Reduction of models of intra-cellular signalling pathways

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Friday, the 20th of November, 2020
On the menu today

1. Context and motivations
2. Case studies
3. Reduction of ordinary differential equations
4. Abstraction of the information flow
5. Model reduction
6. Conclusion
Intra-cellular 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
Interaction maps

Oda et al, 2005
Models of the behaviour of the system

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

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

knowledge representation and models of the behaviour of systems
Site-graphs rewriting

- a language close to knowledge representation;
- rules are easy to update;
- a compact description of models.
Choices of semantics

interaction map

Markov chain

ordinary differential equations

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

concrete semantics

causal traces

information flow

exact projection of the ODE semantics
Contact map
Causal traces
ODE semantics

EGF pathway (reduced ODEs)

Concentration

Time

long
short
sos recruited
Causal traces
A potential breach
A potential breach
On the menu today

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6. Conclusion
Case study
Case study
Law of mass action

We consider that chemical species are elementary particles without any volume, and that they are diffusing in an infinite, perfectly fluid and homogeneous medium without borders.
Let $\mathcal{X}$ be a set of chemical species.
A reaction network is a set of reactions $\mathcal{R}$.
Each reaction $r$ is defined by:
1. $\alpha_r$, a function from $X$ to $\mathbb{N}$ (the reactants);
2. $\beta_r$, a function from $X$ to $\mathbb{N}$ (the products);
3. $k_r$, a non negative real number (the kinetic rate).

With these notations, the law of mass action defines the behaviour of the concentration $[X]$ of each chemical species $X$:

$$\frac{d[X]}{dt} = \sum_{r \in \mathcal{R}} k_r \cdot (\beta_r(X) - \alpha_r(X)) \cdot \prod_{X' \in \mathcal{X}} [X']^{\alpha_r(X')}.$$
Case study

\[
\begin{align*}
\frac{d[(u,u,u)]}{dt} &= -k_c[(u,u,u)] \\
\frac{d[(u,p,u)]}{dt} &= k_c[(u,u,u)]
\end{align*}
\]
\[
\begin{align*}
\frac{d[(u,u,u)]}{dt} &= -k_c \cdot [(u,u,u)] \\
\frac{d[(u,p,u)]}{dt} &= -k_g \cdot [(u,p,u)] + k_c \cdot [(u,u,u)] - k_d \cdot [(u,p,u)] \\
\frac{d[(u,p,p)]}{dt} &= -k_g \cdot [(u,p,p)] + k_d \cdot [(u,p,u)] \\
\frac{d[(p,p,u)]}{dt} &= k_g \cdot [(u,p,u)] - k_d \cdot [(p,p,u)] \\
\frac{d[(p,p,p)]}{dt} &= k_g \cdot [(u,p,p)] + k_d \cdot [(p,p,u)]
\end{align*}
\]
Case study
Case study
Case study

\[
\begin{align*}
[(u,u,u)] &= [(u,u,u)] \\
[(u,p,?)] &\xrightarrow{\Delta} [(u,p,u)] + [(u,p,p)] \\
[(p,p,?)] &\xrightarrow{\Delta} [(p,p,u)] + [(p,p,p)]
\end{align*}
\]

\[
\begin{cases}
\frac{d[(u,u,u)]}{dt} = -k_c \cdot [(u,u,u)] \\
\frac{d[(u,p,?)]}{dt} = -k_g \cdot [(u,p,?)] + k_c \cdot [(u,u,u)] \\
\frac{d[(p,p,?)]}{dt} = k_g \cdot [(u,p,?)]
\end{cases}
\]
What we have learned so far:

We can use the absence of information flow to detect useless correlations between the states of sites in chemical species. We can use this to cut chemical species into fragments.

This transformation loses some information: we cannot compute the concentration of each chemical species anymore.
A model with symmetries

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

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

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

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

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

• Initial system:

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

• Reduced system:

\[
\frac{d}{dt} \begin{bmatrix}
P \\
P^* + P^* \\
0 \\
\end{bmatrix}
= \begin{bmatrix}
-2k_1 & 0 & 0 & 0 \\
2k_1 & -k_1 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & k_1 & 0 & -k_2 \\
\end{bmatrix}
\cdot
\begin{bmatrix}
P \\
P^* + P^* \\
0 \\
\end{bmatrix}
\]
We wonder whether or not:
\[[^*P] = [P^*],\]

Thus we define the difference \(X\) as follows:
\(X \triangleq [^*P] - [P^*].\)

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

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

Thus, if \([^*P] = [P^*]\) at time \(t = 0\), then \([^*P] = [P^*]\) 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

A system of ordinary differential equations is a pair \((\mathcal{V}, F)\) where:

- \(\mathcal{V}\) is a finite set of variables,
- \(F\) is a continuous function from \(\mathcal{V} \rightarrow \mathbb{R}^+\) to \(\mathcal{V} \rightarrow \mathbb{R}\).

Elements of \(\mathcal{V} \rightarrow \mathbb{R}^+\) are called states.

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

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

that is defined over the widest time interval as possible.
1. \( \mathcal{V} \stackrel{\Delta}{=} \{(u,u,u), (u,p,u), (p,p,u), (u,p,p), (p,p,p)\}, \)

2. \( F(\rho) \stackrel{\Delta}{=} \begin{cases} 
(u,u,u) \mapsto -k_c \cdot \rho((u,u,u)) \\
(u,p,u) \mapsto -k_g \cdot \rho((u,p,u)) + k_c \cdot \rho((u,u,u)) - k_d \cdot \rho((u,p,u)) \\
(u,p,p) \mapsto -k_g \cdot \rho((u,p,p)) + k_d \cdot \rho((u,p,u)) \\
(p,p,u) \mapsto k_g \cdot \rho((u,p,u)) - k_d \cdot \rho((p,p,u)) \\
(p,p,p) \mapsto k_g \cdot \rho((u,p,p)) + k_d \cdot \rho((p,p,u)).
\end{cases} \)
Abstraction

An abstraction is a 5-uple \((\mathcal{V}, \mathbb{F}, \mathcal{V}^{\#}, \psi, \mathbb{F}^{\#})\), where:

- \((\mathcal{V}, \mathbb{F})\) is a system of ordinary equations,
- \(\mathcal{V}^{\#}\) is a finite set of observables,
- \(\psi\) is a function from the set \(\mathcal{V} \rightarrow \mathbb{R}\) into the set \(\mathcal{V}^{\#} \rightarrow \mathbb{R}\),
- \(\mathbb{F}^{\#}\) is a function \(C^{\infty}\) from the set \(\mathcal{V}^{\#} \rightarrow \mathbb{R}^{+}\) into the set \(\mathcal{V}^{\#} \rightarrow \mathbb{R}\); such that:
  - \(\psi\) is linear with positive coefficients only and such that each variable \(v \in \mathcal{V}\) occurs in the image of at least one observable \(v^{\#} \in \mathcal{V}^{\#}\) with a non-zero coefficient;
  - the following diagram commutes:

\[
\begin{array}{ccc}
(\mathcal{V} \rightarrow \mathbb{R}^{+}) & \xrightarrow{\mathbb{F}} & (\mathcal{V} \rightarrow \mathbb{R}) \\
\downarrow \psi & & \downarrow \psi \\
(\mathcal{V}^{\#} \rightarrow \mathbb{R}^{+}) & \xrightarrow{\mathbb{F}^{\#}} & (\mathcal{V}^{\#} \rightarrow \mathbb{R})
\end{array}
\]

that is to say that \(\psi \circ \mathbb{F} = \mathbb{F}^{\#} \circ \psi\).
Back to the case study

1. \( \mathcal{V} \overset{\Delta}{=} \{[(u,u,u)], [(u,p,u)], [(p,p,u)], [(u,p,p)], [(p,p,p)]\} \)
   \[ [(u,u,u)] \mapsto -k_c \cdot \rho([(u,u,u)]) \]

2. \( \mathbb{F}(\rho) \overset{\Delta}{=} \left\{ \begin{array}{ll}
   [(u,p,u)] & \mapsto -k_g \cdot \rho([(u,p,u)]) + k_c \cdot \rho([(u,u,u)]) - k_d \cdot \rho([(u,p,u)]) \\
   [(u,p,p)] & \mapsto -k_g \cdot \rho([(u,p,p)]) + k_d \cdot \rho([(u,p,u)]) \\
   \ldots
   \end{array} \right. \]

3. \( \mathcal{V}^\sharp \overset{\Delta}{=} \{[(u,u,u)], [?(p,u)], [?(p,p)], [(u,p,?)], [(p,p,?)]\} \)
   \[ [(u,u,u)] \mapsto \rho([(u,u,u)]) \]

4. \( \psi(\rho) \overset{\Delta}{=} \left\{ \begin{array}{ll}
   [?(p,u)] & \mapsto \rho([(u,p,u)]) + \rho([(p,p,u)]) \\
   [?(p,p)] & \mapsto \rho([(u,p,p)]) + \rho([(p,p,p)]) \\
   \ldots
   \end{array} \right. \)

5. \( \mathbb{F}^\sharp(\rho^\sharp) \overset{\Delta}{=} \left\{ \begin{array}{ll}
   [(u,u,u)] & \mapsto -k_c \cdot \rho^\sharp([(u,u,u)]) \\
   [?(p,u)] & \mapsto -k_d \cdot \rho^\sharp([(p,u)]) + k_c \cdot \rho^\sharp([(u,u,u)]) \\
   [?(p,p)] & \mapsto k_d \cdot \rho^\sharp([(p,p)]) \\
   \ldots
   \end{array} \right. \)
Let us apply the abstraction function

Let:

1. \((V, F, V', \psi, F')\) be an abstraction,
2. and \(X_0 \in V \rightarrow \mathbb{R}^+\) be an initial state.

We have, at any time \(T\) within the time interval \([0, T_{X_0}^{\text{max}}]\):

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

So:

\[
\psi(X_{X_0}(T)) = \psi \left( X_0 + \int_{t=0}^{T} F(X_{X_0}(t)) \cdot dt \right).
\]
Let us push $\psi$ towards the right

Let:

1. $(\mathcal{V}, F, \mathcal{V}^\#, \psi, F^\#)$ be an abstraction,
2. and $X_0 \in \mathcal{V} \rightarrow \mathbb{R}^+$ be an initial state.

We have, at any time $T$ within the time interval $[0, T_{X_0}^\text{max}]$:

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

So:

$$\psi(X_{X_0}(T)) = \psi(X_0) + \psi \left( \int_{t=0}^{T} F(X_{X_0}(t)) \cdot dt \right).$$
Let us push \( \psi \) towards the right

Let:

1. \( (\mathcal{V}, F, \mathcal{V}^\sharp, \psi, F^\sharp) \) be an abstraction,
2. and \( X_0 \in \mathcal{V} \to \mathbb{R}^+ \) be an initial state.

We have, at any time \( T \) within the time interval \( [0, T_{X_0}^{\max}] \):

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

So:

\[
\psi(X_{X_0}(T)) = \psi(X_0) + \int_{t=0}^{T} [\psi \circ F](X_{X_0}(t)) \cdot dt.
\]
Let us push $\psi$ towards the right

Let:

1. $(\mathcal{V}, F, \mathcal{V}^\#, \psi, F^\#)$ be an abstraction,
2. and $X_0 \in \mathcal{V} \to \mathbb{R}^+$ be an initial state.

We have, at any time $T$ within the time interval $[0, T_{\max}^{X_0}]:$

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

So:

$$\psi(X_{X_0}(T)) = \psi(X_0) + \int_{t=0}^{T} [F^\# \circ \psi](X_{X_0}(t)) \cdot dt.$$
Let us push $\psi$ towards the right

Let:

1. $(\mathcal{V}, F, \mathcal{V}^\ast, \psi, F^\ast)$ be an abstraction,
2. and $X_0 \in \mathcal{V} \to \mathbb{R}^+$ be an initial state.

We have, at any time $T$ within the time interval $[0, T^\ast_{X_0}]$:

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

So:

$$\psi(X_{X_0}(T)) = \psi(X_0) + \int_{t=0}^{T} F^\ast(\psi(X_{X_0}(t))) \cdot dt.$$
Abstract semantics

Let \((\mathcal{V}, \mathcal{F}, \mathcal{V}^\#, \psi, \mathcal{F}^\#)\) be an abstraction. The couple \((\mathcal{V}^\#, \mathcal{F}^\#)\) is a system of differential equations. Let us denote by \(Y\) its semantics. For each state \(Y_0 \in \mathcal{V}^\# \rightarrow \mathbb{R}^+\), we denote by \([0, T_{\mathcal{X}_0}^{\#}\max]\) the domain of the function \(Y_{Y_0}\). We have, at any time \(T^\# \in [0, T_{\mathcal{X}_0}^{\#}\max]\),

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

**Theorem 1** For each initial state \(\mathcal{X}_0 \in \mathcal{V} \rightarrow \mathbb{R}^+\), we have:

1. \(T_{\psi(\mathcal{X}_0)}^{\#}\max = T_{\mathcal{X}_0}^{\#}\max\);
2. at any time \(T \in [0, T_{\mathcal{X}_0}^{\#}\max], \psi(\mathcal{X}_0(T)) = Y_{\psi(\mathcal{X}_0)}(T)\).

That is to say that the abstract semantics is the image of the concrete semantics by the abstraction function.
Abstract trajectories

\[ Y(t) \]

\[ t \]
Concrete trajectories
A model with symmetries

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

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

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

• Initial system:

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

• Reduced system:

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

- Initial system:

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

- Reduced system:

\[
\frac{d}{dt} \begin{bmatrix}
P \\
\star P + P^* \\
0 \\
\star P^*
\end{bmatrix} = \begin{bmatrix}
1 & 0 & 0 & 0 \\
0 & 1 & 1 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1
\end{bmatrix} \cdot \begin{bmatrix}
-2 \cdot k_1 & 0 & 0 & 0 \\
k_1 & -k_1 & 0 & 0 \\
k_1 & 0 & -k_1 & 0 \\
0 & k_1 & k_1 & -k_2
\end{bmatrix} \cdot \begin{bmatrix}
P \\
\star P + P^* \\
0 \\
\star P^*
\end{bmatrix}
\]
Pair of projections induced by an equivalence relation among variables

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:

- \( P_r(\rho)(V) = \begin{cases} \sum \{\rho(V') \mid r(V') = r(V)\} & \text{when } V = r(V) \\ 0 & \text{when } V \neq r(V) \end{cases} \)

- \( Z_r(\rho) = \begin{cases} V \mapsto \rho(V) & \text{when } V = r(V) \\ V \mapsto 0 & \text{when } V \neq r(V) \end{cases} \)

We notice that the following diagram commutes:

\[
\begin{array}{c}
P_r \quad \ell^*
\end{array}
\]

\[
\begin{array}{c}
\ell \\
\ell^*
\end{array}
\]

\[
\begin{array}{c}
P_r \\
Z_r
\end{array}
\]
Induced bisimulation

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

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

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

We assume that we are given:

- a concrete system \((\mathcal{V}, \mathcal{F})\);
- an abstraction \((\mathcal{V}^\#, \psi, \mathcal{F}^\#)\) of \((\mathcal{V}, \mathcal{F})\) (I);
- an idempotent mapping \(r\) over \(\mathcal{V}\) which induces a bisimulation (II);
- an idempotent mapping \(r^\#\) over \(\mathcal{V}^\#\) (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:
On the menu today

1. Context and motivations
2. Case studies
3. Reduction of ordinary differential equations
4. Abstraction of the information flow
5. Model reduction
6. Conclusion
Concrete semantics

A rule is a symbolic representation of a multi-set of reactions.

For instance, the rule:

\[
\text{psfrag replacemen ts}
\begin{align*}
\text{psfrag replacemen ts}
k & \text{d}
\end{align*}
\]

denotes the following two rules:

\[
\text{psfrag replacemen ts}
\begin{align*}
\text{psfrag replacemen ts}
k & \text{d}
\end{align*}
\]

The semantics of a set of rules is the semantics of the underlying multi-set of reactions.
Flow of information (in the concrete)

Does the state of a given site influence the capability to modify another site?
Flow of information (in the concrete)
Flow of information (in the concrete)

If there exists a soup of chemical species in which the activation rate of the site of ShC is different in these two contexts, then there may be a flow of information.
Discrimination by a rule

In this case, there exists a rule which makes a difference between these two contexts, for instance the following one:
Flow of information due to a rule
Flow of information due to a rule
Flow of information due to a rule
Flow of information due to a rule
Flow of information due to a rule
Projection on the contact map

EGFR

EGFR
Y68
Y48

ShC
pi
Y7

Grb2
a
b

Sos
d
Projection on the contact map

EGF

ShC

Grb2

Sos

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Projection on the contact map
Projection on the contact map
Projection on the contact map
Direct computation
Direct computation
Direct computation
Direct computation
Direct computation
On the menu today

1. Context and motivations
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6. Conclusion
Which patterns shall we keep?
Which patterns shall we keep?
Pattern annotation
Pattern annotation
**Definition 1 (prefragment)** A pattern is a prefragment if, in its annotated form, there exists a site that it is reachable from every site (following the flow of information).
Definition 2 (fragment) A fragment is a prefragment that cannot be embedded in any bigger prefragment.
Examples
Which patterns are fragments?
Examples: annotated map
Examples: pattern annotation

\[\text{EGF} \quad \text{EGFR} \quad \text{Y48} \quad \text{EGF} \quad \text{EGFR} \quad \text{Y68}\]

\[\text{ShC} \quad \pi \quad \text{Y7} \quad \text{Grb2} \quad \alpha \quad \beta \quad \text{Sos} \]

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Examples

Which patterns are prefragments?
Examples
Prefragments
Examples
Which patterns are fragments?
Examples
Fragments
Examples: fragments
Almost done... 

We are left to express the consumption and the production (in concentration) of each fragment as expressions of the concentration of fragments.

Firstly, we notice that the concentration of each prefragment can be expressed as a linear combination of the concentration of the fragments.
Whenever there is an overlap between a fragment and a connected component in the left hand side of a rule such that the common region contains a site that is modified by the rule, then the connected component embeds in the fragment.
Fragments consumption

Whenever there is an overlap between a fragment and a connected component in the left hand side of a rule such that the common region contains a site that is modified by the rule, then the connected component embeds in the fragment.
For each fragment $F$, for each rule:

$$r: C_1, \ldots, C_n \rightarrow rhs \quad k$$

and for each occurrence of a connected component $C_j$ that is modified by the rule, in the fragment $F$, we have the following contribution:

$$\frac{d[F]}{dt} = \frac{k \cdot [F] \cdot \prod_{i \neq j} [C_i]}{\text{SYM}[C_1, \ldots, C_n] \cdot \text{SYM}[F]}.$$
Whenever there is an overlap between a fragment and the right hand side of a rule, such that the common region contains a site that is modified by the rule.
Whenever there is an overlap between a fragment and the right hand side of a rule, such that the common region contains a site that is modified by the rule...
Fragments production

Whenever there is an overlap between a fragment and the right hand side of a rule such that the common region contains a site that is modified by the rule, each connected component in the left hand side of the refined rule, is a prefragment.
Fragment production

For each overlap $ch$ between a fragment and the right hand side of a rule, such that the common region contains a site that is modified by the rule:

$$r : C_1, \ldots, C_m \rightarrow \text{right hand side} \quad k,$$

we have the following contribution:

$$\frac{d[F]}{dt} \equiv \frac{k \cdot \prod_i [C'_i]}{\text{SYM}[C_1, \ldots, C_m] \cdot \text{SYM}[F]}.$$

where $C'_1, \ldots, C'_n$ is the left hand side of the refined rule.
On the menu today

1. Context and motivations
2. Case studies
3. Reduction of ordinary differential equations
4. Abstraction of the information flow
5. Model reduction
6. Conclusion
### Benchmark

<table>
<thead>
<tr>
<th>Model</th>
<th>early EGF</th>
<th>EGF/Insulin</th>
<th>SFB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of molecular species</td>
<td>356</td>
<td>2899</td>
<td>$\sim 2.10^{19}$</td>
</tr>
<tr>
<td>Number of fragments</td>
<td>38</td>
<td>208</td>
<td>$\sim 2.10^{5}$</td>
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<tr>
<td>(ODEs semantics)</td>
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<tr>
<td>Number of fragments</td>
<td>356</td>
<td>618</td>
<td>$\sim 2.10^{19}$</td>
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<td>(CTMC semantics)</td>
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</tbody>
</table>
In short
Abstraction of the information flow
Abstraction of the information flow
Patterns of interest
Patterns of interest
Related topics and acknowledgements

- Model reduction (ODEs semantics)
  Vincent Danos, Walter Fontana, Russ Harmer, Jean Krivine
- Context-sensitive abstraction of information flow
  Ferdinanda Camporesi
- Model reduction (CTMC semantics)
  Tatjana Petrov, Heinz Koeppl, Tom Henzinger
- Bisimulations metrics
  Norm Ferns.

“AbstractCell” (2009-2013)
“CwC” (2015-2018)
“TGFβSysBio” (2015-2018)