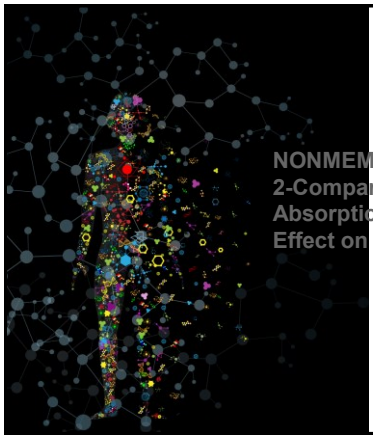


NONMEM to NLME: 2-Compartment Oral Absorption Disease State Effect on V and CL FOCE

Agenda

- Model Description
- Exploratory Data Analysis
- Input Data
- Model in NM-TRAN and PML Code
- Demo
- Summary
- Q&A

2c_oral_cov_categorical_multiple_foce

Structural Model
- 2 compartment model with Oral Single Dose, Covariate relationship between both V and Cl and categorical covariate disease state

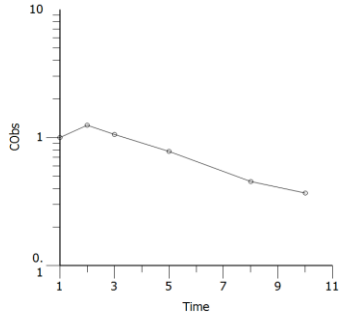
Parametrization
- Clearances and Flows (Ka,V,V2,Cl,Cl2)

Structural Parameters
- All lognormal

Error model
- Multiplicative, 10% CV (Stdev = 0.1)

Covariates
- Categorical, 3 levels of disease:
  - 0 – normal
  - 1 – moderate
  - 2 – severe

2c_oral_cov_categorical_multiple_foce: First Patient



2c_oral_cov_categorical_multiple_foce: Input Data

NONMEM

	CID	TIME	DISEASESTATE	DV	AMT	MDV
1	0	0	0	.	100	1
2	0	1	0	1.00957	.	0
3	0	2	0	1.24863	.	0
4	0	3	0	1.05762	.	0
5	0	5	0	0.779613	.	0
6	0	7	0	0.453543	.	0
7	0	10	0	0.268813	.	0
8	1	0	1	.	100	1
9	1	1	1	0.546788	.	0
10	1	2	1	0.622457	.	0
11	1	3	1	0.552662	.	0
12	1	5	1	0.473607	.	0
13	1	8	1	0.3873	.	0
14	1	10	1	0.342309	.	0

NLME

	id	time	diseasestate	CObs	Aa
1	0	0	0	.	100
2	0	1	0	1.00957	.
3	0	2	0	1.24863	.
4	0	3	0	1.05762	.
5	0	5	0	0.779613	.
6	0	7	0	0.453543	.
7	0	10	0	0.268813	.
8	1	0	1	.	100
9	1	1	1	0.546788	.
10	1	2	1	0.622457	.
11	1	3	1	0.552662	.
12	1	5	1	0.473607	.
13	1	8	1	0.3873	.
14	1	10	1	0.342309	.
15	2	0	2	.	100

Comparison of Code – Defining PK Model

NONMEM	NLME
$PROBLEM TWO COMPARTMENTAL MODEL WITH ORAL BOLUS CL & V DEPENDS ON DISEASE STATE	test(Model Name can be entered here) { Model statements } # Comment can be added here
$INPUT ID TIME DISEASESTATE DV AMT MDV $DATA NONMEM_2C_ORAL_BOLUS_DISEASESTATE_EFFECT_ON_V_CL.csv IGNORE=C	No typing of file name and setting path locations are required. Import the Input data into Data folder in Phoenix project Only Input data mapping required
; DEFINE THE PK MODEL AND ABSORPTION COMPARTMENT	# Define PK model type with dosing point, parameterization and absorption type
$SUBROUTINES ADVAN4 TRANS4	cfMicro(A1, Cl / V, Cl2 / V, Cl2 / V2, first = (Aa = Ka))

Comparison of Code – Defining PK Model

NONMEM	NLME
; =====SPECIFY STRUCTURE MODEL PARAMETERS=======	
$PK	
; KA = ABSORTION RATE	
TVKA = THETA(1)	
KA = TVKA * EXP(ETA(1))	stparm(Ka= tvKa* exp(nKa))

CERTARA

Comparison of Code – Defining Covariate Effects

NONMEM	NLME
; V2 = VOLUME OF DISTRIBUTION OF CENTRAL COMPARTMENT	
TVV = THETA(2)	
	fcovariate(diseasestate())
DVDISEASESTATE1 = THETA(6)	
DVDISEASESTATE2 = THETA(7)	

IF (DISEASESTATE .EQ. 0) THEN
V2 = TVV * EXP(ETA(2))
ENDIF	

IF (DISEASESTATE .EQ. 1) THEN
V2 = TVV * EXP(DVDISEASESTATE1) * EXP(ETA(2))
ENDIF	

IF (DISEASESTATE .EQ. 2) THEN
V2 = TVV * EXP(DVDISEASESTATE2) * EXP(ETA(2))
ENDIF	

	stparm(V = tvV* exp(dVddiseasestate1*(diseasestate==1)) * exp(dVddiseasestate2*(diseasestate==2)) * exp(nV))

CERTARA

Comparison of Code – Defining PK Model

NONMEM	NLME
; V3 = VOLUME OF DISTRIBUTION OF PERIPHERAL COMPARTMENT	
TVV2 = THETA(3)	
V3 = TVV2	stparm(V2 = tvV2)

CERTARA

Comparison of Code – Defining Covariate Effects

NONMEM	NLME
; CL = CLEARANCE RATE FOR CENTRAL COMPARTMENT	
TVCL = THETA(4)	
DCLDISEASESTATE1 = THETA(8)	
DCLDISEASESTATE2 = THETA(9)	

IF (DISEASESTATE .EQ. 0) THEN
CL = TVCL * EXP(ETA(3))
ENDIF	

IF (DISEASESTATE .EQ. 1) THEN
CL = TVCL * EXP(DCLDISEASESTATE1) * EXP(ETA(3))
ENDIF	

IF (DISEASESTATE .EQ. 2) THEN
CL = TVCL * EXP(DCLDISEASESTATE2) * EXP(ETA(3))
ENDIF	

	stparm(Cl = tvCl* exp(dCldiseasestate1*(diseasestate==1)) * exp(dCldiseasestate2*(diseasestate==2)) * exp(nCl))

Comparison of Code – Defining PK & Scaling Parameters

NONMEM	NLME
; Q = INTERCOMPARTMENTAL CLEARANCE	
TVCL2 = THETA(5)	
Q = TVCL2	stparm(Cl2 = tvCl2)
; SCALE PARAMETERS	
S2=V2	C = A1/V Defining the scaling parameter can be incorporated here. Expected to have Dose Information in the same mass units as defined in Concentration mass units.

CERTARA

2c_oral_cov_categorical_multiple_foce

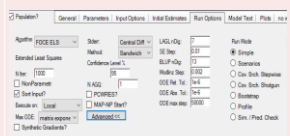
NONMEM	NLME
; =======SETUP INITIAL VALUES FOR THETA AND OMEGA ===	
$THETA	
(0, 1) ;TVKA	fixef(tvKa= c(, 1,))
(0, 50) ;TVV	fixef(tvV= c(, 50,))
(0, 50) ;TVV2	fixef(tvV2 = c(, 50,))
(0, 5) ;TVCL	fixef(tvCl= c(, 5,))
(0, 5) ;TVCL2	fixef(tvCl2 = c(, 5,))
1 ;DVDISEASESTATE1	fixef(dVddiseasestate1(enable=c(0)) = c(, 1,))
-1 ;DVDISEASESTATE2	fixef(dVddiseasestate2(enable=c(0)) = c(, -1,))
0.5 ;DCLDISEASESTATE1	fixef(dCldiseasestate1(enable=c(1)) = c(, 0.5,))
-0.5 ;DCLDISEASESTATE2	fixef(dCldiseasestate2(enable=c(1)) = c(, -0.5,))

CERTARA

2c_oral_cov_categorical_multiple_foce

NONMEM	NLME
$OMEGA	
; INITIAL ESTIMATES FOR VARIANCES OF RANDOM EFFECTS	# Initial estimates variances for random effects
0.3 0.3 0.3	ranef(diag(nV, nCl, nKa) = c(0.3, 0.3, 0.3))
; =====SPECIFY RESIDUAL ERROR MODEL========== ; SETUP INITIAL ESTIMATES FOR THE VARIANCE MATRIX (SIGMA) OF THE RESIDUAL VARIABILITY	# Setup initial estimates for the variance for the residual variability
$SIGMA 0.01	error(CEps= 0.1)
; RESIDUAL ERROR MODEL MULTIPLICATIVE	# Residual error multiplicative
$ERROR Y = F*(1 + EPS(1)) IPRED = F IRES = DV - IPRED	observe(CObs= C * (1 + CEps))

2c_oral_cov_categorical_multiple_foce

NONMEM	NLME
; =====SPECIFIY ESTIMATION METHOD ====== $EST METHOD = CONDITIONAL INTERACTION MAXEVAL=9999 PRINT = 5 ;	Equivalent to **FOCE-ELS** in Phoenix NLME in Algorithm Box in **Run Options** Tab
; ======= CALCULATE SE ======== $COVARIANCE ; THE DEFAULT ONE IS SANDWICH METHOD $TABLE ID TIME IPRED IRES FILE=Residuals.TXT	

Pharmacometrics: Phoenix as The Full package

Textual Mode: Similar to NONMEM control stream

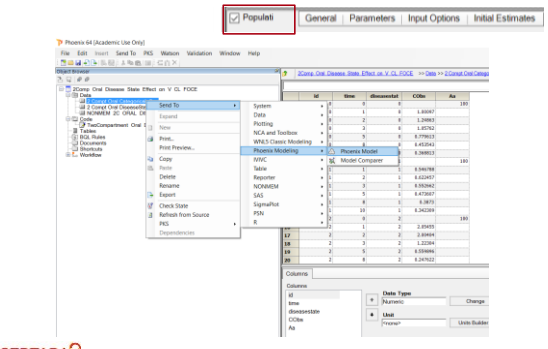
- Now, we will go through an example Population PK model with Categorical Covariate that have been generated using both NONMEM and Phoenix NLME
- In this each model, we will explain the PML code and how we could often generated the PML using the interface (build-in, graphical or both)

Two Compartment, Oral Dosing, Multiple Error model and with Categorical Covariates with FOCE Method

- The model is a 2 compartment model with Oral Bolus and clearance parametrization
- The error model assumes multiplicative error
- Provide Input data and Control file for NONMEM Run
- For NLME do the following
  - Structural model selection
  - Error model selection
  - Fixed effects
  - Covariate relationship: diseasestate is a 3 level covariate with value 0, 1 or 2 linked to both V and Cl
  - Random effects
  - Engine settings and mode (fitting versus simulation)
  - Mapping Input data

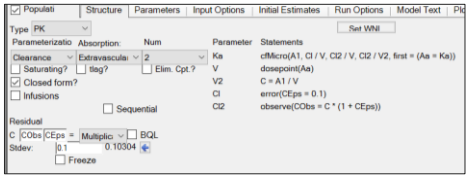
Create a Phoenix Project

Make sure Population Option is enabled.



Pharmacometrics: Phoenix as The Full package

Built-in: Structural and Error Model Selection



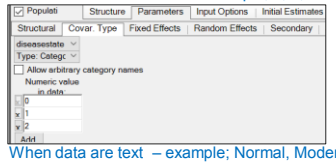
Pharmacometrics: Phoenix as The Full package

Built-in: Covariate and Random effects on Selected Parameters

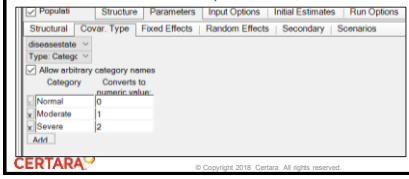
Pharmacometrics: Phoenix as The Full package

Built-in: Selection of Covariate Type for "disease state"

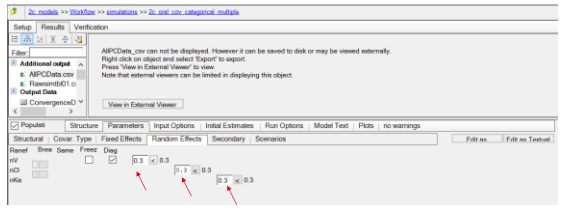
When data are numerical – example, 0, 1, 2



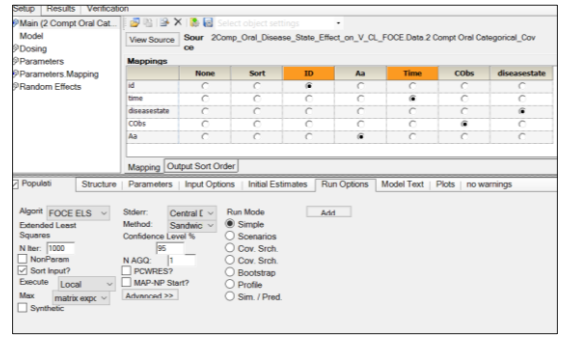
When data are text – example; Normal, Moderate, and Severe



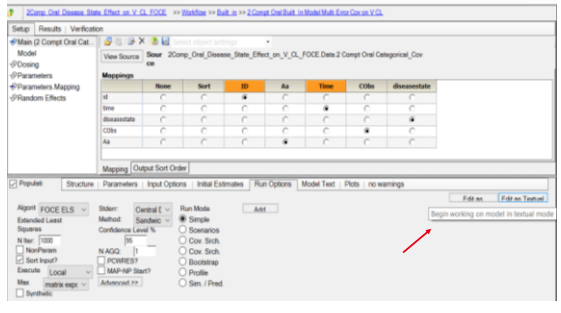
Initial Estimates for Variances of Random Effects



Mapping and Coverting to Textual Mode



Create the pml

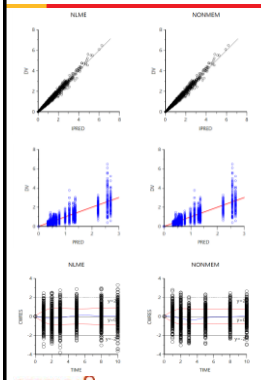


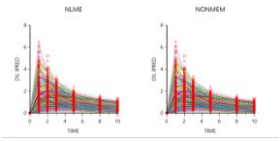
The pml code is created

```
test() {
    cfMicro(A1, Cl / V, Cl2 / V, Cl2 / V2, first = (Aa = Ka))
    dosepoint(Aa)
    C = A1 / V
    error(CEps = 0.1)
    observe(CObs = C * (1 + CEps))
    stparm(Ka = tvKa * exp(nKa))
    stparm(V = tvV * exp(dVddiseasestate1*(diseasestate==1)) * exp(dVddiseasestate2*(diseasestate==2)) * exp(nV))
    stparm(V2 = tvV2)
    stparm(Cl = tvCl * exp(dCldiseasestate1*(diseasestate==1)) * exp(dCldiseasestate2*(diseasestate==2)) * exp(nCl))
    stparm(Cl2 = tvCl2)
    fcovariate(diseasestate())
    fixef(tvKa = c(, 1, ))
    fixef(tvV = c(, 50, ))
    fixef(tvV2 = c(, 50, ))
    fixef(tvCl = c(, 5, ))
    fixef(tvCl2 = c(, 5, ))
    fixef(dVddiseasestate1(enable=c(0)) = c(, 1, ))
    fixef(dVddiseasestate2(enable=c(0)) = c(, -1, ))
    fixef(dCldiseasestate1(enable=c(1)) = c(, 0.5, ))
    fixef(dCldiseasestate2(enable=c(1)) = c(, -0.5, ))
    ranef(diag(nV, nCl, nKa) = c(0.3, 0.3, 0.3))
}
```

Demo

Comparison of Results – NONMEM vs NLME





Parameter	Source			
	NLME		NONMEM	
	Estimate	Stderr	Estimate	Stderr
TVV2	44.481	6.344	43.6	6.57
tvV	48.955	2.446	49.3	2.6
tvKa	0.998	0.039	0.992	0.038
tvCl2	4.844	0.196	4.88	0.207
tvCl	5.267	0.395	5.32	0.414
stdev0	0.09	0.002	0.102	0.022
dVddiseasestate2	-0.923	0.08	-0.928	0.081
dVddiseasestate1	1.021	0.071	1.02	0.074
dCldiseasestate2	-0.443	0.098	-0.436	0.087
dCldiseasestate1	0.558	0.077	0.559	0.08

Summary

- Set up and Run NONMEM & Phoenix NLME model:
  - 2-Compartment Oral
  - Disease State as covariate on CL and Volume
  - Estimation methods: FOCE Interaction vs FOCE ELS
- Postprocessed the NONMEM results and compared them with the NLME results
  - Only small differences

Questions?

Schedule for Q2

Date	Series	Topic
19-Apr	NONMEM-2-NLME	Nonlinear Elimination and Model Validation I: Bootstrap
3-May	NONMEM-2-NLME	Mixed Absorption and Model Validation II: VPC
17-May	NONMEM-2-NLME	Running NONMEM and Phoenix NLME in the Cloud
31-May	NONMEM-2-NLME	PD Emax inhibitory with baseline and shape factor
14-Jun	NONMEM-2-NLME	PD Indirect Response with IV Bolus Dosing
28-Jun	NONMEM-2-NLME	PKPD 1 Compartment-IV Infusion - Emax with Baseline, Shape and Effect

Coming up…

TMDD Model Translated from NONMEM (NM-TRAN) to Phoenix NLME (PML)
March 22, 2018 | 10am EST
Presenter: Loan Pham, Camargo