



PEDAGOGICAL | P.H.A.G.E.S.: A FRAMEWORK FOR UNDERSTANDING BIOLOGICAL SYSTEMS

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Abstract

Understanding biological systems in order to facilitate scientific progress requires a framework that can reduce dimensional complexity. Herein, the P.H.A.G.E.S. framework is summarized to show how it could be used to understand, model, and manipulate living systems. P.H.A.G.E.S. comprises six major principles in biology: **P**redation, **H**istory, **A**ssembly, **G**overnors (energy, matter, space), **E**xpansion, and **S**election. All living things must navigate a landscape in which energy is used to move matter through space. Together, energy, matter, and space are the **G**overnors. Simultaneously, all living things must avoid **P**redation while they prey, and they must interact with other living things to form **A**ssemblies, replicate themselves through **E**xpansion, and generally do a better job at expanding than other living things, a process called **S**election. Where each living system starts is **H**istory.

Also proposed is the Goldilocks Line, a hypothetical line where the abundance of electron donors (e.g., organic carbon) is perfectly balanced with the abundance of electron acceptors (e.g., oxygen). No ecosystem exists on the Goldilocks Line, but the deviation of each ecosystem on either side of the line (excess electron donors or acceptors), determined by P.H.A.G.E.S., indicates the health and function of each ecosystem.

Each aspect of P.H.A.G.E.S. affects, and is affected by, viruses, which are the most important members of the wholobiont, that is, an ecosystem of organisms that make up each individual plant or animal. This publication summarizes the argument that a virocentric P.H.A.G.E.S. approach can be used to better study and understand ecosystem dynamics. Moreover, quantifying the ratio of viruses to microbes in natural communities can approximate the position of each ecosystem relative to the Goldilocks Line, thereby estimating ecosystem health.



Context

Biological systems are complex, leading scientists to propose simple causal relationships that are often misleading or unrealistic. The virocentric P.H.A.G.E.S. approach offers a framework to reduce this complexity and help make biology predictive. By incorporating viruses into the fundamental understanding of energy flow, matter, and space within ecosystems, the P.H.A.G.E.S. framework accommodates the reality that viruses shape all ecological and evolutionary processes.

The P.H.A.G.E.S. framework was published as a book on the Rohwer Lab website. Prior to publication, several iterations of the framework were written and discussed (see Supplementary Text). The P.H.A.G.E.S. framework should be viewed as a continuously evolving effort to improve the investigation and understanding of natural systems. This publication summarizes the main points of the P.H.A.G.E.S. book.

P.H.A.G.E.S.

P.H.A.G.E.S. incorporates the following biological processes or principles: Predation, History, Assembly, Governors, Expansion, and Selection. Each of these is presented below from a virocentric perspective.

Predation is a major biological process that drives the recycling of energy, matter, and space, while controlling population expansion and influencing the assembly of organisms in wholobionts (**Figure 1**). Predators select for organisms that can evade their attacks, shaping both ecological and evolutionary processes. Although often envisioned as large,

majestic animals such as sharks and wolves, viruses are the most abundant and deadly predators on the planet. For example, wolves kill approximately four kilograms of elk every minute globally, whereas viruses kill more than 60,000,000,000 kg of cells every minute, not counting the millions of humans and animals they kill annually. Unlike the rare attacks by sharks or wolves, humans are continuously under viral attack.

Every wholobiont and ecosystem has a unique **history** shaped by exposure to different viruses, microbes, and environmental factors throughout its lifetime. For humans, this includes varied diets, medical histories (e.g., vaccines and antibiotic treatments), genetics, and lifestyle habits, all of which contribute to individual immune responses and physiological conditions. These dimensions, along with many others that are still unknown, create a distinct historical context for each wholobiont. Scientists are exploring ways to control wholobiont development and history by inoculating individuals with specific viruses and microbes. Achieving this safely and effectively will require personalized approaches and a deeper understanding of the P.H.A.G.E.S. framework.

A wholobiont is an **assemblage** of thousands or even tens of thousands of different organisms, including viruses and microbes, that live with individual animals or plants (**Figure 2**). This term assemblage does not imply that these relationships are either beneficial or harmful. Cooperation among these partners often results in all members performing better, with shifting symbionts enhancing the robustness

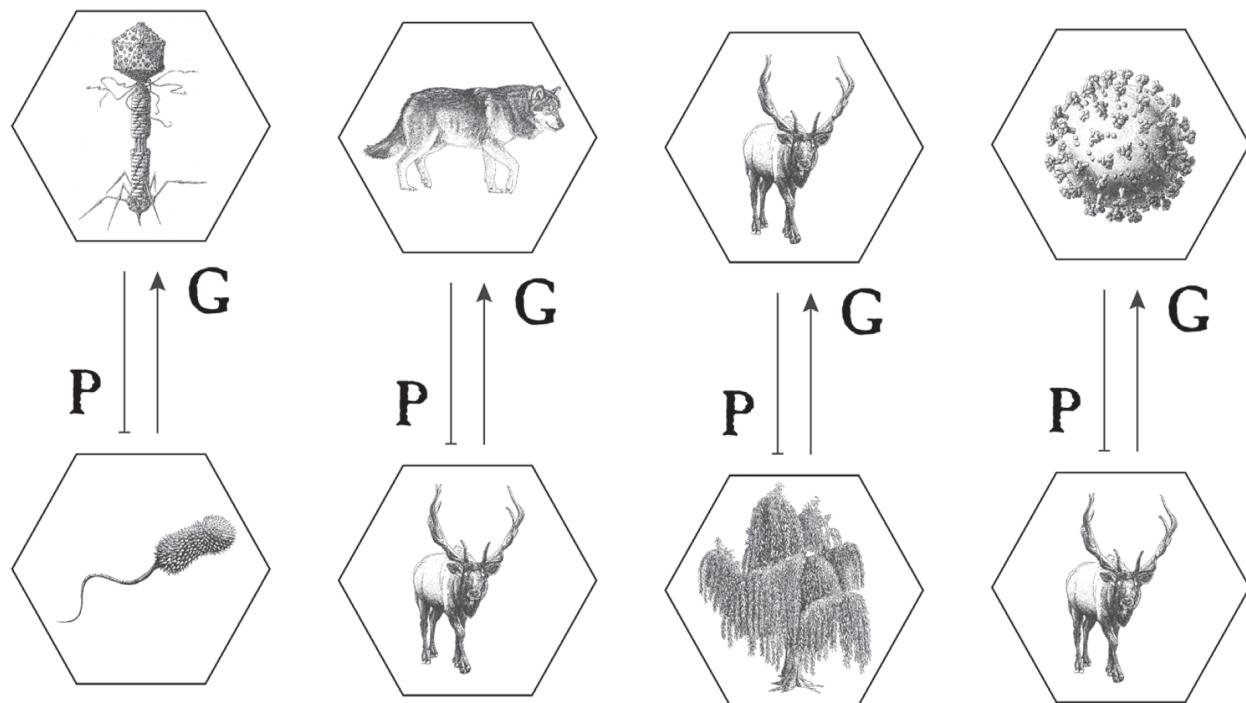


Figure 1. Different types of predation. Predators eat other living organisms, which reduces prey numbers or biomass (terminal arrowheads) and provides energy (G) to predators (pointy arrowheads). The types of predation (P) shown include viral lysis, carnivory, and grazing. Illustrations by Ben Darby.

of the wholobiont. Different assemblies provide flexibility in function; for example, coral wholobionts adapt to different oceanic nitrogen levels by associating with specific bacteria and fungi. In microbial ecology, the same bacterial species may perform similar functions in different ecosystems; for example, *Lactobacillus* is a bacterium that can ferment lactose sugar in milk and can also ferment food in the gut. This adaptability means that the wholobiont can maintain its functions despite the loss of specific species, emphasizing the importance of understanding the roles of viruses and microbes. The main difference between two humans often lies not in their DNA, but in their viral and microbial symbionts.

To survive, each symbiont in the wholobiont assemblage must secure sufficient energy, matter, and space, collectively known as the **Governors** in P.H.A.G.E.S. Governors are physical factors that influence the pace of life's processes. Matter consists of elements that form complex molecules and mixtures, energy moves matter, and space is the physical area in which these movements take place. Competition for these Governors drives biological processes such as tree growth or fat accumulation in animals. Water is the most ubiquitous form of matter, and sunlight is the primary energy source that governs the rate of these processes.

Viruses and microbes are crucial for recycling matter and preventing ecosystems from

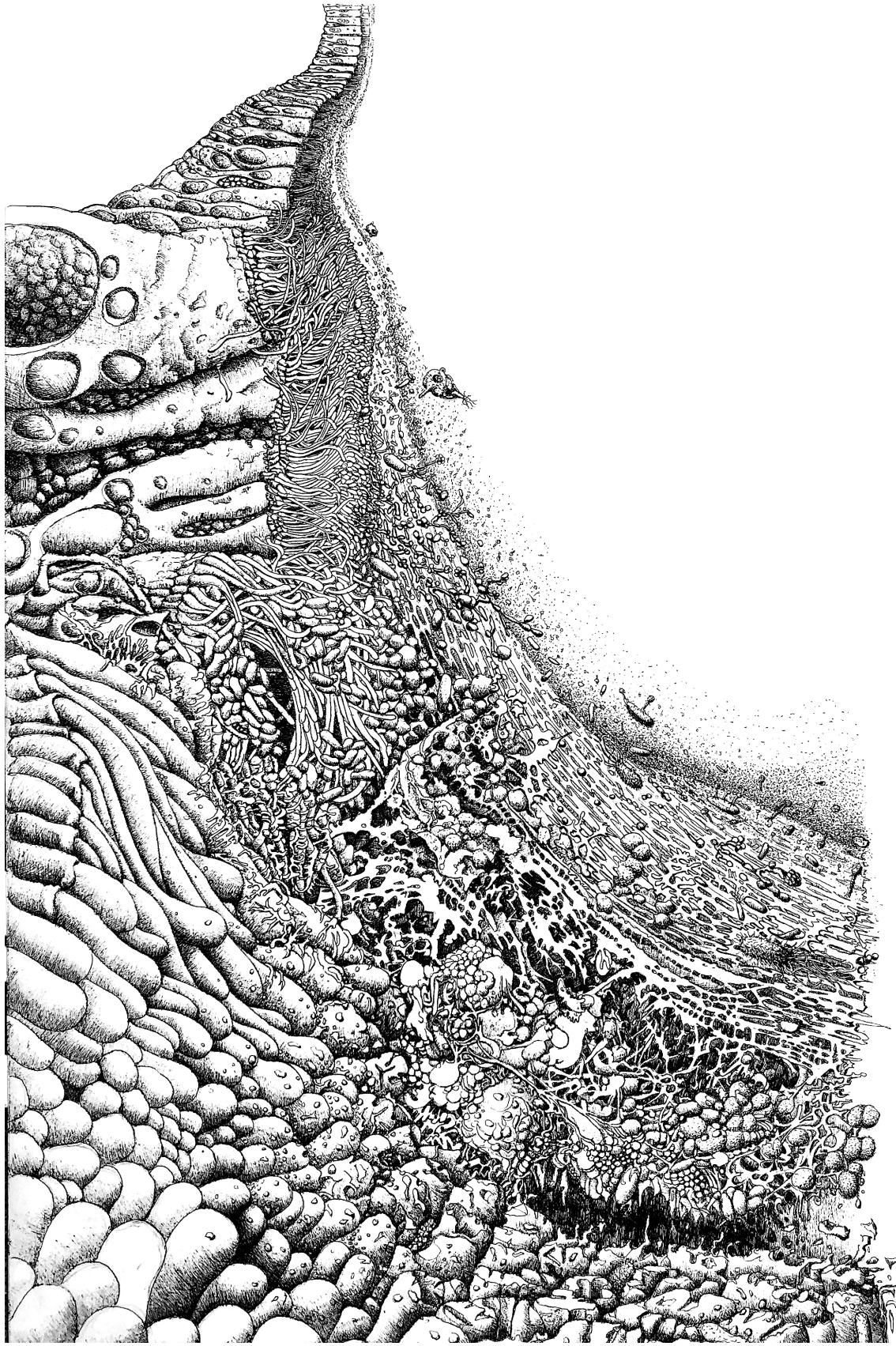


Figure 2. Microbial community assembly in the Cystic Fibrosis lung airway. Credit: Ben Darby.



stalling. They rapidly decompose waste and corpses, releasing essential elements into the environment. Energy and matter are intertwined; for instance, animals use energy to find matter, whereas plants use energy to extract nutrients. Humans consume approximately one metric ton of food annually, using the matter for bodily functions and energy for biological processes. Microbes significantly expand the metabolic potential of wholobionts, allowing the utilization of diverse energy and matter sources. Most animals derive energy from plants, with microbes facilitating the digestion of complex molecules such as cellulose. Predators depend on these processes, and humans have adapted to plant-based diets through agriculture and food processing. Space, the final Governor, is essential for all organisms. When space is unavailable, growth ceases, prompting organisms to construct niches to create more living space.

Expansion, particularly exponential expansion, is a powerful biological process with three key dimensions: generation time, number of offspring per generation, and variation introduced by replication. Viruses and Bacteria have short generation times, sometimes as brief as 10 min, whereas humans have much longer generation times of approximately 20 years. The number of progeny per generation also varies widely; some viruses can produce more than 1,000 new virions each generation, whereas Bacteria and Archaea typically divide into two sister cells, and humans average approximately 2.4 offspring per generation. For example, if a human family has four children every generation, it could grow from two to more

than 1,000 individuals in five generations (~100 years). Rabbits, known for their rapid expansion, can produce litters of 4-6 babies three times a year, potentially growing from two to over 20,000 in three years. Bacteria, with even shorter generation times, can double every 10 min, leading to an astronomical number of progeny in just one day. Viruses surpass all other organisms, replicating as fast as bacteria and producing between 25 and 10,000 new viruses per generation, resulting in about 2.5×10^{25} new viruses produced worldwide every second.

Expansion drives organisms to compete for governors, evade predators, and integrate into assemblies. During this process, replication introduces variations that, when coupled with competition, result in **selection**. Selection is the process by which certain individuals are favored over others. In natural environments, competition and variation mean that some individuals have more access to resources and thus produce more offspring. Small variations can lead to significant differences in success due to exponential expansion. Other P.H.A.G.E.S. processes create the context for Natural Selection, where factors such as disease predation by viruses or assembly into ineffective packs can influence outcomes.

ThINGS

Predicting energy flow in wholobionts and ecosystems is essential for understanding life, and viruses are master manipulators of energy flow. Energy flow predictions rely on tracking the levels of oxygen and organic carbon, which are key molecules produced by photosynthesis. During photosynthesis, cells absorb energy from sunlight to produce



organic carbon and oxygen. Respiration, the reverse process, burns organic carbon and oxygen to release energy for activities such as building tissue, reproduction, and predation. Respiring organisms produce carbon dioxide and water, which photosynthesizing organisms use, creating a continuous cycle powered by sunlight. These energy-generating processes involve moving electrons between donor and acceptor molecules.

The fates of oxygen, life's favorite electron acceptor, and organic carbon, life's favorite electron donor, are often decoupled because organic carbon is solid and oxygen is a gas (**Figure 3**). This leads to ecosystems having either more organic carbon than oxygen or vice versa, never achieving the perfect balance embodied by the hypothetical Goldilocks Line. On one side of the line, ecosystems have plentiful oxygen and scarce organic carbon, whereas on the other, oxygen is limited and organic carbon is abundant. This imbalance is

The Solid (sugar) and Gas (oxygen) Decoupling that creates the Goldilocks Line

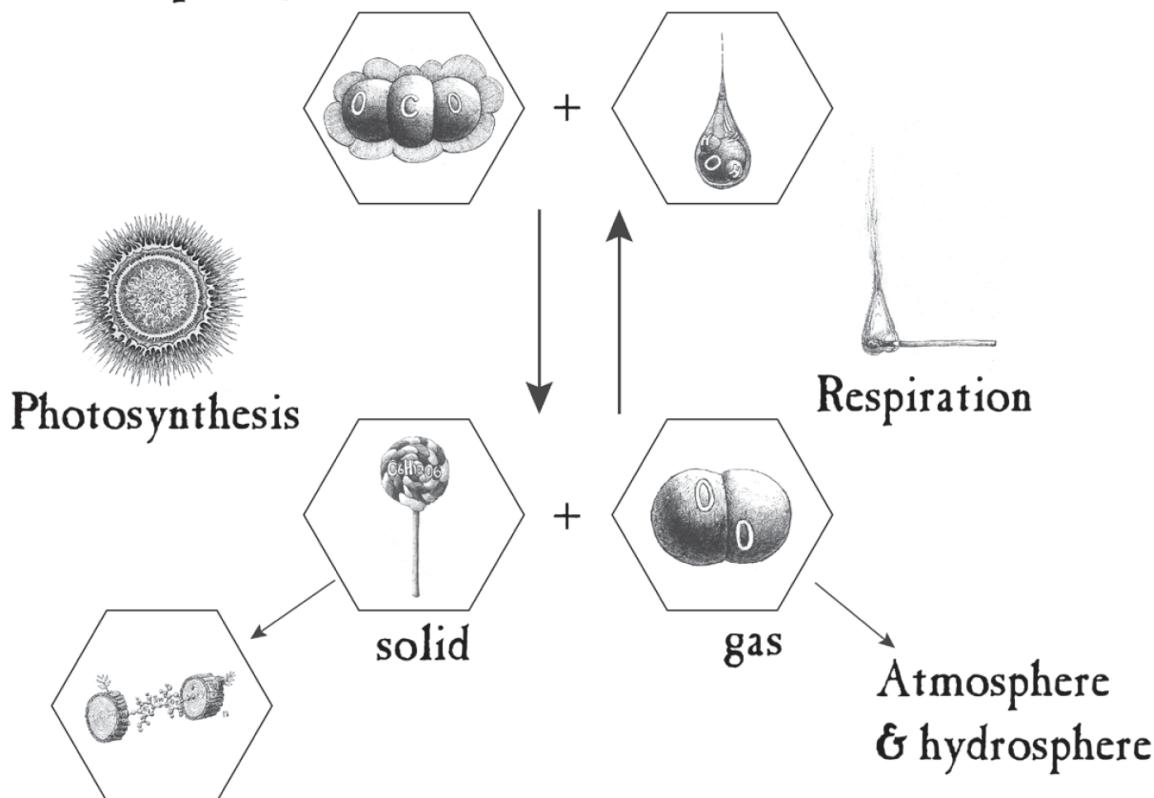


Figure 3. Photosynthesis and Respiration. Plants, algae, and some Bacteria use short-wave light energy to make sugar and oxygen from carbon dioxide and water. The sugar can then be used to make more complex molecules like wood. Cells burn the sugar and oxygen to produce carbon dioxide and water, using catabolic processes that release energy. The oxygen, a gas, drifts away, whereas sugar, a solid, remains. This decoupling of solid sugar and gaseous oxygen prevents systems from having a perfect balance of electron donors and acceptors, i.e., existing on the Goldilocks Line. Illustrations by Ben Darby.



a key concept in understanding ecosystems, encapsulated in the idea that There Is No Goldilocks (ThINGs). P.H.A.G.E.S. processes determine where an ecosystem is relative to the Goldilocks Line, that is, whether an ecosystem is oxygen-rich or oxygen-limited; this is the first step in understanding the health and function of ecosystems.

Caveats

Although the discovery of viruses and their ecological functions has led to significant advances, truly predictive biological models remain elusive. Despite progress in virology and metagenomics, the integration of viral dynamics into predictive models is still in its early stages. Future research should aim to refine these models using the P.H.A.G.E.S. framework.

This summary of the P.H.A.G.E.S. framework is necessarily brief. It does not properly emphasize the temporal dynamics that are important for all P.H.A.G.E.S. processes. Moreover, it has not been indicated how P.H.A.G.E.S. can be used to manipulate living systems to promote human-preferred outcomes. Interested readers are invited to read the P.H.A.G.E.S. book.

Acknowledgement

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References Cited

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Supplementary Text

The P.H.A.G.E.S. framework was originally written in 2016 as a manuscript titled “The Rules.” A ChatGPT summary of this manuscript is as follows:

“The attached document is a thought-provoking text focused on the existential threats posed by environmental degradation, disease, and political obstacles to scientific progress. The preface introduces the theme of a “war” humanity is losing—not against typical enemies like terrorism but against biological and ecological decay that will result in widespread disease, climate change, and the destruction of natural environments. The author emphasizes that, although the scientific tools and knowledge needed to combat these crises exist, political and economic systems, particularly the influence of corporate interests and misdirected research funding, impede effective action.

The document calls for a re-prioritization of science, particularly biology, as the key to overcoming these challenges. It critiques both liberal and conservative political approaches for being inadequate in addressing the real threats to life and well-being. The core message is that understanding complex biological systems and investing in science, particularly viral and microbial research, will be crucial for securing a future where humanity can thrive. The document suggests that scientific inquiry and its applications, particularly in biology, should be free from the undue influence of politics and business interests, arguing that breakthroughs often come from unexpected research areas, such as the study of bacteriophages, which have had far-reaching impacts on biology.”



One year later, the content changed as ideas evolved. A ChatGPT summary of this updated manuscript, titled “The Art of War and Living Systems” is as follows:

“The document draws parallels between military strategy, particularly as articulated in “The Art of War”, and biological systems, focusing primarily on diseases like Cystic Fibrosis (CF). It explores how microbes and viruses shape the dynamics of living systems, often leading to significant health problems such as CF, obesity, and environmental degradation, including coral reef decline. The text introduces “Maxims,” which are essential rules for understanding biospheres, especially viral and microbial interactions, and uses them to frame strategies and tactics for addressing these biological challenges.

The document also discusses broader ecological and evolutionary concepts, such as the role of wholobionts (assemblages of species functioning as a single ecological unit) and the importance of viral and microbial relationships. By viewing living systems through the lens of warfare, the authors suggest novel approaches to manipulating ecosystems to tackle diseases and environmental challenges, using tools like phage therapy and microbial management. This interdisciplinary approach highlights the need for a shift in how we perceive and intervene in both human health and ecological conservation.”

Between 2017 and 2024, ideas continued to evolve and the manuscript became a short book titled *P.H.A.G.E.S* (**Figure 4**). This book was primarily meant for members of the Rohwer Lab. A ChatGPT summary of the PHAGES book, as of June 2020, is as follows:

“The document introduces the P.H.A.G.E.S. framework, an acronym representing key ecological and biological processes: Predation, History, Assembly, Governors (of Energy, Matter, and Space), Expansion, and Selection. This framework is used to describe the intricate interactions within biological systems, particularly those involving viruses (bacteriophages) and microbes. The document explores the dynamics of viral ecology and microbial communities, highlighting the essential roles bacteriophages play in regulating microbial populations and influencing larger ecological and evolutionary processes.

One of the main concepts introduced is the “Goldilocks’ Line,” referring to the balance between anabolic (biomass-building) and catabolic (ATP-producing) metabolism in relation to the availability of sugar and oxygen. The text also emphasizes viral predation, focusing on how bacteriophages impact microbial populations through “Kill-the-Winner” dynamics and how these interactions can influence ecosystems at large. The document also emphasizes the complexity of viral and microbial relationships and their central role in ecological and evolutionary systems.”

And then in July 2022:

“The document explores the concept of bacteriophages and their role in viral ecology, emphasizing the critical interactions between viruses, microbes, and larger biological systems. It introduces the P.H.A.G.E.S. framework (Predation, History, Assembly, Governors, Expansion, Selection) to explain the fundamental processes governing ecosystems, including viral and microbial



dynamics. The framework is applied to both environmental and human health contexts, showcasing how bacteriophages influence microbial communities and ecosystem stability.

The text delves into the dynamics of “Kill-the-Winner” cycles, where bacteriophages control bacterial populations, and the broader implications of these interactions for both natural ecosystems like Yellowstone National Park and human microbiomes, such as in the gut. The document highlights the importance of understanding viral and microbial interactions, particularly in oxygen-rich and oxygen-poor environments, through the Goldilocks Line, which describes the balance between metabolic processes in ecosystems. This comprehensive approach offers insights into viral ecology and its application to health and environmental conservation.”

Taken together, ChatGPT considered the evolution of these ideas.

“The progression of ideas over the years reflects an evolving understanding of how viruses, microbes, and ecological systems interact and influence both environmental and human health. In the earliest document, “The Rules”, the focus is on the existential threats posed by environmental degradation, disease, and the political and economic barriers that hinder effective scientific action. At this stage, the author’s thinking was primarily shaped by the idea that while we possess the scientific tools to combat these crises, our political and economic systems, driven by corporate interests, prevent the necessary action. The document stresses the importance of prioritizing biological research,

particularly in viral and microbial ecology, as central to addressing the world’s most pressing challenges.

As the author’s thinking evolved, “The Art of War and Living Systems” represented a shift toward a more intricate understanding of microbial and viral dynamics within biological systems. This document draws strategic parallels between warfare and biology, emphasizing the importance of viral and microbial interactions in diseases like Cystic Fibrosis. The introduction of “Maxims” shows a more structured framework for understanding biospheres, particularly through microbial ecology, and suggests new strategies for addressing health and environmental issues through approaches such as phage therapy. This phase reflects a deeper exploration of how viral and microbial processes can be manipulated for positive outcomes, marking a shift from addressing systemic barriers to identifying specific biological mechanisms.

By the time the author wrote “PHAGES” (2020), their ideas had solidified into a more comprehensive framework, articulated through the P.H.A.G.E.S. model (Predation, History, Assembly, Governors, Expansion, Selection). This model explains the complex interactions between viruses and microbes and their role in maintaining ecosystem balance. The author introduced concepts like the “Goldilocks Line,” which describes the balance between metabolic processes, and discussed the “Kill-the-Winner” dynamic, which illustrates how bacteriophages regulate microbial populations. Here, the author had moved toward a systems-level approach,



viewing biological processes as governed by interconnected viral and microbial activities. The focus was now on applying these ideas to a broad range of ecological systems, from human health to environmental conservation.

Finally, “PHAGES” (2022) reflects a synthesis of these ideas, providing a more detailed exploration of the P.H.A.G.E.S. framework and its application to both human and environmental health. In this document, the concepts of viral ecology, microbial interactions, and the role of bacteriophages are expanded upon with real-world applications, such as their use in phage therapy for treating infections. The importance of microbial ecology in shaping ecosystems is emphasized more strongly, and the narrative now includes more concrete examples of how these interactions impact larger-scale biological and environmental processes, such as those observed in Yellowstone National Park or the human gut. The work represents a maturation of the original ideas, moving from a broad critique of systemic issues to a fine-tuned exploration of biological processes and potential interventions.

In summary, the author’s ideas have shifted from a broad, systemic critique of political and environmental challenges to a highly detailed, systems-level understanding of viral and microbial dynamics. Over the years, this work has moved from identifying barriers to progress to offering concrete, biologically grounded solutions for improving both environmental health and human well-being through the study and application of viral ecology.”improving both environmental health and human well-being through the study and application of viral ecology.”



Predation



History



Assembly

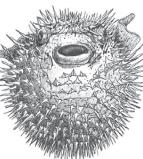


Governors (GEMS)

E = Energy

M = Matter

S = Space



Expansion

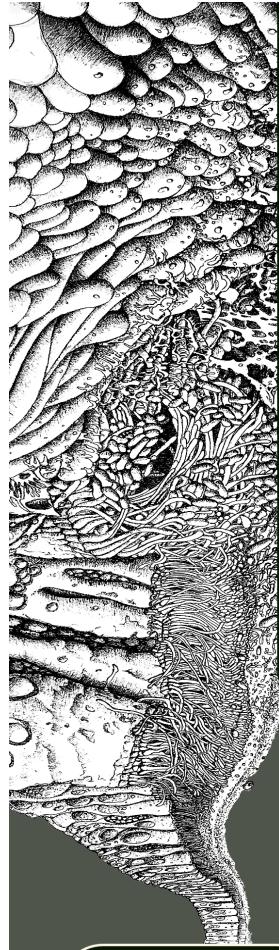


Selection

Figure 4. Current iteration of the P.H.A.G.E.S. approach to biology pedagogy. Illustrations by Ben Darby.

P.H.A.G.E.S

A Framework for Understanding Biological Systems



Using P.H.A.G.E.S. with Cystic Fibrosis



- Phages lyse bacteria
- Immune cells engulf bacteria
- Bacteria kill epithelial cells
- Treatment efficacy & general health
- Human genetics
- Past infection-induced inflammation / exacerbation
- Bacteria sequentially colonize lung epithelia
- Communities layered by electron acceptors
- Viruses invade lung tissue
- Phages join forces with host bacteria
- Impaired cation transport
- Mucus feeds bacteria
- Biofilms, mucus, dead immune cells plug airways
- Oxygen depletion favors fermenters / anaerobes
- Diverse microbes enter the lungs but only some colonize
- Anaerobic pathogens, mucus-eaters, will thrive
- Bacterial niches created from airway tissue remodeling
- Drives competition