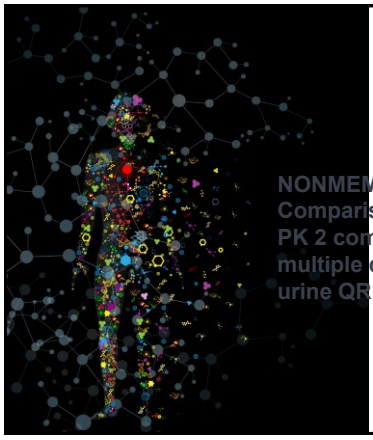

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NONMEM - NLME Comparison: PK 2 compartment IV Bolus multiple dose – plasma – urine QRPEM/IMP

Agenda

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

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NONMEM to NLME: 2c_iv_multiple_plasma_urine

- Model Description
  - Structural Model
    - 2 compartment model with multiple IV Bolus doses
    - Responses in both urine and plasma
  - Parametrization:
    - Clearances and Flows(V,V2,Cl,Cl2)
  - Error model
    - Multiplicative: 10% CV
  - Structural Parameters: All Lognormal
  - Fixed Effects
    - tvV: 1
    - tvV2: 1
    - tvCl:1
    - tvCl2: 1
  - Random Effects
    - nV,NV2,nCl,nCl2: 0.1,0.2,0.2,0.5
  - Engine
    - IMP (NONMEM), QRPEM (NLME)

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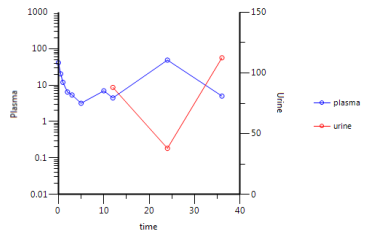
2c_iv_multiple_plasma_urine: Plot First Patient



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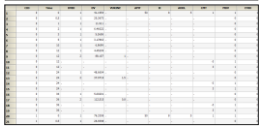
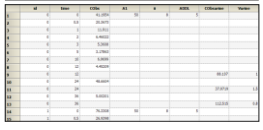
2c_iv_multiple_plasma_urine: Input Data

NONMEM



NLME



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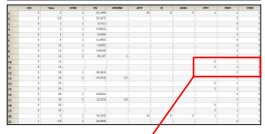
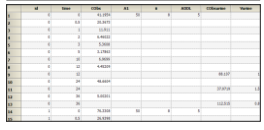
2c_iv_multiple_plasma_urine: Input Data

NONMEM



NLME



CMT	MDV	EVID
-3	1	2
2	1	2
.	0	0

```
observe(CObsurine = Curine * (1 + CEpsurine[
```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NONMEM to NLME: 2c_iv_multiple_plasma_urine

NONMEM

```
;Model Selection
$SUBROUTINES ADVAN6 TOL =6

$MODEL
 NCOMP = 3
 COMP = (CENTRAL)
 COMP = (PERIP)
 COMP = (URINE)
```

NLME

```
# Model Selection
```

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NONMEM to NLME: 2c_iv_multiple_plasma_urine

NONMEM

```
; STRUCTURAL PARAMETERS
$PK
; V = VOLUME OF DISTRIBUTION OF CENTRAL COMPARTMENT
TVV = THETA(1)
V = TVV * EXP(ETA(1))
; CL = CLEARANCE RATE FOR THE CENTRAL COMPARTMENT
TVCL = THETA(2)
CL = TVCL * EXP(ETA(2))
; V2 = VOLUM OF DISTRIBUTION OF PERIPHERIAL COMPARTMENT
TVV2 = THETA(3)
V2 = TVV2 * EXP(ETA(3))
; CL2 = INTERCOMPARTMENTAL CLEARANCE
TVCL2 = THETA(4)
CL2 = TVCL2 * EXP(ETA(4))
```

NLME

```
#Structural Parameters

# V = VOLUME OF DISTRIBUTION OF CENTRAL COMPARTMENT
stparm(V = tvV* exp(nV))

# CL = CLEARANCE RATE FOR THE CENTRAL COMPARTMENT
stparm(Cl = tvCl* exp(nCl))

# V2 = VOLUM OF DISTRIBUTION OF PERIPHERIAL COMPARTMENT
stparm(V2 = tvV2 * exp(nV2))

# CL2 = INTERCOMPARTMENTAL CLEARANCE
stparm(Cl2 = tvCl2 * exp(nCl2)
```

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Using the PML: 2c_iv_multiple_plasma_urine

NONMEM

```
; setup initial values for THETA and OMEGA
$THETA
1 ; TVV
1 ; TVCL
1 ; TVV2
1 ; TVCL2
$OMEGA
0.1 ; ETA1
0.2 ; ETA2
0.3 ; ETA3
0.5 ; ETA4
```

NLME

```
# setup initial values for THETA and OMEGA

fixef(tvV= c(, 1, ))
fixef(tvCl= c(, 1, ))
fixef(tvV2 = c(, 1, ))
fixef(tvCl2 = c(, 1, ))

ranef(diag(nV, nCl, nV2, nCl2) = c(0.1, 0.2, 0.3, 0.5))
```

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Using the PML: 2c_iv_multiple_plasma_urine

NONMEM

```
; ODE MODEL
$DES
DADT(1) = -CL*A(1)/V -CL2*(A(1)/V -A(2)/V2)
DADT(2) = CL2*(A(1)/V -A(2)/V2)
DADT(3) = CL*A(1)/V
```

NLME

```
deriv(A1 = -(Cl * C)-(Cl2 * (C -C2)))
deriv(A2 = (Cl2 * (C -C2)))
urinecpt(A0urine = (Cl * C))
```

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Using the PML: 2c_iv_multiple_plasma_urine

NONMEM

```
; specify residual error model
; setup initial estimates for the variance matrix (SIGMA) of the residual variability
$SIGMA
0.01 ;PLASMA
0.01 ;URINE
; RESIDUAL ERROR MODEL
$ERROR
IF (DVID .EQ. 1) THEN
IPRED = A(1)/V
Y = IPRED*(1 + EPS(1))
ENDIF

IF (DVID .EQ. 2) THEN
IPRED = A(3)/VURINE
Y = IPRED*(1 + EPS(2))
ENDIF

; additional output
IVAR = TIME
IRES = DV – IPRED
```

NLME

```
# residual error model
error(CEps= 0.1)
error(CEpsurine= 0.1)

C = A1/V
observe(CObs = C * (1 + CEps))
Curine = A0urine/Vurine
observe(CObsurine = Curine* (1 + CEpsurine),doafter={A0urine=0})
```

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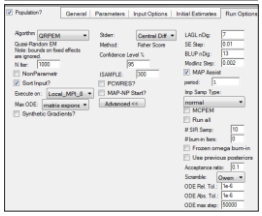
Using the PML: 2c_iv_multiple_plasma_urine

NONMEM

```
; SPECIFIY ESTIMATION METHOD
; DEFAULT VALUES FOR IMP:
 ; NITER = 50; MAXIMUM NUMBER OF ITERATIONS
 ; ISAMPLE = 300;
 ; IACCEPT = 0.4;
 ; CTYPE = 0; (NO TERMINATION TEST, TERMINATE AFTER NITER ITERATIONS)
 ; DF = 0 (NORMAL)
; ------------------------------------------------------------
; CTYPE=1: TEST FOR TERMINATION ON OBJECTIVE FUNCTION, THETAS, AND SIGMAS, BUT NOT ON OMEGAS
; EVERY CINTERVAL ITERATIONS IS SUBMITTED TO THE CONVERGENCE TEST SYSTEM
;------------------------------------------------------------
$EST METHOD = IMPMAP INTERACTION PRINT = 5
CTYPE = 1 CINTERVAL = 10 IACCEPT = 0.1 &
    NITER = 1000 SEED = 123


; CALCULATE SE
$COVARIANCE MATRIX=S
; THE DEFAULT ONE IS SANDWICH METHOD
; NEED FISHER SCORE MATRIX HERE
```

NLME



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Using the PML: 2c_iv_multiple_plasma_urine

NONMEM

```
; OUTPUT
$TABLE ID TVV TVCL TVV2 TVCL2 V CL V2
CL2 NOPRINT NOAPPEND ONEHEADER &
      FILE =
TWO_COMPARTMENT_IV_BOLUS_PLASMA_
URINE.TXT
$TABLE ID IVAR PRED IPRED IRES WRES
CWRES FILE=Residuals.TXT
```

NLME

Table01 [x] [✓]

Add Table

Structural Parameter Estimates

Times: seq(0,36,0.1)

When covr set:

When dose:

When observe: CObs,CObsurine

Variables: C,Curine,IRES

[ ] TAD [✓] IRES [✓] Weight [✓] IWRES

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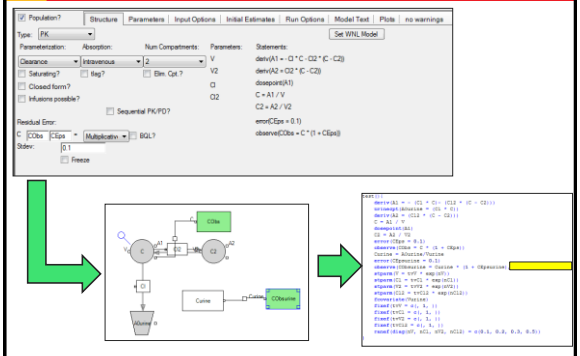
Using the PML: 2c_iv_multiple_plasma_urine



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Demo

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2c_iv_multiple_plasma_urine: Results

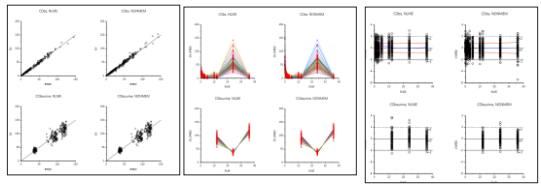

Table 1: Theta

	Source			
	NLME		NONMEM	
Parameter	Estimate	Stderr	Estimate	Stderr
stdev0	0.097	0.003	0.102	0.024
stdev1	0.136	0.005	0.136	0.038
tvCl	1.018	0.030	0.992	0.020
tvCl2	0.996	0.074	0.961	0.093
tvV	0.932	0.031	0.930	0.033
tvV2	0.950	0.052	0.998	0.053

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2c_iv_multiple_plasma_urine: Summary

- Setup and Run NONMEM & Phoenix NLME Model:
  - 2-compartment IV Bolus
  - Multiple Doses
  - Plasma and Urine Observations
  - Sampling methods: IMP and QRPEM
- Postprocessed the NONMEM results and compared them with the NLME results
  - Only small differences

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Questions?

Coming up…

NONMEM-2-NLME
PK 2-compartment oral with Disease State covariate on V and CL
March 8, 2018 | 10am EST
Presenter: Venkateswari Muthukrishnan

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