K-PD models as a flexible modeling tool in non-clinical statistics

T. Jacobs, R. Straetemans,
B. Boulanger, L. Bijnens

29 September 2010


Ying, suffering from allergies

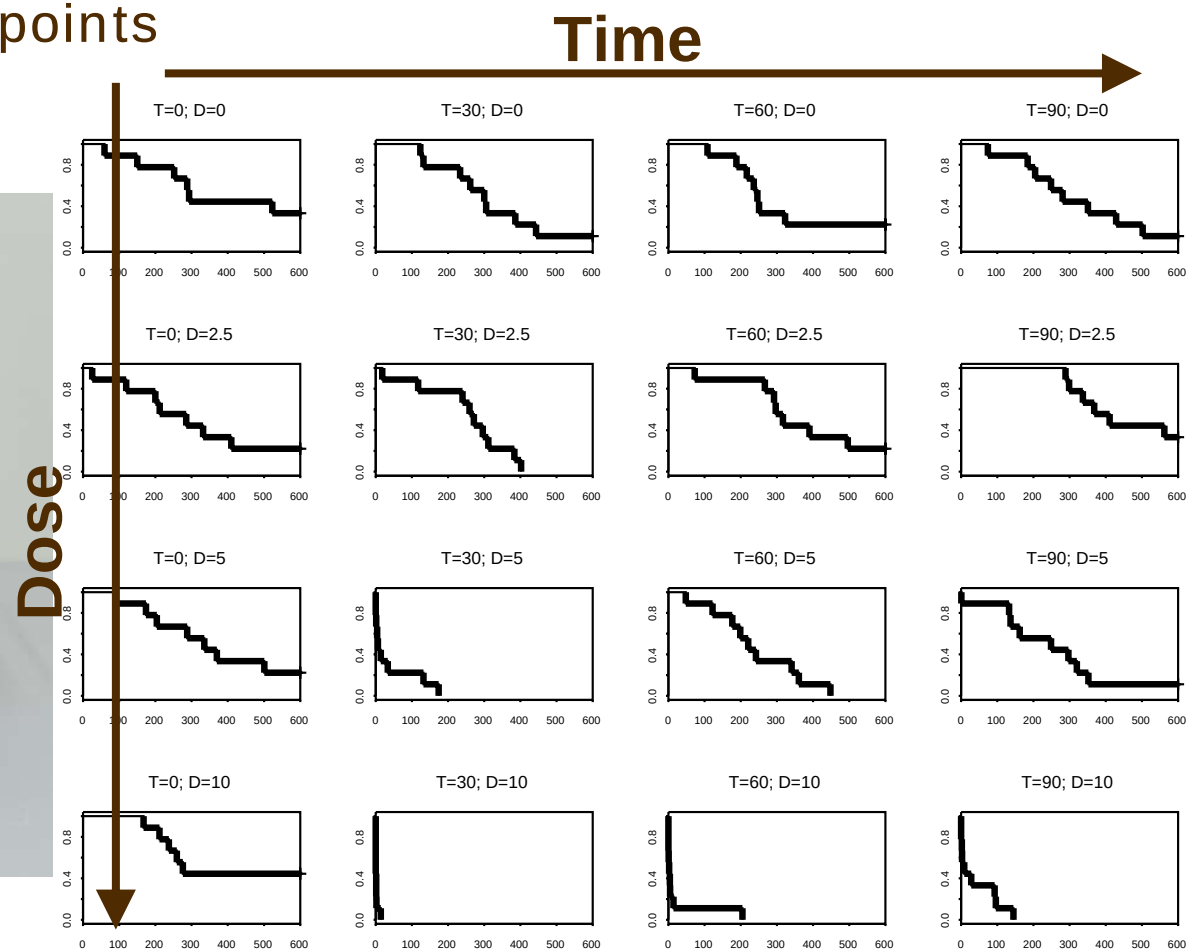
Outline

- Introduction
- Methodology
- Four examples
- Conclusions

Introduction

Pharmacodynamical test: Rotarod (motor coordination)

10 mice/dose, 4 time points



Introduction

- Main question:

  How do we quantify the potential effect on motor coordination in a single value?

  How do we compare different compounds?

- Time to event data
  - Parametric: Accelerated Failure Time (AFT), Polynomials
  - Nonparametric: Cox regression, AFT with Splines

Methodology

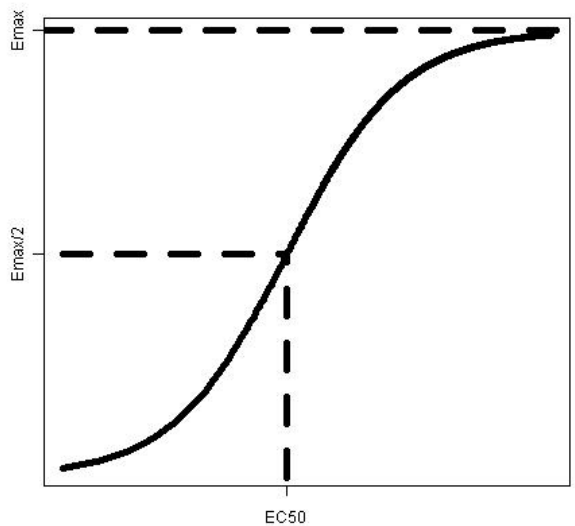
- Traditional statistical techniques (e.g. GLM):
  - Polynomials, random effects

$$E(g(Y_{ij}) \mid b_i, x_{ij}) = \sum_{ij} x'_{ij}\beta + z'_{ij}b_i$$

- Quantification of the effect and comparison of compounds?

- Alternative approach: PK/PD models

$$E(g(Y_{ij}) \mid b_i, x_{ij}) = E_{0i} + \frac{E_{max}c_{ij}}{EC_{50} + c_{ij}}$$



Methodology

KPD

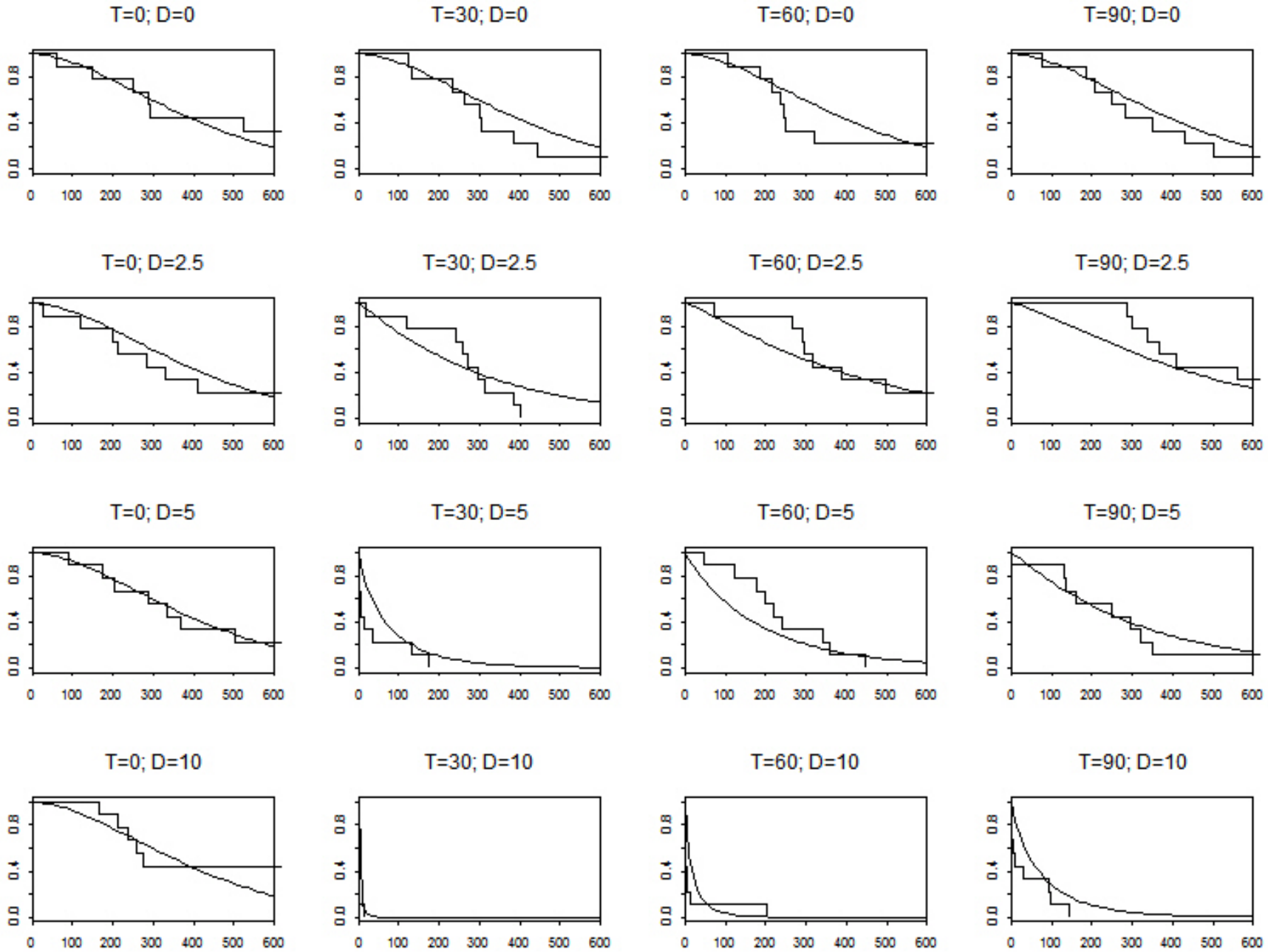
- Fit an Emax model on the scale parameter of the Weibull

$$E(g(Y_{ij}(t)) \mid b_i, x_{ij}) = \exp(\beta_0)\left[1 - \frac{c_{ij}}{EC_{50} + c_{ij}}\right]$$

- Assume a latent PK-profile

$$c_{ij}(t) = \sum_k A_{ik} \exp(-\theta_{ik} t)$$

- Basically, you assume that an unobserved concentration-time profile at the site of action is driving the response
- Number of compartments depends on the model fit, not on external information or physiology
- Confounding of EC_{50} and C_{ij}


T=0; D=0
T=30; D=0
T=60; D=0
T=90; D=0
T=0; D=2.5
T=30; D=2.5
T=60; D=2.5
T=90; D=2.5
T=0; D=5
T=30; D=5
T=60; D=5
T=90; D=5
T=0; D=10
T=30; D=10
T=60; D=10
T=90; D=10
0.0
0.4
0.8
0
100
200
300
400
500
600

Disease Modeling

- What happens if there is a natural evolution over time?
- Holford states that for clinical data

Disease progression

+ Placebo Effect → $E_{0i} = f(t_{ij}, x_{ij})$

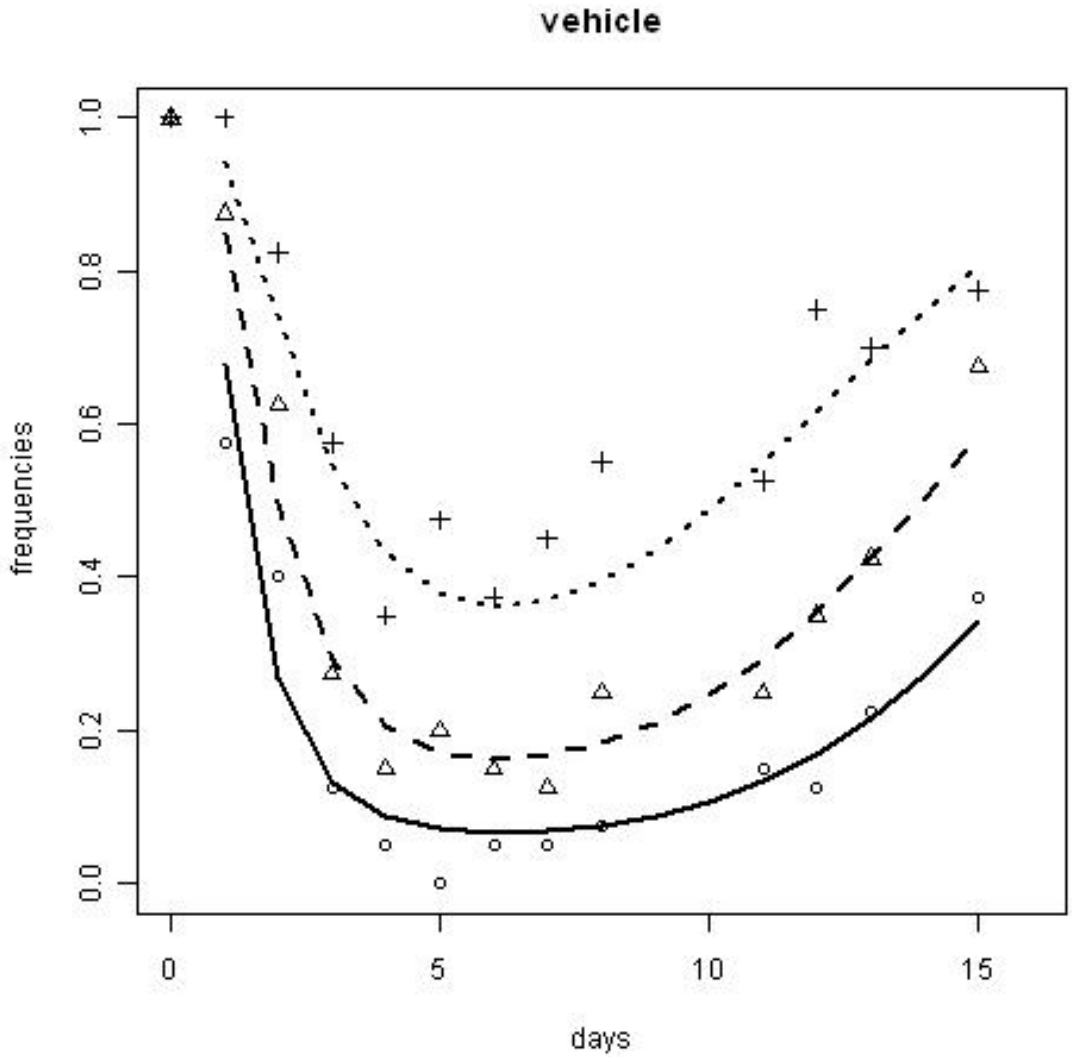
$\frac{E_{max} c_{ij}}{EC_{50} + c_{ij}}$ ← + Treatment Effect

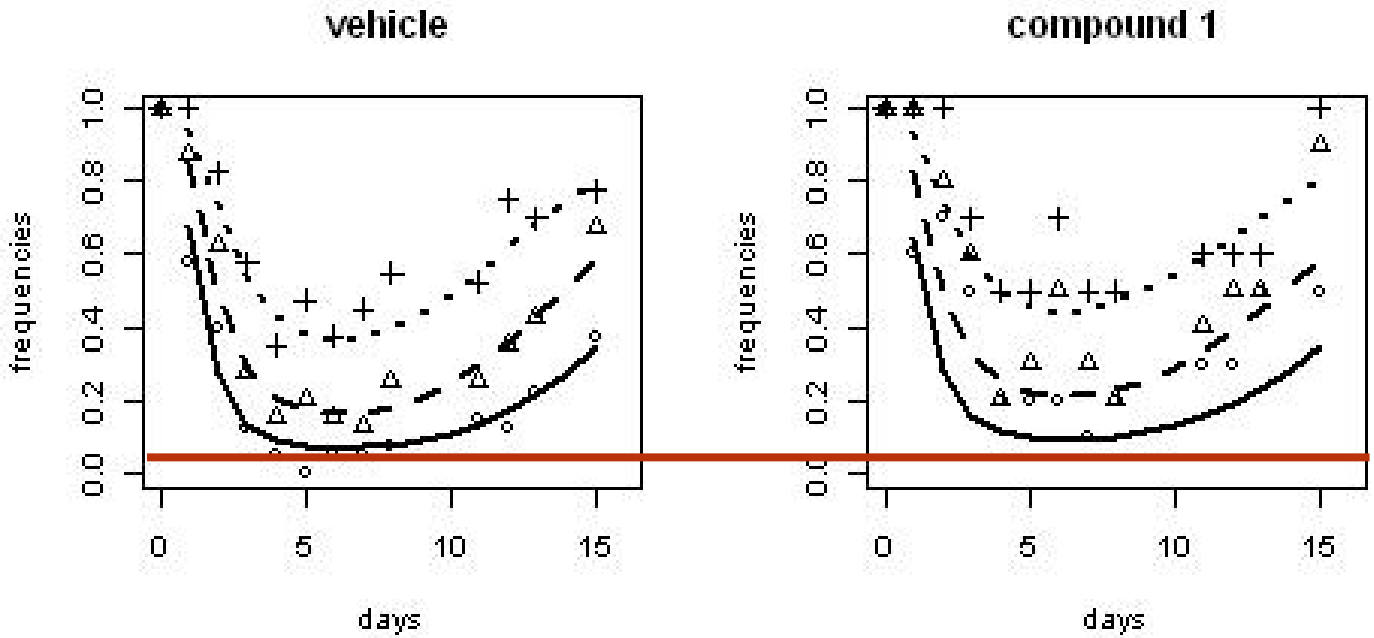
= Response → $E(g(Y_{ij}) \mid b_i, x_{ij})$

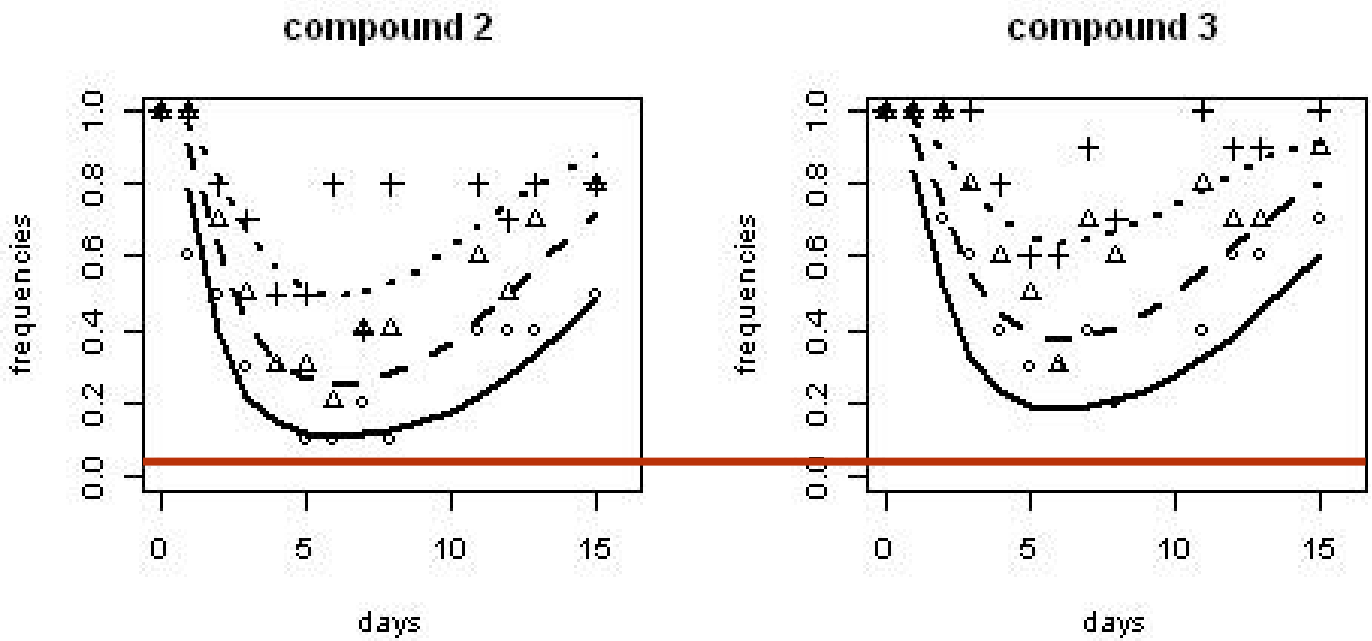
- Model the vehicle data first, then include the treatment impact
- Treatment effect can be additive, or included in the parameters of the vehicle model

Pharmacodynamical test: Pin Prick

- 3+1 compounds add-on to Taxol
- 10 rats / compound
- Score: 0, 1, 2, 3
- How to compare compounds?
- Cum-logit prop odds model (Agresti 2002)
- Model the impact of the compounds on Taxol (E_{max} and/or EC_{50})

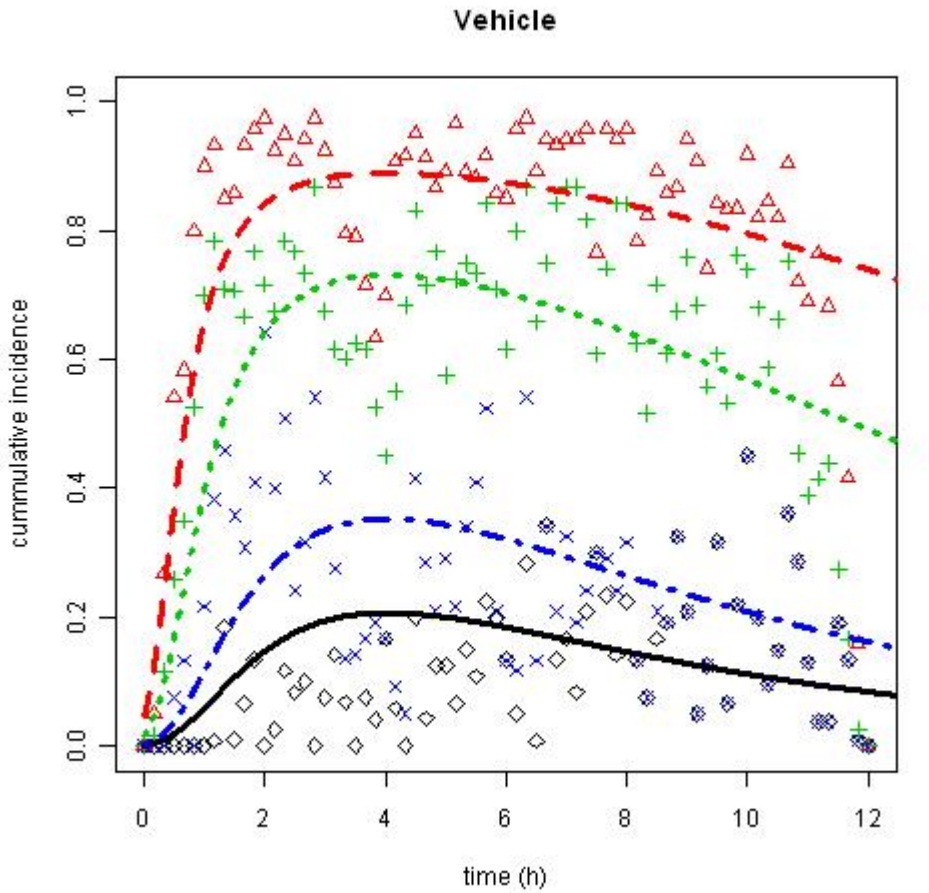


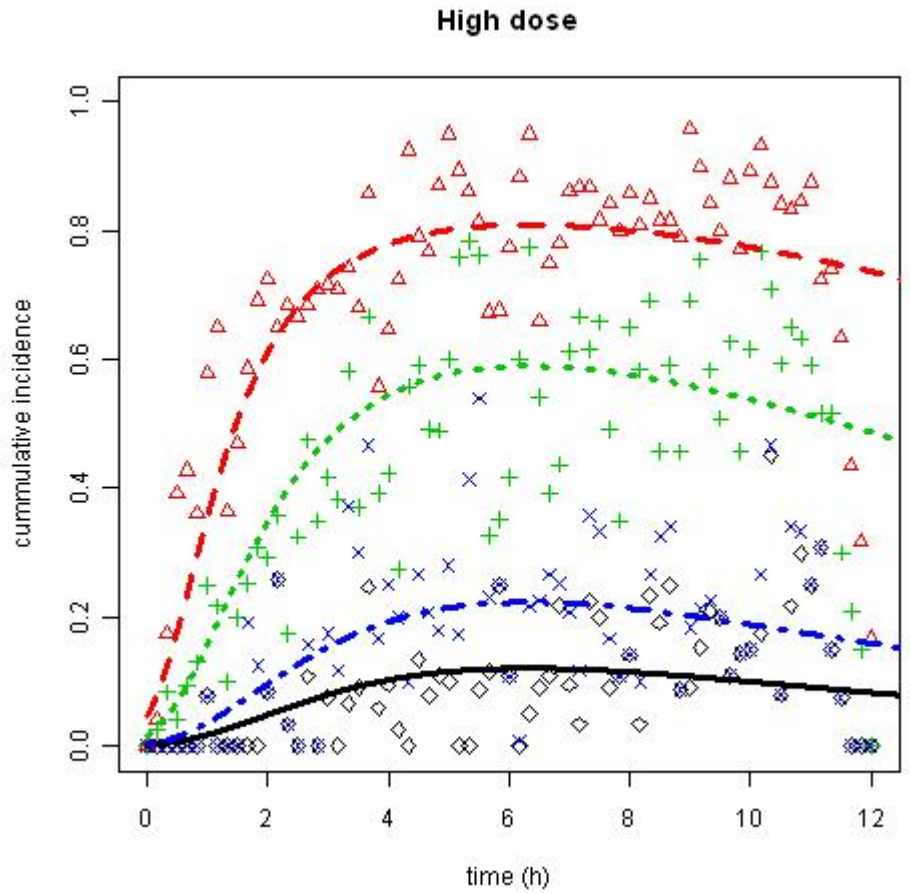

vehicle
compound 1
frequencies
days
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15


compound 2
compound 3
frequencies
days
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15

Another Pharmacodynamic test

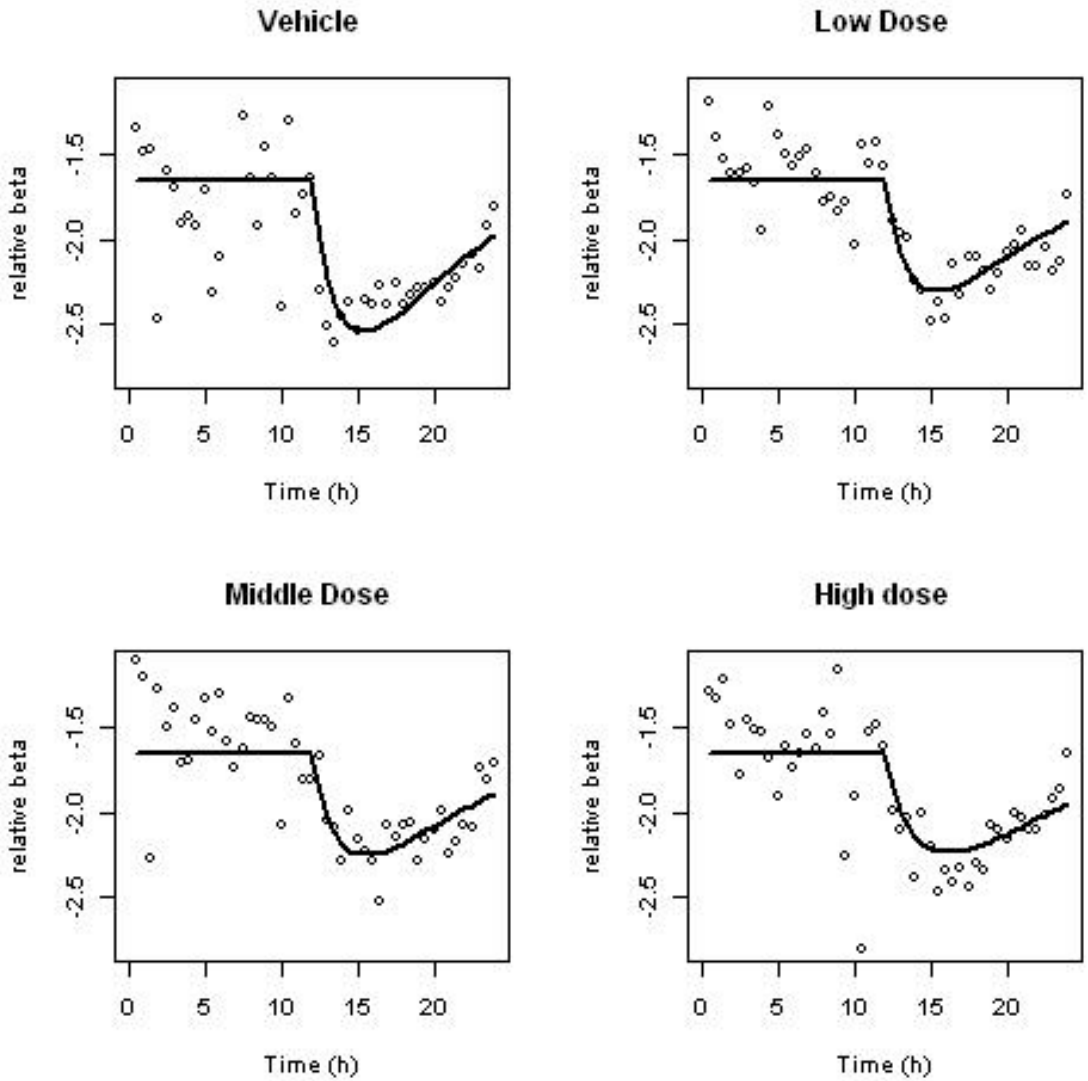
- Design
  - 6 animals
  - 4x4 cross-over
  - 12h evaluation
  - Dose response
- Test procedure: confidential
- Assume a virtual treatment (Emax=disease progression + placebo)
- Incorporate treatment effect at E_{max}, EC_{50} and PK-parameters
- K-PD model for disease progression
- Dose as covariate on the absorption coefficient
- Quantification of change of onset of effect





EEG

- Design
  - 6 animals
  - 4x4 cross-over
  - 24h evaluation
  - Dose response
- Assume after 12h a virtual treatment (Emax=disease progression + placebo)
- Incorporate treatment effect at E_{max} and EC_{50}



Conclusion

Are we statisticians? Are we PK-scientists?

We are pharmacometricians

- Nonlinear mixed effects modeling has been ignored too long by statisticians
- Interpretation of biologically significant effect
- Flexible modeling allows for model-based drug development
- Enabling optimization and integration of data analysis
- Emphasize Generalized Nonlinear Mixed Effects

References

- Jacqmin P, Snoeck E, van Schaick EA, Gieschke R, Pillai P, Steimer JL, Girard P. *Modelling response time profiles in the absence of drug concentrations: definition and performance evaluation of the K-PD model.* J PK PD. 2007, 34, 57-85.
- Jacobs T, Straetemans R, Molenberghs G, Bouwknecht JA, Bijnens L. *A Latent Pharmacokinetic Time Profile to Model Dose-Response Survival Data.* J Biopharm Stat, 2010, 20, 759–767.