



Objective

We propose a new method based on CWRES modelling [1], to assess prediction bias at a given value of an independent variable (IDV). This is done by back-extrapolating the bias in CWRES using to the first order conditional estimation (FOCE) approximation.

We illustrate this method by assessing bias for two glucose homeostasis models: the integrated glucose insulin (IGI) model and the integrated minimal model (IMM) [2,3,4].

Both models were proposed to describe simultaneously the glucose-insulin regulation system following an intravenous glucose tolerance test (IVGTT) in healthy subjects.

Methods

Theory:

At each bin for N number of bins of the IDV:

- let Y^* be the predictions from the true model for the observations y with residuals r .

$$E(r(Y^*)) = 0 \text{ \& \; } Var(r(Y^*)) = 1.$$

- let Y^- be the predictions from a misspecified model and b be the known bias.

$$E(r(Y^-)) = b.$$

- let the distance δ be the difference between Y^* and Y^- .

$$\delta = Y^- - Y^*$$

$$E(r(Y^* + \delta)) = E(Var(Y^*)^{-1/2}(y_i - E(Y^*) - \delta)) = b$$

$$\delta = -Var(Y^*)^{1/2}b$$

At each bin, predictions from misspecified model Y^- need to be corrected by $-\delta$.

How:

- CWRES is treated as a dependent variable.
- A base model estimates mean and variance of the CWRES distribution.

$$\hat{y}_i = \theta_1 + \eta_i + \tilde{\epsilon}_i$$

- The base model is extended to estimate different means for 10 bins of the IDV at cut points $X_1, \dots, X_9$

$$\text{If } (\min(\text{IDV}) < \text{IDV} < X_1) \quad \hat{y}_i = \theta_1 + \eta_i + \tilde{\epsilon}_i$$

$$\text{If } (X_1 < \text{IDV} < X_2) \quad \hat{y}_i = \theta_2 + \eta_i + \tilde{\epsilon}_i$$

.....

$$\text{If } (X_9 < \text{IDV} < \max(\text{IDV})) \quad \hat{y}_i = \theta_{10} + \eta_i + \tilde{\epsilon}_i$$

- Estimates of $\theta_1, \dots, \theta_{10}$ are $b \rightarrow \delta$

- $\Delta OFV_{\text{Bias}} = OFV_{\text{Extended_model}} - OFV_{\text{Base_model}}$

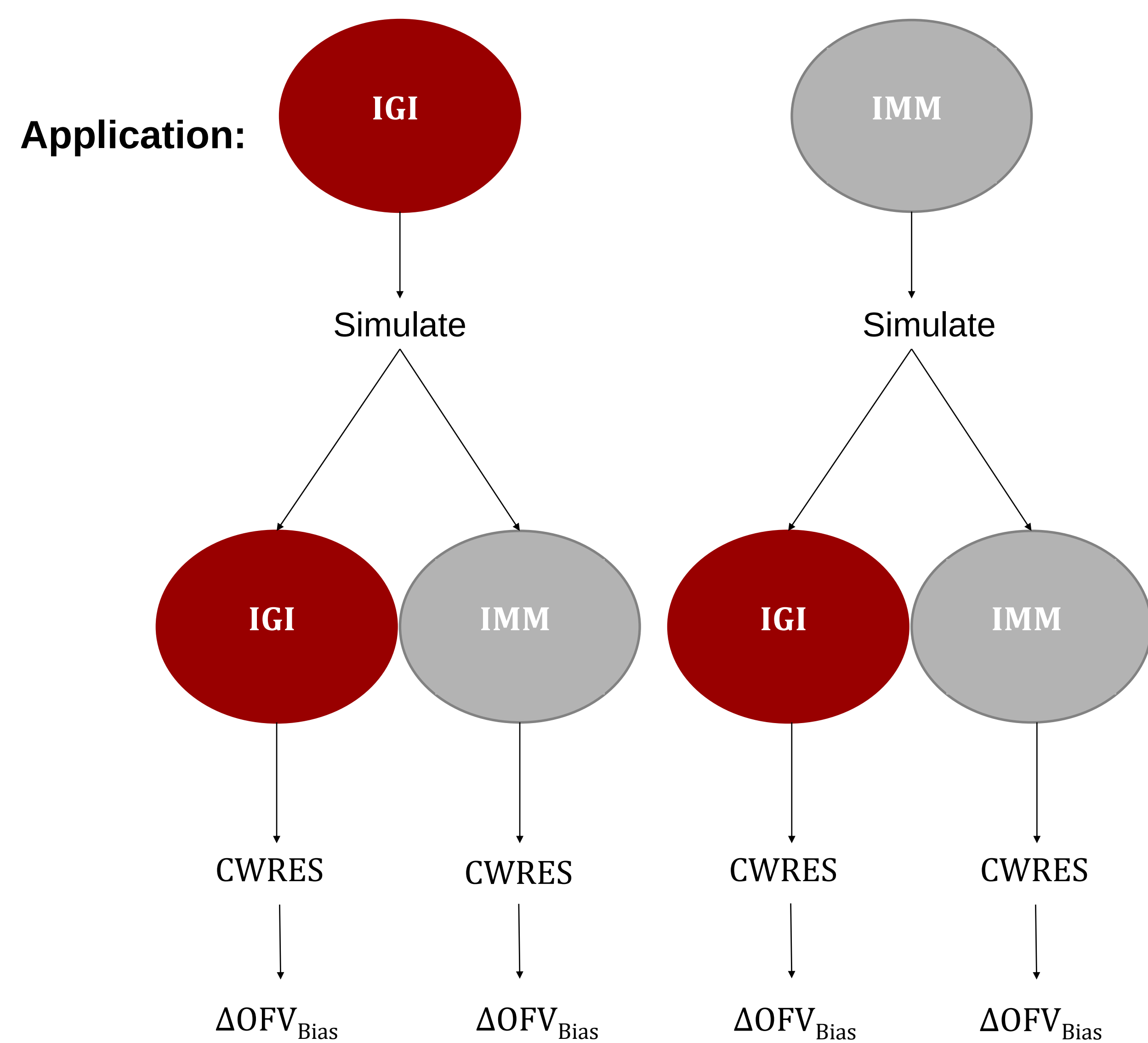


Figure 1: One dataset was simulated from each model according to a standard IVGTT protocol, then analyzed by the two models. CWRES from each model fitting was further analyzed to calculate δ and ΔOFV_{Bias} .

Time, predictions of glucose and insulin were all assessed as IDV (separate estimations) and a random binning technique was implemented to avoid binning introduced bias.

Specification for Random binning technique [5]:

- Number of bins=5
 - Minimum number of observations/bin= 25
- Step 1: Sort CWRES data by the selected IDV
- Step 2: Generate 4 bin boundaries randomly based on IDV
- Step 3: Group CWRES data based on generated bin boundaries
- Step 4: Estimate $b \rightarrow \delta$
- Step 5: Repeat steps 2 - 4 500 times.

Results

Simulation	Estimation	ΔOFV_{Bias}					
		Glucose			Insulin		
		Time	Glucose PRED	Insulin PRED	Time	Glucose PRED	Insulin PRED
IGI	IGI	13.64	6.57	6.26	5.56	2.99	3.77
	IMM	50.15	15.38	13.83	13.07	4.02	3.48
IMM	IGI	6.67	3.66	1.23	10.95	6.48	6.06
	IMM	13.14	6.43	8.58	2.92	3.34	3.69

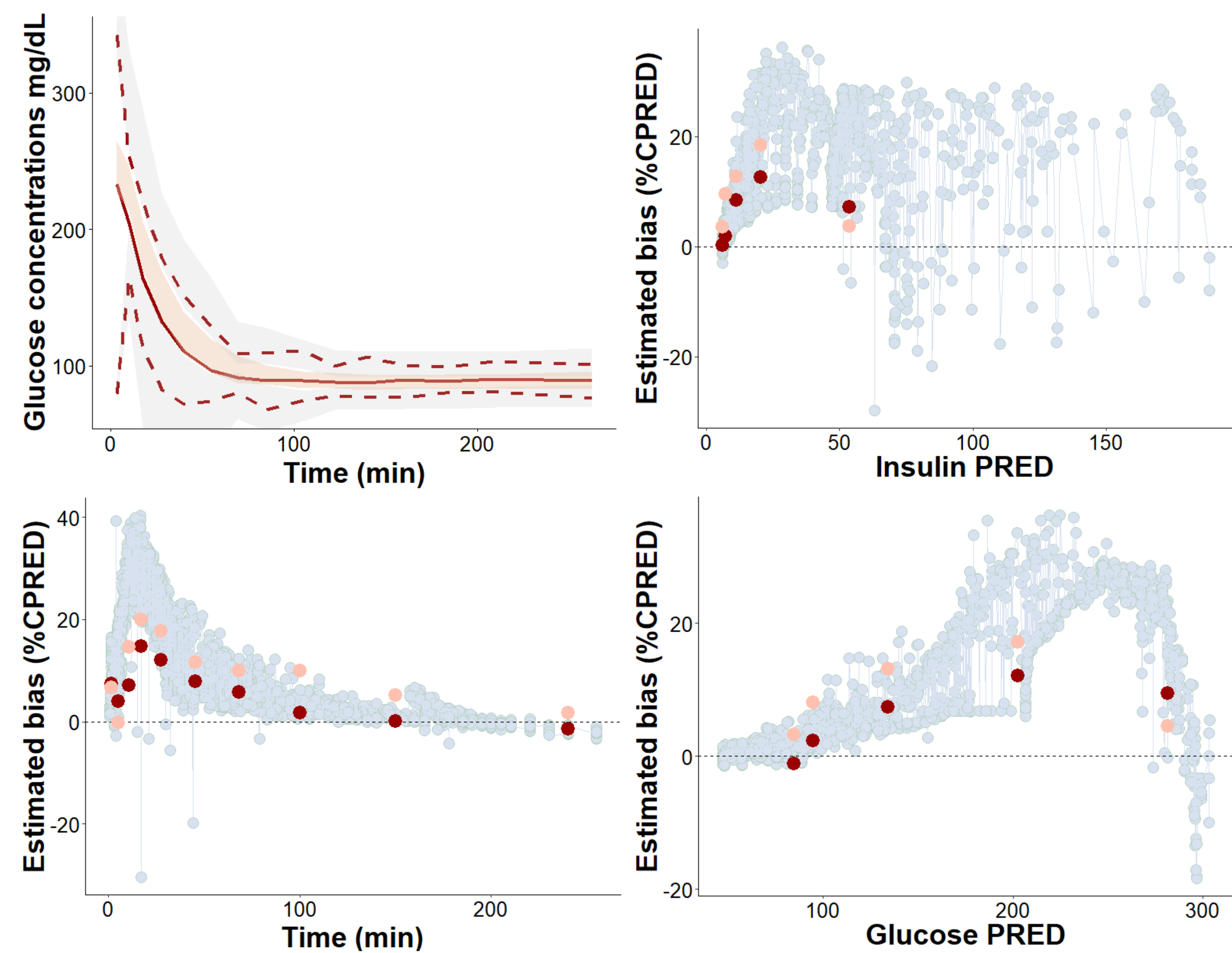


Figure 2: VPC of glucose sub-model of the IMM when fitting to data simulated from the IGI model, and plots of estimated bias (%CPRED) in glucose with standard (red) and random binning (ice blue) versus the different IDVs, over layered by %known bias (rose).

Only when data was simulated with the IGI and analyzed with the IMM was ΔOFV_{Bias} significantly difference when adjusting for the bias; although only for glucose (not insulin, figure 2).

Absolute and proportional magnitude of over prediction bias in glucose sub-model was calculated based on CWRES with three different IDVs e.g. time and predictions of glucose and insulin.

Conclusion

- ✓ New method for predication bias assessment based on CWRES was developed and successfully applied to two integrated, complex models for glucose homeostasis.
- ✓ The new method identified correctly the bias in glucose sub-model of the IMM, when this bias occurred, the magnitude of the resulting bias and the expected improvement of fit after correcting this bias.
- ✓ This new method is already implemented as part of the **qa** tool in PsN.

References

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- [3] Largajolli A., Bertoldo A., Cobelli C., & Denti P., An integrated glucose-insulin minimal model for IVGTT, PAGE 22 (2013) Abstr 2762 [www.page-meeting.org/?abstract=2762].
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- [5] Pavan Kumar V. V., & Duffull S. B. Evaluation of graphical diagnostics for assessing goodness of fit of logistic regression models. Journal of Pharmacokinetics and Pharmacodynamics 2011, 38(2), 205-222.