Computers in Biology and Medicine 108 (2019) 242–248

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/compbiomed

Rapid automatic identification of parameters of the Bergman Minimal Model in Sprague-Dawley rats with experimental diabetes for adaptive insulin delivery

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ARTICLE INFO

Keywords:
Diabetes model
Identification
Adaptive insulin delivery
Minimize comorbidities from diabetes

ABSTRACT

Glucose-Insulin regulation models can be used to individualize insulin therapy. However, the experimental techniques currently used to identify the appropriate parameter sets of an individual are expensive, time consuming, and very unpleasant for the patient. Since there is a wide range of intrapersonal parameter variability, the identified parameters in a laboratory setting (at rest) are not optimal for dynamic conditions of daily activities. In this study we propose a methodology to identify three parameters of Bergman's Minimal Model in streptozotocin-induced diabetic rats from the experimental data of the glucose response to exogenous insulin doses, based on a genetic algorithm (GA). The algorithm requires glucose measurements from a continuous subcutaneous sensor once every 5 min and the amount of injected insulin. The model parameters of 20 *in vivo* experiments (from 19 rats) were identified with high accuracy and the average root-mean squared (RMS) error between predicted and measured glucose concentration was 17.6 mg/dl. Since the algorithm requires a relatively short (60–120 min) observation time it can be used for real-time parameter identification to optimize insulin infusion systems. Model parameter changes due to experimental settings like drug testing or in natural lifestyle changes should be calculable, on-the-fly, using data from only the glucose sensor and the amount of insulin delivered.

1. Introduction

Diabetes mellitus, one of the most important global health problems, is a chronic disease that includes a group of metabolic disorders, characterized by hyperglycemia due to defects in insulin secretion and/or insulin action. Chronic hyperglycemia is responsible for long-term damage and dysfunction of various organs and leads to serious life-threatening complications and death [33]. According to the International Diabetes Federation (IDF) Atlas Report, in 2017, the global prevalence of diabetes was 8.8%. Three quarters of diabetic patients live in low and middle-income countries, and 50% of the adults with diabetes are undiagnosed [16].

There are two main types of diabetes: Type 1 diabetes mellitus (T1DM) and Type 2 (T2DM) [16]. T1DM is usually characterized by an absolute insulin deficiency, due to autoimmune β-cell destruction, and it requires daily administration of insulin to regulate blood glucose, and often presents an abrupt onset of symptoms including hyperglycemia [1,2]. Given current knowledge, this type of diabetes cannot be prevented nor cured. T2DM results from the body's ineffective use of insulin, and this is the most common type of diabetes. Symptoms of T2DM are usually neglected because their onset is less marked, and the patient can spend several years undiagnosed until complications appear [33].

T1DM must be treated with multiple mandatory daily insulin injections whose doses must be individualized according to the metabolic condition of each patient and self-monitored glucose levels [1]. For T2DM there are several treatments, but it has been proven that most of

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https://doi.org/10.1016/j.compbiomed.2019.03.028
Received 20 February 2019; Received in revised form 16 March 2019; Accepted 28 March 2019
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these patients will require treatment with supplemental insulin [29]. The majority of diabetes patients experience glycemic instability that is highly associated with comorbidities, therefore there is an unmet medical need for more effective insulin therapies, optimized to minimize comorbidities [14].

Mathematical models of glucose-insulin dynamics have proven to be useful clinical tools as well as an approach to understanding diabetes mellitus pathogenesis [5]. Models have been developed using complicated methods to identify individual patient parameters, that are uncomfortable for the subject under test.

The Bergman Minimal Model uses a modified version of an intravenous glucose tolerance test (IVGTT) which requires frequent samples of plasma glucose and insulin and it is known as the Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT). This test must be done in a hospital with specially trained personnel while the patient is at rest and it takes 3 h to determine the individual model parameters [5,26].

A more recent model focused on T1DM is the UVA/PADOVA Type 1 Diabetes Simulator. To identify the model parameters a triple tracer protocol is used with oral $[1-^{13}C]$ glucose and intravenous $[6-^{3}H]$ glucose and $[6,\ 6-^{2}H_2]$ glucose [3,20]. To perform the protocol the patient must eat a weight maintenance diet for three days before the procedure and is admitted to the hospital one day before the procedure begins. On the procedure day, the patient must keep his hand in a heated Plexiglass box at 55 °C for blood sampling during the study that lasts 10 h to determine the individual model parameters.

These techniques obtain excellent results but they are expensive, time-consuming and the parameter variability must also be evaluated. In the short term, transitory acute circumstances like Dawn Phenomenon or aerobic exercise can influence the results. Dawn Phenomenon is an excessive increment from nocturnal blood glucose level due to a surge of hormones, 52% and 40% prevalence has been reported in T1DM and T2DM respectively [24,27].

Aerobic exercise can alter the glucose uptake both during the exercise and for several hours afterwards by increasing insulin sensitivity; or in a permanent way when the patient enrolls in a long-term training program [7]. In the case of children, exercise stimulates growth hormone and catecholamine responses. This is especially important in T1DM patients because they are prone to hypoglycemia during exercise. In a study with 50 children 83% of them lower by at least 25% their basal glucose during a 75 min aerobic exercise session, and 15 of them presented hypoglycemia [15].

In this study, we identify three individual parameters of Bergman's Minimal Model, using a Genetic Algorithm, from the glucose response to exogenous insulin measured via continuous glucose sensing, reporting the level every five minutes. Data sets were obtained from 20 *in vivo* experiments in 19 animals in which the initial glucose ($G(0)_{mean}$ = 344 mg/dl), experiment duration was variable (t_{mean} = 80 min), and in most cases the result was good ($RMS_{mean\ error} = 17.26\ mg/dl$).

Since the algorithm requires a relatively short observation time (typically 60–120 min) it can be used for real-time parameter identification to evaluate parameter variation and adapt optimal insulin infusion systems. It can also be used to easily evaluate parameter changes due to experimental settings like drug testing or life style changes using only the glucose sensor and the injected amount of insulin.

2. Methodology

2.1. In vivo experiments

The *in vivo* experiments were conducted according to the national regulations for the care and use of laboratory animals (NOM-062-ZOO-1999). Approval for these studies was granted by the institutional ethical committee.

Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ) solution (40 mg/kg in acetate buffer 0.1 M, pH 4.5) given to 19 overnight fasted female Sprague-Dawley rats (250–300 g). Diabetes was identified by non-fasting plasma glucose of 250 mg/dl or higher 48 h after injection of STZ. The animals had access to water and food *ad libitum* after the STZ injection.

Glucose was measured continuously using a Guardian REAL-Time Monitor (Medtronic). The dorsal area of the rat was shaved and the skin prepped with alcohol. Rats were placed in the prone position on a sterile field. Glucose Sof-Sensor (Medtronic) was implanted in the dorsal area using the manufacturer's insertion device (Sen-Serter, Medtronic). The transmitter was connected to the glucose sensor and covered with Tegaderm. Sensors and transmitters were further secured to the rat dorsum by wrapping them with Vetrap ® wound dressing. The wrapping was checked every twelve hours and renewed if necessary.

Blood glucose levels were manually measured every 12 h using FreeStyle Lite test strips and a hand-held glucometer (Abbott). For each measurement, one drop of blood was collected via a single needle stick (Thin Lancets, Abbott) from the tail vein. The blood glucose measurements were used to calibrate the continuous Guardian REAL-Time Glucose Monitor.

The day after glucose sensor implantation the glucose-insulin response test was performed. Insulin was infused using an insulin pump (Medtronic) until glucose was under 120 mg/dl.

2.2. Bergman Minimal Model

There are several models to describe the glucose-insulin system but the Bergman Minimal Model [6] represents the simplest model that describes the glucose-insulin regulatory system with sufficient accuracy to be useful. It has been used as an approach to understand the effects of insulin secretion and insulin sensitivity on glucose tolerance and risk for diabetes. The original assumptions of the model (T2DM) have led to an understanding of the kinetics of insulin *in vivo*, as well as the relative importance of β-cell compensatory failure in the pathogenesis of diabetes [5]. This model is given by the differential equations

$$\begin{aligned} \dot{G} &= -p_1(G-G_b) - G\,X \\ \dot{X} &= -p_2X + p_3(I-I_b) \\ \dot{I} &= -n(I-I_b) + \gamma\,[G-h]^{+}t + u(t) \end{aligned} \tag{1}$$

where G, X and I are plasma glucose concentration (mg/dl), the insulin mediated reduction of glucose concentration (min^{-1}), and insulin concentration in plasma respectively ($\mu U/ml$). G_b and I_b are the basal values of the plasma glucose and insulin concentration. $u(t)$ represents the insulin infusion rate, p_1 insulin-independent glucose disappearance rate (min^{-1}), also known as glucose effectiveness (S_G). p_2 is the rate of spontaneous decrease of tissue glucose uptake ability (min^{-1}), and p_3 is the insulin-dependent increase in tissue glucose uptake ability per unit of insulin concentration excess over basal insulin $\left(min^{-2}\left(\frac{\mu U}{ml}\right)^{-1}\right)$. The term $\gamma\,[G-h]^{+}t$ represents the pancreatic insulin secretion after a meal at $t=0$. The parameter n represents the disappearance rate of endogenous insulin ($\min^{-1}$) [26]. STZ-induced diabetes is comparable with T1DM [14]. The simplicity of the Bergman Minimal Model permits changing the original assumption of T2DM to also represent Type 1 Diabetes Mellitus by setting $\gamma = 0$, $p_1 = 0$ and a low I_b considering the damage caused by STZ to the $\beta - cells$ [11,19].

3. Parameter identification algorithm

In this section, we present the algorithm used to identify the parameters of the model (1) given that the parameters n, p_2 and p_3 are unknown for all of the rats. Since the T1DM diabetic condition was induced in the subjects, $p_1 = 0$, $G_b = 70$, $X(0) = 0\ I(0) = 0$ [11], and $G(0)$ was set equal to the initial value of the measured glucose of all 20 experiments. The algorithm that is used to find an optimal set of parameter values, given the experimental data, is based on a Genetic Algorithm (GA), that is described next.

3.1. Genetic Algorithms

In this study, we use an approach based on a GA [23,25] to find an individual's model parameters given that only two variables of experimental data are available. This genetic algorithm belongs to the group of so-called Evolutionary Algorithms (EAs) [8,9,23], characterized as methods that mimic the evolution of species, where different genes and chromosomes from *parents* are combined to produce offspring which inherit some of their parental characteristics, but also can suffer mutations from one generation to the next that modify their characteristics [25]. Therefore, a GA is focused on the optimization of a certain objective function called the *fitness function* via an iterative process starting from a set of candidate solutions called a *population*, which in this case is the set of parameters that minimize the mean squared error between the model's output and the experimentally measured glucose level and a known insulin input.

Given their characteristic nature, the GAs are often used in problems where no global convexity is expected, or when the parameter search space is large and numerous local minima could exist [17,31]. In the general practice of identification processes, the root-mean squared error (RMSE) is used as a measurement of the accuracy between the experimental values $G[k]$ and the signal produced by a certain model $\hat{G}[k]$, and is defined as

$$RMSE(G[k], \hat{G}[k]) = \sqrt{\frac{\Sigma_k (G[k], \hat{G}[k])^2}{n}} \quad (2)$$

It can be seen that all observations and output generated values are included in the RMSE and outliers are heavily penalized in the quadratic term. The goal is to find the parameter values n, p_2, p_3 such that (2) is as small as possible. As (1) is given as a continuous-time model and the experimental data is obtained from samples, we use the approximation of the derivative of a certain function $f(t)$ given by

$$\frac{df(t)}{dt} \approx \frac{f(t+T_s) - f(t)}{T_s} := \frac{f[k+1] - f[k]}{T_s} \quad (3)$$

where the time is sampled as $t = kT_s,\ k \in \mathbb{Z}$, k is the sample number and $f[k] := f(T_s k)$, $f[k+1] := f(T_s(k+1))$. In this way, the discrete-time model representation of (1) is given by:

$$G[k+1] = (1 - T_s p_1)(G[k] - G_b) - T_s G[k] X[k]$$

$$X[k+1] = (1 - T_s p_2) X[k] + T_s p_3 (I[k] - I_b)$$

$$I[k+1] = I[k] - n T_s (I[k] - I_b) + T_s u[k] \quad (4)$$

where T_s is the sample time, $t = \{0,\ T_s,\ 2T_s,\ ...,\ kT_s, ..., (N-1)T_s\}$, N is the number of samples taken in the experiment, k is the sample number, $G[k] = G(T_s t)$, $X[k] = X(T_s t)$ and $I[k] = I(T_s t)$.

As it can readily be seen, finding an individual's model parameters can be posed as a minimization problem in a high dimensional space, suitable for the implementation of a GA. While there is no strict definition for a GA [23], some basic requirements must be met:

1. The central goal of a GA is to obtain extreme values of a particular function, called the ***fitness*** **function.** For our case, this is given by (2) and it depends on the unknown parameters $J = RMS(G[k], \hat{G}[k]) = J(n, p_1, p_2)$.
2. For a particular GA, a ***chromosome*** is a candidate solution to the problem typically encoded in an array of values, and also the expected minimum and maximum values. In the presented case, we define that set of values as

$$n \in [\bar{n}, \underline{n}],\ p_2 \in [\overline{p_2}, \underline{p_2}],\ p_3 \in [\overline{p_3}, \underline{p_3}] \quad (5)$$

A *population* is defined as a collection of a fixed number of *chromosomes*. A particular population can be written then as an array containing all possible solutions. For example, in the previous case, a population size of 10 chromosomes may be written as shown in Table 1 and in Fig. 1. When more than one population is considered, we call this a *Multipopulation GA* (MpGA).

Table 1
Coding of 3-genes per chromosome/individual for a possible set of solutions.

Chromosome	n	p_2	p_3
1	0.03	0.02	0.002
2	0.02	0.035	0.004
⋮	⋮	⋮	⋮
10	0.04	0.04	0.005

3. **Crossover and mutation between chromosomes.** A crossover is a process by which two chromosomes generate a new chromosome with a recombination of genes not present in either parent. This is typically done by selecting two chromosomes from the population (randomly or using a specific criteria), called *parents.* Then, a cutting process is done selecting a specific section of the chromosome, that can either be randomly or adaptively selected [30]. Two offspring chromosomes are obtained by joining the alternate parts of the parents, as shown in Fig. 2 for a given chromosome. After the crossover is performed, a *mutation* is done. This means that a given gene or genes of the chromosome will be randomly modified to get another value from the set (5) [18]. This procedure allows the GA to perform a generally wider search on the parameter space or jump out of local minima of the objective function.

In this work, the GA has been defined by the following steps:

1. Choose the number of populations N_P.
2. Choose the number of chromosomes N_c for each generation.
3. Choose the quantization step for each parameter.
4. Initialize chromosomes for the gene set $\{n, p_2, p_3\}$ with random values in the set defined by (5).
5. Choose the N_e chromosomes that achieve the lowest value of the fitness function (2) and pass them to the next generation. This is called an *elitism* procedure, and these chromosomes will be protected from mutation. This process maintains the best chromosomes from the previous generation, while allowing more combinations upon which to search. However, it should not be a large percentage, as it would inhibit the search for new combinations that produce better values of the fitness function.
6. Generate the offspring chromosomes by a random crossing of each one at a random crossover point, as shown in Fig. 2.
7. Mutate the offspring with a Mutation Probability MP. This prevents the algorithm from getting stuck in local minima. However, too large a value of MP can cause the algorithm to discard beneficial genes from generation to generation or repeatedly miss a minimum value during exploration of the parameter space.
8. Repeat for each population until an acceptable minimum value for (2) is obtained, a maximum generation number is reached or the fitness value does not change for a given number of generations.
9. Choose the chromosome that has the minimum fitness value among all populations. In our method, the design parameters are N_P, N_g, N_e and $\%MP$.

4. Experimental results

The algorithm was run such that the results were constrained within the following limits and was initialized with random values within the same range:

$$n \in [0.01, 0.5],\ p_1 = 0,\ p_2 \in [10^{-4}, 0.21],\ p_3 \in [7 \cdot 10^{-5}, 5.1 \cdot 10^{-4}] \quad (6)$$

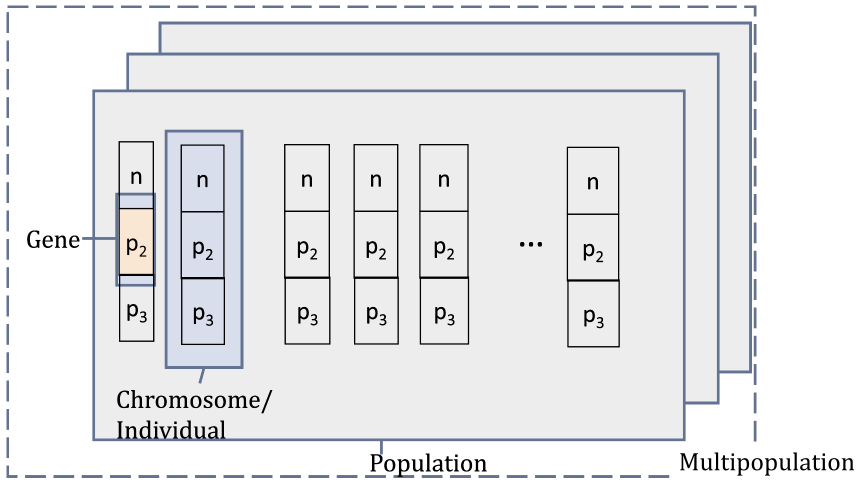

Fig. 1. Graphical representation of a gene, chromosome, population and multipopulation in a GA schema.

considering $I_b = 7$, during 600 generations (or less if the fitness function does not change for 50 gene-rations), with 200 individuals per generation, 10 populations, with 5% of elitism and 1% of mutation probability. The results are shown in Fig. 3 and Table 2, where the experimental data (glucose sensor) is compared with the model output. The mean value of the RMS error is 17.26 mg/dl glucose concentration, with outliers caused by external unmeasurable perturbations that affected both the sensing and the glucose dynamics of the individual. The Varvel performance measures were calculated. These measures are the Percentage Prediction Error (PE), Median Prediction Error (MDPE) that represents bias, Median Absolute Performance Error (MDAPE) that reflects inaccuracy, and Wobble, that is a measure of variability in each subject. These measures are defined as follows [32]:

$$PE[k] = 100\,\frac{G[k] - \hat{G}[k]}{\hat{G}[k]} \tag{7}$$

$$MDPE = median\{PE[k],\ k = 0,1,\ldots,N-1\} \tag{8}$$

$$MDAPE = median\{|PE[k]|,\ k = 0,1,\ldots,N-1\} \tag{9}$$

$$Wobble = median\{|PE[k] - MDPE|,\ k = 0,1,\ldots,N-1\} \tag{10}$$

5. Discussion

We chose a Genetic Algorithm (GA) to identify the parameters of the Bergman Minimal Model because this model includes nonlinear terms, such as $I(t)$ and $X(t)$ that were not available for measurement. Algorithms such as Least-Squares or Gradient-based cannot be used to identify the parameters because they require that the problem be posed with linear parameters. If there are nonlinear terms, these other methods require that the fitness function be at least concave or convex and this is not the case. In this application, Genetic Algorithms only require that the fitness function is well-defined. Access to non-measurable variables is not required.

The experimental goal of this research was to identify the parameters of the Bergman Minimal Model in the transition from hyperglycemia to normoglycemia. In the experiments reported in Fig. 3, this process required approximately 17 glucose measurements, spaced 5 min apart (typically 80 min). This implies the potential of this algorithm to identify model parameters in real-time. This is a significant advantage compared to traditional methods of model parameter identification. For insulin-dependent diabetic patients, model parameter identification and updates can be calculated via data from only an insulin pump and a continuous glucose monitor. Some commercial insulin pumps now integrate a continuous glucose monitor. The system demonstrated here could also be embedded in the pump for a compact single smart unit.

The Bergman Minimal Model was developed in 1979 with mongrel dogs with bodyweight between 20 and 30 kg [6]. It has also been used for cats with bodyweight range 3.7–5.7 kg [10], and mice with bodyweight 25–30 g [28]. The model was validated for different human populations [4]. It has been a valuable clinical and research tool that has helped to understand the interrelated effects of insulin secretion and insulin sensitivity on glucose tolerance [26]. This model

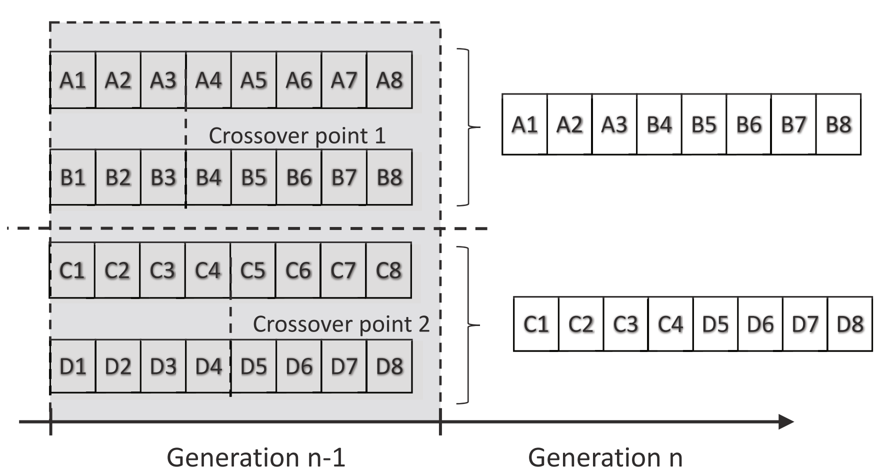

Fig. 2. Gene crossing algorithm for an 8-gene chromosome quantization.

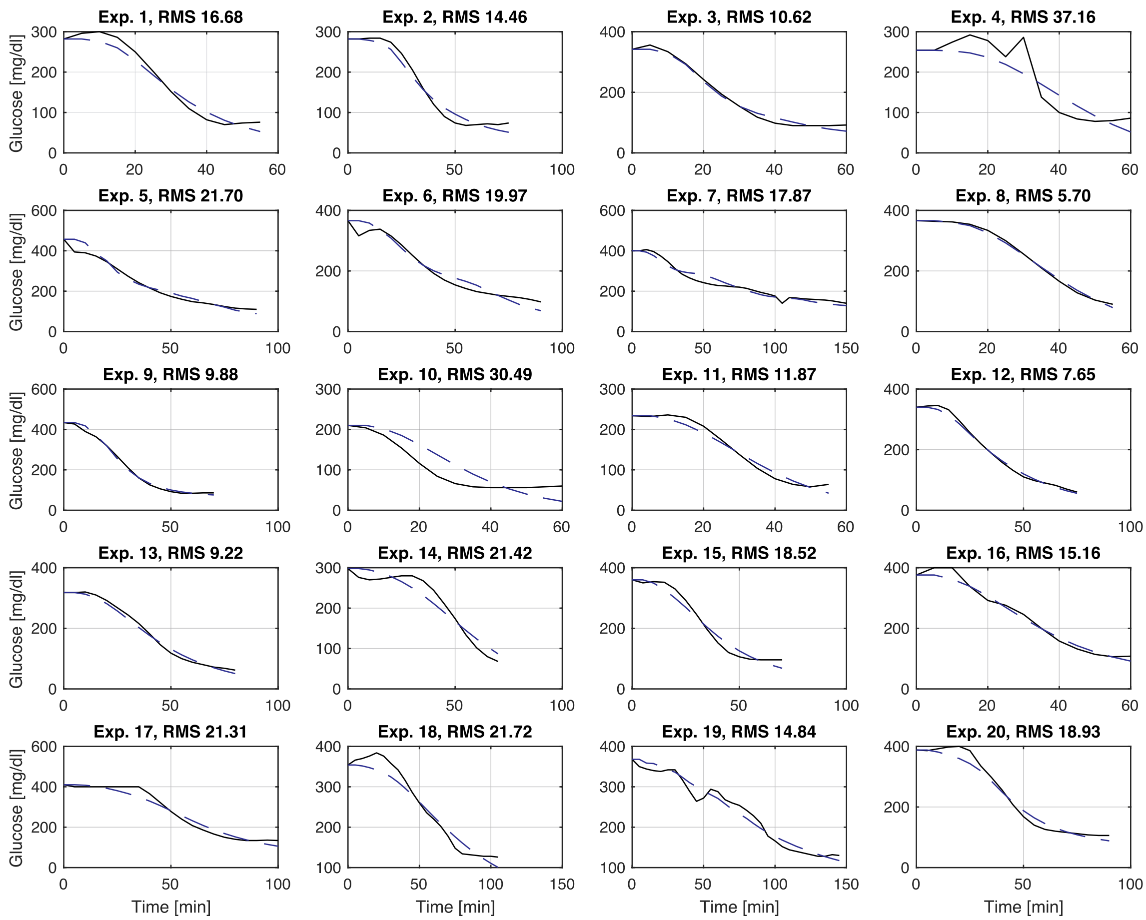

Fig. 3. Identification results and reduction to normoglycemic values. 20 experiments using 19 different animals comparing the model predictions with experimental results. The solid line is the *in vivo* experimental measurement and the output of the model with parameters identified by our genetic algorithm is the dashed line. Normoglycemic values are achieved in 50–100 min in most cases. The mean RMS error is 17.26 mg/dl glucose. The model output has a low bias (MDPE = 1.05) and inaccuracy (MDAPE = 7.85).

Table 2
Identification results with n, p_2, p_3 as unknown parameters.

Individual	n	p_2	p_3	RMS	MDPE	MDAPE	WOBBLE
1	0.03	0.0312	$0.274{\cdot}10^{-3}$	16.68	4.88	9.54	4.67
2	0.05	0.0457	$0.164{\cdot}10^{-3}$	14.46	1.87	8.96	7.09
3	0.07	0.0716	$0.510{\cdot}10^{-3}$	10.62	1.29	3.41	2.11
4	0.01	0.0002	$0.075{\cdot}10^{-3}$	37.16	8.48	17.47	8.98
5	0.21	0.0432	$0.510{\cdot}10^{-3}$	21.70	−0.56	5.78	6.34
6	0.07	0.0664	$0.289{\cdot}10^{-3}$	19.97	0.32	7.34	7.02
7	0.09	0.1373	$0.231{\cdot}10^{-3}$	17.87	2.85	6.28	3.43
8	0.01	0.0086	$0.206{\cdot}10^{-3}$	5.70	0.23	1.15	0.92
9	0.07	0.0552	$0.494{\cdot}10^{-3}$	9.88	−0.51	4.69	5.20
10	0.01	0.0146	$0.510{\cdot}10^{-3}$	30.49	−7.91	28.59	36.50
11	0.01	0.0114	$0.428{\cdot}10^{-3}$	11.87	1.88	6.46	4.57
12	0.05	0.0210	$0.289{\cdot}10^{-3}$	7.65	1.39	3.86	2.47
13	0.06	0.0002	$0.220{\cdot}10^{-3}$	9.22	3.04	4.19	1.15
14	0.01	0.0001	$0.156{\cdot}10^{-3}$	21.42	−0.79	8.32	9.11
15	0.02	0.0257	$0.397{\cdot}10^{-3}$	18.52	1.35	8.30	6.94
16	0.04	0.0342	$0.490{\cdot}10^{-3}$	15.16	0.55	5.68	5.12
17	0.03	0.0234	$0.079{\cdot}10^{-3}$	21.31	−0.35	6.84	7.19
18	0.02	0.0127	$0.087{\cdot}10^{-3}$	21.72	2.79	7.01	4.22
19	0.37	0.0096	$0.339{\cdot}10^{-3}$	14.84	−2.64	6.03	8.67
20	0.04	0.0415	$0.222{\cdot}10^{-3}$	18.93	2.74	7.13	4.40
Mean:	0.06	0.0327	$0.30\cdot10^{-3}$	17.26	1.05	7.85	6.81

incorporates the key physiological concepts, essential to explain the observed glucose dynamics [4], and it is simple enough to modify the configuration to also model T1DM [11,19]. The physiological glucose dynamics of the rat are adequately modeled by the Bergman Minimal Model [4,21,34], therefore it can be used, unmodified, for rats.

Streptozotocin (STZ) was isolated from Streptomyces achromogenes in 1960 and used as a broad-spectrum antibiotic [13]. Its diabetogenic properties were described in 1963. STZ has a selective effect that destroys the pancreatic β cells, responsible for secreting insulin [12]. Structural, functional and biochemical alterations in STZ-induced diabetes in the rat are very similar to those which appear in diabetes in humans [13]. Therefore diabetes induced with streptozotocin in rats is one of the most used animal models in which to study T1DM. It is low cost and allows a large sample size. It has been used to study diabetes prevention, insulin delivery, β cell replacement, gene therapy, artificial pancreas, diabetes complications like retinopathy, heart disease and neuropathy among others [14].

The majority of diabetes patients experience glycemic instability that is significantly associated with comorbidities, thus there is an unmet medical need for more effective insulin therapies, optimized to minimize comorbidities [14]. The majority of basic science to help to meet this medical need will most likely be conducted using the rat STZ induced diabetes model. It is useful to use the Bergman Minimal Model to analyze the resulting data and even more useful when the model parameters can be identified with minimal resources as demonstrated in this study, using, on average, 17 glucose measurements at 5 min intervals and the amount of infused insulin (typically 80 min).

Our purpose was to demonstrate that our genetic algorithm can correctly identify these three parameters of the Bergman Minimal Model *in vivo*, in rats. Not only can our algorithm correctly identify the model parameters, but there is promise that it can do so in real time with a relatively simple, scalable procedure. A limitation of this work is that meal ingestion in rats presents a different glucose dynamic than in humans. With a view toward demonstrating the performance of this genetic algorithm in humans, in a natural setting, we created a simulation using known plausible parameters for the Bergman Minimal Model and it appears in the appendix. This simulation was unlike our *in vivo* experiments in rats in two ways:

1. With the live rats we did not know the physiological Bergman Minimal Model parameters in advance.
2. In the simulation we assigned known model parameters and included a human-like simulated meal ingestion (50 g of carbohydrates) just to visualize the algorithm tracking in both falling and rising blood glucose levels.

The algorithm's accurate tracking of the blood glucose level for the entire simulation is somewhat trivial because once the algorithm calculates correct model parameters the calculated model and the given model are essentially the same. The important point is the accuracy and speed of the algorithm in calculating the model parameters. We placed these simulated results in an appendix to avoid confusion with our *in vivo* rat studies in the main part of this report.

6. Conclusions

In this study we have shown that a Genetic Algorithm can be used to identify an individual's parameters of the Bergman's Minimal Model with minimal resources: a continuous glucose sensor and the insulin profile administered to the subject. The system described here has the capability (although not shown here) to automatically analyze these two variables and provide real-time adjusted model parameters, leading to optimized insulin delivery. The system could also provide compensation for meal ingestion and for activity context-switches, like aerobic exercise, or drug effects which change model parameters. In this way, maintaining glycemic stability and reducing comorbidities, can be achieved in an efficient, economical and practical way.

Conflicts of interest

Authors declare that they do not have any conflict of interest regarding this work.

Acknowledgments

Ana G. Gallardo-Hernández acknowledges Fondo de Investigación en Salud of Instituto Mexicano del Seguro Social (IMSS), Grant FIS/IMSS/PROT/G15/1419. C. Revilla-Monsalve acknowledges CONACyT grant CB-2009-128251 for their financial support for this work. Marcos A. González-Olvera acknowledges Universidad Autónoma de la Ciudad de México and Universidad Nacional Autónoma de México for the support given to this work.

Appendix A

A.1. Simulations that mimic human-like meal ingestion and quantification of algorithm accuracy

Here our purpose is to demonstrate our method's performance with a Bergman Minimal Model (BMM) simulation (human-like parameters) including a meal ingestion. We placed these data apart from our *in-vivo* rat results to avoid confusion with the difference between a rat and a human glucose response to a meal. A rat eating an ethics-approved lab diet would never show a rise in blood glucose like that of a human in a natural setting on an unrestricted diet [22].

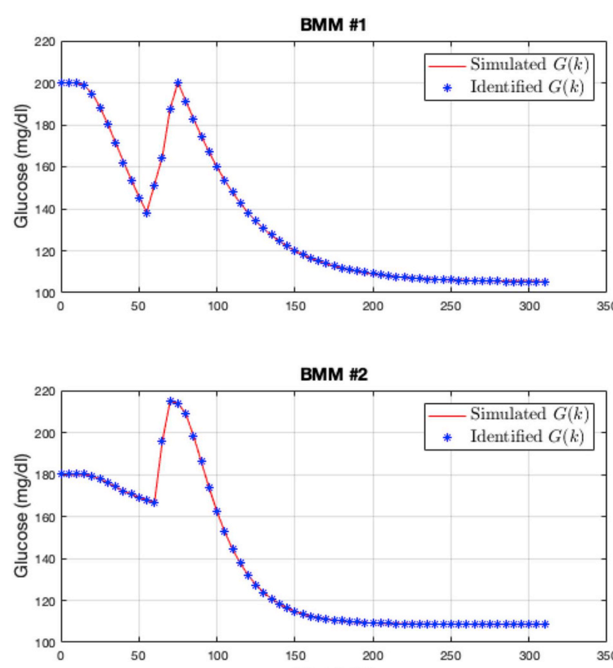

Fig. 4. These two traces visualize BMM simulations (human-like parameters) with meal perturbation (50 g of carbohydrate at minute 55). Starting blood glucose levels were arbitrarily chosen at 200 mg/dl and 180 mg/dl respectively, and the response was controlled by insulin administration with a target of approximately 110 mg/dl. The algorithm accurately identifies the model parameters and therefore mimics the dynamics of the simulation. If the model parameters are the same the blood glucose levels must also be the same. The solid line (red color) is the simulation and the asterisks are the algorithm output.

Fig. 4 time series plots permit visualization of the blood glucose level trajectory during the simulation of the BMM. The sudden rise in blood glucose level at minute 55 is due to a simulated meal ingestion of 50 g of carbohydrate. The blood glucose starting values of the two simulations were arbitrarily chosen at 200 mg/dl and 180 mg/dl respectively, and the response was controlled by insulin administration with a target of approximately 110 mg/dl. The calculated model follows the blood glucose level accurately because with near identical parameters they are essentially the same model. The small errors in the algorithmically determined parameters do not produce significant differences in blood glucose levels. The algorithm correctly identifies the known model parameters in two different simulations and the accuracy of the six (3 2) parameter determinations is listed in Table 3. We are optimistic that our genetic algorithm will perform well in a natural setting wherever the Bergman Minimal Model applies.

Table 3
Comparison of the given simulation parameters versus the algorithmic calculation of model parameters that permit precise tracking of the simulated rats' glucose levels before and after a simulated meal at minute 55. In the *in vivo* study, reported in the main text of this article, the model parameters for all of the rats are unknown. Here we quantify the non-significant error of the algorithm's performance. The maximum parameter error is 2% for simulation 1, and 8.7% for simulation 2.

	Parameter	Simulated	Identified	Error (%)
Simulation BMM 1	**n**	0.03000	0.03051	1.7%
	p_2	0.03120	0.03061	−1.9%
	p_3	0.2740×10^{-3}	0.2734×10^{-3}	−0.02%
Simulation BMM 2	**n**	0.05000	0.04600	−8.7%
	p_2	0.04570	0.04960	7.8%
	p_3	0.164×10^{-3}	0.1639×10^{-3}	0.06%

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