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Cohabitation reaction–diffusion model for virus focal infections

Daniel R. Amor [a,b,*], Joaquim Fort [c]

[a] ICREA-Complex Systems Lab, Universitat Pompeu Fabra, Dr. Aiguader 80, 08003, Barcelona, Spain
[b] Institut de Biologia Evolutiva, CSIC-UPF, Psg Barceloneta, Barcelona, Spain
[c] Complex Systems Lab, Departament de Física, Universitat de Girona, 17071 Girona, Catalonia, Spain

HIGHLIGHTS

- We report an inaccuracy in classical reaction–diffusion models for virus infections.
- We present a new model preventing virion diffusion during intracellular replication.
- Our model yields better results than nondelayed models for two T7 virus strains.
- The predicted infection speed saturates for high values of the virus adsorption rate.
- The predicted infection speed is highly dependent on the death rate of infected cells.

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ABSTRACT

The propagation of virus infection fronts has been typically modeled using a set of classical (noncohabitation) reaction–diffusion equations for interacting species. However, for some single-species systems it has been recently shown that noncohabitation reaction–diffusion equations may lead to unrealistic descriptions. We argue that previous virus infection models also have this limitation, because they assume that a virion can simultaneously reproduce inside a cell and diffuse away from it. For this reason, we build a several-species cohabitation model that does not have this limitation. Furthermore, we perform a sensitivity analysis for the most relevant parameters of the model, and we compare the predicted infection speed with observed data for two different strains of the T7 virus.

1. Introduction

Reaction–diffusion fronts have many applications in Physics, Biology and cross-disciplinary topics [1–4]. Some purely physical examples are superconducting fronts [5] and combustion flames [6]. In this paper we consider a biophysical application, namely the spread of virus infections in a cell culture [7–11]. Very recently, the importance of this research in the context of virus treatments of cancer tumors has been stressed [12]. This interest is due to the fact that some viruses can selectively kill tumor cells and therefore be used in medical treatments of cancer tumors [12]. Therefore, understanding the spatial speed of virus infections is not only a relevant biological phenomenon, but also has potentially relevant clinical applications.

In focal infections a cell in a culture is infected by a virion (i.e., a single virus particle). The virion reproduces inside the cell. Some time later, a new generation of virions leaves the cell, they diffuse away and infect other cells. This cycle is repeated

* Corresponding author at: ICREA-Complex Systems Lab, Universitat Pompeu Fabra, Dr. Aiguader 80, 08003 Barcelona, Spain. Tel.: +34 933160531.
E-mail address: daniel.rodriguez-amor@upf.edu (D.R. Amor).

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many times and a region of dead cells (a plaque) grows at a constant speed, which can be measured experimentally. The propagation of such focal infections has been modeled mathematically [7,13–15]. The interactions between the three species in the system can be summarized as follows

$$V + B \xrightarrow{k_1} I \xrightarrow{k_2} yV, \tag{1}$$

where V, B and I refer to virus, uninfected cells, and infected cells, respectively. k_1 stands for the adsorption rate of a virion into a uninfected cell (the latter is sometimes called the host). k_2 is the rate for the death (or lysis) of an infected cell, a process that releases y new viruses into the extracellular medium (y is called the yield). In the case of cells, diffusion does not take place because cells are immobilized in agar. Thus, the evolution of B and I is governed only by reaction (i.e., population growth) effects, which are well described by the following two equations [7,13–15]

$$\frac{\partial B(r,t)}{\partial t} = -k_1 B(r,t) V(r,t), \tag{2}$$

$$\frac{\partial I(r,t)}{\partial t} = k_1 V(r,t) B(r,t) - k_2 I(r,t). \tag{3}$$

In Eqs. (2) and (3) r is the radial coordinate (distance to the point where the virus was first inoculated), and the symbols [...] denote concentration.[1] In contrast to cells, virions are able to diffuse within the extracellular medium. Furthermore, the delay or lag time T that the virions need to replicate inside the infected cell has been shown to be critically important in order to predict realistic infection speeds [7,14]. In previous models, these features of the virus population were studied by means of the following time-delayed reaction–diffusion equation [7,13,14]

$$\frac{\partial V(r,t)}{\partial t} + \frac{T}{2}\frac{\partial^2 V(r,t)}{\partial t^2} = D_{\text{eff}}\frac{\partial^2 V(r,t)}{\partial r^2} + F(r,t) + \frac{T}{2}\left.\frac{\partial F(r,t)}{\partial t}\right|_g, \tag{4}$$

where F is called the virus growth function, that reads:

$$F(r,t) \equiv \left.\frac{\partial V(r,t)}{\partial t}\right|_g = -k_1 V(r,t) B(r,t) + k_2 y I(r,t). \tag{5}$$

In Eqs. (4) and (5), the subindex $|_g$ remarks that the corresponding time derivatives must take into account growth effects, but not diffusion (see Ref. [16] for a detailed discussion on this point). Moreover, in Eq. (4) we have applied the effective diffusion coefficient D_{eff}, which takes into account the effects of the actual hindered diffusion. In this sense, D_{eff} introduces the corresponding diffusion corrections due to the presence of spheroids (host bacteria) in the medium in which the viruses diffuse. The relation between D_{eff} and the virus diffusivity D in the continuous medium (in our case agar) is given by the Fricke's equation [17]:

$$D_{\text{eff}} = \frac{1-f}{1+\frac{f}{x}} D, \tag{6}$$

where $f = B_0/B_{\max}$ is the initial concentration of bacteria in the experiment relative to its maximum possible value, and x takes care of the shape of the suspended particles (host bacteria). In this paper we will consider the *E. coli* species, for which the shape factor $x = 1.67$ was derived in Ref. [7].

In recent years, single-species reaction–diffusion models have been modified to take into account the cohabitation effect, namely the fact that for some biological species (e.g. humans) newborn individuals cannot disperse away from their parents until a delay time after their birth [18]. Mathematically this leads to a different kind of reaction–diffusion equation, in which the contributions of biological reproduction and dispersal are not added up but computed as separate steps (for example, first reproduction and later dispersal). Clearly, this effect takes place also in virus infections, because it is well-known that after a virus enters a cell, the new generation of viruses does not leave the cell until after a delay time corresponding to the death of the host cell. In the present paper, we build a model that takes this cohabitation effect into account for virus infections. We will also apply it to describe additional experimental data to those analyzed in previous papers [7,13,14].

2. Cohabitation model

Typically, models for virus focal infections are either based in Eq. (4) [7,13,14], or in its classical nondelayed version [15,19], namely Eq. (4) with $T = 0$ (i.e., Fisher's equation). Before modifying Eq. (4), we need first to recall that it can be derived from the following integro-difference reaction–dispersal equation [20,21]

$$V(x,y,t+T) - V(x,y,t) = \iint V(x+\Delta_x, y+\Delta_y, t)\phi_T(\Delta_x,\Delta_y)\mathrm{d}\Delta_x\Delta_y - V(x,y,t) + R_T[V(x,y,t)] - V(x,y,t), \tag{7}$$

[1] An additional, quadratic term has been sometimes added to Eq. (3) in order to describe the so-called one-step experiments [7,14] but is not necessary for the purposes of the present paper, because we are here concerned with the front speed, which is derived by linearizing the reaction–diffusion equations.