# PML Library:
# PD9 - Turnover models with repeated dosing

# PD9: Example 1 Objectives

- Characterize the PD of a new anxiolytic compound Zooparc® after repeated po dosing
- Data were collected during a Phase II study in psychiatric patients at 5mg and 25 mg dose levels
- Establish turnover characteristics of a biomarker.

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

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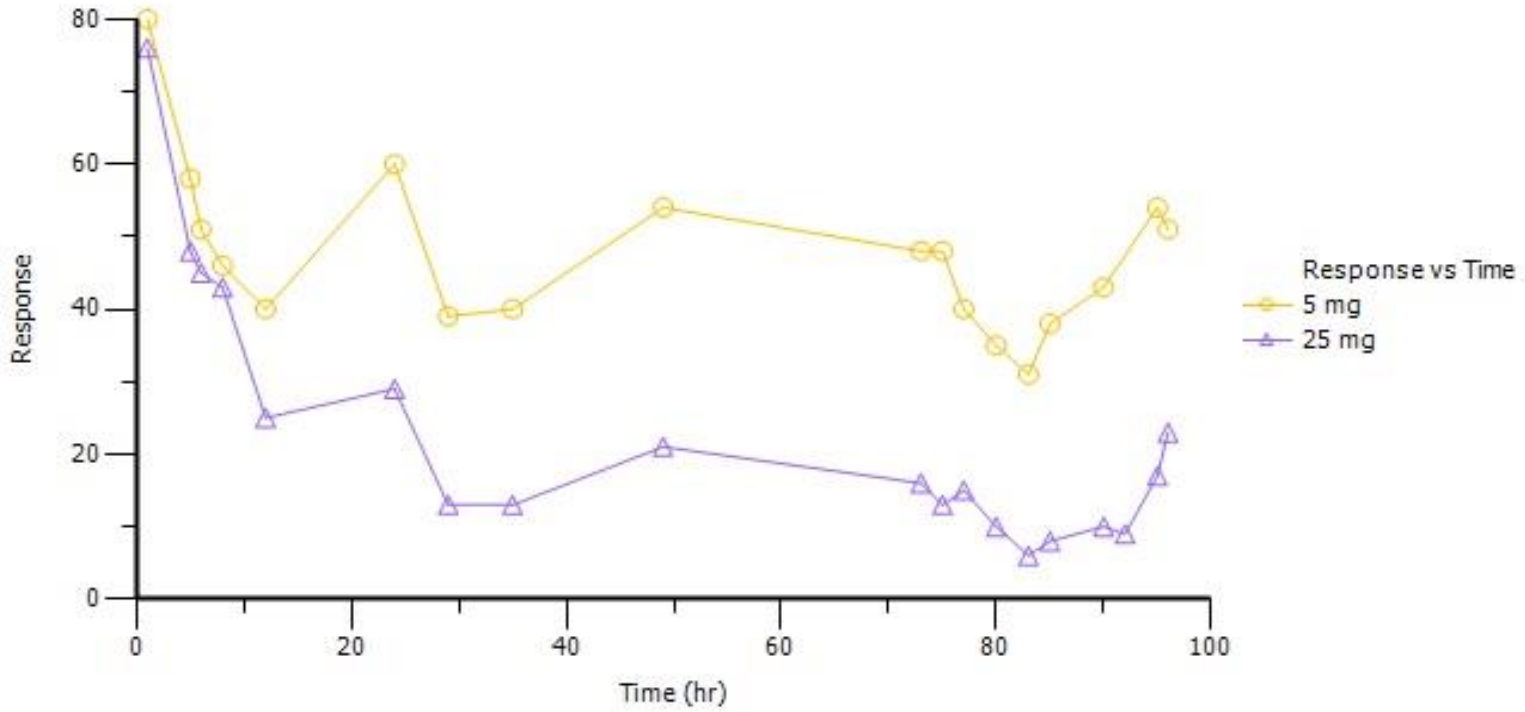
# PD9: Exploratory Data Analysis

- Observed Response-Time data following repeated QD administration of Zooparc® at 5mg and 25mg dose levels




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

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# PD9: PK parameters as fixed effects

- The pharmacokinetics of Zooparc® have been characterized in a previous study.

- Extravascular 1-compartment model:
- dC/dt = Dose*ka/V*(ka-ke)
  - Ka = absorption rate constant, 1.1 1/hr
  - Ke = elimination rate constant, 0.128 1/hr
  - V = volume of distribution, 5 L/kg

- Solve concentration function at different time points for a given dose level.

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

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# PD9: Turnover model: inhibition of kin

- Rate of production is inhibited by the function I(C), assuming Imax = 1
- Animal studies have shown that complete inhibition of response is possible, i.e. I(C) = 0 at high concentrations
- Indirect response is modeled using dR/dt = kin*I(C) – kout*R
  - Kin = zero order rate of production
  - Kout = first order rate of loss
  - I(C) = mechanistic inhibition of Kin

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

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# PD9: Objective: Model drug mechanism using Inhibitory function

- I(C)– typical inhibitory Imax function
- Inhibitory function $I(C) = 1 - Imax*C^{\gamma} / (IC50^{\gamma} + C^{\gamma})$
  - Imax = maximum inhibitory response
  - IC50 = concentration at which 50% of maximum inhibition occurs
  - Gamma = exponent for sigmoid Imax model

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

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# PD9: Objective: Full mechanistic Turnover model

- Full model, substituting in the mechanistic inhibition function:
- $dR/dt = Kin * (1 - Imax * C^{\gamma}/ (C^{\gamma}+ IC50^{\gamma})) - Kout * R$
- Get final estimates for the following parameters:
  - Kin = zero order rate of production
  - Kout = 1st order loss
  - Imax = maximum inhibition
  - IC50 = concentration at which 50% of maximum inhibition occurs
  - Gamma = exponent for sigmoid Imax function

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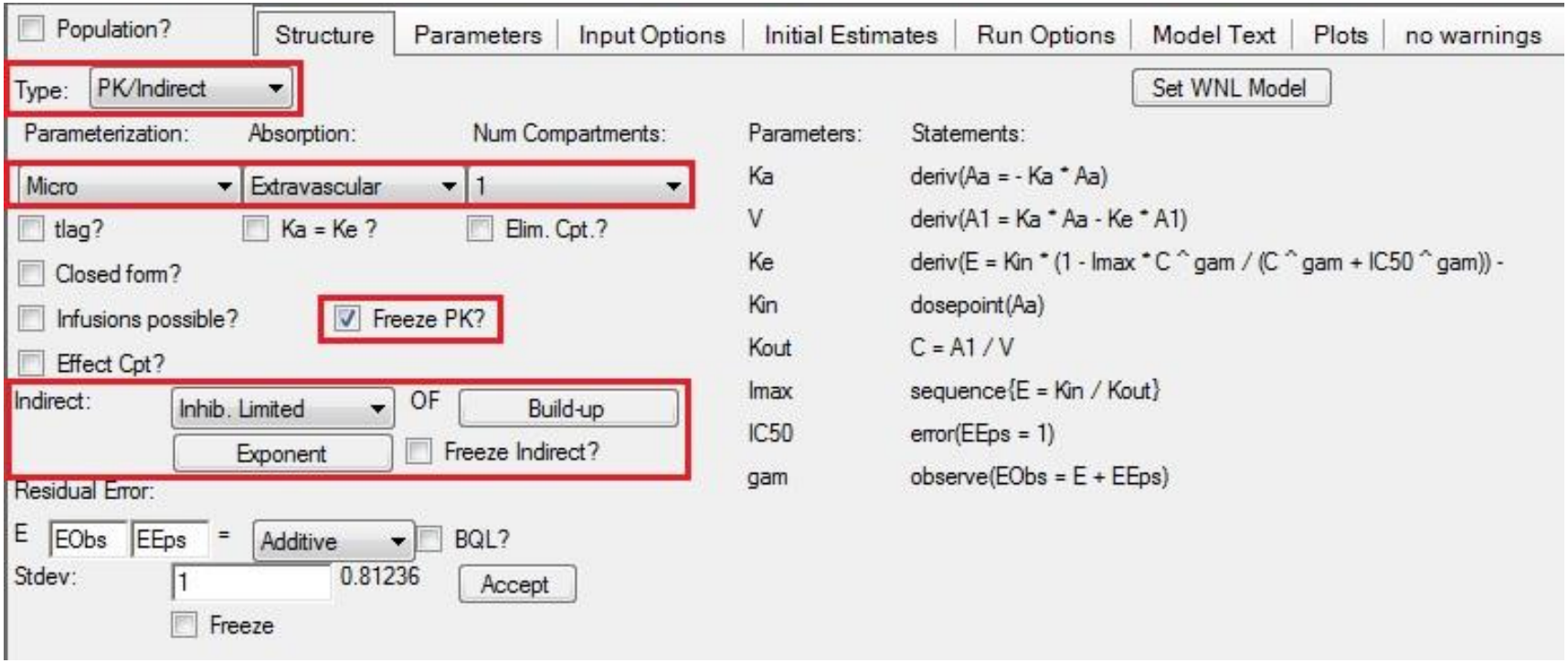
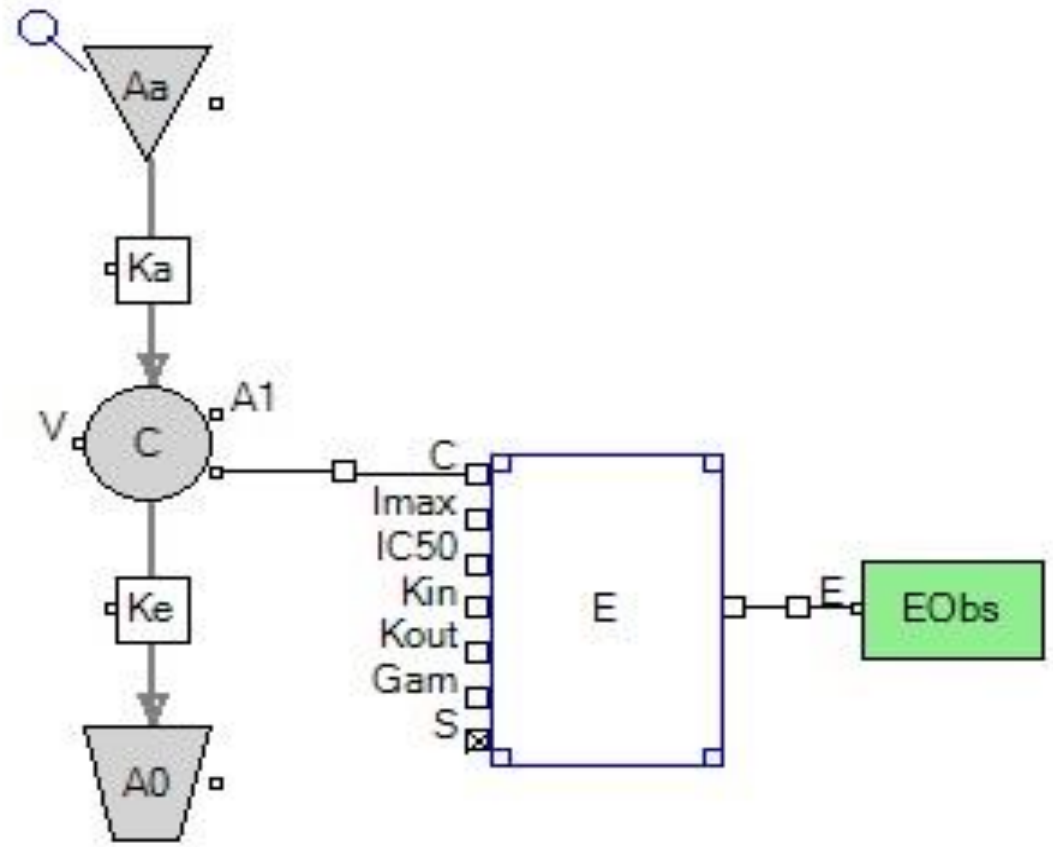
# PD9: Built-in PK/indirect: inhibition of production




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

# PD9: Graphical Model




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

# PD9: Indirect Response Model: PML Code

```
test(){
    # differential equations for PK model
    deriv(Aa = - Ka * Aa)
    deriv(A1 = Ka * Aa - Ke * A1)
    # differential equation for Indirect Response model
    deriv(E = Kin * (1 - Imax * C ^ gam / (C ^ gam + IC50 ^ gam)) - Kout * E)
    # extravascular dose administration
    dosepoint(Aa)
    # concentration in the central compartment
    C = A1 / V
    # baseline response R0
    sequence{E = Kin / Kout}
    # observed response and error model
    error(EEps = 1)
    observe(EObs = E + EEps)
    # PK parameters as frozen fixed effects
    fixef(Ka(freeze) = c(, 1.1, ))
    fixef(V(freeze) = c(, 5, ))
    fixef(Ke(freeze) = c(, 0.128, ))
    # Indirect response parameters with initial estimates
    fixef(Kin = c(, 4.8, ))
    fixef(Kout = c(, 0.06, ))
    fixef(Imax(freeze) = c(, 1, ))
    fixef(IC50 = c(, 0.25, ))
    fixef(gam = c(, 2, ))
}
```

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

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# PD9: Initial Estimates

- R0 = 80, from exploratory plot response at time = 0
- Onset slope = -kout = - (ln(R1) – ln(R2)) / (t1 – t2)
- -Kout = - ln(80/48) / (0-8) = -0.06 $hr^{-1}$
- Kin = R0*kout = 80*0.06 = 4.8 $hr^{-1}$
- Imax = 1
- IC50 is obtained by first finding the time of 50% inhibition, then solving the PK concentration function at that same time point. IC50 = 0.25 mg/L
- Gamma (exponent) = 2, obtained from Initial Estimates tab

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# Example 1 Demo

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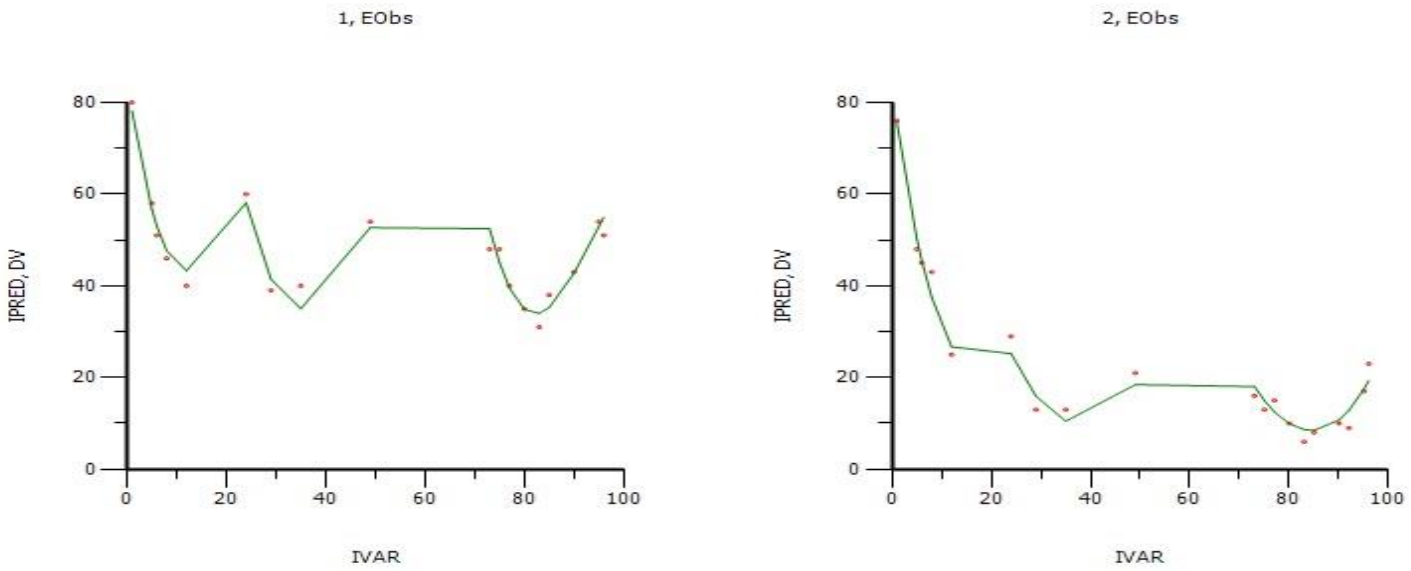
# PD9: Example 1 Results

- Fit




- Final Parameter Estimates

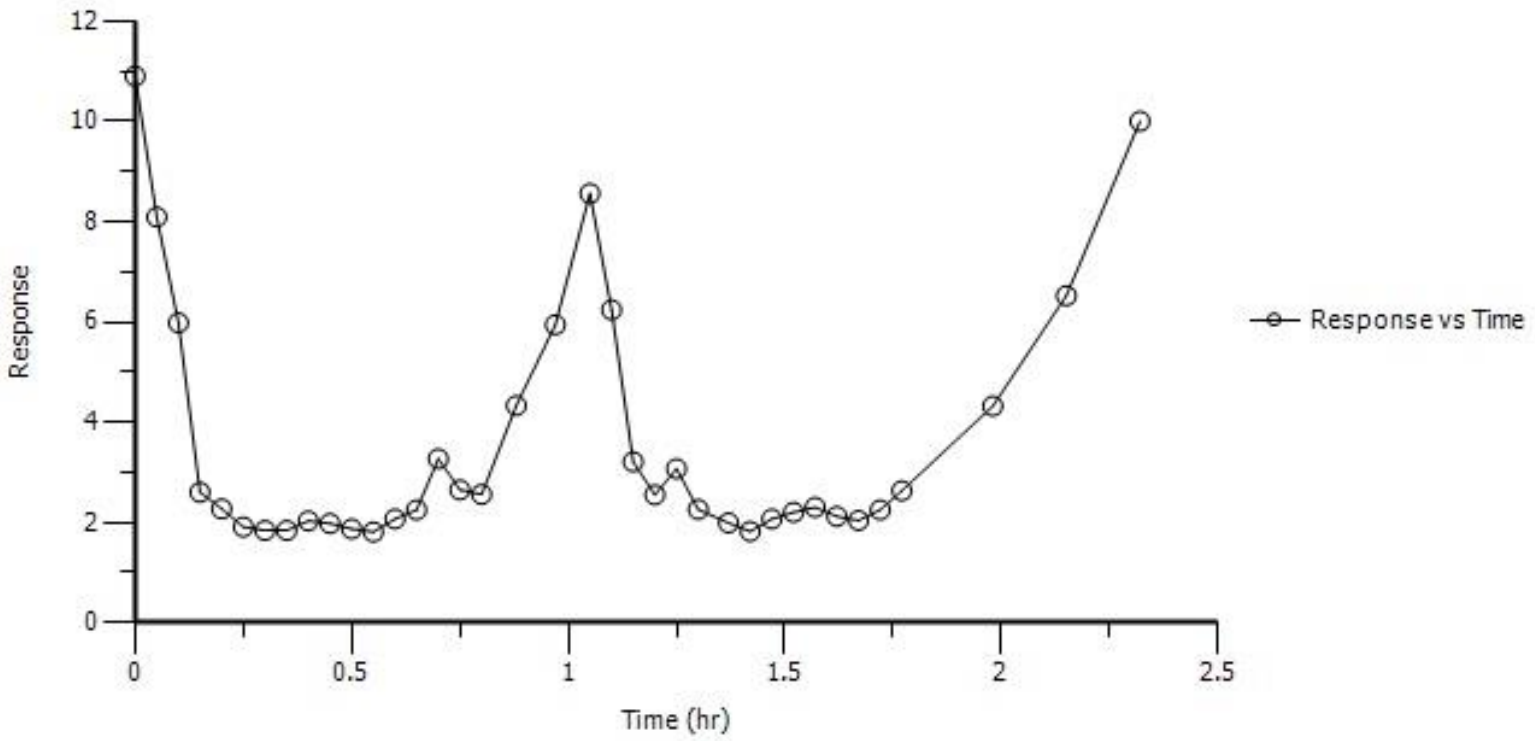
| Parameter | Estimate | Units | Stderr | CV% | 2.5% CI | 97.5% CI | Var. Inf. factor |
|---|---|---|---|---|---|---|---|
| Ka | 1.1 | 1/hr | 0 | 0 | 1.1 | 1.1 | 0 |
| V | 5 | | 0 | 0 | 5 | 5 | 0 |
| Ke | 0.128 | 1/hr | 0 | 0 | 0.128 | 0.128 | 0 |
| Kin | 8.80231 | | 0.31140006 | 3.5377084 | 8.1680101 | 9.4366099 | 0.059228 |
| Kout | 0.105859 | 1/hr | 0.0028807291 | 2.7212888 | 0.099991159 | 0.11172684 | 4.6806E-06 |
| Imax | 1 | | 0 | 0 | 1 | 1 | 0 |
| IC50 | 0.244842 | | 0.0053673085 | 2.1921519 | 0.23390917 | 0.25577483 | 3.2596E-05 |
| gam | 1.38354 | | 0.036746428 | 2.6559715 | 1.3086901 | 1.4583899 | 0.001387 |
| stdev0 | 2.57322 | | 0.0088998876 | 0.34586579 | 2.5550916 | 2.5913484 | |

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

# Example 2 Model 1: Inhibition of Production

# Example 2 Exploratory Data Analysis

- Observed Response-Time data following two rapid infusions




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

# Example 2 Objectives

- Mechanism of action is not known. Develop two different Turnover models for Response-Time data.

- Model 1: inhibition of production
  - dR/dt = kin * I(C) – kout * R

- Model 2: stimulation of loss
  - dR/dt = kin – kout * S(C) * R

- Compare the models using parameter precision and diagnostics (AIC, BIC, -2LL)

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

# Example 2 PK parameters as fixed effects

- The PK of compound 2 has been characterized in a previous study.
- IV infusion 3-compartment model with clearance parameters:
  - dA1/dt = - Cl * C - Cl2 * (C - C2) - Cl3 * (C - C3))
  - dA2/dt = Cl2 * (C - C2))
  - dA3/dt = Cl3 * (C - C3))
  - C = A1 / V
  - C2 = A2 / V2
  - C3 = A3 / V3
- PK parameter estimates:
  - V = 0.7633
  - V2 = 1.72876
  - V3 = 3.43857
  - Cl = 6.2417
  - Cl2 = 5.4595
  - Cl3 = 0.85806

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

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# Ex2: Model 1 drug mechanism using Inhibitory function

- I(C)– typical inhibitory Imax function
- Inhibitory function $I(C) = 1 - Imax*C^{\gamma} / (IC50^{\gamma} + C^{\gamma})$
  - Imax = maximum inhibitory response
  - IC50 = concentration at which 50% of maximum inhibition occurs
  - Gamma = exponent for sigmoid Imax model

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

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# Ex2: Model 1 Full mechanistic Turnover model

- Full model, substituting in the mechanistic inhibition function:
- $dR/dt = Kin * (1 - Imax * C^{\gamma}/ (C^{\gamma}+ IC50^{\gamma})) - Kout * R$
- Get final estimates for the following parameters:
  - Kin = zero order rate of production
  - Kout = 1st order loss
  - Imax = maximum inhibition
  - IC50 = concentration at which 50% of maximum inhibition occurs
  - Gamma = exponent for sigmoid Imax function

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

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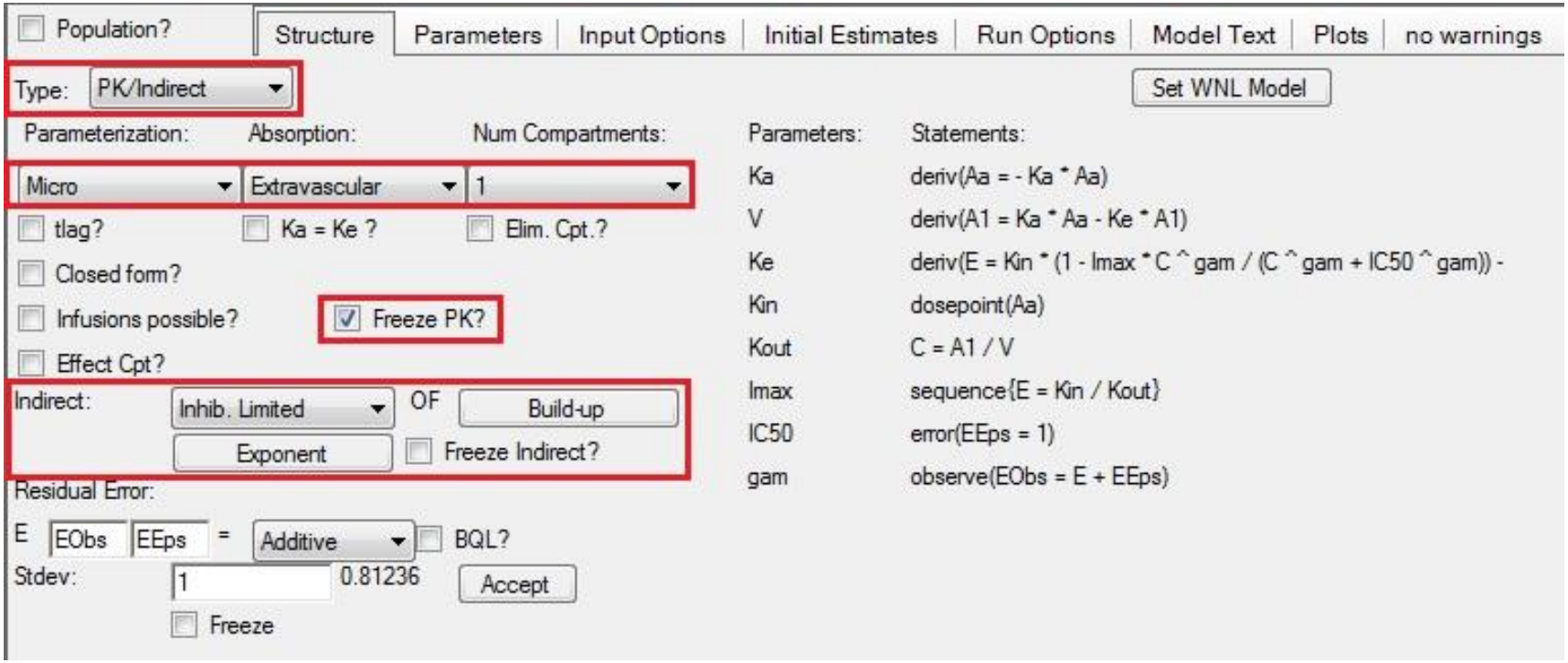
# Ex2: Built-in PK/indirect: inhibition of production

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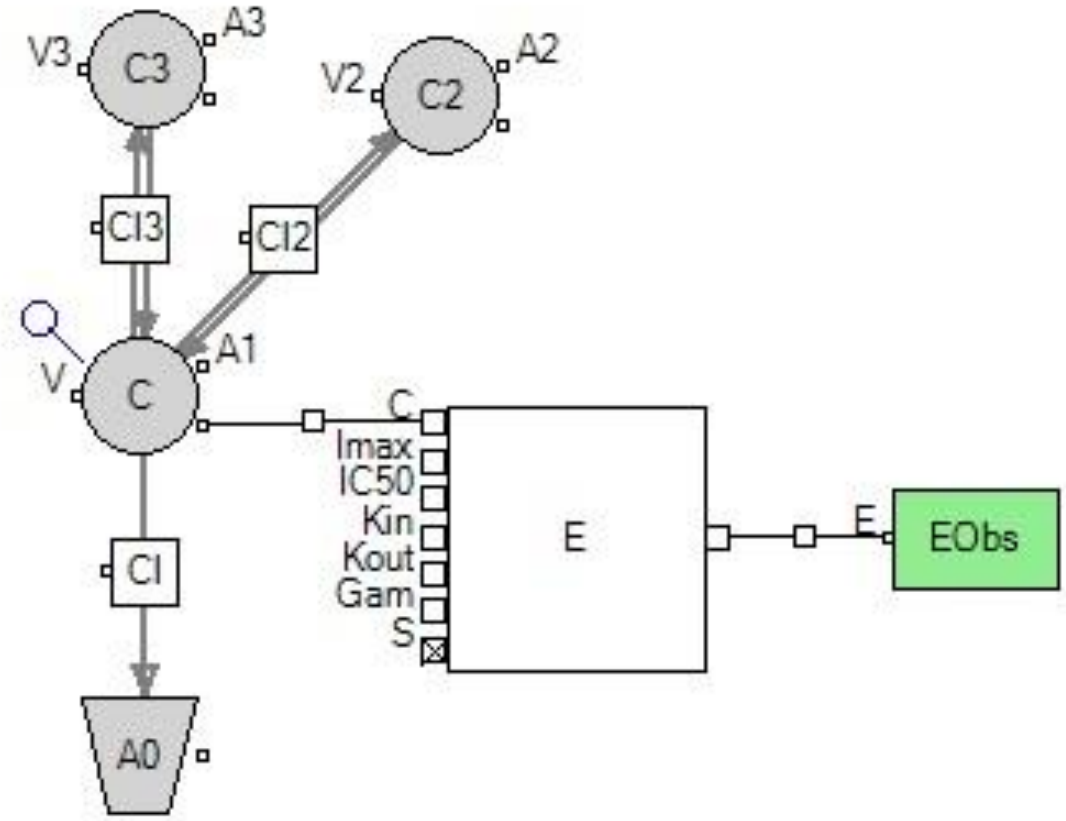
# Ex2: Model 1 Graphical

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# Ex2: Model 1 inhibition of production: PML Code

```
test(){
    # differential equations for the PK model
    deriv(A1 = - Cl * C - Cl2 * (C - C2) - Cl3 * (C - C3))
    deriv(A2 = Cl2 * (C - C2))
    deriv(A3 = Cl3 * (C - C3))
    # differential equation for Indirect Response model
    deriv(E = Kin * (1 - Imax * C ^ gamma / (C ^ gamma + IC50 ^ gamma)) - Kout * E)
    # IV dose administration
    dosepoint(A1)
    # concentrations in central and peripheral compartments
    C = A1 / V
    C2 = A2 / V2
    C3 = A3 / V3
    # baseline response R0
    sequence{E = Kin / Kout}
    # observed response and error model
    error(EEps = 1)
    observe(EObs = E + EEps)
    # PK parameters as frozen fixed effects
    fixef(V(freeze) = c(, 0.7633, ))
    fixef(V2(freeze) = c(, 1.72876, ))
    fixef(V3(freeze) = c(, 3.43857, ))
    fixef(Cl(freeze) = c(, 6.2417, ))
    fixef(Cl2(freeze) = c(, 5.4595, ))
    fixef(Cl3(freeze) = c(, 0.85806, ))
    # Indirect response parameters with initial estimates
    fixef(Kin = c(, 48.4, ))
    fixef(Kout = c(, 4.4, ))
    fixef(Imax = c(, 1, ))
    fixef(IC50 = c(, 300, ))
    fixef(gamma = c(, 4, ))
}
```

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# Ex2 Model 1: Initial Estimates

- R0 = 11, from exploratory plot response at time = 0
- Onset slope = -kout = - (ln(R1) – ln(R2)) / (t1 – t2)
- -Kout = - ln(7.5/2.5) / (0-0.25) = -4.4 $hr^{-1}$
- Kin = R0*kout = 11*4.4 = 48.4 $hr^{-1}$
- Imax = 1 - Rmin/R0 = 1 - 2/11 = 0.82
- IC50 is obtained by first finding the time of 50% inhibition, then solving the PK concentration function at that same time point. IC50 = 250 mg/L
- Gamma (exponent) = 10, obtained from Initial Estimates tab

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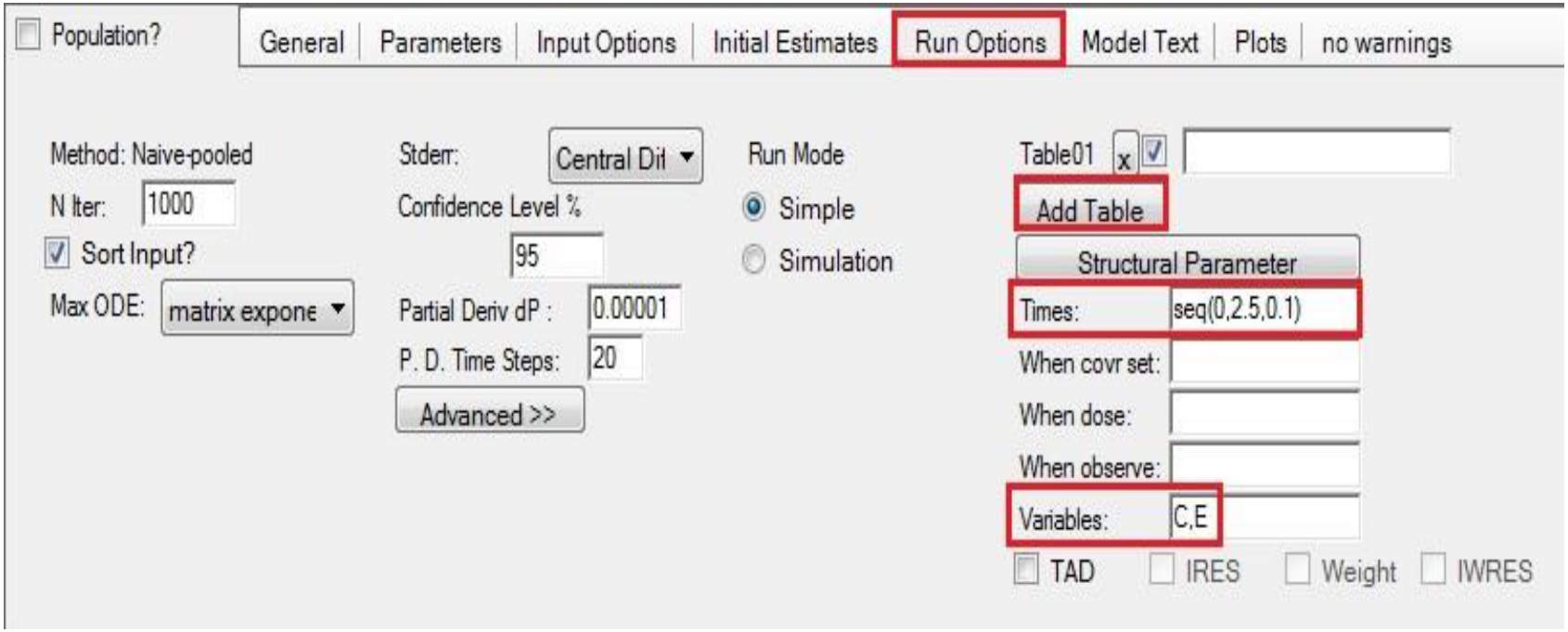
# Ex2 Run Options: add a table with more predicted points




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

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# Example 2 Model 2: Stimulation of Loss

# Ex2: Model 2 drug mechanism using Stimulatory function

- S(C)– typical stimulatory Emax function

- Stimulatory function $S(C) = (1 + Emax * C^{\gamma} / (C^{\gamma} + EC50^{\gamma}))$
  - Emax = maximum stimulatory response
  - EC50 = concentration at which 50% of maximum stimulation occurs
  - Gamma = exponent for sigmoid Imax model

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

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# Ex2: Model 2 Full mechanistic Turnover model

- Full model, substituting in the mechanistic inhibition function:
- $dR/dt = Kin - Kout * (1 + Emax * C^{\gamma} / (C^{\gamma} + EC50^{\gamma})) * R$
- Get final estimates for the following parameters:
  - Kin = zero order rate of production
  - Kout = 1st order loss
  - Emax = maximum stimulation
  - EC50 = concentration at which 50% of maximum stimulation occurs
  - Gamma = exponent for sigmoid Emax function

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

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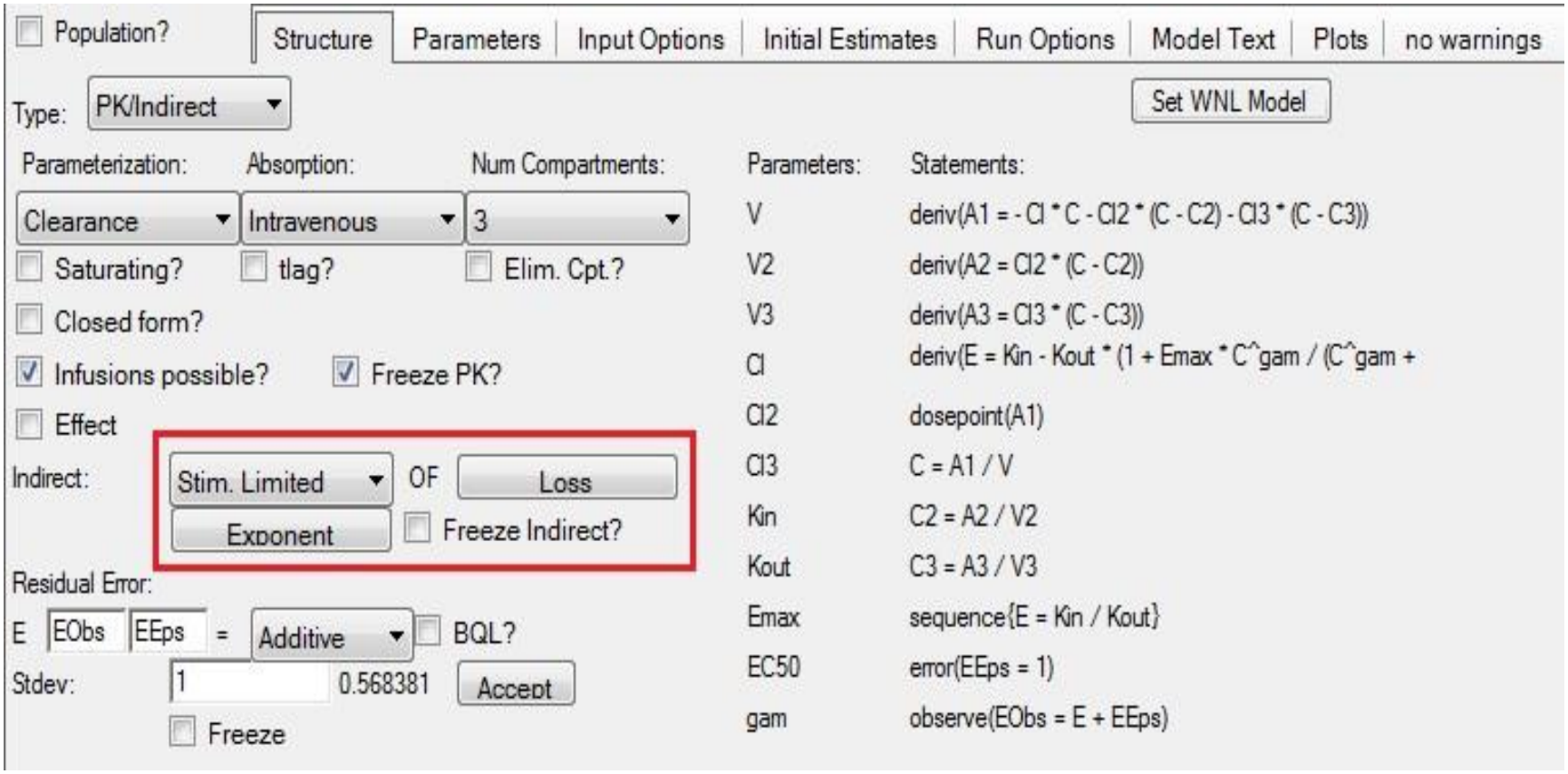
# Ex2: Built-in PK/indirect: stimulation of loss

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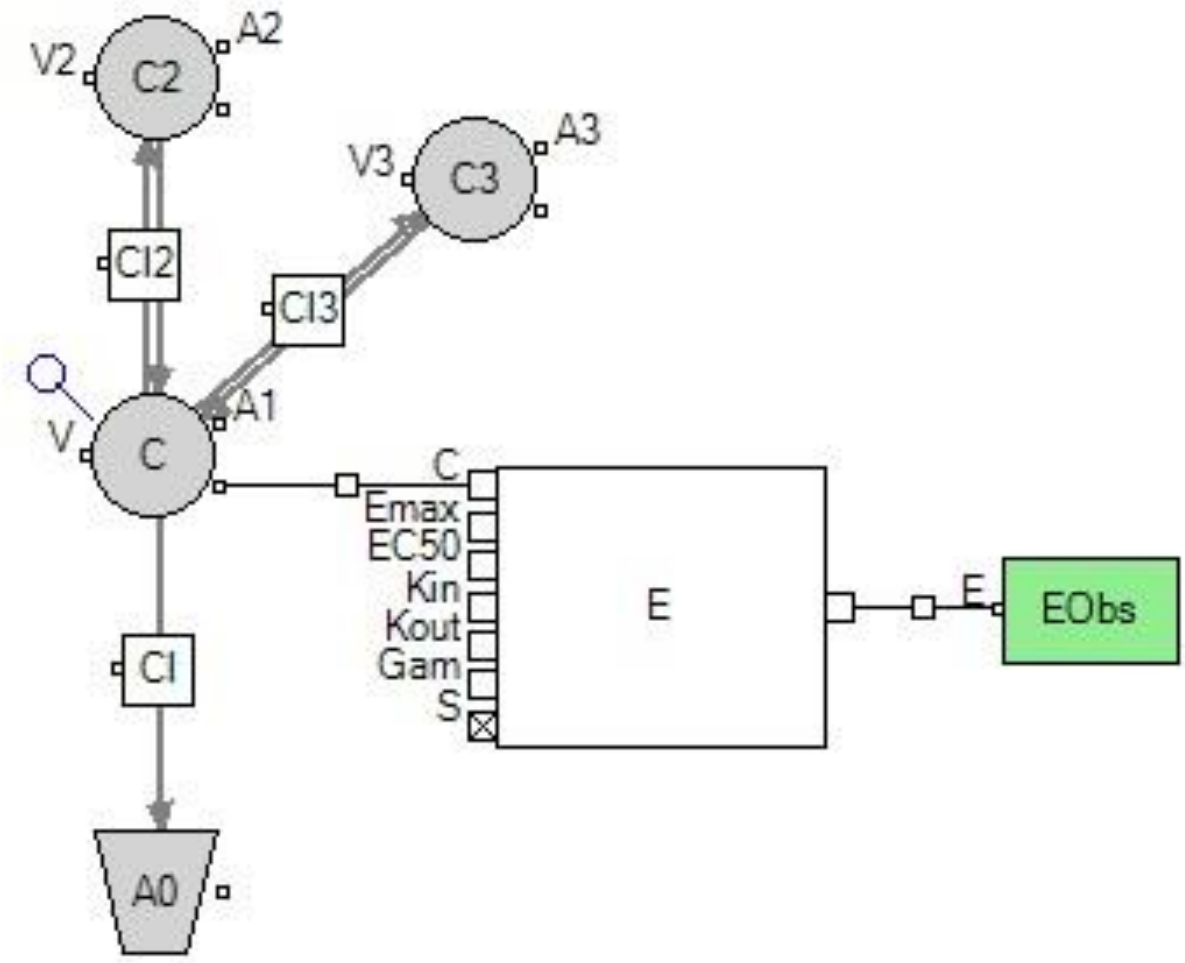
# Ex2: Model 2 Graphical




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

# Ex2: Model 2 stimulation of loss: PML Code

```
test(){
    # differential equations for the PK model
    deriv(A1 = - Cl * C - Cl2 * (C - C2) - Cl3 * (C - C3))
    deriv(A2 = Cl2 * (C - C2))
    deriv(A3 = Cl3 * (C - C3))
    # differential equation for Indirect Response model
    deriv(E = Kin - Kout * (1 + Emax * C^gamma / (C^gamma + EC50^gamma)) * E)
    # IV dose administration to central compartment
    dosepoint(A1)
    # concentrations in central and peripheral compartments
    C = A1 / V
    C2 = A2 / V2
    C3 = A3 / V3
    # baseline response R0
    sequence{E = Kin / Kout}
    # observed response with error model
    error(EEps = 1)
    observe(EObs = E + EEps)
    # PK parameters as frozen fixed effects
    fixef(V(freeze) = c(, 0.7633, ))
    fixef(V2(freeze) = c(, 1.72876, ))
    fixef(V3(freeze) = c(, 3.43857, ))
    fixef(Cl(freeze) = c(, 6.2417, ))
    fixef(Cl2(freeze) = c(, 5.4595, ))
    fixef(Cl3(freeze) = c(, 0.85806, ))
    # Indirect response parameters with initial estimates
    fixef(Kin = c(, 48.4, ))
    fixef(Kout = c(, 4.4, ))
    fixef(Emax = c(, 4.5, ))
    fixef(EC50 = c(, 350, ))
    fixef(gamma = c(, 1, ))
}
```

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# Ex2 Model 2: Initial Estimates

- R0 = 11, from exploratory plot response at time = 0
- Onset slope = -kout = - (ln(R1) – ln(R2)) / (t1 – t2)
- -Kout = - ln(7.5/2.5) / (0-0.25) = -4.4 $hr^{-1}$
- Kin = R0*kout = 11*4.4 = 48.4 $hr^{-1}$
- Emax = R0/Rmin - 1 = 11/2 - 1 = 4.5
- EC50 is obtained by first finding the time of 50% recovery, then solving the PK concentration function at that same time point. EC50 = 350 mg/L
- Gamma (exponent) = 10, obtained from Initial Estimates tab

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# Example 2 Demo

# Example 2 Results comparison

- Overall

| | Source | RetCode | -2LL | AIC | BIC | nParm |
|---|---|---|---|---|---|---|
| 1 | Model inh Kin | 1 | 44.87176 | 56.87176 | 66.537267 | 6 |
| 2 | Model stim Kout | 1 | 63.19406 | 75.19406 | 84.859567 | 6 |

- Final Parameter Estimates

| | Source | Parameter | Estimate | CV% |
|---|---|---|---|---|
| 7 | Model stim Kout | EC50 | 309.902 | 5.4251966 |
| 8 | Model stim Kout | Emax | 4.38766 | 8.6242905 |
| 9 | Model inh Kin | gamma | 7.0629 | 12.506123 |
| 10 | Model stim Kout | gamma | 21.533 | 88.677962 |
| 11 | Model inh Kin | IC50 | 244.203 | 2.2904303 |
| 12 | Model inh Kin | Imax | 0.830643 | 1.423949 |
| 13 | Model inh Kin | Kin | 143.314 | 8.7613725 |
| 14 | Model stim Kout | Kin | 34.3159 | 10.159728 |
| 15 | Model inh Kin | Kout | 12.5528 | 7.2383399 |
| 16 | Model stim Kout | Kout | 2.87789 | 10.617335 |
| 17 | Model inh Kin | stdev0 | 0.443719 | 11.6247 |
| 18 | Model stim Kout | stdev0 | 0.56838 | 11.624738 |

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

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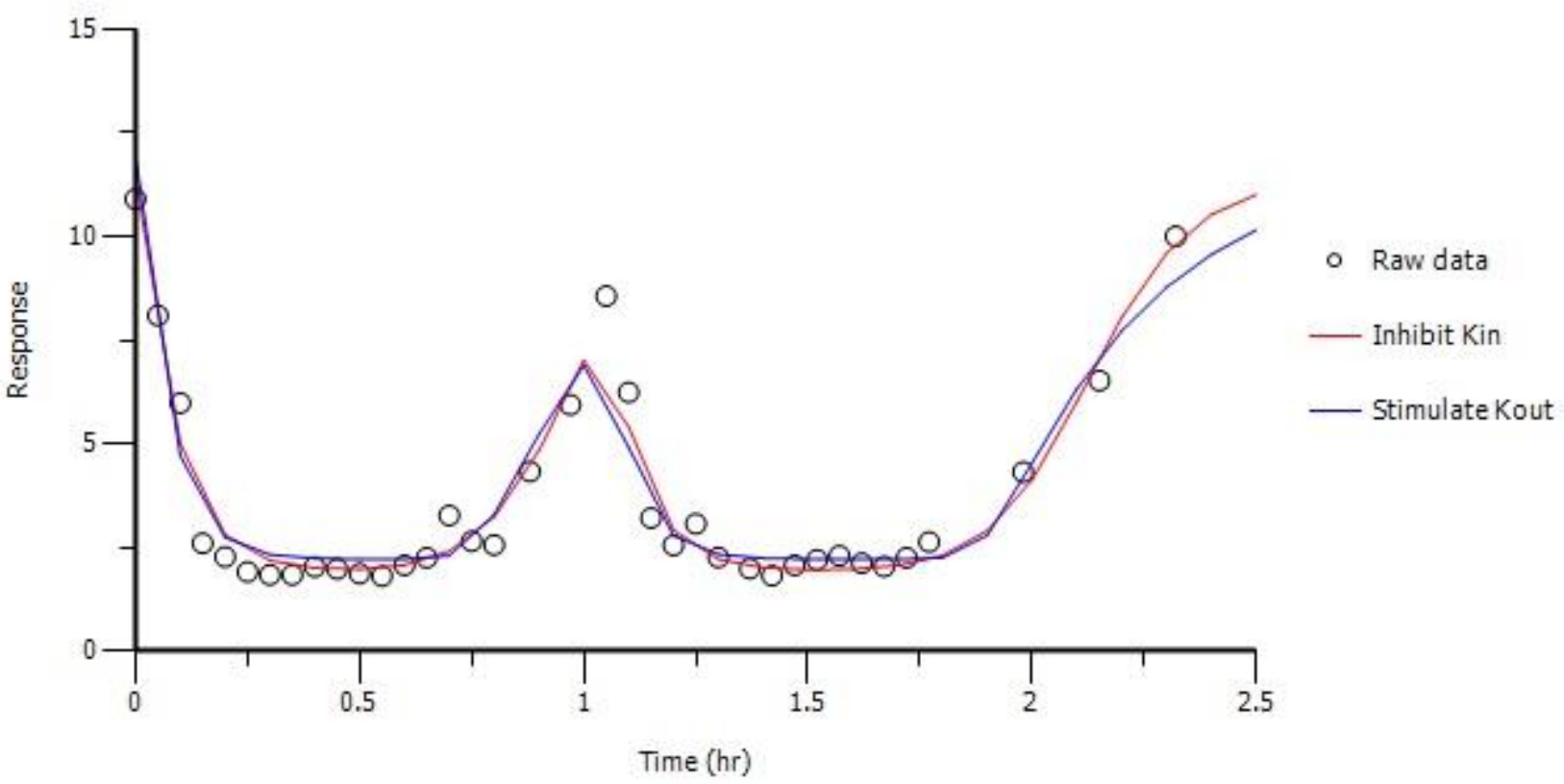
# Example 2: Overlay Plot

- Overlay predicted responses for both models with observed data:




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

# Questions?

# PML School: Materials

- Each model will be made available in Certara Forum
  - Link to live webinar and presentation slides
    - https://support.certara.com/forums/forum/34-pml-school/
  - Model text as file download
    - Can be imported into Phoenix model object to be run on a new dataset
  - Questions and comments can be exchanged in the Forum
    - Or can be entered into the Certara Support portal at:
      - https://support.certara.com/support
    - Or can be sent as emails to support@certara.com

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# PML School: Channels

- Notifications on updates of materials, Q&A and discussions
- Announcements of new sessions
  - PML School on LinkedIn:
    - If you have a LinkedIn Account, please join our new LinkedIn Group:
      - https://www.linkedin.com/groups/8614342
  - PML School on Twitter: @PML_School
  - PML School on Youtube:
    - https://www.youtube.com/user/CertaraLP/videos

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# Certara University

- A wide range of On Demand and Classroom courses are available through Certara University:
  - Introductory, intermediate and advanced instruction in Phoenix WinNonlin, Population Modeling using NLME, IVIVC Toolkit
  - Fundamentals of Pharmacokinetics and Pharmacodynamics
  - Noncompartmental data analysis
  - Programming Bootcamp
  - Partner Lectures and Webinar series
- Please visit our Certara University web site for more information

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# Coming up…


Dose-response-time Analysis I-IV

Analyze dose-response-time data with an instantenous effect model

July 27, 2017 | 10am EST

*Presenter: Bernd Wendt*

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