S1 Appendix: GIGM Model and Parameters

Overview of GIGM Model with Type I Diabetics

We consider the model in [3,4] which is a system of nonlinear differential equations (ODEs). In all equations, $t$ is the physical time (in min), all subscripts $b$ denotes basal state, and all of the parameters are given in the S1 Table. The system of nonlinear differential equations are given below:

**Glucose Subsystem:**

\[
\begin{align*}
\dot{G}_p(t) &= EGP(t) + Ra(t) - U_{ii} - E(t) - k_1 G_p(t) + k_2 G_t(t), \quad G_p(0) = G_{pb} \quad (S1a) \\
\dot{G}_t(t) &= -U_{id}(t) + k_1 G_p(t) - k_2 G_t(t), \quad G_t(0) = G_{tb} \quad (S1b) \\
G(t) &= \frac{G_p}{V_G}, \quad G(0) = G_b \quad (S1c)
\end{align*}
\]

Here $G_p$ (in mg/kg) is the mass of plasma glucose; $G_t$ (in mg/kg) is the mass of tissue glucose; $G$ (in mg/L) is plasma glucose concentration and $V_G$ (in dL/kg) is the distribution volume of glucose; $EGP$ is the endogenous glucose production (in mg/kg/min); $Ra$ (in mg/kg/min) is the rate of glucose appearance in plasma; $U_{ii}$ (in mg/kg/min) and $U_{id}$ (in mg/kg/min) are insulin-independent and insulin-dependent glucose utilizations, respectively. Also $k_1$ and $k_2$ are the parameters.

**Insulin Subsystem:**

\[
\begin{align*}
\dot{I}_p(t) &= -(m_2 + m_4)I_p(t) + m_1 I_l(t) + R_{ia}(t), \quad I_p(0) = I_{pb} \quad (S2a) \\
\dot{I}_l(t) &= -(m_1 + m_3)I_l(t) + m_2 I_p(t), \quad I_l(0) = I_{lb} \quad (S2b) \\
I(t) &= \frac{I_p(t)}{V_I}, \quad I(0) = I_b \quad (S2c)
\end{align*}
\]

Here $I_l$ (in pmol/kg) is the mass of liver insulin; $I_p$ (in pmol/kg) is the mass of tissue insulin; $I$ (in pmol/L) is the plasma insulin concentration; $V_I$ (in L/kg) is the distribution volume of insulin; $R_{ia}$ (in pmol/kg/min ) is the rate of appearance of insulin in plasma; $m_1$, $m_2$, $m_3$ and $m_4$ are the parameters.

**Glucose rate of appearance:**

\[
\begin{align*}
Q_{sto}(t) &= Q_{sto1}(t) + Q_{sto2}(t), \quad G_{sto}(0) = 0 \quad (S3a) \\
\dot{Q}_{sto1}(t) &= -k_{gri}Q_{sto1}(t) + D\delta(t - \tau_D), \quad Q_{sto1}(0) = 0 \quad (S3b) \\
\dot{Q}_{sto2}(t) &= -k_{empt}(Q_{sto})(t)Q_{sto2}(t) + k_{gri}Q_{sto1}(t), \quad Q_{sto2}(0) = 0 \quad (S3c) \\
\dot{Q}_{gut}(t) &= -k_{abs}Q_{gut}(t) + k_{empt}Q_{sto}(t)Q_{sto2}(t), \quad Q_{gut}(0) = 0 \quad (S3d) \\
Ra(t) &= \frac{f k_{abs} Q_{gut}(t)}{BW}, \quad Ra(0) = 0 \quad (S3e)
\end{align*}
\]

\[
k_{empt}(Q_{sto}) = k_{min} + \frac{k_{max} - k_{min}}{2} \left\{\tanh[\alpha(Q_{sto} - bD)] - \tanh[\beta(Q_{sto} - cD)] + 2\right\} \quad (S3g)
\]

Here $Q_{sto}$ (in mg) is the amount of glucose in the stomach, $Q_{sto1}$ (in mg) is the amount of liquid glucose in the stomach, $Q_{sto2}$ (in mg) is the amount of solid glucose in the stomach, $Q_{gut}$ (in mg) is the glucose mass in the intestine; $D$ (in mg) is the amount of ingested glucose at time.
\( \tau_D \); \( BW \) (in kg) is body weight; \( k_{empt} \) is the rate constant of the gastric emptying; \( K_{gri}, k_{abs}, k_{\max}, k_{\min}, f, \alpha, \beta \) are the parameters.

**Endogenous glucose production:**

\[
E_{GP}(t) = k_{p1} - k_{p2}G_p(t) - k_{p3}X^L(t) + \xi X^H(t), \quad E_{GP}(0) = E_{GPb} \tag{S4a}
\]

\[
\dot{I}'(t) = -k_i [I'(t) - I(t)], \quad I'(0) = I_b \tag{S4b}
\]

\[
\dot{X}^L(t) = -k_i [X^L(t) - I'(t)], \quad X^L(0) = I_b \tag{S4c}
\]

\[
\dot{X}^H(t) = -k_H X^H(t) + k_H \times \max[H(t) - H_b, 0], \quad X^H(0) = 0 \tag{S4d}
\]

Here \( X^L \) (in \( \text{L} \)) is delayed insulin action on \( E_{GP} \); \( X^H \) is delayed glucagon action on \( E_{GP} \); \( I' \) is delayed insulin in compartment 1; \( k_{p1}, k_{p2}, k_{p3}, \xi, k_i, k_H \) are the parameters.

**Glucose utilization:**

\[
U_{ii}(t) = F_{cns} \tag{S5a}
\]

\[
U_{id}(t) = \frac{[V_{m0} + V_{max}X(t)]G_i(t)}{K_{m0} + G_i(t)} \tag{S5b}
\]

\[
\dot{X}(t) = -p_{2u} X(t) + p_{2u}[I(t) - I_b], \quad X(0) = 0 \tag{S5c}
\]

Here \( U_{ii} \) (in \( \text{mg/kg/min} \)) and \( U_{id} \) (in \( \text{mg/kg/min} \)) are insulin-independent and insulin-dependent glucose utilization; \( X \) (in \( \text{pmol/L} \)) is insulin in interstitial fluid; \( F_{cns}, V_{m0}, K_{m0}, p_{2u} \) are the parameters.

**Renal excretion:**

\[ E(t) = \begin{cases} k_{c1}[G_p(t) - k_{c2}] & \text{if } G_p(t) > k_{c2} \\ 0 & \text{if } G_p(t) \leq k_{c2} \end{cases} \tag{S6} \]

Here \( E(t) \) (in \( \text{mg/kg/min} \)) is the glucose renal excretion; \( k_{c1} \) is the parameter.

**Glucagon kinetics and secretion:**

\[ \dot{H}(t) = -nH(t) + SR_{H}(t) + Ra_{H}(t), \quad H(0) = H_b \tag{S7a} \]

\[ SR_{H}(t) = SR_{H}^s(t) + SR_{H}^d(t), \tag{S7b} \]

\[ \dot{SR}_{H}^s(t) = -\rho \left[ SR_{H}^s(t) - \max \left( \frac{\sigma[G_{th} - G(t)]}{\max(I(t) - I_{th}, 0) + 1} + SR_{H}^b, 0 \right) \right], \quad SR_{H}^s(0) = nH_b \tag{S7c} \]

\[ SR_{H}^d(t) = \delta \max \left( -\frac{dG(t)}{dt}, 0 \right) \tag{S7d} \]

Here \( H \) (in \( \text{ng/L} \)) is the concentration of plasma glucagon; \( SR_{H} \) (in \( \text{ng/L/min} \)) is the glucagon secretion; \( Ra_{H} \) (in \( \text{ng/L/min} \)) is the rate of appearance of glucagon in plasma; \( SR_{H}^s \) (in \( \text{ng/L/min} \)) and \( SR_{H}^d \) (in \( \text{ng/L/min} \)) is the static and dynamic components of glucagon, respectively; \( n, \rho, I_{th}, \delta \) are the parameters.

**Subcutaneous insulin kinetics:**

\[ R_{ia}(t) = k_{a1}I_{sc1}(t) + k_{a2}I_{sc2}(t) \tag{S8a} \]

\[ \dot{I}_{sc1}(t) = -(k_d + k_{a1})I_{sc1}(t) + IIR(t), \quad I_{sc1}(0) = I_{sc1ss} \tag{S8b} \]

\[ \dot{I}_{sc2}(t) = k_dI_{sc1}(t) - k_{a2}I_{sc2}(t), \quad I_{sc2}(0) = I_{sc2ss} \tag{S8c} \]

\[ IIR(t) = IIR_b + \frac{u_I(t)}{BW} \tag{S8d} \]
Here \( R_{a} \) (in pmol/kg/min) is the rate of appearance of insulin in plasma; \( I_{sc1} \) (in pmol/kg) is the amount of nonmonomeric insulin in the subcutaneous space; \( I_{sc2} \) is the amount of monomeric insulin in the subcutaneous space; \( IIR(t) \) is the insulin infusion rate where \( IIR_{b} \) is the basal infusion rate (in pmol/kg/min) from body and \( u_{I} \) (in pmol/min) is the external insulin infusion rate; \( k_{h3}, k_{a2}, k_{d} \) are the parameters. As the exogenous insulin infusion rate appears in the above equation in pmol/kg/min, we divide \( u_{I} \) by the body weight \( BW \) in the equation. Note that here the \( u_{I} \) is in pmol/min. To convert the unit of insulin infusion rate \( u_{I} \) from U/min to pmol/min, we multiply \( u_{I} \) by 6944.4, that is the unit conversion is 1 U/min = 6944.4 pmol/min.

**Subcutaneous glucagon kinetics:**

\[
\begin{align*}
\dot{H}_{sc1}(t) &= -(k_{h1} + k_{h2})H_{sc1}(t) + GIR(t), \quad H_{sc1}(0) = H_{sc1ss} \quad (S9a) \\
\dot{H}_{sc2}(t) &= k_{h1}H_{sc1}(t) - k_{h3}H_{sc2}(t), \quad H_{sc2}(0) = H_{sc2ss} \quad (S9b) \\
\dot{R}_{uH}(t) &= k_{h3}H_{sc2}(t) \quad (S9c) \\
GIR(t) &= GIR_{b} + \frac{u_{G}(t)}{BV} \quad (S9d)
\end{align*}
\]

Here \( H_{sc1} \) (in ng/L) and \( H_{sc2} \) (in ng/L) are the glucagon concentration in the subcutaneous space; \( GIR \) is the glucagon infusion rate where \( GIR_{b} \) is the basal glucagon infusion rate (in ng/L/min) from the body and \( u_{G} \) is the external glucagon infusion rate (in ng/min); \( k_{h1}, k_{h2}, k_{h3} \) are the parameters. As the exogenous glucagon infusion rate appears in the above equation in ng/L/min, we divide \( u_{G} \) by the body volume \( BV \) in the equation. Note that here the \( u_{G} \) is in ng/min. To convert the unit of glucagon infusion rate from mg/min to ng/min, we multiply \( u_{G} \) by \( 10^{6} \), that is the unit conversion is 1 mg/min = 10^{6} ng/min.

We write the ODEs in Eqs. (S1)-(S9) in the form \( \dot{x}(t) = f(x(t), u(t), \Theta_{G}) \) where \( x \in \mathbb{R}^{17} \) and \( t \) is the physical time (in min). The variable \( x_{1} \) represents \( G_{p} \), the mass of glucose in plasma; the variable \( x_{2} \) represents \( G_{t} \), the mass of glucose in tissue; the variable \( x_{3} \) represents the mass of liver insulin \( I_{l} \); the variable \( x_{4} \) represents the mass of plasma insulin \( I_{p} \); the variable \( x_{5} \) represents the amount of delayed insulin \( I^{d} \) in compartment 1; the variable \( x_{6} \) represents the amount of delayed insulin \( X^{d} \) action on \( EGP \); the variable \( x_{7} \) represents the amount of solid glucose \( Q_{stol} \) in the stomach; the variable \( x_{8} \) represents the amount of liquid glucose \( Q_{sto2} \) in the stomach; the variable \( x_{9} \) represents the glucagon mass \( Q_{gut} \) in the intestine; the variable \( x_{10} \) represents the amount of interstitial fluid \( X \); the variable \( x_{11} \) represents the amount of static glucagon \( SIR_{H}^{s} \); the variable \( x_{12} \) represents the amount of plasma glucagon \( H \); the variable \( x_{13} \) represents the amount of delayed glucagon \( X^{d} \) action on \( EGP \); the variable \( x_{14} \) represents the amount of nonmonomeric insulin \( I_{sc1} \) in the subcutaneous space; the variable \( x_{15} \) represents the amount of monomeric insulin \( I_{sc2} \) in the subcutaneous space; the variable \( x_{16} \) represents the amount of subcutaneous glucagon \( H_{sc1} \) in the subcutaneous space; the variable \( x_{17} \) represents the amount of subcutaneous glucagon \( H_{sc2} \) in the subcutaneous space. Also \( u(t) = [u_{I}(t) \quad u_{G}(t)]^{T} \), where \( u_{I} \) is the external insulin and \( u_{G} \) is the external glucagon. We define \( \Theta_{G} \) as the set of parameters for which the basal glucose level is \( G_{b} \).

**Parameters**

There are a total of 46 parameters in Eqs. (S1)-(S9). The parameters are not given in [3]. We set all the parameters for ‘Glucose subsystem’, ‘Insulin subsystem’, ‘Glucose rate of appearance’, ‘Endogenous glucose production’, ‘Glucose utilization’, ‘Glucose utilization’, ‘Renal excretion’, ‘Subcutaneous insulin kinetics’ from the references [1,2], except \( k_{p1}, V_{m0} \) and \( HE_{b} \). According to [2], the parameters are chosen to satisfy the steady-state constraints in type I diabetes. The parameters \( k_{p1} \) and \( V_{m0} \) are set so that the steady state solutions provide the basal Glucose level \( G_{b} \) and \( EGP_{b} = 2.4 \). In Type I diabetes, the endogenous glucose production is high [2], so we choose \( EGP_{b} = 2.4 \) mg/kg/min. We set \( IIR_{b} = 0 \) and \( GIR_{b} = 0 \) as the model we consider is for Type I diabetes. The commercial version of the UVA/Pavoda simulator [67] allows computing blood glucose responses to supplied dosages of insulin for some patients, but does
not provide all of the parameters. We tune the parameter $HE_b$ so that the blood glucose response to insulin of the patient we consider in this paper is qualitatively similar to the blood glucose response to insulin of a patient from the software [67] (adultaverage.mat). All of the parameters we use are listed in the S1 Table for reproducibility of the results. Our implementation of the model [3] has been published in GitHub [68].

The equations for $k_{p1}$ and $V_{m0}$ are given below:

$$k_{p1} = EGP_b + k_{p2}G_{pb} + k_{p3}I_b$$

$$V_{m0} = \frac{(EGP_b - F_{cns})(K_{m0} + G_{tb})}{G_{tb}}$$

The basal steady states are given below:

$$G_{pb} = G_bV_g$$

$$G_{tb} = \frac{F_{cns} - EGP_b + k_1G_{pb}}{k_2}$$

$$I_{lb} = I_{pb} \cdot \frac{m_2}{m_1 + m_3}$$

$$I_{pb} = \frac{IIR_b}{m_2 + m_4 - \frac{m_1 m_2}{m_1 + m_3}}$$

$$I_{sclss} = \frac{IIR_b}{k_d + k_{a1}}$$

$$I_{sc2ss} = \frac{k_d}{k_{a2}} I_{sclss}$$

$$SR_{Hb} = nH_b$$

$$H_{sc1ss} = \frac{GIR_b}{k_{h1} + k_{h2}}$$

$$H_{sc2ss} = \frac{k_{h1}}{k_{h3}} H_{sc1ss}$$

Here, the basal values $G_b$ (in mg/dL), $IIR_b$ (in pmol/kg/min) and $GIR_b$ (in ng/L/min) are settable by the user.