A formal model for gene regulatory networks with time delays

Jean-Paul Comet, Jonathan Fromentin,
Gilles Bernot, Olivier Roux

Lab. I3S, Université de Nice-Sophia-Antipolis, France
Lab. IRCCyN, Ecole Centrale de Nantes, France
Lab. Labri, Université de Bordeaux, France

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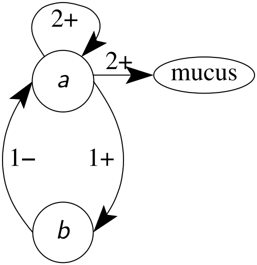
Introduction

- Modelling of genetic regulatory network
  - $\Rightarrow$ deep understanding of how the components interact
  - $\Rightarrow$ non obvious predictions on possible behaviours
- information about interactions increases
  $\neq$ kinetic data not available
- Parameter identification problem is crucial
- Qualitative models : the problem is easier
  $\Rightarrow$ good compromise
- Importance of time in the dynamics of a system
- Qualitative models with time : Hybrid models

Running example : mucus production of the bacterium *Pseudomonas aeruginosa*

- opportunistic pathogen, often encountered in chronic lung diseases such as cystic fibrosis.
- *a* supervises an operon : 4 genes among which one codes for an inhibitor of *a*.
- *a* favours its own synthesis.



Questions

- Is the change of behaviours (production / non production of mucus) due to change of the regulations (mutation) ? Or is due to change of state ?
- What is the shape of the attraction bassin associated to the behavior which does not produce mucus ?

Differential Framework

- with each variable v is associated a value $x_v \in \mathbb{R}$ (concentration)
- ODE : $\frac{dx_v}{dt} = F_v(x) - \lambda_v x_v$ with $\begin{cases} \lambda_v \geq 0 & : \text{degradation} \\ F_v(x) & : \text{synthesis rate} \end{cases}$

  Often, synthesis rate is additive :

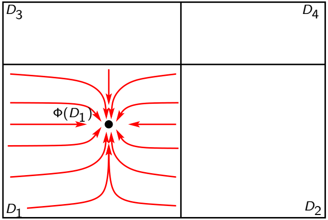
  $F_v(x) = \sum_{u \in G^-(v)} I(u, v)$ contribution of u to the synthesis rate of v

  Sigmoid functions $\Longrightarrow$ Discretization
- Analytical solution in a domain : $x_v(t) = \frac{\mu_v}{\lambda} - (\frac{\mu_v}{\lambda} - x_0^v).e^{-\lambda t}$
- The vector $(\frac{\mu_v}{\lambda_v})_v$ is the **focal point** of the domain
- Derivative : $x'_v(t) = (\frac{\mu_v}{\lambda} - x_0^v).e^{-\lambda t}$

  The sign of derivatives does not change $\Longrightarrow$ **monotonous** trajectories

Discrete Modelling (R. Thomas & E.H. Snoussi)

1. *Taking into account only regular domains*
   - a domain corresponds to a *qualitative* state
   - frontiers are abstracted
2. *Taking into account only qualitative behaviors*



The focal point is in the current domain
Trajectories do not go out of the domain.
$\Rightarrow$ no exit

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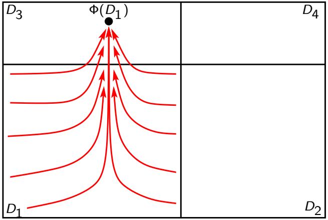

The focal point is in the domain D_3
All trajectories go out of the domain
$\Rightarrow$ in the north direction

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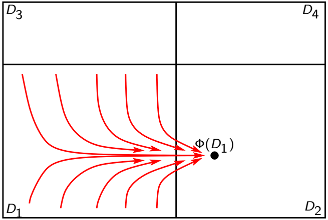

The focal point is in the domain D_2
All trajectories go out of the domain
$\Rightarrow$ in the east direction

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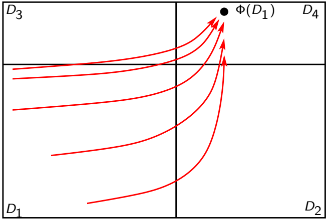
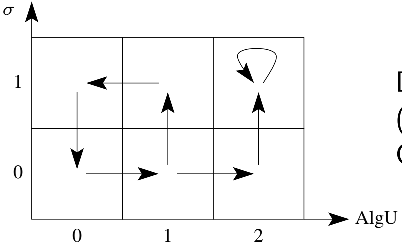


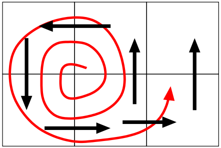
The focal point is in the domain D_4
All trajectories go out of the domain
⇒ in the east direction
⇒ in the north direction

A Discrete Model of the Mucus Production System

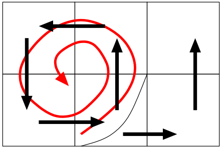


Describes only succession of events (threshold cross-over).
Chronological – not chronometrical

This model can abstract several qualitativelly different continuous models :



Outgoing Spiral



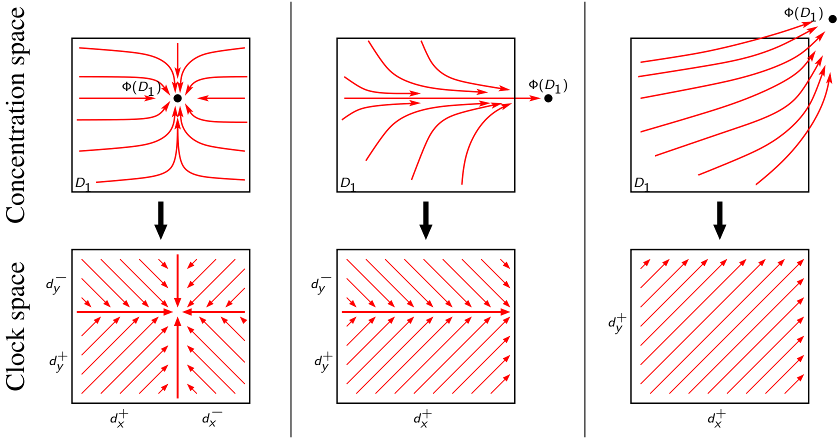
Incoming spiral

Hybrid Modeling

- Notion of delays of activation/inhibition
  1. when an order of activation/inhibition arrives, the biological machinery starts to increase/decrease the corresponding protein concentration,
  2. but this action takes time. $\Longrightarrow$ Clocks
  - $d_v^+(\mu)$ is an approximation of the time necessary to variable v to cross the domain from left to right.
  - $d_v^-(\mu)$ is an approximation of the time necessary to variable v to cross the domain from right to left.
- From differential models to hybrid models :
  - thresholds are given by the differential equations
  - discrete parameters are given by the discretization of focal points
  - delays are deducible :
    - in each domain, the differential model has an analytic solution
    - the time necessary to cross a domain is computable.

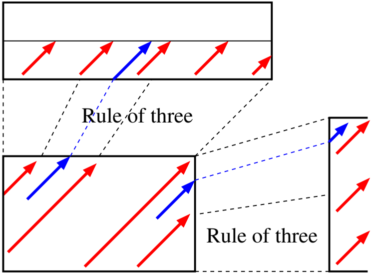
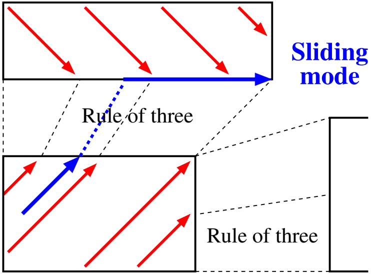
Hybrid models inspired by Diff. models : sketch (1)

- Inside a domain : trajectories are approximated by polylines



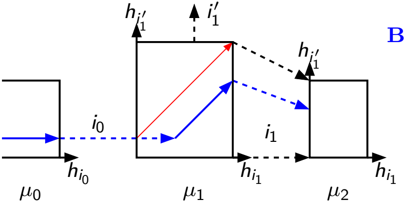
Hybrid models inspired by Diff. models : sketch (2)

- transitions between domains :

if target temporal zone is compatible	if target temporal zone does not accept entering trajectories
	

Building constraints on delays from known trajectories

- Is it possible to build constraints on delays in order to make possible a trajectory passing through a given sequence of domains ?
- Principle : enumeration of constraints due to paths of length 2
- 12 situations
- example $\mu_0 \xrightarrow{i_0} \mu_1 \xrightarrow{i_1} \mu_2$:



Blue trajectory is possible :

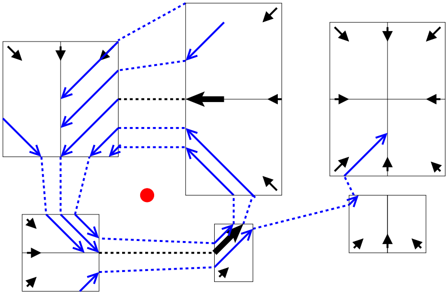
$$(d^+_{i_1}(\mu_1) - clock_{i_1}) < (d^+_{i_1'}(\mu_1) - clock_{i_1'})$$

Constraints on the Mucus Production system

Is it possible to have the discrete cycle
$$(0,0) \rightarrow (1,0) \rightarrow (1,1) \rightarrow (0,1) \rightarrow (0,0)\,?$$

Different kinds of qualitative behaviours :

- a convergent spiral
- a set of cyclic temporal trajectories
- a divergent spiral or
- a limit cycle.



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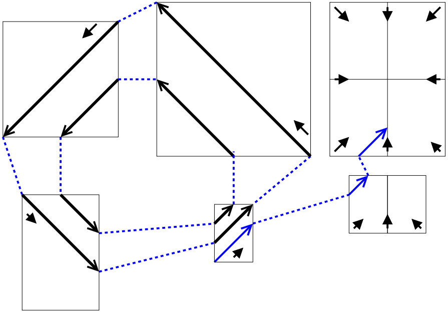

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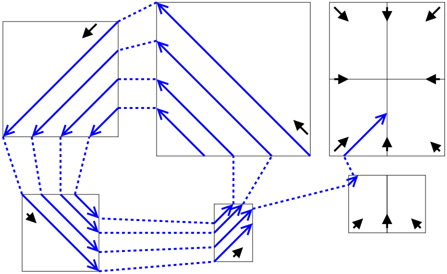

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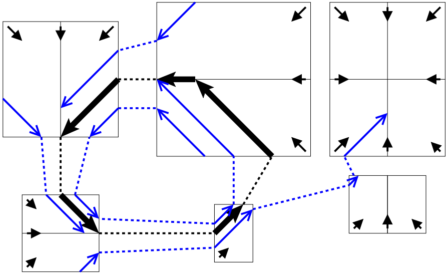

Conclusion

- Distinction of models mixed up in the discrete modeling framework
- Parameter identification problem
- Qualitative information about the behavior :
  - possible automation for discrete models
  - no automation for differential models
- Information about the elapsed time of a trajectory
  - Discrete models do not take into account elapsed time
  - Differential models do, but difficulty for model-checking
- Hybrid models can fill up the gap between discrete models and differential ones.

– Thanks for your attention –

Questions ?

J.-P. Comet – J. Fromentin – G. Bernot – O. Roux