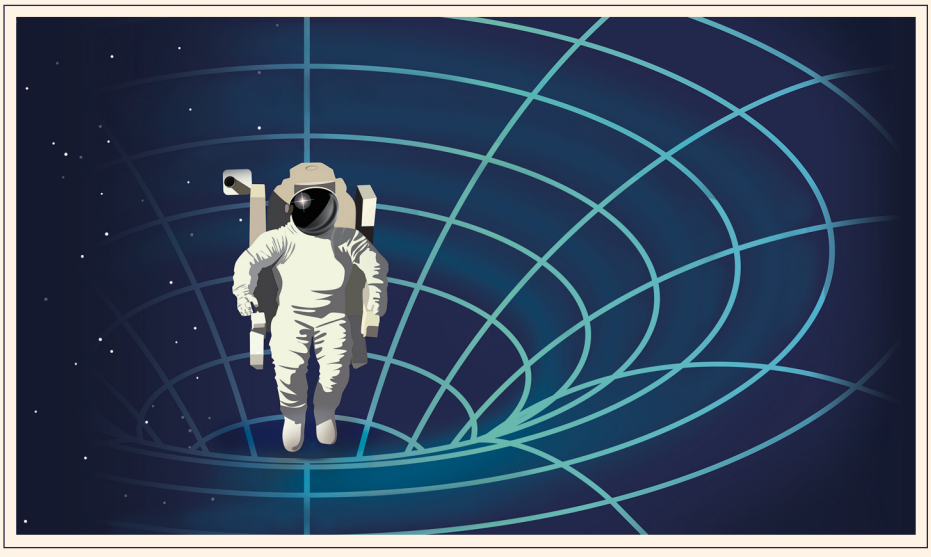
THE GUY FOUNDATION

The health hazards of space travel: novel insights from quantum biology



Driving innovation in medicine through quantum biology

October 2024

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The health hazards of space travel: novel insights from quantum biology

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About The Guy Foundation

The Guy Foundation is a UK-based charitable foundation established in 2018 to facilitate thinking and research on the role of quantum mechanics and thermodynamics in living systems, with the ultimate goal of using this understanding to advance healthcare. We curate, lead and fund an inter-disciplinary research collaboration and have published a number of scientific papers. We support the quantum biology community by convening online symposia on quantum biology and bioenergetics and we host an active network of over 200 scientists and institutions across the globe.

You can find more details on our website, including talks, publications and who we are: **www.theguyfoundation.org**.

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Abbreviations and Glossary

A list of abbreviations is presented on page 74 and a glossary on page 75.

The Guy Foundation Space Health Working Group members

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Foreword

For the last 60 years – since the Kennedy Apollo mission and the Cold War space race and satcomms revolution, space has been the defining frontier of human scientific and technological endeavour. Today, with the NASA Mars mission and an intensifying commercial global race for space, the space industry is booming. Space continues to be one of the most exciting sectors of human endeavour, the equivalent of the oceans to the European discoverers of the post-Renaissance Enlightenment. Space is the ultimate frontier of human endeavour, the ultimate laboratory and testbed for human ingenuity. It is in space that humankind has made the biggest strides in science, technology and engineering, while astronauts have captured the public imagination in a way that few others have.

But with adventure comes risk, and this report is a clear and compelling presentation of the current lack of knowledge and the urgent questions that need to be addressed concerning human space travel for prolonged periods, particularly beyond low-Earth orbit such as to the Moon or Mars. It argues that leaving the quantum environment of Earth with its protective gravitational and magnetic envelope will lead to health problems that lie beyond our adaptive capacity. All life has evolved within Earth's specific environmental conditions over billions of years and it is becoming increasingly clear that manned space activity provides huge challenges and opportunities for human health and life science. Thus, we must ensure that we understand the effects of space travel on the human body and the potential of space to open up a new understanding of the fundamental mechanisms that shape human life, health and disease.

As research science on the International Space Station (ISS) is complemented by accelerating work on the lunar economy and deep space exploration of Mars and beyond, the health impacts on astronauts are beginning to shine a fascinating new light on our lack of understanding of the mechanisms of ageing and disease with many questions remaining unanswered by traditional terrestrial science – and 21st-century life science – with its heavy emphasis on pharmacology and the chemistry of biological systems.

This first became clear to me when I met the UK astronaut Tim Peake on a visit to the Harwell Campus as the first UK Minister for Life Science. Tim told me that while on the space station, he had been conducting a host of experiments on the impact of space on human health – for example, the way that

astronauts experience a rapidly accelerated decline in key aspects of physiology such as retinal function and bone density.

In my time as UK Minister for Life Science in the Coalition government and subsequently as Minister of State for Science, Technology and Innovation, with responsibility for life science, space, quantum, fusion and engineering biology, I have had a hugely privileged insight and access to some of the most exciting science and technology in some of the top labs and companies in the world.

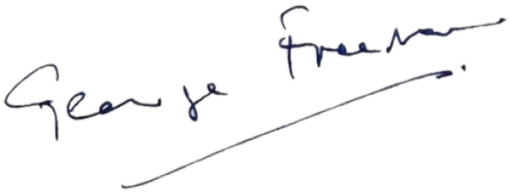
After a 15-year career founding high-growth technology companies developing frontier technologies my long-held fascination with the advances that science and technology can bring – and the extraordinary opportunities that will arise as we start to combine different disciplines and sectors, from AI and biotechnology to quantum and cyber security, grows ever deeper. It was through my work as a Member of Parliament (MP) that I came to know Professor Geoffrey Guy, a physician and polymath, who founded and led several pharmaceutical companies including GW Pharmaceuticals which was known for securing the first worldwide licences for cannabis-based medicines in multiple sclerosis (MS) and childhood epilepsy. Professor Guy is the Founder and Chairman of The Guy Foundation, an independent, UK-based charity that promotes and facilitates thinking and research on the role of quantum mechanics and thermodynamics in biology, with the ultimate goal of using this understanding to advance healthcare.

This report has been prepared by The Guy Foundation's scientific team, with input from scientists who are already researching space medicine and who want to highlight and investigate the health problems that astronauts develop and from scientists from other disciplines who can provide deeper insight. Together they have provided a unifying and compelling rationale which highlights the pressing concerns about the capacity of humans to travel into space without suffering from significant or severe health problems. All this, as many are realising, has serious implications for the many organisations and individuals in the vanguard of the space economy. In parallel, it also offers serious opportunities to improve mankind's understanding of the underlying basis of disease and ageing. The space life sciences may be opening up a whole new field of biology and medicine.

The Guy Foundation and the quantum biology community are keen to assist and to ensure that the safety of human travellers, whether on manned space flights or lunar or Mars bases, can be better assured and their health optimised. Such research will have the additional benefit of serving as a test

bed for biomedical research into some of the modes of action of ageing and disease, thus progressing our understanding and management of ageing and associated diseases here on Earth.

I sincerely hope that the space industry will give due consideration to this report and support the research that is so urgently needed.



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October 2024

1 | Executive summary

1. **This report has been prepared by The Guy Foundation, an independent research body which facilitates the development of quantum biology (QB) to provide further insights into medicine.** The Foundation is supported by a large faculty of internationally recognised scientists from many disciplines, including space research.
2. **The report's principal finding is that space travel seems likely to induce accelerated ageing in astronauts. This "accelerated ageing phenotype" (AAP) needs to be investigated and explained as a matter of urgency.** Furthermore, the report highlights that this space-induced AAP appears to be associated with the disruption of cellular bioenergetics which could have other, perhaps more worrying health consequences.
3. It seems likely that complex long-lived organisms, such as humans, **will not be able to adapt to the unnatural environment of space**, while shorter-lived, rapidly evolving ones, such as bacteria will. This has profound implications for the human microbiome.
4. The Foundation has examined this issue through the lenses of quantum biology, thermodynamics, the origins of life, and bioenergetics. All seem to highlight the importance of understanding the effects of the space environment on mitochondria and the electron transport chain (ETC). At this stage, **the following factors seem particularly significant** in terms of inducing space AAP:
    - **It is likely that reduced, and in particular, zero gravity removes the stimulus to maintain healthy mitochondria** and cellular structural integrity, thereby decreasing metabolic adaptability and increasing oxidative stress.
    - **Increased radiation induces damage in all cellular compartments,** resulting in increased oxidative stress. This is especially the case with high linear energy transfer (LET). Oxidative stress will compound any direct DNA damage and further reduce the capacity to repair and maintain DNA.
    - **The lack of a magnetic field could increase oxidative stress** by altering quantum spin-based homeostasis, putting more stress on cells.
    - A **lack of near-infrared radiation** due to artificial, blue-shifted LED-based lighting may result in increased cellular stress.

- The loss of the circadian environmental cues that underpin an organism's biological rhythms results in cellular stress, **further challenging an already metabolically compromised system**.

5. Although there is openly available pooled data on returning astronauts, **there is much less data on long-term health outcomes**. In particular, there are no multi-year studies of animals in space.
6. At present, there are **no long-term data available** on larger numbers of humans, or even small animals, sufficient for a regulatory environment **to ensure the safety of increasing numbers of space travellers.**
7. Most astronauts have been young, healthy and fit. What happens to less fit and/or older individuals is not well understood, **especially for longer-term missions.**
8. The questions raised in this report may have serious implications. **Further experiments are urgently needed** to improve our understanding of the underlying causes of space-induced ill health, and potential approaches to mitigate it.
9. These experiments should include **biological measures of astronauts' ageing**, as well as the impacts at cellular and sub-cellular levels of **ionising radiation, hyper and hypomagnetic fields, microgravitational fields, non-ionising radiation (light) and disrupted circadian rhythms.**
10. By approaching the issue from an **electrical/quantum mechanical perspective**, we can gain further insights into why the space environment may be adversely affecting bioenergetics.
11. To date, cost and engineering challenges have driven space research to focus on the ability to survive rather than to thrive. **The space AAP is a signal that needs to be understood and addressed. Surviving is not the same as living in optimal health and thriving.**
12. It seems that unless we genetically engineer astronauts, which would have its own legal and ethical considerations, the only way humans may live in optimal health in space is by **reproducing Earth's environment exactly**. More likely given current technology, we need to work out which factors are most important in disease induction and seek to mitigate them or accept the imposed limitations.
13. **We invite scientists and organisations interested in these issues to contact us.** Together we can work to build a better understanding and apply it to improving human health in space.

2 | Introduction

This report, which has been prepared by The Guy Foundation in conjunction with space and quantum biology (QB) scientists, presents findings on space health from the perspective of quantum biology and mitochondrial function. The rationale for our approach is data suggesting that astronauts may be developing an accelerated ageing phenotype (AAP),[1-3] which is similar in some respects to that induced by a modern sedentary lifestyle epitomised by the metabolic syndrome.[4] Critically, like the metabolic syndrome, it seems that going into space results in mitochondrial dysfunction.[5] Very recent data, obtained from a "heart-on-a-chip" platform flown on the ISS for 30 days, indicates that a replicate of the human myocardium developed mitochondrial dysfunction, evidence of oxidative stress and transcriptional changes, as well as weakened contractions – all suggestive of an AAP when compared to controls kept on Earth. Some of these persisted for several days after it was returned to Earth.[6]

As we still do not fully understand the ageing process,[7] understanding space pathology could benefit the field of ageing science in general. In particular, by answering the question "Is an AAP reversible?" It is possible that, in some cases, a stress-induced AAP can reverse naturally.[8] For example, there is evidence that pregnancy can initially result in epigenetic changes similar to an AAP, which can spontaneously reverse after giving birth. Interestingly, the reversal can be slowed by obesity.[9] This raises the question as to whether it is better to prevent the AAP in the first place or try and treat it. In effect, we either build spacecraft that mimic Earth's healthiest conditions exactly or simply accept the unusual conditions and try to treat them. Although it is possible to mitigate some of the negative problems with exercise, diet and some drugs, the effect is minimal. Despite these mitigating strategies, improving the maximum human lifespan is not yet possible.[10]

The problem of astronaut health has been discussed in depth in the recently published NASA-supported paper, '*Thriving in space: Ensuring the future of biological and physical sciences research: A decadal survey for 2023-2032 (2023*)'.[11] In that report, it is suggested that humans, and many of their complex companion organisms, such as plants, may not be able to adapt to space as they evolved on a planet with a very specific set of conditions. In effect, it could be said that space-related physiological changes are an example of failed adaptation, which becomes maladaptive. This might indicate that we must either replicate Earth's conditions exactly in space or else utilise some form of genetic engineering for long-term space exploration. The report also summarises the observation that

although space exploration has been engineering-driven and the spacecraft crewed by pioneers who readily accept the risks, there now needs to be a much greater focus on optimal health as the potential for settlement in space may well become a reality for a more general population. These concepts raise many implications, both medical and legal.

Hence, it is not just about surviving, but thriving in space, which mirrors a question still applicable to living on Earth, namely "What is optimal health?" This can be defined, for any organism, as living in an environment that optimises health span, ensuring morbidity compression at the end of life. In this respect, "end of life" is the recognised maximum achievable age for a species, which is partly determined by genetics and seems to be related to DNA methylation rates.[12] Optimising health span is still not something that has been achieved for many on Earth. For instance, in the USA, it has been estimated that less than 7% of the population displays good cardiometabolic health, which perhaps reflects a sedentary lifestyle.[13] The key message seems to be that much like what happens to humans who live a modern sedentary lifestyle, the AAP associated with space travel is a result of our species living outside their evolutionary-derived "adaptative metabolic envelope" or, to put it another way, outside of our evolutionary "Goldilocks zone". This is encapsulated by the concept of hormesis where just the right amount of stress is key for optimal health, too little reduces robustness, but too much is damaging.[4]

An important gap in our understanding is that it is still unknown whether those returning from space, even after relatively short periods, fully recover and display a normal "health span". At present, there is no readily available long-term health data on the 670 or more people who have been to space. Given this paucity of data, it is likely that this gap could be addressed by employing the emerging medical technologies used to measure biological age as opposed to chronological age. The evidence is that, even in people who have never been in space and who appear healthy by conventional measures, many unseen epigenetic and metabolic changes indicate otherwise.[14] In short, space travel may result in a biological clock that ticks faster than may be indicated by an individual's chronological age.

In this report, we investigate how the intersection between physics and biology, epitomised by quantum biology and focused on mitochondrial function, could provide fresh insight into the detrimental effects of the space environment – especially if we view life as electrical and reliant on redox that evolved under a very specific set of conditions not found in space. So why electrical?

Metabolism is based on the movement of electrons and protons coupled to the generation of ion gradients, giving rise to both dynamic and static electric fields. This makes the electron transport chain (ETC) in mitochondria particularly relevant. Furthermore, as the ETC relies on multiple chromophores (i.e., light-sensitive molecules), it also highlights a less appreciated potential role of photons in day-to-day metabolism. These topics – the movement of charged particles and the role of photons – are central to the field of quantum biology and provide a common starting point with medicine. The movement of electrons, controlled by complex homeostatic mechanisms, is a fundamental life process that if it changes can result in oxidative stress and inflammation. Put simply, if going into space alters an organism's redox, it provides us with a common ground approach.

To date, research has clearly identified increased radiation, reduced gravity and altered circadian rhythms as important in causing ill health in astronauts, but it now also seems that changes in light spectra and magnetic fields could also be key, raising the question, which factor is the most important? Certainly, both microgravity and radiation are high up on the list. One finding that is becoming clear is that going into space seems to induce mitochondrial dysfunction.[5] Mitochondria are not only key in energy management, but also in redox management, and can act as net sinks of reactive oxygen species (ROS) [15-17], suggesting that they serve as good "canaries in the metabolic coal mine".

Thus, understanding which altered factor in space induces mitochondrial dysfunction the most, and how, is perhaps a worthwhile approach. Indeed, all the factors listed can contribute to mitochondrial dysfunction, but likely in different ways. For example, we suggest that a lack of gravity simply removes the stimulus to maintain a higher mitochondrial mass, leading to a greatly reduced metabolic capacity with time, which is then compounded by other factors such as those that directly induce oxidative stress, for instance, radiation, and especially high LET. In addition to this are those factors whose removal also seems to induce stress, such as the Earth's magnetic field, which may directly influence ROS via spin chemistry, or near-infrared light, which might play a role in mitochondrial homeostasis, or the loss of external environmental cues that synchronise an organism's biological rhythms ("zeitgebers"). In short, not only does going into space remove a major stimulus for mitochondrial capacity, gravity, which is coupled to exercise, but it also further overloads the remaining mitochondrial capacity with a variety of non-evolutionary stressors. Mitochondrial health is key for all cellular functions, including genomic stability.

Certainly, taking the above approach, some of the reasons for space-induced mitochondrial dysfunction can be explained using conventional biology, but quantum mechanics can begin to explain other, less obvious causes. In fact, a quantum approach to biology has long been discussed by many leading scientists, including Erwin Schrödinger, Albert Szent-Györgyi, Britton Chance and Roger Penrose. Today, evidence is building that biology indeed employs quantum effects in ways not previously thought possible by many who approach biology from the conventional viewpoint.[18] For example, quantum mechanics is required to explain how coherent electron spin dynamics, and thus magnetic fields, can directly affect ROS production involving mitochondrial function.[19] If we just take this data, it could be predicted that the reduction in magnetic field strength as we move away from Earth may not only increase the risk from radiation but also increase mitochondrial ROS.

In this report, we combine some original thinking with established areas of space health research, to provide fresh insight, and suggest research that needs to be done to advance space health. Unfortunately, it appears that space has a "multi-whammy" effect on life, beyond the well-known radiation hazards. The lack of gravity takes away an essential functional adaptation stimulus that is key in maintaining the structure of complex life such as a healthy population of mitochondria. Also removed are the terrestrial magnetic fields and light spectra which, we are learning, life has evolved to be dependent on. So, although humans can survive in space, all the evidence suggests they will not thrive, and indeed may become increasingly unhealthy, especially on longer trips outside the Earth's protective magnetic field.

3 | Quantum biology and space research

"I suspect that these are not merely simplifications; they are the essence of truth".

- From the Foundation Series by Isaac Asimov.

The above quote suggests we should be looking for a deeper simplicity in biology; on one level, it does appear incredibly complex, but perhaps it is not. Isaac Asimov was not only a good biochemist, but a visionary science fiction writer who has inspired generations of scientists – including the current generation of entrepreneurs who are paving a new way to get into space. We believe there is a way to look for a deeper simplicity and that is to go back in time to life's origins; life arose from the geochemistry of our planet,[20] and although we still do not precisely understand exactly how it started, there are some key clues – such as life's reliance on a proton gradient, which likely reflects its earliest origins.[21]

The roots of The Guy Foundation's experiential expertise lie in both pharmaceutical translational research, in particular around natural products, and the underlying processes of ageing and how this is affected by lifestyle. This has resulted in a primary focus on mitochondrial function, redox and inflammation, and how these are modulated by the adaptive response to stress called hormesis. For instance, the metabolic syndrome could be described as an AAP [4] which, in turn, could explain Fermi's paradox [22] (if life is very common in the galaxy and some of it develops space travel, given the length of time our galaxy has been around, then where is it?). It could also explain how a poor lifestyle could result in reduced mitochondrial function and increased morbidity in individuals infected with SARs-CoV-2.[23,24] These approaches are supported by other theories, such as on the origins of life involving thermal vents, which explains chemiosmosis and mitochondria,[25] plus evidence that not only are bioelectrical fields playing a key role in life,[26] but also that life could well be using quantum effects, giving rise to the field of quantum biology.[18,27,28]

For example, electron tunnelling in biology was championed by Britton Chance in the 1960s.[29] More recently, not only has the role of quantum biology been extended to help explain the origins of life,[30,31] but it is becoming accepted that the thermodynamics of dissipative self-organisation is now perhaps the best way to explain why life is the way it is,[32,33] with new theories incorporating the quantum realm into adaptive thermodynamics coming to the fore.[34] Indeed, recent data indicate that not only is it possible to detect quantum tunnelling in mitochondria, but it can also be manipulated,[35] while

Grover's quantum algorithm has been applied to neuronal functions and other differentiated cell functions, suggesting impacts on normal, diseased, and ageing cellular response regulation on Earth and in off-Earth environments.[36-38] So approaching life from the quantum aspect continues to be useful as even Erwin Schrödinger discussed.[39]

So, to improve our understanding of life, both quantum mechanics and thermodynamics may well be key. This has led to the Foundation developing concepts such as the "quantum mitochondrion",[40] why bioelectricity may have been important at the origins of life,[41] and why dissipative thermodynamics can explain inflammation and hormesis, potentially underlying the process of ageing when viewed from a global perspective.[42] The dissipative concept can also be applied to a possible "photonic homeostatic" system that is integrated with redox via, for instance, chromophoric components of electron transport, which plant compounds have evolved to manipulate and could explain why they can act as medicines.[43,44] As Szent-Györgyi reputedly once said; "life is nothing but an electron looking for a place to rest".[45] Indeed, investigating life from the electrical perspective is potentially highly informative, although it is not a new concept and dates back to the 18th century.[46,47] It is perhaps relevant that the most likely inorganic origins of the central physical process in life, that of electron bifurcation, seem to have been worked out,[48] which perhaps strongly supports this "metabolic" origin of life.

The Guy Foundation originally became interested in space research because of the potential of quantum biology to explain how life interacts with magnetic fields, for instance, in bird navigation,[49,50] which soon led to researchers finding that altering magnetic fields could manipulate mitochondrial function.[51-53] When combined with the discovery that astronauts develop mitochondrial dysfunction[5], this raised the possibility that QB could be an approach to understand space health. The Foundation is not the only group to suggest that hypomagnetic fields could directly affect metabolism in space.[54,55] Indeed, quantum spin might suggest that biology is likely to be sensitive to magnetic fields,[56] and why, as proof, magnetic fields modulate autofluorescence.[57]

Hence, the Foundation believes that a fresh examination of the ways in which the changes in visible and near-visible light spectra, LET of ionising waves and particles, and electromagnetic and gravitational fields associated with the space environment impact astronaut health is needed, which would also include how they affect circadian systems that are tightly integrated with the ageing process. In terms of radiation, which can be defined as the emission or transmission of energy in the

form of waves or particles through space or a material medium, it is all about the energy, how much is transferred into a biological system, and by what mechanism. An iron nucleus travelling at relativistic speeds could cause a lot of damage, while a photon of infrared light, which has a lot less energy, may still cause a vibrational shift in a molecular bond. Both of course could alter cellular homeostasis, and depending on their dose, could either induce an adaptative response (hormesis, which can be both good and potentially bad, depending on the type of cell), immediately catastrophic, or result in delayed effects some 10 years later. Indeed, the short and long-term outcomes could be quite different and sometimes surprising.

There is actually a very long history of studying the biological effects of radiation for medical purposes – ever since the pioneering work of Marie Curie in the late 19th century. The literature is extensive, especially around imaging and cancer treatment, with both low and high LET being used, with a long research focus on working out the relative biological effect (RBE) of the various modalities. Low LET generally refers to ionising photons (electromagnetic), such as gamma and X-rays, while high LET therapy uses heavy charged nuclei and protons. The effects are different, for instance, photonic treatment of cancer can be limited to how deep the photons go with lower energy penetrating less far, while some high LET can penetrate further but because of the Bragg effect, dump more energy in a shorter track, generating a large amount of ROS. Critically, low LET can induce a variety of responses, for instance, an adaptive response, senescence or cell death, which depend both on dose and fluence, but also biological sensitivity. In comparison, although high LET can be more damaging, it can also induce a variety of responses depending on dose and fluence. As treatments, both have advantages and disadvantages.[58]

In terms of the underlying physics, there are fundamental differences between high and low LET, with one of the main ones being that defining dose is difficult, in that low LET tends to deposit energy in a uniform pattern, interacting with many single targets, while high LET can result in a single ionising track, but in a non-uniform way. This is because the heavier, high-energy particles, not only produce a linear track, but branching due to the creation of secondary particles, resulting in greater damage.[59] Indeed, the differences in the effects between high and low LET, fluency and particle type and energy, are reflected in the variability both in gene expression and cell response. For instance, exposure to high Z and high-energy particles (HZE – a component of galactic cosmic rays [GCR]: “H” stands for “high”, “Z” for atomic number, and “E” for “energy” – so ions with +3 *e* charge, hence bigger than

helium) can actually suppress DNA repair mechanisms in the ensuing 8-24 hours, while DNA repair continues following exposure to X-rays. One aspect is that high LET can lead to complex DNA damage, persistent oxidative stress and effects on bystander cells, resulting in altered cellular function, mutation, inflammation and damage to the immune system.[60] This is also reflected in the activation pattern of transcription factors involved in the cell response to damage, such as nuclear factor kappa-B (NF-kB), nuclear erythroid-derived 2-related factor 2 (Nrf2), or p53 and the DNA damage response (DDR) mechanism.[61]

In terms of space travel, it is well recognised that beyond low-Earth orbit (BLEO), the most important source of high LET is likely to be GCR and protons/helium nuclei ejected from the Sun during solar particle events (SPEs). While the latter can be relatively well shielded from, the former is much more difficult to protect from and even if shielding is provided, secondary generation of other particles is important. The main challenge that agencies such as NASA therefore face is how to model this, in particular, for long duration with low fluence and the mixed radiation pattern found in space: most studies to date have used a single energy and particle type, which is usually highly vectored – in space, the radiation is very mixed and often isotropic in direction [62]. Although there has been a focus on radiation exposure for astronauts going to Mars, data from the Chang'e 4 lander suggest that the GCR dose at the lunar surface is 2.6 times higher than inside the ISS.[63]

There is now an emerging consensus, previously underestimated, that both high and low LET can induce damage in all macromolecules, including those in the mitochondrion. Hence, mitochondrial damage may actually be just as important as DNA damage. For example, mitochondria are key in determining cell fate due to epigenetics, retrograde signalling and adaptability, as well as altering the function of bystander cells.[64] This suggests that continual exposure to high LET on the way to Mars, or when staying on the Moon, could result in higher rates of mitochondrial damage, which will accelerate the ageing process leading to chronic inflammation. It is already well-known that excessive radiation accelerates the development of cardiovascular disease [65,66] – a classic inflammatory-based disease of ageing. Perhaps of relevance here are studies done on Hiroshima survivors, which show non-linear effects on cancer at low doses of radiation, especially if latency is taken into account – suggesting a bystander effect.[67] In effect, even at low doses of radiation, negative health effects may appear, albeit with a multi-year latency.

The central point is that the ETC is susceptible to all the factors listed above, which usually results in changes in redox and ROS signalling, leading to the concept of the "mitochondrial canary in the metabolic coal mine".[68] A deeper understanding of the role of the ETC in space-induced pathology could lead to ways to improve the health of astronauts, as well as accelerating progress in quantum biology and the advancement of medicine on Earth. Thus, space-induced AAP serves as a good model for ageing.

The Foundation's **Space Health symposium** and **2023 Autumn Series on Space Health**, as well as the **2024 Spring Series on Ageing,** considered this topic further. All of the Foundation's symposia are structured from the viewpoint of quantum biology and the potential role that non-chemically based homeostasis, such as the role of photons and electromagnetic fields (EMF) might be playing in life. The proceedings and talk recordings are available **here**.

An evaluation of the evidence suggests that while humankind has seen tremendous progress with spacecraft engineering, this has not been matched in associated biological research and so our understanding of the consequences of space travel for human health remains limited. Indeed, there is agreement among those working both within and outside space organisations that a great deal more research needs to be done.[11] Some are even asking the question: "Is gravity deprivation actually ethical for optimal physiology?" given the physiological problems that astronauts develop.[69] This of course raises the question, as non-governmental space exploration expands, and research continues to indicate the very real non-lethal risks, how should the ethics and legality be handled as we send more people into space?[70]

The Foundation has therefore established its Space Health Programme to work in collaboration with scientists and organisations to assess and better understand the effects of space travel and habitation on human health. We are seeking to undertake experiments and review evidence from post-space phenotypes, to the altered electromagnetic and gravitational fields seen in the space environment, to effects at the quantum level.

The following chapters provide a more detailed description of how the space environment differs from that of Earth and the biological implications of this, and how embracing thermodynamics and quantum mechanics may provide fresh insight, not only for astronaut health, but also into the principles of health and medicine in general. For example, what is ageing and why does it occur? We then set out

what further experiments need to be done beyond those already suggested, for instance, to enhance our knowledge when travelling beyond LEO,[71] what this may mean for space travel, and the key questions it raises.

4 | What is optimal health?

There is a clear difference between “thriving” and “surviving” in space, which raises the question, what is optimal health? This is not always a question that has been asked, instead, society tends to focus on disease and how to treat it. Clearly, if going into space results in an AAP, then astronauts are not living in optimal health. One simple definition is that optimal health is a phenotype that maximises healthspan and fitness while demonstrating morbidity compression in relation to its species' maximum lifespan. In effect, the organism is healthy for most of its life, remaining fit, functional and robust with little evidence of disease for its age, until very close to its time of death.

Indeed, data show that “biological age” can be different from “chronological age”. Ageing is associated with a gradual loss of physiological function, accumulation of damage, and increasing disease, which enables a reasonable statistical prediction of mortality. Hence, an organism can have a biological age that can be higher or lower than its chronological age, which it is now possible to measure.[14]

Figure 1 outlines one way of viewing this – we know that a poor lifestyle accelerates the ageing process and is associated with the metabolic syndrome, while a “healthy” lifestyle seems to enable populations to live closer to their known human maximum.[4] What is clear is that many populations do not live in optimal health, for example, a recent assessment by the World Health Organisation (WHO), estimated that 43% of adults were overweight, and 16% were obese (**Obesity and overweight (who.int)**).

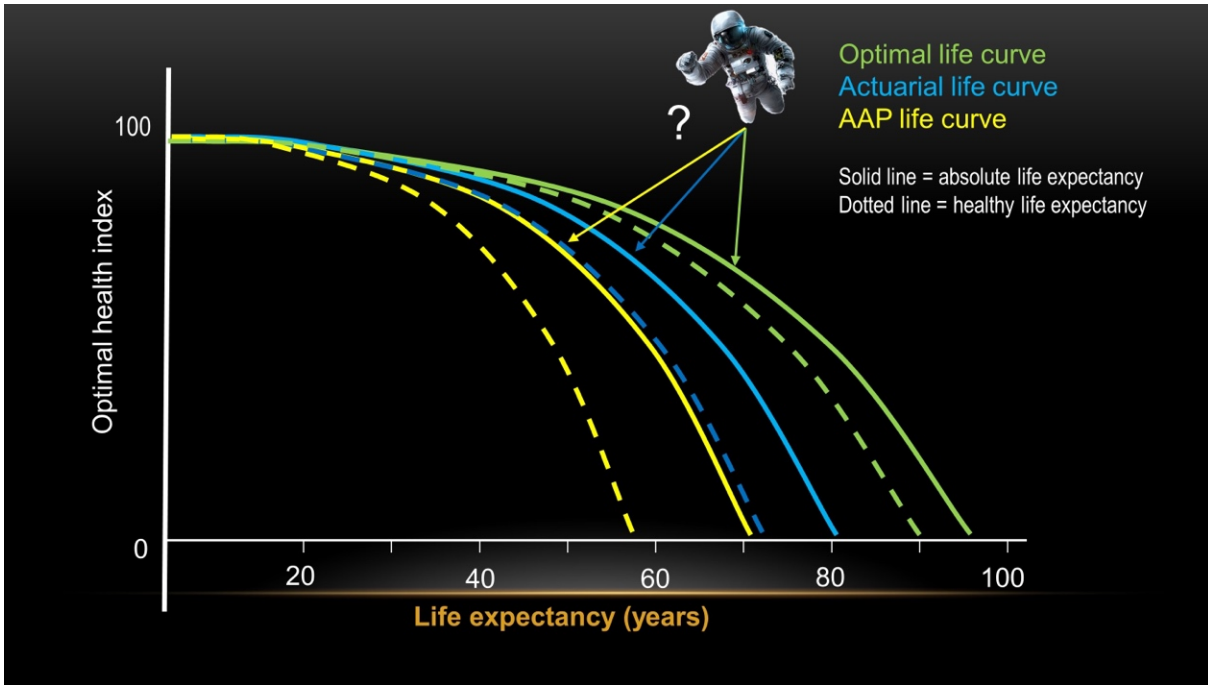

Figure 1. Life in space: what effect may space have on healthy and absolute life expectancy?
Solid lines represent the absolute expected lifespan, while dotted lines indicate "healthspan". While there are certainly genetic effects, the suggestion is that many humans, if they live a very healthy life, could live to 95 or more, only experiencing serious disease in the last few years (green lines). In contrast, a very poor lifestyle reduces life expectancy and expands the time spent living in morbidity (yellow lines). The question is where would, if we had enough data to make a reliable estimate, astronauts end up? The blue lines are what we actually see in developed countries.

Diagram from "Are we trapped on Earth: space and accelerated ageing", Nunn et al., submitted to Nature Microgravity, 2024.

So, in essence, "thriving" in space means doing very well and flourishing, in effect, living in very good health, while "surviving" could simply mean staying alive, but not in good health at all. It may well be that with the current technology, humans, and other organisms, will be biologically challenged by spaceflight to the point that they will not be living in optimal health. We see this as an AAP. A problem with many modern societies is that what many people perceive as being healthy is determined by what they view as normal, which is in fact not the case, as the "normal" phenotype is often the result of a sedentary, high-calorie lifestyle. As is becoming clear, and in fact, has been known for thousands of years, good health comes from taking plenty of physical activity with a balanced diet, which must be maintained throughout life.

5 | Space and the evolved adaptive metabolic envelope

In the previous chapter, we make the point that a large proportion of the world's population is already not living in optimal health. Perhaps the main conclusion from this is that if humans, or any other species, find themselves in an environment they are not adapted to, then they display a sub-optimal health phenotype. This could of course occur because of factors beyond species control, such as a large asteroid impact. But for humans, it seems that we can do this through our own efforts. One of the reasons that many humans are not living in optimal health could be due to a kind of intelligence paradox, as in the process of making our lives more comfortable and safe, we appear to have removed many of the factors that keep us healthy – such as the need for physical activity or diets high in plant compounds.[22] At the other extreme, it seems that by going into space, humans are also putting themselves into another unusual environment for which they are not adapted. We can of course do something about our sedentary comfortable lifestyle, but what about space travel?

This thinking is reflected in the main questions posed in the '*Thriving in space*' report: can humans and their associated flora and fauna adapt to space, and if not, what can be done about it? For humans, the consensus is that adaptation may not be possible, as indicated by evidence of metabolic perturbation, even after relatively short periods off-Earth. While surviving is clearly possible, thriving and living in optimal health may not be – at least with the current level of technology.[11] As several groups have suggested, space travel results in an AAP.[1-3] In effect, going off-Earth in the current type of spacecraft puts humans outside their evolved and canalised adaptative metabolic envelope, or "Goldilocks zone". In short, the conditions are simply too dramatically different to those on Earth for individual humans to adapt to. However, for smaller and much simpler short-lived organisms, it may well be possible that natural selection could result in variants that do not just survive but thrive. This of course raises the question, certainly for humans, of which factors are causing the greatest damage, and whether there is a common underlying mechanism.

To date, the effects of microgravity change in circadian rhythms and radiation are reasonably well described. However, to this, we may need to add the direct effects of hypomagnetism [72] and restricted light spectra.[73] Although there are several biomarkers of ageing, two in particular are perhaps of high importance, and those are mitochondrial dysfunction and epigenetics. Mitochondrial function and DNA methylation are linked, and may well play a role in the ageing process.[74] Indeed, it now seems

that DNA methylation rates scale with maximum lifespan across mammals,[12] while mitochondrial function and epigenetics are tightly integrated.[75] Thus, the effects of the space environment on the ETC could be revealing, especially if quantum mechanics are taken into consideration when considering life as electrical.

In this chapter, we look at space environment factors that are, or could be, different from those on Earth, which include radiation, gravity, magnetic fields, circadian zeitgebers and light spectra, before discussing what this means for living organisms that have been tuned by evolution to their terrestrial environment.

5.1 Ionising radiation

Ionising electromagnetic radiation along with ionising particles, such as alpha and beta particles**,** have been identified by NASA as one of the main spaceflight hazards to humans, which are summarised by the acronym "**RIDGE**": Space **R**adiation, **I**solation and Confinement, **D**istance from Earth, **G**ravity fields, and Hostile/Closed **E**nvironments. Ionising radiation is high-frequency radiation (meaning high energy), which damages biological material (see Figure 2 for details of where this radiation sits on the electromagnetic spectrum). We are protected from this type of radiation by the Earth's magnetic field, which deflects it, as well as by the atmosphere and the ISS sits within this magnetic field. However, going beyond the Earth, or the Moon, is going to put people at much greater risk.

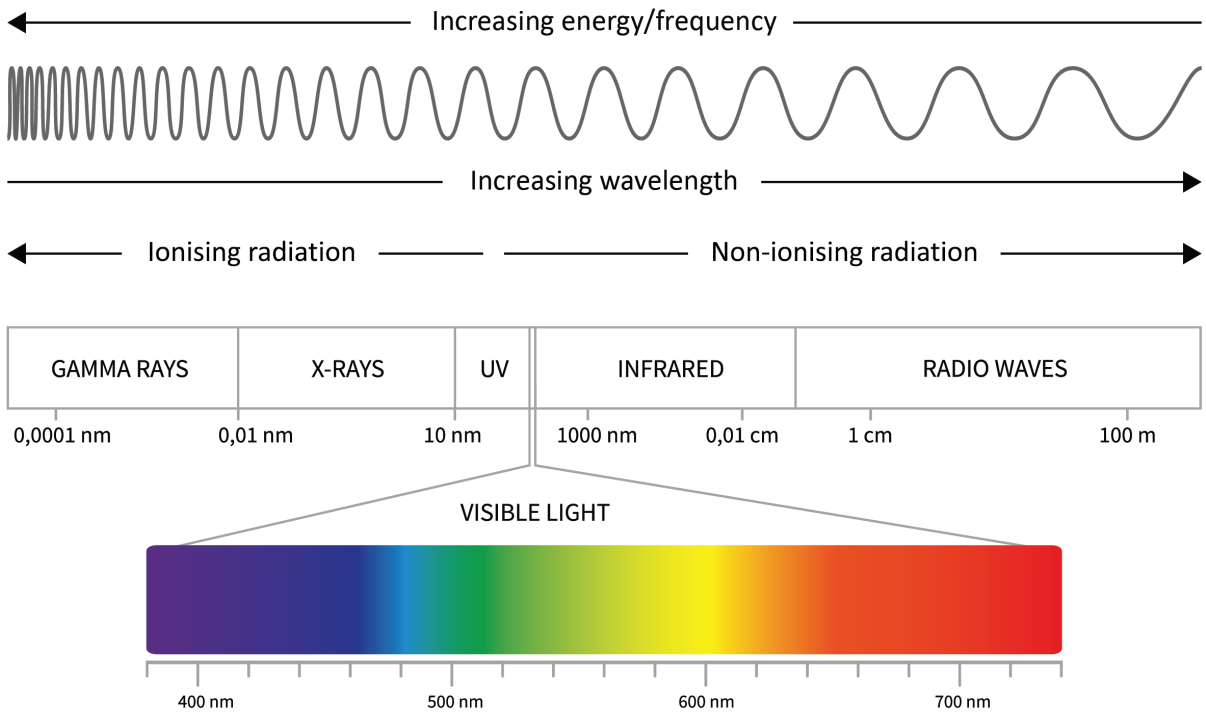

Figure 2. The electromagnetic spectrum.
The diagram illustrates the different frequencies of the electromagnetic spectrum. Frequency is inversely proportional to wavelength. Radiation with high frequency, such as gamma rays, is acknowledged to cause biological damage. At the simplest level, the amount of potential damage is related to the energy each photon carries, as indicated by the equation E=hf. It will also be related to which biological molecules can absorb the energy, and how. Although investigations into the effects of lower-frequency radiation are still ongoing, the prevailing evidence is they could be very important.

Figure provided by The Guy Foundation.

Space contains many different types of radiation, including very high levels of non-ionising, though damaging ultraviolet, due to the existence of biological chromophores that absorb it, such as DNA and even reduced nicotinamide adenine dinucleotide (NADH), a central molecule in cellular redox, which has a very high quantum efficiency for the ejection of a solvated electron when excited by a 340 nm photon.[76] However, as indicated, one of the key concerns is high LET radiation, even in LEO. Although the magnetosphere deflects a great many energetic particles from the Sun, some can get trapped within the magnetic field, while very high energy particles, such as HZE, can penetrate – although at much lower doses than outside of the magnetosphere. LET is a measure of the density of ionisations along a radiation path and is defined as the ratio of energy transferred by a charged particle to the atoms it interacts with per unit length. This generally means that high LET is associated with charged nuclei, which potentially can carry a lot of energy, especially if fast-moving (e.g., approaching relativistic velocities), such as helium nuclei, protons and neutrons, whereas low LET is generally associated with photons, such as gamma and X-rays. In space, high LET has several sources, ranging from solar energetic particles, such as protons released during solar flares and coronal mass ejections also known as SPEs, while GCR is composed of protons, helium and heavier nuclei generated by events beyond the solar system, such as supernovas, and secondary intravehicular radiation when these particles interact with the spacecraft structure itself. Particularly dangerous are those HZE particles present in GCR. The key difference is that GCR is constant, while SPEs are sporadic and can be especially dangerous if astronauts are outside of their spacecraft.[65]

Although the particles found in GCR are known to damage DNA and many signalling pathways, resulting in cancer and inflammation, the underlying science and long-term effects are not well understood.[77-79] Further, there is also evidence of qualitative and risk differences between low and high LET in relation to cancer.[80] Added to this, there are also indications obtained from Earth-based studies that ionising radiation increases the rate of cardiovascular disease, with some qualitative differences noted between high and low doses.[81] Although simulations on the effects of GCR on the brain suggest that astronauts, at least over a month on the Martian surface, might not exceed the current 30-day limit of 500 mGy, those on the lunar surface or in deep space may well do so, implying that shielding is going to be important.[82] There is still, therefore, a great deal of research to be done, especially in relation to chronic exposure BLEO. As discussed in the introduction, the medical applications of high and low LET and the underlying mechanisms are well-researched and continue to

be so. The main problem, however, is modelling exactly that low fluence mixed radiation field which astronauts will be exposed to on any trips to Mars or longer stays on the Moon, which is not something the medical field has focused on as it has generally been focused on short, high fluence therapy.[62] In comparison, a lot of information has been accrued from studying the biological effects of LEO from the ISS and, in particular, working out safe dose limits for various organ systems, such as the eyes, skin, blood-forming organs, circulatory and central nervous systems, both in the short and longer term.[83]

Overall, it is likely that radiation can accelerate the ageing process, especially given that it can result in increased oxidative stress and increased incidence at a younger age in relation to many of the normal conditions associated with ageing, such as cancer, genomic instability, mitochondrial dysfunction, inflammation, telomere shortening, and generalised cellular senescence.[84] Interestingly, as low-level radiation can also induce a protective adaptive response, it has been suggested that prior exposure to low-dose X-rays could be protective before going into space.[85] This is perhaps controversial, as getting the dose right could be difficult, and we simply do not know whether a potentially protective adaptive response induced by what is, essentially, low LET, induces protection against high LET. The other problem is that the exposure is continuous.

Although a single stressor can induce a protective response, continued exposure will likely overcome any ability to adapt. In this regard, it has been observed that the telomeres in the blood cells of astronauts lengthen, but rapidly shorten on returning to Earth, and appear to end up shorter than in those controls who did not venture into space. The effect of radiation on telomeres does appear to be dose-dependent, with high doses shortening them, while low doses potentially increase their length. To investigate this, and the relationship to microgravity, researchers studied a mouse tail suspension model to induce atrophy in muscles in combination with radiation. They found that this did indeed increase telomere length in muscle cells which, unlike the astronauts, did not return to baseline. Interestingly, neither tail suspension nor radiation alone induced the increase in telomere length. The authors suggested that the telomere lengthening was probably not due to increased telomerase activity, but rather to an alternative lengthening of telomeres (ALT) mechanism observed in tumours.[86] Critically, telomeres play a central role in genomic stability, which is why cancer cells can activate mechanisms to protect them, indicating that telomere length is tightly controlled. Indeed, it is now known that telomere length is bi-directionally modulated by stress, wherein mild stress can

lead to their lengthening, while too much shortens them. This has been observed in birds and can aid in their survival, for instance when rearing chicks, but only when plenty of food is available.[87] A key link here is that mitochondrial stress, via a wave of ROS, can cause telomere dysfunction.[88] In turn, ubiquilin 1 (UBQLN1) upregulation can stimulate mitophagy and proteostasis to restore mitochondrial function, protecting telomeres.[89] Furthermore, it seems that dysfunctional components of damaged telomeres generated during replicative crisis can activate a mitochondrially-based innate immunity response that can eliminate potentially neoplastic cells using the Z-DNA binding protein 1 (ZBP1).[90] All in all, this points towards a tightly coupled relationship between both mitochondrial and nuclear DNA damage, possibly suggesting that the telomere lengthening seen in the blood cells of astronauts was a stress response. This could potentially be a double-edged sword as, although it might initially be protective, it could also lead to an increased risk of pathology, including cancer. In the long term, it is well described that ageing is associated with shortened telomeres and is associated with decreased resistance to infections, such as COVID-19,[91] while a healthy lifestyle, and in particular, high cardiovascular fitness, seems to slow the shortening.[92] Critically, data does suggest that chronic oxidative stress in the nucleus does promote telomere loss, but low-level oxidative stress via a hormetic mechanism does appear to lead to lengthening.[93] In effect, telomere homeostasis is tightly integrated with cellular oxidative stress and thus mitochondrial function and health.

What we can probably say is that radiation, especially of higher energy, is likely to induce the production of ROS, both via the radiolysis of water and by damaging multiple cellular components. As redox is a key signalling mechanism, cells adjust to some degree but, ultimately, too much oxidative stress overloads the cell, particularly the mitochondrion, resulting in long-term effects – such as chronic inflammation. Furthermore, information about these effects can be passed between cells and, if they replicate, it can be passed on to their progeny. Central to this mechanism is that mitochondria are not only essential in controlling redox (as they can act as net sinks of ROS), but are also susceptible to DNA damage, in fact, more so than nuclear DNA.[17,94] This is now highlighted by new data indicating just how important mitochondrial DNA mutation is in cancer.[95] This reflects the growing consensus that the effects of radiation on mitochondria may well be important in understanding radiobiology and that via the bystander effect, also affects non-exposed cells.[64]

The overriding message is that high LET, if continuous, is not just going to induce cancer, but also mitochondrial dysfunction – probably in all tissues – resulting in a whole range of pathologies in

multiple tissues. The physiological effect will depend on the role that the mitochondrion plays in a particular cell type, the overall health of the cell, and likely, the rate of division and differentiation state of the tissue. From this, it might be inferred that the prior metabolic status of the astronaut could also influence their response to space travel. In this respect, there is evidence that exercise can offset, to some degree, the risk of secondary cancer following radiation therapy.[96] Even without gravity, the role of exercise in space is still vitally important for potentially protecting astronauts from many more factors than at first realised. A recent review found that exercise could protect, to some degree, against the effects of radiation.[97]

5.2 Non-ionising radiation and circadian rhythms

As indicated, most research has focused on the effects of higher energy photons and particles, but what of near-visible to visible wavelengths, including ultraviolet (UV), blue, green and in particular, red to near-infrared (NIR) and infrared (IR)? Certainly from NASA's perspective, the focus on non-ionising radiation is on radiofrequency emitters, natural and artificial incoherent light sources, and lasers.[98] To this, we might specifically add light-emitting diodes (LEDs). The key here is that life originating from Earth is based on chromophores, which have a range of absorbances from the UV to IR. Depending on the wavelength, and thus resonant frequency and energy, the effects can range from electron excitation to modulation of bond rotation and vibration – all of which will affect electron flow and homeostasis and, depending on dose, result in a biphasic response akin to hormesis. Photosynthesis evolved to capture this energy, quite possibly as an adaptation to the light generated in thermal vents and based on the earlier evolution of the ETC that evolved from a proton gradient.[99] So, although the source of energy is different for most plants and animals, both are environmentally integrated with light, either as a source of energy or as a source of information and/or stress.

There is a lesson here from the field of photobiomodulation (PBM), or low-level light therapy, which utilises wavelengths from 630 nm up to 1,060 nm to reduce inflammation and treat cancer as well as some neuropathological conditions. The mechanism seems to involve modulation of the ETC in the mitochondrion, inducing a redox signal.[100-103] In fact, it has been long known that light modulates components of the ETC and this observation was critical in understanding its function, as many components absorb light at different wavelengths and display a hormetic response to dose.[104]

In terms of space travel, it is well described that one of the problems that astronauts face is a disruption to their circadian rhythms, with light being one of the main zeitgebers (an environmental cue to train circadian rhythm), which is perhaps also linked to accelerated ageing.[105] Critically, ageing and the circadian rhythm are tightly linked, with ageing disrupting the circadian clock, and damage to the circadian clock accelerating ageing.[106]

Again, mitochondrial function may be key here, as mitochondria are involved in the mechanism of light modulation of key hormones involved in controlling the circadian system (e.g., melatonin and cortisol). Mitochondria both produce melatonin and are modulated by it. This has led to the idea that as the majority of melatonin is produced by non-pineal cells, and NIR penetrates far into the body and more than 70% of the photons in sunlight are NIR, and because melatonin is also a powerful antioxidant, modern living indoors, often with light sources that are blue-shifted, could be a cause of ill health.[73] Data certainly suggest that red/NIR light can both enhance bone regeneration, which involves circadian proteins,[107] and reduce blood glucose levels.[108] Indeed, it has been suggested that NIR/red light therapy could be used as a countermeasure for mitochondrial dysfunction in spaceflight-associated neuro-ocular syndrome (SANS).[109] Another stress hormone, cortisol, is also of interest, as its levels respond to blue light and can alter circadian rhythms, especially if an organism is exposed to it at night.[110] Critically, like melatonin, cortisol production involves mitochondria and, in turn, it can also modulate mitochondrial function, with low-dose/short-duration stimulating, but at high doses for a prolonged period inhibiting mitochondrial function.[111]

5.3 The biological requirements for daylight and NIR

The above also suggests that not only are circadian rhythms being disrupted in orbiting spacecraft, but the spectral shift of artificial light in spacecraft, which now eliminates red/NIR wavelengths in the switch from incandescent to LED light sources could also be key, an idea highlighted by Fosbury and Jeffery ('*The Astrophysics of Earth; Light-life interactions beyond photosynthesis. Fosbury & Jeffery, 2024*': **Publications – Herschel Society**). In effect, it is possible that many organisms, including humans, may well be dependent on exposure to NIR for optimal function.

For more than three billion years, life on Earth has evolved in the presence of daylight, a stellar (thermal) spectrum shaped by its passage through the atmosphere and oceans. Even if not directly

illuminated by daylight, life will generally have access to sources that have been exposed. Life establishes a local homeostasis determined by its structure, access to essential nutrients and a temperature of around 310 K. This kinetic temperature is determined by the need for liquid water — a planet in the "Goldilocks zone" around its star — and is optimised to support the biochemistry of life, at least temporarily during darkness. In the presence of daylight, life has access to photons originating in a stellar atmosphere which is close to thermodynamic equilibrium at nearly 6,000 K. By the time these photons reach the biosphere, their density has been greatly diluted over an astronomical unit (the distance between the Sun and the Earth), but they still retain a radiation temperature far higher than that of the local homeostasis. It is this non-equilibrium radiation that provides almost all the energy requirements for life, either directly through photosynthesis on land or at the ocean surface, or indirectly through photosynthetic chemical products consumed as food or fuel. Life has evolved to exploit this large difference between radiation and kinetic temperatures and — from an astrobiological perspective — might be expected to employ all accessible light wavelengths.

The process of photosynthesis is exquisitely complex and its detailed understanding remains a challenge to quantum biology. While it uses light from within the visible spectrum — notably blue and red — to do the 'heavy-lifting' of converting solar photons to chemical energy, it does use other longer wavelengths for directing the growth of plants. Light near the atmospheric ozone cut-off near 300 nm is important to humans and many other animals for the synthesis of the essential hormone vitamin D.

As we move from the UV — where photons can break molecular bonds — towards longer wavelengths and past the range of photosynthesis to the NIR, the behaviour of photons in living tissue changes dramatically above a wavelength of around 700 nm. From being absorption-dominated in the UV and visible spectrum due to the numerous strongly absorbing chromophores, such as chlorophyll and haemoglobin, it transitions to being scattering-dominated in the presence of absorbers that are very much weaker. This band of high translucence extends to beyond 1,000 nm where the vibrational overtones of water become the dominant absorbers. Called the biological (or tissue) transparency window (TTW), this spectral range has been the target of numerous light therapies showing a positive effect on mitochondrial performance, as indicated in Section 5.2.

Scattering of NIR light from refractive index boundaries in cellular structures in the presence of only nanoscale weak absorbers allows photons to travel many scattering-mean-free paths into body tissue until they either escape from a boundary or are absorbed. By spending longer in the tissue, the photon density inside the body can increase above that in the incoming source. As in plant leaves, where regularly spaced nanostructures can increase the probability of absorption of low absorption wavelengths,[112] it appears that regular nanostructures in animal cells, such as the endoplasmic reticulum and mitochondria, can also increase the coupling of external NIR radiation with biochemistry. Thus the body can be considered a highly adapted harvester of NIR light.[73] The light transmission of a hand at a wavelength centred at 850 nm is shown in Figure 3.

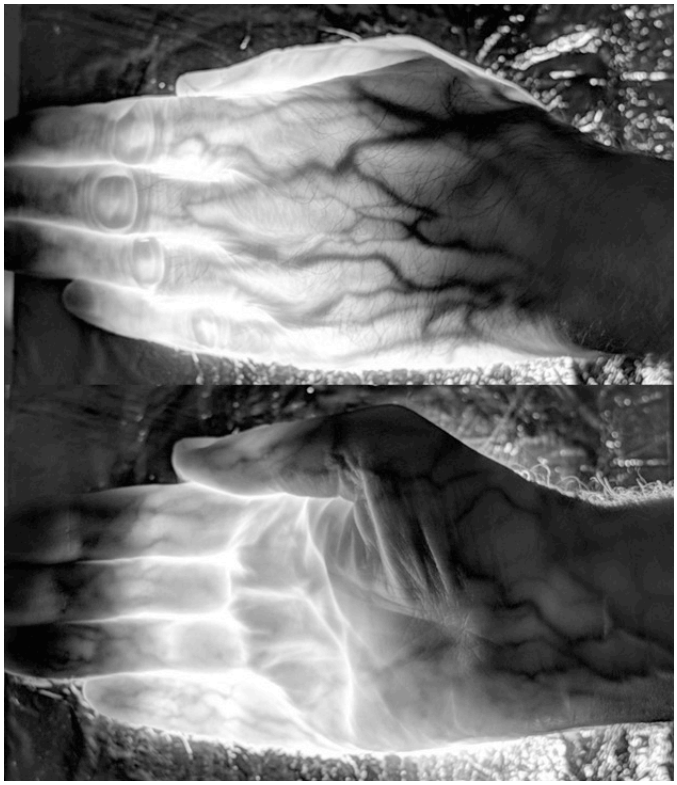

Figure 3. The light transmission of a human hand illuminated by an 850 nm LED source.
Note the appearance of the veins near the upper surface of the hand and the transparency of the bones.
Image supplied by Bob Fosbury and Glen Jeffery.

Work is needed to identify these weak absorbers that couple to the NIR radiation field. It is thought that the excitation of low-lying energy levels in many biomolecules can increase their ability to react

with one another by removing or reducing the kinetic inhibitions imposed by the low temperature of homeostasis. In contrast to photosynthesis, where the solar photons are actually the energy source of the resulting sugars, the lower energy NIR photons act more as a reaction-enabling catalyst driving the mitochondrial ETC. One interaction that has been observed is the direct photon excitation of a ground-state triplet oxygen molecule to the highly reactive singlet state using light in the Fraunhofer telluric A- and B-bands (*work in preparation*).

The regular changes in the brightness and colour of natural light during the circadian cycle alter the balance between the thermal and radiative contribution to homeostasis and so imprint a daily variation in metabolic activity. The importance of the circadian cycle for long-duration spaceflight has been recognised and the current lighting on the ISS is adjusted accordingly by varying brightness and colour temperature of white LED emitters spanning the visible spectrum.[113] However, insofar as we are aware, there are no NIR emitters associated with general lighting at any time during the cycle.

The effects of NIR starvation on the ground, generally associated with extended exposure to the built environment, are becoming increasingly apparent as a slow degradation of general public health, especially in the prominence of diseases associated with ageing and degraded mitochondrial function. For example, a recent double-blind, randomised placebo-controlled study found that PBM treatment using NIR at 850 nm, given for three hours per day, five days per week for four months, resulted in significant improvements in mood, well-being, and reductions in both inflammatory cytokines and resting heart rate – but only when given in the winter. The dose was 6.5 $J.cm^{-2}$ (2.8 x 10^{19} photons cm^{-2}, or 46 $\mu mol.cm^{-2}$). Although the dose was not optimised, the authors made the point that, during the winter, most people would be indoors and not exposed to much NIR, while in the summer they would be as they would be outside more and so the dose would be similar to that possible on a clear summer's day in the Netherlands.[114] Indeed, some authors are now suggesting that the benefits of sunlight may not necessarily all come from the production of vitamin D, but rather from NIR, which explains some of the confounding results from clinical trials looking at the use of vitamin D for health.[115]

With little or no access to light longward of around 750nm, astronauts and experimental animals during long-duration missions are an extreme exemplar of the NIR starvation that is increasingly afflicting the population living in the modern built environment on the ground. In addition to the

almost complete dominance of the NIR-dark white LED lighting, window glass is being tailored, largely for reasons of thermal control, to transmit only visible light, see Figure 4.

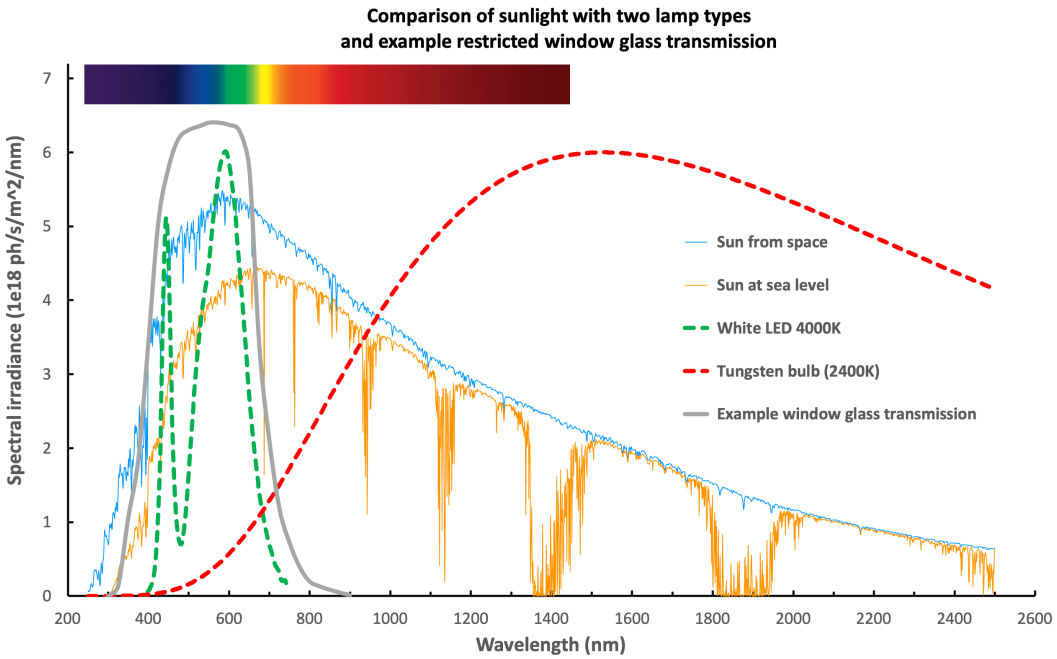

Figure 4. The photon spectral irradiance of the Sun in space (blue line) and the typical solar light reaching the ground through an airmass of 1.5 (orange line).
On an arbitrary scale, two lamp irradiances are shown: a 4000 K white LED (green dashed) and a tungsten filament lamp at 2400 K (red-dashed). The grey line represents the approximate transmission (peaking near 60%) of "visible light only" window glass offered by major window glass manufacturers. This plot illustrates the severely restricted spectrum in the modern built environment on Earth and on the ISS. Note that the tissue transparency window (TTW) extends from ~ 700 nm to around 1300 nm. The dominant absorption bands in the sea-level spectrum are from water vapour but include the Fraunhofer A- and B-bands from molecular oxygen near 760 and 690 nm.

Figure supplied by Bob Fosbury and Glen Jeffery.

While the space environment differs from a ground-based artificially-lit one in terms of gravity and other factors discussed in this report, it would be revealing to compare the health effects experienced by the ISS astronauts with inhabitants of environments on Earth such as submarines and, to some extent, hospitals (especially ICUs), care homes for the elderly, offices, factories, etc. where the lighting is generally artificial and access to daylight very limited. This may greatly aid the task of distinguishing

between the factors contributing to mitochondrial dysfunction and premature ageing on the ground and in space.

History may be repeating itself, as our current long-duration space explorers experience a 21st-century version of scurvy where the absence of vitamin C is replaced by NIR starvation, which suggests that astronauts may require a daily dose of NIR.

5.4 Non-ionising radiation in the radio frequency and microwave ranges

Non-ionising radiation, including radio frequencies (RF) and microwaves, has been an area of growing research in both terrestrial and space environments. On Earth, there is substantial evidence that prolonged exposure to high levels of RF and microwave radiation can lead to thermal effects, including tissue heating and possible disruption of cellular functions.[116-118] However, the non-thermal effects of RF and microwave exposure, especially in long-duration space travel, remain less well understood.[119,120] While astronauts are exposed to a controlled environment, the space setting introduces unique variables, including reduced gravitational forces and altered circadian rhythms, which may influence how the body responds to such radiation.

The state of current knowledge suggests that, while acute exposure to RF and microwaves within regulatory safety limits may not pose immediate threats, the cumulative effects of prolonged exposure in space conditions could exacerbate underlying biological stresses, such as mitochondrial dysfunction or oxidative stress.[121,122] Understanding the molecular mechanisms, particularly how RF and microwave radiation (both its electric and magnetic field components) interact with cellular components like membranes, proteins, and DNA, is crucial. Space missions introduce variables such as altered electromagnetic fields and increased exposure to different radiation spectra, making it imperative to deepen our understanding of how these factors influence astronaut health over time.

Future research must focus on uncovering the molecular pathways affected by non-ionising radiation, especially in space. This includes examining how such radiation might disrupt redox signalling, impact mitochondrial efficiency, or affect cellular homeostasis. A clearer understanding of these mechanisms is, therefore, essential to developing protective measures for long-term human space exploration.

5.5 Electromagnetic fields

Electric and magnetic fields are intimately related and were originally described as separate phenomena but are both components of an EMF. Electric fields are generated by charged particles, for instance in biology, where they are created by charge gradients between positive and negative ions. Magnetic fields can be generated by the movement of charge, such as when a current flows in a wire, or by a permanent magnet in which the magnetic fields generated by the individual electrons of the magnetic material are aligned. In effect, life is electrical, an idea that has been long suggested and is now being proven.[26,46,47]

Life generates both dynamic and quasi-static electric fields, as the movement and gradient of charge result in large electric potentials – in the case of the mitochondrion, the field strength is comparable to a bolt of lightning.[123] In fact, all membranes support a large charge across them, which is maintained by a constant pumping of ions – the result of fundamental dissipative processes. Certainly for the mitochondrion, this has led to it being labelled a "flux capacitor", and is likely reflective of how life started.[25] It therefore seems that not only are these fields important in everyday homeostasis, but it means that, under some circumstances, biology will be sensitive to external fields. Indeed, some organisms have evolved to detect electric fields based on voltage-sensitive ion channels, while others appear to have evolved methods to detect the Earth's magnetic field based on free radical-based electron spin chemistry (see Figure 5). Exactly how much man-made fields, such as those generated by power lines or cell phones, affect life is still being investigated.[26,124]

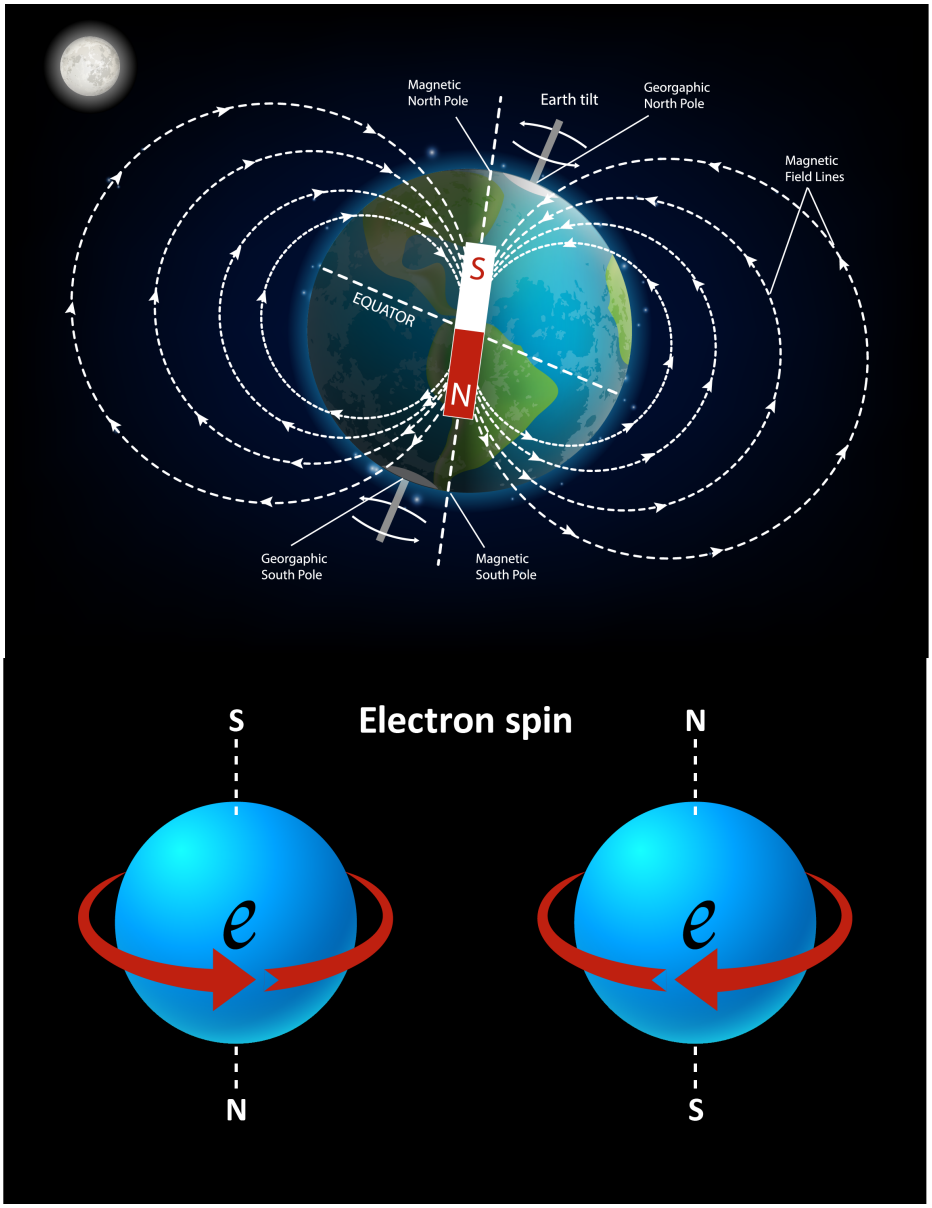

Figure 5. The influence of the Earth's magnetic field on a pair of electrons.
The diagram shows a radical pair, comprising two electrons, in the Earth's magnetic field. The Earth has a static magnetic field with a North and South pole. The chemical outcomes of radical pair reactions are sensitive to external magnetic fields due to the interacting spins of the electrons.

Figure supplied by The Guy Foundation.

This suggests that the "electrome" is just as important as, say, the "proteome" – in that life could not exist without its electrical dimension. In biology, much of the electrome is created by the movement

of ions, including Na^+, K^+, H^+, Ca^{++}, Cl^-, HCO^-, etc. Just as information is stored in genes, so it is in electromagnetic fields. Indeed, when this charge stops flowing, death ensues.[125] Life has long been recognised as electrical since the days of Volta and Galvani,[26,46] and bioelectricity is now recognised as pivotal in cognition, regeneration and cancer, and can be manipulated by altering ion channel activity.[126]

From an origins of life perspective, especially in relation to the movement of charge, there is a modern phenomenon that perhaps reflects this, and that is “uncoupling”, which all life demonstrates. In effect all life seems to have a built-in “short-circuit”, where ions are allowed to leak back through a membrane, thereby forming a futile cycle. Although it seems very wasteful, it generates heat and, from the far from equilibrium, self-organising thermodynamic principle, it describes why life is the way it is. It is key, for instance, in how mitochondria control signalling, membrane potential and redox. It would suggest that the movement of charge, and thus the generation of electromagnetic fields, were integrated right at the beginning of life as a kind of self-organising dissipating homeostatic structure, in effect, a region of negative entropy.[41] Today, these fields could well be essential in everyday homeostasis, with the ETC in the mitochondrion generating a strong field (see Figure 6).

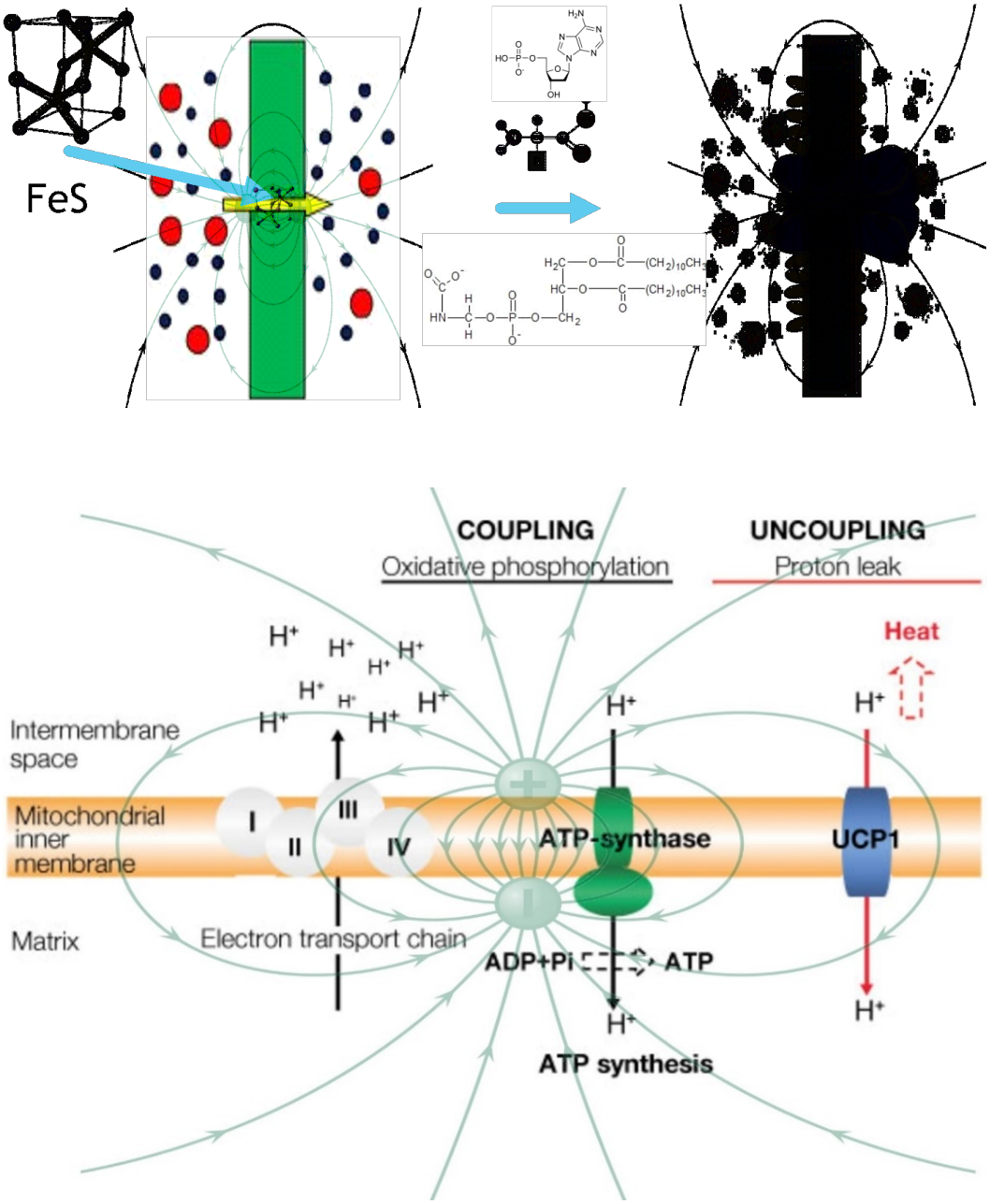

Figure 6. From origins to the electron transport chain – a biofield generator?
The origins of the ETC and fields could arguably be traced back to the beginning of life, where charge flow interacted with molecules to create the first ion channels in a membrane (top panel). In modern times, one of the most important generators of endogenous electric fields in biology could therefore be the electron-driven charge separation of protons across the inner mitochondrial membrane (lower panel). This is integrated with the movement of other ions, such as K^+, Na^+, Ca^{++}, Cl^- and HCO^-, not just within the mitochondrion, but also across all other membranes, hence linking the function of the mitochondrion to the bioelectric fields that surround the entire cell.

Figure supplied by Alistair Nunn

While electric fields act on charge, magnetic fields act on spin. In this sense, the Earth's magnetic field interacts directly with biological systems, rather than merely screening them from radiation. It does this by changing the spin states of molecules and the chemistry that depends on these spin states. This of course does raise questions about what happens to life when the Earth's magnetic field decreases and reverses – and even when it started – the latter question is however still proving difficult to ascertain.[127] Indeed, the jury is still out as to whether the reversal of the Earth's magnetic field has had any effect on biology – although some theories have suggested that it could have had a dramatic effect on weather patterns due to changes in UV irradiation and ozone levels.[128] Certainly, there is evidence that a hypomagnetic field can negatively affect biology, and it has been speculated that reversals of the Earth's geomagnetic fields, for a number of reasons, could have resulted in extinctions, and may have been important in the origins of life.[72]

There is also interest in the relationship between molecular chirality, why life is largely homochiral involving magnetite and spin, and the idea of chiral-induced spin selectivity (CISS).[129,130] Magnetite is thought to have played a key role in the origins of life due to its existence in thermal vents and its ability to catalyse chemical reactions essential for life today.[131] This, again, hints that understanding the origins of life may give clues to the factors that affect it today. Certainly, the Earth's magnetic field varies from place to place,[132] whether this variation locally affects health is an interesting question.

Biological systems have evolved their chemical reactions within the Earth's specific fields and are clearly affected by changes in the field strength, both above, and critically, below. This means that travel to destinations that have no magnetic field, for example, the Moon or Mars, could have fundamental effects on the chemistry integral to life.[54,55] A further aspect is that it is becoming apparent that circadian shifts in the Earth's magnetic field also appear to be a zeitgeber, and likely interact with the classical light-driven cryptochromes also involved in magnetic sensitivity. In short, a hypomagnetic field could interfere with circadian rhythms.[133] The key message is that not only are static electric fields important in biology, but through the property of spin, it would seem so are static magnetic fields – both endogenous and exogenous. Much like the suggested "NIR starvation" idea, astronauts could also suffer from "magnetic starvation", suggesting that, for optimal health, the Earth's magnetic field may need to be reproduced in some way in a spacecraft.

5.6 Gravity – a key organisational stress for life

Life started and evolved under the influence of gravity generated by the mass of the Earth, a primal force that has remained largely unchanged for billions of years. The only variation has been the periodic fluctuations induced by the gravitational effects of other bodies, such as the Moon and the Sun, which could well also have some gravitational influences on life in ways not previously appreciated (see Figure 7 for details).

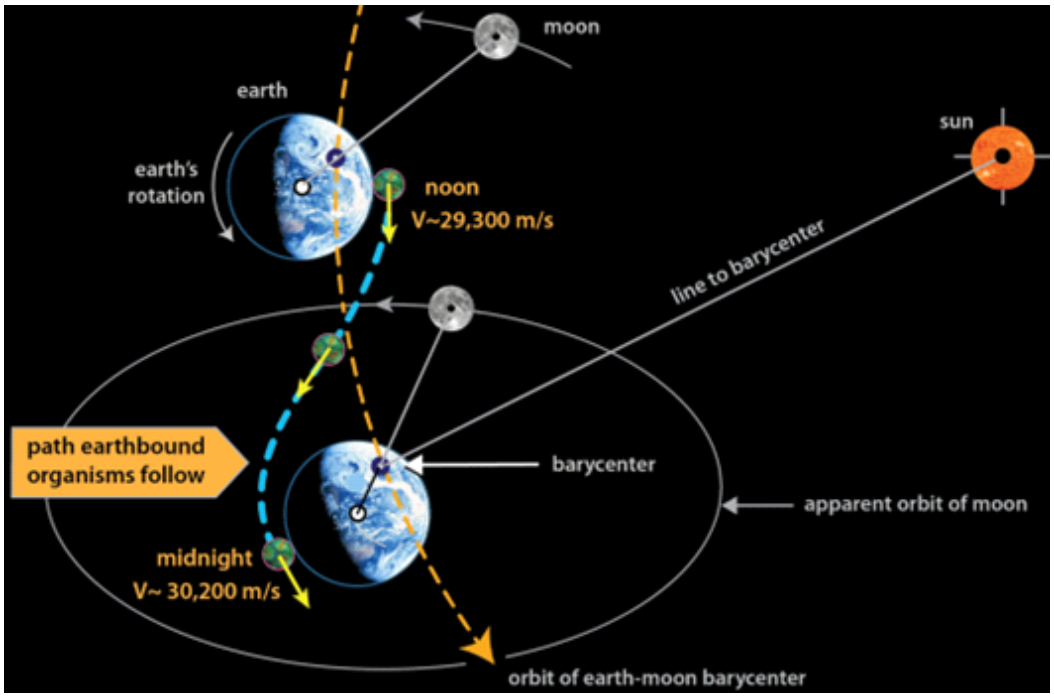

Figure 7. The different gravitational forces experienced on Earth.
This raises the interesting possibility that the wobble generated by the Earth/Moon/Sun barycentre, due to nuclear inertia in the atom (protons and neutrons are much, much heavier than electrons), could affect all atoms in the body – possibly suggesting a way that life could be coupled to this rhythm.

Figure supplied by Steve Thorne, The Copernican Project

However, it has been long recognised that one of the main problems for humans, certainly in orbit, is that astronauts are in free fall, which seems to cause serious physiological changes. One of the most important is the removal of the key organisational "stress" of gravity, a force that life on Earth has never been without. This principle is called "tension-induced integrity" or "tensegrity" (see Figure 8), with the cytoskeleton playing a key role.[134] Critically, mitochondrial function is intimately integrated

with the cytoskeleton and ion channels.[135] Indeed the entire cell is a highly sensitive mechanotransductor system,[136] with redox being pivotal.[137] Interestingly, there is now evidence that the radical pair/spin mechanism can also affect microtubule reorganisation.[138] If this is taken with the observation that prokaryotes also have many antecedents to eukaryotic cytoskeleton proteins, and thus also exhibit mechanotransduction, which could also be important in how they adapt in microgravity,[139] then understanding the evolutionary origins of modern multicellular cytoskeleton and the relationship between spin and redox could be informative. Certainly, the underlying aspects of mechanobiology in microgravity are being applied to its effects on cancer [140] and cardiovascular disease (CVD),[141] as well as plant growth [142] – with microgravity experiments unveiling a role for red light in root phototropism.[143] This all indicates that changes in cell structure caused by reductions in the compressing force of gravity are likely to cause massive alterations in cell biology – particularly in the bioelectric field – but the effect could well be also affected by changes in light spectra and the magnetic field. Although it might well be the case that complex multicellular organisms may be much more sensitive to reduced gravity, as it may affect how their bioelectric fields overlap and interact, given their prokaryotic origins, these factors will also affect them.

Interestingly, a recent experiment on the ISS showed that cells placed in a small centrifuge were much less stressed than those exposed to microgravity, which displayed multiple indicators of ageing, such as inflammation and senescence.[144] Similarly, putting fruit flies into a centrifuge on the ISS also seemed to partially protect them against space-induced neurological defects.[145] A key point here is that one of the best methods to offset some of the problems of microgravity is to exercise, which is well-known to stimulate mitochondrial function throughout the body[146] although, even with this, astronauts still develop an AAP.[3] Hypergravity can evidently induce beneficial changes,[147] and thus serves as an example of hormesis, and it could simply be that, without gravity, routine levels of exercise are insufficient.

However, additional exercise requires fuel and thus additional food and, therefore, carries extra mass, and this could also be a problem in longer space missions, especially if muscle mass needs to be maintained.[148] We also suggest there is a perhaps deeper, and much simpler consideration here, and this is that humans may have likely evolved to have specific ratios of active muscle, which is generally anti-inflammatory, to adipose tissue, which can become inflammatory.[149] It is becoming accepted that fat can be viewed as part of the endocrine/immune system, but so can muscle, which is why having

sufficient actively used muscle likely helps protect against viral infections, such as SARs-CoV-2.[23,24] Simply removing gravity results in loss of muscle and, most likely, a real tendency to put on fat, which could become inflammatory – especially if other space-specific factors induce oxidative stress, say, in mitochondria. Another way to view this is that if life is a dissipative, far-from-equilibrium, self-organising structure, then a human's adaptative metabolic envelope is dependent on a certain amount of energy flux. Thus, removing gravity largely removes this component. From another viewpoint, gravity has been, and remains, a key component driving the energetics around the formation of those dissipative structures we call life.

However, as is well described, there are many other problems, including altered fluid dynamics, which could be contributing – for instance, it is thought to be a central precipitating factor in SANS,[150] although, even in this condition, mitochondrial dysfunction could also be important.[151] The bottom line is that it is very likely that when billion-year-old organising "stress" is removed, a key structural organising force is lost, which is perhaps most obviously exhibited by altering the 3D structure of proteins of say the cytoskeleton of individual cells and of large super-complex components, such as those that make up the ETC. Inter- and intra-molecular distance is pivotal in the chemistry of life. This becomes all the more relevant if life has tuned these distances to optimise for quantum effects, such as coherent electron transfer or tunnelling.[152]

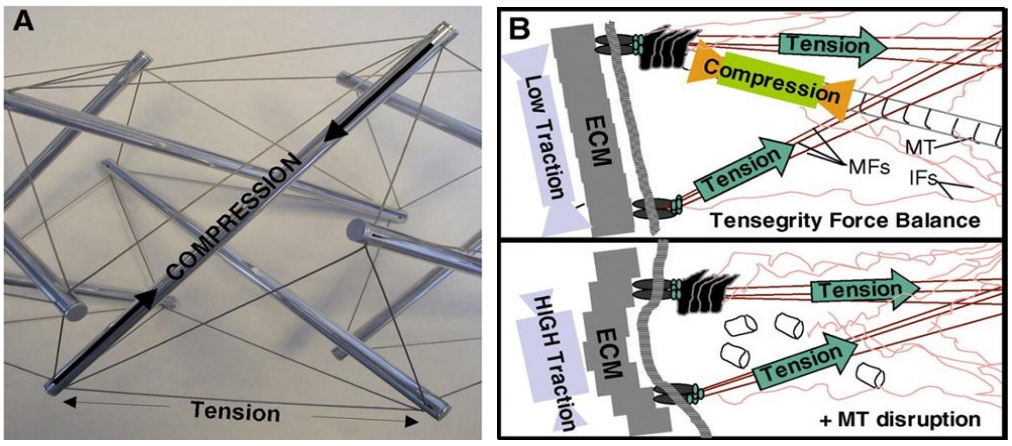

Figure 8. The mechanical forces of tensegrity are likely relevant to life function.
The diagram shows the different mechanical forces of tension and compression in different materials. In biological materials, the extracellular matrix (ECM) and the microtubules, for example, would be involved in maintaining tensegrity. It is likely that life, especially complex life, is reliant on this for optimal function.

Image reproduced with permission, D.E. Ingber, J Cell Sci (2003) 116 (7): 1157–1173 DOI: 10.1242/jcs.00359.

Inertia refers to the fact that matter will remain at rest or will not change its state of motion unless it is subject to an unbalanced force. It is often associated with the gravitational force, which acts on mass but, in general, any force can overcome inertia. The commonly accepted effect is the gravitational pull of the Earth that manifests as weight, which the lack of as discussed, results in problems, especially in orbit. However, the Earth does not exist on its own in the solar system, so there are other gravitational interactions with other objects such as the Sun and Moon. The effects are well described, for instance, in relation to the tides. What is perhaps less appreciated is that, although the Earth appears to move along a highly organised orbital pathway, because it has a centre of gravity that is combined with the Moon, it has an offset barycentre resulting in a gravitational periodicity. In effect, the Earth "wobbles". This raises the question as to whether biological function has become coupled to this periodicity as, in effect, could this wobble also be a zeitgeber. Figure 7 outlines the concept. The question is of course whether organisms are able to detect this as one effect could be related to changes in the magnetic environment due to the wobble, but the possibility does exist that, as the nuclei of atoms have greater mass than their surrounding electron clouds, there could be a subtle nuclear wobble that affects the quantum status of the atom. The cumulative effect of this might result in a biological signal.

5.7 Outside the adaptive metabolic envelope

The apparent message coming from research into the health of astronauts is that they could be developing what appears to be an AAP. Perhaps the simplest explanation is that being in space, at least using the current spacecraft, is placing them outside their evolved Goldilocks zone, and beyond their ability to adapt (Figure 9) – in effect, outside of their own "flight envelope".

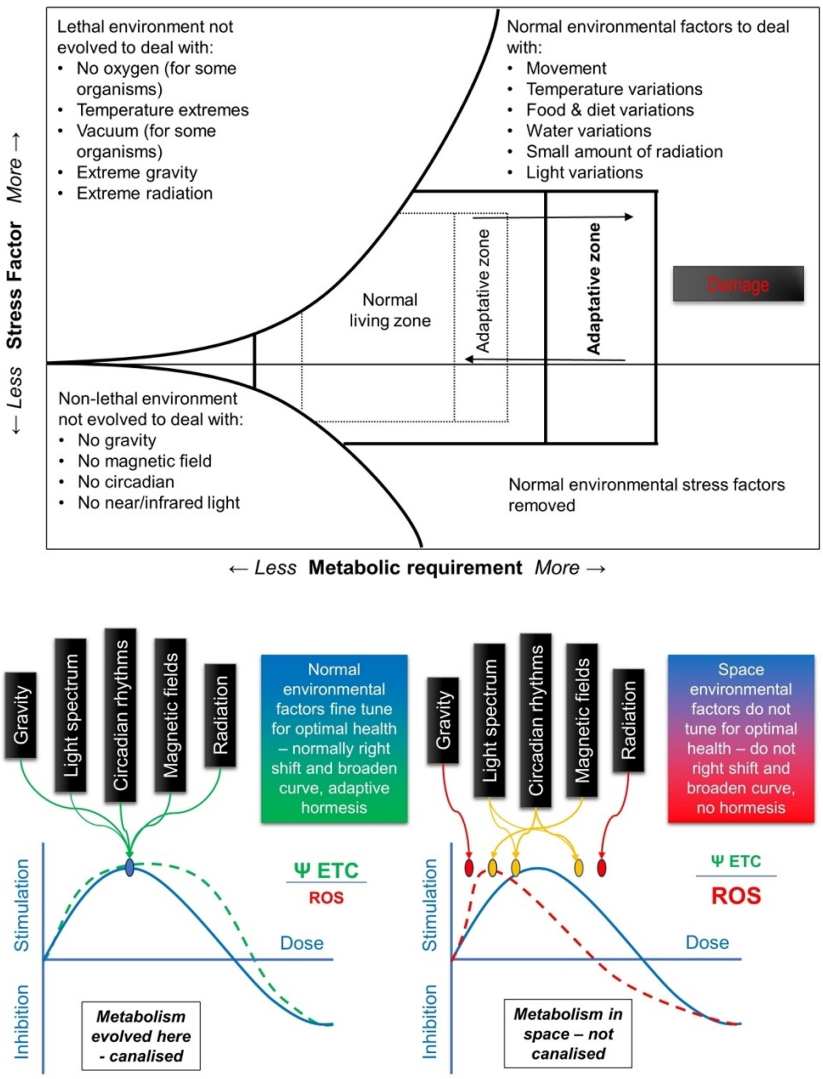

Figure 9. Proposed effects of humans going outside their metabolic envelopes when in space.
Going into space puts astronauts beyond their evolved adaptive metabolic envelope (top panel, based on a classic aircraft flight envelope, lower panel, based on a biphasic adaptive curve). Some factors are required for optimal function, such as gravity, a magnetic field, NIR, and circadian zeitgebers, while others directly cause oxidative stress and damage, such as excessive low, and especially, high LET. The result is inflammation and potentially, an accelerated ageing phenotype due to disrupted electron flow which is not immediately lethal, but may increase the risk of morbidity. Some are almost instantly lethal, such as a vacuum or excessive temperatures.

Figures supplied by Alistair Nunn

The reason is perhaps fairly straightforward. Life has become canalised to function optimally in the conditions in which it evolved and, as the concept of hormesis indicates, the limits are set by upper and lower boundaries of historical environment exposure. When it goes outside these limits, the

system malfunctions, as indicated by alterations in redox, which for complex organisms results in inflammation as a signal of attempted adaptation. The key here is that a lack of a certain kind of stress is just as important as too much, as the former induces optimal structure, while the latter causes damage. This principle can be derived from the thermodynamics around dissipation, adaptation and self-organisation of far-from-equilibrium structures, which is one theory as to how life started, and why, potentially, it ages. This concept is much easier to perceive if life is viewed as an emergent property of the planet and explains why there is such a wide variety of organism lifespans, but also why, within individual organisms, there is a constant turnover of components which reflects natural selection at all scales. Increased inflammation is just a marker for an organism that is not "fit" for its particular niche.[42]

The implications for this are far-reaching, especially in terms of which organisms may be able to adapt. Short-lived prokaryotes may be able to adapt through genetic selection, yet longer-lived complex ones, like humans, or possibly, plants, may not. Clearly, plants do age, although less is known about the mechanisms – but they are capable of extreme longevity[153,154] – which may be an interesting avenue to explore, especially in relation to stem cells. What this might do to the relationship between animals and plants and their respective microbiomes after long periods of space travel is also a significant question. For example, prokaryotes are extremely resilient and can survive in all sorts of habitats, including outer space and various niches in spacecraft. However, as it is for animals and plants, space is stressful for them, but there is a huge variation in how different species adapt, some grow better, while some do not, and some create stronger biofilms or become more virulent. They clearly evolve, and certainly alter their metabolisms and, thereby, how they interact with each other.[155] One particular species, because of its association with humans as an opportunistic pathogen and ability to develop multi-drug resistance, *E. bugandensis,* has been studied on the ISS and has been found to adapt and evolve, not only altering how it interacts with other microbes, but also raising the possibility of increased infection risk.[156] As would be predicted, the microbiome of astronauts does change, and there is evidence of microbiome transfer between astronauts, as well as associated immune system changes and reactivation of viruses – all of which could be of concern on long-duration deep space missions.[157,158] One possibility is that given the ability of prokaryotes to evolve much faster than their hosts, one wonders what might be healthier when humans first arrive on Mars, the astronaut or their microbiota.

Chapter 5 key points

- In this section we outlined how Earth's environment led to the evolution of a specific 'metabolic flight envelope' of life, which when exposed to the unique space environment, may not be able to adapt.
- The space environment differs from Earth in the following broad categories, some of which the spacecraft can compensate for, even if only partially, or not at all in some cases. We list them in order of how well-established the research areas currently are and indicate the degree to which compensation is possible on a spacecraft:
    - Loss of gravity – cannot compensate for with current technology, although could be quite soon (designs for centrifugal systems are well advanced).
    - Increased electromagnetic ionising radiation, such as gamma and X-rays (low LET) – partial shielding.
    - Increased charged particle radiation, such as protons and heavier elements (high LET) – some shielding for protons, but not much for iron nuclei.
    - Increased electromagnetic non-ionising radiation, for instance, ultraviolet and infrared light – nearly complete shielding (but the loss of some IR could be a problem).
    - Loss of Earth's magnetic field away from LEO – cannot compensate for with current technology.
- Some of the effects of this changed environment are the following:
    - Cellular damage and structural changes
    - Increased oxidative stress and reactive oxygen imbalance
    - Metabolic disruption
    - Disrupted circadian rhythms
    - Microbiome changes
    - An AAP

6 | Implications

As discussed, it is possible that astronauts could be developing an AAP.[1,2] This could have far-reaching implications. The recent report, '*Thriving in Space: Ensuring the Future of Biological and Physical Sciences Research: A Decadal Survey for 2023-2032'* confirms the breadth of negative physiological effects that result from being exposed to space environments. These include musculoskeletal, cardiovascular, and pulmonary changes, as well as ocular problems and neurological effects. Some effects occur quickly, such as neurovestibular problems, while there are also post-flight disturbances in perception, spatial orientation, posture, and gait. The immune system experiences profound alterations with latent viruses reactivated. There are also changes in metabolism, likely associated with mitochondrial dysfunction and the development of insulin resistance and prediabetes. The report also raises the question of reproduction and multi-generational physiological outcomes. While some research has been done, very little is known about the effects on sex-dependent physiological function and human reproduction, particularly embryonic and early-stage growth. Ultimately, the report asks the question, "Can humans adapt to living in space?"[11] The similarities and sequelae to other stressors, such as COVID-19 infection and the reactivation of other viruses, and the development of chronic morbidity, for instance, "long-COVID" and a possible role for mitochondrial dysfunction,[23,159] is perhaps a concern here.

Critically, this emerging need for a consolidation of the effects of the space environment on health is becoming increasingly recognised. For example, the journal Nature has worked with a leading group of space scientists to publish, in a coordinated fashion, the Space Omics and Medical Atlas (SOMA) package of scientific papers concerning aerospace medicine and space biology. This has involved more than 100 institutions from multiple countries and is the largest-ever compendium published to date. It covers transcriptome and epigenomic data, information on cellular states and dynamics, advances in our understanding of the microbiome, as well as known mitochondrial changes in response to spaceflight. It also addresses the use of new technologies, such as AI and computational frameworks to study and understand these changes. It also addresses ethics, as well as how we may mitigate the risks of space travel. The index can be found here: **Space Omics and Medical Atlas (SOMA) across orbits (nature.com).**

What is clear is that some systems are probably trying to adapt, but the effect is ultimately maladaptive. For example, in space-flight-induced anaemia, not only does the production of red blood cells decline, but it seems the rate of haemolysis increases. This, in turn, could be related to a fall in antioxidant capacity and increases in ROS, membrane rigidity and a rise in inflammatory tone. There is also an increase of fat in bones and fluid shifts.[160] It is also now being recognised that astronauts appear to be developing clotting problems.[161] A parallel here, again, is the potential for mitochondrial dysfunction to influence this, as platelets are reliant on mitochondrial function. This could explain some of the clotting problems seen in patients with SARs-CoV-2 and the metabolic syndrome – especially when inflammation is taken into account.[23] This suggests that, certainly for humans, our systems cannot adapt, because we have never before been exposed to this particular set of environmental circumstances, and the result is simply a generalised stress response, which is well-known to be associated with an AAP. It might be interesting to directly compare this emerging space-induced AAP with the well-described markers and definers of a poor, lifestyle-induced metabolic syndrome, which are raised blood pressure, insulin resistance, central obesity and reduced HDL-cholesterol, as well as altered blood clotting characteristics. A key underlying mechanism seems to be related to chronic inflammation and mitochondrial dysfunction, which also results in an AAP [4] – potentially a form of "space-induced metabolic syndrome" (SIMS). Clearly, measuring ageing is going to be important, which suggests that other emerging markers, such as miR-29,[162] could be useful.

Perhaps the final point here, which relates to the propensity to develop SIMS and mitochondrial dysfunction, is that the vast majority of astronauts selected have been male, young, and very fit, with top-of-the-class cognitive functioning and hand-eye coordination. As is often quoted in popular culture, they are "the best of the best". In effect, nearly all of the available physiological data is based on a very small population of very healthy individuals, which is not representative of the general population. There is also a dearth of data on females or even those from different ethnic backgrounds. How an "average" human, especially an older unfit one, may react to extended space travel has not really been investigated, but all the evidence would suggest they could be more badly affected than a young, highly trained, and extremely fit test pilot. Their loss of function could have a relatively greater impact on performance, as they would have less metabolic reserve to begin with. The effects of this could be magnified with extended duration, especially in the harsher conditions beyond LEO.

6.1 A focus on mitochondria

Despite the growing evidence that space travel has distinct negative physiological effects, it has so far been difficult to draw conclusions or even to pinpoint the precise mechanisms underlying these physiological changes. However, the observation that going into space appears to precipitate mitochondrial dysfunction is perhaps a clue and, from this, especially if we embrace the quantum aspects relating to redox chemistry, we might be able to suggest a common mechanism. This, in turn, might indicate which factors in space are the most and least important in causing disrupted metabolism, how they may interact and why, and what may need to be done to mitigate these effects. It will likely be a complex interaction.

Accepting that going into space does result in an AAP is a big step forward, as it provides guidance as to both a unifying mechanism, and what may need to be done. It also offers tremendous potential insight into the processes of ageing itself, which are still not fully understood. Perhaps the clearest link here is that continued mitochondrial dysfunction will alter the epigenome, which if it is related to "inflammaging", is likely to be conclusive. Certainly, evidence is that being in space does result in profound immunological changes and increased inflammatory tone.[163] As the "bacteria within", mitochondria are central to inflammation and immune responses,[164] so we must take heed of their dysfunction. Every part of the space environment is likely to challenge them, including microgravity, increased radiation, altered light spectra and magnetic fields, as well as circadian disruption (see Figure 10).

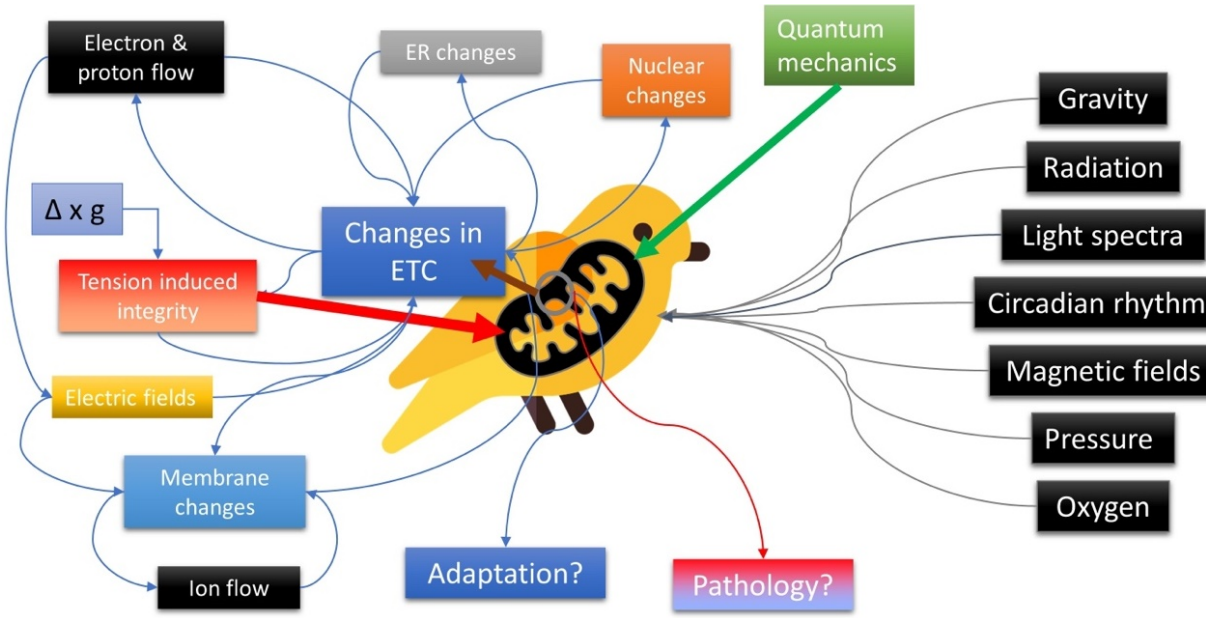

Figure 10. The mitochondrial canary in the metabolic coalmine.
Key – ER: endoplasmic reticulum; ETC: electron transport chain; Δ x g: changes in gravity. Evidence indicates that astronauts develop mitochondrial dysfunction, suggesting it is a good marker for stress. Nearly all normal Earth-bound environmental factors are changed in space, which seems to be stressing organisms by altering electron flow in multiple ways.

Figure supplied by Alistair Nunn

This focus on mitochondria is clearly applicable to animals, but what about plants? Mitochondria are also critical to plant function, in particular, not only being key in energy metabolism but also in controlling oxidative stress.[165] Furthermore, plant cells swap mitochondria and undergo dynamic changes,[166,167] and given their evolutionary common heritage, it is no surprise that they are in many ways very similar to animal mitochondria. This of course raises an interesting, if under-investigated question. Given the importance of the antioxidant effects of phenolic plant compounds in animal cells and potentially astronauts, how important are they in plants? Phenolic compounds are well-known to be part of the plant's stress resistance strategy, perhaps originally arising from their ability to both act as sunscreens and antioxidants, which could certainly begin to explain why they work in animals and modulate their mitochondria – perhaps hinting that their protective effects involve dissipation.[43,44] Critically, there is evidence that phenolic compounds in the plant are also important in protecting mitochondrial enzymes.[168]

Plants become stressed by going into space, as evidenced by the upregulation of heat shock factors (HSFs). These factors are activated in response to almost any stress, are conserved in most organisms, and act to maintain cellular homeostasis.[169] This might suggest that we also need to consider the effects of the space environment on plant mitochondria and whether the upregulation of phenolics by the plant may help to some degree in protecting them, and their host plant, from oxidative stress. But this also suggests that plants grown in space may also provide a more suitable source of compounds that could protect the astronaut. The underlying concept is perhaps explained by the xenohormesis hypothesis, whereby phenolic compounds produced during stress by plants can also activate similar pathways in animals involving the sirtuin pathway, resulting in improved stress resistance and longevity.[170,171] Sirtuins are an ancient group of NAD+-dependent deacetylases found in all phyla of life.[172] Although they are also found in plants, the research is much less developed.[173] As they are metabolic sensors, they play a central role in maintaining mitochondrial function in response to changing conditions.[174] This suggests that studying plant mitochondria and their interaction with their own phenolic metabolism and sirtuin function when exposed to the space environment could be a useful strategy in understanding how they might, in turn, offer some protection to astronauts.

6.2 Availability of medical and physiological data

To date, there doesn't appear to be a readily available database that provides information on the standardisation of tests, medical protocols, or data collection and collation for astronaut health. This probably arises in part from the need to prioritise solving the extreme technical challenge of simply getting people into space and getting them back alive, and thus the pioneering nature of the project means that individuals accept the very real and immediate threats to their lives. This certainly reflects the early days of crew selection, where not only was being a test pilot helpful, but so was having degrees in the sciences. Unfortunately, this has probably resulted in the downplaying of the need to study a full and detailed long-term picture of astronaut health due to other priorities, which is needed to understand impacts on mitochondrial health particularly, as the common factor in many post-space travel pathologies. However, programmes have been set up, including the US Longitudinal Study of Astronaut Health (LSAH, link to newsletters here: **Lifetime Surveillance of Astronaut Health (LSAH) NASA**), which aims to follow up on the health status of astronauts every year. As the space health

research community expands there is a real opportunity to develop an internationally accepted approach, across both private and public enterprises.

There may also be other models which could provide useful data, for instance, on the effects of changing light conditions on captive populations (e.g., in the civilian sector where people are exposed to only natural light in care homes or hospitals). Other potential models of these populations could include crews on ships or those serving on submarines. Data on submariners could be particularly interesting, as their environment does mimic, in many ways, that of spacecraft.

6.3 Current space exposure and astronaut health data limit future health projections

When trying to take the further step of generalising the experience of past astronauts to those in the future who will settle in space, several potential problems arise. The first is that the majority of the 670+ astronauts who have previously travelled to space were not in orbit for more than six months, often for far less time, and most were within LEO. Second, the astronauts were very healthy, having undergone rigorous training to become aerobically fit and cognitively high functioning and thus are not a representative cross-section of the wider population. Third, there is little available metabolic profile data on the astronauts who have already been in space, either in the short term or, in particular, in the long term, to enable us to ascertain whether they are exhibiting an AAP.

6.4 Duty of care

There is also a further problem as space technology matures and becomes safer and more reliable – it will become accessible to a broader selection of people. As is clear, a significant proportion of the population in many countries do not live in optimal health due to a sedentary lifestyle and a poor diet. This lifestyle is associated with poor mitochondrial function, an AAP, and increased rates of numerous diseases, such as cardiovascular disease, cancer and diabetes.[4] This then raises issues of duty of care and legal concerns that, even if space travel in terms of engineering can be made relatively safe, sending less fit individuals into what potentially is an environment that will severely challenge their metabolic health could present a problem.

Chapter 6 key points

- Space travel induces a host of pathologies, ranging from cardiovascular to neurological and immune dysfunction, which could be expressed as an AAP.
- It is yet to be determined what the full effects of space flight might be on the reproductive parameters of humans, and other organisms, both within and across generations.
- Mitochondrial dysfunction could be the “metabolic space canary”, suggesting a common mechanism underlying the variety of pathologies seen in astronauts, as well as other eukaryotic organisms. Mitochondria are known to be sensitive to all aspects of the changed space environment.
- To date, most astronauts have been very fit and healthy. The effects of space travel on a less metabolically healthy population could be more severe.
- There is a lack of comprehensive astronaut health data, especially across a wide range of space environments, travel times, physiologies and follow-up periods.
- There is a lack of comprehensive animal data following long-term exposure to the space environment, especially in a high LET environment.

7 | Questions for space biology and health

There are many questions about what space travel does to organisms, and most are already being investigated, in particular, around the effects of microgravity and radiation. However, many are based on the quite specific and hitherto well-defined aspects of metabolism. These, in turn, have been dictated by the "*zeitgeist*" of genetics and pharmacology-based medicine. As is often the case, more general questions perhaps need to be asked, looking at the bigger picture.

In this chapter, we pose some less obvious questions that might provide further insight into the altered metabolism experienced in space, in particular, from the viewpoints of how life may have started, evolution, quantum mechanics and adaptive metabolic envelopes as indicated by evolutionary canalised hormetic Goldilocks zones. This will include discussion of the direct effects of light and magnetic fields on biology. We will also focus on mitochondrial function and those redox changes which could well be central to understanding an underlying common effect.

One of the simplest overarching questions must be how does going into space in the current fleet of spacecraft accelerate the ageing process? If so, which organisms are most prone to this acceleration and why, and which organ systems will degrade the fastest? Although longer-term effects, for instance, an overall reduction in life expectancy might be important, more immediate effects like immune and reproductive senescence, or accelerating visual and cognitive decline may be paramount to the outcomes of space missions. Although it is likely that all the unusual environmental factors, compared to what life evolved with on Earth, contribute to the unhealthy space phenotype to varying degrees, some are likely to have a greater impact than others. Accordingly, we have listed them in a suggested order of importance – although this could change with further data.

7.1 Gravity and tensegrity

1. What is the influence of gravity on tensegrity, and how does this change the shape of essential biological networks such as chromophore architectures in the cytoskeleton, or components of the ETC, potentially disrupting their functionality? Microtubules, for instance, are sensitive to gravity and rely on it for self-organisation.[175]

2. In neurons, there is a hypothesised connection between the mitochondria bound to axonal microtubules and the fact that microtubules may conduct oscillatory signals from attached mitochondria to generate a pre-excitation state at the synapse. How do these mitochondrial field oscillations integrate with the surrounding cell structure in terms of tensegrity design principles?

3. What is the role of the membrane/cytoskeleton interface and gap junction functionality in multicellular organisms?

7.2 Ionising radiation

1. What are the effects of different kinds of radiation, in particular high-energy protons and HZE ions, on mitochondrial function, and what are the hormetic thresholds?

2. Concerning Q1, how do different cells respond, in particular, from different species? What is the effect of age on this response?

3. Can small doses of radiation enhance protection against larger doses?

4. Given that radiation induces oxidative stress, can antioxidants have a protective effect?

5. Do plants fare better than animals in a space environment?

7.3 Magnetic fields

1. What happens to ROS signalling in the context of space travel beyond the influence of the Earth's magnetic field, in particular, hypomagnetic fields (magnitude and changing alignment)?

2. What are the mechanisms by which magnetic fields interact with oxidative phosphorylation?

3. How do magnetic fields interact with shifts in photon insolation and gravitational shifts?

7.4 Non-ionising radiation

1. What is the light spectrum on the ISS?

2. What is the ideal hourly changing spectrum of light that ensures optimal biological function and homeostasis?

3. What are the effects of different light spectra and intensities on mitochondrial function?

4. Is there an interaction between light spectra, intensity and variations in the magnetic field on mitochondrial function?

5. How does oxidative stress affect the circadian rhythm?

7.5 Electric fields

1. How do applied electric fields change the endogenous electric properties of biological materials, for example through the large dipole moments of tubulin proteins, or in other large complexes, such as those found in the ETC?

2. How is the function of mechanosensitive ion channels altered across different gravitational fields due to changes in tensegrity, and what effect does this have on membrane potential, ROS and bioelectric fields?

3. How do oscillating electromagnetic fields modulate the ETC in mitochondria?

4. Does the morphogenetic bioelectrical field shift when leaving Earth, and does this, in particular, have any effects on embryogenesis?

5. What are the effects of electrostriction and the capacitance of membranes? How do changes in fields have a direct mechanical effect on charged structures (which includes most known structures in biology)?

6. How does the bioelectric field interact with mitochondrial function?

7.6 Integrated theory

The key question is does being in space put most organisms outside their evolutionary-derived adaptive envelope? In effect, does the emerging ageing phenotype represent an inability of individual organisms to adapt to new conditions, and is a marker for this oxidative stress?

1. Can modulation of the ETC by all of the changed known potential factors in space help to provide a more integrated approach to defining the space “phenotype”?

2. Does plant ageing respond in the same way, epigenetically, as mammalian ageing, or are plants more plastic? Can we establish an epigenetic clock for plants? Are plant mitochondria altered in space?

3. Is it possible to define a series of nested “Goldilocks” zones for each organism, so providing a deeper understanding of when each will exceed its adaptative metabolic capacity? This may well include the removal of “normal” stress factors that induce an optimal adaptive response, given that a lack of oxygen, temperature, gravity, light of various frequencies or magnetic fields may be just as important as too much of something.

4. Which of the changed environmental parameters in space is the most important in terms of inducing astronaut ill health? Dissecting the relative contributions of microgravity and increased radiation from altered circadian rhythms, magnetic fields, EMF, and light spectra could be key to identifying which factors, if controlled for, would provide the best health outcomes for astronauts.

5. What are the best blood-borne markers to ascertain an astronaut’s health status?

6. Plants are known to produce more medicinal phenolic compounds under stress. Will plants grown in space produce secondary metabolites better suited to ameliorating AAP?

7. A multi-level investigation of the microbiome-host interaction and, in particular, whether the evolution of the microbiome under the new conditions of space travel will lead to a failure of the host-microbiome cooperation.

Chapter 7 key points

- We posed some less obvious questions that might provide further insight into the altered metabolism experienced in space and how this contributes to accelerating the ageing process.
- These questions challenge conventional viewpoints and suggest that embracing quantum mechanics and thermodynamics in understanding the origins of life and subsequent evolution of the adaptive metabolic envelope and its Goldilocks zone will help explain the physiological phenotype induced by space travel.
- We list these questions in what we believe is the order of importance (subject to further data) of the different effects, as follows:
    - Gravity and tensegrity
    - Ionising radiation
    - Magnetic fields
    - Non-ionising radiation
    - Electric fields
    - Integrated theory (the interaction of different factors and mitigating strategies)
- The key question is whether being in space puts most organisms outside their evolutionary-derived adaptive envelope. In effect, the emerging ageing phenotype represents an inability of individual organisms to adapt to the new conditions and is a marker for this oxidative stress.

8 | Suggested experiments

The experiments that may be needed to answer the key questions raised are set out below.

8.1 Accelerated ageing experiments

Does going into space result in an accelerated ageing process and, critically, does it return to normal when people return to Earth? Moreover, is it dependent on the time spent in outer space and the number of variable space factors an astronaut is exposed to? Does prior health status modify this effect and modulate the recovery process? In short, does staying in space reduce healthy and absolute life expectancy, and are there discernible long-term effects when people return to Earth that are modified by prior health?

Although astronauts develop many conditions that hint at a faster ageing process, actually measuring this may well be possible, for instance, by using epigenetic clock methodologies. We propose the following experiments to measure the extent to which space travel can be considered to produce an AAP; these are listed in order of priority, but these could change with new findings.

1. Obtain blood samples, before, during, and after space missions from astronauts and measure their epigenetic and proteomic age clocks. Repeat at yearly intervals after space flight to ascertain whether the phenotype reverts to normal. The before sample will ascertain, to some degree, how healthy the subjects were, with the sample taken during spaceflight possibly providing insight into the most immediate changes, while the sample taken after measures the extent of the changes. The key here will be to ascertain whether prior health influences the rate and extent of the ageing process. It will also be important to establish lifestyle effects, as these could confound the results, hence the need to measure other key health indices such as visceral fat distribution, standard blood markers, aerobic fitness and strength, and cognitive function (we could use the UK BioBank model here).

2. Develop epigenetic clocks for other, non-mammalian species, including plants and animals.

3. Use blood samples from above to ascertain mitochondrial health, so that epigenetic age can be correlated with mitochondrial function.

4. Correlate mitochondrial function and epigenetic age with more conventional measures of health, such as fat distribution, insulin resistance, cardiorespiratory fitness, balance, inflammation, grip strength, lipid profiles, coagulation, renal function and markers of oxidative stress. If longer term, details of physical activity levels and diet, and if possible, genetic markers of longevity.

5. What is the relationship between the microbiota and ageing? Will mitigation of the various damaging space factors impact humans and microbiota at different rates and in different ways?

6. Check whether telomere length shortens in the cells due to short or long-term exposure to space environment. A similar observation might be important with respect to cellular senescence.

7. What is the effect of social isolation and loneliness on the human AAP during long-term space missions?

8. Check whether long-term mental health has a connection to AAP, as is often the case on Earth.

8.2 Ionising radiation experiments

The main outstanding issues include the differential impacts of high LET versus low LET radiation, the effects of acute versus chronic exposure, and the potential of pharmacological interventions to mitigate these impacts. Given the tight relationship between mitochondrial function, epigenetics, and ageing, understanding these interactions is critical for the health and safety of astronauts on long-duration missions.

1. Exploration of high LET versus low LET radiation on mitochondrial function and epigenetics to investigate how different types of ionising radiation (i.e., high LET vs. low LET) affect mitochondrial bioenergetics, ROS production, and the epigenetic landscape in mammalian cells. This experiment aims to elucidate how these two types of radiation differently impact cellular functions and contribute to DNA damage and repair mechanisms, metabolic flexibility, and chronic inflammation.

2. Investigation of acute versus chronic radiation exposure on epigenetic regulation and mitochondrial health in model systems. Acute radiation exposure delivers a high dose in a short time, whereas chronic exposure involves lower doses over extended periods. Understanding the

differential biological responses to these exposure patterns is critical for assessing risks over long-term space missions. The focus here is on epigenetic regulation and mitochondrial health. This study seeks to understand the relative impacts of short-term high-dose radiation and long-term low-dose radiation on the integrity of cellular structures, ageing phenotypes, and systemic health, particularly in the context of long-duration space missions. There is already a strong focus on studying antioxidant cocktails for this purpose and to control oxidative stress in general.[176]

3. Role of pharmacological agents in mitigating radiation-induced mitochondrial and epigenetic damage. Given the potential of pharmacological interventions in mitigating radiation damage, exploring agents that stabilise mitochondrial function and modulate epigenetic marks could provide protective strategies for astronauts. The objective is to evaluate the efficacy of various pharmacological agents in preventing or reducing the detrimental effects of ionising radiation on mitochondrial function and epigenetic stability. This experiment aims to identify promising compounds that can be used as protective measures for astronauts, potentially enhancing their resilience to radiation-induced damage during space travel.

4. Further studies on the differential effects of acute versus chronic exposure on DNA damage, repair and cancer.

8.3 Magnetic field experiments

The priority is to build on the emerging evidence and show, unequivocally, that magnetic fields can and do modulate metabolism and cell function, both in isolated cells and in whole animals, and whether biology can adapt to these changes. Of greatest interest are hypomagnetic fields that are likely to be experienced by astronauts as they leave the Earth's magnetic field. However, it may also be that the changing alignment/orientation of the field could alter biology.[19] Underlying this are further investigations, for instance, are some organisms more adaptable to changing magnetic fields? Are prokaryotes and single-celled organisms better at adapting to hypomagnetic fields than multicellular life such as humans and plants? What specific adaptations to magnetic fields have biological systems evolved? For example, do we need to investigate the magnetic field properties of the placenta or the role of ferritin in the brain?

1. Repeat experiments using a variety of cell lines, both transformed and primary, with different metabolic profiles, to explore the influence of dose, duration and alignment of static hypo- and hyper-magnetic fields, including rotational effects (chirality may be important). We should then study effects over the longer term – do cells recover, and is there any evidence of hormetic adaptation? Key biomarkers might include mitochondrial morphology; ROS generation (and location, both intra- and extra-mitochondrial); calcium fluxes; mitochondrial membrane potential; oxidative phosphorylation (ox phos) vs glycolysis; epigenetic age; nuclear and mitochondrial genome effects such as genomic stability; mitophagy; cell cycle changes; motility; cell communication; senescence and various forms of cell death; inflammatory markers; heat shock proteins (HSPs) and unfolded protein response (UPR); key transcription factors, such as Nrf2, NfKB, Foxo1, and sirtuins; extracellular vesicle production and content; miRNA; and mtDNA.

2. Repeat experiments in point one with key experimental organisms including *C. elegans*; *Drosophila melanogaster*; planaria; xenobots; frogs, zebrafish and mice; tardigrades; *Arabidopsis* (and other plants); prokaryotes (including magneto-sensitive ones, both anaerobic and aerobic). Depending on the species, key biomarkers (other than those listed in point 1) include behaviour; inflammation; oxidative stress; lipids; fat distribution; growth; regeneration; reproduction; embryology and development; lifespan; epigenetic age; exercise tolerance and resistance to infection; and effects on different organ systems.

3. Repeat some of the experiments in 1 and 2, but with the addition of further factors, such as changing light conditions and, if possible, microgravity (would require experiments on the ISS involving a centrifuge for control), as well as circadian zeitgeber variation, and different doses and types of ionising radiation, as well as dynamic field modulation.

4. Repeat 1 and 2, but with defined factors that might be protective, but also detrimental, such as exercise and calorie restriction vs. sedentary and poor diet (in those animals where this can be done), including natural product/pharmacological manipulation. This might help to identify the limits of adaptative metabolic envelopes. Also study the effects of pre-stress and/or pre-conditioning on organisms, for instance, using pharmaceuticals, metabolic shifts, hormones such as myokines, or exercise in hypergravity. This could be modelled to some degree in cell culture by

studying known biomarkers, such as metabolic adaptability and the ability to maintain redox homeostasis.

5. Human and other organisms could be studied in hypomagnetic rooms originally constructed for magnetoencephalography (MEG) studies, although these would have to operate under low nT (nano Tesla) regimes. Similar to biomarker studies as outlined, we should study the parameters laid out in points 1 and 2.

6. We should study quantum effects such as the measurement, where possible, of tunnelling. Computational and spin simulation is also a possibility. However, direct measurement of quantum effects in biology is still very much a new field, although quantum sensing techniques such as diamond vacancy centres are beginning to be adapted for the biological context. Indirect indices, such as kinetic isotope effects (KIEs), could also be used.

7. Do external magnetic fields affect the recently described NADH anisotropy, hinting at a new order of cristae alignment in mitochondria?[177]

8.4 Gravitational field experiments

The main challenge is that Earth-bound experimentation, such as bed rest inclination and microgravity rotating simulators, are not as good as genuine free fall in space as experienced, for instance, on the ISS. In contrast, it is possible to successfully study the effects of hypergravity on Earth. Thus, it would seem that comparing multiple biological parameters between organisms and cells in a space-based centrifuge, with controls in a microgravity environment, would be key.

1. If possible, explore the experimental parameters outlined in Sections 6.1 and 6.2 using control and centrifuges in space.

2. Theoretical and simulation. Determine the relationship between tensegrity, protein shape and gravity in single-cell and multicellular organisms, looking at how it might affect distances and thus quantum tunnelling in the supercomplexes of the ETC and ROS signalling.

3. As for 2, but looking at the effect on the cytoskeleton, in particular investigating how alterations in chromophore 3D geometries could affect super-radiance and more conventional markers, such as cytoskeleton stability and calcium and ROS signalling.

4. Investigate the effects of gravity on cryptochrome-mediated photomechanical transduction (see reference).[178]

5. Study effects of cytoskeletal changes on nuclear, plasma, mitochondrial and all other membranes in the cell.

6. Investigate whether the Earth's barycentre-induced wobble influences circadian biological function. This may require non-manned automated satellite-based experiments in different orbits, in opposing directions, both equatorial and polar.

8.5 Non-ionising radiation and light experiments

Given the sensitivity of life to light from complex evolved photoreceptors and ancient chromophores, and the fact that living organisms also generate low numbers of biophotons during metabolism and can store photonic energy in the form of delayed luminescence, it is becoming apparent that light plays a much greater role in everyday metabolism than previously thought.[179] Clearly, vision and photosynthesis are well described, as are light-based zeitgeber circadian slaving, but it is now clear that light of different wavelengths can directly and biphasically manipulate metabolism, ranging from their effects on the primary electron-carrying moiety, NADH, to FAD+, to cytochrome C oxidase, as well as other porphyrin and transition metal-containing compounds, in addition to many other cyclic compounds, including cholesterol-based moieties, key amino acids, DNA and RNA. Nearly all are involved in or are capable of fluxing electrons and protons, thus performing energy transfer and dissipation. By definition, most of the key molecules involved in electron transfer have quantum structures that are also commensurate with absorbing a photon, such as double bonds and pi-electron systems.

1. Does life require, for optimal function, a particular spectrum? Under which conditions did life evolve and how important is the circadian variation? A detailed exploration of light spectra on the health of both organisms and individual cells, with experimental conditions outlined in Sections

6.1 and 2, is probably key. The aim would be to answer whether the emergence of humankind's "blue-shifted" light environment is causing more problems than realised, especially if replicated in spacecraft. Although this is likely entrained with circadian rhythms, it has been suggested that a lack of NIR could be causing just as many problems as too much blue light.

2. Further exploration of light on quantum processes, such as tunnelling and spin. This field is already fairly well advanced in relation to the role of cryptochromes and magnetic sensitivity, although there is evidence that only the chromophore (FAD) may be required – for instance, simply increasing levels of FAD in a model of magnetosensitivity can be sufficient,[180] hinting at a much older origin.

3. Investigation of 3D chromophoric superradiance of the cytoskeleton with changes in cell shape (mimicking reduced gravity), changes in gravitational fields, changes in electric and EM fields, and the effects of radiation.

8.6 Therapeutic interventions

Given that ageing results in decreasing robustness and increasing risk of disease, and that stress itself increases the rate of ageing, both prevention and treatment are going to be important. The former clearly comes from a healthy space lifestyle, while treatment is going to have to fundamentally tackle the accelerated process of ageing. The latter, of course, has been the holy grail of research for decades, if not millennia. The problem is that even the most effective treatments, such as rapamycin, only result in marginal improvements in life expectancy, and the question is whether they could ever offset the effects of space travel. Other treatments are being explored, ranging from metformin to resveratrol, as well as other natural products, including mitochondrially targeted antioxidants. Furthermore, most treatments are associated with some kind of side effect. However, there is also the question that, although they may well help in organisms already experiencing sub-optimal health, they might not in apparently very healthy organisms. This question has still not really been answered. This is why understanding optimal health is so important. The following mitigating strategies offer a starting point for discussion.

1. Use of human-sized centrifuges in space to offset microgravity. There might be an effective threshold dose-response between the induced gravity and the amount of exercise.

2. Use of onboard light systems that precisely mimic the average intensity of light and spectrum throughout an Earth day (this might of course vary according to race and skin colour). This could be done ship-wide, although it would be more practical to have a room where astronauts can go to be exposed for shorter durations during the day. The timing and duration could be altered to find the best compromise.

3. Use of a cocktail of compounds that are known to slow the ageing process, in particular, those known to protect or enhance mitochondrial function.

4. Consumption of a diet high in phenolics is known to be healthy. Plants grown in, and adapted to, the space environment might be optimal.

5. Explore the use of either caloric restriction or a ketogenic diet.

6. Beyond LEO, the use of magnetic field generators to mimic Earth's surface magnetic field might be considered.

7. Study plant mitochondria in response to the space environment, and how this is related to upregulation of phenolic production and sirtuin activity.

8.7 Further points on experimental research

As suggested above, as well as human research, research on how plants adapt to space conditions may also be useful, as mitochondria are critical in plant function. Space plant studies also have the benefit of being more advanced than animal studies and so could provide preliminary data that inform future research and experimental protocols. Ultimately experiments that investigate how plants adapt to these environments will also be important to demonstrate the viability and challenges of growing food, necessary for any long-term human settlement in space. The key here, however, will be to develop a much greater understanding of how plants age and whether we can measure it (a surrogate here is to ascertain how stressed a plant is).

Consideration will be needed as to which of the experiments outlined in Section 6 above need to be undertaken in space, with their associated costs and logistic issues, and for which experiments space conditions can be reliably mimicked on Earth. For example, while some experiments into microgravity

conditions take place in real conditions such as the ISS, and others simulate these conditions on Earth, research into microgravity needs to address the limitations of simulating microgravity conditions on Earth. Although some terrestrial microgravity research can be informative, it will never be as good as that undertaken in genuine microgravity. However, the modulation of magnetic fields, radiation and light can all be investigated fairly well on Earth. However, the problem remains as to how they all interact with microgravity, a phenomenon which can only truly be studied in space, hinting that the first step may be to study cells in a small centrifuge in space where the other controlled factors are modified.

Finally, there is also the question of developing a usable regulatory framework for testing which drugs to take into space for treating space-induced illnesses, ascertaining their shelf-life, and the obligation to undertake space-related clinical trials to verify their safety and efficacy and, as is becoming increasingly apparent, off-label use for different indications. Certainly, because of the microgravity-related changes in blood flow and dynamics, the pharmacokinetics and pharmacodynamics need to be explored in more depth.[181] Indeed, there is a much greater need to understand the "pharmacology in space", especially on longer missions.[182] This also crosses over, especially for very long-term missions, to the potential need to develop portable biomanufacturing systems, which could not only generate food, but also pharmaceuticals. In effect, this entails developing technology that makes space exploration independent of the supply chain from Earth. This might, for example, require microbial-based manufacturing systems.[183]

9 | Challenges and opportunities

1. The primary challenge appears to be the acceptance, across a broad range of professional disciplines, ranging not just from biology, but to engineering, finance, legal and management, that going into space does result in an AAP. Once accepted, a unifying approach can be built to find the best way to tackle it. In theory, it should be simpler than tackling the globally developing obesity/poor lifestyle crisis which is currently accelerating the ageing process across large sections of Earth-bound society. This may be because the obesogenic environment has arisen out of a deep-rooted instinct for survival that motivates humans to make their environment as safe and as pleasant as possible, instincts that have been driven by technology and a free market. It is thus extremely complex at a societal level and involves billions of people. In contrast, the health problems of space travel are much more defined in terms of what is causing them, and only affect a very small number of people, hinting that even if humans cannot be genetically adapted soon, it might be possible to mimic the healthy conditions and environment needed to thrive. In effect, there are likely to be technological solutions to remove the need for the individual organism to adapt in space. Critically, there is already a great deal of knowledge garnered from what happens to people's metabolism in a sedentary obesogenic environment that could inform us how to keep astronauts healthy. We may not be able to change lifestyles on Earth any time soon, but we may be able to make spacecraft and other planetary bases as healthy as possible.

2. Research into space biology and health has been viewed through the lens of the Earth-based zeitgeist; this means research has been relatively siloed into established disciplines, potentially missing key parts of the puzzle. For example, the expanding realisation of the importance of mitochondrial function in disease stems from the role of quantum mechanics and thermodynamics in life, the emerging importance of altered electromagnetic and light environments on human health and, indeed, a large part of the healthcare problems on Earth, including AAP, are induced by a poor lifestyle. Accepting that life is electrical does provide a completely new viewpoint. This is emphasised by the point that siloing and a lack of a common language between physicists and biologists have hindered the development of quantum biology.

3. Space biology receives a tiny proportion of the overall space budget, with one estimate suggesting that only approximately 0.3% of the NASA budget is spent on this area.[184] This is perhaps reflective

of the pioneering aspect of space flight which, up until now, has been focused on keeping astronauts alive, whereas keeping them in optimal health will be critical as we venture further.

4. In recent years the space industry has become more fragmented, both in terms of new nations setting up programmes but also within nations. For example, the number of companies now involved with the US's space programme makes the industry an increasingly complex landscape to navigate, resulting in ever greater challenges for coordination and collaboration. This collaboration will likely be made more complex by growing military interest and involvement in space. The US and China have space forces, military branches that are wholly dedicated to operations in outer space. Other countries such as Russia, France, India, Japan and Iran have emerging space entities integrated with their other military branches.

5. Ambitions of space missions BLEO and indeed long-term multi-planetary space habitation involve astronauts being exposed to more extreme environments over a longer timeframe, which moves the goalposts significantly from the relatively short-term visits to the ISS that have been mostly experienced to date. Moreover, habitation plans will ultimately involve a more general population of humans, likely in poorer underlying health than trained astronauts, being exposed to space conditions. These populations will require food and water to sustain them and, if long-term habitation is planned, then it will be necessary to know that reproduction is viable, as the somewhat limited evidence to date raises questions about embryonic development.

6. The enormous complexity of space travel and habitation means that engineering has understandably been at the forefront of the endeavour. Mitigation of the negative effects of the space environment will necessarily need the involvement of engineers in identifying and implementing solutions.

7. Space missions involve a very high level of risk. Success is perhaps viewed in terms of successful launch, mission objectives, and safe return, with the health of astronauts beyond their return to Earth being of lower priority. This focus is understandable in the context, but as many in the industry live with these high levels of risk it may be difficult to attract their interest in effects currently perceived as mild or long-term.

8. To date there appears to be no readily accessible standardisation of tests, medical protocols, data collection and collation concerning astronaut health.

9. Space biology and health evidence can be difficult to obtain, either because it has not been analysed and made publicly available, or else because it is published across a wide range of journals, many of which are often highly specialised. Thus, it may be useful to establish a central resource.

10. To ensure the best use of funds, prioritisation will be needed for key experiments. Coordination and collaboration between different space organisations and research groups would help to maximise the impact and benefits for all concerned.

10 | Conclusions and proposed action

10.1 Conclusions

Quantum biology has taken a hundred years to enter the scientific mainstream. This has been largely because quantum mechanics is simply a difficult subject to understand, the lack of available technology, and the fact that it was considered irrelevant in our quest to understand biology. It has been a century since the early pioneers of quantum mechanics, such as Jordan and Bohr, discussed its role in biology and Alexander Gurwitsch observed that cells could communicate using metabolically produced photons[26] and some 80 years since Schrödinger published his famous book: *What is Life – the Physical Aspects of the Living Cell.*[39]

Today, with the emerging interest in how we can use both quantum mechanics and thermodynamics to better understand biology, we could well be on the verge of a much deeper understanding of what life is, and critically, why it is that most, if not all organisms age. This certainly seems to be correlated with adaptation to a changing environment, both at an individual and population level, and also the challenges of downscaling to the molecular level and upscaling to the entire species. Certainly, in more complex organisms this is related to oxidative stress and inflammation and thus, if we view life as all about the movement of electrons, it hints at why quantum mechanics may provide us with valuable clues. This paradigm shift also puts mitochondrial function centre stage. This may even provide us with an answer to a previous question, namely, will it be easier to solve and mitigate the AAP induced by a poor lifestyle on Earth, or that observed when people spend time in space? It may well be the latter, as this appears to be largely a technological and scientific problem, whereas the former has many more factors, including our evolutionary-derived urges to make life more comfortable, our competitiveness, and the resultant huge asymmetries in wealth distribution. As has been repeatedly shown, longevity is generally related to income but follows a "U-shaped" curve (the obesity Kuznets curve), with obesity and lifestyle-induced disease rising as a country's GDP increases, but then with increasing wealth, the richest then start to invest more in their own health and live longer.[185] The problem is that wealth inequality continues to increase[186] and social inequality is related to accelerated ageing.[187] Health in space does seem to be a much simpler problem to solve, and while it may shed light on what ageing is, whether it will help improve longevity on Earth is perhaps not clear-cut.

Recent breakthroughs in technology are beginning to enable researchers to probe deeper into the extent to which life is using and dependent on physical effects, including those that are quantum-related. However, we need to accelerate progress and apply it to real-life goals, such as space health and advances in terrestrial medicine.

This report has highlighted the key differences of the space environment to that in which we evolved, and how this might be impacting biology and health. The key point seems to be that space travel currently induces something very similar to an AAP in humans, which might also be seen in other complex organisms, including their isolated cells. This raises several questions:

- Can we confirm this phenotype, and if so, which organisms are more prone to it?
- Does this phenotype continue to be exhibited in space, resulting in escalating medical problems?
- Does this phenotype reverse when back on Earth, or will it result in a reduced healthspan and, ultimately, reduced life expectancy?
- How does prior health influence the onset and severity of this AAP?
- Will it ever be possible for human, or companion organism physiology to adapt to this new environment, or will it require genetic manipulation?
- In the shorter term, can this potentially life-shortening phenotype be mitigated and, if so, how? Would reproducing some elements of the correct Earth environment on a spacecraft be sufficient and, if so, which elements are the most important?

Some of the questions we raise may have serious implications, yet some relatively straightforward experiments would take our understanding forward within a reasonable timescale. In short, we suggest the need to understand the deep physics of life in space, the fundamental electrical properties of life, how life must have been canalised into a certain environment, and what likely happens when it is exposed to entirely new environments. To this end, understanding adaptive thermodynamics in relation to how life adapts to stress is key, as is quantum biology, and what this may tell us about bioenergetics. With this knowledge, we might be able to accelerate the ability of humankind to thrive, and not just survive, in space. Ultimately the aim is that space organisations could apply the learnings to mitigating the effects in space, not just at the practical level, but by influencing the key decision

makers that this research is essential. This may well influence the leaders of these organisations to develop future programmes and engineering solutions where maintaining optimal health is vital, especially on long missions, say, to Mars.

10.2 Proposed action

As an independent UK-based science-driven non-profit organisation, The Guy Foundation, with its strong background in relevant research and experience, is well-placed to play a coordinating and collaborative role in this area.

As well as our own scientists, we have established a working group of leading experts, mainly from the UK, Europe, and North America, who are drawn from the fields of space research, quantum biology, mitochondrial research, ageing and pharmaceutical/medical device development. They are lending their expertise by identifying and reviewing evidence, formulating experimental plans, commenting on draft recommendations and reports, and signposting to other relevant contacts and groups.

We are aware that a great deal of money and expertise are already being invested in space research. Having reviewed the scope of current research, there appear to be some less well-investigated areas, such as the effects of weak magnetic fields and exposure to light in the space station environment. For instance, how do these and the effects of gravity, affect mitochondrial function? For this reason, we have chosen these areas and the mitochondrion as our preliminary focus as all the abnormal conditions found in space, can, in one way or another, affect these organelles.

We are embarking on an initial experimental programme with relevant scientists, but we will need additional funding to undertake more in-depth experiments and expand collaborations.

10.3 Invitation to interested parties

If you are interested in the issues we have raised in this report we invite you to contact us to find out more. Please contact Nina Copping (Programme Director) **n.copping@theguyfoundation.org**, or contact Alistair Nunn (Director of Science) **a.nunn@theguyfoundation.org** with thoughts on the science.

11 | List of abbreviations

AAP	accelerated ageing phenotype
ALT	alternative lengthening of telomeres
BLEO	beyond low-Earth orbit
DDR	DNA damage response
ETC	electron transport chain
GCR	galactic cosmic rays
HSF	heat shock factor
HSP	heat shock protein
HZE	high Z and high-energy particles
IR	Infrared
ISS	International Space Station
LED	light-emitting diode
LEO	low-Earth orbit
LET	linear energy transfer
LSAH	The US Longitudinal Study of Astronaut Health
NADH	reduced nicotinamide adenine dinucleotide
NIR	near-infrared
PBM	photobiomodulation
QB	quantum biology
RBE	relative biological effect
RF	radio frequencies
ROS	reactive oxygen species
SANS	spaceflight-associated neuro-ocular syndrome
SIMS	space-induced metabolic syndrome
SPE	solar particle events
TTW	biological or tissue transparency window
UPR	unfolded protein response
UV	ultraviolet

12 | Glossary

An **electrochemical gradient** or membrane potential is a difference in proton or ion concentration across a biological membrane, which results in an electric potential that charged particles experience as a force. This membrane potential is achieved in various ways, including through electron transport chains, and proton pumps such as ATPases or ion channels.

Electromagnetism is the branch of physics that deals with interactions between charged particles with electric and magnetic fields, and their field unification as light. These interactions are mediated by photons, the quanta (discrete packets) of light, which manifest the particulate nature of the electromagnetic wave.

Homeostasis describes the process whereby the organism maintains its internal environment around a set point, and allostasis is the process of how it adapts to its external environment.

Hormesis literally means what does not kill you makes you stronger, and describes a fundamental adaptive response, and is similar in some respects to allostasis. This is the Wikipedia definition: "Hormesis is a two-phased dose-response relationship to an environmental agent whereby low-dose amounts have a beneficial effect, and high-dose amounts are either inhibitory to function or toxic. Within the hormetic zone, the biological response to low-dose amounts of some stressors is generally favourable." A key trigger is a change in redox, usually resulting in the production of ROS, which induces an adaptive programme. Although there is some variability in the pathways involved, most of the central components are shared and one factor, if it is a defined (recognised) biological stressor, can induce robustness against others. The mitochondrion is central to the hormetic process, with important hormetins being physical activity, calorie restriction, plant phenols, and heat and cold.

A **static magnetic field** is a magnetic field that does not change over time and the magnetic field strength at a given point in space remains constant. An example of a static magnetic field is the one produced by a permanent magnet. The Earth's magnetic field is considered a static magnetic field. Static magnetic fields are used in magnetic storage devices like hard drives. An oscillating magnetic field is a magnetic field that varies or fluctuates with time. The strength and direction of the magnetic field change periodically. Magnetic fields can be generated by electric currents. Thus an oscillating magnetic field can be produced by an alternating current flowing through a wire which, in turn,

produces an alternating magnetic field. Oscillating magnetic fields play a crucial role in technologies like transformers and electric generators, as well as in wireless communication systems.

Quantum biology is the application of quantum theory, in particular effects such as superposition, entanglement and tunnelling, to the specific case of biological systems.

Quantum theory describes the discrete, granular nature of wave-particles, such as atoms, electrons, protons and photons, and their aggregates. It was developed out of the need to better describe anomalous experimental observations and is to be distinguished from classical mechanics, which presumes a continuum for all measurements. In particular, classical theory could not accurately and completely explain blackbody radiation. As such quantum theory has roots in the field of thermodynamics. This “ultraviolet catastrophe” led Planck to hypothesise that energy is quantised, or comes in discrete amounts, which was further consolidated by Einstein’s explanation of the photoelectric effect. The result of this is what is often called the “wave-particle” duality of quantum mechanics, where light (and matter) behaves both as a wave and a particle. The exact nature of the underlying reality of the wave-particle phenomena is still not understood, and is still an active area of research and debate. Interestingly, scientists are now starting to use thermodynamics to unpick what quantum mechanics actually represents.

Spin (more formally, spin angular momentum) describes the quantised response of a physical system to a magnetic field, which is not describable by its orbital angular momentum. Spin is not due to any spinning motion of the particles in question. Rather, spin is an intrinsic quantum property, for instance the quantum counterpart of light polarisation for photons. Other intrinsic properties of matter are mass and charge. Mass describes how matter will respond to a gravitational field, charge describes how matter will respond to an electric field, and spin describes how quantum systems such as electrons and protons will respond to a magnetic field. Spin also plays a role in chemical reactions, where electrons that occupy the same orbitals must have opposite spin states (the so-called Pauli exclusion principle). Spin also dictates the magnetic properties of certain materials, for instance paramagnetic materials which have unpaired spins, and diamagnetic materials where all the spins are paired.

Thermodynamics is the branch of physics that deals with phenomena governing temperature, heat, work, energy, and entropy. As a discipline, it was advanced considerably by the invention and refinement of the steam engine. The laws of thermodynamics describe macroscopic "coarse-grained" properties of physical systems in terms of statistical probabilities of arrangements of their microscopic components. Thermodynamics is now essential to our understanding of chemical and biological systems, both in and out of equilibrium. Thermodynamics has also been expanded to include ideas around information for classical and quantum systems, and the energy costs of their manipulation for computing tasks.

Quantum tunnelling falls out of the fundamental principle in quantum mechanics that entities exist in wave-particle duality, which means that they have a probability of being somewhere. Hence, for instance, a proton, or an electron, can exist the other side of a barrier. In effect, there is a finite possibility that they can "tunnel" through it. This is not just a critical process, say, in the Sun's nuclear fusion process, but also in many solid-state electric devices, and, as it turns out, it seems to be key both how biological enzymes work, and how electrons move through cells, in particular, in the ETC.

For other relevant terms, please visit the Glossary on The Guy Foundation website:
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- Maladaptive reversion: does living in space result in an accelerated ageing phenotype? - Professor Alistair Nunn
- Quantum mitochondria and space flight - Professor Douglas C Wallace
- Mitochondrial stress as a central biological hub for spaceflight impact - Dr Afshin Beheshti

Session Three: Microgravity and radiation effects

- Effects of Mars Mission-Equivalent Doses of SEP/GCR Radiation and Simulated Microgravity on
- The Human Hematopoietic System and Astronaut Cancer Risk - Professor Christopher D Porada and Professor Graça Almeida-Porada
- Leveraging gravitation and space biology to model immune ageing and disease - Dr David Furman

Session Four: Potential effects of magnetic fields

- An introduction to the radical pair mechanism - Professor Jonathan Woodward
- Manipulating tissue repair with weak magnetic fields - Professor Wendy Beane

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- Overview of electric fields - Dr Michal Cifra
- Membrane potential and regeneration - Professor Mike Levin
- Overview of magnetic fields – Dr Betony Adams
- Reactive oxygen species (ROS) and stem cells - Professor Wendy Beane
- Overview of oscillating gravitational fields - Steve Thorne
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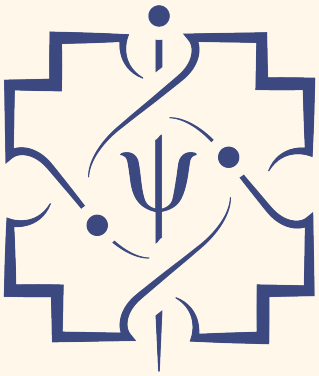

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