Méthodes Formelles pour la Biologie des Systèmes

La Cellule, un Calculateur Analogique Chimique

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Cells compute

- Cells process information from external signals
  - noise filtering, ultrasensitivity
  - analog-digital conversion
- Make decisions
  - metabolism
  - cell division
  - differentiation
  - migration
- Control process execution
  - cell cycle progression
  - DNA repair
  - homeostasis

Chemical Reaction Networks (CRN)
- DNA Genes: digital expression
- RNAs
- Proteins: analog computation
Systems Biology

“Systems Biology aims at systems-level understanding which requires a set of principles and methodologies that links the behaviors of molecules to systems characteristics and functions.”

H. Kitano, ICSB 2000

- After end of Human Genome Project (2001)
- Analyze (post-)genomic data: RNA, proteins
- Data produced with high-throughput technologies
  → Databases GO, KEGG, BioCyc, etc.
- Understand and predict the behaviors of large networks of genes, RNAs, proteins
  → Systems Biology Markup Language (SBML, CellML): model exchange format
  → Model repositories: e.g. biomodels.net thousands of models
  → Modelling & analysis software (Cytoscape, Copasi, Biocham, Kappa,…)
  → Simulation of a whole-cell *mycoplasma genitalium* [Karr Covert et al 12]
Synthetic Biology

Implement useful functions
• in living cells (bacteria, yeast, …)
  – MIT BioBrick standard biological part, IGEM competition since 2004
  – production of Artemisin in yeast (Berkeley Univ., SANOFI)
  – oscillators [Elowitz Leibler 2000 nature], switches [Weiss et al 2012]

• in vitro
  – DNA computing: DNA Strand Displacement [Qian Winfree 2011 science]
  – protein analog computing [Sarpeshkar 2014 Nature]

• in artificial vesicles (non living DNA-free)
  – enzymatic biosensors [Courbet Amar Fages Renard Molina 2018 Mol Sys Biol]
Analog vs Digital Synthetic Biology

[Sarpeshkar 2014 Nature]

- continuous values, e.g. [0,1]
- many bits per variable
- rich basis functions (ODE solutions)
- sensitivity to kinetic parameters
- robust at final signal

Bioelectronics interpretation:
- molecular flux as current
- flux balance as Kirchhoff current law
- enzyme concentration as voltage
- thermodynamic energy balance as Kirchhoff voltage law

- discrete values, e.g. \{0,1\}
- one bit per variable
- poor basis functions (Boolean)
- no or less sensitivity to kinetics
- robust in every signal
Chemical Reaction Networks (CRNs)

**CRN structure**: network of reactants, products, and reactions
  - $2H_2 + O_2 \rightarrow 2H_2O$
  - $C + O_2 \rightarrow CO_2$
  - not necessarily mass balanced
  - synthesis reactions $\_ \rightarrow A$
  - degradation reactions $A \rightarrow \_$
  - hypergraph of reactions (bipartite species-reaction graph)

**CRN dynamics**: several interpretations
  - differential equations, continuous-time Markov chains, Petri net, Boolean net

**CRN theory** [Feinberg77]: interplay between CRN structure and CRN dynamics
  - static analysis of steady states, stable states, oscillations,…
  - reductions by quasi-steady state (QSS) and quasi-equilibrium (QE) approximations
  - Turing completeness and computational complexity of CRNs
Formal Biochemical Reactions

- **Binding, complexation:**
  \[ A + B \rightarrow C \]
  \[ cdk1 + cycB \rightarrow cdk1cycB \]

- **Unbinding, decomplexation:**
  \[ A \rightarrow B + C \]
Formal Biochemical Reactions

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- **Transformation, phosphorylation, transport:** \( A \rightarrow B \)
  
  \( cdk1cycB \rightarrow cdk1cycBp \)
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- **Gene expression, synthesis:**
  \[ A \rightarrow A + B \]
  
  \[ E2Fa \rightarrow E2Fa + RNAcycA \]
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- **Transformation, phosphorylation, transport:** \( A \rightarrow B \)
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- **Gene expression, synthesis:** \( A \rightarrow A + B \)
  \( E2F\alpha \rightarrow E2F\alpha + RNAcycA \)

- **Degradation:** \( A \rightarrow - \)
Biochemical Reaction Rates

- Binding, complexation:
  \[ A + B \overset{k.A.B}{\longrightarrow} C \]
  \[ cdk1 + cycB \rightarrow cdk1cycB \]

- Unbinding, decomplexation:
  \[ A \overset{k.A}{\rightarrow} B + C \]

- Transformation, phosphorylation, transport:
  \[ A \overset{v.A/(k+A)}{\rightarrow} B \]
  \[ cdk1cycB \rightarrow cdk1cycBp \]

- Gene expression, synthesis:
  \[ A \overset{v.A^n/(k+A^n)}{\rightarrow} A + B \]
  \[ E2Fa \rightarrow E2Fa + RNAcycA \]

- Degradation:
  \[ A \overset{k.A}{\rightarrow} \_ \]
Biochemical Reaction Rates

- Binding, complexation:
  \[ cdk1 + cycB \rightarrow cdk1cycB \]

- Unbinding, decomplexation:
  \[ A + B \xrightleftharpoons[^k.A.B]{^k.A} \rightarrow B + C \]

- Transformation, phosphorylation, transport:
  \[ cdk1cycB \rightarrow cdk1cycBp \]

- Gene expression, synthesis:
  \[ E2Fa \rightarrow E2Fa + RNAcycA \]

- Degradation:
  \[ A \xrightarrow[^k.A]{k.A} \rightarrow - \]

Mass action law kinetics
Biochemical Reaction Rates

- Binding, complexation:
  \[ cdk1 + cycB \rightarrow cdk1cycB \]

- Unbinding, decomplexation:
  \[ A + B \xrightarrow{k.A.B} C \]

- Transformation, phosphorylation, transport:
  \[ cdk1cycB \rightarrow cdk1cycBp \]

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  \[ E2Fa \rightarrow E2Fa + RNAcycA \]

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  \[ A \xrightarrow{k.A} \_ \]

Mass action law kinetics

Michaelis Menten kinetics
Biochemical Reaction Rates

- **Binding, complexation:**
  
  \[ cdk1 + cycB \rightarrow cdk1cycB \]

- **Unbinding, decomplexation:**
  
  \[ A + B \xrightarrow{k.A.B} C \]

- **Transformation, phosphorylation, transport:**
  
  \[ cdk1cycB \rightarrow cdk1cycBp \]

- **Gene expression, synthesis:**
  
  \[ E2Fa \rightarrow E2Fa + RNAcycA \]

- **Degradation:**
  
  \[ A \xrightarrow{k.A} \]
Several Semantics $A + B \xrightarrow{k.A.B} C$

Continuous semantics: concentrations, continuous time evolution

Ordinary differential equations (ODE)

\[
\frac{dA}{dt} = -k \cdot A \cdot B \quad \frac{dB}{dt} = -k \cdot A \cdot B \quad \frac{dC}{dt} = k \cdot A \cdot B
\]
Several Semantics $A + B \xrightarrow{k \cdot A \cdot B} C$

**Continuous semantics:** concentrations, continuous time evolution

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\]

**Stochastic semantics:** numbers of molecules, probability and time of transition

Continuous Time Markov Chain (CTMC)

$A, B \xrightarrow{p(S_j), t(S_i)} C++, A--, B--$

Intrinsic variability
(with same genetic and epigenetic parameters)
Continuous semantics: concentrations, continuous time evolution

Ordinary differential equations (ODE)

\[
\frac{dA}{dt} = -k \cdot A \cdot B \\
\frac{dB}{dt} = -k \cdot A \cdot B \\
\frac{dC}{dt} = k \cdot A \cdot B
\]

Stochastic semantics: numbers of molecules, probability and time of transition

Continuous Time Markov Chain (CTMC)

\[ A, B \xrightarrow{p(S_i), t(S_i)} C++, A--, B-- \]

Multi-agent simulation: numbers of molecules, space, diffusion speed, affinity

Random walk (ex. Hsim simulator [Amar 04])
Several Semantics $A + B \xrightarrow{k.A.B} C$

**Continuous semantics:** concentrations, continuous time evolution

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**Stochastic semantics:** numbers of molecules, probability and time of transition

Continuous Time Markov Chain (CTMC)

\[A, B \xrightarrow{p(S_j), t(S_i)} C++, A--, B--\]

**Petri net semantics:** numbers of molecules

Multiset rewriting

CHAM [Berry Boudol 90] [Banatre Le Metayer 86]
Several Semantics $A + B \xrightarrow{\text{k.A.B}} C$

**Continuous semantics:** concentrations, continuous time evolution

Ordinary differential equations (ODE)

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\frac{dA}{dt} = -k \cdot A \cdot B \quad \frac{dB}{dt} = -k \cdot A \cdot B \quad \frac{dC}{dt} = k \cdot A \cdot B
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**Stochastic semantics:** numbers of molecules, probability and time of transition

Continuous Time Markov Chain (CTMC)

\[A, B \xrightarrow{\text{p(S), t(Si)}} C++, A--, B--\]

**Petri net semantics:** numbers of molecules

Multiset rewriting

CHAM [Berry Boudol 90] [Banatre Le Metayer 86]

**Boolean semantics:** presence/absence

Asynchronous transition system

Symbolic model-checking

\[A \wedge B \rightarrow C \wedge \neg A \wedge \neg B\]

\[A \wedge B \rightarrow C \wedge A \wedge \neg B\]

\[A \wedge B \rightarrow C \wedge \neg A \wedge B\]

\[A \wedge B \rightarrow C \wedge A \wedge B\]

Bioregul 2019
Hierarchy of Semantics


**Thm. (approximation)** For large numbers of molecules the ODE semantics approximates the mean stochastic behavior [Gillespie 1971 Kurtz 1978]

**Thm. (abstract interpretation)** Galois connections between the syntactical, stochastic, Petri net and Boolean trace semantics [Fages Soliman Theoretical Computer Science 2008]

*Model cell-to-cell variability Intrinsic and extrinsic variability*

*Animal model Synthetic microreactor*
Practical Work TD1: Lotka-Volterra Enzymatic CRN

BIOCHAM-4: version online [http://lifeware.inria.fr/biocham4/online/](http://lifeware.inria.fr/biocham4/online/)

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**TD1: Lotka-Volterra's prey-predator enzymatic model**

- reaction network
- differential, stochastic and boolean semantics
- addition of immigration/emigration reactions

F. Fages, 18 Jan. 2019

```python
In [1]: clear_model.
In [2]: present(A,a). present(B,b).
In [3]: k1*A*B for A+B => 2*B.
In [4]: k2*A for A => 2*A.
In [5]: k3*B for B => _.
In [6]: parameter(a=1, b=1, k1=2, k2=2, k3=1).
```