Robust model matching control of immune systems under environmental disturbances: Dynamic game approach

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A robust model matching control of immune response is proposed for therapeutic enhancement to match a prescribed immune response under uncertain initial states and environmental disturbances, including continuous intrusion of exogenous pathogens. The worst-case effect of all possible environmental disturbances and uncertain initial states on the matching for a desired immune response is minimized for the enhanced immune system, i.e. a robust control is designed to track a prescribed immune model response from the minimax matching perspective. This minimax matching problem could herein be transformed to an equivalent dynamic game problem. The exogenous pathogens and environmental disturbances are considered as a player to maximize (worsen) the matching error when the therapeutic control agents are considered as another player to minimize the matching error. Since the innate immune system is highly nonlinear, it is not easy to solve the robust model matching control problem by the nonlinear dynamic game method directly. A fuzzy model is proposed to interpolate several linearized immune systems at different operating points to approximate the innate immune system via smooth fuzzy membership functions. With the help of fuzzy approximation method, the minimax matching control problem of immune systems could be easily solved by the proposed fuzzy dynamic game method via the linear matrix inequality (LMI) technique with the help of Robust Control Toolbox in Matlab. Finally, in silico examples are given to illustrate the design procedure and to confirm the efficiency and efficacy of the proposed method.

1. Introduction

A dynamic response of the immune system, which includes innate immune system and adaptive immune system, is induced by infectious microbes or environmental disturbances. The innate immune system provides a tactical response, signaling the presence of ‘non-self’ organisms and activating B cells to produce antibodies to bind to the intruders’ epitopic sites. The antibodies identify targets for scavenging cells that engulf and consume the microbes, reducing them to non-functioning units (Stengel et al., 2002b). The antibodies can also stimulate the production of cytokines, complement factors and acute-phase response proteins that either damage an intruder’s plasma membrane directly or trigger the second phase of immune response. The innate immune system protects against many extracellular bacteria or free viruses found in blood plasma, lymph, tissue fluid, or interstitial space between cells, but it cannot clean out microbes that burrow into cells, such as viruses, intracellular bacteria, and protozoa (Lydyard et al., 2000; Stengel et al., 2002b; Janeway, 2005).

Activated by the innate immune response, the adaptive immune system could provide strategic response to invading microbe and yield protective cells. These protective cells could remember specific antigens and produce antibodies to counter the antigens, and seek for epitopes of antigens on the surfaces of infected cells. It is found that adaptive immune mechanisms depend on the actions of B- and T-lymphocytes that become dedicated to a single antibody type through clonal selection. Meanwhile, killer T-cells (or cytotoxic T-lymphocytes) bind to infected cells and kill them by initiating programmed cell death (apoptosis). In addition, helper T-cells assist naive B-cells in maturing into plasma cells that produce the needed antibody type. Finally, immune cells with narrowly focused memory are generated, ready to respond rapidly if invading microbes with the same antigen epitopes are encountered again. Elements of the innate and adaptive immune systems are shared, and response mechanisms are coupled, even though distinctive modes of operation can be identified (Lydyard et al., 2000; Stengel et al., 2002b; Janeway, 2005).
For clinical treatment of infection, the current therapeutic methods focus on killing the invading microbes, neutralizing their response, and providing palliative or healing care to affected organs of the body. Few biological or chemical agents have adverse side effects; for example, an agent that kills a virus may also damage healthy ‘self’ cells. A critical function of drug discovery and development is hence to identify new compounds that have maximum intended efficacy with minimal side effects on the general population. These examples include antibiotics as microbe killers; interferons as microbe neutralizers; interleukins, oncostatics, and monoclonal antibodies as immunity enhancers; and anti-inflammatory and anti-histamine compounds as palliative drugs (Stengel et al., 2002b).

Recently, there are many models of immune response to infection (Asachenkov, 1994; Rundell et al., 1995; Perelson and Weisbuch, 1997; Nowak and May, 2000) with special emphasis on the human-immunodeficiency virus (Perelson et al., 1993, 1996; Nowak et al., 1995; Stafford et al., 2000). Some papers have discussed immune defense models with moving target strategy (Adler and Karban, 1994). Wiener (1948) and Bellman (1983) appreciated and anticipated the application of mathematical analysis to treatment in a broad sense, and Swan (1981) surveys early optimal control applications to biomedical problems. Notably, Kirschner et al. (1997) offers an optimal control approach to HIV treatment, and intuitive control approaches are presented (De Boer and Boucher, 1996; Bonhoeffer et al., 1997; Wein et al., 1998; Wodarz and Nowak, 1999, 2000).

The dynamics of drug response (pharmacokinetics) have been modeled in several works (Robinson, 1986; Van rossum et al., 1986) and control theory is applied to drug delivery in other studies (Bell and Katusiime, 1980; Carson et al., 1985; Chizeck and Katona, 1985; Jelliffe, 1986; Schumitzky, 1986; Kwong et al., 1995; Polycarpou and Conway, 1995; Parker et al., 1996; Gentilini et al., 2001). Recently, Stengel et al. (2002a) presented a simple model for the response of the innate immune system to infection and therapeutic intervention, reviewed the prior method and results of optimization, and introduced a significant extension to the optimal control of enhancing immune response by solving a two-point boundary-value problem via an iterative method. Their results show not only the progression from an initially life-threatening state to a controlled or cured condition but also the optimal history of therapeutic agents that produces that condition. In their study, the therapeutic method is extended by adding linear-optimal feedback control to the nominal optimal solution. However, the performance of quadratic optimal control for immune systems may be decayed by the continuous exogenous pathogens input, which is considered as an environmental disturbance of the immune system. Furthermore, some overshoots may occur in the optimal control process and may lead to organ failure because the quadratic optimal control only minimizes a quadratic cost function that is only the integration of squares of states and allows the existence of overshoot (Zhou et al., 1996). A series dynamic optimization method is therefore proposed to design the optimal schedule for host defense, immune memory and post-infection pathogen levels in mammals (Shudo and Iwasa, 2001, 2002, 2004; Shudo et al., 2003).

In this study, a robust model matching control of immune response is proposed for therapeutic enhancement to match a desired immune response under uncertain exogenous pathogens input, environmental disturbances and uncertain initial states. Because of the uncertainties of these factors mentioned above, in order to attenuate their detrimental effects, their worst-case effects should be considered in the matching control procedure from the robust design perspective. The worst-case effect of all possible uncertain factors on the matching error to a desired immune response is minimized for the enhanced immune systems, i.e. the proposed robust model matching control is designed from the minimax matching perspective. This minimax matching could be transformed to an equivalent dynamic game problem (Basar and Olsder, 1999). The exogenous pathogens input is considered as a player to maximize (worsen) the matching error, while the therapeutic control agent is considered as another player to minimize the matching error. Since the innate immune system is highly nonlinear, it is not easy to solve the robust model matching control problem by the nonlinear dynamic game method directly. Recently, fuzzy systems have been employed to efficiently approximate nonlinear dynamic systems to solve the nonlinear control problem (Chen et al., 1999, 2000; Lian et al., 2001; Li et al., 2004). A fuzzy model is proposed to interpolate several linearized immune systems at different operating points to approximate the innate immune system via smooth fuzzy membership functions. Then, with the help of fuzzy approximation method, a fuzzy dynamic game scheme is developed so that the minimax matching control of immune systems could be easily solved by the linear dynamic game method, which can be subsequently solved by a constrained optimization scheme via the linear matrix inequality (LMI) technique (Boyd, 1994) with the help of Robust Control Toolbox in Matlab. Because the fuzzy dynamic model can approximate any nonlinear dynamic system, the proposed model matching method via fuzzy game theory can be applied to the robust control design of any model of immune system that can be Takagi–Sugeno (T–S) fuzzy interpolated. Finally, the computational simulation examples considering the side effect of agents are given to illustrate the design procedure and to confirm the efficiency and efficacy of the proposed minimax match control method for immune systems.

2. Model of immune response

For the principal goals to study the general course of a disease and to clarify some observational results, a simple four-nonlinear, ordinary differential equation for the dynamic model of infectious disease is introduced as the following equations to describe rates of change of pathogen, immune cell and antibody concentrations and of an indicator of organic health (Asachenkov, 1994; Stengel et al., 2002a). A more general dynamic model will be given next in sequel:

\[
\begin{align*}
\dot{x}_1 &= (a_1 - a_2 x_3) x_1 + b_1 u_1 + w_1, \\
\dot{x}_2 &= a_2 (x_4) x_2 x_3 - a_3 (x_2 - x_4^2) + b_2 u_2 + w_2, \\
\dot{x}_3 &= a_3 x_2 - (a_3 + a_3 x_1) x_3 + b_3 u_3 + w_3, \\
\dot{x}_4 &= a_4 x_1 - a_4 x_4 + b_4 u_4 + w_4, \\
a_2 (x_4) &= \begin{cases} 
\cos(\pi x_4), & 0 \leq x_4 \leq 1/2, \\
0, & 1/2 < x_4.
\end{cases}
\end{align*}
\]

where \(x_1\) denotes the concentration of a pathogen that expresses a specific foreign antigen, \(x_2\) denotes the concentration of immune cells that are specific to the foreign antigen, \(x_3\) denotes the concentration of antibodies that bind to the foreign antigen, \(x_4\) denotes the characteristic of a damaged organ (\(x_4 = 0\): healthy, \(x_4 \geq 1\): dead). The combined therapeutic control agents and the exogenous inputs are described as follows: \(u_1\) denotes the pathogen killer’s agent, \(u_2\) denotes the immune cell enhancer, \(u_3\) denotes the antibody enhancer, and \(u_4\) denotes the organ healing factor (or health enhancer), and \(w_i\) denotes the rate of continuing introduction of exogenous pathogens. \(w_2-w_4\) denote the environmental disturbances or unmodeled errors and residues. \(a_2 (x_4)\) is a nonlinear function that describes the mediation of immune cell generation by the damaged cell organ. And if there is no antigen, then the immune cell maintains the steady equilibrium value of
3. Robust therapeutic control of immune response

The optimal control is to specify $u(t)$ such that the following cost function is minimized (Stengel et al., 2002a):

$$J = \frac{1}{2} \int_{0}^{T} \left( x^T(t)Qx(t) + u^T(t)Ru(t) \right) dt,$$

where $P$, $Q$, and $R$ are weighting matrices to be specified by designer. Because the quadratic control is only to minimize $J$ in Eq. (3), i.e. the integration of $x^T(t)Qx(t) + u^T(t)Ru(t)$ to be minimized, a control leading to large overshoot of $x(t)$ but with small integration of $x^T(t)Qx(t)$ may be specified in the quadratic optimal control design (Zhou et al., 1996). This therapeutic control will lead to organ failure because $x_d(t) > 1$. Furthermore, the cost function does not include exogenous pathogens and environmental disturbances $w(t)$, which may degrade the performance of the quadratic optimal control. Therefore, it is more appealing to prescribe a desired time response of the disease dynamic in Eq. (2) beforehand. Next, we design therapeutic control agents $u(t)$ to optimally track the desired time response and at the same time the influence of exogenous pathogens and environmental disturbances $w(t)$ on the tracking should be eliminated as much as possible.

Consider a reference model of immune system with a desired time response prescribed as follows:

$$x_{r}(t) = A_{r}x_{r}(t) + r(t),$$

where $x_{r}(t) \in \mathbb{R}^{n \times 1}$ is the reference state vector, $A_{r} \in \mathbb{R}^{n \times n}$ is a specific asymptotically stable matrix, and $r(t)$ is a desired reference signal. It is assumed that $x_{r}(0), \forall t > 0$ represents a desired immune response for Eq. (2) to follow, i.e. the therapeutic control is to specify $u(t)$ such that the tracking error $\hat{x}(t) = x(t) - x_{r}(t)$ must be as small as possible under the influence of uncertain exogenous pathogens and environmental disturbances $w(t)$. Since the exogenous pathogens and environmental disturbances $w(t)$ and the initial state $x(0)$ are uncertain and reference signal $r(t)$ could be arbitrarily assigned, the robust model matching control design should be specified so that the worst-case effect of three uncertainties $w(t)$, $x(0)$, and $r(t)$ on the tracking error could be minimized and set below a prescribed value $\rho^2$, i.e. both the minimax matching and robustness against uncertainties.

$$\min_{\rho^2} \max_{u(t)} \int_{0}^{T} (\hat{x}^T(t)Q\hat{x}(t) + u^T(t)Ru(t))dt \leq \rho^2,$$

where $\rho^2 \leq 0$.

Fig. 1. Innate and enhanced immune response to a pathogenic attack under exogenous pathogens and environmental disturbances.
where the weighting matrices $Q$ and $R$ are assumed diagonal as follows:

$$Q = \begin{bmatrix} q_{11} & 0 & 0 & 0 \\ 0 & q_{22} & 0 & 0 \\ 0 & 0 & q_{33} & 0 \\ 0 & 0 & 0 & q_{44} \end{bmatrix}, \quad R = \begin{bmatrix} r_{11} & 0 & 0 & 0 \\ 0 & r_{22} & 0 & 0 \\ 0 & 0 & r_{33} & 0 \\ 0 & 0 & 0 & r_{44} \end{bmatrix}.$$ 

The diagonal element $q_{ii}$ of $Q$ denotes the punishment on the corresponding tracking error and the diagonal element $r_{ii}$ of $R$ denotes the relative therapeutic cost. Since the worst-case effect of $w(t)$, $r(t)$, and uncertain initial state $x(0)$ on tracking error $\tilde{x}(t)$ and control $u(t)$ is minimized from the energy point of view, the minimax problem of Eq. (5) is suitable for the minimax matching problem under unknown initial $x(0)$, uncertain environmental disturbances $w(t)$ and changeable reference $r(t)$, which are always met in practical design cases. Because it is not easy to solve the Nash dynamic game problem in Eq. (5) subject to Eqs. (2) and (4) directly, we provide an upper bound $\rho^2$ of the minimax problem.

**Remark 1.** Actually, the design idea is the same as the model adaptive control (MRAC) (Åström and Wittenmark, 1995). The desired time response in Eq. (4) is the model reference in Åström and Wittenmark. The difficult of the model reference control design of immune system is that all the immune systems are nonlinear and external disturbances are uncertain. Therefore, the minimax game theory in Eq. (5) and fuzzy interpolation method are employed to simplify the design procedure of the nonlinear MRAC design problem of immune systems in the next approach.

We will first solve the above sub-minimax problem and then decrease the upper bound $\rho^2$ as small as possible to get the real minimax problem. Since the denominator in Eq. (5) is independent of $u(t)$ and is not zero, Eq. (5) is equivalent to (Boyd, 1994; Basar and Olsder, 1999):

$$\min_{u(t)} \max_{w(t), r(t)} \int_0^t (\dot{x}^T(t)Q\dot{x}(t) + u^T(t)Ru(t) - \rho^2 w^T(t)w(t) \ dt - \rho^2 \dot{x}^T(t)r(t) dt \leq \rho^2 \dot{x}^T(0)\dot{x}(0), \quad \forall x(0). \quad (6)$$

Let us denote

$$\min_{u(t)} \max_{w(t), r(t)} J(u(t), w(t), r(t)) = \min_{u(t)} \max_{w(t), r(t)} \int_0^t (\dot{x}^T(t)Q\dot{x}(t) + u^T(t)Ru(t) \ dt - \rho^2 w^T(t)w(t) - \rho^2 \dot{x}^T(t)r(t) dt.$$ 

From the above analysis, the dynamic game problem in Eq. (5) or (6) is equivalent to finding the worst-case disturbance $w^*(t)$ and reference signal $r^*(t)$ which maximize $J(u(t), w(t), r(t))$ and then a minimax control $u^*(t)$ which minimizes $J(u(t), w^*(t), r^*(t))$ such that the minimax value $J(u^*(t), w^*(t), r^*(t))$ is less than $\rho^2\dot{x}(0)^T\dot{x}(0)$, i.e.

$$J(u^*(t), w^*(t), r^*(t)) = \min_{u(t)} J(u(t), w^*(t), r^*(t)) = \min_{u(t)} \max_{w(t), r(t)} J(u(t), w(t), r(t)) \leq \rho^2 \dot{x}(0)^T\dot{x}(0), \quad \forall x(0). \quad (7)$$

Hence, if there exist $u^*(t)$, $w^*(t)$, and $r^*(t)$ such that minimax matching problem in Eq. (7) is solved, then they can satisfy the robust model matching performance in Eq. (5) as well. Therefore, the first step of robust matching control design of therapeutic agents for immune systems is to solve the following dynamic game problem:

$$\min_{u(t)} \max_{w(t), r(t)} J(u(t), w(t), r(t)) \quad (8)$$

subject to the disease dynamic model in Eq. (2) and the desired reference model in Eq. (4). After that, the next step is to check
whether the condition \( f(u^*(t), w^*(t), r^*(t)) < \rho^2 \tilde{x}^T(0) \tilde{x}(0) \) is satisfied or not for any \( \tilde{x}(0) \).

In general, it is not easy to solve the minimax matching problem directly; it should be transformed to an equivalent minimax regulation problem. Let us denote

\[
F(\tilde{x}(t)) = \begin{bmatrix}
 f(x(t)) \\
 Ax(t)
\end{bmatrix}, \quad \tilde{x}(t) = \begin{bmatrix}
x(t) \\
\dot{x}(t)
\end{bmatrix} \in \mathbb{R}^{2n+1},
\u(t) \in \mathbb{R}^{m+1} \quad \text{and} \quad V(t) = \begin{bmatrix}
w(t) \\
r(t)
\end{bmatrix} \in \mathbb{R}^{2n+1}.
\]

Then we can rewrite the minimax matching problem as

\[
\min_{u(t)} \max_{v(t)} [f(u(t), v(t))] = \min_{u(t)} \max_{v(t)} \int_0^T \left( \tilde{x}(t) Q \tilde{x}(t) + u^2(t) R u(t) \right) \, dt \quad \forall \tilde{x}(0) \quad \text{subject to Eq. (10).}
\]

After solving a \( V(\tilde{x}(t)) \) and \( \rho^2 \) from the constrained optimization in Eq. (16), we substitute this solution \( V(\tilde{x}(t)) \) to obtain the minimax matching control \( u^*(t) \) in Eq. (12).

### 4. Robust model matching control of innate immune system via fuzzy interpolation method

Because it is very difficult to solve the nonlinear HJI in Eq. (14), no simple approach is available to solve the constrained optimization problem in Eq. (16) for robust model matching control of innate immune system. Recently (Takagi and Sugeno, 1985; Chen et al., 1999, 2000), the fuzzy Takagi-Sugeno (T–S) model has been widely applied to approximate the nonlinear system via interpolating several linearized systems at different operating points so that the nonlinear dynamic game problem could be transformed to a fuzzy dynamic game problem. Using such approach, the HJI in Eq. (14) can be replaced by a set of LMIs. In this situation, the nonlinear dynamic game problem in Eq. (5) could be easily solved by fuzzy dynamic game method for the design of robust model matching control for innate immune response systems.

Suppose the augmented system in Eq. (10) can be represented by the T–S fuzzy model [Takagi and Sugeno, 1985]. The T–S fuzzy model is a piecewise interpolation of several linearized models through membership functions. The fuzzy model is described by fuzzy ‘If-Then’ rules and will be employed to deal with the nonlinear dynamic game problem for robust model matching control to achieve a desired immune response under exogenous pathogens input and environmental disturbances. The fuzzy model for nonlinear system in Eq. (10) is of the following form (Chen et al., 1999, 2000):

- **Rule i**

If \( x_i(t) \) is \( F_{ij} \) and \( \ldots \) and \( x_g(t) \) is \( F_{ig} \), then

\[
\tilde{x}(t) = A_i \tilde{x}(t) + B_i u(t) + C_i v(t), \quad i = 1, 2, 3, \ldots, L,
\]

in which

\[
A_i = \begin{bmatrix}
A_i & 0 \\
0 & A_i
\end{bmatrix}, \quad B = \begin{bmatrix}
B \\
0
\end{bmatrix}, \quad C = \begin{bmatrix}
D & 0 \\
0 & I
\end{bmatrix}.
\]

and \( F_{ij} \) is the fuzzy set; \( A_i, B, \) and \( C \) are known constant matrices; \( L \) is the number of If-Then rules, \( g \) is the number of premise variables and \( x_1(t), x_2(t), \ldots, x_g(t) \) are the premise variables. The fuzzy system is inferred as follows (Takagi and Sugeno, 1985; Chen et al., 1999, 2000):

\[
\tilde{x}(t) = \sum_{i=1}^{L} h_i(x(t)) A_i \tilde{x}(t) + B_i u(t) + C_i v(t), \quad i = 1, 2, 3, \ldots, L,
\]

with

\[
V(\tilde{x}(0)) \leq \rho^2 \tilde{x}^T(0) \tilde{x}(0), \quad \forall \tilde{x}(0).
\]

**Proof.** See Appendix A.

Since \( \rho \) is the upper bound of Nash game problem in Eq. (5), based on the analysis above, the minimax matching control \( u^*(t) \) and the worst-case disturbance \( v^*(t) \) still need to minimize the upper bound \( \rho^2 \) as follows:

\[
\rho^2 = \min_{\rho, \rho^2 > 0} \rho^2
\]

subject to Eqs. (14) and (15).

After solving a \( V(\tilde{x}(t)) \) and \( \rho^2 \) from the constrained optimization in Eq. (16), we substitute this solution \( V(\tilde{x}(t)) \) to obtain the minimax matching control \( u^*(t) \) in Eq. (12).
The T–S fuzzy model in Eq. (18) is to interpolate linear systems to approximate the nonlinear system in Eq. (10) via the fuzzy basis function $h_i(x(t))$. We specify the parameter $A_i$ easily so that $\sum_{i=1}^{n} h_i(x(t)) A_i \mathbf{r}(t)$ in Eq. (18) can approximate $F(x(t))$ in Eq. (10) by the fuzzy identification method (Takagi and Sugeno, 1985).

After the nonlinear system in Eq. (10) is approximated as the T–S fuzzy system in Eq. (18), the nonlinear dynamic game problem in Eqs. (10) and (11) is replaced by solving the fuzzy dynamic game problem in Eqs. (18) and (11).

**Theorem 2.** The minimax control and the worst-case disturbance for the fuzzy dynamic game problem in Eq. (11) subject to Eq. (18) are solved respectively as follows:

$$u^*(t) = -R^{-1} B^T P r(t)$$ and $$v^*(t) = \frac{1}{\rho} C^T P r(t),$$

where $P$ is the positive definite symmetric matrix solution of the following Riccati-like inequality:

$$PA_i + A_i^T P - P^T B R_i^{-1} B^T P + \frac{1}{\rho^2} P C^T C P \leq 0,$$

$$i = 1, \ldots, L,$$

$$P \leq \rho^2 I.$$ (22)

**Proof.** See Appendix B.

By fuzzy approximation, obviously, the HJI in Eq. (14) can be approximated by a set of algebraic inequalities in Eq. (22).

Since $\rho^2$ is the upper bound of minimax Nash game problem in Eq. (5), the minimax game problem still needs to minimize $\rho^2$ as follows:

$$\rho_0^2 = \min_{\rho > 0} \rho^2$$ (23)

subject to Eq. (22).

In order to solve the above-constrained optimization in Eq. (23) by the conventional LMI method, we let $W = P^{-1} > 0$. Then Eq. (22) can be equivalent to

$$A_i W + W A_i^T + W QQ^T W - BR_i^{-1} B^T + \frac{1}{\rho^2} C C^T \leq 0,$$

or

$$A_i W + W A_i^T + \begin{bmatrix} Q & -Q \\ -Q & 0 \end{bmatrix} W - BR_i^{-1} B^T + \frac{1}{\rho^2} C C^T \leq 0,$$

$$i = 1, \ldots, L,$$

or

$$A_i W + W A_i^T + \begin{bmatrix} Q^{1/2} & -Q^{1/2} \\ -Q^{1/2} & 0 \end{bmatrix} \begin{bmatrix} Q^{1/2} & -Q^{1/2} \\ -Q^{1/2} & 0 \end{bmatrix} W$$

$$- BR_i^{-1} B^T + \frac{1}{\rho^2} C C^T \leq 0,$$

$$i = 1, \ldots, L.$$

By the schur complements (Boyd, 1994), the constrained optimization in Eqs. (22) and (23) is equivalent to the following LMI-constrained optimization:

$$\rho_0^2 = \min_{W > 0} \rho^2$$ (24)

subject to

$$A_i W + W A_i^T - BR_i^{-1} B^T + \frac{1}{\rho^2} C C^T \begin{bmatrix} Q^{1/2} & -Q^{1/2} \\ -Q^{1/2} & 0 \end{bmatrix} \begin{bmatrix} Q^{1/2} & -Q^{1/2} \\ -Q^{1/2} & 0 \end{bmatrix} W$$

$$- I \leq 0,$$

$$i = 1, \ldots, L,$$

$$\rho^2 W \geq I.$$ (25)

**Remark 2.**

1. The fuzzy basis function $h_i(x(t))$ in Eqs. (18) and (20) can be replaced by other interpolation functions, for example, cubic spline functions.
2. By fuzzy approximation, the HJI in Eq. (14) of nonlinear dynamic game problem is replaced by a set of inequalities in Eq. (22), which can be easily solved by LMI-constrained optimization in Eq. (25).
3. The constrained optimization to solve $\rho_0$ and $W = P^{-1}$ in Eqs. (24) and (25) can be easily solved by decreasing $\rho^2$ until there exists no $W > 0$ solution in Eq. (25). After solving $W$ and then $P = W^{-1}$ from the constrained optimization problem in Eqs. (24) and (25), the minimax control can be obtained from Eq. (21).

4. The solution $W > 0$ in LMI-constrained optimization Eq. (25) can be solved by Robust Control Toolbox in Matlab efficiently.

5. If the conventional quadratic optimal control in Eq. (3) is considered (Stengel et al., 2002b), i.e. the effect of disturbance is not considered in the design procedure, the optimal tracking control problem is equivalent to letting $\rho^2 = \infty$ in Eq. (5) (Zhou et al., 1996). Then the optimal control design $u^*(t) = -R^{-1} B P r(t)$ can be solved by a common positive definite symmetric matrix $P$ from Eq. (22) with $\rho^2 = \infty$, i.e. solving a common positive definite symmetric matrix $P > 0$ from the following constrained inequalities: $P A_i + A_i^T P - P B R_i^{-1} B^T P \leq 0$, $i = 1, \ldots, L$ (Boyd, 1994). In order to solve the optimal tracking control by LMI technique, the optimal tracking control is equivalent to solving a common $W = P^{-1}$ from the following constrained inequalities:

$$A_i W + W A_i^T + \begin{bmatrix} Q^{1/2} & -Q^{1/2} \\ -Q^{1/2} & 0 \end{bmatrix} \begin{bmatrix} Q^{1/2} & -Q^{1/2} \\ -Q^{1/2} & 0 \end{bmatrix} W$$

$$- BR_i^{-1} B^T \leq 0,$$

$$i = 1, \ldots, L,$$

or equivalently,

$$A_i W + W A_i^T - BR_i^{-1} B^T W \begin{bmatrix} Q^{1/2} \\ -Q^{1/2} \end{bmatrix} \begin{bmatrix} Q^{1/2} \\ -Q^{1/2} \end{bmatrix} \leq 0,$$

$$i = 1, \ldots, L,$$

which is equivalent to Eq. (25) with $\rho^2 = \infty$.

According to the above analysis, the robust model matching control of innate immune system via fuzzy interpolation method is summarized as follows.

**Design procedure:**

1. Give a desired reference model in Eq. (4) of immune system.
2. Select membership functions and construct fuzzy plant rules in Eq. (17).
3. Give weighting matrices $Q$ and $R$ in Eq. (5).
4. Solve the LMI-constrained optimization in Eq. (25) to obtain $W$ (thus $P = W^{-1}$ can also be obtained) and $\rho_0^2$.
5. Construct the controller under the worst-case disturbance in Eq. (21).

**Remark 3.** The software packages such as Robust Control Toolbox in Matlab can be employed to solve the LMI-constrained optimization problem in Eq. (25) easily.
5. Computational simulation

Example 1. We consider the innate immune system in Eq. (1) and in Fig. 1. The values of the parameters are in Table 1. The environmental disturbances \( w_1 \)–\( w_4 \) are unknown but bounded signals. Under infectious situation, the microbes infect the organ not only by an initial concentration at the beginning but also by the continuous pathogens input. For the convenience of computer simulation, suppose the continuous pathogens input to the immune system is viewed as an environmental disturbance \( w_1 \) shown in Fig. 3. For the convenience of simulation, \( w_2 \)–\( w_4 \) are assumed zero mean white noises with standard deviations all equal to 2. The stochastic noises of immune systems are mainly due to measurement errors, modeling errors and process noises (Milutinovic and De Boer, 2007). The dynamic model of innate immune system under exogenous pathogens input and environmental disturbances is controlled by a combined therapeutic control shown as follows (Stengel et al., 2002a):

\[
\dot{x}_1 = (1-x_3)x_1 - u_1 + 3w_1, \\
\dot{x}_2 = a_{21}(x_4)3x_1x_3 - (x_2 - 2) + u_2 + 3w_2. 
\]

Table 1
Model parameters of dynamic innate immune system (Marchuk, 1983; Stengel et al., 2002b)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a_{11} )</td>
<td>1</td>
<td>Pathogens reproduction rate coefficient</td>
</tr>
<tr>
<td>( a_{12} )</td>
<td>1</td>
<td>The suppression by pathogens coefficient</td>
</tr>
<tr>
<td>( a_{13} )</td>
<td>2</td>
<td>The mean immune cell production rate coefficient</td>
</tr>
<tr>
<td>( a_{14} )</td>
<td>1</td>
<td>The steady-state concentration of immune cells</td>
</tr>
<tr>
<td>( a_{21} )</td>
<td>1</td>
<td>Antibodies production rate coefficient</td>
</tr>
<tr>
<td>( a_{22} )</td>
<td>3</td>
<td>Immune reactivity coefficient</td>
</tr>
<tr>
<td>( a_{23} )</td>
<td>0.5</td>
<td>The rate of antibodies suppress pathogens</td>
</tr>
<tr>
<td>( a_{24} )</td>
<td>0.5</td>
<td>The organ damage depends on the pathogens damage possibilities coefficient</td>
</tr>
<tr>
<td>( b_1 )</td>
<td>2</td>
<td>Organ recovery rate</td>
</tr>
<tr>
<td>( b_2 )</td>
<td>1</td>
<td>Pathogen killer’s agent coefficient</td>
</tr>
<tr>
<td>( b_3 )</td>
<td>1</td>
<td>Immune cell enhancer coefficient</td>
</tr>
<tr>
<td>( b_4 )</td>
<td>1</td>
<td>Antibody enhancer coefficient</td>
</tr>
</tbody>
</table>

The continuous exogenous pathogen disturbances \( w_1 \)

\[
\dot{x}_3 = x_2 - (1.5 + x_1)x_3 + u_3 + 3w_3, \\
\dot{x}_4 = 0.5x_1 - x_4 - u_4 + 3w_4, \\
a_{21}(x_4) = \begin{cases} 
\cos(\pi x_4), & 0 \leq x_4 \leq 1/2, \\
0, & 1/2 < x_4, 
\end{cases}
\]

with the set of the initial condition \( x(0) = [x_1(0) \ x_2(0) \ x_3(0) \ x_4(0)]^T = [3 \ 3.1 \ 1 \ 0.98]^T \). In this example, therapeutic controls \( u_1 \)–\( u_4 \) are combined to enhance the immune system.

Our reference model design objective is that system matrix \( A_r \) and \( r(t) \) should be specified beforehand so that its transient responses and steady state of reference system for innate immune response system are desired. If the real parts of eigenvalues of \( A_r \) are more negative (i.e. more robust stable), the tracking system will be more robust to environmental disturbances. After some numerical simulations for clinical treatment, the desired reference signals are obtained by the following reference model (see Fig. 4):

\[
\dot{x}_r(t) = \begin{bmatrix} -12 & 0 & 0 & 0 \\
-2.3 & 0 & 0 & 0 \\
0 & 0 & -10 & 0 \\
0 & 0 & 0 & -3 
\end{bmatrix} \times x_r(t) + B_r \times u_{\text{step}}(t),
\]

where \( B_r = [0 \ \ 4.6 \ 13.3333 \ 0]^T \) and \( u_{\text{step}}(t) \) is the unit step function.

From the investigation of the uncontrolled innate immune response (lethal case) in Fig. 5, the pathogen concentration is increasing rapidly and causes organ failure. We try to administrate a treatment after a period of pathogens infection to enhance the immune system. The cutting line (black solid line) in Fig. 5 is a proper time to take drugs. Suppose the set of the initial condition of the desired reference model is about \( x_r(0) = [2.9 \ 3.2 \ 1.1 \ 0.9]^T \). The time response of the desired reference model in Eq. (29) is shown in Fig. 4.

To minimize the design effort and complexity for this nonlinear innate immune system in Eq. (28), we employ the T–S fuzzy model to construct fuzzy rules to approximate the nonlinear innate immune system with the innate immune system’s state variables as premise variables in the following.

Time Responses of Reference Model

\[
\begin{align*}
&x_1, \text{Pathogens} \\
x_2, \text{Immune cells} \\
x_3, \text{Antibodies} \\
x_4, \text{Organ}
\end{align*}
\]

Fig. 4. The desired reference model with four desired states in Eq. (29): pathogens \( (x_1, \text{blue, dashed square line}) \), immune cells \( (x_2, \text{green, dashed triangle line}) \), antibodies \( (x_3, \text{red, dashed diamond line}) \), and organ \( (x_4, \text{magenta, dashed circle line}) \). The initial conditions of the reference model are \( x_r(0) = [2.9 \ 3.2 \ 1.1 \ 0.9]^T \).
common positive definite symmetric matrix $P$; performance of the robust model matching control via T–S fuzzy the proposed robust therapeutic control design. model tracking of immune system is attenuated significantly by that the effect of stochastic external disturbances on the reference operating points of $x$. Suppose the concentrations of the pathogens $x_r$ immune cells $x_r$, antibodies $x_r$, and organ index $x_r$ to track the desired reference states $x_r$, $x_r$, $x_r$, $x_r$, respectively. From the simulation results, the tracking performance of the robust model matching control via T–S fuzzy interpolation is quite satisfactory. Fig. 8 shows the four combined therapeutic control signals. Obviously, from Figs. 8 and 9, it is seen that the effect of stochastic external disturbances on the reference model tracking of immune system is attenuated significantly by the proposed robust therapeutic control design.

The control design with considered drug’s side effects is simulated in Figs. 9 and 10. Fig. 9 shows the responses of the controlled immune system by the proposed minimax model matching control with undergoing the side effects of pathogen killer’s agent $u_1$ (i.e. drugs or antibiotics) also degrades organ health. The modified model of Eq. (28) of the organ state $x_4$ becomes

$$ x_4 = 0.5x_1 - x_4 + u_4 + 0.2u_1 + 3w_4. $$

i.e. an increase of 0.2 side effect of the pathogen killer’s agent $u_1$ on the organ state $x_4$. The detailed design of fuzzy approximation is similar to the previous procedure and the parameters are the same except $B$, i.e.

$$ B = \begin{bmatrix} -1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0.2 & 0 & 0 & -1 \end{bmatrix}. $$

After specifying the desired reference model, we need to solve the constrained optimization in Eq. (24) for the robust minimax control in Eq. (21) by employing Matlab Robust Control Toolbox.

Finally, we obtain a minimum attenuation level $\rho_6^2 = 0.98$ and a common positive definite symmetric matrix $P$ for Eq. (22) as follows:

$$ P = \begin{bmatrix} 0.43313 & 0 & 0 & 0 & -0.43313 \\ 0 & 0.56172 & 0 & 0 & 0 & 0 & -0.56172 & 0 \\ 0 & 0 & 0.42678 & 0 & 0 & 0 & 0 & -0.42678 \\ 0 & 0 & 0 & 0.50151 & 0 & 0 & 0 & 0.50151 \\ -0.43313 & 0 & 0 & 0 & 0.28482 & 0 & 0 & 0.28482 \\ -0.56172 & 0 & 0 & 0 & 0 & 0 & 0 & 0.28482 \\ 0 & 0 & -0.42678 & 0 & 0 & 0 & 0 & 0.49526 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0.34567 \end{bmatrix}. $$

and $x_{4r}$, respectively. From the simulation results, the tracking performance of the robust model matching control via T–S fuzzy interpolation is quite satisfactory. Fig. 8 shows the four combined therapeutic control signals. Obviously, from Figs. 8 and 9, it is seen that the effect of stochastic external disturbances on the reference model tracking of immune system is attenuated significantly by the proposed robust therapeutic control design.

Example 2. It is sometime unavoidable for drugs to have adverse side effects. Limiting the impact of side effects should be considered in this therapeutic control design. Suppose the pathogen killer’s agent $u_1$ (i.e. drugs or antibiotics) also degrades organ health. The modified model of Eq. (28) of the organ state $x_4$ becomes

$$ x_4 = 0.5x_1 - x_4 + u_4 + 0.2u_1 + 3w_4. $$

In this design case, we choose

$$ Q = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, R = \begin{bmatrix} 0.002 & 0 & 0 & 0 \\ 0 & 0.002 & 0 & 0 \\ 0 & 0 & 0 & 0.002 \\ 0 & 0 & 0 & 0.34567 \end{bmatrix}. $$

Since the organ health state suffers from the impact of the side effects, we should increase the weighting $q_{44}$ to impose a penalty on the organ health tracking error. Furthermore, we relax the weighting on the control signals to improve the tracking efficiency. By the same design procedure, we obtain a minimum attenuation level $\rho_6^2 = 0.9$ and a common positive definite symmetric matrix $P$ as follows:

$$ P = \begin{bmatrix} 0.29932 & 0 & 0 & -0.29932 & 0 & 0 & 0 \\ 0 & 0.39859 & 0 & 0 & 0 & -0.39859 & 0 \\ 0 & 0 & 0.28408 & 0 & 0 & -0.28408 & 0 \\ 0 & 0 & 0 & 0.30502 & 0 & -0.30502 & 0 \\ 0 & 0 & 0 & 0 & 0.35217 & -0.35217 & 0 \\ -0.29932 & 0 & 0 & 0 & 0 & 0.34567 \\ 0 & -0.39859 & 0 & 0 & 0 & 0.43261 & 0 \\ 0 & 0 & -0.28408 & 0 & 0 & 0 & 0.33088 \end{bmatrix}. $$

Figs. 7 and 8 present the simulation results for the robust model matching control. Fig. 7 shows the responses of the controlled immune system by minimax model matching control with the concentrations of the pathogens $x_r$, immune cells $x_r$, antibodies $x_r$, and organ index $x_r$ to track the desired reference states $x_r$, $x_r$, $x_r$, $x_r$, respectively. From the simulation results, the tracking performance of the robust model matching control via T–S fuzzy interpolation is quite satisfactory. Fig. 8 shows the four combined therapeutic control signals. Obviously, from Figs. 8 and 9, it is seen that the effect of stochastic external disturbances on the reference model tracking of immune system is attenuated significantly by the proposed robust therapeutic control design.

The control design with considered drug’s side effects is simulated in Figs. 9 and 10. Fig. 9 shows the responses of the controlled immune system by the proposed minimax model matching control with undergoing the side effects of pathogen killer’s agent $u_1$. From the simulation result, the organ health state $x_4$ tracks the desired response leisurely at the beginning but it totally matches the desired response at the end. Fig. 10 shows the four combined
therapeutic control signals with the side effects of pathogen killer’s agent $u_1$. At the beginning, the drug of organ health enhancer $u_4$ needs to increase to minimize the side effects from the pathogen killer’s agent $u_1$.

6. Discussion

From the simulation results (Figs. 7 and 8), it is shown that the innate immune system under the continuous intrusion of exogenous pathogens and the corruption of environmental disturbances can be controlled by a robust model matching control design to achieve the desired time response. If we consider the conventional optimal control in Eq. (3), i.e. the effect of the environmental disturbances is not included in the cost function; the optimal tracking control problem is equivalent to letting $p^2 = \infty$ in Eqs. (5) and (22) (Boyd, 1994). From the simulation results (Figs. 11 and 12), the four states of optimal tracking of the immune system are overshooting and diverging without tracking the desired immune time response. Obviously, exogenous pathogens and the environmental disturbances have deteriorated the optimal tracking performance and therefore their effects should be considered in the robust control design procedure. In the situation, the proposed robust matching control design is necessary to achieve a desired time response.

Pathogen killer’s agent $u_1$ has toxic side effect that can damage the organ during the treatment. So, we should consider its detrimental impacts into the innate immune system in the model in Eq. (31). In the robust model matching control design procedure, the element of weighting matrix $q_{44}$ should be increased to impose a penalty on the tracking error of organ health state to eliminate the side effect of $u_1$ on $x_4$. From the simulation results (Figs. 9 and 10), the organ health state $x_4$ tracks the desired response slowly at the beginning but it almost matches the desired response at the end. It is also observed that the innate immune system can be controlled by a combined therapies design to achieve the desired time response under the

![Fig. 5. The uncontrolled immune responses (lethal case) in Eq. (28) are shown to increase the level of pathogen concentration at the beginning of the time period. In this case, we try to administrate a treatment after a short period of pathogens infection. The cutting line (black solid line) is an optimal time point to give drugs. The organ will survive or fail based on the organ health threshold (horizontal dashed line) ($x_4 < 1$: survival; $x_4 > 1$: failure).](image)

![Fig. 6. Membership functions for four states $x_1$, $x_2$, $x_3$, and $x_4$.](image)

![Fig. 7. The tracking of innate immune system to the desired reference model by the robust minimax matching control under the continuous exogenous pathogens and environmental disturbances.](image)
continuous intrusion of exogenous pathogens, environmental disturbances and side effects.

The combined therapies design is an important issue for all human diseases (Villadsen et al., 2003). For a long period, the treatment of inflammatory skin diseases such as psoriasis, contact dermatitis and atopic dermatitis has included agents that alleviate symptoms, but these agents have not been aimed at any specific molecular targets involved in the pathogenesis of the disease. Insights into this immune mechanism may facilitate the development of combination therapies that take advantage of the robust model matching design, with the aim of achieving higher efficacy at a lower drug dosage and with a reduced probability of side effect on organ health. The proposed robust model matching design has used four control variables, i.e. pathogen killer’s agent $u_1$, immune cell enhancer $u_2$, antibody enhancer $u_3$, and health enhancer $u_4$, to achieve a minimax matching performance and to efficiently attenuate the effect of exogenous pathogens and environmental disturbances on the immune system.

In this study, the model of innate immune dynamic system is taken from the literature, which still needs to compare quantitatively with empirical evidence in practical application. For practical implementation, accurate biodynamic models are required for treatment application. However, model identification is not the topic of this paper. Furthermore, we have made an assumption that the four states ($x_1$–$x_4$) of the concentrations or indices can be measured accurately by the medical equipment. With these detectable signals, we can solve these dynamic game problems for robust tracking control design of innate immune system to obtain the drug administration values in real time through medical instrument readout. If measurement is corrupted...
formulated as a minimax problem for an innate immune system to achieve a desired time response prescribed prior under environmental disturbances, unknown initial conditions and side effects. In general, the robust model matching control design for innate immune system needs to solve nonlinear HJI, which is generally difficult to solve for this control design. Based on the proposed fuzzy dynamic game scheme, the design of nonlinear dynamic robust matching control problem for innate immune system is transformed to solve a set of equivalent linear dynamic game problem. Such transformation can then allow us an easier approach by solving an LMI-constrained optimization problem for robust minimax control design. With the help of the Robust Control Toolbox in Matlab instead of the HJI, we could solve these linear dynamic game problems for robust matching control of innate immune system efficiently. From the in silico simulation examples, the proposed minimax match control of immune system could track the prescribed reference time response robustly, which may lead to potential application in therapeutic drug design for a desired immune response during an infection episode.

Acknowledgment

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Appendix A. Proof of Theorem 1

Let us denote a Lyapunov energy function $V(\bar{x}(t)) > 0$. Then Eq. (9) is equivalent to the following minimax problem:

$$
\min_{u(t)} \max_{v(t)} \left\{ V(\bar{x}(0)) - V(\bar{x}(T)) + \int_{0}^{T} \left[ \frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)}^T \bar{x}(t) + \frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} F(\bar{x}(t)) + B^T u(t) + C^T v(t) \right] dt \right\}, \quad \forall \bar{x}(0).
$$

By the chain rule, we get

$$
\frac{dV(\bar{x}(t))}{dt} = \left( \frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} \right)^T \bar{x}(t) + \frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} F(\bar{x}(t)) + B^T u(t) + C^T v(t).
$$

Substituting Eq. (A.2) into Eq. (A.1), we get

$$
\min_{u(t)} \max_{v(t)} \left\{ V(\bar{x}(0)) - V(\bar{x}(T)) + \int_{0}^{T} \left[ \frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)}^T \bar{x}(t) + \frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} F(\bar{x}(t)) + B^T u(t) + C^T v(t) \right] dt \right\}, \quad \forall \bar{x}(0).
$$

$$
\min_{u(t)} \max_{v(t)} \left\{ V(\bar{x}(0)) - V(\bar{x}(T)) + \int_{0}^{T} \left[ \frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)}^T F(\bar{x}(t)) + B^T u(t) + C^T v(t) \right] dt \right\}, \quad \forall \bar{x}(0).
$$

7. Conclusion

Robustness is a significant property that allows the innate immune system to maintain its function despite exogenous pathogens, environmental disturbances and system uncertainties. Based on dynamic game theory, the robust tracking control is...
\[ \begin{align*}
&\times R\left( \begin{bmatrix} 1 & 2 & R^{-1}B^T V(t) \end{bmatrix} \right) \\
&- \left( \begin{bmatrix} \frac{1}{2} B^T V(t) \end{bmatrix} \right) \left( \begin{bmatrix} \frac{1}{2} B^T V(t) \end{bmatrix} \right)^T \\
&\times \left( \begin{bmatrix} \frac{1}{2} B^T V(t) \end{bmatrix} \right) \right) \text{d}r, \quad \forall \tilde{x}(0).
\end{align*} \]

Therefore, the minimax solution is given as follows:

\[ f(u^*(t), v^*(t)) = \left\{ V(\tilde{x}(0)) - V(\tilde{x}(t)) \right\} \]

\[ + \int_0^t \left[ \begin{bmatrix} C_0 & C_1 \end{bmatrix} \tilde{x}(t) + \sum_{i=1}^{L} h_i(t) \tilde{x}(t) \right] \text{d}r, \quad \forall \tilde{x}(0). \]

with

\[ u^*(t) = -\frac{1}{2} R^{-1}B^T \frac{\partial V(\tilde{x}(t))}{\partial \tilde{x}(t)}, \quad v^*(t) = \frac{1}{2} R^{-1}B^T \frac{\partial V(\tilde{x}(t))}{\partial \tilde{x}(t)}. \]

If Eq. (14) holds, then

\[ f(u^*(t), v^*(t)) \leq V(\tilde{x}(0)) - V(\tilde{x}(t)). \]

From the inequality in Eq. (11), this minimax solution should be less than \( \rho^2 \tilde{x}^T(t)P\tilde{x}(t) \), and then we get the inequality in Eq. (15):

\[ \min_{u(t)} \left\{ V(\tilde{x}(0)) - V(\tilde{x}(t)) \right\} \leq \rho^2 \tilde{x}^T(t)P\tilde{x}(t), \quad \forall \tilde{x}(0). \]

**Appendix B. Proof of Theorem 2**

Let us denote a Lyapunov energy function \( V(\tilde{x}(t)) = \tilde{x}^T(t)\tilde{P} \tilde{x}(t) > 0 \). Then Eq. (9) is equivalent to the following:

\[ \min_{u(t)} \{ \max_{v(t)} \left\{ \tilde{x}^T(0)P\tilde{x}(0) - \tilde{x}^T(t)P\tilde{x}(t) \right\} \]

\[ + \int_0^t \left[ \tilde{x}^T(t)Q \tilde{x}(t) + u^T(t)R \tilde{x}(t) \right] \text{d}r \right\}, \quad \forall \tilde{x}(0) \]

\[ = \min_{u(t)} \left\{ \tilde{x}^T(0)P\tilde{x}(0) - \tilde{x}^T(t)P\tilde{x}(t) \right\} \]

\[ + \int_0^t \left[ \tilde{x}^T(t)Q \tilde{x}(t) + u^T(t)R \tilde{x}(t) \right] \text{d}r \right\}, \quad \forall \tilde{x}(0) \]

\[ = \min_{u(t)} \left\{ \tilde{x}^T(0)P\tilde{x}(0) - \tilde{x}^T(t)P\tilde{x}(t) \right\} \]

\[ + \int_0^t \left[ \tilde{x}^T(t)Q \tilde{x}(t) + u^T(t)R \tilde{x}(t) \right] \text{d}r \right\}, \quad \forall \tilde{x}(0) \]

\[ = \min_{u(t)} \left\{ \tilde{x}^T(0)P\tilde{x}(0) - \tilde{x}^T(t)P\tilde{x}(t) \right\} \]

\[ + \int_0^t \left[ \tilde{x}^T(t)Q \tilde{x}(t) + u^T(t)R \tilde{x}(t) \right] \text{d}r \right\}, \quad \forall \tilde{x}(0) \]

\[ \leq \rho^2 \tilde{x}^T(t)P\tilde{x}(t), \quad \forall \tilde{x}(0). \]

In order to simplify the above equation, suppose the inequality in Eq. (22) holds, then

\[ \min_{u(t)} \left\{ \tilde{x}^T(0)P\tilde{x}(0) - \tilde{x}^T(t)P\tilde{x}(t) \right\} \]

\[ \leq \rho^2 \tilde{x}^T(t)P\tilde{x}(t), \quad \forall \tilde{x}(0). \]

From the inequality in Eq. (11), this minimax should be less than \( \rho^2 \tilde{x}^T(t)P\tilde{x}(t) \), and then

\[ \min_{u(t)} \left\{ \tilde{x}^T(0)P\tilde{x}(0) - \tilde{x}^T(t)P\tilde{x}(t) \right\} \]

\[ \leq \rho^2 \tilde{x}^T(t)P\tilde{x}(t), \quad \forall \tilde{x}(0). \]

\[ \text{i.e., } P \preceq \rho^2 I, \]

Since we assume \( \rho^2 \) is the upper bound in Eq. (5), the minimax control becomes how to design \( u(t) \) in Eq. (21) by solving the constrained optimization problem in Eqs. (22) and (23).

**Appendix C. Parameters of the fuzzy system**

The nonlinear innate immune system in Eq. (28) could be approximated by a T–S fuzzy system. By the fuzzy modeling method (Takagi and Sugeno, 1985), the matrices of the local linear system \( A_i \), the parameters \( B \) and \( C \) are calculated as follows:

\[ A_i = \begin{bmatrix} 0.3462 & 0 & 0 & 0 \\ -3.258 & -1.1155 & 0.3433 & 2.1987 \\ -0.2674 & 1.1816 & -1.7724 & 0.1108 \\ 0.6295 & 0 & -1.3994 \\ 0 & 0 & 0 & 0 \\ -12 & 0 & 0 & 0 \\ 0 & -2.3 & 0 & 0 \\ 0 & 0 & -10 & 0 \\ 0 & 0 & 0 & -3 \end{bmatrix}. \]

\[ A_i = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}. \]
\[
\begin{align*}
A_1 &= \begin{bmatrix}
-2.3807 & 0 & 0 & 0 \\
10.616 & -0.9107 & 0.3194 & -1.6078 \\
-2.4789 & 0.5007 & -1.7724 & -0.4134 \\
0.4117 & 0 & 0 & -0.5537 \\
\end{bmatrix}, & A_10 &= \begin{bmatrix}
0.348 & 0.2223 & -2.224 & 0.087 \\
-2.4956 & -1.8301 & -5.6794 & 0.7798 \\
-0.235 & 0.9101 & -2.1142 & -0.0587 \\
0.295 & 0.0728 & 0.0811 & 0.0737 \\
\end{bmatrix}, \\
A_2 &= \begin{bmatrix}
-2.2996 & 0 & 0 & 0 \\
-8.4642 & -0.9355 & -0.4587 & 1.7111 \\
-2.3919 & 0.4936 & -1.6635 & -0.4134 \\
0.1957 & -0.0781 & -0.1643 & -0.5537 \\
\end{bmatrix}, & A_{11} &= \begin{bmatrix}
-2.3807 & -0.0739 & -2.2977 & -0.5749 \\
12.767 & 2.4941 & 11.649 & -1.196 \\
-2.4789 & -0.2104 & -2.1832 & -0.598 \\
0.4117 & 0.1305 & 0.1675 & 0.0489 \\
\end{bmatrix}, \\
A_3 &= \begin{bmatrix}
0.1987 & 0 & 0 & 0 \\
0.6956 & -0.933 & 0.3733 & -3.5255 \\
0.3935 & 1.1816 & -0.4106 & 0.1732 \\
0.2311 & 0 & 0 & -0.3611 \\
\end{bmatrix}, & A_{12} &= \begin{bmatrix}
-2.2996 & -0.9641 & -2.224 & -0.5749 \\
-11.901 & -3.8172 & -11.21 & -3.8954 \\
-2.3919 & -0.2087 & -2.1142 & -0.598 \\
0.1957 & 0.0646 & 0.0811 & 0.0489 \\
\end{bmatrix}, \\
A_4 &= \begin{bmatrix}
0.1981 & 0 & 0 & 0 \\
-2.9804 & -1.0591 & -2.0136 & 3.3337 \\
0.3963 & 1.1644 & -0.3837 & 0.1732 \\
0.1101 & -0.0902 & -0.0619 & -0.3611 \\
\end{bmatrix}, & A_{13} &= \begin{bmatrix}
0.1987 & 0.2243 & -1.0582 & 0.0495 \\
0.5515 & -0.6453 & 3.8238 & 2.1633 \\
0.3935 & 0.9206 & -0.7957 & 0.0991 \\
0.2311 & 0.1473 & 0.0772 & 0.0275 \\
\end{bmatrix}, \\
A_5 &= \begin{bmatrix}
-1.0821 & 0 & 0 & 0 \\
5.3534 & -0.7742 & -0.638 & -0.7012 \\
-0.7249 & 0.5007 & -0.4106 & -0.0417 \\
0.1682 & 0 & 0 & -0.1482 \\
\end{bmatrix}, & A_{14} &= \begin{bmatrix}
-1.0821 & -0.9739 & -1.0582 & -0.2642 \\
3.6655 & 3.8523 & 4.0278 & 4.4254 \\
-0.7249 & -0.2104 & -0.7957 & -0.1756 \\
0.1682 & 0.1305 & 0.0772 & 0.0203 \\
\end{bmatrix}, \\
A_6 &= \begin{bmatrix}
-1.057 & 0 & 0 & 0 \\
-2.8391 & -1.532 & 0.7299 & 0.2814 \\
-0.7023 & 0.4936 & -0.3837 & -0.0417 \\
0.0812 & -0.0781 & -0.0619 & -0.1482 \\
\end{bmatrix}, & A_{15} &= \begin{bmatrix}
-1.057 & -0.9641 & -1.0349 & -0.2642 \\
-6.4434 & -4.5651 & -4.4027 & -6.7461 \\
-0.7203 & -0.2087 & -0.7759 & -0.1756 \\
0.0812 & 0.0646 & 0.0377 & 0.0203 \\
\end{bmatrix}, \\
A_7 &= \begin{bmatrix}
0.3462 & 0.2243 & -2.2977 & 0.087 \\
3.0103 & -0.0287 & 7.6732 & -2.1137 \\
-0.2674 & 0.9206 & -2.1832 & -0.0587 \\
0.6295 & 0.1473 & 0.1675 & 0.0737 \\
\end{bmatrix}, & A_{16} &= \begin{bmatrix}
-1.057 & -0.9641 & -1.0349 & -0.2642 \\
-6.4434 & -4.5651 & -4.4027 & -6.7461 \\
-0.7023 & -0.2087 & -0.7759 & -0.1756 \\
0.0812 & 0.0646 & 0.0377 & 0.0203 \\
\end{bmatrix}, \\
A_8 &= \begin{bmatrix}
-12 & 0 & 0 & 0 \\
0 & -2.3 & 0 & 0 \\
0 & 0 & -10 & 0 \\
0 & 0 & 0 & -3 \\
\end{bmatrix}, & A_9 &= \begin{bmatrix}
-12 & 0 & 0 & 0 \\
0 & -2.3 & 0 & 0 \\
0 & 0 & -10 & 0 \\
0 & 0 & 0 & -3 \\
\end{bmatrix}.
\end{align*}

References


