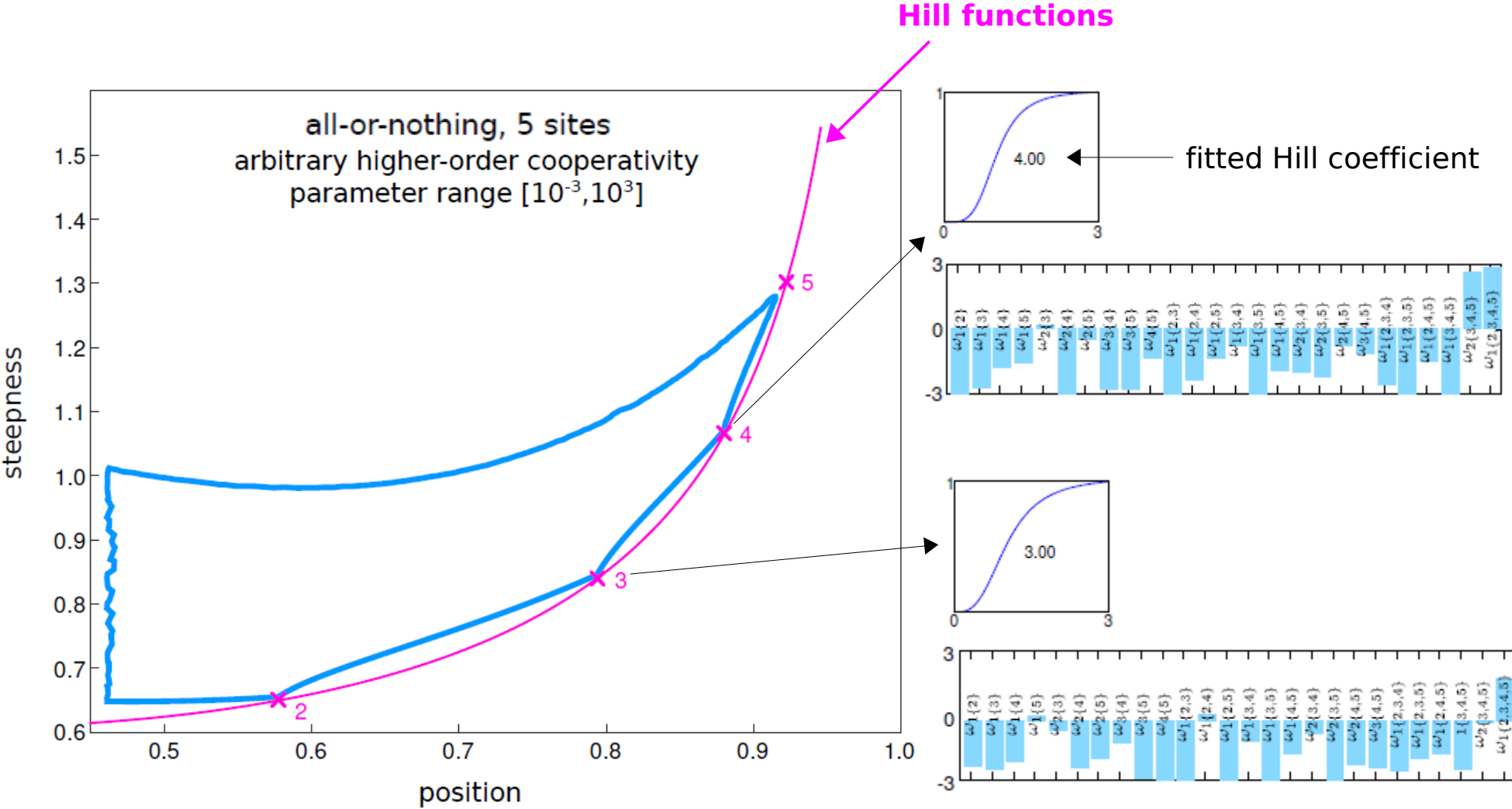


dynamic processes in cells
(a systems approach to biology)

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department of systems biology
harvard medical school

lecture 11
6 october 2016

Hill functions are GRFs



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

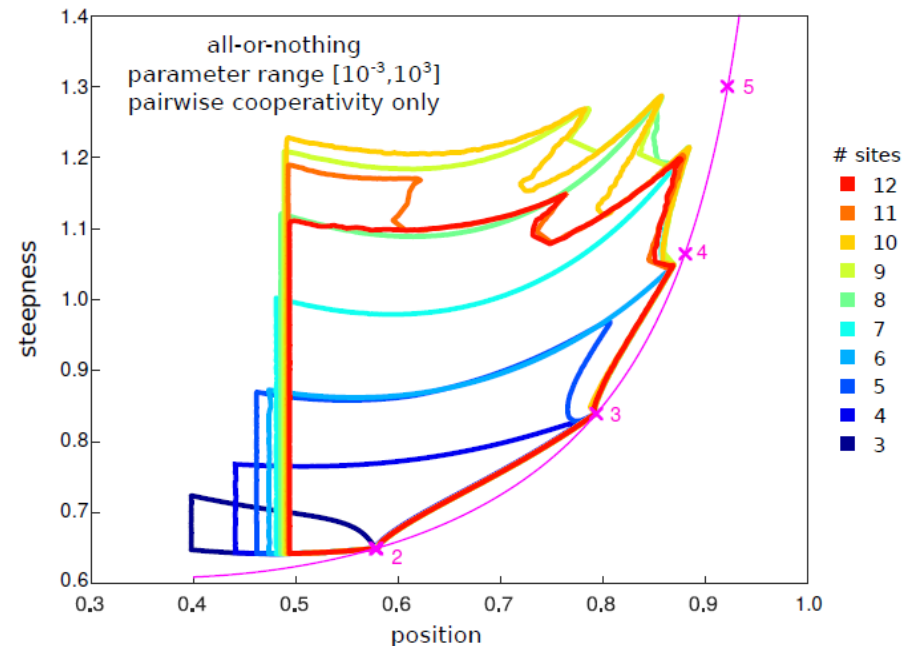
but this needs information integration

Hill functions with an integer Hill coefficient, k , can be closely approximated in shape by GRFs in the all-or-nothing strategy, provided the number of sites, n , exceeds k

however, this requires **higher-order cooperativity** of all orders for n sites.

pairwise cooperativity alone is not sufficient: no matter how many sites, n , are available, the Hill function of coefficient $k = 5$ cannot be matched in position and steepness by a GRF

$$\omega_{i,S} = 1 \text{ for } \#S > 1$$



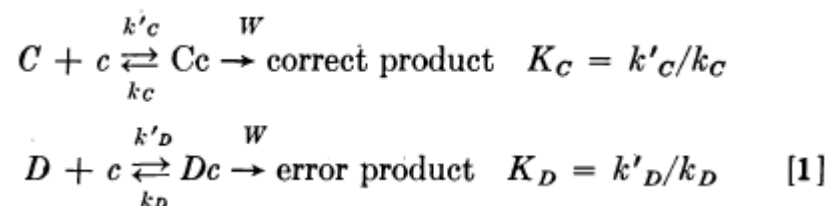
what about energy expenditure?

Hopfield, "Kinetic proofreading: a new mechanism for reducing errors in biosynthetic processes requiring high specificity", PNAS **71**:4135-9 1974



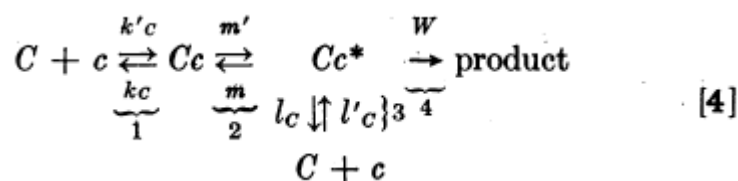
b. 1933

discrimination



equilibrium

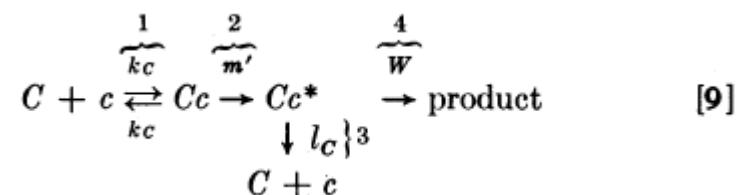
away from equilibrium



Reactions [4] as written, have an equilibrium constraint

$$(m'/m)_{\text{equilib.}} = (l'_c k_c / l_c k'_c) = l'_D k_D / l_D k'_D \quad [6]$$

relating m and m' . Within this constraint, Eq. [5] never yields an error fraction less than f_0 .



the net result is an error fraction $f \approx f_0^2$ expected for a double discrimination. *This driven kinetic pathway using a high energy intermediate achieves an error fraction equal to one achievable by doubling the differences in binding energy between C and D for a simple process like Eq. [1]*

detailed balance

the hopfield barrier in information processing

“THE HOPFIELD BARRIER”

for any information processing task, detailed balance sets an upper bound to how well it can be undertaken by a biochemical system at thermodynamic equilibrium.

the only way to exceed this barrier is to dissipate energy and maintain the system away from equilibrium

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

the problem of history dependence

at thermodynamic equilibrium only one path is needed to calculate steady-state probabilities. history does not matter.

equilibrium GRF for n sites:

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

away from equilibrium, all paths must be evaluated - the matrix-tree theorem does the bookkeeping. **history dependence** leads to a combinatorial explosion.

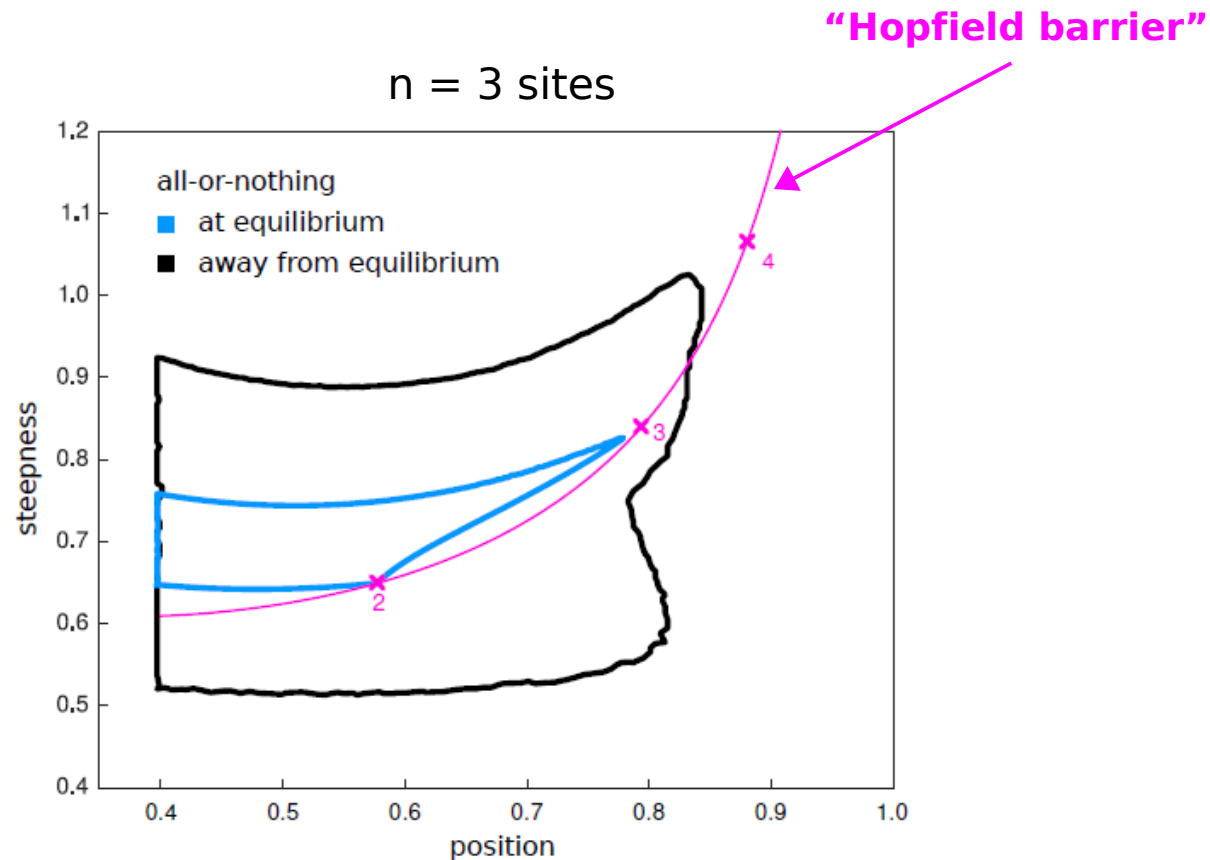
non-equilibrium GRF for n sites:

$$f_n^{ne}(x) = \frac{d_n x^n + \dots + d_{2^n-1} x^{2^n-1}}{e_0 + e_1 x + \dots + e_{2^n-1} x^{2^n-1}} \quad d_{2^n-1} = e_{2^n-1}$$

history dependence leads to a combinatorial explosion

$n = 2$ sites	4 spanning trees
$n = 3$ sites	384 spanning trees
$n = 4$ sites	42,467,328 spanning trees

the hopfield barrier for sharpness

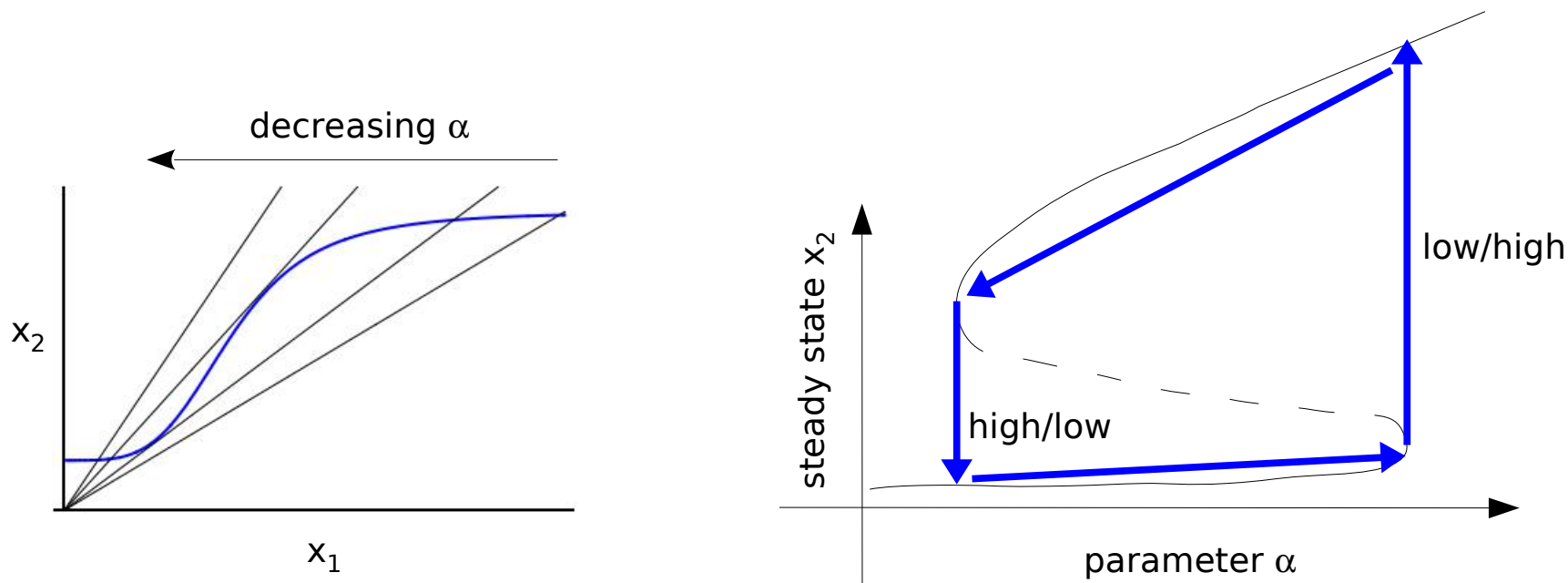


with n sites and with the all-or-nothing expression strategy the Hill line forms the Hopfield barrier for sharpness in gene regulation

with any expression strategy, the Hill function with coefficient $k = n$ forms the Hopfield barrier

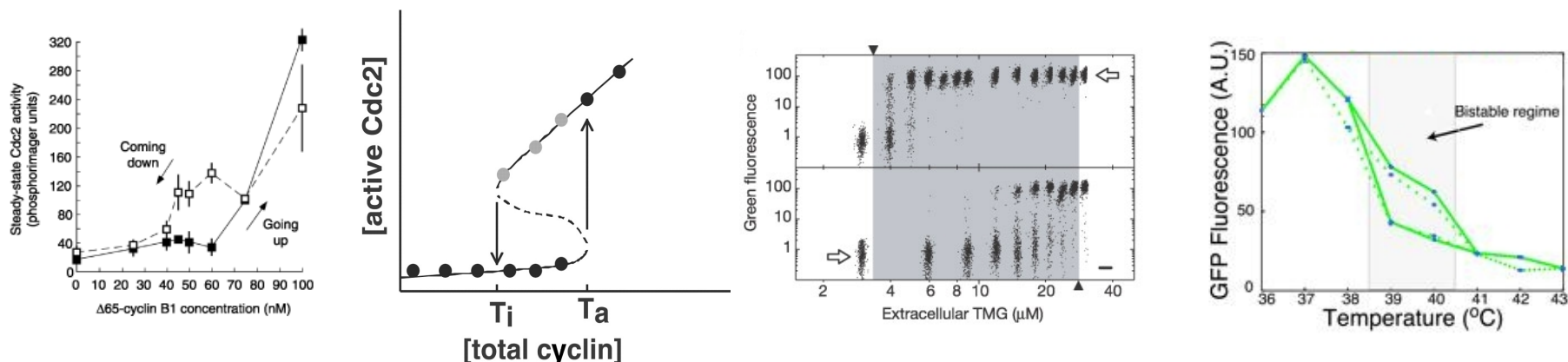
testing bistability by hysteresis

change parameter α slowly (“adiabatically”), so that the system has time to relax back to a steady state after each parameter change



hysteresis: the switch between “low” and “high” (on/off) takes place at different values of the control parameter, depending on the starting state and the direction of change - a signature of a bistable system

in practice



Pomerening, Sontag & James Ferrell “*Building a cell cycle oscillator: hysteresis and bistability in the activation of CDC2*”, *Nature Cell Biol* **5**:346-51 2005

Sha, Moore, Chen, Lassaletta, Yi, Tyson & Sible, “*Hysteresis drives cell-cycle transitions in *Xenopus laevis* egg extracts*”, *PNAS* **100**:975-80 2003

Ozbudak, Thatai, Lim, Shraiman & van Oudenaarden, “*Multistability in the lactose utilization network of *Escherichia coli**”, *Nature* **427**:737-40 2004

Isaacs, Hasty, Cantor & Collins, “*Prediction and measurement of an autoregulatory genetic module*”, *PNAS* **100**:7714-9 2003

types of bifurcation

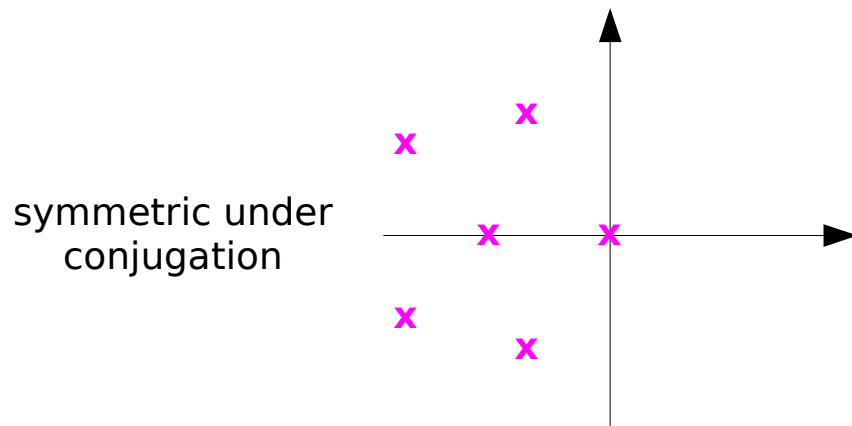
local - the dynamics only changes near a steady state

co-dimension one - requires change in one parameter only

the real part of an eigenvalue of the Jacobian matrix goes through 0

1. a single real eigenvalue becomes 0

eigenvalues of the Jacobian in the complex plane



there are three **normal forms** for this

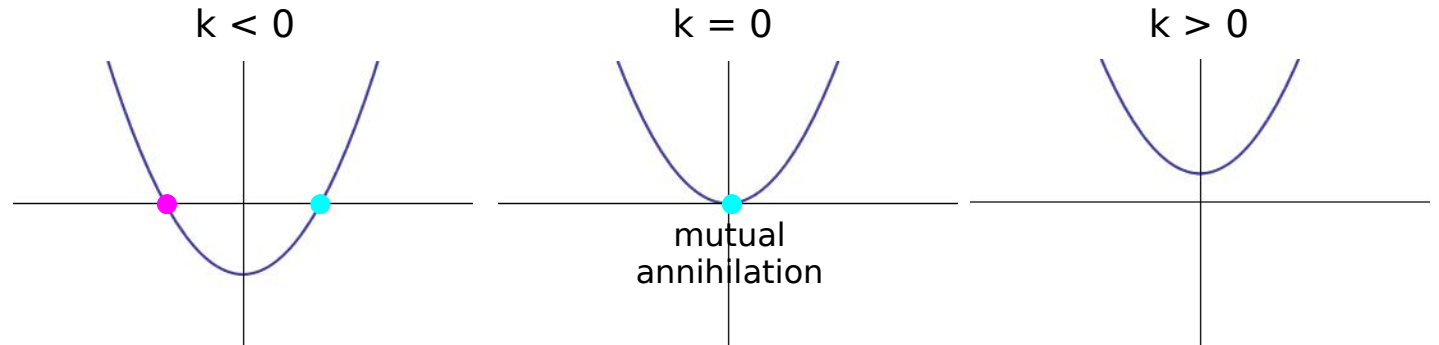


normal forms

in the vicinity of the bifurcation, and in the vicinity of the steady state, the dynamics is given approximately by one of the following forms

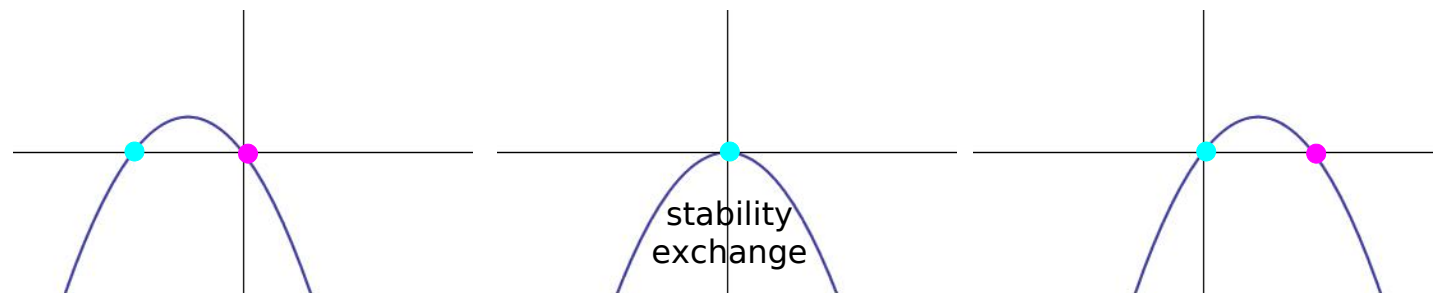
saddle-node

$$\frac{dx_1}{dt} = k + x_1^2$$



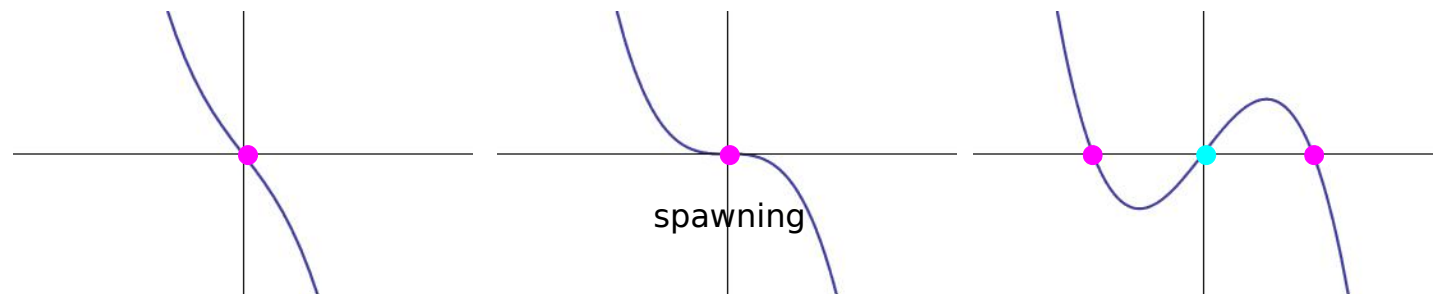
transcritical

$$\frac{dx_1}{dt} = kx_1 - x_1^2$$



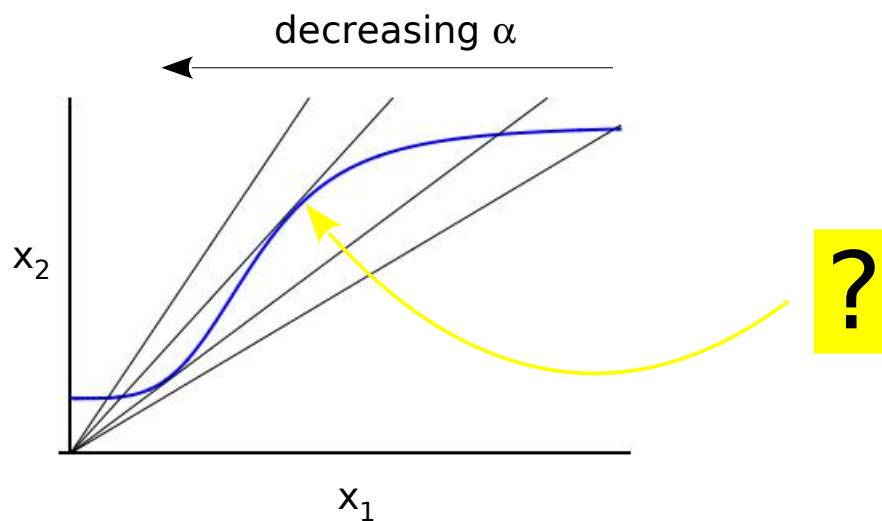
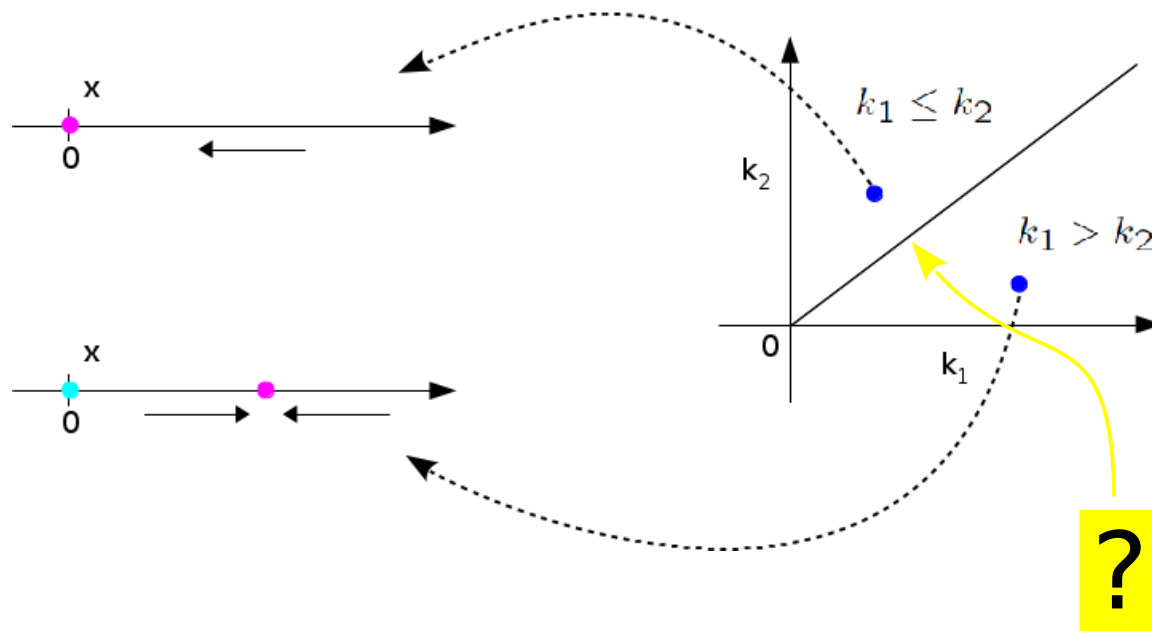
pitchfork

$$\frac{dx_1}{dt} = kx_1 - x_1^3$$



examples

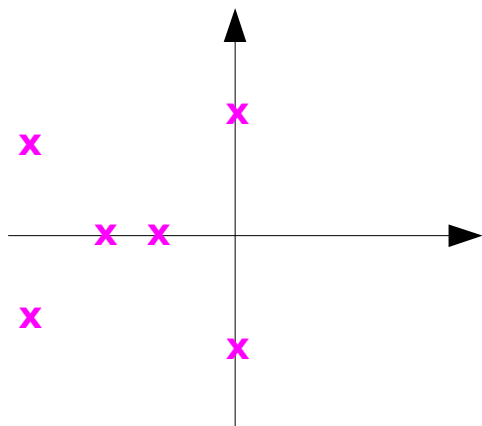
$$\frac{dx}{dt} = k_1 x(1 - x) - k_2 x$$



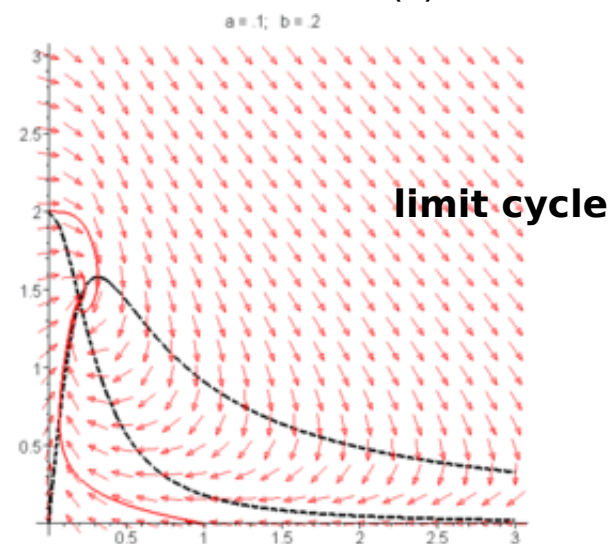
the Hopf bifurcation

2. a pair of complex conjugate eigenvalues reaches the imaginary axis

eigenvalues of the Jacobian in the complex plane



Selkov model (*)



$$\frac{d}{dt} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} \mu & -\omega_0 \\ \omega_0 & \mu \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} - (x_1^2 + x_2^2) \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$$

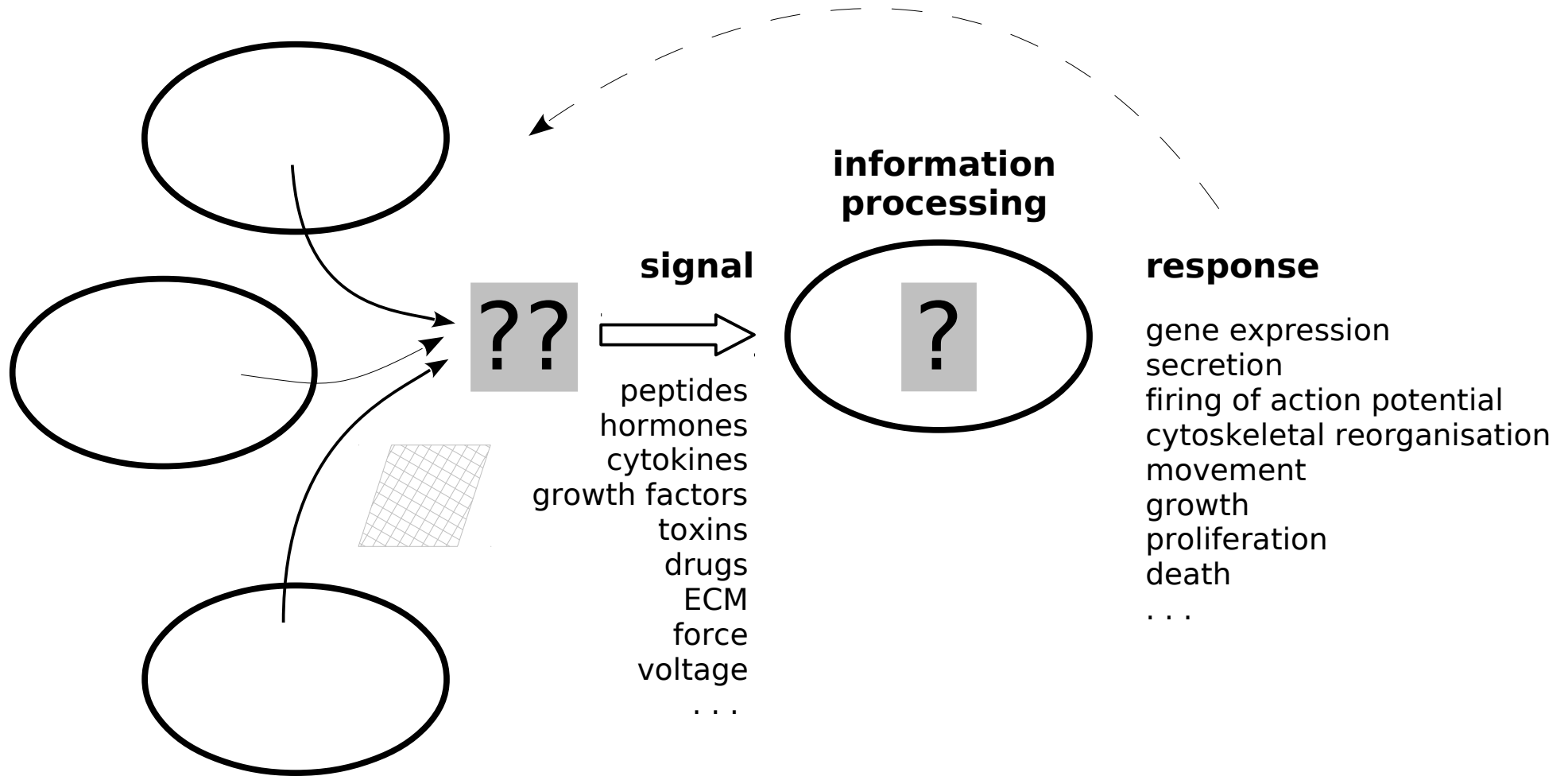
(*) Strogatz, **Nonlinear Dynamics and Chaos: with Applications to Physics, Biology, Chemistry and Engineering**, Westview Press 2001

summary

- cellular identity is determined by the pattern of gene expression
- cellular identity is often modelled as a basin or attractor in a state-space, or potential energy, landscape
- during development of an organism, cellular identity is specified in a hierarchical manner through a series of decisions
- a state-space landscape that exhibits bistability may explain transcriptional priming in hematopoiesis or heterogeneity in embryonic stem cells
- bistability requires positive feedback and sharpness (cooperativity) in gene expression
- sharpness in gene expression is often represented mathematically by some form of Hill function but this has no biophysical interpretation
- the Hill function forms the Hopfield barrier to sharpness in gene expression but reaching this barrier requires all higher-order cooperativities at equilibrium

5. information processing in signal transduction

from the outside to the inside



information processing = computing, not plumbing

signal
→



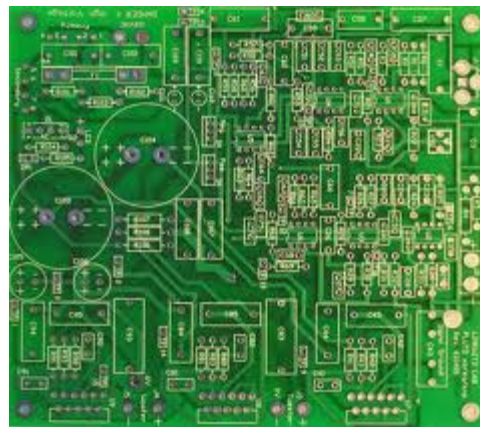
cytoplasm



nucleus

X

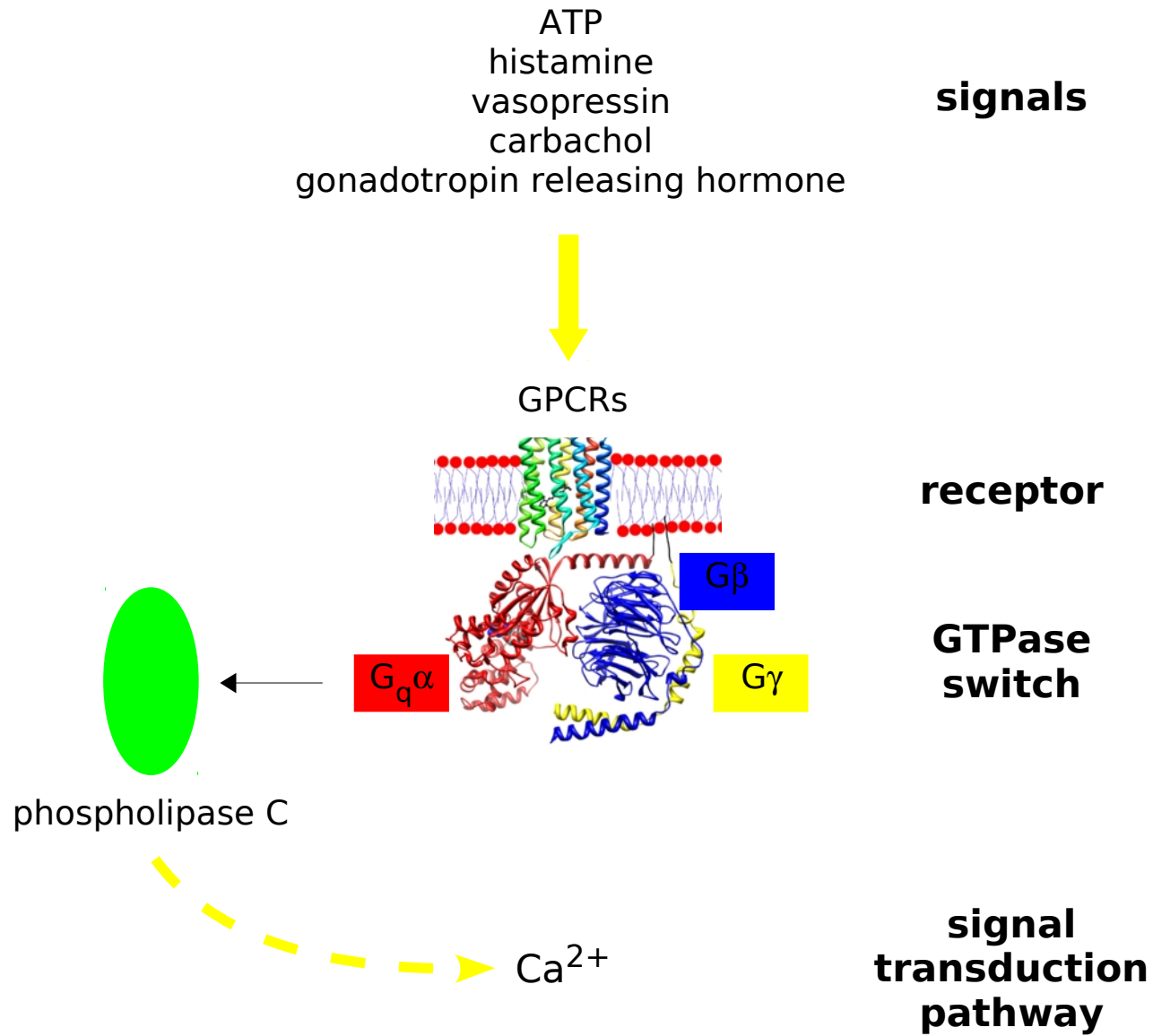
signal
→



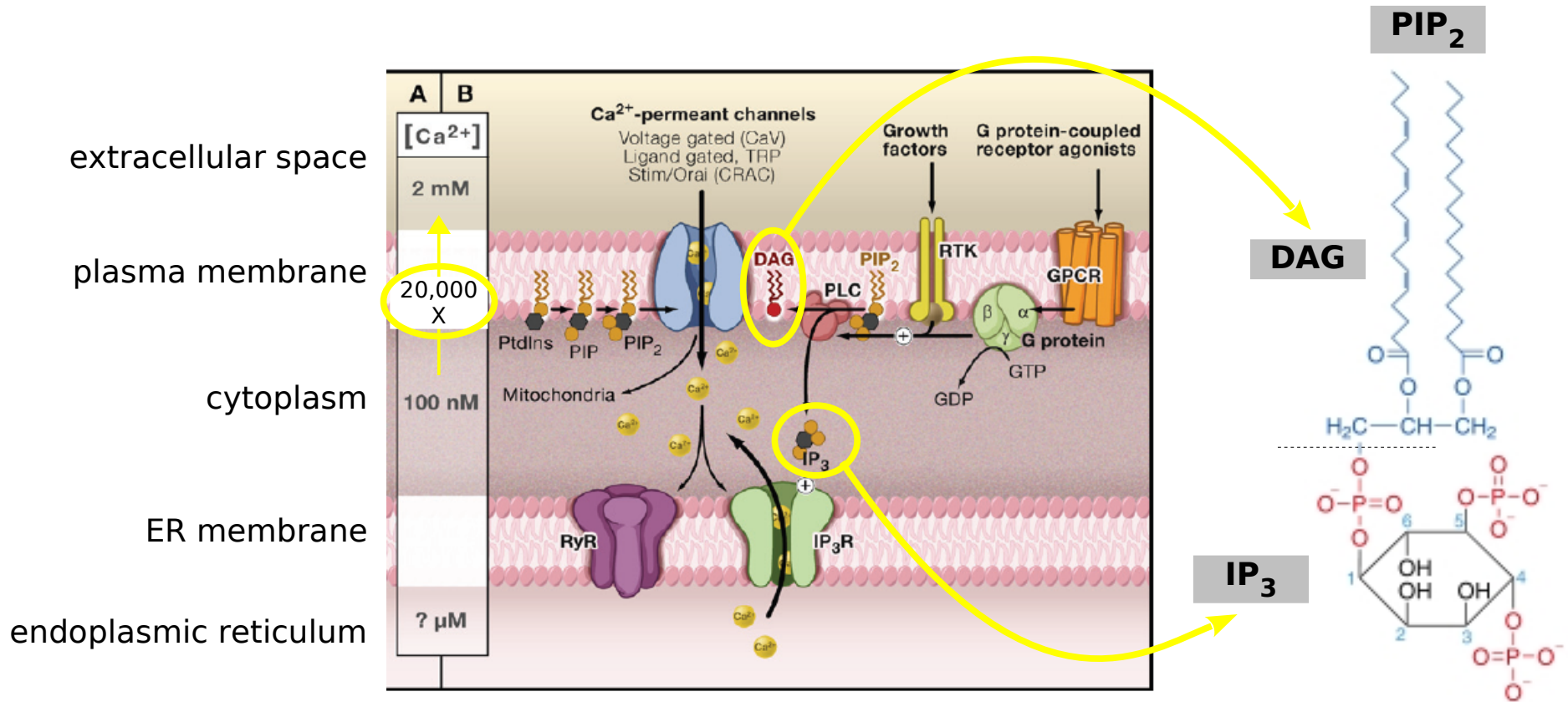
???

✓

Ca²⁺ signalling



a tale of second messengers



Ca²⁺ is toxic and at a 20,000X difference in concentration between extra- and intra-cellular compartments

phosphatidylinositol 4,5-bisphosphate - **PIP₂**
 diacylglycerol - **DAG**
 inositol 1,4,5-trisphosphate - **IP₃**

Clapham, "Calcium signaling", Cell **131**:1047-58 2007

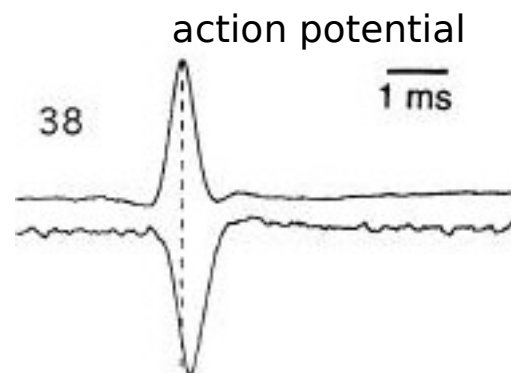
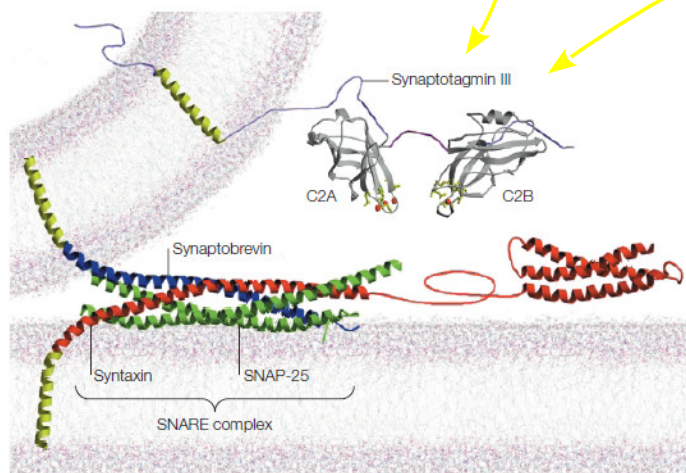
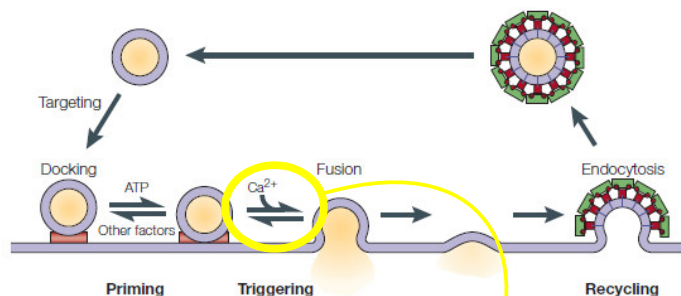
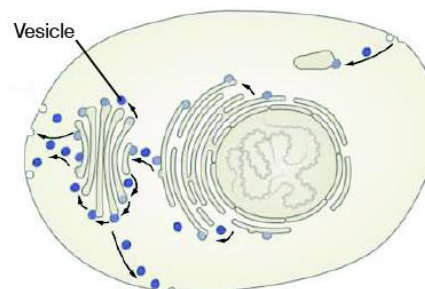
the need for speed

neurotransmitter release from synaptic vesicles

P&M 2013



vesicle trafficking



Ca²⁺ entry - 150 μs @38degC - but is highly temperature sensitive

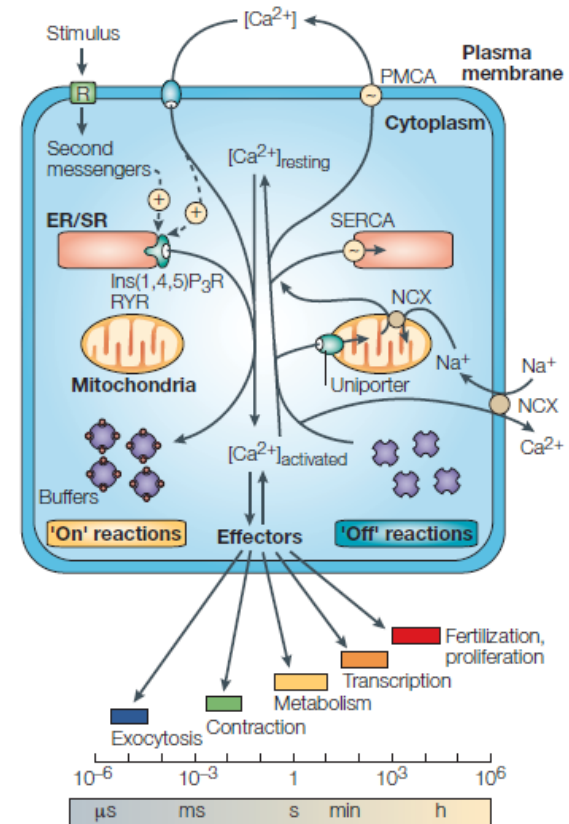
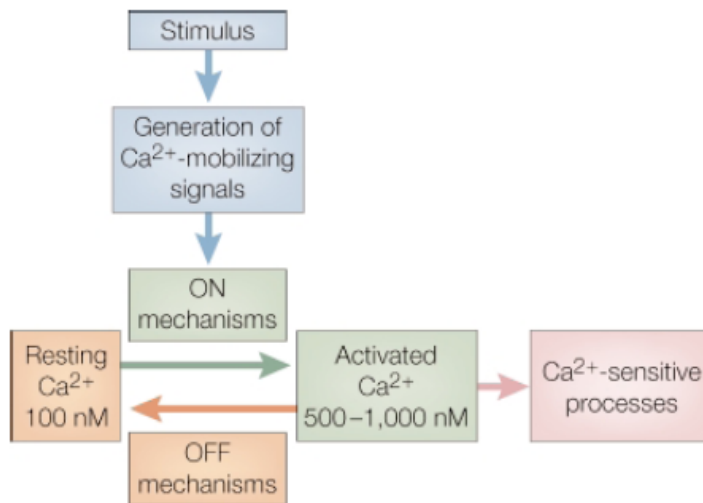
Chapman, "Synaptotagmin: a Ca²⁺ sensor that triggers exocytosis", Nat Rev Mol Cell Biol **3**:1-11 2002; Sabatini, Regehr, "Timing of neurotransmission at fast synapses in the mammalian brain", Nature **384**:170-2 1996

Ca²⁺ signalling “toolkit”

different cell types mix and match components from a “toolkit”

Ca²⁺ handling/sensitive pumps, channels, receptors, buffers, stores

to provide cellular responses appropriate to the cells' physiological roles



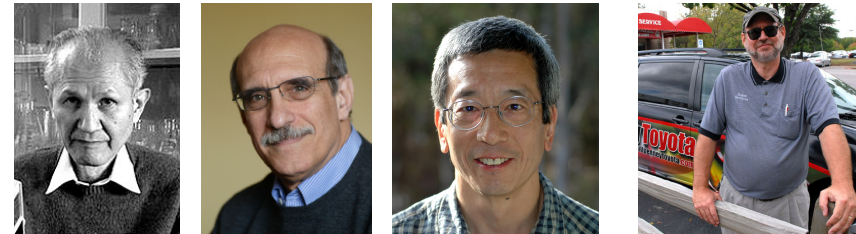
Berridge, Lipp, Bootman, Nat Rev Mol Cell Biol **1**:11-21 2000

Berridge, Bootman, Roderick, Nat Rev Mol Cell Biol **4**:517-29 2003

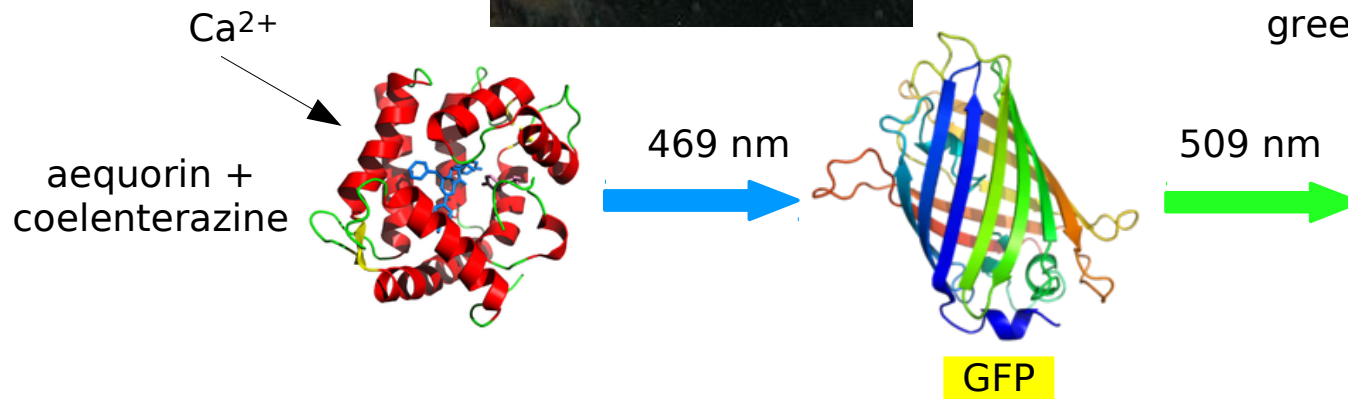
measuring Ca^{2+}



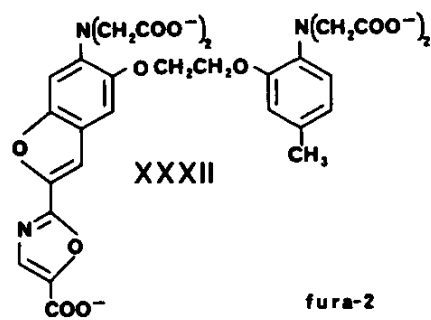
Chem 2008



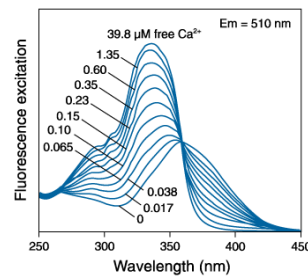
green fluorescent protein



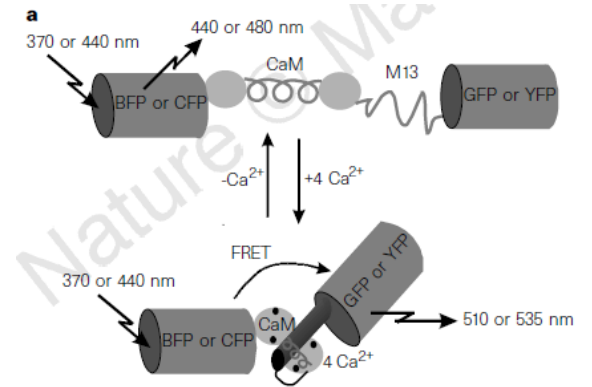
fura2



ratiometric 340/380 excitation

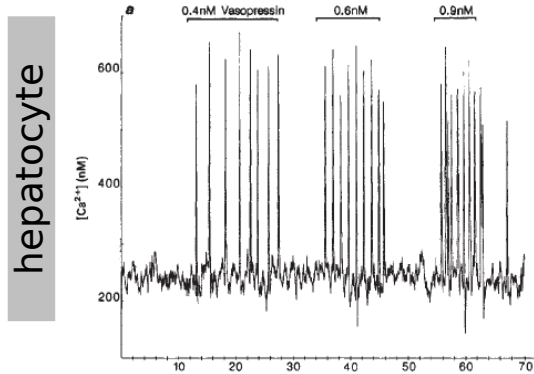


cameleons



Osamu Shimomura, "A short story of aequorin", Biol Bull **2**:3074-92 1988; Grynkiewicz, Poenie, Tsien, JBC **260**:3440-50 1985; Miyawaki et al, Nature **338**:882-7 1997

Ca²⁺ oscillations

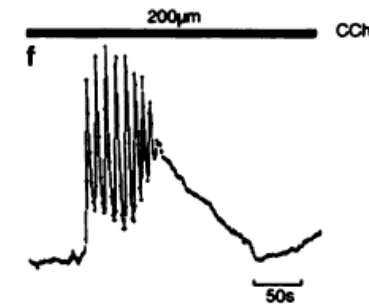
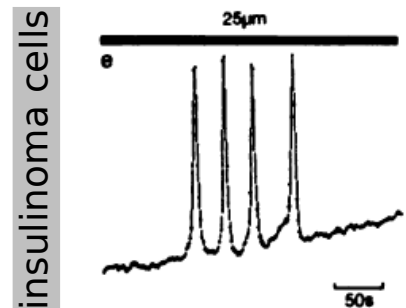
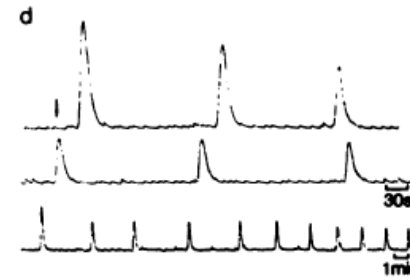
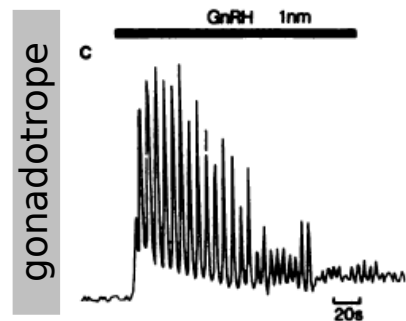
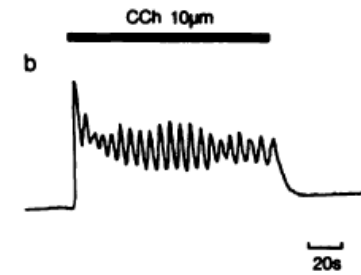
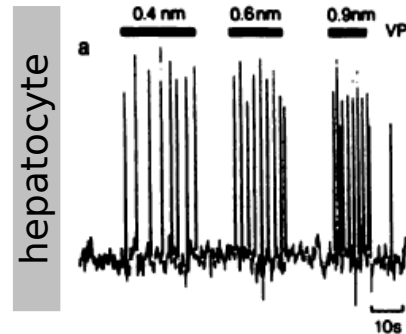
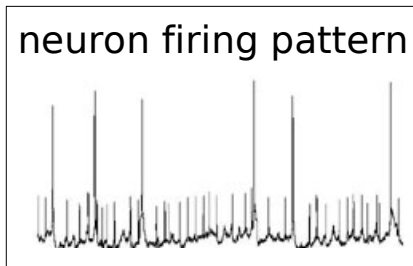


GPCR signalling

VP = vasopressin

CCh = carbachol

GnRH = gonadotropin releasing hormone



Woods, Cuthbertson, Cobbold, "Repetitive transient rises in cytoplasmic free calcium in hormone-stimulated hepatocytes", Nature **319**:600-2 1986

Berridge, Galione, "Cytosolic calcium oscillations", FASEB J **2**:3074-92 1988