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ORDER REDUCTION FOR AN RNA VIRUS EVOLUTION MODEL

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ABSTRACT. A mathematical or computational model in evolutionary biology should necessary combine several comparatively fast processes, which actually drive natural selection and evolution, with a very slow process of evolution. As a result, several very different time scales are simultaneously present in the model; this makes its analytical study an extremely difficult task. However, the significant difference of the time scales implies the existence of a possibility of the model order reduction through a process of time separation. In this paper we conduct the procedure of model order reduction for a reasonably simple model of RNA virus evolution reducing the original system of three integro-partial derivative equations to a single equation. Computations confirm that there is a good fit between the results for the original and reduced models.

1. INTRODUCTION

Due to very high mutation and replication rates combined with high recombination abilities, RNA viruses are able to evolve very fast. This high evolvability presents a serious problem, as viral evolution is probably the most important single factor responsible for the emergence of new pathogens and development of drug resistance by existing. In the same time, this evolvability also makes RNA viruses a convenient experimental model in evolutionary biology. However, mathematical or computational modelling of evolution remains a challenging task even for such a simple object as RNA virus. This difficulty is due to a complex interaction of a range of factors, which drive a natural selection and evolution, and hence must be taken into consideration.

A relatively simple mathematical model of RNA virus evolution was suggested by Korobeinikov and Dempsey [5]. This mechanistic model is an extension of Nowak-May HIV model [6], where viral phenotypes (strains) are assumed to be distributed in a continuous phenotype space, and random mutations are described by dispersion. (For the sake of simplicity, Korobeinikov and Dempsey formulated the model on a basis of the 2-dimensional Wodarz-Christensen-Thomsen model, or Wodarz model [10]; the latter is a reduction of the original 3-dimensional

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Nowak-May model under an assumption that the population of free virus particles is proportional to the infected cells population; this allows to reduce the equation which describes the dynamics of free virus particles.) This model exhibits formation of a pulse travelling wave of evolution, which moves in the phenotype space towards an increasing Darwinian fitness. The model also shows that the speed of evolution depends on (i) the current (average) fitness and (ii) abundance of the resource (which in this case is the uninfected target cells). As a result of a combination of these two factors, the model exhibits the dynamics which closely resembles the dynamics of HIV infection, with a prolonged relatively stable period (which resembles an asymptomatic stage of HIV) ending with an abrupt explosion of the viral load (which resembles the development of AIDS at the end of the asymptomatic stage). However, an analytical study of even this comparatively simple model still is a challenging task. A further development of the model, for instance an addition of factors, such as immune response or a therapy, would make its analysis even more difficult.

As we mentioned above, to a large extent the complexity, which makes the model analysis difficult, arises as a result of the presence of multiple processes progressing at very different time scales. Thus, the original Nowak-May model combines three processes and three time scales, namely (i) the proliferation of the uninfected target cells, (ii) the infectious process and infected cells' life cycle, and, finally, (iii) free virus life cycle. In the Wodarz model, which was used as a basis for model in [5], one of these processes, namely the free virus life cycle, is omitted and replaced by the assumption that the free virus population is proportional to the infected cells population; this makes the model slightly simpler. However, model in [5] includes evolution, which occurs on a comparatively slow timescale, and hence the model is a slow-fast system.

Considerable differences in the timescales indicates that the model can be significantly simplified using the process of time scales separation (for instance, see [1, 7]). In this paper we carry out such a scale separation; as a result of this process, in this case the model RNA virus evolution is reduced to a single equation. Simulations demonstrate that, apart from a comparatively short transition period, there is a good fit of results for both, the full and the reduced models.

2. MODEL

As a basis for modelling, we employ the Nowak-May model of HIV dynamics [6]. This model describes interactions of three populations, namely uninfected target cells (for HIV, the target cells are T helper cells, or Th cells), infected target cells, and free virus particles, of concentrations $u(t)$, $V(t)$ and $X(t)$, respectively, and postulates that there is a continuous influx of the target cells (from the thymus, where they mature) at a rate b , that free virus particles infect target cells at a rate αXu , that the infected cells produce free virus particles at a per capita rate k , and that average life spans of the uninfected cells, infected cells and the free

virus particles are $1/q$, $1/m$ and $1/c$, respectively. Under these assumptions, the model equations are

$$(1) \quad \begin{aligned} \frac{du(t)}{dt} &= b - \alpha X(t)u(t) - qu(t), \\ \frac{dV(t, s)}{dt} &= \alpha X(t)u(t) - mV(t, s), \\ \frac{dX(t, s)}{dt} &= kV(t, s) - cX(t, s). \end{aligned}$$

The global qualitative behaviour of this model is completely determined by the basic reproduction number of the virus (or that of infected cells, as for this model these numbers coincide) $R_0 = b\alpha k/qmc$ [2, 3, 4, 9]). Specifically, if $R_0 \leq 1$, then infection-free equilibrium state Q_0 , where $u_0 = b/q$, $V_0 = X_0 = 0$, is the only equilibrium state of the model, and is globally asymptotically stable (that is, for all non-negative initial conditions, the system eventually converge to this equilibrium state). If $R_0 > 1$, then, apart from equilibrium state Q_0 , the model has a positive (endemic) globally stable equilibrium state Q^* , where $u^* = \frac{b}{q} \frac{1}{R_0}$, $V^* = \frac{c\alpha}{k\alpha}(R_0 - 1)$, $X^* = \frac{q}{\alpha}(R_0 - 1)$; point Q_0 is a saddle point in this case.

We assume now that a viral quasispecies is defined in a continuous phenotype space. For model (1), the basic reproduction number R_0 usually serves as a measure of the Darwinian fitness of the virus. Therefore, it suffices to consider a 1-dimensional phenotype space $M = \{s \in (0, \infty)\}$, where the fitness R_0 is assumed to be a function of variable s (the graph of this function is usually referred to as a “fitness landscape”). Then variables $v(t, s)$ and $x(t, s)$ are density distributions of the infected cells population and the virus in the phenotype space, and the total infected cells population and the total viral load are $V(t) = \int_0^\infty v(t, s)ds$ and $X(t) = \int_0^\infty x(t, s)ds$, respectively. New strains emerge as a result of random mutations, which in a continuous phenotype space can be modeled by dispersion.

In the Nowak-May model, coefficients α, m, k and c are attributed to a phenotype, and hence these are function of s . We assume that $\alpha = \alpha^0\alpha(s)$, $m = m^0m(s)$, $k = k^0k(s)$ and $c = c^0c(s)$, where α^0, m^0, k^0 and c^0 are coefficients of a wild strain (or a phenotype at the begin of evolution), and non-dimensional functions $\alpha(s), m(s), k(s)$ and $c(s)$ such that $\alpha(s), m(s), k(s), c(s) = 1$ hold for this wild phenotype. These assumptions lead to the following system of equations:

$$(2) \quad \begin{aligned} \frac{du(t)}{dt} &= b - u(t) \int_0^\infty \alpha(s) x(t, s) ds - qu(t), \\ \frac{\partial v(t, s)}{\partial t} &= -m(s)v(t, s) + \alpha(s)u(t)x(t, s) + \mu \frac{\partial^2 v(t, s)}{\partial s^2}, \\ \frac{\partial x(t, s)}{\partial t} &= k(s)v(t, s) - c(s)x(t, s). \end{aligned}$$

Note that coefficients b and q are characteristics of target cells, and hence these remain constant.

This system of equations should be complemented by initial and boundary conditions. At $s = +\infty$, the natural boundary conditions for $v(t, s)$ and $x(t, s)$ are zeros. At $s = 0$, for convenience we use no-flux conditions $\frac{\partial v(t, 0)}{\partial s} = \frac{\partial x(t, 0)}{\partial s} = 0$. Initial conditions are $u(0) = u^0, v(0, s) = v^0(s), x(0, s) = x^0(s)$, where $u^0, v^0(s), x^0(s) > 0$. Here, time t is measured in days and variable s is non-dimensional. Furthermore, $u(t)$ is measured in cells \cdot mm $^{-3}$; $v(t, s)$ and $x(t, s)$ are the densities of cells and free virus particles in the phenotype space, and hence these are measured in cells \cdot mm $^{-3}$ and virions \cdot mm $^{-3}$; cell production rate b is measured in cells \cdot mm $^{-3}\cdot$ day $^{-1}$; per capita mortality rates q, m and c are measured in day $^{-1}$, infectivity α is in mm $^3\cdot$ virions $^{-1}\cdot$ day $^{-1}$, and dispersion coefficient μ is in day $^{-1}$.

A model of such type (based on the 2-dimensional Wodarz model, which is, in turn a reduction of the 3-dimensional Nowak-May model) was introduced in [5], and simulations with this model revealed a number of practically relevant outcomes. In particular, the model demonstrates the behaviour which closely recall the observed development of HIV infection. However, an apparent drawback of this model is that even in its present form its analytical study is a challenging task. A further development of the model, which could involve an incorporation of factors such as immune response and a therapy, would make the model more complicated and its analysis even more difficult. The complexity of this model is a result of an interaction of multiple processes with very different time scales. Thus, the original Nowak-May model (1) combines three processes and three time scales, namely (i) the proliferation of uninfected target cells, (ii) the process of infection and infected cells' life cycle, and, finally, (iii) the free virus particles life cycle. Compared with the Nowak-May model, model (2) includes the process of evolution, which, in comparison, is a very slow process, and hence model (2) is a slow-fast system. The presence of four considerably different timescales indicates that model (2) can be significantly simplified, if we separate the timescales.

3. SYSTEM SIZE REDUCTION

Let denote $t = T\bar{t}, s = S\bar{s}$ and

$$u(T\bar{t}) = U\bar{u}(\bar{t}), \quad v(T\bar{t}, S\bar{s}) = \tilde{V}\bar{v}(\bar{t}, \bar{s}), \quad x(T\bar{t}, S\bar{s}) = \tilde{X}\bar{x}(\bar{t}, \bar{s}),$$

and assume that

$$T = \frac{1}{\mu}, \quad S = 1, \quad U = b/q, \quad \tilde{X} = \frac{k^0}{c^0}\tilde{V}, \quad \tilde{V} = 1 \text{ (cells/s)}.$$

Substituting these into system (2), we obtain a non-dimensional system

$$(3) \quad \varepsilon \frac{d\bar{u}}{d\bar{t}} = 1 - \int_0^\infty \frac{1}{q} \alpha(\bar{s}) \frac{k^0}{c^0} \bar{u} \bar{x} d\bar{s} - \bar{u},$$

$$(4) \quad \frac{\partial \bar{v}}{\partial \bar{t}} = \alpha(\bar{s}) \frac{bk^0}{\mu qc^0} \bar{u} \bar{x} - \frac{m(\bar{s})}{\mu} \bar{v} + \frac{\partial^2 \bar{v}}{\partial \bar{s}^2},$$

$$(5) \quad \varepsilon \nu \frac{\partial \bar{x}}{\partial \bar{t}} = \bar{k}(\bar{s}) \bar{v} - \bar{c}(\bar{s}) \bar{x},$$

where $\varepsilon = \mu/q$ and $\nu = q/c^0$. Initial and boundary conditions for this system are, respectively,

$$\bar{u}(0) = \frac{q}{b} u(0), \quad \bar{v}(0, \bar{s}) = \frac{1}{\bar{V}} v(0, s), \quad \bar{x}(0, \bar{s}) = \frac{1}{\bar{X}} x(0, s).$$

and

$$\frac{\partial \bar{v}(\bar{t}, 0)}{\partial \bar{s}} = 0, \quad \lim_{\bar{s} \rightarrow \infty} \bar{v}(\bar{t}, \bar{s}) = 0.$$

Both numbers, $\varepsilon = \mu/q$ and $\nu = q/c^0$, are small parameters; for instance, for parameters which were used in [5] and which correspond to a real life HIV case from [8], $\nu \approx 2 \cdot 10^{-3}$ and ε ranges from $5 \cdot 10^{-5}$ to $5 \cdot 10^{-3}$. That is, system (3)–(5) is a singularly perturbed (“slow-fast”) system, and its size can be reduced using the scale separation technique [1]. This procedure corresponds to assumptions that (i) there is a stable slow manifold such that all solution converge to this manifold, and hence (ii) the values of fast variables $u(t)$ and $x(t, s)$ converge to quasi-equilibrium values which slowly vary as the system progresses along the slow manifold [7].

Let $\nu = 0$; then equality

$$\bar{k}(\bar{s}) \bar{v} = \bar{c}(\bar{s}) \bar{x}$$

holds. Substituting this equality into (3) and (4), we obtain equations

$$(6) \quad \varepsilon \frac{d\bar{u}}{d\bar{t}} = 1 - \int_0^\infty \frac{1}{q} \beta(\bar{s}) \bar{u} \bar{v} d\bar{s} - \bar{u},$$

$$(7) \quad \frac{\partial \bar{v}}{\partial \bar{t}} = \frac{b}{\mu q} \beta(\bar{s}) \bar{u} \bar{v} - \frac{m(\bar{s})}{\mu} \bar{v} + \frac{\partial^2 \bar{v}}{\partial \bar{s}^2},$$

where $\beta(\bar{s}) = \frac{\alpha(\bar{s})k(\bar{s})}{c(\bar{s})}$. System (6), (7) was suggested in [5].

Now let $\varepsilon = 0$; then

$$\bar{u} = \frac{1}{1 + \int_0^\infty \frac{1}{q} \beta(\bar{s}) \bar{v} d\bar{s}} = \frac{1}{1 + \bar{\lambda}(t)},$$

where

$$\bar{\lambda}(t) = \int_0^\infty \frac{1}{q} \beta(\bar{s}) \bar{v} d\bar{s}$$

is the non-dimensional infection force. (Please recall that the dimensional infection force is usually defined as $\lambda(t) = \int_0^\infty \beta(s)v(t, s)ds$.) Substituting this equality into (7), we finally obtain a single equation

$$(8) \quad \frac{\partial \bar{v}}{\partial \bar{t}} = \bar{m}(\bar{s}) \left(\frac{R_0(\bar{s})}{1 + \bar{\lambda}} - 1 \right) \bar{v} + \frac{\partial^2 \bar{v}}{\partial \bar{s}^2},$$

where

$$R_0(\bar{s}) = \frac{b\alpha(\bar{s})k(\bar{s})}{qm(\bar{s})c(\bar{s})}, \quad \bar{m}(\bar{s}) = \frac{m(\bar{s})}{\mu}.$$

When $\lambda(t) \ll q$, that is when the reduction of the uninfected population due to infection is small, equation (8) can be further simplified: in this case we can employ the Taylor expansion and use the approximate equality

$$\frac{1}{1 + \bar{\lambda}(t)} \approx 1 - \bar{\lambda}(t).$$

Then

$$\frac{\partial \bar{v}}{\partial t} = \bar{m}(\bar{s}) [R_0(s)(1 - \bar{\lambda}) - 1] \bar{v} + \frac{\partial^2 \bar{v}}{\partial \bar{s}^2}.$$

4. NUMERICAL SIMULATIONS

Following [5], and for the sake of simplicity, we assume that the diversity of viral phenotypes is described by a single parameter $\alpha(s)$, which can be interpreted as the efficiency of a single virus particle in infecting a target cell; the other parameters are assumed to be constant and the same for all genotypes. To some extent this assumption is justified by the fact that for the Nowak-May model genotype's fitness is defined by a single number $R_0 = \frac{bak}{qmc}$. Under this hypothesis, and taking into consideration that R_0 is a function of all six parameters, it should make no difference which of these six parameters is varying in the phenotype space. The choice of $\alpha(s)$ is just a matter of convenience, because the direct dependence of R_0 on α simplifies the notation.

Results of numerical analysis are presented at the following Figures. (For convenience of comparison, results in these Figures are shown for physical dimensional variables.) For these simulations, we use following values for the system parameters: $b = 20 \text{ cells}\cdot\text{mm}^{-3}\cdot\text{day}^{-1}$, $m = 0.8 \text{ day}^{-1}$, $q = 0.02 \text{ day}^{-1}$, $k = 10^4 \text{ day}^{-1}$ and $c = 8 \text{ day}^{-1}$. These parameters correspond to patient 2 in [8]. For simplicity we assume a linear landscape, postulating that $\alpha(s) = as$. Here, $a = 8 \cdot 10^{-7} \text{ mm}^3\cdot\text{cells}^{-1}\cdot\text{day}^{-1}$; this implies that $R_0 = 1.25s$. All simulations are for $\mu = 10^{-6} \text{ day}^{-1}$.

Simulations demonstrate an excellent fit of results obtained for system (6), (7) and equation (8). Figure 1 shows, that results for these two systems perfectly coincide everywhere apart from a comparatively short transition period. (We have to remind that equation (8) is unable to describe the transition dynamics at all.) If the initial conditions are taken on or near the slow manifold, then the results for these two systems coincide everywhere (see Fig. 2). However, a match of results for systems (3)–(5) and (6), (7) (and hence for equation (8)) is only qualitative; Fig. 3 demonstrates that system (3)–(5) exhibits a slower evolution, producing outcomes which are delayed in time, compared with these for system (6), (7), or equation (8). We conject that this effect is caused by a continuous

accumulation of a small delay, caused by the third equation of the Nowak-May model (2), over a long period of evolution.

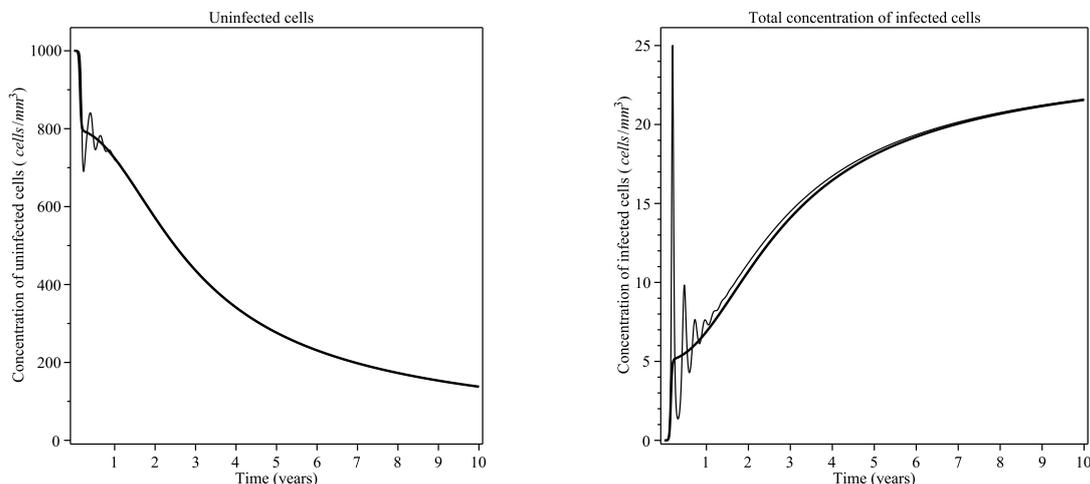


FIGURE 1. Uninfected cells concentration $u(t)$ and total infected cells concentration $V(t)$ for system (6), (7) (thin line) and equation (8) (bold line).

5. CONCLUSION

Due to the fact that a mathematical model in evolutionary biology should necessary combine the factors, which characterize natural selection and drive evolution, and which acts on a comparatively fast time scale, and a very slow process of evolution itself, such a model is complex and its analysis is difficult. However, a combination of several time scales within a model suggests that such a model can be significantly simplified using the scale separation techniques. For ODE, such technique is based on the famous Tikhonov's theorem. The mathematical models in evolutionary biology are usually integro-differential equations and PDE; however the same concepts can be applied to these as well.

In this paper, we execute the scale separation for a RNA virus evolution model, which is based on the 3-dim Nowak-May model. As a result of this procedure, the original system of three integro-partial differential equations is reduced to a single integro-partial differential equation, describing the dynamics of infected target cells $v(t, s)$. The other variables, namely the uninfected cells $u(t)$ and free virus particles $x(t, s)$, are expressed as explicit functions of variable $v(t, s)$. Numerical simulation show an acceptable fit of the solution of the original and the reduced models.

A specific feature of this particular model, which is based on the Nowak-May model specifically tailored to describe the HIV dynamics, is that target cells are assumed to be immigration from the thymus at a constant rate. However, the

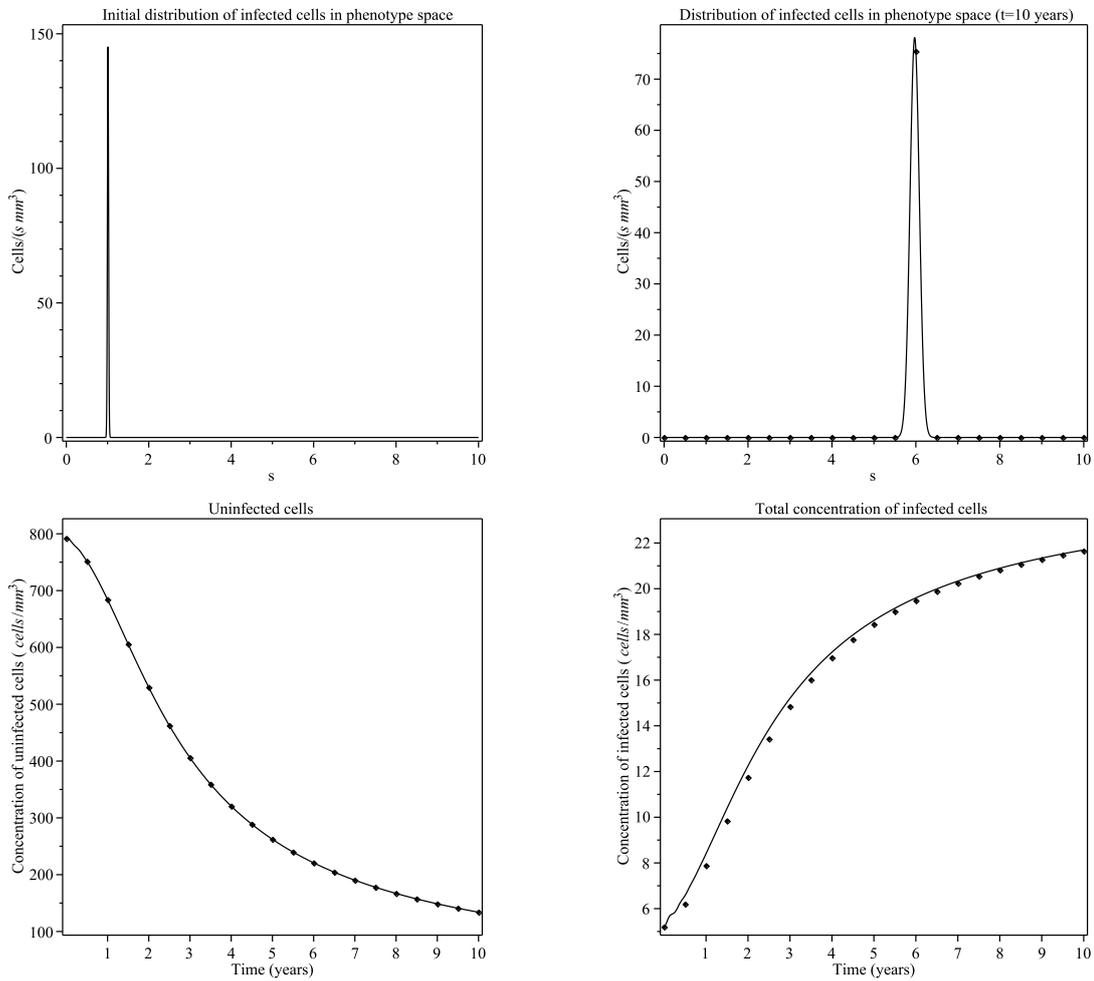


FIGURE 2. Solutions of system (6), (7) (thin line) and equation (8) (markers), when initial condition is taken on the slow manifold.

same concept and the same techniques can be applied to a model of evolution based on any other model of virus dynamics.

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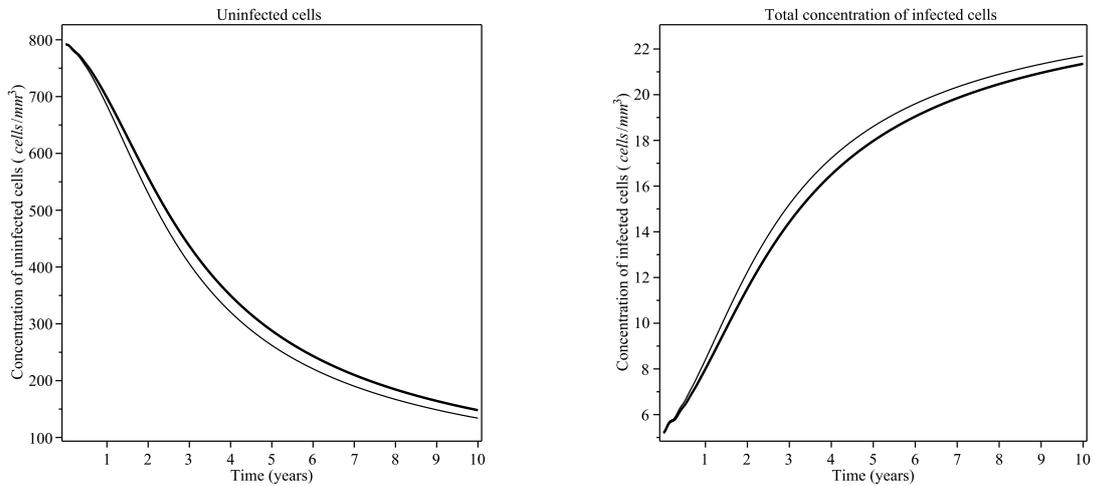


FIGURE 3. Uninfected cells concentration $u(t)$ and total infected cells concentration $V(t)$ for system (3)–(5) (bold line) and (6), (7) (thin line).

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