FEATURE ARTICLE

The Big Evolution of the Little Phage: Teaching Biological Interdependency Through a Virus

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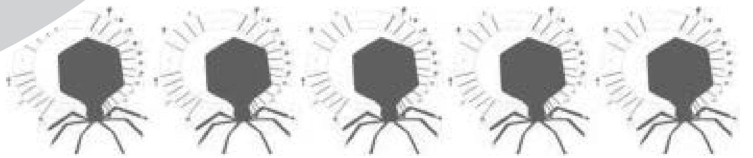

Abstract

Viruses contain some of the most interesting origins, biology, and relationships in the noncellular world. They are also visually alien looking to students and obviously different from cellular life. They are, in their parasitic mode, the consummate intimate associate, the genetic and evolutionary collaborator at the level closest to the cell's inner life. Viruses are, by their very structure and nature, dependent and interdependent. The concept of interdependency is an often-overlooked critical thinking skill, spoken of but rarely consolidated in biology curriculum yet at the root of understanding every tier of biological systems. Interdependency links all life together at all scales. To address the importance of interdependency in biological systems we propose a genomic medicine authentic STEAM-based experience that explores interdependency through the phage viruses. Phages are the most abundant and diverse biological entities on the planet (Batinovic et al., 2019). In this paper we outline the phage's universality and interesting attributes to provide background for a critical thinking prospectus that utilizes fine art skills and biological knowledge for students to experience and discover phage morphology, evolution, and therapy. We explore both the portrait of a phage (its structure and proximal relationships) and the landscape of its interdependence (global relationships) through the GM lens.

Key Words: *phage, bacteria, evolution, STEAM.*

○ Introduction

The history and biology of the phage is fascinating, primarily because of its intermingled and enmeshed global activity with prokaryotic cells in apparently unrelated niches such as the human gut and wetland ecosystems. While we may view their activity as parasitic, their influence on the health of the gut to the ecology of the ocean and their impact on nutrient cycling confirms that they are not a one-way street of parasite and host. Much of their biology places them in highly significant ecosystems functions (Sharma, 2017). Viral ecology is now a full scientific discipline. The environmental bacteriophage is now considered to be the greatest reservoir of non-characterized genetic diversity on Earth (Sime-Ngando, 2014). Viruses, while not cells, can contain genes for photosynthesis, oftentimes structuring, supporting, and driving microbial food webs (Lindell et al., 2005). As symbionts they share the metabolic pathways that govern microbial diversity with a long-lived association that channels the fitness of hosts and the specificity of selection at various stages of ecosystem cycling. The phage viruses appear to wear many hats from parasites to mutualists and may be at the root of much of the biological diversity of cellular life (Hatfull, 2015). Some phages are viral microbial assassins. There are also cell collaborators, cell manipulators, and cell supervisors. Bacteriophages offer us insight into the idea of living entities cross-pollinating and evolving the architecture of biological systems. In introductory biology when we introduce the concept of life to students we rarely defer to viruses. Introducing the concept of life to biology students usually involves some basic ideas around energy, movement, reproduction, and growth. Life processes are more than lists of observations or tables of summarized attributes. Telling the story of the phage, drawing and re-creating it, and understanding its diverse biology and reproductive cycles can stimulate the networked thinking and foundational knowledge about the interdependency of all life. This raises questions of where viral entities begin, and life entities emerge. The focus of this paper is to give a broad background on phages for a phage storytelling introduction that educators can use as introduction to the study of life. We then follow that story with authentic STEAM (science, technology, engineering, art, and math) activities that derive from classical morphological descriptive drawing.

Telling the story of the phage, drawing and re-creating it, and understanding its diverse biology and reproductive cycles can stimulate the networked thinking and foundational knowledge about the interdependency of all life.

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The fuzzy divide that labels viruses and non-life enables us and students to ask when life is life. How much and at what level does the non-living world (water, soil, rocks, viruses) intertwine to generate life forms and their processes? This is akin to the question, "when did life begin." While biology is excellent at categorizing, it is weak in the teaching and research of networked, interdependent systems thinking. Aldo Leopold's land ethic, which is lauded as an extremely influential view in environmental ethics and conservation biology, was dedicated to the assertion that "interdependence between humans, other species, and abiotic entities plays a central role in our ethical responsibilities" (Millstein, 2018). For many indigenous people, interdependence is the foundation of their culture, which often inherently views planetary cycles and intwined existence as critical to life. At the level of epigenetics, interdependency is demonstrated between the behavior of the genome and its environmental imprint where the gene is not a singularity but instead, with its environment becomes a field of possibilities. Viruses give students the opportunity to speculate about definitions, labels, and the divisions humans decide on that separate one species from another, ecosystems from each other, and noncellular entities from cellular entities. In standard evolutionary thinking, interdependency contrasts with the concept of a "biological arms race," a linear competition reflected only between two organisms, without consideration to the meshed landscape that interrelates and orbits around that rivalry. Collaborations throughout the tree of life and even at the level of atoms can be viewed as energetic or biochemical associations and as mutually beneficial relationships at some point in time, and perhaps, in a geological time frame we cannot observe. Regardless of perspective, interdependency seems to be the rule for planetary integrity—it is the only way life can exist. Phage viruses provide a window into such comingled survival, and they provide a line of questioning we can use to initiate discussions early in biology courses about what life might be. This is appropriate for 10th-grade, 12th-grade, and college-level general biology courses. The "What is life?" line of inquiry is best presented as a storytelling activity followed by descriptive drawing of phages. Rather than introduce standard definitions of life, we allow students to start a biology course with an understanding that living systems are connected, dynamic, networked, and ever-evolving. By linking storytelling to the diverse and powerful tools of the classical descriptive art of natural history and morphology, we help students conceptualize the fascinating details of the phage structure linking that structure to relationships, adaptations, interdependency, and the flow of nonliving to living.

○ What Is a Phage?

Bacteriophages are viruses who are specific to bacteria, their lifecycle is acutely focused on bacteria. For students, phages might be best described as the viruses of prokaryotes as they can be found in Archaea as well as the domain of Bacteria. Phage genomes are variable in size (ranging between ~3.5 kb and ~540 kb; Zuppi, 2022). Phages are obligate, intracellular parasites. Their lifecycle includes acellular, extracellular, and intracellular states. Phages, ecologically, have communities, they function as part of ecosystems and are integrated into community ecologies revealing great diversity and interdependency.

Bacteriophages were first discovered in 1915 by William Twort by observing plaque formation, morphology, and growth of bacterial colonies (Hyman 2019). Phages can appear simple, yet they are incredibly diverse and diversity-making quasi-biological symbionts that can contain dsDNA, ssDNA, or ssRNA. Their genome is enclosed within a protein capsid that may be protein only or have a lipid sheath. They typically have tails and variations of tails, and some have no tail at all. All aspects of a phage contribute to its successful entry into bacterial cells. We stress to students that phages are dependent and that they are naturally occurring entities, despite looking like aliens, and they need their host bacterial cell to continue to exist. Phage biology involves two prominent strategies for parasitic infectivity—the lytic and lysogenic cycles; however, those strategies are flexible and can have a range of variations, just like their structural components. Is there an evolutionary relationship between infective cycles and evolving characteristics of phages? This is an intriguing question to pose to students who may wonder what contributes to phage phenotypes. It is also an opportunity to discuss small gradual changes (antigenic drift) in genes that can change a morphological character such as a spike protein. Students may also ponder the last universal common phage ancestor. What did it look like? Was it self-replicating or was it always a parasite? This is a broad question and requires that students step back from the details and look at the larger expanse of evolutionary timescales. Phages also have specificity toward a particular receptor and to a specific bacterium. While they are deadly to that particular bacterium, they are typically harmless to others. Host specificity varies from specificity for one host/receptor or specificity across a range of strains or even genre (Lin, 2019). The term "phage" means "eater," and implies that the virus is consuming the bacteria, when it is infecting it and amplifying its infectivity. Students may have encountered the life cycles of viruses before, that is the lytic infection cycle where a phage virus attaches to a bacterial cell and injects its genetic material. If they have not, we have a storyboard template teachers and students can do together to highlight this feature (see Figure 1). The takeover of cellular machinery explains how a phage virus can rapidly destroy a bacterial infection and cure a patient in a relatively brief period (phage therapy). This cycle contrasts with the lysogenic cycle where the virus remains as a latent entity in the genome of the bacteria and is then inherited by daughter cells through binary fission, camouflaged until conditions are favorable, reverting to the lytic cycle where the stressor or change induces the phage's activity.

Bacteriophages are not simply about diseases or curing them and are part of the larger microbiomes and microbial ecologies of the Earth, which demonstrates a robust example of interdependency. Storytelling the ecology of the phage and the medical potential of the phage can give students a more rounded perspective on viruses. The concept of seeing microbes as significant, important, and integral to the function of a body or to an ecosystem is often a difficult hurdle to overcome in teaching interdependency. Most people, including students, still think microbes are only disease causing. To expand the story further and to make it relatable to biology topics later (DNA),adding in research history with phages can help. The T4 phage was part of the discovery of DNA, that Hershey and Chase utilized in the mid-20th century to reveal that DNA was the genetic material of cells. The T4 phage was further employed to demonstrate the spontaneous nature of mutations (Epstein, 1963). Phages continue to reveal unknowns about ecological systems and themselves. We might say that phage interdependency starts with a host. They evolve along with their bacterial hosts and with animal hosts too. Bacteria have evolved numerous mechanisms for evading infection. In response, the phages continually evolve back diverse strategies in structure and timing for breaking that resistance. New

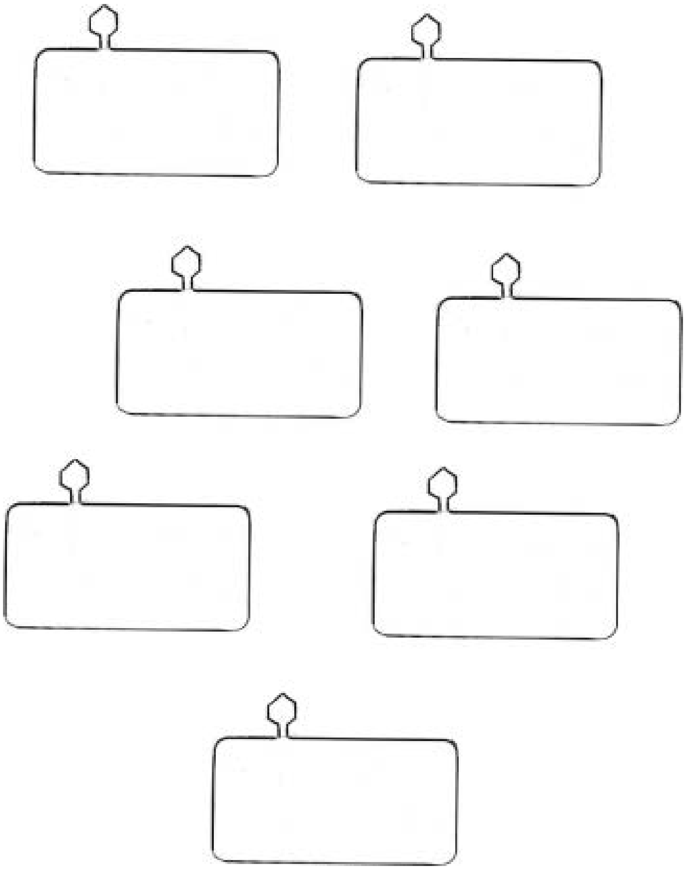

Figure 1. This premade storyboard will prompt students to draw both lytic and lysogenic cycles as well as variations of such cycles.

altered receptors, loss of function of receptors, and receptor variations along with some genomic sleight of hand all lend to the dance of bacterial and viral evolutionary and structural dynamics. Phages and their myriad of structures are uniquely adapted to be interdependent. Their lifecycle, size, and ubiquitous existence mean they are part of all living organisms. Our descriptive STEAM activity will help students make this connection. With a wide array of morphologies, we can examine tailed phages, non-tailed phages, pro-phages, and underlying adaptations in phage geometry, which all lend themselves to a speedy co-evolutionary microscopic drama. This makes the story of phages engaging to students. They are relevant to bacteria, to animals, in global ecologies, gut ecologies, plants, and in recent years have been viewed as a therapy for combating drug-resistant bacterial infections in cases known as compassionate care. There seems to be no other entity on the planet as interdependent as viruses. Students may wonder how ecological phages are connected to humans. Teachers can use the nitrogen cycle in their storytelling to demonstrate that compounds in the nitrogen cycle can be returned to the water cycle via our own human sewage, through phages, which are involved in nutrient release by rupturing the host nitrogen fixing bacterial cell in complex genetic transfers which help regulate the nitrogen cycle. This is another example of how connected and contiguous viruses (phages) are.

○ Morphological & Structural Diversity

The capsid is the most prominent feature of the phage; its geometry is probably one of its most captivating characteristics. Although the capsid is depicted in smooth geometric shapes, it is an elaborate and complex functional structure that makes a great drawing and noticing exercise for students. Capsid shape, ecology, and host are all important aspects of the drawing (see Table 1). The other parts of the phage include its base plate, fibers, arms, "decorative proteins," and sometimes tail apparatus. Previously and still, morphological characteristics are used to classify phages, but genomics has stepped in to help resolve and reorder the families of phages. The majority of phages do have tails, and the tail plays a vital role in delivering the nucleic acid to the host through a flexible protein connector-portal that is situated between the capsid and the tail. This portal adaptation is itself an incredible piece of structural geometry, typically resembling a dodecameric ring form. There are also membrane-containing phages (MCP), which do not have tails to deliver a genome into their host the gram-negative bacteria. They do have a proteolipid tube that connects to the bacteria, and it helps transfer genetic information. Still, there are other phage designs and

Table 1. A survey of just some of the phages and their hosts. Students can examine this table and use it to inform their phage page.

Phage	Bacterial host	Ecosystem
Coliphages	*E. Coli*	Fecal contaminated water
Nanoarchaeum equitans	Crenarchaeota	Hyper saline/hot springs
Oceanospirillum phage vB_OsaM_PD0307	Spirillum	Polar / deep sea
(families) Myoviridae and Siphoviridae (tailed phages)	Firmicutes in the genus Bacillus, though members of the Bacteroidetes, Planctomycetes, Chloroflexi, and delta-Proteobacteria	Desert
(families) Podoviridae Microviridae Corticoviridae	*E. coli* Proteobacteria, Bacteroidetes, and Chlamydiae Gram-negative marine bacteria from the genus Pseudoalteromonas	Soil

(*Continued*)

Table 1. Continued

Phage	Bacterial host	Ecosystem
(families) Siphoviridae, Microviridae, and Myoviridae	SUP05 bacterial symbionts (sulfur oxidizing bacteria found in snails and sponges)	Deep sea sediments
Enterobacterial phage P1	nitrogen-fixing strains of the coliform bacterium Klebsiella pneumoniae	Wet land
dsDNA and ssDNA phages (families), Myoviridae, Podoviridae, Siphoviridae, Ackermannviridae, Corticoviridae, Tectiviridae, and Plasmaviridae	Bacteroides, Bifidobacterium, Blautia, Clostridium, Escherichia-Shigella, Lacto- bacillus, Klebsiella, Roseburia, and Streptococci	Human gut
Tunturi virus (jumbo phage)	Acidobacteria	Tundra
T7-like cyanophages	Cyanobacteria, Synechococcus and Prochlorococcus	Open ocean

architectures, which seem specifically adapted to the bacteria they infect. The shape of phages is featured in our "phage page" activity at the end of this article. There are tail tube proteins, siphonic proteins structures, and variations in sensing fibers. For students, the geometry and structure of phages while constructing the virus through its genome becomes a chance to examine, visualize, and speculate about structure and function and also to learn about this feature of biological systems.

○ Ecology & Evolution Taught Through the Phage

Lytic activity impacts microbial mortality and has deep biogeochemical implications. The populations of lytic bacteria depend on the bacterial host numbers. Most students learn that viruses cause disease and that they need a host to replicate, but this is just a snippet of their life strategies and their interdependent networks. The so-called phages-kill-the-winner hypothesis, imagines the virus as the driver of community structure, indirectly and directly contributing to the cycling of major biogeochemical elements such as carbon and nitrogen. When a phage lyses its hosts it increases the level of detrital material in the environment—it affects respiration and nutrient retention (Zhao, 2025). An interesting question for students relates to predator–prey concepts. Do phages avoid or pursue weakened hosts? In typical predation models, compromised hosts are energetically easier to pursue and capture, but viruses may demonstrate the opposite approach. Is it energetically advisable to pursue a healthy bacterium or a sickly one if you were a phage? The other major reproductive strategy, lysogeny or temperate reproduction, may be an option where host bacteria are in small supply. Either strategy demonstrates that viruses contribute to microbial diversity through pressures that force diversification of metabolism, with new genotypes and phenotypes emerging quickly as they invade various hosts. It has been shown in aquatic ecosystems that viral lysis products shape evolutionary transitions in microbial communities. The range of phage–host interactions are on a gradient, producing varying eco-evolutionary effects. Another major impact of phages is lateral gene transfer (LGT) by transduction. Viromes are a massive reservoir of virally encoded host genes that can reorganize a genome through conjugation and transformation. When lysis happens, free genetic material becomes material into the environment, available for uptake by LGT. Viruses play vital roles in the evolution and ecology of all the domains of life. An example of this can be seen in the sea slug *Elysia chlorotica*. "These are sea slugs that have the unique ability to photosynthesize due to 'kleptoplasty,' where they acquire chloroplasts from their algal prey (*Vaucheria litorea*), a heterokont algae that 'steals' the organelles. It then incorporates them into their own cell. While the exact mechanism is still debated, scientists believe this may involve some level of horizontal gene transfer (HGT), potentially facilitated by a virus. This allows the slug to maintain and utilize the stolen chloroplasts for an extended period" (Battacharya, 2013). This observation was seen in the laboratory and in the field and points to viruses as genetic intermediary agents of gene flow and gene transfer. This complex triad of associations makes for great storytelling and reveals intimate relationships and interdependencies that can illuminate the importance of phages in microbiome communities and build richer conceptual ideas about life in general.

To study phages, like bacteria, scientists rely on metagenomics, but populations of phages possess a high degree of genetic diversity, this can make categorizing them difficult. Combined with microscopy and culturing viruses, the dynamics of viral and bacterial communities emerging is still quite incomplete. Phage communities can be found in the soil of rainforests, in agricultural soils, in deciduous forests, wetlands, marshes, deserts, and even Antarctica. Teachers can incorporate the viral and phage perspective at the beginning of a discussion on evolution and biome ecology with an introductory question like "Why aren't the viruses on the tree of life?," "What are they missing?," or "Do they have a tree of their own?"

○ Evolution & Morphology

Another interesting concept that can help students think more deeply about the drawing activities is the Viral Tiling Theory (VTT). This highly visual and geometric concept links the viral "tiles" of the capsid to its evolutionary potential. VTT coincides with our "phage page," and the 2-D and 3-D drawing exercises (see Figures 2, 3, and 5). In this theory, the tiles or facets of the capsid of a phage or virus represent interactions between capsid protein units (Twarock, 2005). It is a model of where assembly of capsids and the packaging of genomic material with the geometric tile proteins produces protein–protein interactions. As a model, it can capture both structural and biophysical properties and these characteristics may influence how viruses assemble, evolve, and infect their hosts (Twarock, 2005). Students can reflect on this type of model while illustrating and depicting their phages in the later exercise. Architecture in nature is both structural and functional. Viruses are no different in terms of morphology and this is an important teaching point that can tie in well with drawing capsids. Some architectures in viruses have open pores through which viral genomes are circulated and an ability to release the genome, which is a pivotal piece of a virus's success. Since the genome and its replication are the single most important property of viruses, viral genomes must also contain assembly instructions. Many viruses including human pathogens contain assembly code and packaging signals (PS) (Twarock, 2016). The assembly code (nucleotides) is composed of secondary structural elements; these are the packaging signals that coordinate and recognize when and how the virus should assemble its capsid pieces. Another interesting perspective for students is how do bits and pieces of a genome communicate to assemble an entire structure? It is like a package that puts itself together! To visualize this, a student may think of the virus as a set of Russian dolls where one structure or code is enclosed inside another and then another with perhaps a part of the genome activating another part and so on. This concept may be used to build a 3-D model from a schematic sketch or drawing. Students can work in groups to illustrate a 3-D capsid and then they can try and build a cardboard or clay model from it if time permits. The PS exhibits high variation around a sparse capsid recognition motif, as if the PS is camouflaged. This demonstrates that while viruses appear simple some of them have elaborate functional designs. Students can see that the capsid is an evolutionary adaptation, and that geometry informs infection, which can accrue mutations over time. We ask students to storyboard some of the more detailed activities of the virus phage and to consider the evolutionary implications of these stepwise depictions using the storyboard (Figure 1) as well as the big picture image (Figure 6). Students can study all the images together for any of the activities.

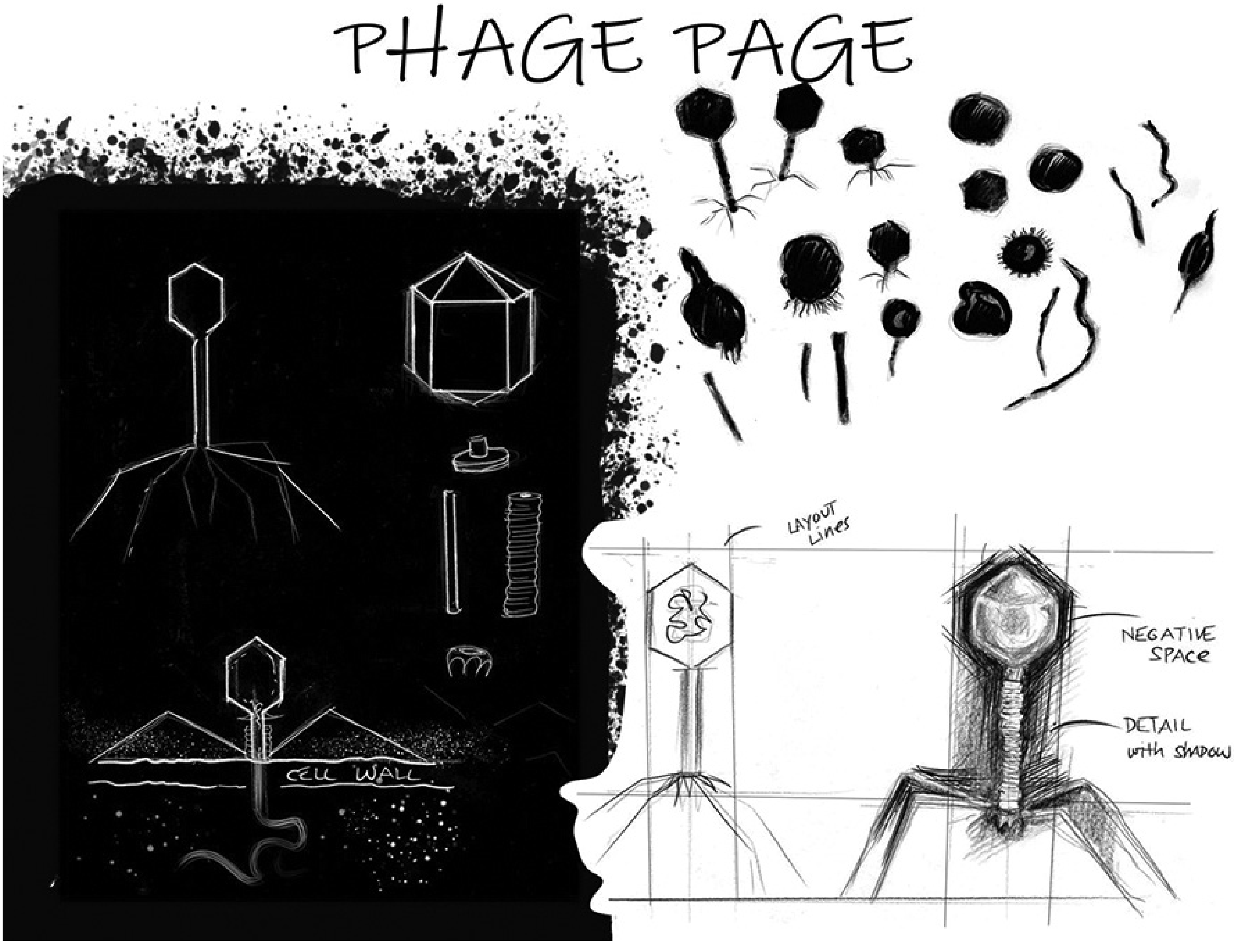

Figure 2. The "Phage page" can serve as a student's exploration into phage interdependence and dependence, on the dynamics of infection, and the wide diversity of morphologies that phages exhibit. Allow students to experiment with creating their own unique page and allow them to add whatever information they think would make this page more informative. They can work alone or in groups. In this image "how to draw" a T4 phage is shown (lower right) along with the silhouettes of different capsid shapes (upper right). The inverted image shows the T4's basic structural parts. Tell students, the phage page is like keeping a nature journal, except it is for making notations about viruses.

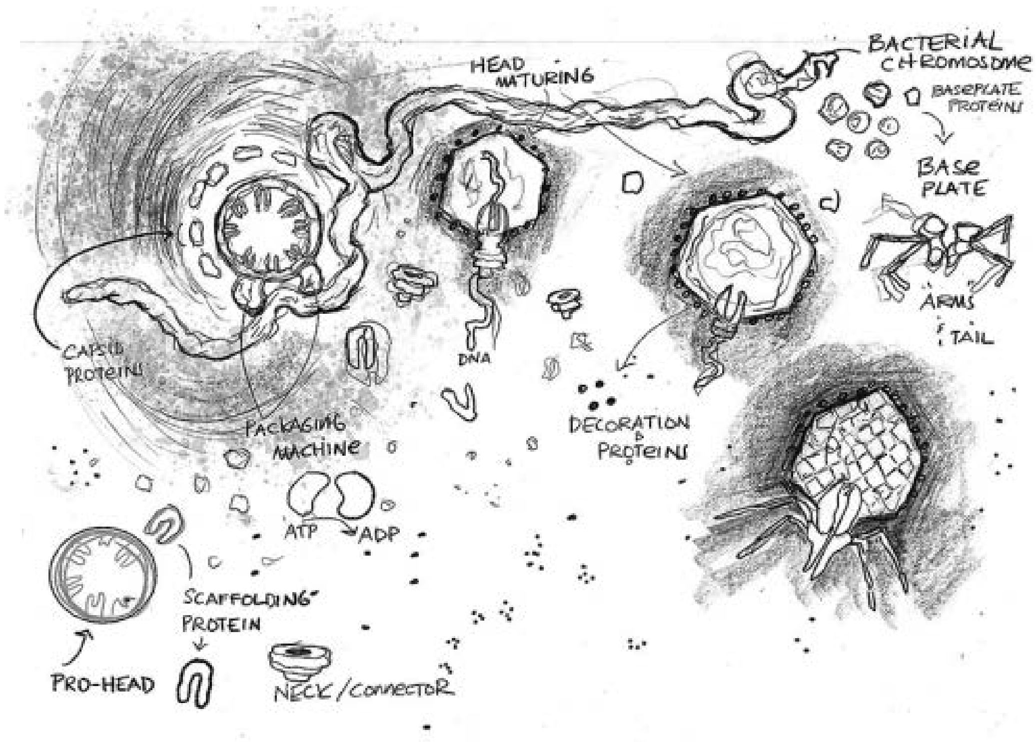

Figure 3. Students can use this drawing to color and familiarize themselves with virus life cycles and structural parts.

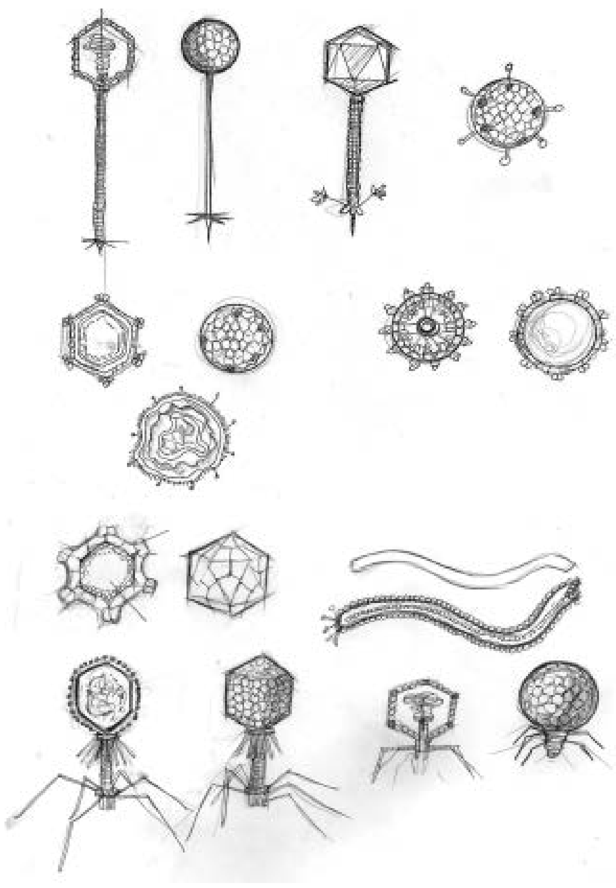

Figure 5. The diversity of phages highlights evolutionary adaptations unique to specific environments and genera of bacteria. Students can color this page and choose a phage to focus on. In class they usually pick a specific type and illustrate it from multiple angles. In this image we see some tailed phages such as *Siphoviridae*, some non-tailed phages such as *Corticoviridae* and *Tectiviridae*, as well as *Plasmaviridae*, *Podoviridae*, and *Inoviridae*.

Figure 6. A T4 phage infecting in the foreground and a host bacterium lysing in the background, presenting a "landscape" of a bacteriophage. Teachers can use this image as a backdrop to their storytelling phage introduction.

○ Phage Discovery & Personal "Phage" Medicine

It might be difficult to imagine that people without the technology of today were able to infer and understand the microbial world, laying foundations for therapies and concepts that are re-emerging into biology and medicine. Almost a decade before the discovery of penicillin by Alexander Flemming in 1928, lesser-known microbiologists Fredrik Twork and Felix d'Herelle made startling discoveries about phages that were successfully applied to infectious diseases (Letarov, 2020). In 1919, d'Herelle successfully treated chickens infected with *Salamonella gallinarum*, he followed this in 1927 with an application of the phage virus to 74 patients with Asiatic cholera (Dublanchet, 2007). In the West, with the discovery of antibiotics, the pursuit of phage therapy fell to the wayside and the widespread use of antibiotics ensued. Despite an understanding of natural selection, the modern Western scientific world continued to rely heavily on antibiotic use, expanding its application to a varied number of industries such as factory farming. Into the 21st century antibiotics are applied to such diverse objects as socks, blankets, and toiletries (Anomaly, 2015). Our excessive dependency and continued imprudent use of antibiotics has ushered in an age of new, deadly antibiotic-resistant strains of virulent bacteria with little or no new antibiotics or methods of treating these life-threatening infections. This dire situation has rekindled an interest in phage therapy, phage ecology, and evolution. Phage therapy is now used to treat some of the most resistant bacterial infections and continues to shed light on the fascinating, rapidly evolving world of phages.

In the human gut, phages appear to have beneficial effects on bacterial populations. Mutualistic interaction as well as predation dynamics happen between bacteria, bacteriophages, and the cells of the human gut. Terms students often see in ecology are applied to phages of the gut, "obligate predator," "phage predation," and "efficient killers," making the gut seem like the African savanna. Interestingly, it appears as if very few bacteria have evaded phage predation, but is phage predation an inevitable evil in bacterial evolution? If we think about this micro world on a larger scale we would say that predation is essential for eco-evolutionary homeostasis. "The phage composition of the gut has been reported to remain stable for up to a 1-year period in healthy adults" (Shkoporov et al., 2019). Alterations have been affiliated with gastrointestinal diseases, such as *Clostridioides* (formerly *Clostridium*) *difficile* infections (CDI) and inflammatory bowel disease (Zuppi, 2022). Phages also can interact with the host's immune cells and modulate immune response (Zuppi, 2022). This ushers in questions about the role death has in life and even the necessity of disease. Are phages harnessing the power of bacteria for the larger human host? Have phages secured a mutualistic relationship in our own bodies? Students may be fascinated to know that the ongoing infection processes between these microscopic denizens are significant drivers of gut immunity, gut health, and the stability of gut microbiomes just like predators maintain the stability of the savanna. Students can learn a lot about evolutionary strategies and interdependent relationships in the gut world of the phage. The undercurrents and forces of these relationships involve such innovative strategies as bacteria committing suicide once infected by a phage virus to ensure it doesn't spread to their community (Berryhill et al., 2021). The dynamics of the phage, virome, or "phageome" of the gut was originally based on studies of bacteriophages in the ocean, but recently greater differences in that paradigm have come into question. The stratifications where levels of organisms create distinct niches were found to be quite different in an ocean than in a gut (Dion, 2020). This is an important teaching point for students, as we might think ecosystem dynamics and terminology can be applied anywhere communities of life exist, but there are many variations of trophic level dynamics, including scale and medium of the habitat that can restructure organization of communities. Students might also wonder how a virus that lyses a bacterial cell could be mutual. In the case of the individual, only the phage would benefit but does the phage infect the "weaker" bacteria or the injured bacteria like macro-scaled predators typically do? Do they benefit the whole of the gut by killing off the so-called weaker bacteria? If this is the case then phage parasites or "predators" could be considered beneficial. Ask students what they think about these scenarios and bring this into a discussion on microscopic ecosystems vs. standard ecosystem dynamics. Regardless, the interactions of phages in the human gut strengthen the idea of interdependency and allow students to gain broader insights into that interdependency at all scales of life.

○ Phage Therapy in the Age of Antibiotic Resistance

For students' antibiotic resistance is a popular discussion topic. It also serves as a real-life, real-time lesson in natural selection. If we introduce the phage into this evolutionary story, we have an added evolutionary dimension, a pathogen killing a pathogen, a battle in the blood stream where the parasite saves the patient's life. From a genomic medicine perspective, phages offer a specific way to approach the increasing threat of antibiotic-resistant microbes on an individual basis. This is critical as novel classes of antibiotics have been stalled for decades (MacNair, 2024). The kinds of phages used in phage therapy are typically lytic and tailed. For therapeutic use the phage must be able to lyse and kill most, if not all the pathogenic bacteria. Obligatory lytic or virulent phages are the best candidates for phage therapy to date. There is, however, more to the story of infectivity than simply host and parasite, phages administered for treating infections may themselves evolve resistance over time. Sometimes when a patient is terminally ill from a drug-resistant bacterial infection, phages are used as "compassionate use," and often with antibiotics present. There are interactions between the antibiotic and the phage as research has shown that the phage sometimes increases the patient's sensitivity to the antibiotic (Hatfull, 2022). This type of synergism is another interesting effect of phage therapy.

Phage Infectivity

When exploring a virus or phage in terms of infectivity, students might consider several other ideas besides just the virus penetrating a cell. Such concepts as the adsorption of the virus, the diffusivity of the virion, the affinity or strength of the virus, the affinity of the virus for a particular genotype, and many other factors determine infectivity including the state of the infection, whether it is early, intermediate, or mature. The virus's activity can also be considered, the rate at which it matures, the duration of its maturing, and the titer of the virus. All of this is just one side of the equation, we have not even considered the host's immunity and the complex variables of diet, stress, preexisting disease, and genetics. One activity that can help students brainstorm about antibiotic resistance, evolution, and phages is designing a protocol for treating a patient with a lethal infection. For our exercise in genomic medicine, we broke students up into groups of three or four and asked them to consider the evolutionary implications of a new therapy, one that would not repeat the mistake of antibiotic resistance. Is it possible to not get resistance? What ideas would you start with to minimize evolutionary pressures on either bacteria or the phage? How would your group approach this?

When it comes to phylogenetic trees, students may not realize that there are huge numbers of phage species across Earth's ecosystems. These may not fit easily into the standard tree model. As influencers of ecosystem change and dynamics, phage participation and contributions to the ecosystems may be less detectable than other types of organisms. Due to their transient nature they may appear more entangled. Phage derived fragments through metagenomic methods can assist in the recovery of the small genomes of phages, but much of their skullduggery remains unaccounted for. Hosts (bacterial cells) are intimate associates of viral phylogenies that involve movement of genomes and genetic material through free-floating genes, HGT, LGT, and other mechanisms (Aminov, 2011). Different fragments of the genome through diversity-making genomic exchanges mean that phages and their hosts are inheriting different evolutionary histories in a rapid timescale and in a variable way. In this entangled history of genomic events, looking for outliers might help identify where a bit of genome came from, and this might be a good place to ask students a "thought question." I asked my students to consider visualizing a tree of phages, and the idea of interdependency by conceptualizing on a piece of paper what a phage tree might look like. How could we model a tree with such transiency and exchange? Ask students to sketch ideas about trees that might consider methods (such as PCR, metagenomics) and visual representations.

○ A Phage Page of Authentic STEAM Activity

From the genetic mapping of the phage revealing spontaneous mutational events back in the early 1960s to the stratification of decomposition in a marine ecosystem, phages will help students conceptualize the interconnectedness of living systems. Drawing and sketching can help students in visualizing and linking such structures as attachment mechanisms and virus geometry to a coevolution (see Figure 4). Structure, morphology, and form in viruses are windows into interdependent relationships. For example, the contractile sheath and the tail tube of phage viruses are an evolved adaptation for their parasitic relationships. They assist to "integrate" the virus with the host; they generate an association/union through time to another organism. We have several interrelated activities to help students see the translation of phage genomes into both process and structure. And because of the viruses' relative simplicity, they serve as an excellent and relatively easy model for the genotype to phenotype concept drawing. Drawing assists in understanding why the virus has a specific morphology and a general morphology (Quillin, 2015). This connects form to the processes of infection. Form, that is the geometry and shape of the virus is an evolutionary adaptation, equipped to deliver the best or most fit infective behavior of the phage, therefore, studying the form can tell us a lot about the virus and its behavior. The not-so-agreeable partner (bacteria) provides the ATP to fuel the timed expression of sequential sets of genes that perpetuate the viral form. Both bacterial phenotype and virus phenotype evolve together. This is why we recommend a "phage page" as well as Figures 3 and 5 to study phage form. Students can make some sketches of various phage shapes and decide which kind of replication strategy might be most effective. In our "phage page" activity students will draw a phage of interest and its parts using multiple image examples. We encourage students to use the drawings provided but to also explore the great diversity of phages through research articles to create their own original drawings. Phages are relatively easy to draw and demonstrate by teachers because they appear to have a simple geometric

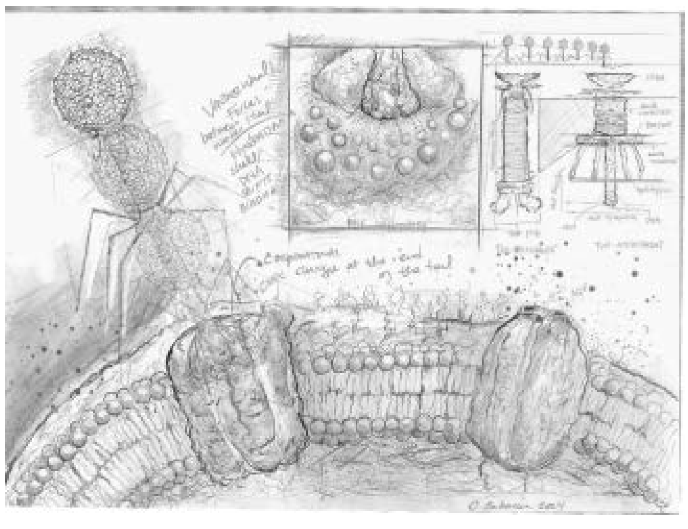

Figure 4. Detailed structure and possible function of the binding mechanism of the tail to the cellular membrane of the bacterium. Students can view this detailed storyboard to devise their own storyboard for one of the many stages of phage virus attachment. This image will help students see a model of the complexity of the viral attachment tail. While viruses may appear simple, their structual adaptations are quite detailed. For students who feel more proficient at drawing, use this image to encourage them to draw the tail sheath, the hollow tube, and the base plate.

shape. If teachers want to further develop an interdisciplinary lesson they can explore the Viral Tiling Theory, which employs mathematical concepts (Twarock, 2005). The illustrations in this paper were meant to provide both educators and students with scientific educational drawings that promote drawing as a skill for learning biology.

Such geometry terms as viral symmetry, three-dimensional lattices, radial dimensions, aperiodicity, vertices, icosahedron, and virus tile theory are all part of the domain of viral replication and virus evolution. The visually fascinating capsid, along with other structures, help determine the viruses' biophysical properties. Architecture and design are key elements of functionality and can help determine how the genome will exit the virus, how the capsid will be copied, whether the genetic code is sparse and reusable, and what tessellations of shape/geometry will be the least expensive in terms of the viruses' energy demands. Form evolves and changes and this is balanced with the virus and its stability in life cycle production, release, and novelty. This overlap of structure and function can easily move into a discussion on evolution and the cost/fitness model of phages, allowing students to see the direct relationship of the genome to the shape of the evolution of a single strain. For students, seeing the direct balance of physical pattern and genetic code is eye opening.

In this activity we have also provided Table 1 to reference diversity of phages for students. We have provided Figure 6, which shows a hypothetical, colorful landscape of phage activity. Figure 2 shows an example of the "phage page." Figure 3 shows a cartoon of phage assembly. Figure 4 shows a close-up of what the infective contraction of the tail sheath mechanism might look like. In Figure 5, we provide a page of diverse phages. Figure 1 includes a storyboard to place a lytic cycle in. All of these images taken together also reveal and showcase how drawing can pull ideas together. Lastly, we provide a page of phage parts and structural components for students to cut out and assemble or to draw (Figure 7).

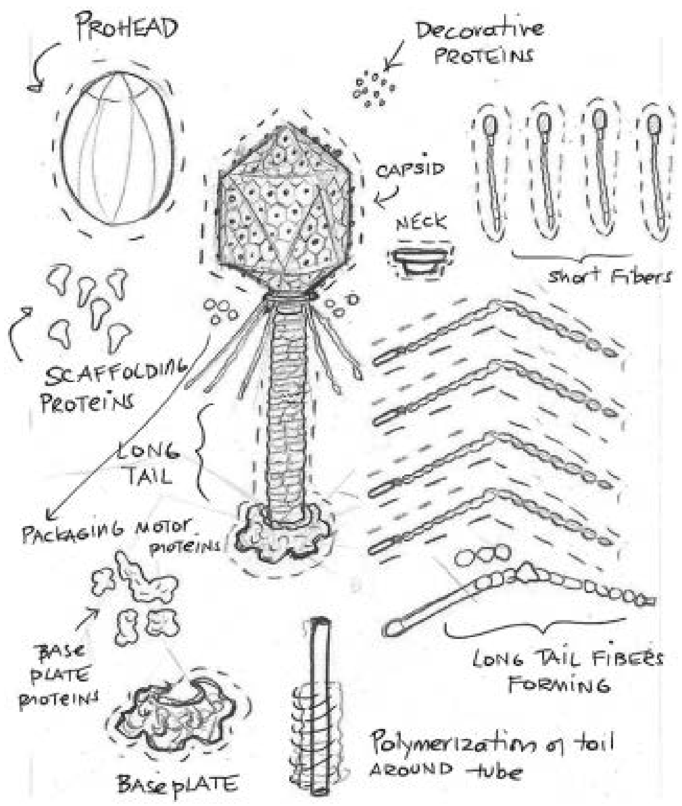

Figure 7. Students can use this image to either construct a paper phage with a cardboard background (just color and glue to thin cardboard). Students can also draw variations of the parts and play with the idea of variation and construct their own cut out virus.

Educators can introduce the phage in the following sequence:

1. Give background on the concept of interdependency and dependency (this article and references). Teacher draws a general bacteriophage on the board.

   Use the virus as a prompt for storytelling. Explain the general features of a bacteriophage and its host. Ask students where one might find viruses. Ask students to give biological examples of dependency and interdependency and ask whether viruses are one or both. For storytelling give background on ecology, structure, and maybe introduce the VTT (in higher-level classes). Provide a half hour of storytelling and structure it according to your class's level or ability. Introduce the concept of antibiotic resistance and biological diversity. Follow this with a brief video on how phages are being used (genomic medicine perspective) in life-threatening cases of antibiotic resistance. Use this video of infectious disease epidemiologist Steffanie Strathdee: https://www.youtube.com/watch?v=XTSJ7pxIhMY. After this video ask students the following: "How does the virus kill the bacterial infection?" "What is this behavior (cycle) called?"
2. Show a brief video on phages: https://www.youtube.com/watch?v=YI3tsmFsrOg.
3. Ask the "what is life?" question. Ask students whether bacteriophages could be living or nonliving? Ask students what dependency and interdependency have to do with the definition of life from cells to ecosystems. Ask them to support their answer. We ask for a 200-word response to this question, which students can easily do in class before or after the phage storytelling.
4. Once the instructor finishes the "what is life" question and the background on phages as a narrative, hand out unlined white drawing paper and construction paper, and ask students to do a search of various viruses (we used the phages). Ask students to describe briefly the host and the ecosystems they are found in (including the human gut). What is similar about the viruses they found? What is unique? Based on some of the shapes, what traits or adaptations make viruses dependent? What traits make them interdependent?
5. Ask students to continue with their exploration by coloring the black-and-white pages and create a phage page of visual and written notes about viruses. Give students the opportunity to explore any aspect of phages (HGT, ecology, microbiomes, morphology, infectivity).
6. Ask students to work in pairs to storyboard a bacteriophage "in action." What part of the phage is uniquely adapted for this? (See Figure 4.)
7. Have students either draw or cut out and construct a phage of interest based on the designed phage from Figure 7. Ask students what part of the phage assists in its infectivity? What role would a phage virus have in the body? In an

ecosystem? After the activity do they consider phages living or nonliving? Are phages part of a larger ecological system or web? How do you think they impact evolution through their relationships?

For supplementary images please visit our website: https://igem.temple.edu/genomicmed/.

○ Conclusion

Phages are fascinating and more than just parasites causing disease. Through the genomic medicine lens, combined with ecological lessons from the microbial world and the interesting history of drug discovery, phages are now emerging as a hot topic in treating antimicrobial resistance. Phages offer more than just an important step in treatment, but a window into the massive diversity of viral genomes on the planet and the essential roles of phages and other viruses in ecological systems and nutrient cycles. Students and educators can incorporate some of the biologically significant aspects of phages into their classrooms via an authentic STEAM activity and through the process of drawing and focus on phage geometry and structure. In both the five kingdoms and the three-domain tree of life, viruses are absent, but their importance to the cycles of life on planet Earth cannot be overstated as new knowledge puts phages and viruses in an eco-evolutionary light.

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