Complex stochastic dynamics in living systems and their regulation

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A fundamental question :

in what respect **living** systems differ from **physical** systems ?

A practical corollary :

how does this difference impact on their analysis/modeling ?

A few clues :

not only dissipative open systems, but also **ecosystems**

evolutionary history ... short cut with the notion of **function**

ubiquitous **regulation** and functional **robustness**

Emergence

Assembly of interacting cells showing **collective** behaviors

The realm of **statistical physics** !

Notion of **effective parameters**, accounting for details/mechanisms at lower scales in a yet integrated way : kinetic rates, elastic coefficients, coupling constant

Consistency between the global variables and the state of the individuals (standard example : ferromagnetism and Ising model)

Complex systems and their circular causality

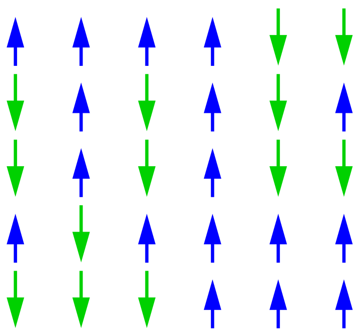
Beyond the generation of mean-fields and emergent/collective variables, elements are able to modify collectively their **micro-environnement**, which in turn exerts a **feedback** on the elements states and dynamics, even on their potentialities and rules

$\Longrightarrow$ **reciprocal** interplay between individual and collective levels

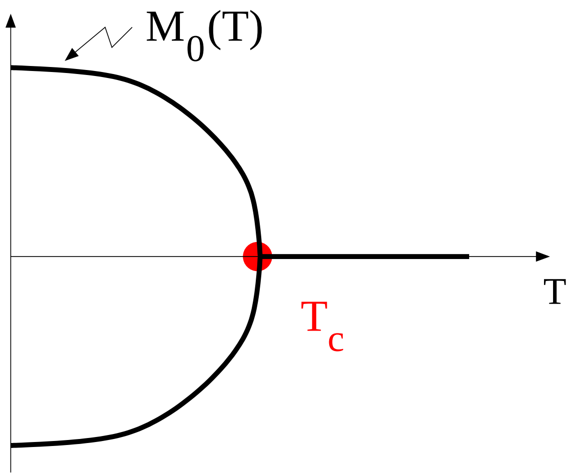
Dunes, canopies ... biofilms, tumors ....

Current in control theory ... and **intrinsically in living systems**

The example of Ising model



coupling $-J\ s_i s_j$



– Scale separation : $T \neq T_c$ free energy $F(T, M)$

$$\langle s_i s_j \rangle = \langle s \rangle^2 \sim M^2$$

– Critical : $T = T_c$, $M(T) \sim (T_c - T)^\beta$, $\xi(T) \sim (T_c - T)^{-\nu}$

– Complex : slaving of T or J to M

A class of examples :

- Assembly of interacting cells showing collective behaviors

  (emergence)

patterns, transitions, spontaneous segregation, localization,

- Able to modify collectively their micro-environnement

  (regulation)

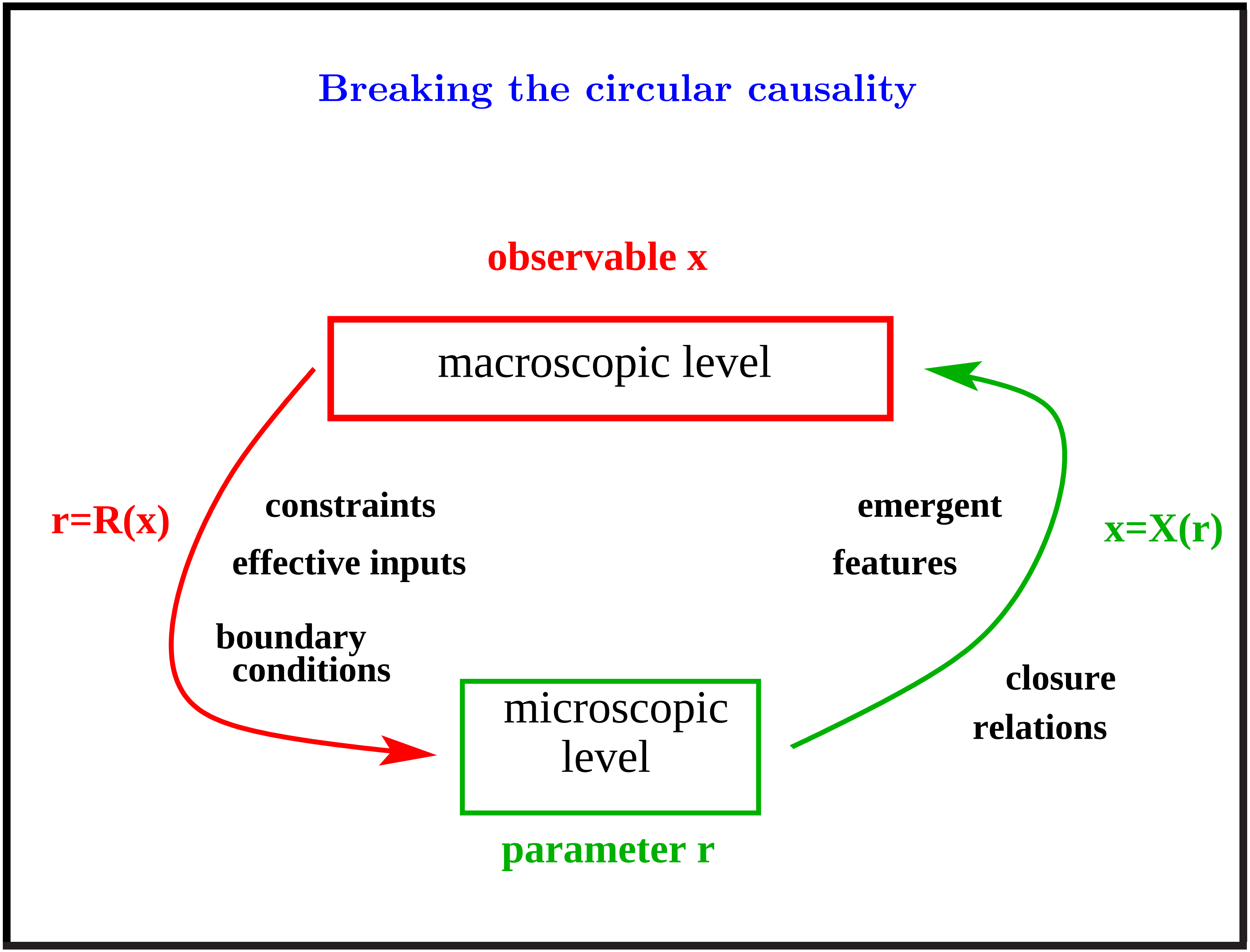
complex interplay between individual and collective levels

Example : **Metastatic escape** (tumor modifies its surroundings)

In a first step : minimal model of **essential mechanisms**

(explanatory purposes, robustness, hypothesis testing ...

... and communication with colleagues from biology)


Breaking the circular causality
observable x
macroscopic level
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When a cell population collective outcome triggers a rare individual event : a mode of metastatic process

Joint work with Georgia Barlovatz-Meimon, Amandine Cartier-Michaud, Franck Delaplace, Guillaume Hutzler and Michel Malo

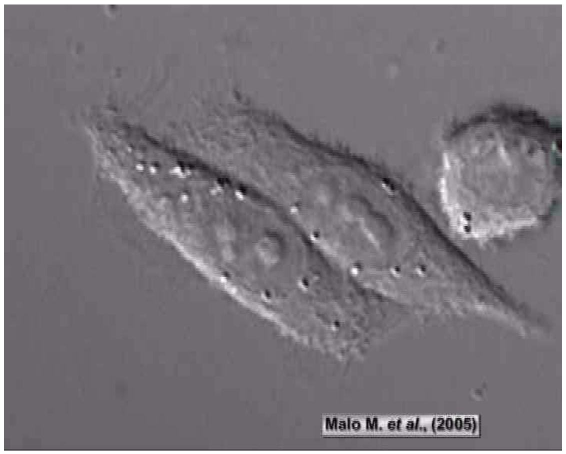
Mathematical Population Studies 17, 136-165 (2010)

Articulating **dynamical systems theory** (for individual cells) and **stochastic population dynamics** (agent-based simulation) to understand a **rare event**

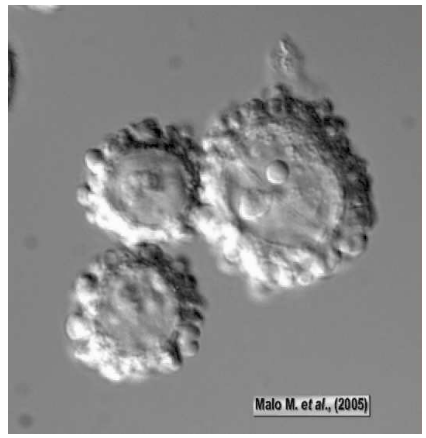
A plausible scenario of (early) metastatic process

Experimental fact : a molecule, PAI-1, controls the cancer cell transition from a proliferative state $\mathcal{M}$ to a migratory state $\mathcal{A}$

through its action on some metabolic pathways, cell morphology, adhesion properties and microenvironment



$$\mathcal{M} \xrightarrow{\quad\text{PAI}-1\quad} \mathcal{A}$$

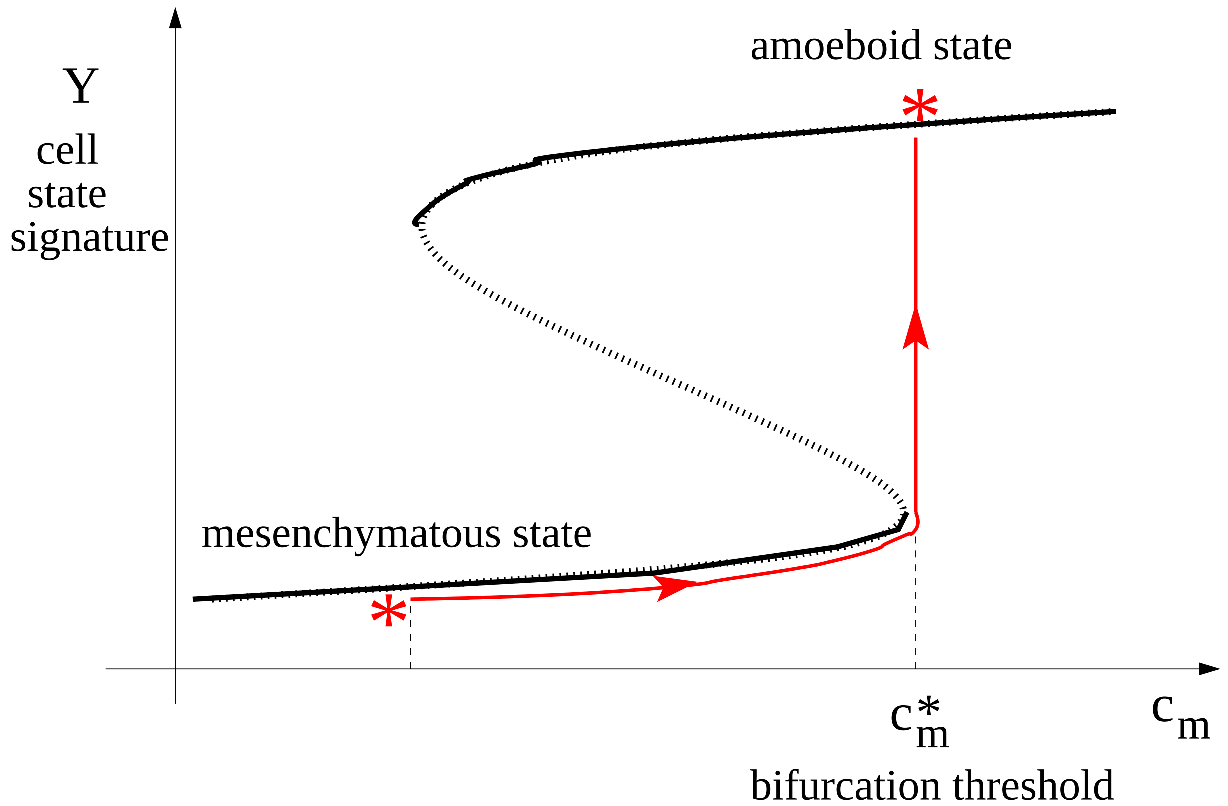


- Some PAI-1 is released outside the cell and binds the matrix
- Matrix-bound PAI-1 is internalized
- mbPAI-1 internalization triggers the transition $\mathcal{M} \rightarrow \mathcal{A}$

Hypothesis : PAI-1-induced bifurcation

Cell transition $\mathcal{M} \rightarrow \mathcal{A}$ controlled by the microenvironment (internalization flux) without any intrinsic specificity

Generic model of bistability : subcritical bifurcation

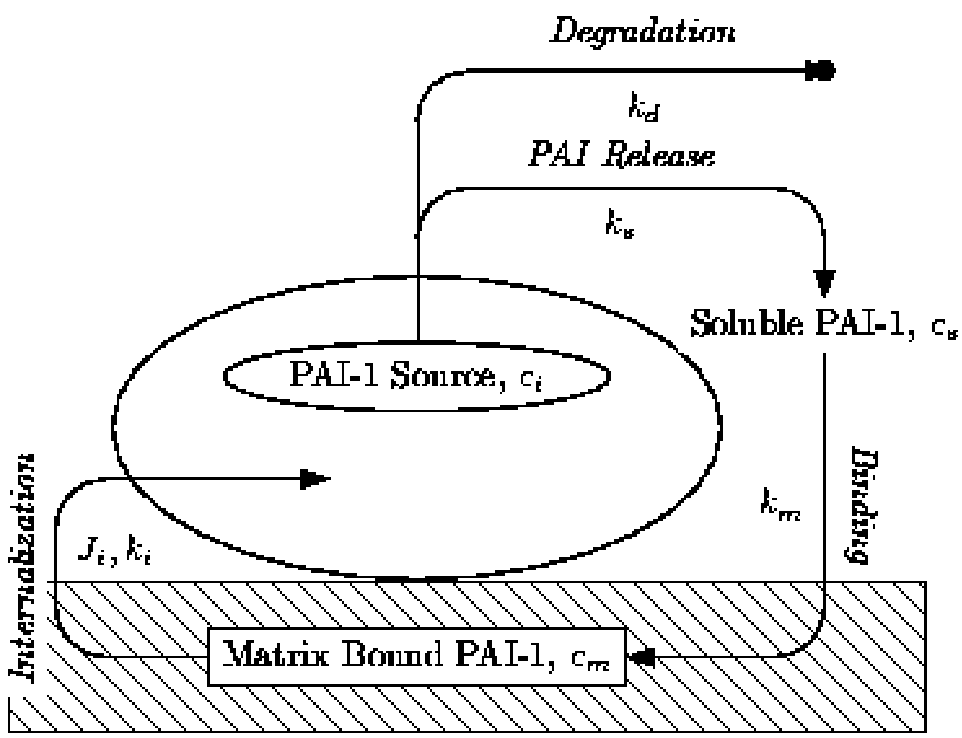


Minimal model of PAI-1 transactions

Three forms : internal, soluble (diffusing) and matrix-bound

internal→ soluble, soluble (diffusing) → matrix-bound

Relevant quantity = matrix-bound-PAI-1 internalization flux



Collective effect with a (randomly) localized consequence

Partial differential equations yield an all-or-none behavior

whereas metastatic escape is a rare event

Hypothesis : essential effect of local fluctuations (cell growth)

No need to invoke some cell specificity (neutral selection)

Random and **history-dependent**

Partial, targeted numerical check with **stochastic simulations** at the cell level

Difficulties : experimentally unknown parameters, lots of factors

$\longrightarrow$ **minimal model**

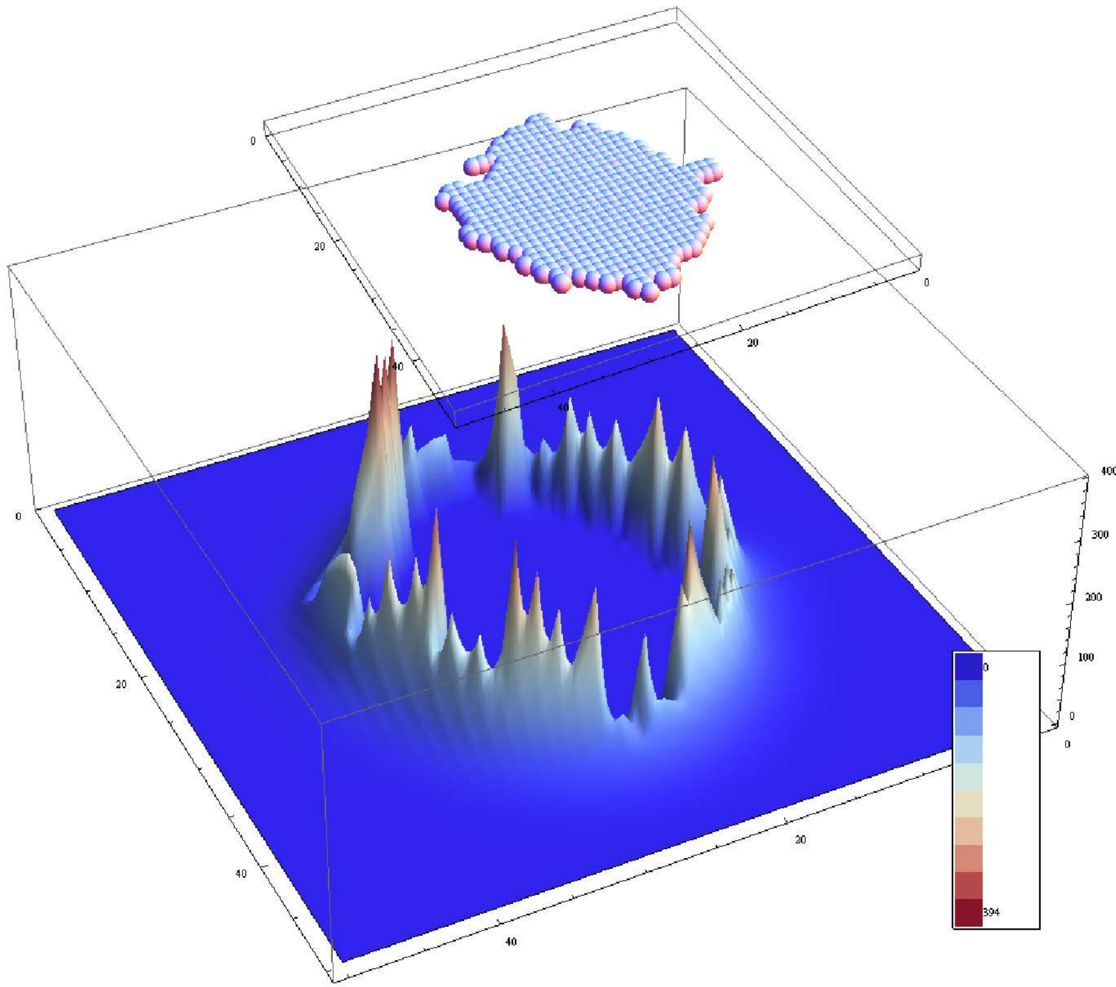
Recursive construction : multi-agent then cellular automata

Partial differential equations

$$
\begin{aligned}
\partial\sigma/\partial t &= k_g\, H(1-\sigma) \int_{\mathbf{R}^3} \sigma(\vec{r}')\Gamma(\vec{r}'-\vec{r})d\vec{r}' && (1)\\
\partial c_i/\partial t &= \sigma f(c_i) - k_s\sigma c_i && (2)\\
\partial c_s/\partial t &= (1-\sigma)D\Delta c_s + k_s\sigma c_i - k_m(1-\sigma)c_s - k_d\sigma c_s && (3)\\
\partial c_m/\partial t &= k_m(1-\sigma)c_s - k_i\sigma c_m && (4)\\
J_i &= k_i c_m \qquad \text{for} \;\; \sigma > 0 && (5)
\end{aligned}
$$

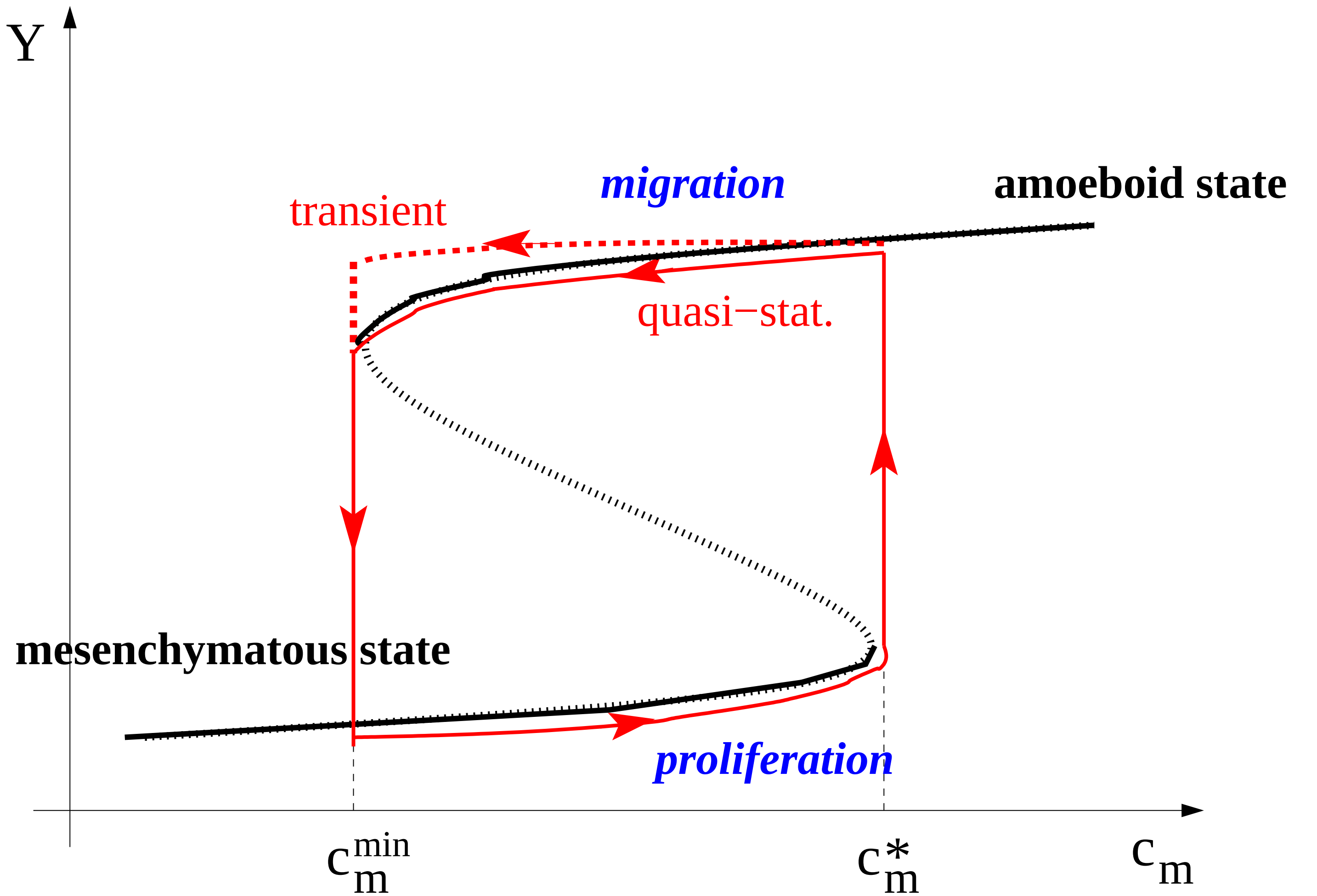
All-or-none behavior whereas metastatic escape is a rare event

Numerical proof-of-principle



spontaneously localized accumulation in a wide range of parameters

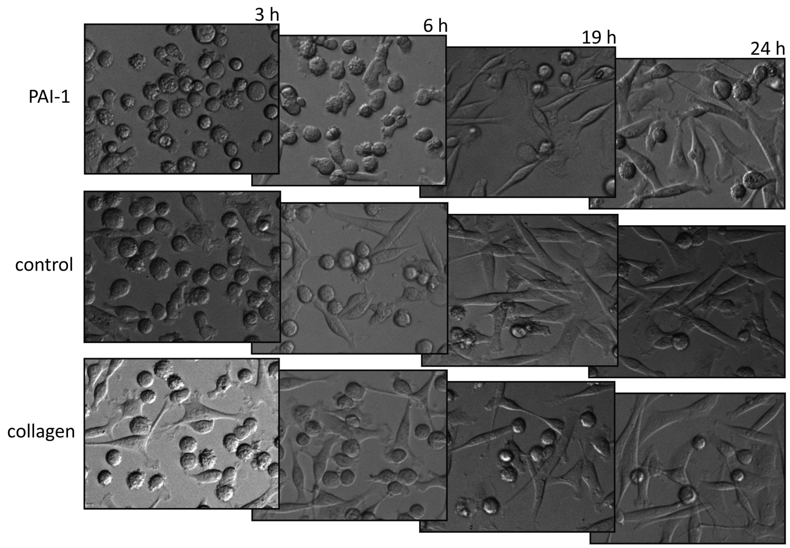
Integrated scenario

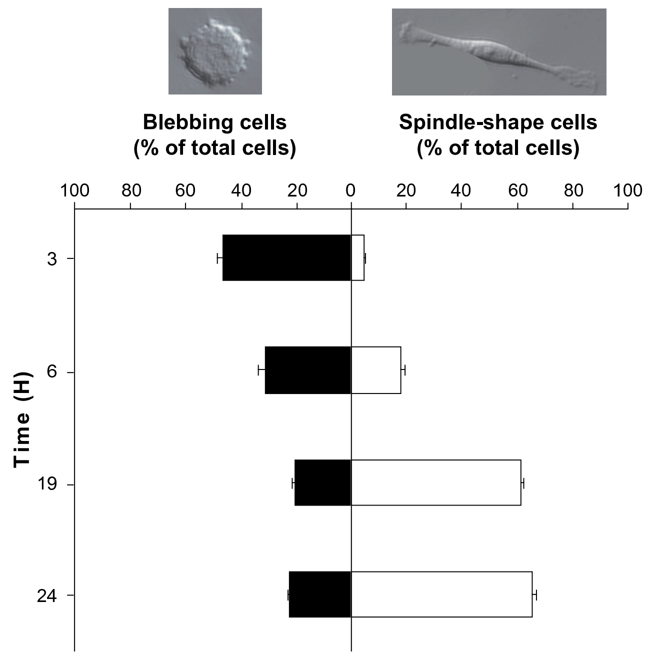


one cell **within** a population that modify the surroundings

Reverse amoeboid-mesenchymal transition

Prediction / validation of the S-shaped bifurcation diagram





In vitro proof-of-principle of **PAI-1-controlled hiving**

Metastatic escape : a case study of a complex system

- a rare event (no direct experimental access)
- interplay of intracellular, extracellular and population levels
- amplification of random and history-dependent fluctuations
- cooperativity yielding singularity
- articulation of various semiquantitative models
- from experiments to other experiments

Multiscale modeling and integration

Bottom-up : emergence

– mean-field, homogenization

– singular perturbations, multiple scales

– criticality, renormalization

Top-down : context-dependence

– effective inputs and fields

– boundary conditions

– conservation laws

Complex/living systems :

– circular causality

– robustness

– adaptation and adaptability

Example of the sand dune

The dune, if enough large, modifies qualitatively (bifurcation) the wind flow in the boundary layer, hence the interaction between the wind and the sand grains is different within the dune (work of **Stéphane Douady**, CNRS MSC Paris 7)

Regulation

feedbacks of emergent features **onto the rules and possibilities** of the elements, allowing for a drift of the state of all levels jointly

$\Longrightarrow$ **adaptive** degree of freedom of the self-consistent state

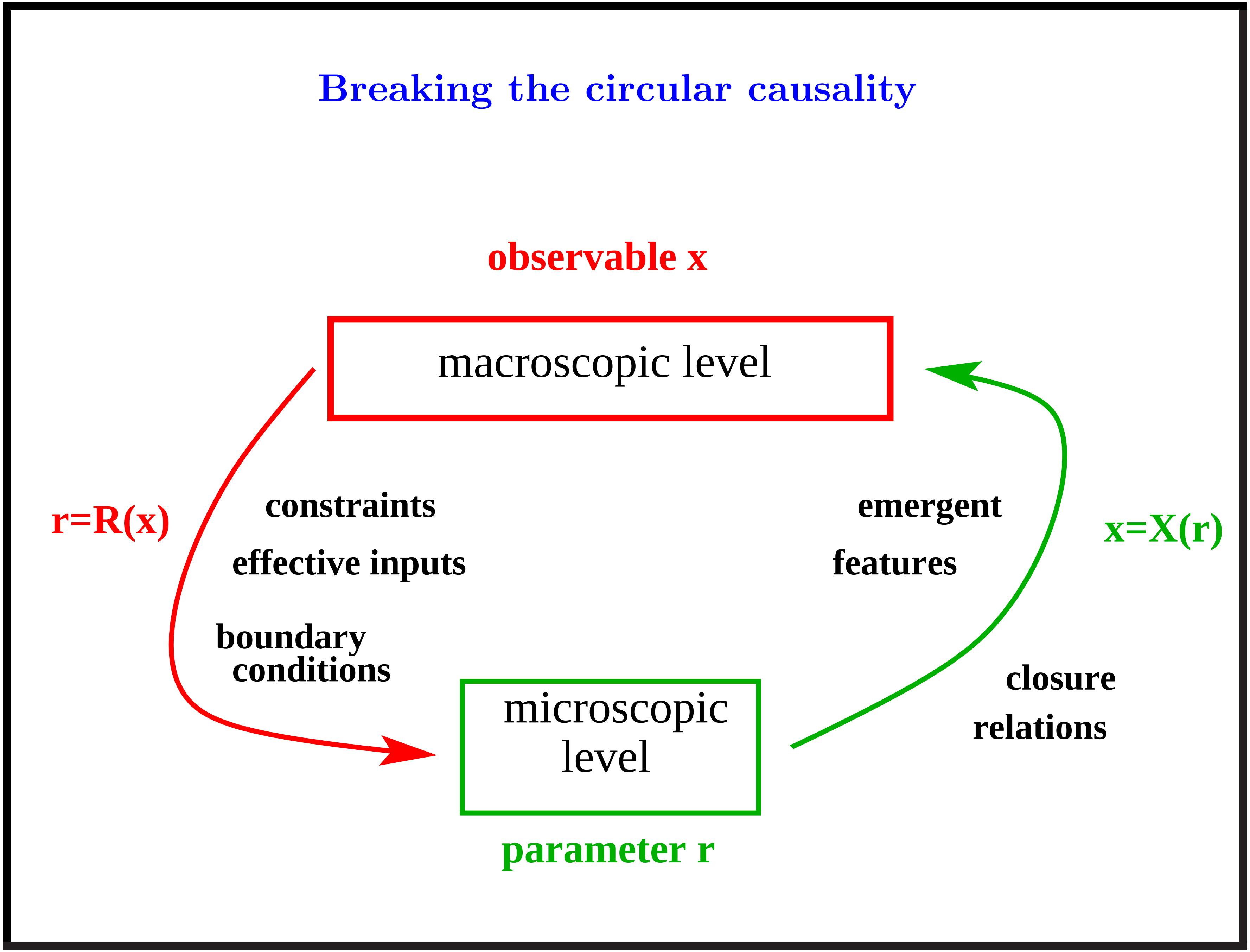
(counter-example : the dune)

specificity of living systems : a posteriori design by natural selection and co-evolution, ensuring robustness and adaptability

A modeling challenge !

dissecting the mechanisms at one level, articulation of several models (interlevel coupling providing effective parameters (bottom-up) and constraints (top-down), hybrid simulation....

A wealth of examples : cell biology and development, neural networks and learning, ecosystems, biofilms ...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observable x
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Modeling of living systems ...

- challenge of **multiscale integration** and capturing **regulation**
- reductionnism in a proper **context** (top-down causation)
- **functional** approach to involve the **evolutionary history**
- one model **for each** biological question (specific pruning of details)
- proofs come from **experiments and data**
- In a first step, no need of sophisticated and technical tools ...

  modeling is abstraction rather than mimicky