dynamic processes in cells (a systems approach to biology)

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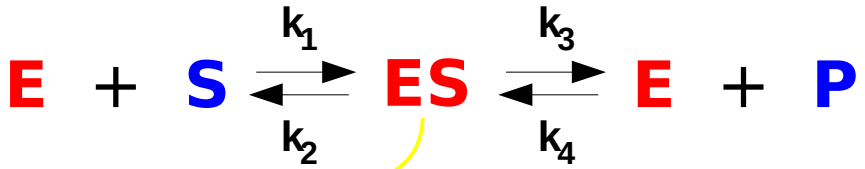
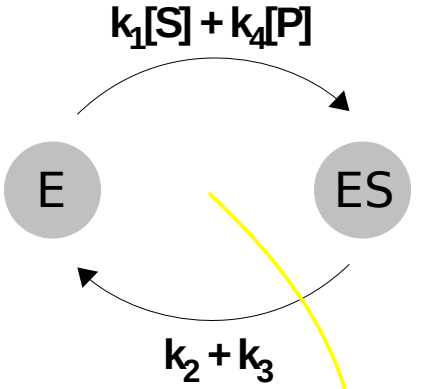
example

reversible Michaelis-Menten scheme





nonlinear dynamics

$$\frac{d[E]}{dt} = (k_2 + k_3)[ES] - k_1[E][S] - k_4[E][P]$$

$$\frac{d[ES]}{dt} = -(k_2 + k_3)[ES] + k_1[E][S] + k_4[E][P]$$

linear Laplacian dynamics

$$\frac{d}{dt}\begin{pmatrix} [E] \\ [ES] \end{pmatrix} = \begin{pmatrix} -(k_1[S] + k_4[P]) & (k_2 + k_3) \\ (k_1[S] + k_4[P]) & -(k_2 + k_3) \end{pmatrix}\begin{pmatrix} [E] \\ [ES] \end{pmatrix}$$

uncoupling condition: a concentration appearing in a label cannot be that of a vertex in the graph (but it can be that of a slow variable or a fast variable that is not a vertex in the graph). this can be dispensed with in some contexts

elimination of internal complexity

when G is strongly connected, so that $\ker \mathcal{L}(G) = \langle \rho \rangle$

if there is a steady state $x^* \in \ker \mathcal{L}(G)$

$$x^* = \lambda \rho \qquad \begin{pmatrix} x_1^* \\ \vdots \\ x_n^* \end{pmatrix} = \lambda \begin{pmatrix} \rho_1 \\ \vdots \\ \rho_n \end{pmatrix}$$

then each of the x_i^* can be **eliminated**

reference node

$$x_i^* = \left(\frac{\rho_i}{\rho_1 + \cdots + \rho_n} \right) x_{tot} \qquad x_i^* = \frac{\rho_i}{\rho_1} x_1^*$$

rational expressions

calculating ρ

1. for any strongly connected graph, ρ can be calculated in terms of the labels, without having to know their numerical values, by the **Matrix-Tree Theorem**.

2. if the steady state of the system is one of thermodynamic equilibrium, then **detailed balance** holds and ρ can be calculated more simply, using a single path in the graph, without having to enumerate all the spanning trees.

3. this gives the same answer as **equilibrium statistical mechanics**.

$$x_i^* = \left(\frac{\rho_i}{\rho_1 + \cdots + \rho_n} \right) x_{tot}$$

partition function

4. the linear framework offers a way to also do **non-equilibrium statistical mechanics**.

calculating ρ using the MTT

Matrix-Tree Theorem: whenever G is strongly connected

$$\ker \mathcal{L}(G) = \langle \rho \rangle \qquad \rho_i = \sum_{T \in \Theta_i(G)} \left(\prod_{j \xrightarrow{a} k \in T} a \right)$$

positive

$\Theta_i(G) =$ set of spanning trees rooted at *i*

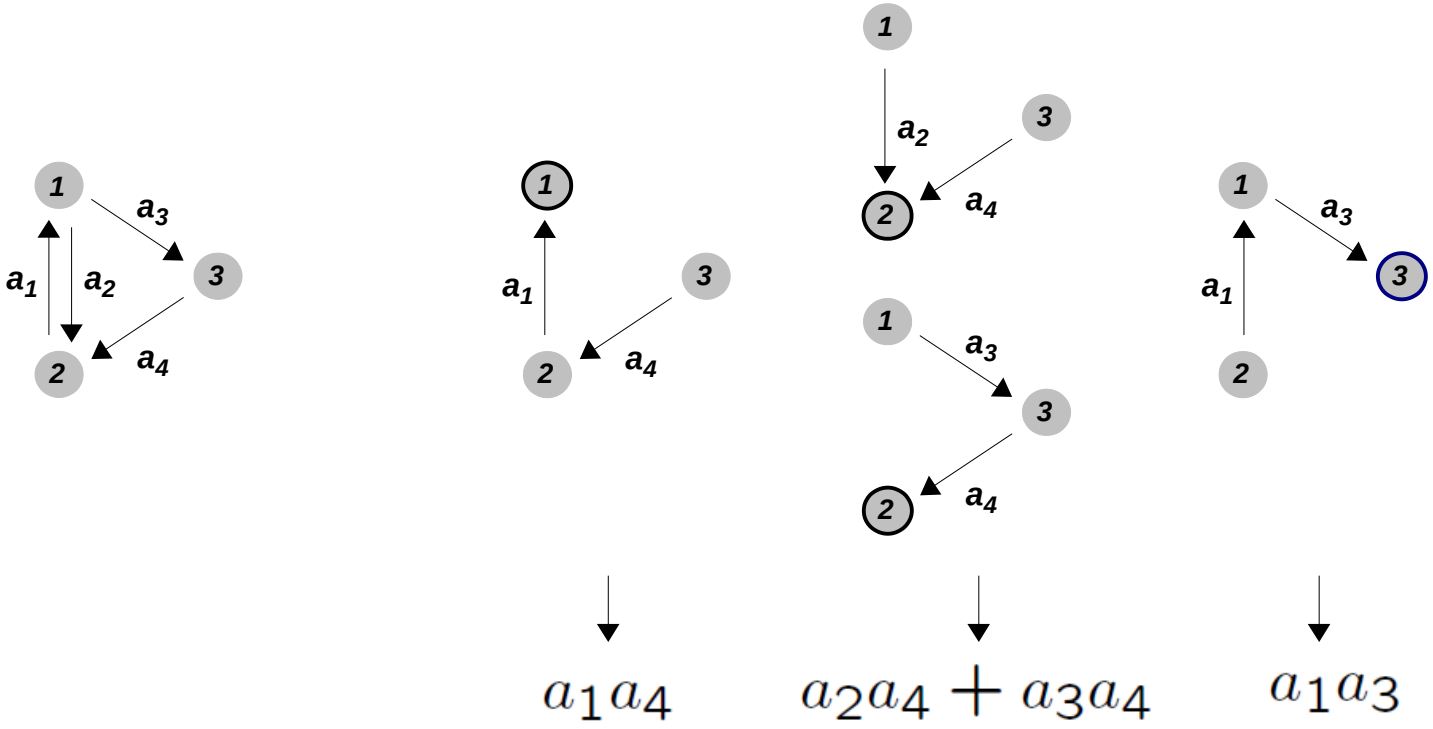
rooted spanning tree – a sub-graph T of G which

SPANS G	–	every node of G is also a node of T
is a **TREE**	–	T has no cycles, ignoring edge directions
is **ROOTED** at *i*	–	*i* is the only node of T with no outgoing edges

Bill Tutte, *"The dissection of equilateral triangles into equilateral triangles"*, Proc Camb Phil Soc **44**:463-82 1948

Mirzaev & Gunawardena, "*Laplacian dynamics on general graphs*", Bull Math Biol **75**:2118-49 2013 – Appendix gives a proof

spanning trees and the MTT



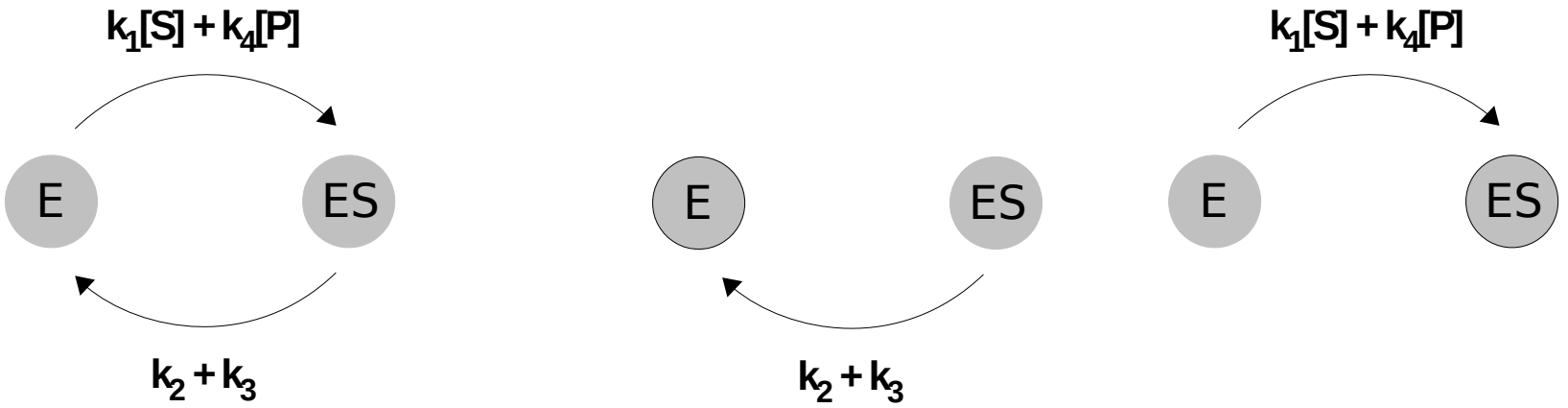
$$\begin{pmatrix} -(a_2+a_3) & a_1 & 0 \\ a_2 & -a_1 & a_4 \\ a_3 & 0 & -a_4 \end{pmatrix} \begin{pmatrix} a_1a_4 \\ (a_2+a_3)a_4 \\ a_1a_3 \end{pmatrix} = 0$$

Laplacian ρ

for a proof, see the Appendix in Mirzaev & Gunawardena, Bull Math Biol **75**:2118-49 2013

reversible michaelis-menten

enumeration of spanning trees

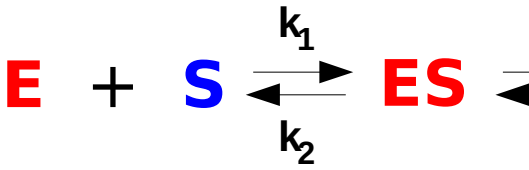


$$\rho = \begin{pmatrix} k_2 + k_3 \\ k_1[S] + k_4[P] \end{pmatrix}$$

elimination

$$[ES] = \left(\frac{k_1[S] + k_4[P]}{k_2 + k_3 + k_1[S] + k_4[P]} \right) E_{tot} \quad [E] = \left(\frac{k_2 + k_3}{k_2 + k_3 + k_1[S] + k_4[P]} \right) E_{tot}$$

reversible michaelis-menten



$$\frac{d[P]}{dt} = k_3[ES] - k_4[E][P]$$

substitute steady-state values from MTT

$$\frac{d[P]}{dt} = \left(\frac{V_f[S]/K_f - V_r[P]/K_r}{1 + [S]/K_f + [P]/K_r} \right)$$

$$V_f = k_3 E_{tot} \quad V_r = k_2 E_{tot} \qquad K_f = \frac{k_2 + k_3}{k_1} \quad K_r = \frac{k_2 + k_3}{k_4}$$

forward & reverse maximal rates

forward & reverse Michaelis-Menten constants

Athel Cornish-Bowden, **Fundamentals of Enzyme Kinetics**, 2nd edition, Portland Press, 2001

in summary

the examples discussed previously can all be treated in this way

there is an underlying graph whose Laplacian dynamics describes the fast sub-system

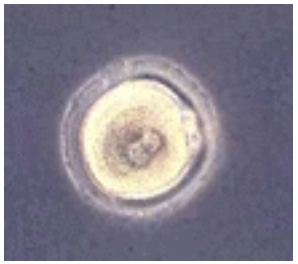
the graph is strongly connected and satisfies the uncoupling condition

the quantities of interest can be calculated by eliminating the fast variables in terms of the labels, as described

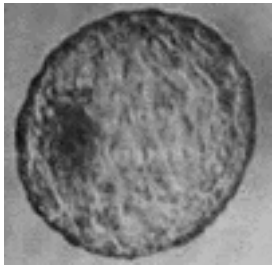
Gunawardena, *"A linear framework for timescale separation in nonlinear biochemical systems"*, PLoS ONE **7**:e36321 2012; Gunawardena, *"Time-scale separation: Michaelis and Menten's old idea, still bearing fruit"*, FEBS J **281**:473-88 2014.

4. cellular identity & gene regulatory networks

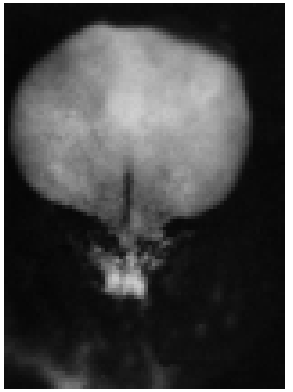
human embryonic development



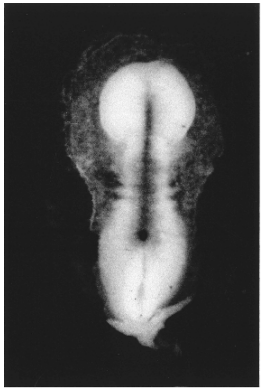
stage 1, day 1
totipotent zygote or
fertilised oocyte



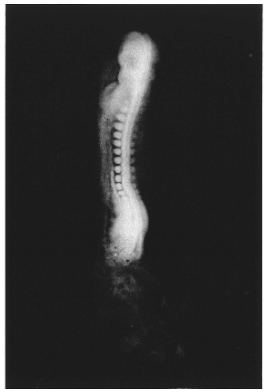
stage 3, day 4-5
pre-implantation
blastocyst



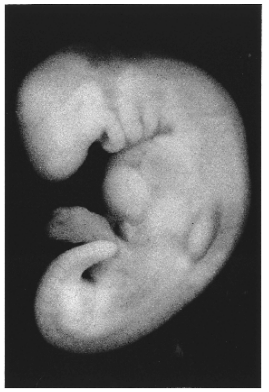
stage 7, day 15-17
gastrulation, notochord



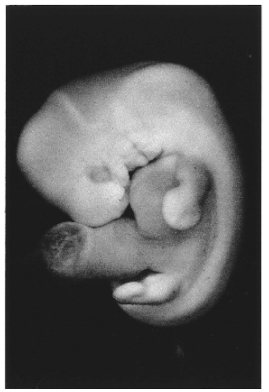
stage 9, day 19-21
neural folds, somites 1-3



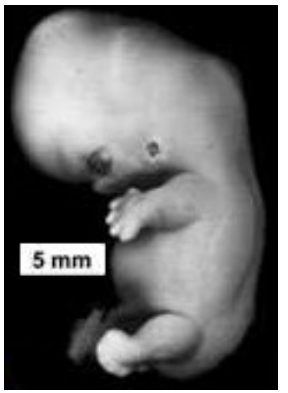
stage 11, day 23-26
13 somites



stage 13, day 28-32
leg buds, pharyngeal
arches, lens placode



stage 17, day 42-44
fingers emerging

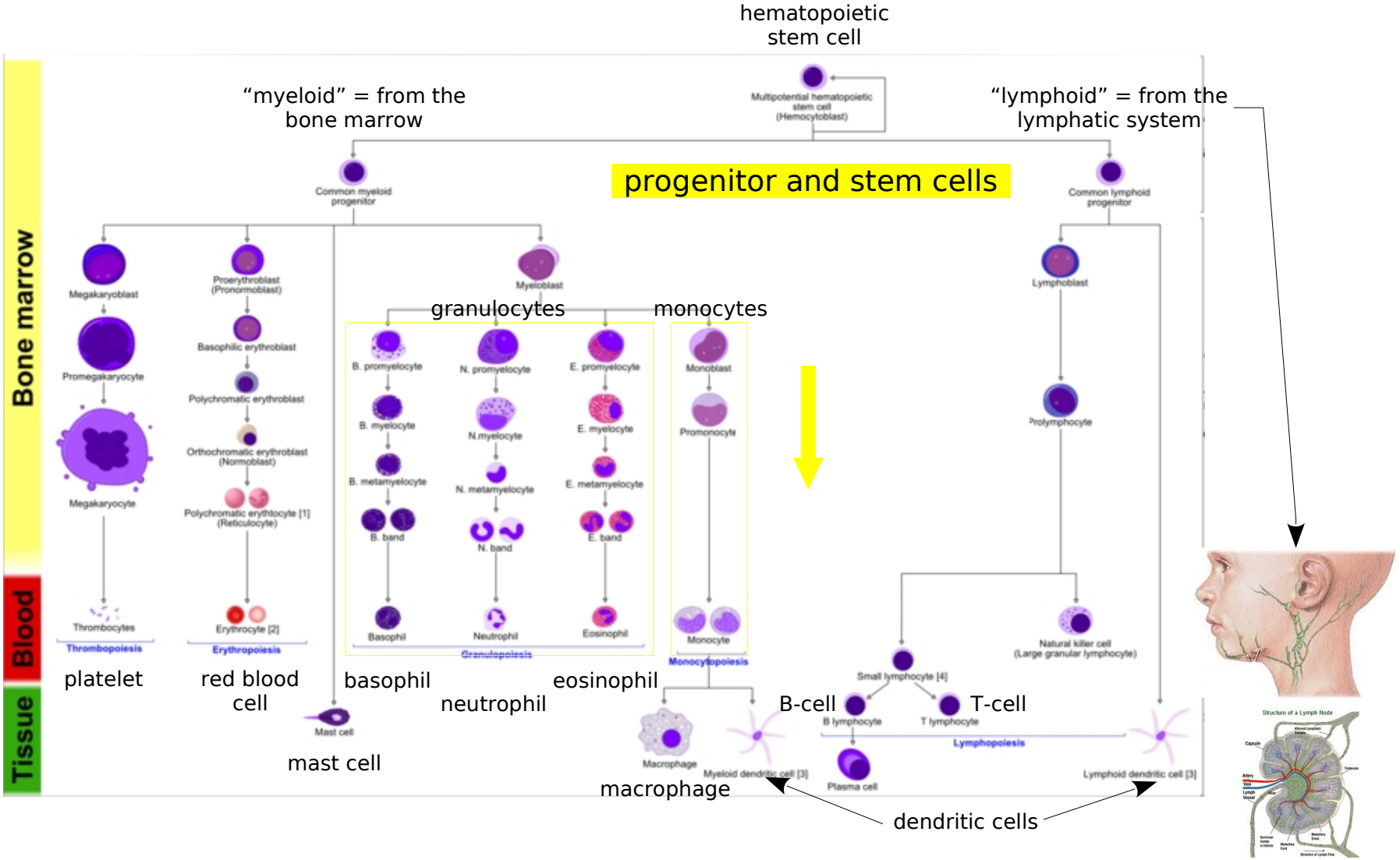


stage 19, day 48-51
fingers emerged, bone
has started to form

UNSW Carnegie Stages
http://php.med.unsw.edu.au/embryology/index.php?title=Embryonic_Development
Kyoto Human Embryo Visualization Project http://bird.cac.med.kyoto-u.ac.jp/index_e.html

hierarchical construction of cellular identity

in the blood (“hematopoietic”) system, which undergoes continuous renewal

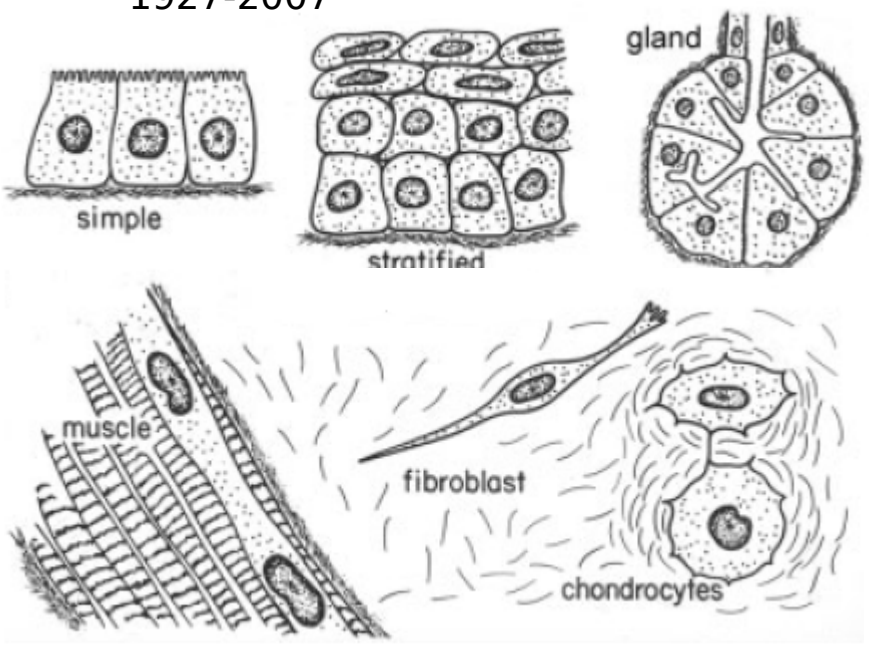


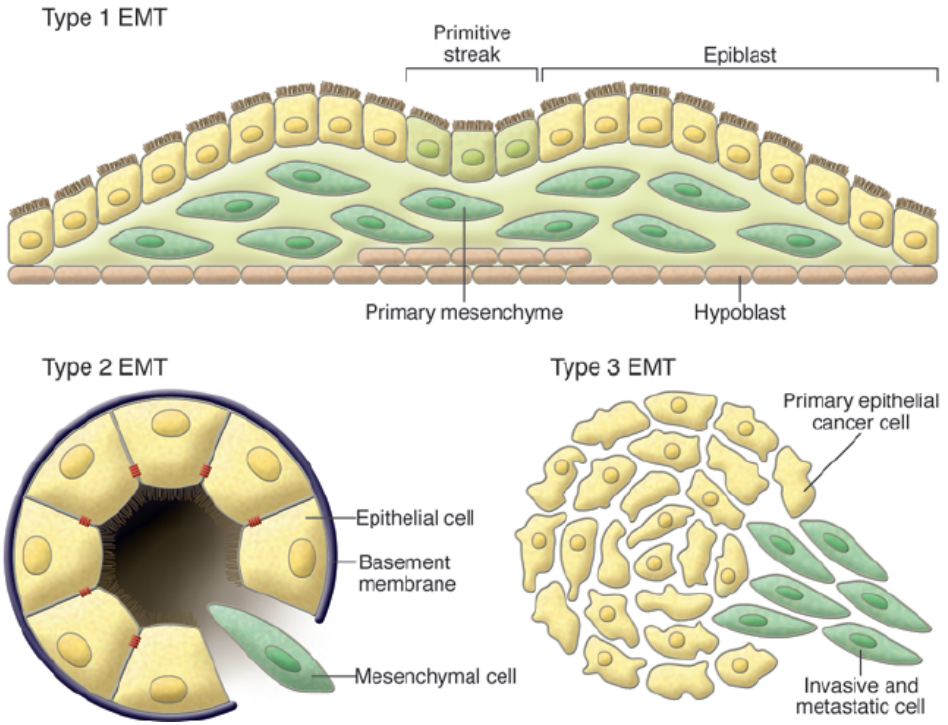
cellular identity is both stable and plastic

Elizabeth “Betty” Hay
1927-2007

EMT – epithelial-mesenchymal transition

MET – mesenchymal-epithelial transition





Hay, *“The mesenchymal cell, its role in the embryo and the remarkable signaling mechanisms that create itr”*, Dev Dyn **233**:706-20 2005; Kalluri, Weinberg, *“The basics of epithelial-mesenchymal transition”*, J Clin Invest, **119**:1420-8, 2009.

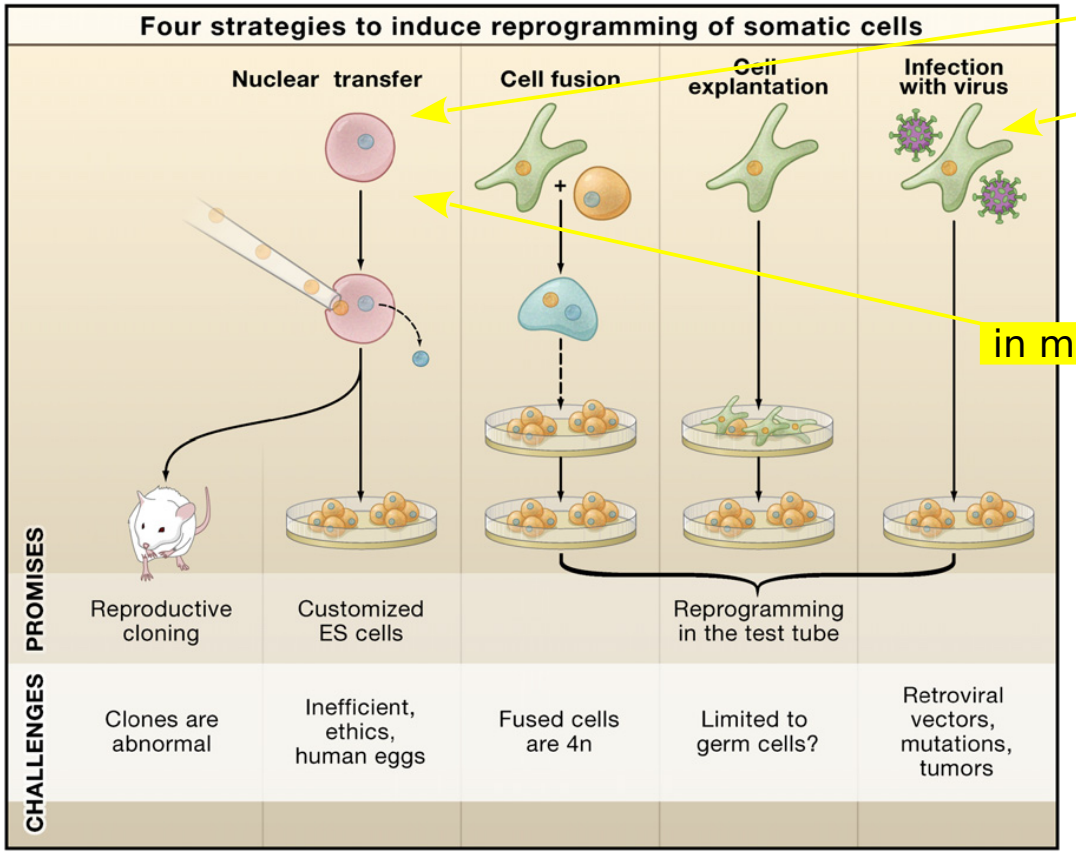
cellular identity can be re-programmed – I

John Gurdon (1933-)
Shinya Yamanaka (1962-)

in frogs

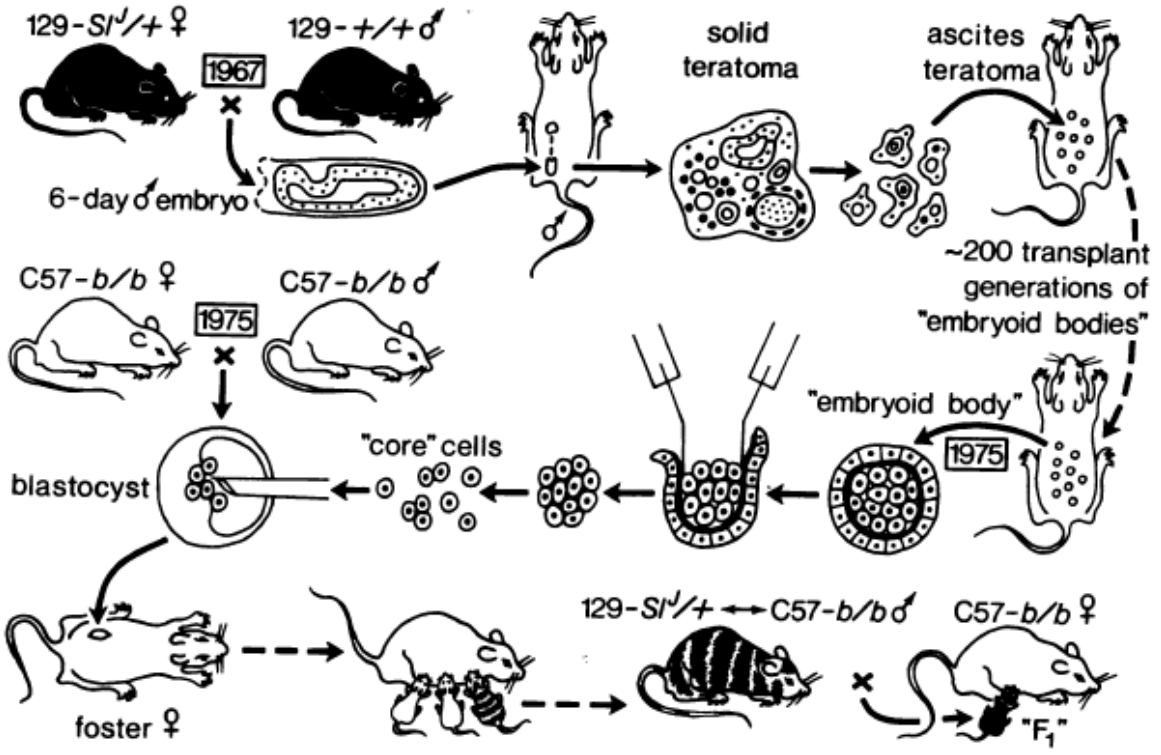
in mammals

(l to r)
Keith Campbell (1954-2012)
Dolly the Sheep (1996-2002)
Fay Weldon
Ian Wilmut (1944-)



Jaenisch, Young, *"Stem cells, the molecular circuitry of pluripotency and nuclear reprogramming"*, Cell, **132**:567-82, 2008; Lensch, Mummery, *"From stealing fire to cellular reprogramming: a scientific history leading to the 2012 Nobel Prize"*, Stem Cell Reports **1**:5-17, 2013

cellular identity can be re-programmed – II

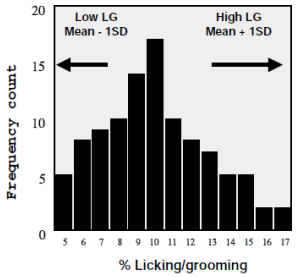


Beatrice Mintz
1921-

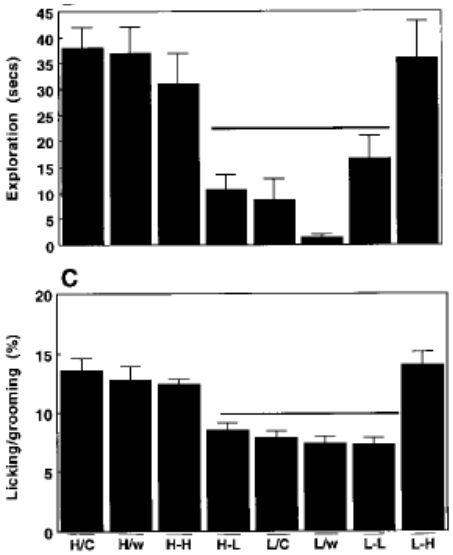
"The results also furnish an unequivocal example in animals of a non-mutational basis for transformation to malignancy and of reversal to normalcy."

Mintz, Illmensee, *"Normal genetically-mosaic mice produced from malignant teratocarcinoma cells"*, PNAS, **72**:3585-9, 1975; Bissell, Radisky, *"Putting tumours in context"*, Nat Rev Cancer, **1**:46-54, 2001

cellular behaviour can also be re-programmed



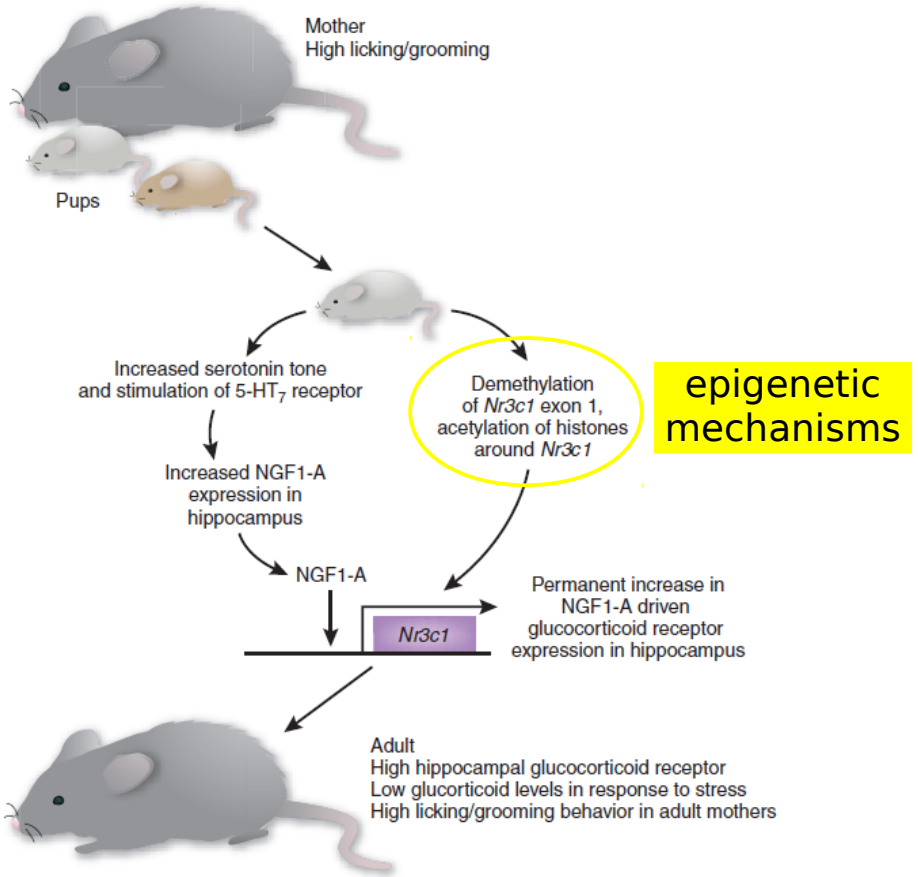
adult female offspring



open field exploration

licking/grooming

cross-fostering group



Francis, Diorio, Liu, Meaney, *"Nongenomic transmission across generations of maternal behaviour and stress responses in the rat"*, Science **286**:1155-8 1999; Szyf, Weaver, Champagne, Diorio, Meaney, *"Maternal programming of steroid receptor expression and phenotype through DNA methylation in the rat"*, Frontiers in Neuroendocrinology **26**:139-62 2005