COSC 348: Computing for Bioinformatics

Lecture 23
Gene Regulatory Networks 3 - ODE

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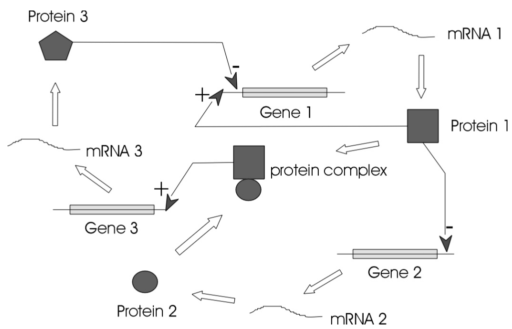
GRN inference and modelling GRN dynamics

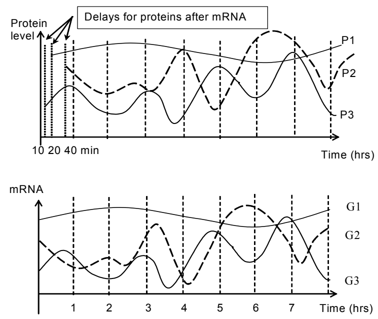
- GRN inference means a reconstruction of GRN based on experimental data from molecular biology.
- Modelling the GRN dynamics means simulating the changes of gene expression levels over time based on some model.
- Types of dynamic GRN models:
  - Boolean Networks
  - Weight matrices
  - Differential equations
  - Bayesian Networks
  - other

Gene regulatory network (GRN)

Genes can either inhibit or activate themselves or other genes. Often products of genes form complexes, which then influence the expression of other genes.



Production of mRNA and proteins is a continuous process



Ordinary Differential Equations (ODE)

- The rate of growth of variable x is the derivative $dx / dt = \dot{x}$.
- Let us assume, the rate of growth of variable x is proportional to the concentration of variable itself, i.e.

$$\frac{dx}{dt} = \dot{x} = k\,x$$

- Where $k > 0$ is the proportionality constant, which is the model parameter (i.e. does not change over time). Time t is the independent variable and x is the dependent variable.
- This equation is ODE because it contains ordinary derivative and not partial derivates and it's a first-order ODE because it contains only the derivative of the 1st order.

Ordinary Differential Equations (ODE)

- The value of variable x at time $t = 0$ is called *initial condition* x_0.
- What does this model predict? What is the solution of this equation?

$$\frac{dx}{dt} = \dot{x} = k\,x$$

- One trivial solution is if $x = 0$, then also $dx / dt = 0$. This is called an equilibrium solution because it is constant forever.
- But what if $x \neq 0$? Then finding the solution of this equation will tell us what will be the value of x at any future time step $t > 0$.

Analytical solution of ODE

- We must find a function $x(t)$ whose derivative is the product $k\,x$.

$$\dot{x} = k\,x$$

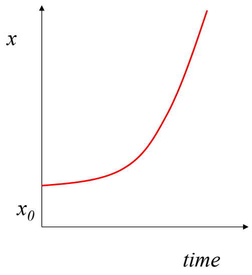
- How? One way is to guess. Let us try the exponential and see where it leads us. Thus, let $x(t)$ be

$$x(t) = x_0\, e^{kt}$$

- Then

$$\dot{x} = x_0\, k\, e^{kt} = k\,x$$

- Which is exactly what we wanted.

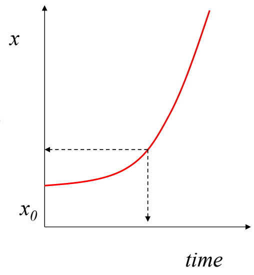


Analytical solution of ODE

- The solution of ODE

$$x(t) = x_0\, e^{kt}$$

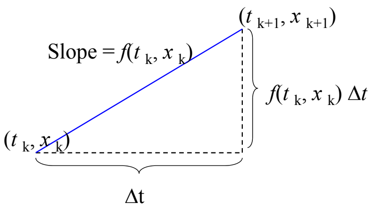
- Means that if we know k and x_0 then we can predict the value of x at each future time step t.
- But most often the analytical solution is very difficult to find or does not exist.
- Then we resort to numerical solutions of ODE.



Numerical solution of ODE: Euler's method

$$\frac{dx}{dt} = f(t,x)$$

- Given the initial condition x_0 and the discrete step size Δt, compute the point (t_{k+1}, x_{k+1}) from the preceding point (t_k, x_k) as follows:
  - Use the ODE to calculate the slope of function $f(t_k, x_k)$.
  - Calculate the next point (t_{k+1}, x_{k+1}) using these formulas:



$$t_{k+1} = t_k + \Delta t$$

$$x_{k+1} = x_k + f(t_k, x_k)\,\Delta t$$

Model of cross-inhibition network

gene 1 $\underset{-}{\overset{-}{\rightleftarrows}}$ gene 2

m_1 = concentration mRNA 1

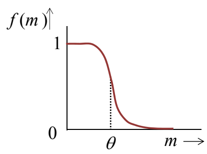
m_2 = concentration mRNA 2

$$\dot{m}_1 = \kappa_1 f(m_2) - \gamma_1 m_1$$

$$\dot{m}_2 = \kappa_2 f(m_1) - \gamma_2 m_2$$

$\kappa_1, \kappa_2 > 0$, production rate constants

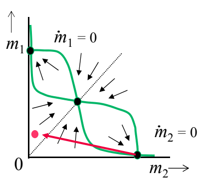
$\gamma_1, \gamma_2 > 0$, degradation rate constants



$$f(m) = \frac{\theta^n}{\theta^n + m^n}\ , \quad \theta > 0 \text{ threshold}$$

Phase-plane analysis

- Analysis of **steady states** in phase plane for given values of κ's and γ's



$$\dot{m}_1 = 0:\ m_1 = \frac{\kappa_1}{\gamma_1}\ f(m_2)$$

$$\dot{m}_2 = 0:\ m_2 = \frac{\kappa_2}{\gamma_2}\ f(m_1)$$

- Two **stable** and one **unstable** steady state. System will converge to one of two stable steady states after many (i.e. $t \rightarrow \infty$) iterations.
- System displays **hysteresis** effect: perturbation may cause irreversible switch to another steady state.

General formulas for genes and their products

For genes (mRNAs):

$$\frac{dm}{dt} = (\text{transcription of regulators terms}) - \text{degradation term}$$

For their products:

$$\frac{dp}{dt} = (\text{translation term}) + (\text{diffusion term}) - \text{degradation term}$$

Formulas for regulators of transcription

Activator: $$\frac{dx}{dt} = \frac{K_{Zx}^{nuZx}}{K_{Zx}^{nuZx} + Z^{nuZx}}$$ $Z \longrightarrow x$

Inhibitor: $$\frac{dx}{dt} = \frac{Y^{nuYx}}{K_{Yx}^{nuYx} + Y^{nuYx}}$$ $Y \multimap x$

Activator-Inhibitor: $$\frac{dx}{dt} = \frac{Z\left(\frac{K_{Yx}^{nuYx}}{K_{Yx}^{nuZx} + Y^{nuYx}}\right)^{nuZx}}{K_{Zx}^{nuZx} + Z\left(\frac{K_{Yx}^{nuYx}}{K_{Yx}^{nuZx} + Y^{nuYx}}\right)^{nuZx}}$$

Formulas for transcription and translation

Transcription:

$$\frac{dr}{dt} = \frac{\tau}{H_r}\left\{\underbrace{\left(1 - \prod_{j=1}^{m}\left(\frac{\alpha_j P_j^{\nu_j}}{K_j^{\nu_j} + P_j^{\nu_j}}\right)\right)}_{\text{Activators}}\underbrace{\left(1 - \frac{\alpha_r P_r^{\nu_r}}{K_r^{\nu_r} + P_r^{\nu_r}}\right)}_{\text{Inhibitor}} - r\right\}$$

Translation:

$$\frac{dP_i(t)}{dt} = \frac{\tau}{H_r}\left(r_i + D_i[(P_{i-1} - P_i) + (P_{i+1} - P_i)] - P_i\right)$$

How to determine all these variables

- It is impossible for large number of genes and proteins;
- For small numbers, they can be determined by experimental evaluation of decay constants and interactions between proteins and genes;
- For individual gene expression measurements we can use the Northern blotting, quantitative real-time PCR, etc;
- For measuring individual protein levels (mass spectroscopy);
- Some parameters can be determined experimentally and some may be optimised by simulated annealing or genetic algorithm.

Evaluation of nonlinear differential equations

- **Pro:** reasonably accurate description of underlying molecular interactions.
- **Contra:** for more complex networks, difficult to analyze mathematically, difficult to know values of parameters.
- **Pro:** approximate solution can be obtained through numerical simulation.
- **Contra:** simulation techniques difficult to apply in practice, due to lack of numerical values for parameters and knowledge of initial conditions !