dynamic processes in cells
(a systems approach to biology)

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lecture 11
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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?


\[
C + c \xrightleftharpoons[k_c]{k'_c} Cc \rightarrow \text{correct product} \quad K_C = \frac{k'_c}{k_c}
\]

\[
D + c \xrightleftharpoons[k_d]{k'_d} Dc \rightarrow \text{error product} \quad K_D = \frac{k'_d}{k_d}
\]  \[1\]

equilibrium

discrimination

Reactions [4] as written, have an equilibrium constraint

\[(m'/m)_{\text{equil.}} = \frac{(l_c'k_c/l_c)k'_c}{l'_c} = \frac{l'_Dk'_D/l_Dk_D'}{4} \]  \[6\]

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

away from equilibrium

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]
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:

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

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:

\[
f^{ne}_n(x) = \frac{d_n x^n + \cdots + d_{2n-1} x^{2n-1}}{e_0 + e_1 x + \cdots + e_{2n-1} x^{2n-1}} \quad d_{2n-1} = e_{2n-1}
\]

history dependence leads to a combinatorial explosion

\[
\begin{align*}
n = 2 \text{ sites} & \quad 4 \text{ spanning trees} \\
n = 3 \text{ sites} & \quad 384 \text{ spanning trees} \\
n = 4 \text{ sites} & \quad 42,467,328 \text{ spanning trees}
\end{align*}
\]
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 $\alpha$ 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.

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


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

![Diagram of eigenvalues in the complex plane](image)

symmetric under conjugation

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

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

k < 0  
mutual annihilation  
k = 0  

k > 0

transcritical

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

k < 0  

k = 0  
stability exchange  
k > 0

pitchfork

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

k < 0  

k = 0  
spawning  
k > 0
Examples

\[ \frac{dx}{dt} = k_1 x(1 - x) - k_2 x \]
2. A pair of complex conjugate eigenvalues reaches the imaginary axis

eigenvalues of the Jacobian in the complex plane

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

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

signal

response
gene expression
secretion
firing of action potential
cytoskeletal reorganisation
movement
growth
proliferation
death

information processing

peptides
hormones
cytokines
growth factors
toxins
drugs
ECM
force
voltage

...
information processing = computing, not plumbing

signal

<image of plumbing system>

→

cytoplasm

→
nucleus

X

signal

<image of electronic circuit>

→

???

✔
Ca\textsuperscript{2+} signalling

ATP
histamine
vasopressin
carbachol
gonadotropin releasing hormone

GPCRs

phospholipase C

G\textsubscript{q} \alpha
G\beta
G\gamma

GTPase

switch

receptor

signal transduction pathway

signals

Ca\textsuperscript{2+}
Ca\(^{2+}\) is toxic and at a 20,000X difference in concentration between extra- and intra-cellular compartments.

the need for speed

neurotransmitter release from synaptic vesicles

**Ca\textsuperscript{2+} signalling “toolkit”**

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

Ca\textsuperscript{2+} handling/sensitive pumps, channels, receptors, buffers, stores
to provide cellular responses appropriate to the cells' physiological roles

measuring $\text{Ca}^{2+}$

Aequoria victoria

$\text{Ca}^{2+}$

eaquorin + coelenterazine

$\text{GFP}$

469 nm

509 nm

Fura2

ratiometric 340/380 excitation

Ca^{2+} oscillations
