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

Jacobian
\[
\begin{pmatrix}
a & b \\
c & d \\
\end{pmatrix}
\]

\[
\text{Tr} = a + d
\]
\[
\text{det} = ad - bc
\]
\[
\Delta = \text{Tr}^2 - 4 \times \text{det}
\]
average rate of production of mRNA \( x = \text{concentration of protein} \)

\[
\begin{align*}
    r &= \frac{r_0 + r_1 (K_1)x^2 + r_2 (K_1K_2)x^4 + r_3 (K_1K_2K_3)x^6}{1 + (K_1)x^2 + (K_1K_2)x^4 + (K_1K_2K_3)x^6}
\end{align*}
\]
\[
\frac{dx}{dt} = \lambda y - ax \\
\frac{dy}{dt} = \frac{\alpha x}{k + x} - by
\]

\[\text{no dimerisation} \quad \text{1 operator site}\]

\[
\begin{align*}
\frac{dx}{dt} &= f(y) - ax \\
\frac{dy}{dt} &= g(x) - by
\end{align*}
\]

\[a, b > 0\]
\[
\begin{pmatrix}
-a & \frac{df}{dy} \\
\frac{dg}{dx} & -b
\end{pmatrix}
\]

\[
\begin{align*}
\text{Tr} &= -(a+b) < 0 \\
\text{det} &= ab - (df/dy)(dg/dx) \\
\Delta &= (a-b)^2 + 4*(df/dy)(dg/dx)
\end{align*}
\]

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

implies \( \text{det} > 0, \Delta > 0 \)

**Jacobian**

**dy/dt = 0 nullcline**

\( y = g(x)/b \)

**dx/dt = 0 nullcline**

\( x = f(y)/a \)

**Tr < 0  det > 0  Δ > 0  →  STABLE NODE**
nullcline plot

stable node

saddle

decreasing $a/\lambda$
dimerisation

2 operator sites

\[
\frac{dx}{dt} = \lambda y - ax
\]

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

two stable steady states

NO BISTABILITY WITHOUT SIGMOIDALITY!
\( y = \text{mRNA concentration} \)

\( x = \text{protein monomer concentration} \)

\[
\begin{align*}
\lambda &= 0.08 \text{(time)}^{-1} \\
a &= 0.02 \text{(time)}^{-1} \\
b &= 0.1 \text{(time)}^{-1} \\
\alpha &= 0.1 \text{(mols)(time)}^{-1} \\
k &= 5 \text{(mols)}^6
\end{align*}
\]
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
dimerisation only
\[ \frac{x^2}{1 + x^2} \]

dimerisation + 2 operator sites
\[ \frac{x^4}{1 + x^2 + x^4} \]

dimerisation + 3 operator sites
\[ \frac{x^6}{1 + x^2 + x^4 + x^6} \]

2 operator sites only
\[ \frac{x^2}{1 + x + x^2} \]
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” 
Sigmoidality in oxygen binding to hemoglobin
Bohr, Hasselbach & Krogh 1904

Data from
Allostery

Monod-Wyman-Changeux model

- Tense ↔ Relaxed

\[ T \leftrightarrow R \]

- \( O_2 \) binds more readily to R than T

\[ T^4 \leftrightarrow R^4 \]

- Concerted change

- Leads to sigmoidality

- Good quantitative agreement with hemoglobin \( O_2 \) binding curve

homodimer of heterodimers

\( (\alpha\beta)(\alpha\beta) \)
phosphofructokinase

ATP inhibits ADP stimulates

citrate inhibits F(2,6)BP stimulates

PFK is stimulated by its own product

F6P + ATP ⇌ 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
S Dane, P G Sorensen & F Hynne, “Sustained oscillations in living cells”
GLYCOLYTIC OSCILLATIONS IN SKELETAL MUSCLE CELLS

K Tornheim
“Are metabolic oscillations responsible for normal insulin secretion?”
Diabetes 46:1375-80 1997
\[
\begin{align*}
\frac{dx}{dt} &= v - sf(x,y) \\
\frac{dy}{dt} &= sf(x,y) - ky
\end{align*}
\]

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

\[ v = 0.1 \quad 0.11 \quad 0.12 \]
\[ s = 40 \]
\[ k = 0.1 \]
\[ L = 5 \times 10^6 \]

initial conditions = (2,16)

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

stable limit cycle has formed
stable spiral
\( v = 0.12 \)
\( s = 40 \)
\( k = 0.1 \)
\( L = 5 \times 10^6 \)
1. **positive feedback** can lead to
   - *one stable steady state*  
   - *two stable steady states*  
   - *stable sustained oscillations*
   
   **PRION GROWTH**

   **GENETIC AUTOREGULATION**

   **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 ...*