



PharmML – An Introduction

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On behalf of the DDMoRe consortium



First specification of DDMoRe Markup Language aka **PharmML**

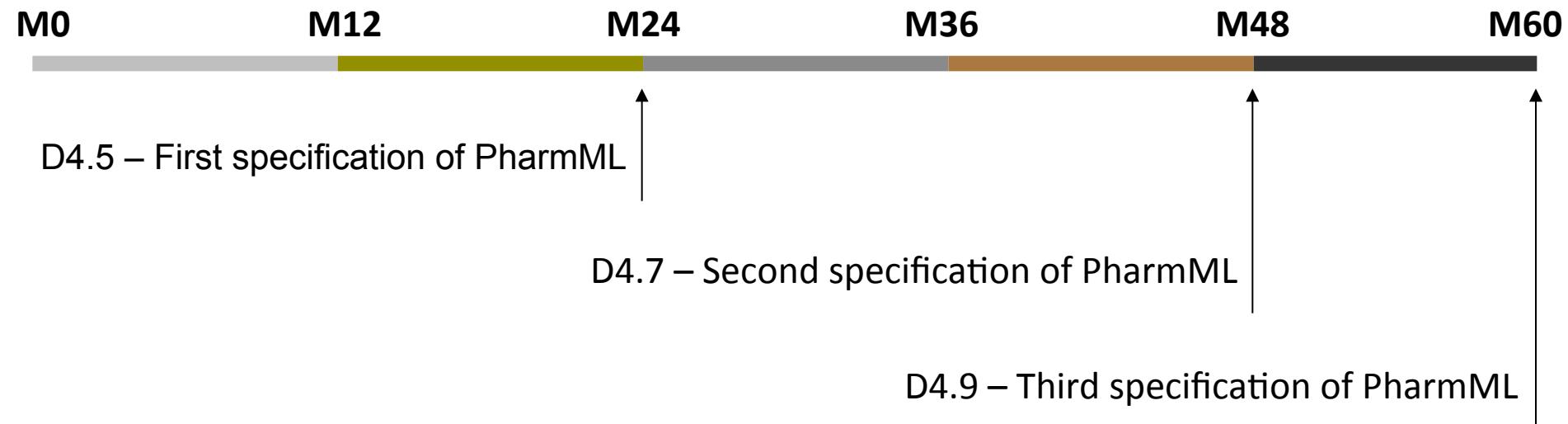
PharmML stands for...



Pharmacometrics Markup Language

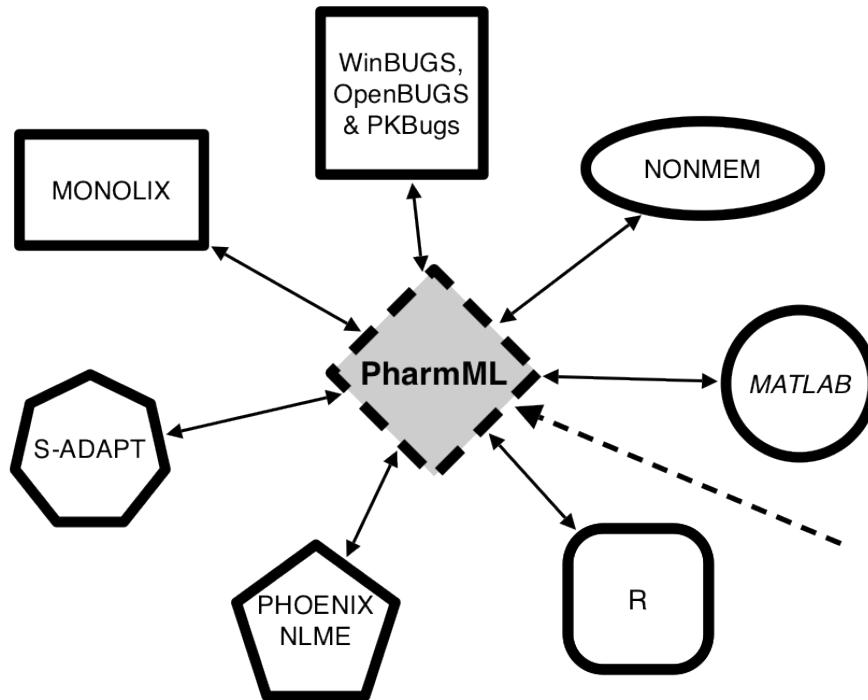
Pharmacokinetics (PK) : “what the body does to the drug”
Pharmacodynamics (PD) : “what the drug does to the body”

PharmML Timeline



PharmML

as element of the interoperability platform



Main objectives

- Encoding of
 - Models
 - Trial design
 - Basic tasks
- Annotation

Status Quo / Motivation

NONMEM code for count data:

\$PROB Generalized Poisson distribution function

\$DATA data.csv IGNORE=@
\$INPUT ID TIME DV

\$PRED

; Parameters

LAMB=THETA(1)*EXP(ETA(1))

LOGIT=LOG(THETA(2)/(1-THETA(2)))

DELTA=2*EXP(LOGIT+ETA(2))/(1+EXP(LOGIT+ETA(2)))-1

; Factorial approximation

IF(DV.LE.1) THEN

LFAC=0

ELSE

LFAC = DV*LOG(DV)-DV +LOG(DV*(1+4*DVG*(1+2*DVG))/6 +LOG(3.1415)/2

ENDIF

; Likelihood definition

LGP = LOG(LAMB)+(DV-1)*LOG(LAMB+DV*DELTA)-LAMB-DV*DELTA-LFAC

Y = -2*LGP

*NONMEM specific
- not part of the model definition*

; Simulation code

IF (ICALL.EQ.4) THEN

LAMB=THETA(1)*EXP(ETA(1))

LOGIT=LOG(THETA(2)/(1-THETA(2)))

DELTA=EXP(LOGIT+ETA(2))/(1+EXP(LOGIT+ETA(2)))

PN=0

N=0

CALL RANDOM (2,R)

DO WHILE (PN.LT.R)

IF(N.LE.1) THEN

LFAC=0

ELSE

LFAC = N*LOG(N)-N +LOG(N*(1+4*N*(1+2*N))/6 +LOG(3.1415)/2

ENDIF

GP=LAMB*(LAMB+N*DELTA)**(N-1)*EXP(-LAMB-N*DELTA)/EXP(LFAC)

PN = GP+PN

IF (PN.LT.R) N=N+1

END DO

DV=N

ENDIF

\$THETA (0,0.50) ; LAMBDA

\$THETA (-1,0.25,1) ; DELTA

\$OMEGA

0.1 ; LAMBDA

1.0 ; DELTA

\$ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE -2LL

\$COV

;\$SIMULATION (361734) (474980 UNIFORM) ONLYSIM NOPRED

\$TABLE ID TIME DV NOAPPEND ONEHEADER NOPRINT FILE = tab

Basic comparison to SB

- 10-12 years behind
- IMI project to start
 - 5 years
 - Top pharmaceutical companies involved
- Different user base
- Different expectations
- Ontology – what is it?

Basic comparison to SB

- Individual based methods versus population based
- Two stage method
 - Stage 1: estimation of pharmacokinetic parameters through nonlinear regression using an individual's dense concentration-time data (data-rich situation)

$$y_j = f(t_j; \psi) + g(t_j; \psi)\varepsilon_j, \quad 1 \leq j \leq n,$$
 - Stage 2: calculation of descriptive summary statistics on the sample, typically, mean parameter estimates, variance, and covariance of the individual parameter estimates
- NLME (sparse data situation)

$$\underbrace{y_{ij}}_{\text{Experimental data}} = \underbrace{f(x_{ij}, \psi_i)}_{\text{Model prediction}} + \underbrace{g(x_{ij}, \psi_i, \xi) \varepsilon_{ij}}_{\text{Error}} \quad 1 \leq i \leq N, \quad 1 \leq j \leq n_i$$

Finishing the spec



PharmML: The Pharmacometrics Markup Language

Language Specification

Version 0.2.0

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Niels R. Kristensen³ and Nicolas Le Novère^{2,4}

13 Sep 2013

Understanding Structure of PharmML

Structure

- Typical **Pharmacometrics project** is usually described by
 - Experimental Data
 - Trial execution model
 - Structural model
 - Population/Individual parameter model
 - Covariate model
 - Correlation structure of the random effects
 - Inter-subject, inter-occasion and higher orders of variability
 - Residual error model
 - Observation model
 - Task model
- **PharmML** is organised in
 - Model Definition
 - Structural Model
 - Covariate Model
 - Parameter Model
 - Variability Model
 - Observations Model
 - Trial Design
 - Structure
 - Population
 - Individual Dosing
 - Modeling Steps
 - Simulation/Estimation Step
 - Step Dependencies

Structure

- **PharmML** is organised in
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Model Definition	Variability Model												
	Covariate Model	Continuous		Categorical									
				Related Covariates									
	Parameter Model			Population Parameters									
				Individual Parameters	Correlation Structure								
	Structural Model												
Trial Design	Observation Model	Residual Error											
	Structure		Epoch	Cell	Segment	Activity							
			Arm	Observation Event									
	Population		Variability Level	Covariate Demographic		Dosing Regimen							
Modelling Steps	Individual Dosing												
	Simulation Step	Initial Assignment				Step Dependencies							
		Observations	Time Points										
			Continuous										
	Estimation Step	Operations											
		Initial Assignment											
		Objective Data											
		Parameters to Estimate											
	Operations												

Structure

```

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2  <PharmML xmlns="http://www.pharmml.org/2013/03/PharmML"
3      xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
4      xsi:schemaLocation="http://www.pharmml.org/2013/03/PharmML http://www.pharmml.org/2013/03/PharmML"
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6      writtenVersion="0.1">
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8      <ct:Description>based on "A Tumor Growth Inhibition Model for Low-Grade Glioma Treated with Chemotherapy or Radiotherapy"
9          Benjamin Ribba, Gentian Kaloshi, Mathieu Peyre, et al. Clin Cancer Res Published OnlineFirst July 3, 2012.</ct:Description>
10     <IndependentVariable symbId="time"/>
11     <ct:FunctionDefinition symbId="constantErrorModel" symbolType="real"> [5 lines]
17     <ModelDefinition xmlns="http://www.pharmml.org/2013/03/ModelDefinition">
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268        <StructuralModel blkId="sm1"> [158 lines]
427        <ObservationModel blkId="om1"> [38 lines]
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561         <EstimationStep oid="estTask1"> [204 lines]
766         <StepDependencies> [4 lines]
771     </ModellingSteps>
772 </PharmML>

```

Model Definition

Model Definition

Structural model This is an oral one compartment model and an indirect response model parameters ka , V , CL , $Imax$, $IC50$, Rin and $kout$.

$$k = \frac{CL}{V}$$

$$\frac{dAd}{dt} = -ka \times Ad$$

$$\frac{dAc}{dt} = ka \times Ad - k \times Ac$$

$$\frac{dE}{dt} = Rin \times \left(1 - \frac{Imax \times Cc}{Cc + IC50}\right) - kout \times E$$

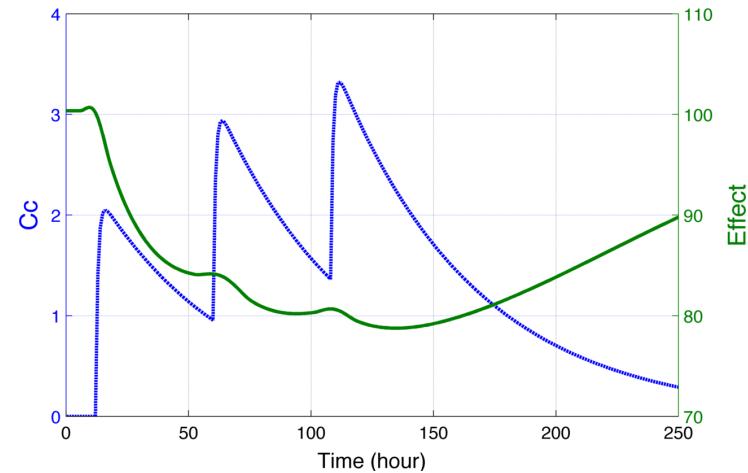
$$Cc = \frac{Ac}{V}$$

initial conditions:

$$E(t = 0) = \frac{Rin}{kout}$$

$$Ad(t = 0) = 0$$

$$Ac(t = 0) = 0$$



Model Definition

Covariate model The only covariate is Weight, W , and it is a continuous covariate:

$$W \sim \mathcal{N}(pop_W, \omega_W)$$

The following transformation is applied:

$$\log(W/70)$$

and the initial values are:

$$pop_W = 70.07, \quad \omega_W = 14.09$$

Model Definition

Parameter model

PK parameters The model uses the following individual parameters:

ka absorption rate constant

V volume of distribution

CL clearance of elimination

All follow a log-normal distribution:

$$\log(ka_i) = \log(pop_{ka}) + \eta_{ka,i}$$

$$\log(V_i) = \log(pop_V) + \beta_{1,V} \log(W_i/70) + \eta_{V,i}$$

$$\log(CL_i) = \log(pop_{CL}) + \beta_{1,CL} \log(W_i/70) + \eta_{CL,i}$$

where

$$\eta_{ka,i} \sim N(0, \omega_{ka}), \quad \eta_{V,i} \sim N(0, \omega_V), \quad \eta_{CL,i} \sim N(0, \omega_{CL})$$

with initial values:

$$\begin{aligned} pop_{ka} &= 1, & \omega_{ka} &= 0.6 & pop_V &= 8, & \omega_V &= 0.2 \\ pop_{CL} &= 0.13, & \omega_{CL} &= 0.2 & \beta_{1,V} &= 1, & \beta_{1,CL} &= 0.75 \\ &&&& \rho_{V,CL} &= 0.7^1 \end{aligned}$$

Model Definition

PK parameters The model uses the following individual parameters:

ka absorption rate constant

V volume of distribution

CL clearance of elimination

PD parameters The model uses the following individual parameters:

I_{max} maximal antagonistic response

IC_{50} concentration giving half the maximal response

R_{in} input (synthesis) rate

k_{out} output (elimination) rate

Variance-covariance matrix The full variance-covariance matrix for the random effects is:

$$\Omega = \begin{pmatrix} \omega_{ka}^2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \omega_V^2 & \omega_{V,CL} & 0 & 0 & 0 & 0 \\ 0 & \omega_{V,CL} & \omega_{CL}^2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \omega_{I_{max}}^2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \omega_{IC_{50}}^2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \omega_{R_{in}}^2 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \omega_{k_{out}}^2 \end{pmatrix}$$

where

$$\omega_{V,CL} = \omega_V \omega_{CL} \rho_{V,CL}$$

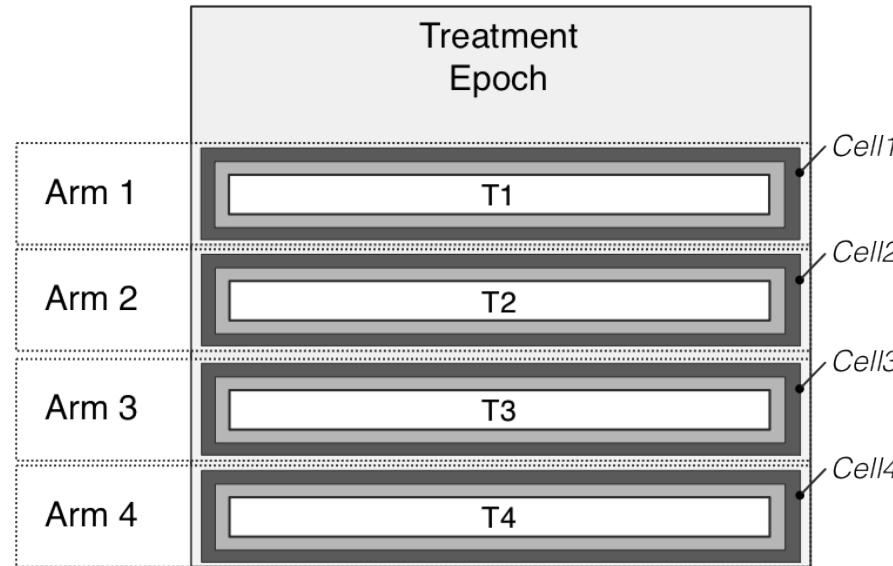
Model Definition

Observation model We apply a residual error model to the output variables Cc and E from the PK and PD models respectively.

Output Variable	Cc	E
Observation Name	Concentration	PCA
Units	mg/l	%
Type	Continuous	Continuous
Model	Combined	Constant
Parameters	$a = 0.5, b = 0.1$	$a = 4$

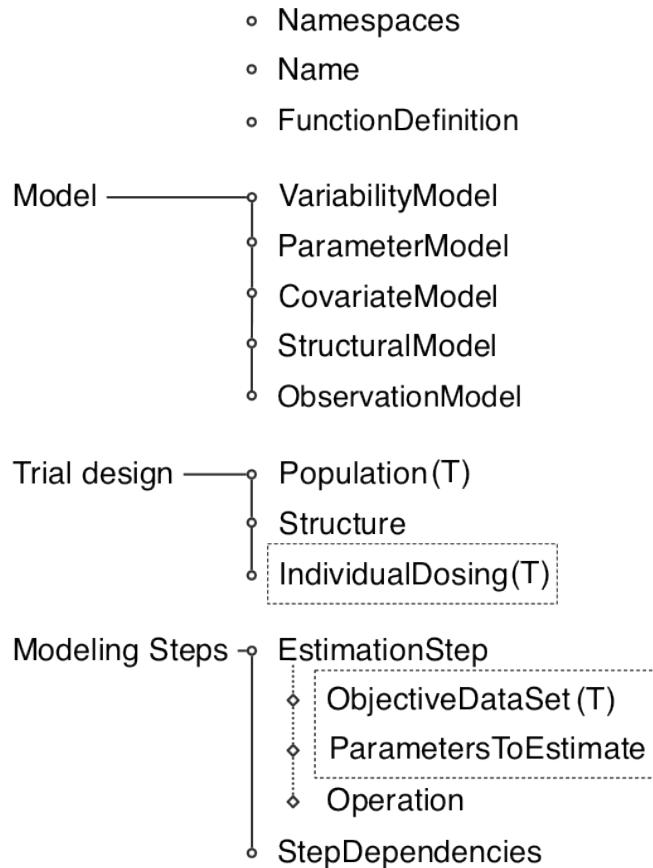
Model Definition

Trial Design

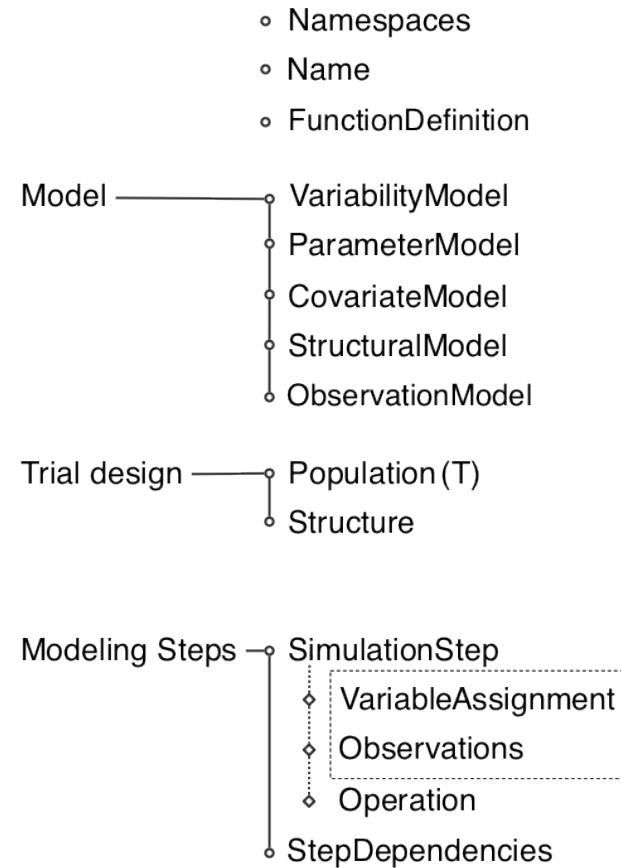


Structure for Estimation/Simulation

Estimation Task



Simulation Task



Use case

Oncology model, Ribba et al. 2012

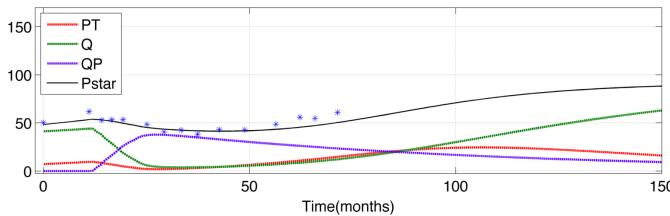
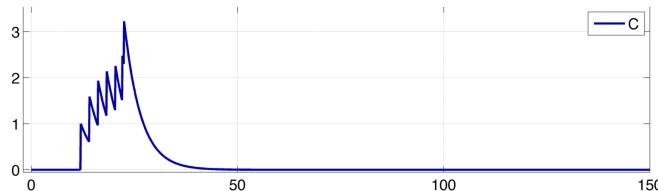
$$\frac{dC}{dt} = -\text{KDE} \times C$$

$$\frac{dP}{dt} = \lambda_p \times P \left(1 - \frac{P^*}{K}\right) + k_{Q_p P} \times Q_p - k_{PQ} \times P - \gamma_p \times C \times \text{KDE} \times P$$

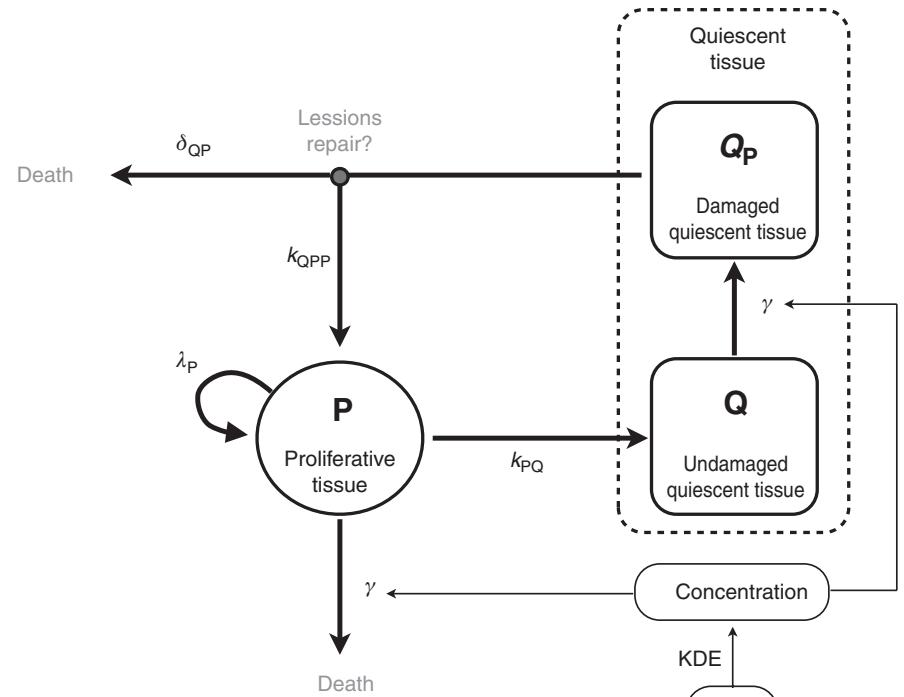
$$\frac{dQ}{dt} = k_{PQ} P - \gamma_Q \times C \times \text{KDE} \times Q$$

$$\frac{dQ_p}{dt} = \gamma_Q \times C \times \text{KDE} \times Q - k_{Q_p P} Q_p - \delta_{QP} \times Q_p$$

$$P^* = P + Q + Q_p$$



* Experimental data for subject #2



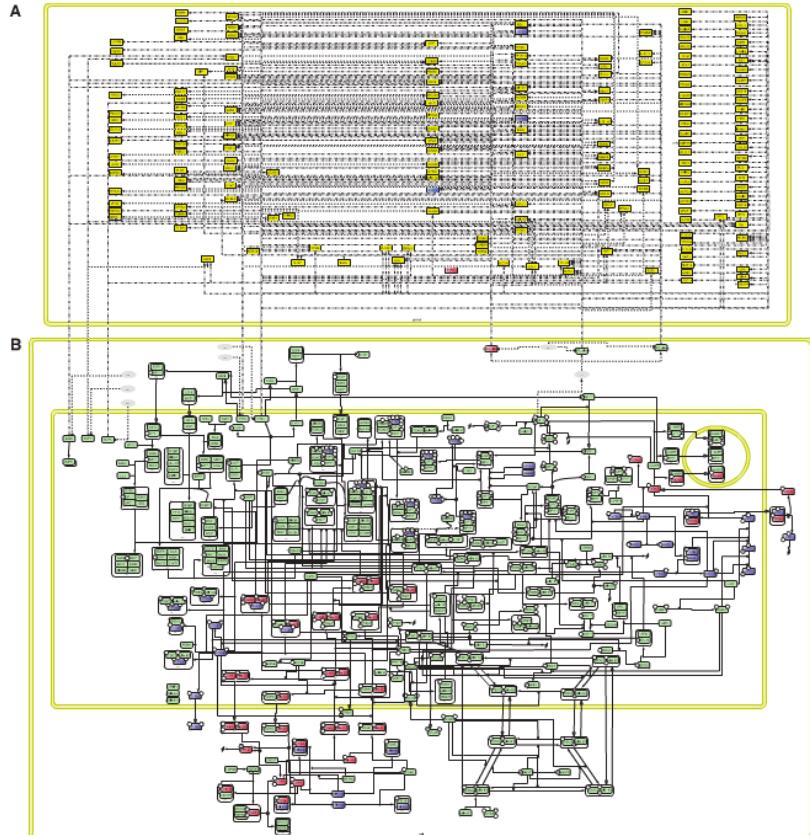
Real data and model simulation for one subject

Model in PharmML

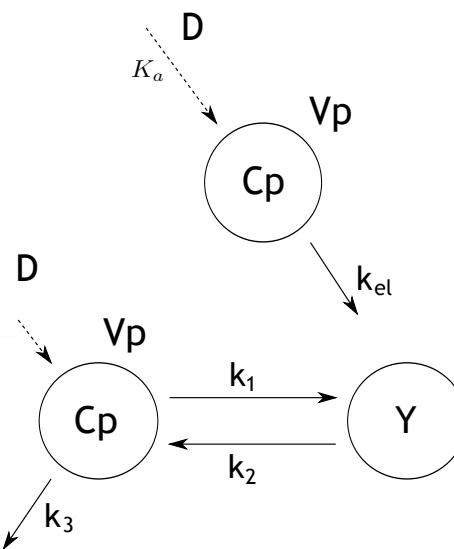
Model Definition extended

```
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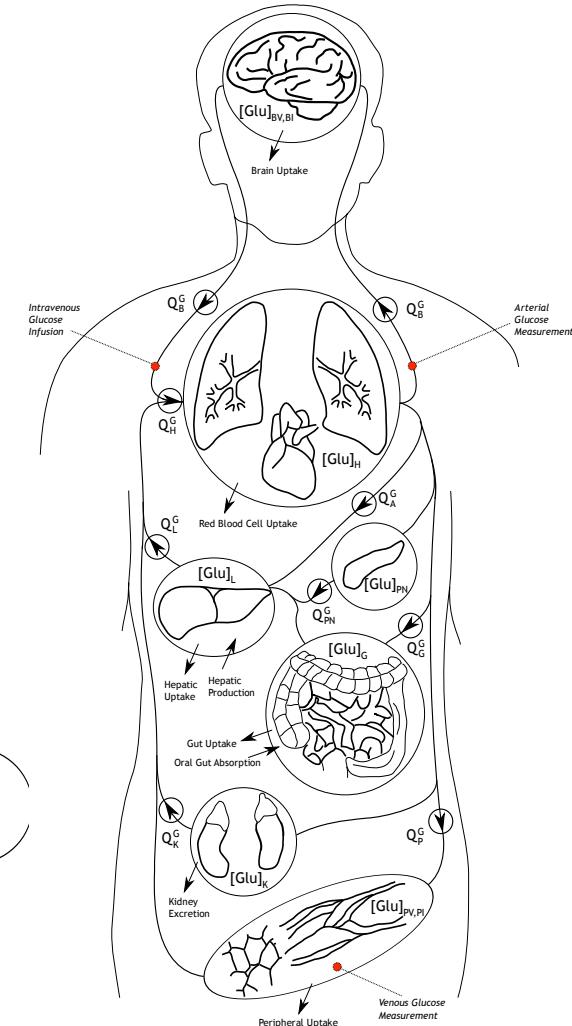
Basic comparison to SB



Compartmental models



PBPK models



Basic comparison to SB

- The details are in the parameter model
 - Population/typical value of a parameter
 - Covariates
 - Continuous – Age, Height, Body weight,...
 - Discrete – Gender, Ethnicity, Pharmacogenomics, ...
 - Correlations
 - Variability, e.g. inter-individual variability
 - Explained – e.g. by covariates
 - Random

Model Definition

Parameter Model

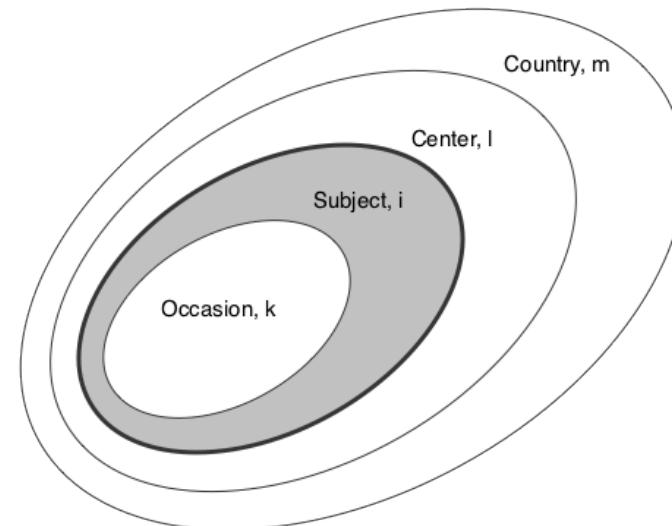
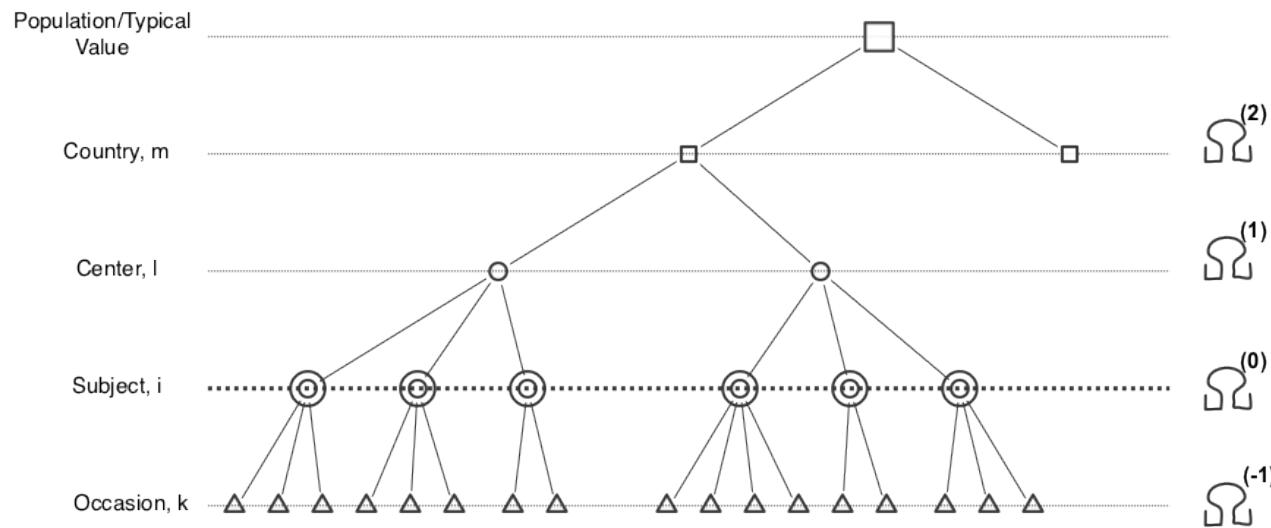
All parameters are log-normally distributed, e.g.

$$\lambda_{P_i} = \lambda_{P_{pop}} e^{\eta_{\lambda_P}};$$

$$\log(\lambda_{P_i}) = \log(\lambda_{P_{pop}}) + \eta_{\lambda_P}; \quad \eta_{\lambda_P} \sim N(0, \omega_{\lambda_P})$$

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Variability – nested hierarchy



Model Definition

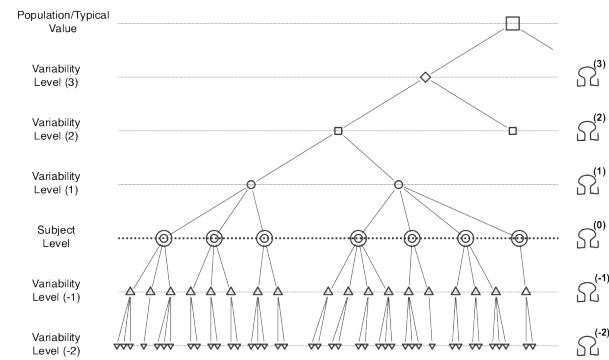
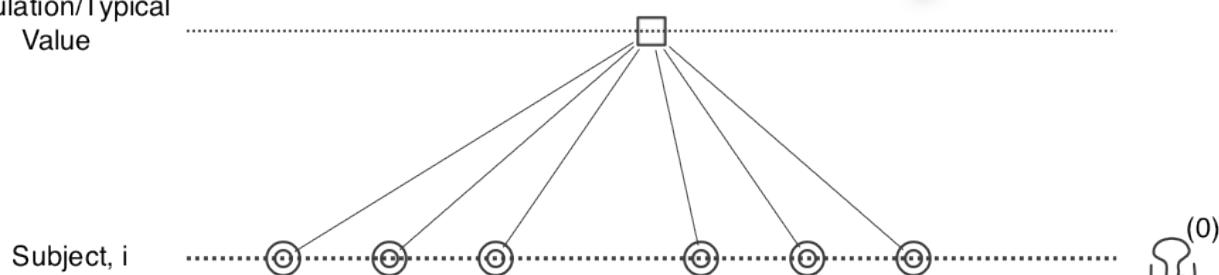
Simple Variability Model

There is only one level of variability
 - inter-individual variability (IIV)

$$\lambda_{P_i} = \lambda_{P_{pop}} e^{\eta_{\lambda_P}};$$

$$\log(\lambda_{P_i}) = \log(\lambda_{P_{pop}}) + \eta_{\lambda_P}; \quad \eta_{\lambda_P} \sim N(0, \omega_{\lambda_P})$$

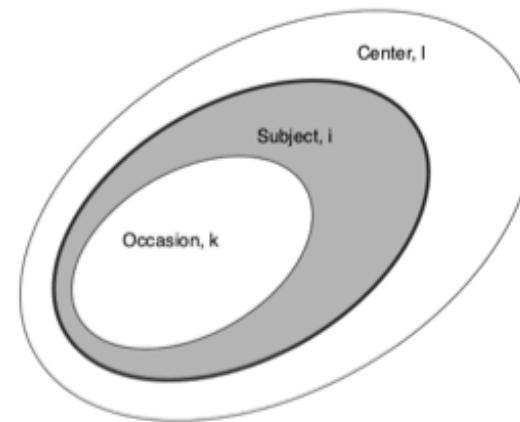
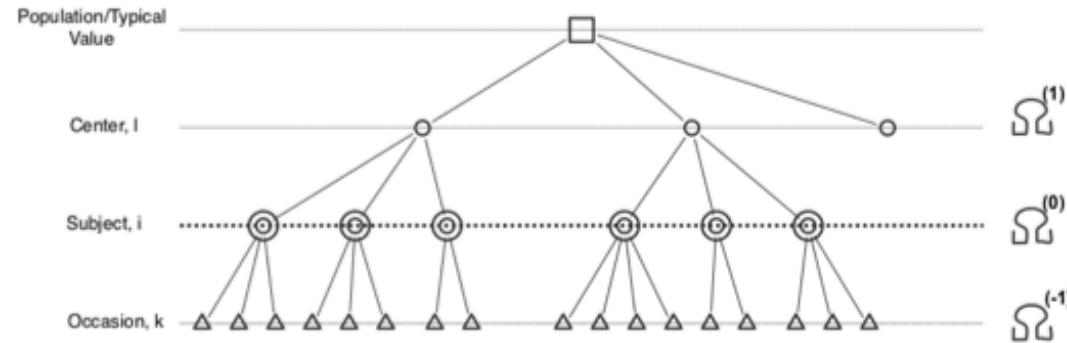
Population/Typical
Value



Complex hierarchy
reduces to

Model Definition

Complex Variability Model

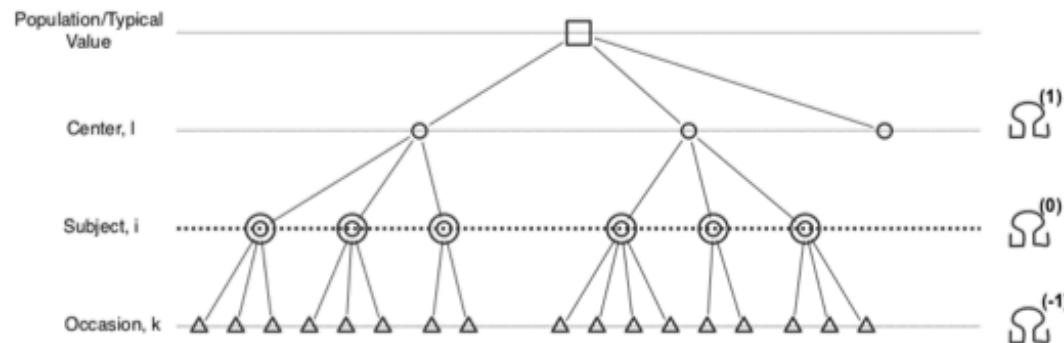


Three levels of variability

- inter-center variability
- inter-individual within center variability
- inter-occasion within individual within center variability

Model Definition

Complex Variability Model



$$\underbrace{\log(V_{lik})}_{\text{transformed individual value}} = \underbrace{\log(V_{pop})}_{\text{transformed typical value}} + \underbrace{\beta_{V,1} 1_{Sex_i=F}}_{\text{categorical covariate model}} + \underbrace{\beta_{V,2} \log\left(\frac{W_i}{70}\right)}_{\text{continuous covariate model}} + \underbrace{\eta_{l,V}^{(1)}}_{\text{inter-centre variability}} + \underbrace{\eta_{li,V}^{(0)}}_{\text{inter-individual within centre variability}} + \underbrace{\eta_{lik,V}^{(-1)}}_{\text{inter-occasion within individual within centre variability}}$$

Three levels of variability

- inter-center variability
- inter-individual within center variability
- inter-occasion within individual within center variability

Trial Design – Example

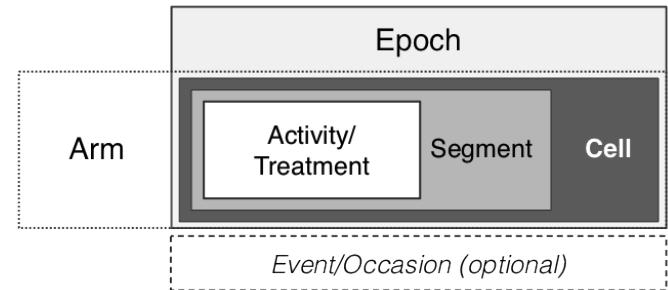
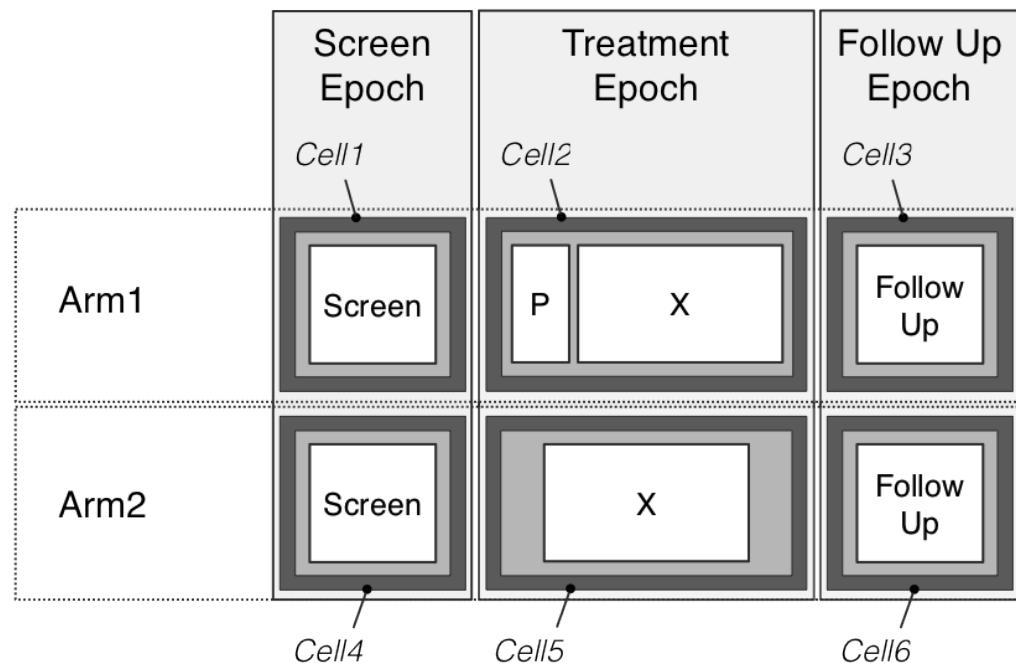
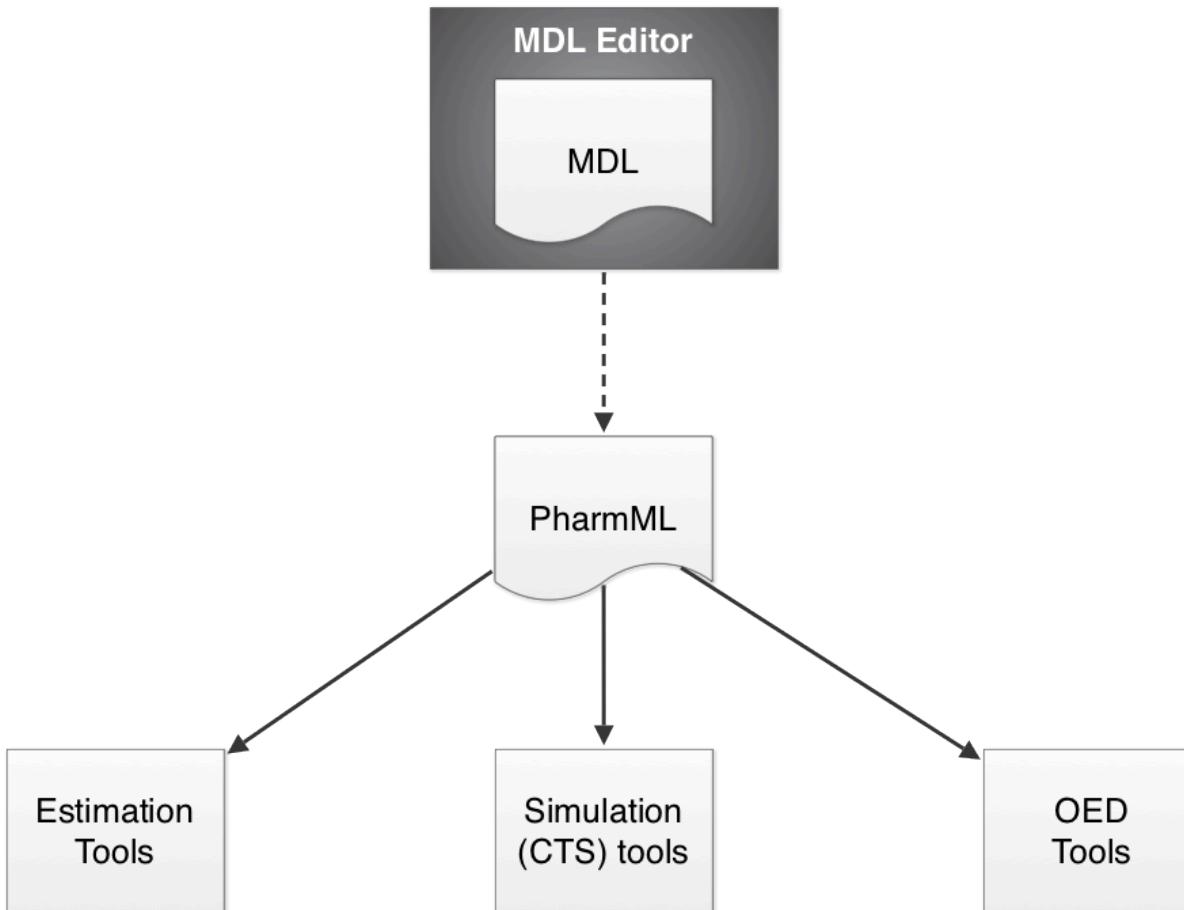


Figure. An example of a study with two arms and three epochs: Screen, Treatment and Follow Up. A segment can contain more than one Activity/Treatment as can be seen in Cell2 with one Pre-Treatment P and one Treatment X . In this particular example no Event/Occasion is specified.

Once you have model encoded in PharmML...

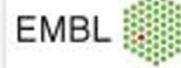


Partners

EFPIA



Academia



SMEs



Reserve slides

