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INVITED REVIEW

Maximizing information from space data resources: a case for expanding integration across research disciplines

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Abstract Regulatory systems are affected in space by exposure to weightlessness, high-energy radiation or other spaceflight-induced changes. The impact of spaceflight occurs across multiple scales and systems. Exploring such interactions and interdependencies via an integrative approach provides new opportunities for elucidating these complex responses. This paper argues the case for increased emphasis on integration, systematically archiving, and the coordination of past, present and future space and ground-based analogue experiments. We also discuss possible mechanisms for such integration across disciplines and missions. This article then introduces several discipline-specific reviews that show how such integration can be implemented. Areas explored include: adaptation of the central nervous system to space; cerebral autoregulation and weightlessness; modelling of the cardiovascular system in space exploration; human metabolic response to spaceflight; and exercise, artificial gravity, and physiologic countermeasures for spaceflight. In summary, spaceflight physiology research needs a conceptual framework that extends problem solving beyond disciplinary barriers. Administrative commitment and a high degree of cooperation among investigators are needed to further such a process. Well-designed interdisciplinary research can expand opportunities for broad interpretation of results across multiple physiological systems, which may have applications on Earth.

Keywords Interdisciplinary research · Adaptation · Extreme environments · Modelling

Introduction

Responses to the unique environment of spaceflight occur in all physiologic systems, with the potential for significant

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interactions and interdependencies among systems. Yet, current investigations are typically limited to one system at a time. Important advancements in understanding of these complex responses could be achieved by interdisciplinary cooperation in planning and executing experiments. Furthermore, irrespective of interdisciplinarity, sharing of data among investigators could accelerate the pace of space physiology research. To address these issues, this paper proposes a programme to systematically archive past and present results and to promote cooperative, interdisciplinary future space and ground-based analogue experiments (e.g. bed rest, water immersion and isolation studies such as Mars500 and those conducted in Antarctica). This article opens the discussion on such issues and introduces several discipline-specific reviews that will extend this discussion. These reviews, in addition to examining current state-of-the-art knowledge in important disciplines of space physiology research, will also highlight how integration of spaceflight research can be accomplished across these disciplines. We provide here a brief synopsis of some of these disciplines and topics that reflect potential areas for coordinated and integrative research.

Neurosciences

Gravitational stress impacts autonomic neural functions. These functions are modified by a lack of gravitational stress in spaceflight and during re-adaptation to gravitational stress after exposure to a gravity-free condition. An obvious example is the vertigo found with gravity transitions. Adaptation to weightlessness involves not just adaptation of vestibular-mediated reflexive and orientation effects (Clément 2003), but also accommodation of the entire postural and muscular control system of the body to a radically different force environment.

Additionally, exposure to microgravity alters the cognitive strategies used in spatially directed tasks (e.g. navigation and the mental representation of three-dimensional space) and inputs to the vestibular system. The latter has effects on the compensatory eye movements (Clément 2003).

Changes in sensory motor function appear to be the most prevalent consequence of spaceflight even in flights of short duration (Kozlovskaya et al. 1981, 2006). In microgravity, the integration of sensory inputs and coordinating motor responses is challenged and these effects become more prominent as spaceflights become longer (Kozlovskaya 2002).

During planetary exploration missions, the neurosensory system will be in a “no gravity” environment for a considerable period of time. It will be exposed not only to the altered sensations of that environment, but also will be challenged by the unique gravitational field found on a new planetary surface. The most basic neuroscience questions must be answered to clarify which nervous system changes could be most critical in these conditions and to identify the best research strategies to compensate for such changes. The results of this research will help minimize risks and optimize crew performance during transit and planetary operations. The improved training methods, countermeasures and treatments associated with adaptation to changes in gravity will also certainly find other applications in medicine and biotechnology.

Cerebral autoregulation and weightlessness

As the development of presyncope or syncope in response to standing could be due to reduced cerebral blood flow (Hainsworth 2004), the high incidence of orthostatic intolerance could be the result of altered cerebral hemodynamics with spaceflight. The development of non-invasive beat-by-beat measures of blood pressure and cerebral blood flow has allowed researchers to assess cerebral autoregulation through transfer function and modelling analysis in greater detail than before. Early results from the shuttle expedition “Neurolab” indicated that cerebral autoregulation remained intact after spaceflight; however, the small sample size and lack of astronauts who presented with presyncope post-flight limited the usefulness of this information. An analysis of a much larger sample size with several astronauts who became presyncopal post-flight provided evidence of a negative effect of spaceflight on cerebral autoregulation and orthostatic tolerance (Blaber et al. 2011). These data were soon followed with similar negative results from long-duration spaceflight (Zuj et al. 2012). Why only some astronauts are affected to the point where they are compromised post-flight and others are not is still not understood and further research is required to better identify the underlying mechanisms.

Cardiovascular deconditioning in space and mathematical modelling

Cardiovascular deconditioning remains a persistent problem associated with spaceflight and its severity increases with spaceflight duration. Upon entering microgravity the cardiovascular system makes homeostatic adjustments to the decrease in gravitational force (Gazenko et al. 1986). While the cardiovascular system adjusts within hours of entry into microgravity, negative orthostatic effects of deconditioning are apparent immediately upon re-entry to the 1-g environment (Buckey et al. 1996) and continue for some time post-flight. The high incidence of orthostatic intolerance post-flight (Buckey et al. 1996; Waters et al. 2002), especially in female astronauts (100 %), and mission specialists (44 %) is of concern if human explorations with extended stays on the Moon (reviewed recently in Goswami et al. 2012) or Mars are to be attempted.

The general condition of orthostatic intolerance is actually a *cardio-postural control system* problem potentially involving many interacting systems and factors including blood volume control, baroreflex control, effectiveness of the skeletal muscle pump, cerebral autoregulation, heart and muscle deconditioning, as well as subtle interactions with sensory motor control including vestibular and somatosensory elements (Blaber et al. 2009).

Orthostatic intolerance has been extensively studied using mathematical modelling both in the context of spaceflight issues as well as Earth-based health contexts (see Sharp et al. 2012, in this series). Given the complexity of system interactions, orthostatic intolerance provides a template example of how mathematical modelling together with other quantitative tools such as meta-analysis can contribute to advancing the goal of increased utilization of the ever-expanding data base of space-related physiology.

Metabolic/endocrine, temperature and circadian effects

While it is broadly recognized that spaceflight is associated with changes in metabolism, the significance and implications of some of these changes are less certain. For example, in broad terms the reductive remodelling of the musculoskeletal system has been well described. Thus for muscle, there is a reductive remodelling of the anti-gravity muscles with a shift in myosin from slow to fast isoforms. Accompanying the shift in fibre type is an increased reliance on carbohydrate metabolism as a source of energy. A frequent ancillary finding is the replacement of muscle protein with fat, and sometimes glycogen. For bone there is a chronic loss of calcium. Ground-based studies have shown that that these changes are associated with complex pattern of poorly understood endocrine changes (National Research Council (2011). Thus, for a comprehensive understanding of the metabolic changes induced by spaceflight, it is important to integrate aspects of both bone and muscle metabolism.

Heat balance, thermoregulation and circadian temperature rhythms are altered in humans during simulated and real spaceflights due to: (1) changes in convective heat transfer from the body surface to the environment, i.e. attenuated heat exchange body surface area; (2) fluid shifts from the periphery to the central core; (3) cardiovascular deconditioning; (4) changes of the autonomous nervous system; (5) changes of metabolism and (6) alterations in body composition. Since these factors are all linked to each other and to thermal regulation, an integrated multidisciplinary approach could again be very productive.

Adverse effects of restricted sleep on well-being and performance accumulate over successive nights of shortened sleep (Dinges et al. 1997). Indeed, there is a close relationship between crew errors and sleep–wake cycle changes (Nechaev and Stepanova 2000). Therefore, an integrative view could also aid in the study of sleep and circadian rhythm disturbances, which are common during spaceflight.

Exercise and physiologic countermeasures for spaceflight

Physical activity is considered necessary to maintain physical fitness during long-term space missions. Certain integrated countermeasures have begun to deliver a broader range of exercise stimuli important for simultaneously impacting the homeostasis of a number of systems. Rodent studies indicate that musculo-skeletal and cardiovascular structure and function depend importantly on weight bearing, as well as gravitational blood pressures and flows within the body (e.g. Delp et al. 2000; Hargens et al. 2012, article VI in this series; Tuday et al. 2007; Zhang 2001).

Radiation effects on humans from space scenarios

Radiation is considered a major hazard for space travel, especially during long-term missions (discussed in Baumstark-Khan et al. 2005, 2007; Goswami et al. 2012). The doses to which an astronaut might be exposed in space are much higher than natural radiation on Earth (Hellweg and Baumstark-Khan 2007; Reitz et al. 2009) and this may cause a number of health-related problems. The effect of ionizing radiation on human beings can be categorized as either acute or delayed, based on the time between exposure and occurrence of symptoms (Durante and Cucinotta 2008). Experts are presently assessing, using data from populations exposed to radiation (accidents), the effects of radiation on cells (Baumstark-Khan et al. 2005, 2007; Sihver et al. 2010) as well as spaceflight data (Hellweg and Baumstark-Khan 2007) to study the radiation risks that the space traveller could be faced with during exploration of Mars. Due to minimal data presently available, the quantification of cancer risk and the level of a safe dose of radiation exposure in space are not clearly specified (Hellweg and Baumstark-Khan 2007). Therefore, in addition to understanding the risks of radiation and the effects they produce, there is a need to merge the spaceflight data with those derived from ground-based analogue data. In this way, appropriate radiation countermeasures can be proposed for long-term spaceflights.

Difficulties and challenges of research in space life sciences

Many of the conditions associated with spaceflight are difficult or impossible to control during space missions, and all lead to time-dependent adaptation processes that are difficult to model in laboratories on Earth. The physiological responses are likely to vary from person to person, even within the same crew. Moreover, subject populations are not uniform, nor do they begin with similar initial physiological states or experience similar conditions in space. In addition, astronauts and cosmonauts use different countermeasures. Since diaries or logs of individual activities are rarely available, major determinants of the physiological state are not always clear. Rarely have spaceflight data been interpreted and compared in light of these uncertainties and varying methodologies.

Problems related to complex systems, such as occurring in biology and health sciences, often occupy the full bandwidth of complexity from the molecular to the global level (Albrecht et al. 1998; Hood 2003; Joyner 2011); a fact that also applies to space life sciences. Within the universe of knowledge, disciplines can be identified that are clustered according to their respective interdisciplinary distance (Choi and Pak 2008). Scientific disciplines as currently organized have emerged from an artificial fragmentation of knowledge (Choi and Pak 2006a, b), leading typically to a programmatic inability to successfully deal with problems that span disciplinary boundaries. As a consequence, disciplinary autonomy, reductionism and super-specialization have often made it difficult for research to rise to overarching scientific challenges (Mommaerts et al. 1968; Long Term Planning Committee 1990; Hood 2003; Joyner 2011).

An additional important factor of increasing relevance to spaceflight research in diverse multinational crews is gender. Taking into account gender-related physiological effects adds an additional level of complexity that can be addressed via integrative study. For example, along with neurobiological and psychosocial effects potentially impacting inflight performance, gender differences in terms of autonomic cardiovascular control are very likely to exist, impinging on post-flight orthostatic intolerance (Deegan et al. 2009; Evans et al. 2001; Iwasaki et al. 2007). A compilation of presyncopal events from 25 female and 140 male astronauts after short duration spaceflight (5–16 days) showed a 28 % incidence in females compared to 7 % in males (Fritsch-Yelle et al. 1996). Another study showed that from 27 returning astronauts, 5 of 7 females were non-finishers, whereas 17 of 20 males were finishers (Blaber et al. 2011).

Clearly, comprehensive and integrated record keeping and coordinated data repositories can only improve the quality of spaceflight data analysis. Such organized treatment of data, including gender comparative studies, together with greater emphasis on interdisciplinary planning of experiments, will provide opportunities for generating convergent insights across disciplines (see Goswami et al. 2012).

Space exploration data: archived, present and future resources

Over the past 50 years, an enormous wealth of physiological data from spaceflight and related ground-based investigations has been collected. In addition, data from the Longitudinal Study of Astronaut Health and current missions continue to grow (see Stein 2012, in this series). While some results have been published in peer-reviewed scientific journals, most of these data either have not been published or are often not easily available or available in a format that limits its usefulness or accessibility (see Stein 2012 in this series). For instance, much of the early spaceflight data is in databases that used software that is now obsolete.

New challenges are now emerging as space-faring nations consider longer missions, such as to Mars, near-Earth asteroids, or long-term stays on the Moon. For example, there is evidence that the musculo-skeletal system of vertebrates changes following acute exposure to weightlessness. What will happen over multiple generations is speculative; only short snapshots are currently available of how small, living organisms' change in the space environment (Clément 2011). However, new perspectives may be required to meet these challenges. Developing these new perspectives will be facilitated by comprehensively understanding and utilizing spaceflight data of the past, present and future.

The need for an integrative approach to space science research

The impact of spaceflight occurs across multiple scales and systems. Traditionally, exploration of integrated physiological systems during spaceflight has been limited to a few systems, such as the musculo-skeletal and cardiovascular systems, with the typical objective of developing more efficient countermeasures to prevent muscle, bone and cardiac deconditioning during long-duration space missions. Interdisciplinarity in research can integrate exploration across disciplines, and at scales incorporating investigations at the molecular, cellular, anatomical, and functional levels. An interdisciplinary approach has in particular worked successfully for exercise physiology, which gained from the understanding of changes in muscle contractility, energy metabolism, perfusion and oxygen supply, as well as the interference between muscle and bone in terms of mechanical forces, blood chemical factors such as growth hormones, and nutritional aspects, including minerals, vitamins, protein, carbohydrates, and fat (Rittweger 2010). Such examples as this provide motivation for expanding interdisciplinary work. To maximize the impact of research and to tap the full potential of interdisciplinary work an integrative approach to data mining, management and interpretation of past data as well as planning for future experiments, seems necessary.

Key focal areas for implementation of integrated research include (a) development of well-defined standards and procedures for conducting experiments (implemented and coordinated via a typical announcement of opportunity call) which can lead to more effective use of data from future studies; (b) development of strategies and paradigms for interaction and cooperation between space life science and earth life science research disciplines; and (c) synergistic collaboration for intensive data mining aimed at synthesizing and testing of hypotheses with existing databases such as the Longitudinal Study of Astronaut Health. These three focal areas, emphasizing an integrative and interdisciplinary perspective, will be further examined and illustrated in the discipline-specific articles that follow this paper. Such an integrative perspective can generate not only great benefits for spaceflight physiological research, but can also lead to new advances for general integrative physiology that may have clinical application on Earth.

The six articles (I–VI) of this series will provide the framework for examining interdisciplinary opportunities. For example, space neuroscience seeks a basic understanding of how gravity affects brain function and strives for prevention of medical issues that originate from dysfunction or mal-adaptation in the nervous system during spaceflight (e.g. space motion sickness and spatial disorientation). A greater integration of neuroscience (article II: Clement and Ngo-Anh 2012), cerebrovascular physiology (article III: Blaber et al. 2012), mathematical modelling (article IV: Sharp et al.), together with the area of metabolism (article V: Stein) and skeletal muscle adaptation (article VI: Hargens et al.), have the potential to lead to new solutions to current problems in space and on Earth, and perhaps even to new disciplines. For instance, there are the intriguing parallels between the physiology of aging and the response to spaceflight (Vernikos and Schneider 2010): both show muscle and strength losses as well as bone loss, leading to increased risk of osteoporosis. Investigation of the common features could lead to new insights into control mechanisms in both of these areas.

Developing an integrated approach in space research

There is often reluctance among individual researchers to “open up” to other investigators’ interests, even within related fields. While agencies recognize this, more emphasis could be given to integrating research during the planning meetings before launch or before a complex experiment, such as those conducted in space analogue environments. Consider a spaceflight agency’s announcement of opportunity: individual groups respond by submitting independent and unrelated proposals that are focused on a certain specific problem, not connected to other proposals’ research questions. Thus, it has often been the case that collections of experimental ideas were organized so that there was minimal interference with other studies—and so often as a consequence, minimal scientific interaction occurs between individual studies. In addition, the application process and review processes tend to isolate individual groups, making it difficult to optimize or coordinate an overall research programme. This sometimes leads to redundant procedures that increase the burden on participants (such as repeated blood samplings or ECG measurements), and to compromised protocol compliance and data quality for overlapping projects.

These barriers can be overcome if additional effort is spent on coordinating, rather than separating, experimental projects within an entire programme. Otherwise, opportunities to organize synergies among different experimental approaches within a common framework may be lost. For example, some joint studies on the cardiovascular and neurovestibular systems were performed successfully during the Neurolab mission, and more recently aboard the ISS. However, only a few systems were integrated.

During the planning phase of projects, therefore, greater attention could be given to searching for ways to share experimental tools and methods so that data could be easily synchronized and compared. In addition, diverse terminology and methodologies of several research disciplines could be reviewed and addressed. Indeed, agencies responsible for funding space research could make project selection contingent upon integration with other protocols.

Furthermore, to encourage interdisciplinarity and integrative research, space agencies could, for example, dedicate a certain percent of effort on the ISS to new experimental designs specifically addressing multiple systems in an integrative perspective. This would help to establish a template for integration of research in general, as recently suggested by the US National Research Council (2011) report (http://www.nap.edu/openbook.php?record_id=13048&page=1).

Experiments involving artificial gravity would be an ideal candidate to test integrative concepts. Countermeasure testing of artificial gravity (article VI) has implications for the vestibular (article II), cardiovascular (article IV), musculo-skeletal, and immune systems, as well as in nutrition, performance, and human factors (Clément and Bukley 2007). Other cross-disciplinary research issues for humans in the space environment could include: food, nutrition and energy balance (article V), radiation effects, gender differences and thermal balance.

Scenario of integrative planning: Concordia research opportunity

As an example of integrative planning, consider the following scenario. The European Space Agency has regularly issued a call for research proposals to conduct biomedical and behavioural research at the Concordia Station outpost in Antarctica. Researchers working in different fields apply for projects to examine the effects of isolation on physiology and psychology. These projects are typically independent, aimed at answering specific questions related to effects of long-term isolation and confinement in an extreme environment.

The *pre-submission meeting* (where submitted letters of intent are discussed) is a good starting place for developing links between projects, as applicants are exposed to all project abstracts. This meeting fosters the idea of inter-, multi-, and transdisciplinary research (see Aboelela et al. 2007; Albrecht et al. 1998; Choi and Pak 2007; Gehlert et al. 2010; Klein 2008; Stokols et al. 2008; Wagner et al. 2011). The information exchanged at this meeting encourages investigators with similar ideas to submit a combined project or modified projects that have interdisciplinary dimensions.

At the *Investigator Working Group* meeting, where approved projects are discussed, the investigators learn about their peers' projects. It is at this point that the potential for collaboration and equipment sharing becomes clearer and detailed planning begins. Investigators who had proposed, e.g. measurements of heart rate variability changes over time could liaise with those who wished to measure sensorimotor changes or urinary and salivary secretion of melatonin during the winter-over period. Not only does cooperation provide more complete and valuable data, but also, due to equipment and cost sharing, reduces overall expenditure. This programme provides a template for how interdisciplinary research can emerge through the programmatic encouragement of the sponsoring agency.

Research integration across missions

In addition to integrating research projects within a single data collection campaign, the relative infrequency and high cost of space and analogue studies necessitates integration across missions. For example, comparison of energy intake for the first 2 weeks of spaceflight for the Skylab mission, a Shuttle mission with voluntary exercise, and a Shuttle mission with heavy exercise requirement showed that dietary intake appears to be mission-related rather than subject-related. Furthermore, food intake correlated negatively with the amount of in-flight exercise, i.e. food intake decreased with increasing exercise (Stein 2000, 2001).

In a more recent study using the Life Sciences Data Archive, Matsumoto et al. (2011) examined the association between observed weight loss during spaceflight and plausible clinical and mission covariates. The analysis found prospective predictors of weight loss including: being a first-time astronaut, pre-flight body weight and BMI, routinely performing pre-flight exercise sessions lasting greater than 1 h, and baseline cholesterol and potassium levels. Severe space motion sickness was significantly associated with greater weight loss. Unexpectedly, a higher number of extra-vehicular activities per mission protected against weight loss. Mission duration had the strongest association with body weight change (-2.4 ± 0.4 % per 100 days in space).

An animal study using rats also demonstrated the power of combining data from multiple investigators (Stein and Wade 2001). Results from 15 spaceflights lasting from 4 to 19 days were analysed. There was no difference in average body weight (206 ± 13.9 vs. 206 ± 14.8 g), body weight gain (5.8 ± 0.48 vs. 5.9 ± 0.56 g/day), caloric intake (309 ± 21.0 vs. 309 ± 20.1 kcal/kg BM/day) or water intake (200 ± 8.6 vs. 199 ± 9.3 ml/kg BM/day) between flight and ground control animals. Compared to standard laboratory animals of a similar body mass, no differences were noted. The observations support previous analysis of human flight data, where it was concluded that the negative metabolic balance observed in humans is due to other factors such as work requirements than the spaceflight environment per se (Wade et al. 2002). These examples were based on small studies exploring foci of investigators' interests. The points favouring integrating data across missions are: (i) the power and potential advantage of doing so, as for example, integration across disparate missions to show that excessive exercise was counterproductive—a result subsequently confirmed experimentally on the ISS; and (ii) the potential for new insights, such as identifying pre-flight walking as a better predictor of less weight loss in space than a heavy exercise regime in-flight. Thus, given adequate data input, investigator expertise and adequate statistical analysis, there exists enough data mining resources to potentially make such an approach highly productive.

From the above discussion it is evident that synergized research, involves cross-subject (within spaceflight research) and cross-discipline collaborations (with other scientific disciplines), requires the merging of various methods, concepts, and viewpoints. Integration of studies, however, is too often a post hoc integration of independent studies in a shared experimental planning at an *investigator group meeting*, without real intellectual integration. There are nevertheless some cases of pre-hoc conjectural integration of experiments. Some of these include, but are not limited to, in chronological order: (1) the 1997 study by

Ferretti and colleagues on the interplay of central and peripheral factors in limiting maximal O_2 consumption in man after prolonged bed rest (Ferretti et al. 1997); (2) the cardiovascular and sympathetic neural responses to various stimuli and how they get affected by spaceflight (Fu et al. 2002); (3) the ensemble of the cardiopulmonary and metabolic experiments of the WISE 2005 bed rest, around the concept of LBNP and exercise as combined countermeasures (Smith et al. 2008); (4) the Berlin bed rest studies around vibration exercise as a countermeasure (see, for example, Blottner et al. 2006).

Tools for synthesizing information

For integrative planning and collaborative use of existing data, several tools are available. Some of these are now explored.

Meta-analysis and data mining

The challenges in coordinating research and tapping interdisciplinary expertise are clearly highlighted in the present difficulty in conducting a meta-analysis of current data. Greater utilization of existing data (especially given current budget constraints) could provide new opportunities for research. However, such an effort requires finding and merging data from disparate disciplines in ways that allow valid inferences to be drawn.

Cooperative efforts in data pooling can maximize the scientific return from flight data, in which the number of subjects per mission is often too small for valid statistical analysis and in which unanticipated confounding variables (such as equipment malfunction) may have arisen. Because of disparities in methods and measurements, valid meta-analysis is not always feasible, as recently exemplified in a focused effort to integrate the literature on psychosocial effects of long-duration confinement in Antarctica (Shea et al. 2009). However, organizing and comparing data collected during past missions in a qualitative fashion is still valuable (e.g. Palinkas et al. 2011). Such data can then be used for future mission planning and countermeasure development and may also have applications in clinical practice.

Meta-analyses are now being used with great success in clinical medicine (see, for example, Singh et al. 2007). Government and insurance company treatment recommendations are frequently based on the results of meta-analyses of a series of clinical trials rather than on a single trial. There is no reason why such an approach should not work equally well for space life science, improving subsequent mission planning and in-flight decision-making. It is mandatory to carefully consider the circumstances under which data have been gathered before conclusions are drawn (Bailar 1997), but even if inferences remain in doubt, meta-analysis can provide indicators of trends or pointers to new observations which can then be followed up by more focused studies.

Meta-analysis can also benefit from better coordination of space-related data. Besides the Life Sciences Data Archive, other initiatives are seeking to maximize the use and exploitation of existing data. For example, *Physionet* is an information base that compiles data usable for signal processing analysis (Costa et al. 2003; see http://www.physionet.org). The Ontology for Biomedical Investigations (OBI) project (Rubin et al. 2006) represents an international effort to build an ontology (methodology that allows for recording, managing and disseminating information) to be used for the annotation of biomedical and clinical investigations. The data thus organized would allow scientists to disseminate information in well-defined computer formats. Many other databases are being developed to provide unambiguous, well-documented data that can be used by researchers beyond those who collected it.

Mathematical modelling

Another powerful tool for synthesizing information about the interaction of physiological systems is mathematical modelling (article IV, Sharp et al.). This tool allows for quantitative studies of the impact of parameter changes or challenges to system stability (Batzel et al. 2012). This quantification also aids the understanding of system dynamics and through parametric sensitivity, provides approaches for developing diagnostic indices. Applications of optimization theory, control theory, and neural network analysis can lead to the development and refinement of treatment strategies.

Space physiology research suffers from no shortage of topics and data that can benefit from coordination of mathematical modelling. For example, the Life Sciences Data Archive offers information on more than 500 astronauts who have flown on US missions alone (Matsumoto et al. 2011) and reveals large variability, for example, in the bone losses induced by spaceflight datasets. Organized modelling efforts could shed light on the reasons for this, and could yield the potential benefits of: (i) obtaining better information on the effectiveness of countermeasures; (ii) selecting subjects less vulnerable to bone loss.

Mathematical models have been developed for many physiological systems as well as for links between systems. Complex global models exist, including the *Digital Astronaut* that extends modelling work of Guyton, Coleman and colleagues (Summers and Coleman 2010). This model has been used to predict certain cardiovascular effects from a Mars mission (see article IV, Sharp et al.).

Reduced models can be developed and studied analytically and model parameter identification carried out using patient-specific data for model adaptation to individual subjects (see Batzel et al. 2012). Examples of such models include those of the baroreflex and cardiovascular control (e.g. Ottesen 1997; Batzel et al. 2009b), including modelling LBNP (lower body negative pressure) and HUT (head-up tilt) challenges; the cardiovascular system and space-related orthostatic intolerance (Broskey and Sharp 2007; Coats and Sharp 2010; Etter et al. 2011); cardiorespiratory interactions (e.g. Ursino and Magosso 2000); cerebral blood flow control (e.g. Olufsen et al. 2005); and heart function. In addition, methods from signal processing provide insights into links between systems or estimates of hard-to-measure quantities (Batzel et al. 2009a).

Models of cerebral autoregulation, blood gas regulation, and orthostatic response have been used to study the control of cerebral perfusion, and its relationship with syncope. One of many application examples is a modelling study (Olufsen et al. 2005) that exhibited different hysteresis patterns in cerebral blood flow during the challenge and recovery phases of healthy controls and subjects with impaired cardiovascular and cerebral autoregulatory mechanisms. A second example is the modelling study by Lu et al. (2001) that considered the application of the Valsalva manoeuvre in diagnosing baroreflex impairment. Such approaches are likely to become increasing more productive with the development of more sophisticated models, improved methods of parameter estimation and increased data availability. These developments will advance the goal of subject-specific model adaptation leading to diagnosis tools and treatment design.

Resources for organizing the ever-increasing body of knowledge in biomedicine include efforts to organize libraries that compile and integrate the very extensive range of models that exist. *Physiome* is an international effort to develop an information base of physiological models in areas such as the cardiovascular system, the respiratory system, and motor-kinetics of anatomical structures (Bassingthwaighte 2000). Physiome seeks to provide standardization and integration over a wide inventory of mathematical models allowing for development of models of integrated systems at various levels of complexity and also allowing for coordination and implementation with archives of experimental data such as Physionet.

Conclusions

Research in spaceflight physiology can benefit from interdisciplinary approaches, merging knowledge and expertise and providing opportunities to develop and test novel approaches to scientific endeavours. Given the level of complexity in individual physiological systems, and the further complexity in interactions among systems, resources that facilitate new insights and novel hypotheses should be fully exploited. To this end, efforts should be made to standardize study designs, allowing for the merging of information, yielding information about individual systems, as well as how they interact (Gerzer and Ruyters 2000). By the same token, empirical knowledge bases for mission planning, countermeasure development, and physiological research in general will profit from overarching planning, procedures, and data interpretation.

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