

## S2 Appendix.

### Ultradian endocrine model

The primary state variables are the glucose concentration  $G$ , the plasma insulin concentration  $I_p$ , and the interstitial insulin concentration  $I_i$ ; these three state variables are appended with a three stage filter  $(h_1, h_2, h_3)$  which reflects the response of the plasma insulin to glucose levels [1]. The resulting ordinary differential equations take the form [2]:

$$\frac{dI_p}{dt} = f_1(G) - E\left(\frac{I_p}{V_p} - \frac{I_i}{V_i}\right) - \frac{I_p}{t_p} \quad (1a)$$

$$\frac{dI_i}{dt} = E\left(\frac{I_p}{V_p} - \frac{I_i}{V_i}\right) - \frac{I_i}{t_i} \quad (1b)$$

$$\frac{dG}{dt} = f_4(h_3) + I_G(t) - f_2(G) - f_3(I_i)G \quad (1c)$$

$$\frac{dh_1}{dt} = \frac{1}{t_d}(I_p - h_1) \quad (1d)$$

$$\frac{dh_2}{dt} = \frac{1}{t_d}(h_1 - h_2) \quad (1e)$$

$$\frac{dh_3}{dt} = \frac{1}{t_d}(h_2 - h_3) \quad (1f)$$

The *major* parameters include: (i)  $E$ , a rate constant for exchange of insulin between the plasma and remote compartments; (ii)  $I_G$ , the exogenous (externally driven) glucose delivery rate; (iii)  $t_p$ , the time constant for plasma insulin degradation; (iv)  $t_i$ , the time constant for the remote insulin degradation; (v)  $t_d$ , the delay time between plasma insulin and glucose production; (vi)  $V_p$ , the volume of insulin distribution in the plasma; (vii)  $V_i$ , the volume of the remote insulin compartment; (viii)  $V_g$ , the volume of the glucose space [3].  $f_1(G)$  represents the rate of insulin production;  $f_2(G)$  represents insulin-independent glucose utilization;  $f_3(I_i)G$  represents insulin-dependent glucose utilization;  $f_4(h_3)$  represents delayed insulin-dependent glucose utilization;

$$f_1(G) = \frac{R_m}{1 + \exp(\frac{-G}{V_g c_1} + a_1)} \quad (2)$$

$$f_2(G) = U_b(1 - \exp(\frac{-G}{C_2 V_g})) \quad (3)$$

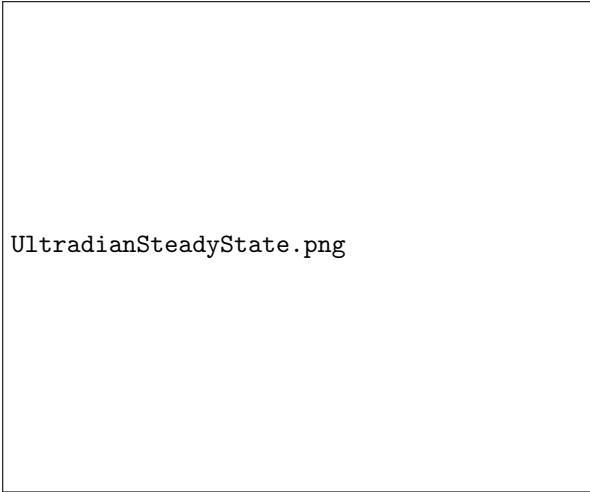
$$f_3(I_i) = \frac{1}{C_3 V_g} \left( U_0 + \frac{U_m - U_0}{1 + (\kappa I_i)^{-\beta}} \right) \quad (4)$$

$$f_4(h_3) = \frac{R_g}{1 + \exp(\alpha(\frac{h_3}{C_5 V_p} - 1))} \quad (5)$$

$$\kappa = \frac{1}{C_4} \left( \frac{1}{V_i} - \frac{1}{E t_i} \right) \quad (6)$$

The nutritional driver of the model  $I_G(t)$  is defined over  $N$  discrete nutrition events [3], where  $k$  is the decay constant and event  $j$  occurs at time  $t_j$  with carbohydrate quantity  $m_j$

$$I_G(t) = \sum_{j=1}^N \frac{m_j k}{60} \exp(k(t_j - t)) \text{ where } N = \#\{t_j < t\} \quad (7)$$



UltradianSteadyState.png

**Fig 1.** Simulation of post-prandial ultradian glucose oscillations returning to equilibrium. This simulation was performed for a 45 g carbohydrate meal, and employed the initial conditions and parameter values reported by Sturis *et al.* [1]

**Table 1.** Full list of parameters for the ultradian glucose-insulin model [2]. Note that IIGU and IDGU denote insulin-independent glucose utilization and insulin-dependent glucose utilization, respectively.

Ultradian model parameters		
Name	Nominal Value	Meaning
$V_p$	3 l	plasma volume
$V_i$	11 l	interstitial volume
$V_g$	10 l	glucose space
$E$	$0.2 \text{ l min}^{-1}$	exchange rate for insulin between remote and plasma compartments
$t_p$	6 min	time constant for plasma insulin degradation (via kidney and liver filtering)
$t_i$	100 min	time constant for remote insulin degradation (via muscle and adipose tissue)
$t_d$	12 min	delay between plasma insulin and glucose production
$k$	$0.5 \text{ min}^{-1}$	rate of decayed appearance of ingested glucose
$R_m$	$209 \text{ mU min}^{-1}$	linear constant affecting insulin secretion
$a_1$	6.6	exponential constant affecting insulin secretion
$C_1$	$300 \text{ mg l}^{-1}$	exponential constant affecting insulin secretion
$C_2$	$144 \text{ mg l}^{-1}$	exponential constant affecting IIGU
$C_3$	$100 \text{ mg l}^{-1}$	linear constant affecting IDGU
$C_4$	$80 \text{ mU l}^{-1}$	factor affecting IDG
$C_5$	$26 \text{ mU l}^{-1}$	exponential constant affecting IDGU
$U_b$	$72 \text{ mg min}^{-1}$	linear constant affecting IIGU
$U_0$	$4 \text{ mg min}^{-1}$	linear constant affecting IDGU
$U_m$	$94 \text{ mg min}^{-1}$	linear constant affecting IDGU
$R_g$	$180 \text{ mg min}^{-1}$	linear constant affecting IDGU

## References

1. Sturis J, Polonsky KS, Mosekilde E, Cauter EV. Computer model for mechanisms underlying ultradian oscillations of insulin and glucose. *Am J Physiol Endocrinol Metab.* 1991;260:E801–E809.
2. Keener J, Sneyd J. *Mathematical physiology II: Systems physiology.* Springer; 2008.
3. Albers D, Elhadad N, Tabak E, Perotte A, Hripcsak G. Dynamical Phenotyping: Using Temporal Analysis of Clinically Collected Physiologic Data to Stratify Populations. *PLoS One.* 2014;6:e96443.