Waddington Redux: Simple Abstract Models and Integrative Biological Explanations

Embryo Physics Course
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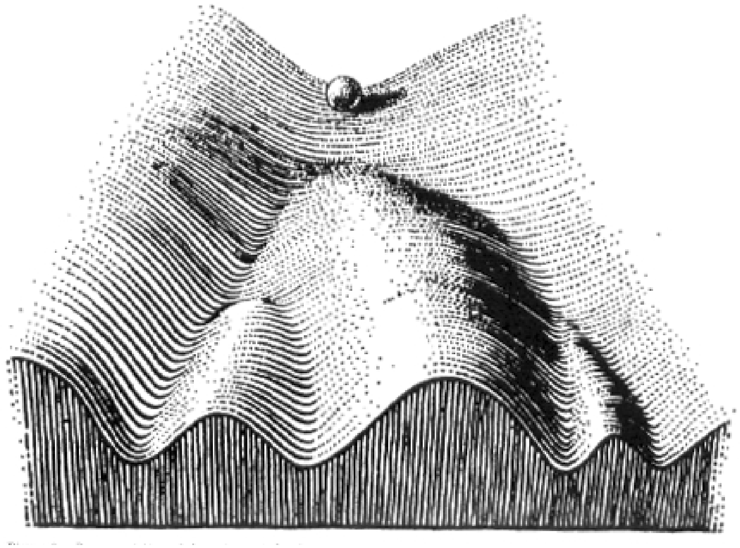
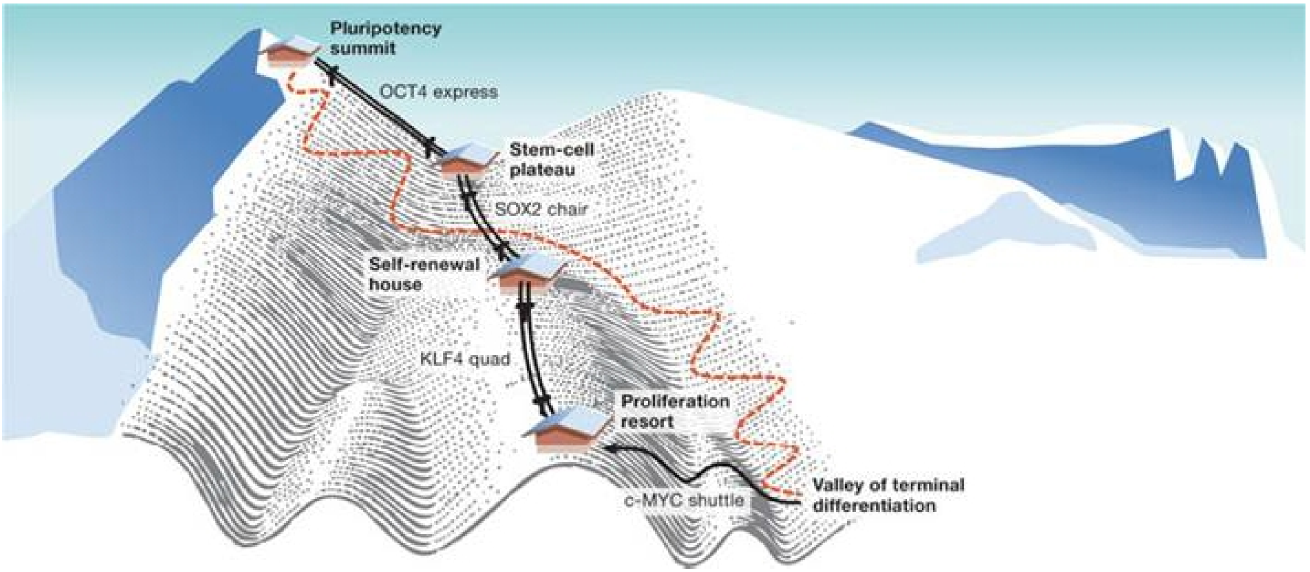
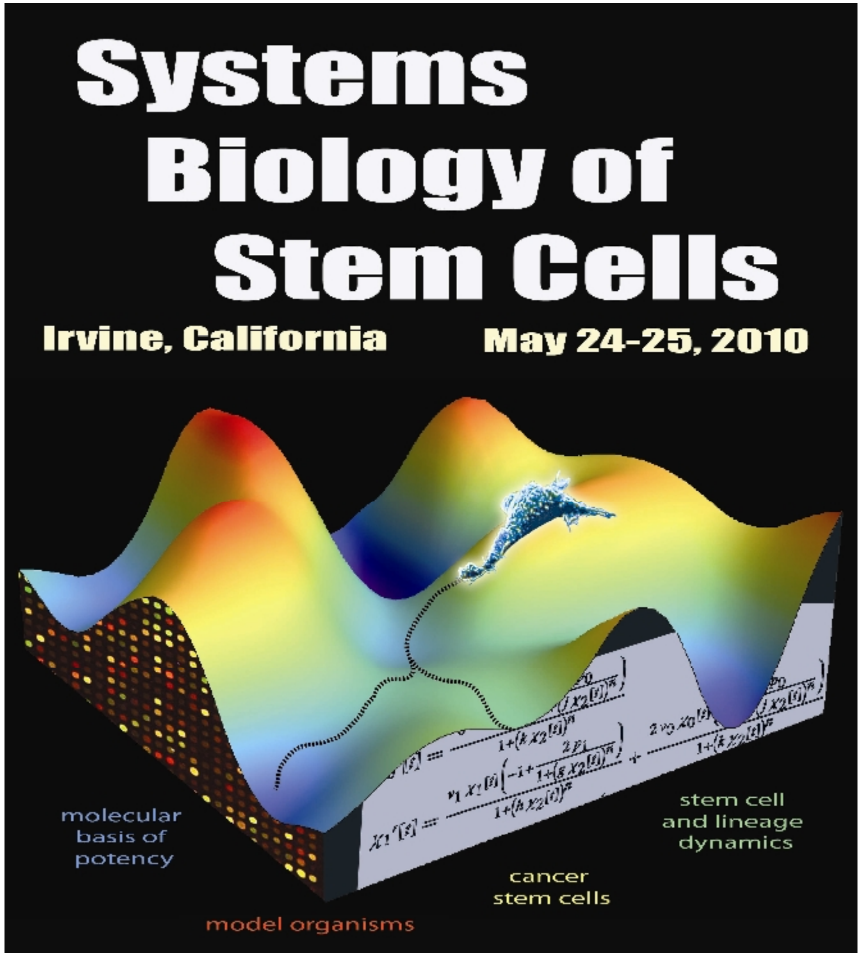


"The epigenetic landscape drawings of Conrad Hal Waddington are models having no grounding in physical reality. They are attempts to present a visual image for the processes by which a population of homogeneous cells differentiate into the diverse cell types of the organism" (Gilbert 1991, 138).

The epigenetic landscape:



(Keystone, Feb 2010)


Systems Biology of Stem Cells
Irvine, California
May 24-25, 2010
molecular basis of potency
model organisms
cancer stem cells
stem cell and lineage dynamics

Outline:

1. The landscape analogy - origins
2. Waddington's model - analysis
3. The landscape in systems biology
4. The landscape in stem cell biology
5. Integrative explanations
6. Conclusions

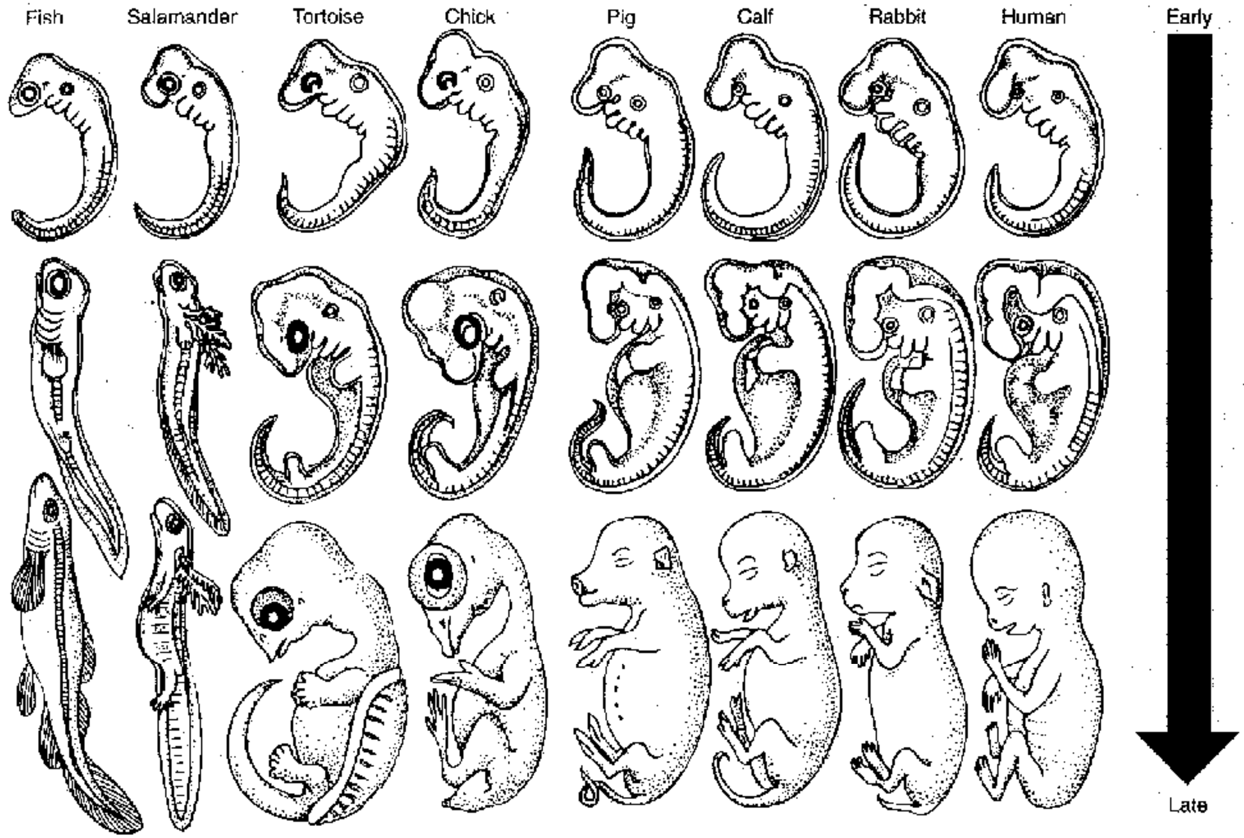
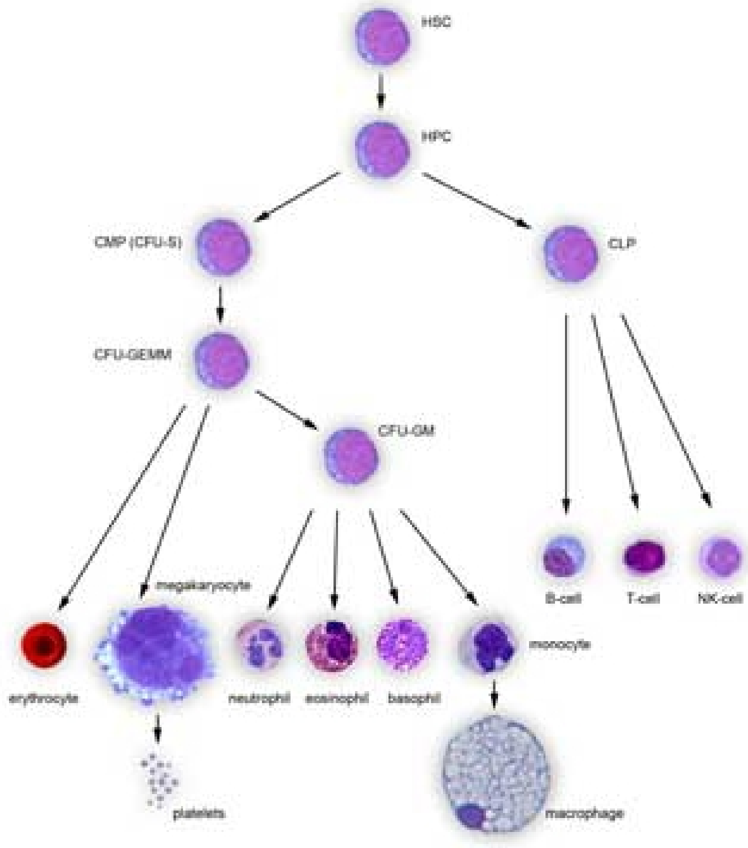
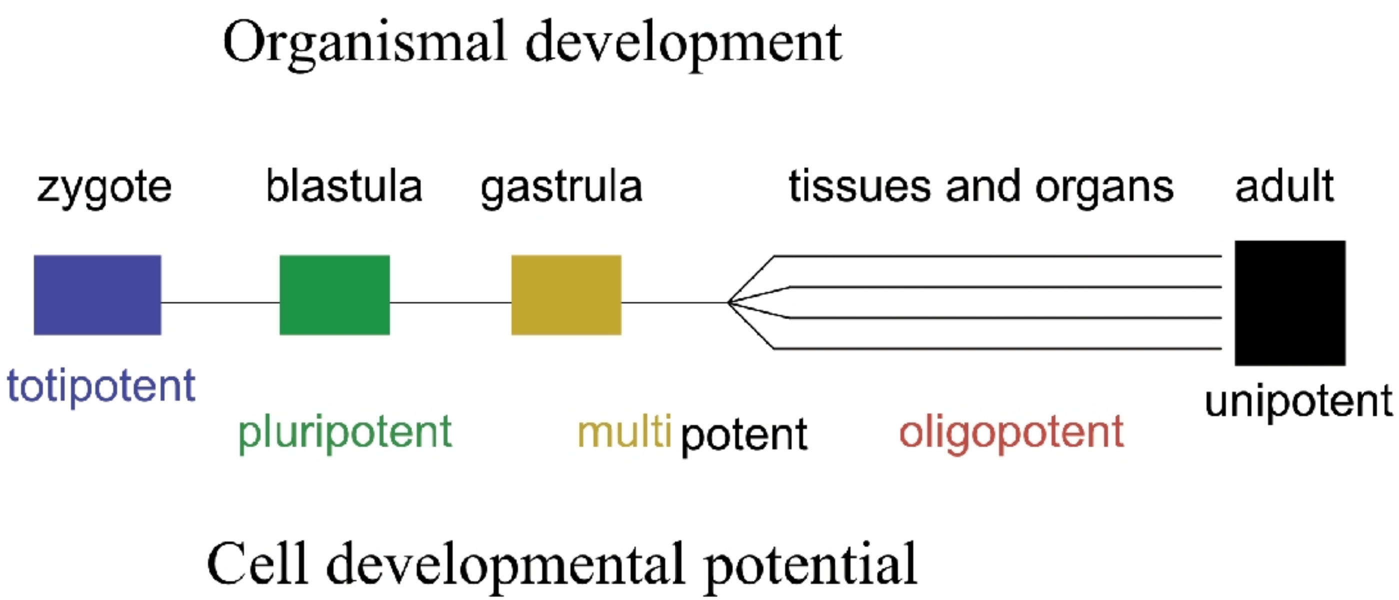


FIGURE 5.38 **Haeckel's comparison of early embryonic stages across vertebrate groups.** Eight species are shown across the figure. The youngest developmental stage of each is at the top of the figure followed by two successively older stages below.



From ISSCR imagefiles (Lensch 2006)


Organismal development
zygote
blastula
gastrula
tissues and organs
adult
totipotent
pluripotent
multipotent
oligopotent
unipotent
Cell developmental potential

Introduction to Modern Genetics (1939):

"Perhaps more important are the cases in which there are several fairly sharply demarcated and alternative developmental processes, *which can only be represented by a system of branching lines*. For instance, we have seen that in Drosophila there is a period of development when the normal vermilion substance is ess-ential for normal eye pigmentation. … at the branching point there are two alternative possible ways in which the mixture can change, according as the vermilion sub-stance is present or not…" (1939, 182).

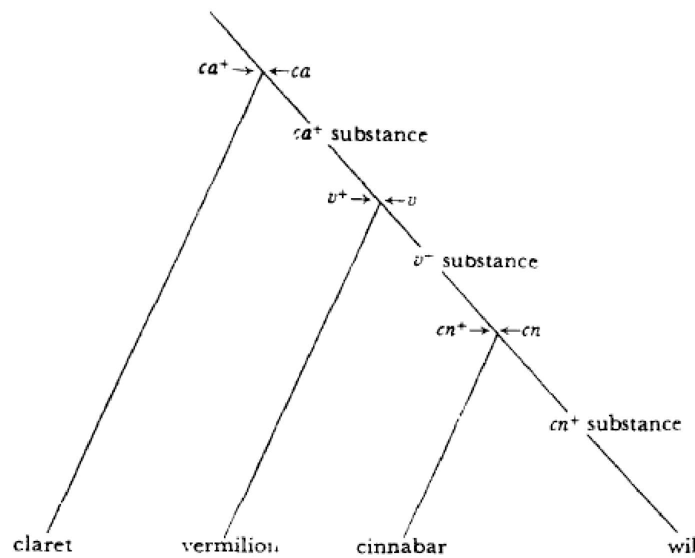
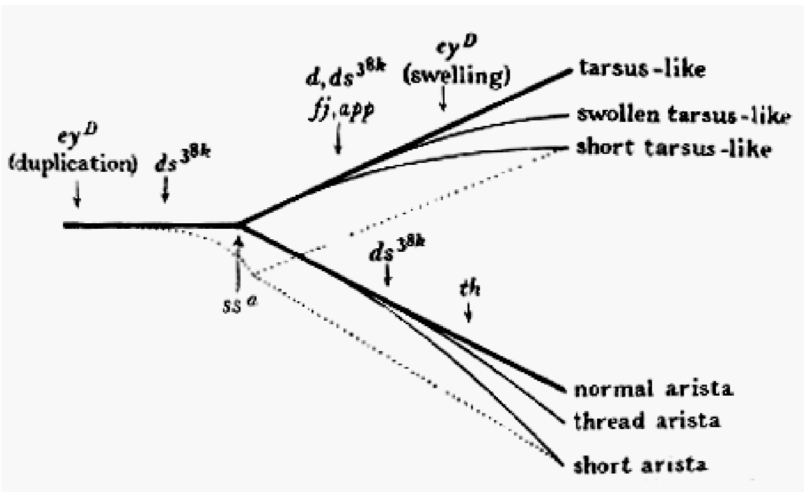
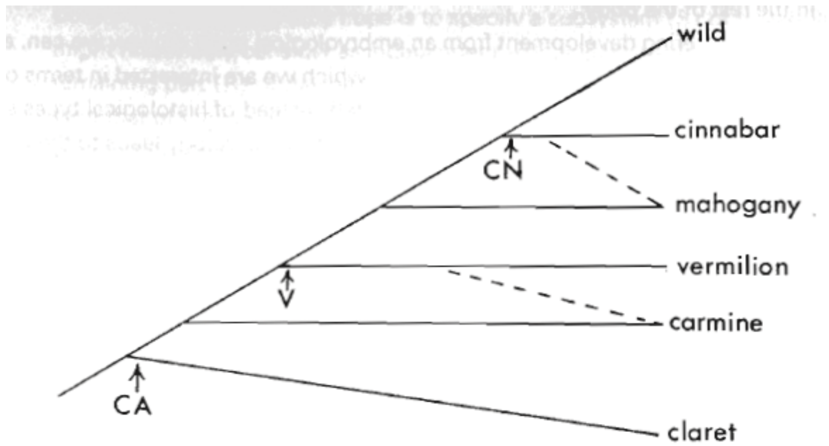


Fig. 1. The formation of eye colours in *Drosophila*. The pigment-forming process normally runs down the line through the ca^+ substance, the v^+ substance, to give wild type pigment. The genes, *ca*, *v* and *cn* interrupt this sequence, so that the process takes an altered course, to give claret, vermilion or cinnabar pigmentation. (Caption from Waddington 1940.)

Introduction to Modern Genetics (cont.):

"If we want to consider the whole set of reactions concerned in a developmental process such as pigment formation, we therefore have to replace the single time-effect curve by a branching system of lines which symbolizes all the possible ways of development controlled by different genes" (1939, 182).





Origin of the landscape (1939):

"Moreover, we have to remember that each branch curve is affected not only by the gene whose branch it is but the whole genotype. *We can include this point if we symbolize the developmental reactions not by branching lines on a plane but by branching valleys on a surface*. The line followed by the process, i.e. the actual time-effect curve, is now the bottom of a valley, and we can think of the sides of the valley as sym-bolizing all the other genes which cooperate to fix the course of the time-effect curve; some of these genes will belong to one side of the valley, tending to push the curve in one direction, while others will belong to the other side and will have an antagonistic effect. One might roughly say that all these genes correspond to the geological structure which moulds the form of the valley." (182, italics mine)

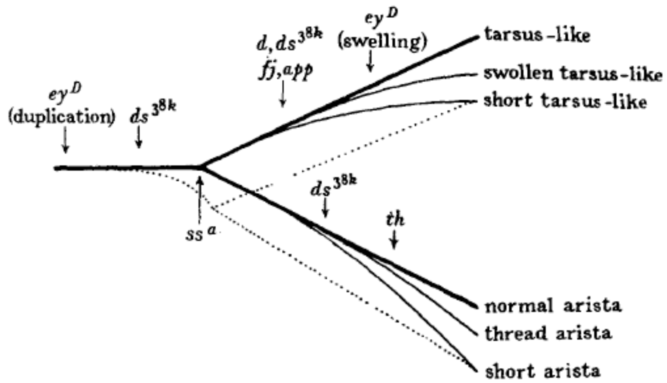
THE EPIGENETIC LANDSCAPE

From a drawing by JOHN PIPER

Looking down the main valley towards the sea. As the river flows away into the mountains it passes a hanging valley, and then two branch valleys, on its left bank. In the distance the sides of the valleys are steeper and more canyon-like. (See p. 91.)

Organisers and Genes (1940):

"One can compare a piece of developing tissue to a ball rolling down a system of valleys which branches downwards, like a delta… The tissue, like the ball…, must move downhill, but at some points there are two downhill paths open to it. At such branching points, it may sometimes require a definite external stimulus, such as an evocator substance, to push the tissue into one of the developmental paths…" (45).



"…it is the track as a whole which, compared with any line lying between the tracks, is a description of an equilibrium" (92).

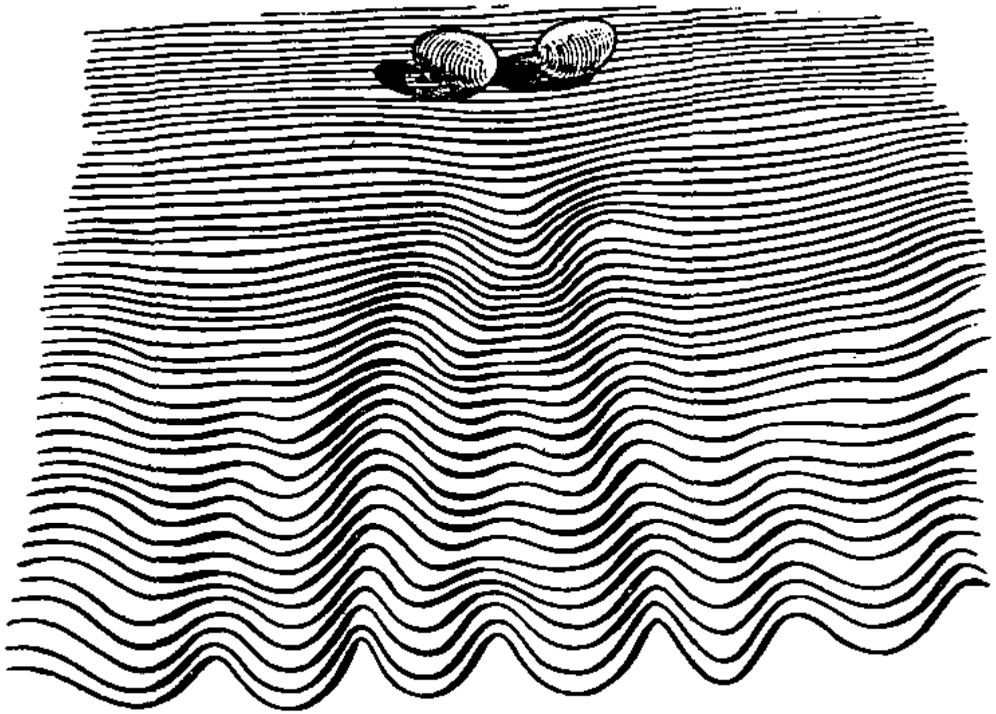
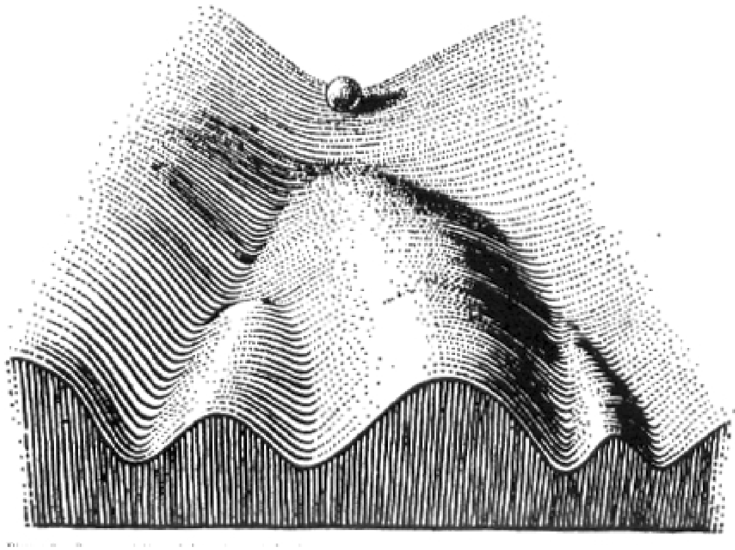


FIGURE 16.2

The 'epigenetic landscape.' A symbolic representation of the developmental potentialities of a genotype in terms of a surface, sloping towards the observer, down which there run balls each of which has a bias corresponding to the particular initial conditions in some part of the newly fertilised egg. The sloping surface is grooved, and the balls will run into one or other of these channels, finishing at a point corresponding to some typical organ. (From Waddington 1954*b*.)

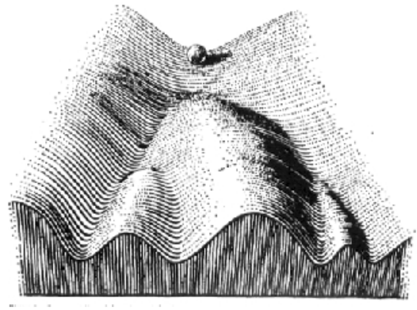
The Strategy of the Genes (1957)



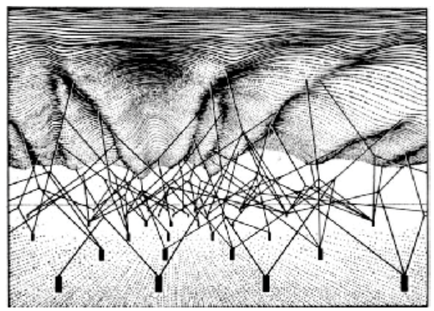
… a more or less flat, or rather undulating surface, which is tilted so that points representing later states are lower than those representing earlier ones [figure 4]. Then if something, such as a ball, were placed on the surface, it would run down toward some final end state at the bottom edge. (Waddington 1957, 29)

Waddington's landscape: purposes

1) represent robust patterns of development
   - developing entity unspecified
   - robust pathways
   - branching track structure
   - visualize generalizations from experiments

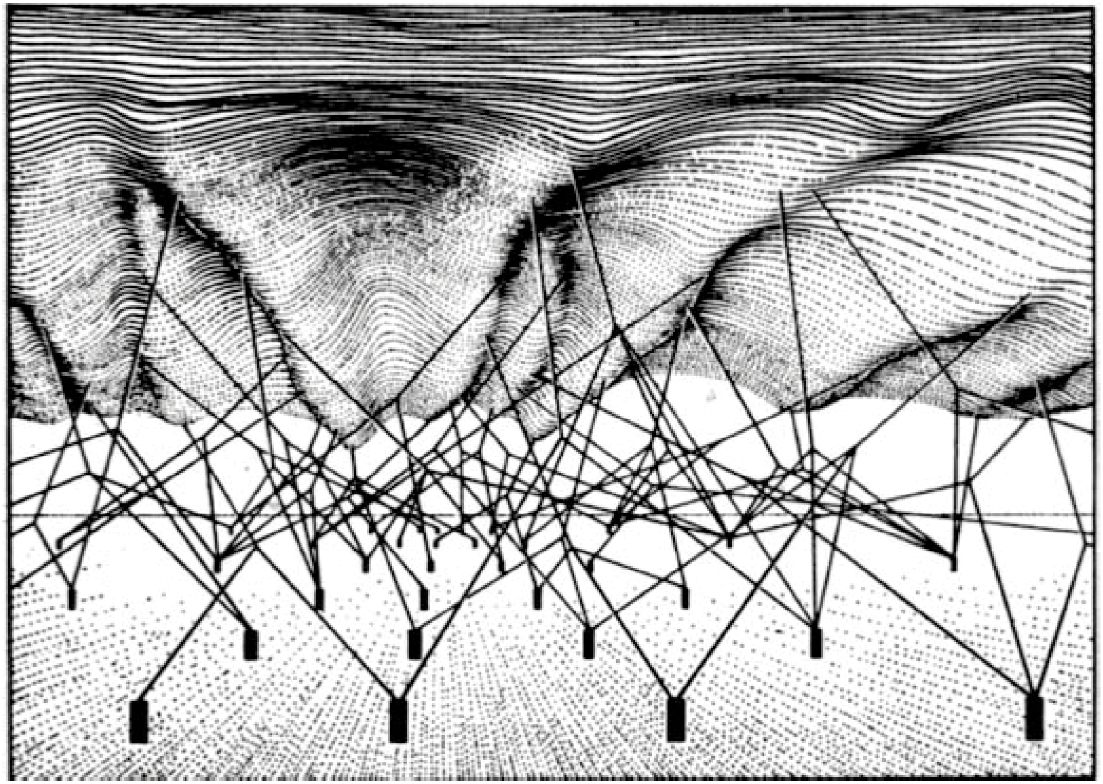


2) express a hypothesis about genetic control of development
   - interacting network of biochem products
   - fixed genes



3) 'conceptual laboratory' for unifying genetics, evolution, development
   - malleable landscape
   - simple, intuitive (3d)

Genetic underpinnings:



The landscape, “which slopes down from above one’s head towards the distance, is controlled by the pull of these numerous guy-ropes which are ultimately controlled by genes” (1957, p.36).

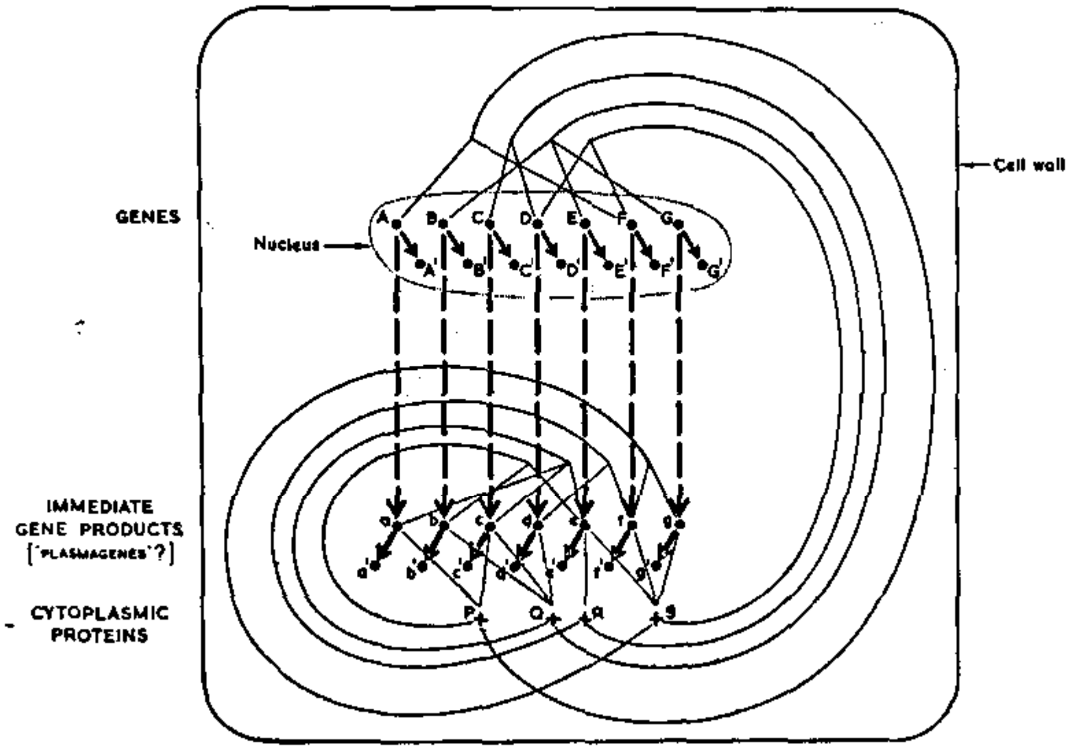
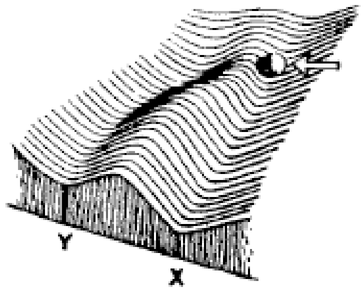


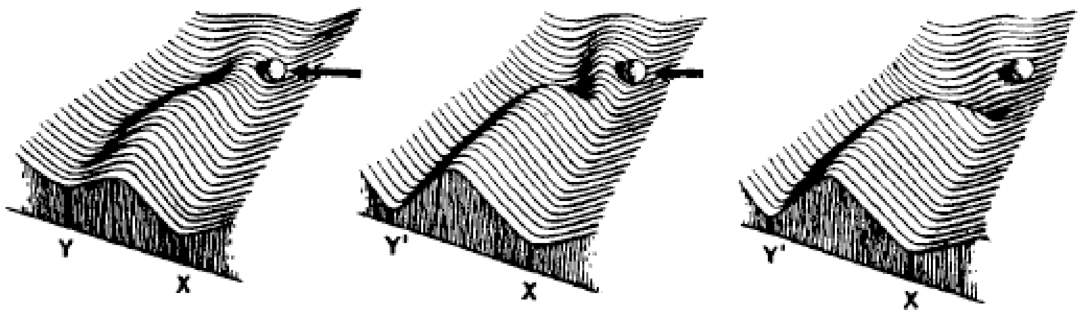
FIGURE 16.1

The double cycle of intra-cellular reactions. The genes in the nucleus acting on cytoplasmic substrates, both reproduce themselves and control the formation of 'immediate gene products', *a*, *b*, *c*, etc. These then use cytoplasmic raw materials (i) perhaps to reproduce themselves identically, in the manner of plasmagenes, and (ii) to elaborate the final cytoplasmic constituents, P, Q, R etc., which are the substrates or raw materials which condition the activity of both the genes and the gene products. (From Waddington 1954*a*.)

Integrated view of genetics, evolution, and development:

- not predictive
- qualitative
- inexact
- abstract
- simple
- non-mathematical





Intended for:
“…a context in which it is more important to employ a system of thought which is flexible and of wide application than to search for a precise formulation of a narrower viewpoint” (31).

Systems biology: cell networks

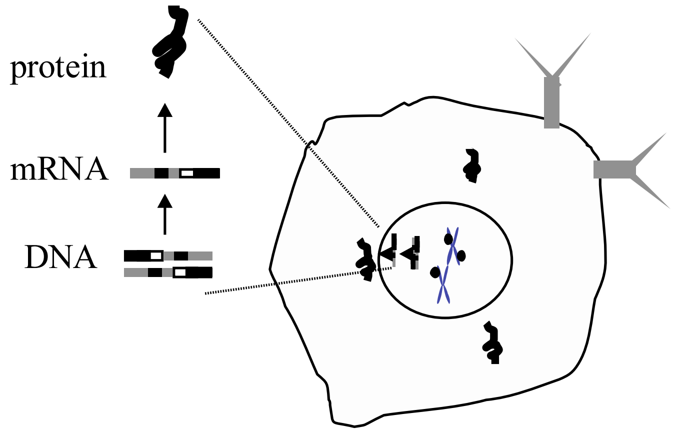
"One can think of the cell as *made of* several superimposed networks"

(Alon 2007, 97)

Cell networks:

transcription
- sensory
- developmental

signal transduction
metabolic
protein-protein interaction

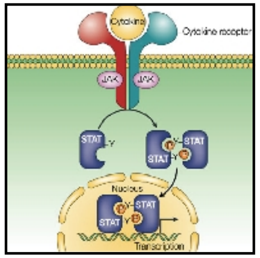


Network models:

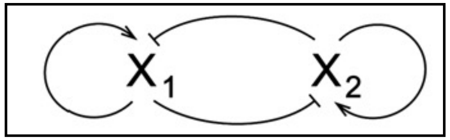
molecular elements $X_1, X_2, \ldots, X_n$
state variable x_i for molecule i at t (concentration, gene expression level)
cell state at t $S(t) = [x_1, x_2, \ldots x_n]$

Cellular systems models: construction

Molecular mechanism



Wiring diagram



Formal representation (ODEs)

$$\frac{dx_1}{dt} = \frac{a_1 x_1^n}{S^n + x_1^n} + \frac{b_1 S^n}{S^n + x_2^n} - k_1 x_1 = F_1(x_1, x_2)$$

$$\frac{dx_2}{dt} = \frac{a_2 x_2^n}{S^n + x_2^n} + \frac{b_2 S^n}{S^n + x_1^n} - k_2 x_2 = F_2(x_1, x_2)$$

Systems models and the landscape:

Solutions to systems of equations

steady-states (dynamic equations set to zero)

local solutions (change from initial conditions)

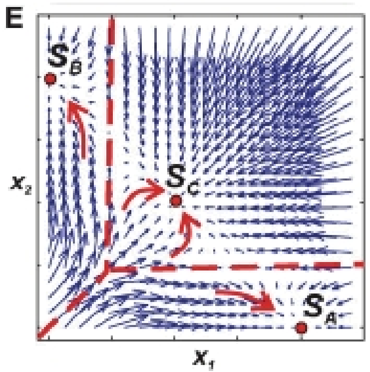
$$\frac{dx_1}{dt} = \frac{a_1 x_1^n}{S^n + x_1^n} + \frac{b_1 S^n}{S^n + x_2^n} - k_1 x_1 = F_1(x_1, x_2)$$

$$\frac{dx_2}{dt} = \frac{a_2 x_2^n}{S^n + x_2^n} + \frac{b_2 S^n}{S^n + x_1^n} - k_2 x_2 = F_2(x_1, x_2)$$

Local solutions describe vectors in state space

steady-states (S_A, S_B, S_C)

local solutions (S_k stable or unstable)

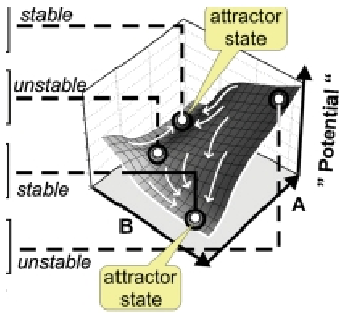


Vectors define

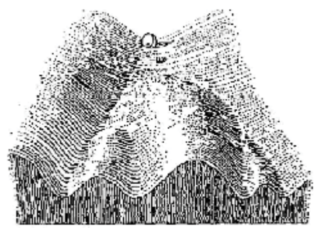
landscape topography

stable steady-states

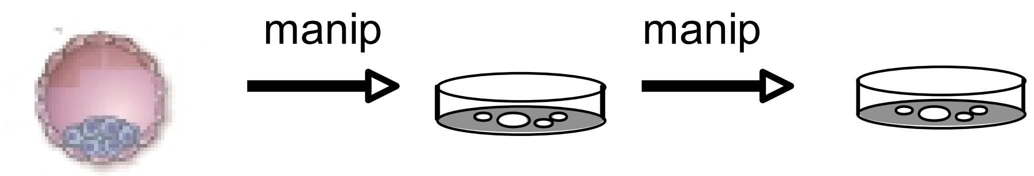
are attractors



From: Huang et al 2009



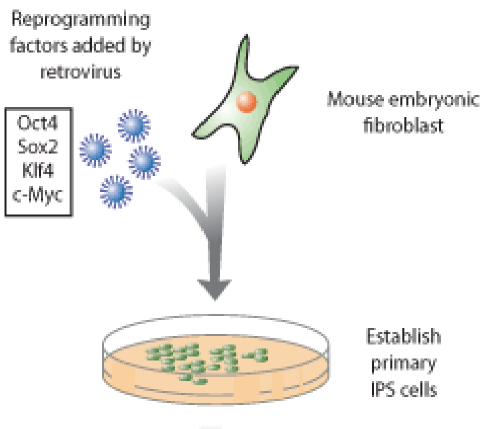
Stem cell experiments: basic design



organismal source

measure cells
- morphology
- biochem

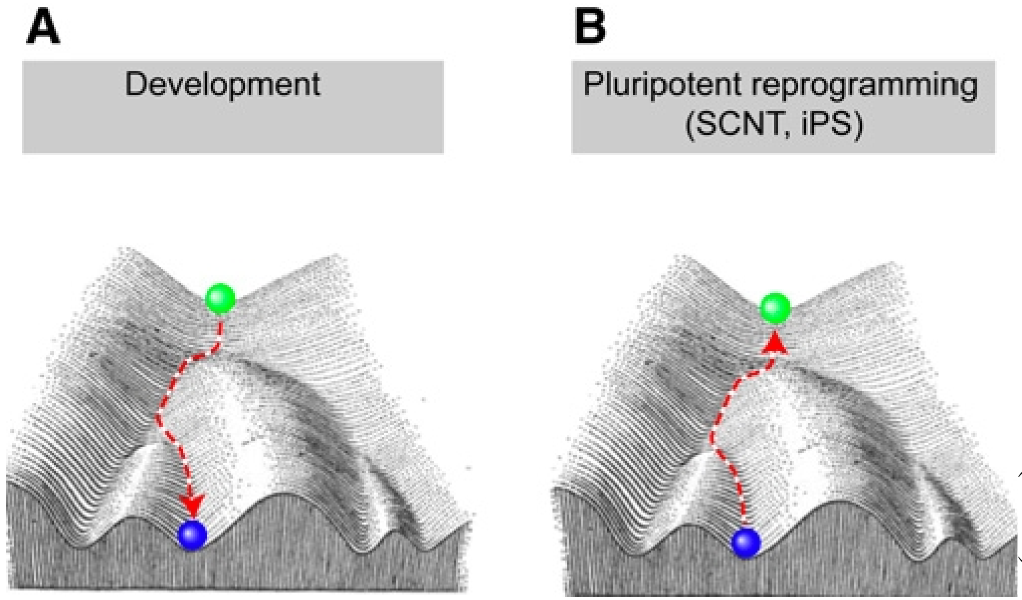
measure progeny
- self-renewal
- differentiation



reprogramming
- add TF genes (2-4)
- grow in culture
- assay for
  self-renewal
  differentiation

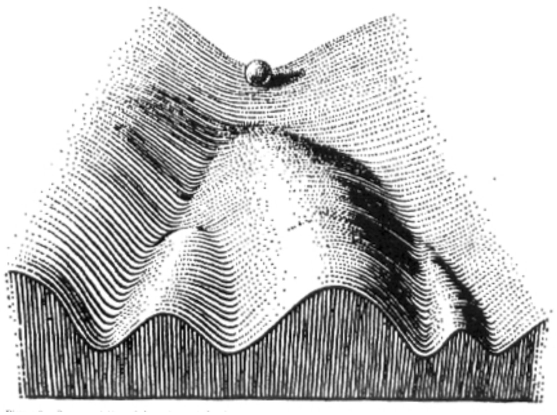
Waddington's landscape and reprogramming

1) visualize shared background assumptions
2) depict generalizations about experiments
3) correlate cell developmental potential and molecular state

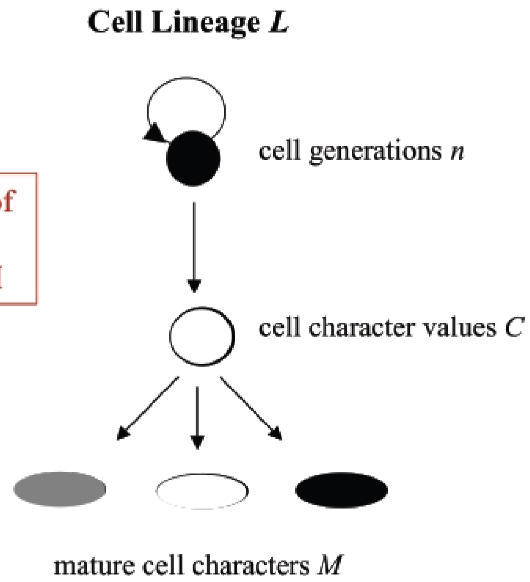


From: Zhou and Melton (2008)

Background assumptions:



Stem cell: unique stem of a cell lineage hierarchy relative to L, n, C and M



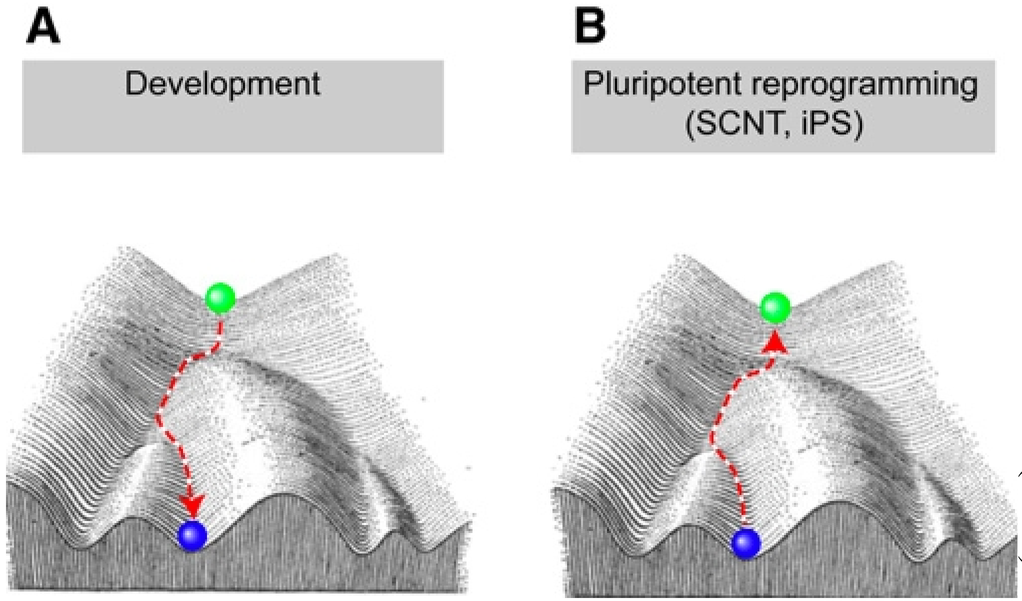
1) unidirectionality

2) single undifferentiated start *stem cell

3) multiple discrete termini

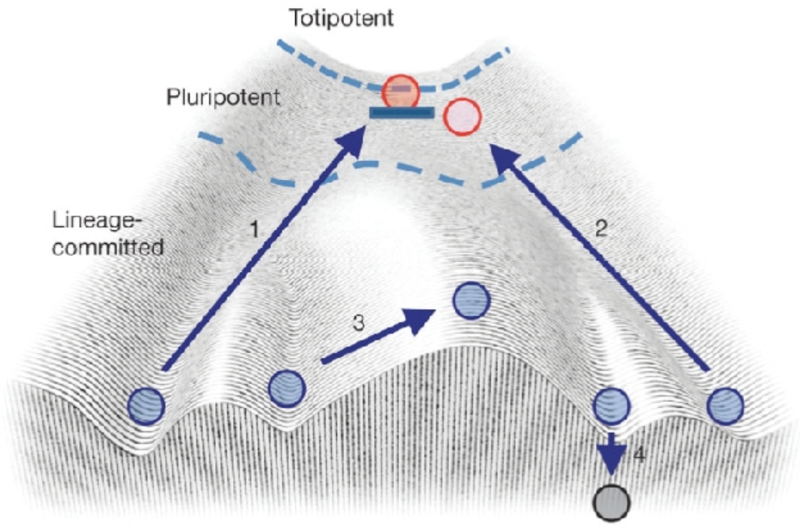
4) robust bifurcating tracks

Generalizing about experiments:



From: Zhou and Melton (2008)

Generalizing about experiments (II):



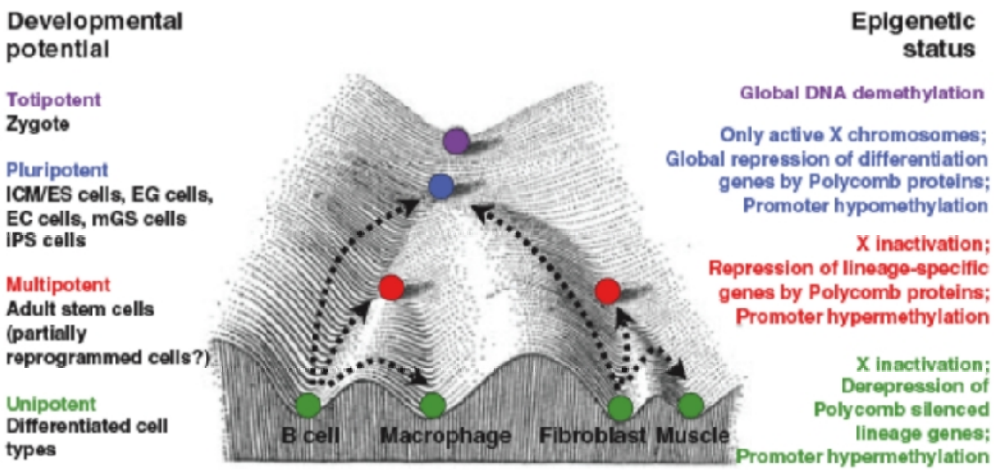
1) complete reprogramming

2) partial reprogramming

3) direct differentiation

4) cell death

Correlating molecular traits and developmental potential:



From Hochedlinger and Plath (2009)

Experimental measurement of cell traits:

physical (size, density)
morphological (shape, inner structure)
physiological (cell cycle status, signaling)
molecular (DNA, RNA, protein, small molecules)

Explanation: the traditional picture

Systems models express hypotheses about underlying molecular networks.

Explanation

Calculation

Prediction

Data

Experimental manipulation

Stem cell experiments articulate phenomena to be explained.

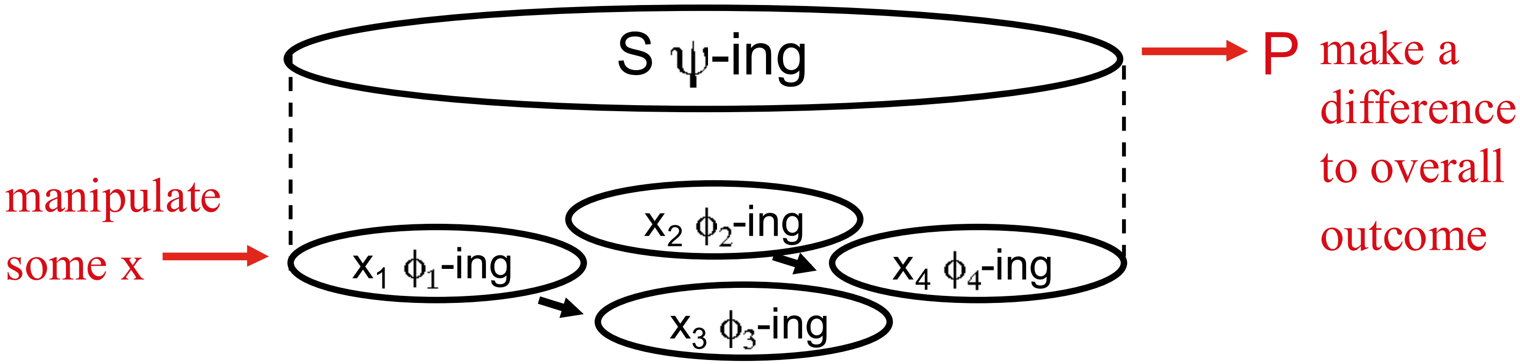
Problems for the traditional picture:

1) Mathematical models of cell development depend on concrete experiments to:
   - identify molecular elements, dependency relations
   - derive predictions

2) Concrete experiments reveal molecular mechanisms underlying cell development.

3) Mechanistic explanations require mathematical predictions.

Mechanistic explanation:



"A mechanism is a structure performing a function in virtue of its component parts, component operations, and their organization. The orchestrated functioning of the mechanism is responsible for one or more phenomena" (Bechtel and Abrahamsen 2005, 423).

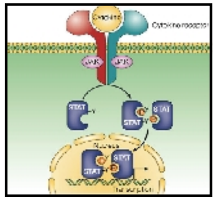
Cell systems models depend on experiments

1) For construction:

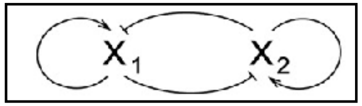
Molecular mechanism

↓

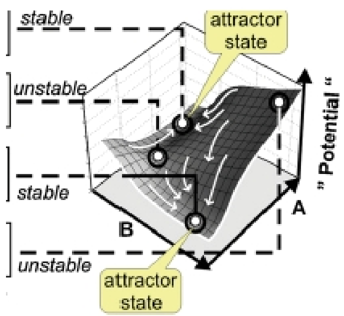
Wiring diagram



Experiments



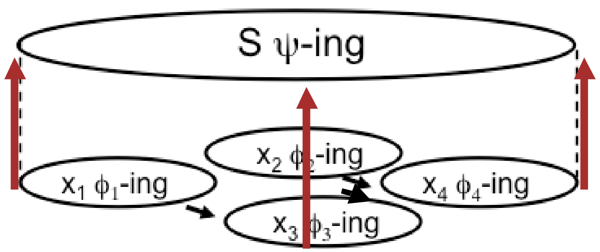
2) For use (prediction)

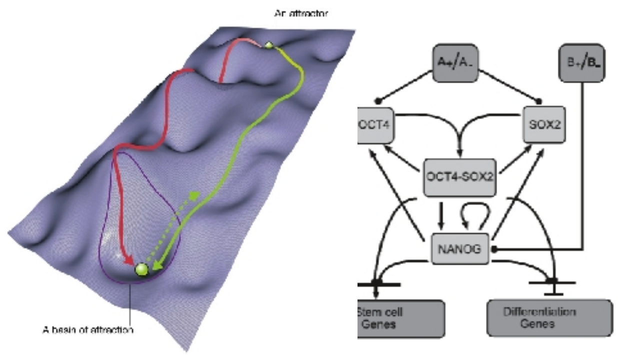


Vector-and-attractor landscape

- need to identify starting point
- a stem cell
- correlation of molecular & cell states (role #3)

Mechanistic explanations depend on mathematical models:





Mathematical models are required to make explicit the connection between cell and molecular levels.

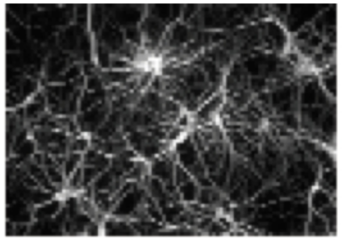
Conclusions:

- Mathematical models and stem cell experiments are interdependent in explanations of cell development.
- Waddington's landscape plays a unifying role, integrating the two approaches.
- Simple abstract models have a distinct role in science, setting the stage for prediction and explanation.
- The landscape model 'visualizes collaboration' between mathematical modeling and concrete experimentation.

Towards a Theoretical Biology:

"Great hopes are often held out for the application to biological problems of new mathematical approaches grouped under the general heading of 'Systems Theory.' I hope some of the mathematicians… can clothe these airy promises with real flesh and blood"

- C.H. Waddington, 1968



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