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Original Article

Minimally-Invasive and Efficient Method to Accurately Fit the Bergman Minimal Model to Diabetes Type 2

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Abstract

Introduction—Diabetes mellitus is a global burden that is expected to grow 25% by 2030. This will increase the need for prevention, diagnosis and treatment of diabetes. Animal and individualized *in silico* models will allow understanding and compensation for inter and intra-individual differences in treatment and management strategies for diabetic patients. The method presented here can advance the concept of personalized medicine.

Methods—Twenty experiments were performed with Sprague-Dawley rats with streptozotocin induced experimental diabetes in which the insulin-glucose response curve was recorded over 60–100 min using only an insulin pump and a percutaneous glucose sensor. The information was used to fit the five-parameter Bergman Minimal Model to the experimental results using a genetic algorithm with a root-mean-squared optimization rule.

Results—The Bergman Minimal Model parameters were estimated with high accuracy, low prediction bias, and low average root-mean-squared error of 15.27 mg/dl glucose.

Conclusions—This study demonstrates a simple method to accurately parameterize the Bergman Minimal Model. We used Sprague–Dawley rats since their physiology is close to that of humans. The parameters can be used to objectively characterize the physiological severity of diabetes. In this way, planned treatments can compensate for natural variations of conditions both inter and intra patients. Changes in parameters indicate the patient's diabetic condition using values of glucose effectiveness ($S_G = p_1$) and insulin sensitivity ($S_I = p_3/p_2$). Quantifying the diabetic patient's condition is consistent with the trend toward personalized medicine. Parameter values can also be used to explain atypical research results of other studies and increase understanding of diabetes.

Keywords—Glucose effectiveness, Insulin sensitivity, Genetic algorithm, Individualized diabetes treatment.

INTRODUCTION

Diabetes is an incurable, chronic disease. There are two main types of diabetes. Diabetes Mellitus Type 2 (DMT2) is the most prevalent worldwide (~ 90%) and is related to environmental factors, like the life-style.[19] The first line of treatments for DMT2 are oral medicines, like metformin, that lower blood glucose, and are usually prescribed together with diet and exercise. Since it is a chronic disease with severe complications, it results in pronounced lifestyle disruption, challenging psycho-social adjustment for the individual, and substantial healthcare expenses.[45]

Diabetes Mellitus Type 1 (DMT1) is characterized by a complete deficiency of insulin secretion, therefore daily insulin injection or infusion is obligatory to avoid exacerbated hyperglycemic episodes that may produce life threatening conditions. DMT1 patients represent only 10% of cases and their treatment is the most complicated.[2] At present DMT1 is an incurable condition, and the treatment includes daily finger pricks for blood glucose tests and insulin injections. Furthermore, it relies on the patient to do the insulin dose calculation, according to the glucose measurements. Considering that the diagnosis is usually made during childhood it imposes a severe burden on the child patients and on their parents, affecting life quality.[20]

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Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation.[46] Considering the prevalence of diabetes is expected to grow, it can be concluded that there are unmet medical needs, like developing new behavioral and medical strategies or drugs for prevention and treatment to help to reduce the global health burden that diabetes complications impose.[17]

According to the International Diabetes Federation, diabetes prevalence is close to half a billion people worldwide and it will increase 51% by 2045. No country in the world has efficiently managed to reduce the cost of long term complications of diabetes. Treating diabetes complications accounts for over 50% of the direct health costs of diabetes.[19] This is a direct consequence of the lack of pharmacological control that is caused by significant interpatient variability. One clear example of this variability is the use of first-line drugs like metformin. It is used worldwide because it has been considered safe and cost effective.[21] However, recent studies demonstrated that 40.5% of the patients do not respond to this treatment.[35] This variability might be easily dose compensated by knowing the correct Bergman Minimal Model of each patient. The GA proposed in this study allows cost effective and quick identification of the individualized Bergman Minimal Model. Identification of the parameters of the model in a simple, cost effective and fast way could lead to more targeted individualized medicine for glucose control.

Animal models are important in diabetes research because they reduce the number of human studies that are costly and ethically challenging. Animal models allow us to obtain better scientific understanding of the disease. Alloxan and streptozotocin are the most often used pharmacological agents to produce artificial diabetic animal models among other methods.[32]

There is an advantage and it is becoming more popular to perform *in silico* trials to further minimize the use of laboratory animals. This technique has been widely used to design new treatments, for example, the design of an artificial pancreas.[25,38]

The implementation of mathematical models for estimation and prediction of glucose-insulin dynamics in conditions like DMT2 has proven to be extremely important. López-Palau *et al.* presented the case of modelling glucose dynamics in DMT2 based on a pharmacokinetic-pharmacodynamic approach that has been demonstrated capable of emulating the pathophysiology of DMT2 metabolism. This includes the effect of gastric emptying and the insulin enhancing effect due to incretin hormones.[24]

In silico trials based on a mathematical models can be used to mimic the insulin response of an animal. In this study we efficiently identified the parameters of the Bergman Minimal Model for Sprague-Dawley rats with experimental diabetes induced by streptozotocin. Using a novel method we created *in silico* or virtual rats. This system identification algorithm can also be used to identify parameters of models for other animals or humans. The virtual rats depicted in this study can be be used to perform preclinical *in silico* trials for insulin therapy for diabetes.

The Bergman Minimal Model has been widely used to understand the pathophysiology of diabetes. It has had great impact in studies of glucose regulation. This approach has helped the medical community have a better understanding of the compound effect of insulin secretion and insulin sensitivity on glucose tolerance and risk for diabetes, as well as in the design of medical devices to regulate glucose more effectively.[5–7]

The Bergman Minimal Model measures insulin sensitivity (SI) and glucose effectiveness (SG) using a very inconvenient, frequently sampled intravenous glucose tolerance test.[5] The Bergman Minimal Model is underused clinically because most endocrinologists are not familiar with mathematical modeling.[6] Here we propose a better method of using the model that may simplify its use for clinical guidance by providing objective values of SG and SI. There are several models to describe glucose regulation, some of them as Sorensen Model,[40] details every system and organ, while the BBM presents a global behaviour of glucose and insulin.[4,13]

Genetic algorithms (GA) have shown good performance in various medical specialties like health care management. These methods have been used for diagnosis, treatment planning or pharmacovigilance.[15] The analysis of the minimal model is widely used in DMT2 to estimate various parameters, like the insulin sensitivity. A GA method for a minimal model called GAMMOD was developed by Morbiducci *et al.* based on these algorithms, for the estimation of the model parameters, this proposed method implements an automated weighting scheme that does not requite any manual intervention.[29] The Extreme Learning Machine Neural Network has been implemented in an automated system for early diagnosis of DMT2 using classification and feature extraction by Alharbi and Alghahtani. This method was implemented on a data set from Saudi Arabian patients with an accuracy of 97.5%.[1] Once again, these studies are based on very inconvenient intravenous glucose tolerance tests (IVGTT). This procedure is time consuming, expensive and very invasive for the patient.

In some cases genetic algorithms can be combined with some traditional approach like nonlinear autoregressive with exogeonous input (NARX) modeling. This model does not require an initial parameterization and it always guarantees convergence, this combined

approach has been implemented in the evaluation of insulin sensitivity with good results (see Ref. [16]). This approach also requires intravenous glucose tolerance tests (IVGTT).

Bergman Minimal Model

The Bergman Minimal Model is the simplest model that effectively describes the glucose-insulin regulatory system. This model has been proven accurate and useful. This model has been used in many studies to analyze and understand the effects of insulin sensitivity on glucose tolerance and risk for diabetes, as well as the effects of insulin secretion.[5]

Understanding of the kinetics of *in vivo* insulin, and the importance of the β-cell failure comes from the original assumptions of the Bergman Minimal Model in the pathogenesis of diabetes.[5] This model is described by the following equations:

$$\begin{aligned} \dot{G} &= -p_1[G - G_b] - GX, \\ \dot{X} &= -p_2 X + p_3[I - I_b], \\ \dot{I} &= -n[I - I_b] + \gamma[G - h]t + u(t). \end{aligned} \tag{1}$$

The parameter and variable descriptions can be seen in Table 1.

The insulin input signal $u(t)$ is an experimental manipulation and does not modify the behavior or solution of the model as long as $u(t)$ is non negative $(u : 0 \rightarrow R_+)$.[11–13,38] There are physiological constraints on the amount of injected insulin to avoid an hypoglycemic episode. The maximal tolerated amount of insulin depends the initial glucose value and conditions.

The insulin sensitivity of the individual is defined by $S_I = p_3/p_2$. The term $\gamma[G - h]^+ t$ represents the pancreatic insulin secretion after a meal at $t = 0$. p_1 is also known as glucose effectiveness (S_G).[7] S_G and S_I are both objective indicators of patients' diabetic condition.

METHODS

In Vivo Experiments

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

Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ) solution (40mg/kg in acetate buffer 0.1 M, pH 4.5) given to 20 overnight fasted female Sprague-Dawley rats (250-300g). Diabetes was identified by non-fasting plasma glucose greater than 250mg/dl 48h after injection of STZ. The animals had access to water and food *ad libitum* after the STZ injection up to the start of the *in vivo* experiment and no food or water during the critical part of the experiment.

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

TABLE 1. Bergman Minimal Model (Eq. 1) description of variables (G, X, I and u) and parameters.

Variable or parameter	Description	Unit
G	Plasma glucose concentration	mg/dl
X	Insulin's effect on the net glucose disappearance	min^{-1}
I	Insulin concentration in plasma	μU/ml
$\mathbf{G_b}$	Basal glucose plasma concentration	mg/dl
$\mathbf{I_b}$	Basal insulin plasma concentration	μU/ml
u(t)	Insulin infusion rate	$\mu U/\text{min}$
$\mathbf{p_1}$	Insulin-independent glucose disappearance rate	min^{-1}
$\mathbf{p_2}$	Spontaneous decreased rate of tissue glucose uptake ability	min^{-1}
$\mathbf{p_3}$	Insulin-dependent increase in tissue glucose uptake ability per unit of insulin concentration increase over basal insulin	$\text{min}^{-2}(\mu\text{U/ml})^{-1}$
h	Threshold value of glucose above which the pancreatic β-cells release insulin (only for DMT2)	mg/dl
γ	Rate of the pancreatic β-cells' release of insulin after the glucose concentration is above the threshold *h*	$(\mu\text{U/ml})/\text{min}^2/(\text{mg/dl})$
n	Disappearance rate of insulin	(min^{-1})

The main value of this method is its accuracy, simplicity, and reliability (see Table 2). Only plasma glucose (G) and infused insulin u(t) are measured so the procedure can be done at home in 60 min for both DMT1 and DMT2 patients..

with Tegaderm. Sensors and transmitters were further secured to the rat dorsum by wrapping them with Vetrap wound dressing. The wrapping was checked every 12 h and renewed if necessary.

To calibrate the continuous glucose monitor, 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 day after glucose sensor implantation the glucose-insulin response test was performed. Insulin was infused using an insulin pump (Medtronic) until glucose was under 120mg/dl (55min to 100min). The total administered insulin I_T was recorded (see Table 2).

Genetic Algorithms for Model Parameter Estimation

Genetic Algorithms (GAs) belong to the so-called Evolutionary Algorithms (EAs), that are computational methods inspired by natural evolution. In this case, using a GA for model parameter estimation is an efficient method to search the parameters' values space to converge on a set of values that minimize an appropriately created *fitness function*. In this way, the model's parameters are tuned so its dynamics fit as closely as possible to the experimental data. The parameter values that achieve the best fit are the best estimates of the biological model for the individual.

The GA presented here finds the values of the set of model parameters $\{p_1, p_2, p_3, n, I_b\}$ of (1) given only plasma glucose concentration and insulin delivered, G and u, that are measured and known from the *in vivo* experiment. The model is the same as (1), except that now the variables are shown as estimated via hats; except for G_b and u:

$$\begin{aligned} \dot{\hat{G}} &= -\hat{p}_1[\hat{G} - G_b] - \hat{G}\hat{X}, \\ \dot{\hat{X}} &= -\hat{p}_2 X + \hat{p}_3[\hat{I} - \hat{I}_b], \\ \dot{\hat{I}} &= -\hat{n}[\hat{I} - \hat{I}_b] + \gamma[\hat{G} - h]t + u(t). \end{aligned} \tag{2}$$

For this problem, the objective is to minimize the root-mean squared (RMS) error function between the predicted plasma glucose concentration and the measured plasma glucose concentration G for the experimental data, taken each T_s given by:

$$RMS = \sqrt{\frac{1}{N}\sum_{k=0}^{N-1}\left(G(kT_s) - G(\hat{kT_s})\right)^2}, \tag{3}$$

where $G(kT_s)$ are the samples taken. Therefore, (3) is defined as the fitness function for this GA.

TABLE 2. The identified parameters of the Bergman Minimal Model (p_1, p_2, p_3, n, I_b).

#R	p_1	p_2	$p_3 \cdot 10^3$	n	I_b	I_T	RMS	MDPE	MDAPE	WOBBLE	Corr.
01:	0.01	0.058	1.00	0.056	13.75	1.70	10.73	0.96	5.47	4.51	0.995
02:	0.02	0.066	0.36	0.066	22.20	4.80	11.81	0.93	6.08	5.14	0.992
03:	0.017	0.048	0.73	0.18	25.95	4.80	14.90	0.00	6.79	6.79	0.990
04:	0.035	0.063	0.73	0.061	24.54	3.20	28.83	0.00	11.20	11.20	0.946
05:	0.02	0.089	0.15	0.088	18.52	6.00	9.21	0.50	3.04	2.54	0.997
06:	0.023	0.129	0.28	0.13	28.08	5.40	11.48	0.53	5.28	4.75	0.992
07:	0.01	0.096	0.01	0.095	4.22	11.50	17.38	2.33	4.95	2.62	0.982
08:	0.044	0.119	0.69	0.11	28.05	1.00	24.81	-0.17	5.58	5.76	0.977
09:	0.01	0.055	0.43	0.058	9.50	2.00	8.33	1.79	3.50	1.71	0.998
10:	0.01	0.060	1.00	0.061	6.04	0.20	7.24	0.63	6.87	6.24	0.993
11:	0.059	0.148	1.00	0.15	25.94	0.20	20.90	1.16	8.90	7.75	0.978
12:	0.038	0.117	1.00	0.12	21.32	1.50	17.08	-1.44	6.18	7.62	0.992
13:	0.016	0.036	0.98	0.037	13.10	1.00	7.93	-0.23	3.40	3.63	0.997
14:	0.06	0.086	0.54	0.066	29.88	0.40	20.93	0.00	8.52	8.52	0.965
15:	0.047	0.117	0.90	0.16	27.11	0.40	18.13	0.49	5.02	4.53	0.988
16:	0.036	0.041	0.94	0.12	17.90	0.80	20.40	0.99	6.31	5.33	0.982
17:	0.011	0.027	0.18	0.089	22.30	3.60	14.61	-0.96	4.72	5.68	0.992
18:	0.012	0.200	0.93	0.029	14.73	1.60	11.22	1.53	2.92	1.40	0.994
19:	0.014	0.010	0.11	0.16	26.67	3.30	13.82	0.06	5.37	5.31	0.986
20:	0.019	0.200	0.60	0.025	22.30	2.60	15.75	0.55	4.59	4.04	0.992
Mean:	0.026	0.088	0.63	0.09	20.11	2.80	15.27	0.48	5.74	5.25	0.986

The term $\boldsymbol{I_T} = \Sigma \boldsymbol{u}(\boldsymbol{t})$ is the total insulin administrated during the *in vivo* experiment. The Varvel Performance Measurements (MDPE, MDAPE, Wobble) evaluate the identification accuracy. It can be seen that there is a low bias (MDPE), and high accuracy (MDAPE). Also shown are Pearson correlations between $G(t)$ of the experimental data and $\hat{\boldsymbol{G}}$, the output of the fitted *in silico* model for each individual. Together with the variable sensitivity to parameter variation shown in Fig. 5, the variability in identified parameters shown here further emphasizes the need for personalized disease management as our method can provide. We believe differences in parameters between individuals are natural variations that work against standard fixed patient care strategies.

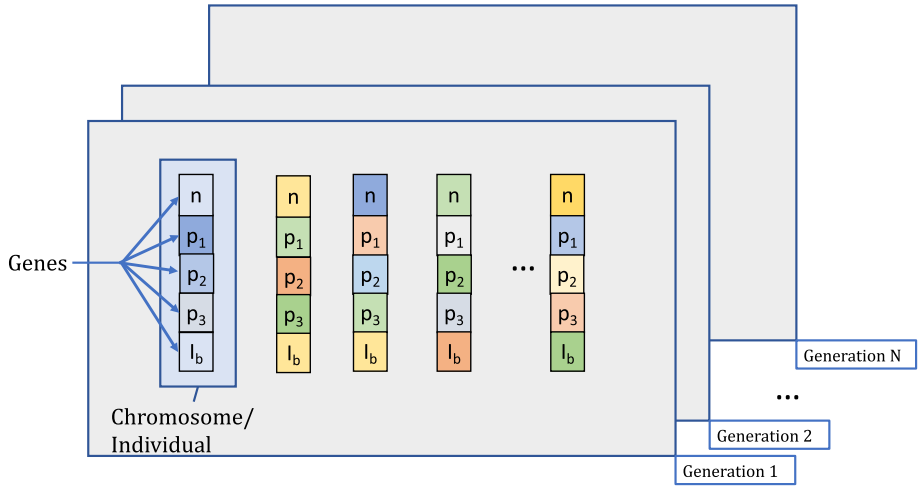


FIGURE 1. Graphic description of the elements of a Genetic Algorithm showing the relationship between genes, chromosomes and a generation. Individuals/chromosomes are composed of genes, in which each gene is a required parameter whose value is to be determined (n, p_1, p_2, p_3 and I_b). Once an initial generation has been randomly assigned different values for its genes in each chromosome, the next generation is obtained following the algorithm described via flowchart in Fig. 3. The different colors of each gene represent the different values that a gene has been assigned.

Resembling genetic information and a reproductive/hereditary evolutionary process, the GA requires a data structure in which the five parameters, or genes are arranged in a vector called a *chromosome*. Each different chromosomal combination of five genes represents an *individual* at a certain iteration or *generation* of the algorithm. In the rest of this paper, the set of parameters coded in chromosomes in a given generation is called an *individual*. These elements are shown in Fig 1.

For each particular experiment, the algorithm begins the parameter search with a given number of individuals called the *population size*. In general, there is not a given rule for selecting this size[36,43]: a small number decreases the genetic diversity, and therefore it can prematurely converge to a suboptimal value; while a high number implies a greater computational load.[10,44] In this case, a reasonable number of 50 individuals per generation is chosen and the initial values are randomly generated with an uniform probability within the boundaries of given intervals. These are discussed in Sect. 3.

The fitness function is evaluated for each candidate chromosomal combination. As the GA proceeds, the next generation of candidate chromosomes is formed via selection based on one of three methods: fitness value, random recombination of genes, or mutation. The evolutionary selective pressure on the individuals is minimizing the fitness function (3) and the process could be described as inbreeding.

The chromosomes that produce the smallest value of the fitness function are called *elite chromosomes*, and a predefined percentage of these are carried to the next generation in a process called *elitism*. This helps the algorithm to preserve the best solutions in each generation and avoid degradation of its overall performance. The remainder of the 50 individuals for the next generation are obtained in two ways: recombination (also known as *crossover*) and by modifying the offspring resulting values via *mutation*.

The recombination is done by randomly selecting two individuals of the present generation, called *parents* to form a new chromosome with a new combination of genes, called *offspring*. Several ways have been reported to do the selection process.[39] In order to find a balance between proper exploration of the parameter space, exploitation of the best genes, and simplicity of the algorithm, we considered a uniform probability selection function for the selection of crossovers and a Gaussian probability selection function for mutations. In the former, a uniform probability is considered so the crossover has no bias and any number of genes can be selected to pass to the offspring. In the latter, the vicinity of the parameter value is explored, while not moving too far from candidate values.[9,10,18,31,36,39,43,44]

The recombination occurs with segments of the parental chromosomes with linked genes or via random selection of individual genes from each of the parents to form offspring, as shown in Fig. 2.

Genes are mutated by randomly adding or subtracting random numeric values to the genes in offspring. The probability density function for the mutation process can be selected in several ways and can even be changed depending on the generation number.[33] In this case, as the number of genes is relatively small, we selected a dynamic Gaussian distribution function

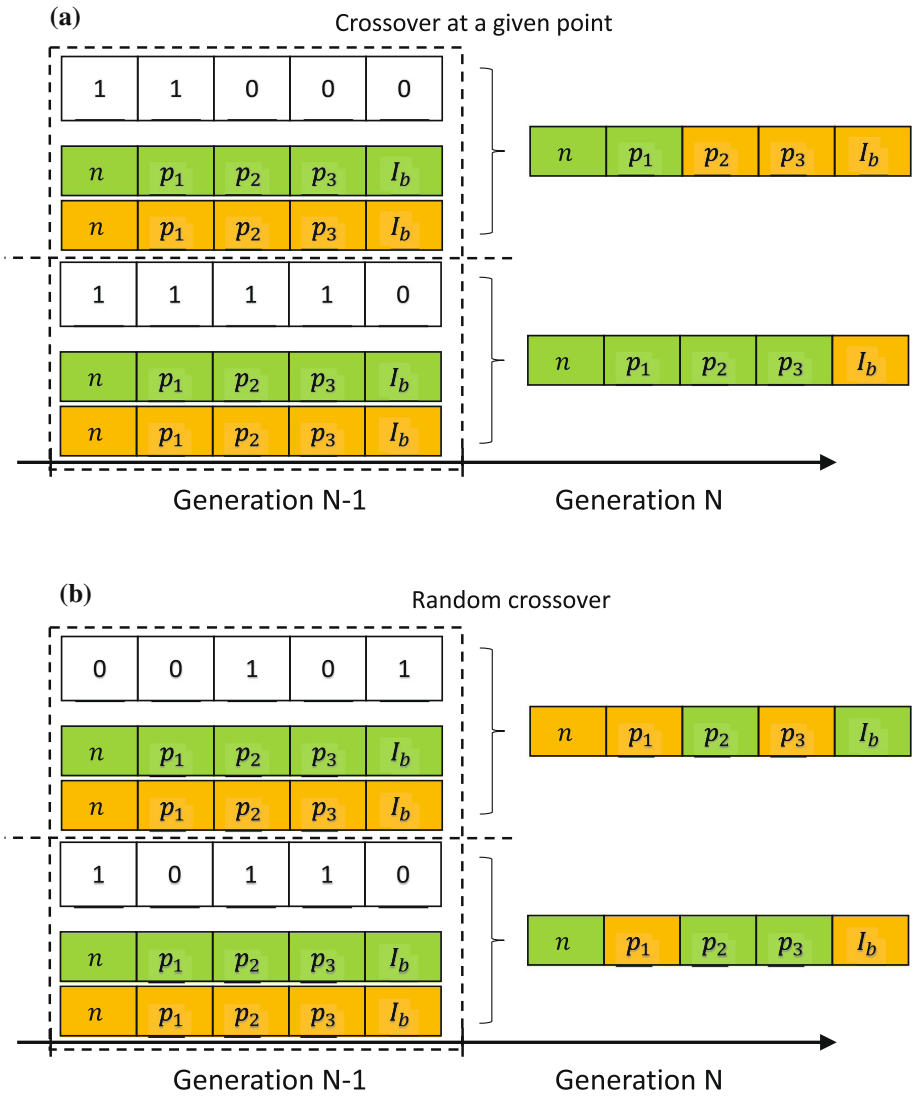


FIGURE 2. Graphic description of the recombination of parent genes to generate a new offspring chromosome with a different set of genes (parameter values). The array of ones and zeros represent which genes are taken from the first parent (ones) and which are taken from the second (zeros) to generate the offspring. a) Crossover done at a random given point on both parents. In this case the first genes are selected from the first parent, and the remaining genes from the second one. b) Crossover done with random and alternate gene selection from both parents.

$$f_m(\theta) = \frac{1}{\sigma_\theta \sqrt{2\pi}} e^{-\frac{\theta^2}{2\sigma_\theta(N_g)^2}},$$

where θ is the given parameter, N_g the generation number, and $\sigma_\theta(N_g)$ the standard deviation with relation to the mean value μ_θ of the search interval that depends on the generation number.

This process is repeated until a predetermined value of the fitness function is achieved or if the best obtained fitness value remains unchanged after a given number of generations. A flow chart of this process is shown in Fig. 3.

For all individuals presented in this report, the initial condition $X(0) = 0$, is assigned, since this represents a stable condition, where there is no insulin-mediated glucose uptake. The algorithm operated according to the following criteria:

1. 50 candidate chromosomal gene (parameter value) combinations for the same rat per generation.
2. An elitism percentage of 5%.
3. 95% of the offspring for the next generation are formed from crossover of 80% of parents and the balance from mutation of parents chosen randomly.
4. A gaussian mutation probability function, with a unit standard deviation with respect to the mean value of the search interval, with a linear reduction

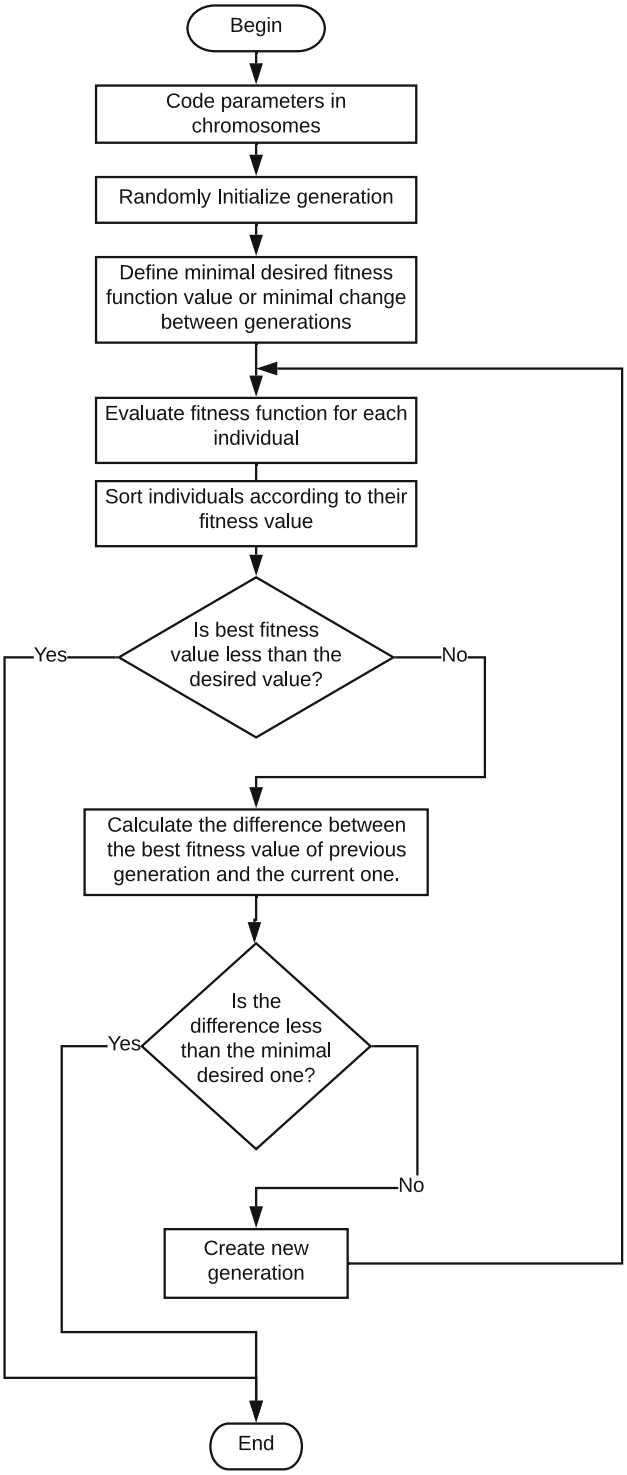


FIGURE 3. Flow chart description of the GA. At first, all individuals are created randomly and after their respective fitness values (RMS error w.r.t. the experimentally determined dynamics) are evaluated, it is decided if the algorithm continues to search for newer individuals or if the best candidate fulfills the conditions to stop. If it is not the case, a new generation is created by elitism, recombination and mutation. All of these occur in the step labeled ''create a new generation''.

factor of the probability tending to zero at the end of the maximum number of generations.

5. The termination condition is given when 500 generations or after 50 consecutive generations without improvement in the value of (3).

RESULTS

The GA was used to estimate the parameters of the Bergman Minimal Model. As described in Fig. 3, the algorithm from Sect. 2.2 was implemented by randomly initializing the values of the parameters and the search in the parameter space was set to the intervals:

$$n \in [0.02, 0.3],\ p_1 \in [0.01, 0.1],\ p_2 \in [0.01, 0.2],$$
$$p_3 \in [10^{-5}, 10^{-3}],\ I_b \in [1, 30].$$

In Fig. 4, the solid line corresponds to the *in vivo* experiment described in Sect. 2.1, and the dotted line is the fitted Bergman Minimal Model output, that mimics the dynamics of the glucose-insulin regulation in streptozotocin induced diabetes. The Figure shows the high accuracy of the Bergman Minimal Model with the identified parameters in all experiments.

The estimated parameters are shown in Table 2, that also includes the Pearson correlation coefficients between the experimental data and the output of the Bergman Minimal Model with the identified parameters and the Varvel performance. The latter is a standard measure to establish the identification quality, both in terms of the error and prePercentage Prediction bias. These measures are the Percentage Prediction Error (PE), Median Prediction Error (MDPE) that evaluates bias, Median Absolute Performance Error (MDAPE) reflects inaccuracy, and Wobble is a measure of variability in each study subject. These measures are defined as[42]:

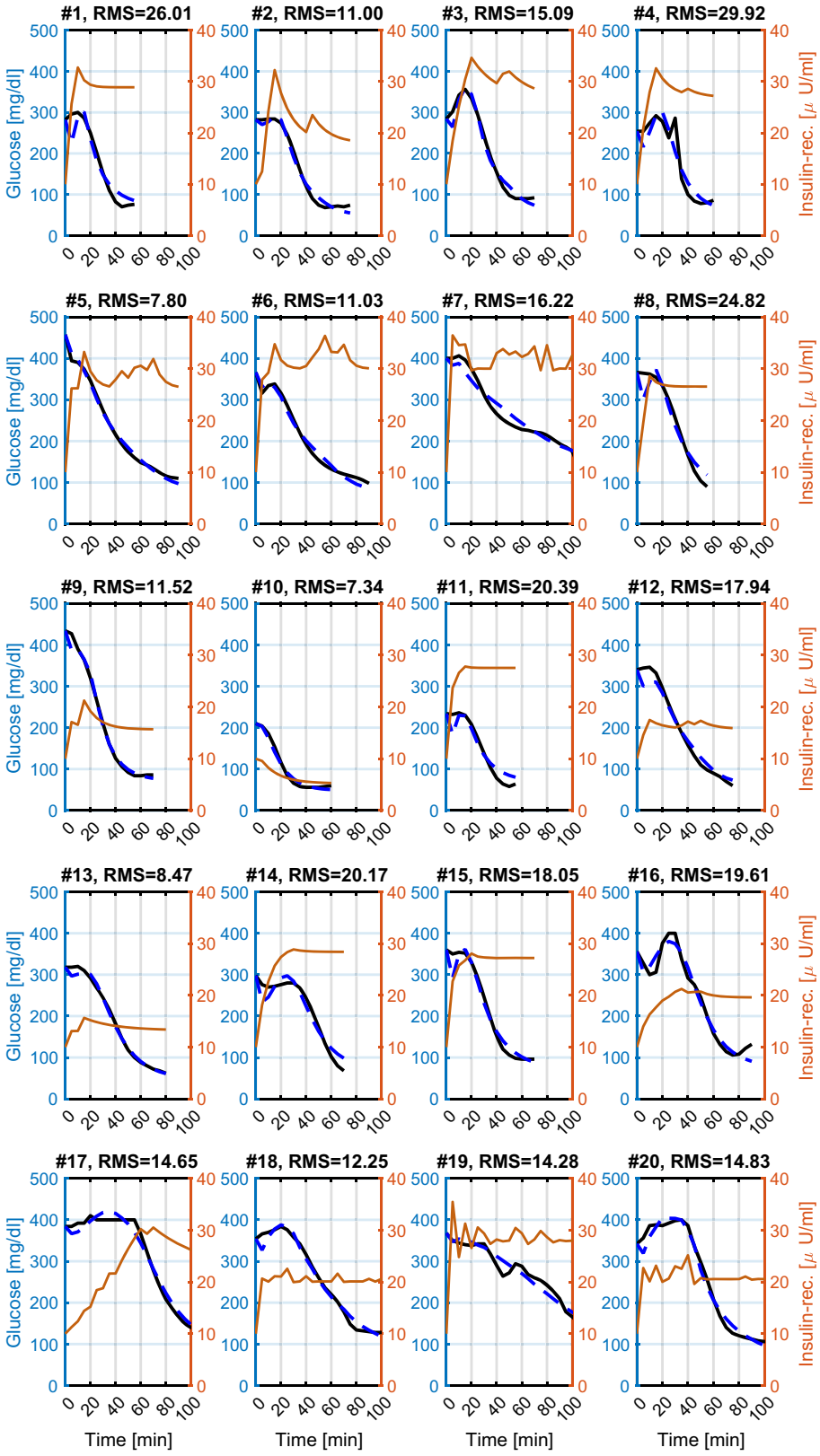
$$PE[k] = 100\frac{G[k] - \hat{G}[k]}{\hat{G}[k]}, \tag{4}$$

$$MDPE = median\{PE[k], k = 0, \dot{s}, N-1\}, \tag{5}$$

$$MDAPE = median\{|PE[k]|, k = 0, \dot{s}N-1\}, \tag{6}$$

$$Wobble = median\{|PE[k] - MDPE|, k = 0, \dot{s}, N-1\}. \tag{7}$$

The transient small glucose elevations, present in very few individuals, are natural stress responses caused by non measurable perturbations that affect both the sensing and the glucose dynamics of the experimental specimens.[26]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#18, RMS=12.25
#19, RMS=14.28
#20, RMS=14.83
Glucose [mg/dl]
Insulin-rec. [μ U/ml]
Time [min]

◀FIGURE 4. Identification results. In solid black line, the *in vivo* measured experimental values of *G*(*t*), in dotted blue line, the reconstruction of the glucose concentration given by the Bergman Minimal Model with identified parameters shown in Table 2, and in solid orange line the reconstruction of the insulin concentration in blood. It can be seen that the identified model follows closely the data of the experiments in most cases, confirming good identification by the genetic algorithm (GA). This means that the GA was able to fit the full Bergman Minimal Model to the *in vivo* experimental results. According to the American Diabetes Association, if the plasma glucose in a random test is over 200 mg/dl, it is sufficient make to a diabetes diagnosis[3]; and it can be seen that all study subjects do fulfill this condition.

In order to evaluate the impact and sensibility of parameter shifts on the fitted model, the parameters were varied within ±10% and ±20% from their identified values and added to Fig. 5. It can be seen that values obtained by this method accurately describe the dynamics of glucose and when parametric variations are introduced. The glucose dynamics envelope is preserved but the identification error tends to grow, as expected.

The average RMS error is 15.27 mg/dl (7.2% of the average glucose level of 212 mg/dl during the experiment) indicating close tracking of the experimentally measured glucose dynamic by the *in silico* model. The average parameter MDPE of 0.48%, is an insignificant bias, meaning the parameters were properly fitted and this is confirmed by the average MDAPE of less than 6% on average. Finally, the average Wobble is close to 5% indicating low variability in the error percentage of each specimen.

The Pearson correlation was calculated for each individual between the glucose data obtained from the *in vivo* experiments and the glucose data generated from the *in silico* experiment using the fitted Bergman Minimal Model. The data is shown in Table 2.

DISCUSSION

Diabetes is a burden for patients, families, and public health systems. The prevalence of diabetes is expected grow 25% worldwide in the next 10 years.[19] This means the health management strategies for this disease are not being properly covered and it is important to develop new treatments and strategies to minimize the long-term complications.[17]

Animal models play a very important role in the development of better treatments since these models allow efficient experimental hypothesis testing, in a well controlled environment.[27] However, before performing expensive animal model experiments an *in silico* trial with a mathematical model can be designed via a process similar to what we have demonstrated here and it can help develop insightful hypotheses to be tested *in vivo* for efficient progress.

The *in silico* model we developed for Sprague-Dawley rats is calibrated in about 60 min for each individual with measured blood glucose and delivered insulin data and it can be used to calculate the complete insulin-glucose response curve. Fitting the five parameter BMM yields insulin sensitivity and glucose effectiveness. Glucose effectiveness was not available in our prior study. Together these derived values can be used to guide a patient's therapy with oral medications, like Metformin, that are used in most of the DMT2 patients that account for 90% of diabetes patients worldwide.

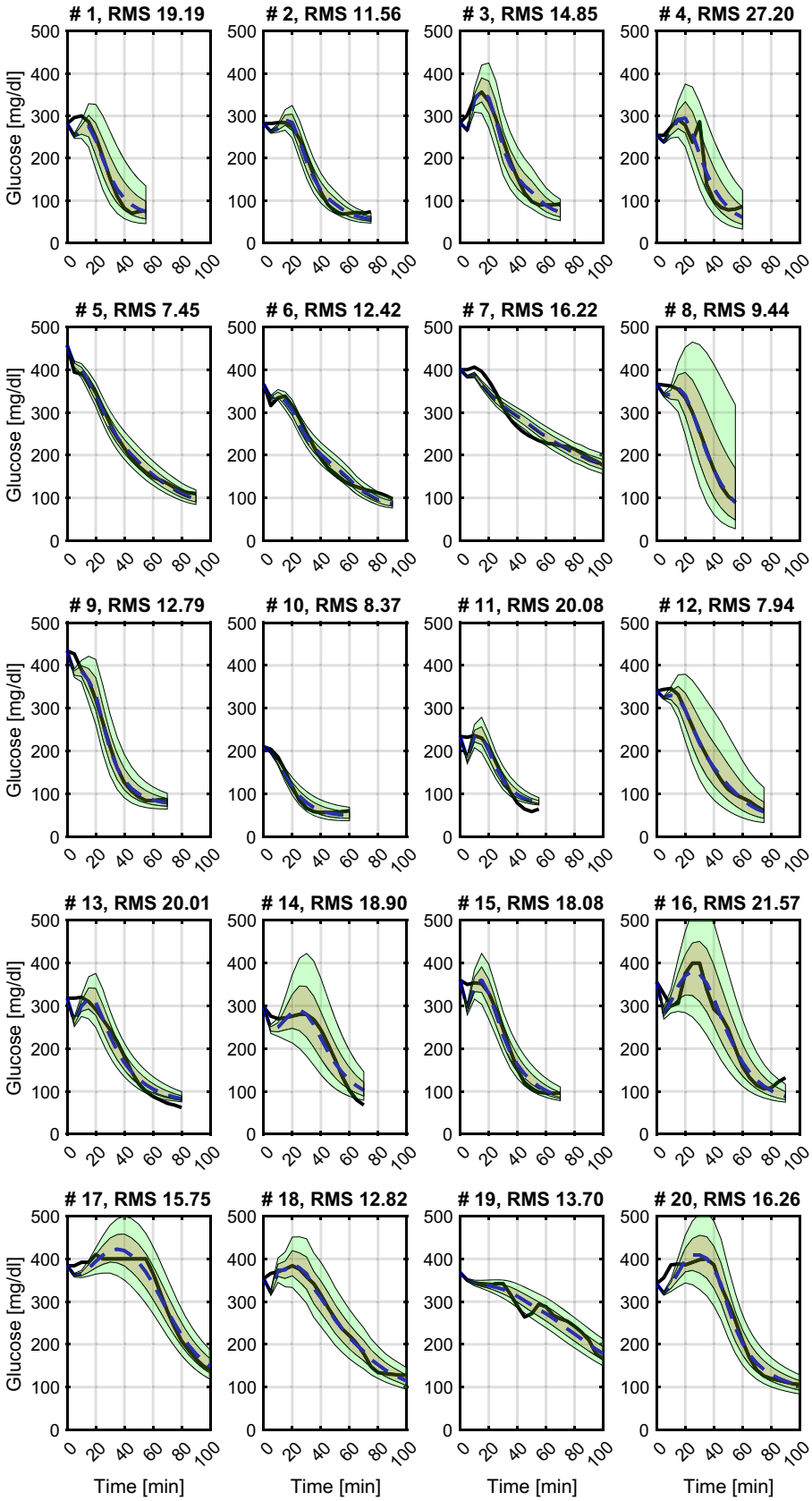
Our previous study fitted just three out of five parameters of the Bergman Minimal Model to describe DMT1 that is characterized by complete deficiency of insulin production.[14] This previous work provided only insulin sensitivity (not glucose effectiveness) and can only be used to individualize insulin delivery systems. The Bergman Minimal Model has been previously validated in the literature for its use for DMT1 by modifying the equations according to the physiological difference of the disease,[12,13,38] and the effect of a limited set of parameter variations has been recently studied.[30] When it is used to describe DMT1 it is assumed that $p_1 = 0$ and $I_b = 0$. This same logic has been used to model other aspects of glucose regulation dynamics like free fatty acid as muscle energy while the body is at rest.[37]

In the present study identification of five individual parameters of a diabetic patient's Bergman Minimal Model can be used to tailor an individualized treatment scheme based on objective information like glucose effectiveness and insulin sensitivity.

The Sprague-Dawley rat was chosen for these experiments because it is it is known to have human-like insulin sensitivity and it is one of the most commonly used strains for insulin-stimulated glucose measurements.[23]

The novel technique used in this study to identify the Bergman Minimal Model is less invasive than any other procedure practiced today. The genetic algorithm for parameterization is fast and accurate. If used clinically, the process to acquire the necessary data could be completed at home rather than in a carefully controlled environment as required by other techniques.

We did not directly measure blood insulin of the rats during our experiment to avoid additional stress to the rats. To check the consistency of our results we compared our calculated mean basal blood insulin level in the study rats to those of Cacho *et al*. Our mean value of 20.11μU/ml is about half the basal insulin reported by Cacho for non diabetic healthy rats.[8] This


1, RMS 19.19
2, RMS 11.56
3, RMS 14.85
4, RMS 27.20
5, RMS 7.45
6, RMS 12.42
7, RMS 16.22
8, RMS 9.44
9, RMS 12.79
10, RMS 8.37
11, RMS 20.08
12, RMS 7.94
13, RMS 20.01
14, RMS 18.90
15, RMS 18.08
16, RMS 21.57
17, RMS 15.75
18, RMS 12.82
19, RMS 13.70
20, RMS 16.26
Glucose [mg/dl]
Time [min]

◀FIGURE 5. Identification results with ±10% (gray area) and ±20% (green area) variation in the obtained parameters. In solid line, the *in vivo* experiment, in dotted line, Bergman Minimal Model output with identified parameters shown in Table 2. Notice the differential sensitivity to parameter variations between individuals which emphasizes the utility of an individualized management strategy that our method makes available. We believe this differential sensitivity is natural variation between individuals.

lower value is consistent with Cacho's report because STZ used with our rats has a β-cell necrosis effect.[34]

The correctness of our model-method is further supported by similar findings in recent work reported by Stefanovski *et al*. They identified parameters for the Bergman Minimal Model based on the data from insulin modified intra-venous glucose tolerance test (IM-IVGTT) of horses. The initial conditions used by Stefanovski *et al*. are within the same ranges of the parameters identified by the genetic algorithm in this study.[41] Excellent correlations between experimental and identified data up to $r = 0.999$ were obtained similar to our results here (see Table 1).

Table 2 shows big inter-specimen variability in parameters. Streptozotocin damages the $\beta - cells$ that produce insulin but it does not do it uniformly.[32] Specimen 6 had 6.6 times higher basal insulin than specimen 7 even when the same dose of streptozotocin was administered to both rats (40 mg/kg). Additional variability comes from different insulin sensitivity of each specimen, given by $S_I = p_3/p_2$. This governs insulin's ability to cause glucose uptake. Another aspect that influenced the variability of the parameters is that before the critical part of the experiment the rats had *ad libitum* access to food and water. Therefore the initial glucose value is different for each rat. To evaluate the sensitivity of the model to parameter changes we ran simulations with random variations within a ±10% and ±20% interval. Notice that while the profile of the glucose response it retained the envelope of the response and the error, as expected, is much wider in a few individuals compared to others. We believe these differences are natural variations.

This behavior resembles the variability observed in diabetic patients that do not follow the dietary recommendations of their physician[28] and each patient has the own sensitivity to medications and insulin.[22] This further emphasizes the need of individualized medicine that may be achieved by fitting individual models for each patient using simple methods like the one presented in this paper.

CONCLUSIONS

Diabetes is among the most challenging health care problems today. While almost half a billion people worldwide suffer its burden and large health care budgets are invested every year to lessen the load of this disease, epidemiological studies show increasing incidence of DMT2. This means there is a strong need to advance prevention, diagnosis, and treatment of diabetes. This can be achieved through better understanding of the disease pathophysiology. Physiological mathematical models can help understand pathopysiology. In this study we demonstrated an efficient, minimally-invasive method to completely parameterize the Bergman Minimal Model for DMT2 which accounts for 90% of diabetes cases worldwide. Our method is much less invasive than IVGTT and calculates the glucose-insulin dynamics and blood insulin using data from only a percutaneous glucose sensor and the quantity of insulin administered by an insulin pump over a period of about 60 min. This contrasts with methods that require frequent samples, not only of blood glucose, but also blood insulin under controlled conditions in a hospital.

The parameters of an accurate, individually identified *in silico* model can serve as an objective indicator of a patient's glucose regulation system and their diabetic condition. With a convenient method to individualize the Bergman Minimal Model which is typically used in research settings,[6] it could become be more widely used in general practice. Clinicians could use insulin sensitivity and glucose effectiveness provided by the model to guide medical management of DMT2 patients and avoid costly complications of uncontrolled hyperglycemia.

Conveniently created virtual rats or other virtual lab animals, as can be created with our method, could allow wide use of *in silico* studies to accelerate hypothesis testing. We chose Sprague-Dawley rats for this study because their glucose-insulin regulatory system is similar to that of humans. *In silico* studies based on individualized mathematical models as we have demonstrated here are an advantageous option to meet the rapidly growing need for better understanding of challenging pathophysiologies like diabetes. We believe modeling research should focus on creating models for other conditions with heavy health care system loads because it is a promising approach. Individualized models can identify study subjects with atypical model parameters and they will have atypical physiologic behavior. Hypotheses based on *in silico* studies can be used to design more focused *in vivo* studies with lab animals and clinical trials with humans. The idea is that more focused clinical trials will more quickly lead to better understanding and

better outcomes for diabetes patients and those at risk for diabetes.

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CONFLICT OF INTEREST

Ana Gabriela Gallardo-Hernández, Marcos A. González-Olvera, Medardo Castellanos-Fuentes, Jésica Escobar, Cristina Revilla-Monsalve, Ana Luisa Hernández-Perez and Ron Leder, declare that they have no conflict of interest

ETHICAL APPROVAL

All animal studies were carried out in accordance with all institutional and national guidelines, and approved by the appropriate institutional committees.

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