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The usefulness of the T1DDS simulator in the context of multi-day type 1 diabetes therapy

Przydatność symulatora T1DDS w kontekście wielodobowej terapii cukrzycy typu 1

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Abstract
The motivation behind the research described in this article was to explore the possibility of using the T1DDS simulator in the context of type 1 diabetes therapy lasting longer than one day. The T1DDS simulator has so far been used within a one-day scope and in this form was employed as the computational engine in the educational application T1DCoach. A natural step in seeking further applications of the simulator is the attempt to use it to support real therapy. The article presents the capabilities of the simulator in its original form regarding therapeutic areas of application.

Keywords: type 1 diabetes; computer simulation; computer aided therapy

Streszczenie
Motywacją prac badawczych opisanych w niniejszym artykule było sprawdzenie możliwości użycia symulatora T1DDS w kontekście terapii cukrzycy typu 1 trwającej dłużej niż jedną dobę. Symulator T1DDS był dotychczas wykorzystywany w zakresie jednej doby i w tej formie został użyty jako silnik obliczeniowy w aplikacji edukacyjnej T1DCoach. Naturalnym etapem poszukiwania kolejnych zastosowań symulatora jest próba użycia go do wspomagania terapii rzeczywistej. W artykule zostały przedstawione możliwości symulatora w jego oryginalnej formie pod kątem terapeutycznych obszarów zastosowania

Słowa kluczowe: cukrzyca typu 1; symulacje komputerowe; terapia wspomagana komputerowo

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1. Introduction to T1DDS simulator

Type 1 Diabetes Direct Simulator (T1DDS) is an original mathematical algorithm describing the physiological response of a type 1 diabetes (T1D) patient to carbohydrates and insulin. The computer program that implements the algorithm is also called T1DDS. For this reason, the simulator can be considered to be a virtual patient. Figure 1 provides a global overview of modern T1D therapy. The goal of the therapy is to maintain a state of the patient (1) within an acceptable range. This state refers to the patient's blood glucose concentration, which should ideally remain between 70 mg/dl and 130 mg/dl. Every meal consumed (2) leads to an increase in concentration, while injected insulin induces a decrease. Currently, the most common method of insulin administration is an insulin pump (3.1) with an infusion set (3.2). The measurement of blood glucose concentration is performed using a Continuous Glucose Monitoring System (CGM), which consists of a sensor (4.1) and a remote reader (4.2).

The therapy is a process that takes place over time. Meals are consumed at specific moments. Each meal initiates the digestion process, which also takes time.

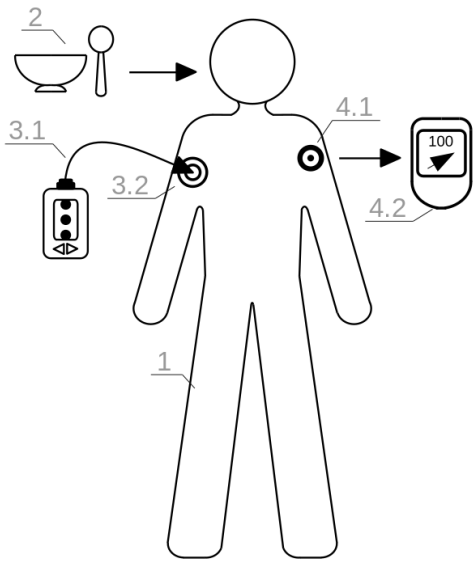

Figure 1: The global view of type 1 diabetes therapy. Actors of the therapy: 1 – a patient, 2 – meals that the patient consumes, 3.1 – an insulin pump, 3.2 – an insulin infusion set, 4.1 – a sensor of a CGM, 4.2 – a reader of the CGM.

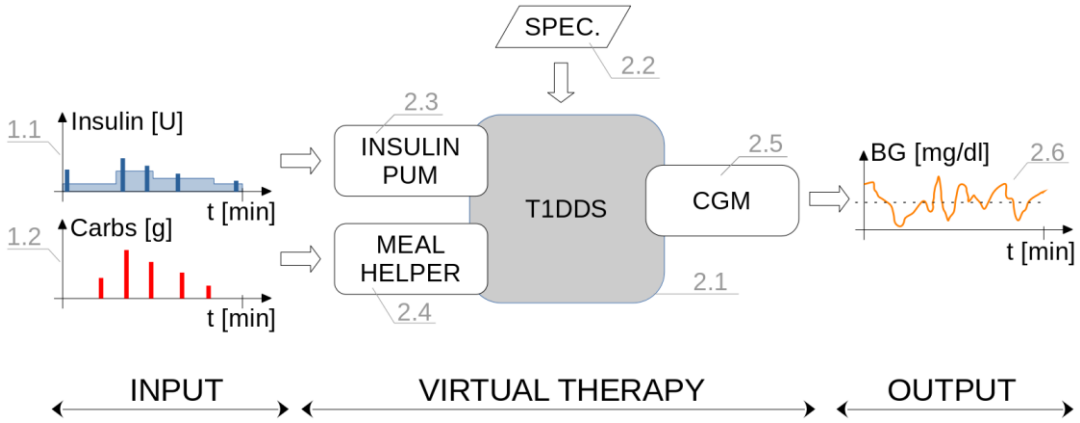

Figure 2: The virtual therapy using T1DDS simulator. Items: 1.1 – a time program of insulin injection, 1.2 – a time program of carbohydrates consumption, 2.1 – T1DDS simulator, 2.2 - specification of the simulator obtained from the calibration process, 2.3 – a virtual insulin pump, 2.4 – a virtual meal provider, 2.5 – a virtual CGM, 2.6 – time record of blood glucose (BG) concentration.

The situation is similar with the insulin. It is injected in single doses, each of which is absorbed through a physiological process that takes several hours. At any given moment, the patient's blood glucose level, which is the result of the two aforementioned processes, can be measured. In real therapy, time passes continuously. It never pauses or returns, making past states impossible to revisit.

The main task of the T1DDS simulator is to act like a real person within the scope described above. Its key characteristic is its ability to adapt to a real patient based solely on therapeutic data recorded during outpatient therapy, which distinguishes it from alternative simulators. Once calibrated to a real patient, the T1DDS simulator can be considered their digital twin. This leads to a virtual T1D therapy, as illustrated in Figure 2. The virtual therapy is analogous to the real therapy shown in Figure 1, with the difference that every real participant is replaced by its virtual counterpart, i.e., a computer program. A real patient is replaced by their digital twin, which is the T1DDS simulator (2.1) calibrated (2.2) using the patient's historical therapeutic data.

The virtual insulin pump (2.3) is able to administer insulin to the T1DDS according to a specified program (1.1). The meal helper (2.4) serves meals at designated times (1.2). The virtual CGM (2.5) reads and records the virtual patient's blood glucose concentration (2.6). The insulin program (1.1) consists of two parallel parts. The first part is single doses given in insulin units (U) at specific moments. These doses are presented as blue bars (see Figure 2, item 1.1). The second part is continuous insulin infusion, represented as a light blue area under the step line. For the meal program (see Figure 2, item 1.2), only single meals at designated times are possible, depicted by red bars. Unlike real therapy, the virtual one allows for various types of experiments without the risk of harming a living individual

2. The calibration of the T1DDS simulator

Before the T1DDS simulator can be used in virtual therapy, it must be calibrated using historical therapy data from a real patient. The result of this calibration is the specification (see Figure 2, item 2.2). The simulator specification consists of three day-cyclic functions describing: the patient's liver activity, insulin sensitivity, and glucose sensitivity. The liver activity function indicates how much glucose the liver releases into the bloodstream throughout the day. Insulin sensitivity quantifies the decrease in blood glucose level in response to injected insulin, while glucose sensitivity reflects the increase in blood glucose level in response to glucose released into the bloodstream by the liver or the digestive system. Both sensitivities change throughout the day. An example model configuration is presented in Figures 10, 11 and 12. Further details on the T1DDS simulator can be found in [1-3].

The virtual set-up used to determine the model specification based on a patient's historical therapy data is shown in Figure 4. In this case, historical data from a real therapy (1.1, 1.2, 1.3) serves as the input. This data, drawn from a typical daily outpatient T1D therapy, must cover at least one day and include records of injected insulin (1.1), consumed carbohydrates (1.2), and blood glucose concentration (1.3). The T1DDS simulator requires this data to be provided with minute-level resolution. Assuming that the historical records of insulin now form the insulin program and the meal records form the meal program, virtual therapy can be performed. However, in this case, the simulator specification is unknown and must be determined. This is the purpose of the calibration. The goal of the calibration is to identify a model specification that makes the simulation output (2.6) as close as possible to the historical records (1.3). For this, an agreement processor (3.1) is needed to compare two records of blood glucose concentration. Mathematically, the challenge lies in comparing two time series of blood glucose levels. The first series contains the historical data (1.3), while the second represents the simulation output (2.6). In the case of blood glucose concentration, discrepancies at lower values are more significant than at higher ones [4]. This aspect must be taken into account. First, the agreement processor (3.1) creates a histogram of the absolute error for the given time series. The absolute error is the absolute difference between the measured value and the value

obtained from the simulation, calculated with an accuracy of 1 mg/dl. If the glycaemia value from the simulation falls outside the specified physiological range of 30–500 mg/dl, the error is set to the penalty value of 1000 mg/dl. This penalty is at least twice as high as any error that can occur within the physiological range. Finally, the error values are discrete and range from 0 to 1000 mg/dl, though not all values may appear. The error histogram shows what fraction of samples (ranging from 0 to 1) from the entire series has a specific error value. In other words, the graph's horizontal axis displays all possible error values from 0 mg/dl to 1000 mg/dl, while the vertical axis shows a value from 0 to 1, representing the occurrence rate of each error. The error rates sum to 1. Secondly, the total weighted absolute error is calculated based on the histogram, which is the sum of the products of the error values and their occurrence rates. Due to the use of the penalty value, the 'working area' of the weighted absolute error is concentrated near the value of 1. The 'working area' refers to the range of glycaemia analyses where values do not exceed physiological limits. To utilize the full range from 0 to 1, a bias function is applied (1):

$$f(x) = \frac{x}{(1/0.95 - 2)(1 - x) + 1} \quad (1)$$

where the value of the total weighted absolute error should be substituted for x. The result of the bias function is a value between 0 and 1, where 0 indicates a perfect fit and 1 no fit. The result is not intuitive and the final fitness value of the processor is obtained by subtracting the value form 1, which reverses the meaning of 0 and 1.

In the T1DDS simulator, it is assumed that the three-day cyclic functions (liver activity, insulin sensitivity, and glucose sensitivity) are represented as polylines defined by six nodes each (see Figure 3). Among the tested methods, the standard genetic algorithm was found to be the most efficient option for finding these functions during calibration. An individual in the genetic algorithm represents the three functions. The horizontal axis boundaries of each zone are simply determined by dividing the day into six equal periods, while the vertical-axis boundary values (V_{min}, V_{max}) are individually and arbitrarily set for each function based on medical guidelines: 0-10 g/min for liver activity, 50-150 (mg/dl)/U for insulin sensitivity, and 5-15 (mg/dl)/g for glucose sensitivity.

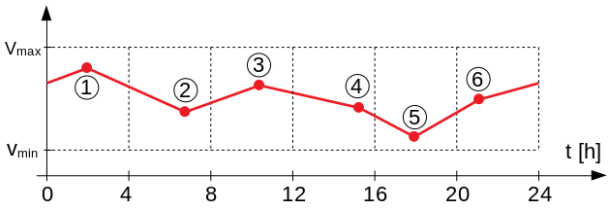

Figure 3: The shape of day cyclic polynomial defined by 6 nodes. (The values at the begging and the end of the day are the same).

Each node is assigned to one of these limited, non-overlapping zones. Thus, identifying the three functions reduces to locating 3×6=18 nodes. The coordinates of these points are normalized to a range from 0 to 1, so finding a solution requires determining a sequence of 36 numbers between 0 and 1. This sequence forms the chromosome of an individual in the genetic algorithm, where each number represents a gene. The calculations has been based on a population of 1000 individuals, with the initial generation generated randomly. Each individual provides a unique specification, allowing virtual therapy to be conducted for each, and their agreement with historical data is evaluated. Consequently, individuals can be ranked from best to worst, which is the key point in the genetic method.

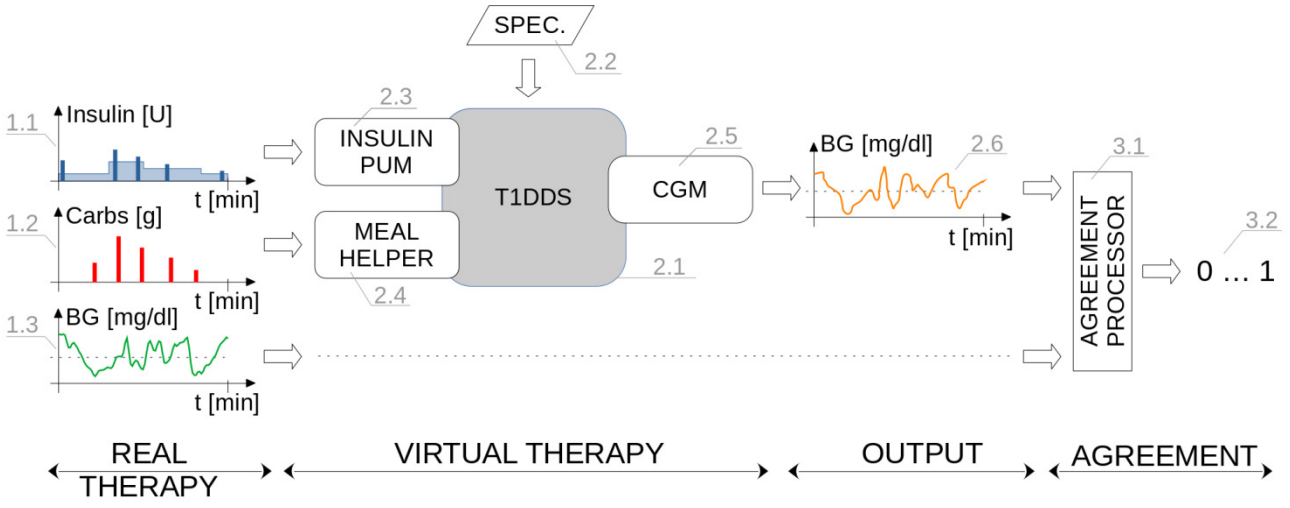

Figure 4: The virtual set-up for T1DDS calibration. Records of real historical therapy: 1.1 – injected insulin, 1.2 – consumed carbohydrates, 1.3 – recorded blood glucose concentration, 3.1 – an agreement processor for 1.3 and 2.6, 3.2 – a fitness value i.e. the output of the agreement processor. The other items has been described in Figure 2.

The final solution is derived by producing successive generations. The top 1% of individuals advance to the next generation without any modifications, while the remainder are replaced by their offspring. For each

individual the second parent is selected using the tournament method (at a rate of 30%) and the descendant is created using the uniform gene mixing method. The stopping condition for generating further generations is met when there is no improvement in the result over the previous 250 generations, so, in practice, the solution is typically achieved between the 550th and 650th generations.

3. Alternative Type 1 Diabetes simulators

Although Type 1 Diabetes (T1D) is a common disease worldwide, only a few diabetes simulators have been developed to date. Undoubtedly, the T1DMS (Type 1 Diabetes Metabolic Simulator) is currently the most advanced and reliable computer simulator in the field of diabetes [5-7]. It is the first (and currently only) in silico diabetes model accepted by the FDA (U.S. Food and Drug Administration) as a substitute for pre-clinical animal testing of new treatment strategies for T1D. The simulator is developed in collaboration between the University of Padova (Italy) and the University of Virginia (USA). It is based on multiple differential equations and several dozen parameters, with the exact number of equations varying by simulator version and functions used. The most popular version incorporates 16 equations and 42 parameters.

According to [8-10], AIDA is a freeware computer program that enables the interactive simulation of plasma insulin and blood glucose profiles for demonstration, teaching, self-learning, and research purposes. Originally developed in 1991, the latest version was published in 2012. The AIDA model uses 4 differential equations along with twelve auxiliary relations.

Configuring either of the above models involves determining values for parameters such as insulin elimination rate, insulin pharmacodynamics parameters, reference basal insulin level, constant for enzyme-mediated glucose uptake, insulin-independent glucose utilization rate, reference glucose utilization value, slope of the peripheral glucose utilization vs. insulin line, rate constant for glucose absorption from the gut, maximal gastric emptying rate, volume of glucose distribution per kg body weight, body insulin sensitivity parameter, and hepatic insulin sensitivity parameter. Unfortunately, determining the values of all these parameters is not feasible in outpatient therapy conditions. This limitation makes these models unsuitable for typical everyday therapeutic use.

4. Research problem and methodology

The T1DDS simulator described above and its calibration method have been successfully used to create an original educational mobile application T1DCoach [11] (see Figure. 5) for learning how to manage type 1 diabetes therapy. For this purpose, a simulator calibrated over a period of 1 day was sufficient. The aim of this research was to investigate the possibility of calibrating the simulator over a period longer than a single day.

Figure 5: T1DCoach mobile application [11].

The research program was based on therapy records from five real patients with T1D. The characteristics of the study group are presented in Table 1. Two distinct 3-day timeframes of real therapy were randomly selected for each patient. For each timeframe, the model was calibrated for periods of 1, 2, and 3 days.

Table 1: Characteristics of the research group

Patient	Sex	Age [years]	Height [cm]	Weight [kg]	Insulin
1	M	11	145	37	Novorapid
2	F	9	136	34	Novorapid
3	M	9	133	43	Novorapid
4	F	6	108	20	Humalog
5	F	6	116	26	Humalog

5. Results

Tables from 2 to 6 contains values of the fitness obtained in the process of calibration of the T1DDS simulator for the group of real patients. The values are given for calibration of 1, 2 and 3 days for the two timeframes.

Table 2: Values of calibration fitness obtained for the Patient 1

Calibration	Timeframe 1	Timeframe 2
1 day	0.645	0.757
2 days	0.501	0.612
3 days	0.344	0.427

Table 3: Values of calibration fitness obtained for the Patient 2

Calibration	Timeframe 1	Timeframe 2
1 day	0.735	0.737
2 days	0.533	0.623
3 days	0.519	0.533

Table 4: Values of calibration fitness obtained for the Patient 3

Calibration	Timeframe 1	Timeframe 2
1 day	0.642	0.590
2 days	0.605	0.449
3 days	0.539	0.401

Table 5: Values of calibration fitness obtained for the Patient 4

Calibration	Timeframe 1	Timeframe 2
1 day	0.680	0.774
2 days	0.573	0.709
3 days	0.563	0.658

Table 6: Values of calibration fitness obtained for the Patient 5

Calibration	Timeframe 1	Timeframe 2
1 day	0.806	0.769
2 days	0.730	0.624
3 days	0.630	0.503

The following diagrams (Figure 6-9) provide a visual representation of the calibration results from selected perspectives. The results has been grouped by patient and by the length of calibration.

The diagrams in Figures 10-12 presents an example of the T1DDS simulator specification obtained in the process of calibration. The specification concerns the case of the 1 day calibration of the Patient 5 in timeframe 1, which is the best fit.

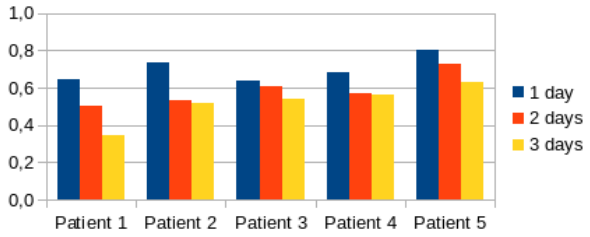

Figure 6: Values of calibration fitness for the timeframe 1 grouped by patient.

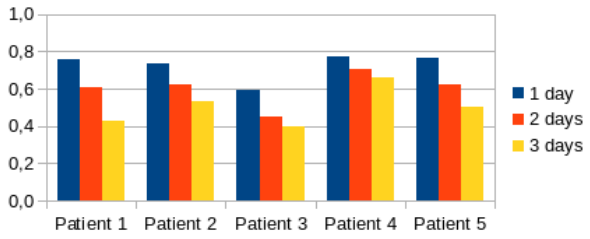

Figure 7: Values of calibration fitness for the timeframe 2 grouped by patient.

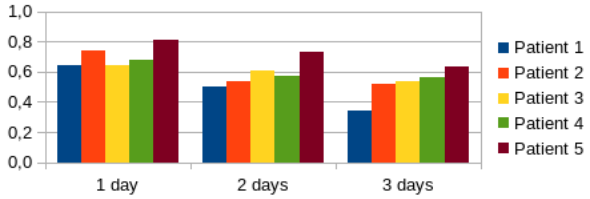

Figure 8: Values of calibration fitness for the timeframe 1 grouped by the length of calibration.

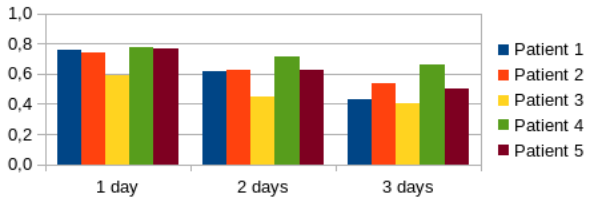

Figure 9: Values of calibration fitness for the timeframe 2 grouped by the length of calibration.

The table summarises the mean values obtained for all patients.

Table 7: Average values of calibration fitness

Calibration	Timeframe 1	Timeframe 2
1 day	0.702	0.725
2 days	0.588	0.603
3 days	0.519	0.504

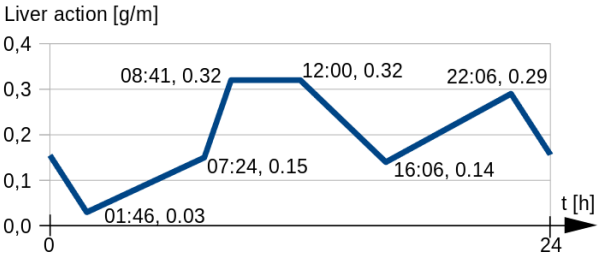

Figure 10: The liver activity obtained for the Patient 5 in 1 days calibration in the timeframe 1.

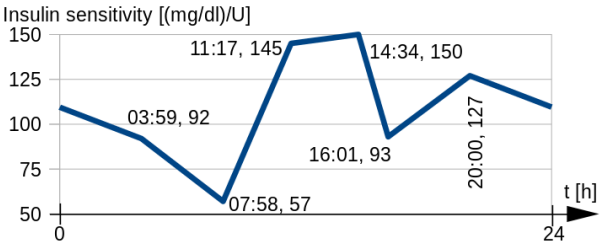

Figure 11: The insulin sensitivity obtained for the Patient 5 in 1 days calibration in the timeframe 1.

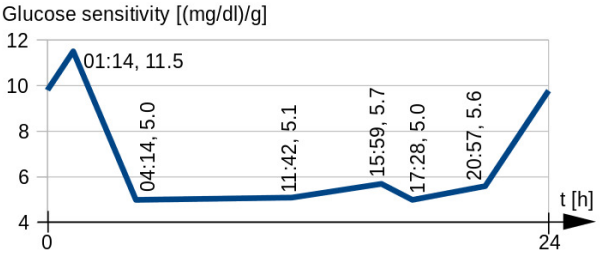

Figure 12: The glucose sensitivity obtained for the Patient 5 in 1 days calibration in the timeframe 1.

Graphs in the Figures 13 and 14 confront historical blood glucose concentration (HIST) with simulation output obtained using T1DDS simulator calibrated for 1, 2 and 3 days (1DAY, 2DAYS, 3 DAYS). The graphs show the best and worst case respectively.

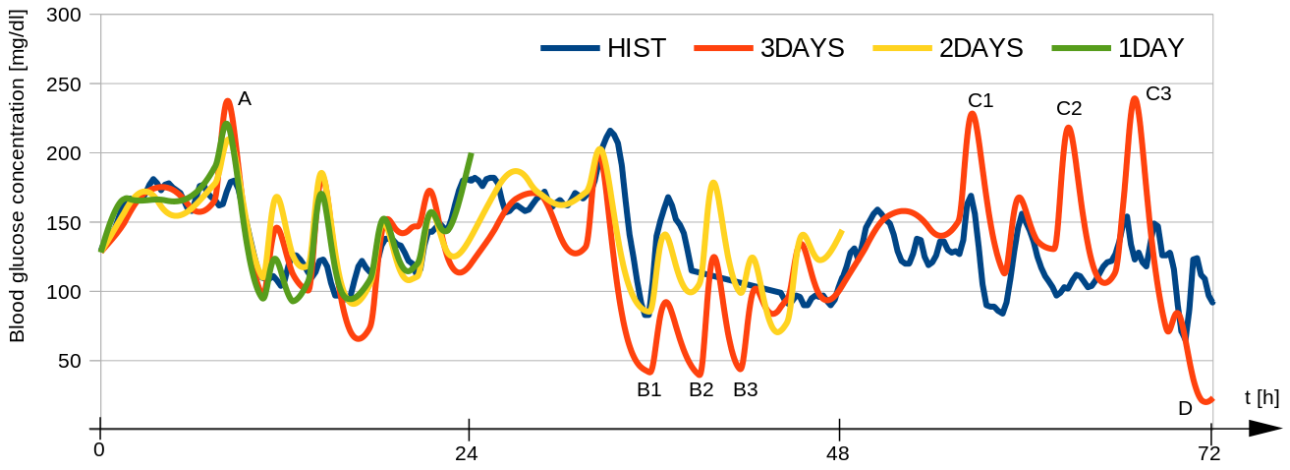

Figure 13: Historical blood glucose concentration (HIST) versus simulation output (1DAY, 2DAYS, 3DAYS). The results relate to Patient 5, timeframe 1, the best case.

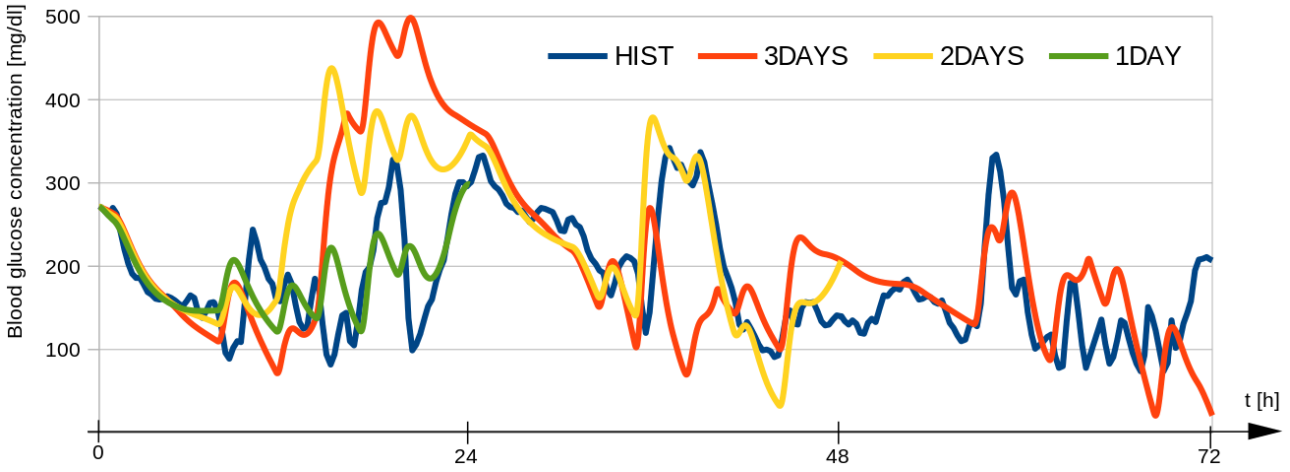

Figure 14: Historical blood glucose concentration (HIST) versus simulation output (1DAY, 2DAYS, 3DAYS). The results relate to Patient 3, timeframe 3, the worst case.

6. Discussion

The T1DDS simulator has been developed to replicate the physiological response of a type 1 diabetes patient. It has been successfully used to create an educational application for teaching type 1 diabetes therapy (see Figure 5). In this context, the model was calibrated using historical data from real patients for a one-day timeframe. Within this scope, the T1DDS model demonstrated satisfactory convergence with real patients.

The aim of the research was to verify whether the T1DDS model can replicate the physiological response of a patient over a period longer than one day. The motivation for this research was to determine whether the model could be applied for therapeutic purposes. The studies were conducted on a sample of 5 real patients, analyzing selected continuous 3-day timeframes of their therapy.

The analysis results showed that the model demonstrates the highest convergence for a single day. For longer periods, this convergence decreases. The average convergence according to the adopted evaluation method was approximately 0.7 for one day, ~0.6 for two days, and ~0.5 for three days (see Table 7). The decline in convergence was observed for all patients and consistently showed a similar pattern, as seen in the charts (see Figures 6 and 7). However, the comparison of results shown in Figures 8 and 9 indicates that the ability of the T1DDS model to represent a patient is an attribute of the patient (specifically, their data) and does not depend on the length of the calibration period. In other words, if patient A's model shows higher convergence than patient B's model, this better convergence applies to all analysis periods, i.e., 1, 2, or 3 days.

The charts in Figures 13 and 14 illustrate example results of retrospective simulations. A retrospective simulation is performed using the calibrated simulator with the same input data that were used for calibration. The outcome of such a simulation is a blood glucose concentration plot that can be compared with the historical plot. Figure 13 shows results for patient 5 analyzed during the first 3-day timeframe, while Figure 14 shows results for patient 3 in the second timeframe, representing the best and worst results, respectively. On both charts, the historical glucose concentration is marked in blue, while the

results of the retrospective simulations for periods of 1, 2, and 3 days are marked in green, yellow, and red, respectively. It is easy to visually assess that for Patient 5, the convergence of the plots is better than for Patient 3.

Let's consider the possibility of using computer simulation results to make therapeutic decisions for patient 5. At point A, all three computer simulation results indicate the occurrence of hyperglycaemia, which would necessitate administering an additional dose of insulin. However, in reality, the hyperglycaemia did not occur. Thus, administering additional insulin to the actual patient would be a therapeutic error. At points B1, B2, and B3, the computer simulation predicted three episodes of hypoglycaemia that did not occur in reality. Similarly, at points C1, C2, and C3, the simulations showed three false episodes of hyperglycaemia. At points D1 and D2, there were false episodes of hypoglycaemia again. After this brief analysis, it must be concluded that making therapeutic decisions based on the direct results obtained from the T1DDS simulator would lead to therapeutic errors.

7. Conclusions

The aim of the conducted research was to assess the usefulness of the T1DDS simulator in the context of multi-day type 1 diabetes therapy. This simulator had previously been successfully used for single-day therapy in educational applications. Extending the context is necessary when using the simulator for therapy support purposes. However, the research showed that extending the context leads to a decrease in the convergence of the simulator's results with actual outcomes. This discrepancy is not significant for educational applications but poses an obstacle for therapeutic use. Therefore, using the T1DDS simulator for supporting type 1 diabetes therapy requires its improvement or the development of a method for interpreting the results obtained through it. The results obtained in this research quantify the loss of convergence of the T1DDS model depending on the time interval of the actual therapy being mapped. This is essential knowledge for further development of the simulator and the method.

Disclaimer

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

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