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Population Approach

Describing The Signal and the Noise

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Pharmacometrics

Science

Pharmacology

Models

Pharmacokinetics

Pharmacodynamics

Experiment

Dose

Concentration

Effect

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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

- Self contained
- Obsi >> Parm
- Structural Mdl
- Residual Error Mdl

Population

- Shared
- Obsi >= 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

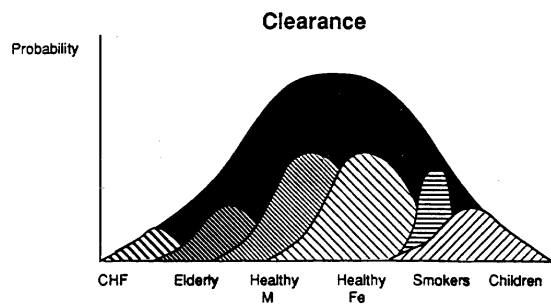
- Fixed Effects (predictable variability)
 - » Covariates and parameters
 - » e.g. renal function and clearance
- Random Effects (unpredictable variability)
 - » Parameter variability e.g. in clearance
 - » Residual error e.g. measurement error

MIXED EFFECT = FIXED EFFECT + RANDOM EFFECT

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Parameter Variability



N.Sambol CDDS/SUMC1997

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Structural Model

$$E = E_0 + E_{MAX} * THEO / (C50 + THEO)$$

Parameters: E_0 , E_{max} , $C50$

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Residual Error Model

RUV=Residual Unidentified Variability

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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Continuous Covariate Model

Theoretical

$$FWT = (WT/70)^{3/4}$$

Empirical

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

Parameters: 3/4 (theory), SLOPE

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Categorical Covariate Model

```
IF (SEX.EQ.1) THEN
  FSEX=1 ; male
ELSE
  FSEX=FFEM ; female
ENDIF
```

Parameter: FFEM

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Multiplicative Covariate Effects

```
GRP_EMAX = FWT * FAGE * FSEX * POP_EMAX
```

FIXED EFFECTS: FWT, FAGE, FSEX

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Parameter Variability Model PPV=Population Parameter Variability

Normal (additive)

$$EMAX = GRP_EMAX + PPV_SD$$

Proportional

$$EMAX = GRP_EMAX + GRP_EMAX * PPV_CV$$

Log Normal

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

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

Parameters: PPV_SD, PPV_CV

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Methods

- Parametric Methods
 - » NONMEM (NONlinear Mixed Effects Model)
 - » R nlme, SAS NL MIXED, Certara Phoenix nlme, nlmixr
- Non-Parametric Methods
 - » NONMEM, NPML, NPEG
- Expectation Maximization Methods
 - » NONMEM, WinBUGS, MCP EM, S-Adapt, Monolix, nlmixr

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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
C PROJECT GROUP. CONTACT: PROF. STUART BEAL, CLINICS 255,
C UNIV. OF CALIFORNIA, SAN FRANCISCO, CA 94143
C COPYRIGHT BY THE REGENTS OF THE UNIVERSITY OF CALIFORNIA
C 1979, 1984, 1985, 1989, 1992, 1998 ALL RIGHTS RESERVED
C
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 METHOD=COND INTER
$COV

$THETA
(0,150.,) ; POP_E0
(0,200.,) ; POP_EMAX
(.001,10.,) ; POP_C50

$OMEGA
0.5 ; PPV_E0
0.5 ; PPV_EMAX
0.5 ; PPV_C50

$SIGMA
100 ; RUV_SD

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

Y = E0 + EMAX*THEO/(C50 + THEO) + EPS(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: POP_E0 POP_EMAX POP_EC50
ETA: PPV_E0 PPV_EMAX PPV_EC50
ERR: RUV_SD
theopd.lst 5801.321 FOCE eval=295 sig=+4.2 sub=153 obs=574 NM7.5.0
THETA = 139 191 8.8
ETASD = 0.099 0.268 1.463
ETAPval = 0.346 0.000 0.605
ETAShrSD% = 81.0 55.8 35.6
EBVshrSD% = 81.8 59.6 29.9
EBVshrREL% = 0.6 5.6 8.6
EPSShrSD% = 9.3
EPSSD = 81.055
THETA:se% = 6.9 9.4 14.9
ETASD:se% = 168.6 20.7 16.9
EPSSD:se% = 5.3
MINIMIZATION SUCCESSFUL
Ttot 0:4.82 Test 0:1.45 Tcov 0:0.57 Ttcl 0:2.78
```

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Ernest Rutherford

*“Science is either
stamp collecting or physics”*

