
Programming languages,
distributed computing systems
and the reconstruction of biological systems

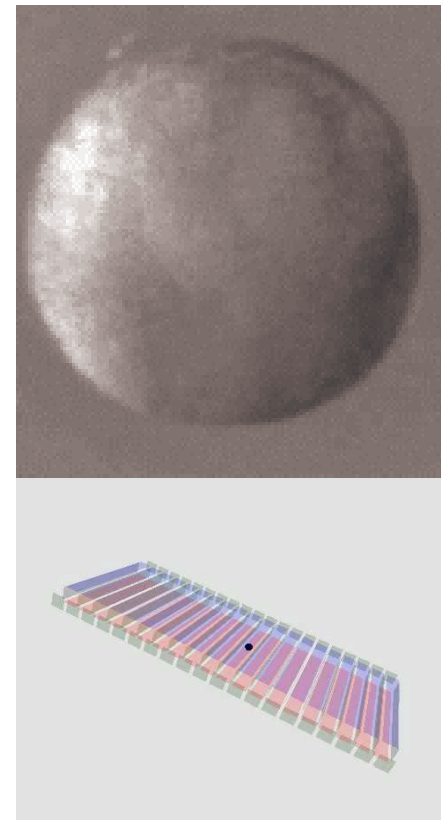
ibiSc

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LIS team, MGS project

<http://mgs.ibisc.fr>



1. Computer modelling of morphogenesis
2. Rewriting systems and abstract transition systems
3. The MGS approach
4. Three examples
 - The growth of a meristeme
 - The modelling of a synthetic multicellular bacterium
 - A schematic sketch of neurulation
5. $(SD)^2$, causality and reductionism

(Computer) Modeling of Morphogenesis

Development =

- cleavage divisions (division without increase in cellular mass)
- + pattern formation (spatial and temporal pattern of activities)
- + morphogenesis (change in 3D form)
- + cellular differentiation (acquisition of different structure & function)
- + growth (increase in size)

Modelling morphogenesis: the approach of A. Turing

THE CHEMICAL BASIS OF MORPHOGENESIS

BY A. M. TURING, F.R.S. *University of Manchester*

(Received 9 November 1951—Revised 15 March 1952)

In this section a mathematical model of the growing embryo will be described. This model will be a simplification and an idealization, and consequently a falsification. It is to be hoped that the features retained for discussion are those of greatest importance in the present state of knowledge.

Mathematical biology after D'Arcy Thompson, Rashevsky, ...

The model takes two slightly different forms. In one of them the cell theory is recognized but the cells are idealized into geometrical points. In the other the matter of the organism is imagined as continuously distributed. The cells are not, however, completely ignored, for various physical and physico-chemical characteristics of the matter as a whole are assumed to have values appropriate to the cellular matter.

Cell-oriented discrete system description

versus

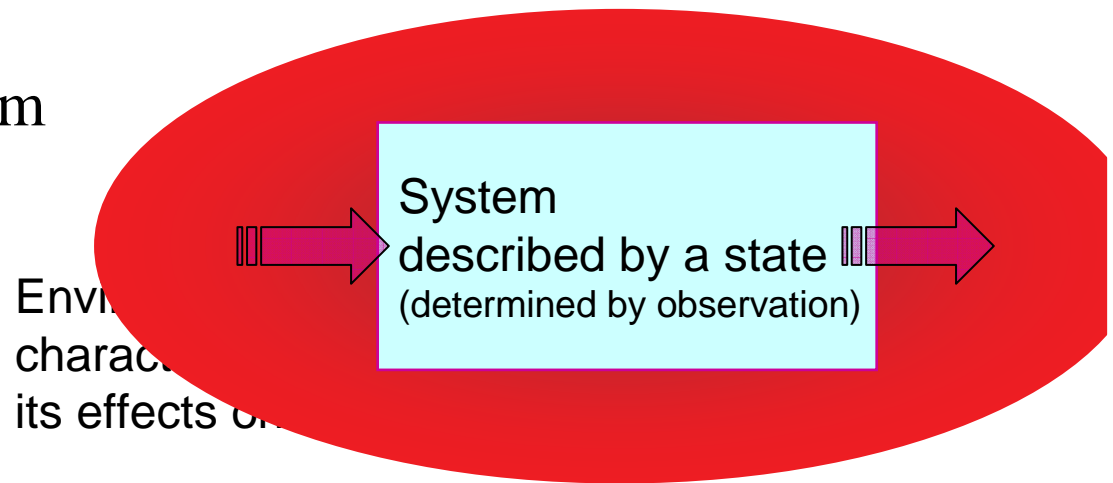
Uniform matter, continuous-oriented system description.

Morphogenesis as a Dynamical System

With either of the models one proceeds as with a physical theory and defines an entity called 'the state of the system'. One then describes how that state is to be determined from the state at a moment very shortly before. With either model the description of the state consists of two parts, the mechanical and the chemical.

Modelling a dynamical system

- state, including space (e.g. fields)
- time
- evolution function



C : continuous, D : discrete	PDE	Coupled ODE	Iteration of functions	Cellular automata	...
<i>state</i>	C	C	C	D	...
<i>time</i>	C	C	D	D	...
<i>space</i>	C	D	D	D	...



The medium/process problem

In determining the changes of state one should take into account

- (i) The changes of position and velocity as given by Newton's laws of motion.
- (ii) The stresses as given by the elasticities and motions, also taking into account the osmotic pressures as given from the chemical data.
- (iii) The chemical reactions.
- (iv) The diffusion of the chemical substances. The region in which this diffusion is possible is given from the mechanical data.

This account of the problem omits many features, e.g. electrical properties and the internal structure of the cell. But even so it is a problem of formidable mathematical complexity. One cannot at present hope to make any progress with the understanding of such systems except in very simplified cases.

A developing
embryo

A falling ball



at any time, a state is a position and a speed

A dynamical system (DS)

the structure of the state (chemical and mechanical state of each cell) is changing in time

**A dynamical system with
a dynamical structure (DS)²**

Modelling morphogenesis: the predefined medium

The interdependence of the chemical and mechanical data adds enormously to the difficulty, and attention will therefore be confined, so far as is possible, to cases where these can be separated.

Suppose, for instance, that a 'leg-evocator' morphogen were being produced in a certain region of an embryo, or perhaps diffusing into it, and that an attempt was being made to explain the mechanism by which the leg was formed in the presence of the evocator. It would then be reasonable to take the distribution of the evocator in space and time as given in advance and to consider the chemical reactions set in train by it.

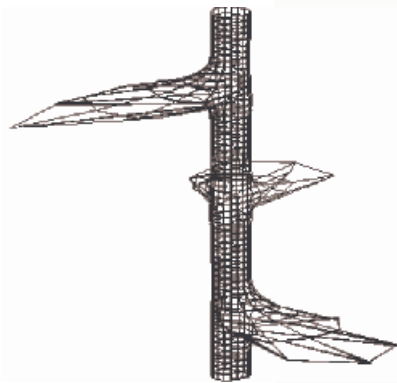
Most of the modelling work has been done in the static carrier setting:

- L. Wolpert
- H. Meinhard
- ...
- cellular automata
- or by considering *continuous deformation* of a predefined space (growth tensor, elastic theory)

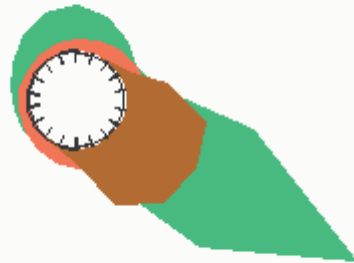
... *except* for the L system approach

What has changed since Turing's time

It might be possible, however, to treat a few particular cases in detail with the aid of a digital computer. This method has the advantage that it is not so necessary to make simplifying assumptions as it is when doing a more theoretical type of analysis. It might even be possible to take the mechanical aspects of the problem into account as well as the chemical, when applying this type of method. The essential disadvantage of the method is that one only gets results for particular cases. But this disadvantage is probably of comparatively little importance.

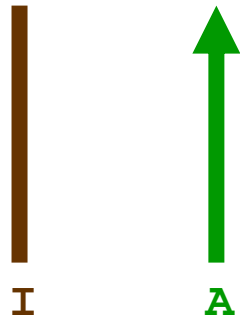


© H. Meinhardt, c.1970
Fixed shape, diffusion and reaction

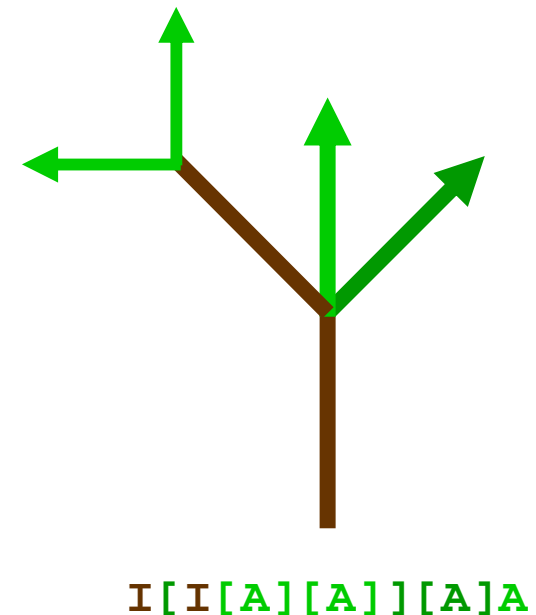
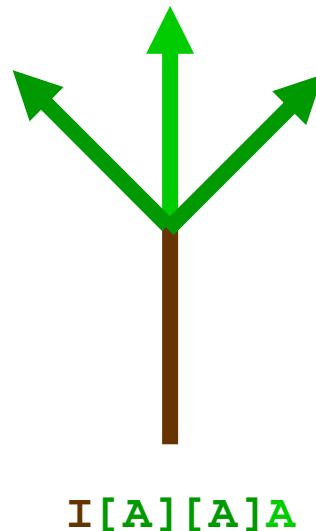
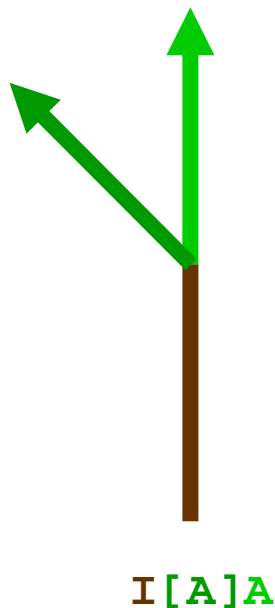


© P. Prusinkiewicz, c.2003
Diffusion and reaction in a deformable surface (E. Coen's *expanding canvas* metaphor). Spring-mass system. No topological change (i.e. real shape creation).

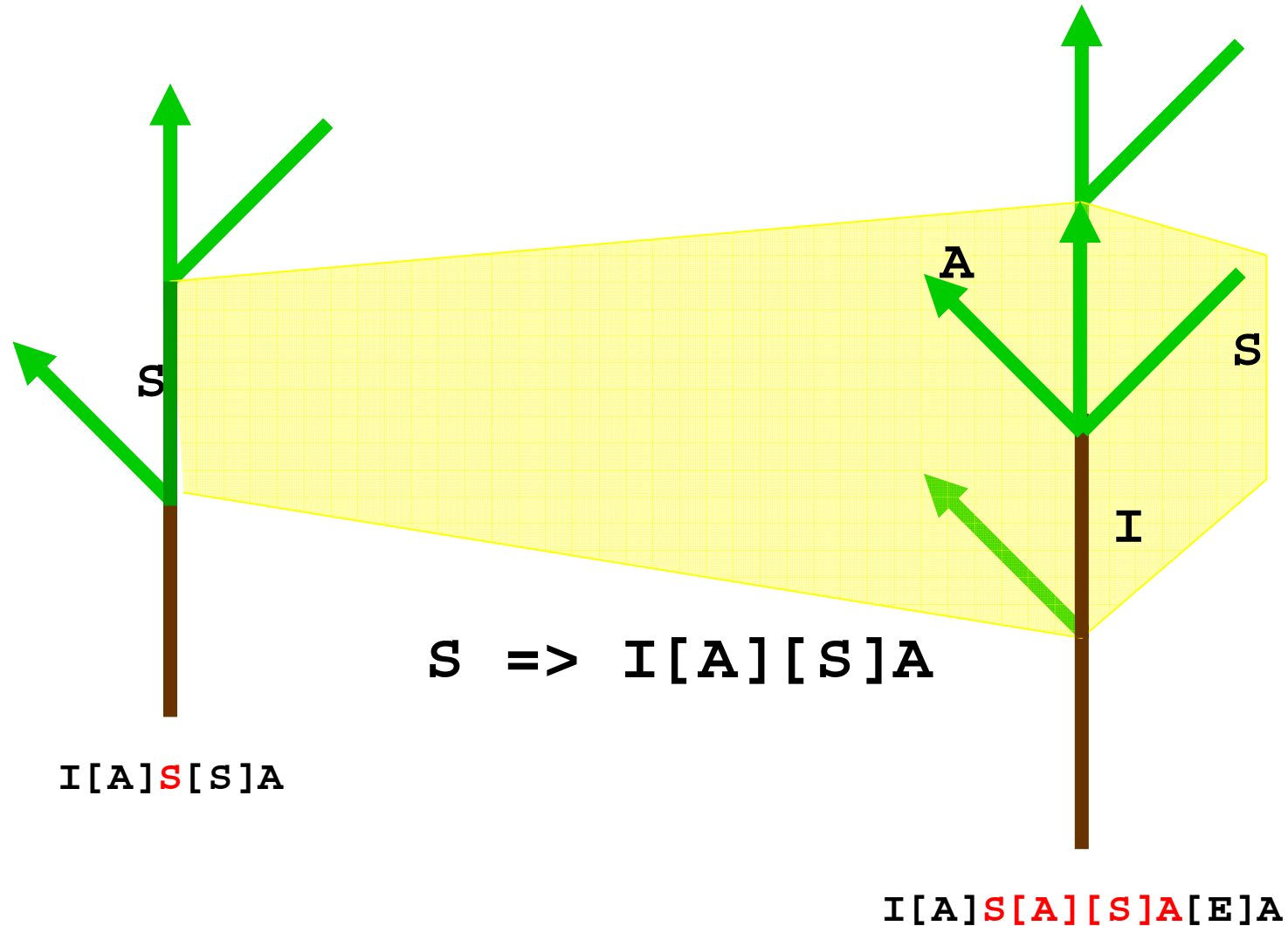
Lindenmayer systems: shape *creation/construction*



- The structure of a tree can be coded by a string of parenthesised symbols
- A symbol is an elementary part of the plant
- The symbol between [and] represents a sub-tree
- Additional conventions are used to represent main axis, orientation, depth, etc.



Lindenmayer systems: grammatical rules



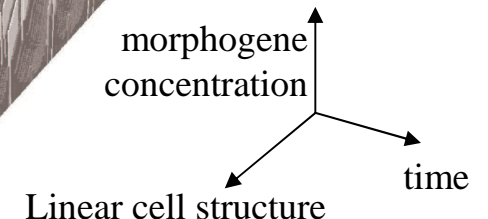
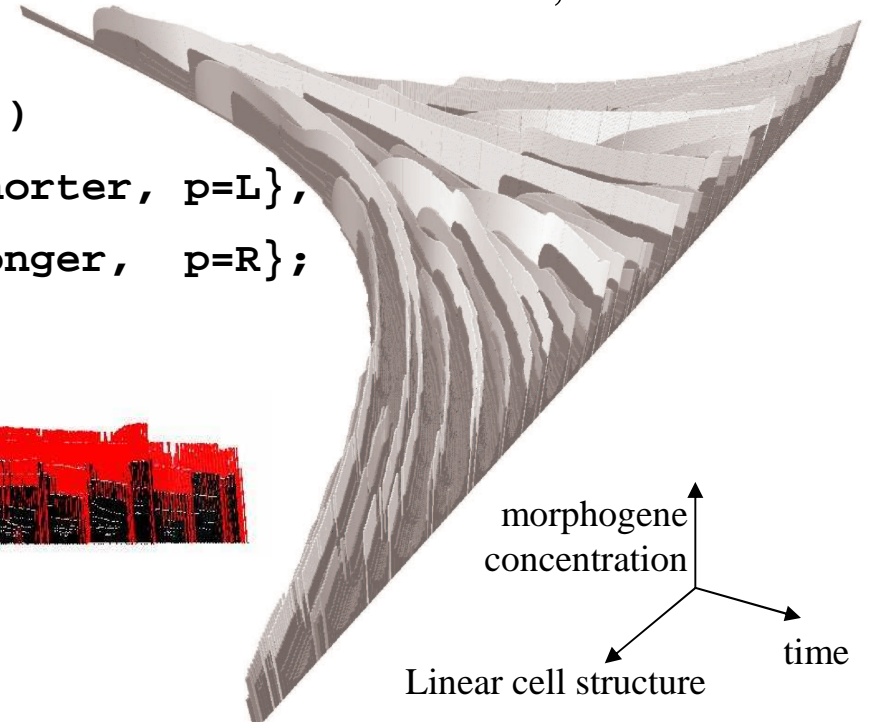
Diffusion and reaction in a linear *growing medium*

The following rules state that a differentiated cell (heterocyst) returns to a vegetative state if the concentration of the activator is too low. In addition, if the cell is large enough, it continues to grow.

```
e / (D(e) & (e.a < thr) | (e.x >= shorter*gr))  
=> {type="C", a=e.a/gr, h=e.h/gr, x=e.x*gr, p=e.p};
```

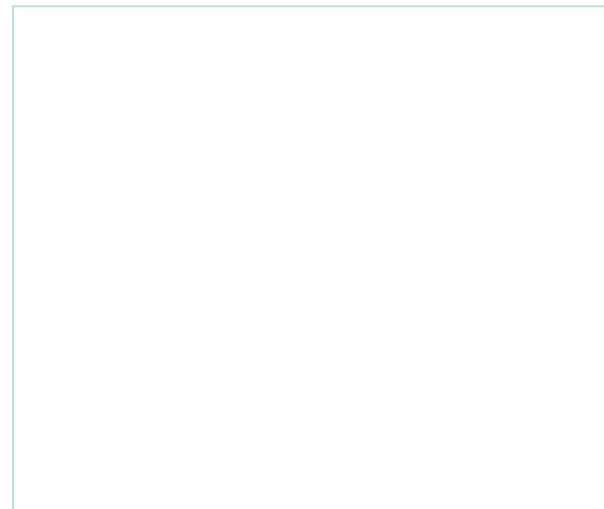
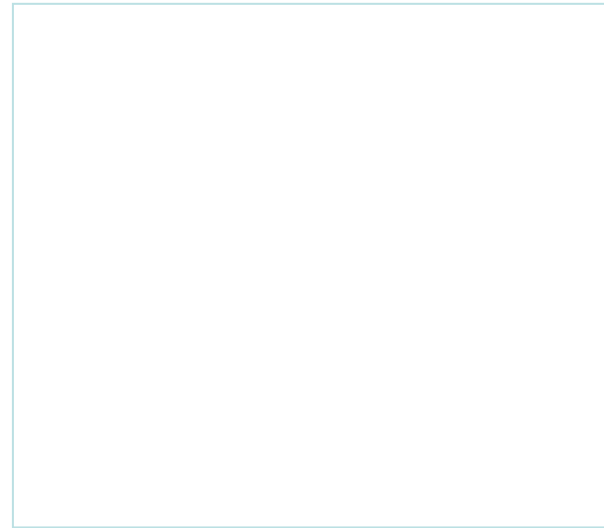
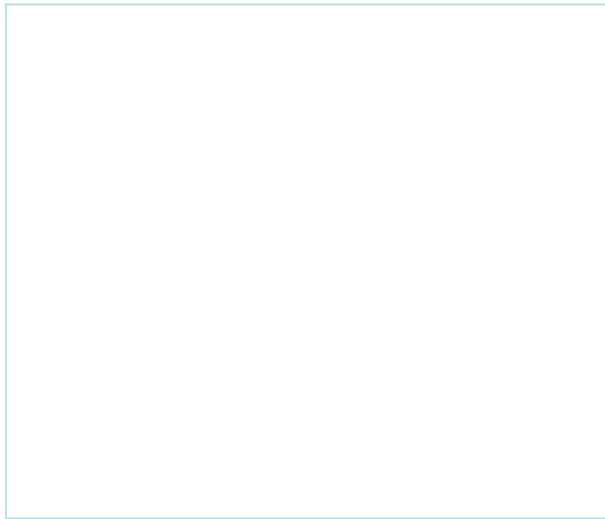
The following rule specifies when a cell with a left polarity divides. Only vegetative cells can divide (hence the predicate C in the rule guard) and it must be large enough. The volume of the two daughter cells remains the same, so there is no variation in the concentration.

```
e / (C(e) & (e.x >= lm) & (e.p == L))  
=> {type="C", a=e.a, h=e.h, x=e.x*shorter, p=L},  
    {type="C", a=e.a, h=e.h, x=e.x*longer, p=R};
```



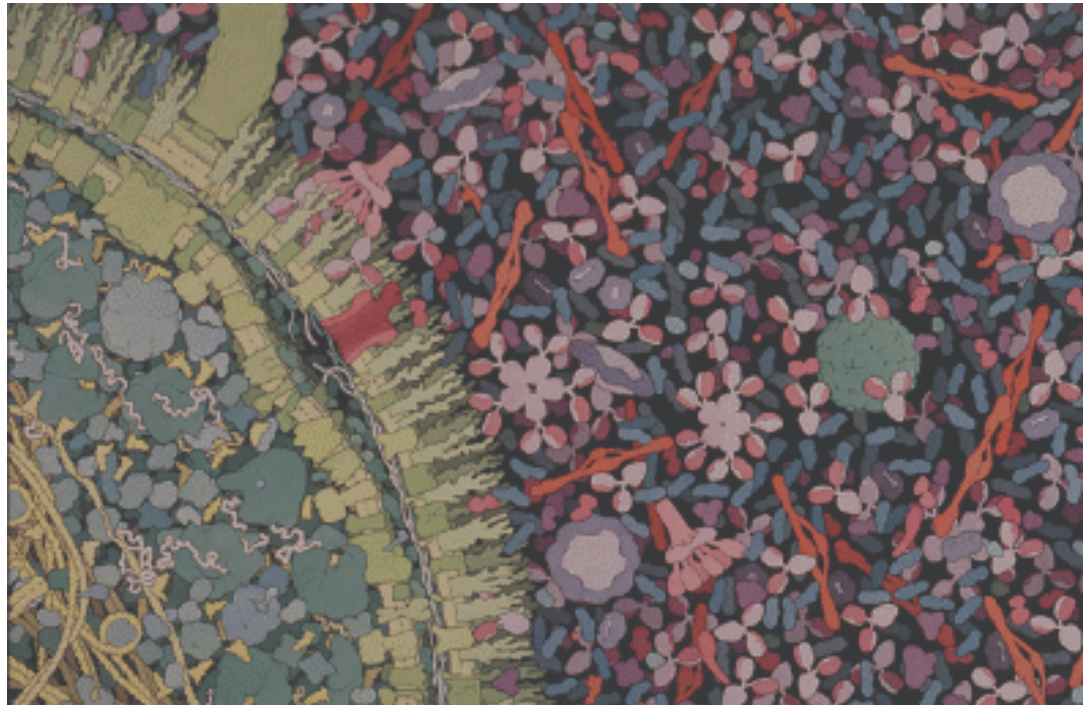
Plant development as grammar rule application

J.-L. Giavitto & O. Michel
IBISC, CNRS FRE 2873
<http://mgs.ibisc.fr>



How to extend to arbitrary spatial structure?

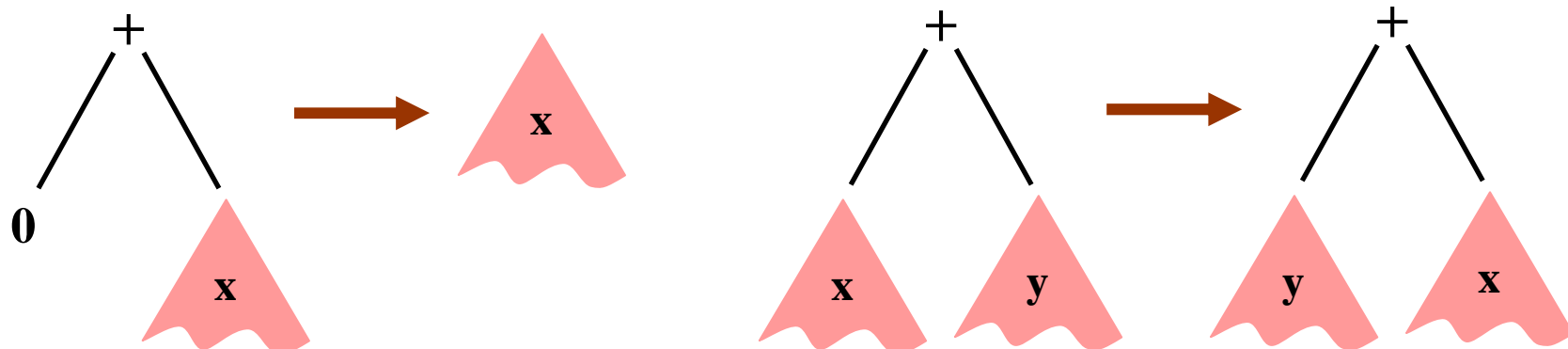
- Anabaena was « easy » because of the linear uniform structure
- How to handle the complex spatial structure of a cell?
- A program is a formal object (and some form of reasoning on it is possible) but a 10^6 lines of codes is not an explanation !



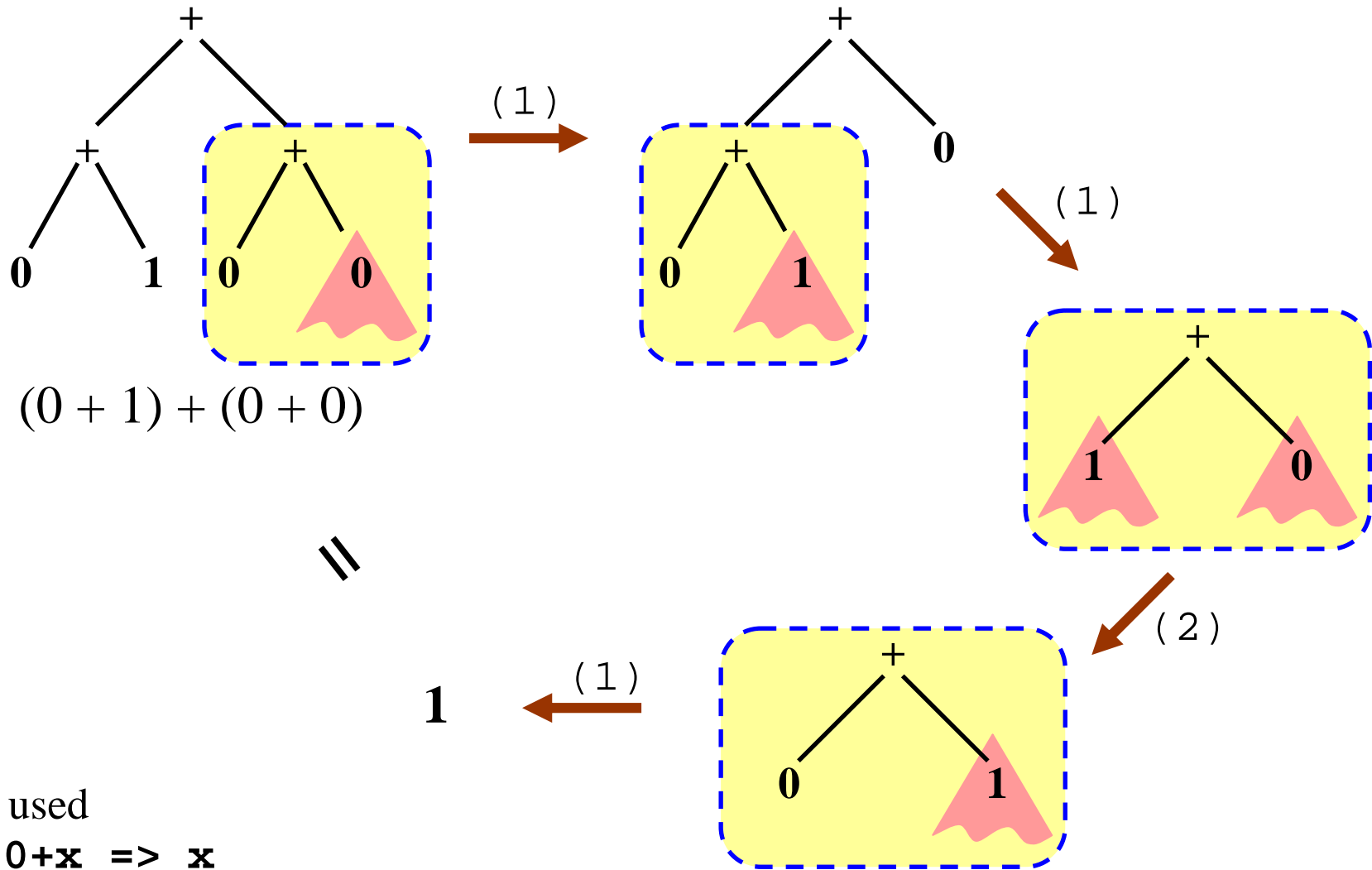
David S. Goodsell

Rewriting systems and abstract transition systems

- Rewriting system
 - Used to formalize equational reasoning
 - A generative device
 - Replace a sub-part of an entity by an other
 - Set of rewriting rules $\alpha \rightarrow \beta$
 - α : pattern specifying a sub-part
 - β : expression evaluating a new sub-part
- Example: arithmetic expressions simplification



Simplification of an expression



Rules used

(1) $0+x \Rightarrow x$

(2) $x+y \Rightarrow y+x$

Trees and spatial structure

- **Associative-commutative term rewriting**

- = multiset
- = *chemical soup*
- = **chemical computing, P systems**

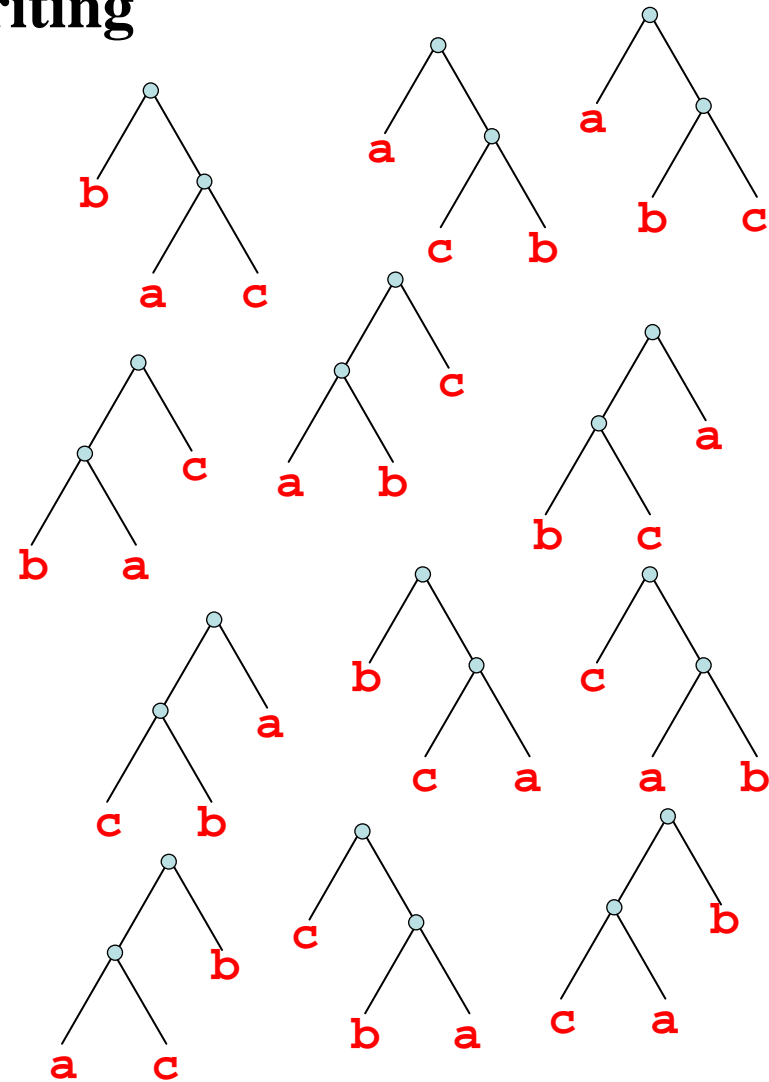
- **Associative term rewriting**

- = string
- = *linear structure*
- = **DNA computing, splicing systems**

- **Term rewriting**

- = tree
- = *branching 1D structure*
- = **L systems**

AC = stirring



$$\begin{aligned}
 a(bc) &= a(cb) = b(ac) = b(ca) = c(ab) = c(ba) = (ab)c = (ac)b = (ba)c = (bc)a = (ca)b = (cb)a \\
 a(bc) &= (ab)c \\
 a(bc) &\neq (ab)c
 \end{aligned}$$

Complex systems \leftrightarrow Rewriting techniques

Modelling

State (space)

hierarchical and tree organizations

arbitrary complex organizations

Evolution function

interactions \rightarrow evolution

local evolution laws

Simulation

Trajectories

Time management

discrete, event-based

synchronous vs. asynchronous

Specification

Data structure

formal trees (or terms)

?

Set of rules

α : pattern \rightarrow β : expression

rewriting rules

Application

Derivations

Rule application strategy

maximal parallel, sequential

deterministic, stochastic

Complex systems \leftrightarrow Rewriting techniques

Modelling

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hierarchical and tree organizations
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Specification

Data structure

formal trees (or terms)

topological collections

Set of rules

α : pattern \rightarrow β : expression

rewriting rules, *transformations*

Application

Derivations

Rule application strategy

maximal parallel, sequential
deterministic, stochastic

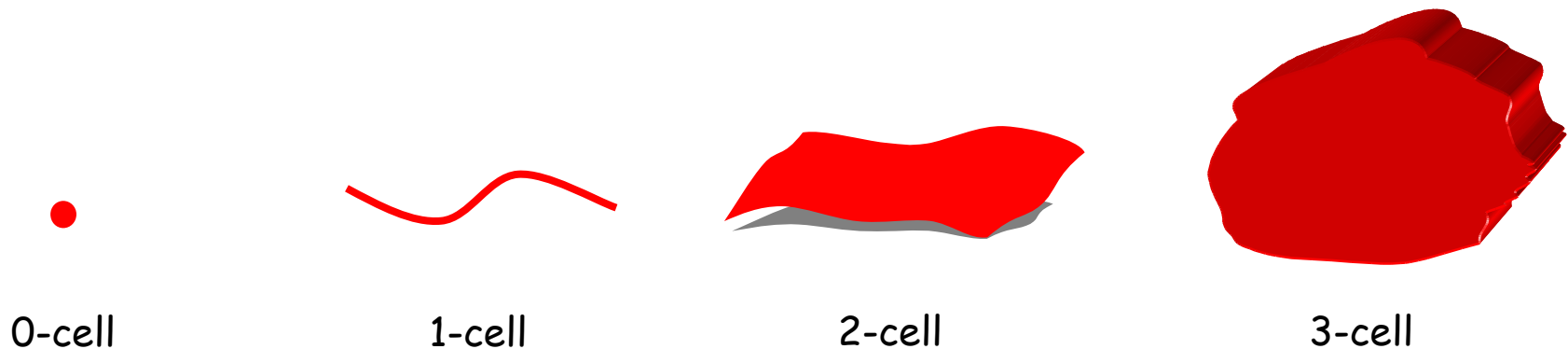
- *local evolution rules* (mandatory when you cannot express a global function because the domain of the function is changing in time)
- the l.h.s. of a rule specifies a set of elements in *interaction*, the r.h.s. the result of the interaction
- *the phase space is well defined but not well known* (a generative process enumerates the elements but membership-test can be very hard)
- *various kind of time evolution* (for the same set of rules)
- *demonstration by induction* (on the rules or on the derivation)

The MGS project

- Language dedicated to the simulation of complex systems models
- Declarative and functional (declarative simulation vs procedural)
- Abstract rewriting of complex spatial structures:
 - Data structure = topological collections
sequence, generalized array, (multi-)set, arbitrary graph, Delaunay triangulation, g-map, ..., abstract complexes
 - Control structure = transformation
 - two powerful languages to specify sub-collections (elements in interaction)
 - Various rule application strategies: maximal parallel, asynchronous, stochastic, Gillespie-like, ...

Representation of space and structure

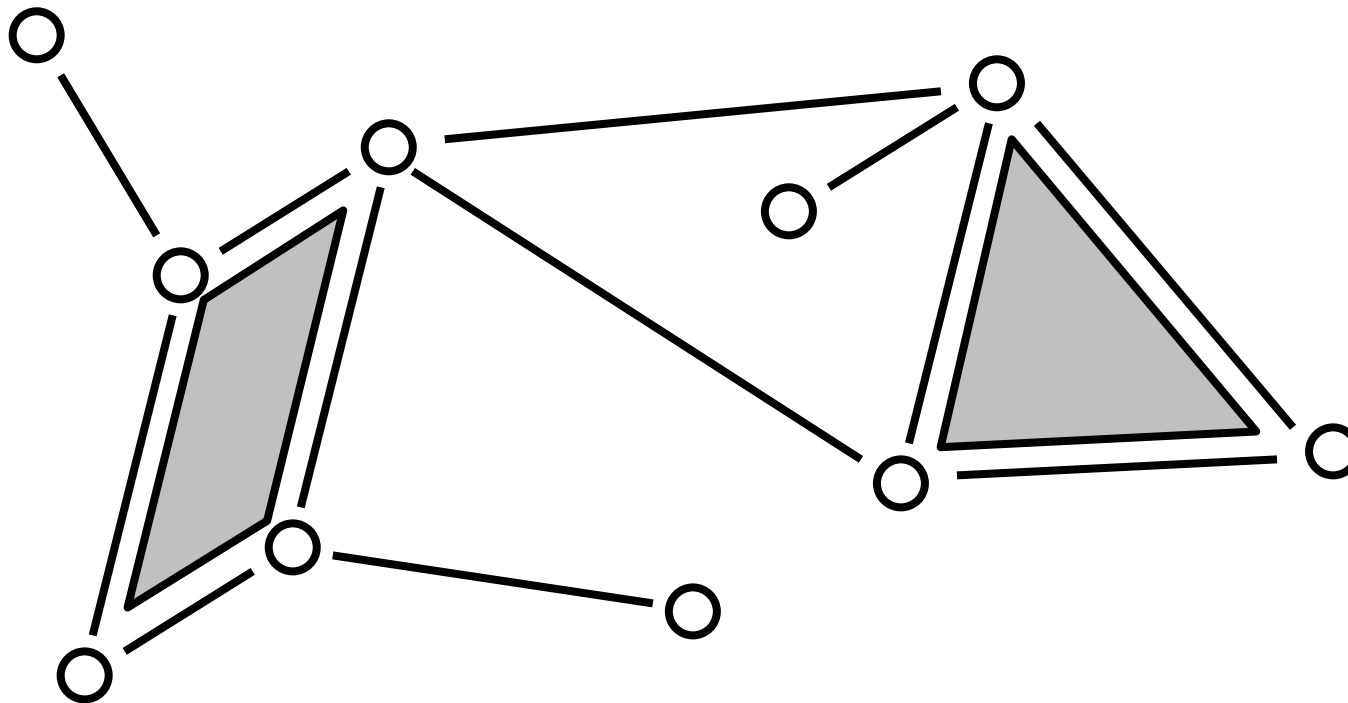
- Structure:
 - Collection of *topological cells*



Topological collection: representing the underlying space

Representation of space and structure

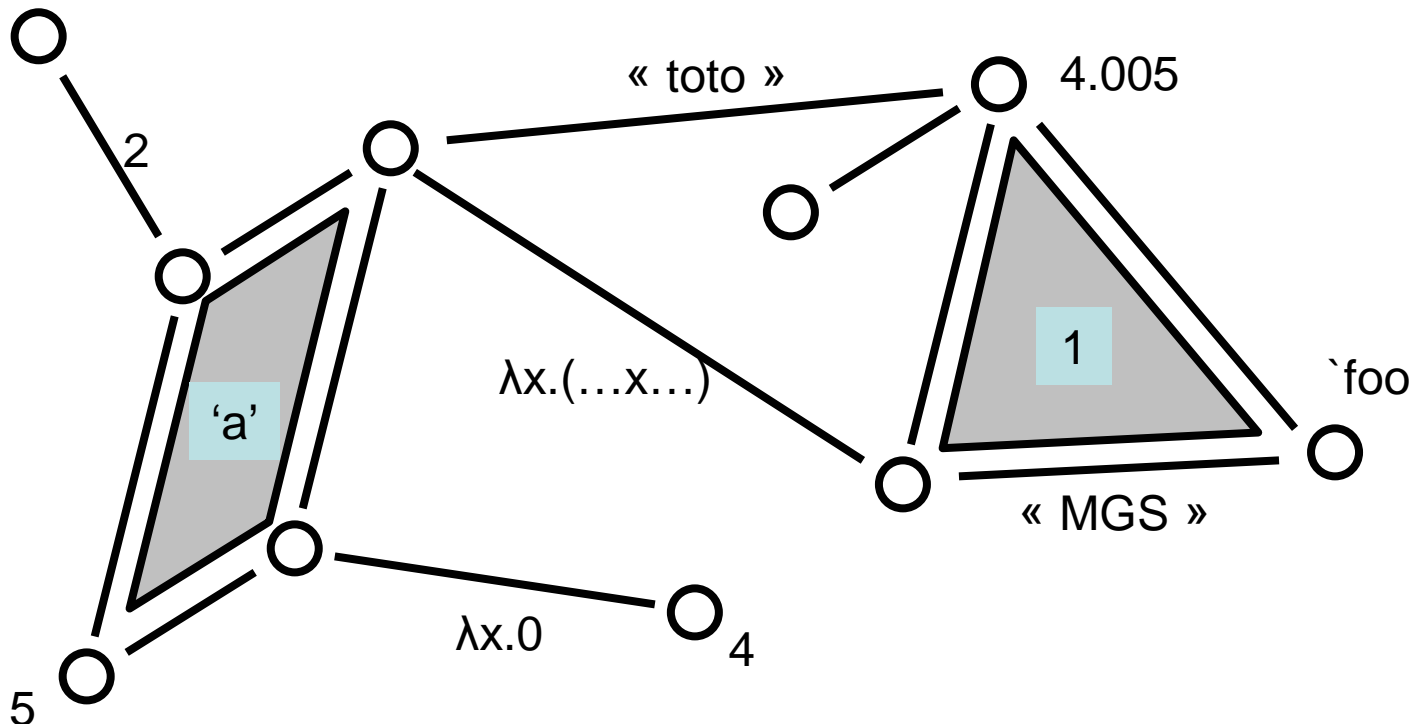
- Structure:
 - Collection of topological cells
 - *Incidence relationship*



Topological collection: a data-field over topological cells

Representation of space and structure

- Structure:
 - Collection of topological cells
 - Incidence relationship
- Data : *associating values with topological cell*



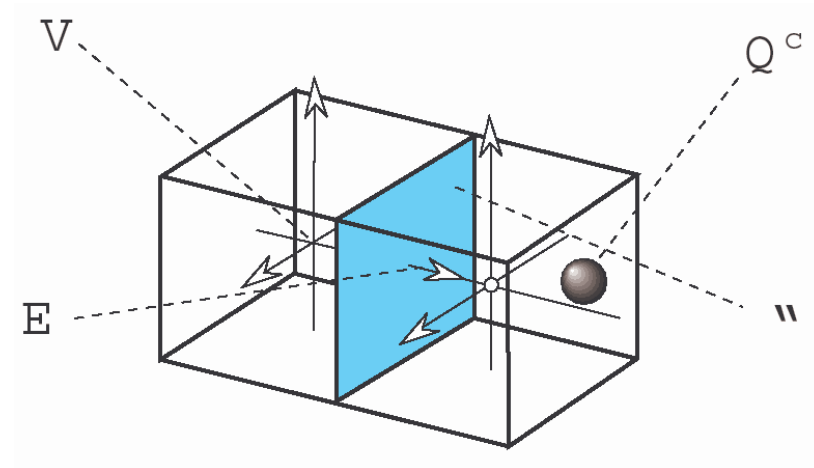
Electrostatic Gauss law [Tonti 74]

- Electric charge content ρ : **dimension 3**
- Electric flux Φ : **dimension 2**
- Law available on a arbitrary complex domain

$$\phi = \oiint w \cdot dS = \frac{Q^c}{\epsilon_0} = \iiint_{(V)} \frac{\rho}{\epsilon_0} d\tau$$

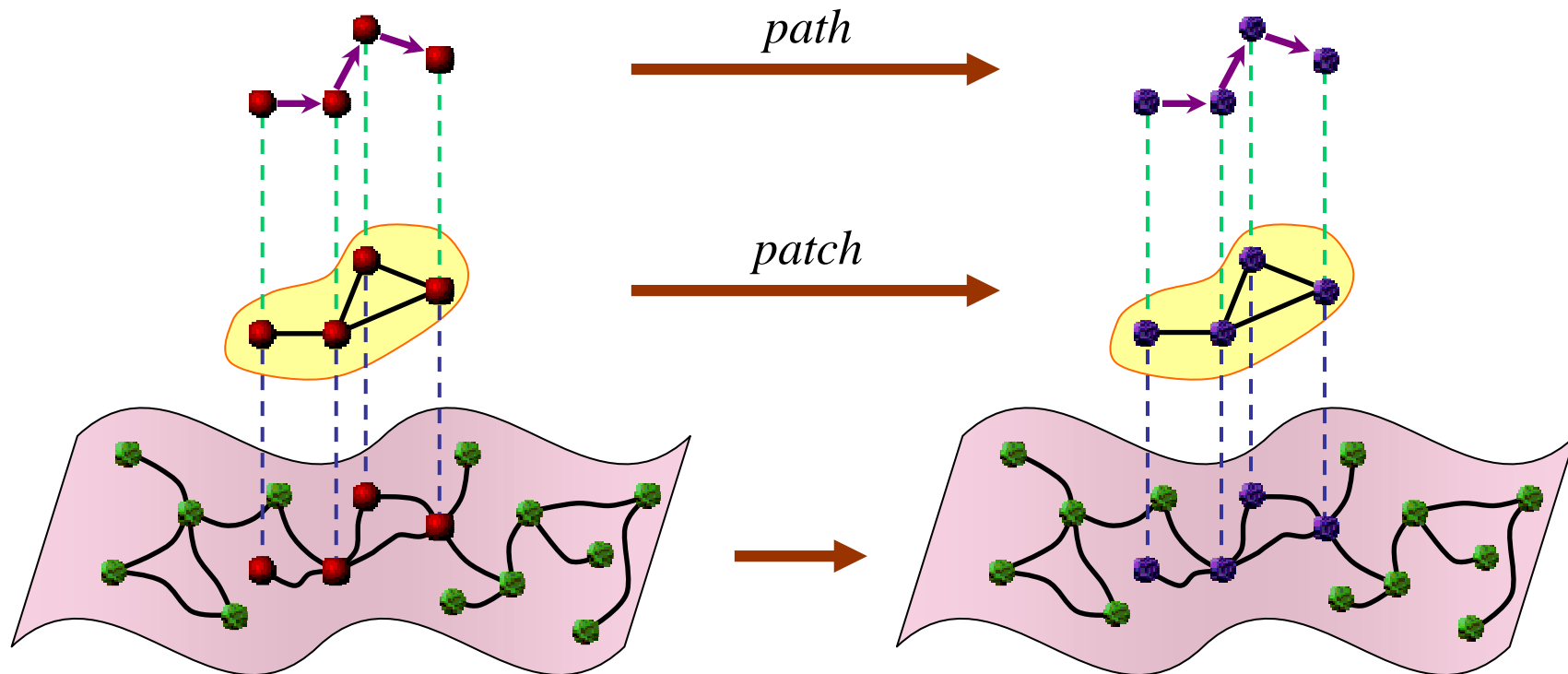
electric field in space:

- V: electric potential (dim 0)
- E: voltage (dim 1)
- w: electric flux (dim 2)
- Qc: electric charge (dim 3)



Pattern matching : specifying a sub-collection of elements in interaction

- *Path transformation* (path = sequence of neighbor elements)
 - Concise but limited expressiveness
- *Patch transformation* (arbitrary shape)
 - Longer but higher expressiveness



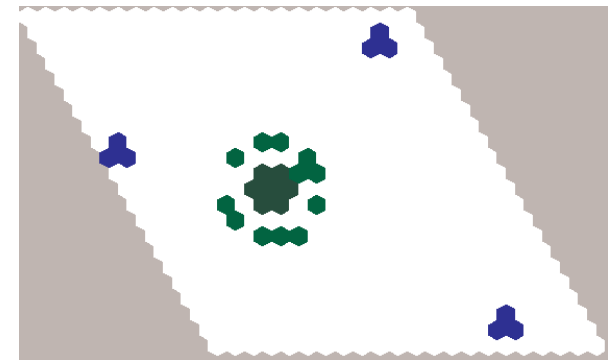
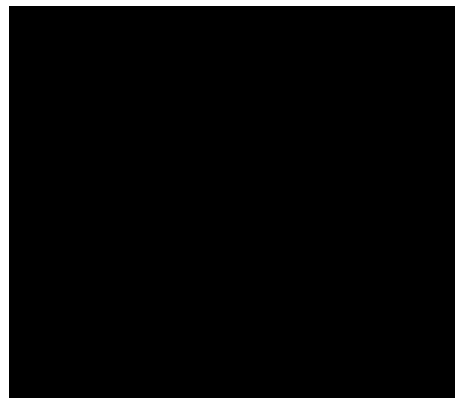
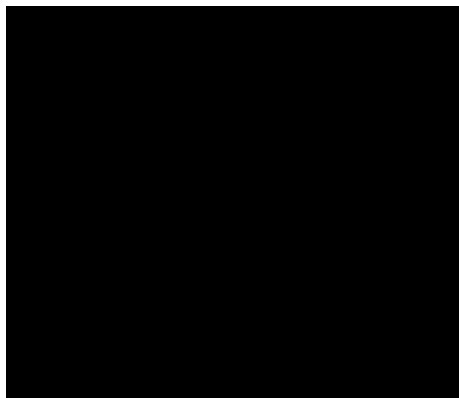
Example: DLA

Diffusion Limited Aggregation (DLA)

- Diffusion: some particles are randomly diffusing; others are **fixed**
- Aggregation: if a **mobile** particle meets a **fixed** one, it stays fixed

```
trans <2,1> dla = {  
    `mobile, `fixed => `fixed, `fixed ;  
    `mobile, <undef> => <undef>, `mobile  
}
```

this transformation is an abstract process that can be applied to any kind of space



The Growth of a Meristem

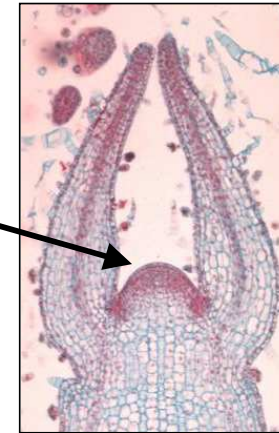
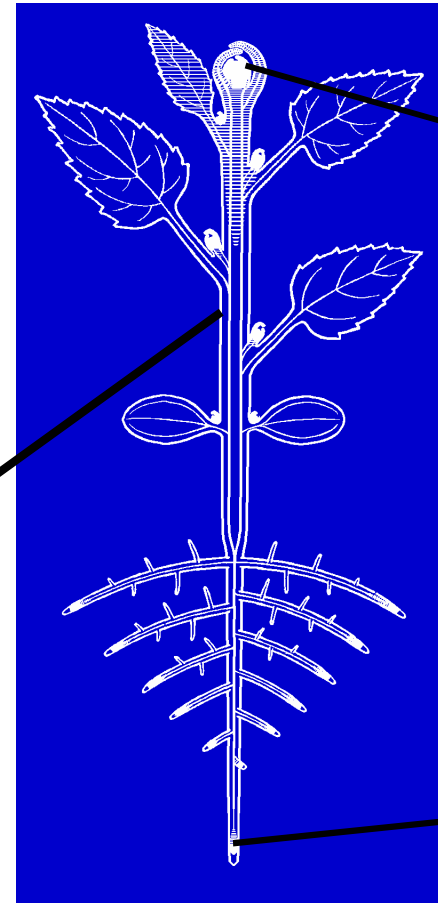
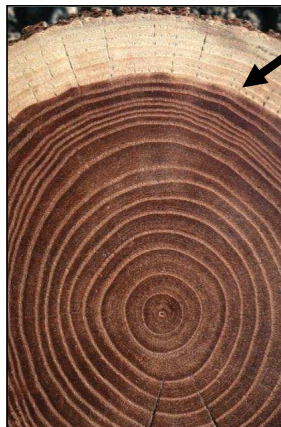
[PNAS 103(5), 1627-1632, 2006]

Pierre Barbier de Reuille
Mikaël Lucas
Jan Traas
Christophe Godin
CIRAD/INRA/INRIA

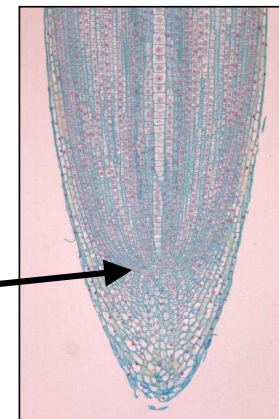


Organs
positioning
at the shoot
apex

Cambium



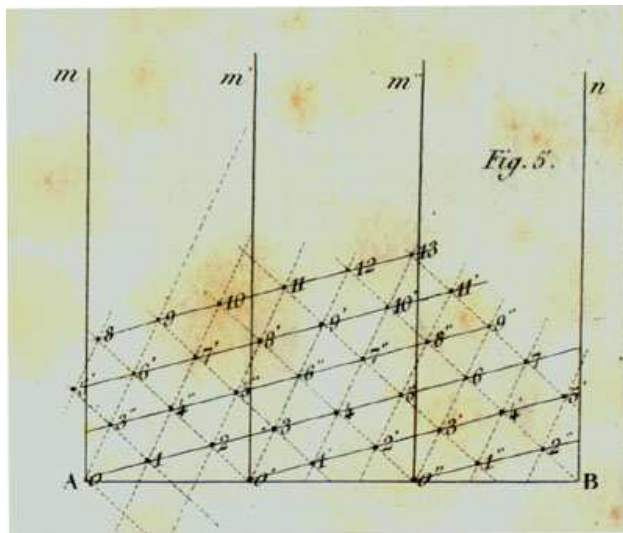
Shoot
apical
meristem



Root apical
meristem

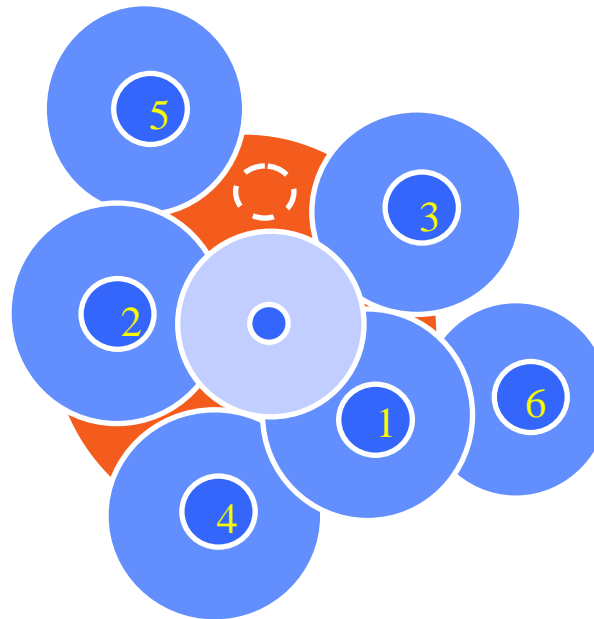
Three kinds of approaches

Geometrical



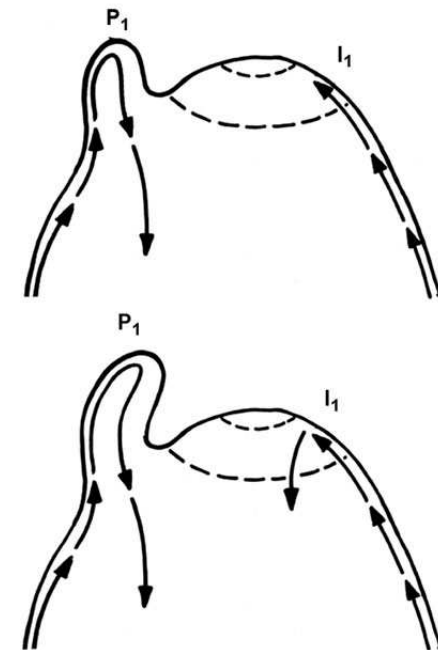
(Bravais & Bravais, 1837)

Optimal (dynamical?)



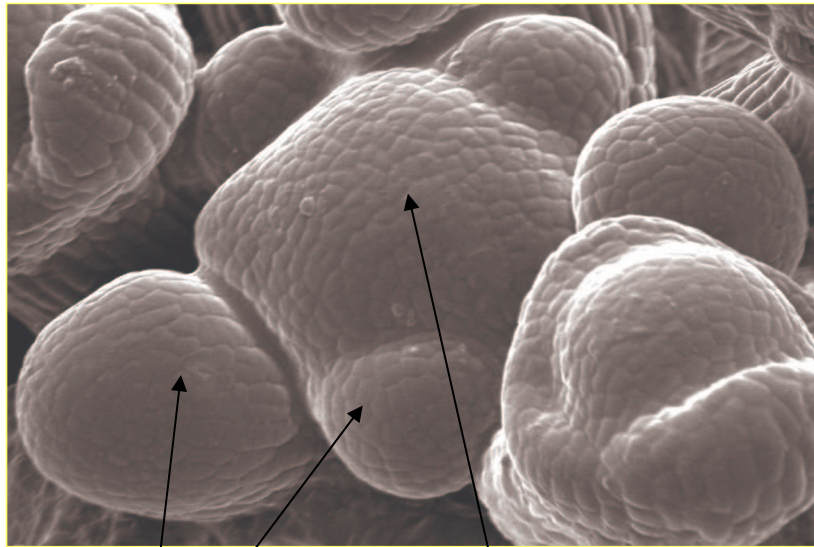
(Hofmeister, 1868)
(Snow and Snow, 1962)

Physiological



(Reinhardt et al., 2000)

A shoot apical meristem



Primordia

Central zone

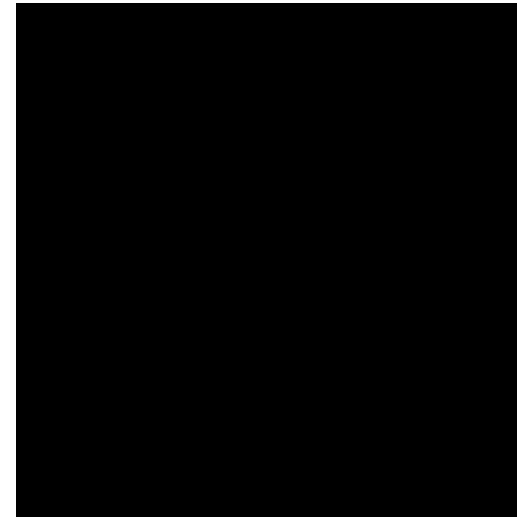
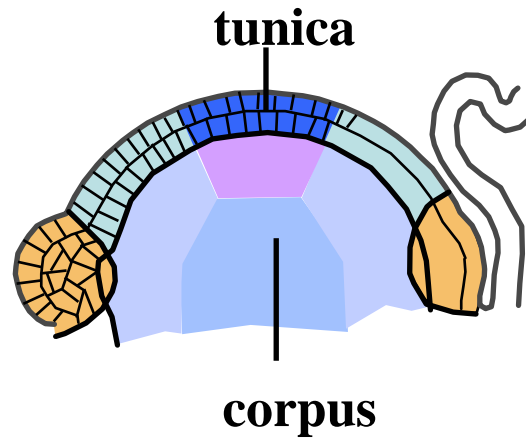
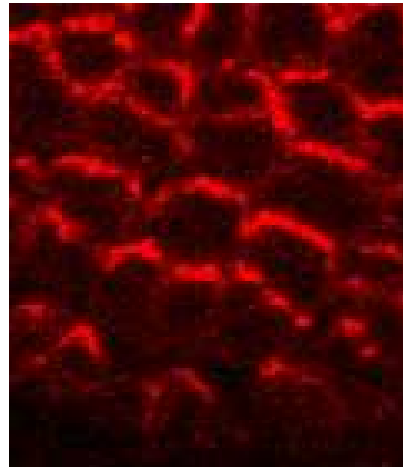


Image sequence showing cell division patterns via membrane-bound PIN1, in Shoot Apical Meristem (SAM), nearby floral meristems, and the boundaries between them. <http://computableplant.ics.uci.edu/>



Active transport of auxine

wild
type

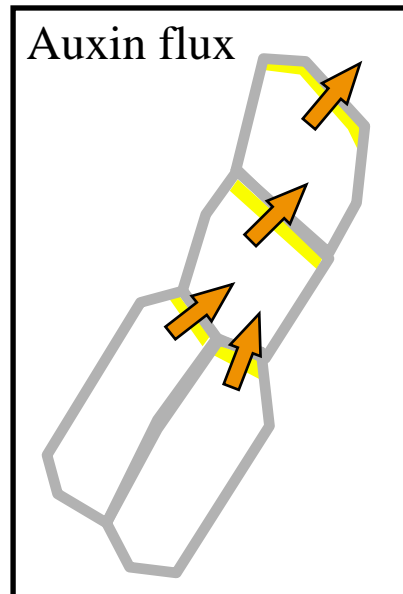


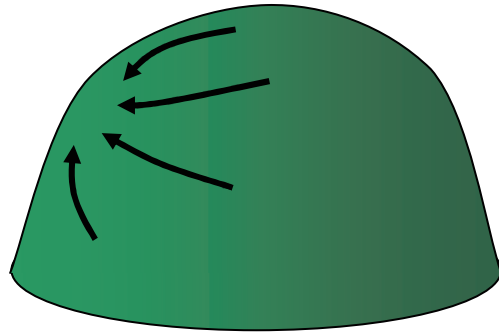
Immunolabelling of
PIN-FORMED1 protein



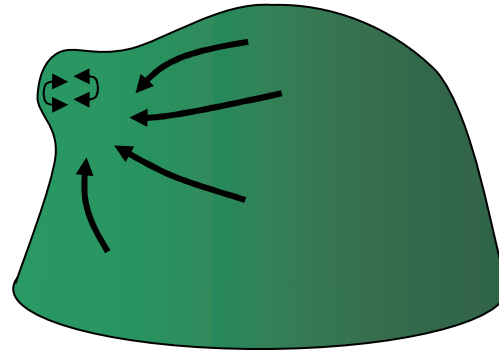
high concentration of
auxine induces organ initiation

pin-1
mutant

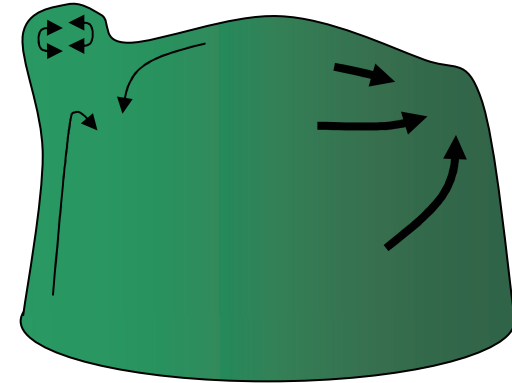




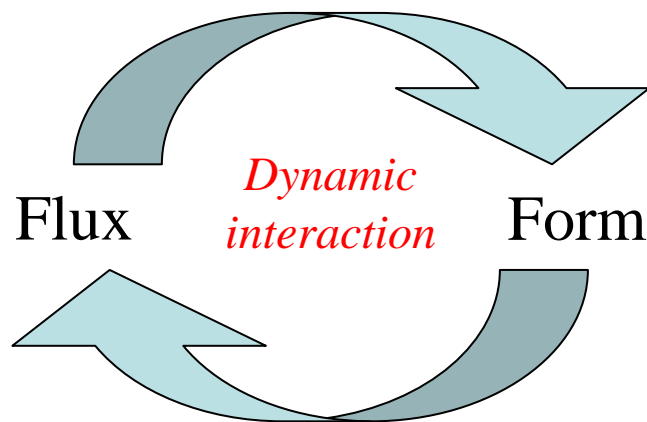
flux...



changes form...



which changes flux...



Model

- Cell internal state and processes

capacity of division, spring relaxed length,
primordium/center,

**concentration of auxin (inhibitor), saturation, auxin
degradation / evacuation, promotion to
primordium, “pump magnetism”**

- Movement (due to cell growth)

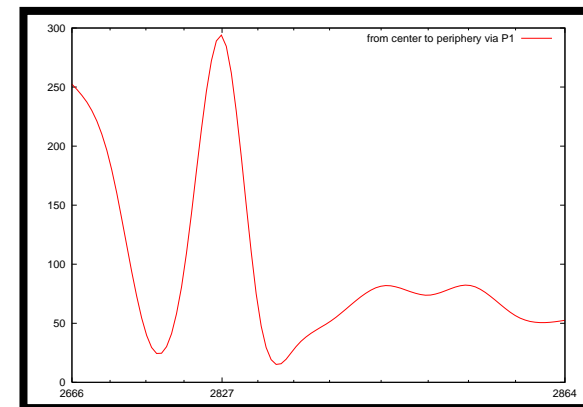
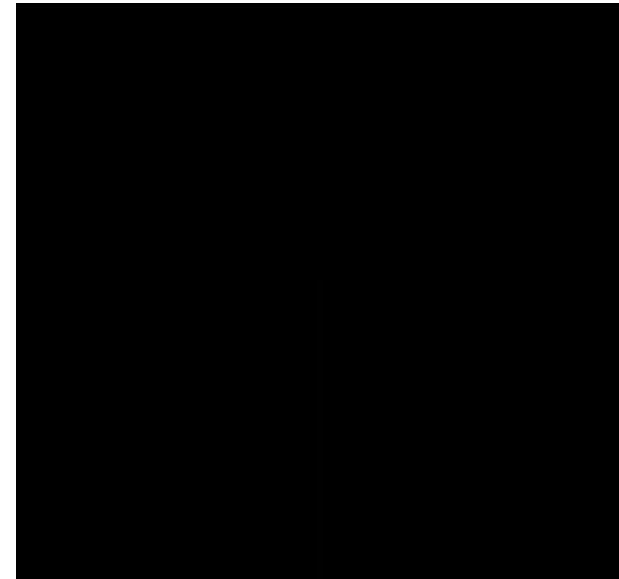
- Growth: increase of spring relaxed length

- Division: when size > threshold

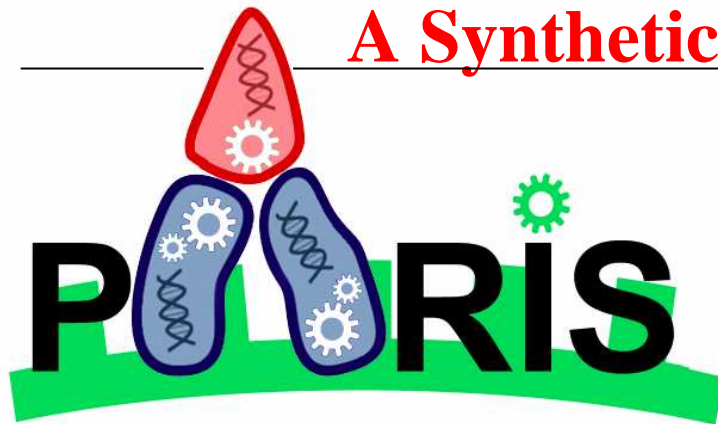
- Cell interaction

Passive diffusion of auxin, active pumping of auxin

```
trans Auxin = {  
  x, y / pump(x,y)  
  → {x.auxin -= δ}, {y.auxin += δ}  
}
```



Auxin level



A Synthetic Multicellular Bacterium

Synthetic Biology is

- A) the design and construction of new biological parts, devices, and systems, and
- B) the re-design of existing, natural biological systems for useful purposes.

(Español)

Synthetic Biology Logo

Home About Conferences Labs Courses Resources FAQ

Community news

- IET Synthetic Biology first issue includes iGEM 2006
- Synthetic Biology 3.0 Zurich proceedings. [Download here.](#)
- BioBricks Foundation first membership drive.
- [Synthetic Biology: Caught between Property Rights, the Public Domain, and the Commons](#)
- US HSPD-18. Guidance on openness and international transparency in biodefense work still needed.

Resources

- Press articles
- Publications: [citavika](#), [connotes](#), [PubMed](#)

Registry of Standard Biological Parts

Massachusetts Institute of Technology

Parts Catalog

Regulatory Reporter Inverter RNA Protein Generator Tag Deleted Cell Strain

RBS CDS Terminator Composite Cell-Cell Signalling Measurement Primer Other Plasmid T7

Web Site Update

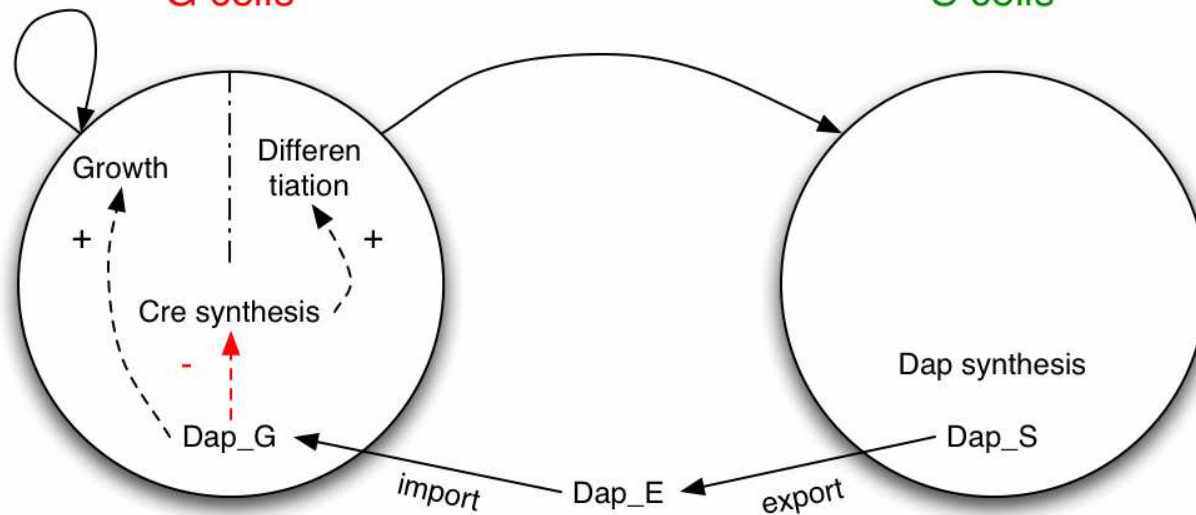
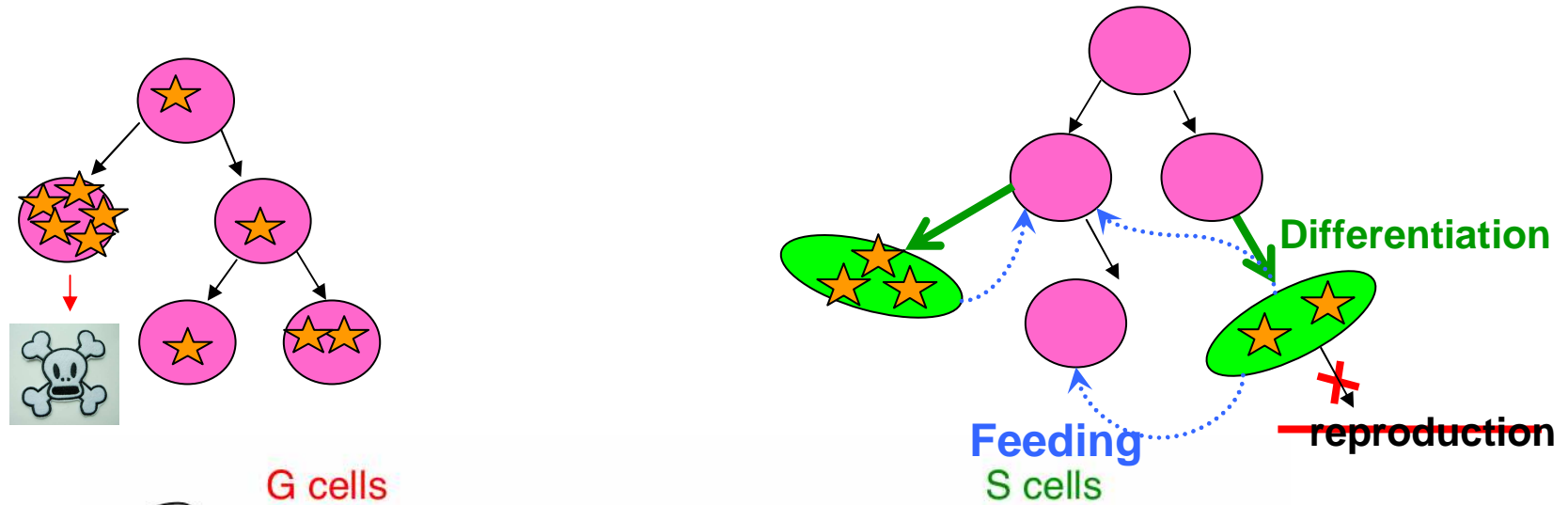
Educational Programs

Employment



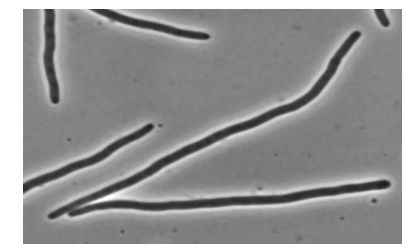
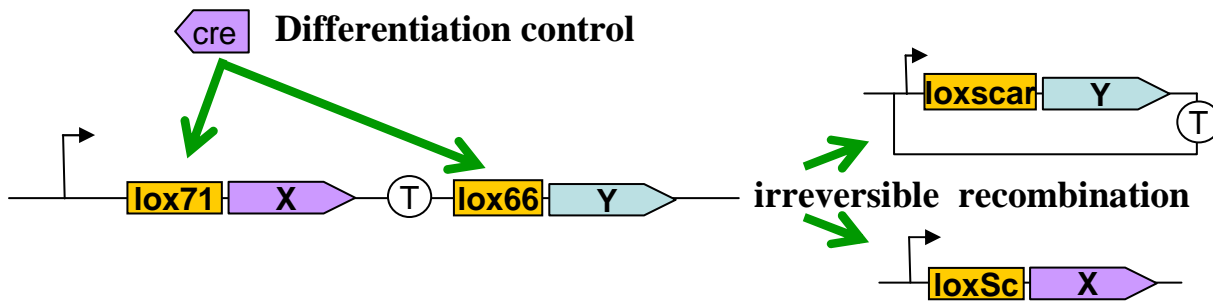
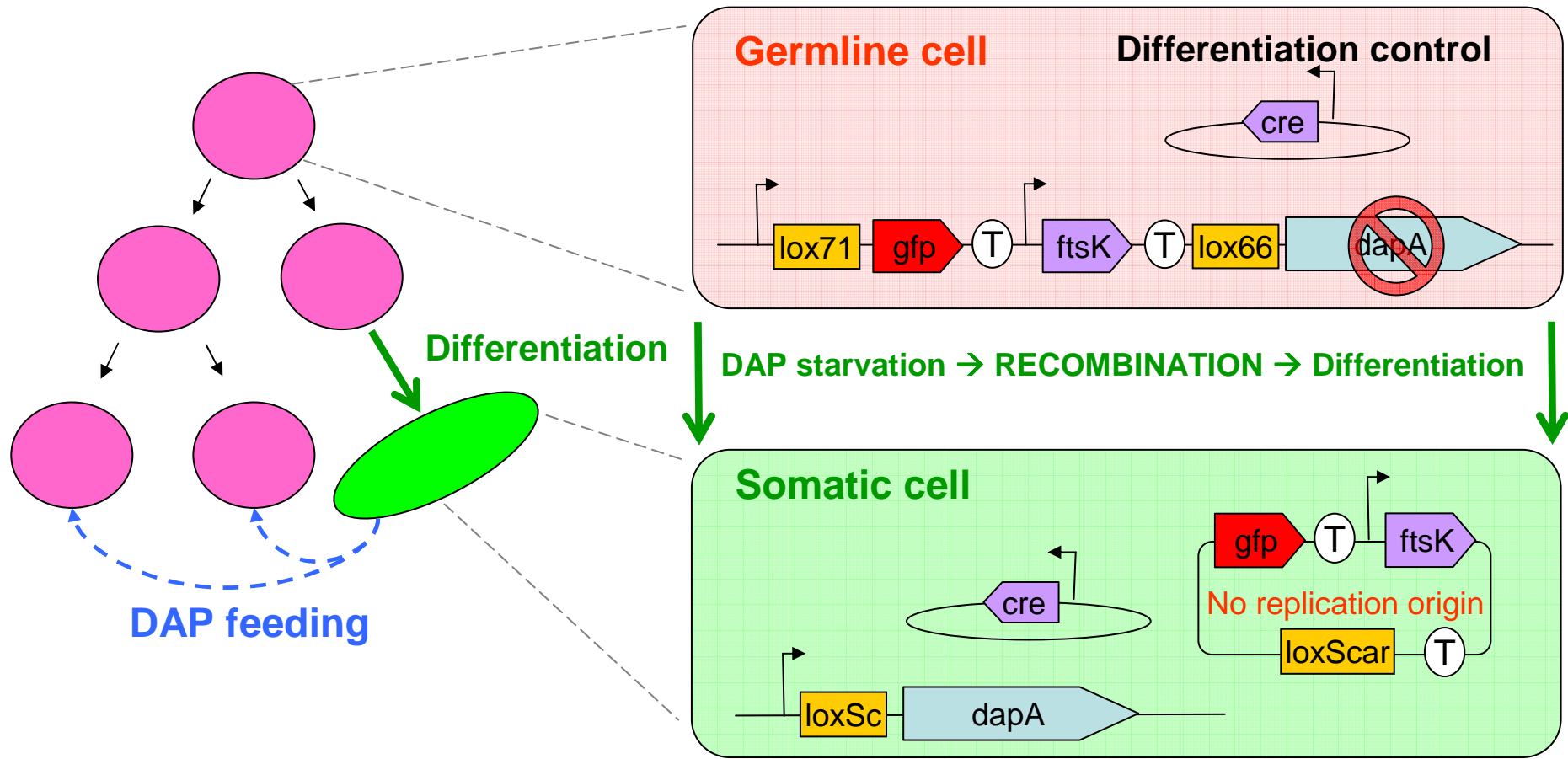
David Bikard, Thomas Landrain, David Puyraimond, Eimad Shotar, Gilles Vieira, Aurélien Rizk, David Guegan, Nicolas Chiaruttini, Thomas Clozel, Thomas Landrain

The Paris iGEM project: decoupling growth and transgene expression



$\overset{+}{-}$: positive/negative influence
 \longrightarrow : process

Implementation using BioBricks



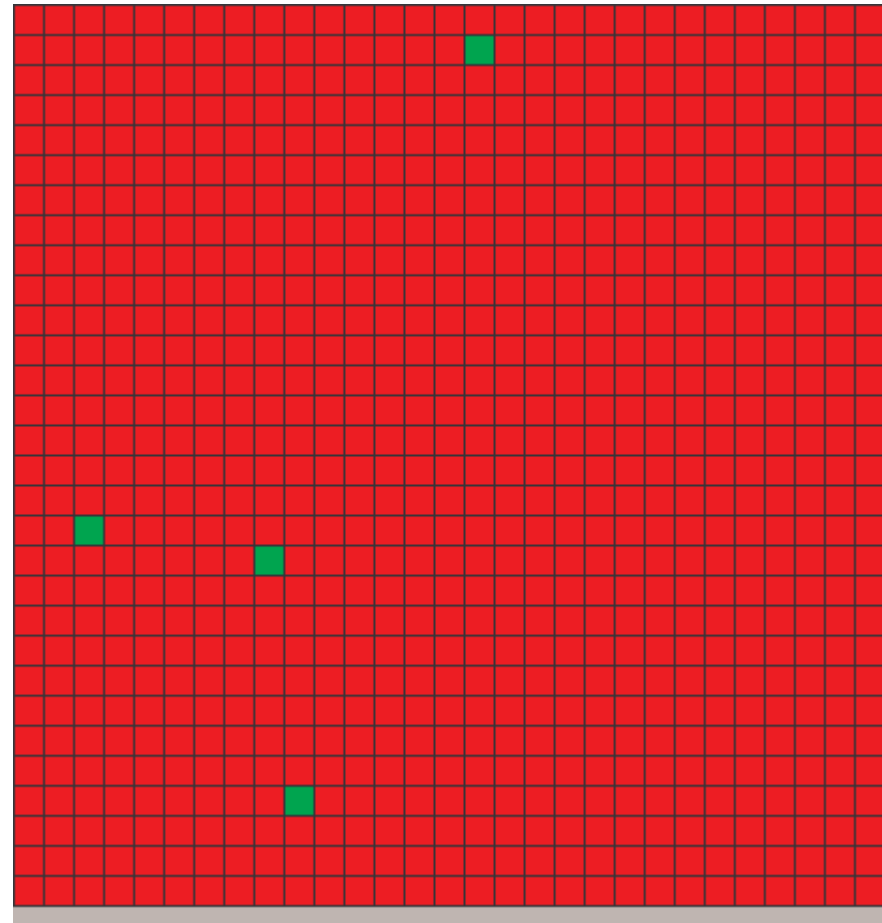
ftsK
 necessary
 for cellular
 division

Simulation to answer 4 questions

- **How does differentiation induces feeding?** (proof of concept)
cellular automaton (in MGS)



diffusion of DAP



somatic and germ cell

Simulation to answer 4 questions

- How does differentiation induces feeding? (proof of concept) cellular automaton (in MGS)
- How do spatial organization and distribution evolve? **agents based system (in MGS)**

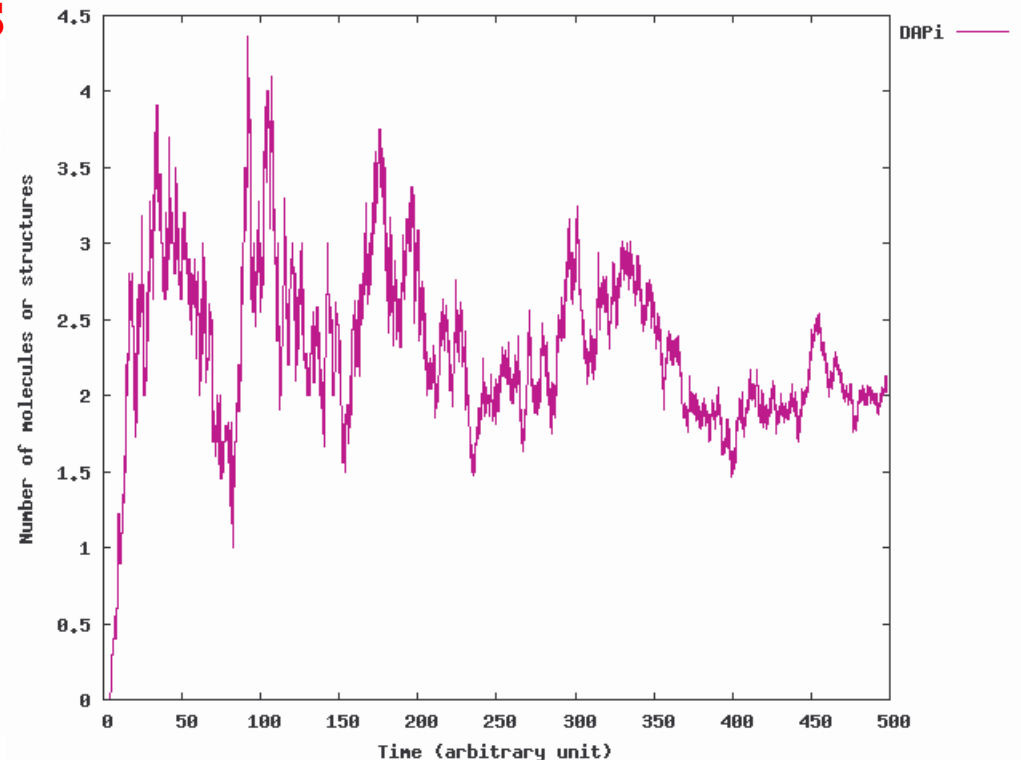
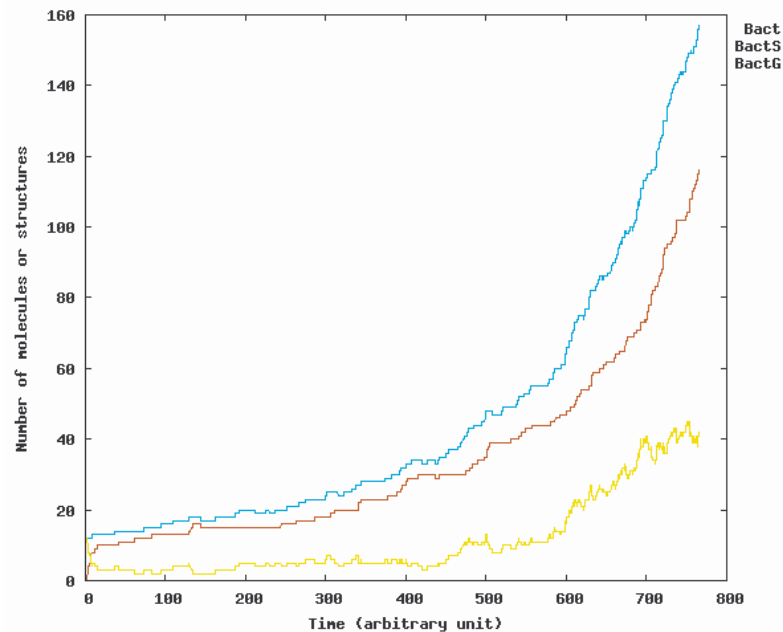


Simulation to answer 4 questions

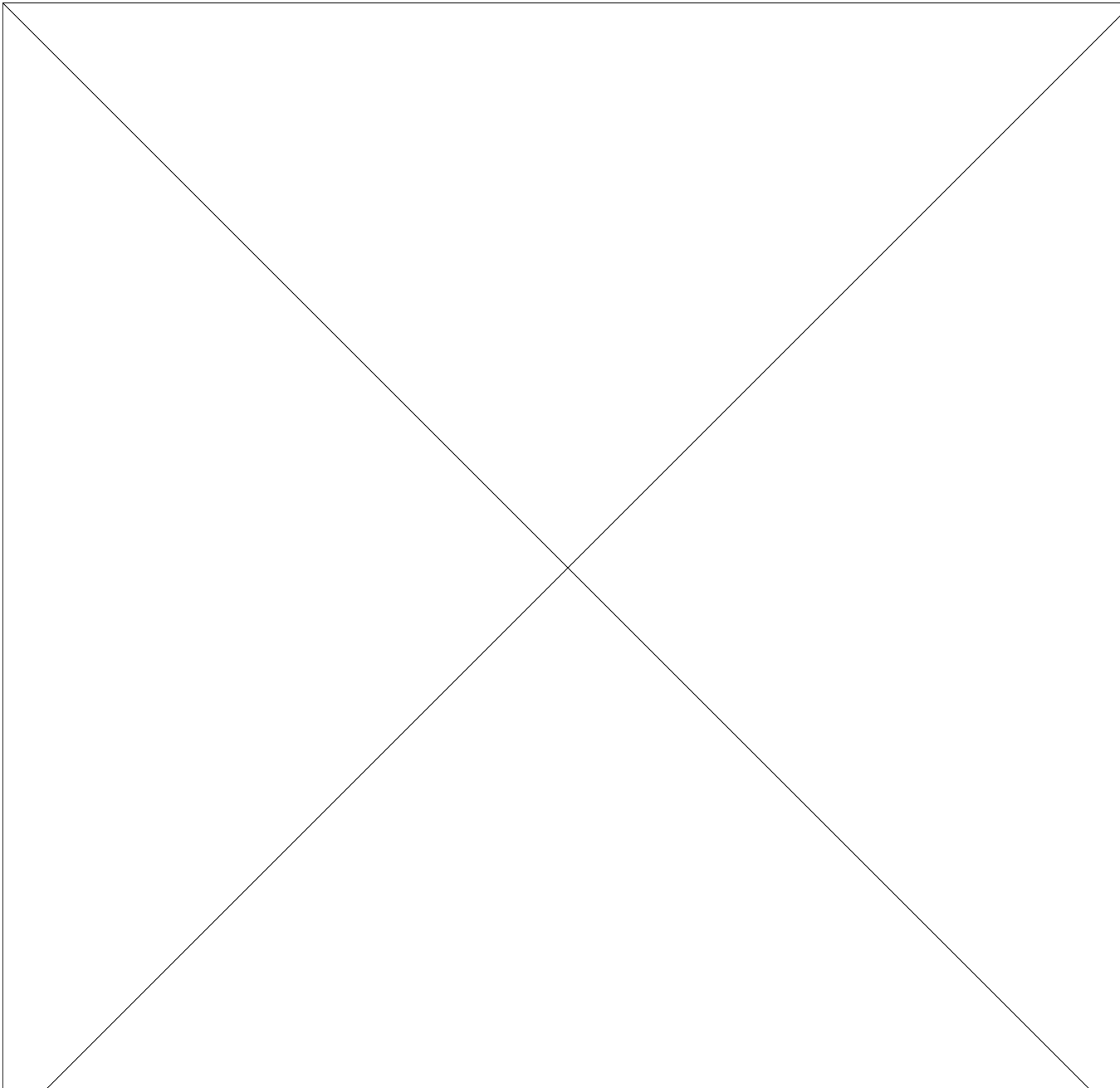
- **How does differentiation induces feeding?** (proof of concept)
cellular automaton (in MGS)
- **How do spatial organization and distribution evolve?**
agents based system (in MGS)
- **How robust and tunable is the model?**
ODE kinetics (matlab)

Simulation to answer 4 questions

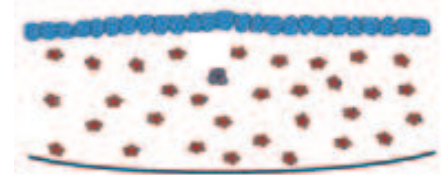
- How does differentiation induces feeding? (proof of concept) cellular automaton (in MGS)
- How do spatial organization and distribution evolve? agents based system (in MGS)
- How robust and tunable is the model? ODE kinetics
- **How sensitive is the system to noise?**
Gillespie based simulation (in MGS)



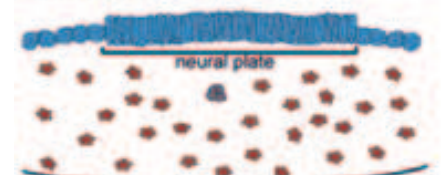
The sketch of a neurulation-like process



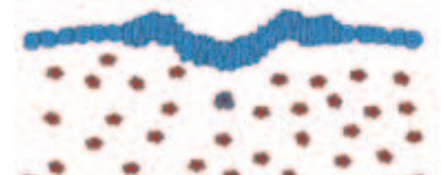
1. Initial epithelium



2. Columnarization



3. Rolling/folding



4. Closure



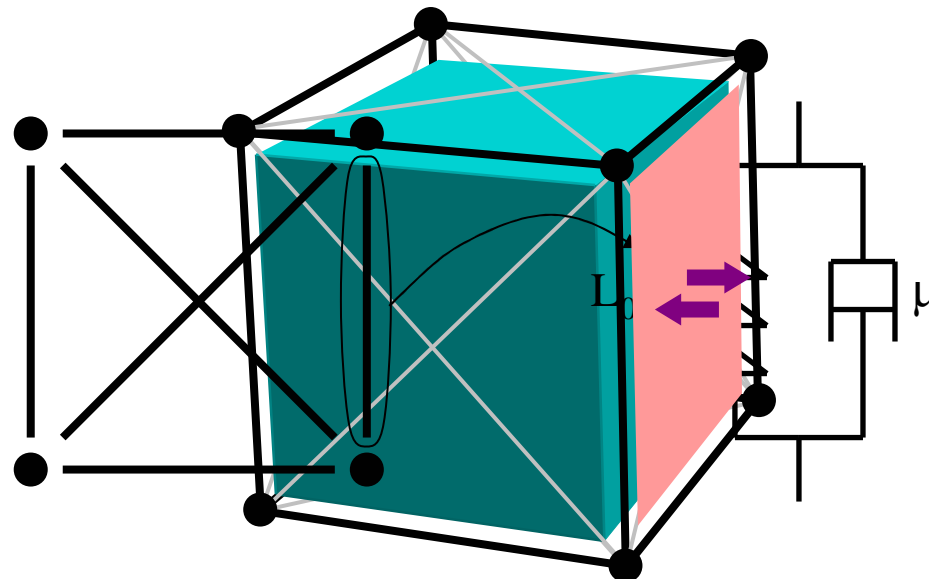
5. Neural tube complete



Mechanical cell model

Shape of cell: given by the cytoskeleton. Basal and apical face.

- 2D Model [Odell *et al.* 1981]: spring-mass system
- Extension to 3D [Nagpal 2001]
- 3D cell
 - Surface \rightarrow cell-cell communication
 - Volume \rightarrow contents of a cell (control)



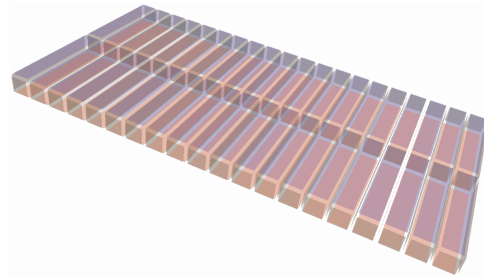
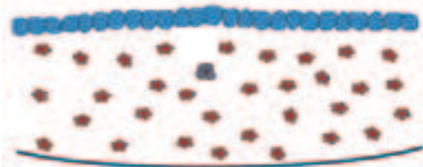
- Computation of mechanical forces
- Integration and translation of masses
- topological surgery

```
trans <0,1> integration [delta_t = 0.01] = {  
  tra patch surgery = {  
    e: f1:[dim=2, (e11,e12,e13,e14) in faces]  
        v11 < e11 > v12 < e12 > v13 < e13 > v14 < e14 > v11  
        f2:[dim=2, (e21,e22,e23,e24) in faces]  
        v21 < e21 > v22 < e22 > v23 < e23 > v24 < e24 > v21  
        [P(v11,v12,v3,v14,v21,v22,v23,v24)] => .in  
        `v1:[dim=0, faces=(),  
            cofaces=(`e1,`e4)@unmatched_cofaces(v11,v12),  
            val=average_0(v11,v21)]  
  } ;;  
  ...  
} ..
```

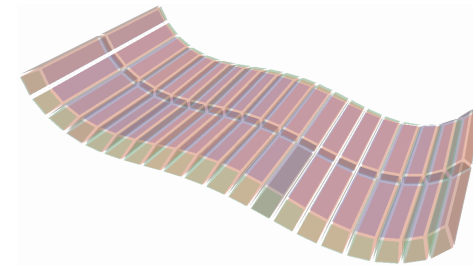
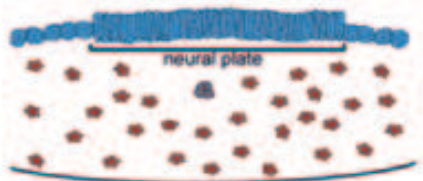
Results

Primary Neurulation

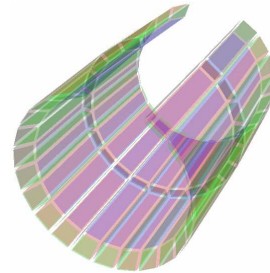
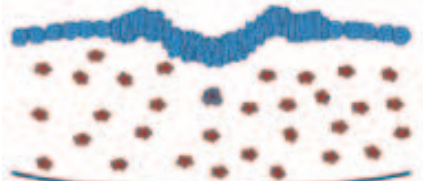
1. Initial epithelium



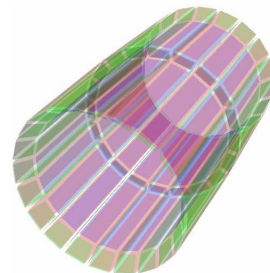
2. Columnarization



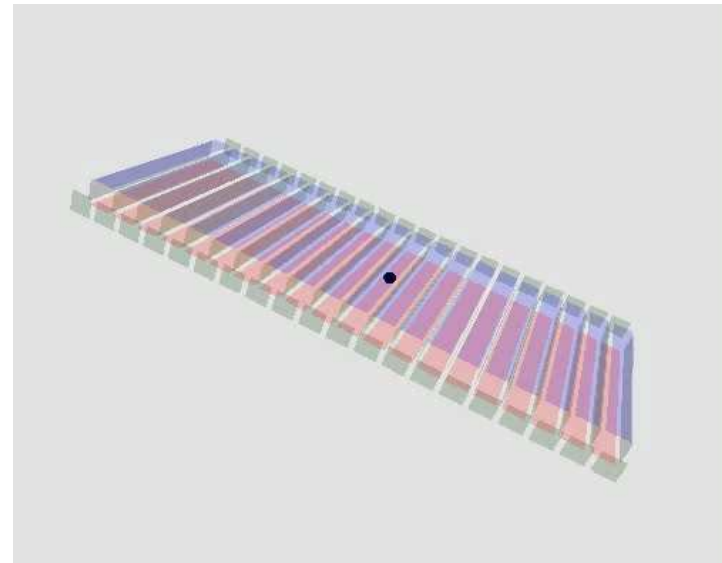
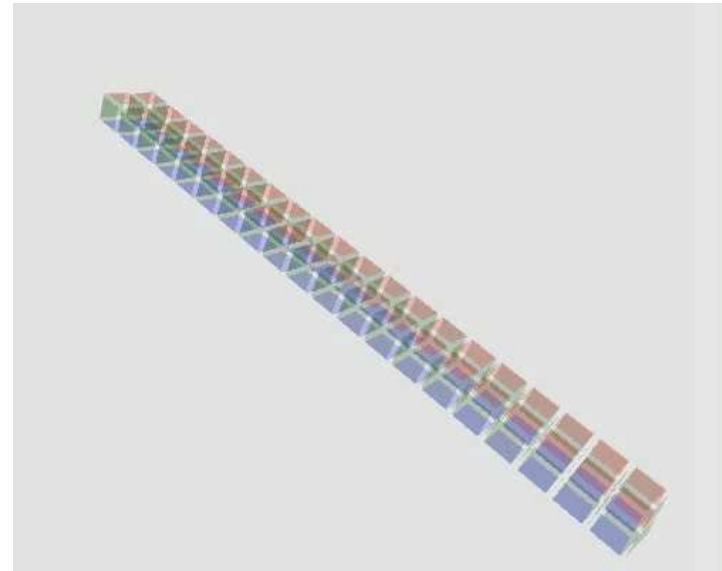
3. Rolling/folding



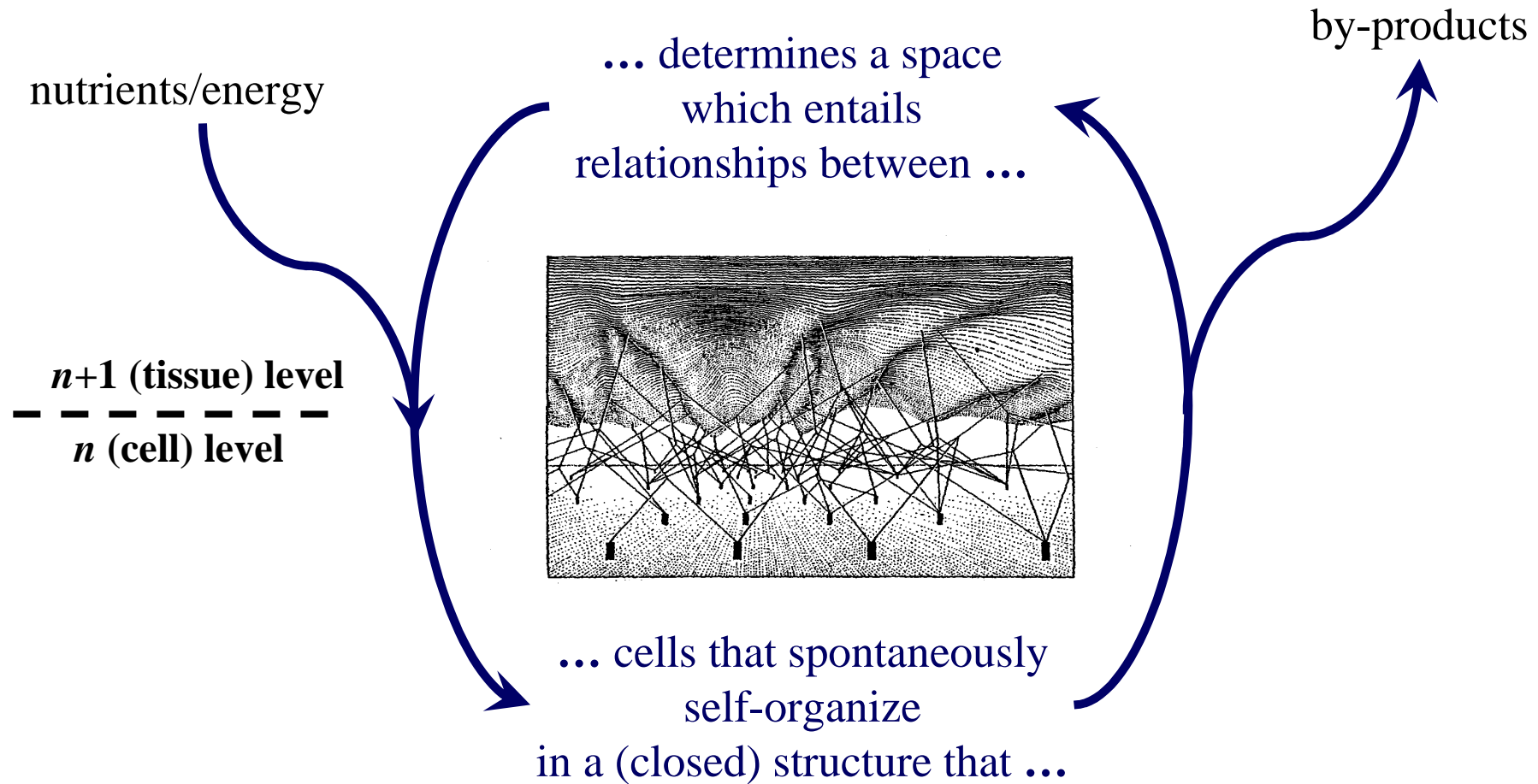
4. Closure



5. Neural tube complete

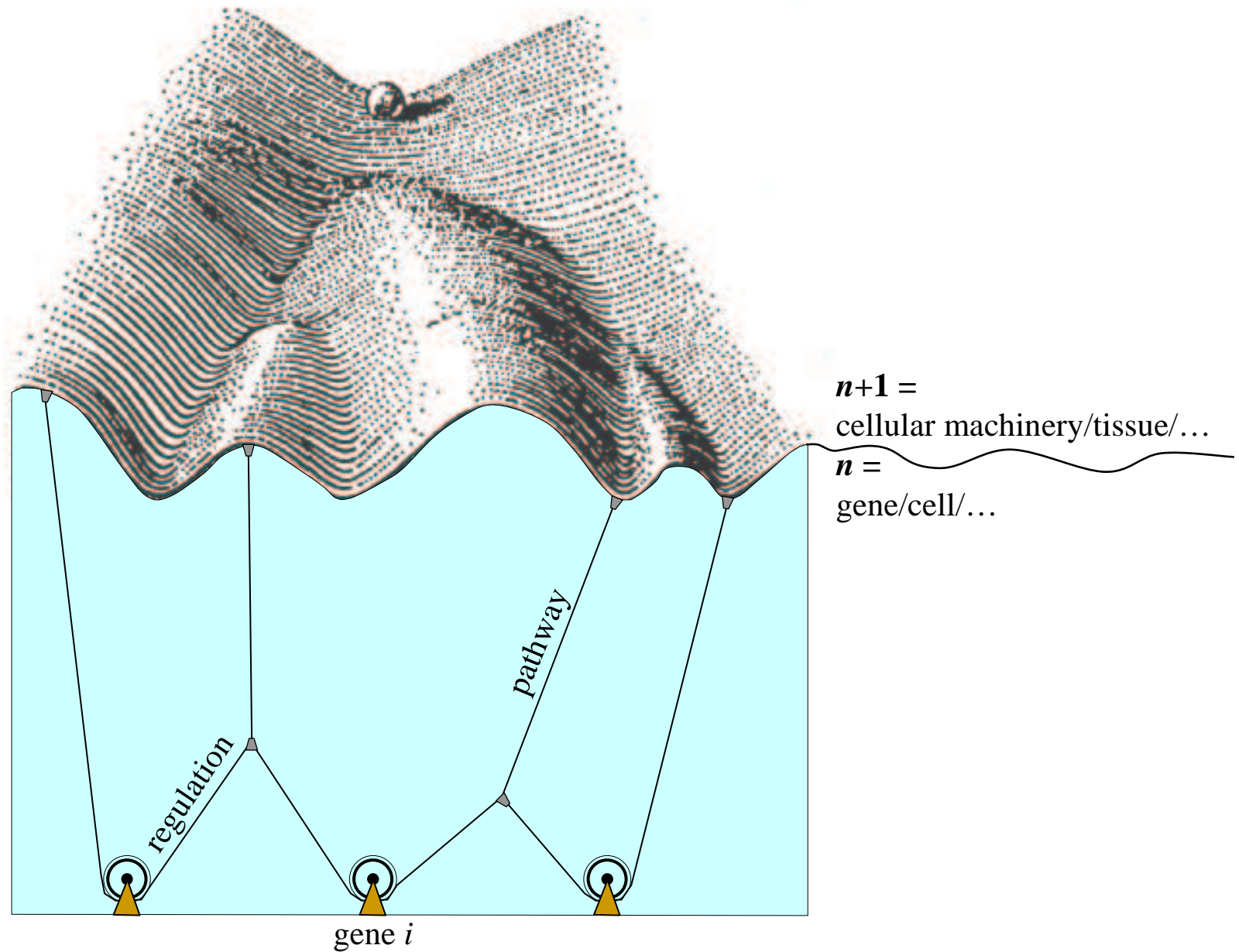


(SD)², Causality and Reductionism



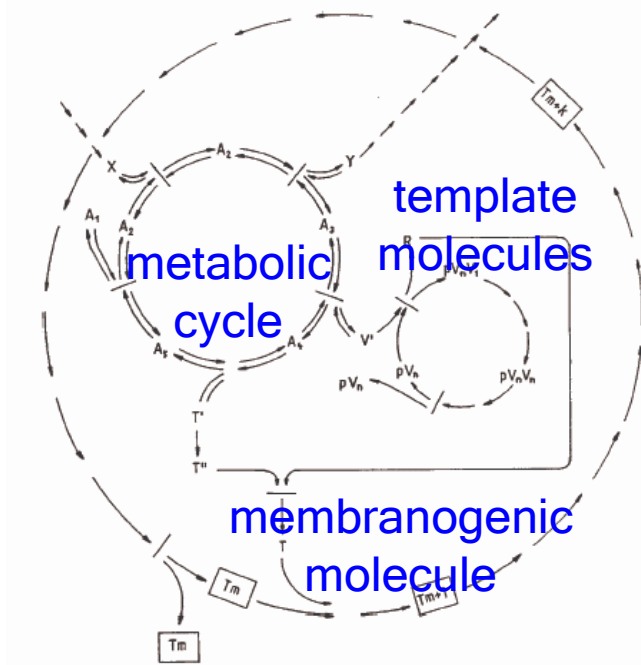
Real or fictional vicious circles?

Waddington



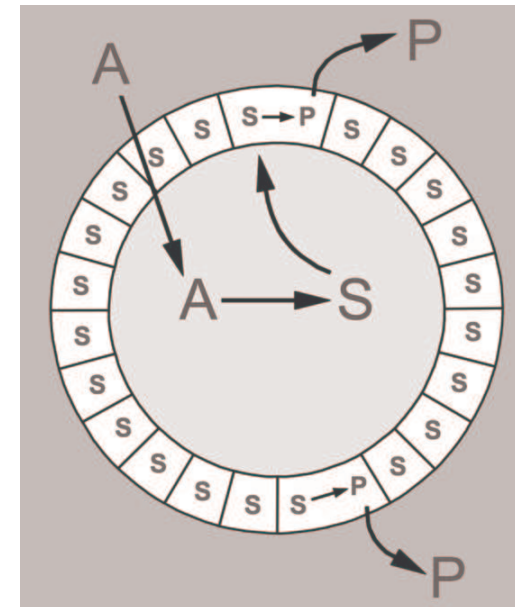
Such cycles are not new in biology

Tibor Ganti's CHEMOTON (1971)



... a “chemical automaton”...
(also called *fluid automata*)

Varela's AUTOPOIESIS (1974)

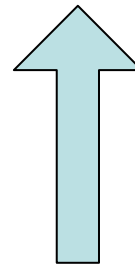
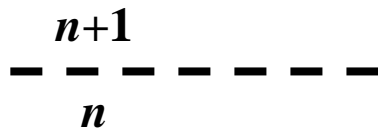


“an autopoietic unity is able to self-generate owing to a reaction network taking place within its own boundary” (the reaction network makes all components of the unit, including the boundary)

M. Eigen & P. Schuster: **hypercycle**,
W. Fontana & L. Buss: **organization**

...

... determines a space
which entails
relationships between ...

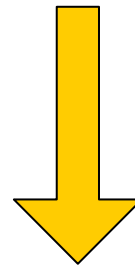
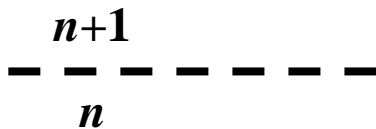


usual **causality**:

- cause always precedes its effect
- a cell is an autonomous entity that exists without a tissue
- a tissue is made of cells

... cells that spontaneously
self-organize
in a closed structure that ...

... determines a space
which entails
relationships between ...



downward causation:

- (the existence of) the tissue determines the behavior of the cells
- the tissue has a kind of autonomy wrt the cell:
 - robustness/ injury or disfunctioning
 - level-specific rules to express own regularities

... cells that spontaneously
self-organize
in a closed structure that ...

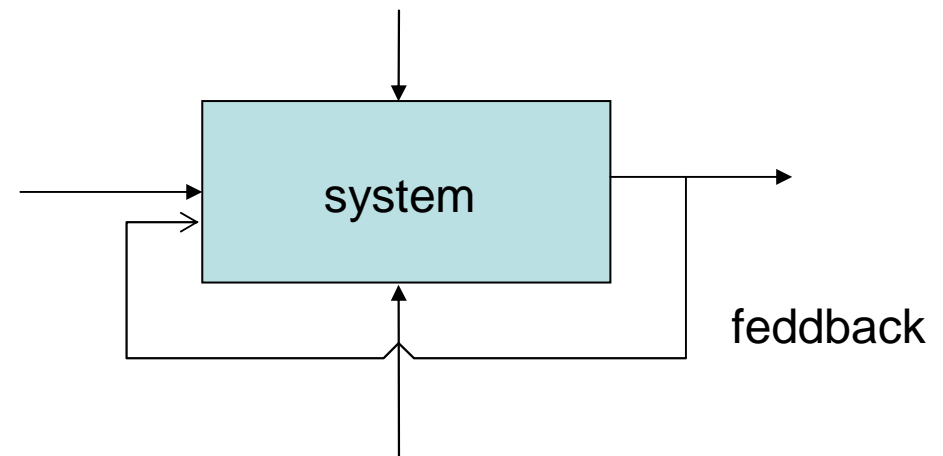
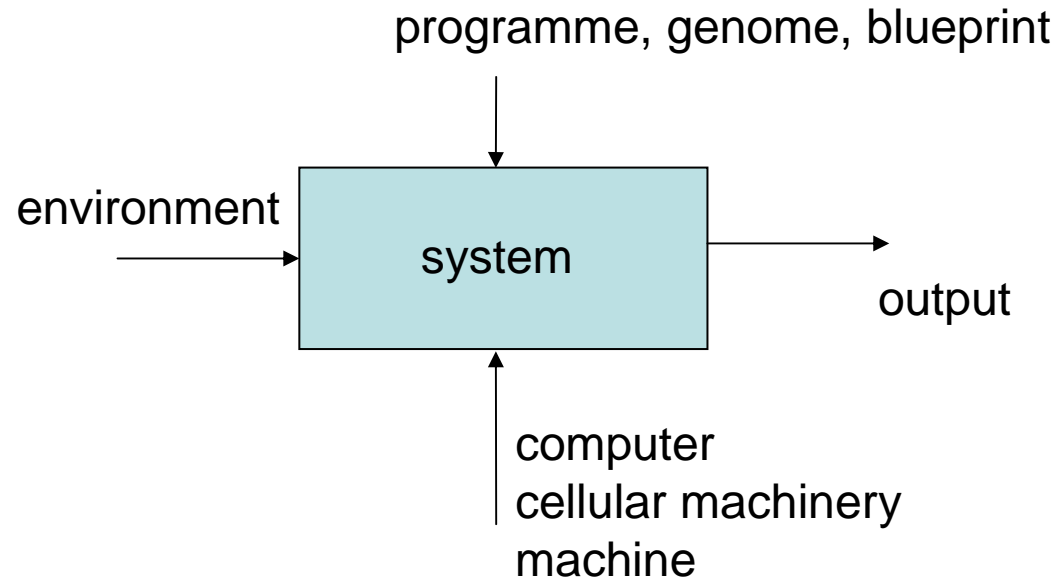
Soto et al.:

“During embryogenesis the generation of form (morphogenesis) is mediated by cellular processes such as the direction and number of cell divisions, changes in cell shape, cell movement, cell growth, cell death and changes in the composition of the cell membrane and extracellular matrix (Gilbert, 1997).

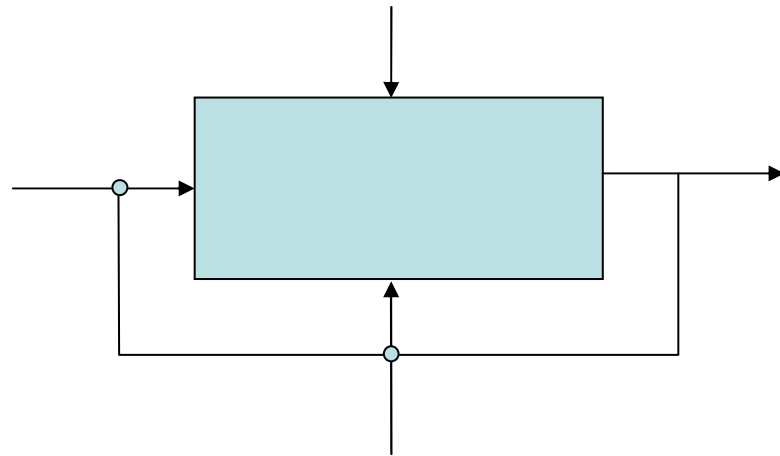
The reductionist view proposes that each of these cellular processes is generated by the differential expression of developmental genes.

We consider instead, that in addition to this upward causation, cellular and tissue events occurring before the expression of a particular set of genes takes place may act downwardly modifying the expression of these genes at a later time (diachronic emergence).”

- **organicism**, theory developed by embryologists following I. Kant for whom the parts of an organism “[. . .] bind themselves mutually into the unity of a whole in such a way that they are mutually cause and effect of one another.”
- complies with **physicalism** (physical facts fixe all the fact) (a tissue is a structured set of cells)
- **no vitalism**
- **no teleology**: building the tissue takes time and “by the time the tissue is formed, the ‘parts’ that we identify in them are no longer the parts that interacted in their formation.”
- **organicism** ≠ **reductionism** on the idea of what is an *explanation*: explanation cannot proceed solely from the properties of fully individuated parts even if properties of the whole are determined by properties of the parts
 - if explanation means prediction, then consider evolution or the trajectories of planets in a 3 body systems
 - each level of organization has its own regularities and principles which are not appropriately described by entities of the lower level:
 - « On ne ramènera jamais les manifestations de notre âme aux propriétés brutes des appareils nerveux pas plus qu’on ne comprendra de suaves mélodies par les seules propriétés du bois ou des cordes du violon nécessaires pour les exprimer » (Claude Bernard).
 - « Toi et moi, Tyler, nous sommes des communautés de cellules vivantes, d’accord ? Et si tu abimes un nombre suffisant de mes cellules, je mourrai, tu m’aura assassiné. Mais si nous nous serrons la main et que je perds quelques cellules de peau dans l’opération, ni toi ni moi ne nous en apercevrons. Cela reste invisible. Nous vivons à certain niveau d’abstraction : nous interagissons en tant que corps, pas en tant que colonie de cellules » (Robert C. Wilson, SPIN).
 - Despite that, we want to clarify/establish/explain as much as possible the relationships between element and whole, individual and population, cell and tissue, local and global.



Cyclic Box-ology



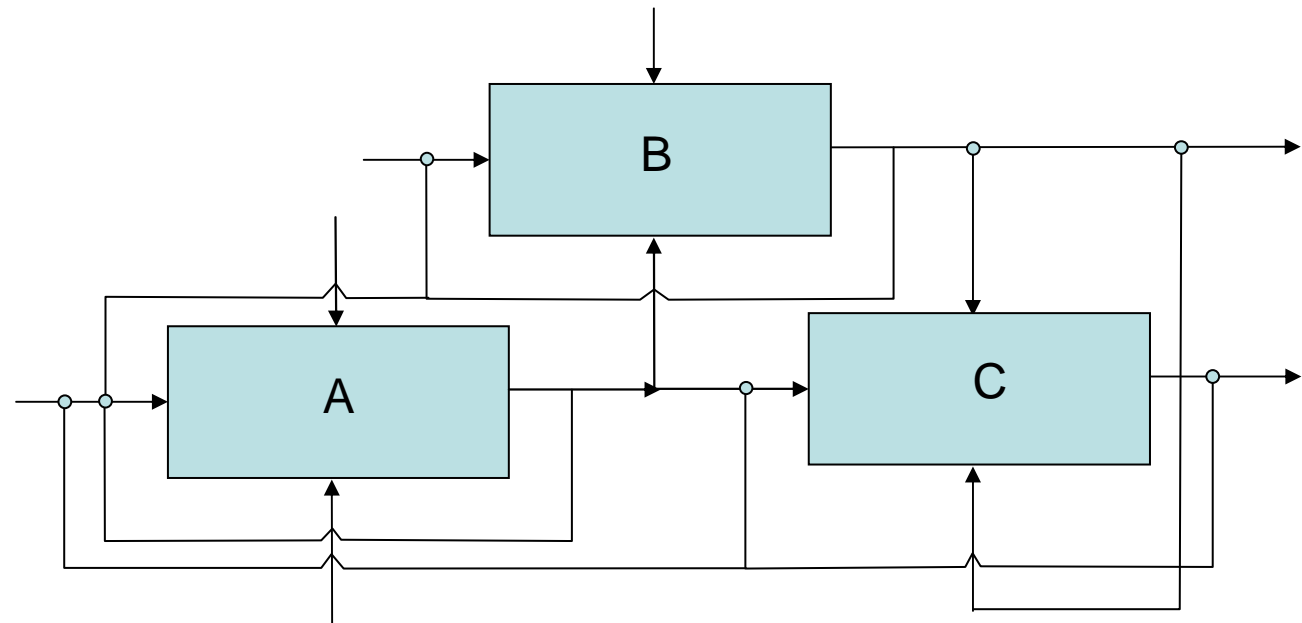
- **at the formal level:** the output of a system can change the environment (including its machine and its programme)
- **if the system is a DS**, and its output changes the environment. Because the environment cannot be characterized by a state, the entity « system+environment » is not a DS.

Feedback can be unfolded in structure:

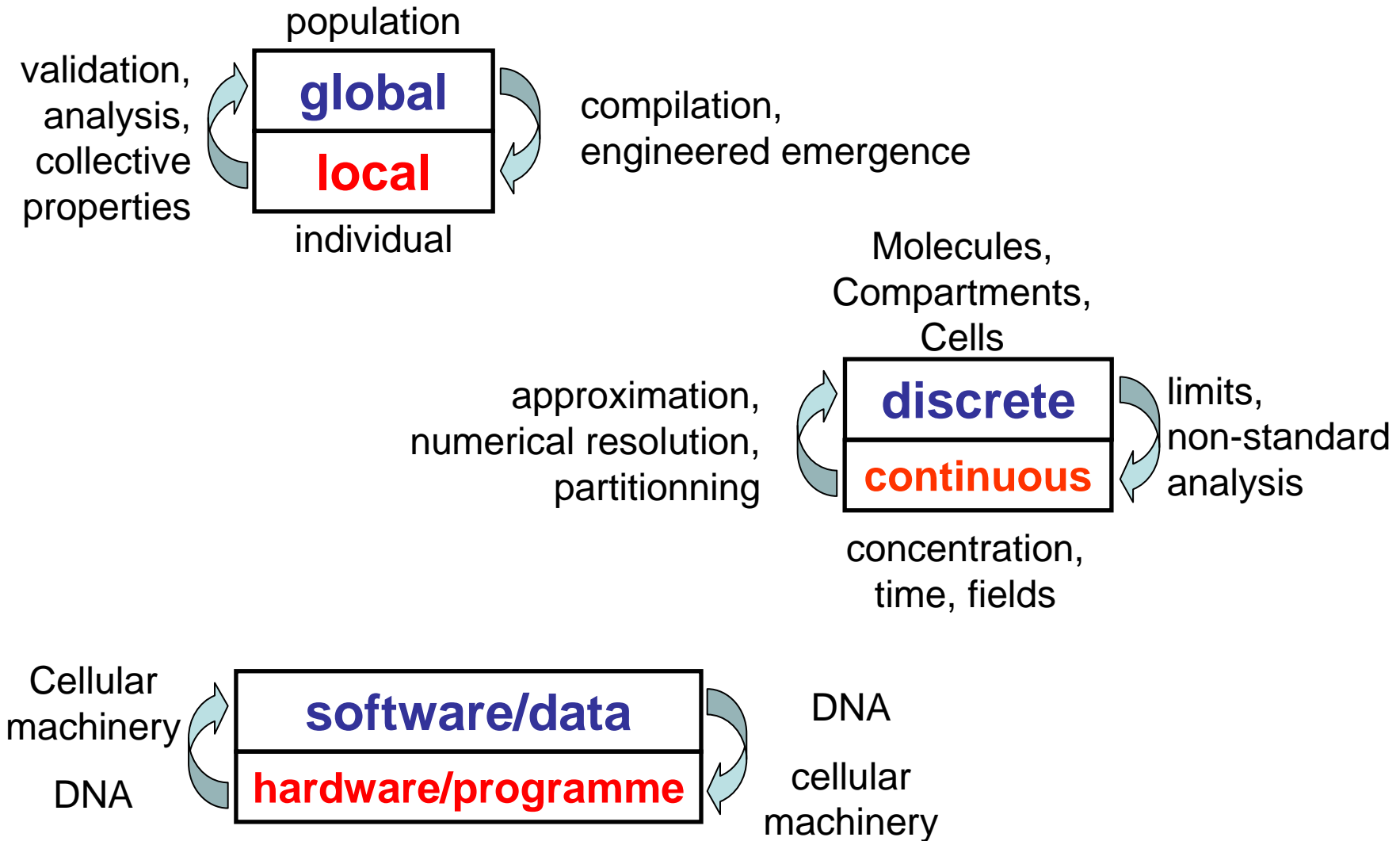
- A: organs
- B: organism
- C: embryo

or unfolded in time:

- A: cell at t
- B: tissue at $t+1$
- C: same cell at $t+2$



Three challenges and some tools



Thanks



J.-L. Giavitto & O. Michel

IBISC, CNRS FRE 2873

<http://mgs.ibisc.fr>

- **Olivier Michel**

- **PhD and other students**

A. Spicher, J. Cohen, P. Barbier de Reuille,
E. Delsinne, V. Larue, C. Bouin, F. Letierce, B. Calvez,
F. Thonerieux, D. Boussié *and the others...*

- **Collaborations**

- J.-P. Banâtre (IRISA, programming)
- H. Berry (LRI, stochastic simulation)
- F. Delaplace (IBISC, synthetic biology)
- P. Dittrich (Jena, chemical organization)
- C. Godin (CIRAD, biological modelling)
- E. Goubault (AS topologie, topological formalization)
- F. Gruau (LRI, langage and hardware)
- P. Liehnard (Poitiers, CAD, Gmap and quasi-manifold)
- G. Malcolm (Liverpool, rewriting)
- P.-E. Moreau (LORIA, compilation of pattern-matching)
- P. Prusinkiewicz (Calgary, declarative modelling)

- **Communities**

- *Berder school*
- *Spring school on Modeling and Simulation in the post-genomic era*
- *ISC-PIF*
- *Epigenomic program and Genopole-Evry*

