Groupe de Travail
Modélisation, Optimisation, et Analyse Statique

Formal model reduction
[PNAS'09, LICS'10, MFPS'10, Chaos'10, MFPS'11]

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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
Bridge the gap between...

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

Oda, Matsuoka, Funahashi, Kitano, Molecular Systems Biology, 2005
Rule-based models

Interaction map

CTMC

ODEs

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

- **number of instances per molecular species**
  - $10^6$
  - 1000
  - 100

- **number of molecular species**
  - 400
  - 80,000
  - 500,000
  - $10^{33}$

- **Combinatorial Wall**
- **Deterministic Differential Equations**
- **Stochastic Master Equations**
- **Agent/rule-based**
- **Event Wall**

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Jérôme Feret

8th January 2013
A breach in the wall(s)?
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A simple adapter

A

B

C
A simple adapter

A, \emptyset B \emptyset \leftrightarrow AB \emptyset \quad k^{AB},k_d^{AB}

A, \emptyset BC \leftrightarrow ABC \quad k^{AB},k_d^{AB}

\emptyset B \emptyset, C \leftrightarrow \emptyset BC \quad k^{BC},k_d^{BC}

AB \emptyset, C \leftrightarrow ABC \quad k^{BC},k_d^{BC}
A simple adapter

\[
\begin{align*}
\frac{d[A]}{dt} &= k^{AB}_d \cdot [AB\emptyset] + k^{AB}_d \cdot [ABC] - k^{AB}_d \cdot [A] \cdot [B\emptyset] - k^{AB}_d \cdot [A] \cdot [BC] \\
\frac{d[C]}{dt} &= k^{BC}_d \cdot ([\emptyset BC] + [ABC]) - [C] \cdot k^{BC}_d \cdot ([\emptyset B\emptyset] + [AB\emptyset]) \\
\frac{d[\emptyset B\emptyset]}{dt} &= k^{AB}_d \cdot [AB\emptyset] + k^{BC}_d \cdot [\emptyset BC] - k^{AB}_d \cdot [A] \cdot [B\emptyset] - k^{BC}_d \cdot [\emptyset B\emptyset] \cdot [C] \\
\frac{d[AB\emptyset]}{dt} &= k^{AB}_d \cdot [A] \cdot [B\emptyset] + k^{BC}_d \cdot [ABC] - k^{AB}_d \cdot [AB\emptyset] - k^{BC}_d \cdot [AB\emptyset] \cdot [C] \\
\frac{d[\emptyset BC]}{dt} &= k^{AB}_d \cdot [ABC] + k^{BC}_d \cdot [C] \cdot [B\emptyset] - [\emptyset BC] \cdot (k^{BC}_d + [A] \cdot k^{AB}_d) \\
\frac{d[ABC]}{dt} &= k^{AB}_d \cdot [A] \cdot [BC] + k^{BC}_d \cdot [C] \cdot [AB\emptyset] - [ABC] \cdot (k^{AB}_d + k^{BC}_d)
\end{align*}
\]
A simple adapter

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

A

B

C
Two subsystems

A

B

B

C
Two subsystems

\[
[A] = [A] \\
[AB?] \triangleq [AB\emptyset] + [ABC] \\
[\emptyset B?] \triangleq [\emptyset B\emptyset] + [\emptyset BC]
\]

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

\[
[C] = [C] \\
[?BC] \triangleq [\emptyset BC] + [ABC] \\
[?B\emptyset] \triangleq [\emptyset B\emptyset] + [AB\emptyset]
\]

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

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

\[
\frac{[ABC]}{[?BC]} = \frac{[AB?]}{[\emptyset B?] + [AB?]}.
\]

Thus we define the dependence index as follows:

\[
\Delta X = [ABC] \cdot ([\emptyset B?] + [AB?]) - [AB?] \cdot [?BC].
\]

We have (after a short computation):

\[
\frac{dX}{dt} = -X \cdot ([A] \cdot k_{AB} + k_{AB} + [C] \cdot k_{BC} + k_{BC}).
\]

So the property:

\[
\frac{[ABC]}{[?BC]} = \frac{[AB?]}{[\emptyset B?] + [AB?]}.\]

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

\[
\begin{align*}
(u,u,u) & \rightarrow (u,p,u) & k^c \\
(u,p,u) & \rightarrow (p,p,u) & k^l \\
(u,p,p) & \rightarrow (p,p,p) & k^l \\
(u,p,u) & \rightarrow (u,p,p) & k^r \\
(p,p,u) & \rightarrow (p,p,p) & k^r
\end{align*}
\]
A system with a switch

\[
\begin{align*}
(u,u,u) & \rightarrow (u,p,u) & k^c \\
(u,p,u) & \rightarrow (p,p,u) & k^l \\
(u,p,p) & \rightarrow (p,p,p) & k^l \\
(u,p,u) & \rightarrow (u,p,p) & k^r \\
(p,p,u) & \rightarrow (p,p,p) & k^r
\end{align*}
\]

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

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

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

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

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

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

Thus we define the dependence index as follows:

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

We have:

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

So the property \((X = 0)\) is not an invariant.
Concentrations evolution with respect to time \((\[(u,u,u)\](0) = 200)\). 
\[
25 \cdot \left( \frac{\((p,p,p)\) - \((p,p,?),(? ,p,p)\)}{\((? ,p,?)\)} \right)
\]
We can use the absence of flow of information to cut chemical species into self-consistent fragments of chemical species:

− some information is abstracted away:
  we cannot recover the concentration of any species;

+ flow of information is easy to abstract;

We are going to track the correlations that are read by the system.
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A model with symmetries

\[ P \rightarrow *P \quad k_1 \]
\[ P \rightarrow P^* \quad k_1 \]
\[ P^* \rightarrow *P^* \quad k_1 \]
\[ *P \rightarrow *P^* \quad k_1 \]

\[ *P^* \rightarrow \emptyset \quad k_2 \]

\[ k_1 \]

\[ k_2 \]
Reduced model

\[ P \rightarrow *P \quad 2 \cdot k_1 \]

\[ *P \rightarrow *P^* \quad k_1 \]

\[ *P^* \rightarrow \emptyset \quad k_2 \]
Differential equations

• Initial system:

\[
\begin{align*}
\frac{d}{dt} \begin{bmatrix} [P] \\
[*P] \\
[P^*] \\
[*P^*] \end{bmatrix} &= \begin{bmatrix} -2 \cdot k_1 & 0 & 0 & 0 \\
0 & k_1 & -k_1 & 0 \\
0 & 0 & k_1 & 0 \\
0 & k_1 & 0 & -k_2 \end{bmatrix} \cdot \begin{bmatrix} [P] \\
[*P] \\
[P^*] \\
[*P^*] \end{bmatrix}
\end{align*}
\]

• Reduced system:

\[
\begin{align*}
\frac{d}{dt} \begin{bmatrix} [P] \\
[*P] + [P^*] \\
0 \\
[*P^*] \end{bmatrix} &= \begin{bmatrix} -2 \cdot k_1 & 0 & 0 & 0 \\
2 \cdot k_1 & -k_1 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & k_1 & 0 \end{bmatrix} \cdot \begin{bmatrix} [P] \\
[*P] + [P^*] \\
0 \\
[*P^*] \end{bmatrix}
\end{align*}
\]
We wonder whether or not:

\[ *[\text{P}] = [\text{P}^*], \]

Thus we define the difference \( X \) as follows:

\[ X \overset{\Delta}{=} *[\text{P}] - [\text{P}^*]. \]

We have:

\[ \frac{dX}{dt} = -k_1 \cdot X. \]

So the property \( (X = 0) \) is an invariant.

Thus, if \( *[\text{P}] = [\text{P}^*] \) at time \( t = 0 \), then \( *[\text{P}] = [\text{P}^*] \) forever.
Conclusion

We can abstract away the distinction between chemical species which are equivalent up to symmetries (with respect to the reactions).

1. If the symmetries are satisfied in the initial state:
   + the abstraction is invertible:
     we can recover the concentration of any species,
     (thanks to the invariants).

2. Otherwise:
   – some information is abstracted away:
     we cannot recover the concentration of any species;
   + the system converges to a state which satisfies the symmetries.
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Differential semantics

Let $\mathcal{V}$, be a finite set of variables; and $F$, be a $\mathcal{C}^\infty$ mapping from $\mathcal{V} \rightarrow \mathbb{R}^+$ into $\mathcal{V} \rightarrow \mathbb{R}$, as for instance,

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

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

The differential semantics maps each initial state $X_0 \in \mathcal{V} \rightarrow \mathbb{R}^+$ to the maximal solution $X_{X_0} \in [0, T_{X_0}^{\max}] \rightarrow (\mathcal{V} \rightarrow \mathbb{R}^+)$ which satisfies:

$$X_{X_0}(T) = X_0 + \int_{t=0}^{T} F(X_{X_0}(t)) \cdot dt.$$
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Abstraction

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

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

such that:

- \(\psi\) is linear with positive coefficients,
- the following diagram commutes:

\[
\begin{array}{ccc}
\mathcal{V} \to \mathbb{R}^+ & \xrightarrow{F} & \mathcal{V} \to \mathbb{R} \\
\psi \downarrow \ell^* & & \downarrow \ell^* \\
\mathcal{V}^\# \to \mathbb{R}^+ & \xrightarrow{F^\#} & \mathcal{V}^\# \to \mathbb{R}
\end{array}
\]

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

- for any sequence \((x_n) \in (\mathcal{V} \to \mathbb{R}^+)^\mathbb{N}\) such that \(||x_n||\) diverges towards \(+\infty\), then \(||\psi(x_n)||^\#\) diverges as well (for arbitrary norms \(||\cdot||\) and \(||\cdot||^\#\)).
Abstraction example

\begin{itemize}
  \item \( \mathcal{V}^\Delta \equiv \{[[u,u,u]],[[u,p,u]],[[p,p,u]],[[u,p,p]],[[p,p,p]]\} \)
  \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]]) \\
    [[u,p,p]] & \mapsto -k_l \cdot \rho([[u,p,p]]) + k_r \cdot \rho([[u,u,u]]) - k_r \cdot \rho([[u,p,u]]) \ldots
  \end{align*}
  \item \( \mathcal{V}^\sharp^\Delta \equiv \{[[u,u,u]],[[?,p,u]],[[?,p,p]],[[u,p,?]],[[p,p,?]]\} \)
  \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]]) \ldots
  \end{align*}
  \item \( \mathcal{F}(\rho) \equiv \{[[u,u,u]],[[u,p,u]],[[u,p,p]],[[p,p,u]],[[p,p,p]]\} \)
  \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]]) \\
    [[u,p,p]] & \mapsto -k_l \cdot \rho([[u,p,p]]) + k_r \cdot \rho([[u,u,u]]) - k_r \cdot \rho([[u,p,u]]) \ldots
  \end{align*}
  \item \( \mathcal{F}(\rho) \equiv \{[[u,u,u]],[[?,p,u]],[[?,p,p]],[[u,p,?]],[[p,p,?]]\} \)
  \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]]) \ldots
  \end{align*}
  \item \( \psi(\rho) \equiv \{[[u,u,u]],[[u,p,u]],[[u,p,p]],[[p,p,u],[[p,p,p]]\} \)
  \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]]) \\
    [[u,p,p]] & \mapsto k_r \cdot \rho([[u,p,p]]) - k_r \cdot \rho([[u,u,u]]) \ldots
  \end{align*}
  \item \( \psi(\rho) \equiv \{[[u,u,u]],[[?,p,u]],[[?,p,p]],[[u,p,?]],[[p,p,?]]\} \)
  \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]]) \ldots
  \end{align*}
\end{itemize}

(Completeness can be checked analytically.)
Abstract differential semantics

Let \((\mathcal{V}, \mathcal{F})\) be a concrete system.
Let \((\mathcal{V}^\#, \psi, \mathcal{F}^\#)\) be an abstraction of the concrete system \((\mathcal{V}, \mathcal{F})\).
Let \(X_0 \in \mathcal{V} \rightarrow \mathbb{R}^+\) be an initial (concrete) state.

We know that the following system:

\[
Y_{\psi(X_0)}(T) = \psi(X_0) + \int_{t=0}^{T} \mathcal{F}^\# \left( Y_{\psi(X_0)}(t) \right) \cdot dt
\]

has a unique maximal solution \(Y_{\psi(X_0)}\) such that \(Y_{\psi(X_0)} = \psi(X_0)\).

**Theorem 1** Moreover, this solution is the projection of the maximal solution \(X_{X_0}\) of the system

\[
X_{X_0}(T) = X_0 + \int_{t=0}^{T} \mathcal{F} \left( X_{X_0}(t) \right) \cdot dt.
\]

(i.e. \(Y_{\psi(X_0)} = \psi(X_{X_0})\))
Abstract differential semantics

Proof sketch

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

\[
X_{X_0}(T) = X_0 + \int_{t=0}^{T} F^\#(X_{X_0}(t)) \cdot dt
\]

\[
\psi\left(X_{X_0}(T)\right) = \psi\left(X_0 + \int_{t=0}^{T} F^\#(X_{X_0}(t)) \cdot dt\right)
\]

\[
\psi\left(X_{X_0}(T)\right) = \psi(X_0) + \int_{t=0}^{T} [\psi \circ F^\#](X_{X_0}(t)) \cdot dt \quad (\psi \text{ is linear})
\]

\[
\psi\left(X_{X_0}(T)\right) = \psi(X_0) + \int_{t=0}^{T} F^\#(\psi(X_{X_0}(t))) \cdot dt \quad (F^\# \text{ is } \psi\text{-complete})
\]

We set \(Y_0 \triangleq \psi(X_0)\) and \(Y_{Y_0} \triangleq \psi \circ X_{X_0}\).

Then we have:

\[
Y_{Y_0}(T) = Y_0 + \int_{t=0}^{T} F^\#(Y_{Y_0}(t)) \cdot dt
\]

The assumption about \(|| \cdot ||, || \cdot ||^\#\), and \(\psi\) ensures that \(\psi \circ X_{X_0}\) is a maximal solution.
Fluid trajectories
Fluid trajectories

Y(t)
X(t)
t
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A model with symmetries

\[ k_1 \]

\[ P \rightarrow \star P \quad k_1 \]
\[ P \rightarrow P^* \quad k_1 \]
\[ P^* \rightarrow \star P^* \quad k_1 \]
\[ *P \rightarrow *P^* \quad k_1 \]

\[ k_2 \]

\[ *P^* \rightarrow \emptyset \quad k_2 \]
Differential equations

- Initial system:

\[
\frac{d}{dt} \begin{bmatrix} [P] \\ [*P] \\ [P^*] \\ [*P^*] \end{bmatrix} = \begin{bmatrix} -2 \cdot k_1 & 0 & 0 & 0 \\ k_1 & -k_1 & 0 & 0 \\ k_1 & 0 & -k_1 & 0 \\ 0 & k_1 & k_1 & -k_2 \end{bmatrix} \cdot \begin{bmatrix} [P] \\ [*P] \\ [P^*] \\ [*P^*] \end{bmatrix}
\]

- Reduced system:

\[
\frac{d}{dt} \begin{bmatrix} [P] \\ [*P] + [P^*] \\ 0 \\ [*P^*] \end{bmatrix} = \begin{bmatrix} -2 \cdot k_1 & 0 & 0 & 0 \\ 2 \cdot k_1 & -k_1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & k_1 & 0 & -k_2 \end{bmatrix} \cdot \begin{bmatrix} [P] \\ [*P] + [P^*] \\ 0 \\ [*P^*] \end{bmatrix}
\]
Differential equations

• Initial system:

\[
\frac{d}{dt} \begin{bmatrix} [P] \\ [*P] \\ [P^*] \\ [*P^*] \end{bmatrix} = \begin{bmatrix} -2 \cdot k_1 & 0 & 0 & 0 \\ k_1 & -k_1 & 0 & 0 \\ k_1 & 0 & -k_1 & 0 \\ 0 & k_1 & k_1 & -k_2 \end{bmatrix} \cdot \begin{bmatrix} [P] \\ [*P] \\ [P^*] \\ [*P^*] \end{bmatrix}
\]

• Reduced system:

\[
\frac{d}{dt} \begin{bmatrix} [P] \\ [*P] + [P^*] \\ 0 \\ [*P^*] \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \cdot \begin{bmatrix} -2 \cdot k_1 & 0 & 0 & 0 \\ k_1 & -k_1 & 0 & 0 \\ k_1 & 0 & -k_1 & 0 \\ 0 & k_1 & k_1 & -k_2 \end{bmatrix} \cdot \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \cdot \begin{bmatrix} [P] \\ [*P] + [P^*] \\ 0 \\ [*P^*] \end{bmatrix}
\]
Let \( r \) be an idempotent mapping from \( \mathcal{V} \) to \( \mathcal{V} \).

We define two linear projections \( P_r, Z_r \in (\mathcal{V} \to \mathbb{R}^+) \to (\mathcal{V} \to \mathbb{R}^+) \) by:

\[
\begin{align*}
\bullet \quad P_r(\rho)(V) &= \begin{cases} 
\sum \{\rho(V') \mid r(V') = r(V)\} & \text{when } V = r(V) \\
0 & \text{when } V \neq r(V)
\end{cases} \\
\bullet \quad Z_r(\rho) &= \begin{cases} 
V \mapsto \rho(V) & \text{when } V = r(V) \\
V \mapsto 0 & \text{when } V \neq r(V)
\end{cases}
\end{align*}
\]

We notice that the following diagram commutes:
Induced bisimulation

The mapping $r$ induces a bisimulation,
\[ \Delta \iff \text{for any } \sigma, \sigma' \in \mathcal{V} \rightarrow \mathbb{R}^+, \ P_r(\sigma) = P_r(\sigma') \implies P_r(F(\sigma)) = P_r(F(\sigma')). \]

Indeed the mapping $r$ induces a bisimulation,
\[ \iff \text{for any } \sigma \in \mathcal{V} \rightarrow \mathbb{R}^+, \ P_r(F(\sigma)) = P_r(F(P_r(\sigma))). \]
Induced abstraction

Under these assumptions \((r(V), P_r, P_r \circ F \circ Z_r)\) is an abstraction of \((V, F)\), as proved in the following commutative diagram:
Overview

1. Context and motivations
2. Handmade ODEs
3. Abstract interpretation framework
   (a) Concrete semantics
   (b) Abstraction
   (c) Bisimulation
   (d) Combination
4. Kappa
5. Concrete semantics
6. Abstract semantics
7. Conclusion
Abstract projection

We assume that we are given:

- a concrete system \((V, F)\);
- an abstraction \((V^\#, \psi, F^\#)\) of \((V, F)\) (I);
- an idempotent mapping \(r\) over \(V\) which induces a bisimulation (II);
- an idempotent mapping \(r^\#\) over \(V^\#\) (III);

such that: \(\psi \circ P_r = P_{r^\#} \circ \psi\) (IV).
Combination of abstractions

Under these assumptions, \((r^\#(V^\#), P_{r^\#} \circ \psi, P_{r^\#} \circ F^\# \circ Z_{r^\#})\) is an abstraction of \((V, F)\), as proved in the following commutative diagram:
Overview

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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

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

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

\[ R(Y_1 \sim u, r!_) \rightarrow R(Y_1 \sim p, r) \]
Creation/Suppression

\[ R(r) \rightarrow R(r!1), R(r!1,l,Y1) \]

\[ R(r!1), R(r!1) \rightarrow R(r) \]
Overview

1. Context and motivations
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We say that $\Phi$ is an embedding between $Z$ and $Z'$ iff:

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

Each rule *rule: lhs → rhs* is associated with a rate constant $k$.

Such a rule is seen as a generic representation of a set of chemical reactions:

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

For each such reaction, we get the following contribution:

$$\frac{d[r_i]}{dt} = k \cdot \frac{\prod [r_i]}{\text{SYM}(\text{lhs})}$$  

and

$$\frac{d[p_i]}{dt} = k \cdot \frac{\prod [r_i]}{\text{SYM}(\text{lhs})}.$$  

where $\text{SYM}(E)$ is the number of automorphisms in $E$. 

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Overview

1. Context and motivations
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   (a) Fragments
   (b) Flow of information
   (c) Abstract counterpart
7. Conclusion
Abstract domain

We are looking for suitable pair \((V^\sharp, \psi)\) (such that \(F^\sharp\) exists).

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

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

- restrict the exploration;
- drive the intuition (by using the flow of information);
- having efficient way to find suitable abstractions \((V^\sharp, \psi)\) and to compute \(F^\sharp\).

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

G
Sh
So

E

R

Y_{68}

Y_{48}

b

a

d

Y_7

pi

r

l

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8th January 2013
Annotated contact map
Fragments and prefragments

A prefragment is a connected site graph for which there exists a binary relations $\rightarrow$ between sites such that:

- **Directed preorder**: for any pair of sites $x$ and $y$ there is a site $z$ such that: $x \rightarrow *z$ and $y \rightarrow *z$.

- **Compatibility**: any edge $\rightarrow$ can be projected to an edge in the annotated contact map.

A fragment is a prefragment $F$ such that:

- **Parsimoniousness**: for any prefragment $F'$ such that $F$ embeds in $F'$, $F'$ also embeds into $F$. 

---

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Are they fragments?
Are they fragments?
Are they fragments?

Thus, it is a prefragment.
Are they fragments?

It is maximally specified. Thus it is a fragment.
Are they fragments?

Thus, it is a prefragment.
Are they fragments?

Thus, it is a prefragment.
Are they fragments?

It can be refined into another prefragment. Thus, it is not a fragment.
Are they fragments?
Are they fragments?

Thus, it is a prefragment.
Are they fragments?

It can be refined into another prefragment. Thus, it is not a fragment.
Are they fragments?

Thus, it is a prefragment.

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Are they fragments?

Thus, it is a prefragment.
Are they fragments?

It is maximally specified. Thus it is a fragment.
Are they fragments?

Yes

No

Yes

No

Yes
What if we were adding this flow?
Are they fragments?

**stage 2**

There is no way to make a path from the first $Y_{68}$ and the second one or to make a path from the second one to the first one. Thus it is not even a prefragment.
There is no way to make a path from the first $Y_{68}$ and the second one or to make a path from the second one to the first one.

Thus it is not even a prefragment.
Are they fragments?

stage 2

There is no way to refine it, while preserving the directedness. Thus it is a fragment.
Are they fragments?

stage 2

Thus it is a prefragment.
Are they fragments?

stage 2

There is no way to refine it, while preserving the directedness.

Thus it is a fragment.
Basic properties

Property 1 (prefragment) The concentration of any prefragment can be expressed as a linear combination of the concentration of some fragments.

We consider two norms $|| \cdot ||$ on $\mathcal{V} \rightarrow \mathbb{R}^+$ and $|| \cdot ||^\#$ on $\mathcal{V}^\# \rightarrow \mathbb{R}^+$.

Property 2 (non-degenerescence) Given a sequence of valuations $(x_n)_{n \in \mathbb{N}} \in (\mathcal{V} \rightarrow \mathbb{R}^+)\mathbb{N}$ such that $||x_n||$ diverges toward $+\infty$, then $||\phi(x_n)||^\#$ diverges toward $+\infty$ as well.

Which other properties do we need so that the function $\mathbb{F}^\#$ can be defined?
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7. Conclusion
We reflect, in the annotated contact map, each path that stems from a site that is tested to a site that is modified.
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7. Conclusion
Whenever a fragment intersects a connected component of a lhs on a modified site, then the connected component must be embedded in the fragment!
For any rule:

\[\text{rule} : \ C_1, \ldots, C_n \rightarrow \text{rhs} \quad k\]

and any embedding between a modified connected component \(C_k\) and a fragment \(F\), we get:

\[
\frac{d[F]}{dt} = \frac{k \cdot [F] \cdot \prod_{i \neq k} [C_i]}{\text{SYM}(C_1, \ldots, C_n) \cdot \text{SYM}(F)}.
\]
Any connected component of the lhs of the refinement is prefragments.

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Any connected component of the lhs of the refinement is prefragments.
For any rule:

\[ \text{rule} : \ C_1, \ldots, C_m \rightarrow \text{rhs} \quad k \]

and any overlap between a fragment \( F \) and \( \text{rhs} \) on a modified site, we write \( C'_1, \ldots, C'_n \) the lhs of the refined rule.

We get:

\[
\frac{d[F]}{dt} = \frac{k \cdot \prod_i [C'_i]}{\text{SYM}(C_1, \ldots, C_m) \cdot \text{SYM}(F)}.
\]
Overview

1. Context and motivations
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## Experimental results

<table>
<thead>
<tr>
<th>Model</th>
<th>early EGF</th>
<th>EGF/Insulin</th>
<th>SFB</th>
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<td>#species</td>
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<td>2899</td>
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<tr>
<td>#fragments (ODEs)</td>
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<td>208</td>
<td>$\sim 2.10^5$</td>
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<tr>
<td>#fragments (CTMC)</td>
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<td>618</td>
<td>$\sim 2.10^{19}$</td>
</tr>
</tbody>
</table>

Both differential semantics
(4 curves with match pairwise)

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Related issues

1. Model reduction of the ODE semantics:
   Joint work with Ferdinanda Camporesi
   • Less syntactic approximation of the flow of information
   • A hierarchy of abstractions tuned by the level of context-sensitivity

2. Model reduction of the stochastic semantics:
   Joint work with Thomas Henzinger, Heinz Koeppl, Tatjana Petrov
   • a framework that preserves the trace distribution
     (lumpability, backward bisimulation, equiprobability of equivalent concrete configurations)
   • Compositionality of the framework
   • Symmetry reduction
SASB 2013

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Seattle, USA

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• Andre Levchenko.

Keynote speakers:
• Eric Deeds,
• ...