Patterns of virus growth across the diversity of life

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Abstract
Although viruses in their natural habitats add up to less than 10 percent of the biomass, they contribute more than 90 percent of the genome sequences (1). These viral sequences or "viromes" encode viruses that populate the Earth's oceans (2, 3) and terrestrial environments (4, 5), where their infections impact life across diverse ecological niches and scales (6, 7), including humans (8-10). Most viruses have yet to be isolated and cultured (11-13), and surprisingly few efforts have explored what analysis of available data might reveal about their nature. Here we compiled and analyzed seven decades of one-step growth and other data for viruses from six major families, including their infections of archaeal, bacterial, and eukaryotic hosts (14-191). We found that the use of host cell biomass for virus production was highest for archaea at 10 percent, followed by bacteria at 1 percent, and eukarya at 0.01 percent, highlighting the degree to which viruses of archaea and bacteria exploit their host cells. For individual host cells, the yield of virus progeny spanned a relatively narrow range (10-to-1000 infectious particles per cell) compared with the million-fold difference in size between the smallest and largest cells. Further, healthy and infected host cells were remarkably similar in the time they needed to multiply themselves or their virus progeny. Specifically, the doubling time of healthy cells and the delay time for virus release from infected cells were not only correlated ($r = 0.71$, $p < 10^{-10}$, $n = 101$); they also spanned the same range from tens of minutes to about a week. These results have implications for better understanding the growth, spread and persistence of viruses in complex natural habitats that abound with diverse hosts, including humans and their associated microbes.

Insight Box
A major challenge in biology is to discover patterns of behavior that describe not just one species, but many. By compiling and analyzing data from over 100 virus-host pairs, we found that cells that take more time to divide also take more time to produce virus progeny. In other words, the same cell type infected with different viruses will release viral progeny on the same

time scale. This relationship underscores the extent to which virus production across the domains of life is coupled with biosynthetic processes needed for cell growth.

Keywords: scaling; biomass; virome; one-step growth, burst size, delay period, kinetics; archaea, bacteria, eukarya

Introduction

The single-cycle or one-step growth behavior of viruses during infection of susceptible cultured host cells have served as a key measure of productive virus infection for 90 years. In pioneering work of 1930, Krueger and Northrop employed a virus or bacteriophage of *S. aureus* to show that host cellular growth was needed in order for phage to grow, that cell lysis correlated with the extracellular appearance of more than 100 infectious phage units per cell, and these phage units grew exponentially with time (192). Within a decade, Ellis and Delbrück refined and extended these methods to study a phage of *E. coli* (193). Later advances in animal tissue and cell cultivation enabled one-step growth measures of eukaryotic viruses (160, 194). Following the discovery and culture of halophilic hosts, such as *Halobacterium cutirubrum* and its phage, one-step growth was measured for a virus from the Archaea (20), the third domain of life.

In general, the one-step growth refers to the level of extracellular virus particles released from infected cells as a function of time post infection, features that may be quantitatively defined by a delay period and burst size (**Fig. 1a**). The variation of such parameters with specific virus strains, host cells and environmental factors reflect the diversity and breadth of virology studies. For example, measures of one-step growth have been used to quantify growth attenuation in gene-order variants of an RNA virus for vaccine applications (195, 196), to quantify how changes in pH, temperature and media constituents affect growth of lactic acid bacteria and their phage (197), and to show how the physiological state of *E. coli* growth impact the timing of phage production (35). Further, one-step growth measures of phage-induced killing of marine bacteria have revealed roles viruses play in biogeochemical and ecological processes (73, 77, 80, 116, 198, 199).

Scaling "laws" arise from patterns or regularities in data from natural or engineered systems that may span many orders of magnitude (200). In animal biology, for example, Kleiber compiled and compared metabolic rates, from mouse-to-whale, where animal masses span 10-to-10^8 grams, and he found that their metabolic rates were proportional to the ¾ power of their mass (201). In virology, Cui *et al.* compiled data from 88 viruses on particle volumes and genome lengths, which span 10^4–fold and 10^3–fold, respectively, and they found volumes scaled with genome length to the 1.5 power (202), and we found comparable scaling (see Supplementary Information). The archival literature contains a large and growing wealth of quantitative data on cells and their infections by viruses, which were tapped for the current study.

Results and Discussion

We initially identified archival one-step growth data for 101 virus-host systems representing diverse virus classifications based on their genomes: dsDNA, dsRNA, ssDNA, ssRNA(+), ssRNA(-) and ssRNA-RT, summarized in **Fig. 1b** and **Table 1**. The number of infectious virus progeny (or plaque forming units, PFU) produced per infected host cell provides at its maximum value an average burst size or PFU per cell. In the absence of information about the number of host cells infected, virus growth curves were quantified based in most cases on PFU per ml, $TCID_{50}$ per ml or FFU per ml (the number of focus-forming units per volume of supernatant), which we defined as the viral yield. All data were used as reported; no assumptions were made regarding loss of PFU from secondary binding of virus progeny particles to cells or cell fragments, particle aggregation, or degradation of infection activity.

The virus growth kinetics reported on a per cell basis spanned about 100-fold range of burst sizes from 10 to 1000, with delay times varying from tens to thousands of minutes. To visualize the broad span of one-step growth curves, data were plotted on logarithm base 10 scales (**Fig. 1c**). For growth kinetics reported on a per volume basis, yields spanned from hundreds to tens of billions of PFU per ml, and delay times varied from tens to tens of thousands of minutes (**Fig. 1d**). Note that the left-most data points on some curves, which correspond with the titers of the earliest samples following the start of infection, appear in some cases to be at high titers of 10^7-10^8 PFU/ml; these likely reflect residual viral inoculum and cell levels (unreported) of 10^8 cells/ml or fractional virus particles per cell. We compared the burst size (PFU/cell) and yield data (PFU/ml, $TCID_{50}$/ml and FFU/ml) by converting their values to log scale and plotting their quantiles against each other. The linearity of the resulting quantile-quantile plot (**Fig. 1e**) provides evidence that the burst-size and yield data were similarly distributed. Based on these similar distributions, we combined the burst-size and yield data by normalizing each data set to its maximum burst size or yield, respectively, so normalized virus production ranged from zero to unity, while times post-infection encompassed the full range of all 101 one-step growth trajectories (**Fig. 1f**).

To quantify how virus growth might depend on host-cell physiology or metabolism, one may consider the amount of material consumed by the production of infectious progeny viruses in comparison with the starting host cell material. Specifically, we estimated what fraction of the host cell volume would be occupied by all the viruses making up a burst of its virus progeny. Such volumes can be employed as a proxy for biomass and thereby reflect how the cell's resources are reclaimed for virus production(203). We found that archaea used the largest fraction of resources for virus production at 10 percent, while bacteria and eukarya were about 10-fold to 1000-fold lower with average volume fractions of 6.5×10^{-3} and 5.0×10^{-5}, respectively (**Fig. 2**). Moreover, bacteria used a maximum of 35 percent of their cellular volume fraction to

make virus; archaea and eukaryotes followed with 11 percent and 1 percent, respectively. Others have estimated volume fractions for eukaryotic virus production of up to 5 percent (203) based on measures of simian immunodeficiency virus (SIV) RNA sequences(204), not functional viral RNA or infectious virus particles. For every 350 viral genomes or virus particles in SIV and HIV infections, it has been estimated that only one virus particle is infectious (205). Thus, the actual volume fraction for SIV and HIV infections may be closer to (5 percent)/350 or 1.4×10^{-4}, which is closer to our estimate of 5.0×10^{-5} for eukaryotic viruses.

As described in our Methods, the one-step growth data were initially used to estimate four parameters: host cell volume (H_V), host cell doubling time (H_T), infected cell burst size or yield associated with virus production (I_{BS} or I_Y), and infected cell delay time associated with virus release (I_T). Distributions of host cell volume (H_V) spanned nearly one million-fold (10^6 or six orders of magnitude) from the smallest bacterial cell to the largest eukaryotic cell, with bacteria spanning almost 10^5-fold and archaeal cells centered with the distribution of bacterial volumes (**Fig. 3a**). Distributions of cell doubling times (H_T) spanned a 10^3-fold range with bacteria represented across the full range, where the longest bacterial doubling times were represented by cyanobacteria, overlapping with the 10^2-fold range of doubling times exhibited by eukaryotic cells (**Fig. 3b**). Both sets of host cell parameters, H_V and H_T, exhibited two peaks in their distributions, represented by bacteria and eukarya centered at lower and higher values, respectively. In contrast with these double-peaked distributions of normal-cell characteristics, parameters associated with the production of viruses by infected cells exhibited distributions with single peaks. Specifically, burst size of virus progeny (I_{BS}) spanned a nearly 10^3-fold range with significant overlap of the distributions from infected bacteria and eukarya (**Fig. 3c**), and the distribution of delay times associated with the release of viral progeny (I_T) spanned a similar 10^3-fold range (**Fig. 3d**).

To explore potential relationships between measures of normal and infected cells, we determined correlation coefficients between all six pairs of cell and infected cell parameters, as shown in **Fig. 3e** (see Supplementary Information for expanded extents of correlation between parameter pairs). A correlation was found between the host cell parameters H_T and H_V ($r = 0.63$, $p < 10^{-5}$, $n = 48$), shown in **Fig. 3f**, as anticipated from laboratory observations, where smaller bacteria typically grow with shorter doubling times (or higher rates) than larger mammalian cells. Based on our past measures of virus production from relatively large eukaryotic and small bacteria cells (35, 196, 206), we expected that larger cells would in general produce more virus progeny. However, as shown in **Fig. 3g**, little correlation was found between burst size and host cell volume ($r = 0.26$, $p = 0.07$, $n = 47$). Instead, we found that delays in the release of virus progeny correlated with the host cell doubling time ($r = 0.71$, $p < 10^{-10}$, $n = 101$), as shown in **Fig. 3h**. (Note that the size of the parameter set for burst sizes is more than two-fold smaller than the set for delay times because they correspond with the data from **Fig. 1c** and **Fig. 1f**, respectively.) We

explored further relationships between rates of virus production and rates of host cell growth, defined using volume equivalents or genome size equivalents, but no correlations were apparent (see Supplementary Information).

Why might cells with longer doubling times (slower growth rates) release virus with longer delays? In a study of phage T7 one-step growth on *E. coli* bacterial hosts, lower rates of cell doubling correlated with lower capacities and rates of protein synthesis (35), a resource that is essential for both cell growth as well as virus replication. The effects of cellular resources on virus growth have yet to be systematically and quantitatively studied for a specific system or across a diversity of virus-host-cell systems. However, progress has been made toward developing data-driven mechanistic models of virus one-step growth for diverse viruses (207-213), as recently reviewed (214). Variation in the productivity of infections of bacterial and mammalian viruses have been found to depend on physiological state of the host cell, with more rapid bacteria growth and pre-division stages of the mammalian cell cycle associated with higher virus yields and shorter times to production of intracellular virus (35, 182, 215). Extensions of such studies to the current work may be to quantify the capacity and rate of protein synthesis for cells of varying size (or physiological state) across the domains of life. The dependence of all viruses on protein synthesis and cell-to-cell differences in the capacity and rate of protein synthesis across diverse host cells may correlate with their associated delay times to virus release when infected.

By employing one-step growth data, our analysis is limited by what it can reveal about viruses in nature. First, in diverse host cells, there can be a complex interplay between ecological and biological factors in both host cellular and virus growth (216), including the prevalence of viral co-infections of the same host (217), infectious virus aggregates (218), defective interfering particles (219), or collective properties of infectivity (220), features not usually considered by one-step growth kinetic behavior measured in the lab. Second, we did not include viruses that are latently carried along with their host genomes; such viruses may contribute a significant fraction of viruses detected by metagenomics analysis (221). Third, longer delays in the release of virus particles from slower doubling cells might well depend on factors beyond the biosynthetic capacity of the host, such as the more complex structure and mechanisms of intracellular transport associated with infections of slower doubling eukaryotic cells (222). Finally, we did not consider any viruses that infect plants, although plants dominate in their contribution to the global biomass (223). Plant viruses typically spread from one infected cell to the next without an extracellular phase (224), or they are transmitted between plant hosts by insect vectors, so one-step growth measures are not used to study viruses that infect plants.

While the current work has focused on virus growth at the level of their cell-level hosts, the growth and spread of viruses in nature entail higher levels of complexity. For example, natural

infections often engage host defensive responses: anti-phage restriction enzymes, acquired immunity(CRISPR) in bacteria, or interferon-mediated innate immune signaling in animal host cells. Such host responses can be triggered on similar time scales as the virus infection, impacting the timing and productivity of subsequent rounds of infection. The mechanisms and dynamics of infections over multiple cycles, within host tissues, and entailing transmission between hosts, combine both physical and biological processes (225, 226). For a limited number of virus-host systems, the dynamics of transmission and immune activation have suggested scaling with host body size (227-229), and efforts for more extensive compilations of data and their analysis, particularly for viruses of human health relevance have begun (230). We anticipate that emerging automated approaches to identify and extract data from the archival literature will in coming years facilitate data-intensive efforts to reveal further facets of virus growth and infection behaviors shared across diverse hosts.

CONCLUSION

The diversity of cellular life is reflected in part by the range of cell sizes and growth rates across the eukarya, archaea, and bacteria. The largest cells occupy a million-fold larger volume than the smallest, and the slowest growing cells double their numbers at a rate that is 100-to-1000 fold less than the fastest. When such cells are infected by viruses, cell size has little impact on the outcome; larger infected cells do not make more virus progeny. Instead, timing appears to be important; cells that normally take longer to double in number, when infected, also take longer to make virus.

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METHODS

Data extraction and estimation of parameters. Healthy host-cell volumes (H_V) and viral particle volumes (V_V) were estimated from their linear dimensions. For example, *Staphylococcus carnosus*, a Gram-positive bacteria used in the ripening of dry sausage, appeared from microscopy images to be spherical with an average diameter of about one micron or volume of $(\pi/6)\times(1\ \mu m)^3$ or 0.523 μm^3 (32). Healthy host-cell doubling times (H_T) were either directly reported values, or they were calculated from reported specific growth rates or generation times:

$$cell\ doubling\ time\ = \frac{ln(2)}{specific\ growth\ rate}\ = ln(2) \times\ generation\ time \qquad (1)$$

Data from virus one-step growth curves were extracted from archival figures using Engauge Digitizer Software (http://markummitchell.github.io/engauge-digitizer/). Parameters of one-step growth were estimated using MATLAB (Mathworks, Natick, MA). Specifically, virus burst size (I_{BS}) or virus yield (I_Y), were estimated using an arithmetic average of all virus titer measures within 95 percent of the maximum reported value. The delay period (I_T) was estimated by linear interpolation between data points of the one-step growth data plotted on a linear scale; the delay period corresponds with the time where virus titer has risen to 50 percent of the virus burst size.

Quantile-quantile analysis. The most informative population measure of one-step growth behavior for production of infectious virus progeny is the average number of plaque-forming units per cell or (PFU/cell) because it can provide the average cell productivity across the population of cells. Less informative, but still valuable, are kinetic measures from synchronized infected cells that do not quantify production of infectious virus particles on a per cell basis, for example: the number of plaque forming units per volume of culture supernatant (PFU/ml), the number of focus-forming units per volume of supernatant (FFU/ml), or the concentration at which 50 percent of the cells are infected by a dilution of sample, also called the tissue-culture infectious dose or ($TCID_{50}$/ml). A quantile-quantile or Q-Q plot enables one to assess whether two data sets arise from a similar or common population. The method compares the population distribution of one data set against the distribution of other data set; the lowest 10 percent of the first data set is plotted against the lowest 10 percent of the second data set, and such plotting is carried out from the lowest to the highest deciles (or more generally, quantiles) of each data set. If the distributions are linearly related, then their Q-Q plot will appear linear. For our extracted one-step growth curves we divided the data into two sets: the first based on measures of PFU/cell (**Fig. 1c)** and the second based on all other measures, including PFU/ml, FFU/ml and $TCID_{50}$/ml (**Fig. 1d)**. Then, virus burst size (I_{BS}) and virus yield (I_Y), were extracted as 95 percent of the maximum reported value of each curve in each data set, and both of the resulting

datasets were sorted based on magnitude; we used the qqplot function in MATLAB to calculate Q-Q plots for I_{BS} and I_Y, as shown in **Fig. 1e**.

Composite parameters. Host-virus interactions may be studied by estimating the level and rate of viral material production. We defined several composite parameters to describe collective viral genomic and molecular material: total viral genomes using the product of infection burst size and viral genome size ($V_{GS}^{tot} = I_{BS} \times V_{GS}$), and total viral volume using the product of infection burst size and viral particle volume ($V_V^{tot} = I_{BS} \times V_V$). Furthermore, we can approximate the time scale of viral production using infection delay time (I_T); the total viral genome production rate (V_{GS}^{tot}/I_T) and total viral volume production rate (V_V^{tot}/I_T) were defined accordingly. Similarly, we approximated the time scale of host cell reproduction using host cell doubling time (H_T); the host cell genome production rate (H_{GS}/H_T) and host cell volume production rate (H_V/H_T).

Statistical analysis and visualization. Linear regressions were estimated by least squares methods and two-tailed t-tests were applied using MATLAB. They were applied to all the systems for which relevant data were available.

Since parameter values often spanned many orders of magnitude, they were reported as their geometric averages with geometric standard deviations instead of arithmetic averages and standard deviations used when values are the same order of magnitude. Geometric average (μ) and geometric standard deviation factor (G) are defined as:

$$\mu = \sqrt[n]{\prod_{i=1}^{n} x_i} \tag{2}$$

$$G = exp\left(\frac{1}{n-1}\sum_{i=1}^{n}(ln(x_i) - ln(\mu))\right) \tag{3}$$

where n is sample size, and x_i is sample value.

Following Kirkwood (231), the uncertainty of the parameters was estimated and reported as [μ÷G, μ×G].

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