GEOCAL'06 – Dynamics and structure of biological networks

A comparison between piecewise-affine and discrete models of gene networks

Etienne Farcot

post-doc – COMORE Project Team

INRIA Sophia Antipolis

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Sketch of the presentation

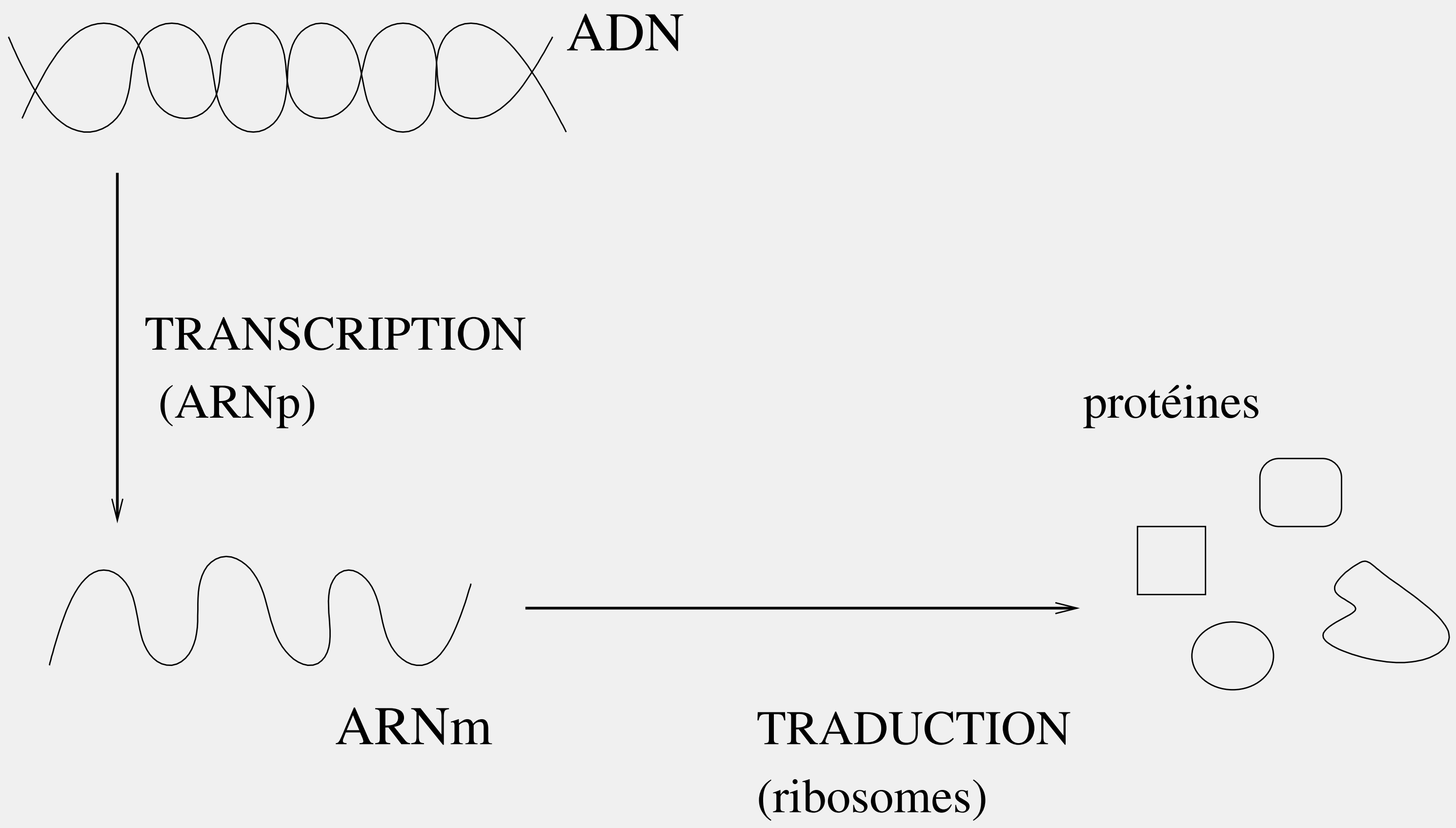
Introduction

1. General discrete models
2. Piecewise-affine models and their discrete analogues
3. Symbolic dynamics as a common framework

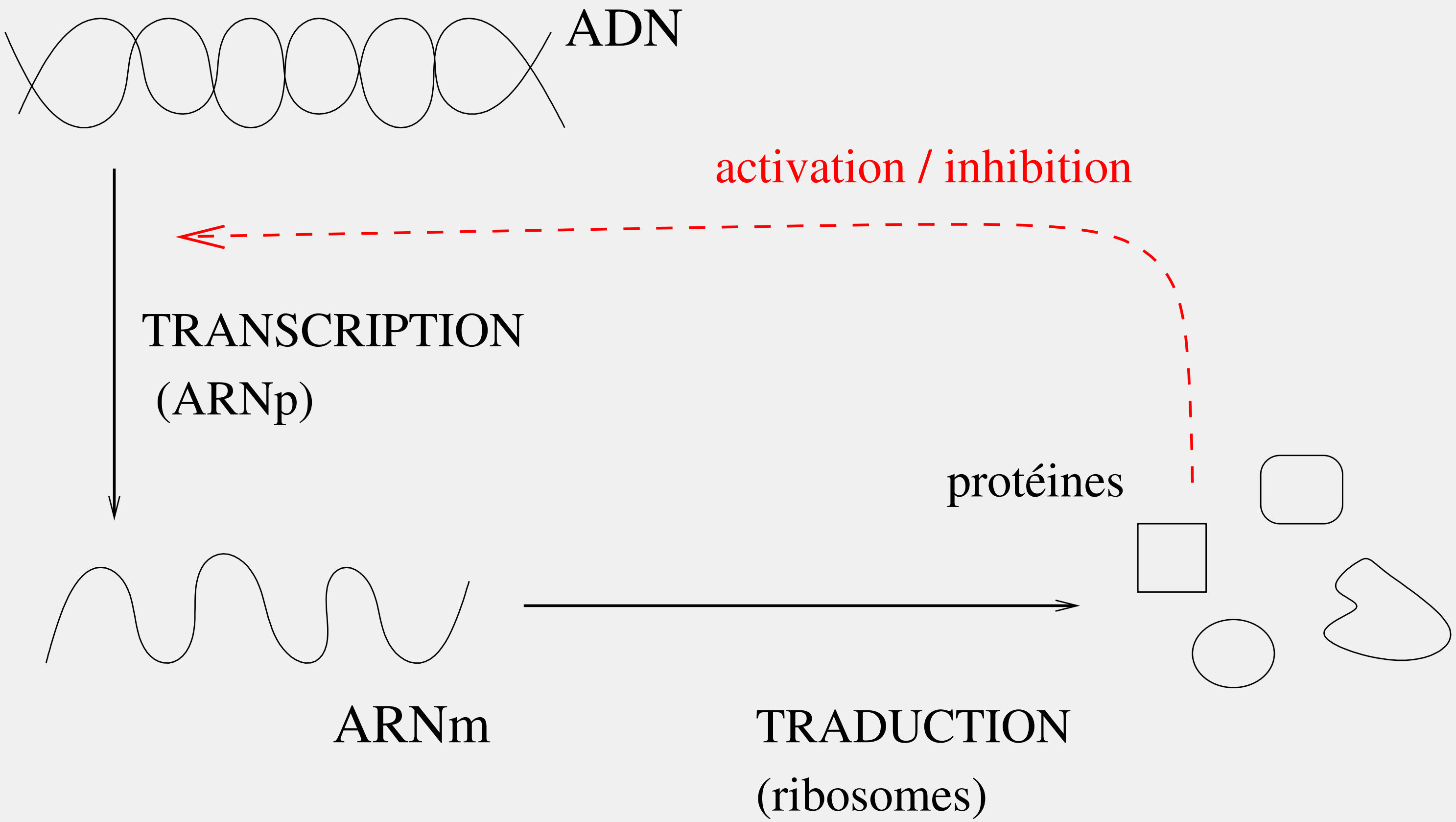
Conclusion

INTRODUCTION

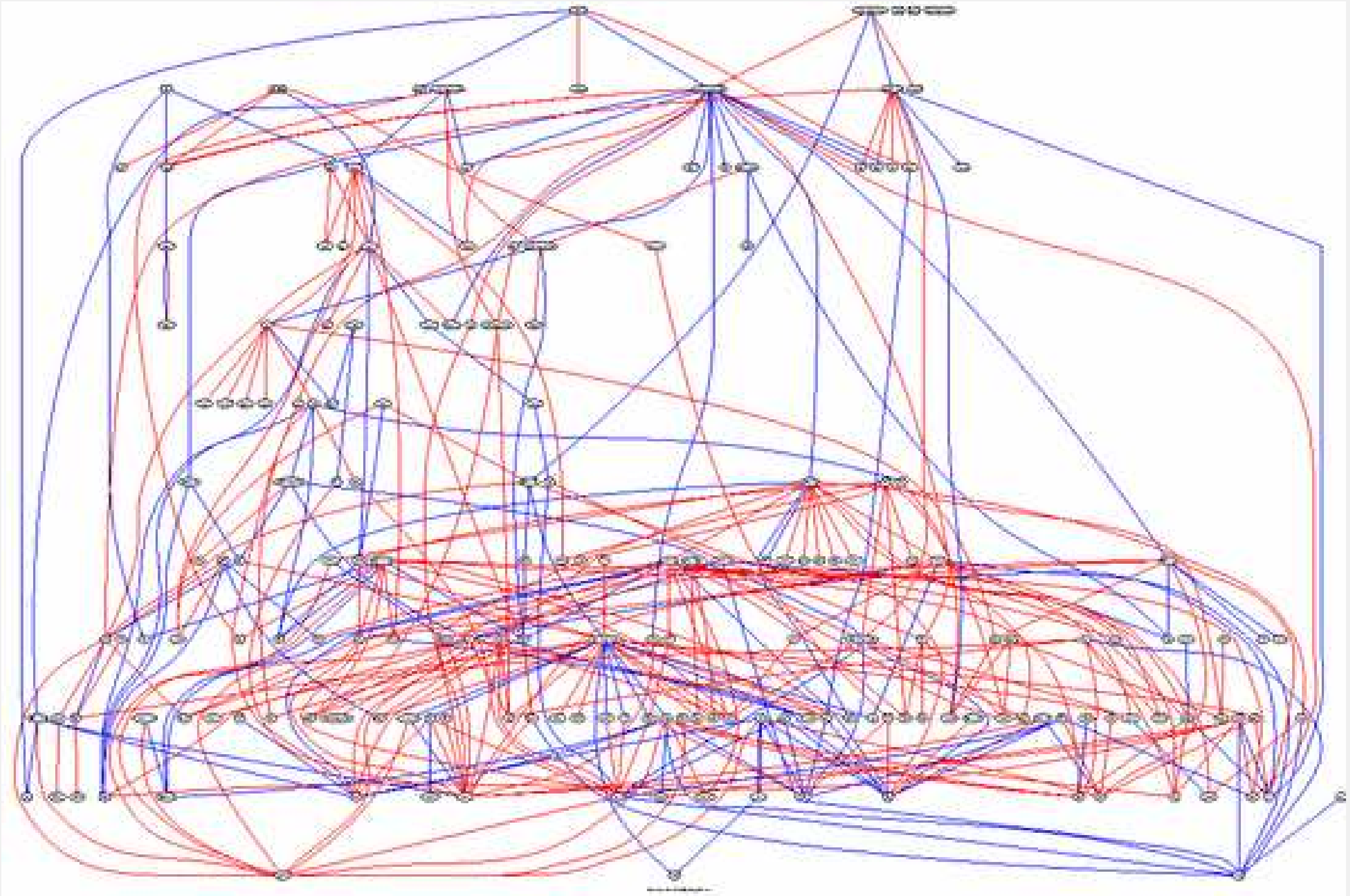
Gene transcriptional regulation: principle



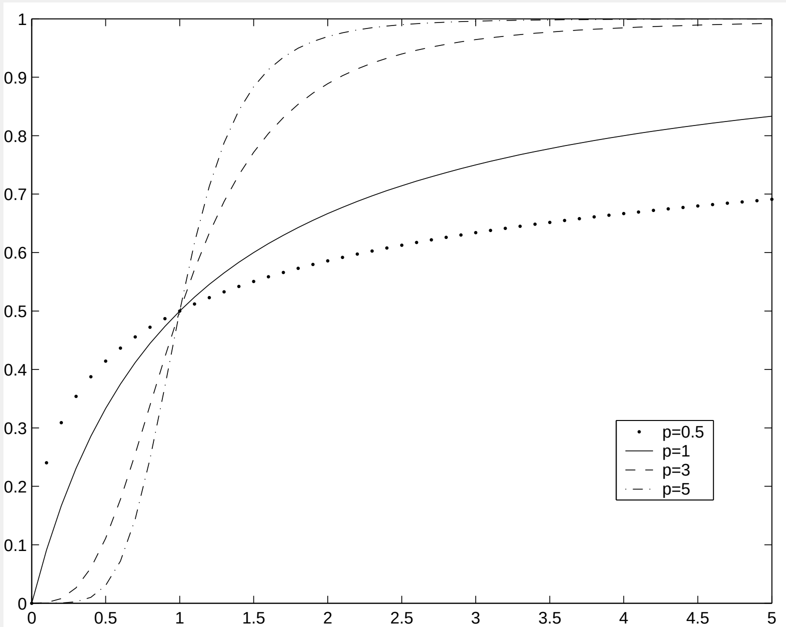
Gene transcriptional regulation: principle



Example of gene network interaction graph



Dynamics of the interactions



$$h^{+}(x) = \frac{x^p}{x^p + \theta^p}$$

$$h^{-}(x) = 1 - h^{+}(x)$$

- x : concentration (mRNA, protein...).
- θ : threshold value.
- p : cooperativity exponent, or "Hill exponent".

- nonlinear differential equations
- high dimension
- uncertain parameters

$\rightsquigarrow$ untractable !

Simplified / Qualitative models needed.

In the 1960's Leon Glass proposed piecewise-linear models.

Use the fact that $[p \to \infty] \implies [h^{\pm} \to \text{step function}]$.

$\longrightarrow$ rapid changes modeled by instantaneous ones.

1. General Discrete Models

Variables : gene expression levels ; finite number.

If n genes interact, for each $i \in \{1 \ldots n\}$:

$$x_i \in E_i = \{1 \ldots q_i\} \quad \text{where } q_i \in \mathbb{N}.$$

Most often $q_i = 2$ *: boolean networks.*

State space of the system : $\mathscr{S} = \prod_{i=1}^{n} E_i$

Discrete time : $t \in \mathbb{N}$.

Trajectories : iteration of a "synchronous successor" mapping :

$$\begin{array}{rccc} F : & \mathscr{S} & \rightarrow & \mathscr{S} \\ & x & \mapsto & F(x) \end{array}$$

deduced from the interaction graph.

Modeling continuity of time in a discrete framework
$\rightsquigarrow$ asynchronous dynamics.

$\rightsquigarrow$ *Partial application* $\widetilde{F}^I$, for $I \subset \{1 \dots n\}$:
applies F_i to coordinates indexed by I ; other x_i's unchanged.

$\rightsquigarrow$ *Update strategy* : $\mathbf{I} = (I_t)_{t \in \mathbb{N}} \in (\mathscr{P}(\{1 \dots n\}))^{\mathbb{N}}$.

Most often *asynchronous strategy* $=$ I_t singleton, for all t.

The strategy $\mathbf{I}$ can be seen as a trajectory in a discrete dynamical system
$\rightsquigarrow$ this system bounds the complexity of the model.

Modeling continuity of space in a discrete framework

$\rightsquigarrow$ Restricting allowed transitions.

$$\textsc{succ}(F, a) = a + \mathtt{sgn}(F(a) - a).$$

Compatibility with asynchronous updating of variables

$$\widetilde{\textsc{succ}}^I(F, a) = \textsc{succ}(\widetilde{F}^I, a).$$

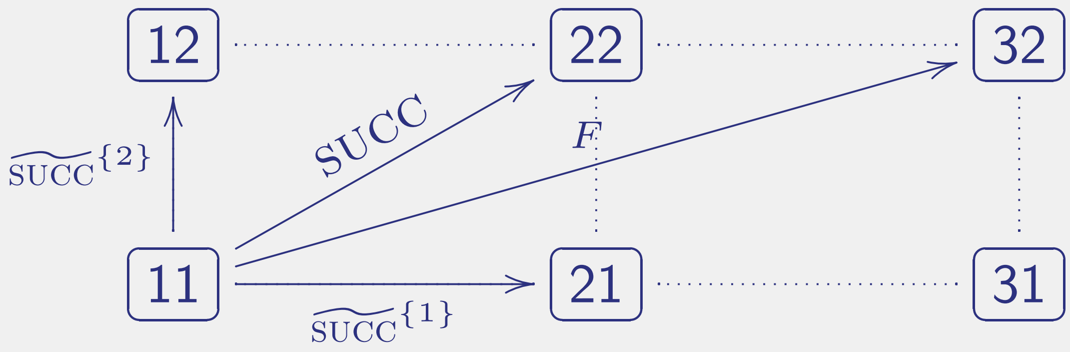
Trajectory from initial condition x^0, with a fixed strategy :

$$\begin{cases} x^0 & \in \mathscr{S} \\ x^{t+1} & = \textsc{succ}\left(\widetilde{F}^{I_t}(x^t)\right), \qquad t \in \mathbb{N}. \end{cases} \tag{1}$$

Example 1

map	image of 11
F	32
$\widetilde{F}^{\{1\}}$	31
$\widetilde{F}^{\{2\}}$	12
SUCC	22
$\widetilde{\text{SUCC}}^{\{1\}}$	21
$\widetilde{\text{SUCC}}^{\{2\}}$	12

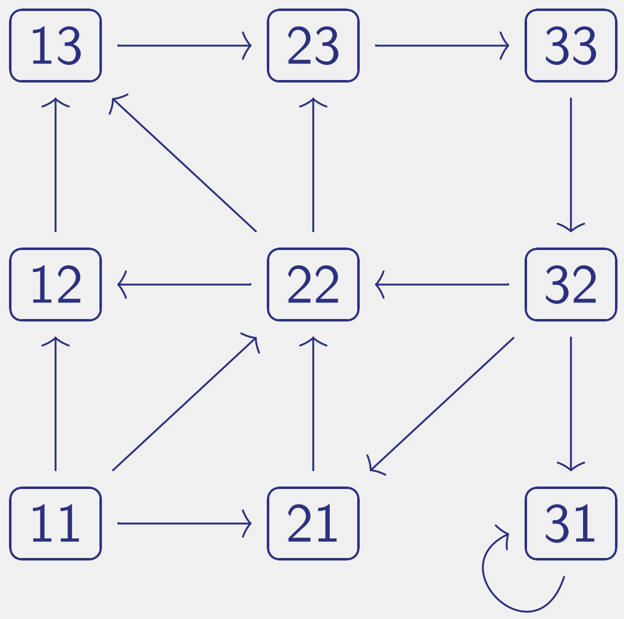
Graphically :



Example 2

a	$F(a)$	$\textsc{succ}(F,a)$	$I(a)$
11	32	22	$\{1,2\}$
12	13	13	$\{2\}$
13	23	23	$\{1\}$
21	23	22	$\{2\}$
22	13	13	$\{1,2\}$
23	33	33	$\{1\}$
31	31	31	$\varnothing$
32	21	21	$\{1,2\}$
33	31	32	$\{2\}$

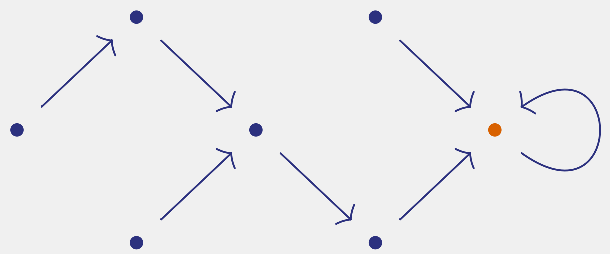
Transition Graph



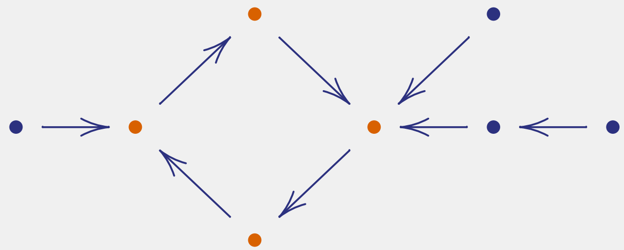
Several possible strategies $\Longrightarrow$ several possible successors for each state.

Three types of attractors in the transition graph :

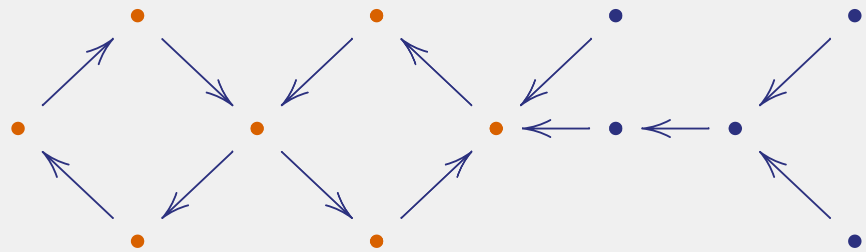
fixed points



simple cycles

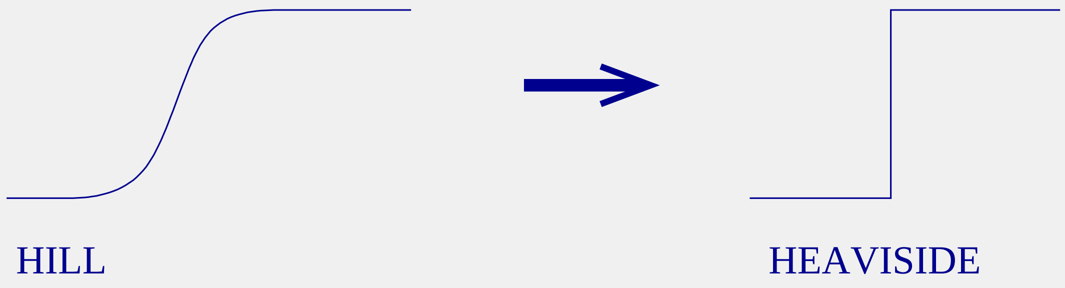


several intricated cycles
"chaotic"



2. Piecewise affine models and their discrete analogues

Principle underlying piecewise affine models :



$\rightsquigarrow$ Differential equations of the form :

$$\frac{dx}{dt} = \Gamma(x) - \Lambda x \qquad (2)$$

$x \in \mathbb{R}_+^n$: vector of concentrations.

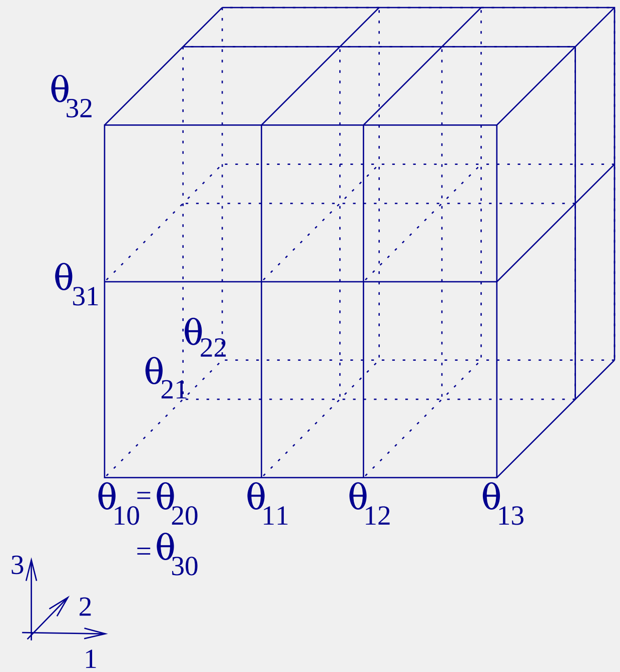
$\Gamma : \mathbb{R}_+^n \to \mathbb{R}_+^n$ production term : piecewise constant.

$\Lambda \in \mathbb{R}_+^{n \times n}$ diagonal matrix : $\lambda_1 \dots \lambda_n$ degradation rates.

Γ constant $\iff$ each x_i between 2 threshold values.

$\rightsquigarrow$ partition of state space into *boxes* :

$$\prod_{i=1}^{n} [\theta_i^-, \theta_i^+]$$

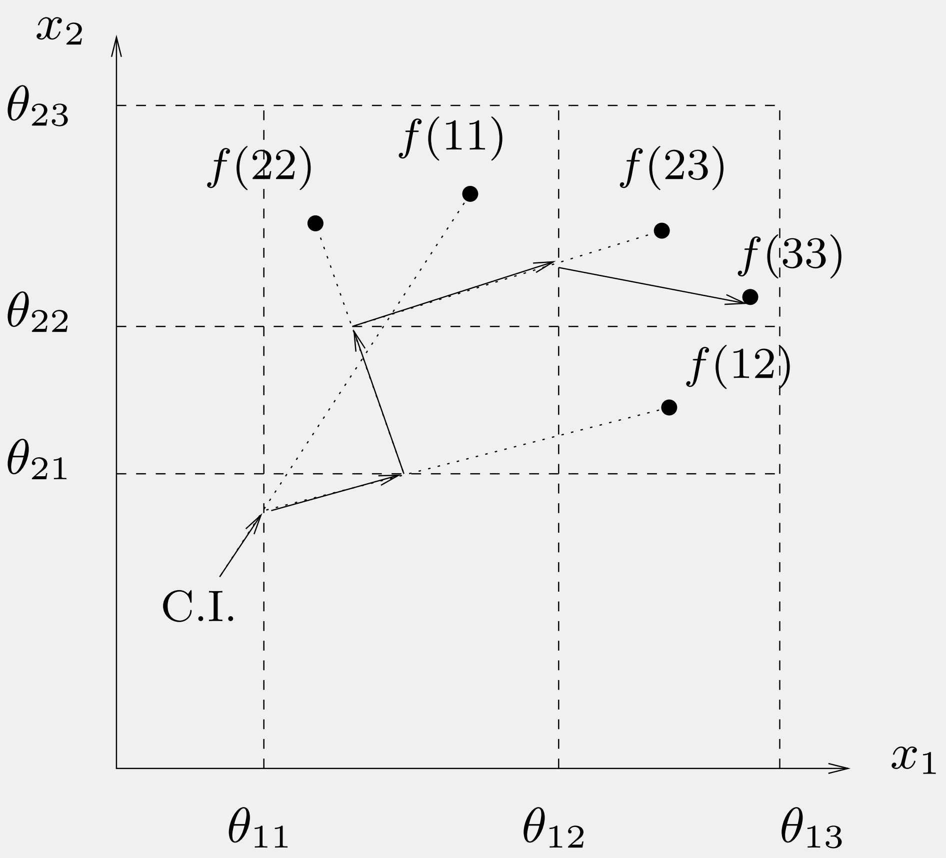


$\rightsquigarrow$ in each box :

$$x_i(t) = f_i + e^{-\lambda_i t}(x_i(0) - f_i)$$

where $f_i = \dfrac{\Gamma_i}{\lambda_i}$ constant.

Reduction to a discrete-time dynamical system



Dynamical system: $(\mathscr{D}, \mathcal{M})$

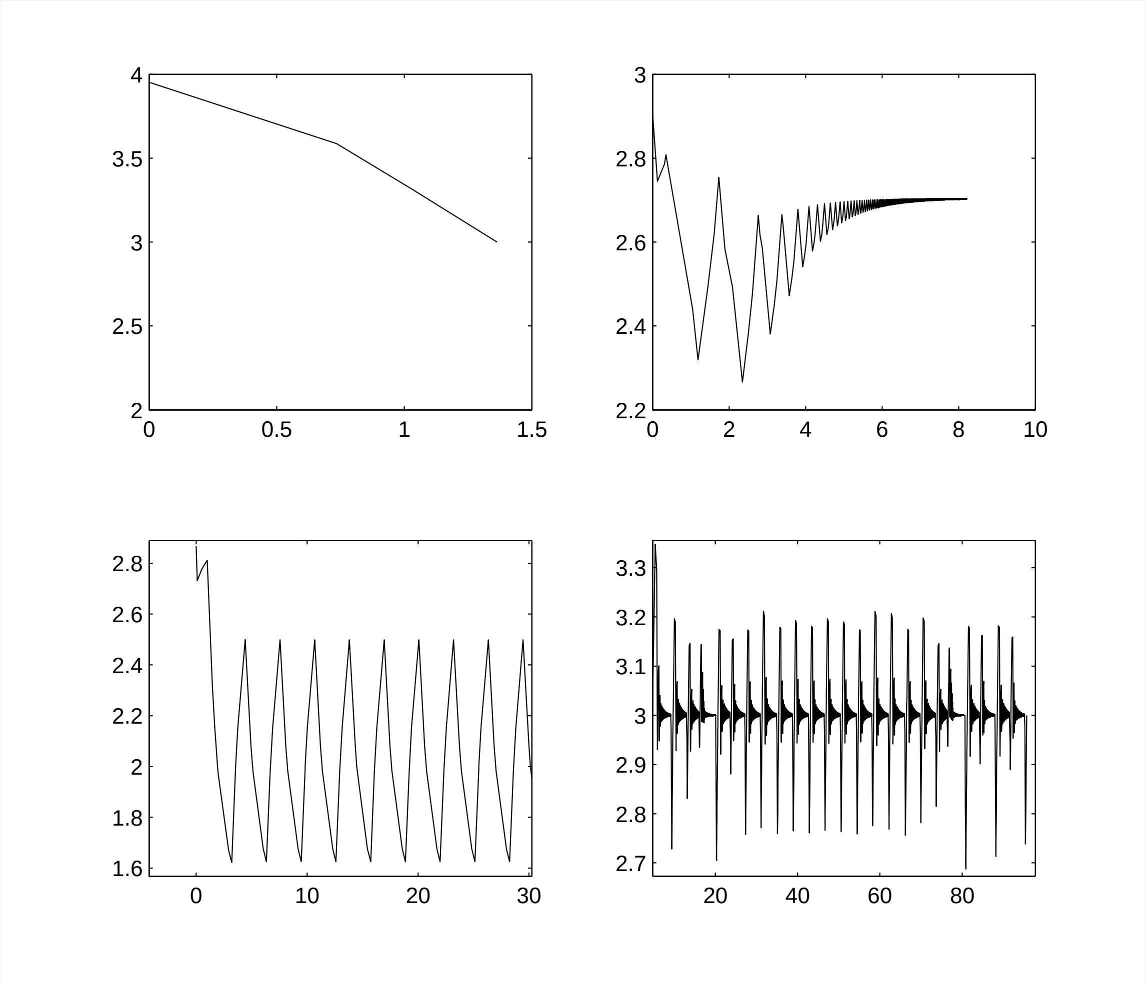
$\mathscr{D}$ union of open facets of boxes : *walls*.

$\mathcal{M} : \mathscr{D} \to \mathscr{D}$, *transition map* deduced from explicit exit time in each box.

In each box $f = (f_1 \dots f_n)$ attracts orbits : often called *focal point*.

$(\mathscr{D}, \mathcal{M})$ can be used for numerical simulations.

Classification of possible attractors :



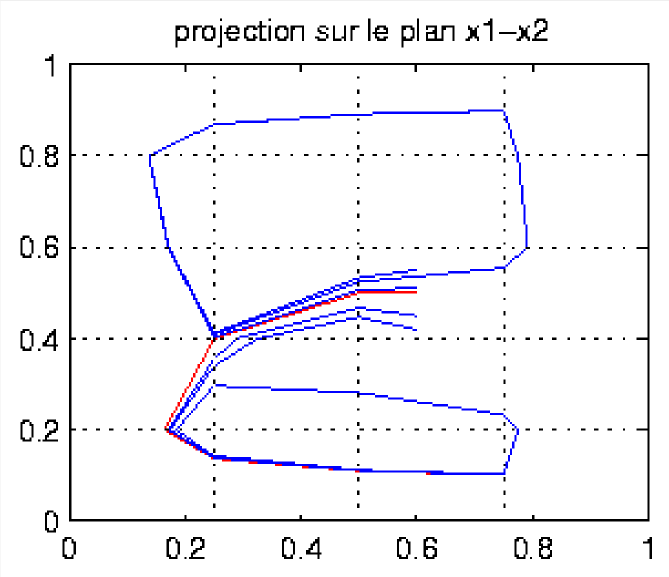
Reduction to a fully discrete system

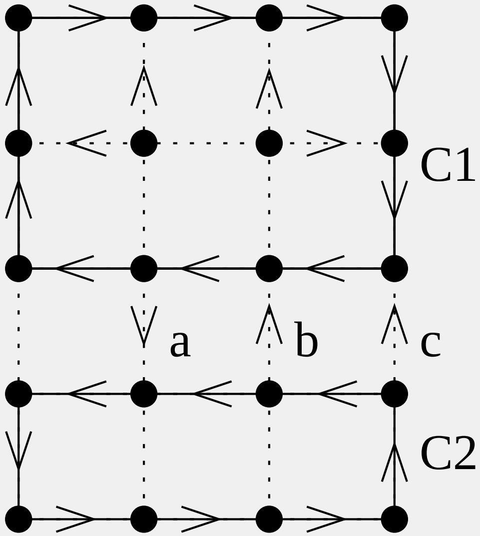
Boxes $\mapsto$ states. Trajectories between adjacent boxes $\mapsto$ transitions.

$\rightsquigarrow$ $\exists$ unique discrete model for each piecewise-affine system.

Continuous trajectory $\mapsto$ fully asynchronous discrete orbit.

Discrete orbits do not always represent continuous trajectories.





3. Symbolic dynamics as a common framework

Some basics of symbolic dynamics

Global viewpoint :

Discrete dynamical system	$\leftrightarrow$	Symbolic dynamical system
$(\mathcal{A}, F)$	$\leftrightarrow$	(Σ_F, σ)
$\mathcal{A}$ finite : *alphabet*	$\leftrightarrow$	$\Sigma_F \subset \mathcal{A}^{\mathbb{N}}$: *language, or "shift space"*
$a \in \mathcal{A}$: *symbol*	$\leftrightarrow$	$\mathbf{a} \in \{a, F(a), F^2(a), \dots\} \in \Sigma_F$: *infinite word*

σ *shift map* : $\boxed{\mathbf{a} = a^0 a^1 a^2 \cdots \longmapsto \sigma(\mathbf{a}) = a^1 a^2 a^3 \cdots.}$

complicated map on a simple space $\ggg$ simple map on a complicated space

Σ_F, endowed with a metric $\rho(\mathbf{a},\mathbf{b}) = \sup_{k\in\mathbb{N}} \frac{\delta(a^k, b^k)}{2^k}$ $\rightsquigarrow$ topological space.

With this metric, σ is continuous $\rightsquigarrow$ (Σ_F, σ) topological dynamical system.

Comparison between topol. dynamical systems (X, f) and (Y, g) :

Continuous $\phi : X \to Y$, such that

$$\begin{array}{ccc} X & \xrightarrow{\phi} & Y \\ {\scriptstyle f}\downarrow & \circlearrowleft & \downarrow{\scriptstyle g} \\ X & \xrightarrow[\phi]{} & Y \end{array}$$

ϕ bijective : *topological conjugacy* $(Y, g) \sim (X, f)$ $\rightsquigarrow$ topologically indistiguishable.

Topological entropy : $h(\Sigma, \sigma) = \lim_{p\to\infty} \frac{\log \#\mathcal{L}_p(\Sigma)}{p}$ conjugacy invariant.

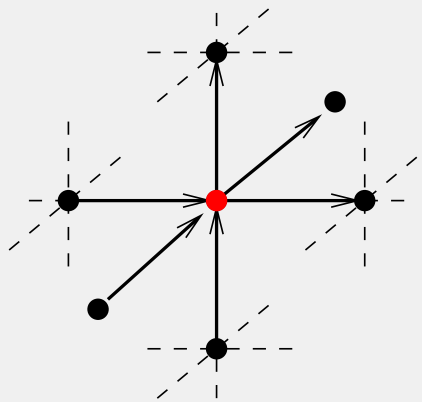
Transition graph induces a symbolic dynamical system (Σ, σ) ; infinite paths.
The "coding" *piecewise-affine* $\rightarrow$ *discrete* induces a mapping $\phi : \mathscr{D} \rightarrow \Sigma$.

We have seen that not all discrete orbits are *admissible* : ϕ not a conjugacy.

But $\phi(\mathscr{D})$ subshift of Σ, *i.e.* $(\phi(\mathscr{D}), \sigma)$ symbolic dynamical system.

We define $h(\mathscr{D}, \mathcal{M}) = h\,(\phi(\mathscr{D}), \sigma) \implies \quad h(\mathscr{D}, \mathcal{M}) \leqslant h(\Sigma, \sigma)$.

For instance, at most one pair of "double transitions" is admissible among the three :



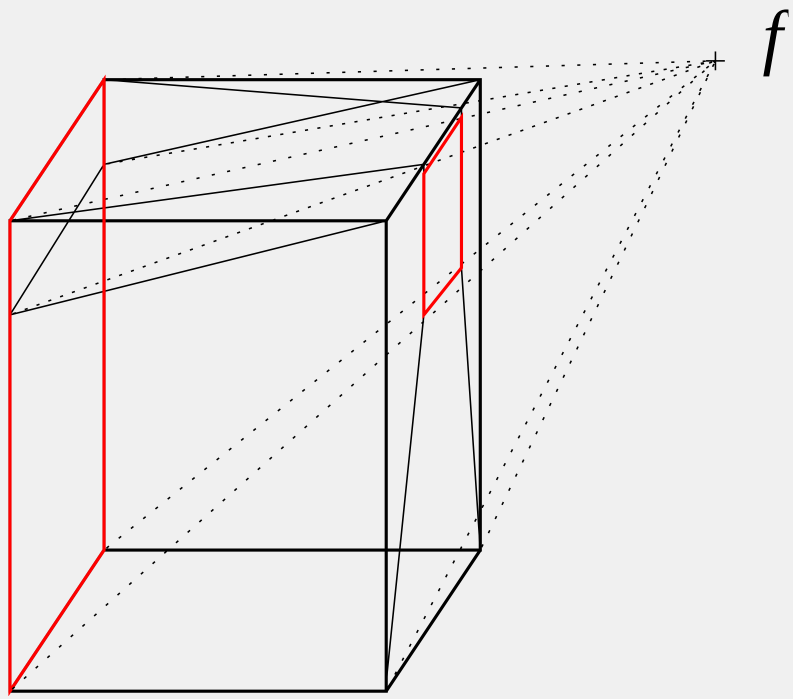
- Due to geometric constraints
- True in any dimension

Intuition in dimension 3

focal point $\equiv$ fixed eye watching a transparent cube.

trajectories $\equiv$ light rays.

Can not see more that one pair of parallel faces as superposed.



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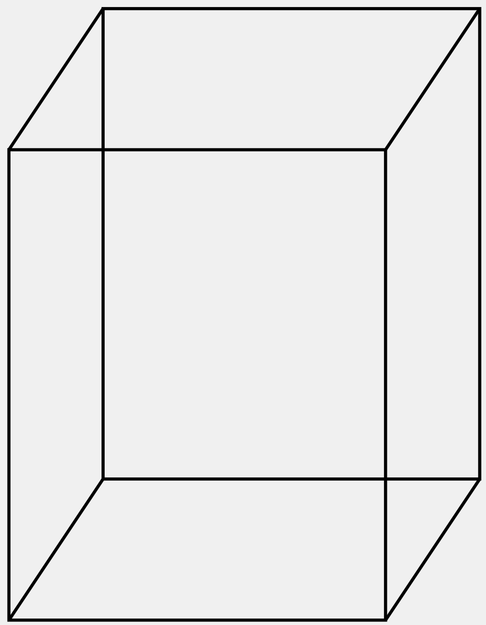

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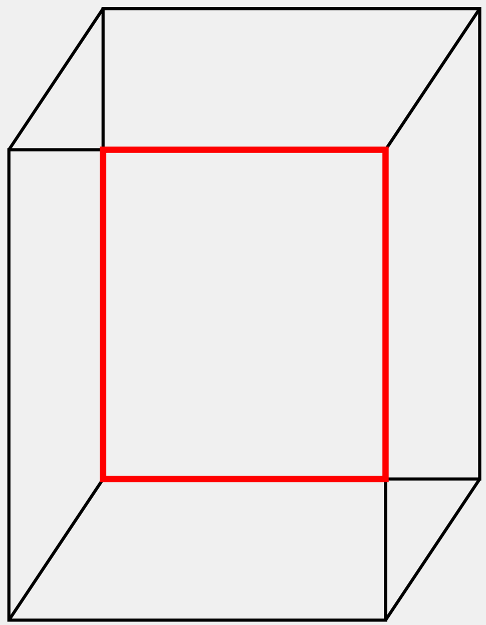
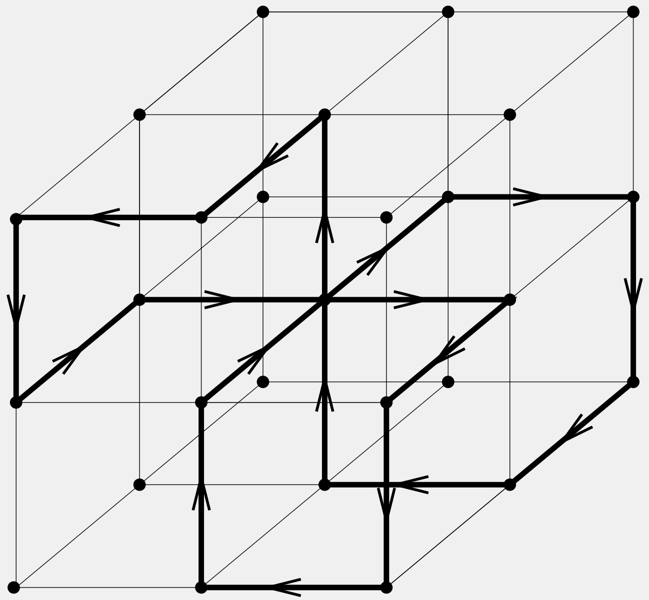


Double transitions inside intricated loops $\rightsquigarrow$ consequence on the entropy :

$$\Longrightarrow \quad h(\mathscr{D}, \mathcal{M}) \; < \; h(\Sigma, \sigma)$$

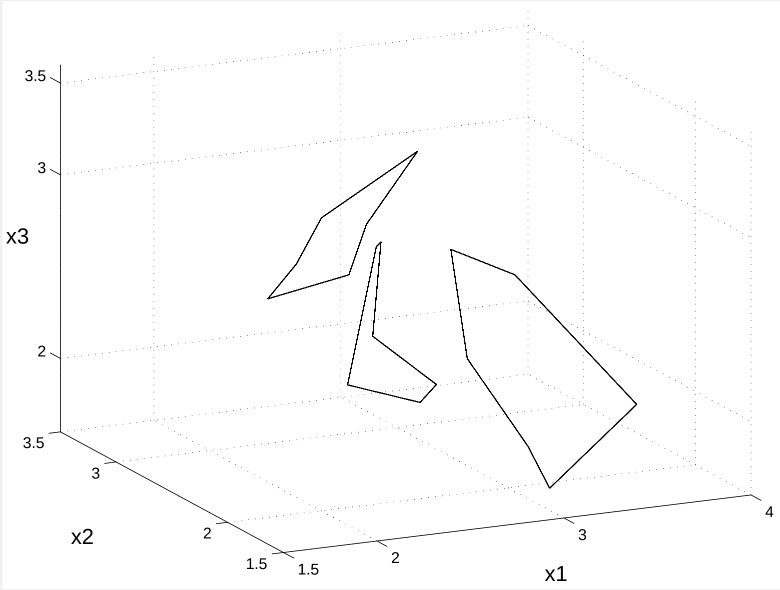
For example:

$h(\Sigma, \sigma) > 0$



and

$h(\mathscr{D}, \mathcal{M}) = 0$



This inequality can be interpreted as follows:

the number of admissible orbits is neglictible among all discrete orbits, asymptotically.

Moreover $h > 0 \implies$ chaos

Chaos observed in piecewise affine systems.

Biologically, the role of deterministic chaos is far from clear :

- existence ?
- due to stochastic events, or noise ?
- useful to generate various (unstable) periodic behaviours ?
- harmful ?

Conclusion

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An important interpretation of biological phenomenons :

mode of behaviour of a biological cell $\Longleftrightarrow$ attractor of a dynamical system

Especially (Waddington, Delbrück) :

multiple stable attractors $\Longleftrightarrow$ cell differentiation

$\leadsto$ Important to describe attractors of those system.

- ⋆ Biological complexity requires a kit of various models.
- ⋆ Piecewise affine models are tractable, and intermediary between discrete and smooth nonlinear ones.
- ⋆ Here : comparison between discrete and piecewise-affine.

Perspectives

⋆ Obtained results require assumptions : no autoregulation, no simultaneous threshold crossings.
⇝ Need to be extended (Fillipov solutions).

⋆ The structure of cubical complex is naturally present
⇝ More elaborate invariants than topological entropy (algebraic topology).

⋆ Confrontation with real biological systems.