Multiscale modelling of viral infection of cells and of interferon resistance

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1. Biological background

For a eukaryotic virus to successfully infect and propagate in cultured cells several events must occur: The virion must identify and bind its cellular receptor, become internalised, uncoat, synthesize viral proteins, replicate its genome, assemble progeny virions, and exit the host cell. The virions bud off from the cell, gaining an envelope from the cell membrane as they exit. The new viral particle infects another cell to repeat the cycle. Usually, during the repeated process of self-replication, the virus destroys host's cells.

While these events are taking place, intrinsic host defenses activate in order to defeat the virus. The first-line defense against viruses is based on innate immunity. This includes, among others, activation of the interferon system, induction of apoptosis, and attempted elicitation of immune responses via chemokine and cytokine production. Interferons are a family of active biochemical species, which help to fight viral infections by spreading from infected to uninfected cells and triggering production of effector molecules. The interferons interact with receptors located on the membrane of uninfected cells, which leads to the activation of the reactions cascade in the uninfected cells and production of some proteins. These latter when activated confer on cells resistance from the virus (Rose et al. 2001).

To get a better insight into the dynamics of the processes described above we developed a mathematical model of dynamics of viral infection in vitro, including infection, cell death, production of interferon and development of resistance. The dynamics of the model can be understood as a combat between the invading virus particles and the ability of the immune system to react to the invasion by producing substances conferring resistance to virus. We concentrate on the case, in which the supply of unexposed cells ceases at the moment of infection. This corresponds to conditions prevalent in cell culture experiments.

The model is motivated by experiments involving vesicular stomatitis virus, (Lam et al. 2005; Rose et al. 2001), and respiratory syncytial virus (Rose et al. 2001) including unpublished experimental results performed in Dr. Allan Brasier's laboratory of the University of Texas Medical Branch in Galvestone.

2. Mathematical models

We consider a model for the dynamics of viral infection, which involves wild-type, i.e., unexposed to virus (W), infected (I) and resistant (R) cells, as well as particles of virus (v) outside cells, and molecules of interferon (i), the substance released by infected cells, which boosts the resistance of wild-type cells. The model consists of five ordinary differential equations for variables W, I, R, i and v, each being a function of time,

$$\begin{aligned} W' &= -\alpha_1 v W - \alpha_2 i W, \\ I' &= -\mu_I I + \alpha_1 v W, \\ R' &= \alpha_2 i W, \\ i' &= -\mu_i i + \alpha_i I - \alpha_3 i W, \\ v' &= -\mu_v v + \alpha_v I - \alpha_4 v W, \end{aligned}$$

with initial conditions

$$(W, I, R, i, v)(0) = (W_0, I_0, R_0, i_0, v_0),$$

To understand influence of the intracellular replication process on the observable spread of infection, we differentiate among the intracellular stages of infection for infected cells using an additional variable describing the age of infection. Infected cells of different age produce interferon at different rates and release virions at different rates. Mathematically, this variant requires an additional transport-type partial differential equation to model the infection-age structure in infected cells,

$$\begin{aligned} \frac{\partial I(t,a)}{\partial t} + \frac{\partial I(t,a)}{\partial a} &= -\mu_I(a) I(t,a), \quad a > 0 \\ I(t,0) &= v(t) W(t), \quad t \geq 0 \end{aligned}$$

However, the transport process can be reduced to distributed delay terms in two of the model equations. Therefore, the model with structure can be analysed using local linearised stability results for the functional (delay) type differential equation system (Diekmann et al. 1995).

3. Results

The methods we used to analyse our models involve both global and local methods. As it happens, a conservation law can be derived for the model without structure, application of which guarantees that the solutions of the model converge to limit values as $t \to \infty$. The same conservation law allows to conclude that unexpectedly, in the case with virus mortality, there is always a residual population of wild-type cells. When the virus mortality rate is equal to zero, this is not necessarily the case.

The conservation law can be extended to the structured case, under some additional hypotheses concerning supports of age-dependent mortality and infectivities. This law is mathematically interesting, since it is not a complete law as frequently used in the epidemics theory, however together with nonnegativity, it provides upper bounds, which sufficiently constrain the solutions.

Let us notice that the system, both in the unstructured and structured versions, is somewhat unusual in that it does not have unique equilibrium points. The limits to which the system is converging strongly depend on initial conditions. This property has an impact on the linearised stability. Attracting properties are limited to the subspace spanned by eigenvectors corresponding to nonzero eigenvalues, while the solution slides along the complementary subspace. In the case of the structured model, considerations of linearised stability can be done using a extension of the Mikhailov criterion.

Conditions of stability, which we obtained, seem to have interesting biological interpretations. First of all, the structure can have a stabilising (respectively, destabilising) effect even if the expected lifetime virus production of an infected cell is higher (respectively, lower) in the structured model than in the unstructured model. Also, delaying and shortening the time of new virus synthesis lead to a stabilising effect of structure. These results illustrate the importance of the dynamics of the process of virus proliferation and death of the infected cells. In the ODE system, duration of these processes can be understood as being described by exponentially distributed random variables. Our results indicate that this is not always sufficient and illustrate the need to understand these processes.

One of the important elements of the model is the presence of a mechanism of interferon-induced virus resistance. Interferon can be produced only by infected cells and confers resistance (in our model a complete resistance) on wild-type cells. It is interesting that setting the interferon production rate to zero does not qualitatively change the behaviour of the system. However, it reduces the total number of wild-type and resistant cells.

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