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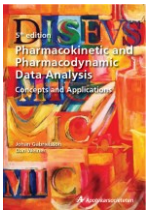
PML School: PD7 Turnover model 4 - IV infusions



Note: The exercise is based on exercise PD7 in the text: Gabrielsson, J. & Weiner, D.L. (5th ed., 2016). *Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications.* Swedish Pharmaceutical Press, Stockholm.

PD7: Objective

- Model response-time data with a turnover-model after iv infusion
- Find estimates for
  - K_{in} – input rate (0-order, turnover rate)
  - K_{out} – output rate (1st order, fractional turnover rate)
  - E_{max} – Maximum response
  - EC_{50} – Concentration at half-maximum response

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PD7: Problem specification

- 3 sets of constant intravenous infusion experiments with increasing doses were performed in a group of patients
- Response-time data was obtained
- Pharmacokinetics of the drug shows mono-exponential disposition with
  - V of 28.6 L
  - Ke of 2.8 1/hr.

➢ Need to simulate PK profiles first!

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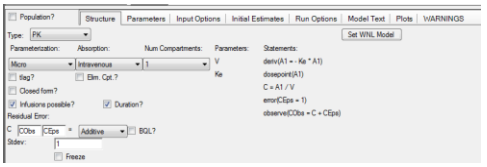
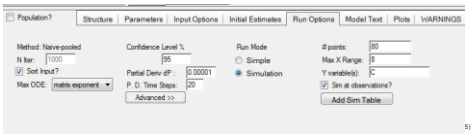
PD7: Simulation of PK Profiles

- Using Built-In options to setup PK model



- Using Run Options to setup Simulation



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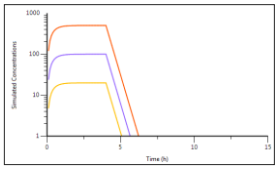
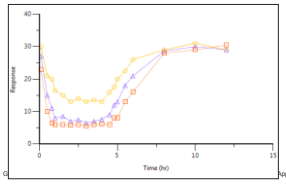
PD7: Exploratory Data Analysis



Plot of simulated PK profiles



Plot of response versus time

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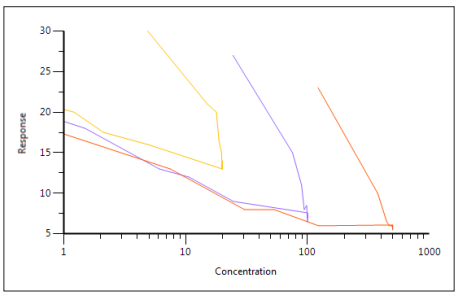
PD22: Exploratory Data Analysis II

- Hysteresis Plot



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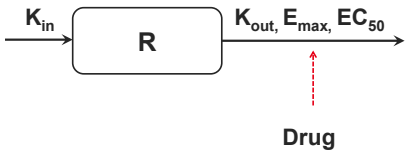
PD7: Turnover model with stimulation of loss



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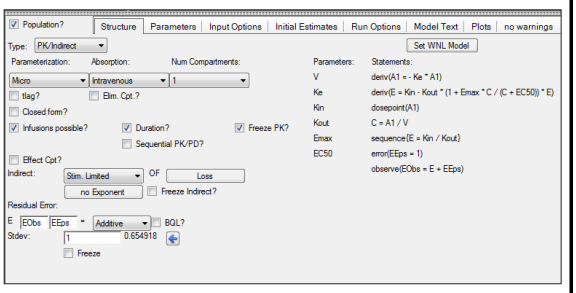
PD7: Built-in PKPD model: Stimulation of Loss



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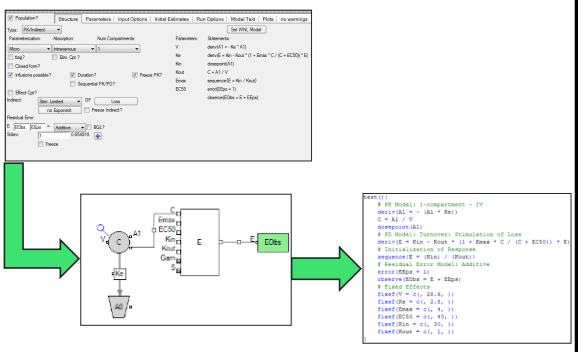
PD7: Graphical and Textual PKPD Model



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PD7: Model Equations + Textual Model

$$V \cdot \frac{dC}{dt} = In - K_e \cdot C$$

1-compartment model with IV input (Micro Parametrization)

$$\frac{dE}{dt} = K_{in} - K_{out} \cdot \left[1 + \frac{E_{max} \cdot C}{EC_{50} + C}\right] \cdot E$$

Turnover Model with Stimulation of Loss

```
test(){
  # PK Model: 1-compartment - IV
  C = A1 / V
  dosepoint(A1)
  # PD Model: Turnover: Stimulation of Loss
  # Initialization of Response
  sequence(E = (Kin) / (Kout))
  # Residual Error Model: Additive
  error(EEps = 1)
  observe(EObs = E + EEps)
  # Fixed Effects
  fixef(V = c(, 28.6, ))
  fixef(Ke = c(, 2.8, ))
  fixef(Emax = c(, 4, ))
  fixef(EC50 = c(, 40, ))
  fixef(Kin = c(, 30, ))
  fixef(Kout = c(, 1, ))
}
```

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PD7: Initial Estimates

- K_{out} – from initial slope (~1)
- K_{in} – from equation: $K_{in} = K_{out} \cdot E_0$ (~30)
- E_{max} – from Plot (~4)
- EC_{50} from steady state equation:
  - $E_{ss} = E_0 \cdot \frac{1}{1+\frac{E_{max} \cdot C_{ss}}{EC_{50}+C_{ss}}}$
  - With C_{ss} ~20 and E_{ss} ~13
  - $13 = 30 \cdot \frac{1}{1+\frac{4 \cdot 20}{EC_{50}+20}}$
  - $EC_{50} = \frac{4 \cdot 20}{\frac{30}{13}-1} - 20 \sim 40$

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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PD7: Summary

- Build Turnover Model
  - Simulated PK profile
  - Turned PK model into PKPD model with frozen PK parameters
  - Fitted the model and examined results

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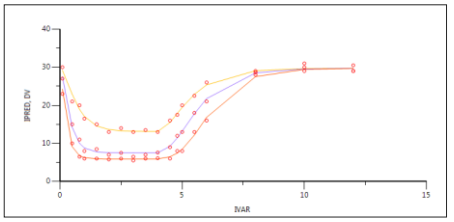
PD7: Results



	Scenario	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
1		V	32.7521		1.0601887	3.2370097	30.61927	34.88493	9.2094E+15
2		Ke	2.66593	L/hr	0.17865889	6.7015598	2.3065137	3.0253463	0.041331
3		Emax	4.43628		0.11100901	2.5022994	4.2129581	4.6596019	0.075749
4		EC50	45.8071		1.4828014	3.2370558	42.82408	48.79012	1.8014E+16
5		Kin	28.79		2.8266219	9.8159845	23.104761	34.475239	6.4185
6		Kout	0.968073	L/hr	0.095599163	9.8752019	0.77575175	1.1603945	0.0075859
7		stdev0	0.649673		0.054429771	8.3780258	0.54017412	0.75917188	

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Questions?

Coming up…

Turnover Model 1: Repeated Dosing I

Apply a turnover model to repeated po dosing response data

July 13, 2017 | 10am EST

Presenter: Chris Mehl

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