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ARTICLE

# A Time-Continuous Model for an Untreated HIV-Infection and a Novel Non-Standard Finite-Difference-Method for Its Discretization

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**ABSTRACT:** In this work, we re-investigate a classical mathematical model of untreated HIV infection suggested by Kirschner and introduce a novel non-standard finite-difference method for its numerical solution. As our first contribution, we establish non-negativity, boundedness of some solution components, existence globally in time, and uniqueness on a time interval $[0, T]$ for an arbitrary $T > 0$ for the time-continuous problem which extends known results of Kirschner's model in the literature. As our second analytical result, we establish different equilibrium states and examine their stability properties in the time-continuous setting or discuss some numerical tools to evaluate this question. Our third contribution is the formulation of a non-standard finite-difference method which preserves non-negativity, boundedness of some time-discrete solution components, equilibria, and their stabilities. As our final theoretical result, we prove linear convergence of our non-standard finite-difference-formulation towards the time-continuous solution. Conclusively, we present numerical examples to illustrate our theoretical findings.

**KEYWORDS:** Convergence; dynamical systems; equilibrium state; existence; finite-difference-method; non-local approximations; numerical analysis; uniqueness

## 1 Introduction

For more than four decades, infections with human immunodeficiency virus (HIV) have become a global epidemic, with approximately 40 million people currently living with this infection [1–3]. However, nearly 5.5 million people do not know about their HIV infection [3]. In the absence of medical treatment of such infections, cellular mechanisms and their time development within human individuals have been well studied and understood [4–7]. Over time, many scientists have developed mathematical models for the evolution of an infection with HIV which are summarized in different reviews [8–10].

### *1.1 Motivation on Mathematical Modeling*

Mathematical models and, in particular, differential equations play an important role in many branches of sciences. A growing field is a mathematical or theoretical biology where, for example, models for brain cancer [11] or models for competing species [12] are considered. Ethanol metabolism in the human body can be described by differential equations as well [13,14]. Temporal development of calcium-ion concentrations in liver cells can be modeled in a similar way as well [15]. In recent years, epidemiology has seen a large growth due to modeling approaches [16–18]. Further fields are chemistry [19–21] or computer science [22,23]. Mathematical modeling has also been an invaluable tool for understanding HIV-1 dynamics within human individuals. Let us first consider one basic mathematical model of untreated HIV dynamics within human hosts described by Stafford and co-workers [24], Perelson [25] or presented in Alizon's and Magnus's review article [8]. Here, we assume human blood as our compartment for our modeling idea as a non-linear system of ordinary differential equations. Since $CD4^+$ T-cells are mainly affected by an HIV infection [4], we denote the density of susceptible, uninfected $CD4^+$ T-cells by $T(t)$, the density of infected $CD4^+$ T-cells by $I(t)$ and the density of virus particles by $V(t)$. Uninfected target $CD4^+$ T-cells are produced by a constant rate $\lambda$ in the bone marrow, transfer to infected $CD4^+$ T-cells by a constant rate $\beta$ and die at a constant natural death rate $d_T$. These infected $CD4^+$ T-cells are also destroyed or die by a constant rate $d_I$. Those infected cells can burst and expose new virus particles by a constant rate $p$. Finally, virus particles are cleared or die naturally from the human system by a constant rate $d_V$. Hence, this fundamental model for the description of untreated HIV dynamics within human individuals reads

$$\begin{cases} T'(t) = \lambda - \beta \cdot T(t) \cdot V(t) - d_T \cdot T(t), \\ I'(t) = \beta \cdot T(t) \cdot V(t) - d_I \cdot I(t), \\ V'(t) = p \cdot I(t) - d_V \cdot V(t), \\ T(0) = T_0 > 0\ ,\ I(0) = I_0 \geq 0\ ,\ V(0) = V_0 > 0, \end{cases} \tag{1}$$

where $T_0$, $I_0$ and $V_0$ denote non-negative initial conditions. Here, we assume $T_0$ and $V_0$ to be positive.

From a mathematical modeling point of view, different adaptations of (1) exist in the literature [8–10]. Let us chronologically summarize some important studies in this regard. In 1991, Nowak and May mainly investigated numerically a simple mathematical model for antigenic variation with multiple virus strains in HIV infections [26]. Based on (1), Perelson, Kirschner and De Boer focused on stability and simulation of an extension of (1) by latently and actively infected $CD4^+$ T-cells and a logistic depletion of susceptible, uninfected $CD4^+$ T-cells [27] two years later. In 1994, Bonhoeffer and Nowak concentrated on the simulation and stability of intra-host time evolution of two HIV strains [28].

Before we continue our chronological summary of different contributions to the field of mathematical modeling of primary HIV infection, we want to introduce our model under consideration which is excellently described by Kirschner [29]. Again, we denote the density of susceptible, uninfected $CD4^+$ T-cells by $T(t)$, the density of infected $CD4^+$ T-cells by $I(t)$ and the density of virus particles by $V(t)$. In contrast to (1), Kirschner modified (1) by a term which represents stimulation of $CD4^+$ T-cells due to presence of virus particle. This adjusted model reads

$$\begin{cases} T'(t) = k_1(t) - k_2 \cdot T(t) + k_3 \cdot \dfrac{T(t) \cdot V(t)}{k_4 + V(t)} - k_5 \cdot T(t) \cdot V(t), \\ I'(t) = k_5 \cdot T(t) \cdot V(t) - k_6 \cdot I(t) - k_3 \cdot \dfrac{I(t) \cdot V(t)}{k_4 + V(t)}, \\ V'(t) = k_7 \cdot k_3 \cdot \dfrac{I(t) \cdot V(t)}{k_4 + V(t)} - k_8 \cdot T(t) \cdot V(t) + k_9 \cdot \dfrac{V(t)}{k_{10} + V(t)}, \\ T(0) = T_0 > 0\ ,\ I(0) = I_0 \geq 0\ ,\ V(0) = V_0 > 0, \end{cases} \tag{2}$$

where $T_0 > 0$, $I_0 \geq 0$ and $V_0 > 0$ stand for initial conditions. All meanings of time-dependent functions are presented in Table 1.

**Table 1:** Explanation of all time-dependent variables of (2)

| Symbols | Meanings |
|---|---|
| $T(t)$ | Density of susceptible, uninfected $CD4^+$ T-cells in blood |
| $I(t)$ | Density of infected $CD4^+$ T-cells in blood |
| $V(t)$ | Density of virus particles in blood |

In the first equation of (2), $k_1(t)$ denotes a time-dependent production rate of susceptible $CD4^+$ T-cells while $k_2$ is a constant natural death rate of these cells. In particular, $k_1(t)$ should be a decreasing function if the virus load becomes larger which means that $k_1(t)$ should be bounded below by zero, bounded above by a positive constant $K_1$ for all $t \geq 0$ and it converges to a non-negative $\widetilde{k_1}$ as $t \to \infty$. In addition to that, $k_3$ symbolizes a constant stimulation rate of the susceptible cells by the presence of virus particles. Here, $k_2 > k_3$ is assumed. $k_5$ is a constant transfer rate of susceptible cells to infected $CD4^+$ T-cells by infiltration of susceptible $CD4^+$ T-cells from virus particles. $k_4$ is an adjustable parameter. In the second equation of (2), $k_6$ symbolizes the clearance and death rate of infected $CD4^+$ T-cells, while the last term $-k_3 \cdot \dfrac{I(t) \cdot V(t)}{k_4 + V(t)}$ represents a bursting term of infected $CD4^+$ T-cells after their infiltration by virus particles. In the last equation of (2), $k_7$ stands for the replication rate of virus particles after division of infected $CD4^+$ T-cells while $k_8$ represents a loss rate of virus particles by immune reactions. At last, $k_9$ is the growth rate of virus particles, whereas $k_{10}$ stands for a saturation rate of this proliferation process. All meanings of constant, positive problem parameters are summarized in Table 2.

**Table 2:** Explanation of all constant or time-dependent, positive problem parameters of (2)

| Symbols | Meanings |
|---|---|
| $k_1(t)$ | Time-dependent production rate of susceptible $CD4^+$ T-cells |
| $k_2$ | Constant natural death rate of susceptible $CD4^+$ T-cells |
| $k_3$ | Constant stimulation rate of susceptible $CD4^+$ T-cells |
| $k_4$ | Adjustable problem parameter |
| $k_5$ | Constant transfer rate of susceptible $CD4^+$ T-cells to infected $CD4^+$ T-cells |
| $k_6$ | Constant clearance and death rate of infected $CD4^+$ T-cells |
| $k_7$ | Constant replication rate of virus particles |
| $k_8$ | Constant loss rate of virus particles |
| $k_9$ | Constant growth rate of virus particles |
| $k_{10}$ | Constant saturation rate of proliferation of virus particles |

Now, we can complete our brief overview on mathematical modeling of primary HIV infections. In 1996, Perelson and co-authors suggested an adjustment of (1) by an infectious pool and a non-infectious pool of virions after introducing a pharmacological therapy [30]. One year later, Perelson and co-workers proposed a changed dynamical model of HIV infection under combination therapy [31]. In 1999, Perelson and Nelson reviewed some fundamental mathematical models, especially regarding the stability of systems of ordinary differential equations concerning primary HIV-infections [32]. In 2000, Stafford and co-authors specifically investigated parameter estimation of model (1) concerning data from different patients [24]. Two years later, Perelson reviewed some basic models regarding primary HIV infection with and without medical treatment [25].

A delay-based system of integro-differential equations of cell-to-cell spread of primary HIV infections was introduced by Culshaw et al. in 2003 [33]. Based on (1), Stilianakis and Schenzle recommended a time-dependent infection rate [34]. In 2009, Kamp examined different strains under HIV coreceptor switch from a dynamical perspective, where investigation of stability was mainly focused [35]. One year later, Elaiw proposed an alternation of (1) by latently infected and actively infected CD4$^+$ T-cells. The main focus of this research work was the proof of globally asymptotic stability [36]. Lythgoe and Fraser came up with a model of three host-cell types, namely susceptible CD4$^+$ T-cells, latently infected memory CD4$^+$ T-cells and macrophages [37]. In the same year of 2012, Alizon and Magnus reviewed the target-cell limitation model (1) and general schemes of the HIV within-host model [8]. Perelson and Ribeiro reconsidered (1) and modifications of within-host HIV models [9]. In 2014, Pourbashash and co-authors examined a global analysis of within-host virus models with cell-to-cell viral transmission [38]. Shen et al. analyzed the global stability of an infection-age structured HIV-1 model linking within-host and between-host dynamics in 2015 [39]. In the same year, Wang and co-authors developed a mathematical model for slow CD4$^+$ T-cell decline in HIV-infected individuals [40]. Based on model (1), Pankavich and Parkinson analyzed a modification with Laplacian operators to include spatial heterogeneity in within-host viral dynamics models [41]. In 2017, Wang and co-authors presented an age-structured within-host HIV model with T-cell competition [42]. One year later, Almocera and co-authors established one multiscale within-host and between-host model for viral infectious diseases [43]. In 2023, D'Orso and Forst reviewed different models for HIV infections [10]. In 2024, Clarke and Pankavich proposed a three-stage model for HIV infections and its implications for antiretroviral therapy [44]. Wacker further investigated a simple mathematical model for primary HIV infection concerning classical mathematical questions [45] in 2024. In 2023, Li and co-authors investigated the impact of standard and non-standard finite-difference methods for between-host dynamics of HIV infections within a population [46], which motivates a quick overview of numerical discretizations of different mathematical models of HIV infection. In 2024, Meetei and co-authors investigated one HIV model against data from real cases [47]. In the same year, Ayele and co-authors examined a population-based model for the co-infection of HIV with tuberculosis [48]. In 2025, Hao and co-workers proposed a mathematical model in order to evaluate an international target strategy against HIV [49]. Recently, Teklu and co-workers have suggested a population-based and age-structured HIV model with optimal control [50].

We also like to briefly highlight stochastic approaches for the solution of within-host HIV models, such as those presented by Mbogo [51] and co-authors in 2013 or by Umar and co-workers [52] in 2022.

### *1.2 Motivation on Numerical Discretizations*

While many works on mathematical models of HIV infections exist, numerical solution of these models, such as time-discrete variants of time-continuous models, is an important research topic as well. We want to summarize some studies with regard to this matter.

Many classical time integration methods such as Runge-Kutta schemes can be applied to such systems of ordinary differential equations [53,54]. As an alternative approach, Mickens popularized the concept of non-standard finite-difference methods for solving differential equations [55,56]. Let

$$\mathbf{y}'(t) = \mathbf{f}(t, \mathbf{y}(t))$$

be a system of ordinary differential equations. Often, we want to find preferably a finite-difference-scheme of the form

$$D_h\left(\mathbf{y}_n\right) = \mathbf{F}_h\left(f, \mathbf{y}_n\right)$$

where $D_h\left(\mathbf{y}_n\right) \approx \mathbf{y}'\left(t_n\right)$, $\mathbf{F}_h\left(\mathbf{f}, \mathbf{y}_n\right) \approx \mathbf{f}\left(t_n, \mathbf{y}_n\right)$ and $\mathbf{y}_n \approx \mathbf{y}\left(t_n\right)$ are appropriate approximations at time grid points $t_n$ for numerical simulations. A discretization scheme is called a non-standard finite-difference-method if at least one of the conditions

1. $D_h\left(\mathbf{y}_n\right) = \dfrac{\mathbf{y}_{n+1} - \mathbf{y}_n}{\varphi\left(h_n\right)}$ is an approximation of the first derivatives of our dynamical system where $\varphi\left(h\right) = h + O\left(h^2\right)$ holds and $h_n = t_{n+1} - t_n$ is a possibly non-equidistant time-step size;
2. $\mathbf{F}_h\left(\mathbf{f}, \mathbf{y}_n\right) = \mathbf{g}\left(\mathbf{y}_{n+1}, \mathbf{y}_n, \ldots, h\right)$ is a non-local approximation of the right-hand-side vectorial function hold.

In 2013, Obaid et al. established a non-standard finite-difference method of development of HIV infections between hosts in a population [57]. In 2016, Yang and co-authors presented one non-standard finite-difference method for a diffusive within-host dynamics model with both virus-to-cell and cell-to-cell transmissions [58]. These authors mainly focused on analyzing stability properties for their suggested discretization method. Elaiw and Alshaikh examined the global stability of different time-discrete HIV dynamical models with three categories of infected $CD4^{+}$ T-cells [59]. Salman introduced a non-standard finite-difference method and an optimal control problem for one HIV model with Beddington-DeAngelis incidence and cure rates [60]. Attaullah and Sohaib suggested one continuous Petrov-Galerkin method and one Legendre Wavelet Collocation method for the discretization of the within-host HIV model [61]. In 2023, Elaiw and co-authors developed a non-standard finite-difference-method for a co-infection model of HIV and another illness where the vectorial right-hand-side function of the dynamical system is a non-linear polynomial [62]. In that work, the authors established the global asymptotic stability of their four different equilibria by providing different Lyapunov functions. In 2025, Namjoo and co-workers proposed a non-standard finite-difference-method for a bounded, time-continuous HIV model of $CD^{+}$ T-cells [63].

### *1.3 Contributions*

All in all, many studies focused mainly on stability properties of (2) and only a few non-standard finite-difference methods exist in the literature. Henceforth, our contributions can be stated as follows:

1. First, we extend some analytical results of (2) by proofs of non-negativity, boundedness of $T\left(t\right)$ and $I\left(t\right)$, at most linear growth of $V\left(t\right)$, global existence in time, global uniqueness in time on a time interval $\left[0, T\right]$ for an arbitrary $T > 0$ and discuss further analytical and numerical investigations on stability properties of model (2). Here, we especially mention all results on the boundedness of solutions, global existence in time, and global uniqueness in time, which were not proved in Kirschner's original work [29]. In particular, we would like to highlight that we, in contrast to Kirschner, establish local stability of equilibria analytically or numerically;

2. As our main contribution, we suggest a novel non-standard finite-difference-method

$$\begin{cases} \dfrac{T_{j+1}-T_j}{h_j} = k_{1,j+1} - k_2 \cdot T_{j+1} + k_3 \cdot \dfrac{T_j \cdot V_j}{k_4 + V_j} - k_5 \cdot T_{j+1} \cdot V_j, \\ \dfrac{I_{j+1}-I_j}{h_j} = k_5 \cdot T_{j+1} \cdot V_j - k_6 \cdot I_{j+1} - k_3 \cdot \dfrac{I_{j+1} \cdot V_j}{k_4 + V_j}, \\ \dfrac{V_{j+1}-V_j}{h_j} = k_7 \cdot k_3 \cdot \dfrac{I_{j+1} \cdot V_j}{k_4 + V_j} - k_8 \cdot T_{j+1} \cdot V_{j+1} + k_9 \cdot \dfrac{V_j}{k_{10} + V_j}, \\ T_1 = T_0 \ , \ I_1 = I_0 \ , V_1 = V_0, \end{cases} \tag{3}$$

with non-equidistant time-step sizes $h_j = t_{j+1} - t_j$ and, for example, $T_j$ denotes time-discrete solutions at grid points $t_j$ on a time mesh and $k_{1,j+1}$ is an appropriate time-discretization of $k_1(t)$. Additionally, we show that many properties of the time-continuous case such as non-negativity, boundedness or at most linear growth transfer to the time-discrete setting and we demonstrate linear convergence of the time-discrete solution components towards the time-continuous ones;
3. Finally, we illustrate our theoretical findings by numerical examples.

Our work is organized as follows. After stating our main goals in Section 1, we provide analytical results of the time-continuous model (2) in Section 2. In Section 3, we examine our proposed non-standard finite-difference-method (3) thoroughly and show evidence of our theoretical results by numerical experiments in Section 4. Conclusively, we summarize our findings and possible future research directions in Section 5.

## 2 Analysis of the Time-Continuous Problem Formulation

Since the vectorial right-hand-side function of (2) is at least continuous, we can conclude that all solution components are at least continuously differentiable.

### *2.1 Preliminaries*

Before providing our analytical results, we want to summarize some important results that we need for our investigation. Let us consider the general initial-value problem

$$\begin{cases} \mathbf{z}'(t) = \mathbf{G}(t, \mathbf{z}(t)), \\ \mathbf{z}(0) = \mathbf{z_0}, \end{cases} \tag{4}$$

where all state variables are included in $\mathbf{z}(t) = (z_1(t), \ldots, z_n(t))$ and all initial values are given by the initial vector $\mathbf{z_0} \in \mathbb{R}^n$. We define a function

$$\mathbf{G}\colon [0,\infty) \times (C([0,\infty) \times \mathbb{R}^n; \mathbb{R}))^n \longrightarrow (C([0,\infty) \times \mathbb{R}^n; \mathbb{R}))^n$$

where $\mathbf{X} := (C([0,\infty) \times \mathbb{R}^n; \mathbb{R}))^n$ denotes the metric space of continuous functions on $[0,\infty)$ equipped with the classical supremum norm $\|\cdot\|_\infty$. Now, we want to summarize important definitions such as local and global Lipschitz-continuity which can be found in [[64], Subsection 3.2.1]. Let $(X, \|\cdot\|_X)$ and $(Y, \|\cdot\|_Y)$ be normed spaces. A function $f\colon X \longrightarrow Y$ is called *globally Lipschitz-continuous* on X if there exists a constant $K \geq 0$ such that the inequality

$$\|f(x_1) - f(x_2)\|_Y \leq K \cdot \|x_1 - x_2\|_X$$

holds for all $x_1, x_2 \in X$. A function $f\colon X \longrightarrow Y$ is called *locally Lipschitz-continuous* if, for every $x \in X$, there exists a neighborhood $U$ of $x$ such that $f$ restricted to $U$ globally Lipschitz-continuous on $U$. Let us recapitulate one important theorem from [[64], Theorem 4.7.1].

**Theorem 1.** *If* $\mathbf{G} : [0,\infty) \times \mathbb{R}^n \longrightarrow \mathbb{R}^n$ *is locally Lipschitz-continuous in both time and state variables and if there exist non-negative real functions* $D : [0,\infty) \longrightarrow [0,\infty)$ *and* $K : [0,\infty) \longrightarrow [0,\infty)$ *such that*

$$\|\mathbf{G}(t,\mathbf{z}(t))\|_{\mathbb{R}^n} \leq K(t) \cdot \|\mathbf{z}(t)\|_{\mathbb{R}^n} + D(t) \tag{5}$$

*holds for all* $\mathbf{z}(t) \in \mathbb{R}^n$ *where* $\|\cdot\|$ *denotes an appropriate norm on the corresponding space. Then it follows a solution of the initial-value problem (4) exists for all* $t \geq 0$ *and moreover, for all finite* $T \geq 0$*, it holds*

$$\|\mathbf{z}(t)\|_{\mathbb{R}^n} \leq \|\mathbf{z}_0\|_{\mathbb{R}^n} \cdot \exp(K_{\max} \cdot t) + \frac{D_{\max}}{K_{\max}} \cdot (\exp(K_{\max} \cdot t) - 1) \tag{6}$$

*for all* $t \in [0,T]$ *where*

$$D_{\max} := \max_{0 \leq s \leq T} |D(s)| \text{ and } K_{\max} := \max_{0 \leq s \leq T} |K(s)|.$$

### *2.2 Non-Negativity, Boundedness of $T(t)$ and $I(t)$ and Linear Growth of $V(t)$ in Time*

First, we want to show that possible solutions of (2) remain non-negative for all $t \geq 0$.

**Theorem 2.** *Solutions of (2) stay non-negative for all* $t \geq 0$.

**Proof.** Since all solution components of (2) are continuous, there exists a time point $t^\star > 0$ such that

$$t^\star = \sup_{t>0} \{t > 0 : T(t) \geq 0 \wedge I(t) \geq 0 \wedge V(t) \geq 0\}$$

holds. Let us assume that $t^\star > 0$ is finite. We can conclude that

$$\begin{aligned} T'(t) &= k_1(t) - k_2 \cdot T(t) + k_3 \cdot \frac{T(t) \cdot V(t)}{k_4 + V(t)} - k_5 \cdot T(t) \cdot V(t) \\ &\geq -k_2 \cdot T(t) - k_5 \cdot T(t) \cdot V(t) \\ &= -T(t) \cdot (k_2 + k_5 \cdot V(t)) \end{aligned}$$

is valid for all $t \in [0, t^\star]$ and by the comparison principle, we obtain

$$T(t) \geq T_0 \cdot \exp\left(\int_0^t (-k_2 - k_5 \cdot V(\tau))\, \mathrm{d}\tau\right).$$

Additionally, we notice that

$$\begin{aligned} I'(t) &\geq -k_6 \cdot I(t) - \frac{k_3}{k_4} \cdot I(t) \\ &= -\left(k_6 + \frac{k_3}{k_4}\right) \cdot I(t) \end{aligned}$$

holds for all $t \in [0, t^\star]$ and this implies

$$\begin{aligned} I(t) &\geq I_0 \cdot \exp\left(\int_0^t -\left(k_6 + \frac{k_3}{k_4}\right) \mathrm{d}\tau\right) \\ &= I_0 \cdot \exp\left(-\left(k_6 + \frac{k_3}{k_4}\right) \cdot t\right) \end{aligned}$$

for all $t \in [0, t^\star]$. Furthermore, we see that

$$V'(t) \geq -k_8 \cdot T(t) \cdot V(t)$$

holds for all $t \in [0, t^\star]$ and the comparison principle yields

$$V(t) \geq V_0 \cdot \exp\left( - \int_0^t k_8 \cdot T(\tau)\, \mathrm{d}\tau \right)$$

for all $t \in [0, t^\star]$. All these inequalities contradict the maximality of $t^\star$ and consequently, all solution components of (2) remain non-negative for all $t \geq 0$. □

Next, we want to prove the boundedness of $T(t)$ globally in time.

**Lemma 1.** *The solution components $T(t)$ and $I(t)$ are bounded for all $t \geq 0$.*

**Proof.** We separate this proof into two parts.

1. It has already been proven that the inequality $T(t) \geq 0$ is valid for all $t \geq 0$. For that reason, we only need to demonstrate that there exists a constant $A > 0$ such that $T(t) \leq A$ for all $t \geq 0$. Since $k_1(t) \leq K_1$ for all $t \geq 0$ and $k_2 > k_3$ hold, we obtain
$$\begin{aligned} T'(t) &= k_1(t) - k_2 \cdot T(t) + k_3 \cdot T(t) \cdot \frac{V(t)}{k_4 + V(t)} - k_5 \cdot T(t) \cdot V(t) \\ &\leq K_1 - k_2 \cdot T(t) + k_3 \cdot T(t) \\ &\leq K_1 - (k_2 - k_3) \cdot T(t) \end{aligned}$$
for all $t \geq 0$ due to the non-negativity of all solution components. By the comparison principle, we get
$$\begin{aligned} T(t) &\leq \frac{K_1}{k_2 - k_3} + \left( T_0 - \frac{K_1}{k_2 - k_3} \right) \cdot \exp\left(-(k_2 - k_3) \cdot t\right) \\ &\leq \max\left\{ T_0 \,;\, \frac{K_1}{k_2 - k_3} \right\} =: T_{\max} \end{aligned}$$
which proves our first assertion.

2. It has also been shown that the inequality $I(t) \geq 0$ holds for all $t \geq 0$. Consequently, we solely need to find a constant $B > 0$ such that $I(t) \leq B$ for all $t \geq 0$. First, by adding $T'(t)$ and $I'(t)$ and applying $k_1(t) \leq K_1$ and $k_2 > k_3$ for all $t \geq 0$, we conclude that
$$\begin{aligned} N'(t) &:= T'(t) + I'(t) \\ &= \left\{ k_1(t) - k_2 \cdot T(t) + k_3 \cdot T(t) \cdot \frac{V(t)}{k_4 + V(t)} - k_5 \cdot T(t) \cdot V(t) \right\} \\ &+ \left\{ k_5 \cdot T(t) \cdot V(t) - k_6 \cdot I(t) - k_3 \cdot I(t) \cdot \frac{V(t)}{k_4 + V(t)} \right\} \\ &\leq K_1 - (k_2 - k_3) \cdot T(t) - k_6 \cdot I(t) \\ &\leq K_1 - \min\{k_2 - k_3 \,;\, k_6\} \cdot (T(t) + I(t)) \end{aligned}$$

holds because of the non-negativity of all solution components. Again, applying the comparison principle, we obtain

$$T(t) + I(t) \leq \frac{K_1}{\min\{k_2 - k_3 \,;\, k_6\}}$$

$$+\left(T_0 + I_0 - \frac{K_1}{\min\{k_2 - k_3\,;\, k_6\}}\right)\cdot \exp\left(-\min\{k_2 - k_3\,;\, k_6\}\cdot t\right)$$
$$\leq \max\left\{T_0 + I_0\,;\, \frac{K_1}{\min\{k_2 - k_3\,;\, k_6\}}\right\} =: N_{\max}$$

for all $t \geq 0$ which shows our second assertion due to the non-negativity of both solution components $T(t)$ and $I(t)$.

This finishes our proof. □

As our last result of this subsection, we prove that $V(t)$ grows at most linearly in time.

**Lemma 2.** *The solution component $V(t)$ grows at most linearly in time.*

**Proof.** The differential equation for $V(t)$ yields the estimate

$$\begin{aligned} V'(t) &= k_7 \cdot k_3 \cdot I(t) \cdot \frac{V(t)}{k_4 + V(t)} - k_8 \cdot T(t) \cdot V(t) + k_9 \cdot \frac{V(t)}{k_{10} + V(t)} \\ &\leq k_3 \cdot k_7 \cdot N_{\max} + k_9 \end{aligned}$$

due to the non-negativity of all solution components. Consequently, it holds

$$V(t) \leq V_0 + (k_3 \cdot k_7 \cdot N_{\max} + k_9)\cdot t$$

by the comparison principle for all $t \geq 0$ which proves our claim. □

### *2.3 Existence Globally in Time*

Let us define

$$\begin{aligned} \mathbf{F}(t,(T(t),I(t),V(t))) &:= \begin{pmatrix} \mathbf{F}_1(t,(T(t),I(t),V(t))) \\ \mathbf{F}_2(t,(T(t),I(t),V(t))) \\ \mathbf{F}_3(t,(T(t),I(t),V(t))) \end{pmatrix} \\ &= \begin{pmatrix} k_1(t) - k_2 \cdot T(t) + k_3 \cdot \dfrac{T(t)\cdot V(t)}{k_4 + V(t)} - k_5 \cdot T(t)\cdot V(t) \\ k_5 \cdot T(t)\cdot V(t) - k_6 \cdot I(t) - k_3 \cdot \dfrac{I(t)\cdot V(t)}{k_4 + V(t)} \\ k_7 \cdot k_3 \cdot \dfrac{I(t)\cdot V(t)}{k_4 + V(t)} - k_8 \cdot T(t)\cdot V(t) + k_9 \cdot \dfrac{V(t)}{k_{10} + V(t)} \end{pmatrix} \end{aligned}$$

as the right-hand-side function of (2). We notice that this function is locally Lipschitz-continuous on $[0,\infty) \times (C([0,\infty)\,;\,\mathbb{R}))^3$ because it is continuously differentiable on this set concerning $t$, $T$, $I$ and $V$ by [[64], Proposition 3.2.2]. Consequently, we can state the following result.

**Theorem 3.** *Solutions of (2) exist for all $t \geq 0$.*

**Proof.** We need to estimate all components of $\mathbf{F}(t,(T(t),I(t),V(t)))$ separately.

1. We see that

$$\begin{aligned} \|\mathbf{F}_1(t,(T(t),I(t),V(t)))\|_\infty &= \left\|k_1(t) - k_2 \cdot T(t) + k_3 \cdot \frac{T(t)\cdot V(t)}{k_4 + V(t)} - k_5 \cdot T(t)\cdot V(t)\right\|_\infty \\ &\leq K_1 + k_2 \cdot T_{\max} + k_3 \cdot T_{\max} + k_5 \cdot T_{\max} \cdot \|V(t)\|_\infty \\ &\leq (K_1 + (k_2 + k_3)\cdot T_{\max}) + k_5 \cdot T_{\max} \cdot \|(T(t),I(t),V(t))\|_\infty \end{aligned}$$

holds.

2. Additionally, we notice that

$$\begin{aligned}\|\mathbf{F}_2(t,(T(t),I(t),V(t)))\|_\infty &= \|k_5\cdot T(t)\cdot V(t)-k_6\cdot I(t)-k_3\cdot\frac{I(t)\cdot V(t)}{k_4+V(t)}\|_\infty\\ &\le k_5\cdot T_{\max}\cdot\|V(t)\|_\infty+k_6\cdot N_{\max}+k_3\cdot N_{\max}\\ &\le (k_3+k_6)\cdot N_{\max}+k_5\cdot T_{\max}\cdot\|(T(t),I(t),V(t))\|_\infty\end{aligned}$$

is valid.

3. Furthermore, we obtain

$$\begin{aligned}\|\mathbf{F}_3(t,(T(t),I(t),V(t)))\|_\infty &= \|k_7\cdot k_3\cdot\frac{I(t)\cdot V(t)}{k_4+V(t)}-k_8\cdot T(t)\cdot V(t)+k_9\cdot\frac{V(t)}{k_{10}+V(t)}\|_\infty\\ &\le k_3\cdot k_7\cdot N_{\max}+k_8\cdot T_{\max}\cdot\|V(t)\|_\infty+k_9\\ &\le (k_3\cdot k_7\cdot N_{\max}+k_9)+k_8\cdot T_{\max}\cdot\|(T(t),I(t),V(t))\|_\infty.\end{aligned}$$

4. Conclusively, these three inequalities yield

$$\begin{aligned}\|\mathbf{F}(t,(T(t),I(t),V(t)))\|_\infty \le{}& (K_1+k_9+(k_2+2\cdot k_3+k_6+k_3\cdot k_7)\cdot N_{\max})\\ &+(2\cdot k_5+k_8)\cdot T_{\max}\cdot\|(T(t),I(t),V(t))\|_\infty.\end{aligned}$$

Finally, this proves the existence of solutions of (2) globally in time since all assumptions of Theorem 1 are fulfilled. □

### 2.4 Uniqueness in Time

By applying [[65], Corollary 2, Subchapter 2.4] and [[65], Theorem 4, Subchapter 2.4], we obtain a uniqueness result globally in time on $[0,T]$ for an arbitrary $T>0$.

**Theorem 4.** *Solutions of (2) exist uniquely for all* $t\in[0,T]$.

**Proof.** Let us construct the open set $E:=\left(-\frac{1}{2}\cdot\min\{k_4;k_{10}\},\infty\right)^3$ for the solution variables $(T,I,V)$. Our initial conditions $(T_0,I_0,V_0)\in[0,\infty)^3\subset E$ are assumed to be non-negative. Furthermore, we have already observed that our right-hand-side function is continuously differentiable on $E$. By Lemmas 1 and 2, we see that

$$(T(t),I(t),V(t))\subset K:=[0,N_{\max}]\times[0,N_{\max}]\times[0,V_0+(k_3\cdot k_7\cdot N_{\max}+k_9)\cdot T]\subset E$$

holds for all $t\in[0,T]$ for an arbitrary $T>0$. If we assume two different solution vectors starting at the same initial condition, we conclude from [[65], Theorem 4, Subchapter 2.4] that all solution components exist uniquely for all $t\in[0,T]$ for an arbitrary $T>0$. As a consequence, uniqueness on $[0,T]$ is established. □

### 2.5 Equilibrium States

For searching equilibrium states of system (2), we need to solve the system of non-linear equations

$$\begin{aligned}0&=\widetilde{k_1}-k_2\cdot T^\star+k_3\cdot\frac{T^\star\cdot V^\star}{k_4+V^\star}-k_5\cdot T^\star\cdot V^\star,\\ 0&=k_5\cdot T^\star\cdot V^\star-k_6\cdot I^\star-k_3\cdot\frac{I^\star\cdot V^\star}{k_4+V^\star},\end{aligned}\tag{7}$$

$$0 = k_3 \cdot k_7 \cdot \frac{I^\star \cdot V^\star}{k_4 + V^\star} - k_8 \cdot T^\star \cdot V^\star + k_9 \cdot \frac{V^\star}{k_{10} + V^\star},$$

where $(T^\star, I^\star, V^\star)$ denotes a possible equilibrium state. Here, we assume that $k_1(t) = \widetilde{k_1}$ is a constant for all $t \geq 0$ for simplicity.

*2.5.1 Virus-Free Equilibrium State*

It can be seen from (7) that the virus-free equilibrium state reads

$$(T_1^\star, I_1^\star, V_1^\star) = \left(\frac{\widetilde{k_1}}{k_2}, 0, 0\right). \tag{8}$$

Let us define the basic reproduction number $R_0$ by

$$R_0 := \frac{k_2 \cdot k_9}{\widetilde{k_1} \cdot k_8 \cdot k_{10}} \tag{9}$$

which is going to be motivated in the proof of our next statement.

**Theorem 5.** *If $R_0 < 1$ of (9) holds, our virus-free equilibrium state (8) of (2) is locally asymptotically stable.*

**Proof.** We divide our proof into different parts.

1. We first calculate the Jacobian matrix, denoted by $DF(T^\star, I^\star, V^\star)$, of the right-hand-side function of our dynamical system at possible equilibria. We notice that

$$DF(T^\star, I^\star, V^\star) = \begin{pmatrix} A_{F,1,1} & A_{F,1,2} & A_{F,1,3} \\ A_{F,2,1} & A_{F,2,2} & A_{F,2,3} \\ A_{F,3,1} & A_{F,3,2} & A_{F,3,3} \end{pmatrix} \tag{10}$$

with entries

$$A_{F,1,1} := -k_2 + k_3 \cdot \frac{V^\star}{k_4 + V^\star} - k_5 \cdot V^\star,$$

$$A_{F,1,2} := 0,$$

$$A_{F,1,3} := k_3 \cdot \frac{T^\star}{k_4 + V^\star} - k_3 \cdot \frac{T^\star \cdot V^\star}{(k_4 + V^\star)^2} - k_5 \cdot T^\star,$$

$$A_{F,2,1} := k_5 \cdot V^\star,$$

$$A_{F,2,2} := -k_6 - k_3 \cdot \frac{V^\star}{k_4 + V^\star},$$

$$A_{F,2,3} := k_5 \cdot T^\star - k_3 \cdot \frac{V^\star}{k_4 + V^\star} + k_3 \cdot \frac{I^\star \cdot V^\star}{(k_4 + V^\star)^2},$$

$$A_{F,3,1} := -k_8 \cdot V^\star,$$

$$A_{F,3,2} := k_3 \cdot k_7 \cdot \frac{V^\star}{k_4 + V^\star},$$

$$A_{F,3,3} := k_3 \cdot k_7 \cdot \frac{I^\star}{k_4 + V^\star} - k_3 \cdot k_7 \cdot \frac{I^\star \cdot V^\star}{(k_4 + V^\star)^2} - k_8 \cdot T^\star + k_9 \cdot \frac{1}{k_{10} + V^\star} - k_9 \cdot \frac{V^\star}{(k_{10} + V^\star)^2},$$

holds.

2. If we plug our virus-free equilibrium state (8), we obtain

$$DF\left(T_1^\star,0,0\right)=\begin{pmatrix}-k_2 & 0 & \dfrac{k_3}{k_4}\cdot T_1^\star-k_5\cdot T_1^\star\\ 0 & -k_6 & k_5\cdot T_1^\star\\ 0 & 0 & -k_8\cdot T_1^\star+\dfrac{k_9}{k_{10}}\end{pmatrix}.$$

Calculating the characteristic polynomial $\chi(\lambda)$ of this Jacobian at the virus-free equilibrium state, we see that

$$\begin{aligned}\chi(\lambda)&=\det\left(DF\left(T_1^\star,0,0\right)-\lambda\cdot\begin{pmatrix}1&0&0\\0&1&0\\0&0&1\end{pmatrix}\right)\\&=(-k_2-\lambda)\cdot(-k_6-\lambda)\cdot\left(-k_8\cdot T_1^\star+\frac{k_9}{k_{10}}-\lambda\right)\\&=0\end{aligned}$$

is valid. Both eigenvalues $\lambda_1=-k_2<0$ and $\lambda_2=-k_6<0$ are negative. The last eigenvalue $\lambda_3=\dfrac{k_9}{k_{10}}-k_8\cdot T^\star=\dfrac{k_9}{k_{10}}-\dfrac{\widetilde{k_1}\cdot k_8}{k_2}$ is negative if $R_0:=\dfrac{k_2\cdot k_9}{\widetilde{k_1}\cdot k_8\cdot k_{10}}<1$ holds.

This finishes our argument. □

*2.5.2 Virus-Endemic Equilibrium State*

Here, we assume that

$$R_0:=\frac{k_2\cdot k_9}{\widetilde{k_1}\cdot k_8\cdot k_{10}}>1$$

holds. From (7), we obtain

$$\begin{aligned}T_2^\star&=\frac{\widetilde{k_1}}{k_2+k_5\cdot V_2^\star-k_3\cdot\dfrac{V_2^\star}{k_4+V_2^\star}}\geq 0,\\ I_2^\star&=\frac{k_5\cdot T_2^\star\cdot V_2^\star}{k_3\cdot\dfrac{V_2^\star}{k_4+V_2^\star}+k_6}\geq 0,\\ V_2^\star\cdot&\left(k_3\cdot k_7\cdot\frac{I_2^\star}{k_4+V_2^\star}-k_8\cdot T_2^\star+\frac{k_9}{k_{10}+V_2^\star}\right)=0.\end{aligned}\tag{11}$$

Since $V_2^\star>0$ should hold in a virus-endemic equilibrium state $\left(T_2^\star,I_2^\star,V_2^\star\right)$, it must hold

$$k_3\cdot k_7\cdot\frac{I_2^\star}{k_4+V_2^\star}-k_8\cdot T_2^\star+\frac{k_9}{k_{10}+V_2^\star}=0.$$

Plugging all results of (11) into our previous equation, we get

$$0 = \frac{\widetilde{k_1} \cdot k_3 \cdot k_5 \cdot k_7 \cdot V_2^\star}{(k_4 + V_2^\star) \cdot \left(k_3 \cdot \frac{V_2^\star}{k_4 + V_2^\star} + k_6\right) \cdot \left(k_2 + k_5 \cdot V_2^\star - k_3 \cdot \frac{V_2^\star}{k_4 + V_2^\star}\right)} - \frac{\widetilde{k_1} \cdot k_8}{k_2 + k_5 \cdot V_2^\star - k_3 \cdot \frac{V_2^\star}{k_4 + V_2^\star}} + \frac{k_9}{k_{10} + V_2^\star} \tag{12}$$

and we can re-establish zeros of (12) by finding zeros of

$$0 = \frac{\widetilde{k_1} \cdot k_3 \cdot k_5 \cdot k_7 \cdot V_2^\star}{(k_3 + k_6) \cdot V_2^\star + k_4 \cdot k_6} - \widetilde{k_1} \cdot k_8 + \frac{k_9 \cdot \left(k_5 \cdot V_2^\star - \frac{k_3 \cdot V_2^\star}{V_2^\star + k_4} + k_2\right)}{V_2^\star + k_{10}} =: G\left(V_2^\star\right). \tag{13}$$

Let us define the coefficients

$$\begin{aligned}
a_3 &:= \widetilde{k_1} \cdot k_3 \cdot k_5 \cdot k_7 - \widetilde{k_1} \cdot k_3 \cdot k_8 - \widetilde{k_1} \cdot k_6 \cdot k_8 + k_3 \cdot k_5 \cdot k_9 + k_5 \cdot k_6 \cdot k_9, \\
a_2 &:= \widetilde{k_1} \cdot k_3 \cdot k_4 \cdot k_5 \cdot k_7 - \widetilde{k_1} \cdot k_3 \cdot k_4 \cdot k_8 - 2 \cdot \widetilde{k_1} \cdot k_4 \cdot k_6 \cdot k_8 - k_3^2 \cdot k_9 \\
&\quad + k_2 \cdot k_3 \cdot k_9 + k_3 \cdot k_4 \cdot k_5 \cdot k_9 + k_2 \cdot k_6 \cdot k_9 - k_3 \cdot k_6 \cdot k_9 \\
&\quad + 2 \cdot k_4 \cdot k_5 \cdot k_6 \cdot k_9 + \widetilde{k_1} \cdot k_3 \cdot k_5 \cdot k_7 \cdot k_{10} - \widetilde{k_1} \cdot k_3 \cdot k_8 \cdot k_{10} - \widetilde{k_1} \cdot k_6 \cdot k_8 \cdot k_{10}, \\
a_1 &:= -\widetilde{k_1} \cdot k_4^2 \cdot k_6 \cdot k_8 + k_2 \cdot k_3 \cdot k_4 \cdot k_9 + 2 \cdot k_2 \cdot k_4 \cdot k_6 \cdot k_9 - k_3 \cdot k_4 \cdot k_6 \cdot k_9 \\
&\quad + k_4^2 \cdot k_5 \cdot k_6 \cdot k_9 + \widetilde{k_1} \cdot k_3 \cdot k_4 \cdot k_5 \cdot k_7 \cdot k_{10} \\
&\quad - \widetilde{k_1} \cdot k_3 \cdot k_4 \cdot k_8 \cdot k_{10} - 2 \cdot \widetilde{k_1} \cdot k_4 \cdot k_6 \cdot k_8 \cdot k_{10}, \\
a_0 &:= k_2 \cdot k_4^2 \cdot k_6 \cdot k_9 - \widetilde{k_1} \cdot k_4^2 \cdot k_6 \cdot k_8 \cdot k_{10} = \widetilde{k_1} \cdot k_4 \cdot k_6 \cdot k_8 \cdot k_{10} \cdot (R_0 - 1).
\end{aligned} \tag{14}$$

Hence, finding zeros of (13) is equivalent to solving

$$a_3 \cdot (V_2^\star)^3 + a_2 \cdot (V_2^\star)^2 + a_1 \cdot V_2^\star + a_0 = 0. \tag{15}$$

Normalizing this cubic polynomial yields

$$(V_2^\star)^3 + \underbrace{\left(\frac{a_2}{a_3}\right)}_{=:A_2} \cdot (V_2^\star)^2 + \underbrace{\left(\frac{a_1}{a_3}\right)}_{=:A_1} \cdot V_2^\star + \underbrace{\left(\frac{a_0}{a_3}\right)}_{=:A_0} = 0. \tag{16}$$

This equation can be solved analytically by applying Tschirnhaus-transformation and setting

$$\begin{aligned}
A &:= 12 \cdot A_1^3 - 3 \cdot A_1^2 \cdot A_2^2 - 54 \cdot A_0 \cdot A_1 \cdot A_2 + 81 \cdot A_0^2 + 12 \cdot A_0 \cdot A_2^3, \\
B &:= \sqrt[3]{36 \cdot A_1 \cdot A_2 - 108 \cdot A_0 - 8 \cdot A_2^3 + 12 \cdot \sqrt{A}}, \\
p &:= \left(-\frac{1}{6}\right) \cdot \left(\frac{B^2 - 12 \cdot A_1 + 4 \cdot A_2^2 - 2 \cdot A_2 \cdot B}{6 \cdot B}\right),
\end{aligned}$$

$$q := \frac{A_1 \cdot A_2 \cdot B - 9 \cdot A_0 \cdot B + B \cdot \sqrt{A} + A_1 \cdot B^2}{3 \cdot B^2} + \frac{-2 \cdot A_1 \cdot A_2^2 - 18 \cdot A_0 \cdot A_2 + 2 \cdot A_2 \cdot \sqrt{A} + 12 \cdot A_1^2}{3 \cdot B^2}. \tag{17}$$

Conclusively, all solutions of (16) read

$$V_{2,1}^{\star} = \frac{B^2 - 12 \cdot A_1 + 4 \cdot A_2^2 - 2 \cdot A_2 \cdot B}{6 \cdot B},$$
$$V_{2,2}^{\star} = -\frac{p}{2} + i \cdot \sqrt{-\left(\frac{p}{2}\right)^2 + q},$$
$$V_{2,3}^{\star} = -\frac{p}{2} - i \cdot \sqrt{-\left(\frac{p}{2}\right)^2 + q}. \tag{18}$$

Since there is a complex interplay between initial values, problem parameters and stability of our possibly three computed equilibrium states, we want to provide a numerical algorithm for solving this problem. Our procedure is given in Algorithm 1.

**Algorithm 1:** Algorithmic summary for computation of all three possible equilibrium points while $R_0 > 1$ holds

1: **Inputs**
2: Define all problem constants $\widetilde{k_1}, k_j \geq 0$ for all $j \in \{2, 3, 4, 5, 6, 7, 8, 9, 10\}$
3: **Computation of helping constants**
4: Define $a_0, a_1, a_2, a_3$ as given by (14)
5: Define $A_0, A_1, A_2$ as done in (16)
6: Compute $A$, $B$, $p$, $q$ as seen in (17)
7: **Calculation of** $V_{2,1}^{\star}$, $V_{2,2}^{\star}$ and $V_{2,3}^{\star}$
8: Calculate $V_{2,1}^{\star}, V_{2,2}^{\star}, V_{2,3}^{\star}$ by (18) or apply a Newton-approach
9: **Remark:** Due to rounding errors, we need to take Remark 1 into account
10: Compute $T_{2,1}^{\star}, I_{2,1}^{\star}, T_{2,2}^{\star}, I_{2,2}^{\star}, T_{2,3}^{\star}, I_{2,3}^{\star}$ by (11)
11: **Outputs**
12: Equilibrium state vectors $\left(T_{2,1}^{\star}, I_{2,1}^{\star}, V_{2,1}^{\star}\right)^T$, $\left(T_{2,2}^{\star}, I_{2,2}^{\star}, V_{2,2}^{\star}\right)^T$ and $\left(T_{2,3}^{\star}, I_{2,3}^{\star}, V_{2,3}^{\star}\right)^T$
13: **Remark:** Rule out those equilibrium state vectors where you have at least one negative component

We want to conclude our analytical results here with this remark.

**Remark 1.** As already mentioned above, we have a complex situation in case of $R_0 > 1$. Later, we are going to demonstrate in Section 4.2 that, depending on initial values and constant problem parameters, we eventually observe different situations such as different equilibrium states or even divergence of $V(t)$ for a large initial amount of virus particles. Additionally, due to rounding errors, there might be a possibility that we obtain complex numbers for the amount of virus particles in equilibrium states. Since our cubic polynomial in (16) has only real coefficients, two complex solutions need to be complex conjugates to each other. If this is not fulfilled, we can neglect the (small) imaginary parts and can solely regard the real parts of those computation solutions. Hence, we notice at this point that further analytical investigations on the stability of these equilibrium states might be of interest for future work on this system of non-linear differential equations. This is a comparable situation to other works [15] on calcium-ion concentrations in liver cells.

### 2.6 Concluding Remark

We would like to point out that all qualitative properties of our time-continuous model are important features that should transfer to the time-discrete setting. For that reason, we note that it is always important to examine properties of the time-continuous case rigorously. Consequently, it becomes easier to build time-discrete approximations which fulfill all these requirements.

## 3 Analysis of the Time-Discrete Problem Formulation Based on a Non-Standard Finite-Difference-Method

Here, we want to consider a non-equidistant partition

$$0 = t_1 < t_2 < \ldots < t_N < t_{N+1} =: T$$

of our simulation time interval $[0, T]$ where $T > 0$ represents our final simulation time. Our non-equidistant time-step size is given by

$$h_j = t_{j+1} - t_j$$

for all $j \in \{1, 2, \ldots, N-1, N\}$. For brevity, we denote $z_j := z\left(t_j\right)$ for time-continuous functions

$$z\colon [0, T] \longrightarrow \mathbb{R}$$

at a time point $t_j$ and $z_{h,j} := z_h\left(t_j\right)$ for time-discrete functions

$$z_h\colon \left\{t_j \,|\, j \in \{1, 2, \ldots, N, N+1\}\right\} \longrightarrow \mathbb{R}$$

at a time point $t_j$ for all $j \in \{1, 2, \ldots, N, N+1\}$.

### 3.1 Time-Discrete Problem Formulation and Unique Solvability

Discretizing (2) by (3), we propose our non-standard finite-difference-method based solely on non-local approximations by

$$\begin{cases} \dfrac{T_{h,j+1} - T_{h,j}}{h_j} = k_{1,j+1} - k_2 \cdot T_{h,j+1} + k_3 \cdot \dfrac{T_{h,j} \cdot V_{h,j}}{k_4 + V_{h,j}} - k_5 \cdot T_{h,j+1} \cdot V_{h,j}, \\ \dfrac{I_{h,j+1} - I_{h,j}}{h_j} = k_5 \cdot T_{h,j+1} \cdot V_{h,j} - k_6 \cdot I_{h,j+1} - k_3 \cdot \dfrac{I_{h,j+1} \cdot V_{h,j}}{k_4 + V_{h,j}}, \\ \dfrac{V_{h,j+1} - V_{h,j}}{h_j} = k_3 \cdot k_7 \cdot \dfrac{I_{h,j+1} \cdot V_{h,j}}{k_4 + V_{h,j}} - k_8 \cdot T_{h,j+1} \cdot V_{h,j+1} + k_9 \cdot \dfrac{V_{h,j}}{k_{10} + V_{h,j}}, \\ \qquad T_{h,1} = T_0 \ , \ I_{h,1} = I_0 \ , V_{h,1} = V_0, \end{cases} \tag{19}$$

for all time indices $j \in \{1, 2, \ldots, N-1, N\}$. Let us first observe that all these difference equations in (19) can be recast in an explicit manner. We see that

$$T_{h,j+1} = \frac{T_{h,j} + h_j \cdot \left(k_{1,j+1} + k_3 \cdot \dfrac{T_{h,j} \cdot V_{h,j}}{k_4 + V_{h,j}}\right)}{\left(1 + h_j \cdot \left(k_2 + k_5 \cdot V_{h,j}\right)\right)} \tag{20}$$

holds from the first equation of (19). The second equation of (19) implies

$$I_{h,j+1} = \frac{I_{h,j} + h_j \cdot k_5 \cdot T_{h,j+1} \cdot V_{h,j}}{\left(1 + h_j \cdot \left(k_3 \cdot \dfrac{V_{h,j}}{k_4 + V_{h,j}} + k_6\right)\right)}. \tag{21}$$

From the last equation of (19), we obtain

$$V_{h,j+1} = \frac{V_{h,j} + h_j \cdot \left(k_3 \cdot k_7 \cdot \dfrac{I_{h,j+1} \cdot V_{h,j}}{k_4 + V_{h,j}} + k_9 \cdot \dfrac{V_{h,j}}{k_{10} + V_{h,j}}\right)}{\left(1 + h_j \cdot k_8 \cdot T_{h,j+1}\right)}. \tag{22}$$

Now, we summarize our solution algorithm for (19) in Algorithm 2.

**Algorithm 2:** Algorithmic summary of our suggested non-standard finite-difference-method for (19)

**Inputs**
Define the vector $\mathbf{k}_1$ for our discretization of $k_1(t)$
Define all problem constants $k_j \geq 0$ for all $j \in \{2, 3, 4, 5, 6, 7, 8, 9, 10\}$
Initialize solution vectors $\mathbf{T_h} := \mathbf{0}, \mathbf{I_h} := \mathbf{0}, \mathbf{V_h} := \mathbf{0} \in \mathbb{R}^{N+1}$
Set the final simulation time $T > 0$
Define our partition $0 := t_1 < t_2 < \ldots < t_N < t_{N+1} =: T$ in our time vector $\mathbf{t} \in \mathbb{R}^{N+1}$
Set initial conditions $\mathbf{T_{h,1}} := T_0$, $\mathbf{I_{h,1}} := I_0$ and $\mathbf{V_{h,1}} := V_0$
**Non-standard finite-difference-method**
**for** $j \in \{1, 2, \ldots, N-1, N\}$ **do**
  Define $h_n := t_{n+1} - t_n$ as our current time step size
  Compute $\mathbf{T_{h,j+1}}$ by (20)
  Calculate $\mathbf{I_{h,j+1}}$ by (21)
  Compute $\mathbf{V_{h,j+1}}$ by (22)
**end for**
**Outputs**
Our calculated vectors $\mathbf{T_h}, \mathbf{I_h}, \mathbf{V_h} \in \mathbb{R}^{N+1}$

Here, we can show the unique solvability of our Algorithm 2.

**Theorem 6.** *Our numerical solution approach in Algorithm 2 is uniquely solvable.*

**Proof.** Since our initial conditions $T_{h,1}, I_{h,1}, V_{h,1}$ are set, we notice from (20)–(22) that $T_{h,2}, I_{h,2}, V_{h,2}$ are uniquely determined as well. Let us assume that $T_{h,j}, I_{h,j}, V_{h,j}$ are known for an arbitrary $j \in \{2, \ldots, N-1, N\}$. Finally, we obtain that $T_{h,j+1}, I_{h,j+1}, V_{h,j+1}$ are uniquely solvable by (20)–(22) as well. By using induction, we conclude that our claim is proven. □

### *3.2 Non-Negativity, Boundedness of $T_h$ and $I_h$ and at Most Linear Growth of Every Component of $V_h$*

Let us first show that all solution components of Algorithm 2 stay non-negative.

**Theorem 7.** *All components of our solution vectors $\boldsymbol{T}_h, \boldsymbol{I}_h, \boldsymbol{V}_h \in \mathbb{R}^{N+1}$, calculated by Algorithm 2, remain non-negative.*

**Proof.** Our initial conditions $T_{h,1} := T_0 \geq 0$, $I_{h,1} := I_0 \geq 0$ and $V_{h,1} := V_0 \geq 0$ are non-negative by our assumptions. From (20)–(22), we can conclude that $T_{h,2} \geq 0$, $I_{h,2} \geq 0$ and $V_{h,2} \geq 0$ hold. Let us assume that $T_{h,j}$, $I_{h,j}$

and $V_{h,j}$ remain non-negative for an arbitrary $j \in \{2, 3, \ldots, N-1, N\}$. We see from (20)–(22) that $T_{h,j+1}$, $I_{h,j+1}$ and $V_{h,j+1}$ stay non-negative as well. Our claim follows from induction. □

Now, we want to prove that every component of $\mathbf{T}_h \in \mathbb{R}^{N+1}$ remains bounded.

**Theorem 8.** *It holds* $T_{h,j} \leq \max\left\{T_0\,;\,\dfrac{K_1}{k_2 - k_3}\right\} =: T_{\max}$ *for all time-discrete indices* $j \in \{1, 2, \ldots, N, N+1\}$.

**Proof.** We separate this proof into two steps. Keep in mind that $k_{1,j+1} \leq K_1$ holds for all $j \in \{0, 1, \ldots, N-1, N\}$ by assumption, $k_2 > k_3$ holds by assumption and that all solution components are non-negative by Theorem 7.

*Step 1:* Let us first consider

$$\frac{T_{h,j+1} - T_{h,j}}{h_j} = k_{1,j+1} - k_2 \cdot T_{h,j+1} + k_3 \cdot T_{h,j} \cdot \frac{V_{h,j}}{k_4 + V_{h,j}} - k_5 \cdot T_{h,j+1} \cdot V_{h,j}$$

for all $j \in \{1, 2, \ldots, N-1, N\}$. We get the estimate

$$\begin{aligned}
\frac{T_{h,j+1} - T_{h,j}}{h_j} &\leq K_1 - k_2 \cdot \left(T_{h,j+1} - T_{h,j}\right) - k_2 \cdot T_{h,j} + k_3 \cdot T_{h,j} \cdot \frac{V_{h,j}}{k_4 + V_{h,j}} \\
&\leq K_1 - k_2 \cdot \left(T_{h,j+1} - T_{h,j}\right) - k_2 \cdot T_{h,j} + k_3 \cdot T_{h,j} \\
&= K_1 - k_2 \cdot \left(T_{h,j+1} - T_{h,j}\right) - (k_2 - k_3) \cdot T_{h,j}
\end{aligned}$$

and this implies

$$T_{h,j+1} \leq T_{h,j} + \frac{h_j \cdot K_1 - h_j \cdot (k_2 - k_3) \cdot T_{h,j}}{1 + h_j \cdot k_2}. \tag{23}$$

*Step 2:* We want to prove our claim by induction. It obviously holds $T_{h,1} := T_0 \leq T_{\max}$. Let us assume that $T_{h,j} \leq T_{\max}$ holds for an arbitrary $j \in \{1, 2, \ldots, N-1, N\}$. Using (23), we obtain

$$\begin{aligned}
T_{h,j+1} &\leq T_{h,j} + \frac{h_j \cdot K_1 - h_j \cdot (k_2 - k_3) \cdot T_{h,j}}{1 + h_j \cdot k_2} \\
&\leq T_{\max} + \frac{h_j \cdot K_1 - h_j \cdot (k_2 - k_3) \cdot T_{\max}}{1 + h_j \cdot k_2} \\
&= T_{\max} + \frac{h_j \cdot K_1 - h_j \cdot (k_2 - k_3) \cdot \max\left\{T_0\,;\,\dfrac{K_1}{k_2 - k_3}\right\}}{1 + h_j \cdot k_2} \\
&\leq T_{\max}.
\end{aligned}$$

Conclusively, our upper bound $T_{h,j} \leq T_{\max}$ is valid for all $j \in \{1, 2, \ldots, N, N+1\}$ and it finishes our proof. □

Next, we want to show that every component of $\mathbf{I}_h \in \mathbb{R}^{N+1}$ stays bounded. Let us define $N_{h,j} := T_{h,j} + I_{h,j}$ for all time-discrete indices $j \in \{1, 2, \ldots, N, N+1\}$ and furthermore, we set $N_{\max} := \max\left\{T_0 + I_0\,;\,\dfrac{K_1}{\min\{k_2 - k_3\,;\,k_6\}}\right\}$.

**Theorem 9.** *It holds* $N_{h,j} \leq N_{\max}$ *for all time-discrete indices* $j \in \{1, 2, \ldots, N, N+1\}$. *Consequently, every component of* $\mathbf{I}_h \in \mathbb{R}^{N+1}$ *remains bounded.*

**Proof.** We separate this proof into two steps. Keep in mind that $k_{1,j+1} \leq K_1$ holds for all $j \in \{0, 1, \ldots, N-1, N\}$ by assumption, $k_2 > k_3$ holds by assumption and that all solution components are non-negative by Theorem 7.

*Step 1:* It holds

$$\begin{aligned}
\frac{N_{h,j+1}-N_{h,j}}{h_j} = \frac{T_{h,j+1}-T_{h,j}}{h_j} + \frac{I_{h,j+1}-I_{h,j}}{h_j} \\
&= k_{1,j+1} - k_2 \cdot T_{h,j+1} + k_3 \cdot T_{h,j} \cdot \frac{V_{h,j}}{k_4 + V_{h,j}} - k_6 \cdot I_{h,j+1} \\
&\quad - k_3 \cdot I_{h,j+1} \cdot \frac{V_{h,j}}{k_4 + V_{h,j}} \\
&\le K_1 - k_2 \cdot \left(T_{h,j+1} - T_{h,j}\right) - k_2 \cdot T_{h,j} + k_3 \cdot T_{h,j} \\
&\quad - k_6 \cdot \left(I_{h,j+1} - I_{h,j}\right) - k_6 \cdot I_{h,j} \\
&\le K_1 - \min\{k_2\,;\,k_6\} \cdot \left(T_{h,j+1} - T_{h,j} + I_{h,j+1} - I_{h,j}\right) \\
&\quad - \min\{k_2 - k_3\,;\,k_6\} \cdot \left(T_{h,j} + I_{h,j}\right) \\
&= K_1 - \min\{k_2\,;\,k_6\} \cdot \left(N_{h,j+1} - N_{h,j}\right) - \min\{k_2 - k_3\,;\,k_6\} \cdot N_{h,j}
\end{aligned}$$

for all time-discrete indices $j \in \{1, 2, \ldots, N-1, N\}$. This implies

$$N_{h,j+1} \le N_{h,j} + \frac{h_j \cdot \left(K_1 - \min\{k_2 - k_3\,;\,k_6\} \cdot N_{h,j}\right)}{1 + h_j \cdot \min\{k_2\,;\,k_6\}} \tag{24}$$

for all $j \in \{1, 2, \ldots, N-1, N\}$.

*Step 2:* We want to prove our claim by induction. It obviously holds $N_{h,1} := T_0 + I_0 \le N_{\max}$. Let us assume that $N_{h,j} \le N_{\max}$ holds for an arbitrary $j \in \{1, 2, \ldots, N-1, N\}$. Using (24), we obtain

$$\begin{aligned}
N_{h,j+1} &\le N_{h,j} + \frac{h_j \cdot \left(K_1 - \min\{k_2 - k_3\,;\,k_6\} \cdot N_{h,j}\right)}{1 + h_j \cdot \min\{k_2\,;\,k_6\}} \\
&\le N_{\max} + \frac{h_j \cdot (K_1 - \min\{k_2 - k_3\,;\,k_6\} \cdot N_{\max})}{1 + h_j \cdot \min\{k_2\,;\,k_6\}} \\
&= N_{\max} + \frac{h_j \cdot \left(K_1 - \min\{k_2 - k_3\,;\,k_6\} \cdot \max\left\{T_0 + I_0\,;\,\frac{K_1}{\min\{k_2 - k_3\,;\,k_6\}}\right\}\right)}{1 + h_j \cdot \min\{k_2\,;\,k_6\}} \\
&\le N_{\max}.
\end{aligned}$$

Conclusively, our upper bound $N_{h,j} \le N_{\max}$ is valid for all $j \in \{1, 2, \ldots, N, N+1\}$ and it finishes our proof because of $N_{h,j} := T_{h,j} + I_{h,j}$ for all $j \in \{1, 2, \ldots, N, N+1\}$ and non-negativity of all solution components. □

Finally, we show that every component of $\mathbf{V}_h \in \mathbb{R}^{N+1}$ grows at most linearly in time.

**Theorem 10.** *It holds* $V_{h,j} \le V_0 + \left(k_3 \cdot k_7 \cdot N_{\max} + k_9\right) \cdot t_j$ *for all time-discrete indices* $j \in \{1, 2, \ldots, N, N+1\}$.

**Proof.** We observe that

$$\begin{aligned}
\frac{V_{h,j+1} - V_{h,j}}{h_j} &= k_3 \cdot k_7 \cdot \frac{I_{h,j+1} \cdot V_{h,j}}{k_4 + V_{h,j}} - k_8 \cdot T_{h,j+1} \cdot V_{h,j+1} + k_9 \cdot \frac{V_{h,j}}{k_{10} + V_{h,j}} \\
&\le k_3 \cdot k_7 \cdot N_{\max} + k_9
\end{aligned}$$

holds for an arbitrary $j \in \{1, 2, \ldots, N-1, N\}$ which implies

$$V_{h,j+1} \le V_{h,j} + h_j \cdot (k_3 \cdot k_7 \cdot N_{\max} + k_9)$$

for an arbitrary time-discrete index $j \in \{1, 2, \ldots, N-1, N\}$ as well.

Now, we want to show our claim by induction. For $j = 1$, it obviously holds

$$\begin{aligned} V_{h,1} &= V_0 \\ &\le V_0 + \left(k_3 \cdot k_7 \cdot N_{\max} + k_9\right) \cdot t_1. \end{aligned}$$

Let us now assume that

$$V_{h,j} \le V_0 + \left(k_3 \cdot k_7 \cdot N_{\max} + k_9\right) \cdot t_j$$

holds for an arbitrary $j \in \{1, 2, \ldots, N-1, N\}$. It follows

$$\begin{aligned} V_{h,j+1} &\le V_{h,j} + h_j \cdot (k_3 \cdot k_7 \cdot N_{\max} + k_9) \\ &\le V_0 + \left(k_3 \cdot k_7 \cdot N_{\max} + k_9\right) \cdot t_j + h_j \cdot \left(k_3 \cdot k_7 \cdot N_{\max} + k_9\right) \\ &= V_0 + \left(k_3 \cdot k_7 \cdot N_{\max} + k_9\right) \cdot \left(t_j + h_j\right) \\ &= V_0 + \left(k_3 \cdot k_7 \cdot N_{\max} + k_9\right) \cdot t_{j+1} \end{aligned}$$

which finishes our claim's proof. □

### *3.3 Equilibrium States*

For simplicity of presentation, let us assume that $k_1(t) = \widetilde{k_1}$ holds for all $t \ge 0$. At first, we want to reformulate (20)–(22). We first observe that

$$\begin{aligned} T_{h,j+1} &= \frac{T_{h,j} + h_j \cdot \left(\widetilde{k_1} + k_3 \cdot \dfrac{T_{h,j} \cdot V_{h,j}}{k_4 + V_{h,j}}\right)}{1 + h_j \cdot k_2 + h_j \cdot k_5 \cdot V_{h,j}} \\ &= T_{h,j} + \frac{h_j \cdot \left(\widetilde{k_1} - k_2 \cdot T_{h,j} + k_3 \cdot \dfrac{T_{h,j} \cdot V_{h,j}}{k_4 + V_{h,j}} - k_5 \cdot T_{h,j} \cdot V_{h,j}\right)}{1 + h_j \cdot k_2 + h_j \cdot k_5 \cdot V_{h,j}} \end{aligned} \tag{25}$$

holds. Furthermore, we notice that

$$\begin{aligned} I_{h,j+1} &= \frac{I_{h,j} + h_j \cdot k_5 \cdot T_{h,j+1} \cdot V_{h,j}}{1 + h_j \cdot k_3 \cdot \dfrac{V_{h,j}}{k_4 + V_{h,j}} + h_j \cdot k_6} \\ &= I_{h,j} + \frac{h_j \cdot \left(k_5 \cdot T_{h,j} \cdot V_{h,j} - k_3 \cdot \dfrac{I_{h,j} \cdot V_{h,j}}{k_4 + V_{h,j}} - k_6 \cdot I_{h,j}\right)}{1 + h_j \cdot k_3 \cdot \dfrac{V_{h,j}}{k_4 + V_{h,j}} + h_j \cdot k_6} \end{aligned}$$

$$+\frac{h_j^2\cdot k_5\cdot V_{h,j}\cdot\left(\widetilde{k}_1-k_2\cdot T_{h,j}+k_3\cdot\dfrac{T_{h,j}\cdot V_{h,j}}{k_4+V_{h,j}}-k_5\cdot T_{h,j}\cdot V_{h,j}\right)}{\left(1+h_j\cdot k_2+h_j\cdot k_5\cdot V_{h,j}\right)\cdot\left(1+h_j\cdot k_3\cdot\dfrac{V_{h,j}}{k_4+V_{h,j}}+h_j\cdot k_6\right)} \tag{26}$$

is valid by using (25). By applying (25) and (26), we obtain

$$\begin{aligned}
V_{h,j+1} &= \frac{V_{h,j}+h_j\cdot\left(k_3\cdot k_7\cdot I_{h,j+1}\cdot\dfrac{V_{h,j}}{k_4+V_{h,j}}+k_9\cdot\dfrac{V_{h,j}}{k_{10}+V_{h,j}}\right)}{1+h_j\cdot k_8\cdot T_{h,j+1}}\\
&= V_{h,j}+\frac{h_j\cdot\left(k_3\cdot k_7\cdot I_{h,j}\cdot\dfrac{V_{h,j}}{k_4+V_{h,j}}-k_8\cdot T_{h,j}\cdot V_{h,j}+k_9\cdot\dfrac{V_{h,j}}{k_{10}+V_{h,j}}\right)}{1+h_j\cdot k_8\cdot T_{h,j+1}}\\
&+\frac{h_j^2\cdot k_3\cdot k_7\cdot\left(k_5\cdot T_{h,j}\cdot V_{h,j}-k_3\cdot\dfrac{I_{h,j}\cdot V_{h,j}}{k_4+V_{h,j}}-k_6\cdot I_{h,j}\right)\cdot\dfrac{V_{h,j}}{k_4+V_{h,j}}}{\left(1+h_j\cdot k_3\cdot\dfrac{V_{h,j}}{k_4+V_{h,j}}+h_j\cdot k_6\right)\cdot\left(1+h_j\cdot k_8\cdot T_{h,j+1}\right)}\\
&+\frac{h_j^3\cdot k_3\cdot k_5\cdot k_7\cdot\left(\widetilde{k}_1-k_2\cdot T_{h,j}+k_3\cdot\dfrac{T_{h,j}\cdot V_{h,j}}{k_4+V_{h,j}}-k_5\cdot T_{h,j}\cdot V_{h,j}\right)\cdot V_{h,j}}{\left(1+h_j\cdot k_2+h_j\cdot k_5\cdot V_{h,j}\right)\cdot\left(1+h_j\cdot\dfrac{k_3\cdot V_{h,j}}{k_4+V_{h,j}}+h_j\cdot k_6\right)\cdot\left(1+h_j\cdot k_8\cdot T_{h,j+1}\right)}\\
&-\frac{h_j^2\cdot k_8\cdot\left(\widetilde{k}_1-k_2\cdot T_{h,j}+k_3\cdot\dfrac{T_{h,j}\cdot V_{h,j}}{k_4+V_{h,j}}-k_5\cdot T_{h,j}\cdot V_{h,j}\right)\cdot V_{h,j}}{\left(1+h_j\cdot k_2+h_j\cdot k_5\cdot V_{h,j}\right)\cdot\left(1+h_j\cdot k_8\cdot T_{h,j+1}\right)}.
\end{aligned} \tag{27}$$

Hence, comparing (7) and (25)–(27), we conclude that our proposed non-standard finite-difference-method possesses the same equilibrium states as the time-continuous model (2).

### *3.4 Convergence towards the Time-Continuous Problem Solution*

To finish our theoretical observations of Algorithm 2, we show that it converges linearly towards the time-continuous solution of model (2). To begin with, we summarize all our assumptions for linear convergence of our time-discrete solution components of Algorithm 2 towards the time-continuous solution components of model (2).

(A1) We consider the time interval $\left[0,\widetilde{T}\right]$ with partition

$$0=t_1<t_2<t_3<\ldots<t_N<t_{N+1}=\widetilde{T};$$

(A2) Initial conditions of the time-continuous and the time-discrete problems coincide;

(A3) The time-continuous rate function $k_1:\left[0,\widetilde{T}\right]\longrightarrow\left[0,K_1\right]$ should be continuously differentiable;

(A4) Time-continuous solution components $T,I,V:\left[0,\widetilde{T}\right]\longrightarrow[0,\infty)$ should be twice continuously differentiable;

(A5) Set $\Delta_{\min}:=\min\limits_{p\in\{1,\ldots,N+1\}}h_p$ and $\Delta_{\max}:=\max\limits_{p\in\{1,\ldots,N+1\}}h_p$.

**Theorem 11.** *Let all aforementioned assumptions (A1)–(A5) be fulfilled. Then the time-discrete solution components converge linearly towards the time-continuous solution components if* $\Delta_{\max} \to 0$.

**Proof.** We briefly outline our proof plan because it is relatively technical. First, let us assume that all time-continuous solution components coincide with all time-discrete solution components at a certain time point $t_p \in \left[0, \widetilde{T}\right]$ for an arbitrary $p \in \{1, 2, \ldots, N-1, N\}$. Our starting step is to examine local error propagation to a time point $t_{p+1} \in \left[0, \widetilde{T}\right]$. Afterward, we investigate error propagation in time and conclusively, and we inspect the accumulation of these errors. We remind ourselves that time-continuous solutions are, for example, denoted by $T\left(t_p\right)$ and time-discrete solution, for example, by $T_{h,p}$ at a time point $t_p \in \left[0, \widetilde{T}\right]$.

1. For local error propagation, we assume that

$$\left(t_p, T_{h,p}\right) = \left(t_p, T\left(t_p\right)\right) \; ; \; \left(t_p, I_{h,p}\right) = \left(t_p, I\left(t_p\right)\right) \text{ and } \left(t_p, V_{h,p}\right) = \left(t_p, V\left(t_p\right)\right)$$

hold for an arbitrary $p \in \{1, 2, \ldots, N-1, N\}$ on the time interval $\left[t_p, t_{p+1}\right]$. Here, we want to apply our relations (25)–(27) where $\widetilde{k_1}$ is replaced by our time-continuous rate function $k_{1,p+1}$ evaluated at the time point $t_{p+1}$. Since we only consider one-time step, we denote the corresponding time-discrete solution components by $\widetilde{T_{h,p+1}}$, $\widetilde{I_{h,p+1}}$ and $\widetilde{V_{h,p+1}}$.

1.1. We see that

$$\begin{aligned}
\widetilde{T_{h,p+1}} &= T_{h,p} + \frac{h_p \cdot \left(k_{1,p+1} - k_2 \cdot T_{h,p} + k_3 \cdot \dfrac{T_{h,p} \cdot V_{h,p}}{k_4 + V_{h,p}} - k_5 \cdot T_{h,p} \cdot V_{h,p}\right)}{1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V_{h,p}} \\
&= T\left(t_p\right) + \frac{h_p \cdot \left(k_1\left(t_{p+1}\right) - k_2 \cdot T\left(t_p\right) + \dfrac{k_3 \cdot T\left(t_p\right) \cdot V\left(t_p\right)}{k_4 + V\left(t_p\right)} - k_5 \cdot T\left(t_p\right) \cdot V\left(t_p\right)\right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right)}
\end{aligned}$$

is valid. Additionally, we observe that

$$\begin{aligned}
&\left|T\left(t_{p+1}\right) - \widetilde{T_{h,p+1}}\right| \\
&\leq \underbrace{\left|T\left(t_{p+1}\right) - T\left(t_p\right) - h_p \cdot T'\left(t_p\right)\right|}_{=:I_{T,1}} \\
&\quad + \underbrace{\left|h_p \cdot T'\left(t_p\right) - \frac{h_p \cdot \left(k_1\left(t_{p+1}\right) - k_2 \cdot T\left(t_p\right) + \dfrac{k_3 \cdot T\left(t_p\right) \cdot V\left(t_p\right)}{k_4 + V\left(t_p\right)} - k_5 \cdot T\left(t_p\right) \cdot V\left(t_p\right)\right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right)}\right|}_{=:II_{T,2}} \\
&=: I_{T,1} + II_{T,2}
\end{aligned}$$

holds. Application of the mean value theorem yields

$$\begin{aligned}
I_{T,1} &:= \left|T\left(t_{p+1}\right) - T\left(t_p\right) - h_p \cdot T'\left(t_p\right)\right| \\
&= \left|\int_{t_p}^{t_{p+1}} T'(\tau) - T'\left(t_p\right) \, \mathrm{d}\tau\right|
\end{aligned}$$

$$= \left| \int_{t_p}^{t_{p+1}} \frac{T'(\tau) - T'(t_p)}{\tau - t_p} \cdot (\tau - t_p) \, \mathrm{d}\tau \right|$$
$$\leq \frac{1}{2} \cdot h_p^2 \cdot \|T''(t)\|_\infty .$$

Another application of the mean value theorem implies

$$II_{T,2} := \left| h_p \cdot T'(t_p) - \frac{h_p \cdot \left( k_1(t_{p+1}) - k_2 \cdot T(t_p) + \frac{k_3 \cdot T(t_p) \cdot V(t_p)}{k_4 + V(t_p)} - k_5 \cdot T(t_p) \cdot V(t_p) \right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V(t_p)\right)} \right|$$
$$= \left| \frac{h_p \cdot \left( \left( k_1(t_p) - k_1(t_{p+1}) \right) + \left( h_p \cdot k_2 + h_p \cdot k_5 \cdot V(t_p) \right) \cdot T'(t_p) \right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V(t_p)\right)} \right|$$
$$\leq h_p^2 \cdot \|k_1'(t)\|_\infty + h_p^2 \cdot (k_2 + k_5 \cdot \|V(t)\|_\infty) \cdot \|T'(t)\|_\infty .$$

After defining our constant

$$C_{\mathrm{loc},T} := \frac{1}{2} \cdot \|T''(t)\|_\infty + \|k_1'(t)\|_\infty + (k_2 + k_5 \cdot \|V(t)\|_\infty) \cdot \|T'(t)\|_\infty ,$$

we obtain

$$\left| T(t_{p+1}) - \widetilde{T_{h,p+1}} \right| \leq C_{\mathrm{loc},T} \cdot h_p^2. \tag{28}$$

1.2. We see that

$$\widetilde{I_{h,p+1}} = I(t_p) + \frac{h_p \cdot \left( k_5 \cdot T(t_p) \cdot V(t_p) - k_3 \cdot \frac{I(t_p) \cdot V(t_p)}{k_4 + V(t_p)} - k_6 \cdot I(t_p) \right)}{1 + h_p \cdot k_3 \cdot \frac{V(t_p)}{k_4 + V(t_p)} + h_p \cdot k_6}$$
$$+ \frac{h_p^2 \cdot k_5 \cdot V(t_p) \cdot \left( k_1(t_{p+1}) - k_2 \cdot T(t_p) + k_3 \cdot \frac{T(t_p) \cdot V(t_p)}{k_4 + V(t_p)} - k_5 \cdot T(t_p) \cdot V(t_p) \right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V(t_p)\right) \cdot \left( 1 + h_p \cdot k_3 \cdot \frac{V(t_p)}{k_4 + V(t_p)} + h_p \cdot k_6 \right)}$$

is valid. This implies

$$\left| I(t_{p+1}) - \widetilde{I_{h,p+1}} \right|$$
$$\leq \underbrace{\left| I(t_{p+1}) - I(t_p) - h_p \cdot I'(t_p) \right|}_{=:I_{I,1}}$$

$$+\underbrace{\left|h_p \cdot I'\left(t_p\right) - \frac{h_p \cdot \left(k_5 \cdot T\left(t_p\right) \cdot V\left(t_p\right) - k_3 \cdot \frac{I\left(t_p\right) \cdot V\left(t_p\right)}{k_4 + V\left(t_p\right)} - k_6 \cdot I\left(t_p\right)\right)}{1 + h_p \cdot k_3 \cdot \frac{V\left(t_p\right)}{k_4 + V\left(t_p\right)} + h_p \cdot k_6}\right|}_{=:II_{I,2}}$$

$$+\underbrace{\left|\frac{h_p^2 \cdot k_5 \cdot V\left(t_p\right) \cdot \left(k_1\left(t_{p+1}\right) - k_2 \cdot T\left(t_p\right) + k_3 \cdot \frac{T\left(t_p\right) \cdot V\left(t_p\right)}{k_4 + V\left(t_p\right)} - k_5 \cdot T\left(t_p\right) \cdot V\left(t_p\right)\right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right) \cdot \left(1 + h_p \cdot k_3 \cdot \frac{V\left(t_p\right)}{k_4 + V\left(t_p\right)} + h_p \cdot k_6\right)}\right|}_{=:III_{I,3}}.$$

By similar argument as before, we obtain

$$I_{I,1} \leq \frac{1}{2} \cdot h_p^2 \cdot \|I''(t)\|_\infty,$$

$$\begin{aligned}
II_{I,2} &= \left|h_p \cdot I'\left(t_p\right) - \frac{h_p \cdot \left(k_5 \cdot T\left(t_p\right) \cdot V\left(t_p\right) - k_3 \cdot \frac{I\left(t_p\right) \cdot V\left(t_p\right)}{k_4 + V\left(t_p\right)} - k_6 \cdot I\left(t_p\right)\right)}{1 + h_p \cdot k_3 \cdot \frac{V\left(t_p\right)}{k_4 + V\left(t_p\right)} + h_p \cdot k_6}\right| \\
&= h_p \cdot \left|\frac{h_p \cdot \left(k_3 \cdot \frac{V\left(t_p\right)}{k_4 + V\left(t_p\right)} + k_6\right) \cdot I'\left(t_p\right)}{1 + h_p \cdot k_3 \cdot \frac{V\left(t_p\right)}{k_4 + V\left(t_p\right)} + h_p \cdot k_6}\right| \\
&\leq h_p^2 \cdot (k_3 + k_6) \cdot \|I'(t)\|_\infty
\end{aligned}$$

and

$$\begin{aligned}
III_{I,3} &= \left|\frac{h_p^2 \cdot k_5 \cdot V\left(t_p\right) \cdot \left(k_1\left(t_{p+1}\right) - k_2 \cdot T\left(t_p\right) + k_3 \cdot \frac{T\left(t_p\right) \cdot V\left(t_p\right)}{k_4 + V\left(t_p\right)} - k_5 \cdot T\left(t_p\right) \cdot V\left(t_p\right)\right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right) \cdot \left(1 + h_p \cdot k_3 \cdot \frac{V\left(t_p\right)}{k_4 + V\left(t_p\right)} + h_p \cdot k_6\right)}\right| \\
&\leq h_p^2 \cdot k_5 \cdot \|V(t)\|_\infty \cdot \left(\|k_1(t)\|_\infty + (k_2 + k_3 + k_5) \cdot \|T(t)\|_\infty\right).
\end{aligned}$$

By defining the constant

$$\begin{aligned}
C_{\mathrm{loc},I} &:= \frac{1}{2} \cdot \|I''(t)\|_\infty + (k_3 + k_6) \cdot \|I'(t)\|_\infty \\
&\quad + k_5 \cdot \|V(t)\|_\infty \cdot \left(\|k_1(t)\|_\infty + (k_2 + k_3 + k_5) \cdot \|T(t)\|_\infty\right),
\end{aligned}$$

we conclude

$$\left|I\left(t_{p+1}\right)-\widetilde{I_{h,p+1}}\right| \leq C_{\mathrm{loc},I}\cdot h_p^2. \tag{29}$$

1.3. It holds

$$\begin{aligned}
\widetilde{V_{h,p+1}} = V\left(t_p\right) &+ \frac{h_p\cdot\left(k_3\cdot k_7\cdot I\left(t_p\right)\cdot\dfrac{V\left(t_p\right)}{k_4+V\left(t_p\right)}-k_8\cdot T\left(t_p\right)\cdot V\left(t_p\right)+k_9\cdot\dfrac{V\left(t_p\right)}{k_{10}+V\left(t_p\right)}\right)}{1+h_p\cdot k_8\cdot\widetilde{T_{h,p+1}}} \\
&+ \frac{h_p^2\cdot k_3\cdot k_7\cdot\left(k_5\cdot T\left(t_p\right)\cdot V\left(t_p\right)-k_3\cdot\dfrac{I\left(t_p\right)\cdot V\left(t_p\right)}{k_4+V\left(t_p\right)}-k_6\cdot I\left(t_p\right)\right)\cdot\dfrac{V\left(t_p\right)}{k_4+V\left(t_p\right)}}{\left(1+h_p\cdot k_3\cdot\dfrac{V\left(t_p\right)}{k_4+V\left(t_p\right)}+h_p\cdot k_6\right)\cdot\left(1+h_p\cdot k_8\cdot\widetilde{T_{h,p+1}}\right)} \\
&+ \frac{h_p^3\cdot k_3\cdot k_5\cdot k_7\cdot\left(k_1\left(t_{p+1}\right)-k_2\cdot T\left(t_p\right)+k_3\cdot\dfrac{T\left(t_p\right)\cdot V\left(t_p\right)}{k_4+V\left(t_p\right)}-k_5\cdot T\left(t_p\right)\cdot V\left(t_p\right)\right)\cdot V\left(t_p\right)}{\left(1+h_p\cdot k_2+h_p\cdot k_5\cdot V\left(t_p\right)\right)\cdot\left(1+h_p\cdot\dfrac{k_3\cdot V\left(t_p\right)}{k_4+V\left(t_p\right)}+h_p\cdot k_6\right)\cdot\left(1+h_p\cdot k_8\cdot\widetilde{T_{h,p+1}}\right)} \\
&- \frac{h_p^2\cdot k_8\cdot\left(k_1\left(t_{p+1}\right)-k_2\cdot T\left(t_p\right)+k_3\cdot\dfrac{T\left(t_p\right)\cdot V\left(t_p\right)}{k_4+V\left(t_p\right)}-k_5\cdot T\left(t_p\right)\cdot V\left(t_p\right)\right)\cdot V\left(t_p\right)}{\left(1+h_p\cdot k_2+h_p\cdot k_5\cdot V\left(t_p\right)\right)\cdot\left(1+h_p\cdot k_8\cdot\widetilde{T_{h,p+1}}\right)}.
\end{aligned}$$

Furthermore, we obtain

$$\begin{aligned}
&\left|V\left(t_{p+1}\right)-\widetilde{V_{h,p+1}}\right| \\
&\quad\leq \underbrace{\left|V\left(t_{p+1}\right)-V\left(t_p\right)-h_p\cdot V'\left(t_p\right)\right|}_{=:I_{V,1}} \\
&\quad+ \underbrace{\left|h_p\cdot V'\left(t_p\right)-\frac{h_p\cdot\left(k_3\cdot k_7\cdot I\left(t_p\right)\cdot\dfrac{V\left(t_p\right)}{k_4+V\left(t_p\right)}-k_8\cdot T\left(t_p\right)\cdot V\left(t_p\right)+k_9\cdot\dfrac{V\left(t_p\right)}{k_{10}+V\left(t_p\right)}\right)}{1+h_p\cdot k_8\cdot\widetilde{T_{h,p+1}}}\right|}_{=:II_{V,2}} \\
&\quad+ \underbrace{\left|\frac{h_p^2\cdot k_3\cdot k_7\cdot\left(k_5\cdot T\left(t_p\right)\cdot V\left(t_p\right)-k_3\cdot\dfrac{I\left(t_p\right)\cdot V\left(t_p\right)}{k_4+V\left(t_p\right)}-k_6\cdot I\left(t_p\right)\right)\cdot\dfrac{V\left(t_p\right)}{k_4+V\left(t_p\right)}}{\left(1+h_p\cdot k_3\cdot\dfrac{V\left(t_p\right)}{k_4+V\left(t_p\right)}+h_p\cdot k_6\right)\cdot\left(1+h_p\cdot k_8\cdot\widetilde{T_{h,p+1}}\right)}\right|}_{=:III_{V,3}}
\end{aligned}$$

$$+\underbrace{\left|\frac{h_p^3\cdot k_3\cdot k_5\cdot k_7\cdot\left(k_1\left(t_{p+1}\right)-k_2\cdot T\left(t_p\right)+k_3\cdot\dfrac{T\left(t_p\right)\cdot V\left(t_p\right)}{k_4+V\left(t_p\right)}-k_5\cdot T\left(t_p\right)\cdot V\left(t_p\right)\right)\cdot V\left(t_p\right)}{\left(1+h_p\cdot k_2+h_p\cdot k_5\cdot V\left(t_p\right)\right)\cdot\left(1+h_p\cdot\dfrac{k_3\cdot V\left(t_p\right)}{k_4+V\left(t_p\right)}+h_p\cdot k_6\right)\cdot\left(1+h_p\cdot k_8\cdot\widetilde{T_{h,p+1}}\right)}\right|}_{=:III_{V,4}}$$

$$+\underbrace{\left|\frac{h_p^2\cdot k_8\cdot\left(k_1\left(t_{p+1}\right)-k_2\cdot T\left(t_p\right)+k_3\cdot\dfrac{T\left(t_p\right)\cdot V\left(t_p\right)}{k_4+V\left(t_p\right)}-k_5\cdot T\left(t_p\right)\cdot V\left(t_p\right)\right)\cdot V\left(t_p\right)}{\left(1+h_p\cdot k_2+h_p\cdot k_5\cdot V\left(t_p\right)\right)\cdot\left(1+h_p\cdot k_8\cdot\widetilde{T_{h,p+1}}\right)}\right|}_{=:III_{V,5}}.$$

By similar arguments as before, we get the estimates

$$\begin{aligned}
I_{V,1} &\le \frac{1}{2}\cdot h_p^2\cdot\left\|I''(t)\right\|_\infty,\\
II_{V,2} &\le \left|\frac{h_p^2\cdot k_8\cdot V'\left(t_p\right)\cdot\widetilde{T_{h,p+1}}}{1+h_p\cdot k_8\cdot\widetilde{T_{h,p+1}}}\right|\\
&\le h_p^2\cdot k_8\cdot\left\|V'(t)\right\|_\infty\cdot T_{\max},\\
III_{V,3} &\le h_p^2\cdot k_3\cdot k_7\cdot\left\|I'(t)\right\|_\infty,\\
IV_{V,4} &\le h_p^2\cdot k_3\cdot k_5\cdot k_7\cdot\left(h_p^2\cdot\left\|k_1'(t)\right\|_\infty+h_p\cdot\left\|T'(t)\right\|_\infty\right)\cdot\left\|V(t)\right\|_\infty
\end{aligned}$$

and

$$V_{V,5}\le h_p^2\cdot k_8\cdot\left(h_p\cdot\left\|k_1'(t)\right\|_\infty+\left\|T'(t)\right\|_\infty\right)\cdot\left\|V(t)\right\|_\infty.$$

Defining the constant

$$\begin{aligned}
C_{\mathrm{loc},V} := {}&\frac{1}{2}\cdot\left\|I''(t)\right\|_\infty+k_8\cdot\left\|V'(t)\right\|_\infty\cdot T_{\max}+k_3\cdot k_7\cdot\left\|I'(t)\right\|_\infty\\
&+k_3\cdot k_5\cdot k_7\cdot\left(h_p^2\cdot\left\|k_1'(t)\right\|_\infty+h_p\cdot\left\|T'(t)\right\|_\infty\right)\cdot\left\|V(t)\right\|_\infty\\
&+k_8\cdot\left(h_p\cdot\left\|k_1'(t)\right\|_\infty+\left\|T'(t)\right\|_\infty\right)\cdot\left\|V(t)\right\|_\infty,
\end{aligned}$$

we obtain

$$\left|V\left(t_{p+1}\right)-\widetilde{V_{h,p+1}}\right|\le C_{\mathrm{loc},V}\cdot h_p^2. \tag{30}$$

2. In general, the points $\left(t_p,T_{h,p}\right)$, $\left(t_p,I_{h,p}\right)$ and $\left(t_p,V_{h,p}\right)$ do not exactly lie on the graph of the time-continuous solution components. For that reason, we have to examine how procedural errors such as $\left|T_{h,p}-T\left(t_p\right)\right|$, $\left|I_{h,p}-I\left(t_p\right)\right|$ and $\left|V_{h,p}-V\left(T_p\right)\right|$ propagate to the $(p+1)$-th time step. Furthermore, we define

$$T_{\max,T,c}:=\left\|T(t)\right\|_\infty\ ;\ I_{\max,I,c}:=\left\|I(t)\right\|_\infty\text{ and }V_{\max,V,c}:=\left\|V(t)\right\|_\infty$$

by boundedness of all time-continuous solution components on our simulation interval $\left[0,\widetilde{T}\right]$ and

$T_{\max,T,d} := \max_{p\in\mathbb{N}} \left|T_{h,p}\right|$ ; $I_{\max,I,d} := \max_{p\in\mathbb{N}} \left|I_{h,p}\right|$ and $V_{\max,V,d} := \max_{p\in\mathbb{N}} \left|V_{h,p}\right|$

by boundedness of all time-discrete solution components for all $p \in \{1,2,\ldots,N+1\}$ on our simulation interval $\left[0,\widetilde{T}\right]$. In addition to that, we define the norms

$$E_{p+1} := \max\left\{\left|T_{h,p+1} - \widetilde{T_{h,p+1}}\right| ; \left|I_{h,p+1} - \widetilde{I_{h,p+1}}\right| ; \left|V_{h,p+1} - \widetilde{V_{h,p+1}}\right|\right\}$$

for all $p \in \{0,1,\ldots,N\}$,

$$F_p := \max\left\{\left|T_{h,p} - T\left(t_p\right)\right| ; \left|I_{h,p} - I\left(t_p\right)\right| ; \left|V_{h,p} - V\left(t_p\right)\right|\right\}$$

and

$$G_p := \max\left\{\left|T\left(t_p\right) - \widetilde{T_{h,p}}\right| ; \left|I\left(t_p\right) - \widetilde{I_{h,p}}\right| ; \left|V\left(t_p\right) - \widetilde{V_{h,p}}\right|\right\}$$

for all $p \in \{1,2,\ldots,N+1\}$.

2.1. We see that

$$\begin{aligned}
&\left|T_{h,p+1} - \widetilde{T_{h,p+1}}\right| \\
&= \left| T_{h,p} + \frac{h_p \cdot \left(k_{1,p+1} - k_2 \cdot T_{h,p} + k_3 \cdot \dfrac{T_{h,p} \cdot V_{h,p}}{k_4 + V_{h,p}} - k_5 \cdot T_{h,p} \cdot V_{h,p}\right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V_{h,p}\right)} \right. \\
&\quad \left. - T\left(t_p\right) - \frac{h_p \cdot \left(k_{1,p+1} - k_2 \cdot T\left(t_p\right) + k_3 \cdot \dfrac{T\left(t_p\right) \cdot V\left(t_p\right)}{k_4 + V\left(t_p\right)} - k_5 \cdot T\left(t_p\right) \cdot V\left(t_p\right)\right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right)} \right| \\
&\le \left|T_{h,p} - T\left(t_p\right)\right| \\
&\quad + h_p \cdot \underbrace{\left| \frac{k_{1,p+1} \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right) - k_{1,p+1} \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V_{h,p}\right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V_{h,p}\right) \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right)} \right|}_{=:I_{T,A}} \\
&\quad + h_p \cdot \underbrace{\left| \frac{k_2 \cdot T_{h,p} \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right) - k_2 \cdot T\left(t_p\right) \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V_{h,p}\right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V_{h,p}\right) \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right)} \right|}_{=:II_{T,A}} \\
&\quad + h_p \cdot \left| \frac{\dfrac{k_3 \cdot T_{h,p} \cdot V_{h,p}}{k_4 + V_{h,p}} \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V_{h,p}\right) \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right)} \right.
\end{aligned}$$

$$
\left. - \frac{\frac{k_3 \cdot T\left(t_p\right) \cdot V\left(t_p\right)}{k_4 + V\left(t_p\right)} \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V_{h,p}\right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V_{h,p}\right) \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right)} \right|
$$

$$
+ h_p \cdot \underbrace{\left| \frac{k_5 \cdot T_{h,p} \cdot V_{h,p} \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right) - k_5 \cdot T\left(t_p\right) \cdot V\left(t_p\right) \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V_{h,p}\right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V_{h,p}\right) \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right)} \right|}_{=:IV_{T,A}}
$$

is valid and $III_{T,A}$ is defined as the remaining summand which is multiplied with $h_p$. Consequently, we obtain the estimates

$$
\begin{aligned}
I_{T,A} &\leq h_p \cdot k_5 \cdot \left\|k_1(t)\right\|_\infty \cdot \left|V_{h,p} - V\left(t_p\right)\right| \\
&\leq h_p \cdot k_5 \cdot \left\|k_1(t)\right\|_\infty \cdot F_p; \\
II_{T,A} &\leq h_p \cdot k_2 \cdot \left(1 + h_p \cdot k_2\right) \cdot \left|T_{h,p} - T\left(t_p\right)\right| + h_p \cdot k_2 \cdot k_5 \cdot \left|T_{h,p} \cdot V\left(t_p\right) - T\left(t_p\right) \cdot V_{h,p}\right| \\
&\leq h_p \cdot k_2 \cdot \left(1 + h_p \cdot k_2\right) \cdot F_p + h_p \cdot k_2 \cdot k_5 \cdot \left|T_{h,p} - T\left(t_p\right)\right| \cdot \left|V\left(t_p\right)\right| \\
&\quad + h_p \cdot k_2 \cdot k_5 \cdot \left|V_{h,p} - V\left(t_p\right)\right| \cdot \left|T\left(t_p\right)\right| \\
&\leq h_p \cdot k_2 \cdot \left(1 + h_p \cdot k_2\right) \cdot F_p + h_p \cdot k_2 \cdot k_5 \cdot V_{\max,V,c} \cdot F_p \\
&\quad + h_p \cdot k_2 \cdot k_5 \cdot T_{\max,T,c} \cdot F_p; \\
III_{T,A} &:= \left| \frac{\frac{k_3 \cdot T_{h,p} \cdot V_{h,p}}{k_4 + V_{h,p}} \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V_{h,p}\right) \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right)} \right. \\
&\quad \left. - \frac{\frac{k_3 \cdot T\left(t_p\right) \cdot V\left(t_p\right)}{k_4 + V\left(t_p\right)} \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V_{h,p}\right)}{\left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V_{h,p}\right) \cdot \left(1 + h_p \cdot k_2 + h_p \cdot k_5 \cdot V\left(t_p\right)\right)} \right| \\
&\leq \frac{k_3}{k_4} \cdot \left|T_{h,p} \cdot V_{h,p} - T\left(t_p\right) \cdot V\left(t_p\right)\right| + \frac{k_3}{k_4^2} \cdot \left|T_{h,p} \cdot V_{h,p} \cdot V\left(t_p\right) - T\left(t_p\right) \cdot V\left(t_p\right) \cdot V_{h,p}\right| \\
&\quad + \frac{h_p \cdot k_2 \cdot k_3}{k_4} \cdot \left|T_{h,p} \cdot V_{h,p} - T\left(t_p\right) \cdot V\left(t_p\right)\right| \\
&\quad + \frac{h_p \cdot k_2 \cdot k_3}{k_4^2} \cdot \left|T_{h,p} \cdot V_{h,p} \cdot V\left(t_p\right) - T\left(t_p\right) \cdot V\left(t_p\right) \cdot V_{h,p}\right| \\
&\quad + \frac{h_p \cdot k_3 \cdot k_5}{k_4} \cdot \left|T_{h,p} \cdot V_{h,p} \cdot V\left(t_p\right) - T\left(t_p\right) \cdot V_{h,p} \cdot V\left(t_p\right)\right| \\
&\quad + \frac{h_p \cdot k_3 \cdot k_5}{k_4^2} \cdot \left|T_{h,p} \cdot V_{h,p} \cdot V\left(t_p\right) \cdot V\left(t_p\right) - T\left(t_p\right) \cdot V\left(t_p\right) \cdot V_{h,p} \cdot V_{h,p}\right| \\
&\leq \frac{k_3}{k_4} \cdot \left(T_{\max,T,d} + V_{\max,V,c}\right) \cdot F_p + \frac{k_3}{k_4^2} \cdot V_{\max,V,c} \cdot V_{\max,V,d} \cdot F_p \\
&\quad + \frac{h_p \cdot k_2 \cdot k_3}{k_4} \cdot \left(T_{\max,T,d} + V_{\max,V,c}\right) \cdot F_p
\end{aligned}
$$

$$
\begin{aligned}
&+\frac{h_p\cdot k_2\cdot k_3}{k_4^2}\cdot V_{\max,V,c}\cdot V_{\max,V,d}\cdot F_p\\
&+\frac{h_p\cdot k_3\cdot k_5}{k_4}\cdot V_{\max,V,c}\cdot V_{\max,V,d}\cdot F_p\\
&+\frac{h_p\cdot k_3\cdot k_5}{k_4^2}\cdot V_{\max,V,c}\cdot V_{\max,V,d}\cdot\left|T_{h,p}\cdot V\left(t_p\right)-T\left(t_p\right)\cdot V_{h,p}\right|\\
&\le\frac{k_3}{k_4}\cdot\left(T_{\max,T,d}+V_{\max,V,c}\right)\cdot F_p+\frac{k_3}{k_4^2}\cdot V_{\max,V,c}\cdot V_{\max,V,d}\cdot F_p\\
&+\frac{h_p\cdot k_2\cdot k_3}{k_4}\cdot\left(T_{\max,T,d}+V_{\max,V,c}\right)\cdot F_p\\
&+\frac{h_p\cdot k_2\cdot k_3}{k_4^2}\cdot V_{\max,V,c}\cdot V_{\max,V,d}\cdot F_p\\
&+\frac{h_p\cdot k_3\cdot k_5}{k_4}\cdot V_{\max,V,c}\cdot V_{\max,V,d}\cdot F_p\\
&+\frac{h_p\cdot k_3\cdot k_5}{k_4^2}\cdot V_{\max,V,c}\cdot V_{\max,V,d}\cdot\left(T_{\max,T,c}+V_{\max,V,c}\right)\cdot F_p
\end{aligned}
$$

and

$$
\begin{aligned}
IV_{T,A}&\le k_5\cdot\left(1+h_p\cdot k_2\right)\cdot\left|T_{h,p}\cdot V_{h,p}-T\left(t_p\right)\cdot V\left(t_p\right)\right|\\
&+h_p\cdot k_5^2\cdot\left|T_{h,p}\cdot V_{h,p}\cdot V\left(t_p\right)-T\left(t_p\right)\cdot V\left(t_p\right)\cdot V_{h,p}\right|\\
&\le k_5\cdot\left(1+h_p\cdot k_2\right)\cdot T_{\max,T,d}\cdot\left|V_{h,p}-V\left(t_p\right)\right|+k_5\cdot\left(1+h_p\cdot k_2\right)\cdot V_{\max,V,c}\cdot\left|T_{h,p}-T\left(t_p\right)\right|\\
&+h_p\cdot k_5^2\cdot V_{\max,V,c}\cdot V_{\max,V,d}\cdot\left|T_{h,p}-T\left(t_p\right)\right|\\
&\le k_5\cdot\left(1+h_p\cdot k_2\right)\cdot T_{\max,T,d}\cdot F_p+k_5\cdot\left(1+h_p\cdot k_2\right)\cdot V_{\max,V,c}\cdot F_p\\
&+h_p\cdot k_5^2\cdot V_{\max,V,c}\cdot V_{\max,V,d}\cdot F_p.
\end{aligned}
$$

By defining the constant

$$
\begin{aligned}
\widetilde{C_{\text{prop},T}}:=&\,h_p\cdot k_5\cdot\left\|k_1\left(t\right)\right\|_\infty+h_p\cdot k_2\cdot\left\{1+h_p\cdot k_2+k_5\cdot V_{\max,V,c}+k_5\cdot T_{\max,T,c}\right\}\\
&+\frac{k_3}{k_4}\cdot\left(T_{\max,T,d}+V_{\max,V,c}\right)+\frac{k_3}{k_4^2}\cdot V_{\max,V,c}\cdot V_{\max,V,d}+\frac{h_p\cdot k_2\cdot k_3}{k_4}\cdot\left(T_{\max,T,d}+V_{\max,V,c}\right)\\
&+\frac{h_p\cdot k_2\cdot k_3}{k_4^2}\cdot V_{\max,V,c}\cdot V_{\max,V,d}+\frac{h_p\cdot k_3\cdot k_5}{k_4}\cdot V_{\max,V,c}\cdot V_{\max,V,d}\\
&+\frac{h_p\cdot k_3\cdot k_5}{k_4^2}\cdot V_{\max,V,c}\cdot V_{\max,V,d}\cdot\left(T_{\max,T,c}+V_{\max,V,c}\right)+k_5\cdot\left(1+h_p\cdot k_2\right)\cdot T_{\max,T,d}\\
&+k_5\cdot\left(1+h_p\cdot k_2\right)\cdot V_{\max,V,c}+h_p\cdot k_5^2\cdot V_{\max,V,c}\cdot V_{\max,V,d},
\end{aligned}
$$

we obtain the estimate

$$\left|T_{h,p+1}-\widetilde{T_{h,p+1}}\right|\le\left(1+h_p\cdot\widetilde{C_{\text{prop},T}}\right)\cdot F_p.$$

2.2. With similar, but lengthier arguments as before, there exist non-negative constants $\widetilde{C_{\text{prop},I}}$ and $\widetilde{C_{\text{prop},V}}$ such that

$$\left|I_{h,p+1}-\widetilde{I_{h,p+1}}\right|\le\left(1+h_p\cdot\widetilde{C_{\text{prop},I}}\right)\cdot F_p$$

and

$$\left|V_{h,p+1} - \widetilde{V_{h,p+1}}\right| \le \left(1 + h_p \cdot \widetilde{C_{\mathrm{prop},V}}\right) \cdot F_p$$

hold. Conclusively, this implies

$$E_{p+1} \le \left(1 + h_p \cdot \max\left\{\widetilde{C_{\mathrm{prop},T}}\,;\,\widetilde{C_{\mathrm{prop},I}}\,;\,\widetilde{C_{\mathrm{prop},V}}\right\}\right) \cdot F_p. \tag{31}$$

3. Let us define

$$C_{\mathrm{prop}} := \max\left\{\widetilde{C_{\mathrm{prop},T}}\,;\,\widetilde{C_{\mathrm{prop},I}}\,;\,\widetilde{C_{\mathrm{prop},V}}\right\} \text{ and } C_{\mathrm{loc}} := \max\left\{C_{\mathrm{loc},T}\,;\,C_{\mathrm{loc},I}\,;\,C_{\mathrm{loc},V}\right\}.$$

It holds

$$\begin{aligned} F_{p+1} &\le E_{p+1} + G_{p+1} \\ &\le \left(1 + h_p \cdot C_{\mathrm{prop}}\right) \cdot F_p + C_{\mathrm{loc}} \cdot h_p^2 \end{aligned}$$

by the results of our first two steps and this can be iterated inductively. Finally, we see that

$$\begin{aligned} F_{p+1} &\le \exp\left(C_{\mathrm{prop}} \cdot T\right) \cdot F_1 + \exp\left(C_{\mathrm{prop}} \cdot T\right) \cdot C_{\mathrm{loc}} \cdot T \cdot \Delta_{\max} \\ &= \exp\left(C_{\mathrm{prop}} \cdot T\right) \cdot C_{\mathrm{loc}} \cdot T \cdot \Delta_{\max} \end{aligned} \tag{32}$$

is valid because $F_1 = 0$ since the initial conditions of the time-continuous and the time-discrete problems coincide.

This finishes our proof of convergence. □

We want to conclude our investigation on our proposed non-standard finite-difference method (19) with one final remark.

**Remark 2.** Here, we managed to show that our proposed non-standard finite-difference-method (19) is unconditionally non-negativity-preserving. Additionally, we were able to demonstrate that this time-discrete version of (2) also preserves upper bounds for $T(t)$ and $I(t)$. Furthermore, our time discretization is also able to capture at most linear growth of $V(t)$. In addition to that, we were able to prove that our numerical solution scheme converges linearly towards the time-continuous solution and we obtain the same equilibrium points as in the time-continuous setting.

However, we would also like to discuss some potential limitations of our time-discrete analysis. In contrast to [62], we were not able to prove the global asymptotic stability of our equilibrium states. While their dynamical system consists of a polynomial right-hand-side vectorial function, we have rational functions. Additionally, we showed that even our time-continuous model possesses at most linear growth of $V(t)$ which is in accordance with numerical results of Kirschner [29]. Conclusively, we can not expect global asymptotic stability of our virus-endemic equilibrium in our time-continuous and our time-discrete settings.

## 4 Numerical Examples

Here, we want to illustrate our theoretical findings by different numerical examples. In our examples, we choose an equidistant mesh, i.e., that our chosen time step size $h > 0$ is equal for all time steps. All loads of cells have unit cells $\mathrm{mm}^{-3}$, compare [29].

### *4.1 Non-Negativity*

First, we want to show that our non-standard finite-difference-method (NSFDM), in contrast to other traditional explicit time discretizations such as the explicit Eulerian method (EE) or a second-order Runge-Kutta scheme (RK2), preserves non-negativity independent of our chosen time step sizes $h > 0$. All problem parameters for these simulations are given by $k_1 = 10$, $k_2 = 0.02$, $k_3 = 0.01$, $k_4 = 100$, $k_5 = 0.000024$, $k_6 = 0.265$, $k_7 = 1000$, $k_8 = 0.00074$, $k_9 = 18.2$, $k_{10} = 1$, $T_0 = 2000$, $I_0 = 0$ and $V_0 = 0.001$ which are inspired by Kirschner's work [29]. Our simulation results for $h = 10$ are seen in Fig. 1.

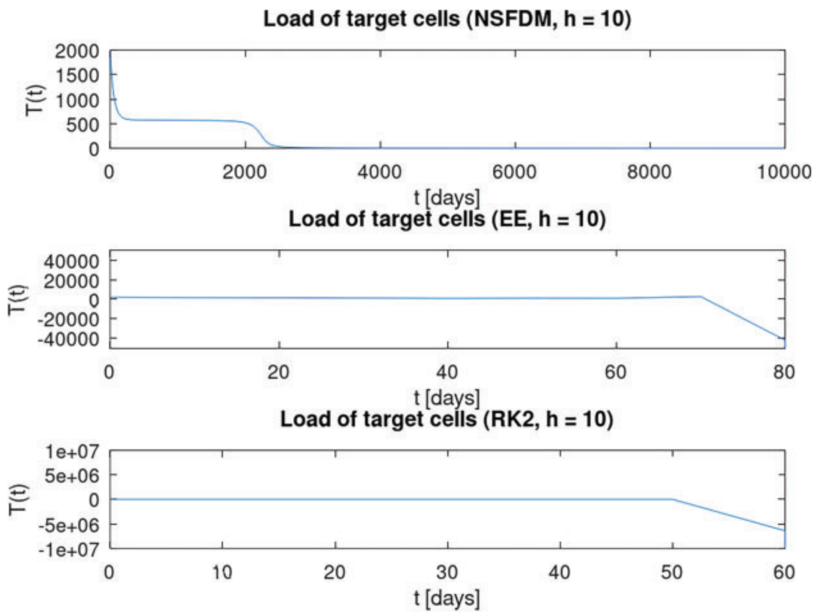


**Figure 1:** Numerical results of a load of target cells for $h = 10$ for all three numerical methods, namely non-standard finite-difference method (NSFDM), explicit Eulerian scheme (EE) and the second-order Runge-Kutta method (RK2)

We observe that only our proposed non-standard finite-difference method from Algorithm 2 can capture non-negativity over a long time interval for a larger equidistant time step size $h = 10$. Both other explicit Runge-Kutta schemes fail to conserve non-negativity after some time steps. However, if we apply a sufficiently small time step size such as $h = 0.1$, we can see that all of these explicit time-stepping methods can capture non-negativity over a large time interval, compare Fig. 2. Conclusively, we want to note that this parameter setting describes a typical untreated HIV infection over the course of time, compared to the simulations given in Kirschner's work [29].

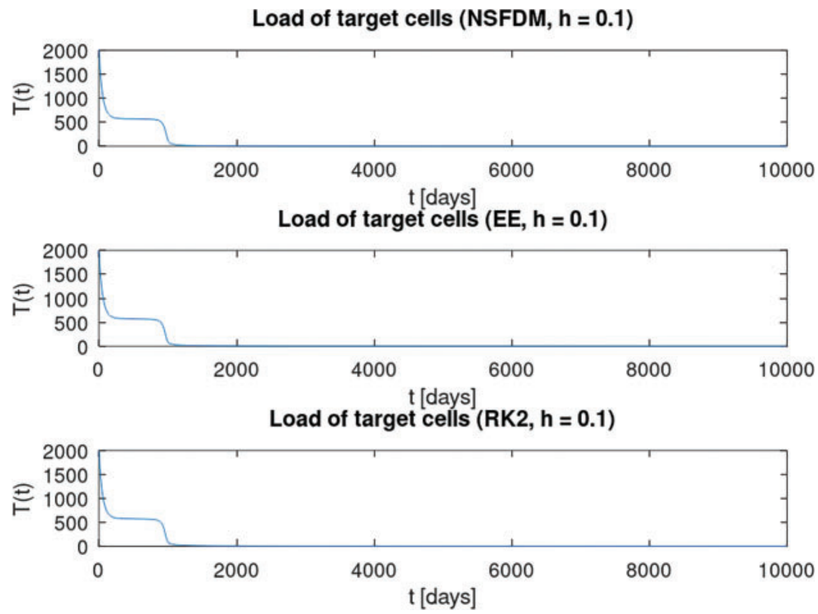


**Figure 2:** Numerical results of a load of target cells for $h = 0.1$ for all three numerical methods, namely non-standard finite-difference method (NSFDM), explicit Eulerian scheme (EE) and the second-order Runge-Kutta method (RK2)

### *4.2 Equilibrium States*

In this example, we want to distinguish three different situations of equilibrium states.

#### *4.2.1 Situation 1: Virus-Free Equilibrium State*

Let us take all problem parameters from Section 4.1. The exceptions are $k_9 = 0.25$, $T_0 = 2000$ and $I_0 = 100$. Let $h = 10$ and our final simulation time $T = 1000$. From our definition of the basic reproduction number in (9), we obtain

$$R_0 \approx 0.6757$$

for our example. Our numerical results can be seen in Fig. 3. Here, solid lines represent our solution components of a load of target cells, a load of infected target cells, and a load of virus cells. Dashed lines give our coordinates of the virus-free equilibrium state which are computed by

$$\begin{aligned} T_1^\star &= \frac{k_1}{k_2} \approx 500, \\ I_1^\star &= 0, \\ V_1^\star &= 0. \end{aligned}$$

We observe that our suggested non-standard finite-difference method converges to the computed coordinates of the virus-free equilibrium state.

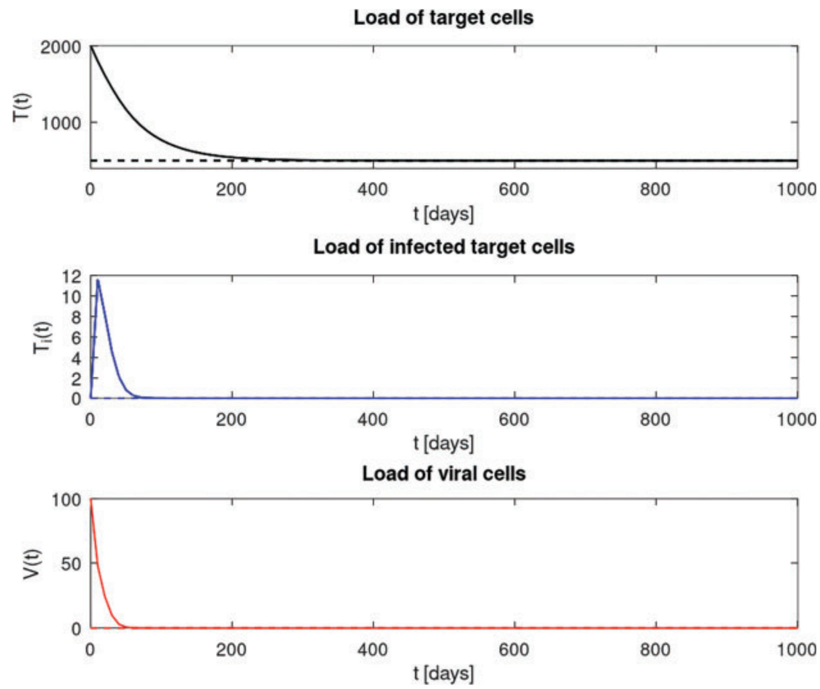


**Figure 3:** Numerical results of our setting in Section 4.2.1 where solid lines represent the solution components while dashed lines stand for the coordinates of the virus-free equilibrium state

*4.2.2 Situation 2: Virus-Endemic Equilibrium State*

Let us take all problem parameters from Section 4.2.1. The exception is $k_9 = 17$. From our definition of the basic reproduction number in in (9), we obtain

$$R_0 \approx 45.946$$

in this example. Our numerical results can be seen in Fig. 4. Here, solid lines represent our solution components of a load of target cells, a load of infected target cells, and load of virus cells. Dashed lines give our coordinates of the virus-free equilibrium state which are computed by

$$T_1^\star \approx 574.5532,$$
$$I_1^\star \approx 4.9362,$$
$$V_1^\star \approx 96.6225.$$

We observe that our suggested non-standard finite-difference method converges to the computed coordinates of the virus-endemic equilibrium state.

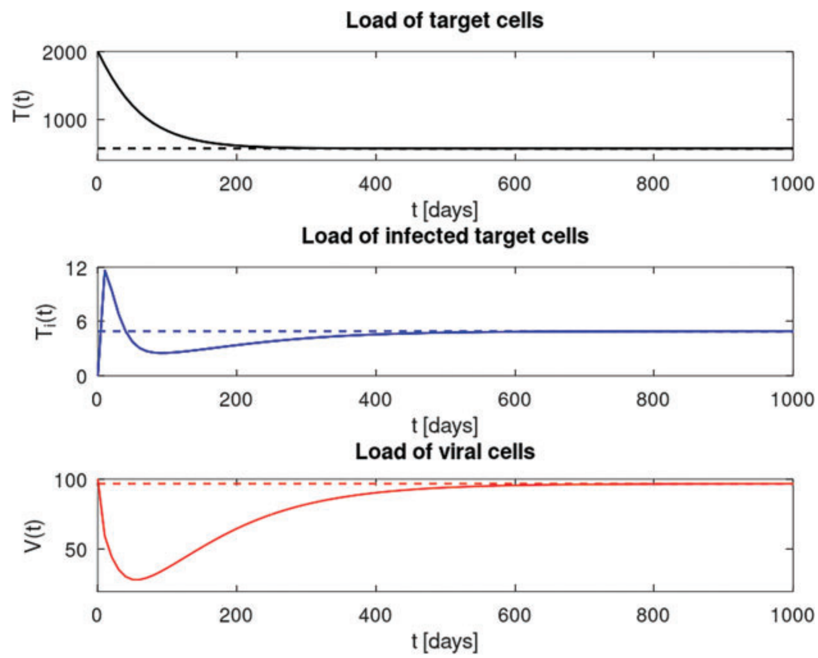


**Figure 4:** Numerical results of our setting in Section 4.2.2 where solid lines represent the solution components while dashed lines stand for the coordinates of the virus-endemic equilibrium state

*4.2.3 Situation 3: Linear Growth of $V(t)$*

Let us take all problem parameters from Section 4.2.1. The exception is $k_9 = 20$. Our numerical results can be seen in Fig. 5. It can be seen that the load of target cells $T(t)$ and the load of infected target cells $I(t)$ remain bounded while we additionally observe that the load of viral cells $V(t)$ grows linearly at most after a certain amount of time. In addition to that, we notice that the number of infected target cells seems to become stationary after a certain period.

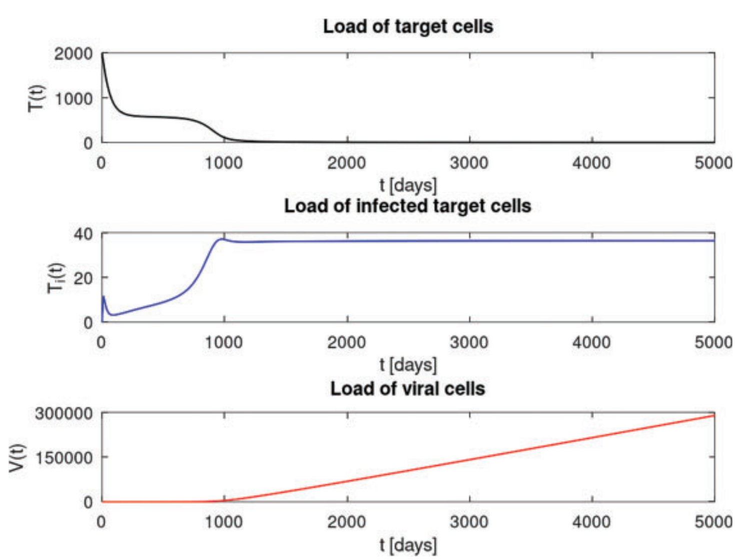


**Figure 5:** Numerical results of our setting in Section 4.2.3 where solid lines represent the solution components

#### *4.2.4 Situation 4: Real-World Application with Some Estimated Parameters from Clinical Trials and Some Calibrated Parameters from Numerical Simulations*

In this numerical experiment, we take some estimated parameter values from Kirschner's work [29] and from [27] which have been evaluated from different clinical trials. Here, we want to show that, in particular, the load of susceptible CD4$^+$ T-cells in the acute phase (first 100 days) and the latent phase (1500–3000 days after the ending of the acute phase) is accurately described by this model, compare [29] and [44]. Our parameter choice reads $k_1 = 10$, $k_2 = 0.02$, $k_3 = 0.01$, $k_4 = 100$, $k_5 = 0.000024$, $k_6 = 0.265$, $k_7 = 1000$, $k_8 = 0.00074$, $k_9 = 17.98$ and $k_{10} = 1.0$. Furthermore, we consider an equidistant time grid with $h = 1$ and final simulation time $T = 4000$.

In Fig. 6, we see numerical approximations of our presented setting. As mentioned in [44], Kirschner's model can capture important features of the acute and the latent phase. We observe a steep decrease of susceptible CD4$^+$ T-cells approximately 8 years after infection with HIV. Hence, Kirschner's model can capture this feature of this steep decrease long after an untreated infection with HIV.

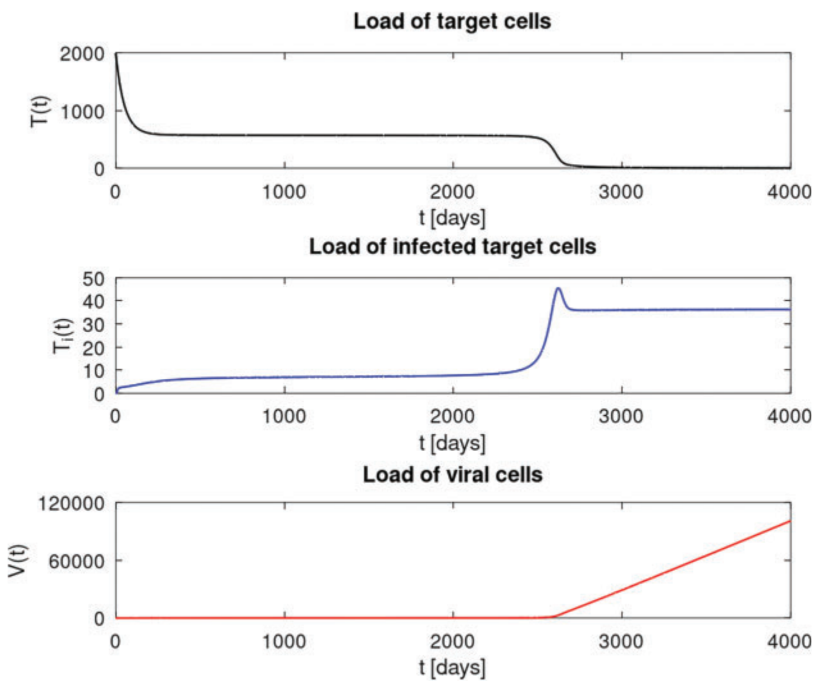


**Figure 6:** Numerical results of our setting in Section 4.2.4 where solid lines represent the solution components

What can be seen as a drawback of Kirschner's model, as we have already noticed from our theoretical results in Section 2, is the linear growth of virus cells which can be explained by the last term $k_9 \cdot \dfrac{V(t)}{k_{10} + V(t)}$. This summand can be interpreted as the growth of load of virus particles by infiltration of other immune cells such as macrophages.

### *4.3 Convergence*

Conclusively, we take all problem parameters from Section 4.2.2. Here, we want to demonstrate that our proposed non-standard finite-difference-method really is a first-order method. For that purpose, we use a fine-scale solution of a fourth-order Runge-Kutta method where all solution components read $T_{\mathrm{RK},j}$, $I_{\mathrm{RK},j}$

and $V_{\mathrm{RK},j}$ for time grid points $t_j$ and equidistant time step size $h_{\mathrm{RK}} = 0.001$. Furthermore, we define the error norm

$$\text{error} := \max_j \left\{ \left| T_{\mathrm{NSFDM},j} - T_{\mathrm{RK},j} \right| ; \left| I_{\mathrm{NSFDM},j} - I_{\mathrm{RK},j} \right| ; \left| V_{\mathrm{NSFDM},j} - V_{\mathrm{RK},j} \right| \right\}.$$

The calculated errors of our non-standard finite-difference method for different equidistant time step sizes are summarized in Table 3.

**Table 3:** Errors of our simulation from Section 4.3 where the rate is defined by $\dfrac{\text{error}_{j+1}}{\text{error}_j}$

| j | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| h | 8 | 4 | 2 | 1 | 0.5 | 0.25 | 0.125 |
| Error | 84.2683 | 43.6746 | 30.4971 | 20.4002 | 11.7250 | 6.3785 | 3.3669 |
| Rate | – | 1.93 | 1.43 | 1.49 | 1.74 | 1.84 | 1.89 |

For small time step sizes, we notice that rate tends to 2 which means that the convergence order is one.

### 4.4 Some Concluding Remarks

Here, we want to summarize some of our theoretical results and of our numerical observations concerning our suggested non-standard finite-difference-method (19).

As we have already proven, our numerical solution algorithm is unconditionally stable and, in particular, it preserves non-negativity for all positive time-step sizes which is one preferable property of the time-continuous model. Hence, this is one main difference from classical Runge-Kutta time-stepping methods which are only conditionally stable and which conserve non-negativity only for a certain range of positive time-step sizes.

In terms of computational cost, since our proposed numerical solution algorithm is explicit and is of convergence order one, it is comparable to an explicit Eulerian time-stepping method concerning computational time. However, in contrast to the explicit Eulerian time-stepping procedure, our algorithm is unconditionally stable and unconditionally non-negativity-preserving. These are features that our algorithm shares with the implicit Eulerian time-stepping method. In contrast to implicit time-discretizations, our numerical solution procedure is explicit and henceforth, it avoids solutions of non-linear systems of equations in each time step.

Conclusively, our proposed non-standard finite-difference method has some interesting numerical properties which transfer from the time-continuous model to our time-discrete setting.

## 5 Conclusion and Outlook

In this work, we re-examined a classical dynamical system for untreated HIV infections proposed by Kirschner. In particular, we proved the non-negativity of all solution components, boundedness of two solution components, at most linear growth of one solution component, existence and uniqueness of solutions, and investigated equilibrium states and local stability for the virus-free equilibrium state. With regard to the time-discrete setting, we suggested a new non-standard finite-difference-method, solely based on non-local approximations. We demonstrated that many properties of the time-continuous case transferred to the time-discrete setting. In particular, we showed that our non-standard finite-difference method is of first order. Conclusively, we strengthened our theoretical findings with different numerical examples.

Let us discuss one important limitation of Kirschner's time-continuous model [29]. Since our proof showed that the viral load $V(t)$ could grow linearly, it might be important to reconsider other potential models. For simplicity, we assumed $k_1(t)$ to be constant for investigation of the equilibrium state. However, as Kirschner mentioned in [29], $k_1(t) = a + \frac{b}{c + V(t)}$ could be chosen in dependence of $V(t)$ with positive constants $a$, $b$ and $c$. This would definitely not disturb many of our analytical results and could be a possible consideration for future research besides examinations of different proposed HIV infection models and their time-discretizations.

Finishing our article, we want to sketch some potential future research directions. At first, it could be of interest to construct higher-order non-standard finite-difference-methods, compare, for example, [66]. In that work, the authors applied Richardson's extrapolation to construct higher-order non-standard finite-difference methods for a model of malware propagation. While they achieve higher rates of convergence, preservation of non-negativity for all time-step sizes was only observed numerically. Henceforth, we stayed with a first-order approach which easily guarantees non-negativity without any restrictions on possible time-step sizes. Furthermore, in contrast to many other works, we applied a non-equidistant time grid.

From a modeling perspective, it seems interesting to add spatial inhomogeneity to Kirschner's model by the introduction of diffusion or reaction terms. This implies that the investigated model transfers to a partial differential equation [67]. Additionally, it might be worth noticing that it is possible to implement further compartments into Kirschner's presented model. Possible extensions might be immune responses from different cells [68] or the total amount of protein levels within a human being [69]. Depending on the structure of these higher-order dynamical systems, our ideas, presented in this article, can be extended to such models as well to create non-standard finite-difference methods which preserve important properties of the time-continuous setting. The implementation of drug therapy into Kirschner's model has already been mentioned by Kirschner herself [29].

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**Author Contributions:** Benjamin Wacker: conceptualization, formal analysis, investigation, methodology, software, validation, visualization, writing—original draft; Jan Christian Schlüter: conceptualization, writing—review & editing. All authors reviewed the results and approved the final version of the manuscript.

**Availability of Data and Materials:** Our GNU Octave codes can be found under the following hyperlink https://github.com/bewa87/2025-Modified-HIV-NSFDM (accessed on 07 July 2025).

**Ethics Approval:** It is not applicable.

**Conflicts of Interest:** The authors declare no conflicts of interest to report regarding the present study.

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