CRM^R

CENTRE DE RECERCA MATEMÀTICA

Order reduction for a model of marine bacteriophage evolution

S. Pagliarini, A. Korobeinikov

ORDER REDUCTION FOR A MODEL OF MARINE BACTERIOPHAGE EVOLUTION

SILVIA PAGLIARINI AND ANDREI KOROBEINIKOV

ABSTRACT. A typical mechanistic model of viral evolution necessary includes several time scales which can differ by orders of magnitude. Such a diversity of time scales makes analysis of these models difficult. Reducing the order of a model is highly desirable when handling such a model. A typical approach applied to such slow-fast (or singularly perturbed) systems is the time scales separation technique. Constructing the so-called quasi-steady-state approximation is the usual first step in applying the technique. While this technique is commonly applied, in some cases its straightforward application can lead to unsatisfactory results.

In this paper we construct the quasi-steady-state approximation for a model of evolution of marine bacteriophages based on the Beretta-Kuang model. We show that for this particular model the quasi-steady-state approximation is able to produce only qualitative but not quantitative fit.

1. INTRODUCTION

Mathematical modelling of biological evolution is a challenging task that modern mathematical science has to address. Due to their comparative simplicity, viruses can serve as an excellent model in evolutionary biology and the most convenient object for such modelling. However, constructing a mechanistic (that is, based on first principles) model and dealing with a typical mechanistic model in evolutionary biology can be a highly non-trivial task. The reason for this is that any mechanistic mathematical model of biological evolution, including models of viral evolution, must comprise a number of factors, including replication of all species involved, random mutations and a mechanism of natural selection. The time scales, on which these factors act, can vary in orders of magnitude. Thus, a mechanistic model of viral evolution can include the dynamics of uninfected and infected target cells, as well as dynamics of virus. An average time scale of the uninfected target cells can be of order of days, whereas the life-span of free virus is of order of hours. These scales have to be compared with evolution, which typically is an extremely slow process. It is this diversity of time scales that makes analytical and numerical study of these systems difficult. That is, a typical mechanistic (that is, based on the first principles) model of biological evolution is unavoidably a slow-fast, or singularly perturbed, system.

1

Reduction of the order is highly desirable for this kind of models. A typical technique of order reduction is the so-called time scales separation technique. However, straightforward application of this technique, and in particularly constructing the so-called quasi-steady-state approximation, can lead to disappointing results.

In this paper we apply this technique to a model of marine bacteriophage evolution and construct a quasi-steady-state approximation of this model. Results of simulation show, that for this particular model the quasi-steady-state approximation does not provide a sufficiently accurate approximation, and terms of higher order are necessary.

2. MODEL OF BACTERIOPHAGE EVOLUTION

We consider the following model of bacteriophage evolution, which is introduced in [5]:

$$
\frac{dS(t)}{dt} = \alpha S(t) \left(1 - \frac{1}{C} \left(S(t) + \int_\Omega I(r,t)dr \right) \right) - \int_\Omega k(r)P(r,t)S(t)dr,
$$

(1)
$$
\frac{\partial I(r,t)}{\partial t} = k(r)P(r,t)S(t) - \lambda(r)I(r,t) + q\Delta I(r,t),
$$

$$
\frac{\partial P(r,t)}{\partial t} = -k(r)P(r,t)S(t) - \mu(r)P(r,t) + b(r)\lambda(r)I(r,t).
$$

This model is based upon the Beretta-Kuang model of marine bacteriophage dynamics [1] and describes interaction of three populations, namely susceptible target bacteria, infected target bacteria and free bacteriophages. The Beretta-Kuang model postulates that the target bacteria reproduce according to the logistic law with reproduction rate α and carrying capacity of the environment C. The susceptible bacteria are infected by the phages in free infective stage at a bilinear rate with coefficient k. Immediately after an instance of infection, the infected bacterium moves into infected bacteria compartment. An average duration of the infective stage is $1/\lambda$, and then the infected bacterium dies. At the moment of death the bacterium released on average b free bacteriophages.

In contrast to the original Beretta-Kuang model where populations in all three compartments are postulated identical, model (1) assume the existence of multiple variants of the bacteriophage and postulate that these are continuously distributed in a continuous variant (phenotype) space Ω. Each of these variants is characterized by its phenotype. In the Beretta-Kuang model, a phage is characterized by four parameters, namely an average number of virions produced by an infected bacterium, b, an average life span of an infected bacterium, $1/\lambda$, an average free phage life span, $1/\mu$, and per capita rate of infection, k. Each of the viral variants in model (1) is characterized by

a corresponding set of parameters k, λ, μ and b as well. In a model of phage evolution, any of these parameters can be variant-dependent, and, hence, the continuous variant space Ω is of dimension up to 4. (Please note that carrying capacity of the environment C and target bacteria per capita reproduction rate α do not depend on viral type, and, therefore, are constant.)

The model is comprises three variables: the susceptible bacterial population $S(t)$ (which is phenotype independent), density distribution in the variant space Ω of free phage population $P(r, t)$, and density distribution of infected bacteria $I(r, t)$ according to viral variants they are infected with. Random mutations in the continuous variant space are modelled by dispersion operator $q\Delta I \equiv q\frac{\partial^2 I}{\partial r^2}$, where coefficient q is assumed to be proportional to a probability of mutation, and is constant and small.

For the sake of simplicity, we assume that the only parameter depending on a phenotype is $k = k(r)$, whereas λ, μ and b are variant-independent (and hence are constant). This allows to reduce dimension of the variant space to 1-dim. For convenience, we assume the variant space Ω is the positive semi-axis of a 1-dimensional real space, $\Omega = \mathbb{R}^1_+ = (0, +\infty)$, and $r \in \Omega$ is the coordinate in this space.

3. Model order reduction

An intrinsic property of model (1), which motivates this study is that the model includes at least four different time scales, namely (i) life-span of the susceptible bacteria, (ii) life-span of the infected bacteria, (iii) life-span of the free phages, and, finally, (iv) a characteristic time scale of evolution. These time scales may differ by orders of magnitude: for instance, an average time for division of the susceptible cells is of order of a day, whereas the life-span of free virus is of order of hours. Such a diversity of time scales makes analytical and numerical study of this system difficult. For such a model, reducing its order is highly desirable. The reduction can be done using a time scales separation technique, which allows to reduce the considered system of three equations to one or two equations. In this section we construct a quasi-steady-state approximation of the system, applying the technique developed in [2,4] for a similar model of RNA virus evolution and the original Beretta-Kuang model.

Let us denote $t = T\bar{t}$ and $r = R\bar{r}$, where T and R are constant scales that have to be defined, whereas $\bar{t}$ and $\bar{r}$ are non-dimensional variables. Furthermore, we denote $S(T\bar{t}) = \tilde{S}\bar{S}(\bar{t})$, $I(T\bar{t}, R\bar{r}) = \tilde{I}\bar{I}(\bar{t}, \bar{r})$ and $P(T\bar{t}, R\bar{r}) = \tilde{P}\bar{P}(\bar{t}, \bar{r})$, where $\tilde{S}$, $\tilde{I}$ and $\tilde{P}$ are also constant scales, while $\bar{S}(\bar{t})$, $\bar{I}(\bar{t}, \bar{r})$ and $\bar{P}(\bar{t}, \bar{r})$ are non-dimensional variables. Let us assume that

$$T = 1/q, \qquad R = 1, \qquad \tilde{S} = C, \qquad \tilde{P} = b\lambda\tilde{I}/\mu, \qquad \tilde{I} = C.$$

Substituting these variables into the system (1), we obtain non-dimensional system

$$\epsilon \frac{d\bar{S}(\bar{t})}{d\bar{t}} = \bar{S}(\bar{t})\left(1 - \bar{S}(\bar{t}) - \int_\Omega \bar{I}(\bar{t},\bar{r})d\bar{r}\right) - \frac{b\lambda C}{\mu\alpha}\bar{S}(\bar{t})\int_\Omega \bar{P}(\bar{t},\bar{r})k(\bar{r})d\bar{r},$$

$$(2) \qquad \frac{\partial \bar{I}(\bar{t},\bar{r})}{\partial \bar{t}} = \frac{b\lambda C}{\mu q}k(\bar{r})\bar{P}(\bar{t},\bar{r})\bar{S}(\bar{t}) - \frac{\lambda}{q}\bar{I}(\bar{t},\bar{r}) + \Delta\bar{I}(\bar{t},\bar{r}),$$

$$\epsilon \nu \frac{\partial \bar{P}(\bar{t},\bar{r})}{\partial \bar{t}} = -\frac{C}{\mu}k(\bar{r})\bar{P}(\bar{t},\bar{r})\bar{S}(\bar{t}) - \bar{P}(\bar{t},\bar{r}) + \bar{I}(\bar{t},\bar{r}).$$

Here $\epsilon = q/\alpha$ and $\nu = \alpha/\mu$ are small parameters. Indeed, ϵ is directly proportional to mutation rate q, which is assumed to be small, whereas ν is ratio of the characteristic time-scales of the free phages and the target bacteria. If ϵ and ν are small, the scale separation technique can be applied to this system.

To obtain a quasi-steady-state approximation of this system, we put $\nu = 0$ (see [2,4]). This yields the following reduced model:

$$\epsilon \frac{d\bar{S}(\bar{t})}{d\bar{t}} = \bar{S}(\bar{t})\left(1 - \bar{S}(\bar{t})\right) - \int_\Omega \left(\bar{S}(\bar{t}) + \frac{b\lambda}{\alpha}\frac{Ck(\bar{r})\bar{S}(\bar{t})}{Ck(\bar{r})\bar{S}(\bar{t}) + \mu}\right)\bar{I}(\bar{t},\bar{r})d\bar{r},$$

$$(3) \qquad \frac{\partial \bar{I}(\bar{t},\bar{r})}{\partial \bar{t}} = \frac{\lambda}{q}\left(b\frac{Ck(\bar{r})\bar{S}(\bar{t})}{Ck(\bar{r})\bar{S}(\bar{t}) + \mu} - 1\right)\bar{I}(\bar{t},\bar{r}) + \Delta\bar{I}(\bar{t},\bar{r}).$$

Here, for simplicity, it is assumed that only one parameter, namely $k = k(r)$, depends on a viral variant, whereas the others parameter are assumed to be constant. Furthermore, here $\bar{r} \in (0, +\infty)$.

4. RESULTS

To explore how well the quasi-steady-state approximation (3) approximates the original model (1), we run simulations for both these models. In these simulations we use the following values for the system parameters: $q = 10^{-6}$ day^{-1}, $\alpha = 1.5$ day^{-1}, $C = 100$ cells, $\lambda = 0.3$ day^{-1}, $\mu = 2$ day^{-1} and $b = 14$. For the sake of simplicity, we assume that $k(r)$ is linearly depending on r, $k(r) = \xi r$, where $\xi = 0.002$ day^{-1}. The value of ξ is chosen in such a way to ensure that the basic reproduction number $R_0 = (b-1)k(r)C/\mu$ is equal to 1 at some r. In simulations we assume that $r \in (0, r_{end})$ and set no-flux boundary conditions for $P(r,t)$ and $I(r,t)$ at $r = 0$ and $r = r_{end}$. For model (1), we set initial conditions $S(0) = C$ and $P(r,0) = 0$, and assume that $I(r,0)$ differs from zero only in a narrow vicinity of $r = 1$. For model (3) we use the corresponding re-scaled initial conditions $\bar{S}(0) = 1$ and $\bar{I}(\bar{r},\bar{0}) = I(r,0)/C$.

Figure 1 shows distributions of the infected bacteria by viral variants which they are infected with in the viral variant space Ω for for model (1) (the left-hand panel) and its quasi-steady-state approximation (3) (the right-hand panel,

respectively). (In Fig. 1, colours corresponds to the density of infected bacteria $I(r, t)$; see legends at the right-hand side of each panel). The formation of a pulse-type travelling wave moving in the right-hand direction in the variant space, that is towards higher Darwinian fitness, is clearly seen for both, the original system and its quasi-steady-state approximation. Please also note that the speed of evolution (the speed of the traveling waves) in Fig. 1 is not constant for either of the systems: it can be seen that evolution goes faster as the Darwinian fitness grows, and then, when some level of the fitness is reached, it abruptly slows down and remans approximately constant thereafter. It is noteworthy that the same effect was observed in [3].
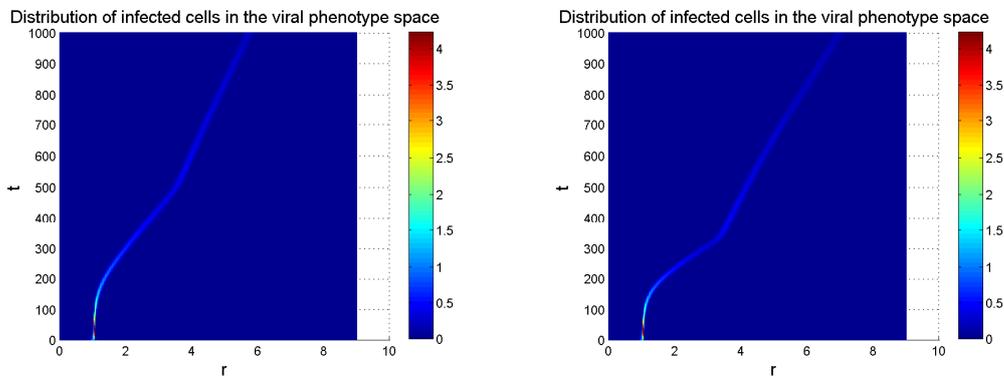

FIGURE 1. Distribution of the infected bacteria by viral type they are infected with in the variant space in time for models (1) (left-hand panel) and (3) (right-hand panel). Here $q = 10^{-6}$, $\alpha = 2$, $C = 100$, $\lambda = 3$ $\mu = 20$, $b = 149.254$, and $\xi = 0.002$. The colours correspond to the density; see the legend on the right-hand sides of both panels. Please note the formation of a pulse-type traveling wave moving in the right-hand direction in the variant space. Please also note that the speed of the waves in both panels is not constant and different for both models.

There is a reasonably good qualitative fit between the data for both models in the sense that the qualitative behaviour of both models is nearly the same. However, the simulations also reviles that the evolution goes faster in the quasi-steady-state approximation than it does in the original model. The disparity in the speed of evolution between the original model and its quasi-steady-state approximation is also seen in Figures 2 and 3. Figure 2 shows distribution of the infected cells by viral variants they are infected with for model (1) (curve #1) and its quasi-steady-state approximation (3) (curve #2) at time $t = 1000$. It can be seen that that the median of distribution (2) is located notably further to the right-hand side than that of distribution (1). This disparity

can be explained only by a faster evolution exhibited by the quasi-steady-state approximation (3) compared with this of the original model (1).

Figure 3 shows the dynamics of the total infected population $\int_\Omega I(r,t)dr$ (left-hand panel) and susceptible population $S(t)$ (right-hand panel) in time. In both these pictures, curves (1) correspond to model (1) and curve (2) corresponds to its quasi-steady-state approximation (3). These pictures also show that, while the qualitative behaviour of both models is very similar, the evolution in the quasi-steady-state approximation progresses faster.
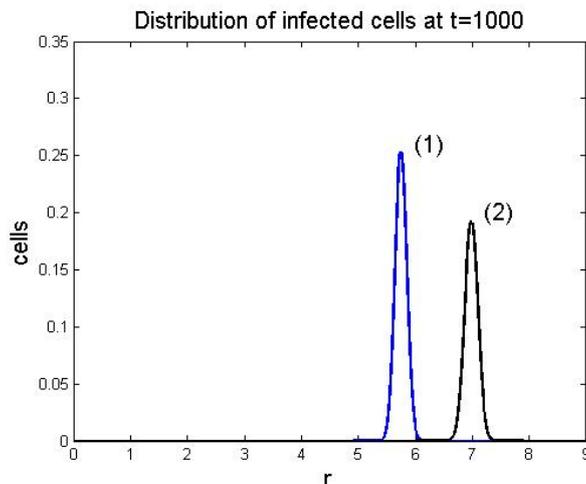

FIGURE 2. Distributions of infected bacteria by the viral variants they are infected with $I(r,t)$ for model (1) (curve #1) and its quasi-steady-state approximation (3) (curve #2) at time $t = 1000$. Please note that the distribution (2) is located further to the right-hand side than distribution (1). This difference reflects the higher speed of evolution that is exhibited by the quasi-steady-state approximation.

An intrinsic property of the Beretta-Kuang model is that, despite the bilinearity of the infection rate, it exhibits a admits a supercritical Hopf bifurcation, with formation of a stable limit cycle in the model phase space [1, 4]. The dynamics of the susceptible population for model (1) and its quasi-steady-state approximation for parameters, which corresponds to the presence of the stable limit cycle in the original model, is shown in Figure 4. Please note the different behaviour of the evolution model and its quasi-steady-state approximation: it is easy to see in these pictures that in both panel curves (2), that correspond to data for the quasi-steady-state approximation, tend to an equilibrium values, whereas curves (1), which correspond to the original model, revile the presence of a stable limit cycle in the system. That is, the Hopf bifurcation occurs
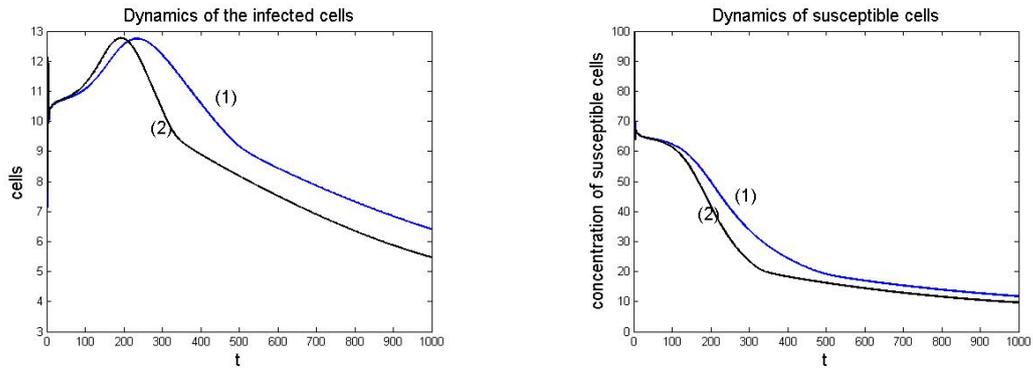
FIGURE 3. Dynamics of the infected ($\int_\Omega I(r,t)dr$) and suscepti-
ble bacteria for model (1) (curves #1) and its quasi-steady-state
approximation (3) (curves #2) in time. Here $q = 10^{-6}$, $\alpha = 2$,
$C = 100$, $\lambda = 3$ $\mu = 20$, $b = 149.254$ and $\xi = 0.002$.

at different parameter values in the original model and in its quasi-steady-state
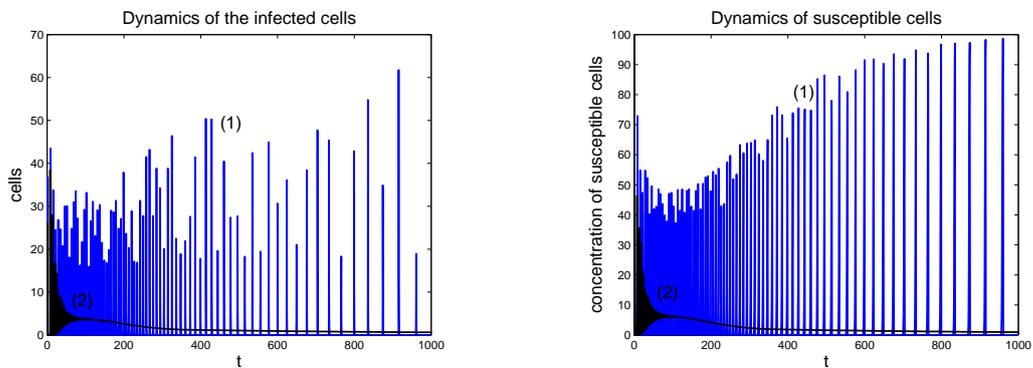approximation. The same observation was reported in [4].

FIGURE 4. Dynamics of the infected ($\int_\Omega I(r,t)dr$) and suscepti-
ble bacteria for model (1) (curves #1) and its quasi-steady-state
approximation (3) (curves #2) in time. Here $q = 10^{-6}$, $\alpha = 2$,
$C = 100$, $\lambda = 3$ $\mu = 20$, $b = 149.254$, and $\xi = 0.02$.

A general conclusion that can be withdrawn from these results is that for
this particular model the quasi-steady-state approximation does not provide
satisfactory quantitative results matching to these for the original model, and
hence terms of higher orders should be taken in account in an reduced model.

5. Conclusions

In this paper we attempted to make a model order reduction for a model of evolution of aquatic bacteriophage, which is based on the Beretta-Kuang model of bacteriophage dynamics. For this we constructed a quasi-steady-state approximation of this model. In many application, constructing such an approximation is sufficient for model order reduction. However, for this particular model, comparison of results for the original model and its quasi-steady-state approximation reviles that the approximation does not produces sufficiently good match to the original model: while qualitative behaviour of both, the model and its approximation, matches, the quantitative outcomes significantly differ. Thus, the approximation produces a notably faster evolution that the original model does. Moreover, Hopf bifurcation appears for different parameter value. The latter observation coincides with observations in [4], where it was shown that a quasi-steady-state approximation of the Beretta-Kuang ODE model, which is the basis for the model of viral evolution considered in this paper, does not preserve totally properties of the Beretta-Kuang model. In general, these results demonstrate that a more accurate approximation, taking into consideration terms of higher order, can be necessary for constructing a reduced model of this particular model. Moreover, these results also show that the widely accepted approach, when the order reduction for a model is limited to construction of a quasi-steady-state approximation, should be applied with significant amount of care and reservations.

References

[1] E. Beretta and Y. Kuang, Modeling and analysis of a marine bacteriophage infection. *Math. Biosci.* **149** (1998), 57–76.

[2] A. Korobeinikov, A. Archibasov, and V. Sobolev, Order reduction for a RNA virus evolution model, *Math. Biosci. Eng.* **12** (2015), 1007–1016.

[3] A. Korobeinikov and C. Dempsey, A continuous phenotype space model od RNA virus evolution within a host. *Math. Biosci. Eng.* **11** (2014), 919–927.

[4] A. Korobeinikov, E. Shchepakina, and V. Sobolev, Paradox of enrichment and system order reduction: bacteriophages dynamics as case study. *Math. Med. Biol.* (2015), (Advance Access pub.) doi:10.1093/imammb/dqv025

[5] S. Pagliarini and A. Korobeinikov, 2016 A mathematical model of marine bacteriophage evolution Math. Biosci. Eng. (submitted) (2016), CRM Preprint.

SILVIA PAGLIARINI
UNIVESTITÀ DEGLI STUDI DI VERONA
VERONA, ITALY
  E-mail address: silvia.pagliarini92gmail.com

ANDREI KOROBEINIKOV
CENTRE DE RECERCA MATEMÁTICA
CAMPUS DE BELLATERRA, EDIFICI C
08193 BELLATERRA, BARCELONA, SPAIN
AND
DEPARTAMENT DE MATEMÀTIQUES
UNIVERSITAT AUTÒNOMA DE BARCELONA
CAMPUS DE BELLATERRA, EDIFICI C
08193 BARCELONA, SPAIN
  E-mail address: akorobeinikov@crm.cat