Controller design based on the use of state observers for blood glucose regulation in patients with type 1 diabetes

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ABSTRACT

In this paper, an observer-based nonlinear controller for regulating blood glucose concentrations (BGC) in type 1 diabetes mellitus (T1DM) is proposed. The virtual patient model considered is the extended Bergmann minimal model, which is augmented by a meal disturbance and adapted to represent the insulin-glucose homeostasis of T1DM. The backstepping (BS) technique is used to design a closed-loop feedback controller. The proposed controller does not need to measure insulin, plasma concentrations, while improving control performance and robustness against uncertainty. Insulin concentration and plasma levels are estimated using state observers. These estimations are used as feedback to the controller. The asymptotic stability of the observer-based controller is proved using the Lyapunov theorem. Moreover, it is proved that the system is bounded input-bounded output (BIBO) stable in the presence of uncertainties generated by uncertain parameters and external disturbances. For realistic situations, we consider only the BGC to be available for measurement, and additionally, inter-and intra-patient variability of system parameters is considered. The results confirm that the proposed controller can asymptotically regulate BGC by appropriate injection of insulin under meal disturbance and $\pm 25\%$ of variations in system parameters.

KEYWORDS

Asymptotic stability; backstepping approach; blood glucose concentration; Lyapunov theorem; observer design.

1. Introduction

Diabetes mellitus (DM), commonly referred to as diabetes, is a persistent medical condition characterized by prolonged periods of elevated blood sugar levels. The classification of diabetes includes type 1 diabetes, type 2 DM, and gestational diabetes. Insufficient insulin production is the underlying cause of type 1 diabetes, also known as "insulin-dependent diabetes" or "juvenile diabetes." On the other hand, type 2 diabetes initiates with insulin resistance, a state where cells fail to respond adequately to insulin, potentially leading to insulin deficiency as the disease advances. This type is also identified as non-insulin-dependent diabetes or "adult-onset diabetes," primarily associated with overweight and insufficient physical activity. Gestational diabetes, the third type, manifests in pregnant women without a history of diabetes, exhibiting elevated blood glucose levels. The glycemic range, denoted by a normal blood glucose concentration of 70-130, serves as a reference point in diabetes management. Hyperglycemia occurs when blood glucose levels exceed the normal range, while hypoglycemia presents when glucose levels fall below the standard threshold. Untreated type 1 diabetes often leads to hyperglycemia, characterized by elevated blood glucose levels, potentially culminating in ketoacidosis, a life-threatening condition. Conversely, hypoglycemia, defined by blood glucose levels below 40 mg/dL, poses a severe risk as glucose represents the primary metabolic fuel for the brain, necessitating a consistent concentration in the bloodstream. In cases where the administered insulin surpasses the blood glucose concentration, hypoglycemia may ensue.

T1DM impacts 5-10% of the population, resulting in the destruction of pancreatic $\beta-$cells and the onset of hyperglycemia. Non-insulin-based diabetes, or Type 2 diabetes, affects 90-95% of individuals and arises from inadequate insulin production. Diabetes is a critical illness that exerts significant economic burdens on societies, with a person affected by diabetes every 8 seconds and a limb lost every 30 seconds. The World Health Organization (WHO) emphasizes that implementing diabetes treatment measures can mitigate its adverse economic effects. Effective diabetes management involves maintaining Blood Glucose Concentration (BGC) within the normal range. Conventional diabetes treatment methods necessitate periodic BGC monitoring and insulin administration as prescribed by healthcare providers. Continuous overnight BGC monitoring poses considerable challenges.

The Artificial Pancreas (AP) represents a sophisticated approach for automated BGC regulation. Ongoing research focuses on refining this treatment modality. Developing an AP controller is complex due to factors like external glucose intake, varying meal consumption, physical activity, drug interactions, and insulin sensitivity, which introduce disturbances complicating diabetes control. The AP functions as a feedback-controlled system comprising three distinct subsystems: a Continuous Glucose Meter (CGM), a feedback control unit for insulin dose determination, and an insulin pump for administering insulin either intravenously or subcutaneously. Designing a stabilizing controller is crucial for adjusting BGC levels within the glycemic range. Mathematical modeling of Type 1 Diabetes Mellitus (T1DM) patients is essential for AP system controller design. Bergman's Minimal Model serves as a straightforward yet effective approach for T1DM mathematical modeling.

Many AP system controllers necessitate monitoring all system states, which may not be practical. Various linear and nonlinear algorithms have been proposed to regulate BGC effectively. For instance, a Linear Quadratic Gaussian controller has been suggested in [1] for maintaining BGC within the normal range, based on a linear parameter-varying model. Similarly, a Linear Quadratic algorithm in [2] is employed to regulate BGC effectively. In [3], a Linear Proportional-Integral-Derivative (PID) controller is implemented to minimize steady-state regulation errors. Meanwhile, in [4], a Linear

Linear control strategies based on Bergman's Minimal Model (BMM) and Extended Bergman's Minimal Model (EBMM) are commonly applied in AP system research. However, as BMM and EBMM are inherently nonlinear, using linear methods to control nonlinear systems may limit controller performance, ensuring stability only in close proximity to the operating point. To achieve global stability, nonlinear control methods are necessary for regulating AP systems effectively. Nonlinear control techniques are employed in [5] to stabilize AP systems.

2. Methodology

The utilization of a backstepping approach is employed in this study for the design of the controller. In the initial stages, the system is depicted in its controllable canonical form, following which an observer is formulated to appraise the remote insulin concentration as well as the plasma insulin concentration. Subsequently, the controller is devised utilizing the backstepping approach.

Backstepping is a systematic control design method used primarily for nonlinear systems. It involves breaking down the control problem into smaller, manageable steps, allowing the designer to construct a stabilizing controller systematically. The backstepping approach builds the controller step-by-step, where each step focuses on stabilizing a particular state variable and incorporates it into the overall control strategy. It explicitly handles the error dynamics by defining virtual control inputs at each step. These inputs are adjusted based on the performance of the previous steps.

The backstepping control approach involves several systematic steps to design a controller for nonlinear systems. First, the system is defined, and a Lyapunov function is selected for the initial state variable to analyze stability. Next, a virtual control law is designed to stabilize this first variable. This process is then recursively applied to subsequent state variables, with each step incorporating the previous virtual control. Finally, all virtual controls are combined into a comprehensive control law for the entire system, ensuring that the closed-loop dynamics remain stable throughout the process. This method allows for a structured and effective way to handle nonlinearities in dynamic systems.

3. Discussion and Results

In this manuscript, a pair of distinct observers are formulated for the purpose of asymptotically estimating the levels of insulin concentration and plasma concentration. The design of the disturbance estimator is aimed at approximating the impact of external disturbances. The primary objective of the controller is to ensure the asymptotic stability of the system, particularly when there is an absence of measurements for remote insulin and plasma insulin concentrations as well as external disturbances. The efficacy of the proposed control technique is evaluated through Control Variability Grid Analysis (CVGA) applied to 100 simulated T1DM patients, with a focus on confirming the reliability and robustness of the method. The key innovations of the proposed control approach encompass:

1- Differing from prior studies, where controllers required measurements beyond Blood Glucose Concentration (BGC), the proposed method solely relies on BGC data easily obtained from BGC sensors. Moreover, the system incorporates two distinct observers dedicated to estimating insulin and plasma concentrations, eliminating the necessity for prior knowledge of external disturbances by utilizing the disturbance estimator.

2- In contrast to previous works, which utilized conventional control techniques, the controller in this study is developed utilizing nonlinear control methodologies. The stability analysis of both the observer and the observer-based controller is conducted concurrently employing the Lyapunov theorem. Consequently, the controller guarantees global asymptotic stability and enhances system performance compared to existing literature.

3- A unique equivalent transformation technique is introduced to facilitate the conversion of system dynamics into a controllable conventional format. The system, now in a controllable canonical configuration, is governed utilizing the BS technique. Consequently, all states pertaining to External Blood-Mass-Moment (EBMM) are effectively regulated, ensuring that internal dynamic instability, as reported in prior studies, is averted.

4. Conclusion

This article introduces a novel approach to blood glucose control in Electrochemical Blood-Monitoring Machines (EBMM) utilizing the Biochemical System theory. Nonlinear observers are employed to estimate plasma and insulin concentrations. A disturbance estimator is developed for assessing external disturbances stemming from physical activity and meal intake. The system's asymptotic stability is established through the application of the Lyapunov theorem. The proposed control mechanism necessitates solely the measurement of Blood Glucose Concentration (BGC) while ensuring the system's asymptotic stability. Simulation outcomes validate the superior performance of the suggested controller in comparison to prior research. Enhanced regulatory outcomes are achieved without the requirement for remote insulin monitoring, plasma insulin levels, or external meal disturbances.

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