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Short-Term Diabetes Blood Glucose Prediction Based On Blood Glucose Measurements

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***Abstract*— Insulin Dependent Diabetes Mellitus (IDDM) is a chronic disease characterized by the inability of the pancreas to produce sufficient amounts of insulin. Daily compensation of the deficiency requires 4-6 insulin injections to be taken daily, the aim of this insulin therapy being to maintain normoglycemia—*i.e.*, a blood glucose level between 4-7 mmol/L. To determine the quantity and timing of these injections, various different approaches are used. Currently, mostly qualitative and semi-quantitative models and reasoning are used to design such a therapy. Here, an attempt is made to show how system identification and control may be used to estimate predictive quantitative models to be used in design of optimal insulin regimens.**

The system was divided into three subsystems, the insulin subsystem, the glucose subsystem and the insulin-glucose interaction. The insulin subsystem aims to describe the absorbtion of injected insulin from the subcutaneous depots and the glucose subsystem the absorbtion of glucose from the gut following a meal. These subsystems were modeled using compartment models and proposed models found in the literature. Several black-box models and grey-box models describing the insulin/glucose interaction were developed and analysed. These models were fitted to real data monitored by a IDDM patient. Many difficulties were encountered, typical of biomedical systems: Non-uniform and scarce sampling, time-varying dynamics and severe nonlinearities were some of the difficulties encountered during the modeling. None of the proposed models were able to describe the system accurately in all aspects during all conditions. However, all the linear models shared some dynamics. Based on the estimated models, short-term blood glucose predictors for up to two-hour-ahead blood glucose prediction were investigated.

PREFACE

In January 2002, the first author was diagnosed with Diabetes Type 1 and soon realized the difficulty of maintaining normoglycemia. The question was raised whether control theory could be applied to the problem. To analyze the system using methods of control theory, a model of the system is essential. This paper is an attempt to estimate such a model based on home-monitored data, typically found in a diabetes diary. The models used were primarily linear and were found to be partly insufficient to describe the system.

I. INTRODUCTION

Diabetes Mellitus is a disease characterized by the inability of the pancreas to produce sufficient amounts of insulin. To cover the deficiency 4-6 insulin injections have to be taken daily, the aim being to keep the blood glucose level as constant as possible. To determine the amount and timing of these injections different approaches are used. Mostly qualitative and semi-quantitative models and reasoning are used to design such a therapy. Most patient monitor their blood glucose using personal glucose meters, and determine their own insulin injections based on these results. Poorly controlled blood glucose levels may result in severe complications. Hypoglycemia, low glucose levels, may lead to brain damage [3], coma and eventually death. Hyperglycemia, high blood glucose, on the other hand, can result in chronic damages such as retinopathy, kidney failure and amputation.

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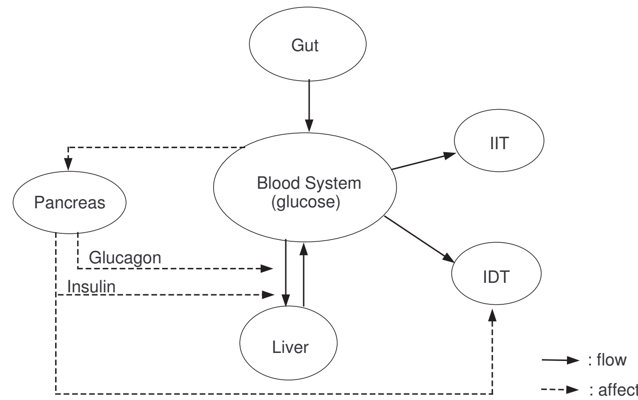

Fig. 1. Overview of the glucoregulatory system.IIT = Insulin Independent Tissue. IDT = Insulin Dependent Tissue.

The purpose of this paper is to evaluate various different data-based modeling approaches to Diabetes Mellitus. Based on daily monitoring of blood glucose, these models will be used for prediction of future blood glucose values as support for determination of insulin therapy. To find the best model different validation criteria will be used. Given data on present and previous blood glucose values, the aim is to predict the glycemic behavior for the next two hours with a reasonable accuracy. This target accuracy is defined as a standard deviation of the prediction error less than 0.5 mmol/l. Although cross validation was used, the models were estimated and validated using primarily one patient's data. It would be preferable to validate the models using other patients data as well, but due to the scarcity of data this was not possible. This is of course a severe limitation, which has to be regarded seriously when evaluating the validity of the models.

The glucoregulatory system controls glucose metabolism and

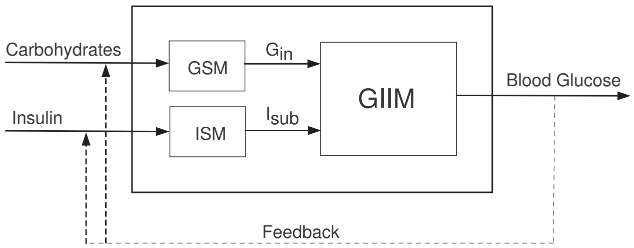

Fig. 2. The partitioning of the system.

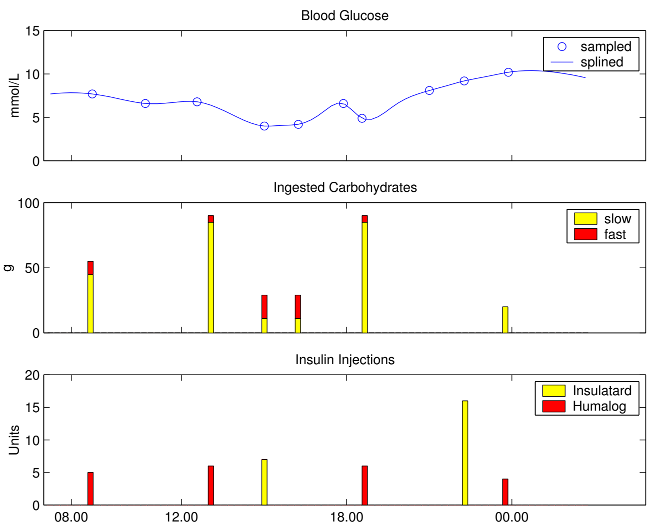

Fig. 3. A typical day.

the insulin/glucose mechanisms needed to maintain normoglycemia [2], [5], [6], [11]. In Fig. 1, a simplified overview of the flow of glucose and insulin between the most important organs relevant for this system. For modeling purposes the system will be considered to consist of three main parts; the Glucose Sub-Model (GSM), the Insulin Sub-Model (ISM) and the Glucose/Insulin interaction Model (GIIM). The GSM describes the absorbtion of glucose from meal, the ISM the absorbtion of insulin from insulin injections and the GIIM the interaction of glucose and insulin in the blood system and organs. These three parts will be modeled separately using mainly compartment models and linear black-box models [10], [9]. Previous quantitative approaches to data-based modeling include [4], [1], [13], [12], [8], [7]. In particular, Sparacino *et al.* presented low-complexity prediction strategies (prediction horizon 30 [min]) based on continuous blood glucose measurement [12].

II. Methods

A. Data Acquisition and Reconstruction

The blood glucose data primarily used in this paper was collected during the first six months of a newly diagnosed type-1 patient. The glucose testing was undertaken using a personal blood glucose tester, Accu-check Compact, Roche Diagnostics. Meals, insulin injections and glucose samples were noted and registered in a diary. In Fig. 3 a typical day can be seen, with the scheduled samplings as well as some unscheduled samplings. The blood glucose curve was reconstructed using spline interpolation with resample period $h = 15$ [min].

B. Input Modeling

The GSM and ISM were modelled using mainly compartment models fitted to absorption profiles found in the literature.

C. System identification

For comparison, a variety of system identification methods were used—*e.g.*, ARMAX-based linear regression, ARMAX-based linear regression, Wiener model identification, subspace-based identification [9]. Subsequently, 8-step-ahead optimal prediction—*i.e.*, two-hour ahead prediction—was made by means of Kalman filter [9].

The subspace-based approach differs from other approaches in using the state-space representation

$$x_{k+1} = Ax_k + Bu_k + \omega_k \quad (1)$$

$$y_k = Cx_k + Du_k + \upsilon_k \quad (2)$$

This system is equivalent to the innovations model:

$$x_{k+1} = Ax_k + Bu_k + Ke_k \quad (3)$$

$$y_k = Cx_k + Du_k + e_k \quad (4)$$

D. Model Validation

The data were divided in two parts; one part for estimation and one for validation. Model validation of the estimated models were made according to statistical model validation criteria including Akaike information criterion (AIC), final prediction error (FPE), minimum description length (MDL), variance accounted for (VAF), root-mean-square error (RMS), residual correlation [9].

III. Results

A. Data Reconstruction Quality

As result of detrending, the glucose data were reduced by the average over the two weeks. No obvious outliers could be found in the data series. To evaluate the reconstruction method 56 patients data records, sampled every 5:th minute using a MiniMed system, were used. These data were resampled up to once every third hour and then reconstructed using the same method as for the Accu-Check data. In Fig. 4, a comparison between the original MiniMed data and the resampled/spline-interpolated data of a representative patient can be seen. Rapid and large fluctuations within the normal range of a diabetic make it suitable as a reference. The sampling of the Accu-Check data during day-time is close to 100 min. The average RMS between the 100 min signal and the original MiniMed signal is less than 1 mmol/L for the 56 patient data records.

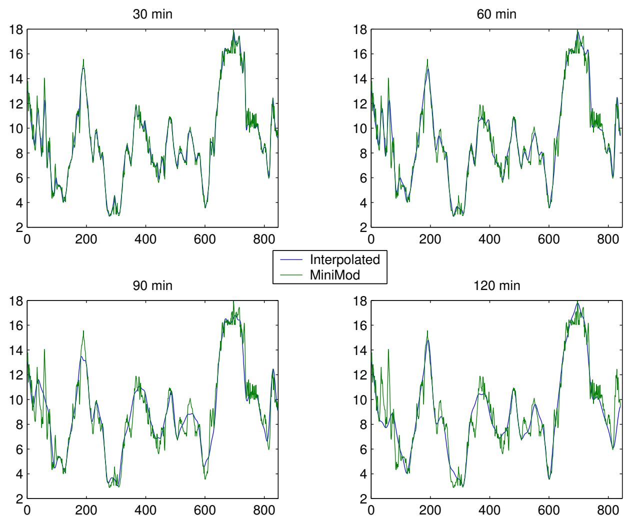

Fig. 4. Comparison between the reconstructed data and the original data for some different resampling frequencies.

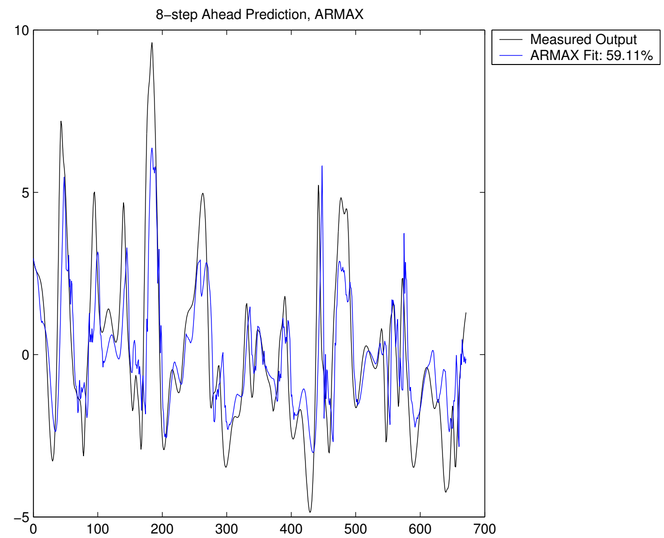

Fig. 6. 8-step-ahead prediction, ARMAX.

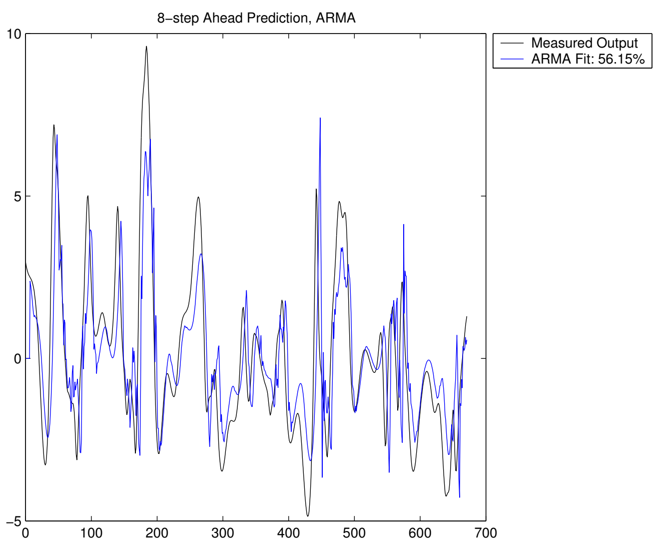

Fig. 5. 8-step-ahead prediction, ARMA.

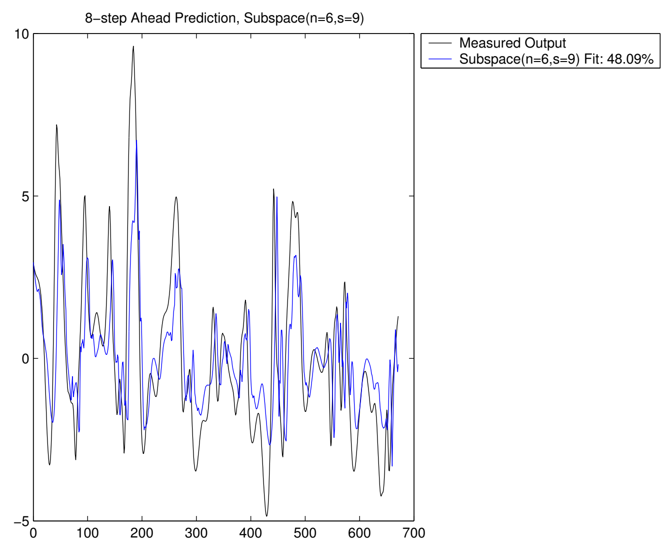

Fig. 7. 8-step ahead prediction, Subspace.

B. *Prediction*

In Fig. 5, the 8-step (or 2h) ahead optimal prediction on the validation data using this model is shown. The predictive capabilities of the subspace-based models and the Wiener-models were impressive. In Figs. 7-9, the 8-step prediction of the $n = 6$, $s = 9$ can be seen. The VAF was significantly lower than for the ARMAX model. Using a Wiener model with a polynomial to represent an output nonlinearity is also rewarding. The prediction now improves somewhat (Fig. 9).

IV. Discussion

The problem of modeling diabetes has many difficulties. The data used in this paper were collected from a newly diagnosed IDDM patient. The fact that only data from one patient was used raises the question of validity for the application of the results in other patients. Many of the problems and properties with the studied system are however general and relevant for modeling of other diabetics as well. The energy intake was considered to consist solely of slow and fast carbohydrates. As food contains two other major sources of energy, (*i.e.*, fat and protein), this assumption is not true. Metabolic conversion of fat and proteins into glucose and free fatty acids (FFA) would also take place.

As for methodology, further efforts need to be spent on system identification for non-uniformly sampled data, meal models, exercise models and logarithmic transformations.

V. Conclusions

The purpose of this paper was to develop and evaluate different models of IDDM, based on one patient's data. The aim was to be able to predict blood glucose values two

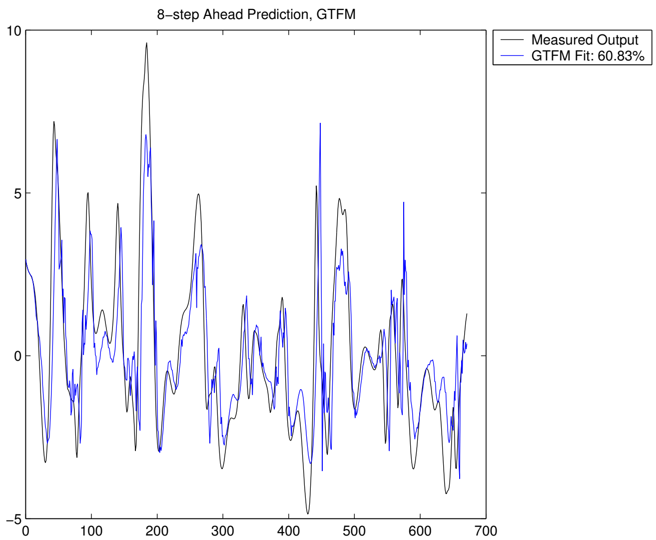

Fig. 8. 8-step ahead prediction, General Transfer Function Model.

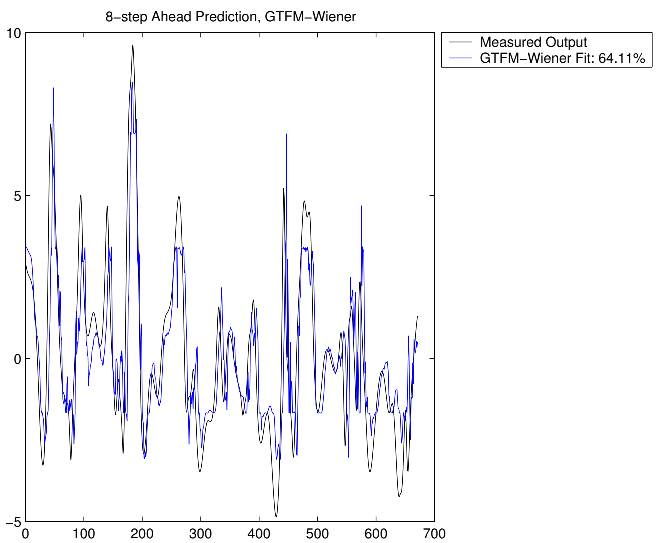

Fig. 9. 8-step ahead prediction, GTFM-Wiener.

hours ahead with a prediction error smaller than 1 mmol/l in 95 % of the cases. Whereas the best models—*i.e.*, the log-normalized linear model based on subspace-based identification and the GTFM-Wiener model—did not quite meet our accuracy target of 0.5 [mmol/l], the predictors of Figs. 5-9 to various degree of accuracy predicting hypoglycemia and hyperglycemia. For a comparison between the different models predictive capability, see Fig. 10. The time variations over of the day have to be considered carefully. If the dynamics shift over the day, different parameter sets of the model have to be considered, one for each segment of the day, for which the parameters can be considered fixed.

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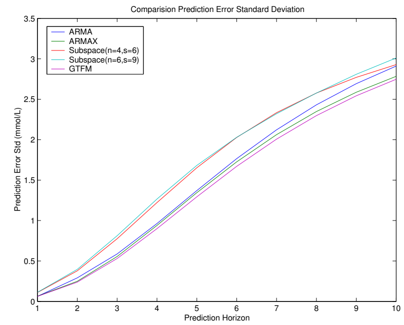

Fig. 10. The prediction standard deviation vs. prediction horizon.

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References

[1] R. Bellazzi, P. Magni, and G. De Nicolao. Bayesian analysis of blood glucose time series from diabetes home monitoring. *IEEE Trans. Biomedical Engineering*, 47(7):pp. 971–975, July 2000.

[2] R.N. Bergman and C. Cobelli. Minimal modeling, partition analysis, and the estimation of insulin sensitivity. *Federation Proceedings*, 39(1):pp. 110–115, January 1980.

[3] G.-J. Biessels. Cerebral complications of diabetes: clinical findings and pathogenetic mechanisms. *The Netherlands Journal of Medicine*, 54:pp. 35–45, 1999.

[4] T. Bremer and D.A. Gough. Is blood glucose predictable from previous values? A solicitation for data. *Diabetes*, 48:pp. 445–451, March 1999.

[5] C. Cobelli and A. Mari. Validation of mathematical models of complex endocrine-metabolic systems. a case study on a model of glucose regulation. *Medical and Biological Eng. and Comput.*, 21:pp. 390–399, 1983.

[6] C. Cobelli, G. Nucci, and S. Del Prato. A physiological simulation model of the glucose-insulin system. *Proc. First Joint BMES/EMBS Conference*, page 999, 1999.

[7] D. J. Cox, L. Gonder-Frederick, L. Ritterband, W. Clarke, and B. P. Kovatchev. Prediction of severe glycemia. *Diabetes Care*, 30(6):1370–1373, 2007.

[8] P. Dua, F. J. Doyle III, and E. N. Pistikopoulos. Model-based blood glucose control for type-1 diabetes via parametric programming. *IEEE Trans. Biomedical Eng.*, 53(8):1478–1491, 2006.

[9] R. Johansson. *System Modeling and Identification*. Prentice Hall, Englewood Cliffs, NJ, 1993.

[10] F. Kajiya, S. Kodama, and H. Abe, editors. *Compartmental Analysis: Medical Applications and Theoretical Background*. Karger, 1984.

[11] G. Nucci and C. Cobelli. Models of subcutaneous insulin kinetics. a critical review. *Computer Methods and Programs in Biomedicine*, 62:pp. 249–257, 2000.

[12] G. Sparacino, F. Zanderigo, S. Corazza, A. Maran, A. Facchinetti, and C. Cobelli. Glucose concentration can be predicted ahead in time from continuous glucose monitoring sensor time-series. *IEEE Trans. Biomedical Eng.*, 54(5):931–937, 2007.

[13] F. Ståhl. Diabetes mellitus modelling based on blood glucose measurements. Master Thesis TFRT-5703, Dept. Automatic Control, Lund University, Sweden, April 2003.