

# Viruses as Modulators of Cellular Metabolism: Implications for Human Health and Life-Support Systems in Space

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## Abstract

Space exploration requires life-support systems for the needs of humans, plants, and their microbial inhabitants. Virus-host interactions in spaceflight are poorly understood, but viral effects on microbes and plants are critical to Earth's biosphere and human health. Viral relationships with their hosts respond to environmental changes in complex ways which are difficult to predict by extrapolating from Earth-based proxies. These relationships must therefore be studied in space to fully understand the effect of spaceflight on human health and life-support systems.

## **How do organisms and virus-host interactions impact human habitability in space environments?**

Microbes and viruses have played an indispensable role in the evolution of Earth's biosphere. Through microbial metabolic processes, microbes are the primary biological drivers for cycling most of the major elements required for life [1] and these roles will be vital for making human-led deep space flight missions possible. Viruses that infect these microbes are responsible for maintaining and promoting diversity and evolution by lysis of dominant hosts and horizontal gene transfer. Contrary to popular belief, a virus infecting a cell is not instantly nor invariably fatal. Rather, viral infection typically changes a microbe's metabolic outputs, in ways that are not yet fully characterized nor understood. The widespread and frequent detection of genes used by viruses to hijack the metabolism of their host cell(s) and manipulate them, in order to either remain intracellular for prolonged periods of time or produce progeny viruses, strengthens the need for a conceptual shift, in which infected cells are understood as unique resulting entities, which can be referred to as virocells [2–3]. Virocells undoubtedly are already an unrecognized component of human environments in spaceflight, and their effects on life support systems should therefore be characterized and understood.

Environmental control and life support systems (ECLSS) are imperative for supporting human spaceflight. These technologies, flight-proven on the International Space Station (ISS), provide or control air composition and temperature, food and water, and waste remediation. However, long duration missions beyond Low Earth Orbit (LEO) will need robust alternatives that do not rely on frequent resupply missions [4]. Closing the carbon loop through bioregenerative technologies is one approach for providing ECLSS for spaceflight beyond LEO. Algal photobioreactors can remove CO<sub>2</sub>, create O<sub>2</sub>, remove or alter waste, and produce edible biomass [5]. These photobioreactors were recently shown to withstand the dynamic temperature environment experienced within the ISS thermal control loops [6–7]. Preliminary spaceflight studies using algae for ECLSS observed thriving cultures [8–9]. Likewise, extremophilic algae, lichen, cyanobacteria and fungi included in experiments mounted on the outside of the ISS and Space Shuttle, survived week to month-long missions [10–11]. However, these studies did not characterize the microbiome within the non-axenic cultures. Understanding potential biome or virome shifts within these systems over long durations may elucidate the need for specific algal species selection, viral or bacterial-based system failures, and any operational considerations [5].

Additionally, biofouling of photobioreactors or any other ISS system, especially wetted surfaces, causes significant system downtime and need for crew time for maintenance and repairs [12]. Including system designs that minimize biofouling through characterization of the composition of these biofilms, their biome evolution, and interaction with spaceflight systems may reduce mission dependency on resupply missions. Chemosynthetic organisms, or those that create their own food not with sunlight but from chemical energy from inorganic compounds [13–14], could be co-opted specifically to remove wastes, recycle nutrients, or even provide an additional energy source to support human life during space flights.

Spaceflight stresses biological systems, including immune systems that fight virus infections, but these effects are not fully understood [15]. The reaction of viruses to microgravity is poorly known,

for not only human viruses, but also for viruses infecting components of the human microbiome and proposed life support organisms. After 6–12 months in space, astronauts have significant changes in their microbiome that lead to rashes and hypersensitivity episodes, warranting further investigation of the effects of long-term exposure from the space environment on humans and their microbes and viruses [16]. Moreover astronauts, subjected to the stresses of spaceflight, experience reactivation of latent viruses, such as herpes simplex virus [17].

Plant viruses are a threat for sustainable agriculture and disease management relies strongly on a fast and accurate identification of the virus. There have been efforts to grow plants on the ISS for CO<sub>2</sub> removal and O<sub>2</sub> production, to provide a source of multivitamins, to reuse urine, and to promote psychological well-being [18]. Many plants have been grown under microgravity including flowers, herbs, and vegetables. Due to the stress of spaceflight, viral infection of these plants is a major concern and a recent study found that spaceflight factors significantly affect tomato plants [18]. They increased the productivity of the plants and the concentration of some vitamins such as carotenoids, which are important for astronauts on long-term space missions. Importantly, plants grown from seeds that were in space for a half of a year, were resistant to viral infection. Moreover, the resilience of seeds from many plant species (among other organisms) were tested by keeping them outside the ISS for 558 or 682 days, exposing them to high levels of radiation [19]. All plant seeds could germinate after the shorter flight, but only plant seeds with a stronger coat could survive the longer radiation exposure. While these studies show promise for plants on long-term spaceflights, there is limited understanding of their viruses on short flights and no information for long-term flights.

Clearly, viruses, microbes, and plants will be critical factors in astronaut health and safety. To enable long-duration crewed missions beyond low Earth orbit, it is essential to understand the influence of the space environment on viruses, their hosts, and their interactions, both within the human body and in life-support systems.

#### *Future directions*

- a) Characterize human, algal, plant, and microbial viruses in space environments, including the ISS
- b) Characterize biofilm composition and growth dynamics in human, algal, and plant systems in space environments
- c) Assess triggers that cause latent infections to become virulent in a space environment

#### **How do microbes and viruses persist in harsh environments including human built spacecraft?**

Extreme environments on Earth, including environments in our daily experience such as plumbing and mining sites, illustrate the remarkable potential for viruses to persist and interact with hosts under unexpected conditions. Diverse viruses have been shown to persist in inhospitable conditions such as droplets suspended in the atmosphere [20], permafrost-associated soils [21–23] or other icy environments such as ice cores or cryoconite holes [24–26] and even ice cubes [27], hot springs [28–29] and domestic hot water systems [30], chemically harsh conditions [31], and

deep-sea sediments [32–33]. Furthermore, virus remnants are present in most cellular genomes, especially in humans where viruses play key roles in human physiology [34–35]. Viruses have evolved multiple mechanisms to survive these conditions and in doing so, often also protect their host. For instance, viruses can confer heat tolerance to their host [36] or carry genes for sporulation so the host can form an inactive spore that is robust to unfavorable conditions [22; 37]. Harsh environments such as polar regions or hydrothermal vents also have a higher incidence of temperate viruses, which have the capability of residing within their microbial hosts (lysogeny) until conditions are favorable for viral replication [38–39]. While in this lysogenic state within their hosts, viruses still can express genes that alter their microbial host’s physiology and metabolism, increasing the host cell’s ability to survive conditions in which resources are limited, including in sea ice environments [40–41].

Microbes have also evolved many mechanisms for surviving harsh conditions even without viral infection. One mechanism for surviving desiccation is anhydrobiosis, in which water is expelled from the cells of the organism and all metabolic processes are stopped [42]. Through anhydrobiosis, these microorganisms can survive a range of chemical and physical conditions over the course of decades [42]. Rotifers, tardigrades, and nematodes have all been shown to use anhydrobiosis to survive the harsh conditions of space [43–50]. Recently, cyanobacteria have been revived after a 672-day exposure to space outside of the ISS [51]. Dormant states such as anhydrobiosis raise the question of how long organisms in these states may remain viable, however. Cyanobacteria in Antarctica have been recorded metabolizing within a week after rewetting following 20–30 years without stream flow [52]. Cyanobacteria are not alone, nematodes have been revived from 30,000 old permafrost in Siberia [53] and rotifers in northeastern Siberia revived from 24,000 year old permafrost [54]. Microbes living in low-energy conditions in the South Pacific Gyre have even retained their metabolic response after 101.5 million years [55]. Some organisms not only survive via dormancy, but actively grow under extreme conditions. In the dry tephra at 6,000 m.a.s.l. on Atacama volcanoes, the thin atmosphere and low precipitation leads to the highest recorded UV fluxes on Earth’s surface and daily fluctuations across the freezing point [56]. The dominant organism in this site is a metabolically-versatile yeast in the genus *Naganishia* that actively grows even during extreme diurnal freeze–thaw cycles [57–58]. This organism provides a template for the type of life that may not just persist but grow in space-like environments [59].

These data show the potential for organisms to survive and even grow in space-like environments, but there is no research on virus, virus-virus, or virus-host interactions in space environments. It is critical to evaluate the effect of viruses on organisms, because in other harsh environments virus-host interactions are fundamentally different [38] compared to ideal environments — for example viruses have been shown to allow photosynthesis in cyanobacteria under desiccating conditions [60]. It is now feasible to computationally integrate how functions encoded in virus genomes interact with material and energy resources of their hosts to predict the timing and levels of virus growth [61]. This capability should be deployed with respect to characterizing viral activity in human-supporting environments in space. Similar virus-host interactions are likely wherever we take life, and it is thus critical to expand our understanding of these interactions on Earth to enable the detection and identification of such phenomena during space missions.

### *Future directions*

- a) Obtain a better molecular understanding of how viruses hijack their host cellular machinery in a space environment
- b) Explore the broad range of virus-host interactions in spaceflight
- c) Quantitatively estimate the role and impact(s) of virocell metabolism in space flight environments

### **Conclusion**

Safe and effective pursuits in deep space travel will require a thorough understanding of the human microbiome in space, including viruses. Viruses are also key contributors to Earth's ecosystems via lysis of microbial cells and modulation of their metabolism, yet there are major unknowns regarding how their dynamics change in a space environment, how they guide the microorganisms that they inhabit, and how they in turn impact life support systems and human microbiomes future human spaceflight missions. This topical white paper raises key questions about viruses that infect humans and microbes across several ecosystems (e.g., human, marine, and soil) that need to be examined specifically in space to understand the effects of the spaceflight environment on biology.

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