A multiagent approach for virtual tissue morphogenesis

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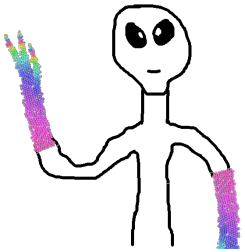

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University of Brest, France

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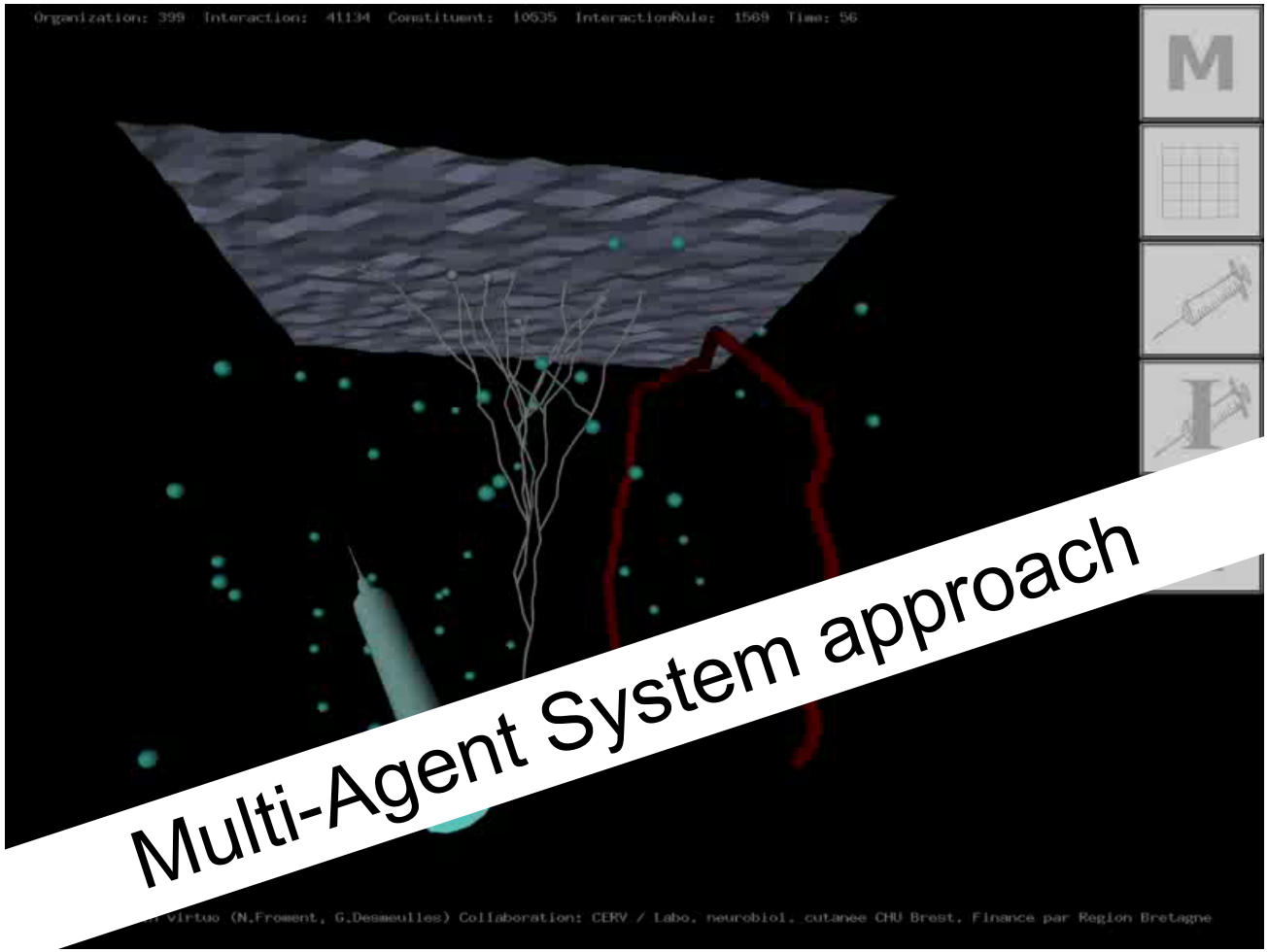
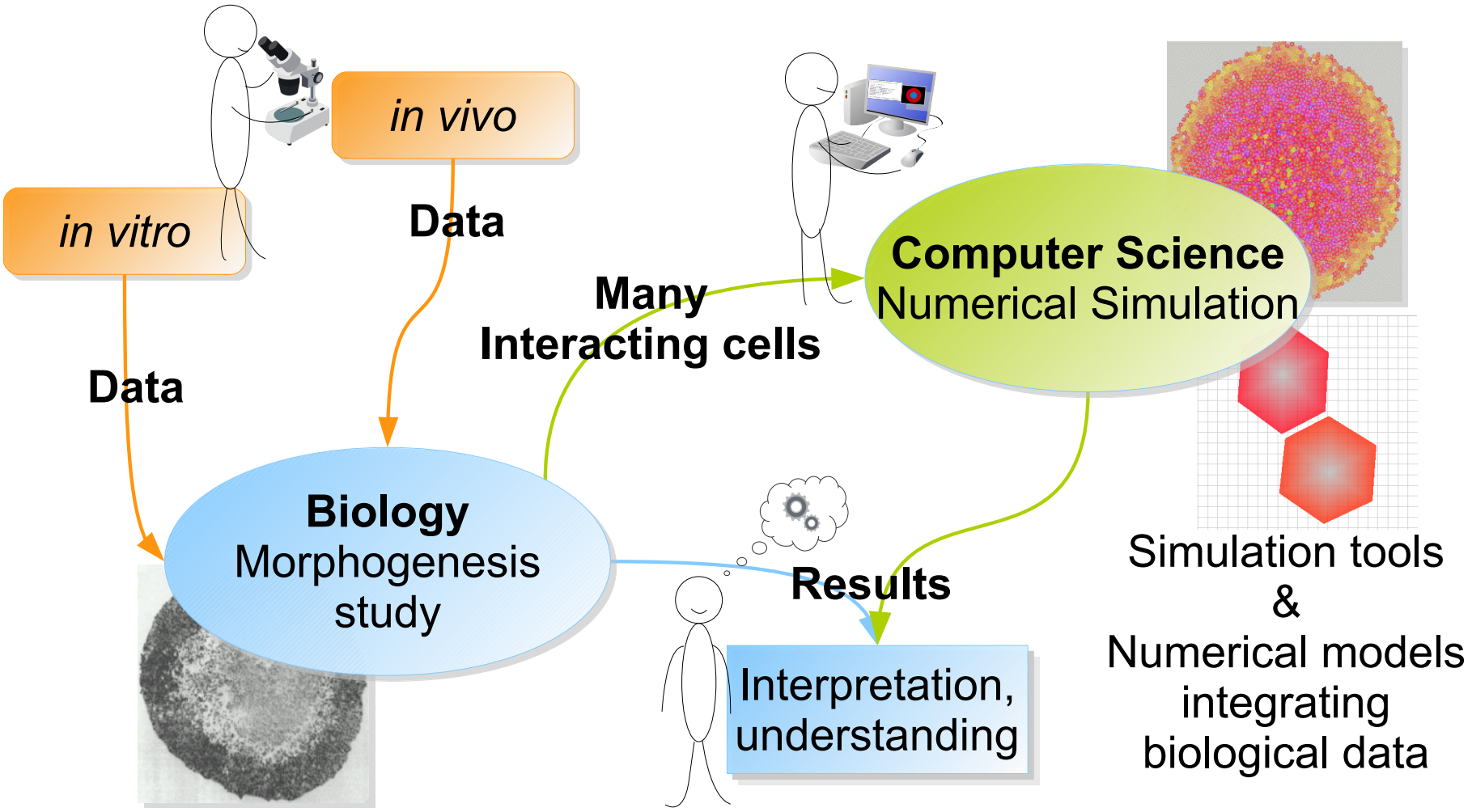
Virtual Reality ➔ Virtual Biology

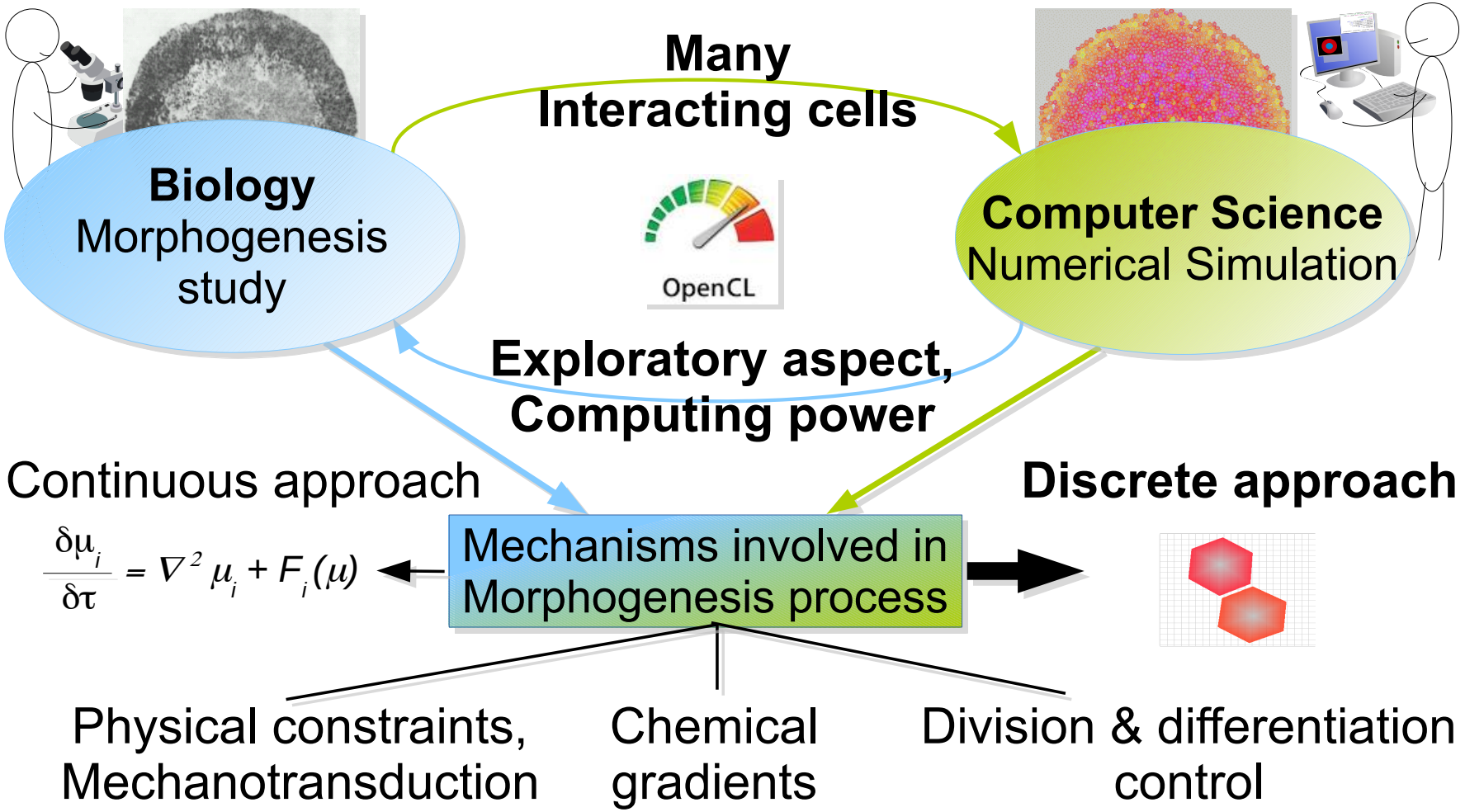


Interaction between virtual cells and/or molecules

Context (1/3)


in vivo
in vitro
Data
Data
Many
Interacting cells
Computer Science
Numerical Simulation
Biology
Morphogenesis
study
Results
Interpretation,
understanding
Simulation tools
&
Numerical models
integrating
biological data

Context (2/3)


Many
Interacting cells
Biology
Morphogenesis
study
OpenCL
Computer Science
Numerical Simulation
Exploratory aspect,
Computing power
Continuous approach
$\frac{\delta \mu_i}{\delta \tau} = \nabla^2 \mu_i + F_i(\mu)$
Mechanisms involved in
Morphogenesis process
Discrete approach
Physical constraints,
Mechanotransduction
Chemical
gradients
Division & differentiation
control

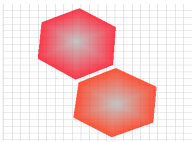
Context (3/3)

Continuous approach

$$\frac{\delta \mu_i}{\delta \tau} = \nabla^2 \mu_i + F_i(\mu)$$

Mechanisms involved in Morphogenesis process

Discrete approach



Physical constraints, Mechanotransduction

Chemical gradients

Division & differentiation control

Ph.D. Anne Jeannin-Girardon

« Research & Technical challenge » work

Ph.D. Abdoulaye Sarr

« Exploratory research » work

A. Jeannin-Girardon et Al, IEEE/ACM Transactions on Computational Biology and Bioinformatics (TCBB), 2015

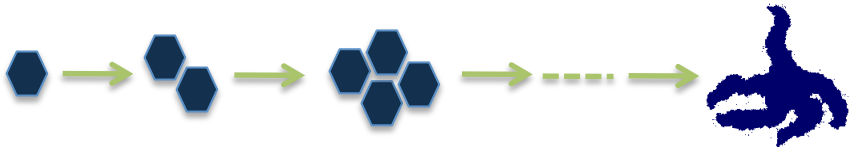
A. Sarr et Al, 3rd international conference on Theory and Practice of Natural Computing (TPNC), 2014

Outline

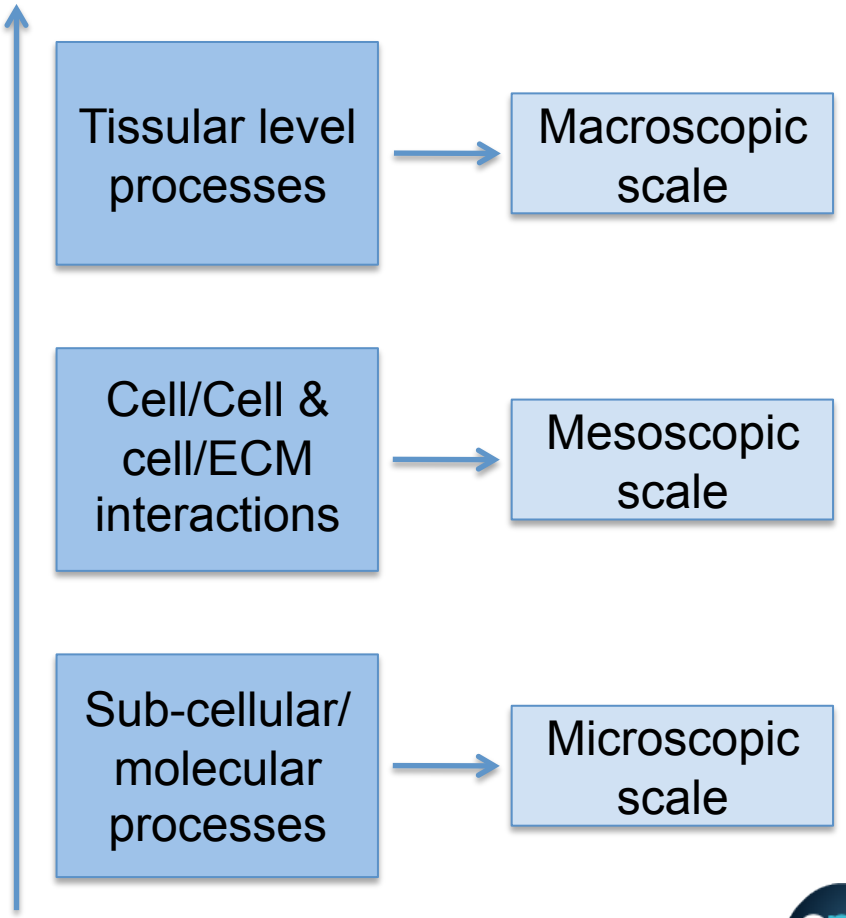
- Introduction
- Virtual cell model
  - ➔ Structure, cycle, abilities, interactions & constraints
- Virtual chemistry model
- Parallel implementation
  - ➔ OpenCL, model coupled with a MAS, 10^6 cells
- Starfish growth… a simplified model
- Towards morphogenesis modeling ?
- Morphogenesis modeling : our approach based on viability
- Morphogenesis modeling : our model, a case study
- Future works

Introduction (1/4)

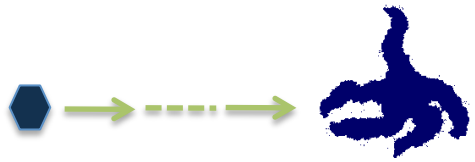
Tissue morphogenesis:



- Is a multi-scale phenomenon
- Can be addressed through continuous/discrete models
- Involves many of interacting entities (cells, molecules, etc.)



Introduction (2/4)



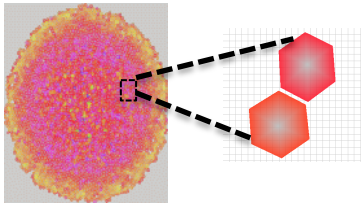
Tissue morphogenesis: continuous VS discrete approaches

Continuous approaches

$$\frac{\delta \mu_i}{\delta t} = \nabla^2 \mu_i + F_i(\mu)$$

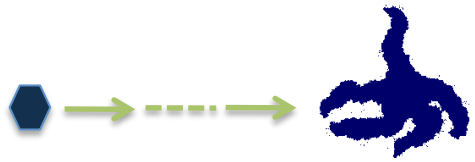
- Consider population instead of individuals
- Adapted for large scale simulation
- Take into account the whole system

Discrete approaches



- Local interactions definition global emerging behaviors
- Require a large amount of computation time
- Can focuse on a small part of the system

Introduction (3/4)

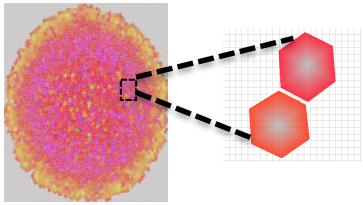


Tissue morphogenesis: our approach is hybrid

Continuous approaches

$$\frac{\delta \mu_i}{\delta t} = \nabla^2 \mu_i + F_i(\mu)$$

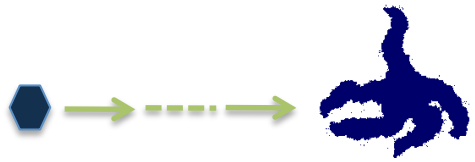
Discrete approaches



But, we choose to favor discrete approaches:

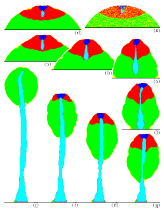
- Discrete modeling of entities allows variability in cell population… and allows cell differentiation
- Individual Based Models (IBM) are often suited for a parallel implementation
- Continous approach can be used when needed (chemical gradient, etc.)

Introduction (4/4)

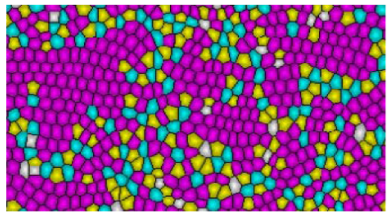


Discrete cellular models

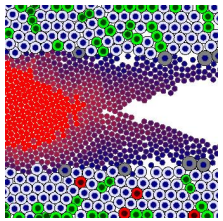
- Some models focus on the internal dynamics of cells
  - ➔ too complex to simulate tissue
- Some models focus on cell behaviors
  - ➔ mitosis, differentiation, etc.



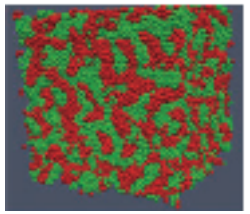
Marée et al, 2001



Li et al, 2012



Macklin et al, 2012



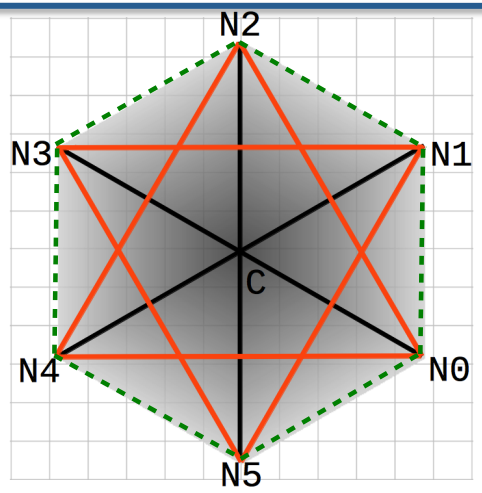
Kang et al, 2014

- Some models are parallelized using various frameworks
  - ➔ OpenMP, MPI, Posix thread, CUDA, openCL, etc.
  - ➔ Laptops, standard PC, Super Computer, Grid, etc.

Virtual cell model (1/6)

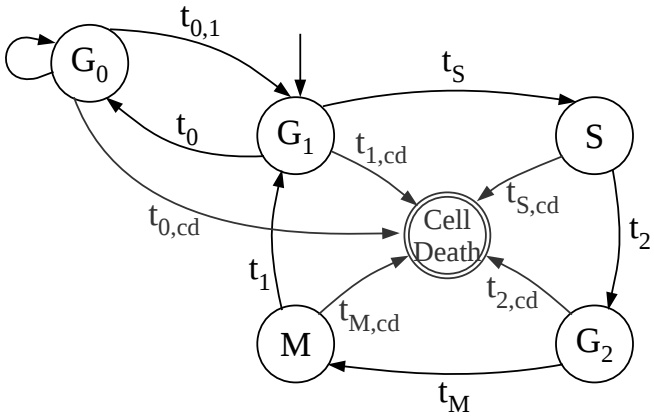
- Virtual cell structure: mass/spring system
  - ➔ n+1 nodes
  - ➔ membrane, cytoskeleton, cortex

Cell deformation



- Virtual cell cycle: very (too) simple one
  - ➔ finite-state machine
  - ➔ no checkpoint

Cell control



- Virtual cell mechanotransduction

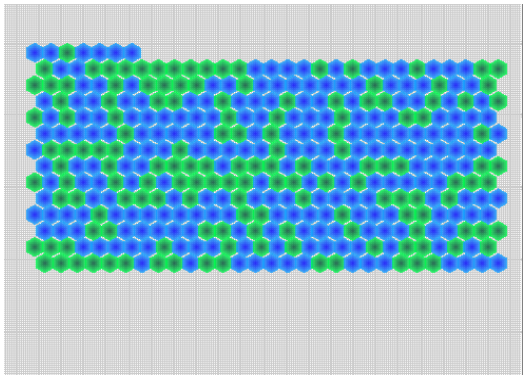
Cell physical constraint evaluation

Virtual cell model (2/6)

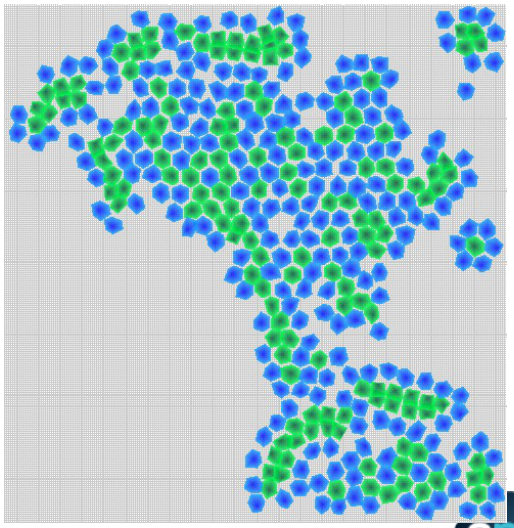
Virtual cells agents behaviors and abilities

- ➔ deformation
- ➔ motility
- ➔ migration along a molecular gradient
- ➔ molecules consumption/production
- ➔ differentiation
- ➔ mitosis
- ➔ apoptosis/necrosis
- ➔ cell interactions
- ➔ mechanotransduction

Interacting cells



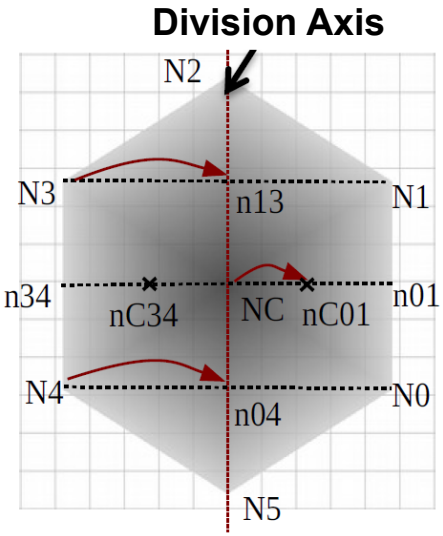
Example: cell sorting

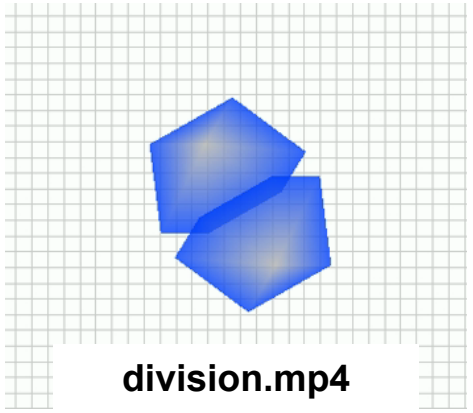


Virtual cell model (3/6)

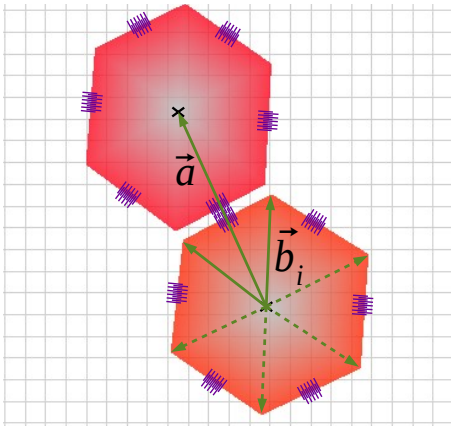
Mitose and cell interactions

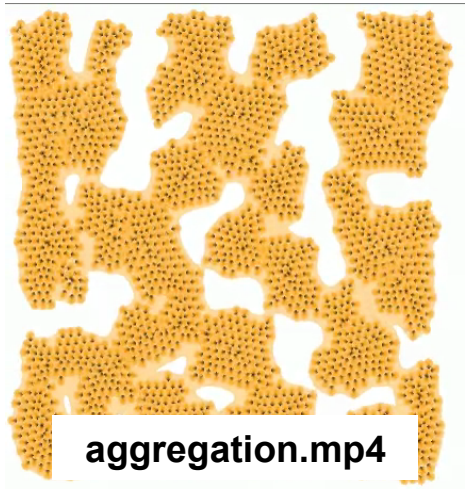
- Mitose
  - ➔ orientated mitosis given an axis





- Cell adhesion/repulsion
  - ➔ differential interaction: simplified mechanism (selected nodes bind with the center of the neighbouring cell)



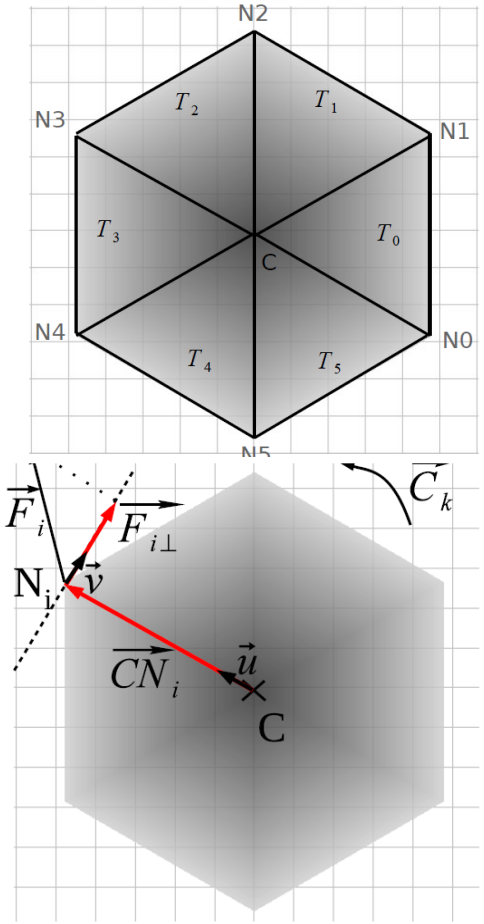


Virtual cell model (4/6)

Mechanical constraints evaluation
➔ Mechanotransduction ➔

- Surface compression/stretching
  - ➔ sum of the area triangles composing the cell

- Shearing constraints
  - ➔ computation of the couple cells ungerdo

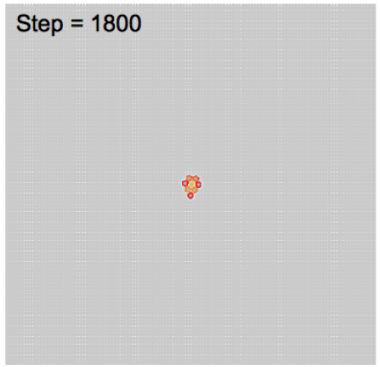


Virtual cell model (5/6)

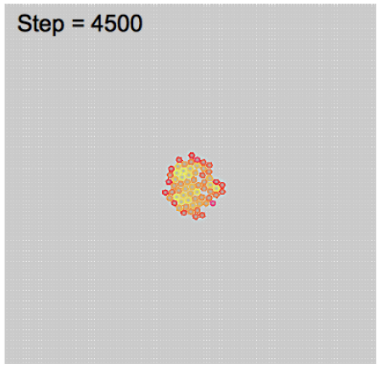
Hypothesis: The **compression/stretching** constraints cells undergo can induce a differentiation

We represent a cell differentiation by a change in the cell's color

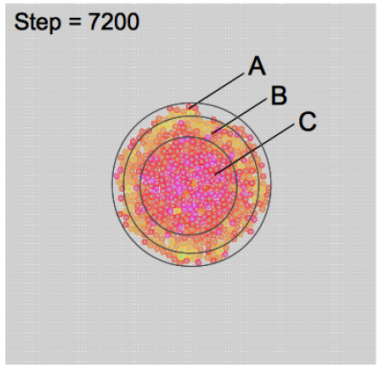
(a)



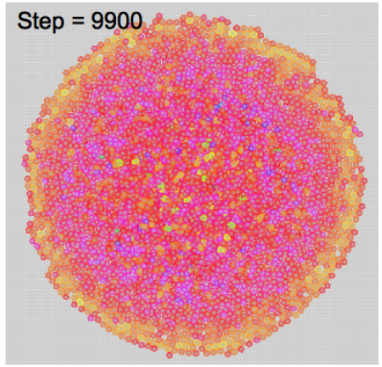
(b)

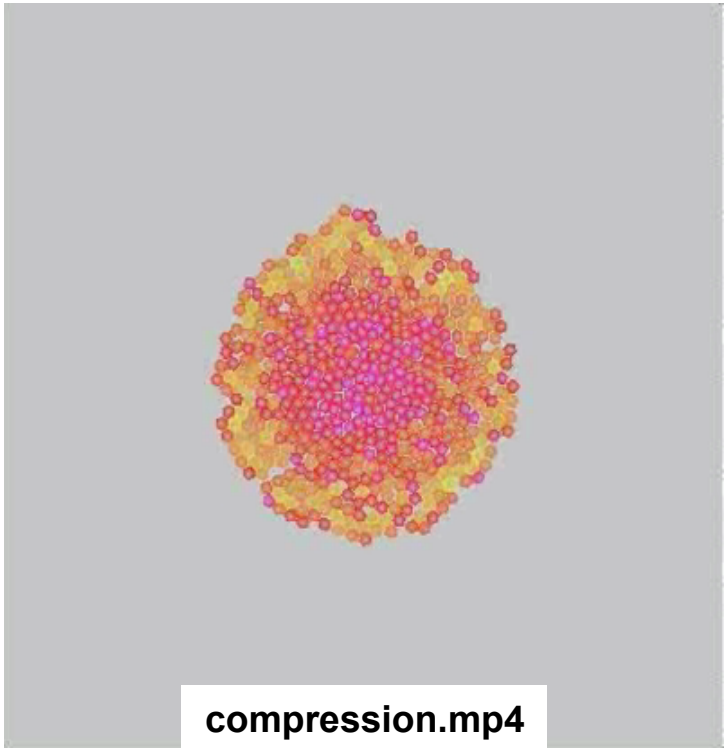


(c)



(d)

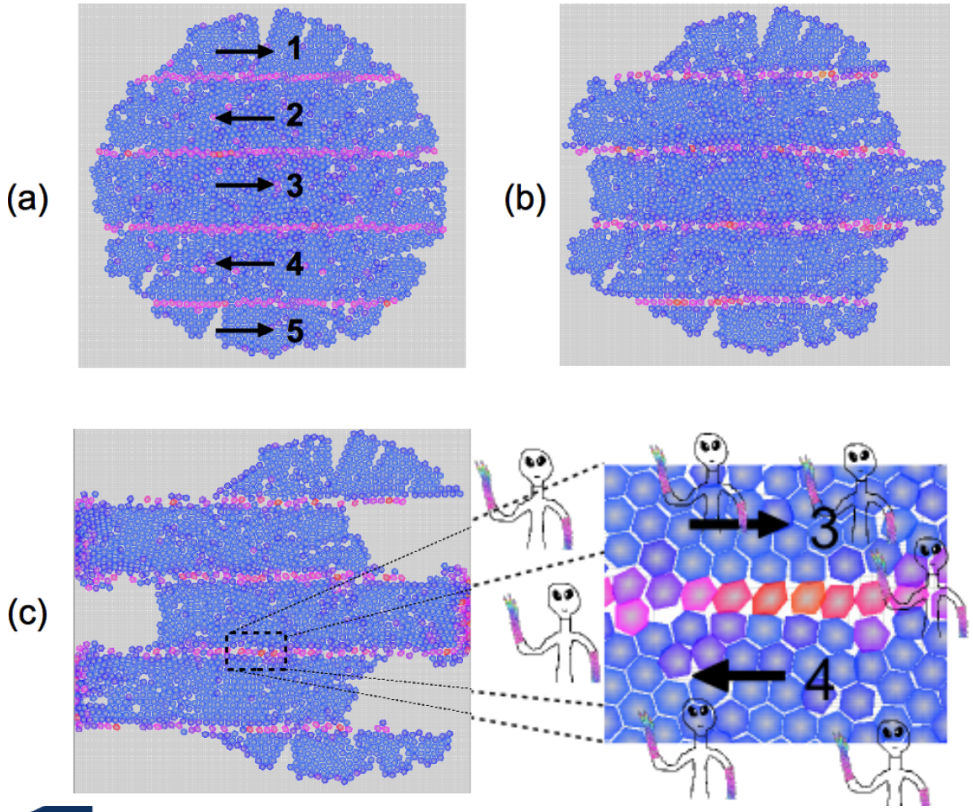


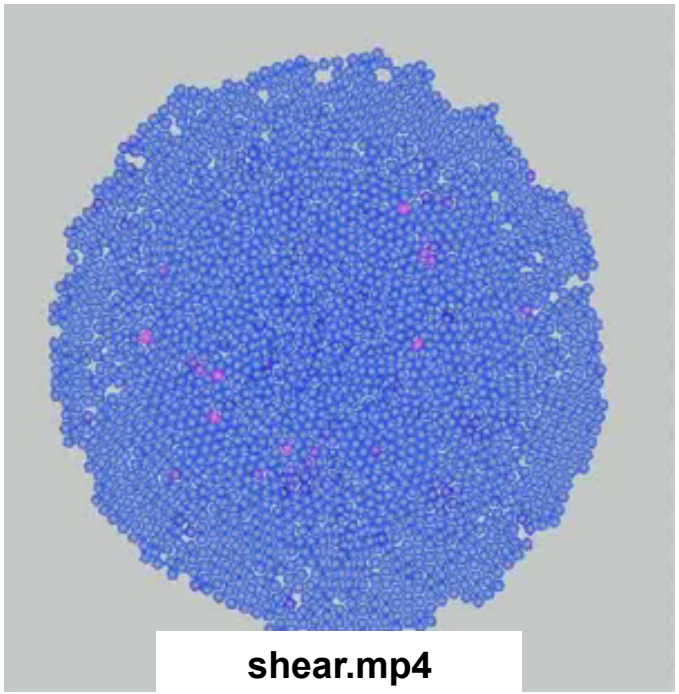


Virtual cell model (6/6)

Hypothesis: The **shearing** constraints cells undergo can induce a differentiation

We represent a cell differentiation by a change in the cell's color



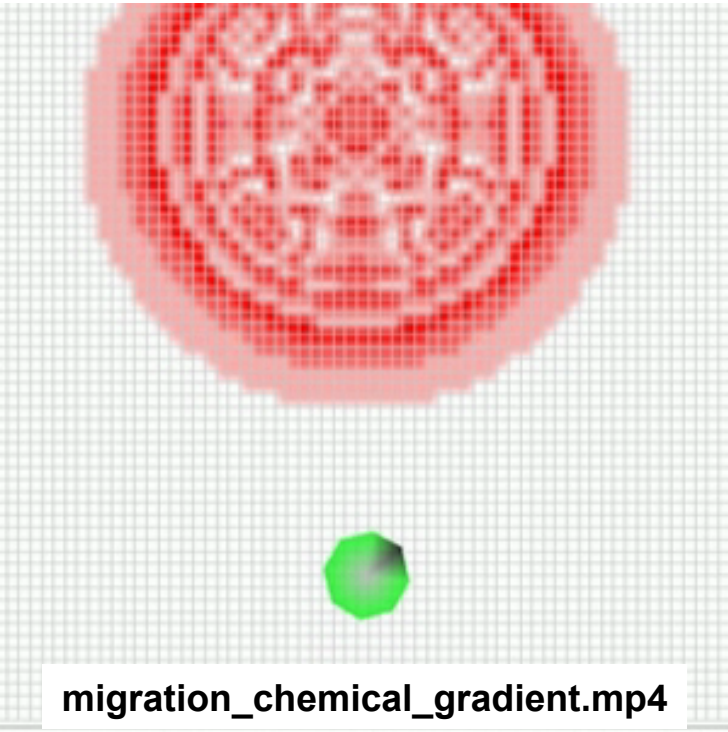


Virtual chemistry model (1/2)

Discrete molecular level modelized with diffusion/reaction equations

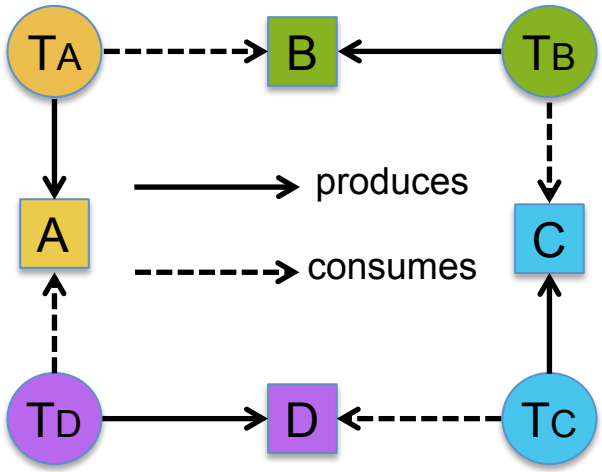
$$\frac{\delta_i(x,t)}{\delta t} = D_i \Delta_i(x,t) - R_i(x,t)$$

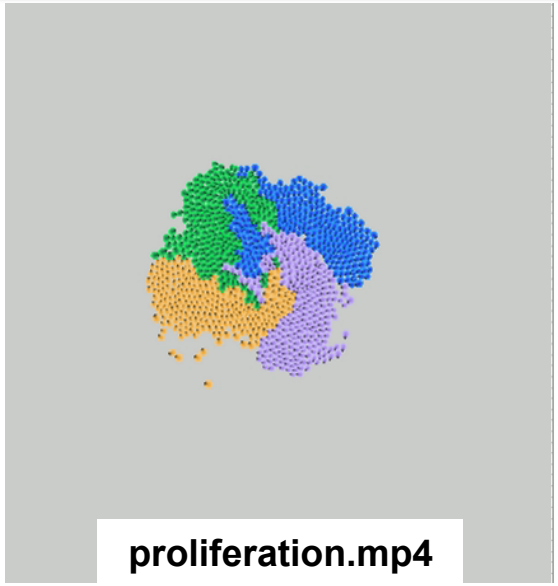
- Set of molecules. Ex: {A, B,C}
- Set of reactions. Ex: {2A + B ➔ C}
- Set of 2D discrete layers.
  One grid layer per molecule type
- Equations solved in 2 steps:
  1) diffusion
  2) reaction

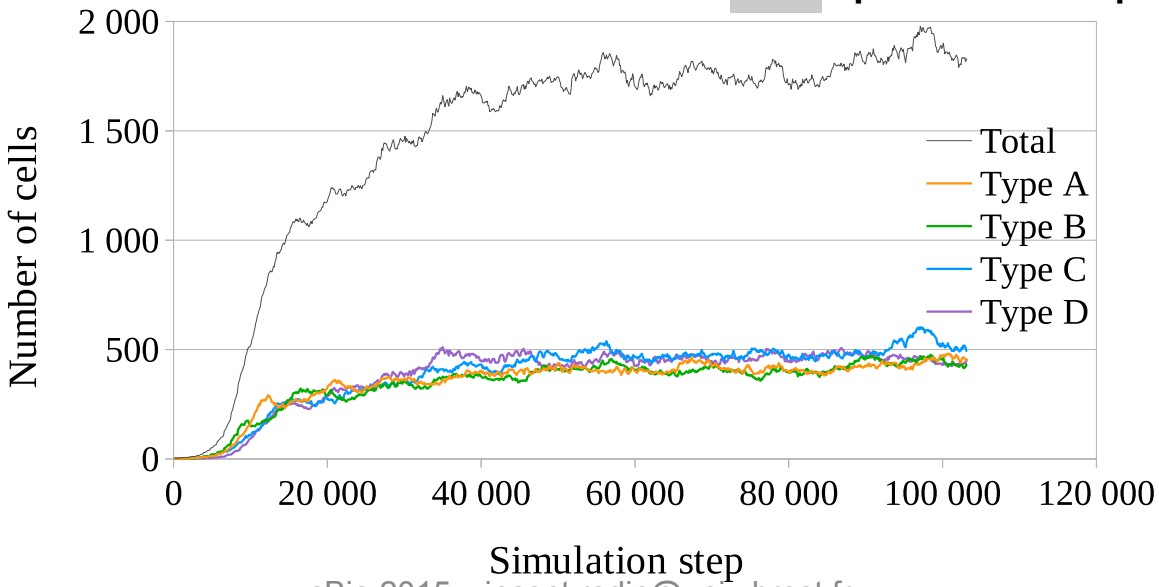


migration_chemical_gradient.mp4

Virtual chemistry model (2/2)







Parallel implementation (1/3)

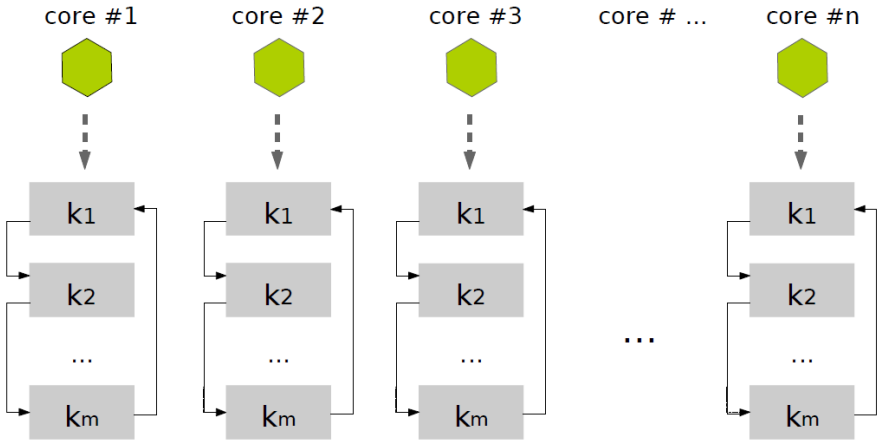
- Parallel hardware and device are everywhere
- Parallel programing gets easier
- Numerous parallel frameworks are available



- Our model seems well adapted to parallel implementation
- We choose to use the **OpenCL framework** to implement it
  ➔ we can use CPUs, GPUs, FPGAs, etc.

Parallel implementation (2/3)

- Fine grained implementation: a cell = an OpenCL core
  - ➔model coupled with a Multi-Agent System



Kernel k1: computes forces
Kernel k2: integrates forces (Euler method)

- Data stored into structures of arrays: nodes, etc.
  - ➔adapted data structure for GPU: a cell = an id
- Cells are located in a discrete 2D environment
  - ➔repulsion: one cell (center node) per grid element

➔ No synchronization required

- Virtual chemistry: a chemistry grid element = an OpenCL core
  - ➔ each core, two synchronized tasks: 1) diffusion and 2) reactions

Parallel implementation (3/3)

Intel Core i7 860

2.8 GHz, quad-core

NVidia GeForce GT 440

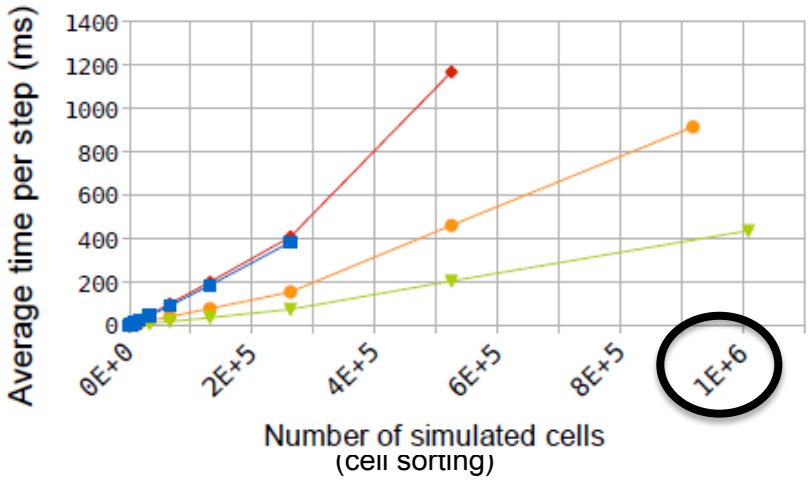
1600 MHz, 96 processing elements

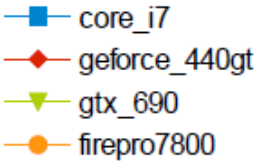
ATI Firepro 7800

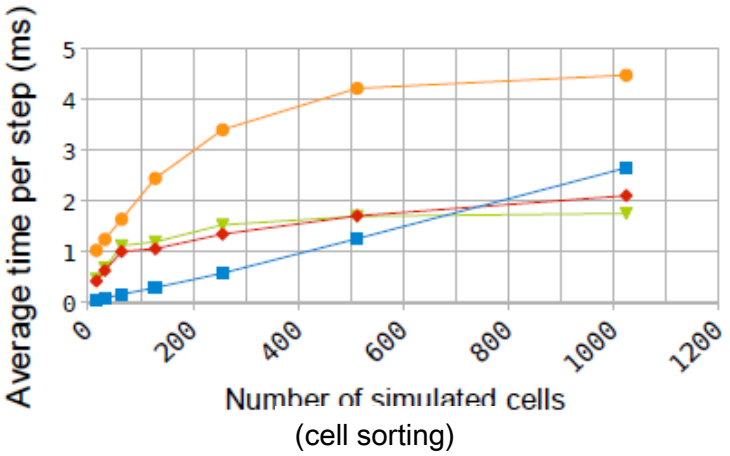
700 MHz, 1440 processing elements

NVidia GeForce GTX 690

900 - 1000 MHz, 1536 processing elements

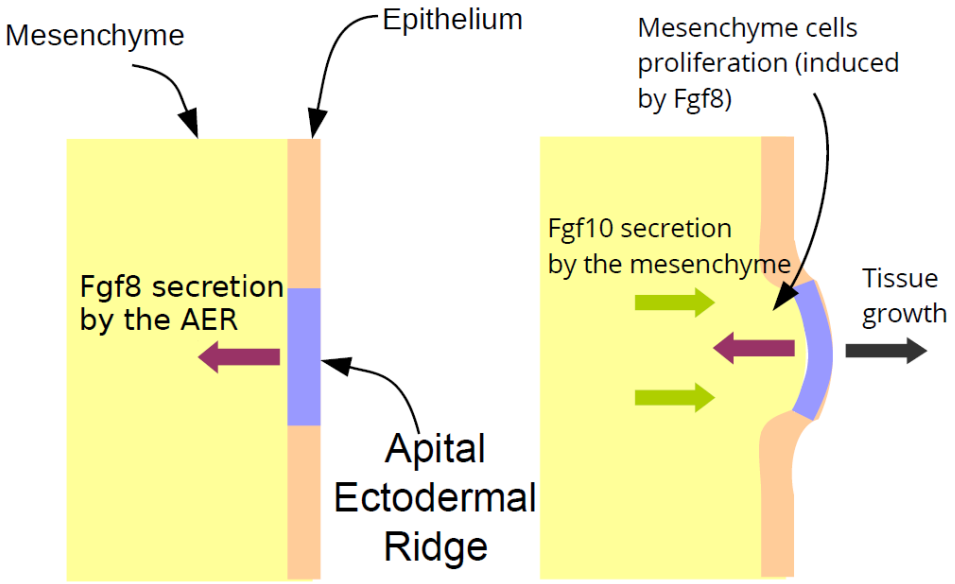


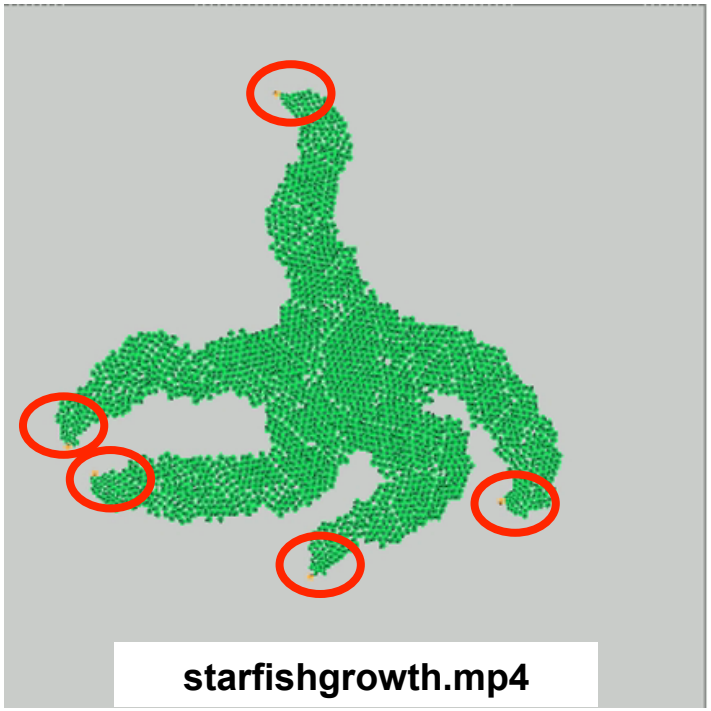




Starfish growth (1/2)

a simplified model



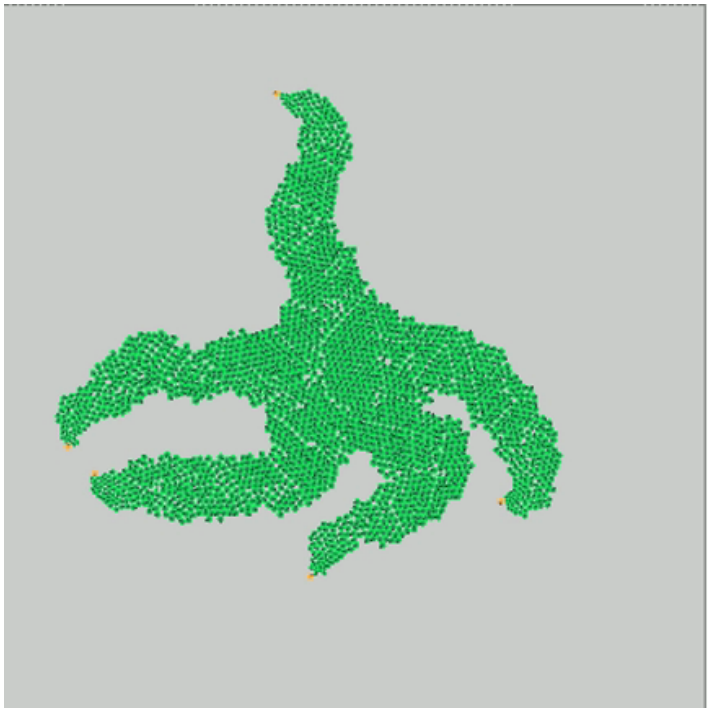


- AER Cells secrete Fgf8 molecules
- Fgf8 molecules induce mesenchyme cells proliferation
- Mesenchyme cells response to Fgf8 by secreting Fgf10 molecules
- Fgf10 molecules maintain Fgf8 secretion

Problem: we put the right cells at the right places….

Starfish growth (2/2)

What is the « program » ?



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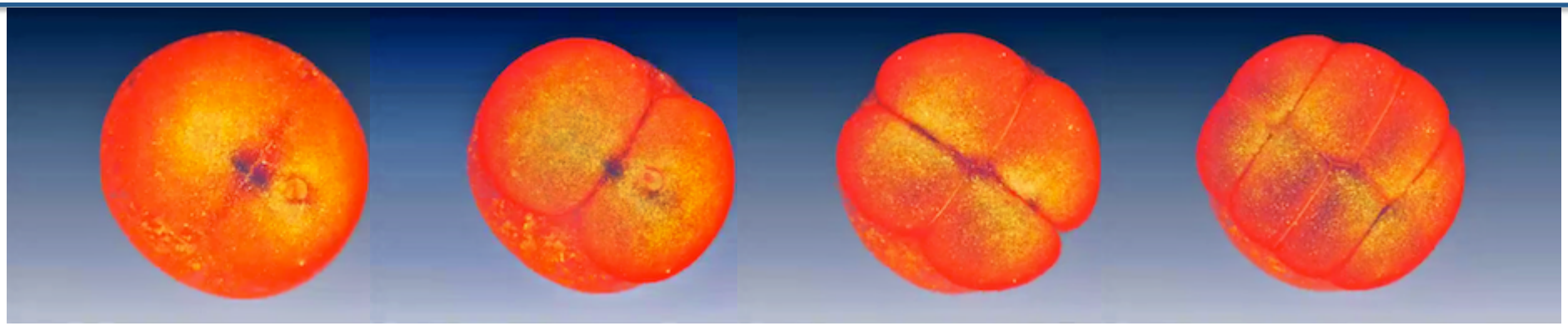
Towards morphogenesis modeling..?(1/2)

occidentale



Early zebrafish embryo, from [N. Olivier et al, 2010]

During early embryogenesis, we can see (probable) :

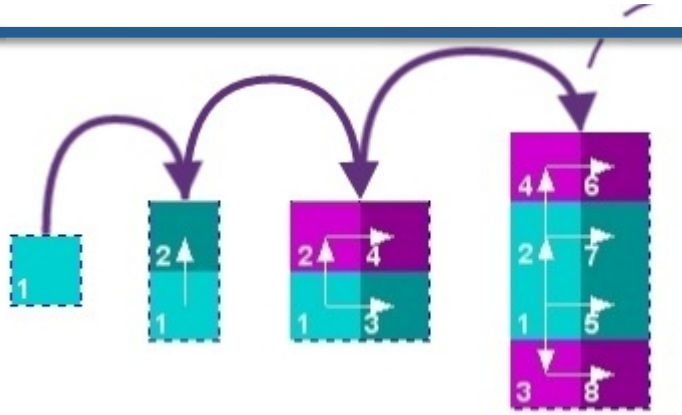
- Geometric segmentation
- Deterministic process

What is the program within cells that controls their placement and their differentiation at the early embryogenesis ?

...

Towards morphogenesis modeling..?(1/2)

occidentale



Idea:

- Find a mathematical model of a well-guided morphogenesis
- Generate, from a single cell, all early tissues and the associate programs

Problem:

- Huge number of possibilities !

Our response:

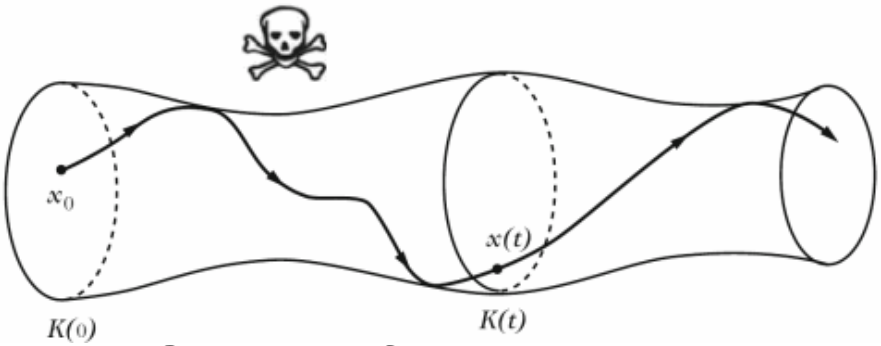
- Tissue morphogenesis is a viability problem !

Morphogenesis modeling :

Our approach (1/2)

Our response:

- Tissue morphogenesis is a viability problem !



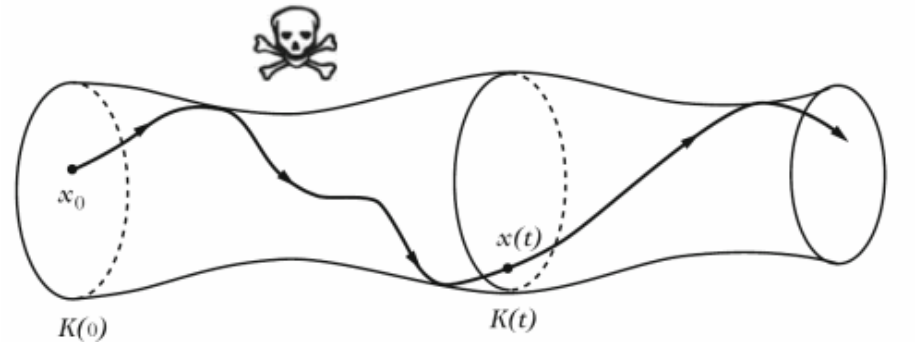
Graph of viable evolution in a *tube*, from [J.P. Aubin, 2001]

Viability Theory (J.P. Aubin, 1991)

- Offers concepts and methods to control a dynamic system to remain in a set of constraints.

Morphogenesis modeling :

Our approach (2/2)



Graph of viable evolution in a *tube*, from [J.P. Aubin, 2001]

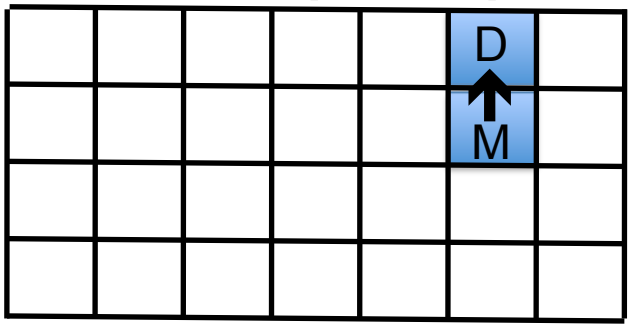
Viability concepts in morphogenesis

- A shape is a **state**
- The directions of division are the **controls**
- The tissues evolve under **constraints**
- A shape can be set as a **target**

Morphogenesis modeling :

Our model (1/2)

- The Environment *E*: a grid



x: **M**other cell
d=1
$x \longrightarrow x + 1$
Create **D**aughter

- A cell *x* : a square which can be placed in the environment 
- A genetic action *d* which can be applied by a cell :

$d \in \{ \uparrow , \downarrow , \rightarrow , \leftarrow , \blacksquare , \varnothing \}$ or simply $d \in \{ 1 , 2 , 3 , 4 , 5 , 6 \}$

A genetic action *d* allow to describe a cell action :

1. Division : $x \longrightarrow x + d$, where $d \in \{ 1 , 2 , 3 , 4 \}$ (action)
2. Quiescence : $x \longrightarrow x + 5 = x$ *(no action)*
3. Apoptosis : $x \longrightarrow x + 6 = 6$ *(programmed cell death)*

Morphogenesis modeling :

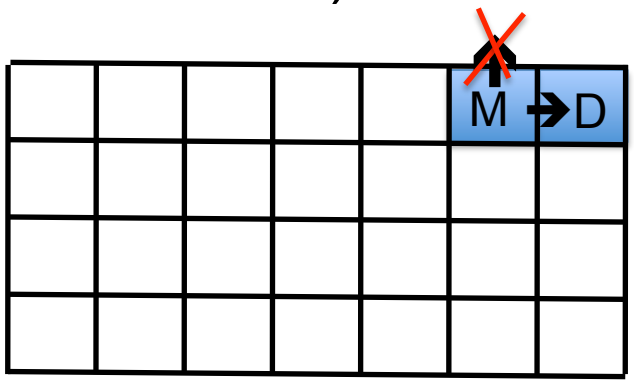
Our model (2/2)

- A genetic process *G* : an ordered list of different genetic actions

  Example: G = { 1 , 3 , 2 , 4 , 5 , 6 } ... A cell control

AT EACH STEP, a cell will apply this algorithm using G:

```
for ( action = 0 ;  action < G.length ; action = action + 1)
{
 if (G[action] can be applied)
 {
   Apply G[action]
   break; /* out of the loop, AT EACH STEP
                only one action is applied ! */
 }
}
```



Currently, when a mitose occurs,
G is transmitted to the daughter cell…

Morphogenesis modeling :

A case study (1/5)

From a single cell  :

- What are the all possible tissues to get after a given number of divisions (phenotypes) ?
- For each attained tissue, what is the minimal underlying genetic process *G* that governed cell division and differentiation (genotypes)?

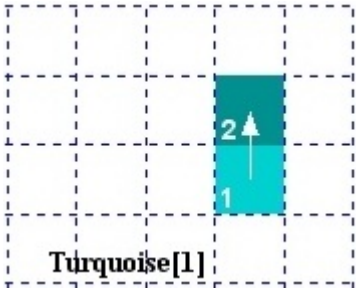
Implementation:

- In 2D, discrete in time and space
- Evolutions of tissues stored using Boost Graph
- Removal of duplicated evolutions : same shapes by geometric transformation… ➡ 87% less !

Morphogenesis modeling :

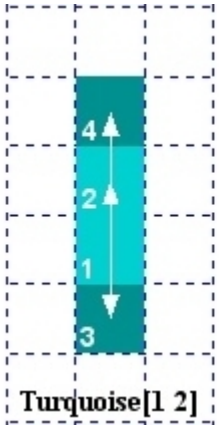
A case study (2/5)

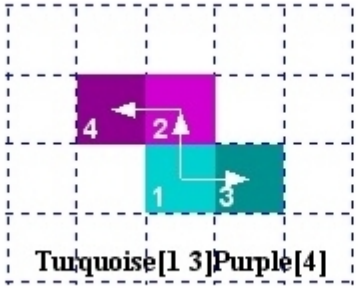
Attainable tissues after 1 division: 1

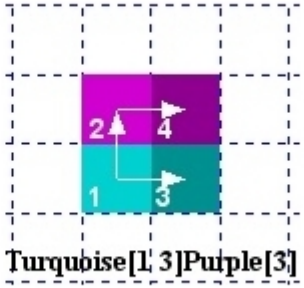


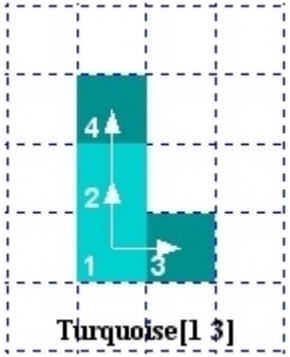
2 cells

Attainable tissues after 2 divisions: 4







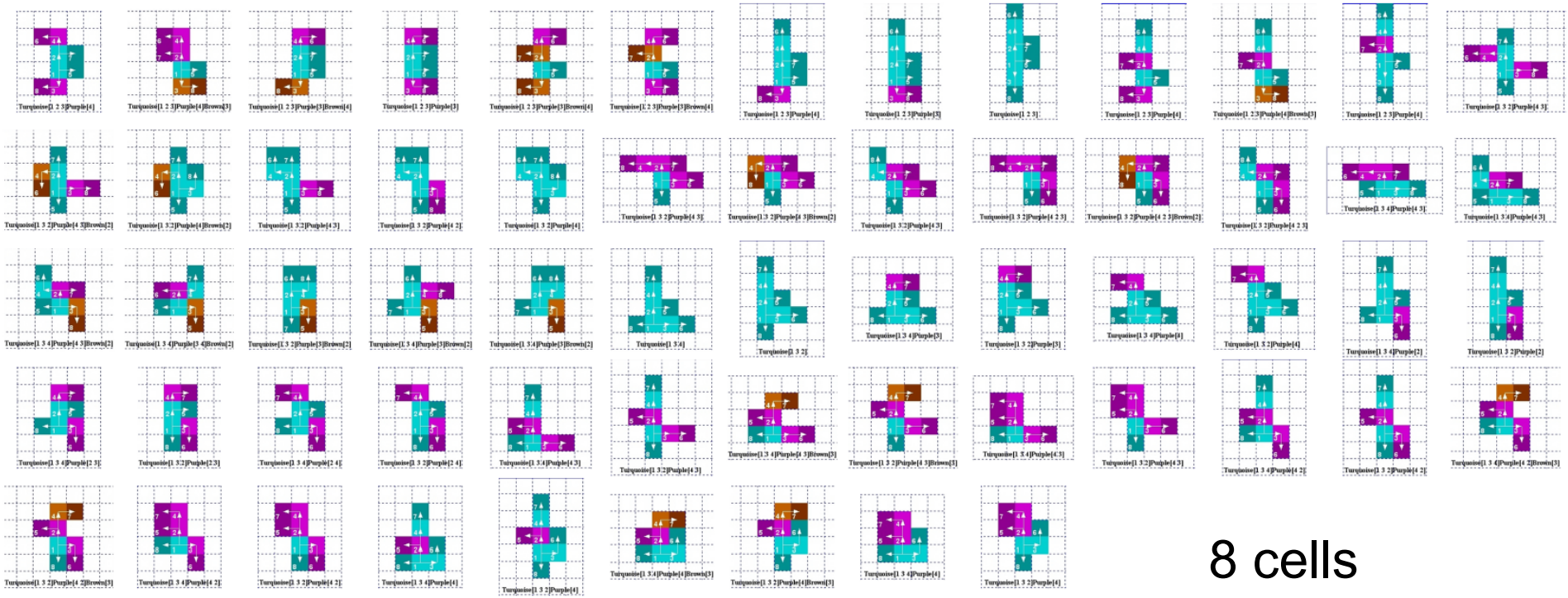


4 cells

Morphogenesis modeling :

A case study (3/5)

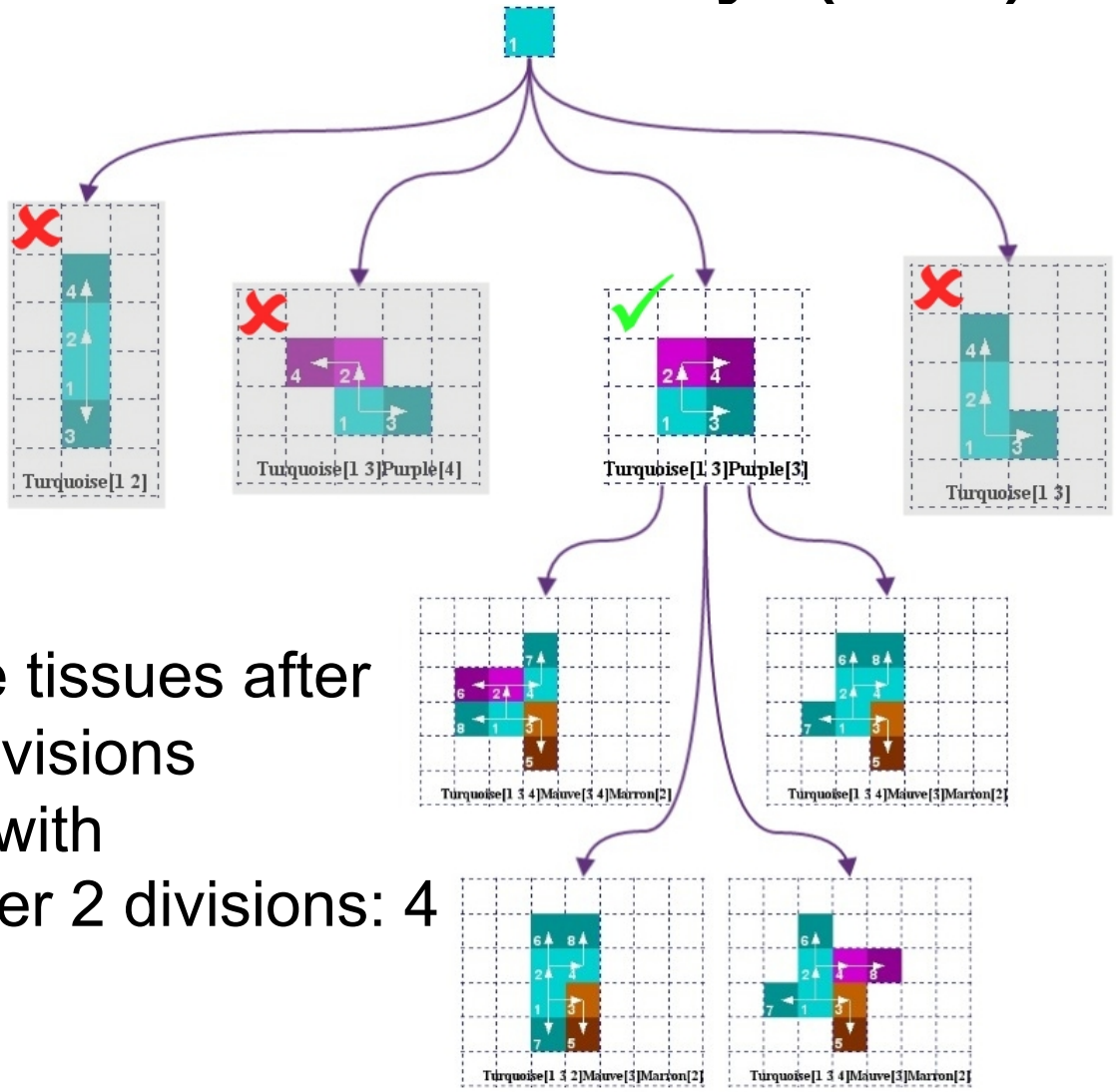
Attainable tissues after 3 divisions: 61



8 cells

Morphogenesis modeling :

A case study (3/5)



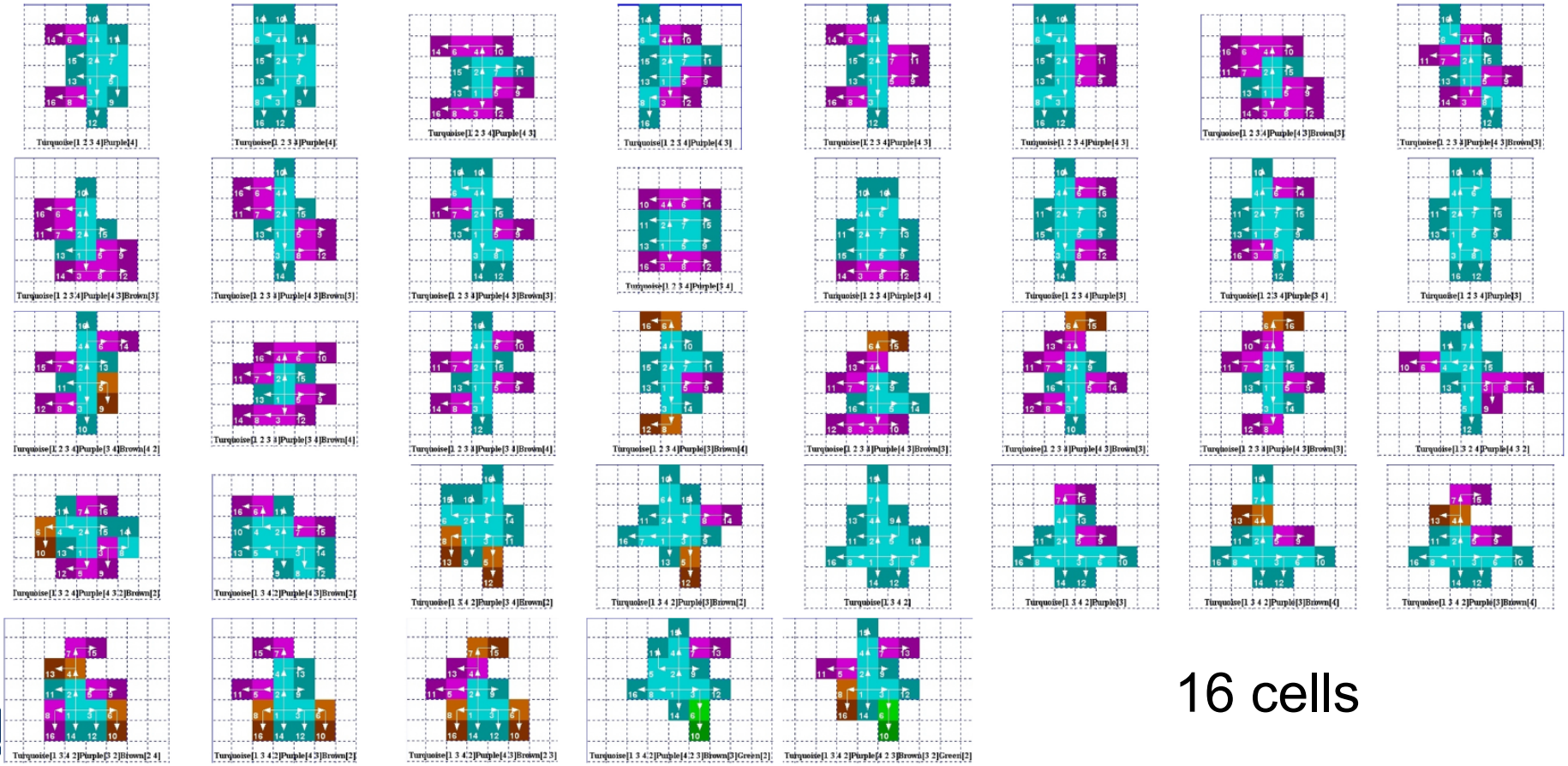
Attainable tissues after
3 divisions
with
selecting after 2 divisions: 4

8 cells

Morphogenesis modeling :

A case study (4/5)

Attainable tissues after 4 divisions: 1029

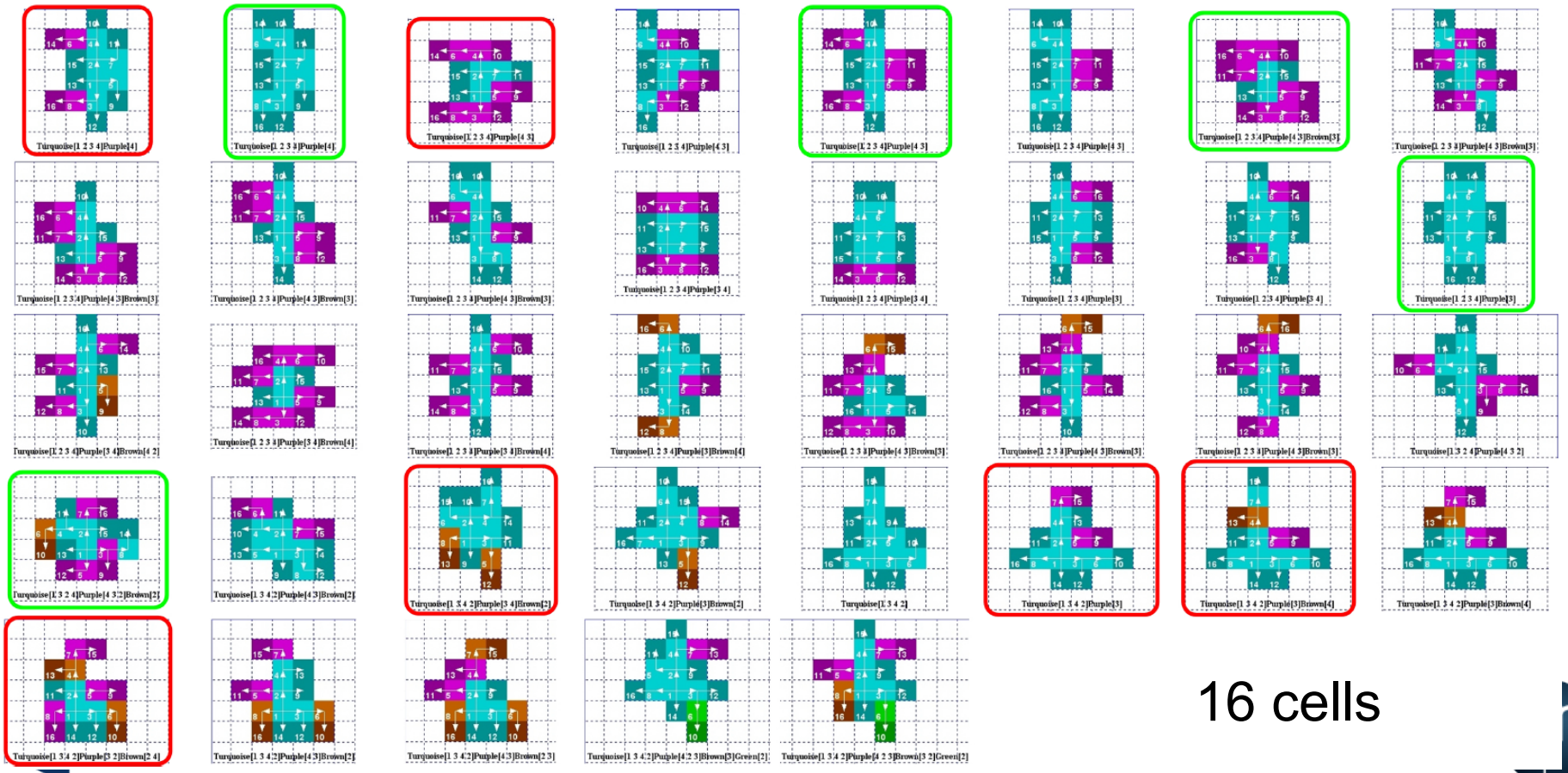


16 cells

Morphogenesis modeling :

A case study (5/5)

Selection with regard to symmetry,
robustness and bio-inspiration of tissues

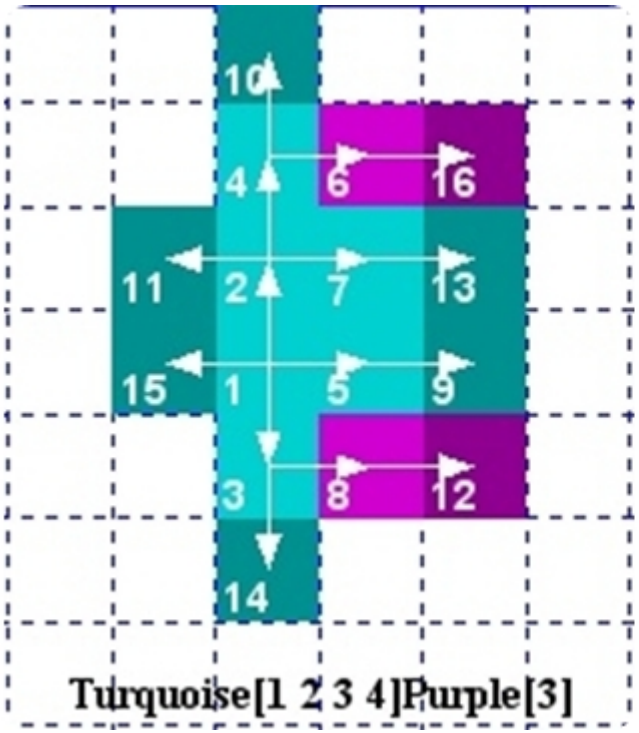


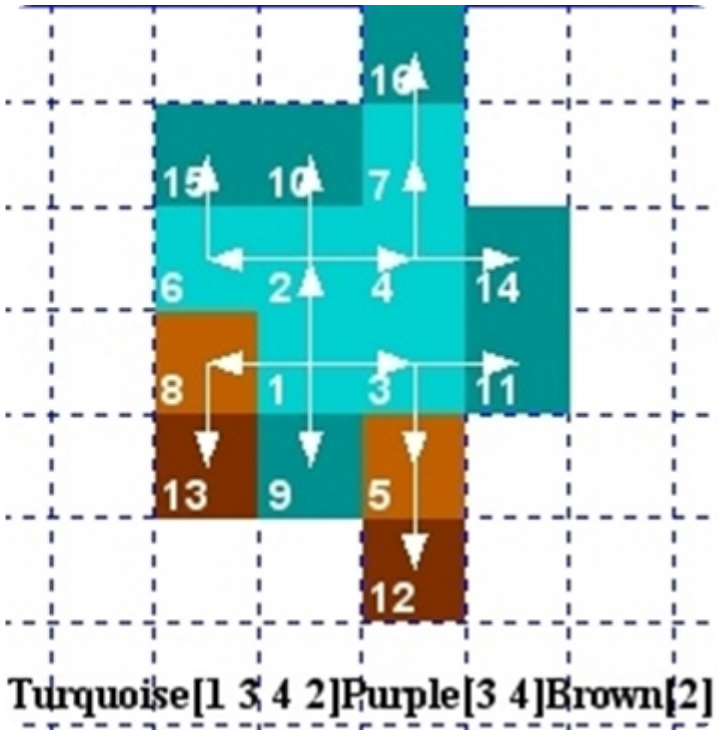
16 cells

Morphogenesis modeling :

A case study (5/5)

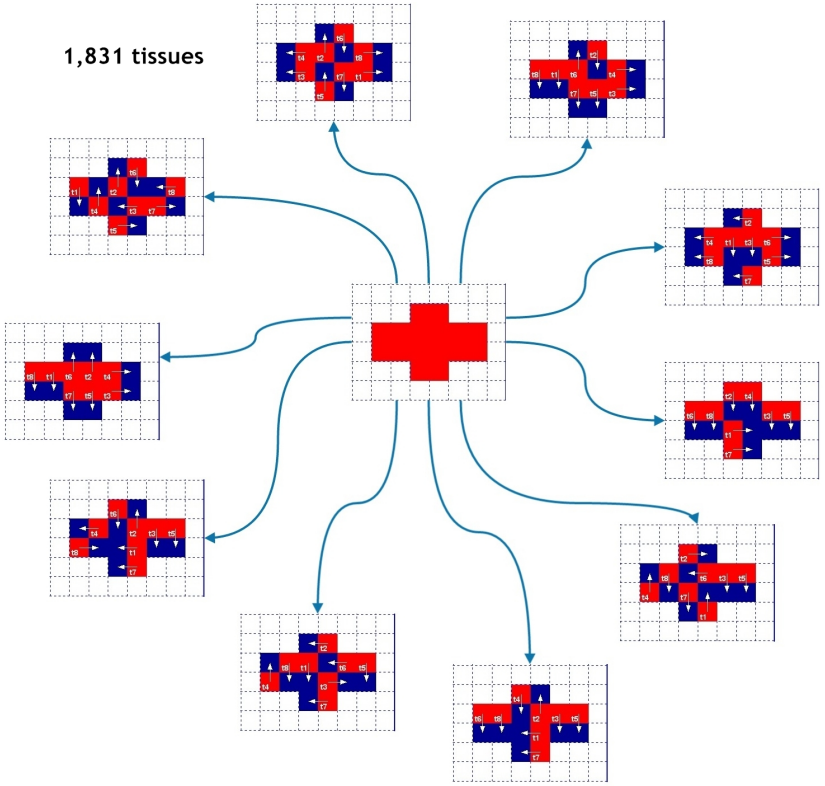
An example that highlights the link between phenotype and genotype



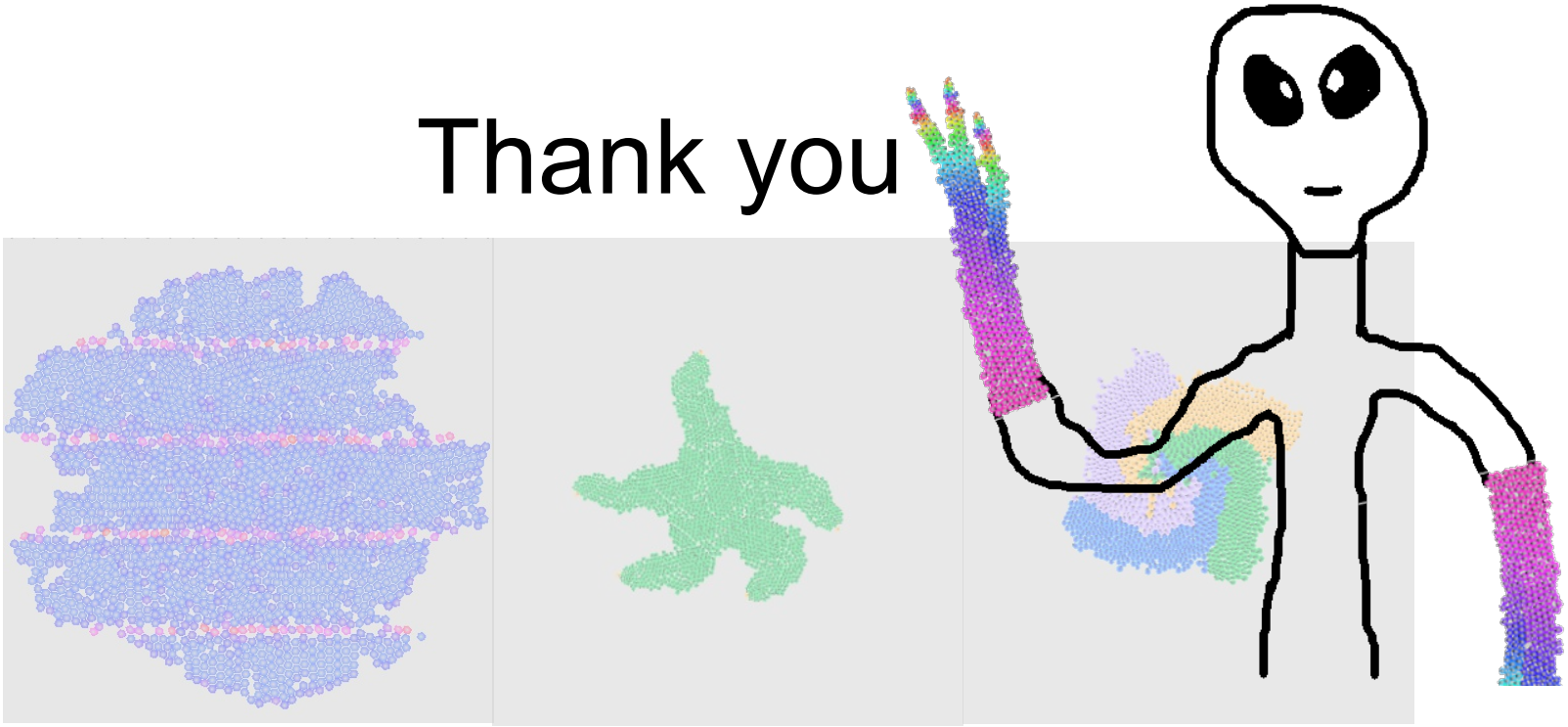


Future works

- Merge our virtual cell model and our morphogenesis approach
- Use more deeply our morphogenesis model …
- And also study backward morphogenesis



Thank you

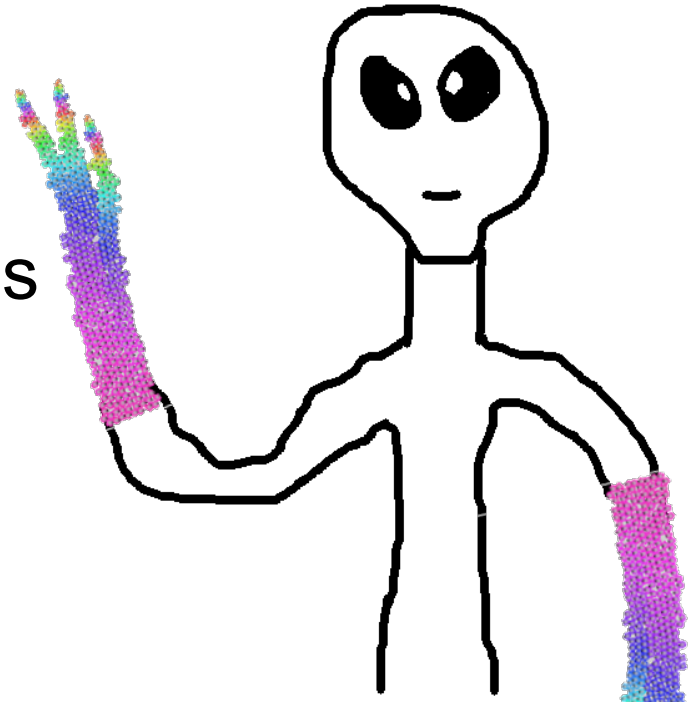


A. Jeannin-Girardon et Al, IEEE/ACM Transactions on Computational Biology and Bioinformatics (TCBB), 2015

A. Sarr et Al, 3rd international conference on Theory and Practice of Natural Computing (TPNC), 2014

Questions?

Vincent, why did you do that ?



➔ Imagine, we integrate in our cells just a part of the works presented in cBio 2015…

➔ We would see, for example, tumor growth taking into account genes, pathways, etc.

➔ We would predict the effect of radiotherapies, chirurgical acts, etc.

A. Jeannin-Girardon et Al, IEEE/ACM Transactions on Computational Biology and Bioinformatics (TCBB), 2015

A. Sarr et Al, 3rd international conference on Theory and Practice of Natural Computing (TPNC), 2014