

Population Pharmacokinetic Model in SAS

Application with proc MCMC

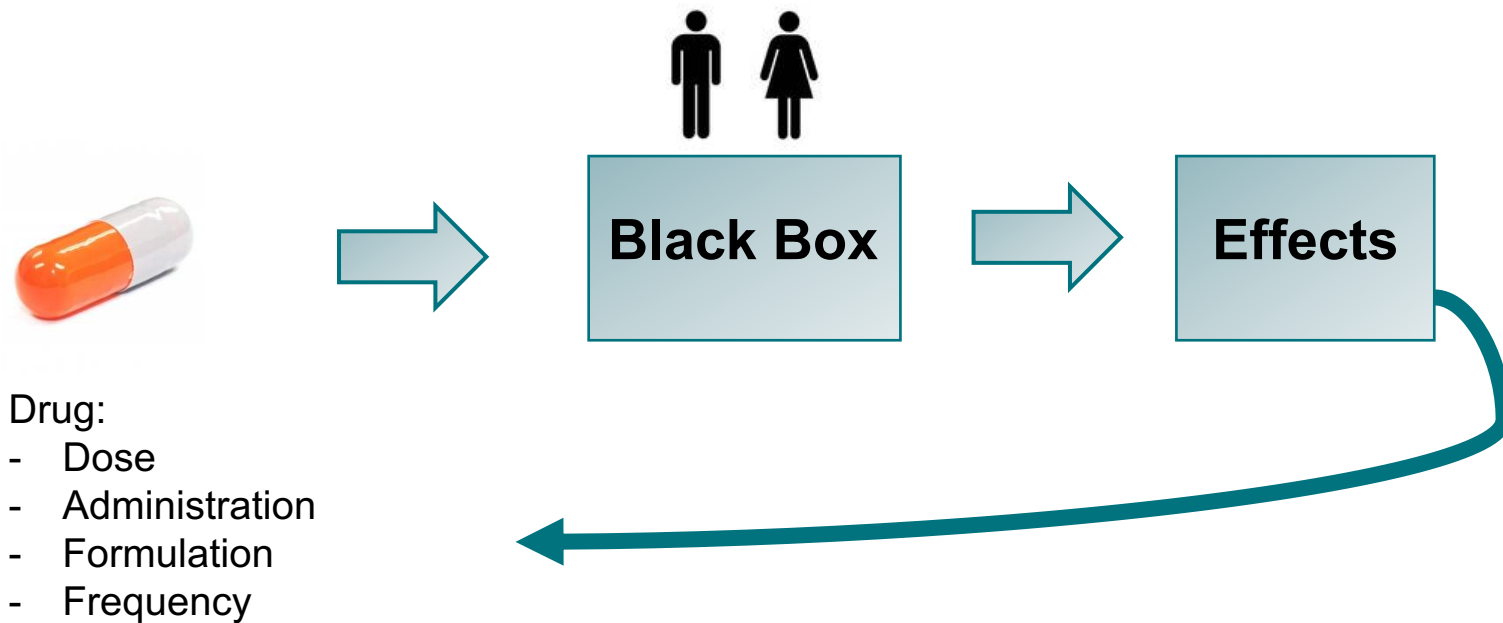
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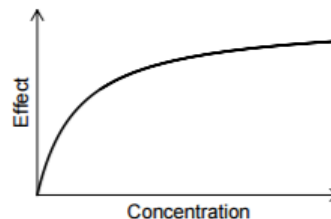
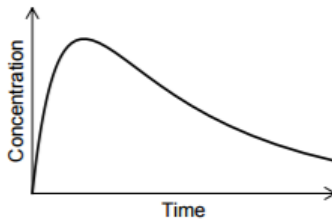
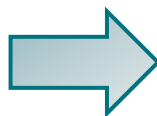
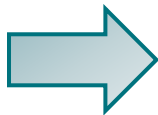
Phuse 2020

● Pharmacokinetic and Compartmental Models

● What's the effect of a drug ?

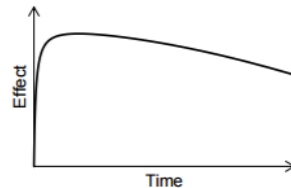


Model the concentration and the effect



Pharmacokinetic (PK)

Pharmacodynamic (PD)



PK/PD

Drug:

- Dose
- Administration
- Formulation
- Frequency



● PK – PD: Definition

- **Pharmacokinetic** describes the drug concentration-time courses in body fluids resulting from administration of a certain drug dose

“ What the body does to the drug? “

- **Pharmacodynamic** describes the observed effect resulting from a certain drug concentration

“ What the drug does to the body? “

- The rationale for **PK-PD modelling** is to link pharmacokinetic and pharmacodynamic in order to establish and evaluate dose-concentration-response relationships and subsequently describe and predict the effect-time courses resulting from a drug dose

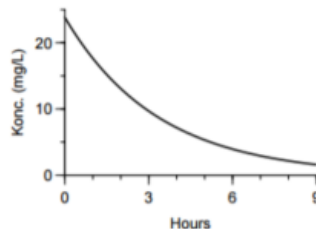


Compartmental Model in Pharmacokinetic

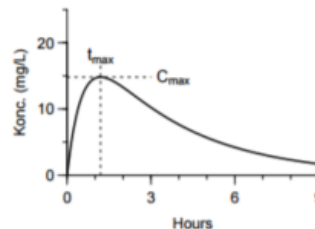
► **Compartmental models** use kinetic models to describe (with approximations) the concentration-time curve. Models take into account

- The type of **administration**

- Oral Administration
- IV Bolus
- Infusion
- ...



(a) Intravenous (iv) bolus dose

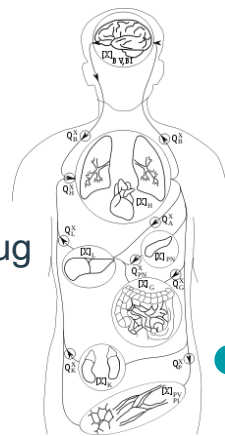


(b) Oral dose

- The **mechanism** of absorption, distribution and elimination

- The **tissues type**: A compartment is a region of the body in which the drug is well mixed and kinetically homogenous.

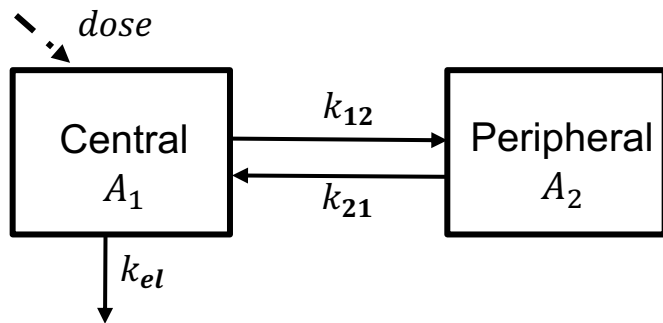
- Bloodstream (= central compartment)
- Poorly-perfused tissues (muscle and skin)
- Brain



Examples of PK compartmental models

$$C_1(t) \sim N(\mu = \frac{A_1(t)}{V_1}, \sigma^2) \text{ where}$$

→ Two compartments model
with iv bolus administration



$$\frac{dA_1(t)}{dt} = -k_{el}A_1(t) - k_{12}A_1(t) + k_{21}A_2(t)$$

$$\frac{dA_2(t)}{dt} = k_{12}A_1(t) - k_{21}A_2(t)$$

$$A_1(0) = dose, A_2(0) = 0$$

Between-subjects variability can be
estimated on the PK parameters:

$$k_{el} = \exp(\beta_1 + b_1), b_1 \sim N(0, \sigma_1^2)$$

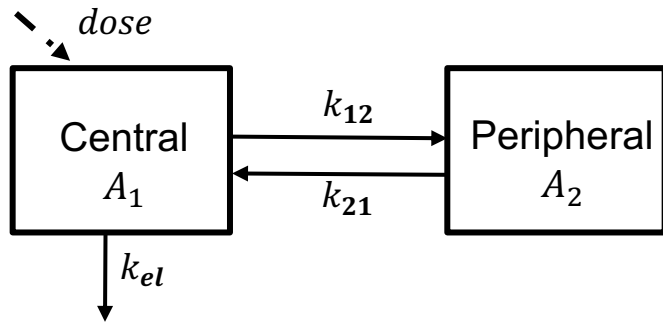
→ **PopPK Models**



Examples of PK compartmental models

$C_1(t) \sim N(\mu = \frac{A_1(t)}{V_1}, \sigma^2)$ where

→ Two compartments model with iv bolus administration



$$\frac{dA_1(t)}{dt} = -k_{el}A_1(t) - k_{12}A_1(t) + k_{21}A_2(t)$$

$$\frac{dA_2(t)}{dt} = k_{12}A_1(t) - k_{21}A_2(t)$$

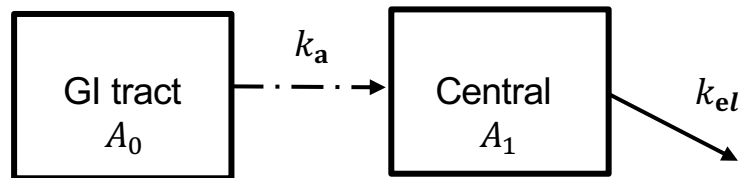
$$A_1(0) = dose, A_2(0) = 0$$

Between-subjects variability can be estimated on the PK parameters:

$k_{el} = \exp(\beta_1 + b_1), b_1 \sim N(0, \sigma_1^2)$

→ **PopPK Models**

→ One compartment model with oral administration



$$\frac{dA_0(t)}{dt} = -k_a A_0(t)$$

$$\frac{dA_1(t)}{dt} = \underbrace{k_a A_0(t)}_{\text{Absorption}} - \underbrace{k_{el} A_1(t)}_{\text{Elimination}}$$



Different parametrization are allowed in PK models

- ▶ Parametrization in terms of **elimination and transfer rate constants**
 - k_{el} is the elimination rate
 - k_{12}, k_{21} ... are the transfer rates
- ▶ Parametrization in terms of **clearance and volumes constants**
 - **Clearance** (CL) is the theoretical volume of plasma that's completely cleared of drug per unit of time
 - **Volume of distribution** is the theoretical volume that would be necessary to contain the total amount of an administered drug at the same concentration that it is observed in the blood plasma

Elimination and transfer rate	Clearance and volume
k_{el}	CL_1/V_1
k_{12}	CL_2/V_1
k_{21}	CL_2/V_2



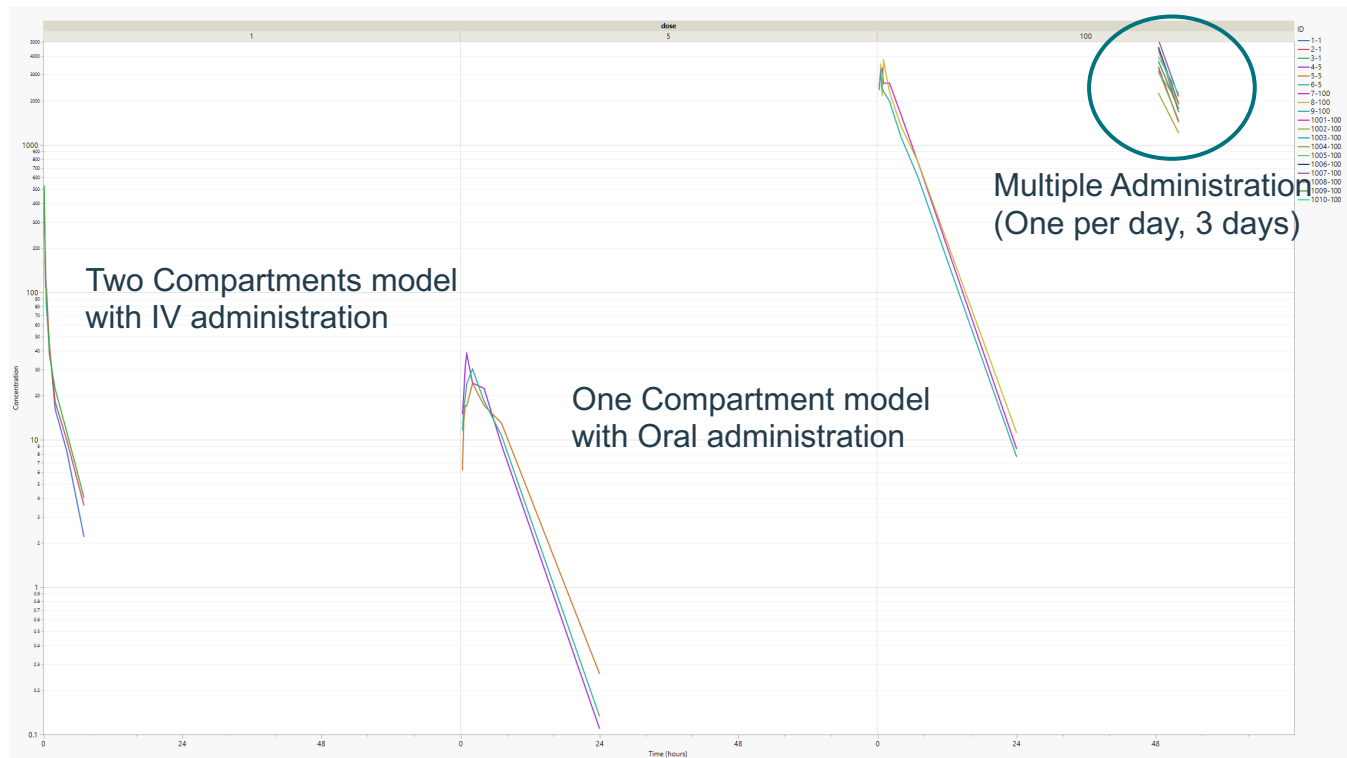


Compartmental Models in Proc MCMC

Example on Preclinical Data

Preclinical data

IV and Oral Administration – Single and Multiple Administration



How to fit Compartmental Model in Proc MCMC (SAS)?

- ▶ `call ode` and `proc fcmp`
 - `proc fcmp` provides the ability to build functions (ODEs in this case).
Use CALL routines and subroutines to use them in other SAS procedures or DATA steps.
 - `call ode` subroutine numerically solves a set of first-order ordinary differential equations (ODEs), including piecewise differential equations.
The subroutine is included in the `proc mcmc` and calls the function built in `proc fcmp`.
- ▶ The `CMPTMODEL` statement computes predicted concentrations from a specified one-, two-, or three-compartment model.
 - Only available in SAS 9.4 - SAS/STAT 15.1
 - Only compartmental model
 - More efficient than `call ode`
 - Available with `proc MCMC` and `proc NLMIXED`



CMPTMODEL Statement

► The CMPTMODEL statement includes three types of options:

- **Required-options:** PCONC=, TIME=, NCOMPS=, ADMTYPE=, and PARMTYPE=
 - PCONC= outcome variable that is the predicted concentration in the first/central compartment
 - ADMTYPE = IVB | INF | ORAL
 - NCOMPS = 1 | 2 | 3
 - PARMTYPE = 1 | 2
 - 1 = parametrizes the compartment model in terms of elimination and transfer rate constants
 - 2 = parametrizes the compartment model in terms of clearance and volumes constants
- **Conditionally-required-options** (depending on the specifications of the *required-options*): CLn=, VOLn=, K12=, K21=, K13=, K31=, KA=, Kn0=, RATE=, and DURN=
 - DURN = duration of the infusion (ADMTYPE = INF)
 - RATE = rate of infusion (ADMTYPE = INF)
 - n = the compartment number
- **Optional-options:** DOSEn=, SCALEn=, PCONC0=, PCONC2=, and PCONC3=.



CMPTMODEL options

- Here is a few examples of the conditionally required options and valid optional options

Model	Required	Conditionally required	Optional
One compartment with bolus dose	NCOMPS = 1 ADMTYPE= IVB PARMTYPE = 1	K10 =	DOSE1= SCALE1=
One compartment with bolus dose	NCOMPS = 1 ADMTYPE=IVB PARMTYPE = 2	CL1 = VOL1 =	DOSE1= SCALE1=
Two compartments with oral dose	NCOMPS = 2 ADMTYPE= ORAL PARMTYPE = 1	K10 = K12= K21= KA =	DOSE1= DOSE2= SCALE1= SCALE2= K20= PCONC2=



Let's fit a compartmental model on the IV data

- Two compartments model with iv bolus administration

$$\frac{dA_1(t)}{dt} = -k_{el}A_1(t) - k_{12}A_1(t) + k_{21}A_2(t)$$

$$\frac{dA_2(t)}{dt} = k_{12}A_1(t) - k_{21}A_2(t)$$

$$A_1(0) = dose, A_2(0) = 0$$

- Solution 1: call ode and **proc fcmp**

```
proc fcmp outlib=sasuser.funcs.PK;  
  subroutine TwoComp_IV(t, y[*], dy[*], kel, k12, k21);  
    outargs dy;
```

```
    dy[1] = -kel*y[1] - k12 * y[1] + k21 * y[2];  
    dy[2] = k12 * y[1] - k21 * y[2];
```

```
  endsub;
```

```
run;
```

```
options cmplib=sasuser.funcs;
```



Proc MCMC with call ode

Random effects on CL1 and V1
→ PopPK Model

```
proc mcmc data=out nmc=300000 nbi =55000 thin = 30;
  array init[2] dose 0;
  array sol[2];
  array mub[2] (0 0);
  array b[2] b1 b2;
  array covb[2,2];
  array S[2,2] (1 0 0 1);

  parms beta1 -6 beta2 -7 beta3 -5 beta4 -5;
  parms s2y 0.1;
  parms covb ;

  prior beta: ~ normal(-5, var = 5);
  prior s2y ~ general(0, lower=0);
  prior covb ~ iWish(2, S);

  random b ~ mvn(mub, covb) subject=id;

  CL1 = exp(beta1 + b1);
  V1 = exp(beta2 + b2);
  CL2 = exp(beta3);
  V2 = exp(beta4);

  kel = cl1/v1;
  k12 = cl2/v1;
  k21 = cl2/v2;

  call ode('TwoComp_IV', sol, init, 0, time, kel, k12, k21);

  m=sol[1]/V1;
  mu = log(m);
  log_dv=log(dv);
  model log_dv ~ normal(mu, var=s2y);
run;
```



Let's fit a compartmental model on the IV data

- Two compartments model with iv bolus administration

$$\frac{dA_1(t)}{dt} = -k_{el}A_1(t) - k_{12}A_1(t) + k_{21}A_2(t)$$

$$\frac{dA_2(t)}{dt} = k_{12}A_1(t) - k_{21}A_2(t)$$

$$A_1(0) = dose, A_2(0) = 0$$

- Solution 2**: CMPTMODEL statement

```
CMPTMODEL ncomps = 2 admtype = ivb time = time pconc = sol  
          parmtime = 2 cl1=cl1 vol1=v1 cl2=cl2 vol2=v2;
```

```
CMPTMODEL ncomps = 2 admtype = ivb time = time pconc = sol  
          parmtime = 1 k10=kel k12=k12 k21=k21;
```



Proc MCMC with CMPTMODEL

```
proc mcmc data=out nmc=300000 nbi =55000 thin = 30;
```

```
array mub[2] (0 0);  
array b[2] b1 b2;  
array covb[2,2];  
array S[2,2] (1 0 0 1);
```

```
parms beta1 -6 beta2 -7 beta3 -5 beta4 -5;  
parms s2y 0.1;  
parms covb ;
```

```
prior beta: ~ normal(-5, var = 5);  
prior s2y ~ general(0, lower=0);  
prior covb ~ iWish(2, S);
```

```
random b ~ mvn(mub, covb) subject=id;
```

```
CL1 = exp(beta1 + b1);  
V1 = exp(beta2 + b2);  
CL2 = exp(beta3);  
V2 = exp(beta4);
```

```
CMPTMODEL ncomps = 2 admttype = ivb time = time pconc = sol parmttype = 2 cl1=cl1 vol1=v1 cl2=cl2 vol2=v2;
```

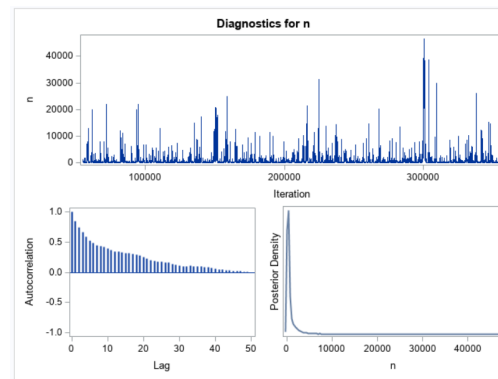
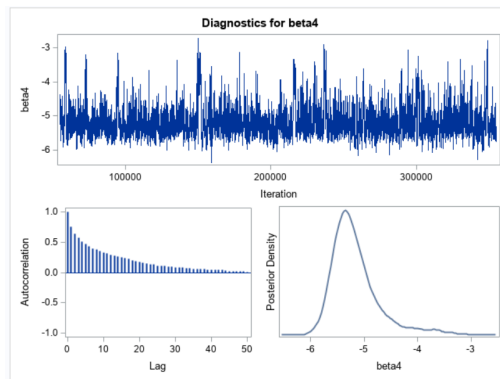
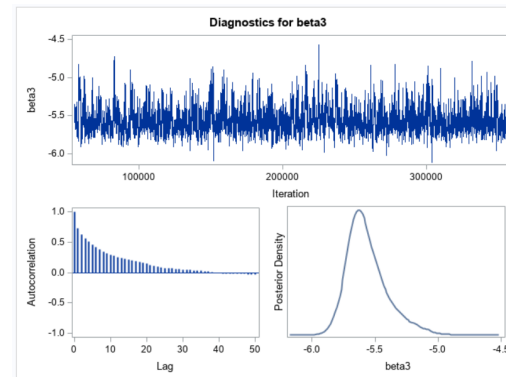
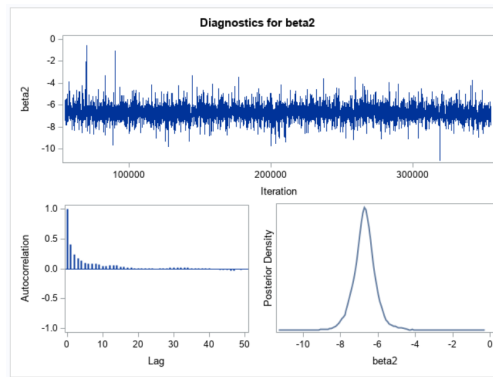
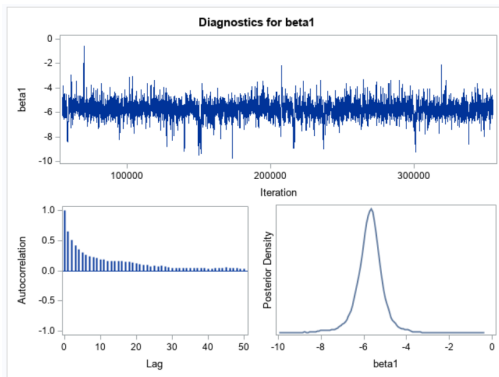
```
m=sol/V1;  
mu = log(m);  
log_dv=log(dv);  
model log_dv ~ normal(mu, var=s2y);
```

```
run;
```

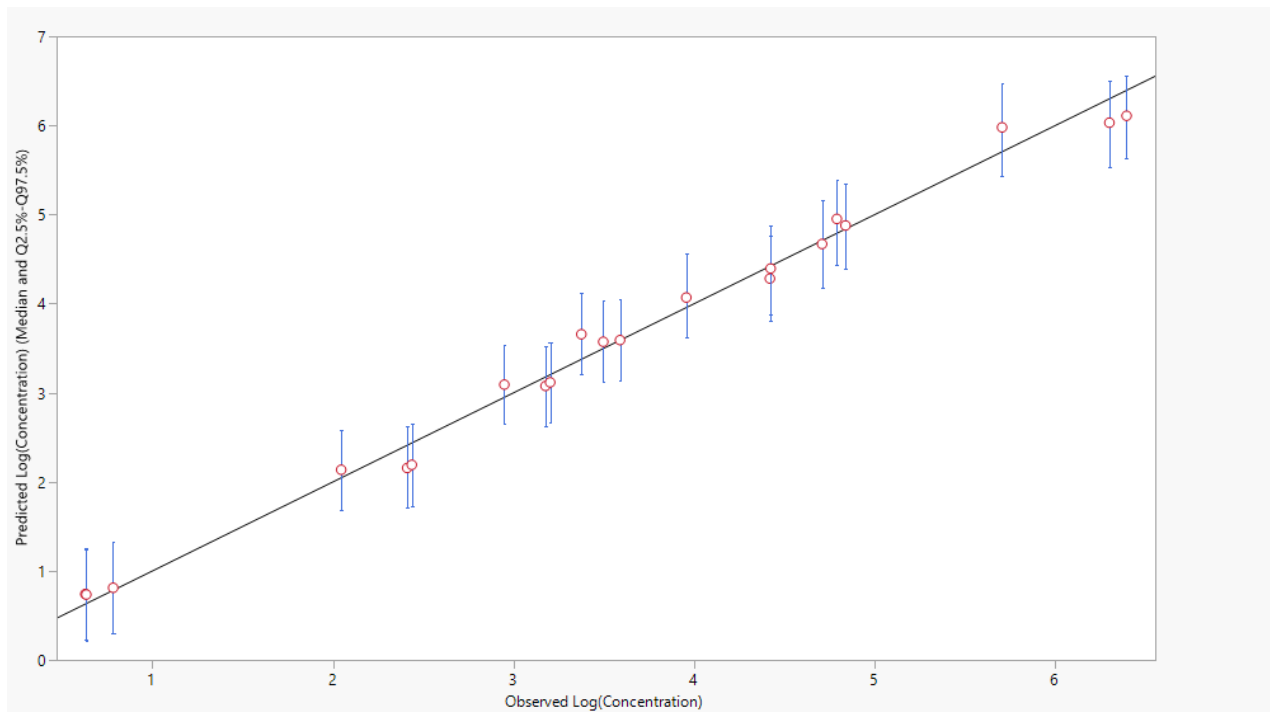
Random effects on CL1 and V1
→ PopPK Model



Output: the two proc mcmc converge to the same solutions



Output: Good fit of the model



- Median of the predictive distribution
- | Interval of Prediction (Q2.5%-Q97.5%)



Comparison solution 1 vs solution 2

► Solution 1: `call` ode and `proc fcmp`

Posterior Summaries and Intervals					
Parameter	N	Mean	Standard Deviation	95% HPD Interval	
beta1	10000	-5.4837	0.4942	-6.3989	-4.4174
beta2	10000	-6.7470	0.6052	-7.8952	-5.4846
beta3	10000	-5.7913	0.2039	-6.1906	-5.4081
beta4	10000	-5.6502	0.1508	-5.9286	-5.3569
s2y	10000	0.0622	0.0318	0.0210	0.1258
covb1	10000	0.8490	1.6871	0.0563	2.7735
covb2	10000	0.0464	1.2761	-1.6612	1.6107
covb3	10000	0.0464	1.2761	-1.6612	1.6107
covb4	10000	1.0905	2.2768	0.0634	3.6236

NOTE: Starting optimization.

NOTE: Tuning the proposal distribution.

NOTE: Generating the burn-in samples.

NOTE: Beginning sample generation.

NOTE: The data set DATA.OUTPOST_IV_FCMP has 10000 observations and 20 variables..

NOTE: PROCEDURE MCMC used (Total process time):

real time 2:14:36.42

cpu time 2:14:33.22

► Solution 2: CMPTMODEL statement

Posterior Summaries and Intervals					
Parameter	N	Mean	Standard Deviation	95% HPD Interval	
beta1	10000	-5.4674	0.4802	-6.4569	-4.4849
beta2	10000	-6.7407	0.5904	-7.9174	-5.5701
beta3	10000	-5.7928	0.1998	-6.1959	-5.4145
beta4	10000	-5.6493	0.1452	-5.9314	-5.3647
s2y	10000	0.0620	0.0324	0.0182	0.1205
covb1	10000	0.8592	2.9203	0.0522	2.6159
covb2	10000	0.0418	2.4036	-1.4168	1.6514
covb3	10000	0.0418	2.4036	-1.4168	1.6514
covb4	10000	1.1195	3.8336	0.0655	3.3156

NOTE: Starting optimization.

NOTE: Tuning the proposal distribution.

NOTE: Generating the burn-in samples.

NOTE: Beginning sample generation.

NOTE: The data set DATA.OUTPOST_IV has 10000 observations and 20 variables.

NOTE: PROCEDURE MCMC used (Total process time):

real time 35.86 seconds

cpu time 35.84 seconds

Let's fit a model on the complete dataset !

- ▶ One model by administration
 - iv bolus administration: 2 compartments model
 - Oral administration: 1 compartment model
- ▶ Parametrizes in terms of clearance and volume constants
- ▶ Use the CMPTMODEL statement

```
CMPTMODEL ncomps = 2 admtype = ivb time = time pconc = sol  
          parmtime = 2 cl1=cl_iv1 voll=v_iv1 cl2=cl_iv2 vol2=v_iv2;
```

```
CMPTMODEL ncomps = 1 admtype = oral time = time pconc = sol  
          parmtime = 2 cl1 = CL_PO voll=V_PO ka=ka;
```



SAS code

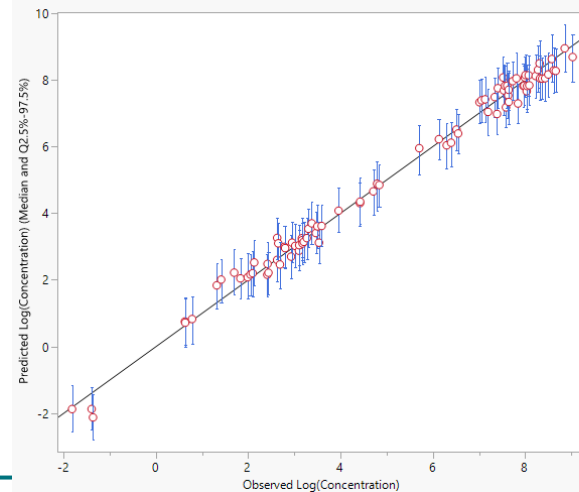
```
proc mcmc data=out nmc=300000 nbi =55000 thin = 30;  
  [ ... ]
```

```
F      = exp(beta0);  
CL_IV1 = exp(beta1 + b1);  
V_IV1  = exp(beta2 + b2);  
CL_IV2 = exp(beta3);  
V_IV2  = exp(beta4);  
CL_PO  = exp(beta1 + b1)/F;  
V_PO   = exp(beta2 + b2)/F;  
ka     = exp(beta5) ;
```

```
if Admin="IV" then do;  
  CMPTMODEL ncomps = 2 admtype = ivb time = time pconc = sol  
  parmttype = 2 cl1=cl_IV1 vol1=v_IV1 cl2=cl_IV2 vol2=v_IV2;  
  m=sol/V_IV1;  
end;  
  
If Admin="PO" then do;  
  CMPTMODEL ncomps = 1 admtype = oral time = time pconc = sol  
  parmttype = 2 cl1 = CL_PO vol1=V_PO ka=ka;  
  m=sol/V_PO;  
end;
```

```
mu = log(m);  
log_dv=log(dv);  
model log_dv ~ normal(mu, var=s2y);
```

run;



F is the bioavailability

Conclusion

- A set of Ordinary Differential Equations (ODEs) can be solved in a Bayesian way thanks to
 - `call ode` + `proc fcmp`
 - `CMPTMODEL` function
- Compartment PopPK model can be handled by the new function `CMPTMODEL` of `proc mcmc`:
 - Ease of implementation: no need to write the system of equations
 - Much faster than `call ode`
 - Multiple administration can be easily modeled (*not shown here*)
 - `%pkconvert` macro should be used to convert the dataset in order to get a structure close to NONMEM structure
 - Limitations:
 - Only available in the latest version of SAS
 - Only classical PK model are available (1-2-3 compartments)
 - Two possibilities for the parametrization



● Contacts

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