Systems Biology: Modeling Gene Networks

Recall the Central Dogma of Biology

DNA has Genes

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↓

mRNA

~~~~~~~~~~ → decays eventually

↓

Protein

ooooo → decays eventually

Ordinary Differential Equations

k → Production rate

γ → Degradation rate

m for mRNA, p for Protein, derivatives wrt time

$$\frac{dm}{dt} = k_m - \gamma_m m$$

k_m is the production rate of mRNA

γ_m is the degradation rate of mRNA (is some fraction of current mRNA abundance)

m is the current abundance of the mRNA

$$\frac{dp}{dt} = k_p m - \gamma_p p$$

$k_p m$ is the production rate of Protein; depends upon current abundance of mRNA
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γ_p is the degradation rate of Protein

p is the current abundance of Protein

At **Steady State,** i.e. no change wrt time in abundance:

$\frac{dm}{dt} = 0$

$m = \frac{k_m}{\gamma_m}$

$\frac{dp}{dt} = 0$

$p = \frac{k_p m}{\gamma_p}$

$$p = \frac{k_p k_m}{\gamma_p \gamma_m}$$

Two-Gene Model: Activation

Gene 1 and Gene 2

~~mRNA1 and mRNA2~~ (for simplicity)

Protein 1 and Protein 2

to simplify Gene → Protein

> *All models are wrong but some are useful*

Let us assume, Gene 1 is facilitating the expression of Gene 2

(Transcription Factor)

$$\frac{dG_1}{dt} = k_1 - \gamma_1 G_1$$

$k1$ is the production rate of Gene 1 (here, DNA → Protein)

γ_1 is the rate of degradation of Protein 1

$$\frac{dG_2}{dt} = \frac{G_1^n}{c^n + G_1^n} k_2 - \gamma_2 G_2$$

γ_2 is the rate of degradation of Protein 2

k_2 is the maximum production rate of Gene 2

$$\frac{G_1^n}{c^n + G_1^n} k_2 \; Hill\ Function\ (start\ at\ 0,\ saturates\ to\ 1)$$

c is a constant that represents the activation threshold of Gene 1 for Gene 2

At $G_1 = c$, the activation function equals 0.5, meaning Gene 2 is being transcribed at half of its maximum rate k_2

In biological terms, c represents the amount of Gene 1 (or its protein) required to significantly activate Gene 2.

n is the Hill coefficient, determining the activation of Gene 2.

Higher n means the function acts more switch-like, meaning Gene 2 is OFF when G1 is below c and turns ON rapidly when G1 exceeds c.

At n = 1, the activation is gradual (Michaelis-Menten-like).

If n > 1, the activation becomes ultrasensitive, meaning Gene 2 is activated only when Gene 1 reaches a high concentration.

$$0\ of\ Gene1 \rightarrow 0\ of\ Gene2$$

Two-Gene Model: Repression

G1 and G2

~~mRNA1 and mRNA2~~

Protein1 and Protein2

Gene1 —| Gene2

$$\frac{dG_1}{dt} = k_1 - \gamma_1 G_1$$

$$\frac{dG_2}{dt} = \frac{c^n}{c^n + G_1^n} k_2 - \gamma_2 G_2$$

Gene1→0

G_1^n →0 ; k_2

G_1^n >> ; $k_2 -> 0$

Three-Gene Model: Negative Feedback Oscillator

DNA

===Gene1===Gene2===Gene3===

$Gene1 \rightarrow Gene2 \rightarrow Gene3$

$Gene3 \dashv Gene1$

$$\frac{dG_1}{dt} = \frac{c^n}{c^n + G_3^n} k_1 - \gamma_1 G_1$$

$$\frac{dG_2}{dt} = \frac{G_1^n}{c^n + G_1^n} k_2 - \gamma_2 G_2$$

$$\frac{dG_3}{dt} = \frac{G_2^n}{c^n + G_2^n} k_3 - \gamma_3 G_3$$

Deterministic v/s Stochastic Modelling

Deterministic models have one trajectory determined by the initial conditions.

Stochastic models involve randomness. Different outcomes each time.

When to use each?

Random variation giving rise to different transcriptional state.

When we want to study random variation in biological system (inherent).

Deterministic model are more “ideal” models which may be used to explain a phenomenon(?)

Gillespie Algorithm

Stochastic Simulation Algorithm (SSA)

The Gillespie algorithm is used to simulate stochastic gene expression models, where reactions occur randomly over time instead of being modeled deterministically.

$$DNA \xrightarrow{k} mRNA \xrightarrow{\gamma} xDecay$$

$rates = [k; production, x\gamma; degradation]$

x is changing, $x\gamma$ is changing

from time $t_1 t\tau$

to randomly pick τ such that it is random but makes sense? and give us correct trajectory

By taking a random draw from a decaying exponential distribution

Probability Density Function

$$P(\tau) = \lambda e^{-\lambda\tau}$$

$Mean = \frac{1}{\lambda}$

How is λ chosen?

$\lambda = k + x\gamma$, represents the sum of all reaction propensities at time t

$P(X \to X + 1) = k/k + \gamma k$

$P(X \to X - 1) = \gamma k/k + \gamma k$

Events	Rates
$X \to X + 1$	k
$X \to X - 1$	γX

Steady state = $\frac{k}{\gamma}$

Mean-field (ODE) approximation,

$$\frac{dX}{dt} = k - \gamma X$$

is valid when stochastic fluctuations are small and describes the average behavior.
