Effect of optimal linear control in human monocytes and macrophages system

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Abstract: Monocytes M and macrophages Mϕ cells are mononuclear essential components of the innate immune system response. M and Mϕ are mononuclear phagocytes that have crucial roles in tissue homeostasis and innate immunity. M Are key players during inflammation and pathogen challenge also are precursor of Mϕ, whereas tissue resident Mϕ has important functions in development, tissue homeostasis and the resolution of inflammation. In previous work, linear optimal control equations with tracking in x2(t) (this is Mϕ) and control only in x1(t), (this is M) were applied obtaining good results. In this work, Linear Optimal Control equations for states x1(t) and x2(t), with tracking in the state x2(t) were applied. It is possible to obtain better convergence results of the states to the asymptotic values (healthy state) when the production rate of (M) and λ into the state equations was modified. Tables and graphics are included.

Keywords: Innate Immune system, linear control, tracking.

1. Introduction

Spite of whole of cases for which has been developed the control equations; it seems that the list of applications is endless. Between the applications, more interesting and related with health are the associated with the immune system of the human body. Mathematical model which represent the behavior of the system of Mϕ and their precursors M, are the “big eaters” into the human body are presented in [1], [2]. Some models of epidemic are presented in literature, but so far, just involve the presence of some virus as you can see in some reports [3], which include the HIV infection [4], these is presented an epidemic model based in population, statistical analysis for stochastic epidemic models is presented as well [5]. However the mathematical model of system of Mϕ and M with infection and without infection was presented also [2]. This model is two dimensional, nonlinear (polynomial of first grade).The M cells arise from myeloid precursor cells in primary lymphoid organs including the fetal liver and bone marrow, during both embryonic and adult hematopoiesis. On the other hand, Mϕ are produced as differentiation from M. Both M and Mϕ cells have crucial and distinct roles in tissue homeostasis and by consequence in the immune system, but they also contribute to a broad spectrum of pathologies and are thus attractive therapeutic targets. Potential intervention strategies that aim to manipulate these cells will require an in depth understanding of
their origins and the mechanisms that ensure their homeostasis. Recent evidence shows that M cells do not substantially contribute to most tissue Mϕ populations in the steady state or during certain types of inflammation. The main interest in this work is to maintain the production levels of these cells properly in a healthy state of the human body through the application of optimum control engineering techniques, when the levels of production are not adequate.

The objective of this work is to obtain the input equations control for the system of differential un homogeneous equations associated to the behavior of M and Mϕ cells. In adding, try its performance when the rate production of M cells and λ is modified (the values of λ can be increased or decreased, which may indicate abnormal healthy conditions or diseases). We believe that the verification of indices of M and Mϕ could provide important information about to discover diseases, which have not yet symptom, or it can help in the recovery after of chemotherapy treatment. The parameter λ in (1), into the state equation, makes that this system be nonlinear. x(t) denotes the population of M in time t, x(t) denotes the population of Mϕ cells. A cost function J is propose to have a measure of the performance of the system, where this cost function contains the energy spent into the system, for the state and for the term of control into the state equation. This cost function can be minimized or maximized obtaining the minimum energy applied, according with the state variable. Dynamic programming (Hamilton Jacobi Bellman) equation, [6] and maximum principle of Pontryagin, [7] are methodologies for obtaining the linear control equations since the 60’s can see in [8], [9] and in [10] it is presented the methodology employed in this work. Some examples and derivation of the control equations via methodologies mentioned can be seen in [11], [12]. For apply the linear control equations in a nonlinear system, it is introduced a parameter - λ; as an equilibrium term into the control law, for get a linear system and apply the equations of the linear control.

In this first steep, it is presented an engineering focus in which the state variables are controlled through the proposed optimal control law. The control input is considering as a medical treatment, which is applied in continuous form via IVs (intravenous fluids), applied each assigned time, in order to normalize the behavior of the state variables (reaching the asymptotic values). In previous work [13], the state x1(t) is controller through the control input, and state x2(t) is tracking to the asymptotic value through x1(t) in equation for x2(t). However the error for the state x2(t) is much greater than the error for x1(t). Now, in this work, it is applied the control input equations in both state variables x1(t) and x2(t) obtaining best results. The traditional control equations are applied and some results obtained, taking 50; 80; 120 percent of λ into the model from [2]. The results are in three tables for some values of parameter λ (rate of production of monocytes). One table presents results for case without control in both states x1(t) and x2(t). The second one with results of [13], with control in state x1(t). Third table contains values of the states with controls in both states. As a future work it is considered, the stochastic dynamic system and apply the stochastic nonlinear control risk-sensitive equations in both states with tracking. This work is organized as following: Section 2 examines a description of the model of monocytes and macrophage cells, in Section 3 is the problem statement, in Section 4 is the methodology, Section 5 the application, Section 6 results and in Section 7 are the conclusions.

2. Description of the model of monocytes and macrophages cells

The M and Mϕ cells originate from a common myeloid progenitor cell in the bone marrow. Under normal conditions, M cells circulate in the bloodstream for a very short time before undergoing spontaneous apoptosis, [14]. In response to differentiation factors, these M cells escape their apoptotic fate by differentiating into Mϕ cells, these with a longer life span found in almost every single organ,
The M cells are the biggest leucocytes, which are in the blood smears, and they can, achieve 12 to 20 μm of diameter with oval nucleus. The M cells originate in the bone marrow. Then they leave to the blood circulation. Some of these cells are in the tissues such as the liver sinusoids or the spleen, being part of the mononuclear phagocytic system. The function of the M and Mϕ is not only as phagocytic; the M and Mϕ are essentials cells for maintaining working adequately the immune system and produce cytokines (IL-1, IL-6 and TNF) as may be seen [16]. M and Mϕ are central cells of the innate immune system, responsible of defending against diverse pathogens. They comprise what was just recently recognized as a heterogeneous family of professional phagocytic cells responsible for the recognition and clearance of pathogens and dead cells, see [17]. The M and Mϕ cells play central roles in the initiation and resolution of inflammation, principally through phagocytosis, release of inflammatory cytokinesis, several reactive oxygen species (ROS) and the activation of the acquired immune system, [18]. Although M cells represent an important part of the host defense, accumulation of M cells can be harmful and aggravate diseases such as atherosclerosis, arthritis and multiple sclerosis, [19]. Recently, the realization that M/Mϕ play fundamental biological roles in development, wound healing, tissue homeostasis and even cancer progression prompted an urgency to understand the molecular mechanisms that determine their life span and cell fate. Excess production of monocytes causes monocytopenia. A low monocyte blood cell count increases susceptibility to infections. Bacteria that normally resides on human skin or those that are in the gastrointestinal and urinary tract cause the most common types of infections, resulting from monocytopenia. The system of two dimensions of linear non-homogeneous differential equations, which describes the population dynamic of monocytes and macrophages in time [2], is given by:

\[
\frac{dx_1(t)}{dt} = \lambda - \mu_1 x_1(t) - \varphi x_1(t),
\]

\[
\frac{dx_2(t)}{dt} = \varphi x_1(t) - \mu_2 x_2(t).
\]

Where \(x_1(t)\), \(x_2(t)\) represent the M and Mϕ cells population respectively at time \(t\). As it may see in table 1, the parameter \(\lambda\) is the index of production of M, approx. 11,000 cell/sec; see [20]. The M cells remain in the bone marrow less than 24 hours, then pass into the bloodstream and they distribute throughout the body. In a normal healthy adult, the average life of M cells, denoted by \(1/\mu_1\), is between 8 to 72 hours, see [20], [21]. When the M cells go out of blood capillaries and they are located in the tissues, they transformed in Mϕ cells.

The step of M to Mϕ cells is denoted by \(1/\varphi\), is often 8 to 12 hours, see [22]. \(1/\mu_2\) of 3 to 6 weeks, see [21] and they are replaced in an index of 1 percent for each day. The initial conditions are: \(x_1(0) = x_{01}; \ x_2(0) = x_{02}\). Figure 1 illustrates the mechanism of differentiation of monocytes to macrophages. The model consider that the macrophages are derived only of monocytes, however recently it was reached in [23], the macrophages are derived from embryonic precursors, are seeded before birth and can maintain themselves in adults by self-renewal. Considering this situation, as future work it should be taken into account and add other parameter in equation for the state \(x_2(t)\), that represent the rate production of macrophages, into the original model.
Figure 1. Diagram of the population of monocytes \((x_1(t))\) and macrophages \((x_2(t))\).

Table 1. Values of the parameters

<table>
<thead>
<tr>
<th>Parameter description</th>
<th>Reference</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\lambda), index of production of ((M))</td>
<td>[7]</td>
<td>(396 \times 10^5) cell/hr.</td>
</tr>
<tr>
<td>(\frac{1}{\mu_1}) Average of life time of ((M))</td>
<td>[7], [10]</td>
<td>8 - 72 hrs.</td>
</tr>
<tr>
<td>(\frac{1}{\phi}) Time in go from ((M)) to ((M\phi))</td>
<td>[23]</td>
<td>8 – 12 hrs.</td>
</tr>
<tr>
<td>(\frac{1}{\mu_2}) Average of life time of ((M\phi))</td>
<td>[10]</td>
<td>336 – 71080 hrs.</td>
</tr>
</tbody>
</table>

3. Problem statement

One particular situation was the large quantities handled in this kind of problems. As a solution of this problem, log transformation (logarithmic in base 10 transformation) is applied to the plot of states \(x_1(t), x_2(t)\), control \(u(t)\), criterion, \(J\). Values of the states in final time may be seen in figures 3 and 4, and errors values are in table 3. In table 2 may be seen the errors values when the control is not present in the states, for certain values of the production rate of monocytes, \(M\). These errors as can be seen are large respect to the errors of table 3, when the control is present in both states: \(M\) and \(M\phi\). The behavior of the states in normal conditions can see in figure 2 (under adequate values of parameter \(\lambda\) ). The initial conditions for the state (see [2]) are: \(x_1(0) = 0.1584 \times 109, x_2(0) = 0.16528 \times 1010; Log(x_1(0)) = (0.1584 \times 109) = 8.199; Log(x_2(0)) = Log(0.16528 \times 1010) = 9.21822030417\). The values of parameters \((\mu_1, \mu_2, \phi)\) in (1) are fixed and they are taken from table 1. The values of the asymptotes for the state are given by \(X_{1\text{max}} = 3168000000; X_{2\text{max}} = 16246487107.42\), (these were obtained in [13]), applying the log transformation, \(log(X_{1\text{max}}) = 8.5091, log(X_{2\text{max}}) = 10.21\). As can be seen in figure 2, the population of macrophages is greater than the population of monocytes because time of live is different, as shown in table 1. These asymptotic values were considered for state as normal in a healthy adult (free of infection).
4. Methodology

The regulator problem for linear tracking systems [11] is determined in this paper. In this case, the desired value of the state vector is not the origin; it is desirable, that the values of the state converge at the asymptotic value in final time. Given the linear state equation

\[ x(t) = Ax(t) + Bu(t). \]  

(2)

The performance measure to minimize takes the form:

\[ J = \frac{1}{2} [x(T) - r(T)]^T H [x(T) - r(T)] + \frac{1}{T} \int_{t_0}^{T} \left( (x(t) - r(t))^T Q (x(t) - r(t)) + u^T(t) R(t) u(t) \right) dt \]  

(3)

The fixed final time is \( T = 720 \text{hrs} = 1 \text{ month} \). \( H, Q \) and \( R \) are weighting matrixes of the state in final time, of the state in each \( t \) and of the control input \( u(t) \) respectively. In addition, \( H, Q \) are real symmetric positive semi definite matrices, and \( R \) is a real symmetric positive defined matrix. \( r(t) \) is the desired or reference value of the state vector, in this case \( r(t) \) take the form of the vector with components \( r_1(t) = X_{\text{max}} = 316800000, r_2(t) = X_{\text{max}} = 16246487107.42784 \) which are the asymptotic values. These values are obtained in [13]. The Hamiltonian equation is

\[ H(x(t), u(t), p(t), t) = \frac{1}{2} k (x(t) - r(t))^2 Q(t) + \frac{1}{2} k u(t)^2 R(u) + p^T(t) A x(t) + p^T(t) B u(t) \]  

(4)

Obtaining the partial derivative respect to \( x, u \) and substituting adequately, the control law equation is obtained, and it is given that

\[ u^*(t) = -R^{-1}(t) B^T K(t) x(t) - R^{-1}(t) B^T s(t). \]  

(5)

Where \( K(t), s(t) \) are the solution of the following matrix and vectorial differential equations:
\[ K(t) = -K(t)A - A^T K(t) - Q(t) + K(t)BR^{-1}(t)B^T K(t), \quad K(T) = H. \]

\[ s(t) = -[A^T - K(t)BR^{-1}(t)B^T]s(t) + Q(t)r(t), \quad s(T) = -Hr(T). \]  

The goal of the control with tracking problem is that the control law \( u(t) \) minimizes the cost function \( J \) and the values of the state converge to the asymptotic values.

5. Application

The methodology mentioned in last section will apply to obtain the control equations, since of the dynamical system (1) is controllable. From system (1), adding the control input \( u_1(t) - \lambda \) into the state \( x_1(t) \), the system (1) takes the form

\[
\frac{dx_1(t)}{dt} = -\mu_1x_1(t) - \phi x_1(t) + u_1(t), \quad \frac{dx_2(t)}{dt} = \phi x_1(t) - \mu_2x_2(t) + u_2(t).\]

Applying the linear control system equations for the tracking problem (5), (6) to the system (1) the control equations are:

\[
\begin{align*}
    u_1(t) &= R^{-1}(k_{11}(t)x_1(t) + k_{12}x_2(t)) - s_1(t), \\
    u_2(t) &= R^{-1}(k_{21}(t)x_1(t) + k_{22}x_2(t)) - s_1(t).
\end{align*}
\]

Where \( K_{ij} \), for \( i,j = 1,2 \) is the solution of the following differential equations of Riccati:

\[
\begin{align*}
    \dot{k}_{11}(t) &= -2k_{11}(t)(\mu_1 + \phi) + 2k_{12}(t)\phi + k_{11}^2(t) + k_{12}^2(t) - Q_{11}(t), \\
    \dot{k}_{12}(t) &= -k_{12}(t)(\mu_1 + \phi) + k_{12}(t)\mu_2 - k_{22}(t)\phi + k_{11}(t)k_{12}(t) + k_{22}(t)k_{12}(t) - Q_{12}(t), \\
    \dot{k}_{22}(t) &= 2k_{22}(t)\mu_2 + k_{22}^2(t) + k_{22}^2(t) - Q_{22}(t).
\end{align*}
\]

Where \( s_i(t), \quad i = 1,2 \) are the solutions of the following differential equations:

\[
\begin{align*}
    s_1(t) &= (\mu_1 + \phi + \frac{k_{11}(t)}{R})s_1(t) + (k_{12}(t) + \frac{\phi}{R})s_2(t) + As_2(t)Q_{12}(t) + As_1(t)Q_{11}(t), \\
    s_2(t) &= (-\phi + \frac{k_{22}(t)}{R})s_1(t) + (\mu_2 + \frac{k_{22}(t)}{R})s_2(t) + As_2(t)Q_{22}(t) + s_1(t)Q_{21}(t).
\end{align*}
\]

The state-weighting matrix \( Q \) and the final state weighting matrix \( H \) are symmetric matrices of design parameters chosen by the designer, depending on the control objectives. For instance, if the elements of \( H \) are selected larger, then the control will force the final state \( x(T) \) to be smaller to keep the values of cost function small. Weight matrices \( Q \) and \( H \) are assumed positive-semi definite \( (Q \geq 0, \quad H \geq 0) \). Thus \( Q \) and \( H \) have nonnegative eigenvalues so that \( x^T Q x \) and \( x^T(T)Hx(T) \) are nonnegative for all \( x(t) \). In other hand, \( R \) is positive definite \( (R > 0) \), that is \( R \) has positive eigenvalues so that \( u^T R u > 0 \) for all \( u(t) \). Then \( J \) is always bounded below by zero, and a sensible minimization problem results, according to [24].
The matrixes \( Q \) and \( H \) take the form:

\[
Q = 0.00001 \begin{pmatrix} 1 & 0 \\ 0 & 0.001 \end{pmatrix}, \quad H = 0.00001 \begin{pmatrix} 0.010 & 0 \\ 0 & 0.001 \end{pmatrix}.
\]

These sets of values were selected according with the dimensions of the problem. They were the best by minimize \( J \) and optimized the behavior of the states. With values less than these, the stability of the solution is broken. With values greater than these, \( J \) value grow even more. The values of \( J \) in tables 3 and 4 are large because the dimensions of the units in the problem are large \((x 10^9)\). In other hand, in this system, the cost for the stability of the state in the asymptotic values is large, for the energy control and for the energy of the states.

The system of equations (7), (8), (9), (10) and cost function equation \( J \) (3) are simulating in Scilab with initial conditions mentioned previously. In figure 2, you can see the asymptotic behavior of the state \((x_1(t) \) and \(x_2(t))\), free of infection and with normal values of parameter \( \lambda \) (rate of production of monocytes, \(x_1(t))\). Both states converge to the asymptotic values. In addition, it can be appreciated in figure 2, the population of macrophages is greater than monocytes, because the time of life for them is greater than the time of life of monocytes (as may be seen in table 1).

6. Results

The values of cost function \( J \) in (3), were minimized and the state reached the asymptotic values through simulation of system of equations (7), (8), (9), (10). In table 2, are the errors for the states \(x_1(t)\) and \(x_2(t)\), when the rate of production of monocytes is altered. These errors are computed as:

\[
e_i = |x_i(t) - r|, \quad \text{for} \quad i = 1, 2.
\]

Table 2. Values of the state variables without control input, for some values of parameter \( \lambda \).

<table>
<thead>
<tr>
<th>Factor *( \lambda )</th>
<th>( e_1 )</th>
<th>( e_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5( \lambda )</td>
<td>1.584E+8</td>
<td>84.8438E+8</td>
</tr>
<tr>
<td>0.8( \lambda )</td>
<td>0.6336E+8</td>
<td>48.2645E+8</td>
</tr>
<tr>
<td>1( \lambda )</td>
<td>0.6E+6</td>
<td>2.426E+9</td>
</tr>
<tr>
<td>1.2( \lambda )</td>
<td>6.336E+7</td>
<td>5.079E+7</td>
</tr>
<tr>
<td>1.5( \lambda )</td>
<td>1.584E+8</td>
<td>37.0873E+8</td>
</tr>
</tbody>
</table>

In table 2 it may be seen the values of errors are greater than when the control input is applied to state \( x_1(t) \) and tracking in the state \( x_2(t) \), which is illustrate in table 4. In table 3 it may be seen the errors and cost function values when control input was applied to state \( x_1(t) \) and \( x_2(t) \) with tracking in both states. As can be appreciated the errors values are smaller in table 3. In figure 3, you may see graphic of states with controls, in both states \( x_1(t) \) and \( x_2(t) \) when rate of production of \( x_1(t) \) (monocytes (M)), the parameter \( \lambda \), is multiplying by 1.5.
Each alteration in the production rate of monocytes (\( \lambda \)), produce a sick in the organism as mentioned before. In this work the goal is to show that the states reach the asymptotic values applying the equations of optimal control with tracking in both states.

Table 3. Errors obtained and value of cost function \( J \), for each value of \( \lambda \) multiplied for each factor: 0.50, 0.80, 1.20, 1.50 and controls in both states: \( x_1(t) \) and \( x_2(t) \) and tracking in both states.

<table>
<thead>
<tr>
<th>Factor *( \lambda )</th>
<th>( e_1 )</th>
<th>( e_2 )</th>
<th>Cost function ( J )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1.4288939</td>
<td>1.258925</td>
<td>3.81\times10^{14}</td>
</tr>
<tr>
<td>0.8</td>
<td>1.258925</td>
<td>1.177605</td>
<td>3.32\times10^{14}</td>
</tr>
<tr>
<td>1</td>
<td>1.1776059</td>
<td>1.129795</td>
<td>3.06\times10^{14}</td>
</tr>
<tr>
<td>1.2</td>
<td>1.0864256</td>
<td>1.096478</td>
<td>2.86\times10^{14}</td>
</tr>
<tr>
<td>1.5</td>
<td>1.0495424</td>
<td>1.009485</td>
<td>2.67\times10^{15}</td>
</tr>
</tbody>
</table>

Table 4: Values of the state variables with control input in \( x_1(t) \) and tracking in \( x_2(t) \) for some values multiplying the parameter \( \lambda \). (From [13]).

<table>
<thead>
<tr>
<th>Factor *( \lambda )</th>
<th>error 1</th>
<th>error 2</th>
<th>( J )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 ( \lambda )</td>
<td>44573.52</td>
<td>1982552.5</td>
<td>1.045E+21</td>
</tr>
<tr>
<td>0.8 ( \lambda )</td>
<td>17514.37</td>
<td>793279.15</td>
<td>1.943E+22</td>
</tr>
<tr>
<td>1 ( \lambda )</td>
<td>526.55</td>
<td>431.44</td>
<td>4.44E+22</td>
</tr>
<tr>
<td>1.2 ( \lambda )</td>
<td>18564.78</td>
<td>792418.27</td>
<td>7.961E+22</td>
</tr>
<tr>
<td>1.5 ( \lambda )</td>
<td>45624.041</td>
<td>1981691.7</td>
<td>1.515E+23</td>
</tr>
</tbody>
</table>
Figure 3. Graphic of states with controls, in states $x_1(t)$ and $x_2(t)$ (7), when production rate of $x_1(t)$ (monocytes (M)), the parameter $\lambda$, is multiplying by 1.5.

Figure 4. Graphic of criterion function $J$ for 1.5$\lambda$.

In figure 4 the values of the exponential quadratic function $J$ are illustrate for 1.5$\lambda$. As you may see the cost for reach the stabilization of the states is expensive, for both, by states and by control.

7. Conclusions
Strategies of linear control with follow-up are apply to the system of dynamic equations that model the monocyte and macrophages system in an adult person. In this case, the control strategy was applied to both states, obtaining better results than when it apply only to one state because the values of the states converges closely to the asymptotic values, that is to say the errors were smaller. We consider this work to be of great importance since the timely detection, through a blood test, of the levels of monocytes and macrophages could prevent terminal diseases. This, before the symptoms appear. Because frequently when the disease is detected is too late since the organs are very damaged, as is the case like with cancer. In this work, we propose the preventive control of diseases with dynamic control of parameters of the immunological processes, that provoke some diseases. This, before the symptoms appear. The expected impact of the control input applied is to make a regulation of the basal biological effect, considered from a medical point of view.

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