Control of Blood Sugar in Diabetes and COVID-19 Comorbidity with Physical Exercise: Modelling by Impulsive System of Differential Equations

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Abstract: - Considerable amount of research effort has been concentrated on modelling and predicting the progress of coronavirus infection, its impacts, and the ramifications of various measures taken by affected nations, such as social distancing, vaccination, and provision of long-term health care. More recently, medical doctors have become aware of an unexpected coronavirus complication that can emerge in a short period of time after the initial COVID-19 infection, or sometimes several months afterward. NHS research confirmed that the risk of death is increased significantly in coronavirus patients with diabetes. Our main purpose is to obtain a better understanding of the impacts of physical exercise on the glucose-insulin dynamics in patients with diabetes-COVID-19 comorbidity. To control diabetes, it is important to keep track, with the aid of an appropriate model, of one's blood sugar levels and to know what levels are too high after a meal, while physical activity can lower your blood sugar by making your body more sensitive to insulin. Here, we, therefore, propose and analyse a model of the glucose-insulin control system, comorbidity of coronavirus infection, that incorporates variations in blood sugar due to food intake as well as the role that exercising can take in keeping plasma glucose at a suitable level. The solutions of the model are shown to be bounded and persistent under suitable conditions on the system parameters. The stability and periodicity of the system are also investigated. The delineating conditions on pertinent physical parameters that allow us to obtain the desired outcome are interpreted and discussed.

Key-Words: - impulsive model, stability, COVID-19 with diabetes, diet and exercise

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1 Introduction

A great deal of research effort has been devoted to modelling and predicting the progress of coronavirus infection and the impacts of social distancing and other measures in various countries hit hard by the pandemic, for example in, [1], [2], [3]. However, according to several recent reports, [4], [5], [6], diabetes types 1 and 2 can increase the patient's risk of serious COVID-19 symptoms and death. Another puzzling connection between the two illnesses has been identified whereby the novel coronavirus may be able to induce diabetes in some patients "from scratch", [7]. Thus, it is most important to carry out more in-depth investigations into this link between coronavirus infection and diabetes mellitus.

Recent medical research and discoveries have improved the way we can supervise and control both types of diabetes, but there is as yet no cure for diabetes. Even though modern medicine has made living with diabetes a lot less challenging than it was before, access to treatment is not always assured and insulin therapy is not affordable for many.

According to, [4], medical doctors have been investigating an unexpected coronavirus complication that can emerge in a short period of time after the initial COVID-19 infection, or sometimes several months afterward. An increasing number of patients have been reported to show life-

threatening symptoms that need prompt medical treatments. This risk factor of coronavirus complication is serious and may last through a patient's entire life. Although most patients will survive coronavirus infection, several of them develop long-term symptoms that regularly demand medical care. Moreover, many of these patients even advance to the multisystem inflammatory syndrome, according to, [4].

In, [5], the author asserted that patients with type 1 diabetes are more likely to die of Covid-19 than those with type 2. Also, NHS research confirmed that the risk of death is increased significantly in coronavirus patients with diabetes. It was stated in, [5], that "Almost one in three of all deaths from coronavirus among people in hospitals in England during the pandemic have been associated with diabetes".

In, [8], the authors studied a model system of nonlinear differential equations exhibiting multiple time scales, which attempted to describe diabetes and COVID-19 comorbidity. The model tracked the levels of plasma glucose $G(t)$, insulin $I(t)$, and functional beta cells $\beta_f(t)$, integrating the actions of insulin resistance I_{RS} and inflammatory response $I_{RP}(t)$. After the variables in the model system have been re-scaled so that they were replaced by their respective dimensionless variables, the authors arrived at the following autonomous system of nonlinear differential equations, [8].

$$\frac{dG}{dt} = R_0 - G\left(E_{G0} + \overbrace{S_I \frac{I}{I_{RS}+i}}^{\text{effect of insulin resistance}}\right) \quad (1)$$

$$\frac{dI}{dt} = \overbrace{\sigma \frac{\beta_f G^{\upsilon_h}}{\alpha + G^{\upsilon_h}}}^{\text{effect of glucose}} - kI \quad (2)$$

$$\frac{d\beta_f}{dt} = -r_0 + r_1 G - r_2 G^2 \beta_f \quad (3)$$

$$\frac{dI_{RP}}{dt} = \overbrace{k_{SARS}\Delta k_{ACE2,0}}^{\text{viral infection}} + \overbrace{k_D[Drug]}^{\text{drug treatment}} + k_G G - \overbrace{k_{eff} I_{RP}}^{\text{anti-inflammatory response}} \quad (4)$$

In equation (1), the first term on the right, R_0, is the net rate of production at zero glucose. The last term is the inhibition of the rise of glucose exerted by the secretion of insulin, [8]. The factor I_{RS} stands for the strength of insulin resistance. In equation (2), the same as that used in [8], [9], the first term on the right accounts for the increase in insulin level due to the increasing level of glucose, while the last term is the rate of removal of insulin by natural means depending on how much insulin is present. Equation (3) describes the rate of change of functional β-cells, following, [6].

Table 1. State variables and parameters appearing in the model equations (1) - (4) with their descriptions

Variable/ Parameter	Description
G	glucose concentration in the bloodstream
I	Insulin concentration in bloodstream
β_f	functional β cells
I_{RS}	insulin resistance
I_{RP}	inflammatory response
R_0	net rate of production at zero glucose
S_I	insulin sensitivity coefficient
E_{G0}	total glucose effectiveness at zero insulin
i	insulin resistance self-inhibition rate
σ	maximal rate secretion of insulin by β cells
α	glucose concentration yielding 50% of insulin secretion
k	combined insulin uptake at the liver, kidneys, and insulin receptors
υ_h	power coefficient for Hill-shaped glycemia effect on pancreatic insulin release
r_0	death rate at zero glucose
r_1	I-order coefficient for β cell replication
r_2	II-order coefficient for β cell replication
k_{SARS}	inflammation rate due to SARS-CoV-2
$k_{ACE2,0}$	normal ACE-catalyzed conversion rate from ANG-II to ANG-(1-7)
Δ	multiple of normal conversion rate $k_{ACE2,0}$
k_D	inflammation rate due to ACEi surplus
$[Drug]$	drug concentration
k_G	inflammation rate constant due to glucose surplus
k_{eff}	anti-inflammatory response rate constant of variable
a_0	II-order coefficient for insulin resistance
b_0	I-order coefficient for insulin resistance
c_0	Insulin resistance at zero glucose

Equation (4) has been adapted from that mentioned in, [6]. The first term on the right accounts for the viral infection, which is expressed as a product of inflammation factor due to SARS-CoV-2 infectivity and the abnormal activity of

ACE2, $\Delta k_{ACE2,0}$. The second term on the right of (4) accounts for the increase in inflammatory response due to drugs that remain in the subject's body. The third term on the right of (4) is the inflammation rate due to glucose surplus. Finally, the last term here accounts for the anti-inflammatory response, which varies directly as the inflammatory response at time *t*.

The authors refer the readers to, [6], [9], for more details concerning the model derivation and description of the model's variables and parameters whose definitions are summarized in Table 1.

The model (1) – (4) was analyzed with the geometric singular perturbation technique, by which conditions on the system parameters were derived to identify regions in which the system exhibits different dynamic behavior. In particular, the authors discovered under what conditions would the system be stable, or eventually oscillate periodically. Discussion of these conditions allowed the authors to explain how comorbidity mediates the development of life-threatening symptoms in a diabetic patient, [8].

Comparatively, the model described in, [6], consists of many equations to track many quantities deemed relevant to the problem at hand and therefore is less tractable than that considered in, [8], which offers more predictive power. Both of them, however, did not take into account the impacts of exercising which can change the course of glucose-insulin dynamics significantly. The model system (1) – (4) needs to be adjusted to take into account the jump in plasma glucose after a meal, named "postprandial" blood glucose, [10]. To manage diabetes, it is important to keep track of one's blood sugar levels and to know what levels are too high after a meal. Experts vary on what the normal number should be, but the ADA says a general goal is a blood sugar level under 180 mg/dl, 1 to 2 hours after a meal. The right insulin or medication program can make a big difference, [11].

On the other hand, according to, [11], physical activity can lower your blood sugar for up to 24 hours or more after your workout by making your body more sensitive to insulin. The American Diabetes Association (ADA) has also explained how exercising can help lower blood sugar, [11]. Firstly, Insulin resistance is decreased, so that one's muscle cells are better able to utilize any available insulin to pick up glucose during and after physical exertion. Secondly, when one's muscles contract during exercise, one's cells use glucose for energy even though insulin is not available, [11].

Paradoxically, an exercise regimen that is not properly designed for each person's physiology can be harmful. Individuals with type 1 diabetes are often unable to adequately alter endogenous insulin levels to maintain normal regulation of blood sugar during and following exercise, [12]. As a result, they are at risk for experiencing early and late hypoglycemia, and hyperglycemia as well. People taking insulin or insulin secretagogues, oral diabetes pills that induce one's pancreas to make more insulin, are at risk for hypoglycemia if one does not properly adjust the insulin dose or carbohydrate intake to take account of exercise, [11].

Thus, it is important to investigate how physical exertions and exercise moderate the glucose-insulin control mechanism. We, therefore, propose a model of the glucose-insulin control system in the presence of COVID-19 comorbidity, which is based on (1) – (4), modified to incorporate the impacts of glucose uptakes after meals and exercise moderation shortly after each meal. The model is analyzed for the boundedness of its solutions and then shown to be persistent under suitable conditions on the model system's parameters. The existence of periodic dynamics in our model is then investigated. Numerical simulations are utilized to compare different scenarios to observe the impacts of exercise on the state variables.

2 Model System

According to [13], those with type 2 diabetes are supposed to keep blood sugar levels at 160 mg/dl within 2 hours of a meal. Because exercising reduces blood sugar, researchers have concluded that it is better to exercise soon after eating and that exercising should start about 30 minutes after the beginning of a meal, [13].

To arrive at a model which considers changes occurring at the scale of minute or hour in time, we will assume that, in such a small time scale, the density of functional beta cells changes very slowly and may be considered constant. Thus, we put $\frac{d\beta_f}{dt} = 0$ and only consider equations (1), (2), and (4), in which the insulin resistance term I_{RS} is now denoted by R(t), taken to vary with time. Also, for simplicity, we denote the magnitude of the

inflammatory response by $C(t)$. Thus, we arrive at the following impulsive system of model equations.

$$\frac{dG}{dt} = R_0 - G\left(E_{G0} + S_I \frac{I}{R+i}\right), G(0) > G_i > 0, \quad (5)$$

$$\frac{dI}{dt} = \sigma \frac{\beta_f G^{\upsilon_h}}{\alpha + G^{\upsilon_h}} - kI, I(0) > I_i > 0, \quad (6)$$

$$\frac{dC}{dt} = k_{SARS} \Delta k_{ACE2,0} + k_D[Drug] + k_G G - k_{eff} C,$$

$$C(0) > C_i > 0 \quad (7)$$

$$\frac{dR}{dt} = -i_0 R + mC + qI, R(0) > R_i > 0 \quad (8)$$

if $t \neq t_n$, $t_n = t_{n-1} + nT, t_0 = 0$, $n = 1,2,3,\ldots$.

$$G(t_n) = (1-p)G(t_n^-), \quad (9)$$

$$I(t_n) = I(t_n^-), \quad (10)$$

$$C(t_n) = C(t_n^-), \quad (11)$$

$$R(t_n) = (1-\rho)R(t_n^-), \quad (12)$$

$n = 1,2,3,\ldots, -1 < p < 1, 0 < \rho < 1$.

Equations (5) and (6) are as explained earlier following (1) and (2), respectively. After each meal, plasma glucose concentration peaks. Its level is reduced by insulin, according to the last term in (1). It could also be scaled down by physical exercise, which we model by Equation (9), where p takes into account the net changes in glucose level due to daily food intake and exercise. We let $p > 0$ when physical exercise is assumed to affect a net reduction in glucose level over the positive increase of glucose due to daily food intake. On the other hand, $p < 0$ means exercising still cannot completely override the increase in plasma glucose due to food intake. Since we have recommendations from researchers mentioned above that it is better to exercise soon after eating, we take here the time interval T between meals to be the same as that between physical activities. The suitable choice of the unit T^* of time t is expected to be in hours, though the state variables in (5) – (12) are assumed to be dimensionless, their dimensions having been scaled out using the same technique as in [8].

Equation (7), the same as (4), follows Equation (12) in the work of [6]. As explained earlier and in more detail in, [6], it models the rate of change of inflammatory response $R(t)$ as a function of contributions from glucose concentration, ACE inhibitor treatments, renal conditions, and viral infections (such as COVID-19) binding to ACE2, while the drug surplus left inside the body may reinforce inflammation. Equation (8) is based on Equation (9) in the work of, [6], taking into consideration what the authors stated in, [14], that pro-inflammatory cytokines can raise insulin resistance $R(t)$ in adipose tissue, skeletal muscle, and liver by inhibiting signal transduction by insulin. We assume here that the level of inflammatory cytokines is directly proportional to the extent of inflammatory response $C(t)$, and hence the second term on the right of (8). Insulin resistance $R(t)$ increases with the increase in insulin concentration according to the last term of (8) and decreases naturally according to the first term on the right of this equation. However, physical exercise can reduce blood sugar as explained in the introduction section, and equation (11) takes this into account. According to (11), blood glucose level takes an impulsive jump with physical exercise shortly after a meal, when $t = t_n, n = 1,2,3,\ldots$, where the parameter p accounts for the net changes in glucose level due to daily food intake and exercise. We incorporate the decrease in insulin resistance by adding equation (12) which ρ takes into account the net changes in insulin resistance I_{RS} due to physical exercise.

In the next section, we consider when the solutions of (5) – (12) are positive and bounded, which is a necessary condition for the model to realistically simulate the system of interest.

3 Model Analysis

3.1 Positivity and Boundedness

Assuming that

$$E_{G0} - k_G > 0, k - q > 0, k_{eff} - m > 0, \quad (13)$$

we define

$$\xi = \min(E_{G0} - k_G, k - q, k_{eff} - m, i_0) > 0,$$

$$R_0^* \equiv R_0 + \sigma\beta_f + k_{SARS}\Delta k_{ACE2,0} + k_D[Drug],$$

and show in the following theorem that, under suitable conditions, all solutions starting from positive initial values are positive and bounded.

Theorem 1 For all solutions $(G(t), I(t), C(t), R(t))$ of (5) - (12) with positive initial conditions, there exists an $M > 0$ such that $0 < G(t) \leq M$, $0 < I(t) \leq M, 0 < C(t) \leq M$, and $0 < R(t) \leq M$ for all large t, provided (13) holds.

Proof

First, we show that $G(t), I(t), C(t),$ and $R(t)$ are positive for all $t > 0$.

To show that G is positive for all $t > 0$, we suppose that there is a $t_1^* > 0$ at which $G(t_1^*) < 0$, then by the continuity of G, there must be a point t_2^*, $0 < t_2^* < t_1^*$, where $G(t_2^*) = 0$ and $G'(t_2^*) < 0$. However, at t_2^*, (5) becomes

$$\left.\frac{dG}{dt}\right|_{t=t_2^*} = R_0 > 0,$$

which is a contradiction and therefore G is positive for all $t > 0$.

To show that I am positive for all $t > 0$, we suppose that there is a $t_1^* > 0$ at which $I(t_1^*) < 0$, then by the continuity of I, there must be a point t_2^*, $0 < t_2^* < t_1^*$, where $I(t_2^*) = 0$ and $I'(t_2^*) < 0$. However, at t_2^*, (6) becomes

$$\left.\frac{dI}{dt}\right|_{t=t_2^*} = \sigma\frac{\beta_f G^{\upsilon_h}}{\alpha + G^{\upsilon_h}} > 0,$$

since G has been shown above to be positive. This is a contradiction and therefore $I > 0$ for all $t > 0$.

To show that C is positive for all $t > 0$, we suppose that there is a $t_1^* > 0$ at which $C(t_1^*) < 0$, then by the continuity of C, there must be a point t_2^*, $0 < t_2^* < t_1^*$, where $C(t_2^*) = 0$ and $C'(t_2^*) < 0$. However, at t_2^*, (7) becomes

$$\left.\frac{dC}{dt}\right|_{t=t_2^*} = k_{SARS}\Delta k_{ACE2,0} + k_D[Drug] + k_G G > 0,$$

since G has been shown above to be positive. This is a contradiction so that C is positive for all $t > 0$.

Finally, to show that R is positive for all $t > 0$, we suppose that there is a $t_1^* > 0$ at which $R(t_1^*) < 0$, then by the continuity of R, there must be a point t_2^*, $0 < t_2^* < t_1^*$, where $R(t_2^*) = 0$ and $R'(t_2^*) < 0$. However, at t_2^*, (8) becomes

$$\left.\frac{dR}{dt}\right|_{t=t_2^*} = mC + qI > 0,$$

since C and I have been shown above to be positive. This is a contradiction and therefore R is positive for all $t > 0$.

Now, to show the boundedness above, we let

$V(t, X) = G(t) + I(t) + C(t) + R(t)$.

When $t \neq t_n$ the right derivative of V is

$$\begin{aligned}
&D^+V(t,X) = G'(t) + I'(t) + C'(t) + R'(t)\\
&= R_0 - G\left(E_{G0} + S_I\frac{I}{R+i}\right) + \sigma\frac{\beta_f G^{\upsilon_h}}{\alpha + G^{\upsilon_h}} - kI + k_{SARS}\Delta k_{ACE2,0}\\
&+ k_D[Drug] + k_G G - k_{eff} C - i_0 R + mC + qI\\
&\le R_0 - (E_{G0} - k_G)G - (k - q)I - (k_{eff} - m)C - i_0 R\\
&+ \left(\sigma\beta_f + k_{SARS}\Delta k_{ACE2,0} + k_D[Drug]\right).
\end{aligned}$$

That is,

$$D^+V(t,X) \le R_0^* - \xi V(t,X), \tag{14}$$

since (13) holds. When $t = t_n$ we consider 2 cases as follows.

$\underline{p > 0}$:

$$V(t^+) = (1-p)G(t) + I(t) + C(t) + (1-\rho)R \le V(t) \tag{15}$$

$\underline{p < 0}$:

When $t = t_n$,

$$\begin{aligned}
V(t^+) &= (1-p)G(t) + I(t) + C(t) + (1-\rho)R\\
&\le V + |p|G(t) < V + |p|V = (1+|p|)V.
\end{aligned} \tag{16}$$

Integrating (14), one obtains,

$$\begin{aligned}
V(t,X) &\le V_0\exp\left(-\int_0^t \xi ds\right) + \int_0^t\left(\exp\left(-\int_s^t \xi du\right)\right)R_0^* ds,\\
&= V_0 e^{-\xi t} + R_0^*\int_0^t e^{-\xi(t-s)}ds = V_0 e^{-\xi t} + R_0^* e^{-\xi t}\int_0^t e^{\xi s}ds\\
&= V_0 e^{-\xi t} + R_0^* e^{-\xi t}\left(\frac{e^{\xi t} - 1}{\xi}\right) = V_0 e^{-\xi t} + \frac{R_0^*}{\xi} - \frac{R_0^* e^{-\xi t}}{\xi}\\
&\le V_0 e^{-\xi t} + \frac{R_0^*}{\xi} \to \frac{R_0^*}{\xi} \text{ as } t \to \infty.
\end{aligned} \tag{17}$$

where $V_0 = V(0, X(0))$. Defining

$$M \equiv (1+|p|)\frac{R_0^*}{\xi} > 0, \tag{18}$$

then (15), (16), and (17) imply

$$V(t, X(t)) \le M, \ \forall t \ge 0.$$

Therefore $G, I, C,$ and R are uniformly bounded. □

3.2 Persistence

The following result concerns the persistence of the model system (5) - (12).

Theorem 2 The model system (5) - (12), with positive initial conditions, is persistent provided (13) holds and

$$\frac{\tilde{q}}{i_0} - \frac{\rho e^{i_0 T}}{e^{i_0 T} - 1} > 0, \tag{19}$$

where

$$\tilde{q} = mm_C + qm_I,\ m_I = \frac{\sigma\beta_f m_G^{\upsilon_h}}{k\left(\alpha + M^{\upsilon_h}\right)},\ \tilde{M} = E_{G0} + \frac{S_I M}{i},$$

$$m_C = \frac{k_{SARS}\Delta k_{ACE2,0} + k_D[Drug] + k_G m_G}{k_{eff}},$$

$$m_G = \min\left(\delta e^{-\tilde{M}T}, \frac{R_0(1-p)\left(1-e^{-\tilde{M}T}\right)}{\tilde{M}}\right)$$

with M as defined in (18), and δ as identified in the proof below.

Proof

For, $t \neq t_n$, (5) gives

$$\frac{dG}{dt} = R_0 - G\left(E_{G0} + S_I \frac{I}{R+i}\right) > R_0 - \left(E_{G0} + \frac{S_I M}{i}\right)G = R_0 - \tilde{M}G.$$

We compare the above with the following system.

$$\frac{dG^*}{dt} = R_0 - \tilde{M}G^*, \text{ if } t \neq t_n, G^*(0) = G_i > 0 \quad (20)$$

$$G^*(t^+) = (1-p)G^*(t), \text{ if } t = t_n$$

Integrating (20), we obtain, for $0 < t < t_1$,

$$G^*(t) = G_i \exp(-\int_0^t \tilde{M}ds) + \int_0^t \left[\exp(-\int_s^t \tilde{M}d\theta)R_0\right]ds$$

$$= e^{-\tilde{M}t}\left[G_i + \int_0^t R_0 e^{\tilde{M}s}ds\right] = e^{-\tilde{M}t}\left[G_i + R_0\left(\frac{e^{\tilde{M}t}-1}{\tilde{M}}\right)\right]$$

$$> G_i e^{-\tilde{M}T} + R_0\frac{\left(1-e^{-\tilde{M}t}\right)}{\tilde{M}} > R_0\frac{\left(1-e^{-\tilde{M}t}\right)}{\tilde{M}}.$$

and

$$G^*(t_1) = (1-p)G^*(t_1^-), \text{ with } t_1 = T,$$

$$> (1-p)R_0\frac{\left(1-e^{-\tilde{M}T}\right)}{\tilde{M}} \square\ \delta > 0.$$

Similarly, for $t_{n-1} < t < t_n$,

$$G^*(t) > G^*(t_{n-1})e^{-\tilde{M}T} + R_0\frac{\left(1-e^{-\tilde{M}(t-t_{n-1})}\right)}{\tilde{M}}$$

$$> \delta e^{-\tilde{M}T} + \frac{R_0\left(1-e^{-\tilde{M}(t-t_{n-1})}\right)}{\tilde{M}} > \delta e^{-\tilde{M}T} > 0$$

and

$$G^*(t_n) = (1-p)G^*(t_n^-) > (1-p)R_0\frac{\left(1-e^{-\tilde{M}(t_n-t_{n-1})}\right)}{\tilde{M}}$$

$$= (1-p)R_0\frac{\left(1-e^{-\tilde{M}T}\right)}{\tilde{M}} > 0$$

Therefore, for $t > 0$,

$$G^*(t) > \min\left(\delta e^{-\tilde{M}T}, \frac{R_0(1-p)\left(1-e^{-\tilde{M}T}\right)}{\tilde{M}}\right) = m_G$$

Hence, by comparison, as $t \to \infty$, there is an $m_G > 0$, and a $\tau_1 > 0$, such that $G(t) \geq m_G - \varepsilon_1, \forall t > \tau_1$, for sufficiently small $\varepsilon_1 > 0$.

Next, for, $t \neq t_n$, (6) gives

$$\frac{dI}{dt} = \sigma\frac{\beta_f G^{\upsilon_h}}{\alpha + G^{\upsilon_h}} - kI > \sigma\frac{\beta_f m_G{}^{\upsilon_h}}{\alpha + M^{\upsilon_h}} - kI \text{ for } t > t_1.$$

We compare the above with the equation:

$$\frac{dI^*}{dt} = \sigma\frac{\beta_f m_G{}^{\upsilon_h}}{\alpha + M^{\upsilon_h}} - kI^*,$$

which, may be solved to yield

$$I^*(t) = \frac{\sigma\beta_f m_G{}^{\upsilon_h}}{k\left(\alpha + M^{\upsilon_h}\right)} + ce^{-kt}$$

for some constant c. Thus,

$$\lim_{t\to\infty} I^*(t) = \frac{\sigma\beta_f m_G{}^{\upsilon_h}}{k\left(\alpha + M^{\upsilon_h}\right)} \equiv m_I.$$

which, by comparison, means that there exists a $\tau_2 > 0$ such that $I(t) \geq I^*(t) > m_I - \varepsilon_2, \quad \forall t > \max(\tau_1, \tau_2)$, for sufficiently small $\varepsilon_2 > 0$.

Now, (7) gives

$$\frac{dC}{dt} = k_{SARS}\Delta k_{ACE2,0} + k_D[Drug] + k_G G - k_{eff}C$$

$$> (k_{SARS}\Delta k_{ACE2,0} + k_D[Drug] + k_G m_G) - k_{eff}C,$$

if $t > t_1$. On comparing with

$$\frac{dC^*}{dt} = \rho^* - k_{eff}C^*,$$

where $\rho^* = k_{SARS}\Delta k_{ACE2,0} + k_D[Drug] + k_G m_G$, we will similarly find that

$$\lim_{t\to\infty} C^*(t) \to \frac{\rho^*}{k_{eff}} \equiv m_C.$$

So, by comparison, we conclude that there exists a $\tau_3 > 0$ such that $C(t) \geq C^*(t) > m_C - \varepsilon_3, \forall t > \max(\tau_1, \tau_3)$, for sufficiently small $\varepsilon_3 > 0$.

Finally, (8) gives

$$\frac{dR}{dt} = -i_0 R + mC + qI > mm_C + qm_I - i_0 R,$$

if $t \neq t_n$, and $t > \max(t_2, t_3)$. With $\tilde{q} \equiv mm_C + qm_I$, we have for $t > \max(\tau_2, \tau_3)$,

$$\frac{dR}{dt} > \tilde{q} - i_0 R, \text{if } t \neq t_n,$$

$$R(t^+) = (1-\rho)R(t), \text{if } t = t_n.$$

We compare the above with the following system.

$$\frac{dR^*}{dt} > \tilde{q} - i_0 R^*, \text{if } t \neq t_n, R(0) = R_i > 0 \quad (21)$$

$$R^*(t^+) = (1-\rho)R^*(t), \text{if } t = t_n.$$

We can show, in a similar manner as for $G(t)$ previously, that

$$R^*(t) > \min\left(\tilde{\delta}e^{-i_0T}, \frac{\tilde{q}(1-\rho)\left(1-e^{-i_0T}\right)}{i_0}\right)$$

where

$$\tilde{\delta} = (1-p)\tilde{q}\frac{\left(1-e^{-i_0T}\right)}{i_0} > 0.$$

This then means there is a $\tau_4 > 0$ such that $R(t) \geq m_R - \varepsilon_4, \forall t > \max(\tau_2, \tau_3, \tau_4)$, for sufficiently small $\varepsilon_4 > 0$.

Thus, all the above results together with that in Theorem 1 yields

$$0 < \liminf_{t\to\infty} G(t) < \limsup_{t\to\infty} G(t) < \infty,$$
$$0 < \liminf_{t\to\infty} I(t) < \limsup_{t\to\infty} I(t) < \infty,$$
$$0 < \liminf_{t\to\infty} C(t) < \limsup_{t\to\infty} C(t) < \infty,$$
$$0 < \liminf_{t\to\infty} R(t) < \limsup_{t\to\infty} R(t) < \infty.$$

That is, the system is persistent. □

3.3 Stability and Periodicity

We next prove the stability of the equilibrium solution of the model system (5) – (12) to ensure that, with little contributions from food intakes or physical exertions, solutions starting sufficiently close to the steady state values will eventually tend towards those values as time passes, provided certain conditions on the system parameters are satisfied. In the case that $p = 0$ and $\rho = 0$, we denote the steady state solution by $S_s = (G_s, I_s, C_s, R_s)$. Equating the right-hand side of (8) to zero yields

$$i_0 R_s = mC_s + qI_s, C_s = \frac{i_0 R_s - qI_s}{m}.$$

Using the above in (7) gives

$$G_s = \frac{k_{eff}(i_0 R_s - qI_s) - m(k_{SARS}\Delta k_{ACE2,0} + k_D[Drug])}{mk_G}.$$

Equation (6) leads to

$$I_s = \frac{\sigma\beta_f G_s^{\upsilon_h}}{k(\alpha + G_s^{\upsilon_h})}.$$

Equation (5) then gives

$$R_0 - G_s\left(E_{G0} + S_I\frac{I_s}{R_s + i}\right) = 0.$$

That is,

$$R_0 - E_{G0}G_s - \frac{\sigma\beta_f S_I G_s^{\upsilon_h+1}}{k(R_s+i)(\alpha + G_s^{\upsilon_h})} = 0$$

Namely,

$$-(\sigma\beta_f S_I + kR_T E_{G0})G_s^{\upsilon_h+1} + kR_0R_T G_s^{\upsilon_h} - k\alpha E_{G0}R_T G_s + k\alpha R_0 R_T = 0,$$

where $R_T = R_s + i$.

In order that (5) – (12) to have a unique non-washout steady state, it is necessary that $\upsilon_h = 1$, in which case we obtain the equation

$$(\sigma\beta_f S_I + kR_T E_{G0})G_s^2 + (k\alpha E_{G0}R_T - kR_0R_T)G_s - k\alpha R_0 R_T = 0.$$

so that the system has only one positive steady state $S_s = (G_s, I_s, C_s, R_s)$ if

$$k\alpha E_{G0}R_T - kR_0R_T > 0 \quad (21)$$

Letting

$$E_s \equiv E_{G0} + S_I\frac{I_s}{R_s + i} = \frac{R_0}{G_s},$$

we obtain the following stability result.

Theorem 3 When $p = 0$, $\rho = 0$, the steady state S_s is locally asymptotically stable if (13), (19), (21) hold and

$$C = ac(k_{eff} + i_0) - b(cq + mk_G) + ki_0(k_{eff} + E_s) + E_s k_{eff}(i_0 + k) > 0. \quad (22)$$
$$D = k_{eff}i_0(kE_s + ac) - b(cqk_{eff} + kmk_G) > 0.$$

Proof

Introducing a small perturbation

$$\underset{\sim}{u} = (\delta G, \delta I, \delta C, \delta R)$$

about S_s;

$\delta G = G - G_s$, $\delta I = I - I_s$, $\delta C = C - C_s$, $\delta R = R - R_s$, we then arrive at the following linearized system of (1)-(4) satisfied by $\underset{\sim}{u}$.

$$\frac{d\tilde{u}}{dt} = J_s\tilde{u},$$

where J_s is the Jacobian matrix of (5) - (8) about S_s:

$$J_s = \begin{bmatrix} -E_s & -a & 0 & b \\ c & -k & 0 & 0 \\ k_G & 0 & -k_{eff} & 0 \\ 0 & q & m & -i_0 \end{bmatrix},$$

where

$$a=\frac{G_s S_I}{R_s+i}, b=\frac{S_I G_s I_s}{\left(R_s+i\right)^2}, c=\frac{\sigma\alpha\beta_f G_s^{\upsilon_h-1}}{(\alpha+G_s^{\upsilon_h})^2}.$$

The eigenvalues μ of J_s satisfy the following characteristic equation:

$$(\mu+E_s)(\mu+k)(\mu+k_{eff})(\mu+i_0)+ac(\mu+k_{eff})(\mu+i_0) - b(cq(k_{eff}+\mu)+(k+\mu)mk_G)=0.$$

Letting $\pi(\mu)$ denote the left-hand side of the above equation, one has

$$\pi(\mu)\equiv\mu^4+A\mu^3+B\mu^2+C\mu+D=0,$$

where

$$A=i_0+k+k_{eff}+E_s,$$

$$B=ac+k(i_0+k_{eff}+E_s)+k_{eff}(i_0+E_s)+E_s i_0,$$

$$C=ac(k_{eff}+i_0)-b(cq+mk_G) + ki_0(k_{eff}+E_s)+E_s k_{eff}(i_0+k),$$

$$D=k_{eff}i_0(kE_s+ac)-b(cqk_{eff}+kmk_G)=\mu_1\mu_2\mu_3\mu_4.$$

We see that $\pi\to\infty$ as $\mu\to\pm\infty$, and

$$A>0, B>0,$$

Thus, by Descartes' Rule of Signs, the characteristic equation has 4 negative eigenvalues if

$$C>0 \text{ and } D>0$$

corresponding to condition (22). Thus, the steady state S_s is locally asymptotically stable if (13), (19),(21), and (22) holds. □

Clinically, the system being persistent means its intractable continuation of characteristic medical state, or durability despite treatment or influence of environmental conditions. In our case, this includes daily food intake in combination with exercising, and persistence and stability are the desirable outcome.

Finally, the existence and stability of a periodic solution of (5) – (12) in the case that $-1<p<1$ and $0<\rho<1$ is given by the boundedness of all solutions of the model system proven in Theorem 1 and the application of the result stated in the article by, [16], which states in Preposition 2 that, for a model satisfying certain suitable conditions, every bounded solution converges to a periodic solution. Their proposition encompasses a wider set of differential equations, and to generalize their result, many terminologies had to be introduced. However, our model equations involve continuous functions which are relatively simple, utilized often in biological models. We, therefore, omit the detailed description of the proposition so that definitions of new terminologies, unnecessary to our purposes, need not be introduced. The following theorem follows straightforwardly.

Theorem 4 If (13) and (19) hold, then every solution of (1) – (8), where $-1<p<1$ and $0<\rho<1$, with positive initial condition converges to a periodic solution.

Proof

It is straightforward to see that our model (5) – (12), with $-1<p<1$ and $0<\rho<1$, satisfies the conditions required by Preposition 2 in the article by [16], while conditions (13) and (19) assure that all solutions of our model with positive initial conditions are positive and bounded. Thus, every solution of (5) – (12) under these conditions converges to a periodic solution. □

4 Numerical Simulation

In this section, we present some numerical simulations of the model system (5) – (12) to support our theoretical predictions.

Figure 1, shows numerical simulations, when the conditions in Theorem 4 hold, comparing the case that there is no contribution from physical exercise, seen here in red, and the case where the effect of physical exercise is felt by the control system, seen here in blue. In both cases, meals are taken every 6 hours (T = 6), leading to spikes in glucose levels. Here, we simulate the situation where a workout is initiated soon after each meal, having the effect of lowering the peaks in blood sugar due to food intake by the factor p from –0.2 to –0.15 , and reducing the insulin resistance by the factor ρ from 0 to 0.14. The time series of all state variables are observed to tend to a periodic solution as theoretically predicted. We see here how exercising has the effect of lowering the glucose peak after each meal as a result of lowering insulin resistance and blood glucose.

In Figure 2, the solution trajectory is shown in various 3-dimensional phase spaces corresponding to the case in Figure 1 where p = –0.15 and ρ = 0,14. The trajectory is seen to approach a limit cycle on which the solution oscillates periodically as theoretically predicted.

For Figure 1 and Figure 2, $R_0 = 0.2$, $E_{G0} = 0.7$, $S_I = 5$, $i = 0.5$, $\sigma = 0.5$, $\beta_f = 0.5$, $\alpha = 0.5$, $k = 0.5$, $\delta = 0.5$, $k_{SARS} = 0.5$, $k_{ACE} = 0.2$, $k_D = 0.1$, $[Drug] = 0.5$, $k_G = 0.15$, $k_{eff} = 0.5$, $i_0 = 0.2$, $m = 0.2$, $q = 0.2$, $v_h = 1$, $T = 6$, $G(0) = 0.144$, $I(0) = 0.17$, $C(0) = 0.2$, $R(0) = 0.3$.

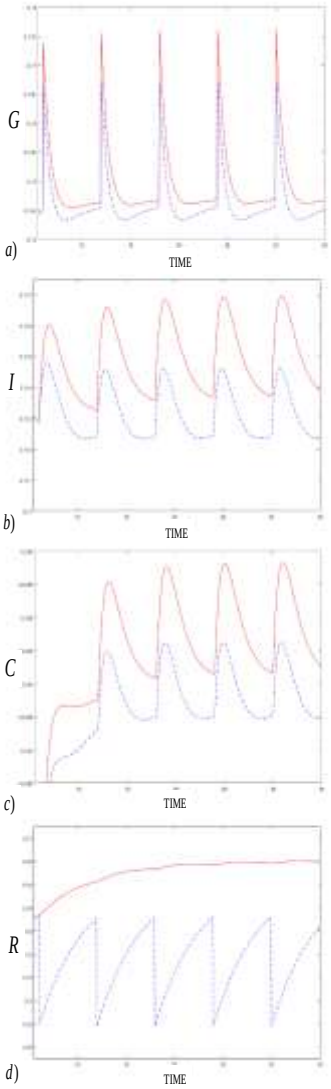

Fig. 1: Numerical simulations of (1) – (8) in the case that the conditions in Theorem 4 hold for different values of p and ρ. Time series are shown for (a) glucose (b) insulin (c) inflammatory response (d) insulin resistance.

$p = -0.2, \rho = 0$, $p = -0.15, \rho = 0.14$.

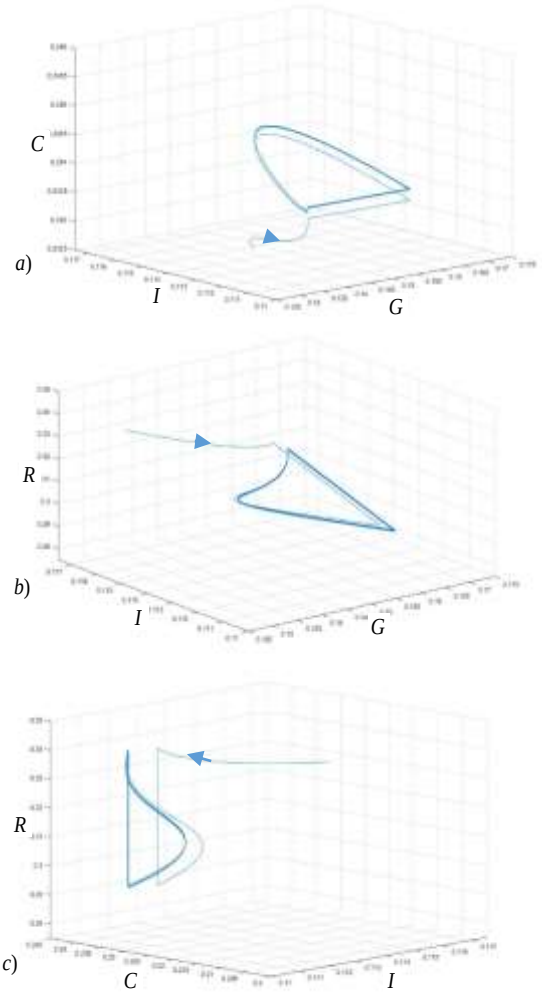

Fig. 2: Solution trajectory plotted in (a) (G, I, C) phase space (b) (G, I, R) phase space (c) (I, C, R) phase space, for the case that $p = -0.15$, and $\rho = 0.14$.

In Figure 3, we show the time series of plasma glucose G for $p = 0.05$, which is the case that physical exercise is able to override the glucose intake from a meal. The glucose level is seen here to take an impulsive drop after every interval of period $T = 6$ before slowly rising back to the original level.

Thus, by varying the values of p and ρ, the extent to which a physical workout induces a drop in blood sugar in different patients with diabetes-COVID-19 comorbidity, each of whom responds to such exertions to varying degrees, a fact that can be accounted for by fitting the parametric values in the model to each specific patient.

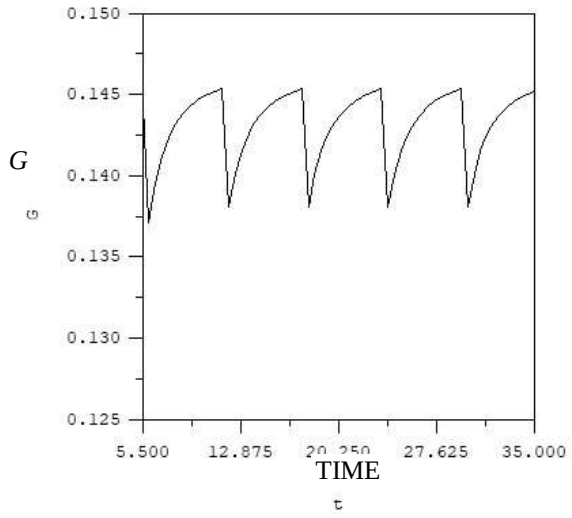

Fig. 3: Time series of plasma glucose $G(t)$ for the case that p is positive, $p=0.05$, while the other parameters have the same values as in Figure 1 and Figure 2.

5 Interpretation and Discussion

We note that exercising and blood glucose control mechanisms work differently in different persons. For the model to be able to simulate individual subjects in different scenarios, it needs to be fitted with data measured from that individual within a controlled environment. Since there are a great deal of factors that may vary unpredictably from moment to moment, or for different activities at that particular moment in time, the result of model predictions must be taken in combination with considerations regarding these random events which may affect the outcome.

According to, [13], some endocrinologists believe that exercising soon after eating has positive effects on blood sugar. However, this can vary from person to person. For a person suffering from diabetes whose body does not manage blood sugar efficiently, sugar level can increase too much during the first half hour of physical exertion before it starts to drop. If one begins to work out with blood sugar which is very much too high, it might have dangerous consequences, [13]. One might need to wait for the level to go down a little before starting to exercise.

Every person reacts a little differently to exercise, so it is advisable to track a person's blood sugar levels for four to five hours after post-meal exercise to see what your reaction to exercising is, [11]. This can help you ascertain whether your levels are currently healthy or dropping too low. It is essential to check our blood sugar levels more frequently before and after exercise so that we may benefit more from physical activity. We also can use the results of our blood sugar checks in combination with the predictions of the model in which the parameters have been calibrated to fit our personal trends, to know how our body would react to different levels of activities. Understanding these patterns can help us keep our blood sugar from becoming too high or too low.

In particular, if you are taking insulin supplementary injections, or oral diabetes pills that cause your pancreas to make more insulin, you are at risk for hypoglycemia if your insulin dose or carbohydrate intake is not adjusted with exercise. Checking your blood sugar before undertaking any physical activity is important to prevent hypoglycemia (low blood sugar). The model can show the extent to which your workout may affect a drop in your blood sugar to below the safe level, or how hard each person should engage in physical workouts to keep blood sugar from rising too high after a big meal.

To achieve certain stability in the system such that each model solution tends asymptotically to a periodic solution as seen in Figure 1 and Figure 2, we need the conditions (13) and (19) to hold so that the system is persistent.

As explained in section 3, persistence and stability are the desirable outcomes, since they ensure the continuation and maintenance of blood glucose so that it does not reach a dangerous level, despite treatment or influence from daily food intake or exercise.

For condition (19) to hold, we see that it puts a restriction on how hard the physical workout should be undertaken. If other parameters in (19) are fixed, then ρ must not exceed the maximum limit $\rho_{\max}$ so that

$$\rho < \frac{\tilde{q}(e^{i_0 T}-1)}{i_0 e^{i_0 T}} \equiv \rho_{\max}. \tag{23}$$

This means, for your particular body type, the limit to how hard you should exercise is limited by the quantity $\rho_{\max}$, given that you choose to exercise every T unit of time. As an example, if you exercise more frequently, T being smaller, then the above formula stipulates that you should not exercise so hard that ρ exceeds $\rho_{\max}$ which is smaller for smaller T.

Moreover, for condition (13) to hold, we need the total glucose effectiveness at zero insulin E_{G0} to be sufficiently large so that it exceeds the specific inflammation rate due to glucose surplus k_G. Also, the combined insulin uptake at the liver, kidneys,

and insulin receptors (k) should exceed the specific rate of increase of insulin resistance due to insulin, and the impact of the inflammatory response on insulin resistance should remain low enough so that m is smaller than the anti-inflammatory response coefficient k_{eff}.

6 Conclusion

Although WHO has said that COVID is no longer a global emergency, many still advocate continued vigil. In [15], the author underscored the importance of ensuring continued accountability especially when an event as devastating as the COVID-19 pandemic is concerned.

Numerous researchers have turned their attention toward Post Covid-19 Syndrome (PCS), considered to be a major cause of morbidity. Specifically, in the article by, [17], a review of the association and consequences of PCS and diabetes was reported. They described the various symptoms of PCS which can be due to organ dysfunction, consequences of hospitalisation and drugs, or other unrelated factors. According to, [17], type 2 diabetes mellitus has a "bidirectional relationship with COVID-19". PCS is influenced by the presence of diabetes symptoms through various pathophysiological mechanisms. Symptoms like tachycardia, sarcopenia as well as muscle fatigue, microvascular dysfunction, and organ damage in patients with diabetes can be exacerbated by COVID-19. Thus, there are numerous ways by which Post Covid-19 Syndrome can be harmful to patients with diabetes. We may conclude from the report in [17], and those by other researchers, that strict control of diabetes involving supervised rehabilitation, physical exercise, and optimal nutrition, which necessitates a nutritional regimen that is suitably adjusted to exercise, could help in reducing the impact of Post Covid-19 Syndrome and raising the efficiency in its control and management.

In this article, we have investigated the role of exercising and food intake in the control of blood sugar in patients with diabetes in relation to COVID-19 symptoms. Utilizing a system of nonlinear differential equations with impulses in the glucose concentration and insulin resistance due to periodic food intakes and physical exercises soon after meals, we have been able to derive delineating conditions which ensure that the sugar level remains in the controllable bounded ranges. The model's numerical simulations show periodic peaks in plasma glucose similar to those observed in clinical data, [18]. Exercising soon after each meal is illustrated to be able to moderate the sharp rise in blood sugar that normally occurs after each meal. The quality and extent to which the responses are observed are unique for each individual patient. Close inspection and interpretation of the conditions derived from our analysis shed light on how the glucose-insulin control system is impacted by COVID-19 infection and how different levels of workouts adjusted with an individual's nutritional program could be utilized for the best outcome for the purposes of the patient's health care.

Although our model appears relatively simple, and the methodologies for its analysis have been applied to other models, the complexity of our work lies in the difficulty in arriving at our conclusions regarding the persistence and boundedness of the system, to make the conclusions regarding its periodicity and stability, a significant characteristic for the control of this complex dynamics complicated by comorbidity which, to our knowledge, has not been investigated before.

For future research, we could use the collected data from patients with diabetes and COVID-19 infection to determine some of the parametric values and make interpretations that are more specific to particular patients turn our attention to the consideration of vaccination policy and possible side effects, in comparison with unvaccinated survivors of coronavirus infection in the future trends of the spread of this virus with its mutations, which is believed by many experts to still pose a serious threat to humankind.

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-Yongwimon Lenbury: conceptualization, verification of analysis, stability analysis, interpretation, and source of funding.

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Conflict of Interest

There is no conflict of interest.