Part II: Building Robust PK/PD Population Models with Bayesian Inference

Clinical neonate example in scientific collaboration with M. Pfister, university children's hospital Basel (UKBB)

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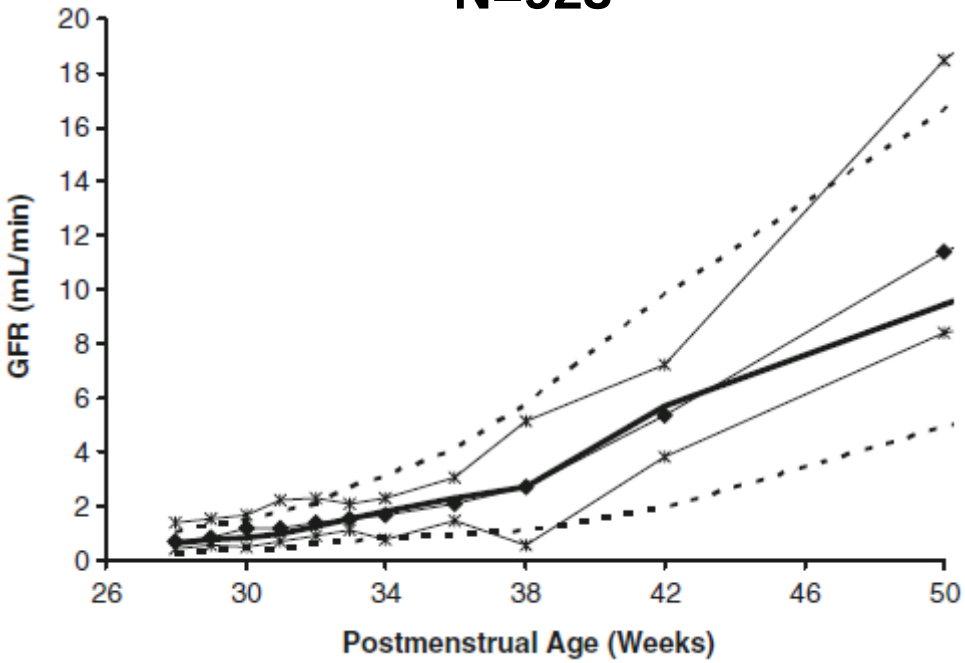
Example: Acetaminophen in Neonates

Very sparse sampling and well-established adult data

- Neonates
  - Newly born babies
  - Very sparse sampling
  - *Organ maturation*
- Pain management in neonates
- Acetaminophen
  - Extensive adult data
  - Parent-Metabolite kinetics

Relevant external information
Human renal function maturation
N=923



Source: Rhodin et. al, Pediatr Nephrol (2009) 24:67–76

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Context for Acetaminophen in Neonates

Extensive adult data, metabolites are essential

- Adult literature data
  - PK: parent V and Cl are known from IV data
  - Main metabolites formed mostly in the liver
    ~60% glucuronidation & ~30% sulfation → G/S ratio ~ 2:1
  - Elimination via kidney → Cl ~ 7.2 l/h/70kg
- **Metabolism vastly different in neonates**
  - Kidney mature at ~1y after birth
  - Glucuronidation (G) quickly matures around birth
  - Sulfation (S) mature long before birth
- Key challenge is to account for changing metabolism

Experimental Data

IV infusions & sparse sampling for (pre-)term neonates

- Joint work with Dept. of Paediatric Research Center, University Children's Hospital Basel
  see for details **poster II-57 & II-56**

- Patient population N=35

	Mean	Min - Max	Unit
Pma	35	23 - 41	weeks
Weight	2.2	0.46 - 4.2	kg
# Obs per pat.	7.2	3 - 11	

- Dosing regimen
  - 30min IV infusions
  - GA ≤ 28: 5x 15mg/kg every 12h
  - GA > 28: 7x 15mg/kg every 8h

Modelling Considerations

Bayesian modelling reflects a quantitative model context with the prior

- Key modeling questions in general
  1. What is the objective of the M&S?
  2. In what aspect is the data at hand informative?
  3. Model checking

- The Bayesian extra is the prior:
  Formulation of the quantitative model context
  - What external information is **relevant for the objective** and can (or must) be taken into account?
  - How can we **parametrize** the model to optimally mirror prior information?
  - Different sources of information can vary in relevance and quality
    → Prior elicitation, see references

The Quantitative Model Context: The Prior

Bayes puts data into a context via the prior

- Priors
  - Use of correct units
  - Are part of the model
  - Often useful to consider plausible 95% CrI
- Technical aspects of priors
  - Similar to regularization
  - Remove non-identifiability if chosen proper
  - Parameterization dependent

Prior	Usage	Example for «$p(\log(\omega_{Cl}))$»
Improper	Easy to use can be problematic	$\propto 1$
Non-Informative	Minimize impact on results can also be problematic	$\sim \text{Normal}(0, 10^2)$ $\omega_{\text{Cl}} \sim (10^{-85}, 10^{85})_{95}$
Weakly-Informative	Identify scale minimal impact, stable inference	$\sim \text{Normal}(\log(0.5), 2)$ $\omega_{\text{Cl}} \sim (0.01, 25)_{95}$
Informative	Contextual domain knowledge (renal clearance)	$\sim \text{Normal}(\log(0.2), \log(3)/1.96)$ $\omega_{\text{Cl}} \sim (0.06, 0.6)_{95}$

Parametrization is Key in Bayesian Modeling

Model parameters must mirror prior knowledge

- Objective for neonate model
  Quantify impact of developing metabolism on PK
- **Strategy**: Relate to adult data with allometric '1/4' power scaling and use known GFR maturation function
- Key facts identified and choices made
  - Metabolites G and S constitute ~90% of Acetaminophen elimination

$$\text{logit}(\pi_{\text{G+S}}) \sim (\text{logit}(0.85), \text{logit}(0.95))_{95}$$

  - Clearance of metabolites via the kidney (~7.2 l/h/70kg)

$$\log Cl_{\text{G,ref}} \sim (\log(5), \log(10))_{95}$$

  - Glucuronidation formation capacity developing with pma

$$Cl_{\text{APAP,G,j}} = Cl_{\text{APAP,G,ref}}\, \pi_{34} \left(\frac{w_j}{70}\right)^{3/4} \exp(\lambda_{\text{G}}\, (pma_j - 34))$$

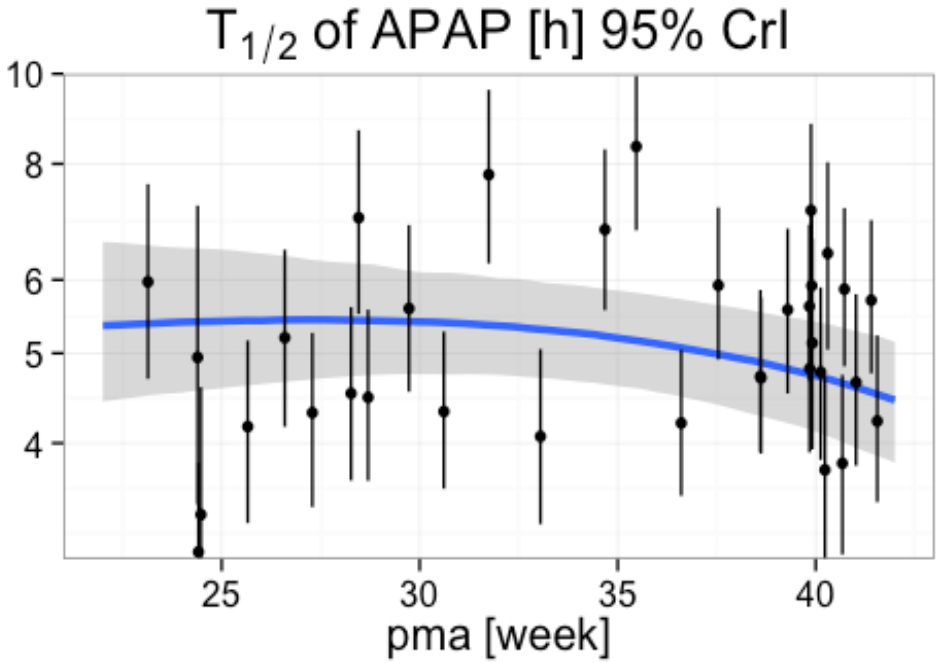
The Developing Metabolism in Neonates

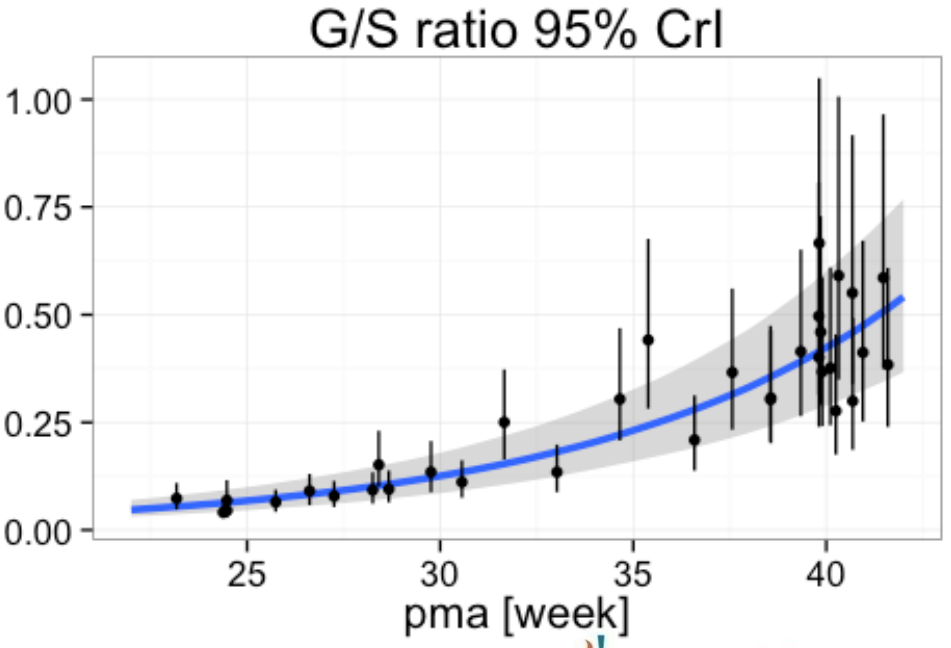
Fast clearance maturation slows down $T_{½}$ decrease with age

- Increase by Cl maturation slows $T_{½}$ weight scaling

$$T_{\frac{1}{2}} = \log(2)\,\frac{V}{Cl}\left(\frac{w}{70}\right)^{\frac{1}{4}}$$

- Considerable uncertainty & variability
- Metabolism changes quickly and is very different from 2:1 G/S adult ratio





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Doing Bayesian PK/PD

The operational & computational hurdles are vanishing

- NONMEM / Monolix (hybrid approach, not full Bayes)
  - No HMC/NuTS available (yet?) → convergence critical
  - Very restrictive in prior choices
- Stan, http://mc-stan.org/
  - PK/PD support growing (stiff ODE solver on Stan GitHub)
  - HMC/NuTS can deal very efficiently with non-linear PK/PD
  - Active community, very responsive user mailinglist
  - Excellent user manual with introductory material
  - ACOP 2015: Workshop from Bill Gillespie on «Getting Started with Bayesian PK/PD Modeling Using Stan»
- WinBUGS/PKBUGS/WBDiff

Key Benefits of a Bayesian Approach

Probabilistic knowledge integration facilitates quantitative decisions

- Bayes provides a quantitative framework to statistically model *uncertain knowledge (including external to dataset)*
  - The prior reflects a **quantitative model context**
  - External information make **models more robust**, yet accounting for **uncertainty is key**
  - **Model parameterization** must mirror prior knowledge
- Results become **conditional** on the **totality of evidence**

$$\mathrm{p}(\theta|\mathcal{D}) \propto \mathrm{p}(\mathcal{D}|\theta)\,\mathrm{p}(\theta)$$

- Neonate example clinical relevance:
  Maturation alters weight scaling, impacting dosing

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References I

Applied Bayesian introduction material

- Stan
  - Stan Dev Team 2015, Version 2.6. http://mc-stan.org
  - Stan User Manual (great introduction, very applied)
- Applied Bayesian Statistics Books
  - Data Analysis Using Regeression and Multilevel/Hierarchical Models A. Gelman, J. Hill (2007)
  - Bayesian Data Analysis, 3. Edition, «BDA3» A. Gelman, J.B. Carlin, H.S. Stern, D.B. Dunson, A. Vehtari, D.B. Rubin (2014)

References II

Prior elicitation

- Prior derivation
  - Pocock's approach (bias model)
    Pocock SJ (1976). The combination of randomized and historical controls in clinical trials. Journal of Chronic Diseases 29, 175-188
  - Ibrahim & Chen Power Priors
    Chen and Ibrahim (2006). The Relationship Between the Power Prior and Hierarchical Models. Bayesian Analysis
  - Meta-Analytic approaches (hierarchical models)
    Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter DJ (2010). Summarizing historical information on controls in clinical trials. Clinical Trials 7, 5-18.
- Combining hierarchical models with data summaries
  http://page-meeting.org/?abstract=3200

References III

Neonate example

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