Kinetic Modeling of Complex Systems

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Simple model: Creation and Degradation

- $$\begin{array}{llll} \emptyset \to X & \textit{transcription} & v_1 = k_1 & (Molecules/minute) \\ X \to \emptyset & \textit{degradation} & v_2 = k_2 A & (minutes^{-1}) \end{array}$$

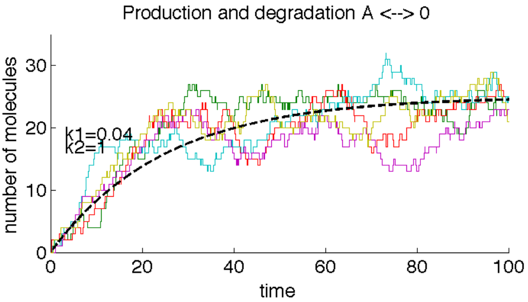
Simple model: Creation and Degradation

- $$\begin{aligned} \emptyset \rightarrow X \quad & \textit{transcription} \quad & v_1 = k_1 \quad & (\textit{Molecules}/\textit{minute}) \\ X \rightarrow \emptyset \quad & \textit{degradation} \quad & v_2 = k_2 A \quad & (\textit{minutes}^{-1}) \end{aligned}$$

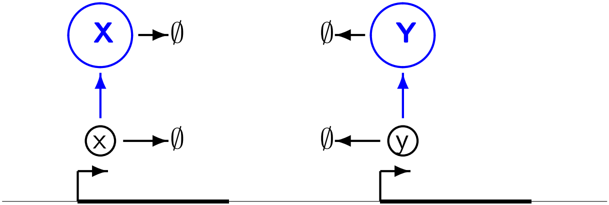
- $$\begin{aligned} \frac{dX}{dt} &= v_1 - v_2 \\ 0 &= k_1 - k_2 X_{ss} \\ X_{ss} &= \frac{k_1}{k_2} \end{aligned}$$

Modeling the differential equations: Stochastic Algorithm

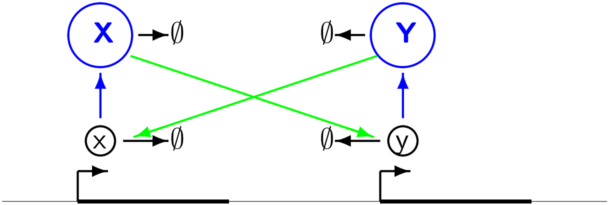
- Sample exponential distribution of times until next reaction
- Randomly choose which reaction occurs next based on abundance of reaction precursors
- Repeat



Model of Genes X and Y



Mutual Inhibition



Chemical reactions

(lowercase=transcripts, Uppercase=Proteins)

$$\emptyset \rightarrow x \quad transcription \qquad v_1 = k_1 \tag{1}$$
$$\emptyset \rightarrow y \quad (txn) \qquad v_2 = k_2 \tag{2}$$

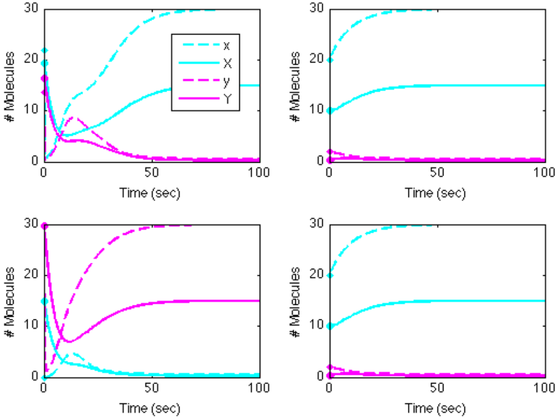
$$x \rightarrow X \quad Translation \qquad v_3 = k_3 x \tag{3}$$
$$y \rightarrow Y \quad (TLN) \qquad v_4 = k_4 y \tag{4}$$

$$x \rightarrow \emptyset \quad transcript\ degradation \qquad v_5 = (k_5 x)(1 + (\frac{Y}{K})^n) \tag{5}$$
$$y \rightarrow \emptyset \quad (deg.) \qquad v_6 = (k_6 x)(1 + (\frac{X}{K})^n) \tag{6}$$

$$X \rightarrow \emptyset \quad Protein\ Degradation \qquad v_7 = k_7 X \tag{7}$$
$$Y \rightarrow \emptyset \quad (DEG.) \qquad v_8 = k_8 Y \tag{8}$$

(9)

Modeling the differential equations: Numerical Solver



After a while, the concentrations end up at their steady-state values.

Then what does it mean to have multiple steady-states?

Steady-state calculations

- $$\frac{dX}{dt} = v_3 - v_7$$
  $$0 = k_3 x_{ss} - k_7 X_{ss}$$
  $$X_{ss} = x_{ss}\frac{k_3}{k_7}\boxed{= x_{ss}\frac{TLN}{DEG}}, \boxed{Y_{ss} = y_{ss}\frac{TLN}{DEG}}$$

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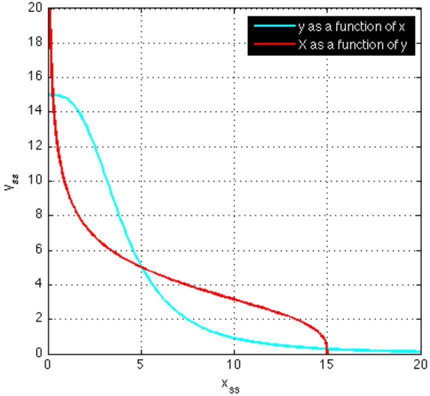
- $$\frac{dx}{dt} = v_1 - v_5$$
  $$0 = k_1 - (k_5 x_{ss})(1 + (\frac{Y_{ss}}{K})^n)$$
  $$x_{ss} = \frac{k_1}{k_5(1 + (\frac{y_{ss}TLN}{K \cdot DEG})^n)}$$

Global steady-state

$$x_{ss} = \frac{k_1}{k_5(1 + (\frac{y_{ss}TLN}{K \cdot DEG})^n)} = \frac{txn}{deg(1 + (\frac{y_{ss}TLN}{K \cdot DEG})^n)}$$



$$txn = 3 \ molecules/sec$$
$$deg = 0.1 \ sec^{-1}$$
$$TLN = 0.1 \ sec^{-1}$$
$$DEG = 0.2 \ sec^{-1}$$
$$K = 4 \ molecules$$
$$n = 3$$ *This is the hill coefficient*

Modeling the differential equations: Stochastic Examples