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LETTER TO THE EDITOR

Bifurcation in a generic model of intracellular viral kinetics

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Abstract

The key steps of intracellular virion reproduction include viral genome replication, mRNA synthesis and degradation, protein synthesis and degradation, capsid assembly and virion release from a cell. Our analysis, incorporating these steps (with no deterioration of the cell machinery), indicates that asymptotically depending on the values of the model parameters the viral kinetics either reach a steady state or are out of control due to an exponential growth of the virion population. In the latter case, the cell is expected to rapidly die or the virion growth should be limited by other steps.

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Interaction between viruses and cells is a complex spatio-temporal phenomenon depending on a multitude of physical, chemical and biological factors [1]. The theoretical works in this field have long been focused on describing the interplay of ensembles of viruses and cells. The corresponding kinetic models are numerous and cover very different situations ranging from temporal evolution of the populations of uninfected and infected cells and virions, x, y and v, described as

$$\mathrm{d}x/\mathrm{d}t = a - k_1 x - k_2 x v$$
$$\mathrm{d}y/\mathrm{d}t = k_2 x v - k_3 y$$
$$\mathrm{d}v/\mathrm{d}t = k_4 y - k_5 v$$

(in these equations, a is the rate of cell replenishment, k_2 is the infection rate constant, k_1, k_3 and k_5 are the death rate constants and k_4 is the rate constant of virion production by infected cells), to complex spatio-temporal schemes taking into account the specifics of diseases [2, 3]. In parallel with this activity, it is now highly desirable to construct the models clarifying various aspects and the whole course of intracellular viral kinetics, because the progress of experimental studies in this area is rapid and impressive [1, 4–6] (the most recent

advances, based on fluorescence of a market molecule, allow e.g., visualization of the pathway of an individual virion in a living cell [7]). The already available relevant models treat plasmid replication [8], protein synthesis [9] and capsid formation [10]. There are also first attempts [11, 12] to describe the interplay between various steps of intracellular virion formation. Despite these efforts, the understanding of the kinetics predicted by the models of the latter type is rather limited. In this letter, we show what may occur in such models.

Viruses are known to consist of a genome in the form of either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), protein coat (capsid) and, in some cases, outer membrane (envelope) [1, 13]. Viral infection of a cell occurs via attachment of a virion to a receptor on the external cell membrane and penetration inside the cell, uncoating in which the viral capsid is completely or partially removed and the virus genome is exposed, followed by genome replication, synthesis of viral proteins, assembly and/or maturation of new virions, and their release from the cell. A minimal set of steps corresponding to this scheme includes genome (e.g., DNA) replication,

$$G \to 2G \tag{1}$$

messenger RNA (mRNA) synthesis and degradation,

$$G \to G + R \tag{2}$$

$$R \to 0 \tag{3}$$

protein synthesis and degradation,

$$R \to R + P \tag{4}$$

$$P \to 0 \tag{5}$$

capsid assembly via association of n proteins with G,

$$G + nP \to V \tag{6}$$

and virion release from the cell,

$$V \to 0. \tag{7}$$

By increasing the number of produced virions, the cell machinery deteriorates and eventually a cell dies. Here we will consider that the virus–cell interaction is not too destructive so that the infected cell may exist a while in the state close to a steady state. Focusing on the transition to the steady-state regime, we exclude the deterioration steps from our present analysis. In addition, we consider that inter-compartment diffusion of all the species participating in the above steps is rapid and accordingly the virus-formation kinetics can be described in terms of the numbers of the species in the cell, N_{G}, N_{R}, N_{P} and N_{G}. Steps (1)–(5) and (7) are treated as elementary (this approximation holds if the virus-induced cell deterioration is negligible). Step (6) is assumed to occur via sequential attachment of P to G. Thus, we have

$$\mathrm{d}N_{\mathrm{G}}/\mathrm{d}t = k_1 N_{\mathrm{G}} - k_6 N_{\mathrm{P}} N_{\mathrm{G}} \tag{8}$$

$$\mathrm{d}N_{\mathrm{R}}/\mathrm{d}t = k_2 N_{\mathrm{G}} - k_3 N_{\mathrm{R}} \tag{9}$$

$$\mathrm{d}N_{\mathrm{P}}/\mathrm{d}t = k_4 N_{\mathrm{R}} - k_5 N_{\mathrm{P}} - n k_6 N_{\mathrm{P}} N_{\mathrm{G}} \tag{10}$$

$$\mathrm{d}N_{\mathrm{V}}/\mathrm{d}t = k_6 N_{\mathrm{P}} N_{\mathrm{G}} - k_7 N_{\mathrm{V}} \tag{11}$$

where k_i ($i = 1$–5 and 7) are the rate constants of steps (1)–(5) and (7), and k_6 is the effective rate constant of step (6).

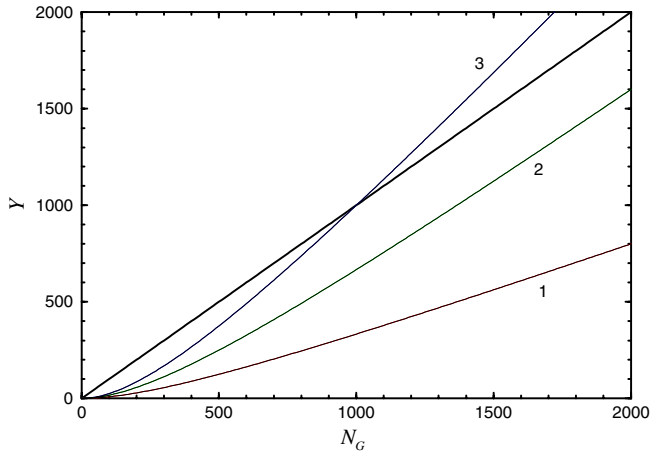

Figure 1. Graphic solution of equation (12) under steady-state conditions for $N_0 = 500$. The thick solid line shows the function $Y_1 = N_G$. Thin solid lines 1, 2 and 3 represent the function $Y_2 = (k_0/k_1)N_G^2/(1 + N_G/N_0)$ for $k_0/k_1 = 0.001$, 0.002 and 0.003, respectively. Lines 1 and 2, corresponding to the conditions $k_0/k_1 < 1/N_0$ and $k_0/k_1 = 1/N_0$, do not cross the thick solid line, and accordingly in these cases there is no steady state. Line 3, constructed for $k_0/k_1 > 1/N_0$, crosses the thick solid line at the point corresponding to a steady state.

Viral capsids (with $n \simeq 100$) are stabilized by attractive lateral protein–protein interactions [1, 13]. Due to these interactions, the kinetics of capsid formation is physically similar to that of first-order phase transitions. Specifically, one can introduce critical concentration of proteins, c_P^{cr}. At $N_P/v < c_P^{cr}$ (v is the cell volume), the capsid formation is thermodynamically forbidden. While for $N_P/v > c_P^{cr}$, it occurs rapidly. Following this line, we use $k_6 = 0$ at $N_P/v < c_P^{cr}$, and $k_6 \simeq \kappa/n$ at $N_P/v > c_P^{cr}$ (the rate constant κ characterizes an elementary association step $G + P \to GP$).

At $t = 0$, the cell is assumed to contain a single uncoated virion, i.e., $N_G(0) = 1$ and $N_R(0) = N_P(0) = N_V(0) = 0$.

The specification above formalizes our generic model of intracellular viral kinetics. Compared to the earlier model [12], our treatment incorporates the mRNA synthesis and degradation. In addition, by introducing c_P^{cr}, we take into account that kinetically the capsid formation occurs in a highly nonlinear fashion. On the other hand, our analysis skips some more specific steps and/or features discussed, e.g., in [11].

To describe the cell at $t > 0$, we note that on the time scale of the genome formation the mRNA and protein synthesis, consumption and degradation are rapid and accordingly equations (9) and (10) can be solved in the steady-state approximation as $N_R = (k_2/k_3)N_G$ and $N_P = k_2k_4N_G/[k_3(k_5 + nk_6N_G)]$. Substituting these expressions into equations (8) and (11) yields

$$\frac{dN_G}{dt} = k_1N_G - \frac{k_0N_G^2}{1 + N_G/N_0} \tag{12}$$

$$\frac{dN_V}{dt} = \frac{k_0N_G^2}{1 + N_G/N_0} - k_7N_V \tag{13}$$

where $k_0 \equiv k_2k_4k_6/(k_3k_5)$ and $N_0 \equiv k_5/nk_6$.

The analysis of equation (12) indicates that it predicts a bifurcation at $k_0/k_1 = 1/N_0$ (figure 1). In particular, equation (12) has and does not have a steady-state solution at

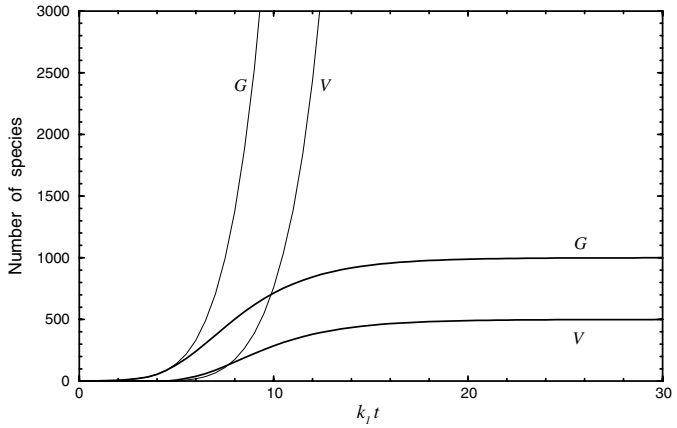

Figure 2. G and V populations inside the cell as a function of time for $vc_{\mathrm{P}}^{\mathrm{cr}} = 100$, $N_0 = 500$ and $k_7/k_1 = 2$. The thick and thin lines correspond to $k_0/k_1 = 0.003$ and 0.001, respectively. In the former case, the cell reaches a steady state. In the latter case, the virion growth is out of control.

$k_0/k_1 > 1/N_0$ and $k_0/k_1 < 1/N_0$, respectively. Thus, the model kinetics asymptotically (at $t \to \infty$) exhibit a steady-state regime for $k_0/k_1 > 1/N_0$ and unlimited exponential growth of the G and V populations for $k_0/k_1 < 1/N_0$ (figure 2).

In summary, the minimal model of intracellular virion reproduction (with no deterioration of the cell machinery) shows that depending on the values of the model parameters the cell either reaches a steady state and exists in this state for a while or the growth of the virion population is out of control. In the latter case, the cell is expected to rapidly die or the virion reproduction should be limited by the steps which were not included in the model.

Finally, it is appropriate to note that despite the abundance of information on various aspects of virus-cell interaction [1] direct measurements of the kinetics of virion reproduction inside single cells are still absent. For this reason, we do not try to compare our predictions with experiment.

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