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Pharmacometrics

Quantitative description of pharmacology

Nick Holford
Dept Pharmacology & Clinical Pharmacology
University of Auckland, New Zealand

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Pharmacometrics

Science

Pharmacology

Models

Pharmacokinetics

Pharmacodynamics

Experiment

Dose

Concentration

Effect

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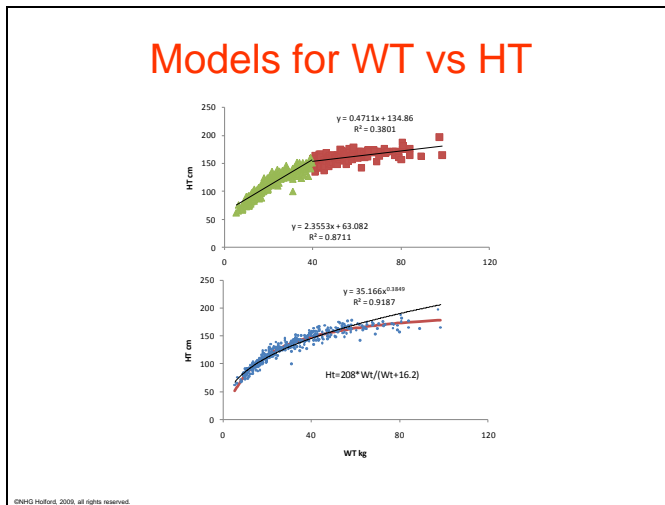
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Model Uses

- **Description**
 - » Correlation
 - » Parameters
- **Prediction**
 - » Interpolation
 - » Extrapolation
- **Explanation**
 - » True science

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George Box

*“All models are wrong
but some models are useful”*

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- ## Modelling
- Simulation
 - » Visualising model predictions
 - » Exploring model properties
 - Parameter Estimation
 - » Non-linear regression (often)
 - » Structural + Error models
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Model Parts

$$Y = \text{slope} * X + \text{intercept}$$

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Model Parts

$$C = \frac{\text{dose}}{V} * e^{-\frac{CL}{V} * t}$$

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Pharmacokinetics

- Drug Elimination

$$\text{RateOut} = CL * \text{Conc}$$

- Bolus Input

$$C = \frac{\text{dose}}{V} * e^{-\frac{CL}{V} * t}$$

- Infusion Input

$$C = \frac{\text{rate}}{CL} * (1 - e^{-\frac{CL}{V} * t})$$

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Receptors/Enzymes

- Ligand Binding

$$Cb = \frac{B_{\max} * Cu}{Cu + Kd} + NS * Cu$$

- Enzyme Velocity

$$V = \frac{V_{\max} * S}{S + Km}$$

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Pharmacodynamics

- Emax

$$E = \frac{E_{\max} * C}{C + EC50} + E0$$

- Sigmoid Emax

$$E = \frac{E_{\max} * C^{Hill}}{C^{Hill} + EC50^{Hill}} + E0$$

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PK Model Building

- One compartment model
 - » First order elimination
 - » Mixed order elimination
 - » Combined First order and Mixed order
- Two compartment model
 - » First order elimination
 - » etc

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PD Model Building

- Single Drug
 - » Linear
 - » Emax
 - » Sigmoid Emax
- Combinations
 - » Competitive
 - » Non-competitive

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PKPD Model Building

- PK Model
 - » One compartment, etc
- Link Model
 - » Immediate
 - » Slow receptor dissociation
 - » Distribution delay
 - » Turnover of mediator
- PD Model
 - » Linear, etc

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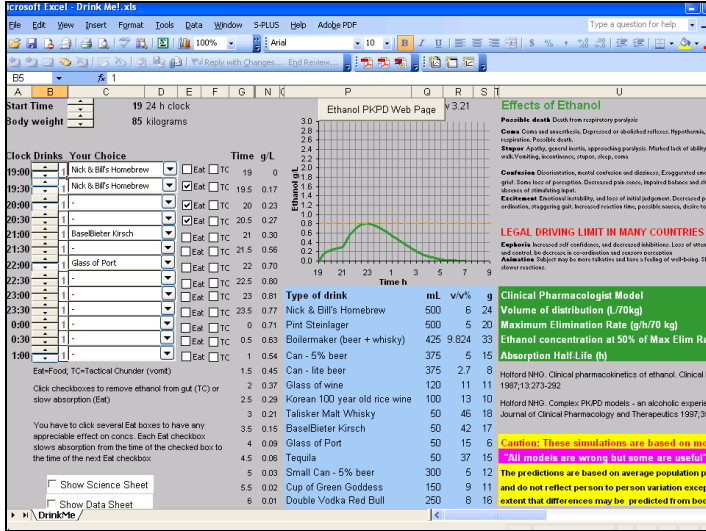
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Pharmacometric Tools

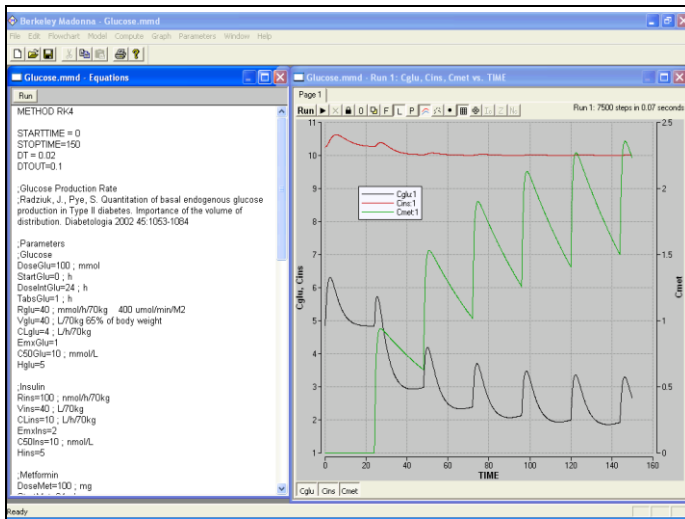
- Simulation
 - » Excel
 - » Berkeley Madonna
 - » Pharsight Trial Simulator
- Individual Non-Linear Regression
 - » WinNonLin
- Population Non-Linear Regression
 - » NONMEM

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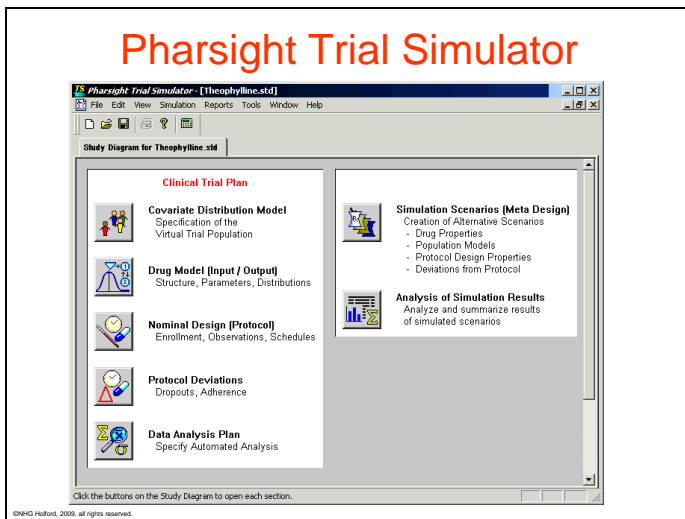
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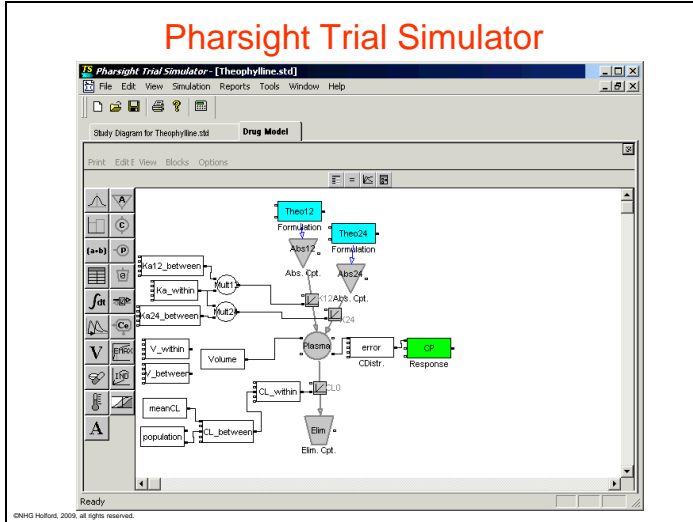
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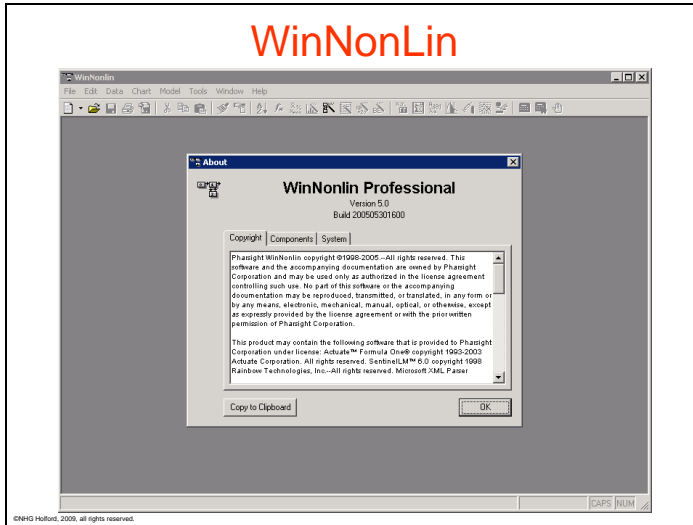
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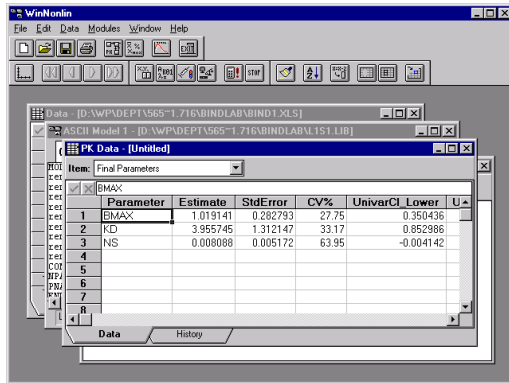
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WinNonLin

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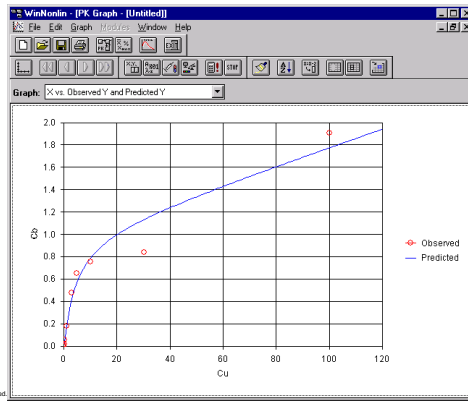
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WinNonLin



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WinNonLin



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NONMEM

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C

PROGRAM NONMEM

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NONMEM

```

$PROB theophylline pharmacodynamics
$DATA theopd.dat IGNORE #
$SIMPT ID TIME THEO AGE WT GEND RACE DIAG PEFR=DV
$ESTIM PRINT=1 POSTHOC MAXEVAL=9999
MSFO=THEOPD.msfc
SCOV

$THETA (0,150,) ; E0
$THETA (0,200,) ; EMAX
$THETA (.001,10,) ; EC50

$OMEGA 0.5 ; CVE0
$OMEGA 0.5 ; CVMAX
$OMEGA 0.5 ; CVEC50

$SIGMA 100 ; SD 1

$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 GEND RACE DIAG
E0 EMAX EC50 Y
NOPRINT ONEHEADER FILE=THEOPD.fit
  
```

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NONMEM

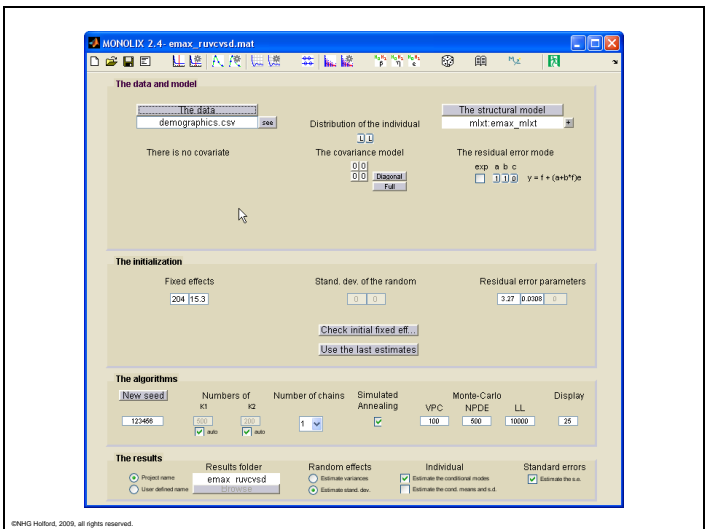
```

THETA:      E0          EMAX          EC50
ETA:        CVE0       CVMAX         CVEC50
ERR:        SD
theopd.lst  5802.086 eval=270 sig=3.3 sub=153 obs=574 CCIL=NNNN NV1.1
THETA      = 146          165          6.57
ETASD      = 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
  
```

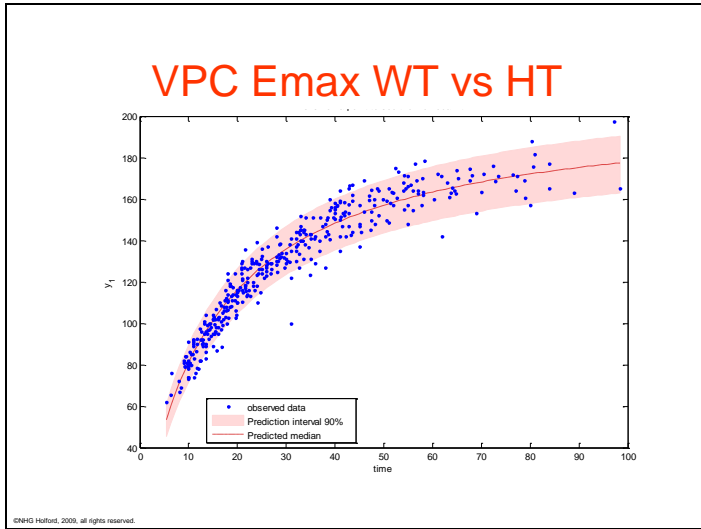
MINIMIZATION SUCCESSFUL

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