A systems approach to biology

SB200

Lecture 8
9 October 2008

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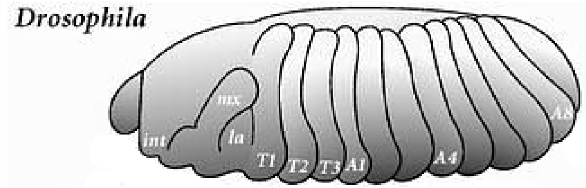
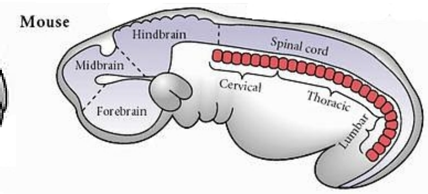
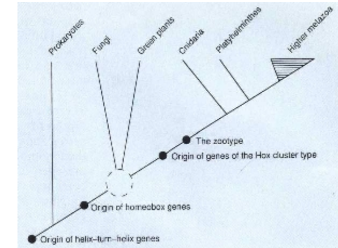
Recap of Lecture 7

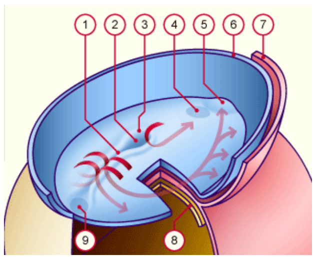
segmentation



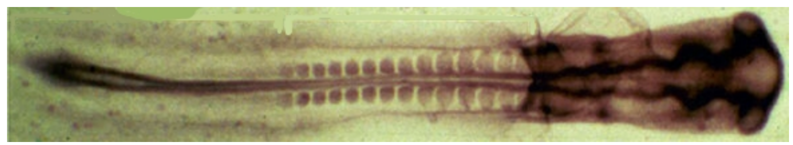


Hox genes

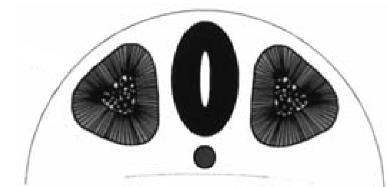


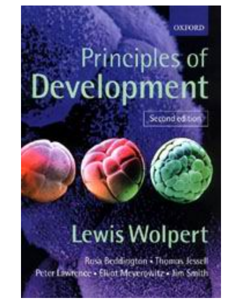


gastrulation & neurulation

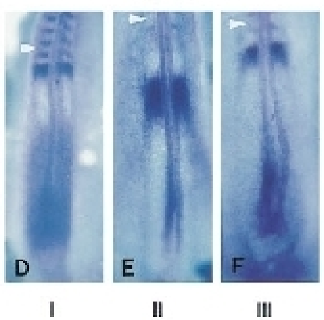


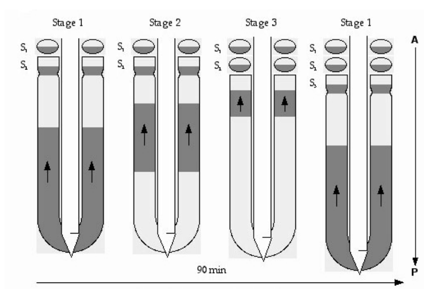
somitogenesis



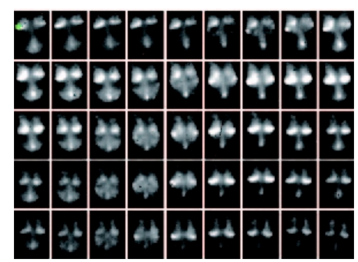


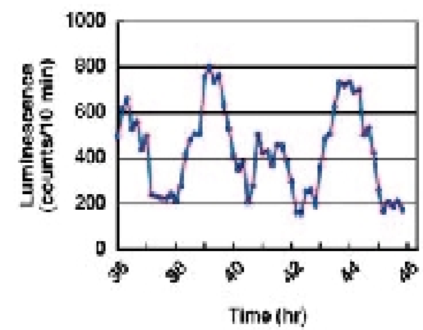
somitogenesis clock

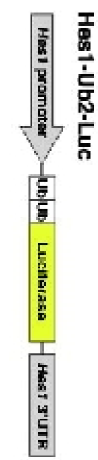




Pourquie, Cell 1997







Kageyama, Science 2002, PNAS 2006

Bendixson's Negative Criterion

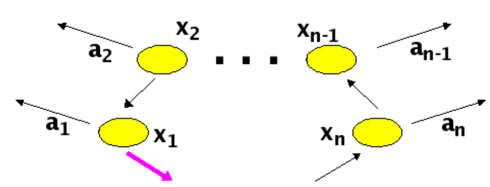
$$\frac{dx_1}{dt} = f_1(x_1, x_2) \qquad \mathrm{Tr}(Df) = \frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2}$$

$$\frac{dx_2}{dt} = f_2(x_1, x_2)$$

either > 0 or < 0 throughout D

then D has no periodic orbits

Tyson-Othmer period formula



$$p < \sec^n(\pi/n)$$

potential alternatives

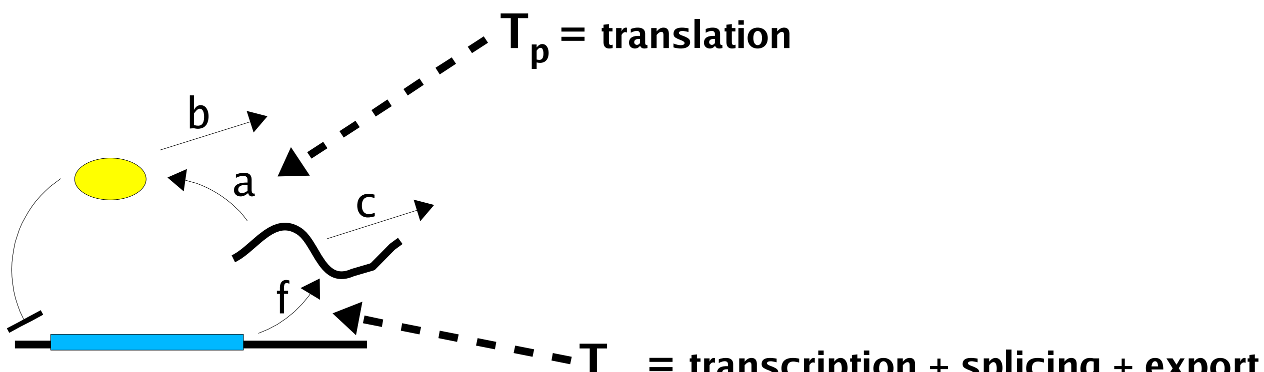
- indirect negative feedback

- explicit accounting for time delays

Julian Lewis
"Autoinhibition with transcriptional delay: a simple mechanism for the zebrafish somitogenesis oscillator"
Current Biology **13**:1398-408 2003

Nick Monk
"Oscillatory expression of Hes1, p53 and NF-kappaB driven by transcriptional time delays"
Current Biology **13**:1409-13 2003

Differential-delay equation (DDE)

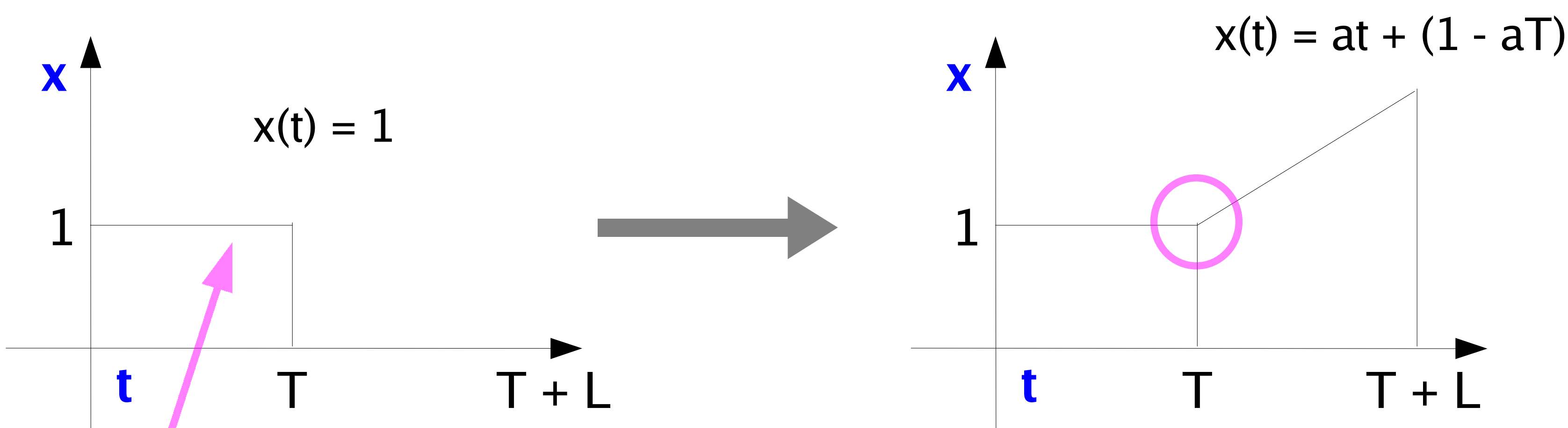


$$\frac{dx_1(t)}{dt} = ax_2(t - T_p) - bx_1(t)$$

$$\frac{dx_2(t)}{dt} = f(x_1(t - T_m)) - cx_2(t)$$

Linear differential-delay equation in 1 variable

$$\frac{dx(t)}{dt} = ax(t - T_0)$$



initial condition
x(t) for $0 \leq t \leq T$
where $T > T_0$

$L < T_0$

solve ODE $\dfrac{dx(t)}{dt} = a$

for $T \leq t \leq T + L$

Initial conditions must be specified over a time interval T which exceeds all time delays in the equation

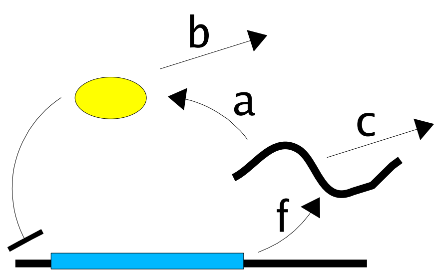
DDEs are infinite dimensional dynamical systems

They can be numerically integrated by reducing to an iterative series of ODEs

Solutions can be discontinuous (kinked)

Kinks may introduce numerical instability

Matlab has a standard dde23 solver while an external package NdelayDSolve is available for Mathematica



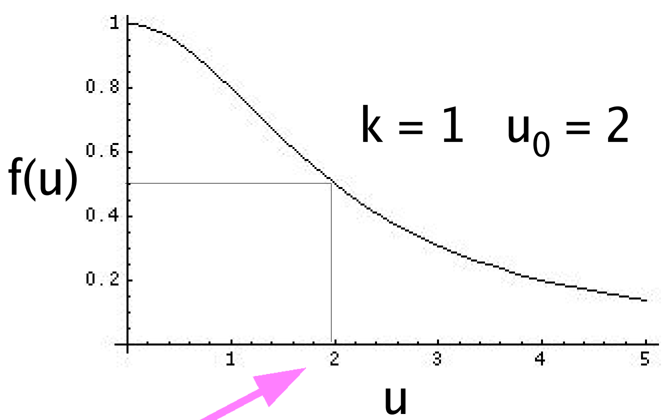
$$\frac{dx_1(t)}{dt} = ax_2(t - T_p) - bx_1(t)$$

$$\frac{dx_2(t)}{dt} = f(x_1(t - T_m)) - cx_2(t)$$

negative feedback

$$f(u) = \frac{k}{1 + (u/u_0)^2}$$

consistent with transcription factor dimerisation



half-maximal dose

$$\frac{dx_1(t)}{dt} = ax_2(t - T_p) - bx_1(t)$$

$$\frac{dx_2(t)}{dt} = f(x_1(t - T_m)) - cx_2(t)$$

$$f(u) = \frac{k}{1 + (u/u_0)^2}$$

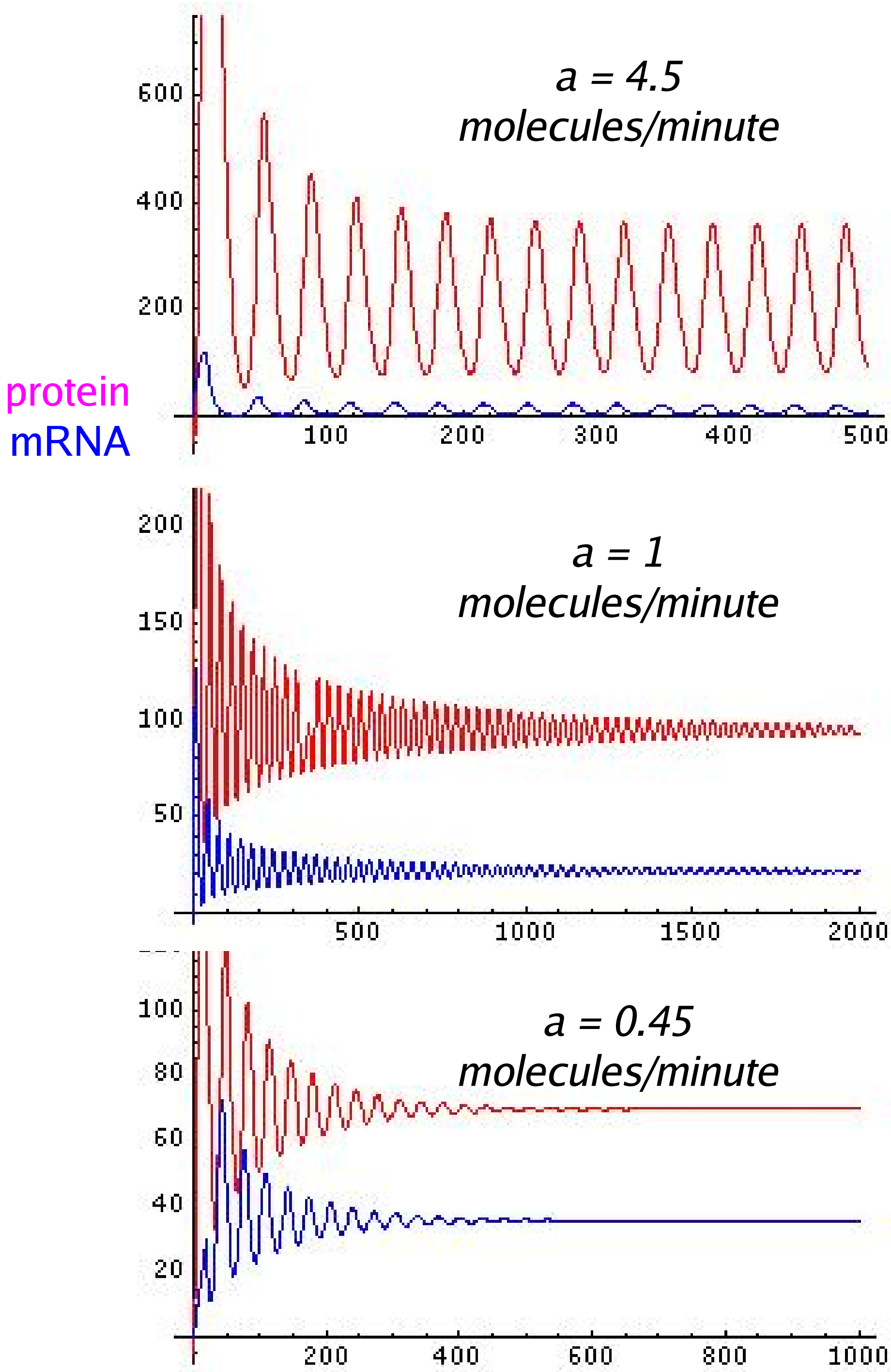
half-life = 3 minutes
$t_{1/2} = 0.7$ / rate

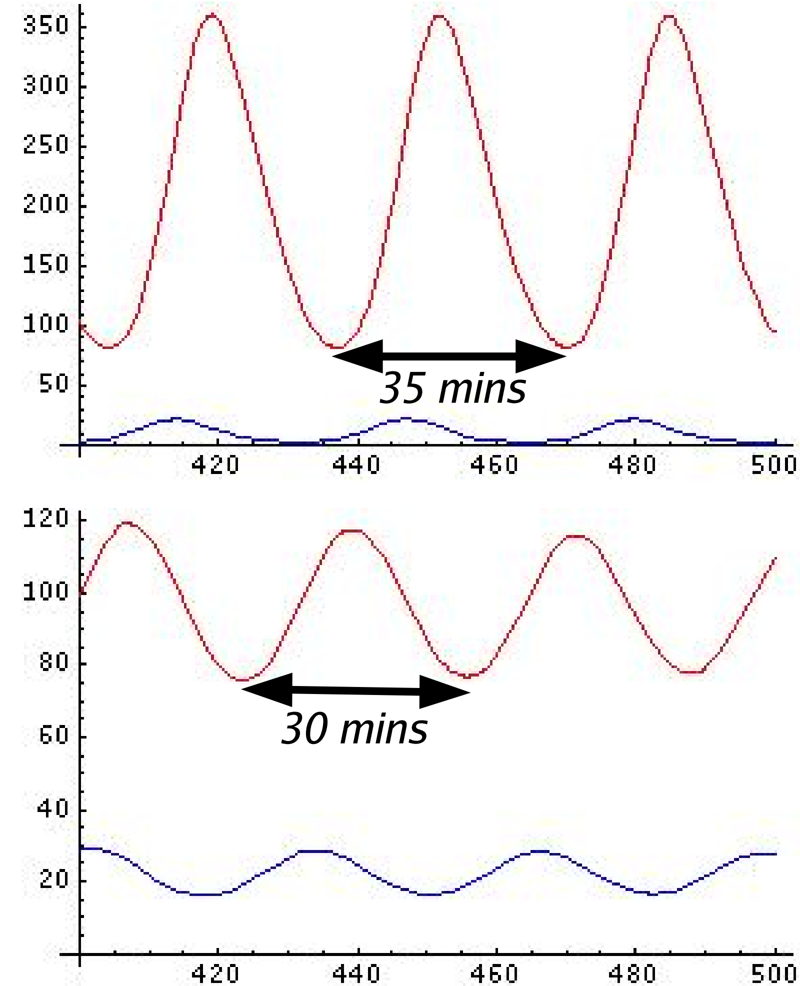
a	protein synthesis rate	4.5 molecules/transcript
b	protein degradation rate	0.23 molecules/minute
c	mRNA degradation rate	0.23 molecules/minute
k	maximal mRNA synthesis rate	33 molecules/minute (1000 transcripts/hour)
u_0	feedback threshold	40 molecules (1nM in a 5 micron diameter nucleus)

RNA Pol II speed	20 bp/sec
intron splicing	1 minute per intron
nucleo-cytoplasmic transport	4 minutes
ribosome speed	6 bp/sec

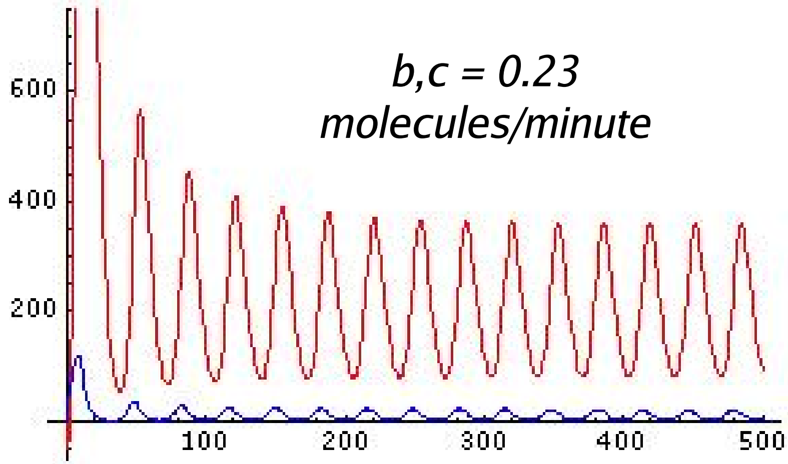
her7 primary mRNA 1280 bp, 2 introns
Her7 204 aa
expected T_m = 7.1 minutes, T_p = 1.7 minutes

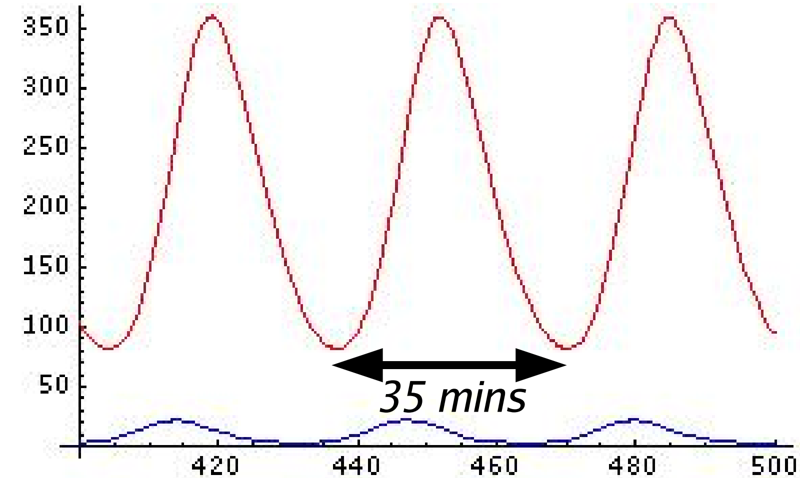
Julian Lewis
"Autoinhibition with transcriptional delay: a simple mechanism for the zebrafish somitogenesis oscillator"
Current Biology **13**:1398-408 2003

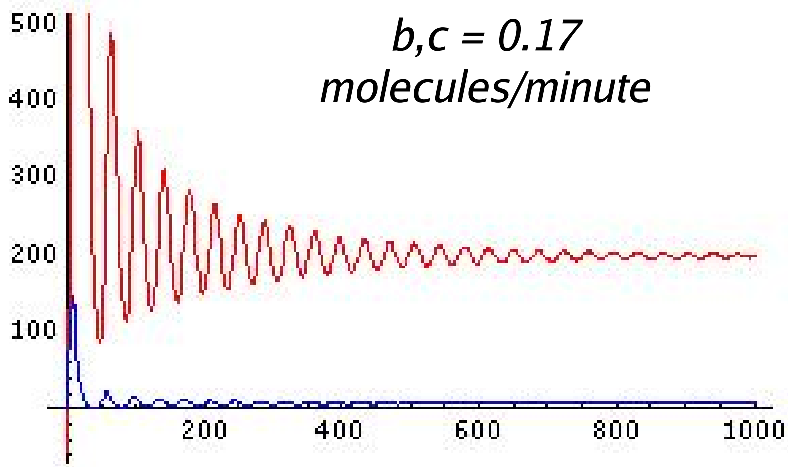




70% reduction in protein synthesis still gives sustained oscillations







25% reduction in degradation rate stops oscillations

oscillation requires $1/b$, $1/c$ $<<$ $T_p + T_m$ (= T the total delay)

in this limit, the period is approximately given by $2(T + 1/b + 1/c)$

similar results for mouse Hes1 oscillation using measured

mRNA half-life = 24.1 + 1.7 minutes

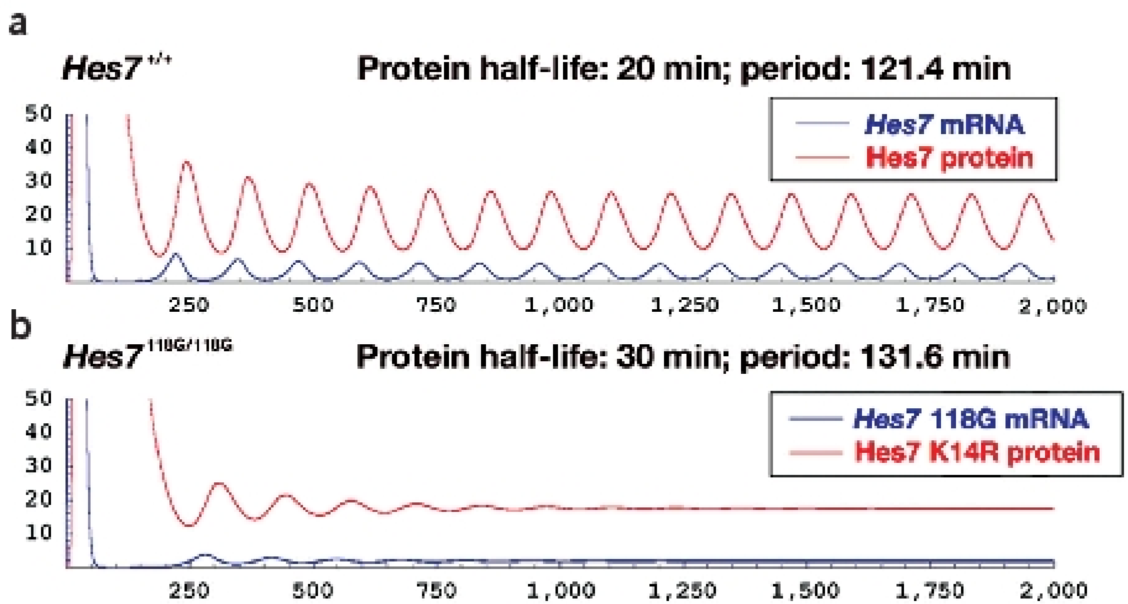
protein half-life = 22.3 + 3.1 minutes

giving oscillations with period ~2 hours

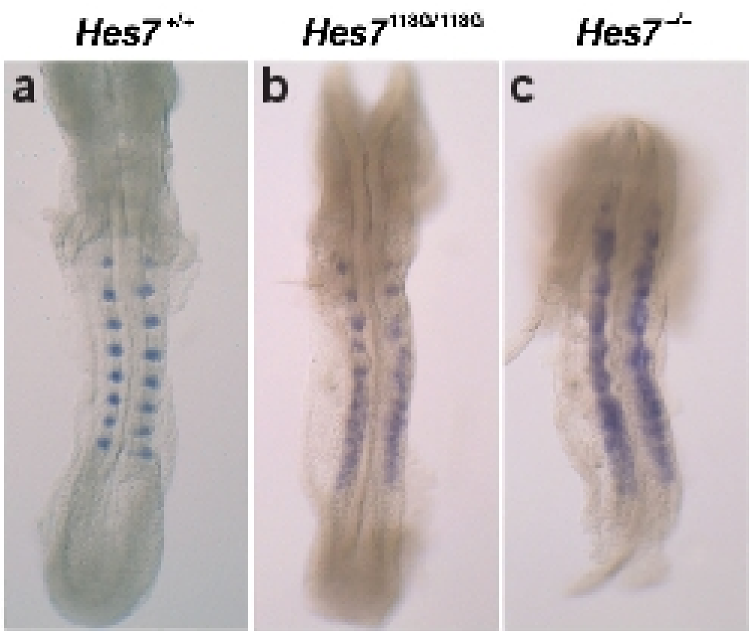
Hirata et al
"Oscillatory expression of the bHLH factor Hes1 regulated by negative feedback loop"
Science **298**:840-3 2002

Monk
"Oscillatory expression of Hes1, p53 and NF-kappaB driven by transcriptional time delays"
Current Biology **13**:1409-13 2003

simulation of the Lewis model

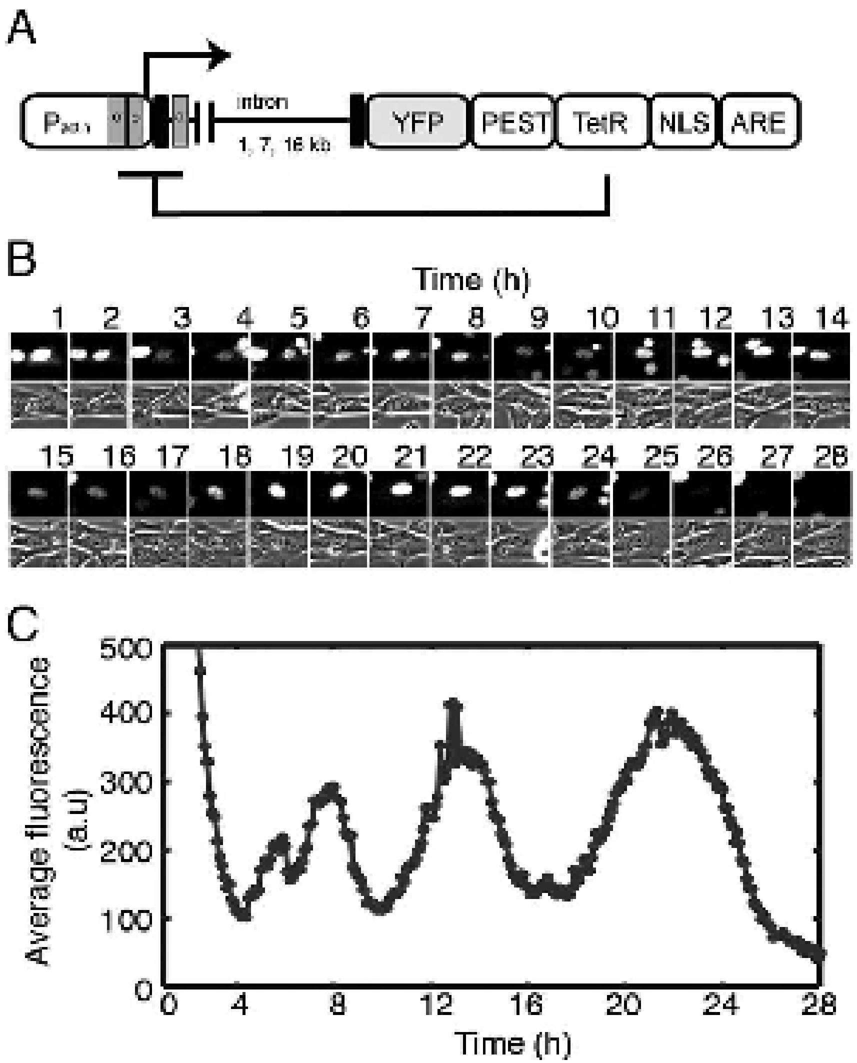


mouse knock-in and knock-out

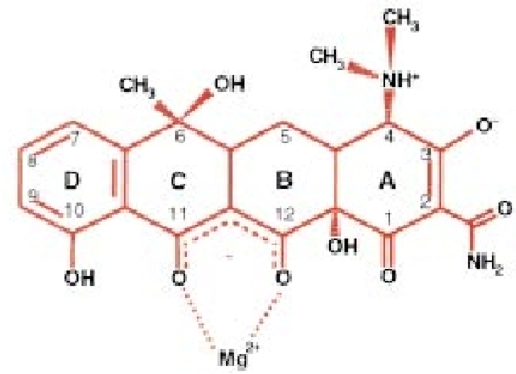


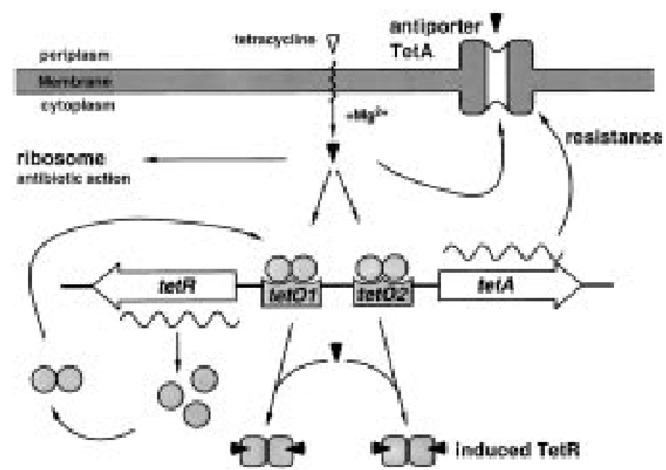
in-situ hybridisation with Uncx4.1

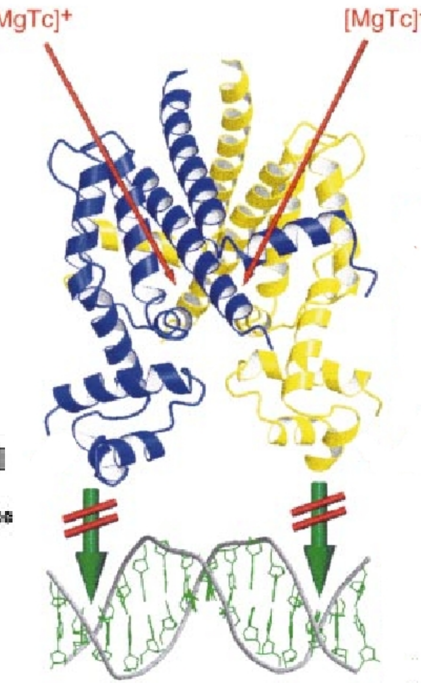
Hirata, Bessho, Kokubu, Masamizu, Yamada, Lewis, Kageyama
"Instability of Hes7 protein is crucial for the somite segmentation clock"
Nature Genetics **36**:750-4 2004



the tetracycline system





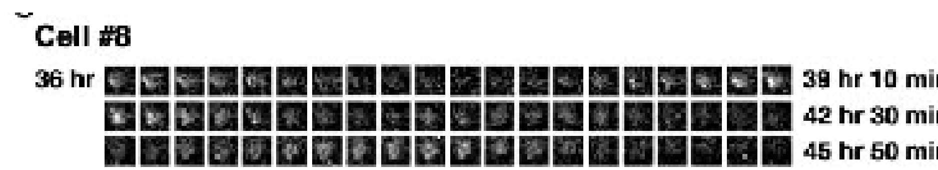


Ian Swinburne, David Miguez, Dirk Landgraf, Pamela Silver
"Intron length increases oscillatory periods of gene expression in animal cells,"
Genes & Development **doi**:10.1101/gad.1696108 2008

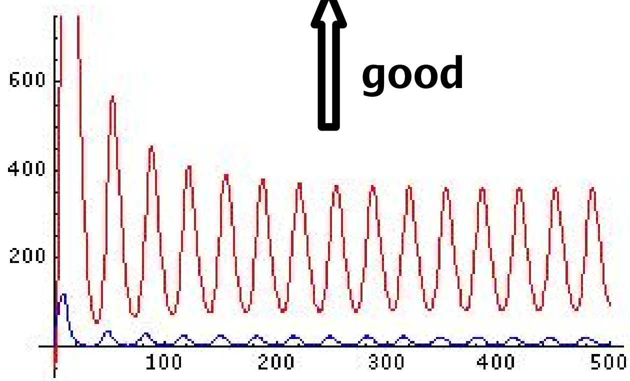
Saenger et al, *"The tetracycline repressor -a parad igm for a biological switch,"*
Angew. Chem. Int. Ed. **39**:2042-52 2000

1. delays can make a significant difference in dynamics

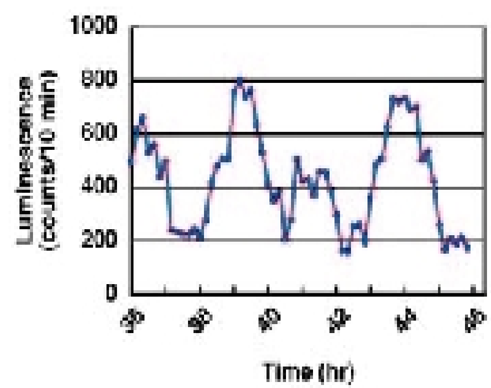
2. DDE models are much better than they ought to be!



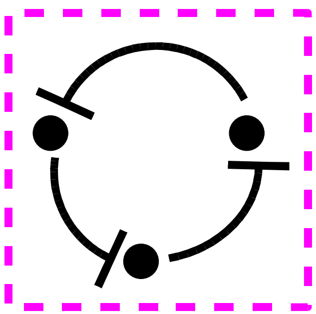
good

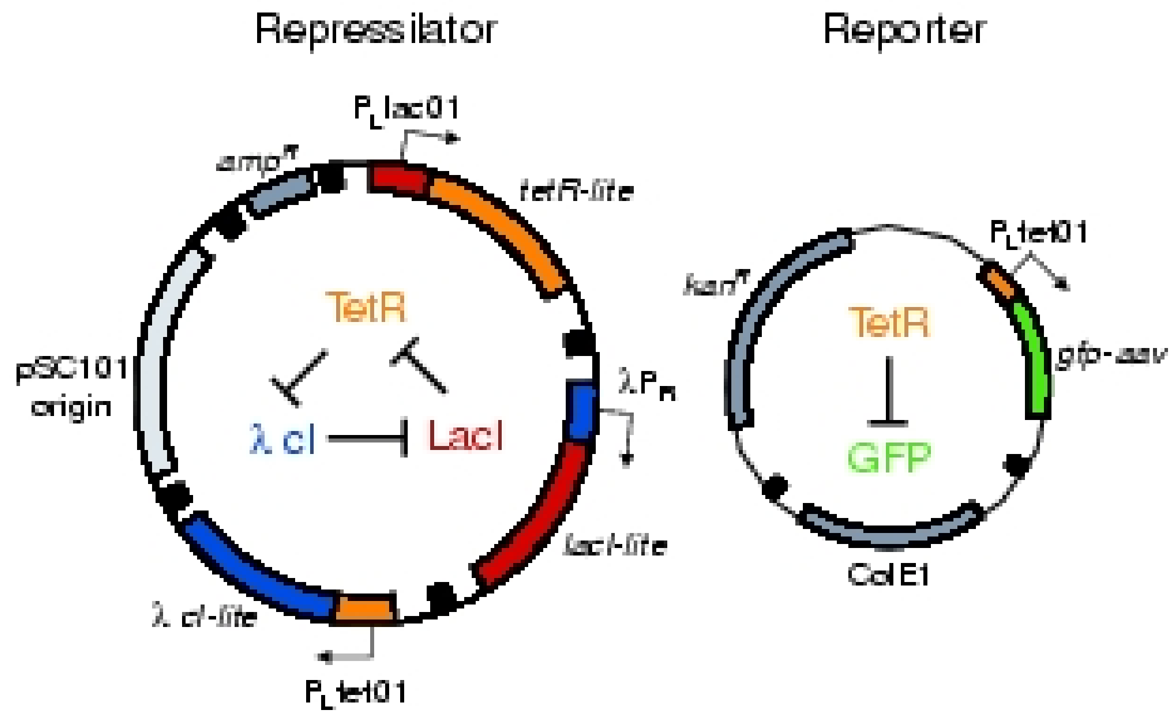


bad



the DDE models represent the biology in a single cell, with no cell-cell interaction or external signals. they describe the behaviour of a single cell very poorly but that of a tissue very well. we do not understand this!

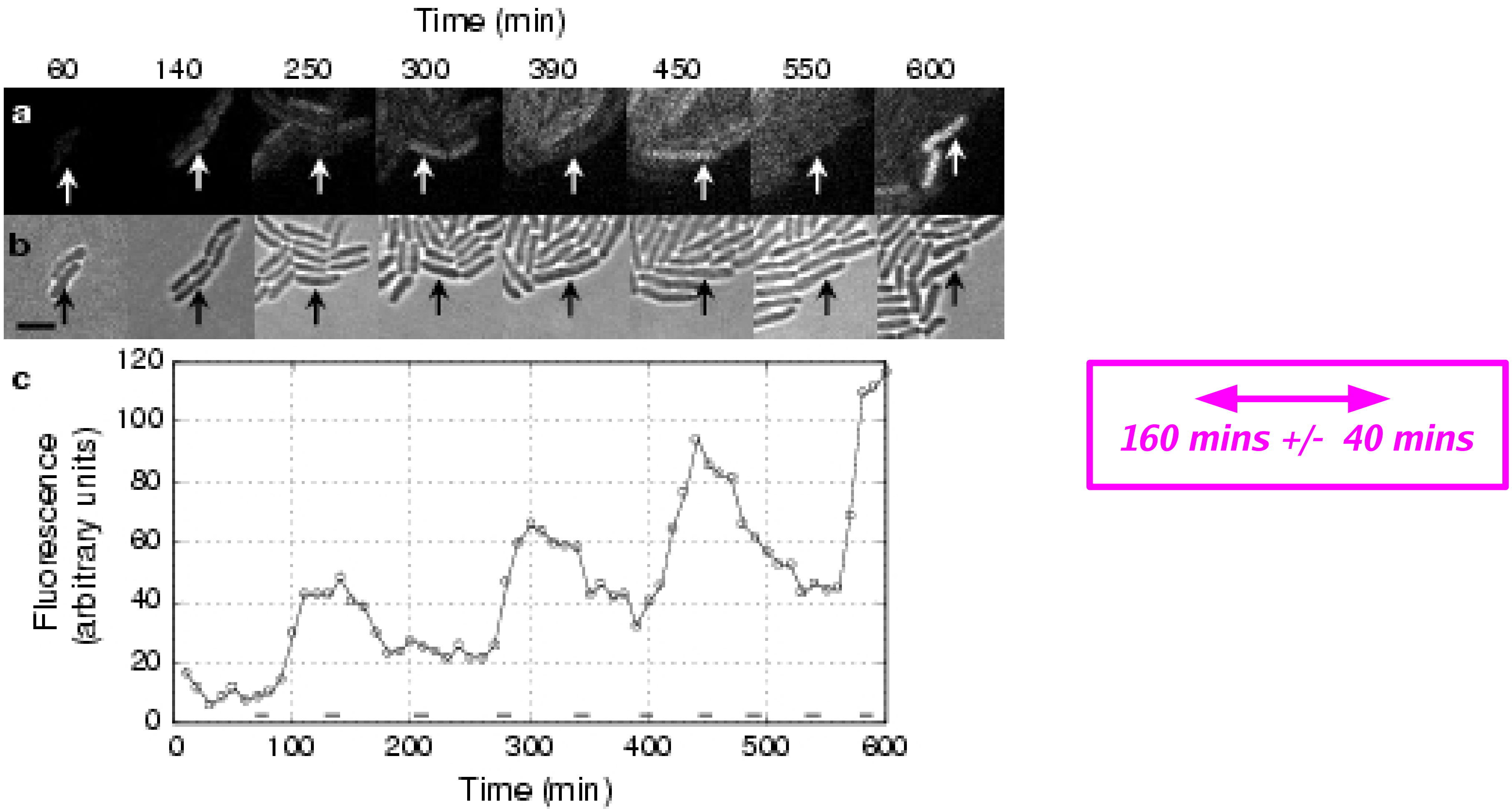




strong promoters, with tight repression

ssrA destruction tags to reduce protein half-lives

Elowitz & Leibler
"A synthetic oscillatory network of transcriptional regulators"
Nature **403**:335-8 2000


Time (min)
60
140
250
300
390
450
550
600
a
b
c
Fluorescence (arbitrary units)
120
100
80
60
40
20
0
0
100
200
300
400
500
600
Time (min)
160 mins +/- 40 mins

pure negative feedback oscillators can be very “noisy” at a single cell level

noise – *variation in period and amplitude within a single cell*
– *variation from cell to cell*

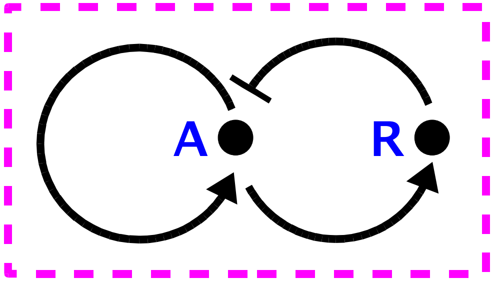
for somitogenesis, such noise may be corrected by cell-to-cell interactions and global morphogen gradients ...

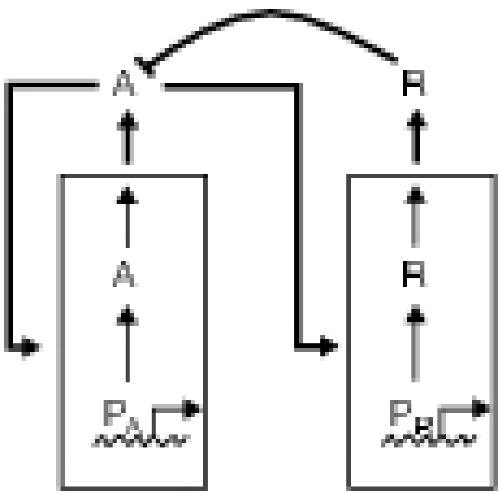
are other oscillator designs less noisy?

circadian oscillation

Barkai-Leibler proposal:
oscillators with interlinked positive and negative feedback loops are

- more robust with respect to parameter change
- more noise resistant





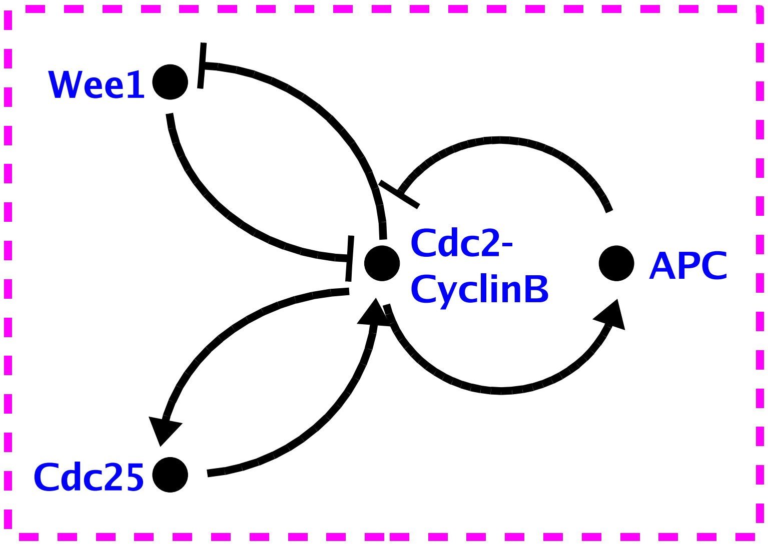
Vilar, Kueh, Barkai & Leibler
"Mechanisms of noise resistance in genetic oscillators"
PNAS **99**:5988-92 2002

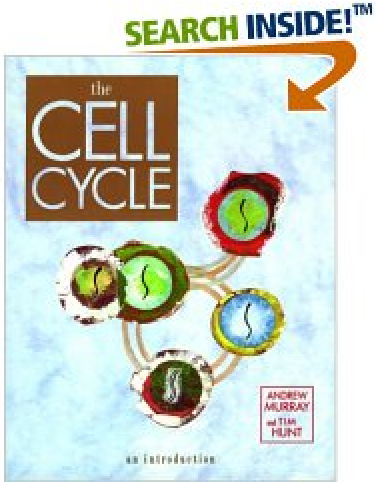
Barkai & Leibler
"Circadian clocks limited by noise"
Nature **403**:267-8 1999

the early embryonic cell cycle

Novak-Tyson model:
early embryonic cell cycle in Xenopus

interlinked positive and negative feedback loops





Andrew Murray & Tim Hunt
The Cell Cycle
OUP, 1994

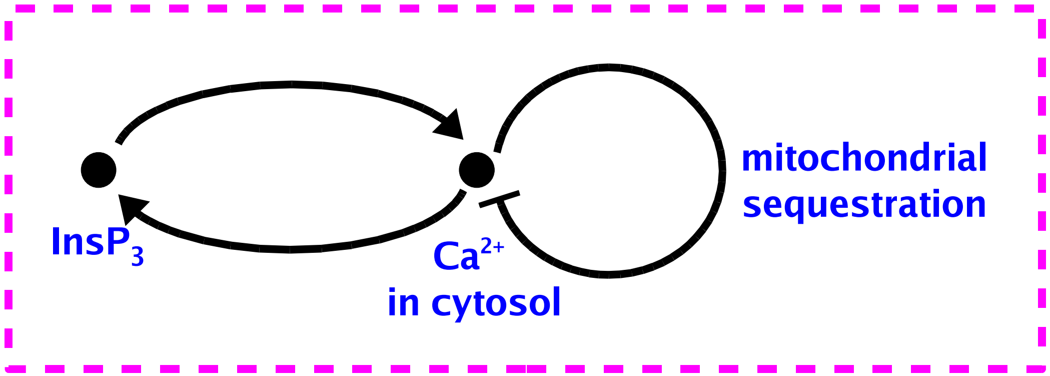
Novak & Tyson
"Numerical analysis of a comprehensive model of M phase control in Xenopus oocyte extracts and intact embryos"
J Cell Sci **106**:1153-68 1993

calcium oscillation

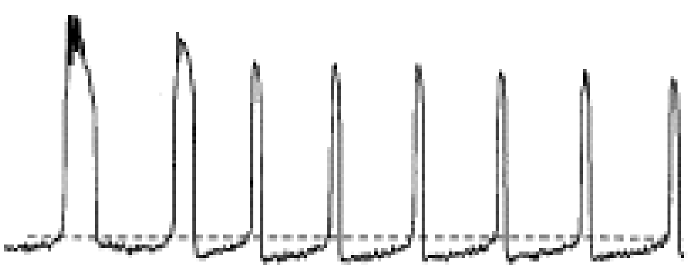
Meyer-Stryer model:
repetitive Ca2+ spikes upon stimulation of some cells by hormone

increasing amplitude of hormone stimulation -> increasing frequency of oscillation

Meyer & Stryer
"Molecular model for receptor-stimulated calcium spiking"
PNAS **85**:5051-5 1988



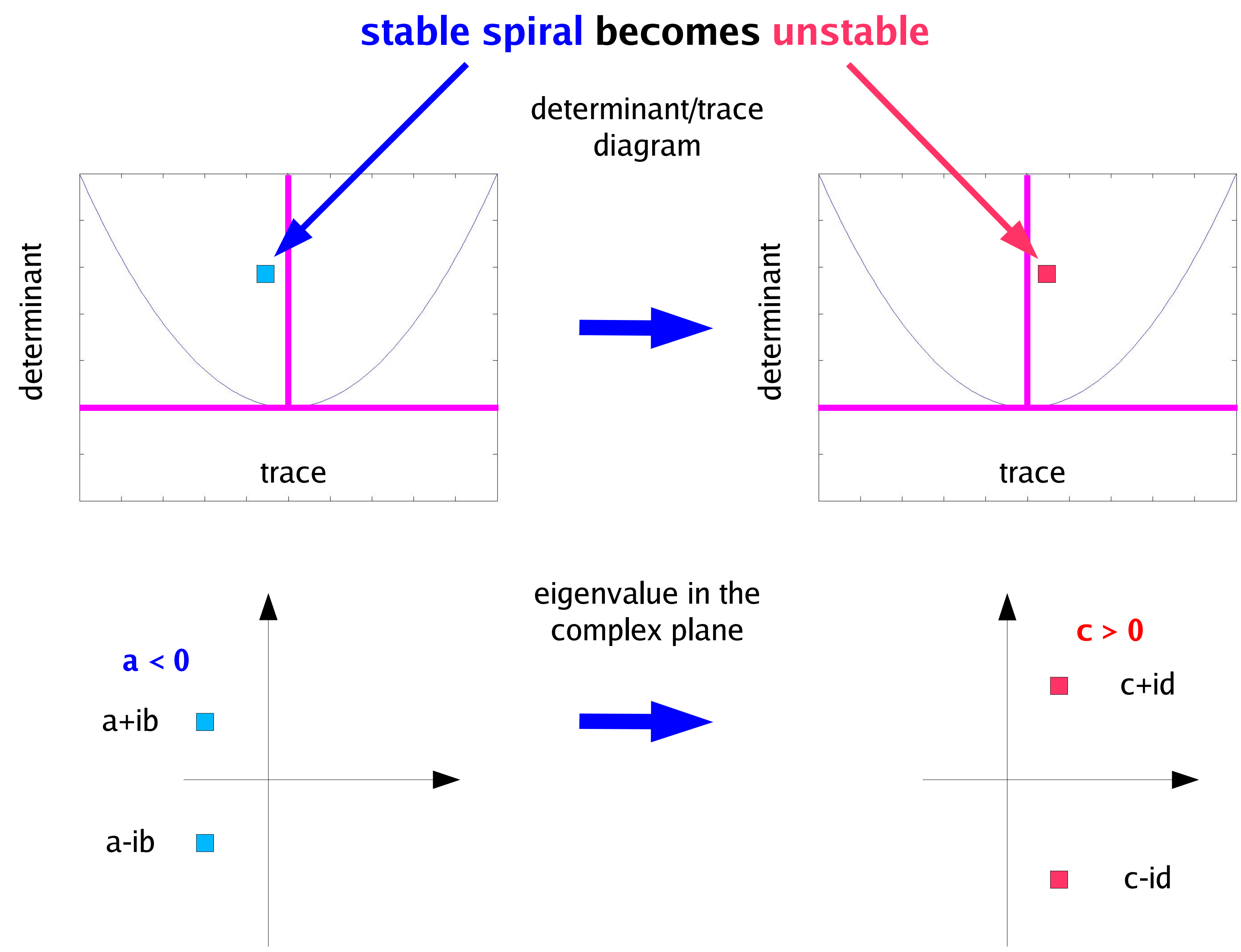
interlinked positive and negative feedback loops



Halet et al, Biochem Soc Trans **31**:907-11 2003
fertilisation induced Ca2+ oscillations recorded in a mouse egg using Fura Red

oscillations can arise through a Hopf bifurcation

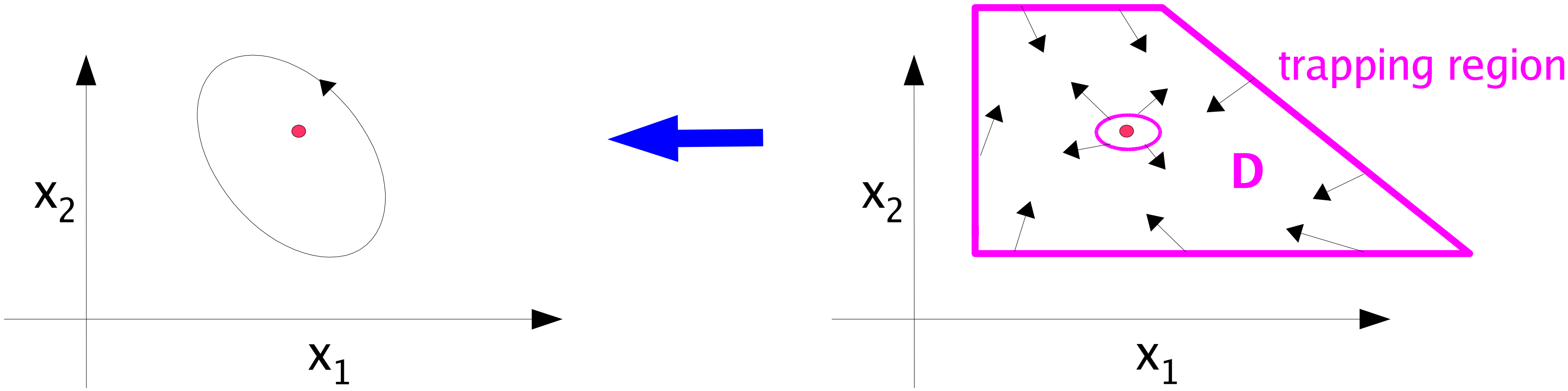
Hopf bifurcation



Poincare-Bendixson Theorem

strictly 2 dimensional !!!

Let D be a closed, bounded region of the state space which contains no steady states of the system. If D is also a **trapping region**, then D contains a periodic orbit (limit cycle).



often used to prove existence of a periodic orbit after a Hopf bifurcation

but it only works in 2 dimensions

Example of a Hopf bifurcation – the Fitzhugh-Nagumo oscillator

2D simplification of 4D Hodgkin-Huxley equation for nerve conduction

$$C_m \frac{dV}{dt} = -g_K n^4 (V - V_K) - g_{Na} m^3 h (V - V_{Na}) - g_L (V - V_L) + I_{appl}$$

Hodgkin-Huxley

$$\tau_n(V) \frac{dn}{dt} = n_\infty(V) - n$$

$$\tau_m(V) \frac{dm}{dt} = m_\infty(V) - m$$

$$\tau_h(V) \frac{dh}{dt} = h_\infty(V) - h$$

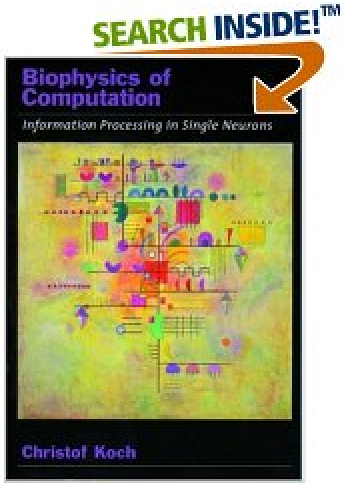
4D

Fitzhugh-Nagumo

$$\frac{dx_1}{dt} = x_2 + x_1 - \frac{x_1^3}{3}$$

$$\frac{dx_2}{dt} = -c(x_1 + b x_2)$$

2D

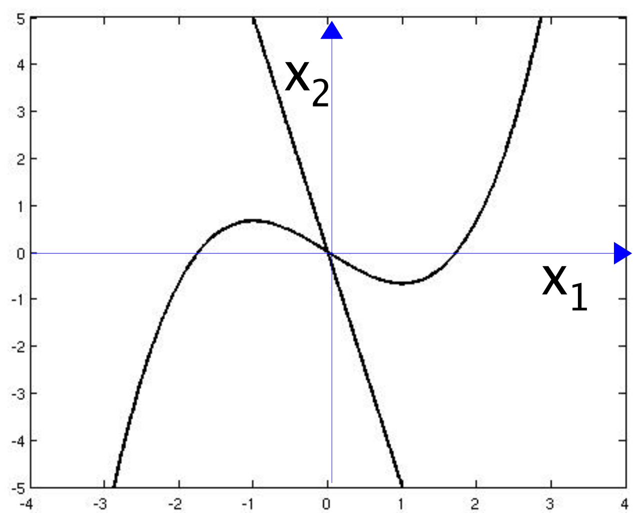


Christof Koch
Biophysics of Computation
OUP, 2004

$$\frac{dx_1}{dt} = x_2 + x_1 - \frac{x_1^3}{3}$$

$$\frac{dx_2}{dt} = -c(x_1 + bx_2)$$

assume b = 0.2



$$Df = \begin{pmatrix} 1 - x_1^2 & 1 \\ -c & -cb \end{pmatrix}$$

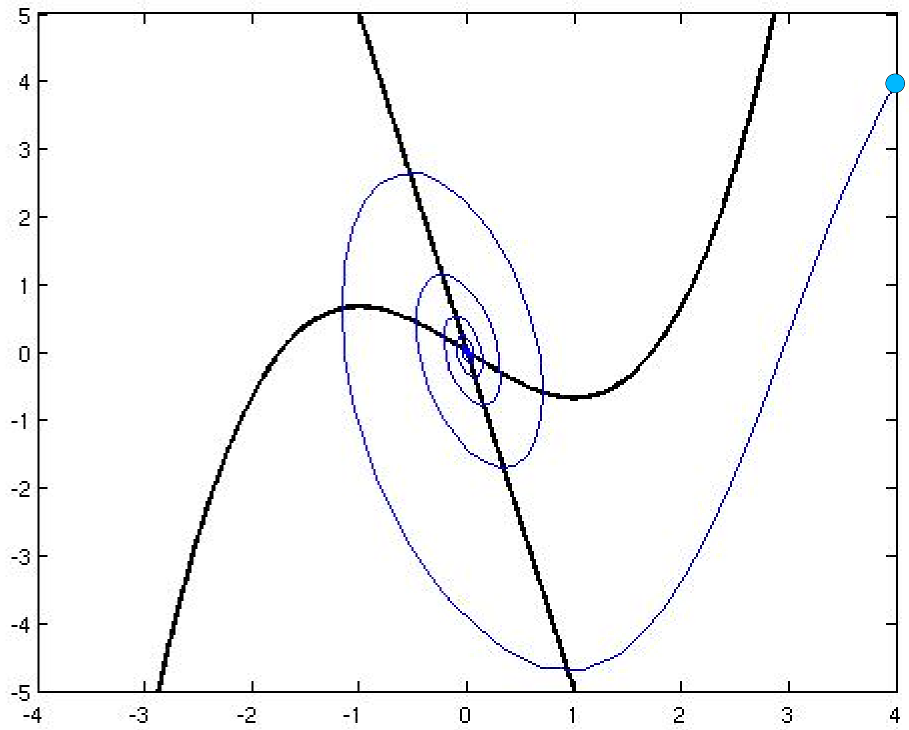
at (0,0)

det Df = c(1 − b)   Tr Df = 1 − cb

if c > 5 then (0,0) is a stable spiral

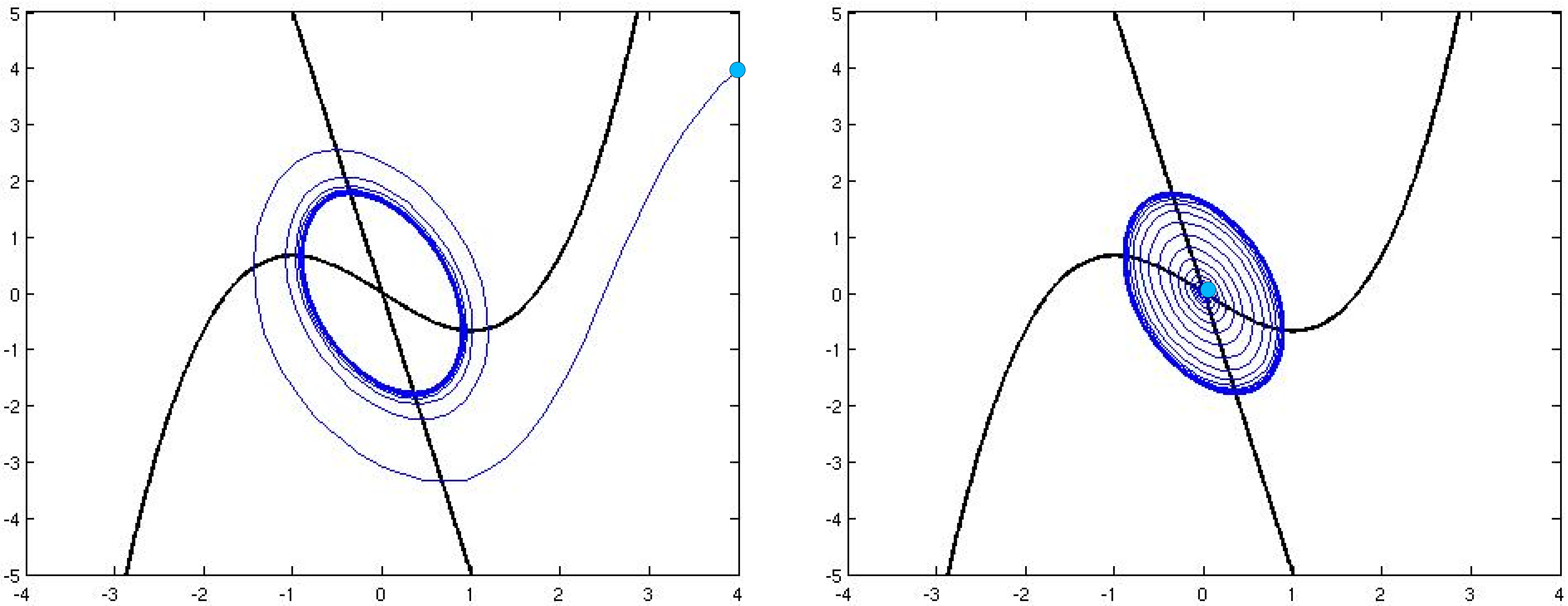
at c = 5 there is a Hopf bifurcation

if c < 5 then (0,0) is an unstable spiral



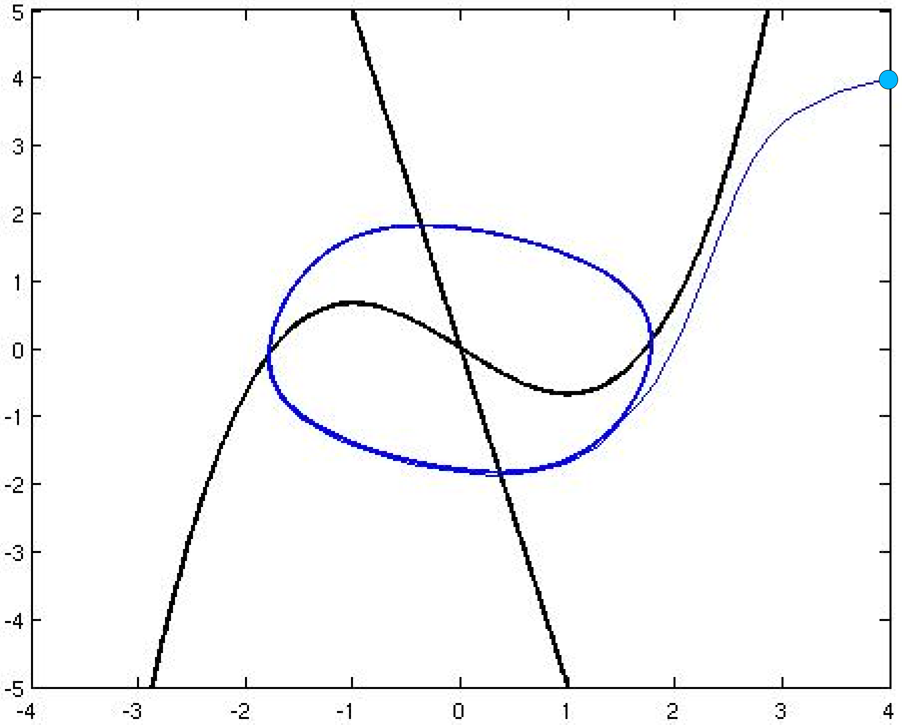
c = 8

stable spiral

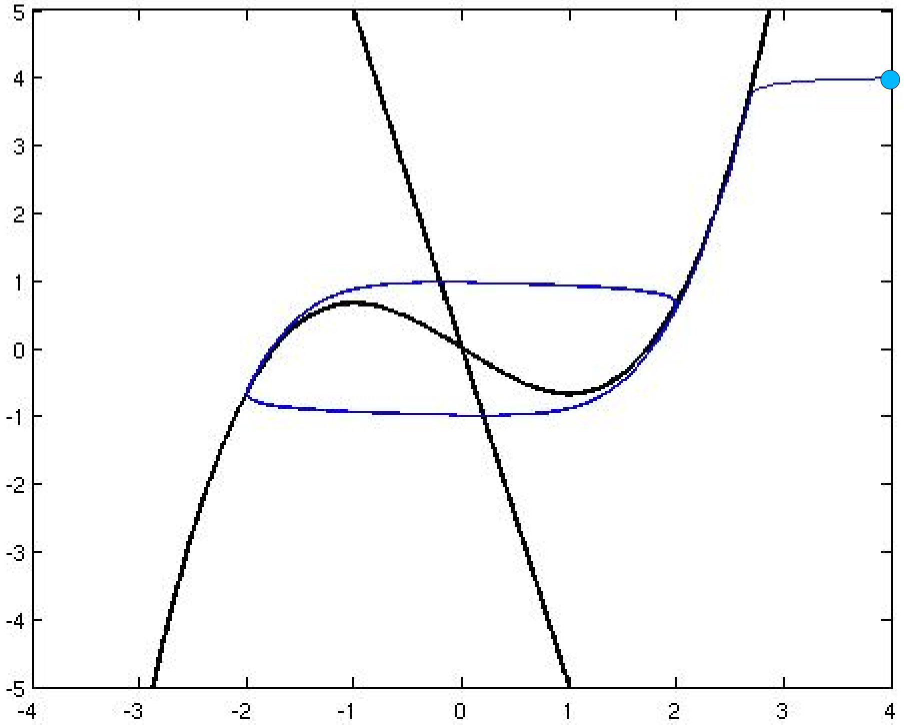


c = 4

unstable steady state surrounded by
stable periodic orbit (limit cycle)
one time scale



c = 1



c = 0.1

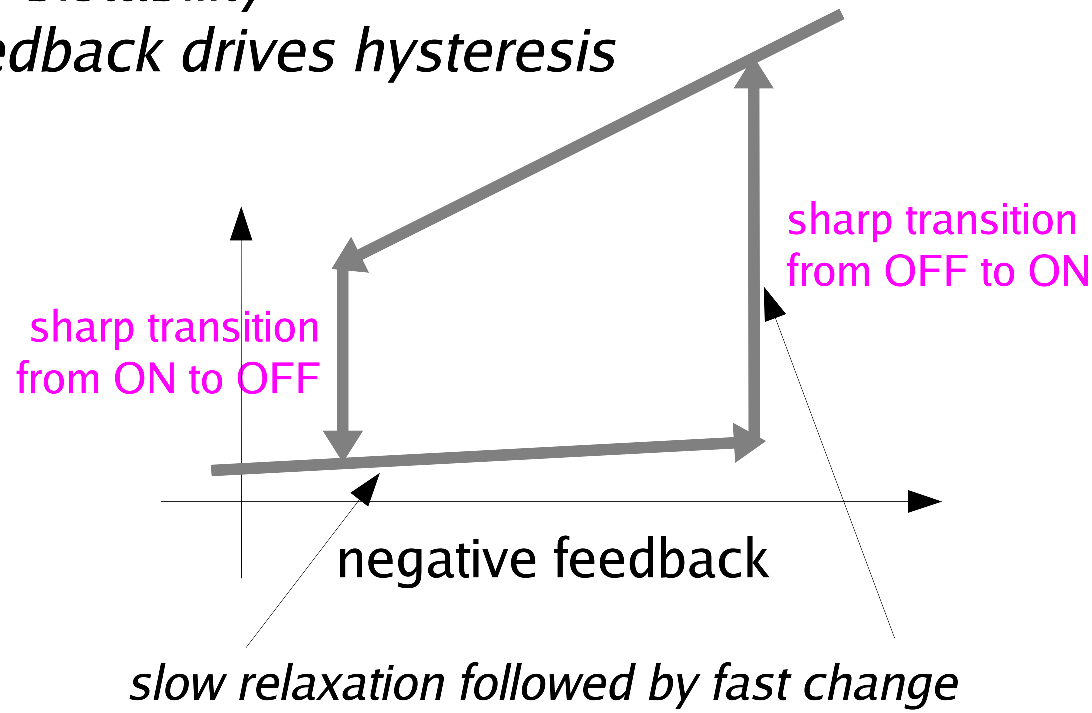
two time scales – fast/slow

relaxation oscillation

relaxation oscillations can arise from
interlinked positive and negative feedback loops

“hysteresis-based oscillation mechanism”

positive feedback gives bistability
interlinked negative feedback drives hysteresis



http://www.iro.umontreal.ca/~eckdoug/vibe/

Barth van der Pol, *“On relaxation oscillations,”* Philosophical Magazine **2**:978-92 1926

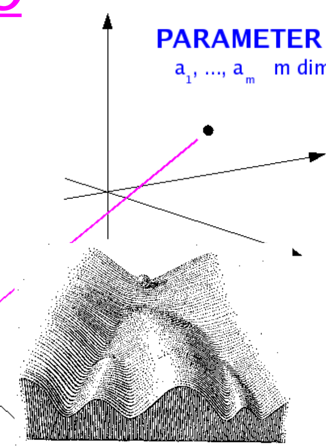
oscillators with interlinked positive and negative feedback loops appear widely in biology

they can give rise to **relaxation oscillations** with fast/slow time scales

such oscillators may have advantages over pure negative feedback loops in some contexts

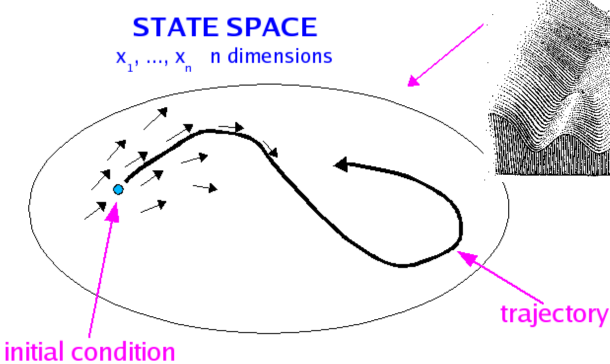
Summing it all up

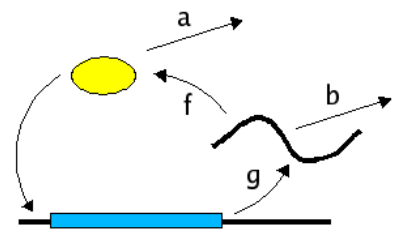
dynamical systems

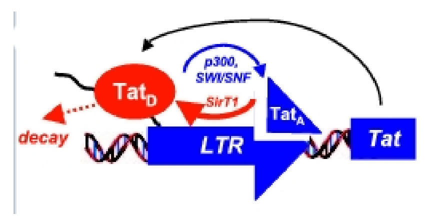


$$\frac{dx_1}{dt} = f(x_2) - ax_1$$

$$\frac{dx_2}{dt} = g(x_1) - bx_2$$

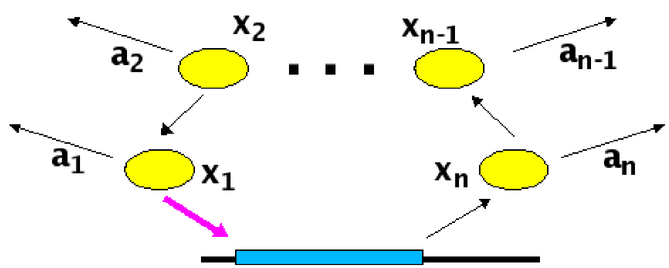




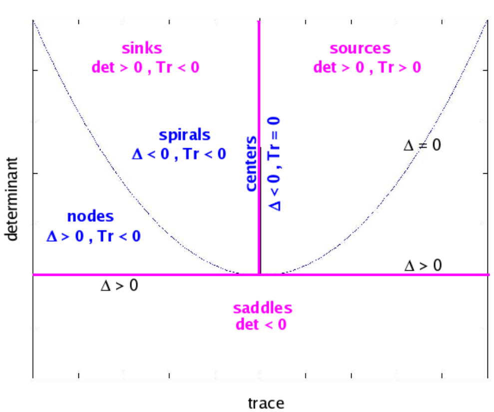


matrix algebra

linear dynamical systems

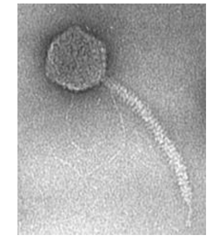


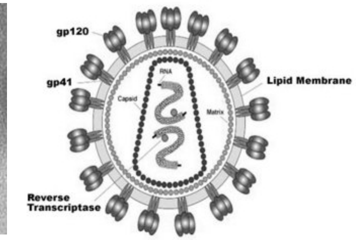
Det/Tr diagram

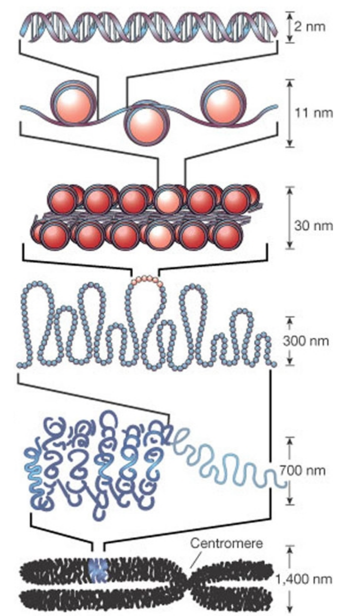


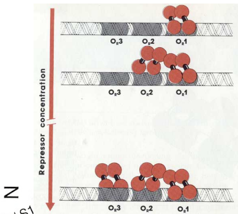
$$\frac{dx_1(t)}{dt} = ax_2(t - T_p) - bx_1(t)$$

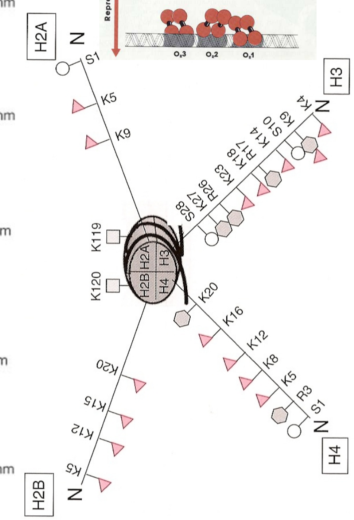
$$\frac{dx_2(t)}{dt} = f(x_1(t - T_m)) - cx_2(t)$$

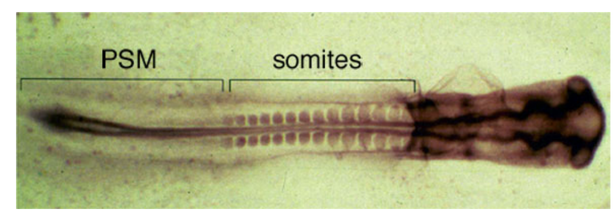


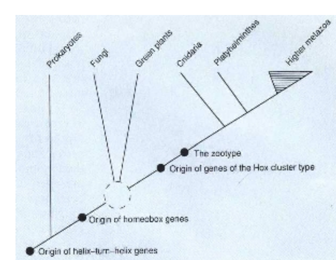


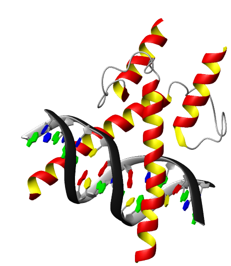






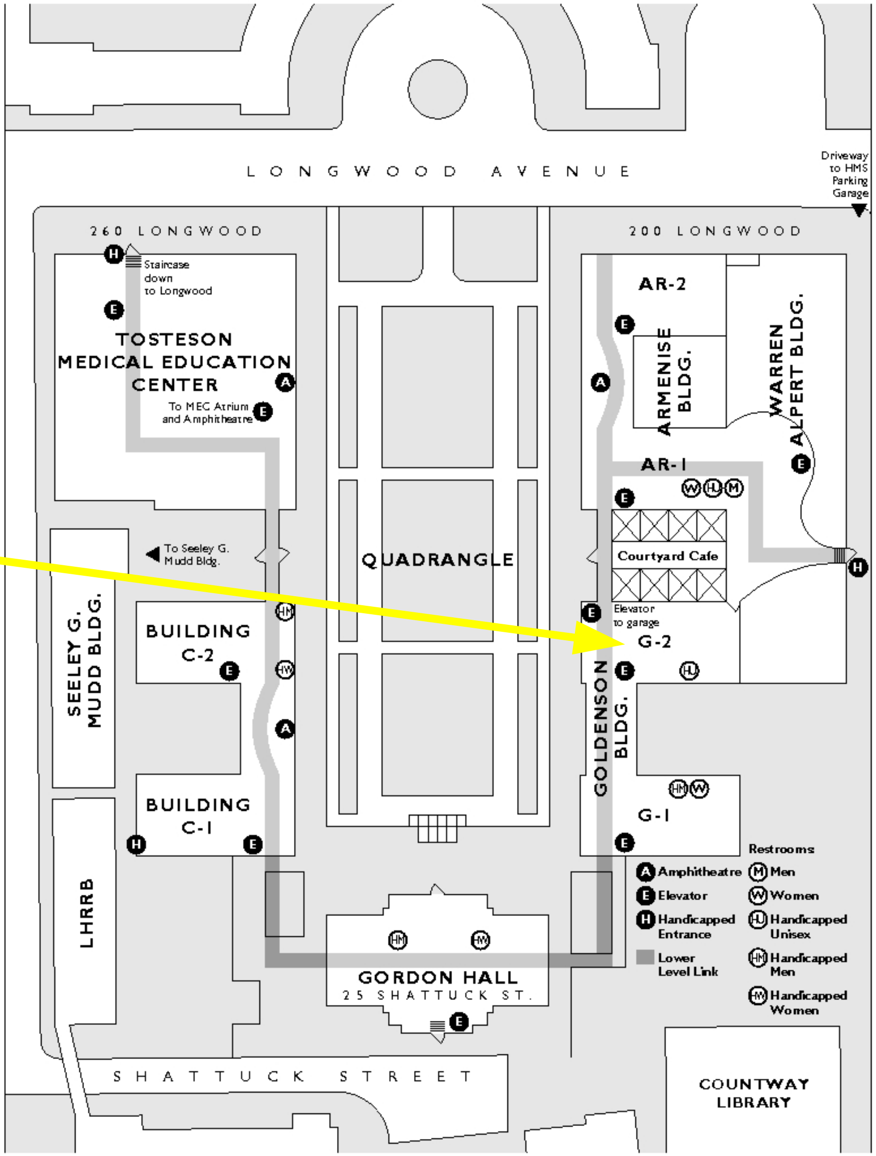






I am always happy to talk about systems biology, either by e-mail or in person. My lab is in Goldenson 504 on the HMS campus but I get over to the College from time to time.

Enjoy the rest of the course.



`jeremy@hms.harvard.edu`

`http://www.hms.harvard.edu/about/maps/quadmap.html`