A systems approach to biology

SB200

Lecture 5
30 September 2008

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Recap of Lecture 4

matrix exponential

$$\exp(A) = 1 + A + A^2/2 + \ldots + A^k/k! + \ldots$$

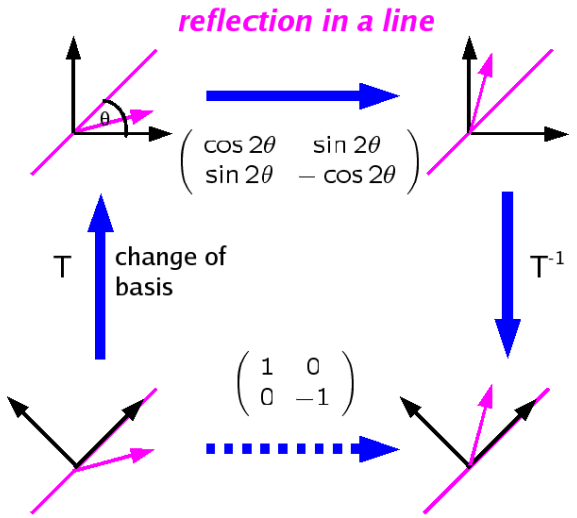
$$dx/dt = Ax$$

$$x(t) = \exp(At)x_0$$

linear transformations

similarity

$$B = T^{-1}AT$$



normal forms

$\Delta > 0$ $\begin{pmatrix} a & 0 \\ 0 & b \end{pmatrix}$

$\Delta < 0$ $\begin{pmatrix} a & -b \\ b & a \end{pmatrix}$

$\Delta = 0$ $\begin{pmatrix} a & b \\ 0 & a \end{pmatrix}$

$$\begin{pmatrix} a & -b \\ b & a \end{pmatrix} + \begin{pmatrix} c & -d \\ d & c \end{pmatrix} = \begin{pmatrix} a+c & -(b+d) \\ b+d & a+c \end{pmatrix}$$

$$(a + ib) + (c + id) = (a + c) + i(b + d)$$

$$\begin{pmatrix} a & -b \\ b & a \end{pmatrix} * \begin{pmatrix} c & -d \\ d & c \end{pmatrix} = \begin{pmatrix} ac - bd & -(ad + bc) \\ ad + bc & ac - bd \end{pmatrix}$$

$$(a + ib) * (c + id) = (ac - bd) + i(ad + bc)$$

$$\exp\begin{pmatrix} a & -b \\ b & a \end{pmatrix}$$

$$\exp(a+ib) = \exp(a)\exp(ib) = \exp(a)(\cos(b) + i\sin(b))$$

$$\exp\begin{pmatrix} a & -b \\ b & a \end{pmatrix} = \exp(a)\begin{pmatrix} \cos(b) & -\sin(b) \\ \sin(b) & \cos(b) \end{pmatrix}$$

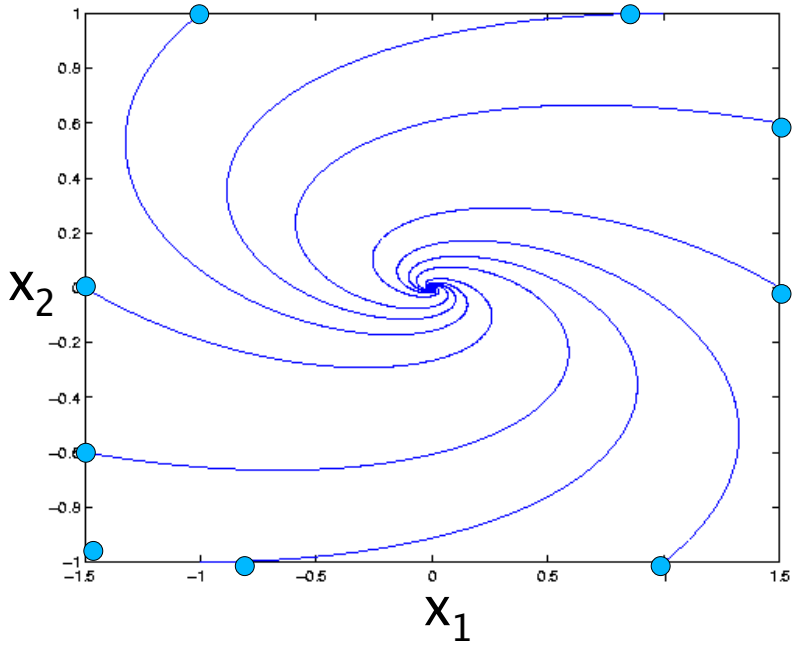
complex case disc < 0 complex eigenvalues

$$\exp\begin{pmatrix} a & -b \\ b & a \end{pmatrix} = \exp(a)\begin{pmatrix} \cos b & -\sin b \\ \sin b & \cos b \end{pmatrix}$$

eigenvalues = a $\pm$ *i b*

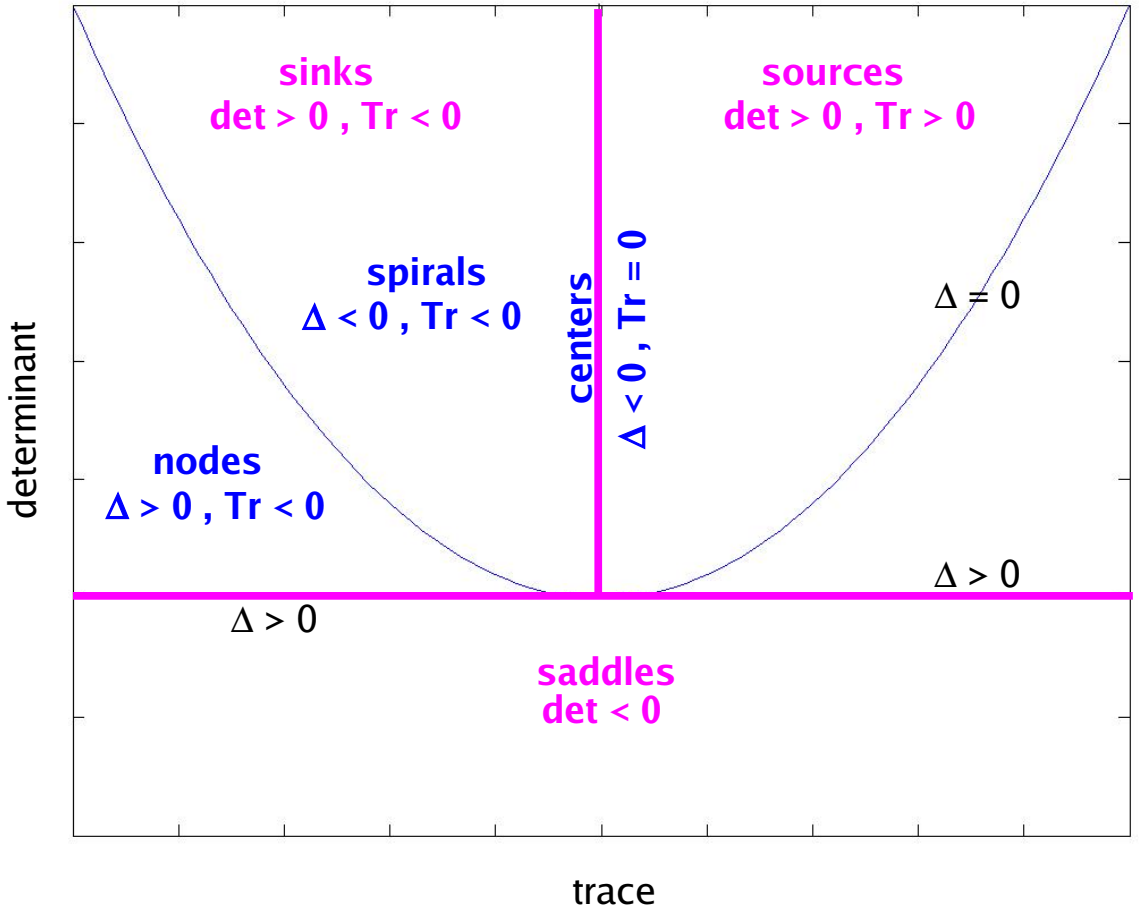
$$\begin{pmatrix} -2 & -5 \\ 1 & -1 \end{pmatrix}$$

Tr = -3 det = 7 **disc = -19**
eigenvalues = -1.5 $\pm$ 2.18 *i*



stable spiral

Complex eigenvalues imply (damped) oscillation, with frequency given by the imaginary part of the eigenvalue


sinks
det > 0 , Tr < 0
sources
det > 0 , Tr > 0
spirals
Δ < 0 , Tr < 0
centers
Δ < 0 , Tr = 0
Δ = 0
nodes
Δ > 0 , Tr < 0
Δ > 0
Δ > 0
saddles
det < 0
determinant
trace

awkward case 1 disc = 0

$$\exp \begin{pmatrix} a & b \\ 0 & a \end{pmatrix} = \begin{pmatrix} \exp a & b \exp a \\ 0 & \exp a \end{pmatrix}$$

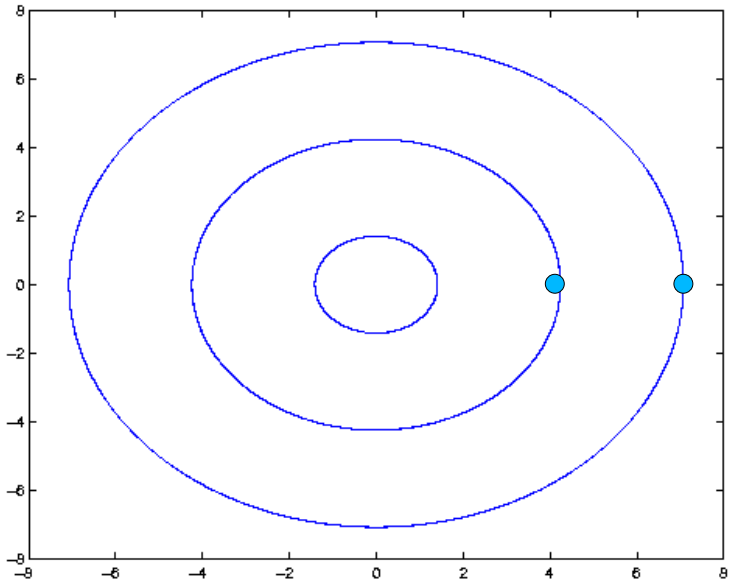
non-generic (degenerate) case

cant make up its mind whether to be a node or a spiral

awkward case 2 disc < 0, Tr A = 0

$$\begin{pmatrix} 0 & 3 \\ -2 & 0 \end{pmatrix}$$

Tr = 0 det = 6 disc = -24
eigenvalues = ± 2.45 *i*

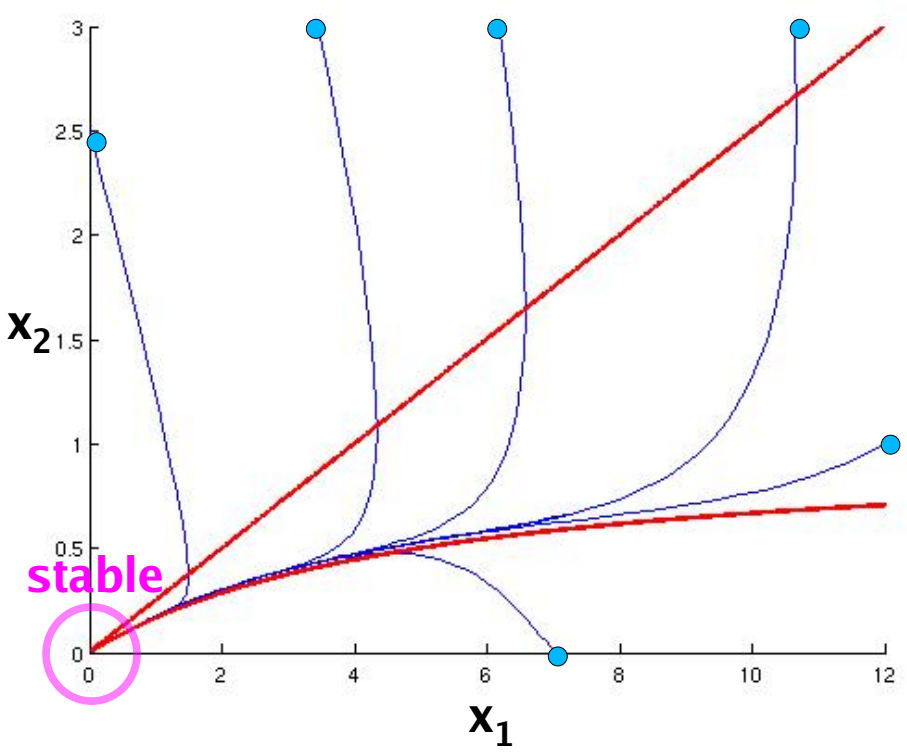


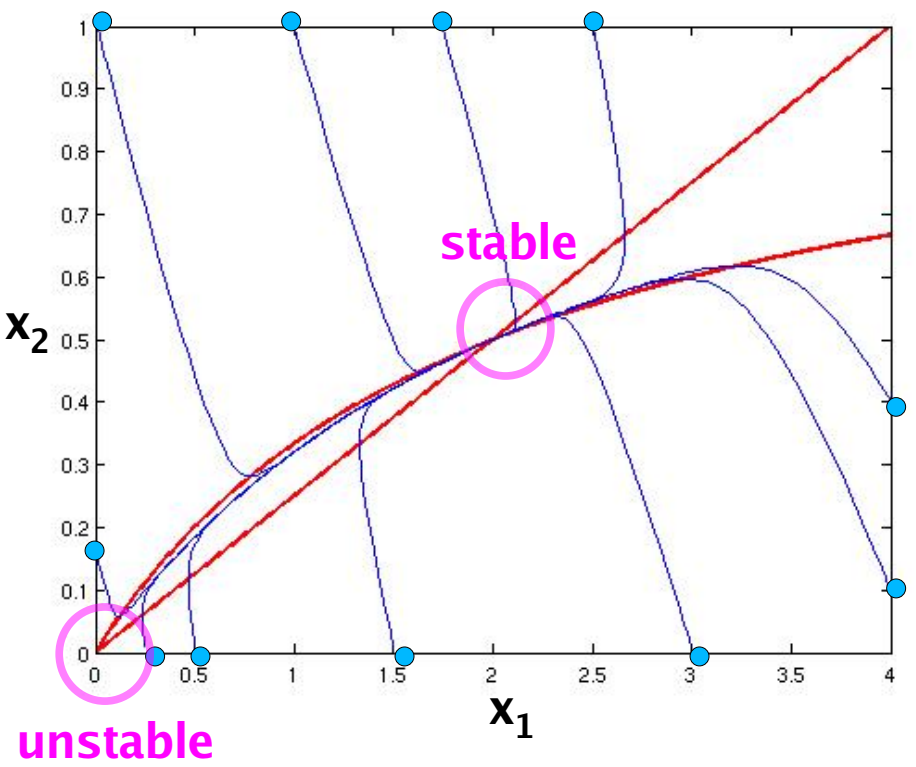
center

cant make up its mind whether to be stable or unstable

robust oscillations require nonlinearity

BACK TO PHAGE LAMBDA

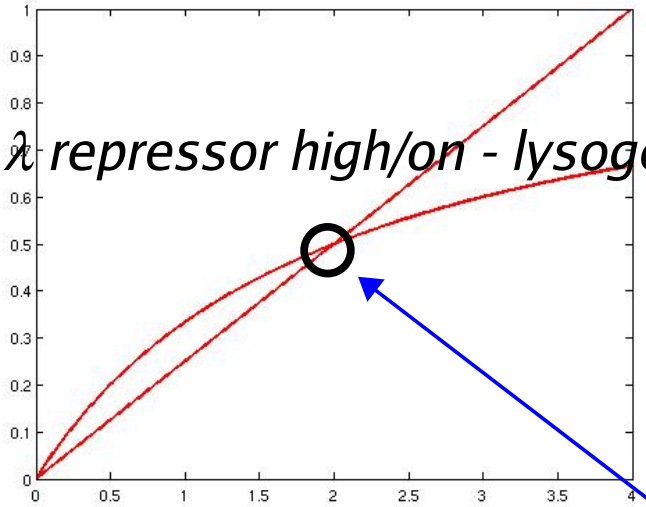




$$\frac{dx_1}{dt} = \lambda x_2 - a x_1$$

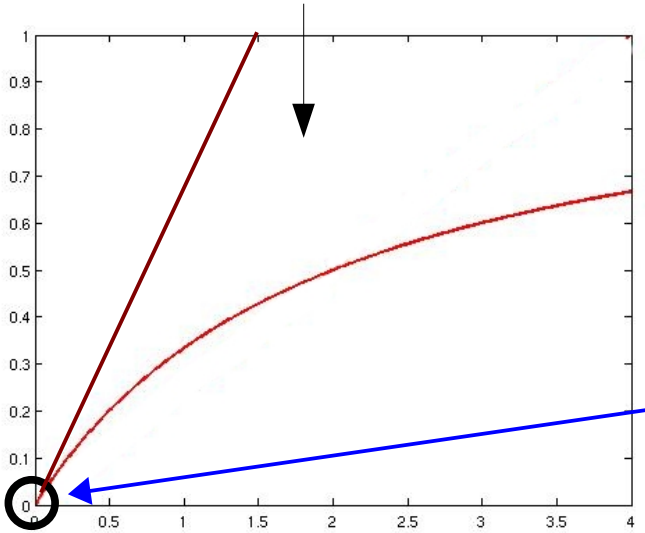
$$\frac{dx_2}{dt} = \frac{\alpha x_1}{k + x_1} - b x_2$$

does this model capture the biology?

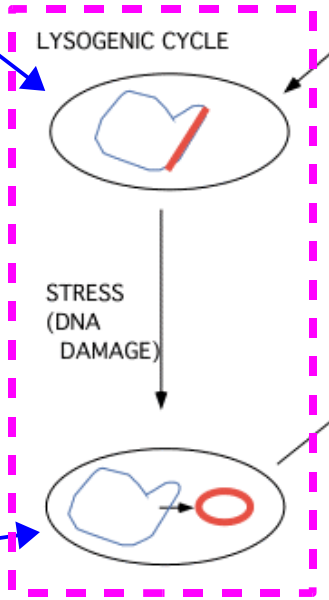


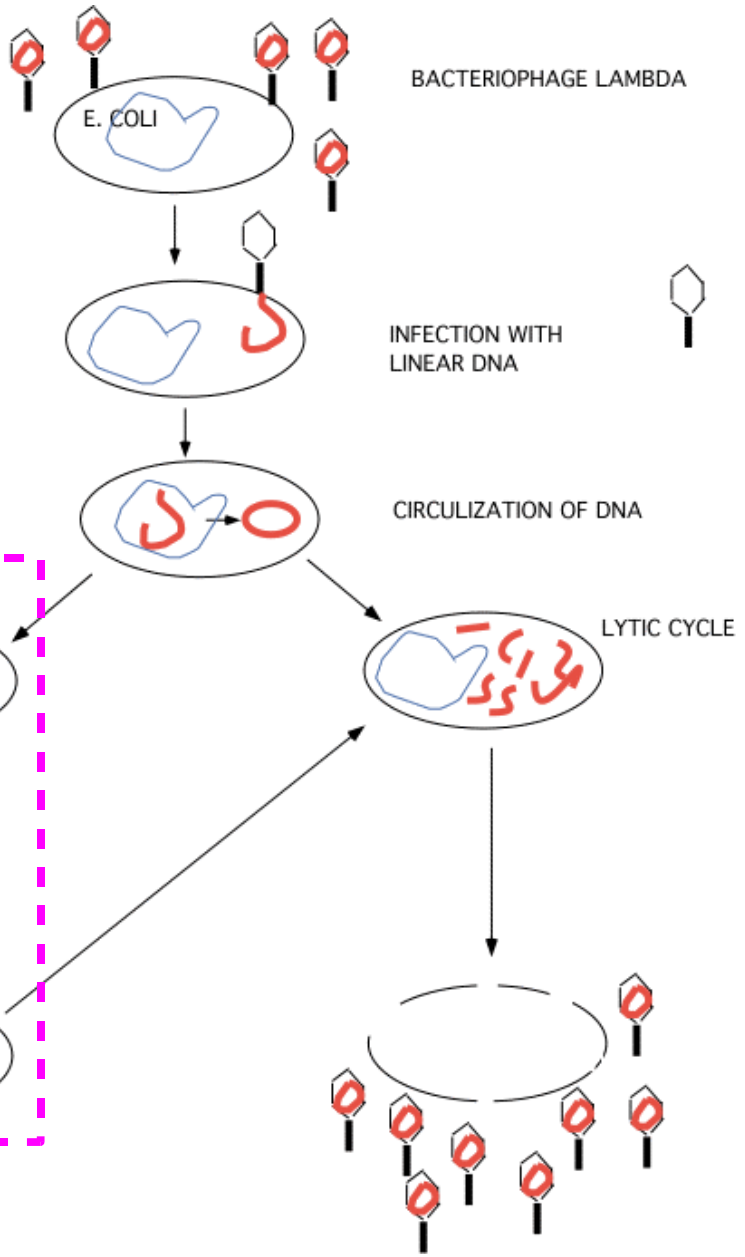
λ repressor high/on - lysogeny

increased degradation of λ

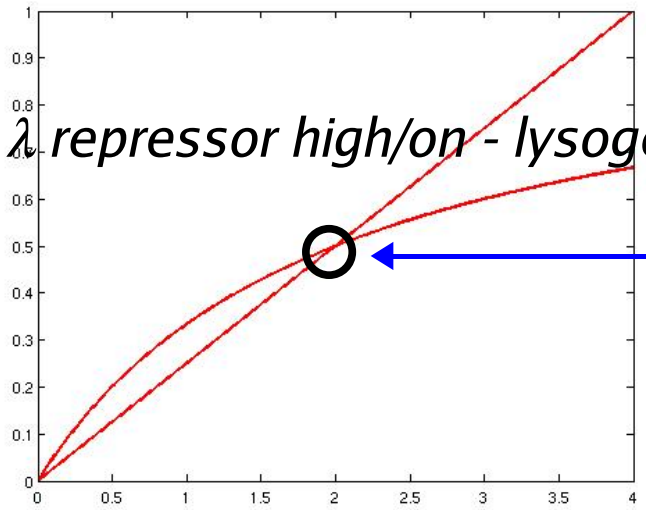


λ repressor off - lysis



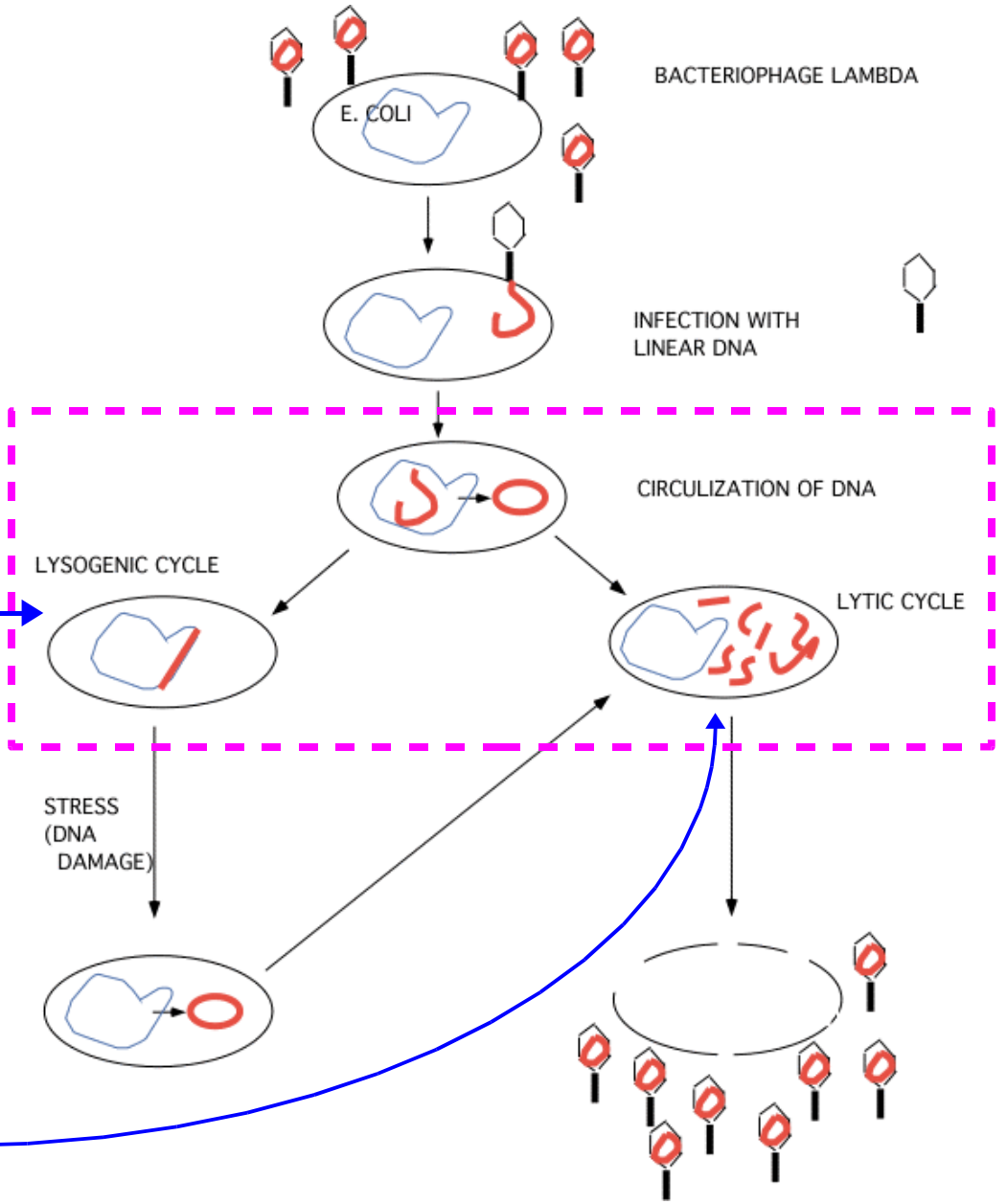


switch is sluggish, not sharp



λ repressor high/on - lysogeny

off state is unstable



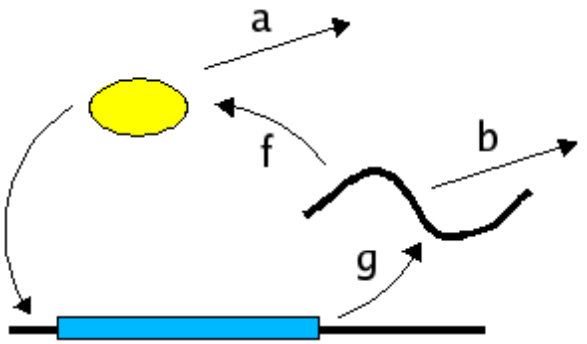
how could the design be changed

to make the switch sharper

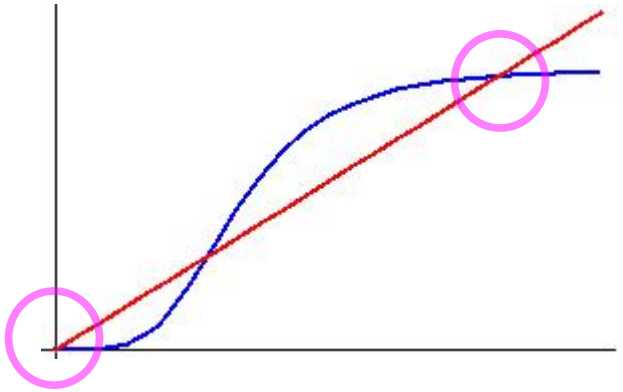
and/or

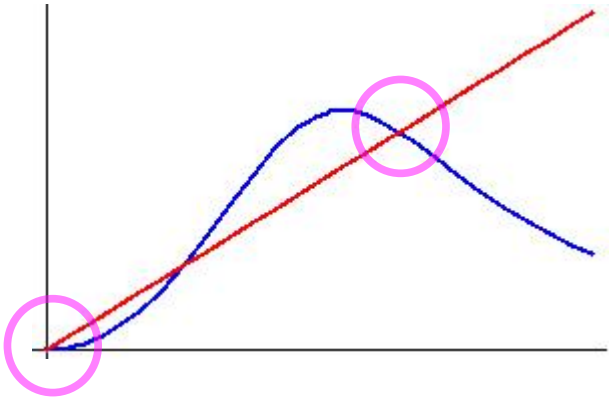
the off-state stable?

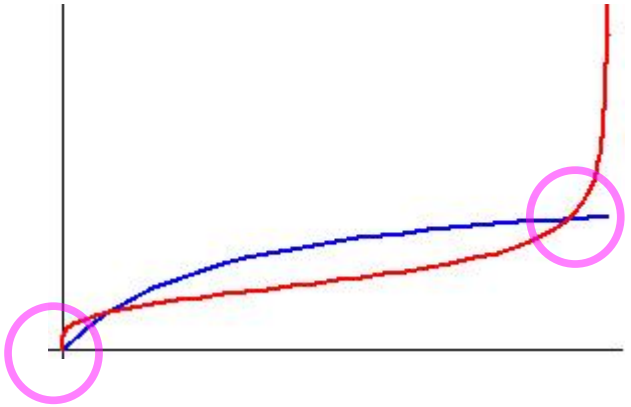
use the same basic design as before



but re-design *f* or *g* to bend the nullcline(s)

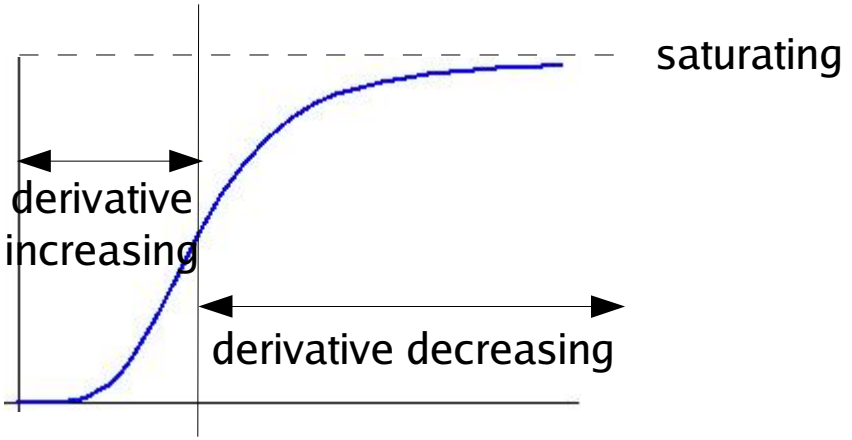






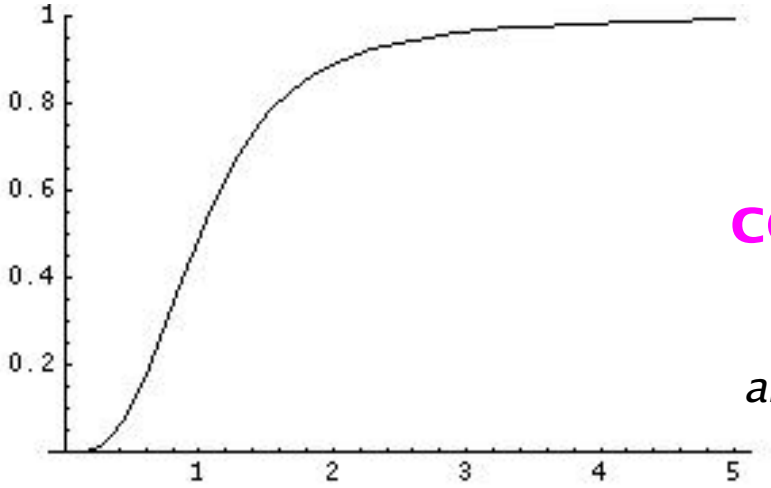
creating two stable nodes
separated by an unstable saddle

a sigmoidal dose-response curve



sigmoidal = S-shaped

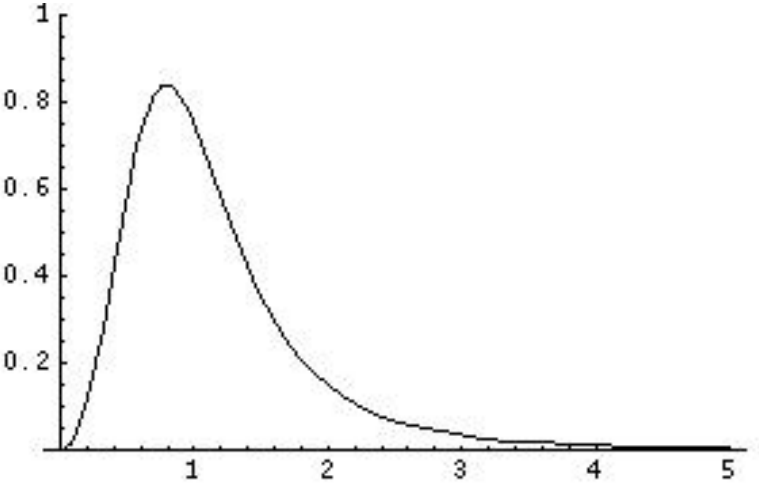
sigmoidal curves correspond to



differentiation

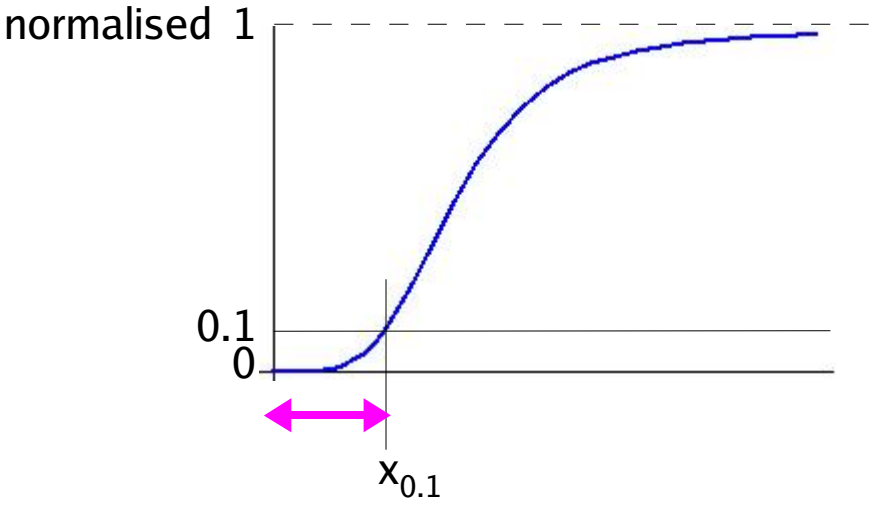
correspond to

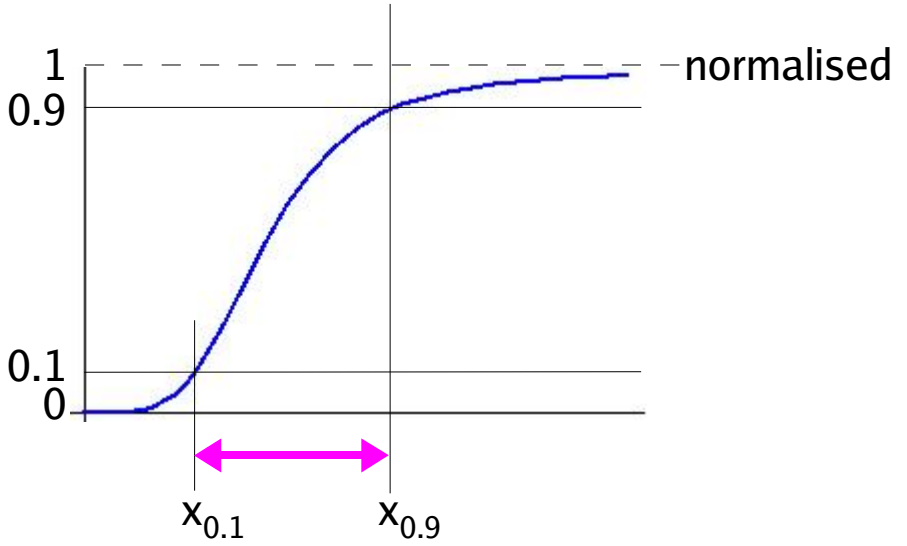
area under the curve (integration)



unimodal probability distributions

sigmoidal curves have two independent features



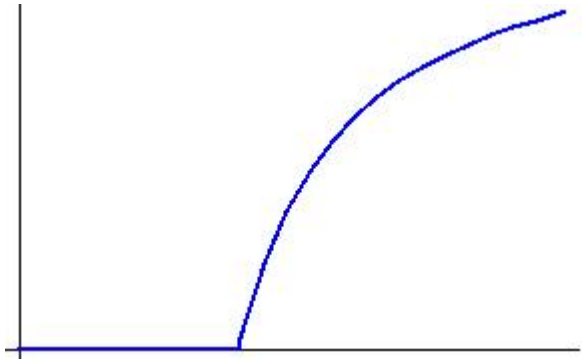


they create a **threshold**

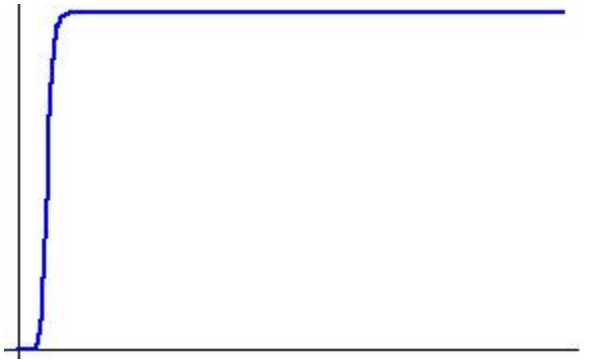
good **threshold** = high $x_{0.1}$

they **switch** from low to high

good **switch** = low ($x_{0.9}$ - $x_{0.1}$)



good **threshold,** poor switch

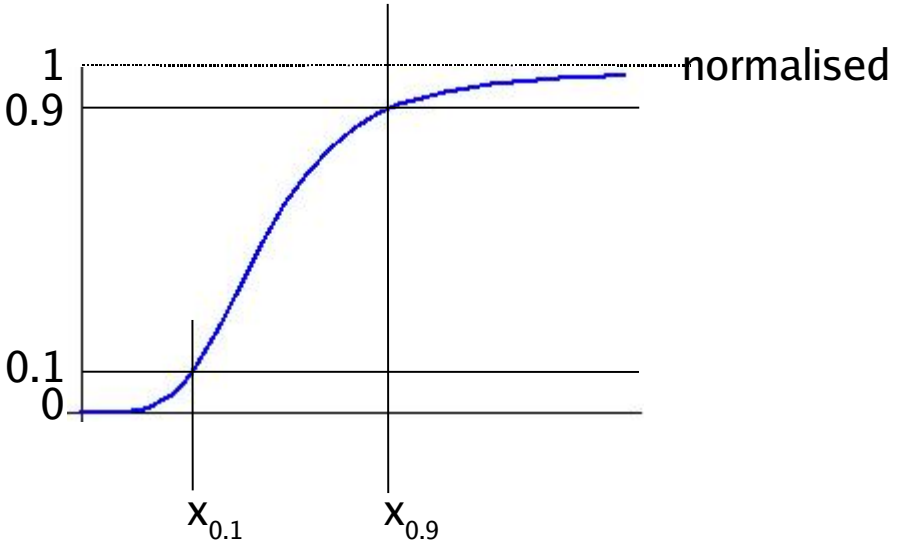


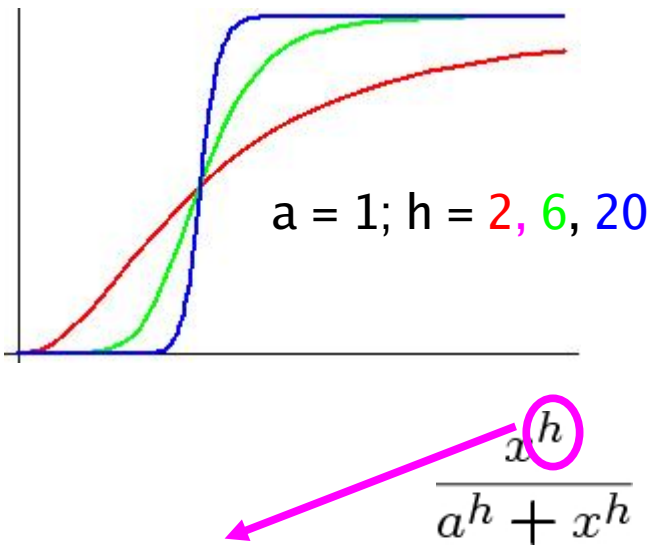
good **switch,** poor threshold

different measures of "switching-ness"

ultrasensitivity - *a small change in dose causes a large change in response*

Goldbeter & Koshland, PNAS **78**:6840-4 1981





$x_{0.9} / x_{0.1}$ - **COOPERATIVITY INDEX**

CI = 81 for the standard hyperbolic curve

ultrasensitive - if CI < 81

HILL COEFFICIENT

$CI = 81^{1/h}$

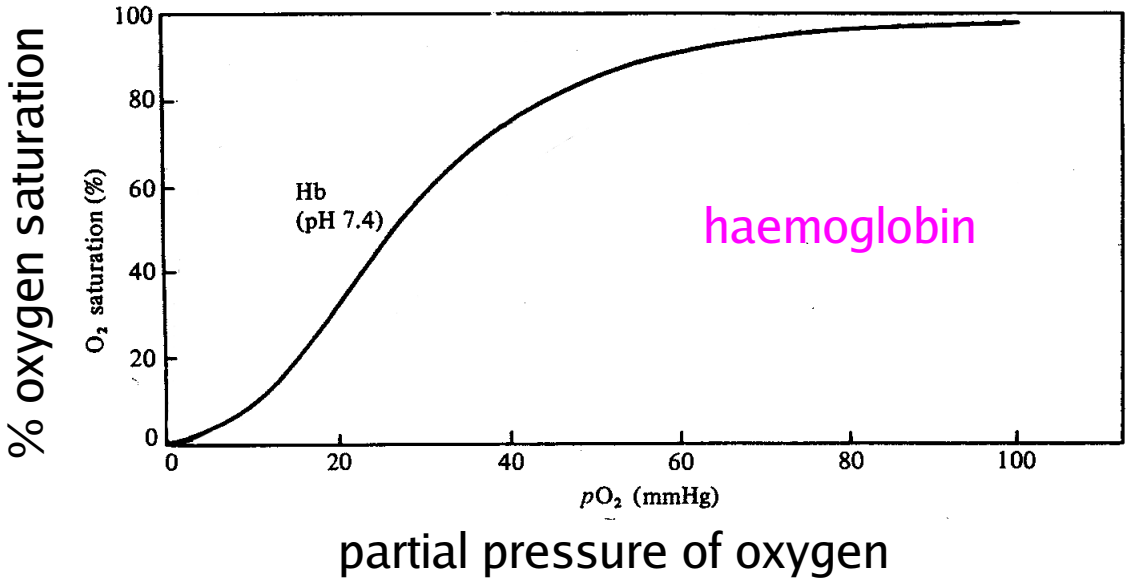
Johan will tell you about another measure in his lectures

cooperativity

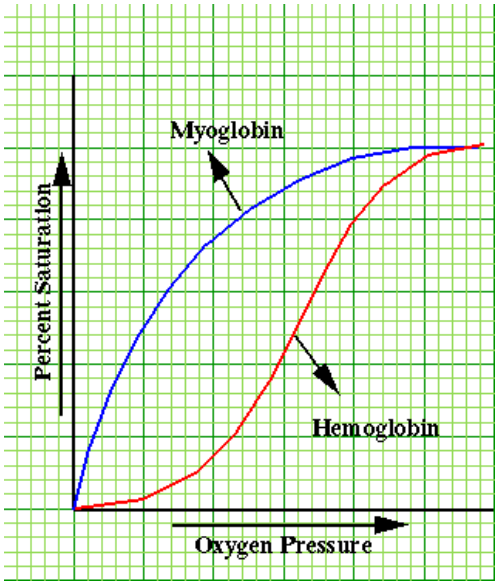
one interaction (eg: a binding event) changes the effect of a subsequent interaction

an important mechanism for creating sigmoidal dose-responses

cooperativity in oxygen binding to haemoglobin

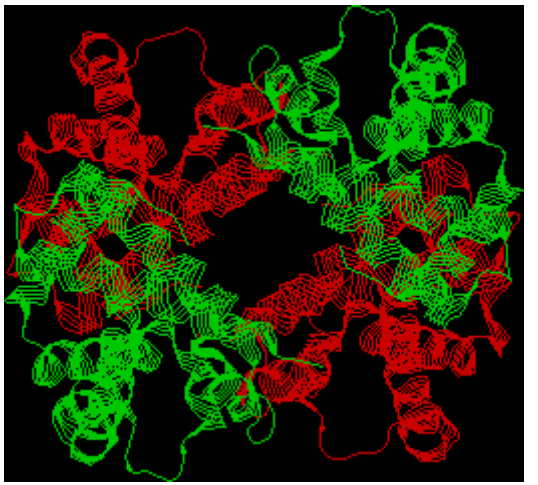


partial pressure of oxygen



Christian Bohr, Boris Hasselbach & August Krogh,
Skand. Arch. Physiol., **16**:401-12, 1904

Haemoglobin cooperativity is based on allostery



August Krogh
Nobel in Physiology
1920

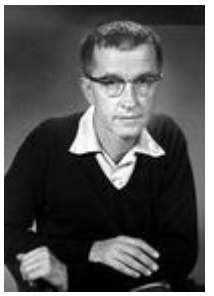
Teacher/student

Christian Bohr

Father/son

Niels Bohr
Nobel in Physics
1922

Teacher/student

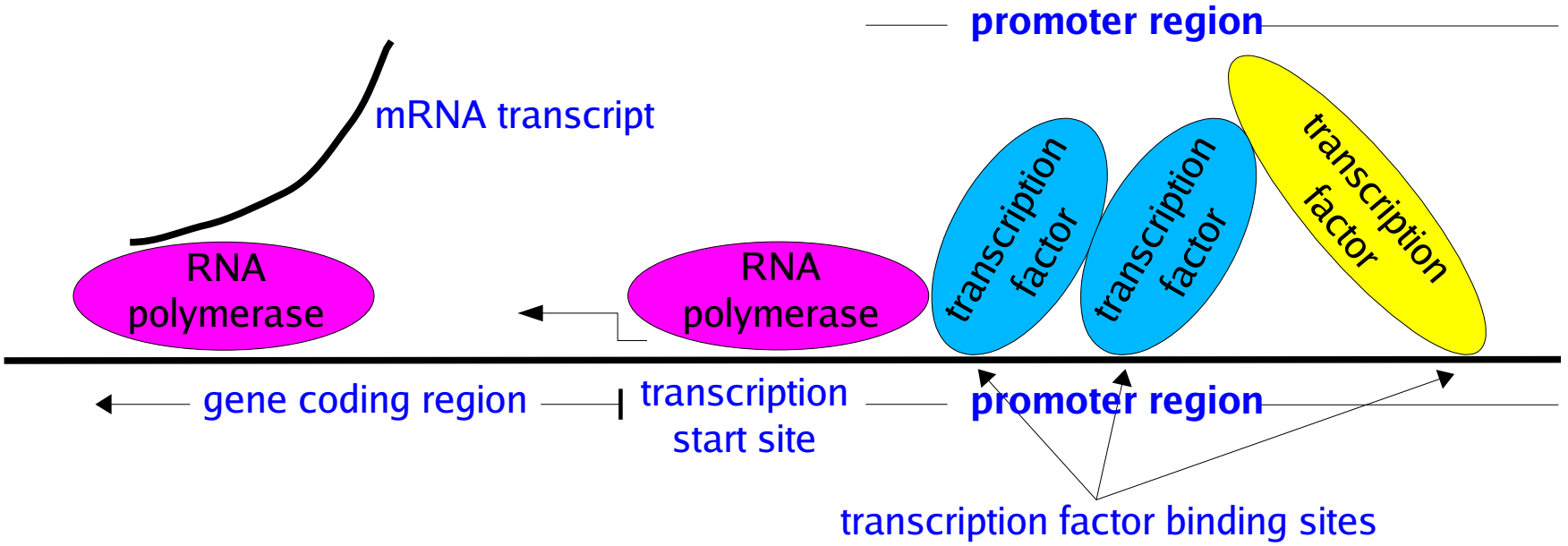


Max Delbruck
Nobel in Physiology
1969

haemoglobin creates cooperativity through
ALLOSTERY

phage lambda creates cooperativity through
PROMOTER STRUCTURE

gene expression depends on promoter structure



proteins

amino acids

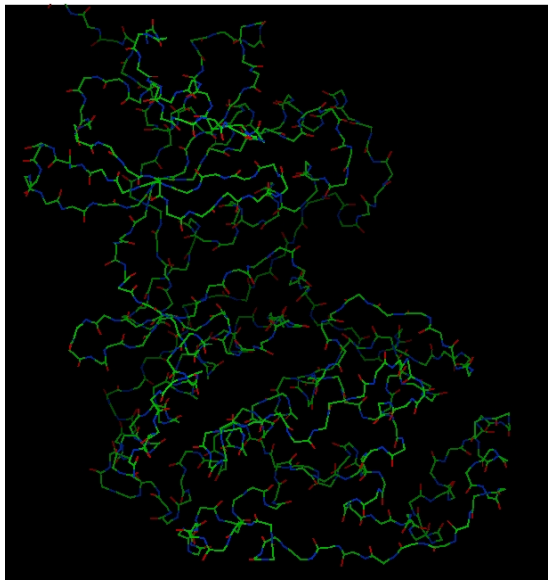
A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y

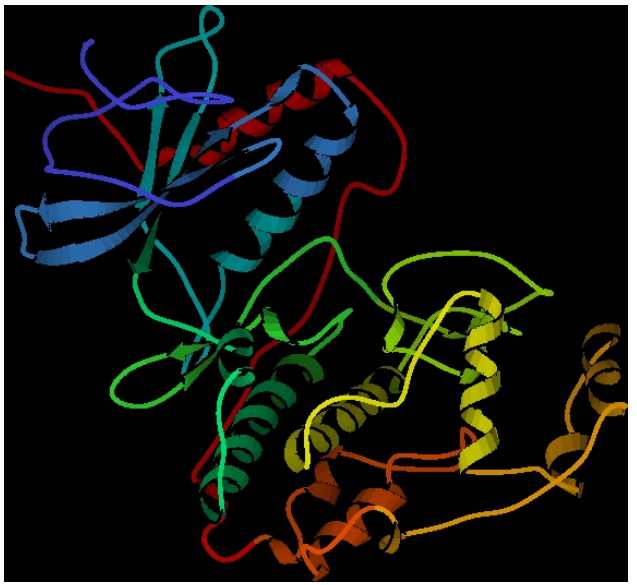
primary sequence

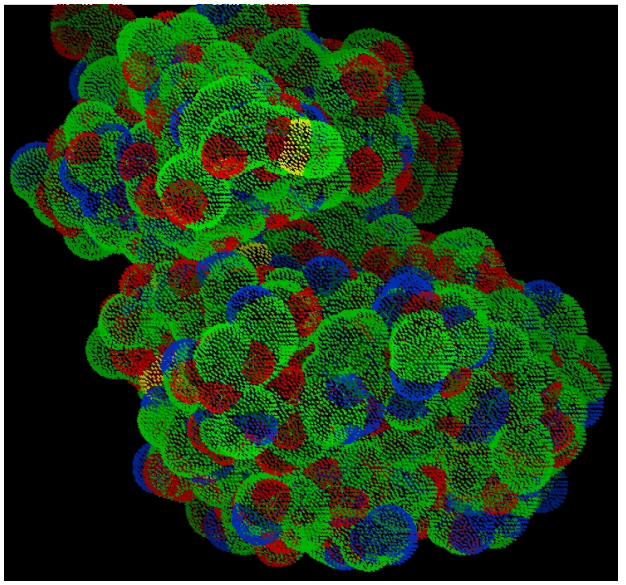
AAAAAAGAGP EMVRGQVFDV GPRYTNLSYI GEGAYGMVCS AYDNVNKVRV AIKKISPFEH
QTYCQRTLRE IKILLRFRHE NIIGINDIIR APTIEQMKDV YIVQDLMETD LYKLLKTQHL
SNDHICYFLY QILRGLKYIH SANVLHRDLK PSNLLLNTTC DLKICDFGLA RVADPDHDHT
GFLTEYVATR WYRAPEIMLN SKGYTKSIDI WSVGCILAEM LSNRPIFPGK HYLDQLNHIL
GILGSPSQED LNCIINLKAR NYLLSLPHKN KVPWNRLFPN ADSKALDLLD KMLTFNPHKR
IEVEQALAHP YLEQYYDPSD EPIAEAPFKF DMELDDLPKE KLKELIFEET ARFQPGYRS

Erk2 – Extracellular signal Regulated Kinase **SwissProt P28482**

secondary structure – α helices and β sheets







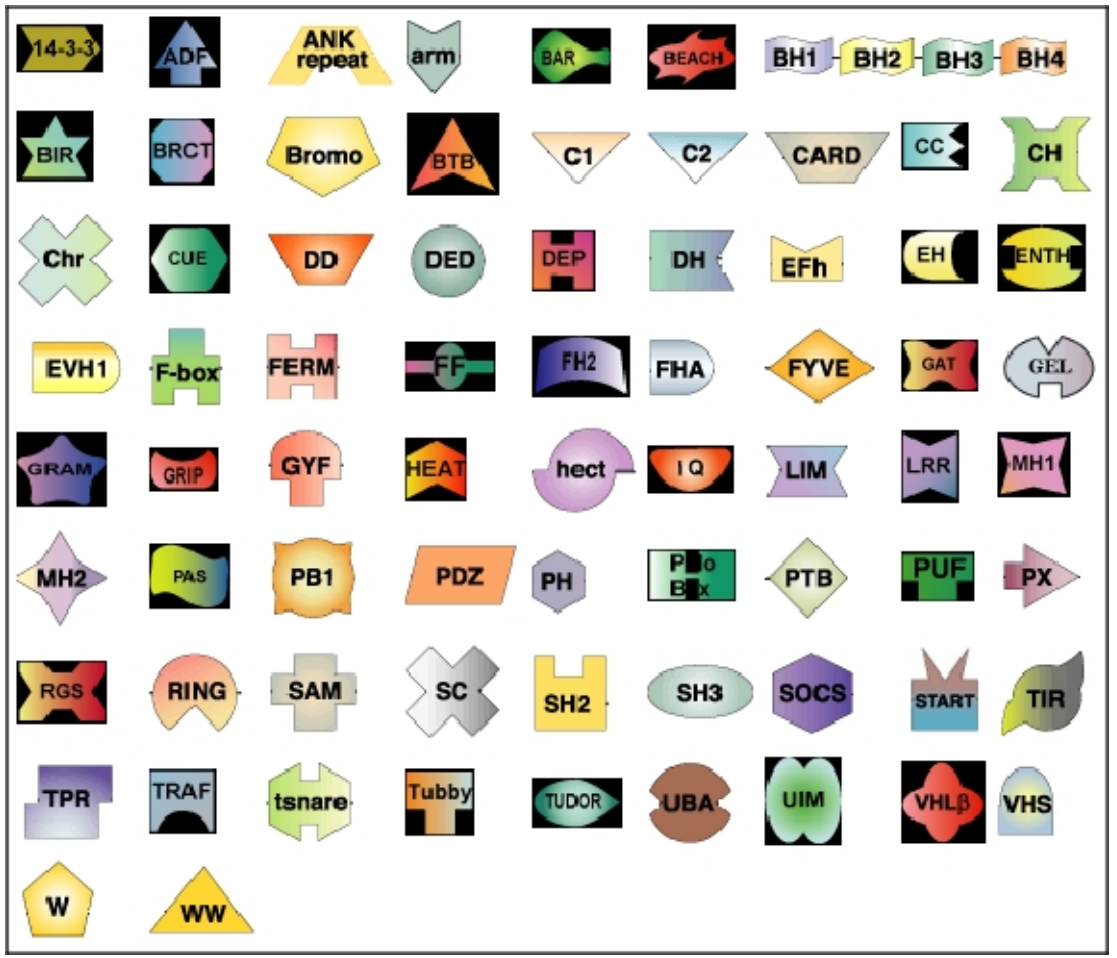
RCSB PDB PROTEIN DATA BANK

http://www.rcsb.org/pdb/

PDB 1ERK

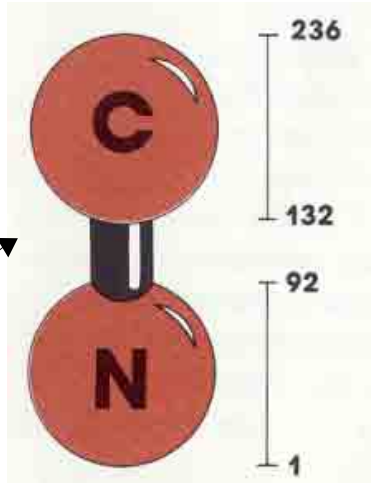
proteins

tertiary structure -do mains



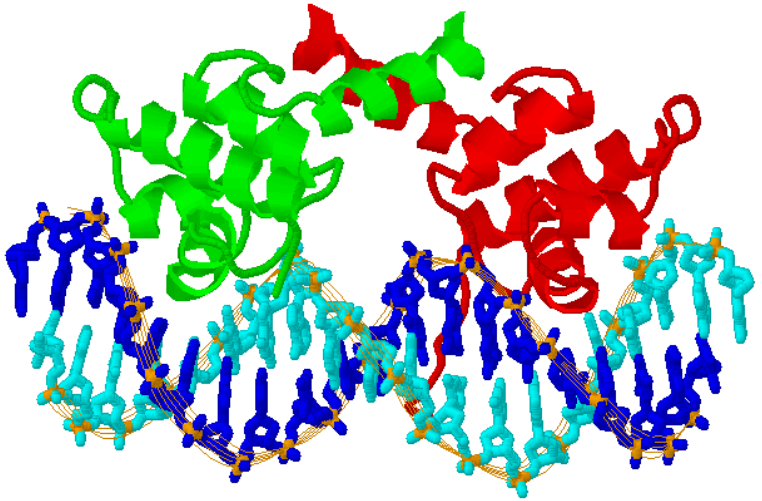
Tony Pawson's lab http://pawsonlab.mshri.on.ca/

lambda repressor – dimerisation and DNA binding

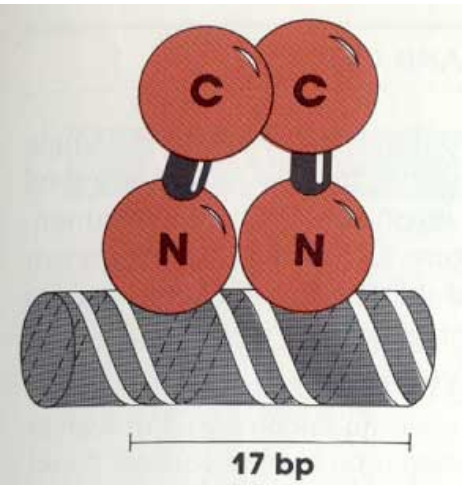


dimerisation

DNA binding

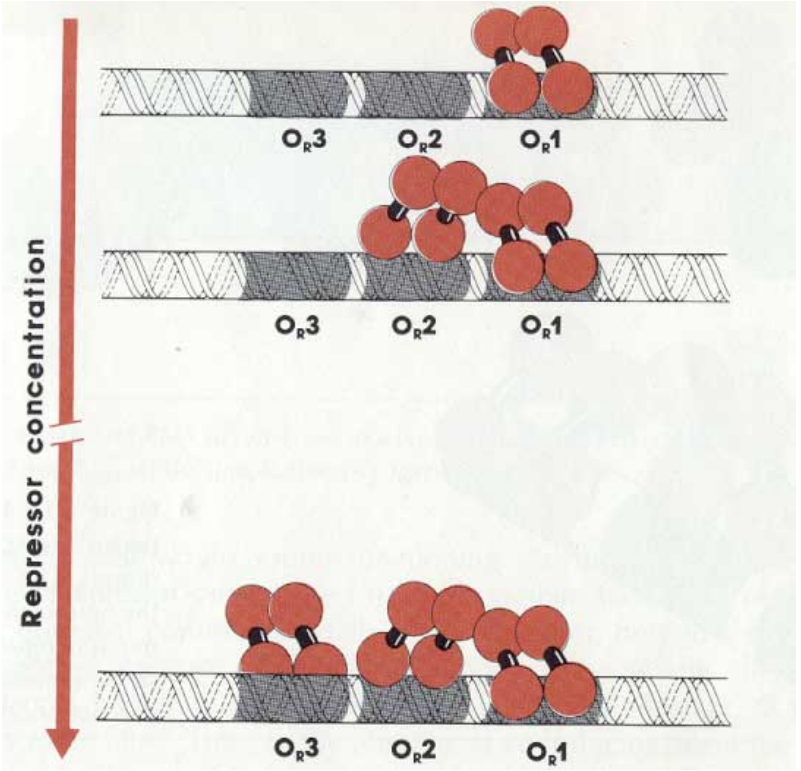


1lmb.pdb Beamer & Pabo J Mol Biol 227:177, 1992



lambda repressor – binding to operator region

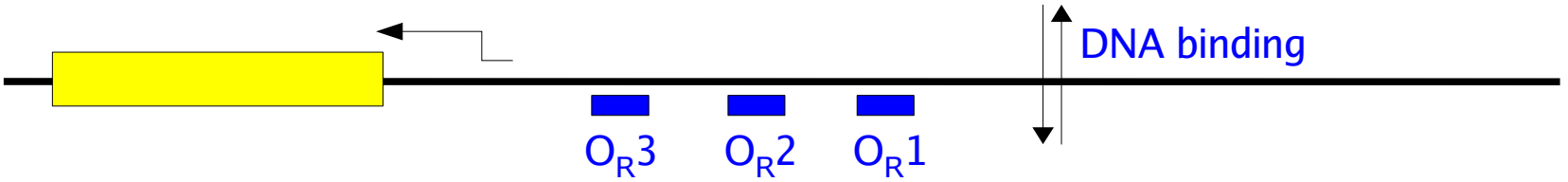
cooperative binding of repressor dimer to O_R1 and O_R2



repressor transcribed at low basal rate

~11x increase in repressor transcription

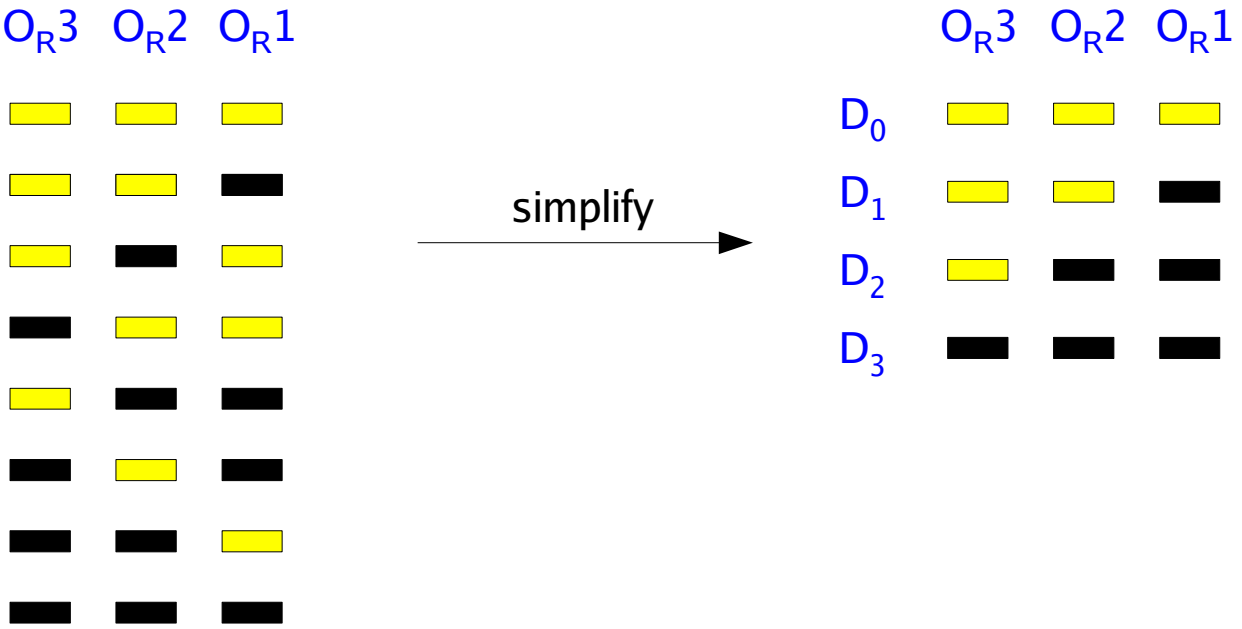
repressor transcription turned off



calculating the rate of repressor expression

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

a general statistical mechanical model for transcription factor binding



calculate the probabilities of finding repressor bound to DNA in each state (D_0, D_1, D_2, D_3)

calculate the rate of gene transcription as an average over this probability distribution