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MPC based optimization applied to treatment of HCV infections.

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Abstract

Background and Objective: The recent introduction of antivirals for the treatment of the hepatitis C virus opens new frontiers but also poses a significant burden on public health systems. This paper presents a simulation study in which model predictive control (MPC) is proposed for optimizing the therapy aiming to obtain a reduction of the costs of therapy, while maintaining the best pharmacological control of the infection. Methods: A dynamic model describing the evolution of hepatitis C is deployed as internal model for MPC implementation, using nominal values of parameters. Different closed-loop simulations are presented both in nominal and in mismatch conditions. In addition, a more easily implementable treatment is proposed, which is based on a discrete dosage approach, where days on/off therapy are considered instead of continuous therapy modulation. Results: Results show that therapy modulation allows one to achieve the same infection evolution as with full therapy, with a reduction of drug consumption between 10% and 40%. The alternative discrete dosage approach shows similar results achieved with therapy modulation, both in terms of therapy effectiveness and drug consumption reduction. Conclusions: The proposed model predictive control therapy optimization strategies appear to be effective, implementable and robust to model errors. It therefore represents a potentially useful approach to alleviate the burden of HCV therapy cost on national health systems.

Keywords: Hepatis C, Model predictive control, Therapy optimization

1. Introduction

Hepatitis C is a liver disease caused by the hepatitis C virus (HCV). The virus can cause both acute and chronic hepatitis, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong disease. HCV is also a major cause of liver cancer. According to World Health Organization (WHO) 1.75 million people newly acquire hepatitis C virus infection each year. Globally, in 2015, WHO estimated that 71 million people have been infected with chronic HCV infection [1]. Recent development of antivirals has made possible to have a positive outcome after treatment in 95% of patients. Although the price of HCV therapies has decreased, it still remains too high for less developed countries especially considering the number of people infected, that stress national healthcare systems. One strategy to reduce therapy costs is to optimize drug delivery in order to preserve therapy efficacy but reducing amount of drug used. Control theory offers a promising solution to achieve this goal through model predictive control (MPC) algorithms. MPC, widely used in many different industrial applications, considers a system model to predict future response of a system and computes a sequence of optimal control inputs, solving an optimization problem including system dynamics. Safety, operational and performance constraints (on state and input variables) are also considered in the optimization problem [2,3]. In the last few years, feedback control technologies, and MPC in particular, have started to gain an increasing attention in the biomedical area [4,5]. Typical biomedical applications of control methods include the glucose insulin system in diabetics [6–10], automatic control of anesthesia [11–13], leukemia treatment [14], anticoagulant therapy [15–17]. In [16] it is shown how an MPC optimization strategy proved to give superior results than other control techniques, where anticoagulant therapy, optimized using MPC in

comparison to a nonlinear PID technique, proved to be more effective in reducing drug delivered amount. In particular it has been proved very effective in dealing with viral dynamics, like those described in [18]. Within the context of an anti-HIV therapy, it is shown in [19–23] how different treatment optimization strategies could be obtained through an MPC approach. A similar result is shown in [24] for hepatitis B therapy, even in presence of structured uncertainties on the model used to describe infection evolution. To the best of the authors knowledge, in literature a similar application in treatment of hepatitis C infections has not been reported, whereas it could potentially reduce the drug consumption and the associated costs for healthcare systems. Hence our purpose is to design an MPC system to optimize the HCV therapy. MPC should rely over a sufficiently accurate model in order to perform good predictions of future state of the plant, i.e. the biological system to be controlled, although it can cope with plant-model mismatch through appropriate feedback mechanisms. The purpose of this work is to propose an MPC strategy to compute an optimized therapy in order to reduce pharmacological treatment cost. The remainder of this paper is organized as follows. In Section 2 three models in the literature are compared and the most appropriate model for our purposes is selected. In Section 3 the MPC method is introduced and adapted to optimize the drug dose. In Section 4 simulation results are presented and commented. In Section 5 the main achievements of this study and possible future directions are summarized.

2. Methods

2.1. HCV modeling

There exist several mathematical models in the literature which describe the HCV evolution [25]. The first model was developed by Neumann et al. [26], based on previous works on HIV [27] and HBV [28]. It describes the HCV evolution based on an α-interferon therapy, showing some typical features of virus infection models, like a three dimensional vector states with healthy hepatocytes T, infected cells I and free virions V. It has quite simple dynamics, where it assumes a (not so realistic constant) reproduction rate of healthy hepatocytes and some canonical population model based for dynamics of (T, I,V). Dahari et al. [29] analyzed the Neumann model and proposed an extended version which improves the accuracy on reproduction rate of healthy and infected hepatocytes and includes Ribavirin [30] in treatment, later improved by Snoeck et al. in [31]. In both Neumann and Dahari models the possibility of a virus eradication without pharmacological treatment is not considered. To overcome this limitation, Aston proposed a new model in [32], which describes in a more accurate way the role of stem cells and the healthy hepatocytes regeneration, even in presence of a great loss of hepatocytes, like after a surgery or during an infection. Liver regeneration mechanism and immune system effects, as modelled in Aston, allow one to consider a reduced amount of drug in order to recover liver healthy conditions. Taking into account the above, Aston model proved to be the most suitable for analyzing possible therapy modulation strategies.

2.1.1. Aston model

The Aston model is considered in this paper and it is described by the following set of differential equations:

$$\begin{aligned}
\dot{T} &= sI + \frac{r_T T_{max}}{T+I} T - (r_T + d)T - (1-\eta)\beta VT \\
\dot{I} &= \frac{r_I T_{max}}{T+I} I - (r_I + \delta)I + (1-\eta)\beta VT \\
\dot{V} &= (1-\rho)(1-\epsilon)pI - cV - (1-\eta)\beta VT \\
\dot{V}_{NI} &= \rho(1-\epsilon)pI - cV_{NI}
\end{aligned} \tag{1}$$

in which T is the concentration of healthy hepatocytes, I is the concentration of infected hepatocytes, V is the concentration of free infectious virions. The term V_{NI} represents the portion of noninfectious virions added due to Ribavirin/DAA (direct-acting antiviral drugs) effect. The maximum number of

healthy hepatocytes is supposed to be T_{max}. The two constants r_T and r_I determine the rate of proliferation of healthy and infected hepatocytes. Coefficients 1/d , 1/δ , 1/c are life span of healthy hepatocytes hepatocytes, infected hepatocytes and virions, respectively. Coefficient p is the production rate of virions. Pharmacological control is described through efficacy of the treatment, a value between 0 and 1, where ε and η are the measured efficacy of interferon effect, while ρ is measured efficacy of Ribavirin and DAA. A complete list of model states and parameters is reported in Table 1. Aston model peculiarity is to consider liver stem cells effects. Such a stem cell action is effective only if liver is damaged or under an infection. Aston introduced the term sI to add this condition in the model assuming that reproduction rate of healthy hepatocytes, due to this mechanism, is directly proportional to I by a constant s. The equation term $r_T T_{max} T/(T+I)$ represents regeneration rate of healthy hepatocytes and it is realistic even if a great loss of hepatocytes occurs, e.g. after surgery or during infection.

Table 1
Symbols used in this work.

Symbol	Meaning
T (IU/ml)	Healthy cells
I (IU/ml)	Infected cells
V (IU/ml)	Free infective virions
V_{NI} (IU/ml)	Free non infective virions
T_{max} (IU/ml)	maximum value of healthy hepatocytes
s (day^{-1})	Stamina cells reproduction rate
d (day^{-1})	hepatocytes death rate
c (day^{-1})	virions death rate
δ (day^{-1})	infected cells death rate
r_T (day^{-1})	proliferation rate of healthy cells
r_I (day^{-1})	proliferation rate of infected cells
β ($IU/ml^{-1}day^{-1}$)	virus infection rate
ρ	virions non-infectious by ribavirin
ϵ	interferon efficacy
η	Ribavirin efficacy
p (day^{-1})	virions production rate

This model can describe different viral load profiles.

• “Sustained Virologic Response” (SVR) shows a rapid viral load decline which becomes undetectable after 24 weeks from the beginning of the treatment.

• “Relapse” shows an initial dynamics similar to SVR except that once the treatment is stopped the viral load rapid increases to pre-treatment levels.

• “Partial Virologic Response” (PVR) occurs if the viral load is quite high before treatment. It is characterized by an initial decline of viral load followed by an increase during treatment. In this condition the final state converges to the infected steady state. A similar condition to PVR is

• “Breakthrough”, but with the exception that the viral load becomes undetectable during treatment and then increases again. It differs from PVR because of the lower viral load at which the infected steady state is reached.

• “Null response” is a dynamics of the infection that occurs when some patients show an undetectable reduction in viral load under treatment. The last condition described by Aston model is called

• “Triphasic Decline” which shows a viral load evolution in treatment where there are two declining phases with a short phase of ascent in the middle.

2.2. MPC algorithm for therapy optimization

2.2.1. Introduction

MPC is an advanced model-based control technique where the process model, at each time sample, is used to compute a control sequence which is optimal according to a chosen cost function n over a finite prediction horizon and the associated sequence of states starting from the current state value [2,3]. The cost function is chosen such that an error variable is minimized while control constraints are fulfilled. The error variable is usually defined as the deviation of the future state sequence from reference target values. The model prediction can be corrected using process measurements, hence closing a feedback

loop [33,34]. Compared to other control techniques, MPC algorithms generally show superior performances and allow one to fulfill system constraints. One potential drawback of MPC is the computational time required, which strictly depends on system model and design parameters, such horizon length and time discretization. Due to this problem, even if it is possible to choose whatever linear or non-linear model, cost function and constraints, these are often chosen as linear models, linear constraints and quadratic cost functions, such that the associated control problem is a quadratic program (QP) or a linear program (LP), which can be solved using efficient available solvers. MPC algorithms are also a flexible instrument, which can handle multi-variable systems and do not require that the number of controlled and manipulated variables to be equal. Optimization goals, like keeping variables close to their reference targets, maintaining all controlled variables within limits and respecting constraints in the manipulated variables, are achieved using all manipulated variables. In this section, a Nonlinear MPC algorithm is presented to determine the "optimal doses" of interferon and Ribavirin/DAA drugs over a finite-prediction horizon.

2.2.2. Nonlinear MPC formulation

As discussed in Section 2.1, HCV dynamics is well described by Aston model. Due to the presence of significant non-linear dynamics in Aston model, it has been decided to implement a nonlinear MPC algorithm rather than considering a linearized model thereof. We recall that the fourth equation in (1) is decoupled from the other ones and can be discarded in the control problem formulation. During system identification some model parameters appear combined in the model and cannot be identified separately as explained in [32], whose identified data are reported in Table 2.

Table 2
Model nominal parameters values.

	PVR	Triphasic
s (day^{-1})	$1.1178 \cdot 10^{-1}$	$3.1259 \cdot 10^{-3}$
$r_T T_{max}$ (IU/ml/day)	$1.0645 \cdot 10^{4}$	$1.1149 \cdot 10^{2}$
$r_T + d$(day^{-1})	$1.9927 \cdot 10^{-3}$	$1.7882 \cdot 10^{-2}$
R	$3.0078 \cdot 10^{1}$	$2.0350 \cdot 10^{-1}$
D	$5.8954 \cdot 10^{1}$	$1.0962 \cdot 10^{1}$
β^* (ml/IU/day)	$8.3376 \cdot 10^{-9}$	$3.3281 \cdot 10^{-8}$
p^* (day^{-1})	$2.0396 \cdot 10^{2}$	$1.1646 \cdot 10^{3}$
c (day^{-1})	$1.7908 \cdot 10^{1}$	1.4294
$T(0)$ (IU/ml)	3.3246	1.9958
$I(0)$ (IU/ml)	$4.1752 \cdot 10^{5}$	$1.0355 \cdot 10^{2}$
η	0.89	0.89
ϵ	0.6	0.6

This led, because of convenience, to a slightly different form of the model. Due to previous considerations the final model used in the control problem formulation and to simulated the patient dynamics is as follows:

$$\begin{aligned} \dot{T} &= sI + \frac{r_T T_{\max} T}{T+I} - (r_T + d)T - \overline{\beta} VT \\ \dot{I} &= \frac{1}{1+R}\left(\frac{r_T T_{\max} I}{T+I} - (r_T + d)I\right) + \overline{\beta} VT - D(r_T + d)I \\ \dot{V} &= \overline{p} I - cV - \overline{\beta} VT \end{aligned} \tag{2}$$

where:

$$\overline{\beta} = (1 - \eta u_1)\beta, \quad \overline{p} = (1 - \epsilon u_2)p, \quad \beta = \frac{1}{(1-\eta)}\beta^*, \quad p = \frac{1}{(1-\epsilon)}p^* \tag{3}$$

in which u_1 and u_2 represent the relative amount of treatment dosage, η and ε represent the efficacy of respectively Ribavirin/DAA and interferon, as described in [35] and reported in Table 2, p^* and β^*

represent the virions production and infection rate in the case of a standard dosage, also reported in Table 2. Treatment efficacy is directly related to the relative drug dosage.

A value of 1 for u_1 or u_2 means that a standard dosage is used, which implies $\underline{p}=p^*$ and $\underline{\beta}=\beta^*$, while a value of zero means that no drug is given to the patient, which implies $\underline{p} = p$ and $\underline{\beta} = \beta$.

This model is in state-space nonlinear time-invariant form:

$$\dot{x} = f(x, u) \tag{4}$$

in which the state $x \in R^3$ and input $u \in R^2$ of the system are defined as follows:

$$x = \begin{bmatrix} T \\ I \\ V \end{bmatrix}, \quad u = \begin{bmatrix} u_1 \\ u_2 \end{bmatrix} \tag{5}$$

This model represents well the condition of the average patient. MPC computation is usually posed and solved as a discrete-time finite horizon optimal control problem in which the prediction is performed over a finite-time horizon divided into N intervals, each having length T_s referred to as the sampling time, that in this approach has the length of one day.
System state and input at each step are x_k and u_k, respectively, and consequently the discretized dynamics can be written as:

$$x_{k+1} = F(x_k, u_k) \tag{6}$$

in which F (·) is defined by (numerical) integration of (4) over the sampling time, that is:

$$F(x, u) = x + \int_0^{T_s} f(x, u)dt \tag{7}$$

Two optimization problems are solved.
First a steady-state problem with set-point x_{sp} is considered, whose result (x_s, u_s) is passed as reference for a dynamic optimization phase.
This steady-state problem is defined as:

$$\begin{aligned} &\min_{x,u} J_{ss} = \tfrac{1}{2}(x + \hat{d}_k - x_{sp})^T Q_{ss}(x + \hat{d}_k - x_{sp}) \\ &\text{subject to} \\ &x = F(x, u) \\ &u_{\min} \le u \le u_{\max} \end{aligned} \tag{8}$$

in which $\underline{d}_k$ is the difference between the actual measured state and the corresponding model state at sample time k, i.e. $\underline{d}_k = x_k - \underline{x}_k$.
This so-called "disturbance" is used to compensate for possible plant-model mismatch, hence embedding feedback in MPC [36] to achieve offset-free tracking.
Then, a quadratic cost dynamic optimization problem is solved:

$$\begin{aligned} &\min_{\mathbf{u},\mathbf{x}} J_{dyn} = \tfrac{1}{2}\sum_{i=0}^{N-1}\big[(x(i) - x_s)^T Q(x(i) - x_s) + \\ &+(u(i) - u_s)^T W(u(i) - u_s)\big] \quad \text{subject to} \\ &x(i+1) = F(x(i), u(i)), \quad x(0) = \hat{x}_k \\ &u_{\min} \le u(i) \le u_{\max} \end{aligned} \tag{9}$$

in which **u** = (u(0), u(1), . . ., u(N − 1)) is an input sequence of the predictive horizon and
x = (x(0), x(1), . . ., x(N − 1)) is the corresponding state sequence.

Cost matrices on states during system evolution and in the steady state problem are Q and Q_{ss}, respectively; W is cost matrix on inputs during system evolution. They are chosen diagonal in both problems:

$$Q = diag(Q_T, Q_I, Q_V) \quad (10)$$

$$Q_{ss} = diag(Q_{ss,T}, Q_{ss,I}, Q_{ss,V}) \quad (11)$$

$$W = diag(W_R, W_I) \quad (12)$$

Reference in steady state optimization is put at zero such that $x_{sp} \rightarrow [0, 0, 0]$. In this way infected cells I and virions V state are pushed to zero. That would also occur to healthy hepatocytes states leading to an unwanted effect of making the infection getting worse but according to the model (2) minimizing I and V has the consequence of increasing the number of healthy cells T.
Thus, the value of Q_T is also set at zero so that T cells are free to evolve following the Aston model dynamics. During optimization the solver has to keep the input variables in a range between 0 and 1. We note that, in order to improve the numerical conditioning of nonlinear optimization problem to be solved, the state variables have been rescaled as follows:

$$\tilde{x} = \begin{bmatrix} \tilde{T} \\ \tilde{I} \\ \tilde{V} \end{bmatrix} = \begin{bmatrix} \sigma_T T \\ \sigma_I I \\ \sigma_V V \end{bmatrix} \quad (13)$$

As pharmacokinetics aspects are not considered in Aston model, it is assumed that drug inputs are constant during the sampling time of 1 day.

2.2.3. Therapy discretization

A continuous therapy modulation is infeasible due to practical reasons. Drugs come in finite amounts such as pills, tablets or vials. It is therefore sensible to derive a discrete sub-optimal therapy that preserves the MPC optimal therapy effectiveness, but can be carried out by the patient. Referring to [19,21–23], we propose a suitable discretization algorithm and discuss its application to the MPC computed interferon and Ribavirin inputs.
To this aim, we introduce the following terminology. “Full therapy” means the traditional drug amount and has a value of 1. “Zero therapy” means no drug intake by the patient, i.e. a value of 0.
The algorithm is based on an iterative loop that computes the difference between MPC percentage of therapy and full therapy and the difference between MPC percentage and zero therapy. The two values are called ”iu” and ”il” and are used to compute upper integral error value, ”integU”, and lower integral error value, ”integL”. These two values are an update of the previous step computed ”integ” value. This value measures the error between the discrete and continuous therapy that has been accumulated over the previous time steps of the prediction horizon. The chosen U_d value is ”full therapy” if ”integU” is lower than ”integL” and is set to ”zero therapy” vice-versa. Such approach is described in Algorithm 1.

3. Results

MPC optimization has been implemented using MPC code [37], an MPC problem tool in Python based on CasADi framework [38]. PVR problem was set with weights shown in Table 3, whereas simulation parameters are reported in Table 4. Results of steady-state optimization in nominal case are reported in Table 5. Scaling factors are $\sigma = [\sigma_T, \sigma_I, \sigma_V] = [10^6, 10^6, 10^6]$.

Both scaling factors and Weights are obtained through a trial and error procedure.

Algorithm 1 Drug discretization algorithm.

```
for therapy length do
    iu = compute_iu
    il = compute_il
    [integU, integL] = UpdateVal(integ, iu, il)
    minV = min(abs(integU), abs(integL))
    if minV == abs(integL) then
        Ud = 1
        integ = integU
    else
        Ud = 0
        integ = integL
    end if
end for
```

Table 3
MPC weights in simulation.

	PVR	Triphasic
$Q_{ss,T}$	0	0
$Q_{ss,I}$	10^5	10^3
$Q_{ss,V}$	10^5	1
Q_T	0	0
Q_I	10^3	10^3
Q_V	10^3	1
W_R	1	0.4
W_I	1	0.4

Table 4
Simulation time parameters.

	PVR	Triphasic
Simulation length (day)	250	60
Horizon (day)	60	30
Time step (day)	1	1

Table 5
Steady state optimization results.

	PVR	Triphasic
T_s (IU/ml)	3.3	6.210^3
I_s (IU/ml)	4.110^5	1.410^2
V_s (IU/ml)	2.010^6	1.210^1

3.1. Nominal case simulations

The results obtained from a traditional therapy and one calculated by MPC are compared. Case studies considered in this work are PVR and Triphasic Decline. In both conditions MPC optimization has proved to give good results in terms of drug dose reduction. Moreover state variables dynamics shows a similar behaviours to the ordinary therapy. Another interesting virological condition is SVR, but no data to identify its dynamics were available.

3.1.1. PVR

In this case, the traditional treatment shows a typical trend in which healthy hepatocytes (T) tend to settle at a value, while infected hepatocytes (I) and free virions (V), after a first decline phase, show a convexity that leads the state variables I and V to return to values similar to the initial ones. In Fig. 1 the result of a traditional therapy, is shown on a logarithmic scale. The treatment calculated by the MPC algorithm provides a significant decrease in dosage between day 10 and day 70, and then resumes, thus

managing to have a dynamics similar to that of traditional dosage, but with much lower drug consumption. It is interesting to note that in this case the healthy hepatocytes are in the order of 10^6 (IU/ml) while the infected hepatocytes and the free virions between 10^5 ad 10^7 (IU/ml), which is why the dosage itself is necessary for a restoration of healthy cells, resulting in functionality, but not a removal of the HCV virus like in SVR case.

The dynamics of PVR in MPC case is shown in Fig. 2, while the drug consumption normalized with respect to the standard one is shown in Fig. 3.

3.1.2. Triphasic decline

In this case, using traditional cure, we can observe a virus load trend divisible into three phases. A first phase of decrease until a local minimum is reached, a second short phase of ascent followed by a final phase of reduction of free virions. Furthermore, with the exception of a short initial time period, there is a constant decrease in the number of infected hepatocytes and a growth of healthy hepatocytes, as shown in Fig. 4. Through the MPC algorithm we are able to obtain the same result, but with a dose reduction of drugs, measured in terms of efficacy, as shown in Fig. 5 and Fig. 6.

3.1.3. PVR and triphasic decline therapy discretization

In this case the therapy discretization algorithm was applied to the results obtained in previous paragraph. As shown in Fig. 8 the state dynamics is similar to the one in Fig. 2, except for a high frequency oscillation in the evolution of virions, due to discretized input shown in Fig. 7. We remark that input oscillations are not computed by the MPC itself, and are the results of discrete (0 or 1) drug administration of the continuous dosage calculated by the MPC. Drug dose mean value, represented in figure through a dashed horizontal line, is preserved among continuous and discretized therapies as expected by using our discretization algorithm. The same considerations remain valid for Triphasic Decline case, as shown in Figs. 9 and 10.

3.2. Model mismatch case simulations

In this section model mismatch is analysed both in PVR and in triphasic conditions. Simulations are performed by varying all the patient model parameters in the disease evolution by the same percentage while keeping at nominal values the parameters used in the MPC optimization model. Overall, 100 different patient simulations are considered for each case. The variation percentage is chosen randomly in each simulation in the range of −100% to 100%.

3.2.1. PVR

In Fig. 11 results are shown proving that despite different situations may arise in case of mismatch, final infection conditions are barely different. In Figs. 12 Ribavirin/DAA and Interferon drug therapy in mismatch condition are shown. In ocher the mean value among the simulations in each day is represented, while the dashed dare red lines represent the confidence intervals at 95%.

3.2.2. Triphasic decline

In Fig. 13 results are shown for Triphasic case, and similar considerations done for PVR remain valid in this condition. In this case the displacement of state variables from nominal condition are less pronounced than in PVR, showing lower sensitivity in parameters mismatch. In particular healthy cells T final values differences are barely noticeable. In Fig. 14, the corresponding interferon and Ribavirin/DAA

drug therapy in mismatch conditions are shown as previously done for PVR therapy. Confidence intervals at 95% are narrower than in PVR case showing a more reliable mean therapy

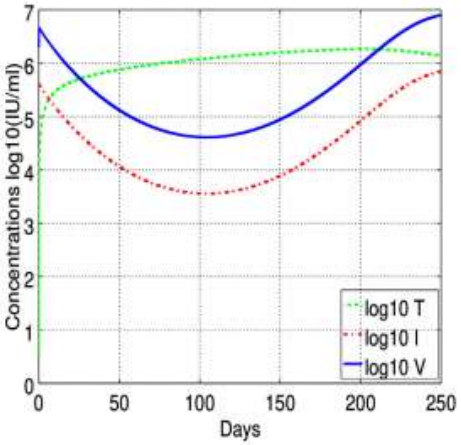


Fig. 1. Time behavior of state variables in PVR conditions (see Table 2) under nominal drug dose.

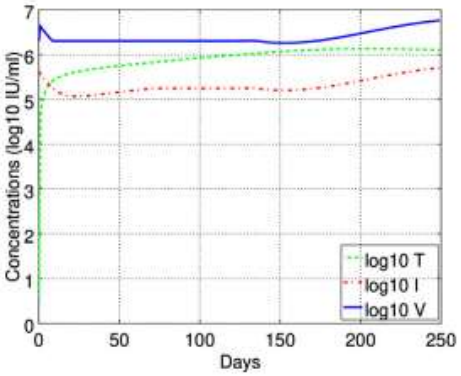


Fig. 2. Time behavior of state variables in PVR conditions under MPC computed drug dose.

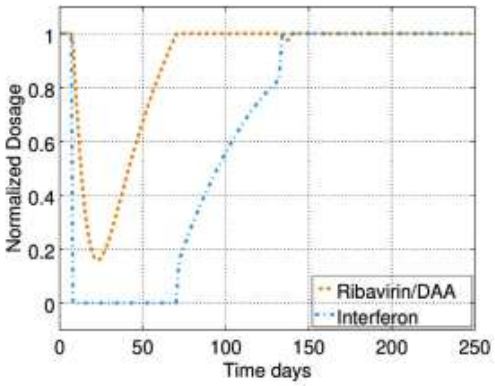


Fig. 3. MPC optimized drug doses in PVR conditions.

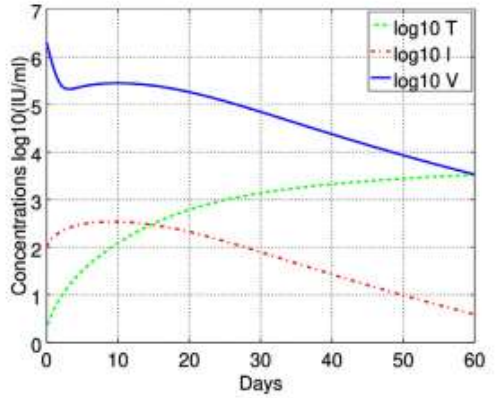


Fig. 4. Time behavior of state variables in Triphasic Decline conditions (see Table 2) under nominal drug doses.

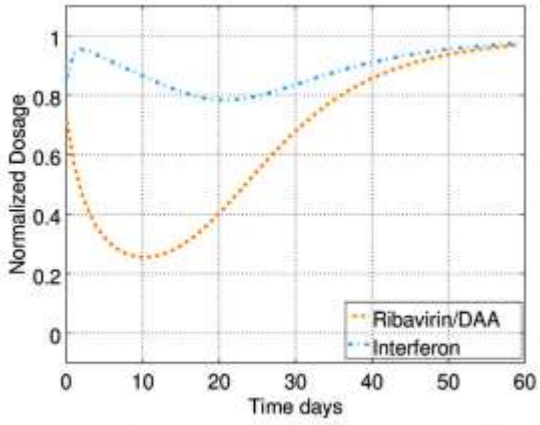


Fig. 5. MPC optimized drug doses in Triphasic Decline conditions.

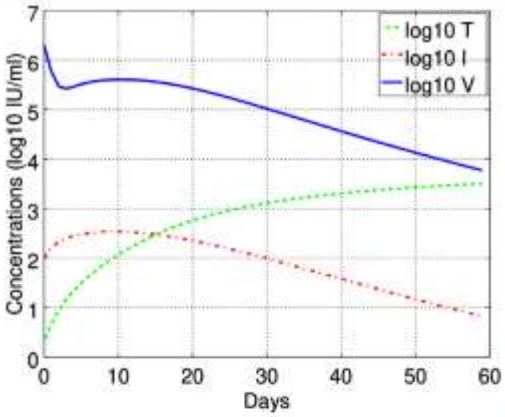
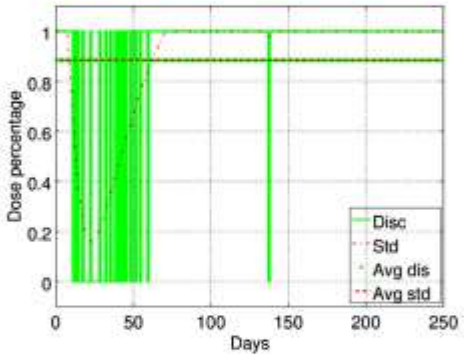
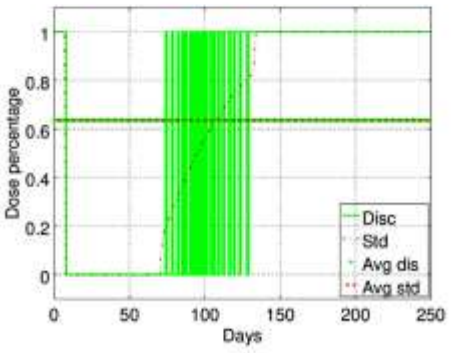


Fig. 6. Time behavior of state variables in Triphasic Decline conditions (see Table 2) under MPC computed drug doses.



(a) Interferon



(b) Ribavirin

Fig. 7. Comparison between continuous and discrete MPC computed drug doses in PVR conditions.

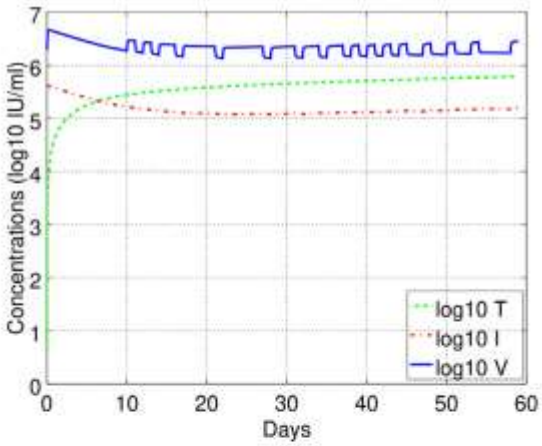


Fig. 8. Time behavior of state variables in PVR conditions under discrete MPC computed drug doses.

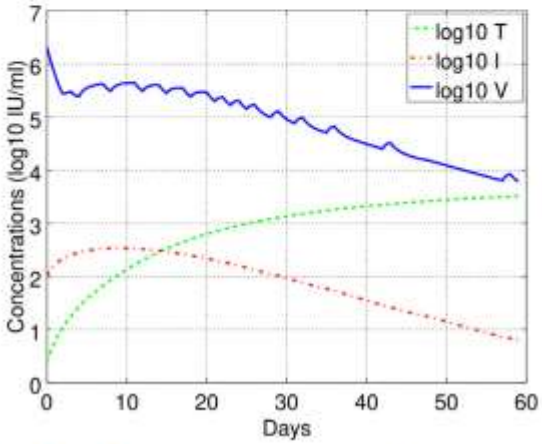
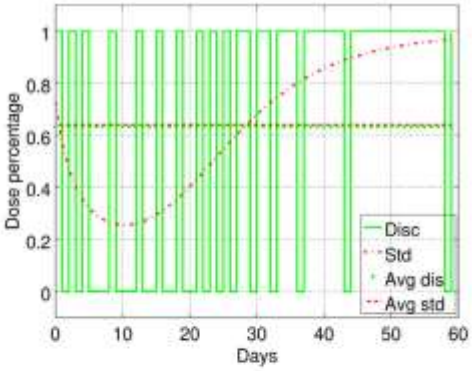
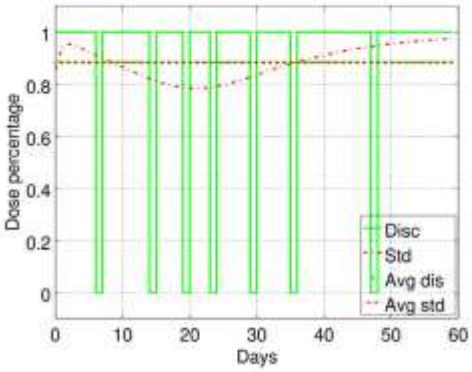


Fig. 9. Time behavior of state variables in Triphasic Decline conditions under discrete MPC computed drug doses.



(a) Interferon



(b) Ribavirin

Fig. 10. Comparison between continuous and discrete MPC computed drug doses in Triphasic Decline conditions.

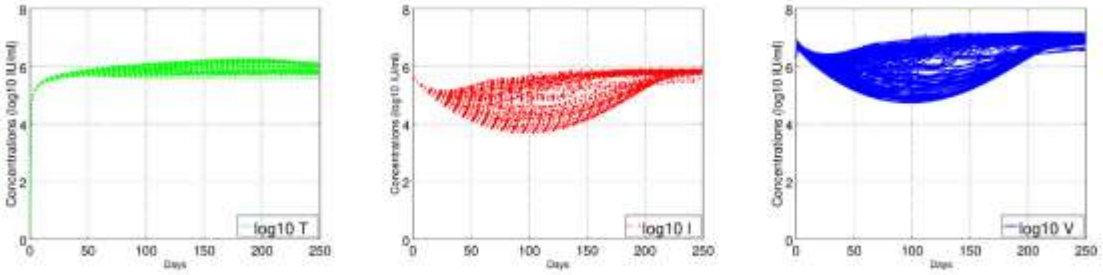


Fig. 11. Time behaviour of state variables in PVR conditions under MPC computed drug doses: 100 patient model cases.

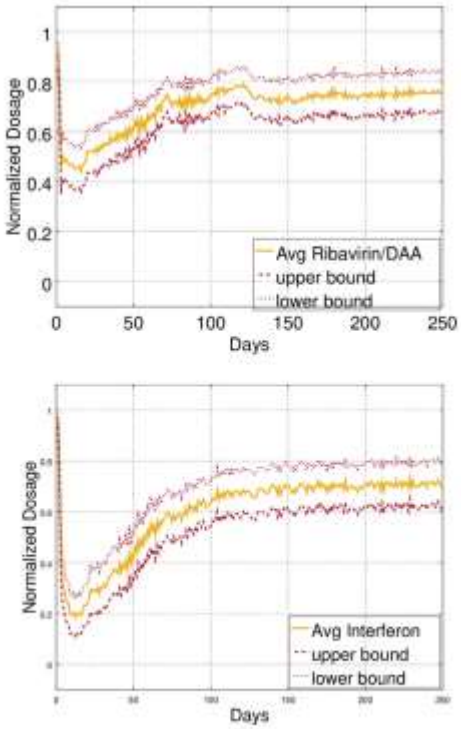


Fig. 12. MPC optimized drug doses in PVR conditions: average, upper and lower bounds of 100 patient model cases.

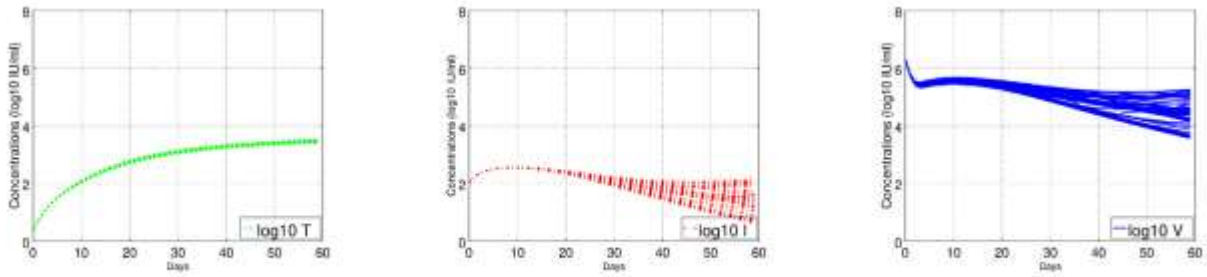


Fig. 13. Time behaviour of state variables in Triphasic Decline conditions under MPC computed drug doses: 100 patient model cases.

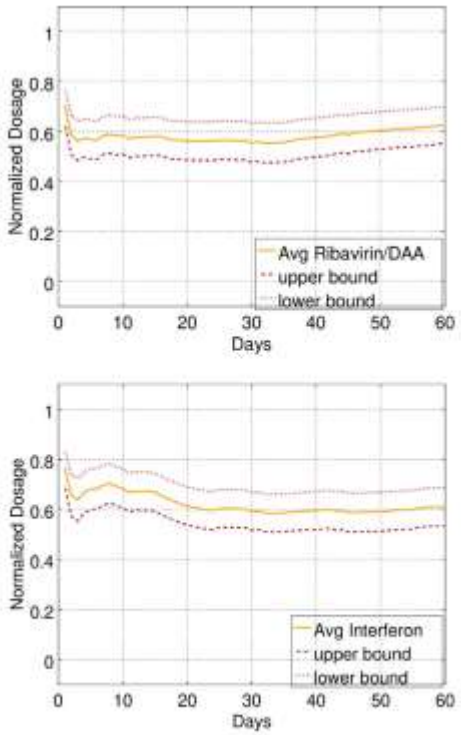


Fig. 14. MPC optimized drug doses in PVR conditions: average, upper and lower bounds of 100 patient model cases.

4. **Discussion**

The work described in this paper refers to the resolution of a medical problem from a mathematical-engineering point of view. In the mathematical model used continuous input refers to the possibility of modulating continuously the drug dose between zero and the standard dose. It is of more practical use to reformulate the optimization problem in terms of a discrete input which can be a direct drug administration (e.g., a pill). It was possible to establish a relationship between continuous administration over time and discrete one expressed in terms of pharmacological normalized dosages, keeping the functionality almost unchanged. As regards the cases studied, described in [32], it was possible to observe a good result in terms of the evolution of disease, maintaining efficacy of drugs, and therefore doses, even considerably lower. The doses computed by our MPC algorithm led to pharmacological Fig. 12. MPC optimized drug doses in PVR conditions: average, upper and lower bounds of 100 patient model cases. therapy savings in variable percentages from approximately 10% up to 40%. Mismatch simulations also proved robustness of our approach to physiological differences in patients response to therapy. The purpose of this work was to set out a therapy optimization strategy which takes into account the pharmacological cost in HCV cases and this appears to be achieved. To simplify the presentation of the main idea of this work, noise-free full state feedback was assumed although in practice this may not be feasible. The use of nonlinear estimators (e.g., Extended Kalman Filter) should be investigated in order to overcome these difficulties. Moreover, the control strategy is robust to model errors, so, through a work of identification of the parameters, an “ad personam” treatment would be possible, but the observations done remain valid in general if the patient is in the aforementioned cases. Identification studies could be focused on treating some model parameters as group dependent and some others as patient dependent, similarly to what was done in [39]. In the Aston model used in this work, pharmacokinetics is not considered, and possible future studies could use a revised model in which the flushing and uptake dynamics of the drugs are taken into account. Such a scenario could benefit from the use of impulsive MPC implementations [40,41].

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