PML Library: PD12 - Modeling inhibition of enzyme activity by means of Turnover

PD12: Study Background

- APP mice produce excess human Amyloid Precursor Protein.
- Cleavage of APP initiates a cascade of secretases, including gamma secretase (GSECR), that results in the formation of amyloid peptide fragments that deposit to form insoluble plaques in the brain.
- By inhibiting GSECR, one hopes to produce less plaque formation via a decrease in formation of amyloid peptide fragments.
- Concentration of soluble beta-amyloid in brain serves as a biomarker of GSECR enzyme activity.

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

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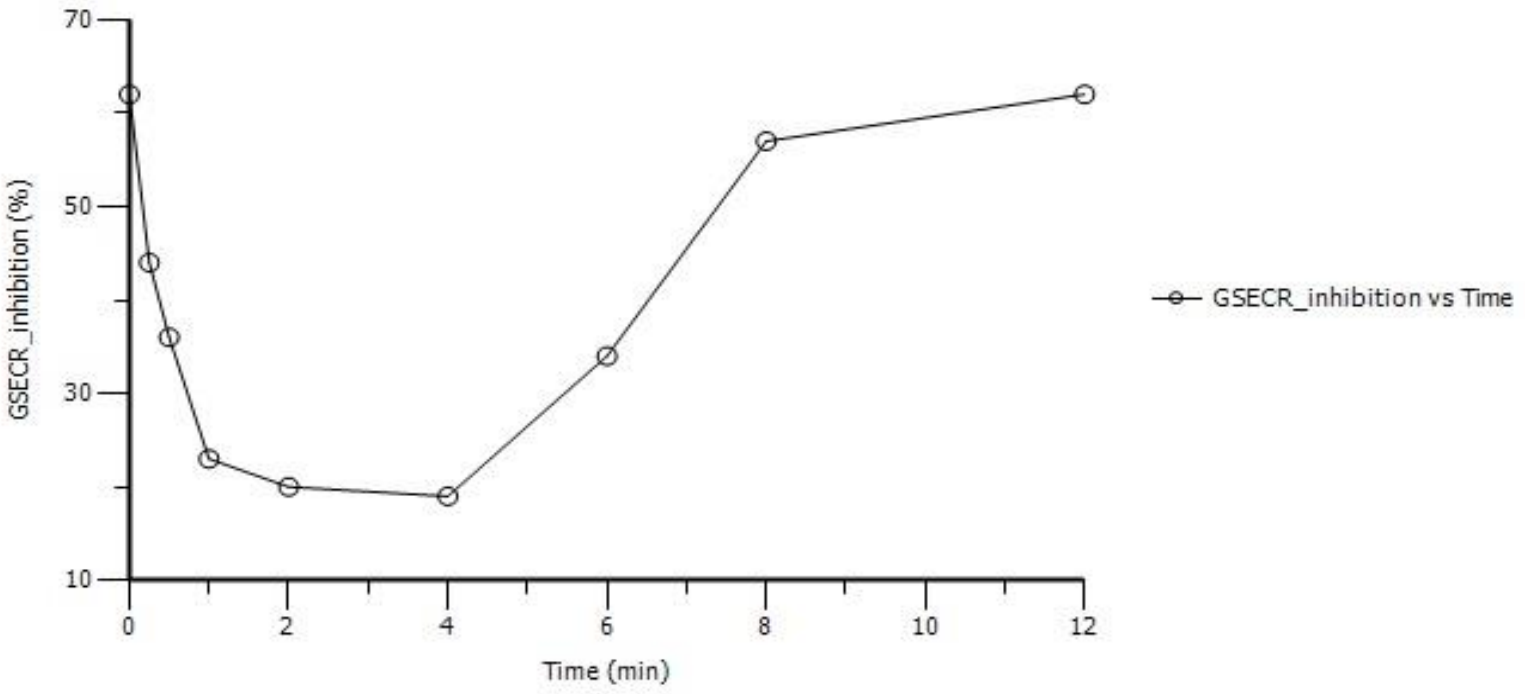
PD12: Exploratory Data Analysis

- Characterize the turnover-driven response to a gamma secretase (GSECR) inhibitor in mice
- Response is measured as % decrease in the biomarker beta-amyloid vs time



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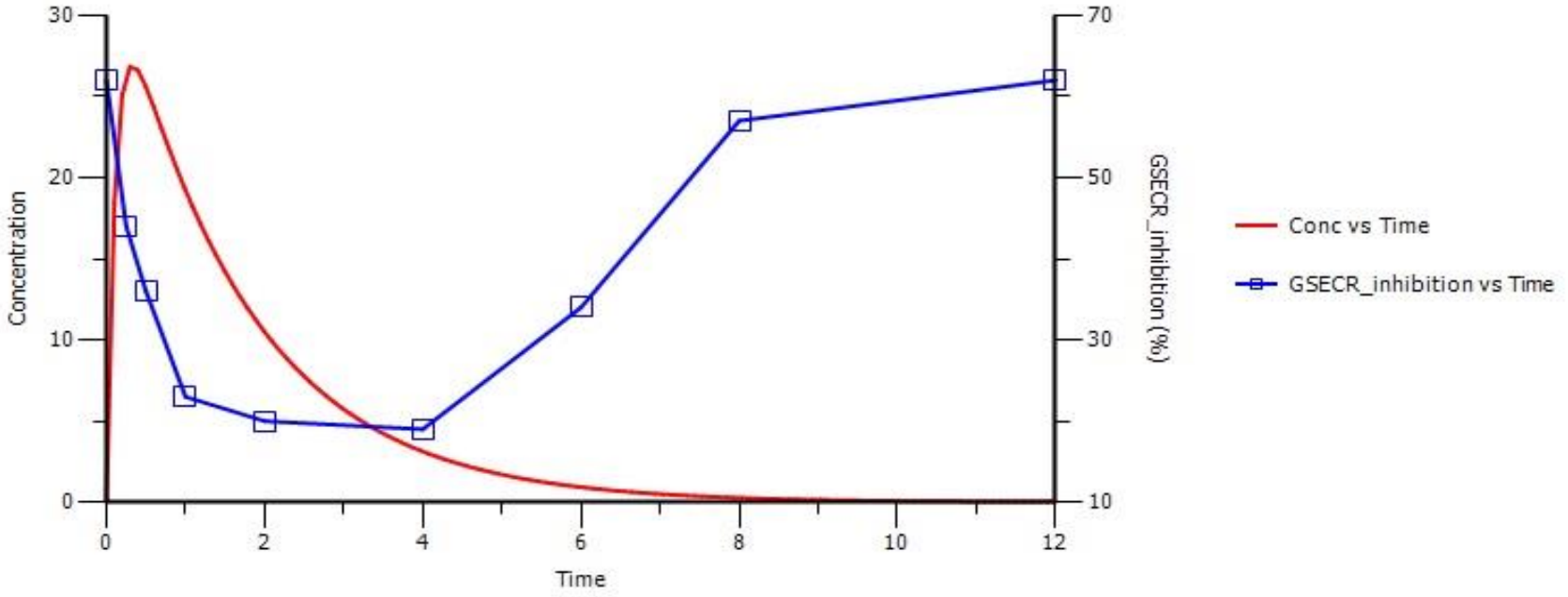
PK12: Protocol

- Previous studies show a delay between peak inhibitor concentration and maximum inhibitory response, suggesting an indirect response model.



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PD12 Objective: use PK from previous study to simulate concentrations

- PK: use fixed parameters from a 1-compartment model obtained from a previous study to simulate concentrations.

- Extravascular 1-compartment model:
- dC/dt = Dose*ka/V*(ka-ke)
  - Ka = absorption rate constant, 8.8 1/hr
  - Ke = elimination rate constant, 0.605 1/hr
  - V = volume of distribution, 3.05 L

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

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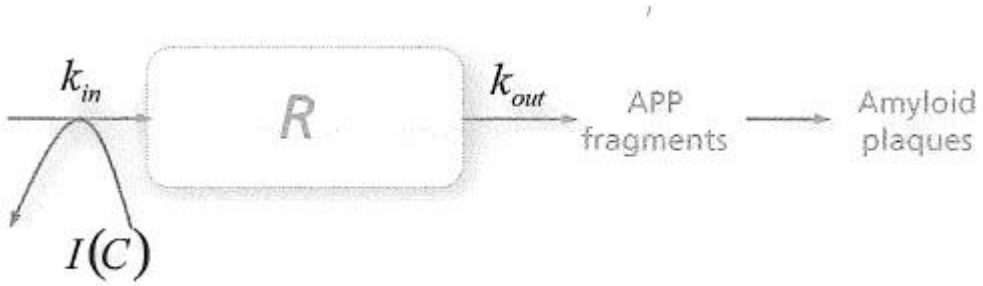
PD12: Objective: Construct mechanistic Turnover model



- Rate of production is inhibited by the function I(C)

- 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

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PD12: 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

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PD12: 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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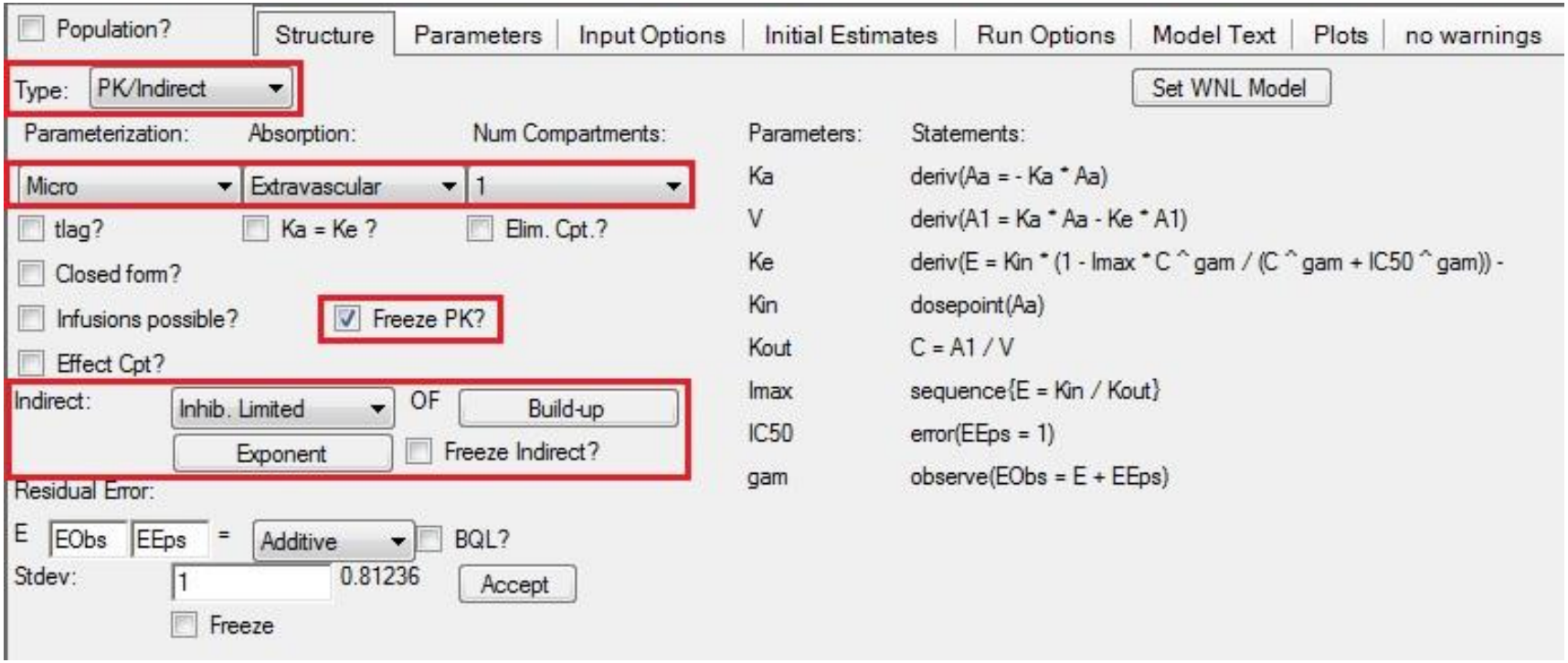
PD12: Built-in PK/indirect: inhibition of production



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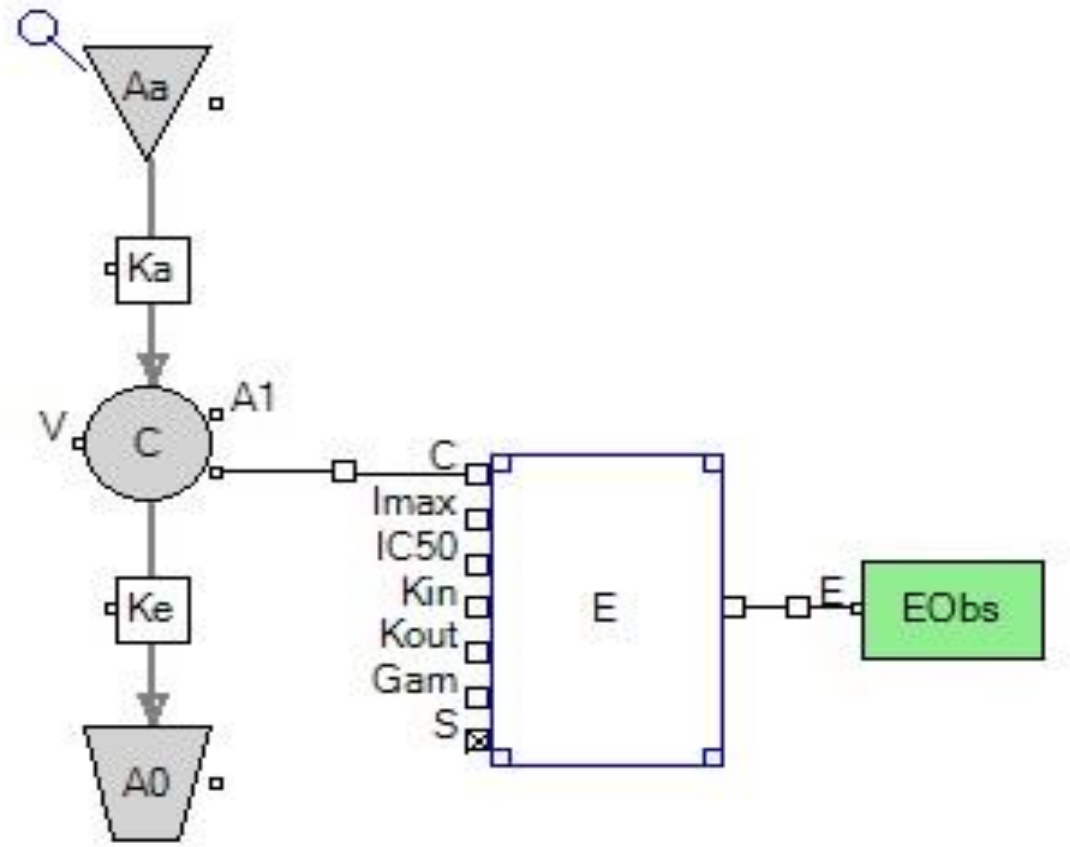
PD12: Graphical Model



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PD12: Indirect Response Model: PML Code

```
test(){
    # differential eq's for PK model
    deriv(Aa = - Ka * Aa)
    deriv(A1 = Ka * Aa - Ke * A1)
    # differential eq 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(, 8.8, ))
    fixef(V(freeze) = c(, 3.05, ))
    fixef(Ke(freeze) = c(, 0.605, ))
    # Indirect response parameters with initial estimates
    fixef(Kin = c(, 60, ))
    fixef(Kout = c(, 1, ))
    fixef(Imax = c(, 0.67, ))
    fixef(IC50 = c(, 1, ))
    fixef(gam = c(, 1, ))
}
```

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PD12: Initial Estimates

- IC50 = 1, derived from overlay plot at 50% inhibition
- Gamma = exponent, arbitrarily set to 1 (from reduced model)
- R0 = 60, from exploratory plot response at time = 0
- Kout = 1, derived from slope of downswing in exploratory plot
- Kin = R0*kout = 60
- ΔR = R0 – Rmin = 60-20 = 40
- Imax = ΔR*kout/kin = 40/60 ~ 0.67

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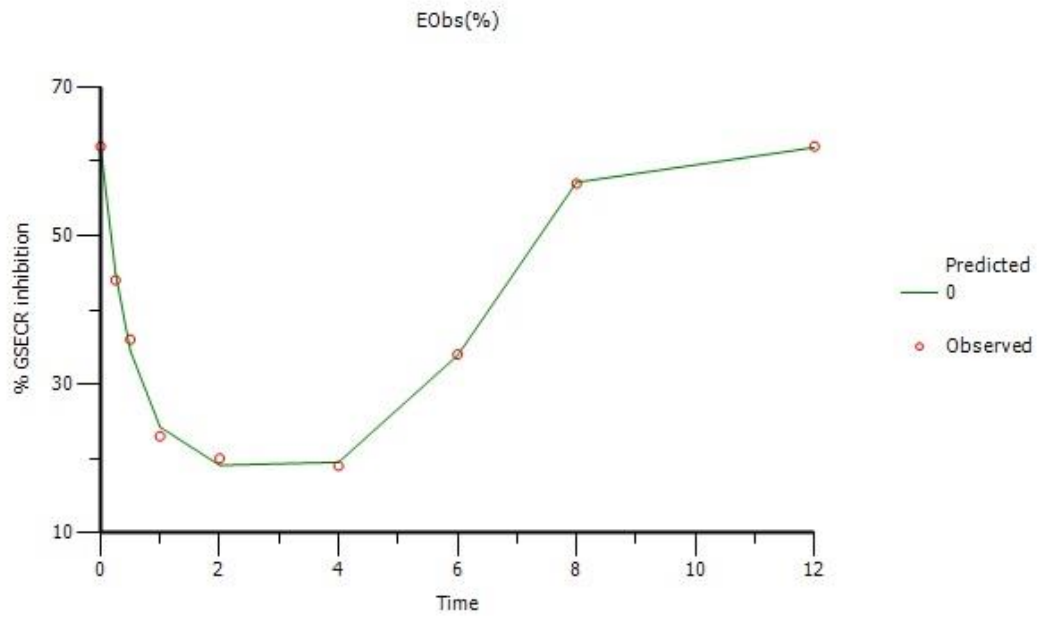
Demo

PD12: Results

- Fit



- Final Parameter Estimates

	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
1	tvKa	8.8	1/min	0	0	8.8	8.8	0
2	tvV	3.05		0	0	3.05	3.05	0
3	tvKe	0.605	1/min	0	0	0.605	0.605	0
4	tvKin	123.196	%/(min)	6.4234726	5.2140269	102.75387	143.63813	62.232
5	tvKout	1.99168	1/min	0.097173042	4.8789485	1.6824354	2.3009246	0.014285
6	tvImax	0.705753		0.011407454	1.6163521	0.66944979	0.74205621	0.00020058
7	tvIC50	0.965352		0.046750401	4.8428346	0.816573	1.114131	0.0032631
8	tvgam	2.49622		0.25736744	10.310287	1.677171	3.315269	0.10257
9	stdev0	0.81236		0.19147585	23.570319	0.20300512	1.4217149	

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PD12: Summary

- Fix PK parameters from previous study
- Develop an indirect response model
- Derive initial estimates
- Fit the model to the data
- Review results
- Simulate response at different dose levels

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
- PML School on Twitter: @PML_School
  - Notifications on updates of materials, Q&A and discussions
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Coming up…

Modeling PK/PD Systems with Distributed Delays

Speaker(s): Wojciech Krzyzanski
Date: May 16, 2017
Time: 11 am EST
Duration: 1 hour

Effect Compartment III: IV infusion
Model response-time data with a link-model
May 11, 2017 | 10am EST
Presenter: Bernd Wendt