Reducing Risk of Closed Loop Control of Blood Glucose in Artificial Pancreas using Fractional Calculus

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Abstract— **Healthcare costs in the US are among the highest in the world. Chronic diseases such as diabetes significantly contribute to these extensive costs. Despite technological advances to improve sensing and actuation devices, we still lack a coherent theory that facilitates the design and optimization of efficient and robust medical cyber-physical systems for managing chronic diseases. In this paper, we propose a mathematical model for capturing the complex dynamics of blood glucose time series (e.g., time dependent and fractal behavior) observed in real world measurements via fractional calculus concepts. Building upon our time dependent fractal model, we propose a novel model predictive controller for an artificial pancreas that regulates insulin injection. We verify the accuracy of our controller by comparing it to conventional non-fractal models using real world measurements and show how the nonlinear optimal controller based on fractal calculus concepts is superior to non-fractal controllers in terms of average risk index and prediction accuracy.**

I. Introduction

Diabetes is one of the fastest growing diseases in the world. Patients suffering from type-1 diabetes have no endogenous insulin production due to malfunctioning of pancreatic beta cells, hence, inability of their body to lower blood glucose (BG) without exogenous insulin. The CDDT study [7] revealed the impact of intensive insulin therapy in comparison with conventional therapy (one or two daily insulin injections and a daily monitoring of BG or urine). They concluded that intensive therapy results in lower mean glycemic level and significantly reduced health complications. This motivates the design of an artificial pancreas (AP) which seeks to improve the quality-of-life for type-1 diabetic people by estimating deviations in BG level from reference value and determining the amount of injected insulin. Adopting a cyber-physical system (CPS) perspective, the AP consists of a continuous time blood glucose sensors, a control algorithm and safety layer, and an insulin injection device. There have been significant advances in BG sensing and insulin injection devices. However, we still lack efficient APs that can control the glycemic level. This can be attributed inaccurate mathematical models and control algorithms. In this work, we present a new control algorithm on the basis of observed fractality in the BG time series.

The paper is organized as follows: Section II overviews the prior work, discusses the pros and cons of the proposed control algorithms and presents our motivation for proposing a fractal controller. Section III presents our formulation of a fractional order model predictive controller. Section IV summarizes our results and contrasts it to the previous conventional integer order model predictive approach.

II. Related Work and Novel Contribution

To control the glycemic level and prevent both short- and long-term medical complications, numerous control algorithms based on proportional-inte-grative-derivative (PID) control [3][19][20][22][23] and model predictive control (MPC) [1][12][13][15] have been proposed. To understand the rationale behind using PID controller in glycemic control [19][20][3][22][23], we explain each of its terms: *i*) a P-controller determines the quantity of insulin as a function of the difference between measured blood glucose and the reference value; *ii*) an I-controller finds the supplement to the P-controller insulin injection rate due to observed errors over a short period of time. This term helps to reduce BG level of insulin resistance patients; *iii*) a D-controller adds a correction to the PI-controller insulin injection rate by multiplying the slope of the errors between the actual BG and the reference value with a derivative gain factor. This distinguishes insulin injection rates for different situations with same current glucose level having different blood glucose increase rate. Despite simplicity in implementation, Renard et al. [17] observed that controlling the BG levels via PID controller in the postprandial period (i.e., two hours after meal intake) remains a significant challenge. In addition, the need of the PID-controller for external intervention (such as programming manually the bolus before meals) critically affects the feasibility of such approaches. Another drawback of PID-controllers is that initial trials revealed that trying to control the meal related hyperglycemia resulted in hypoglycemia in a very short interval of time after meal intake leading to dangerous and life-threatening situations.

Model predictive control (MPC) formulates the BG regulation as a general optimization that can involve many types of models and objective functions. MPC consists of two steps: *i*) a dynamical model (usually linear models are identified from measurements) of the BG dynamics and *ii*) an optimal control signal which is calculated over a predefined time interval by solving an optimization problem. This formalism accommodates delays associated with insulin absorption and can easily account for meal intake and prandial insulin boluses by the patient. The main feature of MPC is that it allows the current timeslot to be optimized while keeping future timeslots into account. This means that the optimization

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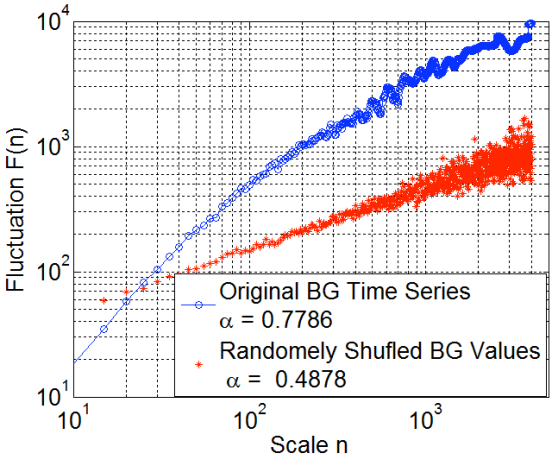

Fig. 1. Detrended fluctuation analysis on real worlds's BG levels and shuffled time series from the real BG values

is achieved on a finite time horizon while implementation is only applied on the current timeslot. Along these lines, Hovorka et al [11] investigated an *in silico* MPC-approach to control the BG during fasting conditions when blood glucose sampling resolution was 15 minute while manual information regarding meal insulin bolus (i.e., meal size) is provided. On a different study, Magni et al. [13] assume that the meal announcement is available and presented an *in silico* linear MPC control approach which determines the insulin injection rate by solving an optimization problem under a linear model for the BG dynamics. Patek et al. [16] described a complete CPS approach to the AP design on the basis of linearized state space model and using MPC formalism. Lee et al. [12] discussed an in silico MPC-approach to blood glucose regulation which relies on detecting the meal size and reduces the overall daily mean glucose for each patient. Similarly, Abu-Rmileh and Garcia-Gabin [1] present a constrained MPC approach to glucose regulation by adopting a linear state space model relating the BG levels to the insulin injection rate and meal intake variable and solving the MPC problem for three glycemic ranges, namely 60, 120, and 200mg/dl.

Several clinical studies [4][6] have assessed the efficacy and benefits of these control algorithms. Clarke et al. [6] studied the benefits of the linear MPC approach proposed in [13] and found that the risk of hypoglycemic events was not always eliminated. In addition, the authors observed that the MPC approach may be highly sensible to BG variability and transmission errors. Similarly, Bruttomesso et al. [4] showed that although MPC is supposed to provide better performance than PID controllers, in reality none of these approaches offered a good postprandial normoglycemic profile.

The vital ingredient of MPC is the model that links insulin delivery and meal ingestion to BG dynamics. This physiological model needs to account for fundamental processes regulating glucose level. Inspired by the observed statistical properties of blood glucose time series in [10] and toward proposing new efficient algorithm for glycemic control, we make the following contributions:

- **Investigation of long-range dependency and time-dependent fractional order derivative:** Fig. 1. shows the detrended fluctuation analysis (DFA) [8] of the blood glucose time series characterized by a Hurst exponent of 0.77 proving the long-range dependence behavior. By randomly shuffling the BG values and performing the DFA on the newly generated series, the Hurst exponent drops to 0.48 which corresponds to a short-range (memoryless) dynamics. We have observed a similar trend for the BG time series [9] indicating the existence of long range dependence property. We have further investigate the fractal behavior and Fig. 2.a shows the computed time dependent fractional order derivative obtained via wavelet method in [21]. As can be seen, assuming a constant fractional order for the derivative makes the model inaccurate and hence reduces the control performance.
- **Investigation of the accuracy of prediction of blood glucose based on fractal model:** We have generated the prediction results on the basis of fractal model and compared the results with non-fractal model in terms of difference risk index of the predicted values and real measurements.
- **Proposing Control Algorithms with average risk as cost function:** We have formulated the closed-loop control algorithm in AP as a model predictive algorithm with risk index as the cost function and reported performance of the fractal controller in comparison to the conventional non-fractal controller.

III. Proposed Mathematical Modeling and Control Algorithm in Artificial Pancreas

The AP control algorithm relies on an accurate model of the BG dynamics to determine the best insulin injection rate and inject the insulin via a specialized pump to maintain the body in normal glycemic range. Toward this end, we first present our novel fractional calculus assisted mathematical model to capture the blood glucose characteristics observed in publicly available real world measurements [9]. Because modeling is a crucial part in the design of any cyber-physical system [2][14], we propose a time dependent fractional model of BG dynamics and formulate the problem of finding the best insulin injection rate as a model predictive control problem in which the average risk index in the finite time horizon is formulated as cost function to minimize.

A. Mathematical Modeling of Blood Glucose

The state-of-the-art control algorithms in AP rely on the memoryless assumption about the blood glucose and ignore the intrinsic physiological variability. In addition, current control algorithms rely on memoryless linear models to find the insulin injection rate. However, the efficacy and performance of such control algorithms are highly dependent on the accuracy of modeling blood glucose dynamics. In this work, rather than, ignoring complex fractal characteristics observed in blood glucose time series, we develop a mathematical model for capturing complex blood glucose

dynamics capable of encapsulating the time dependent fractal behavior. To capture the time dependent fractal behavior shown in Fig. 1 and implicitly the long range memory property, we introduce the fractional derivative (i.e., ${}_0D_t^{\alpha(t)}$) of the BG level $g(t)$ and express its dynamics as follows:

$$ {}_0D_t^{\alpha(t)} g(t) = a(t)g(t) + b(t)u(t) \tag{1} $$

where $\alpha(t)$ is the order of the fractional derivative introduced to model the time dependent memory of the blood glucose dynamics, $a(t)$ is the proportionality coefficient , $u(t)$ denotes the amount of insulin injection rate at time t, $b(t)$ is a coefficient representing the impact of injected insulin on the BG dynamics. The parameter $\alpha(t)$ is obtained by a linear regression of the coefficient of wavelet transform [21].

Intuitively, having time dependent fractional differentiation ${}_0D_t^{\alpha(t)} g(t)$ implies that the current and future BG levels depend on a set of previous values and so it captures the observed long range memory and fractal behavior observed in the power law glucose fluctuations and the spectrum of fractal dimensions[10]. In addition, rather than iteratively searching for the best order of an auto-regressive moving average (ARMA) model and so increasing the number of time dependent parameters in the model, here we only introduce $\alpha(t)$ to capture the effect of past values on current and future BG dynamics. Of note, the introduction of a time dependent fractal (fractional order) exponent $\alpha(t)$ offers also a compact representation of the exhibited intra- (due to meal absorption, subcutaneous insulin absorption, daily physical exercise, stress) and inter- (circadian rhythm, weekly activities) day variability. Consequently, the proposed model in (1) is able to capture the blood glucose variability more adequately then integer order differential equations and addresses the modeling challenges emphasized by the Diabetes Technology Meeting [18].

B. Optimal Control of Blood Glucose with Average Glycemic Risk Index as Cost Function

Aiming to bring the BG within healthy glycemic range, we formulate a finite time horizon optimal control problem in which the objective is to minimize the glycemic risk index:

$$ min_{u(t)} \int_0^{t_f} risk(g(t), g_{ref}(t), u(t))dt \tag{2} $$

subject to glucose-insulin dynamics model in (3), initial value, glucose state and insulin control constraints:

$$ {}_0D_t^{\alpha(t)} g(t) = a(t)g(t) + b(t)u(t) \tag{3} $$

$$ g(t=0) = g_0, \;\; u_{min} \leq u(t) \leq u_{max}, \;\; g_{min} \leq g(t) \leq g_{max} \tag{4} $$

where t_f represents the finite horizon of the control problem, $g_{ref}(t)$ is the time dependent glucose reference value, $u(t)$ denotes the insulin injected at time t, g_0 is the initial glucose level, u_{min} and u_{max} are the minimum and maximum allowed insulin amounts to be injected, g_{min} and g_{max} are the safe bounds imposed on the glucose level. This risk index is motivated by the diabetes literature [5] and is shown in Fig. 2.d.

The goal of the controller is to find the near future best insulin amounts which minimizes average risk. This risk index is defined such that it can capture both chronic and acute risk of glycemic value in a quantitate way; with asymmetric property of being higher for values less than 140 and less for values less than 140. At each control interval only the first insulin value u is injected through the insulin pump and then the optimization problem is solved again to find the next amount for the newly observed BG dynamics.

IV. Results, Discussion and Future Work

To investigate the impact of using proposed fractional order model with respect to conventional integer order model, we compare the predictability ability of both models on real world's measured time series [9]. We generated predictions for both fractal and non-fractal model. Opposed to the conventional comparison of root mean squared error (RMSE), here we compared the distribution of difference of risk index between the prediction and the measured data for fractal and non-fractal model. As can be seen from the distribution of risk index error of fractal and non-fractal approach in Fig. 2.b and Fig. 2.c, fractal model has less proabable risk with non-fractal model having 18% more risk indexo on average. Secondly, the distribution of error of non-fractal approach is more likely to have negative values which means it predicts values which are less risky than the actual glycemic level values and can mislead the control algorithm by being optimistic.

We have also verified the impact of using fractional order controller compared to conventional integer order controller for several control time horizon values. We applied both control algorithms in postprandial scenario and report the difference of obtained blood glucose trajectory with respect to conventional integer order controller in Fig. 2.e. Of note, the non-fractal controller which ignores the long range memory effects has the tendency to reach lower BG values. We have also reported the difference of the average risk index over the finite time horizon in Fig. 2.f. As can be seen, the average risk index resulting from application of fractal controller is less than non-fractal controller. Future directions toward investigation of fractal controller include clinical investigation and modification of current FDA approved patient simulator to account for the fractal complexity of real blood glucose time series.

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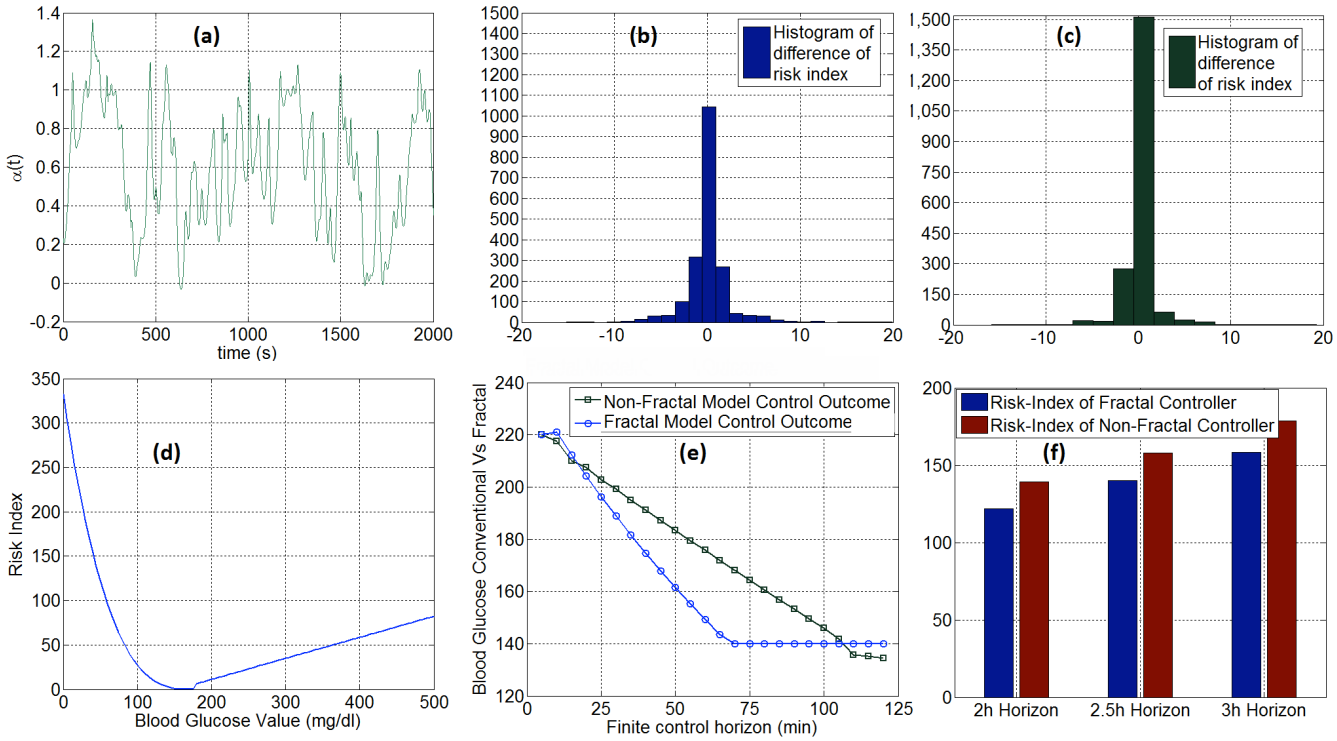

Fig. 2. a) Time dependent fractional order derivative of BG level. Distribution of difference of risk index of actual and predicted glycemic value for b) fractal and c) non-fractal approach. d) The risk index function definition in [5]. e) Comparison between the trajectory blood glucose after applying fractional order controller (blue) and integer order controller (green) with cost function as average risk index. f) Comparison of average risk index over the finite time-horizon for both fractal and non-fractal approach.

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