Bayesian Pharmacokinetic Extrapolation from Dense Adult to Sparse Pediatric Data

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Background

Common situation in early to mid-phase programs

- Large data set for adults available (few dense profiles, many sparse)
- Few and sparse pediatric profiles
- Key question to address for pediatrics is often "Is the PK in pediatrics similar to adults?"

Apart from less data, children are harder to model as the body maturates, possibly altering PK

- Power (3/4 weight-) scaling laws for CL and V
- Possibility of additional maturation processes

Increased modeling need yet less data?

- **Bayesian priors** allow to interpret pediatric data in **larger context** than the data set itself
- Derivation of **informative prior from adult data very attractive**

Objectives

The goal is to characterize pediatric PK accurately in the context of an existing adult PK model. However, the challenge lies in appropriate use of the adult data. A simple pooling approach would lead to a sample size driven inference. This would force the adult model onto the pediatric data. To address this, we suggest a two-step approach which **discounts** the adult prior:

- Derive prior from dense adult data patients using
  - Stable parametrization
  - Based on weakly-informative priors
- Using the adult prior for sparse pediatrics data
  - Discount prior from adults
  - Appropriately scale CL and V
  - Inference with informative prior from adults will be compared to a weakly-informative prior only

Conclusion

Benefits of a Bayesian Population PK Approach:

- Weakly-informative priors help to regularize inference **robustness for numerics/model identifiability**
- Enables evidence synthesis / probabilistic statements for relevant clinical questions; **seamless ability to predict & make probability statements for clinically relevant considerations**
- Allows integration of prior knowledge from adult data in a rigorous statistical framework **especially relevant in pediatric sparse data situation i.e. Leverage adult model for pediatrics.**

Outlook:

- Formalize discounting using sample size arguments
- Introduce multi-variate t-distribution as prior, such that pediatric data can more easily overrule the adult prior in case of marked differences.

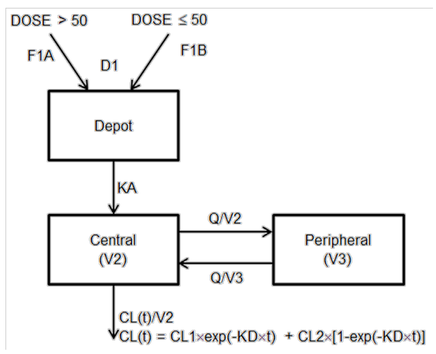
Methods

Study data

- 600 adult patients with PK sampling scheme
  - 25% in absorption phase
  - 50% around Ctrough at 12h post dose
  - 25% in elimination and washout phase
- 22 pediatric patients with wide age range (1y – 18y)
  - Very few samples in absorption phase
  - Most around Ctrough at 12h
  - Almost no samples in elimination or washout phase

Adult PK model

- Oral dosing with dose-dependent bioavailability
- Linear 2cmt elimination model
- Time-changing clearance possibly due to induction processes, i.e. turn-over model on clearance
- Nonmem fit sensitive to initials



Goals of Parametrization chosen for Bayesian Analysis in Stan [1]

- Numerically stabilize the original Nonmem model
- Key step was to de-dimensionalize parameters and express them relative to the overall geometric mean
- Rationale for priors by known time-scales and the fact that the central and peripheral scales are related

Parameter	Unit	Definition	Prior (95% CrI)
$\exp(\theta_1) = \Delta k_a$	1/h	k_a rel. to mean time-scale $k_a = \exp(\theta_1) + \exp(\theta_2 - \theta_3)$.	$1/100 - 100$
$\exp(\theta_2) = \sqrt{\mathrm{Cl}\, Q}$	l/h	Geometric mean of Cl and Q, defines mean clearance	$1/10 - 50$
$\exp(\theta_3) = \sqrt{V_2\, V_3}$	l	Geometric mean of V_2 and V_3	$1 - 100$
$\exp(\theta_4) = \mathrm{Cl/Q}$	none	$\mathrm{Cl/Q} = \mathrm{k}/k_{12}$	$1/5 - 5$
$\exp(\theta_5) = V_2/V_3$	none	$V_2/V_3 = k_{21}/k_{12}$	$1/5 - 5$
$\exp(\theta_6) = \mathrm{F1B}$	none	Relative F for low dose (<=50mg)	$1/10 - 10$
$\exp(\theta_7)$	none	Increase of clearance, $Cl_2 = Cl_1\,(1 + \exp(\theta_7))$	$1/100 - 10$
$\exp(\theta_8)$	h	Doubling time clearance increase, $k_d = \log(2)\exp(-\theta_8)$	$1 - 50 \times 24$

Priors

As weakly-informative priors normal distributions on the log scale were used, with the 95% intervals motived by scientific rationale for this model as shown in the table.

The adult data was fitted with the weakly-informative priors and then the so-obtained posterior was ***discounted*** and used as prior for the pediatric dataset:

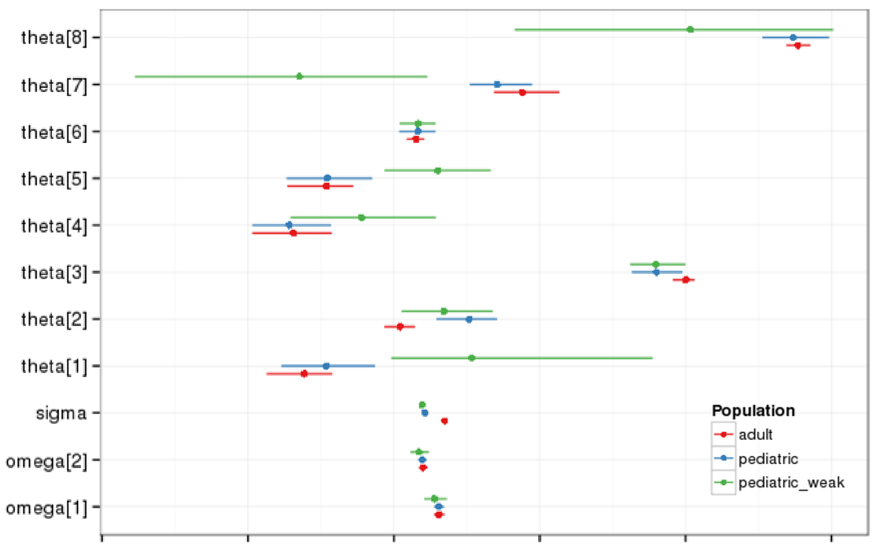
1. Inference from adult data with weak prior gives posterior which we approximate parametrically
$$\phi \equiv \left(\theta_1, \ldots, \theta_8, \log(\omega_1), \log(\omega_2), \log(\sigma_y)\right)$$
$$\phi \sim \mathrm{MultiVariateNormal}(M_\phi, \Sigma_\phi)$$
2. Children are **different but related to adults (parameters are assumed to be at most 2x different here):**
$$\phi' = \phi + \delta.$$
$$\delta \sim \mathrm{MultiVariateNormal}(0, \Sigma_0) \rightarrow \phi' \sim \mathrm{MultiVariateNormal}(M_\phi, \Sigma_\phi + \Sigma_0)$$
with Σ_0 being a diagonal matrix with $(\log(2)/1.96)^2$ elements as trace (allows 2x change), but 0 for the ω's
3. Weight scale CL and V with "¾ power-laws" [2]

Results

We consider the following scenarios for comparisons:

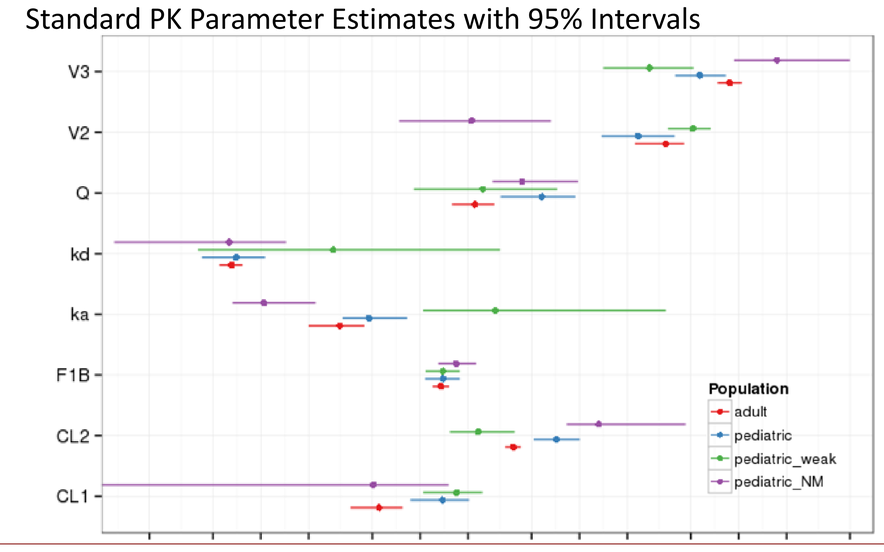
- **Adult**: Posterior when conditioning the weakly-informative prior with the adult data set
- **Pediatric**: Posterior when using the discounted adult posterior as prior
- **Pediatric weak**: Posterior when using only the weakly-informative prior
- **Pediatric NM**: Nonmem estimates for pediatric data set

Model Parameter Estimates with 95% Intervals



- Using discounted adult posterior as prior greatly improves precision of parameter estimates
- Nonmem and the weakly informative priors fail to infer the complex model structure given the sparse pediatric data
- The sparse pediatric data set still updates parameter estimates slightly, i.e. adult data does not overrule.

Standard PK Parameter Estimates with 95% Intervals



References: [1] Stan Development Team (2017). Stan: A C++ library for probability and sampling.

[2] West GB, Brown JH, Enquist BJ, Science. 1997;276(5309):122–6

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