Modelling
Why Model?

Koala, a sluggish, tailless, grey, furry, arboreal marsupial: Marquarie Dictionary

Modelling - Objectives

- Understand the reasons why models are developed and used
- Understand how models can summarise or ‘compress’ data
- Understand how models can be used to study pharmacokinetic mechanisms
- Understand how models can be used to predict concentrations or dosage regimens

Why Model?

- Summarise Data
  – Model and Parameters
- Explore Mechanisms
  – Correlate Parameters with Clinical Correlates
- Make Predictions
  – Calculate Dosage Regimens

Data Compression

Time (hr)	Concentration (mg/L)
1.0	18.6
2.0	15.6
4.0	12.3
8.0	10.1
12.0	7.6
24.0	3.2

Subj #1 Wt 76 kg Dose 200 mg

Time (hr)	Concentration (mg/L)
1.0	19.3
2.0	15.8
4.0	11.5
8.0	9.8
12.0	6.5
24.0	2.1

Subj #2 Wt 74 kg Dose 200 mg

Time (hr)	Concentration (mg/L)
1.0	19.3
2.0	14.5
4.0	12.5
8.0	10.3
12.0	6.9
24.0	3.5

Subj #3 Wt 54 kg Dose 150 mg

Time (hr)	Concentration (mg/L)
1.0	18.9
2.0	14.6
4.0	12.7
8.0	10.3
12.0	7.5
24.0	3.3

Subj #4 Wt 58 kg Dose 150 mg

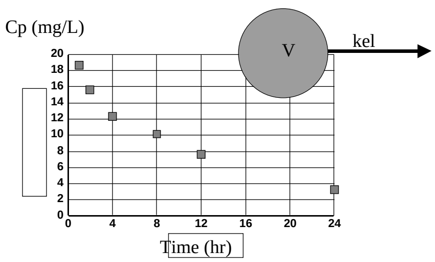
Time (hr)	Concentration (mg/L)
1.0	19.5
2.0	14.7
4.0	12.3
8.0	10.7
12.0	6.9
24.0	4.1

Subj #5 Wt 94 kg Dose 250 mg

Time (hr)	Concentration (mg/L)
1.0	18.7
2.0	14.9
4.0	12.3
8.0	10.3
12.0	7.9
24.0	3.5

Subj #6 Wt 82 kg Dose 225 mg

Data Compression



Data Compression

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

$$Cp = \frac{Dose}{V} \bullet e^{-kel \bullet t}$$

$$kel = 0.076 \pm 0.009 hr^{-1}$$

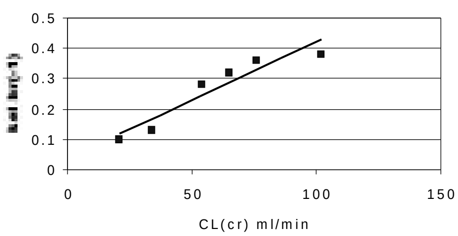
$$V = 10.7 \pm 2.3 L$$

$$V = 0.147 \pm 0.006 L/kg$$

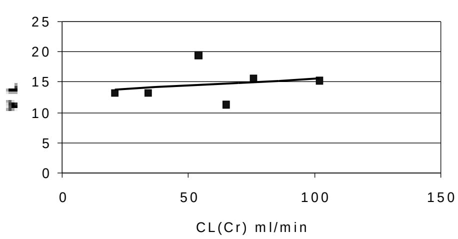
Explore Mechanisms

Subject	Wt.	Sex	CL_{Cr}	Dose	kel	V
1	75	F	102	200	0.38	15.2
2	68	F	34	175	0.13	13.2
3	65	F	21	175	0.10	13.1
4	98	M	54	250	0.28	19.4
5	56	M	65	150	0.32	11.2
6	76	M	76	200	0.36	15.5
…	…	…	…	…	…	…
…	…	…	…	…	…	…

Explore Mechanism



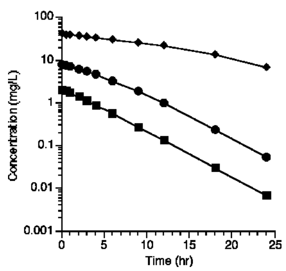
Explore Mechanisms



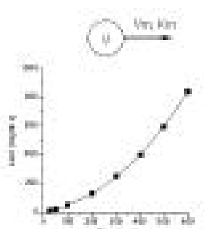
Explore Mechanisms

Dose 25 mg		Dose 100 mg		Dose 500 mg	
Time (hr)	Concentration (mg/L)	Time (hr)	Concentration (mg/L)	Time (hr)	Concentration (mg/L)
0.0	2.03	0.0	8.13	0.0	40.6
0.5	1.83	0.5	7.62	0.5	39.8
1.0	1.65	1.0	7.14	1.0	38.9
2.0	1.34	2.0	6.22	2.0	37.2
3.0	1.07	3.0	5.38	3.0	35.6
4.0	0.86	4.0	4.61	4.0	33.9
6.0	0.54	6.0	3.29	6.0	30.7
9.0	0.26	9.0	1.85	9.0	25.9
12.0	0.12	12.0	0.97	12.0	21.4
18.0	0.02	18.0	0.23	18.0	13.2
24.0	0.01	24.0	0.05	24.0	6.6

Explore Mechanism



Explore Mechanism



Make Predictions

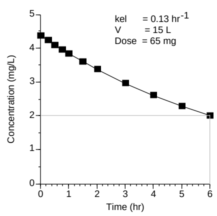
- Dose required to give to Cp = 2 mg/L at 6 hours after an IV dose.
- Given kel = 0.13 hr^{1} and V = 15L

$$Cp = \frac{Dose}{V} \bullet e^{-kel \bullet t}$$

$$Dose = \frac{Cp \bullet V}{e^{-kel \bullet t}}$$

$$= \frac{2x15}{e^{-0.13x6}} = 65mg$$

Make Predictions



Make Predictions

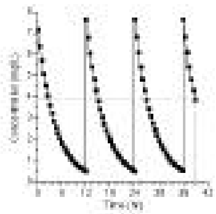
- Calculate Cp after multiple IV doses

$$Cp = \frac{Dose}{V} \bullet \left[\frac{1 - e^{-n \bullet kel \bullet \tau}}{1 - e^{-kel \bullet \tau}} \right] \bullet e^{-kel \bullet t}$$

Calculate Cp, 3 hours after four IV doses of 100 mg every 12 hours given kel = 0.23 hr^{-1} and V = 14 L.

Make Predictions

- Multiple IV dose of 100 mg every 12 hours: kel = 0.23 hr^{-1} and V = 14



Modelling - General Methods

General Methods - Objectives

- Understand the use of formulas as ‘Mathematical models’
- Understand the criteria of least squares
- Understand how parameter adjustment changes the fit to data

Outline

- Mathematical Models
- Error in Y alone
- Least squares criterion
- Parameter adjustment

General Method

- Design Experiment
- Collect Data
- Develop Mathematical Model with 'Parameters'
- Model Data
- Evaluate Fit to the Data
- Use Model

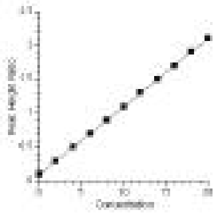
Mathematical Models

Y = f(x,p,c)

- y - dependent variable (observed, calculated data)
- x - independent variable (often time)
- p - parameters [adjustable] (e.g. kel, V)
- c - constants [fixed] (e.g. dose, duration)

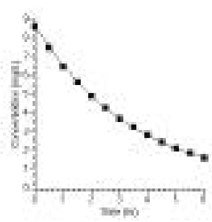
Mathematical Model - 1

- Peak Height Ratio
  = Slope x Concentration + Intercept



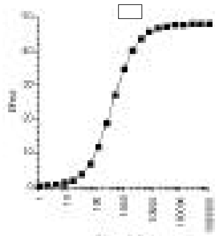
Mathematical Model - 2

$$Cp = \frac{Dose}{V} \bullet e^{-kel \bullet t}$$

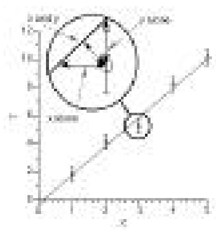


Mathematical Model - 3

$$Effect = \frac{E_{Max} \bullet C^{\gamma}}{EC_{50\%}^{\gamma} + C^{\gamma}}$$



Error in Y alone



Error in Y Alone

- Assume all error in Y (Dependent Variable)
- Need to measure X accurately
- May be appropriate to look at error in X only or in both X and Y

Least Squares Criterion - 1

$$Y_{observed} - Y_{calculated}$$

- Residual - simple difference
- Problems might include high positive and high negative residuals may cancel out
  - An absolute difference would solve this problems

Least Squares Criterion - 2

$$\left(Y_{observed} - Y_{calculated}\right)^2$$

- Square removes problem of sign
- This is the value for one point only

Least Squares Criterion - 3

$$\sum_{i=1}^{i=n}\left(Y_{observed,i} - Y_{calculated,i}\right)^2$$

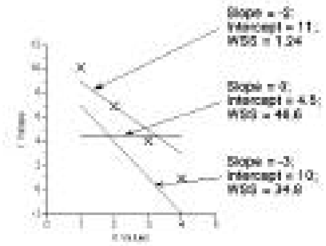
- Sum of the squared residuals
- Calculated over all the data points
- Each data point has the same weight

Least Squares Criterion - 4

$$\sum_{i=1}^{i=n}\left(Y_{observed,i} - Y_{calculated,i}\right)^2 \bullet W_i$$

- Weighted sum of the squared residuals (WSS)
- Program will minimise this term by adjusting parameter values

Parameter Adjustment - 1



Parameter Adjustment - 2