Weighting Data

Why all data are not equal

Weighting - Objectives

- To understand why all data are not equal
- To understand measures of data accuracy
- To understand how to use different weighting schemes
- To understand why different weighting schemes might be used

Weighting Schemes

- Equal Weight
- Reciprocal Variance
- Weighting Schemes
- Iteratively Reweighted Least Squares
- Extended Least Squares

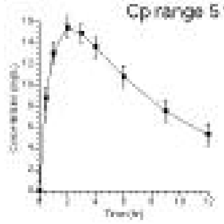
Equal Weight

- Equal (same, similar) error in each data point
- Value of each data point similar
- Error in each data point small

Equal Weight

Data after Oral Administration

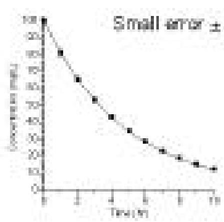
Cp range 5 to 15 mg/L



Equal Weight

Drug stability
Physico-Chemical System

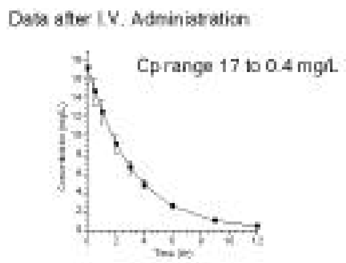
Small error ± 2.5%



Reciprocal Variance

- Large range of data values
- Error in data points variable
- Relatively larger error in data
- Magnitude of data in different sets are quite different

Reciprocal Variance

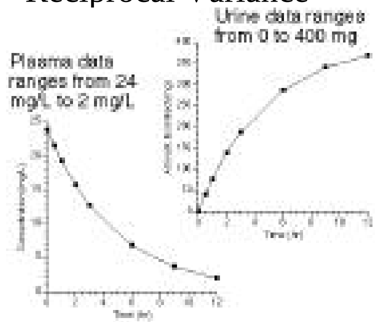


Reciprocal Variance

$$\text{Weight} = \frac{1}{\text{Variance}}$$

- Estimate Variance or at least how Variance varies with Observed Value

Reciprocal Variance



Weighting Scheme

- Variance α Observed Value

$$\text{Weight} = \frac{1}{\text{Observed Value}}$$

- Variance directly proportional to the measured value
  - For example with radioactive counting

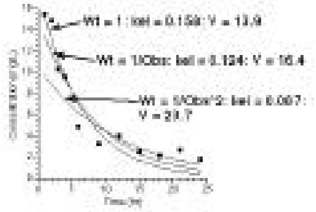
Weighting Schemes

- Variance α Observed Value^2

$$\text{Weight} = \frac{1}{\text{Observed Value}^2}$$

- Variance directly proportional to the square of the measured value
  - For example when the assay involves serial dilutions

Weighting Schemes



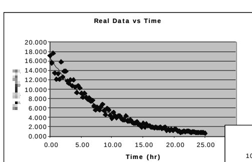
Weighting Schemes

Variance = a•Obs^{b}

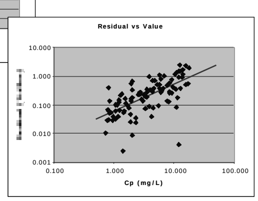
- Plot Variance versus Observed Mean on log-log paper.
  - Determine a and b from intercept and slope, respectively

Wagner, J.G. 1975 *Fundamentals of Clinical Pharmacokinetics*, Drug Intelligence Publications, Hamilton, IL, page289

Estimate Variance from Data



Variance' = $0.0032 \cdot Cp^{1.96}$



Weighting Schemes

$$\text{Variance} = c^b + a \bullet \text{Obs}^b$$

- Assay sensitivity is c and a is a measure of the assay precision

Weighting Schemes

$$\text{Variance} = a \bullet \text{Obs}^b \bullet c^{(t_{last} - t)}$$

- Older assay values, t smaller, have less weight
  - c = 1.05 (useful)
- Could be used for clinical samples collected over a number of days (weeks)

Iteratively Reweighted Least Squares

$$\text{Variance} = f(\text{Calculated Value})$$

- Very low observed value would be given very high weight with weight = 1/Obs^2, for example

Iteratively Reweighted Least Squares

- Variance = $Calc^0$
- Variance = $Calc^1$
- Variance = $Calc^2$

Extended Least Squares

- Weighting Scheme Parameters are obtained from the data DURING the fitting process
- Generally need more data since there are more parameters
- Different Fitting Algorithms needed and not universally available

Extended Least Squares

$$\text{Objective function} = \sum \frac{(Calc_i - Obs_i)^2}{V} + \ln V$$

where

$V = f(vp, \text{Calc or Obs})$

E.g. $V = a \cdot Calc^b$

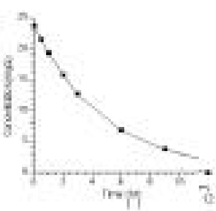
Or $V = a + b \cdot Calc + c \cdot Calc^2$

Weighting Example

- Fitting Plasma and Urine Data together
- Magnitude of the Data quite different
- Error/Variance formula different
  - Plasma - try constant Coefficient of Variation
  - Urine - try constant Standard Deviation

Plasma Data

- Coefficient of Variation = 5%



$$\text{C.V.} = 5\% = \frac{\text{Std.Dev.}}{\text{Value}}$$

$$\text{Std.Dev.} = \text{CV} \bullet \text{Obs}$$

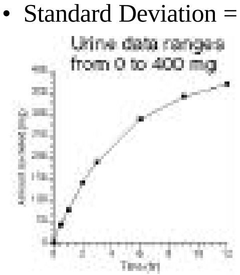
$$\text{Variance} = \text{SD}^2 = \text{CV}^2 \bullet \text{Obs}^2$$

$$\text{Weight} = \frac{1}{(0.05)^2 \bullet \text{Obs}^2} = \frac{1}{a \bullet \text{Obs}^b}$$

$$a = 0.0025 \quad b = 2$$

Urine Data

- Standard Deviation = 5 mg



$$\text{Std.Dev.} = 5\left(\bullet\text{Obs}^0\right)$$

$$\text{Variance} = \text{SD}^2 = 5^2 \bullet \text{Obs}^0$$

$$\text{Weight} = \frac{1}{5^2 \bullet \text{Obs}^0} = \frac{1}{a \bullet \text{Obs}^b}$$

$$a = 25 \quad b = 0$$

Boomer Output

```
Title:  Fit to two lines simultaneously
 Input: From Ch9905b.BAT
 Output:  To Ch9905b.OUT
 Data for [Drug] came from Ch9905bp.DAT
 Data for Drug in Urine came from Ch9905bu.DAT
 Fitting algorithm: DAMPING-GAUSS/SIMPLEX
 Weighting for [Drug]          by 1/a*Cp(Obs )^b
      With a = 0.2500E-02 and b =  2.000
 Weighting for Drug in Urine   by 1/a*Cp(Obs )^b
      With a =  25.00     and b = 0.0000
 Numerical integration method: 2) Fehlberg RKF45
          with  2 de(s)
 With relative error   0.1000E-03
 With absolute error   0.1000E-03
 DT =   0.1000E-02     PC =   0.1000E-04 Loops =     1
 Damping =     1
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