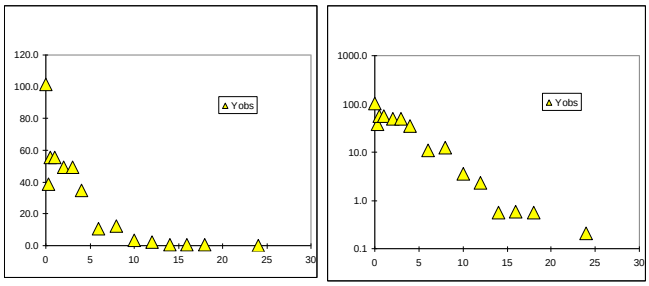
Slide 1	# Pharmacometrics Error Models and Objective Functions 	
Slide 2	# Objective Functions ➢Ordinary Least Squares ➢Weighted Least Squares ➢Extended Least Squares Further background: http://www.xycoon.com/introduction1.htm 	
Slide 3	# The Weighting Problem  	The measurement error is larger at higher concentrations. This arises from dilution errors when measuring high concentrations with a limited range measurement method. Measurement error is a major contributor to the residual error when modelling.

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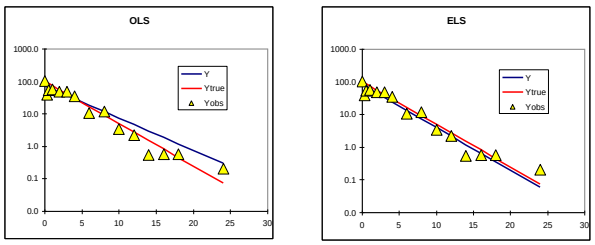
The Weighting Problem



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

When residual error is assumed to be constant (OLS) the half-life estimate is biased (31% too long). When the residual error is allowed to vary with concentration (ELS) the half-life estimate is not biased.

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Ordinary Least Squares

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

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Weighted Least Squares

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

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

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Extended Least Squares

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

$$Var_i = F(f_i, a, b, \ldots)^2$$

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Error Models

WLS	ELS
➢ Additive W=1	➢ Additive Var=a^2 [*f^0]
➢ Poisson W=1/f	➢ Poisson Var=p^2 * f^1
➢ Proportional W=1/f^2	➢ Proportional Var=b^2 * f^2
	➢ General Var=z^2 * f^{PWR}

Residual error models are expressed in various ways. The weights in weighted least squares (WLS) are proportional to the inverse of the variance of the residual error. Extended least squares (ELS) estimates the absolute size of the variance.

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Error Models

ELS	NONMEM	Monolix
➢ Additive Var=a^2	➢ Additive $Y = f + \varepsilon_{SD}$	➢ Additive $Y = f + a \cdot \varepsilon_1$
➢ Poisson Var=p^2 * f	➢ Poisson $Y = f + sqrt(f) \cdot \varepsilon_{SD}$	➢ Poisson ?
➢ Proportional Var=b^2 * f^2	➢ Proportional $Y = f \cdot (1 + \varepsilon_{SD})$	➢ Proportional $Y = f \cdot (1 + b \cdot \varepsilon_1)$
	$\varepsilon_{SD} \approx N(0, {\sigma_{SD}}^2)$	$\varepsilon_1 \approx N(0,1)$

Similar models for the variance may be expressed with different parameterizations by different software. 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. Note that Monolix does not allow users to write their own residual error model. Pre-specified models have to be used (constant (equivalent to additive), proportional, combined1 and combined2.

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.

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NONMEM Code

```
$SIGMA 0.1 ; EPS_SD
```

- Additive
  $Y = f + \varepsilon_{SD}$

```
$ERROR
Y=F + EPS(1)
```

- Poisson
  $Y = f + sqrt(f) \cdot \varepsilon_{SD}$

```
Y=F + SQRT(F)*EPS(1)
```

- Proportional
  $Y = f \cdot (1 + \varepsilon_{SD})$

```
Y=F* (1+ EPS(1))
```

Note: 1 + x is approx exp(x)

```
Y=F* EXP(EPS(1))
```


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.

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Monolix Code

- Additive
  $Y = f + a \cdot \varepsilon_1$
  $\varepsilon_1 \approx N(0,1)$

```
y = f + a * e
```

- Proportional
  $Y = f \cdot (1 + b \cdot \varepsilon_1)$
  $\varepsilon_1 \approx N(0,1)$

```
y = f + b * f * e
```


Additive residual error is always a good starting point. The Monolix model shown here as 'Additive' is called 'constant' in the Monolix naming system. Note the Monolix code on the right hand side is coded internally and not modifiable by the user.

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.

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Combined Error Models

$Y = f + (a + b \cdot f^c) \cdot \varepsilon_1$
$\varepsilon_1 \approx N(0,1)$

Monolix `combined1`

Parameters: a, b, c=1

$Y = f + \varepsilon_{SD} + f \cdot \varepsilon_{CV}$
$\varepsilon_{SD} \approx N(0, {\sigma_{SD}}^2)$ $\varepsilon_{CV} \approx N(0, {\sigma_{CV}}^2)$

NONMEM

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

The combined additive and proportional model is nearly always required for pharmacokinetic residual error models. The combined Monolix model shown here is called 'combined1' in the Monolix naming system.
Note that the variance of the normal distribution of the random effect is fixed to 1 for Monolix and estimated for NONMEM.

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Combined Error Models

$$Y = f + \sqrt{a^2 + b^2 \cdot (f^c)^2} \cdot \varepsilon_1 \qquad \text{Monolix } \texttt{combined2}$$

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

Parameters: a, b, c=1

$$Y = f + \sqrt{SD^2 + (f \cdot CV)^2} \cdot \varepsilon_1 \qquad \text{NONMEM}$$

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

Parameters: SD, CV (THETA) σ_1^2 (SIGMA)

The combined Monolix model shown here is called 'combined2' in the Monolix naming system. Note that the variance of the normal distribution of the random effect is fixed to 1 for Monolix and for NONMEM. The scale of the variance parameter is estimated (Monolix a,b; NONMEM SD,CV).

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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

$CV(X) = \text{sqrt}[Var(X)] / E(X) = \text{sqrt}[\exp(s^2) - 1]$

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

$\text{Sqrt}(\exp(s^2) - 1)$ is approximately $\text{sqrt}((1+s^2) -1)$ i.e. s

The proportional component of random effect models (including population parameter variability and residual error) is often referred to as a coefficient of variation. Most commonly this is approximated by the square root of the estimate of the variance of the proportional error parameter. The square root of the variance is the standard deviation (s). If the random effect is assumed to be log normally distributed then the true coefficient of variation is only approximate. The approximation gets better when the size of s is small.