$ { R(a[.],b[.]),R(a[.]) $\rightarrow$ R(a[.],b[1]),R(a[1]) }

R(a[.],b[2]),R(a[2],b[1]),R(a[1],b[.]) $\in Species_\omega$
But R(a[1],b[1]) $\notin Species_\omega$.

Practical activities

Use static analysis on the following model:



Practical activities

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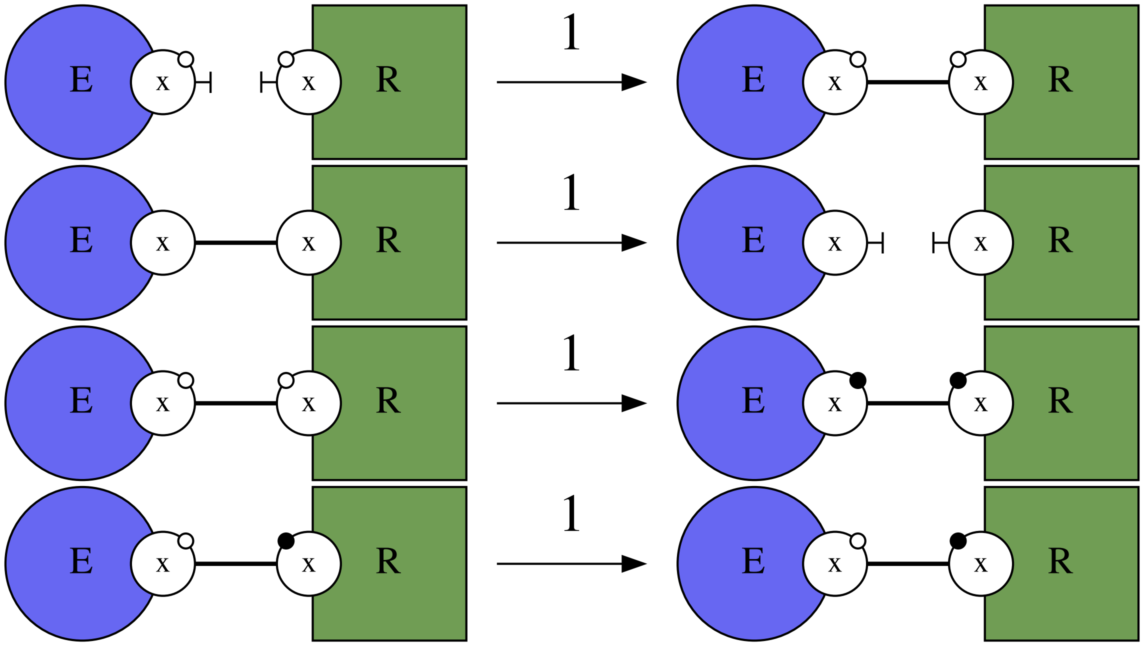
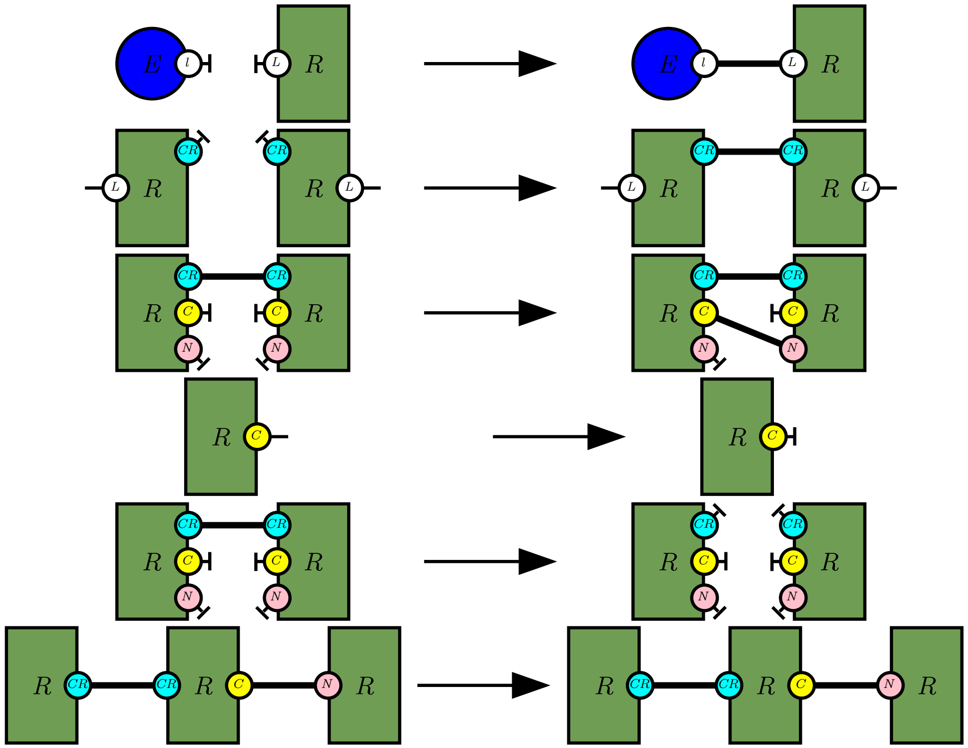


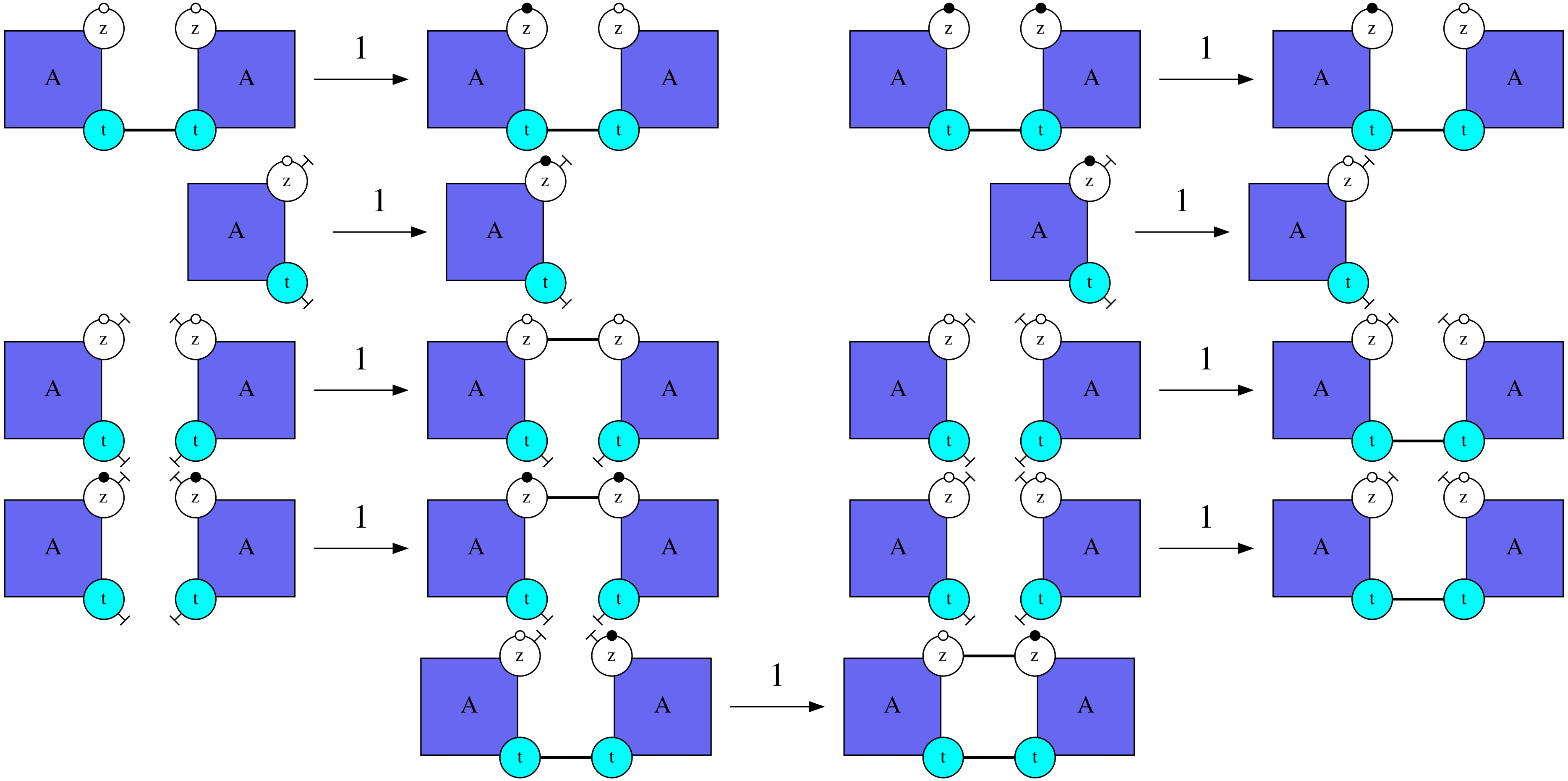
Practical activities

Use static analysis on the following model:



Practical activities

Use static analysis on the following model:



Overview

1. Introduction
2. Abstraction: Local views
3. Completeness: false positives?
4. Local fragment of Kappa
5. 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)

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