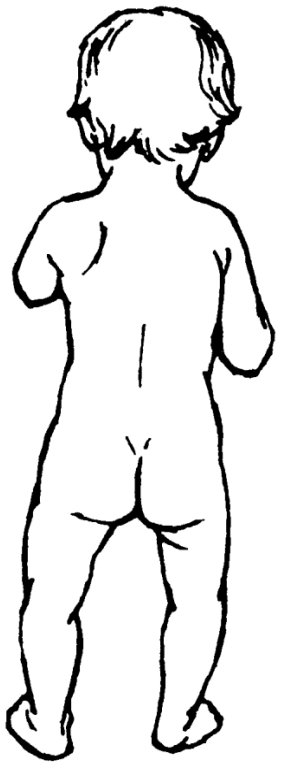
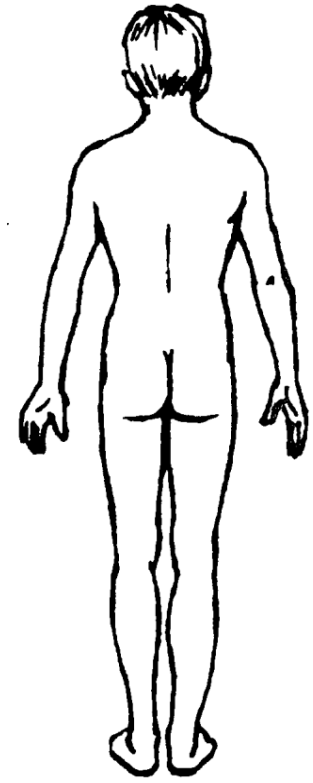
Bayer Technology Services



PBPK/PD modeling with PK-Sim & MoBi in support of the PIP



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Workshop on Modelling in Paediatric Medicines, EMEA, London, 2008-04-15

Outline

- **Why should we use mechanistic, physiology-based modeling in pediatric applications?**
- **Why do we need dedicated software solutions to support clinical applications of physiology-based modeling?**
- **Where software cannot help**
- **Summary and Conclusions**

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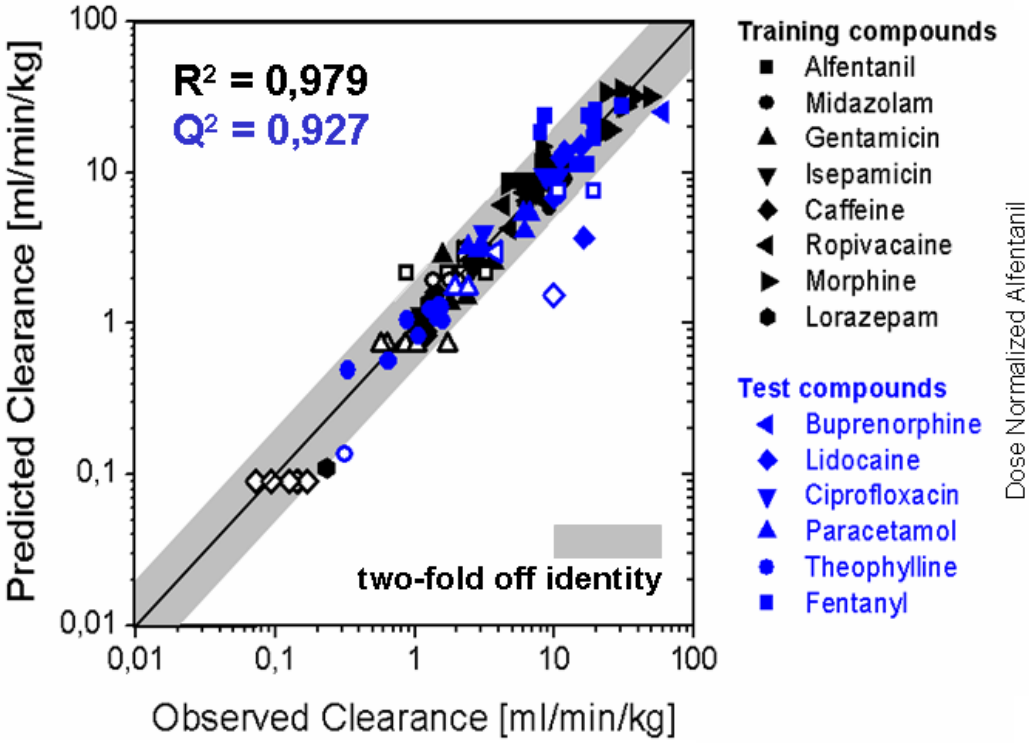
Why mechanistic, physiology-based modeling?

Mechanistic, physiology-based modeling has proven its excellent performance in describing and predicting PK in children!



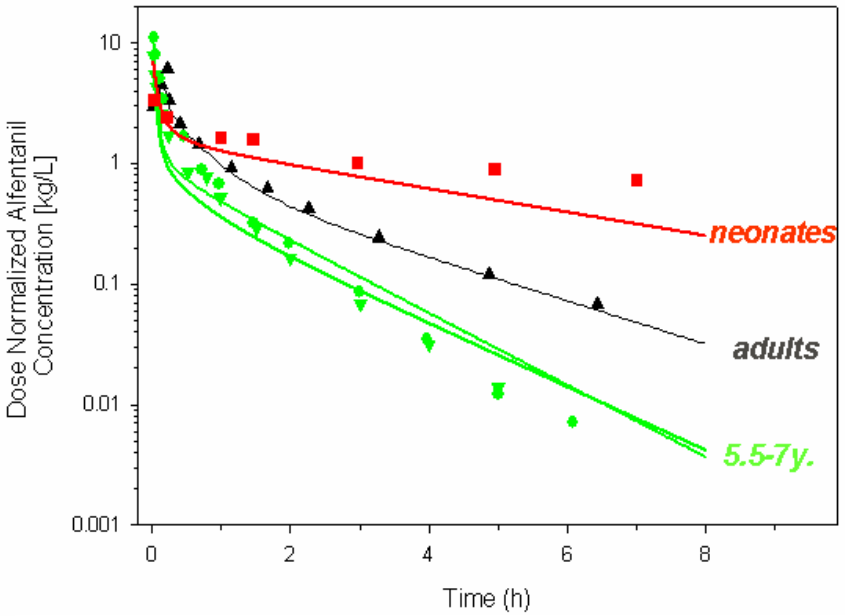
Training compounds
- Alfentanil
- Midazolam
- Gentamicin
- Isepamicin
- Caffeine
- Ropivacaine
- Morphine
- Lorazepam

Test compounds
- Buprenorphine
- Lidocaine
- Ciprofloxacin
- Paracetamol
- Theophylline
- Fentanyl

(closed symbols term neonates/children, open symbols pre-terms)

Edginton et al., Clin. Pharmacokin. 45(7), 683-704 (2006)

Alfentanil PK after IV administration



Edginton et al., Clin. Pharmacokin. 45(10), 1013-34 (2006)

Why mechanistic, physiology-based modeling?

- **Integrate, explicitly represent and exploit knowledge and data about physico-chemistry, (patho-)physiology and other relevant processes**
- **Enforce explicit formulation of crucial assumptions**
- **Reveal discrepancies between current understanding and data**
- **Allow extrapolation and re-use of information between different application scenarios, sub-populations or between different drugs**
- **Foster an improved understanding of pharmaceutics and pharmacology**

and, for ethical reasons,

- **We should simply not allow ourselves to miss opportunities that give us a more holistic picture, reduce risk and increase the chance of optimal therapy**

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Three major constraints in clinicial applications

Ethical and regulatory constraints on the one hand and economic pressure on the other hand lead to three major needs:

- **Reliability**
- **Standardization**
- **Efficiency**

None of these can realistically be achieved by the modeling experts using general purpose modeling tools!

- **A simple PBPK model has >50 compartments, >200 parameters, coupled PBPK/PD models reach 1000 compartments!**

The workflow of PBPK/PD modeling

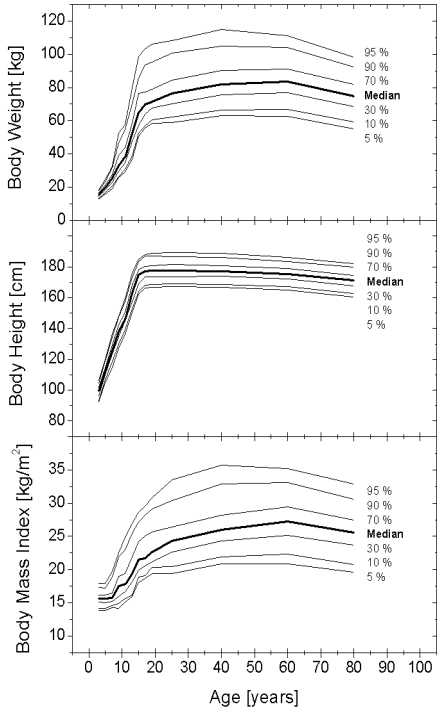
Consequently, the software has to support whole workflows. E.g.

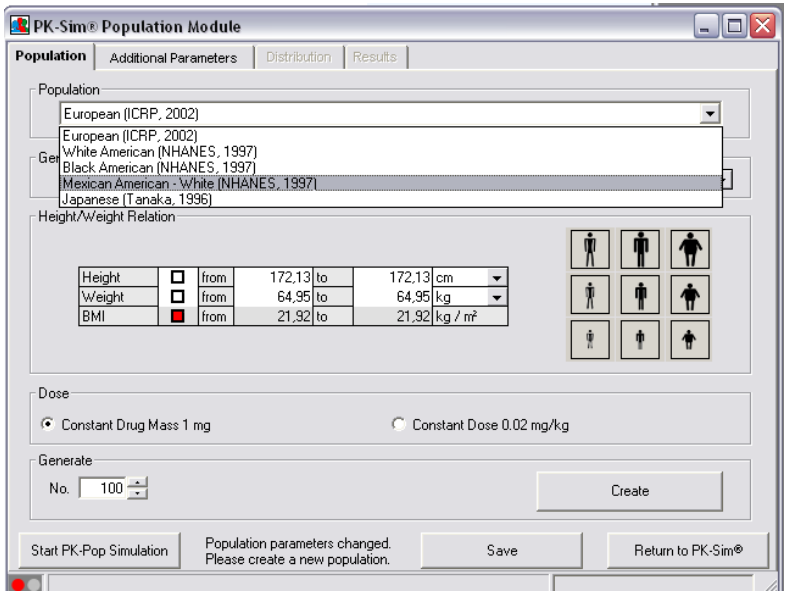
1. **Establishment, parameterization and validation of the adult reference model(s)**
2. **Definition and establishment of in-silico (pediatric) target populations of interest**
3. **Simulation of PK/PD in (pediatric) target populations**
4. **Reporting and documentation of proceding and results**

Establishment of adult reference models I

We need

- **Anatomical and physiological parameters for individuals and populations of different age and ethnic and racial background**
- **Predictive models for partition coefficients and permeabilities**
- **The possibility to integrate**
  - **Transport processes**
  - **Specific binding**
  - **Metabolization in tissue and plasma**

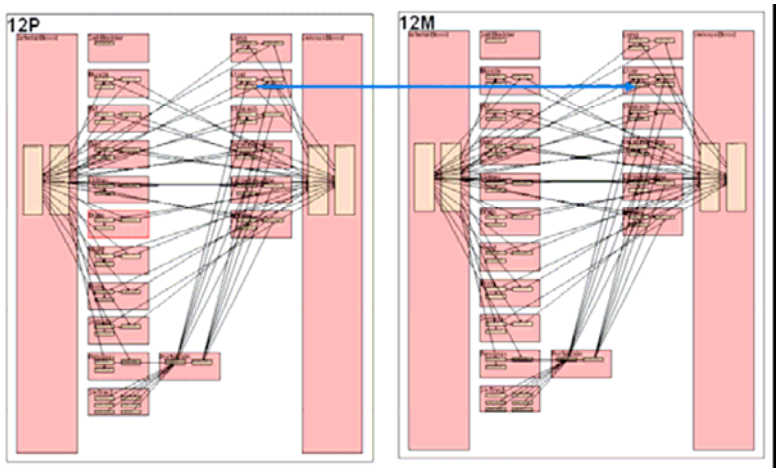


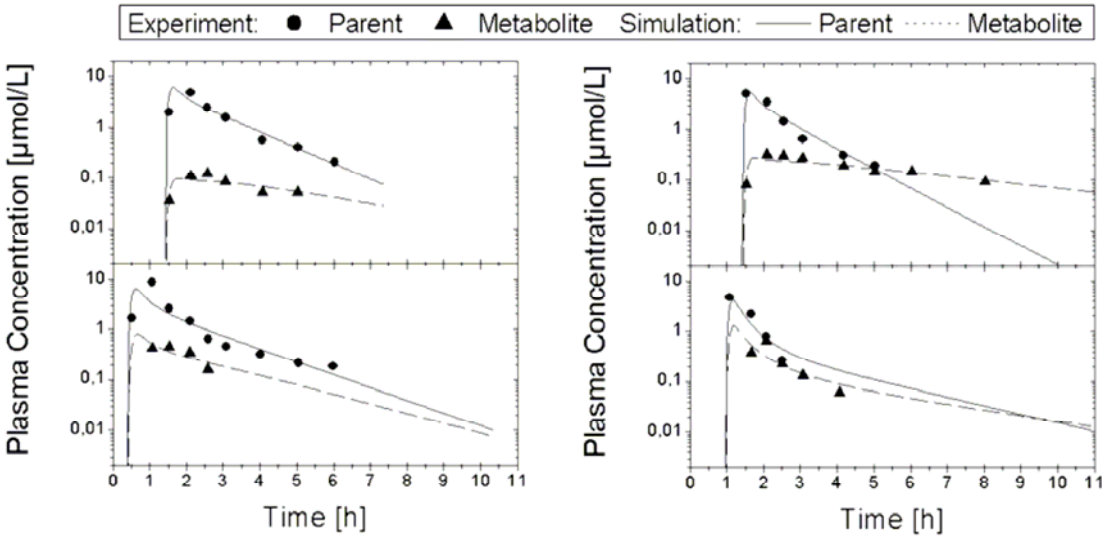


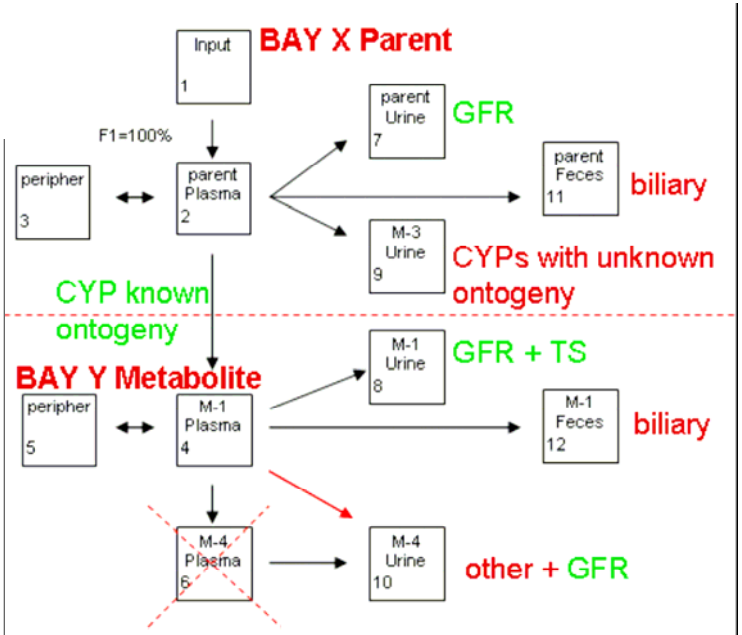
Establishment of adult reference models II

We also need

- **Capabilities for dynamically integrating PBPK models of active metabolites and interacting co-medications into our adult and pediatric simulations**

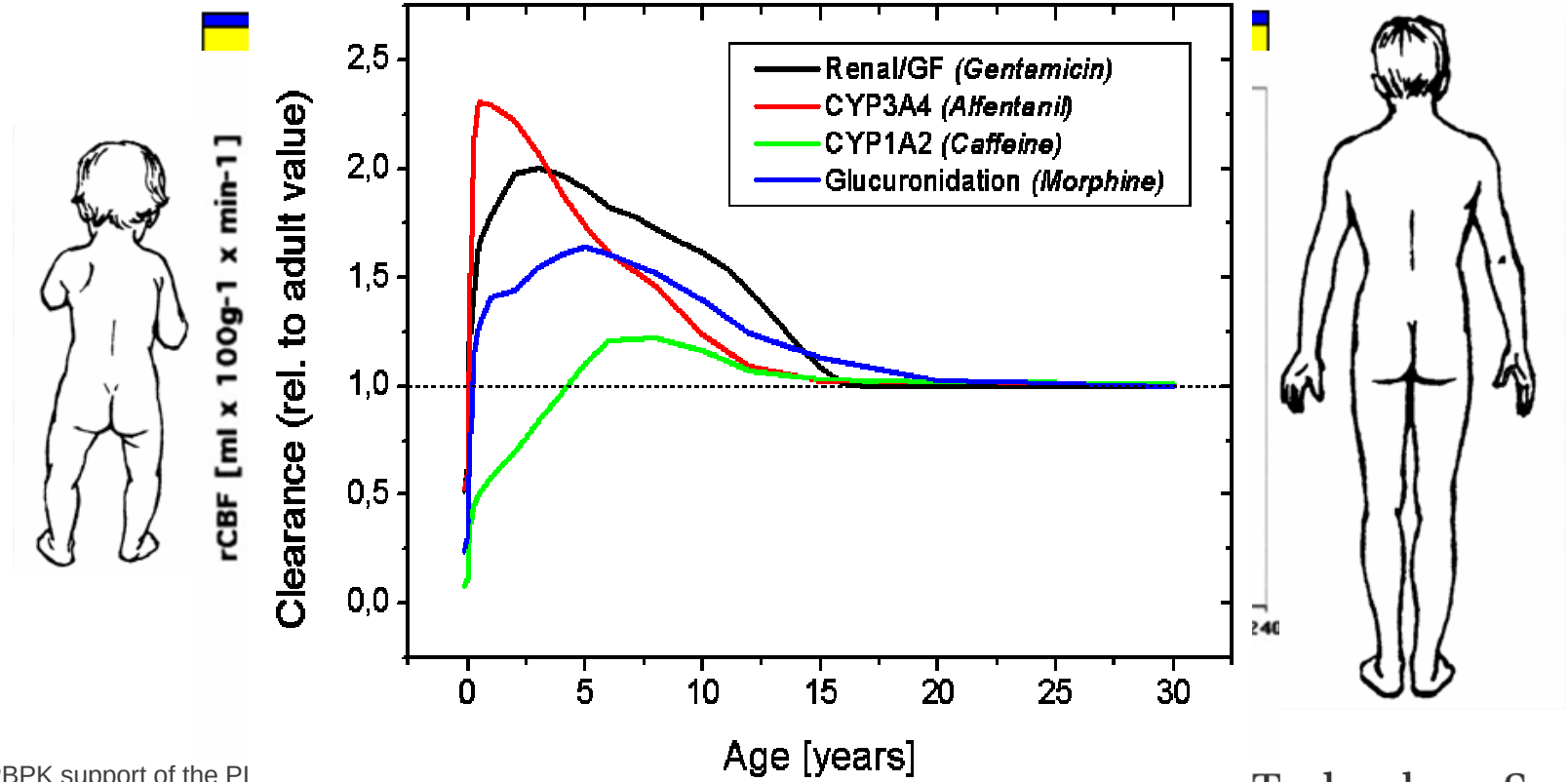






Defining target populations

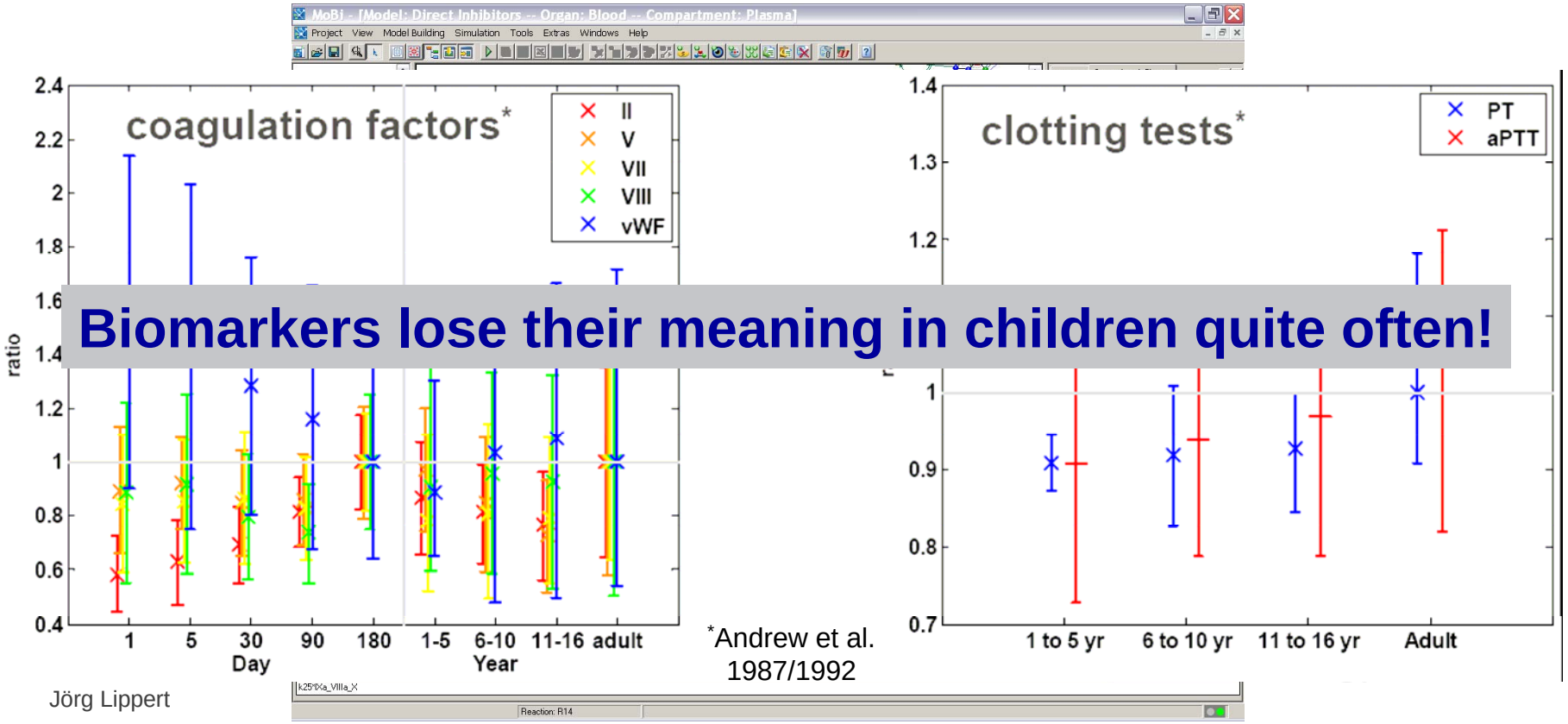
Information about growth and maturation has to be represented and virtual individuals with desired properties have to be generated automatically



Edginton et al., *Clin. Pharmacokin.* 45(10), 1013-34 (2006)

Integrating the ontogeny of pharmacodynamics

For some disease related, pharmacodynamic processes we have prior knowledge and excellent mechanistic PBPD models that we want to integrate and use in the same way as PK information in PBPK models. E.g. blood coagulation:

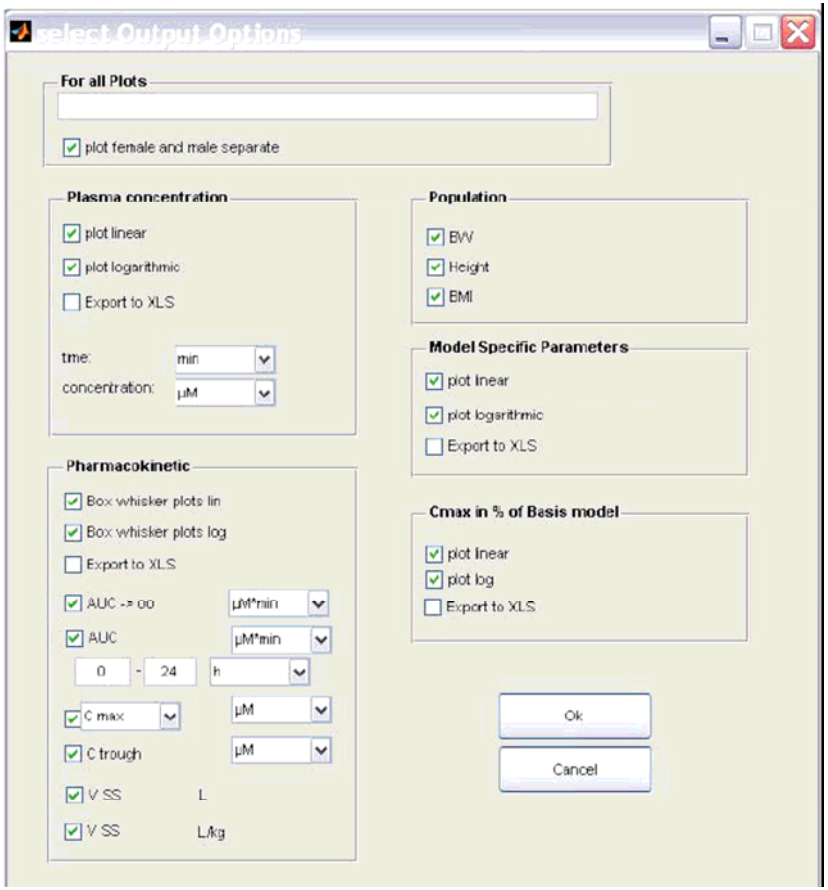


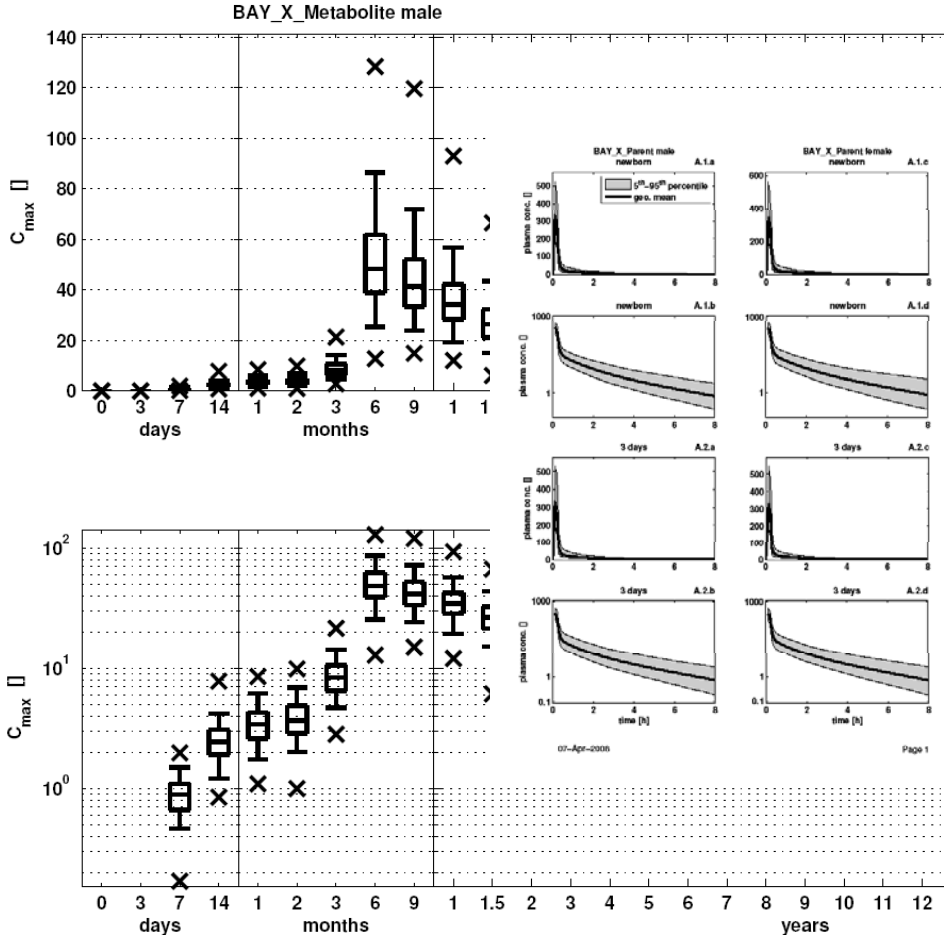
Biomarkers lose their meaning in children quite often!

*Andrew et al. 1987/1992

Simulation, reporting and documentation

For reasons of quality management all these tasks including statistical analyses should be standardized and automated





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Where software cannot help

- **While the number of “well"-studied CYPs is continuously increasing little is known about the ontogeny of transport proteins and binding partners for specific binding yet; the same still holds for some relevant (patho-)physiological processes**
- **High quality raw data is rare and seldomly published; covariances information is usually not reported**
- **Generally accepted criteria for goodness of reference models are lacking and the formulation of such criteria is challenging**
- **So far, most research has focused on population related questions; modeling and simulation of individuals is a rather new application promising**
  - **new insights into driving causes of incidence rates**
  - **new optimization and individualization strategies**

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Summary & Conclusion

- **Mechanistic, physiology-based modeling and our knowledge about growth and maturation have reached a level that allows direct clinical application**
- **Software tools support efficiency and ensure the quality and reliability of results – and they are available**
- **The availability of high quality raw data is still a bottle-neck**
- **Application of PBPK modeling to individualization questions is needed**