Formal Modeling of Biological Systems With Delays

Ph.D. Research Seminar

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Systems Biology

An interdisciplinary field of research regarding:

- the study of the **interactions** between the **components** of *biological systems*, and how these interactions give **rise** to the function and behavior of that system.

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  - via observations / measurements / interactions with experts;
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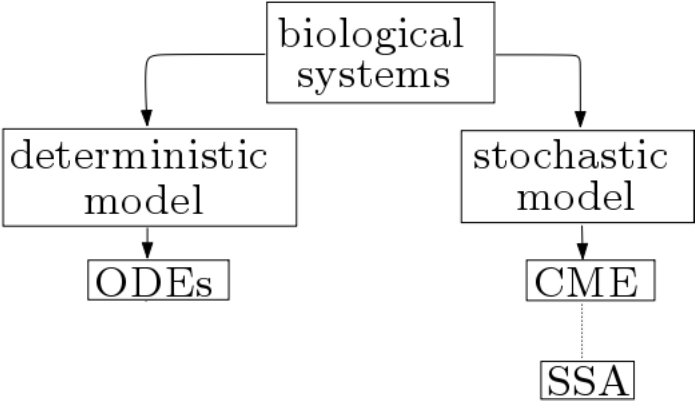
- models have to be analyzed:
  - via **simulation** (deterministic, stochastic);
  - model checking;

Systems Biology Workflow



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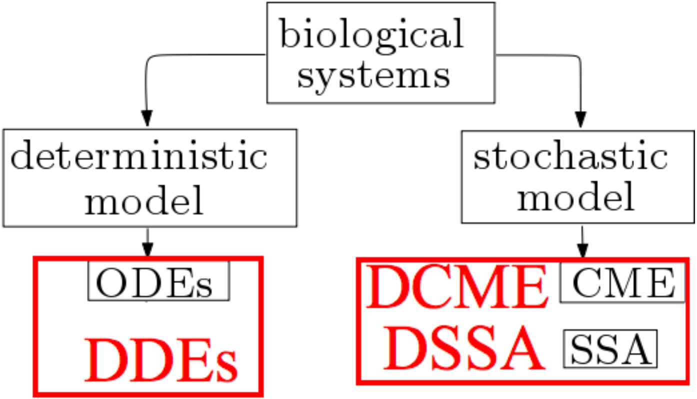
   - Use τ as a **semplification**.

Systems Biology Workflow (extended with delays)



This work needs to be done in two steps:

1. assest the framework for stochastic simulation (almost done);
2. embed delays in formal languages (started);

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Semantics of the application of a reaction transforming A and B in C with a delay τ:

- if $\tau = 0$, delete A and B, add C;
- if $\tau \neq 0$, two **policies**:
  - delete A and B and schedule the insertion of C at τ time units forward in time;
  - schedule the deletion of A and B and the insertion of C at τ time units forward in time;

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A process algebra with delays

Ideas inherited from biologically inspired calculi:

- each molecule is represented by a process;
- a chemical solution becomes a parallelization of processes;
- the firing of a reaction is modeled by a synchronization;
- processes can autonomously spend time;

The semantics provides the *interpretation* of the delays:

- by now, only the one referring to a specific interpretation of the delays;
- and it is not still stochastic (however, the construction of the CTMC is possible by starting from the LTS obtained).

A process algebra with delays: informal definitions

About the processes:

- $(a, \lambda, \sigma).P$ can perform action a with rate λ and delay σ and then becomes P;
- $[\ P\ ]^r$ waits r time units of time and then becomes P;
- classical notions of choice, parallel composition and recursion;

About the semantics:

- embedding the explicit notion of time and stochasticity is not trivial;
- transition system specification defined by rules in the De Simone format;

A process algebra with delays: the semantics

1. $$\frac{t \in \mathbb{R}^+}{(a,\lambda,\sigma).P \xrightarrow{t} (a,\lambda,\sigma).P}$$

2. $$\frac{}{(a,\lambda,\sigma).P \xrightarrow{(a,\lambda)} [\ P\ ]^{\sigma}}$$

3. $$\frac{t < \sigma}{[\ P\ ]^{\sigma} \xrightarrow{t} [\ P\ ]^{\sigma - t}}$$

4. $$\frac{}{[\ P\ ]^{\sigma} \xrightarrow{\sigma} P}$$

5. $$\frac{P \xrightarrow{(a,\lambda)} P'}{P + Q \xrightarrow{(a,\lambda)} P'}$$

6. $$\frac{P \xrightarrow{t} P' \qquad Q \xrightarrow{t} Q'}{P + Q \xrightarrow{t} P' + Q'}$$

7. $$\frac{P \xrightarrow{(a,\lambda)} P'}{P \mid Q \xrightarrow{(a,\lambda)} P' \mid Q}$$

8. $$\frac{P \xrightarrow{t} P' \qquad Q \xrightarrow{t} Q'}{P \mid Q \xrightarrow{t} P' \mid Q'}$$

9. $$\frac{P \xrightarrow{(a,\lambda)} P' \qquad Q \xrightarrow{(\overline{a},\lambda)} Q'}{P \mid Q \xrightarrow{(a,\lambda)} P' \mid Q'}$$

A process algebra with delays: an example

A solution with three molecules A, B, C and one reaction $A \mapsto B$ with rate 10.0 and delay 1.0 is encoded as follows:

- $P_1 \equiv (x, 10.0, 1.0).P_3$ is the process modeling molecule A;
- $P_2 \equiv (\overline{x}, 10.0, 1.0).\mathbf{0}$ is the process modeling molecule B;
- P_3 is the process modeling molecule C.
- synchronization on channel x models the reaction;
- the solution become the process $P_1|P_2|P_3$.

Starting at time 0 the process evolves as follows:

$$P_1|P_2|P_3 \xrightarrow{(x,10.0)} [\ P_3\ ]^{1.0} \,|\, [\ \mathbf{0}\ ]^{1.0} \,|P_3 \xrightarrow{r_1} \ldots \xrightarrow{r_n} P_3|P_3$$

where $\sum_{i=1}^{n} r_i = 1.0$ and, as expected, the new process models the solution $2C$.

Applications

Some **real** applications developed interacting with molecular oncologists and biomathematicians of the *European Institute of Oncology* :

Almost finished:

- tumour–immune system interaction and immunetherapy[2];

In the very beginning:

- insuline prouction and transportation inside the liver;
- p53 (gene) regulatory network;

[2] To be submitted to a journal specific for biologists.

Things to do

Related to the algebra with delays:

- formal properties (i.e. equivalence notions);
- biological operators (i.e. compartments).

And also other stochastic interpretation of delays leading to:

- new simulation algorithms; [3]
- new semantics for the algebra.

[3] supervised a M.Sc. thesis where a new algorithm has been validated sperimentally and formally compared.

References

R.Barbuti, G.Caravagna, A.Maggiolo-Schettini and P.Milazzo **On the Interpretation of Delays in Delay Stochastic Simulation of Biological Systems**. Submitted.

R.Barbuti, G.Caravagna, A.Maggiolo-Schettini and P.Milazzo **A Delay Stochastic Simulation Algorithm with Delayed Propensity Functions**. Draft.

R. Barbuti, G. Caravagna, A. D'Onofrio and P. Milazzo, **Antitumour Immune Surveillance Through Stochastic Oscillations**. Draft.