**Additional File 1: Metabolic System Model and Insulin Sensitivity (SI)**:

This Additional File is designed to present the model and methods used in several referenced studies (e.g. [1-9]) in this paper. The presentation is brief, relying on a separate set of references (from the main article) given at the end of this Additional File, which interested readers can use for explicit details on any aspect of this model and the methods used.

A1-1 Model Definition:

A clinically validated computer model of the metabolic system [10] was used to identify [11] patient-specific, time-varying (hourly) insulin sensitivity (SI) every hour. The model presented is a compartment model, accounting for the appearance of insulin and glucose in blood and interstitial fluid volumes. Figure A1-1 shows this model (Figure 1 in the paper) schematically.

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

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

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

$$P(t) = \min(d_2 P2,\ P_{\max}) + PN(t) \quad (4)$$

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

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

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

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 A1-1. Table A1-2 shows the exogenous input variables to the model.

**Table A1-1**. Parameter values and descriptions for the glucose-insulin model. Abbreviations;

| | VALUE | DESCRIPTION | FIXED? | IDENTIFICATION METHOD | IDENTIFICATION DATA SET | REPORTED RANGE |
|---|---|---|---|---|---|---|
| $S_I(t)$ | l/mU/min | Insulin sensitivity | N | Integral based fitting [1] | Clinical glucose, insulin, nutrition data | - |
| $\alpha_G$ | 1/65 (0.015) l/mU | Saturation of insulin-mediated glucose uptake | Y | Chosen from literature [2]. Sensitivity tested in [3]. | Literature review: [4-7] | 0.001 – 0.025 l/min [8]. |
| $p_G$ | 0.006 $min^{-1}$ | Other non-insulin mediated glucose clearance | Y | Identified: grid search and error minimisation [9] | Grid search: SPRINT cohort [10]<br>Literature review: [11-14] | 0.004 – 0.047 $min^{-1}$ [9] |
| $V_G$ | 13.3 L | Glucose distribution volume | Y | Chosen from literature [9] | - | 10.0 – 15.75 L [15]<br>0.22 L/kg [16] |
| $EGP$ | 1.16 mmol/min | Endogenous glucose production (hepatic) | Y | Grid search and error minimisation [9]. Later (unsuccessful) analysis as function of glucose and time [17]. | Grid search and functional analysis: SPRINT cohort [10]<br>Literature review (critically ill patients): [18-28] | 0.10 – 2.36 mmol/min [17]. |
| $CNS$ | 0.3 mmol/min | Glucose uptake by central nervous system | Y | Chosen from literature [9]. | Literature review: [29-35] | 0.29 – 0.38 mmol/min [9]. |
| $x_L$ | 0.67 | Fractional first pass hepatics insulin clearance from portal vein | Y | Chosen from literature [9] | Literature review: [36-38] | 0.5-0.95 [39]. |
| $n_L$ | 0.1578 $min^{-1}$ | Rate parameter: general hepatic insulin clearance | Y | Chosen based on previous work [9] | Normoglycaemic insulin resistant clamp study participants. [15, 40] | 0.1 – 0.21 $min^{-1}$ [15] |
| $\alpha_I$ | 1.7x$10^{-3}$ l/mU | Saturation of hepatics insulin clearance | Y | Chosen from literature [41]. | Literature review: [42-47] | 0.0005 – 0.0043 L/mU [8]. |
| $n_K$ | 0.0542 $min^{-1}$ | Rate parameter: kidney clearance of insulin | Y | Chosen from literature [9]. | - | 0.053–0.064 $min^{-1}$[15]. |
| $n_C$ | 0.006 $min^{-1}$ | Rate parameter: cellular degradation of internalised insulin | Y | Identified: grid search and error minimisation [3] | Published microdialysis studies [48-53] | Parameter sensitivity: [3]. |
| $n_I$ | 0.006 $min^{-1}$ | Rate parameter: diffusion of insulin between plasma and interstitium | Y | Identified: grid search and error minimisation [3] | Published microdialysis studies [48-53] | 0 – 0.06 $min^{-1}$ [3]. |
| $k_1$ | 14.9 mU·l/mmol/min | Insulin secretion model parameter | Y | Model fit to clinical C-peptide and Insulin data. Compared to results derived from literature [17]. | Clinical sepsis study patients [17].<br>Literature review: [54-61] | 8 - 45.9 mU/min [17]. |
| $k_2$ | -49.9 mU/min | Insulin secretion model parameter | Y | Model fit to clinical C-peptide and Insulin data [17]. | Clinical sepsis study patients [17]. | - |
| $u_{min}$ | 16.7 mU/min | Minimum insulin secretion | Y | Constraint derived from lower range of clinical insulin secretion data [17]. | Clinical sepsis study patients [17]. | - |
| $u_{max}$ | 266.7 mU/min | Maximum insulin secretion | Y | Constraint derived from upper range of clinical insulin secretion data [17]. | Clinical sepsis study patients [17]. | - |
| $V_I$ | 4.0 L | Insulin distribution volume | Y | Chosen from literature [17]. | Literature: [9, 62] | 3.15 – 4.75 L |

**Table A1-2**. Exogenous input variables to the glucose-insulin model.

| Variable | Unit | Description |
|---|---|---|
| PN(t) | mmol/min | Intravenous glucose input rate (parenteral nutrition) |
| D(t) | mmol/min | Oral glucose input rate (enteral nutrition) |
| $u_{ex}(t)$ | mU/min | intravenous insulin input rate |

The insulin sensitivity SI can be identified hourly from blood glucose data along with the clinical insulin and nutritional inputs from all sources [11, 12]. SI is also the critical parameter in predicting the outcome of a nutrition and/or insulin intervention in this model, based on the definition above [2, 3, 11]. It represents the whole body balance of insulin and carbohydrate from all sources. SI can vary with patient-status hour to hour, with larger acute changes or smaller gradual evolution. Thus, the identified SI can be used to characterise metabolic response and evolution for cohorts or specific-patients, enabling more optimal and robust dosing [19-22]. Two example SI profiles and model fit to clinical data can be found in Figure A1-2. Both show stable BG within the 4.4 – 8.0 mmol/L range, despite different underlying insulin sensitivity variability and the insulin and nutrition doses required to achieve comparable BG stability.

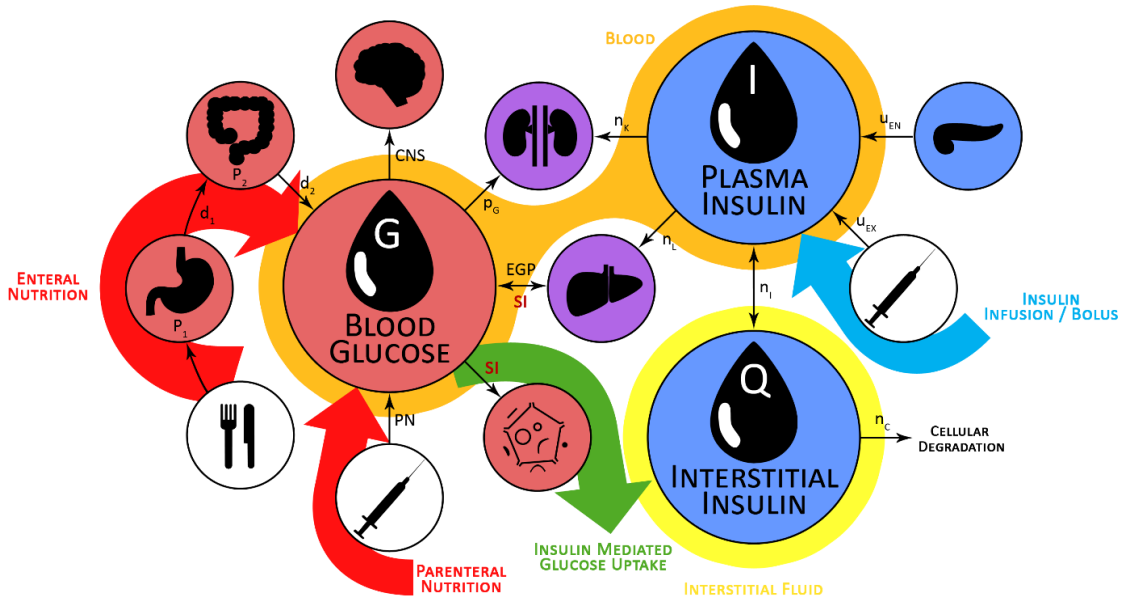


**Figure A1-1**: Model schematic for Equations (1)-(3) showing the physiological compartments and clearances, as well as the appearance of exogenous insulin and carbohydrate, and their kinetic pathways. Insulin sensitivity (SI) can vary over time (hour to hour) thus affecting glycaemic outcomes for a given insulin and/or nutrition intervention.

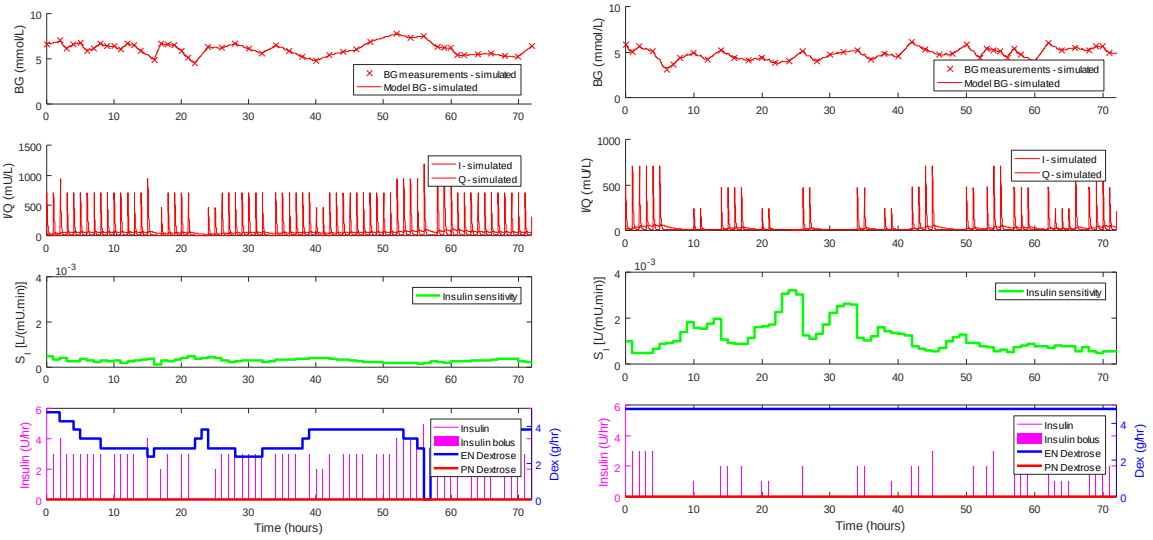


**Figure A1-2**: Example patients from clinical data, showing measured blood glucose (BG), clinically delivered insulin and nutrition, and model fitted insulin sensitivity (SI). A more 'Stable' SI profile (left) and more variable SI profile (right).

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