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Effective drug dosage design for treatment of infectious diseases using dynamic inversion

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Abstract

A generic nonlinear mathematical model describing the human immunological dynamics is used to design an effective automatic drug administration scheme. Even though the model describes the effects of various drugs on the dynamic system, this work is confined to the drugs that kill the invading pathogen and heal the affected organ. From a system theoretic point of view, the drug inputs can be interpreted as control inputs, which can be designed based on control theoretic concepts. The controller is designed based on the principle of dynamic inversion and is found to be effective in curing the 'nominal model patient' by killing the invading microbes and healing the damaged organ. A major advantage of this technique is that it leads to a closed-form state feedback form of control. It is also proved from a rigorous mathematical analysis that the internal dynamics of the system remains stable when the proposed controller is applied. A robustness study is also carried out for testing the effectiveness of the drug administration scheme for parameter uncertainties. It is observed from simulation studies that the technique has adequate robustness for many 'realistic model patients' having off-nominal parameter values as well.

Keywords: Infectious disease, drug administration, dynamic inversion.

1. Introduction

The immune system of living organisms exists to defend it from agents with properties of genetically alien information (such as bacteria, viruses, proteins, tissue and transformed own cells such as tumor cells). For this purpose, there exist three distinct levels of defense against the invading microbes. The first is the outer perimeter of defense–the surface epithelial layers of the body, including the epidermal cells of the skin and the mucosal cells that line the respiratory, gastrointestinal, and genitourinary tracts. Once these have been surpassed, the innate immune system provides a tactical response, signaling the presence of nonself organisms and activating B cells to produce antibodies that bind to the intruder's antigens, reducing them to nonfunctioning units. They also stimulate the production of molecules that either damage the intruder's plasma membrane directly or help trigger the second phase of immune response. The innate immune system protects against many extracellular bacteria or free viruses that are found in blood plasma, lymph, tissue fluid, or interstitial space between cells. The adaptive immune system produces protective cells that

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remember specific antigens and produce antibodies customized to the pathogens. The generation of such defender cells and molecules by the immune system is termed as immune response. Any alien substance which is able to induce such a response is a form of antigen. It is to be noted that even though the innate and adaptive immune systems operate separately, some constituents are shared. An interested reader can refer to [1–3] and the references therein for better understanding of the associated complex mechanism.

When there is an invasion of pathogens in an organ, the immune system responds through the production of plasma cells, which produce antibodies that fight the pathogen. If the concentration of the invading pathogen is high, there is considerable damage to the organ and the body fails to launch a strong immune response. As a result, the immune system becomes weak, leading to a lowered production of plasma cells and antibodies. When this happens, the affected organ fails to recover naturally and there is a need for external medication. The options available for treatment of an infectious disease (once it has been recognized) focus on killing the invading microbes directly, enhancing the efficacy of the immune system (i.e. production of plasma cells and antibodies) or providing healing care to the affected organ directly [4]. Such drugs generally augment the natural ability of the body to fight the infection and eventually cure the damaged organ. However, in this work we have assumed only the availability of drugs that kill the invading microbes and heal the affected organ. We have not considered the drugs that enhance the efficacy of the immune system. This is an advantage because (i) the drugs that enhance the production of plasma cells and antibodies are not readily available (it is still a topic of pharmaceutical research), (ii) the drugs that we have considered are effective enough to achieve our objectives, (iii) elimination of extra drugs also leads to the elimination of side effects and (iv) the treatment plan becomes more cost effective.

Unfortunately, all drugs come with the price of unwanted side effects. Moreover, the response of the body to any external drug is not instantaneous. Hence, a carefully monitored continuous low dosage is always preferable as compared to high dosage at discrete points in time (impulse control), which is currently in practice. However, since it is impossible for a doctor to continuously monitor a patient and decide an appropriate quantity of the drug, the idea can be realized in practice only if the process is made automatic (monitored and controlled by a computer). This is where control systems theory becomes a valuable tool. Using the various advanced control design methods, an appropriate control (drug) requirement history can be found out, which is both effective in treating the disease and distributed over time, leading to minimal side effects.

Perelson and his group [5, 6] have presented a system of differential equations governing the dynamics of antibodies by using binary strings to model reactions between antibodies and antigens. The model also takes into account the fact that the number of state variables is a function of time. A generic nonlinear mathematical model describing the human immunological dynamics is presented in [7]. The model describes the coupled evolution of concentration of pathogens, plasma cells and antibodies and a numerical value that indicates the relative characteristic of a damaged organ. Stengel *et al.* [4] have augmented this model to incorporate the effect of various drug (control) inputs. Further, they have shown a way of control design, following the method of optimal control theory [8]. In [4], a nonlinear optimal controller is obtained by solving the associated two-point boundary value problem, us-

ing the steepest–descent gradient method. The effect of each control, applied separately, is also considered. It is observed that even though each control was effective in arresting explosive growth of the pathogen and preventing organ death, the drug that kills the pathogens and the organ health enhancer are the most effective treatments.

Even though the methods and results presented in [4] have their own merits, there are several drawbacks as well: (i) the steepest descent method (which is relatively an old technique) only leads to an 'open loop' numerical solution for the control variable and hence does not have the beneficial properties of a state-feedback controller (like noise suppression); (ii) the method is numerically intensive and, in general, cannot be applied for online applications since one can never be sure of the convergence of the algorithm within the allotted time interval for control update; (iii) the problem needs to be formulated as a 'finite time' optimal control problem (in order to make use of the steepest descent method). However, the final time (at which the medication needs to be stopped) depends on the patient's condition and, in general, cannot be predicted a priori (this is an important issue). As the authors have themselves pointed out (which is also intuitively obvious), treatment for an insufficient duration of time may not cure the patient completely [4]. On the other hand, fixing a very long treatment time increases both the computational cost and, more importantly, unnecessarily sustains the uneasiness of the patient for a longer duration of time. To address these shortcomings is the main goal of this paper. Taking the help of an advanced technique, namely 'dynamic inversion', we propose a control design strategy which has the following characteristics: (i) it comes up with a closed-form state-feedback control solution; (ii) the approach is computationally non-intensive and implementable in real-time and (iii) there is no need to predict the duration of the treatment a priori (the medication can be continued for arbitrarily long period of time and can be stopped whenever the condition of the patient improves). In addition to these, we have also carried out some simulation studies about the robustness of the proposed controller with respect to parameter uncertainties.

A relatively simpler and popular method of nonlinear control design is the technique of dynamic inversion, which is essentially based on the philosophy of feedback linearization [9]. In this approach, an appropriate coordinate transformation is carried out so that the system dynamics appears in a linear form (in the transformed coordinates). The linear control design tools are then used to synthesize the controller. In this paper, we have used this technique to design a controller (i.e. medication history) based on input–output linearization. We have also proved that the associated internal dynamics (zero dynamics) is stable [9]. Note that as in [4], our approach is generic enough to cater to infectious diseases in general. This shows that the technique presented is capable enough to treat a wider class of problems. For specific diseases, however, the model will have different parameter values. If one concentrates on a particular disease, he can implement the control synthesis algorithm presented here with those parameter values. For example, for influenza the appropriate parameter values can be found in [7].

2. Immunology dynamics and objective of the control design

2.1. *Immunology dynamics*

A generic nonlinear mathematical model describing the human immunology dynamics is presented in [7]. The model describes the coupled evolution of concentration of pathogens,

plasma cells and antibodies and a numerical value that indicates the relative characteristic of a damaged organ. Stengel *et al*. have augmented this model to incorporate the effect of four generic drugs (control inputs), namely, pathogen killer, plasma cell enhancer, antibody enhancer and organ healing factor [4]. An interested reader can see the references for more details. However, in this work we have assumed only the availability of drugs that kill the invading microbes and heal the affected organ. We have not considered drugs that enhance the efficacy of the immune system for the reasons pointed out in Section 1. With the effects of these drugs, the nonlinear mathematical model for the immunology dynamics can be written as

$$\dot{X} = f(X) + BU \tag{1a}$$

where $X = [x_1\ x_2\ x_3\ x_4]^T$, $U = [u_1\ u_2]^T$ are the state and control vectors, respectively. Functions $f(X)$ and matrix B are defined as

$$f(X) \triangleq \begin{bmatrix} (a_{11} - a_{12}x_3)x_1 \\ a_{21}(x_4)\ a_{22}x_1x_3 - a_{23}(x_2 - x_2^*) \\ a_{31}x_2 - (a_{32} + a_{33}x_1)x_3 \\ a_{41}x_1 - a_{42}x_4 \end{bmatrix}, \quad B \triangleq \begin{bmatrix} b_1 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & b_4 \end{bmatrix}. \tag{1b}$$

Here x_1 represents concentration of the pathogen, x_2, the concentration of plasma cells (which are carriers and producers of antibodies), x_3, the concentration of antibodies (which kill the pathogen) and x_4, the relative characteristic of a damaged organ (or organ health factor). Similarly, u_1 represents the drug which is a pathogen killer and u_2, the drug which heals the affected organ. $x_2^* = 2$ represents the steady-state concentration of plasma cells. The parameter a_{21} is a nonlinear function of x_4 that describes the immune deficiency caused by damage to the organ and is given by

$$a_{21}(x_4) = \begin{cases} \cos(\pi x_4), & 0 \le x_4 \le 1/2 \\ 0, & x_4 > 1/2 \end{cases}. \tag{1c}$$

The numerical values of other parameters are given in Table I.

Note that the model in (1a)–(1c) (with the associated numerical values of the parameters in Table I) is a generic one and the numerical values in the model qualitatively describe the

Table I
Parameter values

Parameter	Value	Parameter	Value
a_{11}	1	a_{32}	1.5
a_{12}	1	a_{33}	0.5
a_{21}	See (1c)	a_{41}	0.5
a_{22}	3	a_{42}	1
a_{23}	1	b_1	–1
a_{31}	1	b_4	–1

various effects observed in practice in general. The main motivation of this work, however, is to apply an advanced nonlinear control design technique (namely, dynamic inversion) for automatic treatment of infectious diseases. The model and parameter values considered are sufficient enough to demonstrate this. For specific diseases the model will remain the same, but will have different parameter values [7]. If one concentrates on a particular disease, he can implement the control synthesis algorithm presented here with those parameters.

In the model, parameter a_{11} indicates the exponential growth of the pathogens. The term $(a_{12}x_3x_1)$ designates the number of antigens neutralized by the antibodies x_3, where a_{12} is the coefficient related to the probability of neutralization of the germs by the antibodies upon an encounter. The term $a_{41}x_1$ represents the degree of damage to the organ by the pathogens while the term $a_{42}x_4$ signifies the recuperative capacity of the organ. For more information about the physical meanings of the various terms of the model, the reader is referred to [4, 7, 10].

2.2. *Objective of control design (Medication strategy)*

The objective of this paper is to present a general technique to come up with an appropriate treatment strategy (time history of the required drug dosage) by taking the help of advanced control systems theory so as to completely kill the invading microbes. At the same time, it also makes sure that the affected organ is not fatally damaged at any point of time during the treatment. Hence, in system theory language, our control synthesis strategy for designing an appropriate $U(t)$ must make sure that $[x_1, x_4] \to 0$ as $t \to \infty$ (i.e. as the treatment progresses). This objective should be met without any undesirable behavior in all the states, including the ones for which no specific goal is enforced. Note that meeting the objective as $t \to \infty$ is written only to have a mathematically meaningful formulation. In practice (which will be clear from Section 4), the objective will be much before $t \to \infty$ (i.e. within a meaningful finite time). However, note that this mathematical formulation allows us to apply the drug administration scheme for an arbitrarily long amount of time and more importantly, the duration of the drug administration need not be decided a priori. The mathematical details are discussed in detail in Section 3.

3. Drug dosage scheme (Control design): Mathematical details

As pointed out earlier, the goal is to come up with an effective controller (drug dosage plan) which will meet the goals for the system. Even though we have used the technique of 'dynamic inversion', which is a fairly established technique [9, 11–13], we still outline the basic steps that are relevant to our problem. For completeness of the paper, we outline the generic theory first, which is followed by the specific discussion related to the particular drug dosage design problem.

3.1. *General theory of dynamic inversion*

In this paper, we focus on a class of nonlinear systems which are affine in control and are represented by

$$\begin{aligned} \dot{X} &= f(X) + G(X)\,U \\ Y &= h(X) \end{aligned} \tag{2}$$

where $X \in \Re^n$, $U \in \Re^m$, $Y \in \Re^p$ are the state, control and performance output vectors of the dynamic system, respectively. Here, we assume that $m = p$, i.e. we concentrate on 'square systems' (i.e. systems for which the number of performance outputs are the same as the number of control inputs). We also assume that the system is pointwise controllable. The objective is to design a controller U so that $Y \to Y^*$ as $t \to \infty$, where $Y^*(t)$ is the commanded signal for Y to track. We assume that $Y^*(t)$ is bounded, smooth and slowly varying.

To achieve the above objective, we first notice that from (2), using the chain rule of derivative, the expression for $\dot{Y}$ can be written as

$$\dot{Y} = f_Y(X) + G_Y(X)\,U, \tag{3}$$

where $f_Y \triangleq [\partial h/\partial X]\, f(X)$ and $G_Y \triangleq [\partial h/\partial X]\, G(X)$. We assume that the square matrix G_y is never singular $\forall t$. Next, defining $E \triangleq (Y - Y^*)$ the controller is synthesized such that the following stable linear error dynamics is satisfied

$$\dot{E} + K\,E = 0, \tag{4}$$

where K is chosen to be a positive-definite gain matrix. A relatively easier way is to choose it as a diagonal matrix with positive elements in the diagonal. For better physical interpretation, one can choose $K = \text{diag}(1/\tau_1 \ \ldots \ 1/\tau_m)$, where $\tau_i (i = 1 \ \ldots \ m)$ represents 'time constant' of the i^{th} error channel. Next, using the definition of E and substituting the expression for $\dot{Y}$ from (3) in (4) and carrying out the necessary algebra, we get the solution for the control variable as

$$U = -[G_y(X)]^{-1}\{f_Y(X) + K(Y - Y^*) - \dot{Y}^*\}. \tag{5}$$

Before proceeding further, we wish to mention a few salient points with respect to this technique. First, note that it leads to a closed-form solution for the controller, and hence it can be implemented online without any computational difficulties. Moreover, as long as (5) is satisfied, $E \to 0$ 'asymptotically' (rather exponentially). In other words, asymptotic tracking is achieved. However, there are a few important issues with respect to the dynamic inversion technique as well, which are outlined below:

(i) The assumption $m = p$ (the same number of controls as outputs) need not hold good. In that case, $m < p$, no perfect tracking is possible [14]. However, if $m > p$, additional objectives are usually introduced in the problem objective to obtain a solution for the controller.

(ii) G_Y being nonsingular, $\forall t$ is somewhat a restrictive constraint. If this is violated at small intervals of time, for those durations, the pointwise controllability assumption is not valid. If that happens, usually some approximation (like not updating the controller) is introduced. However, this leads to some performance degradation, which is intuitively obvious.

(iii) Another important issue is the question of 'internal dynamics' (also known as 'zero dynamics'). This is essentially the dynamics of the untracked states. This concept is linked to 'relative degree' μ of the problem, which is defined as the total number of derivatives taken in (3) (a first-order error dynamics in each output error channel is not always possible). Unless $\mu = n$, one explicitly need to answer the question of internal

stability [15]. Unless the internal dynamics is stable, the synthesized controller is of no practical use.

Note that even though the first two difficulties do not arise in our problem, the third one is a concern since in our problem $\mu = 2$ and $n = 4$. Hence, we have explicitly analyzed the question of internal stability and proved that it is stable.

3.2. *Problem specific equations*

With regard to the problem of treatment of infectious diseases, we select the performance output as $Y = [x_1\ x_4]^T$ and from (3), we write the output dynamics as

$$\dot{Y} = \begin{bmatrix} (a_{11} - a_{12}x_3)x_1 \\ a_{41}x_1 - a_{42}x_4 \end{bmatrix} + \begin{bmatrix} b_1 & 0 \\ 0 & b_4 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}. \tag{6}$$

Note that in our case $m = p = 2$, $f_Y(X) = [a_{11} - a_{12}x_3)x_1\ (a_{41}x_1 - a_{42}x_4)]^T$ and $G_Y(X) = \text{diag}(b_1\ b_4)$. Note that $G_Y(X)$ is a diagonal matrix with nonzero constants in its diagonal. Therefore, its inverse always exists $\forall t$. Since the goal is to make sure $Y = [x_1\ x_4]^T \to 0$, $Y^* = 0$ for our problem.

Next, choosing $K = \text{diag}(1/\tau_1\ 1/\tau_2)$, substituting the required expressions in (5) and carrying out the necessary algebra, we get the solution for the control variable as

$$\begin{bmatrix} u_1 \\ u_2 \end{bmatrix} = -\begin{bmatrix} b_1 & 0 \\ 0 & b_4 \end{bmatrix}^{-1} \left\{ \begin{bmatrix} (a_{11} - a_{12}x_3)x_1 \\ a_{41}x_1 - a_{42}x_4 \end{bmatrix} + \begin{bmatrix} 1/\tau_1 & 0 \\ 0 & 1/\tau_2 \end{bmatrix} \begin{bmatrix} x_1 \\ x_4 \end{bmatrix} \right\}. \tag{7}$$

However, as pointed out earlier, since the relative degree for our problem $\mu = 2$, whereas the number of states $n = 4$, it is essential to prove the stability of internal dynamics. It is well known that for this purpose it is sufficient to show that the zero dynamics is stable [9, 15]. In our problem, the zero dynamics is essentially the homogeneous dynamics of the state variable x_2 and x_3 after $Y = [x_1\ x_4]^T \to 0$, which is given by

$$\begin{bmatrix} \dot{x}_2 \\ \dot{x}_3 \end{bmatrix} = \begin{bmatrix} -a_{23} & 0 \\ a_{31} & -a_{32} \end{bmatrix} \begin{bmatrix} x_2 \\ x_3 \end{bmatrix} + \begin{bmatrix} a_{23} \\ 0 \end{bmatrix} x_2^*. \tag{8}$$

Note that (8) is of the form $\dot{X}_z = A_z X_z + B_z x_2^*$ (it turns out to be a linear system), where

$$X_z = [x_{2_d}\quad x_{3_d}]^T,\ A_z = \begin{bmatrix} -a_{23} & 0 \\ a_{31} & -a_{32} \end{bmatrix} \text{ and } B_z = \begin{bmatrix} a_{23} \\ 0 \end{bmatrix}.$$

Since x_2^* is a constant, it is a well-known fact from linear system theory [16] that this dynamics is stable if and only if the eigenvalues of A_z are in the left-half of the complex plane. However, since A_z is a triangular matrix it is obvious that its eigenvalues are its diagonal elements, which are $-a_{23} = -1$ and $-a_{32} = -1.5$ (Table I). Hence, we conclude that the internal dynamics is stable. From this analysis, it is also clear that the internal dynamics remains stable even if there is an uncertainty of parameter values, as long as the signs of the parameters a_{23} and a_{32} are preserved (i.e. they are positive).

4. Numerical results

4.1 *Treatment strategy for patients*

For our numerical study, we selected the initial condition based on the analysis carried out in [4], which in summary is as follows. For a given set of parameter values, the homogenous system responds in four possible ways depending on the initial condition. These are represented by the subclinical, clinical, chronic and lethal cases. External treatment becomes necessary for chronic and lethal cases only as in the subclinical and clinical cases the body's immune system is sufficiently capable to cure the disease. As in [4], we have selected the lethal case for our numerical experiments. Hence, we selected the initial condition as $x(0) = [3\ 2(a_{31}/a_{32})x_2^*\ 0]^T$, where a_{31} and a_{32} are parameters of the system dynamics (Table I) and $x_2^* = 2$ is the steady-state concentration of the plasma cells. *It is important to note that the technique presented in this paper does not depend on the selection of initial condition (it works for any initial condition). However, we have presented the results with the selection of this initial condition for better physical meaning of the results.* An interested reader can see the reference for more justification of this selection.

The control design parameters were chosen as $\tau_{1_d} = 0.5$ and $\tau_{2_d} = 1.5$. Numerical integration of the differential equations was carried out using a fourth-order Runge–Kutta method [17] with constant step size $\Delta t = 1/60$. Even though the controller can be implemented for arbitrarily long duration of time (unlike the one in [4], where the control application cannot be extended beyond the duration that is decided a priori), the treatment duration was fixed at $t_f = 10$, which is sufficient to demonstrate the results.

It can be seen from Fig. 1 that the goal of $[y_1, y_2] = [x_1, x_4] \to 0$ as $t \to \infty$ is met without any problem. In fact, the concentration of pathogen (x_1) decreases asymptotically to zero, which is expected from a dynamic inversion controller. Moreover, the organ remains healthy (the value representing the organ health (x_4) is close to zero) throughout the duration of the treatment. This is an advantage as compared to the results presented in [4]. In their numerical results the organ travels through a bad transient period (despite being healthy initially), even though it eventually recovers and becomes healthy again.

We have shown analytically in Section 3 that the internal dynamics for this problem is stable. This is clearly observed in the simulation plots as well in Fig. 1. The plots for the concentrations of the plasma cells (x_2) and antibodies (x_3) are clearly bounded. Moreover, as expected, they tend towards their respective steady-state values with time.

The associated drug dosages needed (control histories) are shown in Fig. 2. It can be observed that their magnitudes decay smoothly towards zero. In comparison with the results in [4], initially our medication histories are fractionally higher. But the medication is required only for two time units after which it is practically zero. However in [4], the minimum treatment duration required is about four time units (otherwise the treatment is ineffective). Shorter duration for medication is a definite advantage of our approach, since the uneasiness of the patient is not prolonged for a longer period than necessary. The reason for the shorter duration of medication requirement can be attributed to two reasons. As pointed out, initially our medication histories are a bit higher. However, more important, since in our case the healthy organ always remains healthy (i.e. it does not travel through a bad transi-

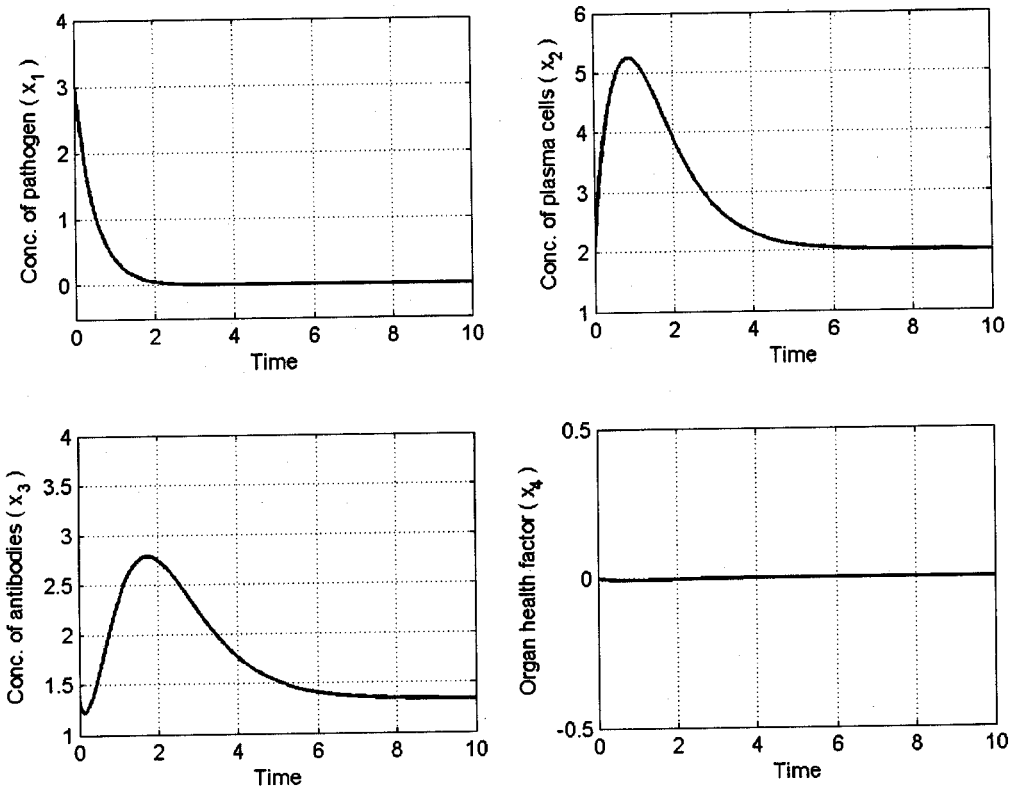

FIG. 1. State trajectories of the patient under treatment.

tion period), there is a higher rate of production of plasma cells and its concentration remains higher (see (1a)–(1c)). This leads to a larger concentration of antibodies that fight with the invading pathogens. Hence the disease gets cured earlier. This intuition is supported by the plots of the histories of the concentration of plasma cells and antibodies in Fig. 3, which are higher in our case (as compared to [4]) during transition.

At this point, we wish to mention that even though we have obtained encouraging simulation results, it is seldom the case that realistic model patients will have the same nominal parameters as used in the model. Rather, in most of the cases the parameter values will not match exactly as their corresponding nominal values. Hence, we wanted to carry out some robustness simulation study (with respect to parameter uncertainties) and experiment with the same off-nominal parameter values in the system. We perturbed all the parameter values in the model and selected numerical values of the parameters randomly within $\pm$ 20% of their nominal values. However, it is important to note that in the control design we still kept the nominal parameter values. Note that in addition to parameter uncertainty, we have perturbed the initial conditions as well and selected random values for them as follows: $x_1(0) \in [3, 3.6]$ and $x_4(0) \in [0, 0.2]$. Note that deviations in these values are within (0–20)% of their corresponding nominal values; the reason for selecting one-sided deviation was

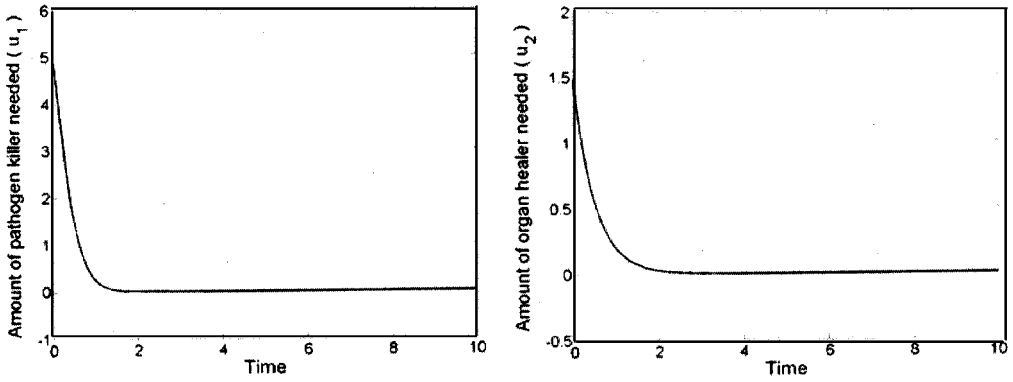

FIG. 2. Drug dosage needed for the patient.

mainly to test the algorithm for patients having worse conditions as compared to an ideal case, in the sense that the organ is already infected and, in addition, it is under more severe pathogen attack. The random value for $x_3(0)$ was automatically selected from the appropriate parameter values as $(a_{31}/a_{32})x_2^*$. However we have retained the initial value for $x_2(0)$ as its steady-state value $x_2^* = 2$, assuming that the steady-state value of the plasma cell concen-

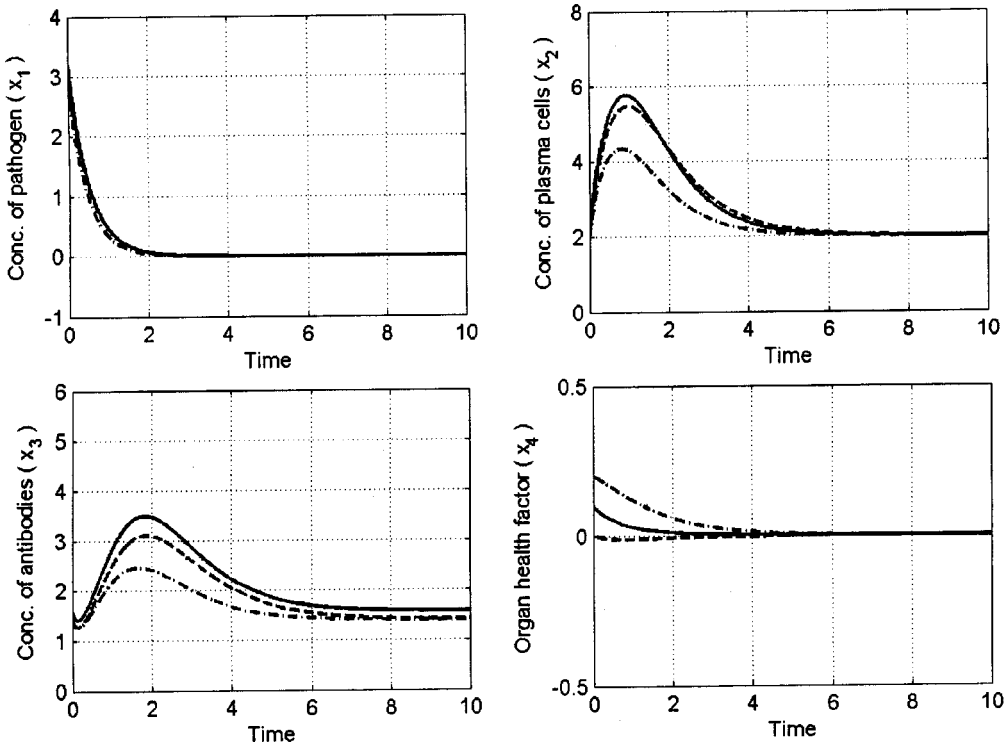

FIG. 3. State trajectories of patients having off-nominal parameter values.

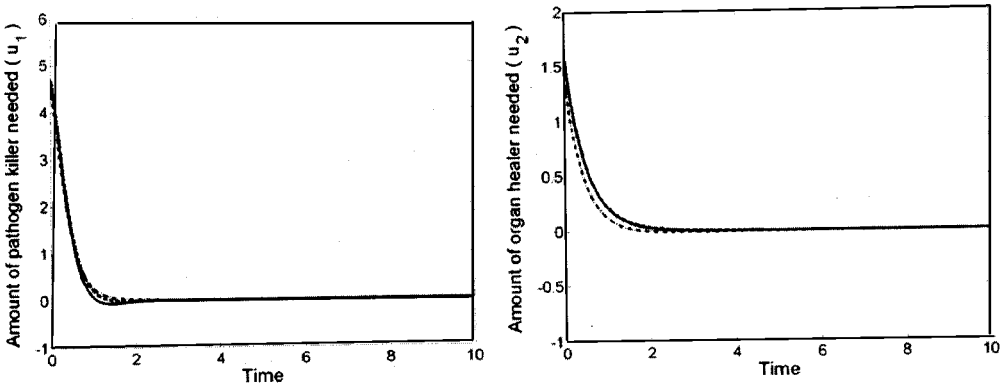

FIG. 4. Drug dosage needed for patients having off-nominal parameter values.

tration remains the same. It is interesting to observe that the resulting drug dosage (controller) still works well. As representative results, we have presented the state trajectories of three such cases in Fig. 3 and the associated control (drug dosage) history in Fig. 4. From these figures it is obvious that the objective of curing the patient is successfully achieved for realistic model patients (i.e. patients having off-nominal parameter values) as well.

Note that the plot in Figs 3 and 4 we have plotted the results for only three random cases for better clarity. However, the trend was observed in a large number of such simulations. In fact, we have run the program 10,000 times and observed that the proposed approach for the automatic drug delivery scheme (with nominal parameter values in the controller formula) failed to cure the patient only 4 times. In other words, from these 10,000 simulation runs, the probability of failure is only 0.04%, which is very low. Hence it is clear that the proposed control synthesis technique (drug administration plan) is sufficiently robust to parametric uncertainties, and hence, it can be used as a viable tool in practice for treating realistic model patients.

5. Conclusions

Using a generic nonlinear mathematical model describing the human immunological dynamics and taking the help of advanced nonlinear control synthesis techniques of dynamic inversion, an effective and robust automatic drug administration strategy is presented in this paper. Note that the state-feedback control solution obtained is in ‘closed form’, which is a major advantage. The proposed drug administration method successfully kills the invading microbes and heals the damaged organ of patients. From a large number of simulation studies with random parameter and initial condition values the probability of failure was found to be very low, which indicates that the proposed drug administration plan is sufficiently robust to be used as a viable tool in practice for actual patients. In addition to meeting this objective, relevant mathematical analysis has been carried out to prove that the internal dynamics (i.e. the dynamics of the concentrations of plasma cells and antibodies) is stable, which is supported from the numerical results as well.

Possible improvements of the paper include (i) using a state observer/filter (since all states are not measurable) and (ii) incorporating a robust/adaptive control synthesis algo-

rithm to systematically address the issues of parametric uncertainty and external noise input (like a situation of continued pathogen attack).

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