

Tradeoffs in bacteriophage life histories

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Viruses are the most abundant biological entities on the planet, yet most classical principles of evolutionary biology and ecology were not developed with viruses in mind. Here, the concept of biological tradeoffs, a fundamental tenet of life history theory, is examined in the context of bacteriophage biology. Specifically, several important parameters of phage life histories—replication, persistence, host range, and adsorption—are evaluated for tradeoffs. Available data indicate that replication rate is strongly negatively correlated with both persistence and host range, suggesting that the well-documented tradeoff in macroorganisms between offspring production and offspring quality also applies to phages. The biological tradeoffs that appear to characterize viruses' life histories have potential importance for viral evolution, ecology, and pathogenesis.

Introduction

Bacteriophages, or viruses that infect bacteria, have been known to science for less than a hundred years and remain at the periphery of our perception of life, but they have proven instrumental to the advancement of biology. Immediately after their discovery (or re-discovery) and promotion by d'Herelle in the late 1910s, the widespread isolation of phages helped to establish that the phenomena observed by Ivanovsky, Beijerinck, and others were attributable not to enzymes or chemical reactions but to biological entities, which we now know to be viruses. Starting roughly 30 y later, many of the pioneers of

molecular genetics, including such luminaries as Delbrück, Hershey, and Watson, studied a handful of phages in great detail in order to elucidate the nature of the gene and usher in the era of molecular biology. Today, we are in the early stages of a second golden age of phage research, one with very different objectives that necessitate a broader view of phage biology. As antibiotic resistance becomes an ever greater threat to public health, phage therapy, or the use of phages to kill bacterial pathogens in medicine, has emerged as an increasingly attractive option to combat drug-resistant bacteria.¹ And as the most numerous biological entities on the planet, with great—if far from fully understood—relevance for global nutrient cycling and gene dispersal, phages and other viruses represent an important and largely unexplored frontier in ecology.²

There are many different aspects of viral ecology. Driven by advances in genome sequencing technology, the phylogeny, taxonomy, comparative genomics, and metagenomics of the virosphere are all the subjects of intense research. These efforts complement more traditional (but by no means obsolete) investigations into phage biology, genetics, and evolution. However, another important issue, one that provides context for all the others, has received comparatively less attention: what is the theoretical framework of viral ecology? More specifically, how are the principles of classical ecology, which were almost exclusively developed by ecologists studying non-microbial life, manifested in viruses and in viral communities?

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This paper discusses the concept of biological tradeoffs, a key component of evolutionary ecology, as applied to phages. Biological tradeoffs occur when a beneficial change in one trait is linked to a detrimental change in another trait.³ Numerous tradeoffs can characterize the life history of any one species, and the same tradeoff can be assessed across multiple species.⁴ Tradeoffs are crucial to explaining the diversity of life that inhabits this planet: although all organisms have finite resource budgets, different organisms manage and deploy those budgets in different ways, leading to differences in morphology, behavior, and life histories. Such tradeoffs are a core tenet of life history theory, have been extensively documented throughout the biosphere, and play a principal role in the maintenance of ecological niches and, more broadly, of biodiversity.^{4,5}

Studying tradeoff evolution in the context of phage biology is both practical and worthwhile. For decades, phages have been used extensively as model organisms because they grow extremely quickly, are readily manipulated, are non-pathogenic, and have simple life cycles with few life history variables to be assessed for tradeoffs. Furthermore, phages are believed to be extremely abundant, diverse, and influential in nature, yet as obligate intracellular parasites lacking metabolic independence, they live very differently than do most other organisms.⁶ Therefore, relatively straightforward experiments *in vitro* can provide insight into the evolutionary and ecological processes that affect a vast number of phages in natural environments.

In that spirit, this paper presents a meta-analysis of phage life history data in order to examine how one of the best-documented biological tradeoffs—between offspring production and offspring quality—is manifested in phages. Such research has both informational and applied value: by exploring the tradeoffs that characterize viral life histories, we better understand the factors that influence viral form and function, and by understanding how viruses look and behave, we gain insight into what has made them the planet's most successful inhabitants⁷ and the most notorious agents of disease.

Life and Death in Phages

From a Darwinian standpoint, any organism's most fundamental goal is to perpetuate its own existence via reproduction. However, producing offspring is a resource-intensive undertaking that carries its own biological costs. One such cost comes in the form of survival: unlike the mythical "Darwinian demon," a fictional creature that produces an infinite number of immortal progeny at no cost to itself, reproduction is, in the real world, often associated with decreased survival.⁸ This survival cost can accrue to one or both parent(s) or to the offspring themselves: mass-produced offspring typically have low rates of survival and a remote chance of maturing to reproductive age (low quality).³ Since a "parent" virus does not itself survive the infection process, the latter tradeoff—between the production of offspring and the quality of those offspring—will be the subject of this analysis.

Phages have been described as the "dark matter" of the biosphere⁶ because our current understanding of their ecology and diversity probably represents just the tip of the iceberg, but the life history variables that govern their reproduction and survival are well-known. In addition to various host and environmental factors, a phage's reproduction rate is principally influenced by three parameters: burst size (the number of viral progeny released per host cell), latent period (the time from infection of a host cell to the release of progeny), and adsorption rate (the rate at which a phage virion irreversibly binds to a host cell, thus commencing the infection).⁹ When hosts are abundant, larger burst sizes, higher adsorption rates, and shorter latent periods all increase absolute virion production. All three variables can be measured relatively easily, and values for latent period and burst size (and, to a lesser extent, adsorption rate) are frequently included in the description of a newly-isolated phage.

Even though the aliveness of viruses remains open to debate, it is clear that phages, like all other biological entities, have functional lifespans. In the extracellular environment, phages can "die" (or be

rendered non-viable) in at least three ways: they can spontaneously degrade, they can be destroyed by environmental stressors (e.g., temperature or pH extremes), or they can irreversibly adsorb to dead bacteria, membrane debris, or other material not capable of supporting their growth. As such, a phage's extracellular existence represents a race between encountering and successfully infecting a permissive host cell and death by degradation or premature adsorption.

Although higher rates of reproduction would, all else being equal, tend to increase fitness, maximizing the number of progeny produced per generation is not necessarily the best way to maximize population levels over the long-term. After all, different phages—even those that infect very similar bacteria—have evolved different absolute rates of replication and produce different numbers of progeny per generation and over time.¹⁰ Since these slower replicators have not been driven to extinction, a phage's absolute replication rate is clearly not the only determinant of its fitness. To the contrary, there are both host- and phage-centric explanations for why a phage would do well to moderate its own replication. Successful viruses must strike a balance between maximizing their own short-term propagation and transmission (effectively, virulence) and preserving the host population for long-term exploitation, meaning that phages might evolve lower productivity in order to avoid eradicating the bacterial population or driving it toward resistance. Multiple studies^{11,12} have demonstrated that such prudence is evolutionarily advantageous in well-structured environments that limit infiltration by more rapacious competitors—the "tragedy of the commons" applies to viruses, too.

Rather than extensively recapitulate the host and environmental factors that influence phage life histories, this piece focuses on tradeoffs among phages' life history variables themselves. In classical ecology, the tradeoff between offspring production and offspring quality is one prominent constraint on the success of organisms whose life history strategies emphasize rapid reproduction. How, and to what extent, is that dichotomy manifested in phages?

Persistence

Available data suggest that a tradeoff exists between a phage's persistence (an obvious component of its quality) and its replication rate. For example, in longitudinal experiments that challenged phage T7 with urea¹³ and phages $\phi 6$ and $\phi X174$ with heat,^{14,15} the evolved strains were found to possess increased resistance to their respective stressors but also decreased fecundity. In a study that assessed numerous physical and physiological properties of 16 coliphages (phages that infect *Escherichia coli*) for covariance with their rates of spontaneous decay, Da Paepe and Taddei found the coliphages' decay rates to be positively correlated with their replication rates.¹⁶ More recently, the replication rate of another coliphage, Q β , was also shown to be inversely proportional to virion stability.¹⁷ A harder virion is not without its costs, and these data suggest that the cost of stability is paid, at least in part, in the form of decreased replication.

Figure 1, which contains data from the lytic (virulent) phages included in the Da Paepe and Taddei study, illustrates the strong positive covariance ($r^2 = 0.8867$, $P < 0.0005$) between lytic coliphages' replication and spontaneous decay rates.

With the exception of reference 16, well-controlled data on the spontaneous decay rates of specific phages is not available. However, more widely-used criteria, such as sensitivity to heat or chloroform, represent another way to evaluate phage persistence. In some cases, drawing conclusions about relative phage stability is fairly straightforward: of four lytic *Vibrio* phages, for example, the slowest replicator had both the highest thermotolerance and the highest resistance to chloroform.¹⁸ When the same phage has different degrees of resistance to different stressors, however, determining that phage's overall "persistence" is a difficult, if not impossible, task. Of four lytic *Rhizobium* phages, for example, the fastest replicator was the most resistant to heat inactivation but the most susceptible to UV irradiation.¹⁹

Ultimately, a specific tradeoff can be most accurately assessed when other key variables are controlled. For example, two lytic *Pseudomonas* phages were

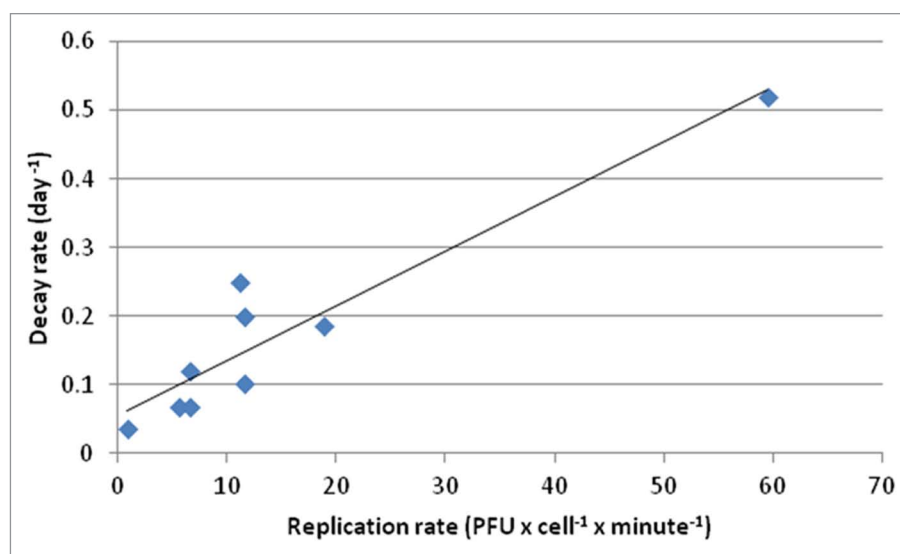


Figure 1. Scatter plot of nine lytic coliphages' replication rates (x-axis) and decay rates (y-axis), as reported by reference 16. Replication rate is defined as burst size divided by latent period, with units of plaque forming units (PFUs) per bacterial cell per minute. Decay rate refers to the loss of viable phage titer per day. The coefficient of determination (r^2) was calculated from the linear line of best fit.

independently isolated from sewage samples and found to have virtually identical host ranges, adsorption rates, and genome sizes but different replication rates; the faster replicator was the more sensitive to thermal inactivation.²⁰ Such data, though piecemeal, suggest that a higher replication rate is associated with lower phage stability, persistence, and quality. In the microscopic world as much as in the macroscopic world, the benefit of increased survival seems to be balanced against the cost of decreased reproduction.

Host Range

Like all viruses, phages must encounter and successfully infect suitable host cells in order to reproduce. As discussed above, greater persistence increases the time that any one phage has to accomplish that objective. Similarly, the ability to productively infect a larger number of hosts increases the likelihood that, over a given period of time, a particular phage will encounter a permissive host. As such, host range breadth and persistence are perhaps the two viral factors that most strongly influence a newly-produced phage's chance of successfully reproducing (its quality). A tradeoff seems to exist between phage replication rate and persistence:

does a similar tradeoff also exist between replication rate and host range?

To investigate that question, the author compiled and analyzed replication and host range data from lytic coliphages in the context of the *Escherichia coli* reference (ECOR) collection. ECOR is comprised of 72 *E. coli* strains from a variety of human and animal sources and is representative of the genotypic diversity of the genus *Escherichia* as a whole.²¹ Since ECOR is large, standardized, and representative, a particular coliphage's ability or inability to productively infect ECOR strains provides (in the author's opinion) a more accurate portrayal of that phage's "true" host range than do tests against smaller or non-reference collections.

To date, eight lytic coliphages for which replication data are available have been tested against the complete ECOR collection. **Figure 2** presents a scatter plot of those eight coliphages' replication rates and the percentage of ECOR strains successfully lysed.

The data indicate a very strong negative relationship between coliphage replication rate and host range: the higher the replication rate, the fewer ECOR strains lysed. Largely due to one influential phage, the line of best fit in **Figure 2** is more strongly logarithmic ($r^2 = 0.9661$, $P < 0.00005$)

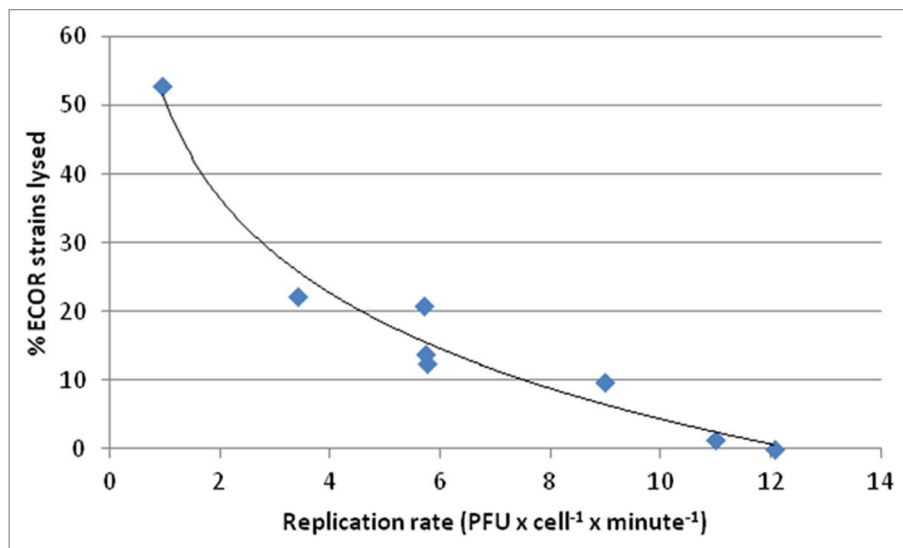


Figure 2. Scatter plot of eight lytic coliphages' replication rates (x-axis) and broadness of host ranges (y-axis). Replication rate is defined as burst size divided by latent period, with units of plaque forming units (PFUs) per bacterial cell per minute. Host range breadth is functionally defined as the ability to infect and lyse members of the *Escherichia coli* reference (ECOR) collection. The coefficient of determination (r^2) was calculated from the logarithmic line of best fit. The figure's data points are derived from references 45–50 in the bibliography.

than linear ($r^2 = 0.8102$, $P < 0.005$), although both are highly significant.

These data suggest the existence of a tradeoff between phage replication rate and host range, at least in lytic coliphages. Though preliminary, this finding corresponds with previous observations. For example, phage mutants with expanded host ranges typically replicate more slowly on the original host than does the wild type, presumably due to antagonistic pleiotropy.^{22,23} When coliphages T1, T4, and ϕ X174 were tested against 69 clinical *E. coli* isolates, the fastest replicator (ϕ X174, a small-genomed ssDNA phage) had by far the narrowest host range against both antibiotic-sensitive and antibiotic-resistant bacterial strains.²⁴ A recent, large-scale study of 32 environmental phages and almost 150 *Klebsiella* strains also found faster replication to be associated with a narrower host range, with slower-replicating phages typically exhibiting the broadest spectrum of lytic activity.²⁵

A tradeoff between replication rate and host range is plausible both evolutionarily (e.g., broader host range as compensation for decreased replication; specialism vs. generalism) and energetically, since producing the structures that physically enable a broader host range (e.g.,

displaying multiple types of receptor-binding tail fibers on a single virion)^{26,27} requires a greater energy expenditure. All in all, it seems that versatility has its drawbacks—even at the edge of life.

Adsorption

Adsorption, or the process by which phages attach to specific bacterial surface receptors, is the first step in infection. Depending on the circumstances, a high adsorption rate can be a blessing or a curse: although adsorption is a requisite part of the phage lifecycle and influences phage replication rate, it can also lead to a phage's premature demise if it irreversibly binds to a dead or non-permissive cell (or to debris) rather than to a viable bacterium. For example, a high adsorption rate was shown to be detrimental to the fitness of phage λ in a biofilm-like environment.²⁸ In a compelling example of how adsorption rate can be rapidly modified in response to changing environmental conditions, Daniels and Wais found that phages infecting the halophile *Halobacterium cutirubrum* had low adsorption rates immediately after isolation but, upon laboratory propagation, quickly mutated to increase their adsorption

rates.²⁹ These mutations increased the phages' virulence without affecting their latent periods or burst sizes. Similarly, a point mutation in *Enterococcus faecalis* phage ϕ EF24C did not affect that phage's latent period, burst size, or host range but did increase its adsorption rate, leading to greater bactericidal activity.³⁰

Other phages, such as the T-even coliphages, modify and detect adsorption via phenotypic plasticity. Phage T4, for example, deliberately retracts its tail fibers in response to adverse environmental conditions, such as low temperature and pH, thereby lowering its adsorption rate and (presumably) its risk of damage.³¹ The phenomenon of lysis inhibition, in which secondary phage adsorption to an infected cell increases both the latent period and the burst size of the original infecting phage, has also been observed in T-even phages.³² By sensing the presence of competing virions via secondary adsorption and producing many more progeny per cell than usual, lysis inhibition allows these phages to maximize their replication when uninfected cells are a rare commodity and the ratio of phages to bacteria is high.³³

Tail fiber-encoding genes are hotspots of mutation within phage genomes, which allows phages to rapidly discriminate among various types of bacterial strains and establish their host ranges.³⁴ Some phages—perhaps many more than previously believed³⁵—even employ VDJ-like recombination in order to generate enormous structural diversity in their tail fiber regions.³⁶ Although these phenomena have frequently been discussed in the context of a co-evolutionary arms race between phages and bacteria, it is interesting to speculate that tail fiber hypermutation might also establish a gradient of adsorption rates within a phage population and serve another purpose. It has long been known that a small percentage of a phage population (the “residual fraction”) has an abnormally low adsorption rate, possibly as a bet-hedging strategy to prevent extinction.³⁷ That phenotype is apparently stochastic and non-heritable,³⁷ but more subtle modifications to adsorption rate might allow phage subpopulations to respond (relatively) rapidly to changes in host abundance. This process could be

driven by the sensing of environmental conditions, leading to real-time phenotypic changes (e.g., lysis inhibition), or by mutations in genes whose products are involved in adsorption. If widespread in nature, such mechanisms might represent an important way by which phages can increase their replication (higher adsorption rate) or persistence (lower adsorption rate) as circumstances dictate.

r/k Selection

Decreased environmental persistence and narrower host range seem to be two biological costs associated with rapid replication in phages. More broadly, viral life histories can be viewed through the prism of r/K selection theory, a concept first developed by MacArthur and Wilson more than four decades ago.³⁸ In a nutshell, r/K selection theory posits that organisms can evolve to either produce large numbers of offspring, most of which die before being able to reproduce (an r-selected life history), or to produce a smaller number of offspring that live longer and have a better chance of successfully reproducing (a K-selected life history).³⁹ Today, r/K selection is considered to be somewhat simplistic, since organisms often display a mixture of r- and K-selected characteristics, but r/K terminology is still used to broadly distinguish between different types of life history strategies, including those of viruses.⁴⁰

Different phages that infect very similar bacteria have evolved to divide a relatively constant resource (i.e., the energy budget of an *E. coli* host cell) between different numbers of offspring. Some phage “parents” produce large numbers of progeny, but because those progeny have comparatively short lifespans and narrow host ranges, it is less likely that any one will successfully replicate (low offspring quality). By contrast, other phages replicate more slowly but endow their offspring with greater stability and host range, thus enabling each to have a better chance of reproduction (high offspring quality). Taken together, these points indicate that even in viruses, there is a tradeoff between the generation of many offspring and the success of any one offspring, between productivity and

efficiency, that lies at the heart of r/K selection theory.

Challenges in Phage Meta-Analyses

Because numerous host and environmental parameters affect phage life history traits, it is important to discuss some of the potential sources of error inherent to meta-analyses. Most obviously, such variation could be procedural, since phage replication and adsorption kinetics can be affected by changes in host cell physiology and size, the multiplicity of infection, the type of growth medium, and other such factors not likely to be well-controlled between studies.⁴¹ This makes studies that utilize an identical procedure to assess the life history parameters of multiple phages, such as reference 16, particularly valuable.

Another potential source of variation, one of greater interest to the microbial ecologist, relates to phages’ niches in natural environments. Many phages are capable of lysing multiple bacterial strains, but the same phage can propagate at very different rates in different permissive hosts. Therefore, it is probable, if ultimately unknowable, that some phages in a meta-analysis would have been tested against more optimal host strains (thus favoring shorter latency, larger burst, or both) and others were measured against less optimal hosts (thus favoring longer latency, smaller burst, or both). In this manner, uncontrollable differences in host suitability could conceivably magnify or obscure what actually occurs in nature.

Since much of the data on phage life history parameters is widely dispersed across the literature (e.g., reports that describe the isolation of a novel phage and its growth characteristics in a particular host), variability will always accompany attempts to discern broad trends in phage biology from multiple studies. That does not mean that such attempts cannot be constructive—after all, drawing conclusions from disparate sources of data is fundamental to the scientific process, and if phage growth parameters had no comparative value there would be little reason to measure them at all—but it is important to recognize their limitations and to analyze their conclusions critically.

Paradox of the Phages?

Finally, it is worthwhile to look back on a classic problem in evolutionary ecology. More than 50 y ago, Hutchinson famously proposed the “paradox of the plankton”⁴² in order to address an apparent dilemma of biodiversity: why does the ocean support an abundance of different phytoplankton species when all have very similar ecological roles and compete for the same limiting resources? Phage biologists could ask the same question, since numerous phage species with different morphologies, genome sizes, and life histories inhabit the same macroenvironments and compete for highly similar bacterial hosts.⁴³

Today, it is recognized that Hutchinson’s paradox, like the competitive exclusion principle on which it is based, is somewhat of a straw man: in practice, a single macroenvironment like the ocean is fragmented into a much larger (and ever-changing) collection of ecological niches, and because no single set of selective pressures is continuously maintained, large numbers of superficially similar organisms can stably co-exist.⁴⁴ Compared with plankton, however, little is known about the niche dynamics and community interactions of phages in natural environments. Basic questions, including those with obvious relevance for explaining and understanding the diversity of the virosphere, remain incompletely resolved. Like viruses generally, phages come in a variety of shapes and sizes: are particular phage morphologies adapted to particular ecological niches? How frequently do speciation and extinction events occur? To what extent do different phages’ host ranges, which presumably contribute to the differentiation of their niches, actually overlap in natural environments? After all, *in vitro* host range experiments shed light on a phage’s fundamental niche (the totality of hosts it can exploit in the absence of competition) but not on its realized niche, or the hosts that it actually does infect under natural conditions.

Ultimately, resolving these and other questions in phage ecology will likely require combining the traditional techniques of phage research with the tools of modern genetics and molecular biology—and with the perspectives of classical

ecology. Perhaps it will be by studying phages in the spirit, if not with the methods, of Darwin and Hutchinson and Wilson, as natural organisms in natural habitats, that we will best come to understand how phages and other viruses interact with each other, with their hosts, and with their shared environments to thrive as some of the planet's most ancient and abundant biological entities.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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