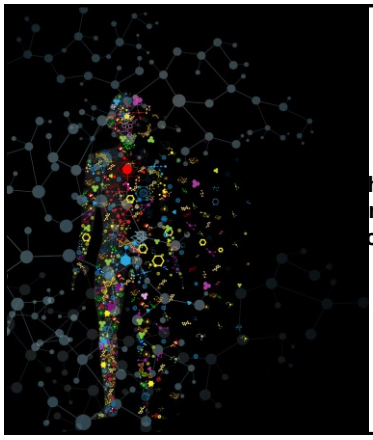

hool:
nonlinear
ce

PK24: Objective

- The drug is known to reduce cardiac output and hepatic blood flow as plasma concentration of the drug increases. Thus we will fit both a static 3 compartment model and a model with flow (concentration) dependent clearance
- Discuss how to obtain initial estimates
- Compare the fits of the two models

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

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PK24: Problem specification

- 1 healthy volunteer received a single intravenous infusion of 10mg/kg (10,000 ug/kg) over 2h
- Plasma samples were collected at various times until 7h after the last dose

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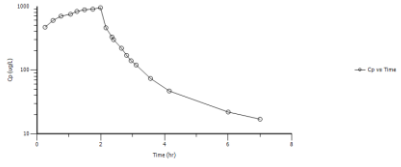
PK24: Exploratory Data Analysis

Semi-log plot of plasma concentrations versus time



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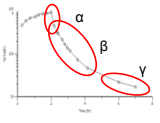
PK24: Results of NCA and Initial Estimates

Lambda_z (1/hr)	AUCINF_pred (hr*ug/L)	Cl_pred (L/hr/kg)	Vss_pred (L/kg)
0.36	1945.98	5.14	4.34



Initial estimates can be derived from the intercepts and slopes associated with the three phases, along with the NCA results. These are derived on Page 592-593 of G&W, 5th ed.

Parameter	Initial Estimate
V	0.5
V2	1.7
V3	1.7
Cl	4.3
Cl2	6.5
Cl3	2.2

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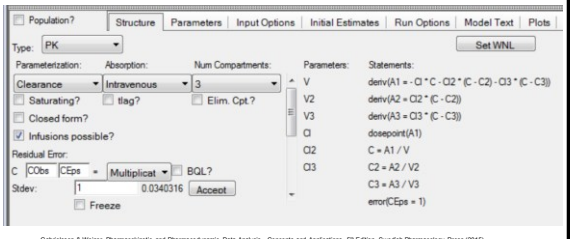
PK24: Built-in 3 Compartment (static Cl) Model

Although only the multiplicative error model is shown here, we will fit both the additive and multiplicative error models and determine the better fit.



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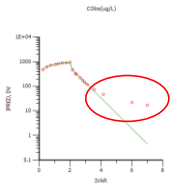
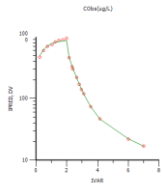
PK24: Static Clearance 3 Cmpt. Model – Additive vs Multiplicative Error

Additive Error



Multiplicative Error



Although the obs.& pred. plot vs. time looks good, the diagnostic plots are not so good and mechanistically (reduced CO and hepatic blood flow) we think Cl is not static

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General Strategy for User Model Building

- Start with a built in library model – (here the three compartment iv infusion model)
- If necessary, convert it to a graphical model and edit further as needed (graphical won't help here – so skip this step)
- If necessary, convert the graphical model to a textual model and edit it as needed

Following this approach speeds up the model building process and reduces the potential for coding errors.

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PK24: Cp Dependent Cl Model

```
test(){
        deriv(A1 = - Cl * C - Cl2 * (C - C2) - Cl3 * (C - C3))  # this is the DE for the amt. in plasma compartment
        deriv(A2 = Cl2 * (C - C2))                              # this is the DE for the amt. in1st tissue compartment
        deriv(A3 = Cl3 * (C - C3))                              # this is the DE for the amt. in 2nd tissue compartment
        dosepoint(A1)                                           # dosepoint specifies where the drug will be input - pl
        C = A1 / V                                              # convert amounts to concentrations
        C2 = A2 / V2
        C3 = A3 / V3
        Cl = Cl0 - a * C                                        # define Cl a a linear function of plasma conc.
        error(CEps = 1)                                         # initial estimate of the within error standard deviation
        observe(CObs = C * (1 + CEps))                          #  use a multiplicative error model
         # structural parameters
        stparm(V = tvV)
        stparm(V2 = tvV2)
        stparm(V3 = tvV3)
        #stparm(Cl = tvCl)
        stparm(Cl2 = tvCl2)
        stparm(Cl3 = tvCl3)
        # fixed effects – the actual parameters to be
        # estimated (lower bound, initial estimate, upper bound)
        fixef(a = c(, 0.0005, ))
        fixef(Cl0 = c(, 4.3, ))
        fixef(tvV = c(, 0.5, ))
        fixef(tvV2 = c(, 1.7, ))
        fixef(tvV3 = c(, 1.7, ))
        #fixef(tvCl = c(, 4.3, ))
        fixef(tvCl2 = c(, 6.5, ))
        fixef(tvCl3 = c(, 2.2, ))
        secondary(Min_Cl=Cl0 - a * 1000)        # optionally add a secondary parameter to predict minimal Cl
}
```

Start with the static model. Make a copy of it, convert it to a textual model and edit the three lines as indicated. Note that a "#" represents a comment (that is, we commented out 2 lines)

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What is a Structural Parameter (stparm)?

- Generally speaking, structural parameters are used for situations when a structural parameter (e.g., V, Cl, EC50, Emax) is not estimated directly. Rather it is some function of other fixed effects and possible between subject effects (etas).
- For example, for a given population model assume V is a function of BW (normalized to a 70kg BW) and incorporates an eta to account for between subject variability in V

$$V = a * \left(\frac{BW}{70}\right)^{b} * e^{\eta_V}$$

Here a and b are parameters (fixed effects) to be estimated, and then V is derived for each individual.

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PK24: Comparison of Models

Source	-2LL	AIC
Model fixed Cl Multiplicative	135.188	149.188
Model C dependent Cl multiplicative	104.2426	120.2426

	Source			
	Model C dependent Cl multiplicative		Model fixed Cl multiplicative	
Parameter	Estimate	CV%	Estimate	CV%
a	0.00251	9.79		
Cl0	6.62	2.32		
tvCl			5.10	1.01
tvCl2	5.91	7.51	6.64	38.70
tvCl3	0.930	3.29	0.725	6.00
tvV	0.685	11.54	0.762	48.45
tvV2	1.77	3.85	1.53	19.97
tvV3	3.20	5.98	2.38	10.72
stdev0	0.0151	16.23	0.0340	16.24

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Demo

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Questions?