Dynamic Systems:
Ordinary Differential Equations

Adapted From:
Numerical Methods in Biomedical Engineering
Stanley M. Dunn, Alkis Constantinides, Prabhas V. Moghe
Chapter 7

Kim Ferlin and John Fisher

Ordinary Differential Equations

Classification of ODEs

- Order
  - Order of the highest derivative in the equation
- Linearity
  - Nonlinear if the ODE includes powers of the dependent variable, powers of derivatives, or products
- Homogeneity
  - Homogenous if \( R(t) = 0 \)
- Boundary conditions
  - Can be initial-value or boundary-value
Ordinary Differential Equations

**General form**

\[ b_n(t) \frac{d^n y}{dt^n} + b_{n-1}(t) \frac{d^{n-1} y}{dt^{n-1}} + \cdots + b_1(t) \frac{dy}{dt} + y_0 b_0(t) = R(t) \]

- Constant coefficients when b’s are scalars
- Variable coefficients when b’s are functions of t

**Nonlinear ODEs**

- Must use numerical methods to solve nonlinear ODEs
  - Euler’s Method
    - Forward marching formula
    - The next value of y is obtained from the previous value
    - Move a step of width h in the tangential direction of y
    - Rather inaccurate
      - If h is large, trajectory can deviate quickly

\[ y_{i+1} = y_i + h \frac{dy_i}{dt} + O(h^2) \]
Nonlinear ODEs

- Runge-Kutta methods
  - Based on the concept of weighted trajectories
  - Derivation is complicated
  - Much more accurate
  - MATLAB utilizes the 4th order Runge-Kutta method to estimate ODE solutions with ode45

\[ y_{i+1} = y_i + \sum_{j=1}^{m} w_j k_j \]

MATLAB functions for nonlinear equations

- \([T, Y] = \text{solver}(@\text{name\_func}, tspan, y0)\)
  - solver
  - ode45
  - name\_func
    - Name of the m-file containing the function that evaluates the right-hand side of the differential equation
    - function name\_func (t, y) must return a vector corresponding to y'
  - tspan
    - Vector specifying interval of integration
    - Can hardcode values or create an evenly spaced vector between two points
  - y0
    - Vector of initial conditions
  - \([T, Y]\)
    - Solver returns values in vectors: T and Y
Solution of enzyme catalysis reactions

- An enzyme, $E$, catalyzes the conversion of a substrate, $S$, to form a product, $P$, via the formation of an intermediate complex, $ES$, as shown below:

$$ S + E \xrightleftharpoons{k_1 \, k_{-1}} ES \rightarrow P + E $$

- Apply the law of mass action to this simple enzymatic reaction to obtain the differential equations that describe the dynamics of the reaction. Use the following values of initial conditions and rate constants to integrate the differential equations and plot the time profiles for all variables in the model:
  - Initial conditions: $[S]_0 = 1.0 \mu M$, $[E]_0 = 0.1 \mu M$, $[ES]_0 = 0 \mu M$, $[P]_0 = 0 \mu M$
  - Constants: $k_1 = 0.1(\mu M)^{-1}s^{-1}$, $k_{-1} = 0.1s^{-1}$, $k_2 = 0.3s^{-1}$
  - Determine the time (in seconds) it takes for the reaction to reach 99% conversion of the substrate

MATLAB example using ode45

```matlab
function kferlin_enzyme
clc, clear all, close all

% set up initial conditions given in the problem, any constants, and also % the time span to be integrated over. Since we are looking for 99%, choose % a large time span to begin with and narrow down from there

S = 1; E = 0.1; ES = 0; P = 0;
k1 = 0.1; k_1 = 0.1; k2 = 0.3;
y0 = [S, E, ES, P];
tspan = [1 1000];
```

MATLAB example using ode45

```matlab
%Kim Ferlin
%BIOE 340
%SOLUTION TO ENZYME CATALYSIS REACTIONS

function kferlin_enzyme
clc; clear all; close all

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S = 1; E = 0.1; ES = 0; P = 0;
k1 = 0.1; k_1 = 0.1; k2 = 0.3;
y0 = [S, E, ES, P];
tspan = [1 1000];
```
%Send the initial values, constants, and time span to the integrating
%function. The vector [t, y] will return the solutions from the ode45
%function

[t, y] = ode45(@enzyme, tspan, y0, [], k1, k_1, k2);
n = length(y);

%Calculate the point in time when the reaction reaches 99.9% completion
for i = 1:n
    if y(i,1) <= 0.001*y0(1)
        fprintf('Reaction is 99.9 percent complete at time = %4.0f seconds', t(i));
        break
    end
end

MATLAB example using ode45

%Plot concentration profiles for all variables
plot(t, y(:,1)) %substrate
hold on
plot(t, y(:,4), 'k') %product
xlabel('Time (s)')
ylabel('Concentration (\textmu{}M)')
title('Concentration Profiles of Substrate and Product')
legend('S','P')
set(legend, 'Location', 'East')
figure
plot(t, y(:,2), 'r') %enzyme
hold on
plot(t, y(:,3), '-.') %enzyme-substrate complex
xlabel('Time (s)')
ylabel('Concentration (\textmu{}M)')
title('Concentration Profiles of Enzyme and Enzyme-Substrate')
legend('E','ES')
set(legend, 'Location', 'East')
MATLAB example using ode45

Results

Reaction is 99.9 percent complete at time = 961 seconds >>

Concentration Profiles of Substrate and Product

%Function that is created to solve the ODE.
%This function must either: (a) go into a separate m-file that is saved
%with the name of the function, or
%(b) go at the end of the same m-file. To do
%this you must use the "@" symbol before the
%name of the function in the calling line

function dy = enzyme(t, y, k1, k_1, k2)

%Define the variables that were sent within the y0 vector
S = y(1);
E = y(2);
ES = y(3);
P = y(4);

dy = [-k1*S*E + k_1*ES
     -k1*S*E + k_1*ES + k2*ES
     k1*S*E - k_1*ES - k2*ES
     k2*ES];
end
end
MATLAB example using ode45

Hodgkin-Huxley Model

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Lab 5 Objectives

- Gain basic understanding of action potential
- Use Hodgkin-Huxley model to simulate cell electrical stimulation and action potentials
- Modify a MATLAB model to investigate a physiological event

Electrochemical Composition of Cells

- Cells have negative potential with respect to extracellular fluid (~-60mV)
- Maintaining resting membrane potential is vital to cell
- Specific concentration of ions within the cell maintain this potential
- These concentrations are maintained through ionic pumps
  - Including active transport mechanisms

<table>
<thead>
<tr>
<th>Ion</th>
<th>Extracellular</th>
<th>Intracellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>142 mEq/l</td>
<td>10 mEq/l</td>
</tr>
<tr>
<td>K⁺</td>
<td>4 mEq/l</td>
<td>140 mEq/l</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>2.4 mEq/l</td>
<td>0.0001 mEq/l</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>1.2 mEq/l</td>
<td>58 mEq/l</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>103 mEq/l</td>
<td>4 mEq/l</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>28 mEq/l</td>
<td>10 mEq/l</td>
</tr>
<tr>
<td>Phosphates</td>
<td>4 mEq/l</td>
<td>75 mEq/l</td>
</tr>
<tr>
<td>SO₄²⁻</td>
<td>1 mEq/l</td>
<td>2 mEq/l</td>
</tr>
<tr>
<td>Glucose</td>
<td>90 mg/dl</td>
<td>0 to 20 mg/dl</td>
</tr>
<tr>
<td>Amino Acids</td>
<td>30 mg/dl</td>
<td>200 mg/dl</td>
</tr>
<tr>
<td>Proteins</td>
<td>2000 mg/dl</td>
<td>16000 mg/dl</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>500 mg/dl</td>
<td>2 to 95 mg/dl</td>
</tr>
<tr>
<td>PO₂</td>
<td>35 mmHg</td>
<td>20 mmHg</td>
</tr>
<tr>
<td>PCO₂</td>
<td>46 mmHg</td>
<td>50 mmHg</td>
</tr>
<tr>
<td>pH</td>
<td>7.4</td>
<td>7.0</td>
</tr>
</tbody>
</table>
Action Potential

- Cell signals are propagated through the action potential

Hodgkin-Huxley Model

- The Hodgkin Huxley Model simulates cellular electrical simulation and action potentials
- Circuit Diagram Model

\[ C_m = \text{membrane capacitance} \]
\[ G_{Na} = \text{sodium conductance} \]
\[ G_K = \text{potassium conductance} \]
\[ G_L = \text{leak conductance} \]
\[ E_{Na} = \text{sodium Nernst potential} \]
\[ E_K = \text{potassium Nernst potential} \]
\[ E_L = \text{leak Nernst potential} \]
\[ V_m = \text{membrane voltage} \]
\[ C_m = \text{membrane capacitance} \]
\[ I_{Na} = \text{sodium current} \]
\[ I_K = \text{potassium current} \]
\[ I_L = \text{leak current} \]
Hodgkin-Huxley Model

- Analyze model using basic electrical circuit theory to get voltage equation
- Ohm’s Law: $I = GV$
- $v = V - V_{rest}$
- So the dynamic current can be written

$$I(t) = g_v(t)(V - E_v)$$

- Adding the currents the current voltage relationship for the cell can be written

$$C_m \frac{dV}{dt} = -g_{Na}(v - E_{Na}) - g_k(v - E_k) - g_L(v - E_L) + I_{app}$$

Hodgkin-Huxley Model

- Conductance of potassium and sodium also modeled using Hodgkin-Huxley
- Potassium Conductance Model

$$g_K(t, v) = \overline{g}_K n^4(t, v)$$

- Where
  - $\overline{g}_K$ is the maximum potassium conductance
  - $n$ is a proportionality constant that represents the probability that one of the four subunits of the potassium channel is open
    - Function of $t$ and $v$ ($V - V_{rest}$)
    - Obey first order kinetics

$$\frac{dn(t, v)}{dt} = \alpha_n(v)(1 - n) - \beta_n(v)n$$
Hodgkin-Huxley Model

- Sodium Conductance Model

\[ g_{Na}(t, v) = g_{Na} m^3 h(t, v) \]

Where

- \( m \) is activation parameter

\[ \frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \]

- \( h \) is inactivation parameter
  - Both probability constants like \( n \)
  - Probability that sodium channel is open is approximately \( m^n h \)

\[ \frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h \]

Table of Constants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane Resting Potential</td>
<td>-90 mV</td>
</tr>
<tr>
<td>Maximum Conductance (K+)</td>
<td>36 mS/cm²</td>
</tr>
<tr>
<td>Maximum Conductance (Na+)</td>
<td>120 mS/cm²</td>
</tr>
<tr>
<td>Leak Conductance</td>
<td>0.3 mS/cm²</td>
</tr>
<tr>
<td>Nernst Potential (leak)</td>
<td>10.6mV</td>
</tr>
<tr>
<td>Nernst Potential (K+)</td>
<td>-12 mV</td>
</tr>
<tr>
<td>Nernst Potential (Na+)</td>
<td>115 mV</td>
</tr>
<tr>
<td>Membrane Capacitance</td>
<td>1 uF/cm²</td>
</tr>
<tr>
<td>V initial value</td>
<td>-82 mV</td>
</tr>
</tbody>
</table>
Assignment

- Create an m-file from the Hodgkin Huxley code posted on the website
  - Label each line with a short comment (<20 words) describing the purpose of the line
- Create a plotting regime that displays:
  - Time profiles of
    - $\nu$
    - gating variables $n$, $m$, and $h$
    - conductance $g_k$ and $g_{na}$
  - Steady-state values of
    - time constants
    - gating variables (as functions of potential voltages)
- The completed m-file should be attached in the appendix of your lab report
- Modify the m-file to investigate a physiological event
- Write a full lab report reporting your findings

- Turn in a paper copy of your lab report in class on October 25, 2012 and an electronic copy of your m-file(s) to kimberly.ferlin@gmail.com by 3:30pm on 10/25/12

Possible Investigation Topics

- What effect does the resting potential ($V_r$) have on the action potential? Is there a range of $V_r$ that must be maintained in order to elicit an action potential?
- What effect do the maximum Na+ and K+ conductance, $g_k$ and $g_{na}$, have on an action potential? What happens when either of these conductances is set to zero?
- Investigate the influence of the Nernst potential for each ion. What happens if the Nernst potential for Na+ and K+ are switched?
- Investigate the influence of the initial gating parameters, $n$. What happens when they approach zero? What happens when $m$ exceeds $h$?
Lab Report

• A full lab report is required for this assignment
• Evaluation will be primarily based on your ability to formulate an hypothesis, develop and experiment to test the hypothesis and to discuss the finding of your experiment
• Include the following sections
  • Title Page
  • Abstract
  • Introduction
  • Experimental
  • Results
  • Discussion
  • Conclusions
  • References
  • Tables and Figures
  • Appendix