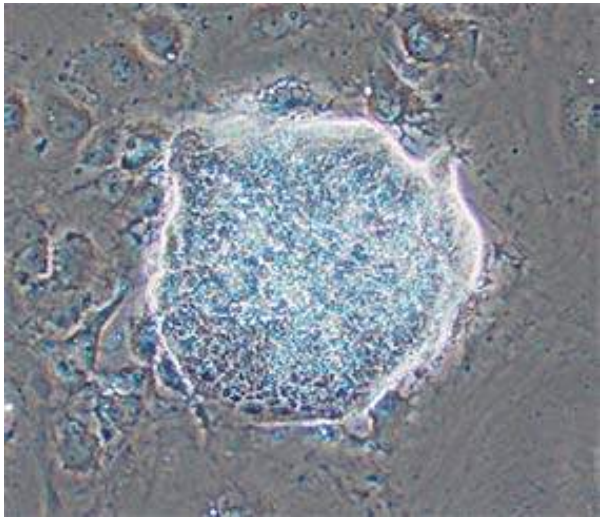
Stem cell models: cell individuality, development, and levels of organization

CNRS, University of Bordeaux
May 2, 2016

Melinda Bonnie Fagan
Department of Philosophy
University of Utah

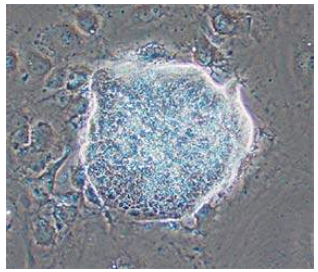
Stem cells: a dual aspect



"Stem cells are functionally defined as having the capacity to self-renew and the ability to generate differentiated cells" (Melton *Essentials of Stem Biology*, 2013, 7).

Philosophy and stem cell biology:

- making explicit assumptions about development
- engaging scientific practice
- challenges: diversity, fragmentation, no general theory



ISSCR 2016 ANNUAL MEETING SAN FRANCISCO

22-25 JUNE CALIFORNIA • USA

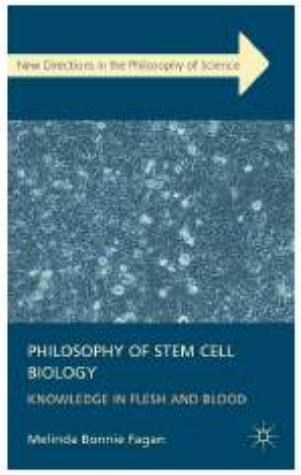
CONCURRENT SESSION IV

13:15-15:15

Road to the Clinic	Tissue Engineering	Stem Cell Metabolism	Regulatory Networks in Differentiation and Disease	Disease Modeling II	Leukemia and Stem Cells	Technology Frontiers
Heather Young, *University Melbourne, Australia*	**Supported by Society for Biomaterials** Milica Radisic, *University of Toronto, Canada*	Daisuke Nakada, *University, USA*	Jian Xu, *University of Texas Southwestern, USA*	Toshiro Sato, *Keio University, Japan*	David Kent, *University of Cambridge, UK*	Mark A. Labow, *Novartis Institutes for Biomedical Research, USA*
Donald B. Kohn, *University of California, Los Angeles, USA*	Shelly Sakiyama-Elbert, *Washington University, USA*	Andrew Dillin, *University of California, Berkeley, USA*	Bertold Göttgens, *University of Cambridge, UK*	Melissa Little, *Murdoch Children's Research Institute, Australia*	Iannis Aifantis, *New York University School of Medicine & HHMI, United States*	Hirohide Saito, *Kyoto University, Japan*

Philosophy and stem cell biology:

- making explicit assumptions about development
- engaging scientific practice
- challenges: diversity, fragmentation, no general theory
- response: a modeling approach
  - inclusive overview of SCB
  - explain general features of SCB
  - implications for philosophy of biology



Outline of talk:

I. Introduction

II. Abstract stem cell model

III. Individuating stem cells

IV. Modeling development

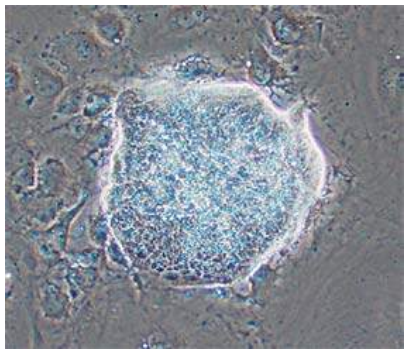
V. Conclusion

Abstract stem cell model:

a modeling approach

- inclusive overview of SCB
- explain general features of SCB
- **implications for philosophy of biology**

- a minimal model
- a cell-level model



Stem cell: general definition

"Stem cells are functionally defined as having the capacity to self-renew and the ability to generate differentiated cells" (Melton 2013, *Essentials of Stem Biology*, 7).

"Stem cells: Cells that have both the capacity to self-renew (make more stem cells by cell division) as well as to differentiate into mature, specialized cells" (ISSCR 2016).

"Stem cell: a cell that can continuously produce unaltered daughters and also has the ability to produce daughter cells that have different, more restricted properties" (EuroStemCell 2016).

Stem cell: general definition

Stem cell: a cell with the capacity to self-renew and to differentiate into one or more specialized cell types

Self-renewal: cell division producing one or more cells similar to the parent

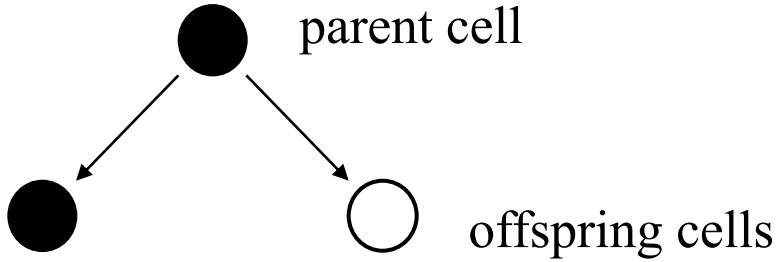
Differentiation: loss of developmental potential and acquisition of specialized traits of a mature cell type

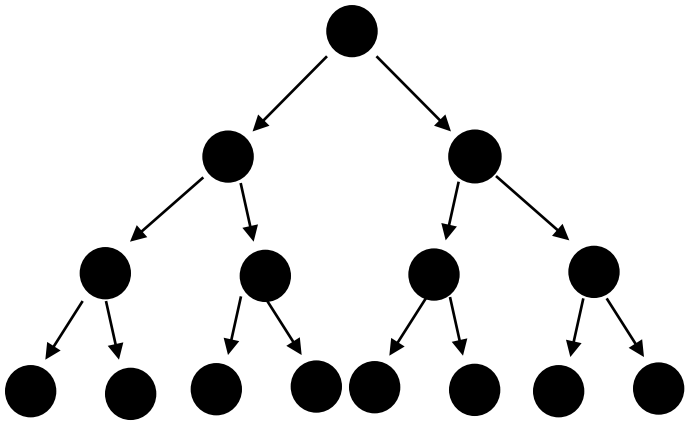
Self-renewal and cell theory:

(i) Cells reproduce by binary division; a parent cell divides to produce two offspring cells.

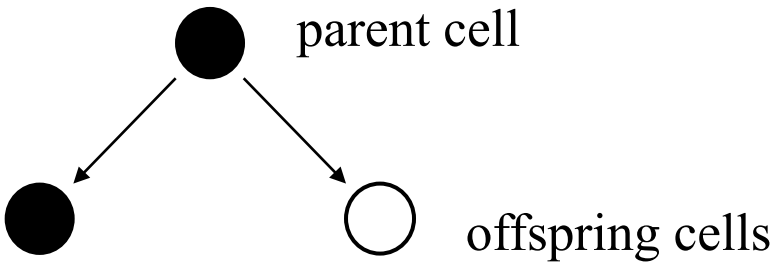
(ii) An individual cell's existence begins with a cell division event and ends with either a second division event (producing two offspring) or cell death (and no offspring).

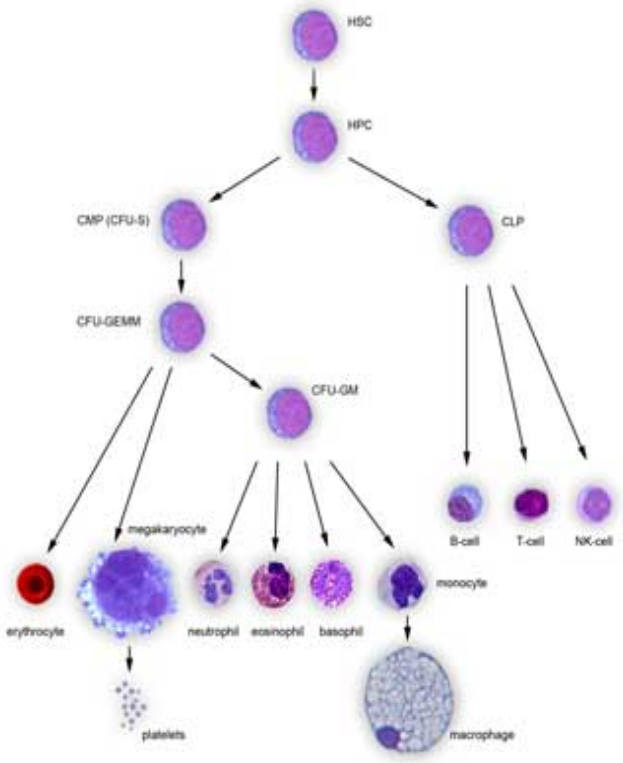
(iii) Generations of cells linked by reproductive division form a lineage.





Self-renewal: comparison across cell generations

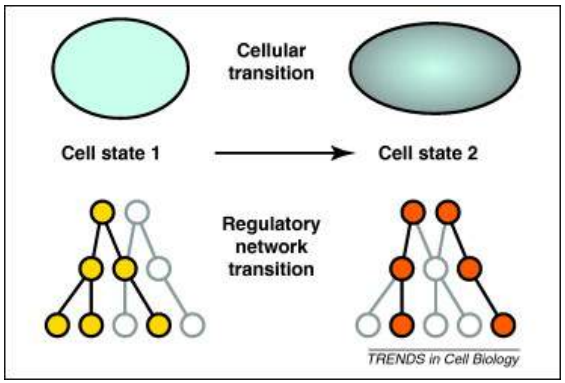


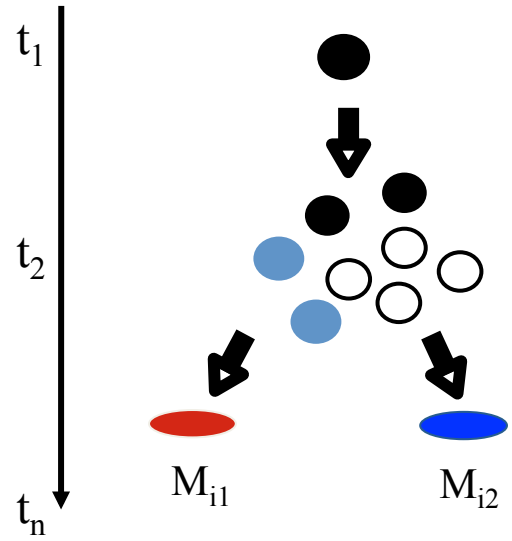


C: a set of variable cell characters, values of which are compared across generations

Differentiation: change in cell state

- an individual cell may differentiate by transforming directly from one 'cell state' to another.

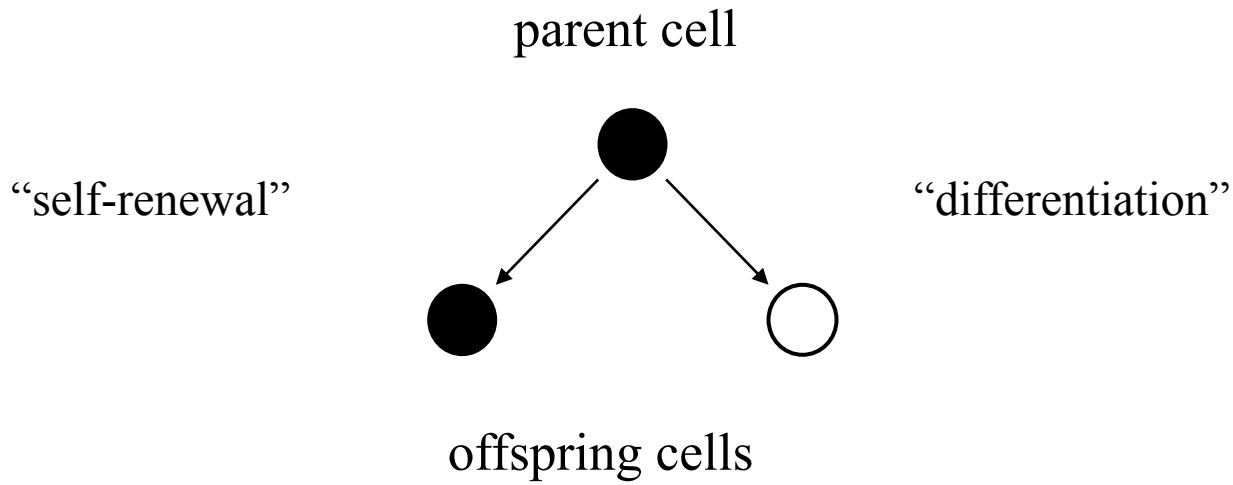




- cell state: a pattern of gene expression and molecular interactions that determines a cell's structural and functional characteristics.

- self-renewal: cell division with no change in cell state.

Stem cell: biologists' minimal model



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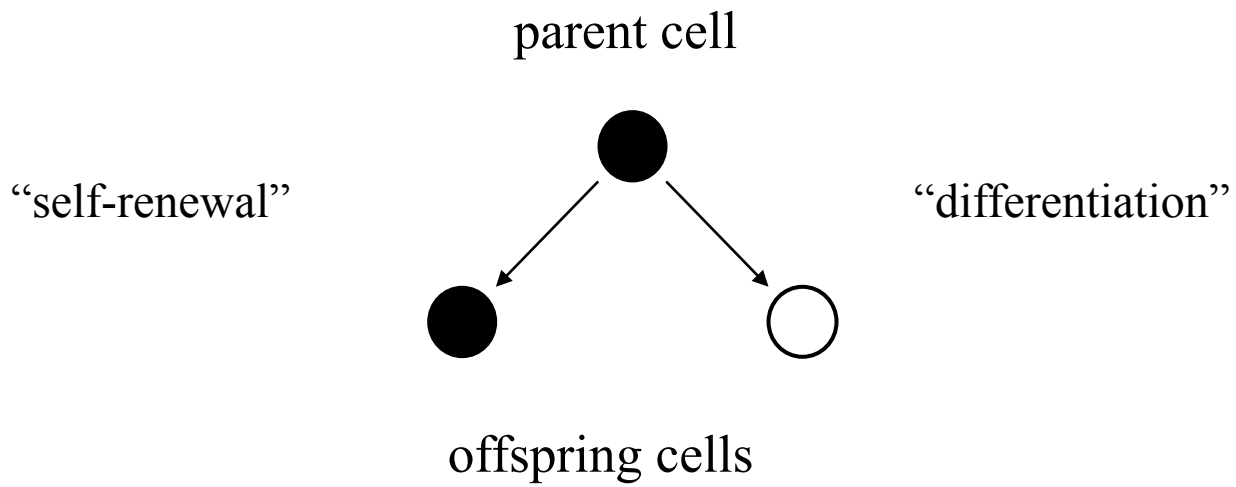
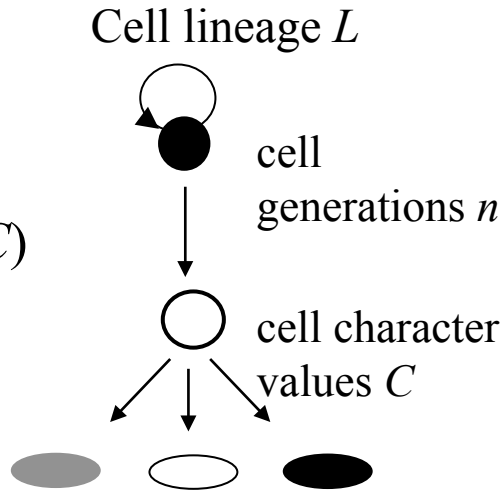


n: number of cell generations; time interval

Stem cell: generalized minimal model

A stem cell is a cell that initiates a cell lineage *L*, which after *n* divisions produces both stem cells (defined as having specific values of characters *C*) and more specialized cells.



Stem cell: generalized minimal model

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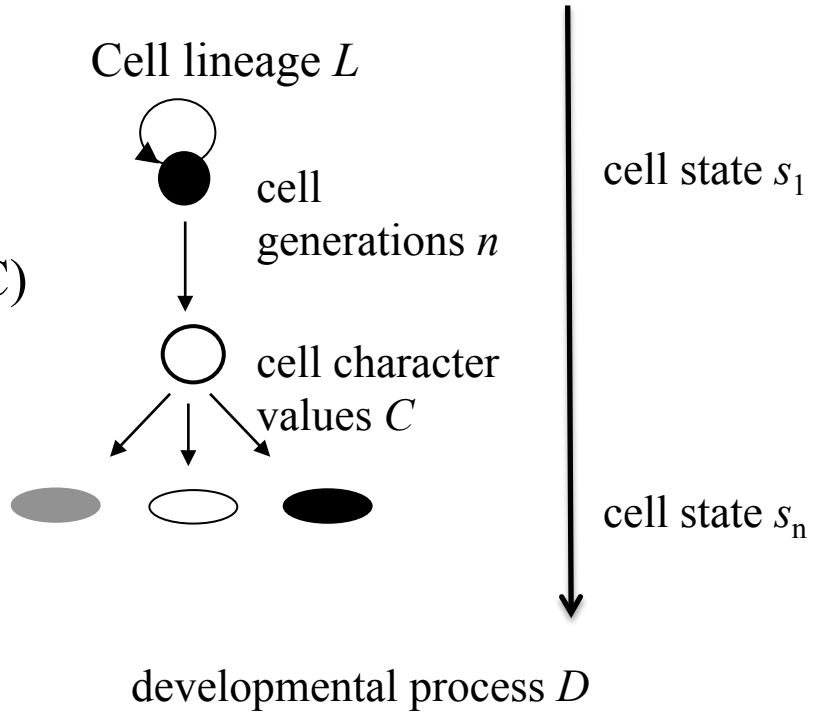
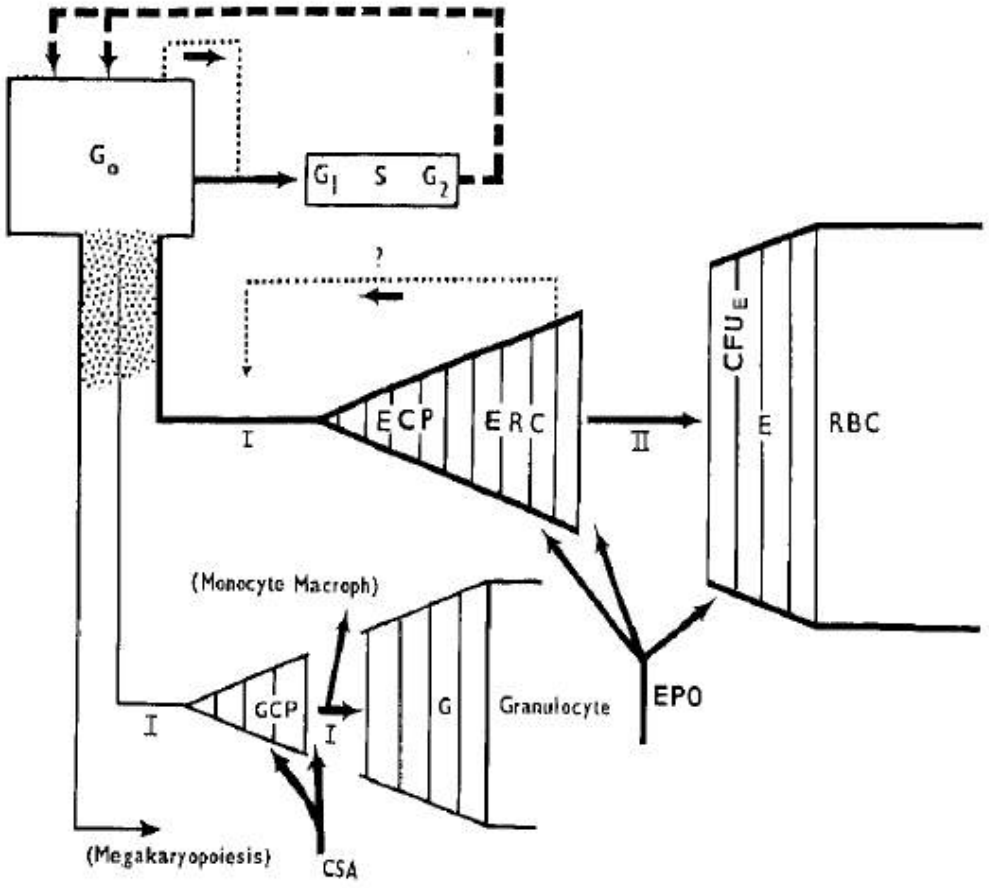
More specialized cells:
- dissimilar to parent
- "directed" to end of development





From: Lajtha and Schofield (1974, 316)

Abstract stem cell model:

Stem cell: a cell that is the origin of a cell lineage *L*, generated by *n* cell divisions and organized by comparison of characters *C*. Character-values of C can be mapped onto a developmental process *D* of ordered cell states $s_1,\ldots s_n$.

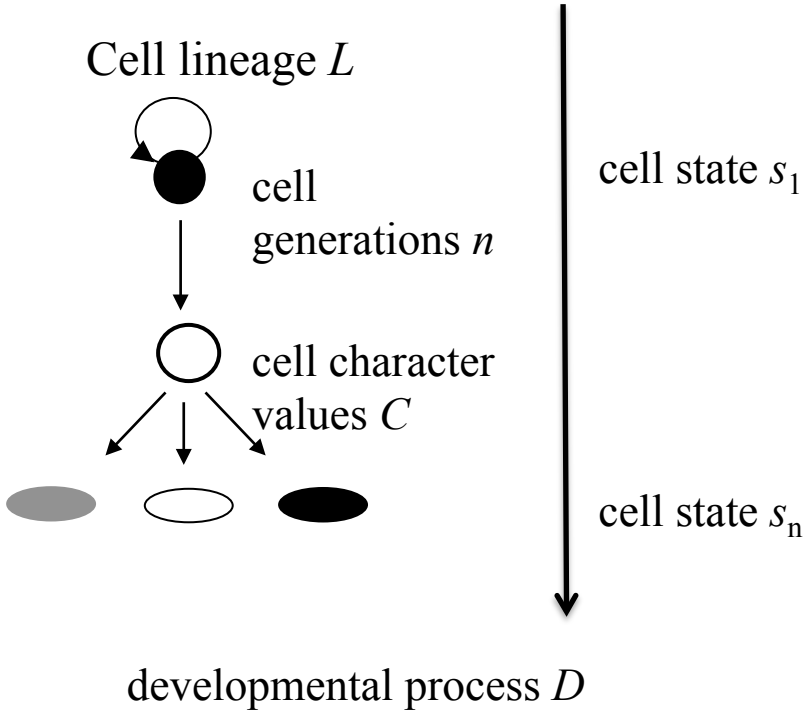


TABLE 1: Model-based classification of stem cells				
Type	**L (source)**	**C**	**n**	**D**
ESC	5d embryo ICM	cell size, cell shape, gene expression, karyotype, telomerase activity, alk-phos, cell surface molecules	≥50 divs	traits of cells from three germ layers
HSC	BM, cord, peripheral blood	cell size, density, light scatter, surface molecules, cell cycle status	>6 months	traits of main blood and immune cell lineages
NSC	basal lamina of ventricular zone	cell morphology, surface markers, gene expression, cytokine response	months to years	traits of neurons, astrocytes, and oligodendrocytes
iPSC	various (relatively mature cells)	colony shape, cell size, cell shape, nucleus/ cytoplasm ratio, cell surface molecules, activity and expression of specific proteins, gene expression (specific and global), histone modifications at key locations	≥50 divs	traits of cells from three germ layers
GSC	5-9wk gonadal ridge	colony shape, alk-phos, surface expression (SSEA-1, SSEA-3, SSEA-4, TRA-1–60,TRA-1–81)	20-25 wks	traits of cells from three germ layers
EC	teratocarcinoma (129)	cell shape, morphology, production of embryoid bodies, surface molecules, enzymes	unlimited	traits of cells from three germ layers, teratocarcinoma

Experimental relativity:

- Stem cells can be individuated only relative to particular experimental methods.

- In practice, the stem cells concept is diverse and context -dependent.

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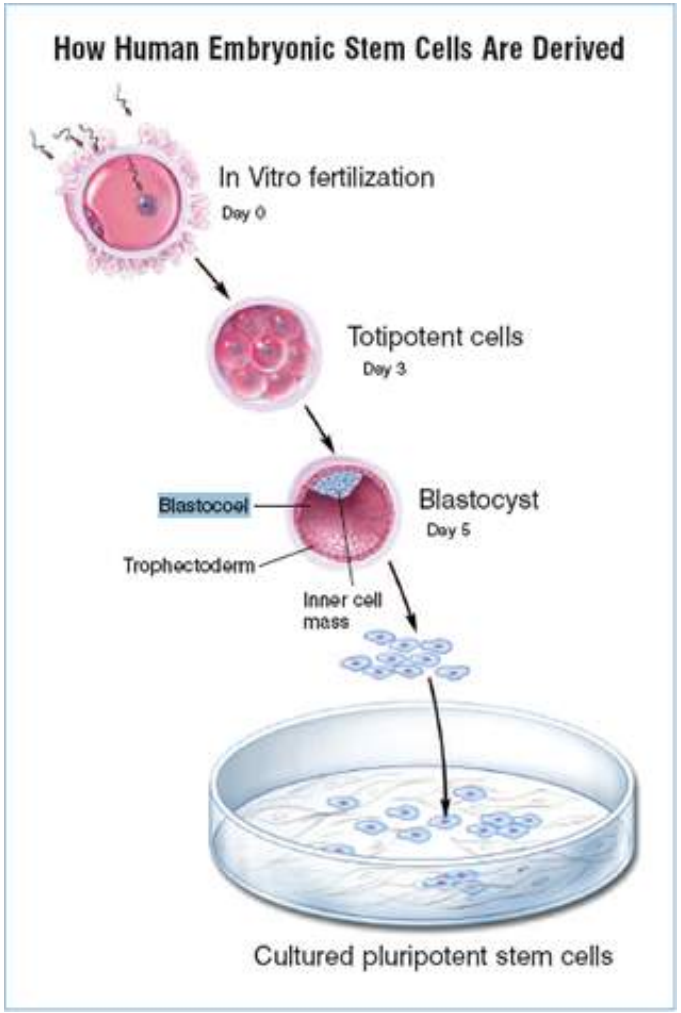

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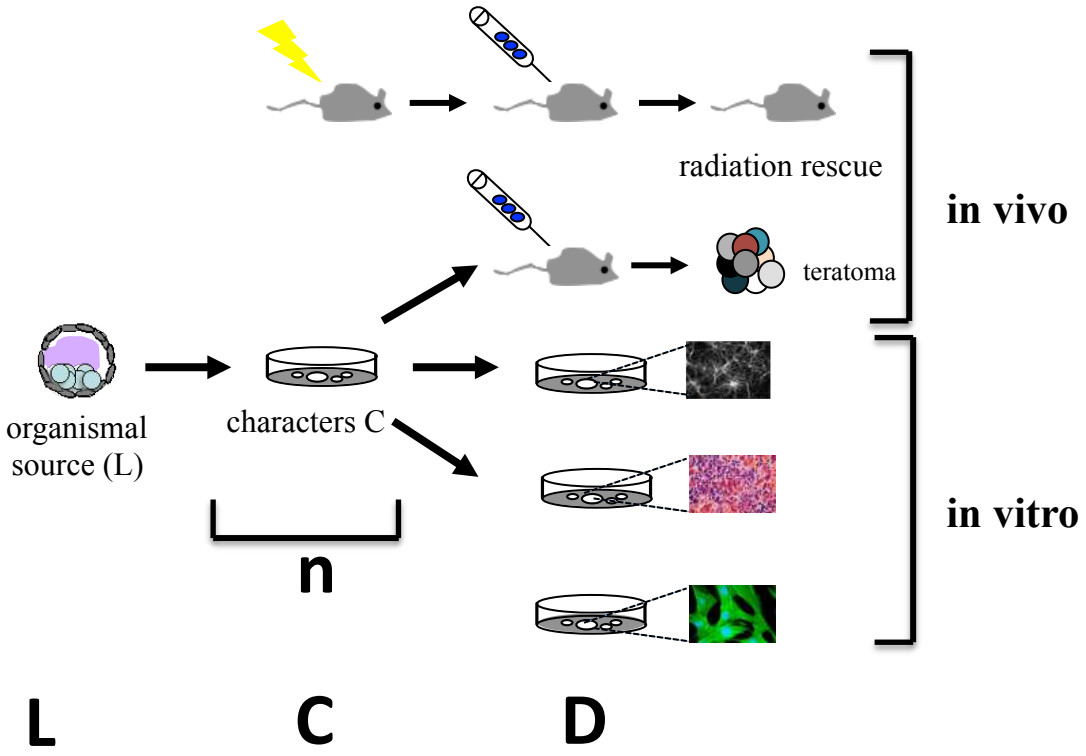
Stem cell experiments: basic design



Stem cell uncertainty:

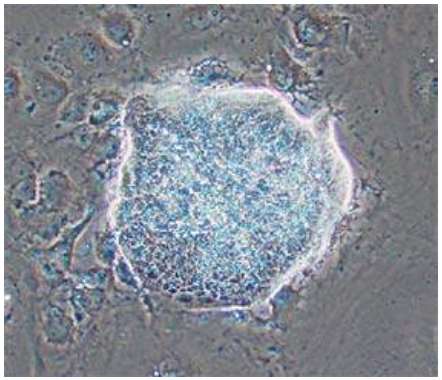
- Cells are measured in two different environments.
- No single cell persists through *both* sets of measurements.
- Self-renewal and differentiation potential cannot both be measured for a single cell.
- A single stem cell can only be identified retrospectively; experimenters ‘don’t know what they’ve got ‘til it’s gone.’

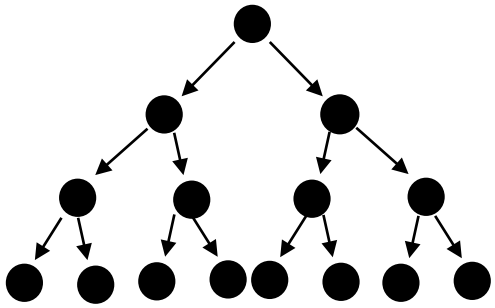
Cell individuation: clear criteria

(i) Cells reproduce by binary division; a parent cell divides to produce two offspring cells.

(ii) An individual cell's existence begins with a cell division event and ends with either a second division event (producing two offspring) or cell death (and no offspring).

(iii) Generations of cells linked by reproductive division form a lineage.





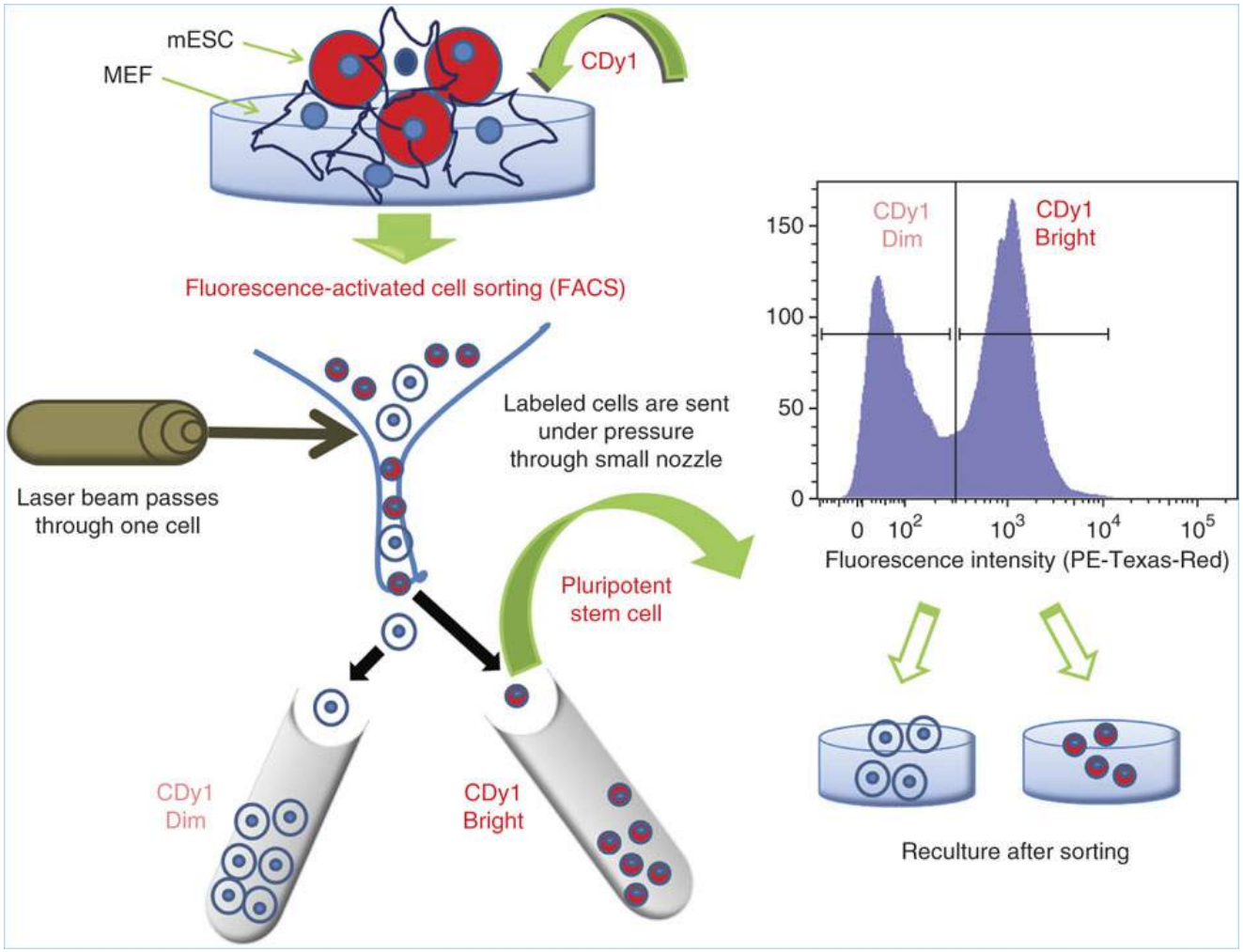
Stem cell individuation:

- The concept of a stem cell involves a cell lineage and differentiated states corresponding to 'future potential.'

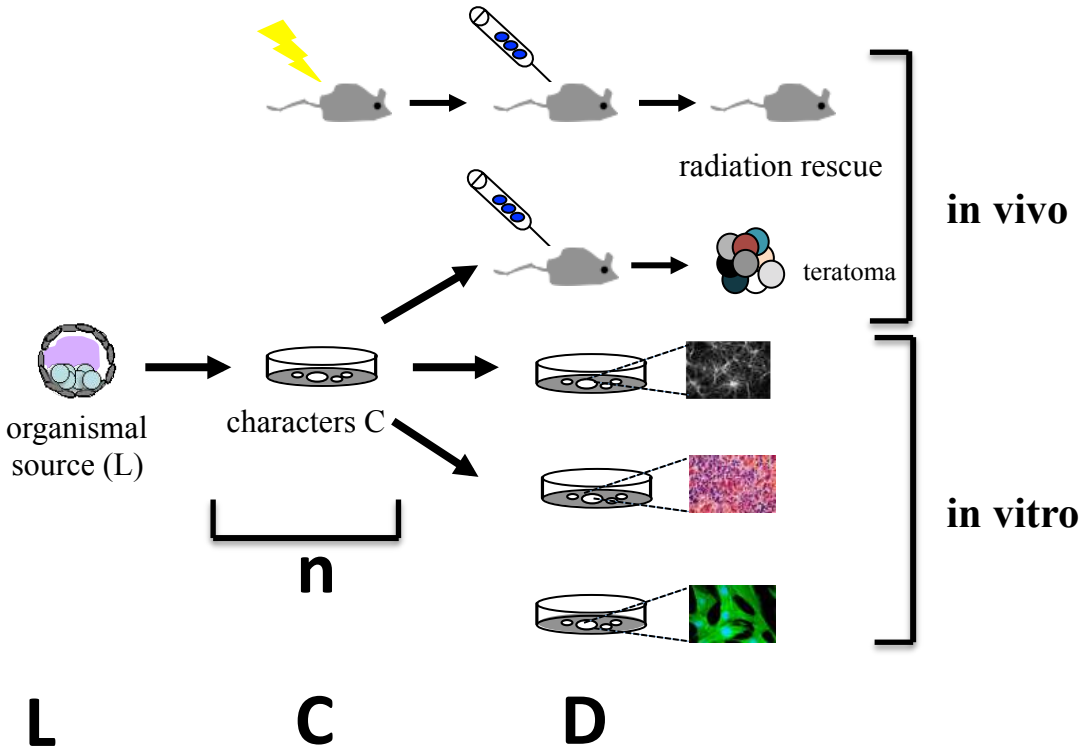
- To show that a given cell is a stem cell, its capacities for self-renewal and differentiation must be realized. But this experiment cannot be performed on a single individual cell.

- Stem cells are individuated at the population level: population of identical stem cells (a clone) allows for a set of perfect replicate experiments – in effect, one tests 'the same cell' across different environments

- So stem cells are individuated relative to relative to a 'homogeneity' assumption about the population of cells used in the experiment.


mESC
MEF
CDy1
Fluorescence-activated cell sorting (FACS)
Laser beam passes through one cell
Labeled cells are sent under pressure through small nozzle
Pluripotent stem cell
CDy1 Dim
CDy1 Bright
150
100
50
0
0
10^2
10^3
10^4
10^5
Fluorescence intensity (PE-Texas-Red)
Reculture after sorting

Stem cell experiments:



Experimental relativity:

- Hypotheses or statements about stem cells are relative to details of the experimental method that specify values for variables in the abstract model, and to the homogeneity assumption for the population of cells tested.

- There is no ‘absolute’ or generally individuated cell type ‘the stem cell.’

- Stem cells are not *cells* –individual ‘units of life’ distinguished from their environment by a bounding membrane.

- Stem cells are the starting points of cell *lineages* associated with particular experimental contexts and hypotheses.

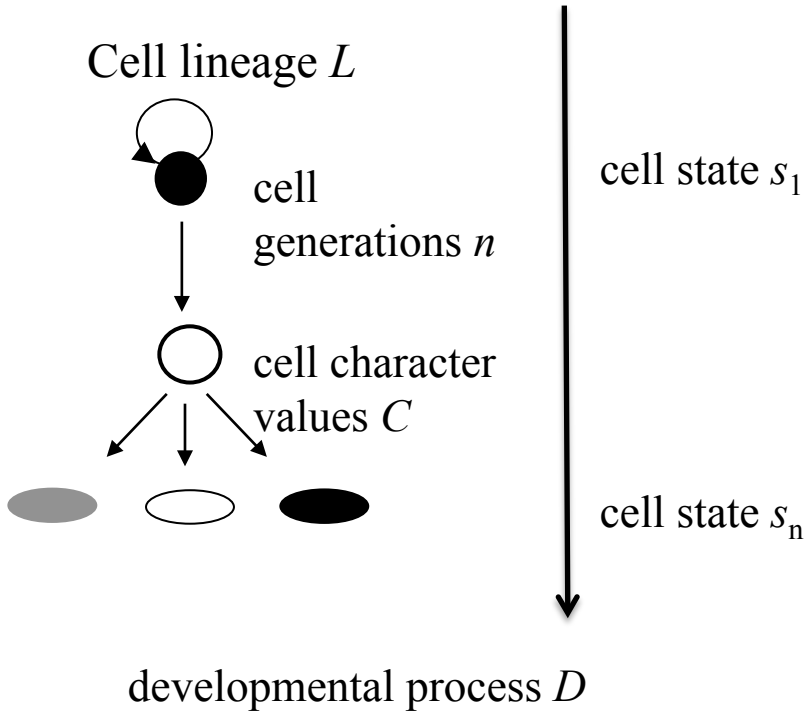
Models of development:

- Stem cell concepts involve substantive assumptions about biological development, at organismal, cellular, and molecular levels.

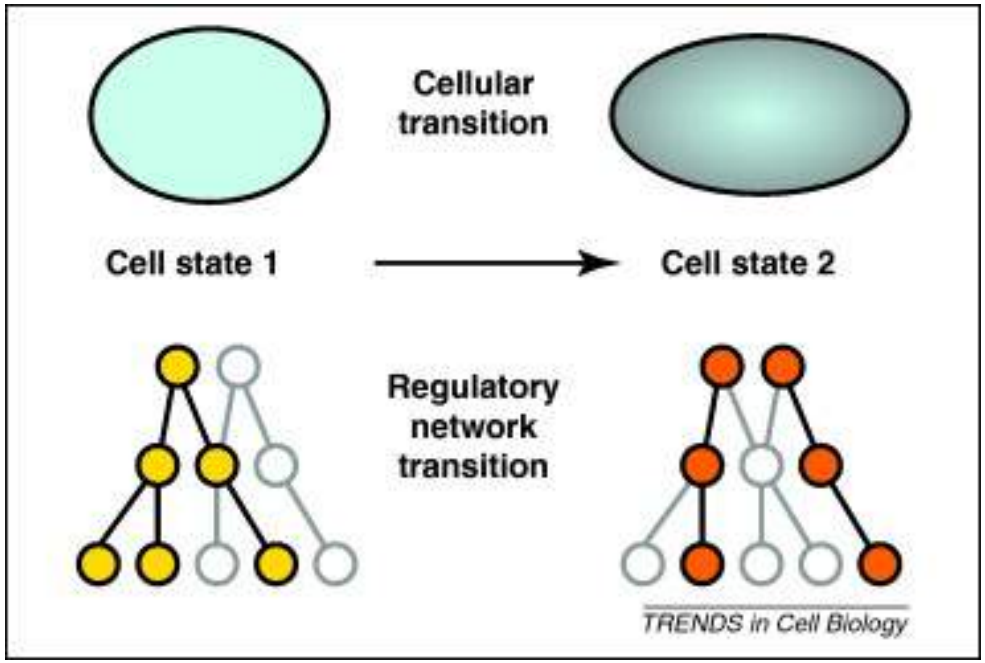
- A stem cell is the origin (or stem) of a cell lineage *L*, generated by *n* cell divisions and organized by comparison of characters *C*, which can be mapped onto a developmental process *D* of ordered cell states $s_1,\ldots s_n$.

- Lineages are modeled using 'tree diagrams' that track relations between generations of reproducing entities.

Developmental process D:

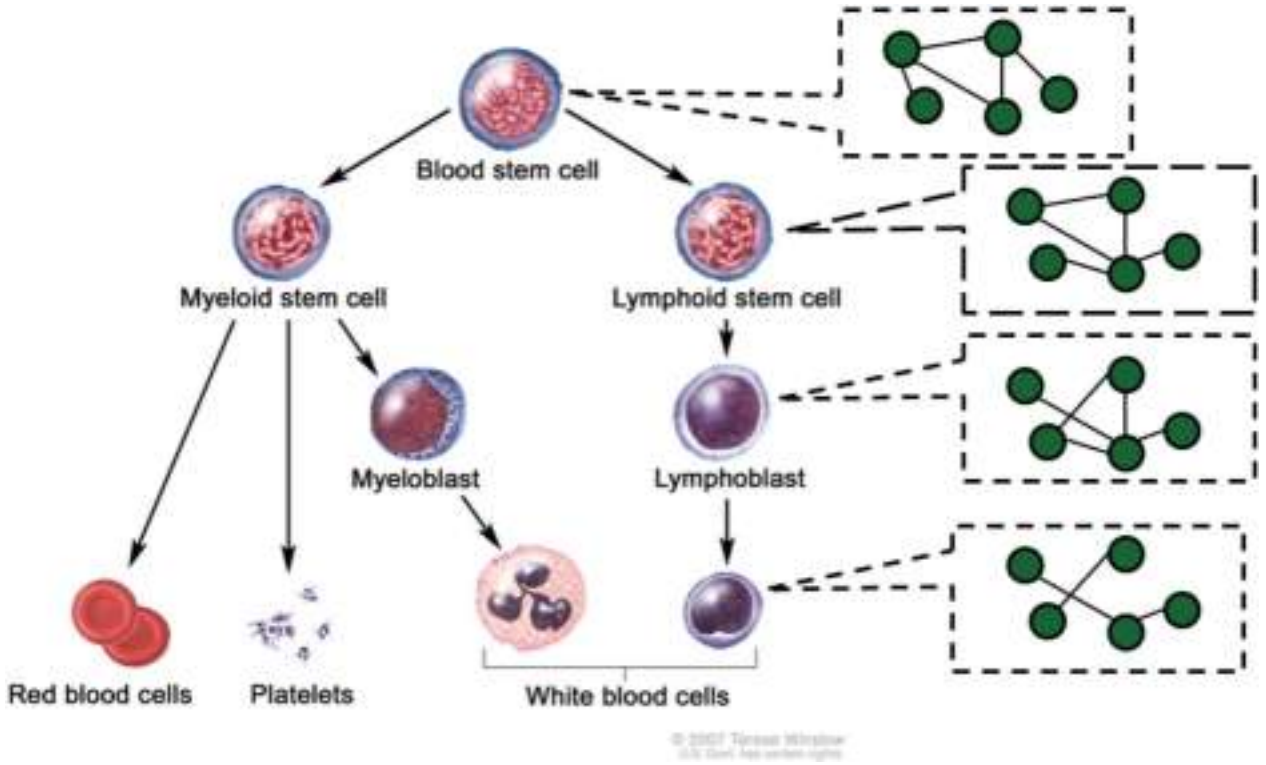


Cell state and cell identity:

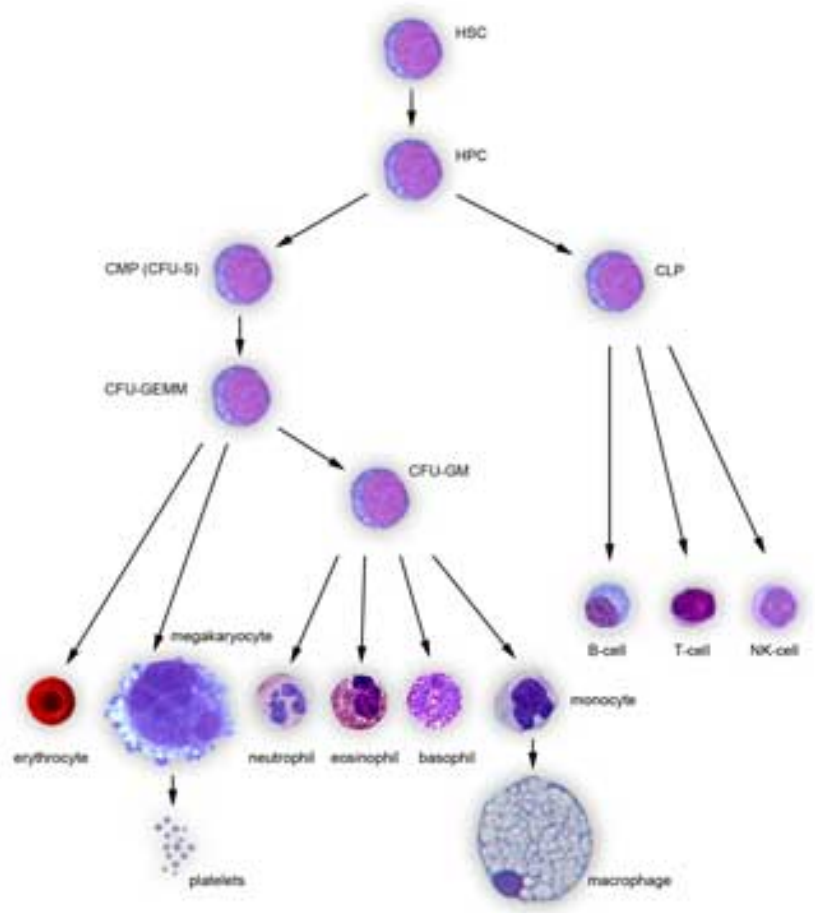


From: Petricka and Benfey (2011, 443)

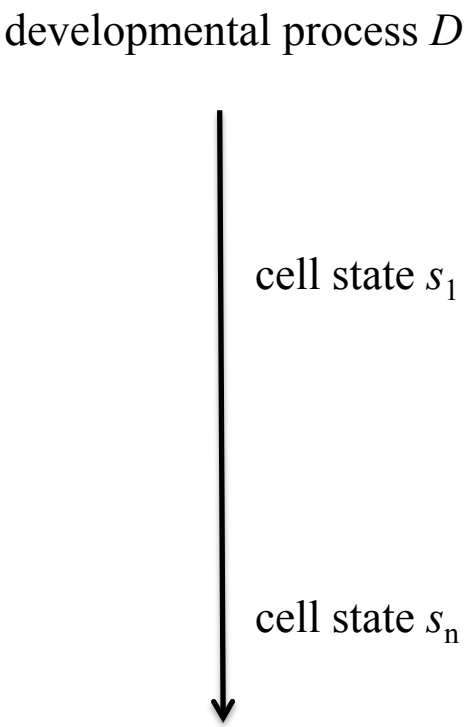
Cell states and regulatory networks:



Cell developmental pathways:

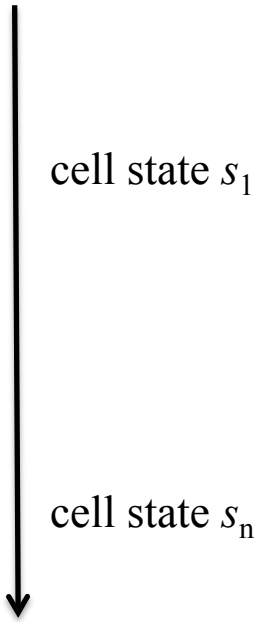


Cell lineage trees: modeling development



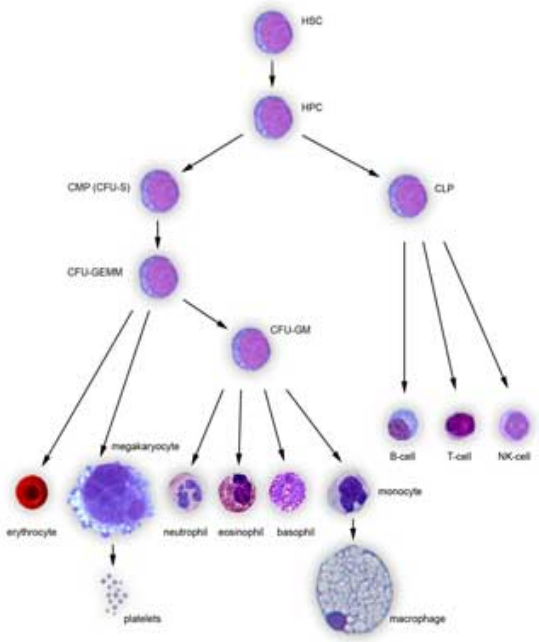
Cell lineage trees: modeling development

developmental process D



cell state s_1

cell state s_n



Cell lineage trees: modeling development

- variable *D*: space of possible tree-models
- Each model has a particular number and arrangement of developmental
  - stages (depth of hierarchy)
  - branch-points (branching cell states)
  - termini (developmental potential)

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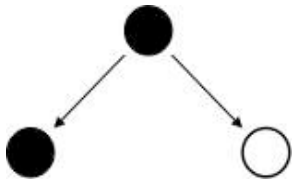

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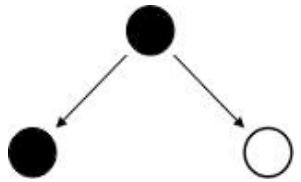
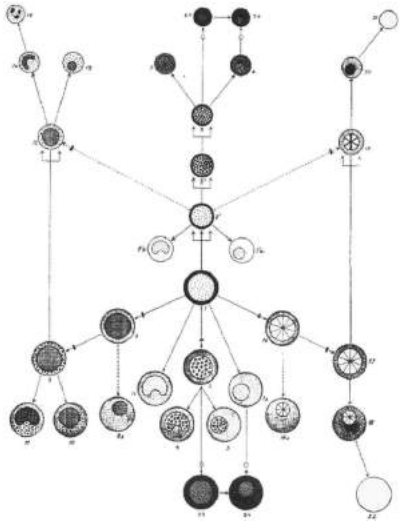
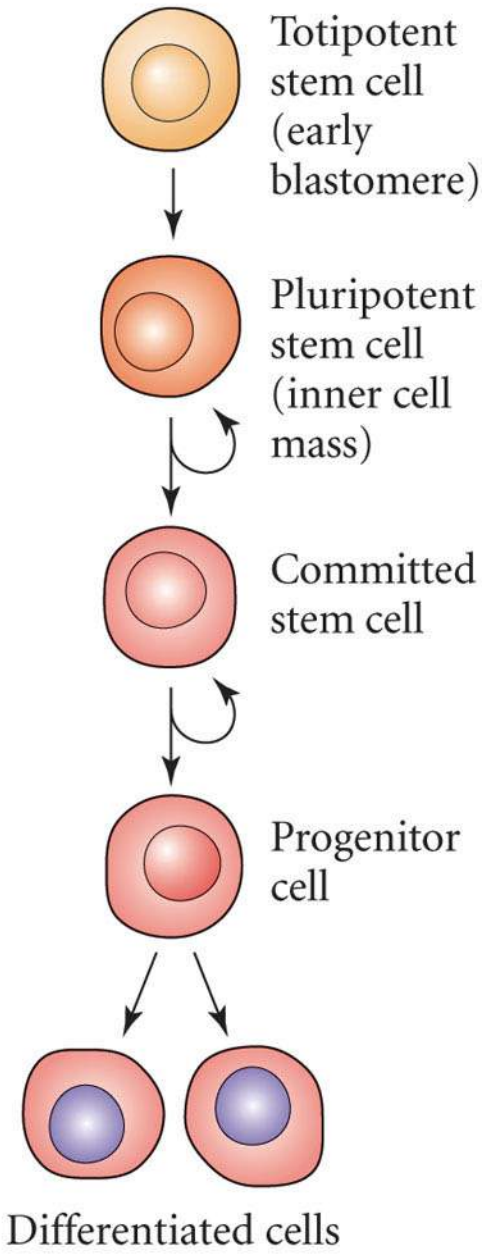
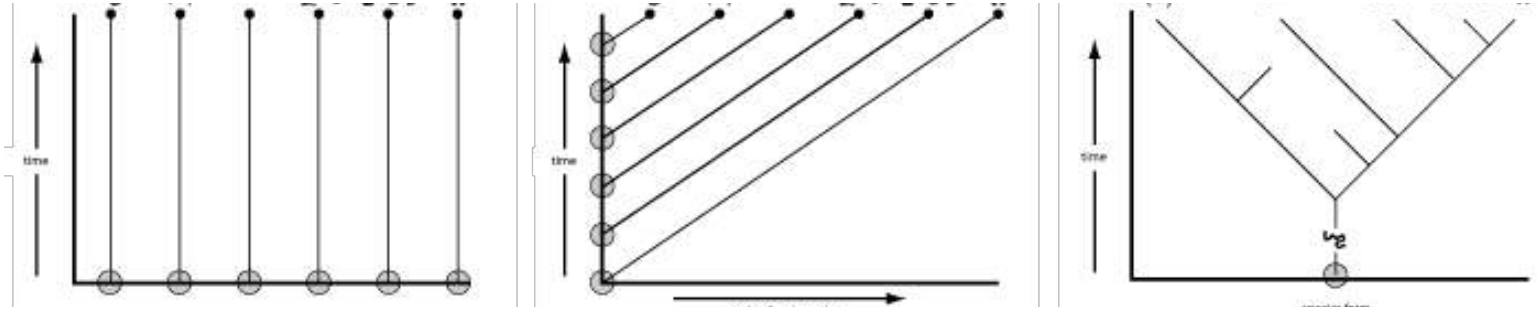




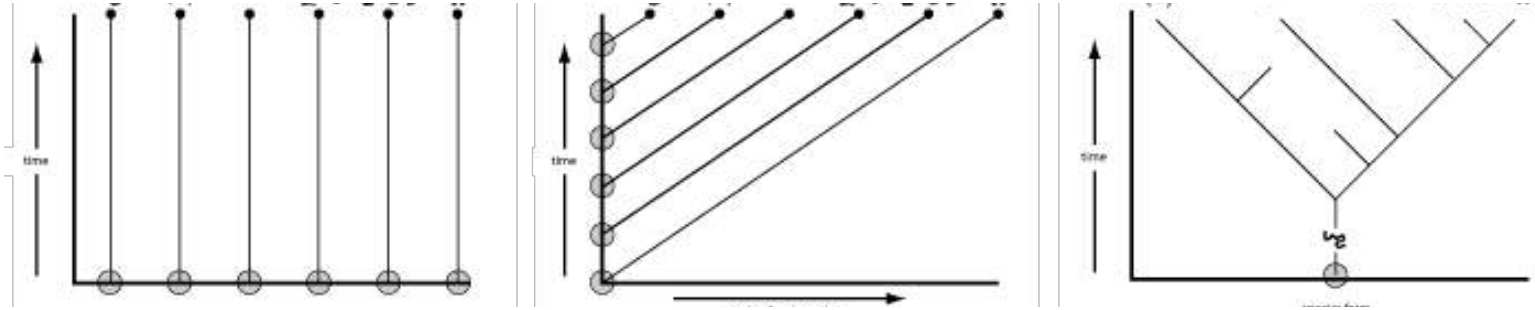


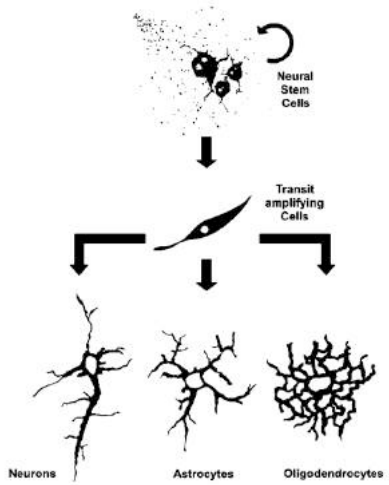
BIOETHICS AND THE NEW EMBRYOLOGY, **Figure 9.1**

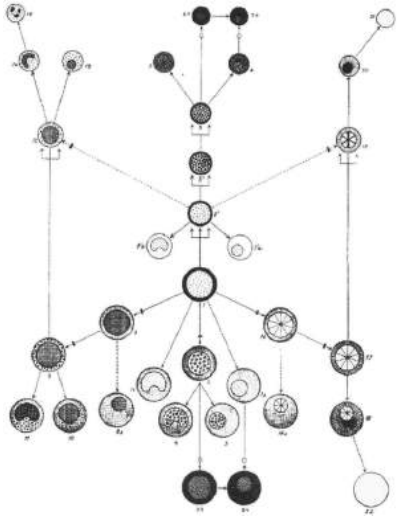
Cell lineage trees: modeling development



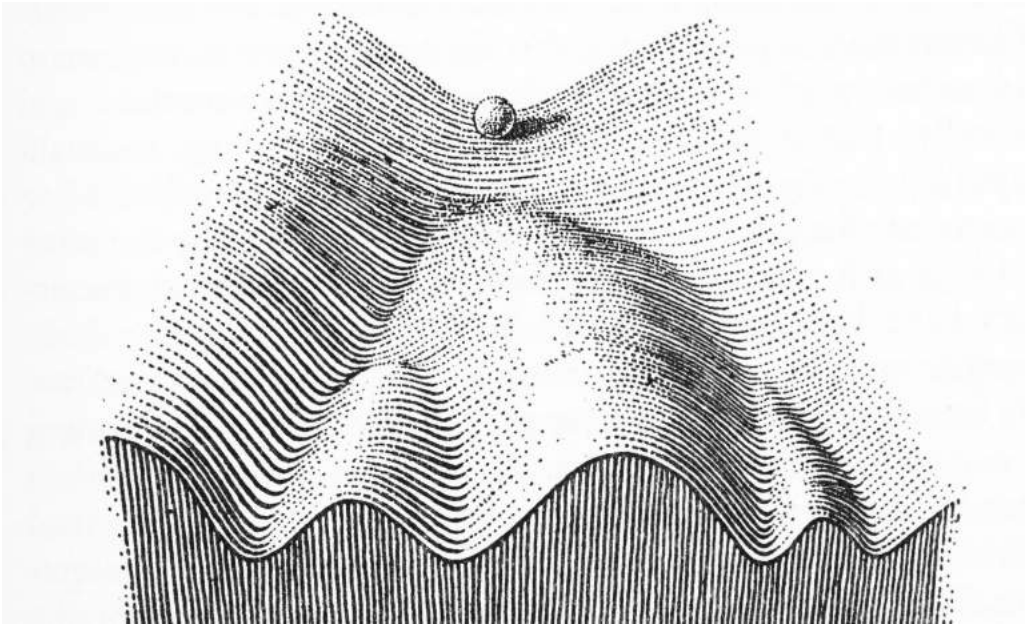
Cell lineage trees: modeling development





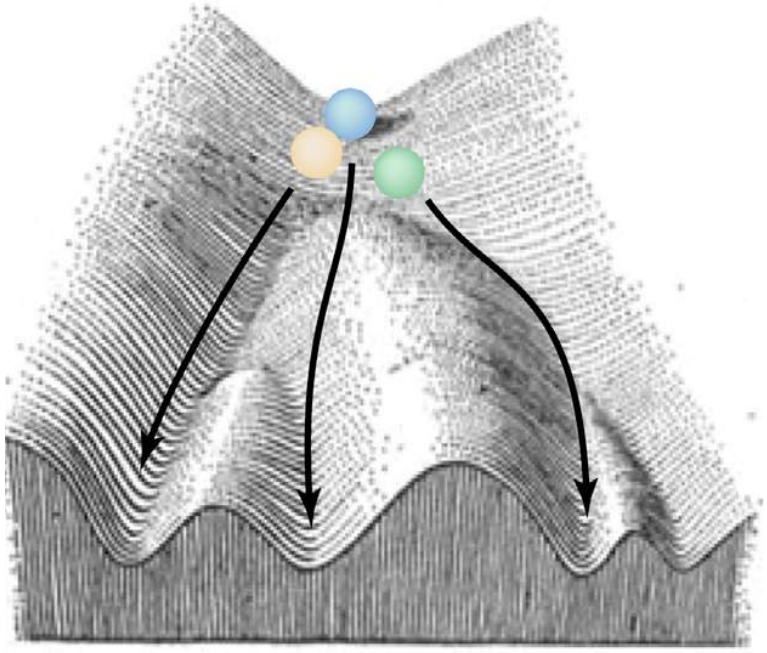


The landscape of development:



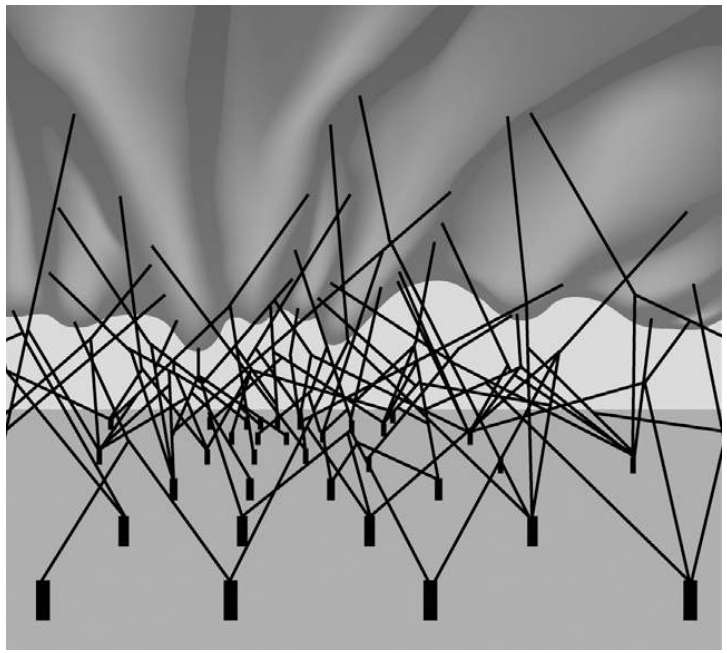
The epigenetic landscape: "…a more or less flat, or rather undulating surface, which is tilted so that points representing later states are lower than those representing earlier ones... Then if something, such as a ball, were placed on the surface, it would run down toward some final end state at the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

The landscape of development:

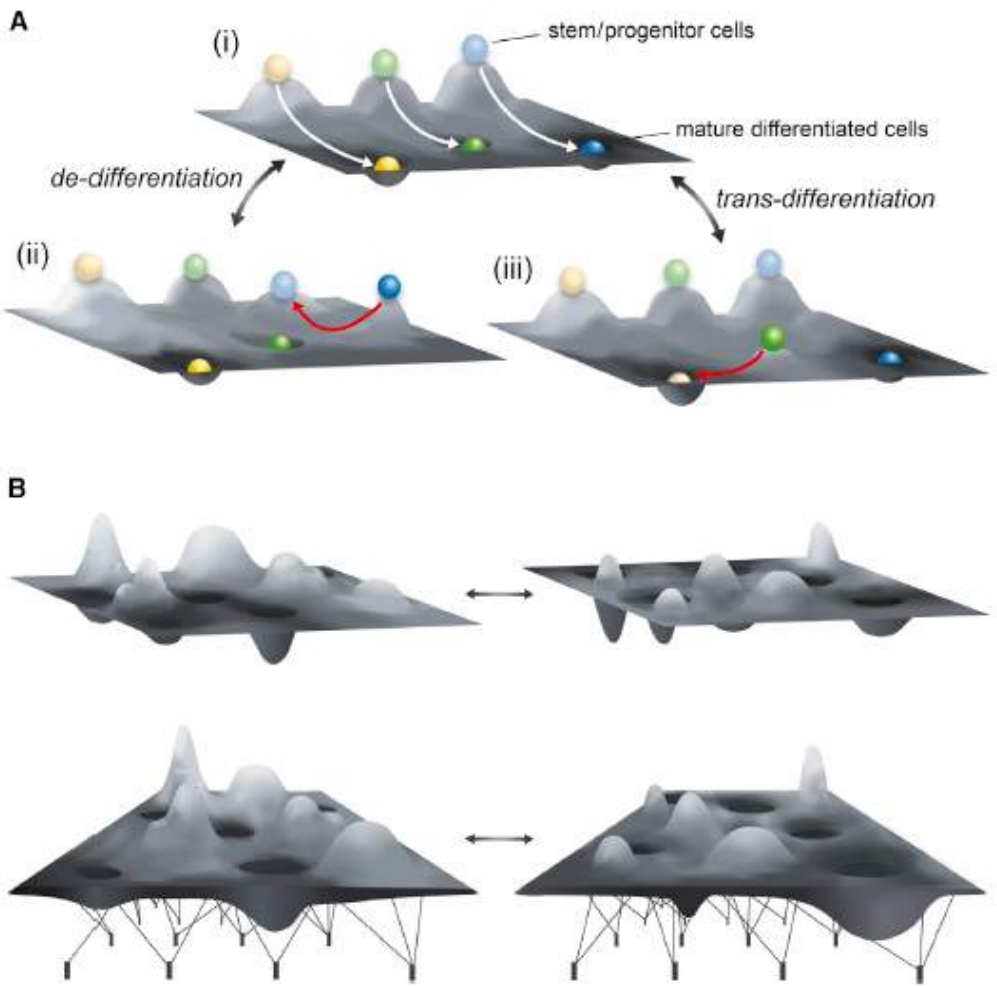


cell lineage level (tree diagram)

underlying molecular network

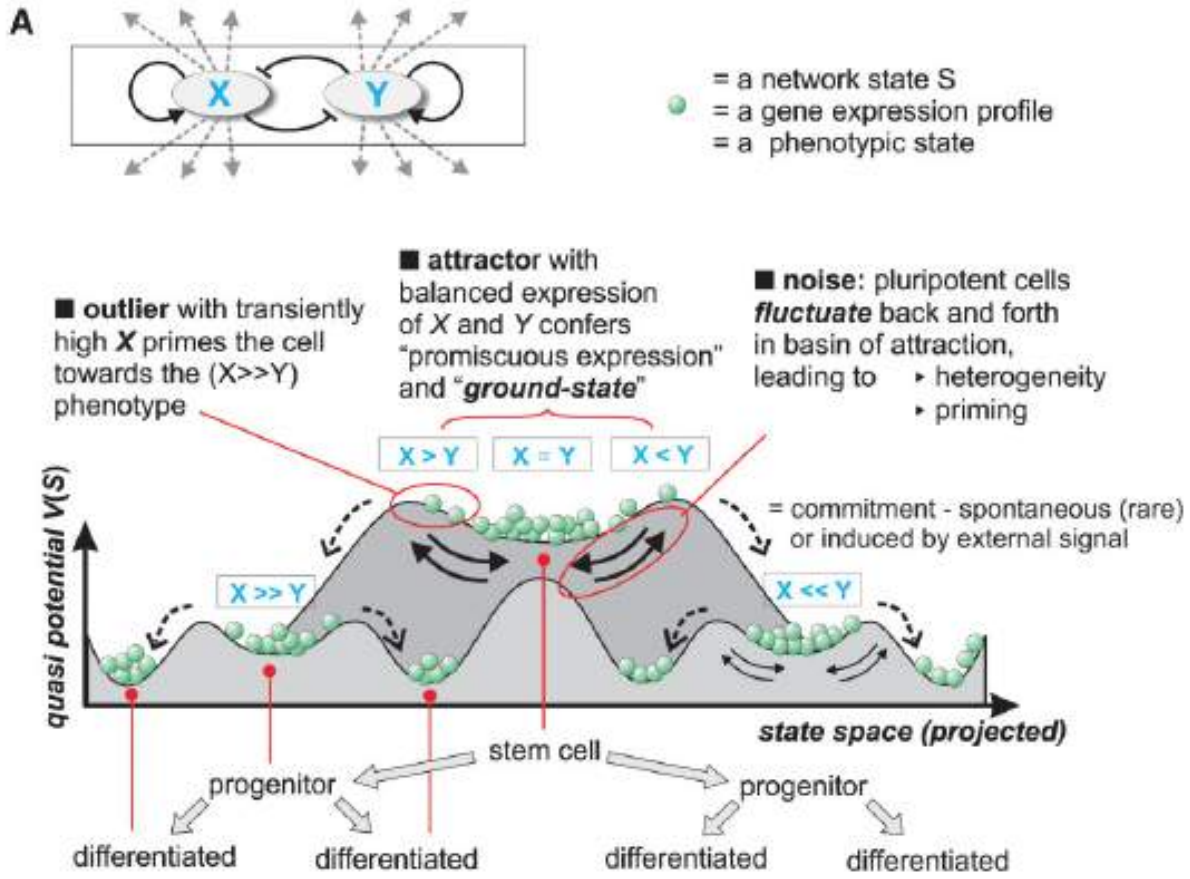


The landscape of development:



From: Rajagopal and Stanger (2016, 136)

Dynamic systems and development:

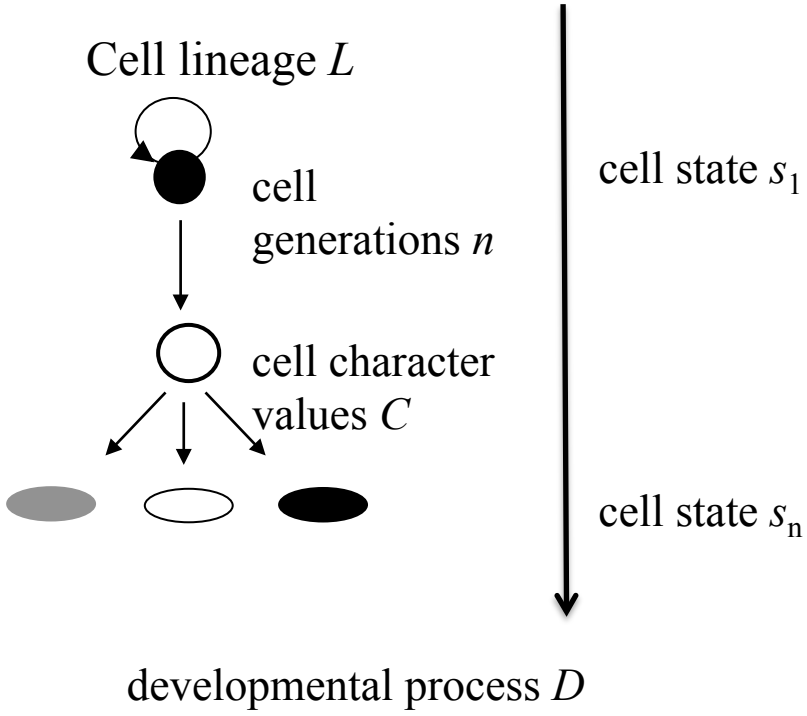


From: Huang (2009, 553)

Cell lineage: organismal source

Lineage L: derived from a multicellular source organism, characterized by:

- species
- developmental stage
- location



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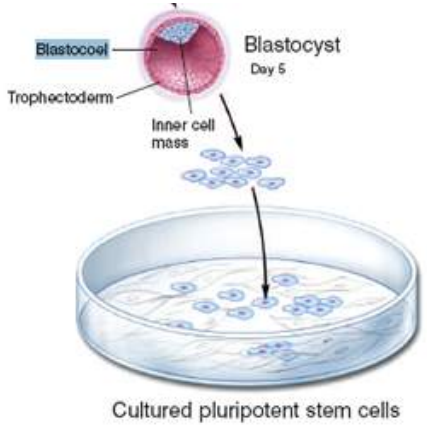
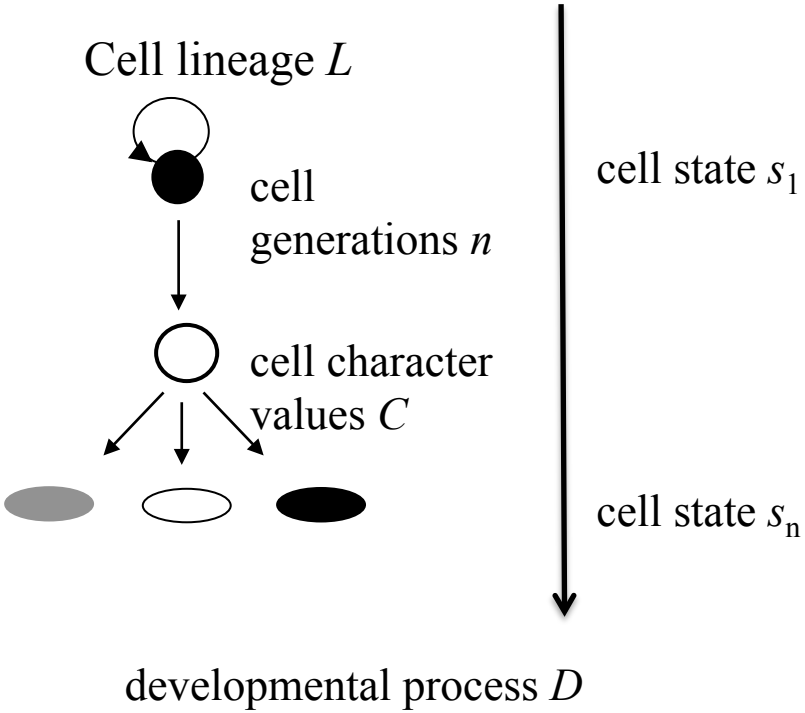
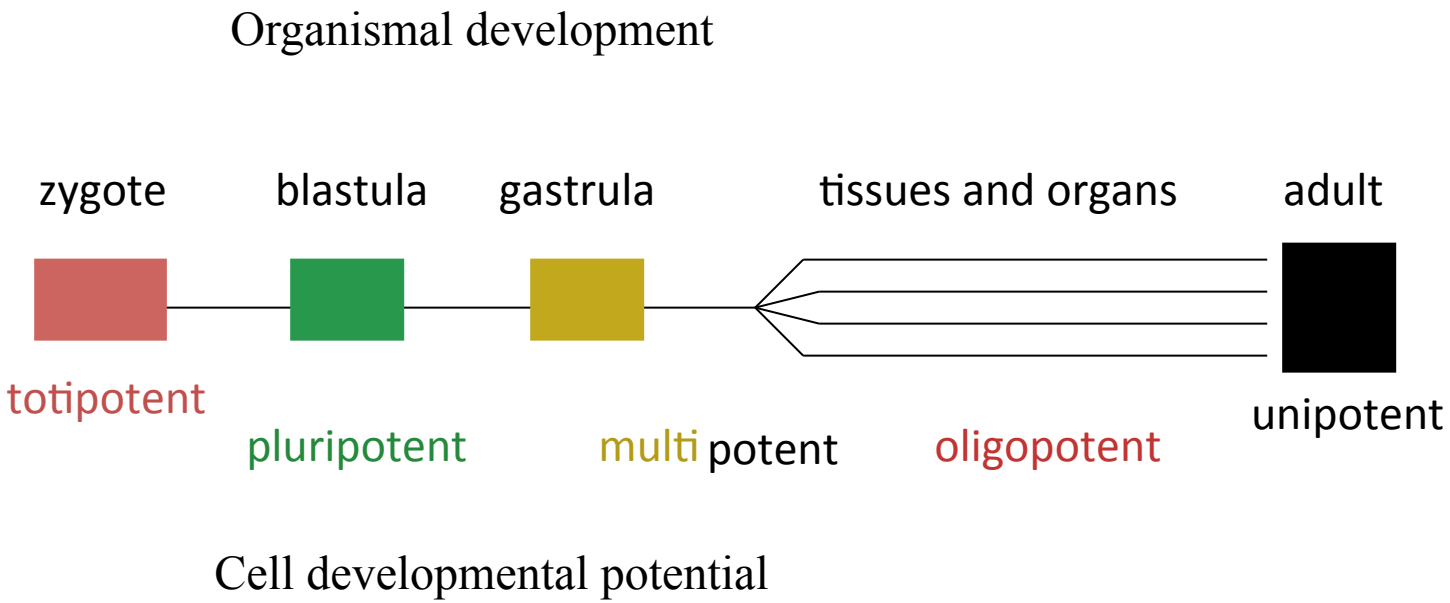
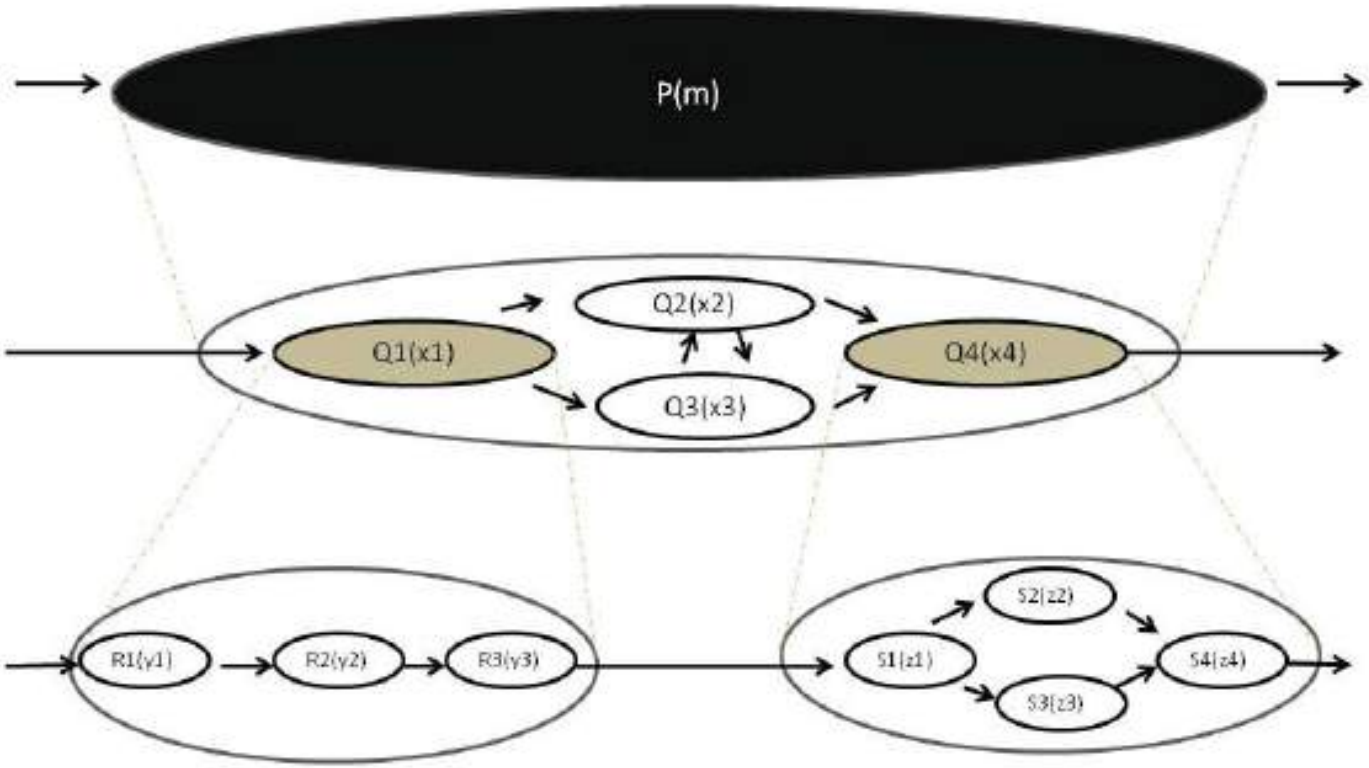




Cell and organismal development:



Multi-level models of development:



organism

cell

molecular network

Concluding summary:

(1) A general account of stem cells - model-based

(2) Stem cells are individuated relative to particular experimental methods.

(3) Stem cells are individuated relative to (provisional) hypotheses about population homogeneity.

(4) Stem cells are the starting points of cell lineages. Tree topology: a general framework for comparing stem cells.

(5) Cell developmental lineages involve changes in cell state (identity). Cell identity: a multi-level concept

(6) Stem cell lineages are derived from and give rise to whole organisms. A multi-level account of development spanning molecular-cell-organism levels is lacking.

Thanks