Characterisation of Optimal Responses to Pulse Inputs in the Bergman Minimal Model

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Abstract: The Bergman minimal model is a dynamic model of plasma glucose concentration. It has two input variables – insulin delivery and carbohydrate intake. We investigate the behaviour of plasma glucose concentration predicted by the model given carbohydrate (CHO) inputs and commensurate insulin inputs. We observe that to maintain plasma glucose above a specified minimum concentration results in an unavoidable peak in plasma glucose. Additionally, we specify the timing and magnitude of a bolus pulse to minimise this unavoidable peak in plasma glucose concentration whilst attaining but not going below the desired minimum glucose concentration. Finally, we obtain necessary and sufficient conditions for the glucose concentration to be minimised.

Keywords: control of constrained systems, non-linear systems, positive systems, performance limitations, blood glucose regulation, diabetes, Bergman minimal model, Artificial Pancreas

1. INTRODUCTION

Diabetes is a chronic disease affecting over sixty million people (Wild et al., 2004). Diabetics are unable to correctly regulate blood glucose concentrations which, if not successfully managed, leads to multiple adverse complications. Typically, management involves subcutaneous administration of insulin to minimise plasma glucose concentration whilst keeping it above a lower bound to avoid hypoglycaemia. Current treatment is invasive and often leads to poor outcomes. Hence, much recent effort has been devoted to developing an artificial pancreas which automates treatment (Harvey et al., 2010) and provides better control of glucose concentrations. The development of such systems and further treatment improvements requires an understanding of the dynamics of glucose regulation and pharmacokinetics of insulin. A number of models of glucose regulation have been proposed (Makroglou et al., 2006). One of these, the Bergman Minimal Model (Bergman (2005); Goodwin et al. (2015a); Kanderian et al. (2009)), is a non-linear continuous-time model for glucose regulation. The model comprises a set of first order linear ordinary differential equations which govern the concentration and effectiveness of insulin:

\[
\frac{d}{dt} I_{sc}(t) = -\frac{1}{\tau_1} I_{sc}(t) + \frac{1}{\tau_1} I_{sc}^0(t)
\]

\[
\frac{d}{dt} I_p(t) = -\frac{1}{\tau_2} I_p(t) + \frac{1}{\tau_2} I_{sc}
\]

\[
\frac{d}{dt} I_{eff}(t) = -p_2 I_{eff}(t) + p_2 S_l I_p(t)
\]

and a non-linear ordinary differential equation which governs the plasma glucose concentration \( g(t) \):

\[
\frac{dg}{dt} = -g(t) \cdot (I_{eff}(t) + G) + r(t) + E
\]

where:

- \( ID(t), I_{sc}(t), I_p(t) \) and \( I_{eff}(t) \) are the delivery, subcutaneous concentration, plasma concentration and insulin effectiveness, respectively.
- \( \tau_1 \) and \( \tau_2 \) are time constants.
- \( C_l, S_l \) and \( p_2 \) are the clearance rate, insulin sensitivity and the insulin motility (Roy and Parker, 2007).
- \( g(t) \) is the plasma glucose concentration.
- \( E \) and \( G \) are the endogenous glucose production and the effect of glucose on the uptake of plasma glucose and the suppression of endogenous glucose production, respectively.
- \( r(t) \) is the glucose absorption from meals.

A variety of physiological values for the above are derived from (Kanderian et al., 2009) and given in Table 1 of (Goodwin et al., 2015a). For notational convenience, we rewrite the Bergman minimal model as the following system of differential equations:

\[
\begin{align*}
\dot{z} &= -dz + duk \\
\dot{y} &= -cy + cz \\
\dot{x} &= -ax + aby \\
\dot{y} &= -hg + w
\end{align*}
\]

where all variables and constants are positive, \( u(t) = ID(t) \) is the input function,

\[
\begin{align*}
h &= x + G \\
w &= r + E
\end{align*}
\]

and the function \( r \) is a given bounded function.
We develop necessary and sufficient conditions, given in Theorem 20, for the glucose response $g(t)$ to a pulse input function, $u(t)$, to be minimised. Additionally, these conditions give a non-linear version of the fundamental control limitation explored in Theorem 2 of Goodwin et al. (2015b), for the specific case of a single input pulse. In Figure 1 we show an example of the glucose responses to two pulse inputs delivered at times $t'_1 > t'_2$. The response which satisfies the conditions of Theorem 20 has a lower maximum glucose concentration for the system whilst still maintaining the glucose concentration above a specified minimum concentration.

![Figure 1](image_url)

Fig. 1. Glucose responses given a fixed function $w$ and two different injection times, where $t'_1$ corresponds to the injection time of the brown response and $t'_2$ the injection time of the blue response.

2. OUTLINE AND NOTATION

In Section 3 we state our assumptions and the constraints on the system. Additionally we prove some facts about the system and develop tools necessary for the subsequent Sections. In Section 4 we prove necessary and sufficient conditions on the plasma glucose response to inputs $w$ and $u$ for the input $u$, comprising a single pulse, to be optimal. Finally, in Section 5 we develop a sufficient condition for an input function, comprising multiple pulses, to be optimal.

3. PRELIMINARIES, ASSUMPTIONS AND CONSTRAINTS

Assumptions

Throughout we impose the following initial conditions: $z(0) = y(0) = ku(0), x(0) = bk(0)u(0)$ and $g(0) > 0$. We assume the function $w$ is positive and bounded. We also assume the input $u(t)$ is positive and bounded and of the form:

$$u(t) = \bar{u} + \tilde{u} \chi_A(t)$$

where the constant $\bar{u}$ is the basal input, $\tilde{u}$ is the magnitude of the bolus input applied at some time $t'$, known as the delivery time. The bolus input is held constant over the interval $A = [t', t' + \tau]$ and $\chi_A$ is the characteristic function of the interval $A$. The boundedness and positivity of $u(t)$ implies that $h$, given by (1) and (2), is a continuous, positive and bounded function. We desire that there exist $\lambda > 0$ such that $g(t) \geq \lambda$ for all $t$. This is achieved if $\lambda$ is a global minimum of $g(t)$. We denote by $t_{\min} \in \mathbb{R}_+$ a point such that $g(t_{\min}) = \lambda$. Note, from (1) that by setting $\bar{g} = 0$ at $t_{\min}$, we have $w(t_{\min}) = \lambda h(t_{\min})$ at such $t_{\min}$.

**Definition 1. (Proper Input).** For some $\lambda \leq g(0)$, an input function, $u(t)$, is proper, if there exists $t_{\min}$ such that $g(h(u(t_{\min})), w) = \lambda, g(t) \geq \lambda$ for all $t$. The existence of a proper input, of the form (3), is established in Theorem 7. Finally, unless otherwise stated we assume that $t_{\max} := \arg \max g(t) < \infty$. The maximal time $t_{\max}$ exists as shown in Corollary 9.

Bounds and System Properties

**Lemma 2. (Bounds).** Suppose $h$ and $w$ are bounded positive real-valued functionals, and $g$ is as in (1). Then there exist $\Gamma, \Lambda \in \mathbb{R}_+$ and constants $c_1$ and $c_2$ depending on the initial condition such that $\Gamma \geq \Lambda$ and:

$$c_1 \exp \left( - \int h \right) + \Lambda \leq g(t) \leq c_2 \exp \left( - \int h \right) + \Gamma$$

**Proof.** A solution for $g$ is given by:

$$g(t) = \exp \left( - \int h \right) \left( c_3 + \int w \exp \left( \int h \right) \right)$$

where $c_3$ is the value of $g$ at the lower extreme of integration. Choose $\Gamma \in \mathbb{R}_+$ such that $w \leq \Gamma h$. Note such $\Gamma$ always exists since $w$ and $h$ are bounded positive functions. We obtain:

$$g(t) = \exp \left( - \int h \right) \left( c_3 + \int w \exp \left( \int h \right) \right) \leq \exp \left( - \int h \right) \left( c_3 + \Gamma \int h \exp \left( \int h \right) \right) = c_2 \exp \left( - \int h \right) + \Gamma$$

where $c_2 = c_3 - \Gamma$. Similarly, for $\Lambda$ such that $\Delta h \leq w$, the lower bound on $g(t)$ is obtained and $c_1 = c_3 - \Lambda$. □

**Remark 3.** The bounds, $\Gamma \geq \sup \{ \frac{w(t)}{h(t)} \}$ and $\Lambda \leq \inf \{ \frac{w(t)}{h(t)} \}$ in Lemma 2, may be improved at any $t$ by taking a finite ordered partition $\mathcal{P} := \{ t_0, \ldots, t_n, t \}$ of the
interval \([0,t]\) and defining \(\Gamma_i\) and \(\Lambda_i\) such that \(\Gamma_i h(t) \geq w(t)\) and \(\Lambda_i h(t) \leq w(t)\) for all \(t \in [i, i+1]\).

Lemma 4. Let \(u(t)\) be as in (3) and choose \(\lambda \leq g(0)\).

(1) The response \(x(t)\) is separable into its basal and bolus responses i.e.

\[
x(t) = x(\bar{u}) + x(\hat{u}) := u \mathcal{Y}(t) + \bar{u} \mathcal{Y}(t)
\]

where \(\mathcal{Y}(t)\) is the response of \(x\) to the input with \(\bar{u} = 1\), \(\hat{u} = 0\) and \(Y(t)\) is the response of \(x\) to the input (3) with \(\bar{u} = 0\), \(\hat{u} = 1\).

(2) Under the assumed initial conditions, \(x(\pi) = bk\pi\) for all \(t\) i.e. \(\mathcal{Y}(\pi) = bk\). Furthermore, if \(A\) is bounded. Then:

\[
\lim_{t \to \infty} x(t) = bk\pi
\]

(3) if \(A\) is empty and the basal input \(\pi \leq \frac{E - \lambda G}{\lambda bk}\) then 

\[
g(t) \geq \lambda \text{ for all } t.
\]

Proof.

Part 1. This follows by linearity of the \((z, y, x)\)-system in (1).

Part 2. Follows from the solutions to the first order linear ordinary differential equations in (1) and \(\mathcal{Y}(t) = bk\) from the specified initial conditions.

Part 3. By Lemma 2 there exists \(\Lambda \in (0, g(0)]\) satisfying \(\Lambda h \leq w\), which guarantees that \(g(t) \geq \Lambda\) for all \(t\). As, from (2), \(w(t) \geq E\) and \(h(t) = h(\pi) = x(\pi) + G \leq G + G\) by Lemma 4, such \(\Lambda\) may be chosen to satisfy the inequality:

\[
\Lambda \leq \frac{E}{bk\pi + G}
\]

Therefore, to ensure that \(\Lambda \geq \lambda\) we require:

\[
\lambda \leq \frac{E}{bk\pi + G} \implies \pi \leq \frac{E - \lambda G}{\lambda bk}
\]

Remark 5. We define the steady-state of \(g\) to be \(g(\infty) := \lim_{t \to \infty} g(t)\), when \(\lim_{t \to \infty} Y(t) = 0\) and \(\lim_{t \to \infty} w(t) = E\) i.e. it is the limit of the response of \(g(t)\) when the only input is the constant input \(\pi\). The steady-state may be set to be any positive real number. Since, if \(\pi\) is constant then \(\dot{g} \to 0\) as \(t \to \infty\). Indeed, assuming that \(A\) is bounded, setting:

\[
\pi = \frac{1}{kb} \left( \frac{E}{g(\infty)} - G \right)
\]

gives the result, where \(g(\infty) \geq \lambda\) is some specified value.

In this case:

\[
h(\pi) := x(\pi) + G \geq \frac{E}{g(\infty)}
\]

We note, the constant, \(c_3\), from Lemma 2 corresponds to the initial plasma glucose concentration, \(g(0)\). Henceforth, we fix \(g(\infty) := g(0)\) and \(\pi\) to be as in (5).

The nature of the system dynamics (1) – (2) and the positivity of the inputs induces a monotonic relationship between the insulin input and glucose concentration. This property is proven in the intermediate Lemma 6. Note, we define \(u_1(t) > u_2(t)\) if there exists such that \(u_1(s) > u_2(s)\) and \(u_1(t) \geq u_2(t)\) for all \(t\).

Lemma 6. Suppose \(w\) is fixed. Then \(g(t)\) is a strictly monotone function of the input \(u(t)\).

Proof. Fix \(w\) and let \(u_1\) and \(u_2\) be two inputs with delivery time \(t'\) such that \(\hat{u}_1 < \hat{u}_2\). Denote by \(h_1\), \(g_1\) and \(h_2\) and \(g_2\) their respective responses. Since \(h\) is a monotone function of the input \(u\) we have that \(h_1 < h_2\) for all \(t > t'\). A solution for \(g(t)\) for \(t \geq t'\) is given by:

\[
g(t) = g_1(t') \exp \left( - \int_{t'}^{t} h(s) \, ds \right)
\]

\[
+ \int_{t'}^{t} w(s) \exp \left( - \int_{s}^{t} h(\xi) \, d\xi \right) \, ds
\]

As \(g_1(t') = g_2(t')\), because the inputs are identical before \(t'\), and:

\[
\exp \left( - \int_{t'}^{t} h_1(s) \, ds \right) > \exp \left( - \int_{t'}^{t} h_2(s) \, ds \right)
\]

\[
\exp \left( - \int_{t'}^{t} h_1(\xi) \, d\xi \right) \geq \exp \left( - \int_{t'}^{t} h_2(\xi) \, d\xi \right)
\]

for all \(t > t'\) and \(l \leq t\), we have that \(g_1(t) > g_2(t)\) for all \(t > t'\). □

Theorem 7 proves the existence of a bolus input delivered at any \(t'\) which achieves a specified minimum \(\lambda > 0\) and thus proves the existence of proper inputs of the form (3).

Theorem 7. (Insulin Bolus). Suppose \(u(t)\) is of the form (3). Fix \(\pi\) and \(t' - \pi\) as the input time i.e. \(A := [\tau', \tau + \tau]\), choose \(\lambda \in (0, g(t'))\) and suppose \(\hat{u}\) such that \(\hat{\hat{u}}(t)\) is as in Remark 5. Then there exists \(\bar{u}\) such that \(u(t)\) is proper.

Proof. Denote by \(g(\hat{u})\) the response of \(g(t)\) to the input \(u(t) := \bar{u} + \hat{\lambda} \hat{\pi} A\). By Lemmas 2 and 6, there exist \(\hat{\hat{u}}\) and \(\hat{v}\) such that \(\min_{\hat{\hat{u}} < \hat{\hat{v}}} \hat{g}(\hat{\hat{u}}) \geq \lambda\) and \(\min_{\hat{\hat{u}}} \hat{g}(\hat{\hat{v}}) \leq \lambda\).

Suppose \(\min_{\hat{\hat{u}} < \hat{\hat{v}}} \hat{g}(\hat{\hat{v}}) < \min_{\hat{\hat{u}}} \hat{g}(\hat{\hat{u}})\). We recursively define the sequences \(\pi := (\hat{\hat{u}})_{n=0}^{\infty}\) and \(\pi := (\hat{\hat{v}})_{n=0}^{\infty}\) by \(\hat{\hat{u}} = \hat{\hat{u}}\) and \(\hat{\hat{v}} = \hat{\hat{v}}\) and \(\hat{\hat{h}}\) the greatest element of the following finite ordered partition of the interval \([\hat{\hat{u}}_{i-1}, \hat{\hat{u}}_{i-1}]\):

\[
L_i := \left\{ \frac{(n-1)\hat{h}_{i-1} + \hat{\hat{v}}_{i-1}}{n}, \ldots, \frac{k_i \hat{h}_{i-1} + (n-k_i)\hat{\hat{v}}_{i-1}}{n} \right\}
\]

where \(n \in \mathbb{N}\) is arbitrary and \(n \leq n\), such that the response:

\[
g \left( \frac{k_i \hat{h}_{i-1} + (n-k_i)\hat{\hat{v}}_{i-1}}{n} \right) \geq \lambda
\]

for all \(t \geq t'\). Similarly, \(\hat{\hat{v}}\) is defined to be the least element of \(L_i\) such that, for all \(t \geq t'\):

\[
g \left( \frac{k_i \hat{h}_{i-1} + (n-k_i)\hat{\hat{v}}_{i-1}}{n} \right) \leq \lambda
\]

The sequence \(\hat{\hat{v}}\) is a monotone increasing sequence bounded above by \(\hat{\hat{v}}\) for all \(\hat{\hat{v}}\) and therefore has a limit \(\hat{\hat{v}}\). Similarly, \(\hat{\hat{h}}\) is a monotone decreasing sequence bounded below by \(\hat{\hat{h}}\) for all \(\hat{\hat{h}}\) and thus has a limit \(\hat{\hat{h}}\). It remains to show that these two limits are equal. If either sequence is eventually constant then both are constant and equal. As either sequence is constant only if \(\min_{\hat{\hat{u}} < \hat{\hat{v}}} g(t) = \lambda\), which case, by construction of the sequences, both sequences would have the same value. Suppose, instead, for all \(i\) that \(\hat{\hat{h}} < \hat{\hat{v}}\). We see that:

\[
\hat{\hat{h}}_{i+1} = \frac{k_i \hat{h}_{i-1} + (n-k_i)\hat{\hat{v}}_{i-1}}{n}
\]
Then, by Lemma 6, $\hat{v}_{i+1}$ must be the next element of $L_i$, that is:

$$\hat{v}_{i+1} = \frac{(k_i - 1)\hat{v}_i + (n - k_i + 1)v_i}{n}$$

Thus:

$$\hat{v}_{i+1} - \hat{v}_i = \frac{1}{n} (\hat{v}_i - \hat{v}_i)$$

$$\vdots$$

$$= \frac{1}{n^{i+1}} (\hat{v}_0 - \hat{v}_0)$$

i.e. $\lim_{i \to \infty} (\hat{v}_{i+1} - \hat{v}_i) = 0$ i.e. $v = 0$. Thus $\lambda \leq \min_{t \geq t} g(v) = \min_{t \geq t} g(0) \geq \lambda$. Setting $\hat{u} = v$ gives $\min_{t \geq t} g(\hat{u}) \geq \lambda$ and $g(\hat{u}) \geq \lambda$ for all $t \geq t'$. □

Corollary 8 provides an explicit expression for the magnitude of the bolus input which achieves the global minimum of the glucose concentration.

Corollary 8. (Insulin Bolus Bound). Fix $t'$ and choose $\lambda > 0$ and let $u = \pi + \hat{u}_A$, see (3), where $\hat{u}$ is as in Remark 5. Suppose the input $\hat{u}$ is as in Theorem 7. Then the input satisfies, $\hat{u} \leq \hat{U}(\lambda)$, where:

$$\hat{U}(\lambda) := \left(\frac{w(t_{\min})}{\lambda} - G - x(\pi, t_{\min})\right) \left(1 - \frac{1}{Y(t_{\min})}\right)$$

and $g(t) \geq \lambda$ for all $t$. In particular, if $\hat{u} = \hat{U}(\lambda)$ then $g(t_{\min}) = \lambda$.

Proof. We have the following:

$$\hat{g}(t_{\min}) = - g(t_{\min})h(t_{\min}) + w(t_{\min}) = 0$$

$$\Leftrightarrow g(t_{\min}) = \frac{w(t_{\min})}{h(t_{\min})}$$

Suppose $g(t_{\min}) < \lambda$. Then, from (2), (4), (7), and as $h(t) > 0$:

$$w(t_{\min}) < \lambda h(t_{\min}) = \lambda (x(\hat{u}, t_{\min}) + \hat{u} Y(t_{\min}) + G)$$

$$\Leftrightarrow \hat{u} > \hat{U}(\lambda).$$

Thus, (6) implies $g(t) \geq \lambda$ for all $t$ and the result follows. □

Corollary 9 proves the existence of a finite global optimum for glucose concentration responses to proper inputs.

Corollary 9. (An Upper Bound). Choose $\lambda \leq g(0)$. Suppose $u(t)$ is proper. Then there exists $t_{\max} \in \mathbb{R}_+ := \mathbb{R}_+ \cup \{\infty\}$ such that $g(t) \leq g(t_{\max}) =: \gamma$ for all $t$ and $\gamma = \lambda$ if and only if $g(t) = \lambda$ for all $t$. Furthermore, if $t_{\max} < \infty$. Then:

$$\gamma = \frac{w(t_{\max})}{h(t_{\max})} = \frac{\alpha_1 \lambda}{\alpha_2 + \alpha_3 \lambda}$$

where $\alpha_1 := w(t_{\max})$, $\alpha_2 := w(t_{\min})$, $\alpha_3 := (G + x(\pi, t_{\max})\left(1 - \frac{1}{Y(t_{\max})}\right) x(\pi, t_{\min}) - x(\pi, t_{\min})).$

Proof. If there is $s \in \{t : g(t) = 0\}$ such that $g(s) \geq g(t)$ for all $t$. Then $t_{\max} = s$. Otherwise $g(t)$ must increase as $t \to \infty$. We may take a monotone increasing sequence $(g(t_i))_{i=0}^{\infty}$, where $t_0 \geq 0$ and $g(t_k) \leq g(t_0)$ only if $g(t_k) = g(t_0)$ for all $t \in [0, t_k]$. $g(t_k)$ is the peak of the function $g$. By Lemma 2 the sequence, $(g(t_i))_{i=0}^{\infty}$ is bounded above and thus converges to $\overline{g} \leq \Gamma$. By construction $g(t) \leq \overline{g}$ for all $t$. We see that $\gamma = \lambda$ if and only if $g(t) = \lambda$ for all $t$ follows by definition of $\gamma$.

Suppose $t_{\max} < \infty$. Then (8) follows from rearranging the differential equation $\dot{y} = -g(t) + w$ evaluated at $t_{\max}$ and substituting in the formula for $\hat{u}$ given by (6). □

Corollary 10 shows that, the higher the minimum glucose concentration, the higher the peak glucose concentration.

Corollary 10. Choose $\lambda < \lambda' \leq g(0)$. Let $u(t)$ and $u'(t)$ be inputs of the form (3), with common delivery time $t'$, which are proper for $\lambda$ and $\lambda'$ respectively. Then $\gamma < \gamma'$.

Proof. Note $\gamma' \geq \lambda'$ and $\gamma \geq \lambda$. Denote by $t_{\min}$ and $t_{\min}'$ the times at which $g(t) = \lambda$ and $g'(t) = \lambda'$ respectively. If for example $h' > h$ for some $t > t'$. Then $h' > h$ for all $t > t'$. This is because $u(t)$ and $u'(t)$ are of the form (3) and have common delivery time. Suppose that $h' > h$ for all $t > t'$. This implies that $g' \geq g$ for all $t > t'$. In particular at $t_{\min} \geq t'$ we have that $\lambda = g(t_{\min}) \geq g'(t_{\min}) \geq \lambda'$ contradicting $\lambda < \lambda'$. Thus $h > h'$ for all $t > t'$. Finally, as $h$ is a monotonous function of the input $u(t)$, we see that $\hat{u} > \hat{u}'$. This implies that $g(t) < g'(t)$ for all $t > t'$. □

4. OPTIMAL INPUTS

In this section we give necessary and sufficient conditions on the delivery time of a proper input such that the glucose response is optimal i.e. the maximum glucose concentration $\gamma$ is minimised. Throughout, we fix the length, $\tau$, of the interval over which the bolus is delivered. This ensures that the function $Y(t-t')$ in (4) is invariant under translation by $t'$ – the delivery time. Under these conditions we establish a property of the function $h$, defined in (2), in Lemma 11.

Lemma 11. For any two distinct proper inputs $u_1$ and $u_2$, delivered at times $t_1$ and $t_2$ respectively, with responses $h_1$ and $h_2$, there exists $t$, such that either:

$$h_1 > h_2, t \in (t_1, t_2)$$

$$h_1 = h_2, t = t_1$$

$$h_1 < h_2, t > t_1$$

Or:

$$h_1 < h_2, t \in (t_1, t_2)$$

$$h_1 = h_2, t = t_1$$

$$h_1 > h_2, t > t_1$$

Proof. Indeed, if $h_2(t) > h_1(t)$ or $h_2(t) < h_1(t)$ for all $t > \min\{t_1, t_2\}$ then, by Lemma 6 there would exist $t$ such that $g_2(t) < \lambda$ or $g_1(t) < \lambda$. Implying that either $u_1$ or $u_2$ are not proper. □

In the subsequent proofs of Lemmas 16, 18, and 19, we only present the first case, (9), as the other case, (10), follows by a similar argument.

Remark 12. For fixed $w$ the functions $h_1$ and $h_2$ satisfy (9) only if $t_1 < t_2$, i.e. only if $u_1$ is delivered before $u_2$ as the function $Y(t)$ is independent of the magnitude $\hat{u}$.

We define the optimal, minimised, glucose response as the input control strategy that ensures that the maximum glucose concentration is minimised given the control and system limitations. Formally:
Definition 13. (Minimised Response). We say the response $g(t) = g(w, h)$ is minimised if $\max_t g(w, h') \geq \max_t g(w, h)$, for all $h' \neq h$.

Definition 14. (Optimal Delivery Time). We say a delivery time $t'$ of a bolus input $\tilde{u}_3[t', x, +\gamma]$, where $\tilde{u}$ is given by (6), is optimal if the response $g(t)$ is minimised.

Lemma 15. Suppose $w(t)$ is a continuous and bounded positive functional and $h(t)$ is the response to a proper input of the form (3). Then, for any $\varepsilon \in [0, g(0) - \lambda)$, there exist at most finitely many $t$ such that the response $g(t) < \lambda + \varepsilon$ and $g(t) = 0$.

Proof. This follows as $w(t)$ is bounded below and the response $Y(t)$ is continuous and converges to 0. □

Lemma 16. Suppose $g(h_1, w) = g_1(t)$ is a response to a proper input with bolus $\tilde{u}_3$ delivered at time $t_1$ such that there is a unique minimum $t^* = t_{1, \text{min}}$ i.e. $g_1(t_{1, \text{min}}) = \lambda$ and $g_1(t) > \lambda$ for all $t \neq t_{1, \text{min}}$. Then there exists a proper bolus input $\tilde{u}_3$ delivered at $t_2$ and a time $t_i \geq \min\{t_1, t_2\}$ at which $h_i(t_i) = h_2(t_i)$ such that the response $g_2(h_2, w) := g_2(t)$ attains its minimum at $\lambda$ and satisfies:

$$
\begin{align*}
g_1 &< g_2, \quad t < t_g \\
g_1 &< g_2, \quad t = t_g \\
g_1 &> g_2, \quad t > t_g
\end{align*}
$$

for some time $t_g \in [t_i, t_{1, \text{max}}]$, where $t_{1, \text{max}} := \max\{s > t_i : g_1(s) \geq g_1(t) \forall t\}$.

Proof. As $g$ is a continuous function of $h$, for all $\varepsilon > 0$ we may find $\delta > 0$ such that $|h_1 - h_2| < \delta$ implies $|g_2 - g_1| < \varepsilon$, for all $t$. Such $h_2$ exists and is of the form $x(t) + G$, where $x(t)$ is as in (4), as $x(t)$ is a continuous function of the input $u(t)$. Thus for all $\delta > 0$ there exists $\delta' > 0$ such that $|x_1 - x_2| < \delta'$ implies $|h_1 - h_2| < \delta$. Furthermore, by Theorem 7, we may assume $u_3$ is proper and of the form (3). Thus, by Lemma 11 and Remark 12, $u_2$ may be chosen such that there exists $t_i$ for which:

$$
\begin{align*}
h_1 &> h_2, \quad t \in (t_i, t_1) \\
h_1 = h_2, \quad t = t_i \\
h_1 < h_2, \quad t > t_i
\end{align*}
$$

Define $X := \min\{g_1(t) : t \neq t_{1, \text{min}} \land g_1(t) = 0\}$ or $g(0)$ if this minimum does not exist. Such $X > \lambda$ exists by Lemma 15 and $X \leq g(0)$, by construction. Choosing $\varepsilon < \min\{\gamma_1 - g(0), \lambda - X\}$ or $\varepsilon < \lambda - \lambda$ if $\gamma_1 - g(0) = 0$, where $\gamma_1 := \max\{g_1(t)\}$, implies that $t_{2, \text{min}} < t_{1, \text{max}}$. Note that $t_{2, \text{min}} > t_i$ as if it were not there would exist $t$ such that $g_1(t) < \lambda$ since $g_1 < g_2$ for all $t \in (t_i, t_1)$. Also, $g_2(t_{2, \text{min}}) = \lambda < g_2(t_{2, \text{min}})$, by assumption. By the Intermediate Value Theorem there is a $t_g \in [t_i, t_{1, \text{max}}]$ such that $g_1(t_g) = g_2(t_g)$. As $h_2 > h_1$ for all $t > t_i$ we see that $g_2(t_g) < g_1(t_t)$ for all $t > t_g$. □

Remark 17. Similarly to Lemma 16, we may show that if $t_{1, \text{max}} < t_{1, \text{min}}$ then there exists $h_2$ with response $g_2$ and $t_g \in [t_i, t_{1, \text{min}}]$ such that:

$$
\begin{align*}
g_1 &> g_2, \quad t < t_g \\
g_1 &< g_2, \quad t = t_g \\
g_1 &< g_2, \quad t > t_g
\end{align*}
$$

Lemma 18. (Single Minimum). Suppose $g(h, w) = g(t)$ is a response, to a proper input $w$, for which there is a unique minimum such that $g(t_{\text{min}}) = \lambda$. Then $g(t)$ is minimised if and only if $\max_{t < \min_t g(t)} g(t) = \max_{t > \min_t g(t)} g(t)$.

Proof. Without loss of generality, suppose that for some $h_1$ we have that:

$$
\gamma_1 := \max_{t < t_{1, \text{min}}} g_1(t) < \max_{t > t_{1, \text{min}}} g_1(t) =: \gamma_1
$$

where $g_1(t) := g(h_1, w)$. The existence of a unique $t_{1, \text{min}}$ implies there is a proper input with non-zero bolus $\tilde{u}_3$ delivered at some time $t'$. Define $t_1 := \max_{t < t_{1, \text{min}}} g_1(t)$ and $t_1 := \max_{t > t_{1, \text{min}}} g_1(t)$. By Lemma 16 there exists $h_2$ such that:

$$
\begin{align*}
g_1 &< g_2, \quad t < t_g \\
g_1 = g_2, \quad t = t_g \\
g_1 > g_2, \quad t > t_g
\end{align*}
$$

Proceeding as in the proof of Lemma 16, choosing $\varepsilon < \min\{\gamma_1 - g(\infty), \lambda - \gamma_1\}$ implies that $g_2 < \gamma_1$ for all $t$, since the choice of $\varepsilon$ ensures that $t_g < t_1$.

Now, suppose that $\max_{t < t_{1, \text{min}}} g_1(t) = \max_{t > t_{1, \text{min}}} g_1(t) := \gamma_1$ and $g_1$ is not minimised. We observe that for $g_2$ not to be minimised there must exist $h_2$ with response $g_2$ such that $g_2(t_1) < \gamma_1$ and $g_2(t) < \gamma_1$, which implies $t_g < t_1$. So $g_2(t_{1, \text{min}}) < g_1(t_{1, \text{min}}) = \lambda$. This contradicts the constraint on $g_2$. Hence no such $h_2$ exists. □

Fig. 2. Glucose response for functions $w$ and $h_1$ showing two unequal maxima about a single minimum, where $\gamma_1 := \max_{t < t_{1, \text{min}}} g_1(t)$ and $\gamma_1 := \max_{t > t_{1, \text{min}}} g_1(t)$.

Lemma 19. (Single Maximum). Suppose $g(h, w) = g(t)$ is a response, to a proper input, for which there exist distinct $t$ and $t$ such that $g(t) = g(t) = \lambda$ but a single $t_{\text{max}} := \arg\max\{g(t)\}$. Then $g(t)$ is minimised if and only if $\arg\max\{g(t)\} \in (t_i, t_1)$.

Proof. Suppose, for some $h_1$, that:

$$
\min_{t < t_{1, \text{max}}} g_1(t) = \min_{t > t_{1, \text{max}}} g_1(t) = \lambda
$$

Define $t_1 := \min\{t < t_{1, \text{max}} : g_1(t) = \lambda\}$ and $t_1 := \max\{t > t_{1, \text{max}} : g_1(t) = \lambda\}$. Suppose $h_2 \neq h_1$ is a response to a proper input $u_2$ as in Lemma 16. As $g_2 \geq \lambda$ for all $t$, the crossing time $t_g$ satisfies either $t_g < t_1$ or $t_g > t_1$. In both cases $g_2(t) > g_1(t)$ for all $t \in [t_1, t_1]$ which implies $\max\{g_2(t)\} > \max\{g_1(t)\}$.

Now, suppose that there are at least two distinct $t$ such that $g_1(t) = \lambda$ and, without loss of generality, that:

$$
\min_{t < t_{1, \text{max}}} g_1(t) < \min_{t > t_{1, \text{max}}} g_1(t)
$$

As in Lemma 16 there exists $h_2$ and $t_i$ with response $g_2$ such that:

$$
\begin{align*}
g_1 &< g_2, \quad t < t_g \\
g_1 = g_2, \quad t = t_g \\
g_1 > g_2, \quad t > t_g
\end{align*}
$$

where $t_g \in [t_i, t_{1, \text{max}}]$. In this case, proceeding as in Lemma 18, there exists $h_2$ such that $g_2(t) < \gamma_1$, where $\gamma_1 := \max\{g_1(t)\}$. □
Lemmas 18 and 19 show that for a given \( w \) and input of the form \( u(t) := \pi + \alpha\lambda t + \gamma t \), see (3), the maximum glucose concentration \( g(t_{\text{max}}) \) is minimised if and only if the maximum occurs between two minima, where \( g(t) = \lambda \), or the minimum between to equal maxima. We state this formally in Theorem 20.

**Theorem 20. (Multiple Extrema).** Suppose \( g(h, w) = g(t) \) is a response to an input of the form (3). Then \( g(t) \) is minimised if and only if there exists \( t_{\min} \) such that \( g(t_{\min}) = \lambda \) and either: arg min\( \{ g(t) \} \in (t, t'] \) where \( t \in \arg \min \{ g(t) \} \) or there is \( t \in \arg \min \{ g(t) \} \) such that max\( \{ g(t) \} = \max_{t\in\mathbb{C}} \{ g(t) \} \).

5. MULTIPLE PULSES

The optimality conditions given in Theorem 20 apply to an input \( u(t) \) with only a single bolus input delivered at some \( t' \in \mathbb{R}_+ \). We provide a sufficient condition for optimality of an input with finitely many bolus inputs i.e. we consider inputs of the form:

\[
u(t, T) := \pi + \sum_{i=0}^{N} u_i \chi_{[t_i', t_{i}'+\tau]} \quad (11)
\]

where \( T := (t_i)_{i=0}^{N} \) is a finite sequence of delivery times and the magnitude \( u_i \) of each bolus input is given sequentially by Theorem 7, if there exists \( t > t_i \) such that \( g(t) > g(0) \) or if \( i = 0 \). Otherwise \( u_i := 0 \). This ensures that each bolus input, and therefore the input, \( u(t) \), is proper and avoids unnecessary inputs. Thus we may assume that each \( u_i > 0 \).

By abuse of notation, we denote \( u(t, N) = u(t, T) \), where \( N \) is the length of the sequence \( T \).

**Lemma 21.** Suppose \( u_1(t, N) \) and \( u_2(t, N) \) are distinct inputs of the form (11). Then there exist at most \( 2N \), \( t_{g,i} \) such that \( g_1(t_{g,i}) = g_2(t_{g,i}) \) and for which one of the following, with either direction or order of the inequalities, is satisfied:

\[
\begin{align*}
g_1 &< g_2, \quad t \in (t_{g,i-1}, t_{g,i}) \\
g_1 &= g_2, \quad t = t_{g,i} \\
g_1 &\geq g_2, \quad t \in (t_{g,i}, t_{g,i+1})
\end{align*}
\]

Or:

\[
\begin{align*}
g_1 &< g_2, \quad t \in (t_{g,i-1}, t_{g,i}) \\
g_1 &= g_2, \quad t = t_{g,i} \\
g_1 &< g_2, \quad t \in (t_{g,i}, t_{g,i+1})
\end{align*}
\]

where \( t_{g,N+1} := \infty \). Furthermore, \( t_{g,0} := \inf \{ t : g_1(t) \neq g_2(t) \} \) must exist.

**Proof.** This follows as \( g \) is a monotonic function of \( h \) which is a monotonic function of the input \( u \).

**Definition 22.** Let \( u_3(t, N) \) and \( u_2(t, N) \) be two distinct inputs of the form (11). The points \( \{ t_{g,0}, t_{g,1}, \cdots, t_{g,2N-1} \} \) defined in Lemma 21 are the intersection points of the responses \( g(h(u_1(t, N))), w = g_1(t) \) and \( g(h(u_2(t, N))), w = g_2(t) \).

**Theorem 23.** Suppose \( u(t, N) \) is proper, the sum of the number of global maxima and minima, of the response \( g(h(u(t, N))), w \), is \( 2N + 1 \) and these minima and maxima are interlaced. Then \( u(t, N) \) is optimal, over inputs of the same \( N \).

**Proof.** Suppose \( g_1 \) is a response as in the statement of the Theorem and that there is an input \( u_2(t, N) \neq u_1(t, N) \) such that \( \max \{ g_2(t) \} < \max \{ g_1(t) \} \). Additionally, assume that \( t_{g,i} \neq t_{1,i,\min} \), where \( t_{1,i,\min} \) is the \( i \)th minimum of \( g_1 \) i.e. the intersection points of \( g_1 \) and \( g_2 \) do not occur at the minima of \( g_1 \). Under this assumption we see that \( \max \{ g_2(t) \} < \max \{ g_1(t) \} \) and if only if each \( t_{1,i,\max} \in (t_{g,i}, t_{g,i+1}) \), where \( t_{g,i} \) and \( t_{g,i+1} \) are two subsequent intersection points of the responses \( g_1 \) and \( g_2 \) and \( t_{1,i,\max} \) is the \( i \)th maximum of \( g_1 \). If this condition were not satisfied there would exist \( t \) such that \( g_2(t) < \lambda \) or \( g_2(t) > \gamma_1 \). Thus we see to ensure that \( g_2 < g_1 \) at \( n \) maxima followed by \( n \) minima and \( g_2 \) and \( g_1 \) must have \( 2n \) intersection points. If the maximum is not followed by a minimum then it requires one intersection point. By assumption, only the final maximum may not be followed by a minimum.

Suppose the first minimum occurs before the first maximum. Either \( t_{g,0} < t_{1,1,\min} \) or \( t_{g,0} \in (t_{1,1,\min}, t_{1,1,\max}) \) i.e. \( u_1(t) = u_2(t) \) for all \( t < t_{g,0} - \epsilon, \epsilon \in (0, t_{g,0}). \) This reduces to the case where the first maximum of \( g_1 \) occurs before the first minimum of \( g_1 \) with distinct inputs \( v_1(t, N - 1) \) and \( v_2(t, N - 1) \), of the form (11).

Suppose \( g_1 \) has \( N + 1 \) minima, and therefore \( N \) maxima. By the above \( t_{g,0} < t_{1,1,\min} \), thus from Lemma 21 \( 2N - 1 \) intersection points remain but \( 2N \) intersection points are required as each maximum is followed by a minimum.

Conversely, suppose \( g_1 \) has \( N + 1 \) maxima, and therefore \( N \) minima, this implies \( g_2 \) must intersect \( g_1 \) at \( 2N + 1 \) points. But by Lemma 21 there exist at most \( 2N \) intersection points.

Finally, suppose that \( m \) of the \( t_{g,i} = t_{1,i,\min} \). This would imply that at least one of the maxima require one fewer intersection points. Indeed, \( n \) maxima followed by \( n \) minima would require \( 2n - m \) intersection points. At such \( t_{g,i} \) we have that \( h_1 = h_2 \) and \( g_1 = g_2 \). Each intersection point after which \( g_2 \) \( g_1 \) corresponds to a pulse of \( u_2(t, N) \). Thus each \( t_{1,i,\max} \) corresponds to a pulse of \( u_2(t, N) \). Either there are \( N + 1 \) maxima of \( g_1 \), in which case \( u_2(t, N) \) does not have sufficiently many pulse inputs, or there are \( N \) maxima and \( N + 1 \) minima of \( g_1 \). In this case \( g_1 \) must start with a minimum. As above we may assume that \( t_{g,0} < t_{1,1,\min} \), which reduces to the case of \( N \) maxima followed by \( N \) minima and only \( N - 1 \) pulses of \( u_2(t, N) \) which we may apply.

Hence, there exists no such response \( g_2 \) and therefore no input \( u_2(t, N) \) exists. Thus \( u_1(t) \) is optimal.

**Remark 24.** The converse of Theorem 23 does not hold for all \( w \). As rapid changes in \( w \) will outpace the response time of \( h \). However the results may be applied over specified bounded intervals, each of which have different maxima, to find the optimal input for each interval.

**Lemma 25.** Suppose \( a < b < c \). Then there exists \( M \geq 1 \) such that the minimised response max\( \{ g(h_n, w) \} = \max \{ g(h_{n+1}, w) \} \) for all \( t \in [a, b] \) and for all \( n \geq M \), where \( h_n \) is the response to the input \( u(t, n) \).

6. EXAMPLE

In the example presented in Figure 3, we consider the following values for the parameters in (1) and (2): \( d = 0.0204, k = 497.5124, c = 0.0213, a = 0.0106, b = 8.11 \times 10^{-4}, G = 0.0032, E = 1.3, \) and \( r(t) = 0.0018f_1(t), \) where
$f_1(t)$ is the response of the system of linear differential equations:
\[
\begin{pmatrix}
\dot{f_1}(t) \\
\dot{f_2}(t)
\end{pmatrix}
= \begin{pmatrix}
\frac{1}{\ell} & 0 & 1 \\
\frac{1}{\ell} & 0 & -1
\end{pmatrix}
\begin{pmatrix}
f_1(t) \\
f_2(t) \\
\end{pmatrix}
+ \begin{pmatrix}
0 \\
\delta(t)
\end{pmatrix}
\]
where $\delta(t)$ is an impulse of magnitude 120 applied at time 500. We take the initial conditions to be as in Section 3 and set $g(\infty) = g(0) = 100 \text{mgdl}^{-1} (5.2 \text{mmolL}^{-1})$. The input is of the form (3) with $\bar{u}$ computed as in (5) and duration $\tau = 10$. The bolus magnitude $\hat{u}$ is computed as in Theorem 7, for the optimal injection time $t'$ that minimises $\gamma$, the global maximum of $g$. The minimum glucose concentration $\lambda$ is chosen to be $80 \text{mgdl}^{-1} (4.4 \text{mmolL}^{-1})$.

The first plot in Figure 3 shows the plasma glucose response to the function, $w(t)$, shown in the second plot of the same Figure, and an optimal bolus input $\hat{u}$ delivered at time 445. Two minima occur at times 500 and 800 bounding the unique maximum which occurs at time 574. The final plot of Figure 3 shows the maximum glucose concentration, $\gamma$, and the magnitude of a proper input bolus as a function of the input time $t'$. We see that $\gamma$ is minimised at the optimal input time 445.

![Figure 3: Glucose Response](image)

**Fig. 3.** The optimal glucose response to the functions $w(t)$ and $b(t)$, which are shown in the second plot, and the magnitude of a proper bolus and the maximum glucose concentration as a function of the delivery time $t'$, shown in the third plot.

### 7. CONCLUSIONS

Current research aims to generalise the presented results to any bounded input function $u(t)$. We are also interested in studying the effect of $\tau$ – the length of the bolus delivery interval $A$, on the response $g(t)$.

We do not know whether similar results to those presented may be shown for other models of glucose metabolism. In particular, those which include other factors such as exercise (Roy and Parker, 2007) or free fatty acid metabolism (Roy and Parker, 2006). Given the general nature of the proofs of the current results we believe it is likely that similar results may hold for other models.

Additionally, we aim to derive a formula for the maximum plasma glucose concentration which is independent of the times $t_{\text{min}}$ and $t_{\text{max}}$ and depends solely on $\lambda$ and the set $A$ i.e. to find $f : \mathbb{R}_+ \times A \rightarrow \mathbb{R}_+$ such that $\gamma = f(\lambda, A)$. This may allow us to extend the results of Corollary 10 by specifying the rate at which the maximum concentration increases with respect to increases in the fixed minimum concentration $\lambda$.

Finally, we desire to prove that there is an optimal partition of $\mathbb{R}_+$ into intervals so that the converse of Theorem 23 holds over each interval and no other partition will produce a lower maximum glucose concentration. Such a result may follow by extending Lemma 16 to cover inputs of the form (11). This would also allow us, in conjunction with Lemma 25 to specify the minimum number of pulses required to achieve the lowest possible maximum glucose concentration over some bounded interval.

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