Dynamical Systems and Chaos
Part II: Biology Applications

Lecture 7: Molecular Systems

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Law of Mass Action

When a reaction happens, the concentrations of the reactants and products are changing. The concentrations of the reactants are decreasing and products are increasing. The law of mass action (Waage and Guldberg, 1864) states that the **rate of a chemical reaction is proportional to the product of concentrations of the reacting molecules**.
For the reaction

$$a\mathrm{A} + b\mathrm{B} \xrightarrow{k} d\mathrm{D} + f\mathrm{F},$$

the reaction rate is

$$v = -\frac{1}{a}\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = -\frac{1}{b}\frac{\mathrm{d}[\mathrm{B}]}{\mathrm{d}t} = \frac{1}{d}\frac{\mathrm{d}[\mathrm{D}]}{\mathrm{d}t} = \frac{1}{f}\frac{\mathrm{d}[\mathrm{F}]}{\mathrm{d}t} = k[\mathrm{A}]^a[\mathrm{B}]^b.$$

Deterministic modeling of chemical reactions

Degradation:

$$A \xrightarrow{k} \emptyset$$

Rate of the reaction is:

$$v = -\frac{d[A]}{dt} = k[A]\,,$$

where $[A]$ is the concentration of A.

Transformation:

$$A \xrightarrow{k} B$$

Rate of the reaction is:

$$v = -\frac{d[A]}{dt} = \frac{d[B]}{dt} = k[A]$$

More complex example:

$$2A \xrightarrow{k} B + C$$

$$v = -\frac{1}{2}\frac{d[A]}{dt} = \frac{d[B]}{dt} = \frac{d[C]}{dt} = k[A]^2$$

Reversible reaction

$$2\mathrm{A} + \mathrm{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C}$$

means that we have two reactions

$$\begin{cases} 2\mathrm{A} + \mathrm{B} \xrightarrow{k_1} \mathrm{C} \\ \mathrm{C} \xrightarrow{k_{-1}} 2\mathrm{A} + \mathrm{B} \end{cases},$$

where A, B, and C are chemical species. k_1 is the forward and k_{-1} the backward rate constant. The reaction rates for forward and backward reaction are

$$v_1 = k_1[\mathrm{A}]^2[\mathrm{B}] \qquad \text{and} \qquad v_{-1} = k_{-1}[\mathrm{C}].$$

The reaction rate for the reversible reaction is

$$v_{1,-1} = v_1 - v_{-1} = k_1[\mathrm{A}]^2[\mathrm{B}] - k_{-1}[\mathrm{C}].$$

The reaction rates for each chemical species are

$$\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = -2v_1 + 2v_{-1} = -2v_{1,-1},$$

$$\frac{\mathrm{d}[\mathrm{B}]}{\mathrm{d}t} = -v_1 + v_{-1} = -v_{1,-1}, \quad \text{and}$$

$$\frac{\mathrm{d}[\mathrm{C}]}{\mathrm{d}t} = v_1 - v_{-1} = v_{1,-1}.$$

The numbers before reaction rates are called stoichiometric coefficients.
In steady state, $\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathrm{B}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathrm{C}]}{\mathrm{d}t} = 0$ which means that $v_1 = v_{-1}$ and $\frac{[\mathrm{A}]^2[\mathrm{B}]}{[\mathrm{C}]} = \frac{k_{-1}}{k_1} = K_d$, where K_d is the equilibrium constant.

Stoichiometric Matrix

One way to present a model is

$$\frac{\mathrm{d}[\mathrm{C}_i]}{\mathrm{d}t} = \sum_{j \in \{J_{to}, J_{out}\}} s_{ij} v_j,$$

where J_{to} and J_{out} are the set of indices of reactions leading to the chemical species C_i (C_i is the product) and out of the chemical species C_i (C_i is the reactant), respectively. s_{ij} are the stoichiometric coefficients and v_j is the reaction rate for the reaction j. One can write in matrix format:

$$\frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t} = \mathbf{S}\mathbf{v},$$

where vector $\mathbf{x}$ describes the concentrations of each chemical species, $\mathbf{S}$ is the stoichiometric matrix, and vector $\mathbf{v}$ describes the deterministic reaction rates for each reaction.

For example, the reversible reaction $2\mathrm{A} + \mathrm{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C}$ can be presented as

$$\frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t} = \begin{bmatrix} \frac{\mathrm{dA}}{\mathrm{d}t} \\ \frac{\mathrm{dB}}{\mathrm{d}t} \\ \frac{\mathrm{dC}}{\mathrm{d}t} \end{bmatrix} = \mathbf{S}\mathbf{v} = \begin{bmatrix} -2 & 2 \\ -1 & 1 \\ 1 & -1 \end{bmatrix} \begin{bmatrix} v_1 \\ v_{-1} \end{bmatrix},$$

where we can easily see that in the forward reaction, 2 moles of A and 1 mole of B are forming 1 mole of C, and in the backward reaction, 1 mole of C is forming 2 moles of A and 1 mole of B. And we get the same result as before:

$$\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = -2v_1 + 2v_{-1},$$

$$\frac{\mathrm{d}[\mathrm{B}]}{\mathrm{d}t} = -v_1 + v_{-1}, \quad \text{and}$$

$$\frac{\mathrm{d}[\mathrm{C}]}{\mathrm{d}t} = v_1 - v_{-1}.$$

Example

Linear chemical equation:

$$\overset{k_1}{\rightarrow} X \overset{k_2}{\rightarrow} Y \overset{k_3}{\rightarrow}$$

Corresponding ODE system:

$$\begin{cases} \dfrac{dX}{dt} = k_1 - k_2 X \\ \dfrac{dY}{dt} = k_2 X - k_3 Y \end{cases}$$

Characteristic equation:

$$\begin{vmatrix} -k_2 - \lambda & 0 \\ k_2 & -k_3 - \lambda \end{vmatrix} = 0 \Rightarrow \lambda^2 + (k_2 + k_3)\lambda + k_2 k_3 = 0$$

$$\Rightarrow \lambda_{1,2} = \frac{-(k_2 + k_3) \pm \sqrt{(k_2 - k_3)^2}}{2} = -k_2 \vee -k_3$$

Time scale of the processes

- Processes can be slow and fast as compared to one another.
- For example, baby's growth can be seen on the scale of **months**, food he/she consumes is digested in **hours**, digested macro-molecules are distributed along the body in **minutes**, the molecules are converted into different molecular species in **micro-seconds** (10^{-6}), the chemical reactions involve movement of charged residues in the scale of **nano-seconds** (10^{-9}), electron density changes in those movements are of the scale of **pico-seconds** (10^{-12}).
- The scale of the process is crucial in the modeling. For instance, we are not interested in modeling chemical reactions in the bodies of hares and wolves in the Volterra equations. We are not even interested in how fast they meet in space, considering this a "faster reaction" than the scale of interest.

Enzyme-Catalyzed reactions (ECR)

Life depends on a series of chemical reactions. Many of these reactions, however, proceed too slowly on their own to sustain life. Hence, there were designed catalysts, which we now refer to as enzymes, to greatly accelerate the rates of these chemical reactions. A typical reaction, where substrate S forms a product P is

$$S \rightarrow P.$$

All enzyme-catalyzed reactions include at least three steps:

1. binding of a substrate S to an enzyme E and formation of an enzyme-substrate complex ES,
2. conversion of ES to an enzyme-product complex EP, and
3. release of the product P from EP to yield free P:

Three steps of the ECR

$$\mathrm{E} + \mathrm{S} \overset{\text{binding}}{\rightleftharpoons} \mathrm{ES} \xrightarrow{\text{catalysis}} \mathrm{EP} \xrightarrow{\text{release}} \mathrm{E} + \mathrm{P}.$$

In the simplest case, when the catalysis stage is very rapid, we can simplify the above reaction equation as follows:

$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k_2} \mathrm{E} + \mathrm{P},$$

where k_1 is the rate constant for the formation of ES from E and S, k_{-1} is the rate constant for ES to dissociate into E and S (dissociation rate) and k_2 is the rate constant for the conversion of ES to product and the subsequent release of P from the E. The first part of the reaction is reversible.

The reaction rates

$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k2} \mathrm{E} + \mathrm{P}$$

The reaction rate for ES formation is

The reaction rates

$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k2} \mathrm{E} + \mathrm{P}$$

The reaction rate for ES formation is

$$v_1 = -\frac{\mathrm{d}[\mathrm{E}]}{\mathrm{d}t} = -\frac{\mathrm{d}[\mathrm{S}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathrm{ES}]}{\mathrm{d}t} = k_1[\mathrm{E}][\mathrm{S}].$$

Once ES is formed the reaction can go backward or forward. The reaction rate for the backward reaction is

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The reaction rate for the forward reaction is

The reaction rates

$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k2} \mathrm{E} + \mathrm{P}$$

The reaction rate for ES formation is

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Once ES is formed the reaction can go backward or forward. The reaction rate for the backward reaction is

$$v_{-1} = \frac{\mathrm{d}[\mathrm{E}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathrm{S}]}{\mathrm{d}t} = -\frac{\mathrm{d}[\mathrm{ES}]}{\mathrm{d}t} = k_{-1}[\mathrm{ES}].$$

The reaction rate for the forward reaction is

$$v_2 = \frac{\mathrm{d}[\mathrm{E}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} = -\frac{\mathrm{d}[\mathrm{ES}]}{\mathrm{d}t} = k_2[\mathrm{ES}].$$

The reaction rates

$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k2} \mathrm{E} + \mathrm{P}$$

Let us write down the ODE's for the rates of the reacting and product molecules.
[S]:

The reaction rates

$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k2} \mathrm{E} + \mathrm{P}$$

Let us write down the ODE's for the rates of the reacting and product molecules.

[S]:

$$\frac{\mathrm{d}[\mathrm{S}]}{\mathrm{d}t} = -v_1 + v_{-1} = -k_1[\mathrm{E}][\mathrm{S}] + k_{-1}[\mathrm{ES}],$$

[E]:

The reaction rates

$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k2} \mathrm{E} + \mathrm{P}$$

Let us write down the ODE's for the rates of the reacting and product molecules.

[S]:

$$\frac{\mathrm{d}[\mathrm{S}]}{\mathrm{d}t} = -v_1 + v_{-1} = -k_1[\mathrm{E}][\mathrm{S}] + k_{-1}[\mathrm{ES}],$$

[E]:

$$\frac{\mathrm{d}[\mathrm{E}]}{\mathrm{d}t} = -\frac{\mathrm{d}[\mathrm{ES}]}{\mathrm{d}t} = -v_1 + v_{-1} + v_2 = -k_1[\mathrm{E}][\mathrm{S}] + (k_{-1} + k_2)[\mathrm{ES}],$$

and [P]:

The reaction rates

$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k2} \mathrm{E} + \mathrm{P}$$

Let us write down the ODE's for the rates of the reacting and product molecules.

[S]:

$$\frac{\mathrm{d}[\mathrm{S}]}{\mathrm{d}t} = -v_1 + v_{-1} = -k_1[\mathrm{E}][\mathrm{S}] + k_{-1}[\mathrm{ES}],$$

[E]:

$$\frac{\mathrm{d}[\mathrm{E}]}{\mathrm{d}t} = -\frac{\mathrm{d}[\mathrm{ES}]}{\mathrm{d}t} = -v_1 + v_{-1} + v_2 = -k_1[\mathrm{E}][\mathrm{S}] + (k_{-1} + k_2)[\mathrm{ES}],$$

and [P]:

$$\frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} = v_2 = k_2[\mathrm{ES}].$$

Michaelis-Menten equation

Goal: *to find the rate of conversion as a function of the substrate concentration* [S], *that is* $v_2 = \frac{d[P]}{dt} = k_2[ES]$.

Enzymes are capable of processing the substrate very effectively. This means that we can reach the **steady state** condition. The steady state is reached if:

1. The enzyme can be in either free form or in the enzyme-substrate complex. Thus, the total enzyme concentration is $[\mathrm{E}]_{tot} = [\mathrm{E}] + [\mathrm{ES}]$.
2. $[\mathrm{S}] \gg [\mathrm{E}]_{tot}$ which means that the formation of ES does not significantly diminish free S. So we can approximate that $[\mathrm{S}] \approx [\mathrm{S}]_{tot}$, where $[\mathrm{S}]_{tot}$ is the total concentration.
3. $\frac{\mathrm{d}[\mathrm{ES}]}{\mathrm{d}t} = 0$ which means that in steady state the reaction rate for ES formation is equal to the reaction rate for ES dissociation ($v_1 = v_{-1} + v_2$).

$$\boxed{\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k2} \mathrm{E} + \mathrm{P}}$$

In steady state

$$v_1 = v_{-1} + v_2$$

$$\Rightarrow k_1[\mathrm{E}][\mathrm{S}] = (k_{-1} + k_2)[\mathrm{ES}]$$

$$\Rightarrow \frac{[\mathrm{E}][\mathrm{S}]}{[\mathrm{ES}]} = \frac{k_{-1} + k_2}{k_1} = K_m \,,$$

where K_m is the Michaelis constant. Given the total enzyme concentration $[\mathrm{E}]_{tot} = [\mathrm{E}] + [\mathrm{ES}]$

$$\Rightarrow [\mathrm{ES}] = \frac{[\mathrm{E}][\mathrm{S}]}{K_m} = \frac{\Big([\mathrm{E}]_{tot} - [\mathrm{ES}]\Big)[\mathrm{S}]}{K_m}$$

$$\boxed{\Rightarrow [\mathrm{ES}] = \frac{[\mathrm{E}]_{tot}[\mathrm{S}]}{K_m + [\mathrm{S}]}}$$

We can shortly write v_2 as v:

$$v = \frac{\mathrm{d[P]}}{\mathrm{d}t} = v_2 = k_2[\mathrm{ES}] \quad \text{and} \quad [\mathrm{ES}] = \frac{[\mathrm{E}]_{tot}[\mathrm{S}]}{K_m + [\mathrm{S}]}$$

$$\Rightarrow v = \frac{\mathrm{d[P]}}{\mathrm{d}t} = \frac{k_2[\mathrm{E}]_{tot}[\mathrm{S}]}{K_m + [\mathrm{S}]}.$$

Because the reaction proceeds at its maximum possible rate when $[\mathrm{ES}] = [\mathrm{E}]_{tot}$, i.e. $v_{max} = k_2[\mathrm{E}]_{tot}$. Other way to see it is

$$v_{max} = \lim_{[\mathrm{S}]\to\infty} \frac{k_2[\mathrm{E}]_{tot}[\mathrm{S}]}{K_m + [\mathrm{S}]} = \lim_{[\mathrm{S}]\to\infty} \frac{k_2[\mathrm{E}]_{tot}}{\frac{K_m}{[\mathrm{S}]} + 1} = k_2[\mathrm{E}]_{tot}.$$

The total concentration for the enzyme and the maximum reaction rate are directly proportional to each other.

Now we will have the Michaelis-Menten (M-M) equation:

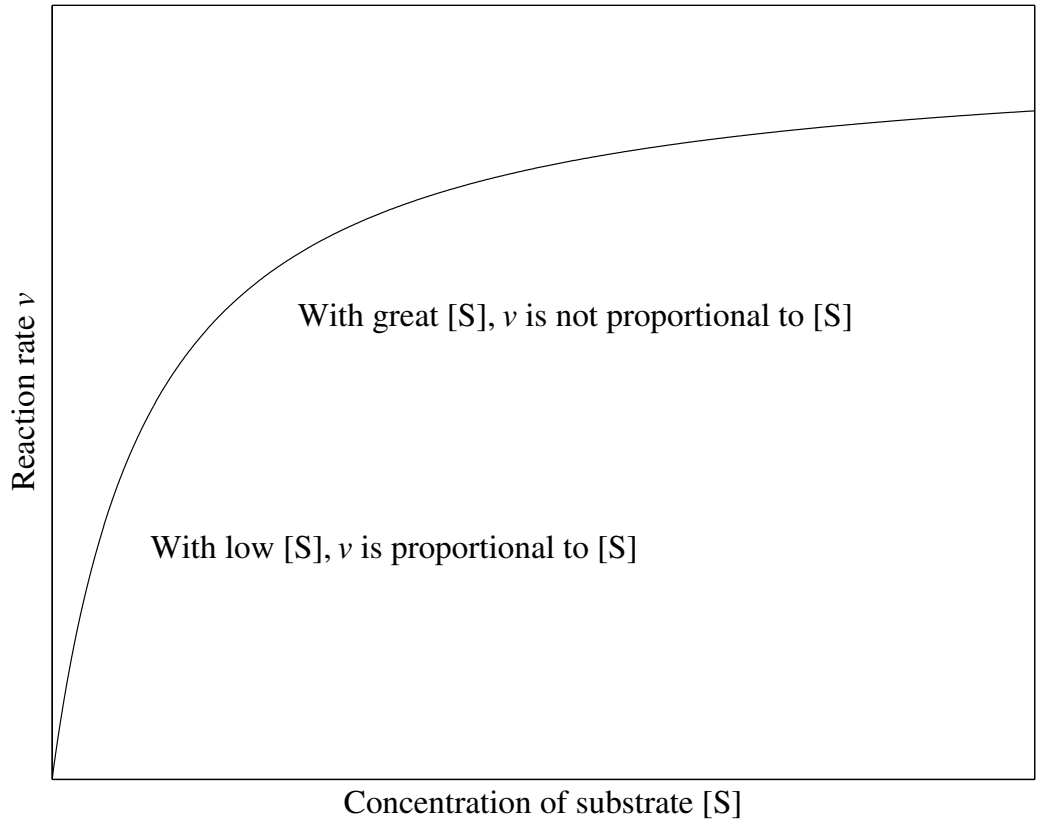
$$v = \frac{v_{max}[\mathrm{S}]}{K_m + [\mathrm{S}]},$$

where $v_{max} = k_2[\mathrm{E}]_{tot}$. M-M model was developed in 1913.
M-M model is still a basic model in enzyme kinetics.
From M-M equation we can see that

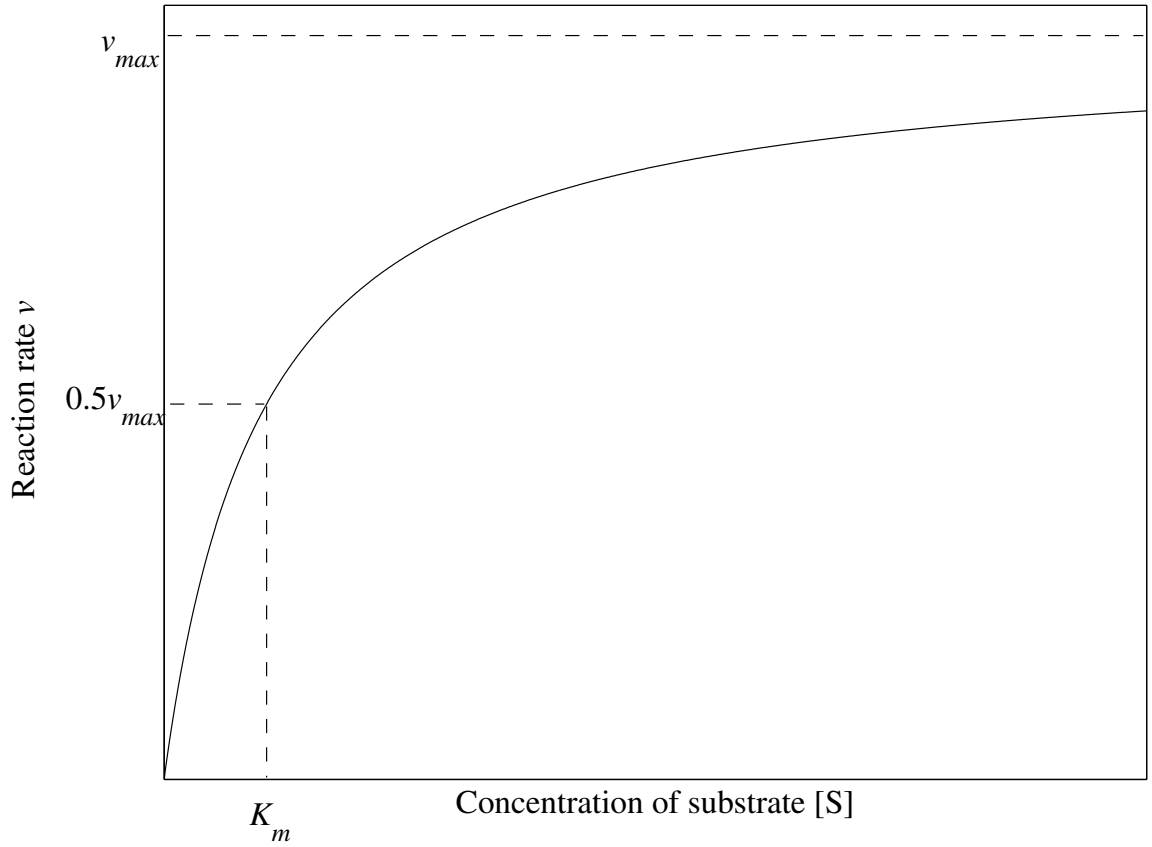
- $[\mathrm{S}] = K_m \Rightarrow v = \frac{1}{2} v_{max}$
- $[\mathrm{S}] \ll K_m \Rightarrow v \approx v_{max} \frac{[\mathrm{S}]}{K_m}$
- $[\mathrm{S}] \gg K_m \Rightarrow v \approx v_{max}$

When we are modeling steady state, we have equations only for [P] and [S]

$$\frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} = -\frac{\mathrm{d}[\mathrm{S}]}{\mathrm{d}t} = \frac{v_{max}[\mathrm{S}]}{K_m + [\mathrm{S}]}.$$



The figure shows how the rate of product formation depends on [S] when $[E]_{tot}$ is kept constant. At low concentrations of S, the reaction rate depends on [S]. As [S] is increased, the rate does not depend on [S], rather, it eventually reaches a maximum rate v_{max} when all E is in a form ES.



v_{max} is the maximal reaction rate at the concentration of which the substrate saturates the enzyme. The concentration of the substrate [S], where the reaction goes on with a half-maximal reaction rate, is the Michaelis constant K_m.

Multi-stability in Dynamical Systems

- The living systems are characterized with multi-stability, which is vital since provide for adaptability in the changing environment.
- Multi-stability is (co)existence of several stable dynamical regimes in a system.
- An organism with the feature of multi-stable dynamics can undergo *differentiation* and *proliferation*, i.e. qualitative changes can occur due to some reason.
- The differentiation and proliferation are inherent properties of life.
- Can dynamical systems account for that?

Genetic toggle switch

- Genetic switch is characterized by two stable states very much in the same way like any other trigger or switch (light switch, bit of computer memory etc).
- The simple genetic switch was constructed experimentally[1] and can be modeled using the following system of ODE's:

$$\begin{cases} \dfrac{du}{dt} = \dfrac{\alpha}{1+v^n} - u \\ \dfrac{dv}{dt} = \dfrac{\alpha}{1+u^n} - v \end{cases}$$

- The switch comprises two genes whose products mutually repress each other.
- α is a max **transcription** rate and n is Hill-coefficient.

[1] Gardner et al, *Nature*, 2000.

Transcription

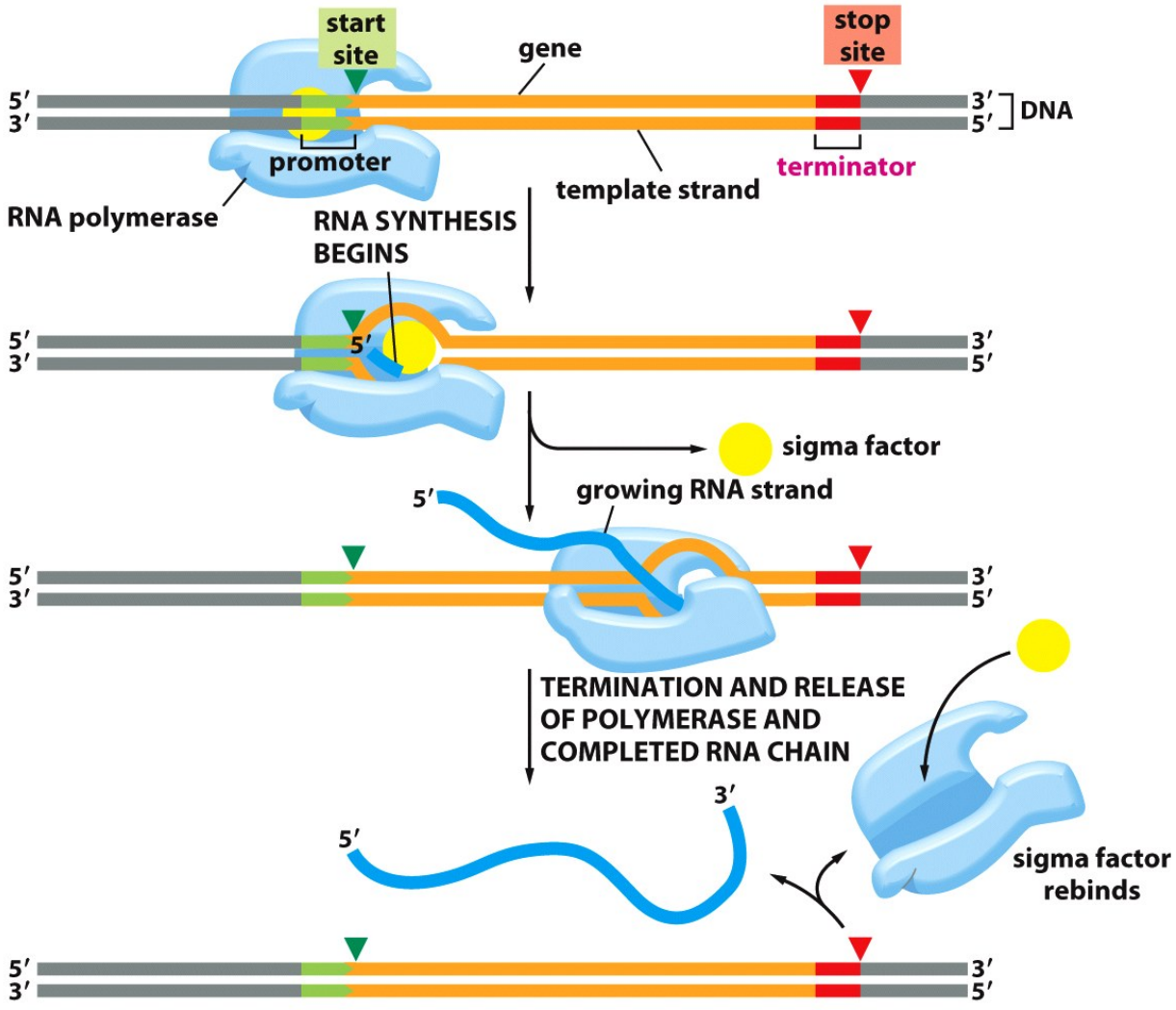


Figure 7-9 Essential Cell Biology 3/e (© Garland Science 2010)

Hill function

- Another type of approximation of molecular interactions.
- Hill function is widely used in molecular genetics modeling.
- Transcription rate = rate constant $\times$ fraction of free promoter sites.
- $\mathrm{n} \cdot \mathrm{T} + \mathrm{D} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{TD}$, where T is a transcription factor (repressor) and D is a DNA region to bind (promoter/operator).
- Fraction of free promoters $= \dfrac{1}{1 + \dfrac{k_1}{k_2}[\mathrm{T}]^{\mathrm{n}}}$
- The general form of the Hill function: $H(x) = \dfrac{1}{1 + x^n}$

Genetic switch: bifurcation diagram

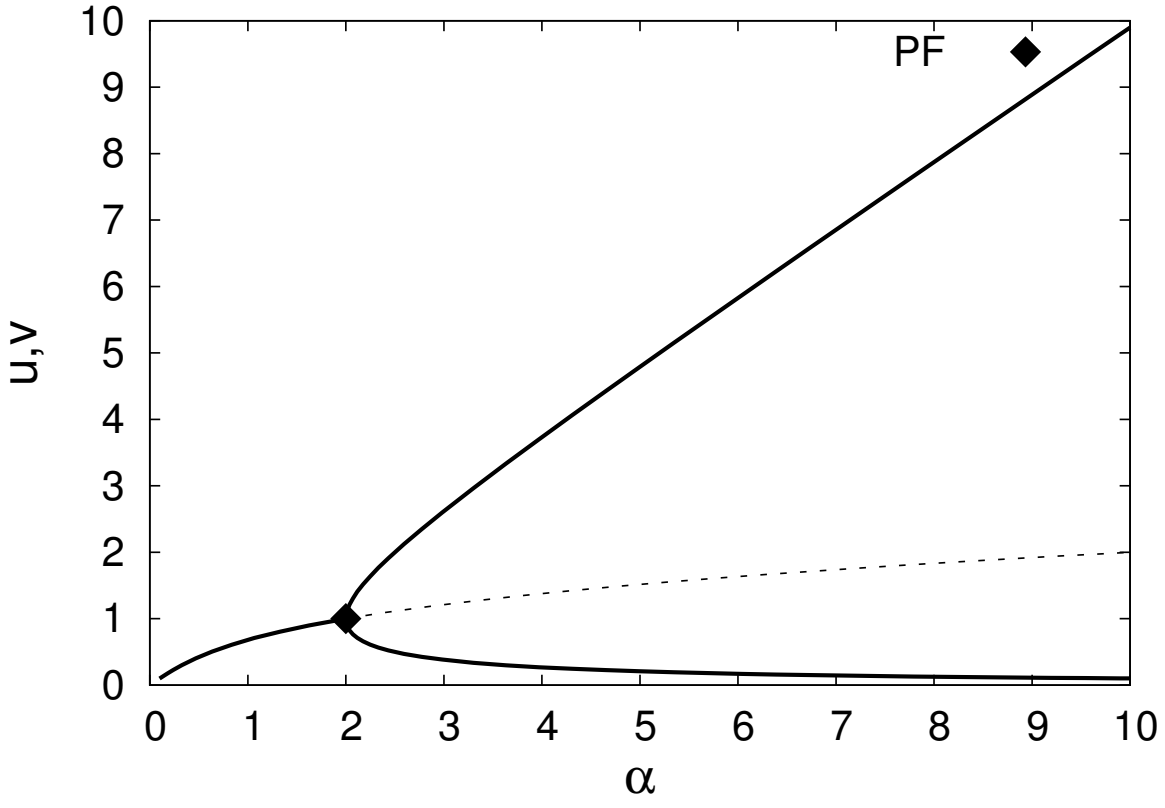
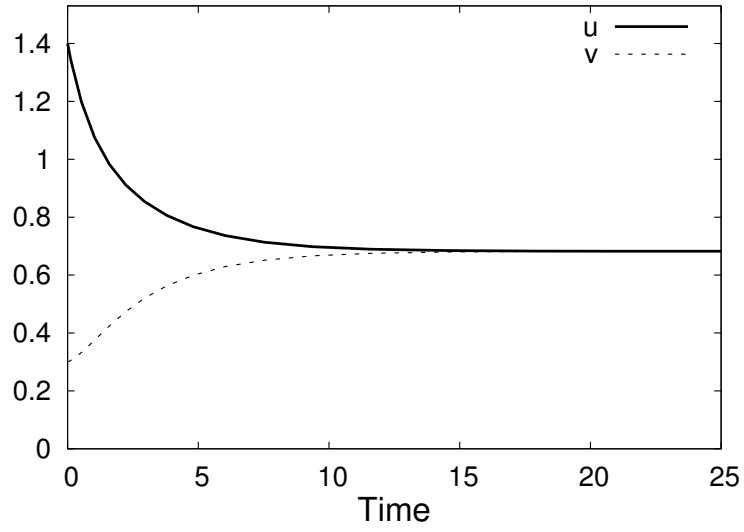
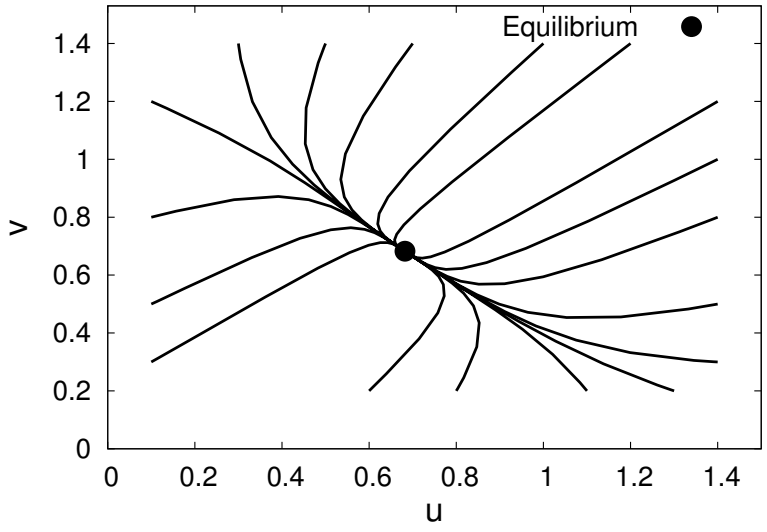


Figure: The bifurcation diagram of toggle switch system for $n = 2$.

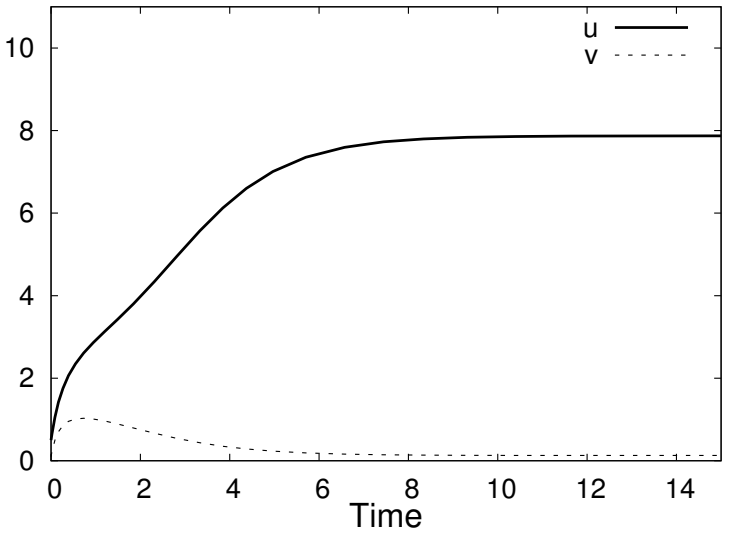
Genetic switch: kinetics

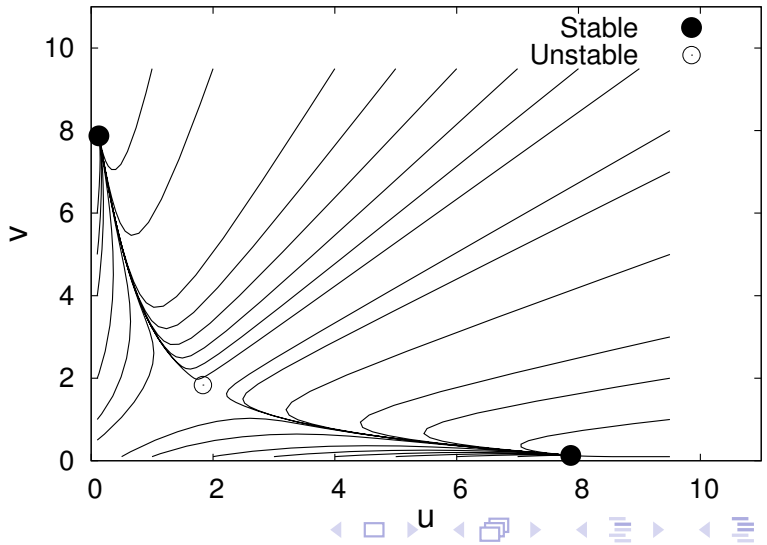
$\alpha = 1, n = 2$





$\alpha = 8, n = 2$





Switching

- How to trigger the switch to change its state?
- First, one can force the system to switch by changing the concentrations (its called *force switching*). Force switching affects the variables of the system.
- Second, it is possible to change the parameters of the system in order to make the phase trajectories move toward the alternative state through consecutive bifurcations changing the number of co-existing steady states and their stability.

Linear analysis of the switch

- Due to the Hill-function it is not easy to do.
- We have to fix some parameters, e.g. $n = 2$.
- General steady state is found from the systems:

$$\begin{cases} u = \dfrac{\alpha}{1 + v^n} \\ v = \dfrac{\alpha}{1 + \left(\frac{\alpha}{1+v^n}\right)^n} \end{cases}$$

- $n = 2$:

Linear analysis of the switch

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- General steady state is found from the systems:

$$\begin{cases} u = \dfrac{\alpha}{1+v^n} \\ v = \dfrac{\alpha}{1+\left(\frac{\alpha}{1+v^n}\right)^n} \end{cases}$$

- $n = 2$:

$$\begin{cases} u = \dfrac{\alpha}{1+v^2} \\ v^5 - \alpha v^4 + 2v^3 - 2\alpha v^2 + (\alpha^2+1)v - \alpha = 0 \end{cases}$$

Two-species population: survives the best

- Volterra-type equations can produce the multi-stable dynamical behavior.
- Consider the following system of equations:

$$\begin{cases} \frac{dx}{dt} = x - xy - ax^2 \\ \frac{dy}{dt} = y - xy - ay^2 \end{cases}$$

Two-species population: survives the best

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- Consider the following system of equations:

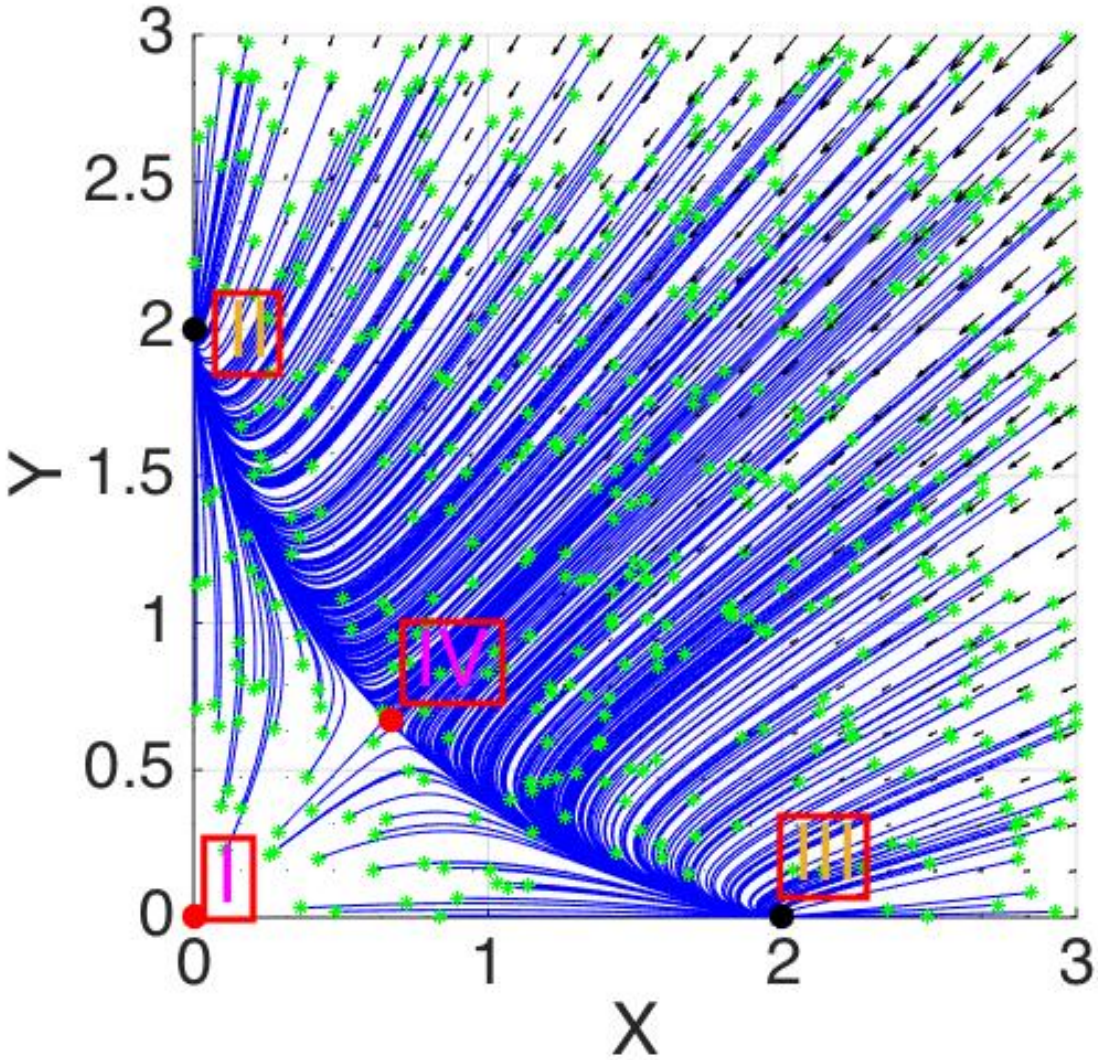
$$\begin{cases} \frac{dx}{dt} = x - xy - ax^2 \\ \frac{dy}{dt} = y - xy - ay^2 \end{cases}$$

- Steady states:

$$\text{i)} \begin{cases} x = 0 \\ y = 0 \end{cases} \wedge \text{ii)} \begin{cases} x = 0 \\ y = \frac{1}{a} \end{cases} \wedge \text{iii)} \begin{cases} x = \frac{1}{a} \\ y = 0 \end{cases} \wedge \text{iv)} \begin{cases} x = \frac{1}{1+a} \\ y = \frac{1}{1+a} \end{cases}$$

- i) and iv) are unstable node and saddle, respectively.
- ii) and iii) are stable nodes.

Two-species population: survives the best



Summary

- The law of Mass Action is based on the physical understanding of molecules *colliding* in space.
- The law gives an apparatus to build ODE-based models of molecular systems.
- Population models are based on the same "collision" approach (individuals meet in space).
- Models of molecular systems are based on certain assumptions (e.g. different time scales).
- These assumptions lead to the standard techniques (Michaelis-Menten, Hill type equations).
- Molecular/population models can account on co-existing states, for example, bi-stable systems with possibility to switch between the states.