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Computer-aided system with machine learning components for generating medical recommendations for type 1 diabetes patients

Abstract

The paper presents an original method for processing medical data from a type 1 diabetes patient, with the aim of generating therapeutic recommendations to improve the quality of patient care. The article summarizes the results of the first phase of research in this area, which focused on identifying mathematical models and selecting algorithmic methods for further verification in clinical settings. The problem under study is characterized by high complexity, the need to tailor the method to the available data, and, in the completed stage of the research, the inability to perform experiments beyond computer simulations. The proposed approach introduces several novel solutions, including the development of a computer model of a person with diabetes, an original time-series similarity criterion for blood glucose concentration, and the innovative application of a genetic algorithm. The use of the genetic algorithm proved to be effective. The method was developed for patients using an insulin pump and a continuous glucose monitoring system. In the research section, data from five real patients were analyzed using the developed method, and the results indicated that it may be effective in supporting real-world therapy.

1. INTRODUCTION

1.1. Therapy of type 1 diabetes as the problem of control

From an engineering perspective, type 1 diabetes (T1D) therapy can be viewed as a control problem involving a human operator and specialized medical equipment (Cobelli et al., 2009; Kovatchev, 2019). The type of equipment used affects both the implementation of medical procedures and the format of therapeutic recommendations. The research presented in this study focuses on therapy using an insulin pump and a continuous glucose monitoring (CGM) system.

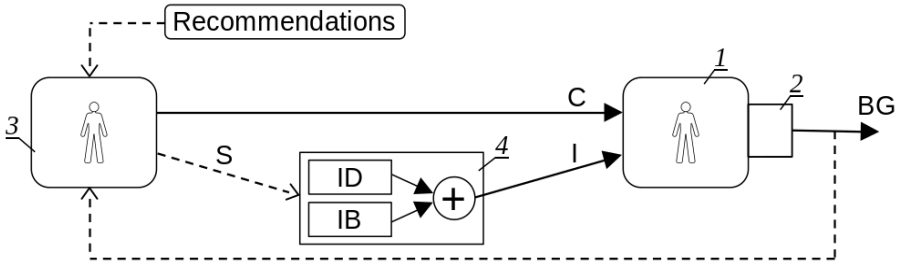

Fig. 1. Therapy of Type 1 Diabetes as a problem of control, 1 – the patient / the object of the control, 2 – CGM / the control object state meter, 4 – the insulin pump, 3 – the caregiver / operator, S – setup, ID – insulin single doses, IB – insulin base (continuous), I – insulin, C – carbohydrates, BG – blood glucose

Figure 1 illustrates the medical scenario analyzed. The therapy is performed for the patient, who also serves as the control object. The condition of this patient/object is their blood glucose concentration (BG), which is monitored by a Continuous Glucose Monitoring (CGM) system worn on the patient's body. In this study, blood glucose concentration is expressed in mg/dl (milligrams of glucose in one deciliter of blood). The operator

may be either the patient's caregiver or the patient. This distinction does not affect the way the therapy is delivered. The operator feeds the patient meals containing carbohydrates (C) and administers insulin (I). The unit of carbohydrate in this study is grams (g). Insulin is delivered by an insulin pump. The operator gives a command (S) to the pump, which then delivers insulin to the patient. In medical practice, insulin is measured in units of insulin U (1U of liquid insulin contains 0.0347 mg of crystalline insulin), and this is the unit used in this study. Insulin is administered in two ways: as an insulin dose (ID) or as an insulin base (IB). Basal insulin is delivered continuously and automatically by the pump according to a programmed schedule stored in the device.

The goal of the control process (therapy) is to maintain the state of the control object (patient) within the target range of BG_{min} = 70 mg/dl to BG_{max} = 130 mg/dl (Hanas, 2022; Kirkman, 2022). Carbohydrates consumed with meals increase blood glucose concentration, while insulin decreases it. In healthy individuals, the body naturally produces adequate amounts of insulin. However, in individuals with impaired insulin production, external insulin administration is necessary. For these patients, each meal represents a disturbance signal *C*, requiring the initiation of a control signal *I*. It is also possible for the blood glucose level to fall below the acceptable threshold. In such cases, carbohydrate must be administered to raise the concentration. In this second scenario, the *C* signal is not considered a disturbance, but rather a control signal. In addition, the supply of glucose to the blood from the patient's liver must be taken into account. This supply is continuous and contributes to an increase in blood glucose levels, which is counteracted by the continuous delivery of basal insulin. However, glucose output from the liver is difficult to estimate.

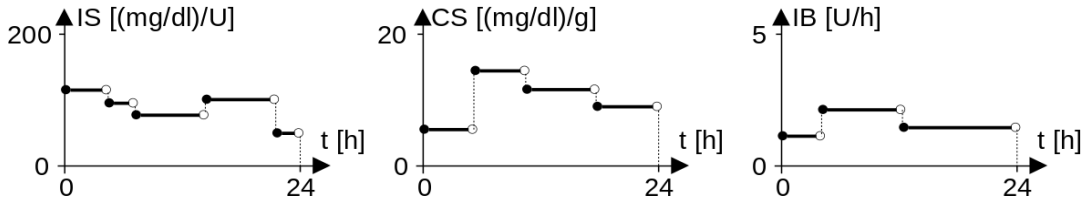

Fig. 2. Typical format of therapeutic recommendations for therapy in diabetes with an insulin pump, IS -insulin sensitivity, CS – carbohydrate sensitivity, IB -insulin base

The procedures performed by the operator are based on therapeutic guidelines provided by medical personnel, referred to as recommendations in the remainder of this paper. In the case of insulin pump use, these recommendations are presented in the form of diurnal-cyclic function step functions, shown schematically in Figure 2. The figure also includes typical ranges for these functions. The recommendations cover insulin sensitivity (IS), carbohydrate sensitivity (CS), and the basal insulin program (IB). Insulin sensitivity defines the decrease in blood glucose concentration following administration of 1U of insulin over the full duration of its action and is expressed in units of (mg/dl)/U. Carbohydrate sensitivity defines the increase in blood glucose concentration following the ingestion and digestion of 1 g of carbohydrate and is expressed in units of (mg/dl)/g. The basal insulin program (commonly referred to as basal insulin) is expressed in units of insulin per hour (U/h). Alternative forms of these parameters may be used in medical practice, but they are derived from those presented here (e.g., insulin-to-carbohydrate ratio, see Equation 3) and are therefore not used in this study. The therapeutic guidelines do not include a meal plan, as the diet of a person with T1D does not differ from that of a healthy person in terms of composition or timing of meals.

After receiving the recommendations (see Figure 1), the caregiver applies them to the treatment process. The basal insulin program is entered into the pump once in the form of a predefined schedule. On the other hand, the caregiver is responsible for performing periodic tasks such as glucose monitoring and meal delivery. Monitoring is performed before each meal, at least twice during the night, and whenever the patient's condition indicates the need. The control procedure involves reading the current blood glucose concentration, referred to as BG_{now}. If this value exceeds the maximum threshold BG_{max}, a correction insulin dose, $ID_{corr,now}$, is administered, calculated according to the following formula:

$$ID_{corr,now} = \frac{BG_{now} - BG_{max}}{IS_{now}} \tag{1}$$

where: IS_{now} – the current value of the insulin sensitivity from the recommendations (e.g. Fig. 2).

If the current blood glucose concentration is below the acceptable threshold BG_{min}, a corrective carbohydrate dose, $C_{corr,now}$, is delivered, calculated using the following formula:

$$C_{corr,now} = \frac{BG_{min} - BG_{now}}{CS_{now}} \tag{2}$$

where: CS_{now} – the current value of carbohydrate sensitivity from the recommendations (e.g. Fig. 2).

The meal delivery action always includes the execution of a control procedure and the administration of an ID_{meal} insulin dose necessary to compensate for the increase in blood glucose resulting from the absorption of the carbohydrates contained in the C_{meal}:

$$ID_{meal} = C_{meal} \frac{CS_{now}}{IS_{now}} \tag{3}$$

where: $\frac{CS_{now}}{IS_{now}}$ can be recognised as an insulin-to-carbohydrate ratio.

1.2. Specifics of type 1 diabetes therapy

T1D is a chronic and incurable disease. Diabetes therapy is ongoing throughout the patient's life, mostly on an outpatient basis. During this time, it is often necessary to modify the therapeutic recommendations. These changes may be due to changes in the patient's lifestyle, environmental conditions, or the emergence of comorbidities. The basis for the development of new therapeutic recommendations is the therapy history record, which includes the carbohydrates consumed *C*, the insulin administered *I=ID+IB*, and the blood glucose levels measured *BG*. An example of such a therapy history record is shown in Figure 3. These data are from the study described in the following sections and correspond to day 4 of the analysis of patient #5. The detailed results presented later in this study refer specifically to this case.

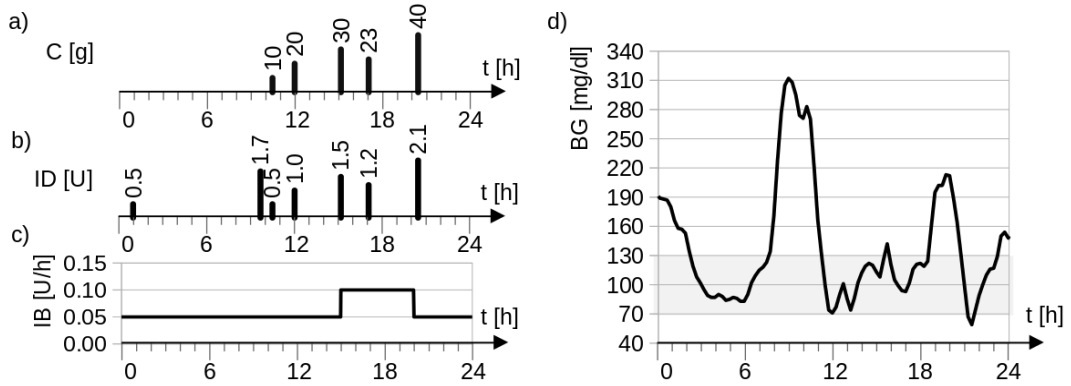

Fig. 3. Example of T1D therapy history record covering a 24-hour period

The sample data comes from the memory of the insulin pump and the CGM system. These data are recorded automatically, without any effort or intervention from the patient. For this reason, they can be referred to as the digital footprint of therapy. In the 24-hour example presented, the patient consumed five meals (Fig. 3a), received seven individual doses of insulin (Fig. 3b), and was given basal insulin according to a simple predefined program (Fig. 3c). The blood glucose concentrations recorded during this period (Fig. 3d) indicate that insulin dosing was inadequate, as glucose levels frequently exceeded the maximum acceptable level, reaching up to 310 mg/dl (!). This patient clearly required the development of new therapeutic guidelines. In all analyses performed, the CGM results were linearly interpolated to determine values for each minute of the day, taking into account the values from the previous and following days.

Figure 4 illustrates the positioning of the expert system designed to generate therapeutic recommendations in the context of ongoing therapy. The time axis emphasizes that the therapy is continuous and cannot be interrupted. The expert system itself is not an active participant in the therapy, which is clearly shown in the diagram. The point labeled „Now” indicates the moment when therapeutic recommendations are changed. It separates the past from the future. The therapy history is known in the context of the recorded digital footprint (e.g. Fig. 3) and serves as input data for the system. Previous therapeutic recommendations are not used as

input data by the system. Once new recommendations are generated, they can be implemented; however, at the moment of implementation, their future effects are not yet known, which is symbolically represented by a „?”. The only possible method to verify the generated recommendations before their implementation is retrospective validation, i.e. validation based on historical data only.

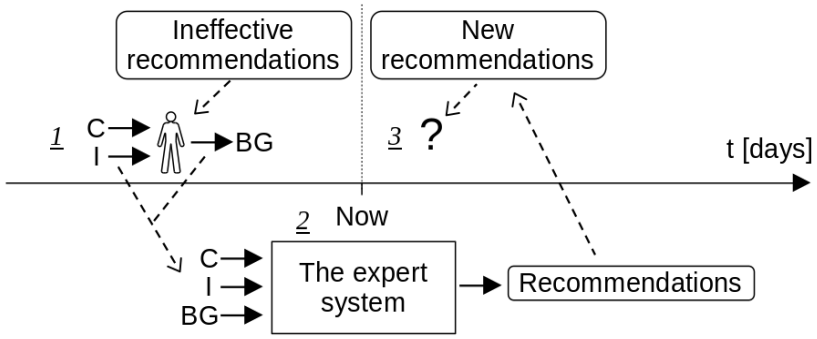

Fig. 4. Positioning of the therapeutic recommendations expert system in the T1D treatment process, 1 – known history of the therapy, 2 – activation of the expert system, 3 – the future therapy

1.3. Modern methods for determining therapeutic recommendations

Each individual with T1D is managed according to personalized recommendations. These recommendations are most often developed by qualified healthcare professionals and communicated to the patient or their caregiver. In clinical settings, they are determined by a physician based on professional experience and general therapeutic guidelines published by medical organizations, such as the American Diabetes Association Professional Practice Committee (2024). Unfortunately, the formulation of such guidelines is often difficult to apply in practice. There are also clinical medical procedures designed to determine patient-specific characteristics e.g. Zhang et.al. (2020) or Pańkowska et al. (2016), but their application in outpatient settings is either burdensome or infeasible. Reliable institutions publish online medical guidelines on how to establish these recommendations, e.g. NHS Tayside (n.d.). These typically advise to search for appropriate therapeutic settings by modifying the current recommendations and observing the results during ongoing therapy.

However, there is a lack of standardized methods for determining therapeutic recommendations based on actual patient treatment outcomes generated by modern medical devices. To the best of the author's knowledge, the method proposed in this publication is pioneering in this regard.

2. METHODOLOGY

2.1. Operation of the proposed system

The goal of this study was to develop an expert system for the automatic generation of personalized therapy recommendations in outpatient settings, based solely on the digital footprint of the therapy. The architecture of the system is shown in Figure 5. The input data for the system includes information about the carbohydrates consumed by the patient *C*, the insulin administered *I* - which includes both insulin for individual doses *ID* and basal insulin *IB* - and the blood glucose levels measured during this period *BG*. An example of such input data has already been presented in Figure 3. The outputs of the system are the therapeutic recommendations “Recommendations” and the corresponding evaluation “Evaluation”. In addition, the system generates intermediate artifacts: a „digital twin” of the real patient and the medical characteristics of this twin „Twin characteristics”. The artifact labeled „device settings” in the diagram corresponds to the therapeutic recommendations; its duplication in the diagram illustrates its internal use within the system. In the diagram, generated artifacts are shown as rounded rectangles, while major computational steps are shown as sharp-edged rectangles. Steps that involve machine learning are marked with an asterisk. The goal of the first computational step “T1D Simulator Personalization” is to create a digital twin of the real patient. In the system, the patient is represented by a computer simulator (described later in the paper). This simulator accepts carbohydrates and insulin as input signals and produces blood glucose levels as output signals. The simulator

has a number of configurable parameters that define its behavior. Adjusting these parameters so that the simulator's response closely matches that of the real patient is called personalization, and the complete set of parameter values is called configuration. The digital twin is thus a properly configured patient simulator that allows for an unlimited number of in silico experiments. The purpose of these experiments is to determine the patient's insulin and carbohydrate sensitivities and basal insulin requirements, collectively referred to as the twin characteristics. Obviously, the quality of the system's output depends on how well these characteristics of the digital twin reflect those of the real patient. However, the characteristics obtained at this stage cannot be used directly in therapy because they are not in the required form of diurnal-cyclic step functions (see Figure 2). Therefore, an adaptation step is necessary to adapt the results to the capabilities of medical devices. The result is therapeutic recommendations in the form of equipment settings that can be practically implemented. An additional step involves retrospective verification of the proposed device settings. At this stage, retrospective verification is the only method of validation available, since the actual effects of the new recommendations are unknown at the time they are generated (as illustrated in Figure 4). This verification consists of applying the new recommendations to past therapy scenarios and assessing how much better the outcomes would have been if these recommendations had been applied. To do this, another in silico experiment is performed using the digital twin. In this experiment, the twin is given the same carbohydrate intake as the real patient, but the insulin doses are determined based on the new recommendations. The result of this experiment is a hypothetical blood glucose profile that is compared to the historical profile. This comparison is used to evaluate the effectiveness of the new therapeutic recommendations.

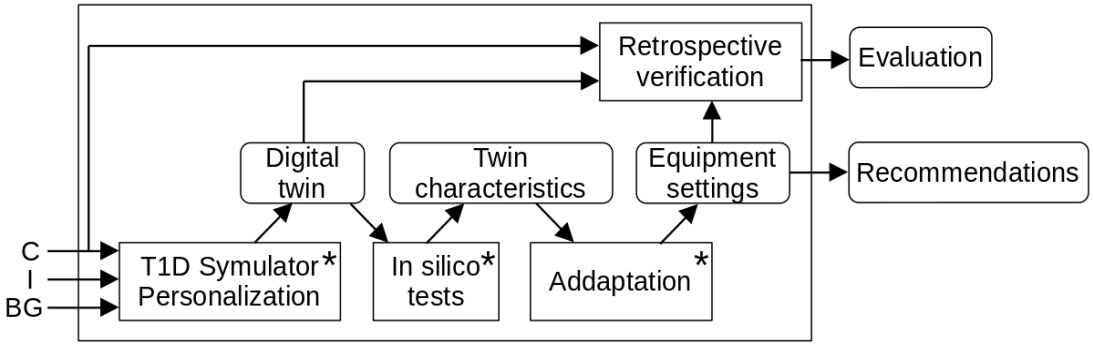

Fig. 5. Internal design of the proposed system and its input and output

2.2. Virtual therapy and computer simulator of type 1 diabetes patient

The basis of the proposed system is virtual T1D therapy. In this work, this term refers to the reconstruction of therapy using computer simulators: a patient simulator and an insulin pump simulator (Fig. 6). In the virtual scenario, the presence of a human operator is not required because all his decisions are already known (e.g. Fig. 3abc). It is also not necessary to know the therapeutic recommendations on which the operator based these decisions. The inputs to the virtual therapy are the carbohydrates consumed by the patient (e.g. Fig. 3a) and the insulin administered (e.g. Fig. 3bc). In virtual therapy, the real patient is replaced by a freely configurable computer-based simulator. The output of the BG_{TWIN} simulation is the blood glucose concentration curve, which reflects the simulator's response to the input. The Insulin Pump Simulator works by delivering basal insulin according to a programmed schedule, as well as single doses. All components of the simulation are controlled and synchronized by a global clock, which is also part of the virtual therapy. The inclusion of a CGM simulator is not required, as the values can be reported directly from the patient simulator. The most critical component of virtual therapy is the patient simulator (virtual patient). The quality of the final therapeutic recommendations generated by the system depends directly on the accuracy and fidelity of this simulation component.

The first advanced physiological mathematical model of a person with type 1 diabetes was presented by Sorensen (1985). Since its publication, many computer simulators have been developed based on this model. Today, the most well-known examples include the Type 1 Diabetes Metabolic Simulator (T1DMS) (Man et al., 2014; Visentin et al., 2018; Cobelli & Kovatchev, 2023; The Elipson Group, n.d.) and the AIDA Simulator (Lehmann, 2004; Lehmann et al., 2007; Wikipedia, n.d.). These simulators share a common goal: to accurately reproduce the physiological and metabolic processes involved in glucose and insulin circulation and

metabolism. This modeling approach is well justified, and the resulting simulators have proven to be valuable tools in research and clinical trials. However, a major limitation of these simulators is their lack of adaptability to individual patients using outpatient therapy data. They rely on individual physiological parameters that cannot be obtained under typical outpatient conditions, such as the insulin elimination rate, parameters of insulin pharmacodynamics, reference basal insulin level, constant for enzyme-mediated glucose uptake, rate of insulin-independent glucose utilization, reference value for glucose utilization, slope of the peripheral glucose utilization vs. insulin curve, rate constant for glucose absorption from the gut, maximum rate of gastric emptying, volume of the intestine, etc. insulin curve, rate constant for intestinal glucose absorption, maximum gastric emptying rate, glucose distribution volume per kilogram of body weight, body insulin sensitivity parameter, and hepatic insulin sensitivity parameter, to name a few. Consequently, there was a need to develop a simplified, original mathematical model and computer simulator that could be personalized based on available outpatient data.

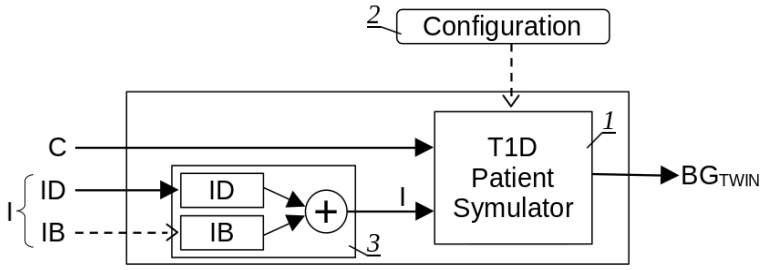

Fig. 6. T1D virtual therapy, 1 – a computer simulator of the patient, 2 – configuration of the simulator, 3 – a simulator of an insulin pump, BG_{TWIN} – blood glucose obtained in the simulation

For the purpose of the proposed expert system, a simplified simulator has been developed and named Type 1 Diabetes Direct Simulator (T1DDS). The operation of the simulator is defined by an equation that describes changes in blood glucose concentration BG_{TWIN} caused by: 1) the appearance of glucose originating from ingested carbohydrates G or released from the liver LA, and 2) the presence of insulin delivered by the pump$I$:

$$\frac{dBG_{TWIN}}{dt} = GA\left(\frac{d}{dt}\sum_i G_i + LA\right) - IA\frac{d}{dt}\sum_j I_j \tag{4}$$

where: $GA = GA(t)$ – the glucose action diurnal-cyclic function,
$LA = LA(t)$ – the liver action diurnal-cyclic function,
$IA = IA(t)$ – the insulin action diurnal-cyclic function,
$G_i = G_i(t)$ – the glucose released from the i-th carbohydrate intake C_i consumed at time $t_{C,i}$,
$I_j = I_j(t)$ – the insulin release from the j-th dose D_j administrated at time $t_{D,j}$.

Glucose emission from the i-th dose of carbohydrates is described by the formulas form (5) to (7) (Cobelli et al., 2009; Hermansson & Sivertsson; 1996; Dalla Man et al., 2007).

$$\frac{dG_i}{dt} = C_i\frac{trp(\tau_i)}{T_{C,i}} \tag{5}$$

$$trp(\tau) = \begin{cases} \frac{h}{r}\tau, 0 \le \tau < r \\ h, r \le \tau \le 1-d \\ \frac{h}{d}(1-\tau), 1-d < \tau \le 1 \end{cases} \tag{6}$$

$$\tau_i(t) = \begin{cases} \frac{t-t_{C,i}}{T_{C,i}}, t_{C,i} \le t \le t_{C,i} + T_{C,i} \\ 0, otherwise \end{cases} \tag{7}$$

where: trp – the trapezoidal distribution defined on the range <0,1>,
$\tau_i = \tau_i(t)$ – relative normalized time for i-th carbohydrate dose,
$T_{C,i}$ – the total time of absorption of the i-th dose of carbohydrates,
$h = 1/(2-r-d)$ – the height of the distribution trapezoid,

r – the section of the left ascending arm of the trapezium $1 < r < 1$,
d – the section of the right descending arm of the trapezium $0 < d < 1 \wedge 0 < r + d < 1$.
Insulin emission from the j-th injection is described by the formulas (Nowicki, 2019):

$$\frac{dI_j}{dt} = D_j \frac{k(\tau_j)}{T_D} \tag{8}$$

$$k(\tau) = \sum_{s=1}^{6} a_s \tau^s \tag{9}$$

$$\tau_j(t) = \begin{cases} \frac{t - t_{D,j}}{T_D}, t_{D,i} \leq t \leq t_{D,i} + T_D \\ 0, otherwise \end{cases} \tag{10}$$

where: k – the normalized insulin curve described on the interval <1,0>,
$\tau_j = \tau_j(t)$ – relative normalized time for j-th carbohydrate dose,
T_D – the total time of absorption of the j-th dose of carbohydrates,
a_s – insulin characteristic values.

The diurnal-cyclic functions *GA*, *LA*, and *IA* used in equation (4) represent the simulator configuration and are not known a priori. The aim of the previously described simulator personalization is to determine these functions based on historical therapy data. In the study conducted, it was assumed that these functions take the form of diurnal-cyclic polylines defined by a finite set of points. Hypothetical *GA*, *LA*, and *IA* functions are shown in Figure 7. The figure also shows typical ranges for these functions. The values of the remaining parameters of the T1DDS simulator are given later in this paper.

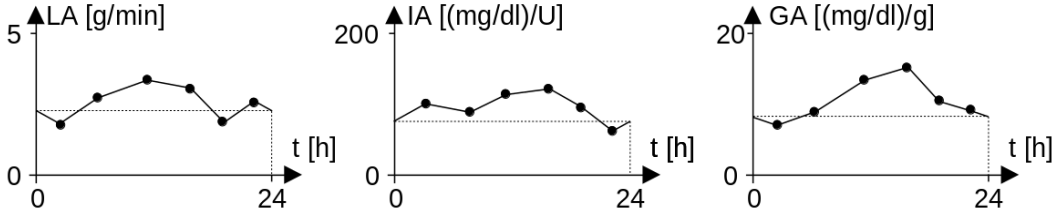

Fig. 7. Hypothetical configuration of the T1DDS simulator

2.3. T1DDS simulator personalization

The personalization of the T1DDS simulator was implemented using machine learning methods. After numerous attempts, it was found that the application of a genetic algorithm gave the best results. A standard genetic algorithm was used (Michalewicz, 2011; Buontempo, 2019), and its schematic representation is shown in Figure 8a. Figure 8b, on the other hand, shows a set of points evenly distributed over the course of a single day. These points can serve as interpolation points for any diurnal-cyclic function (e.g., Fig. 2, Fig. 7). The number of these points can be arbitrary, and they divide the 24-hour day into uniform, disjoint intervals so that each point is assigned to a particular interval. It is also assumed that each point can take any value in the range from v_{min} to v_{max}. Each point can be positioned anywhere within its associated rectangular region. The position of each point within this rectangle can be described by two normalized relative coordinates p and q with values between 0 and 1, where the coordinate (0,0) denotes the lower left corner and (1,1) the upper right corner. Finally, the placement of a set of n points can be represented as a sequence (11). Knowing the values of this sequence and the approximation method uniquely defines any diurnal-cyclic function.

$$p_1, q_1, p_2, q_2, p_3, q_3, \ldots p_n, q_n \tag{11}$$

where: p_i – the relative position of the i-th point in the time direction $0 \leqslant p_i < 1$,
q_i – the relative position of the i-th point in the direction of the value direction $0 \leqslant q_i < 1$,
n – the number of approximation points.

The configuration of the T1DDS simulator consists of three diurnal-cyclic functions (Figure 7). Each of these functions is represented by a sequence defined by equation (11). The concatenation of these sequences forms the chromosome of the genetic algorithm, with a total length of $n_{LA}+n_{IA}+n_{GA}$, where each symbol denotes

the number of interpolation points for the respective functions: *LA*, *IA* and *GA*. Each individual value *p* or *q* is called a gene of this chromosome. It should be emphasized that each chromosome - i.e. any sequence of values between 0 and 1 of the specified length, together with the defined range of each function and the chosen approximation method - uniquely determines the configuration of the T1DDS simulator. This configuration can then be used to perform the virtual therapy procedure shown in Figure 6. The output of this simulation is a glucose concentration profile called BG_{TWIN}. The similarity between the BG_{TWIN} profile and the actual blood glucose profile *BG* (e.g. Fig. 3d) is the measure of the quality of the digital twin.

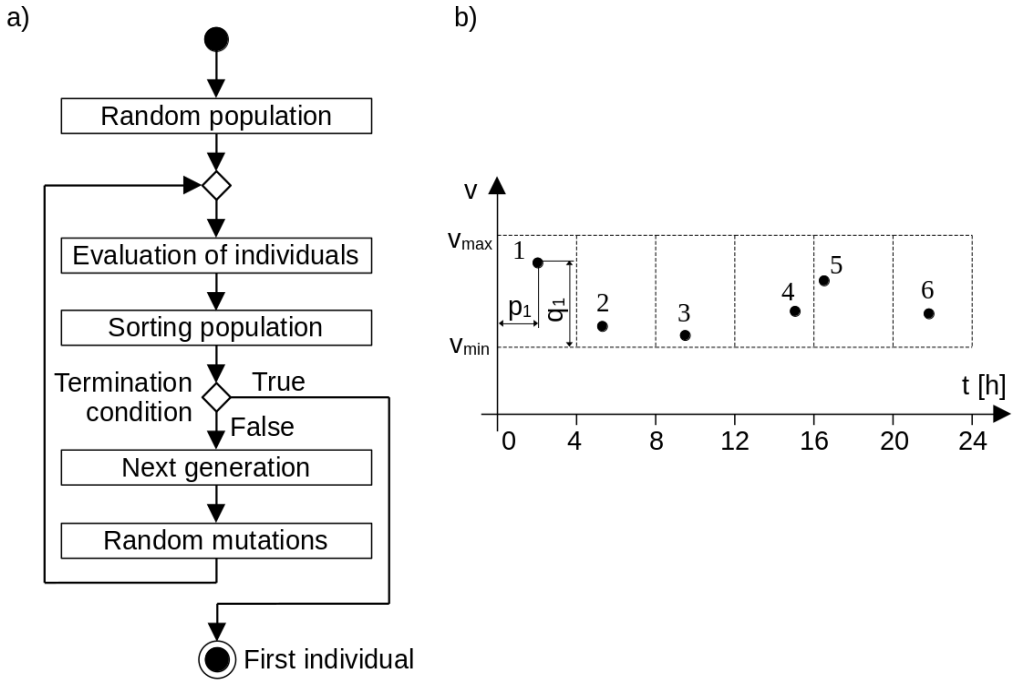

Fig. 8. a) Diagram of the genetic algorithm, b) Approximation points of the diurnal-cyclic function

An original method based on the histogram of absolute error was developed to compare glucose concentration profiles. This was necessary because other methods, such as correlation analysis or mean squared error, did not give satisfactory results. The proposed method suppresses large errors by accepting smaller ones and takes into account the physiological range of the values considered. The proposed approach assumes that the glucose concentration values are quantized, i.e. known for each minute of the considered period and provided with an accuracy of 1 mg/dl. Thus, the task is reduced to comparing two sequences:

$$bg_1, bg_2, \ldots, bg_m \tag{12}$$

$$t_1, t_2, \ldots, t_m \tag{13}$$

where: bg_i – reference (real and interpolated) glucose concentration value in the i-th minute,
t_i – glucose concentration value in the i-th minute from simulation,
m – number of minutes of the analyzed therapy period, both real and virtual.

For each corresponding pair of values bg_i and t_i, the absolute error E_i is calculated according to (14). It is important to take into account the possibility of glucose values outside the physiological range in the computer simulation.

$$E_i = \begin{cases} |t_i - bg_i|, BG_{low} < t_i < BG_{up} \\ PENALTY, otherwise \end{cases} \tag{14}$$

where: $BG_{low} = 30\,mg/dl$ – minimal physiological value
$BG_{up} = 500\,mg/dl$ – maximal physiological value,
$PENALTY = 2 \cdot BG_{up} = 1000\,mg/dl$ – the penalty value.

The absolute error E_i is calculated for each minute of simulation *i=1, 2, ... m*, resulting in a numerical sequence $E_1, E_2, \ldots E$ m of length *m* and values from a discrete set: *{0mg/dl, 1mg/dl, 2mg/dl, ... PENALTY}*. The number of occurrences of each error value is then counted:

$$C_e = \sum_i^m \delta_{e,E_i} \tag{15}$$

where: C_e – the number of occurrences of an error value e,
$e = 1\,mg/dl, 2\,mg/dl, \ldots, PENALTY$ – all possible absolute error values,
δ – Kronecker delta function.

The number of error occurrences divided by the number of all errors forms an absolute error histogram:

$$h_e = \frac{C_e}{m} \tag{16}$$

where: h_e – relative share of an error with an absolute value of e in the number of all errors,
$e = 1\,mg/dl, 2\,mg/dl, \ldots, PENALTY$ – the histogram bins.

In other words, the histogram is constructed so that for each possible absolute error value, i.e. *0mg/dl, 1mg/dl, 2mg/dl, ... PENALTY*, the number of occurrences of that error is assigned, divided by the total number of errors, i.e., the number simulation minutes because for each minute the error is calculated. The histogram allows to determine the relative weighted error *err* according to (17), which can take values from 0 to 1, where 0 means full convergence of the compared sequences.

$$err = \frac{\sum_{e=1mg/dl}^{PENALTY} e \cdot h_e}{PENALTY} \tag{17}$$

In the genetic algorithm, the value of *err* is not used directly, but is converted into the fitness function *fit* using the bias function according to equation (18). The values of the fitness function also range from 0 to 1. However, in this case, a value of 1 indicates a complete match, while 0 indicates a complete mismatch. The use of the bias function allows the full range of values to be used when blood glucose values are within the acceptable physiological range, which facilitates an intuitive assessment of the result obtained.

$$fit(err) = 1 - \frac{err}{(1/0.95-2)(1-err)+1} \tag{18}$$

where: $f(x) = \frac{x}{(1/0.95-2)(1-x)+1}$ – is the bias function used (f:[0,1] →[0,1]).

After defining the fitness function, personalization of the T1DDS simulator becomes an optimization problem, which is solved using a genetic algorithm (Fig. 8a). First, a finite random population is created - a set of randomly generated chromosomes. Each chromosome is called an individual. In the study, the population size was set to 1000. Next, a simulator configuration is created for each chromosome, followed by a virtual therapy simulation that generates a glucose concentration profile. This profile is then evaluated against the real glucose profile by calculating the fitness function value. Once this value is calculated for each individual, the population is sorted from best to worst. After sorting, a termination condition is checked. In the study, the termination condition was reached when one of the following was true: 1) the maximum number of iterations was completed (set to 1000), 2) the maximum computation time was exceeded (set to 3 hours), 3) the target value of the fitness function was reached by the best individual (set to 1.0), or 4) the maximum number of ineffective iterations was exceeded (set to 250). If a termination condition is met, the best individual is considered the final solution. If not, a new population (generation) is created based on the existing one. A subset of the best individuals (5%) is carried over directly to the next generation. A subset of the worst individuals (also 5%) is replaced by newly generated random individuals. Each remaining individual is replaced by its offspring. To select the second parent, the tournament selection method is used: a group of potential candidates (30% of the population) is randomly selected, and the best individual from this group is taken. An offspring chromosome is generated by randomly and uniformly mixing the genes of both parents. In addition, random mutations are introduced after the new generation is created. This is done by randomly selecting 10% of the offspring and randomly changing 10% of the genes in each of their chromosomes. Once the new generation is formed, the individuals must again be evaluated, sorted, and checked against the termination conditions.

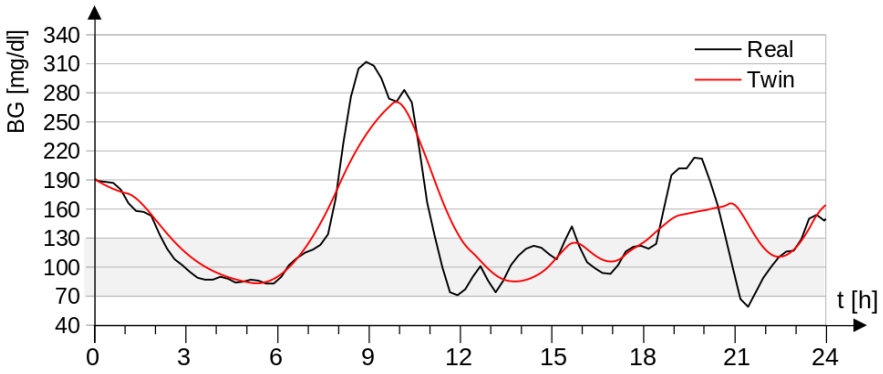

Fig. 9. Glucose concentration for a real patient ("Real") and his virtual twin ("Twin")

The results of the algorithm described above, applied to the data shown in Figure 3, are shown in Figure 9, which shows the glucose concentration of the real patient („Real") and the virtual twin („Twin"). In this case, the obtained value of the fitness function was $fit = 0.711$. The resulting configuration of the T1DDS simulator is shown in Figure 10. In addition, the plots in Fig. 11a illustrate the evolution of the fitness function value over successive generations, as well as the inefficiency parameter of each generation, defined as the number of generations without improvement in the objective function, up to the maximum allowed number of such generations (i.e., 250).

2.4. In silico study of the virtual twin and determination of medical device settings

The T1DDS simulator, together with the configuration obtained as described in the previous section, becomes a virtual twin of the real patient. This enables a series of experiments to be conducted using the virtual twin without posing any risk to the health or life of the real patient. The purpose of these experiments is to determine insulin and carbohydrate sensitivities and to find an optimal basal insulin delivery schedule. Both sensitivities can be assessed using stimulus-response-type experiments. In each case, two copies of the virtual twin must be created. To determine carbohydrate sensitivity, one copy is given a unit dose of carbohydrates, while the other receives none. A virtual therapy is then performed over a time interval covering the complete absorption of carbohydrates T_C, as defined by equation (5). The difference in blood glucose levels between the two copies represents the carbohydrate sensitivity at the moment the unit dose was served t_C. To determine carbohydrate sensitivity over the whole day, this test must be repeated for each minute of the 24-hour period. Insulin sensitivity is determined in an analogous manner, with the difference being that instead of a carbohydrate dose, a unit dose of insulin is administered to one copy of the virtual twin. Examples of the resulting sensitivities obtained using this method are presented in Figure 11b and Figure 11c. These are shown as curves labelled "Characteristic", which in general represent continuous, nonlinear functions.

The basal insulin program for the virtual twin cannot be determined based on stimulus-response tests alone. To solve this problem, the previously described genetic algorithm was applied again. In this case, the goal is to find a diurnal-cyclic stepwise basal insulin delivery function (Fig. 2), represented by form (11). In the calculations, it was assumed arbitrarily that this function would be defined by $n = 24$ points. The desired outcome is a basal insulin program for which the glucose concentration of the virtual twin remains stable, unaffected by hepatic glucose production described by the already known LA function (see Fig. 10a). In other words, the result of equation (4) should be equal to zero throughout the simulation period, assuming both G and ID are zero. An example of the basal insulin program obtained using this method for the data shown in Fig. 3 is presented in Fig. 12c.

The resulting basal insulin program can be directly applied as a therapeutic recommendation. However, the two sensitivities must be approximated using stepwise functions. For this purpose, the previously described genetic algorithm was also used. As with the basal insulin program, it was arbitrarily assumed that the program would be defined by 24 points. In this case, however, a different fitness function was applied: the mean squared error between the continuous (nonlinear) function and its stepwise approximation was minimized. The results of this computation are represented by the curves labelled "Settings" in Fig. 11b and Fig. 11c.

3. NUMERICAL EXPERIMENT

3.1. The experiment program

The developed method was implemented as a original software application called T1DStudio, written in Java. This program was used to generate therapeutic recommendations for real patients. The aim of the study was to evaluate the performance of the method when applied to real-world scenarios.

The research program was based on the therapy records of 5 real patients with T1D. All the patients met the following conditions: 1) using an insulin pump and CGM for at least a year (a guarantee of correct use of equipment resulting from the experience) 2) strictly following the therapy recommendations during the mentioned period of time, 3) agreeing to the use of their data in research in an anonymous form, 4) not suffering from other chronic diseases. The characteristics of the study group has been presented in Table 1.

Tab. 1. Characteristics of the research group

No.	Sex	Age	Height	Weight	Insulin	CGM
		[years]	[cm]	[kg]		
1	M	11	146	38	Novorapid	FreeStyle Libre
2	F	9	136	34	Novorapid	FreeStyle Libre
3	M	9	133	43	Novorapid	FreeStyle Libre
4	F	6	108	20	Humalog	FreeStyle Libre
5	F	6	116	26	Humalog	FreeStyle Libre

Tables 2 and 3 show the numerical values of the parameters adopted for the T1DDS simulator. The values in Table 2 refer to the absorption of carbohydrates consumed in meals (see equations 5, 6 and 7). These values were adopted based on Cobelli et al. (2009), Hermansson and Sivertsson (1996), Dalla Man et al. (2007) and refined through a series of successive experiments. The values in Table 3 are taken from Nowicki (2019) and describe the kinetics of the insulin types used by the patients.

In each analysis, the approximation functions of the T1DDS simulator*(LA*,*IA*,*GA*) were modeled as diurnal-cyclic polyline functions approximated by six vertices. Therapeutic recommendations, on the other hand, were represented as stepwise functions with 24 values.

The time interval of the historical data was one full day. Five consecutive days were randomly selected for each patient. During these periods, only patient #5 had acceptable blood glucose profiles. The remaining patients required adjustments to their therapeutic recommendations as their therapeutic results were unsatisfactory. The proposed in silico experiment involved determining therapeutic recommendations for each patient by analyzing each day separately. In other words, this is a hypothetical scenario in which therapeutic recommendations are generated at 00:00 based on data from the previous day. All generated recommendations were reviewed retrospectively. However, they were not implemented in real-world treatment because the available data were historical rather than current.

Tab. 2. T1DDS simulator parameter values for carbohydrate action

Meal	r	d	T_C
Planned	15min/T_C=0.063	60min/T_C=0.025	240 min
Correction	10min/T_C=0.167	15min/T_C=0.025	60 min

Tab. 3. T1DDS simulator parameter values for insulin action

Insulin	a_1	a_2	a_3	a_4	a_5	a_6	T_D
Novorapid	34.04	−185.9	439.8	−536.6	327.1	−78.44	360 min
Humalog	31.60	−144.7	259.5	−211.3	64.93	0	330 min

3.2. The experiment results

As part of the experiment, the complete computational procedure described in this paper was run 25 times. Figures 10 through 12 show the detailed results obtained for the analysis of day 5 for patient #4. This particular case was selected for detailed presentation because the results were the most representative, i.e., closest to the average outcome of the entire experiment. The historical data used as the basis for this analysis was previously

presented in Figure 3. The configuration of the digital twin created from these data is shown in Figure 10. Therapeutic recommendations resulting from the in silico experiments include insulin sensitivity (Fig. 11b), carbohydrate sensitivity (Fig. 11c), and the basal insulin program (Fig. 12c).

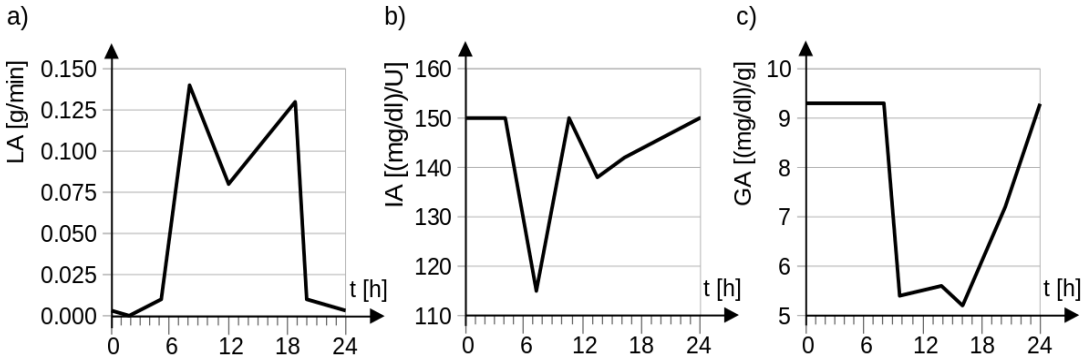

Fig. 10. The configuration functions of digital twin for patient 4 day 5 : a) liver action b) insulin action, c) glucose action

The generated therapeutic recommendations were validated retrospectively. In this case, the virtual twin consumes exactly the same meals as the real patient (Fig. 3a, Fig. 12a), while the basal insulin (Fig. 12c) and bolus insulin doses (Fig. 12b) are administered according to the developed therapeutic recommendations. The therapy simulation results in a blood glucose concentration profile shown as the „Pred" plot in Figure 12d. This is compared with the real historical „Hist" curve, derived from the real patient and previously shown in Figure 3d. To quantitatively assess the improvement in therapy quality, a criterion was proposed based on the calculation of the area between the glucose concentration curve and the acceptable range limits (70 mg/dl to 130 mg/dl). For the historical concentration, the total area was $A_1+ A_2+ A_3+A_4+A_5+ A_6 = 39138$ min-mg/dl, whereas for the predicted scenario, the total area was $B_1+ B_2 = 9116$ min-mg/dl, representing a 77% improvement. This improvement is clearly visible in the figure.

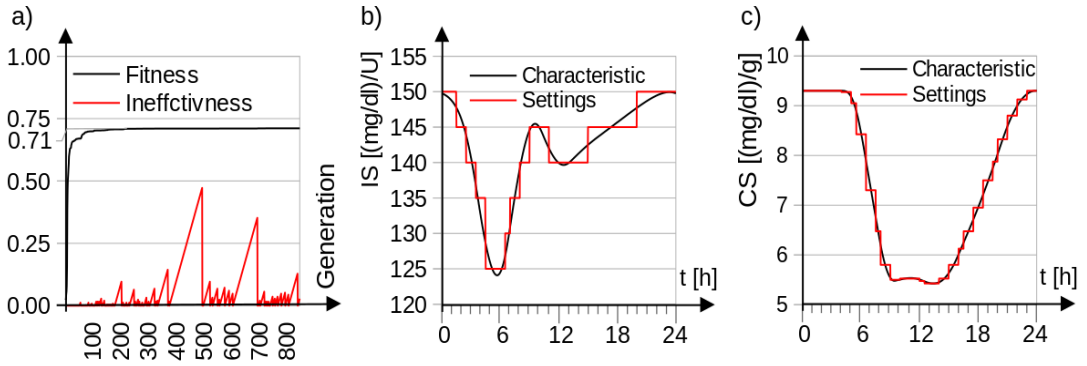

Fig. 11. a) The convergence of the genetic algorithm, b) the insulin sensitivity, c) the carbohydrate sensitivity

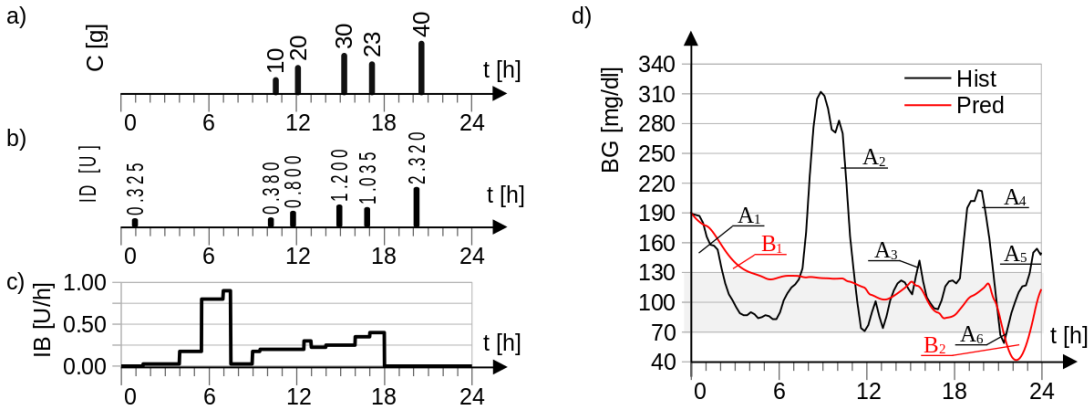

Fig. 12. Retrospective verification a) historical carbohydrate input b) hypothetical single doses of insulin, c) hypothetical insulin base, d) hypothetical "Pred" and historical real "Hist" profile of blood glucose

The results of the remaining analyses are summarized in Tables 4 through 8. Each table corresponds to a different patient in the study group. In these tables, for each application of the method (analysis), the virtual twin calibration report („Virtual Twin Calibration") and the quality of the resulting virtual twin („Virtual Twin Quality") as defined by the fitness function defined earlier in the paper are provided. The report includes the total calibration time („Time"), the number of genetic algorithm steps („Steps") performed during this time, and the number of ineffective steps counted at the time of calibration completion („Ineff."). Next, the total areas of glucose concentration outside the acceptable range are reported for both the historical results („Therapy quality. Historical") and the predicted results assuming the new recommendations had been implemented („Therapy quality. Prediction"). The improvement in glycemic control was calculated as the difference between the historical and predicted values divided by the historical value and is reported in the last column („Therapy quality. Improvement"). The last row of each table („Avg") contains the average result across all calculated cases.

Tab. 4. Experiment results for Patient 1

Day	Virtual twin calibration			Virtual twin quality	Therapy quality		
	Time	Steps	Ineff.		Historical	Prediction	Improvement
	[min]	[count]	[count]	[0-1]	[min·mg/dl]	[min·mg/dl]	[%]
1	180	566	17	0.757	35 668	15 834	56
2	180	583	0	0.828	34 286	7 726	77
3	180	591	14	0.759	19 914	11 673	41
4	180	587	4	0.749	34 737	6 532	81
5	180	541	1	0.786	33 687	7 183	79
Avg	180	574	-	0.776	31 659	9 790	66

Tab. 5. Experiment results for Patient 2

Day	Virtual twin calibration			Virtual twin quality	Therapy quality		
	Time	Steps	Ineff.		Historical	Prediction	Improvement
	[min]	[count]	[count]	[0-1]	[min·mg/dl]	[min·mg/dl]	[%]
1	180	551	70	0.768	106 857	19 196	82
2	180	648	13	0.540	63 549	18 432	71
3	180	620	20	0.744	51 151	0	100
4	180	620	113	0.796	80 586	25 196	69
5	180	627	13	0.685	89 007	8 412	91
Avg	180	613	-	0.707	78 230	14 247	83

Tab. 6. Experiment results for Patient 3

Day	Virtual twin calibration			Virtual twin quality	Therapy quality		
	Time	Steps	Ineff.		Historical	Prediction	Improvement
	[min]	[count]	[count]	[0-1]	[min·mg/dl]	[min·mg/dl]	[%]
1	180	572	8	0.748	87 766	11 239	87
2	180	573	186	0.720	62 596	5 177	92
3	180	599	4	0.694	71 286	10 107	86
4	180	557	1	0.796	86 512	5 391	94
5	180	557	6	0.727	84 858	10 801	87
Avg	180	572	-	0.737	78 604	8 543	89

Tab. 7. Experiment results for Patient 4

Day	Virtual twin calibration			Virtual twin quality	Therapy quality		
	Time	Steps	Ineff.		Historical	Prediction	Improvement
	[min]	[count]	[count]	[0-1]	[min·mg/dl]	[min·mg/dl]	[%]
1	180	635	20	0.733	12 491	4 651	63
2	180	667	219	0.712	12 152	9 010	26
3	180	656	0	0.770	29 413	1 537	95
4	180	659	29	0.680	25 546	2 957	88
5	180	845	7	0.711	39 138	9 116	77
Avg	180	692	-	0.721	23 748	5 454	70

Tab. 8. Experiment results for Patient 5

Day	Virtual twin calibration			Virtual twin quality	Therapy quality		
	Time	Steps	Ineff.		Historical	Prediction	Improvement
	[min]	[count]	[count]	[0-1]	[min·mg/dl]	[min·mg/dl]	[%]
1	155	699	250	0.817	25 987	12 601	52
2	180	742	17	0.771	29 964	11 001	63
3	180	799	98	0.788	7 132	12 773	-79
4	180	650	10	0.828	7	851	-12 057
5	180	658	132	0.770	17 175	21 473	-25
Avg	175	710	-	0.795	16 053	11 740	27

The study showed that the developed method can significantly contribute to the improvement of T1D therapy. Therapeutic recommendations generated by the developed expert system proved to be effective in 22 out of 25 cases analyzed, with an average improvement of 75%. Only in 3 cases the implementation of the proposed recommendations led to a deterioration of the quality of therapy. These cases need to be discussed in more detail. They all concern the same patient, who differs from the others in that the results of his actual therapy were the best of the whole group (see „Historical" column). In case 4, it can be concluded that the patient's historical glucose concentration was within the acceptable range throughout the day. However, the application of the new recommendations resulted in a small deviation compared to the other values in the same column. In this case, the relative deterioration of 12057% does not indicate a life-threatening situation. Cases 3 and 4 should be interpreted in a similar way. Note that in these three cases, the quality of the virtual twins does not differ from the quality of the virtual twins in the other analyses. Thus, the algorithm correctly calibrated the patient model to the historical data. Moreover, comparing the values in the „Prediction" columns, it can be observed that the therapeutic recommendations generated for these three virtual twins are of similar quality to the recommendations in the other analyses. On this basis, it can be concluded that the values obtained in the „Improvement" column result from the limitations of the method used to compare the quality of therapy, which was based on the calculation of the area of the blood glucose curve outside the permissible ranges. With this method, the absolute value derived from the curve carries more information than the ratio of these values. These absolute values clearly indicate that the blood glucose profile either improved or (in three cases) did not significantly worsen. However, the ratio of these areas expressed as a percentage should be considered as additional information.

The adopted criterion for the assessment of therapy quality improvement was introduced specifically for the purpose of retrospective verification. This was due to the fact that typical medical indicators such as TIR (time in range), TBR (time below range) and TAR (time above range) should not be used in this case, since the analyzed period of 24 hours is too short for these measures to be medically meaningful. Furthermore, the effects induced by the introduction of new therapeutic recommendations stabilize only over the insulin action horizon (i.e. 330 or 360 minutes, see Table 3); therefore, approximately 25% of the daily period can be compared in terms of the rate of reaching the target glucose level, which is better reflected by the area-based criterion. The comparison criterion introduced is not perfect, but it serves its purpose and does not pose a risk of medical overinterpretation.

The number of ineffective genetic algorithm steps counted at the end of the virtual twin calibration (column „Ineff.") also requires comment. Low values in this column may suggest that extending the calibration time could improve the result. This is most likely a correct conclusion; however, in each analysis, the convergence process of the genetic algorithm followed the pattern shown in Figure 11 a). Very quickly, i.e. after about 200 iterations, the quality of the digital twin reached a level close to the target. Subsequently, improvements in the fitness parameter were observed, but these changes were insignificant.

4. DISCUSSION

The developed system for generating therapeutic recommendations is entirely based on medical data automatically collected by modern medical devices used in the treatment of T1D, namely, a CGM system and an insulin pump. These data can be considered an individual digital footprint of the patient's daily therapy in outpatient conditions. However, such data do not allow for personalization of the commonly accepted simulators of patients with type 1 diabetes. Therefore, an alternative simplified simulator was proposed.

Personalization of this simulator proved feasible using a genetic algorithm, which was adapted to the problem at hand. The results obtained with this algorithm were satisfactory. The personalized simulator, referred to as a digital twin, was used to conduct a series of in silico experiments. These experiments produced therapeutic recommendations in a form that can be implemented in real-life therapy. During the generation of these recommendations, the developed version of the genetic algorithm was used again. Thus, both the digital twin itself and the therapeutic recommendations generated using it can be regarded as products of machine learning. Considering the available therapeutic data, achieving the intended goal would not have been possible using other methods.

This paper emphasizes the algorithmic aspects of the conducted research and omits several elements not directly related to this aspect. These include, among others: technical details of the medical equipment (operation, data format, integration), justification of the modelling assumptions (exclusion of fat and protein effects in the analysis, lack of direct modelling of all liver functions, absence of a kidney function model), implementation details of the simulator, and the process of its use (e.g., the need for pre-simulation before personalization). At the current stage of the project (i.e., theoretical analysis and computer experiment), the only feasible method of validation was retrospective verification. This validation demonstrated satisfactory results of the developed system and clearly supports a positive recommendation for proceeding to the clinical research stage.

The article summarizes the achievements of the first stage of work on an expert system for the automatic generation of therapeutic recommendations for patients with type 1 diabetes, based solely on the digital footprint of modern therapeutic devices. This stage involved the development of mathematical models applicable in practice and the selection of algorithmic methods for effective work with these models. The exploration was largely conducted using a trial-and-error approach. This stage was highly labor-intensive, due, among other factors, to the need to create successive models, develop original software, and perform time-consuming computer simulations. Ultimately, a method was developed that can automatically generate therapeutic recommendations based only on the available data. The method was successfully verified retrospectively. This indicates that it may be useful in practice, although this does not provide a definitive conclusion.

The next stage of the work involves verifying the developed method in clinical settings with the participation of real patients and under strict medical supervision. Only this verification will provide an answer as to whether the proposed method can be useful in medical practice. At present, research efforts are directed toward this goal. Consequently, in-depth theoretical analyses of the proposed models and methods (including the stability of the T1DDS model, optimization of the genetic algorithm, the impact of approximation assumptions or the blood glucose similarity criterion on the obtained results, cross-day retrospective verification, consideration of periods longer than a single day in retrospective verification, etc.) have been postponed to a subsequent stage of the project. Carrying out these analyses will only be meaningful if the results of the clinical verification indicate the relevance of further work on the proposed solutions. Moreover, the clinical verification will undoubtedly provide rich data for conducting such analyses. At the current stage, it should be emphasized that the method has not yet been fully explored, and therefore any verification involving real patients must be carried out exclusively under medical supervision.

The aim of the clinical verification is to determine whether the assumptions and simplifications on which the method was developed sufficiently reflect reality. However, this verification will necessarily have to be conducted in a manner entirely different from the retrospective validation presented earlier. For reasons of patient safety, changes to the medical device settings should not be made abruptly but rather gradually. In this case, the newly generated therapeutic recommendations will serve only as a basis for modifying the current settings. The patient's response to a modified setting will then form the basis for generating subsequent recommendations, which in turn will be used for further adjustments. From a therapeutic perspective, it is desirable for this process to converge toward a generally understood equilibrium point. Moreover, the optimal time window of historical data to be used in constructing a virtual twin is currently unknown. Most likely, this period will need to extend beyond a single day. In such a case, the patient's virtual twin at a given moment would be constructed based on historical data covering a defined time span in the past (a situation resembling a moving average). It can be assumed that new therapeutic recommendations cause the patient's body to function differently, which leads to the obsolescence of the digital twin. At present, it is unclear whether each new twin should be built independently or derived as a modification of the previous one, as well as how frequently therapeutic recommendations should be updated.

Another issue concerns the method of verifying the effectiveness of the proposed approach in real-world therapy. The criterion proposed in the article, based on calculating the area under the blood glucose curve that exceeds permissible limits, should certainly not be applied. Instead, primarily medical measures such as TIR (Time in Range), TBR (Time Below Range), and TAR (Time Above Range) should be used. In this study, TIR, TAR, and TBR indicators were not applied, as the analyzed periods—namely, one day—were too short for their use. Furthermore, at this stage it is not possible to draw conclusions about the practical usefulness of the proposed method, and the application of these indicators could misleadingly suggest otherwise, potentially leading to erroneous interpretations.

A possible subsequent stage of research will therefore involve the selection of research hypotheses, the development of analytical methods appropriate to medical practice, and the design of corresponding computer applications.

5. CONCLUSIONS

This paper presents an original method for determining therapeutic recommendations for individuals with type 1 diabetes, based on the digital footprint generated by modern insulin pumps and CGM systems used by the patient, using machine learning techniques. The method has been implemented as a computer program that can be classified as an expert system. Numerical experiments conducted with this system showed satisfactory performance. The obtained results clearly support the recommendation of the developed system for further research.

Disclaimer

Any information contained in the paper is not intended to provide personal medical advice. If you need medical advice regarding your diabetic problems, you must contact a diabetes specialist. No human or animal experiments were conducted for the purposes of the presented research.

Conflicts of interest

The author declare no conflict of interest.

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