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A mathematical study on the drug resistant virus emergence with HIV/AIDS treatment cases

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ABSTRACT

HIV/AIDS drug treatments, one of which is highly active anti-retroviral ther-apy (HAART), often fail by the emergence of drug resistant virus. In this paper we study a quantitative method to evaluate the chance of resistant virus gen-eration. To this end we develop a mathematical description of the possibility of the emergence of resistant virus species against drug treatments, depend-ing on the trajectories of the state variables of HIV infection dynamic model. By simulation studies of mathematical models we apply the proposed analy-sis method to HIV/AIDS drug therapies, improved gradual dosage reduction (iGDR) and structured treatment interruption (STI). Based on the analysis it can be explained the reason why STI therapy often fails. Moreover it is con-cluded that iGDR is desirable particularly by decreasing the threat of resistant virus emergence.

1. Introduction

Acquired immune deficiency syndrome (AIDS) is induced by the infection by human immunodeficiency virus (HIV) [1]. When HIV infection progresses further, the function of immune system is considerably disturbed. Accordingly the infected person becomes significantly vulnerable to other infections, for ex-ample, tuberculosis, tumours, and opportunistic infections. Note that these infections usually do not have serious effect on people with proper functions of immune systems [2].

Infected CD4 T-cells can be destructed by direct viral suppression action or by CD8 cytotoxic lymphocytes (CTL) which indicate infection of CD4 T-cells. When the count of CD4 T-cell is less than $200/mm^3$, the infected patient is claimed to be AIDS patient [3]. Cell-mediated immunity of AIDS patient does not perform properly. Thus the human body of AIDS becomes substantially sus-ceptible to other opportunistic infections, resulting in death. The survival time for HIV infected patient is approximately evaluated as 9–11 years, without any HIV/AIDS therapy.

Highly active anti-retroviral therapy (HAART) is able to control the number of HIV effectively in the human body. As a result HAART makes the immunity of the human body to be maintained and thus it can prohibit other opportunis-tic infections [4]. However we know that the therapy cannot exterminate HIV in infected patient, which means that HIV patient has to take long term HAART drug treatment. At the moment it considers that HIV/AIDS treatment is dif-ficult because the cost of anti-retroviral drugs is expensive and also the drug treatment schedule is complicated.

Note that HAART treatment can cause adverse side effects, including fatal liver damage. It is one of the most common causes of infected patients' death. Thus, instead of long term drug treatment of HAART, it is desired to develop such a drug therapy that further drug treatment can be stopped eventually, by helping the immune systems enhanced to work appropriate.

If HIV infected patient has no proper treatment, then the patient is prone to progress towards AIDS status. As a result the patient dies due to other opportunistic infections. Note that, however, all infected patients will not do necessarily. Among the HIV infected patients producing the virus antibodies a few examples of long-term non-progressor (LTNP) have been discussed in [2].

It is known that LTNP patient does not progress towards AIDS status for over 15 years. The count of CD4 T-cell of LTNP patient is maintained signif-icantly higher than that of other HIV patients. This implies that the immune response of LTNP patient is able to work effectively against other opportunistic infections. To explain the LTNP phenomenon, several mathematical models have been proposed and investigated [5, 6].

Such HIV mathematical models have two[1] asymptotic stable equilibria with-out any administration of medicine. One of the equilibrium points corresponds to the full-blown status of AIDS, while the other does to the status of LTNP. When a person is initially infected with

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[1] Refer [7, 8] for HIV mathematical model with three stable equilibrium points.

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HIV, unfortunately the state vector of the infected patient is mostly located in the region of attraction for the equilib-rium corresponding to AIDS status. Only for few exceptions, the state vector is located in the region of attraction for the equilibrium corresponding to LTNP status. In consequence HIV infected patients mostly progress towards the status of full-blown AIDS unless the patient is treated by a therapy specially designed to drive the HIV patient state towards the LTNP status.

For implementation of such a special treatment, the strategy of structured treatment interruption (STI) has been investigated in [5, 6, 9]. This strategy is a scheduling method for drug treatment, switching between zero dosage and full dosage of drug. One of practical problems of the strategy is that it strictly relies on the model parameters, usually hard to be estimated precisely. Hence the result of this strategy is considerably sensitive to the parameter uncertainty. To deal with such a problem we employ control systems perspective. Note that if we apply model predictive control (MPC) method then the feedback property of this method help to solve such a problem to some extent [10, 11].

However even in case that we apply MPC technique the controlled system sta-bility is not still guaranteed if the designed schedule of drug administration is not followed accurately.

In order to solve such a drawback with respect to sensitivity, gradual dosage reduction (GDR) method has been proposed in [12], in which this technique is applied to the 4-dimensional HIV mathematical model of [5]. The technique has been applied in [13] to the 5-dimensional HIV infection model of [6]. GDR is not sensitive to the parameter uncertainty and robust with respect to the schedule of drug treatment. Therefore this method can overcome the drawbacks of STI and MPC.

In the meantime the generation of drug resistant HIV species is a critical problem for HIV drug therapy, because it is one of the most significant rea-sons for the failure of HIV drug treatment [3, 5, 9, 11, 14]. The emergence of resistant virus species is related to the quantity of administered HIV drug [15]. An optimal control problem for the HIV schedules has been addressed in [16] particularly based on the cost function including the constant probability of drug resistance risk, and a more extensive study can be found in [17]. Besides HIV/AIDS disease, it is notable that drug resistance in cancer treatment has been investigated in [18] while antimicrobial resistance in bacterial treatment with antibiotic usage has been researched in [19].

To address the drug resistance problem in HIV/AIDS treatment, improved gradual dosage reduction (iGDR) has been proposed in [20]. Based on GDR, the improved scheduling method is suggested to decrease the amount of admin-istered HIV drug reducing the possibility of generation of drug resistant virus mutation.

Although iGDR has been designed to consider drug resistance in antiretroviral therapy, the reducing effect on the generation of drug resistant species of HIV has been analysed only qualitatively in [20]. Note that any quantitative measure method has not been developed so far to estimate the chance of the emergence of drug resistant virus.

A preliminary study of this research has been presented in [21]. Based on the preliminary study, in this paper we investigate an evaluation method to estimate the risk of drug treatment of HIV infection. The paper shows how our proposed method is designed and how it works for some exemplary cases. Moreover we apply the method to drug scheduling strategies to compare them with respect to the risk of drug resistant generation.

The paper organises as follows. In Section 2 we introduces the HIV math-ematical model studied in this research and provide a short summary of the research from [5, 12, 20]. Then Section 3 suggests a quantitative evaluation method to measure the expectation of the emergence of drug resistant species by HIV drug administration. In Section 4 we present case studies of the appli-cation of the proposed estimation method to the HIV drug scheduling schemes introduced in Section 2, and we discuss the results with additional remarks. The paper concludes in Section 5 with a summary of the main contribution and further research directions.

2. Background and motivation

In this section we present the 4-dimensional HIV mathematical model sug-gested in [5]. Also we provide a summary of the drug scheduling strategies, i.e., STI and iGDR, as well as their simulation results. Finally we introduce the motivation of the research of the paper at the end of this section.

2.1. HIV model

Several mathematical models have been researched so far to describe the dynamic reaction between the immune response and HIV. For a detailed expla-nation on modeling, refer [3, 14].

In particular the mathematical models in [22, 23] do not include any term corresponding to memory CTL. Thus the state is led to the AIDS status in these models if drug administration is stopped. Such models can be considered to study the dynamic response of initial infection of HIV whilst they cannot be used suitably to investigate long term plan for HIV drug treatment.

Note that the model in [5] includes the term describing memory CTL dy-namics, thus it has the equilibrium point which corresponds to the LTNP status.

We here consider the 4-dimensional HIV mathematical model, namely

$$\begin{aligned}
\dot{x}(t) &= \lambda - dx(t) - \eta\beta y(t)x(t),\\
\dot{y}(t) &= \eta\beta y(t)x(t) - ay(t) - pz(t)y(t),\\
\dot{w}(t) &= cx(t)y(t)w(t) - cqy(t)w(t) - bw(t),\\
\dot{z}(t) &= cqy(t)w(t) - hz(t).
\end{aligned} \tag{1}$$

The states, i.e., x, y, w, and z, are the concentrations of uninfected CD4 T-cell, HIV-infected CD4 T-cell, memory CTL, and helper dependent CTL, respectively. Therefore the states are all positive real. In model (1) the virus is not needed to be represented as state directly because the state y approximates HIV proportionally.

The parameters of the model are normalised, which implies that the states do not represent real clinical measures necessarily. For model (1) the time unit is 'day'. For a detailed description of model (1), refer [5].

The η term ($0 \leq \eta \leq 1$) is modified to describe the drug suppression effec-tiveness on model (1). To this end the term is rewritten as

$$\eta = 1 - \eta^* u. \tag{2}$$

The maximum level of the drug effect is presented by the parameter η^*. Thus if a drug is able to prevent maximally 92% of virus infection, then η^* is defined as 0.92. Consequently the control input u ($0 \leq u \leq 1$) describes the amount of administered drug.

The final purpose of HIV drug scheduling in this paper is to drive HIV patient towards the status of LTNP so that the drug treatment can be stopped. The four equilibria of the model is analysed to see whether the purpose can be realised or not. For a detailed description of the analysis on these equilibria, see [12, 20, 24].

For the exemplary model parameters suggested in [5], only two of the equi-libria show asymptotic stability under the condition of no medication, $u = 0$. One of these two points represents the status of AIDS, while the other does the status of LTNP. The point corresponding to the LTNP status is with compara-tively high level of uninfected CD4 T-cell state and memory CTL state. Thus it makes possible for the immune system to work properly, responding effectively to other opportunistic infections.

2.2. Scheduling strategies for HIV drug treatment

To drive the HIV infected patient towards the status of LTNP, STI method has been researched in [5, 6, 9], while GDR and iGDR methods have been investigated in [12, 13, 20].

Here we will not provide the full descriptions of these strategies. Instead we show some simulation studies of the strategies to help to

understand how the strategies' procedures work. For the detailed explanations of the implementation steps, refer [5, 12].

For the simulation studies we employ the initial state and the model param-eters of [5], namely $\lambda = 1$, $d = 0.1$, $\beta = 0.5$, $a = 0.2$, $p = 1$, $c = 0.1$, $q = 0.5$, $b = 0.01$, $h = 0.1$, $\eta^* = 0.9958$, and $[x(0), y(0), w(0), z(0)]^T = [0.52786, 3.5889, 0.035628, 0.063932]^T$. The initial state corresponds to a status of full-blown AIDS patient [5].

A computer simulation of STI scheduling method is carried out, and Figure 1 depicts the result. Drug administration is interrupted twice throughout the simulation of drug scheduling, as shown by the control input $u(t)$ in Figure 1. As a result the STI scheduling technique leads the state of the model to the status of LTNP, described by the point $[9.47, 0.011, 813.96, 4.53]^T$ for the given parameters. This implies that with the enhancement of states w and z the immune system can respond effectively to HIV without further HIV medication. Meanwhile Figure 2 presents the result of a simulation study of iGDR schedul-ing method of [20]. By this scheduling scheme the HIV patient state is driven to the status of LTNP. In the later sections of this paper, we study the results of both simulation examples. While these two scheduling strategies lead the state of HIV patient towards the status of LTNP eventually, comparison research is carried out with respect to the chance of drug resistance generation.

2.3. Motivation of research

Partial HAART is still able to suppress the viral load close to the viral load under full HAART or the viral load of the LTNP status [20]. Moreover the viral load during the therapy suggested in [20] is comparatively lower than the viral load during STI therapy of [5, 6, 11, 15, 25].

In STI protocol the drug dosage is controlled to switch between 'On' Sta-tus and 'Off' status, in other words, between full HAART medication and no administration of drug. It has been suggested in [15] that STI scheduling with such switching method should minimise the possibility of establishment of drug resistant virus due to the following reasons: if HIV patient does not take any administration of anti-retroviral drug, then the HIV level in patient increases. It could be considered that in this case

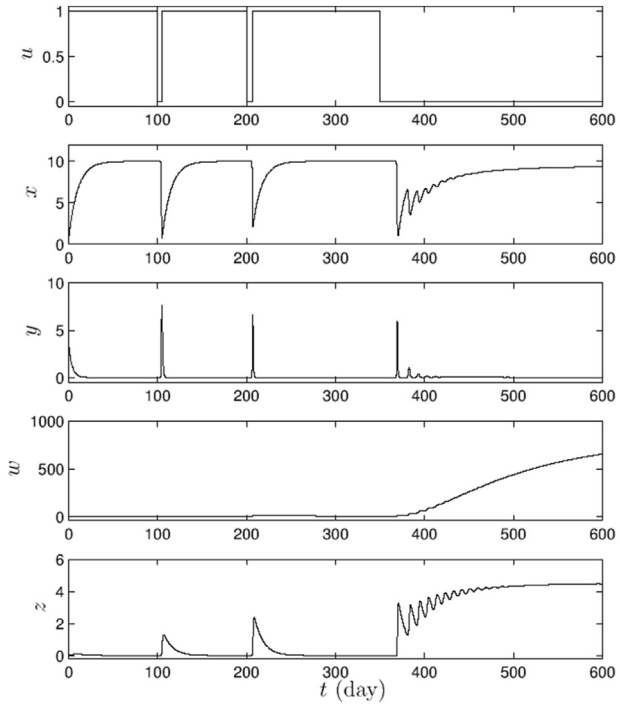

Figure 1. A simulation study of STI scheduling method of [5].

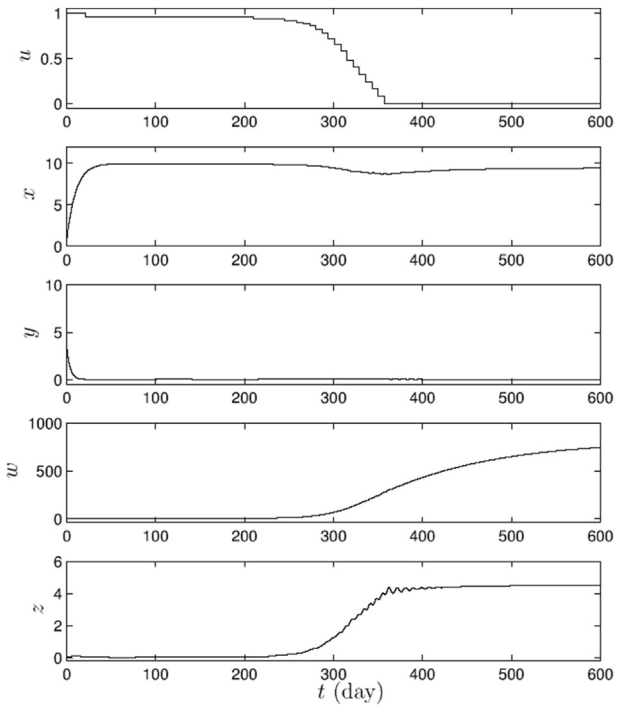

Figure 2. A simulation study of iGDR scheduling method of [20].

the virus strain of wild-type is significantly competitive to survive, compared to any mutation strain. This implies that the mutant HIV cannot continue to survive in such situation. Meanwhile in the case with full medication the viral load is too low for HIV mutant strains to be established. Note that, if any HIV mutant strain is established, then this full medication condition helps the drug resistant virus to survive without difficulty.

Because the STI method utilises only two states of drug dosage, full dosage and zero dosage, it has been suggested that this drug scheduling strategy minimises the risk of emergence of drug resistant virus [15].

However it is notable that the STI scheduling method continues to switch be-tween these two medication states, rather than to stay at one state steadily. For example we here consider the switching instance from no medication treatment to full medication treatment. Note that at this instance the risk of generation of drug resistant strain is maximised by the aforementioned analysis from [15]: according to [15], at this instance the viral load level at the instance is a certain positive so that the drug resistant strain might exist, and such resistant strain becomes more competitive for survival than the wild type strain when switched to full medication treatment.

Meanwhile the GDR and iGDR strategies of [12, 13, 20] exploit partial dosage of suppressive drug therapy. Nevertheless the treatment strategies keep signifi-cantly low level of viral load during the treatments. In the following section we investigate a quantitative evaluation method to see which HIV drug scheduling strategy induces greater risk of generation of drug resistant HIV mutation.

3. Chance of emergence of drug resistant virus

The GDR and iGDR treatments, as illustrated in Section 2, can decrease the total amount of drug administered during the treatments. This could imply that the treatments can reduce the risk of emergence of drug resistant virus, To support the implication quantitatively, we here provide an estimation method for the risk of generation of drug resistant mutation.

3.1. Suggestion of estimation function form

Now we present some results from [26] to be used in this research. Require-ments which the evaluation tool must satisfy is provided in [26]. The require-ments have been derived in [26] based on biological systems perspective.

Requirement 1: The emergence of drug resistant strain has positive relation with viral load.

Requirement 2: Without wild type virus, drug resistant virus does not exist. Requirement 3: The emergence of drug resistant virus is mono-tonically in-creased by administered dosage of HIV drug.

Requirement 4: Without HIV drug administration, drug resistant strain is not generated.

Requirement 2 and requirement 4 represent particular cases of requirement 1 and requirement 3, respectively. Requirements 1 and 2 are induced by the fact that the drug resistant strains are generated from the genetic error of wild type strain [3, 14]. Requirements 3 and 4 come from the fact that the drug resistant virus can survive with stronger competitiveness than wild type virus during drug therapy [15].

In [26] a function form has been defined satisfying the four require-ment conditions. The proposed function form F is described as follows.

$$F\ (t_e) = F\ (y_{[ti,te]},\ u_{[ti,te]},\ t_i,\ t_e). \tag{3}$$

t_i is the instant of time at which drug therapy is initiated while t_e is the instant of time at which we evaluate the possibility of the emergence of drug resistant strain. Consider that t_f is the instant of time at which drug therapy is terminated. If we evaluate the risk during drug therapy, $t_e \leq t_f$. If the risk is estimated after drug therapy, $t_e > t_f$.

The y state of model (1) for time period $[t_i,\ t_e]$ is denoted by $y_{[ti,te]}$. The controlled input u for time period $[t_i,\ t_e]$ is represented by $u_{[ti,te]}$.

Without loss of generality we assume $t_i = 0$. Now the Eq. (3) is rewrit-ten as

$$F\ (t_e) = F\ (y,\ u,\ t_e). \tag{4}$$

Note that we denote $u_{[0,te]}$ and $y_{[0,te]}$ by u and y, respectively, to simplify the notation in (4). By means of function $F\ (t_e)$ of (4) we evaluate the chance of drug resistance emergence at the instant of time t_e based on $y(t)$ and $u(t)$ for $0 \leq t \leq t_e$.

Note that the value of $F\ (t_e)$ of (4) could be greater than one, implying that the value of the function is not considered as probability. One value of the function would not have any practical implication. Instead, values of the function can be used to compare multiple drug scheduling methods with respect to the emerging chance of drug resistant species.

The model (1) can be simulated for different drug scheduling strategies with one initial condition. Then the values of $F\ (\cdot)$ for the drug strategies are calcu-lated. With these values we could compare the strategies. From the perspective of the emergence of drug resistant species, we examine which drug scheduling method is more desirable than other methods. Such a quantitative investiga-tion, for example, with function $F\ (\cdot)$ of (4) has not been reported so far to estimate the risk drug resistant mutation.

The value of function $F\ (\cdot)$ is not related to probability. Instead its implica-tion could be explained as follows: model (1) does not have any term to describe dynamics of drug resistant species. For some examples of mathematical mod-els with mutant HIV strain refer [3, 14, 27, 28, 29]. Thus once drug resistant strain is established, mathematical model including no dynamic term for mu-tant species, such as model (1), cannot represent the behaviour of virus infection dynamics in a proper way anymore.

Consequently the higher the value of function $F\ (\cdot)$ from the state trajectory of model (1) is, the less the simulation up to evaluation time t_e describes the realistic behaviour of the HIV infection dynamics. That is to say, a great value of function $F\ (\cdot)$ is considered that the current simu-lation would not show precise result due to the possible establishment of drug resistant species. Accordingly function $F\ (\cdot)$ increases monotonically with respect to evaluation time t_e.

Now we recall a function from [21], satisfying the four requirements and then we study characteristics of the function.

For the form of (3), a function is suggested in [21] as

$$F(y,\ u,\ t_i,\ t_e) = \int_{t_i}^{t_e} y(t_1)^l u(t_1)^m \left(\int_{t_1}^{t_e} u(t_2)^n dt_2 \right) dt_1. \tag{5}$$

In this equation l, m, and n are positive and real constants. The properties of the function are clearly consistent with all the requirements suggested in this subsection. Also F of (5) is monotonically increased with respect to t_e, as stated above. Noticeably F of (5) is not the only function with which the requirements can be satisfied, that is, there can be other forms of functions.

In [21], the following function has been proposed as one of examples, based on (4) with (5) where $l = 1$, $m = 1$, $n = 1$, and $t_i = 0$:

$$F(y,\ u,\ te) = \int_0^{t_e} y(t_1)u(t_1) \left(\int_{t_1}^{t_e} u(t_2)dt_2 \right) dt_1. \tag{6}$$

The integrations in (6) can be explained term by term as follows: The term $y(t_1)u(t_1)$ is proportional to the emergence of drug resistant virus at t_1 ($t_1 \in [0,\ t_e]$). Note that if the product of virus load and drug adminis-tration increases the possibility of resistance emergence becomes higher [30]. By the discussion in Subsection 2.3, for the drug resistant strain emerging at t_1, the establishment is related to the drug dosage over $t \geq t_1$. Thus it is assumed that the possibility that drug resistant strain has been established and exists at t_e ($t_e \geq t_1$) is proportional to the term $\int_{t_1}^{t_e} u(t_2)dt_2$ describing the accumulation of drug administration for the period $[t_1,\ t_e]$.

In the following section we show how to apply the function F of (6) to some examples, including the cases discussed in Subsection 2.2.

4. Application examples

In the section we demonstrate some applications of F of (6). As a result we illustrate how the suggested function (6) works for exemplary cases of HIV drug treatment. Then we compare the two HIV drug scheduling methods of Subsection 2.2 with respect to the emergence of drug resistance, particularly based on the function (6).

4.1. Application to illustrative cases

In this subsection we provide application examples of function (6) for some illustrative cases of HIV treatment. These application examples show how F of (6) can present the emergence of drug resistant strain, helping to understand the function F.

It is noted that the $y(t)$ and $u(t)$ data employed in this subsection are artifi-cial. Hypothetically the functions of time, $y(t)$ and $u(t)$, are gener-ated in order to demonstrate evaluation of F of (6). We do not obtain the data from com-puter simulations or from clinical cases. Note that in the following subsection we study with $y(t)$ and $u(t)$ obtained from simula-tion result.

At first we discuss two trivial cases, *i.e.,* no drug input case and no HIV infection case. Consider a case with $u(t) = 0$ ($0 \leq t \leq t_e$), no drug administra-tion. Then for any positive value of t_e, $F\ (y,\ u,\ t_e)$ is 0 by (6). Consider a case with $y(t) = 0$ ($0 \leq t \leq t_e$), uninfected by HIV. Then for any positive value of t_e, $F\ (y,\ u,\ t_e)$ is 0 by (6). For these trivial cases we can see that the function works properly as an evaluation method to the emer-gence risk of drug resistant virus.

From Figures 3, 4, 5 and 6, we discuss more realistic 10 scenarios which can occur during HIV drug therapy. We present three examples, *i.e.,* cases 1, 2, and 3 in Figure 3. For the 3 cases, we assume that the drug administration $u(t)$ is $u(t) = 0.5$ ($0 \leq t \leq t_e$) where $t_e = 100$. The top panel of Figure 3 depicts $y(t)$ corresponding to the cases, explained in the legend of Figure 3.

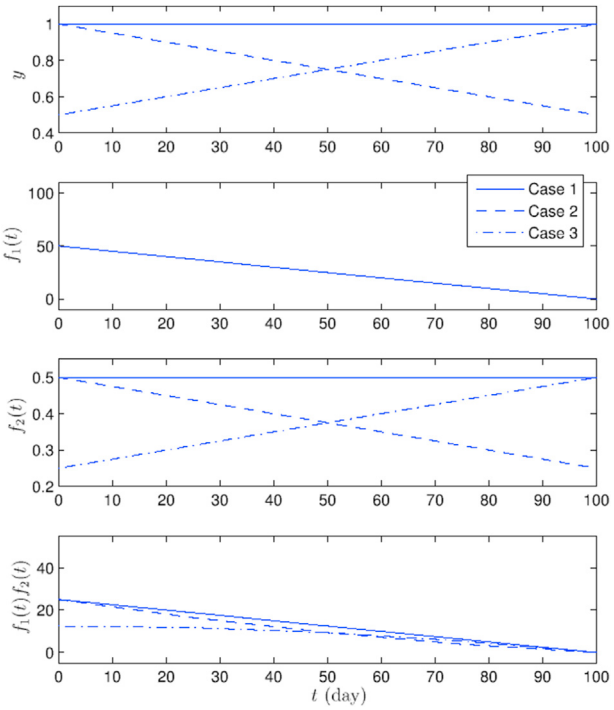

Figure 3. The integrands of function F of (6) corresponding to case 1, case 2, and case 3, respectively. For the cases te = 100 and input u is assumed to be constant. $f_1(t) = \int_t^{t_e} u(t_2)dt_2$ and f2(t) = y(t)u(t). Accordingly the product f1(t) f2(t) is the integrand term of F of (6).

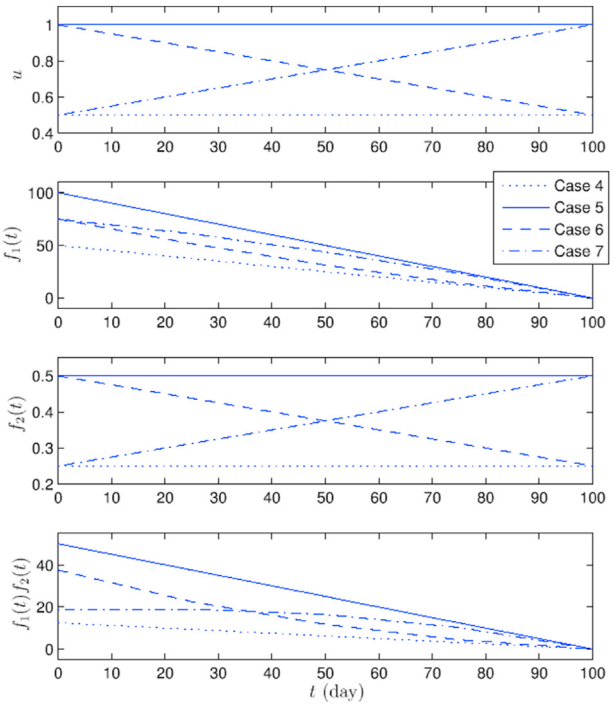

Figure 4. The integrand of the function *F (y, u, te)* of (6) for case 4, case 5, case 6, and case 7. Assume that infected CD4 T-cell *y* is constant. Note that $t_e = 100$, $f_1(t) = \int_t^{t_e} u(t_2)dt_2$ and $f_2(t) = y(t)u(t)$.

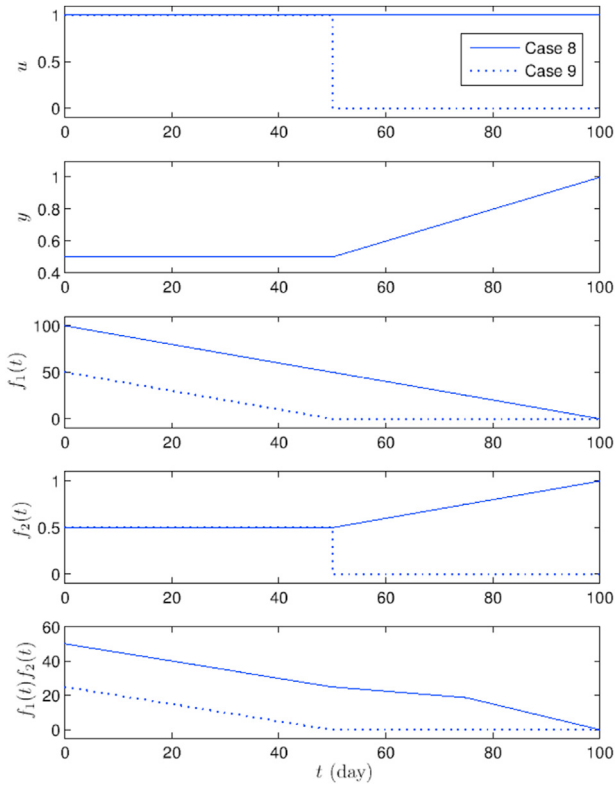

Figure 5. The integrand of the function *F (y, u, te)* of (6) for case 8 and case 9. Both cases employ the same *y(t)* depicted in the second panel. Note that $t_e = 100$, $f_1(t) = \int_t^{t_e} u(t_2)dt_2$ and $f_2(t) = y(t)u(t)$.

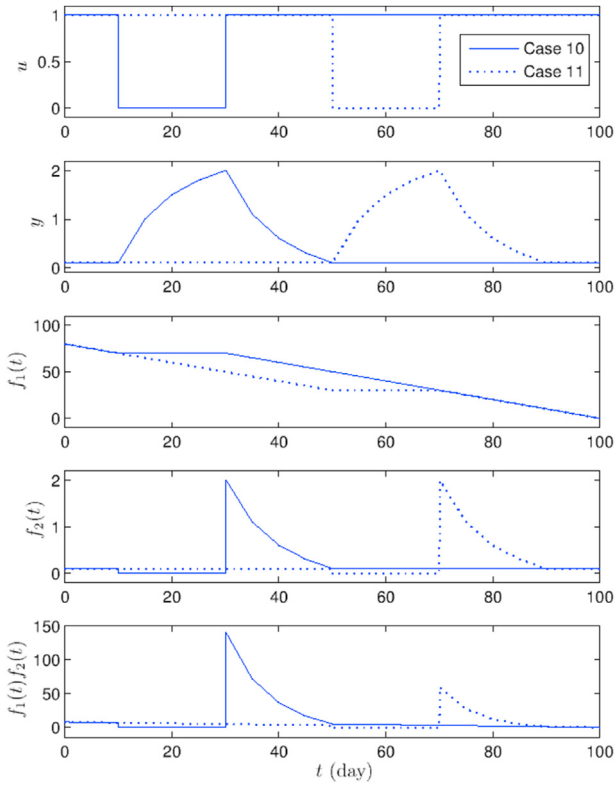

Figure 6. The integrand of the function *F (y, u, te)* of (6) for case 10 and case 11. Note that te = 100, $f_1(t) = \int_t^{t_e} u(t_2)dt_2$ and $f_2(t) = y(t)u(t)$.

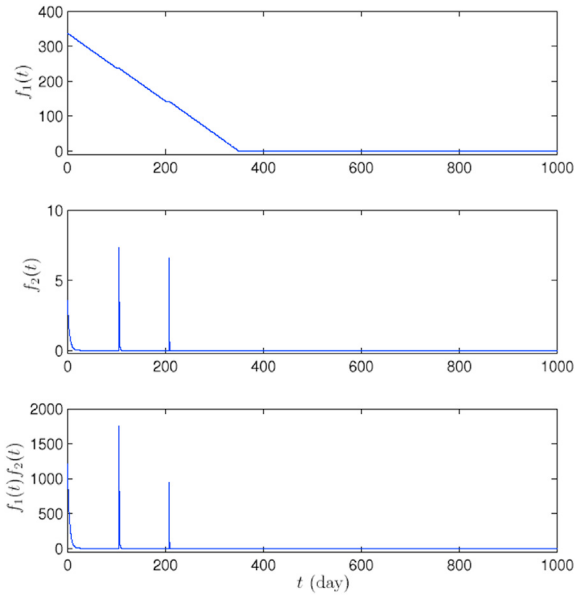

Figure 7. The integrand of the function *F (y, u, te)* of (6) for the STI treatment example of Subsection 2.2. Assume that $t_e = 1,\ 000$. Note that $f_1(t) = \int_t^{t_e} u(t_2)dt_2$ and $f_2(t) = y(t)u(t)$.

Note that $f_1(t) = \int_t^{t_e} u(t_2)dt_2$ and $f_2(t) = y(t)u(t)$ in this figure. This implies that $f_1(t)f_2(t)$ represented in the bottom panel is the integrand term of F of (6). The values of F for case 1, case 2, and case 3 are evaluated as 1250, 1054.7, and 820.31, respectively.

Figure 4 describes four examples, that is to say, case 4, case 5, case 6, and case 7. For these examples $y(t)$ is assumed to be constant, thus $y(t) = 0.5$ for $0 \le t \le t_e$ where $t_e = 100$. The top panel of Figure 4 indicates $u(t)$ employed by each example (see the legend). $F\,(y,\ u,\ t_e)$ of the cases 4, 5, 6, and 7 are obtained as 625, 2500, 1435.5, and 1377.0, respectively.

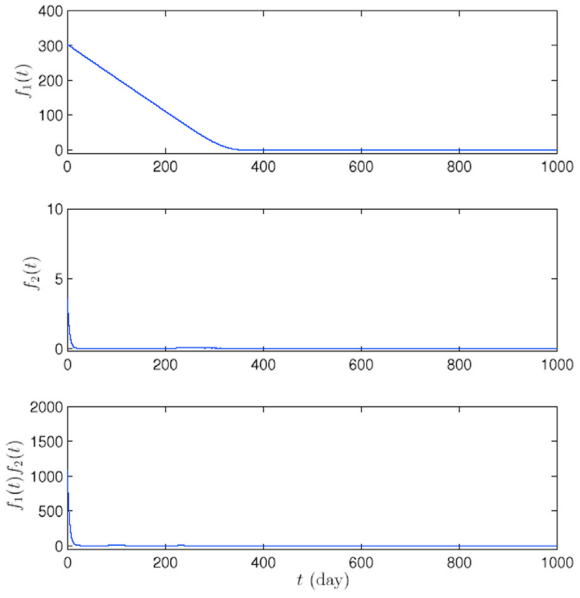

Figure 8. The integrand of the function *F (y, u, te)* of (6) for the iGDR treatment example of Subsection 2.2. Note that $t_e = 1,\ 000$, $f_1(t) = \int_t^{t_e} u(t_2)dt_2$, and $f_2(t) = y(t)u(t)$.

$f_2(t)$ of case 1 is equal to $f_2(t)$ of case 5 whereas $f_1(t)$ of case 1 is not the same with $f_1(t)$ of case 5, because $u(t)$ of case 1 is different to $u(t)$ of case 5. Accordingly the values of F for case 1 and case 5 are different. Likewise the value of F of case 2 is not equal to that of case 6 even though the cases employ the same $f_2(t)$. Note that case 3 and case 7 also show such a result.

Figure 5 shows two examples, *i.e.,* case 8 and case 9. $y(t)$ of the case 8 is equal to that of the case 9 as indicated in the second panel while $u(t)$ is depicted in the top panel (see the legend). The case 8 could be considered as an HIV- infected patient who becomes insensitive to HIV drugs so that the treatment cannot suppress its viral load anymore. The case 9 corresponds to a case where the viral load rebounds after interruption of HIV treatment. $F\,(y,\ u,\ t_e)$ of the cases 8 and 9 are computed as 2656.2 and 625.125, respectively.

Figure 6 presents two examples, *i.e.,* case 10 and case 11. $u(t)$ and $y(t)$ considered in these cases are described in the first and the second panels, re-spectively (see the legend). In the case 10 the drug therapy is interrupted at 10 (day) and $y(t)$ begins to increase and then the HIV treatment reinitiate at 30 (day) and the viral load is controlled to the initial state while in the case 11 $u(t)$ is zero for $50 \le t \le 70$. Note that these cases can describe the process of STI scheduling therapy and also see how this scheduling method influences the value of F of (6). $F\,(y,\ u,\ t_e)$ of the cases 10 and 11 are evaluated as 1178.4 and 650.415, respectively.

4.2. Application to the HIV drug therapy

In this subsection we obtain the values of the function F of (6) for the simulation examples of STI and iGDR scheduling methods in order to compare the two strategies with respect to the risk of drug resistance.

Thus $f_1(t)f_2(t)$ is the integrand.

To calculate the function F of (6) for the STI simulation example we first plot the integrand of the function, as shown in Figure 7. In the figure $f_1(t) = \int_t^{t_e} u(t_2)dt_2$ and $f_2(t) = y(t)u(t)$, assuming that $t_e = 1,\ 000$. Then $F\,(1,\ 000) = 6.6883 \times 10^3$ for the STI example, using the graph of $f_1(t)f_2(t)$.

Note that for this STI example $F\,(t_e) = 6.6883 \times 10^3$ for $t_e \ge 350$ since $u(t) = 0$ for $t \ge 350$. Also note that the integrand goes to high values when the drug administration changes from no dosage to full-dosage, as we predict in 2.3. Based on Figure 8 we also calculate the function F for the iGDR simulation example. Assuming that $t_e = 1,\ 000$, $F\,(1,\ 000) = 4.9584 \times 10^3$ for this example, considerably *lower* than the value for the STI simulation example.

Note that for this iGDR example $F\,(t_e) = 4.9584 \times 10^3$ for $t_e \ge 357$ because $u(t) = 0$ for $t \ge 357$. Mostly this value is obtained from the early stage of the simulation since, compared to the STI example, there is no such a high peak value of the integrand in the middle of the simulation.

Remark: In this paper we develop a method to estimate the possibility of the emergence of drug resistance in HIV therapy. In this section we demon-strate examples to show the applications of our proposed estimation method and the proposed evaluation method is used to compare different drug scheduling methods with respect to the drug resistance emergence. Such a comparison can hardly be found elsewhere in the literature but the estimation method proposed in this paper can be carried out for the comparison study.

5. Conclusions

The paper is now concluded with a summary of the work and further research direction.

Based on the preliminary study in [21], this paper has proposed and investi-gated a quantitative estimation method measuring the emergence possibility of the drug resistant virus. So far such possibility has been qualitatively estimated only. In this paper function of (6) has been developed in Section 3 and then we have applied it to the examples of two HIV drug scheduling schemes, STI and iGDR. According to the

research of this paper we could evaluate these two schemes by a perspective of the risk of drug resistant emergence.

Although the analysis method of the paper can be applied to compare a drug scheduling scheme with other schemes with regard to the possibility of drug resistance emergence, it is assumed that we can obtain the time histories of state variables of dynamic infection model. Note that in this paper we have studied simulation cases for HIV drug treatment. In order to be employed for the clinic treatment cases the method should be further researched with discrete-time measurement of the state variables due to the realistic limitation from the HIV/AIDS drug therapy. This could be one of the most significant future works. In this paper for the analysis of the cases of Section 4 we have mainly em-ployed (6) with $l = 1$, $m = 1$, and $n = 1$, which is one example of the general form (5). This general form can be further investigated with various positive real values of l, m, and n, as a future research direction, to show a possible extension of the evaluation method of this paper.

It is notable that this paper can shed light on the reason why disastrous results have been shown by some STI trials, (*e.g.,* see [31]). Moreover we expect that this paper could inspire other researchers so that advanced quantitative methods will be further developed and investigated.

In the meantime, the primary goal of iGDR scheme studied in [20] is to minimise drug administration subject to a set of given conditions. This approach has been developed considering the emergence of drug resistance, but it is not an approach to minimise such emergence. However, with the help of the study of this paper, we can improve the iGDR scheduling with respect to the emergence of drug resistant virus. To minimise the risk of drug resistance emergence, instead of administered drug dose of HIV therapy, HIV drug scheduling strategy can be researched in the future.

Declarations

Author contribution statement

Hyeygjeon Chang:Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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The authors declare no conflict of interest.

Additional information

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