Rule-based modeling and application to biomolecular networks Abstract interpretation of protein-protein interactions networks Questions set

Jérôme Feret

LIENS (INRIA,ÉNS,CNRS)

1 Abstract Interpretation

Definition 1 (partial order). *A partial order $(D, \leq)$ is given by a set D and a binary relation $\leq \in D \times D$ such that:*

1. *(reflexivity)* $\forall a \in D,\ a \leq a;$
2. *(antisymmetry)* $\forall a, a' \in D,\ [a \leq a' \wedge a' \leq a] \implies a = a';$
3. *(transitivity) and* $\forall a, a', a" \in D,\ [a \leq a' \wedge a' \leq a''] \implies a \leq a".$

Definition 2 (closure). *Given a partial order $(D, \leq)$ and a mapping $\rho : D \to D$.*

1. *We say that ρ is a upper closure operator, if and only if:*
   (a) *(idempotence)* $\forall d \in D,\ \rho(\rho(d)) = \rho(d);$
   (b) *(extensivity)* $\forall d \in D,\ d \leq \rho(d);$
   (c) *(monotonicity)* $\forall d, d' \in D,\ d \leq d' \implies \rho(d) \leq \rho(d').$

2. *We say that ρ is a lower closure operator, if and only if:*
   (a) *(idempotence)* $\forall d \in D,\ \rho(\rho(d)) = \rho(d);$
   (b) *(antiextensivity)* $\forall d \in D,\ \rho(d) \leq d;$
   (c) *(monotonicity)* $\forall d, d' \in D,\ d \leq d' \implies \rho(d) \leq \rho(d').$

Definition 3 (least upper bound). *Given a partial order $(D, \leq)$ and a subset $X \subseteq A$, we say that $m \in D$ is a least upper bound for X, if and only if:*

1. *(bound)* $\forall a \in X,\ a \leq m;$
2. *(least one) and* $\forall a \in D,\ [\forall a' \in X, a' \leq a] \implies m \leq a.$

By antisymmetry, if it exists a least upper bound is unique, thus we call it the least upper bound.

Definition 4 (greatest lower bound). *Given a partial order $(D, \leq)$ and a subset $X \subseteq A$, we say that $m \in D$ is a greatest lower bound for X, if and only if:*

1. *(bound)* $\forall a \in X,\ m \leq a;$
2. *(least one) and* $\forall a \in D,\ [\forall a' \in X, a \leq a'] \implies a \leq m.$

By antisymmetry, if it exists a greatest lower bound is unique, thus we call it the greatest lower bound.

Definition 5 (complete lattice). *Given a partial order $(D, \leq)$, we say that D is a complete lattice if any subset X has a least upper bound $\sqcup X$.*

In a complete lattice, any subset X has a greatest lower bound $\sqcap X$. Moreover,

$$\sqcap(X) = \sqcup\{d \in X \mid \forall x \in X, d \leq x\}.$$

The element $\top = \sqcup(D)$ is the greatest element of D, and the element $\bot = \sqcup(\emptyset)$ is the least element. A complete lattice is usually denoted by $(D, \leq, \bot, \top, \sqcup, \sqcap)$.

Definition 6 (chain-complete partial order). *Given a partial order* $(D, \leq)$*, we say that* $(D, \leq)$ *is a chain-complete partial order if and only if any chain* $X \subseteq D$ *has a least upper bound* $\sqcup X$*.*

A chain-complete partial order is denoted by a triple $(D, \leq, \sqcup)$*.*

Definition 7 (inductive function). *Given a chain-complete partial order* $(D, \subseteq, \cup)$*, we say that a function* $\mathbb{F} : D \to D$ *is inductive if and only if the two following properties are satisfied:*

1. $\forall x \in D,\ x \subseteq \mathbb{F}(x) \implies \mathbb{F}(x) \subseteq \mathbb{F}(\mathbb{F}(x))$*;*
2. *for any chain* C *of elements in* D *such that* $x \subseteq \mathbb{F}(x)$*, for any* $x \in C$*, we have:* $\cup C \subseteq \mathbb{F}(\cup C)$*.*

Proposition 1. *Let* $(D, \subseteq, \cup)$ *be a chain-complete partial order and* $\mathbb{F} : D \to D$ *be a function such that:* $\forall x, y \in D, x \subseteq y \implies \mathbb{F}(x) \subseteq \mathbb{F}(y)$*.*

Then $\mathbb{F}$ *is an inductive function.*

Definition 8 (inductive definition). *Let* $(D, \subseteq, \cup)$ *be a chain-complete partial order,* $x_0 \in D$ *be an element such that* $x_0 \subseteq \mathbb{F}(x_0)$*, and* $\mathbb{F} : D \to D$ *be an inductive function.*

There exists a unique collection of elements (X_o) *such that for any ordinal* o*:*

$$\begin{cases} X_o = x_0 & \textit{whenever } o = 0 \\ X_o = \mathbb{F}(X_{o-1}) & \textit{whenever } o \textit{ is a succesor ordinal} \\ X_o = \cup\{X_\beta \mid \beta < o\} & \textit{otherwise.} \end{cases}$$

The collection (X_o) *is called the transfinite iteration of* $\mathbb{F}$ *starting from* x_0*. For each ordinal* o*, the element* X_o *is usually denoted by* $\mathbb{F}^o(x_0)$*.*

Proposition 2. *Let* $(D, \subseteq, \cup)$ *be a chain-complete partial order,* $x_0 \in D$ *be an element such that* $x_0 \subseteq \mathbb{F}(x_0)$*, and* $\mathbb{F} : D \to D$ *an inductive function.*

Then:

1. *for any pair of ordinals* (o, o')*,* $[o < o'] \implies \mathbb{F}^o(x_0) \subseteq \mathbb{F}^{o'}(x_0)$*;*
2. *for any ordinal* o*,* $x_0 \subseteq \mathbb{F}^o(x_0)$*.*

Lemma 1 (least fix-point). *Let:*

1. $(D, \subseteq, \cup)$ *be a chain-complete partial order;*
2. $\mathbb{F} \in D \to D$ *be a monotonic map;*
3. $x_0 \in D$ *be an element such that:* $x_0 \subseteq \mathbb{F}(x_0)$*.*

Then: there exists $y \in D$ *such that:*

- $x_0 \subseteq y$*,*
- $\mathbb{F}(y) = y$*,*
- $\forall z \in D,\ [[\mathbb{F}(z) = z \wedge x_0 \subseteq z] \implies y \subseteq z]$*.*

This element is called the least fix-point of $\mathbb{F}$ *which is greater than* x_0*, and is written* $lfp_{x_0}\mathbb{F}$*.*

Definition 9 (Galois connexion). *Given two partial orders* $(D, \subseteq)$ *and* $(D^\sharp, \sqsubseteq)$*, we say that the pair of maps* (α, γ) *forms a Galois connection between* D *and* $D^\sharp$ *if and only if:*

1. $\alpha : D \to D^\sharp$*;*
2. $\gamma : D^\sharp \to D$*;*
3. *and* $\forall d \in D,\ \forall d^\sharp \in D^\sharp, [\alpha(d) \sqsubseteq d^\sharp \Leftrightarrow d \subseteq \gamma(d^\sharp)]$*.*

In such a case, we write:

$$D \underset{\alpha}{\overset{\gamma}{\leftrightarrows}} D^\sharp.$$

Proposition 3. *Let $(D, \subseteq)$ and $(D^\sharp, \sqsubseteq)$ be partial orders, and $D \underset{\alpha}{\overset{\gamma}{\leftrightarrows}} D^\sharp$ be a Galois connexion.*
The following properties are satisfied:

1. $\forall d \in D,\ d \subseteq \gamma(\alpha(d))$;
2. $\forall d^\sharp \in D^\sharp,\ \alpha(\gamma(d^\sharp)) \sqsubseteq d^\sharp$;
3. *(α is monotonic)* $\forall d, d' \in D,\ d \subseteq d' \implies \alpha(d) \sqsubseteq \alpha(d')$;
4. *(γ is monotonic)* $\forall d^\sharp, d'^\sharp \in D^\sharp,\ d^\sharp \sqsubseteq d'^\sharp \implies \gamma(d^\sharp) \subseteq \gamma(d'^\sharp)$;
5. $\forall d \in D,\ \alpha(d) = \alpha(\gamma(\alpha(d)))$;
6. $\forall d^\sharp \in D^\sharp,\ \gamma(d^\sharp) = \gamma(\alpha(\gamma(d)))$;
7. $\gamma \circ \alpha$ *is an upper closure operator;*
8. $\alpha \circ \gamma$ *is a lower closure operator.*

Proposition 4. *Let $(D, \subseteq, \bot, \top, \cup, \cap)$ and $(D^\sharp, \sqsubseteq, \bot^\sharp, \top^\sharp, \sqcup, \sqcap)$ be two complete lattices. Let α be a mapping between D and $D^\sharp$ such that for any subset $X \subseteq D$, we have $\alpha(\cup X) = \sqcup\{\alpha(d) \mid d \in X\}$.*
Then there exists a unique mapping γ between $D^\sharp$ and D such that:

$$D \underset{\alpha}{\overset{\gamma}{\leftrightarrows}} D^\sharp$$

is a Galois connexion.
Moreover, for any element $d^\sharp \in D^\sharp$, we have:

$$\gamma(d^\sharp) = \cup\{d \mid \alpha(d) \sqsubseteq d^\sharp\}.$$

Proposition 5. *Given $(D, \subseteq)$ and $(D^\sharp, \sqsubseteq)$ two partial orders, $D \underset{\alpha}{\overset{\gamma}{\leftrightarrows}} D^\sharp$ a Galois connexion, and $X \subseteq D$ a subset of D, if, X has a least upper bound $\cup X$ and $\{\alpha(d) \mid d \in X\}$ has a least upper bound $\sqcup\{\alpha(d) \mid d \in X\}$, then we have:*

$$\alpha(\cup X) = \sqcup\{\alpha(d) \mid d \in X\}.$$

Proposition 6. *Given $(D, \subseteq)$ and $(D^\sharp, \sqsubseteq)$ two partial orders, $D \underset{\alpha}{\overset{\gamma}{\leftrightarrows}} D^\sharp$ a Galois connexion, and $X^\sharp \subseteq D^\sharp$ a subset of $D^\sharp$, if, $X^\sharp$ has a least upper bound $\sqcup X^\sharp$ and $\{\gamma(d^\sharp) \mid d^\sharp \in X^\sharp\}$ has a least upper bound $\cup\{\gamma(d^\sharp) \mid d^\sharp \in X^\sharp\}$, then we have:*

$$\gamma(\sqcup X^\sharp) = \gamma(\alpha(\cup\{\gamma(d^\sharp) \mid d^\sharp \in X^\sharp\})).$$

Lemma 2. *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. *$\mathbb{F} \in D \to D$ be a monotonic mapping;*
4. *$\mathbb{F}^\sharp \in D^\sharp \to D^\sharp$ be mapping such that: $[\forall d^\sharp \in D^\sharp,\ \mathbb{F}(\gamma(d^\sharp)) \subseteq \gamma(\mathbb{F}^\sharp(d^\sharp))]$;*
5. *$x_0 \in D$ such that $x_0 \subseteq \mathbb{F}(x_0)$.*

Then:

$$\alpha(x_0) \sqsubseteq \mathbb{F}^\sharp(\alpha(x_0)).$$

Theorem 1 (soundness). *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: $[\forall d^\sharp \in D^\sharp,\ \mathbb{F}(\gamma(d^\sharp)) \subseteq \gamma(\mathbb{F}^\sharp(d^\sharp))]$;*
4. *$x_0 \in D$ be an element such that: $x_0 \subseteq \mathbb{F}(x_0)$.*

Then, both $lfp_{x_0}\mathbb{F}$ and $lfp_{\alpha(x_0)}\mathbb{F}^\sharp$ exist, and moreover:

$$lfp_{x_0}\mathbb{F} \subseteq \gamma(lfp_{\alpha(x_0)}\mathbb{F}^\sharp).$$

Theorem 2. *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. $\forall d^\sharp \in D^\sharp,\ \mathbb{F}(\gamma(d^\sharp)) \subseteq \gamma(\mathbb{F}^\sharp(d^\sharp))$*;*
6. $x_0, inv \in D$ *such that:*
   - $x_0 \subseteq \mathbb{F}(x_0) \subseteq \mathbb{F}(inv) \subseteq inv$,
   - $inv = \gamma(\alpha(inv))$,
   - *and* $\alpha(\mathbb{F}(\gamma(\alpha(inv)))) = \mathbb{F}^\sharp(\alpha(inv))$*;*

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

Theorem 3. *We suppose that:*

1. $(D, \subseteq, \cup)$ *and* $(D^\sharp, \sqsubseteq, \sqcup)$ *are chain-complete partial orders;*
2. $(D, \subseteq) \underset{\alpha}{\overset{\gamma}{\leftrightarrows}} (D^\sharp, \sqsubseteq)$ *is a Galois connexion;*
3. $\mathbb{F} : D \to D$ *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:

- $lfp_{x_0}\mathbb{F}$ *and* $lfp_{\alpha(x_0)}\mathbb{F}^\sharp$ *exist;*
- $lfp_{x_0}\mathbb{F} \in \gamma(D^\sharp) \iff lfp_{x_0}\mathbb{F} = \gamma(lfp_{\alpha(x_0)}\mathbb{F}^\sharp)$.

Corollary 1 (relative completeness). *We suppose that:*

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

Then, both $lfp_{x_0}\mathbb{F}$ *and* $lfp_{\alpha(x_0)}\mathbb{F}^\sharp$ *exist, and moreover:*

$$lfp_{x_0}\mathbb{F} = \gamma(lfp_{\alpha(x_0)}\mathbb{F}^\sharp).$$

2 Site-graphs

Let $\mathbb{N}$ be a countable set of agent identifiers.
Let $\mathcal{A}$ be a finite set of agent types.
Let $\mathcal{S}$ be a finite set of site types.

Definition 10 (site-graphs). *A site-graph is a triple* $(Ag, Site, Link)$ *where:*

- *Ag* : $\mathbb{N} \rightharpoonup \mathcal{A}$ *is a partial map between* $\mathbb{N}$ *and* $\mathcal{A}$ *such that the subset of* $\mathbb{N}$ *of the elements* i *such that* $Ag(i)$ *is defined is finite;*
- $Site \subseteq \mathbb{N} \times \mathcal{S}$ *is a subset of* $\mathbb{N} \times \mathcal{S}$ *such that for any pair* $(i, s) \in Site$, $Ag(i)$ *is defined;*
- $Link \subseteq Site^2$ *is a relation over Site such that:*
  1. *for any site* $a \in Site$, $(a, a) \notin Link$;
  2. *for any pair* $(a, b) \in Link$, *we have* $(b, a) \in Link$;
  3. *for any sites* $a, b, b' \in Site$, *if both* $(a, b) \in Link$ *and* $(a, b') \in Link$, *then* $b = b'$.

  Whenever $(a, b) \in Link$, *we say that there is a link between the site* a *and the site* b.
  Whenever $a \in Site$, *but there exists no* $b \in Site$ *such that* $(a, b) \in Link$, *we say that* a *is free.*

Definition 11 (embeddings). *An embedding between two site-graphs* $(Ag, Site, Link)$ *and* $(Ag', Site', Link')$ *is given by a partial mapping* $\phi : \mathbb{N} \rightharpoonup \mathbb{N}$, *such that:*

1. *(agent mapping) For any* $i \in \mathbb{N}$, $Ag(i)$ *is defined if and only if* $\phi(i)$ *is defined;*
2. *(well-formedness) For any* $i \in \mathbb{N}$, *if* $Ag(i)$ *is defined, then* $Ag'(\phi(i))$ *is defined;*
3. *(into mapping) For any* $i, i' \in \mathbb{N}$, *if* $\phi(i)$ *and* $\phi'(i)$ *are defined, then* $\phi(i) = \phi(i') \implies i = i'$;
4. *(agent types) For any* $i \in \mathbb{N}$, *if* $Ag(i)$ *is defined, then* $Ag(i) = Ag'(\phi(i))$;
5. *(site types) For any site* $(i, s) \in Site$, $(\phi(i), s) \in Site'$;
6. *(free sites) For any pair* $(i, s) \in Site$ *such that for any* $(i', s') \in Site$, $((i, s), (i', s')) \notin Link$, *then for any* $(i'', s'') \in Site'$, $((\phi(i), s), (i'', s'')) \notin Link$;
7. *(links) For any link* $((i, s), (i', s')) \in Link$, $((\phi(i), s), (\phi(i'), s')) \in Link'$.

Definition 12 (automorphism). *An embedding between a site-graph and itself is called an automorphism.*

Definition 13 (paths). *Let* $\mathcal{G} = (Ag, Site, Link)$ *be a site-graph. We define a path of length* $n > 0$ *in the site-graph* $\mathcal{G}$ *a sequence* $(i_k, s_k)_{0 \leq k \leq 2 \times n - 1}$ *of* $2 \times n$ *pairs of sites in Site such that:*

1. *For any* j *such that* $0 \leq j < n$, $((i_{2 \times j}, s_{2 \times j}), (i_{2 \times j + 1}, s_{2 \times j + 1})) \in Link$.
2. *For any* j *such that* $1 \leq j < n$, $i_{2 \times j} = i_{2 \times j - 1}$ *and* $s_{2 \times j} \neq s_{2 \times j - 1}$.

Proposition 7 (sub-paths). *Let* $\mathcal{G} = (Ag, Site, Link)$ *be a site-graph and* $(i_k, s_k)_{0 \leq k \leq 2 \times n - 1}$ *be a path of length* $n > 0$ *in the site-graph* $\mathcal{G}$. *Let* m, m' *be two integers such that* $0 \leq m < m' \leq n$, *then,* $(i_k, s_k)_{2 \times m \leq k \leq 2 \times m' - 1}$ *is a path in the site-graph* $\mathcal{G}$.

Proposition 8 (path composition). *Let* $\mathcal{G} = (Ag, Site, Link)$ *be a site-graph and* $(i_k, s_k)_{0 \leq k \leq 2 \times n - 1}$ *and* $(i'_k, s'_k)_{0 \leq k \leq 2 \times n' - 1}$ *be two paths of length* $n > 0$ *and* $n' > 0$ *in the site-graph* $\mathcal{G}$ *such that* $i_{2 \times n - 1} = i'_0$ *and* $s_{2 \times n - 1} \neq s'_0$.
Then, the sequence $(i''_k, s''_k)_{0 \leq k \leq 2 \times (n + n') - 1}$ *where:*

$$\begin{cases} (i''_k, s''_k) = (i_k, s_k) & \text{whenever } 0 \leq k \leq 2 \times n - 1 \\ (i''_k, s''_k) = (i'_{k - 2 \times n}, s'_{k - 2 \times n}) & \text{whenever } 2 \times n \leq k \leq 2 \times (n + n') - 1 \end{cases}$$

is a path of length $n + n'$ *in* $\mathcal{G}$.

Proposition 9 (path image). *Let* $\mathcal{G} = (Ag, Site, Link)$ *be a site-graph,* ϕ *be an automorphism of* $\mathcal{G}$, *and* $(i_k, s_k)_{0 \leq k \leq 2 \times n - 1}$ *be a path of length* $n > 0$ *in* $\mathcal{G}$, *then* $(\phi(i_k), s_k)_{0 \leq k \leq 2 \times n - 1}$ *is a path of length* n *in* $\mathcal{G}$.

Definition 14 (connected components). *A site-graph* $(Ag, Site, Link)$ *is a connected component, if and only if, for any pair* $(i, i') \in \mathbb{N}^2$ *of agent identifiers such that* $Ag(i)$ *and* $Ag(i')$ *are defined and* $i \neq i'$, *there exists a pair* $(s, s') \in \mathcal{S}^2$ *of site types, such that* $(i, s) \in Site$, $(i', s') \in Site$, *and there is a path in* $\mathcal{G}$ *between the site* (i, s) *and the site* (i', s').

Definition 15 (cycle). *Let* $\mathcal{G}$ *be a site-graph. A cycle of length* $n > 0$ *is a path* $(i_k, s_k)_{0 \leq k \leq 2 \times n - 1}$ *in the site-graph* $\mathcal{G}$ *such that* $i_0 = i_{2 \times n - 1}$ *and* $s_0 \neq s_{2 \times n - 1}$.

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

Proposition 10. *Let $\mathcal{G} = (Ag, Site, Link)$ be a connected component without any cycle. Let ϕ be an automorphism of $\mathcal{G}$. Let i be an agent identifier such that $Ag(i)$ is defined. Let $(i_k, s_k)_{0 \leq k \leq 2\times n-1}$ be a path between i and $\phi(i)$.*
Then $s_0 = s_{2\times n-1}$.

Lemma 2 (automorphism) *Let $\mathcal{G} = (Ag, Site, Link)$ be a connected component without any cycle.*

- *$\mathcal{G}$ has at most two automorphisms.*
- *If ϕ is a automorphism over $\mathcal{G}$, such that there exists $i \in \mathbb{N}$, such that $Ag(i)$ is defined and $\phi(i) \neq i$, then there exist two agent identifiers $i, i' \in \mathbb{N}$ and a site type $s \in \mathcal{S}$, such that $Ag(i) = Ag(i')$, $(i, s), (i', s) \in Site$, and $((i, s), (i', s)) \in Link$.*

Lemma 3 (Euler) *If a site-graph has no cycle, then it has an agent with at most one bound site.*