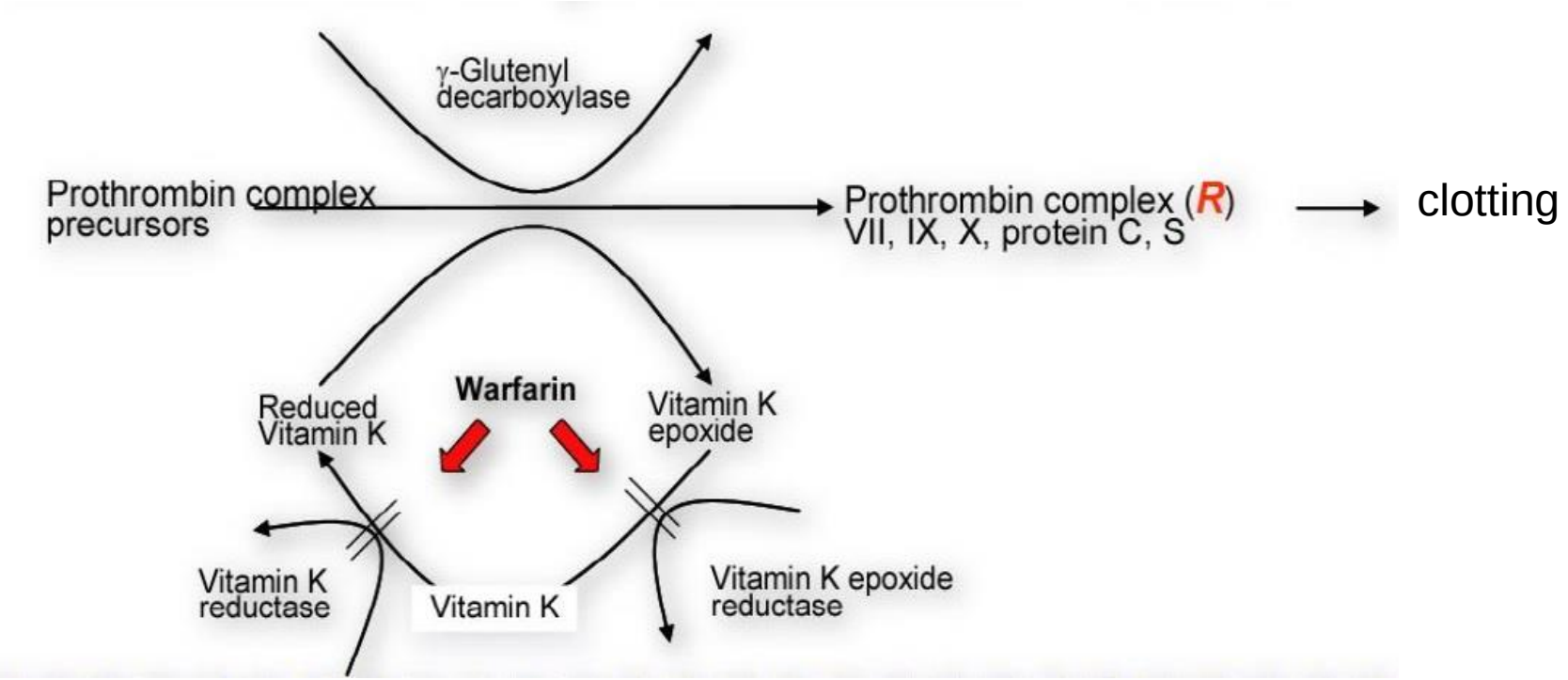
PML Library:
PD4 - Warfarin IV-bolus Turnover Model with Tlag

PD4: Background

- Warfarin is often prescribed as an anticoagulant.
- Warfarin acts indirectly to prevent blood clotting, by inhibiting the production of reduced Vitamin K, that is involved in the formation of the Prothrombin Complex, as shown below:



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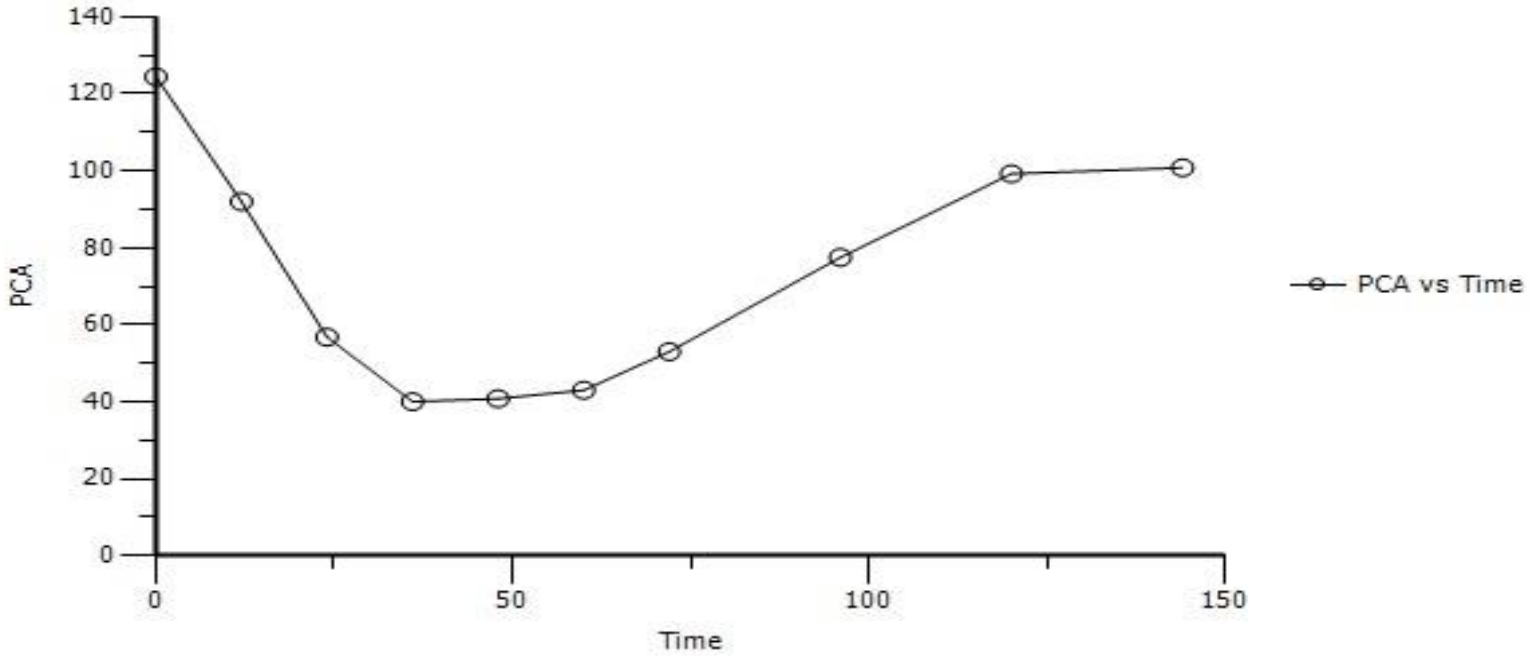
PD4: Protocol

- An IV bolus dose of Warfarin is administered
- Response is measured as % of Prothrombin Complex Activity (PCA) compared to normal (100%)
- % PCA vs Time:



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PD4: Warfarin PK parameters

- Warfarin PK is well characterized from previous studies.
- A 1-compartment bolus model with micro constants (V, Ke) will be used for the PK parameters in the following equation:
- C_w = Dose/V * exp(-Ke*t)
  - Dose = 1.05
  - V = 1
  - Ke = 0.0228

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PD4: Objectives

- Use indirect response to model Warfarin-PCA interaction
- Elaborate on a model with and without lag time in the dynamics
- Compare the two models by AIC and parameter precision
- Optional: extend to a precursor pool model

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PD4: Derivation of Warfarin Inhibitory function

- The empirically found inhibitory function of warfarin on the synthesis rate of PCA (assuming Imax = 1) is:
- $I(C) = 1 - C^{\gamma} / (IC_{50}^{\gamma} + C^{\gamma})$

- Substitute $(IC_{50}^{\gamma} + C^{\gamma}) / (IC_{50}^{\gamma} + C^{\gamma})$ for 1:
- $= (IC_{50}^{\gamma} + C^{\gamma}) / (IC_{50}^{\gamma} + C^{\gamma}) - C^{\gamma} / (IC_{50}^{\gamma} + C^{\gamma})$
- $= IC_{50}^{\gamma} / (IC_{50}^{\gamma} + C^{\gamma})$

- Divide numerator and denominator by IC_{50}^{γ} gives:
- $= 1 / (1 + C^{\gamma} / IC_{50}^{\gamma})$
- $I(C) = 1 / (1 + (C / IC_{50})^{\gamma})$

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PD4: Base Turnover Model

- The turnover rate of PCA is adapted from the base inhibitory turnover model:
- $dPCA/dt = kin * I(C_w) – kout * PCA$
  - Kin = rate of production
  - Kout = rate of loss

- At baseline, $R_0 = kin/kout$, therefore $kin = R_0 * kout$
- Set $R_0 = P_0$, and substitute $P_0 * kout$ for kin:
- $dPCA/dt = P_0 * kout * I(C_w) – kout * PCA$

- Rearranges to:
- $dPCA/dt = kout * (P_0 * I(C_w) – PCA)$

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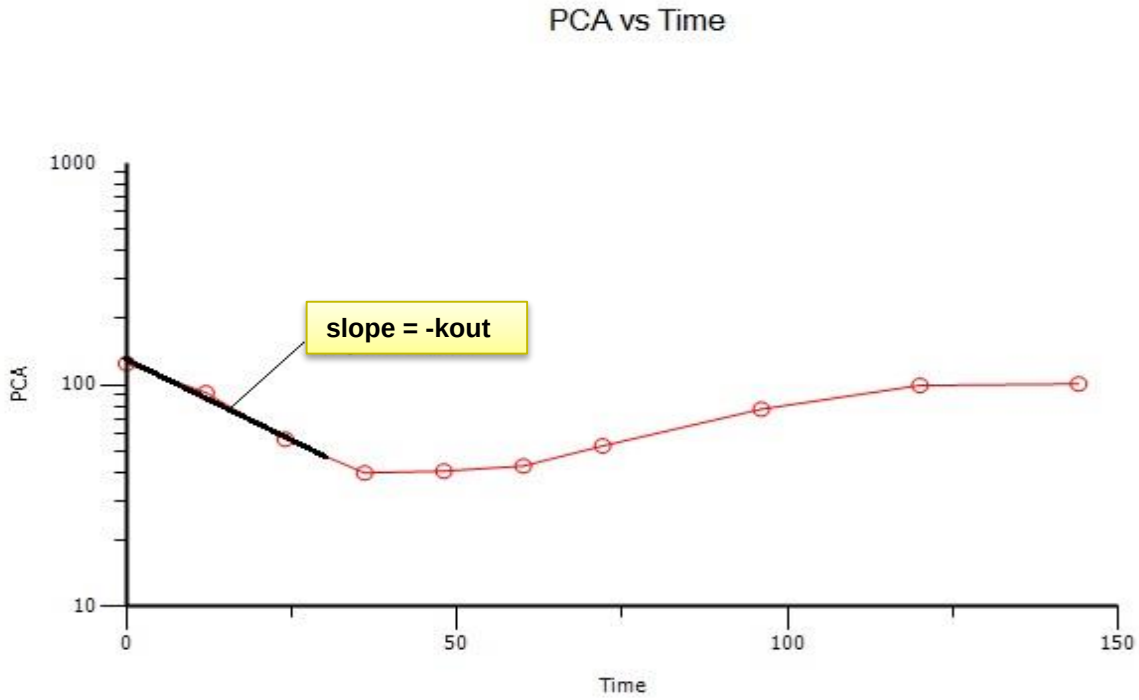
PD4: kout Initial Estimate



$$k_{out} = -\frac{\ln(124.4) - \ln(56.77)}{0 - 24} \approx 0.03\,\mathrm{h}^{-1}$$

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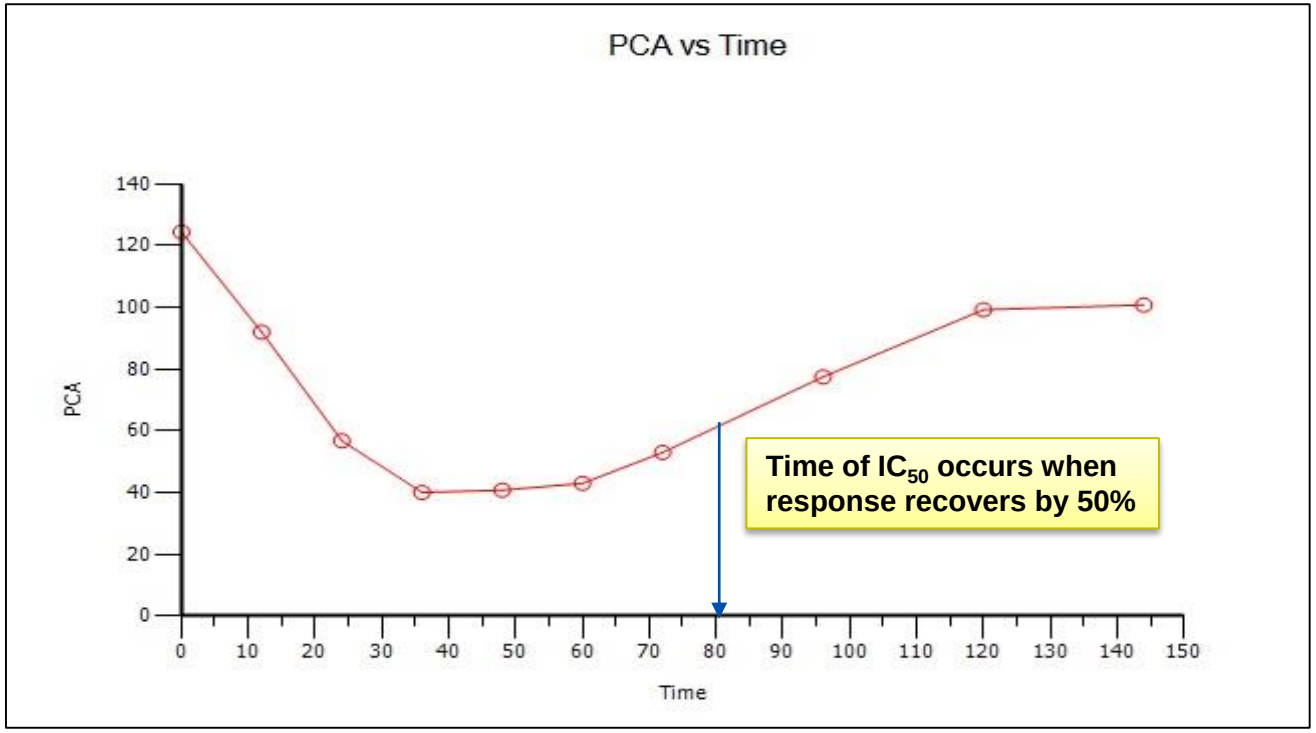
PD4: IC_{50} Initial Estimate



- IC_{50} estimate: solve C_w at time = 80:
- C_w = Dose/V * exp(-Ke*t)
- IC_{50} = 1.05/1 * exp(-0.0228*80) = 0.16

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PD4: Summary of Initial Estimates

- P_0 is baseline PCA activity = 124
- Kout = 0.03, derived from onset slope in exploratory plot
- IC_{50} = warfarin concentration when response recovers by 50% = 0.16
- n = gamma exponent, can be found by fitting built-in inhibitory indirect response model = 4

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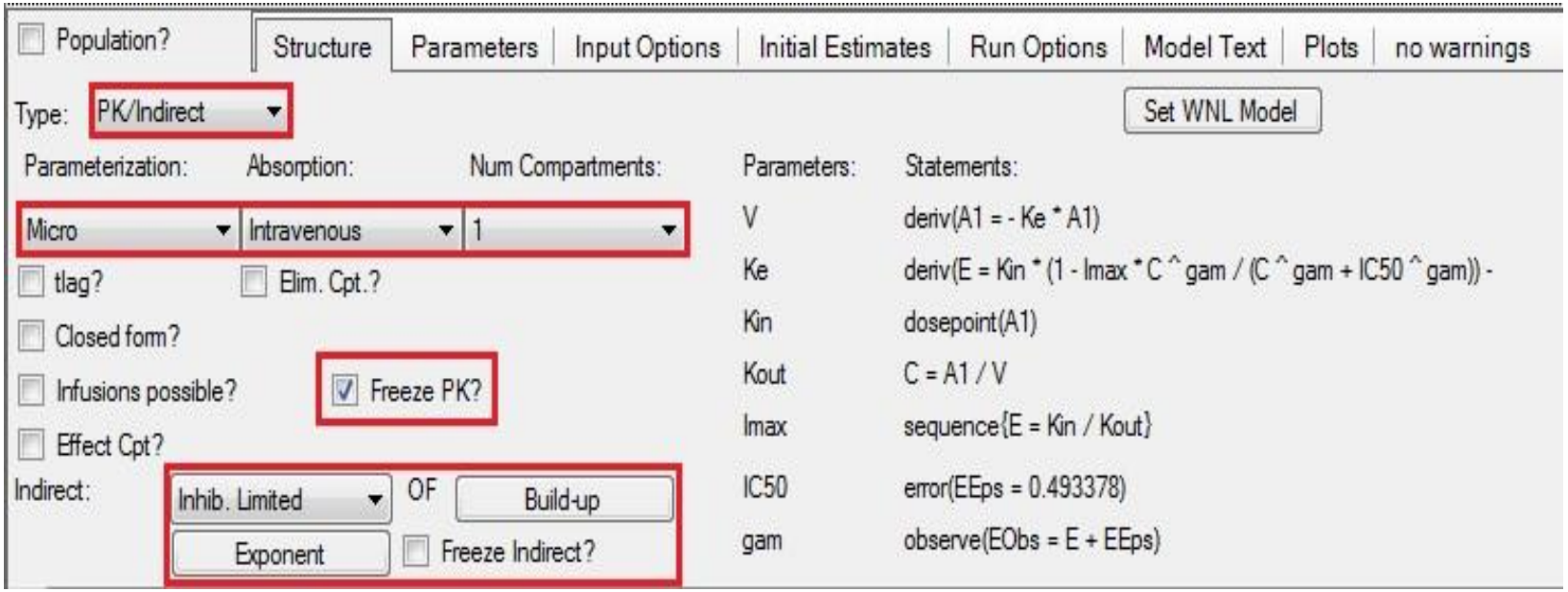
PD4: Built-in PK/indirect: inhibition of production



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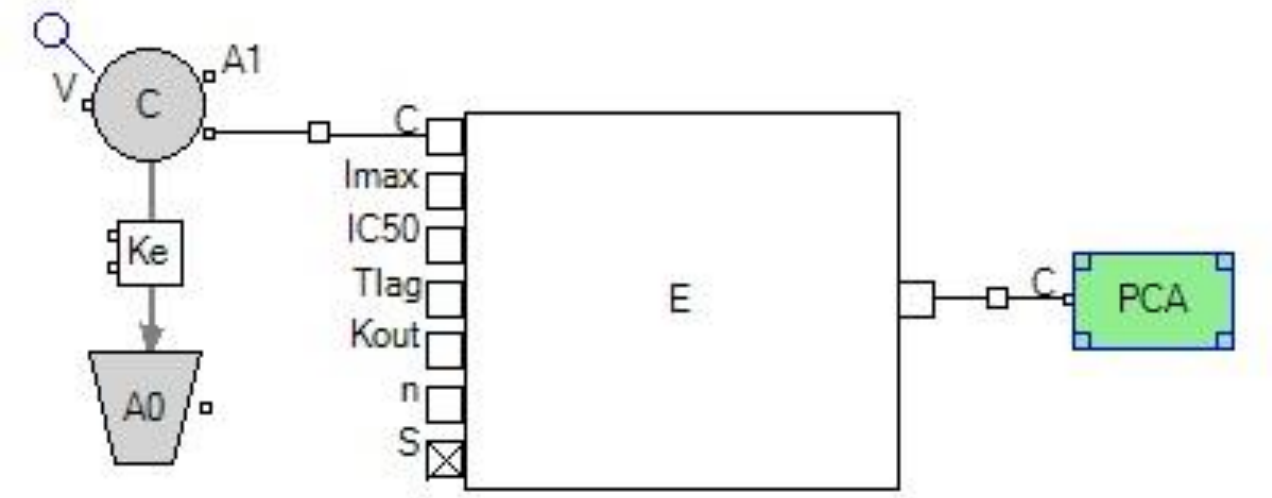
PD4: Graphical Model



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PD4: Base Turnover Model 1: PML Code

```
test(){
    #dose delivered to central compartment
    dosepoint(A1)
    #initial concentration of warfarin
    Cw = A1 / V
    #differential equation for PK model
    deriv(A1 = -Ke * A1)
    #inhibitory function of warfarin
    Inh = 1 / (1 + (Cw/IC50)^n )
    #initial value for PCA set to P0 (baseline parameter)
    sequence{PCA=P0;}
    #differential equation for PCA
    deriv(PCA=Kout*(P0*Inh - PCA))
    #observed PCA with additive error term
    error(Eps=1)
    observe(PCAObs = PCA+Eps)
    #PK parameters as frozen fixed effects
    fixef(V(freeze) = c(, 1, ))
    fixef(Ke(freeze) = c(, 0.0228, ))
    #turnover model parameters as fixed effects with intitial estimates
    fixef(IC50 = c(, .16, ))
    fixef(n = c(, 4, ))
    fixef(Kout = c(, .03, ))
    fixef(P0 = c(, 124, ))
}
```

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PD4: Base Turnover Model 2 with Lag Time: PML Code

```
test(){
    #dose delivered to central compartment
    dosepoint(A1)
    #initial warfarin concentration in central compartment
    Cw = A1 / V
    #differential equation for PK model
    deriv(A1 = -Ke * A1)
    #inhibitory function of warfarin
    Inh = 1 / (1 + (Cw/IC50)^n )
    #time switch for turnover model function
    double(flag)
    #sequence block: initial PCA with on/off switch (flag)
    sequence{
    PCA=P0;
    flag=0;
    sleep(Tlag);
    flag=1;
    }
    #differential equation for PCA
    deriv(PCA = flag*(Kout*(P0*Inh - PCA)))
    #observed PCA with additive error model
    error(Eps=1)
    observe(PCAObs = PCA+Eps)
    #PK parameters as frozen fixed effects
    fixef(V(freeze) = c(, 1, ))
    fixef(Ke(freeze) = c(, 0.0228, ))
    #turnover model parameters as fixed effects with intitial estimates
    fixef(Tlag = c(, 1, ))
    fixef(IC50 = c(, .16, ))
    fixef(n = c(, 4, ))
    fixef(Kout = c(, .03, ))
    fixef(P0 = c(, 124, ))
}
```

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Demo

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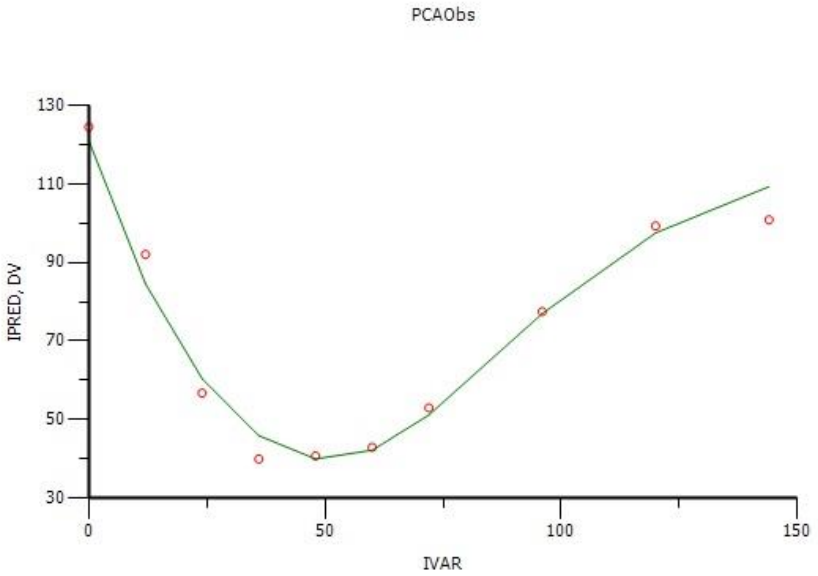
PD4: Summary

- Fix PK parameters from previous study
- Develop an indirect response model
- Derive initial estimates
- Fit turnover models with and without lagtime to the data
- Review results

PD4: Base Turnover Model Results

- Fit



- Final Parameter Estimates

	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
1	V	1		0	0	1	1	0
2	Ke	0.0228		0	0	0.0228	0.0228	0
3	IC50	0.261284		0.020685502	7.9168652	0.20811048	0.31445752	1.5086E-05
4	n	2.99115		1.2677539	42.383495	-0.26769958	6.2499996	0.053706
5	Kout	0.030771		0.0048800615	15.859288	0.018226463	0.043315537	8.8425E-07
6	P0	120.951		4.0632499	3.3594182	110.50613	131.39587	0.63028
7	stdev0	4.4175		0.98778034	22.360619	1.878342	6.956658	

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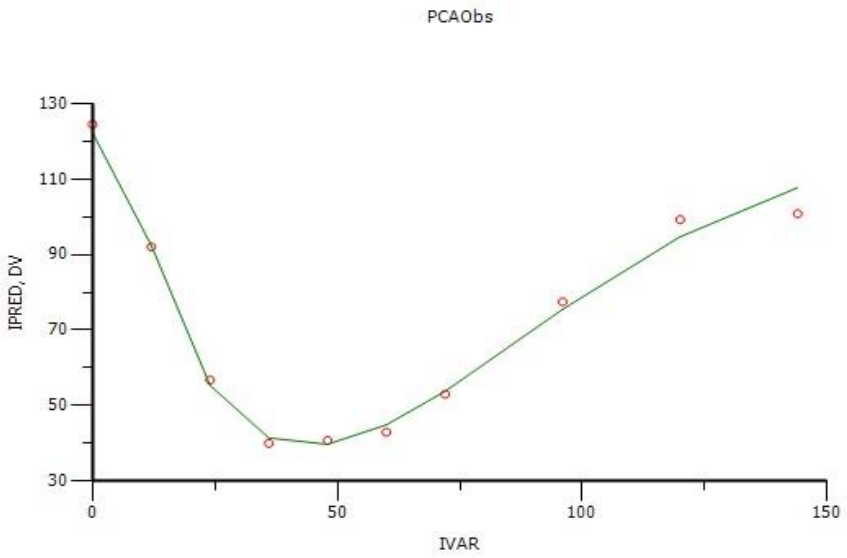
PD4: Base Turnover Model with Lag Time Results

- Fit



- Final Parameter Estimates

	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
1	V	1		0	0	1	1	0
2	Ke	0.0228		0	0	0.0228	0.0228	0
3	Tlag	6.54598		1.0782857	16.472487	3.5521802	9.5397798	0.13878
4	IC50	0.235077		0.013841243	5.8879613	0.19664757	0.27350643	1.9882E-05
5	n	1.51175		0.20318711	13.440523	0.94761239	2.0758876	0.0039438
6	Kout	0.0601138		0.0086395602	14.372008	0.036126545	0.084101055	8.2777E-06
7	P0	122.223		2.9644392	2.4254349	113.9924	130.4536	0.92002
8	stdev0	2.93445		0.65616309	22.360684	1.11265	4.75625	

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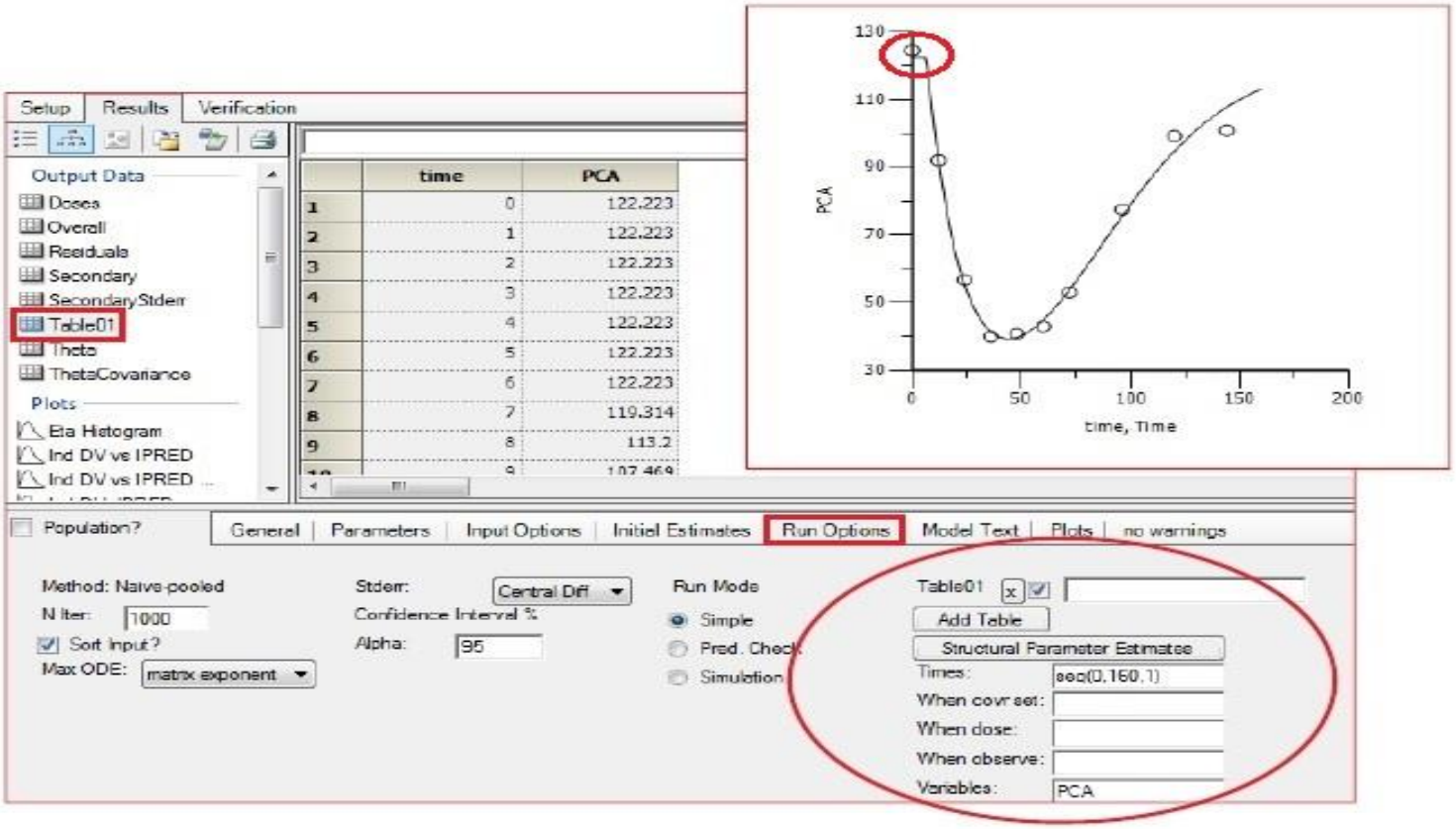
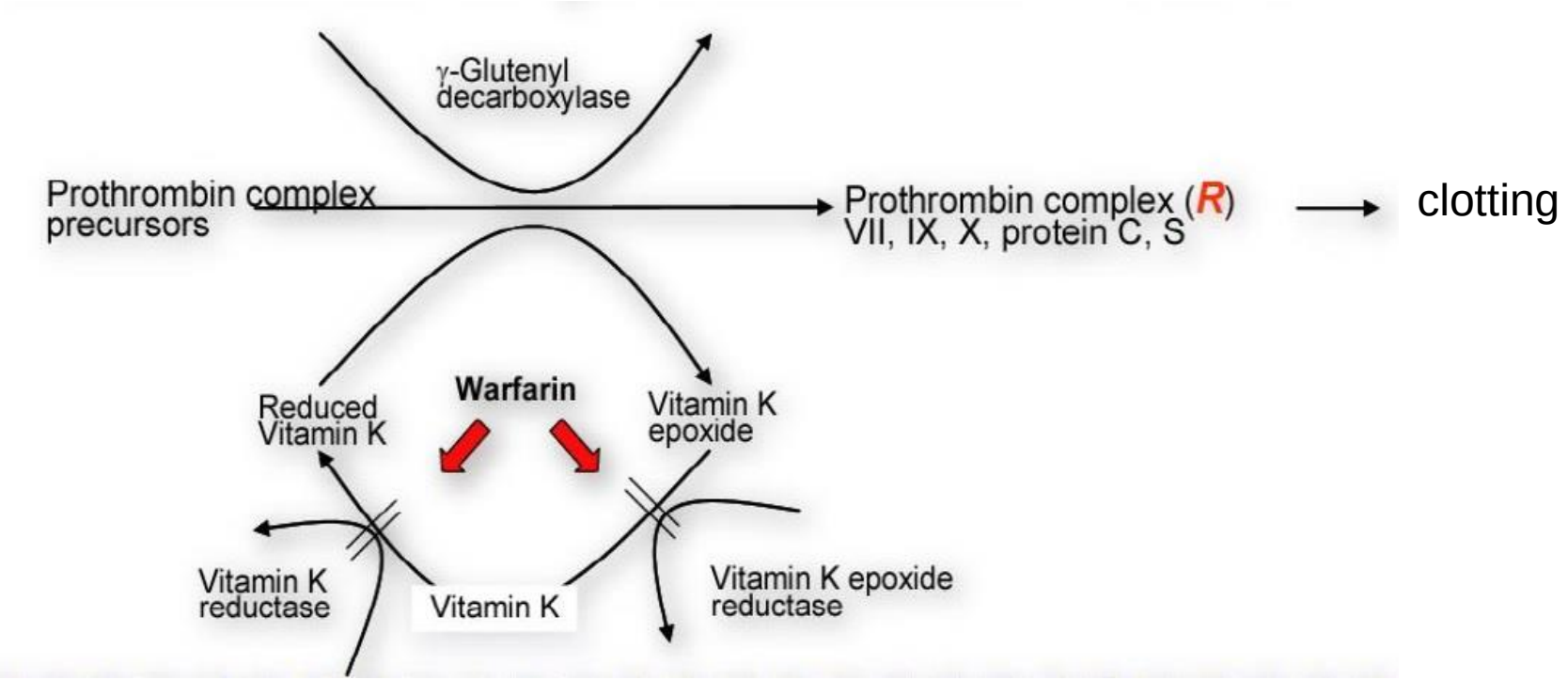
PD4: Use Table function to view fitted lagtime

- In the model Run Options tab, set up a simulation table using the sequence statement.
- Use the result “Table01” to produce an overlay plot with more predicted points to view the lagtime



PD4: Develop a mechanistic precursor pool model

- Warfarin is often prescribed as an anticoagulant.
- Warfarin acts indirectly to prevent blood clotting, by inhibiting the production of reduced Vitamin K, that is involved in the formation of the Prothrombin Complex, as shown below:



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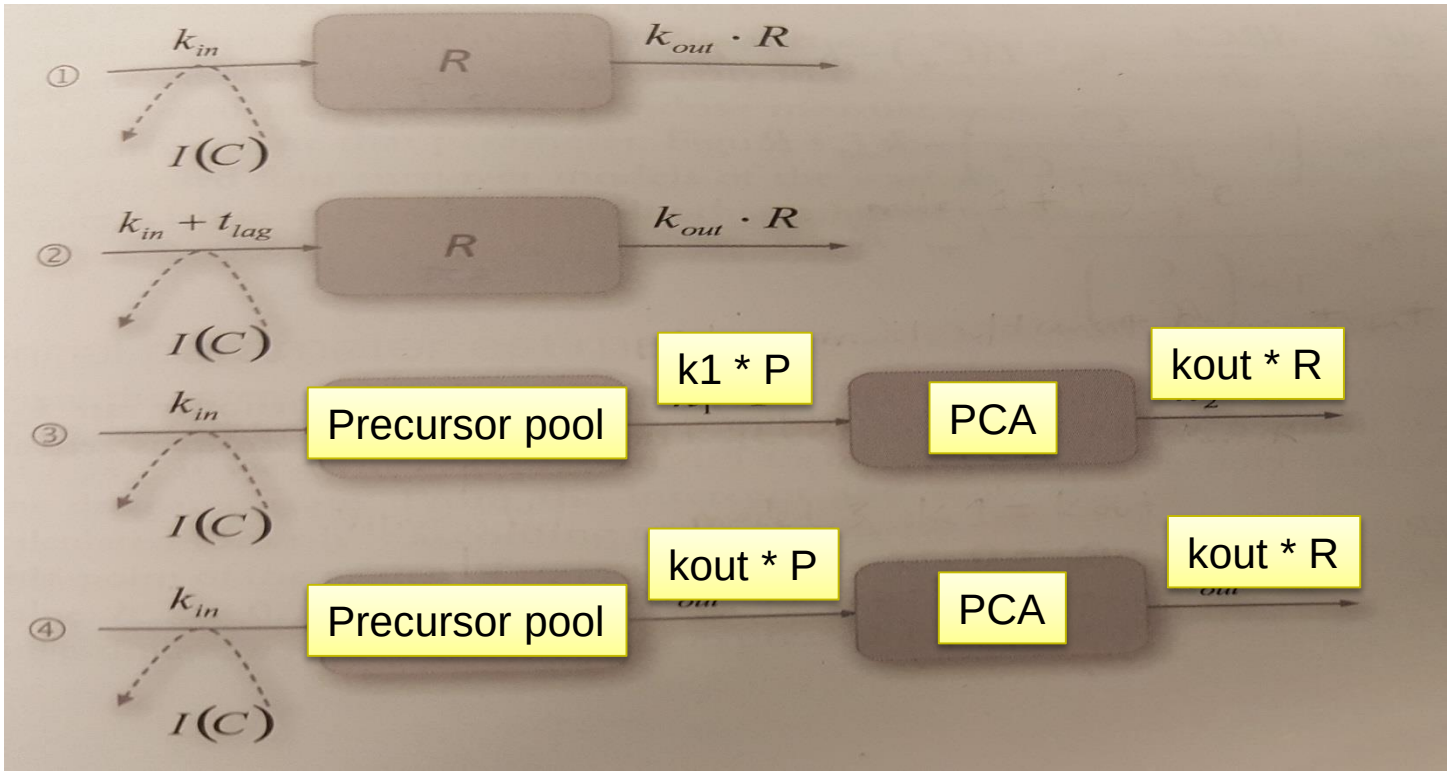
PD4: Develop a mechanistic precursor pool model

- Models 1 & 2 are the basic turnover model both with and without a lag time.
- Warfarin acts one step upstream, inhibiting the formation of reduced Vitamin K, which mediates the formation of PCA from the precursor pool.
- Model 3 is a precursor pool model replacing the lag time with a transit compartment with its own exit rate constant k1.
- Model 4 is similar to 3, but k1 is set equal to kout.



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PD4: Precursor Pool Model 3: PML Code

```
test(){
    #Warfarin PK
    deriv(A1 = -Ke * A1)
    dosepoint(A1)
    Cw = A1 / V
    #Inhibitory function of warfarin
    Inh = 1 / (1 + (Cw/IC50)^n )
    #sequence: initial conditions for PCA and its Precursor pool
    sequence{Precur=P0}
    sequence{PCA=P0}
    #differential equations for PCA and Precursor pool
    deriv(Precur=P0*Kout*Inh - K1*Precur)
    deriv(PCA=K1*Precur - Kout*PCA)
    #observed PCA with additive error model
    error(Eps=1)
    observe(PCAObs = PCA + Eps)
    #PK parameters as frozen fixed effects
    fixef(V(freeze) = c(, 1, ))
    fixef(Ke(freeze) = c(, 0.0228, ))
    #Precursor pool model parameters with initial estimates
    fixef(IC50 = c(, .16, ))
    fixef(n = c(, 4, ))
    fixef(K1 = c(0, .06, ))
    fixef(Kout = c(0, .06, ))
    fixef(P0 = c(, 124, ))
}
```

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PD4: Precursor Pool Model 4: PML Code

```
test(){
    #Warfarin PK
    dosepoint(A1)
    deriv(A1 = -Ke * A1)
    Cw = A1 / V
    #inhibitory function of warfarin
    Inh = 1 / (1 + (Cw/IC50)^n )
    #set Kloss = Kout
    Kloss=Kout
    #Sequence: initial conditions for PCA and its precursor pool
    sequence{Precur=P0}
    sequence{PCA=P0}
    #differential equations for PCA and precursor pool
    deriv(Precur=P0*Kout*Inh - Kloss*Precur)
    deriv(PCA=Kloss*Precur - Kout*PCA)
    #observed PCA with additive error model
    error(Eps=1)
    observe(PCAObs = PCA+Eps)
    #PK parameters as frozen fixed effects
    fixef(V(freeze) = c(, 1, ))
    fixef(Ke(freeze) = c(, 0.0228, ))
    #Precursor pool Kloss eq Kout model parameters with initial estimates
    fixef(IC50 = c(, .16, ))
    fixef(n = c(, 4, ))
    fixef(Kout = c(, .06, ))
    fixef(P0 = c(, 124, ))
}
```

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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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  - Noncompartmental data analysis
  - Programming Bootcamp
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Coming up…

Turnover Model 4: IV Infusions
Apply a turnover model to multiple IV dosing response data
June 22, 2017 | 10am EST
Presenter: Bernd Wendt

- Dr. Wendt will present PD7, which covers a turnover model, using stimulation of loss, at different dose levels.

- Register for future PML School webinars here:
- https://www.certara.com/software/pkpd-modeling-and-simulation/pml-school/

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