# The Glucose-Insulin-Incretin Model for Bariatric Surgery and T2DM Improvement Mechanisms with Two Delays

Puntip Toghaw, Yongwimon Lenbury

***Abstract*—**In 2012 Toghaw *et al.* introduced a mathematical model of the glucose-insulin-incretins system to investigate plausible hypotheses to explain the rapid, weight-independent glycemic effects of bariatric surgery by comparing the pre-surgery simulated time series with those under various hypotheses, namely the lower intestinal hypothesis, the upper intestinal, and the ghrelin hypothesis. The model system has been reduced to a system of 9 differential equations by excluding the plasma ghrelin concentration factor following the discovery made in the work of Toghaw *et al.* in 2012. In the present work, we modify the model system in order to incorporate two time-delays. The model system was analyzed to investigate the effect of delays on the complex dynamic behavior of the system. In addition, the simulations under the three hypotheses will be compared.

***Keywords*—**Bariatric Surgery, delays, glycaemia, mathematical model.

## I. Introduction

ACCOURDING to several recent reports [1]-[3], obese diabetic patients who have undergone bariatric surgery to lose weight, especially Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD), show a rapid improvement of the glucose homeostasis. These two operations have in common the effect of reducing the absorption of nutrients by exclusion of nutrients from the duodenum and proximal jejunum. It has been clinically observed that the blood glucose profile significantly improves only a few days after surgery before any significant weight loss occurs. In order to explain the mechanisms which underly the effect of gastric bypass procedures in normalizing glycaemia uncorrelated with the degree of weight loss, it has been hypothesized that the gut removal itself may play a major role in diabetes remission, due to the fact that important hormones are secreted there, such as the incretin hormones Glucagon-like peptide-1 (GLP-1) and Glucose Insulinotropic Polypeptide (GIP), ghrelin hormones and the unknown hormone anti-incretin.

In healthy subjects, GLP-1 and GIP accounts for 50-70% of the overall insulin secretion in response to oral glucose intake [4]. In patients with type 2 diabetes (T2DM), the effect of administered GIP on insulin secretion is impaired, while the level of plasma GLP-1 is reduced, but the effect of administered GLP-1 on insulin secretion persists [5]. Both GLP-1 and GIP are mainly degraded by the enzyme Dipeptidyl-peptidase IV (DPP4) [6].

In 2009, Cummings reviewed the hypotheses that have been considered so far to explain the mechanisms underlying diabetes remission [7]. His paper discussed various hypotheses proposed in different literatures to explain why the plasma glucose control system shows an improvement at a faster rate than the rate of patient's weight loss after surgery. The main hypotheses proposed in these literatures are the ghrelin hypothesis, the upper intestinal hypothesis and the lower intestinal hypothesis.

The ghrelin hypothesis is based on the observation that the level of plasma ghrelin hormone decreases to approximately 30% of the level before surgery. Ghrelin is a hormone which stimulates hunger and is mainly secreted by the stomach. Its concentration rises before a meal and quickly decreases after meal. The suppression of ghrelin release after surgery may reduce appetite and food intake resulting in an improvement of glycemia.

In the lower intestinal hypothesis, it is claimed that the surgery resulting in the delivery of food to the lower intestine faster increases the release of GLP-1. GLP-1 is an incretin hormone secreted from enteroendocrine L-cells in response to nutrients ingestion which increases insulin secretion in a glucose-dependent manner. The enteroendocrine L-cells can be found throughout the small intestine and in high density in the ileum at the furthest end of the small intestine. As a result of surgery, GLP-1 is secreted sooner in an increased amount leading to glycemic improvement.

For the upper intestinal hypothesis, it is observed that in a diabetes patient, the duodenum and proximal jejunum may have a mechanism which involves the unknown hormone called anti-incretin that works against the function of incretin hormones, and is stimulated when food touches these parts of the small intestines. As a result of surgery, the path of food is

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changed preventing food from passing through the duodenum and proximal jejunum. The anti-incretin does not function leading to diabetes remission.

In 2012, Toghaw *et al*. [8] introduced a mathematical model which describes the dynamics of the glucose-insulin-incretins system, in order to compre these three postulated mechanism with the known physiology. The proposed model is composed of 10 ordinary differential equations, describing the dynamics of the amounts of ingested glucose in the stomach, duodenum and ileum, and the dynamics of plasma glucose, insulin concentrations with GLP-1, GIP, DPP4 and anti-incretin interaction. They evaluated parameter values according to the literature and dependent on a number of assumptions especially in the unknown hormone anti-incretin. They performed numerical experiments to investigate these three plausible hypotheses to explain the weight-independent glycemic effects of bariatric surgery by comparing the pre-surgery simulated time series with those post-surgery under various hypotheses, namely the lower intestinal hypothesis, the upper intestinal, and the ghrelin hypothesis. The modeling results seem to indicate that the suppression of ghrelin release is unlikely to determine major changes in short-term glucose control, while the anti-incretin and the lower intestinal hypothesis simulations both gave higher plasma insulin concentration peaks as well as lower plasma glucose concentration, while the lower-intestinal hypothesis simulations produced greater effect on glycemia levels. However, the mathematical analysis of the model system was not given in this paper.

In 2012, Lueabunchong *et al*. [9] estimated the values of the parameters connected to the dynamics of the plasma glucose and insulin concentrations of the glucose/insulin model with GLP-1 and DPP4 interaction reduced from the model proposed in [8] by using the statistical evaluation.

In 2013, Toghaw *et al*. [10] reduced the model proposed in [8] to a system of 9 differential equations by excluding the plasma ghrelin concentration, in view of the conclusions reached in [8]. Theorems were presented, which show the existence, uniqueness, and local stability of the equilibrium point.

However, sustained fluctuations in insulin and incretins levels are often observed clinically which could be the result of certain delay mechanisms whereby a change in one component does not lead to an immediate change in the other components in the system under study. Such lags in the glucose-insulin dynamics have frequently been reported in the literatures [11]-[13].

The inclusions of time delay terms in many mathematical models have been used in an attempt to better understand the complicated dynamics in natural systems [14]-[18].

In this paper, the impacts of delays are investigated. The organization of the paper is as follows: In Section two, the modification of model system in [10] in order to incorporate two time-delays is presented. Section three deals with the stability properties of the model system. Simulation results and discussion are in Section four. Finally, Section five contains the conclusion.

## II. System Model

We now modify the glucose-insulin-incretin model for bariatric surgery and T2DM improvement mechanisms in [10] in order to incorporate two time delays, $\tau_g$ in the insulin secretion in response to plasma glucose and $\tau_i$ in the insulin-dependent glucose uptake. The model system can then be written as follows:

$$\frac{dS}{dt} = -k_{ds}S(t) - k_{ls}S(t),\ S(T_{\min}) = S_{Tmin} \tag{1}$$

$$\frac{dD}{dt} = k_{ds}S(t) - k_{gd}D(t) - k_{ld}D(t),\ D(T_{\min}) = D_{Tmin} \tag{2}$$

$$\frac{dL}{dt} = k_{ld}D(t) + k_{ls}S(t) - k_{gl}L(t),\ L(T_{\min}) = L_{Tmin} \tag{3}$$

$$\frac{dG}{dt} = -k_{xg}G(t) - k_{xgi}I(t-\tau_i)G(t) + f\frac{k_{gd}D(t) + k_{gl}L(t)}{V_g} + k_g^{liver},\ G(T_{\min}) = G_{Tmin} \tag{4}$$

$$\frac{dI}{dt} = G(t-\tau_g)\left(k_{ig} + k_{iwg}W(t)e^{-\lambda_{01}aA(t)} + k_{iug}U(t)e^{-\lambda_{02}aA(t)}\right) - k_{xi}I(t),\ I(T_{\min}) = I_{Tmin} \tag{5}$$

$$\frac{dW}{dt} = k_{wd}D(t)e^{-\lambda_{04}aA(t)} + k_{wl}L(t) + k_w - k_{xwp}P(t)W(t) - k_{xw}W(t),\ W(T_{\min}) = W_{Tmin} \tag{6}$$

$$\frac{dU}{dt} = k_{ud}D(t)e^{-\lambda_{05}aA(t)} + k_{ul}L(t) + k_u - k_{xup}P(t)U(t) - k_{xu}U(t),\ U(T_{\min}) = U_{Tmin} \tag{7}$$

$$\frac{dP}{dt} = k_p - k_{xp}P(t),\ P(T_{\min}) = P_{Tmin} \tag{8}$$

$$\frac{dA}{dt} = k_{ad}D(t) - k_{xa}A(t) + k_a,\ A(T_{\min}) = A_{Tmin} \tag{9}$$

where:

$t$ [min] is time in minutes;

$\tau_g$ [min] is the time delay in the insulin secretion in response to glucose production in minutes, $\tau_g \geq 0$;

$\tau_i$ [min] is time delay in the insulin-dependent glucose uptake in minutes, $\tau_i \geq 0$;

$T_{\min}$ [min] is starting time for simulations;

$S(t)$ [mmol] is an amount of ingested glucose in the stomach;

$D(t)$ [mmol] is an amount of glucose in duodenum;

$L(t)$ [mmol] is an amount of ingested glucose that appears in the ileum;

$G(t)$ [mM] is plasma glucose concentration;

$I(t)$ [pM] is plasma insulin concentration;

$W(t)$ [pM] is plasma GLP-1 concentration;

$U(t)$ [pM] is plasma GIP concentration;

$P(t)$ [U/L] is plasma DPP4 concentration;

$A(t)$ [pM] is plasma anti-incretin concentration;
$k_{ds}$ [$min^{-1}$] is the rate of ingested glucose from the stomach to duodenum;
$k_{ls}$ [$min^{-1}$] is the rate of ingested glucose from the stomach to ileum;
$k_{gd}$ [$min^{-1}$] is the rate of ingested glucose from the duodenum into the plasma;
$k_{ld}$ [$min^{-1}$] is the rate of ingested glucose from the duodenum to the ileum;
$k_{gl}$ [$min^{-1}$] is the rate of ingested glucose from ileum to the blood;
$k_{xg}$ [$min^{-1}$] is the insulin-independent rate constant of tissue glucose uptake;
$k_{xgi}$ [$min^{-1}$/pM] is the insulin-dependent rate constant of tissue glucose uptake;
$f$ is the fraction of absorbed glucose from ingested meal;
$k_g^{liver}$ [pM/min] is the increase in plasma glucose concentration due to hepatic glucose release;
$k_{ig}$ [pM/min/mM] is the rate of pancreatic release of insulin due to glucose;
$k_{iwg}$ [pM /min/ pM/mM] is the rate of pancreatic release of insulin due to GLP-1;
$k_{iug}$ [pM /min/ pM/mM] is the rate of pancreatic release of insulin due to GIP;
$k_{xi}$ [$min^{-1}$] is the disappearance rate constant for insulin;
$\lambda_{01a}$, $\lambda_{02a}$ [$pM^{-1}$], are the decay rates of insulin secretion via the effect of GLP-1 and GIP as anti-incretin concentrations increase, respectively;
$k_{wd}$ [pM/min/mmol] is the rate of release of GLP-1 per amount of ingested glucose appearing in the duodenum;
$k_{wl}$ [pM/min/mmol] is the rate of release of GLP-1 per amount of ingested glucose appearing in the ileum;
$k_{xw}$ [$min^{-1}$] is the disappearance rate constant for GLP-1;
$k_{xwp}$ [$min^{-1}$/pM] is the disappearance rate constant for GLP-1 due to DPP4;
$k_w$ [pM/min] is the appearance rate constant for GLP-1;
$\lambda_{04a}$ [$pM^{-1}$] is decay rate of GLP-1 production as anti-incretin concentration increase;
$k_{ud}$ [pM/min/mmol] is the rate of release of GIP per unit amount of ingested glucose appearing in the duodenum;
$k_{ul}$ [pM/min/mmol] is the rate of release of GIP per amount of ingested glucose;
$k_{xu}$ [$min^{-1}$] is the disappearance rate constant for GIP;
$k_{xup}$ [$min^{-1}$/pM] is the disappearance rate constant for GIP due to DPP4;
$k_u$ [pM/min] is the appearance rate constant for GIP;
$\lambda_{05a}$ [$pM^{-1}$] is the decay rate of GIP production as anti-incretin concentration increase;
$k_{xp}$ [$min^{-1}$] is the disappearance rate constant for DPP4;
$k_p$ [U/L /min] is the appearance rate constant for DPP4;
$k_{ad}$ [pM/min/mmol] is the appearance rate constant for anti-incretin due to glucose in the duodenum; $k_{xa}$ [$min^{-1}$] is the disappearance rate constant for anti-incretin, supposed to be the same rate as that of DPP-4;
$k_a$ [U/L/min] is the appearance rate constant for anti-incretin.

Equation (1) describes the dynamics of the amount of ingested glucose in the stomach. The first term represents the transfer of the amount of ingested glucose from the stomach to the duodenum which will be zero in the post-surgery situation. The second term is the transfer the amount of ingested glucose from the stomach directly to the ileum, which occurs only after the surgery.

Equation (2) describes the variation of the amount of glucose in the duodenum proximal jejunum, the upper parts of the small intestines. The first term represents the entry of ingested glucose from the stomach, while the second term is the absorption of ingested glucose to the plasmatic glucose compartment and the third term represents the transfer of ingested glucose from these parts to the ileum.

Equation (3) describes the dynamics of glucose in the ileum at the furthest end of the small intestine. The first term represents the entry of ingested glucose from the duodenum which will be zero in the post-surgery situation, while the second term represents the entry from the stomach which occurs only after the surgery. The last term is the absorption of the ingested glucose into the plasmatic glucose compartment.

Equation (4) describes the dynamics of the plasma glucose concentration. The first term represents the insulin-independent glucose tissue uptake. The second represents the insulin-dependent glucose tissue uptake with the time delay $\tau_i$. The third term is plasma glucose entry. The last term is the increase in plasma glucose concentration due to hepatic glucose release.

Equation (5) describes the dynamics of the plasma insulin concentration. All the entry terms are collected in parentheses with the time delay $\tau_g$: the first term accounts for glucose dependent insulin secretion. The second term depends on the plasma glucose and GLP-1 concentration and third terms depend on the plasma glucose and GIP concentration. The action of the incretin hormones GLP-1 and GIP is opposed by the action of plasma anti-incretin with an exponentially decreasing dynamics. The last term accounts for linear plasma insulin elimination.

Equation (6) describes the dynamics of plasma GLP-1 concentration. The first term represents the entry due to the amount of glucose in the duodenum, which is exponentially controlled by plasma anti-incretin concentrations. The second term represents the entry due to the amount of glucose in the ileum. The third term accounts for the elimination depend on plasma DPP4 action, while the fourth term accounts for the natural plasma GLP-1 disappearance. The last term represents the GLP-1 constant secretion.

Equation (7) describes the dynamics of plasma GIP concentration. Each term is similar to (6).

Equation (8) describes the variation of plasma DPP-4 concentration. The first term represents the plasma DPP-4 constant secretion, and the last term accounts for linear plasma DPP-4 elimination.

Equation (9) describes the variation of plasma anti-incretin concentration. The first term represents the entry due to the amount of glucose in the duodenum. The second term

accounts for linear plasma anti-incretin elimination and the last term represents the plasma anti-incretin constant secretion.

The details for the physiological meaning of each variable and the parameter values are described in [8].

**Remark 1.** All model parameters previously defined are strictly positive, except for $k_{ds}$, $k_{ls}$, $k_{ld}$, and $k_{gd}$, which may be zero according to the simulation for pre-surgery or post-surgery situation.

## III. Stability and Bifurcation

We first determine the positiveness, existence and uniqueness of the solution to the model system (1)-(9).

The following theorem ensures that the model system has a positive solution.

**Theorem 1.** System (1)-(9) admits a positive solution for any positive initial condition.

*Proof.* Let $T_{min} = 0$ in this case.

Equation (1) involves only one dependent variable, we have $S(t) = S(T_{\min})e^{-(k_{ds}+k_{ls})t}$.

Hence, if $S(T_{\min}) > 0$, then $S(t) > 0$ for all $t$ and $S(t)$ will approach zero as $t \to \infty$.

Next, let $D(T_{\min}) > 0$. By the continuity of a solution $D(t)$ would become non positive if there exists a $t_2 > 0$ such that $D(t_2) = 0$ and $\left.\frac{dD}{dt}\right|_{t=t_2} \le 0$, which is a contradiction because $\left.\frac{dD}{dt}\right|_{t=t_2} = k_{ds}S(t_2) > 0$.

This proves that, if $D(T_{\min}) > 0$ then $D(t)$ is always positive. Similarly, it can be proven that the system (3)-(9) admits a positive solution for any positive initial condition. By using the same procedure we have, $t_i > 0$, $i = 3,..,9$, such that

if $L(t_3) = 0$, $\left.\frac{dL}{dt}\right|_{t=t_3} = k_{ld}D(t_3) + k_{ls}S(t_3) > 0$,

if $G(t_4) = 0$, $\left.\frac{dG}{dt}\right|_{t=t_4} = f\frac{k_{gd}D(t_4) + k_{gl}L(t_4)}{V_g} + k_g^{liver} > 0$,

if $I(t_5) = 0$,

$$\left.\frac{dI}{dt}\right|_{t=t_5} = G(t_5 - \tau_{5g})\left(k_{ig} + k_{iwg}W(t_5)e^{-\lambda_{01}aA(t_5)} + k_{iug}U(t_5)e^{-\lambda_{02}aA(t_5)}\right) > 0,$$

if $W(t_6) = 0$, $\left.\frac{dW}{dt}\right|_{t=t_6} = k_{wd}D(t_6)e^{-\lambda_{04a}A(t_6)} + k_{wl}L(t_6) + k_w > 0$,

if $U(t_7) = 0$, $\left.\frac{dU}{dt}\right|_{t=t_7} = k_{ud}D(t_7)e^{-\lambda_{05a}A(t_7)} + k_{ul}L(t_7) + k_u > 0$,

if $P(t_8) = 0$, $\left.\frac{dP}{dt}\right|_{t=t_8} = k_p > 0$,

and if $U(t_9) = 0$, $\left.\frac{dA}{dt}\right|_{t=t_9} = k_{ad}D(t_9) + k_a > 0$.

The uniqueness of a non-vanishing equilibrium solution is assured by the following theorem.

**Theorem 2.** System (1)-(9) has a unique non-vanishing equilibrium point

$$\bar{X}_s = \begin{pmatrix} S_s & D_s & L_s & G_s & I_s & W_s & U_s & P_s & A_s \end{pmatrix}^T. \quad (10)$$

*Proof.* Each equilibrium point has to satisfy the following equations

$$-k_{ds}S_s - k_{ls}S_s = 0 \quad (11)$$

$$k_{ds}S_s - k_{gd}D_s - k_{ld}D_s = 0 \quad (12)$$

$$k_{ld}D_s + k_{ls}S_s - k_{gl}L_s = 0 \quad (13)$$

$$-k_{xg}G_s - k_{xgi}I_sG_s + f\frac{k_{gd}D_s + k_{gl}L_s}{V_g} + k_g^{liver} = 0 \quad (14)$$

$$G_s\left(k_{ig} + k_{iwg}W_se^{-\lambda_{01}aA_s} + k_{iug}U_se^{-\lambda_{02}aA_s}\right) - k_{xi}I_s = 0 \quad (15)$$

$$k_{wd}D_se^{-\lambda_{04a}A_s} + k_{wl}L_s + k_w - k_{xwp}P_sW_s - k_{xw}W_s = 0 \quad (16)$$

$$k_{ud}D_se^{-\lambda_{05a}A_s} + k_{ul}L_s + k_u - k_{xup}P_sU_s - k_{xu}U_s = 0 \quad (17)$$

$$k_p - k_{xp}P_s = 0 \quad (18)$$

$$k_{ad}D(t) - k_{xa}A(t) + k_a = 0 \quad (19)$$

From (11)-(13), it is straight forward to find that

$$S_s = D_s = L_s = 0. \quad (20)$$

Furthermore, from (15), we have

$$I_s = \frac{G_sK_1}{k_{xi}} > 0, \quad (21)$$

where $K_1 = k_{ig} + k_{iwg}W_se^{-\lambda_{01}aA_s} + k_{iug}U_se^{-\lambda_{02}aA_s}$.

Substituting (20)-(21) to (14), we obtain the quadratic polynomial

$$k_{xgi}K_1G_s^{\,2} - k_{xg}k_{xi}G_s - k_{xi}k_g^{liver} = 0,$$

which has two roots

$$G_s = \frac{-k_{xg}k_{xi} \pm \sqrt{(k_{xg}k_{xi})^2 + 4k_{xgi}k_{xi}K_1k_g^{liver}}}{2k_{xgi}K_1}.$$

Since the discriminant is positive, we obtain only one positive root

$$G_s = \frac{-k_{xg}k_{xi} + \sqrt{(k_{xg}k_{xi})^2 + 4k_{xgi}k_{xi}K_1k_g^{liver}}}{2k_{xgi}K_1} > 0.$$

Similarly, from (16)-(19), we obtain

$$W_s = \frac{k_w}{k_{xw} + k_{xwp}P_s},$$

$$U_s = \frac{k_u}{k_{xu} + k_{xup}P_s},$$

$$P_s = \frac{k_p}{k_{xp}},$$

and $A_s = \frac{k_a}{k_{xa}}$, which are all positive.

To investigate the effect of delays on the possibility of periodic dynamics in the system, the Jacobian matrix at the equilibrium point $J(\bar{X}_s)$ in (10) is derived as

$$J(\bar{X}_s) =$$

$$\begin{bmatrix} J_{11} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ k_{ds} & J_{22} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ k_{ls} & k_{ld} & -k_{gl} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & J_{42} & J_{43} & J_{44} & J_{45}e^{-\lambda\tau_i} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & J_{54}e^{-\lambda\tau_g} & J_{55} & J_{56} & J_{57} & 0 & J_{59} \\ 0 & J_{62} & k_{wl} & 0 & 0 & J_{66} & 0 & J_{68} & 0 \\ 0 & J_{72} & k_{ul} & 0 & 0 & 0 & J_{77} & J_{78} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & J_{88} & 0 \\ 0 & k_{ad} & 0 & 0 & 0 & 0 & 0 & 0 & J_{99} \end{bmatrix} \tag{22}$$

when

$J_{11} = -k_{ds} - k_{ls}$,

$J_{22} = -k_{gd} - k_{ld}$,

$J_{42} = f\dfrac{k_{gd}}{V_g}$,

$J_{43} = f\dfrac{k_{gl}}{V_g}$,

$J_{44} = -k_{xg} - k_{xgi}I_s$,

$J_{45} = -k_{xgi}G_s$,

$J_{54} = K_1$,

$J_{55} = -k_{xi}$,

$J_{56} = k_{iwg}G_s e^{-\lambda_{01}aA_s}$,

$J_{57} = k_{iug}G_s e^{-\lambda_{02}aA_s}$,

$J_{59} = -\lambda_{01}ak_{iwg}G_sW_s e^{-\lambda_{01}aA_s} + k_{iug}G_sU_s e^{-\lambda_{02}aA_s}$,

$J_{62} = k_{wd}e^{-\lambda_{04}aA_s}$,

$J_{66} = -k_{xwp}P_s - k_{xw}$,

$J_{68} = -k_{xwp}w_s$,

$J_{72} = k_{ud}e^{-\lambda_{05}aA_s}$,

$J_{77} = -k_{xup}P_s - k_{xu}$,

$J_{78} = -k_{xup}U_s$,

$J_{88} = -k_{xp}$,

and $J_{99} = -k_{xa}$.

The characteristic equation of $J(\bar{X}_s)$ is

$$\begin{aligned} p(\lambda) \equiv\ & (-k_{ds} - k_{ls} - \lambda)\cdot(-k_{gd} - k_{ld} - \lambda)\cdot(-k_{gl} - \lambda) \\ & \cdot(-k_{xa} - \lambda)\cdot(-k_{xp} - \lambda)\cdot(J_{77} - \lambda)\cdot(J_{66} - \lambda) \\ & \cdot\left\{(J_{44} - \lambda)(J_{55} - \lambda) - (J_{45}e^{-\lambda\tau_i})(J_{54}e^{-\lambda\tau_g})\right\} \\ =\ & 0 \end{aligned} \tag{23}$$

Hence, the eigenvalues $\lambda_i$, $i = 1,2,...,9$, are

$\lambda_1 = -k_{ds} - k_{ls} < 0$,

$\lambda_2 = -k_{gd} - k_{ld} < 0$,

$\lambda_3 = -k_{gl} < 0$,

$\lambda_4 = -k_{xa} < 0$,

$\lambda_5 = -k_{xp} < 0$,

$\lambda_6 = -k_{xwp}P_s - k_{xw} < 0$,

$\lambda_7 = -k_{xup}P_s - k_{xu} < 0$

and $\lambda_8$, $\lambda_9$ are the solutions of

$$q(\lambda,\tau) \equiv \lambda^2 + b\lambda + c + de^{-\lambda\tau} = 0, \tag{24}$$

with the total delay $\tau = \tau_i + \tau_g \geq 0$,

$b = k_{xg} + k_{xgi}I_s + k_{xi} > 0$,

$c = (k_{xg} + k_{xgi}I_s)k_{xi} > 0$,

and $d = k_{xgi}G_sK_1 > 0$.

If $\tau = 0$,

$$q(\lambda,0) \equiv \lambda^2 + b\lambda + c + d = 0, \tag{25}$$

The solutions of the Eq. (25) are

$$\lambda_8 = \frac{-b - \sqrt{b^2 - 4(c+d)}}{2}$$

and $\lambda_9 = \dfrac{-b + \sqrt{b^2 - 4(c+d)}}{2}$.

Since $b > 0$ and $c + d > 0$, if $b^2 - 4(c+d) < 0$ then the eigenvalues $\lambda_8$ and $\lambda_9$ are complex conjugates with negative real parts. If, on the other hand, $b^2 - 4(c+d) > 0$, then the eigenvalues $\lambda_8$ and $\lambda_9$ are both real and negative, since $c + d > 0$ and so $\sqrt{b^2 - 4(c+d)} < b$.

Therefore, all eigenvalues of the Jacobian matrix have strictly negative real parts. We can conclude that, in the absence of delay, the equilibrium point $\bar{X}_s$ is locally asymptotically stable.

As $\tau$ varies, for a periodic solution to exist, we are looking for a pure imaginary root. Letting $\lambda = i\alpha, \alpha \in \Re$.. That is

$$q(i\alpha) \equiv (i\alpha)^2 + b(i\alpha) + c + de^{-(i\alpha)\tau} = 0$$

We write the exponential in terms of trigonometric functions and break the polynomial into its real and imaginary parts, which yields

$$-\alpha^2 + c + d\cos(\alpha\tau) + i(b\alpha - d\sin(\alpha\tau)) = 0 \tag{26}$$

Equating real and imaginary parts on the right of (26) to zero, we get the pair of equations

$$\alpha^2 - c = d\cos(\alpha\tau) \tag{27}$$

$$b\alpha = d\sin(\alpha\tau) \tag{28}$$

Squaring each equation and summing the results yields

$$\alpha^4 + (b^2 - 2c)\alpha^2 + c^2 - d^2 = 0 \tag{29}$$

Setting $\mu = \alpha^2$, (18) can then be written in terms of $\mu$ as

$$\mu^2 + (b^2 - 2c)\mu + c^2 - d^2 = 0 \tag{30}$$

The equation (24) will have a pair of pure imaginary solutions $\lambda = \pm i\alpha$ if (30) has a positive real solution.

Consider the coefficients in (30),

$$\begin{aligned} b^2 - 2c &= (k_{xg} + k_{xgi}I_s + k_{xi})^2 - 2(k_{xg} + k_{xgi}I_s)k_{xi} \\ &= (k_{xg})^2 + (k_{xgi}I_s)^2 + (k_{xi})^2 + 2k_{xg}k_{xgi}I_s \\ &> 0. \end{aligned} \tag{31}$$

Also, according to (21), $I_s = \dfrac{G_s K_1}{k_{xi}}$,

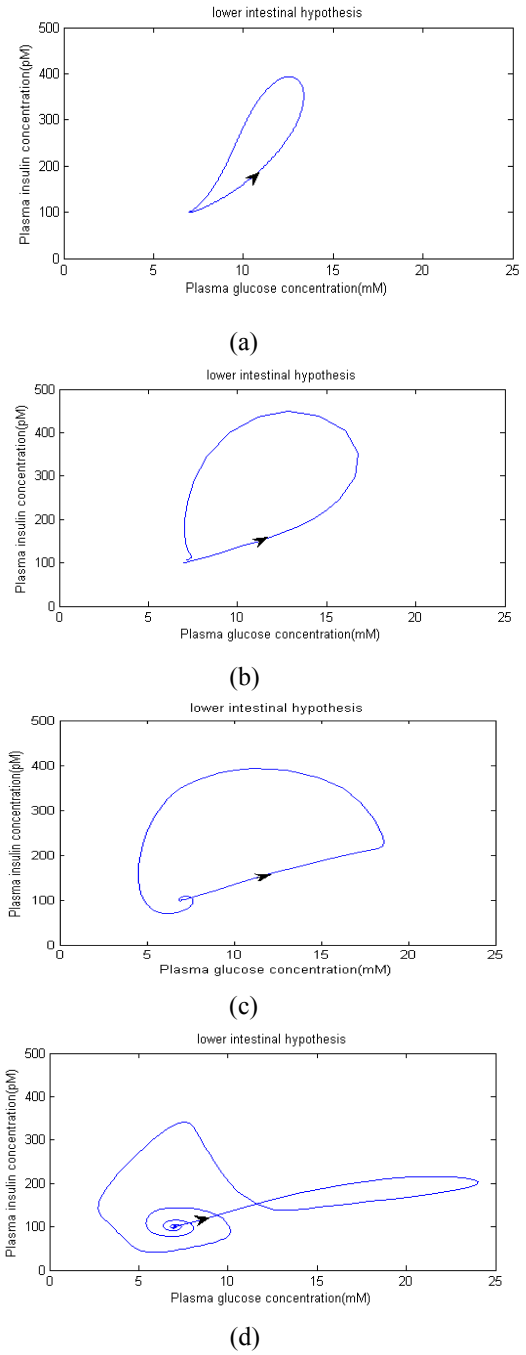


Fig. 1 The solution trajectories of plasma glucose concentration, $G(t)$, and plasma insulin concentration, $I(t)$, of (a) without delay, (b) with delays $\tau_g = 25$ and $\tau_i = 15$, (c) with delays $\tau_g = 70$ and $\tau_i = 25$, and (d) with delays $\tau_g = 200$ and $\tau_i = 100$, all under the lower-intestinal hypothesis.

$$\begin{aligned} d &= k_{xgi} G_s K_1 \\ &= k_{xgi} k_{xi} I_s \\ &< (k_{xg} + k_{xgi} I_s) k_{xi} = c. \end{aligned} \tag{32}$$

Hence, we have $c^2 - d^2 > 0$.

Since, (30) is a quadratic polynomial with positive coefficients, then all roots have negative real part. Equation (30) cannot have any positive real roots for all $\tau \geq 0$. Therefore, the introduction of the delays to the model system (1)-(9) does not lead to a Hopf bifurcation.

**Theorem 3.** The equilibrium point of the model system (1)-(9) is locally asymptotically stable for all $\tau \geq 0$.

## IV. Numerical Results and Discussion

The simulations of the present model has been implemented by using dde23 in MatlabR2011a®. Simulations start at time $T_{min} = 0$ min., and the amount of glucose in the stomach is 600 mmol, while there is no glucose in the duodenum or ileum. Therefore, at time $T_{min}$ we have $S_{Tmin} = 600$ mmol and $D_{Tmin} = L_{Tmin} = 0$ mmol. There are three simulations. One represents the pre-surgery scenario, in which no parameters are changed in the model. In order to simulate the lower intestinal hypothesis and the anti-incretin hypothesis, the parameters that were thought to differ from the pre-surgery situation were changed as described in [8].

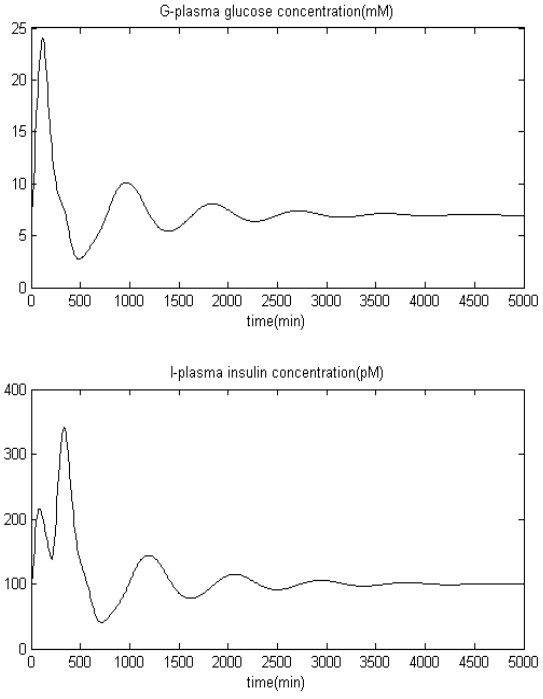


Fig. 2 the simulated time series as $t \to \infty$ of plasma glucose and plasma insulin concentrations with large delays $\tau_g = 200$ and $\tau_i = 100$.

Although the values of the two time-delays do not effect the stability of the equilibrium points of the referenced model, the manner in which the components in tending toward the equilibrium points may depend on the values of the delays. According to the review in [20], it has been clinically observed that the time delay $\tau_g$ was 23.5 minutes and the time delay $\tau_i$ was generally smaller than $\tau_g$. Therefore, in the case of small delays we set $\tau_g = 25$ and $\tau_i = 15$.

First, we study the manner in which the plasma glucose concentration, $G(t)$, and the plasma insulin concentration, $I(t)$ tend towards the equilibrium levels. Since variations in the solution trajectories in the three scenarios are quite similar, only the solution trajectories in the lower-intestinal scenario are shown in Fig. 1. In Fig. 1 (a) the solution trajectories of plasma glucose concentration and plasma insulin concentration without delay tend towards steady state levels in quite a similar manner as in Fig. 1 (b) with small delays, $\tau_g = 25$ and $\tau_i = 15$. Also, in Fig. 1 (c) the solution trajectories with delays $\tau_g = 70$ and $\tau_i = 25$, spiral towards steady state levels in the same manner as in Fig. 1 (d) with delays $\tau_g = 200$ and $\tau_i = 100$. As time passes, the plasma levels of glucose and insulin will settle down towards positive steady state values as shown in Fig. 1-3. However, in the case of large delays, the plasma levels of glucose and insulin will tend to the steady state values in an oscillatory fashion as shown in Fig. 1 (c)-(d) and Fig. 2.

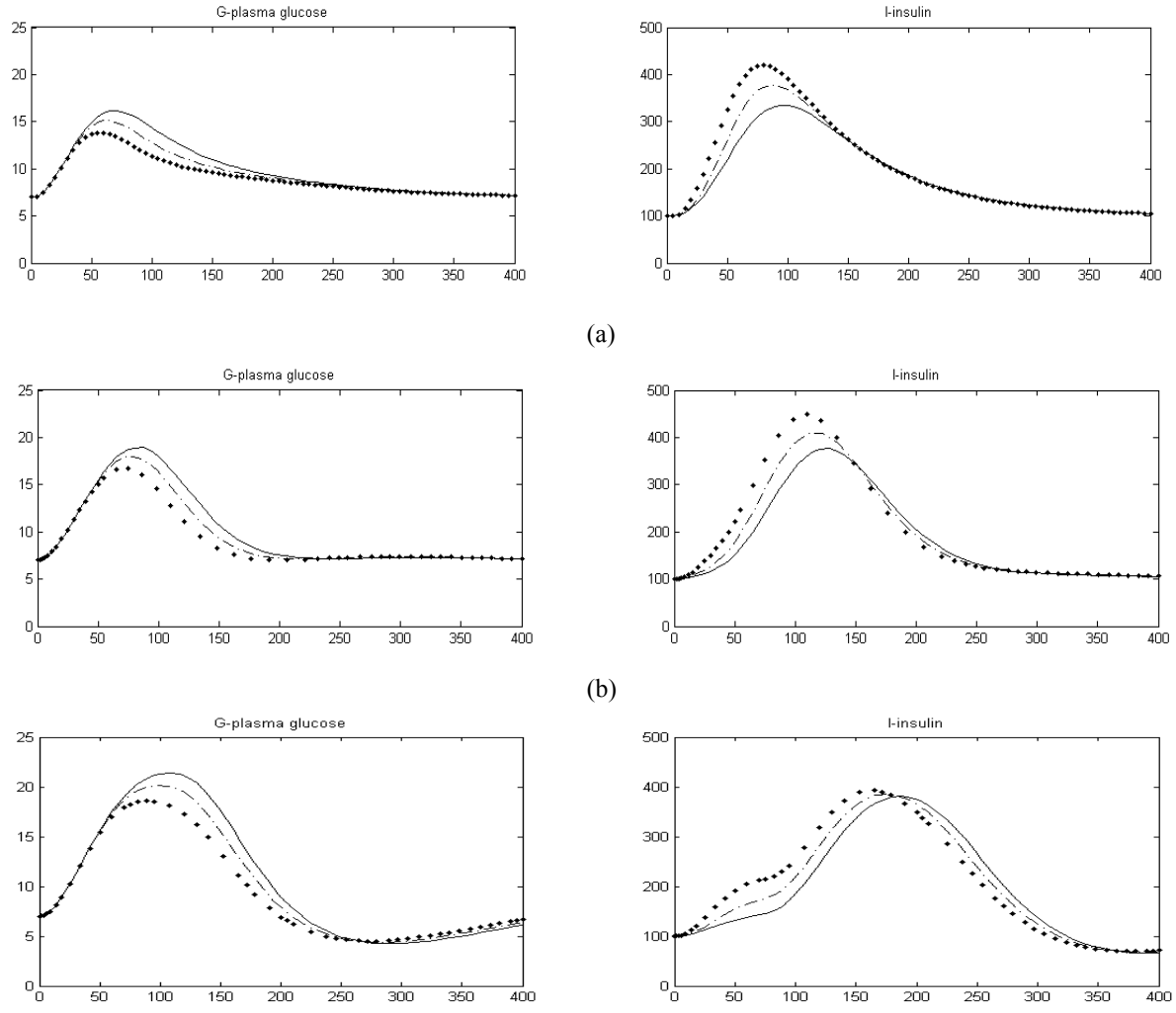


Fig. 3 the simulated time series of plasma glucose on the left panel and plasma insulin concentrations on the right panel, of (a) non-delayed case (upper panel), and (b) delayed case with $\tau_g = 25$ and $\tau_i = 15$ (middle panel), and (c) delayed case with $\tau_g = 25$ and $\tau_i = 70$ (lower panel), for the 3 scenarios are shown together (solid line for the pre-surgery case, dotted line for the lower-intestinal hypothesis, and dash-dot line for the anti-incretin hypothesis).

In Fig. 3, the 3 scenarios are shown together (solid line for the pre-surgery case, dotted line for the lower-intestinal hypothesis, dash-dot line for the anti-incretin hypothesis). The simulated time series of plasma glucose and insulin concentrations with the different delays are shown because the variations of the other components are quite similar as presented in [8].

In Fig. 3 (a), in the upper panel, the simulations of the non-delayed system are shown. In the lower-intestinal (dotted line) and the anti-incretin hypotheses (dash-dot line), the peak of plasma glucose concentration dynamics is lower and the peak of plasma insulin concentration is higher than the pre-surgery curve. However, the lower-intestinal hypothesis curve shows a more marked effect than the anti-incretin hypothesis. In Fig. 3 (b), the delayed case with $\tau_g = 25$ and $\tau_i = 15$ (middle panel), the dynamics of plasma glucose and insulin concentrations for the 3 scenarios are quite similar as in the non-delayed case. However, with delays the peak of plasma glucose and insulin concentration dynamics are higher and elimination is faster. In Fig. 3 (c), the delayed case with $\tau_g = 25$ and $\tau_i = 70$ (lower panel), in the lower-intestinal and the anti-incretin hypotheses the peak of plasma glucose concentration curve is also lower but the curve falls below the equilibrium level before it settles upwards to the equilibrium.

## V. Conclusion

A mathematical model which describes the dynamics of the glucose-insulin-incretins system incorporating time-delays, $\tau_g$ in the insulin secretion in response to glucose production and $\tau_i$ in the insulin-dependent glucose uptake has been investigated in this work. Theorems have been presented which show the existence, uniqueness, and local stability of the equilibrium point, while the values of the two time-delays do not directly effect the stability of the equilibrium points. However, according to simulations, the plasma levels of glucose and insulin will tend to the steady state values in an oscillatory fashion in the case of large delays.

Local stability of the equilibrium point

$$\bar{X}_s = \begin{pmatrix} S_s & D_s & L_s & G_s & I_s & W_s & U_s & P_s & A_s \end{pmatrix}^T.$$

means that if the initial values of each state variables are sufficiently close to the steady state values, then we are assured that, as time passes, the glucose levels in the stomach, the duodenum , and the ileum will eventually vanish, while the plasma levels of glucose, insulin, and other hormones will settle down towards positive steady state values.

In the absence of delay, the manner in which these components tend towards the equilibrium levels depends crucially on the value of the basic number $R_0$ given by

$$R_0 = \frac{4(c+d)}{b^2} = \frac{4k_{xi}(k_{xg} + 2k_{xgi}I_s)}{(k_{xg} + k_{xgi}I_s + k_{xi})^2} \qquad (33)$$

The hormone levels will tend to the steady state values in an oscillatory fashion if $R_0 > 0$, but if the physical parameters can be controlled so that $R_0 < 0$, we could avoid the hormone fluctuations which may be harmful to diabetic patients or difficult to regulate. It is suggested that hormone swings could be minimized if the rate $k_{xgi}$ is kept at a high enough level.

The 3 scenarios have been compared in the cases with and without delays. The weight of evidence accumulated so far would seem to support the lower intestinal hypothesis over the anti-incretin hypothesis which supports the discovery made by the modeling and simulation effort in [8], although the results of a simulation study are dependent on a number of assumptions, both in the simplification of the model structure and in the assessment of the model parameters.

## Acknowledgment

This work has been supported by a grant from the Centre of Excellence in Mathematics, PERDO, Commission on Higher Education, Thailand. The First author would like to thank Kasetsart University, while the second author would like also to thank Mahidol University. Appreciation is moreover extended to the Laboratorio di BioMatematica, Istituto di Analisi dei Sistemi e Informatica "A. Ruberti", Consiglio Nazionale delle Ricerche, Roma, Italy, and Andrea De Gaetano for valuable guidance.

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