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Design Criteria
With Problem Statement Portion revised till Needs and Reference (1.4 not revised)

Partial Gravity Bioreactor

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Abstract

The progress of human exploration to space, the Moon, and Mars is not considered safe due to the limited understanding of how partial gravity affects human cells, nor has it been fully addressed due to cost limitations and the inability to simulate partial gravity on Earth accurately.

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NASA	The National Aeronautics and Space Administration
0g	Zero Gravity
RWV	Rotating Wall Vessel

1. Problem Statement

1.1 Overall Objective

Since the 1960s, space exploration has yielded intriguing discoveries that continue to unfold over time. Yuri Gagarin became the first human in space in 1961, paving the way for thousands of astronauts and cosmonauts to follow him as the years passed [1]. Various theories have been proposed based on space, including the Croatian Barrel Theory, which explains how the solar system, stars, and other celestial bodies formed [2][3]. In 2002, research refuted the theory that gravity alone governs the universe, as it could not explain specific astronomical observations [4]. Sanders and McGaugh modified Newtonian gravity as an alternative to cosmic dark matter, known as Modified Newtonian Dynamics (MOND), correlating a relationship between the acceleration from Newtonian gravity and the observed acceleration at any radius in a galaxy [5][6].

Exploring space not only reveals discoveries beyond our planet, but it also uncovers truths that enhance and govern our lives. Advanced Combustion via Microgravity Experiments (ACME) investigates fuel efficiency and pollutant production in combustion under microgravity conditions on Earth [7]. One of their investigations, Flame Design, studied the quantity of soot produced under different flame conditions [7]. Such a discovery could lead to more efficient combustion, reducing pollution on Earth [7]. In the ongoing Moon exploration, researchers found that the Moon's gravity affects Earth's tides, plant growth, animal behavior, and agricultural practices [8]. Moreover, models have shown that the Earth-Moon coupled magnetospheres provide a buffer against the solar wind, allowing for a reduction in Earth's atmospheric loss to space [9]. The National Aeronautics and Space Administration (NASA) has been exploring Mars for over sixty years to decide whether it is or was a habitable world [10]. Since Mars is the most similar planet to Earth in the Solar System, understanding its surface and evolution is crucial for preparing for future human exploration [11]. With evidence suggesting that Mars was once full of water, warmer, and had a thicker atmosphere, it is highly likely that Mars could be a habitable environment [11].

Traveling outside Earth's atmosphere to explore possible extraterrestrial life is risky and expensive. Since our bodies heavily depend on gravity, any significant change in gravity can cause serious issues [12]. Gravity is a vector that affects every object and determines its weight based on its mass [13]. Biological entities respond to their environment – including gravity – developing their unique shapes, physiology, behaviors, and locations [13]. An organism's sensitivity to gravity increases with size and mass, with single cells surviving 10^5g and humans tolerating 4-5g [14]. At the cellular level, cells consist of organelles, all of which have mass and are therefore reactive to the gravitational vector [14]. Changing the vector could disrupt the homeostasis of cell structure, composition, and orientation, such as the cytoskeleton (which maintains cellular shape) [14]. Additionally, several studies have observed genes that are sensitive to gravity changes, including alterations in cytoskeletal gene expression pathways and gene inhibition after microgravity exposure [15][16]. Without gravity, cellular growth pathways shift, and cellular metabolism adapts due to changes in reactive oxygen species [17][18]. Furthermore, cellular adaptation to gravity influences tissue adaptation, with bones containing cells like osteocytes that sense and adapt to different gravitational loads [14].

Such cellular changes affect the entire human system. Astronauts exposed to microgravity experience physiological deconditioning in systems sensitive to mechanical loading, including the cardiovascular, pulmonary, and musculoskeletal systems [19]. To counteract these effects, current International Space Station (ISS) crew members exercise vigorously; however, despite extensive exercise, astronauts still return from their six-month ISS missions with decreased calf muscle volume and strength, loss of bone mineral density, and reduced peak oxygen uptake [20][21][22][23].

With that, it is highly unethical to send people into space without understanding the effects of gravitational changes on the body. In this paper, a proposed prototype of a device that cultures cells under the influence of partial gravity and microgravity is addressed, allowing for the correlation of certain cell behaviors with the gravitational difference.

1.2 Background

Understanding the effects of partial gravity on humans is less studied due to the high costs associated with conducting tests in a partial or microgravity environment. Between 1960 and 1973, the research experience and studies gained during the Apollo missions, which focused on lunar exploration, provided valuable information summarizing the different effects of partial gravity on the human musculoskeletal, cardiovascular, and respiratory systems, using either microgravity or Earth's gravity as control [24][25]. However, the Apollo missions cost $25.4 billion in 1969, equivalent to roughly $217 billion in 2024 [26]. Following the Apollo missions, with no humans landing on the Moon, the failures in these missions enabled the enhancement of spacecraft design to incorporate additional layers and the development of new, safer materials, along with the integration of computer systems for troubleshooting [27]. In 2019, the health impact of a year-long mission in space was examined in molecular and psychological traits by comparing the DNA sequence of the twin brothers – Mark and Scott Kelly – with Mark Kelly staying on Earth, "the control," and Scott Kelly going to space [28][29]. The study revealed that extensive multisystem and gene expression changes occur in spaceflight [28].

Due to the cost and decommissioning of ISS, researchers aimed to simulate partial gravity on Earth, such as using a pulley-spring system to simulate partial gravity for rats (see Figure 1) [23][30]. However, one of the limitations of the apparatus was that the tail was suspended rather than the whole body, which would provide a weight shift in the rodent's body, thereby not providing a "true" simulation [30].

Figure 1: Experimental Design for Simulated Partial Gravity Apparatus for Rats

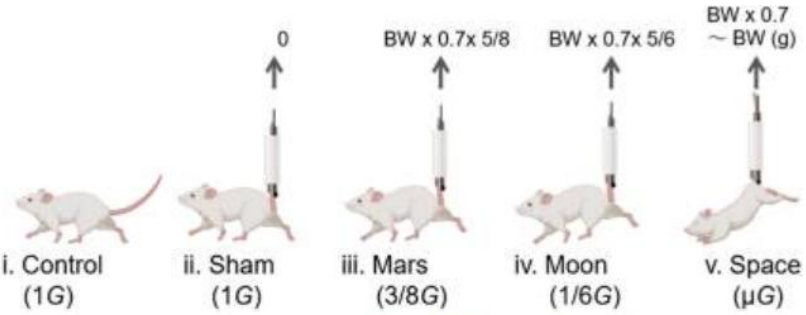

Figure 1 shows the groups of experimental rats with the Control group (1G) (i); the sham group with SA (1G) (ii); the Mars group (3/8G) (iii); the Moon group (1/6G) (iv); and the interplanetary space (μG) group (v) [18].

The impacts of gravity on an object can be either displacement or deformation [31]. Microgravity fosters unique cell growth environments, while partial gravity (such as on the Moon and Mars) may present entirely different effects [32]. To understand the concepts that encompass partial gravity apparatuses, it is essential to differentiate between zero gravity, gravity, microgravity, and partial gravity. Gravity is an abstract phenomenon that can be quantified, but the fundamental cause remains unknown [33]. The gravitational constant is not a force or acceleration but is utilized as a scaling factor for Newton's Law of gravitation, shown in Equation 1: Gravitational Force Equation[33][34].

Equation 1: Gravitational Force Equation

$$F = \frac{Gm_1m_2}{r^2}$$

F is the magnitude of the gravitational force acting between masses m_1 and m_2 separated by distance [33]. G is a universal constant with a value of $6.67384 * 10^{-11}\ \frac{\mathrm{m}^3}{\frac{\mathrm{s}^2}{\mathrm{kg}}}$ [34].

Zero gravity (zero-g) refers to the lack of gravitational force on an object due to its infinitely far distance from another gravitational object or the net sum of all forces acting on the object equaling zero [35]. Microgravity refers to a condition where the net gravitational force acting on an object is minimal, typically within the range of 10^{-4} to 10^{-6}G [36]. The object is still affected by the forces of gravity but is in continuous free fall [36]. The constant free fall occurs when the object falls at a steady rate, but it does not reach a surface [36]. Consequently, the difference between the initial and final velocities is a constant acceleration (g) [36]. Partial gravity refers to the gravitational force that is reduced but not eliminated compared to the force of gravity on Earth, such as that gravity on the Moon is 0.16g, Mars is 0.38g, and Earth is 1g [29]. On Earth, partial gravity can be simulated through centrifugation, parabolic flight, or modified rotation devices that produce acceleration lower than 1g [37].

To study gravitational effects, cell culturing is considered the most effective approach, with bioreactors being the ideal device since they provide controlled nutrients and biomimetic stimulus delivery for cell growth [38]. A bioreactor is a vessel in which a chemical process involving organisms or biochemically

active substances derived from such organisms is carried out, or a system designed to grow cells in the context of cell culture, first developed in 1964 (see Figure 2) [39].

Figure 2: Basic Bioreactor

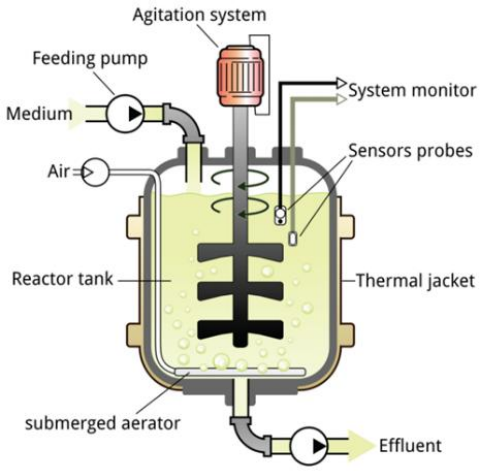

Figure 2 shows the basic bioreactor components. It includes a feeding pump, air, medium, agitation system, reactor tank, and other elements to ensure an automated culturing system [39].

Previous bioreactors were designed as ground-based systems to mimic aspects of weightlessness or reduced gravity experienced by biological organisms in space. Recognizing this potential, in the mid-1980s, NASA researchers at Johnson Space Center needed to develop a way to study the effects of microgravity on human tissues as the shuttle fleet was grounded after the Challenger disaster [40]. They invented a rotating bioreactor to address the challenge of treating injured astronauts in space and to simulate weightlessness on Earth [40]. In microgravity, the bioreactor allows cells to grow in three-dimensional tissue structures that closely resemble natural development, aiding advances in medicine both on Earth and in space [40]. In 2002, Houston-based Regenetech Inc. licensed NASA bioreactor technology and patents [40]. This system can expand adult stem cells (from blood to bone marrow) by 50-200 times in less than a week, providing safer, faster, and more affordable cell sources for therapies [40].

Partial gravity bioreactors, although not extensively studied, have been investigated previously. Research dating back to the 1900s has examined the effects of clinostats, or rotating wall vessels, on biologics [41]. Clinostats were invented by Julius Sachs, who rotated growing plants around their growth axis [41]. Clinostats exist in 1-D or 2-D forms depending on the dimensions of the rotated axial line or the whole experimental area [42]. Enhancing the clinostat with two axes, 3-D clinostats were designed, known as the Random Positioning Machine (RPM) (seen in Figure 3) [42][43].

Figure 3: 3D Clinostat

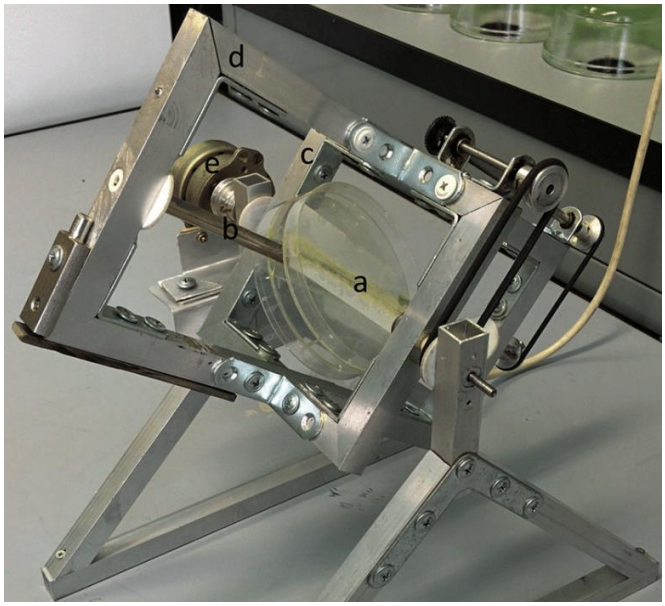

Figure 3 shows a 3D-clinostat used to analyze the effects of microgravity on seed germination: a, insert for Petri plates; b, rotating shaft; c, inner frame; d, outer rotating frame; e, motor [43].

Many early partial gravity bioreactors tested their effects using plant species, which can continuously grow against Earth's gravitational forces [44]. Early renditions included clinostats, which constantly rotate a sample so that the gravitational vector is effectively averaged to near zero [41]. This rendition of a partial gravity bioreactor cannot fully replicate "true" freefall since cells still experience mechanical stimulation and gradients that differ from the actual microgravity environment [41]. Later, rotating wall vessel (RWV) bioreactors were introduced as a specialized form of clinostats [41]. RWVs are fluid-filled cylinders containing cells that create a low-shear, controlled environment, allowing for cellular differentiation in three-dimensional space [45]. By rotating at a terminal velocity, RWVs ensure proper nutrient delivery to the tissue culture, thereby promoting healthy tissue and cell growth [45]. Previous teams have utilized the RWV's cell culturing stability while allowing the incorporation of the partial gravity factor by using an incline plane to cancel a portion of the gravitational vector, enabling the cells to experience partial gravity (seen in Figure 4).

Figure 4: Partial Gravity Bioreactor

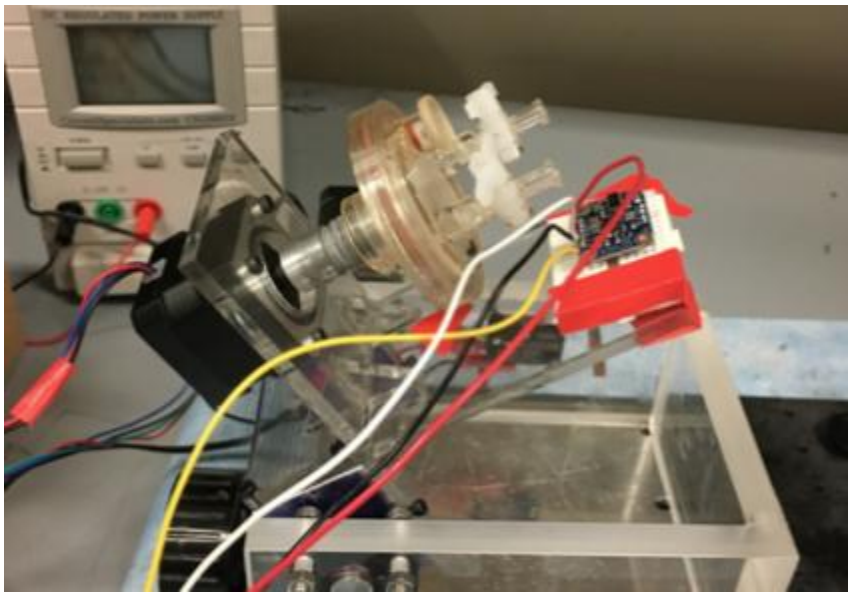

Figure 4 shows the partial gravity bioreactor prototype designed by a previous senior design team, consisting of an RWV attached to an incline plane that stimulates partial gravity.

1.3 Needs Statement

Building a partial gravity cell culturing prototype would enable the study of the relationship between cell properties and different gravitational environments, therefore allowing for correlation between gravitational differences and cell properties.

1.4 Implications of Project Success

In case of the prototype's success, both life in space and on land would be enhanced. Understanding how different gravitational environments influence cells would provide more informed conclusions for human explorations. With such findings, solutions would be developed to ensure the safety of humans beyond Earth. Having humans travel to space, including Mars and the Moon, increases the information we have about outer space and helps answer questions about extraterrestrial life. It could potentially unlock new planets or locations in space where humans can start a new life.

The prototype's success is based on the United Nations Sustainable Development Goals (UNSDG) [46]. A Sustainable Development Goal (SDG) addressed is Life on Land (Goal #15), focusing on ensuring the safety of nature on our planet [47]. The prototype would primarily concentrate on combating desertification by collecting soil from other planets or studying the Moon's role in enhancing agricultural methods. Another SDG addressed is Industry, Innovation, and Infrastructure (Goal #9), which focuses on promoting sustainable industrialization and fostering innovation [48]. With the ability to travel outside Earth, there would be increased innovations, whether by drugs or technologies, to allow humans to

compensate for the gravitational difference. This would not only be required for a limited time, but there would also be a constant need to produce new vital drugs and technologies to sustain human life. For SDGs #12 and #13, the success of the prototype would promote sustainable strategies for space and Earth by demonstrating how biology adapts to reduced gravity and sustains life in space [49][50]. Finally, SDG #3, which refers to "good health and wellbeing," the prototype's success could benefit health and biology in space travel conditions by demonstrating the gravitational effects on cellular development [51].

2. Design Criteria

To ensure prototype viability, the design criteria are categorized as either non-negotiable (mandatory) (see Table 1: Non-Negotiable Needs) or negotiable (desirable) (see Table 2). However, due to the project's complexity, the criteria are divided into three main areas: cell culturing, partial gravity, and prototype.

2.1 Non-Negotiable Criteria

Four criteria should be met to consider cell culturing successful: biological reactivity, environmental conditions, sterility check, and cell viability.

Biological Reactivity: According to the In Vitro Biological Reactivity (Cytotoxicity Testing), USP 87, and Biological Evaluation of Medical Devices—Part 5: Tests for In Vitro Cytotoxicity (ISO 10993-5:2009), there are established tests used to determine the biological reactivity of mammalian cell cultures caused by contact with elastomeric plastics and other polymeric materials [52][53]. Screening the coating materials that will contact the cells ensures they are not toxic [52]. Conducting the Direct Contact Test on the used materials or using materials that have passed this test is crucial to ensure accurate results [52]. The sample meets the requirements if the result is not greater than grade 2 (mildly reactive), according to USP 87 [52].

Environmental Conditions: According to Good Cell and Tissue Culture Practice 2.0 (GCCP 2.0), mammalian cells exposed to temperatures above 39 °C may trigger a heat shock response [54]. Additionally, growing cells at temperatures between 35 °C slows their replication and alters gene expression [54]. Ensuring a stable temperature is crucial for maintaining reproductive biological function [54]. The medium should also be prewarmed to prevent cold shock [54]. Therefore, the optimal culture temperature is 37°C ± 1.0°C [54]. Another vital environmental factor for cell growth is the atmosphere. Excessively high levels of oxygen and carbon dioxide can be toxic to the culture, while low levels may inhibit cell growth or significantly alter gene expression [55]. The commonly used atmosphere is 5% ± 0.5% v/v carbon dioxide in air, with oxygen levels adjusted based on cell type and purpose [54]. To verify the stability of temperature and atmospheric conditions, either a sensor with an alarm or regular testing of the incubator's humidity, temperature, carbon dioxide levels, and vibration absence will be performed before each test [54]. Regarding pH, the optimal physiological pH for mammalian cell cultures is 7.3 ± 0.1, with deviations outside this range affecting cell phenotype, growth, and viability [54]. Media containing pH indicators, such as phenolphthalein, are used to provide alerts for significant pH changes [54].

Sterility Checks: According to GCCP 2.0, it is essential to keep a designated work area dedicated solely to cell culture work and media preparation [54]. Adhering to the Standard Operating Procedures (SOP) for Temple University labs, such as wearing Personal Protective Equipment (PPE) throughout the entire time a person is in the lab, would effectively meet the requirement [56]. Additionally, applying proper cell culture techniques and guidelines would help prevent common issues and improve cell viability [57].

Cell Viability: According to the Standard Guide for Quantifying Cell Viability and Related Attributes within Biomaterial Scaffolds, ASTM F2739-19, dye exclusion techniques are used to determine cell

viability [58]. After removing cells from the scaffold and mixing them with dyes like 0.4% Trypan blue, the cells are manually counted using a hematocytometer [58]. Cells that absorb the dye are considered non-viable [58]. The cell culture is considered healthy if at least 80% of the cells are viable, with viability typically ranging from 80% to 95% [59]. For imaging or visualizing cell viability, one method described in ASTM F2739-19 involves using fluorescent markers to distinguish live from dead cells, which is commonly used to determine the ratio of live to dead cells [58]. A standard live cell stain is calcein acetoxymethyl (calcein-AM), and a standard dead cell stain is ethidium homodimer [58].

Three criteria must be met to consider the partial gravity component in the project successful: gravitational type, movement, and simulation/validation.

Gravitational Type: With NASA deorbiting the ISS, the ability to conduct experiments in the unique microgravity laboratories would be impossible [59]. Therefore, gravitational experiments run on Earth should include the main missions they previously planned. According to NASA, traveling to the lunar surface and around the Moon would enable scientific discoveries that prepare humans for the next exploration, Mars [60]. Since the Moon and Earth are the two most critical gravitational environments, lunar gravity (0.16g) and Martian gravity (0.36g) should be considered [61]. To gather more precise data, Earth's gravity (1g) and microgravity (10-6g) should also be included to ensure the same cells experience all gravity levels and to serve as a cross-reference with previous experiments [61][62].

Simulation: The partial gravity effect on cells has not yet been observed or tested. However, visualizing gravity is not applicable, since gravity is a theory [63]. Using mathematics, fluid mechanics, and particle mechanics, a mathematical model should be developed for partial gravity.

Movement: Since cells are highly sensitive to their environment, the method used to simulate partial gravity should not cause excessive vibrations or inconsistent cell movement [64]. To achieve this, the process for reaching different gravitational levels should operate smoothly, allow the cells to be in free fall, and reduce the shear stress on the cells, all at the same time and in a continuous manner.

Three criteria should be met to consider the prototype successful: size, material, and space.

Size: Since the placement of the prototype may be restricted to the incubator (the usual location according to previous designs), the overall dimensions of the prototype are limited. Nuaire NU-5810E operates at a temperature of 37°C with 98% humidity [65]. The maximum size of the prototype is constrained by the internal dimensions of the incubator, which are 21 by 20 by 20.8 inches [65].

Material: Since there is a possibility that the prototype will be placed inside the incubator, the materials used should withstand room temperature and 37°C, along with 98% humidity [65]. Additionally, the prototype is expected to remain stable for at least 4 months.

Space: Since the prototype is divided into three main categories, its skeleton should have enough room for the cell culturing component to fit in.

Table 1: Non-Negotiable Needs

Priority	Requirement	Metric	Target Values/ Range or Pass/Fail	Justification
Non-negotiable	Direct Contact Test [53]	Biological Reactivity	No more than a grade level of 2 [53]	ISO 10993-5:2009 [53]
Non-negotiable	Temperature, gas exchange, and pH stability	Environmental Conditions	Temperature: 37°C ± 1.0°C Gas exchange: 5% ± 0.5% v/v carbon dioxide in air pH: 7.3 ± 0.1 [54]	GCCP 2.0 [54]
Non-negotiable	Follow the lab SOP [56]	Sterility Checks	Pass/ Fail	GCCP 2.0 [54]
Non-negotiable	Cell Viability	Proper Cell Culturing	>80% [59]	ASTM F2739-19 [58]
Non-negotiable	Gravitational Type	Partial Gravity and Controls	Range: 10-6g to 1g Lunar gravity (0.16g) Martian gravity (0.36g) Earth's gravity (1g) Microgravity (10-6g) [61][62]	NASA's Goals [60]
Non-negotiable	Simulation	Mathematical Model	Pass/ Fail	Accuracy and Validation
Non-negotiable	Partial Gravity Movement Causes Steady Flow	Partial Gravity Accuracy	Pass/ Fail Using Model and Imaging	Inaccuracy of data due to cell sensitivity [64]
Non-negotiable	Size	Dimensions	21 by 20 by 20.8 inches [65]	Nuaire NU-5810E Incubator Restricted Area [65]
Non-negotiable	Material	Strength and Durability	Pass/ Fail to withstand room temperature and 37°C, along with 98% humidity [65]	Project Duration
Non-negotiable	Space	Prototype Assembly	Pass/ Fail	Full Composition of Prototype

Table 1 displays the ten non-negotiable criteria for the prototype's validation. Focusing on the cell culturing section, the biological reactivity, environmental conditions, sterility checks, and cell viability criteria are used to validate the cell culture. For partial gravity, the requirements for its functionality include gravitational type, simulation, and partial

gravity movement. Overall, for the prototype, the base, cell culturing, and partial gravity criteria—including size, material, and space—are essential. The metric, target range, and justification for each criterion are provided.

2.2 Negotiable Criteria

Regarding the negotiable criteria, four factors could improve the prototype if they are met. First, after successfully culturing the cells, sending them for DNA analysis to identify genomic changes would provide additional information about the effects of gravitational variations on the cells. Second, implementing an automated imaging system for the cells would allow the user to assess the cell culture and gain more insights into cell interactions over different time periods. Third, advancing the mathematical models into computational models and simulations would offer a deeper understanding of the fluid dynamics experienced by the cells. Fourth, including a broader range of gravitational conditions would enable a more accurate simulation of human body movements from Earth to other locations in outer space.

Table 2: Negotiable Needs

Priority	Requirement	Metric	Target Values/ Range or Pass/Fail	Justification
Negotiable	DNA Analysis	DNA Sequence Tracking	Pass/ Fail	To find the genomic changes correlating with gravitational changes
Negotiable	Automated Imaging System	Data Tracking	> 30 FPS	To record the cell's activity during culturing
Negotiable	Computational Models	Modeling Accuracy	Pass/ Fail	To have a more sophisticated model for partial gravity
Negotiable	Broader Range of Gravitation	Partial Gravity and Controls	More than three partial gravities achieved	To include minimal gravitational changes during spaceflight

Table 2 lists the four negotiable criteria for enhancing the prototype. These include DNA analysis, an automated imaging system, the development of computational models, and a broader gravitational environment. The table provides the metric, target range, and justification for each criterion.

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