mathematics

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An Evaluation of Propagation of the HIV-Infected Cells via Optimization Problem

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Abstract: Mathematical models have the potential to contribute to design and evaluate the infectivity spreading and growth of human immunodeficiency virus (HIV). Providing a better understanding of the dynamics of HIV infection in vivo and the immune system interactions with the virus can improve the classification of the infected cells and drive to an early diagnosis of the disease and drug evaluations. We analyze a two-dimensional environment HIV model from a new perspective, in terms of a multi-objective optimization problem, by introducing a linear modeling approach and providing numerical evidence for its suitability by introducing a general Instantaneous Control Algorithm.

Keywords: HIV dynamics; multi-objective; instantaneous control algorithm

MSC: 90C05; 58E17; 90C29; 92C50; 35B35

Citation: Granata, D.; Lorenzi, L. An Evaluation of Propagation of the HIV-Infected Cells via Optimization Problem. *Mathematics* **2022**, *10*, 2021. https://doi.org/10.3390/math10122021

Academic Editor: Christina Ramirez Kitchen

Received: 20 April 2022
Accepted: 8 June 2022
Published: 11 June 2022

1. Introduction

Over the past decades, mathematical models have been studied to express the within-host HIV dynamics. These models have become significant in describing the dynamics of HIV and in helping the researchers evaluate the effect of the antiviral drugs and the disease progression. The principal target of HIV infection is a class of lymphocytes or white blood cells that are the $CD4^+$ uninfected T-cells, thus, when the T-cells count drops under 200 mm^{-3}, then the patient is classified as an HIV-infected patient. Furthermore, a number of mathematical models have been developed to represent and define the behavior of the immune system and in particular its interactions with the HIV infestation and consequential decline of $CD4^+$ T-cells.

The HIV infection model, which has become a staple regarding virus replication studies, has been introduced by [1], where three types of variables have been considered: uninfected and infected cells and free virus particles. Infected cells are produced from uninfected cells and free virus at a certain rate, and the free virus is produced by the same uninfected cells at another rate and considering a proper decline rate. This model has been extended during the years by [2–6]. In the present paper, we start with a HIV Diffusion model consisting of ordinary and partial differential equations (see [2]) introduced in Section 2. Such a model admits two steady-state solutions, the uninfected and infected states, whose stability analysis was performed in [2] from a theoretical viewpoint. It turns out that the stability of both steady-state solutions, under sufficiently small and smooth perturbations, depends on the value of the reproduction ratio and, in the case of the infected steady state, also on other parameters (see the forthcoming Theorem 1).

Our aim here is to provide a different way to validate the results obtained in [2] by means of a linear optimization approach.

As it is typical when dealing with stability issues, in Section 2, we linearize the model around the two stationary states, as in [2]. Next, in order to face the computational complex-

ity of the problem, we concentrate our effort on discretizing the problem in Section 3. The resulting two models are approached as multi-objective optimization problems in Section 4 and a general Istantaneous Control Algorithm to efficiently handle the computation complexity is reported in Section 5. Last, some experimental results are presented in Sections 6 and 7 to prove the effectiveness of the introduced algorithm and the correctness of the produced models.

2. HIV Model

As already described before, in the presence of HIV, there are three main actors responsible for virus replication that can be represented by a virus V and two types of possible T-cells: uninfected cells S, infected cells I. The virus V is produced by the infected cells I and it is supposed that, on average, the cells produce N kind of virions. The model presented in [2], which we study in this paper, can be depicted as follows:

HIV-MOD:

$$\begin{aligned}
\frac{\partial S}{\partial t} &= \alpha - \mu_S S + rS\left(1 - \frac{S}{S^{max}}\right) - \gamma VS,\\
\frac{\partial I}{\partial t} &= \gamma VS - \mu_I I,\\
\frac{\partial V}{\partial t} &= N\mu_I I - \mu_V V + d_v \Delta V,
\end{aligned}$$

set on the spatial domain $(0, \ell) \times (0, \ell)$ and with a periodic boundary condition applied to V. Here, Δ represents the two-dimensional Laplace operator. The uninfected cells S are produced at a constant rate α from a set of precursors and are dying at a rate μ_S. It is reasonable to think of the term $rS(1 - \frac{S}{S^{max}})$ as the logistic growth for the S cells, where r is the proliferation rate of these and S^{max} is the maximum concentration of the T-cells. The infected cells I are produced by the uninfected cells S and the virus V at a rate γVS minus the death rate μ_I times the infected cells. Furthermore, the virus V is generated from infected cells I at a rate $N\mu_I$, taking into account the decline rate $\mu_V V$ and the diffusion term. The various terms and parameters are summarized in Table 1.

Table 1. Variables and Parameters.

Variables	**Description**	**Units**
S	Concentration of uninfected $CD4^+$ T-cells population	mm^{-3}
I	Concentration of infected $CD4^+$ T-cells density	mm^{-3}
V	Concentration of HIV virus	mm^{-3}
Constants	Description	Maximum Value
r	Proliferation rate of the $CD4^+$ T-cells population	varies day ($^{-1}$)
N	Number of virus produced by infected cells	300
α	Production rate for uninfected $CD4^+$ T-cells	1.5 day^{-1} mm^{-3}
γ	Infection rate of uninfected $CD4^+$ T-cells	0.001 day^{-1} mm^3
S^{max}	Maximal population level of $CD4^+$ T-cells at which the $CD4^+$ T-cells proliferation shuts off	1500 mm^{-3}
μ_S	Death rate of uninfected $CD4^+$ T-cells population	0.1 day^{-1}
μ_I	Death rate of infected $CD4^+$ T-cells population	0.5 day^{-1}
μ_V	Clearance rate of HIV virus	10 day^{-1}

This HIV-MOD model is a generalization of a previous model by Perelson et al. [5,6] without diffusivity (i.e., $d_v = 0$). The idea of adding a diffusion term in HIV-MOD is strongly inspired by a paper by Funk et al. [7], where the effects of diffusion in a different HIV model have been taken into account to allow for a better understanding of the propagation of the disease into the cells. As a matter of fact, models consisting only on ODEs have been a very good starting point for the mathe-

matical analysis of the HIV infection as well as other viral infections, but it has become clear that such models do not completely capture the dynamics of the viral infection. Considering an environment where cells are densely stuffed, that increases the capacity of the diffusive contamination due to infected cells. In this respect, the diffusive term helps to better investigate the infection dynamics. Nowadays, new models, which take into account the diffusivity have been proposed and thoroughly analyzed (we refer the reader to, e.g., [8–15]).

System HIV-MOD is a mixed problem consisting of two nonlinear ODEs and a linear PDE of parabolic type. The nonlinearity is quadratic due to presence of the logistic growth term VS, so the problem exhibits a critical growth.

One of the most interesting aspects in the study of any HIV model is the analysis of the existence of steady states and their stability, since it provides important information on the evolution of the solutions to the HIV model and, consequently, on the evolution of the HIV infection. Such analysis has been performed for the system HIV-MOD, with no diffusion, in [4,6] and in [2] for the model in its full generality. Both the models with no diffusivity and with a diffusion term admit two steady states, which are also constant in the space. They are the triples (S_0, I_0, V_0) and (S_1, I_1, V_1), where:

$$\begin{aligned} S_0 &= S_0(r) = \frac{r - \mu_S + \sqrt{(r-\mu_S)^2 + \frac{4\alpha r}{S^{max}}}}{2r} S^{max}, \\ I_0 &= 0, \\ V_0 &= 0, \end{aligned}$$

and

$$\begin{aligned} S_1 &= \frac{\mu_v}{\gamma N}, \\ I_1 &= \frac{\alpha}{\mu_I} - \frac{\mu_S \mu_V}{\gamma \mu_I N} + \frac{\mu_V r}{\gamma \mu_I N}\left(1 - \frac{\mu_v}{\gamma N S^{max}}\right), \\ V_1 &= \frac{\alpha N}{\mu_V} - \frac{\mu_S}{\gamma} + \frac{r}{\gamma}\left(1 - \frac{\mu_v}{\gamma N S^{max}}\right). \end{aligned}$$

The steady state (S_0, I_0, V_0), usually referred to as *uninfected steady state*, due to the fact that both the infected cells and the virus are not present in the human body, has physical relevance for every choice of the parameters, since $S_0(r)$ is positive for every choice of such parameters. On the contrary, the second steady state (typically referred to as the *infected steady state*) has physical relevance only for the parameters in a suitable set $\mathcal{I}$, which is the set of all parameters such that the reproduction ratio R_0 is greater than 1, where:

$$R_0(N, r) = \frac{\gamma N S_0(r)}{\mu_V}. \tag{1}$$

One of the main results of [2] is the stability analysis of both the uninfected and the infected steady states. To state such a result, we need to introduce the set:

$$\mathscr{P} = \{(N, r) : N > N_0,\ r_1 \le r \le r_2\}, \tag{2}$$

where N_0 is the largest root of the equation $aN^2 + bN + c = 0$ with:

$$\begin{aligned} a &= \gamma^2 \mu_I S^{max}\{\mu_I \mu_V S^{max} - 4\alpha(\mu_I + \mu_V)\}, \\ b &= -2\gamma \mu_I \mu_V \{(\mu_I^2 + 3\mu_I \mu_V + \mu_V^2) S^{max} - 4\alpha(\mu_I + \mu_V)\}, \\ c &= \mu_V\{\mu_I^4 + 2\mu_I^2 \mu_V(3\mu_I - 2\mu_S) + 6\mu_I \mu_V^3 + \mu_I \mu_V^2(11\mu_I - 4\mu_S) + \mu_V^4\}, \end{aligned}$$

and r_1, r_2 are the roots of the equation $Ar^2 + Br + C = 0$, with:

$$
\begin{aligned}
&A = \mu_V^4(\mu_I + \mu_V),\\
&B = \gamma\mu_V^2 N S^{max}[-\gamma\mu_I\mu_V N S^{max} + 2\alpha\gamma\mu_I N + 2\alpha\gamma\mu_V N + \mu_I^2\mu_V + 3\mu_I\mu_V^2 + \mu_V^3],\\
&C = N^2\gamma^2(S^{max})^2[\alpha\gamma\mu_V^3 N + \alpha\gamma\mu_I\mu_V N(\mu_I + \mu_V) + \alpha^2\gamma^2 N^2(\mu_I + \mu_V) + \mu_I\mu_S\mu_V^3].
\end{aligned}
$$

The stability analysis in [2] reads as follows.

Theorem 1 (Theorems 2.1, 3.1 and 3.2 in [2])**.** *The following properties are satisfied.*

(i) *If the reproduction ratio is less than one, then the uninfected steady state is the unique physically relevant steady state and it is asymptotically stable.*

(ii) *If the reproduction ratio is greater than one, then the uninfected and the infected steady states are both physically relevant. Moreover,*

- *the uninfected steady state is unstable;*
- *the infected steady state is asymptotically stable if the pair (N, r) does not belong to $\mathscr{P}$;*
- *the infected steady state is unstable if (N, r) belongs to the interior of the set $\mathscr{P}$.*

Here, asymptotic stability means that the solutions, which correspond to initial data close to the uninfected steady state, converge to this state exponentially fast. In terms of the infection, this means that the HIV infection can be eliminated if the uninfected steady state is stable and it cannot be eliminated if the infected steady state is stable.

Remark 1. *We stress that, even if the neither N_0, nor the parabola $\mathscr{P}$ depend on the diffusivity constant d_V, the dynamics of the model are crucially influenced by this constant. This is confirmed not only from a theoretical point of view, but also experimentally.*

In this paper, we transform the model HIV-MOD into an optimization problem and test on this model the abstract results in Theorem 1. As a matter of fact, dealing with the HIV transmission HIV-MOD model is very expensive from a computational point of view due to the quadratic growth in two of each constituting equations. For this reasons, we replace such a model with its linearization around the steady states. Such a model is clearly simpler, but still captures the dynamics of the original system near the steady states.

To simplify the final linearized expression, we introduce the new unknowns:

$$\tilde{S} = S - S_k, \qquad \tilde{I} = I - I_k, \qquad \tilde{V} = V - V_k$$

for each $k = 0, 1$, which represent the perturbation of S_k, I_k and V_k. Considering the first steady state (S_0, I_0, V_0), we obtain the system:

$$\frac{\partial \tilde{S}}{\partial t} = \left(-\mu_S + r - \frac{2rS_0}{S^{max}} \right)\tilde{S} - \gamma S_0 \tilde{V}, \tag{3}$$

$$\frac{\partial \tilde{I}}{\partial t} = \gamma S_0 \tilde{V} - \mu_I \tilde{I}, \tag{4}$$

$$\frac{\partial \tilde{V}}{\partial t} = N\mu_I \tilde{I} - \mu_V \tilde{V} + d_v \Delta \tilde{V}. \tag{5}$$

Instead, for the second equilibrium point (T_1, I_1, V_1), we obtain the system:

$$\frac{\partial \tilde{S}}{\partial t} = \left(-\mu_S + r - \frac{2rS_1}{S^{max}} - \gamma V_1 \right)\tilde{S} - \gamma S_1 \tilde{V}, \tag{6}$$

$$\frac{\partial \tilde{I}}{\partial t} = \gamma V_1 \tilde{S} - \mu_I \tilde{I} + \gamma S_1 \tilde{V}, \tag{7}$$

$$\frac{\partial \tilde{V}}{\partial t} = N\mu_I \tilde{I} - \mu_v \tilde{V} + d_v \Delta \tilde{V}. \tag{8}$$

3. Discretization

We discretize the problem using the Lax–Wendroff temporal method [16,17]. To discretize the time horizon $[0, T^{max}]$, we use a set of discretization time points $\mathcal{T}^{max} := \{0 = t_0, t_1, \ldots, t_n = T^{max}\}$ with Δt used as time step size, so that $t_{n+1} = t_n + \Delta t$. To discretize the spatial domain, a grid point $G = \{(m,n) : \forall\, m = 0, \ldots, \ell, n = 0, \ldots, \ell\}$ is introduced. Summing up, we write $S^{t_j}_{m,n}$ to denote the value of $\tilde{S}$ at time t_j for each $j \in \mathcal{T} := \{0 = t_0, t_1, \ldots, t_{n-1} = T^{max} - \Delta t\}$ and at the spatial point of coordinates (m,n). We follow a similar procedure with $I^{t_j}_{m,n}$ and $V^{t_j}_{m,n}$.

Then, the three Equations (3)–(5) may be discretized as follows:

$$\frac{S^{t_{j+1}}_{m,n} - S^{t_j}_{m,n}}{\Delta t} = \left(-\mu_S + r - \frac{2rS_0}{S^{max}} \right) S^{t_j}_{m,n} - \gamma S_0 V^{t_j}_{m,n}, \tag{9}$$

$$\frac{I^{t_{j+1}}_{m,n} - I^{t_j}_{m,n}}{\Delta t} = \gamma S_0 V^{t_j}_{m,n} - \mu_I I^{t_j}_{m,n}, \tag{10}$$

$$\begin{aligned} \frac{V^{t_{j+1}}_{m,n} - V^{t_j}_{m,n}}{\Delta t} =& N\mu_I I^{t_j}_{m,n} - \mu_V V^{t_j}_{m,n} \\ &+ \frac{d_v}{\Delta xy}(V^{t_j}_{m+1,n} + V^{t_j}_{m-1,n} - 4V^{t_j}_{m,n} + V^{t_j}_{m,n+1} + V^{t_j}_{m,n-1}), \end{aligned} \tag{11}$$

for all $t_j \in \mathcal{T}$. Here, Δxy is the spatial step area into the grid G.

Similarly, the three Equations (6)–(8) can be written as:

$$\frac{S^{t_{j+1}}_{m,n} - S^{t_j}_{m,n}}{\Delta t} = \left(-\mu_S + r - \frac{2rS_1}{S^{max}} - \gamma V_1 \right) S^{t_j}_{m,n} - \gamma S_1 V^{t_j}_{m,n}, \tag{12}$$

$$\frac{I^{t_{j+1}}_{m,n} - I^{t_j}_{m,n}}{\Delta t} = \gamma V_1 S^{t_j}_{m,n} - \mu_I I^{t_j}_{m,n} + \gamma S_1 V^{t_j}_{m,n}, \tag{13}$$

$$\begin{aligned} \frac{V^{t_{j+1}}_{m,n} - V^{t_j}_{m,n}}{\Delta t} =& N\mu_I I^{t_j}_{m,n} - \mu_v V^{t_j}_{m,n} \\ &+ \frac{d_v}{\Delta xy}(V^{t_j}_{m+1,n} + V^{t_j}_{m-1,n} - 4V^{t_j}_{m,n} + V^{t_j}_{m,n+1} + V^{t_j}_{m,n-1}), \end{aligned} \tag{14}$$

for all $t_j \in \mathcal{T}$.

4. Multi-Objective Optimization Problems

Combining the results obtained in the previous Sections 2 and 3, we can define, formulate and solve the problems as linear optimization problems. Integration of PDEs into discrete optimization problems is rather new in the literature and is mainly available for some network problems, see, e.g., [18–22]. See also [23], where a general framework is presented. In order to solve the problem for each steady state, we produce some formulations and a general Instantaneous Control algorithm (i.e., Algorithm 1) to efficiently handle the computation complexity, and present them in the next subsections.

4.1. Handle the First Point of Equilibrium (S_0, I_0, V_0)

To approach the Equations (9)–(11), we produce the following linear program and we term this model as Multi-objective First Equilibrium Point (MO-FEP).

MO-FEP:

$$f_1 : \min \psi_1 \geq |S^{t_j}_{m,n}| \qquad \forall t_j \in \mathcal{T},\ (m,n) \in G \tag{15}$$

$$f_2 : \min \psi_2 \geq |I_{m,n}^{t_j}| \qquad \forall t_j \in \mathcal{T},\ (m,n) \in G \quad (16)$$

$$f_3 : \min \psi_3 \geq |V_{m,n}^{t_j}| \qquad \forall t_j \in \mathcal{T},\ (m,n) \in G \quad (17)$$

such that:

$$V_{0,n}^{t_{j+1}} = V_{\ell,n}^{t_{j+1}} \qquad \forall t_j \in \mathcal{T},\ (m,n) \in G \quad (18)$$

$$V_{m,0}^{t_{j+1}} = V_{m,\ell}^{t_{j+1}} \qquad \forall t_j \in \mathcal{T},\ (m,n) \in G \quad (19)$$

$$\frac{S_{m,n}^{t_{j+1}} - S_{m,n}^{t_j}}{\Delta t} \leq \left(-\mu_S + r - \frac{2rS_0}{S^{max}} \right) S_{m,n}^{t_j} - \gamma S_0 V_{m,n}^{t_j} \qquad \forall t_j \in \mathcal{T},\ (m,n) \in G \quad (20)$$

$$\frac{I_{m,n}^{t_{j+1}} - I_{m,n}^{t_j}}{\Delta t} \geq \gamma S_0 V_{m,n}^{t_j} - \mu_I I_{m,n}^{t_j} \qquad \forall t_j \in \mathcal{T},\ (m,n) \in G \quad (21)$$

$$\frac{V_{m,n}^{t_{j+1}} - V_{m,n}^{t_j}}{\Delta t} \geq N\mu_I I_{m,n}^{t_j} - \mu_V V_{m,n}^{t_j} + \frac{d_v}{\Delta xy}(V_{m+1,n}^{t_j} + V_{m-1,n}^{t_j} - 4V_{m,n}^{t_j} + V_{m,n+1}^{t_j} + V_{m,n-1}^{t_j}) \qquad \forall t_j \in \mathcal{T},\ (m,n) \in G \quad (22)$$

$$\psi_1, \psi_2, \psi_3 \geq 0 \quad (23)$$

$$-S_0 \leq S_{m,n}^{t_j} \leq S^{max} - S_0 \qquad \forall t_j \in \mathcal{T}^{max},\ (m,n) \in G \quad (24)$$

$$0 \leq I_{m,n}^{t_j} \leq S^{max} \qquad \forall t_j \in \mathcal{T}^{max},\ (m,n) \in G \quad (25)$$

$$0 \leq V_{m,n}^{t_j} \leq S^{max} \qquad \forall t_j \in \mathcal{T}^{max},\ (m,n) \in G. \quad (26)$$

The objective functions f_1, f_2, and f_3 push perturbation unknowns to converge to zero. However, these objective functions make the problem not linear, so we proceed to linearize them, adding these linear inequality constraints:

$$S_{m,n}^{t_{j+1}} - \psi_1 \leq 0 \qquad \forall t_j \in \mathcal{T},\ (m,n) \in G \quad (27)$$

$$-S_{m,n}^{t_{j+1}} - \psi_1 \leq 0 \qquad \forall t_j \in \mathcal{T},\ (m,n) \in G \quad (28)$$

$$I_{m,n}^{t_{j+1}} - \psi_2 \leq 0 \qquad \forall t_j \in \mathcal{T},\ (m,n) \in G \quad (29)$$

$$-I_{m,n}^{t_{j+1}} - \psi_2 \leq 0 \qquad \forall t_j \in \mathcal{T},\ (m,n) \in G \quad (30)$$

$$V_{m,n}^{t_{j+1}} - \psi_3 \leq 0 \qquad \forall t_j \in \mathcal{T},\ (m,n) \in G \quad (31)$$

$$-V_{m,n}^{t_{j+1}} - \psi_3 \leq 0 \qquad \forall t_j \in \mathcal{T},\ (m,n) \in G, \quad (32)$$

obtaining the linear version of MO-FEP model, namely, MO-FEPL:

MO-FEPL:

$$f_1 : \min \psi_1 \quad (33)$$

$$f_2 : \min \psi_2 \quad (34)$$

$$f_3 : \min \psi_3 \quad (35)$$

such that:

(18)–(26), (27)–(32).

In MO-FEPL, we wish to minimize $S_{m,n}^{t_j}$, $I_{m,n}^{t_j}$ and $V_{m,n}^{t_j}$, We can easily see that the constraints (20) and (21) are local in space. This means that the value $S_{m,n}^{t_{j+1}}$, i.e., the value of the discretization of the perturbation of the uninfected $CD4^+$ cells at time t_{j+1} and at the spatial node (m,n), depends on its value at the same node of the grid G at time t_j, times a constant which depends on the parameters μ_S, r and on the ratio $2rS_0/S^{max}$, and on the value at time t_j and at the same spatial point of the grid G of the discretization of the perturbation of the virus. Similarly, the value of the discretization of the perturbation

of the infected $CD4^+$ cells, i.e., $I_{m,n}^{t_{j+1}}$, depends on the values $I_{m,n}^{t_j}$ and $V_{m,n}^{t_j}$. Different is the case of the constraints (22), which have nonlocal structure. This is not surprising at all, since these constraints come from a partial differential equation of parabolic type and it is well known that such type of equation is not local in space. Even if the initial datum is compactly supported, as time evolves, the support of the solution becomes the whole space. Further, the constraints (23) ensure that ψ_1, ψ_2, ψ_3 only assume non-negative values. Constraints (24) ensure that $S_{m,n}^{t_j}$ are within the interval $[-S_0, S^{max}]$. Last, constraints (25) and (26) impose that the variables values are within $[0, S^{max}]$, respectively, for $I_{m,n}^{t_j}$ and $V_{m,n}^{t_j}$.

The situation changes if we consider optimization problems that arise by decomposing the discretized time steps and considering the time steps separately. Thus, we obtain the Multi-objective First Equilibrium Point Instantaneous Linear model (MO-FEPIL).

MO-FEPIL:

$$f_1 : \min_{t_j} \psi_1 \qquad \forall (m,n) \in G \tag{36}$$

$$f_2 : \min_{t_j} \psi_2 \qquad \forall (m,n) \in G \tag{37}$$

$$f_3 : \min_{t_j} \psi_3 \qquad \forall (m,n) \in G \tag{38}$$

such that:

$$S_{m,n}^{t_{j+1}} - \psi_1 \leq 0 \qquad \forall (m,n) \in G \tag{39}$$

$$-S_{m,n}^{t_{j+1}} - \psi_1 \leq 0 \qquad \forall (m,n) \in G \tag{40}$$

$$I_{m,n}^{t_{j+1}} - \psi_2 \leq 0 \qquad \forall (m,n) \in G \tag{41}$$

$$-I_{m,n}^{t_{j+1}} - \psi_2 \leq 0 \qquad \forall (m,n) \in G \tag{42}$$

$$V_{m,n}^{t_{j+1}} - \psi_3 \leq 0 \qquad \forall (m,n) \in G \tag{43}$$

$$-V_{m,n}^{t_{j+1}} - \psi_3 \leq 0 \qquad \forall (m,n) \in G \tag{44}$$

$$V_{0,n}^{t_{j+1}} = V_{\ell,n}^{t_{j+1}} \qquad \forall (m,n) \in G \tag{45}$$

$$V_{m,0}^{t_{j+1}} = V_{m,\ell}^{t_{j+1}} \qquad \forall (m,n) \in G \tag{46}$$

$$\frac{S_{m,n}^{t_{j+1}} - S_{m,n}^{t_j}}{\Delta t} \leq \left(-\mu_S + r - \frac{2rS_0}{S^{max}} \right) S_{m,n}^{t_j} - \gamma S_0 V_{m,n}^{t_j} \qquad \forall (m,n) \in G \tag{47}$$

$$\frac{I_{m,n}^{t_{j+1}} - I_{m,n}^{t_j}}{\Delta t} \geq \gamma S_0 V_{m,n}^{t_j} - \mu_I I_{m,n}^{t_j} \qquad \forall (m,n) \in G \tag{48}$$

$$\begin{aligned} &\frac{V_{m,n}^{t_{j+1}} - V_{m,n}^{t_j}}{\Delta t} \geq N\mu_I I_{m,n}^{t_j} - \mu_V V_{m,n}^{t_j} \\ &+ \frac{d_v}{\Delta xy}(V_{m+1,n}^{t_j} + V_{m-1,n}^{t_j} - 4V_{m,n}^{t_j} + V_{m,n+1}^{t_j} + V_{m,n-1}^{t_j}) \quad \forall (m,n) \in G \end{aligned} \tag{49}$$

$$\psi_1, \psi_2, \psi_3 \geq 0 \tag{50}$$

$$-S_0 \leq S_{m,n}^{t_j} \leq S^{max} - S_0 \qquad \forall (m,n) \in G \tag{51}$$

$$0 \leq I_{m,n}^{t_j} \leq S^{max} \qquad \forall (m,n) \in G \tag{52}$$

$$0 \leq V_{m,n}^{t_j} \leq S^{max} \qquad \forall (m,n) \in G \tag{53}$$

for all $t_j \in \mathcal{T}$ where $V_{m,n}^{t_j}$, $I_{m,n}^{t_j}$, $S_{m,n}^{t_j}$ refer to the variables of time step Δt. The interpretation of the MO-FEPIL constraints is similar to the MO-FEPL model ones. The changes on the constraints are only regarding the $|\mathcal{T}| = 1$ that here it is reduced to be equal to 1, in fact, at each temporal instant t_j, the only variables values taken into consideration in each grid point $(m,n) \in G$ are those belonging to the previous instant time t_{j-1}. This approach considerably reduces the number of problem constraints, boiling down the problem complexity and resolution time effort.

4.2. Handliing the Second Equilibrium Point (S_1, I_1, V_1)

The same model construction idea may be used to handle Equations (12)–(14), producing the following Multi-objective Second Equilibrium Point Instantaneous Linear (MO-SEPIL) model.

MO-SEPIL:

$$f_1 : \min_{t_j} \psi_1 \qquad \forall (m,n) \in G \tag{54}$$

$$f_2 : \min_{t_j} \psi_2 \qquad \forall (m,n) \in G \tag{55}$$

$$f_3 : \min_{t_j} \psi_3 \qquad \forall (m,n) \in G \tag{56}$$

such that:

$$\frac{S_{m,n}^{t_{j+1}} - S_{m,n}^{t_j}}{\Delta t} \leq \left(-\mu_S + r - \frac{2rS_1}{S^{max}} - \gamma V_1 \right) S_{m,n}^{t_j} - \gamma S_1 V_{m,n}^{t_j}, \qquad \forall (m,n) \in G \tag{57}$$

$$\frac{I_{m,n}^{t_{j+1}} - I_{m,n}^{t_j}}{\Delta t} \geq \gamma S_0 V_{m,n}^{t_j} - \mu_I I_{m,n}^{t_j} + \gamma V_1 S_{m,n}^{t_j}, \qquad \forall (m,n) \in G \tag{58}$$

$$-I_1 \leq I_{m,n}^{t_j} \leq S^{max} - I_1 \qquad \forall (m,n) \in G \tag{59}$$

$$-V_1 \leq V_{m,n}^{t_j} \leq S^{max} - V_1 \qquad \forall (m,n) \in G \tag{60}$$

(39)–(46), (49)–(51).

for all $t_j \in \mathcal{T}$, where $V_{m,n}^{t_j}$, $I_{m,n}^{t_j}$, $S_{m,n}^{t_j}$ refer to the variables of time step Δt. As in the case of MO-FEPL, the constraints (57) and (58) are local in space. Last, constraints (59) and (60) impose that the variables values are within $[-I_1, S^{max} - I_1]$, $[-V_1, S^{max} - V_1]$, respectively for $I_{m,n}^{t_j}$ and $V_{m,n}^{t_j}$.

4.3. Multi-Objective Problems (MOP)

Optimality in multi-objective optimization problems is defined in terms of Pareto dominance and Pareto front. Compared to single-objective optimization, where a single objective function needs to be optimized, in a multi-objective optimization, the goal search is finding a set of so-called non-dominated solutions, knows as a Pareto optimal set. Any solution of this set is optimal in the sense that no improvement can be made on the component of the objective vector without worsening at least another one of its components. To fully understand the dominance, we provide the following definition:

Definition 1 (A solution non-dominated). *A solution x dominates a solution x' if x is at least equally as good as x' with respect to all the objective functions and better than x' with respect to at least one objective function. In formal terms, for each objective function $f_i \in \{f_1, \ldots, f_K\}$ to be minimized, x dominates x' if $f_i(x) \leq f_i(x')$ for all $i = 1, \ldots, K$ and $f_i(x) < f_i(x')$ for at least a i.*

The aim of the resolution methods is to provide a good trade-off between the dimension of the set of efficient solutions and the time and memory requirements to obtain

them. It is crucial to find not just one Pareto-optimal solution, but as many of them as possible, meeting two different types of goals: enhancing the convergence to the true Pareto solutions, and maximizing the spread of the solutions over the Pareto front. Unfortunately, a suitable methodology to find multiple solutions efficiently is not present in the literature, but roughly there are two possible approaches: the former based on the classical methodology that requires to solve repetitive application of the same algorithm, the latter based on bio-inspired search paradigms, whose main advantage is to obtain multiple solutions in a single run, realized by means of Meta-Heuristics procedures [24–28]. Most of these Meta-Heuristics algorithms are based on a priori knowledge of the true Pareto front and, nevertheless, this knowledge is necessary to estimate the measure of convergence of the solutions. For these reasons, it is crucial to have available an exact approach able to provide a good representation of the Pareto front solutions. Among the exact approaches, available in literature, a good methodology that compromises implementation cost, computational burden and parameters analysis is the parameter-based scalarization approach, which solves a multi-objective optimization problem as a single-objective problem by means of a set of weights. The Pareto front is, in general an infinite set of solutions, this means that, in theory, it is necessary to solve the scalarized problem over the whole range of values of weights for the scalarization. Computationally speaking, this is unworkable in any case, because solving each scalarized problem can in itself be very costly. In practice, one may be forced to obtain a reasonable approximation of the Pareto front, solving the scalarized version problem over a partition of the space of weights by finding a subset of Pareto points. Further discussions on the scalarization method can be found in [29,30].

In order to study the Pareto optimal solutions for both problems MO-FEPIL and MO-SEPIL under investigation, we proceed with a scalarization technique analysis, in which we proceed with a convex combination of f_1, f_2 and f_3 to obtain a single objective function $z = \min \lambda_1 \psi_1 + \lambda_2 \psi_2 + \lambda_3 \psi_3$ with $\sum_{k=1,2,3} \lambda_k = 1$, this approach is of easy implementation. Experiments are conducted by varying the λ parameter in the range (0,1].

5. Instantaneous Control Algorithm

To make the most of the instantaneous MO-FEPIL and MO-SEPIL models, we now consider a general Instantaneous Control Algorithm that is stated in an abstract manner in Algorithm 1. Instantaneous control algorithms are useful in approaching challenging control problems, see, e.g., [31]. By such method, given a chosen problem **MOD**, in our case one between MO-FEPIL and MO-SEPIL , the problem can be effectively solved along the discretization time. Hence, the setup of the algorithm at the time $t + \Delta t$, with $\Delta t = 1$, for each $t \in \mathcal{T}$ depends only on the data results obtained by the previous instant time t, all this enables to solve the problem step by step. We only need to generate the initial data necessary at time $t = 0$.

Algorithm 1 Instantaneous Control Algorithm

Input: a discretized time horizon $\mathcal{T}$, initial solutions $V^0_{m,n}$, $I^0_{m,n}$, $S^0_{m,n}$ for all points (m,n) belonging to the grid G at time $t=0$, and a Problem **MOD**

1: $\epsilon \leftarrow 10^{-5}$
2: **for all** $t_j \in \mathcal{T}$ AND ($V^{t_j}_{m,n} > \epsilon$ AND $I^{t_j}_{m,n} > \epsilon$ AND $S^{t_j}_{m,n} > \epsilon, \forall (m,n) \in G$) **do**
3: Setup the problem $\mathbf{MOD^{t_{j+1}}}$ at time step t_{j+1} gathering all the solutions found at step t_j that are $V^{t_j}_{m,n}$, $I^{t_j}_{m,n}$, $S^{t_j}_{m,n}$ $\forall (m,n) \in G$.
4: Solve the problem $\mathbf{MOD^{t_{j+1}}}$.
5: **if** the obtained $\mathbf{MOD^{t_{j+1}}}$ solution is infeasible **then**
6: **return** "No solution is found"
7: **else**
8: Store the found vector solutions $V^{t_{j+1}}$, $I^{t_{j+1}}$, $S^{t_{j+1}}$
9: **end if**
10: **end for**
11: **return** Feasible vector solution ($\{V^0, I^0, S^0\}$,$\{V^{t_1}, I^{t_1}, S^{t_1}\}$, …,$\{V^{t_{n-1}}, I^{t_{n-1}}, S^{t_{n-1}}\}$, $\{V^{t_n}, I^{t_n}, S^{t_n}\}$)

The algorithm iterates over lines 2–10 until it meets the termination conditions that are:

(i) time window $\mathcal{T}$;

(ii) when, for any $(m,n) \in G$, the values $V^{t_j}_{m,n}$, $I^{t_j}_{m,n}$, $S^{t_j}_{m,n}$ are sufficiently small, less than of a chosen tiny quantity ϵ in order to be considered experimentally close to zero values.

To set up, data of the new problem $\mathbf{MOD^{t_{j+1}}}$ at time t_{j+1} are obtained from the data solution of the previous problem $\mathbf{MOD^{t_j}}$ whose results are gathered at line 3.

Remark 2. *In the Algorithm 1, we solve the problems MO-FEPIL or MO-SEPIL at a certain point. At each step, the input data depend only on the produced ones returned by the algorithm execution at a previous instant time. Suppose that we are considering* **MOD** = *MO-FEPIL , if the algorithm stops at line 11, then we can affirm that this solution is also a feasible solution for MO-FEP, but if the Algorithm stops at line 6, then we cannot state anything about the infeasibility found. Thus, this approach cannot guarantee the global optimality of MO-FEP in general.*

6. Computational Testbed

In this section, we present the parameter values used for the computational experiments. The data for $V^{t_j}_{m,n}$, $I^{t_j}_{m,n}$, $S^{t_j}_{m,n}$ at the time $t_j = 0$, where each t_j is the time step expressed in days, for each grid point $(m,n) \in G$ were generated as uniformly distributed. Specifically, for each:

L_S is an experimental value which indicates the upper bound of uninfected S cells at time $t=0$;

L_I is an experimental value which indicates the upper bound of infected I cells at time $t=0$;

L_V is an experimental value which indicates the upper bound of virus V at time $t=0$;

$S^0_{m,n}$ is generated at random with a uniform distribution in the interval $[0, L_S]$;

$I^0_{m,n}$ is generated at random with a uniform distribution in the interval $[0, L_I]$;

$V^0_{m,n}$ is generated at random with a uniform distribution in the interval $[0, L_V]$.

In the generation of the grid G, we consider $\ell = 20$ in order to have a square grid of 21×21 points (according to the numerical simulations in the pioneering paper [7]) and $T^{max} = 25,550$ days. The following parameters have been adopted:

$\epsilon = 1 \times 10^{-5}$ as feasible measurement used as convergence threshold of $V_{m,n}^{t_j}$, $I_{m,n}^{t_j}$, $S_{m,n}^{t_j}$;

$d_v = 0.1$ as diffusion parameter for both models;

$\Delta_{xy} = 1.0 \times 1.0$ is the spatial step area into the grid G;

$\Delta t = 1.0$ is the time interval (expressed in days);

$\gamma = 0.001$ as infection rate of uninfected cells S;

$\alpha = 1.5$ as the production rate of uninfected cells S;

$N = 300$ as the number of the virus produced by the infected cells;

$S^{max} = 1500$ as maximal population level of uninfected cells S;

$\mu_S = 0.1$ as the death rate of uninfected cells S;

$\mu_I = 0.5$ as the death rate of infected cells I;

$\mu_V = 10$ as the death rate of the virus V.

The experiments were executed by using IBM ILOG CPLEX 12.9 on the Intel(R) Core(TM) i7-9750H CPU @2.60GHz processor machine with 16GB of DDR4 memory. In order to appraise the quality of the Pareto front solutions, several convex combinations of the three objective functions were considered and experiments were conducted at varying weight coefficients λ_i , $i = 1, 2, 3$, in the range $(0, 1]$, with such interval divided in 10 steps for each dimension, such that $\sum_{i=1,2,3} \lambda_i = 1$ for each triplet of weight coefficients considered. For this reason, for each triplet (L_S, L_I, L_V), there are solved 66 combinations generated by λ ranges. We denote with T^{min} and T^{max} the found minimum and the maximum amount of days objective values among all the Pareto solutions reached for the configuration (L_S, L_I, L_V). Since we need all the objective function contributions, we consider instead of zero a non-negative sufficiently small number , e.g., a value equal to 10^{-6}. A large set of instances of initial data have been generated for each steady state, in order to evaluate the stability of the two steady states and the instability of the uninfected steady state.

In order to evaluate the time efficiency and effectiveness of the algorithm, we present the execution time in seconds $Time(s)$ and the percentage or the number of the solutions that converge to the steady state. The computational time $Time(s)$ for the scalarization technique convey the sum of all computational times needed to solve the scalarized problem over a the whole range of values of weights λ_i used for the scalarization, where no time limit was applied.

7. Computational Results

The results produced by Algorithm 1 are depicted in the next Tables 2–4, in particular in Tables 2 and 3 are reported the comparisons regarding the solutions values related to the MO-FEPIL model, in Table 4 those regarding to the MO-SEPIL model.

Table 2. Results of Algorithm 1 applied to the triple (L_S, L_I, L_v).

L_S	L_I	L_V	T^{min} [*min-max*]	T^{max} [*min-max*]	*Time*(*s*) Mean	% *Solns Convergent*
1	[1–20]	[1–20]	[39, 711]	[369, 931]	318.41	100
2	[1–20]	[1–20]	[39, 727]	[369, 935]	365.94	100
3	[1–20]	[1–20]	[39, 704]	[375, 935]	372.35	100
4	[1–20]	[1–20]	[39, 656]	[369, 935]	370.69	100
5	[1–20]	[1–20]	[39, 705]	[383, 933]	371.40	100
6	[1–20]	[1–20]	[39, 705]	[383, 933]	371.99	100
7	[1–20]	[1–20]	[39, 622]	[375, 933]	372.00	100
8	[1–20]	[1–20]	[39, 696]	[363, 871]	364.97	100
9	[1–20]	[1–20]	[39, 711]	[375, 932]	324.76	100
10	[1–20]	[1–20]	[39, 705]	[379, 933]	324.51	100
11	[1–20]	[1–20]	[38, 696]	[383, 932]	371.49	100
12	[1–20]	[1–20]	[39, 705]	[369, 934]	371.92	100
13	[1–20]	[1–20]	[39, 636]	[369, 928]	371.93	100
14	[1–20]	[1–20]	[39, 711]	[363, 936]	372.14	100
15	[1–20]	[1–20]	[39, 701]	[363, 934]	370.01	100
16	[1–20]	[1–20]	[39, 688]	[383, 934]	371.22	100
17	[1–20]	[1–20]	[39, 649]	[375, 934]	371.47	100
18	[1–20]	[1–20]	[39, 712]	[375, 930]	371.30	100
19	[1–20]	[1–20]	[40, 672]	[379, 934]	370.96	100
20	[1–20]	[1–20]	[39, 630]	[383, 929]	371.81	100

Table 3. Results of Algorithm 1 applied to the triple (L_S, L_I, L_v).

L_S	L_I	L_V	T^{min} [*min-max*]	T^{max} [*min-max*]	*Time*(*s*) Mean	# *Solns Convergent*
1	[1–30]	[1–30]	[1, 3]	[1, 3]	1.82	0
2	[1–30]	[1–30]	[1, 3]	[1, 3]	1.79	0
3	[1–30]	[1–30]	[1, 3]	[1, 3]	1.97	0
4	[1–30]	[1–30]	[1, 3]	[1, 3]	1.98	0
5	[1–30]	[1–30]	[1, 3]	[1, 3]	2.12	0
6	[1–30]	[1–30]	[1, 3]	[1, 3]	2.14	0
7	[1–30]	[1–30]	[1, 3]	[1, 3]	1.92	0
8	[1–30]	[1–30]	[1, 3]	[1, 3]	1.62	0
9	[1–30]	[1–30]	[1, 3]	[1, 3]	2.00	0
10	[1–30]	[1–30]	[1, 3]	[1, 3]	2.38	0

Table 4. Results of Algorithm 1 applied to the triple (L_S, L_I, L_v).

L_S	L_I	L_V	T^{min} [*min-max*]	T^{max} [*min-max*]	*Time*(*s*) Mean	% *Solns Convergent*
1	[1–10]	[10–150]	[56, 202]	[159, 207]	98.57	100
2	[1–10]	[10–150]	[3, 200]	[157, 207]	93.10	100
3	[1–10]	[10–150]	[2, 198]	[154, 207]	91.33	100
4	[1–10]	[10–150]	[2, 197]	[154, 207]	90.30	100
5	[1–10]	[10–150]	[2, 195]	[150, 206]	86.55	100
6	[1–10]	[10–150]	[2, 192]	[144, 206]	84.13	100
7	[1–10]	[10–150]	[2, 188]	[152, 206]	91.44	100
8	[1–10]	[10–150]	[2, 186]	[149, 206]	88.70	100
9	[1–10]	[10–150]	[2, 184]	[149, 206]	86.34	100
10	[1–10]	[10–150]	[2, 185]	[142, 206]	84.15	100
11	[1–10]	[10–150]	[2, 178]	[138, 206]	81.65	100
12	[1–10]	[10–150]	[2, 181]	[143, 206]	80.13	100
13	[1–10]	[10–150]	[2, 171]	[123, 206]	76.33	100
14	[1–10]	[10–150]	[2, 175]	[142, 206]	73.51	100
15	[1–10]	[10–150]	[2, 155]	[144, 206]	71.87	100
16	[1–10]	[10–150]	[2, 149]	[139, 206]	72.80	100
17	[1–10]	[10–150]	[2, 23]	[135, 206]	69.19	100
18	[1–10]	[10–150]	[2, 159]	[133, 206]	67.00	100
19	[1–10]	[10–150]	[2, 23]	[142, 207]	66.22	100
20	[1–10]	[10–150]	[2, 16]	[134, 206]	63.43	100
21	[1–10]	[10–150]	[2, 16]	[121, 206]	62.40	100
22	[1–10]	[10–150]	[2, 16]	[109, 206]	60.58	100
23	[1–10]	[10–150]	[2, 16]	[21, 205]	58.76	100
24	[1–10]	[10–150]	[2, 15]	[121, 205]	56.00	100
25	[1–10]	[10–150]	[2, 15]	[124, 206]	55.12	100
26	[1–10]	[10–150]	[2, 15]	[24, 206]	53.65	100
27	[1–10]	[10–150]	[2, 15]	[24, 205]	50.21	100
28	[1–10]	[10–150]	[2, 14]	[21, 206]	47.01	100
29	[1–10]	[10–150]	[2, 14]	[22, 206]	45.41	100
30	[1–10]	[10–150]	[2, 14]	[23, 206]	44.74	100

In the next subsections, we describe into details the obtained numerical results. More precisely, in Sections 7.1 and 7.2, we analyze the MO-FEPIL model in both the cases when the reproduction ratio (R_0, see (1)) is less or greater than the crucial threshold of value one. Next, in Section 7.3, we analyze the MO-SEPIL model in a case where the reproduction ratio is greater than one.

In the next Tables 2–4, for presentation reasons, we report the found solutions analyzed into ranges (i.e., L_I, $L_V \in$ [1–20] for Table 2 and L_I, $L_V \in$ [1–30] for Tables 3 and 4. Among all the found Pareto solutions for each triple (L_S, L_I, L_v), we present, in columns 2 and 3, the minimum and maximum number of days (T^{min} and T^{max}) needed to reach the equilibrium, i.e., to converge to the uninfected steady state. Column 4 reports computational time average of Algorithm 1 execution. Last, the percentage of convergence or the number of found feasible solutions is presented in column 5.

7.1. Results for MO-FEPIL Model with $R_0 < 1$

Here, we assume that the proliferation rate of the $CD4^+$ T-cell population (r) is equal to 0.02. Due to the choice of the other parameters already set in Section 6, the value of the reproduction ratio R_0 is equal to 0.56.

Table 2 shows that the MO-FEPIL model produces all the feasible solutions at λ variations for every value of L_S, L_I and L_V, in the range [1–20].

It should be noted that there are few differences in the minimum of the value of T^{min} whereas some differences occur in the maximum values of T^{min} and T^{max} and in the minimum value of T^{max}. The main oscillations are observed in the maximum values of T^{min} and T^{max}, which are respectively equal to 105 and 65 days, whereas the oscillations

of the minimum value of T^{max} are equal to 20 days. No relevant differences are observed in the average time machine needed to solve the Algorithm 1, where the oscillation is less than one minute.

It becomes clear that Table 2 proves the efficacy of the Algorithm 1, because we are able to exploit efficiently the Pareto front in few minutes, obtaining a good number of different solutions that spans effectively over the Pareto front. In addition, all the solutions are given in, on average, under only 7 min. The results in Table 2 are in accordance with the theoretical result in Theorem 1, which states the stability of the uninfected steady state. Furthermore, we can assert experimentally that the found stability of the system is maintained also for instances that are not small compared to the steady state $(S_0, I_0, V_0) = (18.69, 0, 0)$.

7.2. Results for MO-FEPIL Model with $R_0 > 1$

Here, we assume that the proliferation rate of the $CD4^+$ T-cell population (r) is equal to 0.2. Considering the assigned values of the other parameters already set in Section 6, the reproduction ratio is equal to 22.94. Finally, we observe that $S_0 = 764.71$, $I_0 = 0$ and $V_0 = 0$.

The results depicted in Table 3 show that the Algorithm 1 produces no convergent solutions for whichever value of the parameter L_S in the range [1–10] and L_I, L_V in the range [1–30]. This result is in accordance with Theorem 1, which states the instability of the uninfected steady state (S_0, I_0, V_0) when the reproduction ratio R_0 is greater than one.

7.3. Results for MO-SEPIL Model with $R_0 > 1$

To handle the problem from a medical point of view, here, we assume that the proliferation rate of $CD4^+$ T-cells is equal to 0.2, so that the reproduction ratio R_0 is equal to 22.94. Moreover, $N_0 = 140.01$, $r_1 = 2.18$ and $r_2 = 464.12$. Hence, the pair (N, r) does not belong to the interior of $\mathscr{P}$ (see (2)). Finally, we observe that $S_1 = 33.33$, $I_1 = 9.37$ and $V_1 = 140.55$.

Table 4 shows that the MO-SEPIL model produces only feasible solutions for every value of L_S in the range [1–30] and L_I in [1–10] and L_V in [10–150], the latter with a step equivalent to 10.

So far, the results depicted in Table 4 prove once more the theoretical property presented in Theorem 1, which shows that the infected steady state is stable, since the pair (N, r) does not belong to the set $\mathscr{P}$.

Furthermore, Table 4 proves the performance of the Algorithm 1, because we are able to generate the Pareto front solutions in computational times of mostly less than 2 min.

Finally, we stress that no sensible differences in the minimum value of T^{min} occur apart from the case $L_S = 1$. Similarly, no relevant differences are observed in the maximum value of T^{max}, whose oscillation is equal to two days. On the other hand, relevant differences occur in the maximum value of T^{min}: here, the difference between the minimum and maximum value is 188 days. Similarly, the oscillation of the minimum value of T^{max} is 138 days.

8. Conclusions

In this paper, we have analyzed a model proposed to describe the in vivo dynamics of HIV in human beings. We have linearized and discretized the model in order to solve it using instantaneous Control Algorithm. Our computational results, presented in Section 7, agree with the theoretical results presented in Theorem 1, confirming the validity of the MO-FEPIL and MO-SEPIL models. Despite the adopted simplifications, the two models still capture the real dynamics of the infection. An additional outcome of the experiments is assessing the efficiency of the Algorithm 1 and its efficacy in identifying the set of Pareto Optimal solutions for the MO-FEPIL and MO-SEPIL problems.

We played with the values of the proliferation rate, taken in the admissible set of values, to guarantee that the assumptions of point (i) and (ii) of Theorem 1 are satisfied. We found this the easiest way to meet the assumptions of the quoted theorem. Of course, one could rather change the values of the parameter γ, N, μ_S, μ_I and μ_V, but this, of course,

would make the problems much more different from each other. Furthermore, it becomes clear from the presented outcomes the efficacy and the efficiency of the Algorithm 1 to identify the set of Pareto Optimal solutions in few minutes. These performances are quite suitable for an interactive use of the algorithm in the real-time biomedical applications.

Author Contributions: Software, D.G.; Validation, D.G. and L.L.; Writing—original draft, D.G. and L.L.; Writing—review & editing, D.G. and L.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Informed Consent Statement: Not applicable

Data Availability Statement: Not applicable

Conflicts of Interest: The authors declare no conflict of interest.

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