Modeling and Simulation in Computational Systems Biology
Lecture 1: Ordinary Differential Equations and the Applications in Modeling

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Summary

• General Introduction for ODEs

• Modeling with ODEs
A Chemically Reacting System

- Molecules of $N$ chemical species $S_1, \ldots, S_N$
  - In a Volume $\Omega$, at temperature $T$
  - Different conformation or excitation levels are considered different species if they behave differently

- $M$ elemental reaction channels $R_1, \ldots, R_M$
  - Each $R_j$ describes a single instantaneous physical event which changes the population of at least one species. For example,

  $A \rightarrow S_i,$
  or $S_i \rightarrow$ something else,
  or $S_i + S_j \rightarrow$ something else.
For each species, assign a state variable, which describes its concentration or population.

Basic Deterministic Assumption:

The state change is proportional to the state of the reactants and time

\[ \Delta X_1(t) = -kX_1(t)X_2(t)\Delta t \]

\[ X_1'(t) = -kX_1(t)X_2(t) \]
Many scientific applications result in the following system of equations

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

Example: Newton’s Motion Law \( F = m\ddot{x} \)

which is called ordinary differential equations (ODEs).

Two types:

- Initial value problem (IVP)
- Boundary value problem (BVP)
There are a few types of ODEs for which we are able to obtain analytic solution and analyze their properties.

• Equation with separable variables

\[ y' = f(x)g(y) \implies \int \frac{dy}{g(y)} = \int f(x)\,dx + C \]

– example

\[ y' = \lambda y \]

• Total differential equations

\[ P(x,y) + Q(x,y)y' = 0 \]

– example

\[ y' = \lambda y \]
When we cannot find analytic solution

- **Existence**
  - Continuous function

- **Uniqueness**
  - Lipschitz condition
    \[ \left\| f(t, y) - f(t, z) \right\| \leq L \left\| y - z \right\| \]

- **Equilibrium State**
- **Stability**
  - Example: linear system \[ y' = Ay \]
  - Lyapunov function
Numerical Solution

• **Multistep Methods**
  – Euler method
  – Adams method
  – BDF method

• **Runge-Kutta Methods**
  – Explicit RK
  – Implicit RK
Softwares for Numerical Solution

- DASSL (BDF method)
- CVODE (BDF method)
- RADAU5 (RK method)
- MATLAB functions
• Degradation

This process can be modeled as

\[ \frac{dx}{dt} = -kx \]

which can be further formulated into reaction rate equations (RREs).
Isomerization

This process can be modeled as

\[ S_1 \xrightarrow{k} S_2 \]

which can be further formulated into RREs

\[ \frac{dx_1}{dt} = -kx_1 \]
\[ \frac{dx_2}{dt} = kx_1 \]
• Reversible Isomerization

This process can be modeled as

$$\frac{dx_1}{dt} = -k_1 x_1 + k_{-1} x_2$$

$$\frac{dx_2}{dt} = k_1 x_1 - k_{-1} x_2$$

which can be further formulated into RREs
One proposal is that there is a kink in the alpha helices of the pore-lining part of the channel. In the closed state, the kink sticks out to keep ions from passing through the channel. After ACh binds, the subunits rotate so that the kinks are no longer pointed towards the center of the pore.

Keep in mind, though, that this is a cartoon. The detailed structural info needed to support or denounce this model isn't available yet.
Simple Chemical Reaction

- Dimerization (Bi-molecular Reaction)

This process can be modeled as

\[ S_1 + S_2 \xrightarrow{k} S_3 \]

which can be further formulated into RREs

\[
\begin{align*}
\frac{dx_1}{dt} &= -kx_1x_2 \\
\frac{dx_2}{dt} &= -kx_1x_2 \\
\frac{dx_3}{dt} &= kx_1x_2
\end{align*}
\]
Bi-molecular Reaction

Na + Cl = Na Cl
Ionic bond

Covalent bond
Simple Chemical Reaction

• Reversible Dimerization

This process can be modeled as

\[
\begin{align*}
S_1 + S_2 & \quad \xrightleftharpoons[k_1]{k_{-1}} \quad S_3 \\
\end{align*}
\]

which can be further formulated into RRE

\[
\begin{align*}
\frac{dx_1}{dt} &= -k_1 x_1 x_2 + k_{-1} x_3 \\
\frac{dx_2}{dt} &= -k_1 x_1 x_2 + k_{-1} x_3 \\
\frac{dx_3}{dt} &= k_1 x_1 x_2 - k_{-1} x_3 \\
\end{align*}
\]
Example of a Simple System

Each icon represents a chemical species. Each arrow represents a chemical reaction that occurs at a certain rate.

For each species, we can write a rate equation, for example:
\[ d[\text{Cyclin}] / dt = \text{synthesis} - \text{degradation} - \text{binding} + \text{dissociation} \]
Example of a Simple System

1. Synthesis

\[ X(t) = [\text{cyclin}] \]
\[ \frac{dX}{dt} = k_1, \quad X(0) = X_0 \]
\[ X(t) = X_0 + k_1 t \]

Estimate \( k_1 \) from the “red” data:

- Interphase arrested
  - Felix et al. (1990)
  - Nature 346:379, Fig. 1

- Metaphase released
  - Tang et al. (1993)
  - EMBO J 12:3427, Fig. 2
Example of a Simple System

2. Degradation

\[
\frac{dX}{dt} = -k_2 X, \quad X(0) = X_0
\]

\[
X(t) = X_0 e^{-k_2 t}
\]

\[
X(t_{1/2}) = \frac{1}{2} X_0 = X_0 e^{-k_2 t_{1/2}} = \frac{1}{e^{k_2 t_{1/2}}} X_0
\]

\[
2 = e^{k_2 t_{1/2}}, \quad \text{or} \quad t_{1/2} = \frac{\ln 2}{k_2} \approx 0.7
\]

Estimate \( k_2 \) from the “blue” and “green” data above. How can it be that cyclin has different half-lives in different phases of the cell cycle?
Example of a Simple System

3. Dimerization

\[ X(t) = [\text{cyclin}], \quad C(t) = [\text{Cdc2}], \quad M(t) = [\text{dimer}], \]

\[ \frac{dM}{dt} = k_3 C(t) X(t) = k_3 (C_0 - M)(X_0 - M), \quad M(0) = 0 \]

\[ M(t) = \frac{C_0 X_0 (1 - e^{-\alpha t})}{C_0 - X_0 e^{-\alpha t}}, \quad \text{where} \quad \alpha = k_3 (C_0 - X_0) \]

Estimate \( k_3 \) from the data below, given that \( C_0 = 100 \) nM.

![Graph showing dimerization over time](image)
Example of a Simple System

4. Synthesis and Degradation

\[
\frac{dX}{dt} = k_1 - k_2 X, \quad X(0) = 0,
\]

\[
X(t) = \frac{k_1}{k_2} \left(1 - e^{-k_2 t}\right)
\]

Note: as \( t \to \infty \), \( X(t) \to \frac{k_1}{k_2} \) (stable steady state)

From your previous estimates of \( k_1 \) and \( k_2 \), estimate the steady state concentrations of cyclin in interphase and late anaphase (end of mitosis).

<table>
<thead>
<tr>
<th>Phase</th>
<th>( k_1 )</th>
<th>( k_2 )</th>
<th>( X_{ss} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interphase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphase</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary

• General Introduction for ODEs

• Modeling with ODEs
“I SAID that population, when unchecked, increased in a geometrical ratio, and subsistence for man in an arithmetical ratio. “

---- Thomas Malthus

Malthus Model:

Assumption: the reproduction rate is proportional to the size of the population

$$\frac{dP}{dt} = kP, \quad k = \text{growth rate per capita}$$

Solution: $P(t) = P(0)e^{kt}$

$k > 0$: exponential growth, \quad $k < 0$: exponential decay
The reproduction rate is proportional to the population

\[ P(t + \Delta t) = P(t) + kP(t)\Delta t \]

Solve it we have

\[ P(t) = P_0 e^{k(t-t_0)} \]

The population in the United States in year 1790 is $3.9 \times 10^6$. The corresponding population in year 1800 is $5.3 \times 10^6$. With a data fitting, we obtain:

\[ P(t) = 3.9 \times 10^6 e^{0.0307(t-1790)} \]
Logistic Population Model

- Developed by Belgian mathematician Pierre Verhulst (1838) in 1838
- The rate of population increase may be limited, i.e., it may depend on population density

\[ P(t + \Delta t) = P(t) + k(P(t))\Delta t \]

where

\[ k(P(t)) = k_0 \left(1 - \frac{P(t)}{P_m}\right)P(t) \]

The solution is

\[ P(t) = P_0 e^{k_0(t-t_0)} \left( \frac{P_m}{P_0 e^{k_0(t-t_0)} + (P_m - P_0)} \right) = \frac{P_m}{1 + \left(\frac{P_m}{P_0} - 1\right)e^{-k_0(t-t_0)}} \]
Logistic Population Model

The solution of the Logistic model

\[ P(t) = P_0 e^{k_0(t-t_0)} \frac{P_m}{P_0 e^{k_0(t-t_0)} + (P_m - P_0)} = \frac{P_m}{1 + \left(\frac{P_m}{P_0} - 1\right)e^{-k_0(t-t_0)}} \]

With a data fitting

\[ P_m = 197 \times 10^6, \quad k_0 = 0.03134 \]
Model of two species (Competition)

Let the population of two species be \( x(t) \) and \( y(t) \), and they compete in the same environment. If there is no competition, the population of \( X \) will satisfy

\[
\dot{x}(t) = r_1 x(t) \left(1 - \frac{x}{N_1}\right)
\]

With the competition,

\[
\dot{x}(t) = r_1 x(t) \left(1 - \frac{x + \alpha y}{N_1}\right)
\]

For another species, there is a similar equation

\[
\dot{y}(t) = r_2 y(t) \left(1 - \frac{y + \beta x}{N_2}\right)
\]

The physical meaning of \( \alpha \) and \( \beta \) can be understood as:

\[
\alpha = \frac{\text{the resource each } X \text{ species consume}}{\text{the resource each } Y \text{ species consume}}.
\]

Thus we have

\[
\alpha \beta = 1
\]
State Dynamics Plot vs Phase Plot

State Dynamics Plot: state vs time,

Phase Plot: the state space, use arrow to represent the tangent vector

The phase plot reveals the geometric property of a dynamic system represented by a pair of ODEs.

\[
\begin{align*}
\dot{x}(t) &= 0.1x(1 - \frac{x + y}{100}) \\
\dot{y}(t) &= 0.1y(1 - \frac{x + y}{100})
\end{align*}
\]
Example: from different initial value, the trajectory follows the direction of the arrows and reaches its equilibrium state.
However, a slight change of parameters make a big difference in phase plot and lead to a different conclusion

\[ \begin{align*}
    \dot{x}(t) &= 0.1x(1 - \frac{x + y}{100}) \\
    \dot{y}(t) &= 0.1y(1 - \frac{x + y}{90})
\end{align*} \]
State Dynamics Plot vs Phase Plot

\[
\begin{cases}
\dot{x}(t) = 0.1x(1 - \frac{x + y}{100}) \\
\dot{y}(t) = 0.1y(1 - \frac{x + y}{90})
\end{cases}
\]
A direct analysis through the phase plot

\[
\begin{align*}
\dot{x}(t) &= r_1 x (1 - \frac{x + \alpha y}{N_1}) \\
\dot{y}(t) &= r_2 y (1 - \frac{\beta x + y}{N_2})
\end{align*}
\]

The sign of the derivatives are decided by two values

\[N_1 - (x + \alpha y) \quad \text{and} \quad \alpha N_2 - (x + \alpha y)\]

If \(N_1 > \alpha N_2\), X species will win.

If \(N_1 < \alpha N_2\), Y species will win.
Model of two species (Predator and Prey)

- Lotka-Volterra Model
- The simplest model of predator-prey interactions developed independently by Lotka (1925) and Volterra (1926)
- Ancona’s observation on Shark’s population during world war I.
Model of two species (Predator and Prey)

Assumption:

- The predator species is totally dependent on a single prey species as its only food supply,
- The prey species has an unlimited food supply, and there is no threat to the prey other than the specific predator.

Let X represent the prey and Y represent the predator, without the predator, the Malthus model can be applied

\[ \dot{x} = ax \]

However, because of the predator, r has to be modified

\[ \dot{x} = (a - by)x \]

For the predator, the situation is just the opposite.

\[ \dot{y} = (-c + dx)y \]

Thus we get the ODEs for this model

\[
\begin{aligned}
\dot{x} &= (a - by)x \\
\dot{y} &= (-c + dx)y
\end{aligned}
\]
Phase Plot Analysis

\[
\begin{align*}
\dot{x} &= (a - by)x \\
\dot{y} &= (-c + dx)y
\end{align*}
\]

There are two corresponding equilibrium points:

(0,0) \quad \text{or} \quad \left(\frac{c}{d}, \frac{a}{b}\right)
Based on example:

\[
\begin{align*}
\dot{x} &= (1 - 0.2y)x \\
\dot{y} &= (-3 + 0.4x)y
\end{align*}
\]
The solution of the LV predator-prey model is

\[ x = \frac{c}{d}, \quad y = \frac{a}{b} \]

where

- \(a\) : the natural reproduction rate for the prey
- \(b\) : the killing rate because of the predator
- \(c\) : the natural death rate for the predator
- \(d\) : the reproduction rate because of the prey

Question: Why the shark ratio increases during world war I?
Parameter Analysis

\[ x^* = \frac{c}{d}, \quad y^* = \frac{a}{b} \]

When fishing is introduced in the model, their effect will be increase the death rate of the predator and decrease the reproduction rate for the prey. Thus

\[ c \rightarrow c + e, \quad a \rightarrow a - e \]
SIR Model (Kermak – McKendrick Model)

S: Susceptible  
I: Infected  
R: Recovered/Removed

\[
\frac{dS}{dt} = -\beta S(t)I(t) \\
\frac{dI}{dt} = \beta S(t)I(t) - \gamma I(t) \\
\frac{dR}{dt} = -\gamma I(t)
\]

\[S(t)+I(t)+R(t)=N = \text{the total population}\]
SIR Model

From the original model, we have

\[
\begin{align*}
\frac{dS}{dt} &= -\beta S(t)I(t) \\
\frac{dI}{dt} &= \beta S(t)I(t) - \gamma I(t) = [\beta S(t) - \gamma]I(t)
\end{align*}
\]

Note that this type of equations is similar to what we’ve seen before.