dynamic processes in cells (a systems approach to biology)

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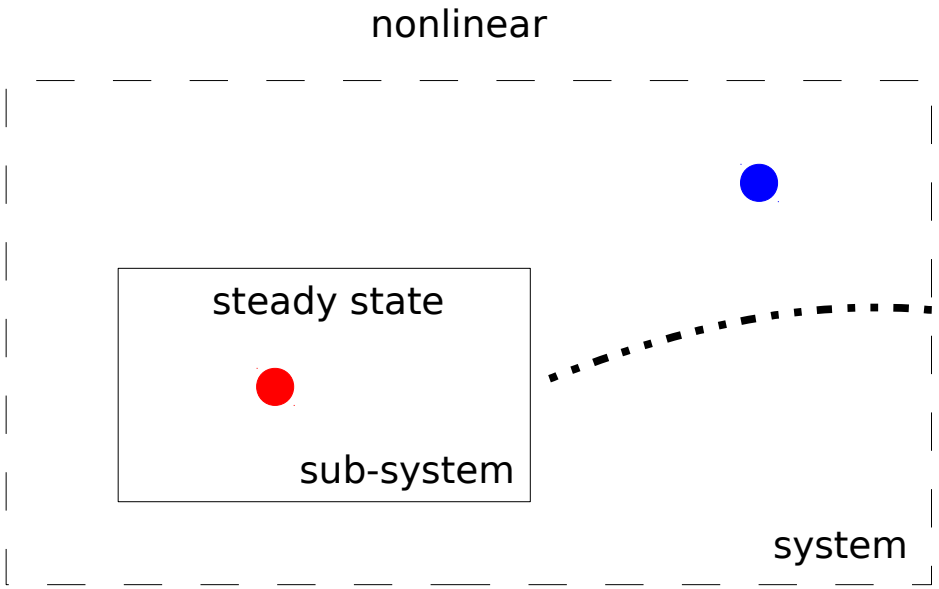
harvard medical school

lecture 7

29 september 2015

time-scale separation



eliminate the complexity arising from the fast components

$$\mathbf{E} + \mathbf{S} \rightleftharpoons \mathbf{ES} \rightarrow \mathbf{E} + \mathbf{P}$$

elimination

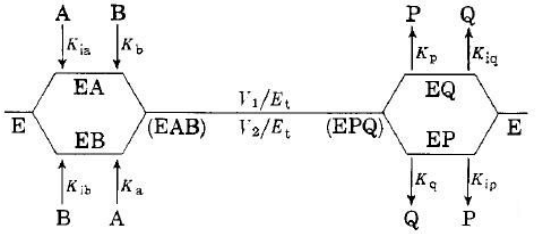
rational expression

$$\frac{d[P]}{dt} = \frac{V_{max}[S]}{K_M + [S]}$$

widely used in biology

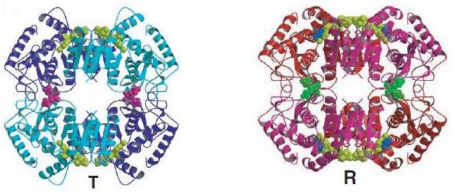
enzyme kinetics

Gulbinsky & Cleland, Biochemistry **7**:566-75 1968;
King & Altman, J Phys Chem **60**:1375-8 1956



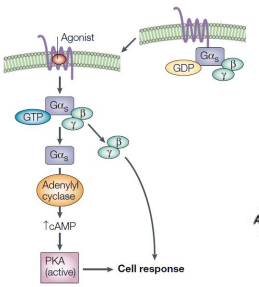
protein allostery

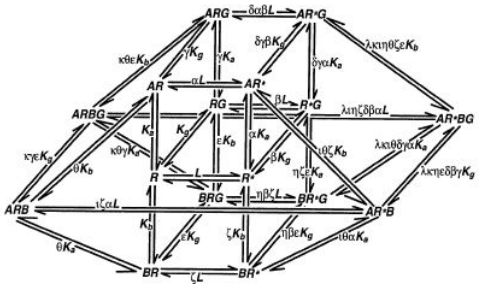
Monod, Wyman & Changeux, J Mol Biol **12**:88-188 1965
Koshland, Nemethy & Filmer, Biochem **5**:365-85 1966



G-protein coupled receptors (GPCRs) and receptor pharmacology

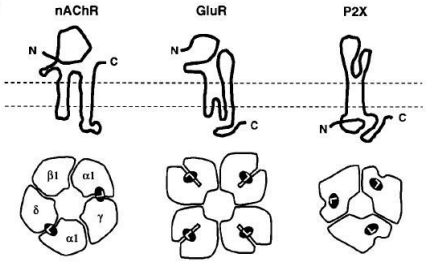
Samama, Cotecchia, Cost, Lefkowitz, J Biol Chem **268**:4625-36 1993; Christopoulos, Kenakin, Pharmacol Rev **54**:323-74 2002





ion-channels and patch-clamp data

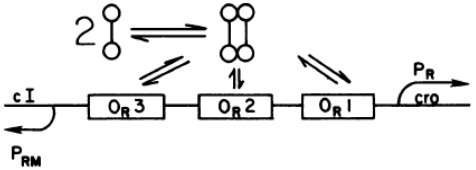
Edelstein, Schaad, Henry, Bertrand, Changeux, Biol Cybern **75**:361-79 1996; Colquhoun, Hawkes, Proc Roy Soc Lond B **211**:205-35 1981



widely used in biology

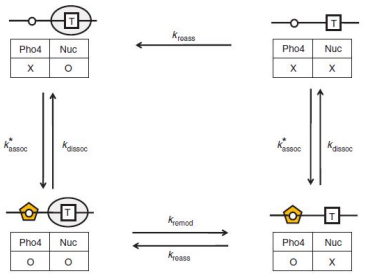
gene regulation in bacteria

Ackers, Johnson & Shea, PNAS **79**:1129-33 1982



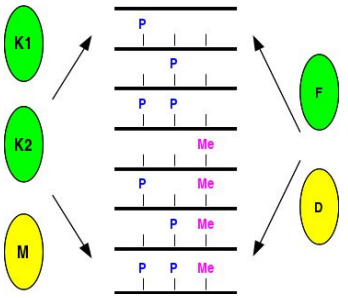
gene regulation in eukaryotes

Kim & O'Shea, Nature Struct Mol Biol **15**:71192-8 2008



post-translational modification

Thomson & Gunawardena, Nature **460**:274-7 2009;
Thomson & Gunawardena, J Theor Biol **261**:626-36 2009



the linear framework

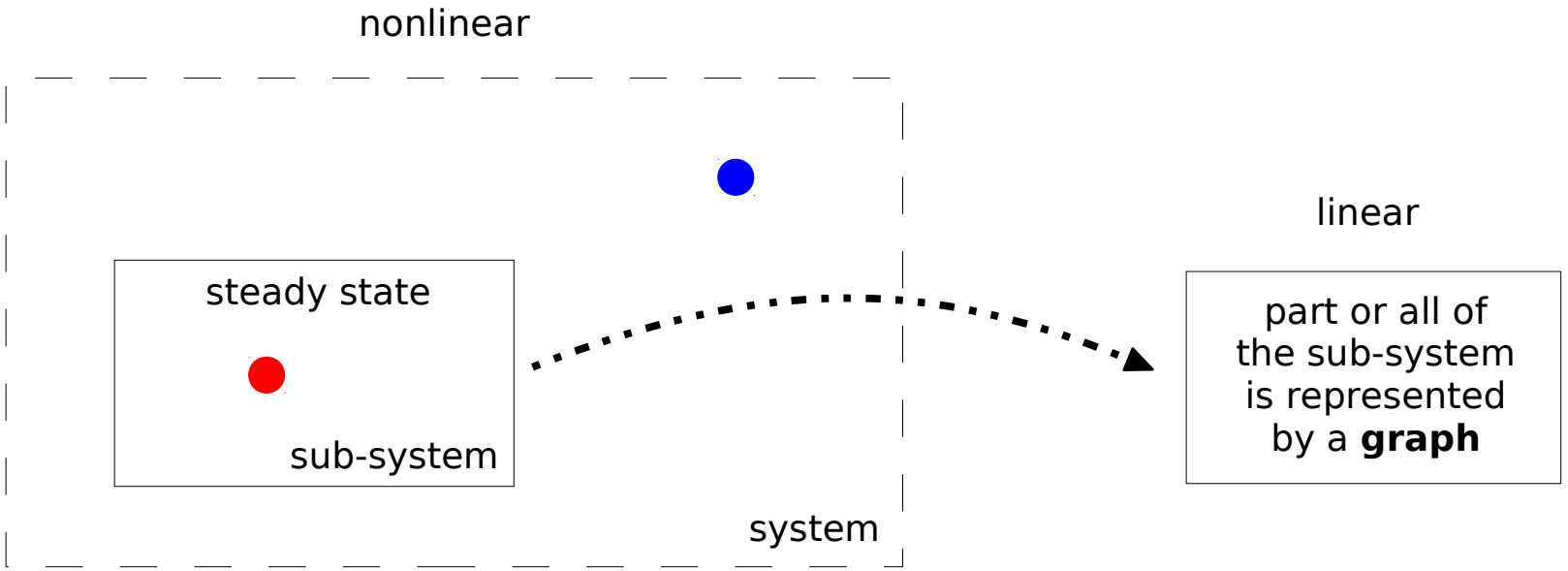
all these calculations look different and independent

in fact, they are all the same calculation

and it is a LINEAR one

Gunawardena, *"A linear framework for timescale separation in nonlinear biochemical systems"*, PLoS ONE **7**:e36321 2012.

the linear framework



$$E + S \xrightarrow{a} ES$$

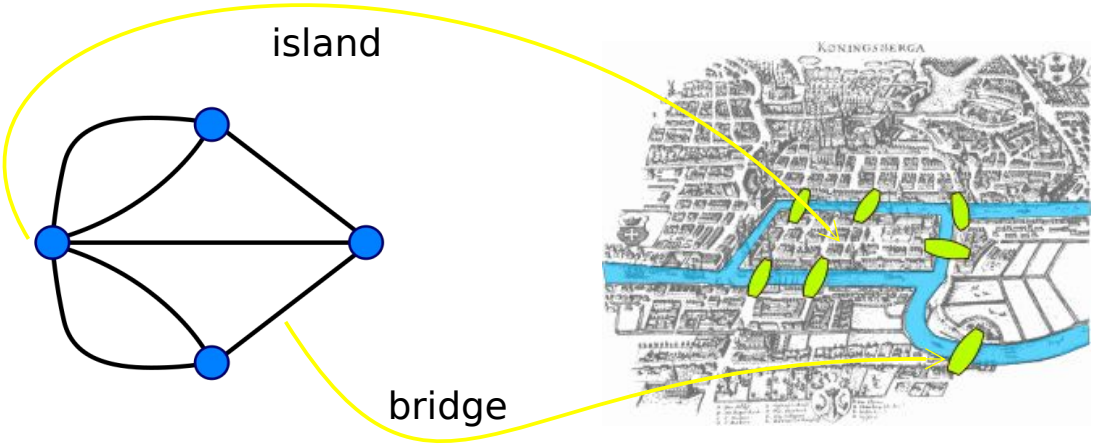
nonlinear with simple rate constants

$$E \xrightarrow{a[S]} ES$$

linear with complex labels subject to an "uncoupling condition"

Gunawardena, *"A linear framework for time-scale separation in nonlinear biochemical systems"*, PLoS ONE **7**:e36321 2012; Mirzaev & Gunawardena, "*Laplacian dynamics on general graphs*", Bull Math Biol **75**:2118-49 2013; Gunawardena, *"Time-scale separation: Michaelis and Menten's old idea, still bearing fruit"*, FEBS J **281**:473-88 2014.

graph theory begins with euler

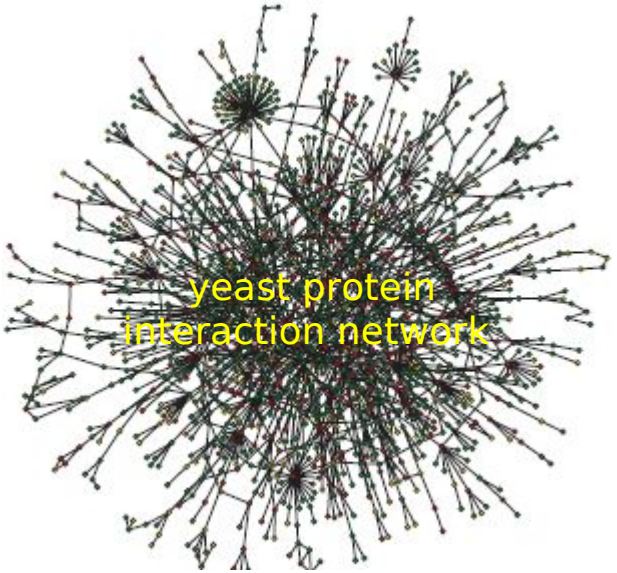


Königsberg, modern Kaliningrad

1707-1783

there is no circuit which traverses each edge once and once only (**eulerian circuit**)

graphs are widely used as mathematical representations of biological organisation



Newman "*The structure and function of complex networks*", SIAM Review **45**:167–256 2003; Barabasi, Oltvai, *"Network biology: understanding the cell's functional organization"*, Nature Rev Genetics **5**:101-13 2004.

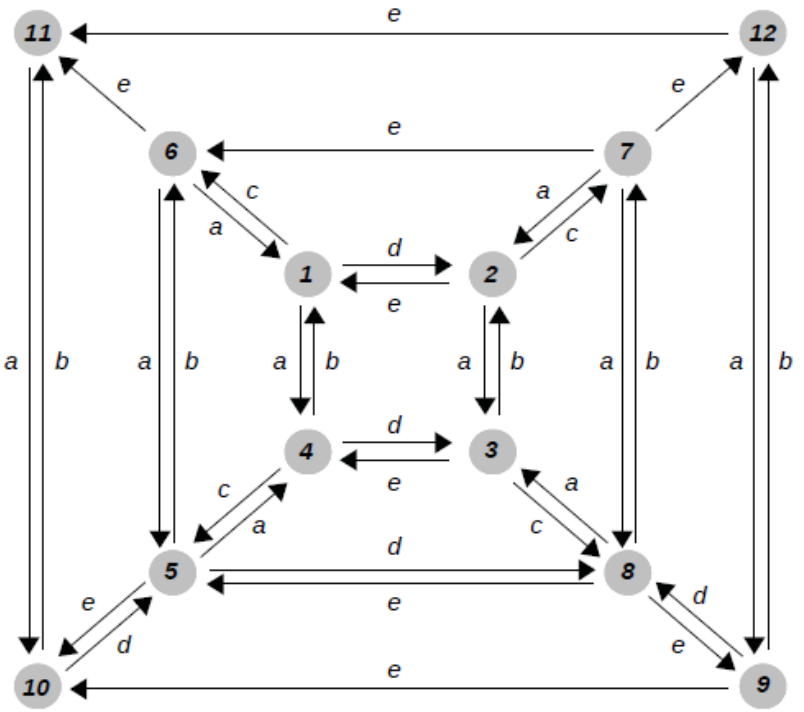
labelled directed graphs

for the linear framework –

a **graph** consists of **vertices** (or **nodes**), with at most one **edge** between any two distinct vertices (no self-loops)

the graph is **directed** – each edge has a specified direction, denoted by an arrow at one end

the graph is **labelled** on each edge

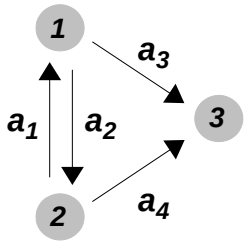


we shall work with graphs which are **connected** (in one piece, forgetting edge directions) and which have **no self-loops**

Laplacian dynamics – macroscopic interpretation

"one-dimensional" chemistry on graphs

consider each edge as a chemical reaction under mass-action kinetics, with the label as the rate constant



Laplacian matrix

$$\frac{d}{dt}\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} -(a_2+a_3) & a_1 & 0 \\ a_2 & -(a_1+a_4) & 0 \\ a_3 & a_4 & 0 \end{pmatrix}\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix}$$

G

$$\frac{dx}{dt} = \mathcal{L}(G).x$$

system of linear ODEs

conservation law:

$$x_1(t) + x_2(t) + \cdots + x_n(t) = x_{tot} \qquad 1.\mathcal{L}(G) = 0$$

Gustav Kirchhoff, *"Uber die Auflosung der Gleichungen, auf welche man bei der Untersuchung der linearen Verteilung galvanischer Strome gefuhrt wird"*, Ann Phys Chem, **72**:497-508 1847

Laplacian dynamics – microscopic interpretation

let $X(t)$ be a time-homogeneous **Markov process** on the states $1, \cdots, n$ for which **infinitesimal transition rates** exist –

$$\lim_{\Delta t \to 0} \frac{\Pr(X(t+\Delta t) = i \mid X(t) = j)}{\Delta t} = a_{ij}$$

define the graph, G_X , with vertices $1, \cdots, n$ and an edge $j \to i$ iff $a_{ij} \neq 0$ give this edge the label a_{ij}

the **stochastic master equation** (Kolmogorov forward equation), for the probability of $X(t)$ being in state i at time t, is identical to Laplacian dynamics on G_X

$$x_i(t) = \Pr(X(t) = i) \qquad \boxed{\frac{dx}{dt} = \mathcal{L}(G_X).x}$$

Mirzaev & Gunawardena, Bull Math Biol **75**:2118-49 2013

basic facts

for any graph, G, Laplacian dynamics always tends to a stable steady state

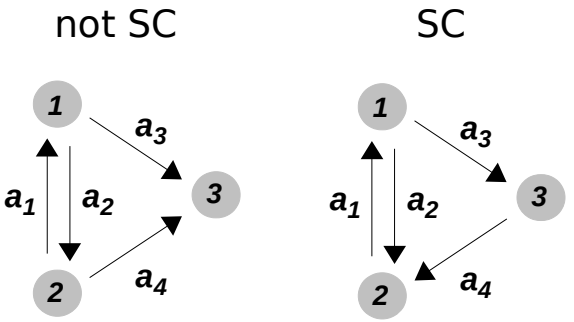
$$x(t) \to x^* \qquad \left.\frac{dx}{dt}\right|_{x=x^*} = 0 \qquad x^* \in \ker \mathcal{L}(G)$$

if G is **strongly connected**, the steady state is unique up to a scalar multiple

$$\ker \mathcal{L}(G) = \langle \rho \rangle$$

where a basis element, ρ , can be calculated in terms of the labels (see later)

strongly connected – there is a directed path between any two distinct vertices



Mirzaev & Gunawardena, Bull Math Biol **75**:2118-49 2013

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's – about which more later

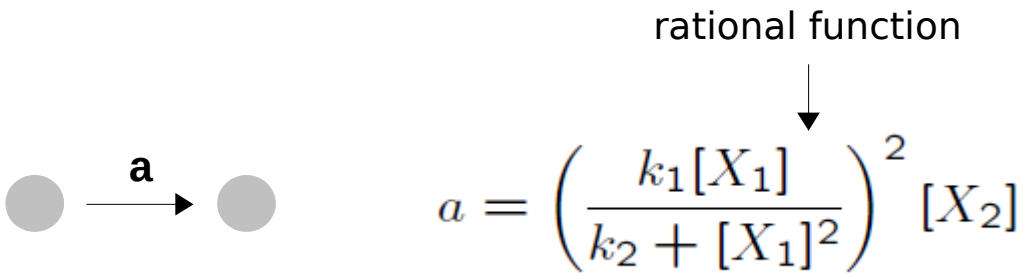
1. if the system reaches thermodynamic equilibrium, then **detailed balance** holds and **ρ** can be calculated using a single path in the graph or by equilibrium statistical mechanics.

2. if the system does not reach equilibrium and the graph is strongly connected, then **ρ** can be calculated by the **Matrix-Tree Theorem**. this requires many paths (or “spanning trees”) in the graph.

3. if the graph is not strongly connected, then a basis for the kernel can be calculated by decomposing the graph into **strongly connected components** (SCCs) and using the MTT on the **terminal** SCCs

nonlinearity goes into the labels

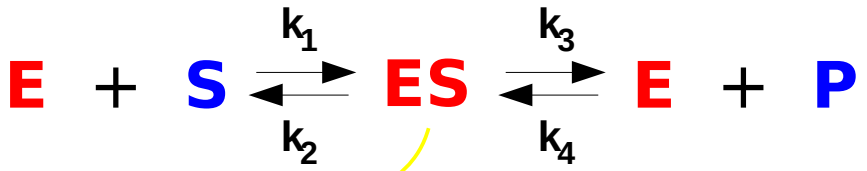
labels are allowed to be complex algebraic expressions, involving rate constants and concentrations

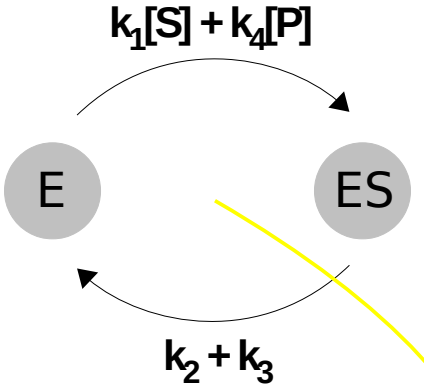


uncoupling condition: no concentration appearing in a label – such as $[X_1]$ or $[X_2]$ above – can be that of a vertex in the graph (but it can be that of a slow variable or a fast variable that is not a vertex in the graph)

uncoupling is essential to keep the dynamics linear

reversible michaelis-menten





uncoupling condition

✓

nonlinear dynamics

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

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

Laplacian (linear) dynamics

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

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

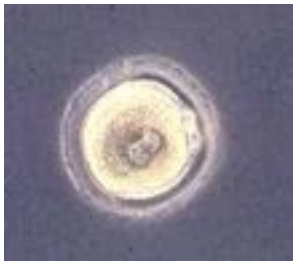
the graph is strongly connected and satisfies the uncoupling condition

the quantities to be calculated are obtained by eliminating the fast variables in terms of the labels, as described

Gunawardena, *“Time-scale separation: Michaelis and Menten's old idea, still bearing fruit”*, FEBS J **281**:473-88 2014.

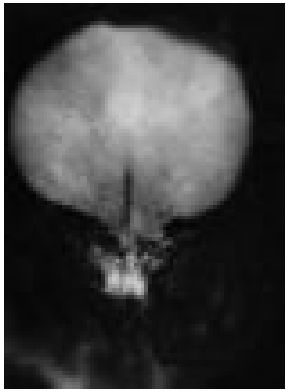
4. cellular identity & gene regulatory networks

human embryonic development

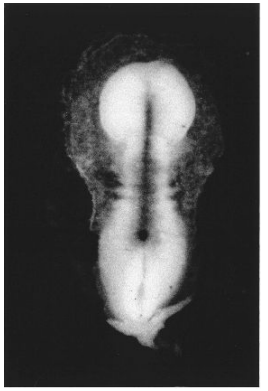


stage 1, day 1
totipotent zygote or
fertilised oocyte

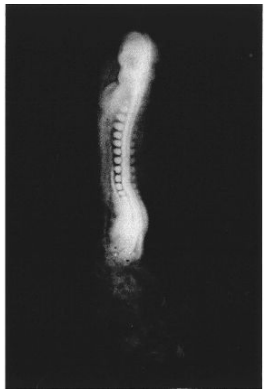
stage 3, day 4-5
pre-implantation
blastocyst



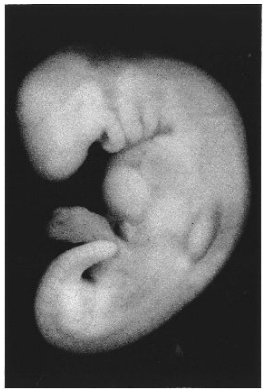
stage 7, day 15-17
gastrulation, notochord



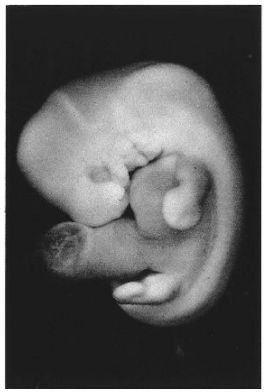
stage 9, day 19-21
neural folds, somites 1-3



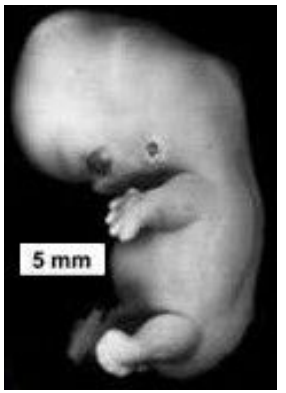
stage 11, day 23-26
13 somites



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



stage 17, day 42-44
fingers emerging

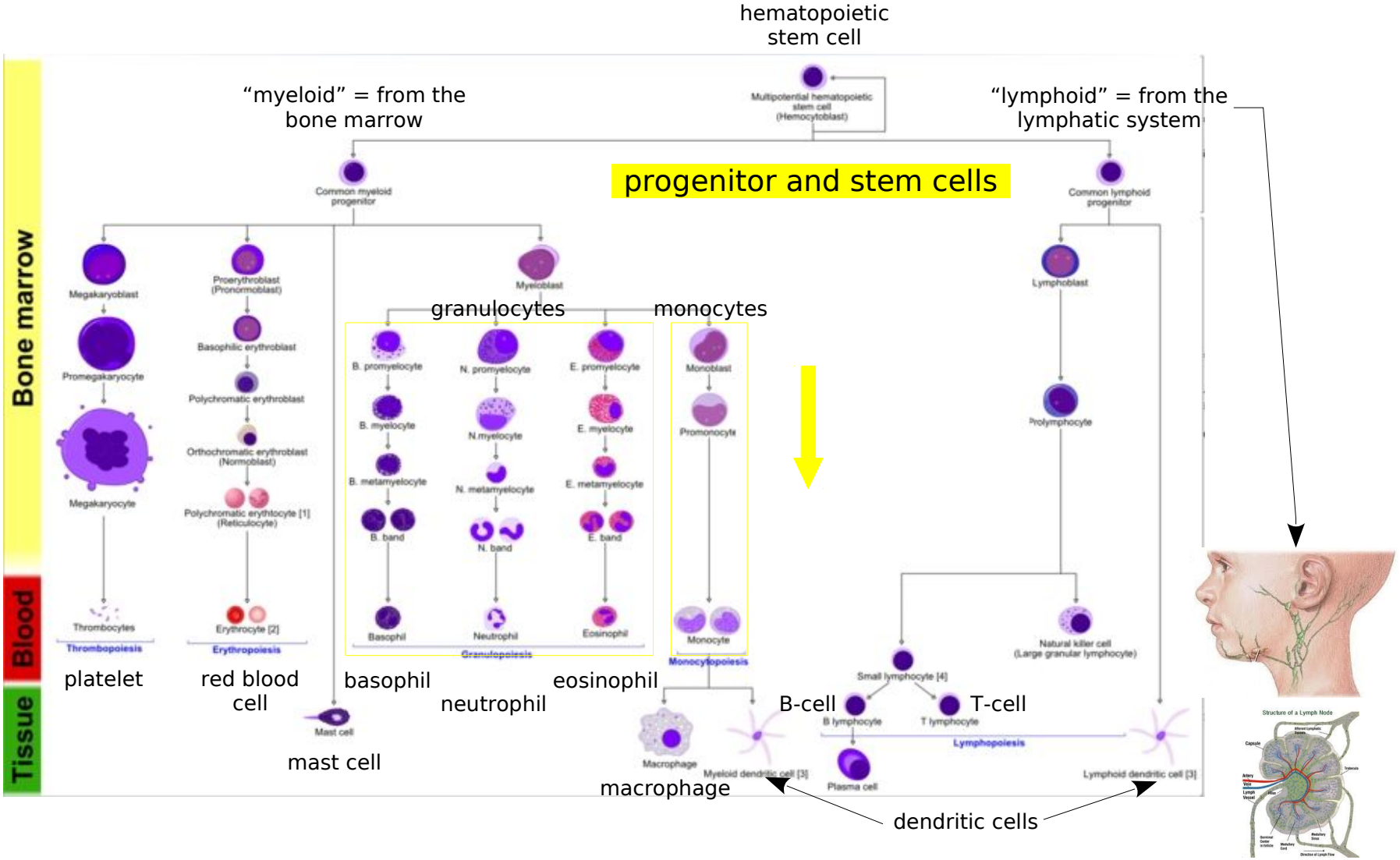


stage 19, day 48-51
fingers emerged, bone
has started to form

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

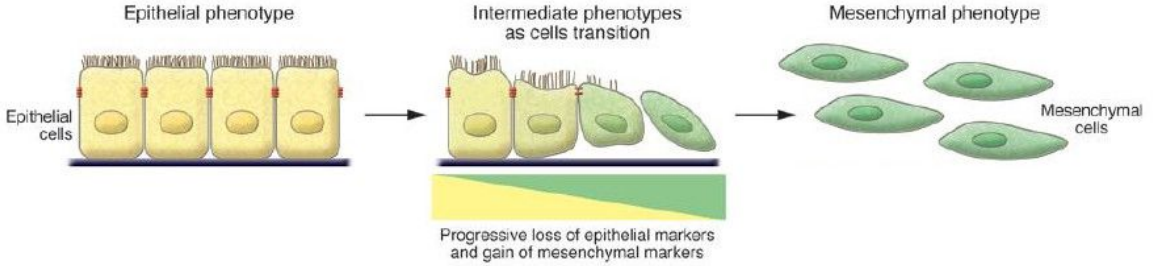
hierarchical construction of cellular identity

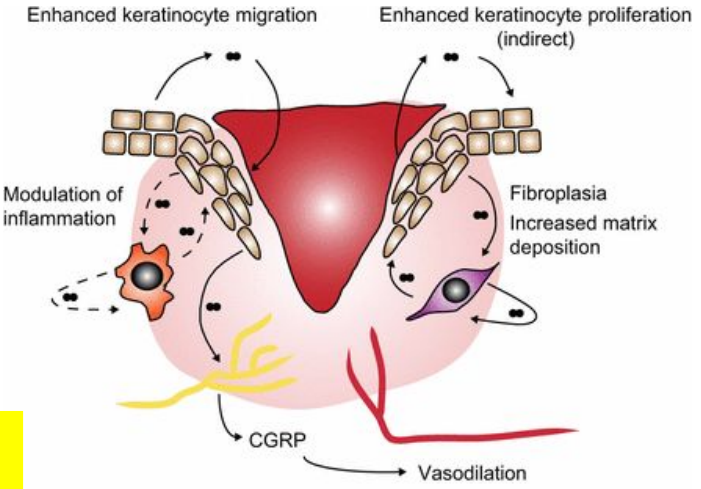
in the blood (“hematopoietic”) system, which undergoes continuous renewal



cellular identity is both stable and plastic

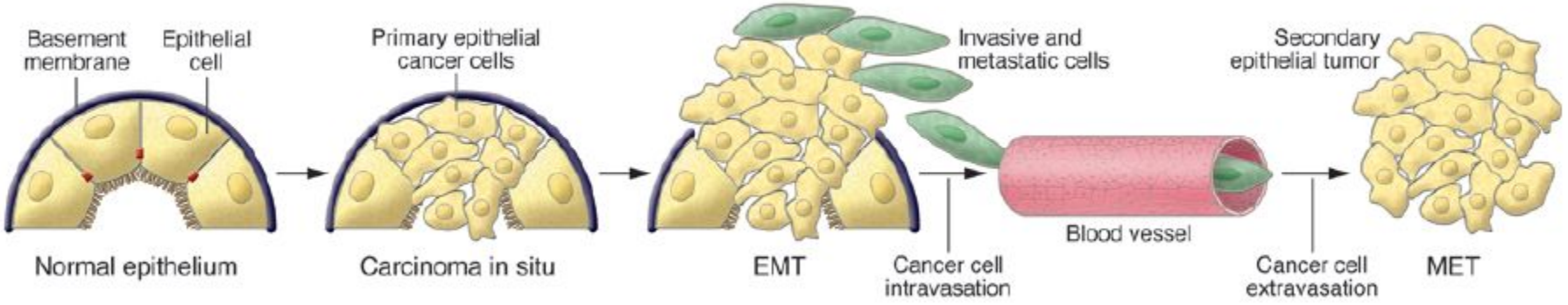
wound healing & tissue regeneration





EMT = epithelial-mesenchymal transition
MET = mesenchymal-epithelial transition

cancer

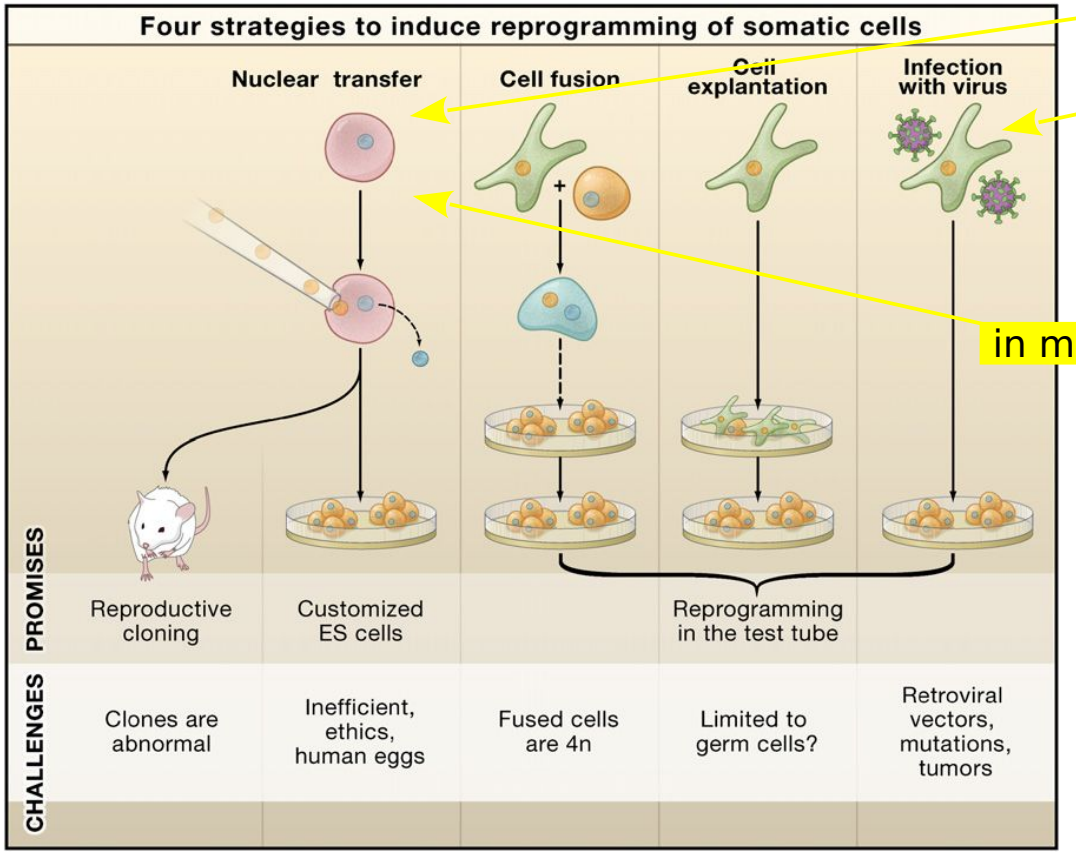


Antsiferova, Werner, *"The bright and dark sides of activin in wound healing and cancer"*, J Cell Sci, **125**:3929-37, 2012; Kalluri, Weinberg, *"The basics of epithelial-mesenchymal transition"*, J Clin Invest, **119**:1420-8, 2009.

cellular identity can be re-programmed – I

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

in frogs

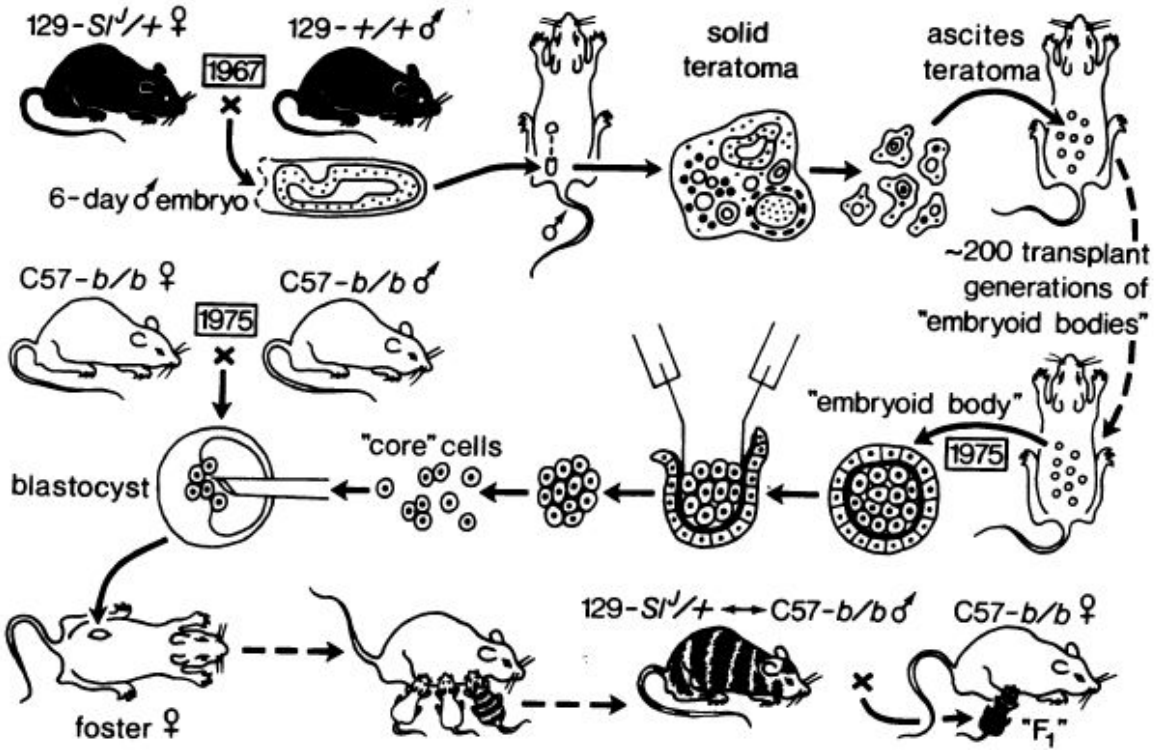


in mammals

(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