Abstract Interpretation Course MPRI

Reachability Analysis of Rule-based Models

[ICCMSE'07, VMCAI'08]

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East China Normal University
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.
Joint-work with...

Walter Fontana
Harvard Medical School

Vincent Danos
Edinburgh

Russ Harmer
Paris VII

Jean Krivine
Paris VII
Overview

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

EGF, TGF-alpha, etc

EGFR

PI3-K
AKT
phosphorylation
mTOR
STAT
GRB2
SOS
RAS
RAF
MEK
ERK
Gene transcription
Cell cycle progression

Cell proliferation
Inhibition of apoptosis
Angiogenesis
Migration, Adhesion, Invasion

Eikuch, 2007
A single story
A concurrent story
Overshoot

When we combine the two stories...

...we get an overshoot.
Overview

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A chemical species

E(r!1), R(ll1,r!2), R(r!2,ll3), E(r!3)
A Unbinding/Binding Rule

\[ E(r), R(l,r) \leftrightarrow E(r!1), R(l!1,r) \]
Internal state

\[ R(Y_1 \sim u, \pi!1), E(r!1) \leftrightarrow R(Y_1 \sim p, \pi!1), E(r!1) \]
Early EGF example

**egf rules 1**

- **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: $R(r^1,Y48) \rightarrow R(r^1,Y48^p)$
    - $R(Y48^p) \rightarrow R(Y48)$

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

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

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

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**receptor type:** $R(l,r,Y68,Y48)$
Early EGF example

**EGF rules 2**

- **G-So binding**
  - 10: $R(Y68p1), G(a1,b), So(d) \leftrightarrow R(Y68p1), G(a1,b2), So(d2)$
  - 12: $G(a,b), So(d) \leftrightarrow G(a,b1), So(d1)$
  - 22: $Sh(\pi,Y7p2), G(a2,b), So(d) \leftrightarrow Sh(\pi,Y7p2), G(a2,b1), S(d1)$
  - 19: $Sh(\pi1,Y7p2), G(a2,b), So(d) \leftrightarrow Sh(\pi1,Y7p2), G(a2,b1), S(d1)$

- **Y48-Sh binding**
  - 13: $R(Y48p), Sh(\pi,Y7) \leftrightarrow R(Y48p1), Sh(\pi1,Y7)$
  - 15: $R(Y48p), Sh(\pi,Y7p) \leftrightarrow R(Y48p1), Sh(\pi1,Y7p)$
  - 18: $R(Y48p), Sh(\pi,Y7p1), G(a1,b) \leftrightarrow R(Y48p2), Sh(\pi2,Y7p1), G(a1,b)$
  - 20: $R(Y48p), Sh(\pi,Y7p1), G(a1,b3), S(d3) \leftrightarrow R(Y48p2), Sh(\pi2,Y7p1), G(a1,b3), S(d3)$

- **Sh-G binding**
  - 17: $R(Y48p1), Sh(\pi1,Y7p), G(a,b) \leftrightarrow R(Y48p1), Sh(\pi1,Y7p2), G(a2,b)$
  - 21: $Sh(\pi,Y7p), G(a,b) \leftrightarrow Sh(\pi,Y7p1), G(a1,b)$
  - 23: $Sh(\pi,Y7p), G(a,b2) \leftrightarrow Sh(\pi,Y7p1), G(a1,b2)$
  - 24: $R(Y48p1), Sh(\pi1,Y7p), G(a,b3), S(d3) \leftrightarrow R(Y48p1), Sh(\pi1,Y7p2), G(a2,b3), S(d3)$

**Refined from**
- $So(d)+G(b)\leftrightarrow So(d1)+G(b1)$
- $Sh(\pi), G(a)\leftrightarrow Sh(\pi1), G(a1)$

**Interface note:** highlight the interacting parts

**Why not simply $G(b3)$??**

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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.
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We write $Z \prec_{\Phi} Z'$ iff:

- $\Phi$ is a site-graph morphism:
  - $i$ is less specific than $\Phi(i)$,
  - if there is a link between $(i, s)$ and $(i', s')$, then there is a link between $(\Phi(i), s)$ and $(\Phi(i'), s')$.

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

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Set of reachable chemical species

Let $\mathcal{R} = \{R_i\}$ be a set of rules. Let $\text{Species}$ be the set of all chemical species ($C, c_1, c'_1, \ldots, c_k, c'_k, \ldots \in \text{Species}$). Let $\text{Species}_0$ be the set of initial chemical species. 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 $\text{Species}_\omega$, the set of all chemical species that can be constructed in one or several applications of rules in $\mathcal{R}$ starting from the set $\text{Species}_0$ of initial chemical species.

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

We define the mapping $F$ as follows:

$$F : \begin{cases} \varphi(Species) & \rightarrow \varphi(Species) \\ X & \mapsto X \cup \left \{ c_j' \mid \exists R_k \in \mathcal{R}, c_1, \ldots, c_m \in X, \ c_1, \ldots, c_m \rightarrow_{R_k} c_1', \ldots, c_m' \right \}. \end{cases}$$

The set $\varphi(Species)$ is a complete lattice.
The mapping $F$ is an extensive $\bigcup$-complete morphism.

We define the set of reachable chemical species as follows:

$$Species_\omega = \bigcup \{ F^n(Species_0) \mid n \in \mathbb{N} \}.$$
Local views

\[ \alpha(\{R(Y1 \sim u, l!1), E(r!1)\}) = \{R(Y1 \sim u, l!r.E); E(r!l.R)\}. \]
Galois connection

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

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

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

Thus, it defines a Galois connection:

$$\wp(\text{Species}) \overset{\gamma}{\leftarrow} \overset{\alpha}{\rightarrow} \wp(\text{Local\_view}).$$

(The function $\gamma$ maps a set of local views into the set of complexes that can be built with these local views).
$\gamma \circ \alpha$ is an upper closure operator: it abstracts away some information.

Guess the image of the following set of chemical species?
\( \alpha \circ \gamma \) is a lower closure operator: it simplifies (or reduces) constraints.

Guess the image of the following set of local views?

\[
\begin{align*}
\{ & R, R, R \} : \{ & S, R, R \}
\end{align*}
\]
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?

\[
\{ \quad R \quad \text{;} \quad R \quad \}
\]
Abstract reactions
Abstract counterpart to $F$

We define $F^\#$ as:

$$
F^\#: \begin{cases}
\varphi(\text{Local\_view}) \rightarrow \varphi(\text{Local\_view}) \\
Y \mapsto Y \cup \left\{ lv_j' \mid \exists R_k \in R, lv_1, \ldots, lv_m \in Y, lv_1, \ldots, lv_m \Rightarrow_{R_k} lv'_1, \ldots, lv'_n \right\}.
\end{cases}
$$

We have:

- $F^\#$ is extensive;
- $F^\#$ is monotonic;
- $F \circ \gamma \subseteq \gamma \circ F^#$;
- $F^\# \circ \alpha = \alpha \circ F \circ \gamma \circ \alpha$ (we will see later why).
Soundness

Theorem 1  Let:

1. \((D, \subseteq, \cup)\) and \((D^\#, \subseteq, \sqcup)\) be chain-complete partial orders;
2. \(D \xleftrightarrow[\gamma][\alpha] D^\#\) be a Galois connection;
3. \(F \in D \to D\) and \(F^\# \in D^\# \to D^\#\) be monotonic mappings such that:
   \(F \circ \gamma \subseteq \gamma \circ F^\#\);
4. \(X_0 \in D\) be an element such that: \(X_0 \subseteq F(X_0)\);

Then:

1. both \(lfp_{X_0} F\) and \(lfp_{\alpha(X_0)} F^\#\) exist,
2. \(lfp_{X_0} F \subseteq \gamma(lfp_{\alpha(X_0)} F^\#)\).
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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?
Which information is abstracted away?

**Theorem 2** We suppose that:

1. \((D, \subseteq)\) be a partial order;
2. \((D^\#, \subseteq, \sqcup)\) be chain-complete partial order;
3. \(D \xrightarrow{\gamma} D^\#\) be a Galois connection;
4. \(F \in D \rightarrow D\) and \(F^\# \in D^\# \rightarrow D^\#\) are monotonic;
5. \(F \circ \gamma \subseteq \gamma \circ F^\#\);
6. \(X_0, \text{inv} \in D\) such that:
   - \(X_0 \subseteq F(X_0) \subseteq F(\text{inv}) \subseteq \text{inv}\),
   - \(\text{inv} = \gamma(\alpha(\text{inv}))\),
   - and \(\alpha(F(\text{inv})) = F^\#(\alpha(\text{inv}))\);

Then, \(\text{Ifp}_{\alpha(X_0)F^\#}\) exists and \(\gamma(\text{Ifp}_{\alpha(X_0)F^\#}) \subseteq \text{inv}\).
Proof I/III

We have seen yesterday (Antoine’s lecture) that:

1. $lfp_{\alpha(\chi_0)}\mathbb{I}^\#$ exists;

2. there exists an ordinal $\delta$ such that $lfp_{\alpha(\chi_0)}\mathbb{I}^\# = \mathbb{I}^\#\delta(\alpha(\chi_0))$. 
Proof II/III

Let us show that $\gamma(lfp_{\alpha(X_0)}^{F^\#}) \subseteq inv$.

Let us prove instead by induction over $\delta$ that $F^\#(\alpha(X_0)) \subseteq \alpha(inv)$.

- If $Y \in D^\#$ is an element such that $Y \subseteq \alpha(inv)$,
  
  \begin{align*}
  F^\#(Y) &\subseteq F^\#(\alpha(inv)) \quad (F^\# \text{ is mon}) \\
  F^\#(\alpha(inv)) &\subseteq \alpha(F(inv)) \quad \text{(assumption)} \\
  \alpha(F(inv)) &\subseteq \alpha(inv) \quad (\alpha \text{ is mon and } inv \text{ is a post})
  \end{align*}

  Thus: $F^\#(Y) \subseteq \alpha(inv)$

- If $Y_i \in D^\#_I$ is a chain of elements such that $Y_i \subseteq \alpha(inv)$ for any $i \in I$,
  then, $\sqcup Y_i \subseteq \alpha(inv)$ (lub).

So: $F^\#(\alpha(X_0)) \subseteq \alpha(inv)$. 
Proof III/III

We have:

$$\FF^{\#\delta}(\alpha(X_0)) \subseteq \alpha(inv).$$

Since $\gamma$ is monotonic:

$$\gamma(\FF^{\#\delta}(\alpha(X_0))) \subseteq \gamma(\alpha(inv)).$$

But, by assumption, $\gamma(\alpha(inv)) = inv$.

Thus,

$$\gamma(\FF^{\#\delta}(\alpha(X_0))) \subseteq inv.$$
When is there no false positive?

**Theorem 3** We suppose that:

1. \((D, \subseteq, \cup)\) and \((D^\#, \subseteq, \cup)\) are chain-complete partial orders;

2. \((D, \subseteq) \xrightarrow{\gamma} (D^\#, \subseteq)\) is a Galois connection;

3. \(F : D \rightarrow D\) is a monotonic map;

4. \(X_0\) is a concrete element such that \(X_0 \subseteq F(X_0)\);

5. \(F \circ \gamma \subseteq \gamma \circ F^\#\);

6. \(F^\# \circ \alpha = \alpha \circ F \circ \gamma \circ \alpha\).

Then:

- \(lfp_{X_0} F\) and \(lfp_{\alpha(X_0)} F^\#\) exist;

- \(lfp_{X_0} F = \gamma(\alpha(lfp_{X_0} F)) \iff lfp_{X_0} F = \gamma(lfp_{\alpha(X_0)} F^\#)\).
Proof I/V

The (transfinite) sequence \((F^{\#0}(\alpha(X_0)))\) is defined and increasing since:

1. \(F^{\#} \circ \alpha = \alpha \circ F \circ \gamma \circ \alpha\), so:
   - \(F^{\#} \circ \alpha\) is monotonic;
   - for any \(X \in D\), there exists \(X' \in D\), such that \(F^{\#}(\alpha(X)) = \alpha(X')\);

2. Moreover, \(\alpha\) is a \(\cup/\sqcup\)-complete morphism, so:
   - for any increasing chain \((\alpha(X_i))_{i \in I}\), there exists \(X' \in D\), such that \(\sqcup \alpha(X_i) = \alpha(X')\).

So there exists an ordinal \(\delta\) such that:

\[
F^{\#}(F^{\#\delta}(\alpha(X_0))) = F^{\#\delta}(\alpha(X_0)).
\]
Proof II/V

Let us show that \( F^\#(\alpha(X_0)) \) is a least fixpoint (greater than \( \alpha(X_0) \)):

Let \( Y \) be such that \( F^\#(Y) = Y \) and \( \alpha(X_0) \subseteq Y \).
Let us prove that \( F^\#(\alpha(X_0)) \subseteq Y \) by (transfinite) induction:

1. If \( \alpha(X) \subseteq Y \), we have: \( F^\#(\alpha(X)) \subseteq Y \).

   Since:
   \[
   \begin{align*}
   F^\#(\alpha(X)) &= \alpha(F(\gamma(\alpha(X)))) \\
   \alpha(F(\gamma(\alpha(X)))) &\subseteq \alpha(F(\gamma(Y))) \quad (\alpha \circ F \circ \gamma \text{ is mon})
   \end{align*}
   \]
   
   \[
   \begin{align*}
   \alpha(F(\gamma(Y))) &\subseteq \alpha(\gamma(F^\#(Y))) \quad (F \circ \gamma \subseteq \gamma \circ F^\# \text{ and } \alpha \text{ mon})
   \end{align*}
   \]
   
   \[
   \begin{align*}
   \alpha(\gamma(F^\#(Y))) &\subseteq F^\#(Y) \quad (\alpha \circ \gamma \text{ is reductive})
   \end{align*}
   \]
   
   \[
   F^\#(Y) = Y \quad \text{(fixpoint)}
   \]

2. If \( (X_i)_{i \in I} \in D^I \) is such that:
   
   • \( (\alpha(X_i))_{i \in I} \) is a chain of elements;
   
   • \( \alpha(X_i) \subseteq Y \) for any \( i \in I \).

   Then \( \sqcup \alpha(X_i) \subseteq Y \) (\( \sqcup \) is a least upper bound)
Proof III/V

By induction, we have proved that:

1. $\text{lfp}_{\alpha(X_0)} F^\#$ exists;

2. $\text{lfp}_{\alpha(X_0)} F^\# = F^\#(\alpha(X_0))$. 
Proof IV/V

Let us now show that:

\[ \text{lfp}_{X_0}\mathbb{F} = \gamma(\alpha(\text{lfp}_{X_0}\mathbb{F})) \iff \text{lfp}_{X_0}\mathbb{F} = \gamma(\text{lfp}_{\alpha(X_0)\mathbb{F}^\#}). \]

• Easy implication: \(\iff\).
  If \( \text{lfp}_{X_0}\mathbb{F} = \gamma(\text{lfp}_{\alpha(X_0)\mathbb{F}^\#}), \)
  then \( \text{lfp}_{X_0}\mathbb{F} = \gamma(\text{lfp}_{\alpha(X_0)\mathbb{F}^\#}) = \gamma(\alpha(\gamma(\text{lfp}_{\alpha(X_0)\mathbb{F}^\#}))) = \gamma(\alpha(\text{lfp}_{X_0}\mathbb{F})). \)

• Other implication:
  - (easy inclusion)
    We always have \( \text{lfp}_{X_0}\mathbb{F} \subseteq \gamma(\text{lfp}_{\alpha(X_0)\mathbb{F}^\#}). \)
Proof V/V

• other inclusion

We assume that \( \gamma(\alpha(\text{lfp}_{X_0} F)) = \text{lfp}_{X_0} F. \)

We have to prove that: \( \gamma(\text{lfp}_{\alpha(X_0)} F^\#) \subseteq \text{lfp}_{X_0} F. \)

We have: \( F^\#(\alpha(\text{lfp}_{X_0} F)) = \alpha(\text{lfp}_{X_0} F). \)

Since:

\[
\begin{align*}
F^\#(\alpha(\text{lfp}_{X_0} F)) &= \alpha(F(\gamma(\alpha(\text{lfp}_{X_0} F)))) \\
\alpha(F(\gamma(\alpha(\text{lfp}_{X_0} F)))) &= \alpha(F(\text{lfp}_{X_0} F)) \\
\alpha(F(\text{lfp}_{X_0} F)) &= \alpha(\text{lfp}_{X_0} F)
\end{align*}
\]

\( F^\# \circ \alpha = \alpha \circ F \circ \gamma \circ \alpha \) (fixpoint)

It follows that: \( \text{lfp}_{\alpha(X_0)} F^\# \subseteq \alpha(\text{lfp}_{X_0} F) \) (lfp and \( \alpha(X_0) \subseteq \alpha(\text{lfp}_{X_0} F) \))

Then, since \( \gamma \) is mon:

\[
\gamma(\text{lfp}_{\alpha(X_0)} F^\#) \subseteq \gamma(\alpha(\text{lfp}_{X_0} F)) = \text{lfp}_{X_0} F.
\]
When is there no false positive?

Theorem 3 We suppose that:

1. \((D, \subseteq, \cup)\) and \((D^\#, \subseteq, \sqcup)\) are chain-complete partial orders;
2. \((D, \subseteq) \xrightarrow{\gamma} (D^\#, \subseteq)\) 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. \(\mathbb{F} \circ \gamma \subseteq \gamma \circ F^\#\);
6. \(F^\# \circ \alpha = \alpha \circ F \circ \gamma \circ \alpha\).

Then:

- \(lfp_{X_0}\mathbb{F}\) and \(lfp_{\alpha(X_0)}F^\#\) exist;
- \(lfp_{X_0}\mathbb{F} = \gamma(\alpha(lfp_{X_0}\mathbb{F})) \iff lfp_{X_0}\mathbb{F} = \gamma(lfp_{\alpha(X_0)}F^\#)\).

We need to understand under which assumptions \(lfp_{X_0}\mathbb{F} = \gamma(\alpha(lfp_{X_0}\mathbb{F}))\).
Swapping relation

We define the binary relation $\sim$ among tuples $Species^*$ of chemical species. We say that $(C_1, \ldots, C_m) \sim (D_1, \ldots, D_n)$ 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 $(C_i)^{\text{SWAP}} \sim (D_j)$;

we have $(D_j) \in X^*$.
Proof (easier implication way)

If:

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

Then:

we have \(\alpha(\{C_i | i \in I\}) = \alpha(\{D_j | j \in J\})\) (because \((C_i) \xrightarrow{\text{SWAP}} (D_j)\))
and \(\alpha(\{C_i | i \in I\}) \subseteq \alpha(X)\) (because \((C_i) \in X^*\) and \(\alpha\) mon);
so \(\alpha(\{D_j | j \in J\}) \subseteq \alpha(X)\);
so \(\{D_j | j \in J\} \subseteq \gamma(\alpha(X))\) (by def. of Galois connections);
so \(\{D_j | j \in J\} \subseteq X\) (since \(X = \gamma(\alpha(X))\));
so \((D_j)_{j \in J} \in X^*\).
Proof: more difficult implication way

For any \( X \in \wp(\text{Local\_view}) \), \( \gamma(X) \) 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 $\mathcal{SWAP} \sim$. 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 $\alpha$, 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

open partial species

$C'' \in X$

$\lambda \in \alpha(X)$

(\text{SWAP})

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Binding two semi-links

\[ C \in X \quad (\text{SWAP}) \]

open partial species

C'' \in X
Consequences

Let $Y \in \wp(\text{Local	extunderscore view})$ 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 $\gamma(Y)$.

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 $F^\# \circ \alpha = \alpha \circ F \circ \gamma \circ \alpha$. 
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We have proved that:

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

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:
   - \( A(a\sim m,S),B(b\sim n,T) \rightarrow A(a\sim m!1,S),B(b\sim n!1,T) \)
   - 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. 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)

\[ C \in \text{Species}_\omega \]

\[ C' \in \text{Species}_\omega \]
First case (II/V)

just before the links are made

$C \in \text{Species}_\omega$

$C' \in \text{Species}_\omega^*$
First case (III/V)

we suppose we can swap the links

$C \in \text{Species}_{\omega}^*$
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 $\sim \, \text{SWAP}$.
First case (V/V)
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:
   - \( A(a \sim m, S), B(b \sim n, T) \rightarrow A(a \sim m!1, S), B(b \sim n!1, T) \)
   - 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. chemical species in \( \gamma(\alpha(Species_\omega)) \) are acyclic,
are satisfied, the set of reachable chemical species is local.
Third case (I/III)

\[ C \in \text{Species}_\omega \]
Third case (II/III)

\[ C \in \text{Species}^*_\omega \]
Third case (II/III)

\[ C \in \text{Species}_{\omega}^* \]
Non local systems

\[ \text{Species}_0 \triangleq R(a \sim u) \]

\[ \text{Rules} \triangleq \left\{ \begin{array}{ll}
R(a \sim u) & \leftrightarrow R(a \sim p) \\
R(a \sim u), R(a \sim u) & \rightarrow R(a \sim u!1), R(a \sim u!1) \\
R(a \sim p), R(a \sim u) & \rightarrow R(a \sim p!1), R(a \sim p!1) \\
R(a \sim p), R(a \sim p) & \rightarrow R(a \sim p!1), R(a \sim p!1)
\end{array} \right\} \]

\[ R(a \sim u!1), R(a \sim u!1) \in \text{Species}_\omega \]
\[ R(a \sim p!1), R(a \sim p!1) \in \text{Species}_\omega \]
But \[ R(a \sim u!1), R(a \sim p!1) \notin \text{Species}_\omega. \]
Non local systems

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

\[ \text{Rules} \triangleq \left\{ \begin{array}{c}
A(a\sim u), B(a\sim u) \rightarrow A(a\sim u!1), B(a\sim u!1) \\
A(a\sim u!1), B(a\sim u!1) \rightarrow A(a\sim p!1), B(a\sim u!1) \\
A(a\sim u!1), B(a\sim u!1) \rightarrow A(a\sim u!1), B(a\sim p!1) \\
\end{array} \right\} \]

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

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

But \[ A(a\sim p!1), B(a\sim p!1) \notin \text{Species}_\omega. \]
Non local systems

Species\(_0\) \(\triangleq\) A(a\(\sim\)u)

Rules \(\triangleq\) \(\{\)

\(A(a\sim u) \leftrightarrow A(a\sim p)\)

\(A(a\sim u), A(a\sim p) \rightarrow A(a\sim u!1), A(a\sim p!1)\) \(\}\)

A(a\(\sim\)u!1), A(a\(\sim\)p!1) \(\in\) Species\(_\omega\)

But A(a\(\sim\)p!1), A(a\(\sim\)p!1) \(\notin\) Species\(_\omega\).
Non local systems

$$\text{Species}_0 \triangleq R(a,b)$$

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

$$R(a,b!2), R(a!2,b!1), R(a!1,b) \in \text{Species}_\omega$$

But $$R(a!1,b!1) \notin \text{Species}_\omega$$. 
Overview

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

- We have seen an example of Galois connection;
- We have played with the corresponding closure operators;
- We have defined a concrete and abstract semantics for set of reachable connected components in site graph rewriting;
- We have given some sufficient conditions for an abstraction to be complete;
- We have deduced a fragment of Kappa for which our abstraction produces no false positive.