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LETTER TO THE EDITOR

A Comment on Amplification and Spread of Viruses in a Growing Plaque

You & Yin (1999) analyse a system in which viruses diffuse to host cells, replicate within and lyse (kill) them. This gives rise to growing regions of dead cells, called plaques. Yin's lucid reaction–diffusion approach to the growth of plaques was solved numerically (You & Yin, 1999), and the results were compared to previous analytic predictions (Yin & McCaskill, 1992). Yin and co-workers have also discovered that mutants can appear and outgrow their precursors (Yin, 1993, 1994; Lee & Yin, 1996), and have proposed a model of hindered diffusion. This leads to *qualitative* agreement between theory and experiment, but *quantitative* agreement has yet to be attained: the predicted speed is 5 times higher than that observed experimentally (You & Yin, 1999). In these papers it has been correctly pointed out that satisfactory agreement may be obtained in the future after the model parameters are precisely measured. In this context, it is important to derive simple and accurate analytical formulae for the virus wavefront speed. Such an equation will be derived here, with the hope that it may be useful to researchers who may want to compare Yin's theory to new experiments in the future.

The model by Yin and co-workers has three species: viruses (V), uninfected host bacteria (B) and virus–host complexes (I). The reactions are

$$V + B \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} I \overset{k_2}{\rightarrow} Y\ V,$$

where Y is the yield. Using dimensionless variables (concentrations V^*, B^* and I^*, distance r^*, time t^* and rate constants κ_1 and κ_{-1}, see You & Yin, 1999) and neglecting curvature effects, the corresponding reaction–diffusion model is

$$\frac{\partial V^*}{\partial t^*} = \frac{\partial^2 V^*}{\partial r^{*2}} - \kappa_1 V^* B^* + (\kappa_{-1} + Y) I^*,$$

$$\frac{\partial B^*}{\partial t^*} = -\kappa_1 V^* B^* + \kappa_{-1} I^*,$$

$$\frac{\partial I^*}{\partial t^*} = \kappa_1 V^* B^* + -(\kappa_{-1} + 1) I^*.$$

You & Yin (1999) assume that the concentration fronts of viruses, hosts and infected bacteria decay exponentially with the same dimensionless decay length $1/\xi$ (see also Yin & McCaskill, 1992). This yields

$$\xi^3 + C_1 \xi^2 + C_2 \xi + C_3 = 0. \qquad (1)$$

In fact, this equation holds without need of the assumption mentioned above that all species have the same decay length $1/\xi$. This is so because, in the linear approximation (wavefront edge), the general solution of any of the species in the system is a linear combination of exponentials with exponents determined by the roots of eqn (1) [for a more detailed explanation see, e.g. Murray (1993), Appendix 1 and Section 12.2]. Thus, in our opinion, the disagreement between the analytic and simulated results for high values of κ_1 (Fig. 4 in You & Yin, 1999) is not due to the assumption mentioned above. In principle, it could be due to the simulations becoming less accurate. However, here we are not interested in analysing this point in detail, simply because the range in which this disagreement appears

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($\kappa_1 > 100$) is far from the independently estimated value of $\kappa_1 = 1.5$ (see Table 1 in You & Yin, 1999).

Real, positive solutions for ξ exist provided that [see eqn (4) and Appendix 1 in Yin & McCaskill, 1992]

$$-4C_1^3C_3 + C_1^2C_2^2 + 18C_1C_2C_3 - 4C_2^3 - 27C_3^2 \geqslant 0, \tag{2}$$

where

$$C_1 = \frac{\kappa_{-1} + 1 - c^{*2}}{c^*}, \tag{3}$$

$$C_2 = -\kappa_{-1} - 1 - \kappa_1, \tag{4}$$

$$C_3 = \frac{Y-1}{c^*}\kappa_1 \simeq \frac{Y}{c^*}\kappa_1, \tag{5}$$

where c^* is the dimensionless front speed (its true speed being $c = \sqrt{Dk_2}\, c^*$, with D the virus diffusion coefficient and k_2 the host death rate). We have applied the large-yield approximation ($Y \gg 1$) because it is rather accurate for a realistic set of parameter values (this will become clear below, specifically from Fig. 2). If we make the assumption that (i)

$$c^{*2} \gg \kappa_{-1} + 1 \tag{6}$$

then we have $C_1 \simeq -c^*$. A stronger assumption is that (ii)

$$c^{*2} \gg \kappa_{-1} + 1 + \kappa_1, \tag{7}$$

which implies that $c^{*2} \gg \kappa_1$, so that for $Y \gg 1$ only the first and last terms in eqn (2) are relevant and it follows immediately that the minimal propagation speed is

$$c^*_{(YM)} = \sqrt{\frac{3}{2}\sqrt{3Y\kappa_1}}, \tag{8}$$

which is eqn (6b) in Yin & McCaskill (1992). However, use of the realistic set of parameter values in You & Yin (1999) (namely, $\kappa_1 = 1.5$, $\kappa_{-1} = 0.5$ and $Y = 50$) into eqn (8) yields $c^*_{(YM)} = 4.74$, from which it is seen that the third term in eqn (2) ($18C_1C_2C_3 = 3733$) is of magnitude similar to that of the first one ($-4C_1^3C_3 = 5402$). It means that the inequality $C_1^2 \gg -C_2$, which is equivalent to eqn (7), does not hold. This shows that assumption (ii) above breaks down for sure. In order to find a more accurate solution for realistic values of the parameters, let us therefore drop assumption (ii) and replace it by the less strong assumption (i). Thus, from now on we assume that eqn (6) holds. Then, eqn (2) becomes

$$f(c^*) \equiv 4c^{*4} + 18(-\kappa_{-1} - 1 - \kappa_1)c^{*2} - 27\,Y\,\kappa_1 \geqslant 0. \tag{9}$$

It is easy to see that the function $f(c^*)$ has a single minimum, which corresponds to a positive value of c^*. On the other hand, $f(c^* = 0) < 0$. Thus, $f(c^*)$ has the shape shown in Fig. 1 and inequality (9) holds for the ranges of c^* labelled in Fig. 1. We now see that negative values for c^* cannot be admitted. In the derivation of eqn (2), it was assumed (Yin & McCaskill, 1992) that the concentration profiles of viruses V^*, hosts H^* and infected bacteria I^* can be written for $z \to \infty$ as

$$V^* = a_1 e^{-\xi z^*},$$
$$B^* = 1 - a_2 e^{-\xi z^*} \tag{10}$$
$$I^* = a_3 e^{-\xi z^*},$$

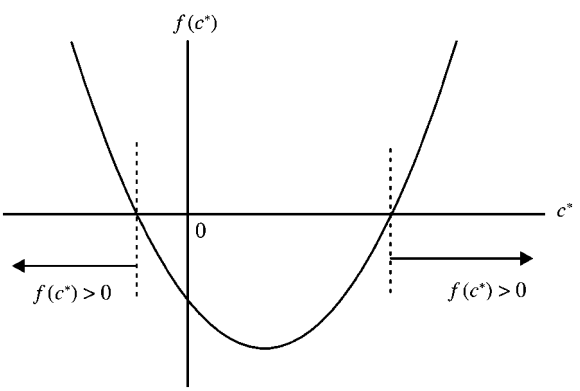

FIG. 1. Plot of the function $f(c^*)$ defined by eqn (9). This plot is used to derive the dimensionless speed of virus and host concentration fronts, eqn (11).

where $z^* = r^* - c^* t^*$ ($r^* = r\sqrt{k_2/D}$ and $t^* = k_2 t$ being dimensionless radial distance and time, respectively). Equation (10) clearly corresponds to a wavefront moving to the right, i.e. $c^* > 0$ (for example, we have $\lim_{z^* \to \infty} V^* = 0$, whereas for a left-moving front we would have $\lim_{z^* \to \infty} V^* \neq 0$). The same conclusion would hold if we considered the general solution, i.e. a linear combination of exponentials for V^*, etc. [see the text below eqn (1)]. Thus in fact, the only allowed range of values for c^* such that $f(c^*) > 0$ is that on the right of Fig. 1. It means that the minimal propagation velocity can be obtained from the conditions $f(c^*) = 0$ and $c^* > 0$. Making use of eqn (9), this yields

$$c^* = \sqrt{9(\kappa_{-1}+1+\kappa_1)\left(-1+\frac{1}{2}\sqrt{\frac{1}{8}+27\frac{Y\kappa_1}{[9(\kappa_{-1}+1+\kappa_1)]^2}}\right)}. \tag{11}$$

We note that the special case $Y\kappa_1 \gg (\kappa_{-1}+1+\kappa_1)^2$ corresponds to the result $c^*_{(YM)}$ by Yin and co-workers [see eqn (8) above]. Moreover, in this special case we see that $c^{*2} \gg \kappa_{-1}+1+\kappa_1$, as it was to be expected, since this is precisely the ansatz, eqn (7), from which we have derived the Yin–McCaskill result [eqn (8)]. In other words, their result corresponds to assuming eqn (7), whereas its generalization [eqn (11)] corresponds to the less strong assumption of eqn (6).

Let us finally enquire to what extent the generalization given by eqn (11) is useful.

(i) We first note that the reduced desorption rate constant κ_{-1} appears in eqn (11), whereas it is not taken into account in the Yin–McCaskill approximation, eqn (8). It means that our new solution can be used to obtain very quickly plots which show the effect of this parameter.

(ii) As far as the dependence on the yield Y is concerned, in Fig. 2 we compare the predictions for the velocity of virus fronts obtained from the simulations (Fig. 3 in You & Yin, 1999), the Yin–McCaskill (1992) result, [eqn (8)], and the new result, [eqn (11)]. It is seen that the new eqn (11) gives a more accurate prediction. For the value of Y stressed in You & Yin (1999), namely $Y = 50$ (see Table 1 in their paper), the error of the previously known analytic result, eqn (8), is about 14%, whereas the error of the new result, eqn (11), is only 2%. Again, this shows the usefulness of the new explicit formula (11). From Fig. 2 it is also found that its error decreases quickly within the most realistic range of values of Y, namely $50 < Y < 200$ (see You & Yin, 1999; Yin & MacCaskill, 1992).

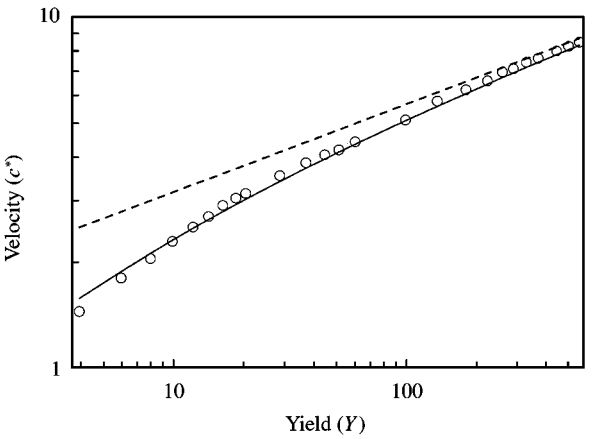

FIG. 2. (○○○) Results of the simulations in Fig. 3 by You & Yin (1999) for the dimensionless speed of plaque growth, (– – –) predictions of the Yin–MacCaskill explicit formula [eqn (8) in the present paper], (——) explicit solution derived here, namely eqn (11). The values of the parameters appearing in eqns (8) and (11) are the same as those used in the simulations, namely $\kappa_1 = 1.5$ and $\kappa_{-1} = 0.5$. Comparing to Fig. 3 in You & Yin (1999), it is seen that the new explicit formula (11) is, for all practical purposes, as accurate as the exact, implicit and very complicated solution [eqns (5a–e) in Yin & McCaskill, 1992].

(iii) Finally, it is also very interesting to note from Fig. 2 that our new result, eqn (11), remains rather accurate even for relatively low values of Y.

(iv) The new formula (11) may be very useful in order to compare to experiment, since one may now readily use the extremely simple eqn (11) to find quick estimates with a pocket calculator, to obtain reliable plots very quickly, to analyse the effect of the parameter values with ease, etc. instead of having to use numerical mathematics computer programs in order to solve the full implicit solution numerically [eqns (5a–e) in Yin & MacCaskill, 1992].

Just to summarize, the contribution of this letter is the improved explicit expression, eqn (11), for the rate of plaque growth. The importance of this result is due to the following facts: (a) the Yin–MacCaskill model is the leading candidate to give a quantitatively correct description of the replication and spread of viruses in growing plaques; (b) our new solution holds in the model by Yin and co-workers; (c) it is explicit, thus much quicker and easier to use than the full implicit solution for future comparisons to experimental data and (d) it is more accurate (for realistic parameter values) than previous explicit approximations.

The compact form of the velocity derived, eqn (11), provides a bridge between a macroscopic real-time measure of the virus spread (rate or velocity of plaque growth) and the microscopic mechanisms that describe the virus–host interaction (adsorption/desorption, intracellular growth, virus yield and diffusion parameters).

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