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Estimating Uncertain Parameters of a Diabetic Model Via Homotopy Optimization Method

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Abstract: One limitation on evaluation of uncertain biological systems is existence of uncertain parameters which are not measurable with noninvasive instrument. In such systems proposing a method which estimates these parameters from measurable outputs of system is a problem of interest. In this paper, we use a Homotopy based estimating method. By decreasing Homotopy parameter the initial problem which has the form of a high gain observer gradually transforms to a parameter estimation problem. This gradual transform to the main problem provides the capability of finding the global optimal value of uncertain parameter. This method is applied to diabetic system to demonstrate the effectiveness of the Homotopy method in obtaining the best estimate of uncertain parameters by finding the global minimum of a proposed optimization problem.
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1. Introduction

The normal blood glucose concentration level in human is in a narrow range$70-110\ mg/dl$. Different factors including food intake, rate of digestion and exercise can affect this concentration. If for some reasons the human body is unable to control the normal glucose-insulin interaction (e.g. the glucose concentration level is constantly out of the above mentioned range), diabetes is diagnosed. The consequences of diabetes are mostly long-term; among others, diabetes increases the risk of cardiovascular diseases, neuropathy and retinopathy, [1]. As regards the generally invasive measurement is not possible to solve this spatial problem; parameter estimation using measurable outputs are useful step in health issues of medical engineering. The problem of identifying the parameters in a mathematical model governed by ordinary differential equations (ODEs), given a set of experimental measurements, is encountered in many fields of physics, chemistry, biology, and engineering [2]. These topics are receiving great attention in the recent systems biology literature. For instance, experimental design and optimal sampling for parameter estimation has been considered by [3, 4]. The important problem of model discrimination and its relation with parameter estimation has been studied by [5], while the key issue of identifiable checking has been illustrated by [6]. In the case of parameter estimation, [7] have highlighted the need of global optimization techniques in order to avoid the spurious solutions often found by traditional gradient-based local methods. [8] has discussed parameter estimation in biochemical pathways: a comparison of global optimization methods. A hybrid approach for efficient and robust parameter estimation in biochemical pathways have also been studied and reported upon [9]. This work focuses on a diabetes model presented by Bergman [10, 11], in which the dynamic concentration profiles of glucose and insulin are modeled. All constants in Bergman model are known, but some of parameters might vary in every patient. Using dynamic patient's data, it is possible to extract the values of these parameters using parameter estimation.

As it is mentioned in the previous paragraph, the problem of parameter identification can be posed as an optimization problem [12], where the arguments of the global minimum of the objective function are the identified parameters. The optimization problems are usually solved using deterministic methods, which require the solution of differential equations at each optimization step. The solution of these ODEs can be obtained using initial-value methods [13]. When deterministic approaches like the steepest descent, Gauss–Newton [14], and Levenberg–Marquardt algorithms are used in the optimization procedure, it is not uncommon to converge to a local minimum rather

than the global minimum [15]. Stochastic methods, such as simulated annealing [16] can be used to find global minima, but these methods typically require a large number of iterations to converge and, thus, are time-consuming, especially for parameter identification problems where the equations of motion are integrated at every optimization step [13].

Homotopy optimization method (HOM) is an effective algorithm for finding global minimum of optimization problems. Homotopy, as a fundamental part of topology, has a relevant place in constructing algorithms for solving systems of algebraic equations, which is referred to as the homotopy method. This method has become much more efficient and powerful since the probability-one homotopies were proposed by Chow et al. [17], and hence was widely applied and improved to solve many problems such as nonlinear systems [18], and nonlinear constrained optimizations [19], etc. Homotopy is a powerful technique that is used in several areas of mathematics, including optimization [20] and nonlinear root finding [17]. It is also successfully applied to ARMAX models [21] for the identification of linear parameters. More details of its development and application in computational science can be found in [22].

In homotopy method, the objective function to be minimized is modified by adding another function whose optimum is known, herein referred to as the known function, and a homotopy parameter is used to transform the modified function into the original objective function. A series of optimizations is performed while slowly varying the homotopy parameter until the modified function is transformed into the original objective function [23]. A new generalized homotopy algorithm for the solving multi objective optimization problems with equality constraints have also been studied and reported upon [20], The mentioned paper gives a necessary and sufficient condition for the set of Pareto candidates to form a (k-1) dimensional differentiable manifold, provides the numerical details of the proposed algorithm, and applies the method to two multi objective sample problems.

The application of homotopy to the general parameter identification in biomedical model has not been studied in the literature yet. In this work, we present a methodology to apply homotopy to the problem of parameter identification for a diabetic model. Also, the application of the homotopy optimization method on diabetes mathematical models are shown and its uncertain parameters to be estimated.

The paper is structured as follows: In the next section, we state the mathematical model of the diabetes. Next, homotopy optimization method (HOM) is presented as a parameter estimation method. The main idea of this paper and the simulation results which show the efficiency of presented algorithm in parameter estimation has been proposed section follows, ending with a set of conclusions.

1. Mathematical Method

Diabetes mellitus is a metabolic disease characterized by irregular glucose metabolism. Patients with diabetes mellitus usually develop serious long-term effects, which increase their risk of developing serious cardiovascular, renal, and neural complications [24]. Several different models of diabetic systems exist in the literature including, for example, the very detailed 21st order metabolic model of Sorensen, [25]. This work focuses on a diabetes model presented by Bergman [10, 11], in which the dynamic concentration profiles of glucose and insulin are modeled. This model has three state variables (as well as outputs) that are the plasma glucose deviation $G(t)$ (mg/dL), remote compartment insulin utilization $X(t)$ $(1/min)$, and plasma insulin deviation $I(t)$ (mU/dL). Equation (1) describes the change in glucose concentration, dG/dt $[mg/dL/min]$, with respect to the current glucose concentration $G(t)$ $[mg/dL]$, the plasma insulin concentration, $X(t)$ $[mU/L]$, the basal glucose value for a healthy human subject, Gb $[mg/dL]$:

$$\frac{dG}{dt} = -P_1 G - X(G + G_b) \qquad (1)$$

Equation (2) describes the change in the plasma insulin concentration, dX/dt $[mU/L/min]$, with respect to the current plasma insulin concentration $X(t)$ and the free plasma insulin concentration above basal value, $I(t)$ $[mU/L]$.

$$\frac{dX}{dt} = -P_2 X + P_3 I \qquad (2)$$

Equation (3) denotes the change in the free plasma insulin concentration above basal value, dI/dt $[mU/L/min]$, with respect to the free plasma insulin concentration above basal value $I(t)$ $[mU/L]$, the basal value of free plasma

insulin, Ib (in $[mU/L]$, the typical free insulin level for controlled diabetic patients), the fractional insulin disappearance rate, *n*. Fisher et al [26] modified this equation of the Bergman model, adding an insulin infusion term and omitting an insulin secretion term:

$$\frac{dI}{dt} = -n(I + Ib) \qquad (3)$$

All constants in this Bergman model are known, but parameters p_1, p_2, p_3 *and* n might vary in every patient. Using dynamic patient data, it is possible to extract the values of these parameters using parameter estimation. Other variables represent parameters of system (1). The physiological parameters are Gb the basal glucose level (mg/dL), Ib basal insulin level (mU/dL), and p_1, p_2, p_3 *and* n represent the model parameters. The nominal values of parameters are determined by [27]:

$$P_2 = 0.025, \quad P_3 = 0.00013, \quad n = \frac{5}{54}, \quad Gb = 110, \quad Ib = 1.5 \qquad (4)$$

In this paper, P_1 is considered as an uncertain parameter and other parameters are supposed to have fixed defined values. So, if the states are assumed as followed:

$$X(t) = x_1 \ , \ I(t) = x_2 \ , \ G(t) = x_3$$

Replacing (4) in (3) yields:

$$\dot{x}_1 = -0.025x_1 + 0.00013x_2$$

$$\dot{x}_2 = -(5/54)(x_2 + 1.5)$$

$$\dot{x}_3 = -P_1x_3 + x_1(x_3 + 110) \qquad (5)$$

After identifying the model, in the next section, we present a new method to estimate uncertain parameter P_1.

2. Estimation Uncertain Parameter Using Homotopy Optimization Method

2.1 Homotopy Optimization Method

In this part, the framework of HOM is briefly presented for solving a nonlinear optimization problem. To clarify the method, at first, we explain how homotopy is applied to a simple algebraic minimization problem. Let $F(p)$ be a convex objective function with a local minimum at p^*. So we apply HOM to find p^* . If we start from an arbitrary point p_0, and if the function has multiple local minimas, it is likely that the optimization procedure will converge to a local minimum. In the homotopy method, we first construct the following function:

$$\mathrm{H}(\mathrm{x}, \lambda) = (1 - \lambda)\mathrm{G}(\mathrm{x}) + \lambda\, \mathrm{F}(\mathrm{x}) \qquad (6)$$

Where$G(x)$, is usually a simple convex function for which the arguments of its global minimum are known. We now begin the process by choosing $\lambda^0 = 1$ and minimizing$H(x, 1) = G(x)$. In the first step, the minimum of $H(p, 1)$ is equal to the minimum of G(x), which is known. Once the minimum has been found for λ=1, λ is declined by a small amount Δ and H(x,λ^1) is minimized, where $\lambda^1=\lambda^0 + \Delta$. Using the converged result from the previous stage as the initial guess for p and using $\lambda^k=\lambda^{k-1} + \Delta$. The process is continued until $\lambda = 0$ is obtained and the objective function has been morphed back into $F(x)$. As we are always finding the minimum of H(x, λ) with an initial guess that is close to its global minimum, it is more likely that we will find the global minimum of the function F(x) (if we choose small enough Δ parameter). Note that the choice of known function G(x) is nontrivial.

In general, the homotopy method is only capable of finding the local minima; however, if the nature of F(x) is known, it may be possible to construct the homotopy transformation in a way that increases the chance of finding the global minimum. Figure 1 presents the details of HOM algorithm.

Algorithm 1 Homotopy Optimization Method

Step 1. Enter the following inputs:
x(0) = x_0,
a local minimizer of G(x);
m ≥ 1;
$\Delta^{(k)} > 0$ (k = 0, ... , m − 1).
Step 2. Initialize: $\lambda^0 = 0$;
Step 3.
for k = 1, ... , m
$\lambda^k = \lambda^{k-1} + \Delta^{(k-1)}$
Use a local minimization method,
starting with $x^{(k-1)}$, to compute
an approximate Solution x (k)
to $min_{x \in X}$ h(x, λ (k)).
End
Step 4. Output: $p^* = x^{(m)}$

2.2 Representing the Parameter Estimation in the form of an Optimization Problem

The nonlinear equations of the physical system for which the parameters must be identified are assumed to be of the following form:

$$\dot{x}_1 = x_2$$
$$\dot{x}_2 = x_3$$
$$\vdots$$
$$\dot{x}_n = f(x_1, \dots, x_n, p, t) \qquad (7)$$

For above system $\boldsymbol{X}(t) = [x_1(t), x_2(t), \dots, x_n(t)]^T$ is the independent coordinates and $\boldsymbol{p}$ is a vector of parameters to be identified. The system is assumed to be nonlinear which is appears in f. Experimental data $\boldsymbol{X}_e(t) = [x_{1e}(t), x_{2e}(t), \dots, x_{ne}(t)]^T$ of all the displacements is assumed to be available over time T. Note that it is possible to identify the system parameters with only a few components of $\boldsymbol{X}_e(t)$ since, in coupled systems, each component of $\boldsymbol{X}_e(t)$ contains information from all the parameters due to the coupling between the system equations. The aim is to estimate the parameters in the mathematical model such that the solution of the differential equations (7) closely matches the experimental data. To identify the parameters, the integral of the squared difference between the experimental and simulated states which is an error indicator should be minimized:

$$\min_p E(\boldsymbol{p}) = \frac{1}{2}\sum_{i=1}^{n}\left\{\int_0^T \left(x_{ie}(t) - x_i(t,p)\right)^2 dt\right\} \qquad (8)$$

Note that a discrete summation can be used in place of the integral in this equation. Given the initial estimates of the parameters, we can use Gauss-Newton [14] which is a fast gradient base optimization method to minimized (8). Using Gauss-Newton algorithm, parameter p is updated according to (9):

$$p^{r+1} = p^r + d^r \qquad (9)$$

Where $\boldsymbol{d}^r$ is the search direction, which can be obtained from the following relation [23]:

$$H(p^r)d^r = -G^T(p^r) \qquad (10)$$

In (10), $\boldsymbol{G}$ and $\boldsymbol{H}$ are the gradient and the approximate Hessian of the objective function, which can be calculated through (11) and (12) by neglecting the higher order terms:

$$G(p) = \frac{\partial V}{\partial p} = -\sum_{i=1}^{n}\left\{\int_0^T \left(x_{ie}(t) - x_i(t,p)\right)\frac{\partial xi}{\partial \boldsymbol{p}} dt\right\} \qquad (11)$$

$$H(p) = \frac{\partial^2 V}{\partial p^2} \approx \sum_{i=1}^{n} \left\{ \int_0^T \frac{\partial xi}{\partial \boldsymbol{p}}^T \frac{\partial xi}{\partial \boldsymbol{p}} dt \right\} \qquad (12)$$

The sensitivity data $\frac{\partial xi}{\partial \boldsymbol{p}} = [\frac{\partial xi}{\partial p_1}, \frac{\partial xi}{\partial p_2}, \ldots, \frac{\partial xi}{\partial p_m}]$ can be obtained by solving the sensitivity differential equations, which can be derived by directly differentiating (7), with respect to the individual parameters:

$$\frac{\partial \dot{x}_1}{\partial p_j} = \frac{\partial x_2}{\partial p_j}$$

$$\frac{\partial \dot{x}_2}{\partial p_j} = \frac{\partial x_3}{\partial p_j}$$

$$\vdots$$

$$\frac{\partial \dot{x}_2}{\partial p_j} = \frac{\partial f(x_1, x_2, \ldots, x_n, p, t)}{\partial p_j} + \frac{\partial f(x_1, x_2 \ldots, x_n, p, t)}{\partial x_1}\frac{\partial x_1}{\partial p_j} + \frac{\partial f(x_1, x_2, \ldots, x_n, p, t)}{\partial x_2}\frac{\partial x_1}{\partial p_j} + \cdots + \frac{\partial f(x_1, x_2, \ldots, x_n, p, t)}{\partial x_n}\frac{\partial x_1}{\partial p_j} \qquad (13)$$

We will briefly explain how homotopy is applied to a simple algebraic minimization problem. Let $F(\boldsymbol{p})$ be the objective function. We are interested in finding parameters $\boldsymbol{p}^*$ at which F has a global minimum.

2.3 Parameter Estimation Using HOM

We now discuss how the homotopy method can be applied to the problem of parameter identification. To modify the objective function, the experimental data is coupled to the mathematical model as follows:

$$\dot{x}_1 = x_2 + \lambda K_1(x_{1e} - x_1)$$
$$\dot{x}_2 = x_3 + \lambda K_2(x_{2e} - x_2)$$
$$\vdots$$
$$\dot{x}_n = f(x_1, x_2, \ldots, x_n, p, t) + \lambda K_n(x_{ne} - x_n) \qquad (14)$$

Initially, when $\lambda = 1$, the coupling term acts as a high-gain observer [28], and if sufficiently high values of Ki are used, the experimental data and simulated response will synchronize. Note that λ is introduced to the traditional definition of a high-gain observer so as to construct the homotopy transformation. Also note that the sensitivity equations (13) must be modified to account for the added coupling term. For very large Ki, the cost function becomes a flat surface with a very small magnitude, and the experimental data x_{1e} and simulated response $\boldsymbol{x}1$ will reach together in the last step. We decrease λ by a small amount $\delta\lambda$ and minimize the objective function (8), treating (14) as the mathematical model. We then decrease λ further to $\lambda - \delta\lambda$; since the parameter guesses have been refined. At each stage in this process, we use the converged result from the previous stage as the initial guess for $\boldsymbol{p}$. This process is repeated until $\lambda = 0$, and (14) has transformed into (7). In summary, the homotopy optimization approach follows the path of minimal error as the observer gain is decreased. We ensure that the error is close to zero in the last stage, with the hope that the refined parameter guesses at the final stage are sufficiently close to the global optimum of the original problem. The process of applying the homotopy method to the problem of parameter identification is summarized in Algorithm 2.

3. Simulation & Discussion

In this paper, HOM is applied to estimate uncertain parameters of a diabetic model which is defined in section two. The state space model of such system is:

$$\dot{x}_1 = -0.025x_1 + 0.00013x_2$$
$$\dot{x}_2 = -(5/54)(x_2 + 1.5)$$
$$\dot{x}_3 = -Px_3 + x_1(x_3 + 110) \qquad (15)$$

Where P is an uncertain parameter. We consider an experimental model with nominal value of P=0.028. Using the state of experimental model (x_{ie}) we construct the cost function as follows:

$$E(\boldsymbol{p}) = \frac{1}{2}\sum_{i=1}^{3} \left\{ \int_0^T \left(x_{ie}(t) - x_i(t,p)\right)^2 dt \right\}$$

Algorithm 2 Parameter identification using homotopy

Input: Experimental data ($\boldsymbol{x}_{1e}$),
Output: Identified parameters ($\boldsymbol{p}$)
Initialize
while $\lambda \geq 0$ **do**
for $i=1:m$
Solve ODEs for $\boldsymbol{x}1$ and $\partial \boldsymbol{x}1\ \partial pj\ \forall j$ Minimize
$E\ (\boldsymbol{p}) = \frac{1}{2}\sum_{i=1}^{n}\left\{\int_0^T (y_{ie}(t) - y_i(t,p))^2 dt\right\}$
Solve $\boldsymbol{H}(\boldsymbol{p})\ \boldsymbol{d} = -\boldsymbol{G}T(\boldsymbol{p})$ for $\boldsymbol{d}$
$\boldsymbol{p} = \boldsymbol{p} + \boldsymbol{d}$
end for
$\lambda=\lambda-\delta\lambda$
end while
return

To estimate the uncertain parameter we use the proposed algorithm 2 for system below:

$$\dot{x}_1 = -0.025x_1 + 0.00013x_2 + \lambda K_1(x_{1e} - x_1)$$

$$\dot{x}_2 = -(5/54)(x_2 + 1.5) + \lambda K_2(x_{2e} - x_2)$$

$$\dot{x}_3 = -Px_3 + x_1(x_3 + 110) + \lambda K_3(x_{3e} - x_3) \qquad (17)$$

The simulation results of optimization algorithm for different values of initial point of P are illustrated in figure 1. For $\lambda = 1$ the described system (17) has the structure of a high gain observer. In this observer we consider large values of K gain which forced the system states to track their related experimental data. This leads to dramatic decline of E(p) as it is shown in figure 1. By decreasing the λ value, the structure of (17) transforms to a parameter dependent equation. Considering the E(p) value for small values of λ shows that the presented algorithm efficiently estimation the uncertain parameter p=0.028, and the accuracy of parameter estimation is not depends on the initial guess of p.

The process of estimated P convergence to its nominal value by decreasing λ is defined in table 1. To indicate the efficiency of algorithm 2, we employ the algorithm for an initial guess $p = 20$. For each fixed value of λ, we consider $m = 3$. According to table 1, estimated p converges to its actual value as λ converges to zero.

Considering this example shows that HOM algorithm is an effective method for estimating uncertain parameters of biological model. Independence on initial value of P is one of the main advantages of this method.

4. Conclusions

In this work, we have presented a new methodology for applying the homotopy optimization method to the parameter estimation. As it was seen in pervious sections, this method could find the global optimization of the uncertain parameter and this estimation is equal to the nominal value of the parameter. The proposed homotopy method can successfully find global minima given a wide domain of initial parameter guesses. The efficient of the proposed method for parameter estimation has been demonstrated by applying to diabetic model. The authors are currently investigating the use of HOM to apply to other biological systems and set the controller up to these systems and identification parameters with controller as next works.

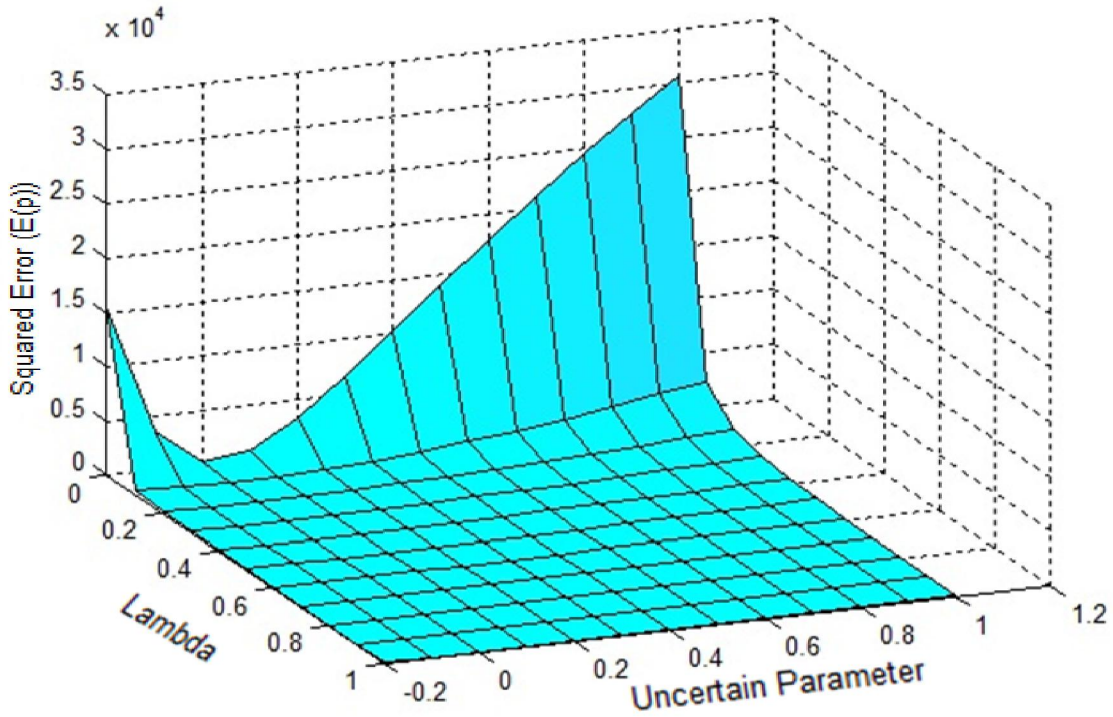

Figure 1. simulation results of optimization algorithm for different values of initial point of P and λ

Table 1. Process of estimated P convergence to its nominal value

Lambda	Uncertain Parameters	Squared Error
1	20	1.6e4
1	**19.25**	1.5e4
1	16.94	1.3e4
0.9	10.24	7.5e3
0.9	3.7	1.4e3
0.9	2.94	942.5
0.8	2.463	836.6
0.8	2.075	608.5
0.8	1.79	462
0.7	1.58	461.9
0.7	1.35	358.2
0.7	1.22	284.5
0.6	1.101	304.9
0.6	0.977	242
0.6	0.876	195.4
0.5	0.79	220.4
0.5	0.71	176.6
0.5	0.63	142.8
0.4	0.574	174.8
0.4	0.51	137.0
0.4	0.455	108.9
0.3	0.41	146.4
0.3	0.357	110.6
0.3	0.315	84.6
0.2	0.28	132.8
0.2	0.236	91.87
0.2	0.20	64.7
0.1	0.17	142.3
0.1	0.133	75.2
0.1	0.1054	41.4
1.4e-016	0.0858	487.0
1.4e-016	0.012	72.7
1.4e-016	0.0282	32.3

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