CHALLENGES AND REQUIREMENTS FOR THE DEVELOPMENT OF BIOREACTORS FOR BONE TISSUE ENGINEERING IN SPACE

Stefano Gabetti (1,2), Liyana I. Popova (3), Umberto Morbiducci (1,2), Michele Balsamo (3), Diana Massai (1,2)

1. Dept. of Mechanical and Aerospace Engineering and PolitoBIOMed Lab, Politecnico di Torino, Italy;
2. Interuniversity Center for the Promotion of the 3Rs Principles in Teaching and Research, Italy;
3. Kayser Italia Srl unipersonale, Italy

Introduction

International space agencies are focusing on long duration crewed missions to the Moon and Mars. Thus, space biomedicine is emerging as a critical field to ensure the health, safety, and performance of astronauts. Among others, reduced gravity represents a major risk factor, as it strongly affects the astronauts' musculoskeletal system, altering bone remodelling mechanisms and increasing the likelihood of fractures [1]. Health monitoring of astronauts and *in vitro* studies carried out on the International Space Station (ISS) have demonstrated that microgravity significantly affects bone cell viability, morphology, and matrix [2]. However, cell-only experiments fail to replicate the three-dimensional (3D) features of bone tissue overlooking the interactions among bone cells and their dynamic environment, thus the processes underlying bone loss remain unclear. In this scenario, *in vitro* modelling inspired by bone tissue engineering (BTE) holds great promise. The development of *in vitro* 3D bone tissue models—featuring bone cells seeded in scaffolds and cultured under bone-like physico-chemical conditions in bioreactors—is crucial for investigating the impact of the space conditions on human bones and for proposing and testing new countermeasures and therapeutic strategies [3]. Here, we analyzed the main challenges concerning the design and use of BTE bioreactors in space, outlining key design requirements.

Methods

To define the basic architecture of the bioreactor for BTE in space, we reviewed the main solutions developed for Earth-based investigations, with a focus on the delivery of bone-like physical stimulations (e.g., fluid-induced shear stress, compression, and electric fields). From a complementary perspective, bioreactors designed for biological research in space were analysed. Lastly, to identify safety and regulatory challenges for in-orbit biological experiments, technical documents and guidelines, including information from NASA and ESA websites, were examined.

Results

A primary requirement for space bioreactors is ensuring compatibility with available on-board facilities and environment constraints. This specification translates into the minimization of bioreactor volume, mass, and power consumption. Moreover, mechanical and electrical interfaces must be compatible with the module intended to accommodate the bioreactor. For its operability, the bioreactor must adopt a gravity-independent circuit for fluid handling and debubbling. To comply with safety requirements, the bioreactor must be equipped with at least one leak-proof level of containment. Furthermore, to enable bone biology investigations, the bioreactor must ensure continuous medium flow through the 3D cultured constructs (Fig. 1). This would both guarantee efficient mass transport during cell seeding / tissue culture and provide fluid-induced shear stress, known to be essential for promoting bone cell proliferation, differentiation, and matrix mineralization [4]. To mimic the native bone environment, additional physical stimulation units could be implemented for providing intermittent compression and/or electromagnetic fields known to promote osteogenic differentiation and bone tissue maturation [5]. To support parallelization for high-throughput studies, the bioreactor units must operate with low power consumption. Finally, to guarantee automation, a feedback-loop monitoring and control unit equipped with in-line sensors must be included. This will enable real-time measurement of the culture conditions and consequently to adapt them, minimizing human intervention while enhancing reliability and safety.

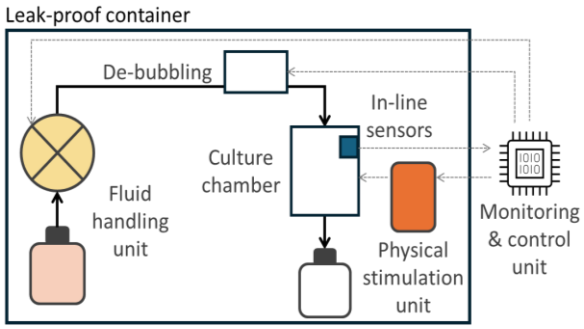


Figure 1: Proposed space bioreactor architecture.

Discussion

Bioreactors that meet the defined requirements could be used as powerful platforms for investigating the effects of space altered gravity on bone cells and tissue. This biomimetic, data-driven approach holds the potential to yield valuable insights for possible countermeasures and therapies in space biomedicine, while advancing BTE and regenerative medicine strategies on Earth. However, developing BTE bioreactors for space demands a robust collaborative effort among experts in stem cell biology, biotechnology, and engineering and between academia and aerospace companies. Thus, we believe it is time to unite efforts and work collectively toward this innovative and transformative goal.

References

1. Stavnichuk et al, Npj Microgravity, 6:1, 2020
2. Gambacurta et al., Sci. Rep., 9: 8343, 2019
3. Scatena et al., IAC Proceedings, 2023.
4. Hoffmann et al., Front. Bioeng. Biotech., 3:10, 2015.
5. Gabetti et al., Sci. Rep. 12:13859, 2022.