

Robust H_∞ Tracking Control of Stochastic Innate Immune System Under Noises

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1. Introduction

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 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 (Janeway, 2005; Lydyard et al., 2000; Stengel et al., 2002b). The innate immune system is a complex system and the obscure relationships between the immune system and the environment in which several modulatory stimuli are embedded (e.g. antigens, molecules of various origin, physical stimuli, stress stimuli). This environment is noisy because of the great amount of such signals. The immune noise has therefore at least two components: (a) the internal noise, due to the exchange of a network of molecular and cellular signals belonging to the immune system during an immune response or in the homeostasis of the immune system. The concept of the internal noise might be viewed in biological terms as a status of sub-inflammation required by the immune response to occur; (b) the external noise, the set of external signals that target the immune system (and hence that add noise to the internal one) during the whole life of an organism.

For clinical treatment of infection, several available methods focus on killing the invading microbes, neutralizing their response, and providing palliative or healing care to other organs of the body. Few biological or chemical agents have just one single effect; for example, an agent that kills a virus may also damage healthy 'self' cells. A critical function of drug discovery and development is 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, antigens from killed (i.e. non-toxic) pathogens, and pre-formed and monoclonal antibodies as immunity enhancers (each of very different nature); and anti-inflammatory and anti-histamine compounds as palliative drugs (Stengel et al., 2002b).

Recently, several models of immune response to infection (Asachenkov, 1994; Nowak & May, 2000; Perelson & Weisbuch, 1997; Rundell et al., 1995) with emphasis on the human-

immunodeficiency virus have been reported (Nowak et al., 1995; Perelson et al., 1993; Perelson et al., 1996; Stafford et al., 2000). Norbert Wiener (Wiener, 1948) and Richard Bellman (Bellman, 1983) appreciated and anticipated the application of mathematical analysis for treatment in a broad sense, and Swan made surveys on early optimal control applications to biomedical problems (Swan, 1981). Kirschner (Kirschner et al., 1997) offers an optimal control approach to HIV treatment, and intuitive control approaches are presented in (Bonhoeffer et al., 1997; De Boer & Boucher, 1996; Wein et al., 1998; Wodarz & Nowak, 1999, 2000).

The dynamics of drug response (pharmacokinetics) are modeled in several works (Robinson, 1986; van Rossum et al., 1986) and control theory is applied to drug delivery in other studies (Bell & Katusiime, 1980; Carson et al., 1985; Chizeck & Katona, 1985; Gentilini et al., 2001; Jelliffe, 1986; Kwong et al., 1995; Parker et al., 1996; Polycarpou & Conway, 1995; Schumitzky, 1986). Recently, Stengel (Stengel et al., 2002a) presented a simple model for the response of the innate immune system to infection and therapy, reviewed the prior method and results of optimization, and introduced a significant extension to the optimal control of enhancing the immune response by solving a two-point boundary-value problem via an iterative method. Their results show that 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 pathogen input, which is considered as an environmental disturbance of the immune system. Further, 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).

Recently, a minimax control scheme of innate immune system is proposed by the dynamic game theory approach to treat the robust control with unknown disturbance and initial condition (Chen et al., 2008). They consider unknown disturbance and initial condition as a player who wants to destroy the immune system and a control scheme as another player to protect the innate immune system against the disturbance and uncertain initial condition. However, they assume that all state variables are available. It is not the case in practical application.

In this study, a robust H_∞ tracking control of immune response is proposed for therapeutic enhancement to track a desired immune response under stochastic exogenous pathogen input, environmental disturbances and uncertain initial states. Furthermore, the state variables may not be all available and the measurement is corrupted by noises too. Therefore, a state observer is employed for state estimation before state feedback control of stochastic immune systems. Since the statistics of these stochastic factors may be unknown or unavailable, the H_∞ observer-based control methodology is employed for robust H_∞ tracking design of stochastic immune systems. In order to attenuate the stochastic effects of stochastic factors on the tracking error, their effects should be considered in the stochastic H_∞ tracking control procedure from the robust design perspective. The effect of all possible stochastic factors on the tracking error to a desired immune response, which is generated by a desired model, should be controlled below a prescribed level for the enhanced immune systems, i.e. the proposed robust H_∞ tracking control need to be designed from the stochastic H_∞ tracking perspective. Since the stochastic innate immune system is highly

nonlinear, it is not easy to solve the robust observer-based tracking control problem by the stochastic nonlinear H_∞ tracking method directly.

Recently, fuzzy systems have been employed to efficiently approximate nonlinear dynamic systems to efficiently treat the nonlinear control problem (Chen et al., 1999,2000; Li et al., 2004; Lian et al., 2001). A fuzzy model is proposed to interpolate several linearized stochastic immune systems at different operating points to approximate the nonlinear stochastic innate immune system via smooth fuzzy membership functions. Then, with the help of fuzzy approximation method, a fuzzy H_∞ tracking scheme is developed so that the H_∞ tracking control of stochastic nonlinear immune systems could be easily solved by interpolating a set of linear H_∞ tracking systems, which can be solved by a constrained optimization scheme via the linear matrix inequality (LMI) technique (Boyd, 1994) with the help of Robust Control Toolbox in Matlab (Balas et al., 2007). Since the fuzzy dynamic model can approximate any nonlinear stochastic dynamic system, the proposed H_∞ tracking method via fuzzy approximation can be applied to the robust control design of any model of nonlinear stochastic immune system that can be T-S fuzzy interpolated. Finally, a computational simulation example is given to illustrate the design procedure and to confirm the efficiency and efficacy of the proposed H_∞ tracking control method for stochastic immune systems under external disturbances and measurement noises.

2. Model of innate immune response

A simple four-nonlinear, ordinary differential equation for the dynamic model of infectious disease is introduced here to describe the rates of change of pathogen, immune cell and antibody concentrations and as an indicator of organic health (Asachenkov, 1994; Stengel et al., 2002a). In general, the innate immune system is corrupted by environmental noises. Further, some state variable cannot be measured directly and the state measurement may be corrupted by measurement noises. A more general dynamic model will be given in the sequel.

$$\begin{aligned}
 \dot{x}_1 &= (a_{11} - a_{12}x_3)x_1 + b_1u_1 + w_1 \\
 \dot{x}_2 &= a_{21}(x_4)a_{22}x_1x_3 - a_{23}(x_2 - x_2^*) + b_2u_2 + w_2 \\
 \dot{x}_3 &= a_{31}x_2 - (a_{32} + a_{33}x_1)x_3 + b_3u_3 + w_3 \\
 \dot{x}_4 &= a_{41}x_1 - a_{42}x_4 + b_4u_4 + w_4 \\
 y_1 &= c_1x_2 + n_1, y_2 = c_2x_3 + n_2, y_3 = c_3x_4 + n_3 \\
 a_{21}(x_4) &= \begin{cases} \cos(\pi x_4), & 0 \leq x_4 \leq 0.5 \\ 0, & 0.5 \leq x_4 \end{cases}
 \end{aligned} \tag{1}$$

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; u_4 denotes the organ healing factor (or health enhancer); w_1 denotes the rate of continuing introduction of exogenous pathogens; $w_2 \sim w_4$ denote the environmental disturbances or unmodeled errors and residues; $w_1 \sim w_4$ are zero mean white noises, whose covariances are uncertain or

unavailable; and $a_{21}(x_4)$ 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 x_2^* . The parameters have been chosen to produce a system that recovers naturally from the pathogen infections (without treatment) as a function of initial conditions during a period of times. Here, y_1, y_2, y_3 are the measurements of the corresponding states; c_1, c_2, c_3 are the measurement scales; and n_1, n_2, n_3 are the measurement noises. In this study, we assume the measurement of pathogen x_1 is unavailable. For the benchmark example in (1), both parameters and time units are abstractions, as no specific disease is addressed. The state and control are always positive because concentrations cannot go below zero, and organ death is indicated when $x_4 \geq 1$. The structural relationship of system variables in (1) is illustrated in Fig. 1. Organ health mediates immune cell production, inferring a relationship between immune response and fitness of the individual. Antibodies bind to the attacking antigens, thereby killing pathogenic microbes directly, activating complement proteins, or triggering an attack by phagocytic cells, e.g. macrophages and neutrophils. Each element of the state is subject to an independent control, and new microbes may continue to enter the system. In reality, however, the concentration of invaded pathogens is hardly to be measured. We assume that only the rest of three elements can be measured with measurement noises by medical devices or other biological techniques such as an immunofluorescence microscope, which is a technique based on the ability of antibodies to recognize and bind to specific molecules. It is then possible to detect the number of molecules easily by using a fluorescence microscope (Piston, 1999).

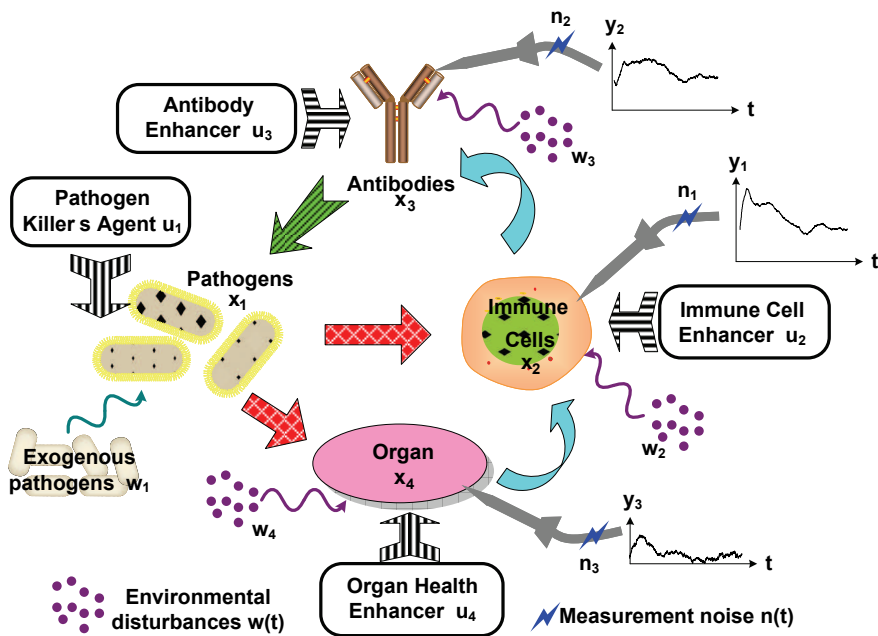


Fig. 1. Innate and enhanced immune response to a pathogenic attack under exogenous pathogens, environmental disturbances, and measurement noises.

Several typical uncontrolled responses to increasing levels of initial pathogen concentration under sub-clinical, clinical, chronic, and lethal conditions have been discussed and shown in Fig. 2 (Stengel et al., 2002a). In general, the sub-clinical response would not require medical examination, while the clinical case warrants medical consultation but is self-healing without intervention. Pathogen concentration stabilizes at non-zero values in the chronic case, which is characterized by permanently degraded organ health, and pathogen concentration diverges without treatment in the lethal case and kills the organ (Stengel et al., 2002b). Finally, a more general disease dynamic model for immune response could be represented as

$$\begin{aligned} \dot{x}(t) &= f(x(t)) + g(x(t))u(t) + Dw(t), \quad x(0) = x_0 \\ y(t) &= c(x(t)) + n(t) \end{aligned} \tag{2}$$

where $x(t) \in \mathbf{R}^{n \times 1}$ is the state vector; $u(t) \in \mathbf{R}^{m \times 1}$ is the control agent; $w(t) \in \mathbf{R}^{n \times 1}$ includes exogenous pathogens, environmental disturbances or model uncertainty. $y(t) \in \mathbf{R}^{l \times 1}$ is the measurement output; and $n(t) \in \mathbf{R}^{l \times 1}$ is the measurement noises. We assume that $w(t)$ and $n(t)$ are independent stochastic noises, whose covariances may be uncertain or unavailable. All possible nonlinear interactions in the immune system are represented by $f(x(t))$.

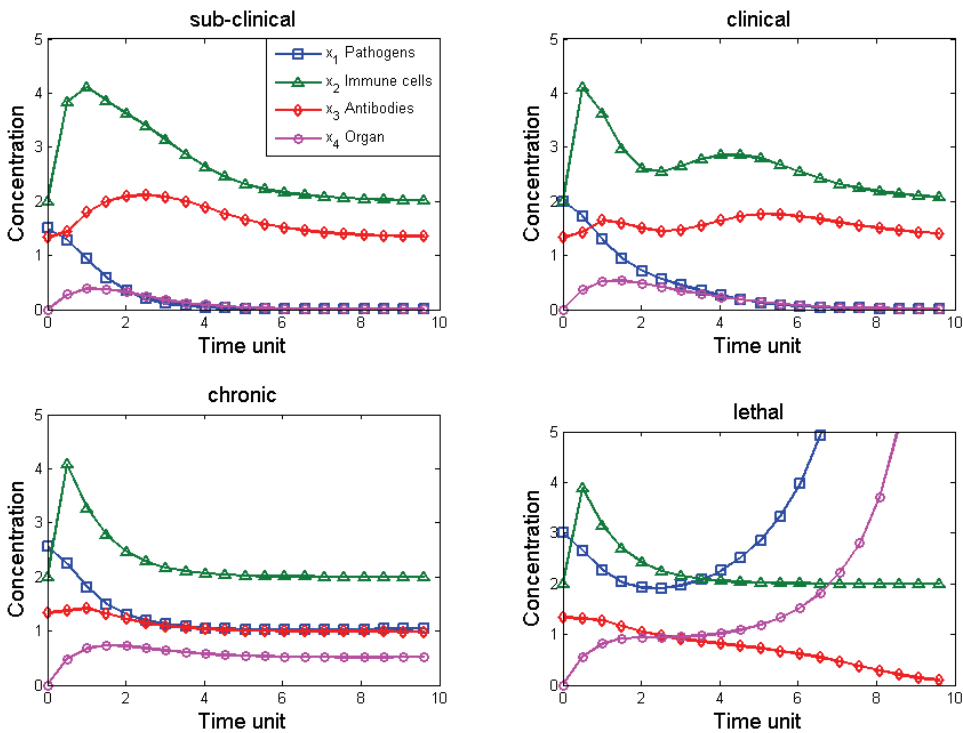


Fig. 2. Native immune responses to attack by different pathogens which are sub-clinical, clinical, chronic, and lethal conditions (Stengel et al., 2002a).

3. Robust H_∞ Therapeutic Control of Stochastic Innate Immune Response

Our control design purpose for nonlinear stochastic innate immune system in (2) is to specify a state feedback control $u(t) = k(x(t) - x_d(t))$ so that the immune system can track the desired response $x_d(t)$. Since the state variables are unavailable for feedback tracking control, the state variables have to be estimated for feedback tracking control $u(t) = k(\hat{x}(t) - x_d(t))$. Suppose the following observer-based control with $y(t)$ as input and $u(t)$ as output is proposed for robust H_∞ tracking control.

$$\begin{aligned} \dot{\hat{x}}(t) &= f(\hat{x}(t)) + g(\hat{x}(t))u(t) + l(\hat{x}(t))(y(t) - c(\hat{x}(t))) \\ u(t) &= k(\hat{x}(t) - x_d(t)) \end{aligned} \tag{3}$$

where the observer-gain $l(\hat{x}(t))$ is to be specified so that the estimation error $e(t) = x(t) - \hat{x}(t)$ can be as small as possible and control gain $k(\hat{x}(t) - x_d(t))$ is to be specified so that the system states $x(t)$ can come close to the desired state responses $x_d(t)$ from the stochastic point of view.

Consider a reference model of immune system with a desired time response described as

$$\dot{x}_d(t) = A_d x_d(t) + r(t) \tag{4}$$

where $x_d(t) \in \mathbf{R}^{n \times 1}$ is the reference state vector; $A_d \in \mathbf{R}^{n \times n}$ is a specific asymptotically stable matrix and $r(t)$ is a desired reference signal. It is assumed that $x_d(t), \forall t > 0$ represents a desired immune response for nonlinear stochastic immune system in (2) to follow, i.e. the therapeutic control is to specify the observer-based control in (3) such that the tracking error $\tilde{x}(t) = x(t) - x_d(t)$ must be as small as possible under the influence of uncertain exogenous pathogens and environmental disturbances $w(t)$ and measurement noises $n(t)$. Since the measurement noises $n(t)$, the exogenous pathogens and environmental disturbances $w(t)$ are uncertain and the reference signal $r(t)$ could be arbitrarily assigned, the robust H_∞ tracking control design in (3) should be specified so that the stochastic effect of three uncertainties $w(t)$, $n(t)$ and $r(t)$ on the tracking error could be set below a prescribed value ρ^2 , i.e. both the stochastic H_∞ reference tracking and H_∞ state estimation should be achieved simultaneously under uncertain $w(t)$, $n(t)$ and $r(t)$.

$$\frac{\mathbf{E} \left[\int_0^{t_f} (\tilde{x}^T(t) Q_1 \tilde{x}(t) + e^T(t) Q_2 e(t)) dt \right]}{\mathbf{E} \left[\int_0^{t_f} (w^T(t) w(t) + n^T(t) n(t) + r^T(t) r(t)) dt \right]} \leq \rho^2 \tag{5}$$

where the weighting matrices Q_i are assumed to be diagonal as follows

$$Q_i = \begin{bmatrix} q_{11}^i & 0 & 0 & 0 \\ 0 & q_{22}^i & 0 & 0 \\ 0 & 0 & q_{33}^i & 0 \\ 0 & 0 & 0 & q_{44}^i \end{bmatrix}, \quad i = 1, 2.$$

The diagonal element q_{ii}^i of Q_i denotes the punishment on the corresponding tracking error and estimation error. Since the stochastic effect of $w(t)$, $r(t)$ and $n(t)$ on tracking error $\tilde{x}(t)$

and estimation error $e(t)$ is prescribed below a desired attenuation level ρ^2 from the energy point of view, the robust H_∞ stochastic tracking problem of equation (5) is suitable for the robust H_∞ stochastic tracking problem under environmental disturbances $w(t)$, measurement noises $n(t)$ and changeable reference $r(t)$, which are always met in practical design cases.

Remark 1:

If the environmental disturbances $w(t)$ and measurement noises $n(t)$ are deterministic signals, the expectative symbol $\mathbf{E}[\cdot]$ in (5) can be omitted.

Let us denote the augmented vector $\bar{x} = \begin{bmatrix} e(t) \\ x(t) \\ x_d(t) \end{bmatrix}$, then we get the dynamic equation of the

augmented stochastic system as

$$\begin{aligned} \dot{\bar{x}}(t) &= \begin{bmatrix} \dot{e}(t) \\ \dot{x}(t) \\ \dot{x}_d(t) \end{bmatrix} \\ &= \begin{bmatrix} f(x) - f(\hat{x}) + k(\hat{x} - x_d)(g(x) - g(\hat{x})) + l(\hat{x})(c(x) - c(\hat{x})) \\ f(x) + k(\hat{x} - x_d)g(x) \\ A_d x_d \end{bmatrix} + \begin{bmatrix} I & 0 & 0 \\ 0 & D & 0 \\ 0 & 0 & I \end{bmatrix} \begin{bmatrix} n(t) \\ w(t) \\ r(t) \end{bmatrix} \end{aligned} \tag{6}$$

The augmented stochastic system above can be represented in a general form by

$$\dot{\bar{x}}(t) = F(\bar{x}(t)) + \bar{D}\bar{w}(t) \tag{7}$$

where $F(\bar{x}(t)) = \begin{bmatrix} f(x) - f(\hat{x}) + k(\hat{x} - x_d)(g(x) - g(\hat{x})) + l(\hat{x})(c(x) - c(\hat{x})) \\ f(x) + k(\hat{x} - x_d)g(x) \\ A_d x_d \end{bmatrix}$, $\bar{w}(t) = \begin{bmatrix} n(t) \\ w(t) \\ r(t) \end{bmatrix}$, and

$$\bar{D} = \begin{bmatrix} I & 0 & 0 \\ 0 & D & 0 \\ 0 & 0 & I \end{bmatrix}.$$

The robust H_∞ stochastic tracking performance in (5) can be represented by

$$\frac{\mathbf{E} \left[\int_0^{t_f} \bar{x}^T(t) \bar{Q} \bar{x}(t) dt \right]}{\mathbf{E} \left[\int_0^{t_f} \bar{w}^T(t) \bar{w}(t) dt \right]} \leq \rho^2 \text{ if } \bar{x}(0) = 0 \tag{8}$$

or $\mathbf{E} \left[\int_0^{t_f} \bar{x}^T(t) \bar{Q} \bar{x}(t) dt \right] \leq \rho^2 \mathbf{E} \left[\int_0^{t_f} \bar{w}^T(t) \bar{w}(t) dt \right]$ where $\bar{Q} = \begin{bmatrix} Q_2 & 0 & 0 \\ 0 & Q_1 & -Q_1 \\ 0 & -Q_1 & Q_1 \end{bmatrix}$

If the stochastic initial condition $\bar{x}(0) \neq 0$ and is also considered in the H_∞ tracking performance, then the above stochastic H_∞ inequality should be modified as

$$\mathbf{E} \left[\int_0^{t_f} \bar{x}^T(t) \bar{Q} \bar{x}(t) dt \right] \leq \mathbf{E} [V(\bar{x}(0))] + \rho^2 \mathbf{E} \left[\int_0^{t_f} \bar{w}^T(t) \bar{w}(t) dt \right] \tag{9}$$

for some positive function $V(\bar{x}(0))$. Then we get the following result.

Theorem 1: If we can specify the control gain $k(\hat{x} - x_d)$ and observer gain $l(\hat{x})$ in the observer-based control law in (3) for stochastic immune system (2) such that the following HJI has a positive solution $V(\bar{x}(t)) > 0$

$$\bar{x}(t)^T \bar{Q} \bar{x}(t) + \left(\frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} \right)^T F(\bar{x}(t)) + \frac{1}{4\rho^2} \left(\frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} \right)^T \bar{D} \bar{D}^T \left(\frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} \right) < 0 \tag{10}$$

Then the robust stochastic H_∞ tracking performance in (5) is achieved for a prescribed tracking performance ρ^2 .

Proof: see Appendix A.

Since ρ^2 is a prescribed noise attenuation level of H_∞ tracking performance in (5), based on the analysis above, the optimal stochastic H_∞ tracking performance still need to minimize ρ^2 as follows

$$\rho_0^2 = \min_{V(\bar{x}) > 0} \rho^2 \tag{11}$$

subject to $V(\bar{x}(t)) > 0$ and equation (10).

At present, there does not exist any analytic or numerical solution for (10) or (11) except in very simple cases.

4. Robust fuzzy observer-based tracking control design for stochastic innate immune system

Because it is very difficult to solve the nonlinear HJI in (10), no simple approach is available to solve the constrained optimization problem in (11) for robust model tracking control of stochastic innate immune system. Recently, the fuzzy T-S model has been widely applied to approximate the nonlinear system via interpolating several linearized systems at different operating points (Chen et al., 1999,2000; Takagi & Sugeno, 1985). Using fuzzy interpolation approach, the HJI in (10) can be replaced by a set of linear matrix inequalities (LMIs). In this situation, the nonlinear stochastic H_∞ tracking problem in (5) could be easily solved by fuzzy method for the design of robust H_∞ tracking control for stochastic innate immune response systems.

Suppose the nonlinear stochastic immune system in (1) can be represented by the Takagi-Sugeno (T-S) fuzzy model (Takagi & 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 H_∞ tracking problem by fuzzy observer-based control to achieve a desired immune response under stochastic noises. The i -th rule of fuzzy model for nonlinear stochastic immune system in (1) is in the following form (Chen et al., 1999,2000).

Plant Rule i :

If $z_1(t)$ is F_{i1} and ... and $z_g(t)$ is F_{ig} ,

$$\begin{aligned} \text{then } \dot{x}(t) &= \mathbf{A}_i x(t) + \mathbf{B}_i u(t) + D w(t), \quad i = 1, 2, 3, \dots, L \\ y(t) &= C_i x(t) + n(t) \end{aligned} \tag{12}$$

in which F_{ij} is the fuzzy set; \mathbf{A}_i , \mathbf{B}_i , and C_i are known constant matrices; L is the number of If-Then rules; g is the number of premise variables; and $z_1(t), z_2(t), \dots, z_g(t)$ are the premise variables. The fuzzy system is inferred as follows (Chen et al., 1999,2000; Takagi & Sugeno, 1985)

$$\begin{aligned}\dot{\hat{x}}(t) &= \frac{\sum_{i=1}^L \mu_i(z(t)) [\mathbf{A}_i \hat{x}(t) + \mathbf{B}_i u(t) + D w(t)]}{\sum_{i=1}^L \mu_i(z(t))} \\ &= \sum_{i=1}^L h_i(z(t)) [\mathbf{A}_i \hat{x}(t) + \mathbf{B}_i u(t) + D w(t)] \\ y &= \sum_{i=1}^L h_i(z(t)) C_i \hat{x}(t) + n(t)\end{aligned}\quad (13)$$

where $\mu_i(z(t)) = \prod_{j=1}^g F_{ij}(z_j(t))$, $h_i(z(t)) = \frac{\mu_i(z(t))}{\sum_{i=1}^L \mu_i(z(t))}$, $z(t) = [z_1(t), z_2(t), \dots, z_g(t)]$, and $F_{ij}(z_j(t))$ is the grade of membership of $z_j(t)$ in F_{ij} .

We assume

$$\mu_i(z(t)) \geq 0 \text{ and } \sum_{i=1}^L \mu_i(z(t)) > 0 \quad (14)$$

Therefore, we get

$$h_i(z(t)) \geq 0 \text{ and } \sum_{i=1}^L h_i(z(t)) = 1 \quad (15)$$

The T-S fuzzy model in (13) is to interpolate L stochastic linear systems to approximate the nonlinear system in (1) via the fuzzy basis functions $h_i(z(t))$. We could specify the parameter \mathbf{A}_i and \mathbf{B}_i easily so that $\sum_{i=1}^L h_i(z(t)) \mathbf{A}_i \hat{x}(t)$ and $\sum_{i=1}^L h_i(z(t)) \mathbf{B}_i$ in (13) can approximate $F(x(t))$ and $g(x(t))$ in (2) by the fuzzy identification method (Takagi & Sugeno, 1985).

By using fuzzy *If-Then* rules interpolation, the fuzzy observer is proposed to deal with the state estimation of nonlinear stochastic immune system (1).

Observer Rule i :

If $z_1(t)$ is F_{i1} and ... and $z_g(t)$ is F_{ig} ,

$$\text{then } \dot{\hat{x}}(t) = \mathbf{A}_i \hat{x}(t) + \mathbf{B}_i u(t) + L_i (y(t) - \hat{y}(t)), \quad i = 1, 2, 3, \dots, L \quad (16)$$

where L_i is the observer gain for the i th observer rule and $\hat{y}(t) = \sum_{i=1}^L h_i(z(t)) C_i \hat{x}(t)$.

The overall fuzzy observer in (16) can be represented as (Chen et al., 1999,2000)

$$\dot{\hat{x}}(t) = \sum_{i=1}^L h_i(z(t)) [\mathbf{A}_i \hat{x}(t) + \mathbf{B}_i u(t) + L_i (y(t) - \hat{y}(t))] \quad (17)$$

Suppose the following fuzzy observer-based controller is employed to deal with the above robust H_∞ tracking control design

Control Rule j :

If $z_1(t)$ is F_{j1} and ... and $z_g(t)$ is F_{jg} ,

$$\text{then } u = \sum_{j=1}^L h_j(z(t))K_j(\hat{x}(t) - x_d(t)) \tag{18}$$

Remark 2:

1. The premise variables $z(t)$ can be measurable stable variables, outputs or combination of measurable state variables (Ma et al., 1998; Tanaka et al., 1998; Wang et al., 1996). The limitation of this approach is that some state variables must be measurable to construct the fuzzy observer and fuzzy controller. This is a common limitation for control system design of T-S fuzzy approach (Ma et al., 1998; Tanaka et al., 1998). If the premise variables of the fuzzy observer depend on the estimated state variables, i.e., $\hat{z}(t)$ instead of $z(t)$ in the fuzzy observer, the situation becomes more complicated. In this case, it is difficult to directly find control gains K_j and observer gains L_i . The problem has been discussed in (Tanaka et al., 1998).
2. The problem of constructing T-S fuzzy model for nonlinear systems can be found in (Kim et al., 1997; Sugeno & Kang, 1988).

Let us denote the estimation errors as $e(t) = x(t) - \hat{x}(t)$. The estimation errors dynamic is represented as

$$\begin{aligned} \dot{e}(t) &= \dot{x}(t) - \dot{\hat{x}}(t) \\ &= \sum_{i=1}^L \sum_{j=1}^L h_i(z(t))h_j(z(t))[\mathbf{A}_i x(t) + \mathbf{B}_i u(t) + D w(t)] - [\mathbf{A}_i \hat{x}(t) + \mathbf{B}_i u(t) + L_i(y(t) - C_j \hat{x}(t))] \\ &= \sum_{i=1}^L \sum_{j=1}^L h_i(z(t))h_j(z(t))[(\mathbf{A}_i - L_i C_j)e(t) - L_i n(t)] + D w(t) \end{aligned}$$

After manipulation, the augmented system in (6) can be expressed as the following fuzzy approximation form

$$\dot{\bar{x}}(t) = \sum_{i=1}^L h_i(z(t)) \sum_{j=1}^L h_j(z(t)) [\bar{\mathbf{A}}_{ij} \bar{x}(t) + \bar{\mathbf{E}}_i \bar{w}(t)] \tag{19}$$

where $\bar{\mathbf{A}}_{ij} = \begin{bmatrix} \mathbf{A}_i - L_i C_j & 0 & 0 \\ -\mathbf{B}_i K_j & \mathbf{A}_i + \mathbf{B}_i K_j & -\mathbf{B}_i K_j \\ 0 & 0 & A_d \end{bmatrix}$, $\bar{x}(t) = \begin{bmatrix} e(t) \\ x(t) \\ x_d(t) \end{bmatrix}$, $\bar{w}(t) = \begin{bmatrix} n(t) \\ w(t) \\ r(t) \end{bmatrix}$, $\bar{\mathbf{E}}_i = \begin{bmatrix} -L_i & D & 0 \\ 0 & D & 0 \\ 0 & 0 & I \end{bmatrix}$.

Theorem 2: In the nonlinear stochastic immune system of (2), if $\bar{P} = \bar{P}^T > 0$ is the common solution of the following matrix inequalities:

$$\bar{\mathbf{A}}_{ij}^T \bar{P} + \bar{P} \bar{\mathbf{A}}_{ij} + \frac{1}{\rho^2} \bar{P} \bar{\mathbf{E}}_i \bar{\mathbf{E}}_i^T \bar{P} + \bar{Q} < 0, \quad i, j = 1, 2, \dots, L \tag{20}$$

then the robust H_∞ tracking control performance in (8) or (9) is guaranteed for a prescribed ρ^2 .

In the above robust H_∞ tracking control design, we don't need the statistics of disturbances, measurement noises and initial condition. We only need to eliminate their effect on the tracking error and state estimation error below a prescribed level ρ^2 . To obtain the best H_∞ tracking performance, the optimal H_∞ tracking control problem can be formulated as the following minimization problem.

$$\rho_0^2 = \min_{\bar{P} > 0} \rho^2 \tag{21}$$

subject to $\bar{P} > 0$ and equation (20).

Proof: see Appendix B.

In general, it is not easy to analytically determine the constrained optimization problem in (21). Fortunately, the optimal H_∞ tracking control problem in (21) can be transferred into a minimization problem subject to some linear matrix inequalities (LMIs). The LMIP can be solved by a computationally efficient method using a convex optimization technique (Boyd, 1994) as described in the following.

By the Schur complements (Boyd, 1994), equation (20) is equivalent to

$$\begin{bmatrix} \bar{\mathbf{A}}_{ij}^T \bar{P} + \bar{P} \bar{\mathbf{A}}_{ij} + \bar{Q} & \bar{P} \bar{L} \\ \bar{L}^T \bar{P} & -\rho^2 (H H^T)^{-1} \end{bmatrix} < 0 \tag{22}$$

where $\bar{L} = \begin{bmatrix} L_i & I & 0 \\ 0 & I & 0 \\ 0 & 0 & I \end{bmatrix}$ and $H = \begin{bmatrix} -I & 0 & 0 \\ 0 & D & 0 \\ 0 & 0 & I \end{bmatrix}$.

For the convenience of design, we assume $\bar{P} = \begin{bmatrix} P_{11} & 0 & 0 \\ 0 & P_{22} & 0 \\ 0 & 0 & P_{33} \end{bmatrix}$ and substitute it into (22) to

obtain

$$\begin{bmatrix} S_{11} & S_{12} & 0 & Z_i & P_{11} & 0 \\ S_{21} & S_{22} & S_{23} & 0 & P_{22} & 0 \\ 0 & S_{32} & S_{33} & 0 & 0 & P_{33} \\ Z_i^T & 0 & 0 & -\rho^2 I & 0 & 0 \\ P_{11} & P_{22} & 0 & 0 & -\rho^2 (D D^T)^{-1} & 0 \\ 0 & 0 & P_{33} & 0 & 0 & -\rho^2 I \end{bmatrix} < 0 \tag{23}$$

where $S_{11} = \mathbf{A}_i^T P_{11} + P_{11} \mathbf{A}_i - C_j^T Z_i^T - Z_i C_j + Q_2$

$S_{12} = S_{21}^T = -P_{22} \mathbf{B}_i K_j$

$S_{22} = (\mathbf{A}_i + \mathbf{B}_i K_j)^T P_{22} + P_{22} (\mathbf{A}_i + \mathbf{B}_i K_j) + Q_1$

$S_{23} = S_{32}^T = -P_{22} \mathbf{B}_i K_j - Q_1$

$S_{33} = A_d^T P_{33} + P_{33} A_d + Q_1$ and $Z_i = P_{11} L_i$.

Since five parameters P_{11} , P_{22} , P_{33} , K_j , and L_i should be determined from (23) and they are highly coupled, there are no effective algorithms for solving them simultaneously till now. In the following, a decoupled method (Tseng, 2008) is provided to solve these parameters simultaneously.

Note that (23) can be decoupled as

$$\begin{bmatrix} S_{11} & S_{12} & 0 & Z_i & P_{11} & 0 \\ S_{21} & S_{22} & S_{23} & 0 & P_{22} & 0 \\ 0 & S_{32} & S_{33} & 0 & 0 & P_{33} \\ Z_i^T & 0 & 0 & -\rho^2 I & 0 & 0 \\ P_{11} & P_{22} & 0 & 0 & -\rho^2 (DD^T)^{-1} & 0 \\ 0 & 0 & P_{33} & 0 & 0 & -\rho^2 I \end{bmatrix} = \begin{bmatrix} \mathbf{A}_i^T P_{11} + P_{11} \mathbf{A}_i - \mathbf{C}^T Z_i^T & 0 & 0 & Z_i & P_{11} & 0 \\ -Z_i \mathbf{C} + Q_2 + \gamma P_{22} & -\gamma_1 I + Q_1 & -Q_1 & 0 & 0 & 0 \\ 0 & -Q_1 & A_d^T P_{33} + P_{33} A_d & 0 & 0 & P_{33} \\ 0 & -Q_1 & +Q_1 + \gamma P_{22} & 0 & 0 & 0 \\ Z_i^T & 0 & 0 & -\rho^2 I & 0 & 0 \\ P_{11} & 0 & 0 & 0 & -\rho^2 (DD^T)^{-1} & 0 \\ 0 & 0 & 0 & 0 & +\gamma P_{22} & 0 \\ 0 & 0 & P_{33} & 0 & 0 & -\rho^2 I \end{bmatrix} + \begin{bmatrix} -\gamma P_{22} & -P_{22} \mathbf{B}_i K_j & 0 & 0 & 0 & 0 \\ (-P_{22} \mathbf{B}_i K_j)^T & (\mathbf{A}_i + \mathbf{B}_i K_j)^T P_{22} & -P_{22} \mathbf{B}_i K_j & 0 & P_{22} & 0 \\ 0 & +P_{22} (\mathbf{A}_i + \mathbf{B}_i K_j) + \gamma_1 I & -P_{22} \mathbf{B}_i K_j & 0 & 0 & 0 \\ 0 & (-P_{22} \mathbf{B}_i K_j)^T & -\gamma P_{22} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\gamma P_{22} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \tag{24}$$

where γ and γ_1 are some positive scalars.

Lemma 1:

If

$$\begin{bmatrix} a_{11} & 0 & 0 & a_{14} & a_{15} & 0 \\ 0 & a_{22} & a_{23} & 0 & 0 & 0 \\ 0 & a_{32} & a_{33} & 0 & 0 & a_{36} \\ a_{41} & 0 & 0 & a_{44} & 0 & 0 \\ a_{51} & 0 & 0 & 0 & a_{55} & 0 \\ 0 & 0 & a_{63} & 0 & 0 & a_{66} \end{bmatrix} < 0 \tag{25}$$

and

$$\begin{bmatrix} b_{11} & b_{12} & 0 & 0 \\ b_{21} & b_{22} & b_{23} & b_{24} \\ 0 & b_{32} & b_{33} & 0 \\ 0 & b_{42} & 0 & b_{44} \end{bmatrix} < 0 \tag{26}$$

then

$$\begin{bmatrix} a_{11} & 0 & 0 & a_{14} & a_{15} & 0 \\ 0 & a_{22} & a_{23} & 0 & 0 & 0 \\ 0 & a_{32} & a_{33} & 0 & 0 & a_{36} \\ a_{41} & 0 & 0 & a_{44} & 0 & 0 \\ a_{51} & 0 & 0 & 0 & a_{55} & 0 \\ 0 & 0 & a_{63} & 0 & 0 & a_{66} \end{bmatrix} + \begin{bmatrix} b_{11} & b_{12} & 0 & 0 & 0 & 0 \\ b_{21} & b_{22} & b_{23} & 0 & b_{24} & 0 \\ 0 & b_{32} & b_{33} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & b_{42} & 0 & 0 & b_{44} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} < 0 \tag{27}$$

Proof: see Appendix C.

From the above lemma, it is obvious that if

$$\begin{bmatrix} \mathbf{A}_i^T P_{11} + P_{11} \mathbf{A}_i - C_j^T Z_i^T & 0 & 0 & Z_i & P_{11} & 0 \\ -Z_i C_j + Q_2 + \gamma P_{22} & & & & & \\ 0 & -\gamma_1 I + Q_1 & -Q_1 & 0 & 0 & 0 \\ 0 & -Q_1 & A_d^T P_{33} + P_{33} A_d + Q_1 + \gamma P_{22} & 0 & 0 & P_{33} \\ Z^T & 0 & 0 & -\rho^2 I & 0 & 0 \\ P_{11} & 0 & 0 & 0 & -\rho^2 (DD^T)^{-1} + \gamma P_{22} & 0 \\ 0 & 0 & P_{33} & 0 & 0 & -\rho^2 I \end{bmatrix} < 0 \tag{28}$$

and

$$\begin{bmatrix} -\gamma P_{22} & -P_{22} \mathbf{B}_i K_j & 0 & 0 \\ (-P_{22} \mathbf{B}_i K_j)^T & (\mathbf{A}_i + \mathbf{B}_i K_j)^T P_{22} + P_{22} (\mathbf{A}_i + \mathbf{B}_i K_j) + \gamma_1 I & -P_{22} \mathbf{B}_i K_j & P_{22} \\ 0 & (-P_{22} \mathbf{B}_i K_j)^T & -\gamma P_{22} & 0 \\ 0 & P_{22} & 0 & -\gamma P_{22} \end{bmatrix} < 0 \tag{29}$$

then (23) holds.

Remark 3:

Note that (28) is related to the observer part (i.e., the parameters are P_{11} , P_{22} , P_{33} , and L_i) and (29) is related to the controller part (i.e., the parameters are P_{22} and K_j), respectively. Although the parameters P_{22} , K_j and γ are coupled nonlinearly, seven parameters P_{11} , P_{22} , P_{33} , K_j , L_i , γ and γ_1 can be determined by the following arrangement.

Note that, by the Schur complements (Boyd, 1994) equation (28) is equivalent to

$$\begin{bmatrix}
 \mathbf{A}_i^T P_{11} + P_{11} \mathbf{A}_i - C^T Z_i^T - Z_i C + Q_2 & 0 & 0 & Z_i \\
 0 & -\gamma_1 I + Q_1 & -Q_1 & 0 \\
 0 & -Q_1 & A_d^T P_{33} + P_{33} A_d + Q_1 & 0 \\
 Z_i^T & 0 & 0 & -\rho^2 I \\
 P_{11} & 0 & 0 & 0 \\
 0 & 0 & P_{33} & 0 \\
 I & 0 & 0 & 0 \\
 0 & 0 & I & 0 \\
 0 & 0 & 0 & 0
 \end{bmatrix} < 0 \tag{30}$$

$$\begin{bmatrix}
 P_{11} & 0 & I & 0 & 0 \\
 0 & 0 & 0 & 0 & 0 \\
 0 & P_{33} & 0 & I & 0 \\
 0 & 0 & 0 & 0 & 0 \\
 -\rho^2 (DD^T)^{-1} & 0 & 0 & 0 & I \\
 0 & -\rho^2 I & 0 & 0 & 0 \\
 0 & 0 & -\gamma^{-1} W_{22} & 0 & 0 \\
 0 & 0 & 0 & -\gamma^{-1} W_{22} & 0 \\
 I & 0 & 0 & 0 & -\gamma^{-1} W_{22}
 \end{bmatrix} < 0$$

where $W_{22} = P_{22}^{-1}$, and equation (29) is equivalent to

$$\begin{bmatrix}
 -\gamma W_{22} & -B_i Y_j & 0 & 0 & 0 \\
 (-B_i Y_j)^T & W_{22} \mathbf{A}_i^T + \mathbf{A}_i W_{22} + Y_j^T \mathbf{B}_i^T + \mathbf{B}_i Y_j & -B_i Y_j & W_{22} & W_{22} \\
 0 & (-B_i Y_j)^T & -\gamma W_{22} & 0 & 0 \\
 0 & W_{22} & 0 & -\gamma W_{22} & 0 \\
 0 & W_{22} & 0 & 0 & -\gamma_1^{-1} I
 \end{bmatrix} < 0 \tag{31}$$

where $Y_j = K_j W_{22}$.

Therefore, if (30) and (31) are all held then (23) holds. Recall that the attenuation ρ^2 can be minimized so that the optimal H_∞ tracking performance in (21) is reduced to the following constrained optimization problem.

$$\rho_0^2 = \min_{P_{11}, P_{22}, P_{33}} \rho^2 \tag{32}$$

subject to $P_{11} > 0, P_{22} > 0, P_{33} > 0, \gamma > 0, \gamma_1 > 0$ and (30)-(31).

which can be solved by decreasing ρ^2 as small as possible until the parameters $P_{11} > 0, P_{22} > 0, P_{33} > 0, \gamma > 0$ and $\gamma_1 > 0$ do not exist.

Remark 4:

Note that the optimal H_∞ tracking control problem in (32) is not a strict LMI problem since it is still a bilinear form in (30)-(31) of two scalars γ and γ_1 and becomes a standard linear matrix inequality problem (LMIP) (Boyd, 1994) if γ and γ_1 are given in advance. The decoupled method (Tseng, 2008) bring some conservatism in controller design. However, the parameters $P_{11}, P_{22} = W_{22}^{-1}, P_{33}, K_j = Y_j W_{22}^{-1}$ and $L_i = P_{11}^{-1} Z_i$ can be determined simultaneously from (32) by the decoupled method if scalars γ and γ_1 are given in advance. The useful software packages such as Robust Control Toolbox in Matlab (Balas et al., 2007) can be employed to solve the LMIP in (32) easily.

In general, it is quite easy to determine scalars γ and γ_1 beforehand to solve the LMIP with a smaller attenuation level ρ^2 . In this study, the genetic algorithm (GA) is proposed to deal with the optimal H_∞ tracking control problem in (32) since GA, which can simultaneously evaluate many points in the parameters space, is a very powerful searching algorithm based on the mechanics of natural selection and natural genetics. More details about GA can be found in (Jang et al., 1997).

According to the analysis above, the H_∞ tracking control of stochastic innate immune system via fuzzy observer-based state feedback is summarized as follows and the structural diagram of robust fuzzy observer-based tracking control design has shown in Fig. 3.

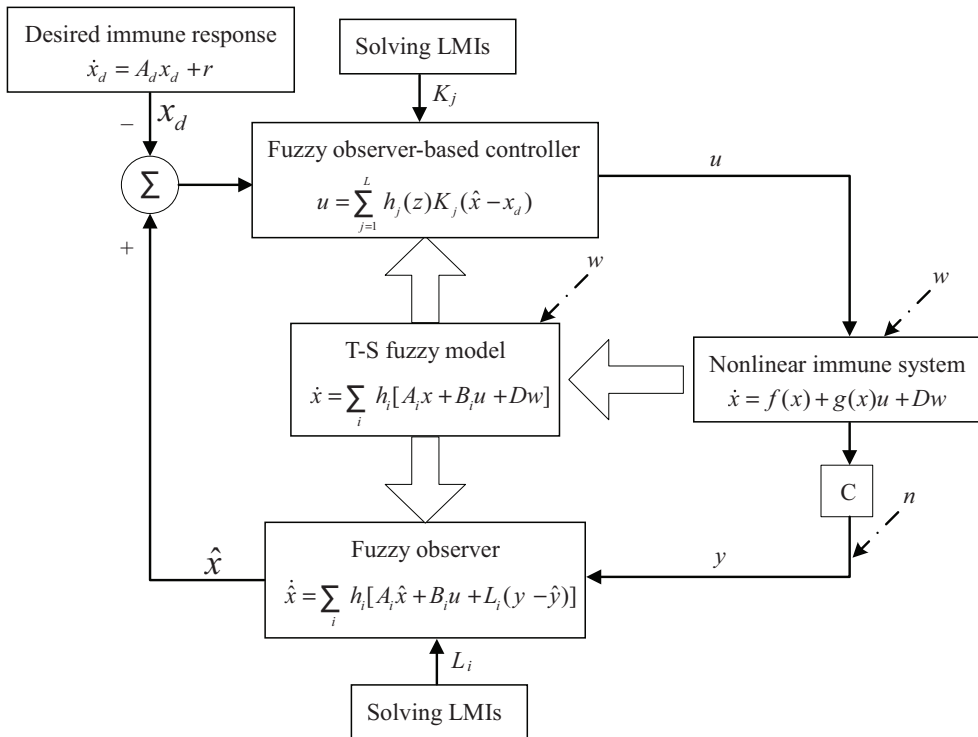


Fig. 3. Structural diagram of robust fuzzy observer-based tracking control design.

Design Procedure:

1. Provide a desired reference model in (4) of the immune system.
2. Select membership functions and construct fuzzy plant rules in (12).
3. Generate randomly a population of binary strings: With the binary coding method, the scalars γ and γ_1 would be coded as binary strings. Then solve the LMIP in (32) with scalars γ and γ_1 corresponding to binary string using Robust Control Toolbox in Matlab by searching the minimal value of ρ^2 . If the LMIP is infeasible for the corresponding string, this string is escaped from the current generation.
4. Calculate the fitness value for each passed string: In this step, the fitness value is calculated based on the attenuation level ρ^2 .
5. Create offspring strings to form a new generation by some simple GA operators like reproduction, crossover, and mutation: In this step, (i) strings are selected in a mating pool from the passed strings with probabilities proportional to their fitness values, (ii) and then crossover process is applied with a probability equal to a prescribed crossover rate, (iii) and finally mutation process is applied with a probability equal to a prescribed mutation rate. Repeating (i) to (iii) until enough strings are generated to form the next generation.
6. Repeat Step 3 to Step 5 for several generations until a stop criterion is met.
7. Based on the scalars γ and γ_1 obtained from above steps, one can obtain the attenuation level ρ^2 and the corresponding P_{11} , $P_{22} = W_{22}^{-1}$, P_{33} , $K_j = Y_j W_{22}^{-1}$ and $L_i = P_{11}^{-1} Z_i$, simultaneously.
8. Construct the fuzzy observer in (17) and fuzzy controller in (18).

5. Computational simulation example

Parameter	Value	Description
a_{11}	1	Pathogens reproduction rate coefficient
a_{12}	1	The suppression by pathogens coefficient
a_{22}	3	Immune reactivity coefficient
a_{23}	1	The mean immune cell production rate coefficient
x_2	2	The steady-state concentration of immune cells
a_{31}	1	Antibodies production rate coefficient
a_{32}	1.5	The antibody mortality coefficient
a_{33}	0.5	The rate of antibodies suppress pathogens
a_{41}	0.5	The organ damage depends on the pathogens damage possibilities coefficient
a_{42}	1	Organ recovery rate
b_1	-1	Pathogen killer's agent coefficient
b_2	1	Immune cell enhancer coefficient
b_3	1	Antibody enhancer coefficient
b_4	-1	Organ health enhancer coefficient
c_1	1	Immune cell measurement coefficient
c_2	1	Antibody measurement coefficient
c_3	1	Organ health measurement coefficient

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

We consider the nonlinear stochastic innate immune system in (1), which is shown in Fig. 1. The values of the parameters are shown in Table 1. The stochastic noises of immune systems are mainly due to measurement errors, modeling errors and process noises (Milutinovic & De Boer, 2007). The rate of continuing introduction of exogenous pathogen and environmental disturbances $w_1 \sim w_4$ are unknown but bounded signals. Under infectious situation, the microbes infect the organ not only by an initial concentration of pathogen at the beginning but also by the continuous exogenous pathogens invasion w_1 and other environmental disturbances $w_2 \sim w_4$. In reality, however, the concentration of invaded pathogens is hardly to be measured. So, we assume that only immune cell, antibody, and organ health can be measured with measurement noises by medical devices or other biological techniques (e.g. immunofluorescence microscope). And then we can detect the numbers of molecules easily by using a fluorescence microscope (Piston, 1999).

The dynamic model of stochastic innate immune system under uncertain initial states, environmental disturbances and measurement noises is controlled by a combined therapeutic control as

$$\begin{aligned} \dot{x}_1 &= (1 - x_3)x_1 - u_1 + w_1 \\ \dot{x}_2 &= 3a_{21}(x_4)x_1x_3 - (x_2 - 2) - u_2 + w_2 \\ \dot{x}_3 &= x_2 - (1.5 + 0.5x_1)x_3 + u_3 + w_3 \\ \dot{x}_4 &= 0.5x_1 - x_4 + u_4 + w_4 \\ y_1 &= x_2 + n_1, y_2 = x_3 + n_2, y_3 = x_4 + n_3 \\ a_{21}(x_4) &= \begin{cases} \cos(\pi x_4), & 0 \leq x_4 \leq 0.5 \\ 0, & 0.5 \leq x_4 \end{cases} \end{aligned} \quad (33)$$

A set of initial condition is assumed $x(0) = [3.5 \ 2 \ 1.33 \ 0]^T$. For the convenience of simulation, we assume that $w_1 \sim w_4$ are zero mean white noises with standard deviations being all equal to 2. The measurement noises $n_1 \sim n_3$ are zero mean white noises with standard deviations being equal to 0.1. In this example, therapeutic controls $u_1 \sim u_4$ are combined to enhance the immune system. The measurable state variables $y_1 \sim y_3$ with measurement noises by medical devices or biological techniques are shown in Fig. 4.

Our reference model design objective is that the system matrix A_d and $r(t)$ should be specified beforehand so that its transient responses and steady state of reference system for stochastic innate immune response system are desired. If the real parts of eigenvalues of A_d are more negative (i.e. more robust stable), the tracking system will be more robust to the environmental disturbances. After some numerical simulations for clinical treatment, the desired reference signals are obtained by the following reference model, which is shown in Fig. 5.

$$\dot{x}_d(t) = \begin{bmatrix} -1.1 & 0 & 0 & 0 \\ 0 & -2 & 0 & 0 \\ 0 & 0 & -4 & 0 \\ 0 & 0 & 0 & -1.5 \end{bmatrix} x_d(t) + B_d u_{step}(t) \quad (34)$$

where $B_d = [0 \ 4 \ 16/3 \ 0]^T$ and $u_{step}(t)$ is the unit step function. The initial condition is given by $x_d(0) = [2.5 \ 3 \ 1.1 \ 0.8]^T$.

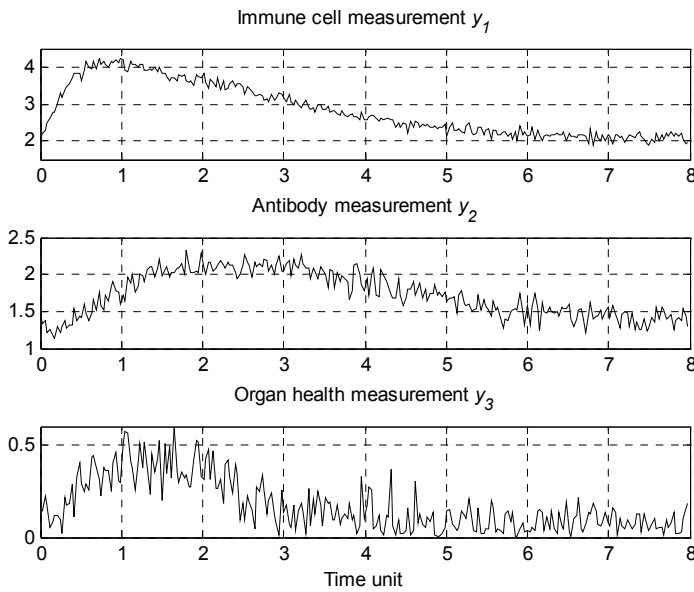


Fig. 4. The measurable state variables $y_1 \sim y_3$ with measurement noises $n_1 \sim n_3$ by medical devices or biological technique.

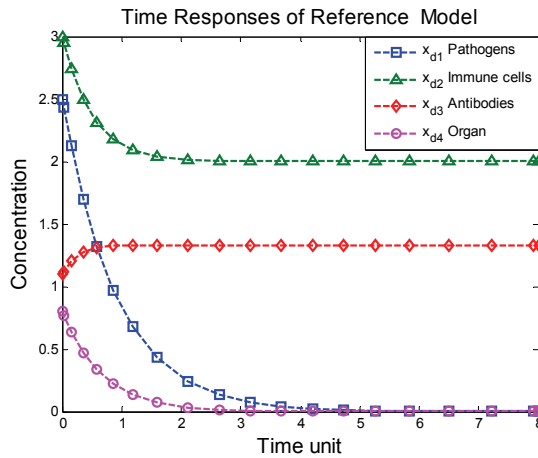


Fig. 5. The desired reference model with four desired states in (34): pathogens (x_{d1} , blue, dashed square line), immune cells (x_{d2} , green, dashed triangle line), antibodies (x_{d3} , red, dashed diamond line) and organ (x_{d4} , magenta, dashed, circle line)

We consider the lethal case of uncontrolled stochastic immune system in Fig. 6. The pathogen concentration increases rapidly causing organ failure. We aim at curing the organ before the organ health index exceeds one after a period of pathogens infection. As shown in Fig. 6, the black dashed line is a proper time to administrate drugs.

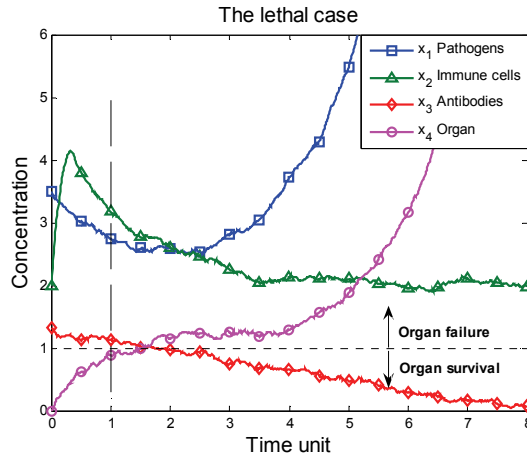


Fig. 6. The uncontrolled stochastic immune responses (lethal case) in (33) are shown to increase the level of pathogen concentration at the beginning of the time period. In this case, we try to administrate a treatment after a short period of pathogens infection. The cutting line (black dashed line) is an optimal time point to give drugs. The organ will survive or fail based on the organ health threshold (horizontal dotted line) [$x_4 < 1$: survival, $x_4 > 1$: failure].

To minimize the design effort and complexity for this nonlinear innate immune system in (33), we employ the T-S fuzzy model to construct fuzzy rules to approximate nonlinear immune system with the measurement output y_3 and y_4 as premise variables.

Plant Rule i :

If y_3 is F_{i1} and y_4 is F_{i2} , then

$$\dot{x}(t) = \mathbf{A}_i x(t) + \mathbf{B}u(t) + Dw(t), \quad i = 1, 2, 3, \dots, L$$

$$y(t) = Cx(t) + n(t)$$

To construct the fuzzy model, we must find the operating points of innate immune response. Suppose the operating points for y_3 are at $\bar{y}_{31} = -0.333$, $\bar{y}_{32} = 1.667$, and $\bar{y}_{33} = 3.667$. Similarly, the operating points for y_4 are at $\bar{y}_{41} = 0$, $\bar{y}_{42} = 1$, and $\bar{y}_{43} = 2$. For the convenience, we can create three triangle-type membership functions for the two premise variables as in Fig. 7 at the operating points and the number of fuzzy rules is $L = 9$. Then, we can find the fuzzy linear model parameters \mathbf{A}_i in the Appendix D as well as other parameters \mathbf{B} , C and D . In order to accomplish the robust H_∞ tracking performance, we should adjust a set of weighting matrices Q_1 and Q_2 in (8) or (9) as

$$Q_1 = \begin{bmatrix} 0.01 & 0 & 0 & 0 \\ 0 & 0.01 & 0 & 0 \\ 0 & 0 & 0.01 & 0 \\ 0 & 0 & 0 & 0.01 \end{bmatrix}, \quad Q_2 = \begin{bmatrix} 0.01 & 0 & 0 & 0 \\ 0 & 0.01 & 0 & 0 \\ 0 & 0 & 0.01 & 0 \\ 0 & 0 & 0 & 0.01 \end{bmatrix}.$$

After specifying the desired reference model, we need to solve the constrained optimization problem in (32) by employing Matlab Robust Control Toolbox. Finally, we obtain the feasible parameters $\gamma = 40$ and $\gamma_1 = 0.02$, and a minimum attenuation level $\rho_0^2 = 0.93$ and a

common positive-definite symmetric matrix \bar{P} with diagonal matrices P_{11} , P_{22} and P_{33} as follows

$$P_{11} = \begin{bmatrix} 0.23193 & -1.5549e-4 & 0.083357 & -0.2704 \\ -1.5549e-4 & 0.010373 & -1.4534e-3 & -7.0637e-3 \\ 0.083357 & -1.4534e-3 & 0.33365 & 0.24439 \\ -0.2704 & -7.0637e-3 & 0.24439 & 0.76177 \end{bmatrix},$$

$$P_{22} = \begin{bmatrix} 0.0023082 & 9.4449e-6 & -5.7416e-5 & -5.0375e-6 \\ 9.4449e-6 & 0.0016734 & 2.4164e-5 & -1.8316e-6 \\ -5.7416e-5 & 2.4164e-5 & 0.0015303 & 5.8989e-6 \\ -5.0375e-6 & -1.8316e-6 & 5.8989e-6 & 0.0015453 \end{bmatrix}$$

$$P_{33} = \begin{bmatrix} 1.0671 & -1.0849e-5 & 3.4209e-5 & 5.9619e-6 \\ -1.0849e-5 & 1.9466 & -1.4584e-5 & 1.9167e-6 \\ 3.4209e-5 & -1.4584e-5 & 3.8941 & -3.2938e-6 \\ 5.9619e-6 & 1.9167e-6 & -3.2938e-6 & 1.4591 \end{bmatrix}$$

The control gain K_j and the observer gain L_i can also be solved in the Appendix D.

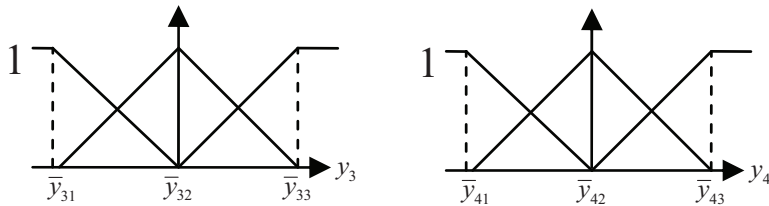


Fig. 7. Membership functions for two premise variables y_3 and y_4 .

Figures 8-9 present the robust H_∞ tracking control of stochastic immune system under the continuous exogenous pathogens, environmental disturbances and measurement noises. Figure 8 shows the responses of the uncontrolled stochastic immune system under the initial concentrations of the pathogens infection. After the one time unit (the black dashed line), we try to provide a treatment by the robust H_∞ tracking control of pathogens infection. It is seen that the stochastic immune system approaches to the desired reference model quickly. From the simulation results, the tracking performance of the robust model tracking control via T-S fuzzy interpolation is quite satisfactory except for pathogens state x_1 because the pathogens concentration cannot be measured. But, after treatment for a specific period, the pathogens are still under control. Figure 9 shows the four combined therapeutic control agents. The performance of robust H_∞ tracking control is estimated as

$$\frac{\mathbf{E} \left[\int_0^{t_f} (\tilde{x}^T(t)Q_1\tilde{x}(t) + e^T(t)Q_2e(t))dt \right]}{\mathbf{E} \left[\int_0^{t_f} (w^T(t)w(t) + n^T(t)n(t) + r^T(t)r(t))dt \right]} \approx 0.033 \leq \rho^2 = 0.93$$

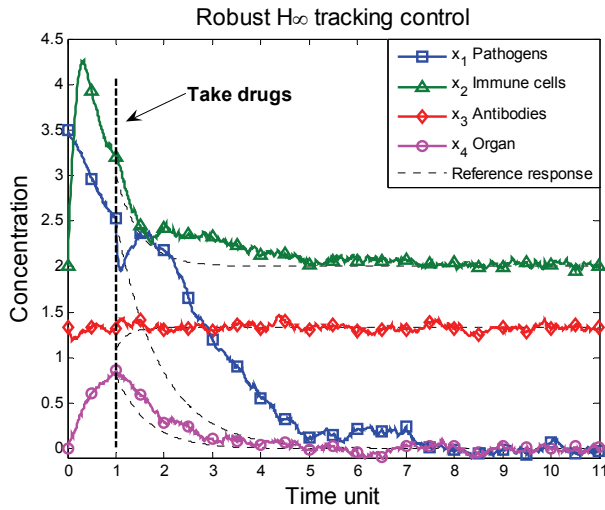


Fig. 8. The robust H_∞ tracking control of stochastic immune system under the continuous exogenous pathogens, environmental disturbances and measurement noises. We try to administrate a treatment after a short period (one time unit) of pathogens infection then the stochastic immune system approach to the desired reference model quickly except for pathogens state x_1 .

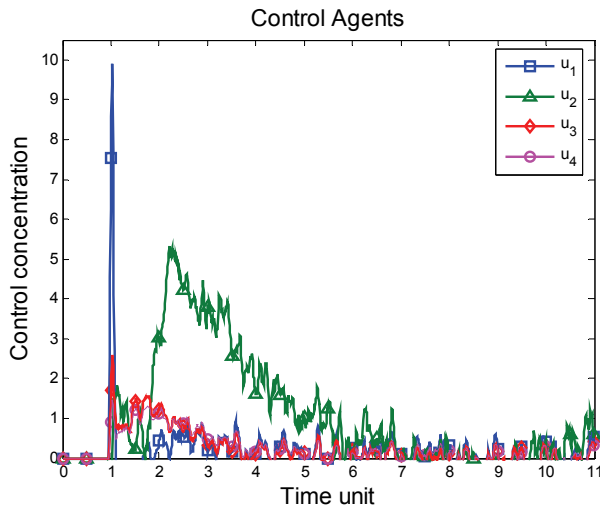


Fig. 9. The robust H_∞ tracking control in the simulation example. The drug control agents u_1 (blue, solid square line) for pathogens, u_2 for immune cells (green, solid triangle line), u_3 for antibodies (red, solid diamond line) and u_4 for organ (magenta, solid circle line).

Obviously, the robust H_∞ tracking performance is satisfied. The conservative results are due to the inherent conservation of solving LMI in (30)-(32).

6. Discussion and conclusion

In this study, we have developed a robust H_∞ tracking control design of stochastic immune response for therapeutic enhancement to track a prescribed immune response under uncertain initial states, environmental disturbances and measurement noises. Although the mathematical model of stochastic innate immune system is taken from the literature, it 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 assume that not all state variables can be measured. In the measurement process, the measured states are corrupted by noises. In this study, the statistic of disturbances, measurement noises and initial condition are assumed unavailable and cannot be used for the optimal stochastic tracking design. Therefore, the proposed H_∞ observer design is employed to attenuate these measurement noises to robustly estimate the state variables for therapeutic control and H_∞ control design is employed to attenuate disturbances to robustly track the desired time response of stochastic immune system simultaneity. Since the proposed H_∞ observer-based tracking control design can provide an efficient way to create a real time therapeutic regime despite disturbances, measurement noises and initial condition to protect suspected patients from the pathogens infection, in the future, we will focus on applications of robust H_∞ observer-based control design to therapy and drug design incorporating nanotechnology and metabolic engineering scheme.

Robustness is a significant property that allows for the stochastic innate immune system to maintain its function despite exogenous pathogens, environmental disturbances, system uncertainties and measurement noises. In general, the robust H_∞ -observer-based tracking control design for stochastic innate immune system needs to solve a complex nonlinear Hamilton-Jacobi inequality (HJI), which is generally difficult to solve for this control design. Based on the proposed fuzzy interpolation approach, the design of nonlinear robust H_∞ observer-based tracking control problem for stochastic innate immune system is transformed to solve a set of equivalent linear H_∞ observer-based tracking problem. Such transformation can then provide an easier approach by solving an LMI-constrained optimization problem for robust H_∞ observer-based tracking control design. With the help of the Robust Control Toolbox in Matlab instead of the HJI, we could solve these problems for robust H_∞ observer-based tracking control of stochastic innate immune system more efficiently. From the *in silico* simulation examples, the proposed robust H_∞ observer-based tracking control of stochastic 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.

7. Appendix

7.1 Appendix A: Proof of Theorem 1

Before the proof of *Theorem 1*, the following lemma is necessary.

Lemma 2:

For all vectors $\alpha, \beta \in \mathbf{R}^{n \times 1}$, the following inequality always holds

$$\alpha^T \beta + \beta^T \alpha \leq \frac{1}{\rho^2} \alpha^T \alpha + \rho^2 \beta^T \beta \text{ for any scale value } \rho > 0.$$

Let us denote a Lyapunov energy function $V(\bar{x}(t)) > 0$. Consider the following equivalent equation:

$$\mathbf{E} \left[\int_0^{t_f} \bar{x}^T(t) \bar{Q} \bar{x}(t) dt \right] = \mathbf{E}[V(\bar{x}(0))] - \mathbf{E}[V(\bar{x}(\infty))] + \mathbf{E} \left[\int_0^{t_f} \left(\bar{x}^T(t) \bar{Q} \bar{x}(t) + \frac{dV(\bar{x}(t))}{dt} \right) dt \right] \quad (\text{A1})$$

By the chain rule, we get

$$\frac{dV(\bar{x}(t))}{dt} = \left(\frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} \right)^T \frac{d\bar{x}(t)}{dt} = \left(\frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} \right)^T (F(\bar{x}(t)) + \bar{D}\bar{w}(t)) \quad (\text{A2})$$

Substituting the above equation into (A1), by the fact that $V(\bar{x}(\infty)) \geq 0$, we get

$$\mathbf{E} \left[\int_0^{t_f} \bar{x}^T(t) \bar{Q} \bar{x}(t) dt \right] \leq \mathbf{E}[V(\bar{x}(0))] + \mathbf{E} \left[\int_0^{t_f} \left(\bar{x}^T(t) \bar{Q} \bar{x}(t) + \left(\frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} \right)^T (F(\bar{x}(t)) + \bar{D}\bar{w}(t)) \right) dt \right] \quad (\text{A3})$$

By Lemma 2, we have

$$\begin{aligned} \left(\frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} \right)^T \bar{D}\bar{w}(t) &= \frac{1}{2} \left(\frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} \right)^T \bar{D}\bar{w}(t) + \frac{1}{2} \bar{w}^T(t) \bar{D}^T \frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} \\ &\leq \frac{1}{4\rho^2} \left(\frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} \right)^T \bar{D} \bar{D}^T \frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} + \rho^2 \bar{w}^T(t) \bar{w}(t) \end{aligned} \quad (\text{A4})$$

Therefore, we can obtain

$$\begin{aligned} \mathbf{E} \left[\int_0^{t_f} \bar{x}^T(t) \bar{Q} \bar{x}(t) dt \right] &\leq \mathbf{E}[V(\bar{x}(0))] + \mathbf{E} \left[\int_0^{t_f} \left(\bar{x}^T(t) \bar{Q} \bar{x}(t) + \left(\frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} \right)^T F(\bar{x}(t)) \right. \right. \\ &\quad \left. \left. + \frac{1}{4\rho^2} \left(\frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} \right)^T \bar{D} \bar{D}^T \frac{\partial V(\bar{x}(t))}{\partial \bar{x}(t)} + \rho^2 \bar{w}^T(t) \bar{w}(t) \right) dt \right] \end{aligned} \quad (\text{A5})$$

By the inequality in (10), then we get

$$\mathbf{E} \left[\int_0^{t_f} \bar{x}^T(t) \bar{Q} \bar{x}(t) dt \right] \leq \mathbf{E}[V(\bar{x}(0))] + \rho^2 \mathbf{E} \left[\int_0^{t_f} \bar{w}^T(t) \bar{w}(t) dt \right] \quad (\text{A6})$$

If $\bar{x}(0) = 0$, then we get the inequality in (8).

7.2 Appendix B: Proof of Theorem 2

Let us choose a Lyapunov energy function $V(\bar{x}(t)) = \bar{x}^T(t) \bar{P} \bar{x}(t) > 0$ where $\bar{P} = \bar{P}^T > 0$. Then equation (A1) is equivalent to the following:

$$\begin{aligned} \mathbf{E} \left[\int_0^{t_f} \bar{x}^T(t) \bar{Q} \bar{x}(t) dt \right] &= \mathbf{E}[V(\bar{x}(0))] - \mathbf{E}[V(\bar{x}(\infty))] + \mathbf{E} \left[\int_0^{t_f} \left(\bar{x}^T(t) \bar{Q} \bar{x}(t) + 2\bar{x}^T(t) \bar{P} \dot{\bar{x}}(t) \right) dt \right] \\ &\leq \mathbf{E}[V(\bar{x}(0))] + \mathbf{E} \left[\int_0^{t_f} \left(\bar{x}^T(t) \bar{Q} \bar{x}(t) + 2\bar{x}^T(t) \bar{P} \left(\sum_{i=1}^L h_i(z(t)) \sum_{j=1}^L h_j(z(t)) [\bar{\mathbf{A}}_{ij} \bar{x}(t) + \bar{E}_i \bar{w}(t)] \right) \right) dt \right] \\ &= \mathbf{E}[V(\bar{x}(0))] + \mathbf{E} \left[\int_0^{t_f} \left(\bar{x}^T(t) \bar{Q} \bar{x}(t) + \sum_{i=1}^L h_i(z(t)) \sum_{j=1}^L h_j(z(t)) [2\bar{x}^T(t) \bar{P} \bar{\mathbf{A}}_{ij} \bar{x}(t) + 2\bar{x}^T(t) \bar{P} \bar{E}_i \bar{w}(t)] \right) dt \right] \end{aligned} \quad (\text{A7})$$

By Lemma 2, we have

$$2\bar{x}^T(t)\bar{P}\bar{E}_i\bar{w}(t) = \bar{x}^T(t)\bar{P}\bar{E}_i\bar{w}(t) + \bar{w}^T(t)\bar{E}_i^T\bar{P}\bar{x}(t) \leq \frac{1}{\rho^2}\bar{x}^T(t)\bar{P}\bar{E}_i\bar{E}_i^T\bar{P}\bar{x}(t) + \rho^2\bar{w}^T(t)\bar{w}(t) \quad (A8)$$

Therefore, we can obtain

$$\begin{aligned} \mathbf{E}\left[\int_0^{t_f} \bar{x}^T(t)\bar{Q}\bar{x}(t)dt\right] &\leq \mathbf{E}[V(\bar{x}(0))] + \mathbf{E}\left[\int_0^{t_f} \left(\bar{x}^T(t)\bar{Q}\bar{x}(t) + \sum_{i=1}^L h_i(z(t))\sum_{j=1}^L h_j(z(t))\left[\bar{x}^T(\bar{P}\bar{A}_{ij} + \bar{A}_{ij}^T\bar{P})\bar{x} + \right. \right. \right. \\ &\quad \left. \left. + \frac{1}{\rho^2}\bar{x}^T(t)\bar{P}\bar{E}_i\bar{E}_i^T\bar{P}\bar{x}(t)\right) + \rho^2\bar{w}^T(t)\bar{w}(t)\right)dt\right] = \\ &= \mathbf{E}[V(\bar{x}(0))] + \mathbf{E}\left[\int_0^{t_f} \left(\bar{x}^T(t)\bar{Q}\bar{x}(t) + \sum_{i=1}^L h_i(z(t))\sum_{j=1}^L h_j(z(t))\bar{x}^T(t)\left[\bar{P}\bar{A}_{ij} + \bar{A}_{ij}^T\bar{P} + \right. \right. \right. \\ &\quad \left. \left. + \frac{1}{\rho^2}\bar{P}\bar{E}_i\bar{E}_i^T\bar{P}\right]\bar{x}(t) + \rho^2\bar{w}^T(t)\bar{w}(t)\right)dt\right] \end{aligned} \quad (A9)$$

By the inequality in (20), then we get

$$\mathbf{E}\left[\int_0^{t_f} \bar{x}^T(t)\bar{Q}\bar{x}(t)dt\right] \leq \mathbf{E}[V(\bar{x}(0))] + \rho^2\mathbf{E}\left[\int_0^{t_f} \bar{w}^T(t)\bar{w}(t)dt\right] \quad (A10)$$

This is the inequality in (9). If $\bar{x}(0) = 0$, then we get the inequality in (8).

7.3 Appendix C: Proof of Lemma 1

For $[e_1 \ e_2 \ e_3 \ e_4 \ e_5 \ e_6] \neq 0$, if (25)-(26) hold, then

$$\begin{aligned} &\begin{bmatrix} e_1 \\ e_2 \\ e_3 \\ e_4 \\ e_5 \\ e_6 \end{bmatrix}^T \left\{ \begin{bmatrix} a_{11} & 0 & 0 & a_{14} & a_{15} & 0 \\ 0 & a_{22} & a_{23} & 0 & 0 & 0 \\ 0 & a_{32} & a_{33} & 0 & 0 & a_{36} \\ a_{41} & 0 & 0 & a_{44} & 0 & 0 \\ a_{51} & 0 & 0 & 0 & a_{55} & 0 \\ 0 & 0 & a_{63} & 0 & 0 & a_{66} \end{bmatrix} + \begin{bmatrix} b_{11} & b_{12} & 0 & 0 & 0 & 0 \\ b_{21} & b_{22} & b_{23} & 0 & b_{24} & 0 \\ 0 & b_{32} & b_{33} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & b_{42} & 0 & 0 & b_{44} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \right\} \begin{bmatrix} e_1 \\ e_2 \\ e_3 \\ e_4 \\ e_5 \\ e_6 \end{bmatrix} \\ &= \begin{bmatrix} e_1 \\ e_2 \\ e_3 \\ e_4 \\ e_5 \\ e_6 \end{bmatrix}^T \begin{bmatrix} a_{11} & 0 & 0 & a_{14} & a_{15} & 0 \\ 0 & a_{22} & a_{23} & 0 & 0 & 0 \\ 0 & a_{32} & a_{33} & 0 & 0 & a_{36} \\ a_{41} & 0 & 0 & a_{44} & 0 & 0 \\ a_{51} & 0 & 0 & 0 & a_{55} & 0 \\ 0 & 0 & a_{63} & 0 & 0 & a_{66} \end{bmatrix} \begin{bmatrix} e_1 \\ e_2 \\ e_3 \\ e_4 \\ e_5 \\ e_6 \end{bmatrix} + \begin{bmatrix} e_1 \\ e_2 \\ e_3 \\ e_5 \end{bmatrix}^T \begin{bmatrix} b_{11} & b_{12} & 0 & 0 \\ b_{21} & b_{22} & b_{23} & b_{24} \\ 0 & b_{32} & b_{33} & 0 \\ 0 & b_{42} & 0 & b_{44} \end{bmatrix} \begin{bmatrix} e_1 \\ e_2 \\ e_3 \\ e_5 \end{bmatrix} < 0 \end{aligned}$$

This implies that (27) holds. Therefore, the proof is completed.

7.4 Appendix D: Parameters of the Fuzzy System, control gains and observer gains

The nonlinear innate immune system in (33) could be approximated by a Takagi-Sugeno Fuzzy system. By the fuzzy modeling method (Takagi & Sugeno, 1985), the matrices of the local linear system A_i , the parameters B , C , D , K_j and L_i are calculated as follows:

$$A_1 = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 3 & -1 & 0 & 0 \\ -0.5 & 1 & -1.5 & 0 \\ 0.5 & 0 & 0 & -1 \end{bmatrix}, A_2 = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 3 & -1 & 0 & 0 \\ -0.5 & 1 & -1.5 & 0 \\ 0.5 & 0 & 0 & -1 \end{bmatrix}, A_3 = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 3 & -1 & 0 & 0 \\ -0.5 & 1 & -1.5 & 0 \\ 0.5 & 0 & 0 & -1 \end{bmatrix},$$

$$A_4 = \begin{bmatrix} -2 & 0 & 0 & 0 \\ 9 & -1 & 0 & 0 \\ -1.5 & 1 & -1.5 & 0 \\ 0.5 & 0 & 0 & -1 \end{bmatrix}, A_5 = \begin{bmatrix} -2 & 0 & 0 & 0 \\ -9 & -1 & 0 & 0 \\ -1.5 & 1 & -1.5 & 0 \\ 0.5 & 0 & 0 & -1 \end{bmatrix}, A_6 = \begin{bmatrix} -2 & 0 & 0 & 0 \\ 9 & -1 & 0 & 0 \\ -1.5 & 1 & -1.5 & 0 \\ 0.5 & 0 & 0 & -1 \end{bmatrix},$$

$$A_7 = \begin{bmatrix} -4 & 0 & 0 & 0 \\ 15 & -1 & 0 & 0 \\ -2.5 & 1 & -1.5 & 0 \\ 0.5 & 0 & 0 & -1 \end{bmatrix}, A_8 = \begin{bmatrix} -4 & 0 & 0 & 0 \\ -15 & -1 & 0 & 0 \\ -2.5 & 1 & -1.5 & 0 \\ 0.5 & 0 & 0 & -1 \end{bmatrix}, A_9 = \begin{bmatrix} -4 & 0 & 0 & 0 \\ 15 & -1 & 0 & 0 \\ -2.5 & 1 & -1.5 & 0 \\ 0.5 & 0 & 0 & -1 \end{bmatrix}$$

$$B = \begin{bmatrix} -1 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & -1 \end{bmatrix}, C = \begin{bmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}, D = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

$$K_j = \begin{bmatrix} 17.712 & 0.14477 & -0.43397 & 0.18604 \\ 0.20163 & 18.201 & 0.37171 & -0.00052926 \\ 0.51947 & -0.31484 & -13.967 & -0.052906 \\ 0.28847 & 0.0085838 & 0.046538 & 14.392 \end{bmatrix}, j=1, \dots, 9$$

$$L_i = \begin{bmatrix} 12.207 & -26.065 & 22.367 \\ 93.156 & -8.3701 & 7.8721 \\ -8.3713 & 20.912 & -16.006 \\ 7.8708 & -16.005 & 14.335 \end{bmatrix}, i=1, \dots, 9.$$

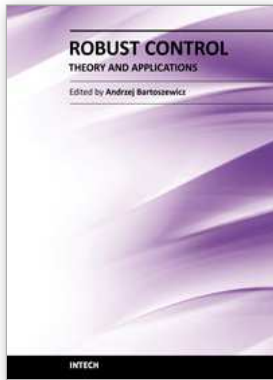
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