A Systems Approach to Biology

MCB 195

Lecture 5
Thursday, 17 Feb 2005

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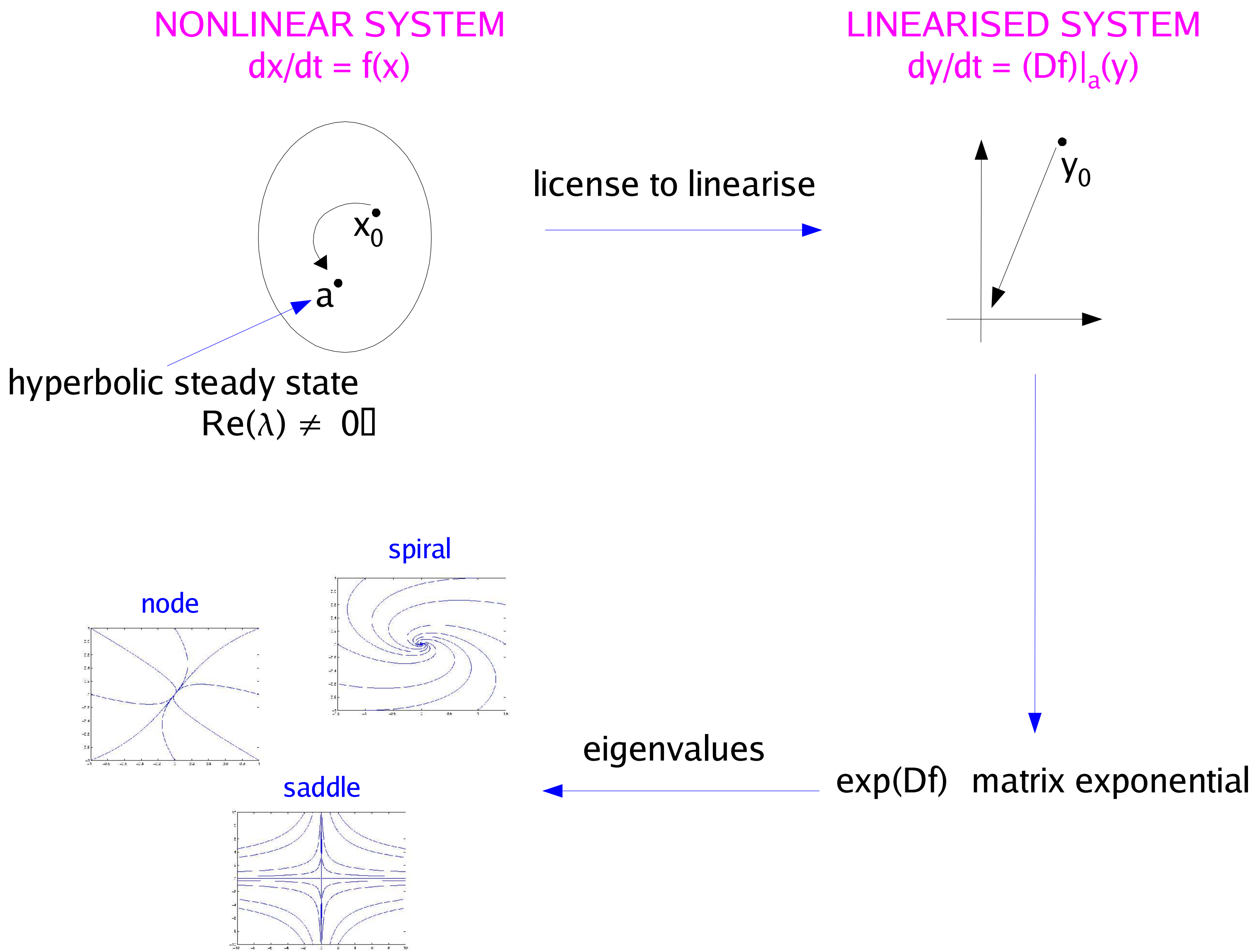
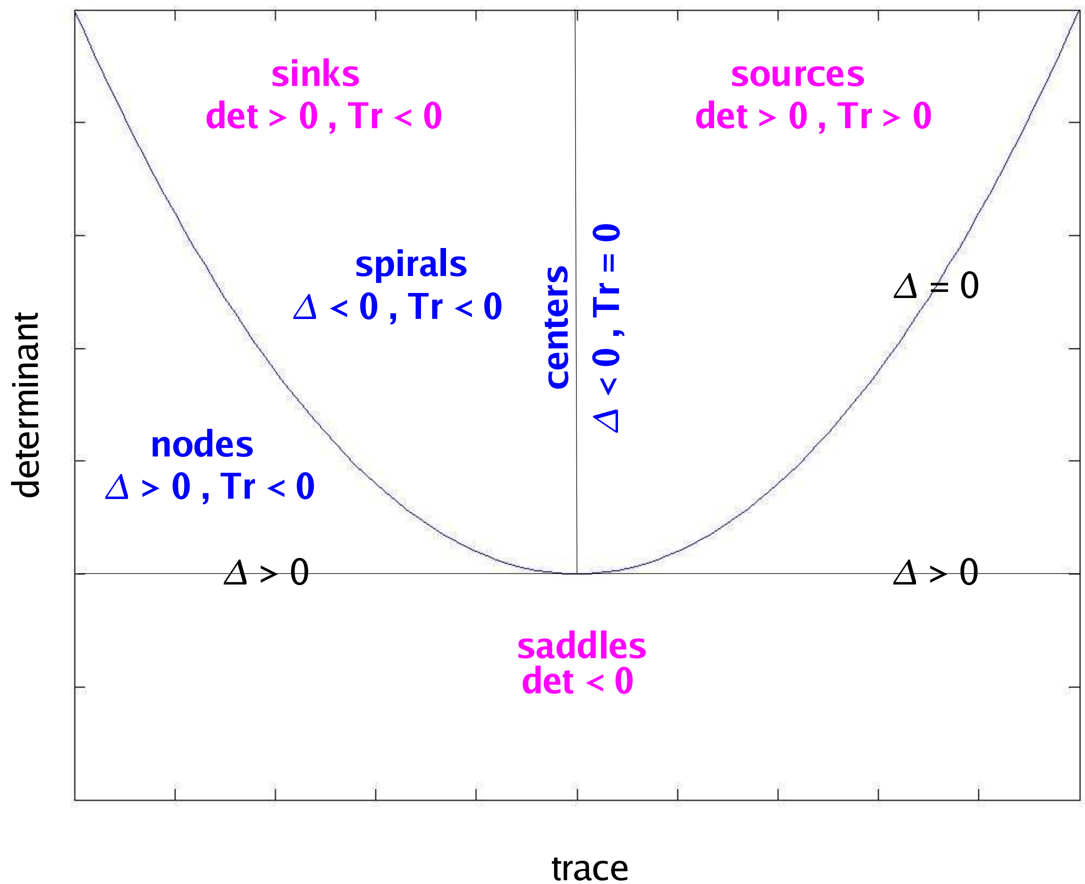
BISTABILITY

in

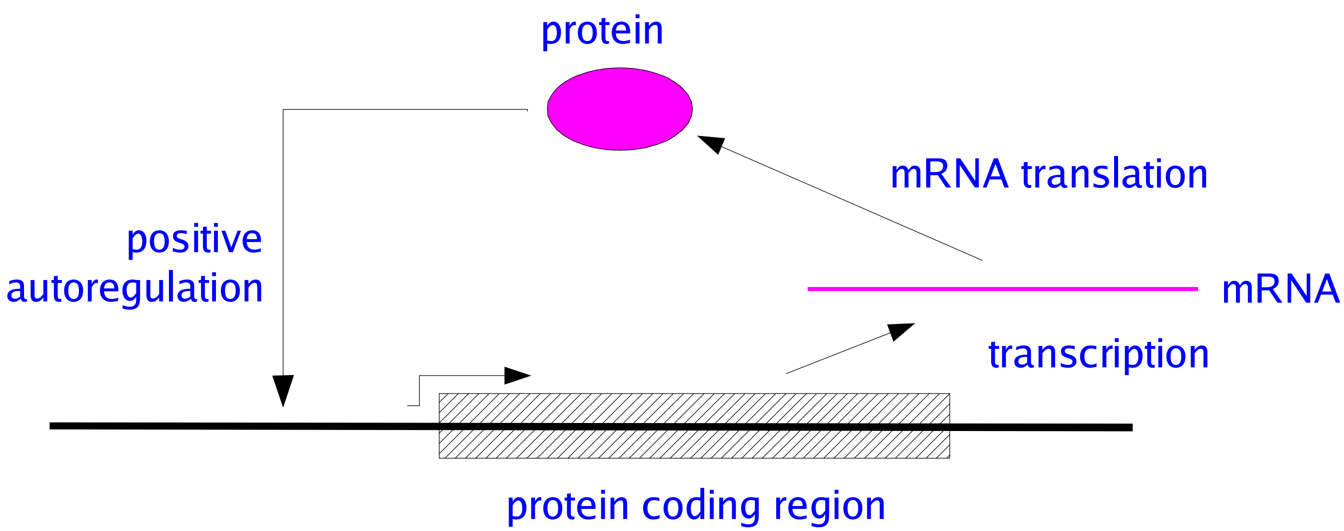
GENETIC REGULATION


NONLINEAR SYSTEM
dx/dt = f(x)
x_0
a
hyperbolic steady state
Re(λ) ≠ 0
license to linearise
LINEARISED SYSTEM
dy/dt = (Df)$|_a$(y)
y_0
exp(Df) matrix exponential
eigenvalues
node
spiral
saddle



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

GENETIC AUTOREGULATORY LOOP



POSITIVE FEEDBACK

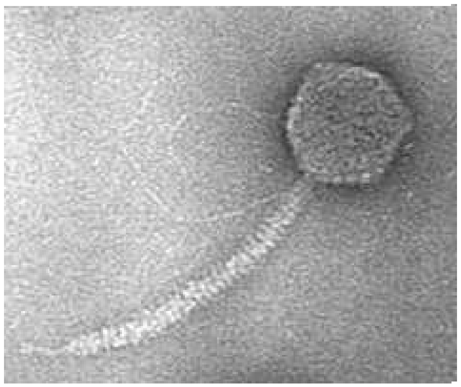
x = protein concentration
y = mRNA concentration

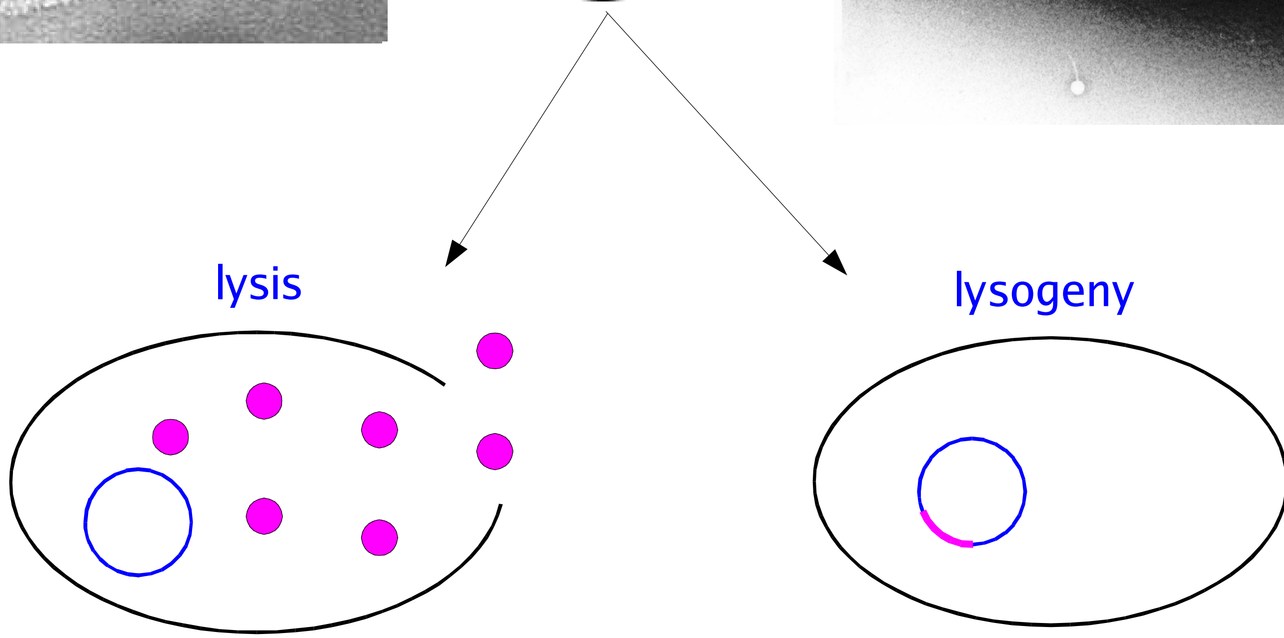
$$\frac{dx}{dt} = \lambda y - ax$$

$$\frac{dy}{dt} = \;?\; - by$$

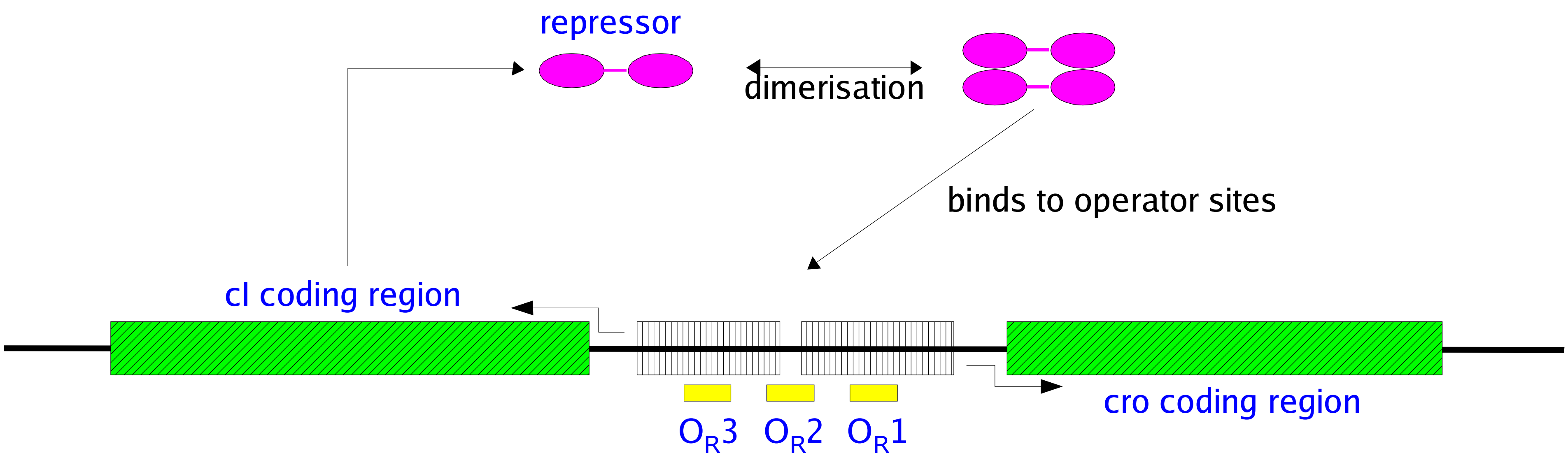
λ	mRNA translation rate	$(\text{time})^{-1}$
a	protein degradation rate	$(\text{time})^{-1}$
b	mRNA dedgradation rate	$(\text{time})^{-1}$

PHAGE LAMBDA





lambda repressor

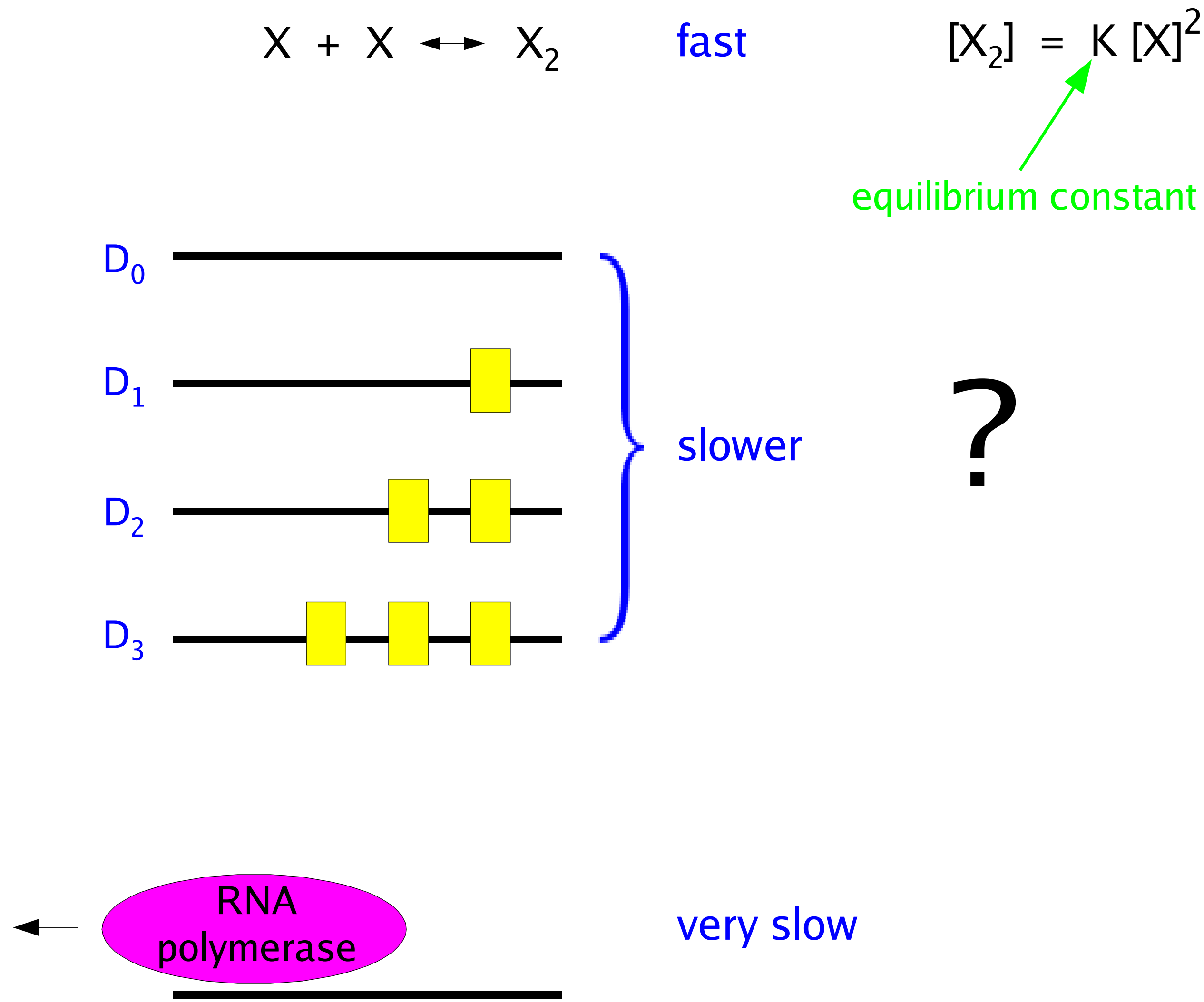


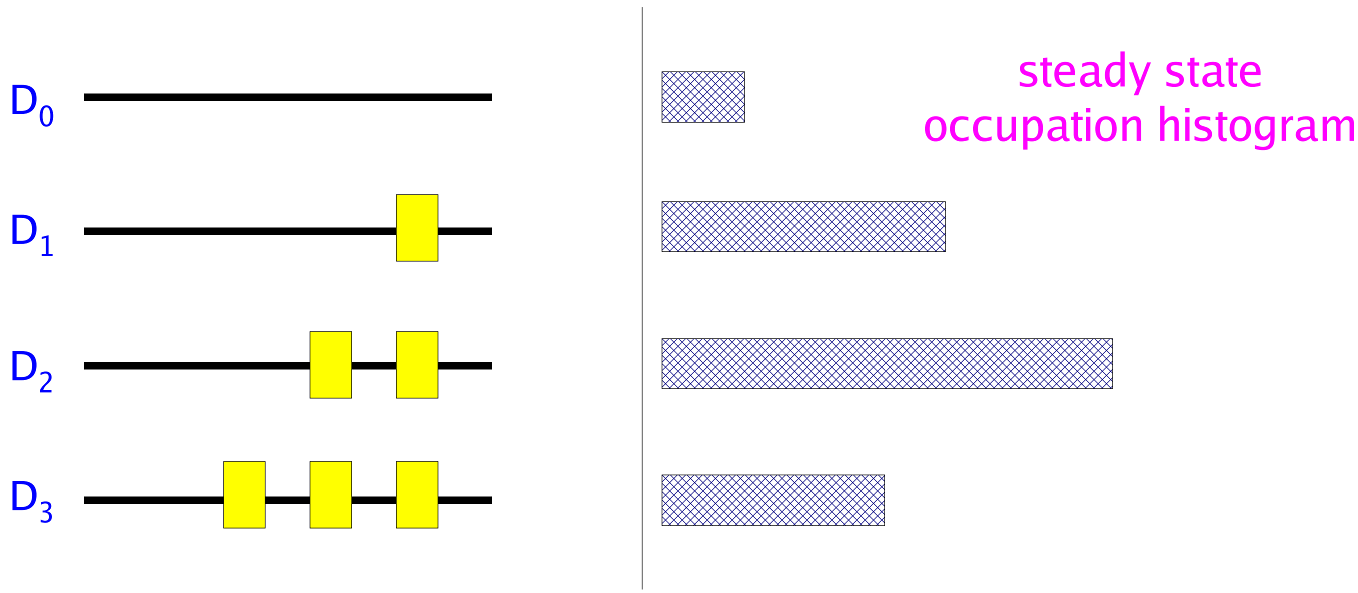
$O_R1 > O_R2 > O_R3$

O_R2 is highly favoured if O_R1 is already bound

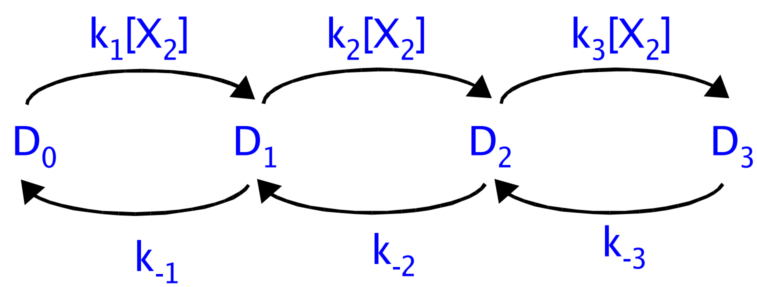
O_R3 is independent of O_R1 and O_R2

O_R1	cI transcribed at low basal rate
O_R2	10x increase in transcription of cI
O_R3	cI transcription turned off


$X + X \leftrightarrow X_2$
fast
$[X_2] = K [X]^2$
equilibrium constant
D_0
D_1
D_2
D_3
slower
?
RNA polymerase
very slow



Markov chain



d_i = probability of state D_i at equilibrium

$$d_i = (k_i[X_2] / k_{-i})\, d_{i-1} = K_i\,[X_2]d_{i-1}$$

$$d_1 = K_1\,[X_2]d_0 \qquad d_2 = K_1K_2[X_2]^2d_0 \qquad d_3 = K_1K_2K_3[X_2]^3d_0$$

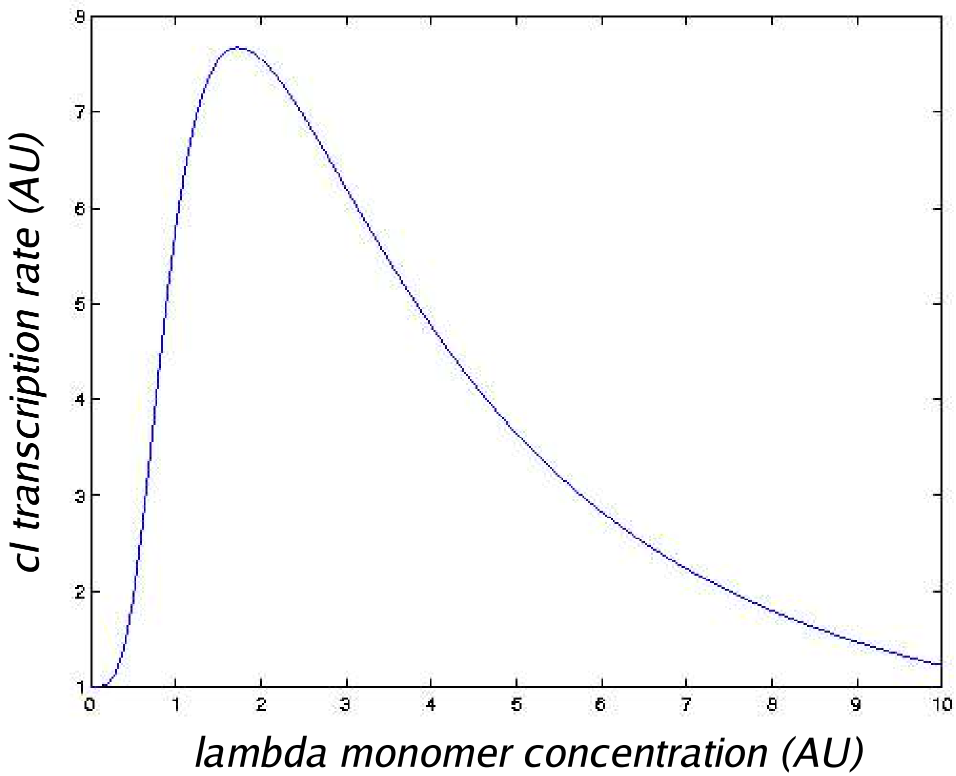
$$d_0 + d_1 + d_2 + d_3 = 1$$

if r_i = transcription rate in state D_i then
the average transcription rate r is

$$r = r_0 d_0 + r_1 d_1 + r_2 d_2 + r_3 d_3$$

$$r = \frac{r_0 + r_1 (K_1 K) x^2 + r_2 (K_1 K_2 K^2) x^4 + r_3 (K_1 K_2 K_3 K^3) x^6}{1 + (K_1 K) x^2 + (K_1 K_2 K^2) x^4 + (K_1 K_2 K_3 K^3) x^6}$$

Effect of lambda repressor on expression of cI



$$\frac{r_0 + r_1 (K_1 K) x^2 + r_2 (K_1 K_2 K^2) x^4}{1 + (K_1 K) x^2 + (K_1 K_2 K^2) x^4 + (K_1 K_2 K_3 K^3) x^6}$$

Hasty et al, *"Designer gene networks: towards fundamental cellular control"*
Chaos **11**:207-220 2001

The Principle of Detailed Balance

in a system at equilibrium each individual loop is at equilibrium

The linear Markov chain satisfies detailed balance

$$d_i = (k_i [X_2] / k_{i-1})\, d_{i-1}$$

Katchalsky & Curran, "Nonequilibrium Thermodynamics in Biophysics"

"(detailed balance) ... is not based on any previous notion and constitutes an additional principle of physical chemistry ... closely related to one of the fundamental principles of statistical mechanics ... microscopic reversibility"

Tolman, "The Principles of Statistical Mechanics"

"Under equilibrium conditions, any molecular process and the reverse of that process will be taking place, on the average, at the same rate"

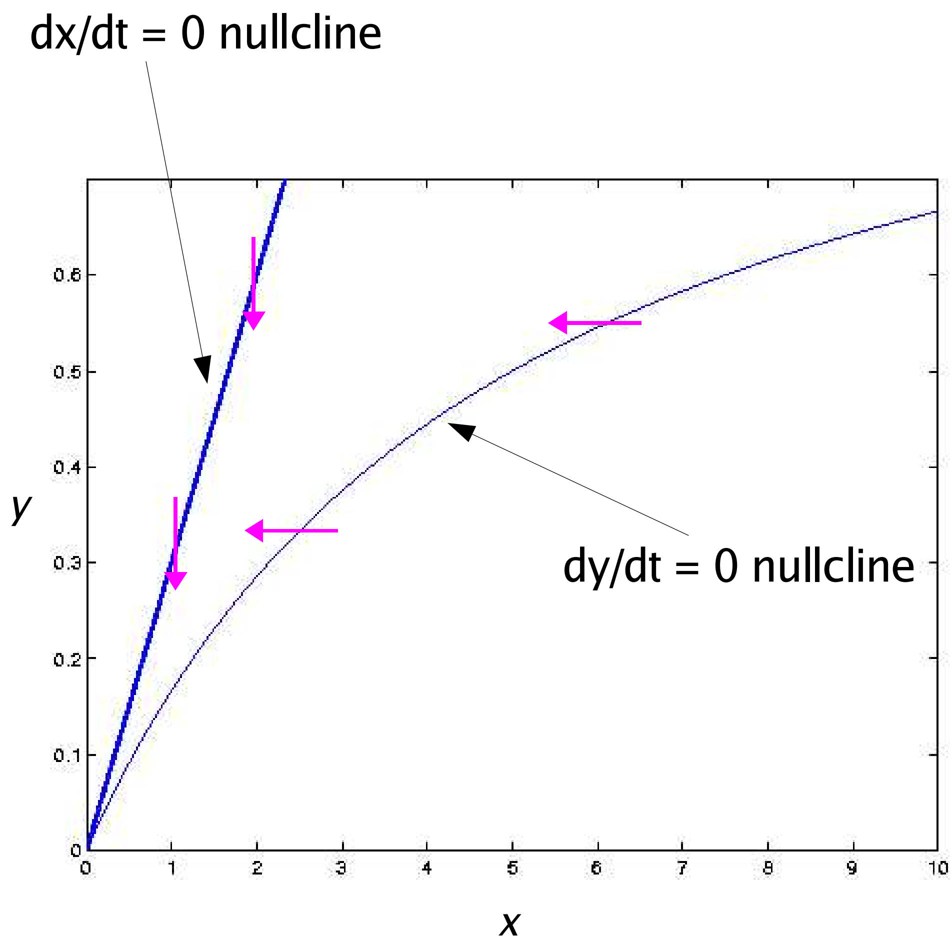
x = protein concentration
y = mRNA concentration

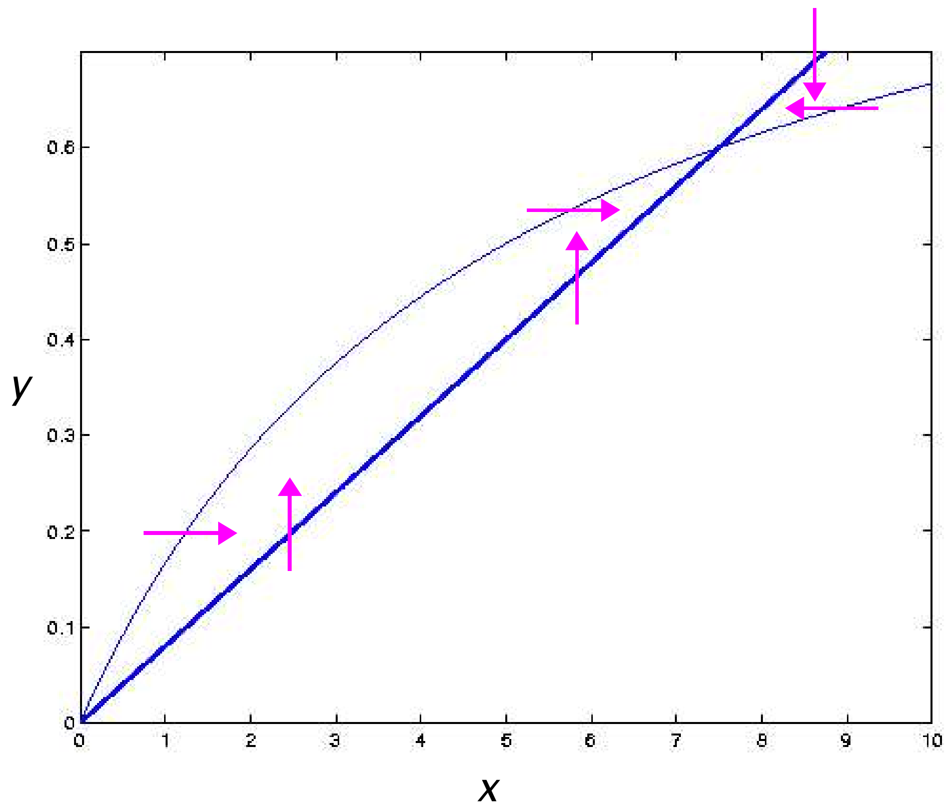
$$\frac{dx}{dt} = \lambda y - ax$$

no dimerisation
1 operator site

$$\frac{dy}{dt} = \frac{\alpha x}{k + x} - by$$

λ	mRNA translation rate	$(\text{time})^{-1}$
a	protein degradation rate	$(\text{time})^{-1}$
b	mRNA dedgradation rate	$(\text{time})^{-1}$
a	maximal gene expression rate	$(\text{mols})(\text{time})^{-1}$
k	“Michaelis-Menten” constant	(mols)


dx/dt = 0 nullcline
dy/dt = 0 nullcline
y
x
0
0.1
0.2
0.3
0.4
0.5
0.6
0
1
2
3
4
5
6
7
8
9
10



0.6
0.5
0.4
0.3
0.2
0.1
0
y
0
1
2
3
4
5
6
7
8
9
10
x

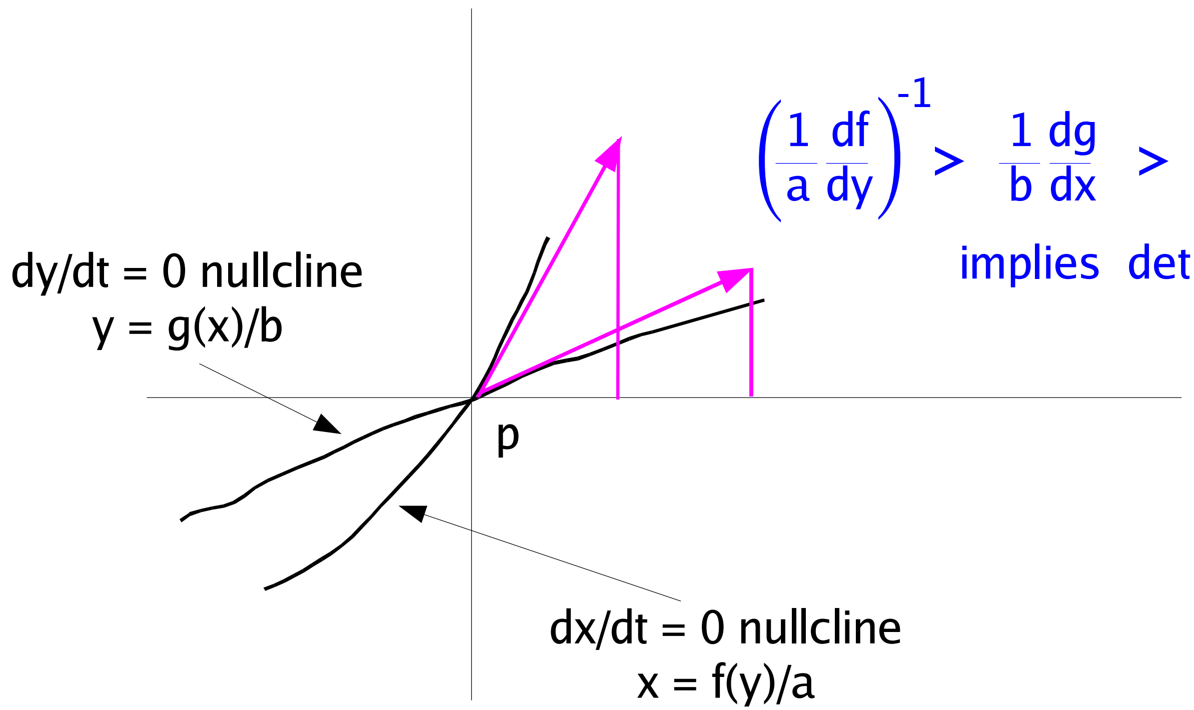
$a, b > 0$

$$\frac{dx}{dt} = f(y) - ax$$
$$\frac{dy}{dt} = g(x) - by$$

Jacobian

$$\begin{pmatrix} -a & df/dy \\ dg/dx & -b \end{pmatrix}$$

$Tr = -(a+b) < 0$



$$\left(\frac{1}{a}\frac{df}{dy}\right)^{-1} > \frac{1}{b}\frac{dg}{dx} > 0$$

implies $\det > 0$

$Tr < 0 \quad \det > 0 \longrightarrow$ stable (node or spiral)