

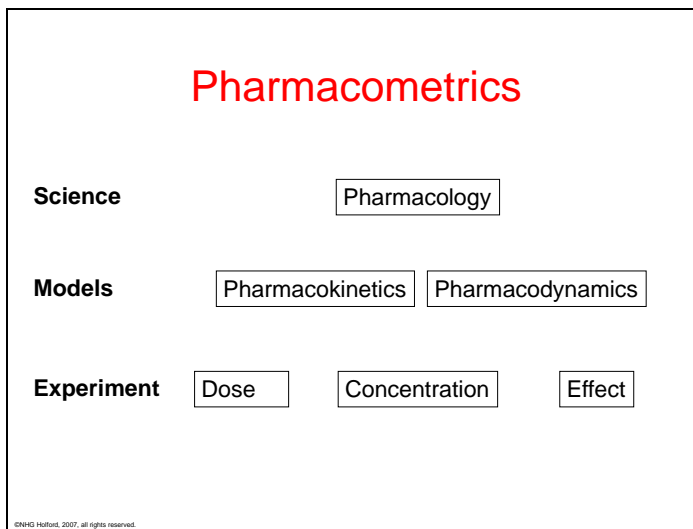
Slide 1

Population Approach

Describing The Signal and the Noise

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Slide 2



Slide 3

Analysis Approaches

ANOVA “Doses”

- Mean/Linear Models
- Limited covariates
- Univariate dose-effect

REGRESSION “Concs”

- Biology is non-linear
- Multiple unrestricted covariates
- Multivariate dose-conc-effect

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Two Approaches

Individual <ul style="list-style-type: none">● Self contained● Obs_i >> Parm● Structural Mdl● Residual Error Mdl	Population <ul style="list-style-type: none">● Shared● Obs_i >= Parm● Structural Mdl● Residual Error Mdl● Covariate Model● Parameter Variability Mdl
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Population Methods

- Naive Pooled Data
 - » Mean (biased)
- Standard Two Stage
 - » Mean + SD (biased)
- Full Population
 - » Mean + SD

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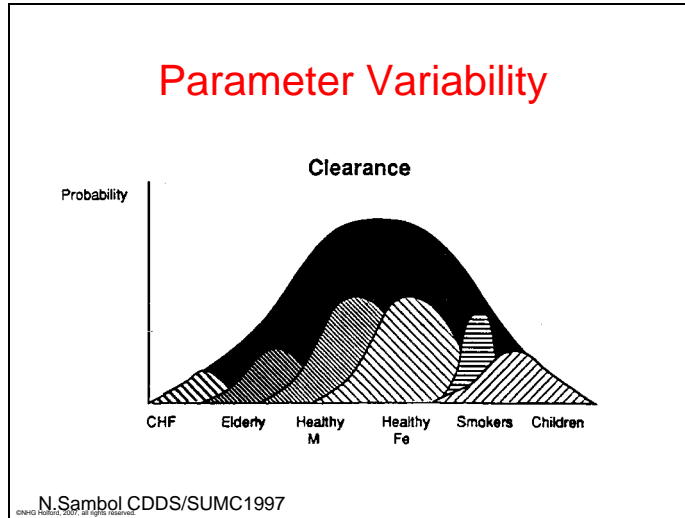
Mixed Effect Model

- Fixed Effects (predictable variability)
 - » Covariates and parameters
 - » e.g. renal function and clearance
- Random Effects (unpredictable variability)
 - » Parameter variability e.g. in clearance
 - » Residual error e.g. measurement error

MIXED EFFECT = FIXED EFFECT + RANDOM EFFECT

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Structural Model

$$E = E_0 + E_{MAX} * THEO / (EC50 + THEO)$$

Parameters: E₀, E_{max}, EC₅₀

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Residual Error Model

RUV=Residual Unidentified Variability

Additive

$$Y = E + RUVSD$$

Proportional

$$Y = E + E * RUVCV$$

Mixed

$$Y = E + E * RUVCV + RUVSD$$

Parameters: RUVSD, RUVCV

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Covariate Model

$$FWT = (WT/70) ** 0.75$$

$$FAGE = 1 + SLOPE * (AGE - 60)$$

$$GRP_EMAX = FWT * FAGE * POP_EMAX$$

Parameters: 0.75, SLOPE

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Parameter Variability Model PPV=Population Parameter Variability

Normal (additive)

$$EMAX = GRP_EMAX + PPVSD$$

Proportional

$$EMAX = GRP_EMAX + GRP_EMAX * PPVCV$$

Log Normal

$$EMAX = GRP_EMAX * EXP(PPVCV)$$

$$\exp(x) \approx 1+x \text{ (small } x\text{)}$$

Parameters: PPVSD, PPVCV

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Methods

- NONMEM
 - » NONlinear Mixed Effects Model
 - » S-Plus NLME, SAS NLMIXED, Pharsight WinNonMix
- NPML, NPEG
 - » NonParametric methods
- WinBUGS, Monolix, MCPM
 - » Monte Carlo Metropolis Hastings/Expectation maximization methods

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Uses

- Covariate Influences
 - » Population Screen
- PKPD
 - » Dose/Conc Response
 - » Disease progress
- Limited Sampling
 - » Paediatrics
 - » Toxicology

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NONMEM

```
C THE NONMEM SYSTEM MAY BE DISTRIBUTED ONLY BY THE NONMEM
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C COPYRIGHT BY THE REGENTS OF THE UNIVERSITY OF CALIFORNIA
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C DO NOT MODIFY CODE
C WITHOUT FIRST CONSULTING WITH THE NONMEM PROJECT GROUP
C
PROGRAM NONMEM
```

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```
$PROB THEOPHYLLINE PHARMACODYNAMICS STANDARD CONTROL STREAM
$DATA theopd.dat IGNORE #
$INPUT ID TIME THEO AGE WT SEX RACE DIAG DV
$ESTIM POSTHOC MAXEVAL=9999
MSFO=theopd.msf
$COV

$THETA (0,150.,) ; POPE0
$THETA (0,200.,) ; POPEMAX
$THETA (.001,10,) ; POPEC50

$OMEGA 0.5 ; ETAE0
$OMEGA 0.5 ; ETAEMAX
$OMEGA 0.5 ; ETAEC50

$$SIGMA 100 ; ERRSD

$PRED

E0=THETA(1)*EXP(ETA(1))
EMAX=THETA(2)*EXP(ETA(2))
EC50=THETA(3)*EXP(ETA(3))

Y = E0 + EMAX*THEO/(THEO+EC50) + ERR(1)

$TABLE ID TIME THEO AGE WT SEX RACE DIAG
E0 EMAX EC50 Y
NOPRINT ONEHEADER FILE=theopd.fit
```

NONMEM

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```
NONMEM
```

```
THETA:      POPE0      POPEMAX      POPECS0  
ETA:        ETAE0      ETAEMAX      ETAEC50  
ERR:        ERRSD  
theopd.lst      5802.086 eval=270 sig=+3.3 sub=153 obs=574 CCIL=NNNN NV1.1  
THETA      = 146      165      6.57  
ETAASD     = 0.0415933 0.487852 1.2083  
ERRSD      = 81.1788  
THETA:se%  = 7.5      12.5      30.0  
OMEGA:se%  = 4300.6   42.9      78.8  
SIGMA:se%  = 10.6  
  
MINIMIZATION SUCCESSFUL  
  
user 0:1.76 real 0:1.76 tcl 0:1.31
```

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Ernest Rutherford
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*“Science is either
stamp collecting or physics”*

```
Stamp Collecting → Models → Physics
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