Abstract interpretation of protein-protein interactions networks

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Joint-work with...

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Signalling Pathways

EGF, TGF-alpha, etc

EGFR

PI3-K
AKT

phosphorylation

mTOR
STAT
GRB2
SOS
RAS
RAF
MEK
ERK

Gene transcription
Cell cycle progression

Cell proliferation
Inhibition of apoptosis
Angiogenesis
Migration, Adhesion, Invasion

Eikuch, 2007
Bridging the gap between... 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

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

![Diagram illustrating complexity walls in molecular species and instances per species.](image-url)
Abstractions offer different perspectives on models

concrete semantics

information flow

causal traces

exact projection of the ODE semantics
Static analysis of reachable species (I/II)

We capture the relationships between the states of the sites of each agent.
Static analysis of reachable species (I/II)

We capture the relationships between the states of the sites of each agent.
Static analysis of reachable species (II/II)

Applications:

1. check the consistency of a model [ICCMSE'07]
2. compute the properties to allow fast simulation [APLAS'07]
3. simplify models,
4. compute independent fragments of chemical species [PNAS'09, LICS'10, Chaos'10]

The analysis is complete (no false positive) for a significat kernel of Kappa [VMCAI'08].
Model reduction

The ground differential system uses one variable per chemical species; We directly compute its exact projection over independent fragments of chemical species.
With a small model, 356 chemical species are reduced into 38 fragments:

On a bigger model, $10^{19}$ chemical species are reduced into 180 000 fragments. [PNAS’09,LICS’10,Chaos’10]