

Modelling Day-to-Day Variability of Glucose-Insulin Regulation over 12-Week Home Use of Closed-loop Insulin Delivery

Yue Ruan, MEng¹, Malgorzata E. Wilinska, PhD¹, Hood Thabit, MD¹, and Roman Hovorka, PhD¹

¹Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK.

Aims

To develop a mathematical model to quantify day-to-day variability of glucose-insulin regulation in adults with type 1 diabetes

Methods

- Conventional clinical data (CGM, insulin delivery and carbohydrate contents) were collected from 12-week home use of closed-loop insulin delivery in 8 subjects with type 1 diabetes (M/F 5/3, age 39.9±9.5 years, BMI 25.4±4.4 kg/m², HbA1c 8.4±0.6%) [1]
- A compartment model was developed comprising five compartments and seven individual parameters

$$\begin{aligned} \frac{dx_1(t)}{dt} &= -\frac{1}{t_{max,IA}} x_1(t) + \frac{u_i(t)}{60} \\ \frac{dx_2(t)}{dt} &= \frac{1}{t_{max,IA}} (x_1(t) - x_2(t)) \\ X(t) &= \frac{1000 \cdot x_2(t)}{t_{max,IA} MCR W} \end{aligned} \quad \begin{aligned} \frac{da_1(t)}{dt} &= -\frac{1}{t_{max,G}} a_1(t) + \delta_{ij}(t) u_G(t_j) \\ \frac{da_2(t)}{dt} &= \frac{1}{t_{max,G}} (a_1(t) - a_2(t)) \\ U_M(t) &= \frac{5.556 \cdot A_G a_2(t)}{t_{max,G} V_G W} \end{aligned} \quad \frac{dG(t)}{dt} = -S_i(X(t) - X_s) + U_M(t) - K(G(t) - G_s)$$

- A Bayesian hierarchical framework was utilized to estimate individual parameters

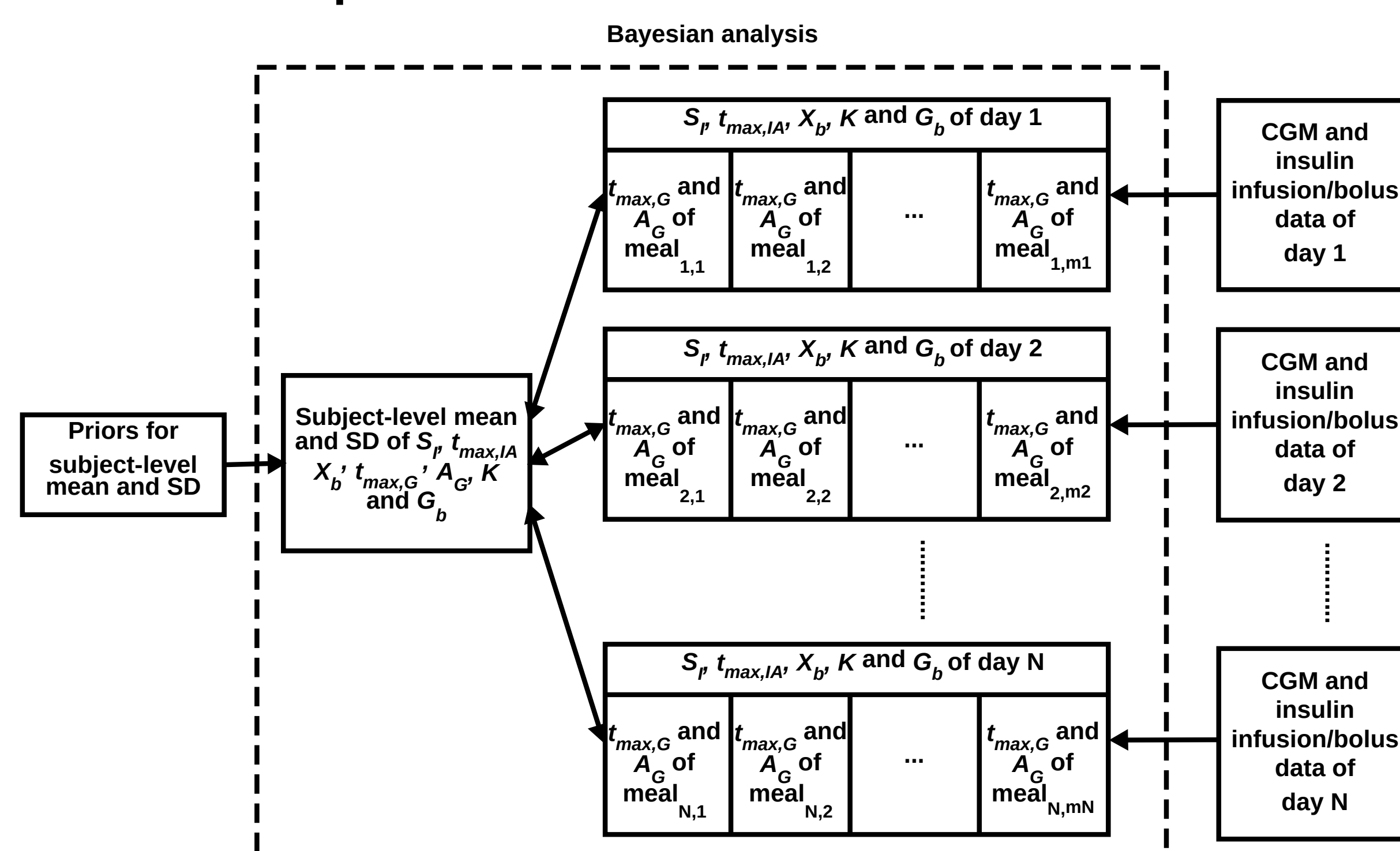


Fig. 1. Bayesian hierarchical analysis of the glucose-insulin regulation. Estimates of the day-level parameters S_p , $t_{max,IA}$, X_b , $t_{max,G}$, A_G , K and G_b were made in parallel with the subject-level mean and SD in one subject over N days. The advantage of Bayesian estimation is the possibility of 'information flow' between days since the day-level estimates rely on the observed glucose-insulin data of that day, and also on the subject-level distribution, which in turn is derived totally of individual day data.

Results

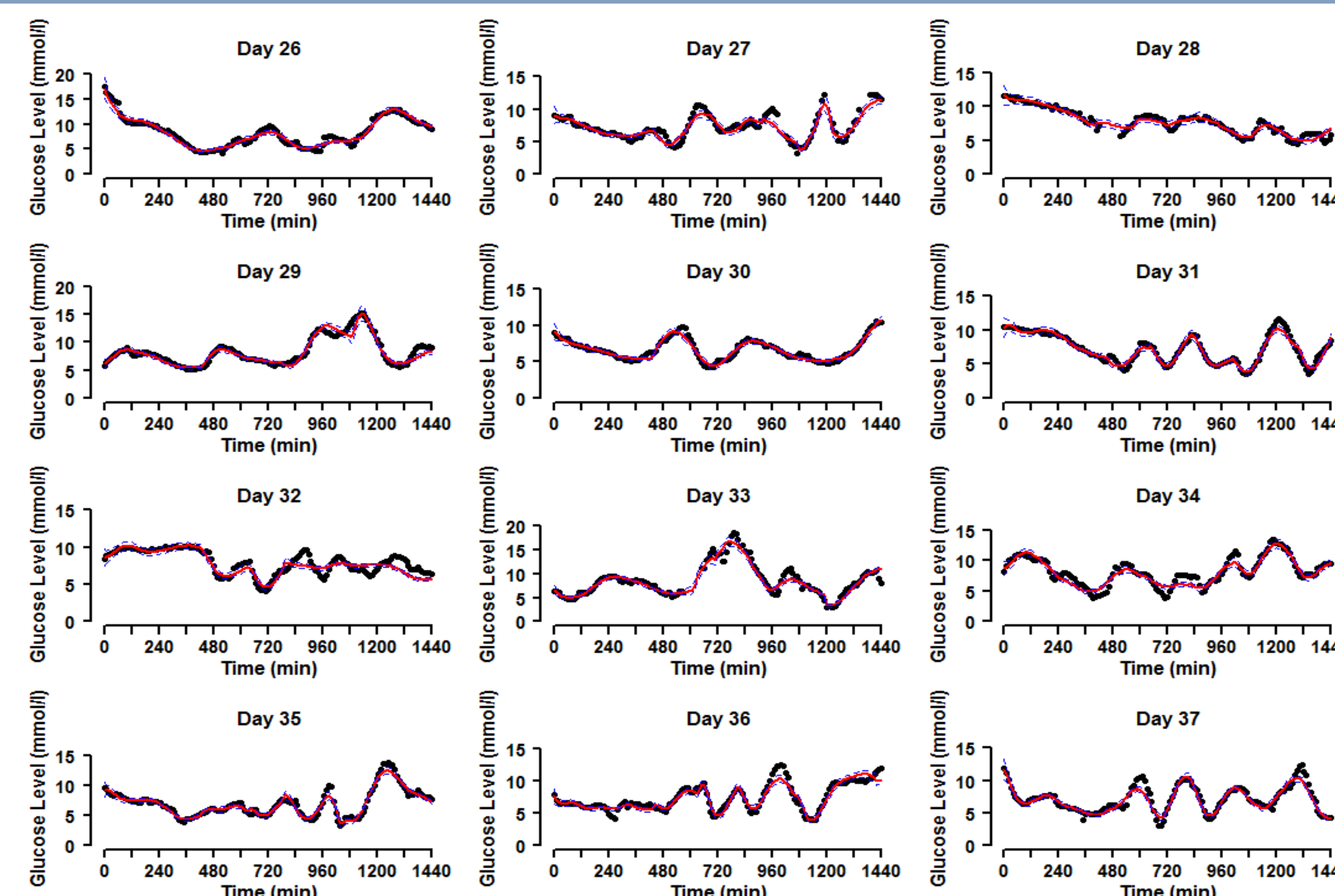


Fig. 2. Model fit of CGM data in a sample subject (sample Day 26 – Day 37 are shown). The black circles are CGM measurements, the red solid lines represent the median of model fit, and the blue dashed lines represent 95% credible intervals of model fit.

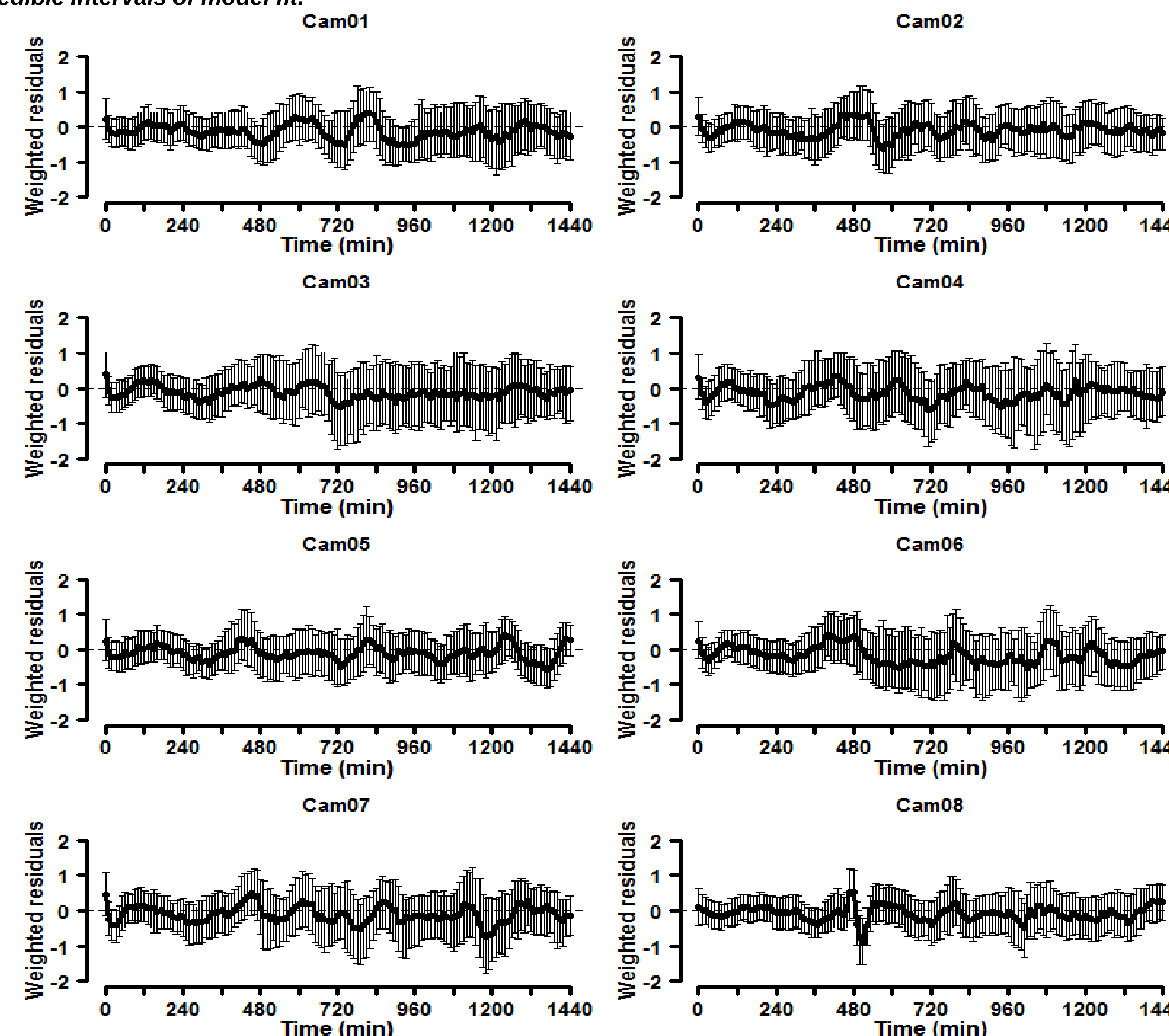


Fig. 3. Weighted residuals (difference between model-predicted and measured CGM values divided by the measurement error) (median [interquartile range]).

Table 1. Estimates of subject-level and population-level model parameters

Subject	Parameter						
	$t_{max,IA}$ (min)	S_i (mmol/min per mU/l)	X_b (mU/l)	$t_{max,G}$ (min)	A_G (unitless)	K (/min)	G_b (mmol/l)
Cam01	93 (43)	0.0055 (69)	8.5 (55)	59 (41)	0.88 (64)	0.0040 (43)	6.5 (32)
Cam02	75 (48)	0.0052 (50)	10.8 (35)	40 (65)	0.85 (69)	0.0041 (40)	7.7 (27)
Cam03	72 (44)	0.0063 (73)	12.2 (28)	39 (68)	0.72 (69)	0.0046 (50)	7.2 (27)
Cam04	70 (43)	0.0044 (69)	11.7 (32)	40 (68)	0.68 (85)	0.0046 (70)	6.8 (26)
Cam05	74 (35)	0.0065 (38)	11.0 (26)	64 (37)	1.11 (39)	0.0033 (11)	6.2 (30)
Cam06	104 (47)	0.0037 (79)	16.2 (30)	47 (56)	0.64 (97)	0.0037 (32)	6.8 (32)
Cam07	68 (42)	0.0035 (58)	17.1 (25)	38 (66)	0.85 (57)	0.0035 (28)	5.5 (29)
Cam08	71 (27)	0.0049 (49)	16.0 (27)	53 (50)	0.96 (50)	0.0033 (13)	6.3 (29)
Population	78±13 (41±7)	0.0050±0.0011 (60±14)	12.9±3.1 (32±10)	48±10 (56±12)	0.84±0.16 (66±18)	0.0039±0.0005 (36±19)	6.6±0.7 (29±3)

Subject-level mean (CV) over days and population parameter values (population CV) mean±SD are reported.

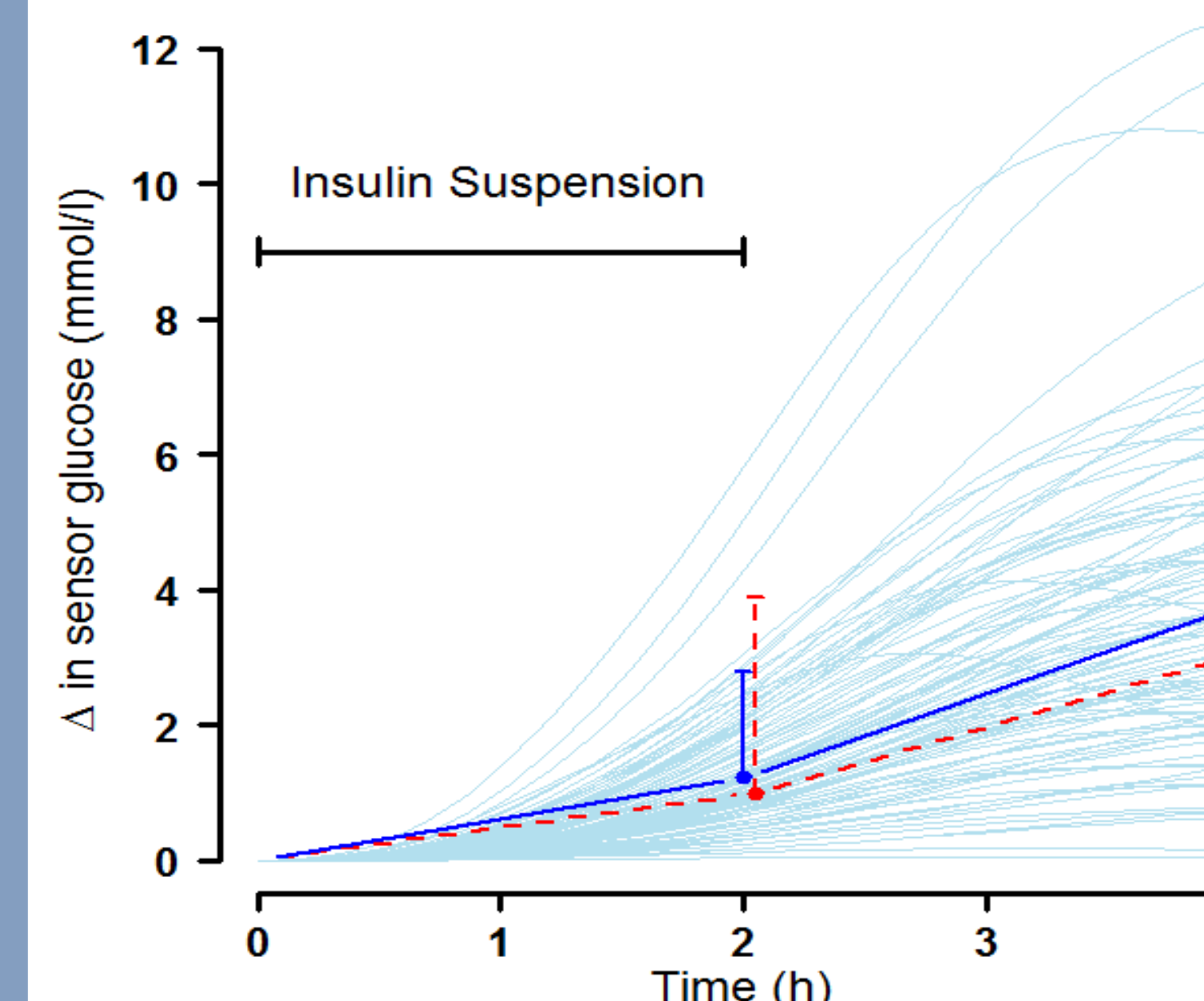


Fig. 4. Comparison between simulation and clinical results of glycemic changes relative to baseline during a 2-hour insulin pump suspension between 0h and 2h monitored over 4 h. The light blue thin solid lines are individual simulation results of glucose changes calculated by the glucose-insulin model using 96 day-level parameter sets estimated from the 8 subjects (12 days chosen randomly from each subject). The dark thick blue solid line with error bars represent mean (SD) of the simulation results. The red dashed thick line with error bars represents mean (SD) clinical results reported by Sherr et al. (99 suspend nights in 17 subjects with T1D) [2].

Conclusions

- We demonstrated the feasibility of a new model to represent 12-week glucose-insulin interactions within a Bayesian hierarchical framework
- The day-to-day variability of physiological parameters was assessed quantitatively
- The model could be implemented in an *in silico* testing environment to simulate realistic data-informed long-term closed-loop insulin delivery trials and to aid the development of closed-loop systems for home use

References

- Thabit H et al. Home use of an artificial beta cell in type 1 diabetes. *N Engl J Med* vol. 373, pp. 2129-40, 2015;
- J.L. Sherr et al. Safety of nighttime 2-hour suspension of Basal insulin in pump-treated type 1 diabetes even in the absence of low glucose, *Diabetes Care*, vol. 37, pp. 773-9, 2014.

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