Biomedical Payloads: A Maturing Application for CubeSats

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Abstract

This paper outlines some of the challenges and opportunities facing the space biomedical community and how CubeSats may (and indeed already are) supporting this research area. A review of current space and microgravity platforms capable of supporting biomedical research is presented alongside a summary of the vital research that this enables. This paper presents biomedical CubeSat enabling technology alongside the critical technology gaps is given, alongside analysis of relevant logistical and bureaucratic factors in the space sector. An overview of the general design requirements for biomedical CubeSat missions is presented to help support potential new developers, alongside a small review of some of the technology gaps and innovations that are present and of importance to the sector's maturity. Finally, we demonstrate that CubeSats do have the potential to become a mature and high-fidelity niche in the NewSpace infrastructure, that could support professionally-credible space biomedical research, complementing traditional platforms such as crewed vehicles, autonomous biosatellites and free-flyers. Biomedical CubeSats have been validated through a well-documented programme of NASA missions, as well as successful flights from at least one commercial company to date, and now these trail-blazers are being followed by a new "mini-space race" among Universities and other groups. This report aims to review the status and estimate in which scenarios a biomedical CubeSat mission would provide cost-effective, worthwhile science return, versus (arguably) the most common current route to space for biomedical payloads – the ISS. It aims to act as a primer and provide information for potential mission planners or scientists that are newer to the space sector and want a ground-up analysis of some of the routes to space. Importantly, this paper compares the biomedical CubeSat versus a payload hosted on a platform like the ISS, and not any of the other high-profile, and potentially very popular, current or developing platforms that are only briefly referenced.

Keywords: CubeSat, space biomedicine, space pharmacy, biomedical payloads, NewSpace

1. Introduction

Space travel is well known to cause a range of problematic effects in astronauts; the most well-known related to their central nervous system, cardiovascular system (in part due to fluid redistribution), musculoskeletal atrophy, immune system dysfunction and increased intracranial pressure [1][2]. On a smaller scale, microorganisms are also affected by microgravity; due to the lack of hydrostatic pressure, sedimentation and convection currents in their culture media, which without stirring will lead to a build-up of metabolites surrounding cells and other effects [3], [4]. The increased levels of ionising radiation present, even in LEO, are also understood to be a factor in most of these effects to humans and microorganisms, in varying capacities [1], [5].

Some of the discovered effects of spaceflight upon microorganisms have a large impact on biomedicine in space. The interaction between microscopic effects and larger *in-vivo* changes in crew members is of critical importance. Pathogens such as *Salmonella, Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA) can exhibit an increased virulence and proliferation [2], drug resistance has been reported in *E. coli* and *E. bugandensis* [6], and biofilms (surface-associated cultures that can arise naturally on Earth or on platforms like MIR and the ISS) also from *E. coli* have been observed to have increased biomass and thickness [3].

One of the other key determinations from these studies is that microgravity alone is not the only driving factor affecting these results, and that unique factors only present in the space environment are in play [7]. Ground controls using simulated microgravity (usually clinostats or rotating wall vessels) often produce similar results to spaceflight samples (compared to ground, 1g controls), although differences are sometimes more significant on levels such as gene expression. It is the topic of further study to what degrees the differences between simulated and real microgravity, or the effects of other space environmental factors (such as radiation, air composition and launch stressors), have on results published in the literature [4], [7]–[11]. While some of these factors (e.g. microgravity) can be simulated in the lab (covered further in section 2), it is difficult to combine more than one stressor at once (e.g. simulating microgravity in an extreme temperature environment while exposing all components to high levels of radiation). It is virtually impossible to completely simulate an entire space mission on a "grounded" payload [4], [8], [9]. This uniqueness is part of why biomedical scientists are so interested in space as a laboratory environment.

Biomedical research in space is hence vital for monitoring the continuing health of astronauts, the development of countermeasures to spaceflight and applications for uses on Earth. However, as often discussed in the space sector, the presence of life in space is set to change in both capacity and diversity in the near and mid-term future [12]. Exploration, space tourism, the foundations of an economy in Low Earth Orbit (LEO) and a greater demand for breakthrough solutions from biotechnology on Earth, are all set to create new, more complex demands and obstacles to the space sector, and the biomedical research that is a centrepiece of it [13], [14].

Typically, biomedical experiments can be placed into at least one of these objective categories:

- Experiments to improve our understanding of the underlying biochemical mechanisms in organisms or other samples that produce changes/adaption to spaceflight
- Experiments that contribute to the development of an application for use in space or on Earth based on these changes. These may:
    - Exploit the changes caused by the space environments to samples (e.g. increased virulence applied to viral vector treatments)
    - Be for a countermeasure to the space environment's effects (e.g. drugs to counteract muscle atrophy)
    - Be a In Orbit Demonstration (IOD) for a system that is desired for biomedical purposes in space or Earth or that benefits from testing in the space environment.
      (e.g. protein crystallisation or secondary metabolite production in bioreactors)

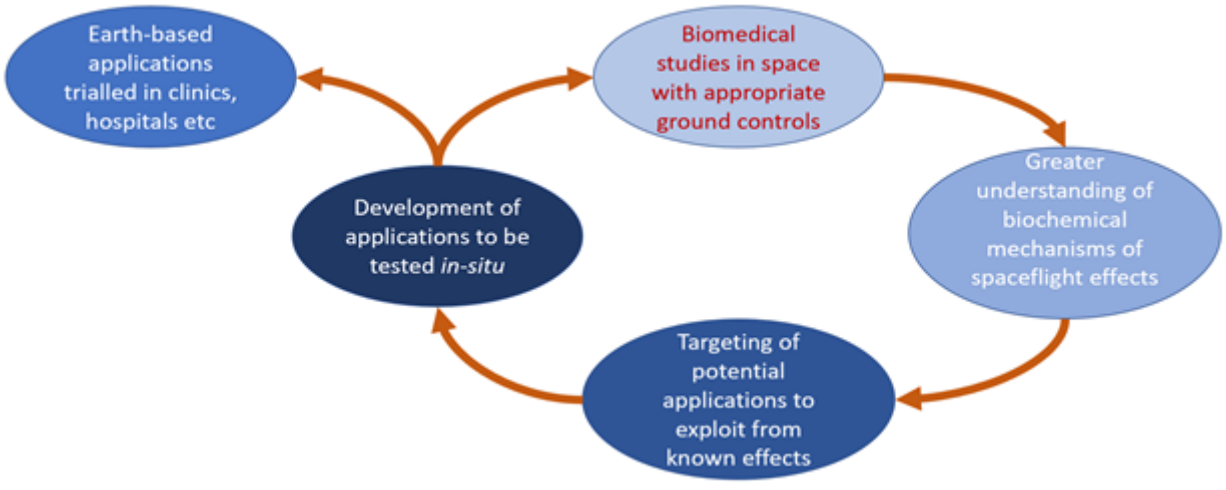

Figure 1: Simplified flow diagram to explain the relevance and methods of how fundamental space biomedical research, produces benefits for both Earth and Space users.

2. Current Supporting Infrastructure of Space Biomedical Research

Space infrastructure consists of many platforms, facilities, and services capable of supporting laboratory studies. Presently, the ISS is foremost among these in addition to the Tiangong programme, and the many historical crewed platforms including MIR, STS, SkyLab and others. While crewed facilities benefit from human researchers being present, there have also been autonomous satellite missions to conduct biomedical studies, such as the Biosatellite, Foton, Bion, Tianzhou and ShiJian programmes as well as free-flying platforms such as LDEF and EURECA. In the future there are plans for more platforms to be added to this list, including the Lunar Gateway, ESA Space Rider, Bion M2, the newly operational Tiangong Station, SpaceTango-42, Nanorack's Outpost, Dream Chaser and sub-orbital vehicles such as those from Virgin Galactic and Blue Origin [1], [15]–[17] In the future there may even be the possibility to conduct research on the surface of other bodies in the solar system too [18]–[20].

Alongside these developments, space agencies are trying to further exploit their valuable platforms through commercialisation of the facilities to outside researchers. Part of the ISS's transition to a commercial space laboratory includes the development and promotion of facilities such as ICE Cubes, the KUBIK Bioreactors, BioChip SpaceLab, CGBA, standardised EXPRESS Racks, NanoRacks' NanoLabs and External Platform, Space Tango's CubeLabs and the Bartolomeo platform – most of which conveniently advertise slots in CubeSat Unit sizes. Commercial experiment slots were also available on STS and MIR missions, and have also produced impactful research in the field of biomedical sciences [3]. These facilities offer laboratory space (as well as supplying power and other resources) to commercial experiments running within the limitations rented to them by ISS partners. These experiments can be in any field the customer wishes, although many of them focus on biomedical research areas including astrobiology, pharmaceuticals and medicine. In addition to these self-contained, automated laboratories, there are also advanced crew-operated instruments including the ISS-hosted WetLab-2 quantitative PCR system, the MinION DNA sequencer and RAZOR EX and MiDASS [1]. Importantly, although the ISS will likely remain at the forefront as the most advanced and capable facility for *in-situ* space research, it will eventually become unusable; either from funding re-direction, retirement, technical problems due to age or commercial buy-out into something like a space hotel. [19]

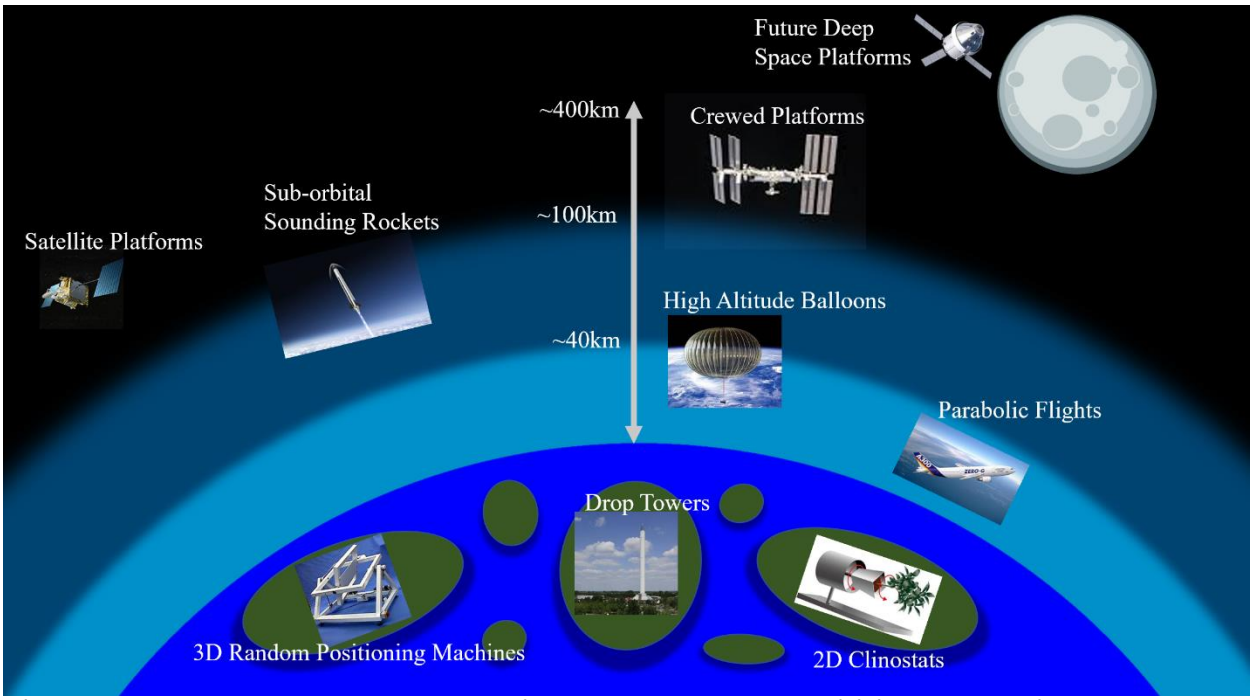

Figure 2: Summary of some of the infrastructure and facilities supporting space-related biomedical research

In addition to space assets, microgravity-analogue facilities exist on Earth that can be accessed for considerably less cost – provided the experiment is suitable for the duration and quality of microgravity exposed [15]. Drop towers, parabolic flights, sounding rockets and high-altitude balloons can all produce minutes or seconds worth of microgravity for payloads – and target

developers with a significant overlap of the CubeSat community (students, low-cost missions etc). So much so in fact, that frequently these facilities are used or advertised as prototype test facilities before an experiment is sent up aboard a CubeSat or other platform [21].

Microgravity analogue facilities including random positioning machines (RPM), rotating wall vessel bioreactors (RWV's or clinostats) and free-fall machines can simulate microgravity to varying degrees of purity, as experienced by samples contained inside, for varying periods of time [1], [22]. These are principally used on Earth for similar research applications to space platforms including microbiology, tissue culturing and crystal growth. One advantage of these tools is that analogue microgravity (or low-shear modelled microgravity, LSMMG) can be set to values experienced on other planetary bodies such as the Moon or Mars, to help prepare for exploration there in the future. They even present the opportunity to conduct experiments in-flight but at simulated 1g using centrifuges [15]. These studies can be particularly informative when conducted alongside true-microgravity, to isolate what other elements of spaceflight are impacting results – radiation, launch stress, enclosed environments etc [4], [23], [24].

3. CubeSats as Alternative Biomedical Platforms

3.1 A Brief Introduction to CubeSats as Space Biomedical Research Platforms

The evolution of CubeSats from educational tools into a highlight of the New Space industry is well documented and is possibly a rare case where many of the predictions made about their future popularity would become true [25]. Reported trends and case studies from various reviews of CubeSats have increasingly seen commercial industry and developing space nations, alongside governmental space agencies and academic institutions, develop their own CubeSat programmes and payloads in a variety of areas [25]–[27]. This application towards more "professional" goals and mission objectives (including biomedical studies), as opposed to their original use as educational systems, is likely to see a growing trend in the future as part of the move to NewSpace. They are quickly becoming recognised as high return-on investment space platforms, with low start-up or "buy-in" costs (costs referring to monetary costs and resources like time, expertise, equipment, and facilities).

In mid-2021, torch-bearing biomedical CubeSat missions have already been flown by NASA and at least one private company, with numerous University-class missions in development - validating the application and returning important results on their own. NASA Ames' has a very successful and well publicised biomedical CubeSat programme and the Swiss-Israeli company SpacePharma has two successful CubeSat launches (DIDO2 and 3) in addition to other ISS-hosted payloads that further validate cube-based biotechnology [28], [29]. The European Space Agency also has plans to develop biomedical CubeSats and payloads, adapting part of the NASA Ames' with their heritage of bio-payloads from the Foton programme. They intend to launch the 6U free-flying CubeSat SpectroCube and two cube-based, multi-payload facilities (SPECTROmodule) in succession to the Bartolomeo platform on the ISS In the future [30], [31]. the start-up SpaceForge aims to include pharmaceutical production as part of its in-orbit manufacturing portfolio using CubeSats [32]. Biomedical CubeSat missions have been identified, at various stages of development, from academia including Cranfield University (BAMMSat)[33], [34], Sapienza University of Rome (AstroBioCubeSat and GreenCube/CultCube)[35]–[37], Wrocław University of Technology (LabSat and a Mars mission) [38]–[40], R V College of Engineering (RVSat-1)[41], KTH Royal Institute of Technology (MIST/MOREBAC)[42], Nanjing University of Science and Technology/Fujian Academy of Agricultural Sciences (unnamed but growing Azolla plants) [43], North Dakota State University (Cabbage growing on a 3U)[44], Ecole Polytechnique de Montréal (Legumes on a 3U)[45], University of Chile (PlantSat)[46], and University of Nottingham (WormSail). Additionally, biomedical cube-payloads including GeMM, MisSt, μTitan (all NASA) [1], BiNOM (Samara NRU)[47], a modular, lab-on-chip payload from the Indian Institute of Science and ISRO [48], MICROCOSM (a joint project from different organisations in Kyiv, Ukraine)[49] and DSPP (Universities of Leicester and Exeter)[50] have been identified so far too. This is in addition to any applicable payloads developed for ISS cube-based facilities such as CubeLab, NanoLab, Bartolomeo or IceCUBES.

3.2 CubeSat Advantages as Alternative Biomedical Platforms

CubeSats as an experiment platform, support different niches in the space research infrastructure than crewed labs, such as the ISS. Crewed labs such as the ISS are arguably the most popular current platform and "route to space". Hence, it is prudent to begin by comparing biomedical CubeSat application. In the future it is entirely possible that some of the developing commercial free-flying platforms that will offer payload slots, could be similarly popular among hopeful biomedical researchers. However, given that very few of these started regular flight operations, this study has been deliberately limited to comparisons to the ISS. Sources such as [17], [25], [26], [28], [29], [51]–[53] review some of the advantages and disadvantages of the alternative platforms – often using comparisons to the ISS as currently the most popular platform and "route to space". There are many arguments to analyse in this discussion, both supporting and refuting the desire to develop novel, alternative space platforms and it most certainly cannot be achieved within the scope (or knowledge) of this particular review.

Some limiting factors, given in the sources, that are faced by those sending scientific experiments to the ISS include: strict regulations, complex legislation and lengthy time and monetary commitments, and even more complex planning requirements (both for safety and operational reasons) when astronauts are involved. These are mentioned here only to highlight the problems that CubeSats are generally described in the literature as having the potential to overcome. A far more measured summary of the situation can be found in section 3.4 and the conclusion.

Biosatellites such as CubeSats have access to different orbits and radiation environments than those found inside (or outside) the ISS, quieter on-orbit vibration environments (giving a more-true microgravity environment) and in some cases can support continuous experiments for months or even years - beyond that of typical ISS experiment durations according to some sources [17]. As a free-flyer commonly launched as a secondary payload, CubeSats may also benefit from an accessible route to deployment in novel space environments, such as different LEO's, missions in the radiation belts or cis-lunar or even Martian space. Another opportunity CubeSats can exploit independently of the ISS is with higher-risk mission payloads that may not be permitted aboard the crewed ISS without significant further investment in time and cost in developing these payloads. This refers to not only biochemical hazards (such as infectious diseases) but also to lower TRL hardware and software – CubeSats are well reviewed tech demonstrator missions as their low investment enables riskier mission objectives with reduced impacts from failures [17], [25]. They also provide an alternative route-to-space for payload developers who may not get access to the ISS for political reasons (e.g. being affiliated with China, which notably can use the ShiJian and Tianzhou for uncrewed experiments).

Alongside this, the oft-cited economic advantages are likely to only improve as laboratory CubeSats become more commonplace and the procedures, services and components required for them become standardised and more accessible. Some researchers envision a day when perhaps entire commercialised payload modules are interchangeable within certain CubeSat buses to support them [53]. However, mission costs for a CubeSat or commercial ISS payloads aren't simply restricted to the bill of parts that designs require, and the launch. Wages must be paid for lead and development times, qualification assessments, various spares and models, ground station time and travel to various facilities required for development and launch integration. Again, these factors are widely variable, and are more closely linked to the mission objectives, partners and resources available to the developer than what platform is selected for the payload.

CubeSats – having evolved from student-led projects - are purposefully designed to be as accessible and broadly appealing as possible and are noted as often requiring less lead time, both from a design and bureaucratic standpoint. Further factors such as these are harder to quantify, but may be highly prioritised figures of merit in certain scenarios. The accessibility of CubeSat missions enables students to become highly competent contributors to the project. Involving students is generally cheaper than professional technicians, and in addition they benefit from gaining valuable technical, project-based experiences. One study of the University of Illinois at Urbana-Champaign's ION CubeSat, estimated that the wages of the 100+ students who worked on it from 2001 – 2006 totalled around $420,000 alone [54]. Students' involvement and education through a CubeSat project is not just a key return on investment, but also a practical advantage in certain cases

too. Further to this student groups are often much more successful at obtaining sponsorship deals from private industry, with models of this approach being seen in University Engineering Faculties' F1 Racing Teams (a common student club in British Universities) and University teams for ESA's REXUS/BEXUS programme. Additional benefits for groups such as these that are harder to quantify or compare accurately are: educational value to developers, useful cooperative links between interdisciplinary organisations, national or institutional pride in building and flying a space asset, reusability of bought assets for other purposes (e.g. ground stations and test facilities), and potential to later commercialise the platform or developed technologies [25].

Overall, the advantages a CubeSat offers over most other platforms can be summarised as: shorter development times, greater accessibility both in expertise, resources and commitment required, lower initial investments, wider choice of location in space, higher tolerances of risk, educational value and prestige [25], [26], [51]. Essentially, they make space more accessible for a wider group of users. These driving factors encourage biomedical applications of CubeSats that are high-risk high-reward, have simple, focused and targeted mission objectives or are heavily impeded by time, cost, logistics or specific science requirements that could be expected with developing an ISS or larger-satellite experiment to a sufficient standard [25], [26], [51]. From this there are certain hypothetical situations and groups that would greatly benefit from using CubeSat platforms as alternatives to the ISS, as well as produce a greater return-on-investment for developers. Examples may include; university student-led projects that seek to enhance or promote their traditional aerospace courses with a space element, emerging space nations wishing to promote their own biotechnology industry or academia, biomedical companies seeking to demonstrate, test or evaluate their products in space, and researchers wishing to utilise the unique environment of space for a relatively low investment. These groups benefit the most in terms of accessibility advantages surrounding biomedical CubeSat missions and, as will be discussed later, have a wide range of valuable experimental opportunities and applications to pursue.

3.3 CubeSat Disadvantages, Obstacles and Limitations

CubeSats however also have several constraints, obstacles and limitations that must be mitigated, overcome or compromised with, in order for a successful mission. These will vary a lot depending on the mission specific science, payload, bus and logistics requirements. There are however some that will be generally applicable to most or all biomedical CubeSat missions and also of importance when discussing their use in comparison to the ISS.

3.3.1 General Issues

Perhaps the most obvious issue with using CubeSats for life science experiments in space is their size and hence the size of life-form that can be fitted aboard. Some of the most useful model organism used on Earth and in space for human analogue research such as rodents and frogs, would be likely too large to ethically live in such a confined space for any usable length of time [52]. As a counter-point however, smaller organisms such as *C. elegans*, tardigrades, zebrafish, extremophiles including bacteria and fungi, and *in-vitro* human or animal tissue (using organ or tissue on chip technology) are all feasible and potentially useful payloads [3], [14], [55].

However, inherent Cube form-factor size limitations also present complex design problems for biomedical payloads, such as thermal and electrical interference as well as physical fitting of instruments and containers in the available envelope. These demands also impact the capabilities of supporting bus sub-systems in what power, data, processing bandwidth etc can be provided to payloads. Clever miniaturisation of components and sub-systems is hence required to maximise the science return of the mission[1], [26]. Furthermore, as there is currently no precedent for returnable CubeSats, the opportunity for further study in Earth labs is removed – again limiting the amount of science that can be achieved while also creating an ethical barrier to flying (and not-returning) higher life-forms.

For a team undertaking their own CubeSat mission, another general obstacle is the requirement to purchase, integrate, test and fly the other satellite sub-systems that support the payload – including structure, Electrical Power Subsystems (EPS) and Tracking, Telemetry and Control (TT&C). Even

with commercial-of-the-shelf "COTS" products and services allowing for "plug-and-play" integration of these parts, a certain level of resources and knowledge is required to ensure these other parts work properly during the mission. If a commercial payload were to be flown on platforms such as the ISS, then the platform provider would typically manage these facets and likely improve the reliability of their performance above a "typical" CubeSat developer. While fully COTS CubeSat buses are available, ready for the payload to be integrated, these can still be prohibitively expensive for certain groups, despite the improved accessibility of commercial CubeSats. The independence a developer gains to devise their own mission increases the responsibility, requirements and risk to themselves and their team.

3.3.2 Thermal Control Systems (TCS)

Many sources identify accurate and power-minimal TCS as being one of the key enabling technologies regarding biomedical CubeSats [26], [51], [52], while also describing the inherent complexities of achieving this in the CubeSat form factor [56], [57]. The supporting of biological samples and reagents at the correct and measurable temperature is important for precise replication of controls back on Earth but also to keep the sample alive. In fact, more important still, if the temperature surges or drops significantly, the samples may die or be rendered inviable due to thermal shock. Further to this, even if the samples do survive seemingly unharmed any temporary deviations from their nominal culturing temperature range must be recorded, as it may affect behaviour or metabolism and hence produce changes to experimental results. Some issues with TCS in CubeSats to highlight are the close proximity of heat dissipating electronics and sub-systems, lower power availability for active measures and larger heat fluxes (heat dissipation versus surface area) compared to larger satellites [57]. L. Zea commented that 60% (500mA) of NASA's GeneSat power demand was required by the heaters alone to maintain the sample at 34°C – demonstrating the significant engineering challenge biomedical CubeSats' TCS require [52]. While this technical challenge is one that NASA has succeeded in mostly solving with their fleet of bio-payload CubeSats, reviewed thoroughly in sources such as [26], [51], [56], it still greatly impacts the design effort. One common solution used in these missions is to thermally insulate the hermetically sealed payload module, but expecting and designing to allow the CubeSat interior to be typically cold during orbits, means that only active heaters, and not coolers are required for TCS [56]. For another example, take NASA's re-flight of PharmaSat payload hardware, from 2009, in EcAMSat in 2014. PharmaSat was a 3U to study Brewer's Yeast (culturing temperature at 27°C [52]), while EcAMSat used E. coli (cultured at approximately 37°C with a selected operating thermal tolerance of ±0.3°C). The CubeSat structure had to be upgraded to 6U for EcAMSat to support the extra solar arrays needed to supply the required power to more active heaters for this change of sample – increasing launch costs and prompting added work to reconfigure for these changes too [58]. This problem is an important case study, as it shows how in a size-limited system, such as a CubeSat, changes to one sub-system can cause larger, cascades of changes to the size, position or even usability of other parts and sub-system components , even if CubeSat-sized payload solutions are available [26].

3.3.3 Advanced Instrumentation

In the past, most instrumentation so far used on biosatellites and CubeSats has been relatively straightforward and limited to sensors that evaluate the ECLSS environment (pH, temperature, gas composition) and measure basic properties of the sample [1], [51]. Biosatellite instruments typically have to be exceptionally miniaturised, automated and reliable to fulfil objectives without crew assistance or sample-return, and within resource limitations. As described previously this is mostly due to the limited space and other resources (mass, power, envelope, data etc) available within a satellite, and particularly a CubeSat. Importantly, experiments involving multi-step assays, which would require extraction of samples, mixing of reagents and various purification and preparation processes are difficult (but not impossible) to reliably achieve in a confined space through teleoperation alone [59]. This means simple, targeted, elegant payload designs are naturally suitable for these missions, as well as being encouraged by the other innate factors in CubeSat applications and industry described in this paper. Crewed platforms like the ISS however, typically benefit from the space to include a laboratory of several instruments and a crew member with which to facilitate studies. However, crew time is at a premium, and advanced, bench-top laboratory instruments – such as quantitative PCR and genomic sequencing are only recently miniaturised and flight-readied enough for successful integration with space platforms [1] meaning more advanced research is still often done on the ground after sample return.

The ISS now supports several modern facilities for miniaturized and often partially-autonomous biomedical study [1], [60], [61]. WetLab-2 features a quantitative PCR system, the MinION is a portable DNA sequencer, and RAZOR EX and MiDASS are capable of *in-situ*, near-real-time environmental monitoring through PCR and nucleic acid analysis respectively; all having been adapted from Earth based COTS instruments [1]. These require some crew operation but were in part selected for their minimal requirements of this, as many of their processes could be automated. In addition to these high-throughput instruments, there are several commercial facilities, such as BioChip SpaceLab, for autonomously culturing and observing samples that uses standardised sample cassettes that can be easily swapped out for new customers samples. *In-situ* environmental monitoring is a critical enabling technology for exploration missions, as well as of interest for science-focused platforms [1], [53]. However, while miniaturisation of Earth-lab-based, COTS instruments is pushing the boundaries of what is considered feasible in space, there is still a significant lag between both the commercialisation of the technology on Earth and then again in its application to space (normally in the ISS) [1]. Evolving technology in this way would also likely involve another lag stage in developing instruments from space-ready or ISS versions of COTS Earth equipment to CubeSat application. Having said that, CubeSats, as discussed previously, being uncrewed, cheaper, with shorter development times and being more directly controlled by their developers, could be used as IOD for such technology, potentially gaining flight validation quicker than safety approval for crewed-vehicle use could be gained – or potentially supporting its approval. For at least the next few years however, it means it is likely that the most in-depth sample analysis, with the greatest variety of instruments and assays, is easier to achieve on the ground upon sample-return. Importantly however, the most accurate time and place to capture flight data from a sample is of course actually still through real-time, *in-situ* analysis of samples.

In so far as miniaturising and modifying Earth equipment for space goes, the other major pathway for space instrumentation development is through the application of innovative and revolutionary (vs evolutionary) technology such as lab-on-chip systems, biochips and sensors and MEMS technology. Such technology is not only valuable for improving the cost, mass and size efficiency of teleoperated research payloads, but for improving the support and research capabilities available to crew on missions, such as using biochips for point of care testing [62]. SporeSat for instance was a major validation of not only lab-on-chip systems, but of miniaturised variable-g centrifuges that functioned within the free-flying CubeSat. [28], [60], [63], [64]. Current technology, in both its evolutionary and revolutionary capacities, dampens the complexity of the instruments flown so far, although there is a push for more advanced instruments to support studies in space [1], [65]. Keeping pace with what the scientific community plans is crucial to future-proofing CubeSats as viable laboratory tools; scientifically compatible with those from more mature platforms [60], [61], [66], [67].

In contrast to how CubeSats are typically described as being accessible, standardised and commercial etc, when it comes to biomedical payloads, very little targeted support is available at the moment due to the application's maturity. It is noteworthy how often bespoke and specialised biomedical payloads are required to be for their chosen mission due to a lack of space-suitable COTS options and specific experiment requirements. The issues this present is that the payloads required for biomedical CubeSats almost invariably need to be developed in-house from scratch, with generally limited mass-produced COTS parts available meeting requirements for both laboratory biology and space appropriateness. Different samples, experiment profiles, instruments, microfluidics and culturing hardware make this process difficult, time-consuming and expensive, and sources are aware of this difficulty [25], [51], [53]. It is hoped with continued investment into CubeSat technology for biomedical applications, COTS components for payloads or even whole modules might become available which would further increase accessibility to the field [53]. In addition to payload requirements for miniaturisation and automation, the data produced from such instruments must be handled by a miniature on-board computer (OBC) and transmitted over a likely limited bandwidth.

Lessons from hardware and operational developments of instruments and payloads from the ISS are valuable to CubeSat payload developers here – even if the ISS instruments themselves are rarely automated, dedicated or unique to particular payload missions. Improving the state of the art for these systems may be less focussed on miniaturising Earth-based or ISS instruments, but rather revolutionising them. Hugely useful sources for presenting an overview of several biomedical

CubeSats' science operations, instruments and results can be found in [28] and [17].

3.3.4 Integration Issues

One other issue that is present when it comes to launching organisms to space for research is that very frequently there can be long pauses between integration into the launcher and experiment "start" in orbit. Weather and engineering delays, waiting for other payloads to be integrated, and the delay between commissioning the satellite and beginning the experiment on-orbit all can present issues to planned mission operations. Sometimes the time between final integration and operation can be days, weeks or even months. Additionally, requirement 3.3.1 of the CubeSat Design Specification (revision 13, 2015) requires P-POD integrated CubeSats to be de-powered before launch and deployment to prevent accidents, which does inhibit certain solutions to this problem [68].

For live samples this creates many problems [25], [26]. Payloads must supply nutrients, atmospheric gases, waste management and various other consumable resources to the organisms, and in the current CubeSat Specification this must all be achieved while de-powered before deployment. If these resources are in limited supply (due to size constraints in the CubeSat for example) then even short delays could consume their stockpile and have significant effects to the outcome of the sample and the experiment. Additionally, time-sensitive experiments and reagents or drugs that can degrade quickly, all suffer greatly from launch delays – particularly if the experiment was only designed to operate for a few weeks anyway. This is a problem that affects all space bioscience platforms including missions to the ISS [26]. A further potential problem is that while CubeSats can be launched on a greater variety of launchers than crew-rated vehicles, these typically induce greater launch stresses on the payloads. This can be an issue for more delicate samples (or payload instruments) that traditionally would go up alongside crew on a more "gentle" launch.

Preserving samples and reagents before integration and then reactivating them when desired on orbit is a critical enabling technology for biomedical CubeSats – importantly these same techniques can be applied in reverse when returning space-flown samples from the ISS and other platforms. These are principally the same systems used on Earth to preserve biological samples when being transported over long-distances between labs. Techniques such as desiccation and keeping samples in more hibernate or resilient states (such as fungal spores) have all been applied both for the ISS and for CubeSats such as SporeSat and EcAMSat [26], [52]. More complex methods such as cryogenic freezing have been accomplished for the ISS (including launch and sample return [69]) although have yet to be applied to biomedical samples in a CubeSat (although CryoCube-1, launched in December 2019 but results pending, aims to demonstrate a CubeSat could be used to produce cryogenic conditions once in orbit for fluid science [70]). In the future as the complexity of organisms or mission profiles (target destination, orbit, launchers, motherships) used increases, these methods may need to advance as well to enable experimental success. All of these techniques are required to be performed reliably without human intervention too, once integration into the launcher is complete. One potential innovation for this is that commercial launch companies are realising the niche in the market for late-access to launcher services and dedicated micro-launchers (for various applications including biomedical science) and are making significant progress towards this [71].

One particular issue currently under study is the probability that biological samples on space missions are affected prolonged exposure to toxic volatile gases in their enclosed environments. While deliberate outgassing is a common requirement for all materials in a spacecraft (to minimize further natural outgassing once in space due to the near-perfect vacuum), enough volatiles can remain within materials, in particular electronics PCBs. When a biological sample has to spend days or even weeks enclosed with materials that may contaminate the experiment before it is even started (even before reaching space itself), it has been found to adversely affect the expected health of the culture compared to control samples not enclosed, both in space and on Earth. As found with NASA's EcAMSat [23].

3.4 Common Trends, Obstacles and Features of Biomedical CubeSat Missions

Biomedical CubeSat developers, whether from academia, private companies or state space agencies all have to overcome certain design problems that come with using the platform for supporting biomedical experiments. Principally these arise from the requirements of integrating a miniaturised, teleoperated and reliably self-contained payload within the CubeSat bus. Some of these payload requirements aren't limited to biomedical CubeSats and would be required in varying degrees for an ISS commercial payload – which themselves can vary even further given the opportunity for crew and crew-based instruments to be involved, so are difficult to generalise accurately.

As described earlier, payloads for these missions are typically developed to fulfil very niche and specific science objectives, hence limiting the number of COTS components available. Although certain multi-mission programmes have used this to launch leftover hardware which, being flexible enough, can be modified to support different samples or experimental methods and take advantage of economies of scale [23], [25]

Table 1: General requirements and design solutions observed during literature review of biomedical cube-payloads. Research from [17], [28], [29], [52], [53]

Common Requirements	**Motivation**	**Validated/Trialed/Developing Solutions**
Sample preservation during sample integration	Unreliable and long durations de-powered on launch pad	Desiccation, withholding of nutrients (stasis buffer)
Sample revival on-orbit	Reliable sample state on "experiment start". Repeatability.	Supply of heat, nutrients and/or moisture/growth medium with microfluidics
Hermetically sealed payload	Sustaining of sample in controlled, repeatable conditions	Insulated seal-before-flight payload modules
Suitable growth media and containers for spaceflight	Sustaining of sample in controlled, repeatable conditions. Prevent anomalies in instrument use or risks to samples or electronics from leaks.	Microfluidics reagents sealed in chambers to prevent leaks, bubbles or air pockets.
Accurate ECLSS (particularly thermal)	Sustaining of sample in controlled, repeatable conditions. CubeSat form factor has innate issues for TCS	Insulated and hermetically sealed payload modules. Use of active micro-heaters on culture wells too.
Miniaturised instruments with tolerance to microgravity and other space factors	Ensure accurate, repeatable results obtained. Difficulties in adapting Earth assay or reagent microfluidics for functioning in microgravity	Observation systems utilising optics and little-no moving parts. Simplified so few multi-reagent or multi-step assays.
Repeatable experiments (on ground or other spacecraft)	Validate Cube-payload results as accurate and not suffering systematic error from form factor	COTS, modular, mass-produced payloads and buses

When reviewing these biomedical CubeSat missions alongside their common trends and features, it becomes clear that stakeholders in the biomedical research community and the CubeSat sector share many common goals and hopes for the application. Examining the larger reviews and individual mission plans given in section 3.1, there are certainly some common directions that researchers seem to be advancing towards. These could be thought of as the "critical technology gaps" of biomedical CubeSats. This wish-list for developers and scientists would remove some of the obstacles and limiting factors affecting the popularity and maturity of the biomedical CubeSat application.

Table 2: Analysis of critical technology gaps or common desired improvements of biomedical cube-payloads, i.e., targets for future development of "next-generation" cube-payloads.	
Remaining Critical Technology Gaps & Desired Innovations for BM Cube Payloads	**Motivation and Promising Examples**
Payload module/sample return capabilities	Enable further, more in-depth study at Earth labs. Confirm *in-situ* observations as accurate.
Advanced instrument capabilities	Advancement and miniaturisation of instruments will improve the value and science-return of cube payloads. Utilisation of Biosensors, lab-on-chip, SporeSat centrifuge, MEMS, microarrays, biochips technology
Flexible (multi-assay) instrument capabilities	Multiple samples, assays, or even whole experiments, can be taken during one flight, enabling improved results capabilities, accuracy and repeatability
COTS, modular and interchangeable biomedical specific payloads, components and services	Respects CubeSats accessibility and affordability which enabled their popularity, encourages commercial industry to boost this further. Standardised payload interfaces would streamline processes for choosing a scientists own route or vehicle to space.
Greater emphasis towards science return instead of IOD	Better coordination with biomedical researchers as "customers" should steer development towards high-value goals
Boundaries analysed to ensure payload slot providers don't "sell-out"	In some situations, cube-payloads are not cost-effective or provide enough science return compared to traditional, monolithic or crew-operated ones.
Validation through analysis and comparison of flight results to other non cube-sat/payload missions	Further validate cube-sat/payloads as professional scientific research tools for use in the space science infrastructure alongside other platforms

3.5 Concluding Table of pros and cons

Excellent reviews of historical and future biomedical CubeSat missions can be found in [17], [25], [26], [28], [29], [51]–[53]. Although given the standard features of mission payloads discussed in this report (namely miniaturised and autonomous ones, capable of *in-situ* analysis), many other relevant material can be found and dissected from non-CubeSat missions such as Eu:CROPIS, the ShiJian, Tianzhou and Bion spacecraft, and the future Space Rider programme [16], [18].

The authors are in agreement with the referenced literature that, when factoring science return, costs and logistics as figures of merit, worthwhile use of biomedical CubeSats is typically only achievable when they "stay in their own lane". That is, they are used for simple, focused, cheap missions with budgetary, space environment or time constraints – i.e., they play to their advantages and do not compete with platforms like the ISS. For more reliable, comprehensive, in-depth studies, with the possibility of sample return, the ISS is likely a more effective and economically suitable platform for now. Although other advantages that greatly benefit specific groups (such as universities) might support motivations to develop a CubeSat mission regardless. This is to say nothing of the predicted future uncrewed platforms that are expected to become available for ride-sharing or payload hosting flights in the coming years. Importantly however, CubeSats and other free-flyers do offer possibilities to conduct experiments in locales with relatively novel (or easier to control) radiation or gravity environments that may not have crewed facilities just yet, such as different LEO's, missions in the radiation belts or cis-lunar space. For cases where using a CubeSat is significantly cheaper for an organisation compared to an ISS mission (e.g., a University that has access to heavily discounted COTS bus products for example), it could even be possibly worthwhile launching multiple CubeSat missions instead. These could give redundancy to the mission, perhaps a good use of resources given academic CubeSats failure rate [72], or allows for an extension to the science goals of the overall mission, while still potentially costing less than one ISS payload life-cycle.

However, an additional point to mention here is that the proliferation of biomedical CubeSats arguably could generate a larger impact on the problem of space debris and may hence increase the risk of triggering a Kessler syndrome event, on a per-payload flow basis.

in certain scenarios CubeSats can be competitive alternatives to ISS-hosted payloads, with advantages including shorter development times, lower buy-in costs, improved accessibility, possibility for use in different locales, COTS products and services and the use of student-workers. However, CubeSats importantly do still require bus sub-systems such as EPS and TT&C to be bought and integrated successfully (even if they are COTS), a thorough campaign of testing, and the development of a bespoke payload – with likely different (both positive and negative) design constraints compared to ISS hardware. Furthermore, there may be less support freely available to CubeSat developers from space agencies compared to commercial ISS payloads – the independence developers gain increases the responsibility, requirements and risk to themselves and their team. It is a damming figure that between 1994 and 2017, ~40% of university-class CubeSats failed to meet their mission objective [72].

Biomedical payloads using CubeSats are likely to have instruments and sample support systems that have limited access to resources such as volume, power, physical movement and, for now at least, the ability to return samples to Earth for post-flight analysis. Notably, payloads must be able to reliably preserve and revive their samples using remote operation after rocket integration and launch. These notable constraints can be somewhat mitigated through careful design, thorough ground testing and sensible expectation and targeting of science returns. In return for these efforts and constraints, CubeSat mission planners will have easier access to orbits and space environments beyond LEO, complete control over their own science objectives and risks and the economic and logistical benefits already discussed.

Similar arguments for a technology push to improve the maturation and uptake of CubeSats as platforms for novel applications is reflected by the case of their use in the astronomy and astrophysics community [26], [73], [74]. Much like with biomedical CubeSats, the application is in its infancy, however remarkable achievements and IOD have still been made such as with the ASTERIA 6U to observe transiting ExoPlanets [75]. They are similar in they have the same advantages and disadvantages of using CubeSats vs larger, monolithic platforms, but still require payloads to be often tailor-made for their missions and built from near-scratch. Providing opportunities and support to new experiments and experimenters by giving accessibility to a horizontal market rather than a vertical market (as in "democratised" NewSpace vs traditional aerospace) – is potentially a successful way to boost these applications in the space sector and produce further, novel innovation. There are likely many more parallels that could be drawn using astronomy applications as an example, but these are best left to other work.

Table 3: Overall Review of CubeSats as platforms for space biomedical research, generally as alternatives compared to the ISS or traditional satellites

Topic	Pro's	Con's	Upcoming Improvements
CubeSats Design and Operations Requirements	Automation, teleoperation and high bandwidth comms enables minimal impact on hosting platform operations or crew time	Limitations to teleoperated *in-situ* modifications or repairs. Although sealed ISS payloads may be similar.	Sample return modules/systems. Maturing COTS industry.
CubeSat Design and Operations Requirements	Smaller size systems generally reduce costs and complexity versus larger satellites. So cheaper and faster to develop and launch.	Limited size constrains available volume for payload samples and instruments. More complex packing issues (e.g. TCS). Condensed payload might affect results.	Lab-on-chip, biosensor, biochip, MEMS and other technologies allowing for miniaturised, advanced, high-throughput instruments

Integration and Launch Issues	Rapid development and integration times. Popular standard enables streamlined ride-share services on more platforms. More opportunities to access space environments beyond LEO	Biomedical samples must be preserved and re-activated remotely. No guarantee of near-launch integration slots and launch delays.	Potential for dedicated Micro/nano launchers which can be tailored to a CubeSat's requirements more closely. Maturing and advancing CubeSat ride-share and deployment commercial services
Independence and Control	More complete project time, cost and design control for development teams.	Requirement to "build your own" supporting bus hardware - EPS, TCS, comms etc. Limited bus resources available (miniaturised sub-systems) for more demanding payloads	Maturing COTS products and services industry providing affordable support to missions. Developing technology enabling more complex samples and payloads with reduced requirements
Flexibility	Greater opportunity to fly low TRL, IOD or risky payloads (e.g. bio-hazard reagents or pathogens). Less investment lost in case of failure.	Difficulty regulating reliable private industries, services, products and test procedures. May lead to space debris issues.	Greater standardisation of testing, maturity and regulation from wealthier industry and state actors demanding reliable products and services.
Accessibility	Greater access to launch or ride-share opportunities, including for space environments beyond LEO and crewed platforms	No demonstrated sample return solution	Interest to demonstrate "in-orbit manufacturing" for pharmaceuticals, crystals, and other products
Accessibility	Standardised, simplified design and supporting sector products and services enables high levels of student involvement	General sector habit to still dismiss CubeSats as "educational tools", rather than scientific platforms. Although this is changing.	Maturing application as shown by various academic, state and industry developers that will increase the tech's popularity and fidelity
Accessibility	Generally good accessibility for researchers (low requirement barriers – expertise, facilities, investment etc).	Too numerous missions might worsen space debris	Building interest in using space for commercial biomedical research – using all platforms with cube-payloads as interchangeable standard
Support Available from Industry	Good availability of COTS products and technical services for CubeSats in general. Developed network of experienced student and teacher training and grants	Less mature commercial industry than ISS "route to space" for biomedical studies	Several start-ups looking to utilise biomedical CubeSats. Increasing space agency and government support for student missions
Politics	Enables alternate routes to space for politically non-ISS partner parties	Proliferation of potentially non-standardised or non-cooperating missions may lead to space debris issues	Increased popularity of application will build bridges using science diplomacy.

4. Further Discussions and Conclusions

As hopefully this review and related sources indicate, there exists a "sweet-spot" in using CubeSats as alternatives to the ISS for biomedical payloads. Where the science operations required are targeted, focussed, able to be constrained enough; and the science, logistics or economics either preclude an ISS mission or otherwise would substantially gain from developing their own CubeSat mission – then perhaps a CubeSat mission would be a suitable alternative. As stated previously, CubeSats should not be thought of as replacements or blanket-alternatives to the ISS. They excel and are more suited in their niche to those missions that would be problematic, undesired or difficult to achieve using other platforms. They complement larger platforms and the whole space sector stands to gain through developing this pathway further. While they may not likely compete in term of pure science return on investment compared to the ISS, it is the other figures of merit (such as prestige and educational value) that can swing the balance in favour of CubeSats for those relevant scenarios. Relevant sources generally advocate for greater CubeSat utilisation and development alongside the continuing refining and growth of other research platforms as well. It is hence not just the mission or hardware or science requirements that impacts the choice, but who is developing them.

Already we can see the first steps towards a more mature biomedical CubeSat community. Missions accomplished by NASA have provided an excellent technological push factor and demonstration of the enabling technology required for such missions. SpacePharma's DIDO-2 & 3 have demonstrated that smaller private-sector teams can accomplish similar missions too, and that there is a market for this amongst biomedical scientists. Thanks to this, many other industrial and academic projects (such as SpaceForge and the others listed in section 3.1) are beginning to occur which will only increase the area's visibility and capabilities, driving a potential whole new sector of the CubeSat industry. Not to mention the benefits the research will bring to the space biomedical community preparing for lunar exploration and private spaceflight. To that end, the novel spacecraft developed for these purposes ([14]–[16], [18], [20]) are hoped to feature commercial payload slots available on them, possibly using CubeSat units as an international standard as is already done for commercial experiment racks on the ISS. Further promoting the credibility, commercialisation and improved development of CubeSat biomedical payloads in a positive feedback loop for the sector.

To take a long-term view it is worth noting that we are only at the early stages of biomedical CubeSat utilisation. The technology is immature and restricted to what payload designers can devise themselves within the current limitations of a CubeSat – all while any arguments made for or against the use of CubeSats as alternate platforms to the ISS are only relevant to the current and very near future state of space infrastructure. The authors recognise that biomedical CubeSats are still on their original (easily-overstated) hype climb, and there are a lot of innovations and realistic solutions that will need to occur before properly realised, highly-capable, scientifically respected, semi-commercial biomedical CubeSats are commonplace – and indeed provide comparable science return on investment to other platforms such as the ISS. At the end of the day, it would be unwise and inefficient to advocate for the total replacement or refilling of the ISS with separated biomedical Cube-payload slots.

In the future it is hoped developments such as in-space manufacturing (of drugs, materials, protein crystals etc), payload return modules, advanced, miniaturised instruments and space biomedical specific COTS products and services will properly enable a mature and high-fidelity biomedical CubeSat industry. While also providing a "killer app" that might encourage further growth and development (potentially commercially) in this sector through a positive feedback loop. These niche applications could and are being exploited by committed NewSpace enterprises or parts of state space agencies, whos' greater demand and budget for reliability and quality in design and operations would further fuel the advancement of biomedical CubeSat technology.

Future work will look into how CubeSats compare to the whole current and future space research infrastructure, not just as alternative niches to crewed platforms such as the ISS. This importantly should include non-crewed, larger biosatellite or free-flyer platforms (such as Space Rider and Dream Chaser), smaller novel platforms (Commercial Lunar Micro-Landers) and new, flagship crewed missions (Gateway and Artemis). This will involve looking at what recommendations we can give to the technology of biomedical CubeSats and in particular cube-payloads, and how that might encourage, and be encouraged by, how the space sector implements things like commercial cube-payload slots in these new

missions (similar to the earlier mentioned ISS facilities today). Overall, between the scientific, technological, political and economic recommendations there is great potential for a biomedical CubeSat/Cube-payload roadmap to be visualised.

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6. References

[1] F. Karouia, K. Peyvan, and A. Pohorille, "Toward biotechnology in space: High-throughput instruments for in situ biological research beyond Earth," *Biotechnology Advances*, vol. 35, no. 7. Elsevier Inc., pp. 905–932, 15-Nov-2017, doi: 10.1016/j.biotechadv.2017.04.003.

[2] P. Ryder and M. Braddock, "Harnessing the Space Environment for the Discovery and Development of New Medicines," in *Handbook of Space Pharmaceuticals*, Springer International Publishing, 2020, pp. 1–35.

[3] L. Zea, "Drug Discovery and Development in Space," 2017.

[4] D. M. Klaus, "Clinostats and Bioreactors," 2001.

[5] J. P. Frippiat *et al.*, "Towards human exploration of space: The THESEUS review series on immunology research priorities," *npj Microgravity*, vol. 2. Nature Publishing Group, 07-Jan-2016, doi: 10.1038/npjmgrav.2016.40.

[6] C. Urbaniak *et al.*, "Detection of antimicrobial resistance genes associated with the International Space Station environmental surfaces," *Sci. Rep.*, vol. 8, no. 1, pp. 1–13, Dec. 2018, doi: 10.1038/s41598-017-18506-4.

[7] M. J. Green, J. W. Aylott, P. Williams, A. M. Ghaemmaghami, and P. M. Williams, "Immunity in Space: Prokaryote Adaptations and Immune Response in Microgravity," *Life*, vol. 11, no. 2, p. 112, Feb. 2021, doi: 10.3390/life11020112.

[8] Y. Zhang, S. E. Richards, J. T. Richards, and and H. G. Levine, "The Use of Microgravity Simulators for Space Research," 2016.

[9] R. Herranz *et al.*, "Ground-based facilities for simulation of microgravity: Organism-specific recommendations for their use, and recommended terminology," *Astrobiology*, vol. 13, no. 1. Mary Ann Liebert, Inc., pp. 1–17, 01-Jan-2013, doi: 10.1089/ast.2012.0876.

[10] L. Shi *et al.*, "Spaceflight and simulated microgravity suppresses macrophage development via altered RAS/ERK/NFκB and metabolic pathways," *Cell. Mol. Immunol.*, pp. 1–14, Jan. 2020, doi: 10.1038/s41423-019-0346-6.

[11] E. E. Higginson, J. E. Galen, M. M. Levine, and S. M. Tennant, "Microgravity as a biological tool to examine host-pathogen interactions and to guide development of therapeutics and preventatives that target pathogenic bacteria," *Pathogens and disease*, vol. 74, no. 8. 01-Nov-2016, doi: 10.1093/femspd/ftw095.

[12] J. Dowling, A. Rosenfeld, J. Waldie, and I. Feain, "Opportunities in space life sciences," *Australasian Physical and Engineering Sciences in Medicine*, vol. 42, no. 3. Springer Netherlands, pp. 663–664, 15-Sep-2019, doi: 10.1007/s13246-019-00769-y.

[13] D. A. Green, "How the UK Can Lead the Terrestrial Translation of Biomedical Advances Arising from Lunar Exploration Activities," *Earth, Moon Planets*, vol. 107, no. 1, pp. 127–146, Dec. 2010, doi: 10.1007/s11038-010-9366-z.

[14] K. R. Brown, P. Hodkinson, N. Smith, A. Hawkey, R. Velho, and P. Carvil, “Why Space The opportunity for Health and Life Science Innovation Why Space?,” UK Space Life and Biomedical Sciences (LABS) Association, May 2021.

[15] V. Pletser, G. De Crombrugghe, and V. Pletser, “Emerging Microgravity Platforms and their Capabilities Compared to the Traditional Offering,” 2017.

[16] A. Fedele *et al.*, “The Space Rider Programme: End user’s needs and payload applications survey as driver for mission and system definition,” *Acta Astronaut.*, vol. 152, pp. 534–541, Nov. 2018, doi: 10.1016/j.actaastro.2018.08.042.

[17] Y. Glick and S. Eyal, “Future of Drug Development in Space: Unmanned Satellites and Vehicles,” in *Handbook of Space Pharmaceuticals*, Springer International Publishing, 2021, pp. 1–29.

[18] S. C. Sun *et al.*, “Lunar Life Sciences Payload Assessment,” 2020.

[19] D. Xiaoci, “China reveals moon station plan with Russia, openness on Space Day - Global Times,” 2021. [Online]. Available: https://www.globaltimes.cn/page/202104/1221948.shtml. [Accessed: 23-Jul-2021].

[20] C. Heinicke *et al.*, “Equipping an extraterrestrial laboratory: Overview of open research questions and recommended instrumentation for the Moon,” *Adv. Sp. Res.*, vol. 68, no. 6, pp. 2565–2599, Sep. 2021, doi: 10.1016/J.ASR.2021.04.047.

[21] ESA, “Biology | Rexus/Bexus,” 2020. [Online]. Available: http://rexusbexus.net/experiments/scientific-research/biology/. [Accessed: 08-Jul-2020].

[22] R. Herranz *et al.*, “Ground-based facilities for simulation of microgravity: Organism-specific recommendations for their use, and recommended terminology,” *Astrobiology*, vol. 13, no. 1. Mary Ann Liebert, Inc., pp. 1–17, 01-Jan-2013, doi: 10.1089/ast.2012.0876.

[23] M. R. Padgen *et al.*, “EcAMSat spaceflight measurements of the role of σs in antibiotic resistance of stationary phase Escherichia coli in microgravity,” *Life Sci. Sp. Res.*, vol. 24, pp. 18–24, Feb. 2020, doi: 10.1016/j.lssr.2019.10.007.

[24] P. W. Taylor, “Infection and Drug Resistance Dovepress Impact of space flight on bacterial virulence and antibiotic susceptibility,” 2015, doi: 10.2147/IDR.S67275.

[25] K. Woellert, P. Ehrenfreund, A. J. Ricco, and H. Hertzfeld, “Cubesats: Cost-effective science and technology platforms for emerging and developing nations,” *Adv. Sp. Res.*, vol. 47, no. 4, pp. 663–684, Feb. 2011, doi: 10.1016/j.asr.2010.10.009.

[26] A. Poghosyan and A. Golkar, “CubeSat evolution: Analyzing CubeSat capabilities for conducting science missions,” *Progress in Aerospace Sciences*, vol. 88. Elsevier Ltd, pp. 59–83, 01-Jan-2017, doi: 10.1016/j.paerosci.2016.11.002.

[27] T. Villela, C. A. Costa, A. M. Brandão, F. T. Bueno, and R. Leonardi, “Review Article Towards the Thousandth CubeSat: A Statistical Overview,” 2019, doi: 10.1155/2019/5063145.

[28] S. Massaro Tieze, L. C. Liddell, S. R. Santa Maria, and S. Bhattacharya, “BioSentinel: A Biological CubeSat for Deep Space Exploration,” *Astrobiology*, p. ast.2019.2068, Apr. 2020, doi: 10.1089/ast.2019.2068.

[29] S. Amselem, “Remote Controlled Autonomous Microgravity Lab Platforms for Drug Research in Space,” *Pharmaceutical Research*, vol. 36, no. 12. Springer New York LLC, pp. 1–15, 01-Dec-2019, doi: 10.1007/s11095-019-2703-7.

[30] A. Elsaesser *et al.*, “SpectroCube: a European 6U nanosatellite spectroscopy platform for astrobiology and astrochemistry,” *Acta Astronaut.*, vol. 170, pp. 275–288, May 2020, doi: 10.1016/j.actaastro.2020.01.028.

[31] A. Sgambati *et al.*, “SPECTROModule: A modular in-situ spectroscopy platform for exobiology and space sciences,” *Acta Astronaut.*, vol. 166, pp. 377–390, Jan. 2020, doi: 10.1016/j.actaastro.2019.10.010.

[32] SpaceForge, “Home - Space Forge.” [Online]. Available: https://spaceforge.co.uk/. [Accessed: 30-Jun-2021].

[33] A. Shamsul *et al.*, “BAMMsat-on-BEXUS: A Technology and Operation Demonstration of a BioCubeSat Platform on a Stratospheric Balloon Flight Educational Program,” *Small Satell. Conf.*, Aug. 2020.

[34] M. Zalasiewicz *et al.*, “A Modular Hardware and Software Architecture for a Student-Designed BioCubeSat Prototype Using Autonomous Operations,” *Small Satell. Conf.*, Aug. 2021.

[35] A. Meneghin, G. Poggiali, and A. Nascetti, “Astrobio CubeSat: A Mini Laboratory Payload for Space Environment Astrobiology Experiments,” 2019, no. September, pp. 2–3, doi: 10.13140/RG.2.2.17952.12801.

[36] F. Santoni *et al.*, “GreenCube: Microgreens cultivation and growth monitoring on-board a 3U cubesat,” in *2020 IEEE International Workshop on Metrology for AeroSpace, MetroAeroSpace 2020 - Proceedings*, 2020, pp. 130–135, doi: 10.1109/MetroAeroSpace48742.2020.9160063.

[37] P. Marzioli *et al.*, “CultCube: Experiments in autonomous in-orbit cultivation on-board a 12-Units CubeSat platform,” *Life Sci. Sp. Res.*, vol. 25, pp. 42–52, May 2020, doi: 10.1016/j.lssr.2020.02.005.

[38] A. Kornakiewicz, J. Mielczarek, and A. Zadrozny, “A concept of biopharmaceutical nanosatellite,” Feb. 2018.

[39] A. Podwin *et al.*, “Lab-on-chip platform as a nanosatellite payload solution for biomedical experiments in outer space,” 2020, pp. 1–3, doi: 10.1109/powermems49317.2019.82063206124.

[40] J. Dziuban, “Polish nano-satellite to explore Mars,” 30-Oct-2019. [Online]. Available: https://pwr.edu.pl/en/university/news/polish-nano-satellite-to-explore-mars-10357.html. [Accessed: 30-Jun-2021].

[41] K. M. Hegde, C. R. Abhilash, K. Anirudh, and P. Kashyap, “Design and Development of RVSAT-1, A Student Nano-satellite with Biological Payload,” in *IEEE Aerospace Conference Proceedings*, 2019, vol. 2019-March, doi: 10.1109/AERO.2019.8742113.

[42] A. Nygren and A. Ramm, “Microfluidics system for the MOREBAC astrobiology experiment module : Design of a cubesat module,” 2018.

[43] Z. Xiang, C. Min, L. Wenhe, Y. Youquan, and Z. Lianxin, “Study on On-Orbit Demonstration Technology for Space-Biology Nanosatellites,” *2014 International Conference on Manipulation, Manufacturing and Measurement on the Nanoscale, Taipei*, 2014. [Online]. Available: https://ieeexplore-ieee-org.ezproxy.nottingham.ac.uk/stamp/stamp.jsp?tp=&arnumber=7057353&tag=1. [Accessed: 30-Jun-2021].

[44] A. Alanazi, A. B. Jones, W. Alsolami, D. S. Anderson, and J. Straub, “The use of a 3u cubesat for the germination of seeds in space,” in *AIAA Scitech 2020 Forum*, 2020, vol. 1 PartF, doi: 10.2514/6.2020-2162.

[45] C. M. Trouillefou *et al.*, “An autonomous plant growing miniaturized incubator for a Cubesat,” *Acta Astronaut.*, vol. 179, pp. 439–449, Feb. 2021, doi: 10.1016/j.actaastro.2020.11.009.

[46] E. Obreque *et al.*, “Space Gardening on Plantsat: Design Challenges and Opportunities for Developing Biological Ecosystems in Low Earth Orbit,” *Small Satell. Conf.*, Aug. 2019.

[47] V. P. Zakharov, V. N. Konyukhov, P. I. Bakhtinov, E. V. Molchkov, D. V. Kornilin, and S. G. Konovalov, “Biological module ‘BiNOM’ for cubesats of the SamSat family,” *Vestn. Samara Univ. Aerosp. Mech. Eng.*, vol. 17, no. 2, p. 80, Jul. 2018, doi: 10.18287/2541-7533-2018-17-2-80-90.

[48] S. Kallapur *et al.*, “Microbial analysis in space: Modular device for biological experiments in microgravity,” *Acta Astronaut.*, vol. 188, pp. 473–478, Nov. 2021, doi: 10.1016/J.ACTAASTRO.2021.08.016.

[49] Brykov, E. Kovalenko, B. Ivanytska, and B. Ivanytska, “MICROCOSM as a perspective model for biological experiment at nanosatellite,” *Sp. Sci. Technol.*, vol. 24, no. 2, pp. 55–59, Mar. 2018, doi: 10.15407/knit2018.02.055.

[50] T. Etheridge, N. J. Szewczyk, L. Dartnell, D. Cullen, L. Rothschild, and J. Holt, “Deep Space Petri-Pod , a new platform for astrobiology experiments beyond the van Allen belts,” pp. 108–109.

[51] National Academies of Sciences Engineering and Medicine, *Achieving Science with CubeSats*. National Academies Press, 2016.

[52] L. Zea, “Microbiological Experiments Onboard CubeSats-A Review and Prospects,” *1 st Lat. Am. IAA CubeSat Work.*, pp. 1–13, 2014.

[53] R. S. M. S. and R. A. J. Zea, Luis, “CubeSats for microbiology and astrobiology research,” in *CUBESAT HANDBOOK: From Mission Design to Operations*, 1st ed., B. K. Cappelletti, Chantal, Battistini, Simone, Malphrus, Ed. Academic Press - Elsevier, 2020.

[54] A. K. Nervold, J. Berk, J. Straub, and D. Whalen, “A Pathway to Small Satellite Market Growth,” *Adv. Aerosp. Sci. Technol.*, vol. 01, no. 01, pp. 14–20, Jun. 2016, doi: 10.4236/aast.2016.11002.

[55] N. Ishioka and A. Higashibata, “Space Experiments Using C. elegans as a Model Organism,” in *Handbook of Space Pharmaceuticals*, Springer International Publishing, 2019, pp. 1–32.

[56] M. F. Diaz-Aguado, S. Ghassemieh, C. VanOutryve, C. Beasley, and A. Schooley, “Small class-D spacecraft thermal design, test and analysis - PharmaSat biological experiment,” in *IEEE Aerospace Conference Proceedings*, 2009, doi: 10.1109/AERO.2009.4839352.

[57] B. Yendler, “Thermal control system,” in *CUBESAT HANDBOOK: From Mission Design to Operations*, 2020.

[58] T. Boone *et al.*, “E. coli AntiMicrobial Satellite (EcAMSat): Science Payload System Development and Test,” *Small Satell. Conf.*, Aug. 2014.

[59] C. Urbaniak *et al.*, “Validating an Automated Nucleic Acid Extraction Device for Omics in Space Using Whole Cell Microbial Reference Standards,” *Front. Microbiol.*, vol. 11, p. 1909, Aug. 2020, doi: 10.3389/fmicb.2020.01909.

[60] A. Kanapskyte, E. M. Hawkins, L. C. Liddell, S. R. Bhardwaj, D. Gentry, and S. R. Santa Maria, “Space Biology Research and Biosensor Technologies: Past, Present, and Future,” *Biosensors*, vol. 11, no. 2, p. 38, Jan. 2021, doi: 10.3390/bios11020038.

[61] E. M. Hawkins, A. Kanapskyte, and S. R. S. Maria, “Developing Technologies for Biological Experiments in Deep Space,” *Proc. 2020, Vol. 60, Page 28*, vol. 60, no. 1, p. 28, Nov. 2020, doi: 10.3390/IECB2020-07085.

[62] A. Roda *et al.*, “Advanced biosensors for monitoring astronauts’ health during long-duration space missions,” *Biosensors and Bioelectronics*, vol. 111. Elsevier Ltd, pp. 18–26, 15-Jul-2018, doi: 10.1016/j.bios.2018.03.062.

[63] J. Park *et al.*, “An autonomous lab on a chip for space flight calibration of gravity-

induced transcellular calcium polarization in single-cell fern spores," *Lab Chip*, vol. 17, no. 6, pp. 1095–1103, 2017, doi: 10.1039/c6lc01370h.

[64] A. Nascetti, D. Caputo, R. Scipinotti, and G. de Cesare, "Technologies for autonomous integrated lab-on-chip systems for space missions," *Acta Astronaut.*, vol. 128, pp. 401–408, Nov. 2016, doi: 10.1016/j.actaastro.2016.07.036.

[65] F. Karouia *et al.*, "Gene Expression Measurement Module (GEMM)-a fully automated, miniaturized instrument for measuring gene expression in space Gene Expression Measurement Module (GEMM) for space application: Design and validation," *Life Sci. Sp. Res.*, vol. 22, pp. 55–67, 2019, doi: 10.1016/j.lssr.2019.07.004.

[66] L. Rutter *et al.*, "A New Era for Space Life Science: International Standards for Space Omics Processing," *Patterns*, vol. 1, no. 9, p. 100148, Dec. 2020, doi: 10.1016/j.patter.2020.100148.

[67] H. Cottin *et al.*, "Space as a Tool for Astrobiology: Review and Recommendations for Experimentations in Earth Orbit and Beyond," *Sp. Sci. Rev. 2017 2091*, vol. 209, no. 1, pp. 83–181, Jun. 2017, doi: 10.1007/S11214-017-0365-5.

[68] California Polytechnic State University, "CubeSat Design Specification Rev. 13 The CubeSat Program, Cal Poly SLO CubeSat Design Specification (CDS) REV 13 Document Classification X Public Domain ITAR Controlled Internal Only," 2015.

[69] NASA, "NASA ISS Cold Stowage," 2017. [Online]. Available: https://ntrs.nasa.gov/api/citations/20170003854/downloads/20170003854.pdf. [Accessed: 15-Apr-2021].

[70] M. Putman, Philip, Walker, Alex, Harris, Michael, Husk, Geoffrey, Haberbusch, "Cryogenic Thermal Management for CryoCube-1," 2015.

[71] P. Luiz Kaled Da Cas, "Launch Vehicle Overview," in *CUBESAT HANDBOOK: From Mission Design to Operations*, 2020.

[72] A. Alanazi and J. Straub, "Engineering Methodology for Student-Driven CubeSats," *Aerospace*, vol. 6, no. 5, p. 54, May 2019, doi: 10.3390/aerospace6050054.

[73] D. R. Ardila and A. Freeman, "Astro2020 APC White Paper SmallSats for Astrophysics," 2019.

[74] R. A. Deepak and R. J. Twiggs, "Thinking Out of the Box: Space Science Beyond the CubeSat."

[75] M. W. Kaufman, Marc, "For First Time, Tiny CubeSat Locates a Distant Exoplanet – Many Worlds." [Online]. Available: https://manyworlds.space/2020/06/08/for-first-time-tiny-cubesat-locates-a-distant-exoplanet/. [Accessed: 27-Jan-2021].