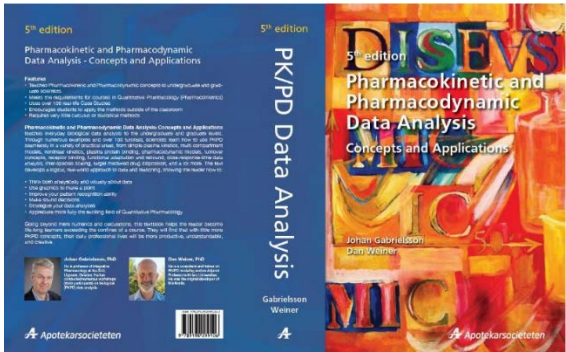
Comparison of Link, Turnover & Receptor Binding Models

PD21



Background

A pharma company had previously used a single point assay for a preclinical screen; measuring the concentration of drug and response at 60min only.

Of course such data are not optimal for determining the time of peak response or duration.

The PK scientist suggested an alternative approach using time-series measurements. We analyze a sample dataset here.

Case Study

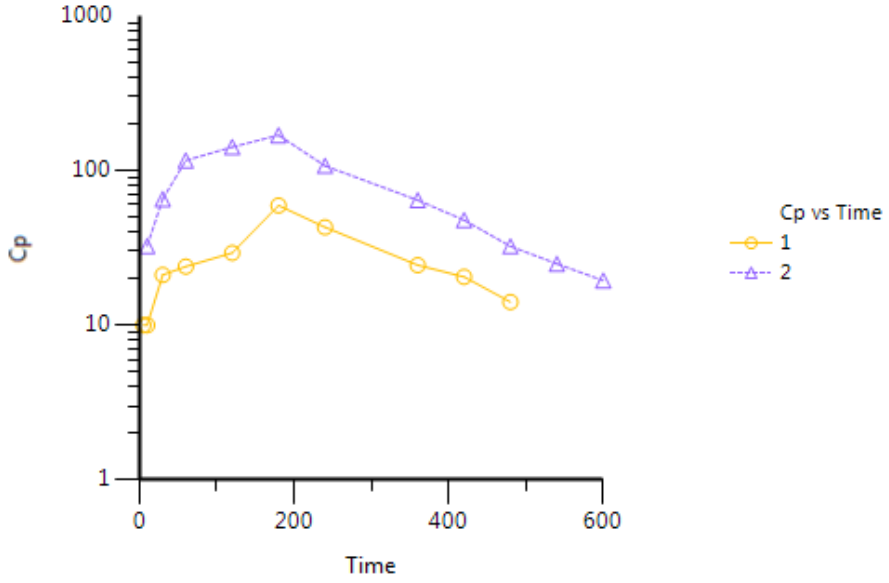
Data were obtained from a study in rabbits after two oral doses of 1 and 2 umol/kg of a drug antagonist X.

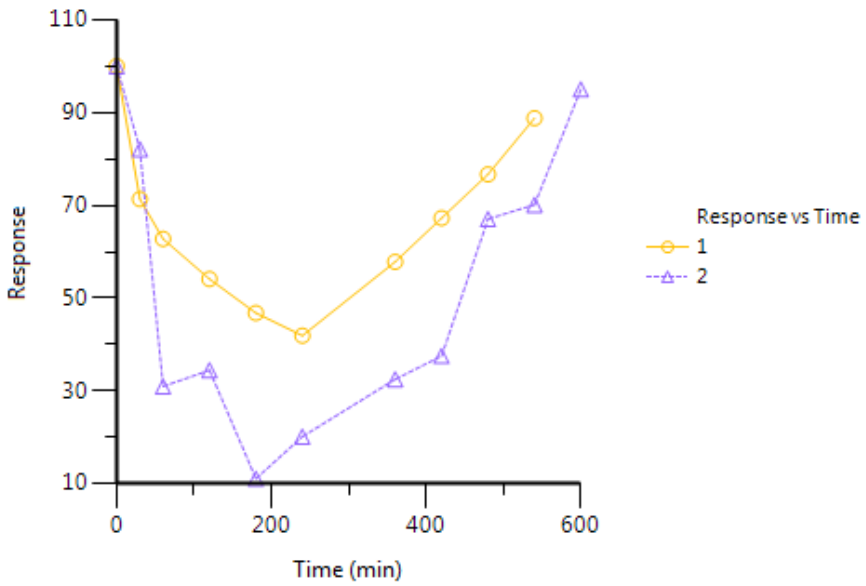
Data displayed both high-intra and inter-subject variability in both rate and extent of absorption. In addition, the PK data did not display a classical PK model profile.

The goal was to come up with an approach that was simple and easy to implement. The solution was to utilize a table function (actual observed data) approach for utilization of the PK data vs fitting an actual model to the PK data. The table function was then used to drive 3 PD models: a link model, a turnover model and a receptor binding model.

Plot of Observed Data

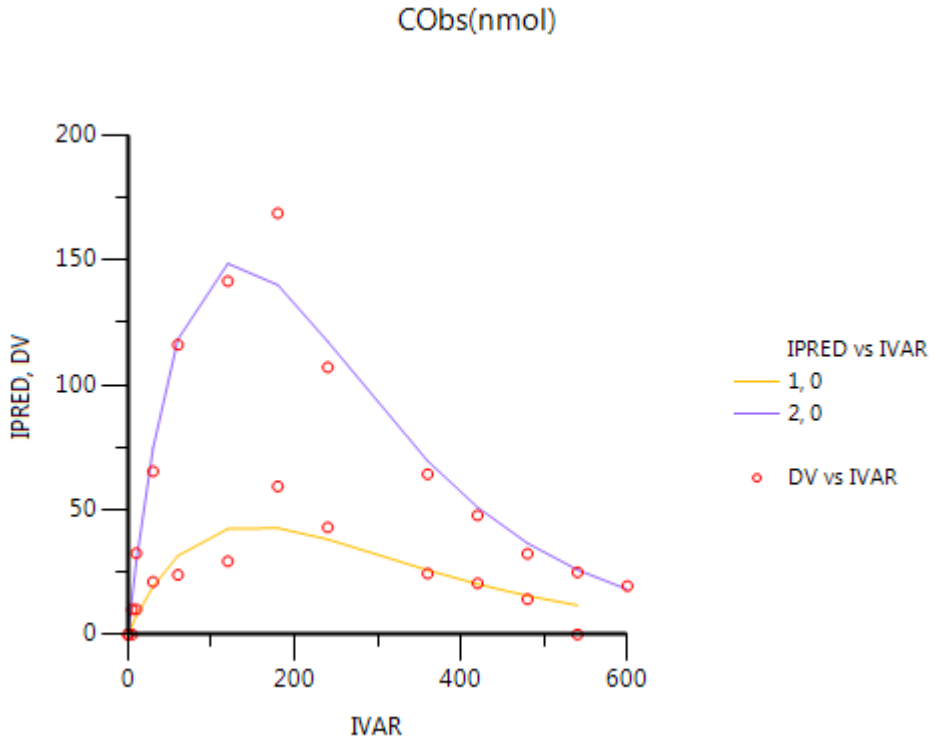
As shown on the next slide, a one compartment model does not fit the Cp absorption phase well and CVs for are parameters are very large.





Results of Fitting a One Compartment PK Model

	Parameter							
	stdev0		tvCl		tvKa		tvV	
Dose_grp	Estimate	CV%	Estimate	CV%	Estimate	CV%	Estimate	CV%
1.00	7.74	20.41	5.65E-05	11.04	0.00665	43.23	0.00849	43.10
2.00	10.3	19.61	3.83E-05	4.45	0.00775	28.65	0.00494	28.61

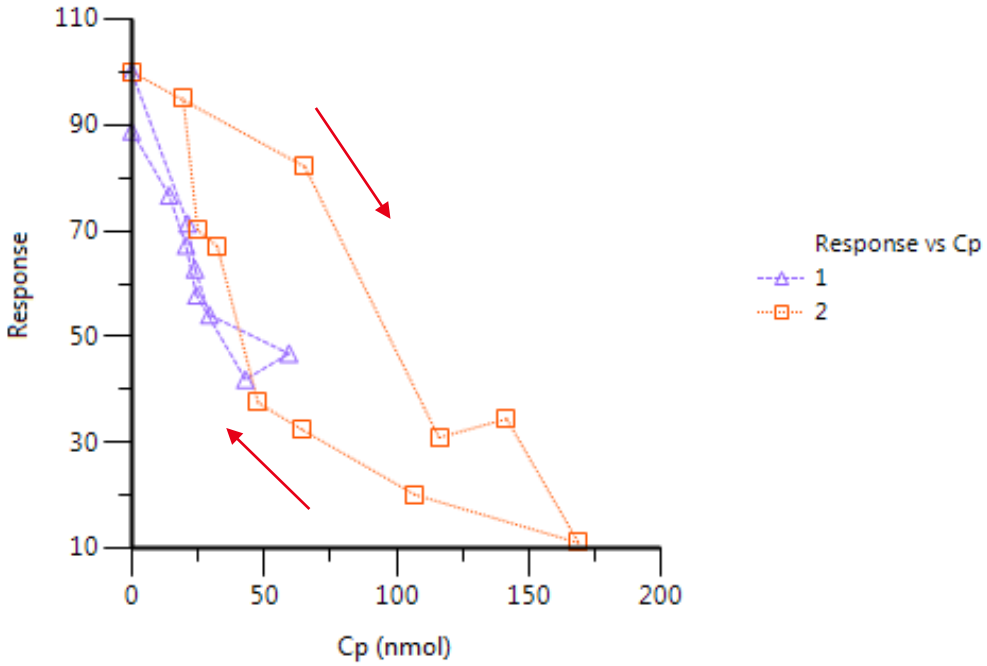


Clearly a one compartment does not fit the data well and there is no evidence of a second compartment? What do we do?

In classical PKPD Models the PK model is used as a smoothing function only. So we will just use the observed PK data!

Plot of Observed Data (cont.)

Note the clockwise histeresis in the plot of the Cp vs R data (for high dose only). Both the link and turnover models can account for histeresis (but in different ways).



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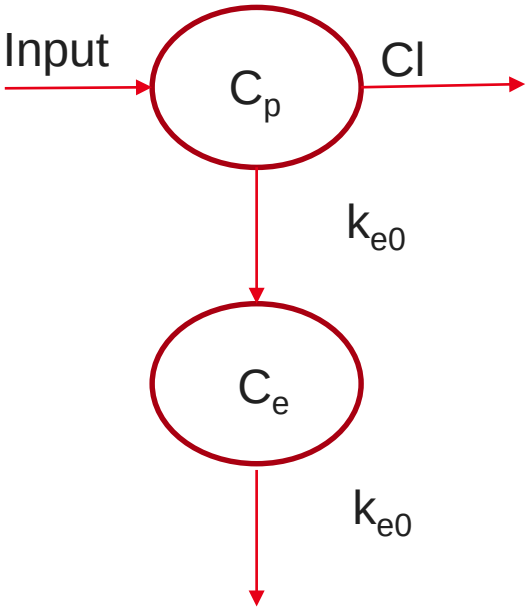
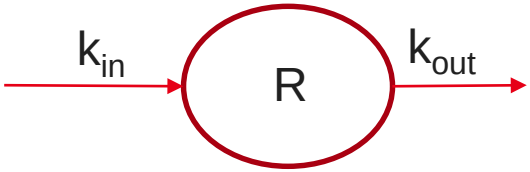
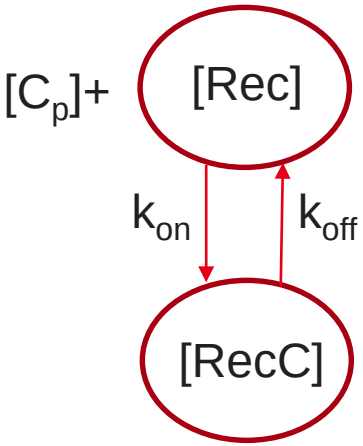
Candidate Models



Effect compartment (link) model



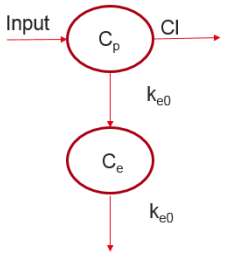
Turnover model



Receptor binding model

Model Equations

For all models the observed Cp data are used



Effect compartment (link) model

$$\frac{dC_e}{dt} = k_{e0} \bullet (C_p - C_e)$$

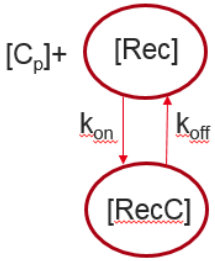
$$R = R_0 \bullet (1 - \frac{I_{\max} \bullet C_p^n}{IC_{50}^n + C_p^n})$$

Turnover model

$$\frac{dR}{dt} = k_{in} \bullet I(C_p) - k_{out} \bullet R \text{ or}$$

$$\frac{dR}{dt} = k_{out} \bullet (R_0 \bullet I(C_p) - R) \text{ and}$$

$$k_{in} = k_{out} \bullet R_0$$



Receptor binding model

Note here R denotes free Receptors and not Response.

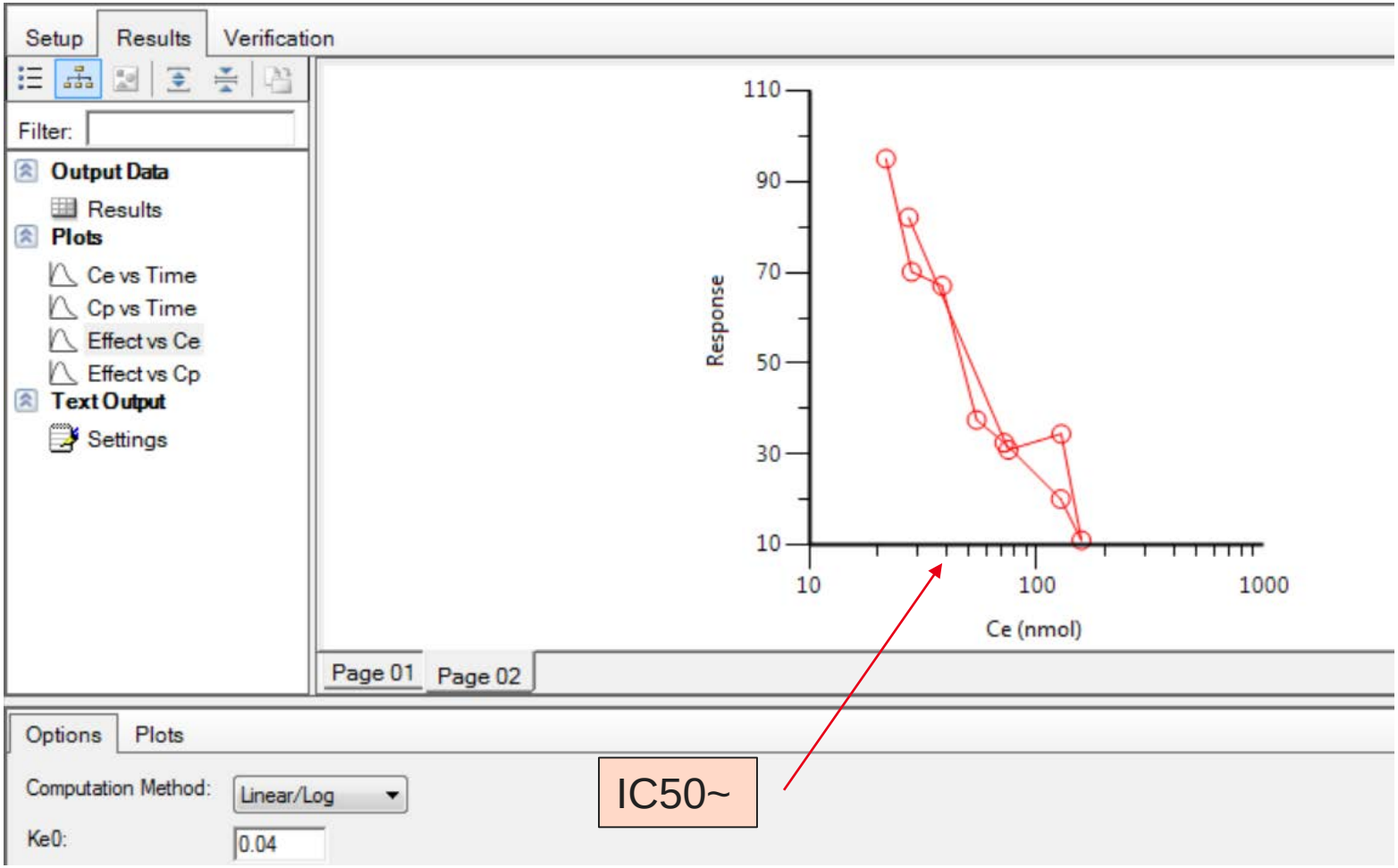
$$\frac{dR}{dt} = -k_{on} \bullet C_p \bullet (B_{\max} - RC) + k_{off} \bullet RC$$

$$\frac{dRC}{dt} = k_{on} \bullet C_p \bullet (B_{\max} - RC) - k_{off} \bullet RC$$

$$\text{Resp} = 100 - [RC]$$

B_{max} denotes the total receptor pool minus the concentration of bound receptors

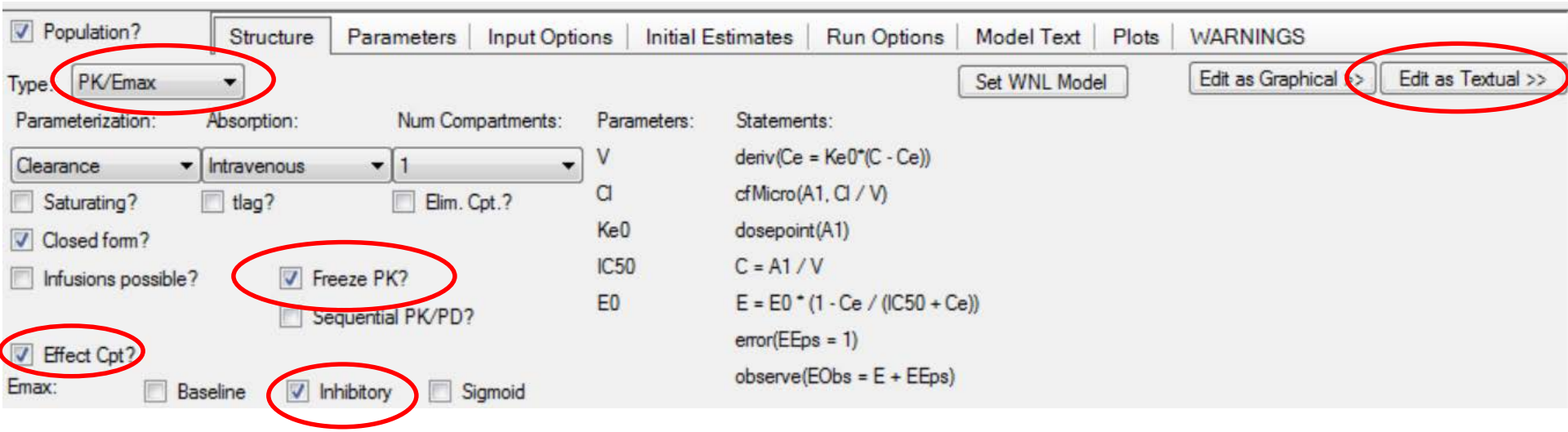
Notes on Initial Estimates for the Link Model



Here is the output from the semi-compartmental routine for the high dose assuming k_{e0}=0.04. Note that the C_e associated with a 50% reduction in response (the IC_{50})~40 uM. R_0 is assumed=100 and I_{max}=1.

Link Model Initial Library Settings

Send the data to a PK/Emax model with the following settings. Then convert it to textual and do the final editing.



Link Model Code Showing Edits in Red

```
test(){
        covariate(C)   # input the observed PK data as a covariate
        deriv(Ce = Ke0*(C - Ce))
        #cfMicro(A1, Cl / V)
        #dosepoint(A1)
        #C = A1 / V
        E = E0 * (1 - Ce / (IC50 + Ce))
        error(EEps = 1)
        observe(EObs = E + EEps)
        #stparm(V = tvV)
        #stparm(Cl = tvCl)
        stparm(Ke0 = tvKe0 * exp(nKe0))
        stparm(IC50 = tvIC50 * exp(nIC50))
        stparm(E0 = tvE0 * exp(nE0))
        #fixef(tvV(freeze) = c(, 1, ))
        #fixef(tvCl(freeze) = c(, 1, ))
        fixef(tvKe0 = c(, 0.04, ))
        fixef(tvIC50 = c(, 40, ))
        fixef(tvE0 (freeze)= c(, 100, ))
        ranef(diag(nIC50, nE0, nKe0) = c(1, 1, 1))
}
```

Delete the equations for the PK model

Note that Phoenix defaults to E (for Effect) for PD models. However, we used R to denote Response in the slide deck equations.

Make sure to select naïve pooled mode in Run Options as we only have two profiles. In naïve pooled model the “ranef” statement is ignored.

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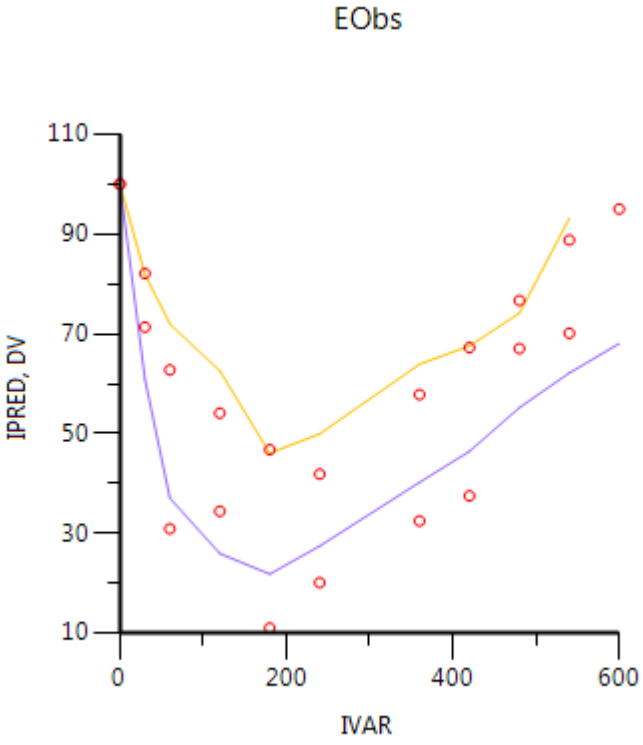
Link Model Output

Parameter	Estimate	Units	Stderr	CV%
tvKe0	0.0259775	1/min	0.0035527454	13.676241
tvIC50	44.8708	nmol	5.4967263	12.250119
tvE0	100		0	0
stdev0	10.2234		2.1357668	20.890964



The fitted curve is clearly deficient

Notes on Initial Estimates for the Turnover Model

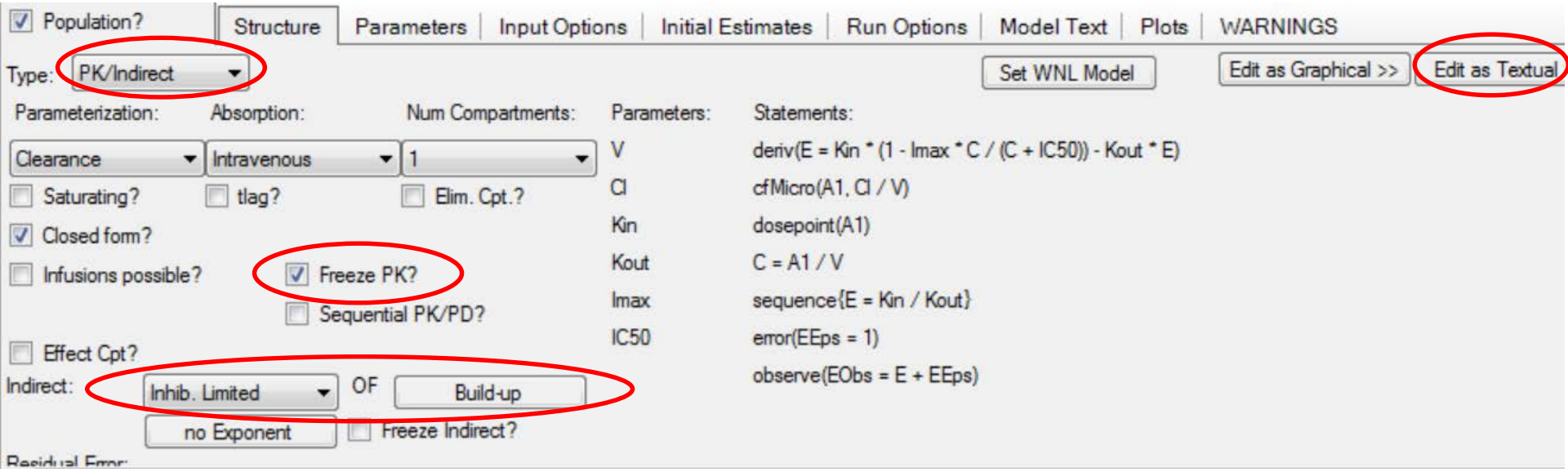
We already derived an estimate of the IC50 ~40 uM. K_{out} can be estimated from a ln-linear plot of R vs t based for the first few points. This gives an estimate of K_{out}~0.01. k_{in} = R0*k_{out} ~ 1.

$$\frac{dR}{dt} = k_{in} \bullet I(C_p) - k_{out} \bullet R$$ for large C_p the input is completely blocked so we have

$$\frac{dR}{dt} = -k_{out} \bullet R$$

Turnover Model Initial Library Settings

Send the data to a PK/Emax model with the following settings. Then convert it to textual and do the final editing.



Turnover Model Code Showing Edits in Red

```
test(){
        covariate(C)
        deriv(E = Kin * (1 - Imax * C / (C + IC50)) - Kout * E)
        #cfMicro(A1, Cl / V)
        #dosepoint(A1)
        #C = A1 / V
        sequence{E = Kin / Kout}
        error(EEps = 1)
        observe(EObs = E + EEps)
        #stparm(V = tvV)
        #stparm(Cl = tvCl)
        stparm(Kin = tvKin * exp(nKin))
        stparm(Kout = tvKout * exp(nKout))
        stparm(Imax = tvImax * exp(nImax))
        stparm(IC50 = tvIC50 * exp(nIC50))
        #fixef(tvV(freeze) = c(, 1, ))
        #fixef(tvCl(freeze) = c(, 1, ))
        fixef(tvKin = c(, 1, ))
        fixef(tvKout = c(, 0.01, ))
        fixef(tvImax(freeze) = c(, 1, ))
        fixef(tvIC50 = c(, 40, ))
        ranef(diag(nKin, nKout, nImax, nIC50) = c(1, 1, 1, 1))
}
```

Note that Phoenix defaults to E (for Effect) for PD models. However, we used R to denote Response in the slide deck equations.

Make sure to select naïve pooled mode in Run Options as we only have two profiles. In naïve pooled model the “ranef” statement is ignored.

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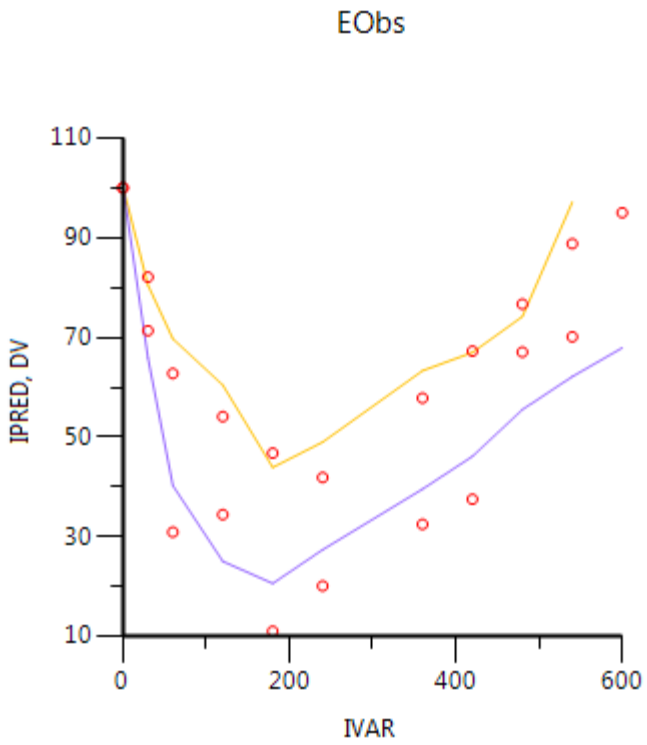
Link Model Output

Parameter	Estimate	Units	Stderr	CV%
tvKin	3.54742		0.19175505	5.4054793
tvKout	0.0353792	1/min	0.0016863867	4.7666049
tvImax	1		0	0
tvIC50	42.1909	nmol	0.88918502	2.107528
stdev0	9.69373		2.0938243	21.599779



The fitted curve is a little better than for the effect compartment model.

Notes on Initial Estimates for the Receptor Model

B_{max} (maximum receptor concentration) is assumed to equal 100. k_{on} and k_{off} were derived from preclinical experiments and were set to 0.0005 and 0.02, respectively.

Receptor Model Code

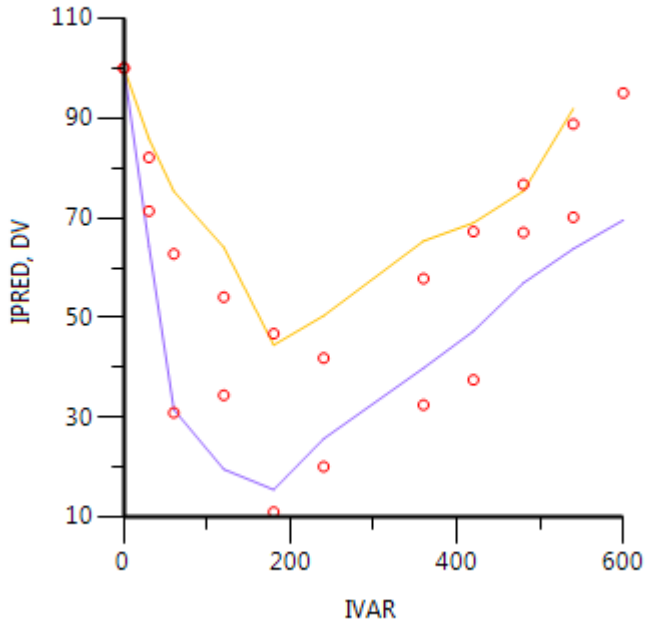
```
test(){
        covariate(Cp)
        deriv(R = -kon * Cp * (Bmax - RC) + koff * RC) # Free receptor
        deriv(RC = kon * Cp * (Bmax - RC) - koff * RC) # Drug-Receptor complex
        E = 100 - RC
        sequence{R = 100}
        error(EEps = 1)
        observe(EObs = E + EEps)
        fixef(kon = c(, 0.0005, ))
        fixef(koff = c(, 0.02, ))
        fixef(Bmax = c(, 100, ))
        secondary(Kd = koff / kon)
}
```

This model is discussed in more detail in G&W, p843. There is no good library model to start with, so just select any model, convert it to textual and edit as shown on this slide. Here, because I cannot estimate random effects for this dataset, I elected to not include the stparm statements.

Receptor Model Output

Parameter	Estimate	Units	Stderr	CV%
kon	0.000325763	1/(nmol*min)	0.00017638027	54.14374
koff	0.018458	1/min	0.0024503673	13.275367
Bmax	112.886		16.806546	14.88807
stdev0	10.0954		1.3536986	13.409064

Secondary	Estimate	Units	Stderr	CV%
Kd	56.661	nmol	23.0719	40.71919



The fitted curve is similar to that for the turnover model.

Extended Dataset

The study was repeated with dose levels of 1, 2, and 4 umol and these data were fitted to the turnover and receptor models.

Turnover

Parameter	Estimate	Units	Stderr	CV%
tvKin	3.29041		0.13269137	4.0326698
tvKout	0.03277		0.0013903237	4.2426723
tvImax	1		0	0
tvIC50	40.5074		1.3839436	3.4165205
stdev0	7.81385		2.453956	31.40521

Receptor

Parameter	Estimate	Units	Stderr	CV%
kon	0.000261093		8.9919408E-05	34.439609
koff	0.0131618		0.0024884734	18.906787
Bmax	106.341		8.517394	8.0095109
stdev0	8.66048		1.7495714	20.201783

Note the improved parameter precision with the turnover model.

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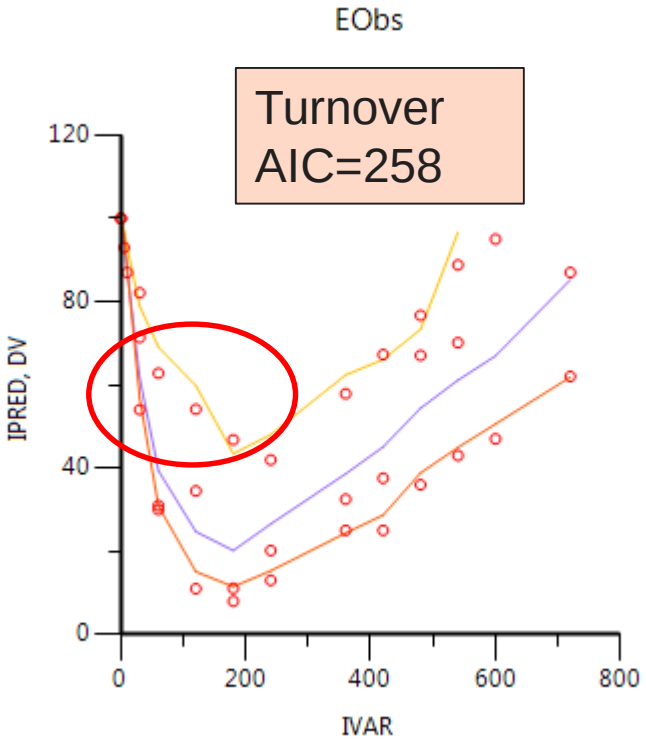
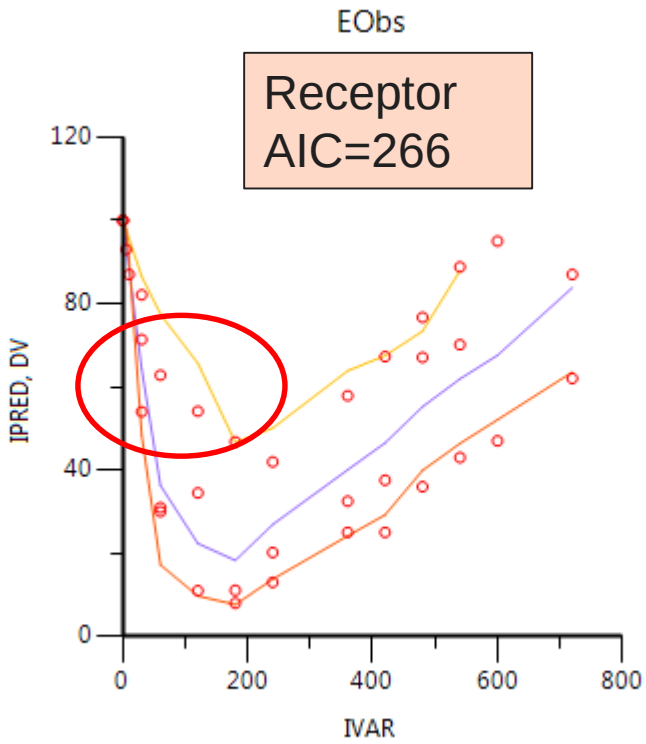
Extended Dataset (cont.)

The study was repeated with dose levels of 1, 2, and 4 umol and these data were fitted to the turnover and receptor models.





The fits for both models were similar but the turnover model had a slightly better fit to the downswing of the low dose and a slightly lower AIC value

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Summary

- When fitting classical PKPD models, the assumption is that the PD data do not impact the fit of the PK model (no PD parameters are shared with the PK models). Thus the PK model only serves as a smoothing function to get PK data at the same times as the PD data
- In such situations we can often use the observed Cp data rather that modeling Cp, even if there are temporal effects (like histeresis).
- For this particular dataset, we see that a turnover model provides a slightly better fit that a link or receptor model.

- We also saw that the fit is improved when we include data from a higher dose.

Questions?

Coming up…

Non-linear Time Scaling for IVIVC: Secrets from an Expert

Speaker(s): Jean-Michel Cardot
Date: March 29, 2017
Time: 11 am EST
Duration: 1 hour

Sigmoidal Concentration-response Models
Apply Gompertz, Weibull, Richards, Morgan-Mercer-Flodin, Hill and logistic models
March 30, 2017 | 10am EST
Presenter: Chris Mehl