Walking the tightrope: The dilemmas of hierarchical instabilities in Turing's morphogenesis

Presented in the Embryo Physics Course
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By

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Abstract

- Alan Turing not only introduced the idea that instabilities in diffusion-reaction processes could lead to spatial patterns of morphogenesis, but also gave us a model for cell differentiation by symmetry breaking. I show that such a model leads to metasymmetries when multiple steps of differentiation are considered. How the embryo chooses from the vast combinatorics in breaking this metasymmetry is an unsolved problem.

2012 THE ALAN TURING YEAR

A Centenary Celebration of the Life and Work of Alan Turing

http://www.mathcomp.leeds.ac.uk/turing2012/give-page.php?302

Seminal papers:

Turing, A.M. (1937). On computable numbers, with an application to the Entscheidungsproblem. *Proc. London Math. Soc.* ***s2-42, 230-265.***

Turing, A.M. (1952). The chemical basis of morphogenesis. *Phil. Trans. Roy. Soc. London* ***B237, 37-72.***

This talk based on:

- Gordon, R. 2011. The dilemmas of hierarchical instabilities in Turing's morphogenesis [invited]. In *The Once and Future Turing - Computing the World [in press].* S. B. Cooper and A. Hodges (eds.): Cambridge University Press.

Bridging the Gap

- Alan Turing made a major contribution in putting forth a model for morphogenesis that attempts to bridge the gap between the molecules we are made of and how we look
- Volumes: 70 liters for an adult human and 0.15 nm^3 for an amino acid
- Ratio to $5x10^{26}$ to 1

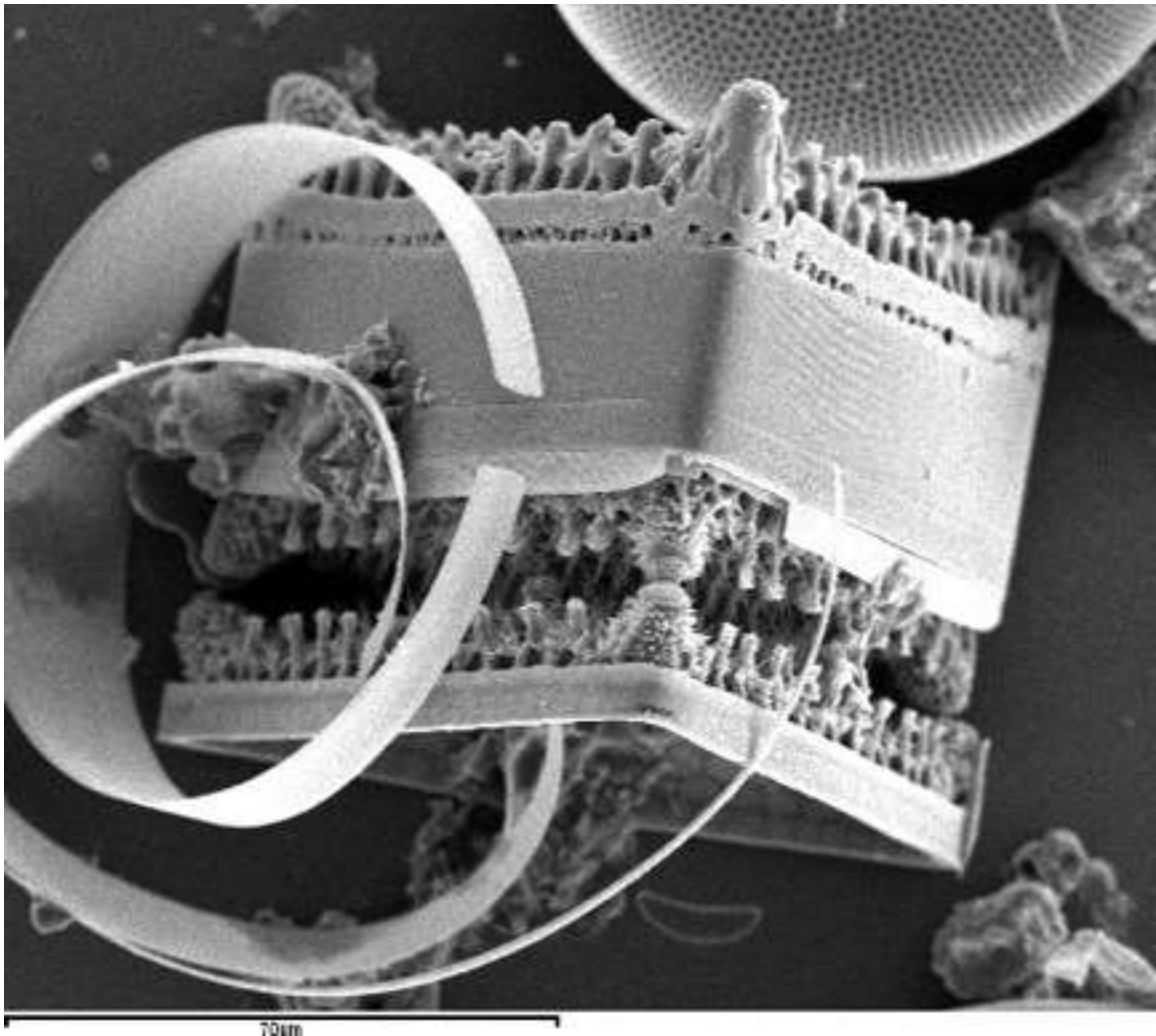
Modularity

- The search has been on to discover just what the modules of life are
- Example:
- Newman, S. A. and Bhat, R. 2009. Dynamical patterning modules: a "pattern language" for development and evolution of multicellular form. *International Journal of Developmental Biology,* **53**, (5-6)**,** 693-705.

Modularity in Bridge Building: Spans & Braces

Contradicting the “Cell Theory” that Cells are Modules in Development:

- 1. Single cell organisms can have quite complex morphologies, such as diatoms
- *Triceratium favus* with permission of Mary Ann Tiffany

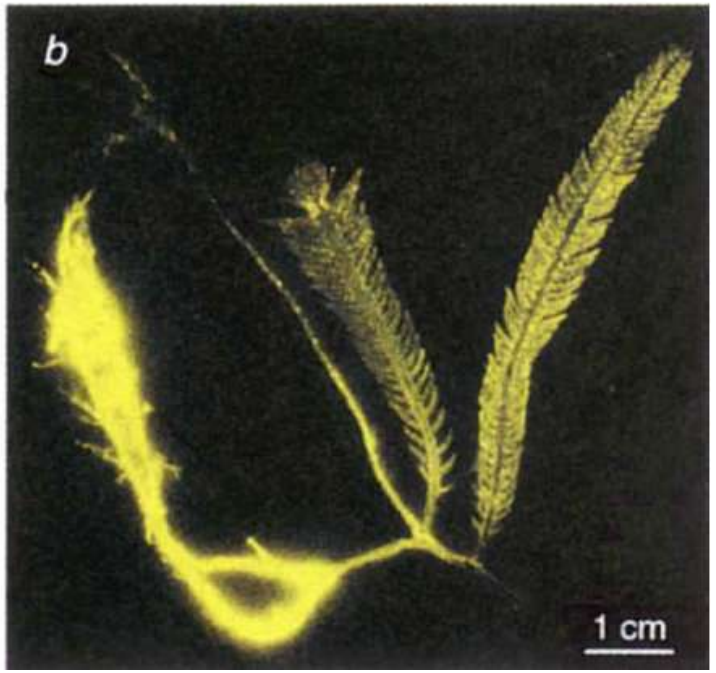


Contradicting the “Cell Theory” that Cells are Modules in Development:

- 2. Some green algae have many nuclei that move in cytoplasmic streaming, unhindered by cell boundaries, yet “…exhibit morphological differentiation into structures that resemble the roots, stems, and leaves of land plants and even have similar functions”.
- Cocquyt, E., Verbruggen, H., Leliaert, F. and De Clerck, O. 2010. Evolution and cytological diversification of the green seaweeds (Ulvophyceae). *Mol Biol Evol,* **27**, (9)**,** 2052-61.

Example: Marine coenocyte (one cell) *Caulerpa taxifolia*

Chisholm, J. R. M., Dauga, C., Ageron, E., Grimont, P. A. D. and Jaubert, J. M. 1996. 'Roots' in mixotrophic algae. *Nature,* **381**, (6581)**,** 382 + (6583) 565 erratum.



Autoradiographs showing transport from rhizoids to stolons and fronds, like roots to leaves

Contradicting the “Cell Theory” that Cells are Modules in Development:

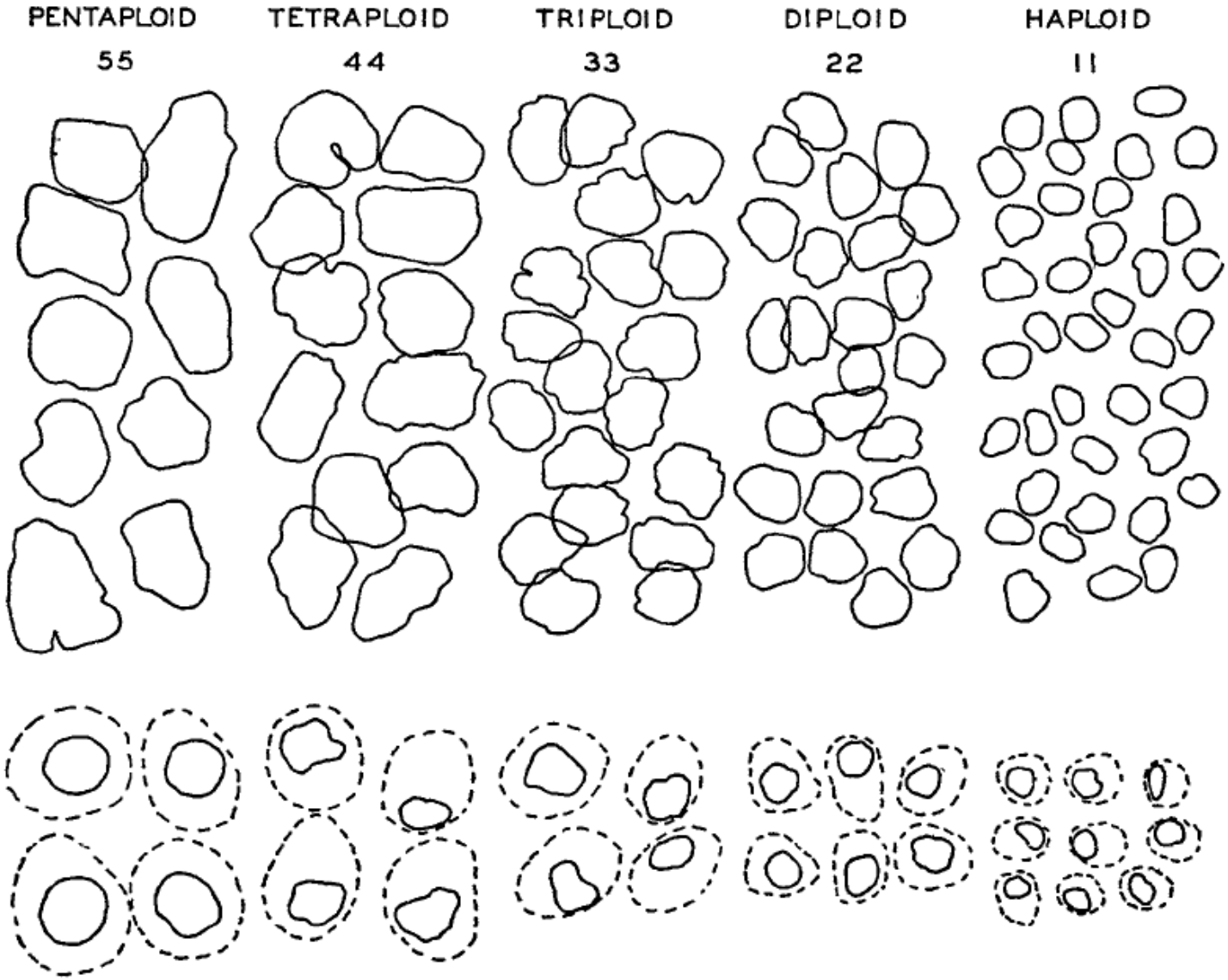
- 3. We can make “polyploid” salamanders with up to 7 copies of their genome per cell. The result is a normal looking adult with fewer larger cells that generally reaches the same size.
- So the adult’s morphology is not dependent on how many cells it is made of (though its intelligence may be).

Example: newt
Notophthalmus (*Triturus*) *viridescens*

http://species.wikimedia.org/wiki/File:Notophthalmus_viridescensPCCA20040816-3983A.jpg

Example: Relative Cell & Nucleus Sizes in this Newt (Animal Size Unchanged)

Fankhauser, G. (1945). The effect of changes in chromosome number on amphibian development. *Quart. Rev. Biol.* ***20(1), 20-78.***



So if not cells,
What are the modules of development?

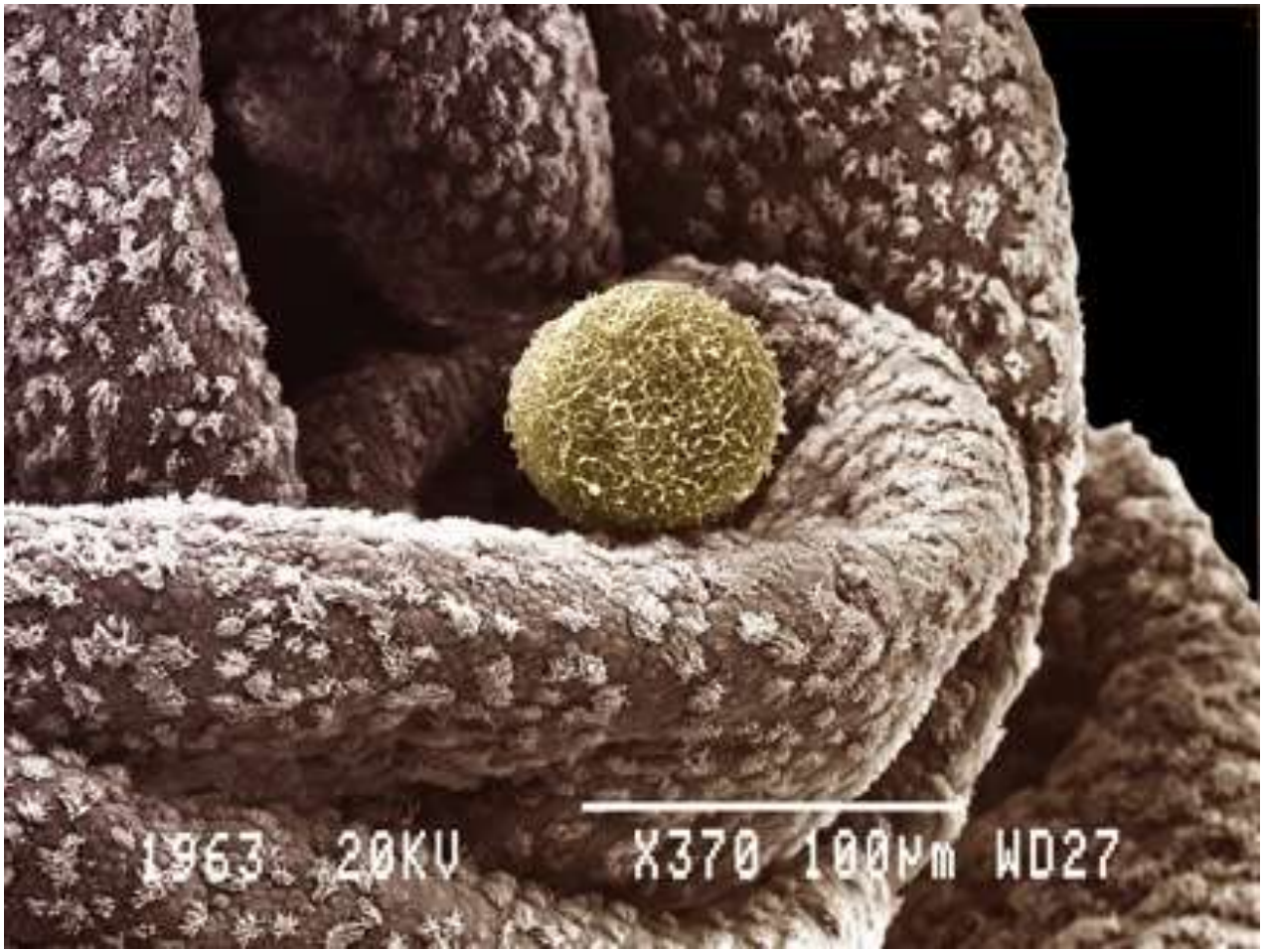
My answer: Tissues

- Organisms are partitioned into cells of different types
- Each group is a module called a”tissue”
- I redefine a “tissue” to be all the cells of a given type in an organism
- Note that mathematically a tissue is an equivalence class

Problem: there are no accepted criteria for placing cells into these equivalence classes

- **Solution**: we need a theory of how cell types form
- The theory will define the equivalence classes
- If the theory is consistent with all observations and its predictions, then the definition of the equivalence classes may be correct

Development starts from one cell: the fertilized egg (zygote)



Nikas, Y. 2011. *Human egg in the fallopian tube [#470]*
http://www.eikonika.net/v2/photo_info.php?photo_id=470

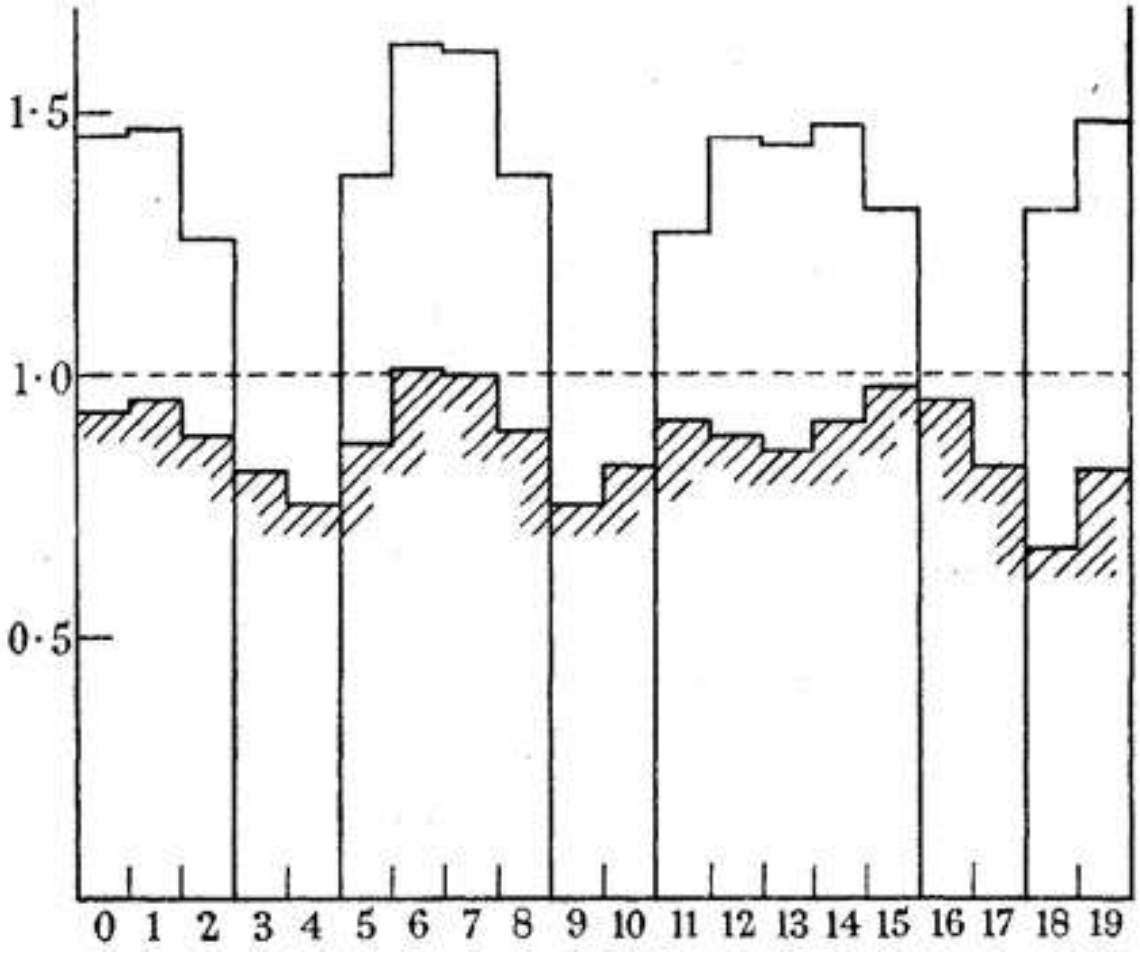
Cells Change Types (or Don't) in Four Ways

- 1. Symmetric cell division.
- Result: two daughter cells of the same type
- 2. Asymmetric cell division.
- Result: two daughter cells of different types
- 3. Stem cell asymmetric division.
- Result: One daughter cell like the mother cell, the other different.
- 4. No cell division, but a hitherto mysterious process call "induction" changes the cell to a new type

Cell Differentiation

- This process (or processes) by which cells change type is called “differentiation”.
- Differentiation is one of the three major outstanding biological problems of our day

Back to Turing's Model for How Cells Change Type (Reaction-Diffusion Equation)



20 cells arranged in a ring

3. Final wave of morphogen concentration

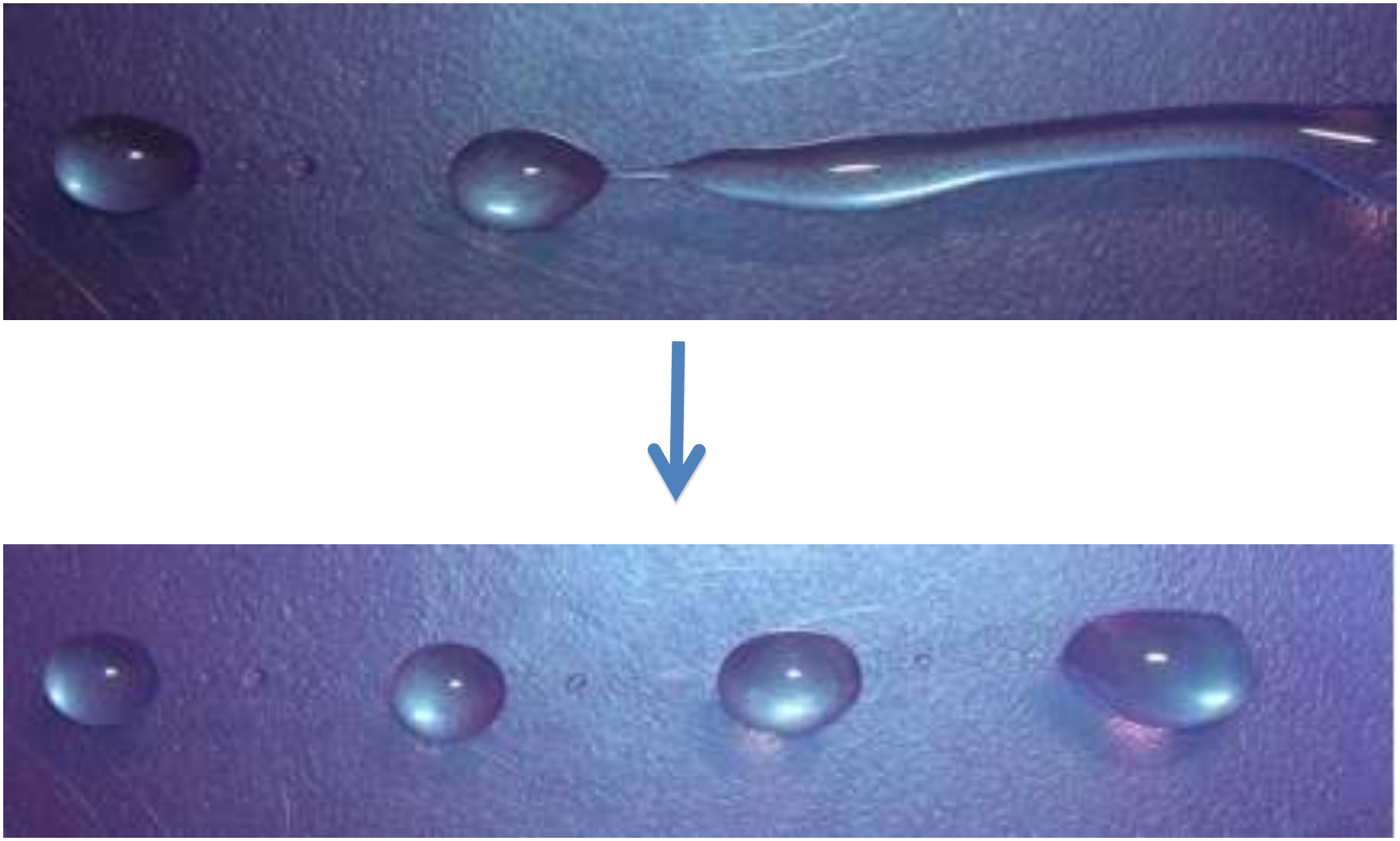
1. Unstable "Equilibrium"

2. Initial random concentration of a morphogen

This is a Symmetry Breaking Model

- Draw a thin string of honey across a dish, and it will break up into drops
- Instability phenomena in “morphogenesis” have been known since 1892:
- Rayleigh, L. 1892. On the instability of a cylinder of viscous liquid under capillary force. *Phil. Mag.,* **34,** 145-54.

Honey Experiment

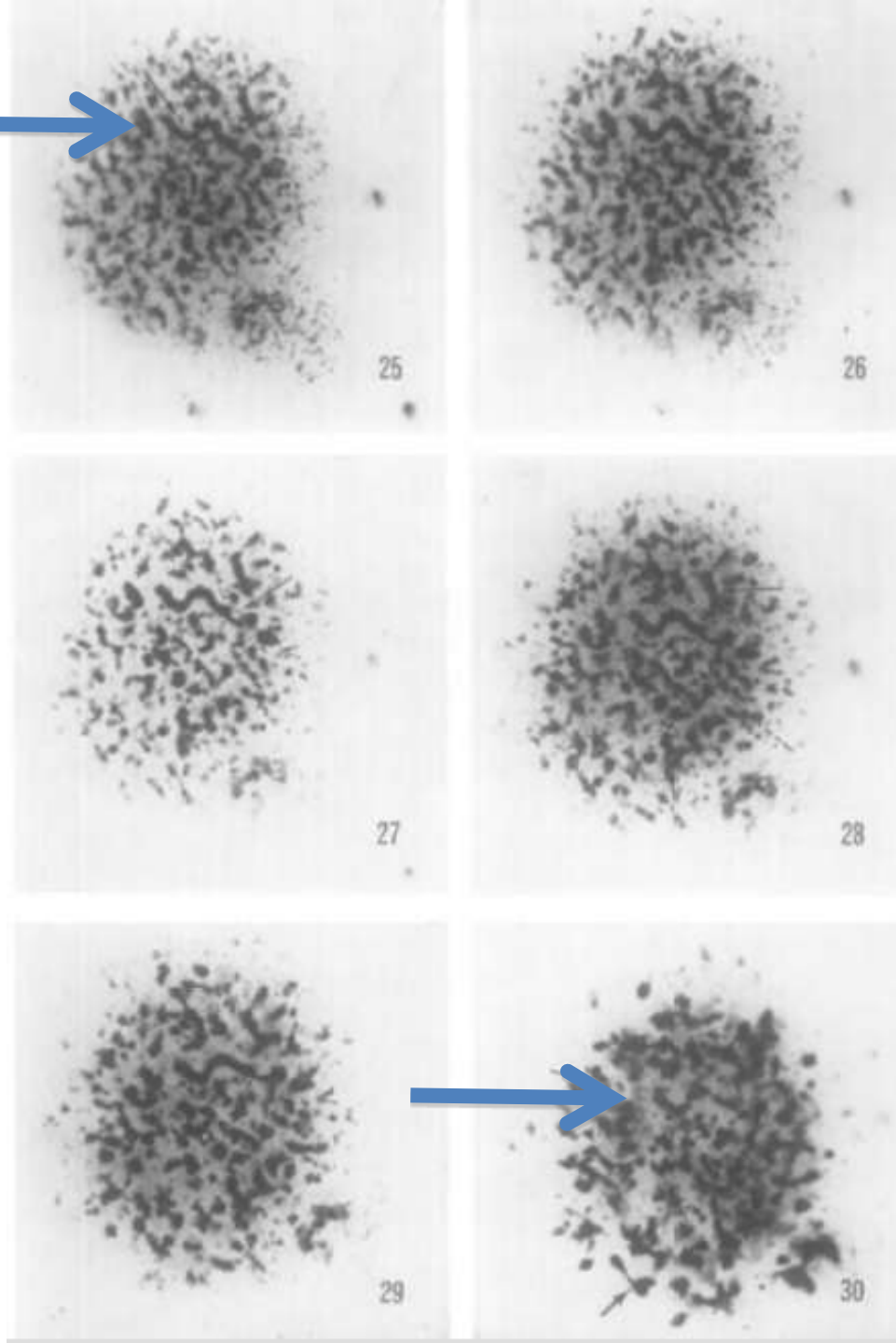


I applied this to self-sorting of embryonic cells

- Gordon, R., N.S. Goel, M.S. Steinberg & L.L. Wiseman (1975). A rheological mechanism sufficient to explain the kinetics of cell sorting. In: *Mathematical Models for Cell Rearrangement. Eds.: G.D. Mostow. New Haven, Yale University Press: 196-230.*
- Estimated tissue viscosities of 0.4×10^6 to 0.7×10^8 poise, compared to water at 10^{-2} poise

"…contraction of clusters will sometimes result in breaking the cellular bridge connecting fused clusters, with consequent separation of the clusters…"

Trinkaus, J.P. & J.P. Lentz (1964). Direct observation of type-specific segregation in mixed cell aggregates. *Developmental Biology* ***9(1), 115-136.***



Can Turing's model handle differentiation?

- Turing showed how just two cells, side by side, with the same morphogens inside, at nearly identical concentrations, can end up having different concentrations of each morphogen:
- "This breakdown of symmetry or homogeneity may be illustrated by the case of a pair of cells originally having the same, or very nearly the same, contents" (Turing, 1952).

Did Turing find the essence of the problem of cell differentiation?

- Start with one cell A, and let us suppose it divides to produce two daughter cells, B and C, that may each be different from A:
-
- A => BC
-
- In the next step, B divides into cells D and E, and C divides into cells F and G:
-
- BC => DEFG

Second Round of Differentiation Creates Problems

- But we have a problem here. Unless cells B and C can somehow influence one another, we could (by symmetry), just as well get:
-
- BC => EDFG
- BC => DEGF
- BC => EDGF

Could be Even Worse

- Furthermore (again by symmetry) cell A could just as well have produced:
-
- A => CB
-
- because BC can differ from CB if there is a left/right polarity to each cell. We thus see that there are even more possibilities:
-
- CB => FGDE
- CB => FGED
- CB => GFDE
- CB => GFED

So 2 steps of differentiation have 8 possible outcomes

- DEFG
- EDFG
- DEGF
- EDGF
- FGDE
- FGED
- GFDE
- GFED

Combinatoric Metasymmetry

- The problem gets exponentially worse with each step of cell division and its symmetry breaking.
- This shows that there is a symmetry to symmetry breaking, and if we are to have a specific organism result, we need to figure out how to break this “higher order” combinatoric “metasymmetry”

Number of Cell Types

- In mouse development estimated as high as 7000 with 8 hierarchical levels
- As $2^{12} < 7000 < 2^{13}$, the number of bifurcations in the cell lineage tree producing a mouse is around 12 to 13 on average, suggesting 4 or 5 more levels are to be found

- Bard, J. B. L., Baldock, R. A. and Davidson, D. R. 1998a. Elucidating the genetic networks of development: a bioinformatics approach. *Genome Res.,* **8**, (9)**,** 859-63.
- Bard, J. B. L., Kaufman, M. H., Dubreuil, C., Brune, R. M., Burger, A., Baldock, R. A. and Davidson, D. R. 1998b. An internet-accessible database of mouse developmental anatomy based on a systematic nomenclature. *Mech. Dev.,* **74**, (1-2)**,** 111-20.

The fundamental question in embryogenesis: Hans Driesch (1867-1941)

- **How is it that cells in an embryo end up**:
- As the *right kinds*
- In the *right place*
- At the *right time*
- To which we now add:
- In the *right numbers*?

http://home.tiscalinet.ch/biografien/biografien/driesch.htm

*Sea Urchin's fertilized egg dividing and growing into a blastocyst, time lapse: http://amazingbeauty.org/Nature/ABbiology02-baby.html.
Also see: http://worms.zoology.wisc.edu/urchins/SUmainmenu.html.

Embryogenesis Combinatorics

- If half of the 7000 mouse cell types are present in the adult mouse, and we arranged them along a line, there would be 3500! (factorial) different arrangements *a priori*, or well over 10^{10000}.
- In three dimensions the possibilities are even greater.
- This is even without considering that there are many cells of each kind.

The Great Module Hunt

- The answer may lie in finding the proper modules for embryonic development, above the single cell level.

Turing's Contribution

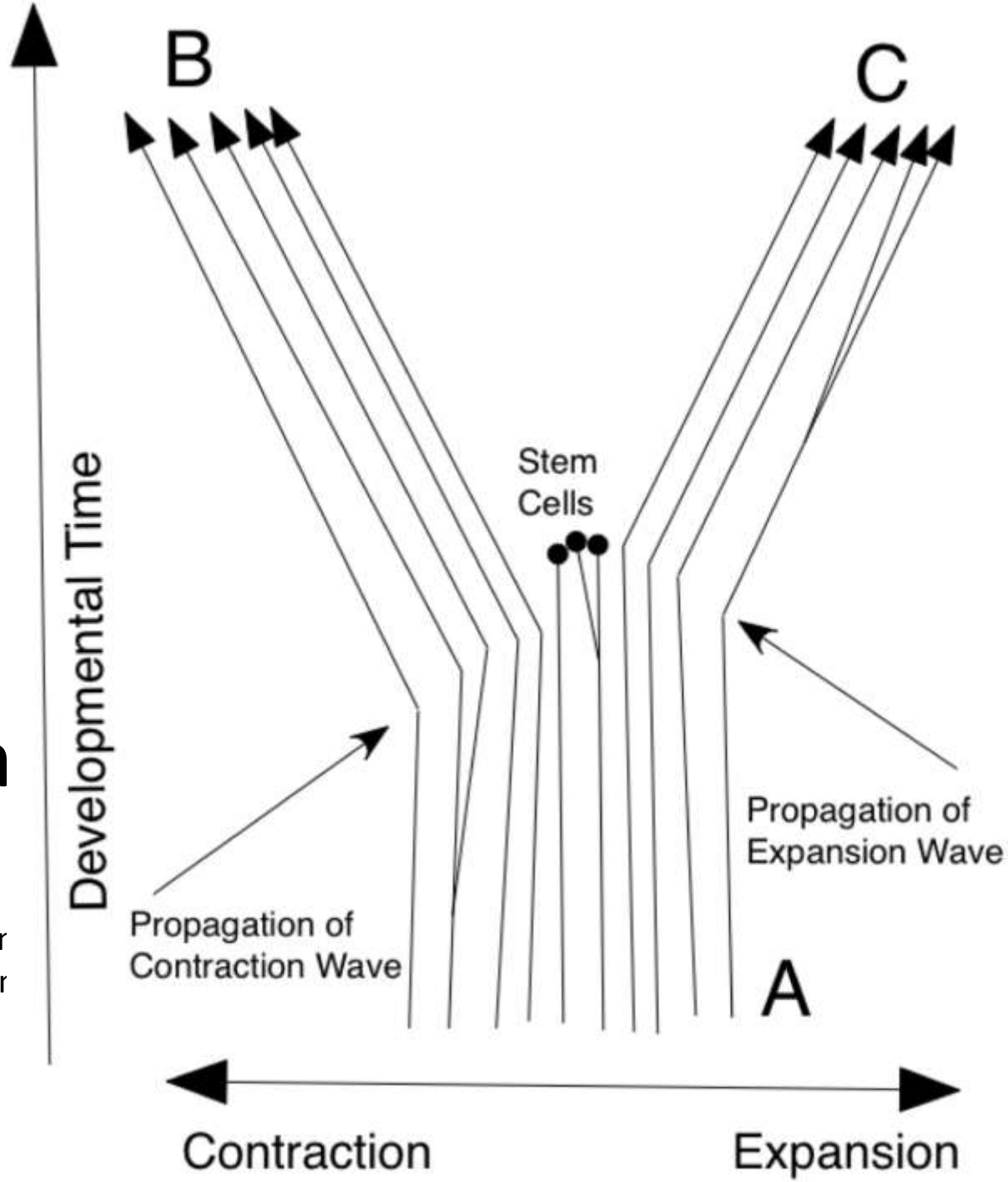
- Turing, in "The chemical basis of morphogenesis", laid the groundwork for one step of how differentiation might come about: symmetry breaking
- But there are metasymmetries to be broken at every level
- …with enough consistency to produce a viable organism
- We don't know yet how this is done.

My own partial solution

- The cell lineage tree can be bundled into a more coarse differentiation tree
- Each branch of the differentiation tree represents a tissue consisting of cells of the same type
- These tissues are the fundamental modules
- Cells are organized into these bundles by differentiation waves

- Gordon, R. (1999). The Hierarchical Genome and Differentiation Waves: Novel Unification of Development, Genetics and Evolution. Singapore & London, World Scientific & Imperial College Press http://www.worldscibooks.com/lifesci/2755.html

A bundle of cells of type A is split into two bundles of cells B and C by a pair of differentiation waves



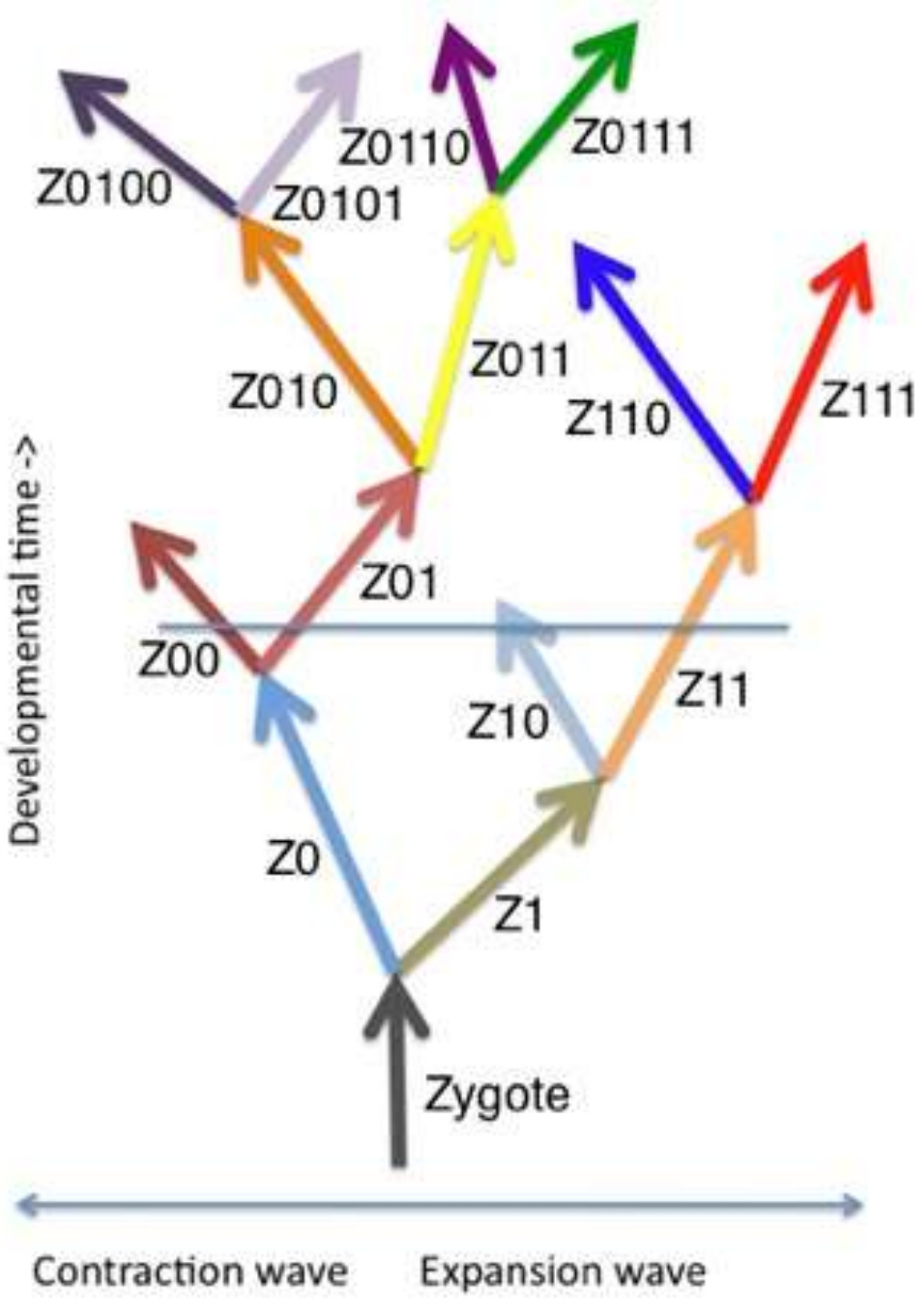
Natalie K. Gordon & Richard Gordor (2012). Embryogenesis Explained [ir preparation]. Singapore: World Scientific Publishing Company.

The Differentiation Tree

Each branch represents a distinct cell type

Note binary differentiation code

Natalie K. Gordon & Richard Gordon (2012). Embryogenesis Explained [in preparation]. Singapore: World Scientific Publishing Company.



Six major events in the evolution of bacteria to people:

1. asymmetric cell division, resulting in differentiated cells, i.e., two cells of different kinds,
2. symbiotic union of certain bacteria to produce eukaryotic cells,
3. invention of continuing differentiation,
4. breaking of metasymmetries to produce fairly unique arrangements of the resulting many cell types,
5. invention of an epigenetic differentiation code,
6. differentiation waves, that allowed the single-cell tissues resulting from asymmetric cell divisions to expand to multicellular tissues.

The Embryo Physics Challenge

- Is it the physics of differentiation waves that somehow start and stop in particular subdomains of the embryo that breaks the metasymmetry?
- If so, what is it that makes this process robust?