2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

Automated Adaptation of Insulin Treatment in Type 1 Diabetes

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Abstract— **Individuals with type 1 diabetes (T1D) need life-long insulin therapy to compensate for the lack of endogenous insulin due to the autoimmune damage to pancreatic beta-cells. Treatment is based on *basal* and *bolus* insulin, to cover fasting and postprandial periods, respectively, according to three insulin dosing parameters: basal rate (BR), carbohydrate-to-insulin ratio (CR), and correction factor (CF). Suboptimal BR, CR, and CF profiles leading to incorrect insulin dosing may be the cause of undesired glycemic events, which carry dangerous short-term and long-term effects. Therefore, correct tuning of these parameters is of the utmost importance. In this work, we propose a new algorithm to optimize insulin dosing parameters in individuals with T1D who use a continuous glucose monitor and an insulin pump. The algorithm was tested using the University of Virginia/Padova T1D Simulator and led to an improvement in the quality of glycemic control. Future efforts will be devoted to test the algorithm in human clinical trials.**

I. Introduction

In type 1 diabetes (T1D), life-long insulin replacement is needed to compensate for the practically absent internal insulin secretion deriving from the autoimmune destruction of pancreatic beta-cells [1]. Consequently, the quality of glycemic control in T1D is heavily dependent on multiple daily treatment decisions by the patient, to account for a wide variety of factors influencing insulin demand, e.g., circadian rhythms, physical activity, food, and stress. In this context, despite the improving accuracy of glucose monitoring devices [2],[3], the availability of modern insulin analogs [4], and the growing proliferation of new technologies [3],[5]-[7], glycemic control remains a challenge in T1D [8], with complication rates and excess mortality still significantly higher when compared to the general population [9],[10].

Traditionally, intensive insulin treatment implemented through continuous subcutaneous insulin infusion (CSII, also referred to as insulin pump therapy), includes *basal insulin* administered to cover the overnight and fasting periods, and *bolus insulin* given with meals to cover carbohydrate consumption and correct postprandial hyperglycemia, in an attempt to mimic insulin secretion in health [11]. However, insulin therapies are not as efficient as the natural endogenous insulin secretion, and suboptimal insulin dosing is still common in the management of T1D, causing potentially life-threatening hypoglycemic episodes [12],[13] and/or sustained hyperglycemia which in turn leads to the development and progression of long-term diabetes comorbidities [14],[15]. Therefore, individuals with T1D face a life-long optimization challenge [16]: to reduce average blood glucose (BG) while simultaneously avoiding hypoglycemia, which has been indicated as the limiting factor in the management of diabetes [13].

To help individuals with T1D solve this problem, technological options are available, in the form of open-loop decision support systems [17],[18] or closed-loop automated insulin delivery (i.e., the artificial pancreas) [19],[20]. Especially in the former case but also in the latter, the optimal trade-off between glycemic control and iatrogenic hypoglycemia is typically achieved through periodical reviews of BG traces, to adjust daily profiles of basal rate (BR) – i.e., the amount of basal insulin delivered throughout the day – and carbohydrate-to-insulin ratio (CR) and correction factor (CF) – i.e., parameters used to dose prandial insulin. If a glycemic pattern is identified, optimized insulin dosing parameters (i.e., optimized BR, CR, and CF profiles) are calculated and implemented. This can be a time-consuming and onerous task, requiring data to be downloaded from multiple devices and subjectively evaluated. In this context, innovative digital technologies represent a promising alternative to lessen the burden on health care providers and provide an objective way to analyze data and extract information otherwise not readily available.

In this work, we introduce a novel method to optimize insulin dosing parameters in individuals with T1D who use a continuous glucose monitoring (CGM) system and follow CSII therapy. The method relies on CGM data (i.e., BG measurements collected and stored every five minutes), basal and bolus insulin records, and meal information to provide weekly recommendations on optimal BR, CR, and CF profiles to be deployed by the user. Here, we present results obtained by testing the optimization algorithm in an FDA-accepted simulation environment known as the University of Virginia/Padova T1D Simulator [21]-[23]. The simulation platform includes a large, fully-identified model of glucose metabolism in T1D and a population of 100 virtual adult subjects displaying key metabolic behaviors observed in the general population of individuals with T1D. In simulation, the algorithm was successful at identifying underlying glycemic patterns and correcting insulin therapy, thereby improving the overall quality of glycemic control.

II. Materials and Methods

A. Optimization of Basal Insulin Dosing

BR is optimized weekly relying on an algorithm which assesses the impact of BR alone (i.e., in the absence of meals and boluses) on the glycemic levels. In summary, the method uses an individualized model of glucose metabolism capable of describing the glycemic response to meals and insulin, thus enabling to parse out the effect of BR and prandial disturbances on BG fluctuations. The model receives as inputs injected insulin (J), consumed meals (M),

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and a residual metabolic signal needed to explain the experimental data (ω). Optimal BR is computed as the insulin input to the model, that allows to maintain the BG response flat at the desired target BG (here, 110 mg/dL), in the presence of ω while setting the meal input to zero.

In detail, the method relies on the following three steps.

1. Individualization of the metabolic model. The metabolic model used within the algorithm can be written as the following discrete-time, linear, time-invariant model:

$$\begin{aligned} x(k+1) &= Ax(k) + B_{ins}J(k) + B_{meal}M(k) + B_{\omega}\omega(k) \\ y(k) &= Cx(k) \end{aligned} \quad (1)$$

where k is the discrete timestamp; x is the metabolic state vector including plasma glucose concentration, insulin concentration in the subcutaneous space and in plasma, insulin action, and amount of carbohydrates in the stomach and gut; y is the model output coinciding with plasma glucose concentration; and A, B_{ins}, B_{meal}, B_{ω}, and C are state-space matrices describing the interaction between glucose and insulin in the presence of a meal. To reflect individual metabolic behaviors, the model is identified on the available CGM data, inputting known J and M to the model, while setting ω to zero. Model identification is performed using maximum-a-posteriori Bayesian estimation, relying on prior knowledge on the metabolic parameters available from the literature. The interested reader is referred to [24] for a more detailed description of the model, the meaning of the various parameters, and the formulation of the estimation problem.

2. Estimation of ω. The residual metabolic signal ω is estimated by regularized deconvolution via inversion of the individualized model outlined above, to capture unmodeled phenomena and glucose dynamics, thereby allowing to well-describe the experimental CGM data. The theoretical bases for the computation of ω are detailed in [24].

3. Estimation of the optimal BR. Upon estimation of ω, a second model inversion is performed, again by regularized deconvolution, to determine the optimal insulin input that allows to obtain a BG profile flat at around 110 mg/dL, in the absence of any meal input but considering ω.

The described procedure is performed for each day, providing daily optimal BR traces. Then, at the end of each week, the median BR across days is computed to determine the final BR profile to be deployed over the following week.

B. Optimization of Prandial Insulin Dosing

In addition to BR, the algorithm provides optimal values of prandial dosing parameters (i.e., CR and CF), based on the placement of the average minimum postprandial BG (*mPBG*) via minimization of its variance while controlling for the amount of tolerated exposure to hypoglycemia.

In the algorithm, *mPBG* is described by a linear model with the classical prandial predictors:

$$\begin{aligned} mPBG = BG_{TGT} + \beta_{BG}(BG_{meal} - BG_{TGT}) + \\ + \beta_{CHO}CHO_{meal} + \beta_{ins}INS_{meal} \end{aligned} \quad (2)$$

where BG_{TGT} is the target postprandial BG (here set at 110 mg/dL); BG_{meal}, CHO_{meal}, and INS_{meal} are mealtime CGM value, meal carbohydrate amount, and meal-related insulin dose; and the βs are model parameters identified using historical data and a weighted least-square estimator with regularization terms on the parameters based on the subject's current CR and CF values. The model is identified for each 30-min timespan of the day (48 identifications in total), with weights assigned to meal events that decrease exponentially with the datapoint absolute age and its distance from the current identification timespan in terms of time of day.

In the *mPBG* model of Eq. (2), INS_{meal} can be controlled through the typical prandial insulin dosing formula:

$$INS_{meal} = \frac{CHO_{meal}}{CR} + \frac{BG_{meal} - BG_{TGT}}{CF}. \quad (3)$$

If Eq. (3) is substituted in Eq. (2), an expression depending on CR and CF is obtained. Thus, the following optimization problem can be formulated to determine CR and CF:

$$\begin{aligned} &\min_{CR,CF} STD(mPBG) \\ &\text{s.t. } AVG(mPBG) - \gamma STD(mPBG) = thHypo \end{aligned} \quad (4)$$

where $STD(\cdot)$ and $AVG(\cdot)$ are the standard deviation and average operators, and γ (set to 1.5) and *thHypo* (set to 70 mg/dL) are aggressiveness parameters determining the amount of tolerated hypoglycemia. If BG_{meal} and CHO_{meal} are assumed to be independent random variables with finite variance, $STD(mPBG)$ and $AVG(mPBG)$ can be written as:

$$\begin{aligned} STD(mPBG) &= \sqrt{\theta_{CHO}^2 VAR(CHO_{meal}) + \theta_{BG}^2 VAR(BG_{meal})} \\ AVG(mPBG) &= BG_{TGT} + \theta_{CHO}AVG(CHO_{meal}) + \\ &+ \theta_{BG}AVG(BG_{meal}) \end{aligned} \quad (5)$$

where $VAR(\cdot)$ is the variance operator, AVG and VAR of CHO_{meal} and BG_{meal} are computed empirically using the same weighting schema used above, and θ_{CHO} and θ_{BG} are:

$$\theta_{CHO} = \beta_{CHO} + \frac{\beta_{INS}}{CR} \text{ and } \theta_{BG} = \beta_{BG} + \frac{\beta_{INS}}{CF}. \quad (6)$$

Given Eq. (5), the minimization problem outlined in Eq. (4) is a quadratic problem in θ_{CHO} and θ_{BG} with constraints. The constraint gives a conic section that is sampled and from which the minimum-$VAR(mPBG)$ point is extracted. From the optimal θ_{CHO} and θ_{BG} (one for each 30-min timespan), relying on Eq. (6) and the values of the βs obtained from the identification of the model in Eq. (2) in the same timespans, optimal CR and CF values are obtained.

The interested reader is referred to [25] for a comprehensive description of the outlined method.

C. Simulation Testing

The optimization algorithm was tested in a 6-week simulation study including 100 virtual subjects with T1D. BG and insulin/meal records were available throughout the study.

Three treatment arms were simulated: a) control arm treated with original insulin dosing parameters built in the simulating platform and factory-designed for each virtual subject (ORIG); b) control arm treated with altered insulin dosing parameters obtained by imposing random deviations with respect to the original parameter configuration (MOD);

c) experimental arm treated with dosing parameters optimized at the end of each study week and deployed over the week following the optimization, starting from the altered parameter configuration defined in the previous arm (OPT).

During each study day, each virtual subject received three meals: breakfast (B), lunch (L), and dinner (D). Meals time and amount were sampled from uniform distributions with the following supports: [0600-0800] and [30-50] grams of carbohydrates (grCHO) for B, [1200-1400] and [60-80] grCHO for L, and [1800-2000] and [40-60] grCHO for D.

Metabolic and behavioral variability were included in the simulations to render the virtual study more realistic. Metabolic variability was generated by imposing daily patterns in insulin sensitivity, based on circadian variability observed in real-world data [23]. Behavioral variability was generated by including snacks given between meals ([15-25] grCHO at [0930-1030] and [1530-1630]), carbohydrate counting errors (up to 30% of the real amount), and bolus delays (up to 60 mins after the meal was consumed).

Treatment arms for each virtual subject were identical, with the same meals and metabolic/behavioral variability.

Algorithm performance was assessed using established metrics of glycemic variability and quality of glycemic control, including: average, standard deviation, and coefficient of variation of BG values; time spent in the target glycemic ranges of 70-140 and 70-180 mg/dL; time spent in the hypoglycemic range <54 and <70 mg/dL; and time spent in the hyperglycemic range >180 and >250 mg/dL. For each arm, these metrics were computed weekly from the BG traces. The comparison of week 6 to week 1 in OPT, focusing on time spent in 70-180 mg/dL (TIR), <70 mg/dL (TBR), and >180 mg/dL (TAR), was the primary analysis. All results are reported as mean ± standard deviation across subjects.

III. Results

Out of the 100 subjects, 50/50 subjects had their original therapy modified to generate insulin over/under dosing.

In OPT, TIR improved from 57.5% ± 21.9% in week 1 to 80.4% ± 13.8% in week 6; TBR improved from 9.3% ± 13.6% to 1.5% ± 3.1%; and TAR improved from 33.2% ± 27.6% to 18.1% ± 14.1%. These results are also summarized in Figure 1, where the evolution of TIR, TBR, and TAR across the six study weeks is displayed for the three treatment arms. An exhaustive comparison between week 1 and week 6 in the OPT treatment arm is presented in Table I.

TABLE I. ALGORITHM PERFORMANCE.

	Week 1	Week 6
BG average [mg/dL]	156.9 ± 47.4	143.4 ± 19.4
BG standard deviation [mg/dL]	44.9 ± 15.6	38.3 ± 14.2
BG coefficient of variation [%]	29.9 ± 10	26.1 ± 6.7
Time in 70-140 mg/dL [%]	35.7 ± 22	55.7 ± 14.4
Time in 70-180 mg/dL [%]	57.5 ± 21.9	80.4 ± 13.8
Time below 54 mg/dL [%]	2.2 ± 3.5	0.2 ± 0.6
Time below 70 mg/dL [%]	9.3 ± 13.6	1.5 ± 3.1
Time above 180 mg/dL [%]	33.2 ± 27.6	18.1 ± 14.1
Time above 250 mg/dL [%]	9.4 ± 15.2	2.9 ± 6.3

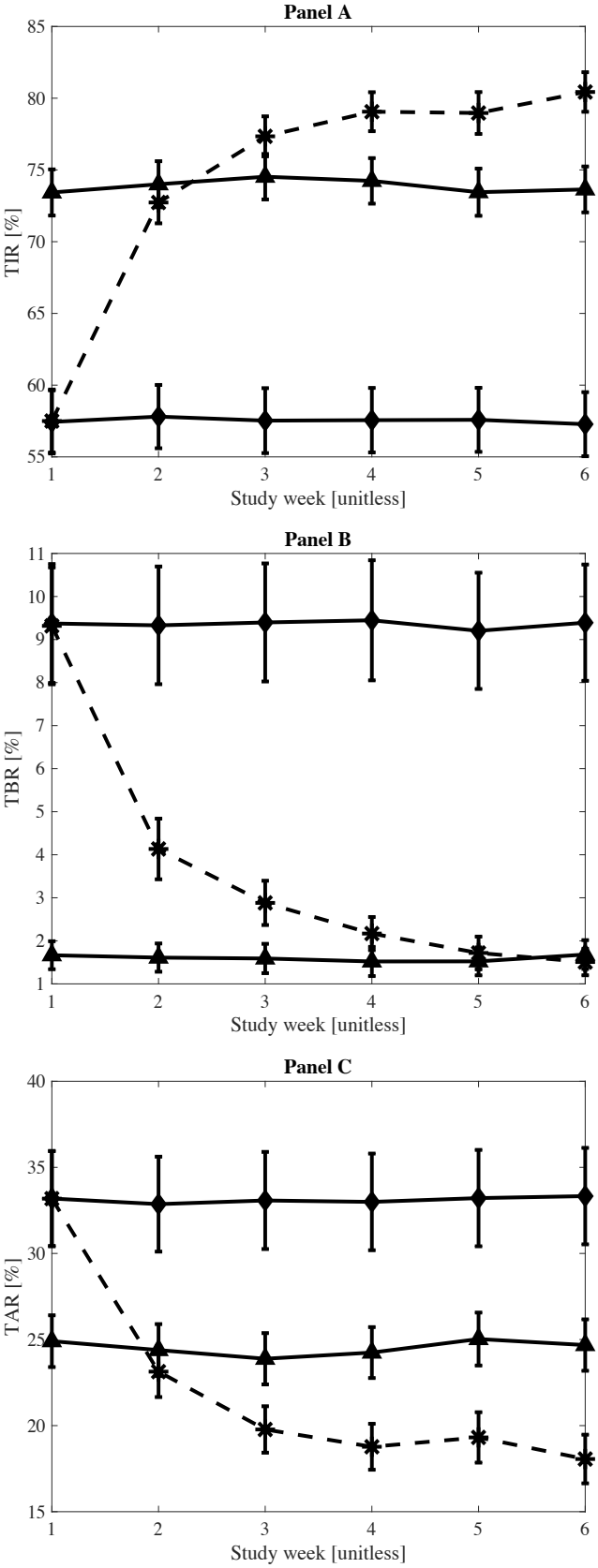

Figure 1. Evolution of TIR (Panel A), TBR (Panel B), and TAR (Panel C) across the six study weeks, comparing the three treatment arms (ORIG: solid line and triangles; MOD: solid line and diamonds; OPT: dashed line and stars).

IV. Discussion

Insulin dosing parameters are needed to make daily treatment decisions in T1D. Wrong parameters are common due to the difficulty of extracting relevant information from the large amount of available data (e.g., CGM, insulin records, meal records). Suboptimal insulin dosing resulting from incorrect dosing parameters may lead to dangerous glycemic events, like hypoglycemia [13] – which if not promptly treated can lead to coma and death – and sustained hyperglycemia and elevated glycemic variability [14] – both identified as independent risk factors for the development and progression of long-term diabetes comorbidities.

New technologies like the artificial pancreas and more general decision support systems have helped the management of T1D and improved the quality of glycemic control [17]-[20]. At the core of these technologies, optimal insulin dosing parameters are needed to maximize system performance and reduce the risk for low/high-BG episodes.

In this work, we proposed an adaptive method to optimize insulin dosing parameters in individuals with T1D who use CGM and follow CSII therapy. The method relies on CGM data, insulin records, and meal information to provide recommendations to patients about optimal dosing parameters to use, based on the analysis of glycemic patterns extracted from previous individual data collected in the field. A proof-of-concept in silico study demonstrated that the method performs well in simulation, increasing time spent in the target euglycemic range, while reducing exposure to hypoglycemia, hyperglycemia, and glycemic variability.

The presented algorithm has large potential if embedded within decision support systems to provide suggestions to patients upon request or on a regular schedule (e.g., weekly), regarding needed therapy modifications. The method can also be personalized to reflect individual treatment preferences (e.g., overnight and postprandial glycemic targets). Further, the method can be extended to work in the presence of different insulin therapies (e.g., multiple daily insulin injections or within an artificial pancreas).

V. Conclusions

This paper introduces a novel algorithm to optimize insulin dosing parameters in individuals with T1D using CGM and CSII therapy. The method was successful in simulation studies. Clinical testing will be performed next, to further validate the technology.

References

[1] American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2014;37(S1):81-90.

[2] Klonoff DC, Prahalad P. Performance of Cleared Blood Glucose Monitors. J Diabetes Sci Technol. 2015;9(4):895-910.

[3] Klonoff DC, Ahn D, Drincic A. Continuous Glucose Monitoring: A Review of the Technology and Clinical Use. Diabetes Res Clin Pract. 2017;133:178-92.

[4] Hirsch IB. Insulin Analogues. N Engl J Med. 2005;352(2):174-83.

[5] Sherwin RS, Tamborlane WV, Genel M, Felig P. Treatment of Juvenile-Onset Diabetes by Subcutaneous Infusion of Insulin with a Portable Pump. Diabetes Care. 1980;3(2):301-8.

[6] Garg S, Brazg RL, Bailey TS, Buckingham BA, Slover RH, Klonoff DC, Shin J, Welsh JB, Kaufman FR. Reduction in Duration of Hypoglycemia by Automatic Suspension of Insulin Delivery: The In-Clinic ASPIRE Study. Diabetes Technol Ther. 2012;14(3):205-9.

[7] Forlenza GP, Li Z, Buckingham BA, Pinsker JE, Cengiz E, Wadwa RP, Ekhlaspour L, Church MM, Weinzimer SA, Jost E, Marcal T, Andre C, Carria L, Swanson V, Lum JW, Kollman C, Woodall W, Beck RW. Predictive Low-Glucose Suspend Reduces Hypoglycemia in Adults, Adolescents, and Children with Type 1 Diabetes in an At-Home Randomized Crossover Study: Results of the PROLOG Trial. Diabetes Care. 2018;41(10):2155-61.

[8] Beck RW, Miller KM, Foster NC. The T1D Exchange Clinic Network and Registry: 10 Years of Enlightenment on the State of Type 1 Diabetes in the United States. Diabetes Technol Ther. 2019;21(6):310-2.

[9] Lind M, Svensson AM, Kosiborod M, Gudbjörnsdottir S, Pivodic A, Wedel H, Dahlqvist S, Clements M, Rosengren A. Glycemic Control and Excess Mortality in Type 1 Diabetes. N Engl J of Med. 2014;371(21):1972-82.

[10] Nishimura R, LaPorte RE, Dorman JS, Tajima N, Becker D, Orchard TJ. Mortality Trends in Type 1 Diabetes. Diabetes Care. 2001;24(5):823-7.

[11] Waldhäusl WK. The Physiological Basis of Insulin Treatment—Clinical Aspects. Diabetologia. 1986;29(12):837-49.

[12] Cryer PE. Hypoglycaemia: The Limiting Factor in the Glycaemic Management of Type I and Type II Diabetes. Diabetologia. 2002;45(7):937-48.

[13] Cryer PE. Hypoglycemia: The Limiting Factor in the Management of IDDM. Diabetes. 1994;43(11):1378-89.

[14] Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN, DCCT/EDIC Research Group. Effect of Glycemic Exposure on the Risk of Microvascular Complications in the Diabetes Control and Complications Trial -- Revisited. Diabetes. 2008;57(4):995-1001.

[15] The Diabetes Control and Complications Trial Research Group. The Relationship of Glycemic Exposure (HbA1c) to the Risk of Development and Progression of Retinopathy in the Diabetes Control and Complications Trial. Diabetes. 1995;44(8):968-83.

[16] Cryer PE. Glycemic Goals in Diabetes: Trade-off Between Glycemic Control and Iatrogenic Hypoglycemia. Diabetes. 2014;63(7):2188-95.

[17] Breton MD, Patek SD, Lv D, Schertz E, Robic J, Pinnata J, Kollar L, Barnett C, Wakeman C, Oliveri M, Fabris C, Chernavvsky D, Kovatchev BP, Anderson SM. Continuous Glucose Monitoring and Insulin Informed Advisory System with Automated Titration and Dosing of Insulin Reduces Glucose Variability in Type 1 Diabetes Mellitus. Diabetes Technol Ther. 2018;20(8):531-40.

[18] Fabris C, Nass RM, Pinnata J, Carr KA, Koravi CLK, Barnett CL, Oliveri MC, Anderson SM, Chernavvsky D, Breton MD. The Use of a Smart Bolus Calculator Informed by Real-Time Insulin Sensitivity Assessments Reduces Postprandial Hypoglycemia Following an Aerobic Exercise Session in Individuals with Type 1 Diabetes. Diabetes Care. 2020;43(4):799-805.

[19] Kovatchev BP, Renard E, Cobelli C, Zisser H, Keith-Hynes P, Anderson SM, Brown SA, Chernavvsky DR, Breton MD, Pelletier MJ, Place J, Bruttomesso D, Del Favero S, Visentin R, Filippi A, Scotton R, Doyle FJ 3rd. Feasibility of Outpatient Fully Integrated Closed-Loop Control: First Studies of Wearable Artificial Pancreas. Diabetes Care. 2013;36(7):1851-8.

[20] Fabris C, Kovatchev BP. The Closed-Loop Artificial Pancreas in 2020. Artif Organs. 2020;44(7):671-9.

[21] Kovatchev BP, Breton MD, Dalla Man C, Cobelli C. In Silico Preclinical Trials: A Proof of Concept in Closed-Loop Control of Type 1 Diabetes. J Diabetes Sci Technol. 2009;3(1):44-55.

[22] Dalla Man C, Micheletto F, Lv D, Breton MD, Kovatchev BP, Cobelli C. The UVA/Padova Type 1 Diabetes Simulator: New Features. J Diabetes Sci Technol. 2014;8(1):26-34.

[23] Visentin R, Campos-Nanez E, Schiavon M, Lv D, Vettoretti M, Breton M, Kovatchev BP, Dalla Man C, Cobelli C. The UVA/Padova Type 1 Diabetes Simulator Goes from Single Meal to Single Day. J Diabetes Sci Technol. 2018;12(2):273-81.

[24] Hughes J, Gautier T, Colmegna P, Fabris C, Breton MD. Replay Simulations with Personalized Metabolic Model for Treatment Design and Evaluation in Type 1 Diabetes. J Diabetes Sci Technol. 2020; https://doi.org/10.1177/1932296820973193.

[25] Gautier T. A Data-Driven Control Strategy Adaptation Applied to Diabetes Meal Glucose Management. Doctoral Dissertation, University of Virginia. 2020.