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Hyperbolic Reaction-Diffusion Model for Virus Infections

Vicenç Méndez*, José Casas-Vázquez

Departament de Física. Universitat Autònoma de Barcelona
E-08193 Bellaterra, Barcelona, Spain.
e-mail: vicenc.mendez@uab.es, jose.casas@uab.es

Abstract

We propose a reaction-diffusion model to study the front propagation of viruses growing in a bacterial colony. From a mesoscopic description we consider that viruses spread according to non-Markovian random walks and thus we obtain a set of hyperbolic reaction-diffusion equations of three components. There is an excellent agreement between our predictions and experimental results. However, this agreement does not exist when random walks are Markovian and the resulting reaction-diffusion equations are of parabolic type.

Keywords: Reaction-diffusion, front propagation, time-delay.

1. Introduction

Reaction-diffusion equations have been studied extensively as mathematical models of systems with reactions and diffusion across a wide scope of applications. Most studies consider that the transport process is described by Fick's law. The resulting parabolic reaction-diffusion equation (Fisher's equation) admits travelling wave solutions propagating with a constant speed which grows unboundedly with the reaction rate. More recently, it has been shown (Fort and Méndez, 2002a) that Fisher's equation always overestimates the value of the front speed in neglecting the waiting time between jumps in comparison with the characteristic evolution time. However, in many processes of biological interest both characteristic times may be of the same order, i.e. cannot be neglected. The first-order correction converts the reaction-diffusion equation into one of hyperbolic type. This equation predicts fronts propagating with constant speed exhibiting an upper bound in the fast reaction limit. In some ecological applications we have shown that the front speed of hyperbolic reaction-diffusion equations (HRD) are in better agreement with the observed data than that obtained from Fisher's equation (Ortega-Cejas et al., 2004). HRD equations can be obtained from the framework of Extended Irreversible Thermodynamics (EIT) (Jou et al., 2001) where the space of thermodynamic variables incorporates the thermodynamic fluxes as well as the equilibrium variables. The existence of a time-delay (linked to the mean waiting time in a mesoscopic description) is the key element to guarantee the causality of the transport equations predicted by EIT. In many physical problems, this time-delay is very small in comparison with the macroscopic time scale. However, the biological system we address here provides a good example where this time-delay is very important and necessary to obtain a good agreement between the theoretical predictions and the experimental results.

We investigate the spreading dynamics of viruses which infect host bacteria. We obtain the same system of equations as in Fort and Méndez (2002b) but from mesoscopic derivation. In particular, we show how non-Markovian random walks for viruses dispersal give rise to macroscopic HRD equations. The process we want to model consists of two steps: (i) the virus-bacteria interaction and (ii) the virus dispersal within the bacterial colony. We derive from a mesoscopic level a hyperbolic reaction-diffusion equation for the virus concentration and we also show that parabolic equations are inadequate as they do not take into account the time elapsed between the adsorption of a virus to a bacterium and the release of newborn viruses to the medium. This time will be estimated to be on the order of 20 minutes which is not negligible with respect to an evolution in time of about a few hours. It is well known from virology that the virus reproduction within host bacteria causes the death of the bacteria and it is observed experimentally that the invaded area (plaque) can be regarded as a propagating front with constant speed (Yin and McCaskill, 1992).

The plaque is formed due to the adsorption of viruses to host bacteria, their replication within and the spread of the new generation after lysis.

* Author to whom correspondence should be addressed.
vicenc.mendez@uab.es

We deal, in particular, with virus phages such as T7 for which plaques grow unboundedly in a medium containing agar-immobilized stationary-phase host bacteria.

Our model consists of three species: viruses (V), host bacteria (B) and infected bacteria (I). Their interactions (lytic cycle) can be summarised as follows:

$$V + B \xrightarrow{k_1} I \xrightarrow{k_2} Y \cdot V \qquad (1)$$

where Y is the number of new viruses released per virus particle (yield or burst size), k_1 is the rate constant of adsorption of viruses to a host bacteria and k_2 is the death rate constant of infected bacteria.

2. Mesoscopic and Macroscopic Equations

2.1. Kinetic equations

In order to deduce the interaction term between the three reacting species, let us consider a homogeneous medium composed initially of infected bacteria and a few free viruses. The adsorption process can be described by the equation

$$\frac{\mathrm{d}[V]}{\mathrm{d}t} = -k_1[V][B], \qquad (2)$$

where brackets mean species' concentrations which depend only on time t. As for each adsorbed bacteria, one virus is "removed" and one has $\mathrm{d}[V]/\mathrm{d}t = \mathrm{d}[B]/\mathrm{d}t$ that can be integrated to obtain $[B] = [V] + C$, where C is an integration constant. Integrating Equation (2) one gets the expression

$$g([V]) \equiv \ln\left(\frac{[V]+C}{[V]}\right) - \ln\left(\frac{[V_0]+C}{[V_0]}\right) = Ck_1 t \,, \qquad (3)$$

where $C = [B_0] - [V_0]$, $[B_0] = [B]_{t=0}$ and $[V_0] = [V]_{t=0}$. For the virus replication we consider the logistic growth equation

$$\frac{\mathrm{d}[V]}{\mathrm{d}t} = k_2[V]\left(1 - \frac{[V]}{[V]_{\max}}\right) \qquad (4)$$

If adsorption takes place at $t = 0$ and we define the delay time τ as the time elapsed from the adsorption and the replication of $V_{\max}/2$ viruses, its solution reads

$$[V(t)] = [V]_{\max}\left(1 + e^{-k_2(t-\tau)}\right)^{-1}. \qquad (5)$$

On the other hand, from the conservation of the number of viruses and infected bacteria one has $[V(t)] + Y[I(t)] = [V]_{\max} = Y[I]_{\max}$ which can be introduced into Equation (4) to yield

$$\frac{\mathrm{d}[V]}{\mathrm{d}t} = -Y\frac{\mathrm{d}[I]}{\mathrm{d}t} = k_2 Y[I]\left(1 - \frac{[I]}{[I]_{\max}}\right). \qquad (6)$$

Finally, the set of kinetic equations reads

$$\frac{\mathrm{d}[V]}{\mathrm{d}t} = F_V([V],[B],[I]), \qquad (7a)$$

$$\frac{\mathrm{d}[B]}{\mathrm{d}t} = F_B([V],[B],[I]), \qquad (7b)$$

$$\frac{\mathrm{d}[I]}{\mathrm{d}t} = F_I([V],[B],[I]), \qquad (7c)$$

with

$$F_V \equiv -k_1[V][B] + k_2 Y[I]\left(1 - \frac{[I]}{[I]_{\max}}\right), \qquad (8a)$$

$$F_B \equiv -k_1[V][B], \qquad (8b)$$

$$F_I \equiv k_1[V][B] - k_2[I]\left(1 - \frac{[I]}{[I]_{\max}}\right). \qquad (8c)$$

2.2. Dispersal equation

In order to propose an equation for the virus dispersal in agar we start form the mesoscopic equation for the virus number at point x at time t obtained from the continuous-time random walk with reaction (Fedotov and Méndez, 2002a)

$$V(x,t) = \phi(t)V(x,0) + \int_0^t \mathrm{d}t' \int \mathrm{d}x' \Psi(x',t')V(x-x',t-t') + \int_0^t \mathrm{d}t' \phi(t')F_V(t-t') \qquad (9)$$

where $\Psi(x,t)$ is the probability density function (PDF) of performing a jump of length x after waiting a time t and $\phi(t)$ is the survival probability which can be written in the form $\phi(t) = 1 - \int_0^t \mathrm{d}t'\varphi(t')$ with $\varphi(t)$ the waiting time PDF. Transforming (9) by Fourier–Laplace and dividing by $\varphi(s)$ one has

$$\frac{1}{\varphi(s)}V(k,s) = \frac{1}{s}\left(\frac{1}{\varphi(s)} - 1\right)V(k,t=0) + \Phi(k)V(k,s) + \frac{1}{s}\left(\frac{1}{\varphi(s)} - 1\right)F_V(k,s) \qquad (10)$$

where we have assumed that jump lengths and waiting times are decoupled random variables, i.e. $\Psi(k,s) = \Phi(k)\varphi(s)$. To be more explicit we take a Gaussian PDF of jumps $\Phi(k) = e^{-2D\tau k^2} \approx 1 - 2D\tau k^2$ in the diffusive limit and the non-Markovian waiting-time PDF $\varphi(t) = (t/\tau^2)e^{-t/\tau}$, where τ stands for the characteristic waiting time between jumps. Note that we have intentionally taken the same notation for this time as for the half reproduction time for viruses because this means that they reproduce

when they are at the sedentary stage only. Introducing the above definitions into Equation (10) and inverting with Fourier–Laplace we get $\frac{1}{2}\tau\partial_t^2 V + \partial_t V = D\partial_x^2 V + F_V + \frac{1}{2}\tau\partial_t F_V$, that is, the hyperbolic reaction-diffusion equation (Jou et al., 2001) for the viruses. As the diffusion of viruses is hindered by the presence of a suspension of spheroids (host bacteria) we must take into account Fricke's equation $D = (1-f)D^*/(1+f/\varsigma)$, where $f = [B_0]/[B]_{\max}$ is the concentration of bacteria relative to its maximum possible value for a fixed nutrient concentration, ς is a parameter which takes care of the shape of bacteria and is equal to 1.67 for E. coli, and D^* is the diffusion coefficient for free viruses in agar.

3. Parameter estimation and results

The adsorption rate between T7 and E. coli was estimated from fitting Equation (3) to experimental data (Shishido et al., 1975) as shown in *Figure 1* (inset). As a result, we obtained $k_1 = (1.29 \pm 0.59)\times 10^{-9}$ ml/min.

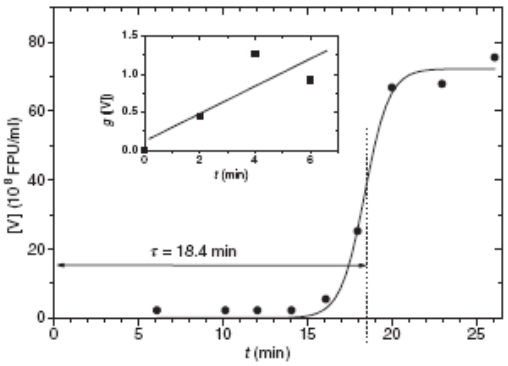

Figure 1. One-step growth curve; inset: adsorption curve; experimental data are obtained for the interaction between T7 and E. coli.

By fitting (5) to the one-step-growth curve for the replication of T7 within E. coli (Yin, 1993) (the main curve in *Figure 1*) we get $k_2 = 1.39\,\text{min}^{-1}$, τ = 18.4 min and $Y = [V]_{\max}/[V_0] = 34.5$. The diffusion coefficient of T7 in agar can be approximated to that of P22 because it is very similar to T7 in size and shape (Ackermann, 1976), and shape (Ackermann, 1976), $D^* = 4\times 10^{-8}$ cm^2/s. The set of evolution equations for the number of viruses, host bacteria and infected bacteria

$$\frac{\tau}{2}\frac{\partial^2[V]}{\partial t^2} + \frac{\partial[V]}{\partial t} = D\frac{\partial^2[V]}{\partial x^2} + F_V + \frac{\tau}{2}\frac{\partial F_V}{\partial t},$$
$$\frac{\partial[B]}{\partial t} = F_B([V],[I],[B]), \qquad (11)$$
$$\frac{\partial[I]}{\partial t} = F_I([V],[I],[B])$$

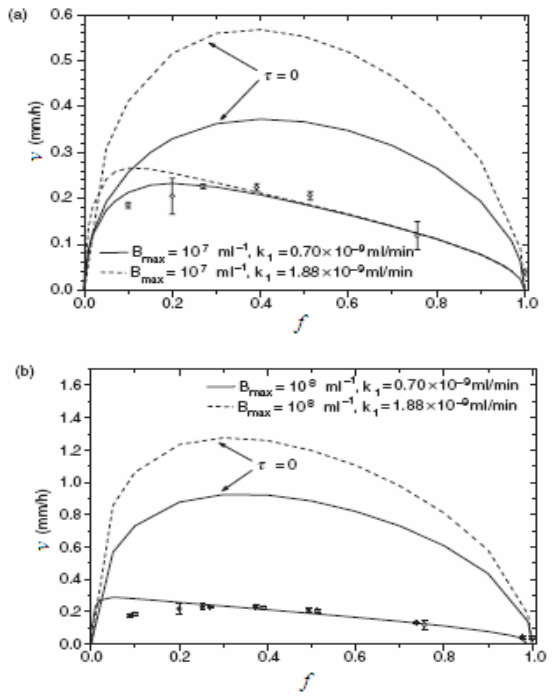

Figure 2. Theoretical (lines) versus experimental results for the front velocity.

with the interaction terms defined as in (7), describes a propagating front invading the unstable state $(0,[B_0],0)$. The dimensionless front speed c (the front speed is calculated by multiplying c by $\sqrt{Dk_2}$) is calculated by computing the minimum value of c for any $\lambda > 0$ from the characteristic equation (Fort and Méndez, 2002b)

$$c\lambda^3\left(1-\tfrac{1}{2}\tau^* c^2\right) + \lambda^2\left\{1-\left[1+\tfrac{1}{2}\tau^*(1+\kappa)\right]c^2\right\}$$
$$-c\lambda\left\{1+\kappa\left[1-\tfrac{1}{2}\tau^*(Y-1)\right]\right\} + \kappa(Y-1) = 0, \qquad (12)$$

where the dimensionless quantities are defined as $\tau^* = k_2\tau$ and $\kappa = k_1 f/(k_2`[B]_{\max})$.

In *Figure 2* we plot our results obtained from Equation (11) for the two extreme values of k_1 (solid and dashed lines) together with the parabolic case where $\tau = 0$. Symbols represent the experimental results (Yin and McCaskill, 1992) for $B_{\max}$ = 10^7 ml^{-1} (*Figure 2a*) and $B_{\max}$ = 10^8 ml^{-1} (*Figure 2b*). As is observed, our hyperbolic model agrees notably better than the parabolic one, reflecting the importance of considering the time-delay τ in the model.

4. Conclusions

Our model provides a satisfactory explanation for the growth of virus plaques. It is based on considering a non-Markovian waiting-time PDF and extends previous models that use parabolic equations (Yin and McCaskill, 1992). From the basis of the experimental knowledge, waiting

times are assumed to be equal to the times elapsed between adsorption and lysis. As a consequence, our model accounts for a dichotomy between dispersal and reproduction processes which has also been observed, for example, in cancer cells (Fedotov and Iomin, 2007). This dichotomy only exists on the level of averages and allows us to identify the mean waiting time as the mean infection time. It is important to stress that this is possible due to the non-Markovian character of the underlying random walk of the viruses. The research reported here can be useful for the characterisation of mutant virus strains in terms of front speeds and the modelling of front shapes in virus infections.

Nomenclature

$[B]$	Concentration of bacteria, cfu/ml
C	Integration constant
c	Dimensionless front speed
D	Effective diffusion coefficient, cm^2/s
D^*	Diffusion coefficient in agar, cm^2/s
f	Concentration fraction of bacteria relative to the maximum value
F_B	Kinetic term for bacteria, cfu ml^{-1} min^{-1}
F_I	Kinetic term for infected bacteria, cfu ml^{-1} min^{-1}
F_V	Kinetic term for viruses, pfu ml^{-1} min^{-1}
g	Arbitrary function
$[I]$	Concentration of infected bacteria, cfu/ml
k	Wave number, cm^{-1}
k_1	Constant rate of adsorption, min^{-1}
k_2	Constant rate of lysis, min^{-1}
s	Laplace variable, cm^{-1}
t	Time, s
$V(x,t)$, $[V]$	Concentration of viruses, pfu/ml
x	Space, cm
Y	Yield, burst size or number of new viruses released per bacteria

Greek symbols

ϕ	Survival probability
Φ	Dispersal kernel, cm^{-1}
φ	Waiting time distribution, min^{-1}
κ	Dimensionless group
λ	Dimensionless front shape
τ	Time delay, min^{-1}
τ^*	Dimensionless time delay, min^{-1}
Ψ	PDF of jump lengths and waiting times, $cm^{-1}min^{-1}$
ς	Bacteria's shape dimensionless parameter

Suffixes

0	Initial time
B	Bacteria
I	Infected bacteria
$t = 0$	Initial time
V	Viruses
max	Maximum value

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