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SURVEY: MATHEMATICAL MODELS FOR THE REGULATION MECHANISM OF GLUCOSE BY PANCREAS'S HORMONES IN THE HUMAN BODY

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Abstract: Optimization algorithms are techniques for solving optimization problems in different areas. Anyone cannot obtain an optimal, precise, and complete solution as those existed in the universe, whether nature behaviour in living creatures, cosmic systems, or at the level of the mechanism of systems in the human body. One of these systems is the system of regulation blood glucose levels in the human body. This system maintains blood glucose levels in a stable condition without increase or decrease. There are many medical, biochemistry, bionic engineering, and physiology researches that have studied the mechanism of regulation of glucose in the human body and the crystallization of the mechanism in the form of mathematical models, which greatly facilitate understanding the mechanism of pancreas hormones and regulation mechanism. However, there is a lack in researches that demonstrate the sequential integrative processes between three main sub-systems and the parallel integrative processes between components of theses sub-systems for managing blood glucose level. Therefore, this research aims to expand on the field of regulation mechanisms of blood glucose. It covers the mechanism with thirteen models that mathematically clarify the mechanism of components of the blood glucose levels regulation in the human body to understand the divine system in the process of the regulation, which may be inspired to create a general method that used to solve optimization problems.

Keywords: Mathematical models, Glucose homeostasis, pancreas hormones

I. INTRODUCTION

Glucose homeostasis is one of the most critical phenomena in the human body. Glucose can originate exogenously from ingestion of food, and, also, endogenously from the liver by glycogenolysis (re-converting stored glycogen). The absorption of glucose in the cells determines the actual concentration of blood glucose. Integrated hormonal and enzymatic processes control all of this. The system comprises of many complicated sub-processes; whose erroneous activity usually leads to common diabetic diseases [1]. The human body system consists of various organs. Those organs have their specific functions and play their roles in maintaining relevant biological activities in the body. Each organ needs a stable and adequate glucose supply from the blood to carry through its function. It is, therefore, important to keep the optimal blood glucose level [2]. The two main organs involved in the maintenance of glucose homeostasis are the pancreas and the liver. The role of the pancreas is to release the two most important hormones that control glucose homeostasis: insulin and glucagon. They are produced in pancreatic-βcells andpancreatic-α-cells, respectively[3], [4], [5]. When the blood glucose level is high, β cells secrete insulin to help cells in the process of glucose absorption. Whereas, α-cells secret glucagon when blood glucose levels fall below normal. It acts as an antagonist of insulin by causing hepatic glucose output to rise[3], [5], [6]. Whereas, the role of the liver acts as a storage organ of excess blood glucose. When blood glucose levels are high, it takes up glucose and converts it into glycogen. When glucose levels are low, it releases glucose by either glycogenolysis or synthesizing new glucose (gluconeogenesis)[7]. Figure 1 illustrates the mechanism of glucose homeostasis

I. INTEGRATION BETWEEN INSULIN AND GLUCAGON TO REGULATE BLOOD GLUCOSE LEVEL

Figure 1 shows the process of glucose absorption that passes through several stages. It further illustrates that several organs intervene in glucose homeostasis. It is preferable to break down the mechanism into partial stages (sub-models) to understand the mechanism of blood glucose regulation in the human body.

This section explains complementary work between insulin and glucagon for managing the process of blood glucose regulation. It consists of three sub-headings: a) The glucose sub-model, b) The insulin sub-model, and c) The glucagon sub-model.

A. The glucose sub-model

Glucose ($C_6H_{12}O_6$) is a monosaccharide used as the main source of energy in the body[8]. Plasma glucose can originate exogenously from the ingestion of food and also endogenously from the liver by glycogenolysis[9]. This plasma passes through the cells, pancreas, and other organs in the body[8]. Glucose enters the cell by facilitated diffusion mechanisms, which represent an example of regulated mass exchange across the cell membrane. Specialized families of membrane proteins called GLUT (i.e., GLUcose Transporters [10]), observed in a large variety of cell types[10], actively operate the removal of free glucose from the interstitial spaces and transport it inside the cytoplasm, with distinct affinities and maximal transport rates [5].The absorption of glucose in the cells determines the actual concentration of blood glucose [1]**.** The pancreas is one of the most important organs in glucose homeostasis. It Continuously monitors blood glucose level that occurs when plasma glucose passes continuously through the pancreas's glucose transporter, the pancreas, in turn, secrete the appropriate hormone (insulin or glucagon) to regulate blood glucose level.

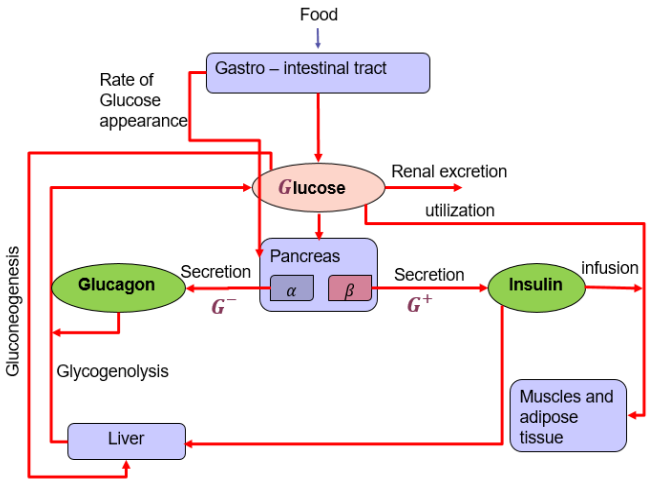

Figure 1. Mechanism of Regulation of Glucose level in the human body: Plasma Glucose enters into Pancreas organs, which can determine the rate of blood glucose. At high glucose concentration, this stimulates pancreatic β-cells to secrete insulin hormone. After plasma insulin is distributed to interstitial fluid, it activates glucose uptake by the target cells (as muscles) by bindinginsulin to cell membrane receptors, which allow it to enter the glucose by target cell's transporter using complicated sub-processes. Whereas, atlow glucose concentration, pancreatic α-cells secrete glucagon hormone that releases glucose by either glycogenolysis (re-converting stored glycogen from the liver) or synthesizing new glucose (gluconeogenesis). The excess proportion of the body is being removed from the body (renal excretion).

B. The insulin sub-model

- ***Insulin***

Insulin is a hormone secreted by the pancreas within the β-cells of the islets of Langerhans.[3],[4],[5] . Insulin has the most important role in maintaining glucose homeostasis. It enables glucose uptake by muscle and adipose tissue cells. It alsoregulates the storage and releases of glucose in the liver and promotes fat synthesis and storage [5]. The pancreas secretes plasma insulin into the portal vein, where it first passes through the liver and subsequently enters systemic circulation [8]. Glucose uptake is activated once plasma insulin is distributed to interstitial fluid, where insulin bind to cell-membrane receptors[8].

- ***Glucose-dependent regulation of Insulin secretion***

Through previous studies, glucose-dependent regulation of Insulin secretion can be summarized into the following steps (Figure 2):

1. Glucose enters into pancreatic β-cells and is metabolized through the glycolytic pathway and subsequently in mitochondria[11].
2. The resultant increase in ATP production leads to closure of the ATP-sensitive potassium (K_{ATP}) channel leading to membrane depolarization[11](depolarizing the membrane potential to a range where the inactivation of voltage-dependent channels takes place. This results in the inhibition of electrical activity, Ca^{2+} influx, and glucagon secretion[12]).
3. This causes Ca^{2+} entry through the voltage-dependent Ca^{2+} channel and elevation of cytoplasmic Ca^{2+} concentration ($[Ca^{2+}c)$, which initiates exocytosis of insulin granules [11].
4. The main feature of insulin secretion is its biphasic secretion pattern[9].
   a. This pattern was earlier described by a mathematical model developed by [14]. The model describes insulin as stored packets inside the β-cells, and each insulin packet has a specific threshold-level to glucose concentration. When the glucose concentration increases, a specific number of insulin packets are secreted into the blood.
   b. Recently, the movement of insulin granules inside β-cells, and the mechanism of exocytosis have been revealed by total internal reflection fluorescence microscopy (TIRFM) [15]–[17].
   c. The insulin granules can be further divided into different insulin pools according to the different movement patterns and relative locations [17].
   d. Readily releasable pools, composed of insulin granules adjacent to the plasma membranes of β -cells, exist in a fully releasable state and are associated with the fast first phase of insulin secretion.
   e. These pools provide quick response of insulin secretion to a sudden glucose increase. In the cell plasma of the β-cells, insulin granules denoted reserve pools secrete insulin granules for maintaining the baseline insulin level and producing the second-phase insulin secretion through the nonstandard secretion pathway and provide supplemental insulin granules to the readily releasable pools [17]. Several other kinetic models have been proposed to describe the biphasic secretion pattern and provided agreement with data from different experimental approaches[9],[18]–[21].
5. Gupta et al. proposed an insulin kinetic model to analyze the insulin kinetics of β-cells, post hepatic insulin delivery, and insulin elimination [22]. The model has detailed descriptions of the insulin pools inside the β-cells and of how glucose affects insulin production and secretion.

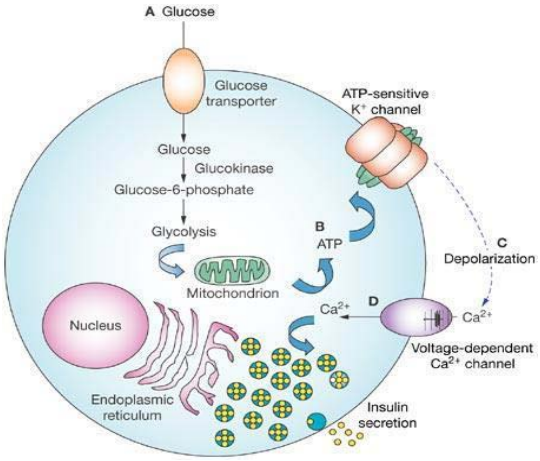

Figure 2: schema of the mechanism of insulin secretion **[23]**

- ***Glucose – Insulin mechanism***

Glucose uptake is activated once plasma insulin is distributed to interstitial fluid, where it binds to cell-membrane receptors.

Figure 3 shows steps of entering glucose to the target cell**,** which is summarized as a following:

1. Cells can communicate with each other by sending and receiving signals, which include hormonal signals from distant endocrine cells, paracrine signals from neighboring cells, or autocrine sensing of signals emitted from the same cell. Cell surface or transmembrane receptors on the plasma

membrane provide cells with the means of sensing different ligands in their environment with relevant signaling cascades, without specific uptake of the respective ligands. [24]

2. Insulin binds to the receptor of the cell[11]
3. The binding process leads to stimulate the signal transduction cascade to stimulate the cell to the Exocytosis process.
4. Exocytosis (moving target cell 's transporter to the cell membrane surface to allow the glucose to enter the cell)
5. The target cell 's transporter enters glucose from the interstitial spaces and transports it inside the cytoplasm with distinct affinities and maximal transport rates [5].

When insulin secretion phases are faded. At that time, the purpose of insulin secretion has been achieved which is to access to desired balancing by reducing blood glucose level.

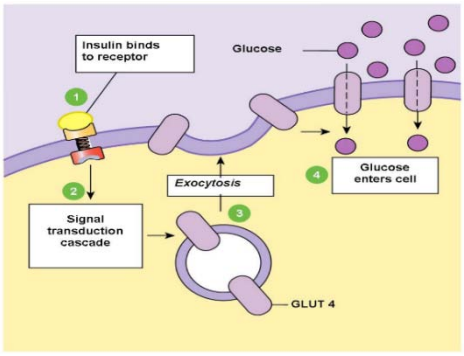

Figure 3: Steps of Glucose entering to target cell [25].

C. Glucagon sub-model

- ***Glucagon***

Glucagon is a hormone that secreted by pancreatic α-cells. Under normal circumstances, the elevation of glucose has opposite effects on the secretion of glucagon from the alpha-cells.When blood glucose levels fall below normal, particularly during fasting and exercise. It also acts as an antagonist of insulin by causing hepatic glucose output to rise. This is either achieved by glycogen breakdown (Glycogenolysis) or increased gluconeogenesis (storing excess circulating glucose as glycogen in the liver). [7]. If glycogen stores are saturated, glucose is converted into fat and stored in the liver and fat cells in the adipose tissue. These processes can be reversed when energy demand is high. Glucose is rapidly released from glycogen via the glycogenolysis process if glycogen stores are used, once the fat is used via the gluconeogenesis process with amino acids to form glucose [8]. Both glycogenolysis and gluconeogenesis are commonly grouped under and described as endogenous glucose production (EGP)). EGP is tightly regulated in the healthy body to maintain basal (minimum) blood glucose concentration. EGP represents net glucose production by the body, primarily by the liver, and released into the blood. EGP is suppressed when blood glucose concentration is considerably high due to external glucose appearance through meals or to a lesser extent via intravenous bolus. However, low glucose concentrations inverse the process by stimulating glucagon secretion via pancreatic α-cells, which activates glycogenolysis and thus rapidly increases glucose concentrations to prevent hypoglycemia. The rate of endogenous glucose production is a function of both stimulus and the availability of substrates. In reality, EGP is modulated by the interaction of many hormones in response to metabolic dysfunctions that cause insulin sensitivity irregularities. As tissue cells fail to respond adequately to insulin, blood glucose concentrations rise. Normally, the liver helps regulate glucose concentrations by reducing glucose production in the presence of insulin. [8]

- ***Glucose-dependent regulation of <u>Glucagon secretion</u>***

Alpha-cell models are not available to the same extent as β-cell models[12], [26]. Through previous studies, which is proposed to be since potential action generation in alpha-cells is dependent on T-type Ca^{2+} channels and Na^{+} channels, which inactivate and cause decreased electrical excitability.

Glucose-dependent regulation of Glucagon secretion can be summarized in the following steps:

1. Glucose is incorporated into the α-cell by the transporter.
2. At low-glucose concentrations, the moderate activity of K_{ATP} channels situates the α-cell membrane potential in a range that allows the opening of voltage-dependent T- and N-type Ca^{2+} channels and voltage-dependent N^{+} channels[12](Figure 4**).**
   - The opening of A-type K^{+} channels is necessary for action potential repolarization.[12]
3. Most of the Ca^{2+} current goes through L-type channels in α-cells, the Ca^{2+} required for exocytosis at low-glucose levels is mediated by N-type channels.[12]**.**
   - Their blockade inhibits glucagon secretion in this range that allows the opening of voltage-dependent T- and N-type Ca^{2+} channels and voltage-dependent Na^{+} channels.[12]**.** However,Their activation triggers action potentials, Ca^{2+} influx, and exocytosis of glucagon granules.[12]
4. Glycogenolysis.
5. Subsequently, blood glucose level rises, and through continuous monitoring of glucose level by the pancreas. It makes the right decision by choosing the appropriate hormone to keep the blood glucose level in the normal range.

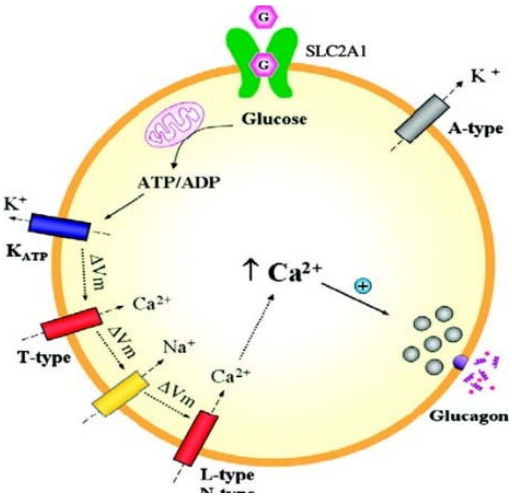

Figure 4: Schematic model for glucose-dependent regulation of glucagon secretion in the mouse a-cell **[12]**

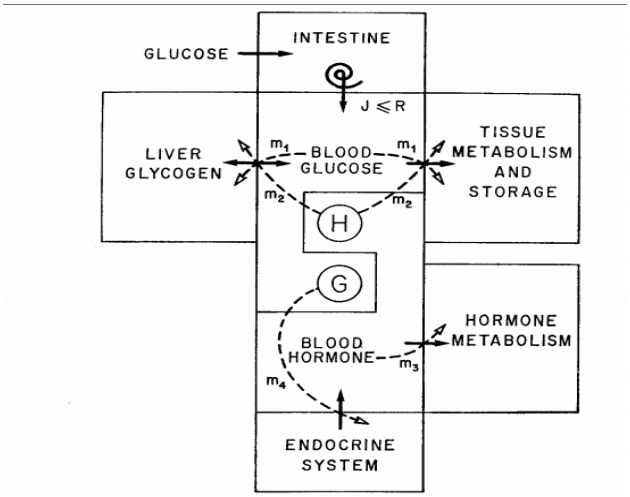

Figure 5: a simplified model of the blood glucose regulatory system using by Ackerman (Ref. **[27]**).

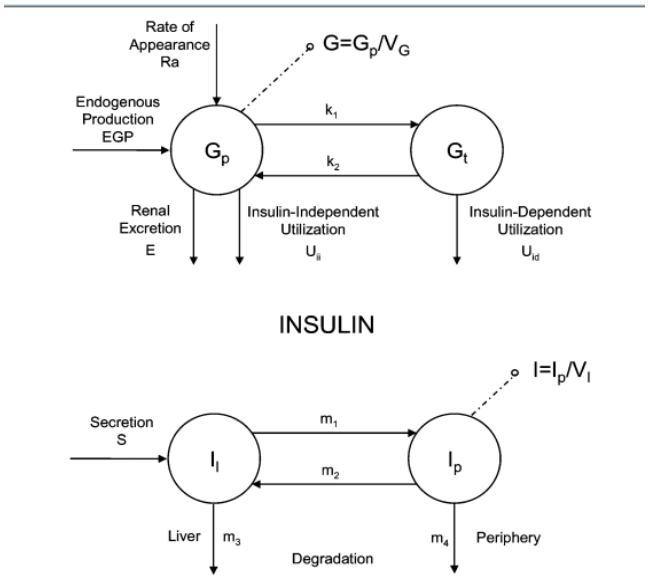

Figure 6: Schema of Glucose and insulin sub-systems in the Dalla Man model (Ref. **[28]**).

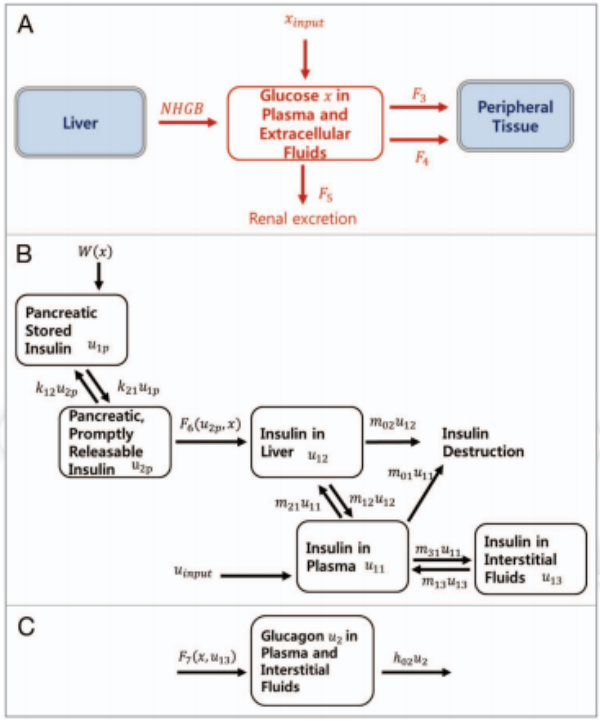

Figure 7: Schematic diagram of the integrated mathematical model consisting of three sub-systems: (A) glucose sub-system, (B) insulin sub-system, and (C) glucagon sub-system. Red and black arrows illustrate the transport of glucose and insulin, respectively (Ref.**[2]**).

II. Mathematical Models for The Regulation Mechanism of Glucose by Pancreas's Hormones in The Human Body **(Table1)**

Table 1: Mathematical models for blood glucose levels regulation

Reference	Equations	Variable description
Cobelli et al. [29]	**Glucose sub model**: $\dot{X_1} = F(x_1 . u_{12} . u_{13} . u_2) + I_X(t)$	X_1 : is a quantity of glucose in the plasma and extracellular fluids. u_{1p} : is a quantity of pancreatic stored insulin. u_{2p} : is a quantity of pancreatic, promptly releasable insulin. u_{11} : is a quantity of insulin in plasma. u_{12} : is a quantity of insulin in the liver. u_{13} : is a quantity of insulin in the interstitial fluids. u_2: is a quantity of glucagon in the plasma and interstitial fluids. W and F_1- F_7 : are nonlinear functions. I_X: is the test input of glucose, m_{ij}, h_{ij}, and k_{ij} are constant rate parameters except for k_{02}, which is a function of X_1. F_7 is the endogenous release of glucagon, dependent on blood glucose and interstitial fluid insulin.
	Insulin synthesis: $\dot{u_{1p}} = k_{21}u_{1p} + k_{12}u_{2p} + W(x_1)u_{1p}(0) = u_{1p0}$ $\dot{u_{2p}} = k_{21}u_{1p} - (k_{12+}k_{02}(x_1))u_{2p}\ u_{2p}(0) = u_{2p0}$ **Insulin secretion**: $\dot{u_{11}} = (m_{01} + m_{21} + m_{31})u_1 + m_{12}u_{12} + m_{13}u_{13}u_{11}(0) = u_{110}$ $\dot{u_{12}} = -(m_{02} + m_{12})u_{12} + m_{21}u_{11} + k_{02}(x_1)u_{2p}u_{12}(0) = u_{120}$ $\dot{u_{13}} = -m_{13}u_{13} + m_{31}u_{11}$; $u_{13}(0) = u_{130}$	
	Glucagon secretion: $u_2 = -h_{02}u_2 + F_7(x_1 . u_{13})u_2(0) = u_{20}$	

Reference	Equations	Variable description
Ackerman et al. [27] The model also used in [30]	**Glucose equation:** ***Hormone equation**:*	$\boldsymbol{G}$: is the glucose concentration. $\boldsymbol{H}$: is glucose-regulating hormones. $\boldsymbol{G_0}$ and $\boldsymbol{H_0}$: are the change in the values of G or H, respectively. $\boldsymbol{m_1}$: rate constant for the removal of glucose above the initial (fasting) level due to its own excess above the initial level. $\boldsymbol{m_2}$: rate constant for the removal of glucose above the initial level due to blood-hormone concentrations above the initial level. $\boldsymbol{m_3}$: rate constant for the removal of hormone above the initial (fasting) level due to its own excess above the initial level. $\boldsymbol{m_4}$: rate constant for the release of hormone above the initial level due to blood-glucose concentrations above the initial level. $\boldsymbol{J}(t)$ and $\boldsymbol{K}(\boldsymbol{t})$: are the rate of infusion of exogenous glucose and insulin, respectively. **Figure 5**
Minimal model (MM) Bergman et al. [31], [32] Other research using MM [31], [33]–[36]	**The physiological factors that determine the restoration of plasma glucose after injection:** Glucose restoration rate = - (glucose effectiveness + remote insulin) G or $\frac{dg}{dt} = -\big(S_G + X(t)\big)G + C$ **The factors that determine the level of insulin in the interstitial.** increase in remote insulin =k_a (plasma insulin) - k_b (remote insulin) or $\frac{dX(t)}{dt} = -\big(k_a I(t) - k_b X(t)\big)$	S_G : is the effect of glucose itself. $X(t)$: is the effect of insulin in the interstitial compartment, which acts synergistically with glucose to return the glycemia to basal levels. $X(t)$ is increased by plasma insulin [$I(t)$ determined by k_a] but decreases by a first-order process proportional by k_b to interstitial insulin itself [$k_b X(t)$]. Parameter C accounts for glucose production at basal insulin.
K. Zarkogianni, et al. [37]	**Compartmental Model for subcutaneous (sc) Insulin Kinetics** $\dot{I}_{sc1}(t) = -(k_d + k_{a1}) \cdot I_{sc1}(t) + u(t)$, $I_{sc1}(0) = I_{sc1ss}$ $\dot{I}_{sc2}(t) = k_d \cdot I_{sc1}(t) - k_{a2} \cdot I_{sc2}(t)$, $I_{sc2}(0) = I_{sc2ss}$ $R_i(t) = k_{a1} \cdot I_{sc1}(t) + k_{a2} \cdot I_{sc2}(t)$ **Compartmental Model for Glucose Absorption From the Gut** $Q_{sto}(t) = Q_{sto1}(t) + Q_{sto2}(t)$, $Q_{sto}(0) = 0$ $Q_{sto1}(t) = -k_{gri} \cdot Q_{sto1}(t) + D \cdot d(t)$, $Q_{sto1}(0) = 0$ $Q_{sto2}(t) = -k_{empt}(Q_{sto}) \cdot Q_{sto2}(t) + k_{sto} \cdot Q_{sto1}(t)$, $Q_{sto2}(0) = 0$ $Q_{gut} = -k_{abs} \cdot Q_{gut}(t) + k_{empt}(Q_{sto}) \cdot Q_{sto2}(t)$, $Q_{gut}(0) = 0$ $Ra(t) = \frac{f \cdot k_{abs} \cdot Q_{gut}(t)}{BW}$, Ra(0) = 0	I_{sc1} and I_{sc2}: represent the amount of nonmonomeric and monomeric insulin in the sc space, respectively. u(t): is the exogenous insulin infusion rate. k_d : is the rate constant of insulin dissociation. k_{a1} and k_{a2}: are the rate constants of nonmonomeric and monomeric insulin absorption, respectively. R_i (t): is the rate of appearance of insulin in plasma. Q_{sto}: is the amount of glucose in the stomach (Q_{sto1}, solid and Q_{sto2}, liquid phase) Q_{gut} : is the glucose mass in the intestine. k_{gri} : is the rate of griding. k_{empt} (Q_{sto}): is the rate constant of gastric emptying, which is a nonlinear function of Q_{sto} . k_{abs} : is the rate constant of intestinal absorption. f (0.90): represent the fraction of intestinal absorption which appears in plasma D: is the amount of ingested glucose. BW: is the body weight. Ra: is the glucose rate of appearance in plasma.
Cobelli et al. [38]	**Static Mode:** $\boldsymbol{IR(t) = RI\left[\frac{y_i(t) - BI}{QI} + 1\right]^2 . \frac{y_i(t) - BI}{QI} + 1 > 0}$ $\boldsymbol{\mathrm{IR(t)} = 0 \quad . \frac{y_1(t) - BI}{QI} + 1 \le 0}$	$\boldsymbol{IR(t)}$: is an insulin infusion rate. $\boldsymbol{y_i}$: is the measured glucose concentration. $\boldsymbol{BI}$: is the steady-state plasma glucose concentration. $\boldsymbol{RI}$: is the steady-state infusion rate (that is, for $\boldsymbol{y_i}$ = $\boldsymbol{BI}$) $\boldsymbol{QI}$: is the inverse of a static gain. $\boldsymbol{m}$: is the slope of the regression line on the last five measured values of glucose concentration (derivative control).

Reference	Equations	Variable description
	Dynamic Mode: $$IR(t) = \frac{k}{10} m(y_i(t) - BI) \frac{RI}{10} \quad . \quad y_i > BI$$ $$IR(t) = 0 \quad . y_i \leq BI$$	k takes on different values depending upon the sign of m (m> 0, m<0, respectively).
El-Khatib et al. [39]	**The control algorithm optimizes the multistage quadratic cost function** $$J_{GPC} = \sum_{k=N_d}^{N_m} \delta_k \| C(r_{t-k} - y_{t-k}) \|^2 + \sum_{k=0}^{N_u} \lambda_k (\Delta u_{t-k})^2$$	GPC: generalized predictive control algorithm to automatically govern the SC administration of insulin and glucagon formulations. $u(t)$: is input signal to regulate the output BG (blood glucose) concentration $y(t)$]: is output signal online. N_d and N_m : are, respectively, the minimum and maximum (output) prediction costing horizon limits, N_u : is the control horizon bound, δ_k : is the weighting on prediction error. λ_k: is the weighting on control signals, and the integrator Δ:=1 - z^{-1}, with z^{-1} playing the role of a one-step delay operator.
Caleb et al. [40]	**The Glucose-Insulin feedback system:** $$\frac{dx}{dt} = f_1(z) - E\left(\frac{x}{V_1} - \frac{y}{V_2}\right) - \frac{x}{t_1}$$ $$\frac{dy}{dt} = E\left(\frac{x}{V_1} - \frac{y}{V_2}\right) - \frac{y}{t_2}$$ $$\frac{dz}{dt} = f_5(h_3) + I - f_2(z) - f_3(z) f_4(y)$$ $$\frac{dh_1}{dt} = \frac{3(x - h_1)}{t_1}$$ $$\frac{dh_2}{dt} = \frac{3(h_1 - h_2)}{t_2}$$ $$\frac{dh_3}{dt} = \frac{3(h_2 - h_3)}{t_3}$$	x : is the amount of plasma insulin. y : is the amount of remote insulin. z : is the amount of glucose. E : is a constant rate of insulin exchange between compartments. V_1, V_2, and V_3: are volumes. $f_1(z)$: represents insulin secretion. $f_2(z)$: represents insulin-independent glucose utilization. $f_3(z)$ and $f_4(y)$ **:** are insulin-dependent utilizations. $f_5(h_3)$: represents glucose production. h_1, h_2, and h_3: are variables representing delay processes between plasma insulin and glucose production. I : is the exogenous glucose delivery rate. t_1 and t_2: are time constants related to insulin degradation. t_3: is the delay time between plasma insulin and glucose production. $\propto (A.G)$ and $\beta(B.G)$: describe the effects of glucagon and insulin on the blood glucose concentration, respectively. $\gamma(R.G)$: Uptake of glucose by muscles and other tissues is, where R is an externally determined quantity describing the activity of the organism. $\emptyset(G)$: is The dependence of the insulin secretion rate on the blood glucose concentration and is a decreasing function of G . $\psi(G)$: represents the dependence of the glucagon secretion rate on the blood glucose concentration and is an increasing function of G . The two functions$h_1(A.B)$ and $h_2(A.B)$ represents the mutual and self-inhibitions of the secretion rates on the insulin and glucagon levels.
Minimal model (piecewise -linear) Dalla Man et al. [33]	**Glucose concentration and Insulin action:** $$\begin{cases} \dot{G}(t) = [p_1 + X(t)]\, G(t) + p_1 G_b + \frac{Ra(t)}{V} \; ; \quad G(0) = G_b \\ \dot{X}(t) = -p_2\, X(t) + p_3 [I(t) - I_b]; \quad X(0) = 0 \end{cases}$$	G : is glucose concentration. X : is insulin action. I : is insulin plasma concentration. Ra : is the glucose rate of appearance in plasma. V : is the volume distribution. suffix " b ": denotes basal (pretest).

Reference	Equations	Variable description
	Piecewise-Linear Model to find Ra(t): $Ra(t) = k_{i-1} + \frac{k_i}{t_i}\begin{cases} k_{i-1} \\ t_{i-1} \end{cases}$; $per\ t_{i-1} \le t \le t_i\ .i = 1 \cdots 7$ $Ra(t) = 0\ .\ otherwise$	values, and p_1, p_2, and p_3 are rate parameters. Specifically, p_1: is the fractional (i.e., per unit distribution volume) glucose effectiveness (GE) measuring glucose ability per se to promote glucose disposal and inhibit glucose production. p_2: is the rate constant of the remote insulin compartment from which insulin action is emanated. p_3 : is a scale factor governing the amplitude of insulin action. $\{k_{i\,j}\}$ is the unknown parameter set representing the values of Ra at the break times.
Minimal model M.E.Fisher et al. [41]	**Plasma glucose concentration:** $\dot{G} = -p_1 G - X(G + G_B) + P(t)$ $G(0) = G_0$ **Plasma insulin concentration:** $\dot{X} = -p_2 X + p_3 I$ $X(0) = X_0$ $\dot{I} = -n(I + I_B) + u(t)/V_I$ $I(0) = I_0$	$G(t)$: represent the differences of plasma glucose concentration. $I(t)$: represent free plasma insulin concentration. $P(t)$: is the rates of infusion of exogenous glucose. $u(t)$: is the rates of infusion of exogenous insulin. $X(t)$: is proportional to the concentration of insulin in the remote compartment. G_B: the value of corresponds approximately to the basal plasma glucose concentration found in normal individuals. G : is basal values of plasma glucose concentration. I : free plasma insulin concentration. V : is the insulin distribution volume. n : is the fractional disappearance rate of insulin.
Kinetic modeling [42]	$\dot{x} = u - b_3 z + G_{exg}$ $\dot{u} = -k_0 u - b_1 b_3 y + b_1 b_3 z + b_1 (b_0 - G_{exg})$ $\dot{z} = -k_2 z + k_2 y$ $G = G_{exg}(t) - GU_1(t) + NEGB(t) - G_{ren}(t)$ $GU_1(t) = \sum_{i=0}^{n} b_3\ z(t_i) - b_3\ z(0)$ $NEGB(t) = \sum_{i=0}^{n} b_3\ u(t_i) - u(0)$	y : is a circulating concentration of insulin. x : is a circulating concentration of glucose. u : is the endogenous glucose balance. z : peripheral insulin-dependent glucose utilization. b_i and k_i : are six parameters that necessary to identify all state variables k_0: is a supplementing time constant. $G_{exg}(t)$: exogenous input of glucose $GU_1(t)$: insulin-controlled peripheral glucose disappearance. NEGB(t): net endogenous glucose balance $G_{ren}(t)$: renal glucose excretion.

Reference	Equations	Variable description
Hyuk Kang et al. [2]	**Glucose equation:** $\frac{dx}{dt} = NHGB(x.u_{12}.u_2) - F_3 - F_4 - F_5 + x_{input}$ **The net hepatic glucose balance:** $NHGB(x.u_{12}.u_2) = F_1(x.u_{12}.u_2) - F_2(x.u_{12})$. **Insulin equations:** $\frac{du_{1p}}{dt} = -k_{21}u_{1p} + k_{12}u_{2p} + W(x)$ $\frac{du_{2p}}{dt} = k_{21}u_{1p} - k_{12}u_{2p} - F_6(u_{2p}.x)$ $\frac{du_{11}}{dt} = -(m_{01} + m_{21} + m_{31})u_{11} + m_{12}u_{12} + m_{13}u_{13} + u_{input}$ $\frac{du_{12}}{dt} = -(m_{02} + m_{12})u_{12} + m_{21}u_{11} + F_6(u_{2p}.x)$ $\frac{du_{13}}{dt} = -m_{13}u_{13} + m_{31}u_{11}$ **Glucagon equation:** $\frac{du_2}{dt} = -h_{02}u_2 + F_7(x.u_{13})$	x: denotes the amount of glucose in the plasma and extracellular fluids. u_{1p}: is the amount of stored insulin in the pancreas. u_{2p}: is the amount of promptly releasable insulin in the pancreas. u_{11}: is the amount of insulin in the plasma. u_{12}: is the amount of insulin in the liver. u_{13} : is the amount of insulin in the interstitial fluids. u_2: is the amount of glucagon in the plasma and interstitial fluids. m_{ij} , h_{ij} and k_{ij} : are appropriate rate constants. W , F_6 and F_7: represent the insulin synthesis rate, insulin secretion rate and glucagon secretion rate, respectively. x_{input} and u_{input} : describe the input rates of glucose and insulin to the plasma, respectively. **Figure 7**
[43]	**The insulin model**: $\frac{dI_p}{dt} = f_1(G) - E\left(\frac{I_p}{V_p} - \frac{I_i}{V_i}\right) - \frac{I_p}{t_p}$ $\frac{dI_i}{dt} = E\left(\frac{I_p}{V_p} - \frac{I_i}{V_i}\right) - \frac{I_i}{t_i}$ **The glucose model:** $\frac{dG}{dt} = G_{in} - f_2(G) - f_3(G)f_4(I_i) + f_5(x_3)$ $f_1(G) = \frac{\boldsymbol{R_m}}{\boldsymbol{1 + exp((C_1 - G/V_g)/a_1)}}$ $f_2(G) = \boldsymbol{U_b(1 - exp(-G/(C_2V_g)))}$ $f_3(G) = \frac{\boldsymbol{G}}{\boldsymbol{(C_3V_g)}}$ $f_4(I_i) = \boldsymbol{U_0} + \frac{\boldsymbol{U_m - U_0}}{\boldsymbol{1 + exp(-\beta ln(I_i/C_4(1/V_i + 1/Et_i)))}}$ $f_5(x_3) = \frac{\boldsymbol{R_g}}{\boldsymbol{1 + exp(\alpha(x_3/V_p)/C_5)}}$ **The receptor model:** $\frac{\boldsymbol{dR_{b.a}}}{\boldsymbol{dt}} = \boldsymbol{k_{bind.a}I_{i.free}R_{f.a} + k_{act.b}R_{b.i} - k_{dis.a}R_{b.a} - k_{in.b}R_{b.a}}$ $\frac{\boldsymbol{dR_{b.i}}}{\boldsymbol{dt}} = \boldsymbol{k_{bind.i}I_{i.free}R_{f.i} + k_{in.b}R_{b.a} - k_{dis.i}R_{b.i} - k_{in.b}R_{b.i}}$ $\frac{\boldsymbol{dR_{f.a}}}{\boldsymbol{dt}} = \boldsymbol{k_{dis.a}R_{b.a} + k_{act.f}R_{f.i} - k_{bind.a}I_{i.free}R_{f.a} - k_{in.f}R_{f.a}}$ $\frac{\boldsymbol{dR_{f.i}}}{\boldsymbol{dt}} = \boldsymbol{k_{dis.i}R_{b.i} + k_{in.f}R_{f.a} - k_{bind.i}I_{i.free}R_{f.i} - k_{act.f}R_{f.i}}$	G: is the amount of glucose in the plasma and intercellular Space. I_p: is the amount of insulin in the plasma. I_i: is the amount of insulin in the intercellular space. $\boldsymbol{x_3}$: represents the delay between insulin in plasma and its effect on the hepatic glucose production. $f_1(G)$: is The pancreatic insulin production controlled by the glucose concentration. $f_2(G)$: is Insulin-independent glucose utilization (glucose uptake by the brain and nerve cells) $f_3(G)$: is The glucose-dependent term in the function describing glucose utilization. $f_4(I_i)$: is The insulin-dependent term. $f_5(x_3)$: is the influence of insulin on the hepatic glucose Production. E : is the transfer rate of The transport of insulin between plasma and intercellular space is assumed to be a passive diffusion process is driven by the difference in insulin concentration between the two compartments. V_p: is the distribution volume for insulin in plasma, and V_i: the effective volume of the intercellular space $\boldsymbol{R_{b.a}}$:is the amount of bound active receptors. $\boldsymbol{R_{b.i}}$: is the amount of inactive bound receptors. $\boldsymbol{R_{f.a}}$: is the amount of free active receptors. $\boldsymbol{R_{f.i}}$: is the amount of free inactive receptors. $\boldsymbol{I_{i.free}}$: is the amount of free insulin in the intercellular space. $\boldsymbol{k_{bind.a}}$: is the active receptor binding rate constant. $\boldsymbol{k_{bind.i}}$: is the inactive receptor binding rate constant. $\boldsymbol{k_{dis.a}}$:is the active receptor dissociation rate constant. $\boldsymbol{k_{dis.i}}$: is the inactive receptor dissociation rate constant.

Reference	Equations	Variable description
		$\boldsymbol{k_{act.b}}$: is the bound receptor activation rate constant. $\boldsymbol{k_{act.f}}$:is the free receptor activation rate constant. $\boldsymbol{k_{in.b}}$: is the bound receptor inactivation rate constant. $\boldsymbol{k_{in.f}}$: is the free receptor inactivation rate constant .
Dalla Man et al. [28]	**Glucose Subsystem:** $\dot{G_P}(t) = EGP(t) + Ra(t) - U_{ii}(t) - E(t) - k_1 \cdot G_P(t) + k_2 \cdot G_t(t)\ ;\quad G_p(0) = G_{pb}$ $\dot{G_t}(t) = -U_{id}(t) + k_1 \cdot G_P(t) - k_2 \cdot G_t(t)\ ;\quad G_t(0) = G_{tb}$ $G(t) = \frac{G_p}{V_G} \qquad ; \qquad G(0) = G_b$ **Insulin Subsystem:** $\dot{I_l}(t) = -(m_1 + m_3(t)) \cdot I_l(t) + m_2 I_p(t) + S(t)\ ;\quad I_l(0) = I_{lb}$ $\dot{I_p}(t) = -(m_2 + m_4) \cdot I_p(t) + m_1 I_l(t)\quad ; I_p(0) = I_{pb}$ $I(t) = \frac{I_p}{V_I} \qquad ; \qquad I(0) = I_b$ **Unit Process Models:** *1)* **Endogenous Glucose Production:** $EGP(t) = k_{p1} - k_{p2} \cdot G_p(t) - k_{p3} \cdot I_d(t) - k_{p4} \cdot I_{po}(t)$ $EGP(0) = EGP_b$ $\dot{I_1}(t) = -k_i \cdot [I_1(t) - I(t)] I_1(0) = I_b$ $\dot{I_d}(t) = -k_i \cdot [I_d(t) - I_1(t)] I_d(0) = I_b$ *2)* **Glucose Rate of Appearance:** $Q_{sto}(t) = Q_{sto1}(t) + Q_{sto2}(t) Q_{sto}(0) = 0$ $Q_{sto1}(t) = -k_{gri} \cdot Q_{sto1}(t)(Q_{sto}) + D \cdot d(t) \quad Q_{sto}(0) = 0$ $Q_{sto2}(t) = -k_{empt} \cdot (Q_{sto}) \cdot Q_{sto2}(t) + k_{gri} \cdot Q_{sto1}(t) Q_{sto2}(0) = 0$ $Q_{gut}(t) = -k_{abs} \cdot Q_{gut}(t) + k_{empt}(Q_{sto}) \cdot Q_{sto2}(t) Q_{gut}(0) = 0$ $Ra(t) = \frac{f \cdot k_{abs} \cdot Q_{gut}(t)}{BW}$ *3)* **Glucose Utilization** $U(t) = U_{ii}(t) + U_{id}(t)$ *4)* **Insulin Secretion:** $S(t) = \gamma \cdot I_{po}(t)$ *5)* **Glucose Renal Excretion:** $E(t) = k_{e1} \cdot [G_p(t) - k_{e2}] \quad if\ G_p(t) > k_{e2}$ $E(t) = 0 \quad if\ G_p(t) \le k_{e2}$	$\boldsymbol{G_P}$ and $\boldsymbol{G_t}$: are glucose masses in plasma and rapidly equilibrating tissues, and in slowly equilibrating tissues, respectively. $\boldsymbol{G}$: plasma glucose concentration. $\boldsymbol{b}$: denotes basal state. $\boldsymbol{EGP}$: is the endogenous glucose production. $\boldsymbol{Ra}$: is the glucose rate of appearance in plasma. $\boldsymbol{E}$: is renal excretion. $\boldsymbol{U_{ii}}$ and $\boldsymbol{U_{id}}$: are the insulin-independent and dependent glucose utilization, respectively. $\boldsymbol{V_G}$: is the distribution volume of glucose. $\boldsymbol{k_1}$ and $\boldsymbol{k_2}$: are the rate parameters. $\boldsymbol{I_p}$ and $\boldsymbol{I_l}$ ::are insulin masses in plasma and liver, respectively. $\boldsymbol{I}$: is plasma insulin concentration. $\boldsymbol{V_I}$: is the distribution volume of insulin. $\boldsymbol{m_1}$, $\boldsymbol{m_2}$and $\boldsymbol{m_4}$: are rate parameters. $\boldsymbol{S}$: is insulin secretion. I_{po} : is the amount of insulin in the portal vein. I_d :is a delayed insulin signal realized with a chain of two compartments. k_{p1} :is the extrapolated EGP at zero glucose and insulin. k_{p2}: is liver glucose effectiveness. k_{p3}: is parameter governing amplitude of insulin action on the liver. k_{p4}: is parameter governing amplitude of portal insulin action on the liver. k_i : is rate parameter accounting for the delay between insulin signal and insulin action. Q_{sto} : is the amount of glucose in the stomach. Q_{sto1} : is solid phase and Q_{sto2} : is liquid phase. Q_{gut} : is the glucose mass in the intestine. k_{gri} : is the rate of grinding. $k_{empt}(Q_{sto})$: is the rate constant of gastric emptying, which is a nonlinear function of Q_{sto}. k_{abs} : is the rate constant of intestinal absorption. f : is the fraction of intestinal absorption, which appears in plasma. D : is the amount of ingested glucose. BW : is the body weight. Ra : is the appearance rate of glucose in plasma. γ : is the transfer rate constant between portal vein and liver. k_{e1} : is the glomerular filtration rate. k_{e2} : is the renal threshold of glucose. **Figure 6**

III. CONCLUSION

This paper explains the general mechanism of the (glucose-insulin –glucagon) system. It extracts the main equations from researches whichshow mathematical models in blood glucose regulatory system that have been done among thirteen research which were studied by biochemistry, medical, biophysical, physiological researchers. Much work can be done in the future to improve the blood glucose regulatory system in diabetes. It is known that science has not found the exact mechanism of how this system works, but it is an ongoing challenge that keeps scientists working continually in order to improve their hypotheses as much as possible to help diabetics in the world.

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