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# A reaction-diffusion model for viral infection and immune response

Mauricio Labadie <sup>1</sup>      Anna Marciniak-Czochra <sup>2</sup>

December 13, 2010

## Abstract

In this work we extend the ODE model for virus infection and immune response proposed by P. Getto *et al* (*Modelling and analysis of dynamics of viral infection of cells and of interferon resistance*, J. Math. Anal. Appl., No. 344, 2008, pp. 821-850) to account for the spatial effects of the processes, such as diffusion transport of virions, biomolecules and cells. This leads to two different nonlinear PDE models, a first one where the cells and the biomolecules diffuse (which we call the reaction-diffusion model) and a second one where only the biomolecules can diffuse (the hybrid model).

We show that both the reaction-diffusion and the hybrid models are well-posed problems, i.e., they have global unique solutions which are non-negative, bounded, and depend continuously on the initial data. Moreover, we prove that there exists a “continuous” link between these two models, i.e., if the diffusion coefficient of the cells tends to zero then the solution of the reaction-diffusion model converges to the solution of the hybrid model.

We also prove that the solutions are uniformly bounded and integrable for all times. We characterize the asymptotic behavior of the solutions of the hybrid system and present several relations concerning the survivability of viruses and cells. Finally, we show that the solutions of the hybrid model converge to the steady state solutions, which implies that the latter are globally stable.

**Keywords:** Reaction-diffusion systems, global solutions, uniqueness, asymptotic behavior, virus, interferon, immune response.

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# 1 Introduction

## 1.1 Spatial effects of viral infection and immunity response

When a virion, i.e., an individual viral particle, enters a healthy cell, it modifies the genetic structure of its host. After infection, the altered biochemical machinery of the host starts to create new virions. The virions are then released from the host cell and may infect other cells. However, the infected cell activates intrinsic host defenses, which include, among others, activation of the innate immunity system and release of biomolecules called interferons (IFN), which communicate with the other cells and induce them to deploy protective defenses. The dynamics of such complex virus-host system results from the intra- and extracellular interactions between invading virus particles and cells producing substances, which confer resistance to virus.

These key processes have been addressed by the mathematical model proposed by Getto, Kimmel and Marciniak-Czochra in [2]. The model was motivated by the experiments involving vesicular stomatitis virus (VSV) [1, 4] and respiratory syncytial virus (RSV). The work of P. Getto *et al* [2] is focused on the study of the role of heterogeneity of intracellular processes, reflected by a structure variable, in the dynamics of the system and stability of stationary states. It is shown that indeed the heterogeneity of the dynamics of cells in respect to the age of the individual cell infection may lead to the significant changes in the behavior of the model solutions, exhibiting either stabilizing or destabilizing effects.

Another interesting aspect of the dynamics of the spread of viral infection and development of resistance is related to the spatial structure of the system and the effects of spatial processes, such as random dispersal of virions and interferon particles. In a series of experiments on the vesicular stomatitis virus infection [1, 4], it was observed that the spatial structure of the system may influence the dynamics of the whole cell population. The role of spatial dimension and diffusion transport of virions and interferon molecules were experimentally studied using two type of experiments: a one-step growth experiment in which all cells were infected simultaneously, and a focal-infection experiment in which cell population was infected by a point source of virus. A spreading circular wave of infection followed by a wave of dead cells was observed. The experiments were performed on two different cell cultures: DBT (murine delayed brain tumor) cells, which respond to IFN and can be activated to resist the replication of viruses, and BHK (baby hamster kidney) cells, which are not known to produce or respond to IFN. In case of focal infection both in DBT and BHK populations spread of infection (rings) was observed. The size of the rings was dependent on the type of the virus (N1, N2, N3, N4 -gene ectopic strains as well as M51R mutant and XK3.1). However, for all virus types, it was observed that in DBT cells the speed of the infection propagation was decreasing with time, while in case of BHK the radius of the infected area was growing linearly in time. Results of the experiments showed that the rate of infectious progeny production in one-step growth experiments was a key determinant of the rate of focal spread under the absence of IFN production. Interestingly, the correlation between one-step growth and focal growth did not apply for VSV strains XK3.1 and M51R in the cells producing IFN. Focal infection in DBT cells led only to the limited infection, the spread of which stopped after a while.

These experiments indicated suitability of focal infections for revealing aspects of virus-cell interactions, which are not reflected in one-step growth curves. Motivated by Duca *et al* experiments, we devise a model of spatio-temporal dynamics of viral infection and interferon production, which involves virions, uninfected, infected and resistant cells, as well as the interferon. We assume that interferon is produced by infected cells and spread by diffusion to neighboring uninfected cells, making them resistant. At the same time, the virus is spread, also by diffusion and the final outcome is the result of competition between these two processes.

## 1.2 The original model

The point of departure for this work is a system of nonlinear ordinary differential equations developed by P. Getto *et al* [2] to model wild-type cells interacting with virions and the consequent interferon-based immune response. The model describes time dynamics of five different types of entities interacting in a culture: three different types of cells (wild-type, infected and resistant) and two different biomolecules (virions and interferons).

P. Getto *et al* [2] considered a culture of wild-type cells infected by virions. When a wild-type cell interacts with a virion it becomes an infected cell. Infected cells produce further virions, but they also release interferons. If an interferon reaches a wild-type cell before a virion does, then this cell becomes a resistant cell. Virions, interferons and infected cells are supposed to have an exponential death rate, whereas there is no death rate associated to wild-type and resistant cells, because they are considered to live longer than infected cells. In the other words, the model describes the time scale of *in vitro* experiments, which is short comparing to the life span of healthy cells.

Under these hypotheses the following nonlinear ODE model was proposed:

$$\begin{cases} W' &= -iW - vW, & \leftarrow \text{wild-type cells} \\ I' &= -\mu_I I + vW, & \leftarrow \text{infected cells} \\ R' &= iW, & \leftarrow \text{resistant cells} \\ v' &= -\mu_v v + \alpha_v I - \alpha_4 vW, & \leftarrow \text{virions} \\ i' &= -\mu_i i + \alpha_i I - \alpha_3 iW, & \leftarrow \text{interferons} \end{cases} \quad (1)$$

where all coefficients are non-negative constants.

## 1.3 Biological hypotheses of the new model

In this work we will modify the ODE model (1) by introducing spatial random dispersion of cells, virions and IFN molecules. We consider two models: In the first model (which we call the reaction-diffusion model) we assume that all cells, virions and interferons diffuse, whereas the second model (which we call the hybrid model) is based on the hypothesis that only virions and interferons diffuse. The diffusion terms are supposed to follow Fick's Law with constant diffusion coefficients and it is modeled by adding Laplacian operators to the ODE system.

Concerning the boundary conditions, we assume that the whole system is isolated within a bounded domain  $\Omega \subset \mathbb{R}^N$  ( $N = 2, 3$ ). This implies no-flux boundary conditions, i.e., homogeneous Neumann conditions, on  $\Gamma = \partial\Omega$ . It is worth to remark, however, that the results presented here are also valid for other boundary conditions such as homogeneous Dirichlet and Robin (mixed).

Since the cells are far bigger than the interferon molecules and the virions, we can suppose that  $d$  is much smaller than both  $d_i$  and  $d_v$ . In order to compare the two latter diffusion coefficients, one can recall that interferons are biomolecules and virions in general have several proteins (including DNA or RNA). Under the light of this argument we assume that  $d_v$  is smaller than  $d_i$ , but both are of the same order. This leads to the following conditions,

$$0 < d \ll d_v \leq d_i.$$

## 1.4 The reaction-diffusion (RD) model

Let  $\Omega \subset \mathbb{R}^N$  ( $N = 2, 3$ ) be a bounded domain with Lipschitz boundary  $\Gamma$ , and let  $T > 0$ . We consider in  $\Omega \times [0, T]$  a reaction-diffusion (RD) system

$$\begin{cases} \partial_t W &= d\Delta W - iW - vW, \\ \partial_t I &= d\Delta I - \mu_I I + vW, \\ \partial_t R &= d\Delta R + iW, \\ \partial_t v &= d_v \Delta v - \mu_v v + \alpha_v I - \alpha_4 vW, \\ \partial_t i &= d_i \Delta i - \mu_i i + \alpha_i I - \alpha_3 iW, \end{cases} \quad (2)$$

with boundary conditions

$$\begin{cases} \nabla W \cdot \mathbf{n}(\sigma, t) &= 0 & \text{on } \Gamma \times [0, T], \\ \nabla I \cdot \mathbf{n}(\sigma, t) &= 0 & \text{on } \Gamma \times [0, T], \\ \nabla R \cdot \mathbf{n}(\sigma, t) &= 0 & \text{on } \Gamma \times [0, T], \\ \nabla v \cdot \mathbf{n}(\sigma, t) &= 0 & \text{on } \Gamma \times [0, T], \\ \nabla i \cdot \mathbf{n}(\sigma, t) &= 0 & \text{on } \Gamma \times [0, T], \end{cases} \quad (3)$$

and initial conditions

$$\begin{cases} W(\mathbf{x}, 0) &= W_0(\mathbf{x}), \\ I(\mathbf{x}, 0) &= I_0(\mathbf{x}), \\ R(\mathbf{x}, 0) &= R_0(\mathbf{x}), \\ v(\mathbf{x}, 0) &= v_0(\mathbf{x}), \\ i(\mathbf{x}, 0) &= i_0(\mathbf{x}). \end{cases} \quad (4)$$

## 1.5 The hybrid model

Since  $d$  is much smaller than both  $d_i$  and  $d_v$  it is plausible to consider that  $d = 0$ . Under this assumption we obtain a hybrid model consisting of PDE equations for the interferons  $i$  and virions  $v$  and ODE equations for the three types of cells  $W, I, R$ . The system takes the form

$$\begin{cases} \partial_t W &= -iW - vW, \\ \partial_t I &= -\mu_I I + vW, \\ \partial_t R &= iW, \\ \partial_t v &= d_v \Delta v - \mu_v v + \alpha_v I - \alpha_4 vW, \\ \partial_t i &= d_i \Delta i - \mu_i i + \alpha_i I - \alpha_3 iW, \end{cases} \quad (5)$$

with boundary conditions

$$\begin{cases} \nabla v \cdot \mathbf{n}(\sigma, t) &= 0 & \text{on } \Gamma \times [0, T], \\ \nabla i \cdot \mathbf{n}(\sigma, t) &= 0 & \text{on } \Gamma \times [0, T]. \end{cases} \quad (6)$$

## 2 Main results

In this Section we formulate main results of the work. The proofs are presented in the following sections.

## 2.1 Existence and uniqueness results

Throughout this work we denote  $\|\cdot\|$  the norm in  $L^2(\Omega)$  and  $\|\cdot\|_\infty$  the norm in  $L^\infty(\Omega)$ .

We will prove that both the RD and the hybrid models are well-posed problems, i.e., they have unique solutions which are non-negative, uniformly bounded, and depend continuously on the initial data.

**Theorem 1** *Fix any  $T > 0$ . If the initial conditions (4) are non-negative a.e. and lie in  $L^\infty(\Omega)$ , then the RD system (2)-(3) has unique solutions  $W(\mathbf{x}, t)$ ,  $I(\mathbf{x}, t)$ ,  $R(\mathbf{x}, t)$ ,  $v(\mathbf{x}, t)$  and  $i(\mathbf{x}, t)$  on  $\Omega \times [0, T]$ . Moreover, these solutions are non-negative, uniformly bounded, and depend continuously on the initial data.*

**Theorem 2** *Fix any  $T > 0$ . If the initial conditions (4) are non-negative a.e. and lie in  $L^\infty(\Omega)$  then the hybrid system (5)-(6) has unique solutions  $W(\mathbf{x}, t)$ ,  $I(\mathbf{x}, t)$ ,  $R(\mathbf{x}, t)$ ,  $v(\mathbf{x}, t)$  and  $i(\mathbf{x}, t)$  on  $\Omega \times [0, T]$ . Moreover, these solutions are non-negative, bounded, and depend continuously on the initial data.*

We also prove that there is a “continuous link” between these two models, as the next result shows.

**Theorem 3** *If  $d \rightarrow 0$  then there is a subsequence  $(W^d, I^d, R^d, v^d, i^d)$  of solutions of the RD system (2)-(3), which converges to the solution  $(W, I, R, v, i)$  of the hybrid system (5)-(6), in the following sense:*

- *Strongly in  $L^2(0, T; L^2(\Omega))$ .*
- *Weakly in  $L^2(0, T; H^1(\Omega))$ .*
- *Weakly- $\star$  in  $L^\infty(\Omega \times (0, T))$ .*

*Moreover, any convergent subsequence  $(W^d, I^d, R^d, v^d, i^d)$  has the same limit  $(W, I, R, v, i)$ .*

## 2.2 Asymptotic results for the RD system

**Theorem 4**

1. *The solutions  $W, I, R, v, i$  of the RD system (2)-(3) are globally-defined and belong to  $L^\infty(\Omega \times (0, \infty))$ .*
2. *If  $W, I, R, v, i$  are non-negative, steady-state solutions of the RD system (2)-(3) then*

$$\begin{aligned}
 W(\mathbf{x}) &= W_0 \geq 0 \quad \text{constant,} \\
 I(\mathbf{x}) &\equiv 0, \\
 R(\mathbf{x}) &= R_0 \geq 0 \quad \text{constant,} \\
 v(\mathbf{x}) &\equiv 0, \\
 i(\mathbf{x}) &\equiv 0.
 \end{aligned}$$

### 2.3 Asymptotic results for the hybrid system

Regularity of solutions  $W, I, R, v, i$  follows from a classical theory for evolution systems and depends on the regularity of initial conditions (see eg. [6], for reaction-diffusion systems coupled with ODEs). In the remainder of this paper we assume that the solutions are (at least)  $C^1$ .

**Theorem 5** *If  $W, I, R, v, i$  are non-negative, steady-state solutions of the hybrid system (5)-(6) then*

$$\begin{aligned} I(\mathbf{x}) &\equiv 0, \\ v(\mathbf{x}) &\equiv 0, \\ i(\mathbf{x}) &\equiv 0. \end{aligned}$$

*Moreover, suppose that the initial conditions belong to  $L^\infty(\Omega)$ . Then the solutions of the hybrid system (5)-(6) are globally-defined and have the following asymptotic properties:*

1.  $I(\mathbf{x}, t)$  belongs to  $L^1(0, \infty; L^2(\Omega))$ , i.e.,

$$\lim_{t \rightarrow \infty} \int_0^t \int_{\Omega} I^2(\mathbf{x}, s) d\Omega ds < \infty.$$

2.  $v(\mathbf{x}, t)$  and  $i(\mathbf{x}, t)$  belong to  $L^1(0, \infty; H^1(\Omega))$ , i.e.,

$$\begin{aligned} \lim_{t \rightarrow \infty} \int_0^t \left( \int_{\Omega} v^2(\mathbf{x}, s) d\Omega + \int_{\Omega} |\nabla v(\mathbf{x}, s)|^2 d\Omega \right) ds < \infty, \\ \lim_{t \rightarrow \infty} \int_0^t \left( \int_{\Omega} i^2(\mathbf{x}, s) d\Omega + \int_{\Omega} |\nabla i(\mathbf{x}, s)|^2 d\Omega \right) ds < \infty. \end{aligned}$$

3.  $v(\mathbf{x}, t)W(\mathbf{x}, t)$  and  $i(\mathbf{x}, t)W(\mathbf{x}, t)$  belong to  $L^1(0, \infty; L^1(\Omega))$ , i.e.,

$$\lim_{t \rightarrow \infty} \int_0^t \int_{\Omega} v(\mathbf{x}, s)W(\mathbf{x}, s) d\Omega ds < \infty \quad \text{and} \quad \lim_{t \rightarrow \infty} \int_0^t \int_{\Omega} i(\mathbf{x}, s)W(\mathbf{x}, s) d\Omega ds < \infty.$$

4. For any  $\mathbf{x} \in \Omega$ ,

$$\lim_{t \rightarrow \infty} I(\mathbf{x}, t) = 0, \quad \lim_{t \rightarrow \infty} v(\mathbf{x}, t) = 0, \quad \lim_{t \rightarrow \infty} i(\mathbf{x}, t) = 0.$$

5. For any  $\mathbf{x} \in \Omega$ ,  $W_0(\mathbf{x}) > 0$  if and only if

$$\lim_{t \rightarrow \infty} W(\mathbf{x}, t) > 0.$$

**Theorem 6** *Consider the hybrid system (5)-(6) and suppose that  $\mu_v = 0$ . Then:*

1. If  $v_\infty(\mathbf{x})$  is a steady-state solution then  $\|\nabla v_\infty\| = 0$ .
2. Define

$$v_\infty(\mathbf{x}) := \limsup_{t \rightarrow \infty} v(\mathbf{x}, t).$$

If  $\alpha_v \geq \alpha_4 \mu_I$  then

$$\int_{\Omega} v_\infty(\mathbf{x}) d\Omega \geq \int_{\Omega} v_0(\mathbf{x}) d\Omega.$$

In particular, if  $v_0 \not\equiv 0$  then  $v_\infty \not\equiv 0$ .



### 3 The fixed point operator and a priori estimates

#### 3.1 Construction of the fixed point operator $\mathcal{R}$

Our approach follows the ideas used by M. Labadie and K. Hamdache in [3].

Define

$$\mathcal{K} := \left\{ (v^\sharp, i^\sharp) \in L^2 \left( 0, T; [L^2(\Omega)]^2 \right) \cap [L^\infty(\Omega \times [0, T])]^2 : v^\sharp(\mathbf{x}, t) \geq 0, i^\sharp(\mathbf{x}, t) \geq 0 \text{ a.e. in } \Omega \times [0, T] \right\}.$$

Fix  $(v^\sharp, i^\sharp) \in \mathcal{K}$  and set

$$\begin{aligned} \partial_t W - d\Delta W + i^\sharp W + v^\sharp W &= 0 && \text{in } \Omega \times (0, T), \\ \partial_t I - d\Delta I + \mu_I I - v^\sharp W &= 0 && \text{in } \Omega \times (0, T), \\ \partial_t R - d\Delta R - i^\sharp W &= 0 && \text{in } \Omega \times (0, T), \\ \nabla W \cdot \mathbf{n}(\sigma, t) &= 0 && \text{on } \Gamma \times [0, T], \\ \nabla I \cdot \mathbf{n}(\sigma, t) &= 0 && \text{on } \Gamma \times [0, T], \\ \nabla R \cdot \mathbf{n}(\sigma, t) &= 0 && \text{on } \Gamma \times [0, T]. \end{aligned} \tag{7}$$

For any finite time interval  $[0, T]$ , the linear system (7) has a unique solution  $(W(\mathbf{x}, t), I(\mathbf{x}, t), R(\mathbf{x}, t))$ , which is non-negative and bounded.

With these functions  $W(\mathbf{x}, t)$ ,  $I(\mathbf{x}, t)$  and  $R(\mathbf{x}, t)$  set

$$\begin{aligned} \partial_t v - d_v \Delta v + \mu_v v - \alpha_v I + \alpha_4 v W &= 0 && \text{in } \Omega \times (0, T), \\ \partial_t i - d_i \Delta i + \mu_i i - \alpha_i I + \alpha_3 i W &= 0 && \text{in } \Omega \times (0, T), \\ \nabla v \cdot \mathbf{n}(\sigma, t) &= 0 && \text{on } \Gamma \times [0, T], \\ \nabla i \cdot \mathbf{n}(\sigma, t) &= 0 && \text{on } \Gamma \times [0, T], \end{aligned} \tag{8}$$

Again, for any finite time interval  $[0, T]$  the linear, uncoupled system (8) has a unique solution  $(v(\mathbf{x}, t), i(\mathbf{x}, t))$ , which is non-negative and bounded.

Our goal is to show that the operator  $\mathcal{R}[(v^\sharp, i^\sharp)] := (v, i)$ , defined for the chain of maps  $(v^\sharp, i^\sharp) \mapsto (W, I, R) \mapsto (v, i)$  constructed above, has a fixed point.

#### 3.2 Positivity of solutions

From now on we will assume that the coefficients

$$d, d_v, d_i, \mu_I, \mu_v, \mu_i, \alpha_3, \alpha_4$$

are all positive, and that the initial conditions (4) are non-negative and bounded.

**Lemma 1** *Let  $(v^\sharp, i^\sharp) \mapsto (W, I, R) \mapsto (v, i)$  be solutions of (7)-(8).*

1. *If  $v^\sharp$  and  $i^\sharp$  are non-negative and bounded then  $W$ ,  $I$  and  $R$  are non-negative and bounded.*

2. If  $W$ ,  $I$  and  $R$  are non-negative and bounded then  $v$  and  $i$  are non-negative and bounded.

**Proof:**

1. The equation for  $W$  is

$$\begin{aligned} \partial_t W - d\Delta W + (i^\sharp + v^\sharp)W &= 0 && \text{in } \Omega \times (0, T), \\ \nabla W \cdot \mathbf{n}(\sigma, t) &= 0 && \text{on } \Gamma \times [0, T], \\ W(\mathbf{x}, 0) = W_0(\mathbf{x}) &\geq 0 && \text{in } \Omega. \end{aligned}$$

Applying Maximum Principle we obtain that  $W(\mathbf{x}, t) \geq 0$  for all  $(\mathbf{x}, t) \in \Omega \times (0, T)$ .

Define  $Z_1 := W - \gamma_1$ , where  $\gamma_1 \in \mathbb{R}$ . Then  $Z_1$  solves

$$\begin{aligned} \partial_t Z_1 - d\Delta Z_1 + (i^\sharp + v^\sharp)Z_1 &= -(i^\sharp + v^\sharp)\gamma_1 && \text{in } \Omega \times (0, T), \\ \nabla Z_1 \cdot \mathbf{n}(\sigma, t) &= 0 && \text{on } \Gamma \times [0, T], \\ Z_1(\mathbf{x}, 0) = W_0(\mathbf{x}) - \gamma_1 &&& \text{in } \Omega. \end{aligned}$$

Choosing  $\gamma_1 = \|W_0\|_\infty$  and using non-negativity of  $i^\sharp$  and  $v^\sharp$  we obtain

$$\begin{aligned} \partial_t Z_1 - d\Delta Z_1 + (i^\sharp + v^\sharp)Z_1 &\leq 0 && \text{in } \Omega \times (0, T), \\ \nabla Z_1 \cdot \mathbf{n}(\sigma, t) &= 0 && \text{on } \Gamma \times [0, T], \\ Z_1(\mathbf{x}, 0) &\leq 0 && \text{in } \Omega. \end{aligned}$$

Hence, Maximum Principle implies that  $Z_1(\mathbf{x}, t) \leq 0$  for all  $(\mathbf{x}, t) \in \Omega \times (0, T)$ , and in consequence  $W(\mathbf{x}, t) \leq \|W_0\|_\infty$  for all  $(\mathbf{x}, t) \in \Omega \times (0, T)$ .

For  $I$ , notice that  $v^\sharp$  and  $W$  are non-negative. Therefore, similarly as above Maximum Principle yields that  $I(\mathbf{x}, t) \geq 0$  for all  $(\mathbf{x}, t) \in \Omega \times (0, T)$ .

Now, due to the boundedness of  $I$ , the function  $Z_2 := I - \gamma_2$  solves

$$\begin{aligned} \partial_t Z_2 - d\Delta I + \mu_I Z_2 &= v^\sharp W - \mu_I \gamma_2 && \text{in } \Omega \times (0, T), \\ \nabla Z_2 \cdot \mathbf{n}(\sigma, t) &= 0 && \text{on } \Gamma \times [0, T], \\ Z_2(\mathbf{x}, 0) = I_0(\mathbf{x}) - \gamma_2 &&& \text{in } \Omega. \end{aligned}$$

Choosing

$$\gamma_2 = \max \left\{ \|I_0\|_\infty, \frac{\|v^\sharp\|_\infty \|W_0\|_\infty}{\mu_I} \right\}$$

and applying Maximum Principle, we obtain that  $W(\mathbf{x}, t) \leq \gamma_2$  for all  $(\mathbf{x}, t) \in \Omega \times (0, T)$ .

Finally, Maximum Principle implies that  $R(\mathbf{x}, t) \geq 0$  for all  $(\mathbf{x}, t) \in \Omega \times (0, T)$ . For the boundedness of  $R$ , define  $Z_3 := R - \gamma_3(t)$ . It yields

$$\begin{aligned} \partial_t Z_3 - d\Delta I &= i^\sharp W - \gamma_3'(t) && \text{in } \Omega \times (0, T), \\ \nabla Z_3 \cdot \mathbf{n}(\sigma, t) &= 0 && \text{on } \Gamma \times [0, T], \\ Z_3(\mathbf{x}, 0) = R_0(\mathbf{x}) - \gamma_3(0) &&& \text{in } \Omega. \end{aligned}$$

Choosing

$$\gamma_3(t) = \|R_0\|_\infty + t\|i^\sharp\|_\infty\|W_0\|_\infty$$

and applying Maximum Principle we obtain that  $R(\mathbf{x}, t) \leq \gamma_3(t)$  for all  $(\mathbf{x}, t) \in \Omega \times (0, T)$ .

2. Using the same argument as before we can prove that  $0 \leq v(\mathbf{x}, t) \leq \gamma_4$  and  $0 \leq i(\mathbf{x}, t) \leq \gamma_5$  for all  $(\mathbf{x}, t) \in \Omega \times (0, T)$ , where

$$\gamma_4 = \max \left\{ \|v_0\|_\infty, \frac{\alpha_v \|I_0\|_\infty}{\mu_v} \right\}, \quad \gamma_5 = \max \left\{ \|i_0\|_\infty, \frac{\alpha_i \|I_0\|_\infty}{\mu_i} \right\}. \quad \square$$

### 3.3 A priori estimates

**Lemma 2** *Let  $(v^\sharp, i^\sharp) \mapsto (W, I, R) \mapsto (v, i)$  be solutions of (7)-(8). Then the functions  $W, I, R, v, i$  belong to  $L^2(0, T; H^1(\Omega))$ .*

**Proof:**

- Multiply (7) by  $W$  and integrate by parts to obtain

$$\frac{1}{2} \frac{d}{dt} \|W\|^2 + d \|\nabla W\|^2 = - \int_{\Omega} (i^\sharp + v^\sharp) W^2 d\Omega.$$

Since  $i^\sharp$  and  $v^\sharp$  are non-negative, it follows that

$$\frac{1}{2} \frac{d}{dt} \|W\|^2 + d \|\nabla W\|^2 \leq 0.$$

Integrating over  $[0, t]$  yields

$$\|W(t)\|^2 + 2d \int_0^t \|\nabla W(s)\|^2 ds \leq \|W(0)\|^2.$$

- Multiply (7) by  $I$  and integrate by parts to obtain

$$\frac{1}{2} \frac{d}{dt} \|I\|^2 + d \|\nabla I\|^2 + \mu_I \|I\|^2 = \int_{\Omega} v^\sharp W I d\Omega.$$

Recall the identity

$$\int_{\Omega} |v^\sharp W I| d\Omega \leq \frac{1}{4\varepsilon} \int_{\Omega} |v^\sharp W|^2 d\Omega + \varepsilon \int_{\Omega} |I|^2 d\Omega.$$

Choosing  $\varepsilon = \mu_I/2$  and using the uniform bounds in Lemma 1, it follows that there is a constant  $C > 0$ , depending on the  $L^\infty$  norm of the initial data, such that

$$\frac{d}{dt} \|I\|^2 + 2d \|\nabla I\|^2 + \mu_I \|I\|^2 \leq C.$$

Here we can keep or discard the term  $\mu_I \|I\|^2$ , leading to two different estimates:

– If we discard the term, the integration over  $[0, T]$  yields

$$\|I(t)\|^2 + 2d \int_0^t \|\nabla I(s)\|^2 ds \leq \|I(0)\|^2 + Ct,$$

which implies that  $I \in L^2(0, T; H^1(\Omega))$ .

– If we keep the term, after multiplying by  $e^{\mu_I t}$  and integrating over  $[0, T]$ ,

$$\|e^{\mu_I t} I(t)\|^2 + 2d \int_0^t e^{\mu_I s} \|\nabla I(s)\|^2 ds \leq \|I(0)\|^2 + C(e^{\mu_I t} - 1).$$

Therefore,

$$\|I(t)\|^2 + 2d \int_0^t e^{-\mu_I(t-s)} \|\nabla I(s)\|^2 ds \leq \|I(0)\|^2 e^{-\mu_I t} + C(1 - e^{-\mu_I t}).$$

This estimate will be useful for the study of the asymptotic behavior when  $t \rightarrow \infty$ .

- Multiply (7) by  $R$  and integrate by parts to obtain

$$\frac{1}{2} \frac{d}{dt} \|R\|^2 + d \|\nabla R\|^2 = \int_{\Omega} iWR d\Omega.$$

Therefore,

$$\frac{d}{dt} \|R\|^2 + 2d \|\nabla R\|^2 \leq C + \|R\|^2.$$

Multiplying by  $e^{-t}$  and integrating over  $[0, t]$  leads to

$$\|R(t)\|^2 + 2d \int_0^t e^{t-s} \|\nabla R(s)\|^2 ds \leq \|R(0)\|^2 e^t + C(e^t - 1).$$

- Repeating the argument for  $v$  and  $i$  yields

$$\begin{aligned} \|v(t)\|^2 + 2d_v \int_0^t \|\nabla v(s)\|^2 ds &\leq \|v(0)\|^2 + Ct, \\ \|v(t)\|^2 + 2d_v \int_0^t e^{-\mu_v(t-s)} \|\nabla v(s)\|^2 ds &\leq \|v(0)\|^2 e^{-\mu_v t} + C(1 - e^{-\mu_v t}), \\ \|i(t)\|^2 + 2d_i \int_0^t \|\nabla i(s)\|^2 ds &\leq \|i(0)\|^2 + Ct, \\ \|i(t)\|^2 + 2d_i \int_0^t e^{-\mu_i(t-s)} \|\nabla i(s)\|^2 ds &\leq \|i(0)\|^2 e^{-\mu_i t} + C(1 - e^{-\mu_i t}). \quad \square \end{aligned}$$

### 3.4 Continuity of the operator $\mathcal{R}$

Let  $(v_1^\sharp, i_1^\sharp) \mapsto (W_1, I_1, R_1) \mapsto (v_1, i_1)$  and  $(v_2^\sharp, i_2^\sharp) \mapsto (W_2, I_2, R_2) \mapsto (v_2, i_2)$  be two solutions of the systems (7)-(8), with the same initial conditions  $(v_0^\sharp = v_0, i_0^\sharp = i_0, W_0, I_0, R_0, v_0, i_0)$ .

Define

$$\begin{aligned}
\hat{v}^\# &= v_2^\# - v_1^\#, \\
\hat{i}^\# &= i_2^\# - i_1^\#, \\
\hat{W} &= W_2 - W_1, \\
\hat{I} &= I_2 - I_1, \\
\hat{R} &= R_2 - R_1, \\
\hat{v} &= v_2 - v_1, \\
\hat{i} &= i_2 - i_1.
\end{aligned}$$

**Lemma 3** *There exists a positive continuous function  $C(t)$  such that*

$$\left[ \int_0^t \left( \|\hat{v}\|^2 + \|\hat{i}\|^2 \right) ds \right] \leq C(t) \left[ \int_0^t \left( \|\hat{v}^\#\|^2 + \|\hat{i}^\#\|^2 \right) ds \right]. \quad (9)$$

**Proof:** The differences  $\hat{v}$ ,  $\hat{i}$ ,  $\hat{W}$ ,  $\hat{I}$ ,  $\hat{R}$  solve the system

$$\begin{aligned}
\partial_t \hat{v} - d_v \Delta \hat{v} + \mu_v \hat{v} + \alpha_4 W_2 \hat{v} + \alpha_4 \hat{v}_1 \hat{W} - \alpha_v \hat{I} &= 0, \\
\partial_t \hat{i} - d_i \Delta \hat{i} + \mu_i \hat{i} + \alpha_3 W_2 \hat{i} + \alpha_3 \hat{i}_1 \hat{W} - \alpha_i \hat{I} &= 0, \\
\partial_t \hat{W} - d \Delta \hat{W} + i_2^\# \hat{W} + W_1 \hat{i}^\# + v_2^\# \hat{W} + W_1 \hat{v}^\# &= 0, \\
\partial_t \hat{I} - d \Delta \hat{I} + \mu_I \hat{I} + W_2 \hat{v}^\# + v_1^\# \hat{W} &= 0, \\
\partial_t \hat{R} - d \Delta \hat{R} + i_2^\# \hat{W} + W_1 \hat{i}^\# &= 0.
\end{aligned}$$

with homogeneous initial and boundary conditions.

Multiply the equation for  $\hat{I}$  by  $\hat{I}$  and integrate by parts to obtain

$$\frac{1}{2} \frac{d}{dt} \|\hat{I}\|^2 + d \|\nabla \hat{I}\|^2 + \mu_I \|\hat{I}\|^2 = - \int_{\Omega} \hat{v}^\# W_2 \hat{I} d\Omega + \int_{\Omega} v_1^\# \hat{W} \hat{I} d\Omega.$$

Noticing that all the functions are in  $L^\infty$ , we deduce that there exists  $C > 0$ , depending on the initial conditions and the model coefficients, such that

$$\frac{d}{dt} \|\hat{I}\|^2 + 2d \|\nabla \hat{I}\|^2 \leq C \left( \|\hat{v}^\#\|^2 + \|\hat{W}\|^2 + \|\hat{I}\|^2 \right). \quad (10)$$

Using the same argument we can show that

$$\begin{aligned}
\frac{d}{dt} \|\hat{W}\|^2 + 2d \|\nabla \hat{W}\|^2 &\leq C \left( \|\hat{i}^\#\|^2 + \|\hat{v}^\#\|^2 + \|\hat{W}\|^2 \right), \\
\frac{d}{dt} \|\hat{R}\|^2 + 2d \|\nabla \hat{R}\|^2 &\leq C \left( \|\hat{i}^\#\|^2 + \|\hat{W}\|^2 \right).
\end{aligned} \quad (11)$$

From (10)-(11) and  $d \geq 0$ , it follows that

$$\frac{d}{dt} \left( \|\hat{W}\|^2 + \|\hat{I}\|^2 + \|\hat{R}\|^2 \right) \leq C \left( \|\hat{i}^\#\|^2 + \|\hat{v}^\#\|^2 + \|\hat{W}\|^2 + \|\hat{I}\|^2 \right).$$

Integrating over  $[0, t]$  we obtain that

$$\|\hat{W}\|^2 + \|\hat{I}\|^2 + \|\hat{R}\|^2 \leq C \left[ \int_0^t (\|\hat{i}^\# \|^2 + \|\hat{v}^\# \|^2) ds \right] + C \left[ \int_0^t (\|\hat{W}\|^2 + \|\hat{I}\|^2) ds \right].$$

Applying Gronwall's Lemma it follows that there exists a positive continuous function  $C(t)$  such that

$$\|\hat{W}\|^2 + \|\hat{I}\|^2 + \|\hat{R}\|^2 \leq C(t) \left[ \int_0^t (\|\hat{i}^\# \|^2 + \|\hat{v}^\# \|^2) ds \right]. \quad (12)$$

On the other hand, multiply the equation for  $\hat{i}$  by  $\hat{i}$  and integrate by parts to obtain

$$\frac{1}{2} \frac{d}{dt} \|\hat{i}\|^2 + d_i \|\nabla \hat{i}\|^2 + \mu_i \|\hat{i}\|^2 + \alpha_3 \int_{\Omega} W_2 \hat{i}^2 d\Omega = -\alpha_3 \int_{\Omega} i_1 \hat{W} \hat{i} d\Omega + \alpha_i \int_{\Omega} \hat{I} \hat{i} d\Omega.$$

Proceeding as before we can show that there exists a constant  $C_1 > 0$  such that

$$\frac{d}{dt} \|\hat{i}\|^2 + 2d_i \|\nabla \hat{i}\|^2 \leq C_1 \left( \|\hat{i}\|^2 + \|\hat{W}\|^2 + \|\hat{I}\|^2 \right).$$

Analogously, we can show that

$$\frac{d}{dt} \|\hat{v}\|^2 + 2d_v \|\nabla \hat{v}\|^2 \leq C_1 \left( \|\hat{v}\|^2 + \|\hat{W}\|^2 + \|\hat{I}\|^2 \right).$$

Using (12) we obtain that

$$\frac{d}{dt} \left( \|\hat{i}\|^2 + \|\hat{v}\|^2 \right) \leq C_1 \left( \|\hat{i}\|^2 + \|\hat{v}\|^2 \right) + C(t) \left[ \int_0^t (\|\hat{i}^\# \|^2 + \|\hat{v}^\# \|^2) ds \right].$$

Integrating over  $[0, t]$  yields

$$\|\hat{i}\|^2 + \|\hat{v}\|^2 \leq C_1 \left[ \int_0^t (\|\hat{i}\|^2 + \|\hat{v}\|^2) ds \right] + C(t) \left[ \int_0^t (\|\hat{i}^\# \|^2 + \|\hat{v}^\# \|^2) ds \right].$$

Applying Gronwall's Lemma, it follows that

$$\|\hat{i}\|^2 + \|\hat{v}\|^2 \leq C(t) \left[ \int_0^t (\|\hat{i}^\# \|^2 + \|\hat{v}^\# \|^2) ds \right].$$

Integrating again over  $[0, t]$  we obtain (9).  $\square$

## 4 Proof of the theorems

### 4.1 Proof of Theorem 1

**Lemma 4** Fix a positive time  $T > 0$ . Then:

1.  $\mathcal{K}$  is a convex closed subset of  $L^2 \left( 0, T; [L^2(\Omega)]^2 \right)$ .

2.  $\mathcal{R} : \mathcal{K} \rightarrow \mathcal{K}$ .
3.  $\mathcal{R} : L^2(0, T; [L^2(\Omega)]^2) \rightarrow L^2(0, T; [L^2(\Omega)]^2)$  is continuous.
4.  $\mathcal{R}(\mathcal{K})$  is relatively compact in  $L^2(0, T; [L^2(\Omega)]^2)$ .

**Proof:**

1. By construction,  $\mathcal{K}$  is convex and closed.
2. If  $i^\# \geq 0$  and  $v^\# \geq 0$  then from Lemma 1 it follows that  $i \geq 0$  and  $v \geq 0$ .
3. By Lemma 3 the operator  $\mathcal{R}$  is continuous.
4. We will use Aubin's compactness theorem (see Theorem 5.1 in Lions [5], Section 5.5, pp. 57-64, and Tartar [7], Chapter 24, pp. 137-141). Suppose that the sequence  $\{(v_n^\#, i_n^\#)\}$  is uniformly bounded in  $L^2(0, T; [L^2(\Omega)]^2)$ . Then, by the continuity of  $\mathcal{R}$ , the sequence  $\{\mathcal{R}[(v_n^\#, i_n^\#)] = (v_n, i_n)\}$  is also uniformly bounded in  $L^2(0, T; [L^2(\Omega)]^2)$ , and the estimates in Lemma 2 imply that  $\{(v_n, i_n)\}$  is uniformly bounded in  $L^2(0, T; [H^1(\Omega)]^2)$ . Furthermore, the sequence of derivatives  $\{(\partial_t v_n, \partial_t i_n)\}$  is uniformly bounded in  $L^2(0, T; [H^{-1}(\Omega)]^2)$ , because the expressions

$$\begin{aligned}\partial_t v_n &= \nabla \cdot (d_v \nabla v_n) - \mu_v v_n + \alpha_v I_n - \alpha_4 v_n W_n, \\ \partial_t i_n &= \nabla \cdot (d_i \nabla i_n) - \mu_i i_n + \alpha_i I_n - \alpha_3 i_n W_n,\end{aligned}$$

define two uniformly bounded sequences of distributions in  $H^1(\Omega)$ . Therefore, applying Aubin's theorem to the spaces  $[H^1(\Omega)]^2 \subset [L^2(\Omega)]^2 \subset [H^{-1}(\Omega)]^2$ , we obtain that the sequence  $\{(v_n, i_n)\}$  is relatively compact in  $L^2(0, T; [L^2(\Omega)]^2)$ .  $\square$

We can now conclude the existence of solutions of the reaction-diffusion system (2)-(3):

From Lemma 4 we see that the operator  $\mathcal{R}$  satisfies Schauder's Fixed Point Theorem (Corollary B.3, p. 262 in Taylor [8]). Therefore, the system (2)-(3) has solutions  $W, I, R, v, i$ . Moreover, from the fact that  $v$  and  $i$  coincide with  $v^\#$  and  $i^\#$ , respectively, we can derive two consequences. First, from Lemma 1 it follows that  $W, I, R, v, i$  are non-negative and bounded. Second, from Lemma 2 we have that  $W, I, R, v, i$  belong to  $L^2(0, T; [H^1(\Omega)]^2)$ .

**Lemma 5** *The solutions  $W(\mathbf{x}, t)$ ,  $I(\mathbf{x}, t)$ ,  $R(\mathbf{x}, t)$ ,  $v(\mathbf{x}, t)$  and  $i(\mathbf{x}, t)$  of the reaction-diffusion system (2)-(3) are unique and depend continuously on the initial data (4).*

**Proof:** Notice that  $v$  and  $i$  coincide with  $v^\sharp$  and  $i^\sharp$ , respectively. Bearing this in mind, and repeating the arguments in Lemma 3, we can show that there is a positive constant  $C$  such that

$$\frac{d}{dt} \left( \|\hat{W}\|^2 + \|\hat{I}\|^2 + \|\hat{R}\|^2 + \|\hat{v}\|^2 + \|\hat{i}\|^2 \right) \leq C \left( \|\hat{W}\|^2 + \|\hat{I}\|^2 + \|\hat{R}\|^2 + \|\hat{v}\|^2 + \|\hat{i}\|^2 \right).$$

Therefore, Gronwall's lemma implies that there exists a positive continuous function  $C(t)$  such that

$$\|\hat{W}\|^2 + \|\hat{I}\|^2 + \|\hat{R}\|^2 + \|\hat{v}\|^2 + \|\hat{i}\|^2 \leq C(t) \left( \|\hat{W}_0\|^2 + \|\hat{I}_0\|^2 + \|\hat{R}_0\|^2 + \|\hat{v}_0\|^2 + \|\hat{i}_0\|^2 \right). \quad \square$$

## 4.2 Proof of Theorem 2

So far we have only considered the reaction-diffusion system (2)-(3). However, for the hybrid system (5)-(6) the same results hold. Indeed, on one hand, in Lemmas 2-5 we have only used that  $d \geq 0$ . On the other hand, we can use the integral representations of  $W$ ,  $I$  and  $R$  in order to deduce that they are bounded and non-negative, which proves Lemma 1 in the hybrid case.  $\square$

## 4.3 Proof of Theorem 3

For any  $0 < d \leq d_0$  let  $(W^d, I^d, R^d, v^d, i^d)$  be a weak solution of (2)-(3) and let  $d \rightarrow 0$ .

First, from Lemma 2 it follows that the sequence  $W^d$  is bounded in

$$L^2(0, T; H^1(\Omega)) \cap L^\infty(\Omega \times (0, T)),$$

which implies that a subsequence, still denoted  $W^d$ , converges weakly in  $L^2(0, T; H^1(\Omega))$  and weakly- $\star$  in  $L^\infty(\Omega \times (0, T))$  to  $W^0$ . This result is also valid for the sequences  $I^d$ ,  $R^d$ ,  $v^d$  and  $i^d$ .

Second, using classical estimates of type

$$\int_0^T \int_\Omega |i^d W^d - i^0 W^0| d\Omega dt \leq C_1 \|i^d - i^0\| + C_2 \|W^d - W^0\|$$

it can be shown that the sequence  $\partial_t W^d$  is uniformly bounded in  $L^2(0, T; H^{-1}(\Omega))$ . In consequence, applying Aubin's compactness theorem yields the strong convergence  $i^d \rightarrow i^0$  in  $L^2(0, T; L^2(\Omega))$ . This result is also valid for the sequences  $I^d$ ,  $R^d$ ,  $v^d$  and  $i^0$ .

Finally, we obtain that a subsequence  $(W^d, I^d, R^d, v^d, i^d)$  of weak solutions of (2)-(3) converges strongly in  $L^2(0, T; L^2(\Omega))$ , weakly in  $L^2(0, T; H^1(\Omega))$  and weakly- $\star$  in  $L^\infty(\Omega \times (0, T))$ . Since the limit  $(W^0, I^0, R^0, v^0, i^0)$  is by construction a weak solution of (5)-(6), the uniqueness of the hybrid system (5)-(6) implies that the limit is the same for any converging subsequence.  $\square$

## 4.4 Proof of Theorem 4

**Lemma 6** *The solutions  $W, I, R, v, i$  of the RD system (2)-(3) are globally-defined and belong to  $L^\infty(\Omega \times (0, \infty))$ .*

**Proof:**



1. Define  $N(\mathbf{x}, t) := W(\mathbf{x}, t) + I(\mathbf{x}, t) + R(\mathbf{x}, t)$ . Then  $N$  satisfies

$$\begin{cases} \partial_t N - d\Delta N \leq 0 & \text{in } \Omega \times [0, T], \\ \nabla N \cdot \mathbf{n} = 0 & \text{on } \Gamma \times [0, T]. \end{cases}$$

Therefore, Maximum Principle provides

$$N(\mathbf{x}, t) \leq \|N_0\|_\infty \quad \forall (\mathbf{x}, t) \in \Omega \times [0, T].$$

Moreover, since this bound is independent of  $t$  and  $T$ , it follows that  $N(\mathbf{x}, t)$  is defined for all  $t \in \mathbb{R}$ . In consequence, the positivity of  $W, I, R$  implies that these three functions exist for all times and that they are uniformly bounded, i.e.,

$$W(\mathbf{x}, t), I(\mathbf{x}, t), R(\mathbf{x}, t) \leq \|N_0\|_\infty \quad \forall (\mathbf{x}, t) \in \Omega \times [0, \infty).$$

2. From Lemma 1 we obtain that  $0 \leq v(\mathbf{x}, t) \leq \gamma_4$  and  $0 \leq i(\mathbf{x}, t) \leq \gamma_5$  for all  $(\mathbf{x}, t) \in \Omega \times (0, T)$ , where

$$\gamma_4 = \max \left\{ \|v_0\|_\infty, \frac{\alpha_v \|I_0\|_\infty}{\mu_v} \right\}, \quad \gamma_5 = \max \left\{ \|i_0\|_\infty, \frac{\alpha_i \|I_0\|_\infty}{\mu_i} \right\}.$$

Again, since the bounds are independent of  $t$  and  $T$ , the solutions  $v$  and  $i$  exist for all times.  $\square$

**Lemma 7** *If  $W, I, R, i, v$  are non-negative, steady-state solutions of the RD system (2)-(3) then*

$$\begin{aligned} W(\mathbf{x}) &= W_0 \geq 0 \quad \text{constant}, \\ I(\mathbf{x}) &\equiv 0, \\ R(\mathbf{x}) &= R_0 \geq 0 \quad \text{constant}, \\ v(\mathbf{x}) &\equiv 0, \\ i(\mathbf{x}) &\equiv 0. \end{aligned}$$

**Proof:** If  $W, I, R, i, v$  are non-negative, steady-state solutions of system (2)-(3), then

$$\begin{cases} -d\Delta W &= -iW - vW, \\ -d\Delta I &= -\mu_I I + vW, \\ -d\Delta R &= iW, \\ -d_v \Delta v &= -\mu_v v + \alpha_v I - \alpha_4 vW, \\ -d_i \Delta i &= -\mu_i i + \alpha_i I - \alpha_3 iW, \end{cases} \quad (13)$$

with boundary conditions

$$\begin{cases} \nabla W \cdot \mathbf{n}(\sigma) &= 0 & \text{on } \Gamma, \\ \nabla I \cdot \mathbf{n}(\sigma) &= 0 & \text{on } \Gamma, \\ \nabla R \cdot \mathbf{n}(\sigma) &= 0 & \text{on } \Gamma, \\ \nabla v \cdot \mathbf{n}(\sigma) &= 0 & \text{on } \Gamma, \\ \nabla i \cdot \mathbf{n}(\sigma) &= 0 & \text{on } \Gamma. \end{cases} \quad (14)$$

Multiplying the equation for  $W$  by  $W$  and integrating by parts we obtain

$$d\|\nabla W\|^2 + \int_{\Omega} (i + v)W^2 d\Omega = 0.$$

Therefore  $iW = vW = 0$  and  $W(\mathbf{x}) = W_0$  constant. Using same argument for  $I$  yields

$$d\|\nabla I\|^2 + \mu_I\|I\|^2 = 0,$$

which implies that  $I(\mathbf{x}) \equiv 0$ . For  $R$  we obtain

$$d\|\nabla R\|^2 = 0,$$

and therefore,  $R(\mathbf{x}) = R_0$  is constant, whereas for  $v, i$  we obtain

$$\begin{aligned} d_v\|\nabla v\|^2 + \mu_v\|v\|^2 &= 0, \\ d_i\|\nabla i\|^2 + \mu_i\|i\|^2 &= 0, \end{aligned}$$

and, in consequence,  $v(\mathbf{x}) = i(\mathbf{x}) \equiv 0$ .  $\square$ .

#### 4.5 Proof of Theorem 5

**Lemma 8** *If  $W, I, R, i, v$  are non-negative, steady-state solutions of the hybrid system (5)-(6) then*

$$\begin{aligned} I(\mathbf{x}) &\equiv 0, \\ v(\mathbf{x}) &\equiv 0, \\ i(\mathbf{x}) &\equiv 0. \end{aligned}$$

**Proof:** The steady-state-solutions of system (5)-(6) solve

$$\begin{cases} 0 &= -iW - vW, \\ 0 &= -\mu_I I + vW, \\ 0 &= iW, \\ -d_v\Delta v &= -\mu_v v + \alpha_v I - \alpha_4 vW, \\ -d_i\Delta i &= -\mu_i i + \alpha_i I - \alpha_3 iW, \end{cases} \quad (15)$$

with boundary conditions

$$\begin{cases} \nabla v \cdot \mathbf{n}(\sigma) &= 0 & \text{on } \Gamma, \\ \nabla i \cdot \mathbf{n}(\sigma) &= 0 & \text{on } \Gamma. \end{cases} \quad (16)$$

From the first three equations in (15)-(16) it follows immediately that

$$iW = vW = \mu_I I = 0.$$

Since  $\mu_i > 0$  then  $I = 0$ . Moreover,  $v$  and  $i$  solve

$$\begin{aligned} -d_v\Delta v &= -\mu_v v, \\ -d_i\Delta i &= -\mu_i i. \end{aligned}$$

In consequence, since  $\mu_v > 0$  and  $\mu_i > 0$  it follows that  $v = i = 0$ . It is worth to mention that in this case we have no restriction on  $W$  and  $R$ .  $\square$

**Lemma 9** *Suppose that the initial conditions belong to  $L^\infty(\Omega)$ . For any  $\mathbf{x} \in \Omega$ , the solutions of the hybrid system (5)-(6) are integrable in the following sense:*

1.

$$\lim_{t \rightarrow \infty} \int_0^t I(\mathbf{x}, s) ds < \infty \quad \text{and} \quad \lim_{t \rightarrow \infty} \int_0^t \int_{\Omega} I(\mathbf{x}, s) d\Omega ds < \infty.$$

2.

$$\lim_{t \rightarrow \infty} \int_0^t v(\mathbf{x}, s)W(\mathbf{x}, s) ds < \infty \quad \text{and} \quad \lim_{t \rightarrow \infty} \int_0^t \int_{\Omega} v(\mathbf{x}, s)W(\mathbf{x}, s) d\Omega ds < \infty.$$

3.

$$\lim_{t \rightarrow \infty} \int_0^t i(\mathbf{x}, s)W(\mathbf{x}, s) ds < \infty \quad \text{and} \quad \lim_{t \rightarrow \infty} \int_0^t \int_{\Omega} i(\mathbf{x}, s)W(\mathbf{x}, s) d\Omega ds < \infty.$$

**Proof:**

1. Adding the equations of  $W, I, R$  we obtain that

$$\partial_t W + \partial_t I + \partial_t R + \mu_I I \leq 0.$$

Integrating over  $[0, t]$  it follows that, for any  $(\mathbf{x}, t) \in \Omega \times [0, \infty)$  we have

$$W(\mathbf{x}, t) + I(\mathbf{x}, t) + R(\mathbf{x}, t) + \mu_I \int_0^t I(\mathbf{x}, s) ds \leq W(\mathbf{x}, 0) + I(\mathbf{x}, 0) + R(\mathbf{x}, 0). \quad (17)$$

Therefore, from (17) and using uniform boundedness of the initial conditions we can deduce that

$$\lim_{t \rightarrow \infty} \int_0^t I(\mathbf{x}, s) ds < \infty \quad \text{and} \quad \lim_{t \rightarrow \infty} \int_0^t \int_{\Omega} I(\mathbf{x}, s) d\Omega ds < \infty.$$

2. Integrating over  $[0, t]$  the equation for  $I$  yields

$$I(\mathbf{x}, t) - I(\mathbf{x}, 0) + \int_0^t I(\mathbf{x}, s) ds = \int_0^t v(\mathbf{x}, s)W(\mathbf{x}, s) ds.$$

Therefore, using the previous result on the integrability of  $I$  we obtain that

$$\lim_{t \rightarrow \infty} \int_0^t v(\mathbf{x}, s)W(\mathbf{x}, s) ds < \infty \quad \text{and} \quad \lim_{t \rightarrow \infty} \int_0^t \int_{\Omega} v(\mathbf{x}, s)W(\mathbf{x}, s) d\Omega ds < \infty.$$

3. Integrating over  $[0, t]$  the equation for  $W$  yields

$$W(\mathbf{x}, t) - W(\mathbf{x}, 0) + \int_0^t vW(\mathbf{x}, s) ds = \int_0^t i(\mathbf{x}, s)W(\mathbf{x}, s) ds.$$

Since the left-hand side has a limit so does the right-hand side, i.e.,

$$\lim_{t \rightarrow \infty} \int_0^t i(\mathbf{x}, s)W(\mathbf{x}, s) ds < \infty \quad \text{and} \quad \lim_{t \rightarrow \infty} \int_0^t \int_{\Omega} i(\mathbf{x}, s)W(\mathbf{x}, s) d\Omega ds < \infty. \quad \square$$

**Lemma 10** *The solutions of the hybrid system satisfy the following properties:*

1.  $\partial_t I$  is uniformly bounded for  $t \in [0, \infty)$ . Moreover, for any  $\mathbf{x} \in \Omega$ ,

$$\lim_{t \rightarrow \infty} I(\mathbf{x}, t) = 0, \quad \lim_{t \rightarrow \infty} \int_{\Omega} I^2(\mathbf{x}, t) d\Omega < \infty \quad \text{and} \quad \lim_{t \rightarrow \infty} \int_0^t \int_{\Omega} I^2(\mathbf{x}, s) d\Omega ds < \infty.$$

2.

$$\lim_{t \rightarrow \infty} \int_0^t (\|v(s)\|^2 + \|\nabla v(s)\|^2) ds < \infty \quad \text{and} \quad \lim_{t \rightarrow \infty} \int_0^t (\|i(s)\|^2 + \|\nabla i(s)\|^2) ds < \infty.$$

3.  $\partial_t v$  and  $\partial_t i$  are bounded distributions in  $L^1(0, \infty; H^1(\Omega))$ .

**Proof:**

1. Since the functions  $I$ ,  $v$  and  $W$  are uniformly bounded in  $\Omega \times (0, \infty)$ , from the equation for  $I$  it follows that  $\partial_t I$  is uniformly bounded as well. Therefore, using

$$\lim_{t \rightarrow \infty} \int_0^t I(\mathbf{x}, s) ds < \infty$$

we can infer that

$$\lim_{t \rightarrow \infty} I(\mathbf{x}, t) = 0 \quad \text{for all } \mathbf{x} \in \Omega.$$

Now consider a sequence

$$0 < t_0 < t_1 < \dots < t_n \rightarrow \infty$$

and define

$$f_n(\mathbf{x}) := I(\mathbf{x}, t_n).$$

We have already proven that

$$\lim_{n \rightarrow \infty} f_n(\mathbf{x}) = 0 \quad \text{and} \quad 0 \leq f_n(\mathbf{x}) \leq N_0(\mathbf{x}),$$

where

$$N_0(\mathbf{x}) := W(\mathbf{x}, 0) + I(\mathbf{x}, 0) + R(\mathbf{x}, 0) \in L^\infty(\Omega).$$

Therefore, we can apply Lebesgue's Dominated Convergence Theorem to obtain

$$\lim_{n \rightarrow \infty} \int_{\Omega} f_n^2(\mathbf{x}) d\Omega = \int_{\Omega} \lim_{n \rightarrow \infty} f_n^2(\mathbf{x}) d\Omega = \int_{\Omega} 0 d\Omega = 0.$$

Since this holds for any arbitrary sequence  $(t_n)_{n \in \mathbb{N}}$  then

$$\lim_{t \rightarrow \infty} \int_{\Omega} I^2(\mathbf{x}, t) d\Omega = 0.$$

For the last statement, if we integrate the equation for  $I$  over  $\Omega \times [0, t]$  we obtain

$$\|I(t)\|^2 + 2\mu_I \int_0^t \int_{\Omega} I^2(\mathbf{x}, s) d\Omega ds = \|I(0)\|^2 + 2\|I\|_{L^\infty(\Omega \times (0, t))} \int_0^t \int_{\Omega} v(\mathbf{x}, s) W(\mathbf{x}, s) d\Omega ds.$$

Since the right-hand side converges as  $t \rightarrow \infty$  then the left converges as well, which implies that

$$\lim_{t \rightarrow \infty} \int_0^t \int_{\Omega} I^2(\mathbf{x}, s) d\Omega ds < \infty.$$

2. Multiplying the equation for  $v$  by  $v$  and integrating by parts yields

$$\frac{1}{2} \frac{d}{dt} \|v(t)\|^2 + d_v \|\nabla v(t)\|^2 + \mu_v \|v(t)\|^2 = \alpha_v \int_{\Omega} I v \, d\Omega - \alpha_4 \int_{\Omega} v^2 W \, d\Omega.$$

Integrating over  $[0, t]$  it can be shown that there is a constant  $C > 0$ , independent of  $t$ , such that

$$\|v(t)\|^2 + 2d_v \int_0^t \|\nabla v(s)\|^2 \, ds + \mu_v \int_0^t \|v(s)\|^2 \, ds \leq \|v(0)\|^2 + C \int_0^t \int_{\Omega} I^2(\mathbf{x}, s) \, d\Omega \, ds.$$

But from the previous results it follows that the right-hand side converges. In consequence, the left-hand side converges, i.e.,

$$\lim_{t \rightarrow \infty} \int_0^t (\|v(s)\|^2 + \|\nabla v(s)\|^2) \, ds < \infty.$$

The proof for  $i$  is exactly the same as for  $v$ .

3. Let  $\varphi(\mathbf{x}, t)$  be a test function in  $L^1(0, \infty; H^1(\Omega))$ . Calculating the dual product in  $L^1(0, t; H^1(\Omega))$  yields

$$\begin{aligned} \langle \partial_t v, \varphi \rangle &= -d_v \int_0^t \int_{\Omega} \nabla v \cdot \nabla \varphi \, d\Omega \, dt - \mu_v \int_0^t \int_{\Omega} v \varphi \, d\Omega \, dt \\ &\quad + \alpha_v \int_0^t \int_{\Omega} I \varphi \, d\Omega \, dt - \alpha_4 \int_0^t \int_{\Omega} v W \varphi \, d\Omega \, dt. \end{aligned}$$

Using the uniform boundedness and integrability of  $I$  and  $W$  it can be shown that there exist three positive constants  $C_1$ ,  $C_2$  and  $C_3$ , independent of  $t$ , such that

$$|\langle \partial_t v, \varphi \rangle| \leq C_1 + C_2 \|\varphi\|_{L^1(0, t; H^1(\Omega))} + C_3 \|v\|_{L^1(0, t; H^1(\Omega))}.$$

This implies that  $|\langle \partial_t v, \varphi \rangle|$  is bounded for any test function in  $L^1(0, t; H^1(\Omega))$  with norm less than one, uniformly in  $t$ . Therefore,  $\partial_t v$  is a bounded distribution in  $L^1(0, \infty; H^1(\Omega))$ .

The proof for  $i$  is exactly the same as for  $v$ .  $\square$

**Lemma 11** *Suppose that the initial conditions belong to  $L^\infty(\Omega)$ . For any  $\mathbf{x} \in \Omega$  fixed, the solutions of the hybrid system (5)-(6) satisfy the following properties:*

1.

$$\lim_{t \rightarrow \infty} v(\mathbf{x}, t) W(\mathbf{x}, t) = 0 \quad \text{and} \quad \lim_{t \rightarrow \infty} i(\mathbf{x}, t) W(\mathbf{x}, t) = 0,$$

2.

$$\lim_{t \rightarrow \infty} v(\mathbf{x}, t) = \lim_{t \rightarrow \infty} i(\mathbf{x}, t) = 0.$$

3.

$$\lim_{t \rightarrow \infty} \int_0^t v(\mathbf{x}, s) \, ds < \infty \quad \text{and} \quad \lim_{t \rightarrow \infty} \int_0^t i(\mathbf{x}, s) \, ds < \infty.$$

**Proof:**

1. Integrating the equation for  $I$  over  $[0, t]$  we obtain

$$\int_0^t v(\mathbf{x}, s)W(\mathbf{x}, s)dt = I(\mathbf{x}, t) - I(\mathbf{x}, 0) + \mu_I \int_0^t I(\mathbf{x}, s)ds.$$

On one hand, using the previous results it follows that the right-hand side is uniformly bounded in  $t$ . In consequence,

$$\lim_{t \rightarrow \infty} \int_0^t v(\mathbf{x}, s)W(\mathbf{x}, s)ds < \infty.$$

On the other hand,

$$\partial_t(vW) = v\partial_t W + W\partial_t v$$

is uniformly bounded because  $v$ ,  $W$ ,  $\partial_t v$  and  $\partial_t W$  are all uniformly bounded. In consequence,

$$\lim_{t \rightarrow \infty} v(\mathbf{x}, t)W(\mathbf{x}, t) = 0.$$

2. Integrating over  $\Omega \times [0, t]$  the equation for  $v$  and using Fubini's Theorem yields

$$\begin{aligned} \int_{\Omega} v(\mathbf{x}, t) d\Omega - \int_{\Omega} v(\mathbf{x}, 0) d\Omega &= \int_0^t \int_{\Omega} \Delta v(\mathbf{x}, t) d\Omega dt - \mu_v \int_0^t \int_{\Omega} v(\mathbf{x}, t) d\Omega dt \\ &\quad + \alpha_v \int_0^t \int_{\Omega} I(\mathbf{x}, s) d\Omega dt + \alpha_4 \int_0^t \int_{\Omega} v(\mathbf{x}, s)W(\mathbf{x}, s) d\Omega dt. \end{aligned}$$

Now recall that  $v$  satisfies homogeneous Neumann boundary conditions. Therefore,

$$\int_0^t \int_{\Omega} \Delta v(\mathbf{x}, t) d\Omega dt = \int_0^t \int_{\partial\Omega} \nabla v(\mathbf{x}, t) \cdot \mathbf{n} dS dt = 0,$$

which implies that

$$\begin{aligned} \int_{\Omega} v(\mathbf{x}, t) d\Omega - \int_{\Omega} v(\mathbf{x}, 0) d\Omega &= -\mu_v \int_0^t \int_{\Omega} v(\mathbf{x}, t) d\Omega dt + \alpha_v \int_0^t \int_{\Omega} I(\mathbf{x}, s) d\Omega dt \\ &\quad + \alpha_4 \int_0^t \int_{\Omega} v(\mathbf{x}, s)W(\mathbf{x}, s) d\Omega dt. \end{aligned}$$

From the previous results and the uniform boundedness of  $W$ ,  $I$  and  $v$  it follows that

$$\lim_{t \rightarrow \infty} \int_0^t \int_{\Omega} v(\mathbf{x}, t) d\Omega dt < \infty.$$

Since  $\partial_t v$  is uniformly bounded it follows that

$$\lim_{t \rightarrow \infty} \int_{\Omega} v(\mathbf{x}, t) d\Omega = 0. \tag{18}$$

Now let  $\varepsilon > 0$  and choose  $\mathbf{x}_0 \in \Omega$ . Define

$$B(\varepsilon, \mathbf{x}_0) = \{\mathbf{x} \in \Omega : |\mathbf{x} - \mathbf{x}_0| < \varepsilon\}.$$

From (18) there exists  $T(\varepsilon) > 0$  such that

$$\int_{\Omega} v(\mathbf{x}, t) d\Omega < \varepsilon |B(\varepsilon, \mathbf{x}_0)| \quad \text{for all } t \geq T(\varepsilon).$$

In consequence,

$$\int_{\Omega} v(\mathbf{x}, t) d\Omega \leq \int_{\Omega} v(\mathbf{x}, t) d\Omega < \varepsilon |B(\varepsilon, \mathbf{x}_0)|,$$

which implies that

$$\frac{1}{|B(\varepsilon, \mathbf{x}_0)|} \int_{\Omega} v(\mathbf{x}, t) d\Omega \leq \varepsilon.$$

Therefore, since  $v(\mathbf{x}, t)$  is continuous, we have

$$v(\mathbf{x}_0, t) = \lim_{|B(\varepsilon, \mathbf{x}_0)| \rightarrow 0} \frac{1}{|B(\varepsilon, \mathbf{x}_0)|} \int_{\Omega} v(\mathbf{x}, t) d\Omega \leq \varepsilon,$$

which implies that

$$\lim_{t \rightarrow \infty} v(\mathbf{x}_0, t) \leq \varepsilon.$$

Since  $\varepsilon > 0$  and  $\mathbf{x}_0 \in \Omega$  are arbitrary it follows that

$$\lim_{t \rightarrow \infty} v(\mathbf{x}, t) = 0 \quad \text{for all } \mathbf{x} \in \Omega.$$

The proof for  $i$  is exactly the same.

3. Define

$$C_{\infty} := \lim_{t \rightarrow \infty} \int_0^t \int_{\Omega} v(\mathbf{x}, s) d\Omega ds.$$

From the previous results we have that  $C_{\infty}$  is well-defined, finite and positive. Now, for any  $n \in \mathbb{N}$  define

$$A_n := \left\{ \mathbf{x} \in \Omega : \lim_{t \rightarrow \infty} \int_0^t v(\mathbf{x}, s) ds > nC_{\infty} \right\}.$$

On the one hand,

$$\lim_{t \rightarrow \infty} \int_0^t \int_{A_n} v(\mathbf{x}, s) d\Omega ds > nC_{\infty} |A_n|.$$

On the other hand,

$$\lim_{t \rightarrow \infty} \int_0^t \int_{A_n} v(\mathbf{x}, s) d\Omega ds \leq \lim_{t \rightarrow \infty} \int_0^t \int_{\Omega} v(\mathbf{x}, s) d\Omega ds = C_{\infty}.$$

Therefore,

$$|A_n| < \frac{1}{n}. \tag{19}$$

Moreover, since

$$A_1 \supset A_2 \supset \dots \supset A_n \supset \dots$$

it follows that

$$A_\infty := \left\{ \mathbf{x} \in \Omega : \lim_{t \rightarrow \infty} \int_0^t v(\mathbf{x}, s) ds \text{ diverges} \right\} = \bigcap_{n=1}^{\infty} A_n.$$

In consequence, from (19) we obtain that  $|A_\infty| = 0$ , which implies that

$$\lim_{t \rightarrow \infty} \int_0^t v(\mathbf{x}, s) ds < \infty \quad \text{a.e. in } \Omega.$$

Finally, since  $t \mapsto v(\mathbf{x}, t)$  is continuous we conclude that

$$\lim_{t \rightarrow \infty} \int_0^t v(\mathbf{x}, s) ds < \infty \quad \text{for all } \mathbf{x} \in \Omega.$$

The proof for  $i$  is the same.  $\square$

**Lemma 12** For any  $\mathbf{x} \in \Omega$ ,  $W_0(\mathbf{x}) > 0$  if and only if

$$\lim_{t \rightarrow \infty} W(\mathbf{x}, t) > 0.$$

**Proof:** Integrating over  $[0, t]$  the equation for  $W$  we obtain

$$W(\mathbf{x}, t) = W_0(\mathbf{x}) \times \exp \left\{ - \int_0^t v(\mathbf{x}, s) ds - \int_0^t i(\mathbf{x}, s) ds \right\}.$$

In consequence, the result follows immediately from Lemma 11.  $\square$

## 4.6 Proof of Theorem 6

**Lemma 13** If  $v_\infty(\mathbf{x})$  is a steady-state solution of the hybrid system (5)-(6) and  $\mu_v = 0$  then  $\|\nabla v_\infty\| = 0$ .

**Proof:** Following the proof of Lemma 8 it follows that

$$d_v \Delta v_\infty = 0.$$

Therefore, integrating by parts yields  $\|\nabla v_\infty\| = 0$ .  $\square$

**Lemma 14** If  $v$  is solution of the hybrid system (5)-(6) and  $\mu_v = 0$  then

$$\lim_{t \rightarrow \infty} \int_\Omega v(\mathbf{x}, t) d\Omega \geq \int_\Omega v_0(\mathbf{x}) d\Omega + (\alpha_v - \alpha_4 \mu_I) \int_0^\infty \int_\Omega I(\mathbf{x}, s) d\Omega dt.$$

**Proof:** Integrating over  $\Omega \times [0, t]$  the equation for  $v$  and using Fubini's Theorem yields

$$\int_\Omega v(\mathbf{x}, t) d\Omega - \int_\Omega v(\mathbf{x}, 0) d\Omega = \int_0^t \int_\Omega \Delta v(\mathbf{x}, s) d\Omega ds + \alpha_v \int_0^t \int_\Omega I(\mathbf{x}, s) d\Omega ds + \alpha_4 \int_0^t \int_\Omega v(\mathbf{x}, s) W(\mathbf{x}, s) d\Omega ds.$$



Now recall that  $v$  satisfies homogeneous Neumann boundary conditions. Therefore,

$$\int_0^t \int_{\Omega} \Delta v(\mathbf{x}, t) d\Omega dt = \int_0^t \int_{\partial\Omega} \nabla v(\mathbf{x}, t) \cdot \mathbf{n} dS dt = 0,$$

which implies that

$$\int_{\Omega} v(\mathbf{x}, t) d\Omega = \int_{\Omega} v(\mathbf{x}, 0) d\Omega + \alpha_v \int_0^t \int_{\Omega} I(\mathbf{x}, s) d\Omega dt + \alpha_4 \int_0^t \int_{\Omega} v(\mathbf{x}, s) W(\mathbf{x}, s) d\Omega dt.$$

On the other hand, integrating the equation for  $I$  yields

$$\int_0^t v(\mathbf{x}, s) W(\mathbf{x}, s) dt = I(\mathbf{x}, t) - I_0(\mathbf{x}) + \mu_I \int_0^t I(\mathbf{x}, s) dt.$$

In consequence,

$$\begin{aligned} \int_{\Omega} v(\mathbf{x}, t) d\Omega &= \int_{\Omega} v_0(\mathbf{x}) d\Omega + (\alpha_v - \alpha_4 \mu_I) \int_0^t \int_{\Omega} I(\mathbf{x}, s) d\Omega dt \\ &\quad + \alpha_4 \int_{\Omega} I(\mathbf{x}, t) d\Omega - \alpha_4 \int_{\Omega} I_0(\mathbf{x}) d\Omega. \end{aligned} \quad (20)$$

Now recall that  $I_0(\mathbf{x})$  is non-negative and

$$\lim_{t \rightarrow \infty} \int_{\Omega} I(\mathbf{x}, t) d\Omega = 0.$$

Therefore, taking the limit  $t \rightarrow \infty$  and applying Lebesgue's dominated convergence theorem in (20) we obtain

$$\lim_{t \rightarrow \infty} \int_{\Omega} v(\mathbf{x}, t) d\Omega \geq \int_{\Omega} v_0(\mathbf{x}) d\Omega + (\alpha_v - \alpha_4 \mu_I) \int_0^{\infty} \int_{\Omega} I(\mathbf{x}, s) d\Omega dt. \quad \square$$

**Lemma 15** *Define*

$$v_{\infty}(\mathbf{x}) := \limsup_{t \rightarrow \infty} v(\mathbf{x}, t).$$

*If  $\alpha_v \geq \alpha_4 \mu_I$  then*

$$\int_{\Omega} v_{\infty}(\mathbf{x}) d\Omega \geq \int_{\Omega} v_0(\mathbf{x}) d\Omega.$$

*In particular, if  $v_0 \not\equiv 0$  then  $v_{\infty} \not\equiv 0$ .*

**Proof:** If  $\alpha_v \geq \alpha_4 \mu_I$  then from Lemma 14 we have

$$\lim_{t \rightarrow \infty} \int_{\Omega} v(\mathbf{x}, t) d\Omega \geq \int_{\Omega} v_0(\mathbf{x}) d\Omega.$$

Recall that  $v(\mathbf{x}, t)$  is uniformly bounded. Therefore, applying Fatou's lemma we obtain

$$\int_{\Omega} v_{\infty}(\mathbf{x}) d\Omega \geq \lim_{t \rightarrow \infty} \int_{\Omega} v(\mathbf{x}, t) d\Omega \geq \int_{\Omega} v_0(\mathbf{x}) d\Omega. \quad \square$$

## 5 Discussion

We proved that both the reaction-diffusion and the hybrid models are well-posed problems, i.e., they have global unique solutions, which are non-negative, bounded and depend continuously on the initial data. We also showed that, when  $d \rightarrow 0$ , the solution of the reaction-diffusion model converges to the solution of the hybrid model.

We provided several asymptotic estimates for the solutions of the hybrid model. First, we proved that the solutions are uniformly bounded and integrable over  $\Omega \times (0, \infty)$ . Second, we showed that virions and wild-type cells cannot coexist, because the product of their concentrations tends to zero as  $t \rightarrow \infty$ . Third, we proved that if  $\mu_v > 0$  then the virus concentration tends to zero as  $t \rightarrow \infty$  and  $W$  tends to a non-zero, non-homogeneous limit. Fourth, if  $\mu_v = 0$  and  $\alpha_v \geq \alpha_A \mu_I$  then the global virus concentration is bigger than the original concentration.

One striking result for the hybrid model is the global stability of the steady-state solutions. Indeed, we characterized the steady-state solutions and showed that they coincide with the limits of the corresponding time-dependent solutions. Indeed, for  $\mu_v > 0$ ,

$$\begin{aligned} \lim_{t \rightarrow \infty} I(\mathbf{x}, t) &= 0 = I_\infty(\mathbf{x}), \\ \lim_{t \rightarrow \infty} v(\mathbf{x}, t) &= 0 = v_\infty(\mathbf{x}), \\ \lim_{t \rightarrow \infty} i(\mathbf{x}, t) &= 0 = i_\infty(\mathbf{x}), \end{aligned}$$

whereas  $W(\mathbf{x}, t)$  has an explicit limit,

$$W_\infty(\mathbf{x}) = W_0(\mathbf{x}) \exp \left\{ - \int_0^\infty v(\mathbf{x}, s) ds - \int_0^\infty i(\mathbf{x}, s) ds \right\}.$$

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