



Background and Objective

The integrated glucose insulin (IGI) model is a semi-mechanistic model that describes glucose and insulin concentrations in humans during glucose tolerance tests¹. The objective of this work was to investigate if the model can be scaled to describe intravenous glucose tolerance test (IVGTT) data from several preclinical species.

Methods

Glucose and insulin concentrations from IVGTTs performed in rats, mice, dogs, pigs and humans as well as the body weight of each subject was available for analysis²⁻⁷. The development was performed in three steps:

1. Allometric scaling based on body weight was investigated. The most suitable value for the allometric exponent was investigated for all parameters in the model, based on objective function value, parameter uncertainty and model complexity.
2. Species adaptations were investigated by scaling parameters with physiological factors relevant to that parameter.
3. Remaining species adaptations that could not be described by allometric scaling was investigated

The glucose and insulin baselines as well as the residual error were estimated separately for all species.

Table 1. Summary of the study designs

Species	Number of individuals	BW (kg) (RSD%)	Glucose dose (g/kg)	Insulin dose (U/kg)
Dog ⁴	11	28.7 (9)	0.3	0.03 @ 20 min
Human ⁵	14	66.5 (10)	0.25-0.33	-
Human ⁶	10	70.0 (0)	0.33	0.03 @ 20 min
Mouse ²	24	0.03 (7)	1.0	-
Pig ⁷	11	21.6 (35)	0.5	-
Rat ³	16	0.29 (7)	0.2, 0.5, 1.0	-

Results

Figure 1 show the results when theoretical values of the allometric exponent of 0.75 for clearance and 1 for volume was used. This model was improved upon and the results from the model development are presented below.

Step 1:

- Exponent for clearances, 0.87
- Exponent for glucose volumes, 0.9
- Exponent for insulin volume, 0.98
- Exponent for rate constants, -0.25 FIX
- Control mechanism power functions (GPRG, IPRG) fix to human values

Step 2:

- None of the investigated relationships improved the fit for all animals simultaneously.

Step 3:

Few parameters were estimated:

- IPRG for dogs, 3.22, higher than human value
- IFST for dogs, 207 mU, lower than scaled value
- k_{IS} for pigs, 0.104 min⁻¹, lower than scaled value
- IFST for pigs, 114 mU, lower than scaled value
- CLGI for pigs, 0.0095 L/min/mU, higher than scaled value

Simulating monkeys

Simulations of a published IVGTT study⁸ in monkeys (figure 3) show that the proposed model accurately can predict glucose and insulin concentrations in another species than the model was developed on.

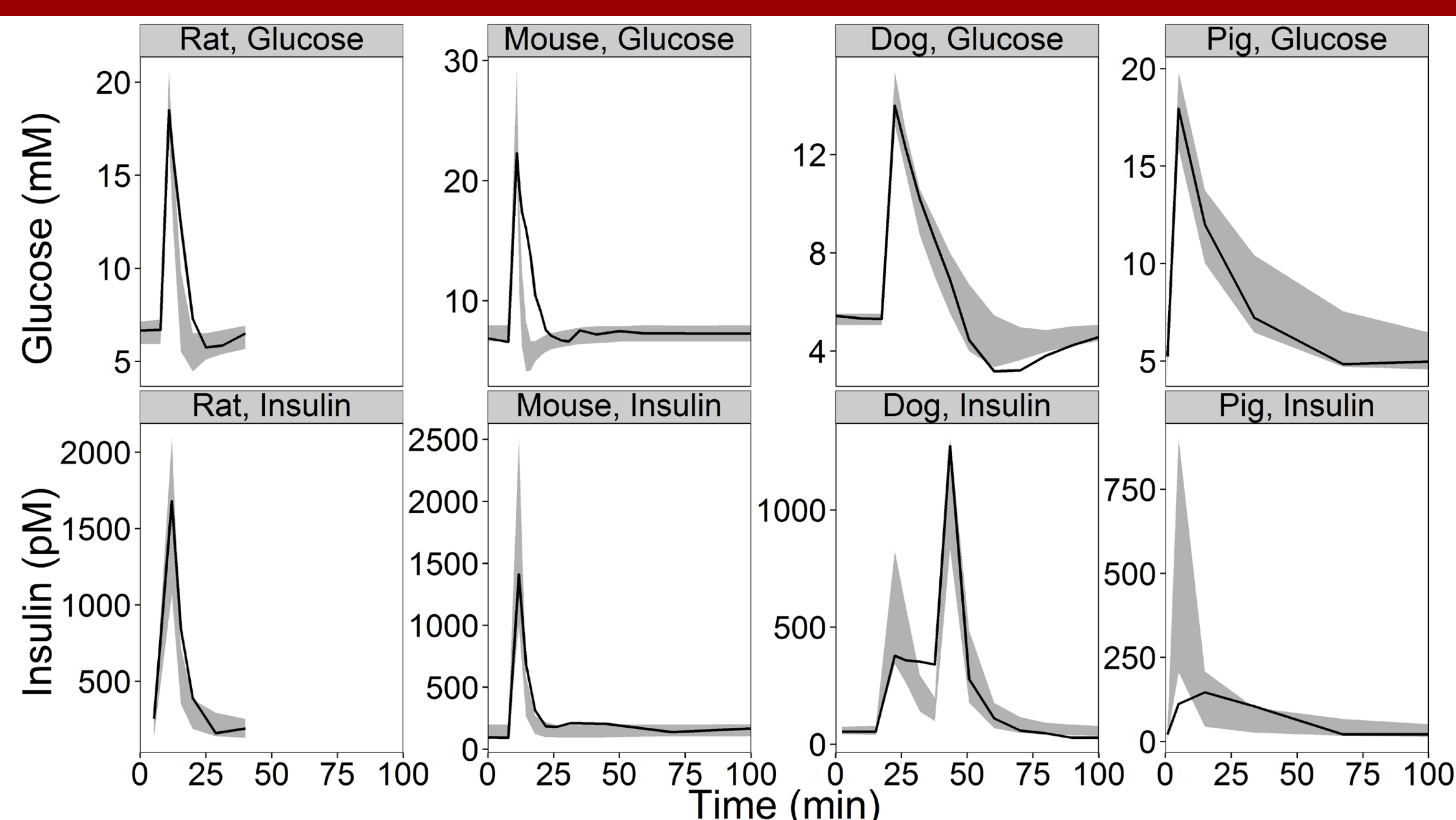


Figure 1. Visual predictive check comparing observations with simulated glucose and insulin data for the different species when the exponent for CL and V are set to the theoretical values of 0.75 and 1. The solid line is the median based on the observed data. Shaded area is the 95% confidence interval around the median based on the simulated data.

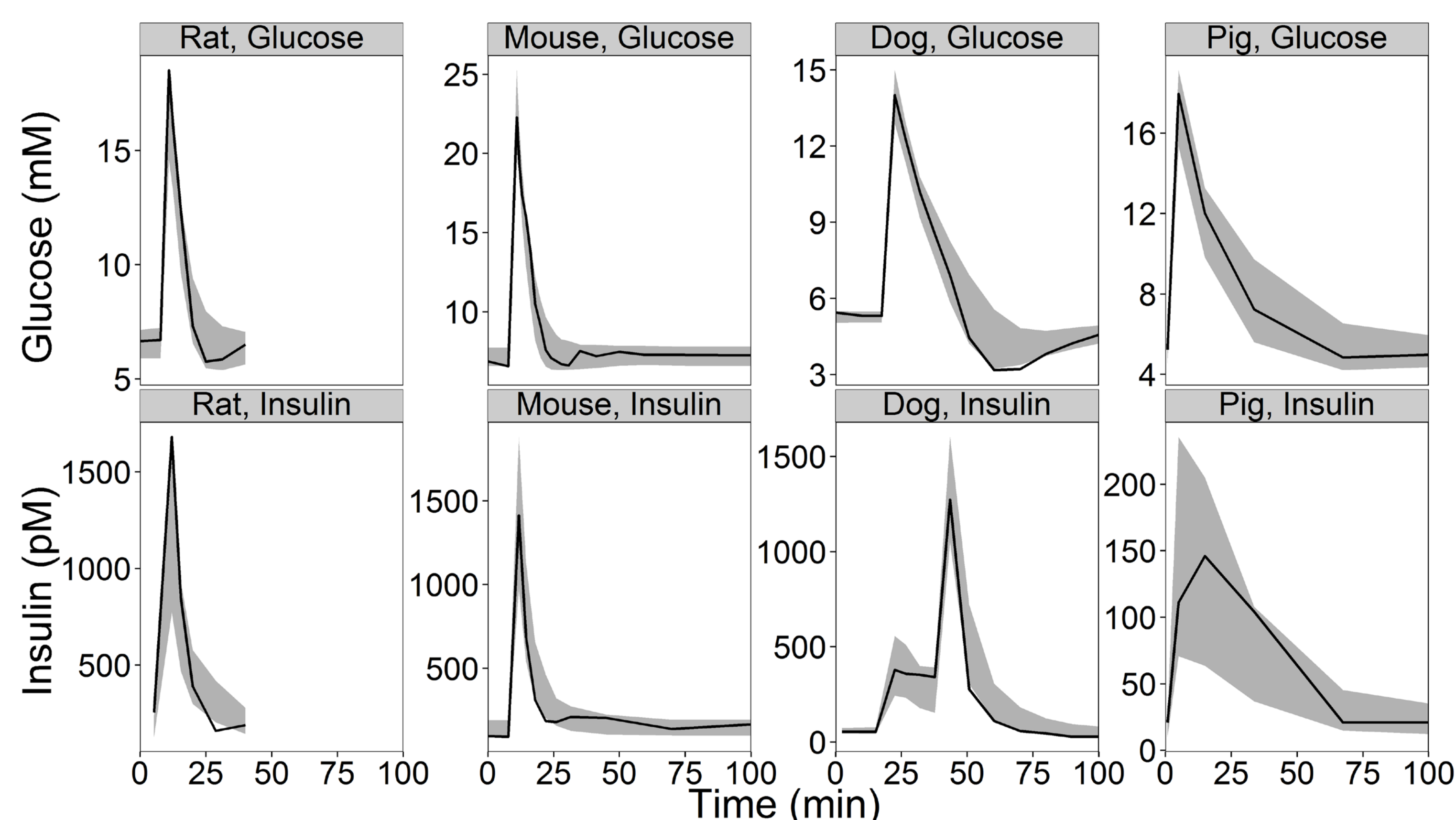


Figure 2. Visual predictive check comparing observations with simulated glucose and insulin data for the different species for the final model. The solid line is the median based on the observed data. Shaded area is the 95% confidence interval around the median based on the simulated data.

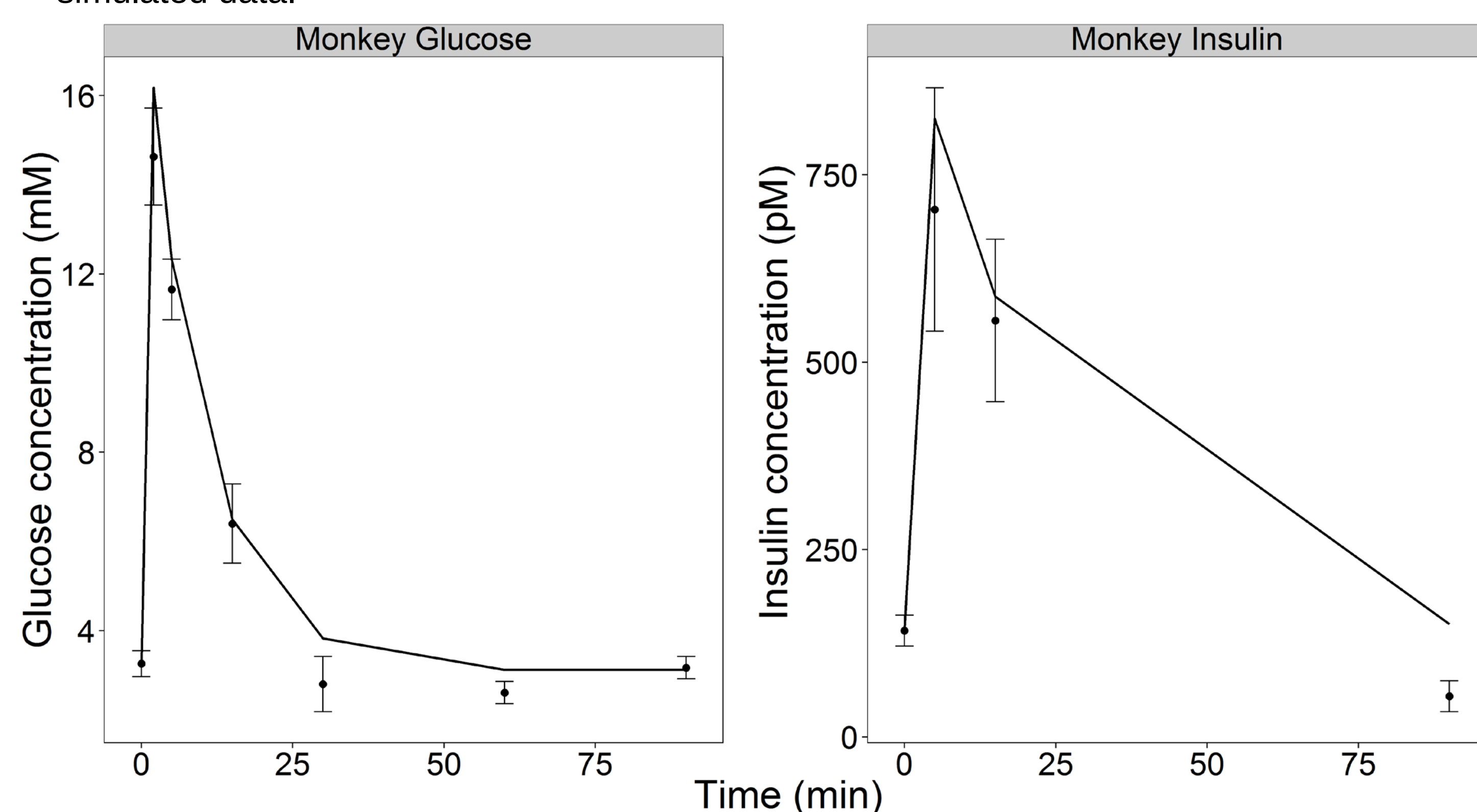


Figure 3. Simulations of a published IVGTT study in monkeys. The black dots and error bars are the observed means and standard deviations. Black line is the mean of 1000 simulated monkeys.

Conclusions

The allometrically scaled IGI model can accurately predict preclinical IVGTT data. The allometrically scaled IGI model can be used in drug development to facilitate better translations of preclinical research into clinic.

References

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