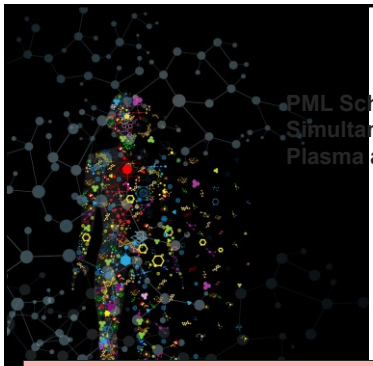

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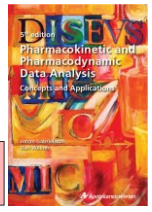
PML School: PK6 Simultaneous Fitting of Plasma and Urine Data



Note: The exercise is based on exercise PK6 in the text: Gabrielsson, J. & Weiner, D.L. (5th ed., 2016). *Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications*. Swedish Pharmaceutical Press, Stockholm.

PK6: Objective

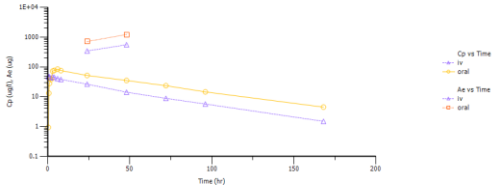
- Simultaneously fit plasma and urine data
  - Simultaneously fit IV and PO data in first step
- Find estimates for
  - Cl - clearance
  - V – volume of distribution
  - F - bioavailability
  - K_a - absorption rate constant
  - t_{lag} – lag time
  - f_e – fraction excreted

PK6: Problem specification

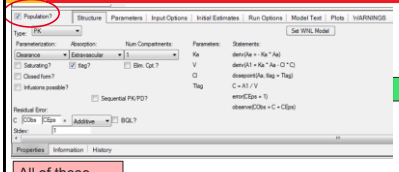
- 1 subject received oral dose of 25 mg
- Followed by IV dose of 12.5 mg
- Plasma and urine samples were collected

PK6: Exploratory Data Analysis

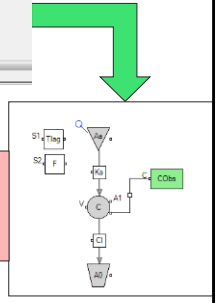
- Linear and semilog plot of concentrations/amount excreted versus time



PK6: Simultaneous Fit of IV and PO Data

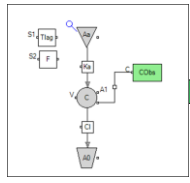


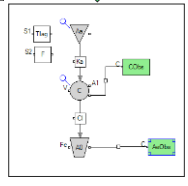
All of these models require Population mode due to simultaneous fitting of IV/PO



Need to add Bioavailability (F) to Aa dosepoint and add A1 dosepoint

PK6: Simultaneous Fit of IV/PO and Plasma/Urine





Need to add continuous observation for elimination compartment

PK6: PML Code

```
test(){
    # structural model
    deriv(Al = - (Cl * C) + (Aa * Ka))          # this is the DE for the amount in plasma compartment
    deriv(Aa = - (Aa * Ka))                     # this is the DE for the amount in absorption compartment
    urineqpt(A0 = (Cl * C), fe=Fe)              # this is the DE for the amount in elimination compartment
    C = Al / V                                  # convert amounts to concentrations
    dosepoint(Al)                               # dosepoint specifies drug amount for IV input
    dosepoint(Aa, tlag = (Tlag), bioavail = (F))  # dosepoint specifies drug amount for oral input
    error(CEps = 4.72921)                           # initial estimate of the within error standard deviation
    error(AeEps = 0.021808)                         # same for Amount excreted
    observe(CObs = C + CEps)                    # use an additive residual error model for plasma conc
    observe(AeObs = A0 + AeEps)                 # same for Amount excreted
    # structural parameters
    stparm(V = tvV)
    stparm(Fe = tvFe)
    stparm(Cl = tvCl)
    stparm(Tlag = tvTlag)
    stparm(Ka = tvKa)
    stparm(F = tvF)
    # fixed effects - the actual parameters to be
    # estimated (lower bound, initial estimate, upper bound)
    fixef(tvV = c(, 294.414, ))
    fixef(tvFe = c(, 0.0711384, ))
    fixef(tvCl = c(, 5.91085, ))
    fixef(tvTlag = c(, 0.316774, ))
    fixef(tvKa = c(, 0.43059, ))
    fixef(tvF = c(, 1.13906, ))
    }
```

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PK6: Initial Estimates

- V = from NCA
- Cl = from NCA
- F = AUC_{po}/AUC_{iv}
- K_a = start with value of 1
- t_{lag} – first measurable concentration after dose
- f_e = Percentage Recovered/100

Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

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Demo

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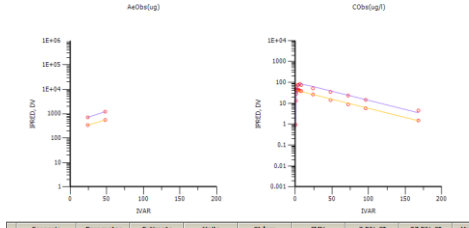
PK6: Results



	Scenario	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
1		tvV	294.414	l	6.3321402	2.1507606	281.28188	307.04612	84307
2		tvFe	0.0711383		1.8965231E-05	0.02665663	0.071098968	0.071177632	7.5628E-07
3		tvCl	5.91085	l/hr	0.12712199	2.150655	5.6672137	6.1744863	33.978
4		tvTlag	0.316774	hr	0.082077402	25.910397	0.14655469	0.48699301	14.165
5		tvKa	0.43059	1/hr	0.014537194	3.3761104	0.40044155	0.46073845	0.44435
6		tvF	1.13906		8.3923179E-05	0.0073677576	1.138886	1.139234	1.4809E-05
7		stdev0	4.72921		0.013314654	0.28154076	4.701597	4.756823	
8		stdev1	0.021808		0	0	0.021808	0.021808	

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PK6: Summary

- Typical one-compartment system
- Simultaneous fit of
  - iv and po administration
  - plasma and urine data
- Derive initial estimates
- Learn how to code the model in PML
- Fit the model to the data
- Examine results

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Questions?