Journal of Space Exploration
ISSN: 2319-9822

Journal of Space Exploration

Research | Vol 13 Iss 1

Suspended Animation for Deep Space Flight

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Received date: 14-Jan-2024, Manuscript No. tsse-24-127550; **Editor assigned:** 16-Jan-2024, PreQC No. tsse-24-127550 (PQ); **Reviewed:** 20-Jan-2024, QC No tsse-24-127550 (Q); **Revised:** 22-Jan-2024, Manuscript No. tsse-24-127550 (R); **Published:** 29-Jan-2024, DOI. 10.37532/2320-6756.2024.13(1).345

Abstract

The discovery of extrasolar planets as well as the growing number of earth-like exoplanets being detected almost routinely, is galvanizing the interest of the public and space agencies alike to plan for exploratory missions to potentially habitable exoplanets. For manned interstellar space flight, ultralow subzero suspended animation strategies will be mandatory since interstellar travel will probably take a number of years measured in 3-digit figures. The rapid progress of cryobiology and freezing technology is giving rise to a growing certainty about the feasibility of reversibly cryopreserving organs and whole organisms at subzero temperatures. Cryopreservation of very small organisms like mammalian embryos, is routinely achieved by fast vitrification and ultrafast rewarming. Studies in lower animals, like the nematode C. elegans, have shown that the nervous system can be successfully cryopreserved and brought back to a functional condition by superfast freezing and thawing procedures, preserving the memory of trained specimens. This article will briefly review the advances in reversible cryopreservation of living organisms and its potential for implementing fully reversible long-term SA as a suitable technology for manned deep-space flight.

Keywords: Space flight; Animation

Introduction

Suspended Animation

Suspended Animation (SA) is the temporary (short- or long-term) slowing or stopping of biological processes. According to the purpose, it may be either hypometabolic or ametabolic in nature. It may be induced by either endogenous natural or artificial means. In its natural form, it is usually reversed when environmental factors return to pre-SA conditions. If it is artificially induced, it may require technologically mediated revival [1]. Long-term SA constitutes a mandatory technology for manned deep (i.e., interstellar) space travel. For manned space flight to Mars and other nearby solar planets and moons, induced torpor is considered a more suitable approach but it will not be discussed here [2-4].

Citation: Goya R. Suspended Animation for Deep Space Flight J Space Explor.2024; 13(1).345.

Deep space travel

Although Mars and other solar bodies like Jupiter's moon Europa are in the relatively near-term plans of space agencies for manned space exploration, the discovery of extrasolar planets, dramatically increased by the Kepler space telescope, a mission to be now continued by the James Webb deep space telescope, as well as the growing number of earth-like exoplanets being discovered almost routinely has galvanized the interest of the public and space agencies alike to plan for exploratory missions to the exoplanets more likely to harbor life and which are orbiting nearby stars [5].

Space agencies like the European Space Agency (ESA) and the US National Aeronautics and Space Administration (NASA) are both interested in implementing feasibility studies about SA for deep-space travel [6, 7]. Thus, the question is not if, but when, those missions would become feasible. Although, undoubtedly, the initial extrasolar missions will be unmanned and only carry advanced AI robots, we humans are explorers by nature and will want to experience the great adventure of visiting other earth-like worlds. Besides, if it is to transcend natural extinction events, the human species will imperatively need to become multi-planetary.

Two general strategies have been considered for implementing manned space travel to promising exoplanets.

Multigenerational space travel

Where very large starships carry a small community composed of passengers and crew. The ship will constitute a sort of biosphere where a few thousand settlers will live until reaching the destination exoplanet where they will try to settle and establish colonies. There are a number of weaknesses this kind of strategy entails.

1. Considering that interstellar travel to extrasolar planets is likely to take many decades, probably over a century, the travellers that start the trip will spend their whole lives traveling, growing old, and dying during the travel. This prospect is likely to discourage many prospective settlers.

2. The monumental mass for a starship that carries a few thousand individuals, as well as all the resources they will need to sustain community life for decades, will require propulsion drives capable of moving these gigantic ships at speeds that represent a significant fraction of the speed of light, maybe 10% C. Developing such kind of technologies may take many decades possibly over a century.

Long-term suspended animation

A more acceptable alternative strategy would be to place the crew and passengers of our interstellar spaceship under SA at the start of the mission and reanimate them upon arrival to the destination exoplanet. For interstellar space flight, ultralow subzero SA strategies will be mandatory since interstellar travel will probably take a number of years measured in 3-digit figures. For instance, at its present speed of 17.3 km/s, it would take 73,000 years for the Voyager 1 spacecraft to reach Proxima Centauri, the closest star to the Sun, at 4.24 light years of distance, some 4 X1012 Km [3].

An interstellar spaceship of the future is likely to be driven by highly advanced robotic AIs and to carry human passengers in SA pods, as already depicted in science fiction movies.

Reversible Suspended Animation

Feasibility of reversible biological cryopreservation

The rapid progress of cryobiology and freezing technology has made it possible to achieve reversible cryopreservation of whole organisms provided they are very small (a few mm^3 in volume). Thus, cryopreservation of whole organisms is routinely achieved in a variety of mammalian embryos, including humans [8, 9]. In the wild, tardigrades constitute a well-known example of animals able to withstand freezing and revive when environmental temperature returns to normal above-zero levels [10, 11].

Vitrification

Although there is a great interest in reversibly cryopreserving organs, mainly for the purpose of creating organ banks, this goal has been elusive until recently [12]. One of the initial hurdles faced by those who attempted organ cryopreservation was ice formation during cooling. The problem was overcome by the development of the process called vitrification [13]. It consists of perfusing the organ of interest with a series of cryoprotective solutions to replace water in the intracellular and extracellular spaces with a solution that at ultralow temperatures will not form sharp needle-like crystals as water does, but an amorphous vitreous solid, thus the name vitrification. To ensure the absence of ice formation the cooling speed during vitrification needs to be within the 1–100°C/min, range.

Nanowarming

Rewarming turned out to be more challenging than cooling, with the Critical Warming Rates (CWR) needed to avoid ice crystallization typically being within the range of 10 °C/min –1000 °C/min. Furthermore, temperature non-uniformity during rewarming must be avoided as it generates thermal stress that can cause cracking. Consequently, speed and uniformity of rewarming are the primary obstacles to achieving successful reanimation after vitrification [14]. This problem does not exist in small organisms where thermal differences and thermal mass are not significant.

Recently, the successful use of nanowarming to achieve ultrafast and homogeneous rewarming in rat kidneys has been reported [14]. The procedure employs alternating magnetic fields to heat Magnetic Nanoparticles (MNP) perfused within the organ vasculature, in order to achieve both rapid and uniform warming, after which the MNP is removed by perfusion. It was further shown that vitrified kidneys can be stored at -150°C for up to 100 days, and successfully recovered by nanowarming to allow transplantation and restore life-sustaining full renal function in nephrectomized rats.

Interestingly, nanowarming rates are not dependent on system size or boundary conditions since the Radio Frequencies (RF) used penetrate tissues without attenuation [15, 16]. In addition, perfusion within the capillary vasculature allows sufficiently uniform delivery of Cryoprotectant Agents (CPAs) and MNPs regardless of organ size. Thus, nanowarming is potentially scalable to human-sized organs for clinical translation and could eventually be adapted for use in deep-space flight to reanimate crewmembers placed in long-term ultracold SA, upon arrival to the destination exoplanet.

Nanowarming in whole animals- The recent demonstration by Han et al. that the combination of vitrification and nanowarming allows the successful cryostorage and subsequent transplantation of rat kidneys opens a new horizon for the implementation of organ banks [14]. Although the procedure is potentially scalable to be used for cryopreserving whole laboratory animals, the achievement of this goal is likely to lie in the distant future. This limitation does not apply to minute animals like C. elegans where successful vitrification and nanowarming were achieved a few years ago by the group led by Ramon Risco at Seville University [17]. In effect, the study demonstrated that while conventional slow freezing and rewarming of this nematode (which is based on a

rewarming method that uses convective airflow or warm water baths) achieves survival rates of around 3% in adults, the average survival rate climbed to an average of 44% when magnetic nanowarming was used.

Cryopreservation and Reanimation in C. Elegans

This section will be devoted to reviewing the characteristics of the nematode C. elegans as a suitable animal model for reanimation studies after cryopreservation.

The free-living worm C. elegans is a simple nematode that can be easily isolated from high microbial substrates such as decaying fruits and stems, compost, and some invertebrates. Its life cycle, from an embryo to an adult, going through four larval feeding stages (L1, L2, L3, and L4), lasts 3 days (at 20°C). Nevertheless, this occurs as far as the animals are under favorable growth conditions. In nature, when the environment is stressful (lack of food, crowding), L1 larvae can enter an alternative stage known as dauer, in which they can live up to 4 months, and then continue their development until a reproductive hermaphrodite [18].

This small free-living worm has been especially useful for the study of developmental biology, cell biology, and neurobiology, thanks to its short but complex life cycle, its small size (1 mm), and the transparency of its neural network. It contains 302 neurons capable of producing highly plastic behavior, including learning (associative and non-associative) and memory [19]. For all those reasons, C. elegans established itself as a standard model organism for a wide variety of investigations.

The traditional way to cryopreserve C. elegans relies on slow freezing (which allows for ice formation) [20]. This method usually achieves survival rates of less than 25-35% for larval stages L1 and L2) [21]. Due to the ice formation previously described, individuals in the adult stage have an extremely low survival rate (4%). The stocks can be cryostored at -80 ºC or -196 ºC for several years avoiding a reduction in the survival rate, and incubation in glycerol and trehalose after the freezing offers tolerance to multiple freeze-thaw cycles [22, 23].

Vitrification is an alternative procedure with higher recovery rates. For vitrification, very fine capillaries (thermoplastic polymeric capillaries that are sealed at both ends during vitrification and reheating, and opened after this step) that maximize cooling and heating rates, are used, allowing the concentration of Cryoprotectant Agents (CPA) to be drastically reduced inside the worm´s body [24]. Then, the worms are hydrated and washed, to be finally transferred to an agar plate with a bed of E. coli and kept at 20°C. Survival rates obtained by this technique are very high (95%) in the case of larvae (L1 - L4). In the case of adults, these rates are close to 83%. These recovery rates make C. elegans, a highly suitable animal model to study memory function after a vitrification-reanimation sequence, a topic of paramount interest in SA research for deep space travel. Within this context, it is important to mention that it has been reported that when C elegans worms are trained in simple tasks, then vitrified and stored at -196 °C in liquid nitrogen, and then reanimated, they fully remember what they have learned [25]. These results revealed that the animals fully tolerated the cryopreservation process, keeping the integrity of their memory and, consequently, of their nervous system structure. It is important to mention that if the worms are killed (by acute anoxia) and then vitrified, none of them revive after rewarming (Girard et al., unpublished results).

This animal model is highly suitable for basic studies of the neuroprotective mechanisms that allow the worms to tolerate ultra-deep hypothermia. Some readers may think that nematodes are so phylogenetically distant from humans, and their nervous system is so much simpler than the human brain that they are highly unlikely to reveal clues that may allow us to develop SA technologies that

preserve memory in deep-space travelers. The response to that concern may be provided considering how neuroscientists began to understand how memory works. The study of the basic cellular and molecular mechanisms underlying memory formation was begun by Nobel laureate Eric Kandel in a simple animal model, the sea slug Aplysia. Starting with this primitive animal model, Kandel could unravel how chemical signals trigger the formation and consolidation of new synapses, a process that is common to all neuronal systems, ranging from simple invertebrates to humans [26].

Conclusion

The existence of planets orbiting other stars had been hypothesized for decades but it was the discovery of the first extrasolar planet, 51 Pegasi b, in 1995 by M. Mayor and D. Queloz that opened a new frontier in space exploration [27]. This pioneering discovery was soon followed by a fast-growing number of other exoplanets, including many earth-like ones. The transcendence of this discovery is difficult to exaggerate and can only be compared to the discovery of the American continent by Christopher Columbus in 1492. Exoplanets represent an opportunity to colonize new habitable spaces and access new natural resources. One major difference from Columbus's discovery is that these new lands are incredibly distant from Earth and reaching them will require a quantum leap in our technological capabilities, including biomedical ones. In fact, interstellar manned travel will require SA technologies capable of cryopreserving deep space passengers for several decades. Upon arrival at the destination planet, SA must be able to return them to their physiological conditions of life prior to the flight, that is, in possession of all their physical and cognitive capacities. Although interstellar travel is far in the future, the initial steps towards a mature SA technology have already been taken. Thus, reversible cryopreservation of very small organisms such as mammalian embryos is routinely achieved by rapid vitrification and ultrarapid rewarming. In addition, the development of efficient vitrification and nanowarming techniques has made it possible to reversibly cryopreserve organs of considerable size, such as rat kidneys. Furthermore, the recent application of nanowarming to the C. elegans nematode may allow us to assess the effectiveness of this novel technique to efficiently revive cryopreserved adult animals, recovering a fully functional nervous system. We believe that these advances are firm steps in the development of an effective SA technology suitable for manned interstellar flight, among other biomedical applications.

Acknowledgments

The authors are grateful to Ms. Yolanda Sosa for editorial assistance.

Funding

The work from the RGG laboratory was supported in part by Grant # SEGR-9-23-21 from the Society for Experimental Gerontological Research (SEGR) and grant # BRLS-2022 from the Biomedical Research and Longevity Society (BRLS) to RGG.

Ethics approval and consent to participate

All authors agree to publish this article and have accepted to abide by the ethical standards of our Institution. All authors grant their consent for the publication of this article.

Availability of data and material

The information reviewed here is public domain.

Declaration of competing interests

None of the authors has competing interests.

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