Literature Research Project

Imperial College London

MEDICINE IN SPACE

Abstract

The forthcoming decades promise humanity a new chance to explore distant planets and experience new frontiers. Through the efforts of organisations and companies such as NASA and SpaceX in recent year, the world is now increasingly interested in adventuring out into space. Clearly, in facing new frontiers, there are additional borders which humanity has to cross to get to its destination. It is henceforth important to look at how mankind can sustain itself throughout the journey to greater pastures. This review sets out to study the ways in which humanity can prepare itself against the realities of space travel. From looking at the effects of microgravity and radiation to nutrition and mental health, the information gathered and its implications are investigated. The way in which personal data about the astronaut's body is also discussed along with monitoring systems such as the Health Analytics System. Subsequently, a proactive approach is looked at for learning more about the stability of medicines in space as well as how to provide personal dosimetry for each astronaut. Finally, more serious injuries are considered through investigating the efficacy of telesurgery and how time delay affects effective communication. The literature is then re-evaluated and discussed for proactive future approaches whilst noting that further research can be done in Virtual Reality and portable diagnosis. It is then concluded that humanity has the necessary tools to begin preparing astronauts to go beyond Earth, to explore new worlds, to boldly go where no one has gone before.

Objectives

The review sets out to shed light and evaluate the state of medicine within the context of space travel. The objectives below have been selected to provide an overview of the topic:

- To evaluate the data collected in regards to the environment of space,
- To review the methods by which data about the human body can be collected and the means of running advanced diagnostics in space,
- To establish the efficacy of pharmaceutical and chemical use aboard long-duration spaceflight,
- To evaluate the technology currently available for conducting complex surgery at a distance and the effect that the distance has on communication.

Contents

1 Introduction

Within the last 70 years, the research done in relation to space has shed light on space medicine. The harder evidence was provided by experiments on board space stations like Mir whilst speculative projects used extreme and simulated environments on Earth.

It is essential to recognise the effects that space can have on the body. One issue is the lack of gravity which can cause issues such as ocular problems, nausea, and bone density loss [1]. Radiation exposure is extremely concerning as risks of immune system dysregulation arise with prolonged exposure [2]. Additionally, astronauts' nutritional needs must be met to counteract issues such as DNA degradation [3] whilst psychological needs must be considered to maintain morale and happiness.

The necessity for attaining metrics about the human body in space is essential for providing personalised medication [4] based on astronaut needs due to factors such as metabolism rates, caloric intake, and sleep. Additionally, activities like spacewalks outside of spacecrafts need constant radiation monitoring to avoid adverse issues associated to high dosages [5].

As such, radiation can also impact the medicines that are on board spacecrafts which causes chemical decomposition due to particle dislocation of the active pharmaceutical [6]. To supplement the loss of this can be done with personal drug delivery through additive manufacturing [7] combined with health monitoring systems as previously described.

In addition to these, trauma and injury in space from accidents or catastrophic events need expert surgery to be performed on astronauts without returning to Earth. Telesurgery was subsequently introduced whilst methods of delivering care were categorised into groups dependent on the amount of time delay between the Earth and the spacecraft [8].

Within this review, the scarcity of relevant papers related to the subject required multiple search engines and search strings to gather ample research. Notable databases were used as described in Table 1 with the corresponding strings related to cited papers. The strings used filtered results to below 250 papers. Further filtering by research article assured that the results provided substantiated papers. However, some cited papers also contained relevant references from Shavers et al., Smith, and Frederiksen et al.

Table 1: Search engines and search strings of selected papers

Science Direct	additive manufacturing AND 3D printing pharmaceuticals; astronaut medication sleep space; "astronaut health" surgery; radiation dosimetry on board the ISS; space astronaut health medication mental; chemicals AND medicine AND space; telepresence surgery telementoring; medicine AND extreme conditions; medicine space station; interplanetary flight AND medicine; interplanetary flight AND health; "outer-space" "time delay" "Exploration-class"; International Space Station telehealth; "Radiation protection" outer space NASA
PubMed	astronaut medication; telemedicine telehealth space surgery; medicine stability extreme conditions space; pharmaceuticals in space; medicine space station; space radiation and the brain; Telesurgery AND health AND medicine; telehealth telesurgery
IEEE	delay time telesurgery; outer space communication; interplanetary astronaut health
Engineering Village	delay time telesurgery; outer space communication; interplanetary astronaut health

2 Astronaut's Health

Throughout mankind's time exploring and investigating space, many questions have been raised concerning the health of astronauts and their survival in space. What impacts would this new environment have on the human body? What do we know about this new unknown? How do we protect our explorers? Despite the relative difficulty of sending researchers into space, the journeys undertaken by the world into LEO led to new insights and collection of vast amounts of data about the human body. As such, this information collected from human spaceflight will help prepare our astronauts for the dangers that may lie far beyond Earth.

2.1 Bone Density

It has been reported that significant bone loss has occurred within cosmonauts spending 5-6 months on board Mir with a rate of 1.35% to 2.0% at the pelvic level [1]. This had occurred despite the cosmonauts receiving regular and extensive exercise on the treadmill and cycle ergometer. This indicated a link between micro-gravity conditions and orthostatic compression of the bones. This is further verified by Sibonga et al. [9] in which 47 astronauts, including the aforementioned Mir cosmonauts, were tested for bone density using DEXA scans. The results are listed in Table 1.

Table 2: Bone Marrow Loss and Recovery of Astronauts post flight [9]

Skeletal site	Loss (L0) at landing %	50% recovery time (days)
Femoral neck	6.8 (5.7, 7.9)	211 (129, 346)
Trochanter	7.8 (6.8, 8.8)	255 (173, 377)
Pelvis	7.7 (6.5, 8.9)	97 (56, 168)
Lumbar Spine	4.9 (3.8, 6.0)	151 (72, 315)
Calcaneus	2.9 (2.0, 3.8)	163 (67, 395)

From this, it can be seen that bone density loss at the pelvis is significantly impacted by micro-gravity. This shows that the pelvis is the most dependent bone structure on orthostatic loading to maintain its bone density. However, this data also displays the rate of recovery of the pelvis to be the fastest followed by the lumbar spine. This is significant in the importance of upright standing in healthy bone density. To generalise, Sibonga et al. developed a relationship between the change in bone density after a flight and the change as a direct outcome of the flight as displayed in Equation 1:

$$L_t = L_0 exp(ln(0.5)t/HL) \tag{1}$$

It is therefore important to note the exponential recovery of bone density post flight as a means of providing astronauts with recuperation routines for spaceflight to external worlds.

2.2 Radiation

For humanity to venture beyond Earth, we must face new risks that come with exiting the Earth's magnetic field. Radiation begins to factor in significantly, which can affect the bodily functions of astronauts. This radiation is known as galactic cosmic radiation (GCR) which originates from heavy, high energy, deep space protons and lighter protons from solar particle events (SPE) [10]. Figures 1 summarise the radiation levels from GCR and SPE activity.

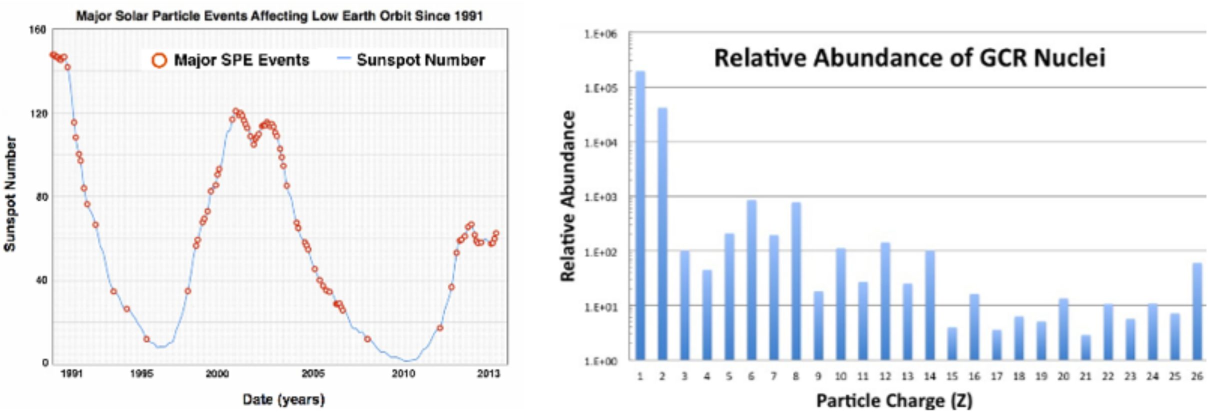


Figure 1: Solar Particle Events and Galactic Cosmic Radiation levels [10]

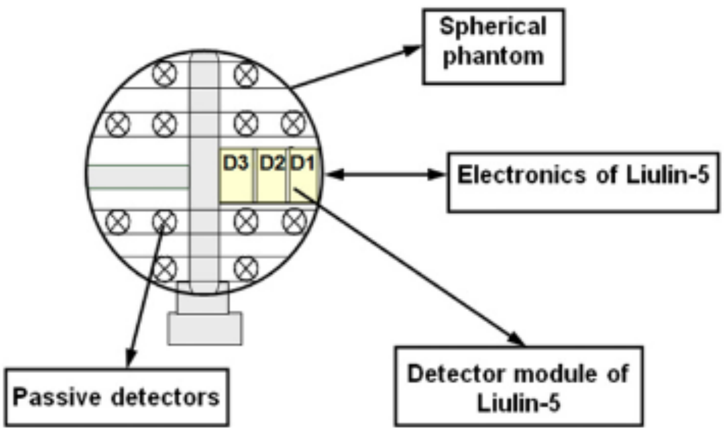


Figure 2: LIULIN-5 and spherical tissue phantom of the MATROSHKA-R experiment [2]

Chancellor et al. describes the ionisation power of GCRs and their dangers to the human body. Combined with the unpredictability of SPEs, radiation poses a great risk for future space exploration. The premise of radiation effects on the human body is supported by Semkova's et al. [2] in which a spherical tissue phantom (Figure 2) fitted with an array of radiation detectors was used as part of the MATROSHKA-R experiment to test the radiation dose on board the Russian part of the ISS. This experiment was conducted during the flight sequence of the station passing through the South-Atlantic Anomaly (SAA) which is a region of the Earth's Van-Allen radiation belt that exposes satellites to higher doses of radiation than usual. This itself provides a more accurate representation of radiation concentration outside of the Earth's magnetic field. The results from Liulin-5 showed an average dose of 190 μGY/day from a combination of 50-60% of SAA protons and 40-50% GCR at 40mm depth of the phantom. At this depth, energy can easily be absored by blood-producing organs which can cause internal damage and increase in cancer cell production which can cause dysfunction of healthy blood circulation. To put this in perspective, this daily dose is the same as that of an average nuclear power station worker's yearly dose of radiation. Additionally, Semkova et al. reported that, at the centre of the SAA, radiation levels reached 800 μGy/h. A day of exposure to said levels is the same as the annual exposure maximum limit of nuclear power station workers.

These results show the imminent radiological dangers of travelling outside of Earth's magnetosphere within missions such as the 2020 Mars expeditions. It also become difficult to shield astronauts from GCR without reducing costs to increase the thickness of the spacecraft shielding [11]. A 2008 paper by Tripathi et al. subsequently proposed a lightweight, low-power electrostatic shield to repel protons before thermal electrons can be attracted.

To put this shielding into effect, a set of charged spheres are to be oriented to direct charged particles away from the space craft. Figure 3 displays a possible orientation of these spheres. These provide a safe space within which the spacecraft can operate. The charged particles would be diverted away from the surrounding region. The simulation of the orientation with charged protons emitted during the time of least solar activity (Solar Minimum 1977) showed a significant decrease in charged particle penetration when compared to normal spacecraft material.

Figure 4 shows the penetration depth and the corresponding annual radiation dose where $\mathrm{g\,cm^{-2}}$ is the "thickness" that the material travels through. This shows significant drops in the exposure levels of astronauts to safer levels. The use of the 1977 Solar Minimum also allowed for the full spectrum of radioactive ions to be tested which factored in the penetrating power of different atomic masses in ranging from a proton of mass 1 to Nickel of mass 28 whilst taking into account 170 isotopes.

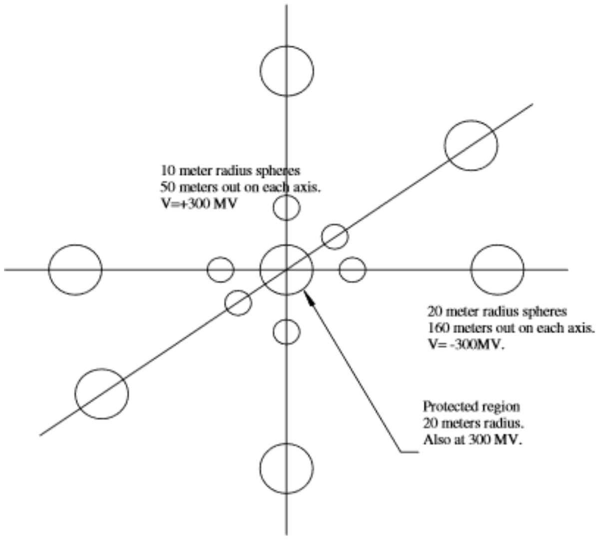


Figure 3: Position of electrostatic spheres around a spacecraft. [11]

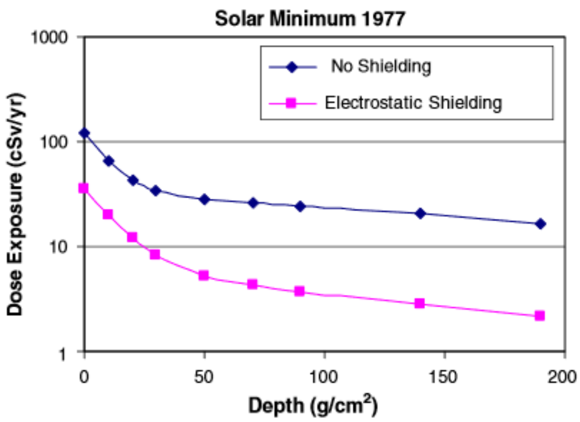


Figure 4: Simulation results of the electrostatic shielding effect. [11]

Another possible method to preventing this is polyethylene shielding as used within the ISS [12] or using lightweight carbon nanotubes [13]. These lightweight materials however do have their limitations within production, costs and implementation as polyethylene would make spacecraft that venture beyond LEO heavy and carbon nanotubes require massive costs for lining the walls of the space craft.

2.3 Nutrition

Smith and Zwart [14] emphasised the importance of providing adequate nutrition to astronauts in their 2008 paper due to factors that relate to maintaining energy and nutrient levels, and also to counteract effects of long-duration spaceflight such as bone density loss. The paper provides key insights into the regulatory levels of key body metrics collected from blood and urine samples of 15 crew members of ISS expeditions between 2000-2006. It was reported that the caloric intake of these crew members was $74 \pm 11\%$ of the WHO recommended value. Urine 8-hydroxy-2'-deoxyguanosin, a biological indicator for oxidation damage to DNA, had also increased by 27% with levels of bone density loss indicators such as excretion of pyridinium crosslinks increased by 72%. Additionally, Smith cites his earlier work [15] in which 14 US ISS crew members of a 2002 expedition had increased ferritin levels at 34% at 27% saturation. These statistics can be explained through the effect of exposure to microgravity and a stressful work environment that the crew members were exposed to. Regardless of the cause of these differences, a key takeaway from Smith and Zwart's paper is that spaceflight has a significant impact on the human body. These unbalanced levels, if applied to longer interplanetary spaceflight, would result in fatigue, aggravation, liver failure, tumor propagation, ageing, and weakened skeletal structure, all of which impact crew productivity, morale, and survival.

To support the importance of nutrition, the advanced Omics (the 5 main fields of study within biology) personalised medicine and treatment system was proposed as a means of delivering optimised nutritional and medical care [16]. Schmidt and Goodwin argue that within future spaceflight, personalised medicine and nutrition can circumvent issues that astronauts and possible space tourists may experience. For example, one-carbon metabolism (the transfer of one-carbon groups within metabolism of amino acids (leucine) and nucleotides (DNA)) requires donors from nutrients such as Folic acid and B12 which are obtained from the diet. One-carbon metabolism is regulated by the genetics of each individual as Schmidt and Goodwin cite Fredriksen et al. [3] whose paper describes a study of 10,610 people in which 86% of people had at least one mutation of the MTHFRC677T allele. This variance can impact ocular vision (as reported by 46% of ISS/Mir crew members), bone density, hypertension, and chromosome stability (impacted by GCR).

2.4 Mental Health

The conditions that astronauts and future space tourists will experiences can add increased psychological stresses and, at worst, severely indirectly impact physiological health. An investigation by Salamon et al. [17] outlined the psychological effects of living in isolated and confined environments (ICE) and the outcomes that transpire as a consequence. The deprivation of the person to new crowds, stimulus, combined with isolation and a lack of privacy can propagate into behaviours such as irritation, impulsiveness, depression, introversion and lack of motivation. As such, asthenia (physiological effects due to mental health) becomes more prevalent as crew members become tired and lack focus. This is also discussed by Tachibana et al. [18] by relating the state of ISS crew members to that of aeroplane pilots. It was stated that even during the short term pilots became increasingly irritated and anxious. Additionally, sea faring journeys are more closely related to interplanetary exploration due to long periods of isolation and remoteness. This means that sea based analogues can be used to further study the effects of remoteness and monotonous routines.

New emerging technologies can help astronauts that undertake long duration flights and interplanetary travel cope with their predicaments by providing an escape from the monotonous and routine life of conducting experiments or other work. One such technology is Virtual Reality (VR) which has recently seen a surge in popularity with the Oculus Rift and smartphone extensions. These can be used alongside a NASA funded virtual ecosystem called ANSIBLE [19] for providing social interactions between humans or with virtual characters. This system was tested using two questions from a Circle of Closeness Survey (-5 to 5 scale) conducted on a control group and an ANSIBLE group over a period of 150 days. Comparing the ANSIBLE group and the test group, an increase closeness between crew members and their family/friends (M = 1.5, M = -0.5) and an increase in satisfaction with their family/friends (M = 3.1, M = -1.3) was reported. However, it was noted that there was no difference between the ANSIBLE and control groups when asked about their closeness to crew members despite the fact that crew members can connect to the system simultaneously.

Figure 5: Simulated environment of crew member's family during festive dinners on long-duration missions. [19]

3 Diagnosis

It is becoming ever more important to know what is actually happening to humans during this transition period as a society. On-Earth examples such as South-Pole expeditions, analogues like HI-SEAS and confined spaces like submarines have become great learning tools which possess non-expert personnel operating medical devices [20]. This is where extensive diagnostics is required to collect the necessary data for monitoring the health and vital systems of astronauts both aboard spacecrafts and external planets.

3.1 Ultrasound

Ultrasound has already been used aboard the ISS for spinal column scans due to reports of back pain within the first few days of NASA missions. [21]. An experiment was conducted on two male astronauts using a portable GE Vivid q ultrasound system which displayed data on the system screen and sent data to ground-based experts with a 1.6s delay. Astronauts had a total of 2 hours of training to familiarise and earn hands-on experience with the device. The results are shown in Figure 6 with emphasis on the identified spinal vertebrae. Although this provides high quality imagery, the experiment did not prove microgravity effects on the spinal column due to the small sample size and no indication of increase in vertebrae spacing.

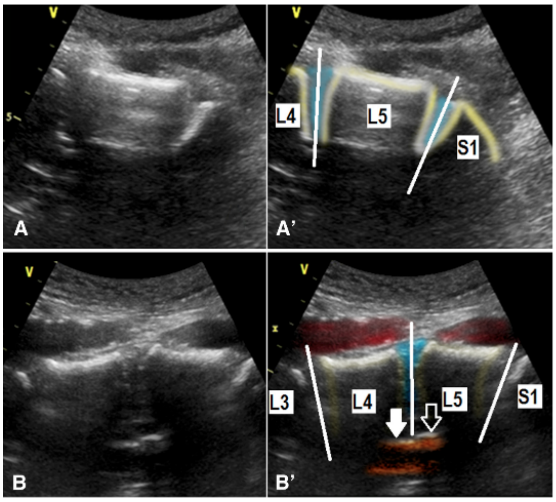


Figure 6: Longitudinal ultrasound scans of the spinal column showing clear, high quality results. [21]

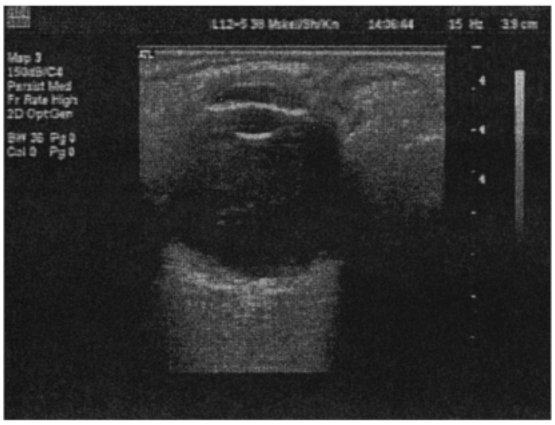


Figure 7: Ocular ultrasound scans showing clear, high quality imagery. [21]

Similarly in 2005, ultrasound was used to retrieve ocular imagery on board the ISS by a non-expert operator with data also being sent back to the Mission Control Centre where an expert was on standby [21]. The results are displayed in Figure 7 and show the clear imagery produced by the ultrasound devices from which trauma can be assessed. These are concrete examples of how ultrasound can be used as a portable and effective imaging tool for injury and trauma evaluation beyond LEO where instant, real-time access to experts is not guaranteed.

3.2 Personalised Care

With increasing distances comes greater autonomy. As astronauts venture farther into the unknown, self-sustainability will become ever more important. Access to professionals and direct care will become increasingly difficult with every second that passes. Thus, personalised health monitoring devices will enable this autonomy and allow astronauts to act accordingly and, if necessary, immediately. As such, projects such as the Prognostic and Health Management for astronauts have developed systems which aim to integrate autonomous health decision technology and biomedical informatics [4]. This shows a shift in paradigms of astronauts from reliance on experts to self-diagnosis and hence this system will combination of different wireless technologies and self-reporting to suit astronaut needs and predict/diagnose problems. One such technology is the electrocardiogram (ECG) wireless sensor as seen in Figure 8.

Figure 8: ECG wireless monitoring device[4]

Additionally, individual's electronic health records will be completely private allowing astronauts to have control of what they share. These records include caloric intake, sleep patterns and logs, cognitive performance, visual and aural metrics, muscle strength and bone density. Other systems also aim to combine real-time on-board diagnosis and delayed mission control analysis as described by Eklund et al. [22] for use in planetary expeditions.

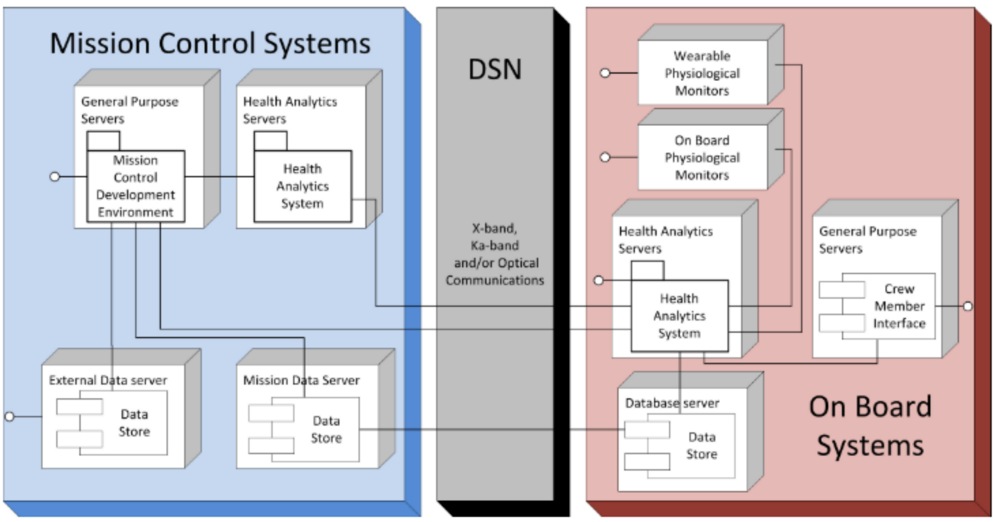


Figure 9: Data transfer of the real-time health system. [22]

The Health Analytics System would provide astronauts with risk assessments with regards to the physiological data acquired by the sensors on the astronaut. The spacecraft would also simultaneously send and receive data from mission control which would allow experts to more accurately draft up plans of action. This can be beneficial for combating emergencies on expeditions to Mars which possess a 44 minute time delay. However, Eklund et al. also state that with large distances comes large decay in signal strength. For example, Mars missions would receive a signal of that is 1 million times weaker than communications to the Moon since the signal strength is proportional to the square of the distance. This implies that expert feedback will not always be available hence this real-time feedback system would aid astronauts in the absence of experts.
These systems can cover a range of well-known health issues that can be resolved using known techniques. However, one must not forget the dangers of travelling outside of the Earth's magnetic field; hence, it is important to measure the personal radiation levels that each astronaut is exposed to. High LET is one such source of risk from radiation as the formation of Hydrogen Peroxide within the human body can damage organic tissue. This can therefore cause complications and cancerous cells to form. Apathy et al. [23] subsequently describe three possible approaches on measuring radiation doses:

- Numerical dose estimation using data from active sensors such as Geiger-Muller counters and Tissue Equivalent Proportional Counters (TEPC)
- Personal small active devices such as ionisation chambers that require power.
- Personal small passive detectors such as thermoluminescent detectors (TLD).

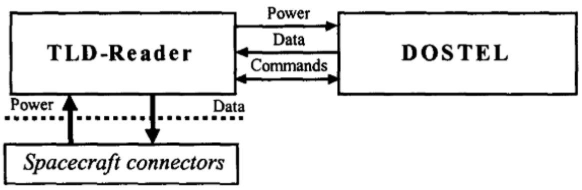


Figure 10: TLD and DOSTEL dosimetry with on-board computer calibration and data display [23]

The most accurate measurements out of these methods is TEPS. However, it is well known that passive detectors are much more beneficial due to their ability to passively measure dose data hence their applications within nuclear power stations. Currently, such detectors are already incorporated on board the ISS. Apathy et al. subsequently propose combining TLDs with DOSTEL (an LET spectrometer) which allows data from TLDs to be processed an output to an on-board computer. This combination can achieve a range of 3 µGy to 10 Gy which allows for personal dosimetry to accurately be conducted. However, such devices have been proven to be obsolete and cumbersome to retrieve readout data with new technology arising that can measure real-time data on a particle-by-particle basis [5]. This technology uses semiconductor radiation imaging pixel detector compactly combined with a Timepix chip that measures the semiconductor electrical activity and counts particle hits. This is described in Figure 11.

Charged particles collide with the semiconductor which causes electrons to be dismembered from their orbitals which cause a current to flow across the p-n type terminals. Bias current is then induced through the solder bump which is then detected on the pixel readout. Essentially, this device acts as a "camera" for radiation but is generally known as a Radiation Environment Monitor (REM).

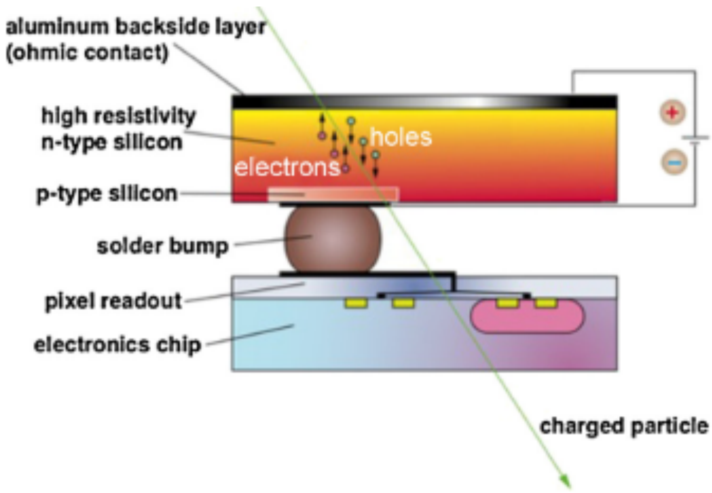


Figure 11: Timepix-semiconductor assembly. [5]

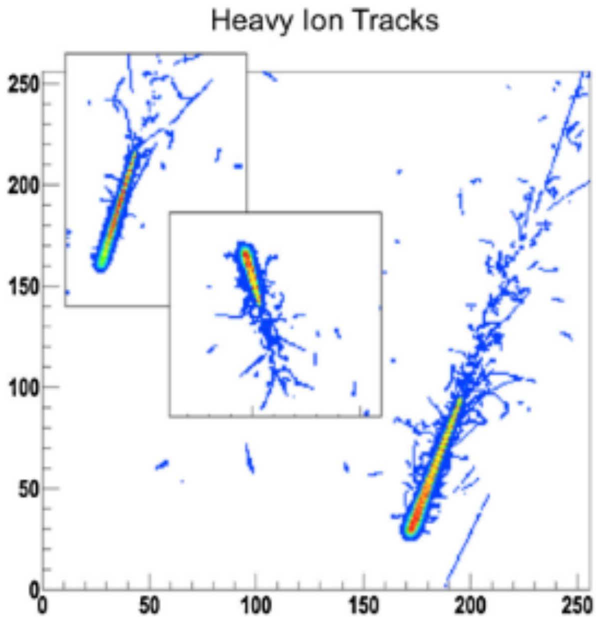


Figure 12: Ionisation Trails on the REM onboard the ISS. [5]

Figure 12 displays the "snapshot" of the REM. The values at each pixel can then be summed over using Equation 2:

$$D_{t,Si} = \frac{1}{m_{sensor}} \cdot \sum_{p_i} E_{p_i} \tag{2}$$

where D represents the overall dose for a time t in Silicon, m is the sensor mass and E is the energy absorbed by a pixel i. The rate can the be calculated by dividing the accumulated dosage by the time at which the recordings were taken. Additionally, the effectiveness of REM was compared to that of TEPC acquisition as seen in Figure 13. As such, there is conclusive evi-

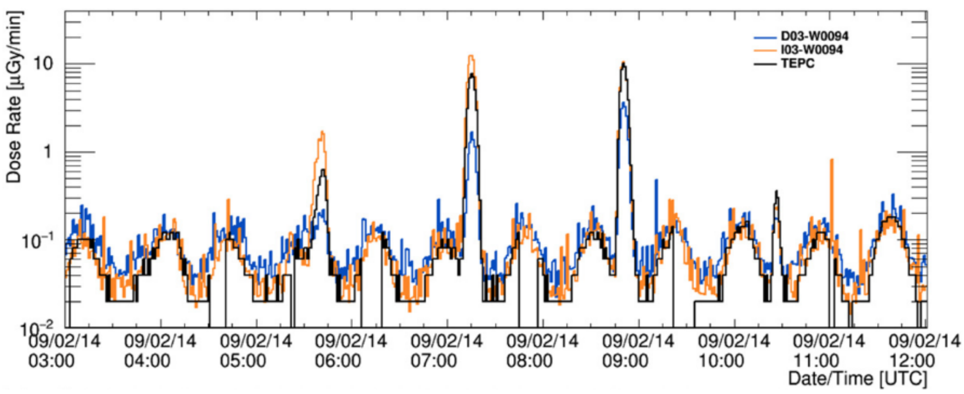


Figure 13: Timepix-semiconductor assembly. [5]

dence to suggest that REM can be used for personal dosimetry of astronauts due to device compactness, weight, and real-data acquisition which can be easily linked up with pre-existing technologies such as smartphones and tablets to present the data.

3.3 Bio- and biomedical sensors

Recent evidence suggests that biological matter can be used indicate symptoms of medical health issues [24]. Additionally, the systems for personal data acquisition and display would allow astronauts beyond Earth to monitor and maintain their health during long-distance journeys. Henceforth, the use of biosensors can prove to be an enticing opportunity to develop a multipurpose analytical device that can take various organic samples and extract multiple metrics out of the sample. Types of independent biosensors which conduct specific tasks are: lateral flow assays, biochemical, electrochemical, microfluidic, arrays, and nucleotide. Due to scope of this review, focus will be placed on a select few sensors that have explicitly been designed for durability and extreme environment purposes. To further understand some of the intrinsic characteristics of how they work, it is important to note the challenges that these sensors need to overcome due to the new environment. Such is caused by microgravity via effects such as bubble formation, convective heat transfer and fluid flow. Additionally, biosensors must be durable, lightweight, reusable, adaptable and stable in order to perform within long-duration spaceflight.

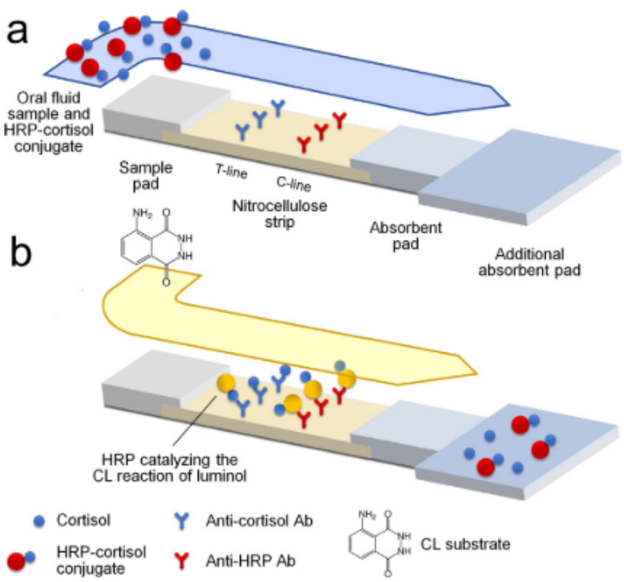


Figure 14: CL array for use in analysing oral-fluid samples with the CL substrate. [25]

The chemiluminescence-based biosensor of Zangheri et al. [25] provides a solution to some of these challenges. Using the effect of capillary flow (the independent flow of fluids within narrow spaces) in a process known as Lateral Flow ImmunoAssay (LFIA) (ImmunoAssay is the decomposition of a complex form into its base constituents). Within the context of cortisol analysis of astronauts, saliva samples were used to test the operation and capillary flow of the device. Cortisol was chosen due to its multipurpose used around the body from regulating blood pressure to controlling stress. The sample is loaded with a cortisol-HRP conjugate and passed on top of two anti-cortisol and anti-HRP biochemicals. The addition of the HRP CL substrate starts the reaction which a CL reader using a charge-coupled-device (CCD) can receive the chemiluminescence and convert electrical signal to digital data. This allowed direct non-invasive measurement cortisol levels due to the proportional relationship to luminescence. As such, this LFIA approach is adaptable for other biomarkers as it counteracts microgravitational effects.

The biosensing system described above holds promise for obtaining accurate information for specific chemicals. However, these have their limitations in the amount of biochemicals that can be stored and used. Hence, it is possible that these biochemicals can run out in space. As such, a prospective approach would be to use spore-based biosensors that can withstand extreme conditions such as Mars and can simultaneously measure multiple metrics. Sangal et al. [26] subsequently describe the use of the Bacillus Subtillis bacterial strain for measuring the levels of arsenite, arsenate, and antimonite, chemicals which are poisonous to humans and can be found in the solar system. The strain was initially tested for control and then stored in microcentrifuge tubes for 12 months under 4 types of harsh environments; wet heat, dry heat, cold, and desiccation. The strain was then sampled every month to observe the effects on such environments and gather data on the change in the detection limit. During sampling, the strain is left to geminate into vegetative cells. This allows for the strain to react with a specific chemical called 6-O-β-galactopyranosyl-luciferin substrate which develops a proportional luminescent effect.

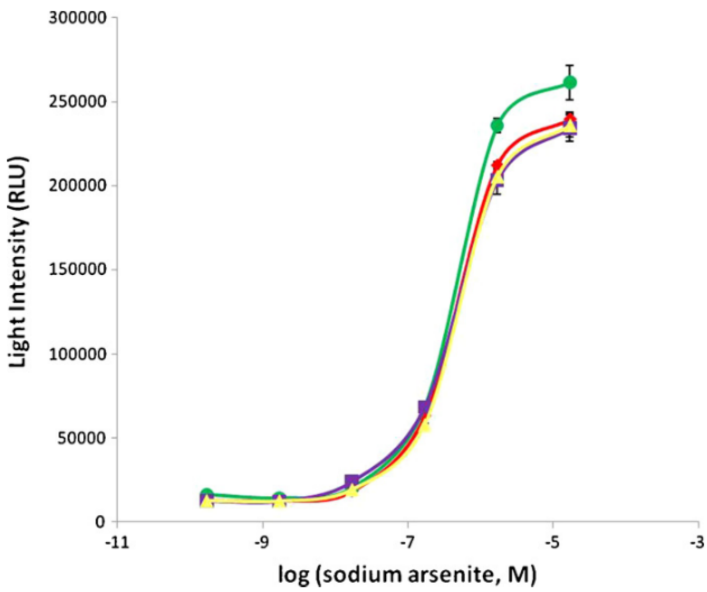


Figure 15: Response of B. Subtilis spores under harsh environments. Green is dry heat, red is cold, yellow iswet heat, and purple is dessication. [26]

At the end of the 12 months, the final sample was taken and the final luminescence data was recorded with different concentrations of arsenite. This is displayed in Figure 15. This clearly shows the level of survivability of the spores within harsh environments that can be found outside of earth; therefore, the spore-based biosensors can be used for more indirect methods of measuring astronaut health during missions on planets such as Mars.

That being said, Sangal's et al. work has greater implications than arsenic sensing. Various spore strains can potentially be used as long lasting sources of testing astronaut health due to their storage capabilities and survival under different conditions if humans are to step foot on new terrain. Indeed, the capabilities of biosensing cannot be understated but further research must be undertaken to ensure easy use and comprehensible data presentation.

4 Remedies and Drugs

Up to now, this review has discussed the issues and concerns that are facing astronauts and the methods by which astronaut health can be monitored, not only in LEO but on long-duration space travel. However, it has not mentioned any possible solutions to the ailments. This section will discuss non-operative treatment of astronauts without direct contact to expert, from pharmaceutical storage and stability, to sleep medication [27] and manufacturing [6, 28].

4.1 Storage and Stability

One key issue that looms over using medicines in space is the potential of expiry and instability. The new conditions such as microgravity were tested by two papers that flew medicines for periods of up to 28-months [6] and 550 days [29] on board the ISS. During the former, Du et al. focused on assessing the change of environment on pharmaceuticals. 4 medicine kits containing solid, semi-solid and liquid drugs were sent up to the ISS with a kit returning within 13, 350, 595, and 879 days whilst 4 identical kits were stored within NASA's laboratory on the ground. 4 analyses were conducted immediately upon the kits return with their ground counterparts to avoid variability. Variables tested were: physical properties such as odour, chemical composition using ultra performance liquid chromatography (UPLC), and dissolution tests according to USP standards. Figure 16 represents only some of the results of the medicines that were tested throughout the 4 trips.

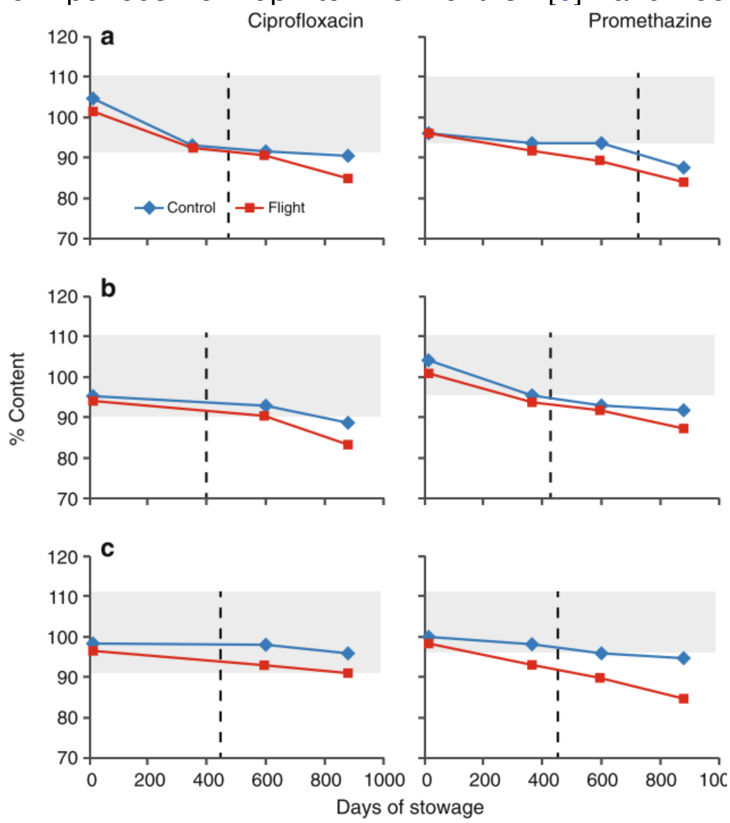


Figure 16: Ciprofloxacin and Promethazine % content of active ingredient in solid, semi-solid and liquid form. Shaded area is the USP active claim, dashed line is expiration date[6]

Note the general decrease in potency of each from. Generally, there is a steeper decline in the solid form. The reasons behind the faster rate of degradation can be down to altered temperature, humidity, microgravity and radiation. It is suggested that radiation is the most likely culprit for these trends as it was recorded that the average radiation dose at the end of the experiment was 20 times that of the control kits.

The later 550 day study, albeit less extensive, which cites Du et al. has supported another observation that the pharmaceuticals taken on board the ISS had met USP regulations well after their expiry date. The testing timeline is shown in Figure 17 [29].

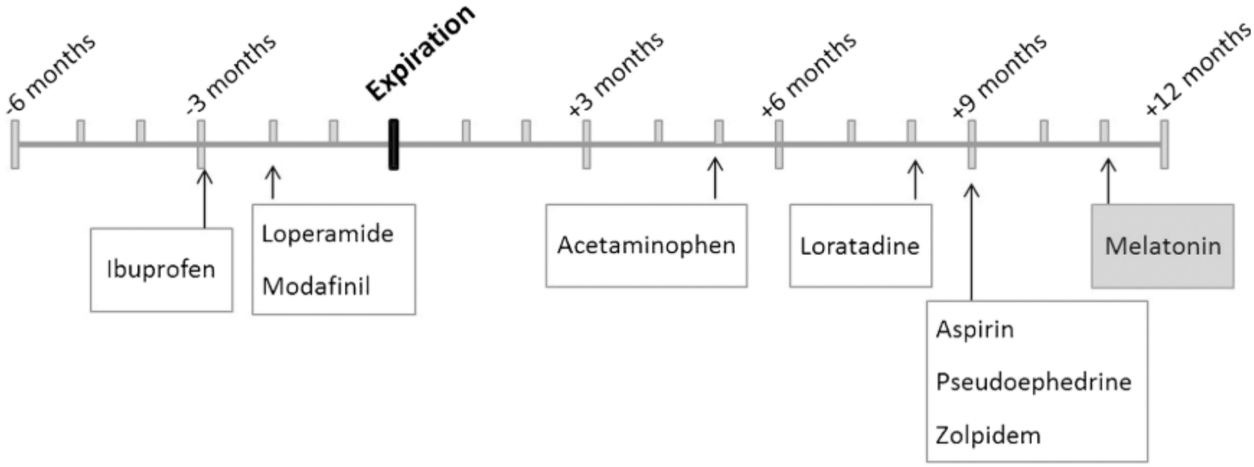


Figure 17: Testing timeline of USP standards of pharmaceuticals flown on the ISS. [29]

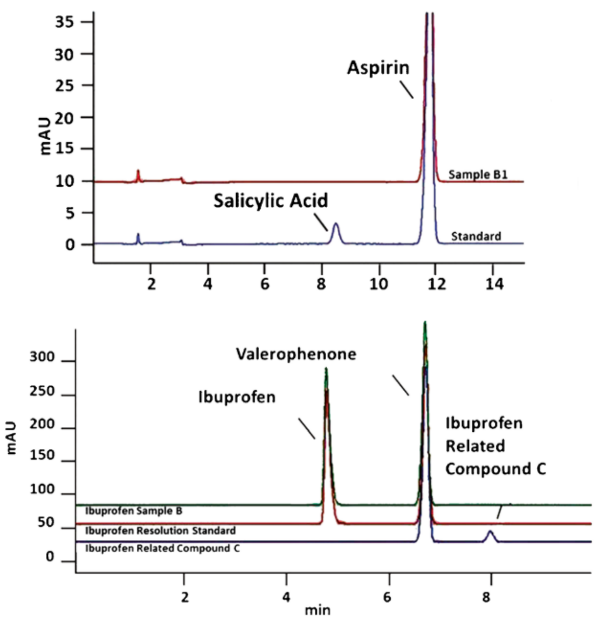


Figure 18: Chromatograms of Aspirin and Ibuprofen with commercial standards. [29]

The testing was achieve using USP monograph High Performance Liquid Chromatography (HPLC). 3 pharmaceuticals were measured with a standard HT HPLC whilst the rest were done using a UV DAD (which is a diode based ultraviolet HPLC method). These measured the absorption spectrum of the pharmaceuticals as exampled by Figure 18. The absorption peaks correlate to the amount of the active compound present in the drug. The graphs on the left display a 96.5% purity of aspirin when compared to a commercial standard with a know contaminant (salicylic acid). Additionally, ibuprofen was found to be 99.9% pure. The two purities are well within the recommended USP purity of 90%.

These results show is that, upon further testing, new expiration dates can be set for medicines flown outside of Earth. This study, however, does not take into account the levels of radiation nor studies the effects of microgravity in space. Rather, it asserts that medicines can still be used aboard spacecraft regardless of expiration dates. On the other hand, these studies shed light on the degradation and deterioration of the active pharmaceutical ingredient (API) within space. Both papers suggest that further controlled studies be undertaken.

4.2 Sleep

The new environment that astronauts experience in space can cause a mismatch of the circadian rhythm and the internal body clock due to the effects of altered exposure times to sunlight and the effect of microgravity on the sleeping pose of astronauts. There have been multiple reports that astronauts experience problems sleeping aboard the ISS dating back to the first Skylab missions in the '70s [30]. As of the past several years, it was found that one of the main pharmaceuticals used aboard the ISS were sleep aids with 71% of 24 crew members over the past 20 years reporting their use. A further 26% of these crew members used sleep aids repeatedly with an average of 2.568 doses taken on the ISS over an average journey length of 160 days [31]. Additionally, data was collected across 80 space shuttle missions and 13 ISS missions using actigraphy monitoring and daily logging of astronauts for sleep duration and patterns [32]. It was found that, generally, Space Shuttle astronauts had an average of 6.32 hours reported and 5.96 hours actigraphy measured sleep whilst ISS astronauts had 6.54 hours reported and 6.09 hours actigraphy measured sleep. 78% of the Space Shuttle astronauts had also reported using sleep aids during the flight. The proportion of nights with less than 6 hours of sleep is displayed in Figure 19. As Space Shuttle missions tend to be shorter than the ISS counterparts the sleep received tends to be less due to higher stress and workload during these missions. An interesting fact to note here is that lack of sleep tends to increase 11 days before space travel. Such sleeplessness cascades down into the mission and hence damage productivity. Barger et al. also reports that astronauts began to make mistakes during extra-vehicular activity (EVA) and some had fallen asleep in front of the keyboard. Levels of anxiety hence caused astronauts on the Space Shuttle to use sleep aids during 500/963 nights. This being said, it is logical to conclude that sleep medication is a useful and demanded crutch by astronauts

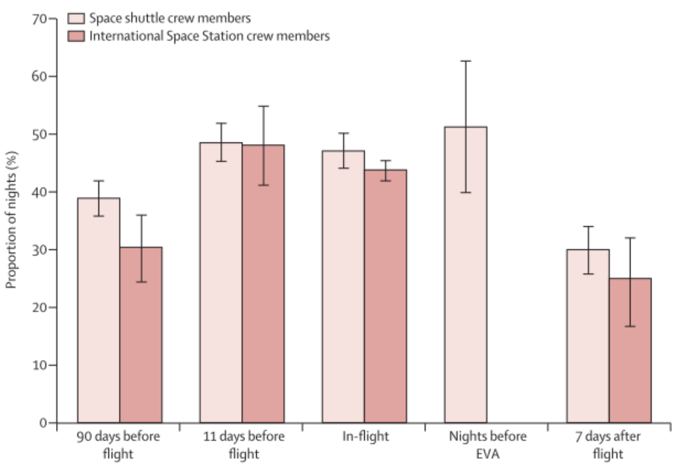


Figure 19: Proportion of actigraphy measured sleep that was less than 6 hours aboard both the ISS and Space Shuttle. [32]

to cope with new environments. Sleep aids must henceforth be regulated and controlled whilst giving astronauts the proper allocated time to sleep. However, the lack of sleep is not only caused by psychological reasons but also due to weightlessness. Gonfalone et al. [33] argue that, as all living beings have various senses around the body to detect the presence of gravity, we have an innate fear of falling. It is argued that rapid eye movement (REM) sleep cannot be achieved if the body cannot verify being grounded. Gonfalone et al. do, however, recognise that astronauts have reported quick adaptation to zero-g environments and that sleep medication would not aid in the case of weightlessness. It is also mentioned that there is no measurable way to test this phenomenon. As such, these studies generally show a lack of sleep and the need for remedying astronauts sleeplessness. Sleep aids must therefore be fine tuned for astronauts and given further attention.

4.3 Additive Manufacturing

With an increase in popularity of 3D printing in the past decade, specific applications have become more and more prevalent. Additionally, the need for precise medical care and personal health care systems would require specific drug dosages for a range of metabolisers. This is where additive manufacturing (3D printing) of pharmaceuticals has been suggested to provide precise dosages by point-of-care delivery [7, 34]. The implementation of this technology can also pave the way for faster patient recovery whilst reducing drug side-effects as is prevalent in standardised medication. As promising as this sounds, there are a few features outlined by Trenfield et al. which a pharmaceutical 3D printer must meet. These are cost, safety, versatility, efficiency, user friendliness, and stability. As of recent, the ideal printer has not been developed. However, there are feasible candidates under development.

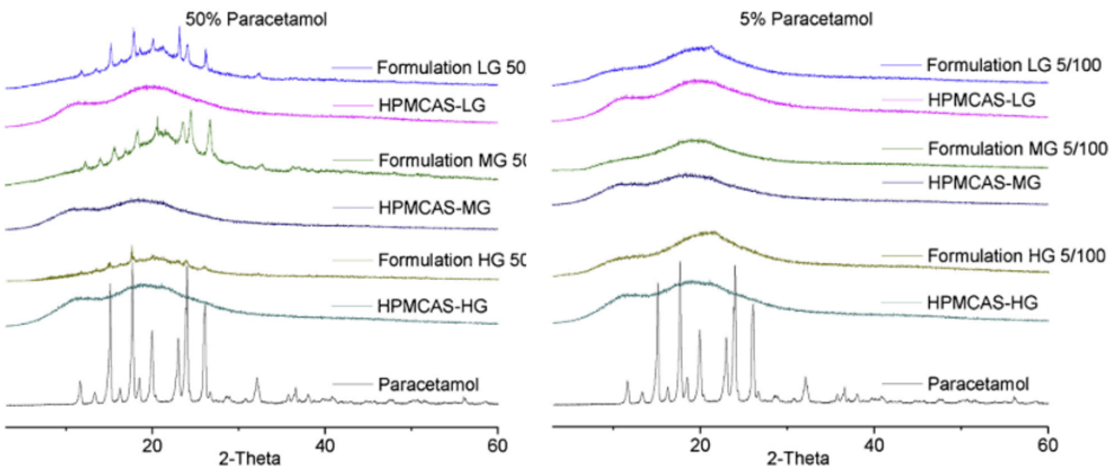


Figure 20: HPLC results for the composition of the tested paracetamol printlet. [28]

Goyanes et al. [28] describe a popular fused deposition modelling (FDM) 3D printing technique using polymer filaments that are pre-packed with drugs. The experiment conducted in this paper used 5 and 50% paracetamol (API), 3 types of hydroxypropylmethylcellulose acetate succinate grains (infill/excipient), methylparaben (plasticiser) and magnesium stearate (lubricant). The ingredients were mixed in a pestle and mortar and hot rolled using hot melt extrusion to create the filament. HPLC analysis was then conducted on the printlets (Figure 20) whilst measuring dissolution within a simulated small intestine (3.5 hours aat 5.6-7.4 pH) and colon (6.5 pH). It was found that the mixtures all complied to the USP recommended delayed release maximum of 10% in the small intestine for the first 2 hours. Lower grade (and hence low pH barrier) polymer grades released the fastest with 50% paracetamol content and 20% infill. This showed that drug release can be controlled by changing the proportions of the composition of the API and infill in 3D printing whilst maintaining weight and stability throughout the heating and drawing processes.

Additive manufacturing was further extended by creating tablets with multiple APIs and release profiles. Khaled et al. [35] proposed a multi-layer tablet with drug compartments (Figure 21). Similarly to Goyanes et al., attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) and X-ray powder diffraction (XRPD) tests were conducted to evaluate the degradation (by interaction of the excipient and the API) and it was found that there was little change during manufacturing.

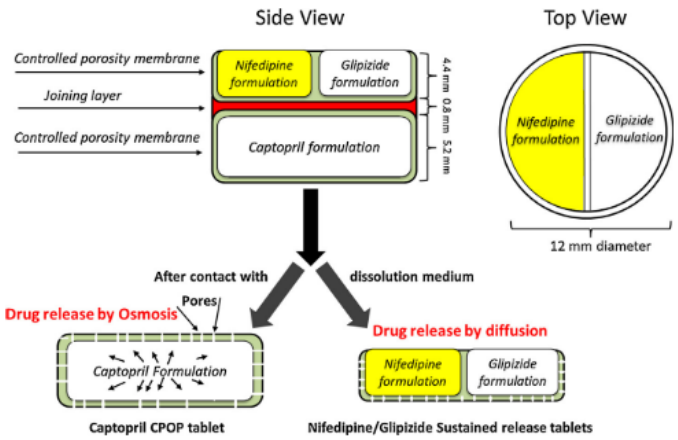


Figure 21: Schematic diagram of multiple API and varied drug release tablet [35]

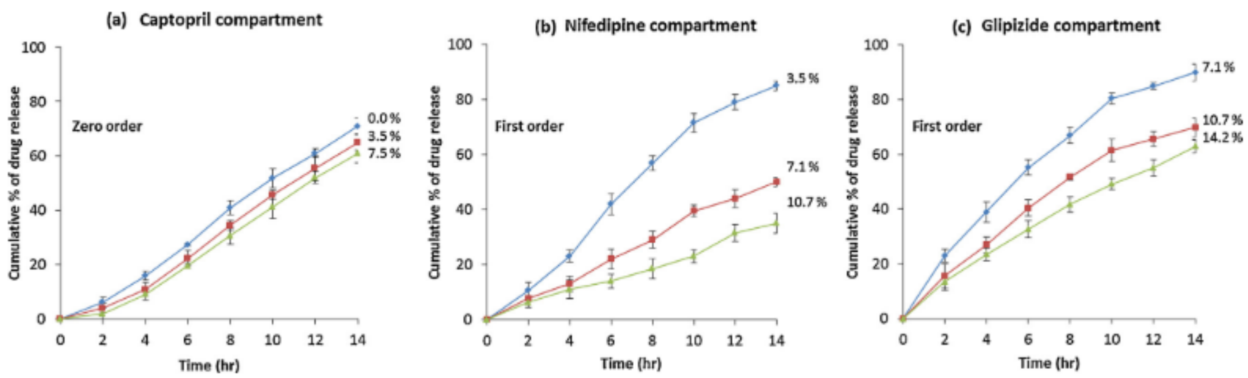


Figure 22: Dissolution results of the 3 APIs of the tablet. [35]

The results in both papers support additive manufacturing as a viable means of delivering and releasing drugs for personalised application. The prospects of applying such technologies in outer space can lead to more efficient use of resources whilst bypassing expiration dates due to additional supplementation of degraded (or irradiated) APIs with more APIs.

5 Telemedicine

Having presented the solutions for resolving mostly non-imminent and biological concerns, it is now important to focus on physical dangers such as trauma and injury. Subsequently, the importance and difficulty of conducting surgery in space cannot be overlooked. As such, we will now discuss surgery and the problems that future astronauts will face when confronted with critical injury as encompassed by the concept of telemedicine. It is now important to lay down the various subsets of telemedicine in regards to distance as described by Haidegger et al. [8] starting with telesurgery (near Earth), telementoring (middle range), and consultancy telemedicine (long distance).

5.1 Telesurgery

Figure 23: Robotic Assisted Microsurgery (RAMS) developed by NASA. [36]

The basic idea of telesurgery is that expert surgeons can conduct complicated surgery at a distance without the presence of a trained expert at the surgery location. The basis of this is using master-slave robotic systems with manipulators at the surgery location and a controller for the surgeon. A prominent example of this is Da Vinci surgical robot currently in use at hospitals around the world [37]. A more suitable example of robotic surgery would be the M7 surgical robot developed by SRI International due to the lightweight, compact design that allows easy portability [8]. Additionally, NASA has already developed a surgical robot back in 1997 [36] with the purpose of conducting small scale surgery which has also been implemented in operations on Earth. This however does have limitations in the scope of the surgery it can conduct and is only limited to on-board control. New methods have been studied over the past two decades to implement teleoperational control within surgery. A recent paper by Aldana et al. [38] proposes a control scheme incorporating time-delay and absence of velocity measurements in master-slave robotics. It serves as a combination of previous work done on eliminating the need for velocity measurements due to the noise created by velocity sensors whilst taking into account lag time which will be experience between spacecraft and the Earth. Using a 3-DoF OMNI master and a 7-DoF LWR slave, the kinematics used in the paper are based on torques for the master and slave robots as shown in Equations 2 and 3:

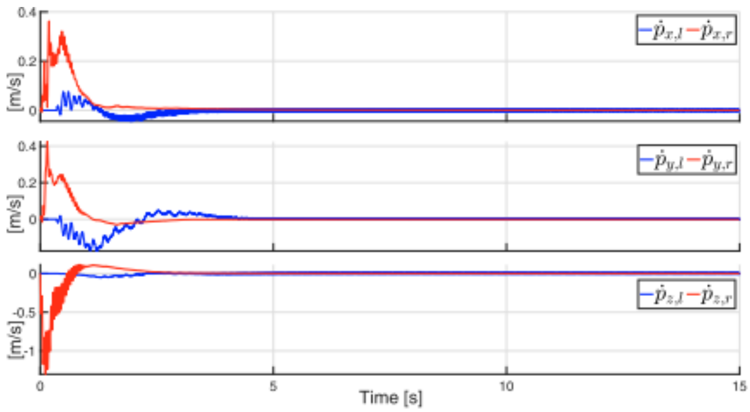
$$M_m(q_m)\ddot{q}_m + C_m(q_m, \dot{q}_m)\dot{q}_m + g_m(q_m) = \tau_h - \tau_m \tag{3}$$

$$M_s(q_s)\ddot{q}_s + C_s(q_s, \dot{q}_s)\dot{q}_s + g_s(q_s) = \tau_s - \tau_e \tag{4}$$

Where M is the symmetric positive definite inertia matrix, C is the Coriolis effect matrix, g is the gravitational torques matrix (not applicable in space for the slave), τ is the toque matrix generated by the master (m) and slave (s) and the induced torque matrix of the human (h) and environment (e) with q representing the joint position matrix and the respective velocity and acceleration. The paper then postulates the problem in which time delay is a time function with an upper limit and requires that (1) the velocities and pose errors are bounded functions in the L_∞ space (generally means that they are measurable functions) and that (2) the velocities and pose error tend to 0 with no human and environmental forces. It then suggests the following dynamic controllers in Equations 4 and 5:

$$\tau_m = -g_m(q_m) + k_m J_m^T(q_m)\Phi^T(\xi_m)(x_m - y_m) \tag{5}$$

$$\tau_s = g_s(q_s) - k_s J_s^T(q_s)\Phi^T(\xi_s)(x_s - y_s) \tag{6}$$



(a) Linear velocities

Figure 24: Linear velocities of the master (red) and slave (blue) [38]

Where τ, g and q were previously described, k is a real constant, J is the geometric Jacobian matrix of the position matrix, Φ is the matrix of diagonal unit-quaternion vectors, ξ, (a 4 dimensional complex space), x is the linear and angular end-effector position and y is the vector of linear and angular controller positions. Implementing the dynamic controllers to the kinematic problem solved the constraints provided by the time delay and the lack of velocity measurements. Simulation results are yielded in Figure 24.
Alternatively, due to the rise popularity of laparoscopic minimally invasive surgery, increasing considerations and research into applications in space have been brought up. Laparoscopic surgery utilises needles inserted into the body to avoid specific critical regions of the body [39]. Similarly to Aldana et al., more simplified dynamic kinematic modelling was used by Dehghan et al. which allowed the control of a 1-DoF master for the linear insertion of a robotic slave needle. This was used to counteract the forces upon piercing and inserting the needle. A closed loop control system was then incorporated which mainly focused on

stability specifically within soft tissue environments to improve fidelity. Taking into account environmental uncertainty, the closed loop control system is represented in Figure 25.

The results from this paper are similar to that found by Aldana et al. (Figure 24) as there was very close similarity in the velocity and force experienced between the needle and motor controller. As such, one can conclude that there is ample opportunity for teleoperated surgery to be conducted in space. However, the two papers presented by Dehghan et al. and Aldana et al. have not incorporated fixed time delays within their work. Such telesurgery can also be incorporated with the previously discussed ultrasound techniques with the additional benefit of the surgeon operating a motorised probe using similar master-slave systems, albeit with much simpler control methods as described by Arbeille et al. [40].

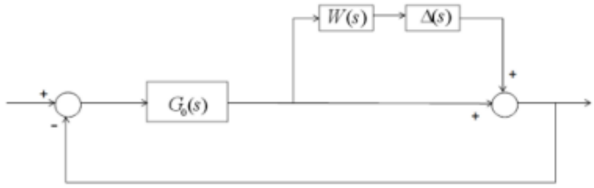


Figure 25: Closed loop control with uncertainty of the robust fidelity and stability system [39]

5.2 Telementoring and Consultancy Telemedicine

Venturing outwards from Earth, time delay becomes a growing issue in real time surgery which makes constant feedback to the surgeon near impossible. A study done by Perez et al. [41] showed that a majority of surgeons cannot conduct surgery normally with more than 350ms delay. The study focused on 15 surgeons trained in laparoscopic surgery conducting 4 different tasks consisting of putting a nuts on bolts, passing a needle through holes, dissecting and closing blood phantoms, and tying a knot. They used 4 different laparoscopic instruments with delays of 150, 200, 250, 300, and 350ms. It was found that 79% and 21% of surgeons could and could not perform procedures respectively at 150ms and 38% and 62% of surgeons could and could not at 350ms. It is interesting to note that surgeons generally ranked the knot as the least possible procedure for all delays and that the procedure possibility had the steepest decline with increasing time delay given that it was the most possible procedure at 150ms. This subsequently shows that even minute delays such as 350ms make it increasingly difficult to perform delicate surgery. Another previous study supports the difficulty of performing time-delayed surgery as conducted by Fabrizio et al. [42]. Within the first phase of a 2-phase trial, a variable time delay of 0-1000ms was implemented within a total of 185 trials using 6 participants that performed 3 precise tasks as part of a game. It was found that there was a linear proportional relationship between errors and the time delay (range of 0.4 to 1.44 errors). In the second phase, a doctor performed tasks in Singapore whilst being based in Baltimore. A learning curve was found for the time taken to complete the tasks of the same game and the repetition of the tasks. However, more errors arose in trials 4 and 5 due to fatigue. This showed that as distance and time delay increased, more errors arose when conducting surgery which cannot happen aboard a spacecraft.

To overcome the need to do surgery from Earth, on-board operations would be conducted by specialised crew members with the help of expert surgeons consulting the procedure and guiding the crew member. It has been shown that in a study done by Moore et al [43] that 22/23 telementored laparoscopic surgeries succeeded with normal recovery of the patient. The experiment set out to prove that telementored surgery can be done by having an expert in laparoscopic surgery be separated by more than 330 metres from a non-expert surgeon. The expert had a movable camera and a speaker to aid the non-expert. The surgeries that took place ranged from more basic procedures such as pelvic lymphadenectomy (n = 5) and renal biopsy (n = 1) to more advanced procedures such as nepherctomy (n = 5) and bladder neck suspension (n = 3). These results suggest that on-board surgery can easily and safely be conducted without the need for an expert to be physically present. However, this experiment did not take into account time delays that would be experienced in space. Subsequently, telementoring applications have already been researched here on Earth within extreme and harsh environments [44]. It was reported that firefighters based in Edmonton were telementored by experts in 4 cities in Canada and America in operating an ultrasound machine (known as knobology) on a simulator of non-compressible torso haemorrhage (NCTH). It was found that the firefighters were 97% accurate despite never operating an ultrasound machine. Additionally, medical military technicians (MedTechs) were placed to perform laparotomy with and without telementoring. The laparotomy was split into 6 phases with a 60s timeframe of procedure for specific tasks to be performed on a Cut Suit. It was found that all of the MedTechs successfully finished the haemorrhage control phases but only 19% succeeded in closing the incision. Overall, telementoring mainly decreased stress levels and hence MedTechs remained calm during the surgery. To conclude, telementoring serves as a viable approach around time lag within mid-range space travel.

Going even deeper out into space, communication becomes increasingly difficult as packets of information can only be received at once due to the large time delays and the degradation of signal strength. At this stage, astronaut training would be a more realistic approach to deal with immediate trauma. The use of Virtual reality or Augmented Reality (VR and AR) has been suggested back in 1997 as an educational means that saves on time and cost [45]. VR can also act as a means of surgeons preparing surgical procedures such as orthopaedic surgery to be uploaded to the spacecraft given patient information [46]. This means that signal strength must be maintained to have fast data uplink which can be achieved using new optical communication methods like error-corrected pulse-position modulation [47].

6 Discussion

In consideration to the health status of astronauts in space, major microgravity effects such as bone density loss would be counteracted by simulating the effect of standing. This would reinforce major bones such as the pelvis in preparation for reentry. Furthermore, the critical risks of radiation add concerns of shielding and the costs incurred to protect the spacecraft [11, 13]. There is ample evidence to support dangerously high radiation dosages within zones such as the SSA hence the need for protection like electrostatic shielding. This must also be in tandem to maintaining astronaut nutrition as the increased levels of ferritin and oxidation damage in space would lead to a plethora of issues to mental and physical health. This can be achieved using the aforementioned advanced Omics system for evaluating personal requirements [16]. Additionally, VR could serve as a good near-realistic approach to keeping crew morale high. However, Salamon et al. [17] recognise that there is currently little research within the field of virtual reality for long duration spaceflight.

The implementation of such solutions will require the use of specialised sensors to measure personal statistics. The research shows that this has already been developed through real-time radiation measurement and on-body sensors. This can potentially enable large data sets to be gathered which can potentially be used for further research into real life applications rather than hypothetical environment testing [4]. Additionally, adequate sensing and diagnosis systems have been developed for use in spacecraft. However, it must be noted that there has not been detail analysis of how to effectively interface hardware with these diagnosis systems within spacecraft as mentioned by Eklund et al. [22]

On remedying health issues in space, one must factor in the specifics of pharmaceuticals in outer space. There is conclusive evidence to suggest that medications like paracetamol are heavily affected in their API content in space [29]. Additionally, countermeasures have already been developed to make personalised medicine through additive manufacturing. This areas of study is exhaustive in stressing the importance and in the supply of adequate medicines to treat issues such as sleeplessness, headaches, and inflammation.

As such, the other side of the coin is to equip our astronauts and our spacecraft for surgery. This topic itself is extensive both within applications of telemedicine in space and on Earth within expertise access from different countries[42]. New control schemes have been developed to take into account time delay and uncertainty due to signal processing causing inaccurate end effector movement. On the other hand, fixed time delays due to large distances have only been explored in regards to statistical studies of surgeries rather than technical reports which show that telesurgery can only be conducted near Earth [41, 39]. However, telemedicine is a promising and thriving topic with direct application to space medicine that fascinates many researchers and organisations like NASA [36].

7 Conclusion

To summarise, this review has looked at the different effects that the environment of space has on the human body. The indirect solutions were then presented for how to go about neutralising threats such as radiation poisoning and degradation of DNA. The ways in which humans can be diagnosed was presented whilst discussing the improvements that were made upon older technologies such as radiation measurement. After setting the scene, the direct intervention by the method of medication was explored to further understand the effect of space on pharmaceuticals and if astronauts can used them. This revealed a trend in applying personalised medicine within long-duration spaceflight. Subsequently, it was shown that personalised medicine can be achieved through additive manufacturing methods which can create a multitude of potent remedies. Finally, critical injuries and trauma were tackled by looking at telemedicine applications into space such as telesurgery and telementoring. However, the challenges that come with enabling surgery in space have yet to be answered.

The extent to which humanity can safely send astronauts beyond LEO as of now is still mostly within a speculative and theoretical phase with research being conducted within laboratories on Earth. However, extensive experiments have already been conducted which covered diverse topics within space medicine such as surgery, diagnosis, and pharmaceutical stability. The findings from spaceflights subsequently provide the groundwork for space medicine to lift off into full effect. Humanity, in general, now has the experience to venture out farther than it has ever gone before. Further research and space missions should attempt to send astronauts beyond LEO to test the technologies and theories covered in this review. This would align humanity to take the first steps to establishing its presence in the solar system. As such, given the research discussed in this review, humans are now well prepared to take on the final frontier and venture out safely, effectively, and rapidly to distant worlds. Our survival in space looks more and more realistic as we prepare for our future outside of this planet.

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