dynamic processes in cells (a systems approach to biology)

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lecture 10

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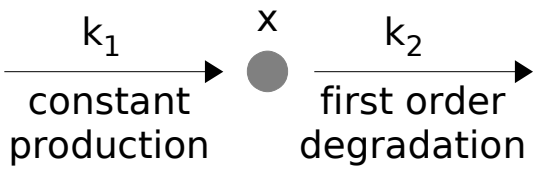
quantitative to qualitative dynamics

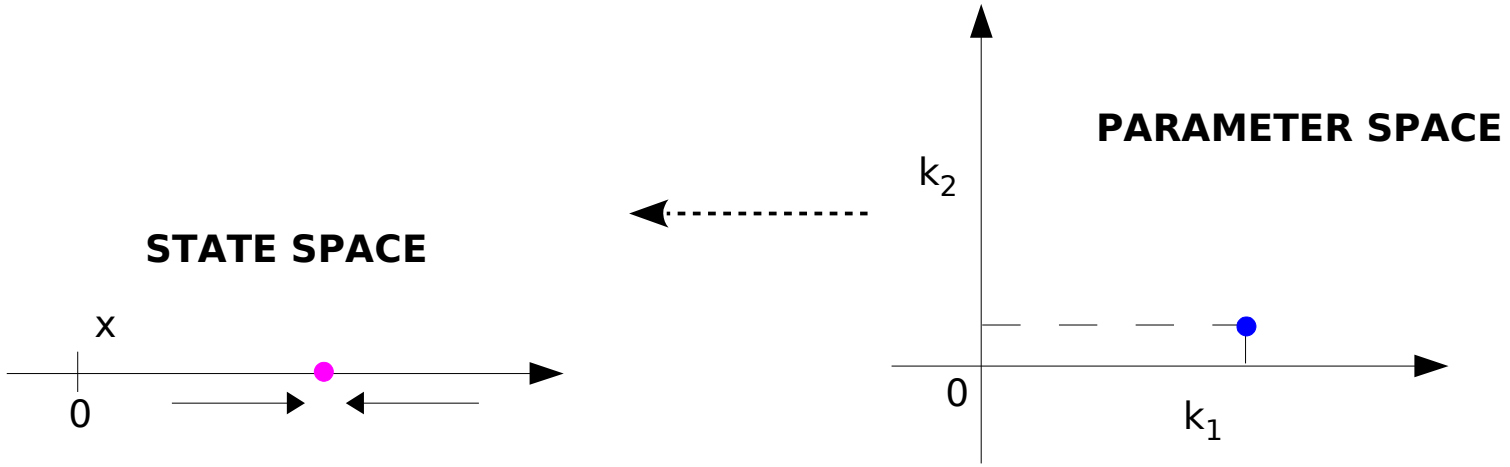


$$\frac{dx}{dt} = k_1 - k_2 x$$

from a quantitative analytical solution

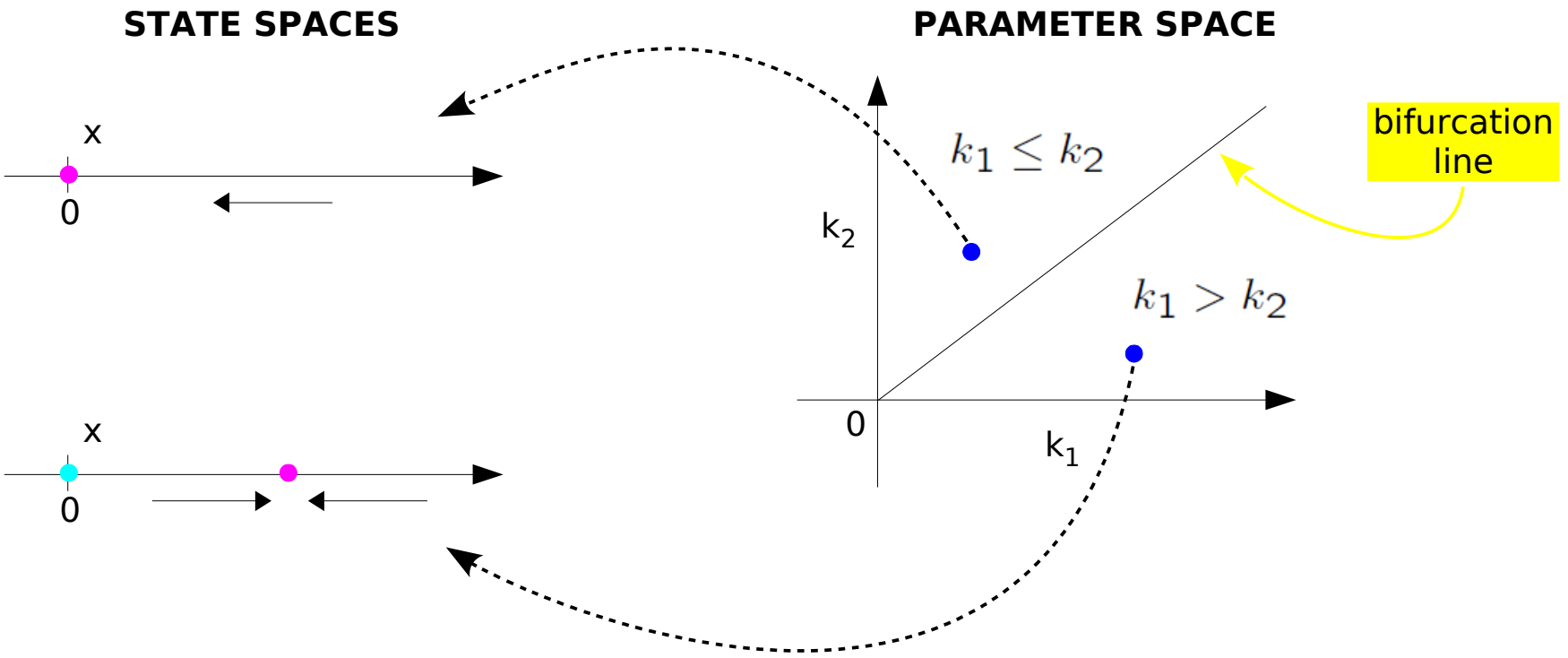
$$x(t) = \frac{k_1}{k_2} + \left(x(0) - \frac{k_1}{k_2} \right) \exp(-k_2 t)$$

to a qualitative geometric perspective



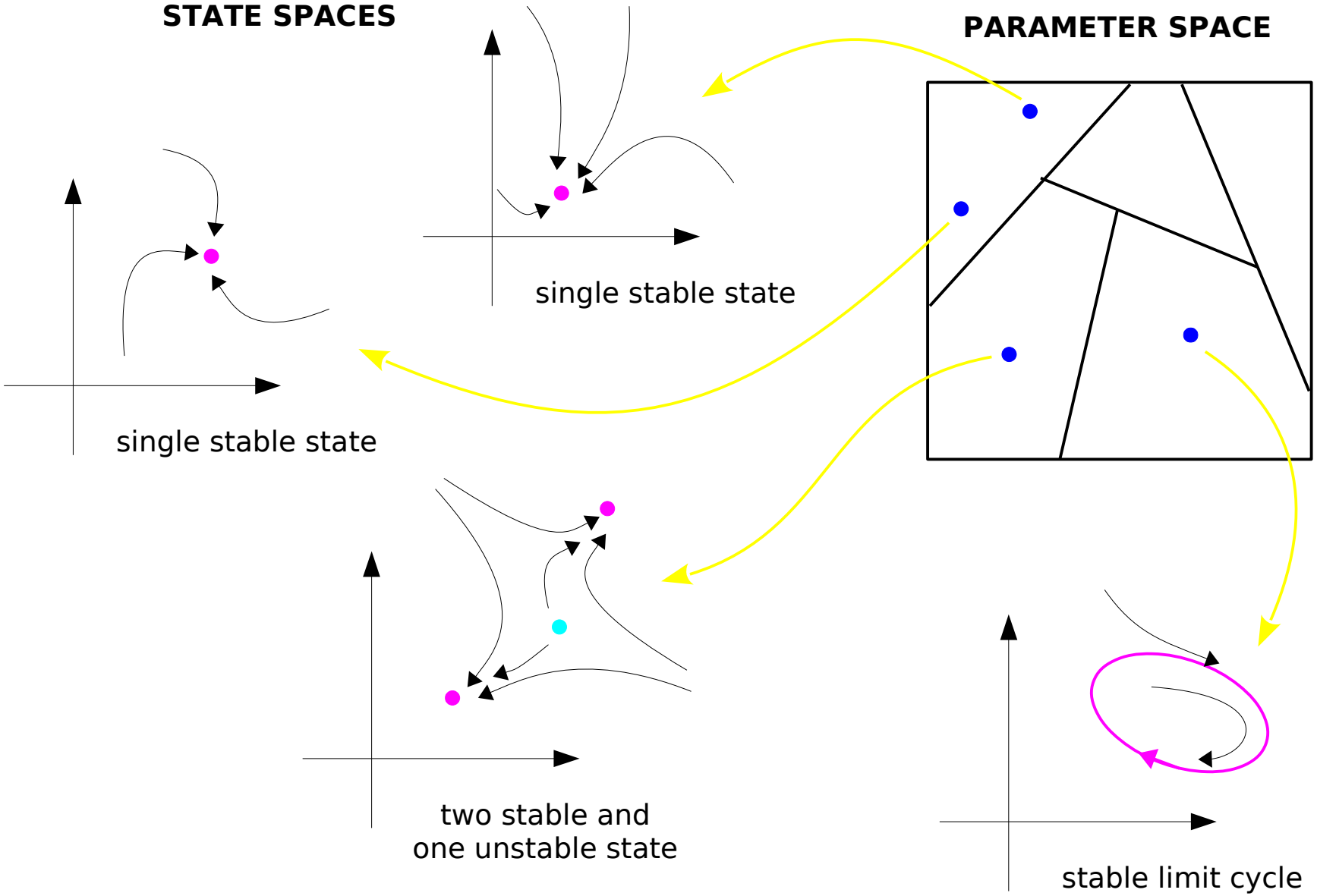
nonlinear qualitative dynamics

$$\frac{dx}{dt} = k_1 x(1-x) - k_2 x$$



bifurcation – change in parameter values that gives rise to a qualitative change of the dynamics in the state space

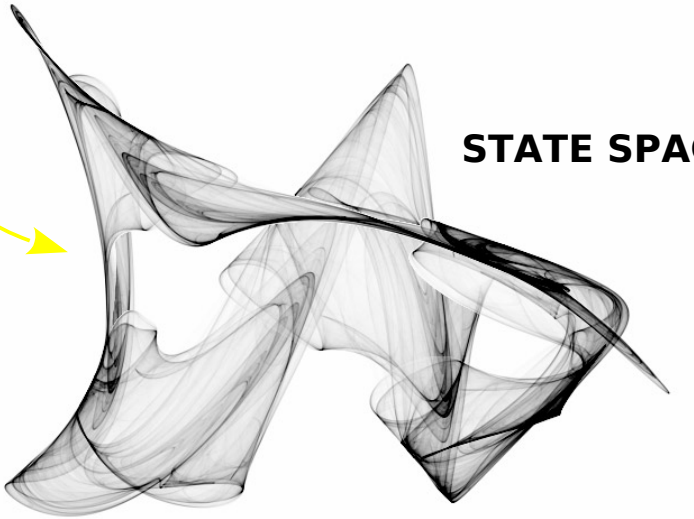
state space “landscapes” and parameter “geography”



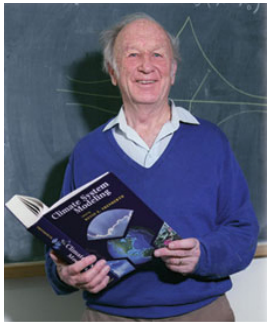
nonlinear dynamics can be very complex

the dynamics may never reach a steady state. a trajectory may exhibit “sensitive dependence to initial conditions” (**“chaos”**) but remain within a bounded region of state space, giving rise to a **“strange attractor”**

$$\frac{dx}{dt} = p_0 + y - z(p_1 + y)$$
$$\frac{dy}{dt} = p_2 + z - x(p_3 + z)$$
$$\frac{dz}{dt} = p_4 + x - y(p_5 + x)$$

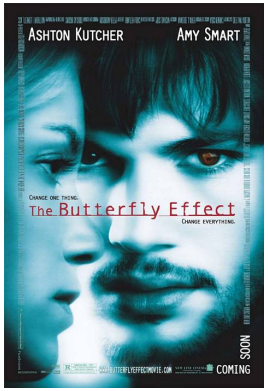


STATE SPACE



1917-2008

“Does the flap of a butterfly's wings in Brazil set off a tornado in Texas?”



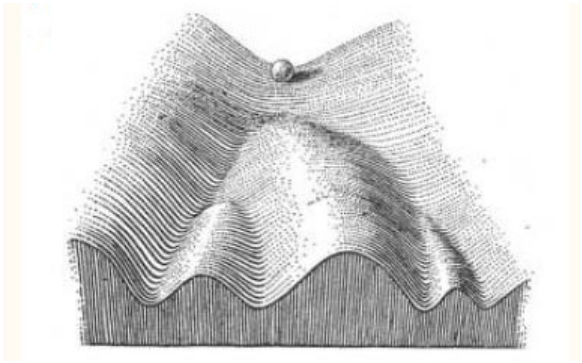
http://www.chaoscope.org/index.htm

Olsen, Degn, *“Chaos in biological systems”*, Quart Rev Biophys **18**:165-225 1985

Scott, **Chemical Chaos**, OUP 1993

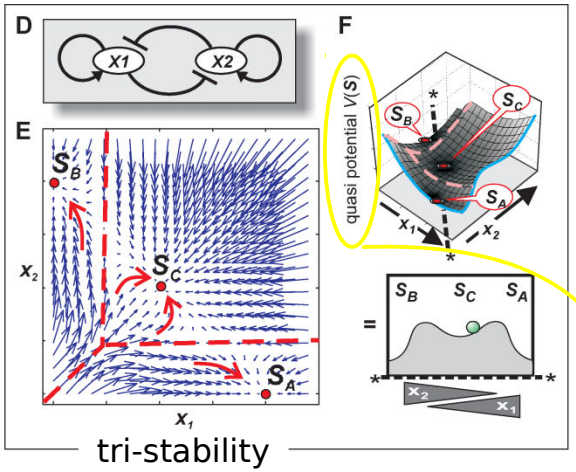
state space landscapes and cellular identity

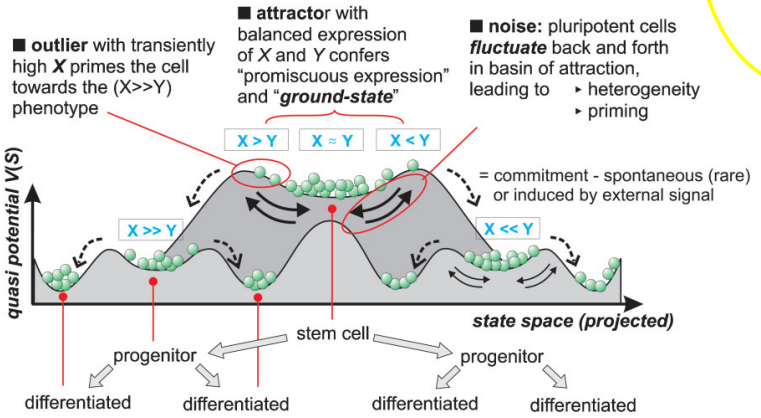
Conrad Waddington



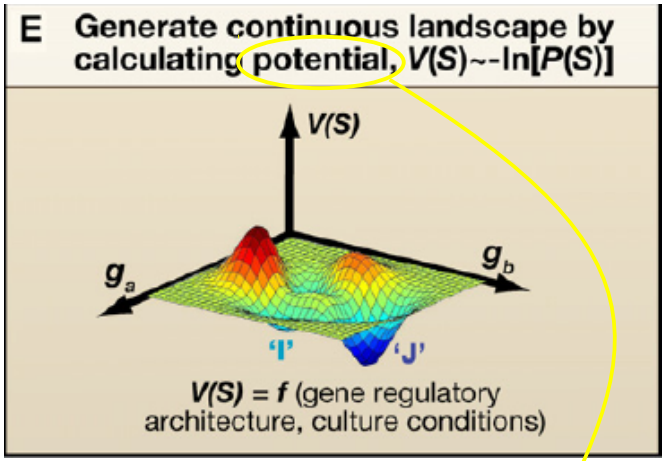
1905-1975

Sui Huang





Rudolf Jaenisch

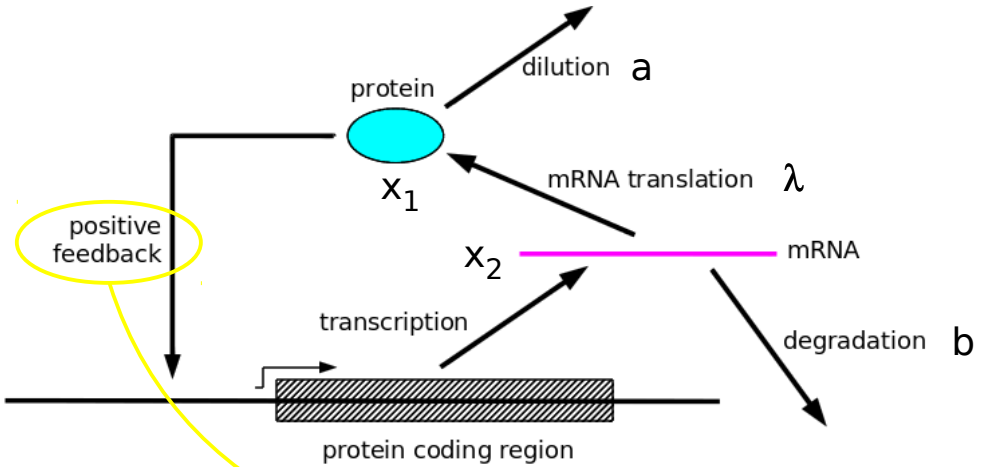


dynamics on a potential surface

Slack, *"Conrad Hal Waddington: the last renaissance biologist?"*, Nature Rev Genetics **3**:889-95 2002. Huang, "*Reprogramming cell fates: reconciling rarity with robustness*", Bioessays, **31**:546-60 2009; Hana, Saha, Jaenisch, "*Pluripotency and cellular reprogramming: facts, hypotheses and unresolved issues*", Cell **143**:508-25 2010.

one gene, two states

positive feedback by a gene on itself is a potential way to create bistability



nonlinear dynamical system

$$\frac{dx_1}{dt} = \lambda x_2 - a x_1$$

$$\frac{dx_2}{dt} = \frac{\alpha x_1}{k + x_1} - b x_2$$

corresponds to GRF for 1 TF binding site, $f_1(x)$

the first thing to calculate are the **steady states** of the dynamical system because they are the skeleton around which the dynamics takes place

method of nullclines (2D systems only)

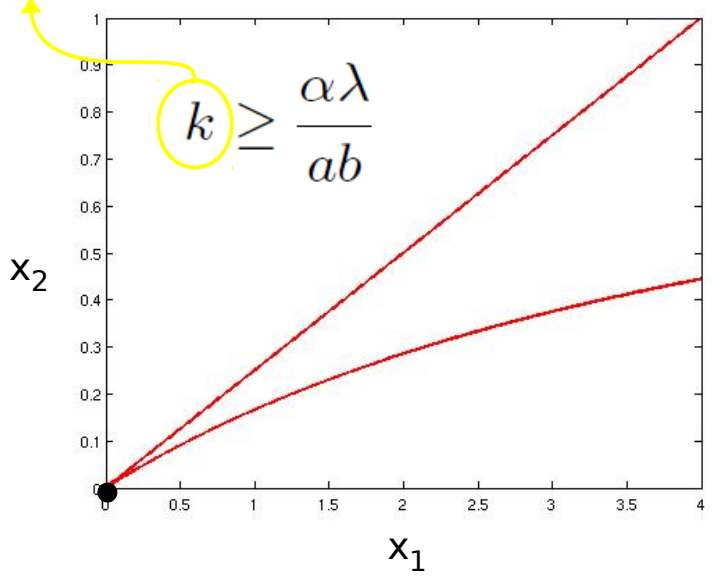
the **x_1 nullcline** is the locus of points satisfying $\frac{dx_1}{dt} = 0$ $\quad x_2 = \left(\frac{a}{\lambda}\right) x_1$

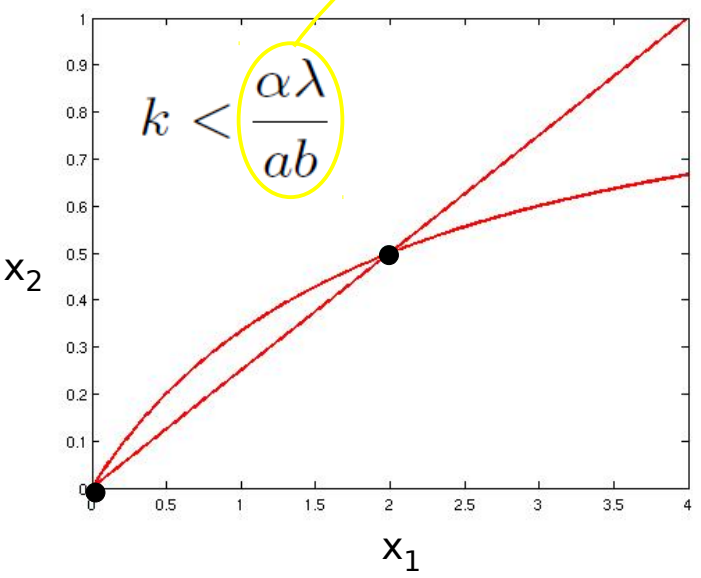
the **x_2 nullcline** is the locus of points satisfying $\frac{dx_2}{dt} = 0$ $\quad x_2 = \left(\frac{\alpha}{b}\right) \frac{x_1}{k + x_1}$

weakness of positive feedback

synthesis rates / degradation rates

STATE SPACES



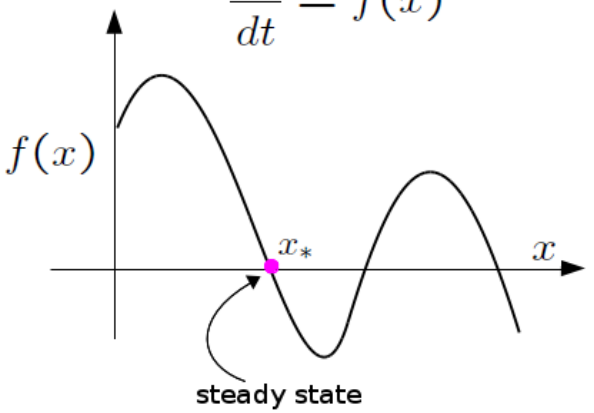


but what is the stability of these steady states?

linearisation (lecture 4-16)

nonlinear system

$$\frac{dx}{dt} = f(x)$$

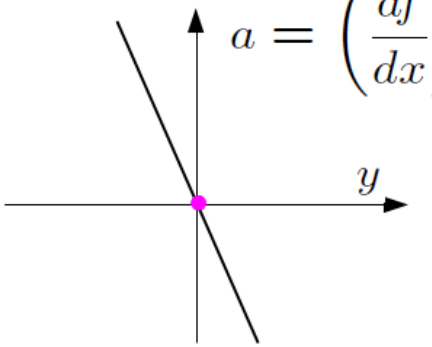


$$f(x_*) = 0$$

linear system

$$\frac{dy}{dt} = ay \qquad y = x - x_*$$

$$a = \left(\frac{df}{dx}\right)\Big|_{x=x_*}$$



nonlinear dynamical system

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1(x_1, x_2, \cdots, x_n; k_1, \cdots, k_m) \\
\frac{dx_2}{dt} &= f_2(x_1, x_2, \cdots, x_n; k_1, \cdots, k_m) \\
&\vdots \quad \vdots \quad \vdots \\
\frac{dx_n}{dt} &= f_n(x_1, x_2, \cdots, x_n; k_1, \cdots, k_m)
\end{aligned}$$

linearisation

$$\frac{dx_i}{dt}\Big|_{x=x_*} = 0$$

linear system

$$\frac{dy}{dt} = A.y \qquad y = x - x_*$$

$$A = \left(\frac{\partial f_i}{\partial x_j}\right)\Big|_{x=x_*}$$

Jacobian matrix of partial derivatives

stability of steady states (lecture 4-4)

$$x_1 = x\,, \quad x_2 = \frac{dx}{dt}$$

$$a_2\frac{d^2x}{dt^2} + a_1\frac{dx}{dt} + a_0 x = 0 \qquad \frac{d}{dt}\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ -\frac{a_0}{a_2} & -\frac{a_1}{a_2} \end{pmatrix}\begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$$

put matrix in triangular form by Gaussian elimination

zeros of the characteristic polynomial ⟷ eigenvalues of the matrix

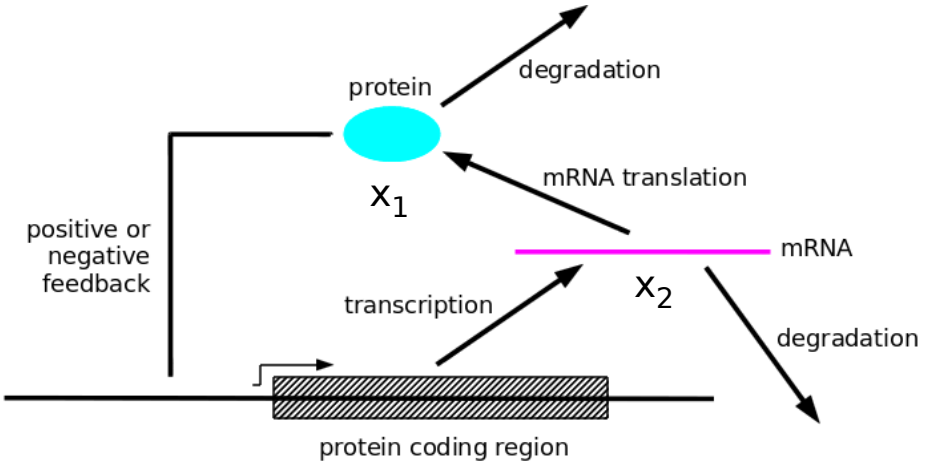
the matrix A has the eigenvalue λ with eigenvector x if $Ax = \lambda.x$

$$\det(A - \lambda.I) = 0$$

a nonlinear dynamical system is stable at a steady state if all the eigenvalues of its Jacobian matrix, evaluated at the steady state, have negative real parts

stability theorem for genetic auto-regulation

assume general transcription & translation functions, linear degradation and arbitrary (positive or negative) feedback



$$\frac{dx_1}{dt} = f(x_2) - ax_1$$

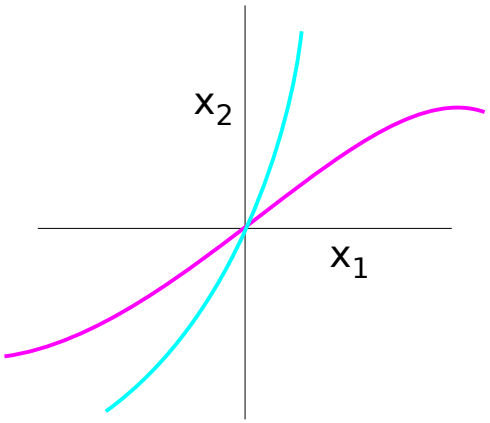
$$\frac{dx_2}{dt} = g(x_1) - bx_2$$

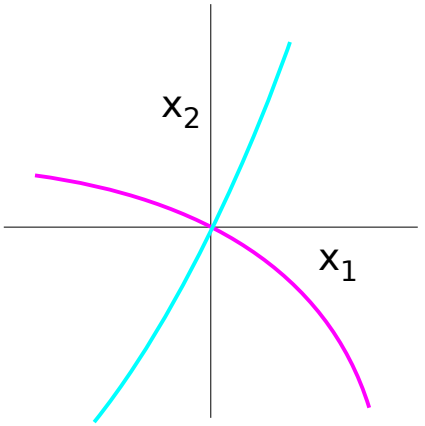
$$a,\ b > 0$$

nullcline geometry determines stability

x_1 nullcline, in the 1st quadrant, crosses above **x_2 nullcline**, in the 1st or 4th quadrants

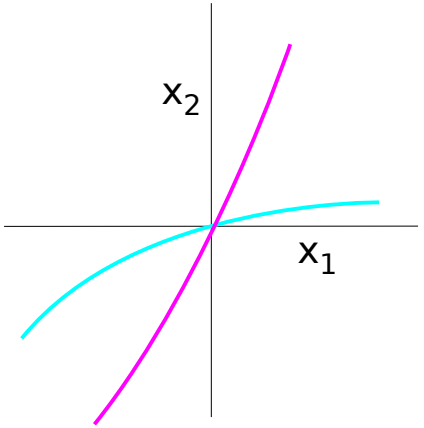
STABLE





x_1 nullcline, in the 1st quadrant, crosses below **x_2 nullcline**, in the 1st quadrant

UNSTABLE



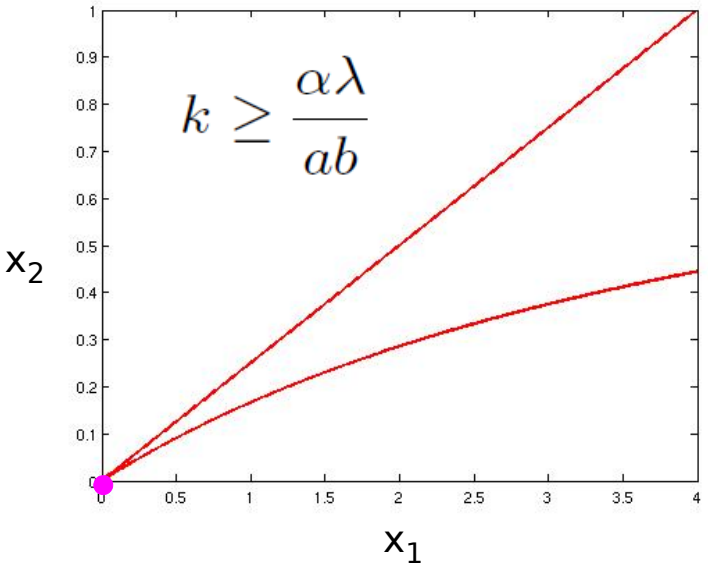
see the "nullcline theorem" handout for details

steady-state stability for positive feedback

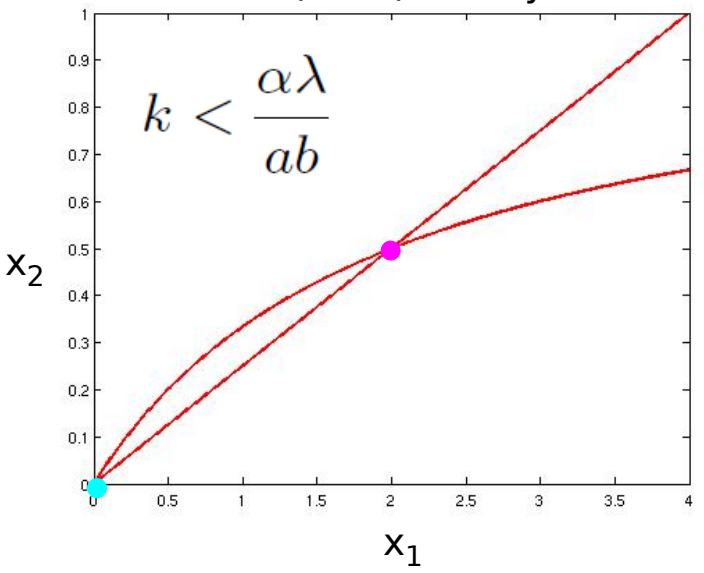
$$\frac{dx_1}{dt} = \lambda x_2 - a x_1$$

$$\frac{dx_2}{dt} = \frac{\alpha x_1}{k + x_1} - b x_2$$

one stable steady state ("off")

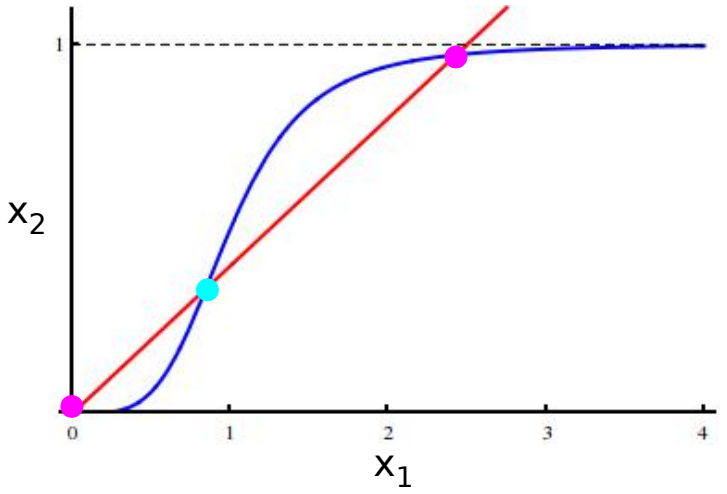


one stable ("on") and one unstable ("off") steady state



how do we make **bistability** with the "off"state and the "on" state both stable?

bistability requires cooperativity (“sharpness”)



positive feedback has to be combined with a sigmoidal (“S-shaped”) nullcline.

this is “**cooperativity**” or “**sharpness**”

a common way to introduce cooperativity is to assume some kind of **Hill function**

$$\frac{dx_1}{dt} = \lambda x_2 - a x_1$$

$$\frac{dx_2}{dt} = \frac{\alpha x_1}{k + x_1} - b x_2 \qquad \frac{\alpha x_1^h}{k^h + x_1^h}$$

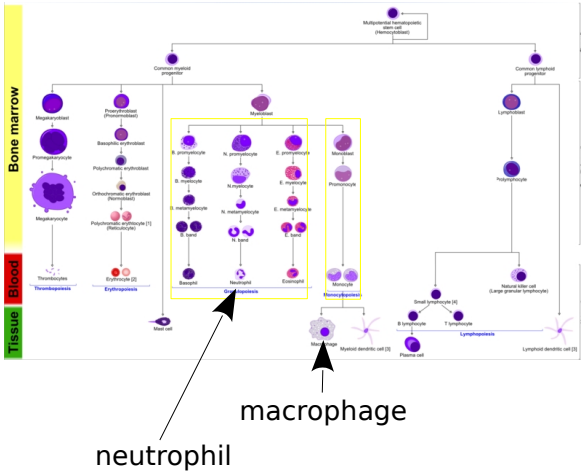
$$\frac{x^h}{1 + x^h}$$

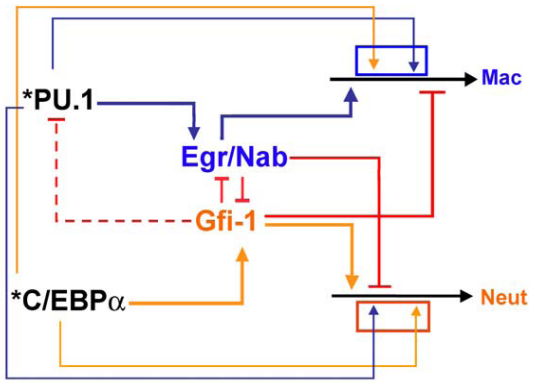
Hill coefficient

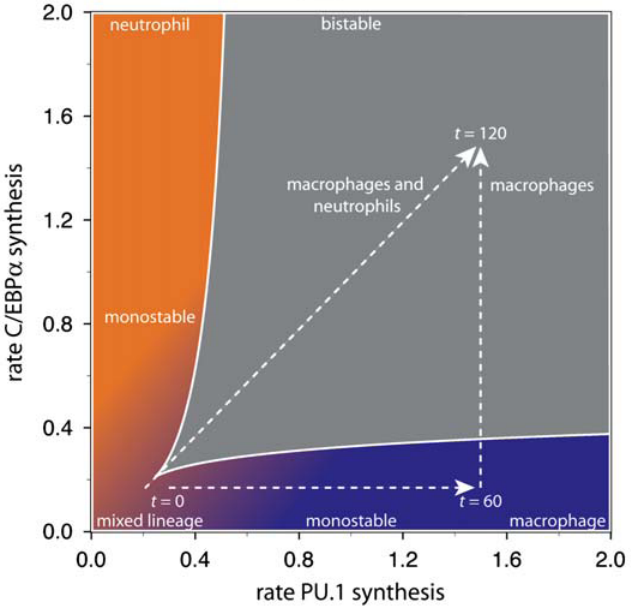
Hill function

hill functions for bistability

transcriptional priming





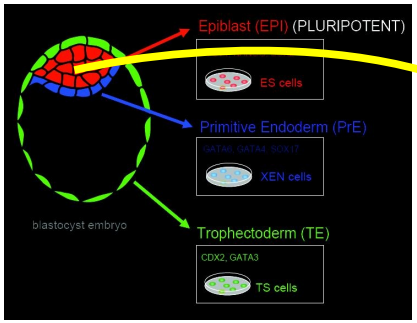


activating $\mathbf{n_A} = 1$ repressing $\mathbf{n_R} = 4$

$$\frac{dx}{dt} = \left(\frac{\alpha A^{n_A}}{K_A{}^{n_A} + A^{n_A}} + e_0 \right) \frac{K_R{}^{n_R}}{K_R{}^{n_R} + R^{n_R}} - \beta x$$

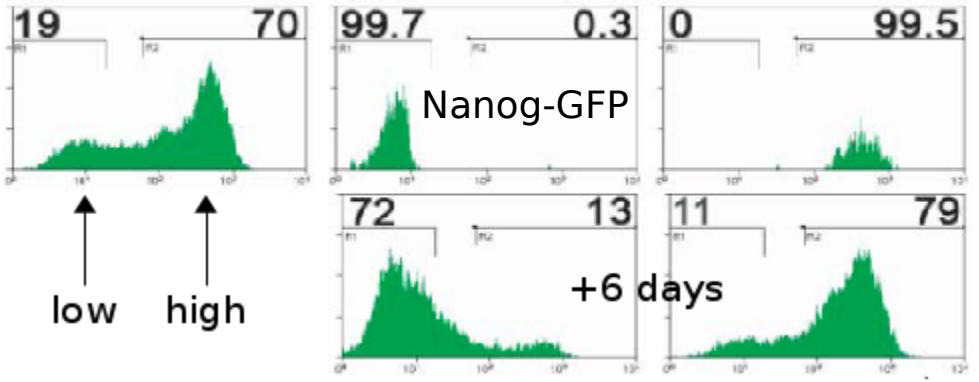
Laszlo et al, "*Multilineage transcriptional priming and determination of alternate hematopoietic cell fates*", Cell **126**:755-66 2006

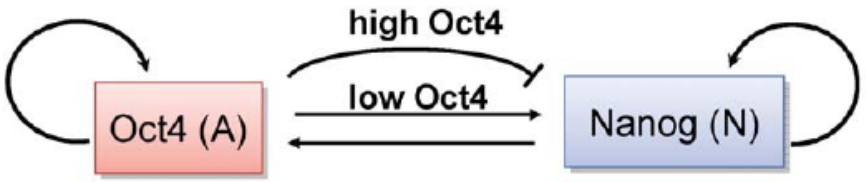
hill functions for excitability



serum + LIF, 2i

embryonic stem cells



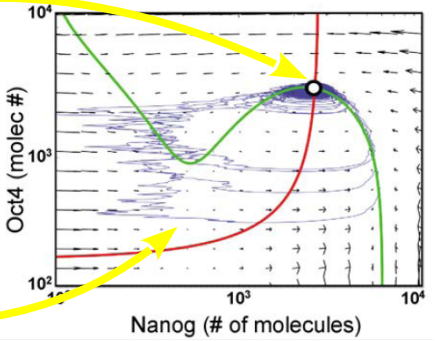


$$\frac{dN}{dt} = \alpha_n + \frac{\beta_n N^n}{k_n^n + N^n} - \delta \frac{A^p}{k_x^p + A^p} N - \gamma_n N$$

$$\frac{dA}{dt} = \alpha_a + \beta_a A N - \gamma_a A$$

n = 2, p = 1.5

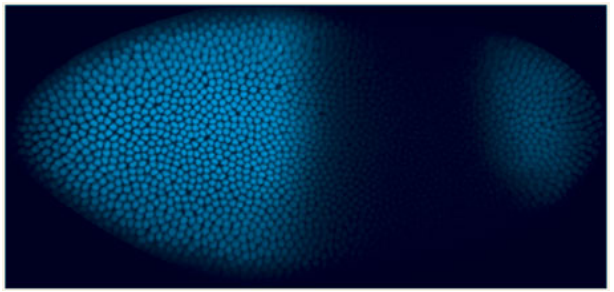
excitability – there is a single, **stable steady state** with a small stability region, outside of which trajectories make **long excursions** before returning to the steady state



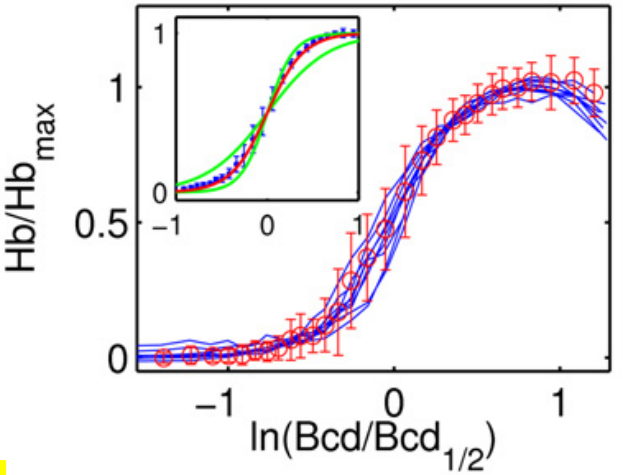
Kalmar, Lim, Hayward, Munoz-Descalzo, Nichols, Garcia-Ojalvo, Martinez-Arias, *"Regulated fluctuations in Nanog expression mediate cell fate decisions in embryonic stem cells"*, PLoS Biol **7**:e1000149 2009

the hill function fits data on sharp gene expression

early Drosophila embryo



Hunchback (Hb) expression



Hill function

$$\frac{[\mathrm{Hb}]}{[\mathrm{Hb}]_{max}} \approx \frac{x^5}{1+x^5} \qquad x = [\mathrm{Bcd}]/[\mathrm{Bcd}]_{0.5}$$

"consistent with the idea that Hb transcription is activated by cooperative binding of effectively five Bcd molecules"

pairwise cooperativity

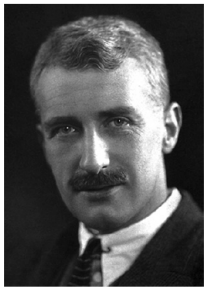
it is widely assumed that gene regulatory sharpness corresponding to a Hill coefficient of ***k*** can be obtained from ***n*** = ***k*** binding sites

Gregor, Tank, Wieschaus, Bialek, *"Probing the limits to positional information"*, Cell **130**:153-64 2007

but the hill function lacks justification

the Hill function was introduced to fit data on oxygen binding to haemoglobin

$$\frac{x^h}{1 + x^h}$$



A V Hill, "*The combinations of haemoglobin with oxygen and with carbon monoxide*", Biochem J **7**:471-80 1913

Archibald Vivian Hill
1886 - 1977

"The Hill equation remains what Hill intended it to be: an empirical descriptor"

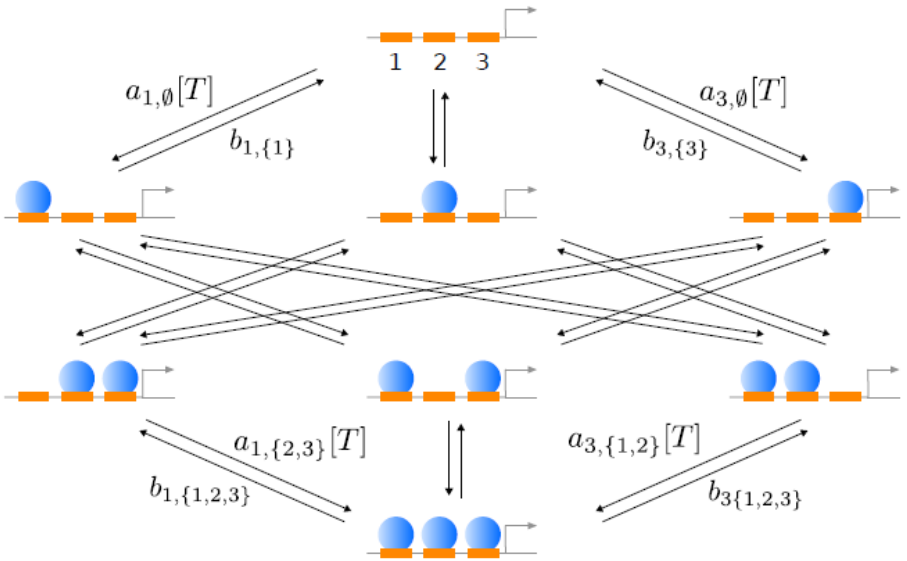
Engel, "*A hundred years of the Hill equation*", Biochem J 2013

"Despite its appealing simplicity, the Hill equation is not a physically realistic reaction scheme, raising the question of whether it should be abandoned in favor of realistic schemes; at the very least, its limitations should be more widely recognized"

Weiss, "*The Hill equation revisited: uses and misuses*", FASEB J **11**:835-41 1997

and is not a valid GRF

$$f_n(x) = \frac{c_n x^n}{1 + c_1 x + \cdots + c_n x^n}$$



the degree ***n*** is the number of sites and the coefficient c_k in the GRF is proportional to the steady-state probability of ***k*** sites out of ***n*** being occupied

this makes no physical sense for the Hill function ... even when the coefficient ***h*** is an integer

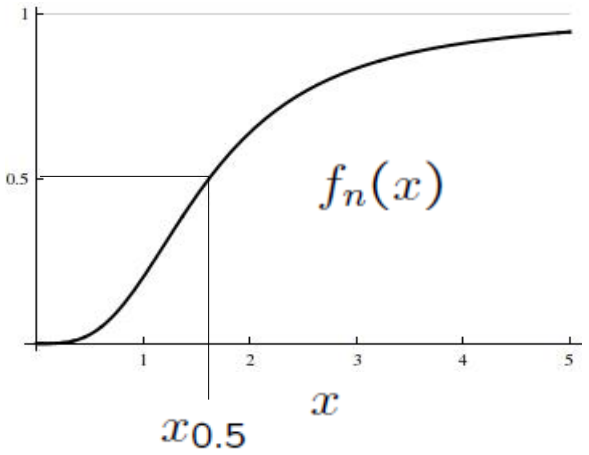
$$\frac{x^h}{1 + x^h}$$

sharpness in gene regulation

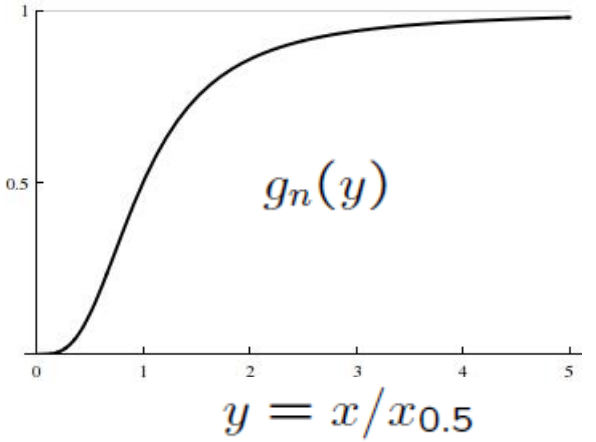
$$f_n(x) = \frac{c_n x^n}{1 + c_1 x + \cdots + c_n x^n}$$

equilibrium GRF for a single TF

measure sharpness of the gene regulation function using two properties – “steepness” and “position”



normalisation



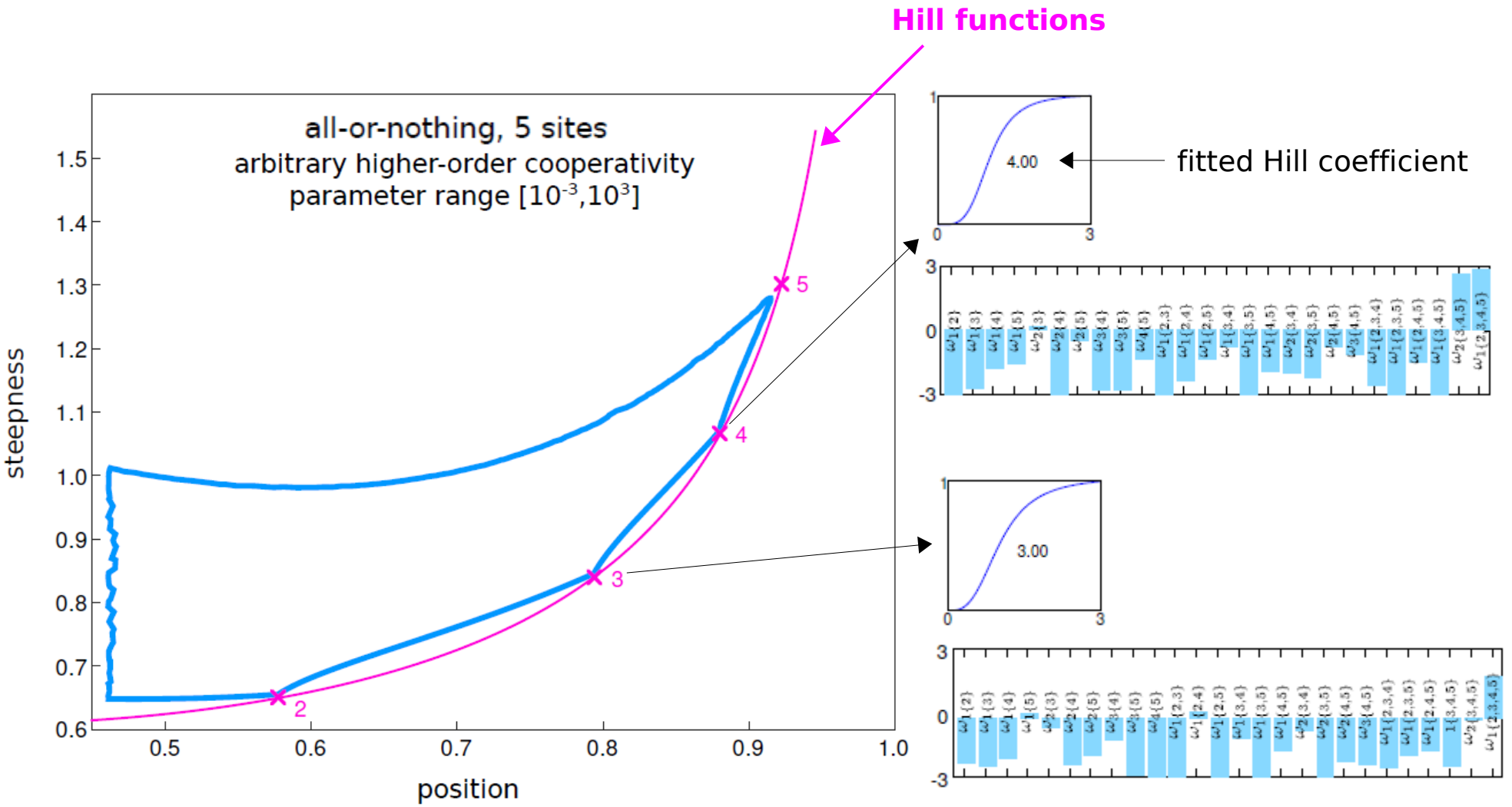
$$\rho(g_n) = \max_{y \geq 0} \frac{dg_n}{dy}$$

$$\gamma(g_n) = z \text{ such that } \left.\frac{dg_n}{dy}\right|_{y=z} = \rho(g_n)$$

“steepness”

“position”

Hill functions are GRFs



Estrada, Wong, DePace, Gunawardena, "*Information integration and energy expenditure in gene regulation*", Cell **166**:234-44 2016