Numerical Integration

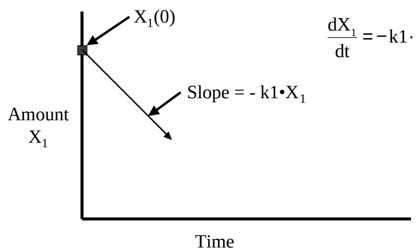
Numerical Integration

- 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



$$\frac{dX_1}{dt} = -k1 \cdot X_1$$

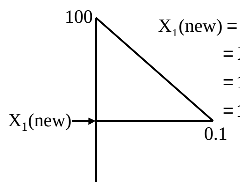
Point-Slope (Euler's) Method

- Point-Slope Method
- Point
  - Initial Value - $X_1(0)$
- Slope
  - Differential Equation - $k1 \cdot X_1$

The Equation $\frac{dX_1}{dt} = -k1 \cdot X_1$

An Example - Euler's Method

- Choose stepsize (ss) = 0.1



$$\begin{aligned} X_1(\text{new}) &= X_1(\text{old}) + \text{slope} \cdot \text{ss} \\ &= X_1(\text{old}) + (-k1 \cdot X_1(\text{old})) \cdot \text{ss} \\ &= 100 + (-0.25 \cdot 100) \cdot 0.1 \\ &= 100 - 2.5 = 97.5 \end{aligned}$$

$X_1(0) = 100$ $k1 = 0.25$

An Example - Euler's Method

Time	ΔX_1	X_1
0.0		100
0.1	-2.50	97.50
0.2	-2.44	95.06
0.3	-2.38	92.68
0.4	-2.32	90.36
0.5	-2.26	88.10

$X_1(0) = 100$ k1 = 0.25

Euler's Method

$$\frac{dCp}{dt} = -kel \cdot Cp$$

$$t_1 = t_0 + \Delta t$$

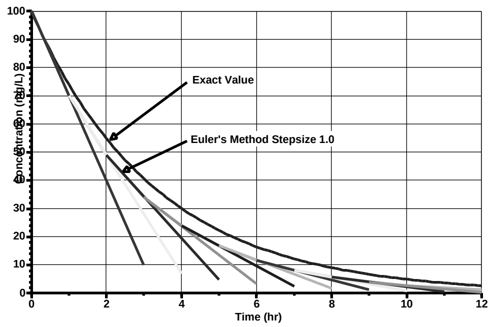
$$Cp_1 = Cp_0 + \frac{dCp}{dt} \cdot \Delta t$$

Euler's Method

- Another Example
  - Cp_0 100 mg/L and kel = 0.3 hr^{-1}

Stepsize	Numerical	Analytical	% Error	Number of Steps
1	70.0	74.08	5.51	1
0.5	85.0	86.07	1.24	2
0.25	92.5	92.77	0.30	4
0.1	97.0	97.04	0.05	10

Euler's Method - Step Size



Euler's Method

- Simple mathematically
- Requires small step size for accuracy

Runge-Kutta Method

- Fourth Order

$$C_1 = C_0 + \frac{1}{6} \cdot \left| k_1 + 2k_2 + 2k_3 + k_4 \right|$$

$$k_1 = \Delta t \cdot f(t_0, C_0) = -kel \cdot C_0 \cdot \Delta t$$

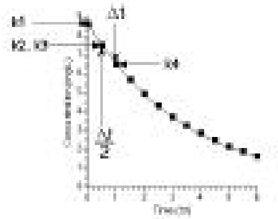
$$k_2 = \Delta t \cdot f\left(t_0 + \frac{\Delta t}{2}, C_0 + \frac{k_1}{2}\right)$$

$$k_3 = \Delta t \cdot f\left(t_0 + \frac{\Delta t}{2}, C_0 + \frac{k_2}{2}\right)$$

$$k_4 = \Delta t \cdot f(t_0 + \Delta t, C_0 + k_3)$$

Runge-Kutta Method

- Fourth Order



Runge-Kutta Method

- Cp_0 = 100 mg/L and kel = 0.3 hr^{-1}

Stepsize	Numerical	Analytical
1	74.084	74.082
0.5	86.071	86.071
0.25	92.774	92.774
0.1	97.044	97.045

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

Runge Kutta Fehlberg

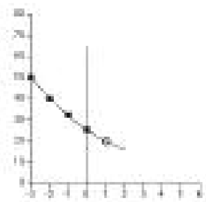
- RKF45
  - Fifth Evaluation used to give Automatic Stepsize Adjustment
  - Very Efficient for Typical Pharmacokinetic Systems
  - Use this Method as default with Boomer

Predictor-Corrector Methods

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

Predictor-Corrector Method

- Adam’s Method



Predictor-Corrector

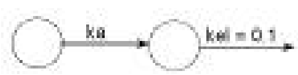
- Gear’s Method
  - Very Efficient for ‘Stiff’ Systems
  - ‘Stiff’ Systems include Both Very Fast and Very Slow Processes (Rate constants)
  - Difference between Fastest and Slowest Extreme

$$\frac{k_{fastest}}{k_{slowest}} \geq 500$$

Numerical Integration

- Comparison between Numerical Integration Methods

	Runge Kutta	RKF45	Adam's	Gear's
ka/kel 1.0	15	2	2	2
ka/kel 10	38	2	3	4
ka/kel 100	174	7	14	4
ka/kel 1000	*	50	110	4



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)