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(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

Environment characterized by its effects on the system

System described by a state (determined by observation)

<table>
<thead>
<tr>
<th>C : continuous, D: discrete</th>
<th>PDE</th>
<th>Coupled ODE</th>
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<tr>
<td>state</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<td>time</td>
<td>C</td>
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<tr>
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<td>C</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>…</td>
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</tbody>
</table>
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 parenthetised 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

S => I[A][S]A

I[A]S[S]A

A

S

I

S =⇒ I[A][S]A

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.

\[
e / (D(e) \land (e.a < \text{thr}) \lor (e.x >= \text{shorter} \times \text{gr}))
\rightarrow \{\text{type} = "C", \ a = e.a/\text{gr}, \ h = e.h/\text{gr}, \ x = e.x/\text{gr}, \ p = e.p\};
\]

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.

\[
e / (C(e) \land (e.x >= \text{lm}) \land (e.p == \text{L}))
\rightarrow \{\text{type} = "C", \ a = e.a, \ h = e.h, \ x = e.x/\text{shorter}, \ p = \text{L}\},
\{\text{type} = "C", \ a = e.a, \ h = e.h, \ x = e.x/\text{longer}, \ p = \text{R}\};
\]
Plant development as grammar rule application

© P. Prusinkiewicz & University of Calgary
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!
Rewriting systems and abstract transition systems

- **Rewriting system**
  - Used to formalize equationnal reasoning
  - A generative device
  - Replace a sub-part of an entity by an other
  - Set of rewriting rules $\alpha \rightarrow \beta$
    - $\alpha$: pattern specifying a sub-part
    - $\beta$: expression evaluating a new sub-part

- **Example: arithmetic expressions simplification**

```
0
x
```

```
x
```

```
x
```

```
+   +
x  y  y  x
```

```
+   +
x  x
```

Simplification of an expression

(0 + 1) + (0 + 0)

Rules used
(1) 0 + x => x
(2) x + y => 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*

\[
\begin{align*}
\text{AC} &= \text{stirring} \\
\text{a(bc) = a(cb) = b(ac) = b(ca) = c(ab) = c(ba) = (ab)c = (ac)b = (ba)c = (bc)a} \\
\text{(a(bc))} &= (ab)c \\
(a(bc)) &\neq (ab)c
\end{align*}
\]
Rewriting systems in simulation

Complex systems $\leftrightarrow$ Rewriting techniques

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<td>hierarchical and tree organizations</td>
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<tr>
<td>arbitrary complex organizations</td>
<td>?</td>
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<tr>
<td>Evolution function</td>
<td>Set of rules</td>
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<td>$interactions \rightarrow$ evolution</td>
<td>$\alpha : \text{pattern} \rightarrow \beta : \text{expression}$</td>
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<td>synchronous vs. asynchronous</td>
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Complex systems ↔ Rewriting techniques

Modelling

State (space)
- hierarchical and tree organizations
- arbitrary complex organizations

Evolution function
- \( \textit{interactions} \rightarrow \text{evolution} \)
- \( \textit{local} \) evolution laws

Specification

Data structure
- formal trees (or terms)
- \( \textit{topological collections} \)

Set of rules
- \( \alpha : \text{pattern} \rightarrow \beta : \text{expression} \)
- rewriting rules, \( \textit{transformations} \)

Simulation

Trajectories
Time management
- discrete, event-based
- synchronous vs. asynchronous

Application

Derivations
Rule application strategy
- maximal parallel, sequential
- deterministic, stochastic
Properties

• *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, …
Topological collection: representing the underlying space

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

\[
\lambda x.(\ldots x \ldots)
\]

\[
\lambda x.0
\]

\[
4.005
\]

\[
\text{« MGS »}
\]

\[
\text{« toto »}
\]

\[
\text{‘a’}
\]

\[
\text{foo}
\]

\[
5
\]

\[
2
\]
Higher dimensional objects for complex simulations

Electrostatic Gauss law [Tonti 74]

- Electric charge content $\rho$ : dimension 3
- Electric flux $\Phi$ : dimension 2
- Law available on a arbitrary complex domain

$$\phi = \iint w \cdot dS = \frac{Q^c}{\varepsilon_0} = \iiint_{(V)} \rho d\tau$$

*electric field in space:*
  - $V$: electric potential (dim 0)
  - $E$: voltage (dim 1)
  - $w$: electric flux (dim 2)
  - $Q^c$: electric charge (dim 3)

A Direct Discrete Formulation of Field Laws: The Cell Method
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

```csharp
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

Shoot apical meristem
Root apical meristem
Camphium
Organs positionning at the shoot apex
Phyllotaxis models

Three kinds of approaches

Geometrical

Optimal
(dynamical?)

Physiological

(Bravais & Bravais, 1837)

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

(Reinhardt et al., 2000)
A shoot apical meristem

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

Immunolabelling of PIN-FORMED1 protein

high concentration of auxine induces organ initiation
Flux... changes form... which changes flux...

Dynamic interaction

Flux Form
- **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)
  \[ \rightarrow \{x.auxin -= \delta\}, \{y.auxin += \delta\}\]
A Synthetic Multicellular Bacterium

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
Implementation using BioBricks

Germline cell

Differentiation control

cre

lox71 gfp T ftsK T lox66 dapA

DAP starvation → RECOMBINATION → Differentiation

Somatic cell

cre

gfp T ftsK

No replication origin

loxCSc

dapA

loxCSc

irreversible recombination

ftsK necessary for cellular division

cre

DAP feeding
Simulation to answer 4 questions

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

![Diagram showing diffusion of DAP and 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 → cell-cell communication
  - Volume → contents of a cell (control)
MGS implementation

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

```ocaml
trans <0,1> integration [delta_t = 0.01] = {

  patch surgery = {
    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
    '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

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

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

Real or fictional vicious circles?
$n+1 = \text{cellular machinery/tissue/…}$

$n = \text{gene/cell/…}$
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 disfunctionning
    - level-specific rules to express own regularities

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

- **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.
Box-ology

Environment → System → Output

Programme, genome, blueprint

Computer, cellular machinery, machine

Feedback
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 $t+2$

• 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 characterized by a state, the entity « system+environement » is not a DS.
Three challenges and some tools

- Global: population, validation, analysis, collective properties
- Local: individual, compilation, engineered emergence

- Discrete: Molecules, Compartments, Cells, limits, non-standard analysis
- Continuous: DNA, concentration, time, fields

- Software/Data: cellular machinery
- Hardware/Programme: DNA, DNA cellular machinery

- DNA, cellular machinery

- Global vs. Local

- Software/Data vs. Hardware/Programme

- Discrete vs. Continuous

- DNA, cellular machinery
Thanks

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