Méthodes Formelles pour la Biologie des Systèmes

La Cellule, un Calculateur Analogique Chimique

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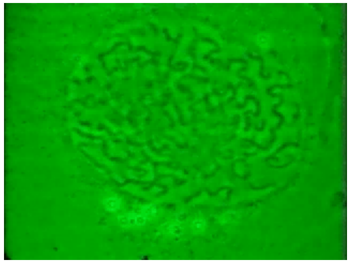
Cells compute

but it's an analog world
[Sauro Kim 2013 Nature]

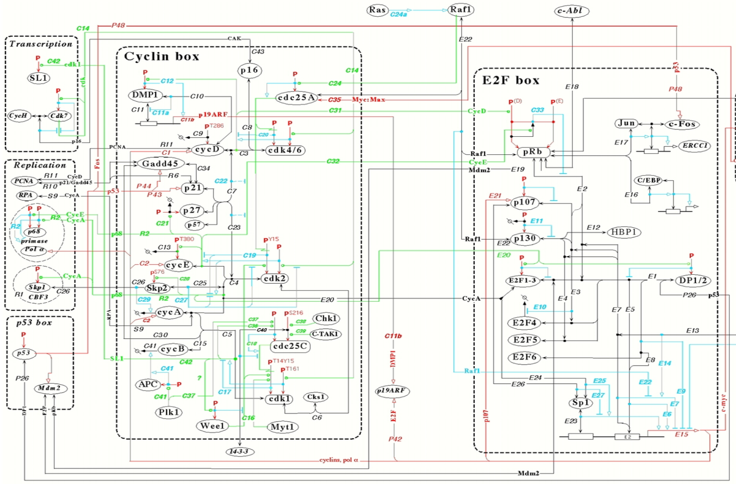
- Cells process information from external signals
  - noise filtering, ultrasensitivity
  - analog-digital conversion
- Make decisions
  - metabolism
  - cell division
  - differentiation
  - migration



- Control process execution
  - cell cycle progression
  - DNA repair
  - homeostasis

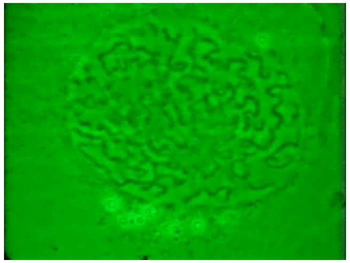
Chemical Reaction Networks (CRN)

- DNA Genes: digital expression
- RNAs
- Proteins: analog computation



Systems Biology

It's not only the genetics



"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.

2 "Bioinformatics" :

- tools for processing biological data
- science of data processing in cells

- 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,…)

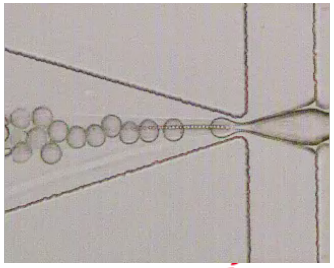
→ Simulation of a whole-cell *mycoplasma genitalium* [Karr Covert et al 12]

Synthetic Biology

Mostly digital circuits with DNA
- **slow**
- **pb interference**

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]



Few analog circuits
- **fast enzymatic reactions**
- **pb sensitivity to reaction rate**

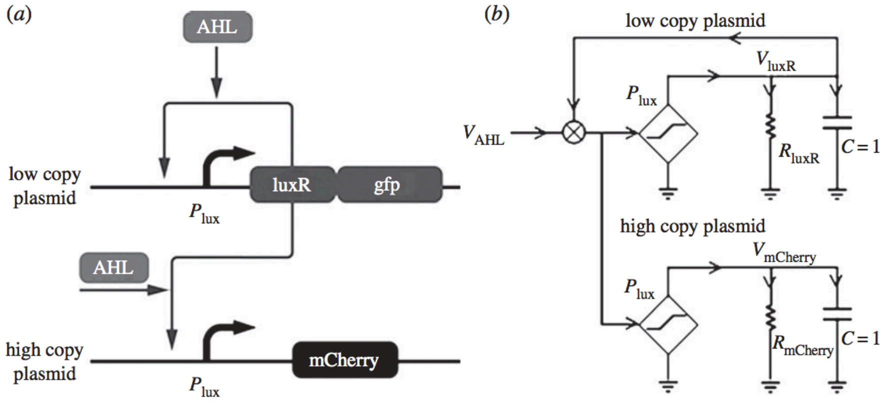
Analog vs Digital Synthetic Biology

[Sarpeshkar 2014 Nature]

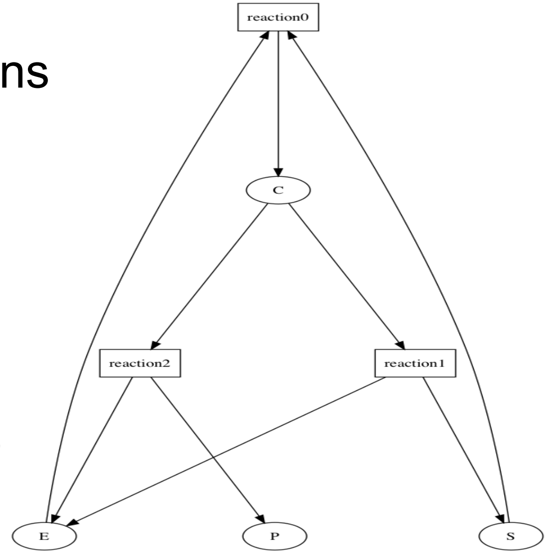
continuous values, e.g. [0,1]	discrete values, e.g. {0,1}
many bits per variable	one bit per variable
rich basis functions (ODE solutions)	poor basis functions (Boolean)
sensitivity to kinetic parameters	no or less sensitivity to kinetics
robust at final signal	robust in every signal

Bioelectronics interpretation:

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



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: $A \rightarrow B + C$

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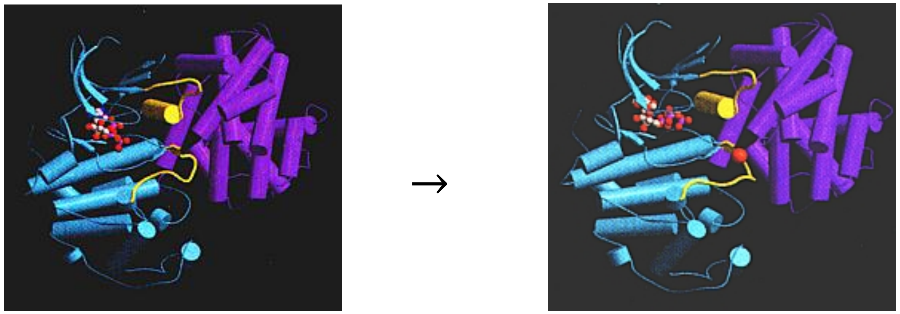

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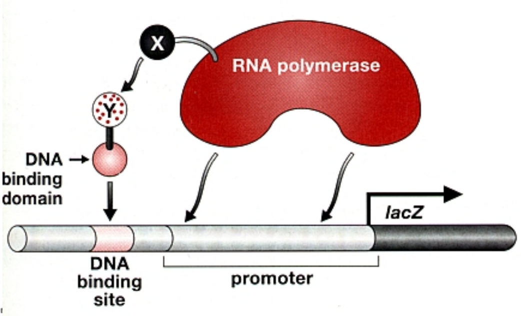
  $E2Fa \rightarrow E2Fa + RNAcycA$



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Biochemical Reaction Rates

Time matters

- Binding, complexation: $A + B \xrightarrow{k.A.B} C$

  $cdk1 + cycB \rightarrow cdk1cycB$

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

- Transformation, phosphorylation, transport: $A \xrightarrow{v.A/(k+A)} B$

  $cdk1cycB \rightarrow cdk1cycBp$

- Gene expression, synthesis: $A \xrightarrow{v.A^n/(k+A^n)} A + B$

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- Degradation: $A \xrightarrow{k.A} \_$

Biochemical Reaction Rates

- Binding, complexation:

  $cdk1 + cycB \rightarrow cdk1cycB$

  $$A + B \xrightarrow{k.A.B} C$$

Mass action law kinetics

- Unbinding, decomplexation:

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Biochemical Reaction Rates

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Mass action law kinetics

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Michaelis Menten kinetics

- Transformation, phosphorylation, transport: $A \xrightarrow{v.A/(k+A)} B$ $(A + E \rightarrow C \rightarrow B + E)$

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- Transformation, phosphorylation, transport: $A \xrightarrow{v.A/(k+A)} B$

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Hill kinetics: switch like behavior

- Gene expression, synthesis: $A \xrightarrow{v.A^n/(k+A^n)} A + B$

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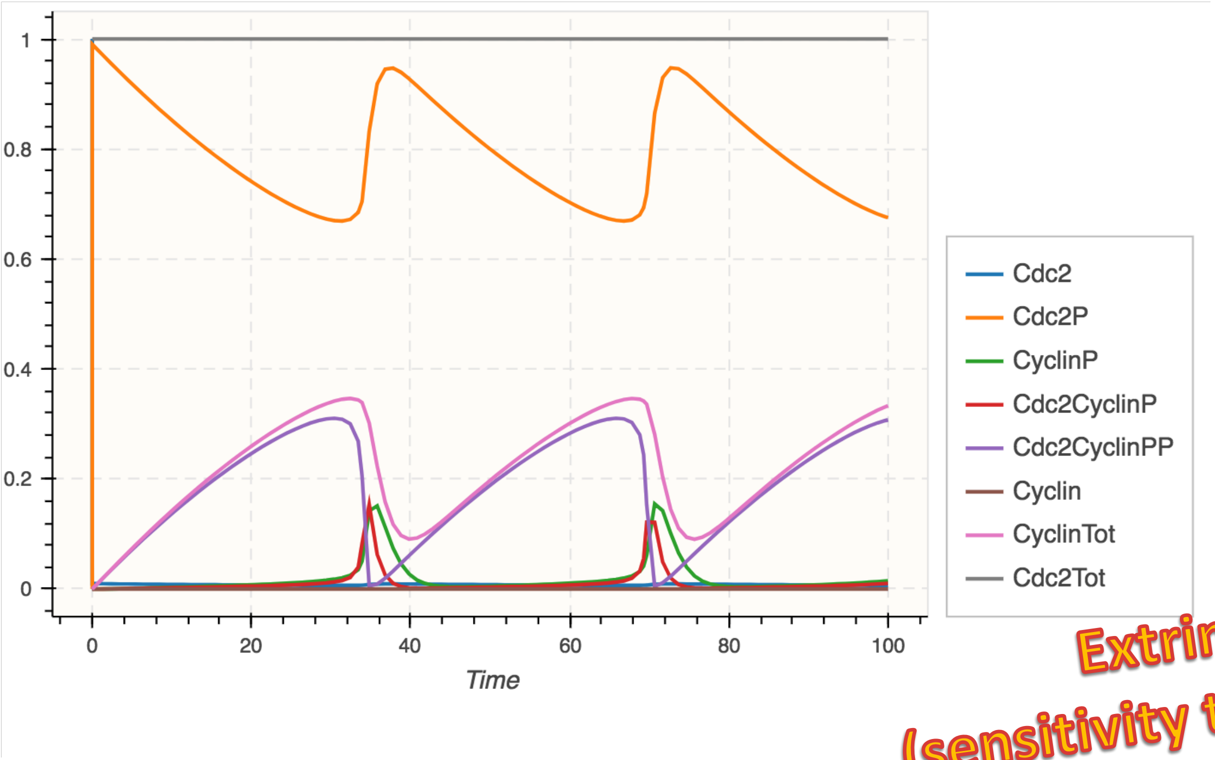
- Degradation: $A \xrightarrow{k.A} \_$

Several Semantics $A + B \xrightarrow{k.A.B} C$

Continuous semantics: concentrations, continuous time evolution

Ordinary differential equations (ODE) $\frac{dA}{dt} = -k.A.B \quad \frac{dB}{dt} = -k.A.B \quad \frac{dC}{dt} = k.A.B$



Extrinsic variability
(sensitivity to parameter change)

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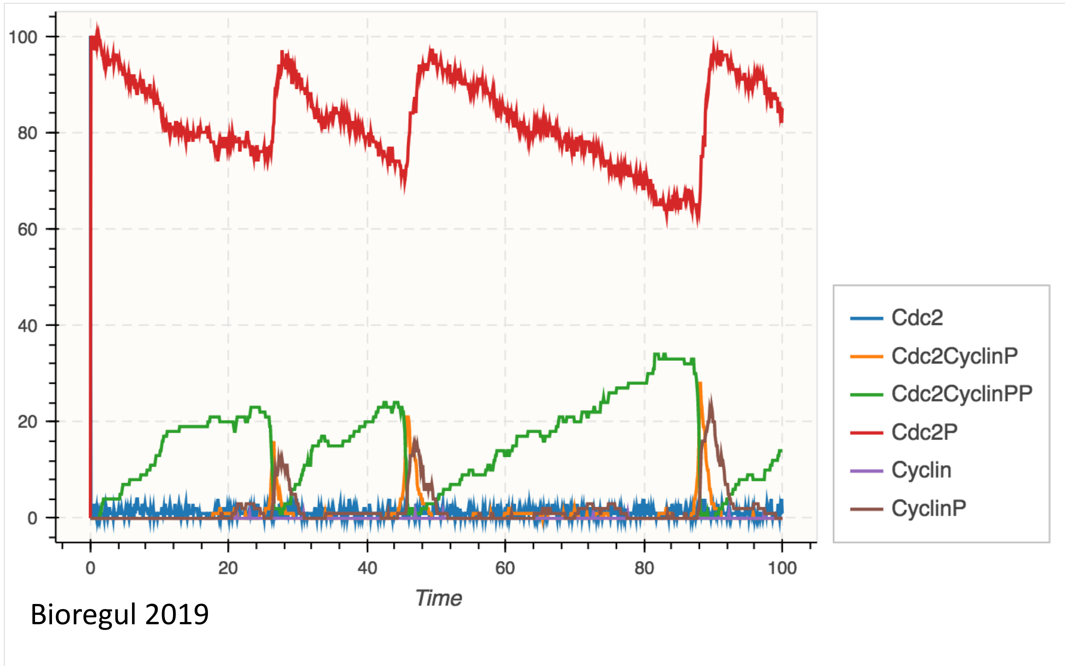
Stochastic semantics: numbers of molecules, probability and time of transition

Continuous Time Markov Chain (CTMC) $A, B \xrightarrow{p(S_i),\, t(Si)} C{+}{+}, A{-}{-}, B{-}{-}$



Bioregul 2019

Intrinsic variability (with same genetic and epigenetic parameters)

François Fages

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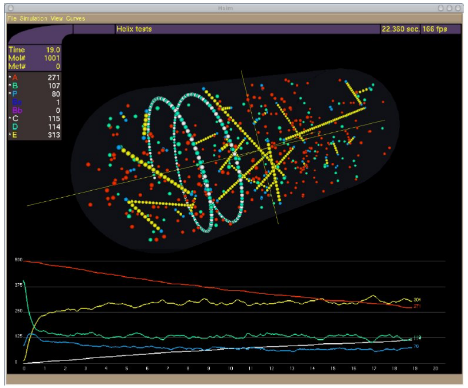
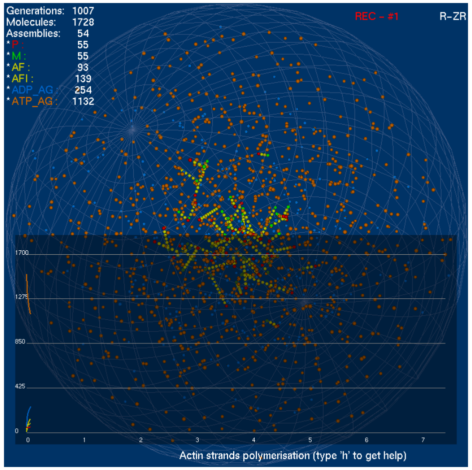
Multi-agent simulation: numbers of molecules, space, diffusion speed, affinity

Random walk (ex. Hsim simulator [Amar 04])



```
Helix tests                22.360 sec. 166 fps
Time    19.0
Mol#    1001
Met#       0
*A       271
*B       107
*P        80
 Ba        1
 Bb        0
*C       115
 D       114
*E       313
```



```
Generations:  1007
Molecules:    1728
Assemblies:     54
*P :            55
*M :            55
*AF :           93
*AFI :         139
*ADP_AG :      254
*ATP_AG :     1132
```

Actin strands polymerisation (type 'h' to get help)

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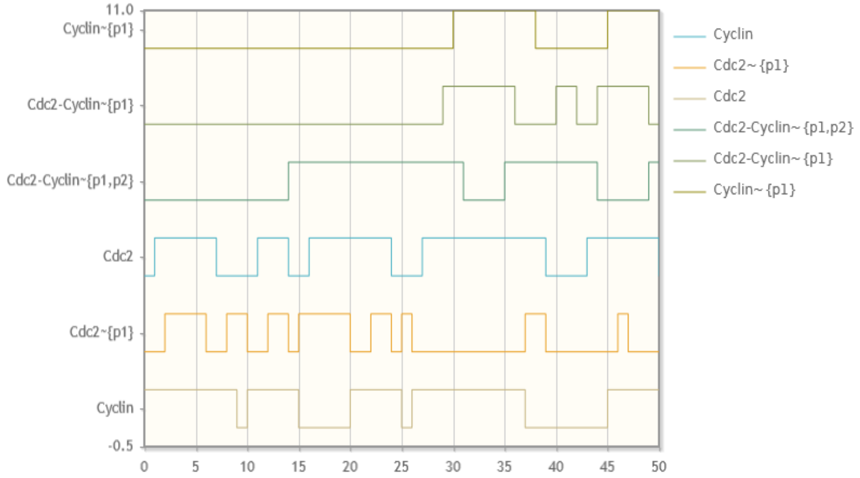
Petri net semantics: numbers of molecules $A\ ,\ B \rightarrow C{+}{+},\ A{-}{-},\ B{-}{-}$

Multiset rewriting

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



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Multiset rewriting

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

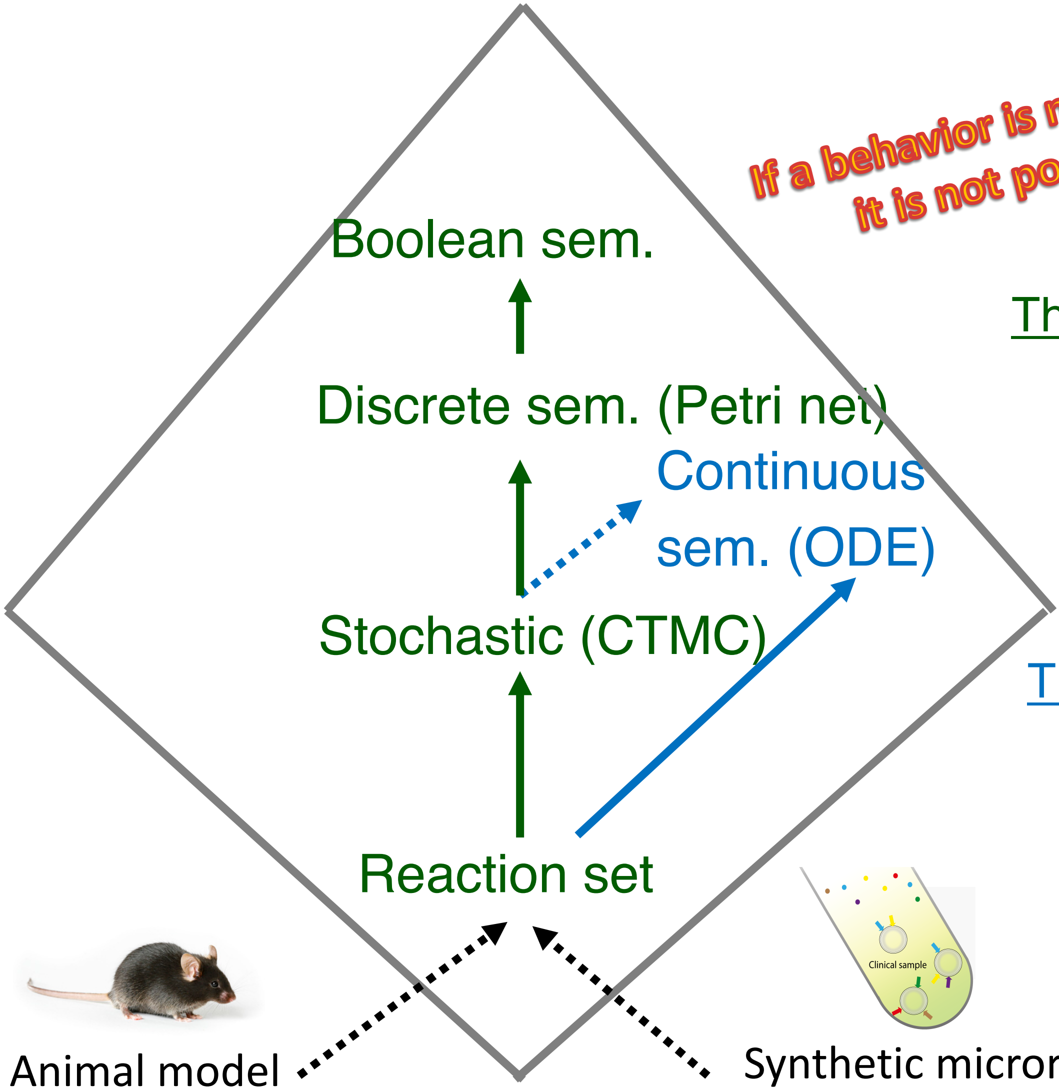
Boolean semantics: presence/absence $A \wedge B \rightarrow C \wedge \neg A \wedge \neg B$

Asynchronous transition system $A \wedge B \rightarrow C \wedge A \wedge \neg B$

Symbolic model-checking $A \wedge B \rightarrow C \wedge \neg A \wedge B$

$A \wedge B \rightarrow C \wedge A \wedge B$

Hierarchy of Semantics



Boolean sem.

Discrete sem. (Petri net)

Continuous sem. (ODE)

Stochastic (CTMC)

Reaction set

Animal model

Synthetic microreactor

If a behavior is not possible in the Boolean semantics
it is not possible in the stochastic semantics
for any reaction rates

Thm. (abstract interpretation ↑) Galois connections between the syntactical, stochastic, Petri net and Boolean trace semantics

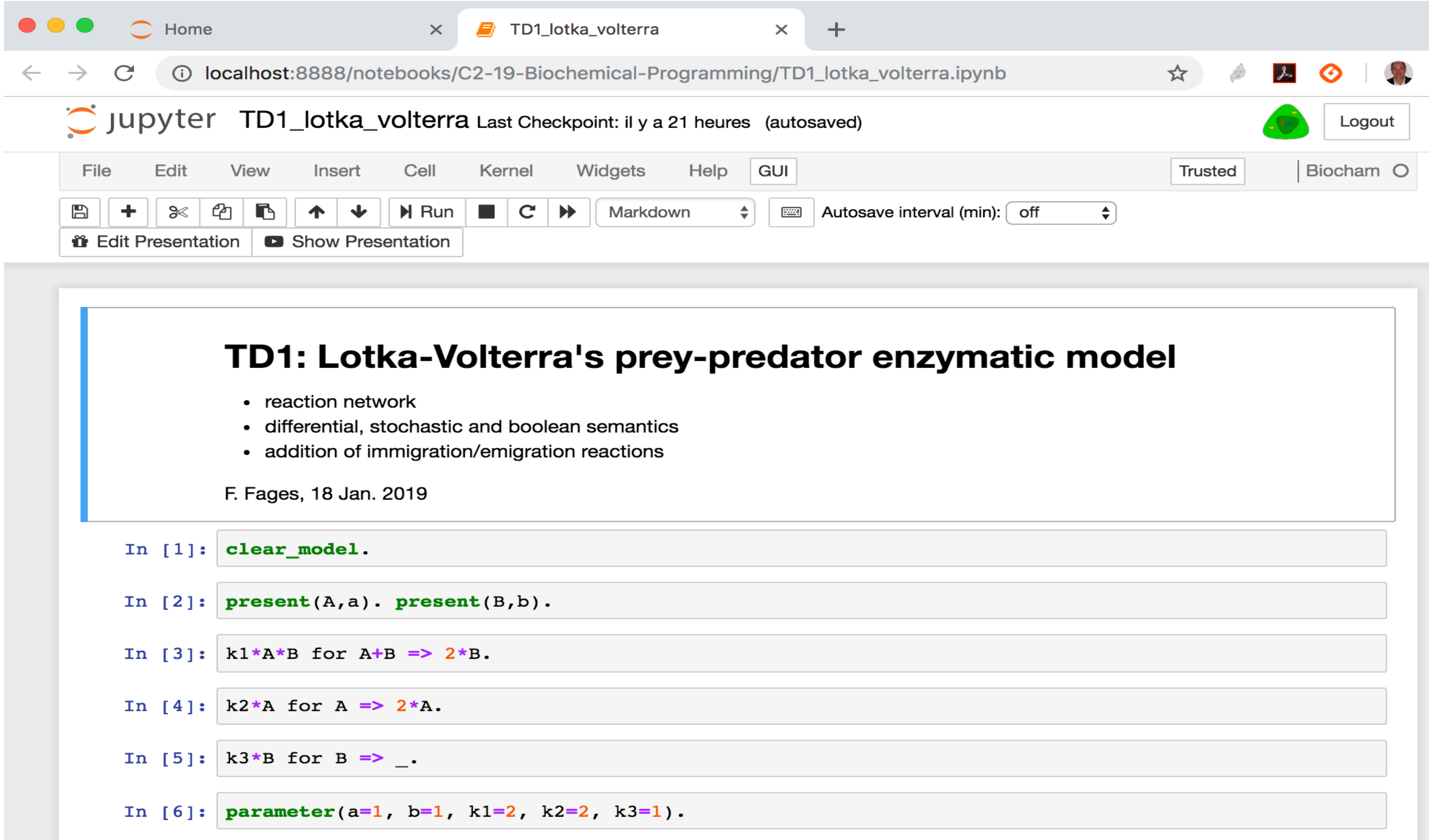
[Fages Soliman Theoretical Computer Science 2008]

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

Model cell-to-cell variability
Intrinsic and extrinsic variability

Practical Work TD1: Lotka-Volterra Enzymatic CRN

BIOCHAM-4: version online http://lifeware.inria.fr/biocham4/online/



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

```
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).
```