CS2Bio

Internal coarse-graining of molecular systems*

[PNAS'09,LICS'10]

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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



Eikuch, 2007

Pathway maps



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

Differential models

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

- 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



A breach in the wall(s) ?





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Case study 1: A simple adapter



Case study 1: A simple adapter



A, $\emptyset B \emptyset$	\longleftrightarrow	A₿∅	k^{AB}, k_{d}^{AB}
A , ∅ BC	\longleftrightarrow	ABC	k^{AB}, k_{d}^{AB}
Ø B Ø , C	\longleftrightarrow	ØBC	k^{BC}, k_{d}^{BC}
AB ∅ , C	\longleftrightarrow	ABC	k^{BC}, k^{BC}_{d}

Case study 1: A simple adapter



\longleftrightarrow	A₿∅	k^{AB}, k_{d}^{AB}
\longleftrightarrow	ABC	k^{AB}, k_{d}^{AB}
\longleftrightarrow	ØBC	k^{BC}, k^{BC}_{d}
\longleftrightarrow	ABC	k^{BC}, k^{BC}_{d}
	$\begin{array}{c} \longleftrightarrow \\ \longleftrightarrow \\ \longleftrightarrow \\ \longleftrightarrow \\ \longleftrightarrow \\ \longleftrightarrow \\ \end{array}$	$\begin{array}{ccc} & & AB \emptyset \\ & \leftarrow & ABC \\ & \leftarrow & \emptyset BC \\ & \leftarrow & ABC \end{array}$

 $\begin{cases} \frac{d[A]}{dt} = k_d^{AB} \cdot ([AB\emptyset] + [ABC]) - [A] \cdot k^{AB} \cdot ([\emptyset B\emptyset] + [\emptyset BC]) \\ \frac{d[C]}{dt} = k_d^{BC} \cdot ([\emptyset BC] + [ABC]) - [C] \cdot k^{BC} \cdot ([\emptyset B\emptyset] + [AB\emptyset]) \\ \frac{d[\emptyset B\emptyset]}{dt} = k_d^{AB} \cdot [AB\emptyset] + k_d^{BC} \cdot [\emptyset BC] - [\emptyset B\emptyset] \cdot ([A] \cdot k^{AB} + [C] \cdot k^{BC}) \\ \frac{d[AB\emptyset]}{dt} = [A] \cdot k^{AB} \cdot [\emptyset B\emptyset] + k_d^{BC} \cdot [ABC] - [AB\emptyset] \cdot (k_d^{AB} + [C] \cdot k^{BC}) \\ \frac{d[\emptyset BC]}{dt} = k_d^{AB} \cdot [ABC] + [C] \cdot k^{BC} \cdot [\emptyset B\emptyset] - [\emptyset BC] \cdot (k_d^{BC} + [A] \cdot k^{AB}) \\ \frac{d[ABC]}{dt} = [A] \cdot k^{AB} \cdot [\emptyset BC] + [C] \cdot k^{BC} \cdot [AB\emptyset] - [ABC] \cdot (k_d^{BC} + [A] \cdot k^{AB}) \\ \end{cases}$

Case study 1: Two subsystems



Case study 1: Two subsystems



Case study 1: Two subsystems

B B $[AB?] \stackrel{\Delta}{=} [AB\emptyset] + [ABC]$ $[?BC] \stackrel{\Delta}{=} [\emptyset BC] + [ABC]$ $[\emptyset \mathbf{B}?] \stackrel{\Delta}{=} [\emptyset \mathbf{B}\emptyset] + [\emptyset \mathbf{B}C]$ $[?\mathbf{B}\emptyset] \stackrel{\Delta}{=} [\emptyset\mathbf{B}\emptyset] + [\mathbf{A}\mathbf{B}\emptyset]$ $\frac{d[A]}{dt} = k_d^{\mathsf{AB}} \cdot [\mathsf{AB}?] - [\mathsf{A}] \cdot k^{\mathsf{AB}} \cdot [\emptyset \mathsf{B}?]$ $\frac{d[C]}{dt} = k_d^{BC} \cdot [?BC] - [C] \cdot k^{BC} \cdot [?B\emptyset]$ $\begin{cases} \frac{d[\mathsf{AB}?]}{dt} = [\mathsf{A}] \cdot k^{\mathsf{AB}} \cdot [\emptyset \mathsf{B}?] - k^{\mathsf{AB}}_{d} \cdot [\mathsf{AB}?] \\ \frac{d[\emptyset \mathsf{B}?]}{dt} = k^{\mathsf{AB}}_{d} \cdot [\mathsf{AB}?] - [\mathsf{A}] \cdot k^{\mathsf{AB}} \cdot [\emptyset \mathsf{B}?] \end{cases}$ $\left\{ \frac{d[?BC]}{dt} = [C] \cdot k^{BC} \cdot [?B\emptyset] - k_d^{BC} \cdot [?BC] \right\}$ $\frac{d[?B\emptyset]}{dt} = k_d^{BC} \cdot [?BC] - [C] \cdot k^{BC} \cdot [?B\emptyset]$

Case study 1: Dependence index

We introduce:

 $[?\mathsf{B}?] \stackrel{\Delta}{=} [?\mathsf{B}\emptyset] + [?\mathsf{B}\mathsf{C}].$

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

 $\frac{[\mathsf{ABC}]}{[\mathsf{?BC}]} = \frac{[\mathsf{ABP}]}{[\mathsf{?BP}]}.$

Thus we define the dependence index as follows:

 $X \stackrel{\Delta}{=} [\mathsf{ABC}] \cdot [?\mathsf{B}?] - [\mathsf{AB}?] \cdot [?\mathsf{BC}].$

We have (after a short computation):

$$\frac{d\textbf{X}}{dt} = -\textbf{X} \cdot \left([\textbf{A}] \cdot \textbf{k}^{\textbf{AB}} + \textbf{k}_{d}^{\textbf{AB}} + [\textbf{C}] \cdot \textbf{k}^{\textbf{BC}} + \textbf{k}_{d}^{\textbf{BC}} \right)$$

So the property:

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

is an invariant (i.e. if it holds at time t, it holds at any time $t^\prime \geq t).$

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Case study 2: A system with a switch



Case study 2: A system with a switch

- $(u,u,u) \longrightarrow (u,p,u) \mathbf{k}^{c}$
- $(u,\mathbf{p},u) \longrightarrow (\mathbf{p},\mathbf{p},u) \mathbf{k}^{\mathsf{l}}$
- $(u,p,p) \longrightarrow (p,p,p) \qquad k^{I}$
- $(u,p,u) \longrightarrow (u,p,p) \quad \mathbf{k}^{\mathbf{r}}$
- $(\mathbf{p},\mathbf{p},\mathbf{u}) \longrightarrow (\mathbf{p},\mathbf{p},\mathbf{p}) \mathbf{k}^{\mathbf{r}}$



Case study 2: A system with a switch

$$(u,u,u) \longrightarrow (u,\mathbf{p},u) \mathbf{k}^{c}$$

$$(u,\mathbf{p},u) \longrightarrow (\mathbf{p},\mathbf{p},u) \mathbf{k}^{\mathsf{l}}$$

$$(u,p,p) \longrightarrow (p,p,p) \qquad k'$$

$$(u,p,u) \longrightarrow (u,p,p) \quad \mathbf{k}^{r}$$

$$(\mathbf{p},\mathbf{p},\mathbf{u}) \longrightarrow (\mathbf{p},\mathbf{p},\mathbf{p}) \mathbf{k}^{\mathbf{r}}$$

$$\begin{aligned} \frac{d[(u,u,u)]}{dt} &= -k^{c} \cdot [(u,u,u)] \\ \frac{d[(u,p,u)]}{dt} &= -k^{l} \cdot [(u,p,u)] + k^{c} \cdot [(u,u,u)] - k^{r} \cdot [(u,p,u)] \\ \frac{d[(u,p,p)]}{dt} &= -k^{l} \cdot [(u,p,p)] + k^{r} \cdot [(u,p,u)] \\ \frac{d[(p,p,u)]}{dt} &= k^{l} \cdot [(u,p,u)] - k^{r} \cdot [(p,p,u)] \\ \frac{d[(p,p,p)]}{dt} &= k^{l} \cdot [(u,p,p)] + k^{r} \cdot [(p,p,u)] \end{aligned}$$

Case study 2: Two subsystems



Case study 2: Two subsystems



Case study 2: Two subsystems

 $[(\mathbf{u},\mathbf{p},?)] \stackrel{\Delta}{=} [(\mathbf{u},\mathbf{p},\mathbf{u})] + [(\mathbf{u},\mathbf{p},\mathbf{p})]$ $[(\mathbf{p},\mathbf{p},?)] \stackrel{\Delta}{=} [(\mathbf{p},\mathbf{p},\mathbf{u})] + [(\mathbf{p},\mathbf{p},\mathbf{p})]$

$$\begin{cases} \frac{d[(u,u,u)]}{dt} = -k^{c} \cdot [(u,u,u)] \\ \frac{d[(u,p,?)]}{dt} = -k^{l} \cdot [(u,p,?)] + k^{c} \cdot [(u,u,u)] \\ \frac{d[(p,p,?)]}{dt} = k^{l} \cdot [(u,p,?)] \end{cases}$$

 $[(?,\mathbf{p},\mathbf{u})] \stackrel{\Delta}{=} [(\mathbf{u},\mathbf{p},\mathbf{u})] + [(\mathbf{p},\mathbf{p},\mathbf{u})]$ $[(?,\mathbf{p},\mathbf{p})] \stackrel{\Delta}{=} [(\mathbf{u},\mathbf{p},\mathbf{p})] + [(\mathbf{p},\mathbf{p},\mathbf{p})]$

$$\begin{cases} \frac{d[(u,u,u)]}{dt} = -k^{\mathsf{c}} \cdot [(u,u,u)] \\ \frac{d[(?,\mathbf{p},u)]}{dt} = -k^{\mathsf{r}} \cdot [(?,\mathbf{p},u)] + k^{\mathsf{c}} \cdot [(u,u,u)] \\ \frac{d[(?,\mathbf{p},\mathbf{p})]}{dt} = k^{\mathsf{r}} \cdot [(?,\mathbf{p},u)] \end{cases}$$

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Case study 2: Dependence index

We introduce:

 $[(?,\mathbf{p},?)] \stackrel{\Delta}{=} [(?,\mathbf{p},u)] + [(?,\mathbf{p},\mathbf{p})]$

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:

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

We have (after a short computation):

$$\frac{\mathrm{d}X}{\mathrm{d}t} = -X \cdot \left(k^{\mathsf{I}} + k^{\mathsf{r}}\right) + k^{\mathsf{c}} \cdot \left[(p, p, p)\right] \cdot \left[(u, u, u)\right].$$

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



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 \mathcal{C}^{∞} mapping from $\mathcal{V} \to \mathbb{R}^+$ into $\mathcal{V} \to \mathbb{R}$.

as for instance,

•
$$\mathcal{V} \stackrel{\Delta}{=} \{[(u,u,u)], [(u,p,u)], [(p,p,u)], [(u,p,p)], [(p,p,p)]\}, \\ \left\{ \begin{bmatrix} (u,u,u)] \mapsto -k^{c} \cdot \rho([(u,u,u)]) \\ [(u,p,u)] \mapsto -k^{l} \cdot \rho([(u,p,u)]) + k^{c} \cdot \rho([(u,u,u)]) - k^{r} \cdot \rho([(u,p,u)]) \\ [(u,p,p)] \mapsto -k^{l} \cdot \rho([(u,p,p)]) + k^{r} \cdot \rho([(u,p,u)]) \\ [(p,p,u)] \mapsto k^{l} \cdot \rho([(u,p,u)]) - k^{r} \cdot \rho([(p,p,u)]) \\ [(p,p,p)] \mapsto k^{l} \cdot \rho([(u,p,p)]) + k^{r} \cdot \rho([(p,p,u)]); \end{cases}$$

we can define the continuous differential semantics as follows:

$$X_{c}: \begin{cases} (\mathcal{V} \to \mathbb{R}^{+}) \times \mathbb{R}^{+} \to (\mathcal{V} \to \mathbb{R}^{+}) \\ (X_{0}, \mathsf{T}) & \mapsto X_{0} + \int_{\mathsf{t}=0}^{\mathsf{T}} \mathbb{F}(X_{c}(X_{0}, \mathsf{t})) \cdot d\mathsf{t}. \end{cases}$$

Abstraction

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

- \mathcal{V}^{\sharp} : a finite set of observables,
- ψ : a mapping from $\mathcal{V} \to \mathbb{R}$ into $\mathcal{V}^{\sharp} \to \mathbb{R}$,
- \mathbb{F}^{\sharp} : a \mathcal{C}^{∞} mapping from $\mathcal{V}^{\sharp} \to \mathbb{R}^+$ into $\mathcal{V}^{\sharp} \to \mathbb{R}$; such that:
 - ψ is linear with positive coefficients,
 - \mathbb{F}^{\sharp} is ψ -complete

i.e. the following diagram commutes:

$$egin{aligned} & (\mathcal{V} o \mathbb{R}^+) & \stackrel{\mathbb{F}}{\longrightarrow} & \mathcal{V} o \mathbb{R} \ & \psi & & & & \downarrow \psi \ & & & & \downarrow \psi \ & (\mathcal{V}^{\sharp} o \mathbb{R}^+) & \stackrel{\mathbb{F}^{\sharp}}{\longrightarrow} & \mathcal{V}^{\sharp} o \mathbb{R} \end{aligned}$$

i.e. $\psi \circ \mathbb{F} = \mathbb{F}^{\sharp} \circ \psi$.

Abstraction example

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

• $\mathbb{F}(\rho) \stackrel{\Delta}{=} \begin{cases} [(u,u,u)] \mapsto -k^{c} \cdot \rho([(u,u,u)]) \\ [(u,p,u)] \mapsto -k^{l} \cdot \rho([(u,p,u)]) + k^{c} \cdot \rho([(u,u,u)]) - k^{r} \cdot \rho([(u,p,u)]) \\ [(u,p,p)] \mapsto -k^{l} \cdot \rho([(u,p,p)]) + k^{r} \cdot \rho([(u,p,u)]) \\ \dots \end{cases}$

•
$$\mathcal{V}^{\sharp} \stackrel{\Delta}{=} \{ [(u,u,u)], [(?,p,u)], [(?,p,p)], [(u,p,?)], [(p,p,?)] \}$$

• $\psi(\rho) \stackrel{\Delta}{=} \begin{cases} [(u,u,u)] \mapsto \rho([(u,u,u)]) \\ [(?,p,u)] \mapsto \rho([(u,p,u)]) + \rho([(p,p,u)]) \\ [(?,p,p)] \mapsto \rho([(u,p,p)]) + \rho([(p,p,p)]) \\ ... \end{cases}$
• $\mathbb{F}^{\sharp}(\rho^{\sharp}) \stackrel{\Delta}{=} \begin{cases} [(u,u,u)] \mapsto -k^{c} \cdot \rho^{\sharp}([(u,u,u)]) \\ [(?,p,u)] \mapsto -k^{r} \cdot \rho^{\sharp}([(?,p,u)]) + k^{c} \cdot \rho^{\sharp}([(u,u,u)]) \\ [(?,p,p)] \mapsto k^{r} \cdot \rho^{\sharp}([(?,p,u)]) \\ ... \end{cases}$

(Completeness can be checked analytically.)

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Abstract continuous trajectories

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

$$\begin{split} X_c(X_0,T) &= X_0 + \int_{t=0}^T \mathbb{F} \left(X_c(X_0,t) \right) \cdot dt \\ \psi \left(X_c(X_0,T) \right) &= \psi \left(X_0 + \int_{t=0}^T \mathbb{F} \left(X_c(X_0,t) \right) \cdot dt \right) \\ \psi \left(X_c(X_0,T) \right) &= \psi(X_0) + \int_{t=0}^T [\psi \circ \mathbb{F}] \left(X_c(X_0,t) \right) \cdot dt \text{ (ψ is linear)} \\ \psi \left(X_c(X_0,T) \right) &= \psi(X_0) + \int_{t=0}^T \mathbb{F}^{\sharp} \left(\psi \left(X_c(X_0,t) \right) \right) \cdot dt \text{ (ψ is linear)} \end{split}$$

We set
$$Y_0 \stackrel{\Delta}{=} \psi(X_0)$$
 and $Y_c \stackrel{\Delta}{=} \psi \circ X_c$.

Then we have:

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

Fluid trajectories



Fluid trajectories



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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



Internal state



 $\mathbf{R}(Y1 \sim u, |!1), \ \mathbf{E}(r!1) \longleftrightarrow \mathbf{R}(Y1 \sim p, |!1), \ \mathbf{E}(r!1)$

Don't care, Don't write



 \neq



Contact map



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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.

Embedding



We write $Z \triangleleft_{\Phi} Z'$ 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'.

Differential system

Let us consider a rule *rule*:

 $\textit{lhs} \rightarrow \textit{rhs}$ 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 $C_i \triangleleft_{\Phi i} r_i$.
- 3. The ground instantiation can be written as follows:

 $r_1,\ldots,r_m \rightarrow p_1,\ldots,p_n$ k.

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

$$\textit{act}_{(r_i,\Phi i)} = \frac{k \cdot \prod [r_i]}{\sharp \{ \Phi \mid \textit{lhs} \lhd_{\Phi} \textit{lhs} \}}.$$

5. Each ground instantiation induces the following contributions:

$$\frac{d[r_i]}{dt} \stackrel{+}{=} -act_{(r_i,\Phi_i)}, \quad \frac{d[p_i]}{dt} \stackrel{+}{=} act_{(r_i,\Phi_i)}.$$

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 - (c) Abstract counterpart

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Abstract domain

We are looking for suitable pair $(\mathcal{V}^{\sharp}, \psi)$ (such that \mathbb{F}^{\sharp} exists)

The set of linear variable changement is too big to be explored.

We introduce a specific shape on $(\mathcal{V}^{\sharp}, \psi)$ so as:

- restrict the exploration;
- drive the intuition;
- having efficient way to find suitable abstractions $(\mathcal{V}^{\sharp},\psi)$ and to compute $\mathbb{F}^{\sharp}.$

Our choice might be not optimal, but we can live with that.

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.



Annotated contact map

















Basic properties

The set of fragments enjoys two convenient properties:

- 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 \mathbb{F}^{\ddagger} can be defined ?

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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.

Fragments consumption Proper intersection



Whenever a fragment intersects a connected component of a lhs on a modified site, then the connected component must be embedded in the fragment!

Fragment consumption Syntactic criteria



We reflect each path that stems from a modified site (in the lhs of a rule) into the annotated contact map.

Connected components



We need to express the "concentration" of any connected component of a lhs with respect to the "concentration" of fragments.

Connected components Sub-fragment



Each connected component of a lhs must be a sub-fragment.

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Connected components Syntactic criteria



Fragments production



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

Fragments production Proper intersection (bis)



Yes, if the connected components of the lhs of the refinement are subfragments, which is already ensured by previous syntactic criteria.

Fragment properties

lf:

- an annotated contact map satisfies the syntactic criteria,
- fragments are defined by this annotated contact map,
- we know the concentration of fragments;

then:

- we can express the concentration of any connected component occuring in lhss,
- we can express fragment proper consumption,
- we can express fragment proper production (eg. see the LICS'2010 paper),
- WE HAVE A CONSTRUCTIVE DEFINITION FOR \mathbb{F}^{\sharp} .

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A binding rule

Let us abstract the contribution of a binding rule:



A binding rule: reactants



For any (F, Φ) such that $C_i \triangleleft_{\Phi} F$,

$$\frac{\mathrm{d}[\mathrm{F}]}{\mathrm{d}\mathrm{t}} \stackrel{+}{=} -\frac{\mathbf{k} \cdot [\mathrm{F}] \cdot [\mathrm{C}_{3-\mathrm{i}}]}{\sharp \{\Phi' \mid \mathrm{C}_1, \mathrm{C}_2 \triangleleft_{\Phi'} \mathrm{C}_1, \mathrm{C}_2\}}.$$

Binding rules: products



If the edge is solid, for any (F_1, Φ_1) and (F_2, Φ_2) , such that $C_1 \triangleleft_{\Phi_1} F_1$ and $C_2 \triangleleft_{\Phi_2} F_2$,

$$\frac{d[F_1 - F_2]}{dt} = \frac{k \cdot [F_1] \cdot [F_2]}{\sharp \{ \Phi' \mid C_1, C_2 \triangleleft_{\Phi'} C_1, C_2 \}}$$

Binding rules: products



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

$$\frac{\mathrm{d}[\mathrm{F}-]}{\mathrm{d}\mathrm{t}} \stackrel{+}{=} \frac{\mathrm{k} \cdot [\mathrm{F}] \cdot [\mathrm{C}_{3-\mathrm{i}}]}{\sharp \{\Phi' \mid \mathrm{C}_1, \mathrm{C}_2 \triangleleft_{\Phi'} \mathrm{C}_1, \mathrm{C}_2\}}.$$
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Experimental results

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



Superposition of the ground and the abstract differential semantics.

On a bigger example, $\approx 2 \cdot 10^{19}$ species are simplified into $\approx 2 \cdot 10^5$ fragments.

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Related issues I: Semantics comparisons



Related issues 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 ?

Joint work with Ferdinanda Camporesi (Bologna)

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

Joint work with Tatjana Petrov and Heinz Koeppl (EPFL)

Announcements

• Call for candidates:

If you are interested in (at least one) of these issues, there are open positions (Internships, PhD students or Post-doc fellows)...

ANR-Chair of Excellence: AbstractCell http://www.di.ens.fr/~feret/abstractcell

• Call for paper/participation:

First Workshop on Static Analysis and Systems Biology (SASB 2010) (co-chaired with Andre Levchenko) 13th Sept 2010, Perpignan http://www.di.ens.fr/sasb2010