Metabolic and biogeochemical consequences of viral infection in aquatic ecosystems

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Abstract | Ecosystems are controlled by 'bottom-up' (resources) and 'top-down' (predation) forces. Viral infection is now recognized as a ubiquitous top-down control of microbial growth across ecosystems but, at the same time, cell death by viral predation influences, and is influenced by, resource availability. In this Review, we discuss recent advances in understanding the biogeochemical impact of viruses, focusing on how metabolic reprogramming of host cells during lytic viral infection alters the flow of energy and nutrients in aquatic ecosystems. Our synthesis revealed several emerging themes. First, viral infection transforms host metabolism, in part through virus-encoded metabolic genes; the functions performed by these genes appear to alleviate energetic and biosynthetic bottlenecks to viral production. Second, viral infection depends on the physiological state of the host cell and on environmental conditions, which are challenging to replicate in the laboratory. Last, metabolic reprogramming of infected cells and viral lysis alter nutrient cycling and carbon export in the oceans, although the net impacts remain uncertain. This Review highlights the need for understanding viral infection dynamics in realistic physiological and environmental contexts to better predict their biogeochemical consequences.

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"A bacterium continually strives to produce two bacteria", wrote François Jacob in *The Logic of Life*, "This seems to be its one project, its sole ambition" (REF.[1]). It is in relentless service of this goal that microorganisms collect substrates from their environment and assimilate them into new forms, harnessing energy from the Sun or chemical disequilibria, while competing with neighbours and relatives seeking to do the same. This globe-spanning effort has generated much of the biogeochemical structure in Earth's environments: our oxygenated atmosphere; the widely nutrient-depleted surface ocean; and sulfide-rich and methane-rich sediments on land and sea[2].

If microbial growth proceeded unchecked, however, global ecology would long ago have exhausted its resources and ground to a halt. Instead, death processes largely keep pace with growth in microbial ecosystems, and, in turn, drive nutrient recycling that fuels the growth of the next generation. In aquatic systems, a complex microbial food web of phytoplankton, heterotrophic bacteria and microscopic consumers was first proposed decades ago[3]. We now recognize additional mechanisms that are crucial for recycling biomass and supporting microbial growth, including lysis from viral infection[4–6]. During infection, the 'sole ambition' of the cell — to reproduce — is commandeered by the virus, which rewires host metabolism for the new goal of producing viral progeny[7,8]. As a result of this reprogramming, viral infection can have substantial biogeochemical consequences well before cellular lysis.

We can now appreciate that in virtually every microbial habitat on Earth, at any given time, there is a substantial portion of microbial cells whose 'one project' has been hijacked by viral infection[4,9]. Early efforts in metagenomics revealed the extensive novel genetic diversity of phages[10,11], and subsequent work has vastly expanded our catalogue of diversity for both phages and archaeal viruses[12–15]. Assessment of eukaryotic viral diversity lags behind, in part due to the challenges of assembling whole eukaryotic viral genomes from marine field samples. Nevertheless, recent studies of eukaryotic viral diversity include genome sequences from cultured algal viruses that infect representatives of several different eukaryotic supergroups[16–19], analysis of individual virally encoded genes[20,21], metagenomic surveys from nature[22] and targeted metagenomic assembly of uncultured viruses of protists[23]. Despite this rapid progress in genomics, our understanding of infection

Transparent exopolymer particle
(TEP). A sticky, gel-like particle consisting predominantly of acidic polysaccharides that originate from microorganisms and can enhance the aggregation of non-sticky particles in marine and aquatic ecosystems.

biology remains limited and is largely based on a few well-studied laboratory model systems; even less is known about infection dynamics in natural ecosystems. In this Review, we focus on cellular-level virus–host interactions and explore their potential impacts on biogeochemistry in aquatic systems. We first summarize how viruses alter the metabolism and composition of their host cells, with the caveat that much of this knowledge is based on a handful of model systems and laboratory growth conditions. We then summarize recent work exploring how host physiology and environmental conditions constrain or alter viral reprogramming of cellular pathways, cell lysis and viral production. Last, we extrapolate from these cellular-level processes to explore how viruses might impact biogeochemistry at the ecosystem scale.

Infection reprogrammes the cell

Viruses employ a range of infection strategies from lysogenic integration into the host genome to acute lytic bursting (BOX 1); the prevalence of these strategies in the wild, and their physiological and environmental controls, are poorly understood. In this Review, we focus on lytic infection, the mode whose cellular and biogeochemical effects are best characterized. Lytic viral infection fundamentally reprogrammes host cell metabolism away from cellular replication towards progeny virus production (FIG. 1). This reprogramming is evident at the transcriptional level, where mRNA synthesis shifts rapidly and almost entirely to viral genes in a highly regulated manner. This transcriptional programme has been described for phages infecting cyanobacteria (cyanophages)[24–26], phages of *Cellulophaga baltica* (marine Bacteroidetes)[27,28] and viruses infecting diverse marine eukaryotic algae, including haptophytes[29,30], prasinophytes[31] and stramenopiles[32]. Comparative studies have found this gene expression programme to be relatively invariant for a given virus infecting different host strains of marine *Synechococcus* (Cyanobacteria)[25] and *C. baltica*[27,28], and for a given virus infecting host cells under phosphorus-replete and phosphorus-limited conditions[31,33], although the onset of this transcriptional reprogramming can vary among individual cells in a population and may be stalled in non-growing or stationary phase cells[34]. Building on this knowledge from model systems, recent work has begun to detect spatiotemporal patterns of active infections in coastal and open ocean environments using metatranscriptomics[35–38]. Despite the relatively invariant viral gene expression programmes observed to date in cultures, the productivity of the infection can vary widely depending on host and environmental factors, as discussed below. Hence, a challenge going forward is to connect gene expression with other cellular markers of infection and viral production.

Beyond gene expression, lytic viral infection alters host cell metabolism and composition in other measurable ways. Cellular changes such as nucleoid degradation, cessation of net RNA synthesis and lipid remodelling are best understood in *Escherichia coli* phage infection systems[39,40], but the extent to which these changes are shared across diverse virus–host systems is unknown. Among marine systems, cellular changes during infection have been best documented in the haptophyte alga *Emiliania huxleyi*. These changes include a shift from carbon fixation to the pentose phosphate pathway for viral nucleic acid synthesis[30,41], extensive lipid remodelling[30,42,43] and alteration of transparent exopolymer particle (TEP) production[44,45]. Similarly, infection has been shown to alter the cellular redox state in the marine cyanobacterium *Prochlorococcus marinus* strain MED4, as metabolism shifts from carbon fixation to the pentose phosphate pathway to supply nucleotides for phage replication[46]. Metabolite profiling has begun to reveal other global changes in cellular metabolism during infection, such as an overall increase in metabolic activity in *Sulfitobacter* spp., along with a stoichiometric shift to higher cellular nitrogen[47]. From these studies, it is clear that lytic infection drastically alters the cellular and metabolic landscape, but more work is needed to determine whether these findings apply to diverse taxa and in relevant environmental conditions. Quantifying how infected cells differ from their uninfected counterparts (for example, in cellular stoichiometry, macromolecular composition and metabolic fluxes) is not only an essential step towards integrating viruses into ecosystem models, but may also lead to new diagnostic biomarkers for measuring infection rates in natural ecosystems. Examples include the distinct lipid signatures[48,49] and intracellular redox conditions[50] of infected *E. huxleyi* cells. Being able to detect and quantify infected cells and their associated metabolic changes is crucial for estimating the pre- and post-lysis impacts of viral infection in aquatic systems.

To date, these features of viral reprogramming have largely been assessed using individual virus–host pairs under laboratory conditions. There is growing evidence that infection outcomes are highly specific to the selected virus–host pair. This specificity is evident in host transcriptional responses to infection, which, in contrast to the relatively fixed viral gene expression programme, appear to be highly variable. The same host strain of marine *C. baltica* shows distinct responses to different viruses[27,28], and, conversely, the same virus elicits distinct responses in different host strains of both *C. baltica*[27,28] and *Synechococcus*[25]. In *Synechococcus* sp. strain WH8102, infection induces expression of both putative host defence genes and genes that the virus may exploit to enhance its replication[51]. Moreover, several host proteins that are synthesized during infection in this same *Synechococcus* strain are also encoded in some phage genomes, suggesting that their expression enhances viral fitness[52]. Host defences against viral infection, and viral counter-defences, are diverse and largely uncharacterized[53,54]. Together, these findings suggest that the outcome of infection may hinge on whether the virus can repress or evade host defences, and potentially exploit host gene expression and metabolism[55], and thereby efficiently produce progeny[27,28]. Given this specificity, a major challenge is to reconcile laboratory findings with ecological reality, in terms of the diversity and abundance of coexisting hosts and viruses.

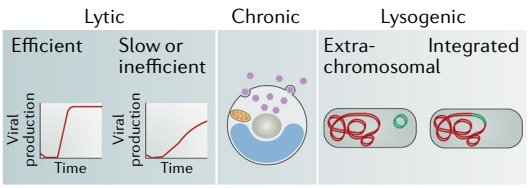
Box 1 | Diversity of viral infection modes

Historically, phages have been classified as obligately lytic or temperate (that is, capable of integrating as a prophage into the host chromosome). Increasingly, however, this dichotomy is thought to be a spectrum[195], with infections ranging from acute and virulent to chronic to lysogenic (see the figure, parts **a** and **b**, and Supplementary information). Lytic infection itself is a continuum of infection modes, from abrupt burst to more gradual release of progeny virions. Efficient lytic infections result in the rapid release of virions concurrent with lysis and death of host cells. Slow or inefficient lytic infections result in the gradual release of virions prior to cell lysis and death. Inefficient lytic infections may be due to localized lysis of the host cell membrane rather than abrupt loss of membrane integrity, suitability of the host (for example, inefficient adsorption or host resistance), or physiological or environmental conditions that slow the rate of virion production and/or release. During chronic infections there is a consistent, minimal release of virions without detectable cell lysis. Extrachromosomal lysogenic (sometimes referred to as 'pseudolysogenic') infections result in a 'carrier state' where virus persists intracellularly without integration into the host genome or replication of the viral genome. Integrated lysogenic infections result in the integration and replication of viral genetic material with the host genome. Temperate phages display both lytic and lysogenic or chronic infection cycles.

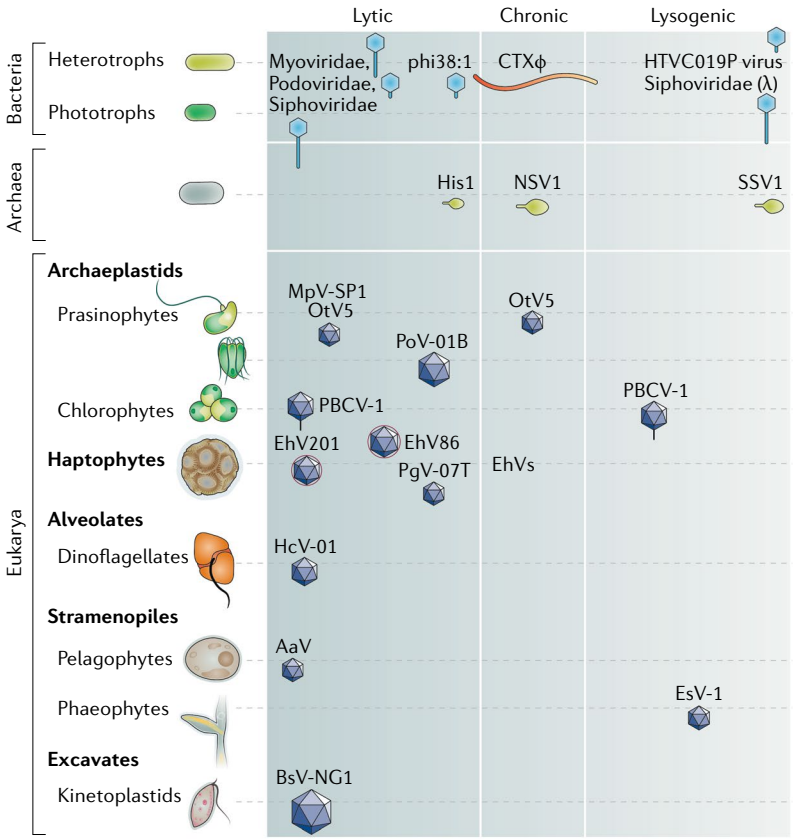
The spectrum of infection strategies can be roughly characterized by how rapidly and directly each leads to release of progeny virions (see the figure, part **a**). At one end, the fitness of obligately lytic viruses depends on rapid host takeover and efficient redirection of cellular metabolism towards synthesis of progeny virions. By contrast, a host cell with a latent lysogenic prophage could be physiologically indistinguishable from an uninfected host cell (however, see below). Thus, we posit that the degree of virus-directed metabolic remodelling is generally proportional to the rate of progeny virion production and release (see the figure, part **c**). The extent to which the metabolism of the infected host cell continues and/or is redirected to producing viral progeny has substantial biogeochemical consequences and varying implications for whether infected cells should be treated as a separate functional class. There are some notable exceptions to this simplified scheme. In lysogenic conversion, for example, a prophage alters its host cell phenotype without phage replication (for example, phage CTXΦ)[196], representing an alternative means by which viruses can reprogramme bacteria[197–199]. Likewise, prior to cell lysis, infection of eukaryotic algae can differentially alter the production of transparent exopolymer particles within and across supergroups[45,165,168], in turn affecting particle aggregation. Some viruses replicate without inducing host cell lysis, including those infecting marine *Nitrosopumilus* ammonia-oxidizing archaeal species, which do not degrade the host chromosome during infection[15]. The degree of metabolic remodelling is also likely constrained by the virus genome size (that is, larger virus genomes have increased potential for encoding metabolic genes) and may be influenced by environmental stability (that is, metabolic manipulation might offer a greater fitness advantage in more stable environments).

Not only do viral taxa vary in their infection strategy (see the figure, part **b**), but individual viruses also exhibit variation across hosts and in response to host physiology[27,28,195,200]. Although many well-studied phage infections tend towards burst-type dynamics, a few, such as *Cellulophaga baltica* phage phi38:1 (REF.[201]), display inefficient lytic infection on different host strains[27,28]. Even the long-studied coliphage T4 was recently shown to have a 'hibernation' mode when infecting stationary-phase *Escherichia coli*, whereby phage replication is paused awaiting additional nutrients[202]. Among algal viruses, enveloped *Emiliania huxleyi* viruses (EhVs) are released by a budding mechanism[203], although infection still culminates in lysis of the host and the rate of lysis depends on the specific virus and host strains involved[191]. Similarly, some cells of the eukaryotic prasinophyte alga *Ostreococcus tauri* develop a 'resistant producer' phenotype in response to infection by OtV5, in which few viruses are produced per cell per day by vesicle budding, but without lysis of the host[204]. Environmental and physiological changes can induce a shift in viral strategy — small increases above the host's optimal growth temperature have recently been found to induce a change from lytic to chronic-like infection in *Micromonas*[68], whereas a similar temperature increase induced an EhV-resistant phenotype in *E. huxleyi*[69]. However, we have limited knowledge of how prevalent the various infection strategies are in nature and how they relate to host abundance and physiology under natural conditions.

a Spectrum of viral infection strategies



b Examples of observed infection strategies



c Corresponding phenotypes of infected cells

[a]Lysogenic conversion is a special case of lysogeny that may involve a greater degree of cellular remodelling, and reduced biochemical similarity between infected and uninfected cells, than shown for other lysogenic infections.

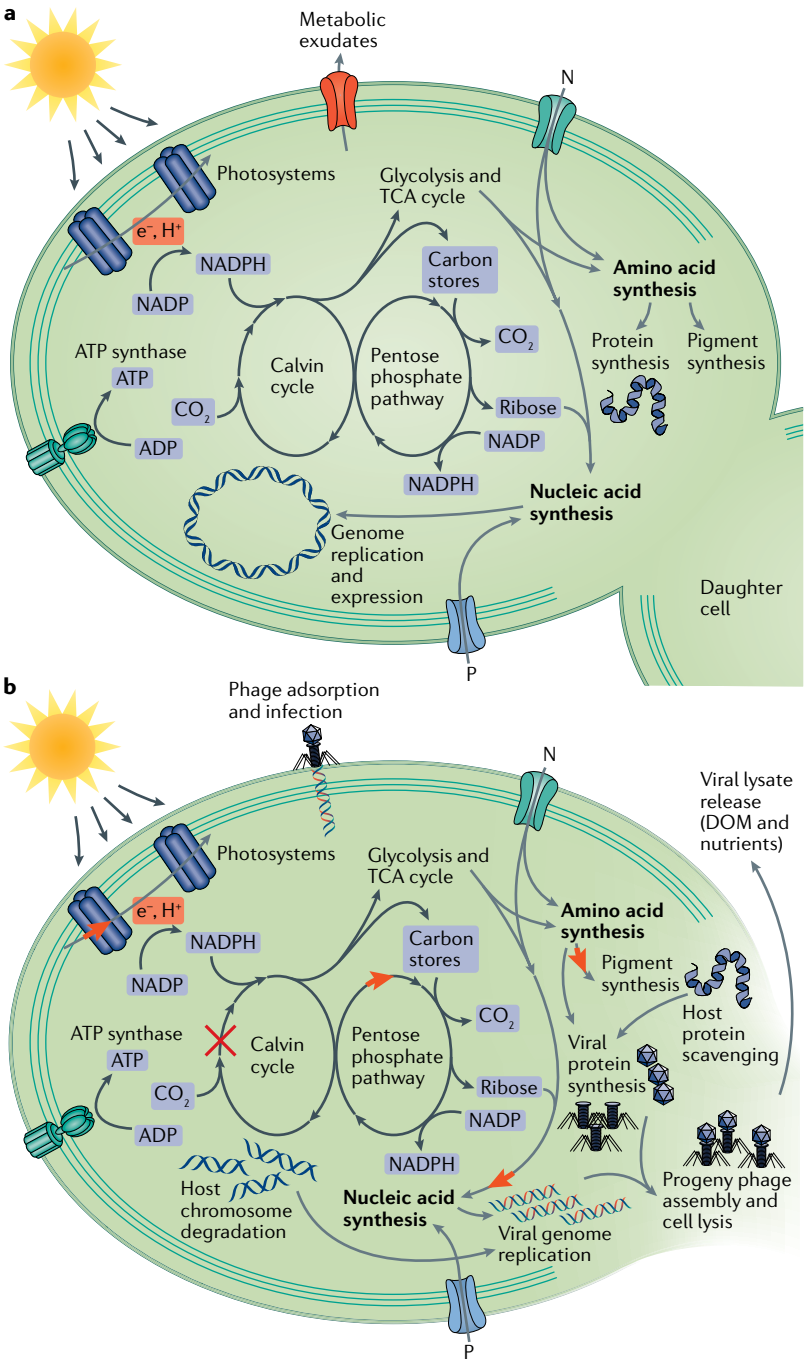


Fig. 1 | **Remodelling of host metabolic pathways during viral infection.** Schematic of selected metabolic fluxes towards biopolymer (nucleic acid and protein) production in a prototypical cyanobacterium, contrasting the metabolic states of an uninfected, replicating cell (part **a**) with a phage-infected, reprogrammed host cell (part **b**). Notable metabolic processes include proton pumping and electron transport by the photosystems in the thylakoid membranes; ATP synthesis; the interlocking carbon-fixing Calvin cycle and carbon-respiring pentose phosphate pathway; biosynthesis of nucleotides and amino acids; synthesis of DNA/RNA and proteins by polymerization; and pigment biosynthesis. These processes can lead to cell growth and replication, producing a daughter cell (part **a**), or lead to assembly of progeny phage particles and cell lysis (part **b**). In both cases, metabolic products are released to the environment, contributing to the dissolved organic matter (DOM) pool; this release is through exudation during growth (part **a**), whereas cell lysis releases cytoplasmic and membrane components of the killed host cell (part **b**). Orange arrows and the red cross (part **b**) indicate pathways stimulated or inhibited, respectively, during infection by expression of virally encoded accessory metabolic genes (note that many additional cellular pathways are affected or redirected by infection). TCA, tricarboxylic acid.

Metabolic constraints on viral infection

In natural environments, microorganisms are often energy or nutrient limited, based on suboptimal growth rates measured in situ[56,57]. This pre-infection physiological state of the host cell has long been known to affect phage production, as documented by studies linking the host growth rate and burst size in *E. coli*[58–60]. Beyond *E. coli*, a multiplicity of relationships between host physiology, environmental conditions and viral productivity have been observed in aquatic bacterial and eukaryotic algal hosts (FIG. 2). Although the data remain sparse and the findings are challenging to compare between studies and organisms (BOX 2), it is clear that viral production can be slowed and/or reduced in light-limited cyanobacteria *Prochlorococcus*[24], freshwater chlorophyte algae[61] and both prasinophyte and haptophyte marine algae[41,62–66]; at suboptimal temperatures in species of the prasinophyte *Micromonas*[62,67,68] and the haptophyte *Emiliania*[69]; and under certain nutrient (for example, nitrogen, phosphorus and iron) limitation conditions for marine bacteria *Pseudoalteromonas* spp.[70], marine cyanobacteria *Synechococcus*[71] and multiple *Phaeocystis* (haptophyte) and *Micromonas* strains[31,63,66,72,73]. By contrast, silicon stress had no detectable effect on viral burst size, but was found to accelerate virus-induced mortality in cultures of the diatom *Chaetoceros tenuissimus* and in natural diatom populations off the California US coast[74]. Extrapolating these trends more broadly remains a challenge in part because the organisms that have been studied represent an unsystematic selection of a few taxa and the conditions studied (including virus and host densities) are not necessarily reflective of those found in nature. The nature of the relationship between the host growth rate or environmental driver and viral production (that is, whether it is linear, monotonic and so forth) also remains unclear because experiments to date often compare only two conditions (for example, nutrient replete versus nutrient deplete). Furthermore, the mechanisms underlying these observed relationships between viral production and the host physiology or environment are poorly understood. It is possible that modulating the host growth rate through different forcing factors (for example, temperature, light availability or nutrient supply) leads to distinct cellular states in terms of biosynthetic machinery, resource allocations and stoichiometry, and may therefore give rise to distinct patterns of viral production. In the following sections we explore the effects of various physiological stressors on host physiology in more detail and, in turn, viral strategies to overcome host constraints, with the goal of elucidating principles that can be applied in biogeochemical models.

Light and energy availability. Photosynthetic microorganisms are commonly studied experimental systems for virus–host interactions because they form the base of the food web, and their energy metabolism can be manipulated instantaneously by turning out the lights or adding specific inhibitors of photosynthesis. Among cyanobacteria, the production of cyanophages has long been known to depend on photosynthesis to varying degrees in both freshwater[75] and marine[76–78] taxa.

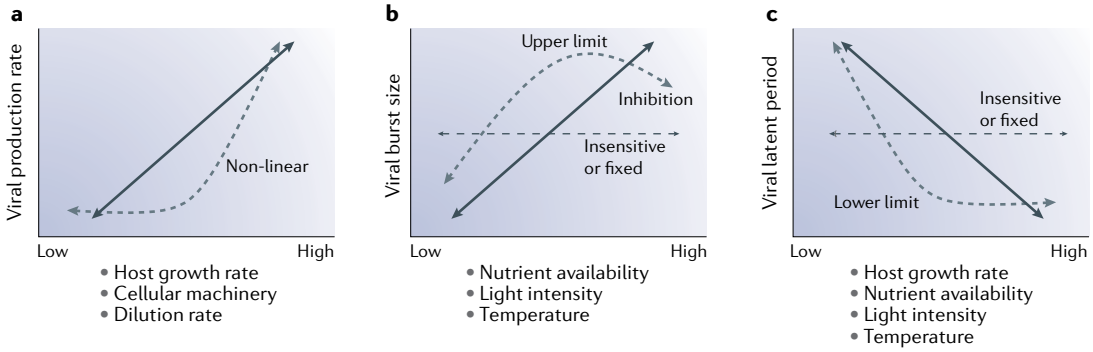


Fig. 2 | **Relationships between viral productivity and host physiology or environment.** Simplified representation of relationships between viral productivity and host physiology or environment, shown in terms of the viral production rate (quantified as accumulation of intracellular genome copies over time[24], linear regression of extracellular virions over time[60,62] or virion growth rate[68]) (part **a**), viral burst size (that is, normalized yield; see BOX 2 for discussion of quantification methods) (part **b**) and viral latent period (for example, the time period to extracellular release of new virions) (part **c**). The host growth rate and cellular machinery (that is, ribosomes and enzymes) can be manipulated by environmental variables (for example, temperature, light intensity or nutrient availability). Nutrient availability has the potential to alter viral production directly through limitation of substrates needed to build progeny virions or indirectly through the host growth rate, which in turn affects production yields or rates, respectively. Linear relationships are shown for simplicity but are intended to represent only the direction of correlation between viral productivity and host physiology. The slope and linearity of the relationship varies in species-specific and environment-specific ways. Interactive effects between environmental variables (for example, light and nutrient availability) can further modify the shape of the relationship. The viral burst size and latent period may be fixed traits or insensitive to the specific variables tested, as shown by the horizontal dashed grey lines (parts **b** and **c**). Data supporting these relationships were obtained from empirical studies across marine and non-marine virus–host model systems: host growth rate[24,62,68], cellular machinery and dilution rate[60,70] (part **a**); nutrient availability[66,72–74,127,215,216], light intensity[61,62,64,66,78] and temperature[67] (part **b**); and host growth rate[68], nutrient availability[66,72,73,216], light intensity[61,62,64,66,78,123] and temperature[67] (part **c**).

Infected cyanobacterial cells direct energy and reducing power away from CO_2 fixation and towards viral protein and DNA synthesis, with CO_2 fixation ceasing well before lysis in some[79,80], although not all[81], freshwater cyanobacteria, and in marine *Synechococcus* sp. WH7803 (REF.[82]).

For some cyanophages, reliance on the pre-existing host energy-generation machinery is insufficient to meet their demands, either because the machinery is not abundant or efficient enough to supply viral energy demand, or because it turns over on short timescales relative to the length of the infection cycle and must be replaced to maintain activity. For these viruses, carrying and expressing their own auxiliary metabolic genes (AMGs) related to energy metabolism can offer an advantage by providing ATP and/or reducing power for viral protein synthesis, which represents the greatest energy demand for relatively small viruses including cyanophages[78,83]. In addition to core reaction centre proteins[84–87], numerous other components of photosynthetic electron transport, along with proteins that are thought to stabilize the reaction centres, are also encoded in cyanophage genomes[88] (FIG. 1b). Cyanophages also appear to contribute to phycobilin pigment biosynthesis, by encoding haeme oxygenase and bilin reductases[89–91] that may enhance light harvesting during infection. Genes that encode core reaction centre proteins are among the best-studied viral AMGs: they are expressed at both the transcript and protein levels[76,84,85,92], they affect photosystem operation and/or electron flow[78,85] and they are predicted to improve cyanophage fitness[93,94]. To date, no single cyanophage has all of these proteins; rather, individual phages likely maintain the genes that are most crucial for viral fitness in the context of their particular host and environment.

Cyanophages also influence phototroph energy and carbon metabolism beyond the photosystems, particularly by redirecting metabolic flows through the interlocking Calvin cycle and pentose phosphate pathways (FIG. 1b). These two pathways share several bidirectional enzymes and can be viewed as running in opposition to one another, with the Calvin cycle trading reducing power (generated by photosynthesis) for fixed carbon and the pentose phosphate pathway doing the reverse. Many cyanophages encode genes for pentose phosphate pathway enzymes, including glucose 6-phosphate dehydrogenase (*zwf*), 6-phosphogluconate dehydrogenase (*gnd*) and transaldolase (*tal*), as well as *cp12*, an allosteric repressor of two Calvin cycle enzymes[95,96]. Expression of these genes during infection of either *Prochlorococcus* or *Synechococcus* hosts appears to promote metabolic flux through the pentose phosphate pathway at the expense of the Calvin cycle, potentially to enhance dNTP synthesis for phage replication[46]. Consistent with this observation, the suppression of CO_2 fixation during infection was more rapid and severe for a *Synechococcus*-infecting cyanophage carrying the pentose phosphate pathway and *cp12* genes than for one without these genes[82].

Analogously, there is some evidence for continuation of host photosynthesis and reduction or cessation of CO_2 fixation in diverse eukaryotic algal–virus systems. Chloroplasts (where photosynthesis is localized in algal cells) are preserved but show altered photosynthetic properties during viral infection of the prasinophyte *Micromonas pusilla*[65] and the stramenopile *Aureococcus*

Core reaction centre
A membrane complex of several proteins, pigments and other cofactors that performs the principal energy conversion reactions of photosynthesis, capturing light energy and converting it into redox potential energy for ATP synthesis and reducing power for reduction of CO_2; also known as the photosynthetic reaction centre.

Phycobilin
Photosynthetic pigments found in cyanobacteria and the chloroplasts of red algae and glaucophytes that aid in absorption of light energy, particularly at wavelengths that are not well absorbed by chlorophylls or carotenoids.

anophagefferens[32,97]. As in some cyanobacteria, CO_2 fixation declines early in infection in freshwater chlorophyte *Chlorella variabilis*[61] and marine *M. pusilla*[98]. Likewise, protein synthesis of CO_2-fixation machinery decreased in infected populations of *E. huxleyi*, but light-driven photosynthetic reactions were maintained[30,41]. Concurrently, expression and activity of the pentose phosphate pathway increased in a light-dependent manner, reflecting a shift towards viral nucleotide biosynthesis, in which the proportion of recycled versus de novo synthesized nucleotides was also controlled by light intensity[30,41]. None of the sequenced algal viruses to date encode photosynthetic reaction centre proteins, although many fewer algal viruses have had their genomes sequenced (examples given in REFS[16–18,99]). We posit that one reason why these algal viruses lack photosynthesis genes is the requirement for the correct transit peptide for proteins that must be imported into the plastid, which increases the barrier to successful protein hijacking by the virus.

There are further hints that viruses manipulate energy metabolism, beyond oxygenic photosynthesis itself, from genomes of marine eukaryotic viruses. The so-called 'giant viruses' (>300 kb genome size) appear to

Box 2 | **Challenges in studying viral infection across experimental systems**

There are several underappreciated challenges and uncertainties in experimental studies of viral infection, which limit our ability to compare experimental systems or laboratory models with natural ecosystems. Viral infection and productivity are historically characterized by several key parameters (listed below) that have operational rather than mechanistic definitions and can therefore only be measured under very specific experimental contexts. Consequently, it is unclear how, or whether, these empirically determined infection parameters can be extrapolated to natural ecosystems. Infection parameters that are typically reported include infectivity or the associated multiplicity of infection (MOI), adsorption rate constant, latent period, burst size and host specificity. These parameters are often treated as intrinsic properties of the virus rather than plastic phenotypes that respond to the host quality and environmental conditions. However, empirical evidence from various virus–host systems suggests that the infectivity, adsorption, latent period and burst size are emergent properties of complex virus and host-associated factors.

Comparisons of viral infection across experiments and systems is complicated by multiple or ambiguous definitions for all of the key viral growth parameters listed above. For example, the burst size can be determined as the number of virions released, on average, over the entire host population or per infected cell[205,206]. The MOI is of particular concern because the relative density of infectious virions to susceptible host cells per unit volume is crucial to inter-experiment comparisons. Yet the MOI is likely the most misinterpreted and misapplied metric[207]. 'Infectivity' conflates several steps of the infection process including attachment, entry, evasion of host defences, transcription and translation of viral proteins, genome replication, virion assembly, lysis and persistence in the environment. Mechanistic insight into viral physiology requires direct assessment of these individual steps. Ambiguous and incongruent definitions for viral growth parameters have developed in part due to limitations in applying specific methods across experimental systems. Some planktonic organisms grow poorly or not at all on solid media and the usual plaque assay for determining infectious titres must be substituted with an endpoint dilution assay[98]. Likewise, not all microbial eukaryotes exhibit the sudden lysis and release of viral progeny common to phage systems[98,203,208] (BOX 1), challenging the essence of the viral 'burst' measurement. The host range is usually reported as a binary metric (that is, host strains are either susceptible or resistant), but with advancements in the molecular tools used to interrogate virus–host interactions[209], a continuous spectrum of infection efficiency and/or a phylogenetic approach to susceptibility may be more appropriate. Whether or not conventional metrics of viral infection are reconsidered and revised, reliable cross-system comparisons of virus–host interactions depend on explicit communication of how key viral infection parameters were quantified, and, where appropriate, how and why system-specific proxies were implemented.

The ability to replicate infection conditions and observed interactions is crucial to identifying key environmental and physiological parameters that influence virus–host interactions. Likewise, inferences about the biogeochemical impacts of viral infection made from molecular characterization of dissolved organic matter[47,147] depend on the replication of infection conditions. It is challenging to reproduce virus–host interactions because the physiological states of both the host and the virus are dynamic and must be controlled. It may be practically difficult to reliably replicate complex phenotypes such as viral infectivity across multiple experiments or laboratories. In addition, host physiology is often defined operationally rather than biologically. For example, low host growth rates can be induced by acute and abrupt starvation or chronic limitation (through continuous culture), but each elicits distinct physiological and molecular responses, as shown for *Prochlorococcus*[210] and *Micromonas*[211] species cultures deprived of phosphorus. By comparison, inducing limitation of micronutrients such as iron may be more straightforward due to the buffering effect of chelating agents (that is, maintaining constant concentrations of free iron) even in batch cultures[212]. Crucially, key infection metrics are usually characterized during rapid host growth in dense cultures and may differ substantially in natural ecosystems, where lower host growth rates and cell densities will alter encounter rates and infection dynamics. Quantification of infection parameters under environmentally relevant conditions and in natural microbial assemblages is an important frontier in understanding virus–host interactions.

Traditional approaches for characterizing infection dynamics collect bulk measurements of cells and viruses, thereby producing population-averaged metrics that ignore spatial heterogeneity and cell-to-cell physiological variation. Consequently, the average properties of an infection may not reflect those experienced by individual cells, such as the MOI[207,213]. Another emerging frontier is the application of single-cell techniques, including microscopy and microfluidics-based approaches, to more accurately describe virus–host dynamics during infection. Continued development and widespread application of single-cell approaches[34,48,132,214] have the potential to resolve some of the uncertainties currently limiting our cross-system synthesis. Likewise, combining these techniques with emerging diagnostic markers of infection[44,50] holds much promise for improving our ability to detect and characterize infection in natural ecosystems.

encode metabolic functions that were formerly considered unique to cellular life[100,101]. Sugar metabolism and fermentation genes were identified in a giant virus of cosmopolitan green alga *Tetraselmis* spp.[102]. Additionally, putative microbial rhodopsin genes have been identified in the marine haptophyte *Phaeocystis globosa* virus PgV and in two putative eukaryotic algal virus metagenomic contigs for which the host is as yet unknown[103]. Rhodopsin and pigment biosynthesis genes were also found in an uncultivated virus of an uncultured choanoflagellate (predatory protist) by targeted metagenomics[23]. Using metagenomics, this study showed that rhodopsins are common components of giant virus genomes and demonstrated that the most common type has proton pumping activity when expressed in *E. coli*[23]. Further, a newly described family of heliorhodopsins, distantly related to known microbial rhodopsins, has also been identified in the Tara Oceans marine viral metagenomes[104]. Presumably, once expressed by the host, the viral rhodopsins function either to establish transmembrane proton gradients for ATP production (that is, energy conversion) or as light sensors, analogous to their microbial counterparts[105,106].

Viruses that infect non-phototrophic, chemoautotrophic bacteria and archaea also appear to manipulate host energy metabolism, but few have been experimentally characterized. Metagenomic analyses have revealed that viruses infecting SUP05 bacteria, a lineage of sulfur oxidizing and denitrifying Gammaproteobacteria common throughout the deep ocean[107], encode *dsrC*, a sulfur redox metabolism enzyme, in habitats that include hydrothermal vents and oxygen minimum zones[108–110]. Likewise, metagenomic evidence suggests that some viruses infecting another abundant marine chemoautotrophic group, the ammonia-oxidizing Thaumarchaeota, carry archaeal-like *amoC* genes that encode a subunit of the ammonia-oxidation machinery[110,111]. Recently, viruses that infect thaumarchaeon *Nitrosopumilus* spp. have been isolated, and although they lack *amoC* genes, they allow host ammonia oxidation to continue for several days post infection, which may enhance their productivity[15]. In all of these cases, the impact of continued host energy metabolism on viral productivity remains to be quantified.

Light can also affect viral dynamics beyond the host cell's energy budget (reviewed in REFS[112,113]), adding another layer of complexity to consider for time- and space-resolved models of viral biogeochemistry. For example, numerous cyanophages[114–116] and a virus of the haptophyte alga *E. huxleyi*[41] show reduced adsorption rates in the dark. Many phototrophs have circadian cell cycles where the time of day influences pools of nucleotides and other resources that could impact viral production[117]. Additionally, high light can reduce viral production in algae through cellular damage caused by reactive oxygen species[41,118], but the relationship between reactive oxygen species and viral production is complex[50]. Light also drives the decay of free viral particles in aquatic systems[119]. Thus, together with its influence on adsorption and viral production, the impact of light extends to non-photosynthetic microorganisms and likely contributes to the distinct depth distributions observed for viral populations in the oceans[120]. Light may also have a key role in governing daily rhythms in viral infection, which have recently been documented both in freshwater[121] and in coastal and open ocean[37,122,123] systems, reflecting the integrated effects of light on viral infection through both phototrophic energy metabolism and photosynthesis-independent mechanisms.

Macronutrient availability. Substrate limitation has the potential to alter viral production in both growth rate-dependent mechanisms (for example, number of ribosomes, and pool sizes of precursors and enzymes)[124,125] and growth rate-independent mechanisms (for example, direct substrate availability) (FIG. 2), depending on the needs of the host and the virus. Few empirical measurements of viral elemental composition have been made, and these values are likely to vary with virion size, morphology and the presence of a lipid envelope. Predictions of stoichiometry for phage[126] and algal virus[127] particles suggest enrichment in nitrogen and phosphorus compared with host cells, implying that viruses must concentrate these elements to reproduce. But to what extent are viruses restricted to recycling intracellular nucleotides and amino acids, compared with de novo synthesis using newly acquired nutrients? Across virus–phytoplankton systems, the host genome size is a strong predictor of viral burst size[128,129], suggesting that viral production depends, in part, on intracellular nucleotide pools. Consistent with this, radiotracer experiments with several marine phage–host pairs suggested that the phosphorus in phage DNA came mostly from host nucleotides[130]. If viruses are limited by intracellular phosphorus availability, then it should be possible to modulate the burst size by changing cellular carbon:phosphorus ratios independent of the growth rate — indeed, this was observed in a freshwater virus–alga system[127]. Thus, at least in some systems, host resource pools have the potential to constrain viral productivity.

At the same time, there is also evidence that some marine viruses can take advantage of resources outside the host cell. Early studies of *E. coli* phages demonstrated that viral replication requires extracellular nitrogen and phosphorus[58], even when the hosts are not starved, as the bulk of coliphage DNA nitrogen is extracellular in origin[131]. Recently, isotopic labelling experiments in the haptophyte *E. huxleyi* and marine *Synechococcus* revealed a similar reliance on extracellular nutrients by tracing the incorporation of carbon and nitrogen into viral particles[132] or of nitrogen into specific viral proteins[52]. Although data are limited, for phosphorus[133] and nitrogen[52], phages infecting *E. coli* and *Synechococcus*, respectively, appear to source relatively more nutrients from the host cell biomass during the early stages of infection, and shift to extracellularly derived nutrients as the infection proceeds. Which pools of host biomolecules are accessible to the virus, which host biomolecules are potentially off-limits (for example, ribosomes) and how this accessibility is controlled are all unknown. Ultimately, the overall balance between intracellular and extracellular resources for viral replication likely varies with environmental nutrient availability as well as with the host growth rate and physiological state at the time of infection.

Viral exploitation of extracellular resources, presumably to alleviate a resource bottleneck during infection, is also reflected in the variety of AMGs related to nutrient acquisition. Many marine cyanophage isolates encode transport machinery for phosphorus, in particular the substrate binding protein PstS and, less commonly, a protein bearing similarity to a putative alkaline phosphatase[134]. Cyanophage phosphorus-uptake genes are upregulated during infection of phosphorus-starved host cells[33] by the host PhoBR two-component system[135], which activates the expression of genes for phosphorus acquisition and metabolism in response to phosphorus limitation[136]. Hence, the phage is able to recognize and specifically respond to phosphorus limitation inside the host cell. Cyanophage-encoded phosphorus-acquisition genes tend to occur more frequently in viral genomes from phosphorus-limited regions of the oceans[134,137]. In these regions, cyanobacterial host cells likely have reduced intracellular phosphorus content[138,139], presumably forcing phages to rely more heavily on extracellular uptake to replicate. Similarly, a haptophyte algal virus isolated from a bloom of *E. huxleyi* in the English Channel encodes a phosphate permease that is absent in a related strain isolated from a Norwegian fjord[99,140], and this gene may help facilitate infection in phosphorus-limited waters.

Transporters for both phosphorus and nitrogen are also present in a subset of viruses that infect prasinophyte algae, interestingly in hosts that generally come from nutrient-replete environments[141,142]. Although there is much unexplored eukaryotic viral diversity in the oceans, the only nitrogen transporter identified among all sequenced viral genomes to date is encoded and expressed by the virus OtV6, which infects the picoeukaryotic prasinophyte alga *Ostreococcus tauri*[141]. Surprisingly, both the host and the virus were isolated from an extremely nitrogen-rich environment, an oyster lagoon in coastal France. The viral protein is related to a broad family of ammonium transporters common to all eukaryotic life, and, in this case, appears to have been acquired directly from the algal host. Functional characterization indicates that the protein broadens the diversity of nitrogen sources that can be accessed by the host and increases substrate affinity over the host transporter[141].

By contrast, AMGs encoding nitrogen transport proteins are absent in phages, at least to date. This absence, along with evidence that phages acquire substantial extracellular nitrogen, suggests that the existing host cell nitrogen uptake machinery and recycling of intracellular stores are generally sufficient to meet the demands of viral production. One major pool of nitrogen that cyanophage may be able to access is phycobilisomes, which can account for up to 50% of the soluble protein in a cyanobacterial cell[143]. Proteins involved in phycobilisome degradation have been identified in several freshwater cyanophage genomes and marine metagenomes, and in some cases biochemically validated[144–146], and their degradation products have been observed in viral lysates[147]. These proteins may help supply nitrogen for viral production, although how viruses balance their need for substrates with their need for continued host photosynthesis and metabolism is unknown.

Micronutrient availability. Besides nitrogen and phosphorus, viruses also appear to influence cellular pathways related to the synthesis of cofactors and other small molecules, highlighting potential bottlenecks in viral production. One such molecule is cobalamin (vitamin B_{12})[148], a cofactor used in the enzymatic reduction of ribonucleotides to deoxyribonucleotides for viral replication. Many marine bacteria produce vitamin B_{12} de novo, whereas eukaryotic phytoplankton do not, making the exchange of these compounds an ecologically important cross-kingdom microbial interaction[149,150]. Several cyanophages and an archaeal virus encode a putative *cobS* gene[134,151], the product of which is predicted to catalyse the last step of vitamin B_{12} synthesis in bacteria. However, the cyanophage *cobS* is phylogenetically distinct from the host gene, suggesting that it was not acquired directly from its host and that it may have different functional properties[152]. As with most AMGs described above, the viral *cobS* protein product has not been biochemically characterized and hence its role in vitamin B_{12} cycling and viral production remains speculative.

Trace metals, in particular iron, are known to limit phytoplankton growth in much of the global ocean[153]. Viral particles are not known to directly incorporate trace metals and other micronutrients, although it has been proposed that viral particles can act as important metal ligands[154]. Trace metals may impact viral production indirectly by controlling the overall host growth rate or the activity of specific cofactor-requiring enzymes. Iron limitation has been shown to reduce the burst size in algal *P. globosa* and *Micromonas* species[73]. However, high trace metal concentrations can also be toxic and inhibit virus replication, as seen for copper and viruses infecting the marine haptophyte *E. huxleyi*[155]. Thus, trace metals undoubtedly impact host physiology and thereby viral infection dynamics, but the molecular mechanisms and ecosystem-level consequences of trace metal–virus interactions are unknown.

Functional divergence in host and viral metabolism. As our catalogue of putative AMGs continues to grow, there is greater need for biochemical characterization to assess viral contributions to the metabolism of infected cells and, by extension, to biogeochemistry. Even for homologous proteins shared by the host and the virus, the version that maximizes viral fitness may not necessarily maximize host fitness, and vice versa, given the different biochemical environments of infected and uninfected cells, and distinct constraints acting on cells and viruses. Hence, homologues encoded by the host and the virus may have very different substrate specificities, kinetics or other properties. Indeed, AMGs characterized to date are often divergent from their host homologues. Examples from cyanophages include phycoerythrobilin synthase (PebS), which combines the activities of two host enzymes[89]; transaldolase (TalC), which is both much shorter in length and less efficient than the host version[46]; and phycobiliprotein lyase (CpeT), which does not appear to catalyse the same reaction as the host version[156]. Examples from algal viruses include the viral-encoded ammonium transporter discussed above[141] and viral serine palmitoyltransferase (vSPT),

an enzyme involved in sphingolipid biosynthesis that differs in substrate specificity from the host version and thereby alters the chemical nature of the infected cell[42]. At an even finer scale, biochemical diversity of vSPT enzymes is evident among viruses that infect a common *E. huxleyi* host, and these biochemical differences can, in turn, influence competitive interactions among viral strains[157]. Functional characterization of viral AMGs, through enzymological[46], physiological[42] and genetic approaches, is essential for understanding how infection alters cellular metabolism, and may point towards new molecular diagnostics of infection that can be applied in natural ecosystems[48].

Viral impacts on biogeochemical cycles

The biogeochemical influence of viruses begins at the moment of infection, due to metabolic remodelling of the host cell[8], and continues even after cellular lysis, as the viral progeny and cellular debris disperse into the surrounding environment where they become food for the wider microbial community, catalyse biogeochemical transformations and initiate new infections[4,158,159]. Competition for resources among the members of this microbial community, in turn, determines the nutrient status and physiological state of the next host cell that viral progeny will ultimately infect. Numerous field studies, primarily in aquatic ecosystems, have documented nutrient stimulation of primary and/or bacterial productivity that is accompanied by increases in viral productivity or abundance[160–162]. It is becoming increasingly clear that viral reproduction in microbial ecosystems is both influenced by and is a contributor to biogeochemical processes at spatial and temporal scales well beyond the infection of individual host cells.

Nutrient recycling versus export. A prevailing concept in considerations of the biogeochemical impact of marine viruses has been the 'viral shunt'[4,5]. This hypothesis emphasizes that lytic infections return lysed host cell biomass back to the dissolved phase, as dissolved organic matter (DOM), which in turn regenerates nutrients for microorganisms and 'shunts' them away from grazers and higher trophic levels (FIG. 3). Although measuring the strength or large-scale impact of the viral shunt is challenging, modelling suggests that it can increase overall productivity of marine ecosystems by enhancing the efficiency of nutrient recycling that enables the majority of marine primary productivity[163], a feature that might be particularly important during nutrient-stimulated bloom events[160]. An ecosystem population dynamics model has recently been used to assess the viral shunt from mortality measurements in the California Current ecosystem, calculating carbon transfer from primary producers to viruses, grazers and the DOM pool[164], and silicon limitation of diatom blooms in this ecosystem has been suggested to accelerate viral termination of the bloom and thereby strengthen the viral shunt[74].

Owing to extensive biochemical remodelling during infection, DOM released by the infected cell or by viral lysis appears compositionally distinct compared with that produced through prey cell breakage during grazing ('sloppy feeding') or exudation by growing phytoplankton[47,147,165]. Although data are limited, it appears that cell wall degradation and stimulated nucleotide synthesis[47], exopolysaccharide degradation[166], lipid remodelling[42,48] and specific proteolysis of abundant protein complexes[147] contribute to these distinct DOM signatures. Relative enrichments of amino acids[47,167] and proteinaceous material[147,165,168] have been observed in multiple types of viral lysate, suggesting that viral lysis may be a particularly important mechanism for nitrogen recycling through the viral shunt[169]. Similarly, viral lysis has been shown to release iron in highly bioavailable forms which can be taken up by other microbial cells[170,171], and organic phosphorus released from viral lysis has been shown to support the phosphorus demand of uninfected but phosphorus-limited cultures of marine *Vibrio* spp.[172]. In addition to these labile components, viral lysis is thought to yield long-lived, recalcitrant DOM as well[173]. To date, most studies of viral effects on DOM have been performed in nutrient-replete laboratory cultures; how these DOM signatures covary with cellular composition, for example, as elemental stoichiometry shifts across resource gradients[174], remains to be tested. More recently, evidence has emerged that viral infection may actually enhance, rather than reduce, carbon export from surface to deep waters, prompting the notion of a 'viral shuttle'[175,176] (FIG. 3). This viral shuttling might happen either because infected cells and/or lysis products aggregate and sink at higher rates, or due to enhanced grazing on viral particles and/or infected cells. Virus-induced production of aggregates is attributed to proteinaceous material in the diatom *C. tenuissimus*[168]. In other hosts, viral infection stimulates production of TEPs — the 'marine snow' known to act as a glue for particulate matter and to enhance aggregation into larger and denser particles[45,165]. Field observations of several mesoscale (~100 km) *E. huxleyi* blooms in the North Atlantic showed that TEP concentrations increased during the early stages of infection, and infected cells were preferentially entrained in sinking aggregates; these aggregates were ballasted by the extracellular calcium carbonate scales characteristic of this host[44,177]. These sinking particles shuttle nutrients out of the surface ocean, which potentially makes them available to larger grazers in the mesopelagic and/or shifts viral lysis and shunt-style nutrient recycling deeper into the water column. The calcified scales covering *E. huxleyi* cells appear to protect some strains from viral infection and scale fragments act as effective adsorbers of viral particles; the viruses, in turn, are able to induce as-yet-unidentified infochemicals that reduce host calcification and render them more susceptible to infection[178], suggesting that export through the viral shuttle can depend on the complex interplay between viral infection and carbonate ballast production.

There is also evidence that two major death processes for aquatic microorganisms — viral infection and predator grazing — can interact in unexpected ways. Virus-infected *E. huxleyi* cells were found to be grazed at higher rates than uninfected cells by the dinoflagellate *Oxyrrhis marina*[179], but at lower rates by the copepod *Acartia tonsa*[180]. Copepods ingested infected *E. huxleyi* cells at high rates under both laboratory conditions and during

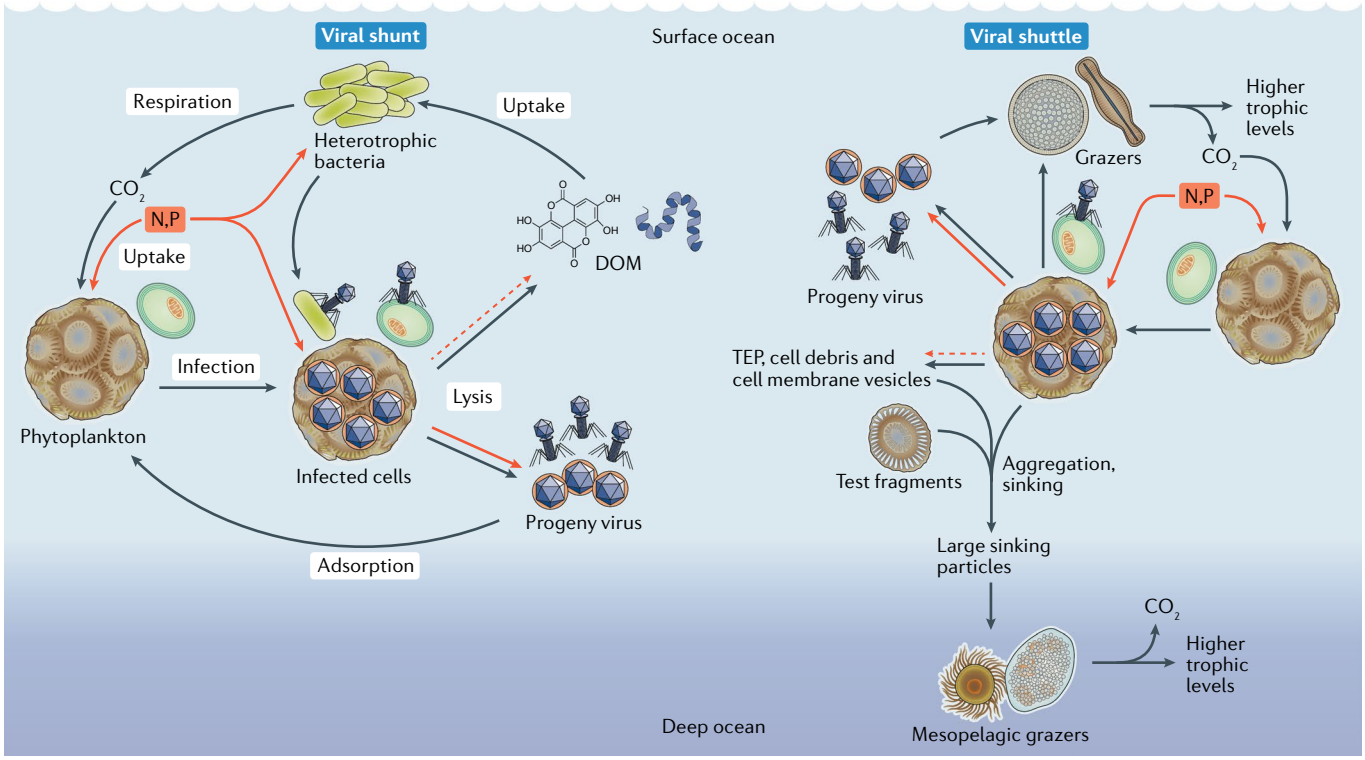


Fig. 3 | **The role of viruses in marine carbon and nutrient cycling.** Schematic of two contrasting scenarios for carbon and nutrient fluxes driven by viral infection of primary producers in aquatic ecosystems. The 'viral shunt' (left) emphasizes release of cellular constituents to the dissolved organic matter (DOM) pool, which fuels heterotrophic microbial production and nutrient recycling through the microbial loop, at the expense of grazing and higher trophic levels. The 'viral shuttle' (right) describes ways in which viral activity could facilitate carbon export to the deep ocean, including direct grazing on viral particles and infected cells, as well as particle aggregation and sinking driven by the release of lysis products and/or virus-induced alterations in host physiology such as transparent exopolymeric polysaccharide (TEP) production. An oversimplification here is that grazers are also known to be infected by viruses (not depicted). Orange arrows indicate uptake of macronutrients (nitrogen and phosphorus), and their preferential incorporation into protein-rich and nucleic-acid-rich viral particles, leaving relatively nitrogen-depleted and phosphorus-depleted byproducts of infection and lysis (dashed arrows).

a bloom event in the North Atlantic, which could act as a vector for viral dispersal[181]. Marine viruses themselves are actively ingested by multiple types of predators[181–183], indicating that viral particles can have a role in the 'classical' marine food web. The rate of removal of virus particles by aquatic protists appears to depend on the specific virus and host strains[183], as well as the feeding mode of the protist[158]. Taken altogether, it seems that the viral shunt and the viral shuttle likely operate simultaneously in many sunlit aquatic ecosystems, their relative importance waxing and waning depending on host traits (for example, cell size or the presence of a ballast), viral effects on metabolism (for example, TEP production) and environmental conditions. Diagnostic biomolecular tools for some aspects of these processes are emerging[48,177] and will provide novel and needed constraints on the rates and variability of viral biogeochemistry.

Viruses in global biogeochemical models. At this point, we have outlined mechanistically and conceptually how viruses potentially alter biogeochemistry through metabolic reprogramming and lysis. At the cellular level, metabolically detailed models of infection physiology have been constructed for a few virus–host model systems[40,41] and could be expanded to others. However, virus impacts on ecosystem-level processes are just beginning to be incorporated into biogeochemical models[163,164,184,185]. A major caveat is that models of viral infection strategies and replication dynamics in natural communities are often based on laboratory studies of select virus–host model systems, in conditions that are physically, chemically and biologically unrealistic. Because our experimental systems are so limited, it has been challenging to extract common principles of infection that can serve as a foundation for improved ecosystem models. Accordingly, none of the models used to predict global responses to CO_2 inputs for the Intergovernmental Panel on Climate Change Assessment Report[186] include an explicit representation of viruses[187]. Instead, some models implicitly represent viral activity, for instance, within the conversion of particulate nutrients to dissolved nutrients[153,188,189]. Yet, given the multifarious ways in which changes in viral activity could either amplify or dampen climate forcing — including influencing the biological carbon pump in the ocean or the production of marine aerosols and reactive trace gases[190], along with the temperature sensitivity of virus–host interactions[68,69] — a mechanistic, quantitative

Euphotic zone
The uppermost layer of water in a lake or ocean characterized by enough sunlight to support photosynthetic carbon fixation.

framework for including viruses in ecosystem and large-scale biogeochemical models is needed. Developing such a framework requires substantial knowledge from both laboratory and field studies, which to date exists for few virus–host systems[157].

Treatment of infected host cells as a separate functional class in biogeochemical models may not be necessary for all purposes, but with the expanding appreciation of how extensive and prolonged remodelling during infection can be, its integration into large-scale productivity models seems warranted. For instance, the global impact of cessation of CO_2 fixation during phage infection of marine cyanobacteria could amount to several petagrams of carbon per year[82], although this estimate does not account for indirect stimulatory effects of infection on productivity[163]. One challenge to achieving this effectively may be the fact that physiologically distinct infection strategies can be pursued by closely-related viruses infecting the same host[45,191,192], so there may be multiple, metabolically distinct 'infected host types' per 'uninfected host type', which could lead to a rapid expansion of model complexity, without necessarily providing better predictive power or greater mechanistic insight. These challenges underscore the importance of elucidating the overarching principles and commonalities that govern viral metabolic remodelling during infection and its consequences for processes such as nutrient recycling, particle aggregation and grazing.

An important area of future exploration is the effect of viruses on the major element stoichiometry (that is, carbon:nitrogen:phosphorus ratios) of organic matter exported from the euphotic zone of the ocean. The export ratios of these elements determine the efficiency of the biological pump that stores vast amounts of carbon in the ocean's deep interior. The relatively high concentration of carbon-rich exopolysaccharides in some infected hosts and viral lysates[44,45,177] would be expected to enhance carbon:nitrogen or carbon:phosphorus ratios in exported organic matter resulting from viral infection; however, other observations that carbon is remineralized more quickly than nitrogen and phosphorus in lysate would suggest that viral activity actually decreases carbon export[171]. Although both observational and modelling studies have shown that changing the elemental stoichiometry of biological particulate material can have a major impact on global biogeochemical cycles[174,193,194], whether viral infection alters the stoichiometry of export on large scales is relatively unexplored. Understanding this potential alteration will require in-depth tracing of nutrient sourcing and flows through the infection process[52] as well as field measurements of virally mediated export events[177] in order to quantify the extent and mechanism of viral alteration of export fluxes.

Conclusions and outlook

Viral replication involves metabolic remodelling of the infected host cell — often, although not always, to a drastic degree — and this remodelling creates a functionally new type of cell for the period of the infection[7,8]. Therefore, the biogeochemical impacts of viral infection are not limited to host cell killing and the release of lysis products, but begin the moment the viral genetic material enters the cell. Although we have focused on lytic infection in this Review, these impacts are likely to be very different depending on the infection strategy, and 'alternative' modes beyond classic lytic infection are probably widespread in nature. This raises the sobering possibility that we have yet to experimentally characterize the infection dynamics most relevant to natural systems. Nevertheless, recent studies have begun to shed light on our blindspots by exploring a broader diversity of virus–host systems, physiological states and environmental conditions, and by beginning to assess viral infection rates and impacts in the wild. Expanding these efforts is essential if we are to elucidate fundamental principles that can guide our efforts to include viral activity in global biogeochemical models. Given the power of viruses to reprogramme cells, and potentially ecosystems, integrating them into global models is an important step towards better predicting the consequences of regional- and global-scale environmental change.

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