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Model-fusion-based online glucose concentration predictions in people with type 1 diabetes

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ABSTRACT

Accurate predictions of glucose concentrations are necessary to develop an artificial pancreas (AP) system for people with type 1 diabetes (T1D). In this work, a novel glucose forecasting paradigm based on a model fusion strategy is developed to accurately characterize the variability and transient dynamics of glycemic measurements. To this end, four different adaptive filters and a fusion mechanism are proposed for use in the online prediction of future glucose trajectories. The filter fusion mechanism is developed based on various prediction performance indexes to guide the overall output of the forecasting paradigm. The efficiency of the proposed model fusion based forecasting method is evaluated using simulated and clinical datasets, and the results demonstrate the capability and prediction accuracy of the data-based fusion filters, especially in the case of limited data availability. The model fusion framework may be used in the development of an AP system for glucose regulation in patients with T1D.

1. Introduction

Type 1 diabetes (T1D) is a chronic disease that is characterized by the inability of the pancreas to produce insulin required for the regulation of blood glucose concentration (BGC). People with T1D must administer exogenous insulin to maintain their BGC within the desired range (70–180 mg/dL). If BGC is not tightly regulated, the glycemic excursions may cause hypoglycemia (low BGC) or hyperglycemia (high BGC), which may lead to a variety of hazardous, long-term complications (Centers for Disease Control and Prevention, 2011).

To mitigate hypo- and hyperglycemic excursions, closed-loop AP systems that incorporate continuous glucose sensors, insulin pumps, and appropriate control algorithms have been developed to automatically calculate and administer the required insulin dosage. A hybrid AP has been announced with availability in 2017 (Garg, Weinzimer, Tamborlane, Buckingham, Bode, Bailey, et al., 2017). However, the conventional AP systems typically involve proportional–integral- derivative control techniques that ordinarily rely on the current glucose measurements and a rudimentary model of the glucose–insulin dynamics (Percival, Zisser, Jovanovic, & Doyle III, 2008). The recent development of accurate continuous glucose monitoring (CGM) systems have increased interest in the predictive modeling of glucose concentrations, which is useful in hypo- and hyperglycemic early warning alarms (Chico, Vidal-Ríos, Subirà, & Novials, 2003) and model-based predictive control in advanced AP systems (Bequette, 2012; Cobelli, Dalla Man, Sparacino, Magni, De Nicolao, & Kovatchev, 2009; Cobelli, Renard, Kovatchev, Keith-Hynes, Ben Brahim, Place, et al., 2012; Dassau, Zisser, Percival, Grosman, Jovanovic, & Doyle III, 2010; Ellingsen, Dassau, Zisser, Grosman, Percival, Jovanovič, et al., 2009; Eren-Oruklu, Cinar, Rollins, & Quinn, 2012; Haidar, Legault, Dallaire, Alkhateeb, Coriati, Messier, et al., 2013; Haidar, Messier, Legault, Ladouceur, & Rabasa-Lhoret, 2017; Hovorka, Canonico, Chassin, Haueter, Massi-Benedetti, Federici, et al., 2004; Jacobs, El Youssef, Castle, Bakhtiani, Branigan, Breen, et al., 2014;

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Kirchsteiger, Jørgensen, Renard, & Del Re, 2015; Kovatchev, Breton, Dalla Man, & Cobelli, 2009; Kovatchev, Tamborlane, Cefalu, & Cobelli, 2016; Pappada, Cameron, Rosman, Bourey, Papadimos, Olorunto, & Borst, 2011; Turksoy, Monforti, Park, Griffith, Quinn, & Cinar, 2017; Wang, Zhang, Zeng, Wang, Chen, Zhang, et al., 2017). Nevertheless, accurately predicting the future glucose trajectories is a challenging problem as BGC is influenced by several factors including meals, administered insulin, exercise (Breton, Brown, Karvetski, Kollar, Topchyan, Anderson, et al., 2014; DeBoer, Cherñavvsky, Topchyan, Kovatchev, Francis, & Breton, 2016; Diabetes Research in Children Network Study Group, 2005; Jacobs, El Youssef, Reddy, Resalat, Branigan, Condon, et al., 2016; Pasieka, Riddell, Turner, Luzio, Gray, Bain, et al., 2017; Peyser, Dassau, Breton, & Skyler, 2014; Turksoy, Kilkus, Hajizadeh, Samadi, Feng, Sevil, et al., 2016a; Turksoy et al., 2017; Turksoy, Samadi, Feng, Littlejohn, Quinn, & Cinar, 2016b) and emotional state (related to the concentration of certain hormones) (Nomura, Fujimoto, Higashino, Denzumi, Miyagawa, Miyajima, et al., 2000). Moreover, different physiological phenomena and the diverse lifestyles of individuals result in significant variability in glucose dynamics over time and among patients (Brazeau, Rabasa-Lhoret, Strychar, & Mircescu, 2008). These causes of glucose variability pose substantial challenges for the accurate prediction of future glucose trajectories.

To address this problem, previous research studies (Eren-Oruklu et al., 2012; Gani, Gribok, Lu, Ward, Vigersky, & Reifman, 2010; Kirchsteiger et al., 2015; Nixon & Pickup, 2011; Pappada et al., 2011; Parker, Doyle, & Peppas, 1999; Pérez-Gandía, Facchinetti, Sparacino, Cobelli, Gómez, Rigla, et al., 2010; Reifman, Rajaraman, Gribok, & Ward, 2007; Turksoy, Quinn, Littlejohn, & Cinar, 2014; Zhao, Dassau, Harvey, Seborg, & Doyle, 2011; Zhao, Dassau, Zisser, Jovanovič, Doyle, & Seborg, 2014; Zhao & Yu, 2015) have utilized various types of models for BGC prediction (or even development of AP systems) that can generally be divided into two main categories: physiological models and data-driven empirical models. Physiological models describe the glucose dynamics based on the fundamental understanding of the biological and chemical phenomena. Despite the abundant use of physiological models (Bergman, 1989; Hovorka et al., 2004; Lehmann & Deutsch, 1992; Parker et al., 1999; Parker, Doyle, Ward, & Peppas, 2000), it may be difficult to develop a model that is personalized to individual patients because the model parameters may not be readily estimated from the limited measurements available (Dalla Man, Micheletto, Sathananthan, Vella, & Cobelli, 2016; Messori, Toffanin, Del Favero, De Nicolao, Cobelli, & Magni, 2016; Piccinini, Dalla Man, Vella, & Cobelli, 2016; Toffanin, Visentin, Messori, Di Palma, Magni, & Cobelli, 2017; Visentin, Dalla Man, & Cobelli, 2016). Daily adaptation of physiological model was proposed recently (Dalla Man et al., 2016; Messori et al., 2016; Piccinini et al., 2016; Toffanin et al., 2017; Visentin et al., 2016). Alternatively, data-driven models offer a simpler structure that is sufficient for online prediction yet computationally tractable for online and adaptive estimation, thus able to capture the time-varying relationships among the system variables (Araghinejad, 2013; Cherkassky & Mulier, 2007; Cinar, Turksoy, & Hajizadeh, 2016; Turksoy et al., 2016a, 2017, 2014, 2016b; Wang, Wu, & Mo, 2013). Once such relationships are identified, they can be used to train models that complement or replace physiological models.

In general, empirical models predict the future glucose values based on a combination of either the predicted or measured current and historical glucose signals. Such types of models can be divided into linear and nonlinear models. For linear models, AR (autoregressive) or ARX (autoregressive with exogenous inputs) modeling methods were developed by using the current and previous BG values or adding exogenous inputs. Since these models usually consider the output predictions to be a linear combination of the model inputs, the model parameters can be readily updated online. The advantages of using linear methods are simplicity, computational tractability, and rapid convergence of the model parameters without the onerous demands of requiring abundant training data. The disadvantage is that, for more reliable prediction results, the ARX models need information that cannot be captured or computed autonomously in real time applications (such as carbohydrate content of meals, concentration of some hormones, etc.). For nonlinear modeling approaches, a large training dataset is typically required to characterize the nonlinear temporal dynamics of blood glucose metabolism, while the learning algorithms may be more time-consuming and computationally expensive. However, a personalized nonlinear dynamic model may result in more accurate predictions, provided the training data are sufficient to identify the nonlinear relationships.

A recent trend is to construct a hybrid data-driven model (Azmi, Araghinejad, & Kholghi, 2010) through the combination of various model types (linear/nonlinear or AR/ARX) obtained from different modeling algorithms (See & Abrahart, 2001). Nevertheless, an inherent challenge of designing the BGC predictor through hybrid models is to ensure that different data-driven models are appropriately combined and coordinated with a suitable decision-making mechanism. Along this direction, recent work (Stahl, Johansson, Renard, & IEEE, 2012) used a probabilistic framework approach to combine three parallel predictors using a soft switcher derived from the Bayesian model averaging technique to find the best individual predictor.

Motivated by the above considerations, an online data-driven prediction strategy is proposed in this work that employs filtering fusion and a decision-making mechanism for accurate glucose concentration predictions in people with T1D. Considering the complexities of glucose dynamics, it is not practical to develop a universal/global prediction model for all subjects. A more suitable approach is to train a personalized model using present and historical data from CGM sensors. Since the characteristics of various kinds of adaptive filters may be better suited to different dynamic processes, training sizes, time-variant and noise environments, the filter fusion methodology is utilized and the parameters of each filter are appropriately designed so that the overall combinational filter can be used in various situations for online glucose prediction. The linear adaptive filters (recursive least squares [RLS] and extended recursive least squares [EX-RLS]) generally require less data for updating the model parameters than the nonlinear kernel-based filters (kernel recursive least squares [KRLS] and extended kernel recursive least squares [EX-KRLS]) (Liu, Principe, & Haykin, 2011). However, kernel-based filters usually have better prediction results than the linear filters if the data are inherently nonlinear. Furthermore, a decision-making mechanism for filter fusion is proposed based on different prediction performance indices to guide the overall output of the filter to have better prediction accuracy than the individual filters. The accuracy of the proposed predictor is demonstrated by predicting the glucose measurements of *in silico* and clinical subjects. The performance of fusion filtering method is also compared with each of the adaptive filtering models for short-term (5–30 min) online glucose prediction. The rest of this paper is organized as follows. Section 2 outlines the four adaptive filtering algorithms and analyzes their characteristics. Then, a detailed description of the model selection and filtering fusion mechanism for online glucose prediction is developed. Section 3 contains the description of the computational experiments and the accompanying results. Section 4 presents the highlights of the experiments as well as a discussion of the findings. Section 5 concludes the paper.

2. Methodology

2.1. Hybrid models with different adaptive filtering algorithms

To improve the accuracy of online prediction, adaptive filters (Goodwin & Sin, 2014), various candidate models with unique and distinguished characteristics are applied to obtain candidate data-driven models. Based on the complex features of the glucose dynamics, recursive least squares (RLS) (Haykin, 2008), extended recursive least squares (EX-RLS) (Sayed, 2003), kernel recursive least squares (KRLS) (Engel,