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:

$$\dot{G}_p(t) = EGP(t) + Ra(t) - U_{ii} - E(t) - k_1 G_p(t) + k_2 G_t(t), \qquad G_p(0) = G_{pb} \tag{S1a}$$

$$\dot{G}_t(t) = -U_{id}(t) + k_1 G_p(t) - k_2 G_t(t), \qquad G_t(0) = G_{tb} \tag{S1b}$$

$$G(t) = \frac{G_p}{V_G}, \qquad G(0) = G_b \tag{S1c}$$

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/dL) 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:

$$\dot{I}_p(t) = -(m_2 + m_4) I_p(t) + m_1 I_l(t) + R_{ia}(t), \qquad I_p(0) = I_{pb} \tag{S2a}$$

$$\dot{I}_l(t) = -(m_1 + m_3) I_l(t) + m_2 I_p(t), \qquad I_l(0) = I_{lb} \tag{S2b}$$

$$I(t) = \frac{I_p(t)}{V_I}, \qquad I(0) = I_b \tag{S2c}$$

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:

$$Q_{sto}(t) = Q_{sto1}(t) + Q_{sto2}(t), \qquad G_{sto}(0) = 0 \tag{S3a}$$

$$\dot{Q}_{sto1}(t) = -k_{gri} Q_{sto1}(t) + D\delta(t - \tau_D), \qquad Q_{sto1}(0) = 0 \tag{S3b}$$

$$\dot{Q}_{sto2}(t) = -k_{empt}(Q_{sto})(t) Q_{sto2}(t) + k_{gri} Q_{sto1}(t), \qquad Q_{sto2}(0) = 0 \tag{S3c}$$

$$\dot{Q}_{gut}(t) = -k_{abs} Q_{gut}(t) + k_{empt} Q_{sto}(t) Q_{sto2}(t), \qquad Q_{gut}(0) = 0 \tag{S3d}$$

$$Ra(t) = \frac{f.k_{abs}.Q_{gut}(t)}{BW}, \qquad Ra(0) = 0 \tag{S3e}$$

$$k_{empt}(Q_{sto}) = k_{\min} + \frac{k_{\max} - k_{\min}}{2}. \tag{S3f}$$

$$\{\tanh[\alpha(Q_{sto} - b.D)] - \tanh[\beta(Q_{sto} - c.D)] + 2\} \tag{S3g}$$

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

τ_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, α, β are the parameters.

Endogenous glucose production:

$$EGP(t) = k_{p1} - k_{p2}G_p(t) - k_{p3}X^L(t) + \xi X^H(t), \qquad EGP(0) = EGP_b \tag{S4a}$$

$$\dot{I}'(t) = -k_i\left[I'(t) - I(t)\right], \qquad I'(0) = I_b \tag{S4b}$$

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

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

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

Glucose utilization:

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

$$U_{id}(t) = \frac{[V_{m0} + V_{mx}.X(t)]G_t(t)}{K_{m0} + G_t(t)} \tag{S5b}$$

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

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

Renal excretion:

$$E(t) = \begin{cases} k_{e1}[G_p(t) - k_{e2}] & \text{if } G_p(t) > k_{e2} \\ 0 & \text{if } G_p(t) \le k_{e2} \end{cases} \tag{S6}$$

Here $E(t)$ (in mg/kg/min) is the glucose renal exertion; k_{e1} is the parameter.

Glucagon kinetics and secretion:

$$\dot{H}(t) = -nH(t) + SR_H(t) + Ra_H(t), \qquad H(0) = H_b \tag{S7a}$$

$$SR_H(t) = SR^s_H(t) + SR^d_H(t), \tag{S7b}$$

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

$$SR^d_H(t) = \delta \max\left(-\frac{dG(t)}{dt}, 0\right) \tag{S7d}$$

Here H (in ng/L) is the concentration of plasma glucagon; SR_H (in ng/L/min) is the glucagon secretion; Ra_H (in ng/L/min) is the rate of appearance of glucagon in plasma; SR^s_H (in ng/L/min) and SR^d_H (in ng/L/min) is the static and dynamic components of glucagon, respectively; n, ρ, I_{th}, δ are the parameters.

Subcutaneous insulin kinetics:

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

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

$$\dot{I}_{sc2}(t) = k_d.I_{sc1}(t) - k_{a2}I_{sc2}(t), \qquad I_{sc2}(0) = I_{sc2ss} \tag{S8c}$$

$$IIR(t) = IIR_b + \frac{u_I(t)}{BW} \tag{S8d}$$

Here R_{ia} (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_{a1}, 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:

$$\dot{H}_{sc1}(t) = -(k_{h1} + k_{h2})H_{sc1}(t) + GIR(t), \qquad H_{sc1}(0) = H_{sc1ss} \tag{S9a}$$

$$\dot{H}_{sc2}(t) = k_{h1}H_{sc1}(t) - k_{h3}H_{sc2}(t), \qquad H_{sc2}(0) = H_{sc2ss} \tag{S9b}$$

$$Ra_H(t) = k_{h3}H_{sc2}(t) \tag{S9c}$$

$$GIR(t) = GIR_b + \frac{u_G(t)}{BV} \tag{S9d}$$

Here H_{sc1} (in ng/L) and H_{sc2} (in ng/L) are the glucagon concentration in the subcutaneous space; IGR is the glucagon infusion rate where GIR_b is the basal glucagon infusion rate (in ng/L/min) from the body and u_I 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 $\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x}(t), \mathbf{u}(t), \Theta_{Gb})$ where $\mathbf{x} \in \mathbb{R}^{17}$ 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' in compartment 1; the variable x_6 represents the amount of delayed insulin X^L action on EGP; the variable x_7 represents the amount of solid glucose Q_{sto1} in the stomach; the variable x_8 represents the amount of liquid glucose Q_{sto2} in the stomach; the variable x_9 represents the glucose 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 SR_H^s; the variable x_{12} represents the amount of plasma glucagon H; the variable x_{13} represents the amount of delayed glucagon X^H 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 $\mathbf{u}(t) = [u_I(t) \quad u_G(t)]^T$, where u_I is the external insulin and u_G is the external glucagon. We define Θ_{G_b} 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:

$$k_{p1} = EGP_b + k_{p2}G_{pb} + k_{p3}I_b \tag{S10a}$$

$$V_{m0} = \frac{(EGP_b - F_{cns})(K_{m0} + G_{tb})}{G_{tb}} \tag{S10b}$$

The basal steady states are given below:

$$G_{pb} = G_b.V_g \tag{S11a}$$

$$G_{tb} = \frac{F_{cns} - EGP_b + k_1 G_{pb}}{k_2} \tag{S11b}$$

$$I_{lb} = I_{pb}.\frac{m_2}{m_1 + m_3} \tag{S11c}$$

$$I_{pb} = \frac{IIR_b}{m_2 + m_4 - \frac{m_1 m_2}{m_1 + m_3}} \tag{S11d}$$

$$I_{sc1ss} = \frac{IIR_b}{k_d + k_{a1}} \tag{S11e}$$

$$I_{sc2ss} = \frac{k_d}{k_{a2}} I_{sc1ss} \tag{S11f}$$

$$SR^s_{Hb} = nH_b \tag{S11g}$$

$$H_{sc1ss} = \frac{GIR_b}{k_{h1} + k_{h2}} \tag{S11h}$$

$$H_{sc2ss} = \frac{k_{h1}}{k_{h3}} H_{sc1ss} \tag{S11i}$$

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.