Simulation of Integrated Physiology Based on an Astronaut Exercise Protocol

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During long-duration spaceflight, the human body faces many risks. Although in-flight exercise protocols have helped to ameliorate the deconditioning effects of microgravity, they have not yet produced postflight conditioning measures equaling those seen preflight. The National Space Biomedical Research Institute convened an Exercise Workshop in 2002 that affirmed the value of producing a simulation of human exercise to study the effects of various exercise protocols. As an initial effort, in collaboration with researchers at three other institutions, APL has developed a prototype integrated simulation of the 25-min cycle ergometer exercise protocol used by U.S. astronauts since the Skylab missions that includes simulations of the cardiovascular system dynamics, tissue-bed blood flows, whole-body metabolism, and respiration. The High Level Architecture standard for simulation interoperability, developed by the DoD and now an Institute of Electrical and Electronics Engineers standard, is used to connect these components.

INTRODUCTION

During long-duration spaceflight, the human body is subjected to many risks, including the microgravity-induced risks of cardiovascular alterations, muscle atrophy, and bone loss. Exercise countermeasures have been used during human spaceflight for decades to help ameliorate the deleterious physiological effects. Nevertheless, postflight physiological measures generally do not duplicate preflight measures, and in-flight exercise remains a time-consuming countermeasure that detracts from mission-related efforts. NASA remains interested in a better understanding of the effects of exercise on astronaut conditioning. This article describes the effort of APL, in collaboration with researchers at three other institutions, to develop a prototype integrated simulation of the 25-min cycle ergometer exercise protocol used by U.S. astronauts since the Skylab missions.

Understanding the prototype simulation development effort requires some understanding of a number of background topics: the biomedical risks associated with human spaceflight, the research that is under way to produce countermeasures for those risks, the role of exercise as a countermeasure, current exercise protocols, background on physiological systems modeling, and techniques to enable simulations to interoperate. Preceding the discussion of the simulation effort and the results obtained from the initial prototype, some background in each of these areas is provided.

BACKGROUND

Biomedical Risks in Human Spaceflight

Spaceflight risks to the human body are associated with the space environment, confined working conditions, and exposure to microgravity. NASA has categorized these risks according to their functional area and criticality, and has produced a Bioastronautics Critical Path Roadmap[1] that shows this categorization. Identified risk areas include bone loss, cardiovascular alterations, muscle atrophy, and radiation effects, among others.

NASA's intent is to eliminate or ameliorate the deleterious effects on the human body associated with these risks to improve the safety of long-duration missions and help ensure the long-term health of returning astronauts. The approach is to identify, through research, appropriate countermeasures that can be applied; to advance the readiness of those countermeasures through ground testing and, eventually, flight testing; and, finally, to make the countermeasures available on a routine basis for long-duration missions.

Countermeasure Research and Development: The Role of the National Space Biomedical Research Institute

The National Space Biomedical Research Institute (NSBRI)[2] was established in 1997 through a NASA competition. The NSBRI is a consortium of 12 institutions, led by the Baylor College of Medicine, working to prevent or solve health problems related to long-duration space travel and prolonged exposure to microgravity. Both APL and the JHU School of Medicine have been members of the NSBRI since its founding. The institute's primary mission is to ensure safe and productive human spaceflight. Its research is intended to lead to countermeasures to the harmful effects of microgravity and space radiation. The NSBRI has research teams focused in 12 areas, both in individual research areas associated with specific effects of long-duration spaceflight on elements of the human body and in several cross-cutting areas.

In 2000, the NSBRI solicited cross-cutting research efforts to develop an understanding of the human body's response to spaceflight from a holistic (i.e., total organism) approach using computer modeling and simulations. One major challenge within this area was to devise strategies and methods for linking appropriate sets of individual physiological models into a system model for understanding the total organism for purposes of space biomedicine. Originally termed Integrated Human Function, the effort included several research projects that were primarily associated with cardiovascular system alterations, muscle alterations, and whole-body metabolism.

As the research evolved, it became apparent that a multisystem countermeasure to the effects of microgravity that deserved additional investigation was the use of exercise during flight. In August 2002, the NSBRI convened an Exercise Workshop. Researchers with specialties in cardiac, cardiovascular, muscle, bone, and whole-body metabolism modeling participated, along with NASA astronaut exercise program representatives and researchers who participated in physiological modeling efforts during the Skylab program in the 1970s. This workshop affirmed the value of producing a simulation of human exercise as a means of studying the effects of various exercise protocols during spaceflight.

Exercise as a Countermeasure and Current Exercise Protocols

The risks (and critical questions) identified in NASA's Roadmap[1] for which exercise has provided, or is believed to provide, a countermeasure cross individual physiological areas of investigation and include

- Loss of skeletal muscle mass, strength, and/or endurance (e.g., What are the appropriate exercise modalities and prescriptions needed to optimize skeletal muscle performance?)
- Impaired cardiovascular response to exercise stress (e.g., Can the aerobic exercise capacity limitation be predicted for individual crew members? What countermeasures can be developed to overcome such limitation?)
- Postlanding alterations in various physiological systems resulting in severe performance decrements and injuries (e.g., How do alterations in cardiovascular functions associated with spaceflight affect the functioning of other systems?)

Most common exercise devices on both U.S. and Russian space missions have included cycle ergometers, treadmills (active and passive), and resistive exercise equipment. Although in-flight exercise protocols employing these devices have helped to ameliorate the physiological effects of exposure to microgravity, their use thus far has not been able to ensure postflight values of bone density, muscle strength, and cardiorespiratory conditioning equal to those seen preflight.[3]

On the International Space Station (ISS), U.S. astronauts spend 1.5 h daily, at least 6 days per week, using a cycle ergometer, a treadmill, and a resistive exercise device. An additional hour per day is spent in the setup and teardown associated with performing the exercise (R. D. Hagan, "Exercise Countermeasures on the International Space Station," presentation at the NSBRI Exercise Workshop, Seattle, WA, Aug 2002). In light of the current reduced ISS habitation levels (now just two or three astronauts) and the time required for normal ISS maintenance activities, the time devoted to exercise reduces by a significant percentage the time available

for research activities. In the long term, a better understanding of the effects of various exercise protocols provides hope for reducing the amount of time that needs to be devoted to exercise.

Physiological Modeling

Just as military simulations have a hierarchy of aggregation levels—often portrayed as a "pyramid" ranging from engineering to campaign simulations—physiological models also have a hierarchy of aggregation ranging from the molecular level to the whole-body level (Fig 1). Historically, physiological modeling of the human body has been performed predominantly by specialists focusing on individual areas of research, and most physiological modeling work has been concentrated at and below the organ level. Significant modeling work has been done at the cellular level to study the function of muscle cells, particularly heart muscle cells. Other work has been performed to aggregate this cellular-level behavior to the whole-heart level, although most simulation implementations have been computationally intensive as a result.

Some high-level multisystem simulations have been produced, but these have been constructed most often to give medical students a basic understanding of physiological functions. During the Skylab program, NASA attempted to develop a "whole-body algorithm"[4] that integrated simulations of several body systems. This effort, which terminated at the end of the Skylab program, noted the interoperability problems encountered, including the differences in structural detail among the models and the lack of correspondence in attributes that needed to be interchanged.

To create a simulation of human exercise, one has to incorporate models of several physiological systems. This can be characterized as a "horizontal integration" of multiple models existing at the "system" level of the physiologica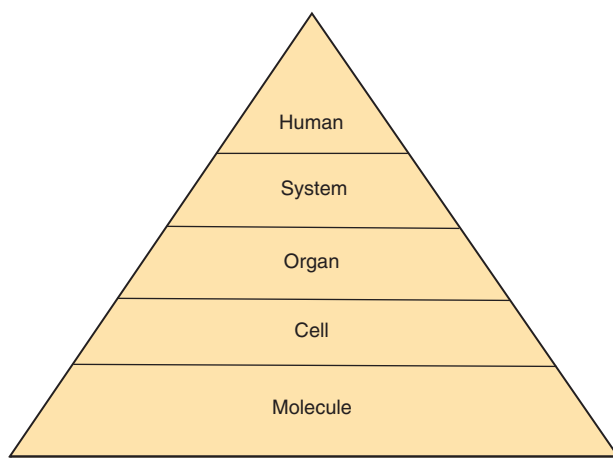l modeling pyramid shown in Fig. 1. Given the historical compartmentalization and level of aggregation of models in the physiological modeling community, the principal challenges were to find appropriate models at the system level and a mechanism for them to operate, over the time dimension, in an integrated simulation.

Interoperable Simulation: The High Level Architecture

The High Level Architecture (HLA)[5] is a general-purpose architecture for simulation reuse and interoperability. It is based on the premise that no simulation can satisfy all uses and users. An individual simulation or set of simulations developed for one purpose can be applied to another application under the HLA concept of the *federation*: a composable set of interacting simulations. Figure 2 is a functional view of the HLA, showing its associated Runtime Infrastructure (RTI). The HLA was mandated for use in the DoD in September 1996, adopted as the Facility for Distributed Simulation Systems 1.0 by the Object Management Group in November 1998, and adopted by the Institute of Electrical and Electronics Engineers (IEEE) as IEEE standard 1516 in September 2000. APL had a significant role in the development of the original DoD HLA Object Model Template and its transition to the IEEE standard.[6]

Based on benefits achieved in the military simulation community by using the HLA, it was felt that similar benefits could be achieved for physiological simulations, and for a simulation of human exercise in particular, because

- Legacy simulations exist for some physiological systems, and portions thereof, that could potentially be adapted to work interoperably.
- In the long term, because of the distributed runtime capability of the HLA, various institutions and
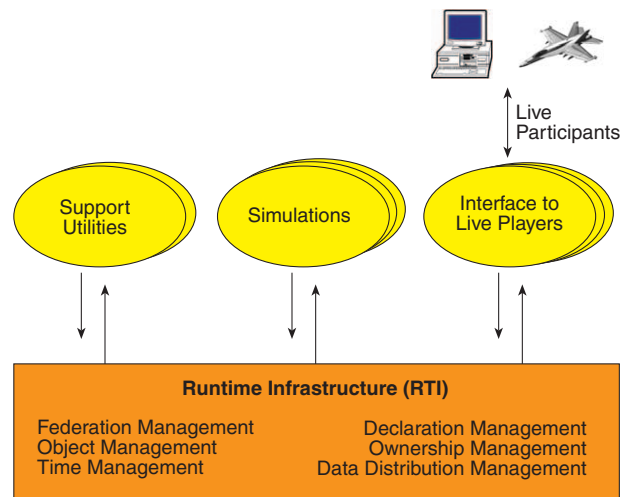

Figure 1. Levels of aggregation in physiological modeling.

Figure 2. A functional view of the High Level Architecture (source: Defense Modeling and Simulation Office).

researchers in the physiological modeling community could share the results of their models while retaining their models locally.
- Some performance increase might be achieved relatively inexpensively by parallel execution of some components. An existing process model for the HLA to aid in the development of interoperable simulations could be tailored to uses in the physiological simulation community.

The process model mentioned above, the HLA Federation Development and Execution Process (FEDEP), is a structured, generic systems engineering approach to the development of distributed simulation systems. APL made significant contributions to the original DoD-developed FEDEP and to its transition to become IEEE standard 1516.3.[7] The seven-step FEDEP is depicted in Fig. 3. The specific intent of the HLA FEDEP is to guide federation developers through the series of activities necessary to design and build HLA federations. Rather than dictating a "one-size-fits-all" solution for all users, the FEDEP provides a common overarching process framework into which lower-level domain-specific management and/or engineering methodologies can be easily integrated.

DESIGN OF THE HUMAN EXERCISE FEDERATION (ExerFed)

Overview of the Simulation Federation

Based on the results of the 2002 NSBRI Exercise Workshop, researchers from APL and three other NSBRI member institutions embarked upon an effort to create a prototype integrated simulation of human exercise that would be a first step in achieving the vision formulated during the workshop. It was decided that a reasonable approach would be to select an existing exercise protocol and construct a simulation that could produce physiological responses which could then be compared to the results of Earth-based exercise tests performed using the protocol.

Of the devices used during manned U.S. and Russian spaceflight missions[3] (Skylab, Soyuz/Salyut, the Space Shuttle, Mir, and the ISS), the most common is the cycle ergometer. Use of the cycle ergometer follows a protocol based on an astronaut's maximum oxygen uptake rate (VO_2max). Prior to flight, each U.S. astronaut's VO_2max is measured during exercise tests, along with the work rate at which that VO_2max is achieved.

The ergometer exercise protocol used on U.S. spaceflights is as follows:

- 5 min of rest
- 5 min at a work level corresponding to 25% of each astronaut's preflight VO_2max
- 5 min at 50% VO_2max
- 5 min at 75% VO_2max
- 5 min of recovery

Because of the frequency and commonality of use of this protocol, it was the exercise protocol of choice to be simulated by the prototype HLA-based human exercise simulation federation, which was named the ExerFed.

In developing the ExerFed, we used a building-block composition approach rather than a top-down functional decomposition approach, which would be desirable if no legacy simulations of value existed. Where simulations of key physiological functions were known to exist within the NSBRI community, we employed them with the minimum possible modifications; where there were gaps, we developed as simple a functional representation as possible to produce the physiological parameters needed by the other simulations.

Using this approach, key elements of the ExerFed were drawn from models developed by NSBRI researchers during prior or concurrent research:

- A computational cardiovascular system model called the Research Cardiovascular Simulator (RCVSIM) developed by R. Mukkamala at MIT as part of the Physionet project (a National Center for Research Resources Program in physiological modeling and signal processing) and used by the NSBRI Cardiovascular Alterations team
- A whole-body lactate metabolism model developed by M. E. Cabrera et al. of Case Western Reserve University (CWRU), a member of the NSBRI Nutrition, Physical Fitness, and Rehabilitation team

Three other physiological representations had to be created by APL to make these two simulations operate in an integrated fashion:
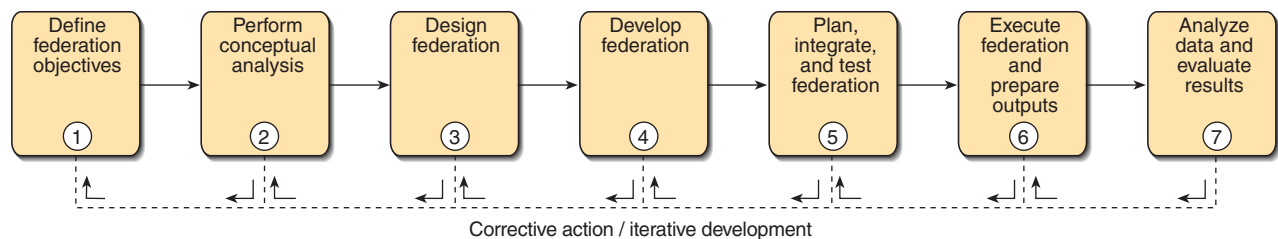

Figure 3. The HLA Federation Development and Execution Process.

- A local blood flow regulator (LBFR), based on earlier modeling work done at MIT, that apportions the overall blood flow rate into several local compartments
- A simple respiratory simulation that transforms the outputs of the whole-body metabolism simulation into a form that can be ingested by RCVSIM
- A rudimentary sympathetic nervous system activator simulation that emulates the brain's and other systems' (e.g., endocrine, thermoregulatory) effects on cardiovascular regulation during exercise and that is implemented by setting a specific targeted blood pressure during the simulated exercise based on work rate

In addition to these, we created two other simulation federates to provide the inputs to, and collect the outputs from, the physiological simulation components:

- An ergometer federate that provides work rate inputs and (for future use) physiological characteristics of the astronaut/subject under test
- A data collection federate that collects physiological data produced by the simulation as well as the corresponding parameter values from the exercise test itself

A block diagram of the ExerFed is shown in Fig. 4. It depicts each of the components discussed above as well as the data that flow between them. The following sections provide conceptual descriptions of the models underlying each simulation component.

The RCVSIM Federate

Conceptual Model of the Original RCVSIM

The RCVSIM model of the cardiovascular system was chosen to simulate the cardiac function and hemodynamics of the human body during exercise. This model was originally used as a "forward" model to develop and evaluate system identification methods ("inverse" models) for characterizing transfer functions between cardiovascular subsystems.[8] As a forward model based on physical principles, it has the potential to simulate accurately system states (e.g., exercise) that it was not originally intended to represent. Indeed, another research group has already employed RCVSIM to perform a cursory investigation of exercise in space (unpublished report, T. Heldt, MIT, 2002). Beyond its capability to generate reasonable physiological signals (including pulsatile hemodynamic waveforms, cardiac function and venous return curves, and beat-to-beat hemodynamic variability), RCVSIM's inclusion in the ExerFed was motivated by its extensibility and its ability to run in near–real time, allowing the simulation of long periods of activity. Furthermore, RCVSIM source code and extensive documentation are readily available from the Physionet Web site.[9,10]

RCVSIM's principal component is a lumped parameter model of the cardiovascular system broken down into six compartments: the left and right ventricles (the principal pumps of the heart), the systemic arteries and veins, and the pulmonary arteries and veins. The mathematical representation of the system is achieved by
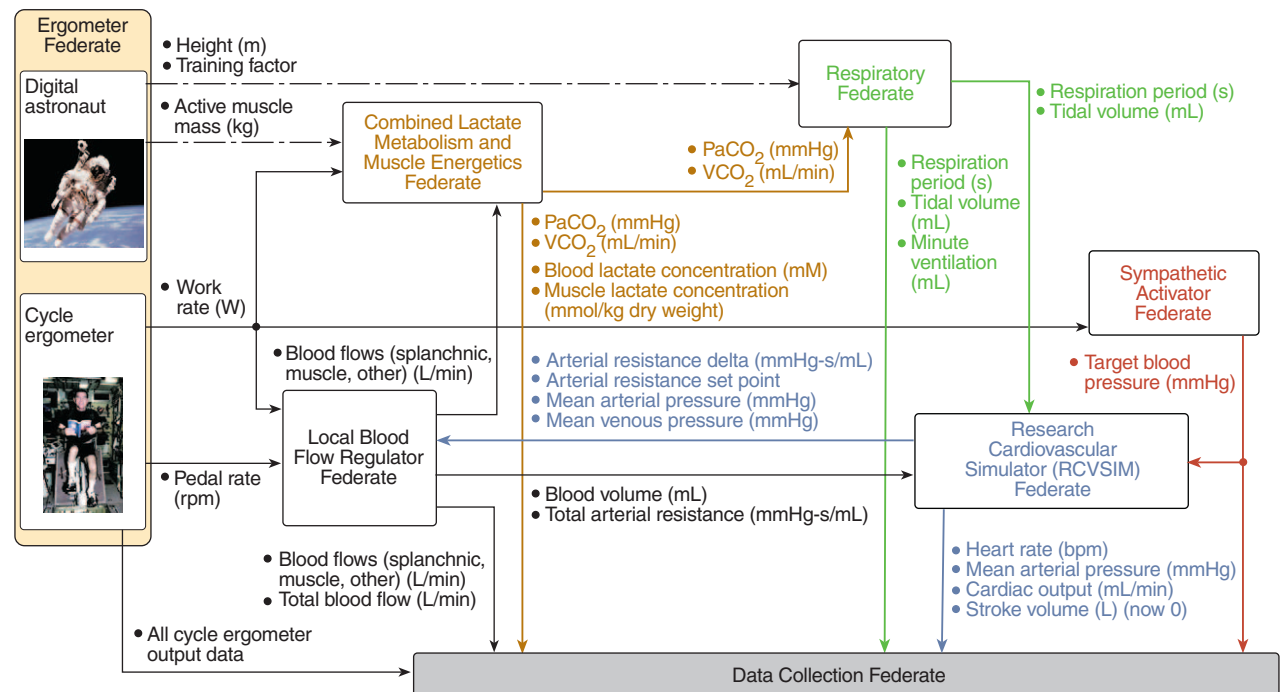

Figure 4. Block diagram of the prototype Human Exercise Federation. (Dashed lines indicate that the data attribute is not currently used by the receiving federate.)

using electrical circuit analogs of the various mechanical system components, with blood volume analogous to charge, current analogous to blood flow rate, and voltage analogous to pressure (Fig. 5). Each compartment allows a certain volume of blood to flow, governed by a linear or nonlinear resistance and a linear or nonlinear compliance, with a corresponding unstressed volume. The time evolution of the cardiovascular system variables (blood pressures, volumes, and flows) is obtained via the solution of the set of coupled first-order differential equations for the circuits. The beating of the left and right ventricles is implemented as a time-varying capacitor. (The atria are omitted. This will impact high-fidelity representation of intense exercise by the model.) In the RCVSIM model, the time-varying capacitance, which determines the stiffness or elastance (capacitance^{-1}) of the ventricles, assumes a simple functional form representative of a normal heartbeat.

Two ancillary RCVSIM components, a short-term regulatory system and resting physiological perturbations, generate the short-term, low-frequency hemodynamic variability seen experimentally during resting conditions. Both components modulate one or more of the following RCVSIM-adjustable system parameters: instantaneous heart rate, ventricular contractility, arterial resistance, and systemic venous unstressed volumes. The short-term regulatory components of RCVSIM implement a feedback control loop involving arterial baroreceptors that serve to adjust cardiovascular parameters (e.g., elastance of the heart muscle during a beat,
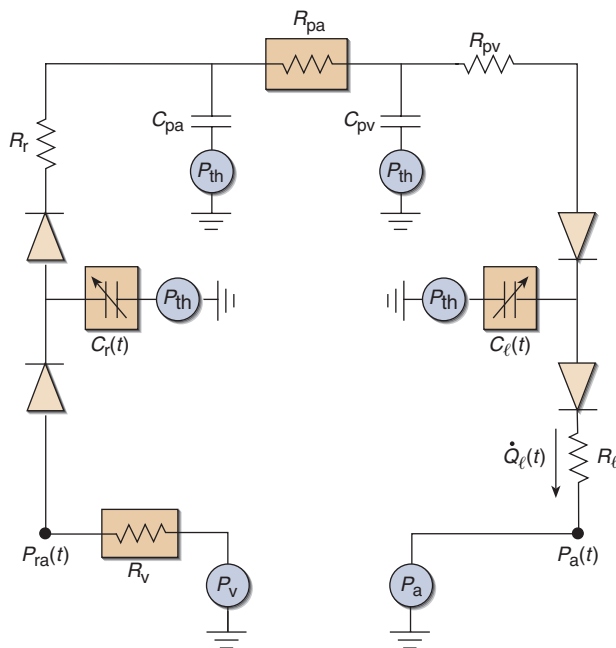
heart rate) in response to an offset of the arterial blood pressure from a pressure set point.

The final system component is a model of normal physiological perturbations to the cardiovascular system parameters, such as those arising from fluctuations in arterial resistance caused by the local regulation of resistance in tissue beds and the effects of higher brain activity on fluctuations in heart rate.

RCVSIM Modifications for the ExerFed

RCVSIM was one of two principal simulations within the ExerFed, directly receiving or exchanging data with every simulation except the Metabolism Federate. Modifications involving time steps and the implementation of respiration were made to RCVSIM for use in the ExerFed.

The original RCVSIM first "reads in" the initialization parameters and precomputes physiological waveforms wherever possible to decrease time spent during the subsequent main simulation loop, which models the behavior of the cardiovascular system. The precision required by the ordinary differential equation (ODE) solver dictates a 1-ms time step for the main simulation loop. To reduce unneeded calculations, the short-term regulatory system and the resting physiological perturbations were band-limited to frequencies within the mean heart rate and sampled at a "slow" rate of 16 samples per second (sps). As the ExerFed update rate is 16 sps, all data required by other federates were simply captured within RCVSIM when a slow update occurred and passed to the RTI. Since the arterial and venous pressures were computed at the "fast" (1000-sps) rate, RCVSIM stores all values of these two variables between successive slow updates and updates the federation with average values.

The largest modification to RCVSIM was made to accommodate the input of continuously varying respiration data. RCVSIM models respiration as a simple electric circuit (Fig. 6), with pressure analogous to voltage and airflow equivalent to current. As the lung volume is modeled (as an approximation) by a sinusoidal function with static amplitude (tidal volume)
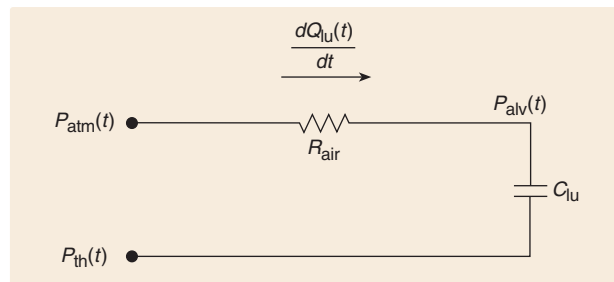

Figure 5. The circuit representation used by RCVSIM to model the human cardiovascular system: a = arterial, C = compliance, ℓ = left ventricle, p = pulmonary, P = pressure, Q = blood flow, r = right ventricle, R = resistance, t = time, th = intrathoracic, and v = venous.[8]

Figure 6. RCVSIM's circuit representation of respiration[8]: alv = alveolar, lu = lung, P = pressure, Q = blood flow, R = resistance, and th = intrathoracic.

and frequency (respiration rate), RCVSIM precomputes all needed respiratory waveforms (lung volume, intrathoracic pressure and its derivative, and alveolar pressure) before entering the main simulation loop. Unfortunately, none of RCVSIM's respiratory options satisfied the ExerFed requirements, and precomputing the respiratory waveforms was not possible. Instead, RCVSIM was modified to receive updated values of the respiration rate and tidal volume every 1/16 s from the Respiratory Federate. It then generated new values for all four respiration waveforms at both temporal granularities (1000 and 16 sps) to extend the existing curves smoothly 1/16 s into the future. RCVSIM subsequently used these updated waveforms to compute the mechanical effects of respiration on the cardiovascular system at the 1-ms resolution.

The Combined Lactate Metabolism and Muscle Energetics Federate

Conceptual Model of the Original Metabolism Simulation

Collaborator M. E. Cabrera of CWRU developed a model of the human bioenergetics system used to represent the metabolism of the entire human body during exercise. References 11–13 fully describe this model, which is shown in Fig. 7. Using a unique, top-down approach to the problem of metabolic simulation, the model links cellular metabolism and its control to processes that occur on the scale of the entire organism (e.g., exercise). This enables an integrated systems approach to analyzing metabolic regulation during exercise, the key reason it was selected for inclusion in the ExerFed.[13]
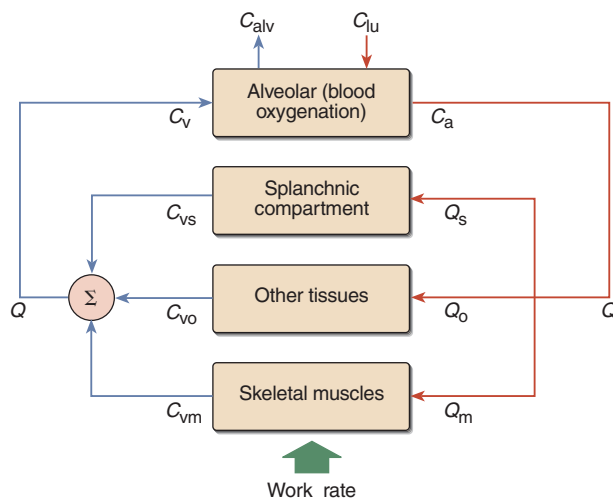

Figure 7. Whole-body human bioenergetics diagram showing a summary of substrate reactions and concentrations C and blood flows Q for the three compartments of the body: a = arterial, alv = alveolar, lu = lung, m = muscle, o = other, s = splanchnic, and v = venous (adapted from Ref. 12).

The principal limitation of the model is that its set of assumptions breaks down during very intense exercise. Specifically, it does not include all relevant mechanisms of anaerobic metabolism that are important under such conditions.

The human bioenergetics system model attempts to balance the production and consumption of adenosine triphosphate (ATP, the body's source of energy) in four different, idealized compartments: the alveolar, representing the lungs as a gas exchanger and the heart as a pump; the splanchnic (liver) and viscera; the skeletal muscles of the lower extremities; and other tissues that include the brain and adipose tissue. Each compartment of the model synthesizes enough ATP to exactly match the amount of energy consumed during rest (the resting metabolic rate). A number of other molecules (substrates) participate in the biochemical pathways of human metabolism and have been included in the model. The biochemical reactions governing the concentrations of each substrate in the four compartments are controlled by Michaelis-Menten kinetics. The rate of these reactions is controlled by a nonlinear function of the concentrations of several metabolic modulator pairs including ADP and ATP, NAD and NADH, and phosphocreatine and creatine.[13]

During exercise, the rate of work done on the cycle ergometer must be the rate of work done by the skeletal muscles. A step increase in the work rate of the active skeletal muscles acts as the input to the human bioenergetics system model. Assuming that only the skeletal muscles can change their ATP synthesis rate and that the only energy available for work is derived from the hydrolysis of ATP, then the muscles maintain homeostasis by increasing their ATP synthesis rate (through metabolism of stored foodstuffs) to match the input work rate. The synthesis of ATP requires oxygen and produces carbon dioxide, both transported by the blood in the circulatory system. In parallel, the input work rate and increased consumption of oxygen by the skeletal muscles cause an increase in the rate of oxygen uptake by the lungs described phenomenologically in the model. These processes are associated with a corresponding increase in the amount of blood being pumped by the heart (cardiac output).[13]

To summarize, dynamic mass balances and chemical kinetic relations describe the transient responses of the concentrations of substrates involved in energy metabolism within various lumped regions of the body (Fig. 7). The substrate concentrations computed include lactate, glycogen, glucose, fatty acids, glycerol, pyruvate, alanine, CO_2, O_2, and H_2O. Within muscle tissue, the concentrations of NAD, phosphocreatine, and ADP are also computed. Numerically, the concentrations of the substrates and metabolic modulators in the model are the state variables of a large system of first-order linear differential equations.

Metabolism Simulation Modifications for the ExerFed

The minor modifications made by APL to the whole-body bioenergetics and metabolism model developed at CWRU allowed it to exchange data successfully with other simulations in the federation. As the federation execution incremented time in 1/16-s increments, the ODE solver used for the metabolism model was configured for the same time step. From the perspective of inputs, the model accepted a new work rate from the Ergometer Federate while also receiving the new blood flow values for the three compartments of the body (splanchnic, muscle, and other) from the LBFR Federate. At first, the metabolism model computed these values internally based on simple, saturating exponential functions. The original code was simply removed, since these variables were now inputs to the model.

Simulation Components Created Specifically for the ExerFed

The Local Blood Flow Regulator Federate

Two different phenomena significantly perturb the human cardiovascular system during a 25-min exercise program on a cycle ergometer: (1) the pumping of stored blood in the venous reservoirs by the rhythmic skeletal muscle contractions in the legs, and (2) the local control of blood flows to various compartments of the body.

With each rotation of the cycle ergometer's pedals, the exercising muscles contract and then relax. These contractions rhythmically compress the blood vessels in the active muscle and create an oscillating increase in blood volume that can help the heart meet the increased circulation (cardiac output) demanded by rigorous exercise. The LBFR Federate models this "muscle pump" indirectly by smoothly varying a net increase in the blood volume sinusoidally. The phase and frequency of this blood volume oscillation are dictated by the cycle ergometer. The amplitude of the volume waveform increases to its targeted steady-state value following a saturating exponential function with a time constant consistent with that of the autoregulation of blood flow by the active muscles (see below).

Regarding local control of blood flows to various compartments of the body, research has shown that muscle blood flow in a well-trained athlete can increase during maximal exercise by a factor of 25 times the resting value.[14] This blood flow to an exercising limb increases exponentially with time constants of 10–20 s, with longer time constants associated with higher exercise intensities. The same researchers also determined that the steady-state blood flow to the exercising muscles was linearly related to the exercise intensity over the range of 10–70 W.[15] While the blood flow to the active skeletal muscles increases, the blood flow to the brain is highly regulated and stays constant (750 mL/min) during rest

and maximal exercise, and blood flows to other regions of the body (such as the viscera) decrease.[16]

In RCVSIM, a single circuit path represents the entire systemic circulation, with single resistors modeling the systemic arterial and venous resistances. In the LBFR Federate, to represent the redistribution of blood flow during exercise more accurately, the single lumped arterial and venous resistances were broken out into a parallel network of resistances similar to that described in Ref. 17. This network represents circulation to muscles, the splanchnic region, and other tissues. (These three compartments were selected because of their use by the whole-body bioenergetics and metabolism model discussed earlier.) Because the resistance to blood flow in the active "working" muscle compartment is under local control (autoregulation) through a signaling mechanism that is not understood, this resistor is decoupled from the RCVSIM peripheral resistance regulation. Its decrease with time is modeled by an exponential function with a time constant of 10–20 s (depending on exercise intensity). RCVSIM retains control of the resistances in the other two body compartments via the computation of a fractional change in resistance applied individually to the resistances in each compartment. This descriptive representation enables simulation of the human body's ability to modulate the amount of blood that flows to different regions of the body independently. In this case, the total arterial resistance realized in the models will reflect the influences of central nervous control and local chemosensors that adjust local blood flow to meet local metabolic demand.

The Respiratory Federate

During exercise, the increased metabolic requirements of the active skeletal and cardiac muscle tissue increase oxygen demand. The lungs, by increasing the frequency of respiration (respiration rate) and the size of each breath (tidal volume), automatically increase minute ventilation (the rate of gas exchange between the lungs and the air) to maintain the homeostasis of critical gases (oxygen and carbon dioxide) in the arterial blood. Unfortunately, despite intense scrutiny, the exact mechanism controlling the regulation of respiration during exercise is unknown. As such, the respiration model used by the ExerFed is phenomenological in nature and assumes that blood gas homeostasis is always achieved (an assumption that is safe for all but the most extreme exercise conditions).

The Respiratory Federate uses two inputs from the whole-body metabolism model—the rate of carbon dioxide production (VCO_2) and the alveolar partial pressure of carbon dioxide ($PaCO_2$)—to compute the alveolar ventilation. The alveolar ventilation is used in conjunction with the dead space volume (150 mL) to compute the minute ventilation. Once minute ventilation has been computed, the needed tidal volume is calculated

based on a curve fit relating tidal volume and minute ventilation.[18] Finally, the respiration rate is computed by dividing the minute ventilation by the tidal volume.

The Sympathetic Activator Federate

Exercise evokes a complex cardiovascular system response, the regulation of which involves central nervous and local control systems, which are both poorly understood. The cardiovascular system model used by the ExerFed did not contain an obvious mechanism through which to initiate exercise. Therefore, a sympathetic activator model was developed that simulates the sympathetic nervous system activation that occurs during exercise by directing RCVSIM to reset its target blood pressure to larger and larger values. These target values are determined for each work rate using an empirically derived relation. In RCVSIM, setting a new target blood pressure triggers baroreflex (mediated by pressure sensors in the cardiovascular system) responses to increase the heart rate and peripheral resistance (in nonactive muscle), as well as venous tone (stiffness). These changes are effected through the autonomic nervous system and result in increased sympathetic flow. By setting the target blood pressure, we use RCVSIM's short-term blood pressure regulation mechanisms to realize the conditions occurring during exercise. Although the use of the empirical work rate versus targeted blood pressure relationship precludes comparison of the model's blood pressure output to that obtained during real exercise tests, other physiological variables of interest, such as heart rate and cardiac output, can be compared to ascertain the model's fidelity.

The Sympathetic Activator Federate sets a new target blood pressure during each 5-min phase of the exercise program, starting from an initial value of 94 mmHg (to match RCVSIM's corresponding initialization parameter) or the last target blood pressure of the previous phase. During each phase, the target blood pressure increases, following an exponential curve with amplitude proportional to the work rate. For all exercise phases, the decay constant was set to 5 s under the assumption that the body could quickly respond to the step increase in work rate. Finally, the time constant for the warm-down period was set to 120 s to mimic the longer sympathetic withdrawal observed after exercise.

The Ergometer Federate

The simulated ergometer supplied two key pieces of data that served as inputs to the rest of the simulations: an exercise work rate in watts and a pedal rate in rotations per minute (rpm). For the first 5 min of the exercise protocol, the work rate was set to 0 W. After this warm-up period, the work rate values for the remaining 20 min of the exercise protocol were read in from a text file. This file contained work-rate values in watts sampled at 10-s intervals during actual experimental exercise protocols conducted with subjects at CWRU. As the Exer-Fed required 1/16-s time steps, adjacent work rate values were linearly interpolated.

As for the second key piece of data, pedal rate, exercise protocols using a cycle ergometer typically fix the angular frequency of pedaling to 1 rev/s or 60 rpm (personal communication, M. J. Kushmerick, Univ. of Washington, Nov 2003). The intensity of the exercise is therefore varied by changing the amount of friction applied to the rotating wheel. Since the cycle ergometer's wheel has inertia, the pedal rate cannot simply jump to 60 rpm the moment an astronaut starts pedaling. Therefore, a saturating exponential with an estimated time constant of 6 s was used to model the increase in pedal rate from 0 to 60 rpm.

The "digital astronaut" (Fig. 4) contains parameters describing static physiologic and anatomic characteristics unique to each person that could potentially affect the simulation outcomes. Two examples of such parameters are an astronaut's height (which could affect lung volume) and weight (which could affect the mass of muscle involved in exercise). As these parameters are static, the Ergometer Federate reads them in from a profile and distributes them to the rest of the federation for simulation initialization purposes before exercise is simulated. These two parameters were planned for future use and do not currently impact the behavior of any federates.

The Data Collection Federate

The Data Collection Federate captures all data interchanged among federates during a federation execution, producing data files and strip-chart recordings of medically significant federation parameters. These parameters include heart rate, blood pressure, tidal volume, respiration rate, and 23 others. This single-source collection and archiving of data enabled the rapid comparison and error analysis of simulated data to published references or experimental data. The real-time visualization of data allowed federation executions to be both controlled and monitored from a single platform. For example, the blood pressure trace can be used to ensure that steady-state conditions have been reached after an exercise run before terminating the execution.

ExerFed HARDWARE AND SOFTWARE IMPLEMENTATION

In biomedicine, the application of HLA to distributed simulation remains a novel methodology. Biomedical research federates do not exist, but a number of useful stand-alone biomedical simulations do exist that were created in vastly different development environments using a diverse set of tools without interoperability in mind. Thus, the two central challenges in implementing

the ExerFed were (1) interfacing the two legacy simulations, RCVSIM and the metabolism model, into a federation, and (2) developing the remaining federates, including their underlying biomedical models.

The creation of the RCVSIM Federate posed unique problems because RCVSIM was developed as a group of MATLAB scripts and functions executed within the MATLAB environment. To overcome this problem with minimal changes to the RCVSIM source code, and with an emphasis on speed, we constructed the RCVSIM Federate as two executables communicating data via a block of shared memory. The first was created using the MATLAB C compiler (mcc). Function calls allowing access to the shared memory block were inserted into the original MATLAB source code of RCVSIM wherever data needed to be exchanged. Using mcc, we translated these modified MATLAB scripts and functions composing the model into C, compiled them, and then linked them to the needed MATLAB libraries to form the first executable. The second executable, developed in C++, was a federate interface capable of reading from and writing to the shared memory block and making the appropriate calls to the RTI software, allowing the MATLAB-based model to participate in the federation execution.

The whole-body metabolism model posed an equally difficult HLA integration problem. It was developed as a system of ODEs using an experimental data-fitting package called Scientist (developed by MicroMath Scientific Software), which was then translated via an automatic algorithm into FORTRAN 95 (F95) code. We had to develop an alternative ODE solver (fourth-order Runge-Kutta) in C++ that could both call the FORTRAN routine and interface with the RTI ambassador. Because of the desire to create a single executable for the federate, we used Microsoft Visual Studio to compile the interface to the RTI and the ODE solver, and to link the C++ objects to the F95 objects. We developed the remaining federates within the ExerFed using JAVA and employed the pRTI 1516 RTI developed by Pitch AB to permit the simulations to interoperate at runtime. A software "wrapper" provided the skeletons for the federate setup, federate ambassador implementations, and thread-safe queues for RTI and federate communications, as well as the foundation of a user interface. The interface included strip charts to monitor the various outputs. In addition, the graphical user interface included a scrollable window to output communications with the RTI. We designed this wrapper to read in federate-specific parameters (such as whether the federate was to be time-constrained) from a text file to minimize the need for federate recompilation.

The selection of computer hardware to execute the ExerFed completed the federation's implementation. To improve performance, we distributed ExerFed federates over five single-processor and dual-processor PC workstations. The RCVSIM Federate ran on a dual-processor 1800+ Athlon workstation running the symmetric-multiprocessor-aware version of Red Hat Linux 8.0. The Metabolism Federate, the other computationally demanding simulation, ran on a dual-processor 2.0-GHz Xeon workstation under Windows 2000. The remaining federates—the Ergometer, LBFR, and Sympathetic Activator—ran on two single-processor 3.0-GHz Pentium 4 workstations, also under Windows 2000. Because of the heavy disk access demands of the Data Collection Federate, it was executed on a dual-processor Xeon workstation with an ultra-SCSI hard drive subsystem that also handled the RTI software. Figure 8 is a graphical representation of federate/workstation assignments.

All computers were connected via two Ethernet networks, enabling the analysis of the effects of network performance on the ExerFed's execution times. The first network was the 100-Mb/s network internal to APL but
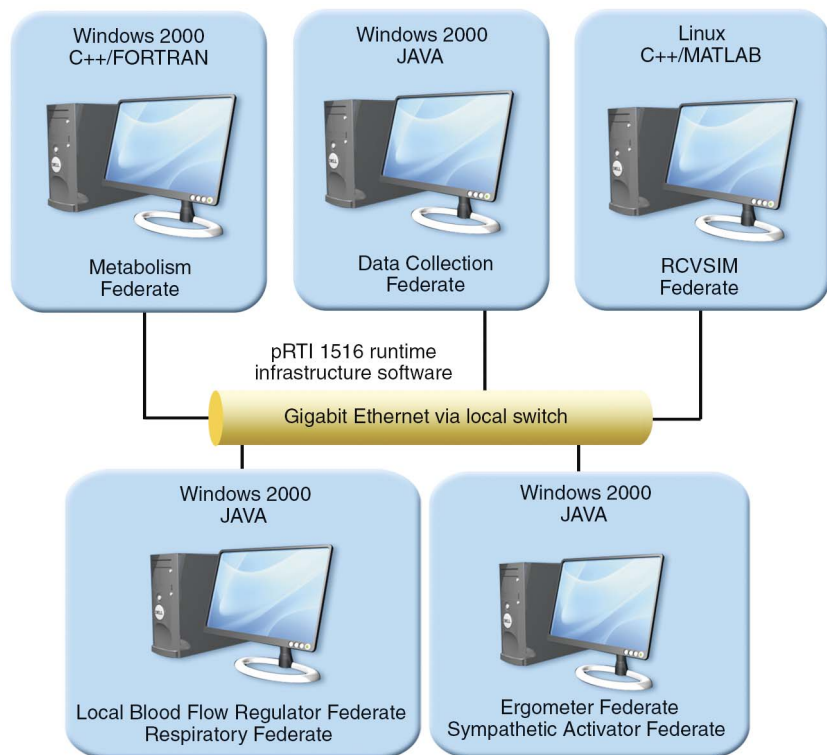

Figure 8. ExerFed hardware and software implementation diagram.

shared on a subnet connecting an entire department of several hundred computers. The second network consisted of all needed workstations connected directly to a 3Com SuperStack 3-Gbit switch via Intel Pro/1000 MT desktop adapters.

RESULTS OF PROTOTYPE TESTING

With the development of all federates completed, an extensive number of federation executions were conducted. The initial set of executions produced promising results, with most of the simulated physiological waveforms (e.g., heart rate, respiration rate, blood pressure)
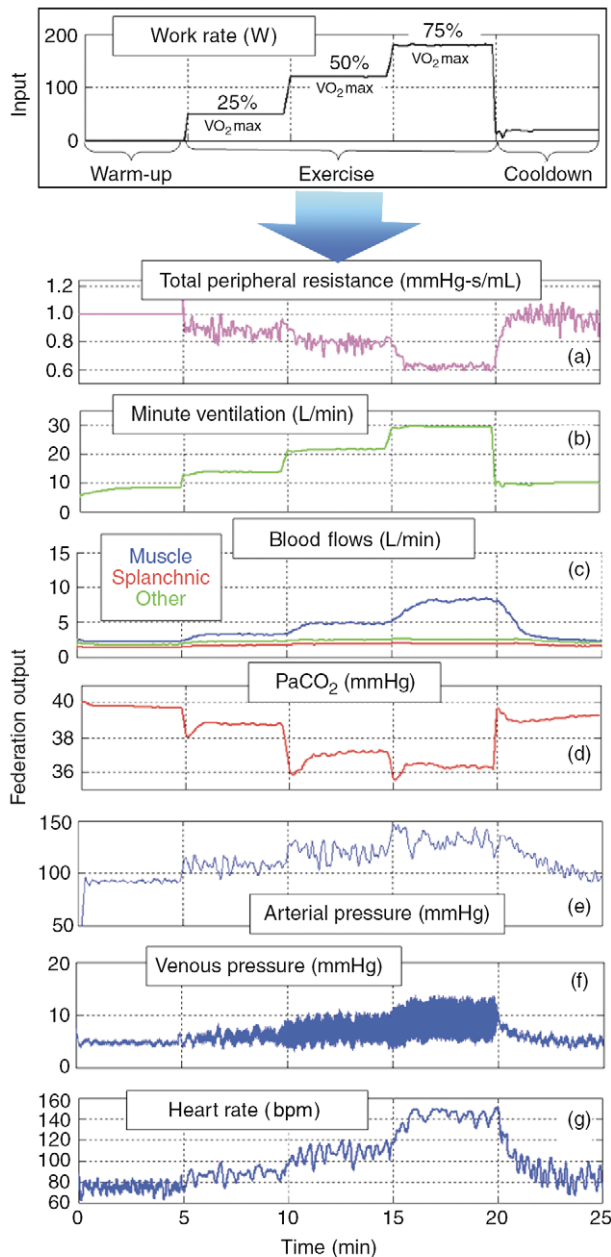
Figure 9. ExerFed execution results during the initial prototype evaluation.

changing in the expected directions. Panels a–g of Fig. 9 show seven simulated variables computed using the work rate curve as input. The total peripheral resistance of the cardiovascular system experienced the expected decrease, causing an increased blood flow to the active muscles while the circulation to other regions of the body stayed approximately constant. Instantaneous values of the mean arterial blood pressure oscillated around the target values, increased during the course of exercise, and returned to normal following the end of the exercise program. Venous pressure oscillated at the approximate frequency of the pedal rotation, and the oscillations increased in amplitude during more intense periods of exercise. The heart rate increased with each successive stage of exercise, conforming to expectations. The only major exception to the general agreement of our model with predicted physiological trends was the simulated lactate concentration in the active skeletal muscle (not shown), which remained constant. For high intensities of exercise, lactate, a by-product of the inefficient anaerobic breakdown of glucose into usable energy, would be expected to increase in concentration when oxygen becomes scarcer. The likely explanation is that the transitioning to the anaerobic threshold within the metabolism model was not implemented with sufficient fidelity.

To gain a quantitative assessment of how well the ExerFed represents the human physiological response to exercise, simulated results were compared to data from exercise tests. Two subjects in Dr. Cabrera's laboratory performed 25-min exercises identical to the NASA cycle ergometer protocol. (Dr. Cabrera's human subject research was approved by an Independent Review Board of CWRU.) Six physiological parameters of interest were collected (oxygen and carbon dioxide consumption rates, heart rate, minute ventilation, respiration rate, and tidal volume) during both the exercise test and while at rest to provide a baseline signal for comparison.

The initial comparison of the ExerFed-generated values to human data prompted several parameter modifications to the ExerFed. The heart rates realized in RCVSIM appeared to be too low at each work rate. To rectify this, the gain of the baroreflex control system was increased at the onset of exercise to emulate an increased sympathetic response. This produced the heart rate signal shown in panel (g) of Fig. 9. Another issue was that intermittent numerical instabilities arose when steady-state blood flows within the whole-body bioenergetics model were replaced with pulsatile waveforms calculated by the LBFR Federate. To remedy this issue, the blood flow values were smoothed using a moving-average filter. In addition, the initial values of the resistance to blood flow in each compartment of the body were slightly modified to produce blood flow values closer to those generated by the original blood flow representation built into the whole-body metabolism model.
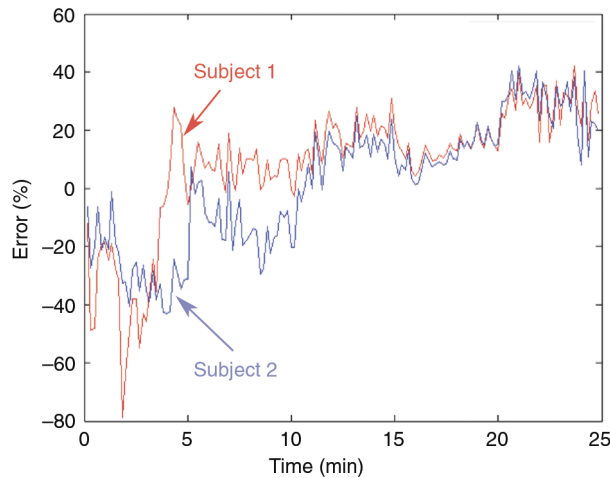
Figure 10. Percentage error between *in vivo* and ExerFed *in silico* heart rates for two subjects during a 25-min cycle ergometer exercise program.

A comparison of the heart rate signals for the Exer-Fed and both human subjects is shown in Fig. 10. As the ExerFed was not tailored to either subject, there remains some difference between the simulated and measured heart rate values. Further research using a larger number of subjects would be required to develop updated model parameters to decrease this difference, but without over-training the model.

CONCLUSION

The completion of the prototype ExerFed has demonstrated the applicability of interoperable simulation techniques, such as the HLA, to the development of simulations for biomedical research. Its development also illuminated several challenges in getting legacy biomedical research simulations to operate together effectively: variations in terminology among different research areas, differences in the number of human body compartments used to represent aspects of human physiology in these areas, sensitivity to the time constants used in the simulations, and various assumptions used in the simulations. These issues will have to be overcome in virtually any endeavor that hopes to use separately developed biomedical simulations, whether or not being used for a space biomedical application.

From a space biomedical research perspective, the prototype development effort was only a proof of principle. As the initial results in the previous section show, additional effort is required to gain better agreement between the simulation and the test data, and more work is needed to show the effects of each subject's physiological characteristics. A validation effort is needed that would compare simulation results to the controlled cycle ergometer test data that are collected in ground tests from the astronaut population. Finally, sensitivity studies are needed to show how aspects of the space microgravity environment may affect the results, which would require comparison to what has thus far been rather limited data collected during spaceflight.

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