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Do Viruses Appear to Cluster Like Created Kinds?

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Abstract

In the book of Genesis, the creation of plants and animals is described, yet the creation of microbes (including viruses) is not mentioned. Some biologists think viruses are on the border between living and non-living organisms, since they cannot exist independently outside of their host. Some propose that retroviruses and the associated mobile genetic elements found in various animal species originated from within the host genome and fulfilled structural and regulatory functions, and were later exogenized.

Previous creationist works have studied the baraminological relationships among insects, fungi, bacteria, and archaea using genomic data, but not that of viruses. This paper aims at performing such a genetic study in order to shed light on the possible baraminic relationships between prokaryotic viruses, otherwise known as bacteriophages.

In this study, 159 bacteriophage strains which had 200 or more orthologous proteins in their genome were examined using the Gene Content Method. Eight phage clusters were found with varying sizes and varying host organisms. Some phage clusters infected only one family of bacterial hosts, whereas others were more promiscuous. Phages within some of the smaller clusters had a tight range for genome size, ORF number, GC%, and host morphology. In two larger clusters, phages infecting different bacterial host genera showed no significant genetic difference. Several smaller phage clusters were found, which were already described in the scientific literature, thereby adding candidate bacteriophage strains to these groups. It appears that God may have created several kinds of bacteriophages to keep various bacterial populations under control.

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Introduction

In Genesis 1:11–12 (NKJV) we read about the creation of plants:

> Then God said, "Let the earth bring forth grass, the herb that yields seed, and the fruit tree that yields fruit according to its kind, whose seed is in itself, on the earth"; and it was so. And the earth brought forth grass, the herb that yields seed according to its kind, and the tree that yields fruit, whose seed is in itself according to its kind. And God saw that it was good.

Similarly, in Genesis 1:21–25 (NKJV) God created the different kinds of animals:

> So God created great sea creatures and every living thing that moves, with which the waters abounded, according to their kind, and every winged bird according to its kind. And God saw that it was good. And God blessed them, saying, "Be fruitful and multiply, and fill the waters in the seas, and let birds multiply on the earth." So the evening and the morning were the fifth day. Then God said, "Let the earth bring forth the living creature according to its kind: cattle and creeping thing and beast of the earth, each according to its kind"; and it was so. And God made the beast of the earth according to its kind, cattle according to its kind, and everything that creeps on the earth according to its kind. And God saw that it was good.

Genesis 1 deals with the different kinds of macroscopic plants and animals, which are observable to the naked eye. More specifically, a living creature, in the biblical sense, is an animal which has a soul, or נֶפֶשׁ (nephesh) in Hebrew. There is no information in the Bible that directly refers to microorganisms or their origin. It has become increasingly evident that microbes aid in digestion, and produce vitamins and minerals as part of a symbiotic relationship with their hosts. According to the biomatrix or organosubstrate theory (Francis, 2003; Linares et al., 2016), microbes were created as a link between multicellular organisms and the physical world to extract inorganic materials and to participate in the geochemical cycling of elements and compounds. Therefore, according to this view, microbes would have been created on days three, five and six, along with their plant and animal hosts (Gillen, 2008). Also, since microorganisms, such as archaea and bacteria show signs of life as defined in modern terms, such as cell division and metabolism, it is possible, that they were also created according to their kind; however, the Bible remains the sole highest authority in this question (Acts 17:10–11). Indeed, two baraminology studies have shown that Nucleocytoplasmic Large DNA Viruses (NCLDVs) and archaea form several species clusters, which are continuous with each other, and discontinuous with all other species (O'Micks, 2016; Yaugh, 2016). NCLDVs may be degenerate bacteria, and not viruses, due to the sheer size of their genomes as well as the presence of genes in their genomes, which have functions characteristic of cellular organisms.

We can now turn to viruses, and ask the question, as to whether they were also created "according to their kind." This we must ask, since virus strains have been known to originate from one another via mutation. For example, HIV has been hypothesized to have originated from SIV (Simian Immunodeficiency Virus) (Sharp and Hahn, 2011). The evolutionary origin of viruses does not make sense, for two good reasons. First, their mutation rate is several orders of magnitude higher than that of cellular organisms, yet viruses have never been observed to evolve into anything other than viruses. For example, the mutation rate of the poliovirus RNA-dependent RNA polymerase is 4.5×10^{-4} per bp (Wells et al., 2001). This despite bacteriophages being the most abundant biological entities on the planet, with an estimated 10^{30} phage particles (Brüssow and Hendrix, 2002). Second, due to this tremendous mutation rate, viruses are theoretically constantly on the verge of mutational catastrophe, meaning that since they mutate so fast, their genome is constantly on the verge of being lethally damaged by mutations.

On the other hand, we must be cautious about whether viruses or other mobile genetic elements can be classified as created kinds, especially in higher organisms. Instead, they could have originated from the host genome (Tomkins, 2015) and then later exogenized. For example, elements such as LINEs, SINEs, Alu repeats and other elements make up more than one third of the human genome (Terborg, 2009). Such a large number of mobile elements present in the human genome could certainly not be due to exogenous origin, since they would certainly have been detrimental to the host genome's stability. Rather, such elements could have originated within the host genome itself. For example, Endogenous Retroviruses (ERVs) take part in gene regulation, DNA repair and recombination (Liu and Soper, 2009), and could have exogenized to form present day retroviruses.

Viruses are mainly known to cause diseases, such as hepatitis, colds, mumps, rabies, polio, and smallpox; therefore, these specific strains could not be part of the original good creation, when there was no pain, death or disease (Genesis 3:17–19). However, the majority of viruses could have possibly played a more benign ecological role as vectors in exchanging genetic elements between microorganisms, like bacteria, a process known as horizontal gene transfer (HGT) (Bergman, 1999). For example, some viruses have been employed today in cancer therapy (Norman and Lee, 2005). After the Fall, viruses would have come under the effect of the curse, and along with certain mutations, would have become pathogenic (Kim, 2006).

Living organisms are defined as being able to reproduce their own species in-

Table 1. List of 19 groups of bacteriophages defined by the bacterial genus that they infect along with the number of bacteriophage strains in that group, as well as the number of clusters with five members or more that they are found in (listed in Table 2).

Bacterial genus	Number of species	Number of clusters found in genus
Enterobacteria	36	4
Synechococcus	25	1
Escherichia	17	2
Bacillus	12	1
Mycobacterium	9	1
Prochlorococcus	7	1
Vibrio	7	1
Klebsiella	6	4
Aeromonas	5	0
Cronobacter	5	2
Cyanophage	5	1
Salmonella	5	2
Shigella	4	1
Staphylococcus	4	0
Yersinia	4	1
Sinorhizobium	3	0
Citrobacter	2	1
Edwardsiella	2	1
Pectobacterium	1	1

dependently. Viruses are somewhere on the border of life and non-life; they are capable of replicating within a cellular context, as are viroids, prions, plasmids and transposons. This means that viruses are incapable of independent existence, but rather are dependent on the cellular machinery of host cells in order to replicate. Viruses also have a non-cellular structure, and a much smaller genome compared to cellular organisms.

In order to further address this question, a recently-developed gene-based baraminology method was applied (O'Micks, 2017) which defines baraminology membership based on gene content similarity. This method has been applied to NCLDVs (O'Micks, 2016), archaea (Yaugh, 2017), insects (unpublished data), and fungi (O'Micks, 2017). Therefore, in this paper this same method will be applied to prokaryotic viruses to see whether these viruses form clusters of species, similar to cellular organisms examined in previous studies. For this, data from the Prokaryotic Virus Orthologous Groups (pVOGs) database (Grazziotin et al., 2017). From here 159 prokaryotic viruses (PVs) were selected that had at least 200 proteins in their genomes, which correspond to pVOGs (see Table 1), and then ran the Gene Content Method (GCM) on them, as detailed in the Materials and Methods section.

A previous analysis on bacteriophage genome content similarity was done on 93 Bacillus bacteriophage strains, uncovering 12 clusters, and 14 singletons (Grose et al., 2014a). What was characteristic of this analysis is that two phages were considered members of the same cluster, if their protein content similarity was at least 40%, which is a cutoff used by the CoreGenes software that determines common gene content for a set of input species (Turner et al., 2013). As we can see in Table 2, the mean JCV for the eight discovered clusters is above this cutoff limit. Furthermore, there is low standard deviation in average basic phage properties, such as genome size, GC%, ORF number, and virus morphotype. Hatfull (2012a) found that GC% varies only slightly within bacteriophage clusters, something which was also reported by O'Micks (2015) in several bacterial genera. Grose and Casjens (2014b) also defined clusters of *Bacillus* subgroups by measuring pairwise genome sequence similarities between pairs of phages, where the sequence similarity was at least 50%, over half of the genome.

Bacteriophages are the most predominant biological entities on the planet. In general, bacteriophages have a preference for a particular host bacterial species, or even strain or serovar; this can also serve as a barrier for the exchange of genes. However, sometimes phages can infect host species from several different genera or families, such as those from *Escherichia*, *Lactococcus*, *Mycobacterium*, *Pseudomonas*, *Staphylococcus*, and *Streptococcus* (Jacobs-Sera et al., 2012). The expansion of host range of phages usually fails, due to the difficulty in the mutation of host attachment proteins (Hall et al., 2013). No phages have been discovered that have jumped the barrier between gram-positive and gram-negative bacteria (Jacobs-Sera et al., 2012).

Table 2. Clusters of bacteriophages with at least five members, predicted by the GCM.

Bacterial host genera	No. strains	Mean JCV ± stdev	JCV range	ORF number range	p-value
Citrobacter, Edwarssiella, Enterobacteria, Escherichia, Klebsiella, Pectobacterium, Salmonella, Shigella, Yersinia	65	0.66±0.14	0.41–1.0	203–288	$2.3x10^{-25}$
Cyanophage, Prochlorococcus, Synechococcus	37	0.54±0.11	0.32–0.98	201–4556	0.0
Vibrio	7	0.88±0.03	0.84–0.93	304–335	$5.6x10^{-35}$
Enterobacteria, Klebsiella	5	0.88±0.06	0.81–0.95	200–210	$6.6x10^{-12}$
Mycobacterium	9	0.63±0.07	0.55–0.81	204–241	$5.3x10^{-35}$
Bacillus	12	0.5±0.22	0.27–0.91	203–272	$6.1x10^{-26}$
Cronobacter, Enterobacteria, Klebsiella, Salmonella	8	0.51±0.24	0.27–0.88	209–241	$2.6x10^{-10}$
Cronobacter, Enterobacteria, Escherichia, Klebsiella	5	0.73±0.12	0.62–0.97	249–293	$6.8x10^{-8}$

Results and Discussion

After running the GCM on the data, we see that eight PV clusters arise of varying sizes, with 5–65 members, and with a different mean JCV and a different range of JCVs (Table 2). Those which infect 19 different families of prokaryotes were analyzed; each cluster had at least five members. These clusters, however, are not homogenous, in that their members infect different host families of prokaryotes. For example, PVs which infect prokaryotes from the families *Enterobacteria* and *Klebsiella* were found in four clusters, and PVs which infect prokaryotes from *Cronobacter*, *Escherichia*, and *Salmonella* were found in two clusters. These results mean that different groups of phages are sometimes capable of infecting the same set of hosts. The predicted virus clusters will be described as to their host range, and similarity to other strains of viruses in the following paragraphs.

Enterobacteria, Escherischia, and other phages

Currently, several hundred *Enterobacteriaceae* phages have been sequenced, many of which infect multiple host genera (Grose and Casjens, 2014b). The first cluster consists of 65 phages (of which 33 have *Enterobacter*, 15 *Eschersichia*, 4 *Shigella*, 4 *Yersinia*, 3 *Salmonella*, 2 *Citrobacter*, 2 *Edwardsiella*, 1 *Klebsiella*, and 1 *Pectobacterium* hosts). Despite the size of the cluster and the variety of bacterial hosts, the phages belonging to this cluster have a mean JCV of 0.66, with a range of 0.41–1.0, and between 203–288 ORFs.

When comparing those phages that infect *Enterobacter* hosts and those that infect *Eschersichia* hosts, we can see that there is hardly any difference between them, meaning that host preference does not play a major role in virus clustering. For example, the mean JCV calculated when one phage infects an *Enterobacter* host and another infects an *Escherischia* host, we get a mean JCV of 0.72, as opposed to 0.7 for only *Enterobacter* hosts, and a slightly higher value (0.79) for only *Escherischia* hosts (see Table 3). The p-value for JCVs between these two genera is 0.79, which is highly insignificant, meaning that the JCV algorithm differentiates between

Table 3. Comparison of bacteriophages, which infect *Enterobacter* and *Escherischia* hosts.

Comparison	Mean JCV ± std. dev.	JCV range
Within *Enterobacter*	0.7 ± 0.13	0.48 – 1.0
Within *Escherischia*	0.79 ± 0.13	0.56 – 1.0
Between *Enterobacter* and *Escherischia*	0.72 ± 0.14	0.48 – 1.0

phages that infect bacteria from these two genera.

Synechococcus + *Prochlorococcus* + cyanophages

In the second cluster there are 25 *Synechococcus* phages, seven *Prochlorococcus* phages, and five Cyanophages; again, similar phages infect different hosts. The reason that *Synechococcus* phages are in the majority compared to *Prochlorococcus* phages is because they have a wider host range (Hambly and Suttle, 2005), making it possible for more strains to arise through HGT. Also striking is that fact that bacteriophages which infect both genera of bacteria cluster well with each other. As we can see in Table 4, the mean JCV and JCV range hardly differs regardless of whether we look at bacteriophages which infect only *Prochlorococcus*, those that infect only *Synechococcus*, or both together. Sullivan (2003) showed that 93% of 58 *Synechococcus* lysates contained *Myoviridae* viruses, 65% of 43 *Prochlorococcus* lysates contained *Myoviridae*, and 98% of 107 *Prochlorococcus* lysates showed *Podoviridae*. Lu and Hodson (2001) found similar results. Although the majority of phages in this group infect *Synechococcus*, the same phages could possibly infect other bacterial hosts.

Table 4. Comparison of bacteriophages, which infect *Synechoccus* and *Prochlorococcus* hosts

Comparison	Mean JCV ± std. dev.	JCV range
Within *Prochlorococcus*	0.52 ± 0.13	0.35 – 0.91
Within *Synechococcus*	0.56 ± 0.13	0.35 – 0.98
Between *Prochlorococcus* and *Synechococcus*	0.56 ± 0.13	0.35 – 0.98

Mycobacterium phages

Mycobacterium phages are very diverse, and more than 200 completely sequenced genomes of these phages form some 20 clusters along with their sub-clusters (Hatfull, 2010, 2012b). The majority of phages which infect *Myocobacterium* species are specific to *M. smegmatis*, but 10% can also infect *M. tuberculosis*, a species with a genome roughly two-thirds the size of *M. smegmatis*, and a longer doubling time (Jacobs-Sera et al., 2012).

The nine *Mycobacterium* phages in this study had a relatively low mean JCV of 0.63. *Mycobacterium* phages are rather diverse, without constituting discrete populations. Their genomes can contain up to 30% orphan genes (Pope et al., 2015), which could account for the relatively low mean JCV. Their genome size has a tight range of 106–110 Kbp, which have 216–247 genes.

Vibrio phages

This smaller groups of phages, which have a similar genetic make-up, have very much the same host range. For example, five of the seven *Vibrio* phages in cluster 3 have a mean JCV of 0.88 and a JCV range of 0.84–0.93. They also have a tight genome size range of 246–248 Kbp, a GC% range of 41.23–42.6, and between 378 and 390 ORFs (Luo et al., 2015).

Bacillus phages

Bacillus bacteriophage Bastille belongs to the L4 subgroup of *Bacillus* phages, whereas four of them (Spock, BigBertha, B5S, and B4) belong to the L5 subgroup, and Bcp1 belongs to the L7 subgroup (Grose et al., 2014a). As we can see in Figure 1, the *Bacillus* bacteriophage cluster consist of two subclusters, L4+L5 and L7. These subclusters also have a similar range for genome size, GC%, and number of ORFS, and all belong to the family *Myoviridae*.

Phages belonging to smaller, mixed clusters

The fourth cluster contains three phages which infect *Klebsiella* hosts, and two which infect *Enterobacter* hosts. They have a mean JCV of 0.88 and between 200–210 ORFs, which is quite a narrow range. Maciejewska et al. (2017) found that from this cluster, *Klebsiella* phage KP27 shows similarity with *Klebsiella* phages KP15, Miro, and Matisse, and *Enterobacter* phage phiEap-3; the latter three were also put in the same cluster by the GCM as well as *Enterobacter* phage RB43, which Maciejewska et al. (2017) did not detect. The phages in this cluster show a highly similar level of genome organization as well. For example, the genomes of phages vB_KpnM_KP15 and vB_KpnM_KP27 are 174,436 and 174,413 bp, respectively, with a DNA sequence identity of 96%.

The genome of *Cronobacter* phage vB_CsaM_GAP31 was determined by Abbasifar et al. (2012). It shows high similarity with *Salmonella* phage SSE-121, which has also been studied here, as well as *E. coli* phages vB_EcoM-FV3 and rV5. Even though only eight phages were found in the seventh cluster, they infect bacteria from four different genera. Their genomes contain 209–241 ORFs. The double-stranded DNA genome of phage GAP31 has 147,940 bp with a GC% of 46.3%.

Enterobacter bacteriophage vB_PcaM_CBB is a member of cluster eight, which has five members, and is classified as a "jumbo-sized phage," characterized by atypical hairy structures along its contractile tail structure. It has a wide host range and is similar to phages *Enterobacter* phage vB_KleM-RaK2,

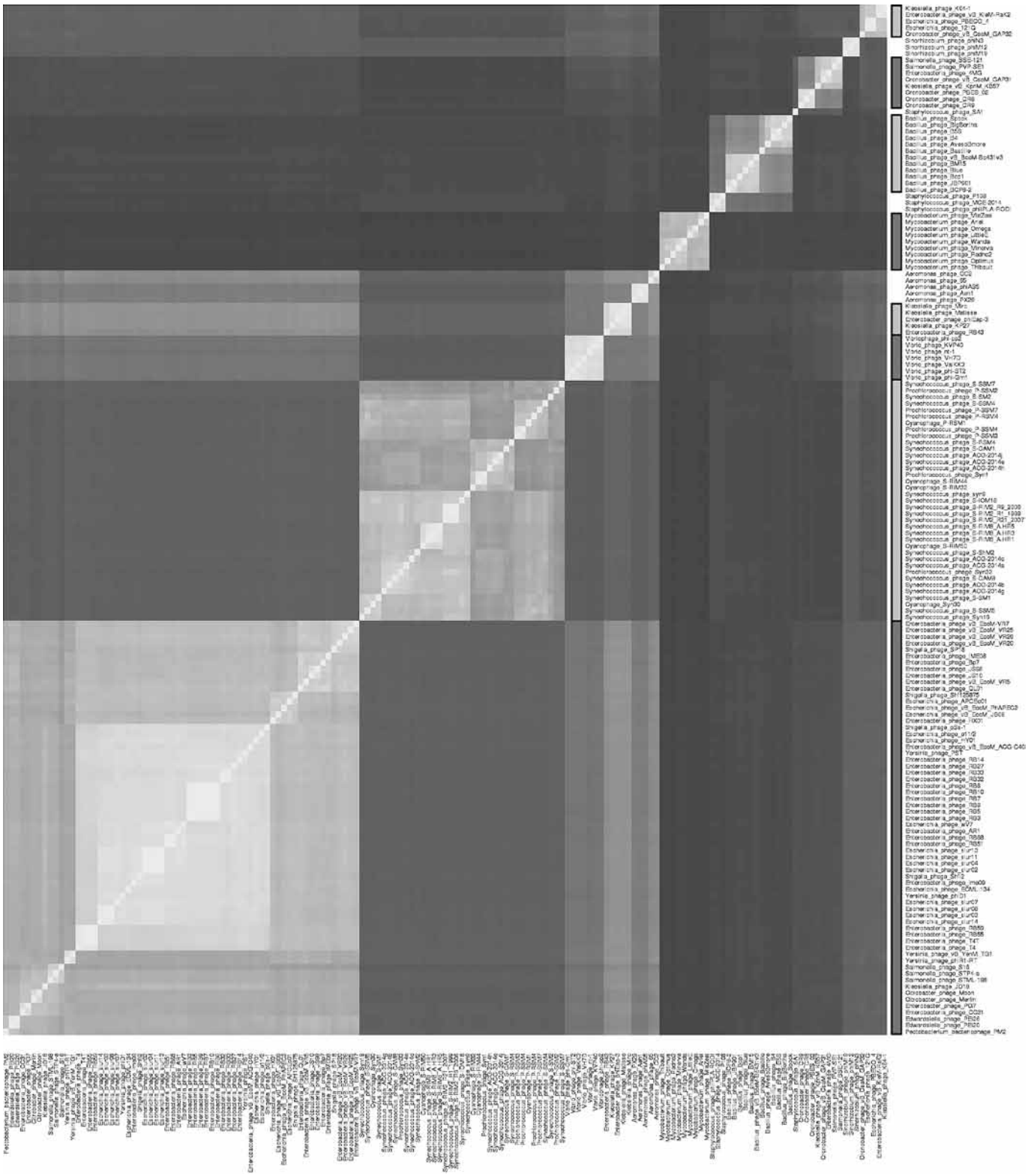

Figure 1. Heatmap of 159 prokaryotic virus strains. Alternating light and dark gray bars show several larger clusters. Lighter colors represent higher JCV values, closer to 1, denoting species which are similar to one another (same group). Darker colors represent lower JCV values, closer to 0, denoting species which are dissimilar to one another (separate group).

Escherichia phage PBECO_4, *Escherichia* phage 121Q, and *Cronobacter* phage vB_CsaM_GAP32 (Buttimer et al., 2017). Phage vB_PcaM_CBB shares 33–38% of its proteins with these other phages, yet a mean JCV of 0.73 was found for the members of this cluster. These phages have been rarely isolated, so they remain to be fully characterized. These phages are unique in that their DNA sequence has low similarity to other phages, and have a high number of species-specific proteins. Abbasifar et al. (2014) suggest putting them into their own virus subfamily.

Conclusion

In conclusion, we can see that bacteriophages form clusters somewhat similar to living organisms. Some are restricted to a single host, whereas others infect several hosts. However, with the extremely large number of phage particles and the speed at which new strains appear across the planet, it would be premature to say that there is a relatively complete picture of bacteriophage genetic diversity. Further, phages replicate differently from living organisms, and their genetic content is also more mosaic due to HGT. However, viruses belonging to the same cluster are highly similar to each other, and have a very similar genome size, genome sequence similarity, number of ORFs, and even GC%, which varies only slightly within a tight range. This could be due to limited HGT and base pair mutations.

Since viruses are not considered to be living organisms by many definitions and replicate differently than plants and animals, the cluster forming pattern could have other causes. Since phages, the focus of this study, seem to be designed to specifically target bacteria, which are not considered living in a biblical (nephesh) sense, they may have existed before the Fall. Thus bacteriophages may have been created according to the kinds of organisms from which they originated, to help modulate populations of bacteria.

Materials and Methods

Data for pVOGs was downloaded from ftp://ftp.ncbi.nlm.nih.gov/pub/kristensen/pVOGs/downloads/All/All-vogtables.tar.gz for 2,976 bacteriophage species. This database contains about 300,000 proteins clustered into 9,518 conserved orthology groups by the COG algorithm (Tatusov, 1997). From this database the top 159 viral strains were selected, which had at least 200 orthologs. The virus strains were analyzed using the Gene Content Method described in O'Micks, 2017. Annotation for different viruses was found at the Actinobacteriophage Database at http://phagesdb.org/.

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