Slide 1

Pharmacometrics

ERROR MODELS and
OBJECTIVE FUNCTIONS

Slide 2

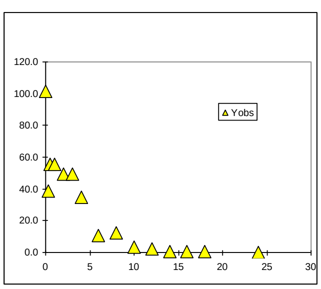
Objective Functions

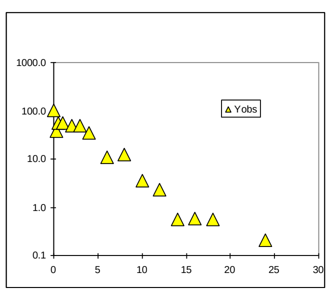
- Ordinary Least Squares
- Weighted Least Squares
- Extended Least Squares

Further background: http://www.xycoon.com/introduction1.htm

Slide 3

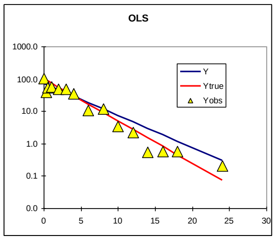
The Weighting Problem

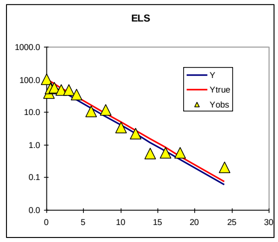




Slide 4

The Weighting Problem





	TRUE	OLS	ELS
Half-life	2.31	3.03	2.30
Error	-	31%	1%

Slide 5

Ordinary Least Squares

$$OLS = \sum_{i=1}^{i=Nobs} \frac{\left(f_i - obs_i\right)^2}{1}$$

Slide 6

Weighted Least Squares

$$WLS = \sum_{i=1}^{i=Nobs} \frac{\left(f_i - obs_i\right)^2}{Var_i}$$

$$Var_i = \frac{1}{W_i} = \frac{1}{F(f_i)} \text{(WLS)} \quad \text{or} \quad \frac{1}{F\left(f_i\right)} \text{(IRLS)}$$

Slide 7

Extended Least Squares

$$ELS = \sum_{i=1}^{i=Nobs} \left[\frac{\left(f_i - obs_i\right)^2}{Var_i} + \ln\left(Var_i\right) \right]$$

$$Var_i = f\left(f_i, SD, \ldots \right)^2$$

Slide 8

Error Models

WLS

- Additive
  - » W=1
- Poisson
  - » W=1/f
- Proportional
  - » W=1/f^2

ELS

- Additive
  - » Var=SD^2 [*f^0]
- Poisson
  - » Var=SD^2 * f^1
- Proportional
  - » Var=SD^2 * f^2
- General
  - » Var=SD^2 * f^{PWR}

Slide 9

Error Models

ELS

- Additive
  - » Var=SD^2
- Poisson
  - » Var=SD^2 * f
- Proportional
  - » Var=SD^2 * f^2

NONMEM / Monolix

- Additive
  - NONMEM: $Y = f + \varepsilon_{SD}$
  - Monolix: $Y = f + a \cdot \varepsilon_1$
- Poisson
  - NONMEM: $Y = f + sqrt(f) \cdot \varepsilon_{SD}$
- Proportional or Exponential
  - NONMEM: $Y = f \cdot (1 + \varepsilon_{SD})$
  - Monolix: $Y = f \cdot \exp(a \cdot \varepsilon_1)$

Note: 1 + x is approx exp(x)

Additive residual error is always a good starting point.

Radioactive disintegration has a Poisson distribution of counting error. The variance of a Poisson distribution is equal to its mean so the variance is directly proportional to the prediction (f).

Most concentration assay systems introduce a proportional error (e.g. due to dilution steps in preparing samples or standards).

When concentration assays are used to measure concentrations close to the background noise of the system then a combined proportional and additive residual error model is needed.

Slide 10

Combined Error Models

$$Y = f + (a + b \cdot f) \cdot \varepsilon_1$$ Monolix

$\varepsilon_1 \approx N(0,1)$

Parameters: a, b

$$Y = f + \varepsilon_{SD} + f \cdot \varepsilon_{CV}$$ NONMEM

$\varepsilon_{SD} \approx N(0,\sigma_{SD}{}^2)$ $\varepsilon_{CV} \approx N(0,\sigma_{CV}{}^2)$

Parameters: $\sigma_{SD}{}^2, \sigma_{CV}{}^2$ (SIGMA)

Monolix and NONMEM take different approaches to expressing residual error models. The results should be the same.

Monolix has a single random effect (epsilon) with mean 0 and variance of 1. The additive (parameter a) and proportional (parameter b) components of the model are estimated.

NONMEM estimates the variance of the additive (sigmaSD) and proportional (sigmaCV) components. NONMEM can also estimate the parameters a and b just like Monolix but it is more usual to estimate the variances of the components.

Slide 11

Coefficient of Variation

If X has a two-parameter lognormal distribution with parameters m and s^2 (i.e. log(X) has a normal distribution with mean m and standard deviation s), then the mean and variance of X are:

E(X) = exp(m + s^2 / 2)

Var(X) = exp(2m +s^2)[exp(s^2)-1]

Therefore, the exact coefficient of variation of X is

CV(X) = sqrt[Var(X)] / E(X) = sqrt[exp(s^2) - 1]

Most commonly the CV is reported as s which is an approximation which only holds when s^2 is small.

Sqrt(exp(s^2) – 1) is approximately sqrt((1+s^2) -1) i.e. s