

Introduction viability algorithms

Genetic Inclusions in discrete time

Alexandra Fronville

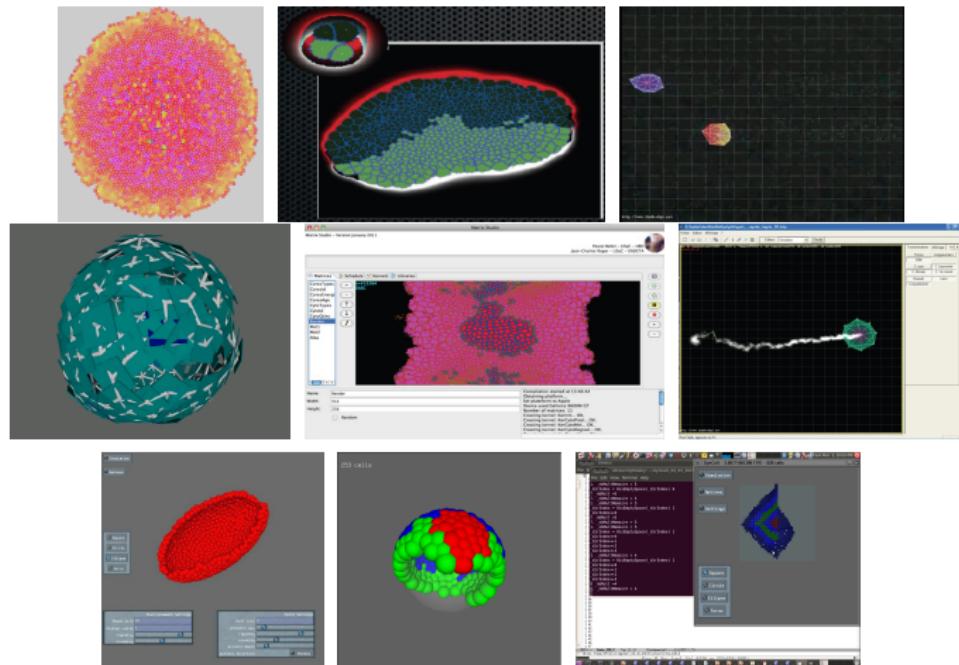
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Equipe Virtulab

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Link between cellular dynamic and multicellular patterns



Mechanical feedback as regulator of tissue growth

1

Introduction

- Multiscale problems

2

Introduction

- Understanding multicellular growth

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Medical imaging

- DynCell : 3D-multi-agent simulation

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Mathematical background

- Controlled Systems
- Morphological Mathematics
- Mutational equations
- Mutational equations

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Morphological dynamic

- Discrete Morphological dynamic

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Morphological dynamic

- Discrete Morphological dynamic

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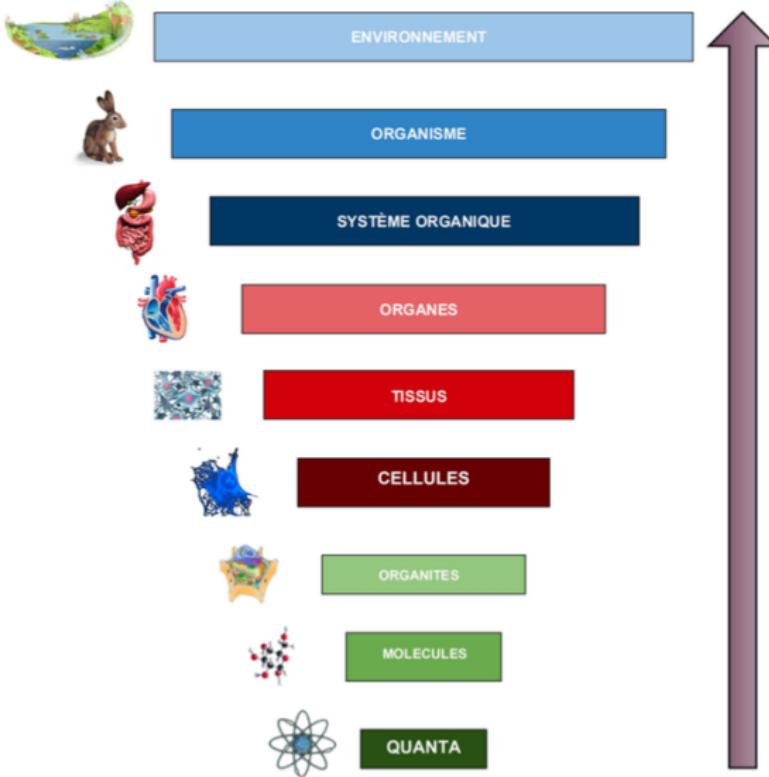
Morphological dynamic

- Discrete Morphological dynamic

8

Morphological dynamic

Biological context



Morphogenesis, Tumor growth :

- Large number of elementary agents interacting locally
- More or less simple individual agent behaviors creating a complex emergent self-organized behavior
- Decentralized dynamics

Heterogeneity in tumor architecture

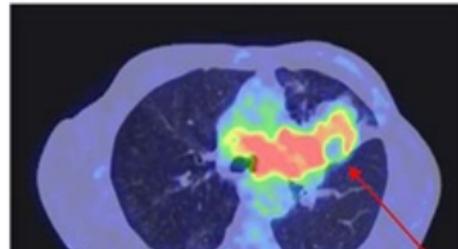
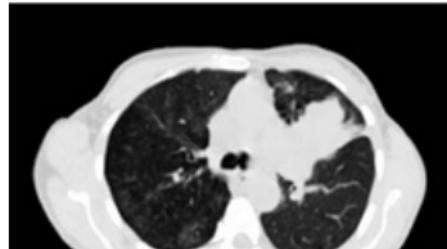
- The majority if solid malignancies studied was found to have the hallmark of a heterogeneous tumor architecture.
- Tumor tissue architecture is an importanat factor that influence drug delivery.
- Complementary involvement of the level of expression and the spatial distibution of Ki67 and PR phenotypes in luminal breast tumours HER2.

[1] B. Plancoulaine, Catherine Bor-Angelier et al.. Etude en histo-imagerie de l'hétérogénéité intra-tumorale des cancers du sein invasifs de sous-type luminal.

[2] Youcef M. Rustum et al. Architectural Heterogeneity in Tumors Caused by Differentiation Alters Intratumoral Drug Distribution.

Medical imaging

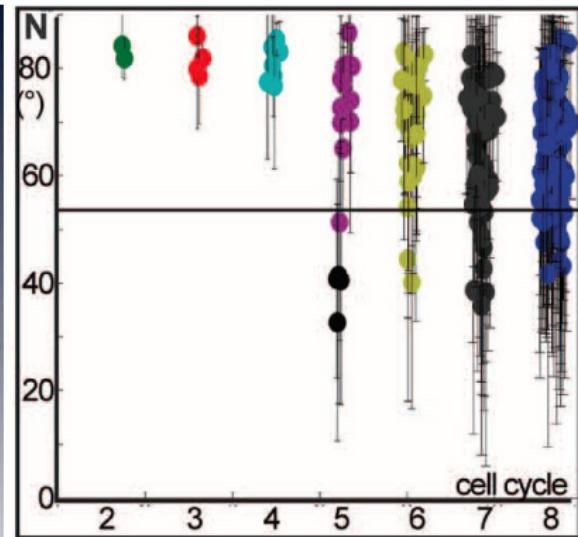
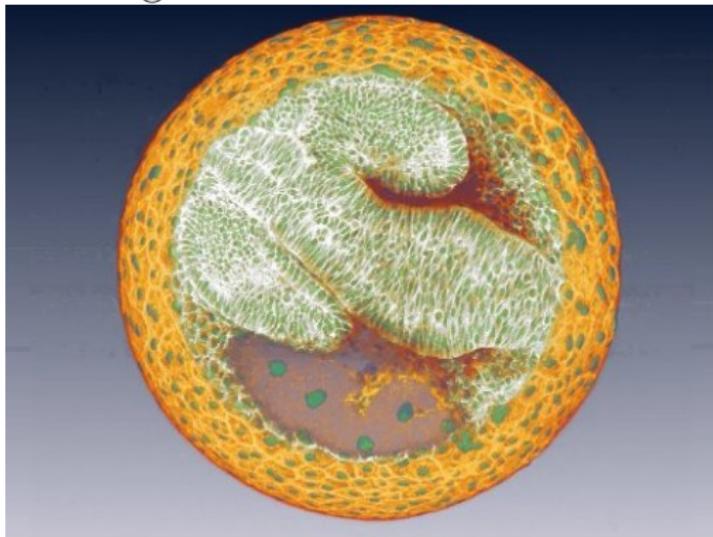
- Positron emission tomography PET (TEP)
 - functional imaging technique that produces a three-dimensional image of functional processes in the body (glucose)
 - used in a quasi-systematic way in oncology
- CT scan, also called X-ray computed tomography (X-ray CT)
 - allow the user to see the shape of the tumor inside the body without cutting.



Confocal imaging

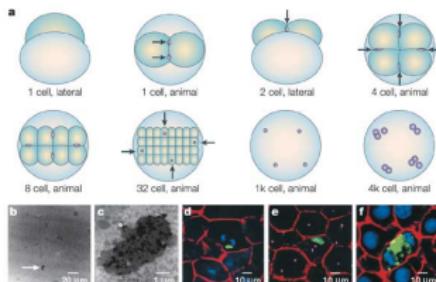
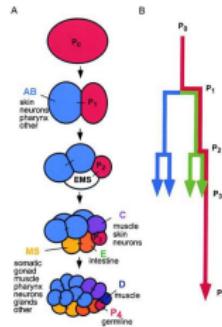
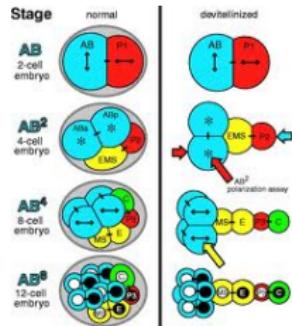
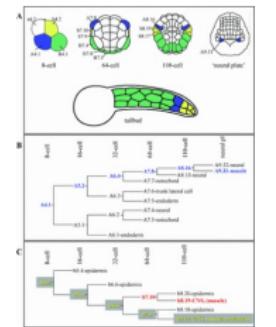
A lot of data from Biologist show the influence of cells dynamic in morphogenesis.

The segmentation axis is not random.



Nadine Peyrieras (DEPSN CNRS)

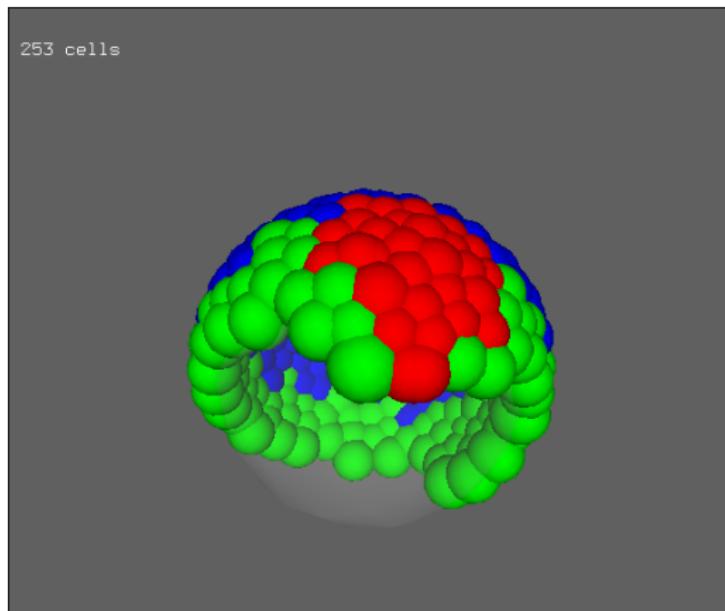
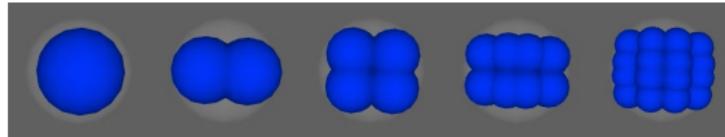
First segmentation



Nature Reviews | Genetics

In virtuo

3D-multi-agent simulation.



Controlled Systems, Controllability

Given a dynamical system which depends on a parameter (named control) and an initial condition, the control theory studies the computation of a control law such that the solution tends to a desired final state. This is the so-called controllability property (in finite or infinite time)

Controlled Systems

A controlled system is given by a state space X , a space of controls U and a evolution law : $\dot{x}(t)/dt = f(t, x(t), u(t))$, where $x(t) \in X$ is the state of the system at time $t \in [0, T]$ and $u(t) \in U$ is the control. This is called controllability (time finite or infinite) . The system is said to be :

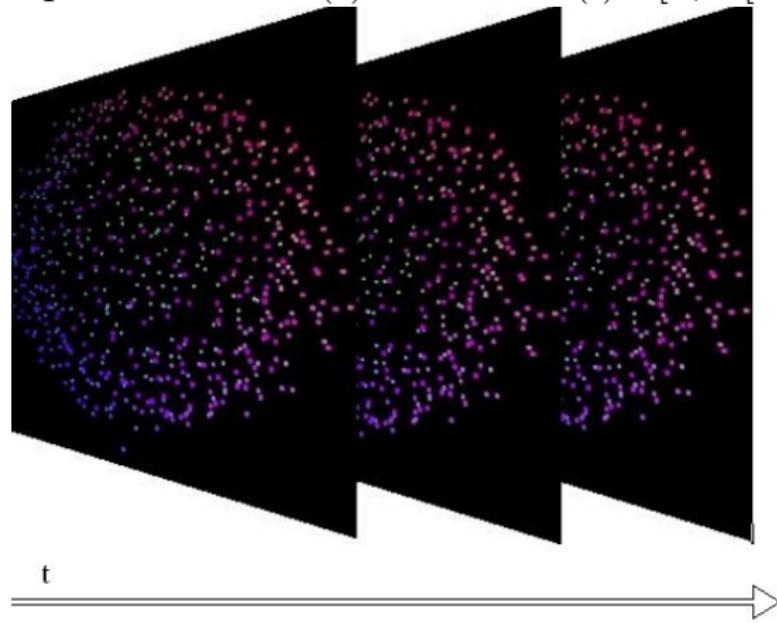
- **controllable** on $[t_0, t_f]$ if given any initial state x_0 , there is a continuous control $u(t)$ that steers the state of the system from $x(t_0) = x_0$ to $x(t_f) = 0$.
- **reachable** on $[t_0, t_f]$ if given any final state x_f , there is a continuous control $u(t)$ that steers the state of the system from $x(t_0) = 0$ to $x(t_f) = x_f$

Morphological Mathematics, J-P Aubin 2000

- We need a "nonvectorial" approach to evolving compact subsets and describing shape dynamics on the basis of distances.
- Evolving compact subsets of \mathbb{R}^N
- No a priori restrictions on the regularity of final contours.
- No parameterization of boundaries while expanding.
- Mitosis need set-valued and morphological analysis
- Morphological transitions.
- Shapes derivative.

Morphological Mathematics, J-P Aubin 2000

A set-valued map which associates each time $t \in [0, T[$ with a nonempty compact subset $K(t) \subset \mathbb{R}^N : K(\cdot) : [0, T[\mapsto K(\mathbb{R}^N)$.



Mutational equations, J-P Aubin 2000

The shape is a target

The task provide a regulation law for regulating the system in order to reach and maintain the dynamic shape.

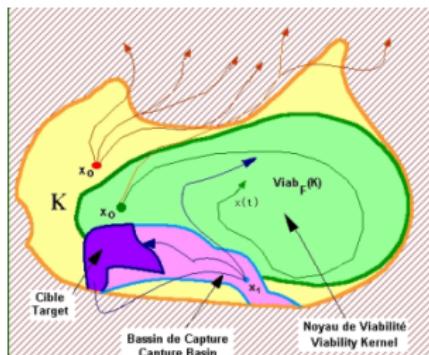
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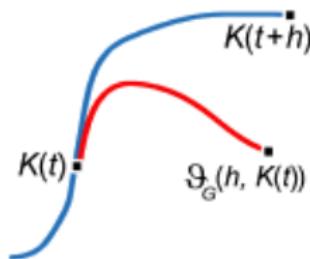
Operability Kernel

It is to characterize the subsets having this property without solving the system and checking the existence of operables solutions for each initial state.



Mutational equations, J-P Aubin 2000

Extending ODE to metric spaces



Transition

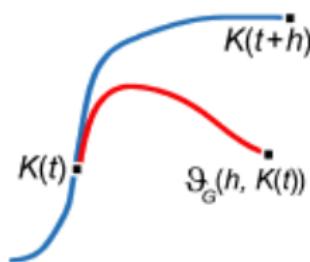
(E, d) metric space

$$\vartheta : [0, 1] \times E \rightarrow E, (h, x) \mapsto \vartheta(h, x)$$

determines to which point $\vartheta(h, x) \in E$ any initial point $x \in E$ is moved at time $h \in [0, 1]$.

Mutational equations, J-P Aubin 2000

Extending ODE to metric spaces

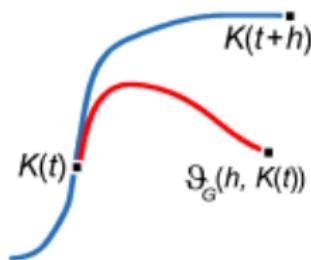


Reachable set

$$\begin{aligned} \vartheta_f : [0, 1] \times \mathcal{K}(\mathbb{R}^N) &\rightarrow \mathcal{K}(\mathbb{R}^N) \\ (t, K_0) \mapsto & \{x(t) \text{ s.t. } \exists x(\cdot) \in C^1([0, t], \mathbb{R}^N) \\ & x'(\cdot) = f(x(\cdot)), x(0) \in K_0\} \end{aligned}$$

Mutational equations, J-P Aubin 2000

Extending ODE to metric spaces



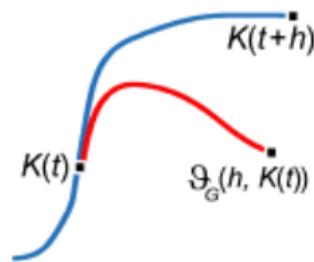
Mutation of $x(\cdot)$ at time t

Let $\Theta(E, d)$ a non-empty set of transitions

$$\mathring{x}(t) := \{\vartheta \in \Theta(E, d) \mid \lim_{h \downarrow 0} \frac{1}{h} \cdot d(\vartheta(h, x(t)), x(t + h)) = 0\}$$

Mutational equations, J-P Aubin 2000

Extending ODE to metric spaces

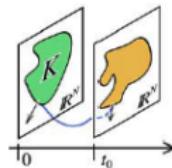


Mutational equation

$$\mathring{x}(t) \ni f(x(.), .)$$

Morphological equations, J-P Aubin 2000

Morphological equations for compact sets in \mathbb{R}^N with
Pompeiu-Hausdorff distance



Morphological transition on $(\mathcal{K}(\mathbb{R}^N), d)$

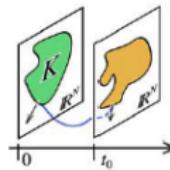
Reachable set

$F : \mathbb{R}^N \rightsquigarrow \mathbb{R}^N$ a set-valued map, we define

$$\begin{aligned}\vartheta_F(t, K_0) := \{x(t) | \exists x(\cdot) \in C^1([0, t], \mathbb{R}^N) : \\ x'(\cdot) \in F(x(\cdot)), x(0) \in K_0\}\end{aligned}$$

Morphological equations, J-P Aubin 2000

Morphological equations for compact sets in \mathbb{R}^N with
Pompeiu-Hausdorff distance



Morphological mutation

$K : t \in [0, T] \rightsquigarrow \mathcal{K}(\mathbb{R}^N)$ is called a tube in \mathbb{R}^N

$$\overset{\circ}{K}(t) = \{F \in LIP(\mathbb{R}^N, \mathbb{R}^N) \mid \lim_{h \downarrow 0} \frac{1}{h} \cdot d(\vartheta_F(h, K(t)), K(t+h)) = 0\}$$

Morphological equation

$$\overset{\circ}{K}(t) \ni \mathcal{F}(K(.), .)$$

Mutational equations, J-P Aubin 2000

- Adaptation of Cauchy-Lipschitz theorem.

Mutational equations, J-P Aubin 2000

- Adaptation of Cauchy-Lipschitz theorem.
- Adaptation of Nagumo theorem for mutational equation with state constraint.

Mutational equations, J-P Aubin 2000

- Adaptation of Cauchy-Lipschitz theorem.
- Adaptation of Nagumo theorem for mutational equation with state constraint.
- Solution to systems : Peano theorem.

Morphological Mathematics, J-P Aubin 2000

Mutational analysis gives the formal framework to this questions.

- Viable differential equations. : $x'(t) = f(x(t), u(t))$.

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- Viable mutational equations : $\dot{x}(t) \ni g(x(t), K(t))$
- Viable morphological equations : $\dot{K}(t) \ni g(x(t), K(t))$

Morphological Mathematics, J-P Aubin 2000

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- Viable mutational equations : $\dot{x}(t) \ni g(x(t), K(t))$
- Viable morphological equations : $\dot{K}(t) \ni g(x(t), K(t))$
- Viable co-evolutions :

$$\begin{cases} \text{(i)} & x'(t) = f(x(t), K(t)) \\ \text{(ii)} & \dot{K}(t) \ni g(x(t), K(t)) \end{cases}$$

Two fundamentals

The inertial principle

States that the regulations evolve when viability is involved.

Viability multiplier :

To reestablish the viability, the cell must at each time :

- Maintain the dynamic but the constraints changes.
- Maintain the constraints but the dynamic changes.
- Maintain the constraints and the dynamic but the initial conditions changes.

Co-viability.

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- Co-viability is the conjoint evolution of $t \mapsto x(t)$ and $t \rightsquigarrow K(t)$
- $\forall t \geq 0, x(t) \in K(t)$

Discrete morphological dynamic

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The subset of eight actions :

$$d \in \mathcal{A} := \{(0, 0, 1), (0, 0, -1), (0, 1, 0), (0, -1, 0) \\ (-1, 0, 0), (1, 0, 0), (0, 0, 0), \emptyset\}$$

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To describe the transitions :

- geometric transition $x \mapsto x + d$
- stationarity, $x \mapsto x + (0, 0, 0) = x$
- apoptosis, $x \mapsto x + \emptyset = \emptyset$

Discrete morphological dynamic

The genetic inclusion

$$x \rightsquigarrow \{x + d^\lambda, x + d^\lambda\}$$

Discrete morphological dynamic

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$$x \rightsquigarrow \{x + d^\lambda, x + d^\kappa\}$$

The cell x , first go to a new place, eventually the same or the death.

$$x + d^\lambda, d^\lambda \in \mathcal{A}$$

and next divide $x + d^\kappa, d^\kappa \in \mathcal{A}$ in an empty space.

Discrete morphological dynamic

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Transitions :

- sterile migration : $d^\lambda \in \mathcal{A}$ and $d^\kappa = \emptyset$
- stationarity division : $d^\lambda := (0, 0, 0)$ and $d^\kappa \in \mathcal{A}$
- migrating division : $d^\lambda \in \mathcal{A} \setminus \{(0, 0, 0)\}$ and $d^\kappa \in \mathcal{A} \setminus \{(0, 0, 0)\}$

Local morphological dynamic

Each permutation of the eight element of \mathcal{A} represent a cellular type.

$$d_\sigma := \{d_{\sigma(1)}, \dots, d_{\sigma(8)}\} \in \mathcal{A}$$

it is a an ordered sequence of actions.

We denote by \mathcal{G} is the set of genetic processes.

Operating the genetic process means that the process scans successively $x + d_{\sigma(1)}, \dots, x + d_{\sigma(8)}$ until it works.

2D

128 cellular types

3D

3912 cellular types

Local morphological dynamic

Regulation is defined as a map associating to each (n, L, x) a pair :

$$(G^\lambda(n, L, x), G^\wedge(n, L, x)) \in \mathcal{G} \times \mathcal{G}$$

with non-overlapping property.

$$\varphi(n, L, x; G^\lambda; G^\wedge) := L \bigcup \{G^\lambda(n, L, x), G^\wedge(n, L, x)\}$$

It transform L at time n for the cell $x \in L$

Global morphological dynamic

Assume that K_n is constructed, it is an ordered list $\{x_1, x_2, \dots, x_{p_{K_n}}\}$ of cells

① We define $K_n(x_1) = \varphi(n, K_n(x_1); G^\searrow, G^\nearrow)$

② $\forall p = 2, \dots, p_{K_n}$

$$K_n(x_1, \dots, x_p) := \varphi(n, K_n(x_1, x_2, \dots, x_{p_{K_n}-1}); G^\searrow, G^\nearrow)$$

③ Then $K_{n+1} = \Psi(n, K_n) := \varphi(n, K_n(x_1, x_2, \dots, x_p); G^\searrow, G^\nearrow)$

Double time dynamic, with non-overlapping property

The algorithm for constructing the shape depend on the type of ordered sequences of cells.

At each time n , each K and each cell $x \in L$, we construct a map (G^\searrow, G^\nearrow)

Global morphological dynamic

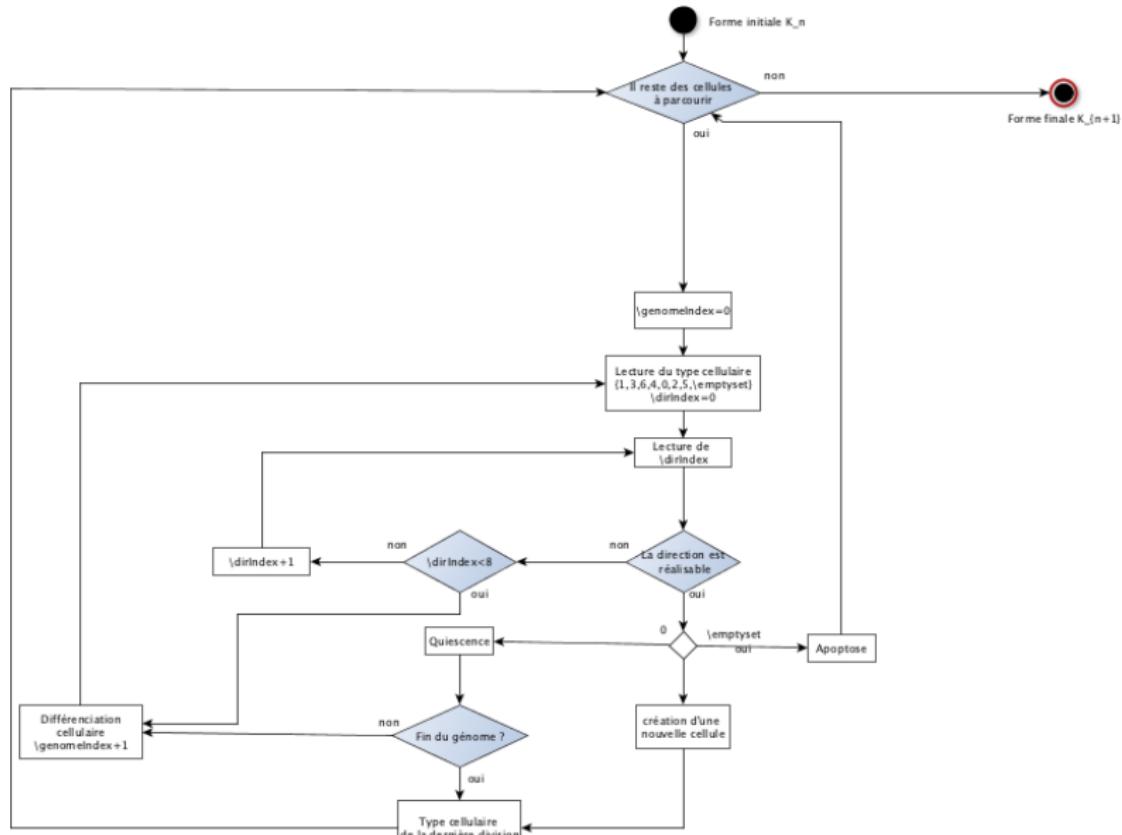
We get the morphological equation governing the evolution of the tube $t \rightsquigarrow K(t)$:

$$\overset{\circ}{K}(t) = \Psi(t, K(t))$$

- To make shape dictionary with different regulation
- To understand how the shape stay the same while the cells are changing.
- To test the robustess of shapes (Driesch and Roux experiments).

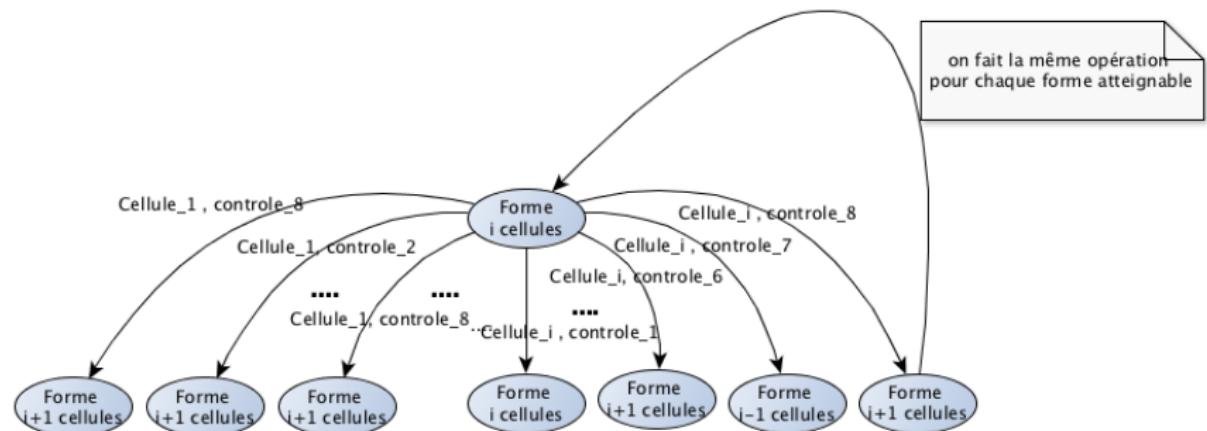
K is a morphological equilibrium of Ψ if the stationary tube $K(t) := K$ is a solution of the morphological equation.

Algorithm



Reachable shapes

With this Morphological equation we can explore the reachable shapes as a state-transition graph.



Basin Capture

The capture basin for a morphological equation $\dot{K}(t) = \Psi(t, K(t))$ is defined as follows

$$\text{Capt}_\Psi(C, K) = \left\{ K \in X \mid \exists T > 0, \exists s \in [0, T] \right.$$

$\exists \dot{K}$ solution of $\dot{K}(t) \in \Psi(K)$ and $K(0) = K_0$

$$\left. \text{s.t. } K(s) \in C \text{ and } \forall \theta \in [0, s[, \quad K(\theta) \in K \right\}$$

Viability and capture basin algorithms have to be adapted to this problem.

Cell Differentiation (Abdoulaye Sarr)

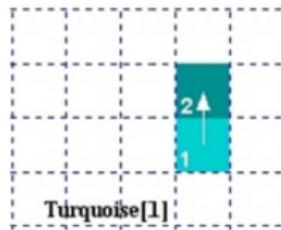


FIGURE: Set of evolutions at 2 cells

Cell Differentiation (Abdoulaye Sarr)

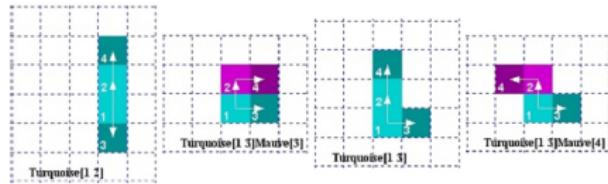


FIGURE: Set of evolutions at 4 cells

Cell Differentiation (Abdoulaye Sarr)

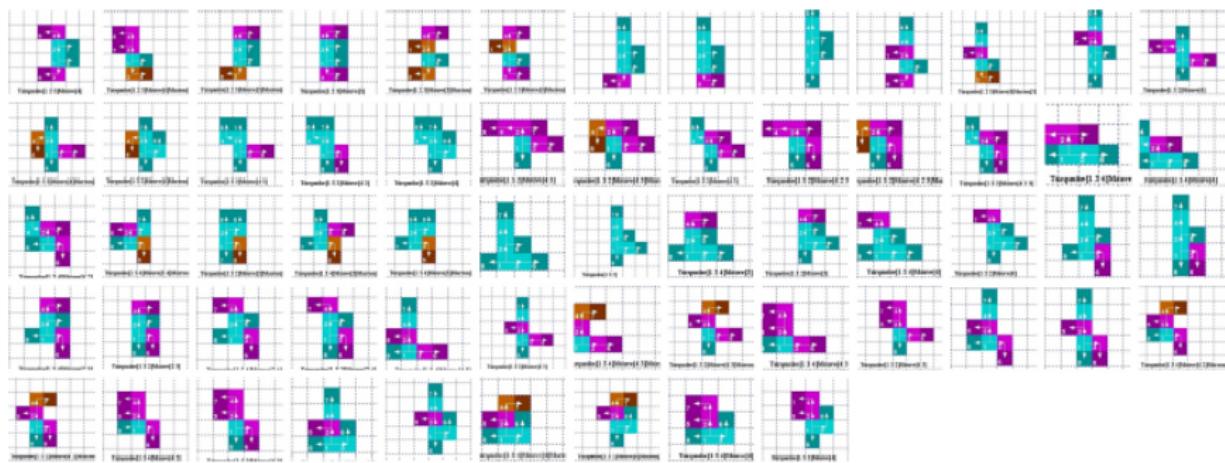


FIGURE: Set of evolutions at 8 cells

Cell Differentiation (Abdoulaye Sarr)

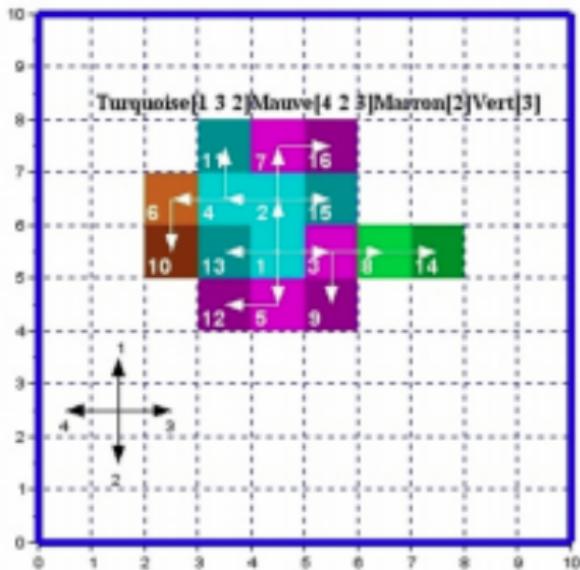
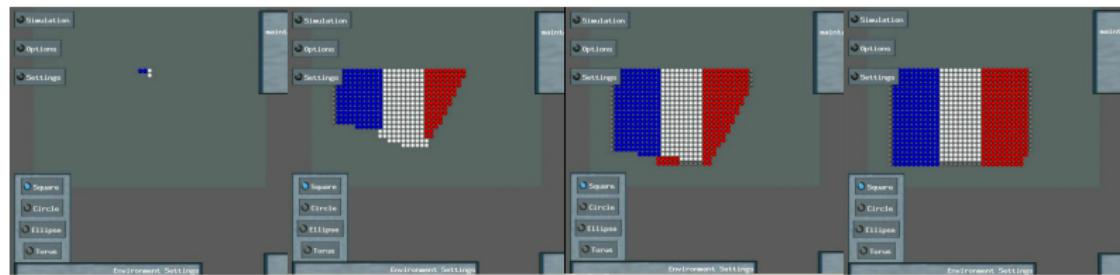


FIGURE: Differentiate cells at 16 cells - The size of the entire set is 1029.

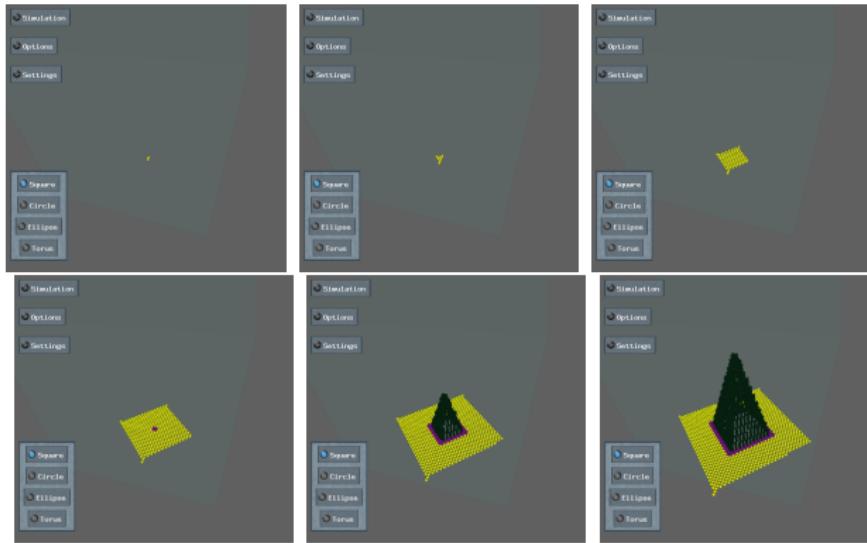
French Flag

A solution to Wolpert French Flag problem.



Gastrulation

A solution to Gastrulation.



Shape robustness (Abdoulaye Sarr)

Shape robustness can be calculated with the potential of regeneration of the shape when we kill some cells and the connectivity degree.

Robustness of a shape is the volume of the capture basin.

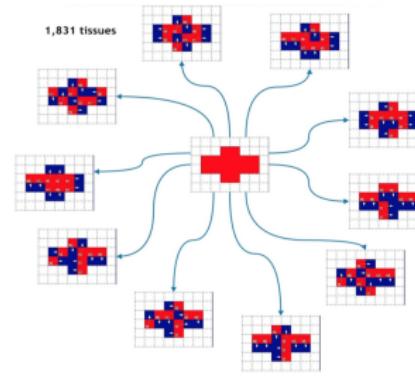


FIGURE: capture basin

Shape robustness (Abdoulaye Sarr)

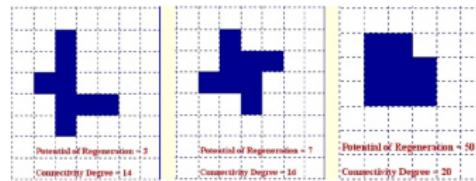


FIGURE: Robustness of Shapes

Tumor irradiation

- Unproductive : irradiation mainly doesn't influence, neither in good, nor in bad way the growth of the tumour (Zero : [0]).
- Dangerous : irradiation mainly accelerates tumour growth (Negative [-]).
- Effective : irradiation mainly stunts the growth of the tumour (Positive [+])
- At Worst Unproductive : irradiation mainly stunts the growth of the tumour or at least maintains it to its normal pace (Zero/Positive : [0+]).
- At Best Unproductive : irradiation mainly accelerates tumour growth or at best maintains it to its normal pace (Zero/Negative : [0-]).
- Effective at Best and Dangerous at Worst : irradiation can either accelerate or stunt the growth of the tumour (Positive/Negative : [+-])

Tumor irradiation

Exemple of classification of 5 tumors.

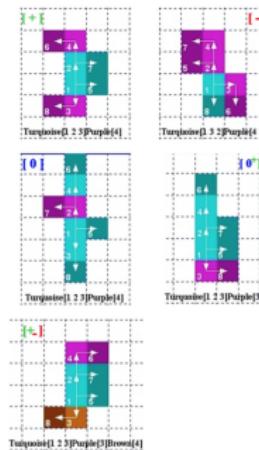


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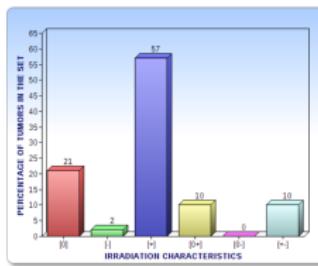


FIGURE: Distribution of the 61 8-cells tissues per tumour category. The cell division cycle for assessing the growth of the tissue after irradiation is set to 10. We can notice that there exists in the studied set any tumour of a category [0-].

Viability kernel (Abdoulaye Sarr)

Cellular dynamics underlying the energy available for the cell coupling mutationnal equation and differential equation.

We define three power thresholds for each of the possible actions of cells.

cells must ensure process that requires energy consumption.

Each cellular type has a different parameter of energy.

Each shape must maintain at least half number of cells.

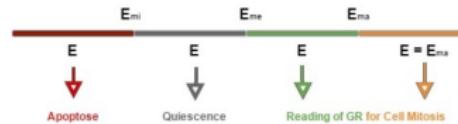


FIGURE: Power Thresholds

Viability kernel (Abdoulaye Sarr)

The viability kernel of the 1029 shapes with 16 cells at 1000 cycles contains 120 shapes

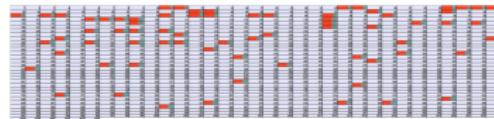


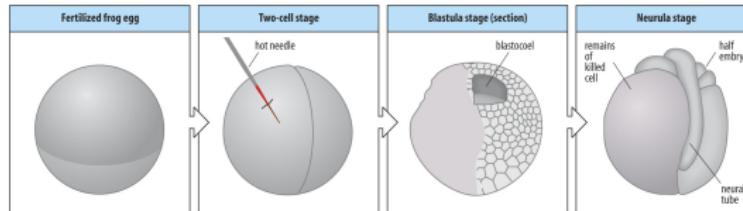
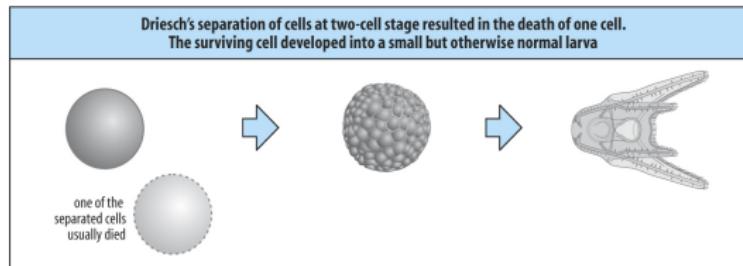
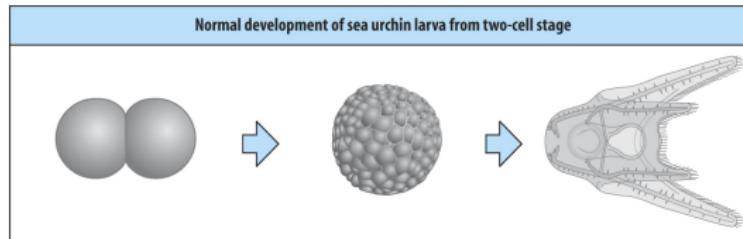
FIGURE: Viability Kernel ar 1000 cycles

and at 10000 cycles contain 5 shapes.



FIGURE: Viability Kernel ar 10000 cycles

Driesch and Roux experimentation



Epigenetic

Link between genotype and phenotype.

- We call regulation, the dynamical mechanisms of ontogenesis and the retro-action with the environment.
- If the environment is in this state then this gene or combinaison of gene will react on the environment.
- How can we code this mechanisms and how the cells read this code.

