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Improved Blood Glucose-Insulin Monitoring with Dual-Layer Predictive Control Design

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***Abstract*—**In response to widely used wearable medical devices equipped with a continuous glucose monitor (CGM) and insulin pump, the advanced control methods are still demanding to get the full benefit of these devices. Unlike costly clinical trials, implementing effective insulin-glucose control strategies can provide significant contributions to the patients suffering from chronic diseases such as diabetes. This study deals with a key role of two-layer insulin-glucose regulator based on model-predictive-control (MPC) scheme so that the patient's predicted glucose profile is in compliance with the insulin level injected through insulin pump automatically. It is achieved by iterative optimization algorithm which is called an integrated perturbation analysis and sequential quadratic programming (IPA-SQP) solver for handling uncertainties due to unexpected variations in glucose-insulin values and body's characteristics. The feasibility evaluation of the discussed control approach is also studied by means of numerical simulations of two case scenarios via measured data. The obtained results are presented to verify the superior and reliable performance of the proposed control scheme with no negative impact on patient safety.

***Keywords*—**Blood glucose monitoring, insulin pump, optimization, predictive control, diabetes disease.

I. Introduction

OVER the past decades, diabetes has received huge attention from different treatments perspective as a chronic disease. In a standard way, the affected patient requires continuous blood glucose monitoring to ensure that blood glucose variation is remained within acceptable limits. The most common recommendation for type-1 and type-2 diabetes is careful insulin therapy meaning regularly injection of insulin via pump insulin in the subcutis. On the other hand, to be able to adjust blood glucose concentration, sufficient injected insulin doses are crucial to prevent individuals from hypoglycemia and its devastating impacts [1], [2].

Nowadays, due to the rapid advancement of electronic devices, the requirement for efficient glucose monitoring in a continuous manner is fulfilled. Although these sensors and wearable devices provide the desired data with enough accuracy; however, there are still some drawbacks in terms of acquired data in longer time for monitoring purposes which are limited to several days as discussed in [2], [3]. Therefore, it is crucial for diagnostic reasons to be able to predict the insulin or glucose profile in a longer horizon.

As explained in [4], by merging an implanted glucose monitor and insulin infusion pump, the system so-called *artificial pancreas* is formed. This concept demands developing an integrated advanced control method comprising of both glucose measurement and insulin injection to deal with the disadvantages of already deployed approaches in clinical trials [5].

To highlight the reported control techniques in literature with the aim of two operational targets mentioned above, we can refer to [4]-[7]. These studies proposed a simple proportional-integral-derivative (PID) controller only to regulate insulin values similar to a lot of researches conducted in the past [6], [7]. It is well-known fact that such techniques based on PID are vulnerable to uncertainties because of the patient's condition changes, leading to inefficient insulin control performance.

Having compared the advanced and closed-loop control methods in this arena, MPC has been pointed out [8]-[10] with its promising features to meet the diabetes treatment requirements.

In spite of significant contributions from many researchers addressing variety of MPC schemes, majority of the available solutions are made up through mathematical representation of the biological glucose control processes. In these models and controllers, physiological structures are the key core of designs without taking crucial constraints like change rate of glucose-insulin levels, longer prediction horizon and patient's body properties into consideration.

This paper tends to develop a two-layer predictive controller incorporating main physiological factors into design for effectively glucose-insulin regulation, whereby an initial controlled variable concerning patient's characteristics is derived via first-layer. The second-layer of the controller is devoted to optimization efforts to enhance overall performance associated with model unknown factors, for instance measurement errors, glucose-insulin dynamics as well as insulin pump response capability. To achieve this objective, an IPA-SQP algorithm is employed in the cost function tuning of the MPC problem, whereas the weighting coefficients are updated accordingly. Once the optimum insulin trajectories are obtained by the two-level predictive design, the most suitable insulin dose pulses are dispatched to the insulin pump for satisfactorily performance.

Two different case scenarios have been simulated using sets of blood-glucose measurement to validate the objectives of the introduced closed-loop predictive controller. Some illustrative results are presented and discussed to conclude this paper.

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II. Predictive Patient's Behavior and Optimization Control

A. Model Predictive Control Design of Blood-Glucose Level

The developed glucose–insulin model includes control states and variables together with control inputs as presented in block diagram shown in Fig. 1. It tends to explain insulin absorption process and dynamics of the glucose-insulin control levels. The wearable medical device provides model inputs by taking all the required measurements for patient's blood glucose-insulin values. The introduced glucose-insulin mathematical model in [8] followed in this study. The main goal of the proposed control scheme here is to take a crucial physiological factor into account; patient blood characteristics such as glucose-insulin dynamics and meal absorption effects.

To establish the proposed control scheme, there are several patient-specific parameters that should be defined in the scale of d (day) and sampling time t as: $G(d,t)$ denotes blood-glucose for the patient acquired from continuous-glucose monitoring device (CGMD).

Based on predictive control technique, the controlled variable $G(d,t)$ is obtained through optimal control steps from the sampling instant at t-1, so becomes $G(d,t$-$1)$ that is the blood-glucose level, and in the same manner the computed value at prior day represented by $G(d$-$1,t)$. In addition, the patient's blood is monitored to figure out the safe limits of the blood glucose, which are named as preferred blood glucose set-points, $G_{ref}(t)$, per each time period. It should be noted that this set-point is varied with respect to whether the patient is taking a meal, e.g. breakfast or lunch or in the absence of meals overnight time. For the control purposes, the generated error is regulated by subtracting $G_{ref}(t)$ from variable blood-glucose function $G(d,t)$. Another important controlled variable $I_n(d,\ t)$ stands for patient's insulin value corresponding to d (day) and time t. Consequently, the introduced control and monitoring system requires to know the difference between individual insulin level, at certain day and time, and the insulin values in the day before, $I_n(d$-$1,t)$. This is shown by $S_I(d,t)=I_n(d,t)-I_n(d-1,t)$ acting as decision index for insulin pump calculated from cost function in the optimization algorithm to identify the variation profile of the patient's glucose-insulin levels. On the other hand, $S_I(d,t)$ determines demand dose of insulin that should be injected via pump, when patient suffers from very low blood-glucose values compared to the target level.

As illustrated in Fig. 1, the value of intended glucose-insulin in each time instant that minimizes the cost function J is chosen at the end to command the insulin pump injection. This is an iterative process involving $G(d,t)$ implying a closed-loop supervisory system.

To summarize, the aforementioned different parameters are expressed mathematically as:

$$\begin{aligned} &G(d,\ t)\big|_{d=d-1\,(day)} = G(d-1,\ t) \\ &G(d,\ t)\big|_{t=t-1\,(moment)} = G(d,\ t-1) \\ &\Rightarrow blood-glucose\ error \begin{cases} G_{ref}(t)-G(d-1,\ t) \\ G_{ref}(t)-G(d,\ t-1) \end{cases} \\ &decision\ index: S_I(d,\ t) = I_n(d,\ t)-I_n(d-1,\ t) \end{aligned} \tag{1}$$

The following quadratic cost function candidate J to apply an optimized insulin pump values considering parameters constraints can be chosen as

$$\begin{aligned} J(k) &= \beta_1.\left\|G_{ref}(d+k,t)-G(d+k,t)\right\|^2 \\ &+\beta_1.\left\|G_{ref}(d+k-1,t)-G(d+k-1,t)\right\|^2 \\ &+\beta_2.\left\|I_n(d+k,t)-I_n(d+k-1,t)\right\|^2 \\ &+\beta_2.\left\|I_n(d,t+k)-I_n(d,t+k-1)\right\|^2+S_I(d,t) \end{aligned} \tag{2}$$

where the desired parameters are predicted at sampling instant of k. β_1 and β_2 are the weighting factors defined based on SQP optimization solution as revealed by the flowchart in Fig. 2.

It is important to indicate that meal is prevalent driving factor as a constraint in varying individual's blood glucose trace either upward or downward. Frankly speaking, in response to various amount of injected insulin, the reaction of blood-glucose system for different patients is distinctly varied.

To overcome this particular type of constraint in (2), the algorithm should compensate the insulin values variations in timely manner by incorporating the decision index. Therefore, the optimization algorithm chooses the appropriate glucose setpoint in each interval as Table I gives these secured values in different daily periods.

TABLE I
Values of Patient Blood Glucose in Different Daily Periods

Time Period	Blood glucose variation	Blood glucose setpoint
7:00 am – 9:00 am	90-198 mg/dL	135 mg/dL
9:00 am – 11:00 am	90-234 mg/dL	180 mg/dL
11:00 am – 1:00 pm	162-342 mg/dL	252 mg/dL
1:00 pm – 5:00 pm	90-198 mg/dL	135 mg/dL
5:00 pm – 8:00 pm	162-342 mg/dL	252 mg/dL
8:00 pm – 7:00 am	72-162 mg/dL	108 mg/dL

A. Proposed Optimization Algorithm with Dose Correction

In this section, the optimization algorithm based on an IPA-SQP is described. The goal is to make a use of this optimization scheme to deal with the parameters constraints and model uncertainties. It is worth mentioning that the types of uncertainty in the model to predict insulin dynamics could be due to unknown patient's characteristics and fluctuation of glucose values, etc. Thus, to make a robust monitoring and performance for the designed control system, the proposed framework in this paper considers the correction factor into glucose-insulin control approach to prevent severe effects by

injecting for example incorrect insulin doses to the patient. As shown in Fig. 2, uncertainty during optimization procedures is performed by second-level control strategy eliminating an extra parameter constraint that is usually in place via conventional control methods.

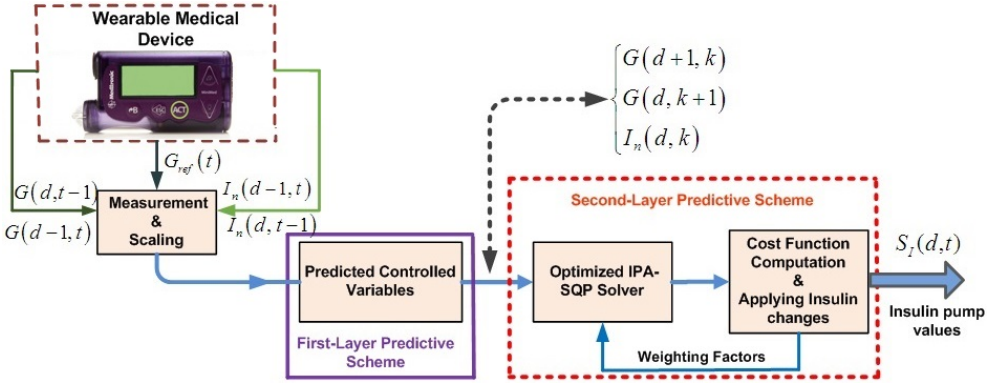

Fig. 1 The proposed two-layer prediction structure generating the optimal insulin patterns, Wearable device shown available at [11]

A procedure of needed variables prediction is separated from the optimized variables with uncertainty and deriving optimal cost function in each sampling time. Through merging IPA-SQP approximations, the predictive formulation is efficiently achieved, while the weighting coefficients are updated respectively. Once the optimum insulin trajectories are obtained by the two-layer predictive scheme, the most suitable insulin levels are dispatched to the insulin pump for acceptable operation considering patient's physiological conditions.

Primarily, whenever at the point $x^i(t)+\delta x^i(t)$, in which i represents the iteration index, the Hamiltonian expression (3) related to the control function $u(t)$ is sufficiently small at prediction time k, leads to the iterative process assumes initial non-zero state perturbation $\delta x^i(t)\neq 0$. The procedure is being completed once the iteration satisfies the following condition for Hamiltonian function through a weighted sum at given threshold value 0.0131.

$$\sum_{k=t}^{t+N-1} \left| H_u(k) \right| \leq 0.0131 \tag{3}$$

where N is the number of measurement taken per each time period for the desired parameters. Further reading and description of how the IPA-SQP algorithm works are provided in [12].

III. Case Study Analysis

A simulated model of exemplary two case studies is developed to validate the theoretical findings of the proposed control strategy with data measurements. The main goal is to investigate the accuracy of blood glucose prediction monitoring against taken measurements through patient's wearable device. For better analysis, a prediction horizon of 30 minutes is calculated by applying the discussed optimized predictive control process. In addition, the measured blood glucose values have deliberately distorted via incorrect insulin doses to fairly judge about compensation of unknown effects on the predicted glucose profile via optimization part of the controller. It is observed from Fig. 3 that the blood glucose measurements are plotted against the predicted profile based on the designed predictive control method over a period of 24-hour (1440 minutes). It shows superior blood glucose control and robustness to measure without providing additional risks, for example overtreatment, due to the side effect of metabolic uncertainties.

In the second case study, the performance of insulin pump with respect to allocated response time is desired during a whole 24 hours slot. The relation of blood glucose trend and insulin values when patient takes a meal is of special interest for this assessment.

To perform the abovementioned case scenario, the acquired data in two complete days have been utilized and the insulin values for the third and fourth days are simulated. In doing so, the blood glucose values for the fifth day have intentionally raised as twice as the fourth day. Consequently, insulin values on the fourth day are approximately two times of the blood glucose values. Furthermore, reduction of the blood glucose levels on the third day will result in decreasing the insulin values accordingly. Based on the recorded data, an excessive rise of blood glucose level denotes a patient's meal-time.

Another imposed change is for the values of blood glucose on the third day, which are dropped by 50% in comparison to that of the fifth day. The insulin profile for the first, third and fifth days associated with respective changes are displayed as a bar graph in Fig. 4. It is revealed that the insulin values on the fifth day (blue-bar chart) are nearly doubled the insulin levels of the third day (red-bar chart). Thus, this trace implies a linear relationship between blood glucose variations and insulin levels.

This is an important feature of the proposed design in particular when there is an insulin overdose status, thus allows injecting pancreatic glucagon in efficient manner. As a result, the control strategy is enabling to regulate patient's glucose variation in both the normal and critical situations.

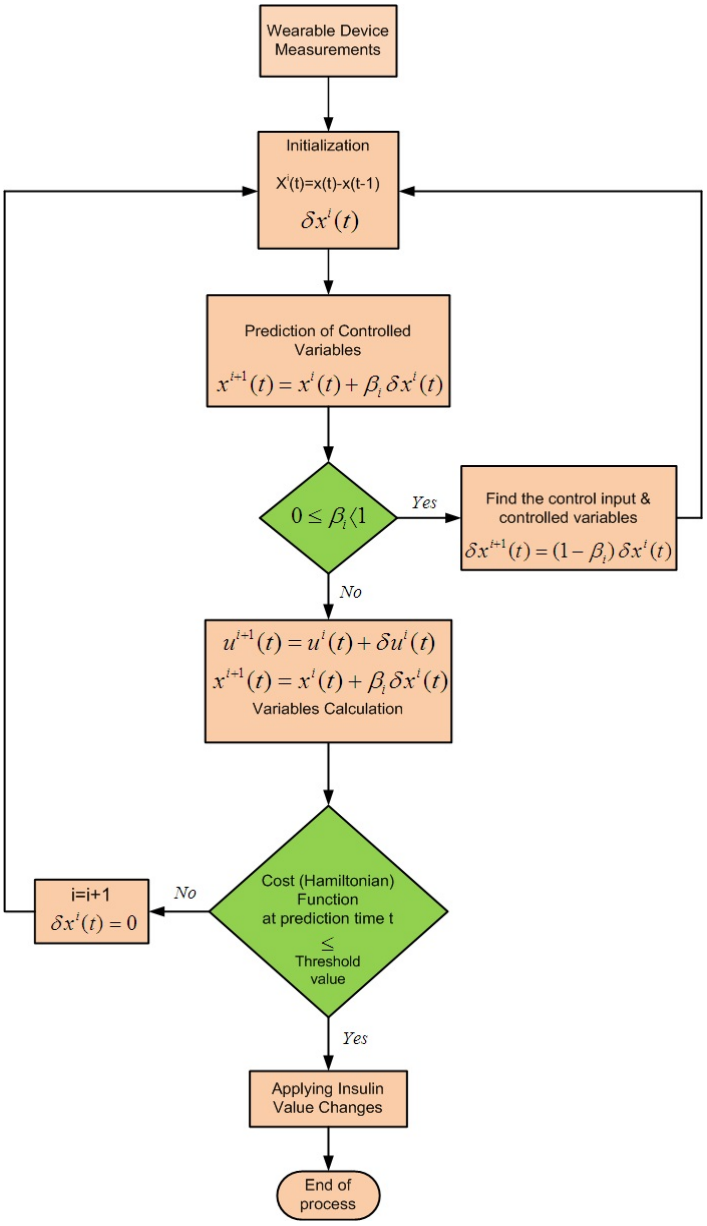

Fig. 2 A flowchart for iterative optimization of predicted glucose formulation using IPA-SQP technique

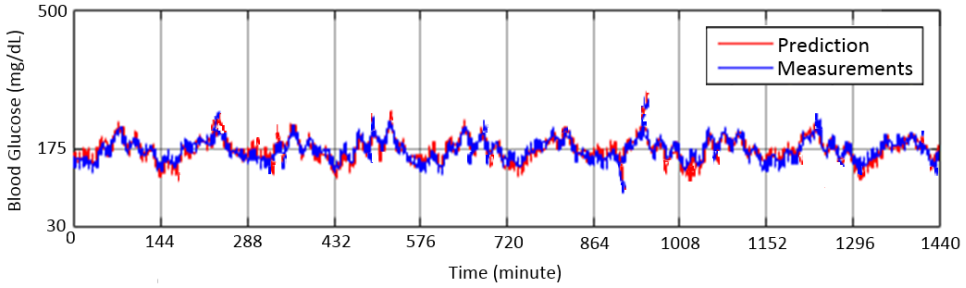

Fig. 3 A simulated blood glucose profile during 24-hour; Measured blood glucose [mg/dL] (Blue curve) compared to the 30-minutes ahead prediction profile (Red curve)

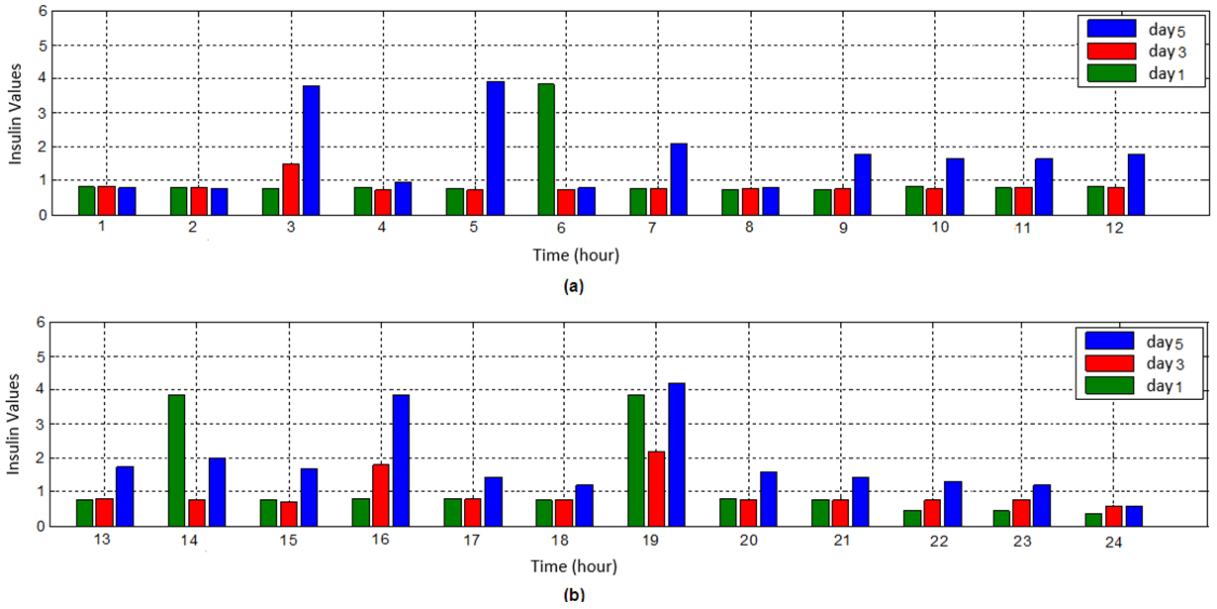

Fig. 4 A representative insulin values corresponding to the applied changes in blood glucose on third and fifth day; Green chart: First-day measured data for one patient sampled every 30-minute during 24-hour period; Red chart: Insulin levels on third day in response to the halved-blood glucose simulated data; and Blue chart: Simulated insulin values for the fifth day after increasing blood glucose level as twice as possible compared to the fourth day values

IV. Conclusion

An effective optimized model predictive control (MPC) methodology has discussed for regulating the blood-glucose profile along with its prediction based on measured data acquired from wearable medical device. Corresponding design principles and control objectives based on various patient's physiological characteristics are explained. Designed control strategy is based on an IPA-SQP optimization of the cost function in each prediction horizon, which is then applied to the control optimization formulation to determine appropriate injection level of the insulin pump. The proposed strategy includes glucose-insulin interactions for diabetic individuals to reduce uncertainties appeared from anthropological features and physiologically controlled variables, hence, improving overall closed-loop control performance. A simulation analysis has performed with respect to 30-minute prediction horizon of blood glucose profile based on measured values. Additionally, the relationship between glucose level variations and insulin deliveries for the full 24-hour period has investigated. From the obtained results and findings, initial objectives of this study have confirmed and further elaboration considering different aspects are the subject of future works.

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