A Systems Approach to Biology

MCB 195

Lecture 6
Tuesday, 22 Feb 2005

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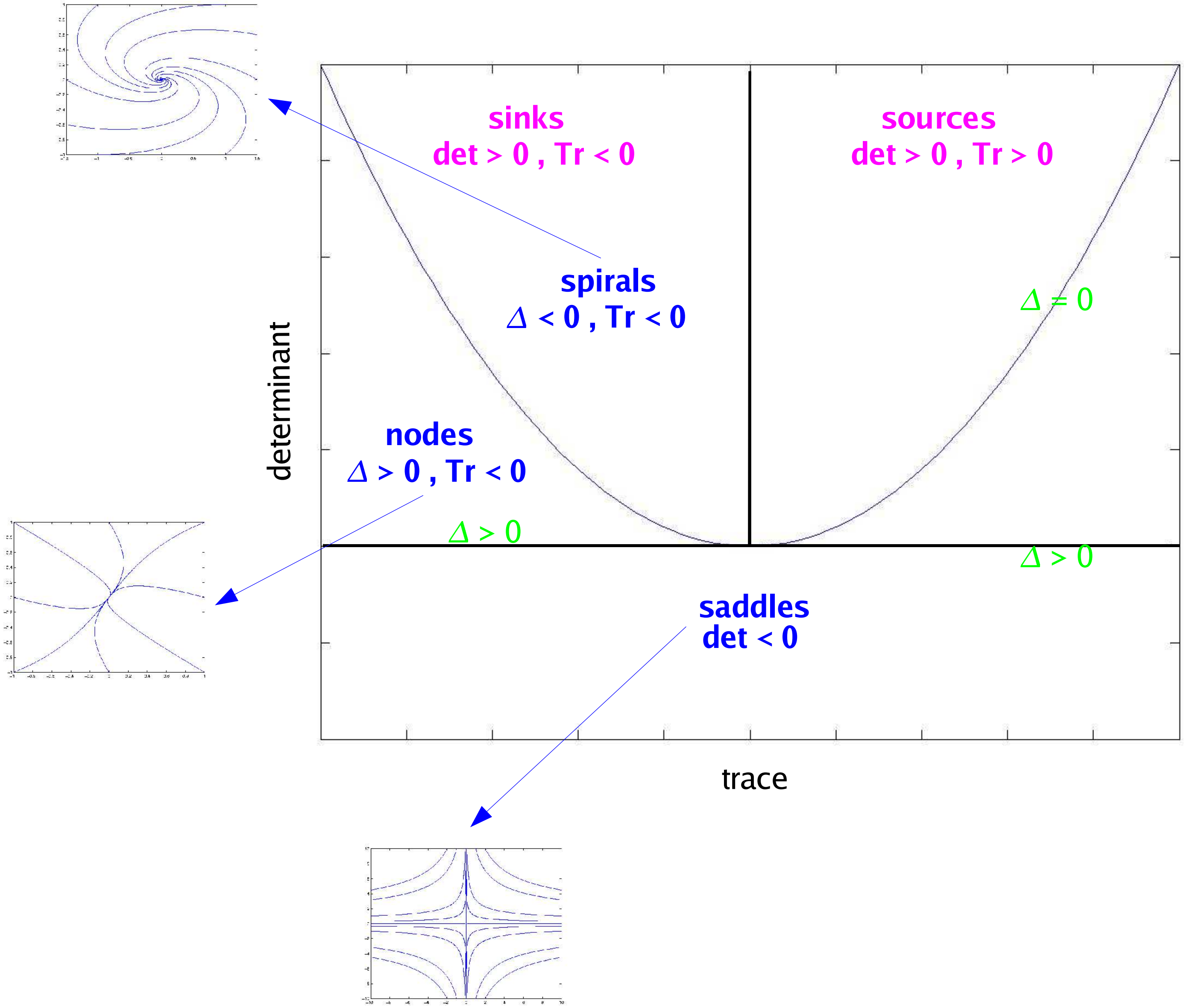
COOPERATIVITY
and its
CONSEQUENCES

Behaviour of 2D nonlinear dynamical systems at a hyperbolic fixed point



sinks
det > 0 , Tr < 0

sources
det > 0 , Tr > 0

spirals
$\Delta < 0$, Tr < 0

$\Delta = 0$

nodes
$\Delta > 0$, Tr < 0

$\Delta > 0$

$\Delta > 0$

saddles
det < 0

determinant

trace

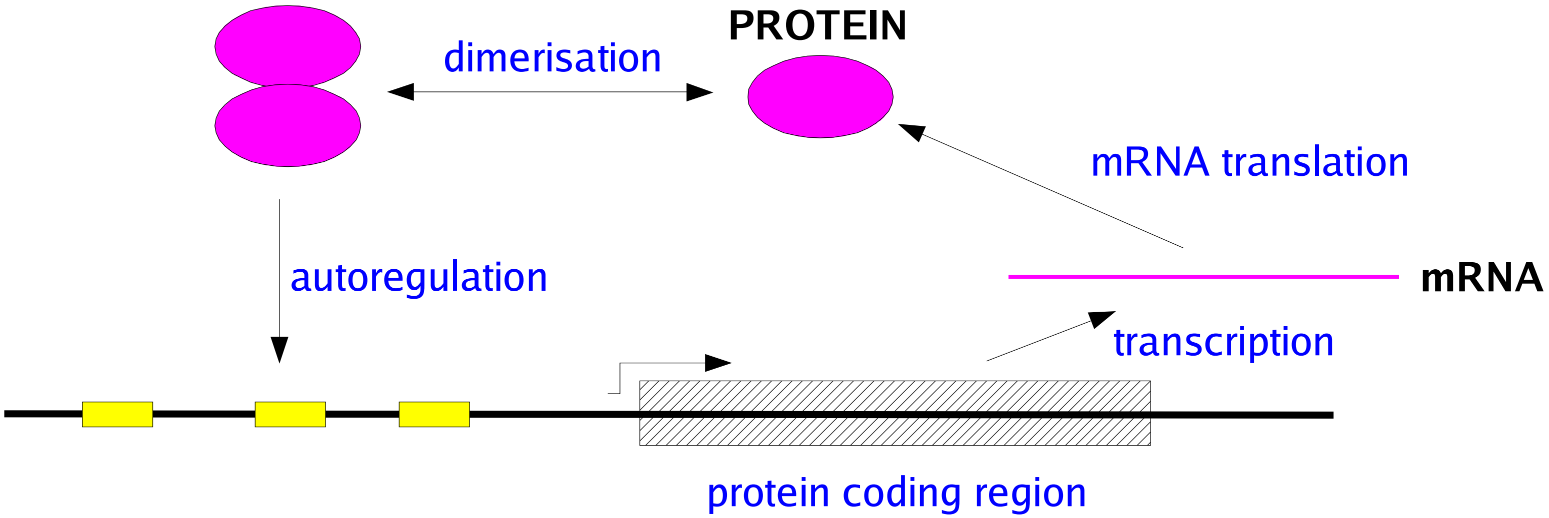
Jacobian

$$\begin{pmatrix} a & b \\ c & d \end{pmatrix}$$

Tr = a + d

det = ad - bc

$\Delta = Tr^2 - 4*det$



average rate of production of mRNA

x = concentration of protein

$$r = \frac{r_0 + r_1 (K_1K)x^2 + r_2 (K_1K_2K^2)x^4 + r_3 (K_1K_2K_3K^3)x^6}{1 + (K_1K)x^2 + (K_1K_2K^2)x^4 + (K_1K_2K_3K^3)x^6}$$

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

no dimerisation
1 operator site

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

a, b > 0

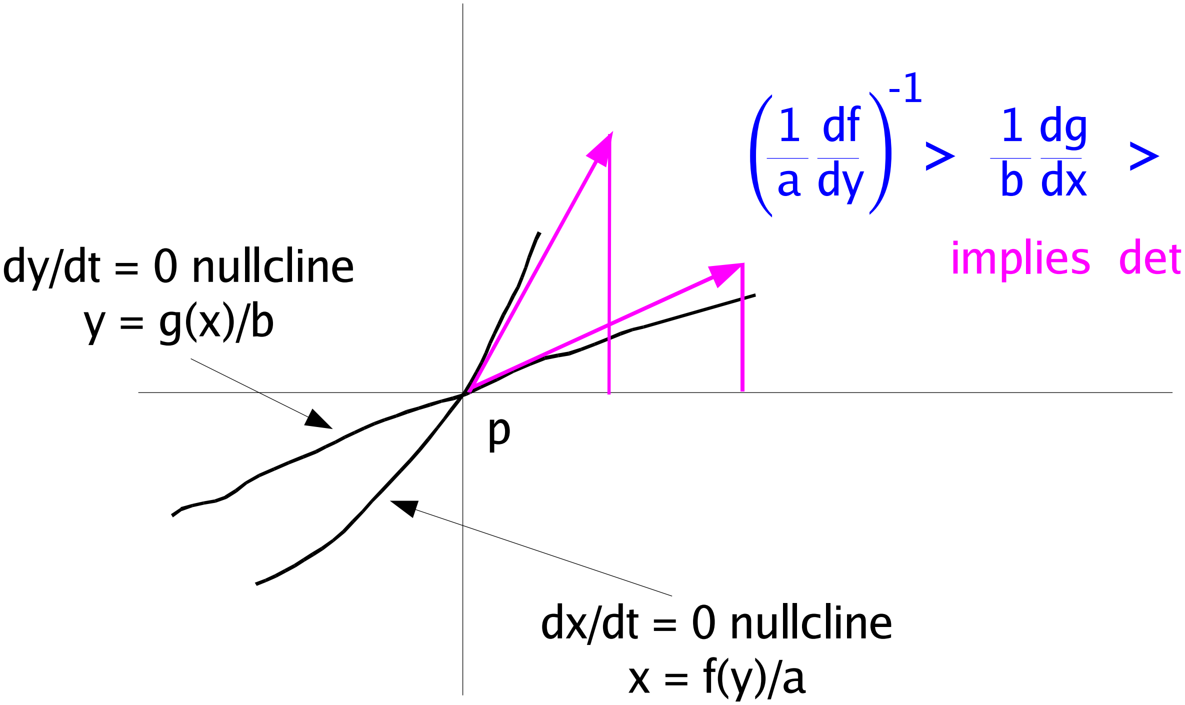
$$\boxed{\begin{aligned} dx/dt &= f(y) - ax \\ dy/dt &= g(x) - by \end{aligned}}$$

Jacobian

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

$Tr = -(a+b) < 0$ $det = ab - (df/dy)(dg/dx)$

$\Delta = (a-b)^2 + 4*(df/dy)(dg/dx)$

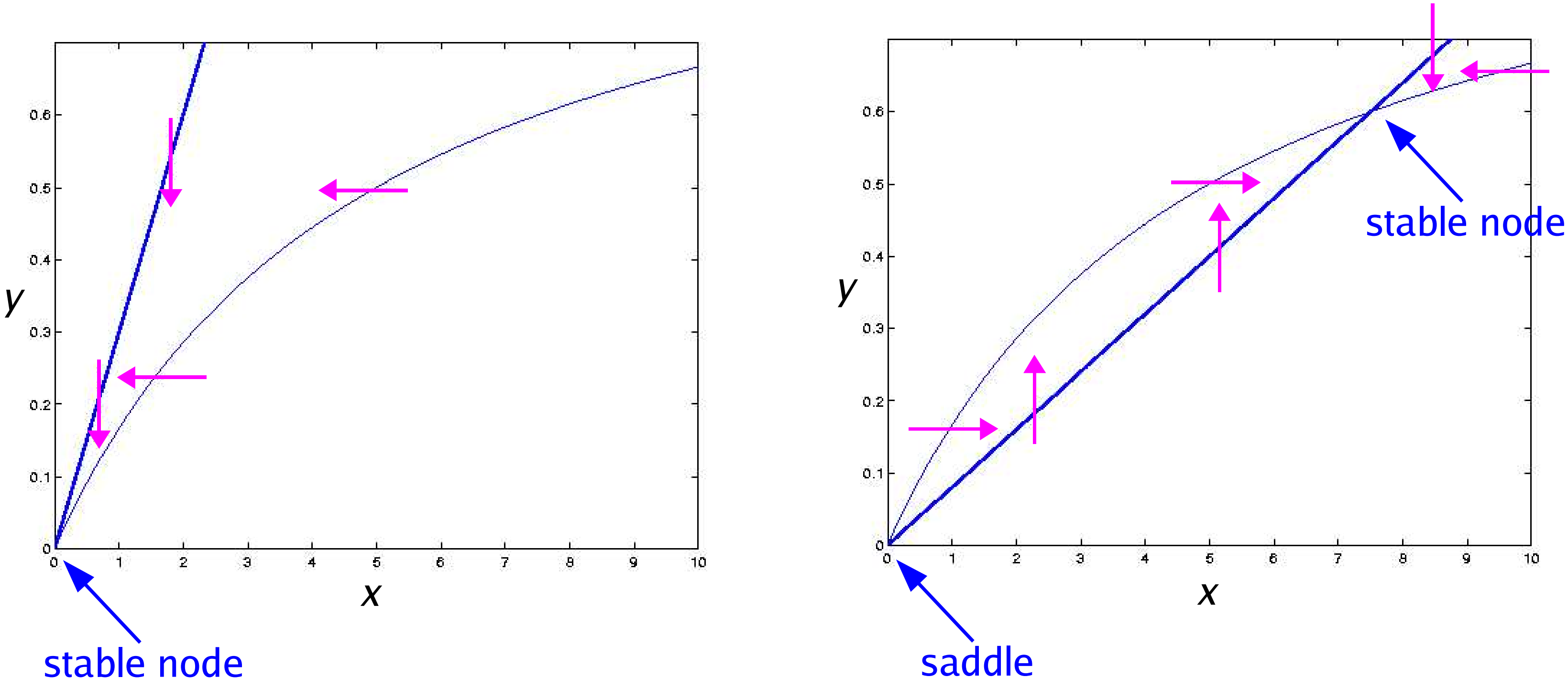


$$\left(\frac{1}{a}\frac{df}{dy}\right)^{-1} > \frac{1}{b}\frac{dg}{dx} > 0$$

implies det > 0, $\Delta > 0$

$Tr < 0$ $det > 0$ $\Delta > 0$ $\longrightarrow$ STABLE NODE

nullcline plot



stable node

saddle

stable node

decreasing a/λ

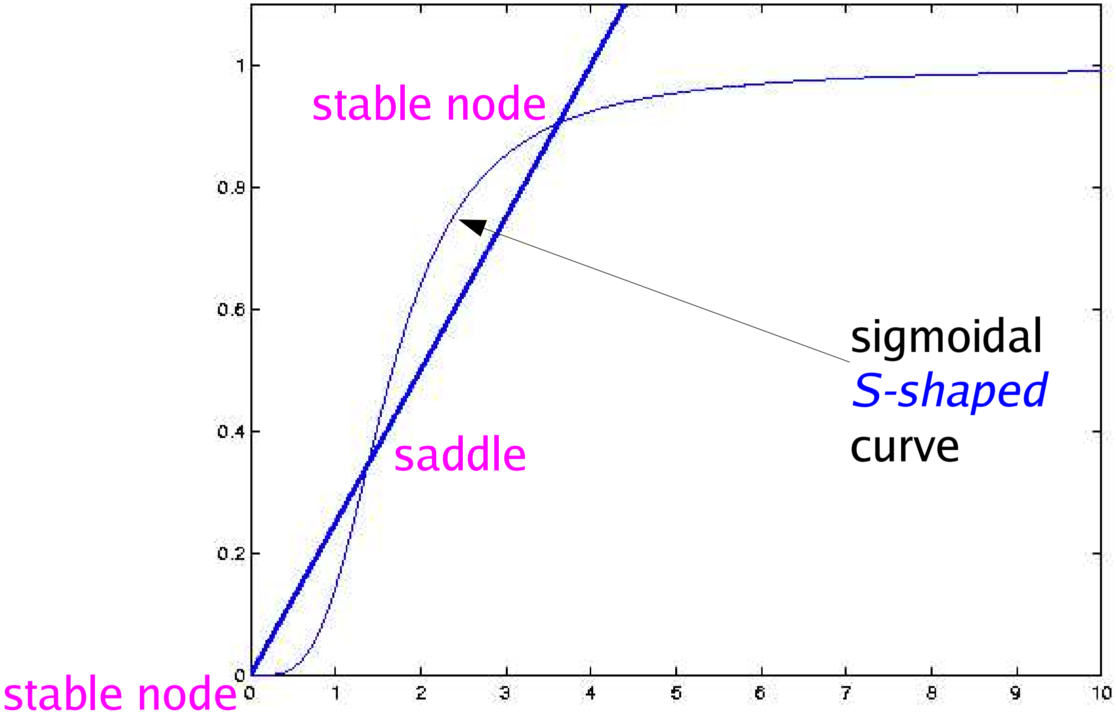
$$\frac{dx}{dt} = \lambda y - ax$$

dimerisation
2 operator sites

$$\frac{dy}{dt} = \frac{\alpha x^4}{k + x^2 + x^4} - by$$

BISTABILITY

two stable steady states



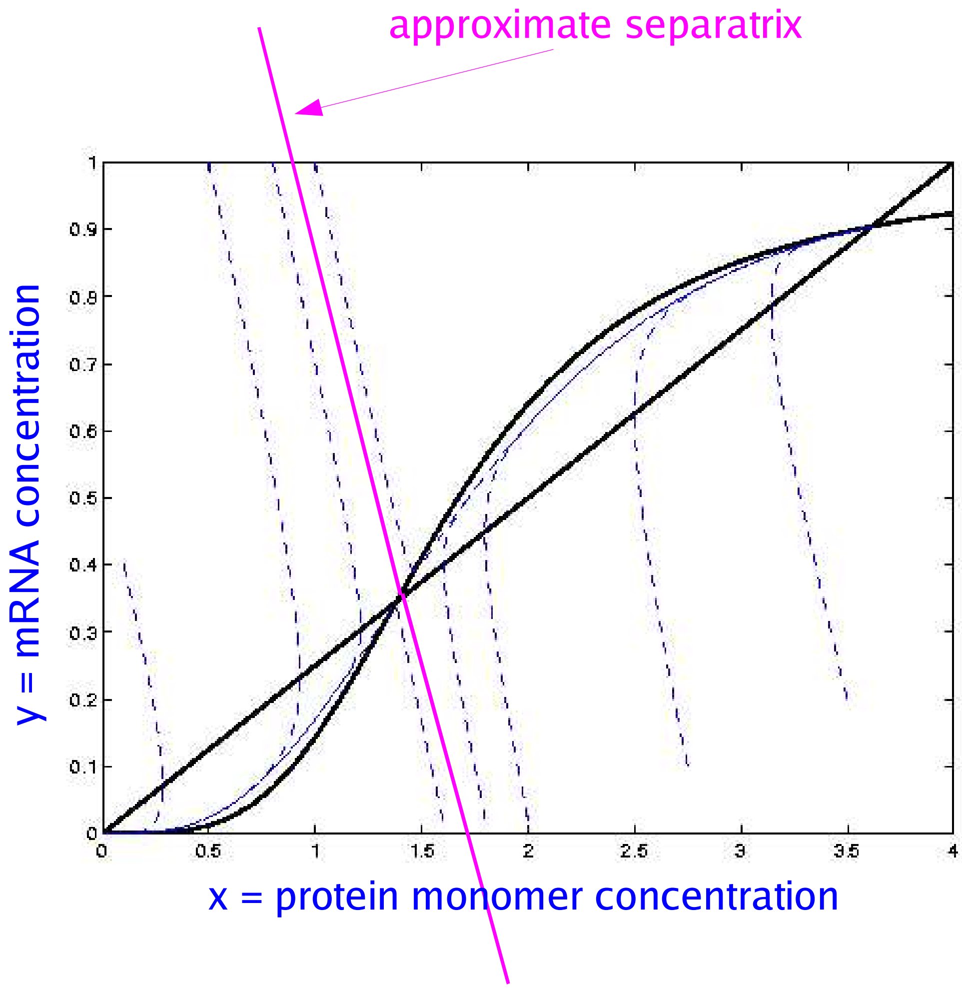
stable node

saddle

stable node

sigmoidal
S-shaped
curve

NO BISTABILITY WITHOUT SIGMOIDALITY !



λ	0.08 $(\text{time})^{-1}$
a	0.02 $(\text{time})^{-1}$
b	0.1 $(\text{time})^{-1}$
α	0.1 (mols)$(\text{time})^{-1}$
k	5 $(\text{mols})^{6}$

stable steady states can be inherited

multistability in genetic networks provides a basis for cellular differentiation

positive autoregulation is only one of many motifs arising in genetic networks

metazoans have much more complex gene regulatory networks than unicellular bacteria and yeasts

as Walter will show you ... soon

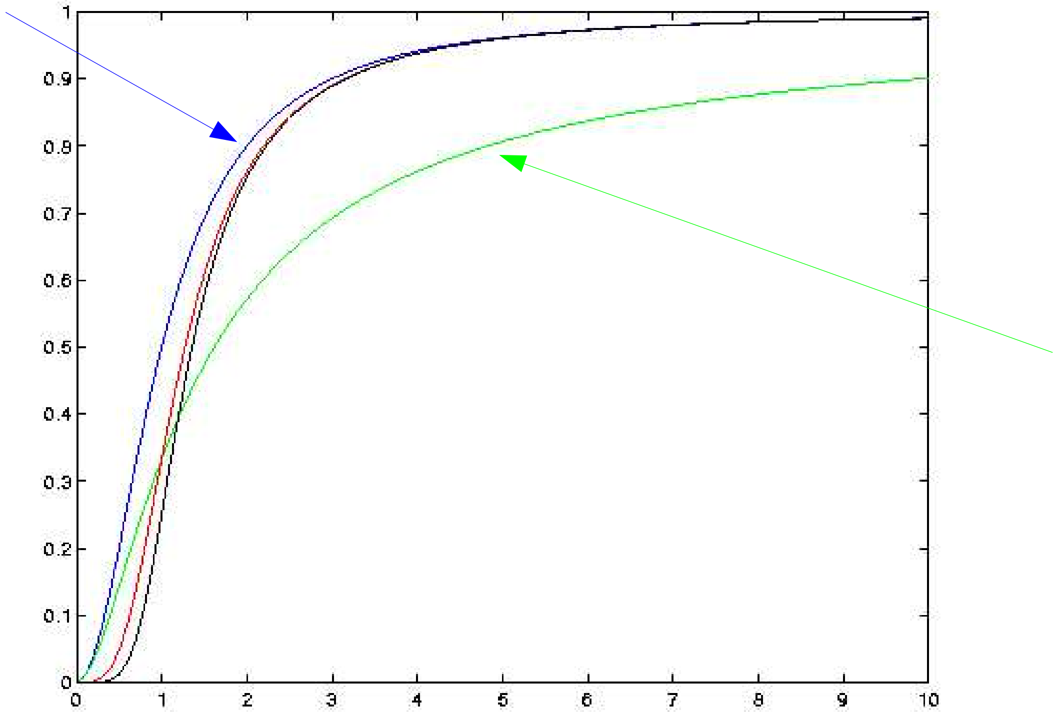
sigmoidality arises from cooperativity

- dimers bind DNA much better than a pair of monomers
- binding at O_R1 makes binding at O_R2 much easier

SHAPING SIGMOIDALITY

dimerisation only

$$\frac{x^2}{1 + x^2}$$



2 operator sites only

$$\frac{x^2}{1 + x + x^2}$$

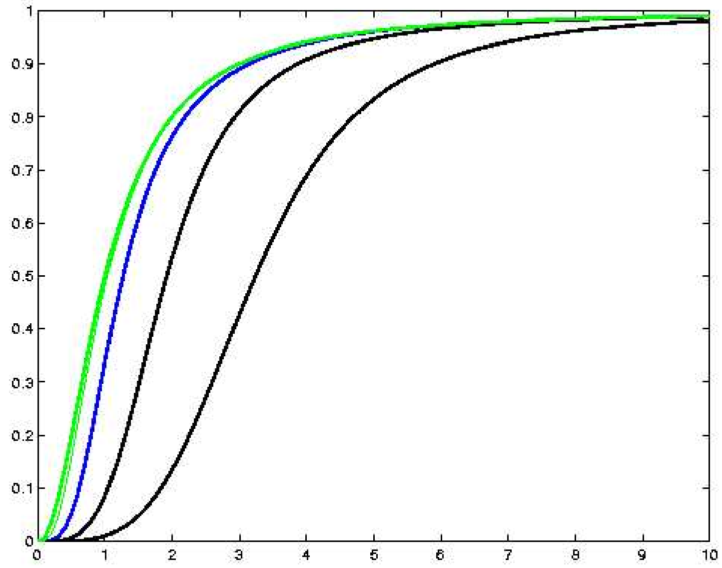
dimerisation + 2 operator sites

$$\frac{x^4}{1 + x^2 + x^4}$$

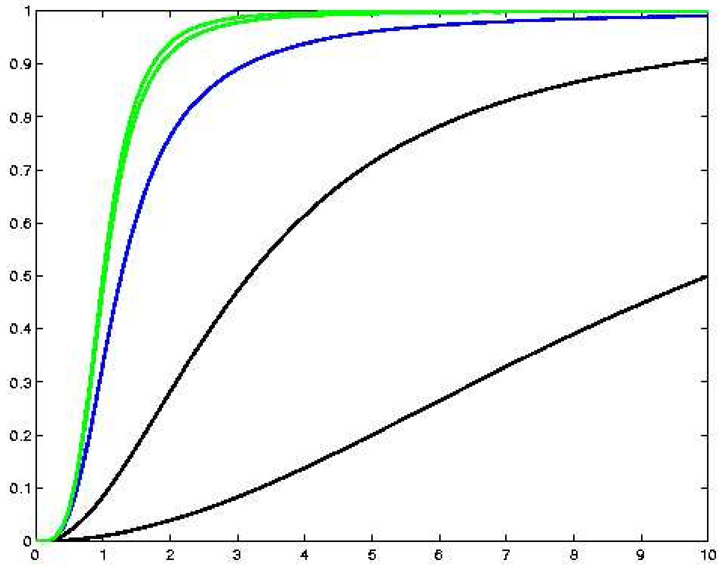
dimerisation + 3 operator sites

$$\frac{x^6}{1 + x^2 + x^4 + x^6}$$

SHAPING SIGMOIDALITY



$$\frac{x^4}{K + x^2 + x^4}$$



$$\frac{x^4}{1 + Kx^2 + x^4}$$

1. positive genetic autoregulation can lead to
    one stable steady state
    two stable steady states

2. positive feedback is necessary for bistability
   but not sufficient (you need sigmoidality)

3. sigmoidality is necessary for bistability
   but not sufficient (you may need a bifurcation)

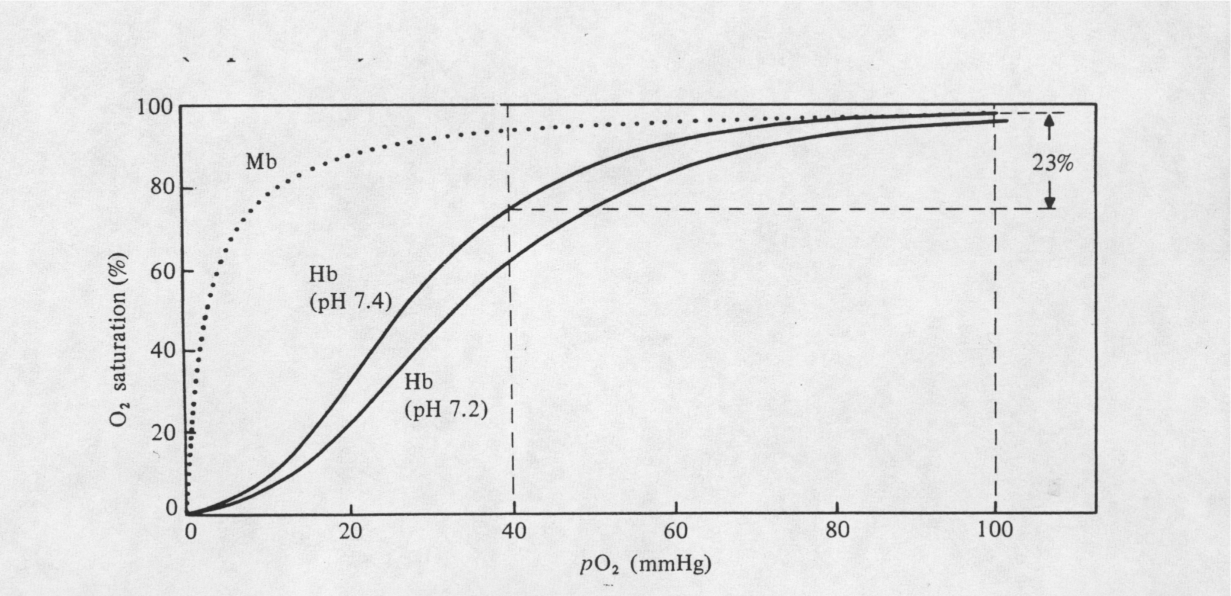
4. dimerisation creates the "steepest" sigmoidal curve

5. positive autoregulation makes a good one-way switch*
    protein degradation can throw the switch
   but it is not so easy to turn it on in the first place

* For a two-way switch see
Gardner, Cantor & Collins, *"Construction of a genetic toggle switch in Escherichia coli"*
Nature **403**:339-42 2000

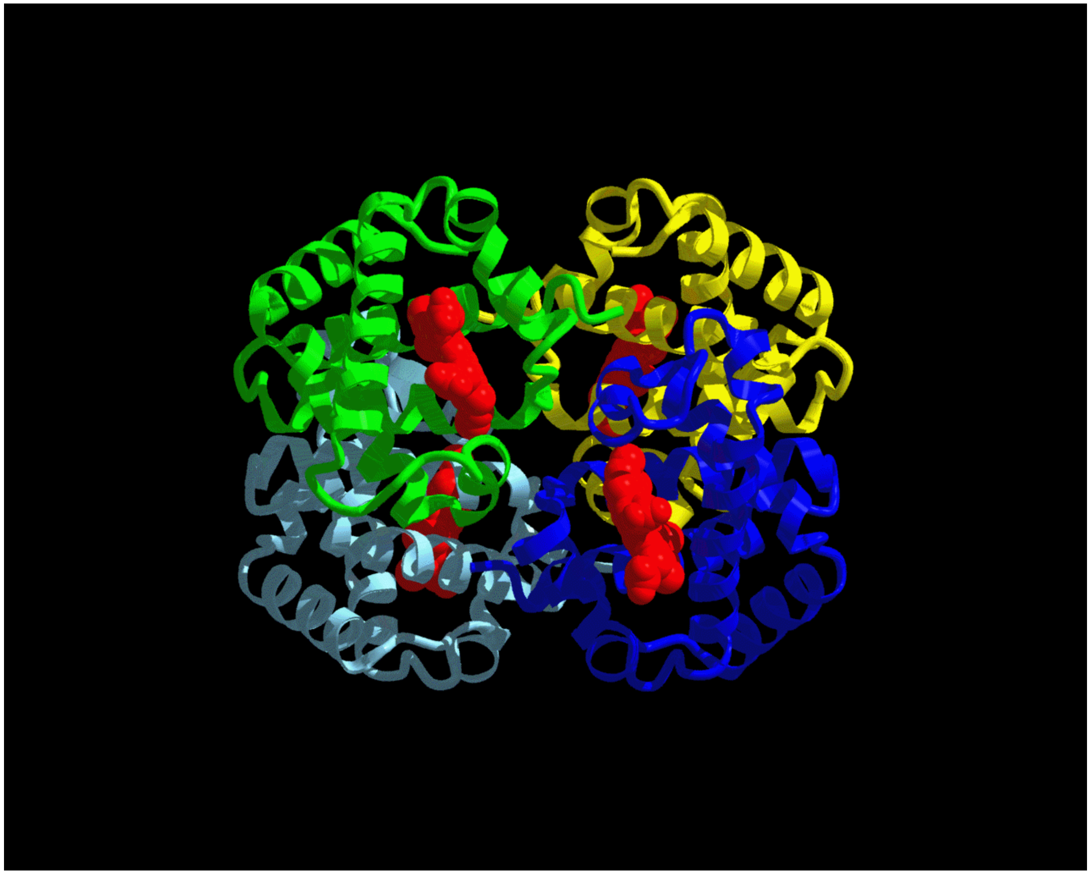
Sigmoidality in oxygen binding to hemoglobin

Bohr, Hasselbach & Krogh 1904



Data from
K Imai, “Allosteric Effects in Haemoglobin”, CUP 1982

Allostery



homodimer of heterodimers

$(\alpha\beta)(\alpha\beta)$

Monod-Wyman-Changeux model

$$\overset{\text{tense}}{T} \longleftrightarrow \overset{\text{relaxed}}{R}$$

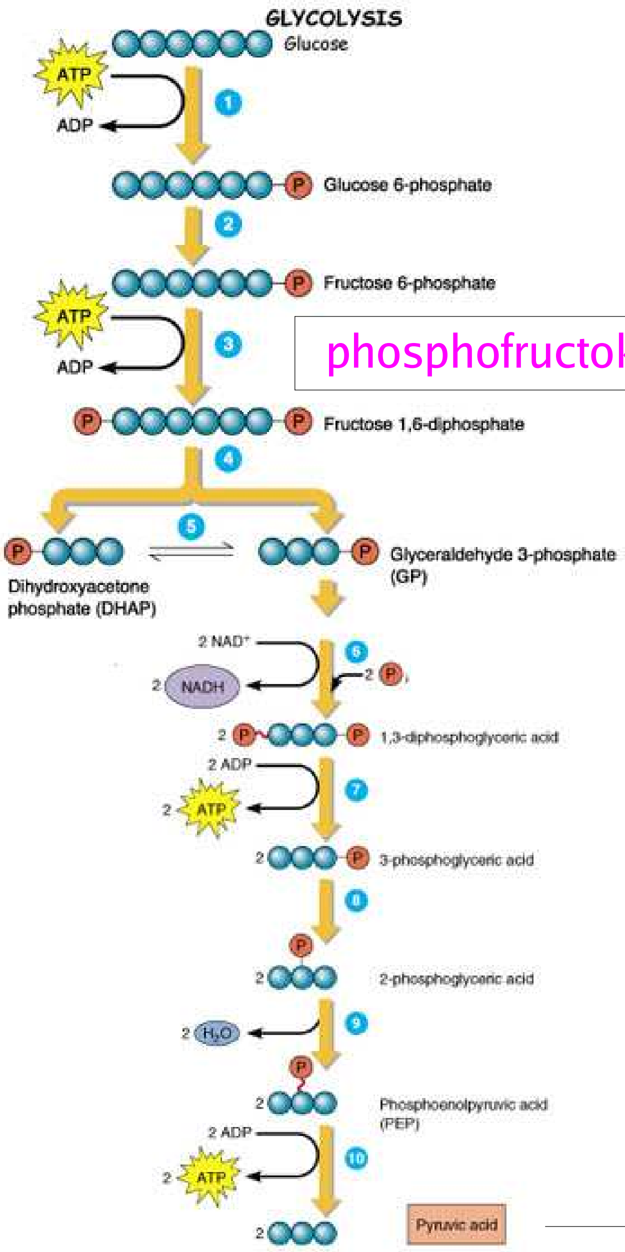
O_2 binds more readily to R than T

$$T^4 \longleftrightarrow R^4$$

concerted change

leads to sigmoidality

good quantitative agreement with hemoglobin O_2 binding curve



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phosphofructokinase

ATP	*inhibits*	ADP	*stimulates*
citrate	*inhibits*	F(2,6)BP	*stimulates*

PFK is stimulated by its own product

$$\mathrm{F6P + ATP} \rightleftharpoons \mathrm{F(1,6)BP + ADP}$$

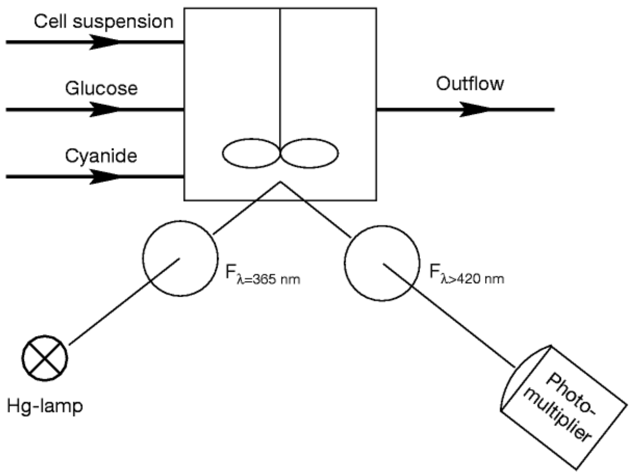
PFK is a tetramer

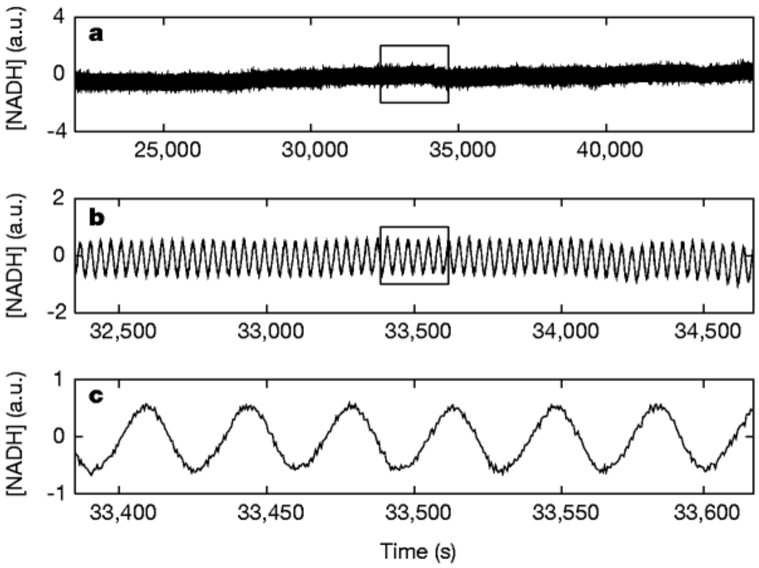
ADP stimulates it allosterically

TCA cycle coupled to electron transport and proton motive force in mitochondria

→ +30 ATPs

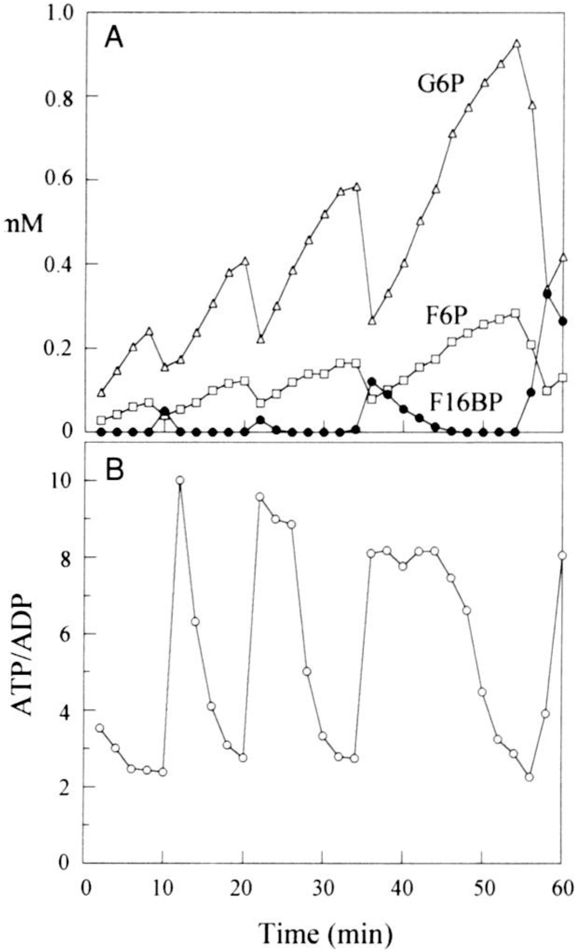
GLYCOLYTIC OSCILLATIONS IN YEAST



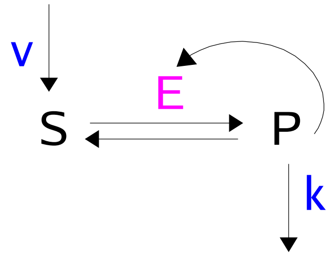


S Dane, P G Sorensen & F Hynne, *“Sustained oscillations in living cells”*
Nature **402**:320-2 1999

GLYCOLYTIC OSCILLATIONS IN SKELETAL MUSCLE CELLS



K Tornheim
"Are metabolic oscillations responsible for normal insulin secretion?"
Diabetes **46**:1375-80 1997



E is a dimer
binds S at the catalytic site
binds P allosterically

f(x,y) = proportion of E with substrate bound

$$f(x,y) = \frac{x(1+x)(1+y)^2}{L + (1+x)^2(1+y)^2}$$

$x = K_R[S] \quad y = K_P[P]$

$$\begin{tikzcd}
 & E_R(S) \arrow[d, leftrightarrow, "K_R"'] & E_R(PS) \arrow[d, leftrightarrow, "K_R"'] \\
E_T \arrow[r, leftrightarrow, "L"'] & E_R \arrow[r, leftrightarrow, "K_P"'] & E_R(P)
\end{tikzcd}$$

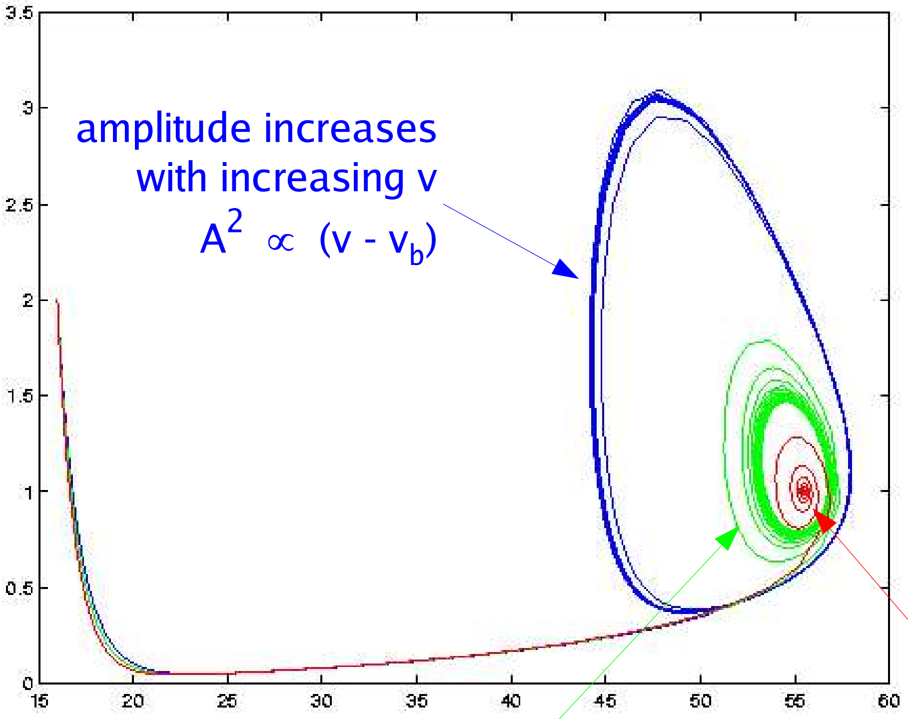
$$\boxed{\begin{aligned} dx/dt &= v - sf(x,y) \\ dy/dt &= sf(x,y) - ky \end{aligned}}$$

s = maximal catalytic rate

A Goldbeter, “Biochemical Oscillations and Cellular Rhythms”, CUP 1997

HOPF BIFURCATION

stable spiral becomes unstable, giving birth to an isolated stable limit cycle



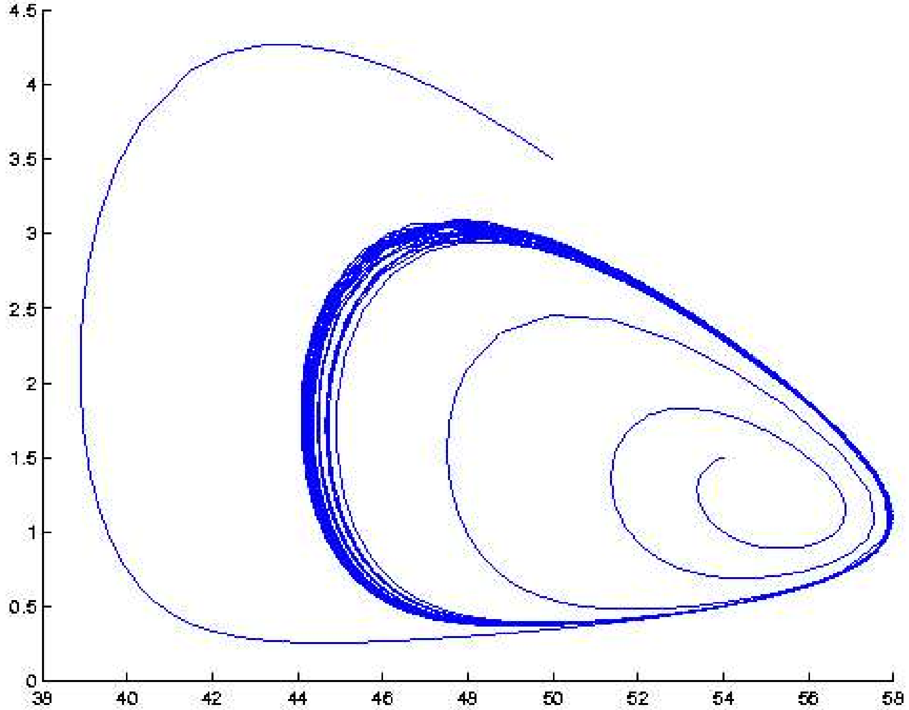
amplitude increases
with increasing v
$A^2 \propto (v - v_b)$

stable limit cycle has formed

stable spiral

v = 0.1   0.11   0.12
s = 40
k = 0.1
$L = 5 \times 10^6$

initial conditions = (2,16)



v = 0.12
s = 40
k = 0.1
L = 5 x 10^6

1. positive feedback can lead to
    - *one stable steady state* — PRION GROWTH
    - *two stable steady states* — GENETIC AUTOREGULATION
    - *stable sustained oscillations* — PFK

2. positive feedback is necessary for bistability
   but not sufficient (you need sigmoidality)

3. sigmoidality is necessary for bistability
   but not sufficient (you may need a bifurcation)

4. complex cooperativity is necessary for oscillation
   but not sufficient

Quantitative measurements and models are necessary to understand cellular mechanisms

but not sufficient ...