A multiagent approach for virtual tissue morphogenesis

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Virtual Reality ➔ Virtual Biology

Interaction between virtual cells and/or molecules
Context (1/3)

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

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Context (2/3)

Biology
Morphogenesis study

Many
Interacting cells

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
Continuous approach

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

Mechanisms involved in Morphogenesis process

Physical constraints, Mechanotransduction

Chemical gradients

Division & differentiation control

Ph.D. Anne Jeannin-Girardon

« Research & Technical challenge » work

Ph.D. Abdoulaye Sarr

« Exploratory research » work

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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
Tissue morphogenesis:

- Is a multi-scale phenomenon
- Can be addressed through continuous/discrete models
- Involves many of interacting entities (cells, molecules, etc.)
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 focus on a small part of the system
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
- Continuous approach can be used when needed (chemical gradient, etc.)
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.

- 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

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Virtual cells agents 
behaviors and abilities

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

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)

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

We represent a cell differentiation by a change in the cell’s color.
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

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

\[
\frac{\delta_i(x,t)}{\delta t} = D_i \Delta_i(x,t) - R_i(x,t)
\]
Virtual chemistry model (2/2)

- **TA** produces **B** consumes **C**
- **B** produces **Tc**
- **A** produces **D** consumes **C**

Simulation step:
- Total
- Type A
- Type B
- Type C
- Type D

Number of cells vs Simulation step

proliferation.mp4

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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

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

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

No synchronization required
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

Graphs showing the average time per step vs. the number of simulated cells (cell sorting) for different hardware configurations.
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 » ?
Towards morphogenesis modeling..? (1/2)

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)

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.
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

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

Our model (1/2)

The Environment $E$: a grid

A cell $x$: a square which can be placed in the environment

A genetic action $d$ which can be applied by a cell:

$d \in \{ \uparrow, \downarrow, \rightarrow, \leftarrow, \mathbf{■}, \emptyset \}$ or simply $d \in \{ 1, 2, 3, 4, 5, 6 \}$

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

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

Our model (2/2)

A genetic process $G$: an ordered list of different genetic actions

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

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

```cpp
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

Attainable tissues after 2 divisions: 4
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
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

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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.

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