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INVITED REVIEW

Space physiology IV: mathematical modeling of the cardiovascular system in space exploration

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Abstract Mathematical modeling represents an important tool for analyzing cardiovascular function during spaceflight. This review describes how modeling of the cardiovascular system can contribute to space life science research and illustrates this process via modeling efforts to study postflight orthostatic intolerance (POI), a key issue for spaceflight. Examining this application also provides a context for considering broader applications of modeling techniques to the challenges of bioastronautics. POI, which affects a large fraction of astronauts in stand tests upon return to Earth, presents as dizziness, fainting and other symptoms, which can diminish crew performance and cause safety hazards. POI on the Moon or Mars could be more critical. In the field of bioastronautics, POI has been the dominant application of cardiovascular modeling for more than a decade, and a number of mechanisms for POI have been investigated. Modeling approaches include computational models with a range of incorporated factors and hemodynamic sophistication, and also physical models tested in parabolic and orbital flight. Mathematical methods such as parameter sensitivity analysis can help identify key system mechanisms. In the case of POI, this could lead to more effective countermeasures. Validation is a persistent issue in modeling efforts, and key considerations and needs for experimental data to synergistically improve understanding of cardiovascular responses are outlined. Future directions in cardiovascular modeling include subject-specific assessment of system status, as well as research on integrated physiological responses, leading, for instance, to assessment of subject-specific susceptibility to POI or effects of cardiovascular alterations on muscular, vision and cognitive function.

Keywords Mathematical modeling · Cardiovascular model · Interdisciplinary research · Control systems · Orthostatic intolerance

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Introduction

The cardiovascular system involves many subsystems that interact with each other and with other physiological systems to insure system homeostasis. Mathematical modeling can play an important role in analyzing these complex interactions and, in particular, in analyzing the cardiovascular system and its response to the stress of microgravity.

Mathematical modeling in physiological research is a powerful tool that allows for:

- Summarizing in a concise way current knowledge on complex systems

- Quantifying the interaction between elements of such systems
- Testing how well current knowledge predicts observations about the system
- Developing and testing new hypotheses where gaps in knowledge exist
- Exploring the value of new experiments and measurements for validating models.

This list illustrates some of the important ways so that modeling can be used to both coordinate and extend current knowledge of physiological systems as well as to complement and support research via experimental investigations.

This article is part of a series of articles in this journal (see Goswami et al. 2012a, in this series) exploring how to exploit in a more efficient manner both past and future data reflecting important physiological systems studied in space life science research. Examples are presented, in the context of the cardiovascular system, showing how the above applications of mathematical modeling can further this goal. A number of other important systems are discussed in this series, such as hormonal control, cerebral autoregulation, regulation of intracranial pressure (ICP), vestibular control, and skeletal-muscular function that generate interacting influences in response to the stresses of spaceflight. Mathematical modeling is an adaptable tool that can be used to reflect and quantify the behavior of these systems and their interactions with each other and with cardiovascular function. A library of mathematical models of physiological systems including various aspects of the cardiovascular system exists, and the Physiome Project (Bassingthwaighte 2000) is underway to catalog and coordinate the integration of this library, while a parallel library of data sources is also being developed [Physionet (Costa et al. 2003)] to organize physiological measurements useful for model development and validation, and also for signal processing analysis.

Cardiovascular risks associated with spaceflight include alterations of (1) cardiac structure and function, including the potential for cardiac atrophy, arrhythmia and disease, (2) vascular features, including fluid balance and diseases such as atherosclerosis, (3) cardiovascular system function, including its impacts on cognitive function, sensorimotor coordination, muscular strength, aerobic performance, circadian rhythms and postflight orthostatic intolerance (POI), and (4) vision impairment by altered intracranial and intraocular pressures and flows. Of these risks, only a few have been studied with mathematical models. Computer modeling was useful in demonstrating that apparent cardiac atrophy during spaceflight that recovered within 3 days postflight may be due to dehydration rather than myocardial remodeling (Summers et al. 2007). A compartmental model of the cranium showed that a microgravity-induced increase in interstitial fluid production across capillaries could cause an elevation in ICP (Lakin et al. 2007), which is an alternative explanation for space sickness (Jennings 1990).

Vision impairment is a recently recognized risk of spaceflight that is only beginning to be actively investigated. Only seven cases of vision impairment in astronauts have been documented in some detail (Mader et al. 2011). Symptoms include optic nerve distension and tortuosity, globe flattening, hyperopic shift, cotton wool spots, papilledema and choroidal folds. Most cases, with one notable exception, support a potential link between elevated ICP and the observed symptoms. A wide range of mechanisms has been forwarded in a comprehensive report by Alexander et al. (2012).

A compartmental model of the cranium applied to the problem of elevated ICP in astronauts (Lakin et al. 2007; Stevens et al. 2005) has followed previous models for relating ICP and cerebral hemodynamics in patients on Earth (Stevens and Lakin 2000; Ursino and Lodi 1997) as well as an integrated model of cranial circulation with the cardiovascular system (Lakin et al. 2003). Stevens et al. (2008) found that adding to the model a collapsible transverse sinus, a postulated cause of vision impairment in astronauts (Alexander et al. 2012), resulted in a bistable state, one of which was mildly elevated ICP characteristic of idiopathic intracranial hypertension in patients on Earth. Further, acute perturbations could cause a jump from normal to elevated pressure states, raising the question whether such a transition could occur in astronauts in response to fluid shifts. An initial finite element and computational fluid dynamics model of the optic nerve and eye has also been formulated to investigate vision impairment (Furlani et al. 2012). Much work remains to be done on this problem, for which mathematical modeling may be particularly appropriate because of the multiple interactions of systems that may provide an explanation.

However, in regard to space life science research, mathematical modeling has primarily been *directly* applied in analyzing the causes of POI and considering potential countermeasures. There are several reasons for this focus, including the early recognition of a connection between POI and cardiovascular function, the complex interactions leading to POI, and the serious implications of POI for future space exploration. In addition, POI has several ground-based analogs, including head-up tilt (HUT), lower body negative pressure (LBNP, reviewed in Goswami et al. 2008), and water immersion. Finally, orthostatic intolerance (OI) is a key problem for our aging population on Earth (the elderly can experience falls and injury from falls), providing an important link between space applications and health issues on earth. Because of the history and

important contributions of modeling to POI, we will review this field in detail and consider it to represent a framework and context for the application of modeling in many other areas of space research.

Two key themes expanded upon in detail in later sections reflect the current state of the art and direction of current research in modeling:

(a) Model validation: New mathematical methods are being developed to match model complexity to experimental data to allow for robust parameter estimation and subject-specific model adaptation (see discussion in Batzel et al. 2013). New extensions of sensitivity analysis, new techniques in optimal experimental design and new tools for physiological measurement, as well as enhanced computational power are together making feasible the adaptation of complex mathematical models for in-depth, subject-specific, real-time assessment of cardiovascular system status (see Batzel et al. 2012). Such developments will have applications for spaceflight research and for the clinical setting as well

(b) The relevance of spaceflight research for broader applications: Information about the mechanisms involved in POI can provide insight into short- and long-term control responses to hypovolemic stress including general OI and syncope, postural orthostatic tachycardia syndrome (POTS), and problems of stabilization of blood pressure during hemodialysis and after acute hemorrhage. Of critical concern, given the aging demographics of the developed world, is that non-accidental falls in the elderly are often associated with impaired baroreflex function and the onset of syncope. In particular, the elderly are often hospitalized in response to falls and fractures associated with such falls, and often they do not recover. Insight provided by modeling the mechanisms related to POI and other related spaceflight effects may also address such clinical problems (Vernikos and Schneider 2010).

In this study then, we will exemplify areas where modeling has been applied to space research, and through the discussion, we highlight key questions that modeling can help address, as well as outline important current mathematical modeling issues related to extending the application of such models.

The modeling process

This process begins with defining both the phenomenon to study and the goals of the modeling effort. These aspects taken together can delineate a set of modeling assumptions that can be utilized in the modeling process. The primary steps involved in modeling include (i) model design, which involves taking into account relevant system details while taking advantage of modeling assumptions to simplify model structure, (ii) model identification, which involves ascertaining the values of model parameters which shape model behavior, and (iii) model validation, which tests whether the model design assumptions lead to system responses that reflect experimental observations of the phenomenon under study. These steps must be carried out not only in the context of the knowledge available regarding the system being modeled and the goals of the modeling effort, but also in the light of the potential for collecting sufficient data to validate the model. Hence, model development is inextricably linked with experimental design (see e.g., Berger and Wong 2005).

Based on data availability and modeling goals, model complexity can vary (Batzel et al. 2012, 2013):

- Minimal models seek to highlight specific mechanisms as simply as possible to maximize the potential for analytic studies
- Global models seek to summarize current state of the art and provide qualitative information on system function. The complexity typically precludes specific parameter identification from data
- Mid-level models seek a compromise between the above two types leading to models that can both explain complex interactions and be accessible to analysis and model adaptation to specific individuals using collected data.

The modeling studies of Guyton et al. (1972) represent a classic global model example and template for examining the modeling process in cardiovascular physiology. The current version developed by Coleman (described in Abram et al. 2007) includes over 4,000 parameters that describe the multiple interaction of the cardiovascular system with neural, endocrine and metabolic control mechanisms. A version of this model (the Digital Astronaut discussed below) has also been adapted for space research. It is clear that it is challenging to adapt such a model with so many parameters to an individual subject, and in general the application of analytic tools (such as stability analysis especially if including system delays) would also be difficult. Hence, a key dimension of modeling is to consider how to design a model that is sufficiently complex to reflect the problem under consideration, but not so complicated as to render the model too difficult to effectively apply to the problem at hand. This in effect represents considering how a model of a complex integrated physiological system can be reasonably reduced in structure by taking into account model goals and assumptions and experimental data available for model validation. A well-motivated and appropriately designed reduced dimension model makes

more feasible model adaptation to individual subjects where data for subject-specific parameter measurements are limited.

Cardiovascular responses to spaceflight

When gravitational forces are no longer acting on the human body, a number of changes occur, leading to physiological adaptive responses in the short term (hours to days) as well as in the long term (days to weeks), as reviewed by Williams et al. (2009). In terms of the cardiovascular system, the influence of gravity changes on cardiovascular control mechanisms is complex (Goswami et al. 2012a, b). For example, the baroreflex control of the heart seems to be unimpaired in microgravity, but the baroreflex vasoconstriction control loop may be impaired (Hargens and Richardson 2009). Cardiac muscle mass is reduced (Convertino 2009) and contractility may be altered (Hughson 2009). The loss of overall muscle mass also contributes to increased lower limb vascular compliance, which could promote a larger volume of blood sequestration in the lower limbs during upright posture under gravitational stress after the return to earth (see e.g., Arbeille et al. 2001). In addition, cardiovascular deconditioning and reduced VO_2max after spaceflight link exercise capacity and POI (Levine et al. 1996).

There is limited research on the effects of spaceflight on cerebral blood flow regulation. The impact of microgravity on cerebrovascular autoregulation is complex and observed to be impaired only in those astronauts exhibiting POI upon return to Earth (Blaber et al. 2012). In addition, astronauts can exhibit changes in ICP even months after return from spaceflight (Alexander et al. 2012).

From a cardiovascular point of view, the major change in microgravity is a redistribution of fluid volumes (i.e., vascular blood volume but also interstitial fluid volume), moving from the lower limbs, which are no longer subjected to gravity, to the trunk and the head. It is estimated that the vascular and tissue volumes of the lower limbs decreased by about 10 % (Leach et al. 1991). This redistribution of fluid volumes to the trunk may lead to complex neuroendocrine responses including distension of volume receptors and suppression of antinatriuretic hormones, but the expected increased in natriuresis is not described in the short-term response to microgravity (Leach et al. 1996).

In fact, the increased vascular pressures in the upper body, associated with a probable decrease in interstitial fluid pressure due to thoracic and abdominal distensions, leads to an increase in fluid filtration across the capillaries of the upper body (Parazynski et al. 1991). This results in decreased plasma volume within the first 24 h of spaceflight (Watenpaugh 2001), which is further confirmed by the observed increase in plasma protein concentration and in hematocrit. The resulting increase in hematocrit and thus in arterial blood oxygen concentration suppresses erythropoietin production by the kidney, leading progressively to decreased red blood cell mass and overall blood volume.

It is thus not surprising that reentry to the Earth is characterized by marked postural orthostatic intolerance. In fact, the situation of relative hypovolemia can be aggravated by the loss of muscle strength and muscle mass with long-term spaceflights (Williams et al. 2009), thereby attenuating the efficiency of the muscle pump in promoting venous return. In addition, the reduction in cardiac muscle mass (Convertino 2009) and contractility (Hughson 2009) as well as the baroreflex impairment of vasoconstriction (Hargens and Richardson 2009) further attenuates the capacity to respond to orthostatic stress. While the hypovolemia of spaceflight is almost certainly a central factor in producing POI (Convertino and Cooke 2005), the explanation of the wide range of times to presyncope among subjects, and the lack of symptoms in others, during postflight stand tests is still far from complete.

From a broader perspective, the emergence of OI, in general, is actually a phenomenon of the *cardiopostural control system* and can involve many interacting systems and factors including blood volume level and blood volume control (Grasser et al. 2009), baroreflex control of heart rate and vasoconstriction, effectiveness of the skeletal muscle pump, cerebral autoregulation (Blaber et al. 2011), heart and muscle deconditioning, and subtle interactions with sensory motor control including vestibular and somatosensory elements.

A comprehensive assessment of the quantitative contribution of each mechanism, as well as the search for additional mechanisms that may potentially be implicated, can be facilitated by the use of mathematical models and computer simulations.

Overview of mathematical models of the cardiovascular system

As mentioned above, the modeling studies of Guyton et al. (1972) represent a classic modeling example representing a global model of mechanisms involved in cardiovascular control. A current variation, the Digital Astronaut has examined the effects of the Mars environment (Summers and Coleman 2010a), the physiological mechanisms associated with adaptation to microgravity (Summers et al. 2008) and for planning emergency treatment in space (Summers and Coleman 2006).

Such global models, representing a comprehensive integration of important effects, can be used to test hypotheses and provide qualitative studies. However, many

other models at diverse scales and levels of complexity have been developed over the last 70 years. The Physiome Project and JSim (Java Simulation resource) within Physiome allows for user-friendly access to a large set of models and methods for analysis. In addition, cost-free teaching models (Hester et al. 2011; Rothe and Gersting 2002) are available on-line. For details, see Batzel et al. (2012).

An overview of the history of modeling of the cardiovascular and respiratory systems and an extensive discussion of models in these areas can be found in Kappel and Batzel (2003). Models of many control systems such as the vestibular, baroreflex, and blood cell growth control systems that include feedback delay (which can influence system function) can be found in Batzel and Kappel (2011). Examples of models developed to study important system responses include:

- Baroreflex control, HUT, and Vasalva maneuver (Lu et al. 2001; Mutsaers et al. 2008; Olufsen et al. 2005; Ottesen 2000)
- Blood volume control, pressure stabilization during dialysis (Cavalcanti et al. 2006; Chamney et al. 2007; Heldt et al. 2002; Kappel et al. 2007; Ursino et al. 1994)
- Cerebral autoregulation, ICP (Giannessi et al. 2008; Lu et al. 2001a; Pope et al. 2009; Stevens et al. 2005; Ursino 1991)
- Electrophysiology of the heart (Ten Tusscher et al. 2007)
- Heart rate variability and complex dynamics (Goldberger et al. 2002)
- Heart mechanics (Ottesen 2000; Ursino 1998)
- Vascular blood flow (Quarteroni and Veneziani 2003)
- Heart and lung modeling from imaging data (Tawhai et al. 2009)
- Cardio-respiratory interactions (Cherniack and Longobardo 2006; Fan and Khoo 2002; Fink et al. 2008)
- Integrative critical care medicine (Heldt et al. 2006).

We consider next the modeling of cardiovascular function in relation to OI and in particular to POI. The purpose is not to comprehensively review the considerable literature on POI (which includes many more experimental investigations than mathematical and physical models), nor to critically assess progress toward the development of countermeasures. Rather, the unique nature of the contributions that modeling can make will be presented with examples taken from current research that demonstrate how modeling and experiments are interdependent, and together can accelerate progress in understanding the problem of orthostatic intolerance in returning astronauts, as well as in the general population and especially the elderly.

Postflight orthostatic intolerance: mathematical and physical models

The following presentation of cardiovascular modeling related to POI will focus primarily on mathematical modeling. However, physical modeling has also played a role in research (see "Physical models").

Mathematical models

Early computer models (e.g., Avula and Oestreicher 1978; Croston and Fitzjerrell 1974; Gillingham et al. 1977; Green and Miller 1973; Snyder and Rideout 1969) of the cardiovascular system for evaluating orthostatic stress, while useful for studying isolated responses, in most cases lacked sufficient detail to mimic the interactions among responses (Table 1). For instance, the effects on cardiac performance of changing venous return, of extravascular pressure, of differences in vascular properties throughout the system and of physiologic control mechanisms were not all included. Melchior et al. (1992) reviewed a number of numerical cardiovascular models and concluded that there was the need for a focused model directed at explaining orthostatic response. Several models were cited that were stimulus specific and, thus, incapable of simultaneously predicting regional fluid shifting, the effect of hydrostatic pressure on the heart and capillary fluid exchange. Subsequently, Melchior et al. (1994) developed an improved model that addressed some of these needs and obtained good agreement with experimental results for LBNP testing with and without leg compression stockings in 1 g for acute responses of mean and systolic arterial pressure and heart rate. The improved model included fluid shifting and its effects on left ventricular diastolic filling, coupled left ventricular performance, and peripheral circulation loading and arterial and cardiopulmonary baroreflexes, but did not include the effects of intrathoracic pressure.

Jaron et al. (1984, 1988) developed a cardiovascular model for predicting the effects of hypergravity maneuvers of aircraft on vision. Peripheral vision loss was predicted for carotid artery pressure at eye level of 50 mmHg, which occurred at approximately 2.7 G, in agreement with observations in pilots. The model included a rather complete system with 27 arterial and 27 venous segments with distributed nonlinear properties and lumped pulmonary and coronary elements. Baroreflex control of heart rate and venous tone were included, but not capillary fluid exchange or the effects of hydrostatic pressure on cardiac performance.

Srinivasan et al. (1992) used computer simulation based on an adaptation of the Guyton model (Guyton et al. 1972) to test variations in countermeasures for reentry orthostatic intolerance. Modeling allowed for testing various time

Table 1 Previous cardiovascular system models

				Control		Heart			Arterial tree			Venous tree				Peripheral beds		
Investigator	**Year**	**Orthostatic Stress Studied**	Total Segments	Arterial baroreceptor	Local regulation	Pulsatile Heart Pump	Extramural pressure	Heart rate	Inertance	Convective term	Nonlinear compliance	Extramural pressure	Venous Valves	Nonlinear compliance	Control of venous tone	Extramural pressure	Resistance control	Capillary filtration
Beneken & DeWit	1967	Hypovolemia	8	x		x			x	x		x	x	x				
Snyder & Rideout	1969	Tilt	86	x		x			x			x	x	x				
Boyers *et al.*	1972	Tilt, hypovolemia	14	x	x													
Hyndman	1972	Tilt	38	x		x			x			x		x				
Green & Miller	1973	+Gz acceleration	30	x											x			
Croston & Fitzjerrell	1974	LBNP, tilt	24	x		x			x		x	x	x	x				
Avula & Oestreicher	1978	+Gz acceleration	6	x					x		x			x				
Leaning *et al.*	1983	Hypovolemia	54	x		x			x	x			x	x				
Jaron *et al.*	1984	+Gz acceleration	40	x		x			x	x		x						
Al-Dahan *et al.*	1985	Hypovolemia	2	x		x			x	x		x	x	x				
Jaron *et al.*	1988	+Gz acceleration	57	x		x		x	x			x	x	x	x			
Srinivasan *et al.*	1992	Tilt	7	x	x									x			x	
Melchior *et al.*	1994	LBNP	9	x							x	x		x				
White & Blomqvist	1998	0G	3				x											
Peterson *et al.*	2002	Tilt, LBNP	36			x	x		x	x		x		x				
Heldt *et al.*	2002	Tilt, LBNP	10	x		x		x					x	x	x		x	x
Broskey & Sharp	2007	Stand test	5				x					x		x				x
Summers *et al.*	2010b	+Gz		x	x	x	x	x				x	x		x	x	x	x
Coats & Sharp	2010	Stand test, centrifuge	7	x	x		x	x				x		x			x	x
Etter *et al.*	2011	Stand test, LBNP	7	x	x		x	x				x		x			x	x

frames for pre-reentry fluid loading and different fluid characteristics such as level of salt concentration. Simulations suggested possible improvements in the countermeasures such as increasing the salt concentration.

The model of White and Blomqvist (1998) focused on the effects of intrathoracic pressure, showing that a decrease in this pressure causes an increase in ventricular volume in spite of a decrease in central venous pressure in astronauts entering weightlessness. This study explained the mechanism for this otherwise counterintuitive result and showed that intrathoracic pressure is an important parameter in modeling the acute effects of posture and gravity on the cardiovascular system.

Cirovic et al. (2001) developed a model of cerebral perfusion only and found that cerebral flow can be reduced, even if aortic pressure is maintained constant, by collapse of the jugular vein during high-gravity maneuvers. Specifically, they predicted that jugular vein collapse begins to dominate total cerebral resistance and cut cerebral flow in half at about 4 g. Such collapse may not be a major factor in causing POI, since their model predicted only a 5 % reduction in cerebral flow due to jugular collapse at 1 g. However, because collapse depends on jugular transmural pressure, the influence of collapse would tend to increase as right atrial pressure is decreased in a volume-depleted astronaut.

Peterson et al. (2002) utilized a relatively detailed model of the arterial system in combination with a three-compartment model of the systemic vasculature and compartments for the atria, ventricles and pulmonary circulation. Posture-dependent intrathoracic pressure and intramural hydrostatic pressure were included. Three gravity levels, three postures and LBNP were simulated, with resulting cardiac output consistent with observed acute responses. A unifying finding was that cardiac output was proportional to cardiac diastolic transmural pressure for all conditions tested, suggesting that to accurately model cardiovascular response to orthostatic stress, models must include the effects of the two pressures that determine cardiac diastolic transmural pressure, i.e., intrathoracic pressure and cardiac diastolic intramural pressure.

Heldt et al. (2002) simulated the transient response of mean cardiovascular parameters during orthostatic stress (tilt or LBNP). The model incorporated a relatively simple hydraulic model, but a more comprehensive reflex control model including regulation of cardiac contractility and heart rate, peripheral resistance and venous tone. Dependence of intrathoracic pressure on posture was not included. A posture-dependent rate of plasma volume loss by capillary filtration was included, but the influence of different rates of loss was not investigated. Perhaps more importantly, responses were simulated for only 2 min of

orthostatic stress, too short in the case simulated to predict syncope. Good agreement was obtained of simulated short-term response of stroke volume, heart rate and arterial pressure with population-averaged human results. Promising results were found in a case study in which model parameters were adjusted in an effort to fit the heart rate response of a particular astronaut. This application of computer modeling to individual subjects demonstrated the potential for not only investigating mechanisms of POI in groups of similarly afflicted subjects, but also to help diagnose contributors to POI in a particular subject.

The development of the previously mentioned large model of the circulation by Guyton et al. (1972) represented a major step in the understanding of whole body cardiovascular control. The model consisted of several hundred mathematical equations aiming primarily at understanding the long-term regulation of blood pressure and cardiac output, with the complex interplay of interstitial fluid dynamics, renal function and neuroendocrine control. Guyton continued to improve his model over the next decades, mainly by developing the kidney components and incorporating more recent cardiovascular discoveries (Guyton et al. 1988; Montani et al. 1989; Montani and Van Vliet 2009).

However, one major drawback of applying Guyton's model to space exploration was that the model did not include the effect of gravity. The Guyton model of fluid and electrolyte regulation (Guyton et al. 1972) was thus modified by other investigators to incorporate elements of gravitational stress (Leonard and Grounds 1977) and was used to study adaptations to 0 g, bed rest and water immersion (Leonard et al. 1985), and fluid loading as a countermeasure for POI (Srinivasan et al. 1992).

Guyton's model had other drawbacks. First, the model only used mean arterial pressure and did not consider the pulsatile nature of blood pressure. Similarly, there was no pulsatile blood flow and no stroke volume analysis. Second, although Guyton's model could be used to simulate acute challenges such as fluid load or physical exercise still, the model was primarily designed to understand long-term cardiovascular control and was thus not the most appropriate for simulating orthostatic tolerance.

Major structural modifications were made to Guyton's model by Thomas G. Coleman and colleagues to incorporate stroke volume analysis, pulse pressure and to include many other factors that may impact cardiovascular control, such as glucose and insulin, fat metabolism, body weight gain and control of temperature. Over the years, the model evolved to include today over 4,000 parameters and variables that describe the multiple interaction of the cardiovascular system with neural, endocrine and metabolic control mechanisms (Abram et al. 2007; Hester et al. 2011). With such a model, it was, for example, possible to hypothesize that increased venous capacitance in the lower limbs related to the loss of external compressive forces by decreased interstitial fluid volumes in the lower limbs could play an important role in the genesis of POI (Summers and Coleman 2002). This mechanism may also explain the greater propensity of females for POI (Summers et al. 2010). These results represent important theoretical insights. Model reduction from such comprehensive models is an important step when considering model adaptation (estimation of individualized model parameters) to specific individuals using measured data.

The models outlined in Table 1 implement effects of gravity in various ways typically by modeling the pooling of blood volume in lower limbs by changes in various compartment transmural pressures. For example, in the Heldt et al. (2002) model, a negative transmural bias pressure was applied in the lower body to model LBNP and produce pooling of blood. The degree of negative bias was correlated with sequestration of blood at various levels of HUT or orthostasis. In this case, the blood volume shift to the lower body represented the initiating orthostatic challenge and the focus of the model was on the cardiovascular control response to the resulting transient drop in blood pressure.

All the models described so far have contributed to our understanding of the effects of gravity on the cardiovascular system; however, none directly simulated the postflight occurrence of presyncope, which is the greatest cardiovascular problem of spaceflight (Convertino 2002).

Unless the simulation is carried out to the actual occurrence of presyncope, the mechanistic connections between the simulated cardiovascular responses and POI are uncertain. We provide next an example of modeling research that links overall cardiovascular function and cerebral circulation to explore the phenomenon of presyncope and syncope.

POI, presyncope and syncope

Sharp's group (Broskey and Sharp 2007; Coats and Sharp 2010; Etter et al. 2011) used a simple model of syncope based on cerebral arterial pressure dropping below a threshold. Broskey and Sharp (2007) noted that most astronauts can stand postflight for several minutes without symptoms of presyncope. Because intravascular fluid shifting and cardiac and autonomic responses occur much more rapidly, these effects cannot provide a complete explanation of POI. The gradual hypovolemia caused by capillary transport, on the other hand, provides a mechanism with long time constant compatible with experimental observations. Broskey and Sharp (2007) used a five-compartment model with nonlinear venous compliance to find that elevated capillary hydraulic conductance can explain

syncope in nonfinishers of a 10-min stand test, while normal capillary hydraulic conductance did not produce syncope. Another contribution of Broskey and Sharp (2007) was a parametric sensitivity study which showed that reduced circulating volume had by far the greatest impact on arterial pressure. All other factors, including venous capacitance, peripheral resistance and cardiac function were less significant by comparison.

Coats and Sharp (2010) expanded the Broskey and Sharp (2007) model to seven compartments to compare with human regional volume measurements. The effects of peripheral resistance, heart rate and stroke volume control were also added. Simulated stand tests on the Moon and Mars were compared to those on Earth, and cardiovascular response to the radius-dependent stress on a centrifuge was simulated. It was found that capillary transport could cause syncope on the Moon and Mars after much longer standing times than on Earth, which presents a unique safety hazard because of the uncertainty of when symptoms may occur. In addition, it was found that times to syncope comparable to those in uniform gravitational acceleration conditions were obtained in the centrifuge at lower gravity values at heart level. Gender effects were also simulated. A common elevated capillary filtration value differentiated nonfinishing males and females from finishing males. The greater susceptibility of females was explained by lower initial arterial pressure (83 mmHg for females versus 93 mmHg for males) and a higher arterial pressure threshold for syncope (40 mmHg for females versus 30 mmHg for males).

Etter et al. (2011), using a further development of the Coats and Sharp (2010) model, took advantage of time-resolved measurements of regional blood volume in 12 subjects to compare predicted and experimental orthostatic tolerance times during tilt with graded LBNP (Grasser et al. 2009). Inputs to the simulations were subject-specific measured regional blood volume changes, heart rate, stroke volume and peripheral resistance. Syncope was predicted when modeled cerebral arterial pressure dropped below a fixed threshold (30 mmHg—all subjects were male). Simulated and actual orthostatic stress tolerance times (Fig. 1) were in statistically significant agreement.

Because only initial and final measured values of hemodynamic parameters were available from the experiments (Grasser et al. 2009) to which the model was matched, simple linear changes in heart rate, stroke volume, blood volume and peripheral resistance were used in the Etter et al. (2011) model. Though other experiments (Goswami et al. 2009; Levenhagen et al. 1994) suggest that these responses are reasonably linear, better agreement might be obtained by more complex relationships based on more finely time-resolved data. Further, additional insights might be gained from a more mechanistic model based on the chemical and hormonal changes (e.g., Grasser et al. 2009) underlying these hemodynamic responses.

It was noted that, particularly for the longer orthostatic tolerance times, the difference between simulated syncope (loss of consciousness) and experimental presyncope (dizziness, nausea, tachycardia and a wide range of other symptoms) may explain the larger mismatches for these subjects. The Etter et al. (2011) study included a simple threshold of cerebral arterial pressure as the predictor of syncope and as a proxy for inadequate cerebral perfusion. Certainly, much remains to be learned about the distinctions between presyncope and syncope and the mechanisms that compromise cerebral blood flow (see Hainsworth

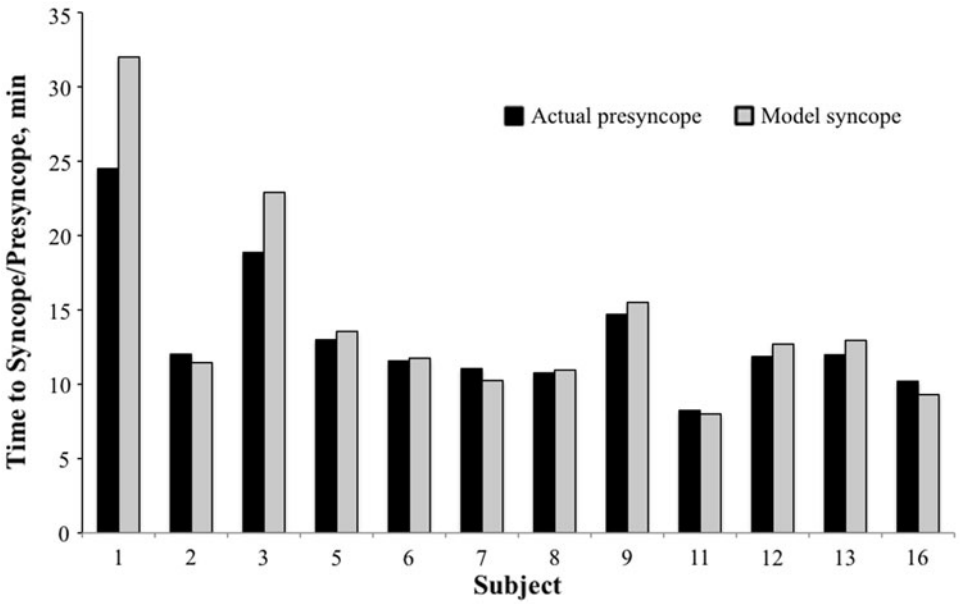

Fig. 1 Comparison of subject-specific simulated syncope and experimental presyncope times during tilt with graded LBNP (from Etter et al. 2011)

2004). These mechanisms include cerebral autoregulation, metabolic local flow control and carbon dioxide reactivity, ventilation, ICP, and the interconnection between cerebral and arterial blood pressure and blood volume. Blaber et al. (2011) suggested that a mismatch between cerebral flow and pressure related to autoregulatory function may play a role in presyncope in astronauts returning from space. Mathematical models can aid in analyzing the interaction of the many factors influencing cerebral blood flow and one can examine these mechanisms through models at various levels of complexity. Such analysis of factors influencing cerebral blood flow is exemplified in the model studies of Banaji et al. (2005), Giannessi et al. (2008), Lu et al. (2004), and Olufsen et al. (2005). These issues are further explored in "System response and parameter sensitivity".

Physical models

Physical models of the cardiovascular system have also been used for investigating responses to spaceflight. This work draws on experience with building models for testing of artificial hearts and other devices (Donovan 1975; Ferrari et al. 2005; Kolff 1959; Rosenberg et al. 1981; Sharp and Dharmalingham 1999; Sharp et al. 2008). The Sharp and Dharmalingham model was adapted for experiments in microgravity, aboard both the NASA KC-135 and the Space Shuttle (O'Leary et al. 1999; Pantalos et al. 1998b, 2005; Woodruff et al. 1997). These experiments confirmed the significance of intramural hydrostatic pressure on cardiac diastolic filling and helped explain human responses to changes in gravity (Pantalos et al. 1996, 1998a; Videbaek and Norsk 1997).

Parameter identification and parameter sensitivity

Computer models have several advantages over physical models, perhaps the greatest of which is the capability to repeat the simulations with different inputs quickly and easily. In contrast, exploring a range of parameter values with physical models typically requires adjustment of the experimental setup and/or protocol, which may be cumbersome and time consuming, particularly for parameters such as gravitational acceleration. With a computer model, thousands of cases can be simulated in seconds, which facilitates two processes that expand the usefulness of the models.

First, *parameter identification* comprises the estimation of the values of coefficients in equations within the model by fitting the model response to a target (e.g., human) response. Depending on the model, the parameters may correspond to anatomical characteristics that can be measured and verified. Second, *parameter sensitivity* describes the relative effects of the model parameters on the response of the model. Parameter sensitivity can be used to deduce mechanisms of complex responses such as POI by recognizing that the most sensitive parameters are those most likely involved in the cause and effect. Further, parameter sensitivity can be used to efficiently refine models. Improvements in estimates of the most sensitive parameters lead to greater model fidelity, and better subject-specific model adaptation. On the other hand, less sensitive parameters may affect model output so little that the parameter value can be chosen from general correlations based on height, weight, etc., or perhaps can be deleted from the model without loss of accuracy. Finally, higher sensitivity also suggests that matching of the model to in vivo response will lead to accurate estimation of this parameter for a given subject. It is a principle of modeling that the ability to identify parameter values decreases with the complexity of the model and with the incorporation of nonlinearities, but that the chances of properly identifying the most sensitive parameters increases with the completeness of the model. For a general overview of these issues, see Batzel et al. (2006) and Batzel et al. (2009a) and for a discussion of these model identification issues with regards to the Guyton model, see Sagawa (1975).

Because of the large number of factors that have been implicated in producing orthostatic intolerance, and due to the nonlinearity of a number of these factors, the usefulness of parameter identification may be limited to problems in which most parameter values are fixed and only a few are identified (see, for instance, De Cecco and Angrilli 1998; Faes et al. 2008). On the other hand, parametric sensitivity analysis is broadly useful, and this tool should become for model-based investigation the standard procedure as grid sensitivity studies are for finite element methods and error propagation for experiments. Indeed, parameter identification and sensitivity analysis can be combined to enhance the processes of model validation and model application. In particular, parametric sensitivity analysis can be used to categorize insensitive parameters, the values of which can be fixed to facilitate the identification of a smaller set of remaining sensitive parameters (Ataee et al. 2010; Ellwein et al. 2008).

System response and parameter sensitivity

A modeling application involving sensitivity analysis

Parametric sensitivity analysis has also been utilized to compare the importance of parameters determining arterial pressure (which was directly related to times to presyncope) in subject-averaged models of finishers and male and female nonfinishers of stand tests on Earth (Broskey and Sharp 2007), in subject-averaged models on centrifuges

and in stand tests on the Moon and Mars (Coats and Sharp 2010), and in subject-specific models of graded orthostatic stress (tilt and LBNP) (Etter et al. 2011). In all three modeling studies, blood volume and its gradual reduction by capillary transport during the orthostatic stress event, was found to be by far the most sensitive system parameter. This factor has received little attention in most prior research on POI, which has focused on a number of other mechanisms, including plasma volume loss in microgravity (Leach et al. 1996), changes in vascular compliance (Arbeille et al. 2001), gravity-induced intravascular and extravascular fluid shifting (Norsk 2005; Thornton et al. 1977), baroreceptor dysfunction (Fritsch-Yelle et al. 1994), venous compliance (Freeman et al. 2002), systemic vascular resistance (Buckey et al. 1996; Fritsch-Yelle et al. 1996; Waters et al. 2001), cardiac atrophy (Fu et al. 2004a; Levine et al. 1997), body composition (Fortrat et al. 2007), cerebral autoregulation (Blaber et al. 2011) and skeletal muscle tone (Belin de Chantemele et al. 2004). Convertino (2009) noted a lack of evidence for some of these mechanisms, and added reduced vasoconstrictor reserve to the list (Fu et al. 2004b). Yet, by simulating the full time course of the typical gradual descent to presyncope, it becomes clear that these other responses that act immediately or are completed within a minute or two after the imposition of the orthostatic challenge cannot explain the typical ability of subjects to tolerate several minutes of orthostatic stress before developing symptoms. A number of investigators recognized this mismatch as early as two decades ago. For instance, Hildebrandt et al. (1993) measured increased capillary filtration in endurance-trained athletes by as much as 13 ml/min and proposed that this accumulated fluid loss may explain late presyncope. Hildebrandt et al. (1994) found that fainters exhibited four times greater capillary filtration rates than nonfainters in tilt tests after a day of bed rest. Bonde-Petersen et al. (1994) found approximately three times higher capillary filtration in the legs after 3 days of bed rest (but returned to normal after 10 days of bed rest). Lundvall et al. (1996) documented filtration loss as high as 700 ml after 10 min of standing. Brown and Hainsworth (1999) found capillary filtration during tilt tests in patients with orthostatic intolerance to be twice that of normal subjects. Studying the time course of heart rate in postural tachycardia led Diehl (2005) to the conclusion that capillary filtration may be the cause. Lindenberger and Länne (2007) measured higher capillary filtration in women than men, which [supported by the modeling result of Coats and Sharp (2010)] suggests that this factor contributes to the greater susceptibility of females to POI.

In astronauts, three times higher postflight capillary transport was measured in one Gemini astronaut (Charles et al. 1994), and elevated inflight capillary filtration was documented (Baisch et al. 2000), but this phenomenon has been largely overlooked recently.

Modeling: advantages and limitations

Experiments, by their very nature, include all the physics and biophysics of the problem. Yet, practical instrumentation provides measurements of a limited set of variables. Thus, interpretation of mechanisms can be speculative. Correlation, or lack thereof, between orthostatic tolerance and measured parameter differences may be a secondary effect of a factor that was not measured. A good example of this potential problem with experimental studies is the Lindenberger and Länne (2007) finding that measuring only beginning and ending calf volumes during orthostatic stress masks the fact that venous compliance is lower and capillary transport is higher in women than men. Models, on the other hand, allow monitoring and determination of the relative importance of each parameter and combinations of parameters in affecting results from an arbitrary number of baselines. Such information can be particularly valuable in guiding future experiments into areas that maximize the return on the experimental effort.

The advantage of models in providing the time history of every parameter value, and their sensitivity in determining the results, is tempered by the need to incorporate in the model the most important parameters using validated algorithms. Model reduction should take advantage of circumstances or conditions that can allow for the neglecting of specific mechanisms or the imposition of reasonable constraints on behavior. Sensitivity analysis tools described in "Current research in extensions of sensitivity analysis" can aid in choosing appropriate model complexity and designing matching experiments to arrive at a well-motivated model simplification that allows for validation against data.

An extreme example of model simplification is found in Summers et al. (2010) (here, simplification refers not to the model itself, which incorporates some 4,000 parameters, but to the modifications to simulate females). The authors found that lowering the center of gravity of the male body, with no other changes, resulted in a drop in arterial pressure upon standing within about 40 s to 40 mmHg, which is the approximate threshold for presyncope for females. While it is enticing to conclude that this difference may be a mechanism for the greater propensity of women to suffer orthostatic intolerance, the observed effect may not reflect the entire story, given the number of other differences between women and men that were not included that could either contribute to, or counteract, the drop in arterial pressure. For instance, a question remains regarding whether decreased venous compliance (Lindenberger and Länne 2007) or the shorter average height of women might

prevent arterial pressure from dropping to the presyncope threshold, disproving the relevance of the lower center of gravity hypothesis. On the other hand, the lower resting arterial pressure in females might promote presyncope. Further, this hypothesis alone provides a potential cause only for early presyncope, and not for symptoms that occur minutes after standing. Including a sufficient level of validated detail, while avoiding inclusion of extraneous effects that only contribute to increased computational time and effort, embodies perhaps the greatest challenge in modeling (see "Current issues in parameter sensitivity, model validation, and experimental design"), which can only be addressed by collaborative experiments that quantify the relationships among parameters.

Finally, one limitation of parametric sensitivity that should be noted is that low sensitivity does not necessarily identify that parameter as unimportant, only that its variation must be larger to affect the results as much as a small change in a parameter with high sensitivity. Since plasma volume loss in fainters during a 10-min stand test is in the order of 10 % of total circulating volume, which means that to have a similar effect, cardiac atrophy (which is a roughly 10 times less sensitive parameter in the Sharp model) would have to reduce cardiac pumping effectiveness to 10 % of normal, an extreme reduction for this parameter. On the other hand, peripheral resistance, which is known to increase by a factor of two or more, has a greater chance of being an important factor, given that its sensitivity relative to circulating volume is similar.

Models are powerful tools in verifying mechanistic pathways for system responses, and for differentiating strong versus weak factors, but experimental validation is still required to confirm the necessary magnitude of parameter variation and to test countermeasures. Expanded use of parametric sensitivity is encouraged in all modeling efforts to diagnose and treat orthostatic intolerance. One must also keep in mind that such sensitivities vary with the choice of nominal parameters chosen for the model analysis. In addition, parameter sensitivities are influenced by model structure and this structure could lead to effects that are model-based rather than being reflective of physiological behavior. This is one of the challenges of modeling: an ongoing testing and verification of model validity is required. As with physiological evidence, over time an accumulating body of consistent results points toward the correct conclusions.

The validity of a complex model is supported by testing the internal consistency of the model in the sense that all model outputs and parameters are physiologically reasonable and provide reasonable responses under a wide range of varying conditions (difficult to achieve if the model is inaccurate). When this test fails in a well-designed model, this information can potentially point to missing knowledge leading to suggestions and insights for future research. When validated, mathematical modeling allows for examining complex interactions between mechanisms and provides quantitative predictions that could lead to diagnosis and treatment. See also "Future directions in cardiovascular system modeling".

Current issues in parameter sensitivity, model validation, and experimental design

As illustrated in the above discussion, effective modeling requires establishing a compromise between two competing factors. On one hand, models reflecting complex system interactions must be comprehensive enough to reflect all known factors relevant to a phenomenon under study, as well as rich enough to allow for discovery of unexpected links among factors. On the other hand, if a model is too complex, then analytic tools may not be applicable and interactions between specific factors may also be hard to delineate. In addition, complex models typically incorporate a large number of parameters and typically there are not enough data to identify all the given parameters. Parameter sensitivity analysis provides one approach for grappling with the issue of how to reduce model complexity and parameter count to render the process of model validation and eventually applicability to individual subjects tractable (see e.g., Batzel et al. 2009a, b, 2012). An example of a reduced model study related to central venous pressure and cardiac function during spaceflight is given by White and Blomqvist (1998).

Current research in extensions of sensitivity analysis

In addition to parameter sensitivity, a second issue in the analysis of model parameters is the degree to which a set of parameters might be *interdependent* in the sense that different combinations of values of the parameters create the same effect on model output. For example, if the ratio of two parameters appears in a model, then as long as each is increased by the same factor the net effect on model output will be unchanged. *Model identifiability* analysis refers to the process of searching for such parameter dependencies and this topic is a key area of current research.

Methods to analyze model identifiability include

- Structural identifiability (see e.g., Bellu et al. 2007), which tests how parameters are interrelated in the structure of the model equation
- Subset selection, which seeks to select from all model parameters (incorporating sensitivity information) a subset that includes parameters both sensitive and independent so that the estimation process is well defined. Of course, this analysis depends on the type

and quality of data available and methods are being developed that allow for subset selection to be considered in the light of data availability so that one can examine how the parameter identification problem can be improved by measuring additional states or changing the experiment for data collection. See e.g., Burth et al. (1999), Catchpole and Morgan (1997), Catchpole et al. (1998), Fink et al. (2008) and Pope et al. (2009)

- Other sensitivity analysis methods such as generalized sensitivity analysis seek to examine how parameter estimation is influenced by the experimental design and the manner in which data are collected (how often during various intervals, which intervals are most important). See e.g., Banks et al. (2010) and Thomaseth and Cobelli (1999, 2000).

New research results in the above areas should help foster the application of models for assessing patient-specific system status, thus leading potentially to new methods for designing clinical treatment (Heldt et al. 2006).

Future directions in cardiovascular system modeling

In this section, we examine important dimensions of future research in mathematical modeling of the cardiovascular system (and, indeed, other physiological systems) for spaceflight research.

New modeling applications for space science cardiovascular research

Two areas will be highlighted. First, modeling may be particularly important in identifying the mechanisms for vision impairment in astronauts, because so many systems may be involved. Similarly, muscular performance, in particular power and endurance, but not strength, may be affected by cardiovascular alterations due to spaceflight.

Vision impairment

When astronauts enter the microgravity environment, the loss of hydrostatic pressure in the arteries, veins, cerebrospinal column and lymphatic vessels causes fluid shifts that may acutely affect ICP and biomechanical responses within the eye and optic nerve. In addition, the new state may influence interstitial and cerebrospinal fluid production and resorption, which could alter fluid volume and pressure in the cranium, eye and optic nerve over a much longer time scale. Furthermore, the symptoms of vision impairment include tissue responses, in particular, optic nerve distension, globe flattening and choroidal folds (Alexander et al. 2012; Mader et al. 2011; Marshall-Bowman 2011), which will require model components other than classic fluid mechanical elements. Future efforts in this area may require models not only of cardiovascular flows, but also cerebrospinal fluid circulation, lymphatic circulation and aqueous humor circulation. Examples of patient-based models that might be adapted to build a model for studying vision impairment in astronauts include cerebrospinal fluid flow in the spine (Loth et al. 2001) and in the ventricles in the brain (Kurtcuoglu et al. 2005), flow in cranial subarachnoid spaces (Gupta et al. 2010), coupled cardiovascular and cerebrospinal flows (Martin et al. 2012), pumping in the initial lymphatics (Galie and Spilker 2009, Mendoza and Schmid-Schonbein 2003) and in larger lymphatic vessels (Reddy 1986), combined osmotic and hydraulic transport across microvessels (Levick and Michel 2010), and biomechanical models of the eye and optic nerve (e.g., Cirovic et al. 2006).

Skeletal muscle performance

Spaceflight causes loss of muscle volume, strength and endurance (Gopalakrishnan et al. 2010) and changes in the structure and function of muscle fibers (Fitts et al. 2010), which can affect fulfillment of mission tasks and constitute deconditioning that impacts performance upon return to a gravitational environment on Earth, Moon or Mars. These deficits may, in part, be related to cardiopulmonary function through impacts on the transport of oxygen to muscles, as well as on the delivery of muscle activation signals. Potential mechanisms are many, with the dehydration of spaceflight perhaps being an important factor, and exercise countermeasures alone have been incompletely effective (Hargens et al. 2012). Because muscle performance is due to multiple interactions of the cardiovascular, pulmonary, muscular and neurological systems, computer modeling can be helpful in comparing the feasibility of mechanisms and the potential effectiveness of countermeasures. To simulate this problem, at least two subsystems must be added to a basic cardiovascular model, including an integrated model of tissue mechanics, gas transport and blood flow in lung (Liu et al. 1998) and a model of muscle activation, fatigue and recovery (Liu et al. 2002). The multiscale, multiphysics lung model of Burrowes et al. (2008) represents part of a more detailed approach, and Bonjour et al. (2011) provide validation data demonstrating a decrease in cardiac output and an increase in oxygen consumption during exercise with increasing gravitational acceleration.

Other new applications

In addition, there are many other areas related to consequences of long-term spaceflights that could be covered by modeling, such as loss of bone mass, loss of red blood cell

mass, immune dysregulation, effects of radiation, and alterations in circadian rhythms. This last point is of particular interest because disruption of circadian rhythms is a clear cardiovascular risk factor and astronauts in zero gravity show blunting in blood pressure circadian variation (Agarwal 2010; Karemaker and Berecki-Gisolf 2009).

Multiscale integrative research

Given the complexity of the cardiovascular system (and other physiological systems as well), it is clearly advantageous to draw on all available resources to examine these systems (Goswami et al. 2012a, in this series). In addition, as brought out in the introductory article of this series, comparison of the space-normal and Earth-normal steady states can provide insight into both. Development of a comprehensive strategy of research can be furthered by greater coordination of current resources:

- Integration of modeling resources: A large number of cardiovascular, respiratory and other physiological system models have been developed over the last 50 years. To tap into this resource, a comprehensive effort *Physiome* is underway to coordinate and integrate these models to allow for combining and exploiting them (Bassingthwaighte 2000) in the study of complex systems and system interactions
- Integration of data resources: In a spirit similar to that of the Physiome Project, *PhysioNet* (Costa et al. 2003) seeks to generate and coordinate a broad database of physiological measurements useful for model development and validation, and signal processing. The Longitudinal Study of Astronaut Health (LSAH) represents a complementary resource on physiological data from the astronaut community
- Integration of model and data in real time: Heldt et al. (2006) argued that better coordination of data and models in critical care can lead to better decision making
- Development of comprehensive models that summarize information: The development of comprehensive models can play an important role in testing hypotheses of system interactions, effects of currently untestable situations, and development of tools for spaceflight. Important studies with the Digital Astronaut have examined the effects of the Mars environment (Summers and Coleman 2010), the physiological mechanisms associated with adaptation to microgravity (Summers et al. 2008) and for planning emergency treatment in space (Summers and Coleman 2006). Additional comprehensive models that can serve such purposes include the cardio-respiratory Pneuma model (Fan and Khoo 2002), the cardiovascular model by Rothe and Gersting (2002), and a model of cerebral vascular action (Giannessi et al. 2008). For further discussion regarding these, see Batzel et al. 2012.

Such initiatives and resources all support a transition to greater integration of current knowledge leading to greater insight into physiological systems and decision making. Clearly, this integration can also be furthered by correlating information on both the space-normal and Earth-normal initiatives. This can generate important synergies as discussed in the next section.

New applications of advanced mathematical tools

In addition to efforts at increased integration of information, innovative approaches including interdisciplinary research that involves application of advanced mathematical tools can also hasten understanding. There are many examples of how methods from mathematics can be applied to cardiovascular physiology (see Batzel et al. 2012, 2013). Important current areas of interdisciplinary interaction include applications of chaos theory to understand variability in hemodynamic variables (Costa et al. 2008), and new uses of signal processing to develop tools for estimating key cardiovascular system parameters (e.g., Mukkamala et al. 2006). In addition, research using fractals to analyze changes in the characteristics of physiological complexity (complexity in the time series dynamics of measured states) due to aging (e.g., Goldberger et al. 2002) might also be applicable as a tool for examining returning astronauts. Control theory has often been employed to examine cardiovascular control and as this area advances, new insights into physiological control are possible. Compare, for example, the control theory approaches taken in Mutsaers et al. (2008) and Hoyer et al. (2007). Hence, as outlined in the first article of this series (Goswami et al. 2012a), mathematical modeling research that links various mathematical and physiological skills in interdisciplinary research can expand and accelerate the returns from modeling (Batzel et al. 2009a).

Linking models from Earth life science research to spaceflight responses

As mentioned in "the Introduction", Earth-based analogs, including bed rest with head-down tilt, whole body immersion, drug-induced dehydration, blood volume reduction, LBNP, centrifuge exposure and parabolic flight, have been applied specifically to study the effects of gravity, reduced gravity and microgravity for spaceflight applications (see Goswami et al. 2012a, b). Many of these conditions have been investigated by computer simulation, as well. However, extensive opportunities also exist to

leverage Earth life science research to advance the understanding of responses to spaceflight in areas such as

- Blood volume control
- Orthostatic intolerance
- Cerebral autoregulation
- Peripheral vascular control
- Effects of aging.

Aging is an overarching focus of many of these studies that may provide important perspectives for spaceflight responses. Potential parallels between deconditioning due to microgravity and aging have recently been reviewed (Vernikos and Schneider 2010). Of particular relevance for this review is the relationship between orthostatic intolerance emerging as a result of aging and that caused by microgravity. Models integrating the mechanisms of both types of responses might be used to merge information and test hypotheses about how cardiovascular deconditioning due to aging and microgravity could be seen in a unified light, leading potentially to better countermeasures for both subject groups.

The sensitivity of modeled syncope to blood volume reflected in Broskey and Sharp (2007), Coats and Sharp (2010) and Etter et al. (2011) suggests that studies of mechanisms of regional and total blood volume control, including not just resistive and compliance-based fluid shifting, but also dehydration, hydraulic and osmotic transcapillary transport, and mobilization of unstressed volume (Kappel et al. 2007) may provide insight into factors influencing POI.

Patient- or subject-specific model adaptation

A key goal of modeling under active research is model adaptation to the specific patient or subject for individualized system analysis and diagnosis. This implies model parameter identification at the level of accuracy that can provide a reliable basis for diagnosis or design of treatment.

Model identifiability and experimental design

The sensitivity analysis approach discussed above provides one example of how model design and experimental design can be coordinated to improve model parameter estimation:

- Subset selection provides a subset of all model parameters (exploiting in various ways sensitivity information) that includes parameters both sensitive and independent so that the estimation process is well defined, given the available data. In addition to the classical methods exemplified by Burth et al. (1999), Catchpole and Morgan (1997), Catchpole et al. (1998), Fink et al. (2008), and Pope et al. (2009), new research is providing insight and new approaches (Banks et al. 2013; Olufsen and Ottesen 2012)
- Generalized sensitivity analysis provides an important example of how sensitivity information (via the Fisher information matrix) can be applied to examine how parameter estimation is influenced by experimental design. Research on global sensitivity analysis has begun to address the local nature of sensitivity information.

Model reduction and experimental design

In spite of the discussion above emphasizing a more integrated modeling resources, Einstein's principle should be considered, which applied to modeling states, "a model should be as simple as possible, but not simpler." (Einstein's advice is essentially a restatement of Occam's Razor, which dates to the thirteenth century.) The reasons for following Einstein's principle include reduced model development time, reduced run time, simpler specification of inputs and easier interpretation of results. For a particular problem such as POI, the challenge of following Einstein's principle is to include in the model all significant mechanistic pathways to the final response, but none of the insignificant ones. The obvious question, then, is how to determine a priori which mechanisms will be important. An essential step in model development is, therefore, to reason causes and effects so that these hypotheses can be tested with the appropriate mechanisms included. A temptation inherent in using existing complex models, such as the Guyton model, is that this essential step may be omitted, and results attributed only to the mechanisms already in the model, which may not include the correct ones. The development of new approaches for analyzing model complexity (for e.g., methods employing subset selection or generalized sensitivity) in the context of issues related to experimental constraints, measurement feasibility, and data quality can play a key role in making precise the analysis of model complexity and the process of model reduction.

Development and application of new simulation tools

With the possible spatial scales underlying physiologic modeling ranging from molecular (picometers) to organism (meters) level, and time responses varying from molecular reactions (femtoseconds) to long-term organism responses such as aging (years), models can easily become cumbersome and time intensive. A logical resolution of the dichotomy between comprehensiveness and practicality is to have extensive data and modeling resources from which to assemble reduced models to test particular hypotheses. An attractive foundation for realizing these capabilities is an object-oriented user interface (OOUI), wherein modular components are selected from a library and connected graphically, such as in the commercial packages SimuLink

(Mathworks, Natick, MA) and LabView (National Instruments, Austin, TX) and the more academically based TRNSYS (Madison, WI), which has so far been applied primarily to solar energy system simulation. Mangourova et al. (2011) adapted the Guyton model to SimuLink and noted that physiologic modeling lags behind many other research areas in applying the latest simulation tools. An additional advantage of OOUI is that multiple investigators can contribute subsystem modules without jeopardizing the function of the rest of the simulation (see also the discussion of the Physiome Project above).

Summary

The primary focus of modeling in space physiology has been POI, a problem that has been central to orbital spaceflight to date and may be even more important for long-term flights to the Moon and Mars. Yet, modeling has the potential to contribute to solutions in other areas, in particular, interactions of the cardiovascular system with the muscular and pulmonary systems to understand inflight and postflight deficits in aerobic capacity (Convertino 2009), and the neurological and vision systems to determine the causes of elevated ICP and visual impairment. This review has presented trends that may expand the usefulness of modeling. These trends are summarized in the following.

Future directions for modeling research

- Development of techniques for model adaptation to individual subjects. This includes methods for matching model design and experimental design, and for formulating subject-specific countermeasures
- Collaborative space and Earth physiology research to develop models for testing new hypotheses arising from interdisciplinary insights
- Development of a framework and standards for coupling models from multiple investigators and for archiving and using data bases for validation
- Greater focus on modeling various potential mechanisms relating orthostatic intolerance to presyncope
- Standardized use of parametric sensitivity and parametric identification to refine and validate models.

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