A systems approach to biology

SB200

Lecture 8
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Recap of Lecture 7

gastrulation & neurulation

Hox genes

segmentation

somitogenesis

Bendixson's Negative Criterion

\[
\frac{dx_1}{dt} = f_1(x_1, x_2) \\
\frac{dx_2}{dt} = f_2(x_1, x_2)
\]

\[ \text{Tr}(Df) = \frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2} \]

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)

new notation!

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

\[ \frac{dx_2(t)}{dt} = f(x_1(t - T_m)) - cx_2(t) \]
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 \( T > T_0 \)

Solve ODE \( \frac{dx(t)}{dt} = a \)

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 \texttt{dde23} solver while an external package \texttt{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

\[ k = 1 \quad u_0 = 2 \]
\[ \frac{dx_1(t)}{dt} = ax_2(t - T_p) - bx_1(t) \]
\[ \frac{dx_2(t)}{dt} = f(x_1(t - T_m)) - cx_2(t) \]

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

\begin{align*}
\text{rate} & \quad \text{value} \\
a & \quad \text{protein synthesis rate} & 4.5 \text{ molecules/ transcript} \\
b & \quad \text{protein degradation rate} & 0.23 \text{ molecules/ minute} \\
c & \quad \text{mRNA degradation rate} & 0.23 \text{ molecules/ minute} \\
k & \quad \text{maximal mRNA synthesis rate} & 33 \text{ molecules/ minute (1000 transcripts/hour)} \\
u_0 & \quad \text{feedback threshold} & 40 \text{ molecules (1nM in a 5 micron diameter nucleus)} \\
RNA \text{ Pol II speed} & \quad 20 \text{ bp/sec} \\
\text{intron splicing} & \quad 1 \text{ minute per intron} \\
\text{nucleo-cytoplasmic transport} & \quad 4 \text{ minutes} \\
\text{ribosome speed} & \quad 6 \text{ bp/sec} \\
\text{her7} & \quad \text{primary mRNA 1280 bp, 2 introns} \\
\text{Her7} & \quad 204 \text{ aa} \\
\text{expected } T_m & \quad 7.1 \text{ minutes, } T_p = 1.7 \text{ minutes}
\end{align*}

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.
oscillation requires $1/b, 1/c \ll T_p + T_m \ (= T \ \text{the total delay})$

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
Hirata, Bessho, Kokubu, Masamizu, Yamada, Lewis, Kageyama

“Instability of Hes7 protein is crucial for the somite segmentation clock”
Nature Genetics 36:750-4 2004
Ian Swinburne, David Miguez, Dirk Landgraf, Pamela Silver
“Intron length increases oscillatory periods of gene expression in animal cells;”

Saenger et al, “The tetracycline repressor – a paradigm for a biological switch,”
1. delays can make a significant difference in dynamics

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

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
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 ...
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

“Numerical analysis of a comprehensive model of M phase control in Xenopus oocyte extracts and intact embryos”

J Cell Sci 106:1153-68 1993

Andrew Murray & Tim Hunt
The Cell Cycle
OUP, 1994
calcium oscillation

Meyer-Stryer model: repetitive Ca\(^{2+}\) 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

fertilisation induced Ca\(^{2+}\) oscillations recorded in a mouse egg using Fura Red
oscillations can arise through a Hopf bifurcation
Hopf bifurcation

stable spiral becomes unstable

determinant/trace diagram

eigenvalue in the complex plane

\[ \begin{align*}
\text{a < 0} \\
a + ib \\
a - ib
\end{align*} \]

\[ \begin{align*}
\text{c > 0} \\
\text{c} + \text{id} \\
\text{c} - \text{id}
\end{align*} \]
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

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

\[ \tau_n(V) \frac{dn}{dt} = n_\infty(V) - n \]
\[ \tau_m(V) \frac{dm}{dt} = m_\infty(V) - m \]
\[ \tau_h(V) \frac{dh}{dt} = h_\infty(V) - h \]

\[ \frac{dx_1}{dt} = x_2 + x_1 - \frac{x_1^3}{3} \]
\[ \frac{dx_2}{dt} = -c(x_1 + bx_2) \]

Hodgkin-Huxley

Fitzhugh-Nagumo

Christof Koch
Biophysics of Computation
OUP, 2004
\[
\begin{align*}
\frac{dx_1}{dt} &= x_2 + x_1 - \frac{x_1^3}{3} \\
\frac{dx_2}{dt} &= -c(x_1 + bx_2)
\end{align*}
\]

Assume \( b = 0.2 \)

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

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

At \((0,0)\)

\[
det Df = c(1 - b) \quad Tr Df = 1 - cb
\]
c = 8

stable spiral
c = 4

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

slow relaxation followed by fast change

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

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.

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