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Radhakant Padhi

S. N. Balakrishnan
Missouri University of Science and Technology, bala@mst.edu

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Development and Analysis of a Feedback Treatment Strategy for Parturient Paresis of Cows

Radhakant Padhi and S. N. Balakrishnan

***Abstract*—An intelligent on-line feedback treatment strategy based on nonlinear optimal control theory is presented for the parturient paresis of cows. A limitation in the development of an existing nonlinear mathematical model for the homogeneous system is addressed and further modified to incorporate a control input. A neural network based optimal feedback controller is synthesized for the treatment of the disease. Detailed studies are used to analyze the effectiveness of a feedback medication strategy and it is compared with the current 'impulse' strategy. The results show that while the current practice may fail in some cases, especially if it is carried out before the condition of a patient deteriorates, the proposed continuous medication process may be initiated at any time. Moreover the proposed on-line continuous infusion strategy never leads to severe hypercalcemic problems, thereby avoiding an associated disastrous consequence of cardiac arrest. A comparison study with linear quadratic regulator theory brings out the advantages of the nonlinear control synthesis approach.**

***Index Terms*—Biomedical system, calcium homeostatis, neural networks, optimal control, parturient paresis.**

I. Introduction

THE idea of using mathematical control theory to solve problems in biological sciences is relatively old [7]. However, in recent years, activities based on this idea is growing fast. This is primarily due to development of more mathematical models for various biological systems [5], [14]. 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 [10] and the references therein.

In this paper we address a control problem associated with the treatment strategy of parturient paresis of cows, which is related to the Calcium (Ca) dynamics of the animal. Ca has various crucial physiological roles in animals. Besides maintaining the integrity of the bone structure, intracellular Ca ions are involved in the activity of a large number of enzymes. They are also involved in conveying information from the surface to the interior of the cell. Extracellular Ca ions are necessary for neuromuscular excitability, blood clotting and hormonal secretions etc. We cite [6] for an interested reader. A systematic mathematical model for the calcium homeostatis problem of cows was first developed by Ramberg *et al.* [18]. The one-dimensional (1-D) model has recently been modified to a two-dimensional (2-D) model, with appropriate justifications, by El-Samad *et al.* [3], [4]. This model clearly explains the Ca homeostatis phenomenon in healthy cows. Besides, it also attempts to explain a disease with the onset of parturition (calving), commonly known as parturition paresis (milk fever), experienced by some animals. This disease is caused by hypocalcemia which occurs when the complex internal control mechanism in cattle for maintaining calcium homeostatis fails due to a sudden and severe outflow of calcium. As pointed out in [16], parturient paresis is one of the most common metabolic diseases of the dairy cattle, with about 6% of the dairy cattle in USA being affected annually.

From a system theoretic point of view, the parturient paresis problem of dairy cows can be thought of as follows Fig. 1: prior to onset of parturition, the internal Ca homeostatis mechanism operates at a stable equilibrium point. However, after the parturition, due to the outflow of Ca the equilibrium point shifts to a new value. With respect to this new equilibrium point, the earlier one can be thought of as an initial condition. Depending on the system parameters, the dynamics may drive the system from this initial condition toward the *domain of attraction* [19] of new equilibrium point and is eventually driven to the new equilibrium point (which happens for a 'healthy' animal). In some cases, however, the dynamics may drive the system away from this domain of attraction of the new equilibrium point and in that case the Ca dynamics goes unstable and the animal suffers from the parturient paresis disease. As pointed out in [16], a common treatment strategy for the cows with milk fever is the intravenous infusion of Ca salt. However, as the authors have pointed out, it should always be administered "slowly" to prevent sudden cardiac arrest due to hypercalcemia.

The major objectives of this paper are twofold: to develop a system theoretic model of calcium homeostatis to accommodate feedback control and, more important, to devise an optimal on-line feedback control (medication) strategy based on nonlinear optimal control theory. Many difficult real-life control problems can be formulated within the framework of optimal control. It is well known that the dynamic programming formulation offers the most comprehensive solution approach to nonlinear optimal control in a state feedback form [2], 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. There is a technique in the current literature which yields optimal feedback control for nonlinear systems. An innovative idea was proposed in [20] to get around the computational complexity of the dynamic programming formulation by using Ap-

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The authors are with the Department of Mechanical and Aerospace Engineering and Engineering Mechanics, University of Missouri—Rolla, MO 65409 USA (e-mail: padhi@umr.edu; bala@umr.edu).

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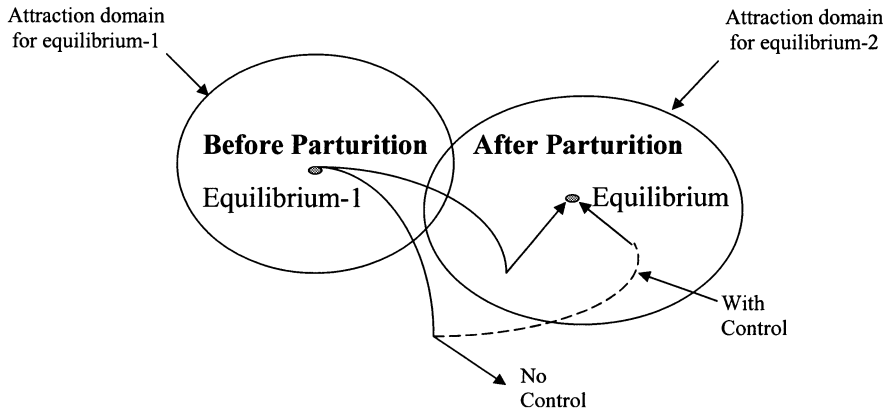

Fig. 1. System theoretic view of parturient paresis.

proximate 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 adaptive critic approach, called the Dual Heuristic Programming (DHP), one network (called the action network) captures the mapping between the state and control variables while 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, since the control computation requires a few multiplications of the network weights (which are trained off-line). Among many successful use of this method for nonlinear control design found in the literature, we cite [1] in which the authors solved an aircraft control problem using this technique. Proofs for both convergence of networks at each step of the training process as well as the fact that the process will eventually lead to the optimal control is found in [12] for linear systems. A related but separate development toward the stability and global convergence proofs is found in [15] for input-affine nonlinear systems (the nonlinear system discussed in this paper is input-affine). Note that a significant improvement to the adaptive critic technique is proposed in this paper (see Section III) by eliminating one of the two networks in the structure.

The medication strategy presented in this paper assures that the initial condition (earlier equilibrium point) of almost all the sick animals are safely driven toward a new safe equilibrium point. The intravenous Ca treatment is treated as an on-line process with the rate of infusion being the control variable. Detailed studies are used to show the effectiveness of a feedback strategy and compared with an 'impulse' strategy which is currently carried out by manually injecting Ca salt to the blood pool of a sick animal (by a veterinary surgeon). A comparison study was carried out with the standard linear quadratic regulator theory [2], [11], which clearly brought out the advantage of the proposed nonlinear control synthesis approach.

Rest of the paper is organized as follows: Section II deals with the mathematical modeling aspects of the problem. We point out a limitation of the mathematical model developed in [3], [4] and modify the model to address that and expand the basic homogeneous model to accommodate control inputs. In Section III we discuss the necessary conditions of optimality from a discrete dynamic programming perspective. We describe the main idea of a neural network based controller synthesis procedure in this section. We outline our proposed on-line medication strategy for parturient paresis in detail in Section IV. In Section V, we discuss the numerical results and outline some of the relevant comments and derive some conclusions in Section VI.

II. Calcium Homeostatis in Cows: Mathematical Models

A. Existing Model

A systematic dynamic model for the Ca homeostatis problem was first developed by Rabmerg *et al.* [18]. The model has recently been modified to the following 2-D model, by El-Samad *et al.* [3], [4]

$$\begin{aligned}\dot{z}_1 &= \frac{1}{Vol}\left[Sat_1\left\{K_p(r-z_1)\right\} + f(z_1)Sat_2\left\{z_2\right\} - V_{cl}\right]\\ \dot{z}_2 &= K_1(r-z_1)\end{aligned} \tag{1}$$

where z_1 is Ca concentration (gm/L) in the blood plasma; z_2 is the rate (gm/d) (where d stands for day) at which Ca is supplied to blood plasma from intestine $\dot{z}_1$; $\dot{z}_2$ is the rate of change of z_1 and z_2, respectively, with respect to time (t); Vol is the total plasma volume (L); V_{cl} is the total Ca clearance from the plasma (gm/L); r is the set point, for Ca concentration regulation (gm/L); K_p is the constant, for the internal proportional block (L/d); K_I is the constant, for the internal integral block (L/d ^{2}); $Sat_1(\cdot)$, $Sat_2(\cdot)$ are the saturation values; $f(z_1) = \{1/12\,[(\alpha_1+\alpha_2 z_1)(\alpha_3+\alpha_4 z_1)], z_1 < r \text{ and } 1, z_1 \geq r\}$ is a multiplicative reduction factor, reflecting the effect of plasma Ca concentration on rate of Ca supply from intestine, where α_1, α_2, α_3, α_4 are constants. For more details on the model and its validity, refer to [3], [4].

B. Refinement to the Model

In [3], [4], the authors have relied on the model given by (1) to explain the parturient paresis problem in dairy cows. One can notice that the model consists of *saturation nonlinearity* functions which fall under the class of *hard nonlinearities* (having discontinuities in derivatives). However, biological systems seldom exhibit this behavior. At worst, they can have *strong nonlinearities* (consisting of higher order terms in a power series expansion). Thus, the nonlinear model for the

problem should ensure gradual saturation, rather than a sudden saturation. To incorporate this effect, the *hard-nonlinear* saturation functions should be replaced by some *gradually* saturating functions. Besides, the modified model should have the same saturation values as (1) and moreover, near the equilibrium point, it should closely represent the original linear model as predicted by (1). To account for the above factors, we propose to change the hard-nonlinear saturation functions to *hyperbolic tangent* function, and rewrite the system dynamics as:

$$\begin{aligned}\dot{z}_1 &= \frac{1}{Vol}\left[A_1 \tanh\left\{\frac{K_p(r-z_1)}{A_1}\right\} + f(x_1)A_2 \tanh\left\{\frac{z_2}{A_2}\right\} - V_{cl}\right] \\ \dot{z} &= K_I(r-z_1) \end{aligned} \tag{2}$$

where $A_1 = Sat_1$, $A_2 = Sat_2$. We consider A_1, A_2, K_p, K_I as system parameters. At this point, we point out that in (1) the equilibrium point is given by $[\,z_1^0 \quad z_2^o\,]^T = [\,r \quad V_{cl}\,]^T$ whereas in (2), the equilibrium point is given by

$$\begin{bmatrix} z_1^0 \\ z_2^0 \end{bmatrix} = \begin{bmatrix} r \\ A_2 \tanh^{-1}\left(\frac{V_{cl}}{A_2}\right) \end{bmatrix}. \tag{3}$$

Note that in our modified model, the final equilibrium point (after parturition) is *parameter dependent*. Intuitively this makes more sense, since different animals are supposed to settle at different equilibrium points.

C. Model in Terms of Deviated State Values From Equilibrium

Our main aim is to regulate the system about its equilibrium point. For convenience, we rewrite the system dynamics in deviation terms by defining

$$\begin{bmatrix} z_1 \\ z_2 \end{bmatrix} = \begin{bmatrix} z_1^0 \\ z_2^0 \end{bmatrix} + \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} \tag{4}$$

where x_1, x_2 are the deviations of z_1 and z_2, respectively, from their equilibrium values. The equations in terms of x_1 and x_2 can be written as

$$\begin{aligned}\dot{x}_1 &= F_1(X) \\ \dot{x}_2 &= F_2(X) \end{aligned} \tag{5}$$

where $X = [\,x_1 \quad x_2\,]^T$ and $F_1(X)$, $F_2(X)$ are given by

$$\begin{aligned} F_1(X) &= \frac{1}{Vol}\left[A_1 \tanh\left\{\frac{-K_p x_1}{A_1}\right\} + f(z_1^0 + x_1)A_2 \tanh\left\{\frac{z_2^0 + x_2}{A_2}\right\} - V_{cl}\right] \\ F_2(X) &= -K_1 x_1. \end{aligned} \tag{6}$$

Note that the phase plots (not included in this paper) of the new model closely followed that of [3], [4].

D. Model With External Control

The models discussed in (1) and (2) do not contain the effects of external inputs (control). Our main objective is to develop an on-line medication strategy for the sick animals affected with parturient paresis, so we need to develop a mathematical model that includes a control term. Toward this goal, we observe that we are primarily interested in a medication strategy with intravenous Ca infusion (assumed as the control variable) which is infused directly to the blood plasma. Due to direct infusion, the *rate of change* of Ca $(\dot{x}_1)$ in the blood plasma is assumed to be changed *instantaneously*. However, the externally infused Ca is assumed to reflect in the blood plasma with efficiency η; the body rejects the rest. A block diagram for the system reflecting these points is given in Fig. 2. Combining (5) and (6), we arrive at

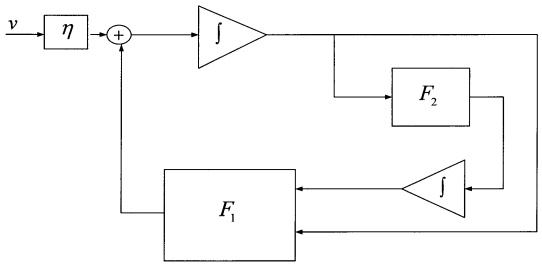

Fig. 2. Block diagram representation of Ca regulation.

$$\begin{aligned}\dot{x}_1 &= \frac{1}{Vol}\left[A_1 \tanh\left\{\frac{-K_p x_1}{A_1}\right\} + f(z_1^0 + x_1)A_2 \tanh\left\{\frac{z_2^0 + x_2}{A_2}\right\} - V_{cl}\right] + \eta\nu \\ \dot{x}_2 &= -K_1 x_1 \end{aligned} \tag{7}$$

where η is the efficiency of external control and ν is the external control.

E. Model With Normalized Variables

For better training of neural networks (Section III-B), we normalize the neural network inputs. For this reason, we define the new variables $\tilde{x}_1 \equiv x_1/x_{1nom}$, $\tilde{x}_2 \equiv x_2/x_{2nom}$, where $x_{1_{nom}}$ and $x_{2_{nom}}$ are the *nominal values* of x_1 and x_2, respectively, (chosen appropriately so that the values of $\tilde{x}_1$, $\tilde{x}_2$ becomes roughly of same order). After writing the system dynamic equation in terms of $\tilde{x}_1$ and $\tilde{x}_2$, for convenience we redefine $[\,x_1 \quad x_2\,]^T \equiv [\,\tilde{x}_1 \quad \tilde{x}_2\,]^T$ and arrive at the following equations

$$\begin{aligned}\dot{x}_1 &= \frac{1}{\text{Vol}\, x_{1nom}}\left[g_1(x_1) + \tilde{f}(x_1)\, g_2(x_2) - V_{cl}\right] + \eta u \\ \dot{x}_2 &= -K_I\left(\frac{x_{1nom}}{x_{2nom}}\right) x_1 \end{aligned} \tag{8}$$

where

$$\begin{aligned} u &\equiv \frac{v}{x_{1nom}}, \quad \tilde{f}(x_1) \equiv f(z_1^0 + x_1 x_{1nom}) \\ g_1(x_1) &\equiv A_1 \tanh\left\{\frac{(-K_p x_1 x_{1nom})}{A_1}\right\} \\ g_2(x_2) &\equiv A_2 \tanh\left\{\frac{(z_2^0 + x_2 x_{2nom})}{A_2}\right\}. \end{aligned} \tag{9}$$

Note that the equilibrium point of the homogeneous system dynamics in (8) and (9) now corresponds to the *origin* (for nor-

malized and deviated states) and the control term $\nu = ux_{1nom}$ represents the *rate of infusion* of Ca per unit volume of blood plasma. Accordingly, the actual rate of Ca infusion u_a (gm/d) and the amount of Ca infused to the blood plasma m_a (gm) by time $t > t_0$ are given by

$$\begin{aligned} u_a &= Vol \cdot u \cdot x_{1nom} \\ m_a &= \int_{t_0}^{t} u_a dt. \end{aligned} \tag{10}$$

III. Optimality Conditions and Neural Network Synthesis

A. Optimality Conditions for Calcium Regulation Problem

For use with neural networks, the Ca regulation medication dynamics is first discretized as

$$X_{k+1} = X_k + \Delta t F^k(X_k, u_k) \tag{11}$$

where Δt is the step size in time, $X = \begin{bmatrix} x_1 & x_2 \end{bmatrix}^T$ is the state vector and F^k is given by

$$F^k(X_k, u_k) = \begin{bmatrix} \frac{1}{Vol x_{1nom}} \left[g_1(x_{1k}) + \tilde{f}(x_{1k}) g_2(x_{2k}) - V_{cl} \right] + \eta u_k \\ -K_1 (\frac{x_{1nom}}{x_{2nom}}) x_{1k} \end{bmatrix}. \tag{12}$$

It is clear that the medication problem falls under the class of *regulator problems*, the regulation being carried out about the *origin*. We assume a discrete cost function of the form

$$J = \frac{1}{2} \sum_{k=1}^{(N \to \infty)} \left[X_k^T (Q \Delta t) X_k + u_k^T (R \Delta t) u_k \right] \tag{13}$$

where $Q \geq 0$, $R > 0$ 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 Ca 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 [2], [11], the equations for optimal control and costate dynamics are given by

$$u_k = -R^{-1} \begin{bmatrix} \eta & 0 \end{bmatrix} \lambda_{k+1} \tag{14}$$

$$\lambda_k = \lambda_{k+1} + \Delta t \left[Q X_k + \left(\frac{\partial F^k}{\partial X_k} \right)^T \lambda_{k+1} \right] \tag{15}$$

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

At each time step k the coupled equations (12), (14) and (15) 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 [8].

B. Procedure for Neural Network Synthesis

In this section, a neural network based optimal control synthesis is presented. The schematic of the controller synthesis procedure is shown in Fig. 1. We propose a neural network structure that solve the optimal control problem contained in (11) and (12), (14) and (15), while satisfying the boundary conditions as well. The controller is essentially obtained through what we call as a set of "critic networks". This is to retain the terminology of the *adaptive-critic* methodology [1], [8], [17], [20]. Note that, as pointed out earlier in Section I, the need for a second network has been eliminated.

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 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 nonzero probability*, the controlled states with different magnitudes, including the ones *close to zero*. For this reason, we follow a telescopic procedure outlined here.

Define, for $i = 1, 2, 3, \ldots$, $S_i = \{\text{all } X_k : \|X_k\|_\infty \leq c_i\}$, where c_i is a positive constant. Notice that for $c_1 \leq c_2 \leq c_3 \leq \cdots$, $S_1 \subseteq S_2 \subseteq S_3 \subseteq \cdots$. 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 $c_i = c_I = 1$.

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 two neural networks (separate networks for each element of the vector λ_{k+1}). We have assumed that the parameters of the problem (K_p, K_I, A_1, A_2) are not fixed and they can vary, within known minimum and maximum values. Thus, $K_p \in [K_{p\min}, K_{p\max}]$, $K_I \in [K_{I\min}, K_{I\max}]$, $A_1 \in [A_{1_{\min}}, A_{1_{\max}}]$ and $A_2 \in [A_{2_{\min}}, A_{2_{\max}}]$. However, we have assumed that the parameters remain constant for any particular animal and, hence, for a typical state trajectory. Thus, to capture the relationship between X_k and λ_{k+1}, we construct an augmented vector $X_k^{inp} = \begin{bmatrix} X_k^T & \vdots & P^T \end{bmatrix}^T$ (P is the vector containing parameters), which serves as the input to the neural networks. However, since the individual elements of X_k^{inp} vary widely in magnitude, we construct a

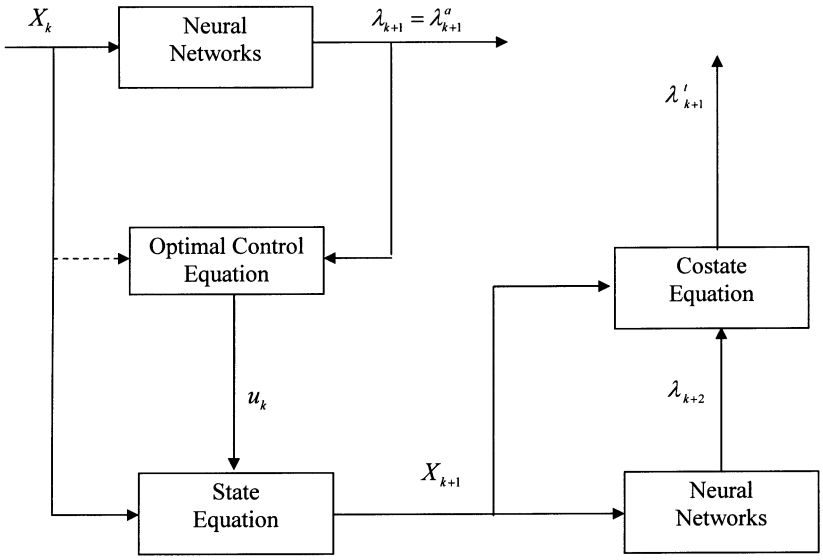

Fig. 3. Schematic of optimal control synthesis using neural networks.

normalized vector to serve as the input. Thus we have $X_k^{inp} = [x_{1k}\ x_{2k}\ K_p/K_{1nom}\ K_I/K_{Inom}\ A_1/A_{1nom}\ A_2/A_{2nom}]^T$ where $K_{p_{nom}}$, $K_{I_{nom}}$, $A_{1_{nom}}$ and $A_{2_{nom}}$ are the normalizing values for K_p, K_I, A_1 and A_2, respectively. Note that after successful training of the networks, we can directly calculate the associated optimal control u_k from (14) for each X_k^{inp}. We synthesize the neural networks in the following manner (Fig. 3)

1) Generate S_i, as described in Section III-B.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* (14).
   - Get X_{k+1} from the *state equation* (11) and (12), 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* (15). 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 III-B.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 $[\beta\lambda^t_{k+1} + (1-\beta)\lambda^a_{k\cdot j+1}]$, $[\beta \in \lambda^t_{2k+1} + (1-\beta)\lambda^a_{2k,j+1}]$ 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. One also notices that although S_i should ideally contain an infinite number of profiles, we generate S_i with a finite, yet large number of random states. For the biomedical problem under consideration, we have followed these ideas (selecting $\beta = 0.5$).

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_i^c, generate the target outputs, as described in Section III-B.1. Let the outputs be $\lambda_1^{t_i}$, $\lambda_2^{t_i}$
4) Generate the actual output from the networks, by simulating the *trained* networks with the profiles from S_k^c. Let the outputs be $\lambda_1^{\alpha_i}$, $\lambda_2^{\alpha_i}$.
5) Check whether $(\|\lambda_1^{t_i} - \lambda_1^{a_i}\|_2/\|\lambda_1^{t_i}\|_2) < tol$ and $(\|\lambda_2^{t_i} - \lambda_2^{a_i}\|_2/\|\lambda_2^{t_i}\|_2) < tol$. If these conditions are satisfied simultaneously, we assume that the networks have converged.

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 smaller network may not be adequate to capture the nonlinearity of the problem whereas a larger network choice may lead to a slower training and a greater probability of getting trapped in a local minimum. For this particular problem, we took two $\pi_{6,6,4,1}$ neural networks, one each for each of the costates. Note that a $\pi_{6,6,4,1}$ neural network means six neurons in the input layer, six neurons in the first hidden layer, 4 neurons in the second hidden layer and 1 neuron in the output layer. For activation functions, we took *tangent sigmoid* function for all the hidden layers and *linear* function for the output layer. Simulation results indicate that this was an appropriate choice. For initializing the weights, we solved the problem with the well-known linear quadratic regulator optimal control theory [2], [11], after linearizing the system dynamics, and trained the

networks based on the associated relationship between state and costate variables.

IV. Medication Strategy for Parturient Paresis

As pointed out by Oetzel *et al.* [16], the milk fever can be categorized as stage I, II, or III, depending on the Ca concentration in blood. Stage I milk fever has blood Ca concentration in the range of 0.055–0.075 gm/L, stage-II in the range of 0.035–0.065 gm/L and stage III can have as low as 0.01 gm/L. Stage I milk fever, considered to be a milder disease, is treated either with oral Ca supplement or intravenous Ca salt infusion. Cattle in stage II or III require immediate treatment with intravenous Ca salt. In [16] it is also pointed out that the intravenous Ca should always be administered "slowly" to prevent sudden cardiac arrest due to hypercalcemia. Another fact pointed out by the authors is that 75% of all cases of the milk fever occur within 24 h of calving, with additional 12% occurring within 24 to 48 h.

One may notice that our proposed medication procedure assumes the rate of intravenous Ca infusion as a continuous process. The parameters for a typical animal are assumed to be known and both states are assumed to be measurable. Before we describe the details of our proposed medication strategy, we observe the following: if the Ca concentration in the blood pool is 0.05 gm/L or higher, the milk-fever problem falls under stage I and is not considered serious. Since the value at the new equilibrium point is 0.08 gm/L, this essentially translates to (a deviation from equilibrium) $x_1 x_{1nom} \geq -0.03$. When $x_1 x_{1nom} \leq -0.03$, the animal runs into the danger of stage II-III milk fever and hence, our goal should be to assure that the deviation of the Ca concentration level (from the new equilibrium point) never drops below -0.03 gm/L after stopping the medication. Moreover since most of the milk fever cases have been observed to occur within a day or two of the parturition, medication is important at this early period after calving. Based on the above observations, we propose the following medication strategy.

1) Monitor the condition of an animal after parturition, showing the sign of milk fever; i.e., keep measuring the Ca concentration in the blood pool. Note that the parameters for a typical animal are supposed to be known and assumed to remain fixed.
2) If $x_1 x_{1nom}$ value drops below a specified level, say -0.03, bring the sick animal under the medication scheme.
3) The medication is carried out for a fixed amount of time, say for 1 h. During that period, the following steps are carried out.
   - At any time step k, the control magnitude u_k is computed on-line, using the neural networks as synthesized in Section III.
   - If the computed control $u_k < 0$, we forcefully make $u_k = 0$, since a negative infusion rate is impossible to implement. However, $u_k < 0$ essentially indicates that the blood pool already contains more Ca than necessary and, hence, there is no requirement of additional intravenous infusion. For this reason, forcefully making $u_k = 0$ will not lead to any catastrophic consequence.
   - The Ca infusion process is continued at a rate u_k until the next time step $k+1$.
4) At the completion of Step 3, the condition of the patient animal is projected for some specified future time, say for a week (which is normally required for an animal to restore the Ca regulation internally [3], [4]). This is done using the homogeneous part of system dynamics.
5) If the projected states show $x_1 \to 0$ and $x_2 \to 0$ (i.e., the patient recovers without further medication) *and* x_1 trajectory never enters the region $x_1 x_{1nom} < -0.03$, STOP medication. Otherwise, go to Step 3 and continue medication for another fixed amount of time (in this case, 1 h).

One should note that this paper does not deal with any new drug development. It simply attempts to make use of the advanced control theory concepts to optimally use an available drug, thereby improving its effectiveness substantially.

V. Numerical Results and Discussion

A. Parameter Values

For our numerical experimentation, we have fixed $r = 0.08$ gm/L, $V_{clo} = 20$ gm/d (before parturition), $V_{cl} = 70$ gm/d (after parturition), $Vol = 30$ L as in [3], [4]. Values of K_p, K_I, A_1, A_2 for healthy cattle are given in these references are based on minimizing a mean square error function from actual experiment data. However for animals having milk fever, which is the focus of our study, this reference only outlines a *qualitative* study. Based on those qualitative arguments, we have chosen $K_{p_{\min}} = 2000$ L/d, $K_{p_{\max}} = 2100$ L/d, $K_{I_{\min}} = 2100$ L/d^2, $K_{I_{\max}} = 2200$ L/d^2, $A_{1_{\min}} = 55$ gm/d, $A_{1_{\max}} = 65$ gm/d, $A_{2_{\min}} = 85$ gm/d, $A_{2_{\max}} = 95$ gm/d. For normalization, we have chosen $x_{1nom} = 0.01$ gm/L, $x_{2nom} = 10$(gm/L/d, $K_{p_{nom}} = 2000$ L/d, $K_{I_{nom}} = 2000$ L/d^2, $A_{1_{nom}} = 60$ gm/d, and $A_{2_{nom}} 90$ gm/d. For the neural network training purposes, we have assumed $x_{1_{\min}} = -0.07/x_{1_nom}, x_{1_{\max}} = 0.02/x_{1nom}$ and $x_{2_{\max}} = 20/x_{2nom}$. However, depending on the parameter value A_2, we have fixed $x_{2\min} = (1.2\ A_2/x_{2nom}) \left[\tanh^{-1}(V_{clo}/A_2) - \tanh^{-1}(V_{cl}/A_2)\right]$. The factor 1.2 is chosen to allow a 20% overshoot. The weights in the cost function are

$$Q = \begin{bmatrix} Q_{11} & Q_{12} \\ Q_{21} & Q_{22} \end{bmatrix} = \begin{bmatrix} 4/\left(0.01/x_{1_{nom}}\right)^2 & 0 \\ 0 & 1/\left(50/x_{2_{nom}}\right)^2 \end{bmatrix}$$

and $R = (\eta/20)^2 Q_{11}$.The time interval Δt was chosen as 30 s. We have assumed the control efficiency factor $\eta = 20\%$

B. Analysis of Simulation Results

We first assumed $K_p = 2000$ L/d, $K_I = 2100$ L/d^2, $A_1 = 60$ gm/d, and $A_2 = 90$ gm/d. These parameters lead to an unstable trajectory for the initial condition $x_1 = 0$, $x_2 = (A_2/x_{2nom}) \left[\tanh^{-1}(V_{do}/A_2) - \tanh^{-1}(V_{cl}/A_2)\right]$ (the values at parturition), indicating a diseased animal. First, we experimented with these parameter values. However, since the infusion process is supposed to be carried out only for patient animals, starting with this initial condition, we first propagated

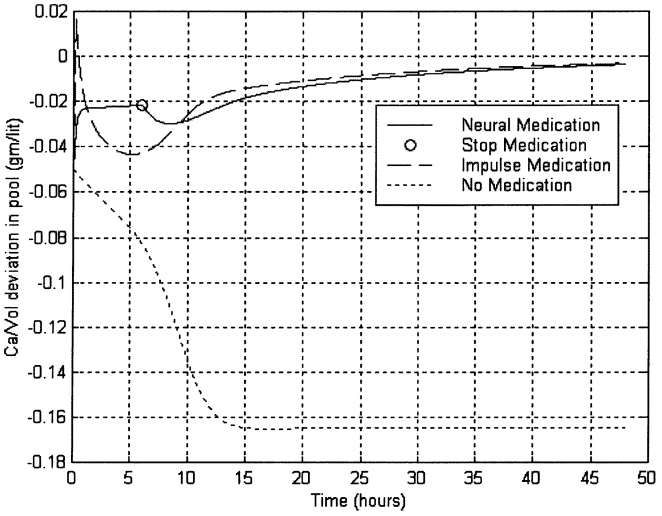

Fig. 4. Calcium/Vol. deviation in the pool; case-1.

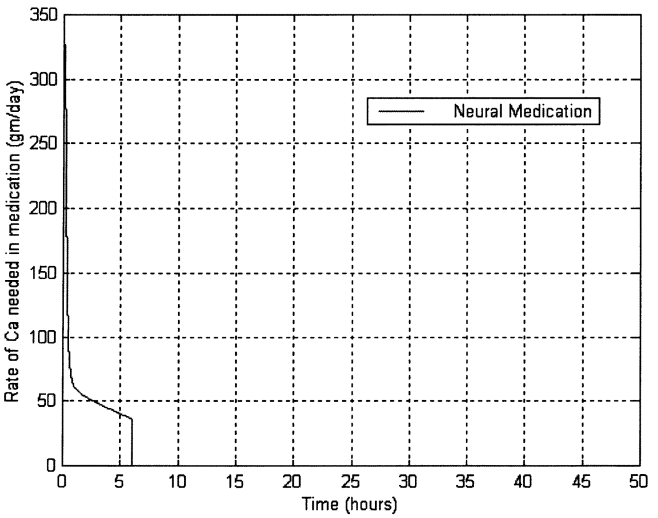

Fig. 6. Rate of Ca needed in medication; case-1.

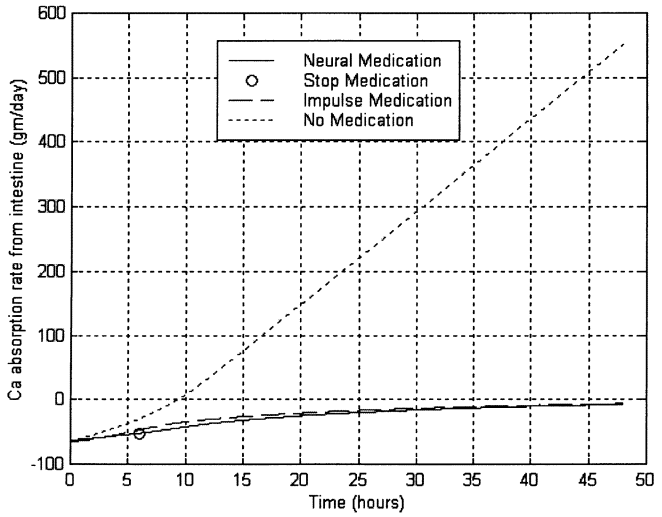

Fig. 5. Calcium absorption rate in intestine; case-1.

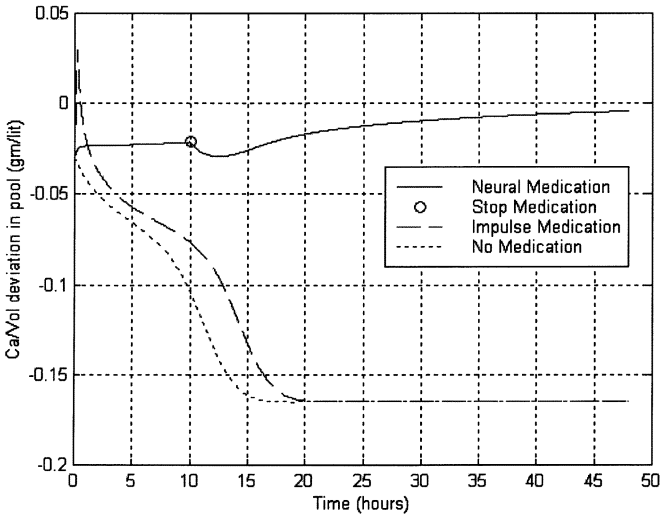

Fig. 7. Calcium/Vol. deviation in the pool; case-2.

the homogeneous system until x_1 dropped below x_{1cut}, a known value. Then we collected the corresponding value of x_2 at that time and considered the state values at that time as our initial condition for the application of control.

As mentioned in [16], the current practice of Ca infusion to treat parturient paresis is to infuse 10.8 gm of Ca in 12 min. So, it becomes necessary to compare our results not only with the homogeneous system behavior, but also with this current practice of medication. However one can notice, because of the high rate of infusion, this process is completed very quickly as compared to our proposed on-line continuous medication. In systems theory, this can be termed as an "impulse" input. Thus, we refer to this as *impulse medication*, in our attempt to compare the results. For the numerical simulation, we just assume a constant rate of infusion (control) of 10.8 gm /12 min for 12 min, and then assume it to be zero for rest of the time.

Figs. 4–6 show the results with $x_{1cut} = -0.05/x_{1nom}$. It is clear that both the continuous and the impulse medication work fine in recovering the patient animal. Moreover the actual amount of Ca infused to the system in the 6-h long medication is $m_a = 15.78$ gm, a comparable value to 10.8 gm. However, as seen in Fig. 4, the trajectory of the deviated amount of Ca per unit volume of the blood pool from its equilibrium value enters the positive domain, which means the presence of extra Ca in the pool than necessary. This may lead to a potential danger of hypercalcemia [16]. Moreover, the same trajectory for the impulse medication again drops below -0.04 gm/L, a low value that could cause some concern, before recovering back. On the other hand, the continuous medication shows a much smoother trajectory. It never goes to the positive side either. Moreover after termination of the medication, even though the trajectory drops a little before recovering back, it always remains above the danger level of -0.03 gm/L (meeting the condition we set in Section IV) for all future time. About 1 h after terminating the medication, the trajectory drops close to -0.03 gm/L (but remains above it in strict mathematical sense). This is significantly better than the impulse medication. Fig. 5 depicts the trajectory of the rate of Ca resorption from intestine. The two plots for impulse and continuous control are quite close to each other,

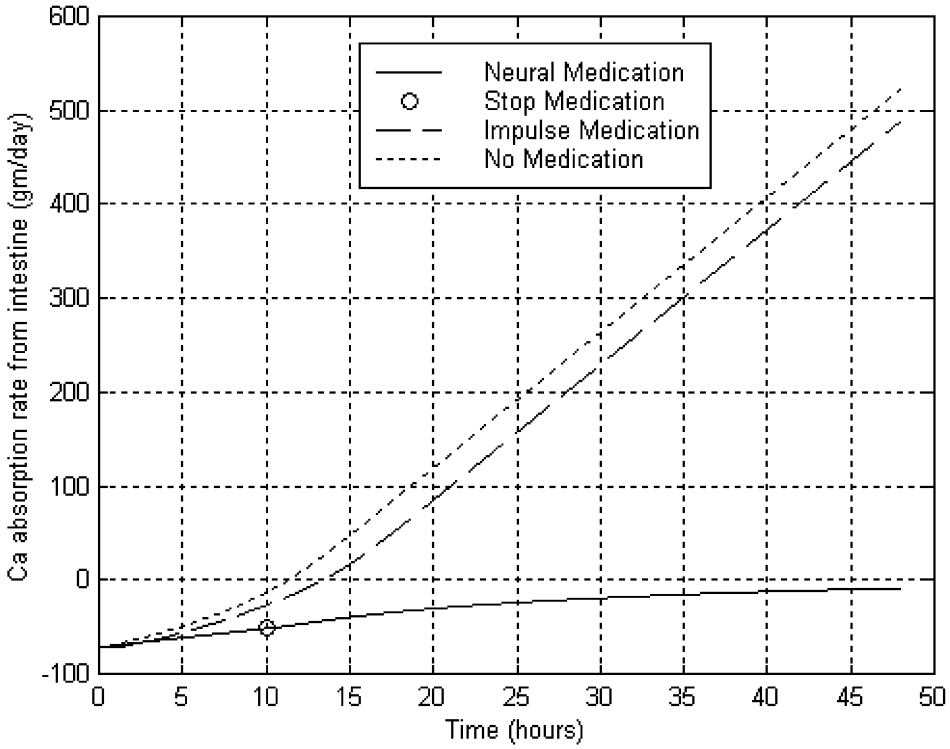

Fig. 8. Calcium absorption rate in intestine; case-2.

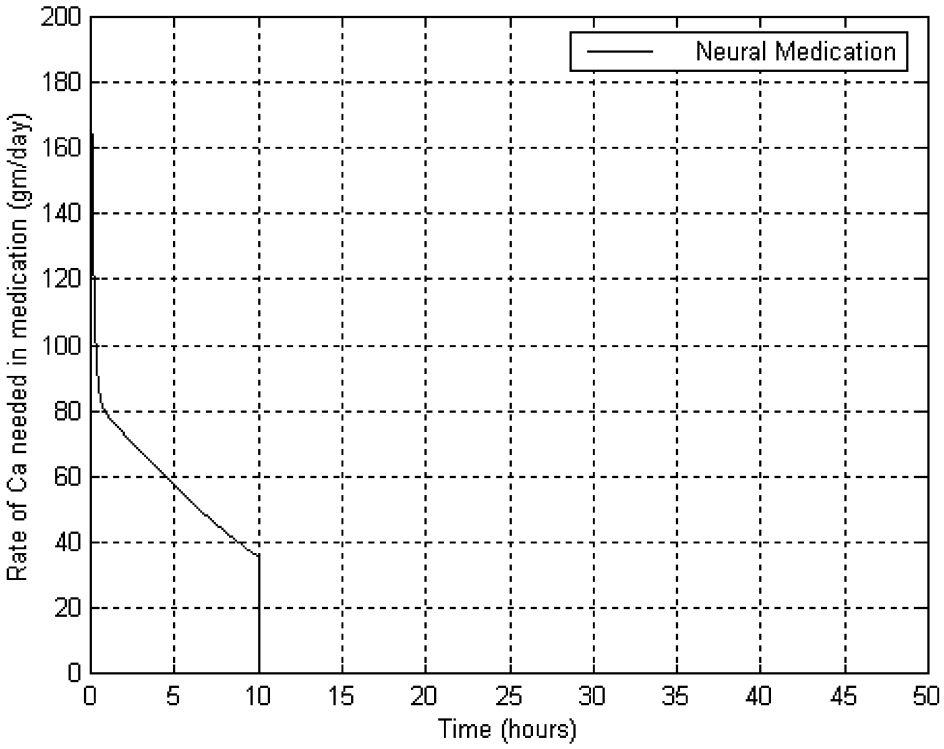

Fig. 9. Rate of Ca needed in medication; case-2.

which indicate that by continuous control, we are not doing anything drastically wrong to the intestine. Fig. 6 depicts the control trajectory under the on-line optimal medication. At time $t = 6$ h, the control is terminated. Note that as compared to the impulse input of 10.8 gm/12 min, which is 1296 gm/d, the control magnitude in the continuous scheme is much lesser. Thus the system is pulled toward the equilibrium point in a much smoother way.

In Figs. 7–9 we used the same value of the parameters. However, this time we simulated the system with

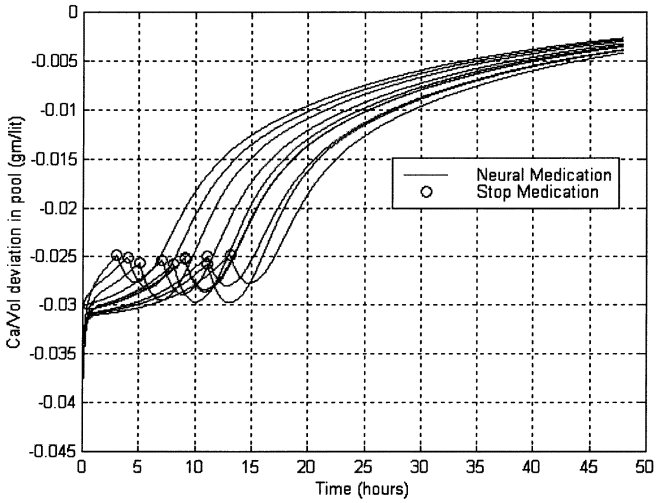

Fig. 10. Calcium/Vol. deviation in the pool from various initial conditions.

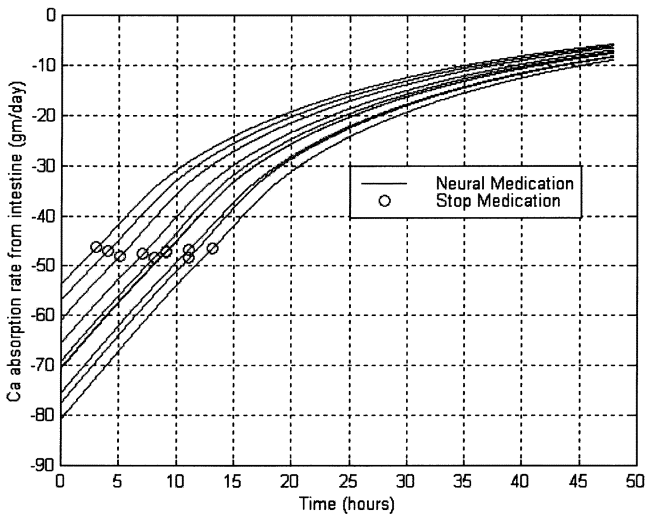

Fig. 11. Calcium absorption rate in intestine from various initial conditions.

$x_{1cut} = -0.03/x_{1nom}$. It was surprising to see that the impulse control did not work. This implies that if the current practice of impulse infusion is carried out before the condition of the patient animal becomes sufficiently bad, in some cases (depends on system parameters) it may not work. However, the on-line continuous scheme was successful in achieving its goal and recovered the animal successfully. In this case, however, the duration of control application was longer and the amount of Ca infused was $m_a = 25.02$ gm. Note that although the continuous medication scheme works from any initial condition, one may consider starting the medication a little later for easier drug administration if the animals have to be kept static (by strapping, putting under anesthesia, etc.) for the duration of continuous infusion of Ca injection. Even if it is feasible, it is always better for the animal to minimize the duration of medication as much as possible to minimize the associated risks (e.g., high doses of anesthesia may lead to death).

One of our objectives, however, was to see that the proposed methodology and the synthesized controller work from a large number of initial conditions from the domain of interest. Toward this end, we assumed a large number of random parameter values and random initial states and simulated the system repeatedly (Monte Carlo simulation). Figs. 10–12 show some of the simulated results indicating that the proposed scheme works for many different possible cases. Even though only ten such cases are shown (for clarity of the figures), similar results were obtained for a very large number of cases. In fact, the controller was successful in all the cases. Furthermore, the trajectory of Ca deviation per unit volume of blood pool never entered the positive domain (dangerous hypercalcemic problem) in any simulation.

For comparison, we have solved this problem with the well-established Linear Quadratic Regulator (LQR) optimal control theory [2], [11], where the control synthesis is carried out after linearizing the system dynamics. We present two sets of representative results in Figs. 13–18. In Figs. 13–15 we present a case where the linear control works but the nonlinear control works better. It can be observed from Fig. 13 that with the application of linear control the Ca deviation level drops below -0.04 gm/L, a dangerously low value, before recovering back whereas the nonlinear controller keeps this deviation relatively small. In Figs. 16–18 we present a case where the linear control actually fails and the system becomes unstable (i.e., the cow dies), whereas the nonlinear control was successful in pulling the system into a stable region (i.e., it recovers the sick animal). From this comparison study it is clear that the proposed nonlinear control synthesis approach has a clear advantage over the existing LQR approach based on linear theory.

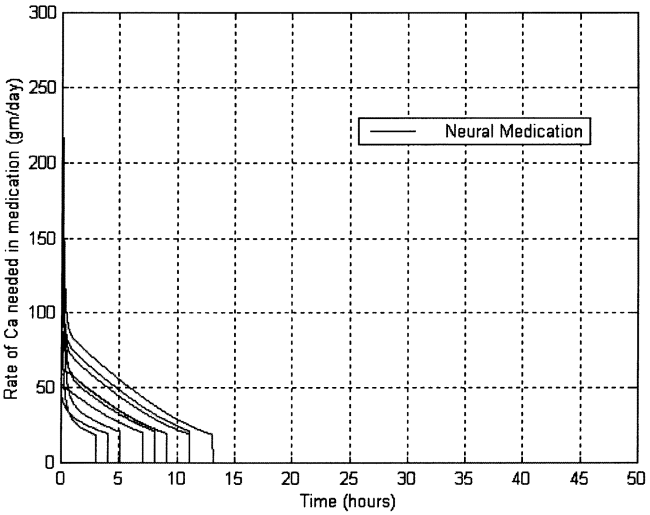

Fig. 12. Rate of Ca needed in medication, from various initial conditions.

C. Some Relevant Comments

- In our control synthesis, we have assumed that both the states x_1 and x_2 are available. Where as x_1 can readily be measurable, currently no technique exists to measure x_2. For this reason, in actual implementation of the proposed medication strategy, it may be necessary to design an observer or filter to have an estimate of x_2. Similarly, it may also be helpful to incorporate a parameter estimation technique to carry out an on-line estimation of the parameters.

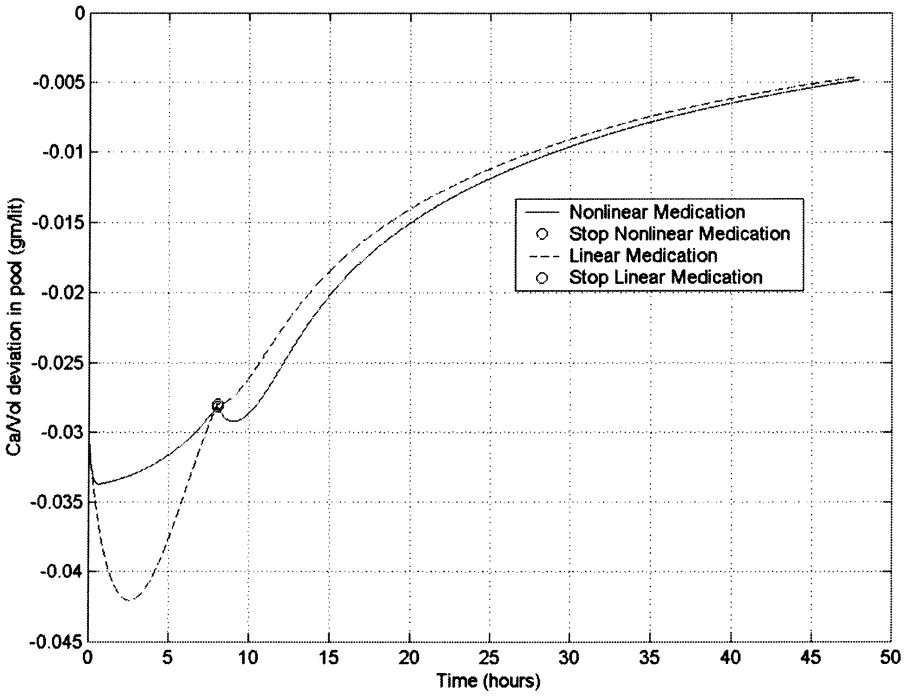

Fig. 13. Calcium/Vol. deviation in the pool: A comparison study; case-1.

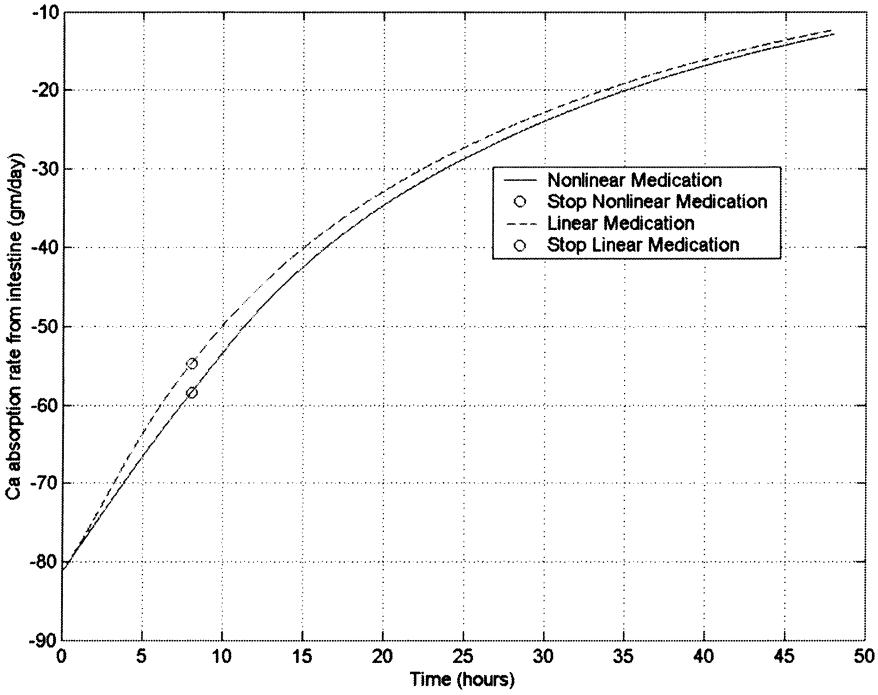

Fig. 14. Calcium absorption rate in intestine: A comparison study; case-1.

These are possibilities for further refinement of the proposed on-line medication technique.

- In order to analyze the effects of the control efficiency factor on the process, we made $\eta = 30\%$. The results are similar to the case when $\eta = 20\%$. As expected, when the control efficiency is higher, the actual amount to be infused to the system was observed to be lower, which in some sense validated the fact that our control synthesis approach was proper.
- In simulations, we observed that the even if the impulse medication pushed the Ca deviation to as high as $+0.05$ gm/L, the system was still stabilizable in some cases whereas in some other cases even about $+0.025$ gm/L lead to instability. This is because as long as a point in the state space (dependent on *all* state variables) falls within the "domain of attraction" of an equilibrium point, the evolution of the trajectory from that point will be stabilizing. We point out that one may use

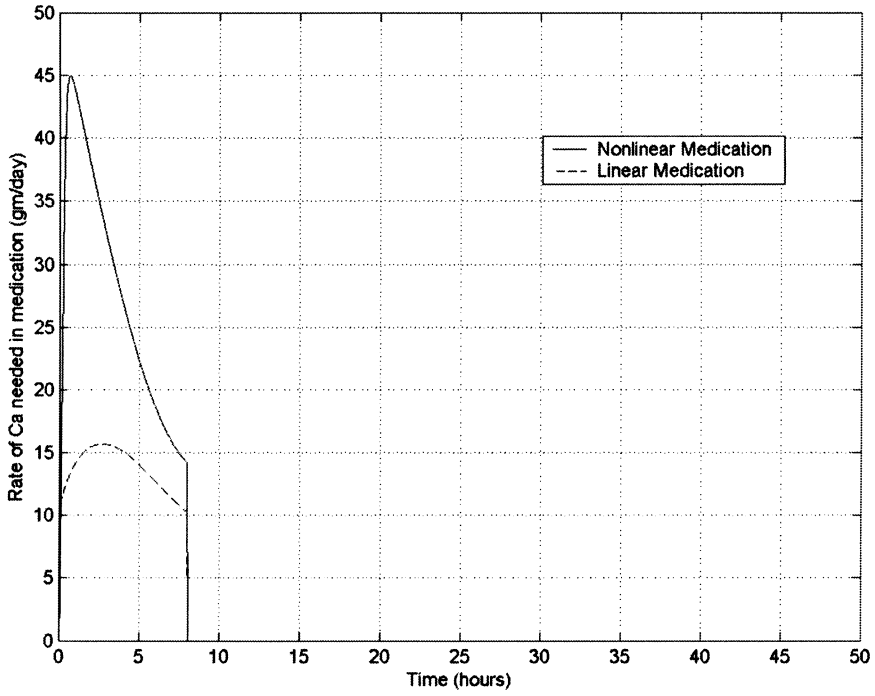

Fig. 15. Rate of Ca needed in medication: A comparison study; case-1.

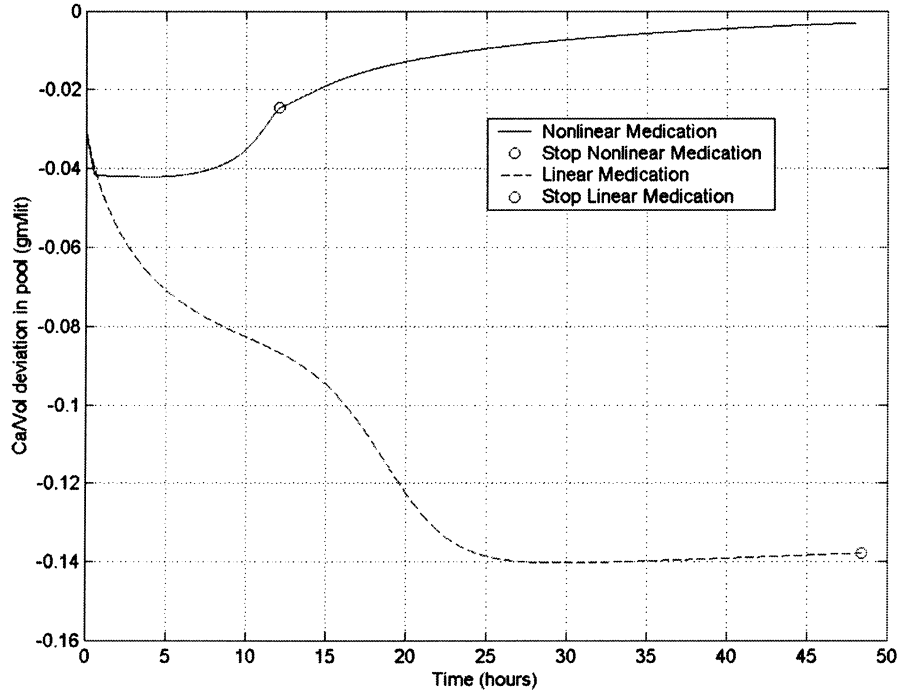

Fig. 16. Calcium/Vol. deviation in the pool: A comparison study; case-2.

Lyapunov theory [19] to estimate the domain of attraction. Note that with collaborative work with experimentalists in the area will definitely lead to more accurate models and help interpret the validity of the mathematical results better.

- Even though the paper deals with the particular biomedical problem related to parturient paresis, the idea of an on-line feedback medication can be applied to any other linear/nonlinear problem, provided an appropriate mathematical model is available.

VI. Conclusion

We have developed a more realistic model for the calcium homeostatis problem of cows in this study, which both accounts for a limitation in an existing (recently developed) model as well

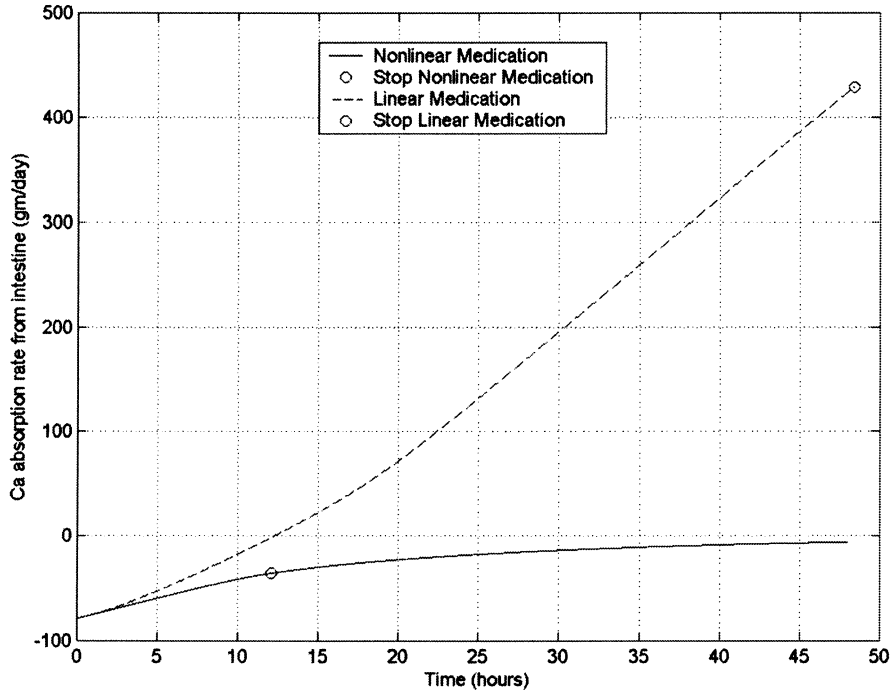

Fig. 17. Calcium absorption rate in intestine: A comparison study; case-2.

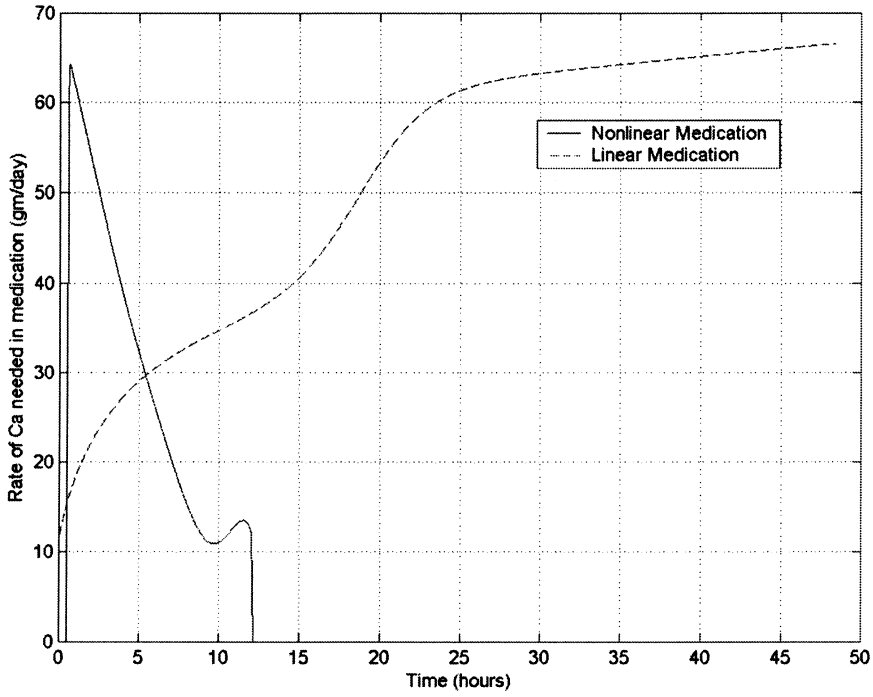

Fig. 18. Rate of Ca needed in medication: A comparison study; case-2.

as incorporates the effects of external medication (control). We have successfully synthesized an on-line feedback optimal medication strategy for the parturient paresis problem of cows commonly observed on the onset of parturition. The proposed computerized automatic medication scheme has been shown to improve the effectiveness of an existing drug substantially as compared to the impulsive manual quick infusion process, which is currently in practice. It was found that whereas the current practice failed in some cases (leading to the death of the animal), the proposed medication process was successful in saving the animals. Unlike the current practice which should start only after the animal actually develops the disease (otherwise the medicine flows out of body and hence becomes ineffective) the proposed on-line continuous infusion strategy can be initiated at any time. Moreover, it never leads to severe hypercalcemic problems, thereby avoiding the associated disastrous consequences such as cardiac arrest. Furthermore, a comparison study with the linear quadratic regulator theory clearly brings out the ad-

vantage of the proposed nonlinear control synthesis approach. We conclude the paper with the comment that although the results are quite promising, collaborative work with veterinarians is needed to assess problems in implementations.

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Radhakant Padhi received the B.E. degree in mechanical engineering from University College of Engineering-Burla, Orissa, India, in 1994, and the M.E. degree in aerospace engineering from the Indian Institute of Science, Bangalore, in 1996. He received the Ph.D. degree in aerospace engineering from the University of Missouri—Rolla, in 2001.

He has been a Postdoctoral Fellow with the Department of Mechanical and Aerospace Engineering and Engineering Mechanics, University of Missouri—Rolla. He worked as a scientist with the Defense Research and Development Organization, Hyderabad, India, from April 1996 to July 1997. He will be joining the Aerospace Engineering Department of the Indian Institute of Science, Bangalore, as an Assistant Professor in January 2004. His research interests are in the broad area of systems theory and applications. Specifically, he is interested in optimization and optimal control, distributed parameter systems, neural networks, control and guidance of aerospace vehicles, and application of control theory to biomedical systems.

Dr. Padhi received a Best Student Paper Award (third place) in the 2001 IEEE Joint Conference on Control Applications and International Symposium on Intelligent Control, held in Mexico City, Mexico, where he has presented a shorter version of this paper.

S. N. Balakrishnan received the Ph.D. degree in aerospace engineering from the University of Texas at Austin.

He has been with the University of Missouri—Rolla since 1985. Currently, he is a Professor with the Department of Mechanical and Aerospace Engineering and Engineering Mechanics. His nonteaching experience includes work as a Lead Engineer in the Space Shuttle program, Fellow, Center for Space Research at the University of Texas at Austin, Summer Faculty Fellow at Air Force Research Laboratory, Eglin, FL, and Engineer, Indian Space Program. His research interests are in the areas of system theory and applications. His current research uses neural netowrks and classical methods in the identification and robust control of missiles, airplanes, rockets, and other "interesting" systems. His work has been sponsored by the National Science Foundation, the Air Force, the Naval Surface Warfare Center, the Army Space and Missile Defense Command, and NASA.

Dr. Balakrishnan is a member of Sigma Gamma Tau. He is an Associate Fellow of AIAA and serves as a Director, American Automatic Control Council. He has been a Program Chair, AIAA Guidance, Navigation and Control Conference, a Vice Chair, American Control Conference, and a General Chair, AIAA Atmospheric Flight Mechanics Conference.