Estimating the similarity between adult and pediatric dose-toxicity curves to inform pediatric dose-finding

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PEDIATRIC PHASE I CLINICAL TRIALS IN ONCOLOGY

- Phase I clinical trials are the first step in testing a new therapy in the target population.
  - The aim is to find a dose that is safe *and* effective.
  - This maximum tolerable dose (MTD) should have a certain toxicity probability (often around 30%).
- Due to strong ethical concerns and small sample sizes, pediatric dose-finding trials are often not even conducted.

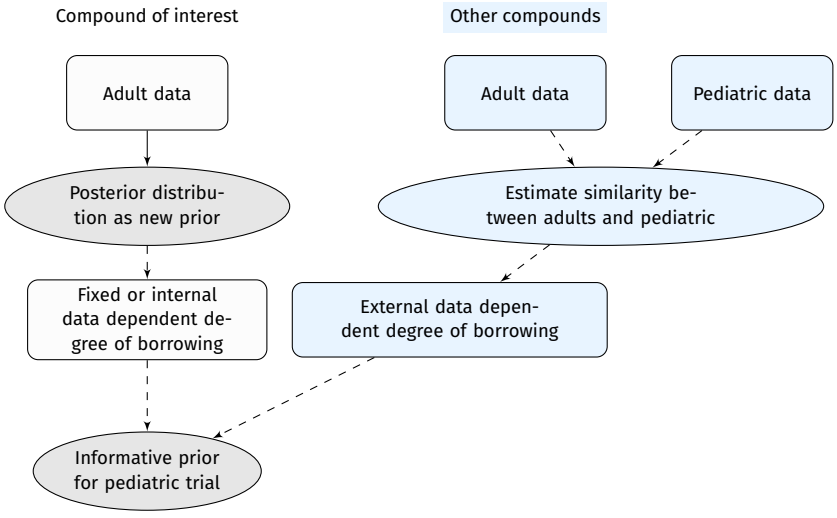
Mahmood and Burckart (2016)

"The fundamentals of pediatric drug dosing are still evolving. While this may sound strange in the twenty-first century, it is a true statement."

Borrowing from adults to children

- Information from adults can be "borrowed" to support the pediatric trial.
- But how much borrowing of the adult information is appropriate?
- What if there were other compounds with similar mechanism action, from which the similarity between adults and children could be estimated?

CONTROLLING THE DEGREE OF BORROWING



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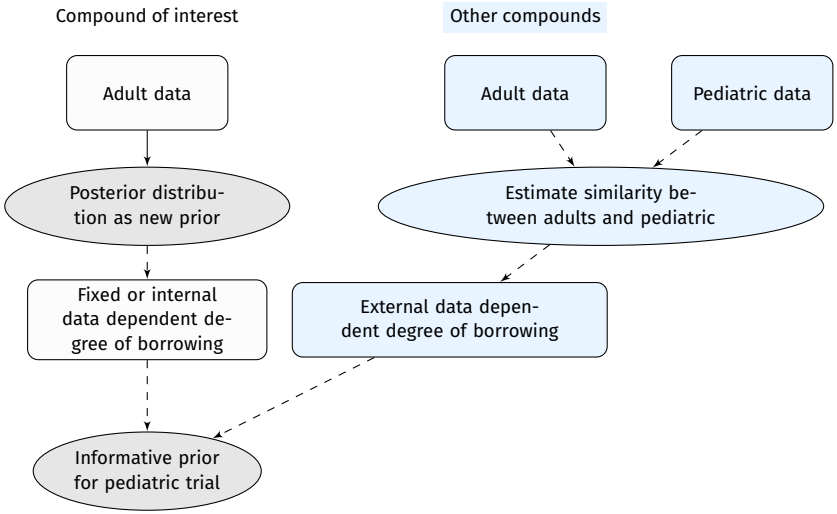

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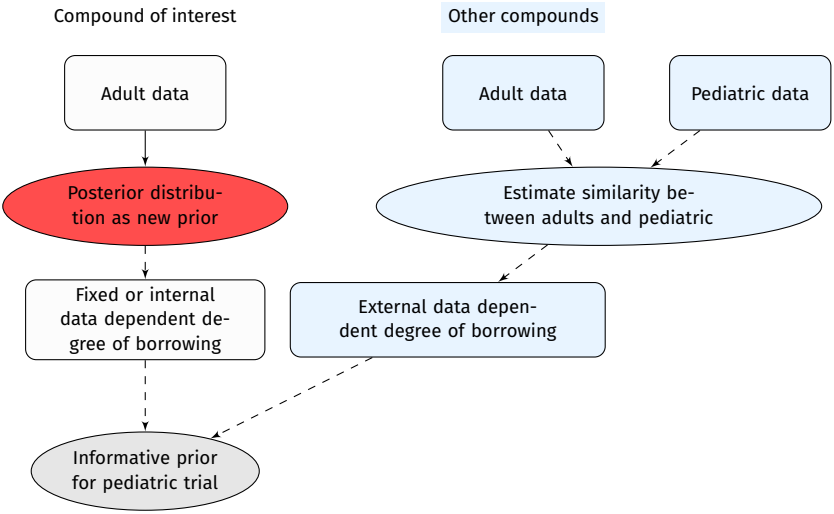
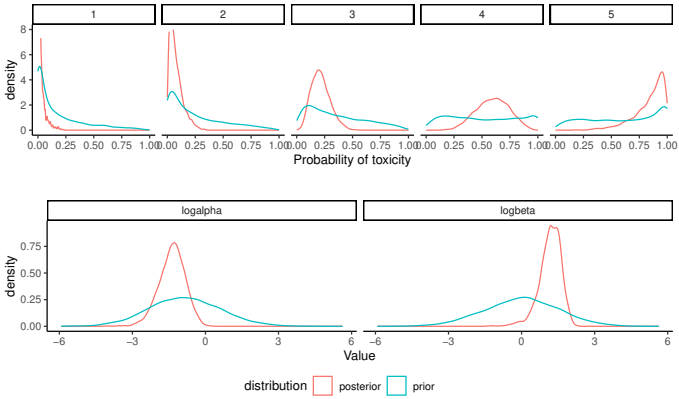


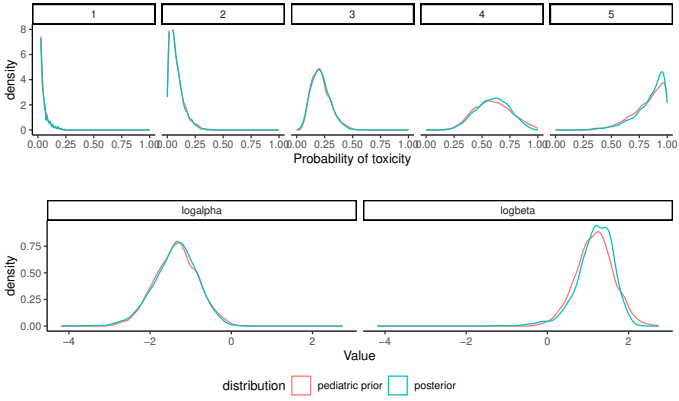
SIMPLE EXAMPLE OF A DOSE-FINDING TRIAL

- Doses in mg/m²: 5, 10, 15, 25, 40; dR = 15; N = $\{6, 6, 12, 6, 3\}$; toxicities = $\{0, 0, 3, 3, 3\}$
- Model: BLRM (Neuenschwander et al. 2008): $\text{logit}\left(p_i\left(D_i; \alpha, \beta\right)\right) = \log(\alpha) + \beta \log(D_i / D_R)$



CONSTRUCT AN INFORMATIVE PEDIATRIC PRIOR

Using normal priors with posterior means and variances are often a good approximation.
This assumes adult and children are exchangeable, without possibility to detect a prior-data conflict.



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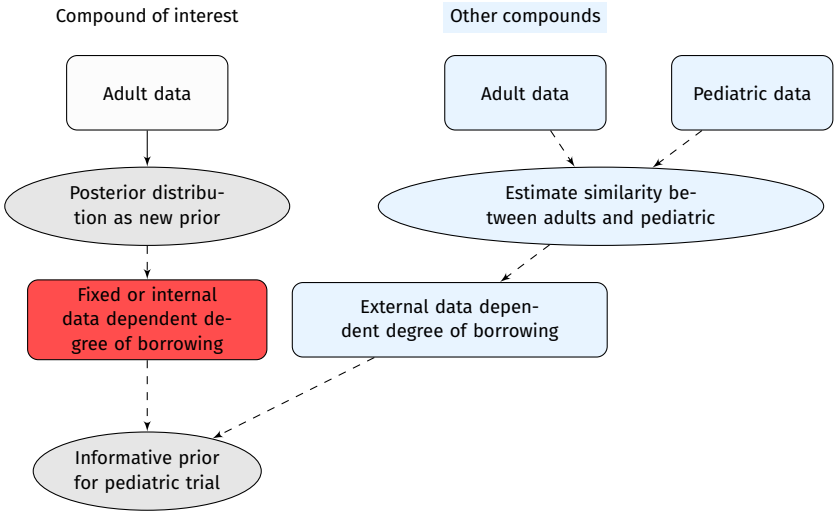


CONTROLLING THE DEGREE OF BORROWING

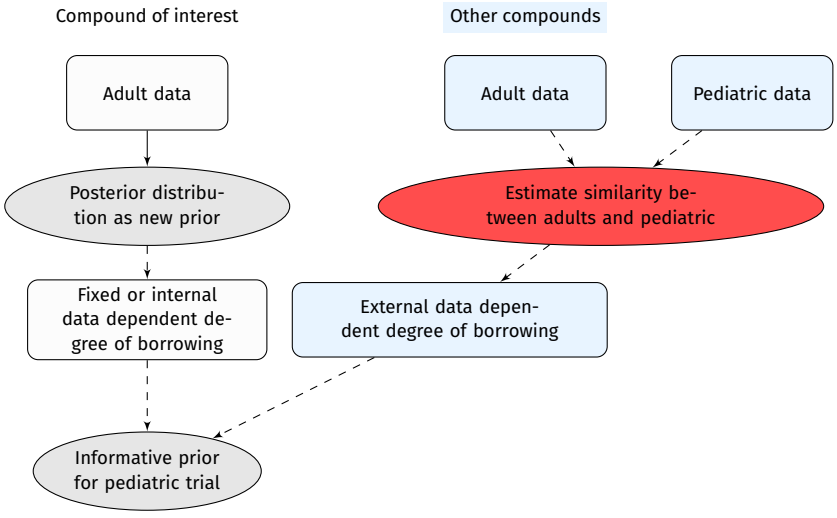
- Robustify priors via mixtures of strongly and weakly informative distribution [1]:

$$\log(\alpha) \sim \delta_\alpha \times P_{\text{adult}}(\log(\alpha)) + (1 - \delta_\alpha) \times P_{\text{weak}}(\log(\alpha))$$

$$\log(\beta) \sim \delta_\beta \times P_{\text{adult}}(\log(\beta)) + (1 - \delta_\beta) \times P_{\text{weak}}(\log(\beta))$$

- The closer δ is to 0 the less informative the prior, $\delta = 1$ means full borrowing.

CONTROLLING THE DEGREE OF BORROWING



APPROACH 1: HIERARCHICAL MODEL

- First level: population-specific and compound-specific means, variance τ^2 expresses population heterogeneity (within-compound-variability):

$$\begin{pmatrix} \log(\alpha_{A,j}) \\ \log(\beta_{A,j}) \end{pmatrix}, \begin{pmatrix} \log(\alpha_{P,j}) \\ \log(\beta_{P,j}) \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{\alpha_j} \\ \mu_{\beta_j} \end{pmatrix}, \begin{pmatrix} \tau_\alpha^2 & \tau_{\alpha,\beta} \\ \tau_{\alpha,\beta} & \tau_\beta^2 \end{pmatrix} \right)$$

- Second level: distribution of compound-specific means (between-compound-variability):

$$\begin{pmatrix} \mu_{\alpha_j} \\ \mu_{\beta_j} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_\alpha \\ \mu_\beta \end{pmatrix}, \begin{pmatrix} \sigma_\alpha^2 & \sigma_{\alpha,\beta} \\ \sigma_{\alpha,\beta} & \sigma_\beta^2 \end{pmatrix} \right)$$

- with some priors, e.g. $\mu_\alpha \sim N(-0.84, 1.5^2)$, $\mu_\beta \sim N(0, 1.5^2)$ and $\tau_\alpha \sim \Gamma(1, 1/10)$, $\tau_\beta \sim \Gamma(1, 1/10)$, $\rho_\tau \sim \text{Unif}(-1, 1)$, $\sigma_\alpha \sim \Gamma(1, 1/10)$, $\sigma_\beta \sim \Gamma(1, 1/10)$, $\rho_\sigma \sim \text{Unif}(-1, 1)$.
- The similarity (or heterogeneity) parameters are then estimated as standard intraclass correlation coefficients:

$$\zeta_\alpha = \frac{\tau_\alpha^2}{\tau_\alpha^2 + \sigma_\alpha^2} \text{ and } \zeta_\beta = \frac{\tau_\beta^2}{\tau_\beta^2 + \sigma_\beta^2}$$

APPROACH 2: EXNEX-MODEL

- **Exchangeable component (Ex)**
  - With probabilities ζ_α and ζ_β, the parameters for adult and pediatric patients come from the same compound-specific distribution, i.e.:

$$\alpha_{P,j}, \alpha_{A,j} \sim N(\mu_{\alpha,j}, \sigma_\alpha^2)$$
$$\beta_{P,j}, \beta_{A,j} \sim N(\mu_{\beta,j}, \sigma_\beta^2)$$

- **Non-exchangeable component (Nex)**
  - With probability $1 - \zeta_\alpha$ and $1 - \zeta_\beta$, the parameters for adult and pediatric patients come from different compound-specific distributions, i.e.:

$$\alpha_{P,j} \sim N(\mu_{\alpha_{P,j}}, \sigma_\alpha^2), \alpha_{A,j} \sim N(\mu_{\alpha_{A,j}}, \sigma_\alpha^2)$$
$$\beta_{P,j} \sim N(\mu_{\beta_{P,j}}, \sigma_\beta^2), \beta_{A,j} \sim N(\mu_{\beta_{A,j}}, \sigma_\beta^2)$$

- Each parameter is modeled as a mixture between Ex and Nex, for the weights a Beta prior is used:

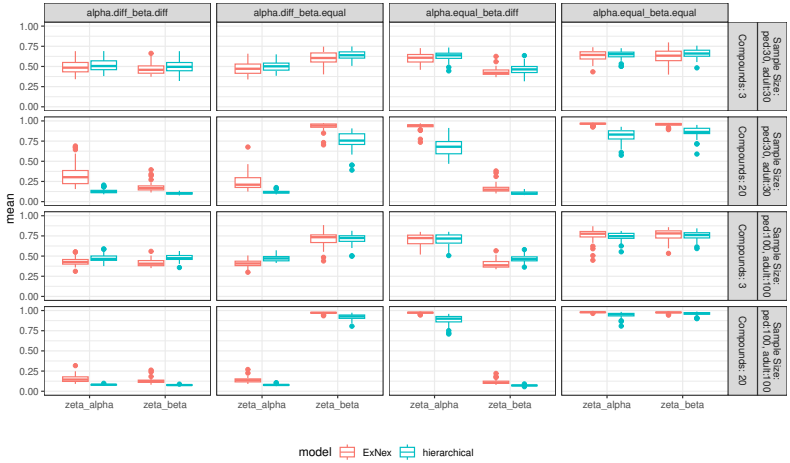
$$\zeta_\alpha \sim \text{Beta}(0.5, 0.5) \text{ and } \zeta_\beta \sim \text{Beta}(0.5, 0.5)$$

- The variance parameters are assigned vague Gamma priors, $\Gamma(1, 1/10)$.

SIMULATION STUDY – ESTIMATING SIMILARITY IN OTHER COMPOUNDS

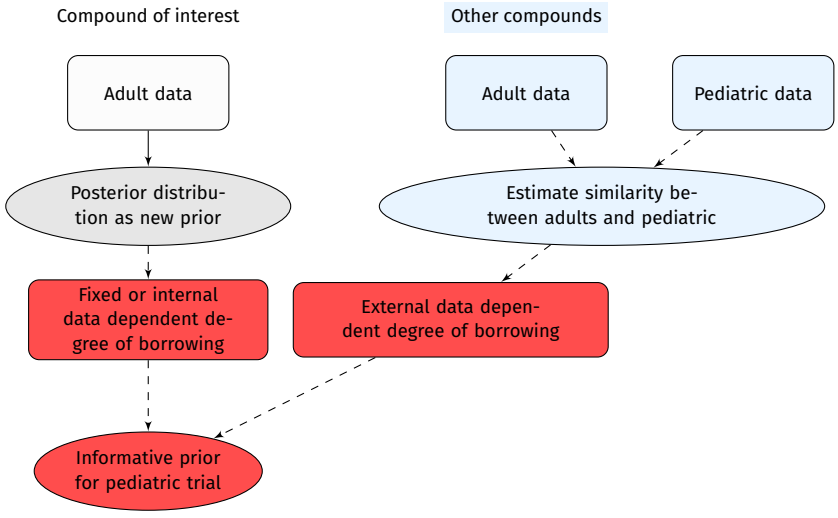
- Four similarity scenarios:
  - α and β equal
  - α equal, β different
  - α different, β equal
  - α and β different
- Two values each for $\log(\alpha) \in \{-2.5, -0.84\}$ and for $\log \beta \in \{0, 1.5\}$, so 4x4 dose-toxicity curves.
- 3 vs. 20 compounds
- Sample size of 30 vs. 100 patients per trial
- For simplicity, the following is applied to all compounds:
  - The same 5 doses.
  - Equal distribution of the sample size to the dose levels.

SIMULATION RESULTS: POSTERIOR MEANS OF SIMILARITY PARAMETERS



Note: later in the simulations, only the posterior mean will be used as weight for the prior information.

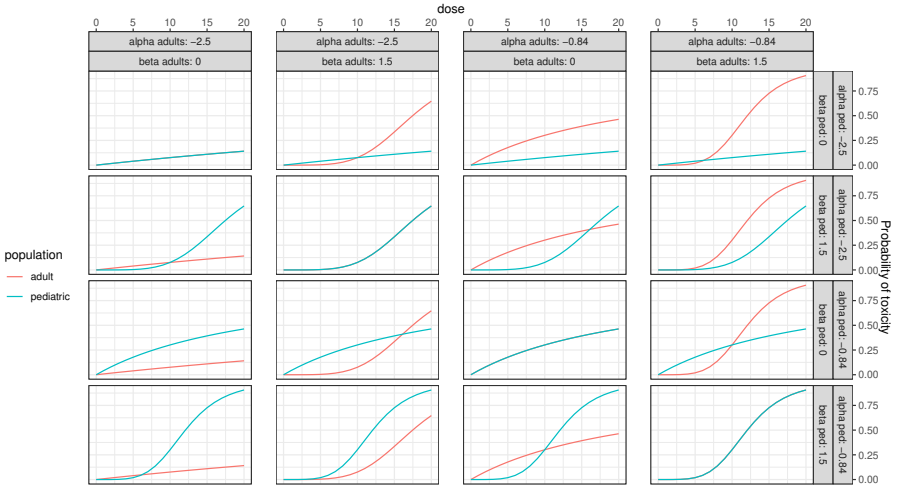
THE FINAL STEP TOWARDS AN INFORMATIVE PEDIATRIC PRIOR



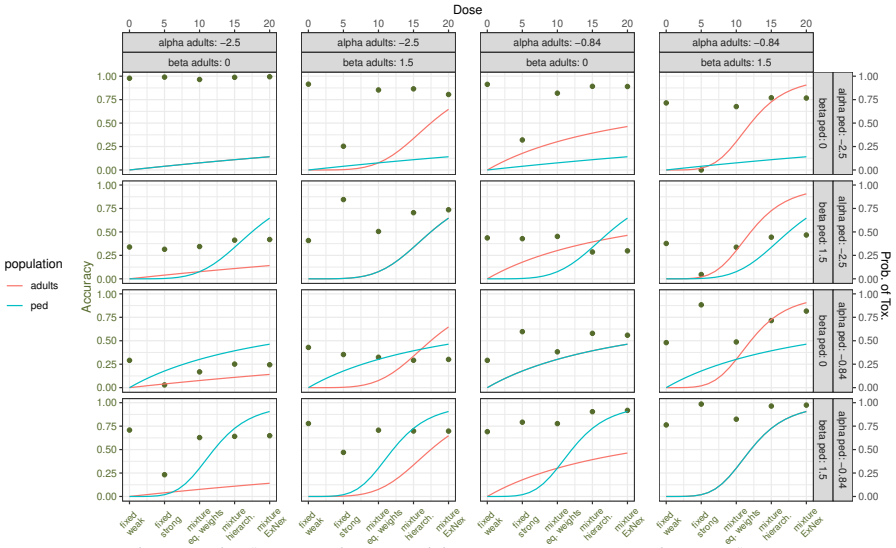
SIMULATION STUDY – NEW PEDIATRIC TRIAL

- We assume an adult trial has been conducted with N=40, and we want to test the same compound in N=12 pediatric patients.
- We assume an ideal case of 20 historical compounds with pediatric and adult data available.
- Similarity between pediatric and adult dose-toxicity curves is the same for the new compound as for the historical compounds.
- The following model approaches are considered:
  - Weakly informative priors borrow posterior means but not posterior variance from the adults.
  - Strongly informative priors borrow posterior means and posterior variances from adults.
  - The weights for mixture priors are determined by one the following strategies:
    - Fixed at 0.5,
    - Estimated from historical data with 20 cohorts using the ExNex model.
    - Estimated from historical data with 20 cohorts using the hierarchical model.

SIMULATION RESULTS – NEW PEDIATRIC TRIAL

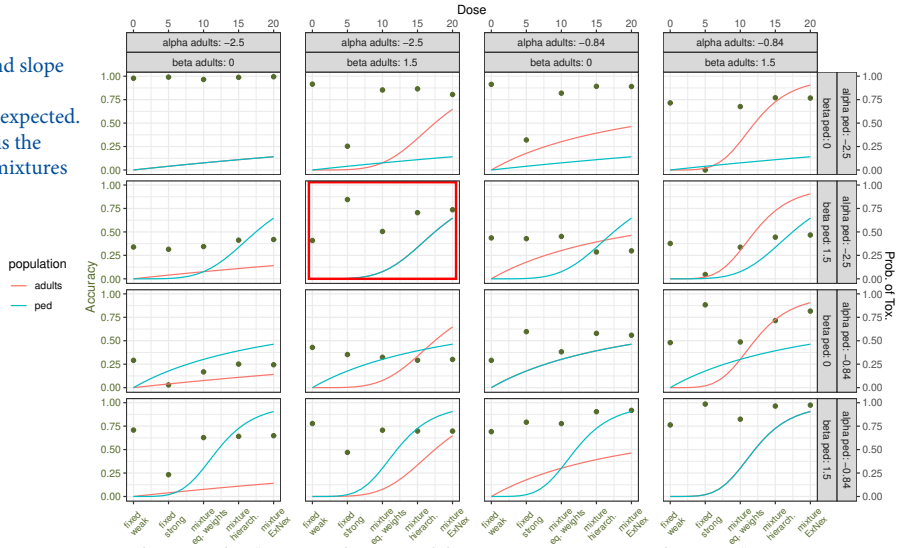


SIMULATION RESULTS – NEW PEDIATRIC TRIAL



SIMULATION RESULTS – NEW PEDIATRIC TRIAL

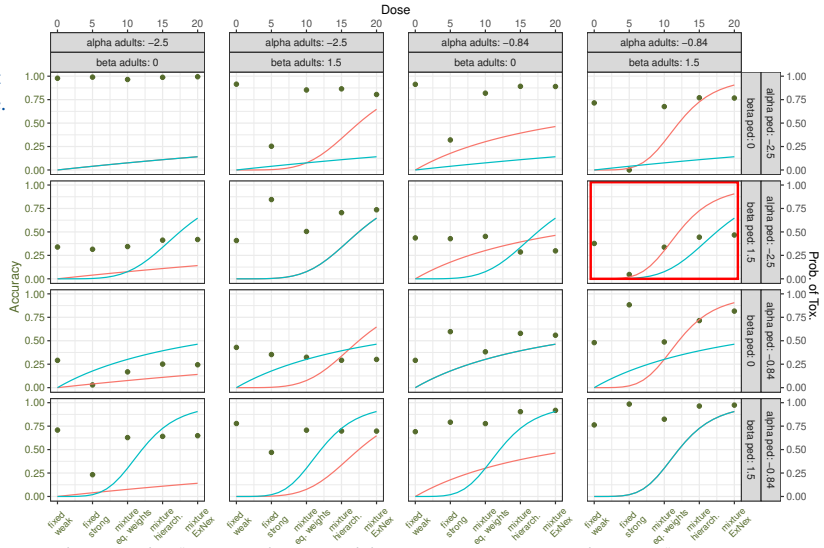
The intercept and slope are the same.
Performance as expected.
Full borrowing is the best, informed mixtures come close.



SIMULATION RESULTS – NEW PEDIATRIC TRIAL

The intercept is different and the slope is the same. Informed mixtures perform best, probably since they borrow information about the slope.

Full borrowing performs very poor, because the intercept is fully borrowed, which was the adult MTD.



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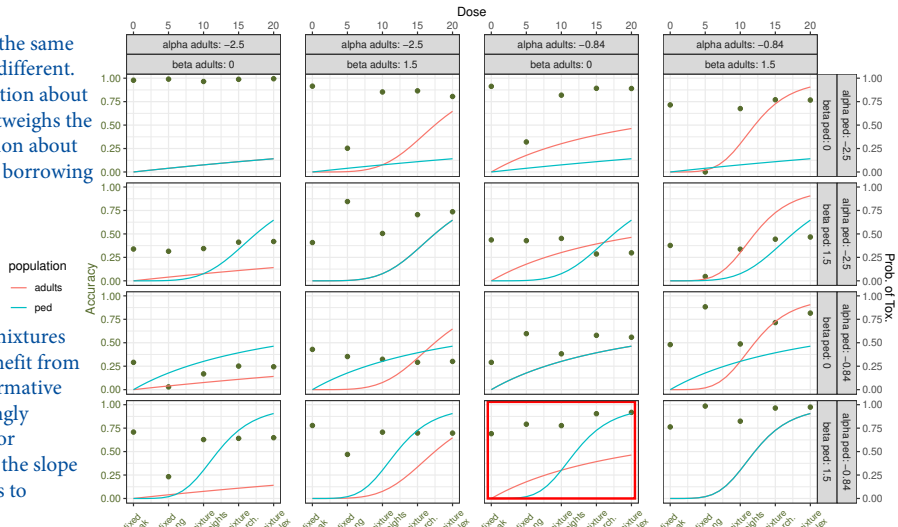
SIMULATION RESULTS – NEW PEDIATRIC TRIAL

The intercept is the same and the slope is different. Correct information about the intercept outweighs the wrong information about the slope, so full borrowing performs good.

The informed mixtures additionally benefit from the weakly informative slope. The strongly informative prior underestimates the slope and hence tends to overdose.



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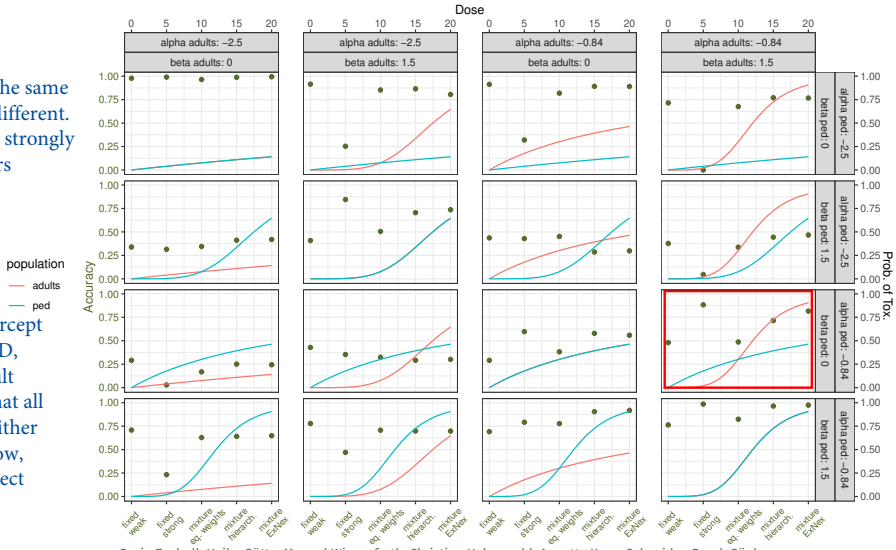
Informing pediatric dose-finding using adult information and data from other compounds

SIMULATION RESULTS – NEW PEDIATRIC TRIAL

The intercept is the same and the slope is different. Interestingly, the strongly informative priors performs best.

Reasons: the intercept is at the true MTD, and the large adult slope indicates that all other doses are either too high or too low, which is not correct but still helpful.



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PRELIMINARY CONCLUSIONS

- Both the hierarchical and the ExNex approach seem to enable reliable estimation of similarity between adults and pediatric dose-toxicity curves, if enough data is available.
- In most practical situation, to acquire this amount of data may be challenging, though.
- Prior information about the intercept often has much higher impact than prior information about the slope.
- Informing the borrowing by the estimated similarity achieved almost always accuracy close to the best optionof no or full borrowing, and was sometimes even superior.
- The effect of borrowing on the dose selection can be counter-intuitive at first. Thorough investigation of all relevant scenarios is important.

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