Nonlinear Regression Programs

Model Specification
Program Set-up

Objectives

• To understand the steps required to input a model into various programs
  – Boomer, SAAM II, WinNONLIN, and ADAPT II
• To understand how to complete a nonlinear regression problem using each of these programs

General Approaches

• Draw/Sketch Diagram of Model
• Derive Equation - Differential or Integrated
• Define Model in the Program
  – Selection of Model from Library (WinNONLIN)
  – Selection of Parameters of Model (Boomer, SAAM II)
  – Describe Model using Computer Language (ADAPT II, WinNONLIN, SAAM II)
Using Boomer - Macintosh/Windows

• Draw Diagram of the Model

![Diagram]

Boomer - Define the Model

<table>
<thead>
<tr>
<th>Parameter Name</th>
<th>Parameter Type</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>1 Initial Value</td>
<td>Into 1</td>
</tr>
<tr>
<td>kel</td>
<td>2 First Order</td>
<td>From 1 To 0</td>
</tr>
<tr>
<td>V</td>
<td>18 Volume</td>
<td>From 1 To 1</td>
</tr>
</tbody>
</table>

Boomer - Running the Problem

• Start Boomer
• Select Input/Output option and Normal Fitting
• Describe Model
• Select Algorithms
• Enter Data
• Run the Analysis
• Read the Output
Using SAAM II - Macintosh/Windows

- Graphical User Interface to Define the Model by Parameter Selection

SAAM II - Running the Problem

- Start SAAM II
- Describe Model
- Describe Experiment
- Enter Data
- Run the Analysis
- Read the Output
SAAM II - Model Defined

Define Model - Experiment

Add Data and Parameter Estimates
Using WinNONLIN Pro - Windows

- Model Selected from Library

<table>
<thead>
<tr>
<th>Model</th>
<th>Input</th>
<th># Compartment</th>
<th>micro/macro Lag</th>
<th>Elimin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>iv-bolus</td>
<td>1</td>
<td>-</td>
<td>no</td>
</tr>
<tr>
<td>2</td>
<td>iv-infus</td>
<td>1</td>
<td>-</td>
<td>no</td>
</tr>
<tr>
<td>3</td>
<td>1st ord</td>
<td>1</td>
<td>-</td>
<td>no</td>
</tr>
<tr>
<td>4</td>
<td>1st ord</td>
<td>1</td>
<td>-</td>
<td>yes</td>
</tr>
<tr>
<td>5</td>
<td>1st ord</td>
<td>1</td>
<td>k10=k01</td>
<td>no</td>
</tr>
<tr>
<td>6</td>
<td>1st ord</td>
<td>1</td>
<td>k10=k01</td>
<td>yes</td>
</tr>
<tr>
<td>7</td>
<td>iv-bolus</td>
<td>2</td>
<td>micro</td>
<td>no</td>
</tr>
</tbody>
</table>

WinNONLIN Pro - Running the Problem

- Start WinNONLIN Pro
- Enter Data
- Select Model
- Enter Parameters
- Run the Analysis
- Read the Output

WinNONLIN Pro - Enter Data
Select Model from Library

WinNONLIN Pro - Data Defined

Add Parameter Estimates and Dose
Using ADAPT II - VAX VMS / Windows

- Model Defined by Subroutine
  
  ```c
  C-------- inDIFFEQ ---------------C
  C 1. Enter Differential Equations Below
  C   (e.g. XP(1) = -P(1)*X(1) ) C
  C 2.--------------------------------------------------------C
  xp(1) = -p(1)*x(1)
  C 3. Enter Output Equations Below   (e.g. Y(1) = X(1)/P(2) )
  C--------------------------------------------------------C
  Y(1) = x(1)/p(2)
  ```

ADAPT II - Running the Problem

- Set up class directory, copy files
- Start ADAPT II
- Enter Options
- Edit Model (in subroutine as needed)
- Enter Doses, Data, and Parameters
- Run the Analysis
- Read the Output

ADAPT II - Dose Information Entered

----- SUPPLY MODEL INPUT INFORMATION ----- 

Enter the number of model inputs: 0
Enter the number of bolus inputs: 1
Enter the compartment number for each bolus input (e.g. 1,3,...): 1
Enter the number of input event times: 1
For each input event enter as required:
  Time  Value for all Inputs
  Event  Units,  B(1)
  1.  0.250
ADAPT II - Enter Data

----- SUPPLY MODEL OUTPUT INFORMATION -----

Enter the number of model output equations: 1
Enter the number of observation times: 5
For each observation enter as required:

<table>
<thead>
<tr>
<th>Observation</th>
<th>Units</th>
<th>Measured Value for Each Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2,5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3,2,6</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5,0,9</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6,0,56</td>
<td></td>
</tr>
</tbody>
</table>

Add Parameter Estimates

----- INITIALIZE ESTIMATION PROCEDURE -----

Read parameter values from a file (Y/N)? n
Enter initial values for parameters & specify those to be estimated:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (Y/N)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>kel</td>
<td>.5,y</td>
</tr>
<tr>
<td>V</td>
<td>20,y</td>
</tr>
<tr>
<td>IC(1)</td>
<td>0,n</td>
</tr>
</tbody>
</table>

Comparison of Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Boomer</th>
<th>SAAM</th>
<th>WinNONLIN</th>
<th>ADAPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>kel</td>
<td>0.5407</td>
<td>0.5406</td>
<td>0.5406</td>
<td>0.5407</td>
</tr>
<tr>
<td>V</td>
<td>18.06</td>
<td>18.07</td>
<td>18.07</td>
<td>18.06</td>
</tr>
</tbody>
</table>