OPTIMAL CONTROL APPLICATIONS AND METHODS
Optim. Control Appl. Meth. (2009)
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/oca.920

Optimal blood glucose regulation of diabetic patients using single network adaptive critics

Sk. Faruque Ali[‡] and Radhakant Padhi*[, †, §]

Department of Aerospace Engineering, Indian Institute of Science, Bangalore-560012, India

SUMMARY

Diabetes is a long-term disease during which the body's production and use of insulin are impaired, causing glucose concentration level to increase in the bloodstream. Regulating blood glucose levels as close to normal as possible leads to a substantial decrease in long-term complications of diabetes. In this paper, an intelligent online feedback-treatment strategy is presented for the control of blood glucose levels in diabetic patients using single network adaptive critic (SNAC) neural networks (which is based on nonlinear optimal control theory). A recently developed mathematical model of the nonlinear dynamics of glucose and insulin interaction in the blood system has been revised and considered for synthesizing the neural network for feedback control. The idea is to replicate the function of pancreatic insulin, i.e. to have a fairly continuous measurement of blood glucose and a situation-dependent insulin injection to the body using an external device. Detailed studies are carried out to analyze the effectiveness of this adaptive critic-based feedback medication strategy. A comparison study with linear quadratic regulator (LQR) theory shows that the proposed nonlinear approach offers some important advantages such as quicker response, avoidance of hypoglycemia problems, etc. Robustness of the proposed approach is also demonstrated from a large number of simulations considering random initial conditions and parametric uncertainties.

Received 28 March 2009; Revised 10 October 2009; Accepted 20 October 2009

KEY WORDS: blood glucose regulation; diabetes control; optimal neuro control; nonlinear optimal control; adaptive critic design; single network adaptive critics

1. INTRODUCTION

The idea of using mathematical control theory to solve problems in biological sciences is relatively old [1–3]. However, in recent years activities based on this idea is growing fast. This is primarily owing to the development of more mathematical models for various biological systems [1, 2]. This rapid growth can also be attributed to the advancement in control theory. Some of the recent biomedical applications of control engineering can be found in [2] and the references therein. In the present study, an attempt has been made to regulate blood glucose concentration in diabetic patients following a nonlinear optimal control design approach.

Diabetes is a disease in which the blood sugar level increases in patients and a significant effort is directed toward finding better ways to manage diabetes [3, 4]. The normal blood glucose concentration level in a human is in the narrow range of 70–110 mg/dl [5]. Keeping blood glucose levels as close to normal as

*Correspondence to: Radhakant Padhi, Department of Aerospace Engineering, Indian Institute of Science, Bangalore-560012, India.
†E-mail: padhi@aero.iisc.ernet.in
‡Research Associate.
§Assistant Professor.

possible leads to a substantial decrease in long-term complications of diabetes. A higher value as well as a lower value can lead to a serious illness in human beings. A higher blood sugar level leads to hyperglycemia, whereas a low blood sugar level results in hypoglycemia. Hyperglycemia in the long run can create problems such as stroke, cardiac arrest, blindness, etc. Hypoglycemia (less than 50 mg/dl of blood sugar concentration), on the other hand, has more serious consequence as it can rapidly lead to brain failure and hence death of the patient. The blood sugar concentration is normally controlled within these limits by different factors in the body. The most important regulators of the glucose level in the body are insulin and glucagon hormones that suppress and increase the blood sugar level, respectively. Insulin is anabolic and stimulates the glucose uptake capacity in tissues and thereby lowers the glucose level in the blood. Conversely, glucagon is catabolic. It stimulates the glucose production from fatty acids and amino acids when needed and results in increasing the blood sugar level. Different factors including food intake, rate of digestion, and exercise affect the glucose concentration in the blood.

Diabetes mellitus is a disease in which blood glucose concentration is elevated because of deficient insulin secretion or abnormal insulin action. Diabetic patients require lifetime exogenous insulin injections to monitor the glucose concentration in blood within safe limits. Traditionally, managing diabetes has been through intermittent monitoring of blood glucose and then administering an appropriate dose of insulin into the blood stream. This method of intermittent monitoring and administration of insulin cannot ensure that blood glucose remains at near normal levels at all times and therefore there is considerable interest in managing diabetes on a continuous basis [5, 6]. The current treatments include 3–4 daily glucose measurements and an equivalent number of insulin injections.

An alternative approach is to replicate the function of pancreatic insulin, i.e. to have a continuous measurement and situation-dependent insulin injection to the body based on a feedback strategy using an external device such as an insulin pump and a sensor [3, 5–8]. This pump, which acts like an artificial pancreas, includes a sensor and an insulin container. The sensor provides the measurements of the blood glucose concentration and passes the information to a feedback-control system that would decide on the necessary insulin delivery rate using control algorithms to keep the patient under metabolic control. The pump injects insulin through a catheter placed under the patient's skin. The ultimate goal in closed-loop control of blood glucose is not just finding the optimal insulin rates that can effectively reduce the high blood glucose, but to infuse it in such a way that the blood glucose level can mimic the body's natural excursion [7, 8]. In this study we apply a nonlinear optimal control approach using the recently developed single network adaptive critic (SNAC) philosophy [9, 10] to regulate blood glucose concentration.

Several methods have been previously employed to design the feedback controller for insulin delivery. These include classical linear control design ideas such as PID and pole placement designs, linear quadratic regulator (LQR) control, etc. [5, 6], where a linearized model of the system is used for the feedback-control design. Nonlinear control design ideas such as model predictive control (MPC) [11, 12] and higher order sliding mode (HOSM) control [13, 14] have also been proposed in the recent literature. However, an important issue in blood glucose regulation using linearized plant is the hypoglycemia problem (blood glucose level below 50 mg/dl) [13], which is typically not addressed in the existing literature. In fact, our comparison simulation study with the LQR control clearly shows that such an approach does lead to hypoglycemia problems (see Section 4 for the comparison results). On the other hand, this issue does not arise in the proposed SNAC-based nonlinear optimal drug delivery approach.

Many difficult real-life control problems can be formulated within the framework of optimal control theory. It is well known that the dynamic programming formulation offers the most comprehensive solution approach to nonlinear optimal control problems in a state-feedback form [15], which is desirable because of its beneficial properties (e.g. robustness with respect to noise suppression). However, a huge (infeasible) amount of computational and storage requirements are needed to solve the associated Hamilton–Jacobi–Bellman (HJB) equation. An innovative idea has been

DOI: 10.1002/oca

proposed in [16] to get around the computational complexity of the dynamic programming formulation by using approximate dynamic programming (ADP) formulations. The solution to the ADP formulation is obtained through a two-neural network approach called adaptive critic (AC). In one version of the AC approach, called the dual heuristic programming (DHP), one network (called the action network) captures the mapping between the state and control variables, whereas a second network (called the critic network) captures the mapping between the state and costate variables. More important, this solution can be implemented on-line, as the control computation requires a few multiplications of the network weights (which are trained off-line). Recently, a significant improvement to the adaptive critic technique is proposed in [9] by eliminating one of the two networks in the structure and therefore named as SNAC. The action network in adaptive critic design is eliminated and only the critic network is preserved. As a consequence, the SNAC architecture offers three potential advantages: a simpler architecture, lesser computational load and elimination of the approximation error associated with the eliminated network. This approach is applicable to a wide class of nonlinear systems where the optimal control (stationary) equation can be explicitly expressed in terms of the state and costate variables. The efficiency of the technique has been reported for a class of nonlinear systems [10] and treatment of Parturient Paresis in cows [9].

In the present study we apply SNAC to regulate blood glucose concentration in diabetic patients. The advantages of the proposed continuous medication strategy using SNAC include (i) it provides nonlinear optimal treatment strategy for diabetic patients which does not lead to any hypoglycemic conditions (unlike linear quadratic controller) and hence avoids the associated severe consequences such as brain failure, (ii) it is computationally efficient and hence can be implemented in real time and (iii) it brings down the glucose level in blood to a safe level (less than 110 mg/dl) within approximately 1 h (and to the basal value within approximately 3–4 hours) of food intake. The proposed approach has sufficient robustness to parameter uncertainties as well. Note that a small change in some of the sensitive parameters can dramatically drive the patient's blood glucose level to instability and may even result in the patient's death. Therefore, it is vital for the patients that controller used in the closed-loop system should be capable of handling these uncertainties in parameters, which we demonstrate from sufficiently large number of simulations.

The remainder of the paper is organized as follows: Section 2 deals with the mathematical modeling aspects of the problem. Nonlinear minimal model is considered for the present analysis with exogenous glucose intake as food. In Section 3 the necessary conditions of optimality from the ADP perspective is described, followed by the main idea of SNAC synthesis. Results from the simulation studies are discussed next in Section 4 and some conclusions of this research are derived in Section 5.

2. MATHEMATICAL MODEL FOR INSULIN–GLUCOSE REGULATION

Blood glucose regulation for a diabetic patient is done using empirical and model-based approaches. In the empirical approach to control algorithm design, the relationship between the input (insulin) and the output (desired glucose level) is determined based on experimental data, not on a mathematical theory. A control rule is then formulated either as a curve fitting technique or as a look-up table using the experimental data as the basis.

The model-based approaches involve the use of a mathematical model in the control of blood glucose level. The models describe the complex interaction of glucose and insulin. Various linear and nonlinear models are available for controller design [5]. In this paper, the insulin–glucose regulatory system dynamics in the human body as described by the 'minimal model' is used. Bergman minimal model [17, 18] is a commonly referenced model in the literature and approximates the dynamic response of a diabetic patient's blood glucose concentration to the insulin injection using nonlinear differential equations.

2.1. Minimal model for insulin–glucose regulation

Minimal model is composed of two parts: the first part describes the glucose plasma concentration considering

DOI: 10.1002/oca

Table I. Minimal model variables.

Variable	Meaning	Unit
$G(t)$	The blood glucose concentration at time t (min)	mg/dl
$I(t)$	Blood insulin concentration at time t (min)	μU/ml
$Z(t)$	Represents insulin-excitable tissue glucose uptake activity	$\min^{-1}$
$D(t)$	Exogenous glucose infusion rate after meal	mg/dl/min
G_b	Basal glucose level	mg/dl
I_b	Basal insulin level	μU/ml
γ	The rate of pancreatic release of insulin after bolus	μU/ml/(mg/dl)/min
h	The pancreatic target glycemia [5]	mg/dl
n	The time constant for insulin disappearance	$\min^{-1}$
$u(t)$	Insulin injection rate (the control variable)	μU/ml/min

'U' indicates insulin strength. For example, U-100 reflects the number (100) of active insulin units in each ml of liquid.

the dynamics of glucose uptake and independent of circulating insulin. It treated insulin plasma concentration as a known forcing function [5].

$$\begin{aligned}\dot{G}(t) &= -p_1[G(t)-G_b]-Z(t)G(t)+D(t)\\ \dot{Z}(t) &= -p_2Z(t)+p_3[I(t)-I_b]\end{aligned} \tag{1}$$

where $t=0$ shows the time glucose enters blood, $G(t)$ is the glucose concentration in the blood plasma in (mg/dl), $Z(t)$ is the insulins effect on the net glucose disappearance, the insulin concentration in the remote compartments in (1/min). G_b is the basal pre-injection level of glucose in (mg/dl). Parameter p_1 is the insulin-independent rate constant of glucose uptake in muscles and liver in (1/min), p_2 is the rate for decrease in tissue glucose uptake ability (in 1/min), p_3 is the insulin-dependent increase in glucose uptake ability in tissue per unit of insulin concentration above the basal level in $((\mu\text{U/ml})^{-1}\min^{-1})$. The term p_1G_b accounts for the body's natural tendency to move toward basal glucose levels.

Insulin kinetics is given by a single equation which describes the plasma insulin concentration considering the dynamics of pancreatic insulin release in response to the glucose stimulus.

$$\dot{I}(t)=-n[I(t)-I_b]+\gamma[G(t)-h]^+t \tag{2}$$

where '+' sign shows the positive reflection to glucose intake, i.e. when $[(G(t)-h)>0]$ the term $\gamma[G(t)-h]^+$ in Equation (2) acts as an internal regulatory function that formulates the insulin secretion in the body, which does not exist in diabetic patients [5] (and therefore assumed not present in simulations carried out with diabetic patients). $I(t)$ is the insulin concentration in plasma at time t in (μU/ml), I_b is the basal pre-injection level of insulin. The definition of variables used in the minimal model and their units are given in Table I. It is worth noting that all the values are calculated for a person of average weight and these are not constant numbers and vary from patient to patient, which makes the design of the controller a more challenging task.

To show the complete dynamics of the glucose–insulin regulatory system, a food intake term is considered in Equation (1). $D(t)$ shows the rate at which glucose is absorbed to the blood from the intestine, following food intake. This glucose absorption is considered as a disturbance to the system dynamics owing to the absence of normal insulin regulatory system in diabetic patients. This disturbance can be modeled by a decaying exponential function, whose dynamics is given by the following equation.

$$\dot{D}(t)=-BD(t), \quad B>0 \tag{3}$$

where t is in (min) and $D(t)$ is in (mg/dl/min) [5, 7, 14].

The objective of the study is to develop a nonlinear control technique to compensate the uncertainties and disturbances and to stabilize the blood plasma glucose concentration of a diabetic patient at the basal value.

DOI: 10.1002/oca

It should be noted that the control term is not yet considered in the model introduced in Equation (2).

2.2. Model for control design

The system of equations introduced in Equations (1)–(3) can be combined to get following equations

$$\begin{aligned}\dot{x}_1 &= -p_1[x_1 - G_b] - x_1 x_2 + x_4 \\ \dot{x}_2 &= -p_2 x_2 + p_3[x_3 - I_b] \\ \dot{x}_3 &= -n[x_3 - I_b] + u(t) \\ \dot{x}_4 &= -B x_4\end{aligned} \tag{4}$$

In Equation (4), x_1, x_2, x_3 and x_4 represent $G(t)$, $Z(t)$, $I(t)$ and $D(t)$, respectively. Note that the term $\gamma[G(t)-h]^+$ in Equation (2) is removed from Equation (4) as it does not exist in diabetic patients [5, 18]. $u(t)$ defines the insulin injection rate and replaces the normal insulin regulation of the body [14], which acts as the control variable. The exogenous infusion of glucose (Equation (3)) is considered as an additional state variable (x_4) in Equation (4).

The aim of the present study is to design the control system such that the system variables in Equation (4) reach their equilibrium values (i.e. basal values in the present case). Therefore, for convenience, system dynamics is rewritten in its deviation terms. For this we define,

$$\begin{aligned}[x_1 \;\; x_2 \;\; x_3 \;\; x_4]^{\mathrm{T}} = [x_{1_0} \;\; x_{2_0} \;\; x_{3_0} \;\; x_{4_0}]^{\mathrm{T}} \\ + [x_{1_d} \;\; x_{2_d} \;\; x_{3_d} \;\; x_{4_d}]^{\mathrm{T}}\end{aligned} \tag{5}$$

where $[x_{1_d} \;\; x_{2_d} \;\; x_{3_d} \;\; x_{4_d}]^{\mathrm{T}}$ is the 'deviated state' about the equilibrium point $[x_{1_0} \;\; x_{2_0} \;\; x_{3_0} \;\; x_{4_0}]^{\mathrm{T}}$ of the system. From Equation (4) the equilibrium is obtained as

$$[x_{1_0} \;\; x_{2_0} \;\; x_{3_0} \;\; x_{4_0}]^{\mathrm{T}} = [G_b \;\; 0 \;\; I_b \;\; 0]^{\mathrm{T}} \tag{6}$$

Equation (4) can be rewritten in terms of x_{1_d}, x_{2_d}, x_{3_d}, and x_{4_d} as

$$\begin{Bmatrix} \dot{x}_{1_d} \\ \dot{x}_{2_d} \\ \dot{x}_{3_d} \\ \dot{x}_{4_d} \end{Bmatrix} = \begin{Bmatrix} -p_1 x_{1_d} - (x_{1_d} + G_b) x_{2_d} + x_{4_d} \\ -p_2 x_{2_d} + p_3 x_{3_d} \\ -n x_{3_d} + u(t) \\ -B x_{4_d} \end{Bmatrix} \tag{7}$$

2.3. Model with normalized variables

For better training of neural networks (see Section 3.2), we normalize the neural network inputs. For this reason, we define the new variables $\bar{x}_1 \triangleq x_{1_d}/x_{1_n}$, $\bar{x}_2 \triangleq x_{2_d}/x_{2_n}$, $\bar{x}_3 \triangleq x_{3_d}/x_{3_n}$, $\bar{x}_4 \triangleq x_{4_d}/x_{4_n}$, where subscript $(_n)$ denotes nominal values of the variables (chosen appropriately so that the values of the normalized variables becomes roughly of same order). The system dynamics can now be written in terms of the normalized variables as follows

$$\begin{Bmatrix} \dot{\bar{x}}_1 \\ \dot{\bar{x}}_2 \\ \dot{\bar{x}}_3 \\ \dot{\bar{x}}_4 \end{Bmatrix} = \begin{Bmatrix} -p_1 \bar{x}_1 - (\bar{x}_1 + G_b/x_{1_n}) \bar{x}_2 x_{2_n} + \bar{x}_4 x_{4_n}/x_{1_n} \\ -p_2 \bar{x}_2 + p_3 \bar{x}_3 x_{3_n}/x_{2_n} \\ -n \bar{x}_3 + \bar{u}(t) \\ -B \bar{x}_4 \end{Bmatrix} \tag{8}$$

Note that the equilibrium point of the homogeneous system dynamics in (8) now corresponds to the origin (for normalized and deviated states) and the control term $\bar{u}(t) = u(t)/x_{3_n}$ represents the normalized rate of insulin infusion. For convenience redefining $[x_1 \;\; x_2 \;\; x_3 \;\; x_4]^{\mathrm{T}} \triangleq [\bar{x}_1 \;\; \bar{x}_2 \;\; \bar{x}_3 \;\; \bar{x}_4]^{\mathrm{T}}$ and $\bar{u}(t)$ as $u(t)$, the normalized dynamics in Equation (8) can be written as

$$\dot{X} = F(X, u) = f(X) + g u(t) \tag{9}$$

where, $X = [x_1 \;\; x_2 \;\; x_3 \;\; x_4]^{\mathrm{T}}$ and

$$f(X) \triangleq \begin{Bmatrix} -p_1 x_1 - (x_1 + G_b/x_{1_n}) x_2 x_{2_n} \\ \quad + x_4 x_{4_n}/x_{1_n} \\ -p_2 x_2 + p_3 x_3 x_{3_n}/x_{2_n} \\ -n x_3 \\ -B x_4 \end{Bmatrix} \tag{10}$$

$$g \triangleq [0 \;\; 0 \;\; 1 \;\; 0]^{\mathrm{T}}$$

Note that the control term appears only in the insulin dynamics, i.e. only the rate of insulin injection is modified by the state feedback-control theory. As only the plasma glucose concentration has to reach its basal value, an output regulator problem is considered for the

DOI: 10.1002/oca

medication problem. Glucose concentration in blood is considered as the output (y), where

$$y = CX = [1\ 0\ 0\ 0]X \tag{11}$$

3. OPTIMAL CONTROL DESIGN USING SNAC

A brief overview of the SNAC technique is presented in this section. Even though the discussion is purposefully biased toward the blood glucose regulation problem, attempt has been made to preserve sufficient generality for the larger benefit of the readers. As mentioned in Section 1, SNAC falls into the larger basket of adaptive critic methods, which in turn rely on the ADP philosophy and provides a state feedback optimal control solution within a domain of interest. However, SNAC eliminates one of the two networks in the adaptive critic structure for a class of problems for which the optimal control (stationary) equation can be explicitly expressed in terms of the state and costate variables. This provides a simpler architecture, lesser computational load and reduction in the approximation error. Even though only a brief overview of this fairly recent technique is provided here for completeness, an interested reader can find more details on the technique in [10].

3.1. Optimality conditions

For use with neural networks, the insulin–glucose regulation medication dynamics (i.e. the system dynamics) is first discretized using Euler integration scheme [19]) as

$$X_{k+1} = X_k + \Delta t\, F^k(X_k, u_k) = X_k + \Delta t[f_k + g u_k] \tag{12}$$

where Δt is the step size in time. The discretized output vector (y_k) is given as

$$y_k = CX_k = [1\ 0\ 0\ 0]X_k \tag{13}$$

Note that X_k represents the 'normalized state vector' at time t_k.

A standard regulator cost function with output weighting is considered. An approximate (using trapezoidal rule [19]) following discrete cost function is obtained.

$$J = \frac{1}{2}\sum_{k=1}^{N\to\infty}[Q_d y_k^2 + R_d u_k^2] \tag{14}$$

where $Q_d = Q\Delta t \geqslant 0$, $R_d = R\Delta t > 0$ are the weighting matrices on state and control, respectively, and Δt is the step size in time. The goal of this control synthesis approach is to administer insulin slowly into the blood stream which means one should not choose too high values of Q or very small values for R. Appropriate choice of these values is problem dependent and can be adjusted with relative ease after a few simulations. Applying the standard discrete optimal-control theory [15], the equations for optimal control and costate dynamics are given by

$$u_k = -R^{-1}[0\ 0\ 1\ 0]\lambda_{k+1} \tag{15}$$

$$\lambda_k = \lambda_{k+1} + \Delta t\left[C^{\mathrm{T}} Q C X_k + \left(\frac{\partial F^k}{\partial X_k}\right)^{\mathrm{T}}\right] \tag{16}$$

where, λ_k is the costate variable at time step t_k, the dynamics for which evolves backwards in time.

At each time step k the coupled Equations (9), (10), (12), (15) and (16) have to be solved simultaneously, together with the boundary conditions (X_1 specified and $\lambda_N = 0$ as $N \to \infty$), to obtain the optimal control solution u_k. In an infinite horizon of the problem, we can essentially capture the steady state relationship between state and costate in a single network (or set of networks, if one network is assumed for each element of the output vector, as done in this work). For finite horizon problems, however, one needs a series of such networks to capture this relationship at every time step [10].

3.2. Procedure for neural network synthesis

In this section, the procedure for synthesizing a set of neural networks, called as 'critic networks', is presented. The neural network structure solves the optimal control problem contained in Equations (12), (15) and (16), while satisfying the boundary conditions as well.

The blood glucose regulation problem discussed in this paper is solved assuming two different cases. First, it is assumed that complete information about the model

DOI: 10.1002/oca

parameters for individual patients is available (with the assumption that a sufficiently fast parameter identification procedure can be augmented in parallel). In the second case, it is assumed that no specific information about the model parameters for individual patients is available (hence one must rely on the nominal parameters for all patients). In the first case the model parameters (p_1, p_2, p_3, n, B, etc.) are assumed to be constant and only the initial conditions of the state variables are assumed to vary. In the second case, the model parameters p_2, p_3, n, B are also varied in addition to the initial condition variation of states (p_1 is not varied as p_1 is assumed zero for diabetic patients [5]). Note that the first case will be more easier (and realistic) for implementation, whereas the second case is expected to come up with 'tailor made' drug dosage for individual patients. As it is evident from this discussion, in the first case we only need to give the state information for the feedback control (i.e. input to the neural networks), whereas parameter values are also needed as input to the networks in the second case.

3.2.1. State generation for neural network training. In the controller synthesis process, we first fix a particular time step k. Then we choose a set of states $S=\{X_k: X_k \in \text{Domain of interest}\}$ for which the critic networks are to be trained. Obviously it is a difficult task, mainly because of the fact that prior to the controller solution, we do not have an idea so as to how exactly a system evolves in the presence of control. However, for all practical purposes, one can just choose a sufficiently large number of random states in the domain of interest for training the neural networks. One can notice, however, that for regulator problems, as time increases the states tend to zero. Thus the set S must also contain, with non-zero probability, the controlled states with different magnitudes, including the ones close to zero. For this reason, we follow the same 'telescopic procedure' proposed earlier [9, 10], which is outlined below.

Define, $S_i=\{\text{all } X_k : \|X_k\|_\infty \leqslant c_i\}$, for $i=1,2,3,\ldots$, where c_i is a positive constant. Notice that for $c_1 \leqslant c_2 \leqslant c_3 \leqslant \cdots$, $S_1 \subseteq S_2 \subseteq S_3 \subseteq \cdots$. Thus, for some $i=I$, S_I will include the domain of interest for initial conditions. Hence, to begin the synthesis procedure, we fix a small value for the constant c_1 and train the networks for the states, randomly generated within S_1. Once the critic networks converge for this set, we choose c_2 close to c_1 and again train the networks for the profiles within S_2 and so on. We keep on increasing the constant c_i this way until the networks are trained for states in S_1. In this paper, we have chosen $c_1=0.05$, $c_i=c_1+0.01(i-1)$ for $i=2,3,\ldots$ and continued until $c_i=c_I=1$.

3.2.2. Neural network training. The critic neural network(s) essentially capture the relationship between X_k and λ_{k+1}. For faster training, we have synthesized four neural networks (separate networks for each element of the vector λ_{k+1}). Separate neural networks are trained for the two different cases (first with random initial conditions and the second one with random initial conditions and random model parameters). Discussion for the training in second case is presented here as it is more general. We have assumed that the parameters of the problem (p_2, p_3, n, B) are not fixed and they can vary, within known minimum and maximum values. Thus, $p_2 \in [p_{2\min}, p_{2\max}]$, $p_3 \in [p_{3\min}, p_{3\max}]$, $n \in [n_{\min}, n_{\max}]$ and $B \in [B_{\min}, B_{\max}]$. The parameter range are shown in Table II. However, we have assumed that the parameters remain constant for any particular patient and hence, for a typical state trajectory. Thus, to capture the relationship between X_k and λ_{k+1}, we construct an augmented vector $X_k^{\text{inp}}=[X_k^{\text{T}} \vdots P^{\text{T}}]^{\text{T}}$ (P is the vector containing parameters), which serves as the input to the neural networks. However, as the individual elements of X_k^{inp} vary widely in magnitude, we construct a normalized vector to serve as the input. Thus we have $X_k^{\text{inp}}=[x_{1k}\ x_{2k}\ x_{3k}\ x_{4k}\ p_2/p_{2_n}, p_3/p_{3_n}, n/n_n, B/B_n]^{\text{T}}$, where p_{2_n}, p_{3_n}, n_n and B_n are the normalizing values for p_2, p_3, n and B, respectively. Note that for first case (i.e. for which only nominal parameter information is available), X_k is used as X_k^{inp}. With the availability of

Table II. Nominal parameter values.

Parameter	Value	Parameter	Value
p_1	0	p_2	0.0142
p_3	1.54×10^{-5}	B	0.05
n	0.2814	γ	0

DOI: 10.1002/oca

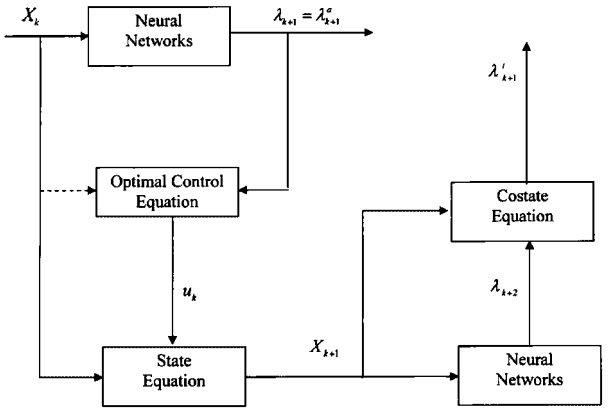

Figure 1. Schematic of optimal control synthesis using neural networks.

X_k^{inp} information, the steps of synthesizing the neural networks is as follows (Figure 1) [10]:

1. Generate S_i, as described in Section 3.2.1:
2. For each element X_k of S_i, follow the steps below,
   - Construct X_k^{inp},
   - Input X_k^{inp} to the networks to get λ_{k+1}: let us denote this actual output as λ^a_{k+1} as well,
   - Calculate u_k, knowing X_k and λ_{k+1}, from optimal control equation Equation (15),
   - Get X_{k+1} from the state equation (12 and 10, using X_k and u_k,
   - Construct X_{k+1}^{inp},
   - Input X_{k+1}^{inp} to the networks to get λ_{k+2},
   - Calculate the target λ_{k+1}, from the costate equation Equation (16). Let us denote this as λ^t_{k+1}.
3. Train the networks, with all X_k^{inp} as input and all corresponding λ^t_{k+1} as output.
4. Check for convergence, as described in Section 3.2.3.
5. If proper convergence is achieved, stop and revert to step 1, with $i = i+1$. If not, go to step 1 and retrain the networks.
6. Continue the process till $i = I$; i.e. until $c_i = c_I = 1$.

One can notice that for faster convergence, one can take the convex combinations $[\beta\lambda^t_{k+1} + (1-\beta)\lambda^a_{k,j+1}]$, $[\beta\lambda^t_{2k+1} + (1-\beta)\lambda^a_{2k,j+1}]$ as target outputs for training, where $0 < \beta < 1$ is the learning rate for the neural network training. Moreover, to minimize the chance of getting trapped in a local minimum, one can follow the philosophy of batch training, where a network is trained for all of the elements of S_i together [10]. For the blood glucose regulation problem under consideration, we have followed these ideas (selecting $\beta = 0.5$). One also notices that although S_i should ideally contain an 'infinite' number of X_k^{inp} vectors, a large yet finite number of random states is usually sufficient.

3.2.3. Convergence condition. Before changing c_i to c_{i+1} and generating new profiles for further training, it should be assured that proper convergence is arrived for c_i. This can be done in the following manner.

1. Fix c_i to the same values that have been used for the training of the networks. Generate a set S_i^c of profiles, exactly the same manner used to generate S_i. This set will be used to check or the convergence of the network.
2. Choose a tolerance value tol (we have selected $tol = 0.1$).
3. By using the profiles from S_c^c, generate the target outputs, as described in Section 3.2.1. Let the outputs be $\lambda_1^{t_i}$, $\lambda_2^{t_i}$, $\lambda_3^{t_i}$ and $\lambda_4^{t_i}$.
4. Generate the actual output from the networks by simulating the trained networks with the profiles from S_k^c. Let the outputs be $\lambda_1^{\alpha_i}$, $\lambda_2^{\alpha_i}$, $\lambda_3^{\alpha_i}$ and $\lambda_4^{\alpha_i}$.
5. Check whether $[\|\lambda_i^{t_i} - \lambda_i^{\alpha_i}\| / \|\lambda_i^{t_i}\|] < tol$, where $i = 1, 2, 3, 4$. If these conditions are satisfied simultaneously, we assume that the networks have converged.

Note that after successful training of the networks (i.e. after successfully meeting the convergence condition), one can directly calculate the associated optimal control u_k from Equation (15) for each X_k^{inp}.

3.2.4. Choice of neural network structure and initialization. Choosing a neural network structure is not a science yet; one mostly relies on experience and intuition. The choice of a network is a trade-off between

DOI: 10.1002/oca

accuracy and computational complexity. A relatively smaller network may not be adequate to capture the nonlinearity of the problem, whereas a larger choice of network may lead to a slower training and a greater probability of getting trapped in a local minimum. For this particular problem, we took four $\pi_{4,6,4,1}$ neural networks, one each for each of the costate variables in the training where the model parameters are assumed unchanged. Note that a $\pi_{4,6,4,1}$ neural network means four neurons in the input layer, six neurons in the first hidden layer, four neurons in the second hidden layer and one neuron in the output layer. Similarly, for random parameters and states four $\pi_{8,6,4,1}$ neural networks, one each for each of the costate variables, are considered.

For activation functions, we took *tangent sigmoid* functions for all the hidden layers and a *linear* function for the output layer. Simulation results indicate that this is an appropriate choice. For initializing the weights, we solved the problem with the well-known LQR optimal control theory [15], after linearizing the system dynamics, and trained the networks based on the associated relationship between state and costate variables. For more details on SNAC, one can refer to [9, 10].

4. NUMERICAL RESULTS

In this section, numerical results from extensive simulation studies are presented to evaluate the performance of the proposed nonlinear optimal drug delivery (continuous insulin injection) strategy. The simulation studies presented here can be broadly classified into three categories. First, studies are carried out with nominal model with fixed parameters (both for control design as well as simulations). Next, the concentration is on realistic models with randomly chosen parameters. This replicates a more realistic situation as different patients are supposed to have different physiological property and hence different parameters. However, this set of simulation studies is done with the assumption that the parameters are 'known' for individual patients (which can possibly come from a parameter identification scheme implemented in parallel). Finally, a robustness study is carried out by repeatedly applying the nominal controller to the realistic models with randomly chosen parameters. This situation is more realistic as it retains the advantage of eliminating the parameter identification requirement (hence making it easier practical realization), while simultaneously showing the robustness of the control design over a broad class of patient parameters. Comparison studies with LQR-based medication scheme is also carried out as part of the simulation studies that clearly brings out some important advantages of the proposed SNAC approach over the LQR approach.

4.1. Case-I: simulation studies with nominal model

For this set of simulation studies (including training of the neural networks), the parameter values considered are shown in Table II, which are taken from [5, 6]. For all simulation studies, the basal value of glucose (G_b) and insulin (I_b) concentrations in plasma are considered as 70 mg/dl and 7 μU/ml, respectively. For the neural network training purposes, the range of values for the state variables that are accounted for in the neural network training are shown in Table IV. The normalizing variables $[x_{1_n}, x_{2_n}, x_{3_n}, x_{4_n}]^{\mathrm{T}}$ are taken as $[150, 0.01, 100, 10]^{\mathrm{T}}$. Note that for training purposes the lower bound for some of the deviation states are taken as negative with the expectation of some overshooting during transient. However, these correspond to positive values of the actual physical state variable. The time interval Δt is chosen as 10 s, which is compatible with the sampling time of the available apparatus to monitor the blood glucose and inject the insulin [5]. The output weight Q is taken as $5 \times (x_{1_n})^2$ and the control weight is considered as $400 \times (x_{3_n})^2$. Q and R are chosen such so as not to change the values of Q and R with the change in nominal state values.

The parameters used here leads to an undesirable glucose trajectory for the untreated condition (i.e. without exogenous insulin supply) as seen in Figure 2. Hence, this is a case where the external medication is a necessity. Figure 2 also shows the glucose history for both linearized system and nonlinear system with LQR-based medication and proposed SNAC-based medication. Figure 3 shows the trajectory of plasma insulin concentration in the patient and Figure 4 shows the corresponding control input required. It is

DOI: 10.1002/oca

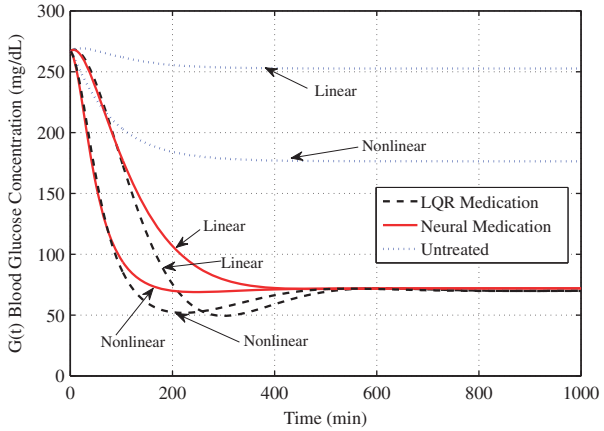

Figure 2. Trajectories of blood glucose concentration.

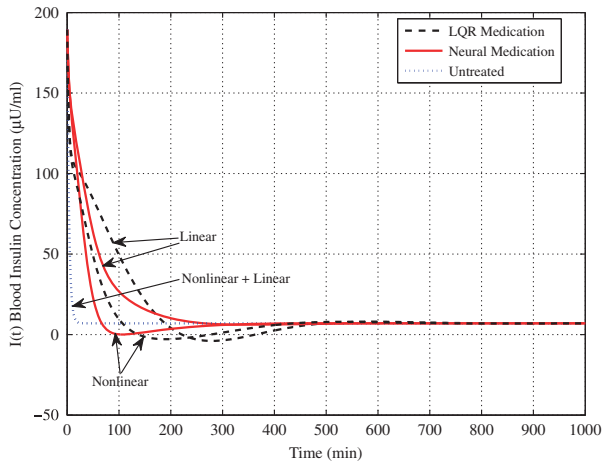

Figure 3. Trajectories of blood plasma insulin concentration.

evident form these figures that, as expected, the linearized system and the nonlinear system differ in their response and the SNAC-based medication performs better than LQR-based medication because of the following reasons:

- The LQR-based medication strategy leads to overshooting during transient. The overshooting is rather high (very close to the dangerous 50 mg/dl level) and may trigger hypoglycemia (a major concern for diabetic patients, which may lead to brain failure [5]). This dangerous trend is completely absent in the proposed SNAC-based medication.

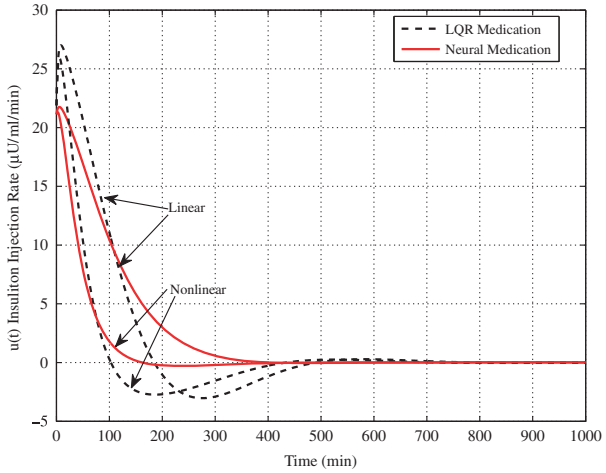

Figure 4. Required insulin injection rate for blood glucose regulation.

- From Figure 4 one can observe that the LQR control input demand goes to negative during transient. However, implementation of a negative control is difficult as it would rather mean a backup system through which glucagon can be injected to the blood plasma. However, such a requirement is not there in the SNAC-based medication. In fact, this trend is observed in all of our numerous simulation studies, including many randomly selected initial conditions and parameter perturbations, which will be clear from subsequent discussions in this section. We claim this as rather an important advantage as the requirement of an emergency negative control (i.e. glucagon injection) is completely avoided.
- The SNAC medication leads to a faster closed-loop response of the blood glucose trajectory towards its steady state value. One can see from Figure 2 that in SNAC medication, one can essentially stop the medication after about 200 minutes (approximately three hours) of its initiation as the control required after that is zero. This is however with

DOI: 10.1002/oca

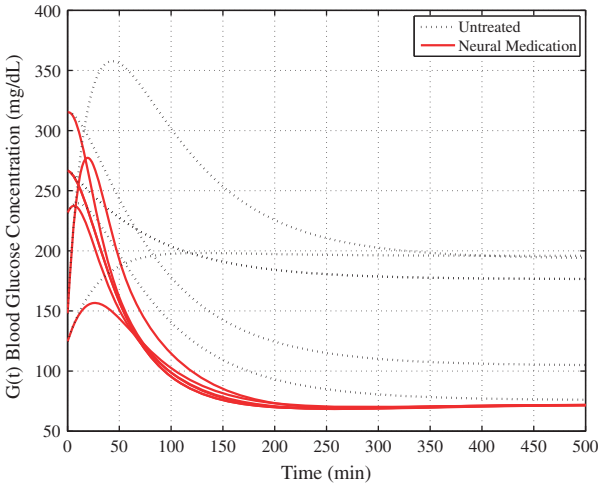

Figure 5. Blood glucose trajectories with random initial conditions.

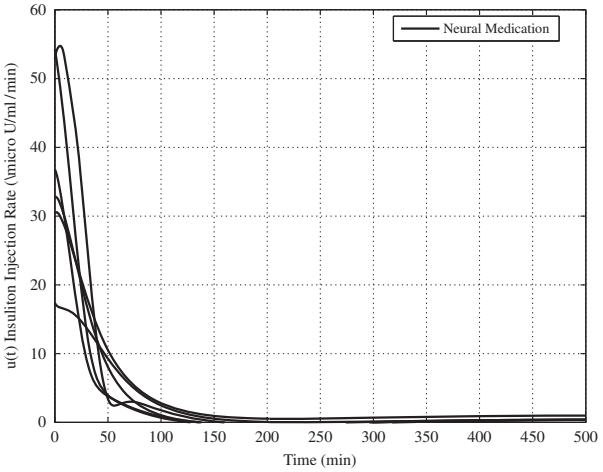

Figure 6. Rate of insulin injection for random initial conditions.

the assumption that there is no further disturbance input to the system (such as fresh food intake).

- The SNAC medication also brings down the blood glucose level of a initial high value to within the safe limit (which we assume to be below 110 mg/dl) within approximately one hour of initiation of medication, which is adequate.

The above observations clearly indicates that the SNAC approach is a much better alternative compared with the LQR approach. Next, to gain confidence on the results, a large number of simulation studies were carried out from different initial conditions. For clarity of pictures, however, we include only five such cases in Figures 5 and 6.

Blood glucose concentrations with random initial conditions are shown in Figure 5. Figure 5 shows the glucose trajectories for untreated patients and for patients with neural medication. As shown in Figure 5, neural medication never leads to overshooting of the closed-loop response and hence never leads to hypoglycemic conditions. It is to be observed that in all cases the blood glucose concentration is reduced to the basal value (70 mg/dl) within about 200 min (i.e. approximately three hours) of initiation of medication and to the safe limit (below 110 mg/dl) within approximately one hour. More important, the control requirement never becomes negative, thereby eliminating the additional requirement of emergency glucagon injection. In summary, all advantages pointed out above are maintained in all of our numerous simulation studies.

Figures 2–6 indicate that the proposed SNAC-based medication scheme leads to good (rather substantially improved) blood glucose management. However, these results are based only on the nominal model. Further simulation studies need to be carried out with realistic models (i.e. models with parameter variations) before gaining sufficient confidence of the robustness of the proposed approach, which is discussed next.

4.2. Case-II: simulation studies with realistic models with known parameters

In this exercise, the model parameters (p_2, p_3, n and B) are considered random from a range of values about their nominal values (as suggested in [5]), which are given in Table III. However, as mentioned before, these parameters are assumed to be 'known' and hence are accounted for in the control design.

For the neural network training purposes, we have assumed a range of values for the state variables (X_k) as given in Table IV. Numerical values of the normalizing variables are selected as the nominal values i.e.

DOI: 10.1002/oca

Table III. Range of parameter values for realistic model.

Parameter	Min value	Max value	Nominal value	Deviation (%)
p_2	$0.01/p_{2_n}$	$0.02/p_{2_n}$	0.015	± 33
p_3	$1\times10^{-6}/p_{3_n}$	$3\times10^{-6}/p_{3_n}$	2×10^{-6}	± 50
n	$0.12/n_n$	$0.30/n_n$	0.21	± 42
B	$0.01/B_n$	$0.10/B_n$	0.05	$+100, -80$

$[p_{2_n}, p_{3_n}, n_n, B_n]$: Nominal parameters.

Table IV. Range of values for state variables.

State	Value	State	Value
$x_{1\,\max}$	$220/x_{1_n}$	$x_{1\,\min}$	$-80/x_{1_n}$
$x_{2\,\max}$	$0.03/x_{2_n}$	$x_{2\,\min}$	$-0.001/x_{2_n}$
$x_{3\,\max}$	$200/x_{3_n}$	$x_{3\,\min}$	$-10/x_{3_n}$
$x_{4\,\max}$	$20/x_{4_n}$	$x_{4\,\min}$	$0/x_{4_n}$

$[p_{2_n}, p_{3_n}, n_n, B_n]^{\mathrm{T}}$. Basal value of glucose concentration in blood (G_b) is another parameter, which is assumed to be an input to the control computation. This is because the ideal basal glucose concentration varies from patient to patient (depending on other factors such as body weight, age, etc.) and is assumed to be determined by the physicians from a prescribed chart [5]. This gives a choice to the physician for better diabetes management for individual patients. In this paper, however, three basal values are selected as possible options to a physician without loss of generality. Accordingly, three separate set of networks are synthesized for different ideal basal values of blood glucose. The basal values considered here are 70 mg/dl, 80 mg/dl and 90 mg/dl, respectively. Basal value of blood plasma insulin concentration, however, is considered as 10 μU/ml for all cases.

Blood glucose concentration with random model parameters and $G_b = 70$ mg/dl are shown in Figure 7. The trajectories of blood glucose concentration without treatment and with neural treatment are shown together for better comparison. The controlled glucose trajectories are observed to reach the basal value and reach there in short time. The corresponding control inputs (rate of insulin injection) are shown in Figure 8. As evident from Figure 7, the insulin injections can be stopped after 200 min as all the control trajectories

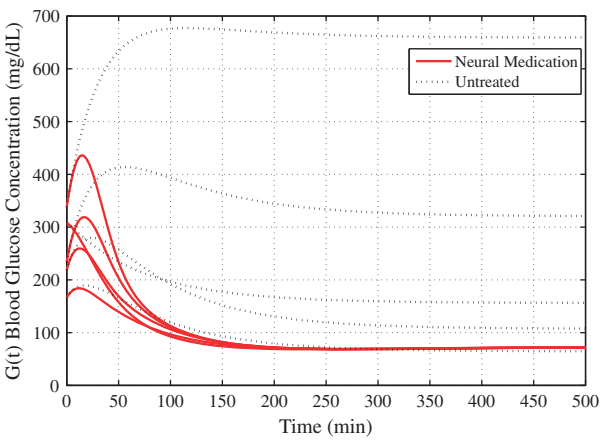

Figure 7. Blood glucose trajectories with random parameters, ($G_b = 70$) mg/dl.

are seen to reach zero within this time (in some cases, it can even be stopped in about 100 min). Note that in this set of simulation results, we have also made a comparison study with the LQR controller, as applied to the nonlinear system. The blood glucose response in one such representative case is shown in Figure 9, whereas the associated control (insulin injection) history is shown in Figure 10. It is evident from these plots that the LQR medication shows a

DOI: 10.1002/oca

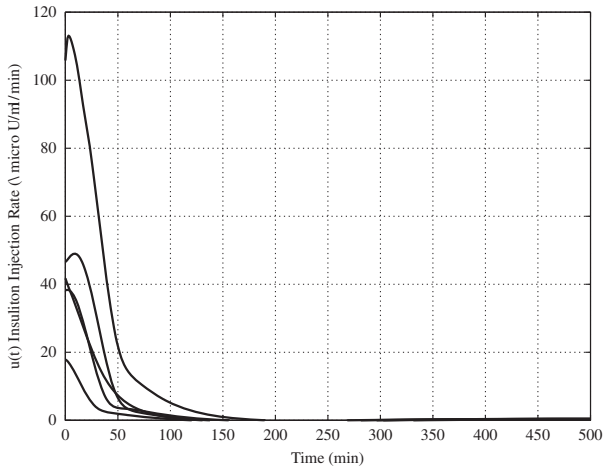

Figure 8. Rate of insulin injection for random parameters, ($G_b = 70$) mg/dl.

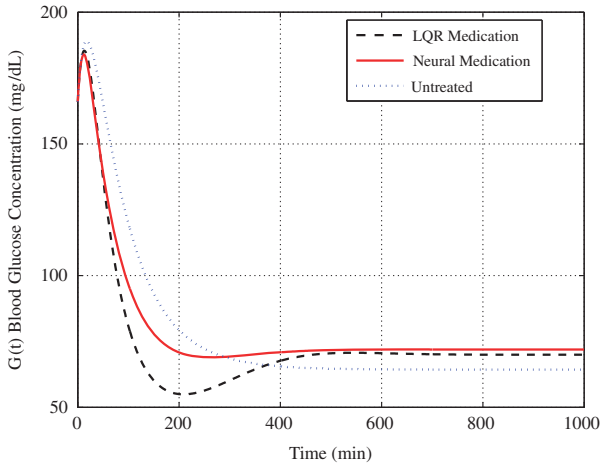

Figure 9. Glucose trajectories with random parameters, ($G_b = 70$) mg/dl.

drop down in blood glucose concentration near to 50 mg/dl, which has the potential danger of triggering the serious hypoglycemic condition. It should be noted that it appears better to give no treatment rather than to use LQR. Similar to what was observed before, this behavior is absent in neural medication in this case as well, thereby avoiding the necessity of having a glucagon infusion mechanism in addition to the insulin

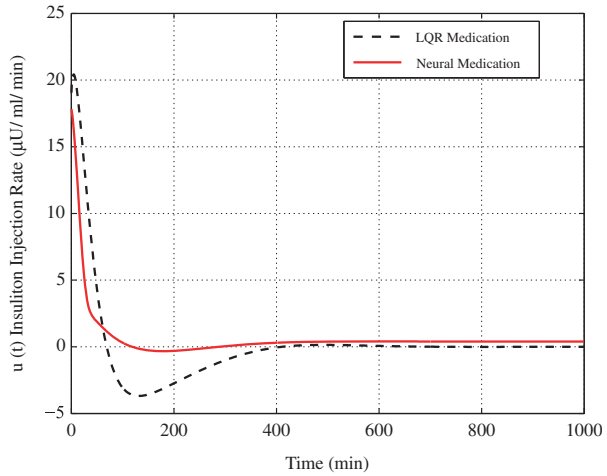

Figure 10. Rate of insulin injection for random parameters, ($G_b = 70$) mg/dl.

pump. In other words, the advantages of the proposed SNAC-based nonlinear design retains the advantages over the LQR design for a wide range of parameter values as well.

It should be noted that Figures 5 and 6 are generated with random initial conditions with basal glucose value (G_b) as 70 mg/dl, whereas, Figures 7 and 8 are generated with both random initial conditions and random parameters for $G_b = 70$ mg/dl. Figures 11 and 12 show the simulation results for the trained network with $G_b = 80$ mg/dl, with similar advantages.

4.3. Case-III: simulation studies with realistic models with unknown parameters

Even though the numerical results of Case-II are quite promising, such a strategy can be implemented in practice, only if the basic design proposed in this paper can be augmented with an online system (parameter) identification scheme. Hence, such a strategy is rather a bit unrealistic and complicated to realize in practice. A more realistic strategy is perhaps to have the controller design based on nominal parameters, whereas it can guarantee sufficient robustness for inaccuracies in the model parameters and retain its generality for a large number of patients (see Figure 13 for a conceptual diagram of the philosophy). The purpose of the

DOI: 10.1002/oca

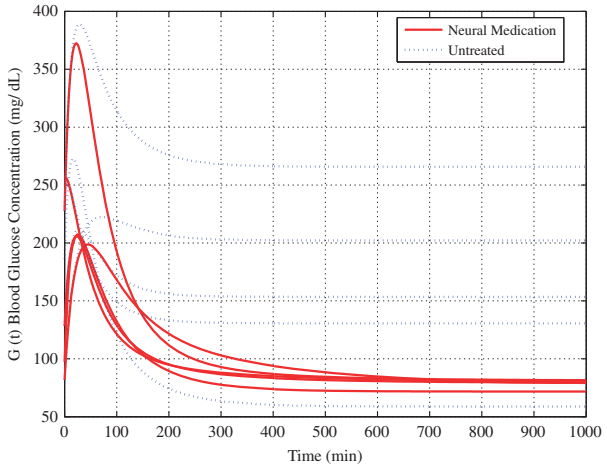

Figure 11. Blood glucose trajectories with random parameters, $(G_b = 80)$ mg/dl.

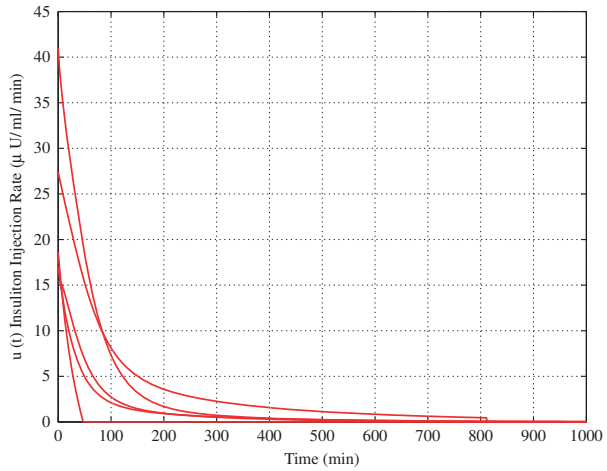

Figure 12. Rate of insulin injection for random parameters, $(G_b = 80)$ mg/dl.

following set of results is to investigate such robustness property of the proposed nominal controller.

Here simulations are run with random system parameters and random initial conditions, selected from the range of values as mentioned in Tables III and IV, respectively. The control design, however, is based on the nominal parameters, as mentioned in Table II. Note that the random patient parameters are unknown to the

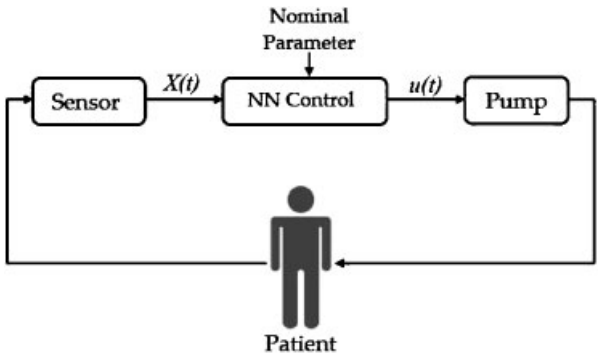

Figure 13. Schematic of diabetic control system with nominal parameters.

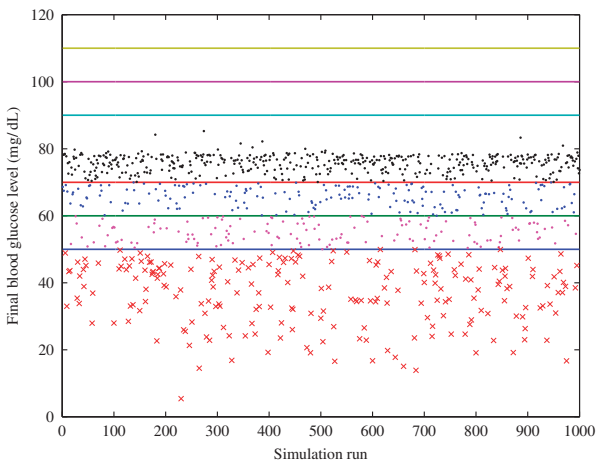

Figure 14. Simulation results with $G_b = 70$ mg/dl.

controller and therefore, this analysis shows robustness of the control design under parametric uncertainty. In this set of simulation results and associated analysis, depending on the achieved steady state values of the blood glucose, we propose to define different levels of success in the following manner: (i) failure (either > 110 mg/dl or < 50 mg/dl), (ii) marginally successful (between 100–110 and 50–60 mg/dl), (iii) fairly successful (between 90–100 and 60–70 mg/dl) and (iv) successful (between 70–90 mg/dl). Simulations are run for 1000 random parametric values and for different basal values of $G_b = 70$, 80, 90 mg/dl. Figures 14, 15 and 16 show the steady state blood glucose level

DOI: 10.1002/oca

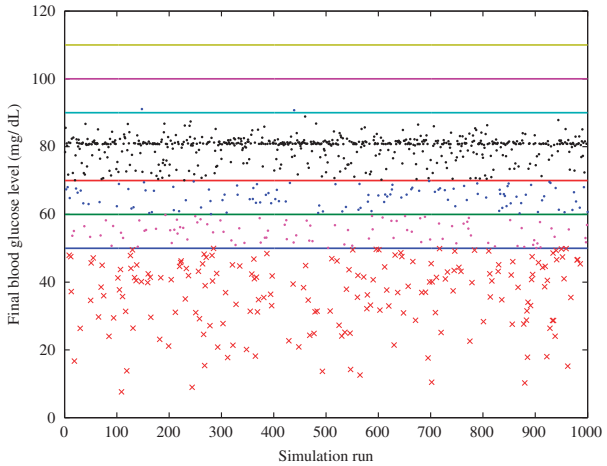

Figure 15. Simulation results with $G_b = 80\,\text{mg/dl}$.

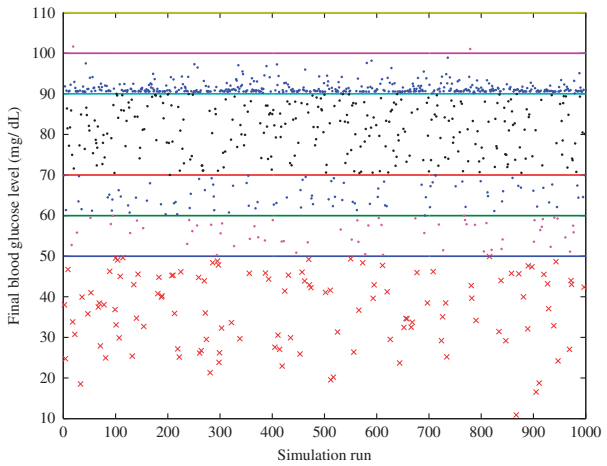

Figure 16. Simulation results with $G_b = 90\,\text{mg/dl}$.

after 1000 min of simulation run for $G_b = 70$, 80, 90 mg/dl, respectively. Note that 200 min is roughly the settling time of the closed-loop system. However, simulations are run for much longer time to ascertain that the actual steady state value is picked up in this analysis. Horizontal lines are drawn at glucose level of 100, 90, 70, 60 and 50 mg/dl to clearly show the number of cases falling between different segments. In Figures 14, 15 and 16, the dots signify the successful cases (patients do not get hypoglycemia) and the cross signifies the unsuccessful cases of robustness test (simulation results to hypoglycemic condition).

Table V shows the values of the respective number of cases falling in each group. For the case of $G_b = 80\,\text{mg/dl}$, simulation results show that out of 1000 simulations, 598 cases are successful with very good response and 115 more cases lead to fairly successful results. This means the nominal controller performs fairly good for 713 cases (i.e. it leads to 71.3% success). If one includes the additional 96 marginal cases as well within the definition of acceptable performance, the success rate rather goes to 809 cases (i.e. 80.9% success). Only about 191 (19.1%) failure runs are observed from the 1000 simulation runs. The results from other cases (i.e. $G_b = 70$, 90 mg/dl) are also fairly similar. Note that a lesser number of cases are observed to fall within the range 70–90 mg/dl for $G_b = 70$ and 90 mg/dl basal values because only one-sided spread is allowed in both the cases. If both side spread is allowed in the definition of successful cases, much more cases will fall within the proper range. From Table V it is evident that the proposed SNAC-based nominal control design has fairly adequate robustness for parameter inaccuracies of the model. In the strict definition of failure, i.e. for steady state values of blood glucose concentration of either $> 110\,\text{mg/dl}$ or $< 50\,\text{mg/dl}$, only the maximum percentage of failure cases observed was only 22.3 %.

5. CONCLUSIONS

An intelligent online feedback insulin infusion strategy is presented in this paper for the control of blood glucose levels in diabetic patients using single network adaptive critic neural networks with the intension of replicating the function of pancreatic insulin, i.e. to have a fairly continuous measurement and situation-dependent insulin injection to the body using an external device. Detail studies are carried out to analyze the effectiveness of this adaptive critic-based feedback medication strategy. The efficiency and the robustness of the proposed nonlinear controller is shown taking random initial conditions and random parameters. A comparison study with LQR theory shows that the proposed nonlinear medication strategy

DOI: 10.1002/oca

Table V. Results of simulation for robustness study (out of 1000 simulations).

Basal value	Ranges of blood glucose concentration			
G_b	70–90 mg/dl	60–100 mg/dl	50–110 mg/dl	>110 and <50 mg/dl
70	447	634	777	223
80	598	713	809	191
90	280	817	879	121

offers the following potential advantages: (i) it never leads to the hypoglycemia problem, thereby avoiding the severe consequences associated with it, (ii) the necessity of a negative control (glucagon infusion) is eliminated and (iii) it is capable of bringing down the blood glucose level to safe level quickly (within an hour's time of initiation of insulin injection). The sampling time chosen is compatible with the available apparatus. Moreover, as the computational demand in using the trained neural networks is typically very minimal, the necessary computations can very well be carried out online (this is a major advantage of the adaptive critic approach in general). Because of these important advantages, the proposed nonlinear optimal control theoretic approach is a potential option for implementation in the continuous insulin infusion apparatus for continuous regulation of blood glucose in diabetic patients, leading to potential benefits in the long run. Possible topics of further research would include: (i) state estimation from output information (as measurement of all state variables is typically not feasible), (ii) parallel system (parameter) identification, thereby making the drug dosage specific to the patients (i.e. fully tailor made drug dosage) and (iii) experimental clinical trial and subsequent development of the hardware (insulin pump) implementing this logic.

REFERENCES

1. Grodins F. *Control Theory and Biological Systems*. Columbia University Press: Columbia, 1963.
2. Wellstead P, Bullinger E, Kalamatianos D, Mason O, Verwoerd M. The role of control and system theory in systems biology. *Annual Reviews in Control* 2008; **32**:33–47.
3. Rother K. Diabetes treatment—bridging the divide. *New England Journal of Medicine* 2007; **365**(15):1499–1501.
4. WHO. Definition, diagnosis and classification of diabetes mellitus and its complications. *World Health Organisation Department of Noncommunicable Disease Surveillance* 1999; Available from: http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf.
5. Chee F, Fernando T. *Closed Loop Control of Blood Glucose*. Springer: Berlin, 2007.
6. Chee F, Fernando T, Savkin A, Heeden V. Expert PID control system for blood glucose control in critically ill patients. *IEEE Transactions on Information Technology in Biomedicine* 2003; **7**:419–425.
7. Fisher M. A semi closed-loop algorithm for the control of blood glucose levels in diabetics. *IEEE Transactions on Biomedical Engineering* 1991; **38**:57–61.
8. Jaremco J, Rorstad O. Advances toward the implantable artificial pancreas for treatment of diabetes. *Diabetes Care* 1998; **21**:444–450.
9. Padhi R, Balakrishnan SN. Development and analysis of a feedback treatment strategy for perturient paresis of cows. *IEEE Transactions on Control Systems Technology* 2004; **12**(1):52–64.
10. Padhi R, Unnikrishnan N, Wang X, Balakrishnan S. A single network adaptive critic (snac) architecture for optimal control synthesis for a class of nonlinear systems. *Neural Networks* 2006; **19**:1648–1660.
11. Parker R, Doyle F, Peppas N. A model-based algorithm for blood glucose control in type I diabetic patients. *IEEE Transactions on Biomedical Engineering* 1999; **46**:148–157.
12. Lynch S, Bequette BW. Model predictive control of blood glucose in type I diabetes using subcutaneous glucose measurements. *Proceedings of American Control Conference*, Anchorage, U.S.A., 2002; 4039–4040.
13. Kaveh P, Shtessel Y. Blood glucose regulation using higher order sliding mode control. *International Journal of Robust and Nonlinear Control* 2008; **18**:557–569.
14. Kaveh P, Shtessel Y. Blood glucose regulation via double loop higher order sliding mode control and multiple sampling rate. In *Modern Sliding Mode Control Theory*, Bartolini G (ed.). Lecture Notes in Computer Information Sciences. Springer: Berlin, 2008; 427–445.
15. Bryson A, Ho Y. *Applied Optimal Control*. Taylor & Francis: London, 1975.
16. Werbos P. Approximate dynamic programming for real-time control and neural modeling. *Handbook of Intelligent Control*,

White D, Sofge D (eds). Van Nostrand Reinhold: New York, 1992.
17. Bergman R, Philips L, Cobelli C. Physiological evaluation of factors controlling glucose tolerance in man. *Journal of Clinical Investigation* 1981; **68**: 1456–1467.
18. Fuler S, Kraegen E, Smallwood R, Chisolm D. Blood glucose control by intermittent loop closure in basal mode: computer simulation studies with a diabetic model. *Diabetes Care* 1985; **8**:553–561.
19. Carnahan B, Luther H, Wilkes J. *Applied Numerical Methods*. Wiley: New York, 1969.

DOI: 10.1002/oca