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Mathematical Modeling of Glucose homeostatic regulatory system for Type II diabetic patients

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Abstract:

One of the most important and crucial physiological control systems in humans is the glucose homeostasis regulatory system. The malfunctioning of this system may cause type II diabetes mellitus (T2DM) in humans. Proper functioning of this complex and highly sensitive system is essential for human life. In the present paper we propose a simulation model of glucose homeostasis by incorporating the control theory principles and mathematical modeling by using which the proper functioning of this system is presented. This model uses differential equations and Proportional (P) and Integral (I) Controller [PI Controller]. The biological hormonal effects, causing the Glucose homeostasis in human body for regulation of glucose levels in normal values, are considered as parameters in the model. The validation of this model is possible through in vivo data.

Introduction:

In glucose homeostasis a good number of organs and hormones play an important role[1]. The secretion of the β-cells of the pancreas, insulin, has been recognized as a hypoglycemic factor of prime importance. Insulin secretion is thought to be controlled via signals from the G.I. tract after carbohydrate ingestion, in addition to direct stimulus of the β-cells by glucose [2]. The impaired insulin secretion results the irregularity in glucose homeostasis and causing type 2 diabetes mellitus. Many biological phenomena at physiological and molecular levels are described by regulation and feedback concepts. The homeostasis or the ability of biological mechanisms to restore their equilibrium in the presence of disturbances is done through the feedback control present in these mechanisms. This concept was described by Wiener in 1948[3].

In the present research understanding of biological organization and systems is done through the mathematical methods and models. This motivation is due to the renewed interest of advances in molecular biology over the past decade have made it possible to experimentally probe cause-and- effect relationships between micro and macro level molecules within a cell

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and their organisms. At the physiological level the hormone (like insulin) and protein (like BDNF) levels maintain the integrity of Glucose in plasma to maintain the sugar levels normal. The physiological role of glucose necessitates that its concentration is precisely monitored and regulated from any deviations of the set points (say 110 mg/dL in fasting) in human beings should be perfectly controlled.

Type 2 Diabetes Mellitus:

Diabetes mellitus (DM) is characterized by hyperglycemia resulting from defects in insulin secretion and/or action. The chronic hyperglycemia of DM can lead to long-term dysfunction, damage or failure of various tissues and organs such as the eyes, kidneys, heart, vascular tissue, and nerves. The DM is classified into two types, based on the primary mode of onset and pathobiology of the disease process. The younger onset insulin dependent diabetes mellitus (IIDM) is called *type 1 diabetes*, and the older onset insulin not dependent diabetes mellitus (NIIDM) is also called *type 2 diabetes*. In type 1 diabetes mellitus, the development of DM is due to autoimmune destruction of pancreatic β cells with consequent insulin deficiency. These patients are dependent on insulin that needs to be administered from external sources. The patients with type 2 diabetes mellitus are not insulin deficient but show peripheral insulin resistance and consequent hyperinsulinemia. But, over a period of time, these patients also become insulin deficient due to the exhaustion of pancreatic β cells and hence, may eventually become insulin dependent [4]. The hypothalamic neurons play a critical role in energy homeostasis regulating gut and pancreatic β islet activity in response to plasma levels of glucose, protein, fatty acids, insulin and leptin [5, 6]. BDNF has been implicated in the regulation of food intake and body weight both in experimental animals and humans. For instance, systemic administration of BDNF decreased non fasted blood glucose in obese, non-insulin-dependent diabetic mice, with a concomitant decrease in body weight [7].Bioinformatics and experimental studies revealed that BDNF (brain-derived neurotrophic factor) prevents diabetes mellitus by acting on the pancreatic β cells and hypothalamus.

Proposed Model:

If the total volume of glucose accumulated into the plasma is represented by $V_T(t)$ per unit time, and the total glucose consumed from blood as $V_C(t)$.

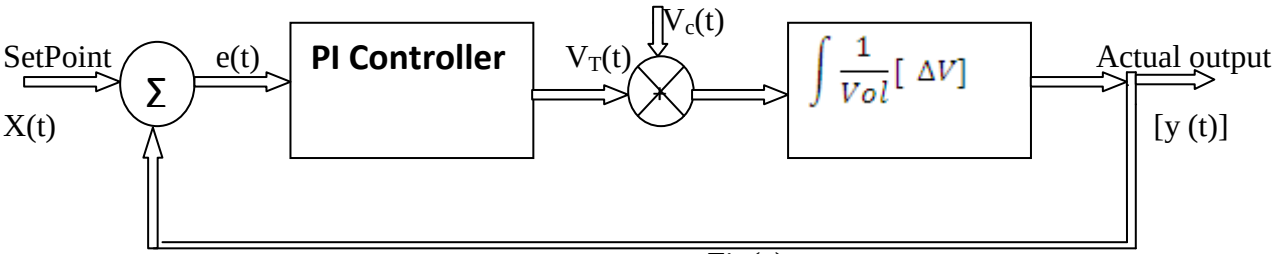
Then the rate of change of glucose concentration in plasma is given by

$$\frac{d}{dt}[\text{Glucose}]p = \frac{1}{Vol}[\ VT(t) - VC(t)] = \frac{1}{Vol}[\Delta V] \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(1)$$

Or $[\text{Glucose}]p = \int \frac{1}{Vol}[\ \Delta V] \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(2)$

Where vol is the plasma volume, $[Glucose]_p$ is called plasma Glucose or y(t).

The system satisfying the above equations is shown in fig(a),



Fig(a)

According to the feedback control theory the difference of the actual output and the set point is called the error value e(t).This error value is proportional to the volume of the glucose introduced into the plasma. The error zero means the PI controller controls the system properly and the levels of the glucose in the plasma maintain the normal values.

Otherwise, $e(t)\ \alpha\ V_T(t)$ or $V_T(t) = K_p\ e(t) = K_p\ [y(t)-x(t)]$……..3

But, the basic PI control equation for the above system is given by

$$V_T(t) = K_p\ e\ (t) + K_I \int e(t) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots..4$$

Where K_p, K_I are called proportional and integral constants, e(t) is called the glucose regulation error.

The physiological basis of PI control is used here to set the Glucose homeostasis. Since the glucose level is controlled harmonically and we hypothesized that an investigation is possible for hormonal or protein interactions to explain through the PI control.

For this consider two hormones or proteins M (say Insulin) and N (say BDNF) and realized the PI control system with these elements. If we hypothesize that the total Glucose (V_T) introduced into the plasma is proportional to the concentrations of hormones M and N, because for more glucose levels in the plasma need more production of Insulin and BDNF.

from 3 and 4,

$V_T(t)\ \alpha\ [M]$, then $\frac{d}{dt}[M]\ \alpha\ \frac{d}{dt}[Kp\ e\ (t) + KI\ \int e(t)]$

$\frac{d}{dt}[M]\ \alpha\ \{error + \frac{d}{dt}[\text{Kp e (t)}]\}$.....(5)

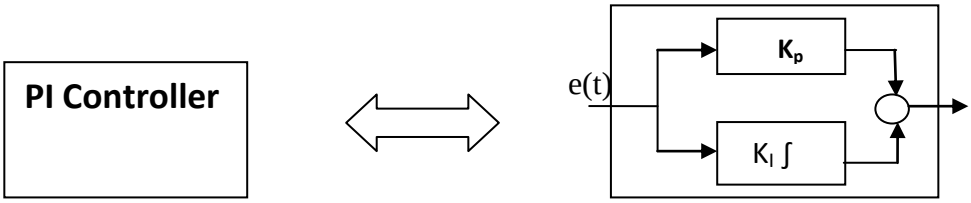
From 5, the production rate of Hormone M is proportional to the error plus the error derivative. It indicates that the production rate of Hormone M depend on two individual processes. Also it is difficult achieve the error derivative relation with the Hormone M and hence the concentration of Hormone M is proportional to error only. That is if error is more the system needing more concentration of Hormone M to regulate the homeostasis state.

Suppose that the following condition is satisfied:

- The production rate of Hormone N depends on the concentration of Hormone M; that is
- [Hormone M] α [error] and d/dt[Hormone N] α [Hormone M]
- $V_T=V_M+V_N$ where V_M α [Hormone M] and V_N α [Hormone N]

This indicates the proportional component of PI control (Eq 5) is given by V_M ,while the integral component is given by V_N. The concentration of Hormone M provides the measure of error and the concentration of Hormone N provides the measure of the integral of the error.

Thus the simulation model indicates that the two hormones regulate the Glucose homeostasis with PI controller. The simple block of PI controller is shown in the fig(b).



Fig(b)

Conclusions:

Generally there are specific set points for glucose levels for normal humans, like 110mg/dL for fasting glucose, these normal levels are continuously regulated by the hormones and proteins. This regulation is described here in terms of PI controller of the control theory. But for T2DM patients these set points are changed so that the normal levels are not sustained. Thus the controller elements, proportional (P) and integral (I) are assigned with reference to the error values obtained during feedback mechanism. This study describes the multi level

hormonal controller to accomplish blood glucose homeostasis. This simulation model needs to be validated with experimental data.

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