Journal of Theoretical Biology 345 (2014) 32–42

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Evolutionary comparison between viral lysis rate and latent period

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HIGHLIGHTS

- Delay models representing viral infection and their simplified lysis-rate versions provide similar qualitative ecological results.
- Although they are interchangeably used to describe marine viruses, they show very different evolutionary behaviors.
- Phages with infection cycles represented by the lytic-rate model have ecological and evolutionary advantages over those described by the delay model.
- Evolutionary runaway observed for a standard form of the trade-off between released progeny and infection duration may prevent the rate model from reliably predicting bacteriophage long-term behavior.
- New theoretical frameworks are needed to properly analyze the eco-evolutionary interactions of microbial systems beyond steady environments.

ARTICLE INFO

Article history:
Received 15 August 2013
Received in revised form
2 December 2013
Accepted 3 December 2013
Available online 17 December 2013

Keywords:
Bacteriophage
Phytoplankton
Burst size
Evolutionarily stable strategy
Eco-evolutionary dynamics

ABSTRACT

Marine viruses shape the structure of the microbial community. They are, thus, a key determinant of the most important biogeochemical cycles in the planet. Therefore, a correct description of the ecological and evolutionary behavior of these viruses is essential to make reliable predictions about their role in marine ecosystems. The infection cycle, for example, is indistinctly modeled in two very different ways. In one representation, the process is described including explicitly a fixed delay between infection and offspring release. In the other, the offspring are released at exponentially distributed times according to a fixed release rate. By considering obvious quantitative differences pointed out in the past, the latter description is widely used as a simplification of the former. However, it is still unclear how the dichotomy "delay versus rate description" affects long-term predictions of host–virus interaction models. Here, we study the ecological and evolutionary implications of using one or the other approaches, applied to marine microbes. To this end, we use mathematical and eco-evolutionary computational analysis. We show that the rate model exhibits improved competitive abilities from both ecological and evolutionary perspectives in steady environments. However, rate-based descriptions can fail to describe properly long-term microbe–virus interactions. Moreover, additional information about trade-offs between life-history traits is needed in order to choose the most reliable representation for oceanic bacteriophage dynamics. This result affects deeply most of the marine ecosystem models that include viruses, especially when used to answer evolutionary questions.

1. Introduction

Viruses are the most numerous organisms on Earth. They play diverse roles in the biotic component of practically any ecosystem. Especially remarkable is the case of marine ecosystems. Marine viruses are important sources of mortality at every trophic level. Potential hosts range from whales and commercial fish species to zooplankton, heterotrophic bacteria and microbial autotrophs (Suttle, 2007). Viruses are key components of the microbial loop and, therefore, the biogeochemical cycle of elements such as nitrogen or phosphorus (Fuhrman, 1999). They are responsible for more than 40% of marine bacterial mortality (Fuhrman, 1999), contributing importantly to shaping the community (Suttle, 1994; Winter et al., 2010; Wommack and Colwell, 2000). The relevance of *virioplankton* stems not only from the "predatory" pressure they exert, but also from the subsequent release of organic nutrients (able to supply a considerable amount of the nutrient demand of, e.g. heterotrophic bacterioplankton, Wilhelm and Suttle, 1999); or their contribution to microbial genetic diversity in the ocean through horizontal gene transfer (Wommack and Colwell, 2000; Marston et al., 2012; Abedon, 2009).

The vast majority of these roles are assumed by marine viruses that eventually kill the host cell (Wilcox and Fuhrman, 1994). The standard *lytic infection* can be summarized in the following steps

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http://dx.doi.org/10.1016/j.jtbi.2013.12.006

(Weinbauer, 2004): (i) free viruses diffusing in the medium encounter and attach to cells at a certain *adsorption rate*; (ii) after injecting its nucleic acid into the host cell, the virus takes control of the host synthesis machinery in order to replicate its genetic material (DNA or RNA, depending on the type of virus, Abedon, 2009) and produce the proteins that will form the components of the viral offspring (*eclipse period*); (iii) during the *maturation* stage (or *rise period*), the new *virions* are assembled; (iv) finally, the virus synthesizes the *holin* protein, which perforates the plasma membrane allowing viral endolysins (lysoenzymes) to reach and lyse the cell wall, thereby releasing offspring and cellular organic compounds to the medium.

The *latent period* (steps (ii)–(iv) above), controlled by the so-called *gene t* (or holin gene) (Abedon et al., 2003), is one of the most important viral life-history traits. So are the *burst size* (offspring number, intimately related to the duration of the infection) and the adsorption rate. The latent period is studied intensively in the viral literature not only due to its ecological importance, but also owing to the small pleiotropic effect that its evolutionary change has on other phenotypic traits (Bull, 2006).

On the other hand, the latent period links ecological and evolutionary change, as mutations in this trait influence the demography of the population and the environment influences which latent periods are favored by selection (Abedon et al., 2003; Bull et al., 2006), closing in this way an eco-evolutionary feedback loop (Pelletier et al., 2009). Furthermore, the short generation times and numerous offspring of viruses facilitate rapid evolution (Lennon and Martiny, 2008), and a possible overlap between ecological and evolutionary timescales. All these factors provide evidence for the importance of using a proper description of the ecological interactions between virus and host in order to make reliable evolutionary predictions.

In the theoretical literature for marine viruses, mostly centered on viruses that infect bacteria (*bacteriophages*), host–virus interactions are represented in two different ways. One approach explicitly considers the latent period imposing a fixed delay between the adsorption and the release of the offspring (Levin et al., 1977). In the other approach, new viruses are continuously released at a certain *lytic rate*, with cells that are simultaneously infected bursting at different post-infection times, exponentially distributed (Beretta and Kuang, 1998; Middelboe, 2000). Thus, in the delay model the survival of each and every infected cell is ensured up to an infection age that equals the fixed latent period, whereas survival responds to a probabilistic rule in the rate model. The latter can actually be seen as a simplification of the former that facilitates mathematical and computational analysis of the interactions. Indeed, the ecological outcome of the two approaches seems to be, a priori, qualitatively similar in spite of the obvious difference in the timing of the infection (Weld et al., 2004). While in the delay model progeny shows periods of no release (e.g. initial stages of viral culture experiments), in the rate model viral offspring are liberated at all times. However, little attention has been paid to quantifying thoroughly how these differences affect the long-term predictions by the two kinds of models. Here, we aim to fill this gap.

In this paper, we focus on the eco-evolutionary differences between the two approaches to the description of the lytic infection cycle. This comparison may prove very useful to assess the evolutionary consequences of the simplifying assumptions in these models, and therefore the long-term reliability of a whole group of different models for host–virus dynamics available in the literature. The rate-based approach is used to model not only diverse aspects of host–lytic virus interactions (Weitz et al., 2005), but also other types of viral infection cycles such as lysogeny (Evans et al., 2010) or shedding (Pearson et al., 2011). In the latter, viruses continuously produce and release virions during the entire infection period. Some examples include filamentous phages, and viruses of an enormous importance for humans such as Ebola, SARS, smallpox, varicella-zoster virus, and HIV (Nowak and Bangham, 1996). In some retroviruses such as HIV, both burst and continuous production modes have actually been suggested (Pearson et al., 2011). Thus, this question transcends purely technical matters such as model selection. Indeed, this study can potentially serve to compare the evolutionary strategies of a wide selection of viruses with very different infection cycles.

As a model case, we use bacteriophages, due to their importance for biogeochemical cycles; it also allows us to resort to the extensive modeling bibliography available, in which the two approaches to the infection cycle are used. On the other hand, we consider mutations only in the holin gene, in order to isolate the effects of evolution on the key differentiating trait for the two strategies: the latent period (or, equivalently, lysis rate). Thus, we first present the two models for lytic infection. After briefly comparing them from an ecological perspective, we turn our attention to their evolutionary divergences. Under this framework, we discuss the ecological and evolutionary contrast between the two forms for the life-history *trade-off* between latent period and burst size that have been proposed in the literature. Finally, we comment on the implications of all the above for the descriptions of host–virus interactions in general, and marine bacteriophages in particular. This study will contribute to the reliability of long-term predictions regarding the interaction between a wide variety of viruses and their hosts.

2. Modeling host–virus interactions

2.1. Environment

In order to compare the two approaches to the infection cycle, we first set common idealized environmental conditions by using two-stage chemostats (Husimi et al., 1982).

Two-stage chemostats are basically composed of a continuous culture for bacterial hosts, coupled to a continuous culture of co-existing bacteria and viruses. A flow of nutrients from a fresh medium to the first chemostat facilitates bacterial growth, and a flow of "fresh" hosts from the first chemostat to the second chemostat allows for the development of the viral population. Finally, both virus and bacterial cells are washed out from the second chemostat at a certain rate. The described flows, which can loosely resemble e.g. the continuous passage or migratory events occurring in the mammalian gastrointestinal tract (Abedon, 1989), enable a steady state for the overall system. From the perspective of marine bacteriophages, *quasi*-stationary conditions may be found in stratified waters where cyanobacteria, among the most common targets for virioplankton, dominate.

Such a steady state is very convenient from the mathematical standpoint, as is the continuous source of hosts, which helps alleviate the oscillations that are frequently observed in standard predator–prey models (Husimi et al., 1982) (see below). In addition, the continuous flow of uninfected hosts constitutes a relief for the bacterial population from the evolutionary pressure of the virus and, therefore, prevents bacteria from embarking on an otherwise expected co-evolutionary arms race (Bull et al., 2006; Weitz et al., 2005). This allows us to focus on viral evolution only. Thus, two-stage chemostats provide a controlled environment whose conditions are easily reproducible in the laboratory; they also offer general results that can be adapted to other environments, as discussed below.

Lastly, the environmental parameters are chosen to avoid multiple infections (see Table A1 in Appendix A), preventing in this way any kind of intra-cellular competition among viruses.