Bayesian non-linear PK modelling applied to dose escalation studies using WinBUGS

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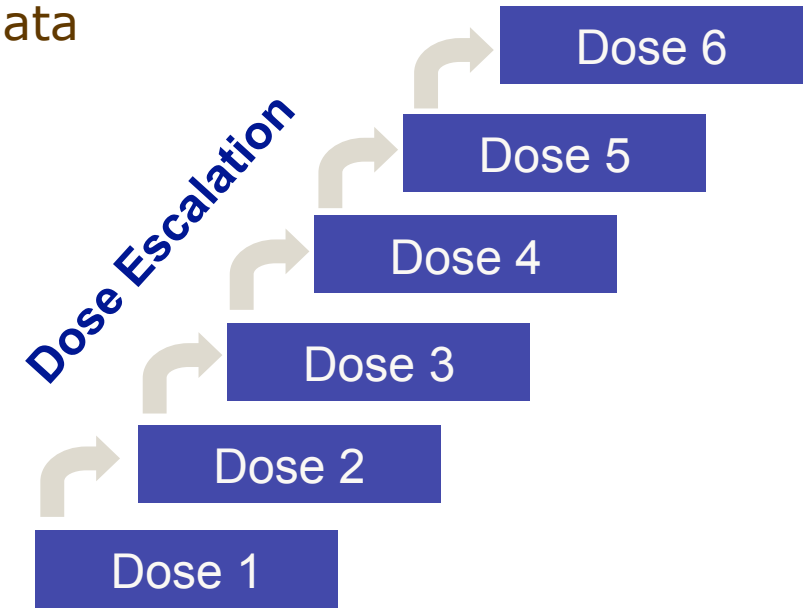
Véronica, living with epilepsy

Outline

- What is the problem? Predict AUC at the next dose level.
- What is the model? Two-compartment model with linear and nonlinear elimination kinetics.
- Why Bayesian framework? What are the priors?
- Results
- WinBUGS implementation

The Study

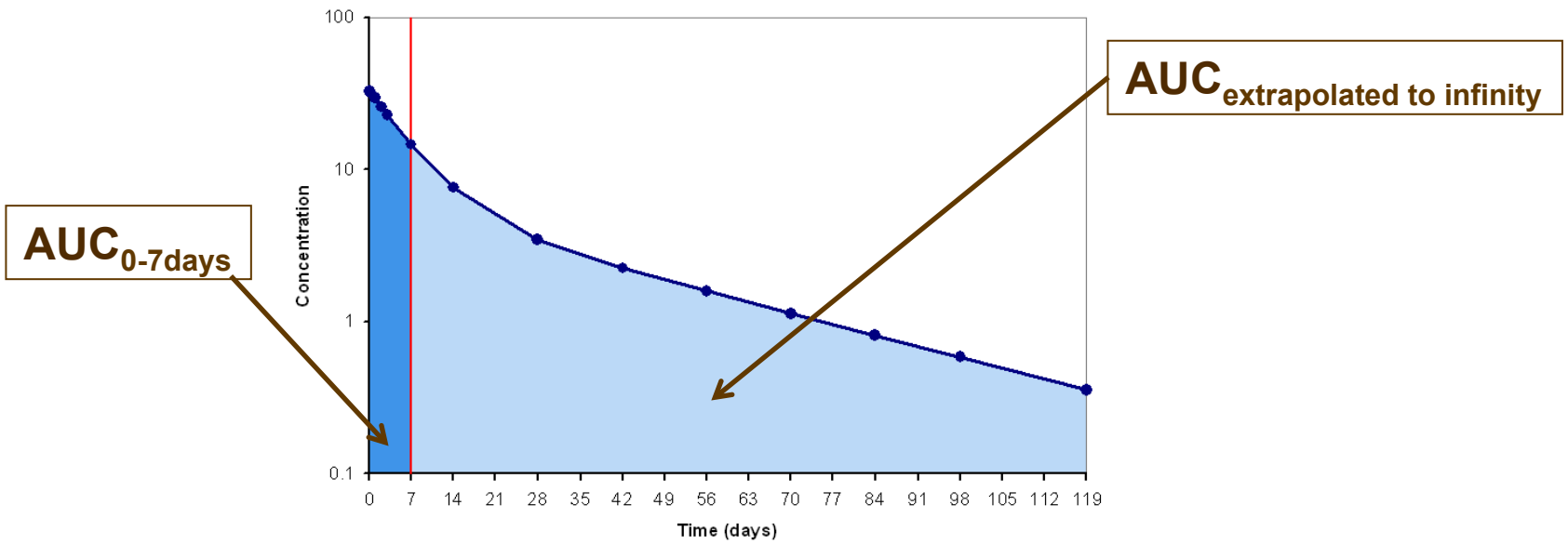
- Single dose, dose escalating study
- Objectives: safety, tolerability and PK
- 1 placebo and 3 actives at each dose level
- Data review meeting before each dose escalation:
  - 14 day safety data & 7 day PK data
- Dose adaptation:
  - Safety and tolerability
  - PK
- Drug: Monoclonal antibody
- IV administration



The Problem

Predict exposure (AUC) at the next dose level when limited data are available

- Extrapolate $AUC_{0\text{-}7days}$ to $AUC_{0\text{-}inf}$



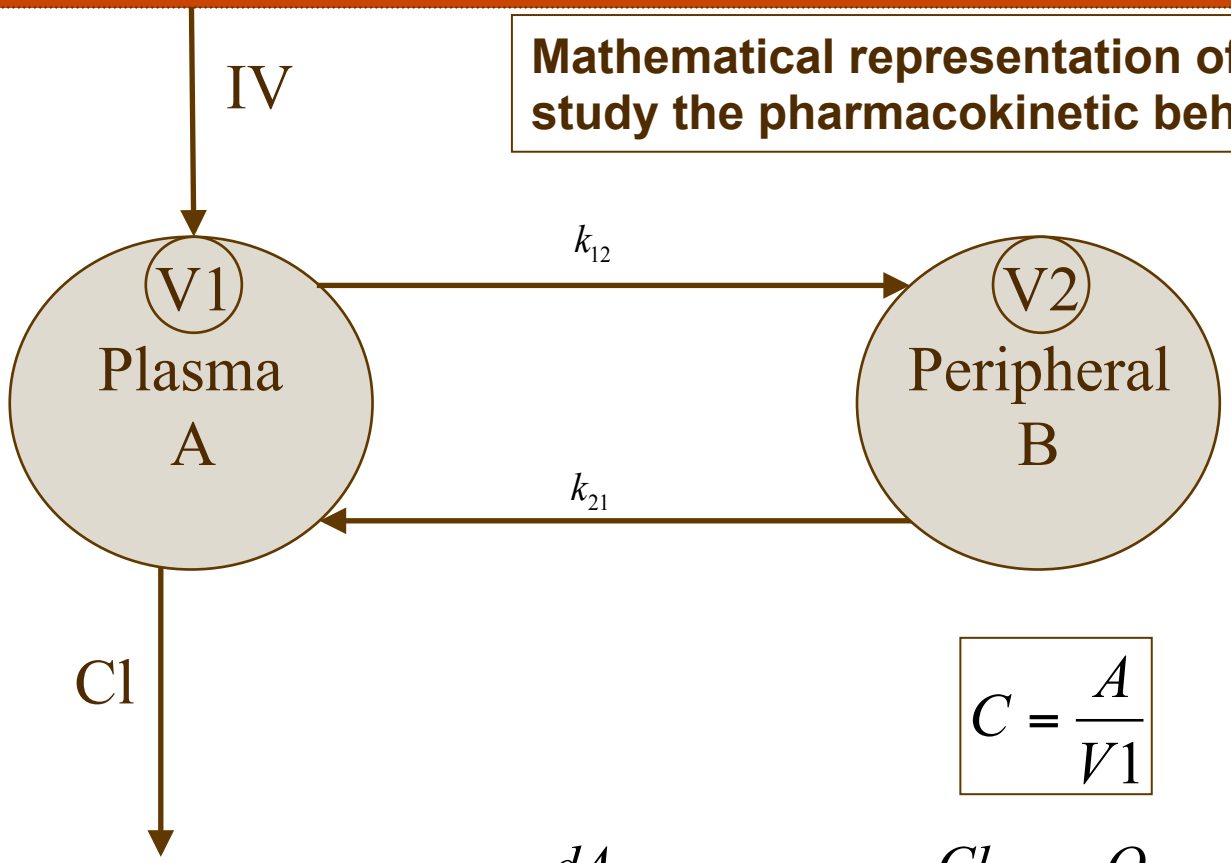
- Find the predicted probability that the $AUC_{0\text{-}inf}$ of the next planned dose level exceeds pre-specified threshold (NOAEL AUC value)

The Solution

- Make use of what we have observed/learned:
  - The PK of Monoclonal antibodies is in general well predicted from preclinical species.
  - In humans, antibodies with similar formats tend to have similar PK.
- Use the Bayesian approach that allows the use of the above information and, so, borrows strength to give good parameter estimates when we have limited data.
- Assume a stochastic model (nonlinear mixed effect model) that describes the Pharmacokinetics of the drug and accounts for inter-individual variability.

The Pharmacokinetics Model

Mathematical representation of the body created to study the pharmacokinetic behaviour.



$$k_{12} = \frac{Q}{V1}$$

$$k_{21} = \frac{Q}{V2}$$

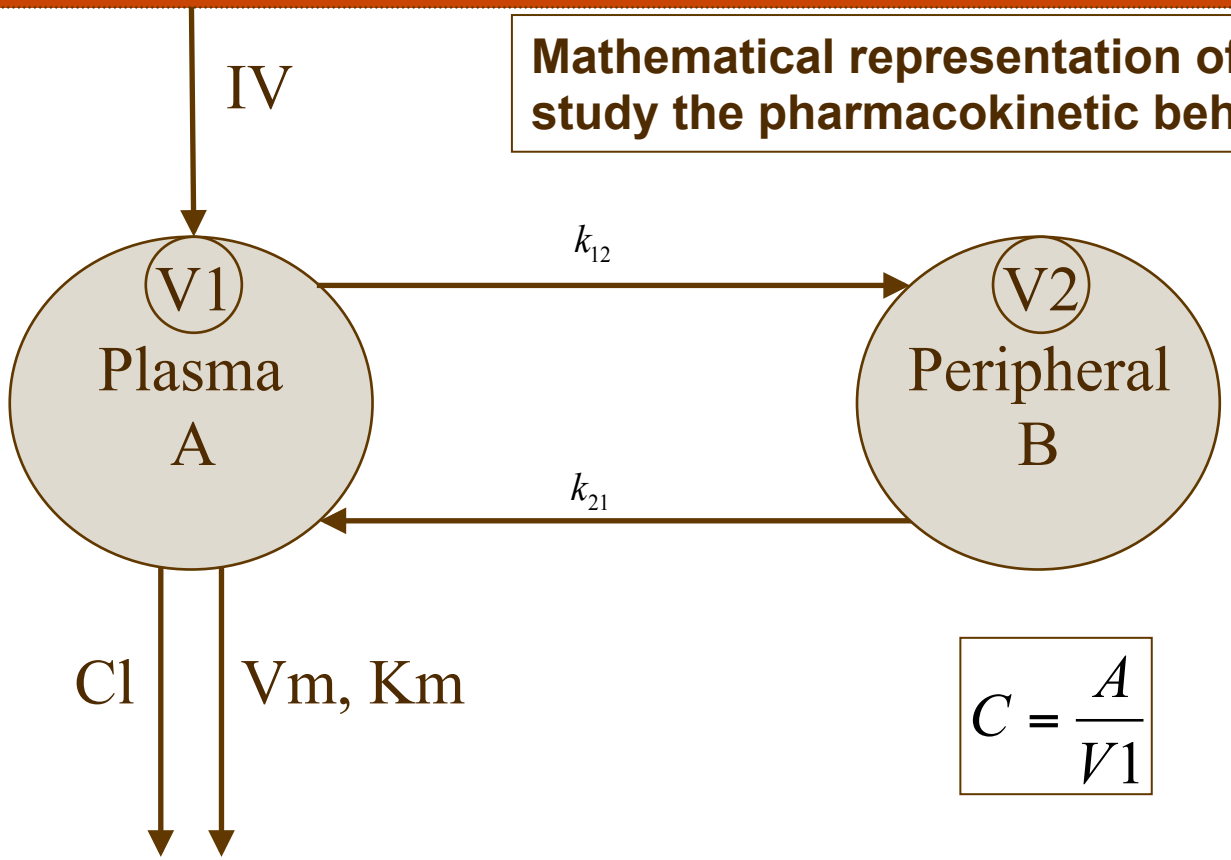
$$C = \frac{A}{V1}$$

$$\frac{dA}{dt} = Rate(t) - A\frac{Cl}{V1} - A\frac{Q}{V1} + B\frac{Q}{V2}$$

$$\frac{dB}{dt} = A\frac{Q}{V1} - B\frac{Q}{V2}$$

The Pharmacokinetics Model

Mathematical representation of the body created to study the pharmacokinetic behaviour.



$$k_{12} = \frac{Q}{V1}$$

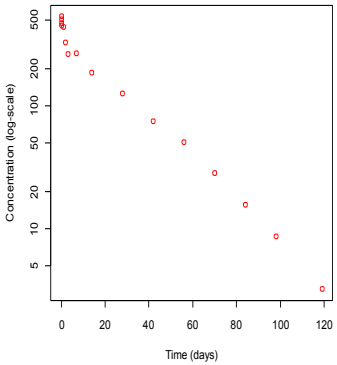
$$k_{21} = \frac{Q}{V2}$$

$$C = \frac{A}{V1}$$

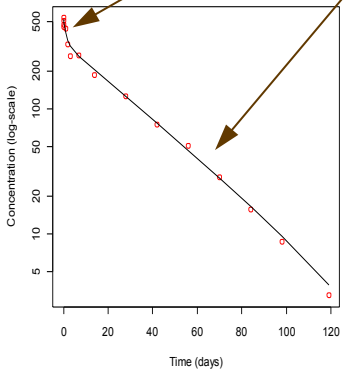
$$\frac{dA}{dt} = Rate(t) - A\frac{Cl}{V1} - A\frac{Q}{V1} + B\frac{Q}{V2} - Vm\frac{A/V1}{Km + A/V1}$$

$$\frac{dB}{dt} = A\frac{Q}{V1} - B\frac{Q}{V2}$$

Linear vs. Nonlinear Elimination



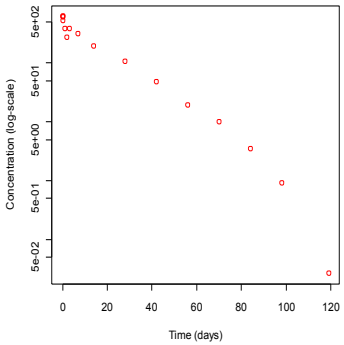
linear



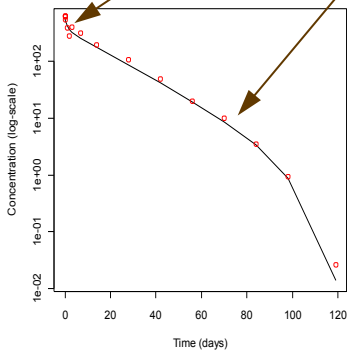
Distribution phase

Linear Elimination phase

Analytical solution for concentration at any given time point.



nonlinear



Distribution phase

Nonlinear Elimination phase

No Analytical solution. Requires solving ODEs.

The Statistical Model

- **Concentration for the jth subject at ith time point is**

$$C_{ij} = \frac{A_{ij}}{V1_j} * \varepsilon_{m,ij} + \varepsilon_{a,ij}$$

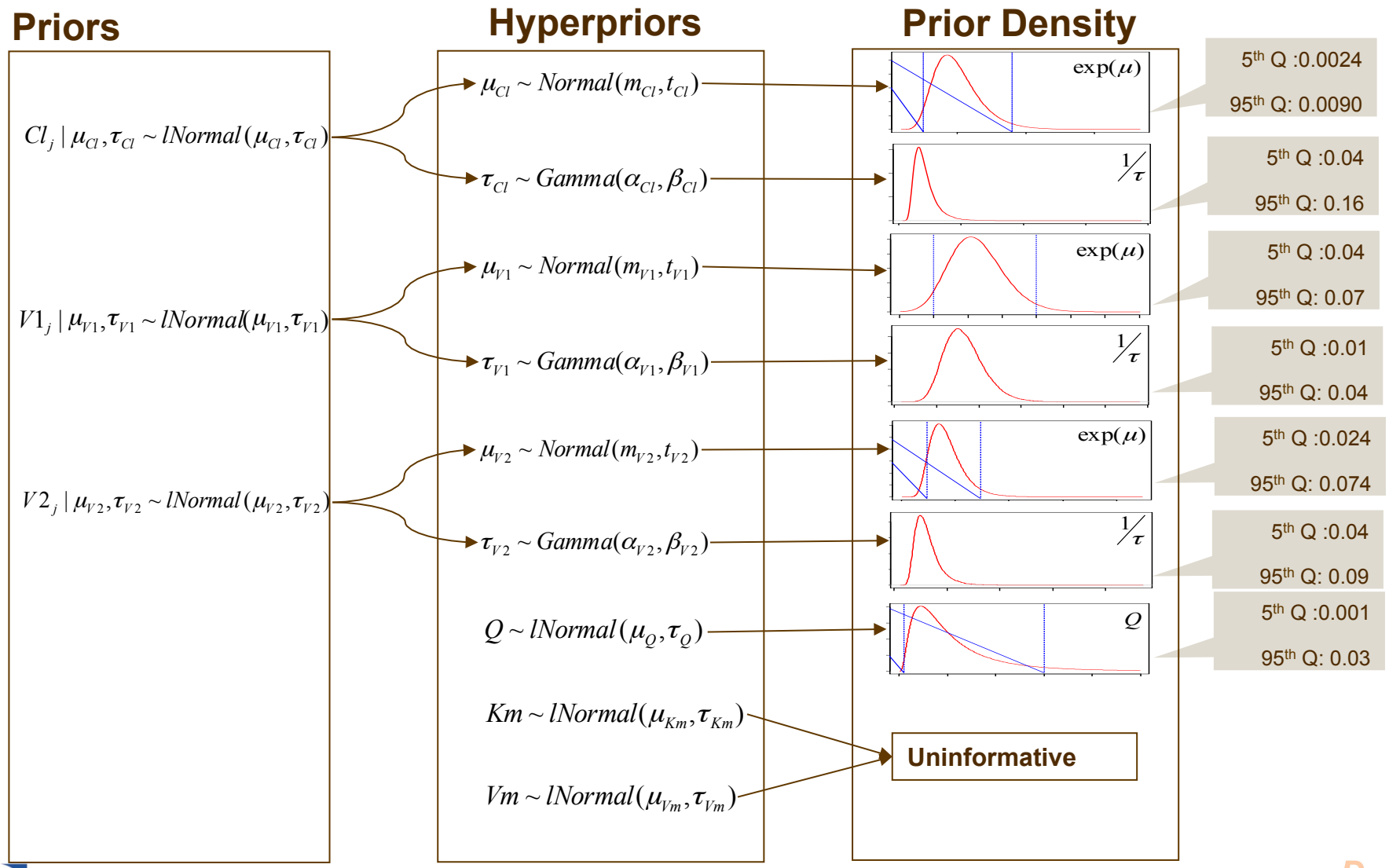
- **With multiplicative and additive errors**

$$\varepsilon_{m,ij} \sim Normal(1, \sigma_m^2) \qquad \varepsilon_{a,ij} \sim Normal(0, \sigma_a^2)$$

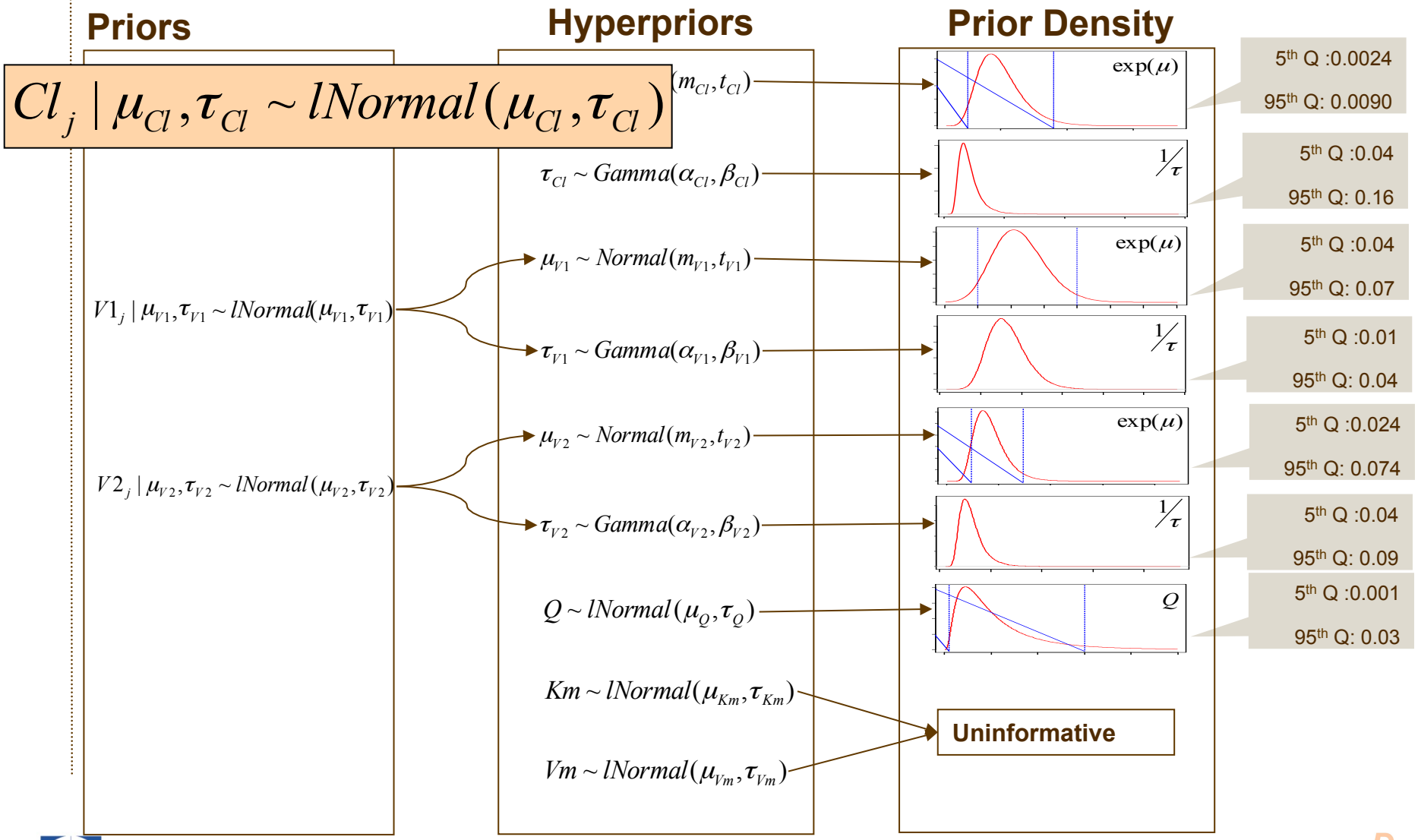
- **So the model is**

$$C_{ij} \sim Normal\left(\frac{A_{ij}}{V1_j}, \sigma_m^2\left(\frac{A_{ij}}{V1_j}\right)^2 + \sigma_a^2\right)$$

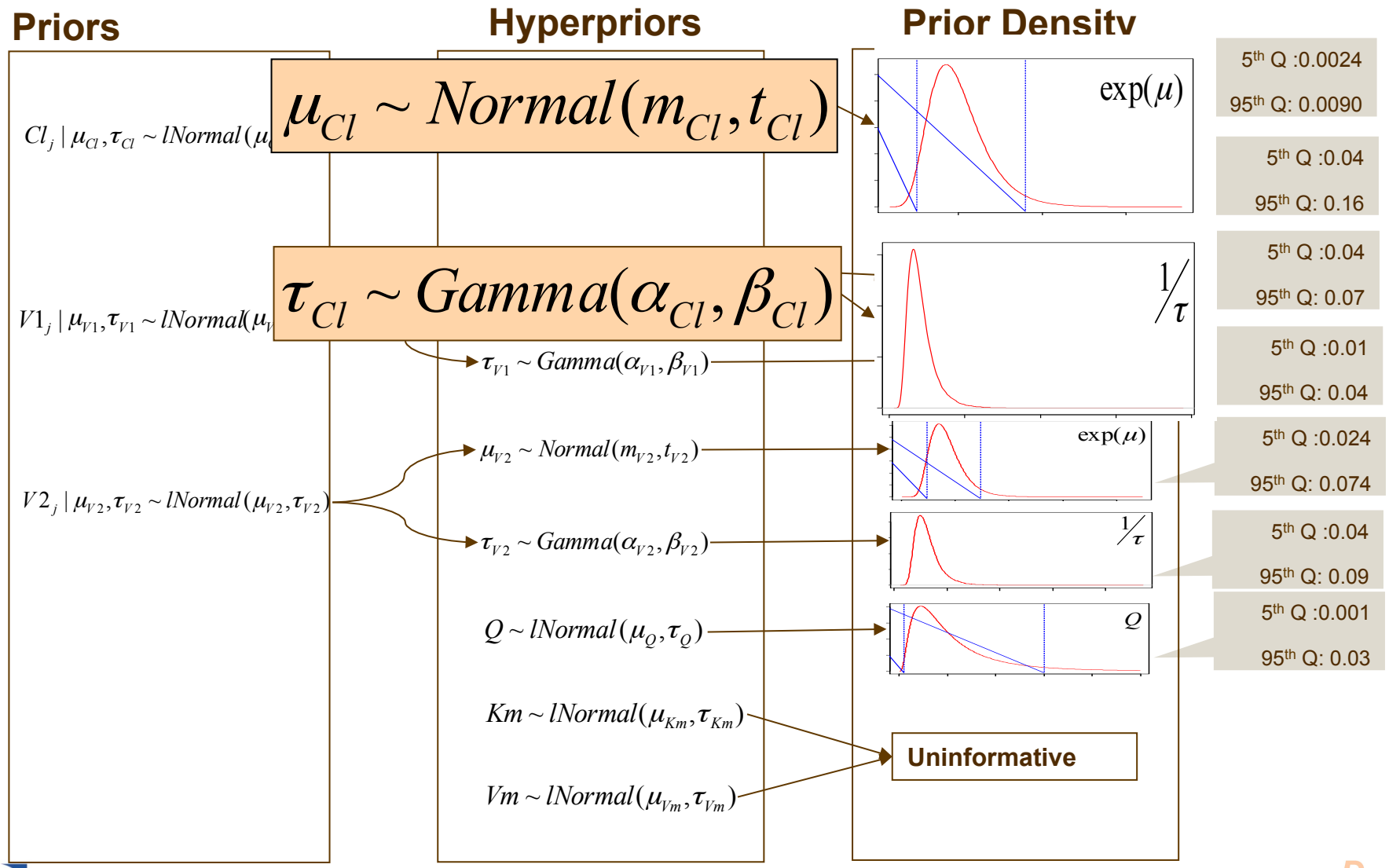
Prior Specifications



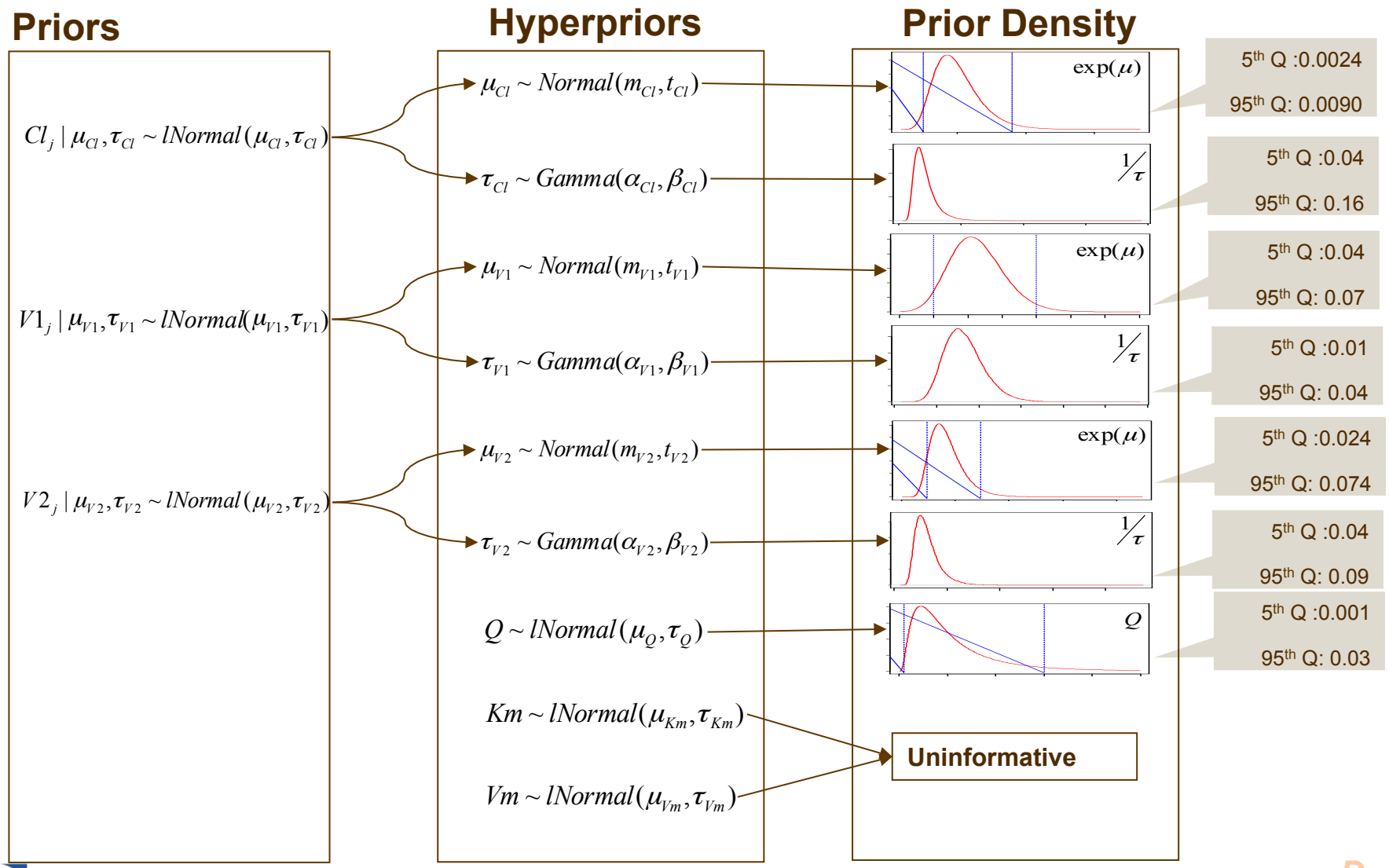
Prior Specifications



Prior Specifications

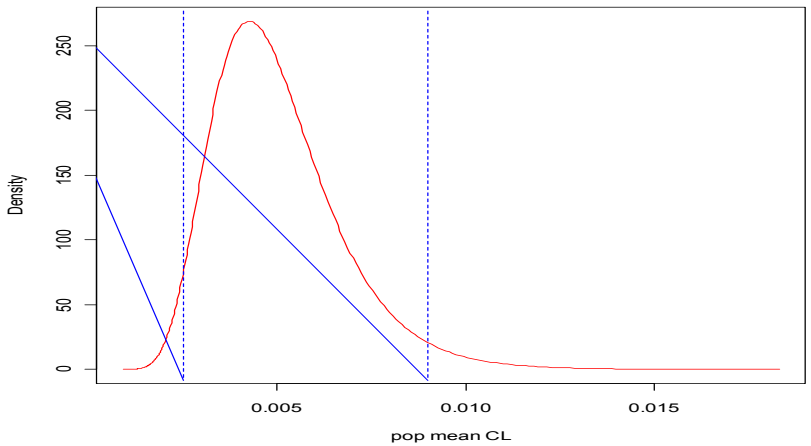


Prior Specifications

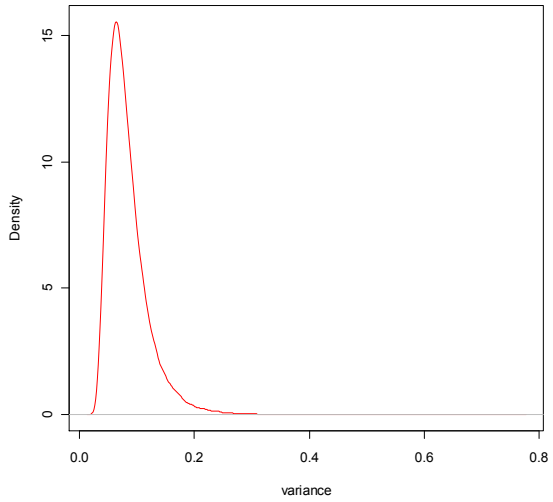


Details on Prior Selection - Clearance

- Prior knowledge for population mean:
  - Drug X pre-clinical CL allometrically scaled to human: 0.00364 L/kg/day
  - Drug Y pre-clinical CL allometrically scaled to human: 0.0058 L/kg/day
  - Drug Z CL in healthy volunteers: 0.0059 L/kg/day
  - literature data range of CL from other antibodies: 0.0024 to 0.0086 L/kg/day
  - Data were combined to get 95% of CL values to be between 0.0024 and 0.0090 L/kg/day:
    - popCL ~ logNorm(mu=log(0.00475),sd=0.33)



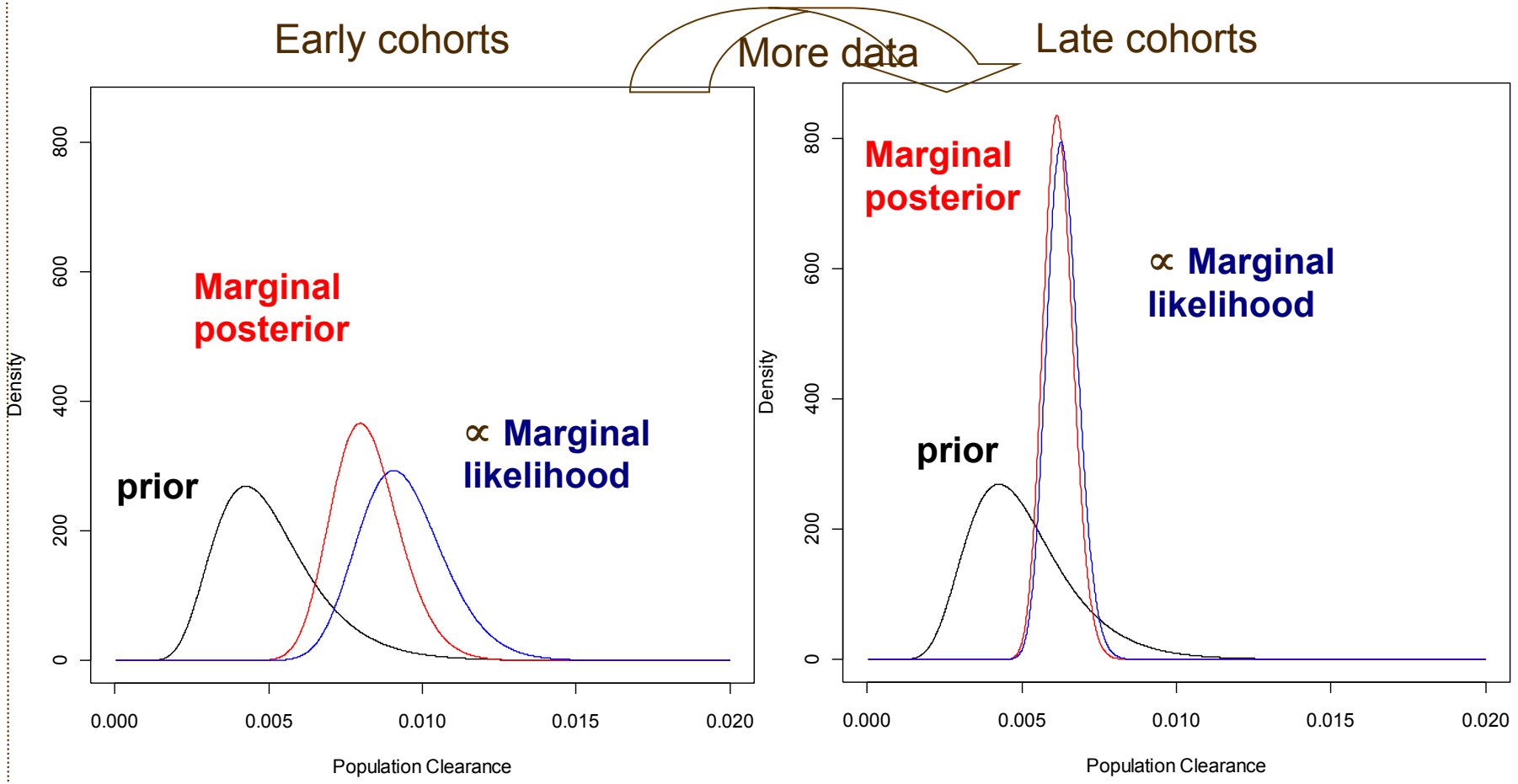
- Prior knowledge for interindividual variability:
  - Drug X in healthy volunteers CV%=38.2
  - Drug Y in healthy volunteers CV%=27%
  - Range of plausible values 20% (var=0.04) to 40% (var=0.16)
    - varCL~InvGamma(shape=7, rate=0.5)



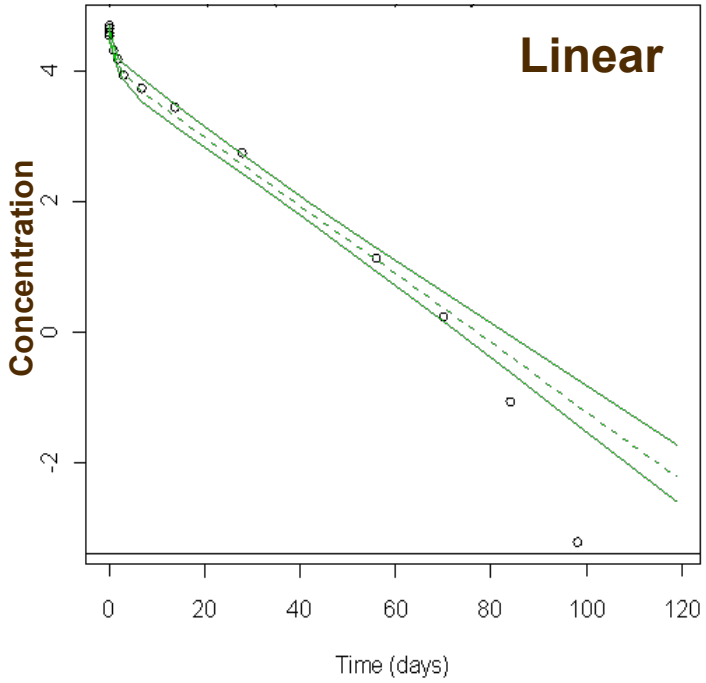
Results: Parameter Estimates

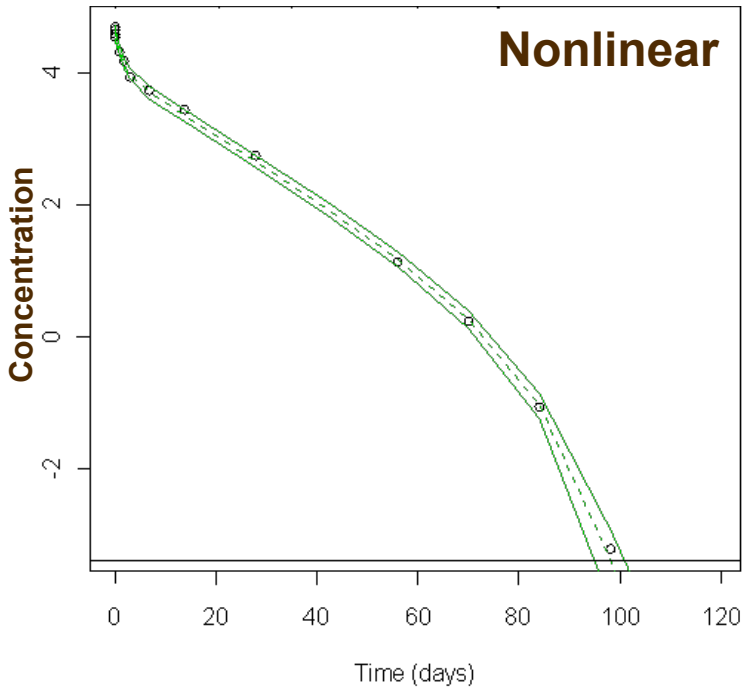
	WinBUGS
	Posterior mean (95% Credible Interval)
CL (L/kg/day)	0.0045 (0.004, 0.005)
Variance CL	0.0495 (0.029, 0.084)
V1 (L/kg)	0.0535 (0.0492, 0.058)
Variance V1	0.025 (0.018, 0.034)
Q (L/kg/day)	0.0139 (0.011,0.017)
V2 (L/kg)	0.036 (0.031, 0.042)
Variance V2	0.073 (0.041, 0.126)
Km (ug/mL)	0.173 (0.084, 0.348)
Vmax (mg/kg/day)	0.0037 (0.0027,0.0051)

Prior Influence on Posterior for the Population Clearance

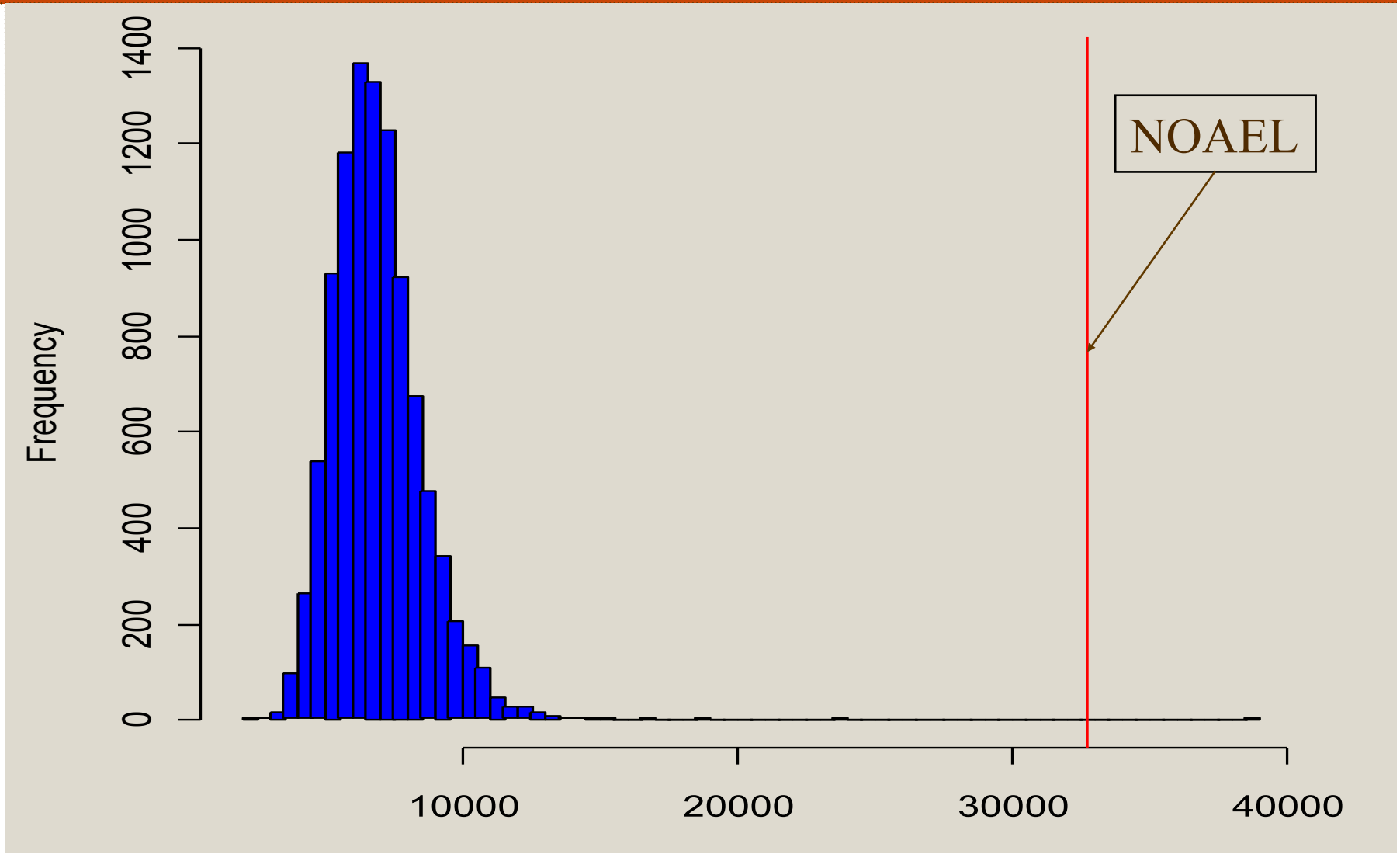


Linear vs. Nonlinear Fitting for an Individual Profile





AUC Predictive Distribution for Next Dose



How to Implement this in WinBUGS? Pre-requisites

- **WinBUGS 1.4 (of course!)**
- **Optional: R version 2.13.1 and package 'R2WinBUGS'**
- **WBDiff: WinBUGS differential interface (see Appendix 1)**
  - **Allows the numerical solution of arbitrary systems of ordinary differential equations (ODEs) within WinBUGS (1.4) models.**
- **BlackBox Component builder (see Appendix 2)**
  - **What is it? The BlackBox Component Builder is an integrated visual development environment for the rapid development of software components.**
  - **Translation: Use this to write your own WinBUGS functions → Pascal language→ makes WinBUGS run in minutes instead of hours…**
  - **Do I need to program in BlackBox????? No, as someone else has already done it for the functions we will be using here.**

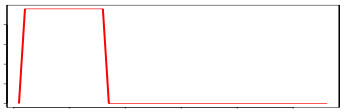
Ode.block

- Simple ‘ode’ command solves ODEs that are composed of smooth functions over time.
- ‘ode.block’ function solves ODEs in blocks (used when discontinuities occur). For example, in situations when we have multiple subcute/bolus dosing.
- Breaking down the WinBUGS ‘ode.block’ command
  - Inputs
    - Initial conditions values: matrix with rows corresponding to the time points that there is a change in the system (e.g. bolus dose) and columns that correspond to the different compartments.
    - Times: a vector with the time points where the ODE will be evaluated (at which time points we want to know what is the amount of drug at compartment A).
    - ODE equations: a vector with as many elements as the number of ODE equations. In our case that is two (one for each compartment).
    - Origins: a vector with the time points that correspond to a change in the system.
    - Tolerance: a small value
  - Output
    - Amount of drug in each compartment at each time point: a matrix with elements the solution of the system of ODEs. Columns correspond to the compartment (# columns = 2) and rows correspond to time points of the ODE evaluation.

WinBUGS Model

```
model{
for(j in 1:M){                # For each subject

for(i in 1:ntp[j]){           # For each time point
    Y[j,i]~dnorm(Mean[j,i],Prec[j,i])        # Give the model
    Mean[j,i] <- CompA[j,i,1]/V1[j]          # Mean
    Var[j,i] <- (varmult*pow(Mean[j,i],2)) + varadd        # Variance
    Prec[j,i]<-1/Var[j,i]     #Precision
}

CompA[j,1:ntp[j], 1:dim] <- ode.block(init[j,1:2,1:dim], x[j,1:ntp[j]], D(C[j,1:dim], t), origins[j,1:n.block], 1.0E-3)

# Set the differential equations
D(C[j,Ac],t) <- RA[j] - C[j,Ac]*CL[j]/V1[j] - C[j,Ac]*Q[j]/V1[j] + C[j,Bc]*Q[j]/V2[j] - Vmax[j]*(C[j,Ac]/V1[j])/(KM1[j]+C[j,Ac]/V1[j])
D(C[j,Bc],t) <- C[j,Ac]*Q[j]/V1[j] - C[j,Bc]*Q[j]/V2[j]

RA[j] <- piecewise(vec.RA[j,1:n.block])
vec.RA[j,1] <- rate[j]
vec.RA[j,2] <- 0

 init[j,1,1] <- 0
 init[j,1,2] <- 0
 init[j,2,1] <- 0
 init[j,2,2] <- 0

origins[j,1] <- 0
origins[j,2] <- 2/24

CL[j]~dlnorm(logmuCL,tauCL)
V1[j]~dlnorm(logmuV1,tauV1)
V2[j]~dlnorm(logmuV2,tauV2)
Vmax[j]<-exp(logmuVmax)
KM1[j]<-exp(logmuKM1)
Q[j]<-exp(logmuQ)

}
```

$$Y_{ij} \sim Normal\left(\frac{A_{ij}}{V1_j}, \sigma_m^2\left(\frac{A_{ij}}{V1_j}\right)^2 + \sigma_a^2\right)$$



$$\begin{array}{c} \\ t_1 \\ t_2 \end{array} \begin{array}{c} \begin{array}{cc} A & B \end{array} \\ \begin{bmatrix} 0 & 0 \\ 0 & 0 \end{bmatrix} \end{array}$$

$$\begin{array}{c} t_1 \\ t_2 \end{array} \begin{bmatrix} 0 \\ \frac{2}{24} \end{bmatrix}$$

$$Cl_j \mid \mu_{Cl}, \tau_{Cl} \sim lNormal(\mu_{Cl}, \tau_{Cl})$$

$$V1_j \mid \mu_{V1}, \tau_{V1} \sim lNormal(\mu_{V1}, \tau_{V1})$$

$$V2_j \mid \mu_{V2}, \tau_{V2} \sim lNormal(\mu_{V2}, \tau_{V2})$$

WinBUGS Model

```
model{
for(j in 1:M){                                          # For each subject
```

```
for(i in 1:ntp[j]){                                     # For each time point
    Y[j,i]~dnorm(Mean[j,i],Prec[j,i])                   # Give the model
    Mean[j,i] <- CompA[j,i,1]/V1[j]                     # Mean
    Var[j,i] <- (varmult*pow(Mean[j,i],2)) + varadd     # Variance
    Prec[j,i]<-1/Var[j,i]                               # Precision
}
```

$$Y_{ij} \sim Normal\left(\frac{A_{ij}}{V1_j}, \sigma_m^2\left(\frac{A_{ij}}{V1_j}\right)^2 + \sigma_a^2\right)$$

WinBUGS Model

```
# Calculate the amount of drug at each compartment (ode.block)

CompA[j,1:ntp[j], 1:dim] <- ode.block(
                                        init[j,1:n.block,1:dim],   # Initial conditions
                                        x[j,1:ntp[j]],             # Times
                                        D(C[j,1:dim], t),          # ODEs
                                        origins[j,1:n.block],      # Origins
                                        1.0E-3                     # Tolerance
                                      )
```

```
# Set the differential equations

D(C[j,Ac],t) <- RA[j] - C[j,Ac]*CL[j]/V1[j] –
                C[j,Ac]*Q[j]/V1[j] +
                C[j,Bc]*Q[j]/V2[j] -
                Vmax[j]*
                (C[j,Ac]/V1[j])/(KM1[j]+C[j,Ac]/V1[j])

D(C[j,Bc],t) <- C[j,Ac]*Q[j]/V1[j] - C[j,Bc]*Q[j]/V2[j]
```

$$\frac{dA}{dt} = Rate(t) - A\frac{Cl}{V1} - A\frac{Q}{V1} + B\frac{Q}{V2} - Vm\frac{A/V1}{Km + A/V1}$$

$$\frac{dB}{dt} = A\frac{Q}{V1} - B\frac{Q}{V2}$$

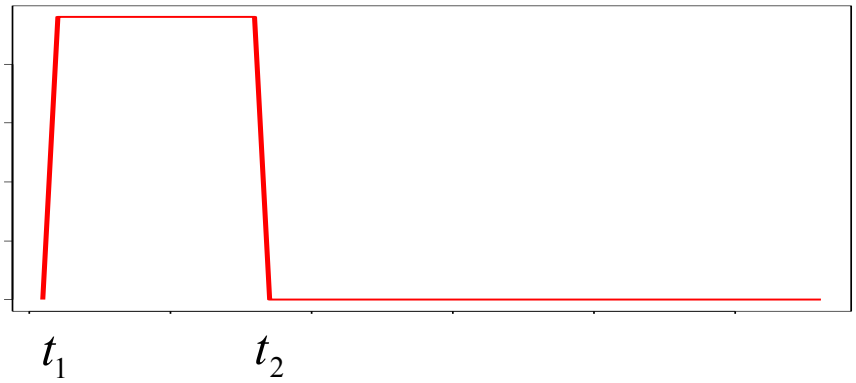
WinBUGS Model

- origins[j,1] <- 0
- origins[j,2] <- 2/24

$$\begin{matrix} t_1 \\ t_2 \end{matrix}\begin{bmatrix} 0 \\ \frac{2}{24} \end{bmatrix}$$

- RA[j] <- piecewise(vec.RA[j,1:n.block])

- vec.RA[j,1] <- rate[j]
- vec.RA[j,2] <- 0



- init[j,1,1] <- 0
- init[j,1,2] <- 0
- init[j,2,1] <- 0
- init[j,2,2] <- 0

$$\begin{matrix} & A & B \\ t_1 & 0 & 0 \\ t_2 & 0 & 0 \end{matrix}$$

WinBUGS Model

```
# Priors
CL[j]~dlnorm(logmuCL,tauCL)
V1[j]~dlnorm(logmuV1,tauV1)
V2[j]~dlnorm(logmuV2,tauV2)
Vmax[j]<-exp(logmuVmax)
KM1[j]<-exp(logmuKM1)
Q[j]<-exp(logmuQ)

}
```

$$Cl_j \mid \mu_{Cl}, \tau_{Cl} \sim lNormal(\mu_{Cl}, \tau_{Cl})$$

$$V1_j \mid \mu_{V1}, \tau_{V1} \sim lNormal(\mu_{V1}, \tau_{V1})$$

$$V2_j \mid \mu_{V2}, \tau_{V2} \sim lNormal(\mu_{V2}, \tau_{V2})$$

```
# Hyperpriors
logmuCL ~ dnorm (CLmean,CLprec)                 tauCL~dgamma (CLa,CLb)
logmuV1 ~ dnorm (V1mean,V1prec)                 tauV1~dgamma (V1a,V1b)
logmuV2 ~ dnorm (V2mean,V2prec)                 tauV2~dgamma (V2a,V2b)
logmuVmax~dnorm (Vmaxmean,Vmaxprec)
logmuKM1~dnorm (KM1mean,KM1prec)
logmuQ ~ dnorm (Qmean,Qprec)
taumult ~ dgamma (varmulta,varmultb)            varmult<-1/taumult
tauadd ~ dgamma (varadda,varaddb)               varadd<-1/tauadd
}
```

Appendix 1: Installing WBDiff

- Download WBDiff from:
  - http://www.winbugs-development.org.uk/download_wbdiff.html
  - and follow the instructions.
- Start your copy of WinBUGS 1.4 and open the .txt file from within it.
- Select "Decode" from the "Tools" menu -- the "Decode" dialogue box should appear.
- Click on the "Decode All" button to install the WinBUGS Differential Interface (WBDiff). You may be prompted to create five new directories in total during the installation process -- click on "OK" for each one.
- Quit WinBUGS to complete the installation. (You may delete this file afterwards if you wish.)
- After installation, documentation for this interface can be found in: Program Files/ WinBUGS14/WBDiff/Examples/WBDiff_example.pdf

Appendix 2: (Installing BlackBox)

- Download *BlackBox Component Builder* from the following web-page: http://www.oberon.ch/blackbox.html
- Unzip the downloaded file, if necessary. Install 'BlackBox' by double-clicking on the Setup.exe icon and following the instructions. The software should be installed into the new directory Program Files/BlackBox.
- Open My Computer (or its equivalent) and navigate to the Program Files/WinBUGS14 directory; then press Ctrl+A (or select Select All from the Edit menu) to select all files and sub-directories within the WinBUGS14 directory. Now press Ctrl+C (or select Copy from the Edit menu) to copy those files and sub-directories.
- Continue using My Computer to navigate to the Program Files/BlackBox directory and then press Ctrl+V (or select Paste from the Edit menu) to paste the copied files and sub-directories to this location. Select "Yes to All" if prompted about replacing existing files.
- Now your copy of BlackBox should include the *full* functionality of WinBUGS 1.4 within it, and so the BlackBox.exe icon on the desk-top or that in the Program Files/BlackBox directory can be used either to run WinBUGS in the normal way or to conduct WinBUGS development work (or even more general Component Pascal programming).

Conclusions

- The proposed Bayesian approach allows the prediction of $AUC_{(0\text{-inf})}$ and the probability to exceed a predefine AUC threshold by integrating information from:
  - 7 days PK data from the latest dose level
  - the PK data from previous dose levels
  - prior knowledge
- A PK model Bayesian approach for dose escalations implemented for the first time
- Computationally demanding approach (takes a few hours to run)

Acknowledgments

- Astrid Jullion
- Bruno Boulanger
- Muriel Boulton

Questions?