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Patient-specific performance evaluation for insulin control systems

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Abstract— **We consider an assessment of various insulin control systems through classification by means of different performance characteristics, such as risk of hypoglycemia, hyperglycemia and overall risk. The approach is based on specific, measured patient data under standard insulin therapy. An adaptive prediction technique is used to estimate the differences in blood glucose values produced by control actions that differ from the standard therapy.**

I. INTRODUCTION

Diabetes disturbs a natural metabolic control mechanism which uses endogenous insulin production to keep blood glucose (BG) in the correct range, and so it is natural that the basic therapeutic approach consists of approximating the natural control action by having the patient deciding on the external insulin amount to be delivered. To be more exact, the patient estimates the correct amount of insulin in order to keep his BG in an euglycemic range, which is commonly understood between 70 and 180 mg/dl. Too high doses lead to BG under 70 mg/dl (hypoglycemia) and too small doses can cause the BG to be above 180 mg/dl (hyperglycemia). Unfortunately, this estimation is not always correct, as both the quality of the information on the state of the patient and the delivery channels are very different from the natural ones.

Against this background, there has been much work over decades to develop an automatic replacement for the natural metabolic system, a so-called artificial pancreas, and intensive research has been conducted to develop suitable control algorithms [1], [2], [3], [4]. As experiments cannot and frequently may not be performed on humans in a fully reproducible way, different approaches have been developed to allow the evaluation of control methods, in particular the *in silico* testing approach developed by Italian and US researchers [5], [6], [7], [8], [9] and accepted as a preliminary step for the initial testing.

The only disadvantage of this approach is that *in silico* testing is based on plausible models, but on no specific patient. To estimate the impact of different control strategies on a specific patient, for whom measurements but no individual model are available, a different approach is needed. For preliminary, raw classification we refer the reader to control variability grid analysis [10], a graphical representation of minimum / maximum glucose values in a population of patients either real or virtual.

As the natural bottom line of a new control approach is the performance of the actual one, this paper is based on a comparison of the performance of the standard therapy - as measured - with the modified advice a control would have provided. To do this, the paper first proposes a classification of the control performance of any control approach (including the standard therapy) based on risk of hypoglycemia, hyperglycemia and overall risk. Then it uses these measures together with an adaptive prediction to estimate the differences consequent upon a different dosage as produced, for instance, by a distinct control action.

Automatic comparison between different strategies using real data is shown to coincide with the medical evaluation.

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II. DATA COLLECTION

The data collection was reviewed and approved by the Centre d' Investigation Clinique de Montpellier, France. It includes six separate datasets (patients: P101, P102, P104, P115, P119, P130), which were recorded under disturbance free conditions. This study population consists of subjects with type 1 diabetes receiving multiple daily injection therapy. We randomized 2 women and 4 men with a mean ($\pm$SD) age 42.00$\pm$16.55 years, BMI 23.15$\pm$4.14 kg/m^2, and body weight 66.42$\pm$13.21 kg. The subjects are healthy apart from their diabetes. Their diabetes-related characteristics are the mean duration after diagnosis of diabetes 15.83$\pm$3.66 years and the mean hemoglobin A1c 8.08$\pm$1.18. Likewise, they do not present clinically overt diabetes complications.

Subjects were hospitalized for 72-hours and kept their standard insulin therapy. It included insulin injections (control actions), which were delivered before every meal. The insulin dosage was adjusted by patients and was based on the current BG value and the amount of meal carbohydrates. Abbott FreeStyle Navigator^{TM} [11] was used as continuous BG monitoring system. The BG information was taken at ten minute intervals. If hyperglycemic events occurred, the subjects were prescribed a dose of correction insulin.

III. METHODS

A. Performance Evaluation

The performance evaluation is based on patient-specific postprandial BG values. After each control action, that is, an insulin advice given at the meal time, postprandial BG values, which are measured within a previously selected time of interest, are recorded. In our case, the time of interest starts

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ten minutes after an insulin injection and ends three hours after the injection time. Since the main impact of the control actions is represented in the postprandial BG values, other values are not taken into consideration.

It is well known, that the BG scale is asymmetric: the hyperglycemic range is much wider than the hypoglycemic range (see e.g. [5]). To be more exact, we have hypoglycemic BG $\in [0, 70]$ mg/dl and hyperglycemic BG $\in [180, \infty)$ mg/dl with the median of about 100 mg/dl. In order to estimate the risk due to hypo- and hyperglycemic BG values, we normalize the values according to [12] by using:

$$f(BG, \alpha, \beta) = (\ln(BG))^{\alpha} - \beta, \tag{1}$$

where $\alpha, \beta > 0$ are sample independent parameters determined from the assumptions:

$$f(800, \alpha, \beta) = -f(20, \alpha, \beta), \tag{2}$$

and

$$f(180, \alpha, \beta) = -f(70, \alpha, \beta). \tag{3}$$

These assumptions give $\alpha = 1.084$ and $\beta = 5.381$. Now, the centrum of the BG values is 0, negative values correspond to lower than median BG values, positive values to higher than median BG values, respectively. The BG measurements which are symmetrized in this way can be transformed to risk values by using the risk function:

$$r(BG) = 10 \times (\gamma f(BG, \alpha, \beta))^2 \times \text{sign}(f(BG, \alpha, \beta)), \tag{4}$$

with a scaling parameter $\gamma = 1.509$. Note, that we have modified the original risk function (cf. [5], [13]) by the signature term in order to emphasize the difference between hyper- and hypoglycemic BG values. The risk function ranges from -100 to 100. We obtain negative risk values for hypo- and positive risk values for hyperglycemic BG measurements.

The controller performance can be easily evaluated by three indexes that are defined below. Consider a series of $n \geq 1$ postprandial BG values $x_1, x_2, ..., x_n$. The low BG risk index ($LBGI$) is defined as:

$$LBGI = -\frac{1}{n} \sum_{i=1}^{n} \left(r(x_i) \times I_{\{r(x_i)<0\}} \right), \tag{5}$$

with the indicator function $I_{\{A\}}$, where $I_{\{A\}} = 1$ if the condition A holds, and 0 otherwise. According to [14] this index provides a classification of patients with regard to their long-term risk for hypoglycemia. To be more exact: minimal-risk for $LBGI \in [0.0, 1.1)$, low-risk for $LBGI \in [1.1, 2.5)$, moderate-risk for $LBGI \in [2.5, 5.0)$ and high-risk for $LBGI \in [5.0, \infty)$. It has also been used for short term prediction of hypoglycemia [14], [15], [16]. The second index is the high BG risk index ($HBGI$):

$$HBGI = \frac{1}{n} \sum_{i=1}^{n} \left(r(x_i) \times I_{\{r(x_i)>0\}} \right). \tag{6}$$

TABLE I
STANDARD THERAPY PERFORMANCE FOR PATIENT P102

	LBGI	HBGI	OBGI
P102	0.21	5.93	6.14

The third one - the overall BG risk index ($OBGI$)- we define as $OBGI = LBGI + HBGI$. Table I gives an example of the performance of the standard insulin therapy for patient P102. Obviously, these performance characteristics can be calculated for every proposed controller on condition that the consequent BG values are given. Clearly, lowest risk indexes characterize the best controller.

B. Blood Glucose Prediction

The BG values that are dependent on insulin advices that differ from the standard therapy have to be calculated, in order to apply the proposed performance evaluation. The calculation method presented in this section is based on measured postprandial BG values, on a patient-specific insulin sensitivity factor, and on a personal rate of appearance of insulin.

Note that any other prediction technique can be employed here (see for example [18]). For the sake of simplicity we give the preference to a conventional method resting upon parameters as used by clinicians in practice.

The personal insulin sensitivity factor (ISF), or correction factor, gives the amount by which the blood glucose is reduced by one unit of short-acting insulin in a period of two to three hours. It is typically between 30 and 50 mg/dl. This parameter can be estimated from the collected data or provided by the clinician in charge. Please note, that ISF is a stochastic value. It gains on accuracy with increasing sample size $m \geq 1$. Consider a series of m different ISF measurements $ISF_1, ISF_2, ..., ISF_m$. Obviously, ISF is normally distributed. This implies the following $100(1-\epsilon)\%$ asymptotic confidence interval $ISF \in$

$$\Big[\sum_{i=1}^{m} \frac{ISF_i}{m} + t_{\frac{\epsilon}{2}} \sqrt{\frac{m}{m-1} \left(\sum_{i=1}^{m} ISF_i^2 - \left(\sum_{i=1}^{m} \frac{ISF_i}{m^2} \right)^2 \right)}, \sum_{i=1}^{m} \frac{ISF_i}{m} - t_{\frac{\epsilon}{2}} \sqrt{\frac{m}{m-1} \left(\sum_{i=1}^{m} ISF_i^2 - \left(\sum_{i=1}^{m} \frac{ISF_i}{m^2} \right)^2 \right)} \Big], \tag{7}$$

where $t_{\frac{\epsilon}{2}}$ is obtained from Student's t-distribution tables. Thus, the accuracy of the prediction depends on the accuracy of estimation of ISF.

Furthermore, ISF can also be calculated by the 1500-rule developed by P. Davidson (see e.g. [17]). According to this rule the personal ISF is given by $ISF=$ 1500/(TotalDailyInsulinDose).

We use the rate of appearance of insulin $Ra(t)$ which is calculated from specific patient parameters, such as weight and plasma insulin, according to [6], [19]. Clearly, this rate

represents the insulin absorption process, which starts at time $t = 0$ of an insulin injection and ends after about three hours, that is, $t = 180$. Fig. 1 illustrates this rate for patient P102. The change in the BG values due to an insulin injection that differs from the standard injection can be calculated as follows: Let, for $t \in [0, 180]$, $x(t)$ denote the measured BG values, $\hat{x}(t)$ the estimation of BG values which result from non-standard injection, and ΔI the difference in the insulin amount. We obtain

$$\hat{x}(t) = x(t) - \Delta I \int_0^t \theta Ra(t)dt, \tag{8}$$

with the scaling parameter θ which is determined from

$$\int_0^{180} \theta Ra(t)dt = ISF. \tag{9}$$

Fig.2 illustrates the original and predicted BG of patient P102 for $ISF = 26.31$ and $\Delta I = -3$. We apply this technique to every control action and get an estimation of postprandial BG values, which are then used for performance evaluation.

IV. Results

We consider the comparison of the performance characteristics of the standard therapy, as described in the second section, with the modified control advices. The results serve as an example of assessment of an arbitrary number of distinct controllers. We start with a short description of the controller which we employ in this paper as our example. Note that any controller can be examined analogously.

A. Modified Controller

We illustrate the concept of performance comparison on modified control advices which are based on a transfer function model of the patient with two inputs (cf. [20]): carbohydrate impulses $u_1(t)$ and insulin impulses $u_2(t)$

$$y(t) = \frac{K_1}{(1+sT_1)^2 s} u_1(t) + \frac{K_2}{(1+sT_2)^2 s} u_2(t). \tag{10}$$

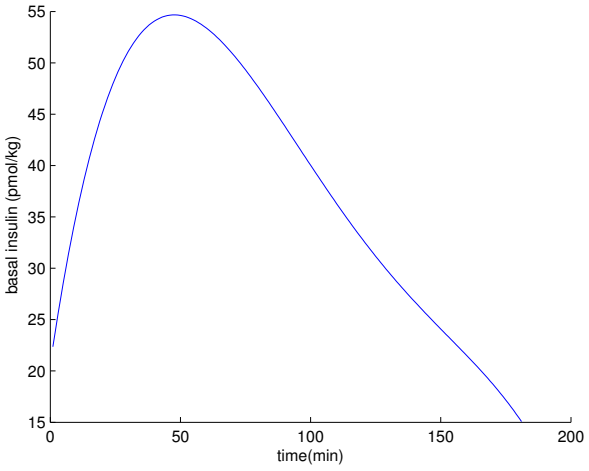

Fig. 1. Rate of appearance of insulin of patient P102

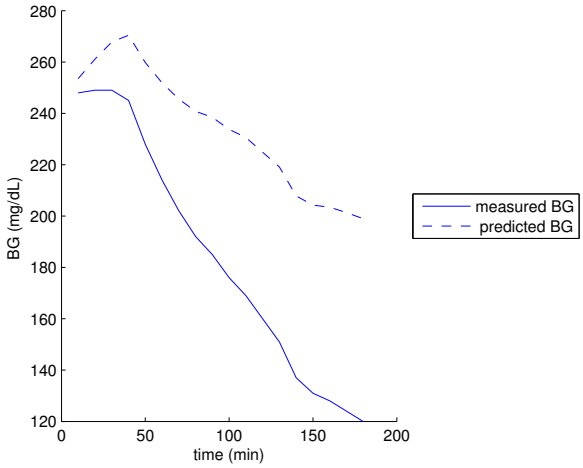

Fig. 2. Measured BG and predicted BG of patient P102

The two parameters used to calculate control advices are the carbohydrate sensitivity K_1 and the insulin sensitivity K_2, that are estimated from postprandial-breakfast data. In the event of a meal, the controller calculates an insulin advice I_{meal} according to (11) where $BG_{current}$ is the latest available BG value, BG_{ref} is the defined target (blood) glucose concentration to reach, and CHO is the amount of meal carbohydrates. Note that this advice only relies upon a single BG measurement.

$$I_{meal} = \frac{CHO \times K_1 + BG_{current} - BG_{ref}}{-K_2} \tag{11}$$

In the absence of meals, the controller might give correction advices on both insulin I_{corr} (12) and carbohydrates CHO_{corr} (13), if the blood glucose exceeds a target range. Note that therefore, continuous BG measurements are necessary to monitor the actual glucose concentration. The threshold values of 200 mg/dl and 80 mg/dl were chosen according to current clinical practice.

$$I_{corr} = \frac{BG(t) - BG_{ref}}{-K_2}, \text{ if } BG(t) > 200 \text{ mg/dl} \tag{12}$$

$$CHO_{corr} = \frac{BG(t) - BG_{ref}}{-K_1}, \text{ if } BG(t) < 80 \text{ mg/dl} \tag{13}$$

For a more detailed description of this controller, we refer the interested reader to [20].

Fig.3 illustrates the results for patient P102: Continuous BG values and the carbohydrate intakes are shown at the top, the standard therapy insulin advices in the middle, and the modified control advices at the bottom of the figure. Since our performance evaluation is based on meal time insulin advices, we omit the carbohydrate correction intakes here. Consider area a): The BG value is about 100 mg/dl, the patient applies 6 units of insulin (standard therapy), and the modified controller suggests to use 12 units, that is $\Delta I = 6$. Obviously, this control advice would result in a

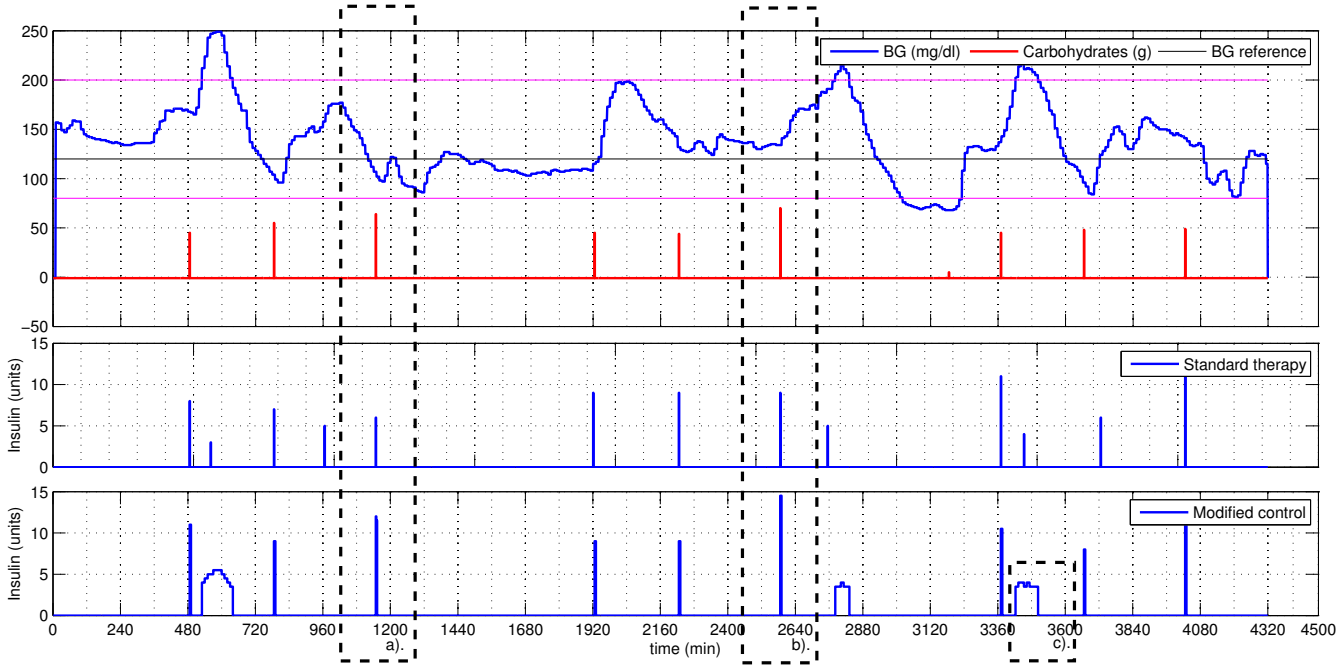

Fig. 3. Standard therapy vs. modified controller insulin advices together with BG time series and carbohydrate intakes for the hospitalization period of patient P102

TABLE II
STANDARD THERAPY PERFORMANCE

	LBGI	HBGI	OBGI
P101	0.06	5.77	5.83
P102	0.21	5.93	6.14
P104	0.14	14.84	14.98
P115	0.35	6.84	7.19
P119	0.01	7.15	7.17
P130	0.47	19.19	19.66

rapid decrease in BG values. Consider area b). now: The BG value is 130 mg/dl, clearly the patient applies more insulin than in a)., that is, 8 units. The modified controller suggests 14.5 units ($\Delta I = 6.5$). For the sake of clarity, view area c).: The modified controller repeatedly recommends a dose of 4 units insulin. Note that this recommendation will last until the patient applies insulin or the BG value reaches an euglycemic range.

B. Performance Evaluation and Assessment

The performance characteristics of the standard therapy can directly be evaluated from the measured BG data. Table II illustrates the indexes $LBGI$, $HBGI$, $OBGI$ for patients under study.

In order to evaluate the performance of the modified controller, the proposed blood glucose prediction technique is applied to all measured postprandial blood glucose values before computing the risk indexes (see Fig.4). The insulin correction factor ISF is computed using the 1500-rule or estimated from the breakfast-data (cf. modified controller parameter K_2). The modified controller performance characteristics for both cases are shown in Table III and Table IV, respectively.

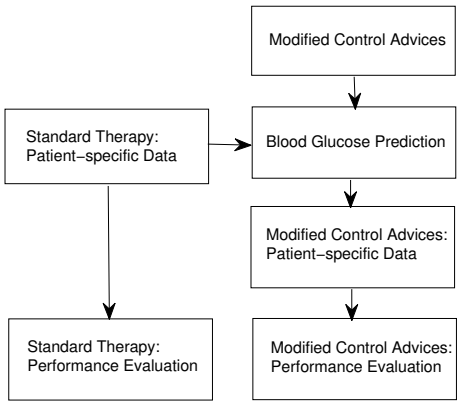

Fig. 4. Flowchart - performance evaluation

It can be easily seen, that the indexes strongly depend on the chosen ISF. Note that the sample size (72 hours) for

TABLE III

MODIFIED CONTROLLER PERFORMANCE (1500-RULE ISF)

	LBGI	HBGI	OBGI
P101	0.00	13.17	13.17
P102	3.27	3.86	7.14
P104	0.11	20.92	21.03
P115	4.61	4.41	9.02
P119	0.11	6.01	6.12
P130	3.84	14.94	18.78

TABLE IV

MODIFIED CONTROLLER PERFORMANCE (ISF ESTIMATED FROM THE DATA)

	LBGI	HBGI	OBGI
P101	0.00	21.21	21.21
P102	3.00	3.87	6.87
P104	0.11	28.58	28.69
P115	9.09	3.57	12.66
P119	0.04	6.08	6.12
P130	5.98	16.04	22.02

ISF which is calculated from the data could be insufficient for a precise estimation. We recommend a bigger sample size. This parameter has to be estimated very carefully or be evaluated by a clinician. Nevertheless, the qualitative results, which we present next, are only marginally affected.

In order to evaluate the controls, single performance indexes have to be compared. Next two tables (Table V, Table VI) illustrate the results of the controller assessment. A "$+$" denotes risk indexes that were reduced by the modified controller, a "$-$" denotes risk indexes that were raised by the modified controller, and "0" means a change of risk index of less than 20%.

The proposed modified control advices cause a decrease

TABLE V

MODIFIED CONTROLLER ASSESSMENT (1500-RULE ISF)

	LBGI	HBGI	OBGI
P101	+	-	-
P102	-	+	0
P104	0	-	-
P115	-	+	-
P119	-	0	0
P130	-	+	0

TABLE VI

MODIFIED CONTROLLER ASSESSMENT (ISF ESTIMATED FROM THE DATA)

	LBGI	HBGI	OBGI
P101	+	-	-
P102	-	+	0
P104	+	-	-
P115	-	+	-
P119	-	0	0
P130	-	0	0

TABLE VII

MODIFIED CONTROLLER ASSESSMENT - BREAKFAST DATA (1500-RULE ISF)

	LBGI	HBGI	OBGI
P101	0	-	-
P102	0	+	+
P104	0	0	0
P115	-	+	+
P119	0	0	0
P130	0	+	+

TABLE VIII

MODIFIED CONTROLLER ASSESSMENT - BREAKFAST DATA (ISF ESTIMATED FROM THE DATA)

	LBGI	HBGI	OBGI
P101	0	-	-
P102	0	+	+
P104	0	-	-
P115	-	+	+
P119	0	0	0
P130	-	+	0

in risk of hyperglycemia $HBGI$, but also an increase in risk of hypoglycemia $LBGI$ for most subjects under study. Since more weight is attached to low BG values, it is clear that slightly lower BG values, which result in a decrease in $HBGI$, make the $LBGI$ significantly increase and the overall risk becomes much higher.

Note, that the presented modified controller uses estimators K_1, K_2 computed from breakfast-postprandial BG values, that is, it is optimized for breakfast data. Thus, the risk indexes calculated for the breakfast values (see Table VII and Table VIII) are smaller than in the overall case.

V. CONCLUSIONS

The present contribution was concerned with the patient-specific assessment of insulin control systems based on a risk based performance evaluation and on adaptive BG prediction. Performance results were shown for the standard therapy, applied by the patients, and for the modified control advices, which were automatically evaluated. The results illustrated a patient-specific increase or decrease in risk values.

The presented approach can analogously be applied not only to two, but to an arbitrary number of distinct controllers. For use in practice the authors recommend big sample sizes for parameter estimation, risk calculation and validation. Due to the easy interpretation this assessment technique points out the best (patient-specific) controller, and, by this means, can be used for a faster development of insulin control systems.

VI. ACKNOWLEDGMENTS

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REFERENCES

[1] R.S. Parker, E.P. Gatzke,F.J. Doyle, "Advanced Model Predictive Control (MPC) for Type I Diabetic Patient Blood Glucose Control", in *American Control Conference*, Chicago, Illinois, USA, pp. 3483 - 7,2000.

[2] Y. Wang, E. Dassau, F.J. Doyle, "Closed-Loop Control of Artificial Pancreatic -Cell in Type 1 Diabetes Mellitus Using Model Predictive Iterative Learning Control ", *IEEE Transactions on Biomedical Engineering*, vol. 57, no. 2, pp. 211 - 9,2010.

[3] H. Kirchsteiger, L. Del Re, E. Renard,M. Mayrhofer, "Robustness Properties of Optimal Insulin Bolus Administrations for Type 1 Diabetes", in *American Control Conference (ACC)*, St. Louis, MO, USA, pp. 2284 - 9, 2009.

[4] E. Ruiz-Velazquez, R. Fermat, D.U. Campos-Delgado, "Blood Glucose Control for Type 1 Diabetes Mellitus: A Robust Tracking H inf problem", *Control Engineering Practice*, vol. 12, no. 9, pp. 1179 - 95,2004.

[5] C. Cobelli, C. Dalla Man, G. Sparacino, L. Magni, G. De Nicolao, B.P. Kovatchev, "Diabetes: Models, Signals, and Control", *IEEE Reviews in Biomedical Engineering*, vol. 2, pp 54 - 96 , 2009.

[6] C. Dalla Man, R. A. Rizza, C. Cobelli, "Meal Simulation Model of the Glucose-Insulin System", *IEEE Transactions on Biomedical Engineering*, vol. 54, pp. 1740 - 1749, 2007.

[7] G. Castillo Estrada, H. Kirchsteiger, L. Del Re, E. Renard, "Innovative Approach for Online Prediction of Blood Glucose Profile in Type 1 Diabetes Patients", in *American Control Conference*, Baltimore, Maryland, USA, pp. 2015 - 20, 2010.

[8] J.T. Sorensen, "A Physiologic Model of Glucose Metabolism in Man and its use to Design and Assess Improved Insulin Therapies for Diabetes", PhD thesis, University of California, Berkeley, 1978.

[9] F. Stahl, R. Johansson, "Diabetes mellitus modeling and short-term prediction based on blood glucose measurements", *Mathematical Biosciences*, vol. 217, pp. 101 - 17, 2009.

[10] L. Magni, D. M. Raimondo, C. Dalla Man, M. Breton, S. Patek, G. De Nicolao, C. Cobelli, and B. P. Kovatchev, "Evaluating the Efficacy of Closed-Loop Glucose Regulation via Control-Variability Grid Analysis", *Journal of Diabetes Science and Technology*, vol. 2, pp. 1 - 6, 2008.

[11] Abbott Diabetes Care, *www.abbottdiabetescare.com.*

[12] B. P. Kovatchev, D. J. Cox, L. A. Gonder-Frederick, and W. L. Clarke, "Symmetrization of the blood glucose measurement scale and its applications", *Diabetes Care*, vol. 20, pp. 1655 - 1658, 1997.

[13] B. P. Kovatchev, M. Straume, D. J. Cox, and L. S. Farhy,"Risk analysis of blood glucose data: A quantitative approach to optimizing the control of insulin dependent diabetes", *J. Theoretical Medicine*, vol. 3, pp. 1 - 10, 2001.

[14] B. P. Kovatchev, D. J. Cox, A. Kumar, L. A. Gonder-Frederick, and W. L. Clarke, "Algorithmic evaluation of metabolic control and risk of severe hypoglycemia in type 1 and type 2 diabetes using Self-Monitoring Blood Glucose (SMBG) Data", *Diabetes Technol. Therapeutics*, vol. 5, no. 5, pp. 817 - 828, 2003.

[15] D. J. Cox, L. A. Gonder-Frederick, L. Ritterband, W. L. Clarke, and B. P. Kovatchev, "Prediction of severe hypoglycemia", *Diabetes Care*, vol. 30, pp. 1370 1373, 2007.

[16] B. P. Kovatchev, D. J. Cox, L. S. Farhy, M. Straume, L. A. Gonder-Frederick, and W. L. Clarke, "Episodes of severe hypoglycemia in type 1 diabetes are preceded, and followed, within 48 hours by measurable disturbances in blood glucose", *J. Clin. Endocrinol. Metab.*, vol. 85, pp. 4287 - 4292, 2000.

[17] P. C. Davidson, H. R. Hebblewhite, R. D. Steed, B. W. Bode, "Analysis of Guidelines for Basal-Bolus Insulin Dosing: Basal Insulin, Correction Factor, and Carbohydrate-to-Insulin Ratio", *Endocrine Practice*, vol. 14, no.9, pp. 1095 - 1101, 2008.

[18] V. Naumova, S. Pereverzev, S. Sampath, "Reading Blood Glucose from Subcutaneous Electric Current by Means of a Regularization in Variable Reproducing Kernel Hilbert Spaces", to be published in *IEEE Conference on Decision and Control and European Control Conference*, Orlando, FL, USA, 2011.

[19] H. Trogmann, H. Kirchsteiger,L. Del Re, "Hybrid Control of Type1 Diabetes Bolus Therapy", in *IEEE Conference on Decision and Control*, Atlanta, GA, USA, 2010.

[20] H. Kirchsteiger, G. Castillo Estrada, S. Plzer, E. Renard, L. Del Re, "Estimating Interval Process Models for Type 1 Diabetes for Robust Control Design", to be published in *IFAC World Congress*, Milano, Italy, 2011.

[21] DIAdvisor,*www.diadvisor.eu*