IJAMEC
e-ISSN: 2147-8228

INTERNATIONAL JOURNAL OF APPLIED MATHEMATICS ELECTRONICS AND COMPUTERS

www.dergipark.org.tr/ijamec

International Open Access

Volume 08
Issue 04

December, 2020

Research Article

Robust Constrained Drug Dosage Regulation of Acute Inflammation Response Under Disturbances

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ARTICLE INFO

Article history:
Received 23 October 2020
Accepted 1 December 2020

Keywords:
Aseptic and septic cases,
Disturbance,
Inflammation response,
Sliding mode control,

ABSTRACT

Mathematical modelling of the biological processes, diseases and organs are important for the model-based control of diseases. Due to unmodeled dynamics, unknown and external disturbances, the performance of controllers based on these models are degraded for the accurate control. Therefore, robust controllers are need especially for the applications on patients. Inflammation, the cause of many complex biological phenomena and diseases, is a nonlinear process that is difficult to control. In this paper, continuous-time sliding-mode controller has been designed for the control of acute inflammation response (AIR) and antibacterial drug infusion under external disturbances both for septic and aseptic cases. Sliding-mode controller (SMC) is mostly used to control nonlinear systems against external disturbances and parametric uncertainties. Beside the control signal generation, we propose constraints on the control signals based on the clinical experiences such that the applied control signal is suitable for the health and improves the performance of the controller. Due to the multiple equilibrium point on the behavior of the acute inflammation response, it is difficult to design such model-based controllers without input constraints. In the numerical applications, septic death case and aseptic death case with disturbances are controlled and acceptable performances are obtained for future clinical applications.

1. Introduction

Inflammation is the center of complex biological processes such as autoimmune diseases, depression, chronic lung disease, coronary heart disease, Alzheimer and several types of cancer [1]. The immune system's response to pathogenic infection caused by invading bacteria and the secreted inflammatory mediators, such as activated phagocytes and pro-inflammatory cytokines occurs as inflammation [2, 3]. Control of this process is very important for the recovery of critical patients, as inflammation can destroy the immune system [4]. It is possible to eliminate tissue-damaging inflammation with anti-inflammatory drugs [5], but for some critical conditions, therapy optimization is required in the response of the immune system [6].

Recently, most diseases have been mathematically modeled in differential equations as nonlinear time-varying processes. There are some studies in the literature with predictive or optimal control content for optimization of anti-inflammatory and antibacterial drug infusion. In [7], nonlinear model predictive control was applied to determine the appropriate therapeutic intervention for silico patients with complex inflammatory conditions. In [8], a nonlinear optimal control approach has been proposed for the acute inflammatory model of the human body that describes the reaction to bacterial infection. An optimal control strategy given with a pro-inflammatory and anti-inflammatory drug therapy was presented in [9]. In [10], an algorithm for state estimation in nonlinear acute inflammation models has been developed using the particle filter.

Sliding-mode controller (SMC), which is mostly used to control nonlinear systems against external disturbances and parametric uncertainties, is known as a robust controller [11, 12]. SMC is used for reference tracking in

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DOI: 10.18100/ijamec.815606

systems whose mathematical model is known. However, for unknown models or much noised systems, it is preferred to generate a control input together with the identifier modeling the system. In addition, there are several studies in the literature where biological phenomena or diseases are controlled by the sliding mode controller. For example, in [13], closed loop control algorithm has been proposed based on SMC for optimal control of blood glucose concentration in type-1 diabetes patients. In [14], in the presence of model uncertainties, a robust nonlinear adaptive sliding-mode control strategy was presented for influenza epidemics to reduce the number of susceptible and infected humans to zero. In [15], robust super-twist sliding-mode controller has been designed based on output information for an uncertain human immunodeficiency virus (HIV) infection model. In addition to the aforementioned studies, research on SMC-based acute inflammation control is still limited.

In this study, continuous-time sliding-mode controller is designed for the control of anti-inflammatory and antibacterial drug infusion under external disturbances. The disturbance function has been considered as a total uncertainty function such that it includes internal and external disturbances such as parameter uncertainties, noises, temperature, humidity and etc. In numerical applications, aseptic and septic case treatment results are shown that very accurate control results are obtained for future applications. The rest of the paper is organized as follows. In Section 2, the mathematical model of the acute inflammation response and its parameters are given. Then, sliding mode controller is described in Sections 3. Numerical results and conclusion are presented in Section 4 and Section 5, respectively.

2. Mathematical Modeling of Inflammation Response

The control of the acute inflammatory, which occurs with biological factors such as severe infection or trauma, ensures the adaptation of the organism to stress, eliminates pathogens, promotes tissue repair and healing. The dynamics of the acute inflammatory response to the pathogenic infection was proposed in [2] as

$$\begin{aligned}
\dot{P} &= k_{pg}P(1-\frac{P}{P_\infty}) - \frac{k_{pm}s_mP}{\mu_m + k_{mp}P} - k_{pn}f(N^*)P, \\
\dot{N}^* &= \frac{s_{nr}R}{\mu_{nr}+R} - \mu_nN^* + u_p(t), \\
\dot{D} &= k_{dn}\frac{f^6(N^*)}{x_{dn}^6 + f^6(N^*)} - \mu_dD, \\
\dot{C}_A &= s_c + k_{cn}\frac{f(N^* + k_{cnd}D)}{1+f(N^*+k_{cnd}D)} - \mu_cC_a + u_a(t),
\end{aligned} \tag{1}$$

where

$$R = f(k_{np}P + k_{nn}N^* + k_{nd}D), \tag{2}$$

and

$$f(x) = \frac{x}{1+(\frac{C_A}{c_\infty})^2}. \tag{3}$$

where P represents the bacterial pathogen population that causes inflammation. N^* is associated with managing activated phagocytes and early pro-inflammatory mediators produced by N^*. D refers to tissue damage that helps to determine the response outcomes. C_A is the anti-inflammatory mediators such as cortisol and interleukin-10 [16]. The production of anti-inflammatory mediator is associated with the presence of activated phagocytes and markers of high tissue damage. This mediator is responsible for preventing excessive tissue damage caused by severe inflammation. In this way, inflammation is directly alleviated. While N^* and C_A represent multiple mediators with similar inflammatory properties, D is an indication of collateral tissue damage caused by inflammatory by-products. These mediators are crucial in mitigating severe inflammation and are also responsible for preventing organ damage and high proliferation of the pathogen. u_a and u_p are time-varying input controls for the anti-inflammatory and pro-inflammatory therapy, respectively. $f(x)$ term in Eq. (3) models the effect of activated phagocytes and their by-products on the formation of damaged tissue. The defined parameter values for the inflammation response given in Eq. (1), (2) and (3) are presented in Table 1.

As mentioned in [16], the acute inflammation response model has three stable equilibrium points: healthy, aseptic and septic which can be interpreted consistent with clinical outcomes. In the healthy case; $P = N^* = D = 0$ and C_A is at the background level. In the aseptic case; N^*, C_A and D mediators are elevated and pathogen P has been eliminated. In the septic case; all mediators (N^*, C_A and D) with pathogen P are at high levels.

3. Sliding-Mode Control

The control law is based on the known mathematical model of the nonlinear system and the design of the sliding-mode controller has two phases. The first one is to select the sliding surface (or manifold), so that the states are restricted to the sliding surface with desired dynamics. The second phase consists in designing a control law that drives the states to the sliding surface and then keeps the states there. An n th-order nonlinear system can be

described as

$$\begin{aligned} \dot{x}_1 &= x_2, \\ \dot{x}_2 &= x_3, \\ &\vdots \\ x^{(n)} &= f(x) + g(x)u \\ y &= x_1 \end{aligned} \tag{4}$$

Table 1. Parameters of the acute inflammatory response model [2].

k_{pm}	0.6	M units hr
k_{mp}	0.01	P units hr
s_m	0.005	M units hr
μ_m	0.002	hr
k_{pg}	various in range $(0.021 - 2.44)$	hr
p_∞	20×10^6	cc
k_{pn}	1.8	N^* units hr
k_{np}	0.1	P units hr
k_{nn}	0.01	N^* units hr
s_{nr}	0.08	$N_R$unitshr
μ_{nr}	0.12	hr
μ_n	0.05	hr
k_{nd}	0.02	D units hr
k_{dn}	0.35	units of Dhr
x_{dn}	0.06	N^* units
μ_d	0.02	hr
c_∞	0.28	C_A units
s_c	0.0125	$C_A$unitshr
k_{cn}	0.04	$C_A$unitshr
k_{cnd}	48	N^*units$D$ units
μ_c	0.1	hr

For nth-order nonlinear system defined in (4), $u \in \mathbb{R}$ and $y \in \mathbb{R}$ are input and output values, respectively and $\boldsymbol{x} = [x_1, x_2, , x_n]^T \in \mathbb{R}$ is state vector. $f(x)$ and $g(x)$ are nonlinear functions that determine system properties, assuming that their nominal values and bounds are known. The control task is to track the reference signal x_d, where the tracking error is defined as $e = x - x_d$. In addition, the derivatives of the e is defined as $e = [e, \dot{e}, \dots, e^{(n-1)}]^T$. The sliding surface $s(x,t) = 0$ with initial conditions $e(0) = 0$ can be defined as [11]

$$s(x;t) = (\frac{d}{dt} + c)^{n-1} e, \tag{5}$$

where c is a positive real constant that determine the slope of the sliding surfaces. Lyapunov's direct method can be used to obtain a control signal that can keep the trajectory on the sliding surface. Thus, the tracking error will asymptotically reach zero. $V = \frac{1}{2}s^2$ is a candidate Lyapunov function with $V(0) = 0$ and $V(s) > 0$ for $s > 0$ [11]. To keep the value of sliding surface at zero, the input signal is designed to satisfy

$$\dot{V} = \frac{1}{2}\frac{d}{dt}s^2 \leq -\eta|s|, \tag{6}$$

$$s\dot{s} \leq -\eta|s|, \tag{7}$$

where η is a strictly positive real constant. Ensuring the inequality in equation (6) means that the system is stable and will always be controlled by moving towards the sliding surface. For a second-order system ($n = 2$), the dynamics of the sliding mode can be written as follows:

$$\dot{s} = \ddot{e} + c\dot{e} = f_0(x) + g_0(x)u - \ddot{x}_d + c\dot{e} \leq -\eta|s|, \tag{8}$$

To achieve $\dot{s} = 0$, the equivalent control input of the system is derived as

$$u_{eq} = \frac{1}{g(x)}(-\hat{f}(x) + \ddot{x}_d - c\dot{e}), \tag{9}$$

To satisfy the dynamics in (7) and to reach the desired states in finite time a discontinuous control part is added to input (9) as

$$u = u_{eq} + u_c = \frac{1}{g(x)}(-\hat{f}(x) + \ddot{x}_d - c\dot{e}) - k\text{sgn}(s), \tag{10}$$

where k is a strictly positive real constant with a lower bound depending on the estimated system parameters. u_{eq} term in (10) is based on estimated system parameters and compensating for the estimated undesirable dynamics of the system. In addition, the second term (u_c) with the signum function requires infinite switching on the intersection of the error trajectory and the sliding surface.

sgn(.) is the signum function

$$\text{sgn}(s) = \begin{cases} +1 & s \geq 0, \\ -1 & s < 0, \end{cases} \quad (11)$$

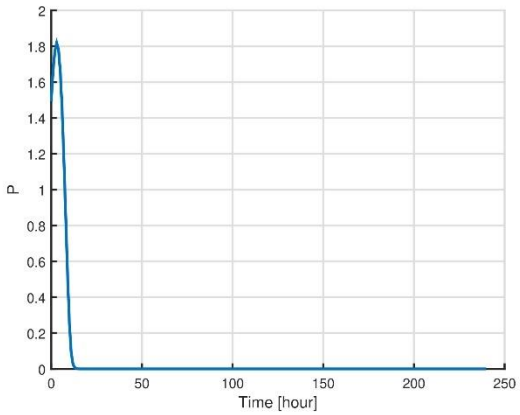
$$k \geq \beta(F + \eta) + (\beta - 1)|u_{eq}| \quad (12)$$

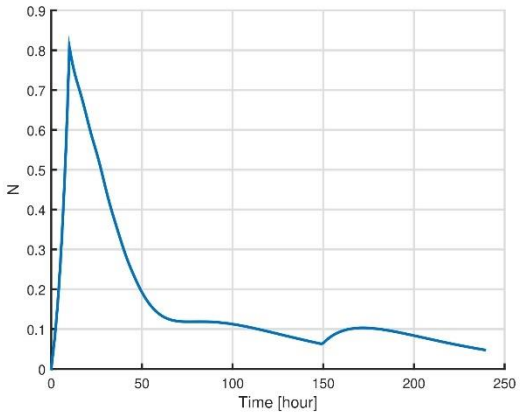
where $\beta = \sqrt{\frac{g_{max}(x)}{g_{min}(x)}}$ is a positive constant. By using (10) with k satisfying (12), one obtains

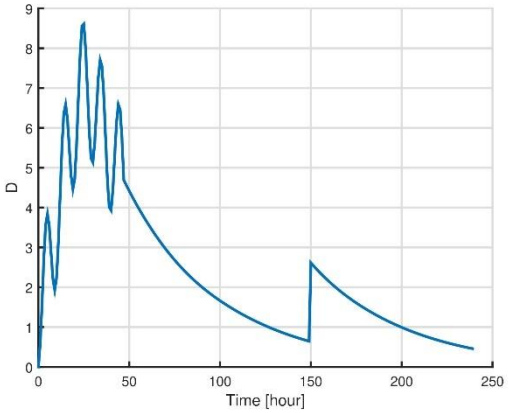
$$\dot{s}s \leq -\eta|s| = -\eta s\text{sgn}(s) \quad (13)$$

The value of k is an important design parameter of the sliding-mode controller. It must satisfy equation (6) and it influences the convergence of the tracking error. The control input eventually drives the dynamics of s and e to zero. However, it may cause oscillations (or chattering) on the sliding surface. To avoid the chattering effect, the signum function can be replaced with other functions. The well−known approach is to use a saturation function [11]

$$\text{sat}(\sigma) = \begin{cases} \sigma & \sigma < |1|, \\ \text{sgn}(\sigma) & \text{otherwise}, \end{cases} \quad (14)$$







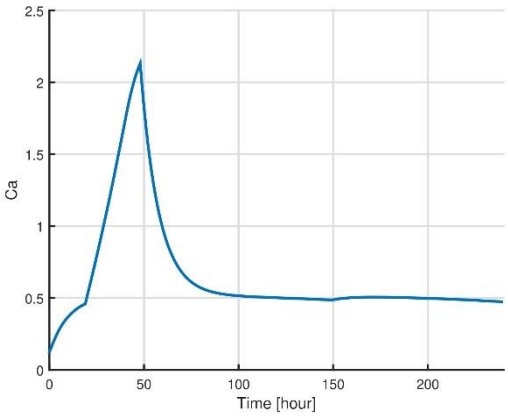


Figure 1. Aseptic case: sliding-mode control of inflammation response.

a) Pathogen b) Activated Phagocytes c) Tissue Damage d) Anti-inflammatory Mediator

4. Numerical Applications

In this section, numerical results obtained by sliding-mode controller are presented for regulating the drug dosage of acute inflammatory response in aseptic and septic cases under disturbances. The sliding-mode controller is designed in conventional form without any modifications. The measured states of acute inflammatory response model are N^* and C_A and in simulations, the sampling time is chosen clinically appropriate as 1-hour. The simulations have evaluated as 240-hours to observe 10-day period under disturbances. According to acute inflammatory response model, the k_{pg} parameter of the pathogen status makes it very difficult to control the septic case. The sliding-mode controller designed here effectively controls both cases, even under disturbances.

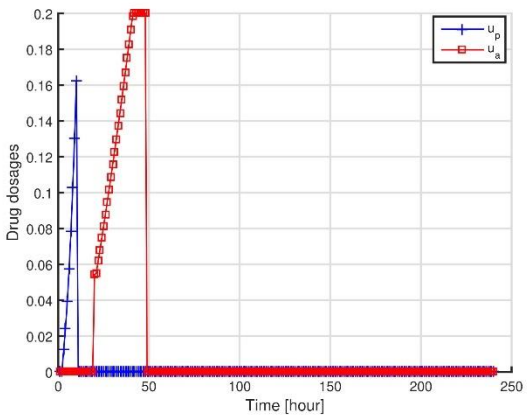
4.1. Constraints on the control dosages

Constraints of drug doses (anti-inflammatory and pro-inflammatory therapy) calculated with the acute inflammation response model are very important for the

clinical compatibility. Overdose medication given at once may cause death of the patient, and lower doses may prolong the recovery period of the disease. In addition, it is known that maintaining high levels of anti-inflammatory doses for a longer period plays a major role in the predisposition to secondary infections that can lead to the death of patients [17, 4]. In this study, a protocol was followed in which anti-inflammatory therapy was initiated at the 10th hour of therapy and the dose of both anti-inflammatory and pro-inflammatory therapy was discontinued at the 50th hour of treatment. Eventhough, the control dosages are generated nonzeore after 50th hour by the designed controller, the dosages are constraint to zero value.

4.2. Aseptic case

The non-infectious levels of all variables ($P = 0$) except the pathogen for the inflammatory response model constitute the aseptic case. Exceeding the limits of inflammatory dynamics (P, N^*, D, C_A) forces the patient to stabilize the healthy state with optimum therapy. Otherwise, the immune system becomes unable to cope with this increased pathogen attack. In this study, simulation results of the sliding-mode control used to calculate the drug dosages with optimum therapy are shown in Figure 1. The initial conditions for aseptic case of the inflammatory response dynamics are selected as $P = 1.5, N^* = 0, D = 0, C_A = 0.125$ and $k_{pg} = 0.3$. Results from Fig. 1 (a) to Fig. 1 (d) express the dynamics of acute inflammatory response obtained using the initial conditions in aseptic case. Anti-inflammatory ($u_a(t)$) and pro-inflammatory ($u_p(t)$) therapy signals obtained in the presence of disturbance are shown in Fig. 2 (a). Disturbance signal and shot noise are shown in Fig.2 (b).



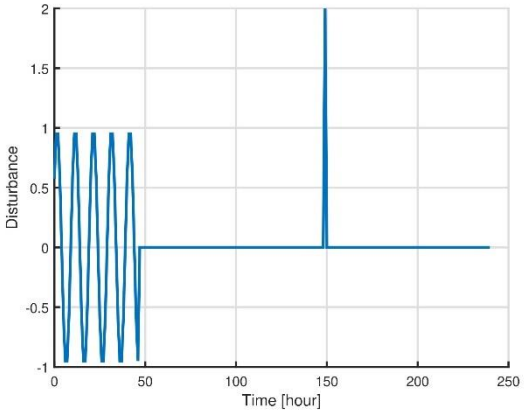


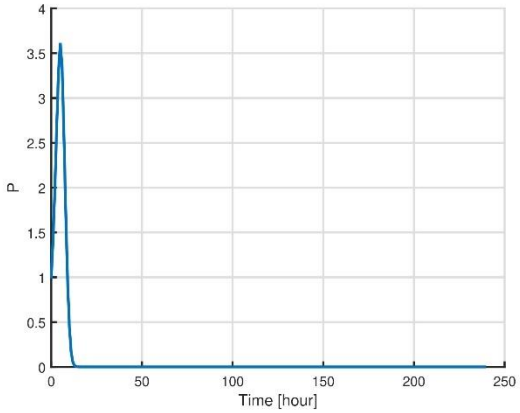
Figure 2. Control dosages of aseptic case and unknown disturbance for septic and aseptic case.

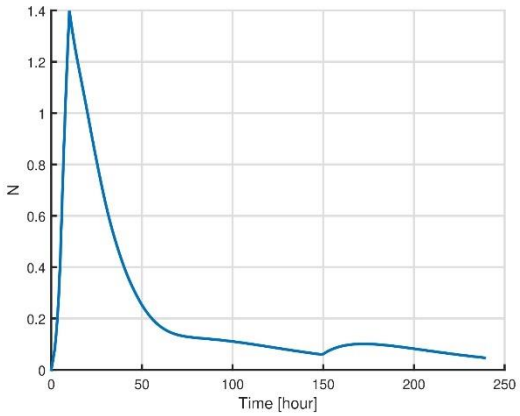
a) Control signals b) Disturbance signal and shot noise

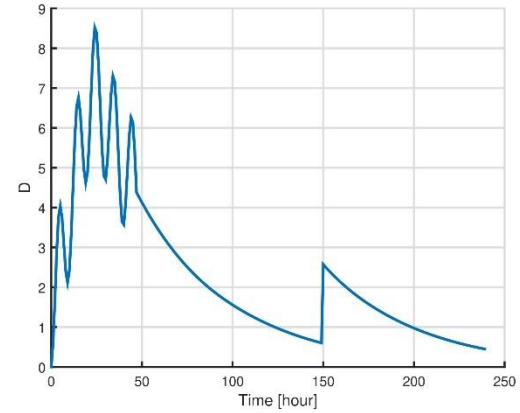
4.3. Septic case

The increase of the pathogen with other variables causes septic condition, that is, all mediator and pathogen values are at high levels. The aim of optimal therapy based on SMC in septic case is to use the lowest drug dosages by minimizing the levels of pathogen and damage so that $P = 0$ and $D = 0$. The simulation results related to septic case are shown in Figure 3. The initial conditions for septic case of the inflammatory response dynamics are selected as $P = 1, N^* = 0, D = 0, C_A = 0.125$ and $k_{pg} = 0.6$. Results from Fig. 3 (a) to Fig. 3 (d) express the dynamics of acute inflammatory response obtained using the initial conditions in septic case. Anti-inflammatory ($u_a(t)$), pro-inflammatory ($u_p(t)$) therapy signals obtained in the presence of disturbance are shown in Fig. 4, respectively and the same disturbance function has been applied in septic case as in aseptic case.

According to the simulation results, the occurrence of a pro-inflammatory response (N^*) is related to increase in the amount of pathogen (P). The large N^* value causes tissue damage, destroying the pathogen faster. This result also reduces N^* while activating the anti-inflammatory response (C_A). C_A inhibits D tissue damage caused by N^*, while there is no need to have $N^* = 0$. The aim is to provide a balance between $P = 0$ and $D = 0$ targets, and to make the patient in healthy case.







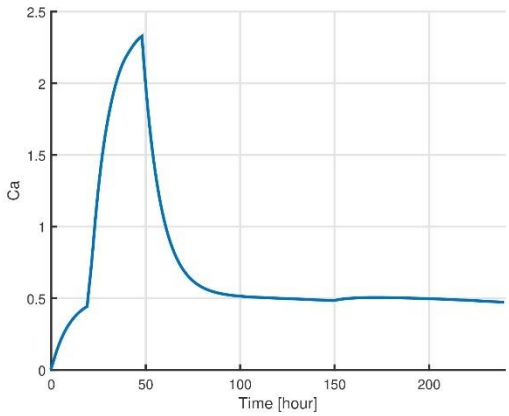


Figure 3. Septic case: sliding-mode control of inflammation response.

a) Pathogen b) Activated Phagocytes c) Tissue Damage d) Anti-inflammatory Mediator

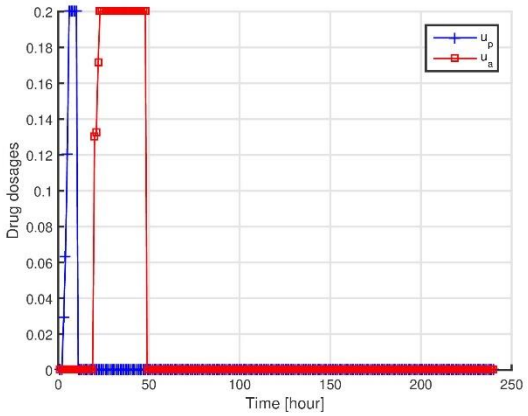


Figure 4. Control dosages of septic case.

5. Conclusion

This paper proposed sliding-mode controllers for the treatment of acute inflammation response under unknown disturbances. Due to the robust structure of the sliding-mode control, disturbances are suppressed and accurate stabilization performances are obtained with constraint drug dosage inputs. These constraints on the input dosages provide confidence of the treatment and improve the effectiveness of the control method. In future applications, the constraints and robust performance of the proposed controllers with observer-based and adaptive structures can be proposed for more flexible and accurate treatments.

Author's Note

Abstract version of this paper was presented at 9th International Conference on Advanced Technologies (ICAT'20), 10-12 August 2020, Istanbul, Turkey with the title of "Robust Constrained Drug Dosage Regulation of Acute Inflammation Response Under Disturbances".

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