EMBL-EBI

Drug Disease Model Resources
ddmore

Development of new representation standards in PK/PD

Maciej J Swat
Stuart Moodie
Nicolas le Novère

EMBL-EBI, Hinxton, UK

1. **Pharmacokinetics**, PK, and **pharmacodynamics**, PD, are branches of science dealing with drug related simulation and modeling. The former explains the time course of concentration in the human body, the latter the drug action.

2. This can be done using both phenomenological or mechanism based models. Although the complexity of human body is enormous, **compartment based methods** have been successfully applied in drug discovery and design for decades and remain indispensable today.

3. Their application is straight forward for frequently measured individual data and results in subject specific set of physiologically meaningful parameters.

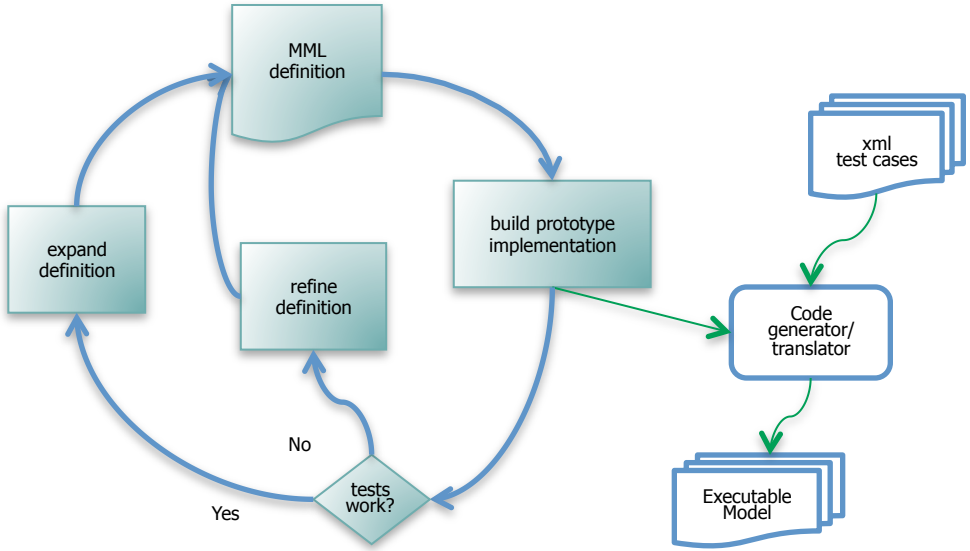
4. However, **clinical data** come often with few measurement point per subject, inter-subject and inter-occasion variability and one has to resort to population approaches which provide both population and individual parameters estimates. The statistical modeling framework called '**Nonlinear Mixed Effects**' is the most popular one used in this context.

5. Surprisingly all this activities in this vital field of research has not seen much of **standardization** efforts so far. There is number of tools, such as Monolix, NONMEM or WinBUGS whose code has to manually transcribed in order to use them in parallel. The recently launched **DDMoRe** (www.ddmore.eu) project is a pioneer IMI founded effort to feel this gap. EMBL-EBI has the lead in the work package dedicated to the design of a set of **system-to-system** Modeling Markup Languages, MMLs.

6. The goal is to use where possible existing standards, such as **SBML**, **SED-ML**, **UncerML** etc. The aspects one has to account for in the new standards are the structural model, parameter distribution, covariate model, correlation between parameters, clinical trial design and others. The **MMLs** will enable researchers in industry and academia to **share** their models, **verify** the results obtained with different tools and allow effective control vocabulary/ontology based **search**.

7. For example the work on notation and encoding of **probability distributions** is crucial for the former and missing in the latter field. DDMoRe project has already an important impact on the **unification** efforts in M&S in Life Sciences. We present here an overview of our ongoing efforts, highlight the challenges and issues.

8. Developing the Specification….



Collection of Models and Tasks

- Trial design model
- Parameter model
  - Correlation Structure
- Structural model
  - Compartmental
  - Physiology-Based
- Residual error model
- Observation model
- Covariate model
- Tasks
  - Simulation
    - PK & PD
    - Single individuals &virtual population
  - Estimation
    - …

Example Task – Simulating Virtual Patients

- Observation model
  - *Continuous data* – ODE based PK/PD models
  - *Discrete data* – mainly Generalized Linear Models
    - *Count data* – e.g. number of seizures, coughs, heart attacks
    - *Categorical data* – two or more categories such as age group, sex, ethnicity, disease type
    - *Time-to-event data* – time to death, discharge from hospital
- Parameter values for a study necessary – based on prior knowledge, i.e. sample from distributions
  - continuous and discrete with known
    - Probability Density Function, PDF
    - Probability Mass Function, PMF
  - non-parametric distributions

Trial Design Model – An example

- There are four study arms with different number of patients
  - Subjects per arm = 20, 20, 40, 40
- Dosing depends on the arm. For example, in the first arm, dosing starts on 0h and repeats every 24*h*
  - *Arm A* – 0:24:192*h*
  - *Arm B* – 0:48:192*h*, etc.
- Dosing is adjusted to body weight, here 1 mg per 1 kg of body weight
- Time of measurement for PK and PD happens according to different schedules, in *arm A*
  - PK Observation Times: 0.5, 4:4:48, 52:24:192,192:4:250 *h*
  - PD Observation Times: 0:24:288 *h*

Parameter Model

Parameter model allows to define population distribution of individual parameters, their dependence on subject specific and extrinsic factors and possible correlation with other parameters

Here, e.g.

- Parameter distribution

$$k_a \sim LogNormal(pop_{k_a}, \omega_{k_a})$$

$$V \sim LogNormal(pop_V, \omega_V)$$

etc.

- Covariate model – intrinsic factors (inherited, genetically determined), such as age, weight, height, and race, or extrinsic factors (subject to outside environmental influences), such as smoking status, and presence of concomitant medications
  - here scaled body weight is used

$$C(\beta, Weight_i) = \beta \log(Weight_i/70)$$

Parameter Model

Parameter model allows to define population distribution of individual parameters, their dependence on subject specific and extrinsic factors and possible correlation with other parameters

Here, e.g.

- Parameter distribution

$$k_a \sim LogNormal(pop_{k_a}, \omega_{k_a})$$

$$V \sim LogNormal(pop_V, \omega_V)$$

etc.

- Covariate model – intrinsic factors (inherited, genetically determined), such as age, weight, height, and race, or extrinsic factors (subject to outside environmental influences), such as smoking status, and presence of concomitant medications
  - here scaled body weight is used

$$C(\beta, Weight_i) = \beta \log(Weight_i/70)$$

- Correlation structure
  - Correlation between volume and clearance $\rho_{V,CL} = 0.7$

Parameter Model – Correlation Structure

e.g. correlation between volume and clearance $\rho_{V,CL} = 0.7$ using

- Correlation matrix

$$\rho = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ & 1 & \rho_{V,CL} & 0 & 0 & 0 & 0 \\ & & 1 & 0 & 0 & 0 & 0 \\ & & & 1 & 0 & 0 & 0 \\ & & & & 1 & 0 & 0 \\ & & & & & 1 & 0 \\ & & & & & & 1 \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0.7 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

Parameter Model – Correlation Structure

e.g. correlation between volume and clearance $\rho_{V,CL} = 0.7$ using

- Correlation matrix

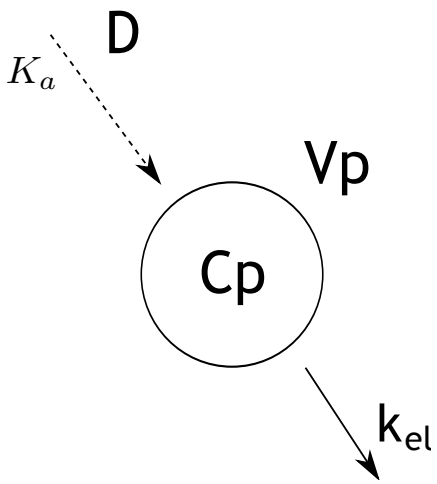
$$\rho = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ & 1 & \rho_{V,CL} & 0 & 0 & 0 & 0 \\ & & 1 & 0 & 0 & 0 & 0 \\ & & & 1 & 0 & 0 & 0 \\ & & & & 1 & 0 & 0 \\ & & & & & 1 & 0 \\ & & & & & & 1 \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0.7 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

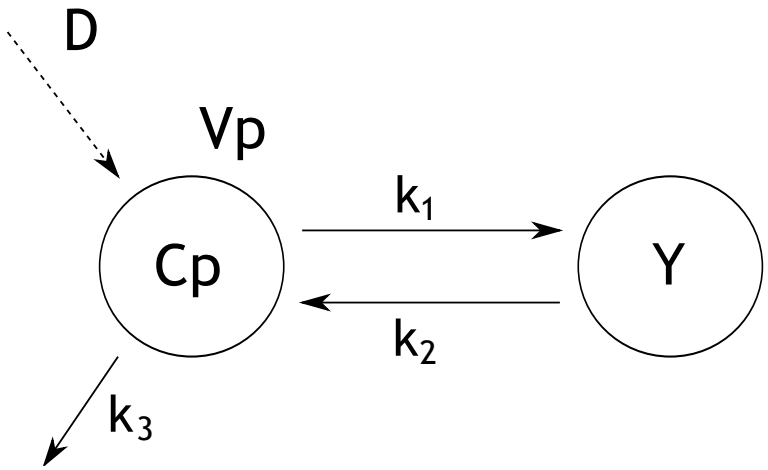
but other forms are possible, such as

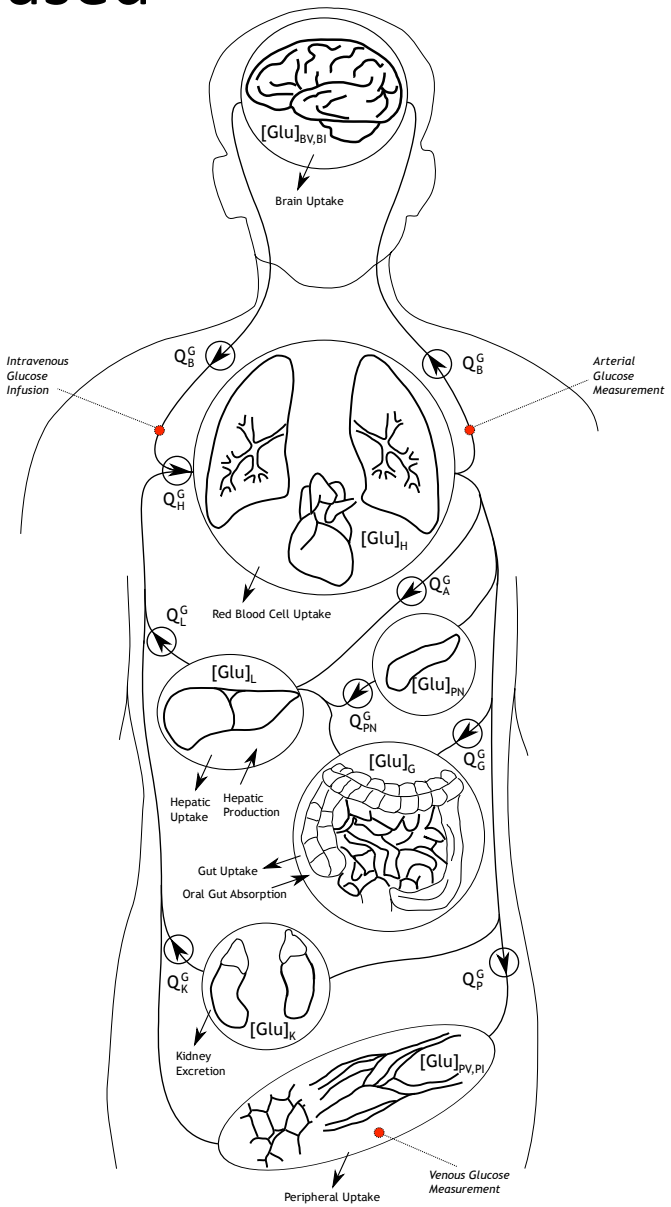
- Variance-covariance matrix

$$\Sigma = \begin{pmatrix} \omega_{ka}^2 & \omega_{ka,V} & \omega_{ka,CL} & \omega_{ka,Imax} & \omega_{ka,IC50} & \omega_{ka,Rin} & \omega_{ka,kout} \\ & \omega_V^2 & \omega_{V,CL} & \omega_{V,Imax} & \omega_{V,IC50} & \omega_{V,Rin} & \omega_{V,kout} \\ & & \omega_{CL}^2 & \omega_{CL,Imax} & \omega_{CL,IC50} & \omega_{CL,Rin} & \omega_{CL,kout} \\ & & & \omega_{Imax}^2 & \omega_{Imax,IC50} & \omega_{Imax,Rin} & \omega_{Imax,kout} \\ & & & & \omega_{IC50}^2 & \omega_{IC50,Rin} & \omega_{IC50,kout} \\ & & & & & \omega_{Rin}^2 & \omega_{Rin,kout} \\ & & & & & & \omega_{kout}^2 \end{pmatrix}$$

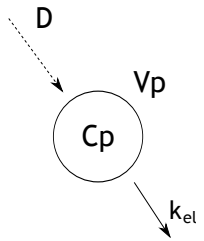
Structural Model – Compartmental versus Physiology-Based







Structural model



- PK – 1-comp, oral

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

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

$$Cc = Ac/V$$

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

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

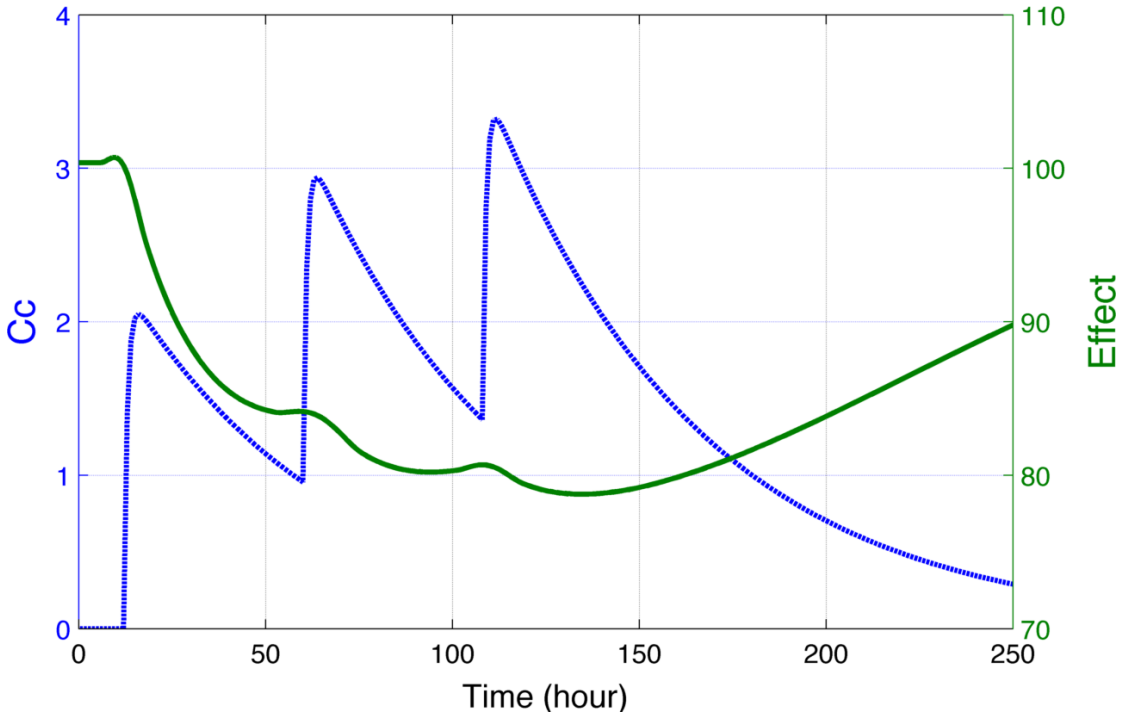
- PD – indirect response model with impact on the input, *Rin*

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

$$E(t=0) = Rin/kout$$

Structural model

- PK – 1-comp, oral
- PD – indirect response model with impact on the input



Continuous data model

The following general model applies to continuous output

$$y_{ij} = f(x_{ij}, \Psi_i) + g(x_{ij}, \Psi_i)\epsilon_{ij}, 1 \leq i \leq N, 1 \leq j \leq n_i$$

y_{ij} – observations

- i – number of subjects
- j – time points of measurements

f – structural model

gε – residual error model with standard deviation, g, and residual errors, ε ~ N(0,1)

Residual error model

Here we assume

- Concentration (Cc) – '*Combined*'

$$a1 = 0.5, b1 = 0.1$$

- Effect (E) – '*Constant*'

$$a2 = 4$$

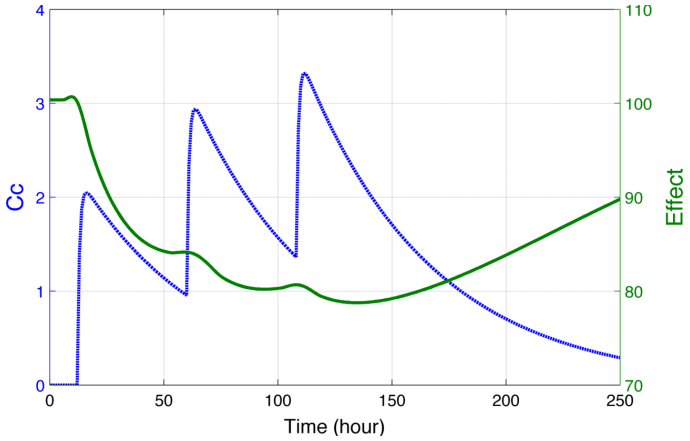
The residual can be user defined or taken from the residual error model library, e.g.:

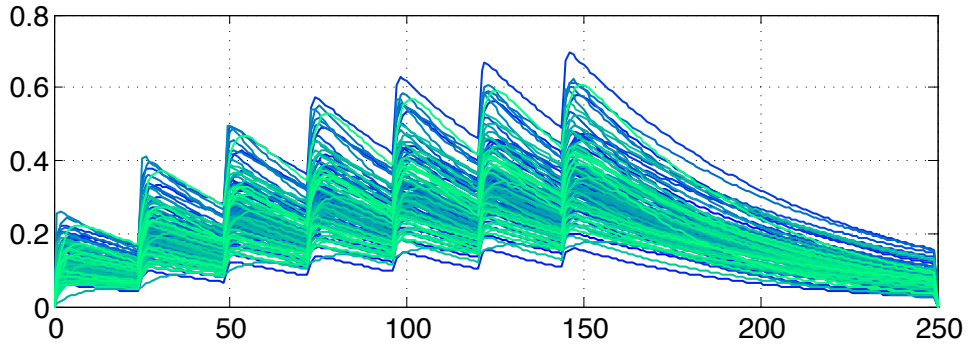
- *Constant* – $g(x_{ij}, \Psi_i) = a$
- *Proportional* – $g(x_{ij}, \Psi_i) = bf$
- *Combined* – $g(x_{ij}, \Psi_i) = a + bf$
- Alternative combined – $g(x_{ij}, \Psi_i) = \sqrt{a^2 + b^2 f^2}$
- Etc.

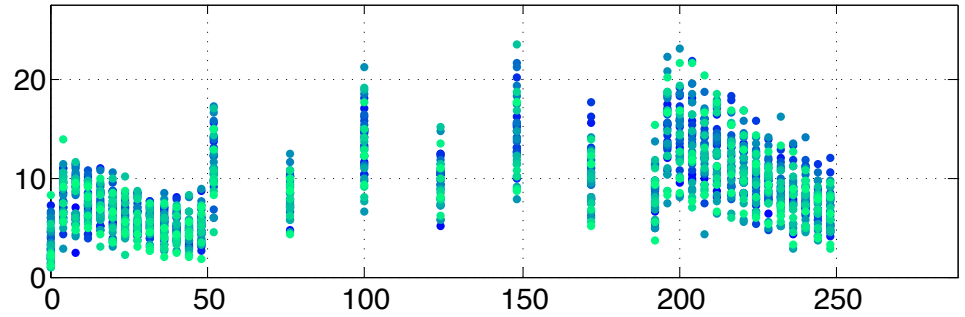
Observation Model and Task

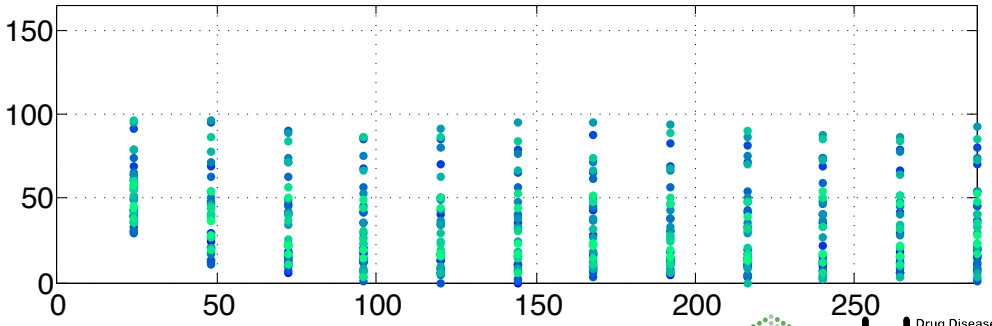
- Observation name
  - Concentration, Cc
  - Effect, E
- Observation unit
- Observation type
  - Continuous
  - Continuous
- Task:
  - Simulate Cc & E
  - Plots for Cc & E

Continuous Data – Plots









EMBL-EBI

Drug Disease Model Resources
ddmore

Categorical Data Models

two or more categories such as age group, sex, ethnicity, disease type

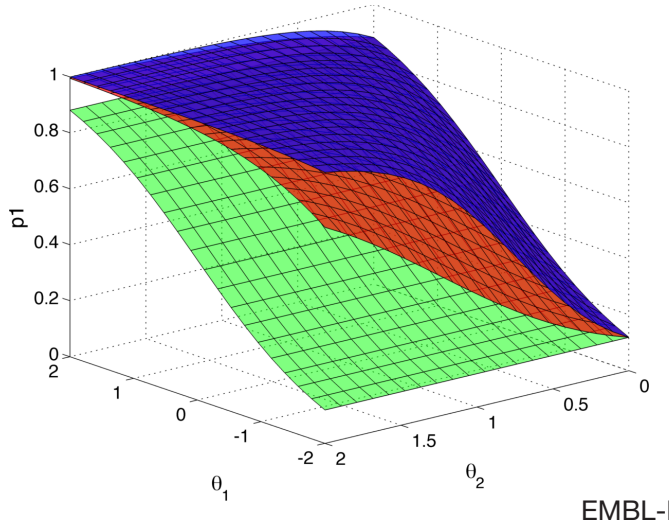
Categorical Data Models

For example, *k in {1,2}*, i.e. the effect outcome is either 1 or 2.

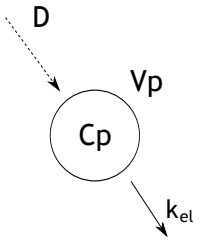
We simulate the probability that the outcome is 1 using e.g. logistic equation

$$p1 = \frac{1}{1 + \exp(-\theta_1 - \theta_2 \log(Cc))}$$

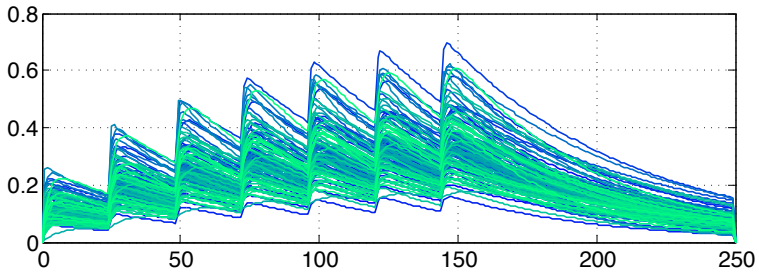
As before, the underlying PK model is 1-compartmental oral model.
This p1 – surface is function of Θ_1, Θ_2 and *log(Cc)* and this is visualized by it for three different values of *Cc = {1,5,15}:*

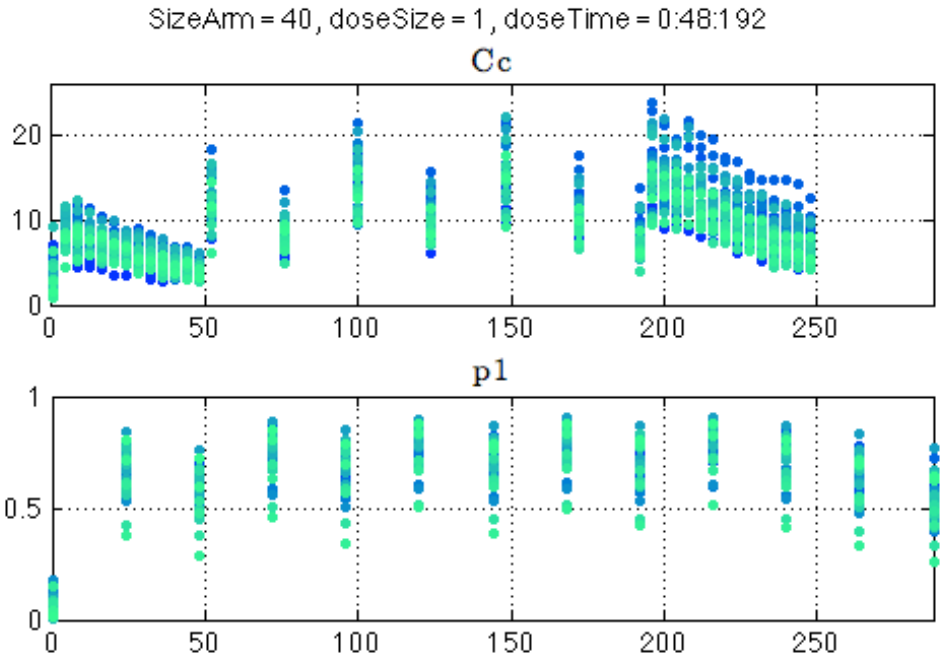


Categorical Data Models – Plots & Animation

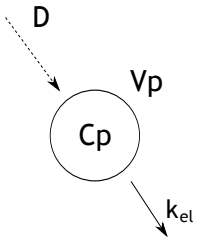


$$p1 = \frac{1}{1 + \exp(-\theta_1 - \theta_2 \log(Cc))}$$

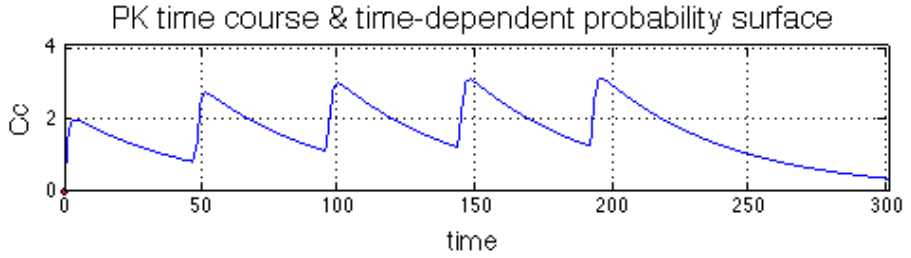


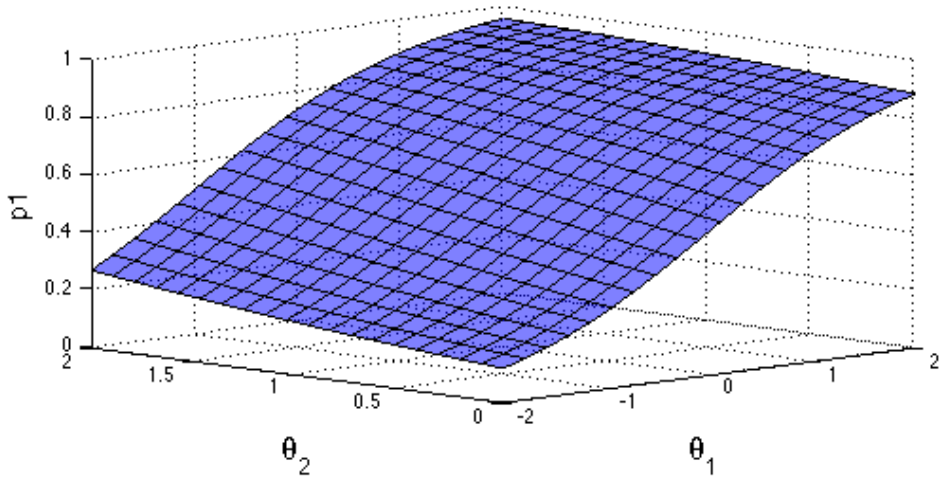


Categorical Data Models – Plots & Animation



$$p1 = \frac{1}{1 + \exp(-\theta_1 - \theta_2 \log(Cc))}$$





Count Data Models

e.g. number of seizures, coughs, heart attacks

Count Data Models

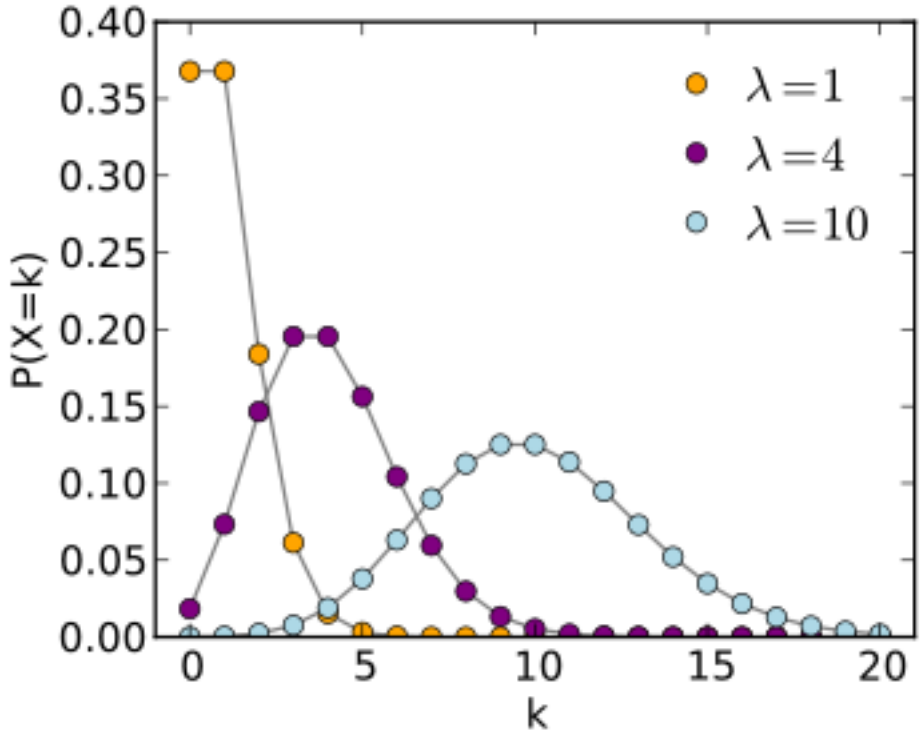
We deal with count data, for example number of seizures, coughs, heart attacks. Here k in {1,2, .., n}.

As before, the underlying PK model is 1-compartmental oral model.

We estimation the probability that the outcome is k using the non-homogeneous Poisson model

$$P\left(Y_{ij} = k | C_{ij}, \psi_i\right) = \frac{e^{-\lambda_{ij}} \lambda_{ij}^{k}}{k!}$$

Count Data Models – Poisson model



$$P(Y = k) = \frac{e^{-\lambda}\lambda^{k}}{k!}$$

Count Data Models

We deal with count data, for example number of seizures, coughs, heart attacks. Here k in {1,2, .., n}.
As before, the underlying PK model is 1-compartmental oral model.
We estimation the probability that the outcome is k using the non-homogeneous Poisson model

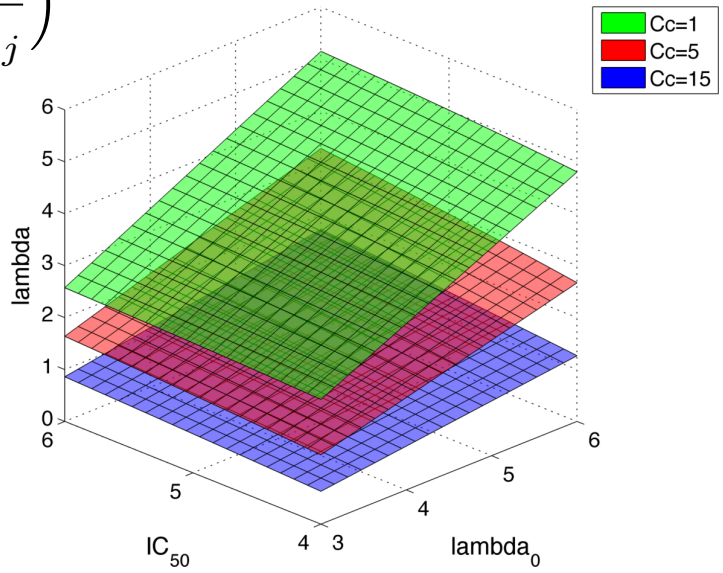
$$P\left(Y_{ij} = k | C_{ij}, \psi_i\right) = \frac{e^{-\lambda_{ij}} \lambda_{ij}^{k}}{k!}$$

with concentration dependent mean λ, defined as

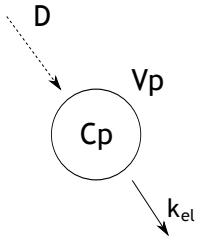
$$\lambda_{in} = \lambda_0 \left(1 - \frac{C_{ij}}{IC_{50} + C_{ij}}\right)$$

also called Poisson intensity.

λ – depends on the parameters λ_0 and IC_{50}. λ is constant, IC_{50} is sampled from log-normal distribution
λ_0 – stands for the baseline seizure count prior to any drug.

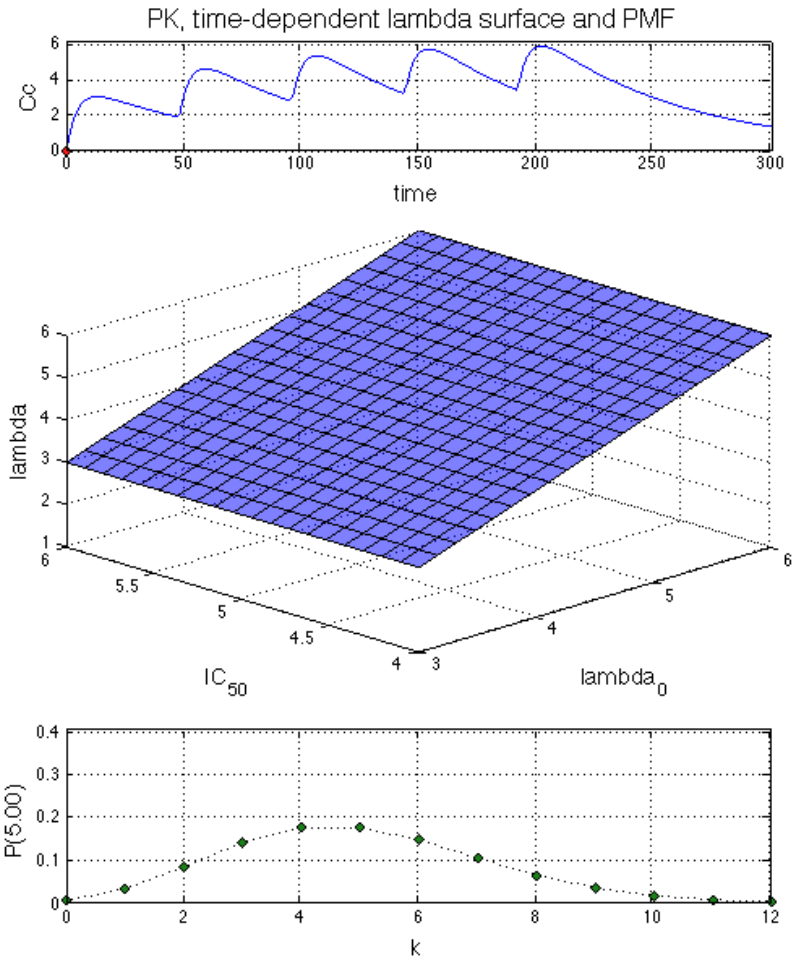


Count Data Models – Animation



$$P\left(Y_{ij} = k | C_{ij}, \psi_i\right) = \frac{e^{-\lambda_{ij}} \lambda_{ij}^{k}}{k!}$$

$$\lambda_{in} = \lambda_0 \left(1 - \frac{C_{ij}}{IC_{50} + C_{ij}}\right)$$



Minimal Information

a model for ***continuous data*** is completely defined by

- design x_{ij}
- structural model f
- residual error model g
- probability distribution of the residual errors ε_{ij}
- transformation of the data

a model for ***categorical data*** is completely defined by

- design x_{ij}
- probability distribution of each observation y_{ij}

a model for ***count data*** is completely defined by

- design x_{ij}
- probability distribution used to represent the distribution of the data
- parameters of this distribution

Conclusion

1. New standard necessary for the PK/PD field
    - Interoperability
    - Annotation
    - Storing
2. Reusing existing standards – SBML, SED-ML, PharML, UncertML
3. Driving development of new packages – such as *distrib*
4. Synergies between Systems Biology and Pharmacometrics
5. More efficient drug design and testing

Acknowledgments

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115156, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution. The DDMoRe project is also financially supported by contributions from Academic and SME partners.

EMBL-EBI

ddmore Drug Disease Model Resources