Oscillations & Poincaré Map

Repressilator Elowitz & Leibler; Nature 403, 335 (2000)

Solution depends on: transcription rate, translation rate, decay rates

→ 1 stable state; or sustainable limit cycle

Oscillator: strong promoter, good RBS, good repression, cooperativity, comparable decay rates

mRNA decay rates ~ 2 min in E. coli

Protein rates ~ 60 min → 4 min @ protease tag

150 min ~ 3 x Think
- Repressilator stopped in stationary phase coupled to global cell growth

**Theory**

\[
\frac{dm_i}{dt} = -m_i + \frac{\alpha}{1 + p_i^n} + \alpha_0
\]

\[
\frac{dp_i}{dt} = -\beta (p_i - m_i)
\]

**Note:**

- \( n = 2 \)
- Promoter strength \( m = 5 \times 10^{-4} \rightarrow 0.5 \)
- avg transcript eff = 20 proteins transcript
- Protein half life = 10 min
- mRNA half life = 2 min
- \( \text{Km} = \# \text{ of rep} \) for \( 1/2 \text{ max} = 40 \)

Stable \( \Rightarrow \) Unstable when \( \frac{(\beta + 1)^2}{\beta} < \frac{3X^2}{4 + 2X} \)

Where

\[
X = \frac{\alpha \times p_i^{n-1}}{(1 + p_i^n)^2}
\]

\( P \) is solution to \( \alpha \) \( P = \frac{\alpha}{1 + p_i^n} \)

**Diagram:**

- Stable
- Unstable
- Dashed line
- \( n = 2.5 \)
- \( k = 0.02 \)
- \( \alpha = 0.01 \)
- \( \beta > 0.5 \)
- \( 10^5 \)
Oscillators - 2 slow variables + delay

- Lots of bio oscillators!
  - Cell cycle, circadian rhythms, metabolic oscillations, heart beat

- Glycolytic oscillations (Metabolism) (sustained oscil 1969)

Remember: glucose $\rightarrow$ enzymes $\rightarrow$ 2-ATP + pyruvate

$\text{(F-6-P)}$  $\text{(S)ugar PFK (P)}$

$\text{ATP} \rightarrow \text{ADP} \rightarrow \text{ATP}$

$\text{phospho fructokinase}$

[SHOW FIGURES]

allosteric enzyme = binds ligand which makes it activity change

2 eqns @ +ve & -ve feedback (key)

\[ x = -x + ay + xy \]
\[ y = b - ay - xy \]

(Goldbeter & LeFever 1972)

argue: \[ P \uparrow \text{s} \downarrow \text{as } P \uparrow \] i.e. P↑ & s↑
phase plane

fixed point: \[ y = \frac{x}{a+x^2} \quad \text{and} \quad y = \frac{b}{a+x^2} \]

\[ \Rightarrow \quad x^* = b \quad \text{and} \quad y^* = \frac{b}{a+b^2} \]

(Finish) Want to show: 

oscillations

no oscillations
Oddlines:

\[ y = \frac{x}{a + x^2} \quad ; \quad y = \frac{b}{a + x^2} \]

\[ \Rightarrow \text{one fixed pt:} \quad x^* = b \quad \& \quad y^* = \frac{b}{a + b^2} \]

Stability:

\[ \frac{\partial f}{\partial y} = f(x, y) = -x + ay + x^2y \]

\[ f = y(x, y) = b - ay - x^2y \]

\[ A = \begin{pmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{pmatrix} = \begin{pmatrix} 1 + 2x^*y^* & a + (x^*)^2 \\ -2xy^* & -(a + (x^*)^2) \end{pmatrix} \]

Stability: need \[ \Delta = \text{det}(A) > 0 \]

\[ \zeta = \text{Tr}(A) < 0 \]

so \[ \zeta = -(a + b^2 + 1) + \frac{2b^2}{b^2 + a} \]

and \[ \Delta = a + b^2 \]
Limits: 

\[ T(b=0) = -(a+1) < 0 \] 
\[ T(b=\infty) = -(b^2+a+1)+2 < 0 \] 

- Small \( b \) and large \( b \) \( \Rightarrow \) stable fixed point

Cross-over: \( \text{Tr} = 0 \)

\[ \Rightarrow \quad \frac{2b^2}{b^2+a} = a + b^2 + 1 \]

\[ \Rightarrow \quad b_2^2 = \frac{1}{2} \left( 1 - 2a + \sqrt{1-8a} \right) \]

\[ \Rightarrow \quad b_2^2 = \frac{1}{2} \left( 1 - 2a - \sqrt{1-8a} \right) \]
Eigenvalues:

\[ \lambda_{1,2} = \frac{\text{Tr} \pm \sqrt{\Delta^2 - 4\Delta}}{2} \]

@ bifurcation \( \lambda_{1,2} = \pm i\omega \); \( \tau = 0 \)

where \( \omega = \sqrt{\Delta} = \sqrt{a^2 + b^2} \)

Show limit cycle!?!?

Synthetic Oscillators Elovitch & Leibler (Repressilator)

\[
\begin{align*}
\frac{dp_1}{dt} &= -p_1 + \frac{\alpha}{1 + p_3^n} + \delta_0 \\
\frac{dp_2}{dt} &= -p_2 + \frac{\alpha}{1 + p_1^n} + \delta_0 \\
\frac{dp_3}{dt} &= -p_3 + \frac{\alpha}{1 + p_2^n} + \delta_0
\end{align*}
\]
Now symmetry: \( p = p_1 = p_2 = p_3 \) for so \( \theta \) steady-ski (skier) \[ P = \frac{\alpha}{1 + p^n} + \alpha_0 \]

Jacobian:
\[
A = \begin{bmatrix}
-1 & 0 & x \\
x & -1 & 0 \\
0 & 0 & -1
\end{bmatrix}
\]

where
\[
X = -\frac{\alpha n p^{n-1}}{(1+p^n)^2} \quad (<0)
\]

evaluates:
\[
-(1+X)^3 + X^3 = 0
\]

\[ \lambda_1 = x-1 \quad \text{(decays)} \]

\[ \lambda_2 = -1 - \frac{1}{2} X + i \frac{\sqrt{3}}{2} X \quad \text{(could oscillate)} \]

\[ \lambda_3 = -1 - \frac{1}{2} X - i \frac{\sqrt{3}}{2} X \]
Need $\text{Re}(A) < 0$ for stability

$X < 0$

so

$-1 - \frac{1}{2} X < 0 \Rightarrow X > -2$

so

$-2 < X < 0$

or $\frac{\alpha n p^{n-1}}{(1 + p^n)^2} < 2 = 2$ @ boundary

gives $\alpha = f(\alpha_0)$ & $p = g(\alpha, \alpha_0)$

---

[Graph showing stable fixed point and limit]
Existence of Limit Cycles

"Want to show the existence of an attracting stable closed orbit"

Theorems for systems that cannot have limit cycles:

1. 1D systems
2. \( x = -\Delta V(x) \) \( \Leftrightarrow \) no oscillation

**Poincaré–Bendixson Theorem (Existence of cycle) (2D)!!!**

(\( \equiv \) no chaos in 2D !!!)

\( R \) is closed bounded set

b) \( \vec{x} = f(x) \) is differentiable vector field on \( R \)

c) No fixed points in \( R \)

\[ \implies \text{Then there is a 'closed' orbit} \]

Physicist Intuitive Thm:

If boundaries are repelling, then there will be a closed orbit.

\[ \text{Fixed pt in here} \]
$$(b, b/2)$$

want

want to show repelling line

repelling region

large $$x, y$$:

$$x \approx x^2 y$$

$$y \approx -x^2 y$$

so

$$\frac{dy}{dx} = \frac{y}{x} = -1$$

compare $$x$$ with $$y$$:

$$y - x = -b + ay + x^2 y + x - ay - x^2 y$$

$$= x - b > 0$$ for $$x > b$$

$$\Rightarrow$$ can draw a line from $$x=b$$ with slope of $$-1$$ & know it's repelling

Need inferior boundary that is also repelling

unstable & repelling (did this last class!)
Fig. 1. The glycolytic oscillator. (a) A summary of the glycolytic pathway (thick arrows) together with the NAD and adenine nucleotide cycles (thin arrows). The dotted lines represent the allosteric control of phosphoglycerate kinase (PGK) by ATP, ADP, AMP and fructose-6-phosphate (F6P). The circles indicate those enzymes which seem to be important for oscillatory activity. GDH, glyceroldehyde dehydrogenase; PGK, phosphoglycerate kinase; PK, pyruvate kinase. (b) and (c) Changes in the concentration of key intermediates at two points during the oscillatory cycle. Large font lettering of metabolites is used to indicate high
Fig. 2.4. Control of glycolytic oscillations in yeast extracts by the substrate injection rate. (a) The diminution of the rate of injection of fructose from 40 to 20 mM/h causes a lengthening of the period as well as a change in the waveform of oscillations; this change is reversible. (b) Decreasing the injection rate below 20 mM/h causes the reversible suppression of the oscillations (Hess & Boiteux, 1968b).

[Reproduced from Goldbeter (1996).]