Slide 1

The Population Approach

Describing The Signal and the Noise

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Slide 2

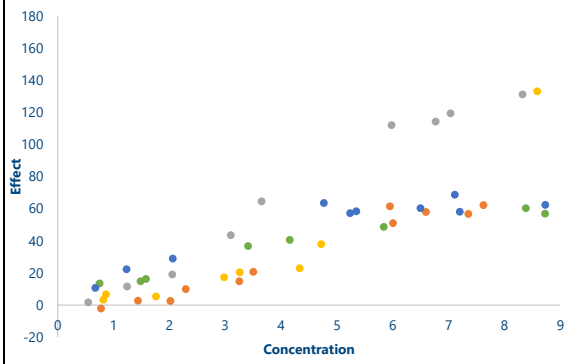
Objectives

- To describe the naïve-pooled, two-stage and population approaches to analysis of (PKPD) data.
- To learn how covariate models are specified using NM-TRAN.
- To provide practical experience of performing population analysis using NONMEM.

Slide 3

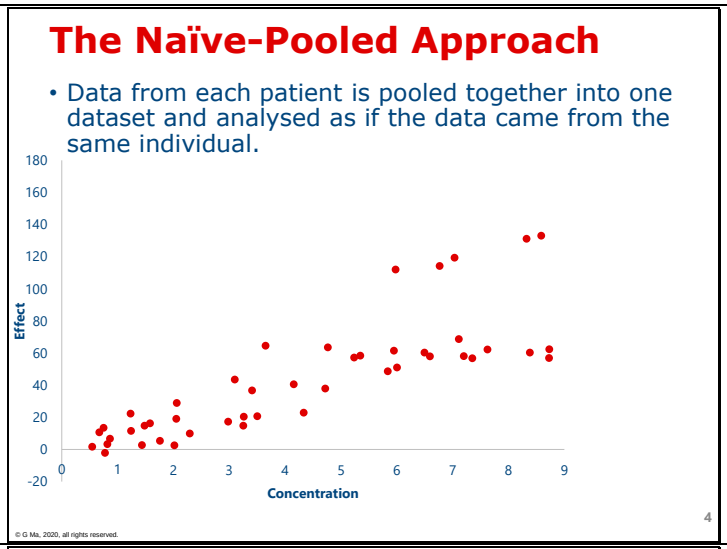
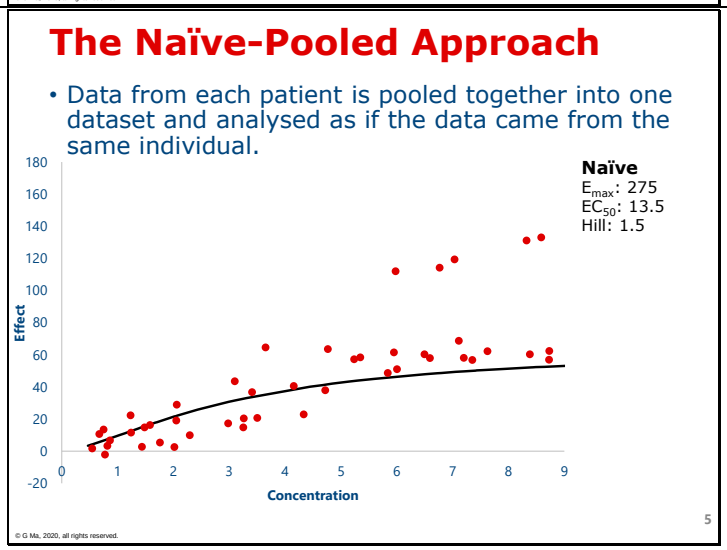
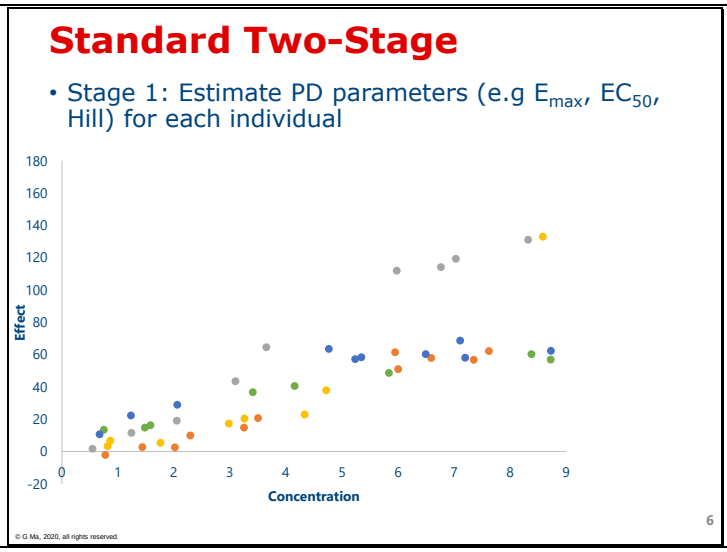
Motivating Example

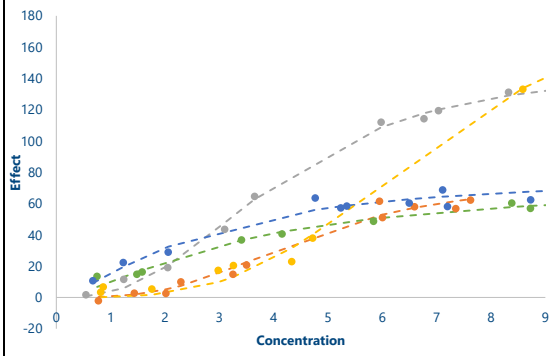
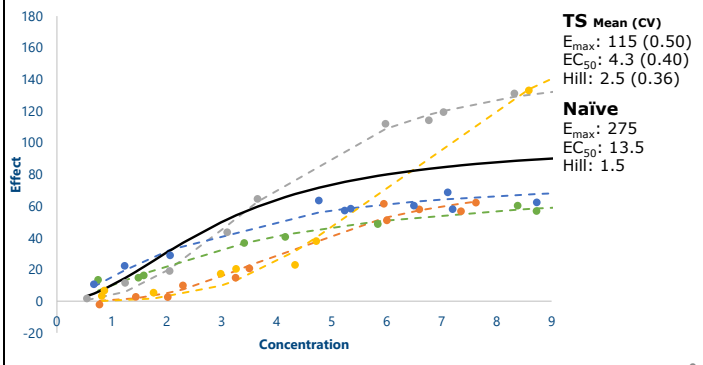
- How can population data be analysed to obtain unbiased parameter estimates?



Previously in the course, analysis has focussed on data from a single individual. Clinical data however comes from a population.
How can population data be analysed to obtain unbiased estimates of our parameters?

A simulated PD dataset of five individuals will be used to illustrate the different approaches to data analysis. Here measured concentration is plotted against effect with each individual in a different colour.

Slide 4		One approach may be to ignore the fact that the data comes from different individuals.
Slide 5		In a naïve pooled approach, the data from each individual is pooled together, thus we assume the data comes from the same individual. We may fit models to the data and obtain parameter estimates, the black red line shows the predicted concentration-effect curve under the naïve pooled parameter estimates. Parameter estimates from this approach are likely to be biased. Indeed the estimates of EMAX (275), EC50 (13.5) and HILL (1.5) differ noticeably from the values used to simulate this data (Emax: 100, EC50: 3, HILL: 2). Treating the data as if it comes from one individual ignores sources of variation between individuals. Outlier individuals or individuals with missing data can bias parameter estimates as data from each individual is weighted equally.
Slide 6		A standard two-stage approach recognises that the dataset comprises of different individuals. There are 5 individual PD profiles in this plot.

Slide 7	**Standard Two-Stage** • Stage 1: Estimate PD parameters (e.g E_{max}, EC_{50}, Hill) for each individual  7 	Parameters may be estimated for each individual, the dashed lines show the predicted concentration-effect curve under each individuals' parameter estimates.
Slide 8	**Standard Two-Stage** • Stage 2: Calculate measures of central tendency and variability from the individual parameters ID EMAX EC50 HILL 1 201 7.0 3.5 2 149 4.1 2.7 3 75 4.6 3.2 4 72 3.3 1.5 5 79 2.6 1.5 **Average 115 4.3 2.5** **Std Dev 58 1.7 0.9** **CV 0.50 0.40 0.36** 8 	Measures of central tendency (Average) and variability (Std Dev) and CV (Std Dev/Average) can be calculated from the individual parameter estimates.
Slide 9	**Standard Two-Stage** • Stage 2: Calculate measures of central tendency and variability from the individual parameters  9 	The dashed lines show the predicted concentration-effect curve under each individuals' parameter estimates, the black line illustrates the predicted concentration-effect curve under the average value of the parameter estimates. The average of the parameter estimates from the standard two-stage approach are now closer to the values used for simulation (Emax: 100, EC50: 3, HILL: 2). It is possible to estimate population parameter variability using the standard two-stage approach but it is confounded with parameter uncertainty.

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Mixed-Effect (Nested) Model

- Fixed Effects (predictable variability)
  - Structural model & parameters

$$E = \frac{E_{max} \cdot C^{HILL}}{C_{50}^{HILL} + C^{HILL}}$$

- Random Effects (unpredictable variability)
  - Parameter variability e.g. on E_{max}
  - Residual error e.g. measurement error

MIXED EFFECT = FIXED EFFECT + RANDOM EFFECT

- $True\ Effect_{ID} = \begin{bmatrix} Pop\ E_{max} + \eta_{E_{max}} \\ Pop\ C_{50} + \eta_{C_{50}} \\ Pop\ HILL + \eta_{HILL} \end{bmatrix}$
- $Effect_{obs,\,ID} = True\ Effect_{ID} + \varepsilon_{obs,ID}$

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A (non-linear) mixed-effect approach overcomes the disadvantages of the naïve pooled and standard two-stage approaches.

A mixed effect model incorporates fixed and random effects. The fixed effects describes the predictable sources of variability such as the structural model, the model that we believe describes the underlying process under which our data arises. Random effects account for unexplainable/random sources of variability. Random effects includes parameter variability such as between-subject variability (biological differences between individuals), within-subject variability, and residual unexplained variability (e.g. assay error, measurement error).

In this slide text in green is used to denote the fixed effect and red to denote the random effect component.

Mixed-effect models are often referred to as nested or hierarchical. In this example there are two layers.

The first layer describes the true effect for an individual (ID) as a function of the sigmoid Emax model, with each parameter equal to the population value plus population parameter variability (PPV; eta, η). Thus in this layer, the fixed effect is the sigmoidal Emax model and the population parameters, while the PPV component is a random effect. While parameter variability is random in nature, this can be described using a probability distribution such as a normal distribution with mean zero and standard deviation of omega (ω). It may not be plausible for a parameter to be negative, thus a log-normal distribution, exp(η), may be used instead.

The second layer of the model describes an effect observation for an individual. Each observation is equal to the true effect for the individual (first layer) plus residual unexplained variability (RUV; epsilon, ε). Again, because residual variability is random, this is described by a normal distribution with mean zero and standard deviation of sigma (σ).

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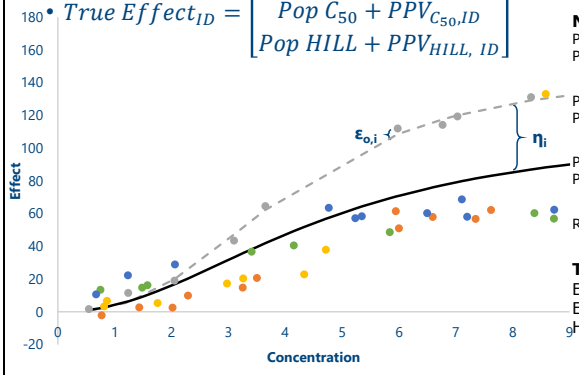
Mixed-Effect (Nested) Model

- $Effect_{obs,\,ID} = True\ Effect_{ID} + RUV_{obs,ID}$
- $True\ Effect_{ID} = \begin{bmatrix} Pop\ E_{max} + PPV_{E_{max},ID} \\ Pop\ C_{50} + PPV_{C_{50},ID} \\ Pop\ HILL + PPV_{HILL,\ ID} \end{bmatrix}$



NLME PPV, RUV as SD
POP_E_{max}: 112
PPV_E_{max}: 0.39
SIM: 100, 0.45
POP_EC_{50}: 4.6
PPV_C_{50}: 0.27
SIM: 3, 0.45
POP_Hill: 2.1
PPV_Hill: 0.49
SIM:2, 0.45
RUV: 4.42 (5)
SIM: 5

TS Mean (CV)
E_{max}: 115 (0.50)
EC_{50}: 4.3 (0.40)
Hill: 2.5 (0.36)

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Thinking about the PD example again, each observation of effect is based upon the true effect plus residual variability ($RUV_{observed,\ individual}$; $\varepsilon_{o,\,i}$).
The true effect is based upon the structural model and the individual parameter estimates which are related to the population parameter value plus population parameter variability ($PPV_{parameter,\ individual}$; η_i)

The non-linear mixed effect estimates of the population parameters (i.e. POP_EMAX, POP_EC50, POP_HILL) are closer to the values used to simulate the data (SIM) compared to the two-stage estimates.

For reference this data was simulated under a sigmoidal Emax model with the parameter values below. PPV (population parameter variability) and RUV (residual unexplained variability) are expressed as variances.

POP_EMAX: 100
POP_C50: 3
POP_HILL: 2
PPV_EMAX (lognormal): 0.2
PPV_C50 (lognormal): 0.2
PPV_OMEGA (lognormal): 0.2
RUV_SD (additive): 25

Note that this example uses a small sample (n=5) to succinctly illustrate the methodology; a larger dataset would be expected to yield more unbiased estimates by the mixed-effect method.

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Structural & Residual Error Models

- Structural Model

```
E = E0 + EMAX * THEO/(C50 + THEO)
```

  - Parameters: E0, Emax, C50

- Residual Error Model
  - Additive `Y = E + RUV_SD`
  - Proportional `Y = E + E * RUV_CV`
  - Mixed `Y = E + E * RUV_CV + RUV_SD`

  - Parameters: RUV_SD, RUV_CV

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The Population PD workshop uses an Emax model to describe the relationship between theophylline concentration (THEO) and effect (E). The following slides illustrate how the different components of a mixed effect model can be coded in NONMEM.
The structural model describes the process under which we believe the data arises.
We may use an additive, proportional or mixed residual error structures to describe the relationship between observed effect (Y) and the predicted effect under the structural model (E).
Additive error models describes residual error which tends to be fixed in magnitude, this error model will fall over when the data covers several orders of magnitude.
A mixed (additive + proportional) residual error model describes two sources of error, fixed error such as that near the assay limit of detection, and error which is proportional to concentration.

Slide 13	**Covariate Models**
	• Covariates are variables specific to an individual that may explain PKPD variability
	  • e.g. weight, renal function, age
	• Covariates are used to describe predictable sources (fixed effects) of variability.
	• A useful covariate is expected to explain some of overall variability and should lead to a decrease in unpredictable (random effects) variability.
	• Why Model Covariates?
	  • To identify and explain between subject and within subject variability
	  • Predict subject specific differences
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		See also: Principles of Covariate Modelling. holford.fmhs.auckland.ac.nz/docs/principles-of-covariate-modelling.pdf

Slide 14	**Covariate Models**
	• Continuous Covariates
	  • Weight `FWT=(WT/70)**(3/4)`
	  • Age `FAGE= 1 + SLOPE*(AGE-60)`
	  • Parameters: ¾ (theory), SLOPE
	• Categorical Covariates
	  • Sex
	`IF (SEX.EQ.1) THEN`
	`  FSEX=1  ; male`
	`ELSE`
	`  FSEX=FFEM ; female`
	`ENDIF`
	  • Parameter: FFEM
	• Multiplicative Covariate Effects
	  • FIXED EFFECTS: FWT, FAGE, FSEX
	`GRP_EMAX=FWT * FAGE * FSEX * POP_EMAX`
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		POP_EMAX=THETA(1)

Slide 15	**Parameter Variability Model**
	• Normal (additive)
	`EMAX = GRP_EMAX + PPV_SD`
	• Proportional
	`EMAX = GRP_EMAX + GRP_EMAX*PPV_CV`
	• Log Normal
	`EMAX = GRP_EMAX *EXP(PPV_CV)`
	• Parameters: PPV_SD, PPV_CV
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		A proportional error model describes the random variability in a parameter as a proportion of the typical group value. This may result in negative individual parameters, thus a log-normal distribution is more biologically plausible.
		
		EMAX = GRP_EMAX *EXP(ETA(1))

Slide 16	**Modelling Workflow**
	• Run an Initial Model with No Estimation:
	  • Check model predictions versus observations
	  • Look for outliers
	• Identify Base Model
	  • Estimate residual error models (additive, proportion or combined)
	  • Estimate structural model (e.g. 1 or 2 cpt)
	  • Estimate random effects components (e.g. BSV, BOV)
	• Identify Potential Covariate Relationships
	• Include Covariates one at a time to build the model
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Slide 17	**Covariate Selection**
	• Which Covariate to Select
	  • Biological plausibility: Does the covariate have a biologically plausible explanation?
	  • Extrapolation plausibility: Does the model extrapolate sensibly outside the range of observed covariates?
	  • Statistical plausibility: Is the covariate statistically significant?
	  • Clinical relevance: Is the covariate effect size clinically important?
	• Likelihood Ratio Test (LRT)
	  • For nested models the difference of two log-likelihoods is asymptotically chi-squared distributed, thus for 1 parameter difference (1 df) the critical value from the chi-squared distribution is 3.84 (P=0.05)
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Slide 18	**Methods**
	• Parametric Methods
	  • NONMEM (NONlinear Mixed Effects Model)
	  • R nlme, nlmixr
	  • SAS NLMIXED
	  • Certara Phoenix nlme
	• Non-Parametric Methods
	  • NONMEM
	  • NPML
	  • NPEG
	• Expectation Maximization Methods
	  • NONMEM
	  • WinBUGS
	  • MCPEM
	  • S-Adapt
	  • Monolix
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		There are many methods and software available to do non-linear mixed effects modelling.