Morpheus – Hypometabolic Stasis in Humans for Long Term Space Flight

MARK AYRE[1], CARLO ZANCANARO[2] AND MANUELA MALATESTA[3]
1. *Advanced Concepts Team, ESTEC, Keplerlaan 1 - 2201 AZ, Noordwijk, The Netherlands.*
Email: Mark.ayre@esa.int
2. *Department of Morphological and Biomedical Sciences, Anatomy and Histology Section, University of Verona, Italy.*
Email: carlo.zancanaro@univr.it
3. *Institute of Histology and Laboratory Analyses, University of Urbino, Italy.*
Email: malatesta@uniurb.it

An overview of the application of hypometabolic stasis (HS) to humans for long-term space flight is presented. In the first section, the paper begins with a discussion of why HS in humans would be, from a resource-driven perspective, desirable during long-term space flight. The second section then reviews mammalian hibernation, covering behavioural, physiological and genetic strategies. The third part presents a general review of the effects on human physiology of the space environment, and the overlapping areas between the likely physiological effects of human-hibernation and the space environment are briefly discussed. In the fourth section, possible hibernation strategies for humans are considered, including pharmacological, genetic and environmental tactics. The fifth section briefly discusses the impact of human hibernation at a system level, particularly with regards to life support. The report finishes by concluding that the achievement of the goal of human hibernation on the Earth will probably take decades of research. Hibernation in space, with the concomitant increases in the complexity of the problem caused by the space environment, will be substantially more difficult to achieve. But, if realised, it will be of significant benefit to the extension of human presence in space.

Keywords: Human, hibernation, space, travel, flight, extended

1. Introduction

Whilst the current and near-term focus on space exploration centres around unmanned missions, human voyages back to and beyond the moon can be considered an inevitable feature of our activity in space at some point in the future. Work is already taking place at ESA under the Aurora program with the final goal (via precursor missions and a manned Moon outpost) of a manned Mars mission circa 2033. Beyond the Moon and Mars, human presence in space will hopefully extend throughout the solar system, to the outer planets and their moons, the belts and perhaps beyond.

Transit times to astronomical bodies within the solar system for manned missions will be a complex function of relative positions, transfer-type, spacecraft mass, technology and so on, and therefore will vary considerably from mission to mission. However, we can discuss likely transit durations by taking precedent from existing missions and mission concepts. To get to the moon in the 1960s a journey of just a few days was required. To travel to Mars using currently envisaged technology will take of the order of 6-9 months. For farther flung destinations such as the asteroid belts and the outer planets, travel times for manned missions could quite easily take a period of the order of a decade.

The enabling technologies to send unmanned missions to such distant destinations obviously already exist. For human missions minimisation of transit time will be a key driver, and further advances in propulsive efficiency will work to reduce journey times. However, upper limits to this efficiency (assuming reaction propulsion and ignoring the prospect of exotic propulsion concepts) in the near-term are likely to place lower limits on journey times. This is especially true when considering the mass penalty associated with human missions. Life support system (LSS) costs will be a significant part of the mission payload, and life-support related masses will be strong drivers of the propulsion requirements for the mission [1].

The presently envisaged mass penalties associated with life support are considerable. Taking as an example a manned mission to Mars composed of 6 persons, with a total mission time of a little over 2 years, an Equivalent System Mass (ESM) – a measure taking into account both the quantity of consumable and the equipment required to maintain/deliver/manage it - of 30 tonnes over the total mission duration for food stowage alone is representative. In addition to this are the mass penalties associated with water and atmosphere provision and waste management.

Apart from these basic physiological resource requirements, the journey would challenge human ability to live and work for an extended period of time in an enclosed environment, imposing significant psychological pressures on the crew (for a discussion of these pressures, see [2]). Therefore an environment would be required that is conducive to the maintenance of the mental and physical health of the astronaut (*75m³* of pressurised living space per astronaut for a manned Mars mission [ESA HMM internal study], including facilities such as exercise machines, recreational facilities and so forth). The mass penalty associated with providing life support and a suitable environment would therefore undoubtedly be considerable (recently calculated as approximately 40% of total wet mass within an ESA internal study). The impact of the LSS mass penalty on mission design is summarised in fig. 1.

Given these likely problems associated with life support and the associated mass penalty, an alternative approach is to somehow reduce LSS load to a minimum (whilst still maintaining crew health and effectiveness to acceptable levels). Again taking the Mars mission as an example, between establishment of the interplanetary trajectory and insertion into Mars orbit virtually complete automation is not an unreasonable goal for a well-designed mission. If this were the case, the mission requirement for crew activity during this period would collapse to zero, introducing the possibility of some form of hypometabolic stasis, by which both the physical and psychological requirements of the crew could be minimised. Induction of a state similar to hibernation observed in certain animals, with a concomitant reduction in resource consumption, would reduce drastically the requirements imposed on the LSS in virtually every area (see Table 1). This is with the possible exception of crew safety, where some augmentation could be necessary to compensate for the inability of dormant astronauts to respond to contingency events.

Looking to the natural world, hibernation is a common tactic for organisms that wish to survive in an environment where the normal pace of life is not possible or practical. The length of hibernation is dependent upon the periodicity of the environmental change that requires it; hibernation is normally based around seasonal variation, and therefore normally has an annual periodicity. However, shorter and longer term suspension of life is observable, for example in the case of seeds, which commonly can remain in the dormant phase for several years or more until the right environmental conditions prevail.

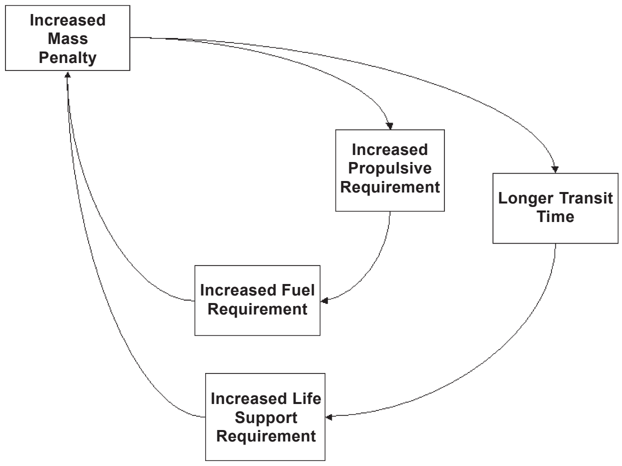


Fig. 1 The impact of the LSS mass penalty on mission design.

Attainment of the ability to place human beings into stasis has application beyond that of LSS load reduction in manned space missions. There are several other areas in which human stasis would be useful. This fact has been recognised by, for example, the US military, who have sponsored research into rapid induction of a hibernation-like state to aid in treatment of wounded soldiers. The application extends to other therapeutic measures such as induction of an analogue-anaesthetised state in patients during surgery, the development of therapeutic measures to combat obesity, and organ preservation techniques based on hibernation biochemistry [3].

2. Hibernation

Hibernation is one of five recognised forms of dormancy displayed by animals. The five states of dormancy are:

- Sleep
- Torpor
- Hibernation
- Winter sleep
- Aestivation ('summer sleep').

It is difficult to establish clear-cut boundaries between hibernation and other types of dormancy. Many animals, including poorwills, some bats, and some ro-

TABLE 1: *The Effect of HS on the Requirements Placed on the Main Areas of Life Support.*

Life Support Area	Purpose	Effect of HS
Atmosphere Management	Atmosphere composition control, temperature and humidity control, pressure control, atmosphere regeneration, contamination control, ventilation	Reduced heating requirement, reduced regeneration requirement
Water Management	Provision of potable and hygienic water, recovery and processing of waste water	Reduced drastically
Food Production and Storage	Provision and, potentially, production of food	Reduced Drastically
Waste Management	Collection, storage, and processing of human waste and refuse	Reduced Drastically
Crew Safety	Fire detection and suppression, radiation shielding	Augmented?
Crew Psychology	Maintenance of crew mental health	Reduced Drastically

dents, can enter either hibernation or what appears to be a daily torpor. While active, most mammals have an average body temperature around 37° C (99° F). In hibernation, the body temperature generally falls below 10° C (50° F) and, in many species, may drop as low as 5° C (41° F). The body temperature of a hibernating Arctic ground squirrel for example may be as low as –2° C (27° F), depending on the season of the year and other environmental conditions. Some desert ground squirrels that aestivate during the hottest part of the year remain inactive throughout the winter, so it is difficult to mark when aestivation ends and hibernation begins in these animals. These grey areas between the classifications of dormant behaviours make classification difficult; it must therefore be appreciated that individual species often do not fall cleanly into a specific dormancy classification.

Hibernators exist in every phylum, and the behavioural and physiological mechanisms that animals use to hibernate are as diverse as the animals themselves (for examples of general metabolism suppression, see [4]). In this review, because of their phenotypical/genotypical similarity to humans (belonging to the *mammalia* class), only mammalian hibernation is considered. Within the class *mammalia* hibernators exist in the orders *Monotremata, Marsupialia, Primates, Insectivora, Chiroptera, Carnivora* and *Rodentia*. There exist many different behavioural and physiological mechanisms peculiar to specific species within these orders, but there also exists a wide range of common behaviour and mechanisms that characterise mammalian hibernators as a whole. The typical mechanisms of small true hibernators (such as the ground squirrel *Spermophilus tridecemlineatus*) and those of larger winter sleepers (such as the Brown bear *Ursus arctos*) are of most interest in terms of application to HS.

2.1 Pre-Bout Strategies

Well before the actual dormancy event, a sequence of physiological events months in advance marks the beginning of preparation for hibernation/winter-sleep. For seasonal hibernators, entrance into hibernation is preceded by changes in behaviour and physiology that lead to the accumulation of energy stores. Hibernators store energy either exogenously through storing food in caches or endogenously through the accumulation of fat reserves, with many species employing both tactics. Food caches are used by true hibernators, and drawn from during periodic arousal, whilst winter sleepers rely more on endogenous reserves of energy.

In storing energy endogenously, white adipose tissue is the most efficient form of fuel storage. During the pre-hibernation fattening period, increased deposition of lipids is stimulated by increased plasma insulin content. Insulin both stimulates the synthesis and inhibits the breakdown of glycogen, triglycerides and protein. High insulin levels also decrease the activity of lipase, the major lipolytic enzyme that releases fatty acids from triglyceride stores. In addition to laying down of white fat reserves, in some mammals a specialized tissue known as brown fat is also accumulated. Brown fat is found in patches along the neck and major blood vessels, and between the shoulders of newborn mammals (including human infants), and in adult hibernating animals. Cells that contain ordinary fat burn fuel and use the energy to power various life processes. Brown fat cells differ in that they burn fuel and release the energy directly as heat in a process known as nonshivering thermogenesis.

2.2 Entry into Bout and Bout Strategies

As the time to enter hibernation approaches, all hibernators and winter sleepers select a specially chosen or constructed place within which to hibernate, termed the *hibernaculum*. For example, alpine marmots (*Marmota marmota*) retreat in family groups into their hibernacula during late September, closing the entrance with a plug constructed out of stones, clay and faeces. Examples of hibernacula are diverse and include caves, tree bowls, buildings etc. However, all these locations are related in that they provide some measure of environmental protection and regulation that is conducive to the hibernation process.

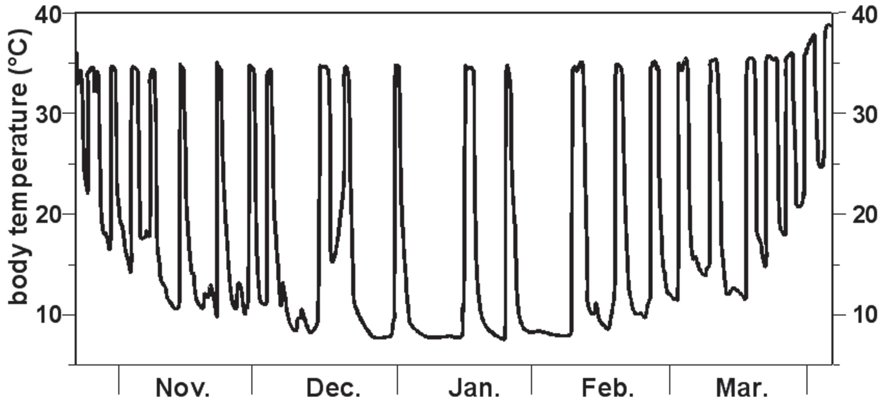
How the time to commence hibernation is chosen is poorly understood. Hibernation cues vary with species, and include photoperiod (day length) and circannual rhythm. With regards to selection of hibernation time, two types of hibernators can be broadly defined - permissive and obligatory. For example, Syrian hamsters (*Mesocricetus auratus*) fall into the permissive category; they have the option to hibernate depending on conditions of temperature and food supply (suggesting some internal mechanism for selecting the time to hibernate). Obligatory hibernators do so regardless of conditions and are generally obese before entering hibernation. The existence of a hypothesised ‘trigger molecule’ that initiates hibernation has been hypothesised since 1969 [5]. One such molecule has been found in the plasma of deeply hibernating woodchucks, ground squirrels, bats, and black bears, and has been termed the Hibernation Induction Trigger (HIT). It is a natural proto-opioid whose chemical identity is not yet completely clarified and which can act as a powerful metabolic inhibitor in non hibernators [6, 7]. Entry into hibernation proper is characterised by a drastic reduction in metabolism. In the ground squirrel, for example, the respiratory rate drops from a normal of 200 breaths per minute to 4 to 5 per minute, and the heart rate from 150 to 5 beats per minute. Breathing can become episodic with bouts of apnoea. The slow breathing and heart rate reduces cerebral blood flow to levels that would cause brain damage and neuronal death in non-hibernators. However, in hibernators, the drastic drop in cerebral metabolic rate and thus demand for oxygen allows such a reduction to be tolerated.

In most hibernators, the body temperature is closely checked by internal systems (the set-point). If the body temperature drops dangerously close to the freezing point, the animal will wake, or initiate compensatory heat generation mechanisms such as shivering or non-shivering thermogenesis. Some hibernators, such as the arctic ground squirrel (*Spermophilus parryii*) actually cool to below freezing, at –2°C. These hibernators avoid freezing by supercooling their body fluids, entering a metastable state where crystallisation in avoided through the absence of freezing catalysts and nucleators (principally proteins, which are sequestered into non-freezing regions of the body [8]).

In contrast to true hibernators, winter sleepers do not experience such drastic drops in metabolic rate and body temperature. Winter sleepers are larger, and therefore have less need to save energy since their normal Body Mass Ratios (BMRs) are low relative to their energy stores. In addition, larger mammals have relatively low metabolic rates compared to small mammals; combined with their large body mass, this would indicate a large metabolic effort to raise body temperature from near ambient to euthermic levels. It is thought that the bear uses a number of strategies for countering muscle atrophy during wintering periods; protein synthesis through recycling urea, rhythmical muscle stimulation (isometric), and drawing on labile (non-fixed) protein reserves.

True hibernators awaken at regular intervals throughout the hibernation period to eat, drink and eliminate wastes before returning to hibernation. During these periodic arousals, physiological parameters such as body temperature are rapidly returned to euthermic levels (see fig. 2); an energy intensive process at odds with the energy-conserving function of hibernation. The energy expended in warming up and maintaining high body temperatures during these euthermic periods is estimated to be as much as 90% of the total energy expenditure over the entire hibernation event. These periodic arousals should therefore play a key role in survival during hibernation. Animals emerging from a bout of hibernation appear to be sleepy, and spend most of their euthermic time between bouts in NREM (i.e. deep) sleep. Additionally, the intensity of this sleep decreases as the euthermic period progresses [9]. These observations have led some scientists to hypothesize that animals may actually become sleep deprived during hibernation and that they arouse periodically in order to catch up on their sleep [10]. Periodic arousal from torpor is thought to be necessary for the neural

Fig. 2 Variation in body temperature of marmota marmota, showing periodic arousals throughout hibernation period.



conditioning that sleep provides, a hypothesis strengthened by evidence of sleep-inducing substances that accumulate in the brain during wakefulness [11].

During the hibernation/winter-sleep bout, heat generation, although suppressed, does continue. The mechanisms for heat generation are shivering and non-shivering thermogenesis. Shivering thermogenesis involves activating mutually antagonistic muscle groups such that ATP is hydrolysed to produce energy, whilst producing no directed physical work; the released energy thus appears as heat. Non-shivering thermogenesis is based on 'brown fat' accumulated during the pre-bout period. Brown fat is characterised by extensive vascularisation and a high number of mitochondria (the brown colouration being caused by mitochondrial cytochrome oxidase). Non-shivering thermogenesis is fuelled by oxidation of fatty acids and glucose, such that hardly any of the energy released is directed towards ATP synthesis.

Winter sleepers stay dormant throughout the hibernation period without eating, drinking, urinating or defecating. Over-wintering bears use ursoeoxycholic acid to avoid problems with gallstones. Bears also reduce kidney function; they do not urinate for months but don't suffer from urea poisoning. Urea is broken down and the resulting nitrogen used to build protein, which is then used to alleviate muscle atrophy. To illustrate the differences between winter sleepers and true hibernators, Table 2 shows a summary of the body temperature and respiratory rate differences between black bears and arctic ground squirrels.

At the cellular level, animal cells obtain energy in the form of ATP (produced in the mitochondria) by oxidizing nutritional substrates through the process of respiration. The hydrolysis of ATP then supplies the energy needed for cellular processes, such as the transport of molecules or cellular movement.

TABLE 2: *Compared Physiological Rates of Black Bears and Arctic Ground Squirrels.*

	Summer respiratory rate	Hibernating respiratory rate
Black bear	30 breaths/minute	2 breaths/minute
Ground squirrel	60 breaths/minute	Holds breath ½ hour, takes 10-15 breaths, repeats
	Summer body temperature	**Hibernating body temperature**
Black bear	37 °C	30 °C
Ground squirrel	37 °C	-2 °C

The main consumers of ATP are ion pumping, protein synthesis and protein degradation processes. During hibernation, suppression of both energy production and energy consumption processes is necessary to maintain cellular homeostasis and prevent loss of electrical activity and eventual cell death.

A considerable percentage of the basal metabolic rate (i.e. ATP consumption) of a cell is attributed to ion pumping in order to maintain ion gradients across cell and mitochondrial membranes. These gradients are necessary for facilitation of diffusion or secondary active transport of metabolites, and mitochondrial ATP production itself. During hibernation, in order to maintain ion homoeostasis under reduced metabolic conditions, functional downgrading of ion channels occurs and ion-pumping activity is markedly suppressed. Membrane conductance for ions can either be affected through changing channel density or changing channel properties. The most important method of ion channel suppression is phosphorylation of ion-channel proteins. Protein synthesis is also regulated via reversible protein phosphorylation. Reversible phosphorylation involves the addition or removal of covalently bound phosphate to/from enzymes and functional proteins, drastically suppressing their activity, and is one of the most important mechanisms used by hibernators [12].

2.3 Gene Expression Changes in Hibernation

From an evolutionary perspective, there exist two hypotheses for hibernation [13]. A common mammalian ancestor which had the ability to hibernate which was subsequently lost in all but a few ancestors, or convergent evolution, where different mammalian heritages have independently arrived at the ability to hibernate. Hibernating species are frequently closely related to non-hibernating species. This, coupled with the phylogenetic distribution of hibernating species across the mammalian order lends credence to the hypothesis that hibernation is based molecularly upon differential mechanisms of common genes rather than creation of new genes. In this case, a small number of regulatory changes determine the phenotype of hibernation, rather than creation or loss of numerous hibernation-specific biochemical mechanisms, encoded by a selection of hibernation specific genes. Therefore, hibernation is thought to be the result of a reprogramming of existing mammalian biochemical capabilities through the differential expression of existing genes [14].

The low body temperatures associated with hibernation reduces rates of molecular synthesis and degradation, with a reduction in activity of all enyzmes related to protein homeostasis. Rates of transcription, translation, mRNA degradation and protein degradation should all decrease proportionally as a function of body temperature, and hence this could be expected to be sufficient to maintain protein homeostasis. However, the preferential synthesis and blocking of specific gene products indicates the existence of hibernation control mechanisms based on differential gene expression.

2.4 Post Bout Strategies

Upon termination of the bout, the biochemistry and metabolism of the hibernator returns to euthermic levels. However, the hibernation bout will have had a somewhat deleterious effect on the physical condition of the hibernator/winter-sleeper. Principal amongst these is a large loss in body mass (both lean-muscle and fat). Post-bout behavioural imperatives therefore centre on the consumption of food in order to improve physical condition.

As a final aside, one of the most exciting issues in hibernation is the possible hibernation-associated increase in longevity of the whole animal. There is some descriptive evidence showing convincingly that hibernating hamsters live longer than non-hibernating individuals of the same species [15]: in fact, a positive correlation was found between the length of life of 288 Turkish hamsters and the amount of time spent in hibernation, suggesting that the process of aging is slowed during hibernation; quite recently, it has been found that bat life span significantly increase with hibernation [16]. From these data, the conclusion that hibernation per se prolongs life does not necessarily follow: an alternative explanation could be that non-hibernating animals were undergoing a greater stress (at the individual/organ/cellular level) and hence would age faster. However, the obvious relevance of a possible hibernation-associated increase in life span to any exploitation of hypometabolic states to manned space missions strongly suggests the need for close investigation of the involved mechanisms. An interplay between hibernation mechanisms involved in increased longevity and those responsible for the protection of key organs and systems during hibernation bout is likely. Albeit the precise mechanisms underlying the hibernator's ability to maintain life in the extreme conditions of the hibernation bout are still matters of research, several lines of evidence indicate that multiple metabolic and regulative adaptations mediate such a phenomenon.

3. The Space Environment

The human space environment (a typical environment aboard a spacecraft or space station away from Earth orbit) imposes several different stressors on the human organism. These can be identified as the following:

- Isolation
- Altered social interactions
- Confinement
- Reduce afferent flow in the central nervous system (CNS)
- Hypokinesia
- Removal of circadian cues
- Increased radiation
- Micro-gravity.

Because these factors are all present, it is very difficult to isolate and quantify the degree to which different stressors are responsible for the observed physiological and behavioural changes associated with spaceflight. Many physiological changes observed in subjects during microgravity experiments (full stressor range) are similar to those observed in bed-rest studies (due to hypokinesia but also psychological stressors), which in turn have physiological effects partially similar to those observed during confinement and isolation studies (psychological stressors only). Table 3 shows the partitioning of stressors between these three main types of study conducted.

Investigation of the psychological stressors associated with the space environment has been conducted through isolation studies such as the EXEMSI study [17]. These have produced effects such as, for example, loss of body weight, and the same pattern of changes in parameters such as blood volume and regulating hormones renin and aldosterone as bed rest [18]. Confinement also has a major effect on the immune system of both animals and humans, principally through an increase in stress response [19]. Hypokinesia and reduced afferent flow in the CNS have been investigated through bed-rest studies, such as [20]. Additionally, the use of 'tilt-down' bed-rest studies has allowed investigation of some of the physiological effects that accompany microgravity (principally body fluid redistribution [21]).

Microgravity is the principle stressor in the human space environment. Animal and plant physiology is a tuned response to the huge diversity of environments present on the earth, with environmental differences encompassing ranges of temperature, water supply, pressure and so forth. However, gravity is effectively constant over the entire range of terrestrial environments (and has been so over the entire evolutionary period of life on Earth). It is therefore readily apparent that the constant presence of gravity during the evolution of life on earth has influenced and indeed largely dictated a substantial fraction of the evolved physiological strategies and mechanisms that biological agents use in order to survive. This influence extends from the macro-scale physiological adaptation of large muscle groups, the musculo-skeletal system, motor adaptation, through to the cellular and molecular level, where gravitic field fluid dynamics (buoyancy, convection, sedimentation, hydrostatic pressure) have ordered the structure and mechanisms of life at a cellular level (for example plants require positional cues from gravity in order to direct growth, both at a macro and cellular level [22]). All life forms are predominantly composed of liquids, and employ surfaces to isolate their different constituents and facilitate/mediate the enormous number of biochemical reactions that are essential to support life. With this in mind, it is obvious that a change in the magnitude or removal of gravitation will have a substantial effect on biological systems.

TABLE 3: *Space Environment Stressors and Their Spread Across Studies.*

<table>
<tr><td>Isolation</td><td rowspan="3">Confinement Studies</td><td rowspan="5">Bed-Rest Studies</td><td rowspan="8">Space Environment Studies</td></tr>
<tr><td>Altered Social Interactions</td></tr>
<tr><td>Confinement</td></tr>
<tr><td>Reduced Afferent flow in CNS</td><td></td></tr>
<tr><td>Hypokinesia</td><td></td></tr>
<tr><td>Removal of circadian cues</td><td></td><td></td></tr>
<tr><td>Increased Radiation</td><td></td><td></td></tr>
<tr><td>Micro-gravity</td><td></td><td></td></tr>
</table>

In addition to microgravity, the ionising radiation environment of interplanetary space is a source of danger to astronaut health. The radiation environment is principally composed of galactic cosmic rays (protons, alpha particles, HZEs) and is very difficult to shield against. Additional radiation load is provided by solar particle events (solar flares) composed mainly of protons and helium ions. However, particulate energy of solar flares is much less than that of cosmic radiation (typically less than 1 GeV/nucleon) and so shielding is more effective. Nevertheless, secondary particle production can be important in higher energy events. Galactic cosmic radiation (GCR) can however be fragmented by the shielding, and the GCRs and their products can penetrate further into the shielding and expose the astronaut. Curtis *et al.*, [23] estimate that over a three year journey to Mars at solar minimum, between 40 and 50% of neural cells in certain critical areas (retina, hippocampus, thalamus) will be traversed by a particle with a Z greater than or equal to 15. Ionising radiation can act both directly and indirectly to promote carcinogenesis and oncogenesis. Direct impact of nuclear or electromagnetic radiation can produce physical lesions in DNA; indirectly, radiation effects on the cell structure may be equally important, through the production of intracellular electrophiles and reactive oxygen species (ROS) [24], which can cause genetic damage themselves, by causing nucleotides to cross link each other.

Generally, exposure to the space environment induces two types of response:

- Adaptive – neuromotor adjustments, occur as the body compensates for the lack of gravitational pull and or stimuli, and taper off as the body adapts to microgravity
- Pathophysiological – disuse osteoporosis or chromosomal damage from radiation exposure arise as space environment induced changes to the body proceed.

3.1 Hibernation Mechanisms and the Space Environment

In the case of humans hibernating in space, some of the stressors will effectively be obviated (see Table 4).

In the hibernation instance, the psychological stressors are effectively obviated, since the hibernating subject is not awake to worry about his or her situation. This can extend to the circadian cue stressor, since circadian cueing is mediated in humans by photonic sensing. However, in hibernation, afferent flow through the nervous system is likely to collapse to effectively zero; this might have several physiologically (and particular neurologically) undesirable effects. In addition to this the degree of hypokinesia experienced will be increased, again with muscle use effectively collapsing to zero; this is likely to increase the atrophic effects on muscles. Of course, significant remedy to such a drawback would come from proper mimicking in the human of the strategies used by natural hibernators, which apparently do not present significant neural or musculoskeletal deficit at arousal from hibernation. The microgravity and radiation effects are obviously left unchanged.

The potential of an artificially induced hypometabolic state is enormous in the field of manned space missions, although a full hibernation state (very low body temperature, a few heart beats per minute, striking reduction of brain electrical activity) is not needed to get consistent benefits in terms of energy saving. A hypometabolic state could in fact contrast the negative effects of low gravity and reduced physical activity on the musculoskeletal apparatus, reduce the overall energy requirement and help with the stress associated with long-term missions. It is likely that reduced ventilation, heart rate, kidney filtration and CNS activity could make the organism less sensitive to the deleterious effects of microgravity. Appropriate light/dark cycles could help cells and tissues to keep normal circadian rhythms during the hypometabolic period, although it is possible that no significant degradation of the internal clock would occur in the absence of a deeply hibernating state. As for the periodic interruptions of the hypometabolic state, they could have conflicting consequences: they could allow to reset organic functions similarly to true hibernators but, on the other hand, they would imply both important energy expense and increased sensitivity to space environment effects.

4. Strategies For Human Hibernation in Space

In common with natural hibernators, human hibernation strategies will encompass techniques before, during and after the hibernation event. We can classify hibernation strategies as being divided into three groups:

- Pre-bout
- Bout (including actions taken to enter and exit hibernation)
- Post-bout.

Additionally, these can be further divided into the following areas:

- Genetic
- Biochemical/physical
- Environmental (hibernacula).

4.1 Pre-bout

Pre-bout strategies will involve preparative efforts to ready the hibernator for the hibernation event. A high level of physical fitness would obviously be desirable, in order to maximise the body's ability to deal with the stress of the hibernation event, and to start from a 'higher' point so that physical mission effectiveness is as high as possible after the unavoidable deleterious effects of the hibernation bout. Therefore, physical conditioning will probably play an important role in preparation for hibernation. Physical conditioning could incorporate not only exercise to improve lung and heart efficiency, but also perhaps accumulation of fat reserves if fat conversion is to be used as a bout hibernation strategy. This could range from simple accumulation of white adi-

TABLE 4: *Interactions Between Hibernation and Space Environment Stressors.*

Space Environment Stressor	Obviated by hibernation	Exacerbated by hibernation	Unaffected by hibernation
Micro-gravity			X
Increased Radiation			X
Reduced afferent flow		X	
Hypokinesia (reduced muscle use)		X	
Removal of circadian cues	X		
Confinement	X		
Isolation	X		
Altered Social Interactions	X		

pose tissue, for which humans are already fully adapted, or accumulation of brown adipose tissue, effected through genetic engineering means. In tandem with physical training, the administration of compounds to induce desirable effects within the body could be employed. This could include use of steroids to improve muscle tissue growth rates during preparative physical conditioning, or to stimulate lipid accumulation.

Psychological preparation will also play an important part. An astronaut typically possesses a high level of mental resilience. However, coming to terms with a potentially high-risk event whereby you effectively lose six months of your life (although decreased metabolism would probably lead to decreased oxidative stress, cellular division and hence possibly increased lifespan) will require psychological preparation. Closer to the event, it may be necessary to place the hibernator into space for a time period sufficient for certain adaptive reactions to occur, for example vestibular adaptation to weightlessness.

4.2 Entry into Bout and Bout

Previously mentioned, brown adipose tissue, used by various mammalian hibernators to produce heat through non-shivering thermogenesis, is also present in humans (and is used extensively by babies). Therefore it is possible that this could be a possible mechanism used by hibernating humans in space. However, hibernation strategies for human spaceflight, which is not a winter survival situation (environmental temperature is under the control of spacecraft designers), may not require survival strategies associated with body-temperature maintenance, such as non-shivering thermogenesis, freeze avoidance (animals which maintain body fluids in a liquid state well below the expected environmental minima for their habitat, dangerous because there is a danger of both endogenous and exogenous nucleative freezing events) and freeze tolerant hibernators (those which can tolerate partial freezing of body fluids [25]).

Pharmaceutical measures are likely to play a central role in maintaining both the hibernative state, both through initiating and regulating suppression of the metabolism and also protecting against the atrophic effects of hibernation (again, the overlap between space-environment countermeasures and hibernation-effect countermeasures should be remembered).

One possible compound that could be used to induce a hypometabolic state is the synthetic compound DADLE (Ala-(D)Leu-Enkephalin), which has been found to extend the time organs can be kept viable before transplantation, and more directly can induce hibernation in animals by mimicking the action of the HIT molecule. DADLE, a synthetic product of amino acids, is a modified form of a naturally occurring opiate substance called an enkephalin, found in the brains of mammals. Opioids have been shown to cause bradicardia, hypotension, respiratory suppression and lowering of set-point in thermoregulation, all changes similar to those observed during the annual cycle of mammalian hibernators. Another compound that has received interest is the neurotoxin Tetrodotoxin, which is commonly associated with the tetraodon pufferfish, and is the active component behind the ritualised ‘zombification’ practised in Voodoo. Tetrodotoxin selectively blocks the voltage-sensitive sodium ion channels of excitable tissues, and as a result disrupts nervous function, leading to paralysis (although this would not appear a desirable result).

Examples of compounds that could maintain physiology during hibernation include dobutamine, which has been shown to induce and maintain conditioning effects in muscles similar to those seen with exercise training [26]. Administration of dynamically composited fluids and electrolytes through a drip could allow compensation for changes in blood composition. For example, the use of diphosphonates could prevent increases in urinary calcium and inhibit bone reabsorption. Hormonal compounds in particular will also be important due to their principal role in regulating homeostasis and physiological function. Examples of possible application include use of Insulin-like growth factor (IGF-1), which has the potential to ameliorate space-flight induced immune problems and therefore also the reduction of leukocytes which may occur in human hibernation. Spaceflight reduces the activity of naturally forming IGF-1 in the body, and supplementation could allow the hibernator to benefit more greatly from IGF-1; IGF-1 is an important cytokine for growth process regulation, acting on peripheral tissue to promote growth. IGF-1 is also an important component in erythropoiesis (red blood cell formation) and marrow blood cells that develop into immune cells are also responsive to IGF-1 [27].

Re-introduction of the gravity vector through using artificial gravity could be used to alleviate the physiological problems associated with the microgravity stressor – by far the most influential stressor in the space environment. There may be certain undesirable effects on the Neurovestibular system, through the Coriolis forces induced by the rotation, as yet largely unquantified. In the hibernation instance, use of artificial gravity will leave just the afferent flow and hypokinesia stressors, which already share a large degree of commonality with the physiological effects of hibernation. These reduce the problem to that of a bed-rest situation. Crucially, this would then allow more development of the required technology to be conducted on Earth.

The depth to which the metabolism is suppressed may make periodic arousal, as practised by many small hibernators, a necessary action. Periodic arousal would allow mitigation of physiological deterioration through various waking behaviours (exercise, mental activity, nutrient consumption, hydration etc.), but would not be advantageous, due to the likely difficulties associated with entering and exiting the hypometabolic state. This difficulty would be a combination of the operational complexity of entering the hypometabolic state (which could be a very complex and physiologically stressful process) and the associated risk; entry and exit of the hypometabolic state, like take-off and landing in aviation, could be high-risk events (and furthermore could have a cumulative negative impact on the hibernator's physiology), which it would be operationally undesirable to undertake repeatedly. Periodic arousal would also have consequences for the LSS. From this perspective, it may be more preferable to place the astronaut into a mode of dormancy closer to winter sleep rather than true hibernation.

4.3 Genetic

Pre-bout strategies could conceivably encompass the entire life span of the hibernating agent in the form of gene therapy to produce human beings with an innate capability to hibernate with very little requirement for environmental control beyond that required by natural hibernators. The focus would be on gene therapy that introduces desirable characteristics such as sensitivity to certain environmental cues to induce hibernation, genetic suppression of metabolism and so forth. It is likely that humans already possess at least some of the genes associated with hibernation techniques, such as those that involved with fat metabolism (PL and PDK-4).

It could be expected that as knowledge of genetic engineering increases, the ability to internalise hibernation mechanisms e.g. gene-driven enzyme phosphorylation within the phenotype would increase (Fig. 3). However, reliance on environmental techniques will still play a part (for travel in the hostile environment of space, the hibernator is obviously going to be reliant on the hibernaculum to some degree).

4.4 Post-bout

Upon revival, the astronauts would be required to rapidly reacquire a nominal level of mission effectiveness. Physical conditioning in the form of exercise, optimal nutrition, and post-bout drug therapy are likely elements of a post-bout programme of 'rehabilitation'.

5. Engineering/System Issues

In analogy to the animal world, a specific region or regions of the ship will be required to provide a suitable environment within which the astronauts can enter, sustain and exit torpor safely – their hibernaculum. Because at present the hibernation technique is unknown, it is impossible to determine exact requirements placed on the hibernaculum. However, the peculiar state of the hibernating human is likely to be analogous to that of a medical patient, and as such will likely require continuous monitoring and intervention, through administration of pharmaceutical compounds, and so forth. Such

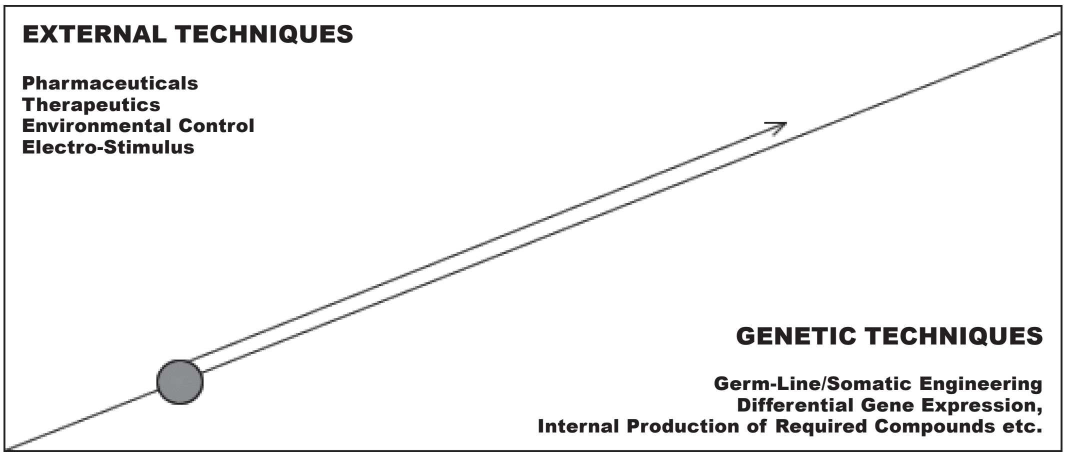


Fig. 3 Increasing maturity of biotechnology and genetic engineering will result in increasing internalisation of hibernation mechanisms.

external control will also likely extend to the mechanisms by which the hibernation is entered and exited. Additionally, the hibernaculum will of course also have to provide a basic life support function in lieu of the shipwide LSS that is in some areas augmented whilst in other areas reduced. The essential requirements on the hibernaculum are therefore:

- Control of entry, maintenance and exit of the torpid state
- Life support.

5.1 Hibernation Control

Hibernation control will require a range of medical sensing and administration equipment for each individual astronaut that will be driven by the requirements for external intervention into the hibernating astronauts' state. It seems reasonable that data provided to the agent and the ground station in order to monitor hibernating astronauts include at least the following:

- Body temperature
- Electrocardiogram & heart rate
- Electroencephalogram
- Gas exchange (respirometry)
- Capillary blood pressure.

All such data are provided non-invasively by current medical technology. Further, useful information (blood glucose and metabolite levels, haemogas-analysis, blood levels of drugs, clotting time etc) could be obtained at definite intervals by means of available minimally invasive procedures (e.g., finger puncture for capillary blood).

Additionally, an agent (a nurse) would be required to interpret and act upon the information acquired in a timely manner. In order to fill the agent role, one or more crew members could conceivably remain awake in order to monitor and control the condition of the remaining hibernating astronauts. However, for the small crew sizes envisaged for future deep space missions, this would significantly obviate the resource saving gained from the hibernation tactic, as well as introduce potential psychological issues due to the reduced *effective* crew size (including possible situation-specific psychological responses such as resentment towards the hibernators).

Communication delays between the vessel and Earth would be of the order of minutes to hours. Relay of medical monitoring information to Earth, decision making and then relay of the decisions back to the spacecraft for implementation would be possible, but would be dependent upon the time-scale of possible adverse effects and problems during the hibernation process (as well as a very robust communication link with no down-time). Looking to examples of reactive timescales in ordinary medicine applied to patients in a vegetative state (intensive care, coma), although a nurse is not continuously involved in monitoring the patient, medical staff are available to administer reactive measures in response to alarms from monitoring equipment in a matter of minutes, if not less. Thus in-situ monitoring and control of the hibernative state is required, and therefore so is an automated AI agent.

An AI agent (the agent paradigm includes all types of AI implementation, neural nets, expert systems etc.) can be defined as an entity capable of carrying out goals, perceiving and acting autonomously. The key concepts are therefore autonomous operation, i.e. the ability to carry out certain functions without help from other agents, and community, where within the agent cooperates with other agents (in this the ground segment) to some degree to synergistically achieve high level goals [28]. Agent technology is already finding increasing application within health care in functions such as coordinating distributed data, maintaining autonomy of collaborating participants, scheduling and monitoring [29]. Examples of agent technology specifically applied to patient monitoring and administration include GUARDIAN [30], which monitors and diagnoses intensive-care patients recovering from heart surgery. The GUARDIAN potentially has the ability to operate independently, but is aimed at supplementing human agents in diagnostic decision-making. Work has also been performed on using neural networks as intelligent agents for medical diagnosis [31].

As previously outlined, the tasks of the agent would involve automated monitoring of the hibernator and environmental parameters, and automated control actions such as therapeutic drug delivery and environmental regulation. These task responsibilities would cover not just maintenance of hypometabolic stasis, but also perhaps initiation and termination of the bout, through the administration of chemical or environmental cues (depending on the mechanics of the hibernation strategy, and the task division between the hibernator and the agent).

5.2 Life Support

The basic life support function of the hibernaculum will be much reduced with respect to the ship-wide LSS (the reason it would be used). This reduction takes two forms; redundancy of certain LS functions, and a scale reduction and localisation of the remain-

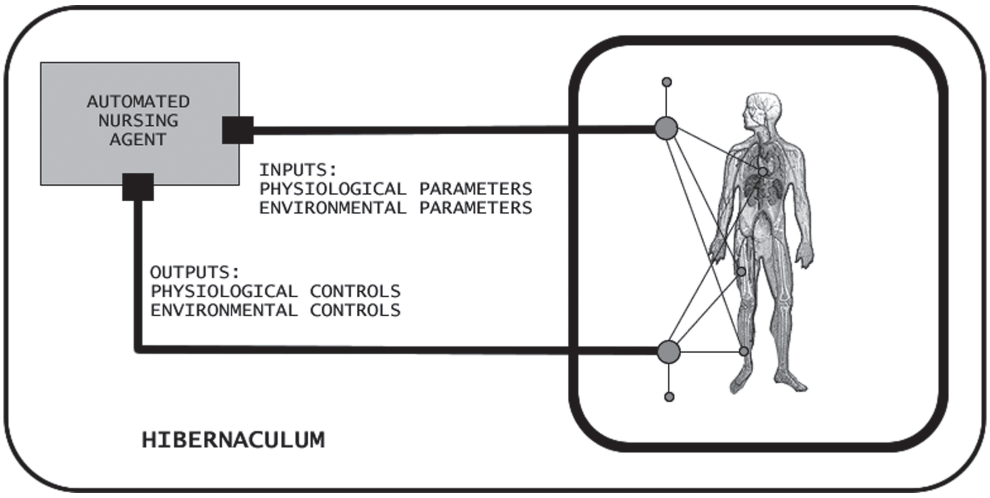


Fig. 4 Human hibernation system.

ing functions. The crew complement of a deep space mission will invariably include more than one astronaut; thus during periods of hibernation there are likely to be several hibernators. It is envisaged that there will be some common areas between astronauts regarding the LS function (such as radiation shielding) and that the majority of basic LS functions during hibernation would be combined.

Figure 5 shows the main life support functions and their interrelationships, with the greyed-out areas corresponding to those elements of LS that are not required during hibernation. Food production and preparation are obviously redundant during hibernation, as is the use of hygiene facilities such as showers and toilets. The major physiological process that the hibernating astronaut will continue is of course respiration from breathing and through the skin. Thus the main component of life support that will have to be maintained is atmosphere revitalisation. All the normal atmosphere management processes associated with a life support system will be required (control and supply, temperature and humidity control, atmospheric monitoring, ventilation, fire detection and suppression).

In tandem with this will be the need for some degree of water management due to the requirement for processing atmospheric condensate, and maintaining moisture balance in the atmosphere. Additionally, there might exist some requirement for hydration due to moisture loss through respiration, although this is envisaged to be dealt with by the hibernation control system in tandem with administration of other compounds (through for example a drip). Both the atmospheric revitalisation and water management functions themselves will require waste processing. Wastes from the hibernaculum will be in the form of particulates (outgassing from the astronaut and the hibernaculum environment), and concentrated absorbed or absorbed gases (Carbon Dioxide, Methane etc.)

These remaining LS functions will of course be radically descaled. For example the metabolic and breathing rate of a hibernating human will be drastically lowered compared to even a normal sleeping human, thus moisture transfer to the atmosphere through respiration/perspiration will be much lower. The quantities of waste generated from the atmospheric and water management functions are likely to be very small (perspired and respired moisture are very 'pure' sources of waste water), so waste stabilisation and storage rather than processing would appear to be more suitable, although this is of course a function of time spent in torpor.

The choice of technologies for the LS functions mentioned above will be dictated by the peculiarities of the required environment and the specific parameters associated with each loop (impossible to define at present). However, the general conclusion can be made that physico-chemical (PC) systems would be more suitable for life support in a hibernaculum. This is primarily due to the requirement for high responsiveness (the hibernaculum will be activated and deactivated at least four times during a round trip mission) which biological LS systems could not accommodate. Furthermore, PC systems are generally more compact, a key advantage should the hibernaculum LS systems run separately from ship-wide LS. PC systems are also well understood and typically low maintenance, of crucial importance when the astronauts cannot intervene in their function. PC systems are more energy hungry than biological systems, but the extremely low load associated with a hibernating astronaut would indicate that energy consumption would still be very low.

If hibernation is entered after leaving orbit, hibernation would occur over periods in which there are just minor course-corrective manoeuvres. In-transit course corrections for deep space missions are likely to be

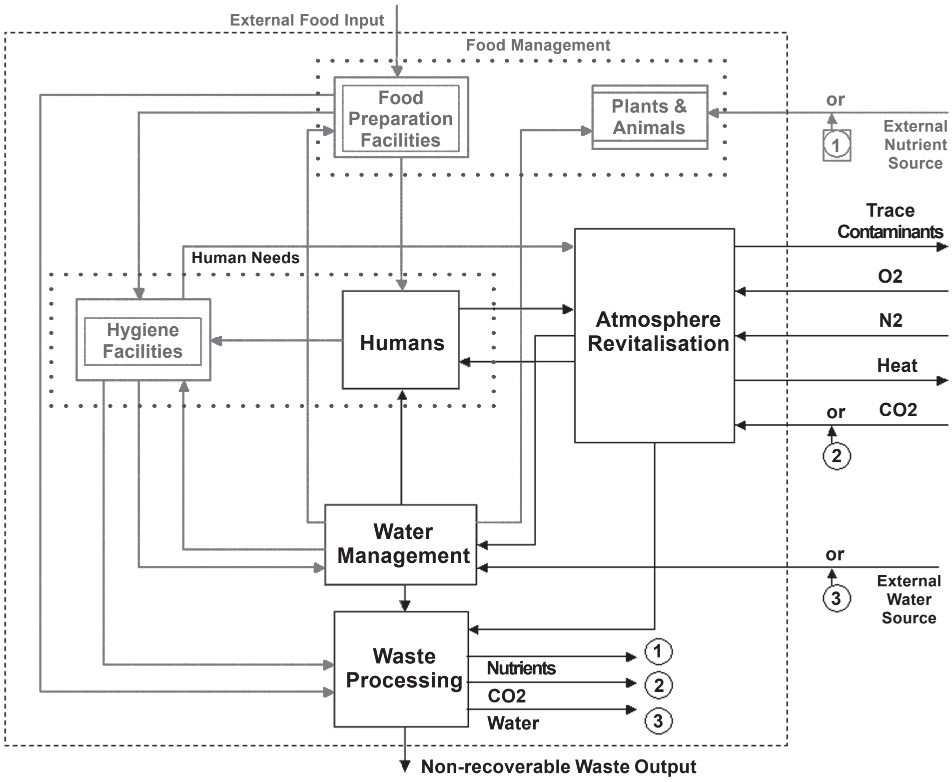


Fig. 5 Human hibernation impact on life support functions and their interrelationships.

achieved using low thrust propulsion (and this would probably be the preferred case due to requirements for propulsive efficiency), with accelerative loads of the order of 0.01 ms^{-2}. Such small loads would be unlikely to upset the hibernation state, but would still need to be transmitted to the hibernator in an acceptable manner. If hibernation took place during waypoint manouvres (departure/arrival/aerobraking), and/or if artificial gravity were employed to obviate problems with micro-gravity, the hibernaculum would face additional design pressures associated with the existence of substantial accelerative loads.

In artificial gravity, there would be problems associated with prolonged immobility of the astronaut in a gravitic environment. For example, bed sores (decubitus ulcers) form when a person is sitting or lying in one position for too long, and are caused by sustained pressure on one area, leading to reduced blood flow to the skin and subdermal tissues, and subsequent damage. Possible solutions to this are use of electrostimulus or another mechanism (perhaps behavioural) to effect periodic (or as necessary) postural change.

5.3 Integration of Hibernacula with Spacecraft LSS

Integration of one or more hibernacula into a ship-wide LSS will have a number of important consequences. The role of life support will be split between the ship-wide LSS (which will now be sized to accommodate the astronauts over the duration of their waking periods) and the LS function of the hibernaculum designed to support a hibernating astronaut (discussed in the previous section). Consequently in order to obtain the benefit from hibernation, the life support function of the hibernaculum should be as localised as possible, whilst ship-wide LS should be dormant to the largest extent possible (although some elements of ship-wide life-support function are likely to be maintained during stasis, such as pressurisation).

This arrangement will by necessity lead to what is essentially a two-phase ship-wide LSS. Any LSS would require complex control strategies that can maintain stable system performance and balance resources [32]. This requirement for dynamic response would be considerably increased with the presence of hypometabolic stasis. The dynamic variability of the life support load would be increased, as for at least one extended period the life support requirement on board the spacecraft will be reduced drastically. LSS function will then have to mirror (and to some degree anticipate) the physiological function of the astronauts as stasis is entered and exited.

Simple consideration of the principle characteristics of physical-chemical and bio-regenerative LSS (Table 5) indicates that a hypometabolic stasis system would be most suited to integration with PC systems. Food production (the principle advantage of a biological regenerative system) is not a requirement for hibernating crew, and in any case, crew maintenance of food production (an envisioned requisite for the foreseeable future) would be impossible. Biological systems would have trouble providing the required environmental changes due to typically slow response times (start-up of a biological life-support system can take weeks/months).

This responsiveness of the ship-wide LSS would rapidly increase if the hibernation strategy adopted involved periodic arousal (in which case life support would have to be extended from the hibernaculum to a sufficient portion of the spacecraft to allow the crew to perform inter-bout activities), or provision for an astronaut reaction to contingency events.

6. Summary

The ability to place astronauts into hibernation during the transit periods of deep space missions can be seen as a potentially enabling technology, due to the drastic reduction in LSS mass it would allow and the resultant relaxation of requirements on the propulsion subsystem. As such, in addition to the other terrestrial applications of human hibernation such as organ preservation, it is seen as a worthy subject for evaluation.

Mammalian hibernation mechanisms are intuitively seen as the most promising for application to humans, but are still quite poorly understood. A wide range of strategies are called upon in parallel, ranging from pre-hibernation behaviour; lipid accumulation; genomic and proteomic events that occur in both the hypothalamus and the peripheral tissues; the use of trigger compounds that are capable of inducing a hypometabolic state; protective mechanisms that preserve lean tissue mass in hibernators during torpor and so forth. No less importantly, many questions concerning the secondary effects of hibernation will have to be answered. For example the effects of hypometabolism on cognitive function and memory and the influence of hypometabolism on the immune system.

The interaction between the hibernating human and the deep space environment will be of crucial importance. The deleterious effects of microgravity, when combined with the inactivity of hibernation, may well prove to be an insurmountable showstopper. In such a case artificial gravity would be required. Alternatively, it may result that the protective mechanisms hibernators have developed to counter physiological atrophy during torpor can be reproduced effectively in hibernating (and perhaps non-hibernating) astronauts, and may well lead to amelioration

TABLE 5: *Principle Characteristics of Physical Chemical and Bioregerative Life Support Systems.*

Physical-Chemical	Bio regenerative
Well understood,	Not well understood,
Compact,	Large volume,
Low maintenance,	Maintenance intensive,
Quick response times,	Slow response time,
Cannot replenish food stocks	Can provide food

of the negative effects of the deep space environment on the body. In this case, human hibernation during deep space flight may have the very desirable secondary role of physiological maintenance.

The extent to which the hibernation state is induced, established, regulated and exited through using the external environment is a key question. The construction of a suitable hibernaculum for the human will have to take into account the operational scenario, the peculiarities of the space environment as well as the degree of 'engineering' that has gone into the hibernator (invariably leaving a shortfall in capability which will have to be addressed by the hibernaculum, through the use of a controlled environment, monitoring and drug administration equipment and so forth). The subsequent requirement will be for completely automated monitoring, decision-making and administration of environmental control and compounds to the hibernating human.

A human hibernation system would result in redundancy and localisation of life support. Life support during hibernation would probably be supplied by PC LS systems, as the dynamic response requirement imposed by entry and exit into hibernation would preclude the use of biological systems. This reasoning would furthermore extend to the ship-wide LSS, which would be subject to the same dynamic response requirements. This does not however completely preclude biological LS systems, and LS on-board a vessel employing hibernacula would likely be hybrid in nature.

To conclude, human hibernation for long-term space travel will make use of a wide variety of techniques, in a combination that is currently unknown. These fields include pharmacology, genetic engineering, environmental control, medical monitoring, AI and agent technology, radiation shielding, therapeutics, spacecraft engineering, life support and more. Integrating these disparate disciplines in such a way as to successfully create a safe, effective and space-borne human hibernation system will be an enormous challenge. But, if realised, it will be of significant benefit to the extension of human presence in space.

References

1. A.E. Drysdale, M.K. Ewert, A.J. Hanford, "Life Support Approaches for Mars Missions", *Advances in Space Research*, **31**, No. 1, pp.51-61, 2003.
2. E. Rosnet, G. Cazes, A. Vinokhodova, "Study of the Psychological Adaptation of the Crew during a 135 Days Space Mission", *Acta Astronautica*, **42**, No.1-8, pp.265-272, 1998.
3. H.V. Carey, J.H. Southard, M.J. Mangino, "Changes in gut function during hibernation - implications for bowel transplantation and surgery", *Gut*, **49**, pp.459-61, 2001.
4. K.B. Storey, "Turning down the fires of life: Metabolic Regulation of Hibernation and Aestivation. Molecular Mechanisms of Metabolic Arrest", BIOS Scientific Publishers, Oxford, pp.1-21, 2000.
5. B. Boyer, B.M. Barnes, "Molecular and Metabolic Aspects of Mammalian Hibernation", *Bioscience*, **49**, No. 9., 1999.
6. K. Bolling, M. Kronon, B.S. Allen, T. Wang, S. Ramon, H. Feinberg, "Myocardial protection in normal and hypoxically stressed neonatal hearts: the superiority of blood versus crystalloid cardioplegia", *Journal of Thoracic Cardiovascular Surgery*, **113**, pp.994-1003, 1997.
7. P.E. Benedict, M.B. Benedict, T.P. Su, S.F. Bolling, "Opiate drugs and delta-receptor-mediated myocardial protection", *Circulation*, **100**, pp.357-360, 1999.
8. N.A. Azzam, J.M. Hallenbeck, B. Kachar, "Membrane Changes During Hibernation", *Nature*, **407**, pp.317-318, 2000.
9. S. Daan, B.M. Barnes, A.M. Strijkstra, "Warming up for sleep? – ground squirrels sleep during arousals from hibernation", *Neuroscience Letters*, **128**, pp.265-268, 1991.
10. L. Trachsel, M.E. Dale, H.G. Heller, "Are Ground Squirrels Sleep Deprived During Hibernation?", *American Journal of Physiology*, **260** (Regulatory Integrative Comparative Physiology 29), pp.1123-1129, 1991.
11. R. Eckert, D. Randall, "Animal Physiology: Mechanisms and Adaptations", Freeman Publishing, 1998.
12. J.A. MacDonald, K.B. Storey, "Regulation of Ground Squirrel Na+ K+ ATPase Activity by Reversible Phosphorylation during Hibernation", *Biochemical and Biophysical Research Communications*, **254**, pp.424-429, 1999.
13. S.F. Eddy, K.B. Storey, "Gene expression in hibernation: testing skeletal muscle of little brown bats, Myotis Lucifugus, using commercially available cDNA microarrays", *Proceedings of the Virtual Conference on Genomics and Bioinformatics*, 2001.
14. H.K. Srere, L.C.H. Wang, S.L. Martin, "Central Role for Differential Gene expression in mammalian hibernation", *Proceedings of the National Academy of Science USA*, **89**, pp.7119-7123, 1992.
15. C.P. Lyman, R.C. O'Brien, G.C. Greene, E.D. Papafrangos, "Hibernation and longevity in the Turkish hamster Mesocricetus Brandti", *Science*, **212**, pp.668-70, 1981.
16. G.S. Wilkinson, J.M. South, "Life history, ecology and longevity in bats", *Aging Cell*, **1**, pp.124-31, 2002.
17. A. Maillet, S. Normand, H.C. Gunga, A.M. Allerard, J.M. Cottet-Emard, E. Kihm, F. Strollo, C. Pachiandi, K.A. Kirsch, C.A. Bizollon, G. Gauquelin, C. Gharib, "Hormonal, Water Balance, and electrolyte changes during sixty-day confinement", *Advances in Space Biology and Medicine*, **5**, pp.123-143, 1996.
18. H.C. Gunga, K.A. Kirsch, L. Rocher, A. Maillet, C. Gharib, "Body Weight and Body Composition during 60 Days of isolation", *Advances in Space Biology and Medicine*, **5**, pp.167-185, 1996.
19. D. Husson, M. Abbal, M. Tafani, D.A. Schmitt, "Neuroendocrine system and Immune responses after confinement", *Advances in Space Biology and Medicine*, **5**, pp.91-109, 1996.
20. Y. Ishizaki, T. Ishizaki, H. Fukuoka, C. Kim, M. Fujita, Y. Maegawa, H. Fujioka, T. Katsura, Y. Suzuki, A. Gunji, "Changes in Mood Status and Neurotic Levels During a 20 Day Bed Rest", *Acta Astronautica*, **50**, pp.453-459, 2002.
21. Y.G. Zorbas, K.P. Charapakhin, V.J. Kakurin, V.A. Deogenov, "Electrolytes in Femur and Plasma of Rats during prolonged restriction of motor activity", *Acta Astronautica*, **47**, pp.781-788, 2000.
22. A. Sievers, W. Hensel, "Fundamentals of Space Biology", Japan Scientific Societies Press and Springer-Verlag, 1990.
23. S.B. Curtis, M.E. Vazquez, J.W. Wilson, W. Atwell, M. Kim, J. Capala, "Cosmic Ray hit frequencies in critical sites in the central nervous system", *Journal of Advanced Space Research*, **22**, pp.197-207, 1998.
24. M. Stanford, J.A. Jones, "Space Radiation Concerns for Manned Exploration", *Acta Astronautica*, **45**, pp.39-47, 1999.
25. K.B. Storey, J.M. Storey, "Natural Freezing Survival in Animals. Annual Review of Ecological Systems", **27**, pp.365-386, 1996.
26. B. Girten, C. Oloff, P. Plato, E. Eveland, A.J. Merola, L. Kazarian, "Skeletal Muscle Antioxidant Enzyme Levels in Rats After Simulated Weightlessness, Exercise and Dobutamine", Proceedings of the 13th Annual Meeting of the IUPS Commission on Graviational Physiology, 1996.
27. S.K. Chapes, S.J. Simske, A.D. Forsman, T.A. Bateman, R.J. Zimmerman, "Effects of Space Flight and IGF-1 on Immune Function", *Advances in Space Research*, **23**, pp.1955-1964, 1999.
28. C.C. Hayes, "Agents in a Nutshell – A very Brief Introduction", *IEEE Transactions on Knowledge and Data Engineering*, **11**, No 1, 1999.
29. J.L. Nealon, A. Moreno, "The Application of Agent Technology to Health Care", AgentCities Working Group on Health Care, 2000.
30. B. Hayes-Roth, J.E. Larsson, "Guardian: an intelligent autonomous agent for medical monitoring and diagnosis", *IEEE Intelligent Systems* (January/February), pp. 58-64, 1998.
31. M.E. Cohen, D.L. Hudson, "Meta Neural Networks as Intelligent Agents for Diagnosis", *IEEE 0-7803-7278-6/02*, 2002.
32. D. Kortenkamp, R.P. Bonasso, "Distributed, Autonomous Control of Space Habitats", *IEEE 0-7803-6599-2/01*, 2001.

(Received 12 February 2004)