Adaptive Borrowing of Adult Data for Pediatric Trials: Collaborative Research at the Intersection of Pharmacometrics and Statistics

Joint Statistical Meetings

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Outline

- Motivation
- A Simulation Study
  - Study Design
  - Simulation Results
- Remarks and Conclusions

Motivation

- **Use of historical control data for assessing treatment effects in clinical trials**

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- To review the key issues of history borrowing, and to compare several methods
  - Consider 6 methods for *hypothesis testing*
    1. Separate: ignore historical data
    2. Pooling
    3. Test-then-pool: to pool or not to pool via hypothesis testing
    4. Power priors: discounting historical information
    5. Hieratical modelling: dynamic borrowing
    6. Single arm trial

Application/Extension → Pediatric Studies

- About pediatric studies

  Extensive data in adult subjects are often available before initiation of pediatric studies. ***Efficiency can be greatly enhanced, if adult information can be utilized***.

  Two popular analysis practices in pediatrics development programs:

  – utilize ped data alone (*0%* borrowing from adult data)

  – pool adult and ped data together (*100%* borrowing): with explicit or implicit assumptions of the similarity between two populations

- Key questions

  – How to apply historical borrowing methodology to pediatric studies with focus on ***estimation***?

  – How do the approaches compare with regard to relevant operating characteristics, e.g., bias, efficiency (sample size), etc., at various levels of similarity between the adult and paediatrics populations?

  – Under what conditions can adult data be/not be leveraged for pediatrics inference?

Possible Approaches for Utilizing Adult Data in Ped PK

- **No borrowing (0%)**
  - **M1**: utilizing ped data only
- **Full borrowing (100%)**
  - **M2**: pooling adults and ped data, using allometric scaling to account for differences
- **Partial borrowing:** level of borrowing depends on similarity between two populations
  - **M3.1**: Using **covariates** to differentiate certain model parameters between adults and ped, e.g. TVCL $^{\text{is.adult}}$
  - **M3.2: power priors** – $\pi_P(\theta|\, D_A, \gamma_0) \propto \pi_A(\theta)\, L(\theta|D_A)^{\gamma_0}$, pediatric prior π_P proportional to adult prior π_A times adult likelihood to γ_0 power; common θ for adults and pediatrics; γ_0 will be determined by the adult and pediatric data
  - **M3.3**: **commensurate power priors**

    e.g. $\log(TVCL_A) \sim N(\mu_A, \sigma_{A^2})$,

    $\log(TVCL_p) \sim N(\mu_P, \sigma_{p^2})$,

    $\mu_P \sim N(\mu_A, \sigma_{0^2})$
- **Other potential methods: test for statistical significance of difference between adults and pediatrics – 100% pooling or no pooling, accordingly**

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Simulations

Simulation Design

- Trial Design
  - A single dose PK study: 1 mg for both adults and paediatrics
  - Sample sizes
    - Adults: N=100 with a median body weight of ***70 kg*** and CV of 30-%
    - Paediatrics: two age groups, N=7 per age group
      - age group 1: median body weight = ***20 kg*** and CV=30%
      - age group 2: median body weight = ***45 kg*** and CV=30%
    - *Adults : Paediatrics = 100:14 ~* ***7:1***
  - PK samples
    - Adults: 5 PK samples: @ 0.05, 0.15, 0.3, 0.6 and 1
    - paediatrics:3 samples (D-opt): at 0.05, 0.3, and 1
    - Adults: Paediatrics = (100*5) : (14*3) ~ ***12:1***

Simulation Design (cont.)

- Assumed PK model
  - One-compartment model with first-order input
    - CL_i = TVCL $(WT/70)^{\square}$ $e^{\eta 1,i}$
    - V_i = *TVV (WT/70)* $e^{\eta 2,i}$
    - $C_i(t) = \mu_i(t)\, e^{\varepsilon\, i,t}$
- Model fitting
  - One compartment model was fitted to the data
    - For pooling method: no additional parameter was included to account for possible differences in PK parameters
    - For covariate and commensurate priors approaches, parameters to address potential PK ***differences*** in ***CL*** and ***V*** between two populations were included
  - Parameters of interest: CL at 20 and 45 kg
  - Metrics
    - Percent bias
    - MSE, relative efficiency, and relative efficiency gain over ped alone

Simulation Design (cont.)

- Data generating: ***576*** different sets of adult PK profiles (scenarios), one pediatrics

Parameter	Pediatrics	Adults
Ka	10	10, 5
TVCL	0.5	0.5, 0,55, 0.60, 0.65, 0.70, 0.75
TVV	0.2	0.2, 0.22, 0.24, 0.26, 0.28, 0.30
(allometric parameter)	0.75	0.75
$_{LogCL}$	30%	30%, 15%
$_{logV}$	30%	30%, 15%
	30%	30%, 15%

- Note
  - 1,000 simulated PK studies for each of 576 adult scenarios, and 5,000 for pediatrics

No Borrowing

Simulation Results - Pediatric data alone (no borrowing)

- Based on 5,000 simulated trials

Parameter	Assumed	Estimate	95% Creditable Interval
Ka	10	9.27	(3.82-14.30)
TVCL	0.5	0.47	(0.30-0.70)
TVV	0.2	0.19	(0.08-0.26)
□ (allomeric parameter)	0.75	***0.65***	(0.18-1.08)
$\square_{LogCL}$	30%	33%	(0.14-0.51)
$\square_{logV}$	30%	32%	(0.12-0.53)
□	30%	31%	(0.20-0.43)
CL at 20 kg	0.195	0.204	(0.156-0.264)
CL at 45 kg	0.357	0.347	(0.260-0.442)

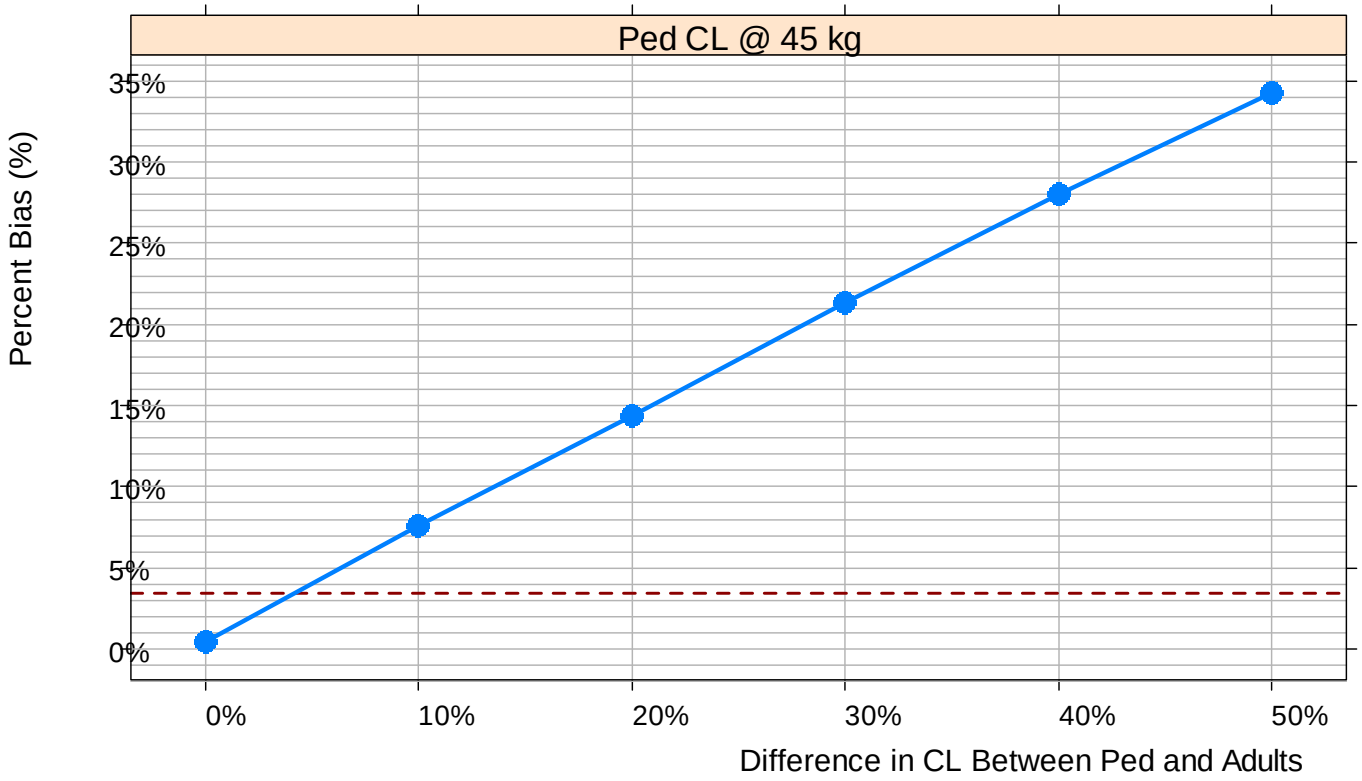
- Limited number of pediatic subjects with body weight around 70kg → may introduce bias

Full Borrowing

Simulation Results – pooling (full borrowing)

Percent bias: CL @ 45kg

- When two populations can only differ in clearance

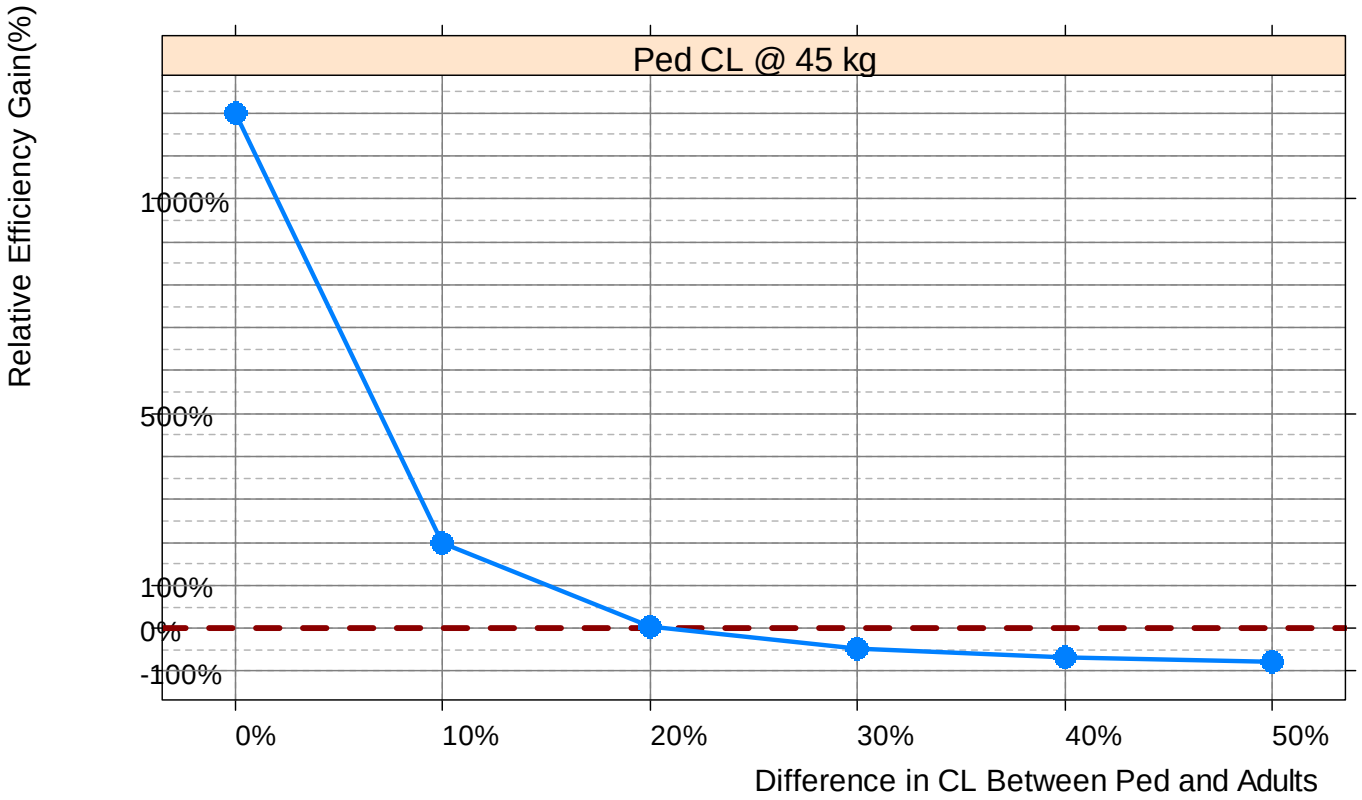


- bias increases as difference in CL increases
- Note: percent bias = -3.5% for no borrowing (ped. data only)

Simulation Results – pooling (full borrowing)

Relative efficiency gain: CL @ 45kg

- When two populations can only differ in clearance

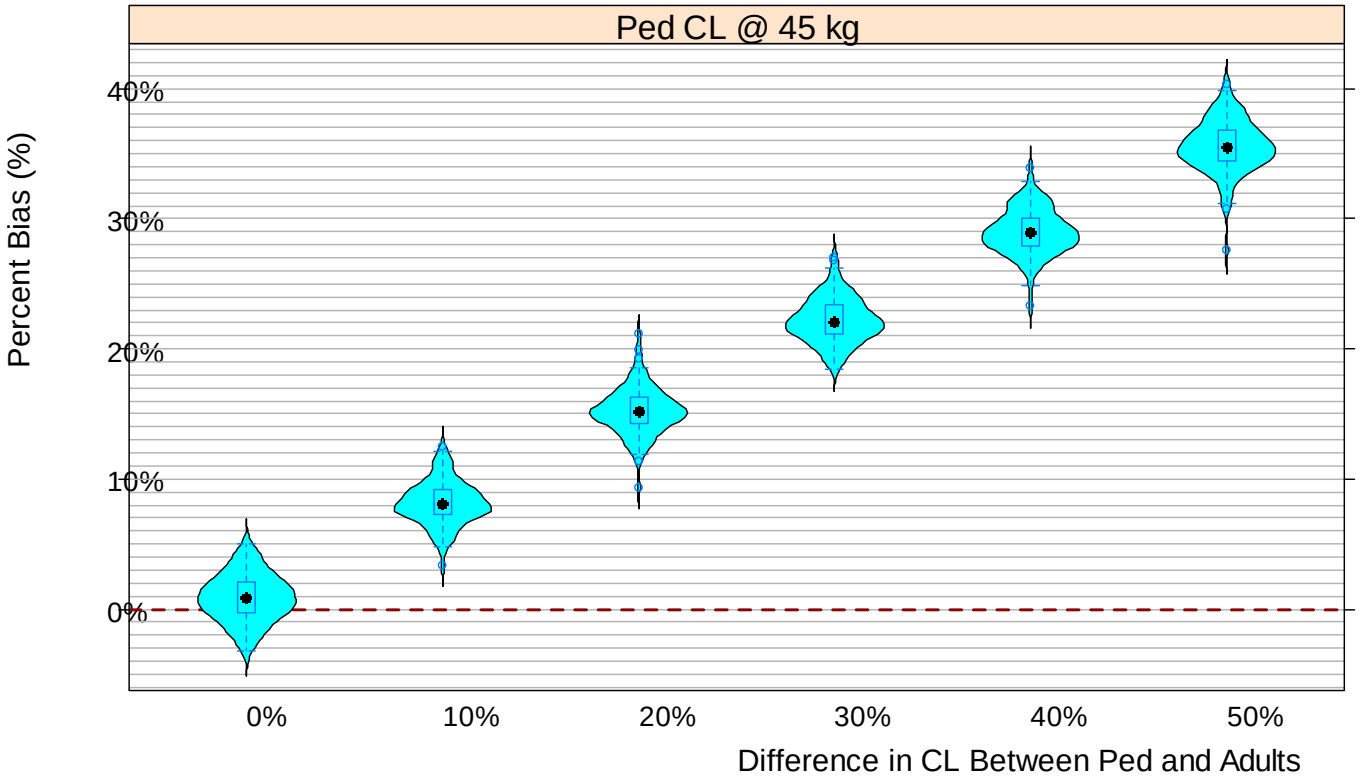


- Tremendous gains → popPK models are identical
- Trade-off between bias and efficiency

Simulation Results – pooling (full borrowing)

Percent bias: CL @ 45kg

- Considered all 576 scenarios

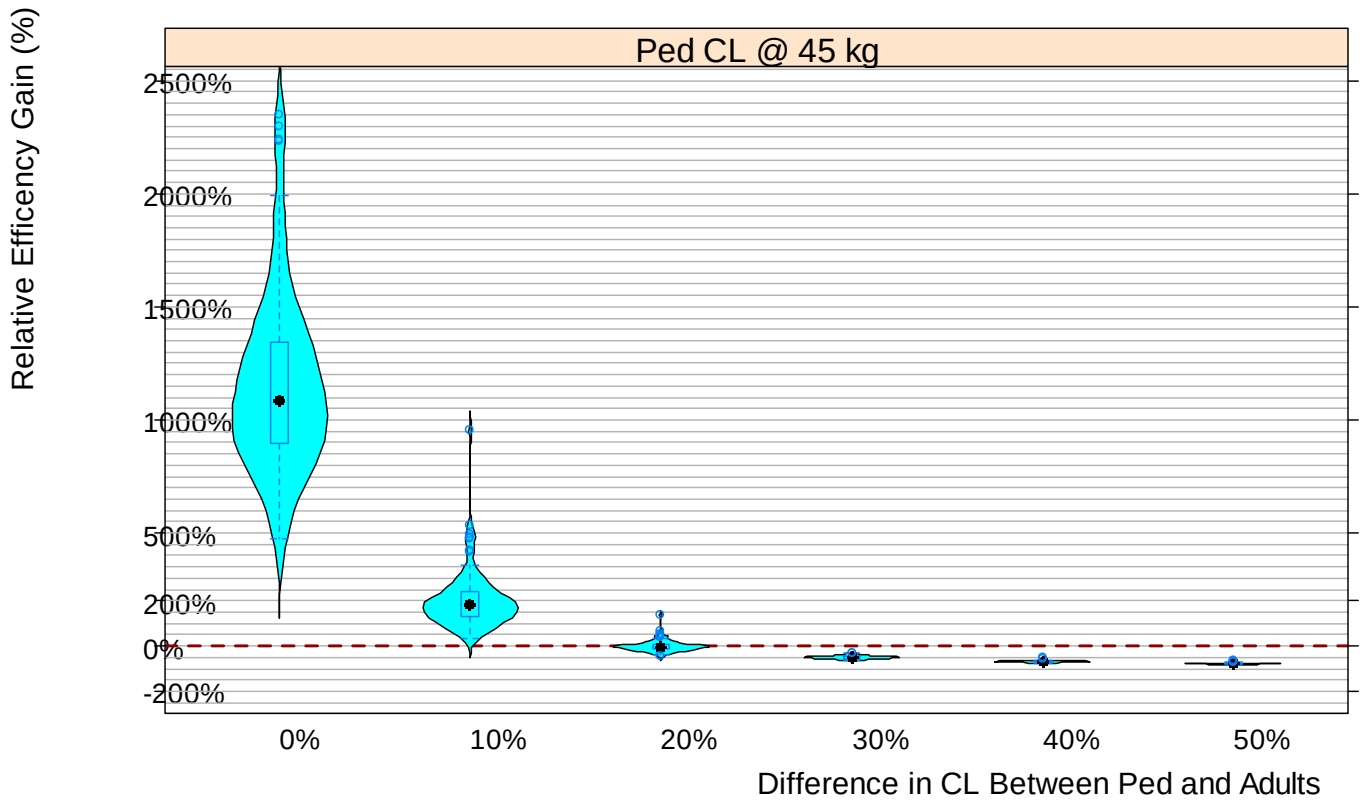


- As expected, bias increases as difference in CL increases

Simulation Results – pooling (full borrowing)

Relative efficiency gain: CL @ 45kg

- Considered all 576 scenarios



- Pooling can enhance efficiency greatly, if difference in clearance is rather moderate

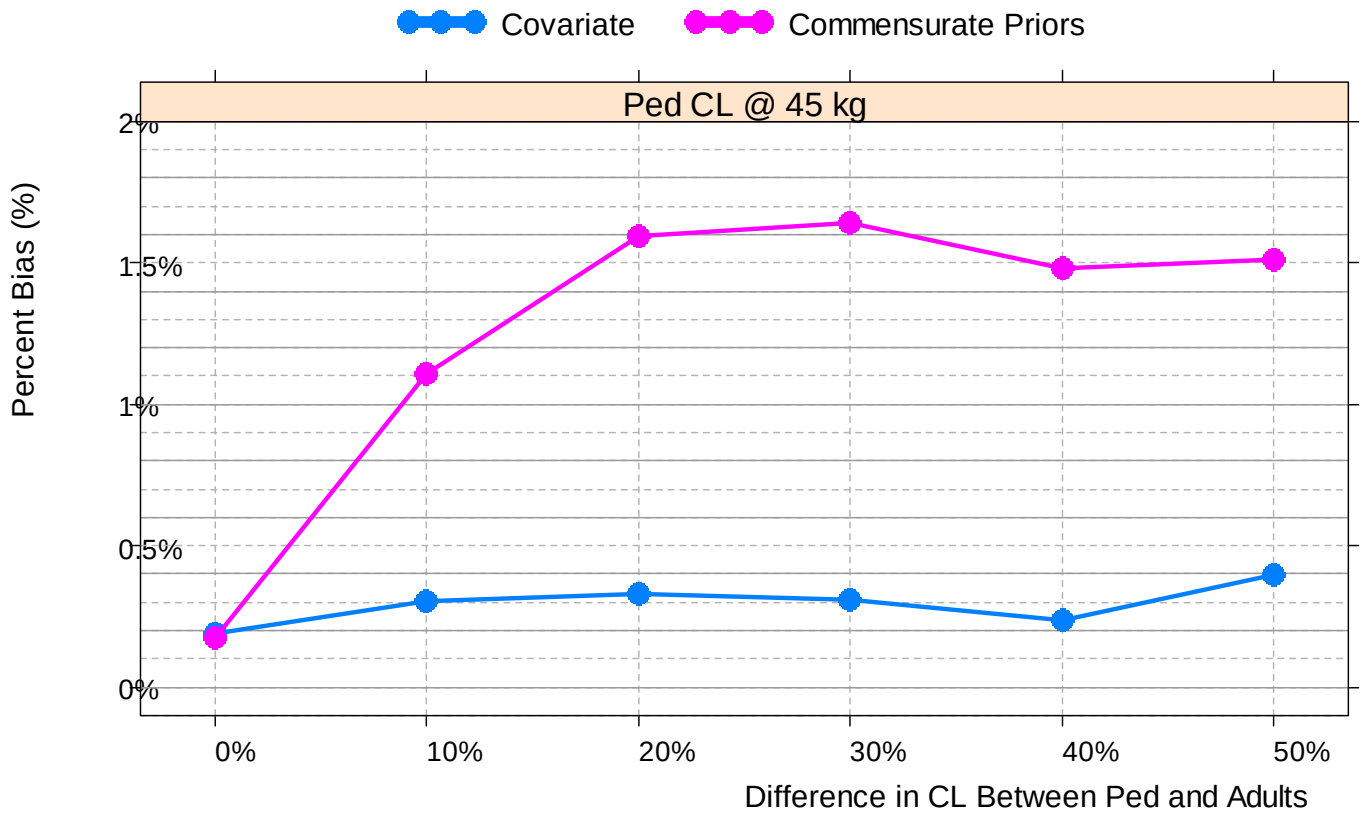
Partial Borrowing:

covariate and commensurate priors

Simulation Results – partial borrowing

Percent Bias: CL @ 45kg

- When two populations can only differ in clearance

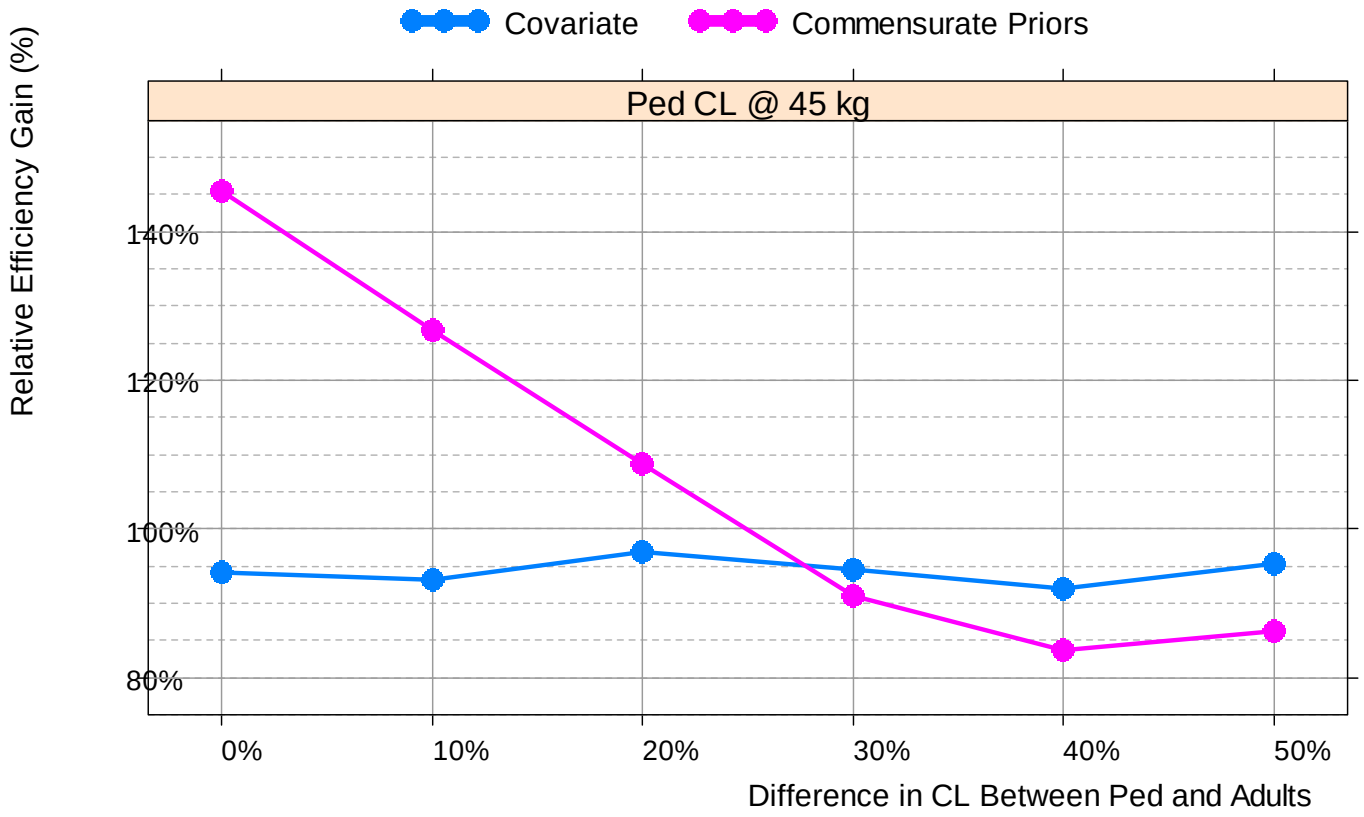


- Minimal bias from both methods

Simulation Results – partial borrowing

Relative efficiency gain: CL @ 45 kg

- When two populations only differ in clearance

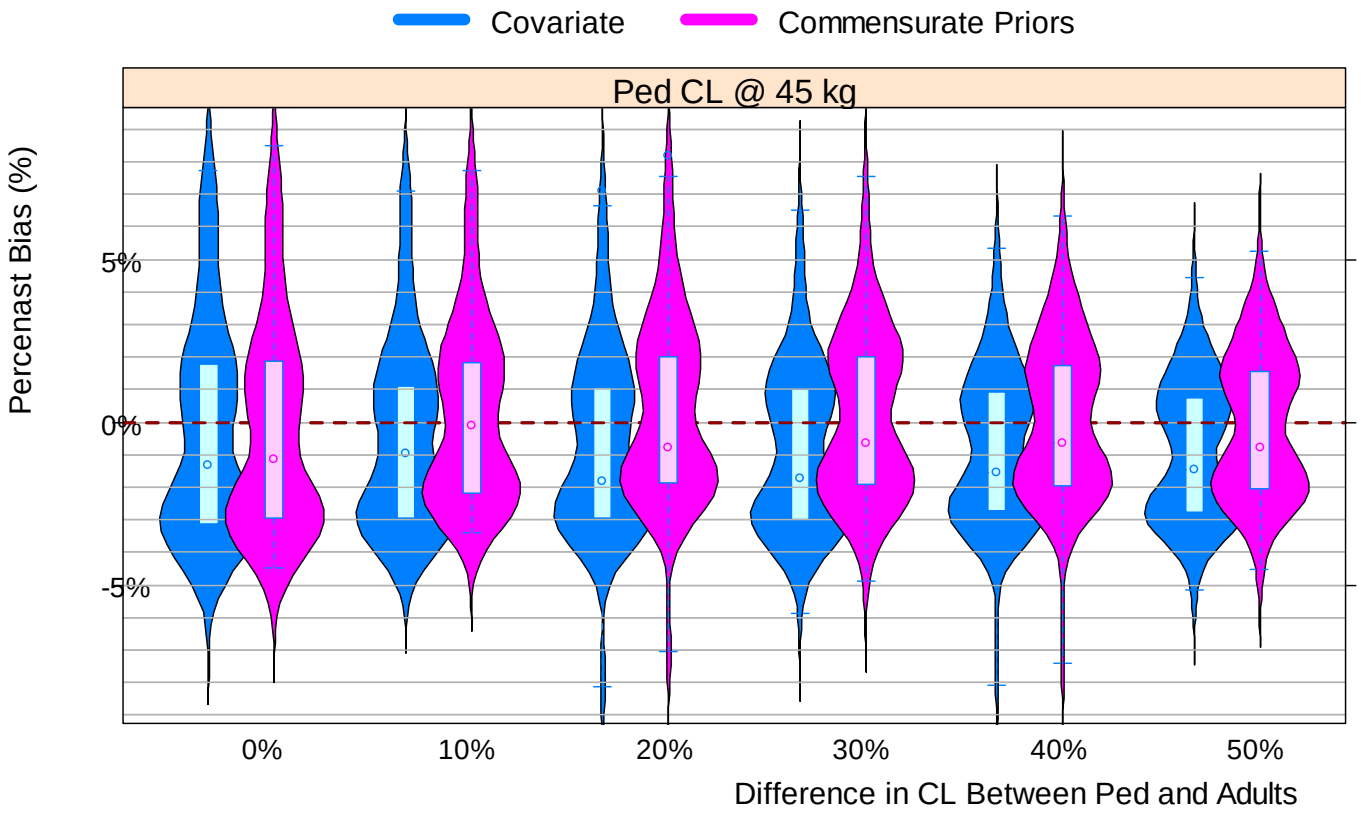


- Efficiency gains were observed – more from commensurate priors when two means are closer to each other

Simulation Results – partial borrowing

Percent Bias: CL @ 45 kg

- Considered all 576 scenarios

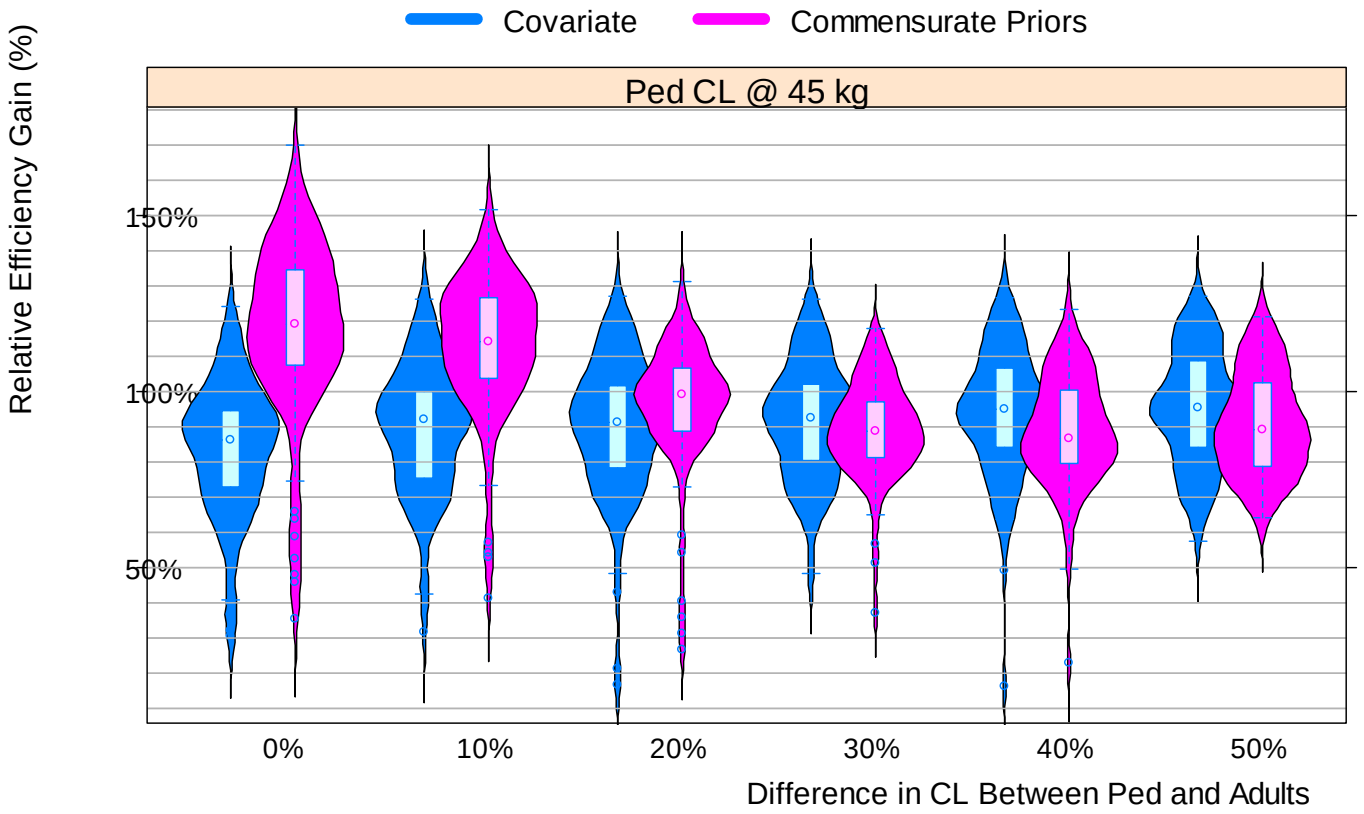


- bias are within +/- 10%

Simulation Results – partial borrowing

Relative efficiency gain: CL @ 45 kg

- Considered all 576 scenarios



- Efficient gain in all cases

Concluding Remarks

- Ped data alone (no borrowing) might not be sufficient to characterize the PK profiles due to limited number of subjects studied and limited PK samples collected. Leveraging adults' data could be helpful

- Pooling (full borrowing)
  - when the PK of adults and pediatrics was similar after adjusting for body size, tremendous efficiency gain was observed,
  - when the PK of adults and pediatrics was different ($\geq$ 20%), no gain or loss of efficiency, and significant increase in bias

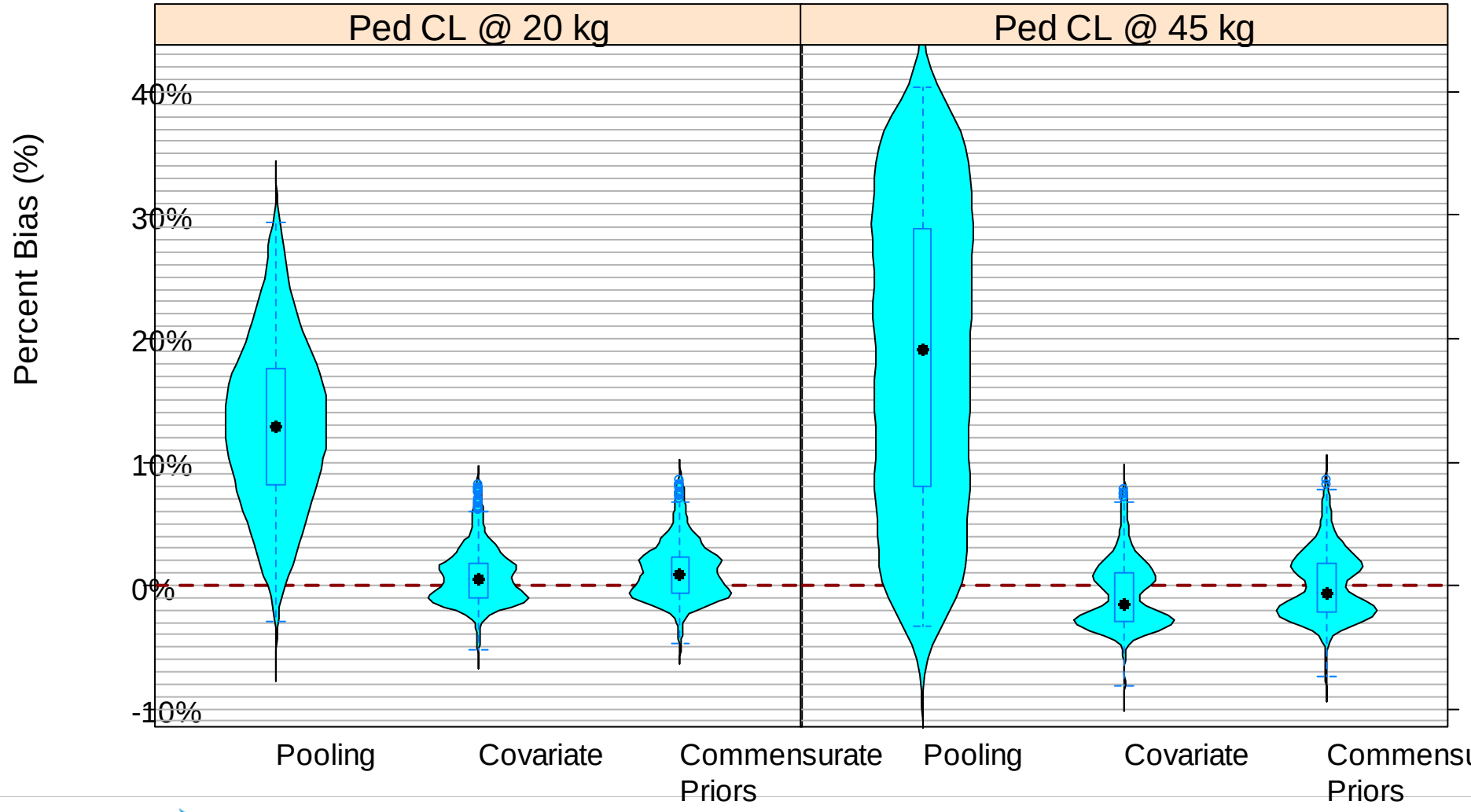
Concluding Remarks

- For partial borrowing (covariate and commensurate priors approaches)
  - the percent bias are within +/- 10% in all 576 scenarios
  - relative efficiency gain was observed in all scenarios with a median gain of 82%
  - comparisons between methods
    - covariate approach seems to produce estimates with slightly less bias (~ 1% better)
    - When PK profiles are similar, commensurate priors approach is more efficient than that of covariate -- up to 50% more efficient
- Overall, our simulation results suggest
  - leveraging adult data can greatly enhance the ability to characteristics ped PK profile
  - the commensurate priors approach is the most robust and efficient method

Backup

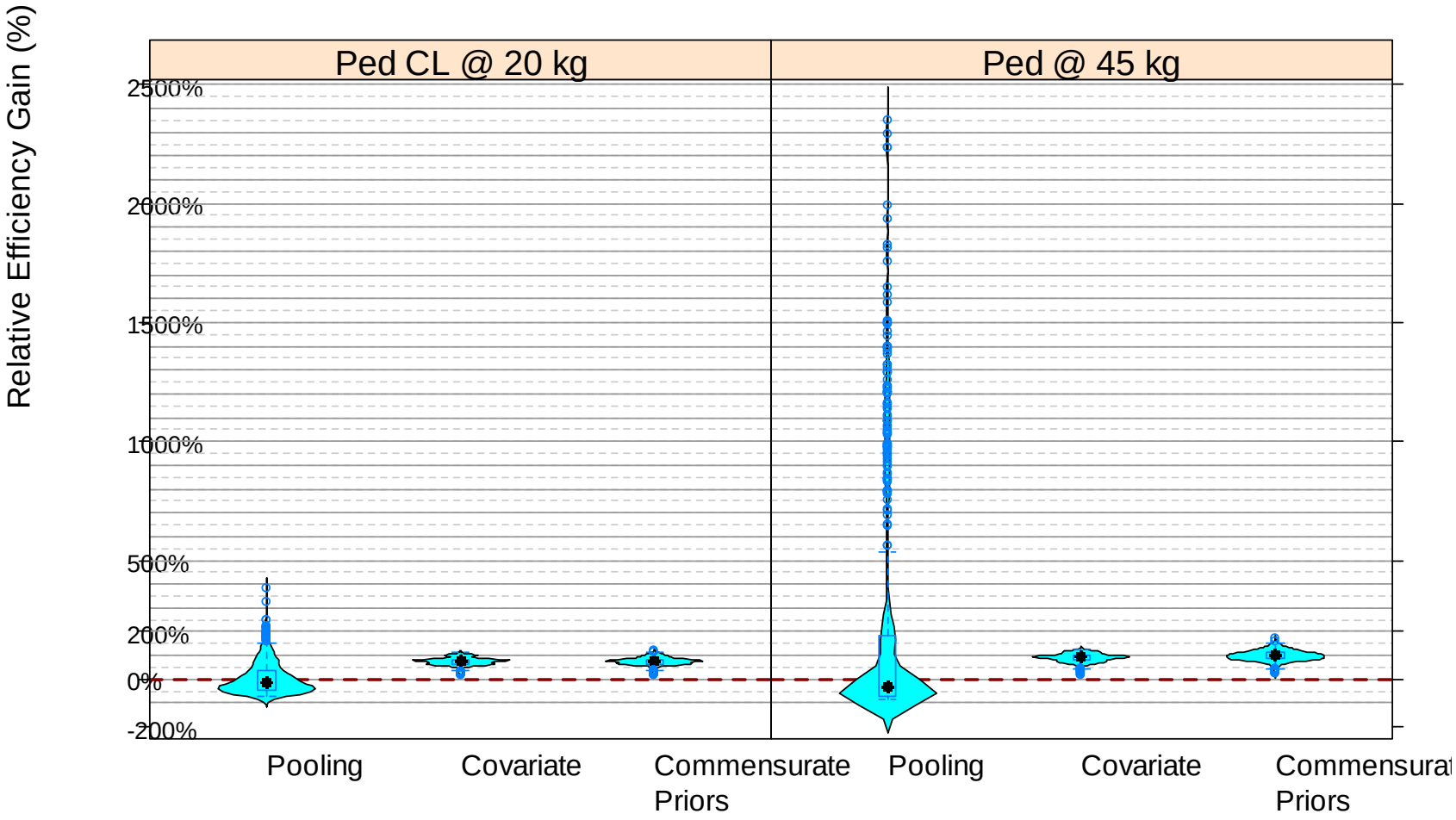
Simulation Results

Percent bias in estimation



Simulation Results – pooling (full borrowing)

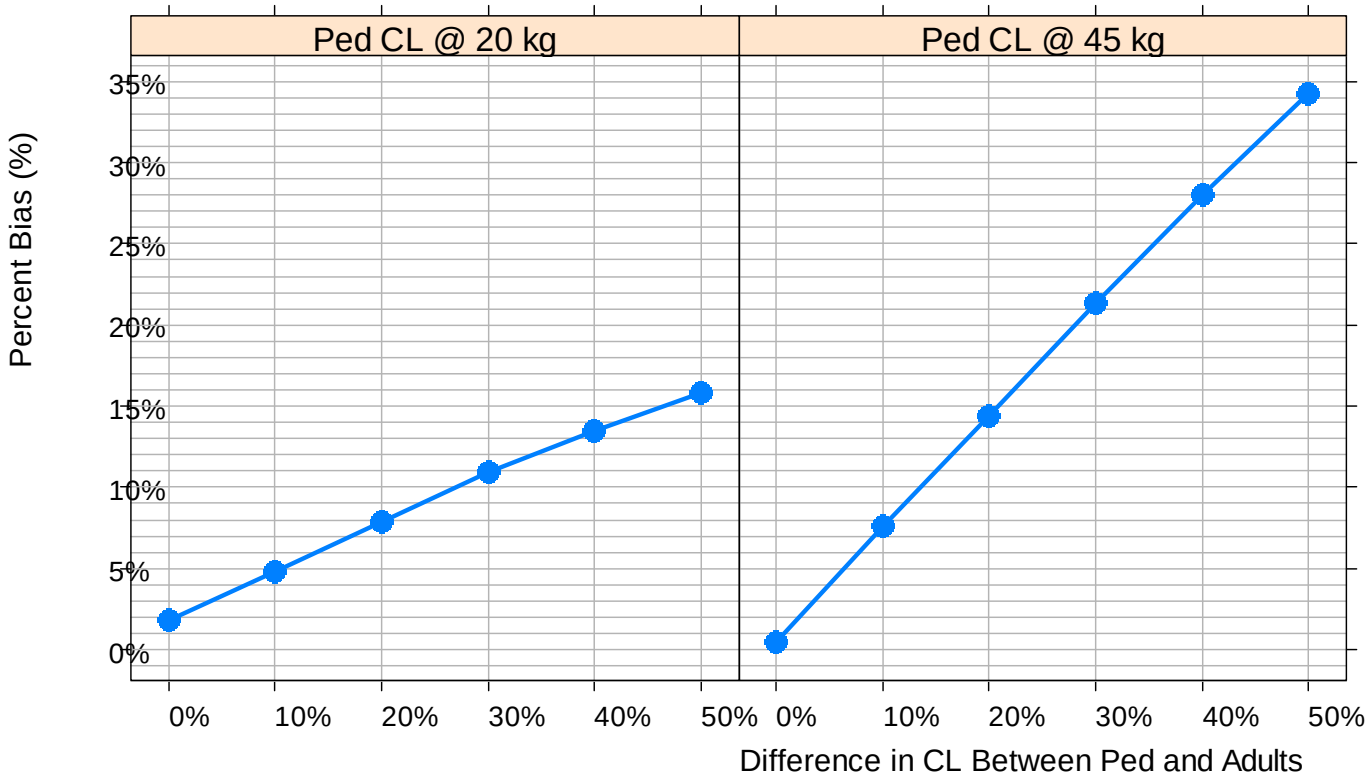
Relative efficiency gain



Simulation Results – pooling (full borrowing)

Percent bias in estimation

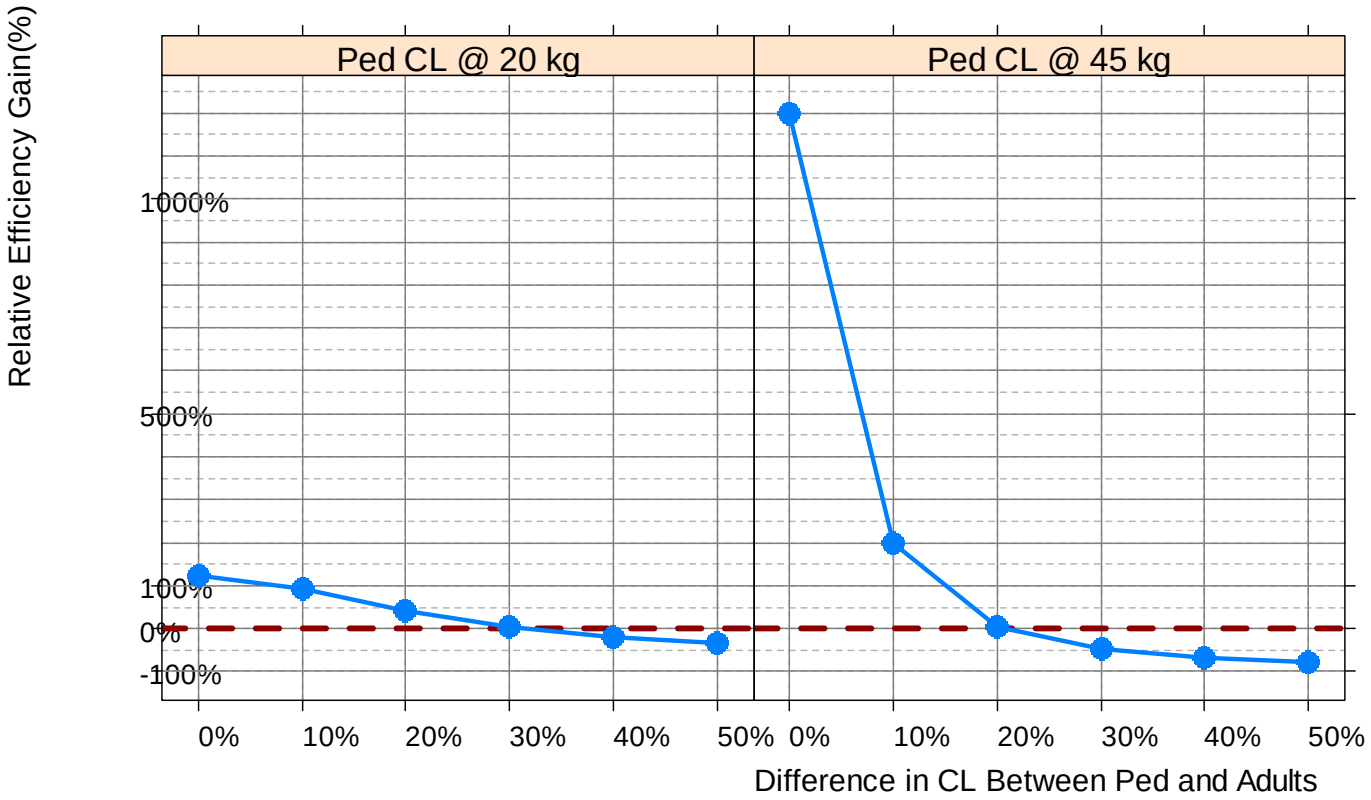
- Assumed only difference in clearance



Simulation Results – pooling (full borrowing)

Relative efficiency gain

- Assumed difference only in clearance between adults and pediatrics



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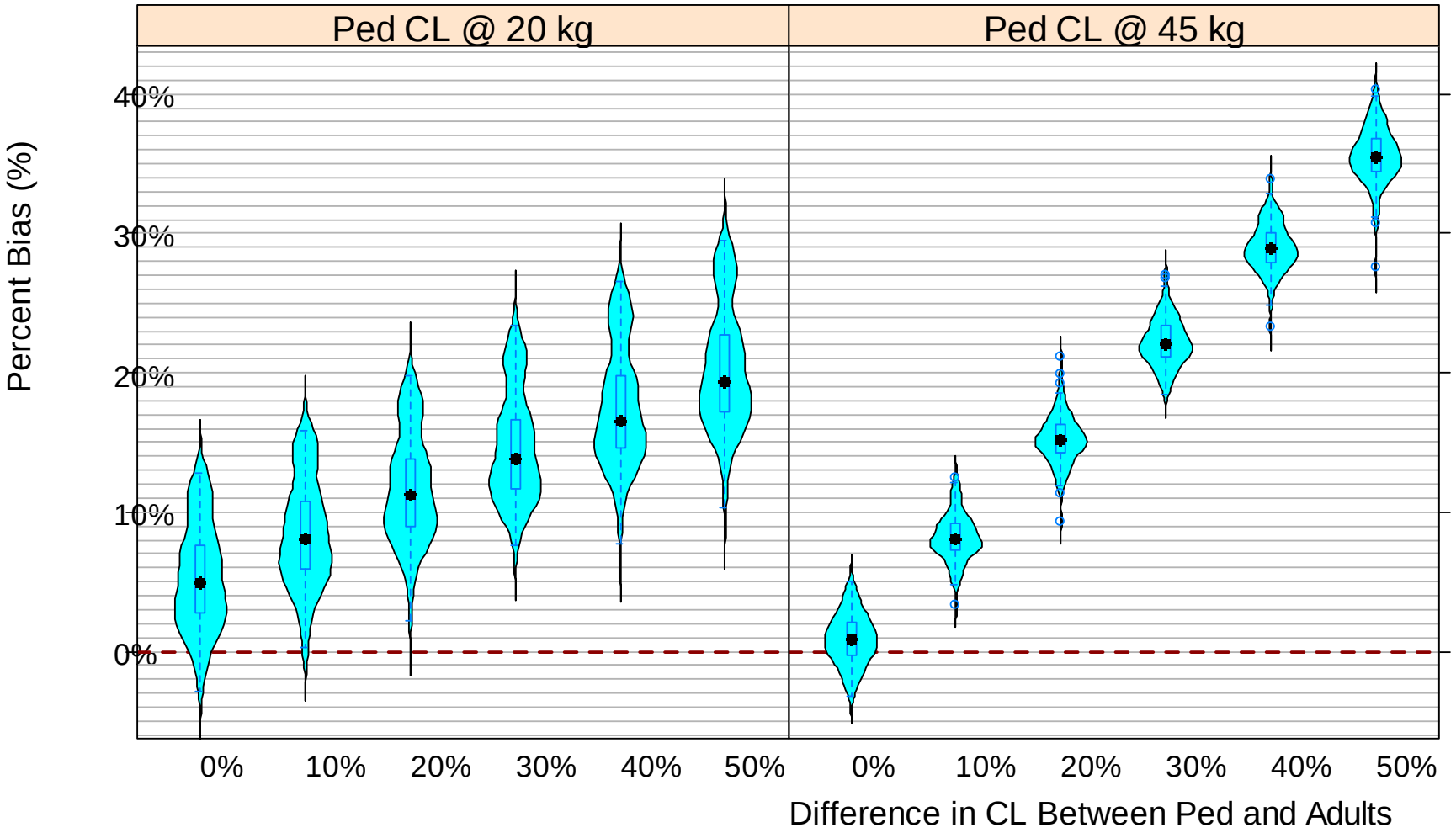
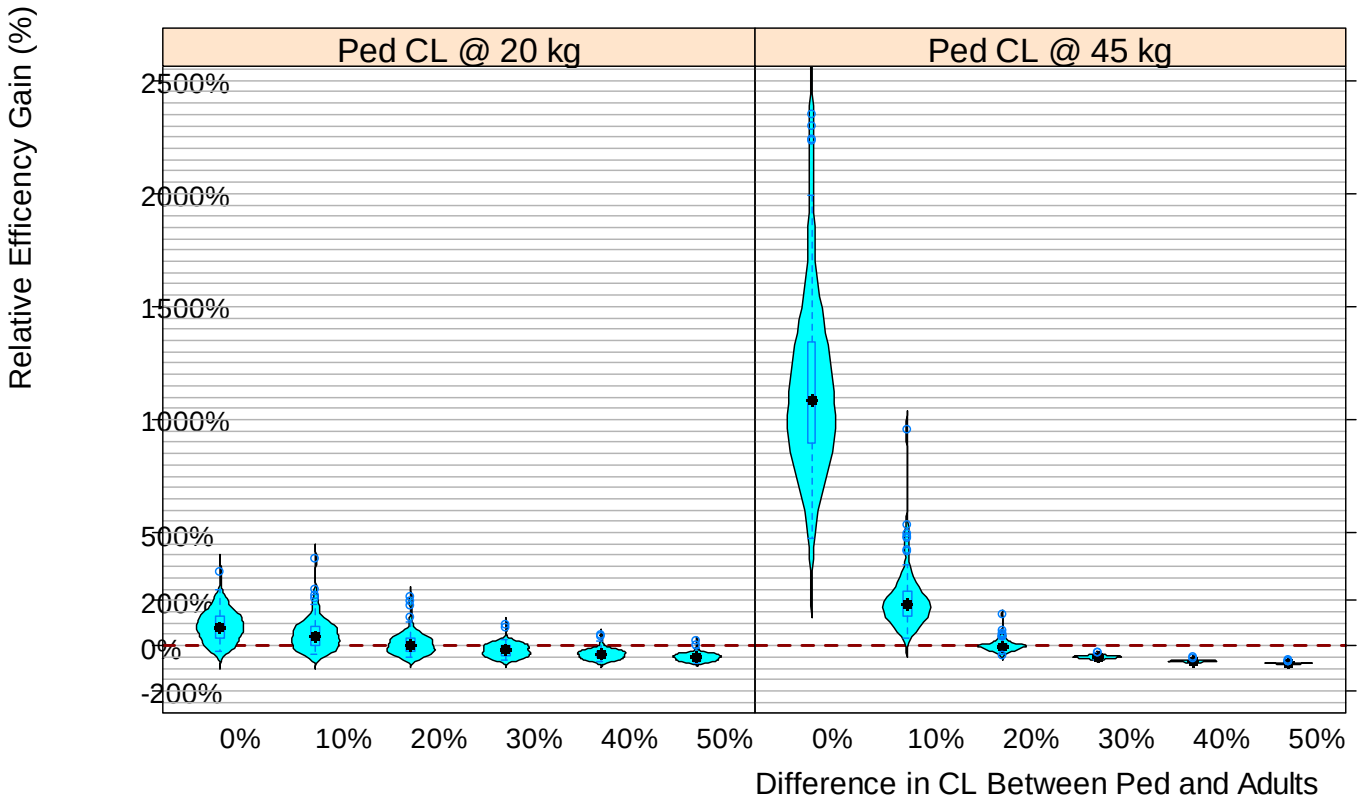


Simulation Results – pooling (full borrowing)

Relative efficiency gain

- Considered all 576 scenarios



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