Numerical Integration

- Objectives:
  - Understand the process of Numerical Integration
  - Understand some of the Numerical Integration methods (algorithms)
  - Consider the Advantages and Disadvantages of some these methods

Numerical Integration Methods

- Point-slope (Euler’s) Method
  - Step-Size
- Runge-Kutta Methods
- RKF45 Method
- Predictor-Corrector Method
- Gear’s Method
Simple Numerical Integration

\[ \frac{dX_1}{dt} = -k_1 X_1 \]

Point-Slope (Euler’s) Method

- Point-Slope Method
- Point
  - Initial Value - \( X_1(0) \)
- Slope
  - Differential Equation - \( k_1 X_1 \)

The Equation \( \frac{dX_1}{dt} = -k_1 X_1 \)

An Example - Euler’s Method

- Choose stepsize (ss) = 0.1

\[ X_1 \text{(new)} = X_1 \text{(old)} + \text{slope} \times \text{ss} \]
\[ = X_1 \text{(old)} + (-k_1 \times X_1 \text{(old)}) \times \text{ss} \]
\[ = 100 + (-0.25 \times 100) \times 0.1 \]
\[ = 100 - 2.5 = 97.5 \]

\( X_1(0) = 100 \quad k_1 = 0.25 \)
An Example - Euler’s Method

<table>
<thead>
<tr>
<th>Time</th>
<th>ΔX₁</th>
<th>X₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>0.1</td>
<td>-2.50</td>
<td>97.50</td>
</tr>
<tr>
<td>0.2</td>
<td>-2.44</td>
<td>95.06</td>
</tr>
<tr>
<td>0.3</td>
<td>-2.38</td>
<td>92.68</td>
</tr>
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<td>0.4</td>
<td>-2.32</td>
<td>90.36</td>
</tr>
<tr>
<td>0.5</td>
<td>-2.26</td>
<td>88.10</td>
</tr>
</tbody>
</table>

X₀(0) = 100  k₁ = 0.25

Euler’s Method

\[ \frac{dC_p}{dt} = -k_e C_p \]

\[ t_i = t_{i-1} + \Delta t \]

\[ C_{p_i} = C_{p_{i-1}} + \frac{dC_p}{dt} \Delta t \]

Euler’s Method

Another Example

- \( C_{p_0} \) = 100 mg/L and \( k_e \) = 0.3 hr⁻¹

<table>
<thead>
<tr>
<th>Stepsize</th>
<th>Numerical</th>
<th>Analytical</th>
<th>% Error</th>
<th>Number of Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70.0</td>
<td>74.08</td>
<td>5.51</td>
<td>1</td>
</tr>
<tr>
<td>0.5</td>
<td>85.0</td>
<td>86.07</td>
<td>1.24</td>
<td>2</td>
</tr>
<tr>
<td>0.25</td>
<td>92.5</td>
<td>92.77</td>
<td>0.30</td>
<td>4</td>
</tr>
<tr>
<td>0.1</td>
<td>97.0</td>
<td>97.04</td>
<td>0.05</td>
<td>10</td>
</tr>
</tbody>
</table>
Euler’s Method - Step Size

Euler’s Method
- Simple mathematically
- Requires small step size for accuracy

Runge-Kutta Method
- Fourth Order

\[
\begin{align*}
C_0 &= C_0 + \frac{1}{6} \left[ k_1 + 2k_2 + 2k_3 + k_4 \right] \\
k_1 &= \Delta t \cdot f(t_0, C_0) = -k_0 + C_0 \cdot \Delta t \\
k_2 &= \Delta t \cdot f(t_0 + \frac{\Delta t}{2}, C_0 + \frac{k_1}{2}) \\
k_3 &= \Delta t \cdot f(t_0 + \frac{\Delta t}{2}, C_0 + \frac{k_3}{2}) \\
k_4 &= \Delta t \cdot f(t_0 + \Delta t, C_0 + k_4)
\end{align*}
\]
Runge-Kutta Method

- Fourth Order

\[ \text{Cp}_0 = 100 \text{ mg/L and } \text{k}_e = 0.3 \text{ hr}^{-1} \]

- More Accurate with Four Evaluations per step
- No Automatic Stepsize Control

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<tr>
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<th>Numerical</th>
<th>Analytical</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74.084</td>
<td>74.082</td>
</tr>
<tr>
<td>0.5</td>
<td>86.071</td>
<td>86.071</td>
</tr>
<tr>
<td>0.25</td>
<td>92.774</td>
<td>92.774</td>
</tr>
<tr>
<td>0.1</td>
<td>97.044</td>
<td>97.045</td>
</tr>
</tbody>
</table>

Runge-Kutta Fehlberg

- RKF45
  - Fifth Evaluation used to give Automatic Stepsize Adjustment
  - Very Efficient for Typical Pharmacokinetic Systems
  - Use this Method as default with Boomer
Predictor-Corrector Methods

- Adam’s Method and variations
  - Larger Step size Possible
  - More Complex Calculations

Predictor-Corrector Method

- Adam’s Method

![Graph showing predictor-corrector method]

Predictor-Corrector

- Gear’s Method
  - Very Efficient for ‘Stiff’ Systems
  - ‘Stiff’ Systems include Both Very Fast and Very Slow Processes (Rate constants)
  - Difference between Fastest and Slowest Extreme

\[
\frac{k_{\text{fastest}}}{k_{\text{slowest}}} \geq 500
\]
Numerical Integration

• Comparison between Numerical Integration Methods

<table>
<thead>
<tr>
<th>Runge-Kutta</th>
<th>RKF45</th>
<th>Adam's</th>
<th>Gear's</th>
</tr>
</thead>
<tbody>
<tr>
<td>ka/kel 1.0</td>
<td>15</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ka/kel 10</td>
<td>38</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>ka/kel 100</td>
<td>174</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>ka/kel 1000</td>
<td>59</td>
<td>113</td>
<td>4</td>
</tr>
</tbody>
</table>

Numerical Integration

• Boomer
  – RK, RKF45, Adams’, Gear’s
• SAAM II
  – Rosenbrock (Stiff), RKF45, Pade (Special)
• WinNONLIN
• ADAPT
  – LSODA (Switches between Adam’s and Gear’s Method)