Dynamical Systems and Chaos
Part II: Biology Applications

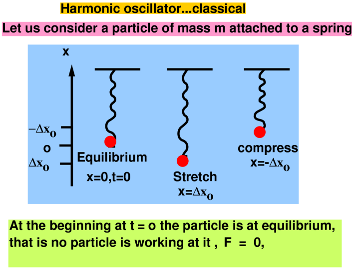
Lecture 8: Oscillations in life

Ilya Potapov
Mathematics Department, TUT
Room TD325

Harmonic oscillator: linear oscillations

- Famous example from physics:

$$m\frac{d^2x}{dt^2} = -kx \Rightarrow \begin{cases} \dfrac{dx}{dt} = y \\ \dfrac{dy}{dt} = -\dfrac{k}{m}x \end{cases}$$



- Steady state: $x = 0$ and $y = 0$
- Characteristic equation

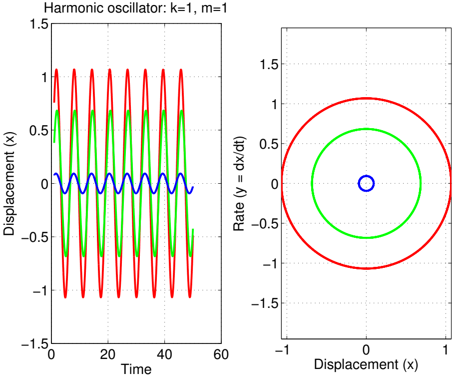
$$\begin{vmatrix} -\lambda & 1 \\ -k/m & -\lambda \end{vmatrix} = 0 \Rightarrow \lambda^2 + \frac{k}{m} = 0$$

- Given $k > 0$ and $m > 0$ (physical constants)

$$\Rightarrow \boxed{\lambda_{1,2} = \pm i\sqrt{\frac{k}{m}}}$$

Harmonic oscillations

- The amplitude is dependent on the initial conditions.
- There is no notion of an oscillatory attractor.
- Period of oscillations is $\frac{2\pi}{\sqrt{\frac{k}{m}}}$.



Nonlinear oscillations

- In general appear through the Hopf bifurcation.
- Hopf bifurcation (HB) is a codim-1 bifurcation, that is it requires only one parameter to be changed for the bifurcation to occur.
- Limit cycle is another type of attractor in the dynamical systems with nonlinear evolution operator.

Limit cycle

- Limit cycle is a closed trajectory in the phase space (at least 2D).
- Limit cycle is an attractor, thus, having the basin of attraction.
- Trajectories from the limit cycle's basin of attraction tend toward the limit cycle either in forward or backward time.
- Limit cycle corresponds to a periodic behaviour. For a system:

$$\begin{cases} x' = P(x, y) \\ y' = Q(x, y) \end{cases}$$

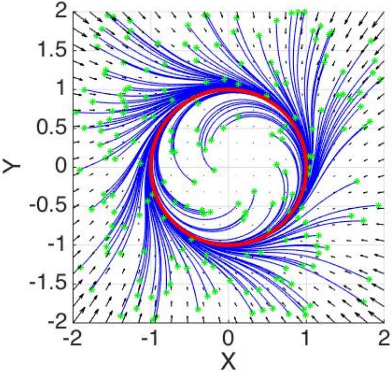
- $x(t+T) = x(t)$ and $y(t+T) = y(t)$: periodic movement with period $T > 0$.

Limit cycle

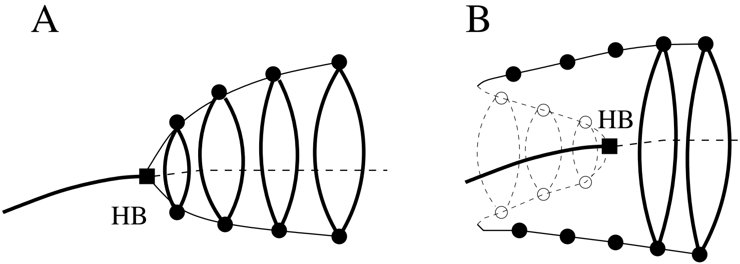
- Consider the system:

$$\begin{cases} x' = y + x[1 - (x^2 + y^2)] \\ y' = -x + y[1 - (x^2 + y^2)] \end{cases}$$

- Trajectory $x^2 + y^2 = 1$ is a limit cycle.



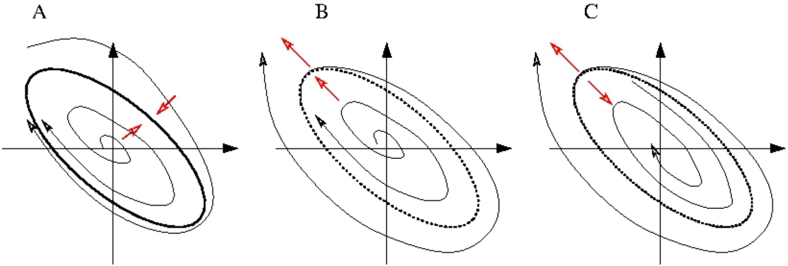
Two types of Hopf bifurcation



Two types of the Hopf bifurcation: super- (A) and sub-critical (B).

Stability of the limit cycles

- Limit cycles can be stable or unstable (semi-stable).
- Figure below shows the schematic of the stable (A), semi-stable (B), and unstable (C) limit cycles.
- The unstable limit cycles usually demarcate regions of attraction for two other stable attractors (equilibrium and limit cycle, see the sub-critical Hopf bifurcation).



Stability of the limit cycles

- Periodic solution: $\bar{x}(t) = \bar{x}(t+T)$, where T is period.
- Matrix of linearization is periodic too: $A(t) = A(t+T)$.
- Stability is determined by how the small perturbation $\bar{y}(t_0)$ changes during the period T.

$$\bar{y}(t_0 + T) = M_T \bar{y}(t_0)$$

  where M_T is a constant monodromy matrix.
- The eigenvalues of M_T ($\mathrm{Det}[M_T - \mu I] = 0$) are called (Floquet) *multipliers*.
- Stable limit cycles imply all $|\mu_i| \leq 1$.
- Lyapunov exponents:

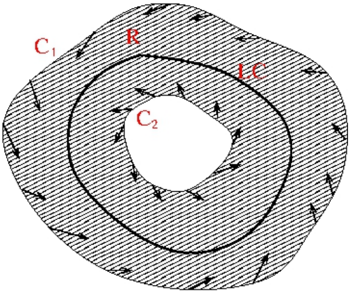
$$\lambda_i = \frac{1}{T} \ln |\mu_i|$$

- $\lambda_i = 0$ corresponds to $\mu_i = \pm 1$. For the limit cycles one λ is always zero, hence, $|\mu| = 1$.

Finding limit cycles

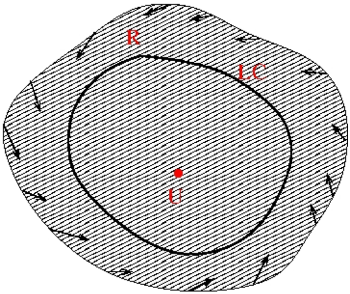
- Poincaré-Bendixson theorem: Suppose R is a regions between two simple closed curves C_1 and C_2. If
  1. at each point of C_1 and C_2 the vector field points toward the interior of R and
  2. R contains no critical points

  then the system has a closed trajectory LC lying inside R.



Finding limit cycles

- If there is a continous region R containing an unstable equilibrium U and the vector field on the region's boundary points toward the interior of the region, then there is at least one stable limit cycle LC in the region.



Non-existence criteria

There are no closed trajectories in a system if:

- No equilibrium points
- One equilibrium other than node, focus, or center (e.g. saddle)
- Bendixson criterion: if P_x and Q_y are continuous in a region R which is simply-connected (i.e. without holes) and

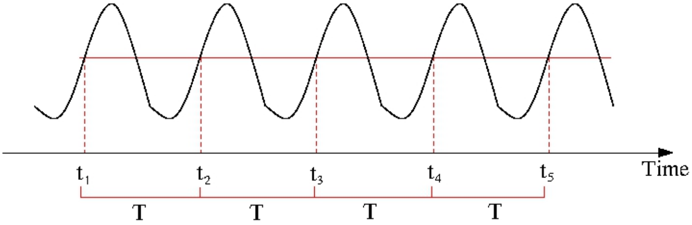
$$\frac{\partial P}{\partial x} + \frac{\partial Q}{\partial y} \neq 0$$

at any point of R, then the system

$$\begin{cases} x' = P(x, y) \\ y' = Q(x, y) \end{cases}$$

has no closed trajectories inside R.

Finding period of oscillations



Calculating the Poincaré map and period T (return times) of the trajectory. $T = t_{i+1} - t_i$ (e.g. $T = t_5 - t_4$).

Bifurcations of the limit cycles

- One multiplier is always ± 1.
- Among others the bifurcation criteria (codim-1) are three:
  1. $\mu(\alpha^*) = +1$ (saddle-node bifurcation of the limit cycles)
  2. $\mu(\alpha^*) = -1$ (period doubling bifurcation)
  3. $\mu(\alpha^*) = \exp(\pm\phi i)$ (Neimark-Sacker bifurcation)

Biochemical and Cellular cycles

Table 9.1 Biochemical and Cellular Rhythms Sources: Goldbeter (1996), Rapp (1979).

Rhythm	Period
Membrane potential oscillations	10 ms–10 s
Cardiac rhythms	1 s
Smooth muscle contraction	seconds – hours
Calcium oscillations	seconds–minutes
Protoplasmic streaming	1 min
Glycolytic oscillations	1 min–1 h
cAMP oscillations	10 min
Insulin secretion (pancreas)	minutes
Gonadotropic hormone secretion	hours
Cell cycle	30 min–24 h
Circadian rhythms	24 h
Ovarian cycle	weeks–months

C. Fall, Computational Cell Biology, Springer. Chapter 9.

Brusselator

- Brusselator is a model systems mimicking some molecular interactions involving tri-molecular chemical reactions (usual case for biology):

$$A \xrightarrow{1} X$$
$$2X + Y \xrightarrow{1} 3X$$
$$B + X \xrightarrow{1} Y + D$$
$$X \xrightarrow{1} E$$

- All reaction for simplicity have the same rate constant equal to 1. System is resolved in regard to variables X and Y, whereas A and B are the parameters:

$$\begin{cases} \dfrac{dX}{dt} = A - (B+1)X + X^2Y \\ \\ \dfrac{dY}{dt} = BX - X^2Y \end{cases}$$

Brusselator

- Steady state:

$$\begin{cases} \bar{X} = A \\ \bar{Y} = \dfrac{B}{A} \end{cases}$$

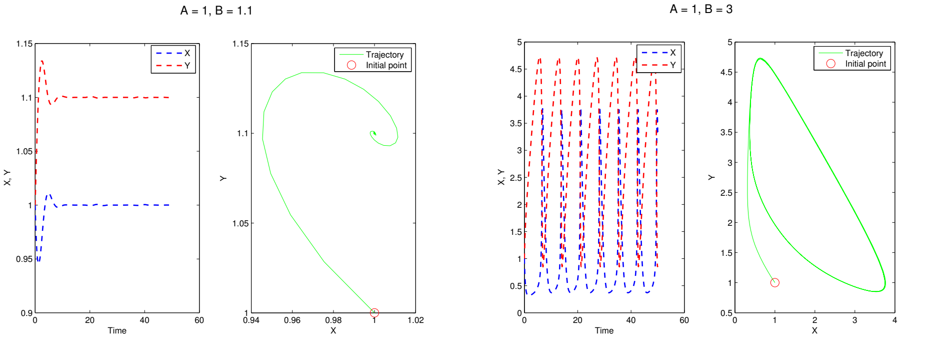
- Characteristic equation:

$$\begin{vmatrix} B - 1 - \lambda & A^2 \\ -B & -A^2 - \lambda \end{vmatrix} = 0 \Rightarrow$$

$$\lambda_{1,2} = \frac{B - 1 - A^2 \pm \sqrt{(B - 1 - A^2)^2 - 4A^2}}{2}$$

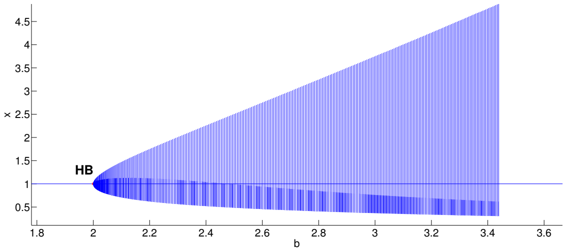
- $\operatorname{Re} \lambda > 0$ (SS is unstable), when $B > 1 + A^2$.

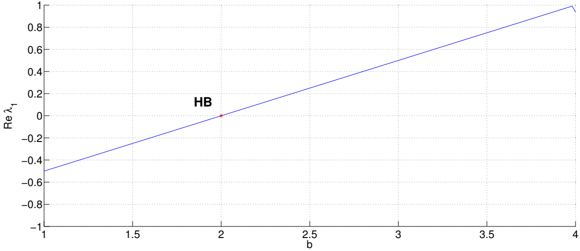
Brusselator dynamics



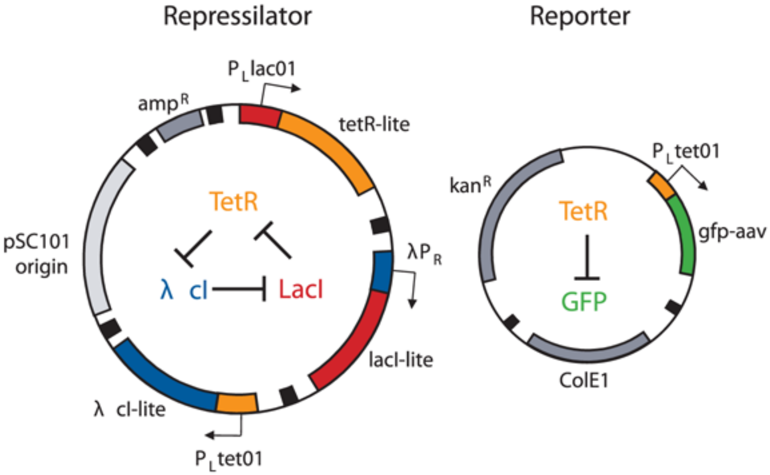
Hopf Bifurcation: Brusselator

$$A = 1$$





Genetic oscillator: experimental setup



M. Elowitz and S. Leibler, *Nature*, 2000.

Genetic oscillator: model

m_i is a mRNA and p_i is a protein.

$$\begin{aligned}\frac{dm_i}{dt} &= -m_i + \frac{\alpha}{1+p_j^n} + \alpha_0 \\ \frac{dp_i}{dt} &= -\beta(p_i - m_i)\end{aligned} \qquad \begin{pmatrix} i = lacI, tetR, cI \\ j = cI, lacI, tetR \end{pmatrix} \qquad (1)$$

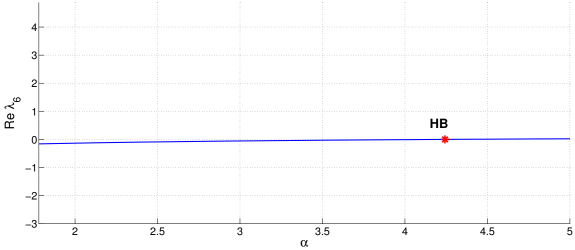
Parameters:

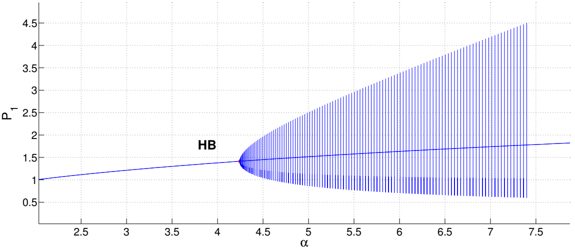
- α is a transcription rate
- α_0 is a leaky transcription rate
- n is the Hill-coefficient
- β is the ratio between mRNA and protein lifetimes = inverse degradation rates

M. Elowitz and S. Leibler, *Nature*, 2000.

Genetic oscillator dynamics

$\beta = 1,\ n = 2,\ \alpha_0 = 0$

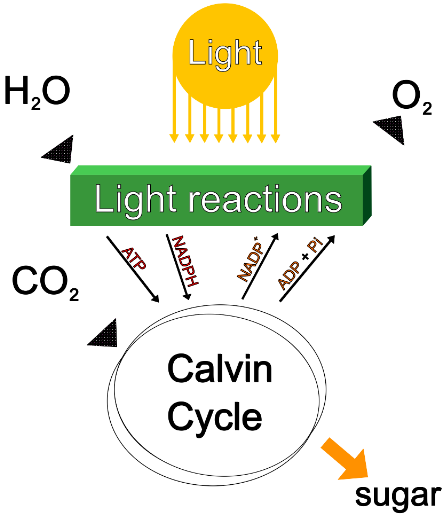




Photosynthetic oscillator

- **Photosynthesis** is a process of transform of the light energy to the energy of the chemical bonds accompanied with emission of O_2 and consumption of CO_2. The process takes place in plant(-like) organisms.
- The chemical energy is stored in carbohydrate molecules, such as sugars.
- The process of O_2 emission is periodic given the periodicity of the day-and-night cycle. However, periodicity is persistent for long time even in the constant light conditions.

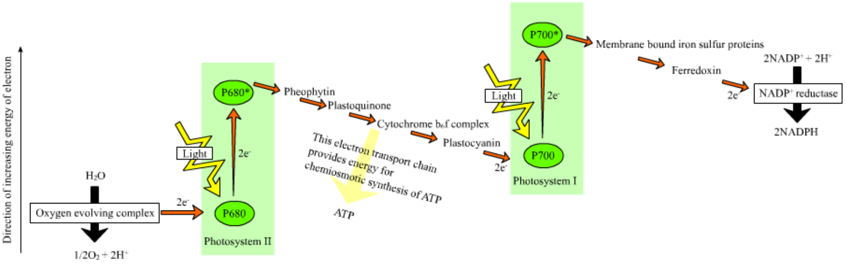
Photosynthesis: two stages



Wikipedia

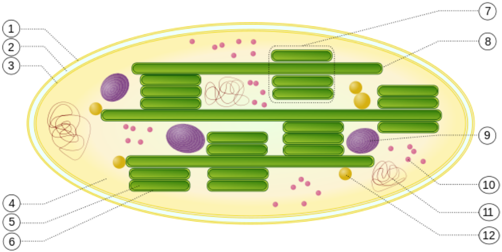
- Photosynthesis consists of two stages: light and dark.
- Light stage involves fast electron chain reactions.
- Dark reactions (Calvin cycle) are slow chemical transformations.
- Cycle implies the initial chemical is regenerated inside the cycle.

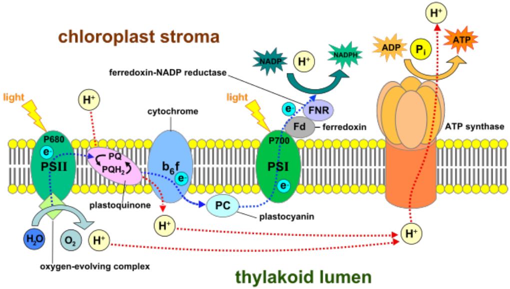
Z-scheme



Wikipedia

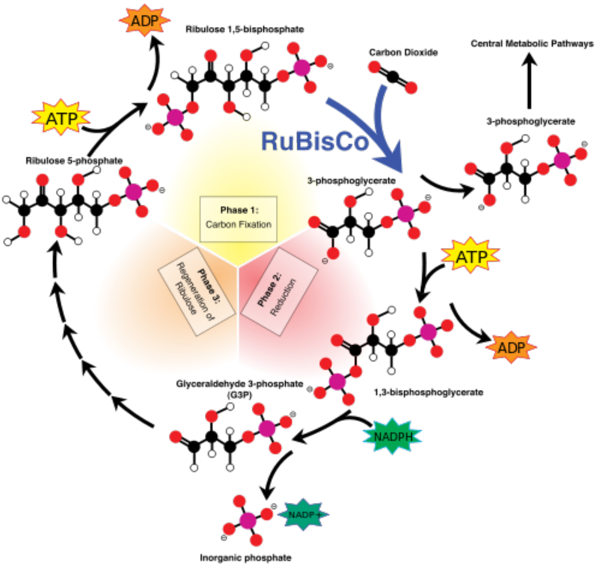
Thylakoid





Wikipedia

Calvin cycle: dark reactions



Wikipedia

Photosynthetic oscillator: dark reactions

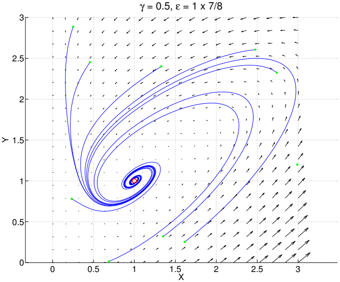
- Dark reactions involve various types of rearrangements between sugars of different size conventionally measured in number of C atoms they contain.
- The system is reduced to describe the dynamics of C_3 (X) and C_6 (Y) sugars.
- The system describes various types of transformations, e.g. $C_3 + C_3 \rightarrow C_6$

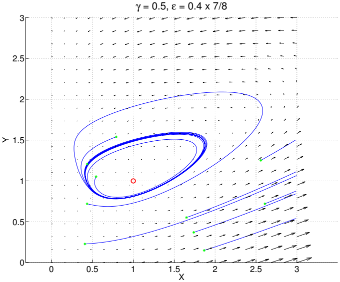
$$\begin{cases} \dfrac{dX}{dt} = X^2 - (1+\gamma)XY + \gamma \\ \\ \dfrac{dY}{dt} = \dfrac{1}{7}\epsilon(7X^2 - Y^2 - 6XY) \end{cases}$$

Photosynthetic oscillator: steady states

- $\dfrac{dX}{dt} = 0$ and $\dfrac{dY}{dt} = 0$ give:
- $\bar{X} = \bar{Y} = 1.$
- The eigenvalues for the equilibrium:
- $$\lambda_{1,2} = \frac{1 - \gamma - \frac{8}{7}\epsilon \pm \sqrt{(1 - \gamma - \frac{8}{7}\epsilon)^2 - \frac{64}{7}\epsilon\gamma}}{2}$$
- Steady state is *focus*.

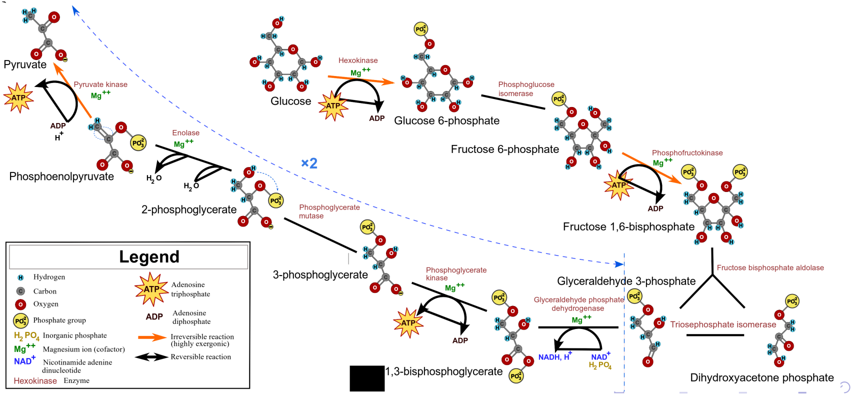
Photosynthetic oscillator: dynamics



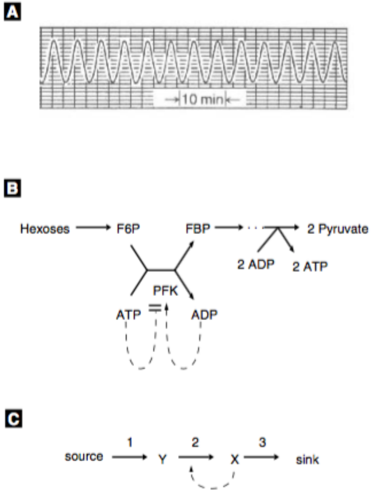


Glycolysis oscillations

- **Glycolysis** is a process of a chemical decomposition of glucose and other sugars, into three-carbon chemicals, e.g Pyruvate.
- The process entails the liberation of 2 molecules of ATP (the main energy currency of a cell) for each glucose molecule.



Glycolysis oscillations: PFK-reaction



The reaction [Fructose-6-phosphate → Fructose-1,6-bisphosphate] is governed by the enzyme **Phospho Frukto Kinase** (PFK) and is an oscillatory reaction.

C. Fall, Computational Cell Biology, Springer.

Two-subunit enzymes

- Analogously to one subunit enzymes (Michaelis-Menten equation).

$$\begin{aligned} \mathrm{EE} + \mathrm{S} &\rightleftharpoons \mathrm{EES} & \text{dissociation constant} &= k_{-1}/k_1 \\ \mathrm{EES} &\rightarrow \mathrm{EE} + \mathrm{P} & \text{rate constant} &= k_3 \\ \mathrm{EES} + \mathrm{S} &\rightleftharpoons \mathrm{SEES} & \text{dissociation constant} &= k_{-2}/k_2 \\ \mathrm{SEES} &\rightarrow \mathrm{EES} + \mathrm{P} & \text{rate constant} &= k_4 \end{aligned}$$

- The rate of the reaction:

$$v = \frac{d[P]}{dt} = -\frac{d[S]}{dt} = \frac{[EE]_T\left(\frac{[S]}{K_{m1}}\right)\left(k_3 + k_4\left(\frac{[S]}{K_{m2}}\right)\right)}{1 + \left(\frac{[S]}{K_{m1}}\right) + \left(\frac{[S]^2}{K_{m1}K_{m2}}\right)}$$

where $[EE]_T = [EE] + [EES] + [SEES]$,
$K_{m1} = (k_{-1} + k_3)/k_1$, and $K_{m2} = (k_{-2} + k_4)/k_2$. K_{m1}/K_{m2} is the inverse affinity of substrates to the enzyme.

Cooperative binding

- *Hill equation*: $K_{m1} \to \infty$, $K_{m2} \to 0$, such that $K_{m1}K_{m2} = K_m^2 = \text{Constant}$

$$v = \frac{V_{\max}\left([S]/K_m\right)^2}{1 + \left([S]/K_m\right)^2}, \ V_{\max} = k_4[EE]_T$$

- *Substrate inhibition*: $k_3 \to \infty$, $K_{m1} \to \infty$, $K_{m2} \to 0$, such that $K_{m1}K_{m2} = K_m^2 = \text{Constant}$, $k_3K_{m2} \to \infty$ and $k_3[EE]_T K_m/K_{m1} = V_{\max} = \mathit{constant}$

$$v = \frac{V_{\max}[S]/K_m}{1 + \left([S]/K_m\right)^2}$$

- *No cooperation*: the same Michaelis-Menten equation: $v = \dfrac{V_{\max}[S]}{K_m + [S]}$

Glycolytic oscillator

- Given x is Fructose-6-phosphate and y is Fructose-1,6-bisphosphate, the system of equations can be written in the form:

$$\begin{cases} \dfrac{dx}{dt} = k - \chi \dfrac{x}{K_{mx} + x} \dfrac{y}{K_{my} + y} \\ \\ \dfrac{dy}{dt} = \chi \dfrac{x}{K_{mx} + x} \dfrac{y}{K_{my} + y} - q \dfrac{y}{K'_{my} + y} \end{cases}$$

- NOTE the Michaelis-Menten terms! Reaction is dependent upon the PFK enzyme.

Glycolytic oscillator

Given $K_{mx} \gg x$ and $K_{my} \gg y$ we can substitute the variables and get:

$$\begin{cases} \dfrac{dx}{dt} = 1 - xy \\ \\ \dfrac{dy}{dt} = \alpha y \left(x - \dfrac{1+r}{1+ry} \right) \end{cases}$$

where $\alpha = \dfrac{(q-k)^2 K_{mx} K_{my}}{\left(K'_{my}\right)^2 k\chi}$ and $r = \dfrac{k}{q+k}$.

Glycolytic oscillator

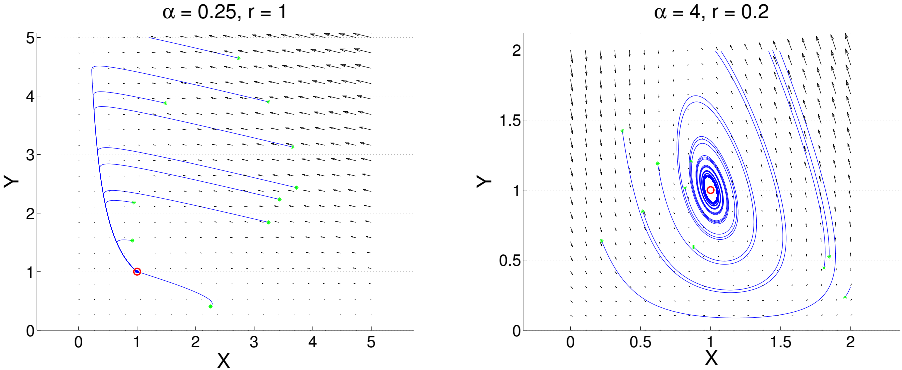
- Steady state is $\bar{x} = \bar{y} = 1$.
- The characteristic equation:

$$\begin{vmatrix} -1-\lambda & -1 \\ \alpha & \frac{\alpha r}{1+r} - \lambda \end{vmatrix} = 0$$

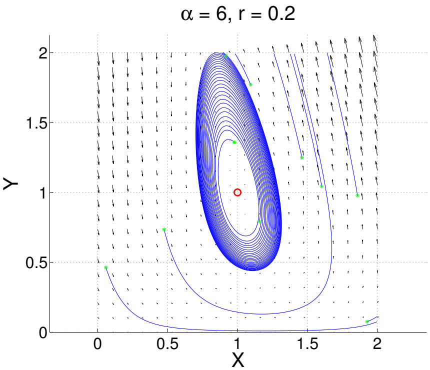
- $\Rightarrow$Roots:

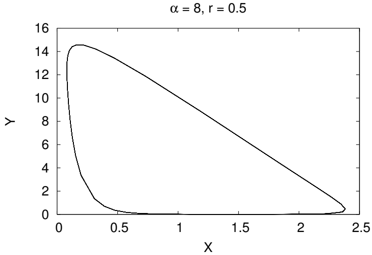
$$\lambda_{1,2} = \frac{r(\alpha-1) - 1 \pm \sqrt{(r(\alpha-1)-1)^2 - 4\alpha(1+r)}}{2(1+r)}$$

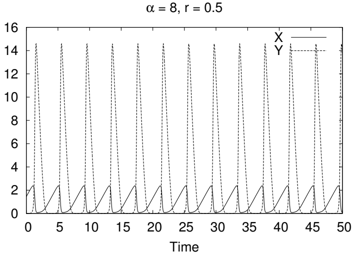
Glycolytic oscillator: dynamics



Glycolytic oscillator: dynamics







Summary

- Oscillations are abundant in life.
- This ranges on the scale from the ecological to the cellular and molecular levels ...
- as well as on the time span from the periods of miliseconds (e.g. brain) to the months and even years (e.g. seasonal migrations).
- There are specific biological functions that ultimately depend on oscillatory behaviors (photosynthesis, glycolysis, circadian rhythms etc.).

Further reading

- C. Fall, Computational Cell Biology, Springer. **Chapter 9 (“Biochemical Oscillations”)**.
- J.D. Murray, Mathematical Biology: I. Intoroduction, Springer, 3rd ed., **Chapter 6, 7**.