Journal of Biochemical Engineering & Bioprocess Technology

Commentry A SCITECHNOL JOURNAL

Mathematical Model for the Combined Effect of Medications and Life Style

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Received date: 19 August, 2022, Manuscript No. JBEBT-22-73156;

Editor assigned date: 22 August, 2022, Pre QC No. JBEBT-22-73156(PQ);

Reviewed date: 31 August, 2022, QC No. JBEBT-22-73156;

Revised date: 16 September, 2022, Manuscript No. JBEBT-22-73156(R);

Published date: 28 September, 2022, DOI: 10.4172/jbebt.1000059

Introduction

To propose a new mathematical model for the combined effect of different treatments and lifestyles on the glucose-insulin dynamics of Type 2 diabetes patients. The model gives the possibility to take into consideration physical activity, stress, meals, and medications while evaluating or designing treatment plans for diabetes patients. The model is proposed by combining and modifying some of the available models in the literature. Simulations were performed for the modifications to show how the model confirms with literature on type 2 diabetes patients. Additionally, a discussion is provided to demonstrate the ability of the model to be used in the assessment of treatment plans and in the design for robust insulin dose guidance algorithms. An open source code for the model is additionally provided. One of the greatest health challenges which faces humanity in the 21st century is the emergence of type 2 diabetes as a global pandemic. More than 463 million were reported to suffer from diabetes in 2019 and the number is expected to reach 700 million by 2045. Moreover, the global expenses related to diabetes are estimated to be 760 billion USD in 2019 and they are expected to increase. T2D is characterized by high levels of glucose concentration in the blood. This increase in glucose levels can cause cardiovascular, kidney, and eye diseases and, if left untreated, will lead to organ failures. For T2D patients, low sensitivity to insulin, which is the hormone responsible for lowering glucose concentration in the blood, causes the beta cells in the pancreas to produce insulin to compensate. This will eventually weaken the cells and damage them, which in turn will make the body fail to regulate glucose concentration. Insulin based treatment is initiated at later stages of the T2D disease when changes in diets and physical activities accompanied with oral medications have failed. Clinically, it is difficult to calculate suitable insulin doses and oral medication treatment plans for each specific patient.

Robust Control Methods

Many patients experience uncontrolled for a long period of time until they reach a safe level of glucose. Having a model to simulate the combined effect of oral medications, insulin doses, and lifestyle changes can help medical professionals in the evaluation of different treatment plans. Moreover, such models can be used together with robust control methods to design automatic insulin guidance algorithms that ensure safe reach to the desired glucose concentrations. In general, there are two main categories of methods to model systems: first principles methods, or data driven methods derived by fitting data to general mathematical structures such as ARMAX models. The glucose-insulin dynamical models for T2D patients based on first principles can vary with different degrees of complexity. In the literature, there exist two main categories of such models: minimal models and maximal models. Maximal models are very detailed models, which model metabolic functions at a molecular level. On the other hand, minimal models are less detailed and rely mostly on compartments and mass balance equations. While maximal models provide a great level of accuracy, the amount of different data, which is required to estimate parameters for these models is large and difficult to obtain from patients undergoing typical treatment plans. Moreover, the high accuracy of maximal models provides little relevance to the accuracy of the general glucose-insulin dynamics within the human body.

In contrast, minimal models consist of compartments to represent the distribution, diffusion, and production of glucose and insulin in the body with terms to represent the interaction between them. Furthermore, these models include pharmacokinetic equations to describe exogenous insulin injections and the intake of other medications. Several mathematical structures have been developed for the glucose-insulin dynamics in T2D patients. Some of them have a simple structure with less than ten states such as the ones presented in. These models consider simple insulin injections and meal models. Their simplicity makes them good candidates for patient specific parameter estimation and control design. Nevertheless, the few number of states force them to consider generic insulin and glucose states without considering other metabolic hormones (e.g. glucagon). Thus, making the process of augmenting them with oral medications and stress difficult. On the other hands, the models in are larger and more complex. The model in has recently been proposed and confirmed with patient data. Parameters were estimated as mean and covariance matrices of a normal distribution from patients' data. Only the mean and the diagonal elements of the covariance matrices were reported. The model includes a glucose ingestion model that takes into account only glucose meal given after fasting conditions. The model was also augmented with an insulin degludec linear pharmacokinetic model in. As for the model in, it is based on and includes the effect of oral medications (metformin and vildagliptin), Glucagon, and Glucagon-like peptide-1. The model uses the same glucose ingestion model from and it is only for glucose meals after fasting conditions. Only mean parameters were reported. The work in focused on the glucose dynamics in the brain and provided a mathematical description for the effect of stress in diabetic patients. Physical activity has been modeled before but mainly for type 1 diabetes patients. It has been included in simple models such as the one in or more complicated ones such as the one in.

Analyzing Treatment Plans

Heart beat rate data from smart watches and data regarding stress levels from self-assessment questionnaires are becoming more feasible to be obtained from patients during treatment. Therefore, having a model to simulate the combined effect of different types of treatments together with the effect of stress and physical activity can improve the process of evaluating and developing treatment plans for diabetic patients. Therefore, in this work, it is intended to present a mathematical structure for the combined effect of multiple glucose

meals with no fasting conditions, insulin injections and multiple oral doses of metformin with different sizes, physical activity, and stress. Additionally, a Matlab toolbox is developed to simulate patients is provided as an open source code on GitLab1 for others to use the model easily and have a better chance to contribute for the development of the model. This structure can help with analyzing treatment plans depending on lifestyle conditions. Moreover, the structure can be used with robust control strategies to obtain algorithmic insulin dose. As for the glucagon and the incretins, a single compartment is used for each one of them as it is assumed that glucagon and incretins have equal concentration in all the body parts. In addition, the model contains metabolic production and uptake rates for different compartments. These metabolic rates are generally defined as their basal values multiplied with scaling variables that depend on the concentrations of insulin, glucose or glucagon. The pancreas has a different nonlinear and hybrid model. In addition, a glucose ingestion model based on is included as in but modified to handle multiple meals along the day. Moreover, metformin and vildagliptin oral treatment models are included based on and respectively, as in but with a modification on the oral metformin model to handle different oral doses along the treatment. Additionally, a physical activity model based on is added to the model. Furthermore, long acting and fast acting insulin injection models.