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ORIGINAL ARTICLE

Application of covariance matrix adaptation–evolution strategy to optimal control of hepatitis B infection

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Abstract To avoid the cirrhosis and liver cancer, antiviral treatment for chronic hepatitis is necessary. In the literature, several mathematical models have been used to describe the dynamics of viral infections. In addition, several control strategies have been reported in the literature to deal with optimal antiviral therapy problem of infectious diseases. In this paper, three controller structures with optimized parameters using covariance matrix adaptation–evolution strategy algorithm are proposed for optimal control of basic hepatitis B virus (HBV) infection dynamical system. The first structure is an optimized neural-type sigmoid-based closed-loop controller, which is a nonlinear feedback controller. The second structure is an optimized open-loop time-based fuzzy controller in which the control input is approximated using the mixture of Gaussian membership functions. Finally, an optimized closed-loop fuzzy controller is used as the third control structure. After designing the controllers, some parameters of the HBV infection model are considered to be unknown and the robustness of the controllers is studied. Experimental results show that the optimized neural-type sigmoid-based closed-loop controller has the best performance in terms of healthy hepatocytes and free HBVs concentration among the investigated controllers and the optimized closed-loop fuzzy controller is the best in terms of minimum mean control input signal that is the drug usage. Concerning the robustness, the optimized neural-type sigmoid-based closed-loop controller has the best performance.

Keywords Optimal control · Covariance matrix adaptation–evolution strategy · Optimal treatment · Hepatitis B

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1 Introduction

Hepatitis is usually caused by a viral infection, toxic agents, or other diseases such as metabolic diseases. By replicating in hepatocytes, the normal functioning of the liver is interfered by hepatitis type B virus (HBV). The pathological damage and liver inflammation are caused by the response of immune system to combat and potentially eliminate the infectious agent [1]. HBV infection is among the most common causes of hepatitis and can result in serious liver diseases such as chronic hepatic insufficiency, hepatocellular carcinoma, and cirrhosis (scarring of the liver) [2–4].

HBV is transmitted through contact with infected blood or body fluids [5]. It may spread from an infected mother to her child during the birth process [6], between children in overcrowded regions [7], from a needle stick, or by sexual contact [8]. It is also noted that hepatitis B has been one of the most significant infectious risks for health care providers for the past few decades [9]. Modes of HBV transmission are the same for the human immunodeficiency virus (HIV), but HBV is 50–100 times more infectious. Unlike HIV, HBV can survive outside the body for at least 7 days. During that time, the virus can still cause infection if it enters the body of a person who is not infected. The virus incubation period is 90 days on average, but can vary from about 30–180 days. HBV may be detected

30–60 days after infection and persist for widely variable periods of time [10, 11].

Hepatitis type B virus (HBV) occurs when there is a weak antiviral response, which is more common at a younger age of infection. Nearly 90 % of HBV-infected children during the first year of life develop chronic infections, 30–50 % of children infected in the age range 1–4 years develop chronic infection, and 90 % of healthy adults who are infected will recover and be rid of the virus within 6 months [8]. HBV typically resolves within 3 months, but over 10 % of cases become asymptomatic carriers or experience chronic HBV infection. People who develop chronic HBV are at increased risk of developing cirrhosis and/or liver cancer [12].

The hepatitis B vaccine has an outstanding record of safety and effectiveness. Chronic carriage of HBV is related to the age when the infection occurs; the younger the age, the higher the chronicity rate. Hence, vaccination should be given in early childhood. People vaccinated in infancy have a protection of more than 20 years, and hepatocellular carcinoma decreases in them [13, 14].

Chronic hepatitis B may be treated with drugs. Drugs licensed for treating persons with chronic HBV include adefovir dipivoxil [15], alpha-interferon [16], lamivudine [16], pegylated interferon [17], entecavir [18], telbivudine [19], and tenofovir [20]. Although none of hepatitis antiviral drugs are able to completely remove the infection, they prevent replication of HBVs and save the liver from cirrhosis and cancer. During the treatment, the viral load is reduced and consequently the viral replication in liver is decreased [21].

In the literature, several mathematical models have been used to describe the dynamics of viral infections, such as HIV infection [22–24] and hepatitis C virus (HCV) infection [22, 25–28]. In addition, several control strategies have been reported in the literature to deal with optimal antiviral therapy problem of infectious diseases.

In this paper, three different control structures are employed to design optimal controllers for basic HBV infection dynamical system: (a) neural-type sigmoid-based closed-loop controller, which is a nonlinear feedback controller, (b) open-loop fuzzy controller in which the control input is approximated using the mixture of Gaussian membership functions, and (c) closed-loop fuzzy controller. It is noted that the fuzzy logic has emerged as a powerful tool to employ knowledge about the systems for implementing an appropriate control law [29–31].

Nowadays, determining optimal values of unknown design parameters of controllers is considered as a state-of-art subject in control theory and applications, such as optimized proportional-derivative (PD) controller [32], genetic algorithm (GA)-optimized fuzzy proportional-integral-derivative (PID) controller [33], differential evolution (DE)-optimized fuzzy controllers [34, 35], big bang–big crunch (BB–BC)-optimized fuzzy controller [36], GA- and particle swarm optimization (PSO)-optimized fuzzy controllers [37–39], evolutionary algorithms (EAs)-optimized fractional-order PID controllers [40, 41], chaotic DE-optimized PI and PID controllers [42], ant colony-optimized PI controller [43], GA- and PSO-optimized neural-based controllers [44–46].

In this paper, covariance matrix adaptation–evolution strategy (CMA–ES) algorithm [47, 48] is used for parameters optimization of controllers. The CMA–ES algorithm has been widely used as a powerful optimization algorithm in recent years in multidimensional problems [49–51] such as solar energy optimization [52] and filter design [53]. Furthermore, CMA–ES has been used in real parameter optimization [54–57] and designing PID controller [58]. In this paper, after designing the controllers, some parameters of the HBV infection model are considered to be unknown and the robustness of controllers is statistically studied.

The rest of the paper is organized as follows. Related work is reviewed in Sect. 2. Section 3 describes the mathematical model of hepatitis B infection. Section 4 includes the statement of optimal control problem. The control strategies are described in Sect. 5. The description of CMA–ES algorithm is provided in Sect. 6. Experimental results are given in Sect. 7. Finally, Sect. 8 concludes the paper.

2 Related work

In recent decades, several dynamic models have been developed to mathematically describe the HBV infection and antiviral therapy [22, 59–61]. These models can be classified to the following groups: (a) models based on antiviral drugs and/or immunotherapeutic approaches [60, 61], (b) spread and transmission models under certain conditions [62–67], and (c) replication models based on molecular biological information [68]. It is noted that the mathematical model used in this paper is a model based on antiviral drugs [69].

As sample models based on antiviral drugs and/or immunotherapeutic approaches, Le Guerhier et al. [60] used the duck HBV (DHBV) infection model to evaluate the efficacy of the combination of adefovir with DNA immunization by comparison with the respective monotherapies. Ciupe et al. [61] focused on HBV dynamics during the acute stages of infection and analyze the immune mechanisms responsible for viral clearance. They presented a basic model used to interpret HBV therapy studies conducted in chronically infected patients and then introduced additional models to study acute infection.

As sample researches on HBV spread and transmission models, Thornley et al. [62] used the model described by

Medley et al. [70] on the prevalence of chronic HB (CHB) in adults, together with estimates of vaccine coverage levels, to estimate population-specific infection transmission parameters. In the model, the host population was divided into five different epidemiological classes, expressed as the proportion: susceptible, infected but not infectious (latent), with acute infection, with CHB (carriers), and with protective immunity. In this way, a system of differential equations (DEs) was formed. Qiao and Qi [63] developed a delayed reaction–diffusion model to describe HBV infection and control, where the diffusion is confined to a finite domain. By using the method of upper–lower solutions, they obtained the sufficient conditions for the existence of traveling wave solutions of reaction–diffusion systems with delay. Qiao et al. [64] modeled and analyzed the HBV infection with impulsive vaccination and time delay, according to the epidemic state, propagation mode, and transformation between HBV infection states. They adopted control methods of impulsive vaccination and active therapy and derived the sufficient conditions that HBV can be eliminated eventually or be persistent. Luzyanina and Bocharov [65] developed a computational methodology for the analysis of the impact of random forcing on the patterns of virus persistence in HBV infection. They examined the issue of robustness versus sensitivity in models of chronic infections (which relates to a fundamental question in immunology) and presented the practical details of implementation of stochastic ordinary differential equation (ODE) models in the analysis of spontaneous recovery. These included the effect of sampling of the parameter space, the number of simulation runs needed for a robust estimation of mean and variance of the spontaneous recovery pattern, the impact of noise intensity, and type on the response of models. Pang et al. [66] developed a model to explore the impact of vaccination and other controlling measures of HBV infection. The model had simple dynamical behavior with a globally asymptotically stable disease-free equilibrium. Finally, Zhang and Zhou [67] formulated a mathematical model, in terms of an ODEs system, to describe the spread of HBV and applied it to HBV transmission in China.

As sample replication model based on molecular biological information, Nakabayashi and Sasaki [68] constructed a mathematical model of the intracellular replication of HBV based on the molecular biological information. Two different intracellular replication patterns of HBV, "explosive" and "arrested," were switched depending on the viral gene expression pattern. In the explosive replication, prominent growth of HBV is observed. On the other hand, the virion production is restricted in the arrested replication.

As mentioned before, several control strategies have been used to deal with optimal antiviral therapy problem of infectious diseases. As sample researches, the optimal control of HIV infection using classic approaches [71, 72] and model predictive control [73, 74] have been studied in the literature. However, the optimal control of hepatitis B infection has not been studied so much. As a rare example, Hattaf et al. [75] studied the optimal control of hepatitis B infection using classical optimal theories.

3 Mathematical model of hepatitis B infection

The following mathematical model of hepatitis B infection is used in this paper [69]:

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta xv \\ \dot{y} &= \beta xv - \delta y \\ \dot{v} &= [1 - \mu u(t)]py - cv \end{aligned} \tag{1}$$

in which state variables x, y, and v represent the concentration of healthy hepatocytes, the concentration of infected hepatocytes, and the concentration of free HBVs, respectively. In the first state equation in (1), λ is the constant production rate of healthy hepatocytes, d is the proportional death rate of healthy hepatocytes, and β is the aggressiveness of HBVs. In the second state equation in (1), δ indicates the proportional death rate of infected hepatocytes. In the third state equation in (1), μ is the efficacy of antiviral drug and $u(t)$ is the control input signal, which indicates the drug usage. Furthermore, p and c are the proportional production rate and the proportional death rate of free HBVs, respectively.

The values of control input $u(t)$ and efficacy of antiviral drug μ are considered normalized:

$$0 \le u(t) \le 1 \tag{2}$$

$$0 \le \mu \le 1 \tag{3}$$

So, when the drug usage is maximum [i.e., $u(t) = 1$] and the antiviral drug efficacy is maximum (i.e., $\mu = 1$), then $[1 - \mu u(t)] = 0$ and based on (1), the free HBVs are exponentially decayed to zero.

The parameter values of dynamical model defined in (1) are listed below [69]:

$$\begin{aligned} &\lambda = 2.5251 \times 10^5, \quad d = 0.0038, \quad \beta = 1.9810 \times 10^{-13}, \\ &\delta = 0.0125, \\ &\mu = 0.8, \quad p = 842.0948, \quad c = 0.67 \end{aligned} \tag{4}$$

In addition, the initial values of states are considered as follows [69]:

$$\begin{aligned} &x(0) = 5.5556 \times 10^7, \quad y(0) = 1.1111 \times 10^7, \\ &v(0) = 6.3096 \times 10^9 \end{aligned} \tag{5}$$

4 Optimal control problem

Maximization of the treatment performance and minimization of the drug usage are two main objectives in the optimal treatment problem. Maximization of the treatment performance is completely dependent on the trajectory of system (1) in the state space. Minimization of the infected hepatocytes and free HBVs, and maximization of the healthy hepatocytes result in optimization of the treatment performance. From a clinical point of view, optimization of treatment performance is the main objective of treatment and clinical actions. Considering the side effects of antiviral drugs and costs of drugs and treatment, the minimization of drug usage is defined as the secondary objective.

Maximization of a signal, namely $s(t)$, at each moment could be achieved by maximization of each of the following objective functions:

$$\bar{s} = s_{\text{mean}} = \frac{1}{T}\int_0^T s(t)\,\mathrm{d}t \tag{6}$$

$$s_{\min} = \min_{0 \le t \le T} s(t) \tag{7}$$

$$s_{\text{f}} = s(T) \tag{8}$$

where T indicates the time-span (herein the treatment time-span). The expressions defined in (6), (7), and (8) are the average value, minimum value, and final value, respectively. Each of these expressions is focused on certain features of the objective signal.

A mixture of the mentioned expressions can also be formed by means of a weighted linear combination:

$$\breve{s} = w_{\text{mean}} s_{\text{mean}} + w_{\min} s_{\min} + w_{\text{f}} s_{\text{f}} \tag{9}$$

where w_{mean}, $w_{\min}$, and w_{f} are the corresponding weighting factors that satisfy (10) and (11):

$$w_{\text{mean}} + w_{\min} + w_{\text{f}} = 1 \tag{10}$$

$$w_{\text{mean}}, w_{\min}, w_{\text{f}} \ge 0 \tag{11}$$

Similarly, if it is desired to minimize the values of signal $s(t)$ at each moment, the minimization of following weighted sum is equivalent to the minimization of $s(t)$:

$$\hat{s} = w_{\text{mean}} s_{\text{mean}} + w_{\max} s_{\max} + w_{\text{f}} s_{\text{f}} \tag{12}$$

where $s_{\max}$ is defined as follows:

$$s_{\max} = \max_{0 \le t \le T} s(t) \tag{13}$$

In addition, the weighting factors satisfy equations similar to (10) and (11).

Maximization of the treatment quality is equivalent to the following optimization problems:

$$\max \breve{x} = w_{\text{mean}} x_{\text{mean}} + w_{\min} x_{\min} + w_{\text{f}} x_{\text{f}} \tag{14}$$

$$\min \hat{y} = w_{\text{mean}} y_{\text{mean}} + w_{\max} y_{\max} + w_{\text{f}} y_{\text{f}} \tag{15}$$

$$\min \hat{v} = w_{\text{mean}} v_{\text{mean}} + w_{\max} v_{\max} + w_{\text{f}} v_{\text{f}} \tag{16}$$

Furthermore, minimization of the drug usage is equivalent to the following optimization problem:

$$\min u_{\text{mean}} \tag{17}$$

which simply means the minimization of average drug usage in the treatment time-span.

All of the above objective functions are combined to form an objective function that maximizes the treatment performance and also minimizes the drug usage. This objective function is defined as follows:

$$\min w_x J_x + w_y J_y + w_v J_v + w_u J_u \tag{18}$$

in which weighting factors w_x, w_y, w_v, and w_u are positive and satisfy the following condition:

$$w_x + w_y + w_v + w_u = 1 \tag{19}$$

From a different point of view, the problem in hand is a multi-objective optimization problem that we want to solve it by defining sub-objective functions to maximize the treatment performance and minimize the drug usage.

The sub-objective functions J_x, J_y, J_v, and J_u are defined as follows:

$$J_x = \frac{x(0)}{w_{\text{mean}} x_{\text{mean}} + w_{\min} x_{\min} + w_{\text{f}} x_{\text{f}}} \tag{20}$$

$$J_y = \frac{w_{\text{mean}} y_{\text{mean}} + w_{\max} y_{\max} + w_{\text{f}} y_{\text{f}}}{y(0)} \tag{21}$$

$$J_v = \frac{w_{\text{mean}} v_{\text{mean}} + w_{\max} v_{\max} + w_{\text{f}} v_{\text{f}}}{v(0)} \tag{22}$$

$$J_u = u_{\text{mean}} \tag{23}$$

To evaluate the success of treatment procedure of hepatitis B, the final values of healthy hepatocytes concentration, infected hepatocytes concentration, and free HBVs concentration are more important than the minimum/maximum/mean value of mentioned concentrations in the treatment time-span. So, w_{f} as the same weight factor of x_{f}, y_{f} and v_{f} in (20)–(22) is selected three times more than $w_{\min}$, $w_{\max}$ and w_{mean} weight factors in our simulations to consider this importance.

In addition, the importance of healthy hepatocytes concentration sub-objective function is emphasized in this paper by selecting larger value for w_x (as compared tow_y, w_v and w_u). The sample values in our simulations are listed in (24) and (25). It is noted that all above weighting factors are positive and satisfy (10) and (19).

$$w_{\text{mean}} = 0.2, \quad w_{\min} = w_{\max} = 0.2, \quad w_{\text{f}} = 0.6 \tag{24}$$

$$w_x = 0.8, \quad w_y = 0, \quad w_v = \frac{1}{15}, \quad w_u = \frac{2}{15} \tag{25}$$

Based on the equation of $\dot{v}$ in (1), the concentration of free HBVs (v) is proportional to the concentration of infected hepatocytes (y) when the drug usage is not considered. On the other hand, the diagnosis of infected hepatocytes is a hard task as compared to counting the HBVs. So, the weight factor for J_y (i.e., w_y) is set to zero in our simulations. In addition, due to the importance of healthy hepatocytes concentration (x) in the treatment time-span, the weight factor w_x is set to a large value as compared to w_v and w_u.

5 Proposed control strategies

In this paper, three approaches are used to form the control input signal. One of these approaches is an open-loop scheme and the others are closed-loop feedback approaches. Description of these control strategies is provided in this section.

5.1 Closed-loop sigmoid-based strategy

In this approach, the control input signal $u(t)$ is calculated using the following mathematical relation:

$$u(t) = S[\theta_1 x(t) + \theta_2 v(t) + \theta_3] \tag{26}$$

in which weighting factors θ_1, θ_2, and θ_3 are unknown controller parameters and should be determined by designer and the sigmoid function $S(\xi)$ is defined by:

$$S(\xi) = \frac{1}{1 + e^{-\xi}} \tag{27}$$

In fact, (26) is a nonlinear feedback rule and resembles a single artificial neuron, with the sigmoid activation function, defined in (27).

5.2 Open-loop fuzzy strategy

Suppose that $A_i;\ i \in \{1, 2, \ldots, N\}$ are the fuzzy sets, defined in the time domain. Membership function of A_i is indicated by $\mu_{A_i}(t)$. The fuzzy set A_1 is related to "early stages of treatment time-span" and A_N is related to "late stages of treatment time-span."

It is possible to define an open-loop fuzzy control strategy as follows:

$$u(t) = \frac{\sum_{i=1}^{N} U_i \mu_{A_i}(t)}{\sum_{i=1}^{N} \mu_{A_i}(t)} \tag{28}$$

which implements a Takagi–Sugeno (TS) fuzzy system with N rules as follows [39, 76]:

$$\text{Rule } i: \ \text{If } t \text{ is } A_i, \ \text{then} \quad u(t) = U_i; \quad i \in \{1, 2, \ldots, N\} \tag{29}$$

The constant parameters $U_i;\ i \in \{1, 2, \ldots, N\}$ are unknown control parameters and should be determined by the designer. In our simulations, N is set to 20 in this strategy. The fuzzy sets A_i are assumed to have Gaussian membership functions as shown in Fig. 1.

As can be seen, the width of each Gaussian function in this strategy is set to 0.0275 and the center of 20 Gaussian functions is determined as follows:

$$m_{i+1} = m_i + \frac{1}{N-1}; \quad i = 1, \ldots, N-1, \quad m_1 = 0, \quad N = 20 \tag{30}$$

5.3 Closed-loop fuzzy strategy

A closed-loop fuzzy controller is used as the third approach in this study. Assume that N fuzzy sets are defined to describe the concentration of healthy hepatocytes x, namely $X_i;\ i \in \{1, 2, \ldots, N\}$. Similarly, the fuzzy sets $V_j;\ j \in \{1, 2, \ldots, N\}$ are defined to describe the concentration of free HBV copies. In our simulations, N is set to 7 in this strategy. This strategy has N^2 rules of the form:

$$\text{Rule } (i,j): \ \text{If } x \text{ is } X_i \text{ and } v \text{ is } V_j, \ \text{then} \quad u(t) = U_{ij}; \quad i,j \in \{1, 2, \ldots, N\} \tag{31}$$

which is a T–S fuzzy system and can be simplified as follows:

$$u(t) = \frac{\sum_{i=1}^{N} \sum_{j=1}^{N} U_{ij} \mu_{X_i}[x(t)] \mu_{V_j}[v(t)]}{\sum_{i=1}^{N} \sum_{j=1}^{N} \mu_{X_i}[x(t)] \mu_{V_j}[v(t)]} \tag{32}$$

Parameters of the closed-loop fuzzy controller are $U_{ij};\ i,j \in \{1, 2, \ldots, N\}$ and must be specified by the designer to optimize the performance of closed-loop system. In this paper, the fuzzy sets X_i and V_j are assumed to have Gaussian membership functions as shown in Figs. 2 and 3.

In generating fuzzy sets X_i and V_j, the normalization is performed (i.e., $\frac{x(t)}{x(0)} \to x(t)$ and $\frac{v(t)}{v(0)} \to v(t)$) and the following boundaries are considered:

$$X_i \in [0.4,\ 1.1], \quad V_j \in [0.2,\ 1.1] \quad \forall i,j \in \{1, 2, \ldots, N\}, \quad N = 7 \tag{33}$$

It is noted that if healthy hepatocytes concentration becomes lower than $0.4x(0)$, then it will be harmful for the patient.

The width of each Gaussian function in this strategy is set to 0.0968 and the center of 7 Gaussian functions for fuzzy sets X_i and V_j is determined as (34) and (35), respectively:

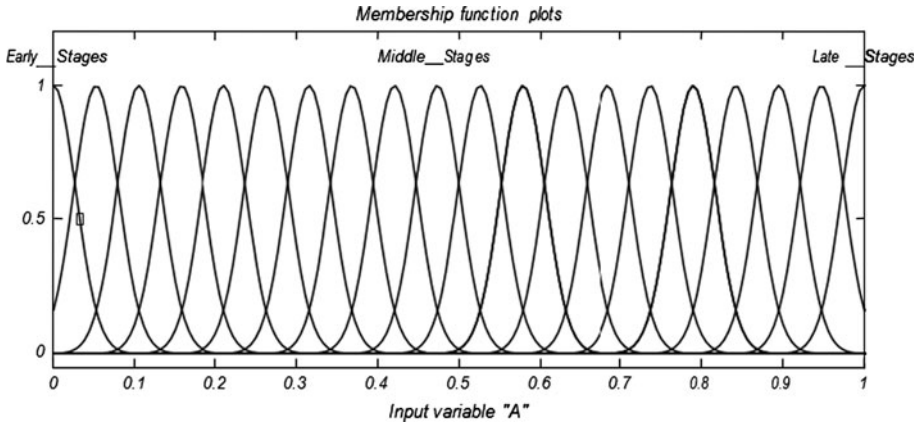

Fig. 1 Gaussian membership functions used in open-loop fuzzy strategy

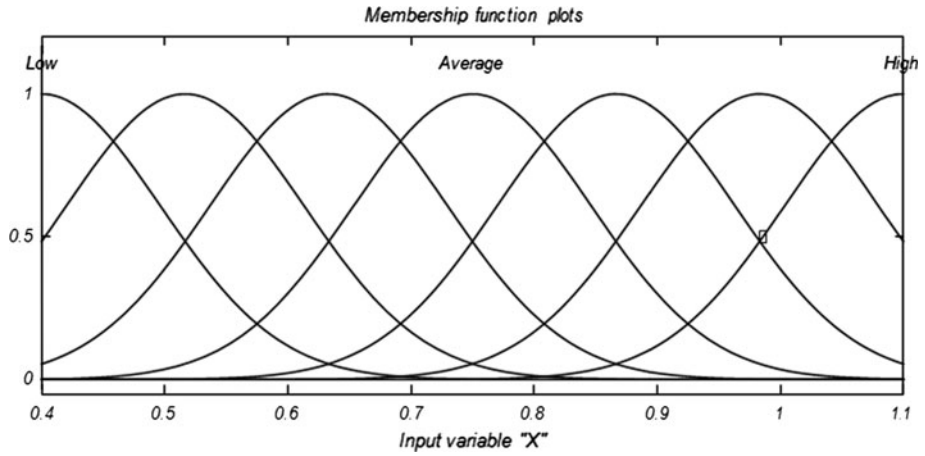

Fig. 2 Gaussian membership functions of fuzzy set X_i in closed-loop fuzzy strategy

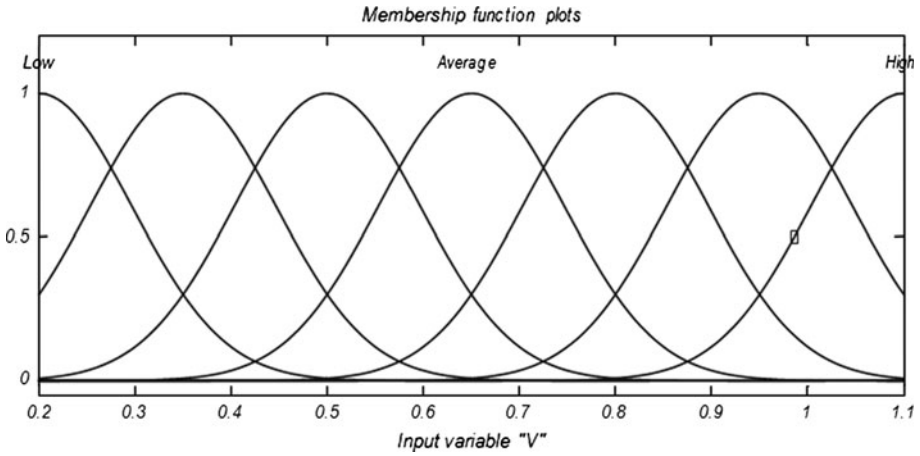

Fig. 3 Gaussian membership functions of fuzzy set V_i in closed-loop fuzzy strategy

$$m_{i+1} = m_i + \frac{0.7}{N-1}; \quad i = 1, \ldots, N-1, \quad m_1 = 0.4, \quad N = 7 \tag{34}$$

$$m_{j+1} = m_j + \frac{0.9}{N-1}; \quad j = 1, \ldots, N-1, \quad m_1 = 0.2, \quad N = 7 \tag{35}$$

6 Covariance matrix adaptation–evolution strategy (CMA–ES) algorithm

CMA–ES is a stochastic method for real continuous-parameter optimization of nonlinear, non-convex functions. The CMA–ES algorithm includes adaptation of covariance

matrix, which is an alternative method of traditional Quasi–Newton method for optimization based on gradient method [56]. Evolution strategies (ES) for real-valued optimization usually rely on Gaussian random variations. Appropriately adapting the covariance matrices of these mutations during optimization allows for learning and employing a variable metric for the search distribution. It is well known that such an automatic adaptation of the mutation distribution drastically improves the search performance on non-separable and/or badly scaled objective functions [77, 78]. In general, altering the mutation distribution aims at making beneficial steps in the search space more likely. The so-called covariance matrix adaptation (CMA) explicitly employs this concept and has proven to be an effective adaptation mechanism for ES [47, 48, 78].

Comparisons between evolutionary techniques such as GA, DE, and CMA–ES show that CMA–ES is the most efficient search algorithm with comparable search quality as DE [79]. In addition, performance comparison of swarm intelligence (SI)-based algorithms such as PSO and CMA–ES algorithm shows that the CMA–ES algorithm is more consistent in obtaining the best solution with reduced computation time. Furthermore, CMA–ES outperforms PSO on non-separable and ill-conditioned functions by orders of magnitude in terms of function evaluations number [80].

Assume the objective function $f : IR^n \rightarrow IR$ and a sequence of $(x^{(t)})_{t=1,2,\ldots} \in IR^n$, which minimizes $f(x^{(t)})$.

$$f : x \subseteq IR^n \rightarrow R \quad x \rightarrow f(x) \tag{36}$$

The objective function f is nonlinear, non-separable, non-convex, and non-smooth. The goal is to find a new point to minimize the cost function. This new search point is sampled normally distributed as:

$$x_i \sim m + \sigma N_i(0, C); \quad i = 1, 2, \ldots, \lambda \tag{37}$$

in which $m \in IR^n$, $\sigma \in IR_+$, $C \in IR^{n \times n}$, and m are the mean vector represents the favorite solution. Also, σ is the step size and C is the covariance matrix that determines the shape of distribution ellipsoid. This matrix is updated such that the likelihood of previously successful search steps is increased and followed by:

$$\{x \in IR^n | x^T C^{-1} x = 1\} \tag{38}$$

The candidate solutions x_i's are evaluated on the objective function to be minimized:

$$x_{i:\lambda} \rightarrow f(x_i); \quad i = 1, 2, \ldots, \lambda \tag{39}$$

The results are sorted by fitness and then the weighted mean is computed as follows:

$$x_{i:\lambda} \rightarrow \text{sort}(x_{i:\lambda}),\ m_{k+1} = m_k + \sum_{i=1}^{\mu} w_i (x_{i:\lambda} - m_k); \quad k = 1, 2, \ldots, K \tag{40}$$

where K is the number of iteration and $\mu \leq \lambda/2$.

The w_i's are positive weights as follows:

$$w_1 \geq w_2 \geq \cdots \geq w_\mu > 0, \quad \sum_{i=1}^{\mu} w_i = 1 \tag{41}$$

The step-size σ_k is updated using cumulative step-size adaptation (CSA), sometimes also denoted as path length control. The evolution path (or search path), p_σ, and step size, σ_k, are updated as follows [47, 81, 82]:

$$\begin{aligned} p_\sigma &\leftarrow (1 - c_\sigma) p_\sigma + \sqrt{1 - (1 - c_\sigma)^2}\sqrt{\mu_w} C_k^{-1/2} \frac{m_{k+1} - m_k}{\sigma_k}; \\ \mu_w &= \lambda/4 \\ \sigma_{k+1} &= \sigma_k \times \exp\left(\frac{c_\sigma}{d_\sigma}\left(\frac{\|p_\sigma\|}{E\|N(0,I)\|} - 1\right)\right) \end{aligned} \tag{42}$$

where $\frac{1}{c_\sigma} \approx n/3$ is the backward time horizon for the evolution path and larger than one, and d_σ is the damping parameter usually close to one. The step size is increased if and only if $\|p_\sigma\|$ is larger than the expected value $E\|N(0, I)\|$ and decreased if it is smaller. Finally, the covariance matrix is updated as follows [48, 83, 84]:

$$\begin{aligned} p_c &\leftarrow (1 - c_c) p_c + \text{IF} \times \sqrt{1 - (1 - c_c)^2}\sqrt{\mu_w} \frac{m_{k+1} - m_k}{\sigma_k}; \\ \text{IF} &= \begin{cases} 1 & ; \|p_\sigma\| \in [0, \alpha\sqrt{n}] \\ 0 & ; \text{otherwise} \end{cases} \\ C_{k+1} &= (1 - c_1 - c_\mu + c_s) C_k \\ &\quad + c_1 p_c p_c^T + c_\mu \sum_{i=1}^{\mu} w_i \frac{x_{i:\lambda} - m_k}{\sigma_k} \left(\frac{x_{i:\lambda} - m_k}{\sigma_k}\right)^T \end{aligned} \tag{43}$$

It is noted that IF term in (43) is indicator function, which is defined on a set X that indicated membership of an element in a subset A of X, having the value 1 for all elements of A and the value 0 for all elements of X not in A. In addition, T denotes the transpose and $\frac{1}{c_c} \approx n/4$, $\alpha \approx 1.5$, $c_1 \approx 2/n^2$, and $c_\mu \approx \mu_w/n^2$. c_s is also given by:

$$c_s = (1 - \text{IF}) c_1 c_c (2 - c_c). \tag{44}$$

7 Experimental results

All of the three employed control strategies are optimized using CMA–ES algorithm to obtain the optimal treatment strategies for hepatitis B infection.

In the closed-loop neural-type sigmoid-based strategy (referred to as SIG), variation range of the weighting parameters θ_1, θ_2, and θ_3 is assumed to be $[-10, 10]$. In the open-loop fuzzy strategy (referred to as OLF), it is assumed that $0 \leq U_i \leq 1;\ i \in \{1, 2, \ldots, N\}$ and $N = 20$. In the closed-loop fuzzy strategy (referred to as CLF), it is assumed that $0 \leq U_{i,j} \leq 1;\ i,j \in \{1, 2, \ldots, N\}$ and $N = 7$. The best cost values against iteration number for the three mentioned control strategies are shown in Fig. 4. The simulation results of final sub-optimal solutions for the three mentioned control strategies are also shown in Fig. 5. As can be seen, in the results for state variable x, the CMA–ES-optimized SIG controller has the best performance in increasing the concentration of healthy hepatocytes in the treatment time-span. In decreasing the concentration of infected hepatocytes, all strategies perform well; however, the CMA–ES-optimized SIG controller performs slightly better. In terms of drug usage, the CMA–ES-optimized CLF controller performs better; however, the drug usage for CMA–ES-optimized OLF controller is nearly zero for a short time interval in treatment time-span.

Detailed numerical information of the final sub-optimal solutions is also reported in Table 1. The corresponding ranks of the three methods are also provided inside the parenthesis in Table 1.

According to the information provided in Table 1, considering J_x, J_y, and J_v, the sub-optimal closed-loop neural-type sigmoid-based controller has the best performance as compared to other strategies. Whereas, the closed-loop fuzzy uses minimum drug amount as compared to other methods. Combining all of the partial costs, using the weighted sum defined in (18), the open-loop fuzzy strategy is in the first rank and the closed-loop fuzzy controller is in the second rank. However, the difference between the values of total cost z in three control strategies is very small.

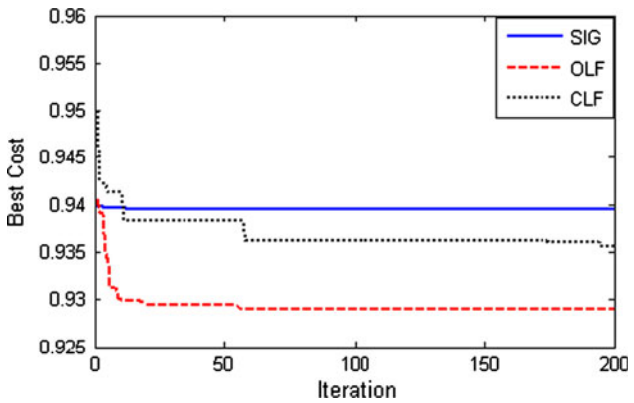

Fig. 4 Best cost against iteration number for the three proposed control strategies

To analyze the robustness of sub-optimal controllers, provided by CMA–ES, three parameters of the model (1) are considered to have uncertainty. It is assumed that β, p, and μ are uncertain and statistically distributed according to the following uniform distributions:

$$\beta \sim U(\beta_{\min}, \beta_{\max}) \tag{45}$$

$$p \sim U(p_{\min}, p_{\max}) \tag{46}$$

$$\mu \sim U(\mu_{\min}, \mu_{\max}) \tag{47}$$

where the lower and upper bounds of the above uniform distributions are defined as follows:

$$\begin{aligned} &\beta_{\min} = 1.9810 \times 10^{-13}, \quad p_{\min} = 842.0948, \quad \mu_{\min} = 0.72, \\ &\beta_{\max} = 1.25\beta_{\min}, \quad p_{\max} = 1.25p_{\min}, \quad \mu_{\max} = 0.8 \end{aligned} \tag{48}$$

According to (4) and (48), $\beta_{\min}$, $p_{\min}$, and $\mu_{\max}$ are equal to the nominal values of parameters β, p, and μ, respectively. The values of lower and upper bounds are defined such that the values of uncertain parameters have destructive effects on the performance of pre-designed controllers.

Using Monte Carlo simulation, 50,000 samples are drawn from uniform distributions defined in (45), (46), and (47), and each of the sub-optimal controllers are tested on the system using new values of uncertain parameters. It is noted that Monte Carlo simulation is a method for iteratively evaluating a deterministic model using sets of random numbers as inputs. The obtained values of total cost z and partial costs (J_x, J_y, J_v, and J_u) are statistically modeled and the corresponding approximate probability density functions (PDFs) are shown in Figs. 6, 7, and 8 for the three mentioned control strategies. It is noted that the nominal values of cost components, the mean values of obtained costs for non-nominal sampled systems, and the corresponding variance range are also shown in Figs. 6, 7, and 8.

It is noted that because of open-loop nature of the open-loop fuzzy control strategy, the value of control input partial cost J_u remains fixed for all values of uncertain parameters. For the three mentioned control strategies, numerical and statistical information of the Monte Carlo simulation results are provided in Table 2. In Table 2, STD stands for standard deviation and nominal values are also included from Table 1. ERR and ERRP indicate error and error percentage, as the difference between mean and nominal values, respectively.

As can be seen in Fig. 6, the mean value in statistical description of total cost (z) is 0.962 and the nominal value is 0.939. So, the mean value of total cost is only 2.45 % more than the total cost value when $\beta_{\min}$, $p_{\min}$, and $\mu_{\max}$ are

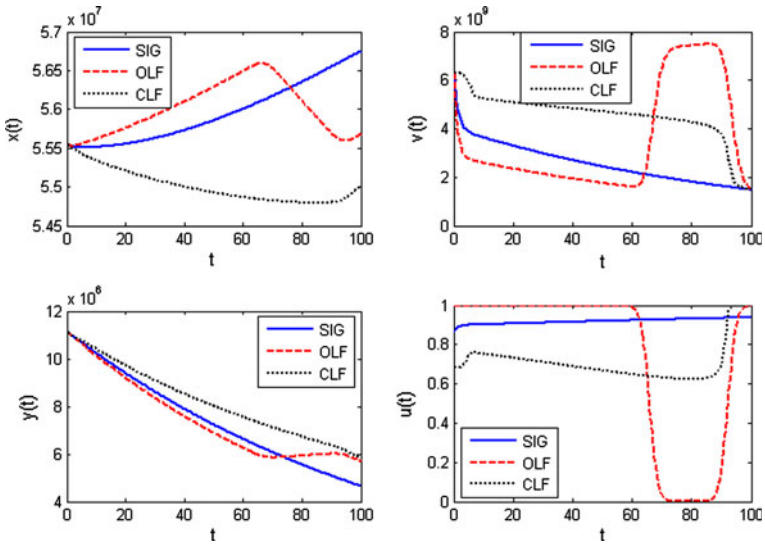

Fig. 5 Simulation results of final sub-optimal solutions for the three proposed control strategies

Table 1 Numerical information of sub-optimal solutions for the three proposed control strategies

State variables	CMA–ES-optimized control strategies		
	SIG	OLF	CLF
$x(t)$			
x_{mean}	5.5509×10^7 (2)	5.6010×10^7 (1)	5.5009×10^7 (3)
$x_{\min}$	5.5951×10^7 (1)	5.5532×10^7 (2)	5.4792×10^7 (3)
x_{f}	5.6755×10^7 (1)	5.5688×10^7 (2)	5.5007×10^7 (3)
J_x	**0.9860 (1)**	0.9970 (2)	1.0108 (3)
$y(t)$			
y_{mean}	7.4570×10^6 (1)	7.4616×10^6 (2)	8.1965×10^6 (3)
$y_{\max}$	1.1111×10^7 (1)	1.1111×10^7 (1)	1.1111×10^7 (1)
y_{f}	4.6476×10^6 (1)	5.6912×10^6 (2)	5.8310×10^6 (3)
J_y	**0.5852 (1)**	0.6416 (2)	0.6624 (3)
$v(t)$			
v_{mean}	2.5807×10^9 (1)	3.5079×10^9 (2)	4.5382×10^9 (3)
$v_{\max}$	6.3096×10^9 (1)	7.4880×10^9 (3)	6.3125×10^9 (2)
v_{f}	1.4800×10^9 (1)	1.5194×10^9 (3)	1.4936×10^9 (2)
J_v	**0.4225 (1)**	0.4930 (3)	0.4860 (2)
$u(t)$			
u_{mean}	0.9186 (3)	0.7382 (2)	0.7096 (1)
J_u	0.9186 (3)	0.7382 (2)	**0.7096 (1)**
Total			
z	0.9394 (3)	**0.9289 (1)**	0.9356 (2)

used as the best parameters in (1), that is, minimum aggressiveness of HBVs, minimum proportional production rate of free HBVs, and maximum antiviral drug efficacy, respectively. This percent for CMA–ES-optimized OLF and CLF strategies, based on Figs. 7 and 8, is 3.66 and 8.10 %, respectively. The STD in Fig. 6 is 0.010, which shows low variability exists from the mentioned acceptable mean value. This value for CMA–ES-optimized OLF and CLF strategies, based on Figs. 7 and 8, is 0.014 and 0.023, respectively. So, the CMA–ES-optimized SIG strategy performs the best in terms of error percentage as compared to CMA–ES-optimized OLF and CLF strategies.

As can be seen in Figs. 6, 7, and 8 for J_x, the STD in SIG, OLF, and CLF strategies is 0.009, 0.011, and 0.018, respectively. So, the SIG strategy is in the first rank of robustness when considering J_x sub-objective function. Similarly, the SIG strategy is placed in the first rank of

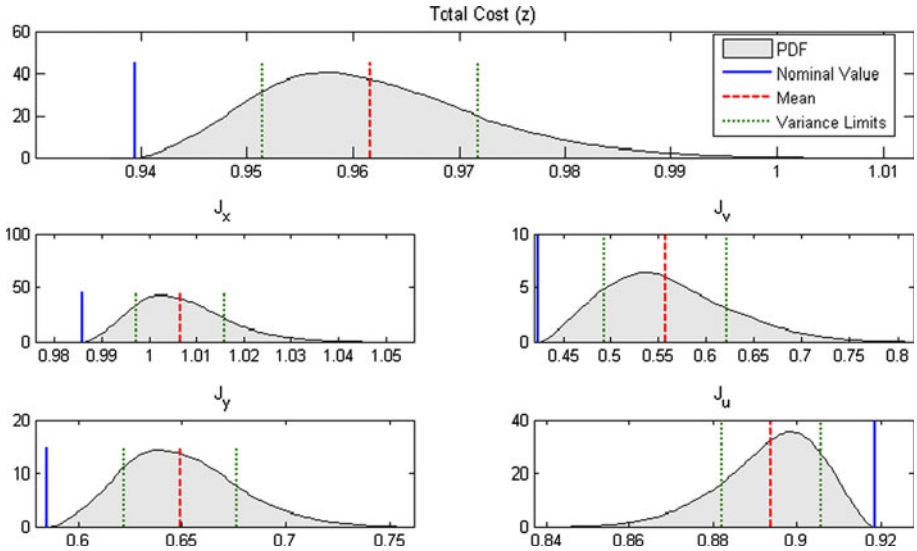

Fig. 6 Statistical description of obtained cost components from Monte Carlo simulation of SIG strategy

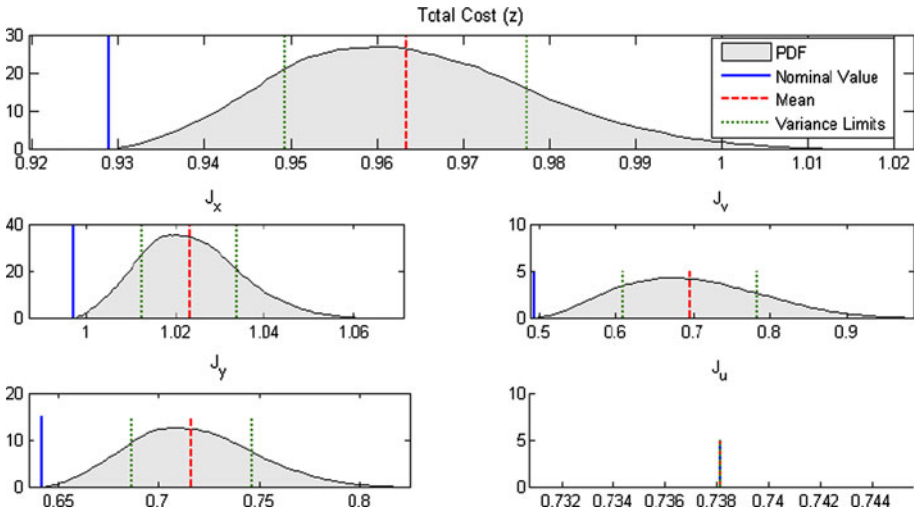

Fig. 7 Statistical description of obtained cost components from Monte Carlo simulation of OLF strategy

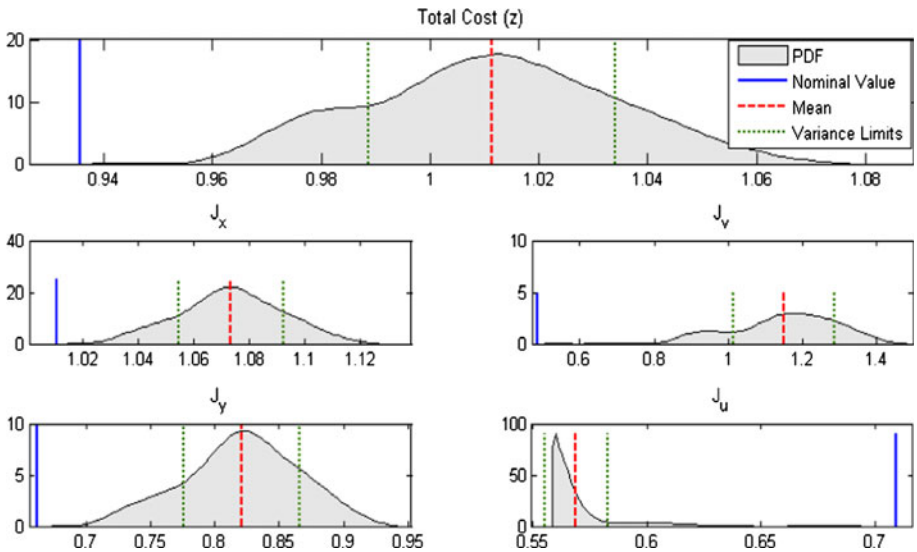

Fig. 8 Statistical description of obtained cost components from Monte Carlo simulation of CLF strategy

Table 2 Numerical and statistical information of Monte Carlo simulation results

Statistical description of sub-objective functions	CMA–ES-optimized control strategies		
	SIG	OLF	CLF
J_x			
Mean	**1.0067 (1)**	1.0232 (2)	1.0734 (3)
Min.	0.9864 (1)	0.9975 (2)	1.0139 (3)
Max.	1.0451 (1)	1.0605 (2)	1.1271 (3)
STD	**0.0094 (1)**	0.0107 (2)	0.0182 (3)
Nominal	0.9860 (1)	0.9970 (2)	1.0108 (3)
ERR	**0.0207 (1)**	0.0262 (2)	0.0626 (3)
ERRP (%)	**2.1004 (1)**	2.6248 (2)	6.1931 (3)
J_y			
Mean	**0.6493 (1)**	0.7165 (2)	0.8212 (3)
Min.	0.5865 (1)	0.6435 (2)	0.6724 (3)
Max.	0.7535 (1)	0.8168 (2)	0.9430 (3)
STD	**0.0273 (1)**	0.0299 (2)	0.0452 (3)
Nominal	0.5852 (1)	0.6416 (2)	0.6624 (3)
ERR	**0.0641 (1)**	0.0749 (2)	0.1587 (3)
ERRP (%)	**0.9535 (1)**	11.6732 (2)	23.9652 (3)
J_v			
Mean	**0.5570 (1)**	0.6962 (2)	1.1516 (3)
Min.	0.4246 (1)	0.4967 (2)	0.5022 (3)
Max.	0.8085 (1)	0.9764 (2)	1.4822 (3)
STD	**0.0637 (1)**	0.0867 (2)	0.1331 (3)
Nominal	0.4225 (1)	0.4930 (2)	0.4860 (3)
ERR	**0.1344 (1)**	0.2032 (2)	0.6656 (3)
ERRP (%)	**31.8100 (1)**	41.2145 (2)	136.9645 (3)
J_u			
Mean	0.8940 (3)	0.7382 (2)	**0.5689 (1)**
Min.	0.8455 (3)	0.7382 (2)	0.5580 (1)
Max.	0.9182 (3)	0.7382 (2)	0.6947 (1)
STD	0.0118 (2)	**5.9453×10^{-13} (1)**	0.0137 (3)
Nominal	0.9186 (3)	0.7382 (2)	0.7096 (1)
ERR	−0.0247 (2)	**0 (1)**	−0.1407 (3)
ERRP (%)	−2.6847 (2)	**0 (1)**	−19.8255 (3)
z			
Mean	**0.9617 (1)**	0.9634 (2)	1.0114 (3)
Min.	0.9398 (3)	0.0926 (1)	0.9372 (2)
Max.	1.0027 (1)	1.0119 (2)	1.0779 (3)
STD	**0.0101 (1)**	0.0141 (2)	0.0227 (3)
Nominal	0.9394 (3)	0.9289 (1)	0.9356 (2)
ERR	**0.0222 (1)**	0.0345 (2)	0.0758 (3)
ERRP (%)	**2.3663 (1)**	3.7130 (2)	8.0994 (3)

robustness when considering J_y and J_v sub-objective functions with a smaller error percentage as compared to OLF and CLF strategies. However, as can be seen in Fig. 8, the performance of proposed CMA–ES-optimized CLF strategy is noticeable in minimization of drug usage. It is noted that the mean value in statistical description of J_u sub-cost is 0.569 and is lower than its nominal value (i.e., 0.710) with an STD equals to 0.014.

It is noted that in our simulations, λ is set to 100, K as the maximum number of iterations is set to 200, μ as the number of positive weights is set to 100, and d_σ as the damping parameter is set to 0.98. The dimension of search

Table 3 Optimal parameter values in the three proposed control strategies

Control strategy	Parameter	Parameter value							
SIG	θ_i	$i = 1$			$i = 2$			$i = 3$	
		10.0000			−0.7551			−7.3551	
OLF	U_i	$i = 1$	1.0000	$i = 6$	1.0000	$i = 11$	0.8358	$i = 16$	0.2002
		$i = 2$	1.0000	$i = 7$	1.0000	$i = 12$	0.5053	$i = 17$	0.3813
		$i = 3$	1.0000	$i = 8$	1.0000	$i = 13$	0.7119	$i = 18$	0.0676
		$i = 4$	1.0000	$i = 9$	1.0000	$i = 14$	0.1829	$i = 19$	1.0000
		$i = 5$	1.0000	$i = 10$	0.8892	$i = 15$	0.2592	$i = 20$	1.0000
CLF	U_{ij}	i, j	$j = 1$	$j = 2$	$j = 3$	$j = 4$	$j = 5$	$j = 6$	$j = 7$
		$i = 1$	0.3569	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
		$i = 2$	1.0000	0.9257	1.0000	1.0000	1.0000	1.0000	1.0000
		$i = 3$	1.0000	0.5960	0.7815	1.0000	0.4168	0.6904	0.4603
		$i = 4$	0.7426	0.7023	0.6679	0.5527	1.0000	1.0000	1.0000
		$i = 5$	0.4339	0.7045	0.4283	0.7164	0.9277	1.0000	0.9985
		$i = 6$	0.4999	0.9999	0.0553	0.7322	1.0000	1.0000	1.0000
		$i = 7$	0.6552	0.1000	0.5949	0.8091	1.0000	1.0000	1.0000

for closed-loop sigmoid-based strategy, open-loop fuzzy strategy, and closed-loop fuzzy strategy is set to 3, 20, and 7, respectively.

According to the numerical information reported in Table 2, considering the total cost z, SIG strategy has the best performance in terms of the number of infected hepatocytes, free HBVs, and the number of healthy hepatocytes in average. It should be mentioned that the closed-loop neural-type sigmoid-based controller uses only three optimized parameters as compared to other two controllers with 20 and 49 parameters (Table 3).

8 Conclusion

In this paper, three different forms of CMA–ES-based optimal controllers have been designed to perform the optimal antiviral therapy on hepatitis B infection model. Among the proposed controllers, CMA–ES-based open-loop fuzzy controller has the best nominal performance and the closed-loop fuzzy controller is in the second rank. After designing the controllers, aggressiveness of HBVs, replication rate of HBVs, and efficacy of the antiviral drug have been considered to be unknown and uniformly distributed random numbers. Variation range of these parameters has been chosen such that they had destructive effect on the controller performance.

Then, the robustness of controllers has been analyzed and studied statistically. Concerning the robustness, the CMA–ES-based closed-loop neural-type sigmoid-based controller is the best and the CMA–ES-based open-loop fuzzy controller is in the second rank. Thus, for the optimal control of HBV infection model, CMA–ES-based closed-loop neural-type sigmoid-based controller is more reliable than other investigated controller structures.

It is noted that the problem in this paper is a multi-objective optimization problem. In this way, EAs such as one introduced in [85], multi-objective self-organizing algorithm (MOSOA) [86], multi-objective particle swarm optimization (MOPSO) [87], and multi-objective DE algorithm (MODEA) [88] can be used as future work instead of solving the problem by defining sub-objective functions to maximize the treatment performance and minimize the drug usage. Study of more complex models, which include the response of immune system, and employing other types of control strategies are examples of future research directions.

References

1. Robinson WS (1994) Hepatitis B viruses. General features (human). In: Webster RG, Granoff A (eds) Encyclopedia of virology. Academic Press, London, pp 554–569
2. Robinson WS (1995) Hepatitis B virus and hepatitis D virus. In: Mandell GL, Bennett JE, Dolin R (eds) Principles and practice of infectious diseases, 4th edn. Churchill Livingstone, New York, pp 1406–1439
3. Ganem D, Schneider RJ (2001) Hepadnaviridae: the viruses and their replication. In: Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B et al (eds) Fields virology, 4th edn. Lippincott Williams & Wilkins, Philadelphia, pp 2923–2969
4. Wong VWS, Wong GLH, Chu WCW, Chim AML, Ong A, Yeung DKW, Yiu KKL, Chu SHT, Chan HY, Woo J, Chan FKL, Chan HLY (2012) Hepatitis B virus infection and fatty liver in the general population. J Hepatol 56:533–540
5. Mahoney FJ, Kane M (1999) Hepatitis B vaccine. In: Plotkin SA, Orenstein WA (eds) Vaccines, 3rd edn. WB Saunders Company, Philadelphia, pp 158–182

6. Pan CQ, Duan ZP, Bhamidimarri KR, Zou HB, Liang XF, Li J, Tong MJ (2011) An algorithm for risk assessment and intervention of mother to child transmission of hepatitis B virus. Clin Gastroenterol Hepatol. doi:10.1016/j.cgh.2011.10.041. Available online 9 Nov 2011
7. Kapoor A, Bhatia V, Gopalan S, Sibal A (2011) Hepatitis B in children-current status. Apollo Med 8:287–293
8. World Health Organization (2008) Hepatitis B. Who is most at risk for chronic disease? Available at: http://www.who.int/mediacentre/factsheets/fs204/en/, accessed 30 Mar 2012
9. Michelin A, Henderson DK (2010) Infection control guidelines for prevention of health care-associated transmission of hepatitis B and C viruses. Clin Liver Dis 14:119–136
10. World Health Organization (2008) Hepatitis B. Transmission. Available at: http://www.who.int/mediacentre/factsheets/fs204/en/, accessed 30 Mar 2012
11. Delfino CM, Berini C, Eirin ME, Malan R, Pedrozo W, Krupp R, Blejer J, Espejo R, Fierro L, Puca A, Oubiña JR, Mathet VL, Biglione MM (2012) New natural variants of hepatitis B virus among Amerindians from Argentina with mainly occult infections. J Clini Virol. doi:10.1016/j.jcv.2012.02.023. Available online 22 Mar 2012
12. Ganem D, Prince AM (2004) Hepatitis B virus infection-natural history and clinical consequences. N Engl J Med 350:1118–1129
13. Romano' L, Paladini S, Van Damme P, Zanetti AR (2011) The worldwide impact of vaccination on the control and protection of viral hepatitis B. Dig Liver Dis 43(Supplement 1):S2–S7
14. Huang LM, Lu CY, Chen DS (2011) Hepatitis B virus infection, its sequel, and prevention by vaccination. Curr Opin Immunol 23:237–243
15. Lok ASF, McMahon BJ (2001) Chronic hepatitis B. Hepatology 34:1225–1241
16. Marcellin P, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML et al (2003) Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med 348:808–816
17. Piccolo P, Lenci I, Demelia L, Bandiera F, Piras MR, Antonucci G et al (2009) A randomized controlled trial of pegylated interferon-alpha2a plus adefovir dipivoxil for hepatitis B e antigen-negative chronic hepatitis B. Antivir Ther 14:1165–1174
18. Matthews SJ (2006) Entecavir for the treatment of chronic hepatitis B virus infection. Clin Ther 28:184–203
19. Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y et al (2007) Telbivudine versus lamivudine in patients with chronic hepatitis B. N Engl J Med 357:2576–2588
20. Woo G, Tomlinson G, Nishikawa Y, Kowgier M, Sherman M, Wong DK et al (2010) Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. Gastroenterology 139:1218–1229
21. Lai CL, Yuen MF (2007) The natural history and treatment of chronic hepatitis B: a critical evaluation of standard treatment criteria and end points. Ann Intern Med 147:58–61
22. Nowak M, May R (2001) Virus dynamics: mathematical principles of immunology and virology. Oxford University Press, New York
23. Wodarz D, Nowak M (2002) Mathematical models of HIV pathogenesis and treatment. BioEssays 24:1178–1187
24. Landi A, Mazzoldi A, Andreoni C, Bianchi M, Cavallini A, Laurino M, Ricotti L, Iuliano R, Matteoli B, Ceccherini-Nelli L (2008) Modeling and control of HIV dynamics. Comput Methods Prog Biomed 89:162–168
25. Perelson AS (2002) Modeling viral and immune system dynamics. Nat Rev Immunol 2:28–36
26. Wodarz D (2003) Hepatitis C virus dynamics and pathology: the role of CTL and antibody responses. J Gen Virol 84:1743–1750
27. Perelson AS, Hermmann E, Micol F, Zeuzem S (2005) New kinetic models for the hepatitis C virus. Hepatology 42:749–754
28. Debroy S (2010) Evaluating treatment of hepatitis C for hemolytic anemia management. Math Biosci 225:141–155
29. Yasini S, Naghibi-Sistani MB, Karimpour A (2008) Active insulin infusion using fuzzy-based closed-loop control. In: Proceedings of the international conference on intelligent systems and knowledge engineering, pp 429–434
30. Coban R (2011) A fuzzy controller design for nuclear research reactors using the particle swarm optimization algorithm. Nucl Eng Des 241:1899–1908
31. Frantti T (2012) Expert system for open-loop power control of wireless local area networks. Expert Syst Appl. doi:10.1016/j.eswa.2012.02.105. Available online 19 Feb 2012
32. Jagodnik KM, van den Bogert AJ (2010) Optimization and evaluation of a proportional derivative controller for planar arm movement. J Biomech 43:1086–1091
33. Das S, Pan I, Das S, Gupta A (2012) A novel fractional order fuzzy PID controller and its optimal time domain tuning based on integral performance indices. Eng Appl Artif Intell 25:430–442
34. Oh SK, Kim WD, Pedrycz W (2012) Design of optimized cascade fuzzy controller based on differential evolution: simulation studies and practical insights. Eng Appl Artif Intell 25:520–532
35. Meidanshahi V, Karimi G (2012) Dynamic modeling, optimization and control of power density in a PEM fuel cell. Appl Energy 93:98–105
36. Kumbasar T, Eksin I, Guzelkaya M, Yesil E (2011) Adaptive fuzzy model based inverse controller design using BB-BC optimization algorithm. Expert Syst Appl 38:12356–12364
37. Oh SK, Jang HJ, Pedrycz W (2011) Optimized fuzzy PD cascade controller: a comparative analysis and design. Simul Model Pract Theory 19:181–195
38. Oh SK, Jang HJ, Pedrycz W (2011) A comparative experimental study of type-1/type-2 fuzzy cascade controller based on genetic algorithms and particle swarm optimization. Expert Syst Appl 38:11217–11229
39. Cococcioni M, Lazzerini B, Marcelloni F (2011) On reducing computational overhead in multi-objective genetic Takagi–Sugeno fuzzy systems. Appl Soft Comput 11:675–688
40. Pan I, Das S, Gupta A (2011) Handling packet dropouts and random delays for unstable delayed processes in NCS by optimal tuning of $PI^{\lambda}D^{\mu}$ controllers with evolutionary algorithms. ISA Trans 50:557–572
41. Das S, Pan I, Das S, Gupta A (2012) Improved model reduction and tuning of fractional-order $PI^{\lambda}D^{\mu}$ controllers for analytical rule extraction with genetic programming. ISA Trans 51:237–261
42. dos Santos Coelho L, Wicthoff Pessôa M (2011) A tuning strategy for multivariable PI and PID controllers using differential evolution combined with chaotic Zaslavskii map. Expert Syst Appl 38:13694–13701
43. Sundareswaran K, Srinivasarao Nayak P (2012) Ant colony based feedback controller design for soft-starter fed induction motor drive. Appl Soft Comput 12:1566–1573
44. Sheikhan M, Shahnazi R, Hemmati E (2012) Adaptive active queue management controller for TCP communication networks using PSO–RBF models. Neural Comput Appl. doi:10.1007/s00521-011-0786-0. Available online 4 Jan 2012
45. Sheikhan M, Shahnazi R, Garoucy S (2011) Hyperchaos synchronization using PSO-optimized RBF-based controllers to improve security of communication systems. Neural Comput Appl. doi:10.1007/s00521-011-0774-4. Available online 16 Dec 2011
46. Sheikhan M, Shahnazi R, Garoucy S (2011) Synchronization of general chaotic systems using neural controllers with application to secure communication. Neural Comput Appl. doi:10.1007/s00521-011-0697-0. Available online 19 Jul 2011
47. Hansen N, Ostermeier A (2001) Completely derandomized self-adaptation in evolution strategies. Evol Comput 9:159–195

48. Hansen N, Müller SD, Koumoutsakos P (2003) Reducing the time complexity of the derandomized evolution strategy with covariance matrix adaptation (CMA–ES). Evol Comput 11:1–18
49. Bledsoe KC, Favorite JA, Aldemir T (2011) A comparison of the covariance matrix adaptation evolution strategy and the Levenberg–Marquardt method for solving multidimensional inverse transport problems. Ann Nucl Energy 38:897–904
50. Chu W, Gao X, Sorooshian S (2011) A new evolutionary search strategy for global optimization of high-dimensional problems. Inf Sci 181:4909–4927
51. Piotrowski AP, Napiorkowski JJ, Kiczko A (2012) Differential evolution algorithm with separated groups for multi-dimensional optimization problems. Eur J Oper Res 216:33–46
52. Kämpf JH, Robinson D (2009) A hybrid CMA–ES and HDE optimization algorithm with application to solar energy potential. Appl Soft Comput 9:738–745
53. Baskar S, Suganthan PN, Ngo NQ, Alphones A, Zheng RT (2006) Design of triangular FBG filter for sensor applications using covariance matrix adapted evolution algorithm. Opt Commun 260:716–722
54. Hou S, Li Y (2009) Short-term fault prediction based on support vector machines with parameter optimization by evolution strategy. Expert Syst Appl 36:12383–12391
55. Villasana M, Ochoa G, Aguilar S (2010) Modeling and optimization of combined cytostatic and cytotoxic cancer chemotherapy. Artif Intell Med 50:163–173
56. Ghosh S, Das S, Roy S, Minhazul Islam SK, Suganthan PN (2012) A differential covariance matrix adaptation evolutionary algorithm for real parameter optimization. Inf Sci 182:199–219
57. Piotrowski AP, Rowinski PM, Napiorkowski JJ (2012) Comparison of evolutionary computation techniques for noise injected neural network training to estimate longitudinal dispersion coefficients in rivers. Expert Syst Appl 39:1354–1361
58. Iruthayarajan MW, Baskar S (2010) Covariance matrix adaptation evolution strategy based design of centralized PID controller. Expert Syst Appl 37:5775–5781
59. Nowak M, Bonhoeffer S, Hill AM, Boehme R, Thomas HC, Mc Dade H (1996) Viral dynamics in hepatitis B infection. Proc of Natl Acad Sci USA 93:4398–4402
60. Le Guerhier F, Thermet A, Guerret S, Chevallier M, Jamard C, Gibbs CS, Trépo C, Cova L, Zoulim F (2003) Antiviral effect of adefovir in combination with a DNA vaccine in the duck hepatitis B virus infection model. J Hepatol 38:328–334
61. Ciupe SM, Ribeiro RM, Nelson PW, Perelson AS (2007) Modeling the mechanisms of acute hepatitis B virus infection. J Theor Biol 247:23–35
62. Thornley S, Bullen C, Roberts M (2008) Hepatitis B in a high prevalence New Zealand population: a mathematical model applied to infection control policy. J Theor Biol 254:599–603
63. Qiao M, Qi H (2009) Dynamics of the HBV model with diffusion and time delay. In: Proceedings of the international workshop on chaos-fractals theories and applications, pp 297–300
64. Qiao M, Qi H, Chen Y (2011) Qualitative analysis of hepatitis B virus infection model with impulsive vaccination and time delay. Acta Math Sci 31:1020–1034
65. Luzyanina T, Bocharov G (2011) Stochastic modeling of the impact of random forcing on persistent hepatitis B virus infection. Math Comput Simul. doi:10.1016/j.matcom.2011.10.002. Available online 14 Oct 2011
66. Pang J, Cui JA, Zhou X (2010) Dynamical behavior of a hepatitis B virus transmission model with vaccination. J Theor Biol 265:572–578
67. Zhang S, Zhou Y (2012) The analysis and application of an HBV model. Appl Math Model 36:1302–1312
68. Nakabayashi J, Sasaki A (2011) A mathematical model of the intracellular replication and within host evolution of hepatitis type B virus: understanding the long time course of chronic hepatitis. J Theor Biol 269:318–329
69. Hollinger F, Lau D (2006) Hepatitis B: the pathway to recovery through treatment. Gastroenterol Clin N Am 35:895–931
70. Medley GF, Lindop NA, Edmunds WJ, Nokes DJ (2001) Hepatitis-B virus endemicity: heterogeneity, catastrophic dynamics and control. Nat Med 7:619–624
71. Adams BM, Banks HT, Davidian M, Kwon H, Tran HT, Wynne SN, Rosenberg ES (2005) HIV dynamics: modeling, data analysis, and optimal treatment protocols. J Comput Appl Math 184:10–49
72. Costanza V, Rivadeneira PS, Biafore FL, D'Attellis CE (2009) A closed-loop approach to antiretroviral therapies for HIV infection. Biomed Signal Process Control 4:139–148
73. Zurakowski R, Teel AR (2006) A model predictive control based scheduling method for HIV therapy. J Theor Biol 238:368–382
74. Pannocchia G, Laurino M, Landi A (2010) A model predictive control strategy toward optimal structured treatment interruptions in anti-HIV therapy. IEEE Trans Biomed Eng 57:1040–1050
75. Hattaf K, Rachik M, Saadi S, Yousfi N (2009) Optimal control of treatment in a basic virus infection model. Appl Math Sci 3:949–958
76. Ying H (1998) General SISO Takagi–Sugeno fuzzy systems with linear rule consequent are universal approximators. IEEE Trans Fuzzy Syst 6:582–587
77. Beyer HG, Schwefel HP (2002) Evolution strategies: a comprehensive introduction. Nat Comput 1:3–52
78. Kern S, Müller S, Hansen N, Büche D, Ocenasek J, Koumoutsakos P (2004) Learning probability distributions in continuous evolutionary algorithms-a comparative review. Nat Comput 3:77–112
79. Li C, Heinemann PH (2007) A comparative study of three evolutionary algorithms for surface acoustic wave sensor wavelength selection. Sens Actuators B Chem 125:311–320
80. Hansen N, Ros R, Mauny N, Schoenauer M, Auger A (2011) Impacts of invariance in search: when CMA–ES and PSO face ill-conditioned and non-separable problems. Appl Soft Comput 11:5755–5769
81. Hansen N, Ostermeier A (1996) Adapting arbitrary normal mutation distributions in evolution strategies: the covariance matrix adaptation. In: Proceedings of the IEEE conference on evolutionary computation, pp 312–317
82. Jastrebski GA, Arnold DV (2006) Improving evolution strategies through active covariance matrix adaptation. In: Proceedings of the IEEE world congress on computational intelligence, pp 9719–9726
83. Hansen N, Kern S (2004) Evaluating the CMA evolution strategy on multimodal test functions. In: Yao X et al (eds) Parallel problem solving from nature-PPSN VIII, LNCS 3242. Springer, Berlin, pp 282–291
84. Igel C, Hansen N, Roth S (2007) Covariance matrix adaptation for multi-objective optimization. Evol Comput 15:1–28
85. Thapar A, Pandey D, Gaur SK (2012) Satisfying solutions of multi-objective fuzzy optimization problems using genetic algorithm. Appl Soft Comput. doi:10.1016/j.asoc.2012.03.002. Available online 13 Mar 2012
86. Fotakis D, Sidiropoulos E (2012) A new multi-objective self-organizing optimization algorithm (MOSOA) for spatial optimization problems. Appl Math Comput 218:5168–5180
87. de Carvalho AB, Pozo A (2012) Measuring the convergence and diversity of CDAS multi-objective particle swarm optimization algorithms: a study of many-objective problems. Neurocomputing 75:43–51
88. Musrrat A, Patrick S, Millie P (2012) An efficient differential evolution based algorithm for solving multi-objective optimization problems. Eur J Oper Res 217:404–416