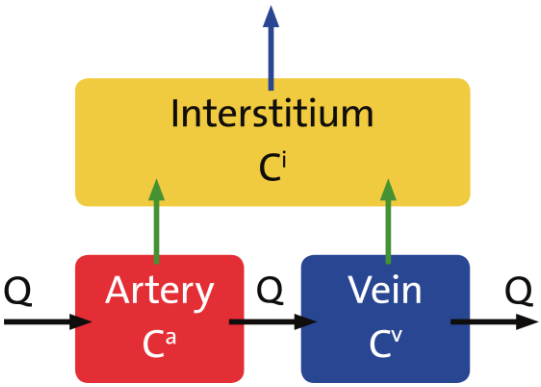
Compartmental Model for Intra-Arterial Microdosing of Insulin



Supplemental Figure 1: Schematic Diagram of the Computational PK/PD Model. Superscripts i, a, v denote interstitium, artery, and vein, respectively. Subscripts 'ins' and 'glu' denote insulin and glucose, respectively. C denotes insulin or glucose concentration. Q denotes blood flow through the model vessels. Green arrows denote vascular fluxes; blue arrow denotes cellular uptake of insulin or glucose.

The model represents a pair of artery and vein that perfuse the target tissue or organ. Each vessel is represented as a compartment; see Supplemental Figure 1. The vessels interact with the interstitium, which is represented as a separate compartment. Blood enters the model artery at a given rate, carrying glucose and insulin, and exits the system via the model vein. Cellular uptake of glucose and insulin is represented in the interstitial compartment. The compositions of the arterial blood, venous blood, and interstitial fluid are assumed to be homogeneous. The model predicts the concentrations of insulin and glucose as functions of time in each of the compartment.

Solute conservation equations

To determine insulin and glucose concentrations in the arterial compartment (denoted $C_k^a(t)$, where k = ins or glu, the model imposes solute conservation, given by

$$V^a \frac{\partial}{\partial t} C_k^a(t) = Q\left(C_k^0(t) - C_k^a(t)\right) - P_k\left(C_k^a(t) - C_k^i(t)\right)$$

where V^a denotes arterial compartment volume, taken to be 0.108 mL. Q is the rate of blood entering the model artery, taken to be 1.458 mL/min. If the compartments are assumed to be non-compliant, then the same volume must flow between the artery and vein, and exit the system from the vein. The second term on the right-hand-side represents transmural solute flux, which depends on arterial and interstitial solute concentrations, and is characterized by transmural permeability P_k. Vascular permeabilities to glucose and inulin are set to 1.1 and 1.0 mL/min, respectively. $C_k^0(t)$ is the solute concentration in the blood that enters the model artery at time t. Blood glucose concentration is assumed to be constant in time at 2.3 mg/mL, where $C_{ins}^0(t)$ can be varied in time to simulate a bolus of insulin. The

left-hand-side of the equation represents the rate of change of total insulin in the arterial compartment. That change is driven by the incoming blood which carrying insulin and glucose (the term $QC_k^0(t)$).by capillary flow which carries blood from the model artery into the vein ($-QC_k^a(t)$), and by transmural flux.

An analogous equation applies to the vein:

$$V^v \frac{\partial}{\partial t} C_k^v(t) = Q\left(C_k^a(t) - C_k^v(t)\right) - P_k\left(C_k^v(t) - C_k^i(t)\right)$$

Here the rate of change of total insulin in the venous compartment is given by the blood entering the vein at rate Q carrying insulin or glucose at a concentration of $C_k^a(t)$, leaving the system at rate Q at concentration $C_k^v(t)$, and transmural flux. Venous volume V^v, is taken to be 0.162 mL.

In the interstitial compartment, conservation of glucose is given by

$$V^i \frac{\partial}{\partial t} C_{glu}^i(t) = -m_1 C_{glu}^{i'}(t) - m_2 C_{ins}^{i'}(t) + P_{glu}\left(C_{glu}^{a'}(t) - C_{glu}^{i'}(t)\right) + P_{glu}\left(C_{glu}^{v'}(t) - C_{glu}^{i'}(t)\right)$$

where the prime notation (in $C_k^{i'}$) denotes deviation from baseline glucose or insulin concentration levels. V^i denotes the volume of the interstitium not occupied by the artery, vein, or target cells, and is set to 0.432 mL. The term $-m_1 C_{glu}^{i'}$ represents passive glucose diffusion into cells; $-m_2 C_{ins}^{i'}$ represents facilitated update of glucose via GLUT4, with GLUT4 expression mediated by insulin; the remaining terms represent vascular glucose fluxes. m_1 and m_2 are model parameters (see below).

Conservation of insulin is given by

$$V^i \frac{\partial}{\partial t} C_{ins}^i(t) = -m_3 C_{ins}^{i'}(t) + P_{ins}\left(C_{ins}^{a'}(t) - C_{ins}^{i'}(t)\right) + P_{ins}\left(C_{ins}^{v'}(t) - C_{ins}^{i'}(t)\right)$$

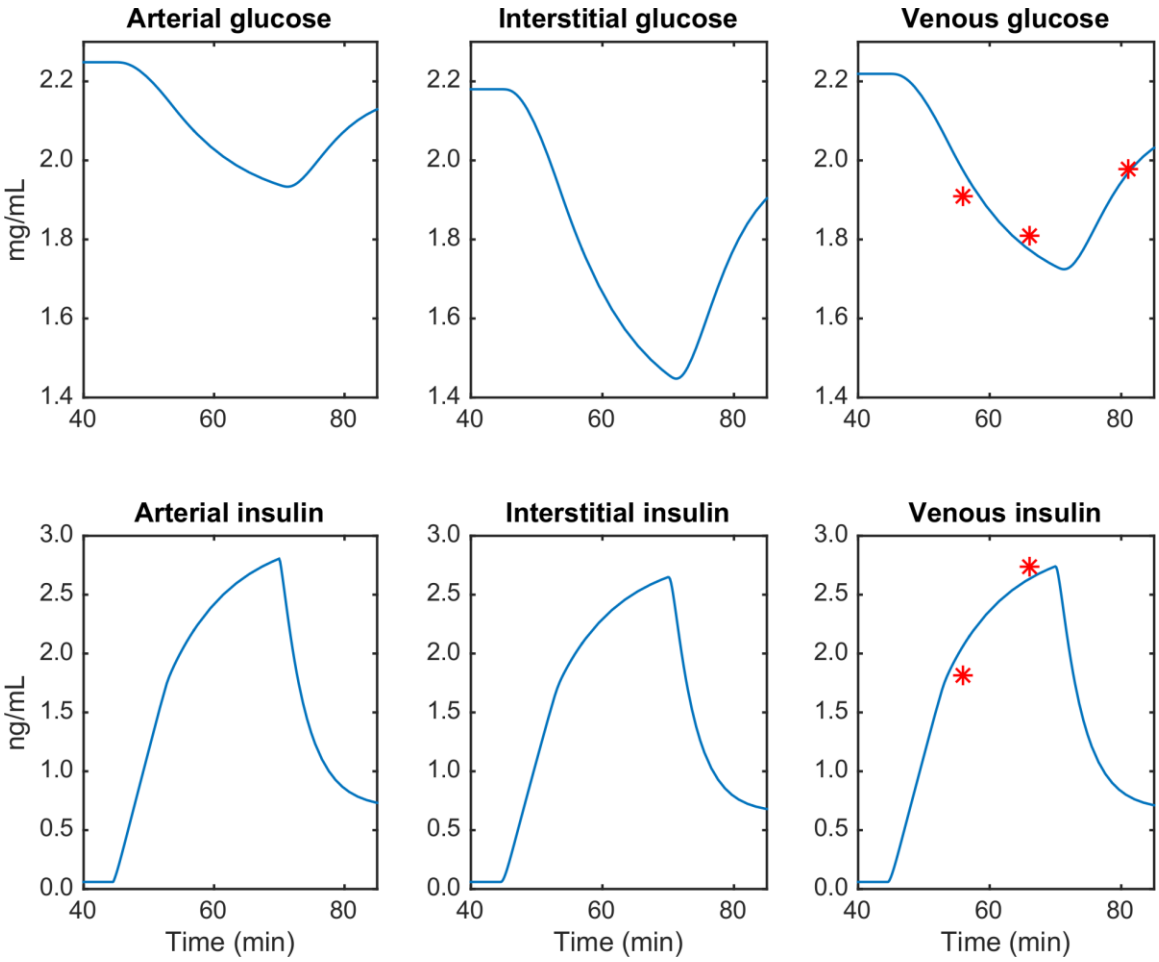
where the term $-m_3 C_{ins}^{i'}$ represents cellular uptake of insulin.

Simulation Results

To simulate the insulin bolus, inflow insulin concentration C_{ins}^0(t) (in mg/mL) is approximated by:

$$C_{ins}^0(\mathrm{t}) = \begin{cases} 0.06 & t < 44.5\ s \\ 0.06 + (t - 44.5) \times 1.74/(52.5 - 44.5) & 44.5 \le t < 52.5\ s \\ 1.8 + 1.35 \times \left(1 - e^{-\frac{t-52.5}{10}}\right) & 52.5 \le t < 70\ s \\ 1.8 + 1.35 \times \left(1 - e^{-\frac{70-52.5}{10}}\right) - 2.2 \times \left(1 - e^{-\frac{t-70}{4}}\right) & 70\ s \le t \end{cases}$$

The parameters m_1, m_2, and m_3 are fitted using experimental data. Specifically, they are taken to be 0.1, 0.33, and 0.1 mL/min, respectively. A comparison between model predictions and measured data is shown in Supplemental Figure 2.



Supplemental Figure 2. Predicted Glucose and Insulin Concentrations.
Predicted glucose and insulin concentrations in the arterial, venous, and interstitial compartments as functions of time. Red asterisks mark experimental data.

Supplemental Table 1. Supplemental Information. Post-IAM Changes in Insulin and Glucose Plasma Levels.

Sample site	Insulin AUC (*ng/mL•min/0.2IU/kg)*		
	AUC_{last}	T_{last} (min)	AUC_{0-16}
CLFV	6.03	16	6.03
FV	17.27	16	17.27
Sys	28.53	37	9.81
	Glucose AUC (mg/dL•min)		
	AUC_{last}	T_{last} (min)	AUC_{0-19}
CLFV	127	34	185.8
FV	-1108.5	31	-666.9
Sys	410.5	37	356.5

Plasma insulin and glucose levels after IAM insulin administration into the ipsilateral femoral artery. The table describes 3 sets of data (ipsilateral, contralateral, and systemic) obtained simultaneously in the same animal (animal # V in Table 2). Area Under the Curve (AUC) of insulin and glucose levels in Ipsilateral Femoral Vein (FV) vs. Contralateral Femoral Vein (CLFV) and Systemic Data (Sys – Superior Vena Cava). *Unit for Insulin AUC is ng/mL•min/0.2IU/kg.*