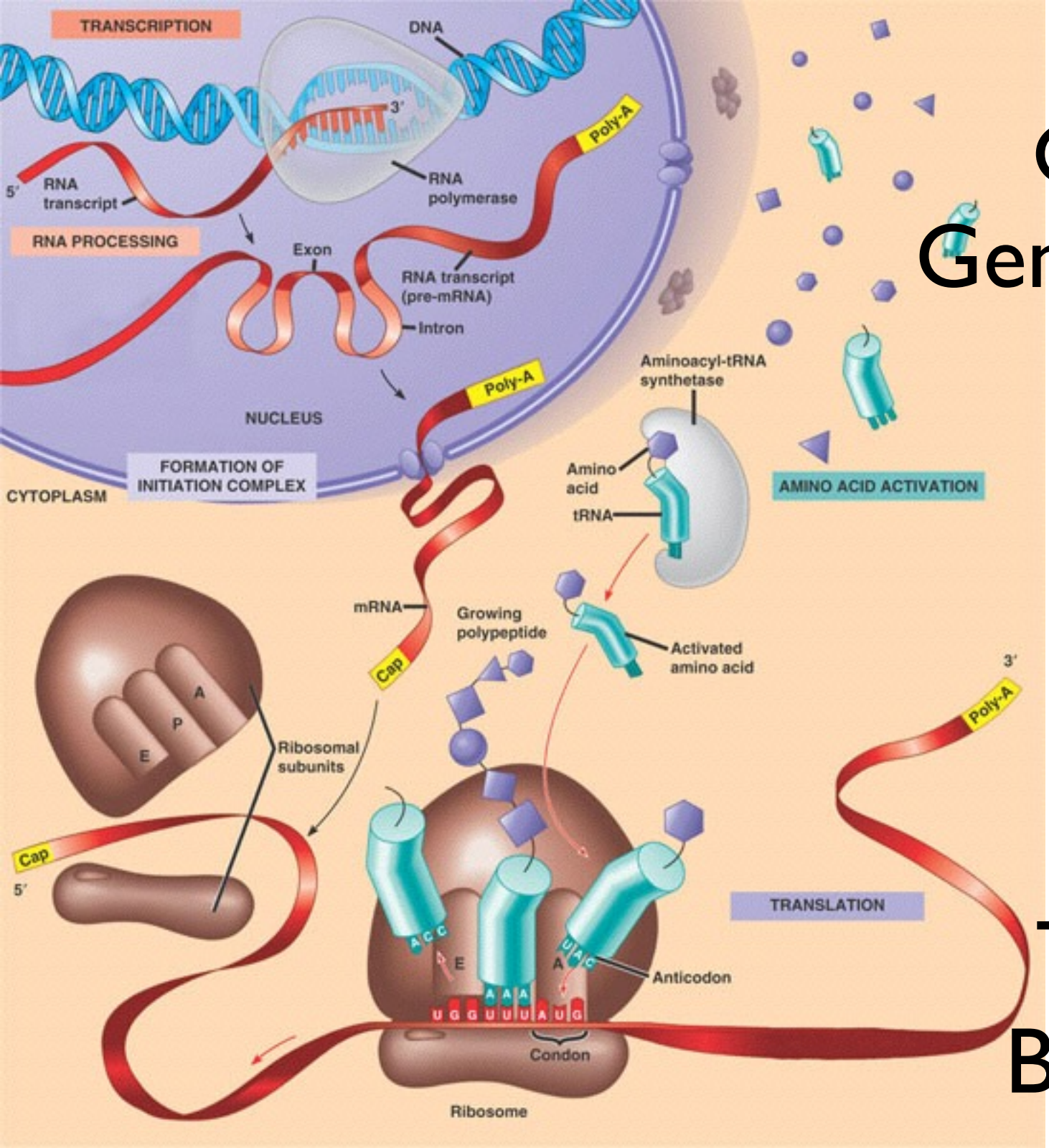
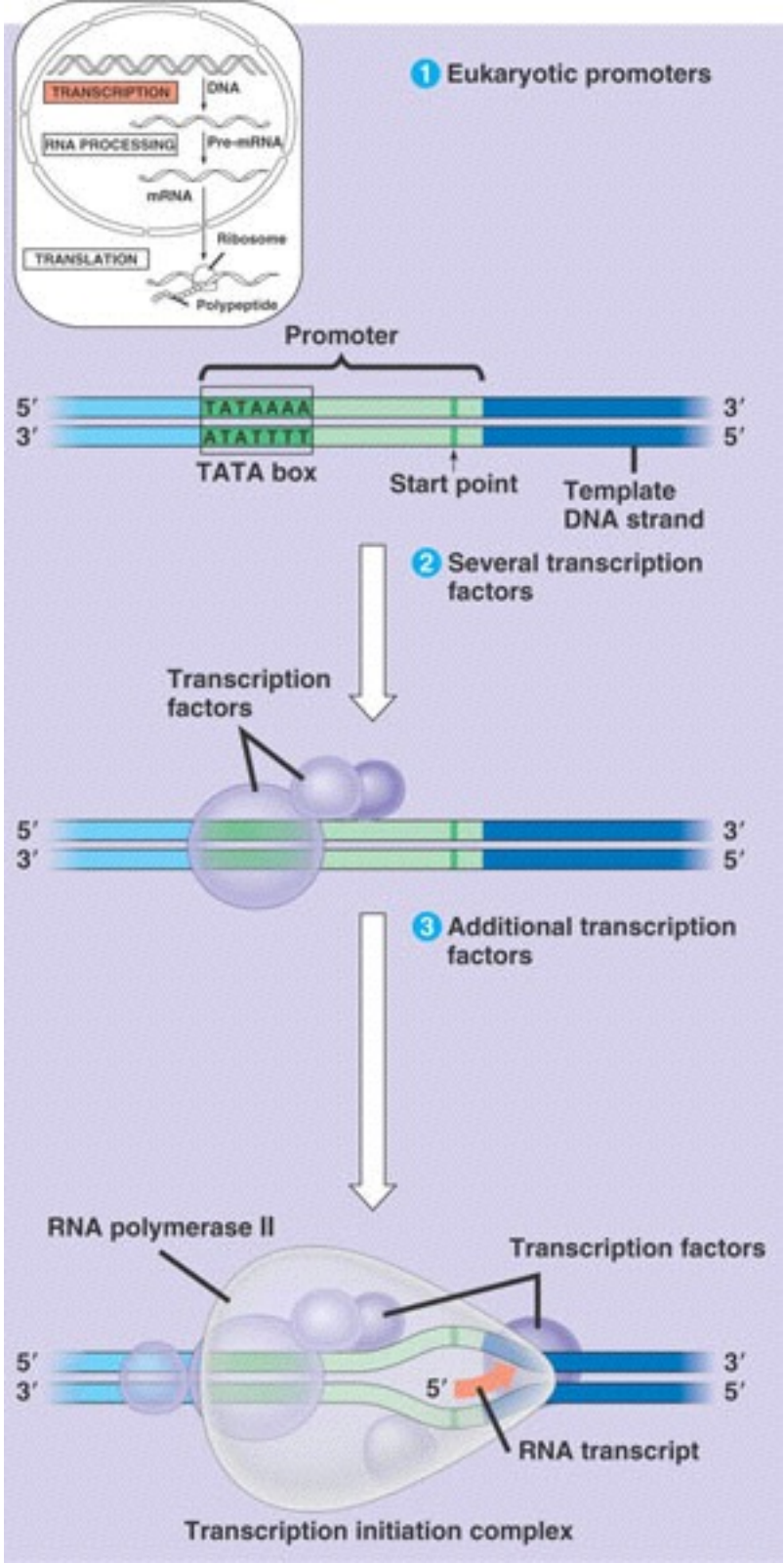


Chapter 7
Gene regulation

Theoretical Biology 2016

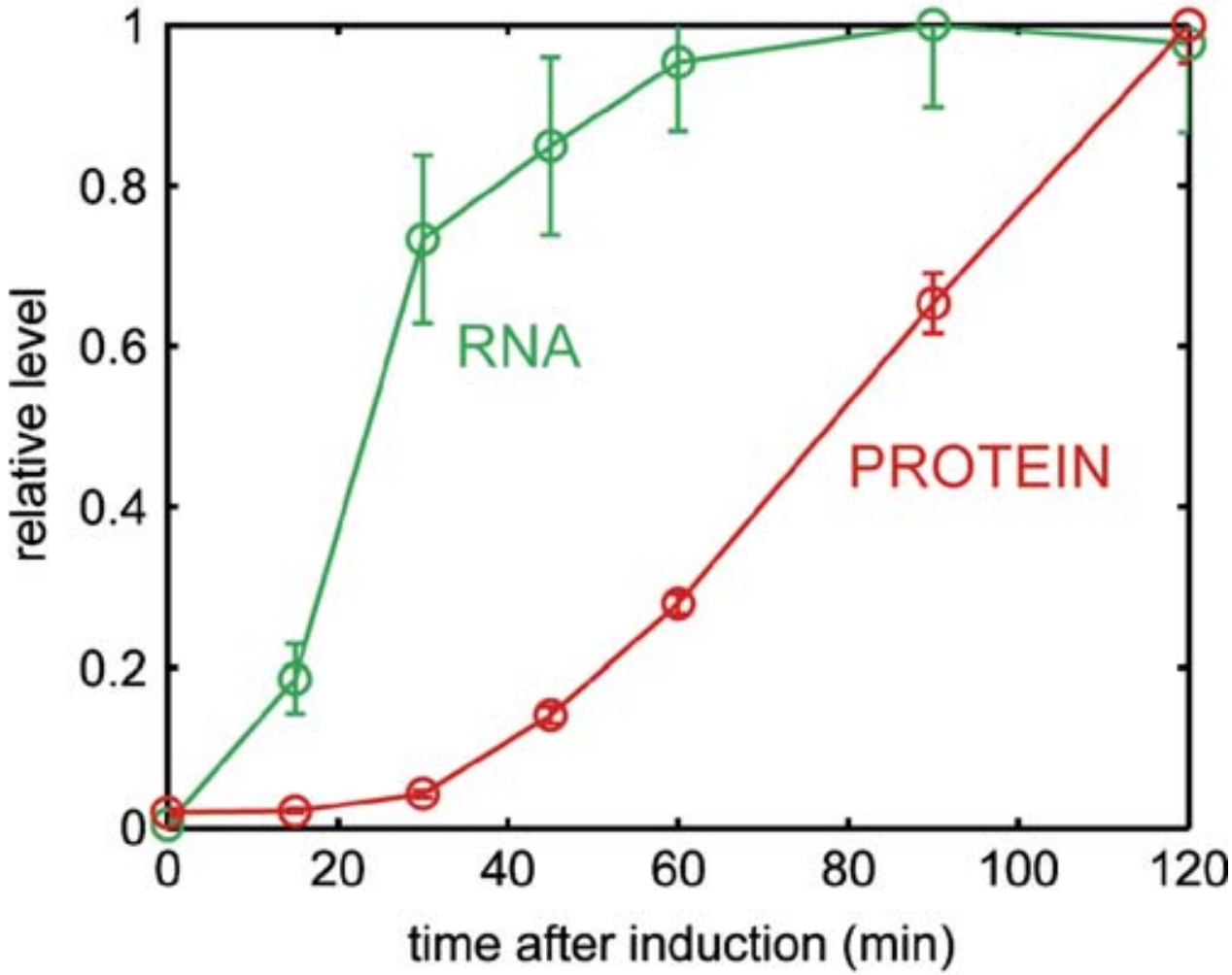


Transcription factors

bind DNA
to block or enhance transcription

From Campbell

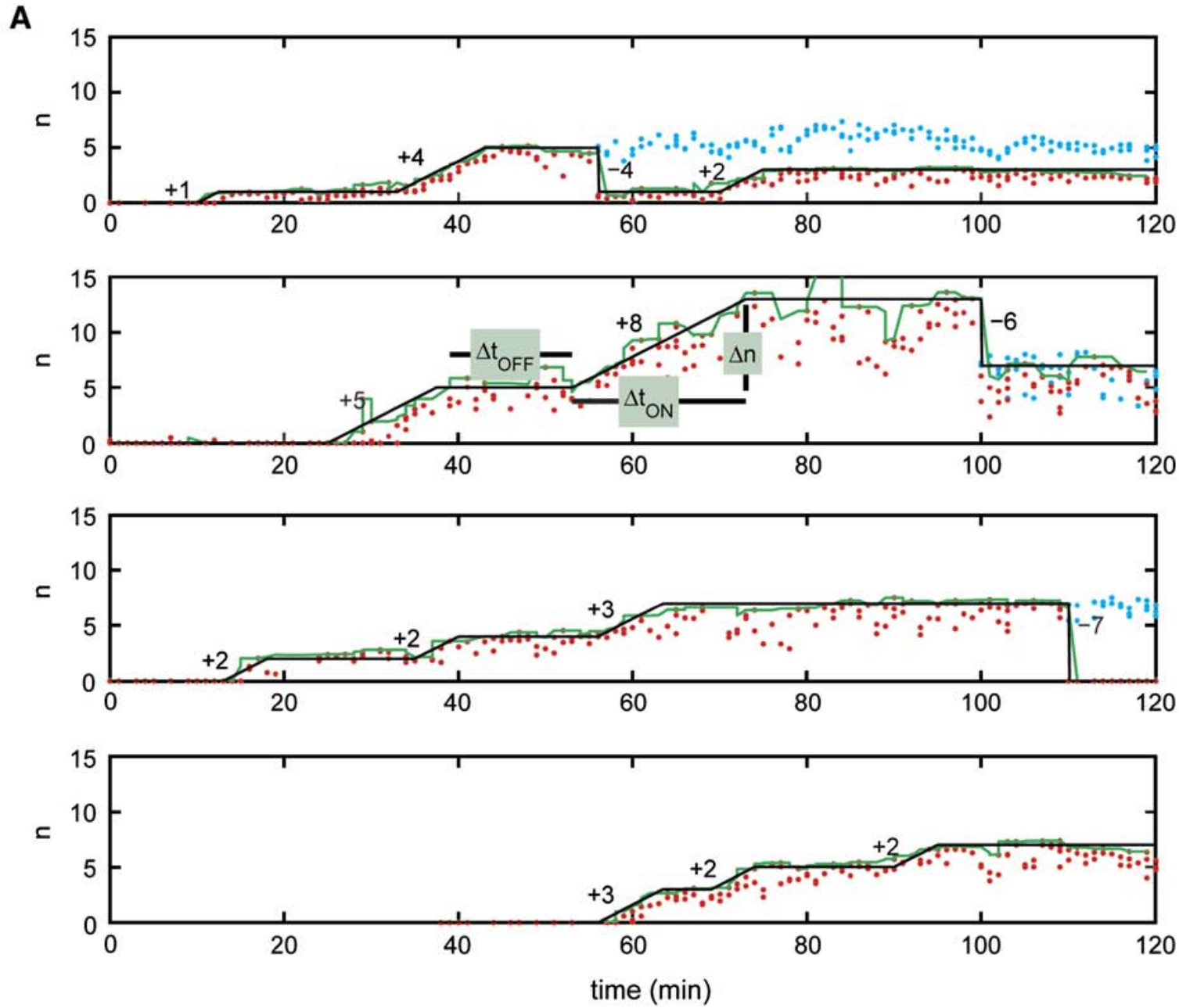
DNA makes RNA makes protein



Golding et al. Cell 2005

$$\frac{\mathrm{d}M}{\mathrm{d}t} = c - dM \quad \text{and} \quad \frac{\mathrm{d}P}{\mathrm{d}t} = lM - \delta P$$

mRNA formation occurs in bursts

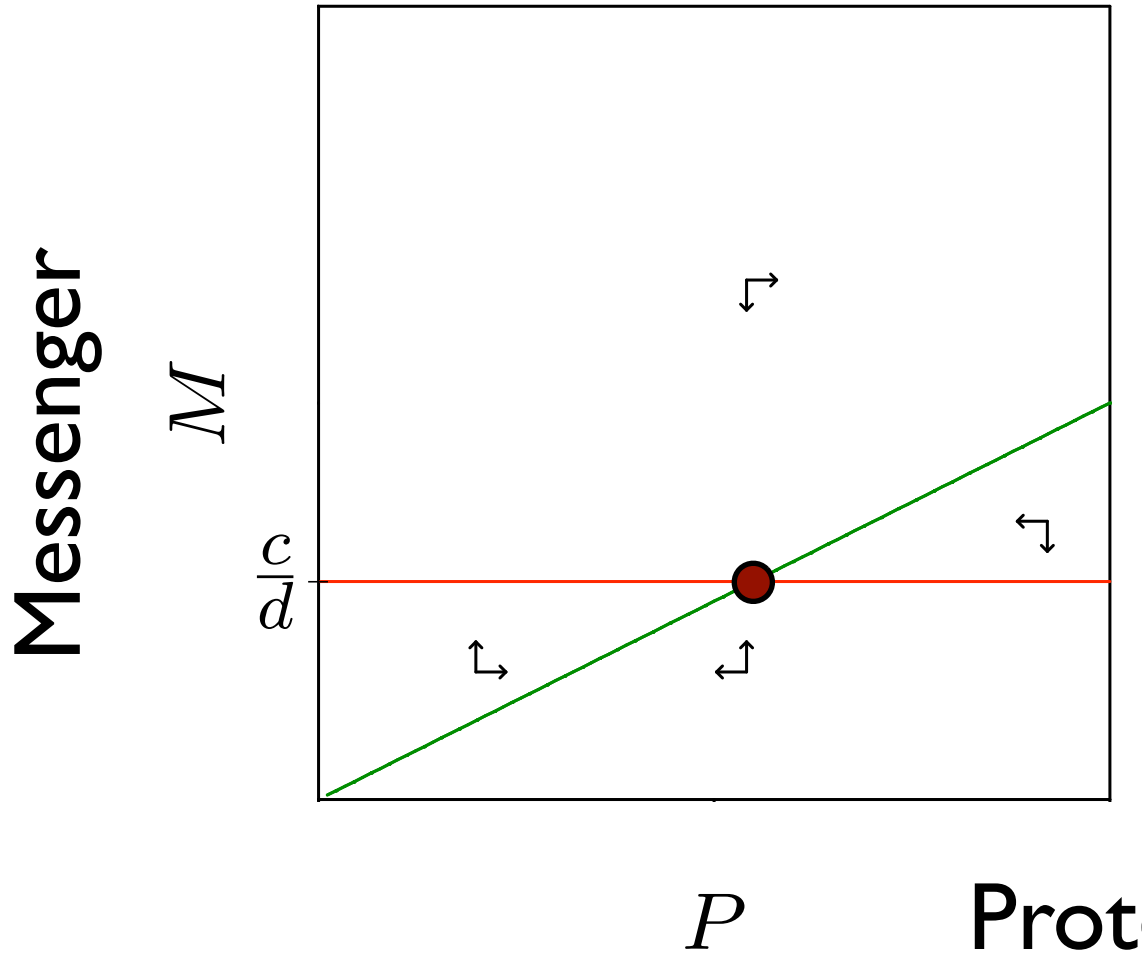


Golding et al. Cell 2005

Number of mRNA transcripts in individual cells over time.

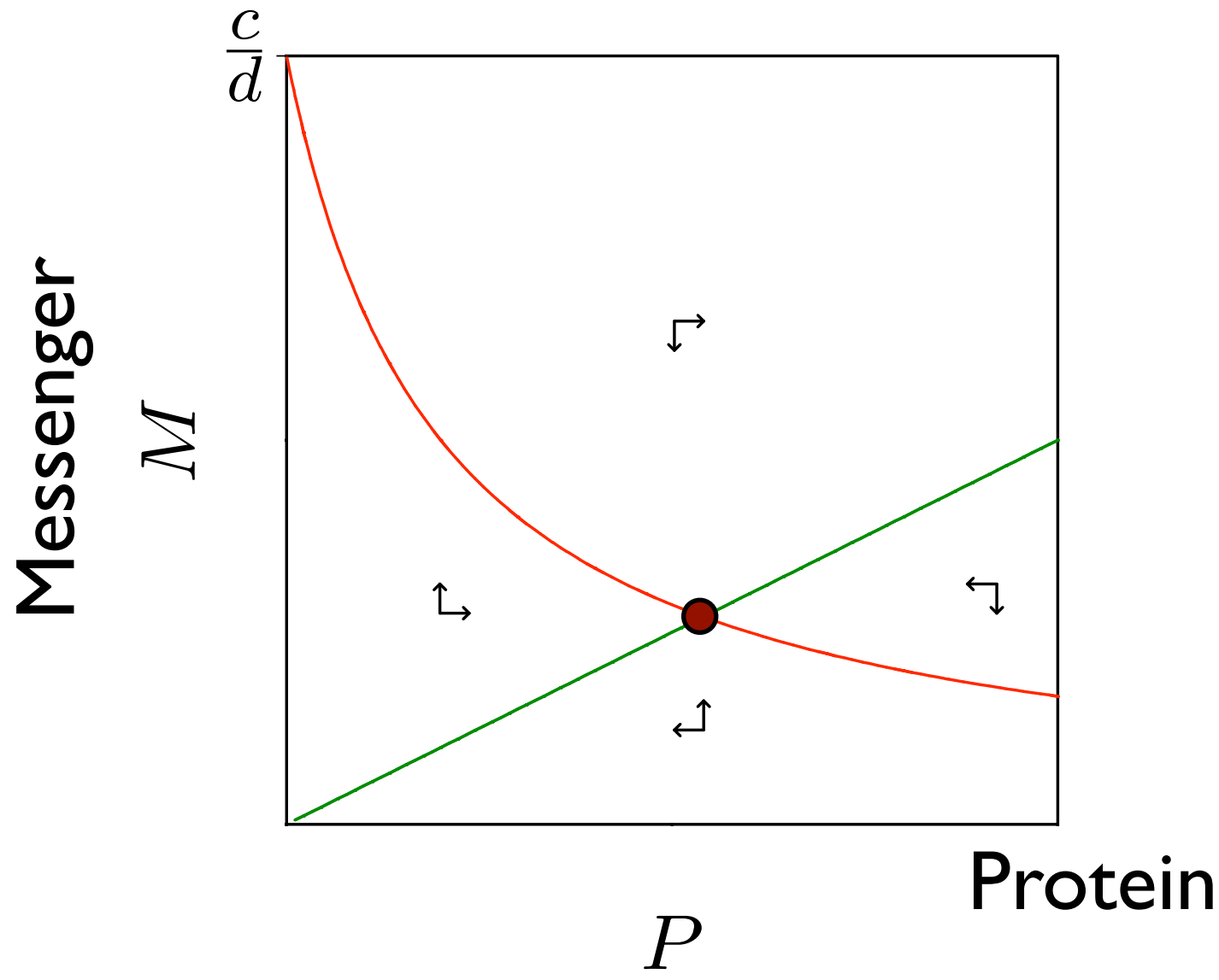
Red: data, blue: daughter cells, drops: cell division.

Mathematical model: mRNA & protein



$$\frac{\mathrm{d}M}{\mathrm{d}t} = c - dM \quad \text{and} \quad \frac{\mathrm{d}P}{\mathrm{d}t} = lM - \delta P$$

Now with negative feedback on transcription



$$\frac{\mathrm{d}M}{\mathrm{d}t} = \frac{c}{1 + P/h} - dM \quad \text{and} \quad \frac{\mathrm{d}P}{\mathrm{d}t} = lM - \delta P$$

Quasi steady state assumption

$$\frac{\mathrm{d}M}{\mathrm{d}t} = \frac{c}{1 + P/h} - dM \quad \text{and} \quad \frac{\mathrm{d}P}{\mathrm{d}t} = lM - \delta P$$

Suppose turnover of protein much faster than that of mRNA

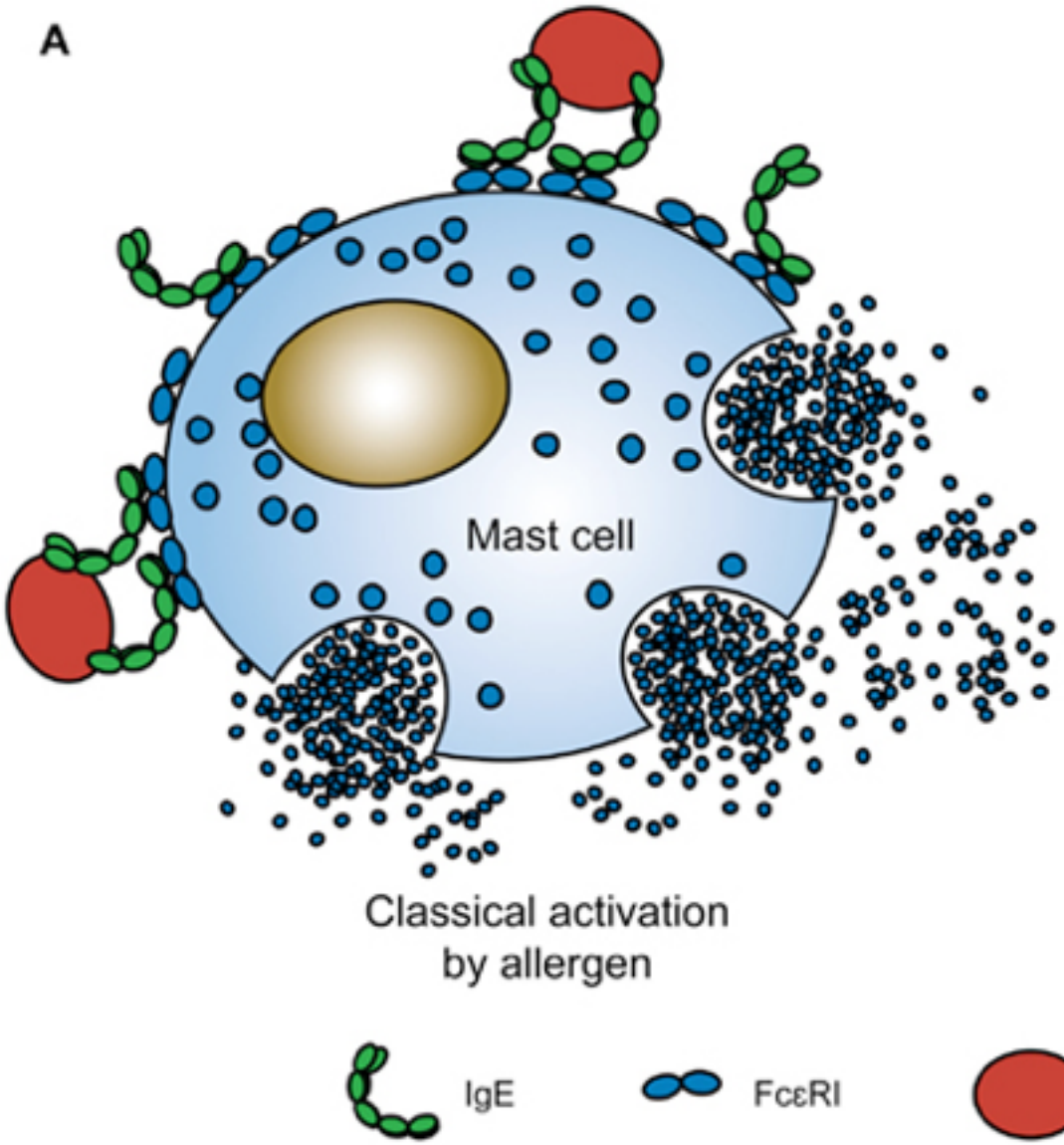
$$\frac{\mathrm{d}P}{\mathrm{d}t} = lM - \delta P = 0 \qquad \text{or} \qquad P = \frac{l}{\delta} M$$

Substituting this into d*M*/d*t* gives:

$$\frac{\mathrm{d}M}{\mathrm{d}t} = \frac{c}{1 + (l/\delta)M/h} - dM = \frac{c}{1 + M/h'} - dM$$

with $h' = h\delta/l$

Cross linking of receptors activates cells



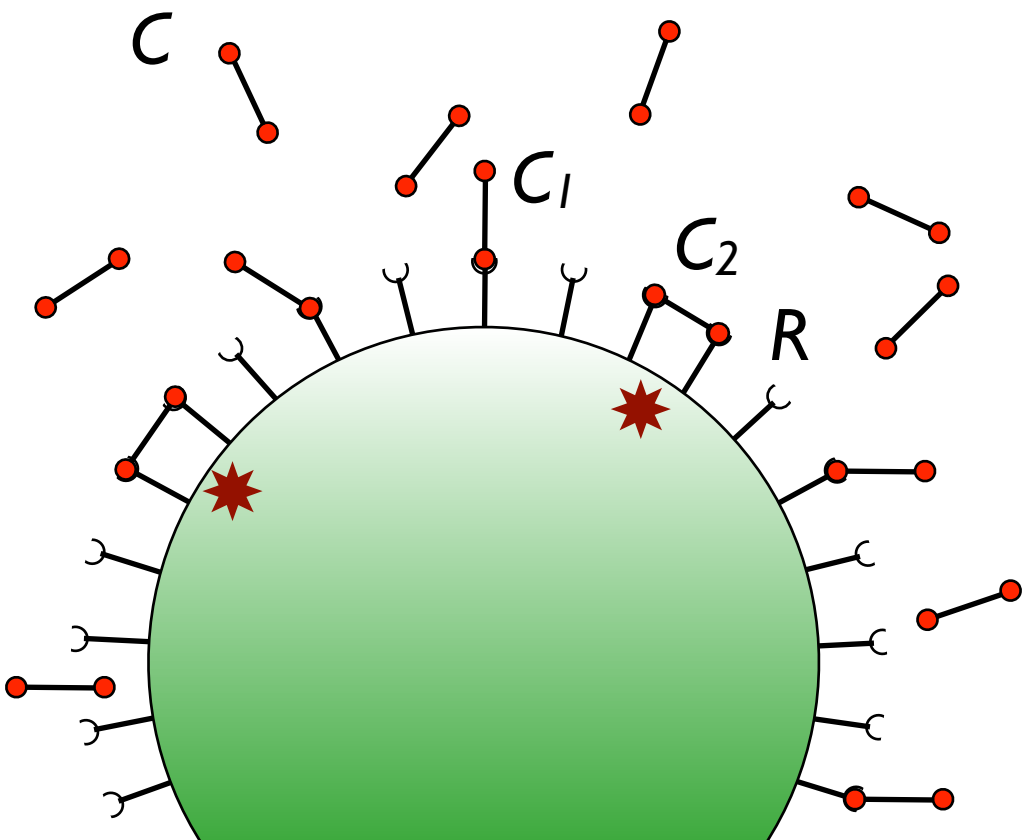
Mast cell degranulation

B cells activate and start to divide

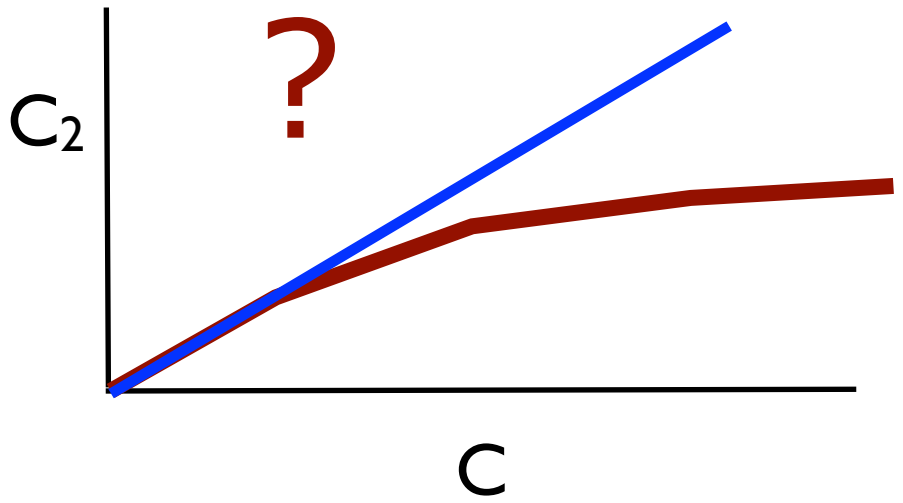
Bivalent ligand binding a monovalent receptor

$$\frac{\mathrm{d}N}{\mathrm{d}t} = bN\frac{2C_2}{R_T} - dN$$

C: free ligand (*C* > *NR*$_T$),
R: free receptors,
R$_T$: total receptors,
C$_1$: single bound ligand,
C$_2$: double bound ligand:
R$_T$ = *R* + *C*$_1$ + 2*C*$_2$



How does *C*$_2$, and hence the growth rate, depend on *C*?



$$
\begin{aligned}
R_T &= R + C_1 + 2C_2 \ , \\
\frac{\mathrm{d}C_1}{\mathrm{d}t} &= 2k_{\mathrm{on}}RC - k_{\mathrm{off}}C_1 - x_{\mathrm{on}}RC_1 + 2x_{\mathrm{off}}C_2 \ , \\
\frac{\mathrm{d}C_2}{\mathrm{d}t} &= x_{\mathrm{on}}RC_1 - 2x_{\mathrm{off}}C_2 \ .
\end{aligned}
$$

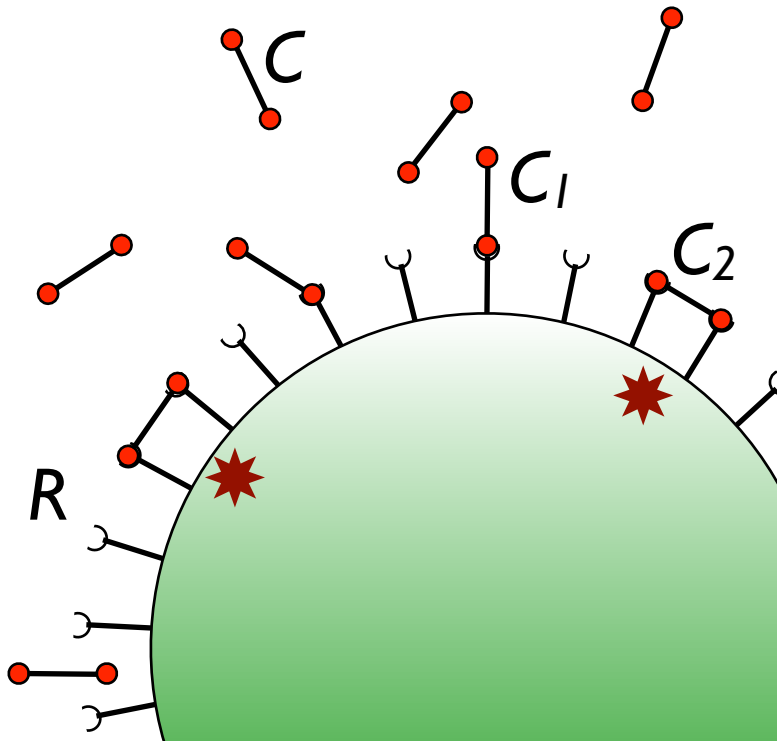
To study the steady state we set $\mathrm{d}C_2/\mathrm{d}t = 0$ and add this to $\mathrm{d}C_1/\mathrm{d}t$:

$$
\frac{\mathrm{d}C_1}{\mathrm{d}t} = 0 = 2k_{\mathrm{on}}RC - k_{\mathrm{off}}C_1 = 2KRC - C_1 \ ,
$$

where $K = k_{\mathrm{on}}/k_{\mathrm{off}}$ and $R = R_T - C_1 - 2C_2$.

Solving this gives

$$
\overline{C_1} = \frac{2CK(R_T - 2C_2)}{1 + 2CK} \ ,
$$



$$\overline{C_1} = \frac{2CK(R_T - 2C_2)}{1 + 2CK}\ , \qquad \frac{\mathrm{d}C_2}{\mathrm{d}t} = x_{\mathrm{on}} R C_1 - 2x_{\mathrm{off}} C_2\ .$$

which can be substituted into $\mathrm{d}C_2/\mathrm{d}t = 0$ to solve $\overline{C_2}$ as a function of C:

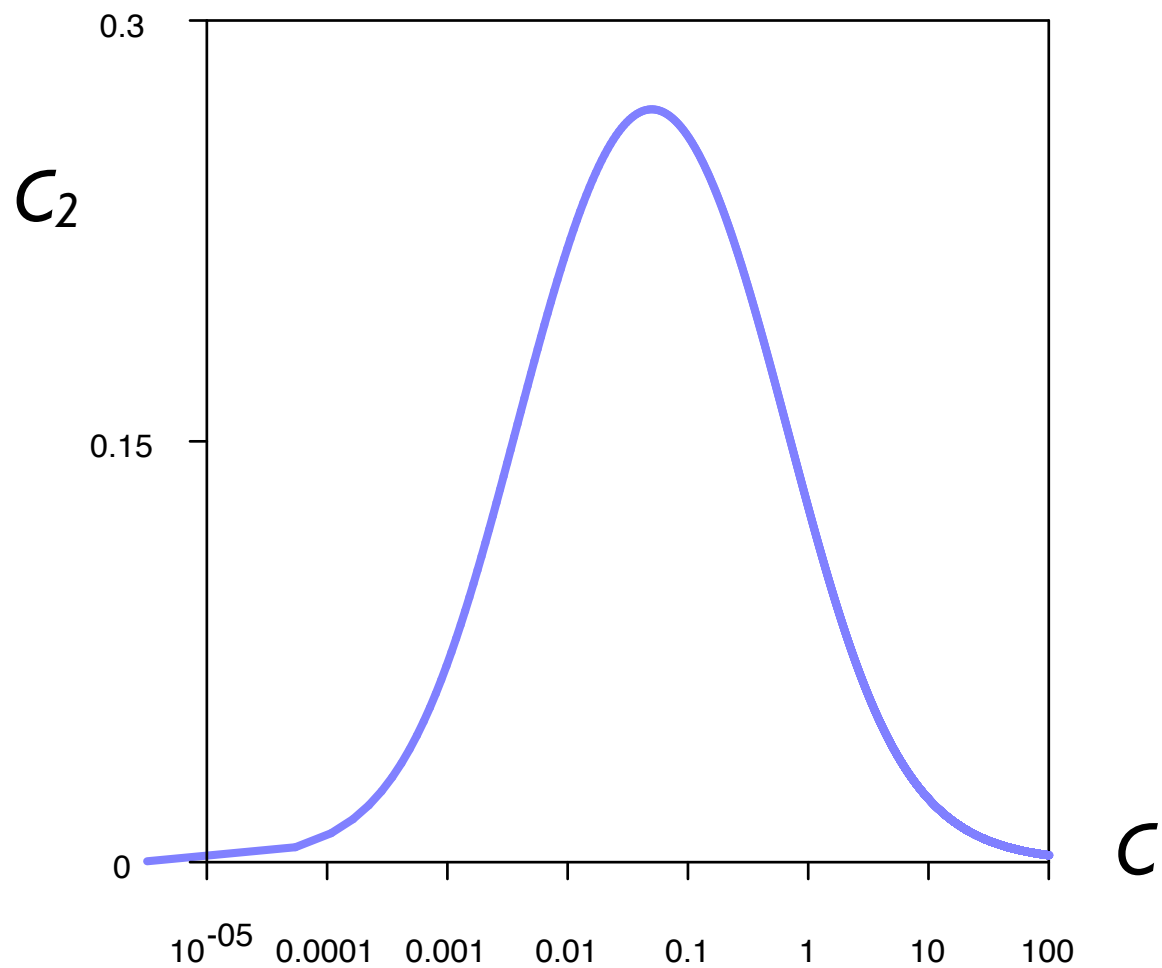
$$\overline{C_2} = \frac{1 + 4CK + 4C^2K^2 + 4CKR_TX - (1 + 2CK)\sqrt{(1 + 2CK)^2 + 8CKR_TX}}{8CKX}$$

where $X = x_{\mathrm{on}}/x_{\mathrm{off}}$.

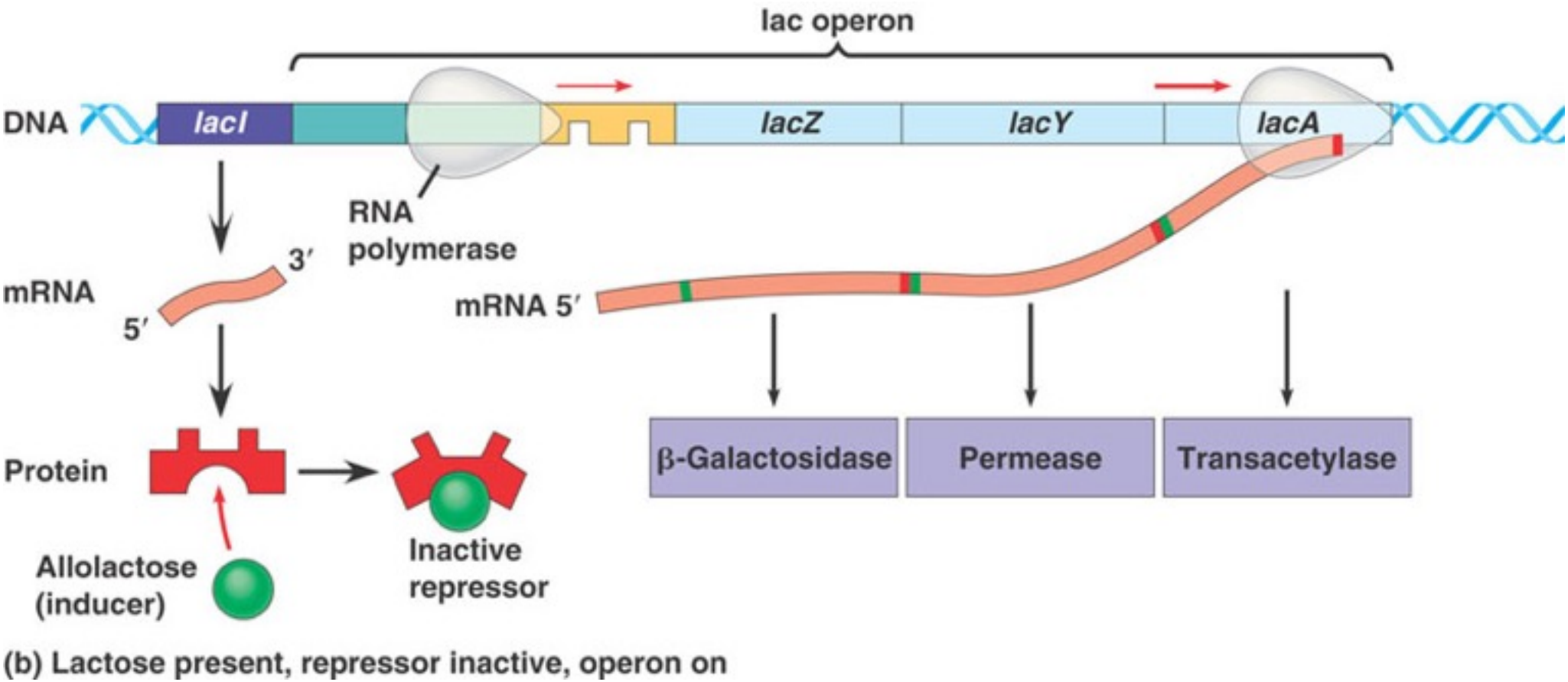
Thus, the number of crosslinks is a bell-shaped function of the ligand concentration C.

Cells grow best at intermediate ligand concentrations

$$\frac{\mathrm{d}N}{\mathrm{d}t} = bN\frac{2C_2}{R_T} - dN$$

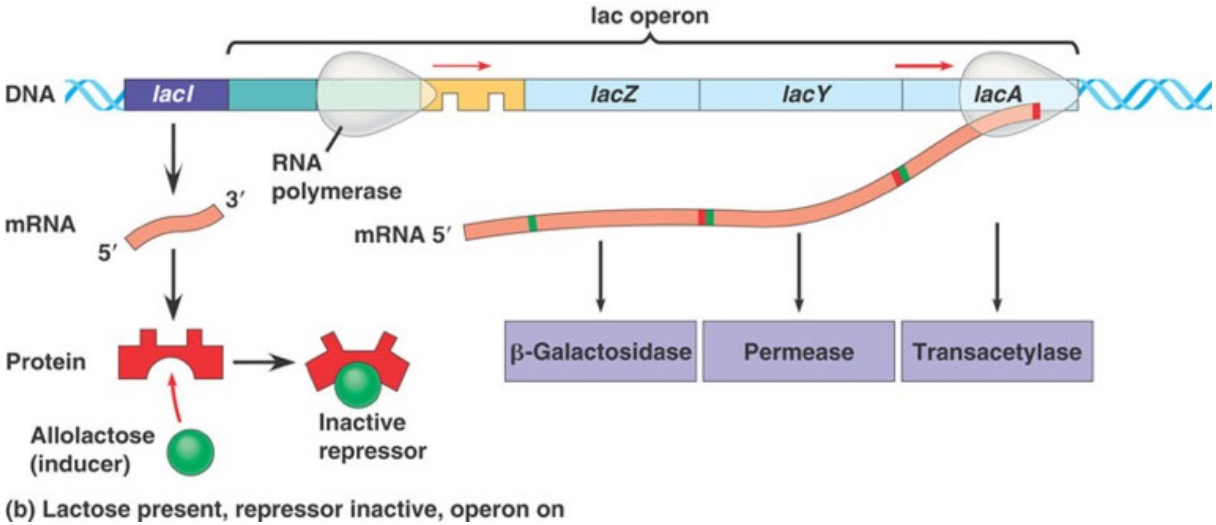


Lac operon, Jacob & Monod (1961)

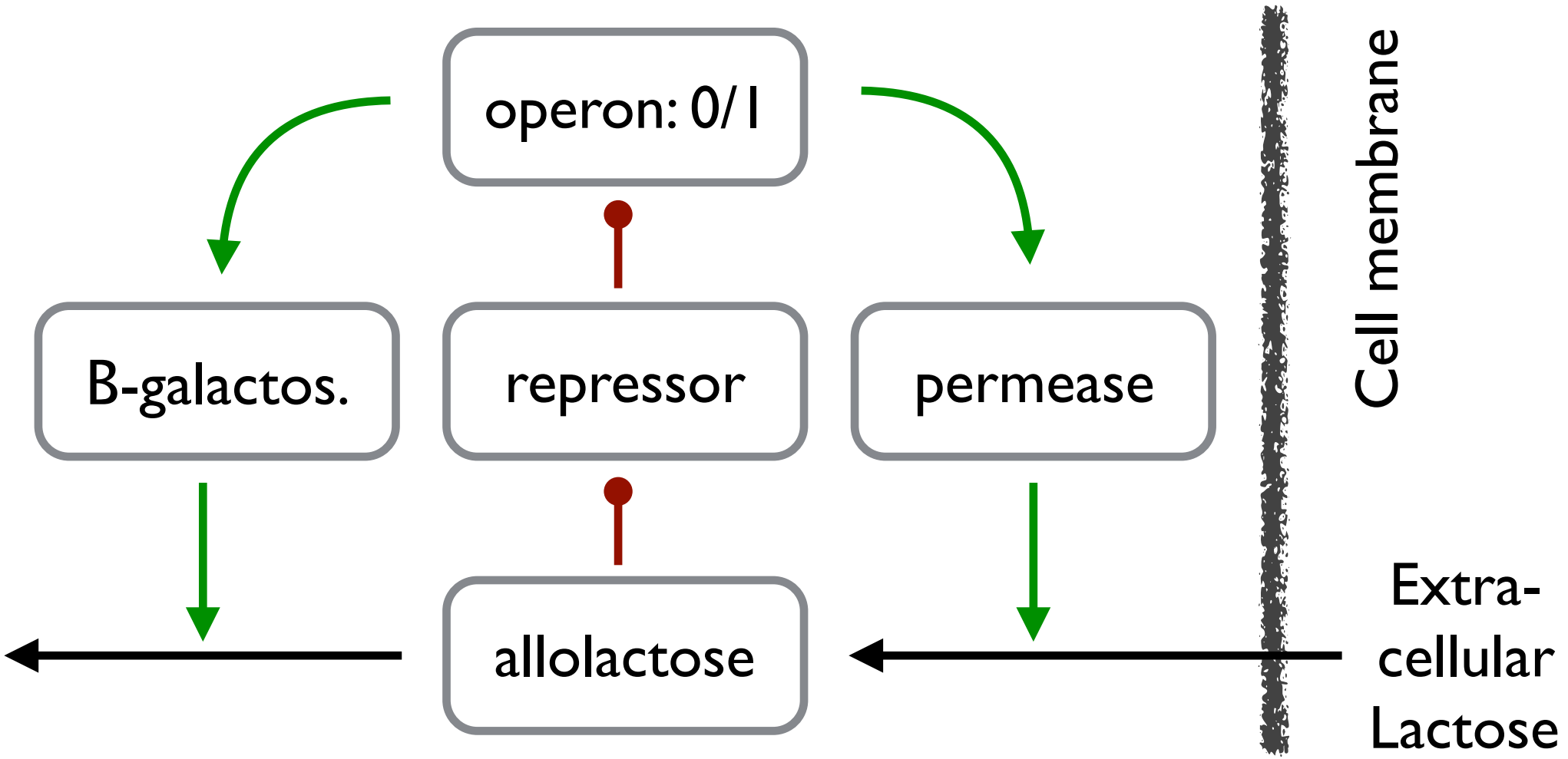


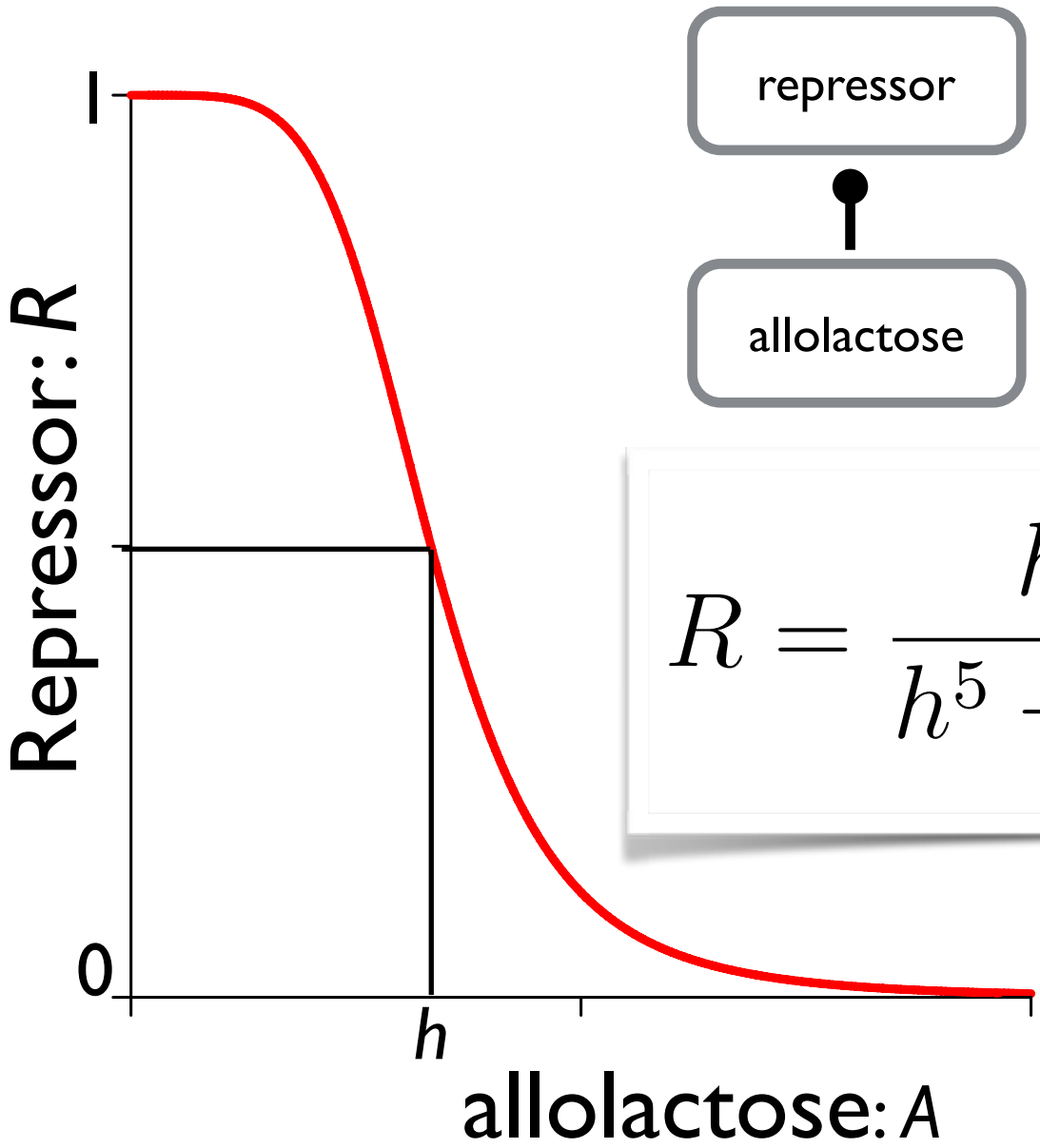
(b) Lactose present, repressor inactive, operon on

From Campbell



Translate this into simple scheme





Towards a phenomenological mathematical model

$$R = \frac{h^5}{h^5 + A^5} = \frac{1}{1 + (A/h)^5}$$

Repressor is modeled as a declining sigmoid Hill function.
We will even scale the allolactose concentration such that $h=1$

Complete mathematical model

R: repressor, *M*: messenger & *A*: allolactose:

$$R = \frac{1}{1+A^n} ,$$

R=0: operon "on"
R=1: operon "off"

$$\frac{\mathrm{d}M}{\mathrm{d}t} = c_0 + c(1-R) - dM = c_0 + \frac{cA^n}{1+A^n} - dM ,$$

$$\frac{\mathrm{d}A}{\mathrm{d}t} = ML - \delta A - vMA ,$$

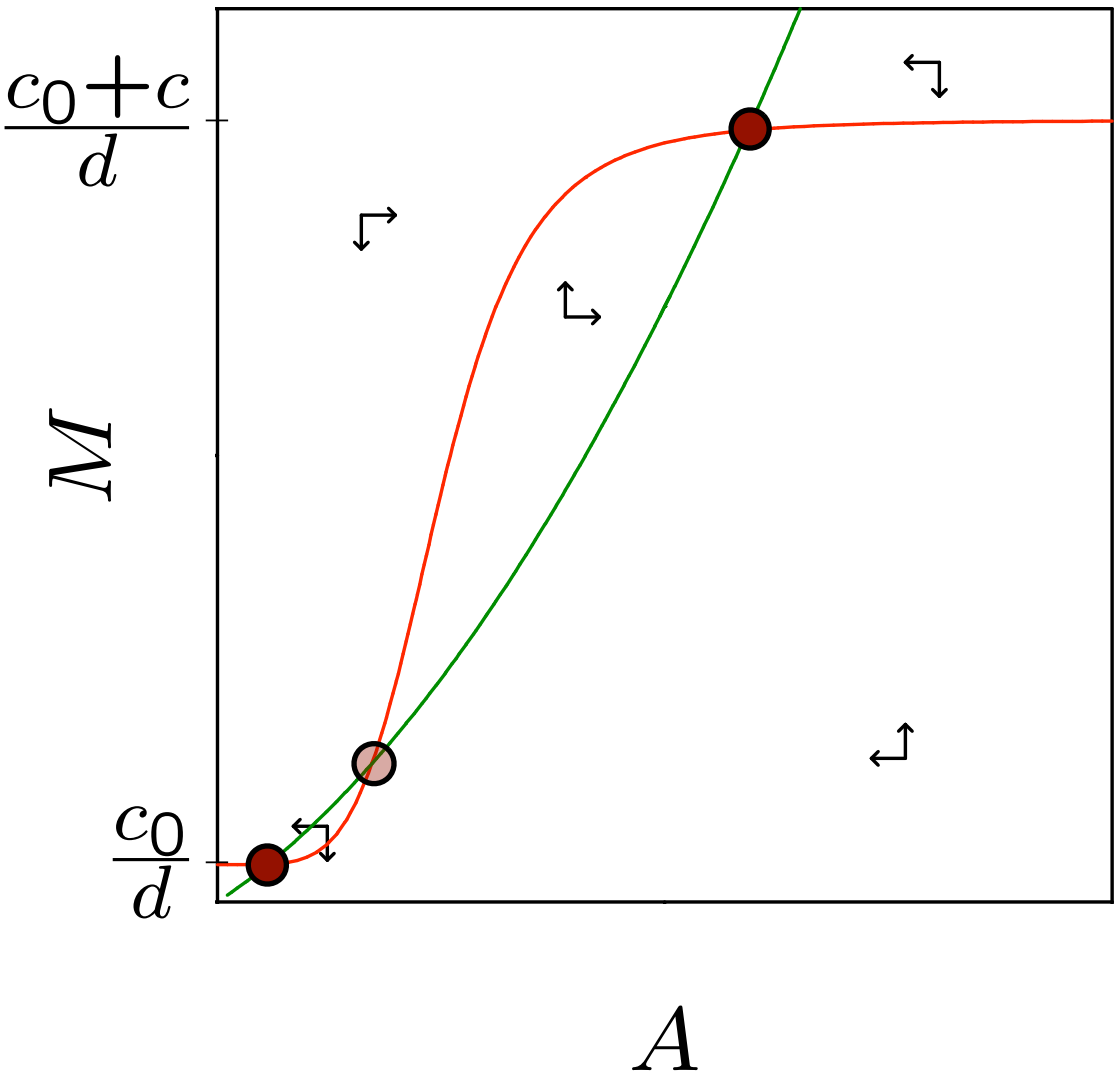
c_0: basal transcription rate,
c_0+c: transcription rate when operon is "on",
d and δ are decay rates of mRNA and allolactose,
ML is the permease mediated influx
-vMA term: B-galactosidase hydrolizes allolactose.

Nullclines

A'=0:

$$M = \frac{\delta A}{L - vA}$$

Origin: M = (δ/L)A



M'=0:

$$M = \frac{c_0}{d} + \frac{(c/d)A^n}{1 + A^n}$$

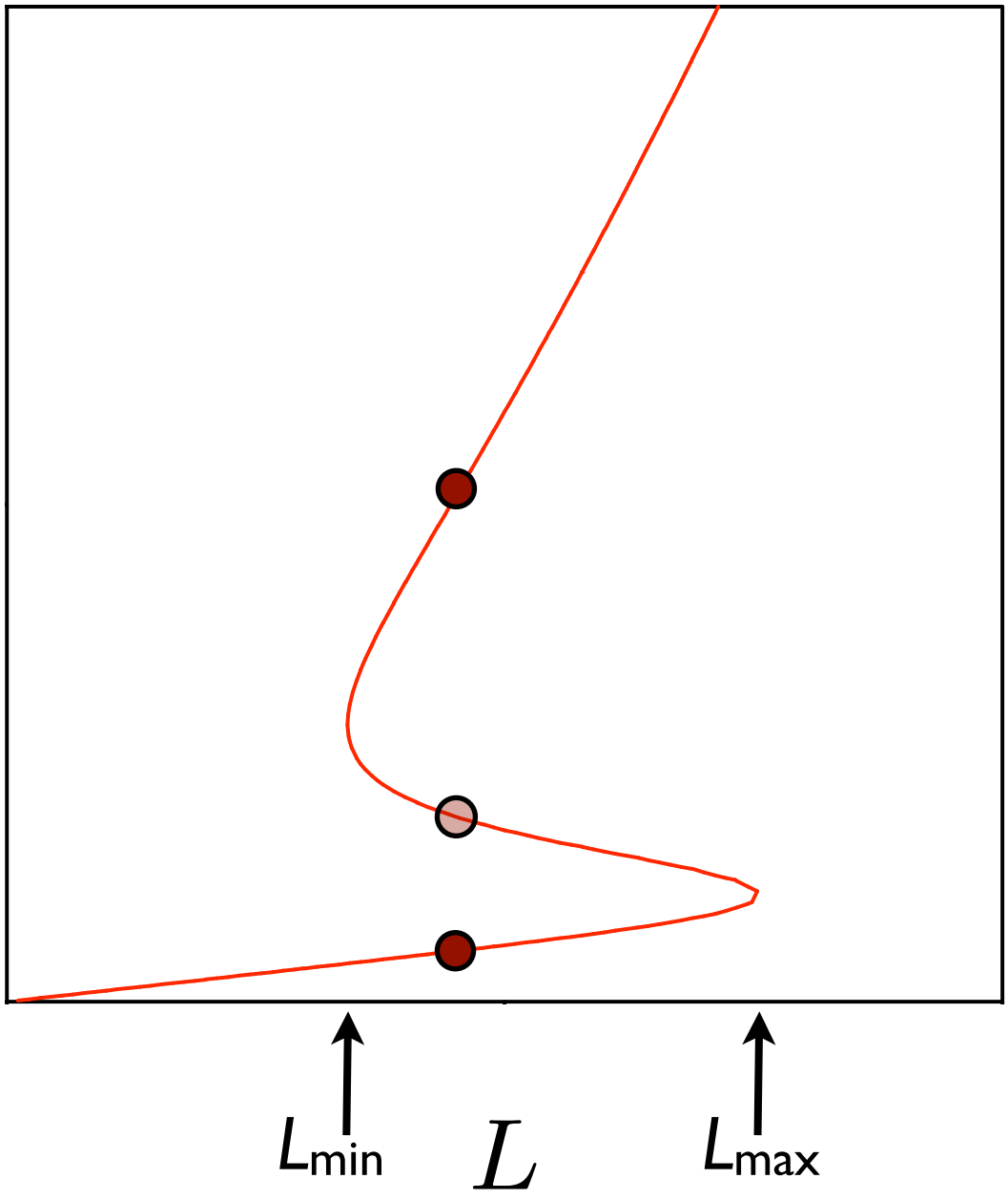
sigmoid Hill function

Quasi steady state d*M*/d*t* = 0

$$\frac{\mathrm{d}A}{\mathrm{d}t} = ML - \delta A - vMA$$

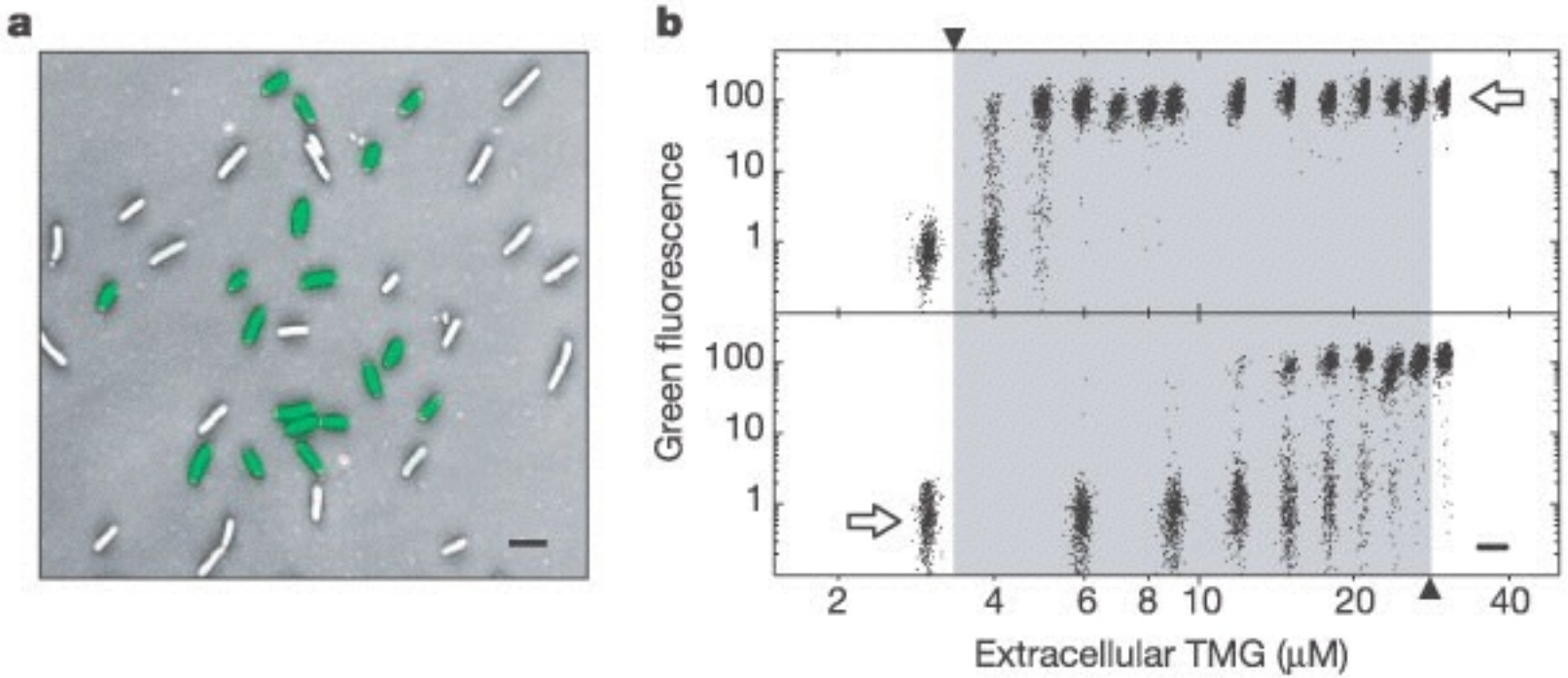
with

$$M = \frac{c_0}{d} + \frac{(c/d)A^n}{1 + A^n}$$



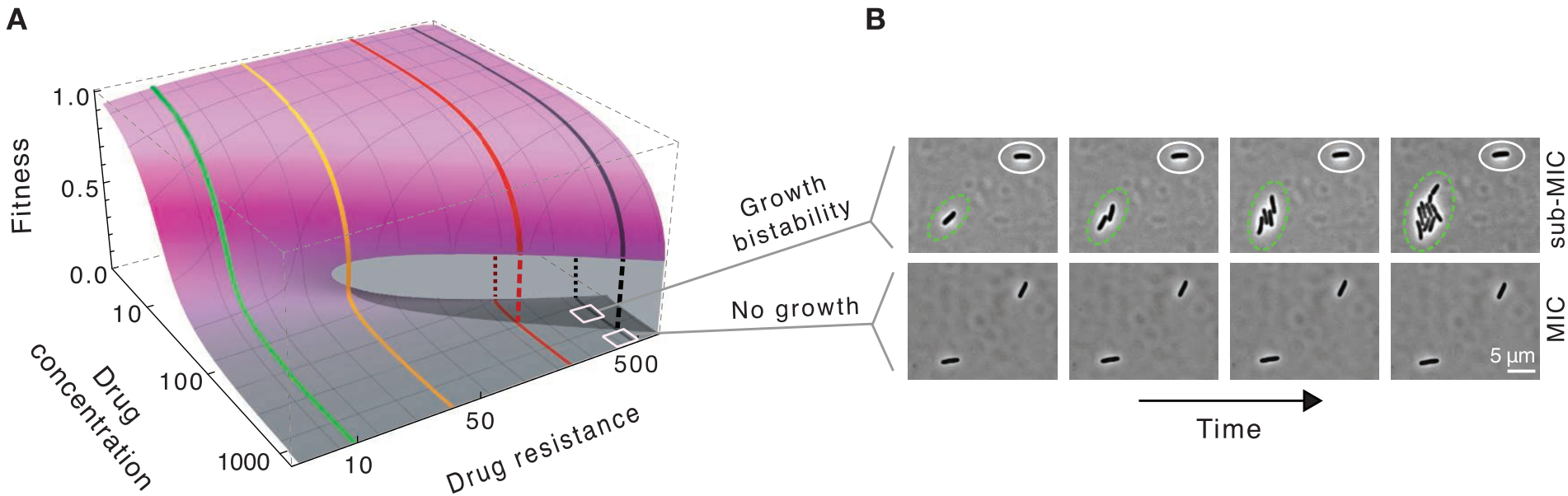
For one concentration of *L* three concentrations of *A*

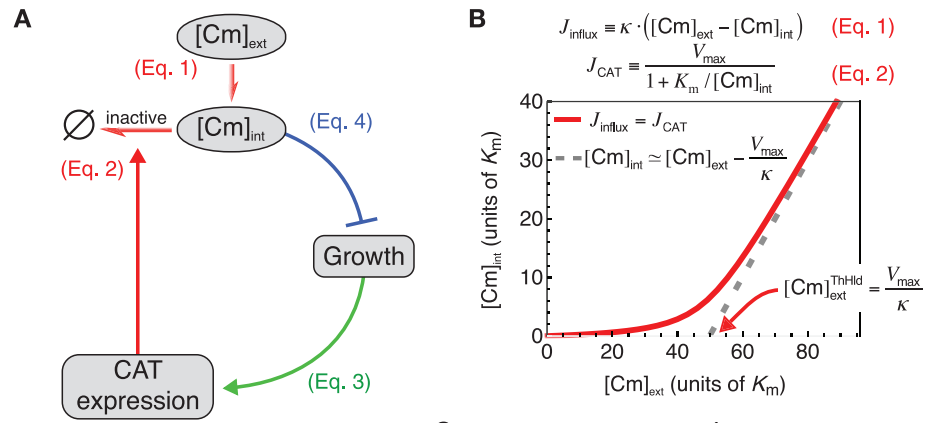
Observed bi-stability in *E. coli*



Green: E. coli with high expression of lac operon
From: Ozbudak *et al*. Nature, 2004 (see the reader)

Bi-stability in growth of *E. coli*



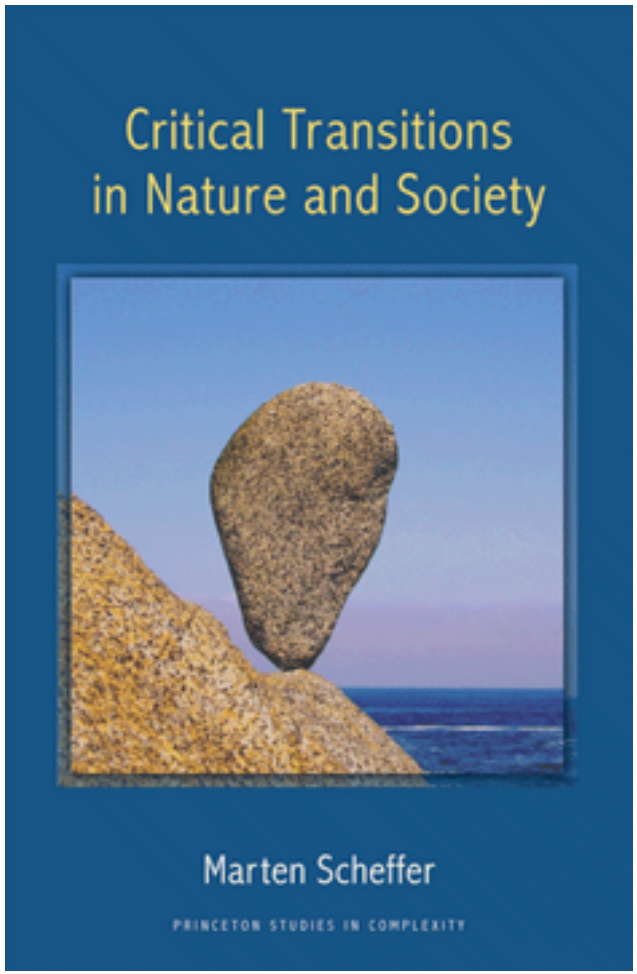


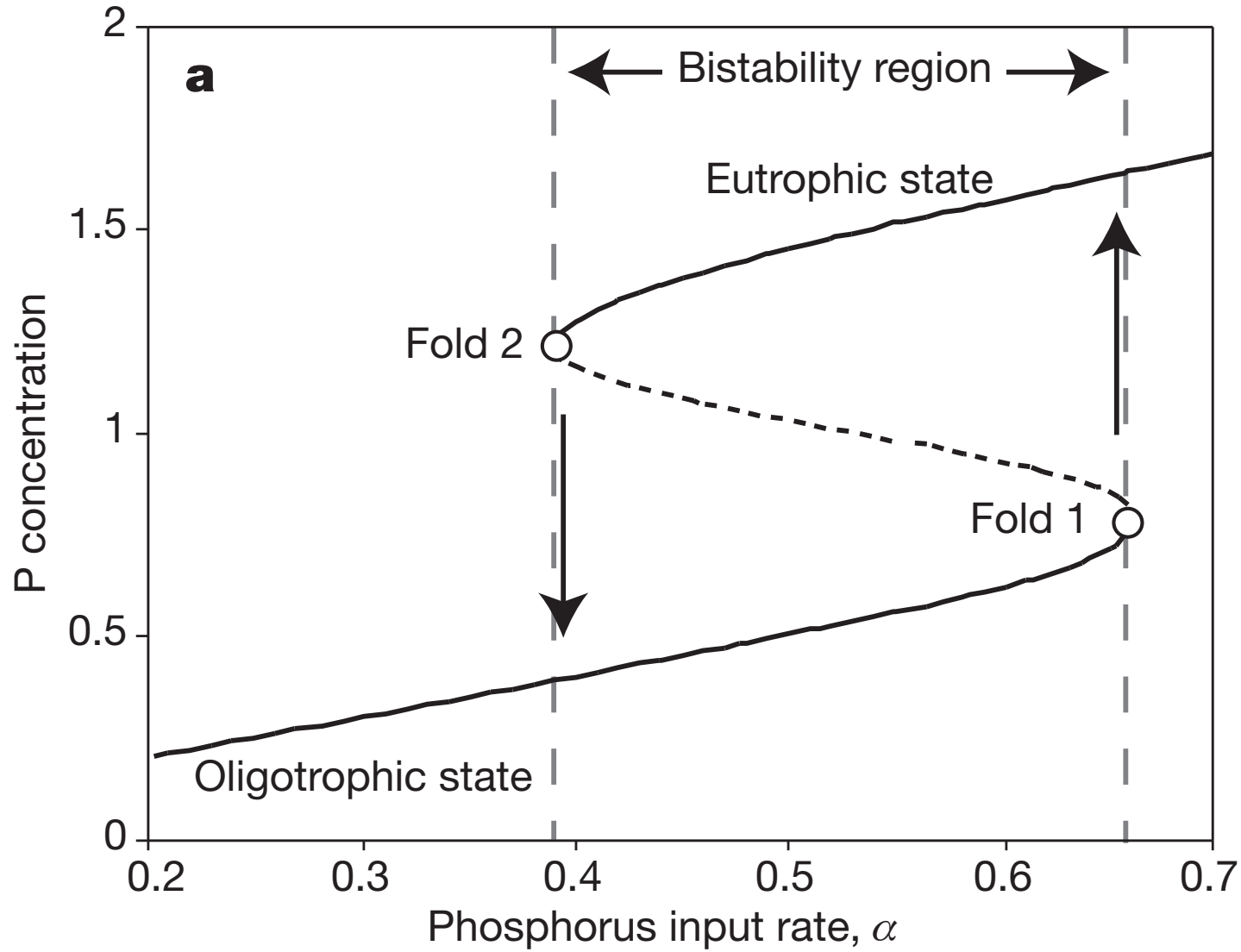
The Innate Growth Bistability and Fitness Landscapes of Antibiotic-Resistant Bacteria

J. Barrett Deris,[1,2]* Minsu Kim,[1]*† Zhongge Zhang,[3] Hiroyuki Okano,[1] Rutger Hermsen,[1,2]‡ Alexander Groisman,[1] Terence Hwa[1,2,3]§

Science 2013

bi-stability in algal densities in lakes





LETTER

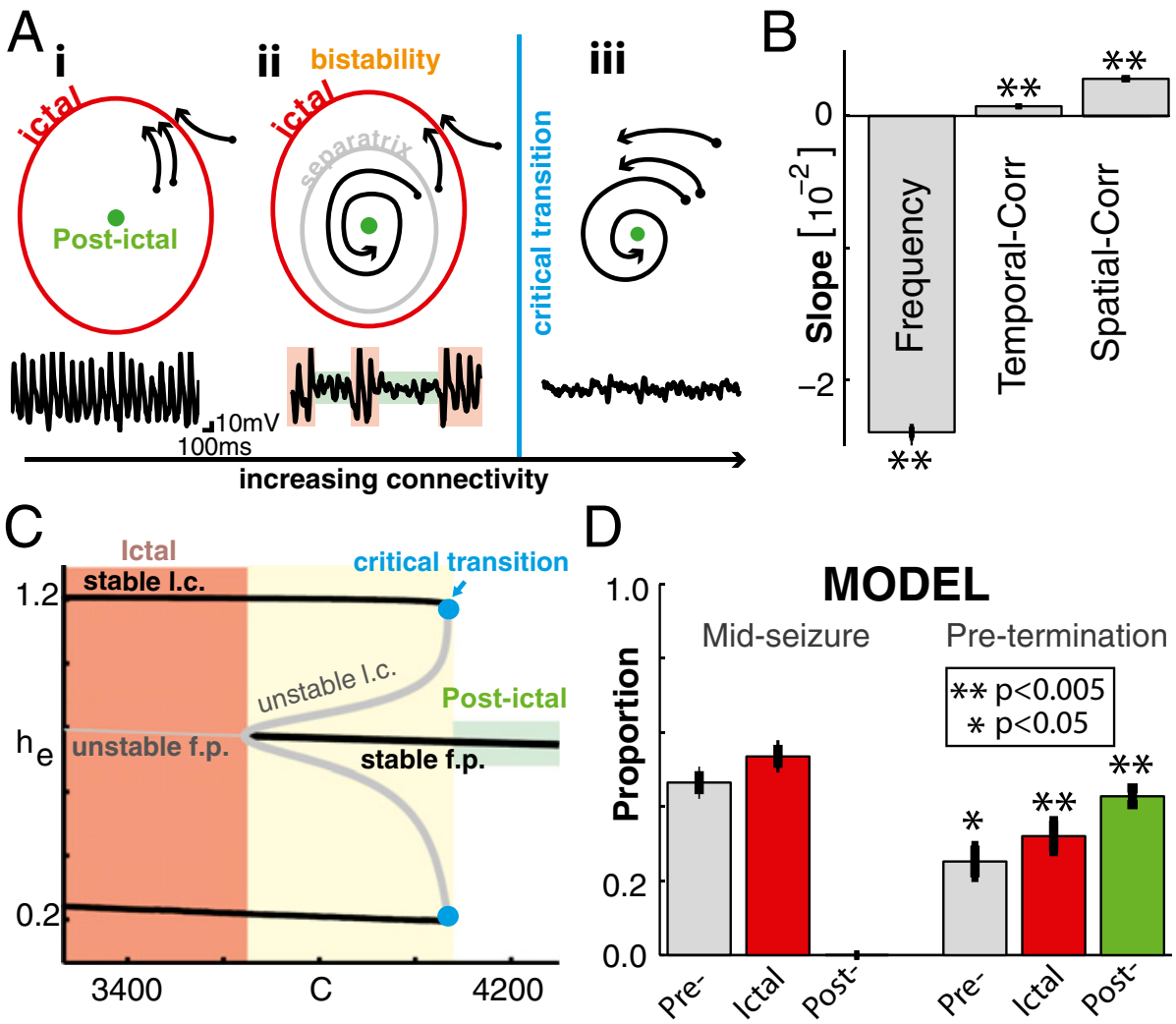
doi:10.1038/nature11655

Flickering gives early warning signals of a critical transition to a eutrophic lake state

Rong Wang[1,2], John A. Dearing[1], Peter G. Langdon[1], Enlou Zhang[2], Xiangdong Yang[2], Vasilis Dakos[3,4] & Marten Scheffer[3]

Nature 2012

Initiation and termination of epileptic seizures

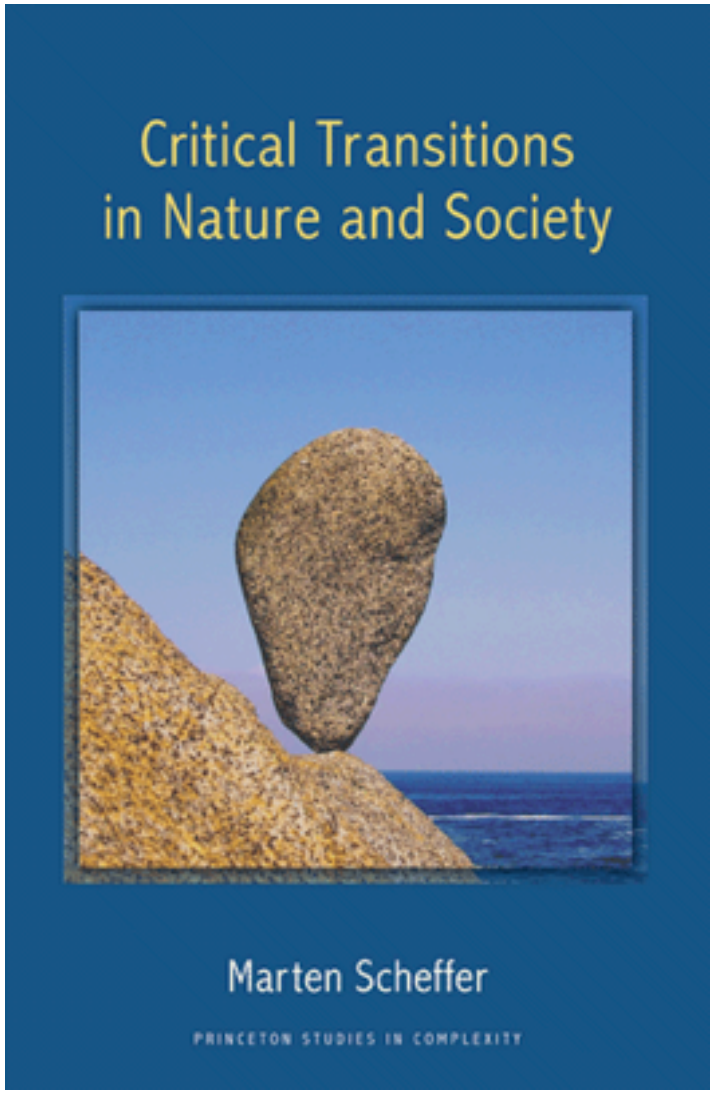


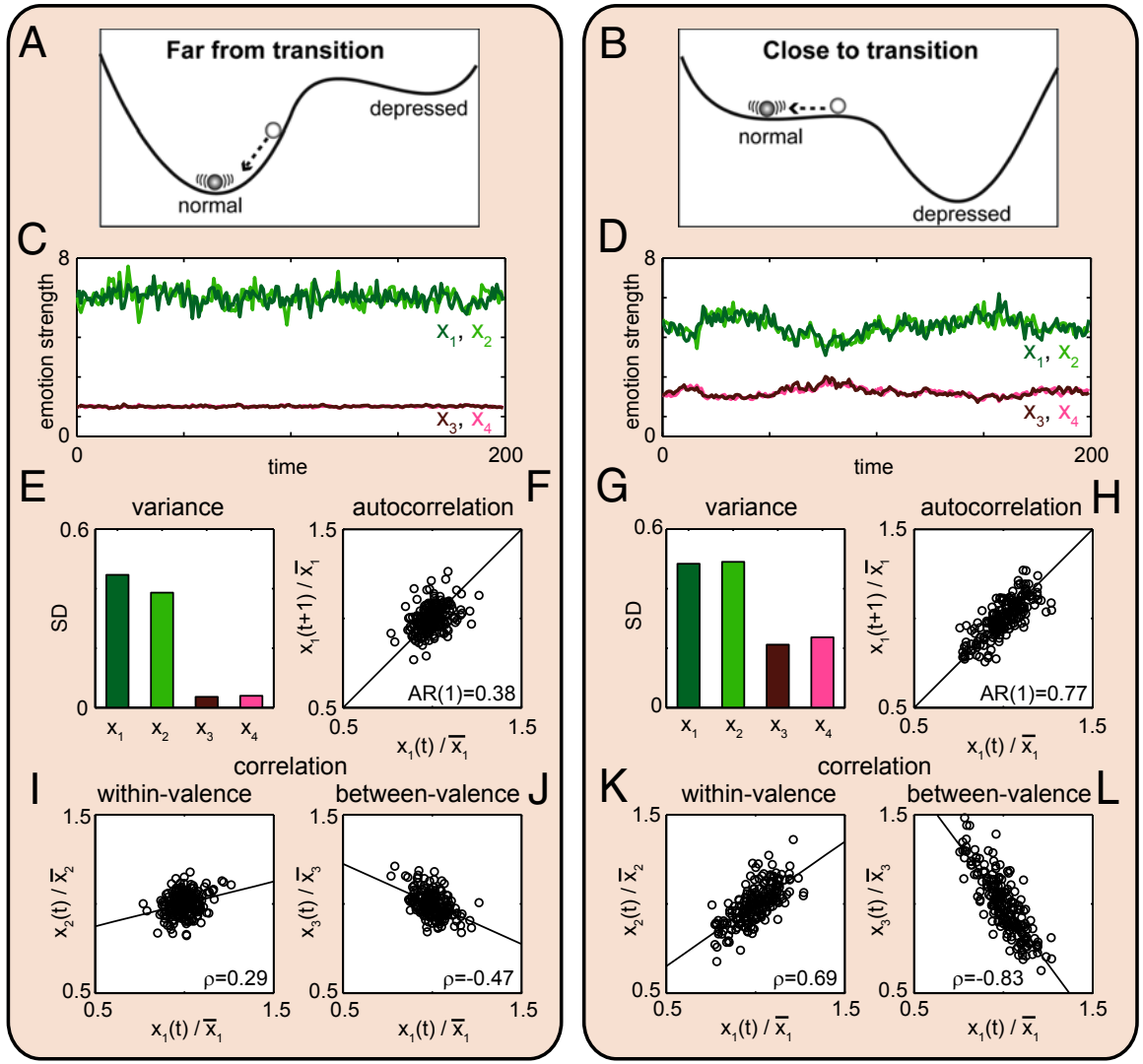
Human seizures self-terminate across spatial scales via a critical transition

Mark A. Kramer[a,1], Wilson Truccolo[b,c,d,e], Uri T. Eden[a], Kyle Q. Lepage[a], Leigh R. Hochberg[c,d,e,f,g], Emad N. Eskandar[f,h], Joseph R. Madsen[i,j], Jong W. Lee[k], Atul Maheshwari[d,f], Eric Halgren[l], Catherine J. Chu[d,f], and Sydney S. Cash[d,f]

PNAS: 2012

Initiation and termination of depression





Critical slowing down as early warning for the onset and termination of depression

Ingrid A. van de Leemput[a,1,2], Marieke Wichers[b,1], Angélique O. J. Cramer[c], Denny Borsboom[c], Francis Tuerlinckx[d], Peter Kuppens[d,e], Egbert H. van Nes[a], Wolfgang Viechtbauer[b], Erik J. Giltay[f], Steven H. Aggen[g], Catherine Derom[h,i], Nele Jacobs[b,j], Kenneth S. Kendler[g,k], Han L. J. van der Maas[c], Michael C. Neale[g], Frenk Peeters[b], Evert Thiery[l], Peter Zachar[m], and Marten Scheffer[a]

PNAS: 2014

Catastrophic shifts in ecosystems

2001

Marten Scheffer*, Steve Carpenter†, Jonathan A. Foley‡, Carl Folke§ & Brian Walker‖

* *Department of Aquatic Ecology and Water Quality Management, Wageningen University, PO Box 8080, NL-6700 DD Wageningen, The Netherlands*
† *Center for Limnology, University of Wisconsin, 680 North Park Street, Madison, Wisconsin 53706, USA*
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All ecosystems are exposed to gradual changes in climate, nutrient loading, habitat fragmentation or biotic exploitation. Nature is usually assumed to respond to gradual change in a smooth way. However, studies on lakes, coral reefs, oceans, forests and arid lands have shown that smooth change can be interrupted by sudden drastic switches to a contrasting state. Although diverse events can trigger such shifts, recent studies show that a loss of resilience usually paves the way for a switch to an alternative state. This suggests that strategies for sustainable management of such ecosystems should focus on maintaining resilience.