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Mathematical Biology

Viral infection dynamics with immune chemokines and CTL mobility modulated by the infected cell density

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Abstract

We d a i al i fec i m del i c a i g b h cell- -cell i fec i a d imm e chem ki e . Ba ed e e ime al e l i he li e a e e make a a di g a m i ha he c ic T l m h c e (CTL) ill m e a d he l ca i i h m e i fec ed cell hile he diff i a e f CTL i a dec ea i g f c i f he de i f i fec ed cell . We e abli h he gl bal e i e ce a d l ima e b ded- e f he l i ia a i ie e g e ima e . We he de e he ba ic e d c i mbe f i al i fec i R_0 a d e (b he if m e i e ce he , L a f c i ech i e a d LaSalle i a ia ce i ci le) ha he i fec i -f ee ead a e E_0 i gl ball a m icall able if $R_0 < 1$. Whe $R_0 > 1$, he E_0 bec me able, a d a he ba ic e d c i mbe f CTL e e R_1 bec me he d amic h e h ld i he e e ha if $R_1 < 1$, he he CTL-i ac i a ed ead a e E_1 i gl ball a m icall able; a d if $R_1 > 1$, he he imm e e e i if m e i e a d, de a addi i al ech ical c di i he CTL-ac i a ed ead a e E_2 i gl ball a m icall able. T e abli h he gl bal abili e l e eed e i di i a i i , b ai if m e i e ce, c c i able L a f c i , a d a l he LaSalle i a ia ce i ci le.

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1 Introduction

Ma hema ical m del ha e bee la i g a im a le i de a di g i al d amic (Pe el a d Nel 1999 d i (Halle e al. 2016), CTL e d mig-a e m -e lw l w hile -ec g i i g i fec ed cell . He ce e ill a me i -m del ha he diff i -a e f CTL i a dec-ea i g f c i f he de i f i fec ed cell . M -e eci call e - e d he f llw i g -eac i -diff i em i h ge e-al i cide ce f c i :

$$
\begin{cases}
\partial_t T = d_T \Delta T + b(T) - f(T, I) - g(T, V), & x \in \Omega, t > 0,\\
\partial_t I = d_I \Delta I + f(T, I) + g(T, V) - r_1 I Z - \mu_I I, & x \in \Omega, t > 0,\\
\partial_t V = d_V \Delta V + kI - \mu_V V, & x \in \Omega, t > 0,\\
\partial_t Z = \Delta[d_Z(I) Z] + r_2 I Z - \mu_Z Z, & x \in \Omega, t > 0,\\
\partial_\nu T = \partial_\nu I = \partial_\nu V = \partial_\nu Z = 0, & x \in \partial\Omega, t > 0,\\
\{T, I, V, Z\}(x, 0) = \{T_0, I_0, V_0, Z_0\}(x), & x \in \Omega,
\end{cases}
\tag{1.1}
$$

w he-e $\Omega \subset \mathbb{R}^2$ i a b ded d mai w i h m h b da- $\partial\Omega$. $T(x, t)$, $I(x, t)$, $V(x, t)$ a d $Z(x, t)$ de e he de i ie f i fec ed a-ge ed cell , i fec ed a-ge ed cell , i- e a d c ic T l m h c e (CTL), -e ec i el . d_T, d_I a d d_V a-e i i e diff i c a f -T, I a d V, -e ec i el . The g-w h f c i f - i fec ed a-ge ed cell i gi e b $b(T)$. The cell- -cell a d i- - -cell -a mi - i a-e cha-ac e-i ed b he li ea- f c i $f(T, I)$ a d $g(T, V)$, -e ec i el . $r_1 I Z$ a d f - he -em al -a e f i fec ed cell b CTL a d kI i he i-i - - d c i -a e. The -ec-i me -a e f CTL i $r_2 I Z$. U cali g $\widetilde{Z} = (r_1/r_2) Z$ w e ma a me w i h l f ge e-ali ha $r_1 = r_2 = r$. The c a e- ca i al dea h -a e f I, V a d Z a-e de ed b μ_I, μ_V a d μ_Z, -e ec i el . Fi all , he f c i $d_Z(I) > 0$ cha-ac e-i e he de e de ce f CTL m ili he de i f i fec ed cell . N e ha $\Delta[d_Z(I)Z] = \nabla \cdot [d_Z(I)\nabla Z] + \nabla \cdot [d_Z'(I) Z \nabla I]$. The - e-m $\nabla \cdot [d_Z(I)\nabla Z]$ im lie ha he CTL diff e m -e lw l if he de i f i fec ed cell i highe-w hile he ec d e-m $\nabla \cdot [d_Z'(I) Z \nabla I]$ ge he-w i h he a m i $d_Z'(I) \le 0$ i dica e ha he CTL e d m e w a-d he l ca i w i h highe- de - i f i fec ed cell . The e-m $\Delta[d_Z(I)Z]$ i al -ela ed he de i - - -e ed m ili w hich ma - d ce m -e c m le d amic a d a e- (F e al. 2012; Li 2011). The de i - - -e ed m ili ha bee died e e i el i he c - e f chem a i (Kelle- a d Segel 1970, 1971) a d -e - a i (Ka-ei a a d Odell 1987). M -e -eci el , i ha bee - ed ha he de i - - -e ed m ili ca -e e he blw - f l i (Ta a d Wi kle- 2017; Ji e al. 2018; Jia g e al. 2022; F jie a d Jia g 2020, 2021), e ha ce he diff i (Wi kle- 2020), a d -igge- a e- f -ma i (Ma e al. 2020; Ji a d Wa g 2021; Li a d Wa g 2021).

Notations: Fi $p_0 > 2$ a d le $\mathbb{X} = W^{1,p_0}(\Omega, \mathbb{R})$ be he ha e ace f - i i ial c di i . M -e e-w e e a l mb l i he b c-i de e he - ega i e c e f he c -e di g Ba ach ace; f - i a ce, $\mathbb{R}_+ = [0, \infty)$ a d $\mathbb{X}_+ = W^{1,p_0}(\Omega, \mathbb{R}_+)$. F - $1 \le p \le \infty$, $\|\cdot\|_p$ de e he L^p- -m i $L^p(\bar{\Omega})$. Gi e a li ea- e-a - L, he ec-al b d a d ec-al -adi f L a-e de ed b $s(L)$ a d $\rho(L)$, -e ec i el . We a a li ea- d amical em $u'(t) = Lu$ (- he li ea- e-a - L) i able if $s(L) < 0$ a d able if $s(L) > 0$. We e ∂_ν a d dS de e he -mal de-i a i e a d diffe-e ial f -m $\partial\Omega$. The mb l ∇, ∇^2, a d Δ a d f - he g-adie ec -, He ia ma-i , a d La lacia , -e ec i el . E eciall , Δu

i he ace f $\nabla^2 u$. The a i $|\cdot|$ i dica e he E clidea m f a ec hile $|\cdot|_E$ i he F be i m f a ma i . The l i emi f (1.1) i de ed a $\Theta(t) : \mathbb{X}_+^4 \to \mathbb{X}_+^4$ f $t \geq 0$. F a i i ial c di i $\phi \in \mathbb{X}_+^4$, he mega limi e f ϕ i $\omega(\phi) = \cap_{s\geq 0}\overline{\cup_{t\geq s}\Theta(t)\phi}$. F a b e $D \subset \mathbb{X}_+^4$, he mega limi e f D i $\omega(D) = \cup_{\phi\in D}\omega(\phi)$. We a he b e D i i i el i a ia if $\Theta(t)D \subset D$. Ob i l , if a i i el i a ia b e D i cl ed he $\omega(D) \subset D$. Gi e a ead a e $E \in \mathbb{X}_+^4$ ch ha $\Theta(t)E = E$ f all $t \geq 0$, he able e f E i $W^s(E) = \{\phi \in \mathbb{X}_+^4 : \lim_{t\to\infty}\Theta(t)\phi = E\}$.

Basic assumptions: Th gh hi a e e e $r_1 = r_2 = r$, a d make he f ll i g bi l gicall ele a a m i .

- (H1) $b \in C^2(\mathbb{R}_+)$ i h $b' < 0$ $\mathbb{R}_+$. M e e , he e e i (a i e) $T_0 > 0$ ch ha $b(T_0) = 0$.
- (H2) $f, g \in C^2(\mathbb{R}_+ \times \mathbb{R}_+)$ ch ha f a d g a i h he b da f ad a , he - de a ial de i a i e $\partial_T f, \partial_I f, \partial_T g$, a d $\partial_V g$ a e ic l i i e i he i e i f he ad a , he ec d- de a ial de i a i e $\partial_{II} f$ a d $\partial_{VV} g$ a e - i i e i he ad a , a d he e e i $K > 0$ ch ha $f(T, I) \leq KTI$ a d $g(T, V) \leq KTV$ f all $T, I, V \in \mathbb{R}_+$.
- (H3) $d_Z \in C^2(\mathbb{R}_+)$ ch ha $d_Z > 0$ a d $d_Z' \leq 0$ $\mathbb{R}_+$.

Main results: O mai e l ca be mma i ed i he f ll i g he em .

Theorem 1.1 (Gl bal e i e ce a d i di i a i i) *Let* $\Omega \subset \mathbb{R}^2$ *and* $\mathbb{X}_+ = W^{1,p_0}(\Omega, \mathbb{R}_+)$. *Assume (H1)-(H3). For any initial value in* $[\mathbb{X}_+ \setminus \{0\}]^4$, *the system (1.1) has a unique nonnegative classical solution* (T, I, V, Z) *satisfying*

$$(T, V, Z) \in [C([0, \infty) \times \bar{\Omega}) \cap C^{2,1}((0, \infty) \times \bar{\Omega})]^3$$

and

$$I \in C([0, \infty) \times \bar{\Omega}) \cap C^{2,1}((0, \infty) \times \bar{\Omega}) \cap L^\infty_{loc}([0, \infty); W^{1,\infty}(\Omega)).$$

Moreover, there exists $C > 0$ *independent of initial conditions such that*

$$\lim_{t\to\infty} (\|T(\cdot, t)\|_{\mathbb{X}} + \|I(\cdot, t)\|_{\mathbb{X}} + \|V(\cdot, t)\|_{\mathbb{X}} + \|Z(\cdot, t)\|_{\mathbb{X}}) \leq C.$$

Here, $\mathbb{X} = W^{1,p_0}(\Omega, \mathbb{R})$ *and* $\|u\|_{\mathbb{X}} = \|u\|_{p_0} + \|\nabla u\|_{p_0}$ *for* $u \in \mathbb{X}$.

Theorem 1.2 *(Global dynamics) Assume (H1)-(H3) and define*

$$R_0 := \frac{\partial_I f(T_0, 0)}{\mu_I} + \frac{k\partial_V g(T_0, 0)}{\mu_V \mu_I}.$$

Let $(T(t), I(t), V(t), V(t))$ *be any solution to (1.1) with initial value in* $[\mathbb{X}_+ \setminus \{0\}]^4$.

- *If* $R_0 \leq 1$, *then the solution will converge to the infection-free steady state* $E_0 = (T_0, 0, 0, 0)$ *as* $t \to \infty$.

- *If* $R_0 > 1$, *then there exists a unique CTL-inactivated steady state* $E_1 = (T_1, I_1, V_1, 0)$. *We define* $R_1 := rI_1/(\mu Z_1)$ *and assume that* $f(T, I) = h_0(T)h_d(I)$ *and* $g(T, V) = h_0(T)h_i(V)$, *where* $h_0, h_d, h_i \in C^2(\mathbb{R}_+)$.
  - *If* $R_0 > 1$ *and* $R_1 \leq 1$, *then the solution will converge to* E_1.
  - *If* $R_0 > 1$ *and* $R_1 > 1$, *then there exists a unique CTL-activated steady state* $E_2 = (T_2, I_2, V_2, Z_2)$. *Moreover, the solution converges to* E_2 *provided*

$$d_I \geq \frac{Z_2}{4I_2} \max_{0 \leq I \leq \infty} \frac{|Id_Z'(I)|^2}{d_Z(I)}.$$

Outline of the paper: I Sec . 2, e e abli h he b ded e a d gl bal e i e ce f l i . The ke e i e he f he a i f (1.1) b ai he b ded e f $\int_t^{t+\tau} \int_\Omega Z^2 dxds$ f me ed $\tau \in (0, 1]$. Wi h hi i ha d e ca f he h $\geq \subset$ ha $\int_t^{t+\tau} \|\Delta I\|_2^2 ds$ i if ml b ded. A di ec a lica i f L^2 e ima e Z gi e

$$\frac{d}{dt}\|Z\|_{L^2}^2 \leq K0$$

2.1 Global existence

Fi w e a e he f ll w i g lemma w hich i a ge e ali a i f (S i e e al. 2014, Lemma 3.4) a d G w all i e ali .

Lemma 2.1 *Let $t_m > 0$, $\tau \in (0, t_m)$, $c_1 > 0$ and $c_2 > 0$. Assume that y is a non-negative and continuously differentiable function on $[0, t_m)$ satisfying $y'(t) + c_1 y(t) \le h(t)$ for all $t \in (0, t_m)$, where h is a non-negative and locally integrable function on $(0, t_m)$ such that $\int_{t-\tau}^{t} h(s)ds \le c_2$ for all $t \in [\tau, t_m)$. Denote $c_3 = \text{ma }\{y(0), c_2/(c_1\tau) + c_2\}$. We then have $y(j\tau) \le c_3$ for all non-negative integer $j < t_m/\tau$, and $y(t) \le c_3 + c_2$ for all $t \in [0, t_m)$.*

Proof We l eed e he a e i beca e he ec d e f ll w imme-dia el f m he - ega i i f h a d y ge he w i h a i eg a i f he i e ali $y' + c_1 y \le h$. Ob i 1 , $y(0) \le c_3$. A me $y(j\tau) \le c_3$ a d $j + 1 < t_m/\tau$. We c - ide w ca e : (i) $y(s) \ge c_2/(c_1\tau)$ f all $s \in [j\tau, (j+1)\tau]$; a d (ii) $y(s_0) < c_2/(c_1\tau)$ f me $s_0 \in [j\tau, (j+1)\tau]$. I he ca e w e i eg a e $y' + c_1 y \le h$ b ai $y((j+1)\tau) \le y(j\tau) \le c_3$; w hile i he ec d ca e, a i eg a i f $y' + c_1 y \le h$ gi e $y((j+1)\tau) \le y(s_0) + c_2 \le c_3$. Thi c m le e he f. ☐

N w w e a e ead e he gl bal e i e ce f cla ical l i a f ll w .

Theorem 2.2 *Let $\Omega \subset \mathbb{R}^2$ and $\mathbb{X}_+ = W^{1,p_0}(\Omega, \mathbb{R}_+)$. Assume (H1)-(H3). For any initial value in $[\mathbb{X}_+ \setminus \{0\}]^4$, the system (1.1) has a unique nonnegative classical solution (T, I, V, Z) satisfying*

$$(T, V, Z) \in [C([0, \infty) \times \bar{\Omega}) \cap C^{2,1}((0, \infty) \times \bar{\Omega})]^3$$

and

$$I \in C([0, \infty) \times \bar{\Omega}) \cap C^{2,1}((0, \infty) \times \bar{\Omega}) \cap L^{\infty}_{loc}([0, \infty); W^{1,\infty}(\Omega)).$$

Proof B ad i g he idea i (Ta a d Wi kle 2011, Lemma 2.1) a d (Ji e al. 2018) w e ca e he e i e ce f l cal l i b i g he Scha de ed i he em a d he a ab lic eg la i he ; amel , he e e i $t_m \in (0, \infty]$ ch ha he blem (1.1) ha a i e ega i e cla ical l i (T, I, V, Z) a i f i g

$$(T, V, Z) \in [C([0, t_m) \times \bar{\Omega}) \cap C^{2,1}((0, t_m) \times \bar{\Omega})]^3$$

a d

$$I \in C([0, t_m) \times \bar{\Omega}) \cap C^{2,1}((0, t_m) \times \bar{\Omega}) \cap L^{\infty}_{loc}([0, t_m); W^{1,\infty}(\Omega)).$$

M e e w e ha e ei he $t_m = \infty$

$$\lim_{t \to t_m^-} (\|T(\cdot, t)\|_{L^\infty} + \|V(\cdot, t)\|_{L^\infty} + \|Z(\cdot, t)\|_{L^\infty} + \|I(\cdot, t)\|_{W^{1,\infty}}) = \infty.$$

N e ha $[0, t_m)$ i he ma im m i e al f he e i e ce f cla ical l i . I f ce e ha he l i d e bl a $t \to t_m^-$. De e $\tau = $ mi $\{1, t_m/2\}$. F c e ie ce e ill e c de e a ge e ic (la ge) i i e c a ha i i de e de f t. We ceed i he f ll i g i e e .

Step 1. $\|T(\cdot, t)\|_\infty \leq c.$

I ie f he - ega i i f he l i a d (H2) e b ai f m he e a i f (1.1) ha $\partial_t T \leq d_T \Delta T + b(T)$. B (H1) a d ma im m i ci le e ha e $T(x, t) \leq$ ma $\{\|T(\cdot, 0)\|_\infty, T_0\}$.

Step 2. $\|I(\cdot, t)\|_1 + \|V(\cdot, t)\|_1 + \|Z(\cdot, t)\|_1 \leq c.$

F m (1.1) e b ai

$$\frac{d}{dt}\int_\Omega (T + I + Z)dx = \int_\Omega [b(T) - \mu_I I - \mu_Z Z]dx$$
$$\leq \int_\Omega [b(0) + c - T - \mu_I I - \mu_Z Z]dx.$$

I he f ll f m G all i e ali ha $\|I(\cdot, t)\|_1 + \|Z(\cdot, t)\|_1 \leq c$. I eg a i g he f h e a i f (1.1) a d a l i g G all i e ali ield $\|V(\cdot, t)\|_1 \leq c$.

Step 3. F a $p > 1$, $\|I(\cdot, t)\|_p + \|V(\cdot, t)\|_p \leq c.$

M l i l i g he ec d e a i f (1.1) b I^{p-1} a d i eg a i g e he d mai Ω, e b ai

$$\frac{1}{p}\frac{d}{dt}\int_\Omega I^p dx = d_I \int_\Omega (\Delta I) I^{p-1} dx + \int_\Omega [f(T, I) + g(T, V)] I^{p-1} dx$$
$$- \int_\Omega (r_1 Z + \mu_I) I^p dx.$$

The G ee ide i gi e

$$\int_\Omega (\Delta I) I^{p-1} dx = -\int_\Omega (\nabla I) \cdot ((p-1) I^{p-2} \nabla I) dx = -\frac{4(p-1)}{p^2}\int_\Omega |\nabla I^{p/2}|^2 dx.$$

O acc f (H2) e ha e

$$\int_\Omega [f(T, I) + g(T, V)] I^{p-1} dx \leq \int_\Omega KT(I^p + I^{p-1} V) dx \leq c \int_\Omega (I^p + V^p) dx.$$

He ce,

$$\frac{1}{p}\frac{d}{dt}\int_\Omega I^p dx + \frac{4(p-1)d_I}{p^2}\int_\Omega |\nabla I^{p/2}|^2 dx \leq c \int_\Omega (I^p + V^p) dx. \tag{2.1}$$

Simila l e m l i l he hi d e a i f (1.1) b V^{p-1} a d he a l G ee ide i ha e

$$\frac{1}{p}\frac{d}{dt}\int_\Omega V^p dx + \frac{4(p-1)d_V}{p^2}\int_\Omega |\nabla V^{p/2}|^2 dx \leq c \int_\Omega (I^p + V^p) dx. \tag{2.2}$$

N w w e e he Gaglia d -Ni e be g i e ali a d b ded e f $\|I\|_q + \|V\|_q$ d

$$\|I^{p/2}\|_2^2 \le c(\|\nabla I^{p/2}\|_2^{2(1-1/p)}\|I^{p/2}\|_{2/p}^{2/p} + \|I^{p/2}\|_{2/p}^2) \le \frac{1}{c}\|\nabla I^{p/2}\|_2^2 + c, \tag{2.3}$$

a d imila l ,

$$\|V^{p/2}\|_2^2 \le \frac{1}{c}\|\nabla V^{p/2}\|_2^2 + c, \tag{2.4}$$

Taki g a eigh ed m f i e ali ie (2.1), (2.2), (2.3), a d (2.4), a d he a l i g G w all i e ali w e b ai $\|I(\cdot,t)\|_p^p + \|V(\cdot,t)\|_p^p \le c$.

Step 4. $\|I(\cdot,t)\|_\infty + \|V(\cdot,t)\|_\infty \le c$.

I f ll w f m he hi d e a i f (1.1) ha

$$V(\cdot,t) = e^{(d_V\Delta-\mu_V)t}V(\cdot,0) + k\int_0^t e^{(d_V\Delta-\mu_V)(t-s)}I(\cdot,s)ds.$$

B e ima e f Ne ma hea emig (H ma a d Wi kle 2005; K w alc k a d S ma ka 2008) a d if m b ded e f $\|I\|_3$ w e d $\varepsilon > 0$ ch ha

$$\|V(\cdot,t)\|_\infty \le \|V(\cdot,0)\|_\infty + c\int_0^t [1+(t-s)^{-1/3}]e^{-\varepsilon(t-s)}ds \le c.$$

Simila l , i g he a m i i (H2) w e b ai f m he e a i f (1.1) a d he if m b ded e f $\|I\|_3 + \|V\|_3$ ha $\|I(\cdot,t)\|_\infty \le c$.

Step 5. $\int_{t-\tau}^t\int_\Omega Z^2(x,s)dxds \le c$ f all $t \in [\tau, t_m)$.

T hi e d w e hall e he d ali a g me ba ed me ice idea de el ed i (Ta a d Wi kle 2017). De e $\delta_1 = \mu_Z/[2d_Z(0)]$ a d le $\mathcal{A}$ be he elf-adj i i i e ea $-\Delta + \delta_1$ w i h Ne ma b da c di i $L^2(\Omega)$. The $\mathcal{A}^{-1}$ i a b ded a d i i e ea $L^2(\Omega)$. Addi g he ec d a d he f he e a i f (1.1) gi e (ecalli g ha $r_1 = r_2 = r$)

$$\begin{aligned}\partial_t(I+Z) + \mathcal{A}[d_I I + d_Z(I)Z] &= \delta_1[d_I I + d_Z(I)Z]\\ &\quad + f(T,I) + g(T,V) - \mu_I I - \mu_Z Z \le c,\end{aligned}$$

w he e w e ha e made e f (H2), $\delta_1 < \mu_Z/d_Z(0) \le \mu_Z/d_Z(I)$, a d he if m b ded e f $\|T\|_\infty + \|I\|_\infty + \|V\|_\infty$. M l i l i g he ab e i e ali b $2\mathcal{A}^{-1}(I+Z) \ge 0$ gi e

$$\frac{d}{dt}\int_\Omega |\mathcal{A}^{-1/2}(I+Z)|^2dx + 2\int_\Omega (I+Z)[d_I I + d_Z(I)Z]dx \le c\int_\Omega \mathcal{A}^{-1}(I+Z)dx. \tag{2.5}$$

Si ce $\|I\|_\infty$ i if ml b ded, i f ll w f m (H1) ha $d_Z(I) \geq d_Z(c_2) > 0$. Le $\delta_2 > 0$ be f cie l mall ch ha

$$d_I I + d_Z(I) Z \geq \delta_2 (I + Z). \tag{2.6}$$

I f ll w f m b ded e f $\mathcal{A}^{-1}$ a d $\mathcal{A}^{-1/2}$ $L^2(\Omega)$ ha

$$\|\mathcal{A}^{-1}(I + Z)\|_1 \leq c\|\mathcal{A}^{-1}(I + Z)\|_2 \leq c\|I + Z\|_2 \leq \delta_3 \|I + Z\|_2^2 + c, \tag{2.7}$$

a d

$$\|\mathcal{A}^{-1/2}(I + Z)\|_2^2 \leq c\|I + Z\|_2^2, \tag{2.8}$$

w he e $\delta_3 > 0$ i f cie l mall. A c mbi a i f he ab e f i e ali ie (2.5 2.8) ield

$$\frac{d}{dt} \int_\Omega |\mathcal{A}^{-1/2}(I + Z)|$$

B (H1) a d if m b ded e f $\|I\|_{\infty}$ e ca d a mall $\delta_4 > 0$ ch ha $d_Z(I) \geq \delta_4$. I he f ll f m he ab e i e ali a d Ca ch i e ali ha

$$\frac{d}{dt}\int_\Omega Z^2 dx + 2\delta_4 \int_\Omega |\nabla Z|^2 dx \leq \delta_4 \int_\Omega |\nabla Z|^2 dx + c\int_\Omega (Z^2|\nabla I|^2 + Z^2)dx.$$

B H lde i e ali e b ai

$$\frac{d}{dt}\|Z\|_2^2 + \delta_4\|\nabla Z\|_2^2 \leq c(\|Z\|_4^2\|\nabla I\|_4^2 + \|Z\|_2^2).$$

The igh -ha d ide f he ab e i e ali ca be f he e ima ed ia he Gaglia d - Ni e be g i e ali a d elli ic eg la i he . He ce e b ai

$$\begin{aligned}\frac{d}{dt}\|Z\|_2^2 + \delta_4\|\nabla Z\|_2^2 &\leq c(\|\nabla Z\|_2\|Z\|_2 + \|Z\|_2^2)(\|\Delta I\|_2\|\nabla I\|_2 + \|\nabla I\|_2^2) + c\|Z\|_2^2\\
&\leq c(\|\nabla Z\|_2\|Z\|_2 + \|Z\|_2^2)(\|\Delta I\|_2 + c)\\
&\leq c\|\nabla Z\|_2\|Z\|_2\|\Delta I\|_2 + c\|\nabla Z\|_2\|Z\|_2 + c\|Z\|_2^2\|\Delta I\|_2 + c\|Z\|_2^2\\
&\leq \delta_4\|\nabla Z\|_2^2 + c\|Z\|_2^2(\|\Delta I\|_2^2 + 1).\end{aligned}$$

Thi ge he i h he if m b ded e f $\int_{t-\tau}^t \|\Delta I\|_2^2 ds$ a d Lemma 2.1 im lie ha $\|Z(\cdot,t)\|_2^2 \leq c$.

S e 8. F a $p > 1$, $\|Z(\cdot,t)\|_p \leq c$.

Si ce $\|Z\|_2$ i if ml b ded, a a lica i f a ab lic eg la i (K alc k a d S ma ka 2008, Lemma 1) he ec d e a i f (1.1) gi e he if m b ded e f $\|\nabla I\|_4$. Recall ha $d_Z(I) \geq \delta_4 > 0$. We m l i le he f he a i f (1.1) b Z^{p-1} a d a l G ee ide i d

$$\frac{1}{p}\frac{d}{dt}\int_\Omega Z^p dx + (p-1)\delta_4 \int_\Omega Z^{p-2}|\nabla Z|^2 dx \leq c\int_\Omega Z^{p-1}|\nabla Z||\nabla I| dx + c\int_\Omega Z^p dx.$$

A l i g Ca ch i e ali , H lde i e ali , a d he Gaglia d -Ni e be g i e ali e b ai

$$\begin{aligned}&\frac{1}{p}\frac{d}{dt}\int_\Omega Z^p dx + \frac{1}{c}\int_\Omega Z^{p-2}|\nabla Z|^2 dx + \int_\Omega Z^p dx \leq c\int_\Omega Z^p(|\nabla I|^2 + 1)dx\\
\leq& c\|Z^{p/2}\|_4^2 \leq c(\|\nabla Z^{p/2}\|_2^{2(1-1/p)}\|Z^{p/2}\|_{4/p}^{2/p} + \|Z^{p/2}\|_{4/p}^2)\\
\leq& c(\|\nabla Z^{p/2}\|_2^{2(1-1/p)} + 1) \leq \frac{1}{c}\|\nabla Z^{p/2}\|_2^2 + c.\end{aligned}$$

B G all i e ali e ha e $\|Z(\cdot,t)\|_p \leq c$.

S e 9. $\|Z(\cdot,t)\|_\infty \leq c$.

Si ce $\|Z\|_3$ i if ml b ded, a im le a lica i f a ab lic eg la i (K al- c k a d S ma ka 2008, Lemma 1) he ec d e a i f (1.1) gi e he if m b ded e f $\|\nabla I\|_\infty$. Ba ed a m di ed M e i e a i a i (Ta a d Wi kle (2012), Lemma A.1) e ca b ai $\|Z(\cdot,t)\|_\infty \leq c$ di ec l .

Si ce $\|T\|_\infty + \|I\|_\infty + \|\nabla I\|_\infty + \|V\|_\infty + \|Z\|_\infty$ i if ml b ded, he l i ca bl a $t \to t_m^-$. Th , $t_m = \infty$; amel , he l i e i gl ball . Thi c m le e he f. □

2.2 Point dissipativity

I hi b ec i e ill h ha he l i i l ima el b ded b a c a i de e de f i i ial c di i . H e e , he c a $0 \le t_0 \le t_1 \le \cdots$ ma de e d he i i ial c di i . We a e a lemma ha i a al g Lemma 2.1.

Lemma 2.3 *Let $y(t) \ge 0$ be continuously differentiable, $h(t) \ge 0$ be locally integrable on $[t_0, \infty)$, and $y'(t) + C_1 y(t) \le h(t)$ for all $t \ge t_0$, where $C_1 > 0$ and $t_0 \ge 0$. Assume $\lim_{t\to\infty} \int_{t-1}^{t} h(s)ds \le C_2$, then we have $\lim_{t\to\infty} y(t) \le C_2/C_1 + 2C_2$.*

Proof F a f cie l mall $\varepsilon > 0$, he e e i $t_1 \ge t_0$ ch ha $\int_{t-1}^{t} h(s)ds \le C_2 + \varepsilon$ f all $t \ge t_1$. We claim ha he e e i $t_2 \ge t_1$ ch ha $y(t_2) \le (C_2 + 2\varepsilon)/C_1$; he i e, $y(t) > (C_2 + 2\varepsilon)/C_1$ f all $t \ge t_1$ hich im lie ha $y'(t) < h(t) - (C_2 + 2\varepsilon)$ a d $y(t+1) < y(t) - \varepsilon$ f all $t \ge t_1$, a c adic i . S e ha e $y(t_2) \le (C_2 + 2\varepsilon)/C_1$ f me $t_2 \ge t_1$ hich ge he i h Lemma 2.1 im lie ha $y(t) \le$ ma $\{(C_2 + 2\varepsilon)/C_1 + C_2, C_2/C_1 + 2C_2\}$ f all $t \ge t_2$. E eciall , $\lim_{t\to\infty} y(t) \le$ ma $\{(C_2 + 2\varepsilon)/C_1 + C_2, C_2/C_1 + 2C_2\}$. Si ce $\varepsilon > 0$ i a bi a il mall e ma ch e $\varepsilon < C_1 C_2/2$ a d b ai $\lim_{t\to\infty} y(t) \le C_2/C_1 + 2C_2$. Thi c m le e ha f. □

N e a e ead h ha he em i i di i a i e.

Theorem 2.4 *Let $\Omega \subset \mathbb{R}^2$ and $\mathbb{X}_+ = W^{1,p_0}(\Omega, \mathbb{R}_+)$. Assume (H1)-(H3). Let (T, I, V, Z) be the classical solution of system (1.1) obtained in Theorem 2.2. There exists $C > 0$ independent of initial conditions such that*

$$\lim_{t\to\infty} (\|T(\cdot,t)\|_{\mathbb{X}} + \|I(\cdot,t)\|_{\mathbb{X}} + \|V(\cdot,t)\|_{\mathbb{X}} + \|Z(\cdot,t)\|_{\mathbb{X}}) \le C. \tag{2.11}$$

Here, $\mathbb{X} = W^{1,p_0}(\Omega, \mathbb{R})$ and $\|u\|_{\mathbb{X}} = \|u\|_{p_0} + \|\nabla u\|_{p_0}$ for $u \in \mathbb{X}$.

Proof We ceed i he f ll i g 12 e . The i e e a e imila he f f The em 2.2 a d he de ail a e mi ed. A e hall ee i he la e , he mai dif c l lie i he e ima e f $\|\nabla Z\|_{2p}$ i h $p > 1$. F c e ie ce, e e C_i (i h $i = 1, 2, \cdots$) de e la ge i i e c a ha a e i de e de f he i i ial c di i .

S e 1. F m he e a i f (1.1) e ha e $\partial_t T \le d_T \Delta T + b(T)$. B (H1) e b ai f m he c m a i i ci le ha $\lim_{t\to\infty} \|T\|_\infty \le T_0$.

S e 2. The e e i $C_1 > 0$ a d $t_0 \ge 0$ ch ha $\|T\|_\infty \le C_1$ f all $t \ge t_0$. F m he em (1.1) e ha e

$$\frac{d}{dt}\int_\Omega (T + I + Z)dx \le \int_\Omega [b(0) + C_1 - T - \mu_I I - \mu_Z Z]dx, \quad t \ge t_0$$

w hich im lie ha $\lim_{t\to\infty}(\|I\|_1 + \|Z\|_1) \le C_2$. A i eg a i f he hi d e a i f (1.1) gi e $\lim_{t\to\infty} \|V\|_1 \le C_3$.

S e 3. The e e i $C_4 > 0$ a d $t_1 \ge t_0$ ch ha $\|I\|_1 + \|V\|_1 + \|Z\|_1 \le C_4$ f all $t \ge t_1$. F a $p > 1$, i f ll w f m he ec d a d hi d e a i f (1.1) a d Gaglia d -Ni e be g i e ali ha

$$\frac{d}{dt}\int_\Omega (I^p + V^p)dx + C_5 \int_\Omega (I^p + V^p)dx \le C_6, \quad t \ge t_1$$

w hich im lie ha $\lim_{t\to\infty}(\|I\|_p + \|V\|_p) \le C_7$. N e ha C_7 de e d p.

S e 4. The e e i $C_8 > 0$ a d $t_2 \ge t_1$ ch ha $\|I\|_3 + \|V\|_3 \le C_8$ f all $t \ge t_2$. Si ce w e ha e ed $p = 3$, he c a

F a $t \ge t_4 + 1$, he e e i $s \in [t-1, t]$ ch ha $\|Z(\cdot, s)\|_2^2 \le C_{17}$. I he f ll f m he ab e i e ali ha $\|Z(\cdot, t)\|_2^2 \le C_{17} e^{C_{18}(C_{17}+1)}$ f all $t \ge t_4 + 1$. E eciall , $\lim_{t\to\infty}$ $\|Z\|_2 \le C_{19}$.

S e 8. The e e i $C_{20} > 0$ a d $t_5 \ge t_4$ ch ha $\|Z\|_2 \le C_{20}$ f all $t \ge t_5$. A a lica i f (K alc k a d S ma ka 2008, Lemma 1) he ec d e a i f (1.1) gi e $\|\nabla I\|_4 \le C_{21}$ f $t \ge t_5$. F a $p > 1$, b he f he a i f (1.1) a d Gaglia d -Ni e be g i e ali w e b ai

$$\frac{d}{dt}\int_\Omega Z^p dx + \int_\Omega Z^p dx \le C_{22}, \quad t \ge t_5,$$

w hich im lie ha $\lim_{t\to\infty}$ $\|Z\|_p \le C_{23}$.

S e 9. The e e i $C_{24} > 0$ a d $t_6 \ge t_5$ ch ha $\|Z\|_3 \le C_{24}$ f all $t \ge t_6$. A l i g (K alc k a d S ma ka 2008, Lemma 1), e ca de i e ha $\|\nabla T\|_\infty + \|\nabla I\|_\infty + \|\nabla V\|_\infty \le C_{25}$ f $t \ge t_6$. Ba ed a m di ed M e i e a i a i (Ta a d Wi kle (2012), Lemma A.1), e ca h ha $\|Z(\cdot, t)\|_p$ i 1 ima el b ded f a i e $p > 0$. Thi ge he i h (D g 1997, The em 1) he gi e $\lim_{t\to\infty}$ $\|Z\|_\infty \le C_{26}$.

S e 10. The e e i $C_{27} > 0$ a d $t_7 \ge t_6$ ch ha $\|Z\|_\infty \le C_{27}$ f all $t \ge t_7$. I he f ll f m he f he a i f (1.1) a d he Gaglia d -Ni e be g i e ali ha

$$\frac{d}{dt}\int_\Omega |\nabla Z|^2 dx + \int_\Omega |\nabla Z|^2 dx \le C_{28}, \quad t \ge t_7,$$

w hich im lie ha $\lim_{t\to\infty}$ $\|\nabla Z\|_2^2 \le C_{28}$.

S e 11. The e e i $C_{29} > 0$ a d $t_8 \ge t_7$ ch ha $\|\nabla Z\|_2 \le C_{29}$ f all $t \ge t_8$. De e $J := \nabla I$. I f ll f m he ec d e a i f (1.1) ha

$$\partial_t J = d_I \Delta J - \mu_I J + \Psi(T, I, V, Z, \nabla T, J, \nabla Z),$$

w he e

$$\Psi = (\partial_T f + \partial_T g)\nabla T + \partial_I f J + \partial_Z g \nabla Z - rJZ - rI\nabla Z.$$

I i ea il ee ha $\|\Psi\|_2 \le C_{30}$ f $t \ge t_8$. F each $p \in [1, \infty)$, e a 1 he me h d f a ia i f c a he e a i f J a d e he e ima e f Ne ma hea emig (H ma a d Wi kle 2005; K alc k a d S ma ka 2008) b ai $\|\nabla J\|_p \le C_{31}$ f all $t \ge t_8$. E eciall , $\lim_{t\to\infty}$ $\|\Delta I\|_p \le C_{32}$.

S e 12. F each $p > 1$, he e e i $C_{33} > 0$ a d $t_9 \ge t_8$ ch ha $\|\Delta I\|_{2p} \le C_{33}$ f all $t \ge t_9$. I f ll f m he f he a i f (1.1) a d G ee ide i ha

$$\frac{1}{2p}\frac{d}{dt}\int_\Omega |\nabla Z|^{2p} dx = \int_\Omega |\nabla Z|^{2p-2}\nabla Z \cdot \nabla(\partial_t Z) dx = K_1 + K_2 + K_3, \qquad (2.12)$$

w here

By (Mizoguchi and Souplet 2014, Lemma 4.2), we have $|\partial_\nu(|\nabla Z|^2)| \le 2\kappa(\partial\Omega)|\nabla Z|^2$, where $\kappa(\partial\Omega)$ is the maximum of curvature of $\partial\Omega$. It follows that

$$\begin{aligned} K_{12} \le& \kappa(\partial\Omega)d_Z(0)\int_{\partial\Omega}|\nabla Z|^{2p}dS + C_{37}\int_\Omega |\nabla Z|^{2p-2}|\nabla(|\nabla Z|^2)|dx \\ &- \frac{d_Z(C_{11})(p-1)}{2}\int_\Omega |\nabla Z|^{2p-4}|\nabla(|\nabla Z|^2)|^2dx. \end{aligned}$$

In view of the trace inequality (Souplet and Quittner 2007, Remark 52.9):

$$\|u\|_{L^2(\partial\Omega)} \le \varepsilon\|\nabla u\|_{L^2(\Omega)} + C(\varepsilon)\|u\|_{L^2(\Omega)}$$

and Cauchy's inequality: $2uv \le \varepsilon u^2 + (1/\varepsilon)v^2$ with a small $\varepsilon > 0$, we further obtain

$$K_{12} \le C_{38}\int_\Omega |\nabla Z|^{2p}dx - \frac{d_Z(C_{11})(p-1)}{3}\int_\Omega |\nabla Z|^{2p-4}|\nabla(|\nabla Z|^2)|^2dx. \tag{2.17}$$

Another application of Cauchy's inequality to (2.15) gives

$$K_{11} \le C_{39}\int_\Omega |\nabla Z|^{2p}dx + \frac{d_Z(C_{11})(p-1)}{9}\int_\Omega |\nabla Z|^{2p-4}|\nabla(|\nabla Z|^2)|^2dx. \tag{2.18}$$

Note that $|\Delta Z| \le \sqrt{2}|\nabla^2 Z|_E$. We apply Cauchy's inequality again to K_2 and make use of $\|\Delta I\|_{2p} \le C_{33}$ to find

$$\begin{aligned} K_2 \le& \frac{d_Z(C_{11})(p-1)}{9}\int_\Omega |\nabla Z|^{2p-4}|\nabla(|\nabla Z|^2)|^2dx \\ &+ \frac{d_Z(C_{11})}{2}\int_\Omega |\nabla Z|^{2p-2}|\nabla^2 Z|_E^2dx + C_{40}\int_\Omega |\nabla Z|^{2p}dx + C_{40}. \end{aligned} \tag{2.19}$$

A combination of (2.12), (2.13), (2.14), (2.16), (2.17), (2.18), and (2.19) yields

$$\begin{aligned} &\frac{1}{2p}\frac{d}{dt}\int_\Omega |\nabla Z|^{2p}dx + \frac{d_Z(C_{11})(p-1)}{9}\int_\Omega |\nabla Z|^{2p-4}|\nabla(|\nabla Z|^2)|^2dx \\ &\quad + \frac{d_Z(C_{11})}{2}\int_\Omega |\nabla Z|^{2p-2}|\nabla^2 Z|_E^2dx \le C_{41}\int_\Omega |\nabla Z|^{2p}dx + C_{41}. \end{aligned}$$

Fi all w e e G ee ide i , $|\Delta Z| \le \sqrt{2}|\nabla^2 Z|_E$ a d Ca ch i e ali b ai

$$
\begin{aligned}
&(C_{41}+2)\int_\Omega |\nabla Z|^{2p}dx\\
&\quad=(C_{41}+2)\int_\Omega (|\nabla Z|^{2p-2}\nabla Z)\cdot\nabla Z dx\\
&\quad=-(C_{41}+2)\int_\Omega Z[|\nabla Z|^{2p-2}\Delta Z+(p-1)|\nabla Z|^{2p-4}\nabla(|\nabla Z|^2)\cdot\nabla Z]dx\\
&\quad\le \frac{d_Z(C_{11})(p-1)}{9}\int_\Omega |\nabla Z|^{2p-4}|\nabla(|\nabla Z|^2)|^2dx\\
&\qquad+\frac{d_Z(C_{11})}{2}\int_\Omega |\nabla Z|^{2p-2}|\nabla^2 Z|_E^2dx+C_{42}\int_\Omega |\nabla Z|^{2p-2}dx,
\end{aligned}
$$

a d

$$
C_{42}\int_\Omega |\nabla Z|^{2p-2}dx \le \int_\Omega |\nabla Z|^{2p}dx + C_{43}.
$$

C e e l w e ha e

$$
\frac{1}{2p}\frac{d}{dt}\int_\Omega |\nabla Z|^{2p}dx+\int_\Omega |\nabla Z|^{2p}dx \le C_{44},
$$

w hich im lie $\lim_{t\to\infty}$ $\|\nabla Z\|_{2p}^{2p} \le C_{44}$.

The ef e w e ha e ed he i di i a i f he em. □

C li g The em 2.2 a d The em 2.4 gi e The em 1.1.

3 Global dynamics

I hi ec i w e i e iga e he l g- ime beha i f he l i he em (1.1). Fi w e d he c a ead a e $E=(T,I,V,Z)$ ha a i e he f ll w i g e ilib i m e a i

$$
b(T)=f(T,I)+g(T,V)=(rZ+\mu_I)I,\quad V=kI/\mu_V,\quad (rI-\mu_Z)Z=0. \tag{3.1}
$$

I ie w f (H1) a d (H2), e ca ea il check ha (3.1) ibl ha h ee e f h m ge e ead a e : he i fec i -f ee ead a e $E_0 := (T_0,0,0,0)$, he CTL-i ac i a ed ead a e $E_1 := (T_1,I_1,V_1,0)$, a d he CTL-i ac i a ed ead a e $E_2 := (T_2,I_2,V_2,Z_2)$. I he f ll w i g b ec i w e w ill a al e he e i - e ce a d abili f he e ead a e .

3.1 Basic reproduction numbers and local analyses

I hi b ec i e ill e abli h he e i e ce a d l cal abili e l f c a ead a e . I ie f (H1) a d (H2), he e e i a i e i fec i -f ee ead a e $E_0 = (T_0, 0, 0, 0)$ f (1.1). Li ea i i g he em (1.1) ab E_0 gi e e a i

$$\partial_t T = d_T \Delta T + [b'(T) - \partial_T f(T_0, 0) - \partial_T g(T_0, 0)]T - \partial_I f(T_0, 0)I - \partial_V g(T_0, 0)V$$

a d $\partial_t Z = d_Z(0)\Delta Z - \mu_Z Z$, hich d affec he abili f E_0, a d a dec led em

$$\begin{cases} \partial_t I = d_I \Delta I + \partial_I f(T_0, 0)I + \partial_V g(T_0, 0)V - \mu_I I, \\ \partial_t V = d_V \Delta V + kI - \mu_V V. \end{cases}$$

The li ea e a he igh -ha d ide f he ab e e a i ca be dec m ed a $\mathcal{F} - \mathcal{V}$, he e

$$\mathcal{F} = \begin{pmatrix} \partial_I f(T_0, 0) & \partial_V g(T_0, 0) \\ 0 & 0 \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} -d_I \Delta + \mu_I & 0 \\ -k & -d_V \Delta + \mu_V \end{pmatrix}.$$

N e de e he ba ic e d c i mbe f i al i fec i a $R_0 = \rho(\mathcal{F}\mathcal{V}^{-1})$, he ec al adi f he e ge e a i e a $\mathcal{F}\mathcal{V}^{-1}$ he Ba ach ace $\mathbb{X}^2 = W^{1,p_0}(\Omega, \mathbb{R}^2)$. Le $\mathcal{B}_d = \partial_I f(T_0, 0)(-d_I \Delta + \mu_I)^{-1}$ be he e ge e a i e a f di ec a mi i a d $\mathcal{B}_i = k\partial_V g(T_0, 0)(-d_V \Delta + \mu_V)^{-1}(-d_I \Delta + \mu_I)^{-1}$ be he e ge e a i e a f i di ec a mi i . A im le calc la i gi e $R_0 = \rho(\mathcal{B}_d + \mathcal{B}_i)$. N e ha he c a f c i $1 \in \mathbb{X}$ i a eige f c i f $\mathcal{B}_d + \mathcal{B}_i$. I f ll f m K ei -R ma he em ha he c e di g eige al e i a i ci al eige al e; amel ,

$$R_0 = \frac{\partial_I f(T_0, 0)}{\mu_I} + \frac{k\partial_V g(T_0, 0)}{\mu_V \mu_I}. \tag{3.2}$$

Remark 3.1 The bi l gical i e e a i f he ab e f m la i clea . The f ac i gi e he a e age mbe f e l i fec ed cell h gh cell- -cell a mi i d i g he life a f a i fec ed cell hich i i d ced he i fec ed a ge cell i h de i T_0. The ec d f ac i c he a e age mbe f e i e d ced d i g he i di ec a mi i c cle he a i i i d ced he i fec ed a ge cell i h de i T_0. The e f ac i , de ed b R_d a d R_i, a e al efe ed a he ba ic e d c i mbe f di ec a d i di ec a mi i , e ec i el . The ab e f m la c i cide i h he ea lie k i al m del i h a ial diff i (Lai a d Z 2014, 2015; P ba ha h e al. 2014); ee al (Magal e al. 2019) f a imila f m la f R_0 f a HIV m del i h imm e e e. Si ce $R_0 = R_d + R_i$, i i c cl ded ha he ig a ce f ei he a mi i mecha i ill de e ima e he ba ic e d c i mbe f i al i fec i .

Proposition 3.2 *Assume (H1)-(H3). If $R_0 < 1$, then the infection-free steady state E_0 is linearly stable. If $R_0 > 1$, then E_0 is linearly unstable.*

Proof Si ce he li ea i ed e a i f T a d Z a e able, i f ce h ha a d

$$\lim_{T \to T_0} \frac{kg(T, v(T))}{}$$

b he ig f $R_1 - 1$, he-e

$$R_1 := \frac{rI_1}{\mu_Z} \tag{3.6}$$

i he ba ic -e -d c i mbe- f he imm e-e e. We mma-i e he ab e -e l i he f ll i g- ii .

Proposition 3.3 *Assume (H1)-(H3). The CTL-inactivated steady state E_1 exists uniquely (i.e., $0 < T_1 < T_0$, $I_1 > 0$ and $V_1 > 0$) if and only if $R_0 > 1$. Moreover, if $R_0 > 1$, then E_1 is linearly stable when $R_1 < 1$ and linearly unstable when $R_1 > 1$.*

Fi all e hall d he e i e ce a d l call a m ic abili f he CTL-ac i a ed ead a e $E_2 = (T_2, I_2, V_2, Z_2)$. I fac e ha e he f ll i g- ii .

Proposition 3.4 *Assume (H1)–(H3). The CTL-activated steady state E_2 exists uniquely (i.e., $0 < T_2 < T_0$, $I_2 > 0$, $V_2 > 0$ and $Z_2 > 0$) if and only if $R_0 > 1$ and $R_1 > 1$. Moreover, E_2 is linearly stable whenever it exists.*

Proof F- m (3.1) e ha e $I_2 = \mu_Z/r$ a d $V_2 = k\mu_Z/(r\mu_V)$. T - e he e i e ce f E_2, i f ce h ha $H(T, I_2, V_2) = 1$ ha a i e l i $T_2 \in (0, T_0)$ ch ha $b(T_2) > \mu_I I_2$ a d he $Z_2 = [b(T_2)/I_2 - \mu_I]/r$, he-e

$$H(T, I, V) = \frac{f(T, I) + g(T, V)}{b(T)}$$

i -ic l i c-ea i g i T, I, V d e (H1)-(H2). T achie e hi e b e- e ha $R_1 > 1$ gi e $I_1 > \mu_Z/r$, hich e ail $I_1 > \mu_Z/r = I_2$ a d $V_1 = kI_1/\mu_V > V_2$. C e e l , $H(T_1, I_2, V_2$

w he e he a iable f $\partial_T f$ a d $\partial_I f$ a e (T_2, I_2) w hile he a iable f $\partial_T g$ a d $\partial_V g$ a e (T_2, V_2). We w ill e b c adic i ha all eige al e f he li ea e a c e di g he ab e li ea em ha e ega i e eal a . A me he c a ha he e e i $\lambda \in \mathbb{C}$ w i h $\mathrm{Re}\lambda \geq 0$ a d $\xi \geq 0$ ch ha de $(\lambda + B) = 0$, w he e

$$B = \begin{pmatrix} d_T\xi - b'(T_2) + \partial_T f + \partial_T g & \partial_I f & \partial_V g & 0 \\ -\partial_T f - \partial_T g & d_I\xi + \mu_I + rZ_2 - \partial_I f & -\partial_V g & rI_2 \\ 0 & -k & d_V\xi + \mu_V & 0 \\ 0 & -[r - d_Z'(I_2)\xi]Z_2 & 0 & d_Z(I_2)\xi \end{pmatrix}.$$

A im le calc la i gi e

$$\left(1 + \frac{\partial_T f + \partial_T g}{\lambda + d_T\xi}\right)\left(1 + \frac{\lambda + d_I\xi}{\mu_I + rZ_2} + \frac{rI_2[r - d_Z'(I_2)\xi]}{(\mu_I + rZ_2)[\lambda + d_Z(I_2)\xi]}\right)$$
$$= \frac{\partial_I f}{\mu_I + rZ_2} + \frac{k\partial_V g}{(\mu_I + rZ_2)(\lambda + d_V\xi + \mu_V)}.$$

Taki g m d l b h ide gi e

$$1 < \frac{\partial_I f}{\mu_I + rZ_2} + \frac{k\partial_V g}{\mu_V(\mu_I + rZ_2)} \leq \frac{f}{(\mu_I + rZ_2)I_2} + \frac{kg}{\mu_V(\mu_I + rZ_2)V_2} = 1,$$

a c adic i . Thi c m le e he f. □

3.2 Global dynamics: global attractivity and uniform persistence

I hi b ec i w e w ill e abli h gl bal d amic f he l i emi w $\Theta(t)$ f em (1.1) w i h a i i ial c di i i $\mathbb{X}_+^4$. T b ai he c m ac e f he l i emi w w e im e he eg la i f he l i b ai ed i The em 2.2. M e eci el w e ha e he f ll w i g e l :

Lemma 3.5 *Assume (H1)-(H3). Let (T, I, V, Z) be the non-negative global classical solution of the system (1.1) obtained in Theorem 2.2. Then there exist $\sigma \in (0, 1)$ and $c > 0$ such that*

$$\|(T, I, V, Z)\|_{C^{2+\sigma, 1+\frac{\sigma}{2}}(\bar{\Omega}\times[1,\infty))} \leq c.$$

Proof F m The em 2.2 w e ca d w i i e c a c_1, c_2 ch ha

$$0 < T(x, t), I(x, t), V(x, t), Z(x, t) \leq c_1, \quad |\nabla I(x, t)| \leq c_2 \text{ f all } x \in \Omega \text{ a d } t > 0.$$

We e w i e he f he e a i f (1.1) a $\partial_t Z = \nabla \cdot A + B$, w he e $A = d_Z(I)\nabla Z + d_Z'(I)Z\nabla I$ a d $B = rIZ - \mu_Z Z$. Ob i 1 , $|B| \leq c_3$ a d $|A| \leq d_Z(0)|\nabla Z| + c_4$.

B (H3) a d Ca ch i e ali w e al ha e

$$A \cdot \nabla Z = d_Z(I)|\nabla Z|^2 + d_Z'(I) Z \nabla I \cdot \nabla Z \geq \frac{d_Z(c_1)}{2}|\nabla Z|^2 - c_5.$$

Th w e a l he H lde eg la i f a ili ea a ab lic e a i (P i a d Ve i 1993, The em 1.3 a d Rema k 1.4) b ai $\|Z\|_{C^{\sigma,\frac{\sigma}{2}}(\bar{\Omega}\times[1,\infty))} \leq c_6$. M e- e , a l i g he a da d a ab lic Scha de he (Lad he ka a e al. 1968) he em (1.1), e ha

$$\|(T, I, V, Z)\|_{C^{2+\sigma,1+\frac{\sigma}{2}}(\bar{\Omega}\times[1,\infty))} \leq c_7,$$

w hich c m le e he f. □

F m Lemma 3.5 w e b e e ha , f a $t > 1$ a d a b ded e B i $\mathbb{X}_+^4$, he e $\Theta(t)B$ i b ded i $C^2(\Omega, \mathbb{R}_+^4)$ a d h ec m ac i $\mathbb{X}_+^4 = W^{1,p_0}(\Omega, \mathbb{R}_+^4)$ f $p_0 > 2$. Thi im lie ha he l i ma $\Theta(t) : \mathbb{X}_+^4 \to \mathbb{X}_+^4$ i c m ac f all $t > 1$. Recall f m The em 2.4 ha $\Theta(t)$ i i di i a i e. I he f ll w f m (Hale 1988, The em 3.4.8) ha he em admi a em gl bal a ac i $\mathbb{X}_+^4$. Ne w e b ai he if m e i e ce f l i w hich w ill be ed e he gl ball a m ic abili f ead a e .

Proposition 3.6 *Assume (H1)-(H3). Let (T, I, V, Z) be the non-negative global classical solution of the system (1.1) with an initial value in $[\mathbb{X}_+ \setminus \{0\}]^4$. There exists $\delta_0 > 0$ such that*

$$\liminf_{t\to\infty} \min_{x\in\bar{\Omega}} T(x,t) \geq \delta_0.$$

If $R_0 > 1$, then there exists $\delta_1 > 0$ such that

$$\liminf_{t\to\infty} \min_{x\in\bar{\Omega}} \min\{I(x,t), V(x,t)\} \geq \delta_1.$$

Proof I ie w f he e a i f (1.1), (H2) a d (2.11) w e d $C_0 > 0$ a d $t_0 > 0$ ch ha $\partial_t T \geq d_T \Delta T + b(T) - C_0 T$ f all $t > t_0$. B (H1), he e e i $\delta_0 \in (0, T_0)$ ch ha $b(\delta_0) - C$

c a ha he e e i a l i (T, I, V, Z) i h i iial c di i i $\mathcal{X}_1$ ch ha $\lim_{t\to\infty}(T, I, V, Z) = (T_0, 0, 0, 0)$. The e e i $t_1 > 0$ ch ha

$$
\begin{aligned}
&\partial_t I \geq d_I \Delta I + (1-\varepsilon)[\partial_I f(T_0, 0)I + \partial_V g(T_0, 0)V] - \mu_I I,\\
&\partial_t V = d_V \Delta V + kI - \mu_V V,
\end{aligned}
$$

he e $\varepsilon = (1 - 1/R_0)/2 > 0$. O acc f Pe -F be i he em e le $(I_\varepsilon, V_\varepsilon) \in \mathbb{R}^2_+$ be a i i e eige ec f he ma i

$$
\begin{pmatrix} (1-\varepsilon)\partial_I f(T_0, 0) - \mu_I & (1-\varepsilon)\partial_V g(T_0, 0) \\ k & -\mu_V \end{pmatrix}
$$

c e di g he i ci al eige al e $\lambda_1 > 0$. The e e i $c_1 > 0$ ch ha $c_1 I(x, t_1) \geq I_\varepsilon$ a d $c_1 V(x, t_1) \geq V_\varepsilon$ f all $x \in \Omega$. I he f ll f m c m a i i ci le ha $I(x,t) \geq e^{\lambda_1(t-t_1)} I_\varepsilon / c_1$ a d $V(x,t) \geq e^{\lambda_1(t-t_1)} V_\varepsilon / c_1$ f all $t > t_1$. Thi c adic he a m i ha $I(x,t) \to 0$ a d $V(x,t) \to 0$ a $t \to \infty$. Th , he able e f E_0 d e i e ec $\eta_1^{-1}(0, \infty)$. B (Smi h a d Zha 2001, The em 3), he e e i $\delta_1 > 0$ ch ha $\liminf_{t\to\infty} p(\Theta(t)\phi) \geq \delta_1$ f a $\phi \in \mathcal{X}_1$. □

N e a e ead e he gl bal a ac i e e f ead a e ia he L a- f ci ech i e a d LaSalle i a ia ce i ci le. T ge he i h l call a m ic abili b ai ed i Sec . 3.1 e ill ac all b ai gl ball a m ic abili f ead a e (de ce ai c di i). Fi e hall e abli h gl bal a ac i e e f he i fec i -f ee ead a e $E_0 = (T_0, 0, 0, 0)$ ba ed he f l- l i g L a f ci :

$$
\mathcal{L}_0(T, I, V, Z) := \frac{1}{2}\int_\Omega [kI^2 + \partial_V g(T_0, 0)V^2]dx. \tag{3.7}
$$

He e, a d i he f hc mi g c e , a L a f ci i a diffe e iable a d - ega i e f ci al a b e f $\mathbb{X}^4_+$ hich i i i el i a ia i h e ec he l i ma $\Theta(t)$. F i a ce e de e $\mathcal{L}_0$ he b e

$$
D_0 = \{\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in \mathbb{X}^4_+ : \phi_1(x) \leq T_0\}. \tag{3.8}
$$

The i i e i a ia ce f D_0 f ll f m he - ega i i f f a d g, (H1) a d a di ec a lica i f he c m a i i ci le he e a i f (1.1). M e e , he mega limi e $\omega(\phi) \subset D_0$ f a $\phi \in \mathbb{X}^4_+$. The mai e i he L a f c- i ech i e i c c a i able L a f ci ha i -i c ea i g al g he l i ajec . Whe e ic ed al g a l i (T, I, V, Z), he L a f ci ca be al a ega ded a a i gle- a iable f ci f $t \in \mathbb{R}_+$.

Theorem 3.7 *Assume (H1)–(H3). If $R_0 \leq 1$, then the infection-free steady state E_0 is globally attractive. If $R_0 < 1$, then E_0 is globally asymptotically stable.*

Proof O acc r f he ec d a d hi-d e r a i f em (1.1)w e b ai fr m (3.7) a d Gree ide i

$$\frac{d\mathcal{L}_0}{dt} = -kd_I\int_\Omega |\nabla I|^2dx - \partial_V g(T_0,0)d_V\int_\Omega |\nabla V|^2dx - rk\int_\Omega I^2Zdx - k\mu_I\int_\Omega I^2dx$$
$$- \mu_V\partial_V g(T_0,0)\int_\Omega V^2dx + k\int_\Omega If(T,I)dx + k\int_\Omega I(g(T,V)+\partial_V g(T_0,0)V)dx,$$

Si ce D_0 i (3.8) i i i el i a-ia w e ha e $\|T\|_\infty \le T_0$. I he f llw fr m (H2) ha $f(T,I) \le f(T_0,I) \le \partial_I f(T_0,0)I$ a d $g(T,V) \le g(T_0,V) \le \partial_T g(T_0,0)V$. S b i r i g he e i he ab e e r a i gi e

$$\frac{d\mathcal{L}_0}{dt} \le \int_\Omega k[\partial_I f(T_0,0)-\mu_I]I^2dx + \int_\Omega 2k\partial_V g(T_0,0)IVdx - \int_\Omega \mu_V\partial_V g(T_0,0)V^2dx$$
$$= -\mu_V\partial_V g(T_0,0)\int_\Omega (V-\frac{k}{\mu_I}I)^2dx + k\mu_I(R_0-1)\int_\Omega I^2dx \le 0,$$

beca e $R_0 \le 1$. The la-ge i i el i a-ia ce e f $d\mathcal{L}_0/dt = 0$ i D_0 i a i - gle $\{E_0\}$. Ob i r 1 , $\omega(\phi) \in D_0$ f r a $\phi \in D_0$. B LaSalle i a-ia ce -i ci le, E_0 i gl ball a -ac i e i D_0; amel , D_0 i a r b e f $W^s(E_0)$, he able e f E_0. Nw , f r a i i ial al e $\phi \in \mathbb{X}^4_+$, he mega limi e $\omega(\phi)$ i i e- all chai -a i i e (Zha 2017, Lemma 1.2.1) a d $\omega(\phi) \subset D_0$. O acc r f (Zha 2017, The -em 1.2.1), E_0 i gl ball a -ac i e i $\mathbb{X}^4_+$. If f -he-, $R_0 < 1$, he P- i i 3.2 im lie ha E_0 i ac r all gl ball a m icall able. □

If $R_0 < 1$, e ma r e a imila- a-g me a i (Bai a d Wi kle- 2016) e he gl bal a -ac i e e f E_0. Hw e e-, f r he c-i ical ca e $R_0 = 1$w e hall a 1 he LaSalle i a-ia ce -i ci le a i he ab e f.

Ne w e w ill e 1 -e he c di i f r he gl bal abili f $E_1 = (T_1, I_1, V_1, 0)$ a d $E_2 = (T_2, I_2, V_2, Z_2)$. T hi e dw e a r me ha he i cide ce f c i ake he f llw i g f -m :

(H4) $f(T,I) = h_0(T)h_d(I)$ a d $g(T,V) = h_0(T)h_i(V)$w he-e $h_0, h_d, h_i \in C^2(\mathbb{R}_+)$.

Remark 3.8 We h r ld i r ha h he i (H4) i -i ge , beca e i ca be a i ed b ma f -m f $f(T,I)$ a d $g(T,V)$ i cl di g he ma ac i i cide ce $f(T,I) = \beta_d TI$, $g(T,V) = \beta_i TV$ r ed i im la i , ee Sec . 4.1 f r de ail . I fac , h he i (H4) i 1 r ed r e he gl bal abili f he h m ge e r ead a e E_1 a d E_2. F r he li ea- abili f E_0, E_1, E_2 a d he li ea- abili f E_0, h he i (H4) ca be-em ed. He ce, i i a r -al r d he gl bal abili f he CTL-i ac i a ed/ac i a ed ead a ew i h r a r m i (H4) i r -f r -e w -k.

N e f m (H2) a d (H4) ha $h_0' > 0$. Thi ge he i h G ee ide i im lie ha he i eg al i he e e i f $d\mathcal{L}_1/dt$ i m e ha e . Simila l , i f ll f m G ee ide i ha he ec d a d hi d i eg al a e i i e hile he f h i eg al e al e . The ef e, $d\mathcal{L}_1/dt \le \int_\Omega \mathcal{M}_1 dx$.

Ne e ill h ha $\mathcal{M}_1 \le 0$. Si ce $E_1 = (T_1, I_1, V_1, 0)$ a i e he e a i (3.1) a d $R_1 = rI_1/\mu_Z$ e ca e i e $b(T) = b(T) - b(T_1) + h_0(T_1)[h_d(I_1) + h_i(V_1)]$, $\mu_I = h_0(T_1)[h_d(I_1)+h_i(V_1)]/I_1$, $k = \mu_V V_1/I_1$, a d $rI_1 - \mu_Z = \mu_Z(R_1 - 1)$. C e e 1 ,

$$\begin{aligned}\mathcal{M}_1 = &\left[1 - \frac{h_0(T_1)}{h_0(T)}\right][b(T) - b(T_1)] + \mu_Z(R_1 - 1)Z \\ &+ h_0(T_1)[h_d(I_1)\mathcal{M}_{11} + h_i(V_1)\mathcal{M}_{12}],\end{aligned} \tag{3.11}$$

he e

$$\begin{aligned}\mathcal{M}_{11} =& 1 - \frac{h_0(T_1)}{h_0(T)} + \frac{h_d(I)}{h_d(I_1)} - \frac{I_1 h_0(T) h_d(I)}{I h_0(T_1) h_d(I_1)} + 1 - \frac{I}{I_1}, \\ \mathcal{M}_{12} =& 1 - \frac{h_0(T_1)}{h_0(T)} + \frac{h_i(V)}{h_i(V_1)} - \frac{I_1 h_0(T) h_i(V)}{I h_0(T_1) h_i(V_1)} + 1 - \frac{I}{I_1} + \frac{I}{I_1} - \frac{V}{V_1} - \frac{V_1 I}{V I_1} + 1.\end{aligned}$$

B addi g a d b ac i g $2 - \frac{I h_d(I_1)}{I_1 h_d(I)}$ e b ai

$$\begin{aligned}\mathcal{M}_{11} =& \left[3 - \frac{h_0(T_1)}{h_0(T)} - \frac{I_1 h_0(T) h_d(I)}{I h_0(T_1) h_d(I_1)} - \frac{I h_d(I_1)}{I_1 h_d(I)}\right] + \left[\frac{h_d(I)}{h_d(I_1)} - 1 - \frac{I}{I_1} + \frac{I h_d(I_1)}{I_1 h_d(I)}\right], \\ =& \left[3 - \frac{h_0(T_1)}{h_0(T)} - \frac{I_1 h_0(T) h_d(I)}{I h_0(T_1) h_d(I_1)} - \frac{I h_d(I_1)}{I_1 h_d(I)}\right] + \left[\frac{h_d(I)}{h_d(I_1)} - 1\right]\left[1 - \frac{I h_d(I_1)}{I_1 h_d(I)}\right].\end{aligned}$$

Simila l , b addi g a d b ac i g $3 - \frac{V h_i(V_1)}{V_1 h_i(V)}$ e b ai

$$\begin{aligned}\mathcal{M}_{12} =& \left[4 - \frac{h_0(T_1)}{h_0(T)} - \frac{I_1 h_0(T) h_i(V)}{I h_0(T_1) h_i(V_1)} - \frac{V h_i(V_1)}{V_1 h_i(V)} - \frac{I V_1}{I_1 V}\right] \\ &+ \left[\frac{h_i(V)}{h_i(V_1)} - 1 - \frac{V}{V_1} + \frac{V h_i(V_1)}{V_1 h_i(V)}\right] \\ =& \left[4 - \frac{h_0(T_1)}{h_0(T)} - \frac{I_1 h_0(T) h_i(V)}{I h_0(T_1) h_i(V_1)} - \frac{V h_i(V_1)}{V_1 h_i(V)} - \frac{I V_1}{I_1 V}\right] \\ &+ \left[\frac{h_i(V)}{h_i(V_1)} - 1\right]\left[1 - \frac{V h_i(V_1)}{V_1 h_i(V)}\right].\end{aligned}$$

O acc f (H2) a d (H4) e ha e $h_d' > 0$ a d $h_d'' \le 0$. Thi ge he i h Ca ch i e ali im lie $\mathcal{M}_{11} \le 0$. Simila l e b ai f m (H2), (H4) a d Ca ch i e ali ha $\mathcal{M}_{12} \le 0$. M e e , i ie f (H1), (H2) a d (H4) e ha e $b' < 0$ a d $h_0' > 0$. He ce, he e m i he e e i f $\mathcal{M}_1$ i (3.11) i i i e. The ec d e m i al m e ha e he $R_1 \le 1$. C mbi i g he e i h i i e e f $\mathcal{M}_{11}$ a d $\mathcal{M}_{12}$ ield $\mathcal{M}_1 \le 0$ a d $d\mathcal{L}_1/dt \le 0$.

The la-ge i i el i a-ia e f $d\mathcal{L}_1/dt = 0$ i D_1 i a i gle $\{E_1\}$. Si ce $\omega(D_1) \subset D_1$ b P- i i 3.6, w e a l LaSalle i a-ia ce -i ci le d $D_1 \subset W^s(E_1)$. Nw w e c ide- he i i ial c di i $\phi \in [\mathbb{X}_+ \setminus \{0\}]^4$. I agai f llw f- m P- i i 3.6 ha $\omega(\phi) \subset D_1$. B (Zha (2017), Lemma 1.2.1), $\omega(\phi)$ i i e- all chai -a i i e. A a lica i f (Zha 2017, The -em 1.2.1) ield $\omega(\phi) = E_1$. Thi - e gl bal a -ac i e e f E_1 i $[\mathbb{X}_+ \setminus \{0\}]^4_w$ he $R_0 > 1$ a d $R_1 \le 1$. If f- he-, $R_1 < 1$, he w e b ai f- m P- i i 3.3 ha E_1 i gl ball a m icall able i $[\mathbb{X}_+ \setminus \{0\}]^4$. □

The f llw i g -e l gi e if -m e- i e ce i Zw he b h $R_0 > 1$ a d $R_1 > 1$.

Proposition 3.10 *Assume (H1)-(H4). Let (T, I, V, Z) be the solution of (1.1) with initial condition in $[\mathbb{X}_+ \setminus \{0\}]^4$. If $R_0 > 1$ and $R_1 > 1$, then there exists $\delta_2 > 0$, independent of initial condition, such that*

$$\mathop{\mathrm{lim\,i\ f}}_{t\to\infty} \mathop{\mathrm{mi}}_{x\in\bar{\Omega}} Z(x,t) \ge \delta_2.$$

Proof De e $\mathcal{X}_2 = \mathbb{X}_+ \times [\mathbb{X}_+ \setminus \{0\}]^3$ a d $\partial\mathcal{X}_2 = \mathbb{X}_+ \times [\mathbb{X}_+\setminus\{0\}]^2 \times \{0\}$. Le M_2 be he la-ge i i el i a-ia e i $\partial\mathcal{X}_2$. U i g a imila- a-g me a i he - f f P- i i 3.6, w e d ha $E_1 = (T_1, I_1, V_1, 0)$ i gl ball a -ac i e M_2. Nw, w e i - d ce a ge e-ali ed di a ce f c i $\eta_2(u) = \mathrm{mi}_{x\in\bar\Omega}\, u_4(x)$ f - $u \in \mathbb{X}_+^4$. I f llw f- m - g ma im m -i ci le ha $\eta_1(\Theta(t)\phi) > 0$ f - all $\phi \in \mathcal{X}_2$. N e ha $\eta_2^{-1}(0,\infty) \subset \mathcal{X}_2$. He ce, he c di i (P) i (Smi h a d Zha 2001, Sec i 3) i e-i ed. We a-e lef hw ha $W^s(E_1)\cap\eta_2^{-1}(0,\infty) = \emptyset$. A me he c -a- ha f - me i i ial c di i i $\mathcal{X}_2$, he l i $(T, I, V, Z) \to (T_1, I_1, V_1, 0)$ a $t \to \infty$. The-e e i $t_2 > 0$ ch ha $\partial_t Z \ge \Delta[d_Z(I)Z] + \varepsilon_2 Z$, w he-e $\varepsilon_2 = (rI_2 - \mu_Z)/2 > 0$. B c m a-i -i ci le, w e ha e $\int_\Omega Z(x,t)dx \ge e^{\varepsilon_2(t-t_2)}\int_\Omega Z(x,t_2)dx$, w hich c -adic he a m i $Z \to 0$ a $t \to \infty$. The-ef -e, w e b ai f- m (Smi h a d Zha 2001, The -em 3) ha $\mathop{\mathrm{lim\,i\ f}}_{t\to\infty} p_2(\Theta(t)\phi) \ge \delta_2$ f - me $\delta_2 > 0$ i de e de f he i i ial c di i $\phi \in \mathcal{X}_2$. □

Ne w e hall - e he gl bal a -ac i e e (a w ell a gl ball a m ic abili) f $E_2 = (T_2, I_2, V_2, Z_2)$ ba ed he f llw i g L a f c i :

$$\begin{aligned}\mathcal{L}_2(T, I, V, Z) := & \int_\Omega \left(T - T_2 - \int_{T_2}^{T} \frac{h_0(T_2)}{h_0(\theta)} d\theta\right) dx + \int_\Omega \left(I - I_2 - I_2 \mathrm{l}\ \frac{I}{I_2}\right) dx \\ & + \frac{h_0(T_2) h_i(V_2)}{\mu_V V_2} \int_\Omega \left(V - V_2 - V_2 \mathrm{l}\ \frac{V}{V_2}\right) dx \\ & + \int_\Omega \left(Z - Z_2 - Z_2 \mathrm{l}\ \frac{Z}{Z_2}\right) dx\end{aligned}$$

de ed he i i el i a-ia e

$$D_2 = \{\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in \mathbb{X}_+^4 : \phi_i(x) > 0 \text{ f - all } i = 1, 2, 3, 4 \text{ a d } x \in \bar{\Omega}\}.$$

Simila D_1 de ed i (3.10), he e D_2 i i i el i a ia b cl ed. F a $\phi \in D_2$ w e ha e $\Theta(t)\phi \in D_2$. H w e e, h w ha $\omega(\phi) \in D_2$ w e eed make e f he e i e ce e l i P i i 3.6 a d 3.10.

Theorem 3.11 *Assume (H1)–(H4). Let (T, I, V, Z) be the solution of (1.1) with initial condition in $[\mathbb{X}_+ \setminus \{0\}]^4$. If $R_0 > 1$ and $R_1 > 1$, then the CTL-activated steady state E_2 is globally asymptotically stable provided*

$$d_I \geq \frac{Z_2}{4I_2} \max_{0 \leq I \leq \infty} \frac{|I d_Z'(I)|^2}{d_Z(I)}. \tag{3.12}$$

Proof U i g a imila a g me a i he f f The em 3.9 w e b ai af e a edi calc la i a d a a lica i f G ee ide i ha $d\mathcal{L}_2/dt = \int_\Omega \mathcal{M}_2 dx$, w he e

$$\begin{aligned}
\mathcal{M}_2 = &-\frac{d_T h_0(T_2) h_0'(T)}{h_0^2(T)}|\nabla T|^2 - \frac{d_V h_0(T_2) h_i(V_2)}{\mu_V V^2}|\nabla V|^2 \\
&- \frac{d_I I_2}{I^2}|\nabla I|^2 - \frac{Z_2 d_Z(I)}{Z^2}|\nabla Z|^2 - \frac{Z_2 d_Z'(I)}{Z}(\nabla I \cdot \nabla Z) \\
&+ h_0(T_2) h_d(I_2) \left(\frac{h_d(I)}{h_d(I_2)} - 1\right)\left(1 - \frac{I h_d(I_2)}{I_2 h_d(I)}\right) \\
&+ h_0(T_2) h_i(V_2) \left(\frac{h_i(V)}{h_i(V_2)} - 1\right)\left(1 - \frac{V h_i(V_2)}{V_2 h_i(V)}\right) \\
&+ \left(1 - \frac{h_0(T_2)}{h_0(T)}\right)[b(T) - b(T_2)] \\
&+ h_0(T_2) h_d(I_2) \left(3 - \frac{h_0(T_2)}{h_0(T)} - \frac{I_2 h_0(T) h_d(I)}{I h_0(T_2) h_d(I_2)} - \frac{I h_d(I_2)}{I_2 h_d(I)}\right) \\
&+ h_0(T_2) h_i(V_2) \left(4 - \frac{h_0(T_2)}{h_0(T)} - \frac{I_2 h_0(T) h_i(V)}{I h_0(T_2) h_i(V_2)} - \frac{V h_i(V_2)}{V_2 h_i(V)} - \frac{I V_2}{I_2 V}\right).
\end{aligned}$$

The li e i he e e i f $\mathcal{M}_2$ i b i l m e ha e . The ec d li e i b ded b e d e (3.12). The la e li e a e al m e ha e beca e $h_0' > 0$, $h_d' > 0$, $h_i' > 0$ a d $b' < 0$. C e e l w e ha e $\mathcal{M}_2 \leq 0$ a d $d\mathcal{L}_2/dt \leq 0$. The la ge i i el i a ia e f $d\mathcal{L}_2/dt = 0$ i D_2 i a i gle $\{E_2\}$. F a $\phi \in D_2$, i f ll w f m P i i 3.6 a d 3.10 ha $\omega(\phi) \in D_2$. B LaSalle i a ia ce i ci le, $D_2 \subset W^s(E_2)$. N w , f a $\phi \in [\mathbb{X}_+ \setminus \{0\}]^4$, ha k P i i 3.6 a d 3.10 w e ill ha e $\omega(\phi) \subset D_2$. M e e , (Zha 2017, Lemma 1.2.1) im lie ha $\omega(\phi)$ i i e all chai a i i e. B (Zha 2017, The em 1.2.1), E_2 MM

4 Simulations and discussions

4.1 Simulations

I hi b ec i w e c d c me me ical im la i f m del w i h eci c f c i

$$b(T)=\lambda_c-\mu_T T+\lambda_l T(1-T/K_T),\quad f(T,I)=\beta_d TI,\quad g(T,V)=\beta_i TV,\quad d_Z(I)=d_0e^{-I}.$$

The a ame e al e a e ch e be c i e w i h he die i he li e a e (K ma a e al. 2003; Li a d Sh 2012; Sh e al. 2014):

$$\begin{aligned}&\lambda_c=10,\ \mu_T=0.02,\ \lambda_l=0.005,\ K_T=1500,\ \beta_d=0.003,\ \beta_i=0.0027,\\&\mu_I=3,\ \mu_V=2.4,\ \mu_Z=0.3,\ r_1=r_2=r=0.3,\ k=3,\\&d_T=0.01,\ d_I=0.01,\ d_V=0.1,\ d_0=0.01.\end{aligned}$$

O e f he im le i i e a d dec ea i g f c i i he e e ial f c i , w e ch e $d_Z(I)=d_0e^{-I}$ w i h $d_0=0.001$. The al e f he diff i c ef cie d_T, d_I, a d d_V a e a bi a il ch e . Ba ed he he e ical e l , he diff i c ef cie d affec he gl bal d amic . The c a g w h a e λ_c a d he l gi ic g w h a e λ_l f he a ge ed cell a w ell a he cell- -cell i fec i a e β_d a e al a bi a il ch e . The em al a e f i fec ed cell r_1 a d he ec i me a e f CTL r_2 w ill be a i g f m 0.3 1 im la e w ca e $R_1<1$ a d $R_1>1$, e ec i el ; i g ha $r_1=1$ i (Li a d Sh 2012; Sh e al. 2014). The de c i i a d efe e ce f he a ame e a e li ed i Table 1.

I ca be calc la ed ha $T_0\approx 589$. The d mai i e be $\Omega=(0,1)\times(0,1)$. We ch e he i i ial c di i a a e ba i f i fec i -f ee ead a e $E_0=(T_0,0,0,0)$:

$$T(x,0)=T_0,\ I(x,0)=V(x,0)=Z(x,0)=e^{-100[(x_1-0.5)^2+(x_2-0.5)^2]}.$$

Table 1 Pa ame e al e a d de c i i

Pa ame e al e	De c i i	Refe e ce
$\mu_T=0.02$	Dea h a e f a ge ed cell	(Li a d Sh 2012)
$K_T=1500$	Ca i g ca aci f a ge ed cell	(Li a d Sh 2012)
$\beta_i=0.0027$	Vi - -cell a mi i a e	(Li a d Sh 2012)
$\mu_I=3$	Dea h a e f i fec ed cell	(Li a d Sh 2012)
$\mu_V=2.4$	Dea h a e f i	(Li a d Sh 2012)
$k=3$	P d c i a e f i	(Li a d Sh 2012)
$\mu_Z=0.3$	Dea h a e f CTL	(K ma a e al. 2003)

4.2 Discussions

We c ide-ed a ge e-al i-al i fec i m del i h cell- -cell -a mi i a d imm e chem ki e . The gl bal e i e ce a d l ima el b ded e f he l i e-e b ai ed ia a -i -i e e-g e ima e. We i -d ced he ba ic -e -d c i m-be- f i fec i R_0 a d ed ha i i he h-e h ld a-ame e- de e-mi e e i c i a d e- i e ce f i-al i fec i ; amel , he i e i fec i -f-ee ead a e E_0 i gl ball a m icall able if $R_0 < 1$ a d gl ball a -ac i e if $R_0 = 1$ hile he i-al i fec i ill be if -ml e- i e if $R_0 > 1$. Whe $R_0 > 1$, he-e e i a i e CTL-i ac i a ed ead a e E_1. We de ed a he- ba ic -e -d c i m-be- f he CTL imm e-e e R_1 hich de e-mi e he h-e h ld d amic f CTL. T be m -e eci c, if $R_1 < 1$ he E_1 i gl ball a m icall able; if $R_1 = 1$ he E_1 i gl ball a -ac i e; a d if $R_1 > 1$ he he-e e i a i e CTL-ac i a ed ead a e E_2 hich i gl ball a m icall able.

The a m i (H1) (H4) a-e bi l gicall -ele a a d ma hema icall b- ad. F -i a ce, he li ea- i fec i -a e $f(T, I)$ a d $g(T, V)$ ge e-ali e m c mm l ed f c i al -e e f H lli g e I a d II; a d he g- h f c i $b(T)$ i cl de a li ea- f c i $b_l(T) = \lambda_c - \mu_T T$ l a ible li ea- mi i -a e $b_m(T)$ a l g a $b_m'(T) < \mu_T$ f - all $T > 0$. I he me-ical im la i e ch e a l gi ic g- h $b_m(T) = \lambda_l T(1 - T/K_T)$ i h $\lambda_l < \mu_T$. I i -h -ema-k ha H f bif -ca i ma cc - if $\lambda_l > \mu_T$; ee (Li a d Sh 2012). Th , he m ici c di i $b'(T) < 0$ i im -a e abli h he abili -e l f ead a e . I he -f f The -em 3.11 e made a ech ical a m i (3.12) a c -c a i able L a f c i hich i -i c-ea i g al g he l i emi . N me-ical im la i (h he-e) gge ha hi a m i c ld be -em ed; amel , he a eme f The -em 3.11 -emai alid i h he ech ical a m i (3.12). We lea e hi -blem f - f - he- i e iga i .

The-e a-e me ible ge e-ali a i f -m del. O e e e i i i c -a e he i -acell la- dela d -i g i-al i fec i (Lai a d Z 2014; Li a d Sh 2012; Sh e al. 2013) a d ime lag i he -ce f imm e -e e (Fe e al. 2006; Sh e al. 2014). A he- e e i i -e lace he e-m $\Delta[d_Z(I)Z] = \nabla \cdot [d_Z(I)\nabla Z + d_Z'(I)Z\nabla I]$ i h a m -e ge e-al e-m f diff i a d chem a i $\nabla \cdot [d_Z(I)\nabla Z - \chi(I)Z\nabla I]$; ee (Ji a d Wa g 2021). I i e ec ed ha he e e ded m del i h ime dela a d m -e ge e-al chem a i ill e hibi m -e-ich d amic . We ill - ide a de ailed d f hi e e ded m del i a f - hc mi g a e-. O he he- ha d, f - he -c m e em i h dege e-a e m ili , he gl bal e i e ce f eak a d ge e-ali ed l i f - a la-ge cla f $d_Z(I)$ i h a-i deca beha i - (Wi kle- 2023a, b, c; Li a d Wi kle- 2023; Li a d Wa g 2023) ha e bee e abli hed, he ce i i a i e-e i g i e d he l i beha i - f - he em (1.1) i h he dege e-a e m ili , ha i $d_Z(I) = 0$ a $I = 0$.

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