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Optimal control and stability analysis of a glucose-insulin-FFA dynamic model with GLP-1 incretin effects

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Abstract. Obesity and its associated metabolic dysregulations, particularly Type 2 Diabetes Mellitus (T2DM), constitute a global health crisis. Understanding the intricate interplay of key metabolic components is crucial for effective management strategies. This study presents a novel mathematical model capturing the dynamic interactions among plasma glucose, insulin, and free fatty acids (FFAs), critically integrating the regulatory influence of Glucagon-Like Peptide-1 (GLP-1).

Through qualitative analysis, we established the model's physiological relevance and demonstrated the existence of a stable equilibrium point, confirmed by numerical simulations across various initial conditions. Sensitivity analysis revealed that FFA-related parameters (e.g., lipolysis rates and FFA-induced insulin impairment) and insulin secretion/clearance rates profoundly affect glucose homeostasis, underscoring the detrimental role of elevated FFAs in hyperglycemia. Furthermore, we applied optimal control theory, using Pontryagin's Maximum Principle, to design GLP-1 receptor agonist intervention strategies. We evaluated two scenarios that balance the cost of intervention with the effectiveness of glucose regulation. Results show that GLP-1 agonism effectively lowers glucose and FFA levels, with greater glucose reduction achieved when control cost and glucose deviation are equally weighted.

This research provides a comprehensive mathematical framework for analyzing complex glucose-insulin-FFA-GLP-1 dynamics. Our findings highlight the interconnectedness of insulin sensitivity, lipid metabolism, and incretin action in metabolic health and offer valuable insights for optimizing therapeutic interventions. The developed optimal control strategies suggest potential to improve glycemic control and to inform future clinical approaches to prevent and manage metabolic disorders.

Keywords: mathematical model; glucose; insulin; free fatty acids; GLP-1; sensitivity analysis; optimal control.

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1 Introduction

The global burden of obesity has reached epidemic proportions, posing an immense public health challenge. Projections indicate a staggering increase, with obesity expected to affect 186 million children and young adolescents, 175 million older adolescents, 838 million men, and 1.1 billion women by 2050 [20]. Defined by a body mass index (BMI) of 30 kg/m^2 or higher, obesity is characterized by excessive fat accumulation. It is a primary driver of numerous severe comorbidities, including type 2 diabetes (T2DM), cardiovascular disease, specific cancers, and nonalcoholic steatohepatitis (NASH) [15].

The intricate interplay between glucose, insulin, and free fatty acids (FFAs) is central to metabolic homeostasis, and its disruption is a hallmark of obesity and T2DM. Insulin, a key anabolic hormone, promotes lipogenesis and FFA uptake by adipocytes, thereby mitigating excessive circulating FFAs [16]. However, persistently elevated FFAs, common in obesity, impair insulin signaling, leading to insulin resistance and increased hepatic glucose production [27]. Chronic exposure to high FFAs can also induce oxidative stress and inflammation, leading to pancreatic beta-cell dysfunction and reduced insulin secretion, thereby exacerbating hyperglycemia [13]. Understanding this delicate yet dynamic balance among glucose, insulin, and FFAs is therefore crucial for deciphering the pathogenesis of metabolic diseases.

Glucagon-like peptide-1 (GLP-1), an incretin hormone, adds another crucial layer to this metabolic regulatory network. Secreted post-prandially, GLP-1 enhances glucose-dependent insulin secretion, suppresses glucagon release, slows gastric emptying, and promotes satiety [15,19]. These multifaceted effects make GLP-1 a pivotal target for T2DM therapeutics, with GLP-1 receptor agonists widely used to improve insulin sensitivity, lower glucose levels, and aid in weight management [14]. Given its profound impact on metabolic control, integrating GLP-1's role is essential for a comprehensive understanding of metabolic dysregulation.

Numerous studies have investigated the complex relationship between glucose and insulin as mathematical models, for example, [3, 9, 10]. Other models utilized fractional derivatives for glucose-insulin regulation as in [17]

While previous mathematical models have significantly advanced our understanding of glucose-insulin-FFA dynamics [2,12,21], there remains a critical need for integrated models that comprehensively capture the synergistic effects of key hormones, such as GLP-1, within the context of persistent metabolic dysregulation observed in obesity and T2DM. Such models are essential for unraveling the precise mechanisms underlying insulin resistance and identifying more effective therapeutic targets.

This study, therefore, aims to develop a novel mathematical model that describes the regulation of glucose levels, explicitly integrating the complex interactions among glucose, insulin, and FFAs, as well as the crucial regulatory role of GLP-1. In Section 2, we establish the model's fundamental structure, defining the system of equations and the underlying biological assumptions governing these metabolic interactions. We then conduct a rigorous qualitative analysis in Section 3 to assess the model's physiological relevance by exam-

ining its positivity, boundedness, and stability properties. Section 4 presents numerical simulations to validate our theoretical findings and includes a comprehensive sensitivity analysis to identify the key parameters driving glucose homeostasis. Finally, in Section 5, we introduce an optimal control strategy that regulates glucose levels by minimizing external intervention (represented by the control function u), thereby offering potential avenues for optimizing metabolic balance. By providing a more comprehensive representation of these intricate metabolic pathways, our model offers a deeper understanding of the mechanisms contributing to insulin resistance and hyperglycemia, ultimately laying a critical foundation for optimizing therapeutic strategies for metabolic disorders.

2 Model structure

The proposed mathematical model captures the dynamic interactions among plasma glucose concentration ($G(t)$), plasma insulin concentration ($I(t)$), and plasma FFAs concentration ($F(t)$). These state variables are functions of time (t) and represent key components of metabolic regulation. The core assumptions governing the model's dynamics are outlined as follows:

(S1) Glucose enters the plasma at a constant intake rate, k_1. Its entry is attenuated by the action of GLP-1, represented by the control function $u(t)$. Glucose is removed from the plasma via two primary mechanisms: a glucose-effectiveness rate (μ_2) and an insulin-mediated uptake rate (μ_1). However, the presence of FFAs in the plasma directly impairs glucose absorption, a process quantified by the rate γ_1 [5].

(S2) Insulin secretion into the bloodstream is stimulated by both glucose concentration (at rate σ_2) and the incretin hormone GLP-1 (represented by the term $\sigma_1 u(t)$, where we have made an optimistic assumption regarding the switch-like behavior of GLP-1). Once secreted, insulin is subsequently cleared from the body by the liver and kidneys at a degradation rate d_1. Importantly, elevated plasma FFAs are assumed to impair insulin secretion, a detrimental effect modeled at rate γ_2 [5, 28].

(S3) FFAs primarily enter the plasma through lipolysis, occurring at a rate δ_1 [6]. Additionally, plasma glucose is assumed to have a secondary effect, elevating lipolysis at a rate δ_2. Plasma FFAs are oxidized (removed) at a rate k_2, a process enhanced by GLP-1 action [22, 28, 29]. Peripheral uptake of FFAs, independent of insulin, occurs at a rate α_2 [6]. Conversely, insulin plays a crucial inhibitory role in lipolysis, reducing FFA release into circulation at a rate α_1 [28].

The dynamics of the model are described by the following system of nonlinear ordinary differential equations:

$$\begin{aligned} G' =& k_1(1-u(t)) - \mu_1 GI - \mu_2 G + \gamma_1 F, \\ I' =& \sigma_1 u(t) + \sigma_2 G - d_1 I - \gamma_2 F, \\ F' =& \delta_1 F + \delta_2 G - \alpha_1 IF - \alpha_2 F - k_2 u(t) F. \end{aligned} \tag{2.1}$$

The structure of these interactions is illustrated in Figure 1, and the parameters are summarized in Table 1.

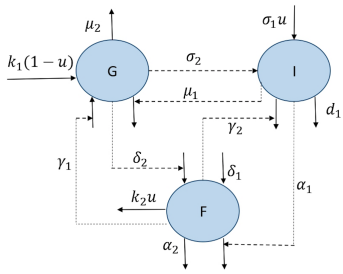


Figure 1. Flowchart of model (2.1).

Table 1. The model parameters and their description.

Parameter	Description
k_1	Intake rate,
u	GLP-1 action
μ_1	Insulin dependent glucose elimination rate
μ_2	Insulin independent glucose elimination rate
γ_1	Impaired glucose uptake rate due to FFAs
σ_1	Insulin secretion stimulating rate due to incretins
σ_2	Insulin secretion stimulating rate due to glucose
d_1	Insulin elimination rate
γ_2	Impaired insulin secretion rate due to FFAs
k_2	Oxidation rate due to GLP-1 action
δ_1	Lipolysis rate
δ_2	Secondary elevate rate of FFAs due to glucose
α_1	Inhibiting rate of lipolysis due to the presence of insulin
α_2	Uptake rate of FFAs by cells

3 Qualitative analysis

In this section, we provide a qualitative analysis of model (2.1) with the assumption that $u(t) = u$ is a scalar. First, we identify the region where the state variables remain positive and have finite values. Next, we calculate the model's steady-state solutions and evaluate their stability. The main investigations are presented in the following subsections.

3.1 Positivity and boundedness

Theorem 1. *If* $(G(0), I(0), F(0)) \in R^3_{\geq 0}$ *then the set* $\Omega = \{(G, I, F) \in R^3_{\geq 0} : 0 \leq G + I + F \leq \Big([G(0) + I(0) + F(0)] + \frac{1}{h}[k_1(1-u) + \sigma_1 u]\Big)\mathrm{e}^{hz}\}$ *is positively invariant for model* (2.1)*, where* $z \in [0, T]$*,* T *is any positive number and* $h = min\{\sigma_2 + \delta_2, \delta_1 + \gamma_1\}$.

Proof. This theorem can be proved by applying standard differential inequality arguments; however, we provide a full derivation here to ensure maximum transparency and utility for the reader.
First, we will demonstrate that the state variables have non-negative values. Let $(G(0), I(0), F(0)) \in \Omega$. Rewrite the first equation in (2.1) as:

$$\begin{aligned} &G' - k_1(1-u) + \mu_1 GI + \mu_2 G - \gamma_1 F = 0, \\ &G' - \big[k_1(1-u)/G - \mu_1 I - \mu_2 + \gamma_1 F/G\big]G = 0. \end{aligned} \tag{3.1}$$

Multiply both sides of (3.1) by $\exp\{-\int_0^t \big(\frac{k_1(1-u)}{G(s)} - \mu_1 I(s) - \mu_2 + \frac{\gamma_1 F(s)}{G(s)}\big)\,\mathrm{d}s\}$, then we can express (3.1) as:

$$\frac{d}{dt}\Big(G\ \exp\{-\int_0^t \Big(\frac{k_1(1-u)}{G(s)} - \mu_1 I(s) - \mu_2 + \frac{\gamma_1 F(s)}{G(s)}\Big)\,\mathrm{d}s\}\Big) = 0.$$

Integration from 0 to t yields

$$\begin{aligned} \Big[G\ \exp\Big\{-\int_0^t \Big(\frac{k_1(1-u)}{G(s)} - \mu_1 I(s) - \mu_2 + \frac{\gamma_1 F(s)}{G(s)}\Big)\,\mathrm{d}s\Big\}\Big]_0^t &= 0, \\ G(t)\ \exp\{-\int_0^t \Big(\frac{k_1(1-u)}{G(s)} - \mu_1 I(s) - \mu_2 + \frac{\gamma_1 F(s)}{G(s)}\Big)\,\mathrm{d}s\} - G(0) &= 0. \end{aligned}$$

Hence,

$$G(t) = G(0)\ \exp\Big\{\int_0^t \Big(\frac{k_1(1-u)}{G(s)} - \mu_1 I(s) - \mu_2 + \frac{\gamma_1 F(s)}{G(s)}\Big)\,\mathrm{d}s\Big\} \geq 0.$$

In a similar fashion, we can prove that $I(t)$ and $F(t)$ are non-negative. Therefore, all solutions that are greater than or equal to zero will continue to be greater than or equal to zero in Ω
Next, we demonstrate the bounded nature of the solutions. From the first, second, and third equations in (2.1), we have

$$G' + I' + F' \leq k_1(1-u) + \sigma_1 u + (\sigma_2 + \delta_2)G + (\delta_1 + \gamma_1)F.$$

Let $h = \max\{\sigma_2 + \delta_2, \delta_1 + \gamma_1\}$, then,

$$\begin{aligned} G' + I' + F' &\leq k_1(1-u) + \sigma_1 u + (\sigma_2 + \delta_2)G + (\delta_1 + \gamma_1)F + hI, \\ &\leq k_1(1-u) + \sigma_1 u + h(G + I + F), \end{aligned}$$

that is,

$$G' + I' + F' - h(G + I + F) \leq k_1(1-u) + \sigma_1 u.$$

By solving it using the integrating factor method, we obtain

$$\frac{d}{dt}\Big(\mathrm{e}^{-ht}[G+I+F]\Big) \leq (k_1(1-u)+\sigma_1 u)\mathrm{e}^{-ht}.$$

Integrating both sides from 0 to t, we obtain

$$G(t)+I(t)+F(t) \leq \Big([G(0)+I(0)+F(0)]+[k_1(1-u)+\sigma_1 u] \\ \big(-\frac{1}{h}(\mathrm{e}^{-ht}-1)\big)\Big)\mathrm{e}^{ht}.$$

Therefore,

$$G+I+F \leq \Big([G(0)+I(0)+F(0)]+\frac{1}{h}[k_1(1-u)+\sigma_1 u]\Big)\mathrm{e}^{hz},$$

where $z \in [0,T]$, and T is any positive number. Hence, all solutions of model (2.1) are bounded and non-negative. Thus, Ω is positively invariant. □

3.2 Equilibrium point

The equilibrium point of the system, (G^*, I^*, F^*), corresponds to the steady-state solutions that are obtained by equating the rates of the equations in (2.1) to zero, that is,

$$k_1(1-u)-\mu_1 G^* I^* - \mu_2 G^* + \gamma_1 F^* = 0, \tag{3.2}$$
$$\sigma_1 u + \sigma_2 G^* - d_1 I^* - \gamma_2 F^* = 0, \tag{3.3}$$
$$\delta_1 F^* + \delta_2 G^* - \alpha_1 I^* F^* - \alpha_2 F^* - k_2 u F^* = 0. \tag{3.4}$$

From Equation (3.4), we have

$$I^* = \frac{\delta_2 G^* + F^*(\delta_1 - \alpha_2 - k_2 u)}{\alpha_1 F^*}. \tag{3.5}$$

Substituting (3.5) into (3.2), we obtain

$$\alpha_1 k_1(1-u)F^* + \gamma_1\alpha_1 F^{*2} = \mu_1\delta_2 G^{*2} + \mu_1(\delta_1 - \alpha_2 - k_2 u)G^* F^* + \alpha_1\mu_2 G^* F^*. \tag{3.6}$$

Substituting (3.5) into (3.3), we get

$$G^* = \frac{\alpha_1\gamma_2 F^{*2} + (d_1(\delta_1 - \alpha_2 - k_2 u) - \alpha_1\sigma_1 u)F^*}{(\sigma_2\alpha_1 F^* - d_1\delta_2)}. \tag{3.7}$$

Substituting (3.7) into (3.6), we obtain the following equation for F^*,

$$a_3 F^{*3} + a_2 F^{*2} + a_1 F^* + a_0 = 0, \tag{3.8}$$

where

$$a_3 = \mu_1\delta_2\alpha_1^2\gamma_2^2 + \mu_1\alpha_1^2\gamma_2\sigma_2(\delta_1 - \alpha_2 - k_2 u) + \alpha_1^3(\mu_1\gamma_2\sigma_2 - \gamma_1\sigma_1^2),$$
$$a_2 = 2\mu_1\delta_2\alpha_1\gamma_2(d_1(\delta_1 - \alpha_2 - k_2 u) - \alpha_1\sigma_1 u) - [\sigma_2^2\alpha_1^3 k_1(1-u) - 2\gamma_1\alpha_1^2\sigma_2 d_1\delta_2]$$

$$+ [\mu_1(\delta_1 - \alpha_2 - k_2u) + \alpha_1\mu_2][\sigma_2\alpha_1(d_1(\delta_1 - \alpha_2 - k_2u) - \alpha_1\sigma_1u) - d_1\delta_2\alpha_1\gamma_2],$$

$$a_1 = \mu_1\delta_2(d_1(\delta_1 - \alpha_2 - k_2u) - \alpha_1\sigma_1u)^2 - [\gamma_1\alpha_1d_1^2\delta_2^2 - 2\sigma_2\alpha_1^2d_1\delta_2k_1(1-u)]$$
$$+ [\mu_1(\delta_1 - \alpha_2 - k_2u) + \alpha_1\mu_2][-d_1\delta_2(d_1(\delta_1 - \alpha_2 - k_2u) - \alpha_1\sigma_1u],$$

$$a_0 = -d_1^2\delta_2^2\alpha_1k_1(1-u).$$

It is observed that $a_3 > 0$ if $\delta_1 > \alpha_2 + k_2u$, and $\mu_2\gamma_2\sigma_2 > \gamma_1\sigma_1^2$. Also, $a_2 > 0$ if $\sigma_2\alpha_1(d_1(\delta_1 - \alpha_2 - k_2u)) > \alpha_1^2\sigma_1\sigma_2u + d_1\delta_2\alpha_1\gamma_2$, and $\gamma_1d_1\delta_2 > \sigma_2\alpha_1k_1(1-u)$. Clearly, $a_0 < 0$. Therefore, by using Descartes' rule of signs [4], Equation (3.8) has a unique positive root despite the sign of a_1. Hence, F^* is positive if the following conditions are satisfied:

$$\delta_1 > \alpha_2 + k_2u, \quad \mu_2\gamma_2\sigma_2 > \gamma_1\sigma_1^2,$$
$$\sigma_2\alpha_1(d_1(\delta_1 - \alpha_2 - k_2u)) > \alpha_1^2\sigma_1\sigma_2u + d_1\delta_2\alpha_1\gamma_2, \ \gamma_1d_1\delta_2 > \sigma_2\alpha_1k_1(1-u)$$

In a similar fashion, Equation (3.6) can be expressed as:

$$b_2G^{*2} + b_1G^* + b_0 = 0,$$

where

$$b_2 = \mu_1\delta_2 > 0, \quad b_1 = (\mu_1(\delta_1 - \alpha_2 - k_2u) + \alpha_1\mu_2)F^* > 0,$$
$$b_0 = -(\alpha_1k_1(1-u) + \gamma_1\alpha_1)F^* < 0.$$

Clearly, there exists a unique positive root G^*. Also, from (3.5), I^* is positive under the same conditions.

Theorem 2. *Model* (2.1) *has a unique equilibrium point,* $E = (G^*, I^*, F^*)$*, if* $\delta_1 > \alpha_2 + k_2u$*,* $\mu_2\gamma_2\sigma_2 > \gamma_1\sigma_1^2$*,* $\sigma_2\alpha_1(d_1(\delta_1 - \alpha_2 - k_2u)) > \alpha_1^2\sigma_1\sigma_2u + d_1\delta_2\alpha_1\gamma_2$*, and* $\gamma_1d_1\delta_2 > \sigma_2\alpha_1k_1(1-u)$*.*

Theorem 2 states that the equilibrium point E exists under certain biological conditions. The balance of lipids is maintained when the rate of fat release (δ_1) is greater than the rate of fat removal (uptake by cells α_2 plus GLP-1-induced oxidation k_2u). In addition, a balance between insulin-independent glucose removal (μ_2) and secretion (σ_1 and σ_2) should be maintained against the damaging effects of FFAs (α_1 and α_2). This inequality ($\mu_2\gamma_2\sigma_2 > \gamma_1\sigma_1^2$) ensures that the basic biological machinery (basal glucose uptake and natural insulin response) is strong enough to withstand interference caused by FFAs. Furthermore, lipid balance ($\delta_1 - \alpha_2 - k_2u$) should overcome insulin inhibition of lipolysis (α_1) and glucose stimulation of fat release (δ_2). Finally, to ensure the existence of a steady-state, the glucose intake (k_1) adjusted for the effect of GLP-1 ($1-u$) must be less than the rate at which FFAs alter glucose uptake (γ_1) and are elevated by glucose (δ_2).

3.3 Stability

Theorem 3. *The equilibrium point* $E = (G^*, I^*, F^*)$ *is locally asymptotically stable if* $\mu_1 > \alpha_1$*,* $\mu_2d_1 > \gamma_1\delta_2 + \alpha_1\sigma_1u$*,* $\gamma_1\alpha_1\sigma_2 > \gamma_2\mu_1(\delta_1 - \alpha_2 - k_2u) + \gamma_2\alpha_1\mu_2$*, and* $\delta_2\mu_2G^* > (d_1\delta_1\gamma_1 + 2\gamma_2\delta_2\mu_1G^*)F^*$*.*

Proof. The Jacobian matrix of model (2.1) at E is given by

$$J(E) = \begin{bmatrix} -\mu_1 I^* - \mu_2 & -\mu_1 G^* & \gamma_1 \\ \sigma_2 & -d_1 & -\gamma_2 \\ \delta_2 & -\alpha_1 F^* & \delta_1 - \alpha_1 I^* - \alpha_2 - k_2 u \end{bmatrix}.$$

Solving the characteristic equation $det(J(E) - \lambda I) = 0$, the eigenvalues $\lambda_{1,2,3}$ satisfy the following equation

$$a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0,$$

where

$$\begin{aligned} a_3 &= -1, \quad a_2 = \delta_1 - \alpha_1 I^* - \alpha_2 - k_2 u - (\mu_1 I^* + \mu_2 + d_1), \\ a_1 &= \gamma_1\delta_2 + \gamma_2\alpha_1 F^* - d_1(\mu_1 I^* + \mu_2) - \sigma_2\mu_1 G^* \\ &\quad + (\mu_1 I^* + \mu_2 + d_1)(\delta_1 - \alpha_1 I^* - \alpha_2 - k_2 u), \\ a_0 &= -\gamma_1\alpha_1\sigma_2 F^* + \gamma_1\delta_2 d_1 + \gamma_2\alpha_1 F^*(\mu_1 I^* + \mu_2) \\ &\quad + \gamma_2\delta_2\mu_1 G^* + (\delta_1 - \alpha_1 I^* - \alpha_2 - k_2 u)[d_1(\mu_1 I^* + \mu_2) + \sigma_2\mu_1 G^*]. \end{aligned}$$

Clearly, $a_3 < 0$. Also, $a_2 < 0$ since we can rewrite it by using (3.4) as:

$$a_2 = -\delta_2 G^*/F^* - (\mu_1 I^* + \mu_2 + d_1).$$

Similarly, using (3.3), we express a_1 as:

$$\begin{aligned} a_1 &= \gamma_1\delta_2 + \alpha_1\sigma_1 u + \alpha_1\sigma_2 G^* - \alpha_1 d_1 I^* - d_1(\mu_1 I^* + \mu_2) - \sigma_2\mu_1 G^* \\ &\quad + (\mu_1 I^* + \mu_2 + d_1)(\delta_1 - \alpha_1 I^* - \alpha_2 - k_2 u). \end{aligned}$$

In order for a_1 to be less than zero, we must have $\mu_1 > \alpha_1$ and $\mu_2 d_1 > \gamma_1\delta_2 + \alpha_1\sigma_1 u$. Using (3.4) again, we rewrite a_0 as:

$$\begin{aligned} a_0 &= -\gamma_1\alpha_1\sigma_2 F^* + \gamma_1\delta_2 d_1 + \gamma_2\alpha_1 F^*(\mu_1 I^* + \mu_2) \\ &\quad + \gamma_2\delta_2\mu_1 G^* - \delta_2 G^*/F^*[d_1(\mu_1 I^* + \mu_2) + \sigma_2\mu_1 G^*]. \end{aligned}$$

Also, from (3.4), we have

$$\alpha_1 I^* F^* = \delta_1 F^* + \delta_2 G^* - \alpha_2 F^* - k_2 u F^*.$$

By using the above equation, we rewrite a_0 as:

$$\begin{aligned} a_0 &= F^*(-\gamma_1\alpha_1\sigma_2 + \gamma_2\mu_1(\delta_1 - \alpha_2 - k_2 u) + \gamma_2\alpha_1\mu_2) + \gamma_1\delta_1 d_1 + 2\gamma_2\delta_2\mu_1 G^* \\ &\quad - \frac{\delta_2}{F^*} G^*[d_1\mu_1 I^* + \sigma_2\mu_1 G^*] - \frac{\delta_2}{F^*} G^*\mu_2. \end{aligned}$$

For a_0 to be less than zero, $\gamma_1\alpha_1\sigma_2 > \gamma_2\mu_1(\delta_1 - \alpha_2 - k_2 u) + \gamma_2\alpha_1\mu_2$, and $\delta_2\mu_2\frac{G^*}{F^*} > d_1\delta_1\gamma_1 + 2\gamma_2\delta_2\mu_1 G^*$. Since $a_0, a_1, a_2,$ and a_3 are all negative under the stated conditions, then by using Descartes' rule of signs [4], the eigenvalues $\lambda_1, \lambda_2,$ and λ_3 are all negative. Hence, E is locally asymptotically stable under the stated conditions. □

Biologically, Theorem 3 means that if the system (metabolism) suffers a small temporary disturbance, it has the internal strength to return to its steady equilibrium state provided that some conditions are satisfied. For stability, the body must prioritize using insulin to remove glucose from the blood (μ_1) over using it to lock fat in adipose tissue (α_1). In addition, the ability to clear up glucose (μ_2) and insulin (d_1) must be stronger than the complex signals such as FFA-induced resistance ($\gamma_1\delta_2$) and the incretin-driven hormonal loop ($\alpha_1\sigma_1 u$). Furthermore, the healthy loop: glucose triggers insulin (σ_2) which stops fat release (α_1) must overcome FFAs impairment (γ_1 and γ_2) that interfere with glucose uptake (μ_1 and μ_2). Finally, the last condition identifies the maximum fat threshold (F^*) that the body can tolerate before metabolism collapses, given the patient's glucose level (G^*).

Theorem 4. *The equilibrium point $E = (G^*, I^*, F^*)$ is globally asymptotically stable if*

$$\frac{2}{3}\mu_2 d_1 \alpha_1 I^* > \frac{2}{3}\mu_2 d_1 \delta_2 \frac{G^*}{F^*} + d_1\gamma_1\delta_2 + \mu_2\gamma_2\alpha_1 F^*.$$

Proof. Define the Lyapunov function as

$$L(G, I, F) = \frac{A_1}{2}(G - G^*)^2 + \frac{A_2}{2}(I - I^*)^2 + \frac{A_3}{2}(F - F^*)^2,$$

where A_1, A_2 and A_3 are positive defined as follows

$$A_1 = \frac{-b_1 + \sqrt{b_1^2 - 4a_1c_1}}{2a_1}, \quad A_2 = 1, \quad A_3 = \frac{-b_2 + \sqrt{b_2^2 - 4a_2c_2}}{2a_2}$$

and

$$a_1 = \mu_1^2 G^{*2}, \;\; b_1 = -(2\mu_1\sigma_2 G^* + \frac{4}{9}\mu_2 d_1), \;\; c_1 = \sigma_2^2, \; a_2 = d_1\delta_2^2 + A_1\mu_2\alpha_1^2 F^{*2},$$
$$b_2 = 2d_1A_1\gamma_1\delta_2 + 2A_1\mu_2\gamma_2\alpha_1 F^* - \frac{4}{3}A_1\mu_2 d_1(\alpha_1 I^* - \delta_2\frac{G^*}{F^*}),$$
$$c_2 = d_1A_1^2\gamma_1^2 + A_1\mu_2\gamma_2^2.$$

It is easy to demonstrate that L is a positive definite function. Evaluating the derivative of L yields

$$L' = A_1(G - G^*)G' + A_2(I - I^*)I' + A_3(F - F^*)F'.$$

Using Equations (3.2)–(3.4) at equilibrium E, we get

$$\begin{aligned} L' =& A_1(G - G^*)[k_1(1 - u) - \mu_1 GI - \mu_2 G + \gamma_1 F - k_1(1 - u) + \mu_1 G^* I^* \\ &+ \mu_2 G^* - \gamma_1 F^*] + A_2(I - I^*)[\sigma_1 u + \sigma_2 G - d_1 I - \gamma_2 F - \sigma_1 u - \sigma_2 G^* \\ &+ d_1 I^* + \gamma_2 F^*] + A_3(F - F^*)[\delta_1 F + \delta_2 G - \alpha_1 IF - \alpha_2 F - k_2 uF - \delta_1 F^* \\ &- \delta_2 G^* + \alpha_1 I^* F^* + \alpha_2 F^* + k_2 uF^*]. \end{aligned}$$

Rearranging the terms and letting $A_2 = 1$, we get

$$L' = -A_1\mu_1(G - G^*)(GI - G^*I^*) - A_1\mu_2(G - G^*)^2 + A_1\gamma_1(G - G^*)(F - F^*)$$

$$+\sigma_2(I-I^*)(G-G^*)-d_1(I-I)^2-\gamma_2(I-I^*)(F-F^*)+A_3\delta_1(F-F^*)^2$$
$$+A_3\delta_2(F-F^*)(G-G^*)-A_3\alpha_1(F-F^*)(IF-I^*F^*)-A_3\alpha_2(F-F^*)^2$$
$$-A_3k_2u(F-F^*)^2.$$

Rewriting

$$GI-G^*I^*=GI-G^*I+G^*I-G^*I^*=(G-G^*)I+(I-I^*)G^*,$$
$$IF-I^*F^*=(I-I^*)F^*+(F-F^*)I.$$

Collecting terms, we obtain

$$L'=-A_1\mu_1(G-G^*)^2I-(A_1\mu_2G^*-\sigma_2)(G-G^*)(I-I^*)-A_1\mu_2(G-G^*)^2$$
$$+(A_1\gamma_1+A_3\delta_2)(G-G^*)(F-F^*)-d_1(I-I^*)^2-(\gamma_2+A_3\alpha_1F^*)(I-I^*)$$
$$\times(F-F^*)-A_3\alpha_1(F-F^*)^2I+A_3(\delta_1-k_2u)(F-F^*)^2-A_3\alpha_2(F-F^*)^2.$$

Equivalently,

$$L'=-A_1\mu_1(G-G^*)^2I-(A_1\mu_2G^*-\sigma_2)(G-G^*)(I-I^*)-\frac{A_1\mu_2}{3}(G-G^*)^2$$
$$-\frac{A_1\mu_2}{3}(G-G^*)^2-\frac{A_1\mu_2}{3}(G-G^*)^2+(A_1\gamma_1+A_3\delta_2)(G-G^*)(F-F^*)$$
$$-\frac{d_1}{3}(I-I^*)^2-\frac{d_1}{3}(I-I^*)^2-\frac{d_1}{3}(I-I^*)^2-(\gamma_2+A_3\alpha_1F^*)(I-I^*)(F-F^*)$$
$$-A_3\alpha_1(F-F^*)^2I+A_3(\delta_1-k_2u)(F-F^*)^2-A_3\alpha_2(F-F^*)^2.$$

Completing the squares in the terms,

$$L'=-\frac{A_1\mu_2}{3}(G-G^*)^2-A_1\mu_1(G-G^*)^2I-\frac{d_1}{3}(I-I^*)^2-\frac{A_1\mu_2}{3}\left[(G-G^*)^2\right.$$
$$+\frac{3(A_1\mu_1G^*-\sigma_2)}{A_1\mu_2}(G-G^*)(I-I^*)+\left(\frac{3(A_1\mu_1G^*-\sigma_2)}{2A_1\mu_2}\right)^2(I-I^*)^2$$
$$\left.-\left(\frac{3(A_1\mu_1G^*-\sigma_2)}{2A_1\mu_2}\right)^2(I-I^*)^2\right]-\frac{d_1}{3}(I-I^*)^2-\frac{A_1\mu_2}{3}\left[(G-G^*)^2\right.$$
$$-\frac{3(A_1\gamma_1+A_3\delta_2)}{A_1\mu_2}(G-G^*)(F-F^*)+\left(\frac{3(A_1\gamma_1+A_3\delta_2)}{2A_1\mu_2}\right)^2(F-F^*)^2$$
$$\left.-\left(\frac{3(A_1\gamma_1+A_3\delta_2)}{2A_1\mu_2}\right)^2(F-F^*)^2\right]-\frac{d_1}{3}\left[(I-I^*)^2+\frac{3(\gamma_2+A_3\alpha_1F^*)}{d_1}(I-I^*)\right.$$
$$\times(F-F^*)+\left(\frac{3(\gamma_2+A_3\alpha_1F^*)}{2d_1}\right)^2(F-F^*)^2-\left.\left(\frac{3(\gamma_2+A_3\alpha_1F^*)}{2d_1}\right)^2(F-F^*)^2\right]$$
$$+A_3(\delta_1-k_2u)(F-F^*)^2-A_3\alpha_1(F-F^*)^2I-A_3\alpha_2(F-F^*)^2.$$

From

$$\delta_1F^*+\delta_2G^*-\alpha_1I^*F^*-\alpha_2F^*-k_2uF^*=0,$$

we have $\delta_1 - \alpha_2 - k_2 u = -\delta_2 \frac{G^*}{F^*} + \alpha_1 I^*$. Simplifying,

$$L' = -\frac{A_1\mu_2}{3}(G-G^*)^2 - A_1\mu_1(G-G^*)^2 I - \frac{d_1}{3}(I-I^*)^2 - \frac{A_1\mu_2}{3}\Bigg[(G-G^*) + \left(\frac{3(A_1\mu_1 G^* - \sigma_2)}{2A_1\mu_2}\right)(I-I^*)\Bigg]^2 - \frac{A_1\mu_2}{3}\Bigg[(G-G^*) - \left(\frac{3(A_1\gamma_1 + A_3\delta_2)}{2A_1\mu_2}\right) \times (F-F^*)\Bigg]^2 - \frac{d_1}{3}\Bigg[(I-I^*) + \left(\frac{3(\gamma_2 + A_3\alpha_1 F^*)}{2d_1}\right)(F-F^*)\Bigg]^2 - A_3\alpha_1(F-F^*)^2 I + \left[\frac{3(A_1\mu_1 G^* - \sigma_2)^2}{4A_1\mu_2} - \frac{d_1}{3}\right](I-I^*)^2 + \left[\frac{3(A_1\gamma_1 + A_3\delta_2)^2}{4A_1\mu_2} + \frac{3(\gamma_2 + A_3\alpha_1 F^*)^2}{4d_1}\right] \times (F-F^*)^2 + A_3(\alpha_1 I^* - \delta_2 \frac{G^*}{F^*})(F-F^*)^2.$$

It can be seen that all terms of L' are negative, except for the last three. To ensure that L' becomes negative, then A_1 and A_3 must satisfy the following equations:

$$\frac{3(A_1\mu_1 G^* - \sigma_2)^2}{4A_1\mu_2} - \frac{d_1}{3} = 0, \tag{3.9}$$

$$\frac{3(A_1\gamma_1 + A_3\delta_2)^2}{4A_1\mu_2} + \frac{3(\gamma_2 + A_3\alpha_1 F^*)^2}{4d_1} + A_3(\alpha_1 I^* - \delta_2 \frac{G^*}{F^*}) = 0. \tag{3.10}$$

Rearranging Equation (3.9), we obtain

$$\mu_1^2 G^{*2} A_1^2 - (2\mu_1\sigma_2 G^* + \frac{4}{9}\mu_2 d_1)A_1 + \sigma_2^2 = 0.$$

Solving for A_1, we have

$$A_1 = c\big(-b_1 + \sqrt{b_1^2 - 4a_1c_1}\big)/2a_1,$$

where $a_1 = \mu_1^2 G^{*2}$, $b_1 = -(2\mu_1\sigma_2 G^* + \frac{4}{9}\mu_2 d_1)$, $c_1 = \sigma_2^2$. Clearly, A_1 is positive. Similarly, rearranging Equation (3.10), we get

$$(d_1\delta_2^2 + A_1\mu_2\alpha_1^2 F^{*2})A_3^2 + (2d_1A_1\gamma_1\delta_2 + 2A_1\mu_2\gamma_2\alpha_1 F^* - \frac{4}{3}A_1\mu_2 d_1(\alpha_1 I^* - \delta_2 \frac{G^*}{F^*}))A_3 + d_1A_1^2\gamma_1^2 + A_1\mu_2\gamma_2^2 = 0.$$

Solving for A_3, we get

$$A_3 = \big(-b_2 + \sqrt{b_2^2 - 4a_2c_2}\big)/2a_2,$$

where

$$a_2 = d_1\delta_2^2 + A_1\mu_2\alpha_1^2 F^{*2}, \quad c_2 = d_1A_1^2\gamma_1^2 + A_1\mu_2\gamma_2^2,$$
$$b_2 = 2d_1A_1\gamma_1\delta_2 + 2A_1\mu_2\gamma_2\alpha_1 F^* - \frac{4}{3}A_1\mu_2 d_1(\alpha_1 I^* - \delta_2 \frac{G^*}{F^*}).$$

A_3 is positive if

$$\frac{2}{3}\mu_2 d_1 \alpha_1 I^* > \frac{2}{3}\mu_2 d_1 \delta_2 \frac{G^*}{F^*} + d_1 \gamma_1 \delta_2 + \mu_2 \gamma_2 \alpha_1 F^*.$$

Hence, under this condition, L is positive definite and L' is negative definite; therefore, the equilibrium point E is globally asymptotically stable. □

Global stability, in biological terms, means that the system is sufficiently robust that, even after a severe metabolic shock, it will always return to an equilibrium state. The condition for global stability, with rearrangement, is the following:

$$\alpha_1 I^* > \delta_2 \frac{G^*}{F^*} + \frac{3\gamma_1 \delta_2}{2\mu_2} + \frac{3\gamma_2 \alpha_1 F^*}{2d_1}.$$

To explain the condition biologically, we begin by interpreting each term in the inequality. The first term on the right side ($\delta_2 G^*/F^*$) represents how much of the current glucose level (G^*) is trying to force fat out into the blood (δ_2), relative to how much fat is already there (F^*). If an individual has high sugar but little fat, this term becomes massive. This is why even if the individual is lean, high-carb diets are so stressful on the system. The second term ($3\gamma_1\delta_2/(2\mu_2)$) shows that glucose intake creates fat (δ_2) and that fat creates resistance (γ_1), but this is proportioned by insulin-independent clearance rate of glucose (μ_2). If the body is naturally good at clearing glucose without insulin (μ_2 is high), the strain on insulin is low. However, if clearance is low, even a small amount of resistance (γ_1) forces insulin to work much harder to maintain stability. The last term ($3\gamma_2\alpha_1 F^*/(2d_1)$) demonstrates the lipotoxicity stress. High levels of circulating FFAs (F^*) directly affect the pancreatic beta cells at a rate of γ_2, reducing the body's ability to produce insulin. This damage is compounded by the factor α_1, because as the pancreas struggles to function, it is simultaneously under pressure to provide enough insulin to slow the release of even more fat into the bloodstream. The entire burden is balanced against the insulin elimination rate (d_1). Hence, global stability is maintained if insulin's ability to lock away fat ($\alpha_1 I^*$) exceeds the combined pressure from diet, resistance, and toxicity.

4 Numerical analysis

In this section, we utilize numerical techniques to solve model (2.1) and present various simulations of the model using MATLAB. Additionally, we analyze the parameters' sensitivity to gain a deeper understanding of the key parameters that could inform the most effective therapeutic strategies.

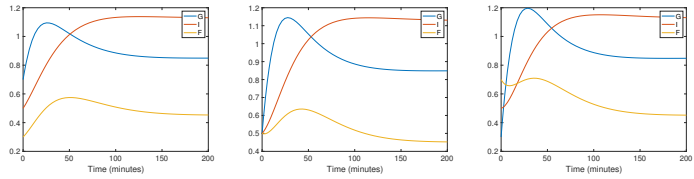
4.1 Numerical simulations

To investigate the dynamics of model (2.1), numerical simulations were performed using varying initial conditions for glucose (G), insulin (I), and free

Table 2. Parameter values and units.

Parameter	Assumption value	Unit
k_1	1×10^{-1}	mmol $L^{-1}min^{-1}$
u	3×10^{-1}	-
μ_1	7×10^{-2}	$min^{-1}mmol^{-1}L$
μ_2	3×10^{-2}	min^{-1}
γ_1	5×10^{-2}	min^{-1}
σ_1	2×10^{-2}	mmol $L^{-1}min^{-1}$
σ_2	2×10^{-2}	min^{-1}
d_1	2×10^{-2}	min^{-1}
γ_2	1×10^{-3}	min^{-1}
k_2	5×10^{-2}	min^{-1}
δ_1	5×10^{-2}	min^{-1}
δ_2	2×10^{-2}	min^{-1}
α_1	2×10^{-2}	$min^{-1}mmol^{-1}L$
α_2	5×10^{-2}	min^{-1}

fatty acids (F). Specifically, three distinct sets of initial values were tested. All simulations utilized the fixed parameter values detailed in Table 2. As depicted in Figure 2, the numerical solutions consistently converge to a stable equilibrium point, irrespective of the initial conditions.



(a) (IC1) $G = 0.7$, $I = 0.5$, $F = 0.3$. (b) (IC2) $G = 0.5$, $I = 0.5$, $F = 0.5$. (c) (IC3) $G = 0.3$, $I = 0.5$, $F = 0.7$.

Figure 2. Numerical simulations of model (2.1) illustrating the temporal variation of plasma glucose (G), insulin (I), and FFAs (F) under different initial conditions. Parameter values from Table 2 were used for all simulations.

The converged equilibrium values for the respective initial conditions were found to be: $E_{(a)} = (0.8492, 1.1304, 0.4533)$, $E_{(b)} = (0.8486, 1.1307, 0.4527)$, and $E_{(c)} = (0.8480, 1.1310, 0.4521)$. The proximity of these equilibrium values, despite varying starting points, strongly supports the existence of a globally stable equilibrium point. This numerical finding robustly corroborates our qualitative analysis of the model's stability properties.

4.2 Parameter sensitivity analysis

This section analyzes the influence of individual model parameters on plasma glucose concentration (G). A comprehensive sensitivity analysis was conducted by systematically varying one parameter at a time while keeping all other parameters fixed at their baseline values (from Table 2). The resulting impact on G is illustrated in Figure 3.

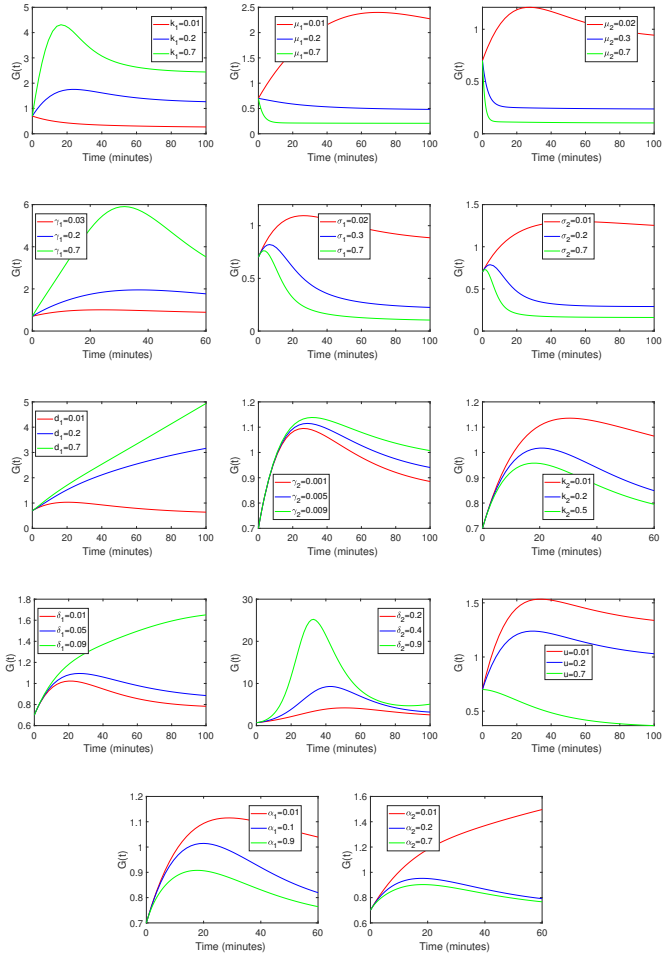


Figure 3. The effect of the parameters in model (2.1) on G.

As demonstrated in Figure 3, insulin-related parameters critically influence plasma glucose concentration. An increase in the insulin elimination rate (d_1) elevates plasma glucose, indicating that faster insulin degradation compromises glucose regulation. Conversely, an increase in either the insulin-dependent glucose uptake rate (μ_1), the insulin-independent glucose effectiveness rate (μ_2), or the pancreatic insulin secretion rate (σ_2) all result in a reduction in plasma

glucose concentration, highlighting their roles in glucose clearance and insulin production.

Regarding the impact of plasma FFAs on glucose levels, the figure reveals that an increase in parameters associated with FFA-induced impairment (e.g., the effect of FFAs on glucose absorption (γ_1), the lipolysis rate (δ_1), the glucose-induced FFA release rate (δ_2), or the FFA-mediated insulin impairment rate (γ_2)) consistently leads to an elevation in plasma glucose. This underscores the detrimental role of elevated FFAs in exacerbating hyperglycemia. In contrast, higher rates of lipolysis inhibition by insulin (α_1) and increased FFA uptake by adipose tissue (α_2) both contribute to a decrease in plasma glucose, emphasizing mechanisms that mitigate FFA-induced metabolic dysfunction. These observed effects are consistent with previously reported findings in the literature [5, 6, 28].

Furthermore, the analysis shows that an increase in the intake rate (k_1) predictably raises plasma glucose. However, the simulation demonstrates that GLP-1 action (u) effectively lowers glucose levels. Similarly, an increase in the insulin release rate, dependent on gut glucose content (σ_1), and an increase in the FFA oxidation rate, enhanced by GLP-1 action (k_2), also contribute to reducing plasma glucose concentration. These results align closely with outcomes presented in recent studies concerning metabolic regulation [5, 22, 28, 29].

5 Optimal control

Optimal control theory provides a robust framework for enhancing the performance of dynamic systems by identifying the most effective strategies to achieve desired outcomes [8]. In our model, the objective is to regulate blood glucose levels by optimally adjusting the control variable, $u(t)$, which represents the influence of glucagon-like peptide-1 (GLP-1) receptor agonist treatment. GLP-1 receptor agonists, such as semaglutide and liraglutide, are injectable medications widely used for managing type 2 diabetes and obesity. These agents mimic the physiological actions of GLP-1, resulting in improved glycemic control, significant weight loss, and reduced cardiovascular risk for patients with type 2 diabetes [11, 26]. However, the clinical benefits of these therapies often come at a high cost. By applying optimal control techniques, we aim to identify strategies that effectively maintain glucose homeostasis while minimizing treatment costs.

5.1 Problem formulation

To formulate the optimal control problem, we define an objective function that minimizes both fluctuations in glucose levels and the economic cost of the control intervention, subject to the inherent constraints of the metabolic system. The primary goal of this control strategy is to keep the plasma glucose concentration, $G(t)$, as close as possible to a desired physiological reference level, G_{target}, while simultaneously minimizing the control effort, such as medication dosage or frequency.

The objective function, J, is formally expressed as:

$$J = \min \int_0^{t_f} [Au(t)^2 + B(G(t) - G_{target})^2] \, \mathrm{d}t, \quad 0 \le u(t) \le 1. \tag{5.1}$$

This minimization is subject to the dynamics of model (2.1) with the initial conditions: $G(0) = G_0$, $I(0) = I_0$, and $F(0) = F_0$. The parameters within the objective function (5.1) are detailed in Table 3. We employ Pontryagin's Maximum Principle [8] to derive the necessary conditions for determining the optimal control $u(t)$.

Table 3. Parameters of the objective function and their descriptions.

Parameter	Description
$u(t)$	The control variable, representing the effect of GLP-1 receptor agonist intervention.
G_{target}	The desired target plasma glucose level.
A	Weighting coefficient balancing the cost associated with the control effort (u).
B	Weighting coefficient balancing the deviation of plasma glucose from its target level (G_{target}).
t_f	The final time of the simulation/treatment period.

The Hamiltonian, H, for this control problem is defined as:

$$H = Au^2 + B(G - G_{target})^2 + \Lambda_1 G' + \Lambda_2 I' + \Lambda_3 F'.$$

Applying the optimality condition ($H_u = 0$) yields the expression for the optimal control $u(t)$:

$$u(t) = \frac{k_1 \Lambda_1 + k_2 F \Lambda_3 - \sigma_1 \Lambda_2}{2A}, \tag{5.2}$$

where $\Lambda_1(t)$, $\Lambda_2(t)$, and $\Lambda_3(t)$ are the adjoint variables satisfying the following system of differential equations:

$$\begin{aligned}
\Lambda_1' &= -\frac{\partial H}{\partial G} = -2B(G - G_{target}) + \Lambda_1(\mu_1 I + \mu_2) - \Lambda_2 \sigma_2 - \Lambda_3 \delta_2, \\
\Lambda_2' &= -\frac{\partial H}{\partial I} = \Lambda_1 \mu_1 G + \Lambda_2 d_1 + \Lambda_3 \alpha_1 F, \\
\Lambda_3' &= -\frac{\partial H}{\partial F} = -\Lambda_1 \gamma_1 + \Lambda_2 \gamma_2 - \Lambda_3(\delta_1 - \alpha_1 I - \alpha_2 - k_2 u),
\end{aligned} \tag{5.3}$$

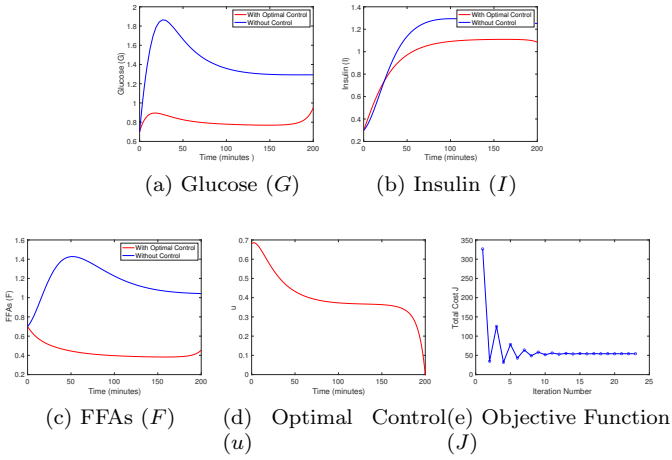
with the transversality (or boundary) conditions: $\Lambda_1(t_f) = \Lambda_2(t_f) = \Lambda_3(t_f) = 0$.

5.2 Numerical results

The optimality system, comprising the state equations (2.1), the adjoint equations (5.3), and the characterization of the optimal control (5.2), was solved

numerically using the Forward-Backward Sweep Method [8]. All simulations employed the baseline parameter values specified in Table 2. Our focus here is to analyze the impact of varying the weighting coefficients A and B on the optimal control profiles and the resulting trajectories of glucose, insulin, and FFAs.

We investigate two distinct scenarios for the optimal management of glucose levels using simulated GLP-1 receptor agonist interventions.



(a) Glucose (G) (b) Insulin (I)

(c) FFAs (F) (d) Optimal Control (u) (e) Objective Function (J)

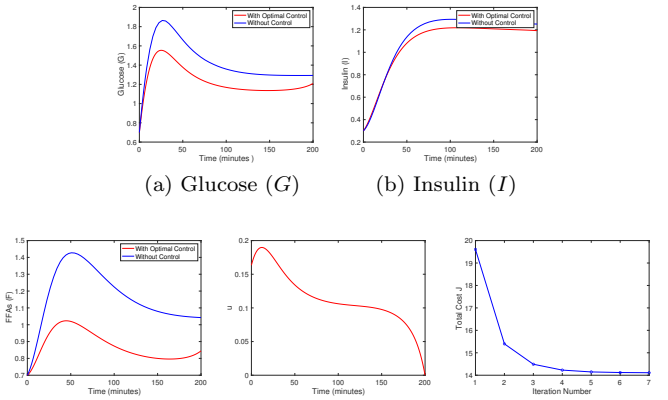
Figure 4. Simulations of optimal control for Scenario 1: Balanced weighting, with $A = 1$ (control cost) and $B = 1$ (glucose deviation cost).

Scenario 1: Balanced control and glucose regulation

In this scenario, the cost associated with GLP-1 intervention and the objective of glucose management are considered equally important, reflected by setting the weighting coefficients to $A = 1$ and $B = 1$. Figure 4 illustrates the dynamic responses of glucose, insulin, and FFAs under this optimal control strategy. Both plasma glucose and FFA levels decrease significantly following the implementation of optimal control. To achieve this, the optimal control profile ($u(t)$) suggests an initial high intervention level (approximately 0.68) for a brief period, followed by stabilization at a moderate level (around 0.4) for approximately 150 minutes, before sharply decaying to its minimum value of 0 towards the end of the observation period. This profile effectively drives both glucose and FFAs towards lower, more desirable levels.

Scenario 2: Prioritizing control cost minimization

This scenario investigates the outcome when the cost of GLP-1 intervention is weighted more heavily than the deviation in glucose levels, by setting $A = 1$ and $B = 0.1$. Figure 5 presents the corresponding variations in glucose, insulin, and FFAs. While glucose levels decrease, the reduction is notably less pronounced than in Scenario 1, whereas the decrease in FFAs remains significant. The optimal control profile for this scenario suggests starting with a relatively low control value ($u \approx 0.16$), gradually increasing it to about 0.19



(a) Glucose (G) (b) Insulin (I)

(c) FFAs (F) (d) Optimal Control (u) (e) Objective Function (J)

Figure 5. Simulations of optimal control for Scenario 2: Higher emphasis on minimizing control cost, with $A = 1$ and $B = 0.1$.

after 12 minutes, then reducing it to approximately 0.11 for about 70 minutes, and finally tapering to 0 by the end of the simulation. This demonstrates that prioritizing cost results in a less aggressive, yet still beneficial, reduction in glucose levels.

The simulated results indicate that both scenarios effectively help manage glucose levels. However, Scenario 1, which balances control cost and glucose regulation equally, is more effective at achieving substantial glucose reduction than Scenario 2. This greater efficacy in glucose management is, as expected, achieved with a higher overall control effort, reflecting the trade-off between strict glucose control and minimization of intervention cost.

6 Discussion and conclusions

This study uniquely captures the dynamic interactions among plasma glucose, insulin, and FFAs, crucially integrating the regulatory role of glucagon-like peptide-1 (GLP-1). Through a combination of qualitative analysis, numerical simulations, and optimal control strategies, this work significantly enhances our mechanistic understanding of metabolic regulation, offering promising insights for the management of disorders such as type 2 diabetes.

WE developed and analyzed a novel mathematical model to unravel the complex mechanisms governing glucose homeostasis by moving beyond the bipartite glucose-insulin framework characteristic of classic models such as the Bergman minimal model [1]. By uniquely capturing the tripartite interactions among glucose, insulin, and FFAs while crucially integrating the regulatory role of GLP-1, we derived conditions for a unique equilibrium $E = (G^*, I^*, F^*)$, specifically, $\delta_1 > \alpha_2 + k_2 u$. This suggests that metabolic steady states are not solely determined by glucose clearance but are fundamentally dependent

on the balance between lipid flux and GLP-1-driven oxidation, extending the foundational work of Topp et al. [23] by identifying the specific lipid triggers that precede long-term beta cell failure.

Our analysis of local stability further formalizes the concept of metabolic flexibility described initially by Kelley and Mandarino [7], where the condition $\mu_1 > \alpha_1$ identifies a critical biological requirement: for the system to remain stable, the body must prioritize insulin-dependent glucose clearance over its role in inhibiting lipolysis. Furthermore, the global stability analysis defines the mathematical tipping point where the system's hormonal shield ($2\mu_2 d_1 \alpha_1 I^*/3$) must outweight the combined pressures of the dietary load ($2\mu_2 d_1 \delta_2 G^*/(3F^*)$), the resistance tax ($d_1\gamma_1\delta_2$), and the toxicity tax ($\mu_2\gamma_2\alpha_1 F^*$). This provides rigorous mathematical proof for Unger's Lipotoxicity theory [24] and aligns with FALCON study findings regarding the lethal potency of specific lipids on beta cells [25].

Our findings from the three-compartment model underscore the profound impact of elevated plasma FFA levels on glucose dynamics. We demonstrated that elevated FFAs critically impair insulin sensitivity, thereby reducing glucose uptake and elevating plasma glucose concentrations. The sensitivity analysis further highlighted key parameters, such as lipolysis and insulin secretion rates, as pivotal determinants of glucose regulation within this intricate system.

A significant contribution of this research is the exploration of optimal control strategies for robust glucose regulation while accounting for intervention costs. By applying Pontryagin's Maximum Principle, we identified effective control profiles representing GLP-1 receptor agonist interventions. These strategies demonstrate the potential to minimize glucose fluctuations and guide optimal therapeutic efforts, balancing glycemic control with treatment costs.

The outcomes of this research unequivocally emphasize the necessity of a holistic and multi-pathway approach to understanding glucose regulation. Our model emphasizes the critical and interconnected roles of insulin sensitivity, lipid metabolism, and incretin hormones (such as GLP-1) in maintaining metabolic balance. These findings strongly suggest that therapeutic interventions targeting these integrated pathways are essential for the effective management of metabolic disorders.

Future research efforts should focus on expanding the scope and predictive accuracy of this model. Incorporating additional physiological factors, such as the influence of stress hormones (e.g., cortisol) and growth hormones, could provide a more comprehensive understanding of their systemic effects on glucose metabolism. Moreover, the evolution of this model could employ switch-like behavior in GLP-1 secretion patterns (using a switched system approach [18]), stochastic differential equations, and multi-objective optimal control to address additional complexities. Furthermore, the clinical utility of these models could be substantially enhanced by personalizing model parameters using individual patient data, enabling tailored assessments and highly individualized treatment optimization. Ultimately, the successful translation and implementation of this mathematical model into real-world clinical decision support systems would represent an invaluable advancement, empowering healthcare professionals to refine and optimize treatment plans for individuals with glucose dysregulation.

In conclusion, this study provides a vital mathematical perspective on glucose regulation, comprehensively illustrating the dynamic interactions among glucose, insulin, FFAs, and GLP-1. The proposed optimal control strategies offer a compelling pathway to improved glycemic control and hold significant promise for informing future clinical interventions aimed at preventing or managing the escalating burden of metabolic disorders.

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