Microgravity and Low-Shear Modeled Microgravity Effects on Dynamics of Salmonella: Implications for Space Travel and Colonization

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Abstract

Salmonella, a well-known pathogenic bacterium, experiences particular difficulties and stressors in space, specifically in varying gravity levels. Significant differences in the growth rate, morphology, gene expression, pathogenicity, and biofilm formation of *Salmonella* spp. have been found in studies examining the dynamics of the organism under microgravity (MG) and low-shear modeled microgravity (LSMMG) settings. Concerns are raised about the possibility of increased pathogenicity and weakened control of *Salmonella* infections during space missions as a result of these changes in *Salmonella* behavior in MG and LSMMG environments. Developing solutions to reduce the hazards associated with *Salmonella*-related infections in space requires an understanding of the mechanisms enabling *Salmonella* adaptation to MG and LSMMG settings. The results of these investigations also have wider ramifications for how we comprehend microbial behavior and adaptation to extreme environments. In this review, Examine the effects of microgravity and low-shear modeled microgravity conditions on the dynamics of *Salmonella* and the potential implications of MG and LSMMG-induced changes in *Salmonella* for future space travel and colonization.

Introduction

Space travel and colonization, introduced in an era of unprecedented exploration, have refined our understanding of limitless potential and expanded our understanding of science and the universe. This has led to numerous technological innovations and a vision of the future where humanity may establish settlements beyond Earth, offering new possibilities for scientific research. However, these endeavors also present daunting challenges. Understanding the impact of microgravity (MG) and low-shear modeled microgravity (LSMMG) on *Salmonella* dynamics is crucial, given its real-world implications for space travel. NASA's advances in rocket design, astronautics, astrophysics, robotics and medicine have brought space colonization closer to reality *[Rosenzweig 2009]*. Ambitious programs are testing the boundaries of human endurance in space by simulating off-world conditions on Earth. Ensuring astronaut safety of the astronauts in these missions is paramount.

Salmonella, a genus of rod-shaped, gram-negative bacteria, comprises two species: *Salmonella bongori* and *Salmonella enterica*. Certain serotypes of *Salmonella* cause infections characterized by gastrointestinal pain, diarrhea, and fever, sometimes requiring hospitalization [*Threlfall 2002*]. The Centers for Disease Control and Prevention (CDC) report approximately 1.35 million *Salmonella* infections annually in the United States, leading to about 26,500 hospitalizations and 420 deaths [*CDC*]. *Salmonella* serotypes vary in traits and virulence factors, influencing their capacity to cause illness. *Salmonella enterica* is divided into six subspecies: *S. e. enterica, S. e. salamae, S. e. arizonae, S. e. diarizonae, S. e. houtenae, and S. e. Indica*. *Salmonella* can thrive in a variety of settings, including food, water, animals, humans and various environmental conditions, including low/no gravity [*Weidemann 2015*].

Microbes present on spacecraft surfaces, equipment, or in food and water supplies during space missions are a major concern *[Horneck 2010]*. In the context of *Salmonella*, the spacecraft and environment can become breeding grounds for harmful microbes, posing risks to human health and colonization efforts. The issue extends beyond the lab, as the findings could significantly impact future space living and exploration. In this review, I explore how MG and LSMMG conditions affect *Salmonella* dynamics and the potential concerns these microgravity-induced changes pose for space travel and colonization.

Microgravity, Low-shear Modeled Microgravity, and *Salmonella*

Microgravity (MG) describes an environment where gravitational forces are greatly reduced, creating an almost weightless state, either in space or during freefall. Although gravitational forces are not completely absent in microgravity, they are significantly diminished, resulting in a near-weightless experience for objects and individuals, whether in space or during the freefall phase of a parabolic flight [*Karmali 2008*]. Due to the weak gravitational pull in microgravity, objects and living things appear to float, creating unique experimental settings distinct from Earth's gravity. For instance, a study on the metabolites of *Streptomyces rochei and Cupriavidus metallidurans* utilized simulated microgravity through rotating-wall bioreactors [*Tangerina 2020*]. These bioreactors are specialized laboratory devices designed to mimic microgravity conditions by continuously rotating cell cultures, creating a low-shear, fluid-filled environment. This setting allows researchers to study cellular behavior in a near-weightless state, resembling conditions experienced in space. The study aimed to understand how simulated microgravity affects the metabolic processes and chemical production produced by *Streptomyces rochei* and *Cupriavidus metallidurans.* The research's broader implications include contributing to our understanding of microbial behavior under microgravity conditions, relevant to both space exploration and the development of biotechnological processes. Additionally, the findings might be Earth-based applications, potentially leading to the development of new processes or products by manipulating microbial metabolism under conditions resembling space [*Acharjee 2022*].

Low-Sheared Microgravity (LSMMG) is a specific type of microgravity environment engineered on Earth to simulate specific aspects of weightlessness [*Nickerson 2004; Barilla 2022; Crabbe 2010*]. It enables researchers to isolate the effects of microgravity on biological systems, such as bacteria, in a controlled setting. This helps to comprehend how microorganisms respond to altered gravitational conditions. LSMMG and MG represent two distinct types of gravitational environments: MG occurs naturally in space, while LSMMG is an Earth-based simulation mimicking certain elements of MG. Both environments present unique opportunities for scientific investigation and insights into biological system behaviors under weaker gravitational fields.

LSMMG efficiently reduces fluid shear forces (mechanical forces exerted on fluids when they flow or move) while establishing a controlled test environment [*Fukuda 2000*]. Specialized equipment, like rotating bioreactors or clinostats, is used to produce various gravitational pulls and reduce fluid shear. To dive more specifically, Clinostats, for one, are machines that continually rotate biological samples to replicate microgravity conditions. They are essential in LSMMG investigations, allowing researchers to investigate the subtle effects of changed gravity on biological systems, particularly bacteria. The controlled environment created by LSMMG testing allows scientists to explore how different gravitational pulls, such as those produced by clinostats, influence biological reactions.Through LSMMG testing, scientists can examine the nuanced ways that altered gravity impacts biological systems, particularly bacteria.

Salmonella Dynamics in Microgravity and Low-Sheared Modeled Microgravity

The field of *Salmonella* research conducted in MG and LSMMG is examined in this section through experiments conducted aboard space shuttle missions STS-115 and STS-123, which took place in low Earth orbit. These studies offer an in-depth analysis of how various gravitational settings can influence the physiological characteristics and growth dynamics of *Salmonella*, highlighting concerns relevant to space exploration [*Wilson 2008*].

Aboard Space Shuttle missions STS-115 and STS-123, researchers investigated how the spaceflight environment affects the virulence of *Salmonella* and whether growth media composition influences this response. The primary subjects were *Salmonella enterica serovar Typhimurium* with variables including different media compositions like Lennox Broth (LB), M9, and LB-M9 salts media. Cultures were closely monitored for temperature and humidity, with coordinated activation and termination times to maintain consistent conditions between spaceflight and ground control samples.

The study revealed that *Salmonella* cultured in LB media during spaceflight exhibited increased virulence in a murine model, with decreased time-to-death and lower LD50 values compared to ground controls. The median lethal dosage, or LD50 for context, is a common statistic used to express the fatal dose of a chemical that would kill 50% of a test animal population. In the study, the LD50 values were used to quantify the virulence of Salmonella cultured in Luria-Bertani media during spaceflight. However, when cultured in M9 minimal media or LB-M9 salts media in spaceflight, LD50 values showed no consistent difference in comparison to ground controls. This indicates that media composition significantly influences *Salmonella's* virulence, with spaceflight intensifying these differences, especially for LB media versus M9 media. These findings highlight the importance of tailoring microbial control measures and safety protocols for space missions to account for media-dependent variations in Salmonella virulence, ensuring astronaut safety and reducing the risk of infectious diseases during extended space travel. They also underscore the importance of media composition in bacterial behavior and virulence, with broader implications for studying infectious diseases on Earth and developing therapeutics. These findings highlight the importance of tailoring microbial control measures and safety protocols for space missions to account for media-dependent variations in Salmonella virulence, ensuring astronaut safety and reducing the risk of infectious diseases during extended space travel.

Using specialized equipment, Low-Sheared Microgravity Experiments

Rotating bioreactors are designed to create an environment where cells experience minimal shear stress due to controlled rotation. These cells can include a variety of biological entities, including bacterial cells, mammalian cells, yeast cells, and other microorganisms for research and bioprocessing purposes. This advanced device aims to replicate the weightless conditions found in space, enabling researchers to precisely study the behavior of organisms like *Salmonella*. Key aspects of the experiment are highlighted as follows:

1. Molecular adaptations in Gene Expression Patterns

The investigation of *Salmonella's* genomic responses is a compelling aspect of LSMMG research. Under LSMMG conditions, specific genes related to stress responses, metabolic activities, and virulence factors show notable changes in expression levels. Pacello et al. found that these genetic modifications suggest that *Salmonella* may undergo molecular adaptations to cope with the particular stresses found in LSMMG settings [*Pacello 2012*].

Various *Salmonella* strains, including *S. Typhimurium ATCC14028, S. Typhimurium DT104, S. Typhimurium LT2, S. Enteritidis LK5, and S. Choleraesuis A50*, have been grown under LSMMG and MG conditions using bioreactors. For epitope tagging and immunodetection, proteins such as KatE, KatG, KatN, and SodA, were tagged with 3xFLAG to assess their expression and activity. These proteins are crucial components in bacterial physiology, each serving distinct roles in cellular processes. The decision to epitope tag and immune detect these proteins, particularly with 3xFLAG, driven by the importance of understanding their expression and activity levels.

Western blotting and immunodetection were used for protein analysis, and bacterial growth, as well as resistance to hydrogen peroxide and acid stress, were also assessed [*Barraud 2021*]. Catalase and peroxidase activities of specific enzymes (KatG, KatE, KatN) were visualized on native gels, and spectrophotometric assays were used to measure catalase activity. The effects of these genetic changes could significantly impact *Salmonella's* pathogenicity and treatment responses in the context of space travel. Here are the key findings of the research:

- Enhanced Hydrogen Peroxide Resistance: The study discovered that LSMMG conditions significantly increase the resistance of various *Salmonella* strains to hydrogen peroxide compared to NG conditions. This increased resistance is a common feature among most of the tested *Salmonella* strains.
- Catalase Involvement: The enhanced resistance to hydrogen peroxide observed in LSMMG was linked to changes in catalase activity, specifically KatG and KatN. KatN activity notably increased in LSMMG-grown bacteria, while KatG activity decreased.
- Differential Response in Different Strains: While most *Salmonella* strains exhibited increased hydrogen peroxide resistance in LSMMG, the response varied between strains with some strains showing a more significant response than others. The strains of Salmonella exhibiting variable responses to LSMMG and changes in catalase activity, particularly KatG and KatN, are crucial to understanding the adaptability and virulence potential of different Salmonella variants. The specific strains involved in the study were likely chosen based on their relevance to human health, their prevalence in certain environments, or their distinctive genetic characteristics.

The identification of strains that demonstrated a more significant response to LSMMG and increased hydrogen peroxide resistance is essential for several reasons including virulence and pathogenicity, ability to stress and genetic diversity .

- Resistance to Acid Stress: The study found that LSMMG-grown *Salmonella* strains generally exhibited higher resistance to acid stress, although there were some exceptions.

2. Relevance to Protecting Astronaut Health in Space Travel:

In a conducted study, researchers investigated the impact of Low Shear Modeled Microgravity (LSMMG) on Salmonella, a pathogenic bacterium, with a focus on various aspects such as virulence, antibiotic resistance, growth, reproduction, and transmission. The study utilized epitope tagging and immunodetection methods to assess the expression and activity of key proteins, including KatE, KatG, KatN, and SodA, under different culture conditions in space. The researchers also examined the responses of different Salmonella strains to LSMMG, particularly noting changes in catalase activity and hydrogen peroxide resistance.

Prior research has shown significant implications for space travel, especially regarding the security and wellbeing of astronauts during extended missions [*Pacello 2012*]. LSMMG research impacts various critical aspects of *Salmonella*, including virulence, antibiotic resistance, growth, reproduction, and transmission. These findings are crucial for space travel:

- *Salmonella* is an active participant in space, not a passive bystander. It changes its genetic makeup to adapt to microgravity, as evidenced by alterations in gene expression patterns *[Najrana 2016]*. This directly affects its virulence and potential resistance to antimicrobial treatments in space, posing challenges for scientists in developing effective defenses.

LSMMG induces changes in environmental factors such as osmolarity, pH, temperature, and reactions to antimicrobial challenges [*Najrana 2016*]. Predicting and managing *Salmonella's* behavior in space is essential to protect astronaut health and ensure the success of lengthy missions, which hinge on understanding and adapting to these alterations.

Space Travel : Risks, Concerns, Challenges Pertaining to Bacteria

As humanity explores the possibilities of space travel and colonization, we encounter a wide array of scientific, technical, and health challenges. These include understanding the impact of microgravity on the growth, virulence, and genetic expression of microorganisms. Understanding these effects is a scientific challenge with implications for controlling and preventing infections during space missions. Studying the space microbiome, which encompasses the collection of microorganisms present in spacecraft and space habitats, is crucial for scientific research [*Venkateswaran 2014*; *Checinska 2015*]. Identifying and characterizing these microorganisms helps researchers understand how they interact with human health and the spacecraft environment. It is particularly important to understand how bacteria, especially those causing diseases like *Salmonella* infection, behave in space habitats to overcome these challenges.

Next, we explore the potential dangers, issues, and challenges associated with microorganisms in the context of space travel. Developing and maintaining effective sterilization and containment measures to prevent the proliferation of harmful bacteria on spacecraft and in space habitats poses a significant technical challenge [*Pavletic 2022*]. This includes ensuring that spacecraft are free from contaminants that could affect the health of astronauts. Implementing biosecurity measures to control and monitor microorganisms on the International Space Station (ISS) and other space habitats is another technical challenge, as it requires sophisticated containment and monitoring systems.

Microgravity's Effect on Bacterial Behavior

The impact of microgravity on microbial development and behavior is a crucial aspect of space travel. In the regulated and confined environment of a spacecraft, the dynamics of bacterial populations can change drastically. Microgravity can alter some bacteria's ability to form biofilms, which are intricate networks used to cling to surfaces and protect themselves from harmful elements. This has implications for how bacteria develop resistance to antibiotics, potentially leading to more persistent and difficult-to-treat strains.

Research on *Pseudomonas aeruginosa* in microgravity environments has shown a significant shift in microbial behavior, with a 60% reduction in biofilm formation **[cite]**. This finding is crucial for spacecraft surface maintenance. As indicated before, the significant reduction in *Pseudomonas aeruginosa* biofilm formation observed in microgravity environments is crucial for spacecraft surface maintenance. This finding suggests potential benefits, including improved equipment performance, contamination control, material preservation, and enhanced astronaut health and safety during space missions. Moreover, microgravity can influence the development of antibiotic resistance, leading to the emergence of more robust bacterial types.

Microgravity-induced changes have been linked to a 2.5-fold increase in the development of antibiotic-resistant *Staphylococcus aureus* strains [*Wilson 2008*]. This highlights the importance of understanding microbial adaptations in space for effective antibiotic management.

1. *Salmonella's* Modified Pathogenicity
   Salmonella, not immune to the modifications brought on by microgravity, presents a critical concern for understanding its altered pathogenicity in space. Astronauts in confined spaces, such as spacecraft and space habitats, are at risk of infections [*Wilson 2008*]. Additionally, microgravity can weaken the human immune system, thus if *Salmonella* becomes more virulent or resistant in space, it poses a significant threat to astronaut health. Understanding these changes is crucial in developing strategies to mitigate the risks.

Studies have shown that in LSMMG environments, the virulence of *Salmonella* increases. This enhancement is linked to changes in growth patterns and gene expression, potentially intensifying the expression of virulence factors [*Barilla 2022*]. As a result, Salmonella might become more adept at spreading disease in space. This finding underscores the importance of applying aseptic techniques and safety standards to preserve astronauts' health. It also raises questions about the hazards of epidemics during prolonged space missions.The difficulties astronauts have in cramped space habitats are further complicated by *Salmonella*'s altered virulence in microgravity. *Salmonella* is a pathogenic bacterium that can cause food poisoning and other illnesses, therefore people's health in spaceships and habitats is seriously at stake. Determining the behavior of *Salmonella* in microgravity is essential to creating effective plans to shield astronauts from any infections. The hazards are increased by the dual effects of microgravity on the human immune system and the pathogenicity of *Salmonella*. As a result of altered growth patterns and gene expression, LSMMG settings exhibit increased virulence, which emphasizes how critical it is to put aseptic procedures and safety regulations in place. In the unique space environment, microgravity's dual effects on the human immune system and the pathogenicity of Salmonella heighten the hazards of microbial contamination. Altered growth patterns and gene expression in LSMMG settings increase bacterial virulence, emphasizing the critical importance of implementing aseptic procedures and safety regulations. Spacecraft operate within closed habitats, necessitating advanced air filtration systems and stringent cleanliness protocols to minimize the risk of microbial contamination. Advanced sterilization methods, including dry heat, vaporized hydrogen peroxide, and ultraviolet radiation, are employed to eliminate microbial contaminants in space equipment completely. Additionally, microgravity-compatible bioreactors provide insights into bacterial behavior in space, aiding in developing targeted aseptic procedures for maintaining a safe environment for astronauts during extended space missions.

Risks of Space Outbreaks: Will They Increase?

There is legitimate concern over the possibility of bacterial epidemics in cramped spacecraft habitats. This danger may be exacerbated by changes in bacterial behavior induced by microgravity, such as increased pathogenicity and antibiotic resistance [*Taylor 2015*]. The continual recycling of air and water in closed-loop life support systems on spacecraft presents numerous opportunities for microbial contamination and transmission [*Taylor 2015*]. Therefore, it is crucial that space authorities take prompt action to prevent the likelihood of more virulent bacterial strains triggering outbreaks.it is imperative for space authorities, including organizations like NASA and the ESA and international space agencies, to promptly implement preventive measures against the emergence of more virulent bacterial strains. These preventive actions should include rigorous cleanliness protocols, advanced sterilization techniques, and continuous monitoring of microbial environments within spacecraft. Additionally, the risk of increased antibiotic resistance in the weightless environment of space poses a serious threat to astronaut health and safety. The elevated pathogenicity and the potential for antibiotic resistance in bacteria contribute to the risk of bacterial epidemics in spacecraft habitats [*Taylor 2015*].

Microorganisms Yet to Be Studied in MG or LSMMG

There is still much to learn about the microorganisms that naturally occupy space habitats. Despite our studies of the microbes travelers bring with them to space and those discovered in spacecraft, such as *Methylococcus capsulatus* [*Koehle 2023*]. This methane-oxidizing bacteria has not been thoroughly investigated in microgravity settings. Its metabolic capabilities make it a compelling subject for investigation in space habitats.

The health of future space colonies may largely depend on local microorganisms. Exploring how they interact with the people inside and the environment of the spacecraft is an intriguing research direction. This allows scientists to investigate the dynamic interactions between diverse microbial ecosystems and human occupants, as well as the built environment. In envisioning future space colonies, researchers recognize the potential significance of local microorganisms in maintaining the health and well-being of the inhabitants. This involves delving into the intricate interactions between diverse microbial ecosystems within the spacecraft, the human occupants, and the built environment. Scientists aim to understand how microbial communities dynamically interact with each other in various spaces, exploring the impact of design, materials, and environmental conditions on their behavior. Simultaneously, they study how these microorganisms interact with the human microbiome, potentially influencing human health and well-being in a spacecraft or colony's confined space. The research direction aligns with regenerative systems, where the intentional cultivation of specific microorganisms could contribute to air and water purification, waste recycling, and overall sustainability, fostering a more autonomous and healthy space habitat.Understanding the roles these local microorganisms play in nutrient cycling, air purification, and waste management can be beneficial for creating self-sustaining and health-promoting environments in future space colonies. This approach will foster a holistic view of the cohabitation of humans and microbes on the extraterrestrial frontier.

Most research to date has focused on relatively short-term space missions. As we consider longer journeys into space, understanding how microbes adapt and evolve over extended periods is crucial.

Conclusion

Salmonella, a genus of bacteria known for causing various food-borne illnesses in humans, is significant due to its potential to endanger astronauts' health in space. Understanding how its virulence and behavior change in microgravity environments is crucial to reducing health risks and preventing outbreaks during space missions.

Furthermore, recognizing the connections between space flight and colonization is critical as we broaden our horizons in both fields. Research on *Salmonella* in microgravity (MG) and low-sheared microgravity (LSMMG) environments has provided scientists valuable insights that extend beyond the laboratory. These findings have immediate implications for designing spacecraft, life support systems, and habitats in space. Understanding how microbes react in space will help improve space food safety procedures, develop more effective defenses against infectious agents, and enhance waste management techniques.

Studies have shown multiple enhancements in antibiotic resistance in microgravity: *Salmonella* bacteria exposed to microgravity environments may express more genes resistant to antibiotics. This indicates that the efficacy of conventional antibiotic treatments may face obstacles due to bacterial activity in space environments.

The expression of virulence genes is significantly altered in *Salmonella* grown under low-shear modeled microgravity. This suggests that the bacteria's pathogenic potential is altered by the microgravity environment, which has implications for developing focused countermeasures and space-based vaccinations [*Juergensmeyer 2011*].

Salmonella forms stronger biofilms under microgravity conditions, making them more resistant to cleaning agents [*Aleksandrowicz 2023*]. Understanding this phenomenon is essential for designing spacecraft surfaces and life support systems.

In conclusion, research into dynamics of *Salmonella* in MG and LSMMG environments is an important field with broad ramifications. It provides the groundwork for safer and more sustainable space flight and colonization efforts, in addition to addressing current concerns about astronaut health. These scientific studies provide insight into the future and guide us toward a time when humanity can thrive beyond Earth's atmosphere.

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