Supplementary File: ICING model and parameters

The clinically validated ICING (Intensive Care Insulin-Nutrition-Glucose) model of glucose-insulin metabolism [1-5] was used to identify [6] patient-specific, time-varying hourly-hour insulin sensitivity (SI). The model presented is a physiological compartment model, accounting for the appearance and clearance of insulin and glucose in blood and interstitial fluid volumes. Figure S-1 shows this model (Figure 2 in the paper) schematically.

Model equations are defined:

$$\dot{G}(t) = -p_G G(t) - S_I G(t)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t) + EGP - CNS}{V_G} \quad (1)$$

$$\dot{Q}(t) = n_I\big(I(t) - Q(t)\big) - n_C \frac{Q(t)}{1+\alpha_G Q(t)} \quad (2)$$

$$\dot{I}(t) = n_K I(t) - n_L \frac{I(t)}{1+\alpha_I I(t)} - n_I\big(I(t) - Q(t)\big) + \frac{u_{ex}(t)}{V_I} + (1-x_L)\frac{u_{en}(G)}{V_I} \quad (3)$$

$$P(t) = \min(d_2 P_2,\ P_{\max}) + PN(t) \quad (4)$$

$$\dot{P1}(t) = -d_1 P1 + D(t) \quad (5)$$

$$\dot{P2}(t) = -\min(d_2 P2,\ P_{\max}) + d_1 P1 \quad (6)$$

$$u_{en}(G) = \min\left(\max\left(u_{min}, k_1 G(t) + k_2\right), u_{max}\right) \quad (7)$$

Where *G(t)* [mmol/L] is plasma glucose concentration, *I(t)* and *Q(t)* [mU/L] are plasma and interstitial insulin concentrations. Pancreatic insulin secretion is modelled as a function of plasma glucose and is denoted $u_{en}(G)$. The associated parameter values and descriptions are listed in Table S-1.

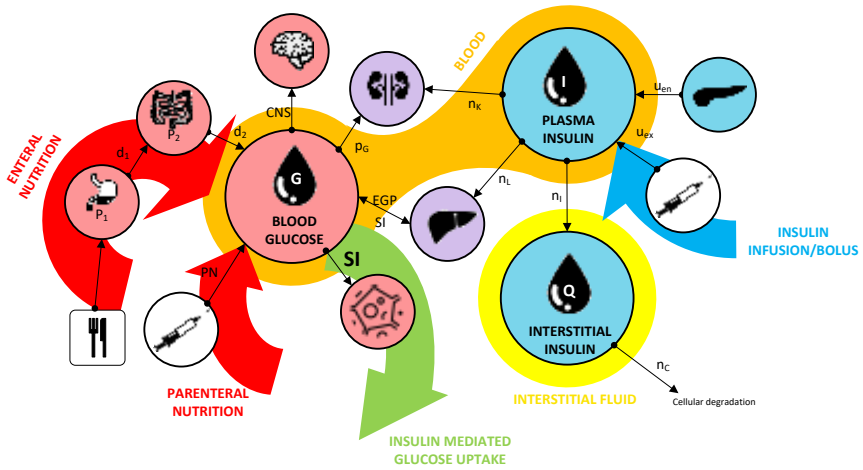

Figure S-1: Illustration of key dynamics of the glucose-insulin model, where key compartments include blood glucose, plasma insulin, and interstitial insulin. Arrows show the direction of glucose flux, and key abbreviations include central nervous system (CNS), Endogenous glucose production (EGP), parenteral nutrition (PN), insulin sensitivity (SI). Figure originally published in [7].

Table S-1: Parameter values, inputs, and model state descriptions for the glucose-insulin model.

	UNITS	DESCRIPTION
$G(t)$	mmol/L	Plasma glucose concentration
$I(t)$	mU/L	Plasma insulin concentration
$Q(t)$	mU/L	Interstitial insulin concentration
$P(t)$	mmol/min	Total glucose appearance from enteral and parenteral sources
$PN(t)$	mmol/min	Parenteral (IV) glucose appearance
$P_1(t)$	mmol	Glucose in the stomach
$P_2(t)$	mmol	Glucose in the gut
$D(t)$	mmol/min	Glucose appearance in stomach from enteral (oral) nutrition
$u_{ex}(t)$	mU/min	Exogenous IV insulin input rate.
	VALUE/UNITS	DESCRIPTION
$S_I(t)$	l/mU/min	Insulin sensitivity
α_G	1/65 (0.015) l/mU	Saturation of insulin-mediated glucose uptake
p_G	0.006 min^{-1}	Other non-insulin mediated glucose clearance
V_G	13.3 L	Glucose distribution volume
EGP	1.16 mmol/min	Endogenous glucose production (hepatic)
CNS	0.3 mmol/min	Glucose uptake by central nervous system
x_L	0.67	Fractional first pass hepatics insulin clearance from portal vein
n_L	0.1578 min^{-1}	Rate parameter: general hepatic insulin clearance
α_I	$1.7x10^{-3}$ l/mU	Saturation of hepatics insulin clearance
n_K	0.0542 min^{-1}	Rate parameter: kidney clearance of insulin
n_C	0.006 min^{-1}	Rate parameter: cellular degradation of internalised insulin
n_I	0.006 min^{-1}	Rate parameter: diffusion of insulin between plasma and interstitium
k_1	14.9 mU·l/mmol/min	Insulin secretion model parameter
k_2	-49.9 mU/min	Insulin secretion model parameter
u_{min}	16.7 mU/min	Minimum insulin secretion
u_{max}	266.7 mU/min	Maximum insulin secretion
V_I	4.0 L	Insulin distribution volume

Further reading:

Model development: [4, 5], summarised in a supplementary file within [7]

Model validation: [1, 8]

STAR protocol development: [9, 10]

Clinical outcome validation: For the SPRINT protocol [2, 11, 12] and STAR protocol [3, 13]

Insulin sensitivity and its variability: Statistical forecasting [14, 15] and relationship with clinical variables [16-21].

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