Master AIV

Internal coarse-graining of molecular systems

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Overview

1. Context and motivations
2. Handmade ODEs
3. Abstract interpretation framework
4. Kappa
5. Concrete semantics
6. Abstract semantics
7. Conclusion
Signalling Pathways

EGF, TGF-alpha, etc

EGFR

PI3-K

AKT

mTOR

STAT

GRB2

SOS

RAS

RAF

MEK

ERK

Gene transcription
Cell cycle progression

Cell proliferation
Inhibition of apoptosis
Angiogenesis
Migration, Adhesion, Invasion

Eikuch, 2007
Pathway maps

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

\[
\begin{align*}
\frac{dx_1}{dt} &= -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
\frac{dx_2}{dt} &= -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
\frac{dx_3}{dt} &= k_1 \cdot x_1 \cdot x_2 - k_{-1} \cdot x_3 + 2 \cdot k_2 \cdot x_3 \cdot x_3 - k_{-2} \cdot x_4 \\
\frac{dx_4}{dt} &= k_2 \cdot x_3^2 - k_2 \cdot x_4 + \frac{v_4 \cdot x_5}{p_4 + x_5} - (k_3 \cdot x_4 - k_{-3} \cdot x_5) \\
\frac{dx_5}{dt} &= \ldots \\
\vdots \\
\frac{dx_n}{dt} &= -k_1 \cdot x_1 \cdot c_2 + k_{-1} \cdot x_3
\end{align*}
\]

- 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

- deterministic differential equations
- stochastic master equations
- agent/rule-based

number of instances per molecular species

number of molecular species

400 80,000 500,000 $10^{33}$
A breach in the wall(s) ?
Overview

1. Context and motivations
2. Handmade ODEs
   (a) Independent subsystems
   (b) Self-consistent subsystems
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Case study 1: A simple adapter
Case study 1: A simple adapter
Case study 1: A simple adapter

\[
\begin{align*}
\frac{d[A]}{dt} &= k_{dB}^{AB}([AB] + [ABC]) - [A] \cdot k_{dB}^{AB} ([\emptyset B] + [\emptyset BC]) \\
\frac{d[C]}{dt} &= k_{dB}^{BC} ([\emptyset BC] + [ABC]) - [C] \cdot k_{dB}^{BC} ([\emptyset B] + [AB]) \\
\frac{d[\emptyset B]}{dt} &= k_{dB}^{AB} [AB] + k_{dB}^{BC} [\emptyset BC] - [\emptyset B] \cdot ( [A] \cdot k_{dB}^{AB} + [C] \cdot k_{dB}^{BC}) \\
\frac{d[AB]}{dt} &= [A] \cdot k_{dB}^{AB} [\emptyset B] + k_{dB}^{BC} [ABC] - [AB] \cdot (k_{dB}^{AB} + [C] \cdot k_{dB}^{BC}) \\
\frac{d[\emptyset BC]}{dt} &= k_{dB}^{AB} [ABC] + [C] \cdot k_{dB}^{BC} [\emptyset B] - [\emptyset BC] \cdot (k_{dB}^{BC} + [A] \cdot k_{dB}^{AB}) \\
\frac{d[ABC]}{dt} &= [A] \cdot k_{dB}^{AB} [\emptyset BC] + [C] \cdot k_{dB}^{BC} [AB] - [ABC] \cdot (k_{dB}^{AB} + k_{dB}^{BC})
\end{align*}
\]
Case study 1: Two subsystems

A

B

C
Case study 1: Two subsystems

A

B

B

C
Case study 1: Two subsystems

\[ [AB?] \overset{\Delta}{=} [AB\emptyset] + [ABC] \]
\[ [\emptyset B?] \overset{\Delta}{=} [\emptyset B\emptyset] + [\emptyset BC] \]

\[
\begin{align*}
\frac{d[A]}{dt} &= k_d^{AB} \cdot [AB?] - [A] \cdot k^{AB} \cdot [\emptyset B?] \\
\frac{d[AB]}{dt} &= [A] \cdot k^{AB} \cdot [\emptyset B?] - k_d^{AB} \cdot [AB?] \\
\frac{d[\emptyset B]}{dt} &= k_d^{AB} \cdot [AB?] - [A] \cdot k^{AB} \cdot [\emptyset B?] \\
\end{align*}
\]

\[ [?BC] \overset{\Delta}{=} [\emptyset BC] + [ABC] \]
\[ [?B\emptyset] \overset{\Delta}{=} [\emptyset B\emptyset] + [AB\emptyset] \]

\[
\begin{align*}
\frac{d[C]}{dt} &= k_d^{BC} \cdot [?BC] - [C] \cdot k^{BC} \cdot [?B\emptyset] \\
\frac{d[?BC]}{dt} &= [C] \cdot k^{BC} \cdot [?B\emptyset] - k_d^{BC} \cdot [?BC] \\
\frac{d[?B\emptyset]}{dt} &= k_d^{BC} \cdot [?BC] - [C] \cdot k^{BC} \cdot [?B\emptyset] \\
\end{align*}
\]
Case study 1: Dependence index

We introduce:

\[ \Delta \equiv [?B?] + [?BC]. \]

The binding with A and with C would be independent if, and only if:

\[ \frac{[ABC]}{[?BC]} = \frac{[AB?] - [AB?] \cdot [?BC]}{[?B?]}. \]

Thus we define the dependence index as follows:

\[ X \equiv [ABC] \cdot [?B?] - [AB?] \cdot [?BC]. \]

We have (after a short computation):

\[ \frac{dX}{dt} = -X \cdot ( [A] \cdot k^{AB} + k^{AB}_d + [C] \cdot k^{BC} + k^{BC}_d ) \]

So the property:

\[ [ABC] = \frac{[AB?] \cdot [?BC]}{[?B?]} \]

is an invariant (i.e. if it holds at time \( t \), it holds at any time \( t' \geq t \)).
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Case study 2: A system with a switch
Case study 2: A system with a switch

\[(u,u,u) \rightarrow (u,p,u) \quad k^c\]
\[(u,p,u) \rightarrow (p,p,u) \quad k^l\]
\[(u,p,p) \rightarrow (p,p,p) \quad k^l\]
\[(u,p,u) \rightarrow (u,p,p) \quad k^r\]
\[(p,p,u) \rightarrow (p,p,p) \quad k^r\]
Case study 2: A system with a switch

\[
\begin{align*}
\frac{d[u,u,u]}{dt} &= -k^c \cdot [u,u,u] \\
\frac{d[u,p,u]}{dt} &= -k^l \cdot [u,p,u] + k^c \cdot [u,u,u] - k^r \cdot [u,p,u] \\
\frac{d[u,p,p]}{dt} &= -k^l \cdot [u,p,p] + k^r \cdot [u,p,u] \\
\frac{d[p,p,u]}{dt} &= k^l \cdot [u,p,u] - k^r \cdot [p,p,u] \\
\frac{d[p,p,p]}{dt} &= k^l \cdot [u,p,p] + k^r \cdot [p,p,u]
\end{align*}
\]

\[
\begin{align*}
(u,u,u) &\rightarrow (u,p,u) \quad k^c \\
(u,p,u) &\rightarrow (p,p,u) \quad k^l \\
(u,p,p) &\rightarrow (p,p,p) \quad k^l \\
(u,p,u) &\rightarrow (u,p,p) \quad k^r \\
(p,p,u) &\rightarrow (p,p,p) \quad k^r
\end{align*}
\]
Case study 2: Two subsystems
Case study 2: Two subsystems
Case study 2: Two subsystems

\[
A[(u,p,?)] = [(u,p,u)] + [(u,p,p)]
\]

\[
A[(p,p,?)] = [(p,p,u)] + [(p,p,p)]
\]

\[
\frac{d[(u,u,u)]}{dt} = -k_c \cdot [(u,u,u)]
\]
\[
\frac{d[(u,p,?)]}{dt} = -k_l \cdot [(u,p,?)] + k_c \cdot [(u,u,u)]
\]
\[
\frac{d[(p,p,?)]}{dt} = k_l \cdot [(u,p,?)]
\]

\[
\frac{d[(?,p,u)]}{dt} = -k_c \cdot [(u,u,u)]
\]
\[
\frac{d[(?,p,p)]}{dt} = -k_r \cdot [(?,p,u)] + k_c \cdot [(u,u,u)]
\]
\[
\frac{d[(?,p,p)]}{dt} = k_r \cdot [(?,p,u)]
\]
Case study 2: Dependence index

We introduce:

\[ [(?,p,?)] \overset{\Delta}{=} [(?,p,u)] + [(?,p,p)] \]

The states of left site and right site would be independent if, and only if:

\[ \frac{[(p,p,p)]}{[(p,p,?)]} = \frac{[(?,p,p)]}{[(?,p,?)]}. \]

Thus we define the dependence index as follows:

\[ X \overset{\Delta}{=} [(p,p,p)] 
\cdot 
[(?,p,?)] 
- 
[(?,p,p)] 
\cdot 
[(p,p,?)]. \]

We have (after a short computation):

\[ \frac{dX}{dt} = -X \cdot (k^l + k^r) + k^c \cdot [(p,p,p)] 
\cdot 
[(u,u,u)]. \]

As a consequence, the property \( X = 0 \) is not an invariant. We can split the system into two subsystems, but we cannot recombine both subsystems without errors.
Case study 2: Erroneous recombination

Concentrations evolution with respect to time \( ([u,u,u])(0) = 100 \).

\( [(p,p,p)] \) and \( [(p,p,?)] \cdot [(?,p,p)] \)
Conclusion

1. Independence:
   + the transformation is invertible:
     we can recover the concentration of any species;
   – it is a strong property
     which is hard to prove,
     which is hardly ever satisfied.

2. Self-consistency:
   – some information is abstracted away
     we cannot recover the concentration of any species;
   + it is a weak property
     which is easy to ensure,
     which is easy to propagate;
   + it captures the essence of the kinetics of systems.

We are going to track the correlations that are read by the system.
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Continuous differential semantics

Given $\mathcal{V}$, a finite set of variables; and $\mathbb{F}$, a $C^\infty$ mapping from $\mathcal{V} \rightarrow \mathbb{R}^+$ into $\mathcal{V} \rightarrow \mathbb{R}$.

as for instance,

- $\mathcal{V} \triangleq \{(u,u,u), (u,p,u), (p,p,u), (u,p,p), (p,p,p)\}$,

- $\mathbb{F}(\rho) \triangleq \begin{cases} 
((u,u,u)) \mapsto -k^c \cdot \rho((u,u,u)) \\
((u,p,u)) \mapsto -k^l \cdot \rho((u,p,u)) + k^c \cdot \rho((u,u,u)) - k^r \cdot \rho((u,p,u)) \\
((p,p,u)) \mapsto k^l \cdot \rho((u,p,u)) - k^r \cdot \rho((p,p,u)) \\
((p,p,p)) \mapsto k^l \cdot \rho((u,p,p)) + k^r \cdot \rho((p,p,u)) \\
\end{cases}$

we can define the continuous differential semantics as follows:

$$X_c : \left\{ \begin{array}{c}
(\mathcal{V} \rightarrow \mathbb{R}^+) \times \mathbb{R}^+ \rightarrow (\mathcal{V} \rightarrow \mathbb{R}^+) \\
(X_0, T) \mapsto X_0 + \int_{t=0}^{T} \mathbb{F}(X_c(X_0, t)) \cdot dt.
\end{array} \right\}$$
Abstraction

An abstraction \((\mathcal{V}^#, \psi, F^#)\) is given by:

- \(\mathcal{V}^#\): a finite set of observables,
- \(\psi\): a mapping from \(\mathcal{V} \rightarrow \mathbb{R}\) into \(\mathcal{V}^# \rightarrow \mathbb{R}\),
- \(F^#\): a \(C^\infty\) mapping from \(\mathcal{V}^# \rightarrow \mathbb{R}^+\) into \(\mathcal{V}^# \rightarrow \mathbb{R}\);

such that:

- \(\psi\) is linear with positive coefficients,
- \(F^#\) is \(\psi\)-complete
  i.e. the following diagram commutes:

\[
\begin{array}{ccc}
\mathcal{V} & \xrightarrow{F} & \mathcal{V} \\
\downarrow \psi & & \downarrow \psi \\
\mathcal{V}^# & \xrightarrow{F^#} & \mathcal{V}^#
\end{array}
\]

i.e. \(\psi \circ F = F^# \circ \psi\).
Abstraction example

• \( \mathcal{V} \overset{\Delta}{=} \{ [(u, u, u), (u, p, u), (p, p, u), (u, p, p), (p, p, p)] \} \)

\[ \begin{align*}
(u, u, u) & \mapsto -k_c \cdot \rho([(u, u, u)]) \\
(u, p, u) & \mapsto -k_l \cdot \rho([(u, p, u)]) + k_c \cdot \rho([(u, u, u)]) - k_r \cdot \rho([(u, p, u)]) \\
(p, p, u) & \mapsto -k_l \cdot \rho([(u, p, p)]) + k_r \cdot \rho([(u, p, u)]) \\
(p, p, p) & \mapsto -k_r \cdot \rho([(u, p, p)]) + k_l \cdot \rho([(u, p, p)])
\end{align*} \]

• \( \mathcal{V}^\# \overset{\Delta}{=} \{ [(u, u, u), (? , p , u), (? , p , p), (u, p, ?), (p, p, ?)] \} \)

\[ \begin{align*}
(u, u, u) & \mapsto \rho([(u, u, u)]) \\
(?, p , u) & \mapsto \rho([(u, p, u)]) + \rho([(p, p, u)]) \\
(?, p , p) & \mapsto \rho([(u, p, p)]) + \rho([(p, p, p)])
\end{align*} \]

\[ \begin{align*}
(?, p , u) & \mapsto -k_c \cdot \rho^\#([(u, u, u)]) \\
(?, p , p) & \mapsto -k_r \cdot \rho^\#([(?, p , u)]) + k_c \cdot \rho^\#([(u, u, u)]) \\
(?, p , p) & \mapsto k_r \cdot \rho^\#([(?, p , p)])
\end{align*} \]

(Completeness can be checked analytically.)
Abstract continuous trajectories

Given an abstraction $\mathcal{V}^\#, \psi, \mathbb{F}^\#$, we have:

$$X_c(X_0, T) = X_0 + \int_{t=0}^{T} \mathbb{F} (X_c(X_0, t)) \cdot dt$$

$$\psi (X_c(X_0, T)) = \psi \left( X_0 + \int_{t=0}^{T} \mathbb{F} (X_c(X_0, t)) \cdot dt \right)$$

$$\psi (X_c(X_0, T)) = \psi(X_0) + \int_{t=0}^{T} [\psi \circ \mathbb{F}] (X_c(X_0, t)) \cdot dt \quad (\psi \text{ is linear})$$

$$\psi (X_c(X_0, T)) = \psi(X_0) + \int_{t=0}^{T} \mathbb{F}^\# (\psi (X_c(X_0, t))) \cdot dt \quad (\mathbb{F}^\# \text{ is } \psi\text{-complete})$$

We set $Y_0 \triangleq \psi(X_0)$ and $Y_c \triangleq \psi \circ X_c$.

Then we have:

$$Y_c(X_0, T) = Y_0 + \int_{t=0}^{T} \mathbb{F}^\# (Y_c(X_0, t)) \cdot dt$$
Fluid trajectories

$Y(t)$

$t$
Fluid trajectories

Y(t)
X(t)
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A species

\[ E(r!1), R(l!1,r!2), R(r!2,l!3), E(r!3) \]
A Unbinding/Binding Rule

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

\[ R(Y_1 \sim u, \ll 1), E(r!1) \leftrightarrow R(Y_1 \sim p, \ll 1), E(r!1) \]
Don’t care, Don’t write

\[ R \quad Y_1 \quad u \quad \Leftrightarrow \quad R \quad Y_1 \quad p \]

\[ R \quad Y_1 \quad u \quad \neq \quad R \quad Y_1 \quad p \]
Contact map

So

Sh

G

b

E

G

a

d

Y_7

Y_{68}

Y_{48}

E

r

R

l

r

pi
Overview

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Requirements

1. Reachable species
   A set $\mathcal{R}$ of connected site-graphs such that:
   - $\mathcal{R}$ is finite;
   - $\mathcal{R}$ is closed with respect to rule application: i.e. applying a rule with
     a tuple of site-graphs in $\mathcal{R}$ gives a tuple of site-graphs in $\mathcal{R}$;

2. Rules are associated with kinetic factors
   - the unit depends on the arity of the rule as follows:
     \[ \left( \frac{L}{mol} \right)^{arity - 1} \cdot s^{-1} \]
     where $arity$ is the number of connected components in the lhs.
We write $Z \triangleleft_{\Phi} Z'$ 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 $i = i'$. 
Differential system

Let us consider a rule *rule*:

\[ \text{lhs} \rightarrow \text{rhs} \quad k. \]

1. We write *lhs* as a multi-set \( \{C_i\} \) of non empty connected components.
2. A ground instantiation of the rule *rule* is defined by a tuple \( (r_i, \Phi_i) \) such that \( \forall i, r_i \in \mathcal{R} \) and \( C_i \prec_{\Phi_i} r_i \).
3. The ground instantiation can be written as follows:

\[ r_1, \ldots, r_m \rightarrow p_1, \ldots, p_n \quad k. \]

4. The activity of a ground instantiation is defined as:

\[ \text{act}_{(r_i,\Phi_i)} = \frac{k \cdot \prod[r_i]}{\#\{\Phi \mid \text{lhs} \prec_{\Phi} \text{lhs}\}}. \]

5. Each ground instantiation induces the following contributions:

\[ \frac{d[r_i]}{dt} = -\text{act}_{(r_i,\Phi_i)}, \quad \frac{d[p_i]}{dt} = \text{act}_{(r_i,\Phi_i)}. \]
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   (a) Fragments
   (b) Soundness criteria
   (c) Abstract counterpart
7. Conclusion
Partial species

Fragments are well-chosen partial species.

A partial species is a connected site-graph such that:

- the set of the sites of each node of type $A$ is a subset of the set of the sites of $A$;
- sites are free, bound to an other site, or tagged with a binding type.

For instance:

$$G(b!d, So, a!1), Sh(Y_7!1, pi!2), R(Y_{48}!2, r)$$
Annotated contact map

The set of fragment is described by an annotated contact map.
Are they fragments?
Are they fragments?
Are they fragments?
Are they fragments?
Are they fragments?
Are they fragments?

Yes or no?
Basic properties

The set of fragments enjoys two convenient properties:

1. Closure with respect to the operational semantics:
   When we apply a rule with a tuple of fragments, we get a tuple of fragments.

2. Subfragments:
   We can express the concentration of any sub-fragment as a linear combination of the concentration of some fragments.

Which other properties do we need so that the function $F^\#$ can be defined?
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7. Conclusion
Fragments consumption

Can we express the amount (per time unit) of this fragment (bellow) concentration that is consumed by this rule (above)?
Fragments consumption

No, because we have abstracted away the correlation between the state of the site $r$ and the state of the site $l$. 
Whenever a fragment intersects a connected component of a lhs on a modified site, then the connected component must be embedded in the fragment!
We reflect each path that stems from a modified site (in the lhs of a rule) into the annotated contact map.
We need to express the “concentration” of any connected component of a lhs with respect to the “concentration” of fragments.
Each connected component of a lhs must be a sub-fragment.
Each connected component of a lhs must be a sub-fragment.
Can we express the amount (per time unit) of this fragment (below) concentration that is produced by the rule (above)?
Yes, if the connected components of the lhs of the refinement are subfragments, which is already ensured by previous syntactic criteria.
Fragment properties

Whenever the annotated contact map satisfies the syntactic criteria, fragments enjoy the following properties:

1. the concentration of any sub-fragment is a linear combination of the concentration of some fragments;
2. Any connected component of a lhs is a sub-fragment;
3. Whenever a fragment intersects a connected component of a lhs on a modified site, then the connected component is embedded in the fragment,
   This ensures that we can express fragment consumption;
4. Whenever a fragment intersects a connected component of a rhs on a modified site, any connected component of the lhs of the refined rule is a subfragment,
   This ensures that we can express fragment production.
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A binding rule

Let us abstract the contribution of a binding rule:

\[ \text{Sh} \] \quad \text{G} \quad \text{Sh} \]

\[ \begin{array}{c}
\text{Y}_7 \\
\text{Y}_{48} \\
\text{R} \\
\text{C}_1 \\
\text{pi} \\
\end{array} \quad \begin{array}{c}
a \\
b \\
\text{C}_2 \\
\end{array} \quad \begin{array}{c}
\text{Y}_7 \\
\text{Y}_{48} \\
\text{R} \\
\text{C}_1 \\
\text{pi} \\
\end{array} \quad \begin{array}{c}
a \\
b \\
\end{array} \]

\[ k \]
A binding rule: reactants

For any \((F, \Phi)\) such that \(C_i \triangleleft_\Phi F\),

\[
\frac{d[F]}{dt} = -\frac{k \cdot [F] \cdot [C_{3-i}]}{\#\{\Phi' | C_1, C_2 \triangleleft_\Phi' C_1, C_2\}}.
\]

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If the edge is solid, for any \((F_1, \Phi_1)\) and \((F_2, \Phi_2)\), such that \(C_1 \ll_{\Phi_1} F_1\) and \(C_2 \ll_{\Phi_2} F_2\),

\[
\frac{d[F_1 - F_2]}{dt} = k \cdot [F_1] \cdot [F_2] / \#\{\Phi' \mid C_1, C_2 \ll_{\Phi'} C_1, C_2\}
\]
Binding rules: products

If the edge is dotted, for any \((F, \Phi)\) such that \(C_i \triangleleft_{\Phi} F\),

\[
\frac{d[F \rightarrow]}{dt} = \frac{\kappa \cdot [F] \cdot [C_{3-i}]}{\#\{\Phi' \mid C_1, C_2 \triangleleft_{\Phi'} C_1, C_2\}}.
\]
Soundness

If:

1. the annotated contact map satisfies the criteria on slides 50 and 54;
2. the abstraction $\psi$ gives the concentration of fragments, knowing the concentration of species;
3. the abstract dynamic $\mathbb{F}^\#$ is defined as in slides 58 to 60.

Then, the abstract dynamic $\mathbb{F}^\#$ is $\psi$-backward complete.
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Experimental results

On early egfr, 356 species are simplified into 38 fragments:

Wiggly curves: stochastic semantics.
Steady curves: abstract differential semantics.
Future works I: Semantics comparisons

Species–based semantics  ⊆  Rule–based semantics  ⊆  Abstract semantics

refinements

limit

refinements

limit

refinements

#
Future works II: Semantics approximations

1. ODE approximations:
   • Because of the use of annotated contact map, fragments have a homogeneous structure (or signature).
     Can we design and use heterogeneous fragments?

2. Stochastic semantics approximations:
   • Can we design abstraction?
   • Find the adequate soundness criteria.