

# Metabolic Modeling in Altered Gravity

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**Abstract**—This paper explores the extension of an existing 21-compartment lumped-parameter hemodynamic model of the cardiovascular system to incorporate pulmonary function and metabolic gas transport. The existing model allows study of the acute responses of cardiovascular system parameters (pressures, volumes, resistances, heart rate) with and without exercise under a variety of gravitational conditions, including constant gravity as well as scenarios where gravity gradients are artificially induced, such as centrifugation or lower body negative pressure. The extended model can provide additional insight into human physiology in space as well as future development of integrated countermeasures, especially with regards to the identified reduced aerobic capacity risk for future exploration class missions.

We propose to enhance the existing model by incorporating pulmonary function, a gas transport model, and a respiratory control system. Thus, the model will be able to generate gravitational dose-response curves for additional parameters such as respiration rate, tidal volume, oxygen uptake, and carbon dioxide output. The modeling effort will follow a six-stage development process using techniques and elements either newly developed or adapted from a broad range of human and animal physiological modeling studies. This paper outlines the motivation for developing such a model, and it includes a thorough literature review of various aspects of pulmonary and metabolic modeling physiology, before describing in detail our approach to building the model.

Future work includes completing the development effort and validating our model via human experiments using a tilt platform and a short-radius centrifuge. This research effort will generate acute responses to altered-gravity with and without exercise, providing important insight into the operational risks of altered-gravity on aerobic performance for future exploration class missions as well as the development of integrated countermeasure protocols. Finally, our modeling efforts also have many applications outside the space domain.

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## 1. INTRODUCTION

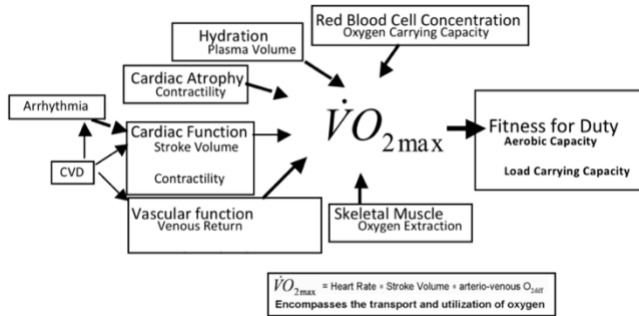
### *Background*

Exposure to microgravity causes decrements in cardiovascular fitness, including maximal aerobic capacity [1]. In current near-Earth spaceflight operations, the degradation can be mitigated with exercise protocols and layered countermeasures [2]; however there is significant variability among crew members and there remains a residual risk that decreased fitness could potentially impair mission operations. Furthermore, when future planetary design reference missions (DRM), or other exploration class missions of longer duration with reduced countermeasure availability, are considered, the long duration implications are unknown and the risk to both operations and astronaut health increases, thus requiring further understanding and mitigation [3].

*Risk evidence*—The NASA Human Research Program (HRP) evidence report “*Risk of reduced physical performance capabilities due to reduced aerobic capacity*” [4] contains a summary of experimental evidence collected from Project Mercury through current International Space Station (ISS) operations. Data show that, whilst  $\dot{V}O_{2max}$  can be maintained during short duration spaceflight, there is a significant impairment on landing, which is hypothesized to be due to the combined influence of hypovolemia and orthostatic stress. Recovery can take up to 30 days post flight.

Whilst there are multiple studies on cardiovascular deconditioning (e.g., an excellent overview of older flight studies is given by Charles et al. [5] as part of the Extended Duration Orbiter Medical Project), flight data on aerobic performance is sparse as  $\dot{V}O_{2max}$  has only been effectively measured in-flight in one ISS study [5] (an attempt was made in Skylab 3 and 4 but equipment difficulties inhibit confidence in the results). Prior to this, heart rate response to submaximal exercise was used as a (not particularly effective) predictor, with errors ranging from -24% to +58% [4]. A number of ground-based analogs (including bed rest studies) have also shown decrements in  $\dot{V}O_{2max}$ , showing the highest decrements in subjects with a high pre-study fitness level and no percentage difference based on gender [6]. Most decrements in  $\dot{V}O_{2max}$  are hypothesized to be related to changes in cardiac output ( $Q_c$ ), venous return, and plasma volume; however, deficits in arteriovenous  $O_2$  difference, hematocrit, cerebral perfusion, orthostatic tolerance, and

thermoregulation are also factors under consideration [4]. Figure 1 shows the main physiological contributors to  $\dot{V}O_{2max}$ . The most effective countermeasures against cardiovascular deconditioning and fitness decrements come from reversing the cephalad fluid shift occurring during microgravity or bed rest studies. These countermeasures include, artificial gravity [7] and lower body negative pressure [8], coupled with an efficient and effective exercise protocol (SPRINT [9] is one attempt to develop such a protocol).



**Figure 1. Major physiological contributors to  $\dot{V}O_{2max}$ .**  
 Reprinted from “Evidence Report: Risk of Reduced Physical Performance Capabilities Due to Reduced Aerobic Capacity,” by M. Downs et al., 2015, *Human Research Program Human Health Countermeasures Element, NASA-HRP-47072*, p. 7. Credit 2015 NASA [4].

All of the data collected to date refer to current exercise countermeasures in a near-Earth, weightless environment. There exists no  $\dot{V}O_{2max}$  data in varying gravitational levels such as Moon’s gravity (1/6g) and Mars’s gravity (3/8g). In addition, the  $\dot{V}O_{2max}$  changes when current exercise suites will not be available (due to mass/volume constraints, i.e., in a planetary DRM) have not currently been determined. The HRP evidence report alludes to this: “The minimum exercise requirements required to maintain [ $\dot{V}O_{2max}$ ] at or near pre-flight levels is not known and will require a much larger data set to provide any recommendations regarding exercise prescriptions.” [4].

**Aims**—In order to develop and understand the required integrated countermeasure suite for exploration missions, it will be necessary to deduce and comprehend the gravitational dose-response curves that describe how the cardiopulmonary system will perform in micro-, Lunar-, and Mars-gravity. Additionally, with both artificial gravity and lower body negative pressure suggested as potential countermeasure elements [7], [8], the effect of gravity gradients on the body must be explored. Furthermore, whilst studies have considered the effects of hypogravity on the cardiovascular system, the long duration physiological changes of hypovolemia and reduced hematocrit [10], [11] likely have composite effects on aerobic capacity.

## Modeling Approach

**Usage**—Modeling is a powerful tool that can provide unique insights into these considerations. As Heldt succinctly summarizes: “the physiological interpretation of limited experimental data can benefit substantially from the concomitant use of a reasonably complete mathematical model” [12]. NASA uses a large multi-system model in the form of the digital astronaut project (DAP), which has replicated the cardiovascular results found by Levine [1], [4], [13]. By extending existing cardiovascular models to include metabolic transport and pulmonary function, we enhance their reach beyond hemodynamics to help answer the questions “how does aerobic performance change in hypogravity?” and “how can we prevent performance decrements?”.

**Baseline model**—The cardiovascular system in altered gravity environments has previously been modeled by Heldt [12], [14] as a 21-compartment lumped-parameter hemodynamic transport model incorporating detailed cardiac function, systemic circulation, pulmonary circulation, and two control systems (the arterial baroreflex and cardiopulmonary reflex), but only a rudimentary lung model. Whilst several other cardiovascular models were designed to look at the effects of gravity (for example [15]–[17]), Heldt built on much of their work to develop a comprehensive systemic model. He followed this with a detailed parameter estimation to develop a model that has been validated in a number of scenarios. Heldt’s model was later extended first by Zamanian [18] to include the effects of centrifugation, and then by Diaz-Artiles [19], [20] to incorporate the effects of exercise.

**Limitations**—It is important to mention briefly both the general limitations of modeling as well as the specific limitations that apply to this model. In general, models are designed to perform a specific function, and caution should be taken extrapolating performance to scenarios outside of the designed range. Furthermore, the principle of “garbage in, garbage out” (GIGO) applies particularly with the selection of model parameters. This creates a challenging scenario as 10 different literature sources could give 10 relatively different ranges for a particular physical parameter, and sometimes they must be estimated based on animal studies. The danger here can be mitigated with a sensitivity analysis to determine the most important parameters (as has been done for the baseline model by Whittle, Alonso, and Diaz-Artiles [21]). In particular for this model, it should be noted that some of the assumptions around certain linearities modeled in the cardiac cycle may be invalid at high pressures outside of normal physiological ranges (e.g., those displayed in subjects with untreated pathological hypertension). We generally assume modeled subjects are healthy individuals representative of the current astronaut population.

## 2. LITERATURE REVIEW

The current state of the baseline model enables simulation of both rest and exercise in constant and artificially generated

gravitational fields to obtain beat-to-beat cardiac parameters including cardiac output, stroke volume, and heart rate, along with specific pressures, volumes, flows, and compliances at any point on the model. The intent of the present modeling effort is to extend Heldt's model to include metabolic function, which could include but is not limited to: oxygen uptake, carbon dioxide excretion, hemoglobin oxygen saturation, expiratory minute ventilation, respiratory exchange ratio, alveolar ventilation, and tidal volume. This will require expanding Heldt's model to include pulmonary function and gas transport, and as such this literature review will cover two related areas. First, the physiology of aspects of the cardiopulmonary system where applicable to the intended modeling effort; and second, the current state of systemic metabolic modeling with some specific examples, including the interface of pulmonary and cardiovascular models.

Whilst the combined work of Prisk and West [22], [23], widely regarded as experts in the field of pulmonary physiology, conclude that pulmonary function itself may not be grossly affected by gravity, the overall dose response curves of aerobic capacity have been shown to be impacted [24]. Furthermore, due to the coupling of the cardiovascular and pulmonary systems, modeling of gaseous transport properties can provide insight into long duration changes in metabolic performance during exercise in microgravity. This is done by allowing us to model additional degrading effects such as hypovolemia [10] and hematocrit changes [11] on aerobic capacity.

#### *Modeling individual aspects of cardiopulmonary physiology*

*Respiratory ventilation*—Respiratory ventilation modeling typically includes two important aspects: first, the actual model of the lungs inspiring and expiring air, and its impact on cardiopulmonary parameters in the thoracic cavity; and second, how this relates to gaseous concentrations in the pulmonary volume. Many of the papers discussed below include some form of ventilation mechanics, typically as a function of changing pleural pressure. Morgenstern and Kaiser [25] provide a general approach explaining how complexity in ventilation modeling can be built up by connecting more and more lumped parameter compartments in series.

The alveolar gas equation (AGE) relates the fraction of inspired  $O_2$  from the atmosphere and the concentrations of  $O_2$  and  $CO_2$  in the alveoli. It was first characterized in a classic paper by Fenn et al. in 1946 [26]. More recently, adjustments have been made by West [27] and Cruickshank and Hirschauer [28]. The aim of these adjustments was to account for the effects of apneic mass-transfer oxygenation, which whilst a minor consideration under normal

circumstances, can become important in cases of carbon dioxide toxicity. The AGE is shown in equation 1.

$$p_{A_{O_2}} = F_{I_{O_2}} (P_{ATM} - p_{H_2O}) - \frac{p_{a_{CO_2}}}{RER} \quad (1)$$

Where  $p_{A_{O_2}}$  is the alveolar partial pressure of Oxygen,  $F_{I_{O_2}}$  is the fraction of inspired Oxygen,  $P_{ATM}$  is atmospheric pressure,  $p_{H_2O}$  is the saturated vapor pressure of water,  $p_{a_{CO_2}}$  is the arterial partial pressure of Carbon dioxide, and RER is the respiratory exchange ratio.

*Pulmonary microcirculation and Gaseous diffusion*—Heldt's original thesis [12] models the lung as set of parallel Starling resistors distributed homogenously across the height of the lung. At a minimum, a model that included pulmonary ventilation would need to return to this distributed model due to ventilation induced variation in intrathoracic and alveolar pressure. Vieyres, Moore, and Jaron [29] use such a model to look at pulmonary perfusion under acceleration stress, modeling the pulmonary vasculature into a series of perfusion zones to study changes in regional flow driven by gravitational gradients.

With respect to gaseous diffusion, many different models exist, including some that are discussed below in the context of more systemic models. For work that purely focusses on diffusion, there appear to be three main approaches. As an example of the first, Wagner and West [30] give the time course of diffusion of both  $O_2$  and  $CO_2$  through the alveoli membranes into pulmonary capillaries as differential equations, giving a range of time constants to model concentration changes with flow along the capillary length. They also account for the effects of pulsatile capillary flow. Reynolds, Ermentrout, and Clermont's paper [31] belongs to the set of work that focuses on the biochemical reactions between hemoglobin (Hb) and  $O_2/CO_2$  including the effect of catalytic enzymes on  $CO_2$  in the bloodstream. Finally, some papers take a much more discrete approach, for example Petrassi et al. [32] conduct a hypobaric experimental study but discuss theory in which they model the effect of individual gas bubbles (formed in the low pressure environment due to Henry's Law) based on Epstein and Plesset's [33] model of bubble formation.

*Gas transport*—Modeling of gas transport primarily relates to biochemical modeling of Hb and the oxygen-hemoglobin dissociation curve (ODC). Whilst the curve, shown in Figure 2, was derived empirically, models exist that calculate fractional saturations ( $S_{HbO_2}$  and  $S_{HbCO_2}$ ) mathematically. One example is given by Dash and Bassingthwaighe [34] who model  $S_{HbO_2}$  as a function of partial tensions, acidity, temperature, hematocrit, and erythrocytic 2,3-diphosphoglycerate (2,3-DPG) concentration<sup>1</sup> (equation 2):

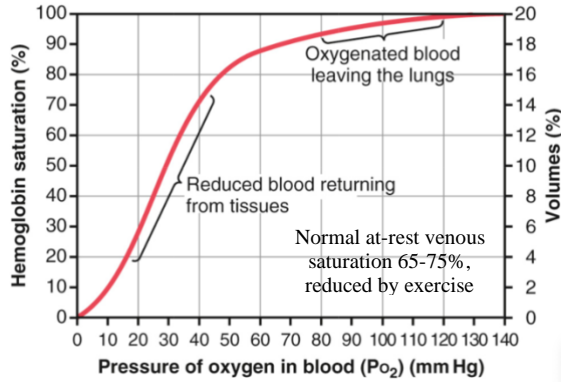
<sup>1</sup> See MacDonald [110] for an extensive paper on the importance of 2,3-DPG for Hb oxygen affinity and whether iatrogenic manipulation in vivo could produce metabolic changes.

$$S_{\text{HbO}_2} = \frac{[\text{HbO}_2]}{[\text{Hb}]} = \frac{K_{\text{HbO}_2}[\text{O}_2]}{1 + K_{\text{HbO}_2}[\text{O}_2]} \quad (2)$$

Where the apparent Hill coefficient  $K_{\text{HbO}_2}$  is given by equation 3:

$$K_{\text{HbO}_2} = \frac{K'_4 \left( K'_3 [\text{CO}_2] \left\{ 1 + \frac{K''_3}{[\text{H}^+]} \right\} + \left\{ 1 + \frac{[\text{H}^+]}{K''_6} \right\} \right)}{\left( K'_2 [\text{CO}_2] \left\{ 1 + \frac{K''_2}{[\text{H}^+]} \right\} + \left\{ 1 + \frac{[\text{H}^+]}{K''_5} \right\} \right)} \quad (3)$$

With the various  $K$  parameters modeled or estimated from an extensive literature review.



**Figure 2. The HbO<sub>2</sub> dissociation curve. Modified from Guyton and Hall: *Textbook of Medical Physiology*, 13<sup>th</sup> Ed. (p. 530), by J. E. Hall, 2016, Philadelphia, PA: Elsevier [39].**

Plenty of modeling has also been done relating to transport of carbon dioxide. Older models such as those of Kelman [35] make use of the Henderson-Hasselbalch equation to derive CO<sub>2</sub> content of whole blood based on temperature and metabolic acidosis or alkalosis. The importance of modeling CO<sub>2</sub> tension does not relate to saturation levels in the same way as studying O<sub>2</sub> transport, as the CO<sub>2</sub> transport mechanism is relatively unstressed under homeostatic conditions due to the high solubility of CO<sub>2</sub> [36]. Rather, the key factor is the relationship between CO<sub>2</sub> content and blood acidity, which is sensed as dissociated H<sup>+</sup> and HCO<sub>3</sub><sup>-</sup> ions by chemoreceptors as part of the respiratory control system. One example of this modeling approach is given by Tanford, Swanson, and Shore [37], who fit curves to experimental dissociation studies of bovine serum albumin (BSA) as an analog for human blood. A more detailed study is presented by Wooten [38] using the Van Slyke equation and strong-ion difference (SID) method to theoretically model CO<sub>2</sub>-pH interaction. As a side note, most literature on this subject covers both O<sub>2</sub> and CO<sub>2</sub> transport due to the cross-coupled interaction of both the Bohr effect (increased CO<sub>2</sub> driving O<sub>2</sub> displacement) and the Haldane effect (binding O<sub>2</sub> promoting CO<sub>2</sub> displacement and transport) [39].

*Oxygen usage and carbon dioxide production in the systemic circulation*—An important part of any metabolic model involving O<sub>2</sub> and CO<sub>2</sub> transport is understanding their use/production by the tissues surrounding the systemic

circulation (be that the brain, the splanchnic and renal circulations, or the musculoskeletal system). Many papers give base tissue consumption/production rates at rest, for example Dyachenko et al. [40] use a single systemic compartment with an overall tissue oxygen consumption level (Qiu and Bai [41] and Olszowka and Rahn [42] are two further examples that are discussed below). However, there appears to have been much less human modeling of organ level consumption/production of O<sub>2</sub> and CO<sub>2</sub> during exercise (though a plethora of experimental studies). Many models exist at a microscopic level, for example Lai et al. [43], [44] consider a cellular level model based on the rates of adenosine triphosphate (ATP) breakdown at various exercise intensities. Similarly, Lyabakh [45] uses Michaelis-Menten kinetics to look at the limits of oxygen usage at high intensities.

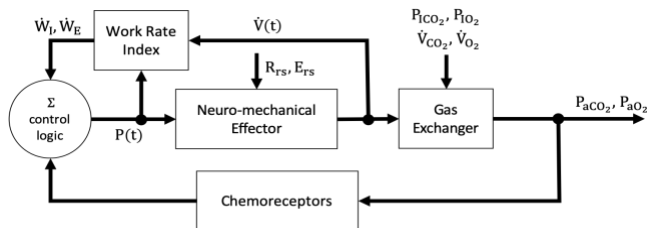
In terms of experimental data, at the organ level several studies give values for base consumption/production rates, including Leach and Treacher [46], Samaja [47], and Wang et al. [48] in humans, and many more papers cover animal data (Liu et al. [49] is one example of a murine study). At the organism level, Mitchell, Stolwijk, and Nadel [50] provide parameters for oxygen consumption at upright rest and maximal exercise, and fit models relating heart rate and cardiac output to total  $\dot{V}\text{O}_2$  based on experimental data. Regarding organ modeling there is a significant amount of literature related to sea mammals during aerobic diving, these are discussed separately at the end of this review. In summary, for our purposes, any modeling of tissue or organ gas exchange would require a mixture of experimental and theoretical data. Then, we would need to fit parameters for oxygen usage and carbon dioxide production in systemic compartments as a function of exercise intensity. This is one of the major challenges that requires further investigation and research.

*Control systems*—Respiratory control is divided between 1) the dorsal respiratory group (DRG) and ventral respiratory group (VRG) in the medulla, and 2) the pontine respiratory group (PRG) consisting of the pneumotaxic center and the apneustic center in the upper and lower pons respectively [39]. Specific modeling efforts related to the respiratory control system fall into two categories: those that aim to model individual systems to control individual inspirations and expirations (e.g., the VRG, see for example Ben-Tal and Smith [51] described below), and those that aim to model overall control. An example in the latter category is the model of Milhorn, Jr. et al. [52], who model the total control system mainly focusing on biochemical changes in blood pH due to the concentrations of HCO<sub>3</sub><sup>-</sup> ions sensed by the pneumotaxic center.

An example of a neuron level model is given by Molkov et al. [53], who model the interaction of the retrotrapezoid nucleus/parafacial respiratory group (RTN/pFRG) along with the central pattern generator (CPG) (all parts of the medulla) to provide both chemical and mechanical closed loop feedback control. Whilst their implementation is perhaps too

detailed for our purposes, they demonstrate the level of fidelity that can be achieved. Furthermore, a review of 12 separate control models is given by Bidani and Flumerfelt [54], which could be used as a starting point for a detailed study of respiratory control systems (however, further consideration will not be given here due to space constraints).

It is also worth mentioning here the work of Heldt [14], who elegantly models the cardiovascular control systems (the arterial baroreflex and cardiopulmonary reflex) as two feedback control loops, each with a sympathetic and parasympathetic arc (with associated time delayed impulse response functions), and an external set point to provide feedback control. A similar methodology could also be used to provide feedback control for the pulmonary system with an external parameter (say base respiration rate) used to adjust involuntary (unforced) breathing; one such similarly elegant example is given by Poon, Lin, and Knudson [55] and is shown in Figure 3 (as adapted by Serna et al. [56]).



**Figure 3. Respiratory closed-loop feedback control system. Adapted from “Optimization techniques in respiratory control system models,” by L. Y. Serna et al., 2016, *Applied Soft Computing*, 48, p. 435 [56].**

### Cardiopulmonary modeling

**Overview**—Huo and Fu [57] provide a good review paper overviewing recent developments in respiratory modeling. On a macroscopic level, they note the work of Halsey et al. [58] in modeling the respiratory system as a black box to assess respiratory efficiency under acceleration for different animal species. They also highlight the models of Schumann et al. [59] and Kent et al. [60], which consider non-linearities in the time varying compliance, resistance, and viscoelasticity, of the lungs under mechanical ventilation. Huo and Fu also describe several microscopic models incorporating the complexity of gas flow into the alveolar spaces. Whilst many of these are interesting as, like Heldt’s work, they are based on lumped parameter models [61]–[63], they are potentially unnecessarily high fidelity and thus computationally intensive, especially if we consider that these are beat-to-beat and breath-to-breath models where the outputs are time-averaged parameters. Another example of a highly complex microscopic model is given by Clark, Kumar, and Burrows [64], where they use computed tomography (CT) to model alveoli structure and computational fluid dynamics (CFD) to examine pulmonary flow.

Whilst Huo and Fu also discuss some models of gas exchange, many of these have already been considered

above. Their final section is of prime interest as it discusses integrated dynamic system models i.e., linking the lungs with either the cardiovascular system or neural control systems. They note that most models of either the cardiovascular or pulmonary systems use the outputs of one process as inputs to another process, but that “*investigating the interaction between [multiple] systems is an exciting advancement in respiratory mechanics*”. Specifically, several models are mentioned, all of which are discussed in the ‘coupled dynamic models’ section below.

**Static models**—One complete static model of cardiopulmonary function comes from Bretherick et al. [65] in the form of a web based clinical calculator for diagnostic purposes. This is built from multiple individually modeled elements, many of which are described above. Their model also incorporates model atmospheres given by West [66] to determine fraction of inspired O<sub>2</sub> at different altitudes for hypobaric uses. This model is an excellent static calculator, giving output transport and metabolic parameters based on physiological inputs, yet it contains no dynamic elements, and has no control system, or capability for modeling changes due to either position (supine, upright etc.), gravity levels, or exercise.

**Coupled dynamic models**—Ben-Tal and Smith [51] consider a coupled model of the lung gas exchange system. In their model brainstem neural circuits provide control of ventilation via the pre-Bötzinger complex (pre-BötC) neurons in the rostral ventrolateral medulla (rhythm generation). The pre-BötC complex then drives the VRG (inspiratory motor output). This provides a level of feedback control over pulmonary ventilation, although as discussed above, control of ventilation also depends on additional unmodeled neural activity.

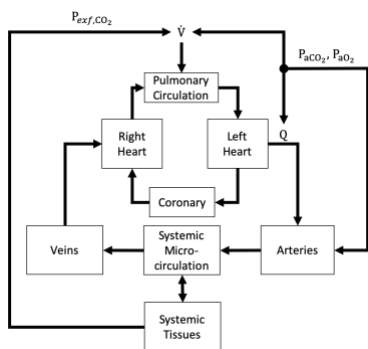
Regarding the coupling of cardiovascular and pulmonary systems, both Montebelli [67] and Jallon et al. [68] use very minimal circulatory models to address dynamic interaction. Montebelli simulates cardiopulmonary interaction during spontaneous breathing to study the effects of chronic obstructive pulmonary disease (COPD), whereas Jallon et al. model the coupling of pleural pressure and intrathoracic blood volume. Whilst both models are complete, they can be considered low-fidelity and they include no models of gas transport, preventing their use in determining metabolic performance. The advantages of these two modeling approaches are in their simplicity, allowing fast simulations for rapid diagnostic means.

Lu et al. [69] provide a highly detailed analysis of linking a pulmonary model to a lumped parameter model of the cardiovascular system. They have a complex pulmonary model, and their cardiovascular model also incorporates the arterial baroreflex. The authors use this model to study a Valsalva maneuver. Their circulatory system is simply a scaled-up model of a canine systemic circulation and they do not incorporate the effects of gravity gradient on hemodynamic transport or blood flow to interstitial spaces. They also include no control feedback of the ventilation

mechanics as a Valsalva maneuver is a forced, deliberate action.

Olszowka and Rahn [42] also developed a compartmentalized lumped-parameter model of the circulatory system to study gas transport. What is interesting about their work is that whilst most other approaches appear to group organs into compartments via location (e.g., Heldt [14] uses a splanchnic compartment to represent all of the lower trunk organs and a separate compartment to represent the legs and pelvis), the authors form four parallel systemic compartments based on tissue type (kidneys, musculoskeletal and integumentary systems, brain and visceral organs, and fat). This model is used to study repetitive breath hold diving, and was later adapted to study sea mammals (see below). From a metabolic perspective, the useful insight comes from their parameterization of CO<sub>2</sub> production in tissues, though they focus equally on CO<sub>2</sub> and N<sub>2</sub> changes. Furthermore, their work demonstrates the ability to link changes in tissue respiratory exchange ratio with gaseous diffusion between the lungs and cardiovascular system.

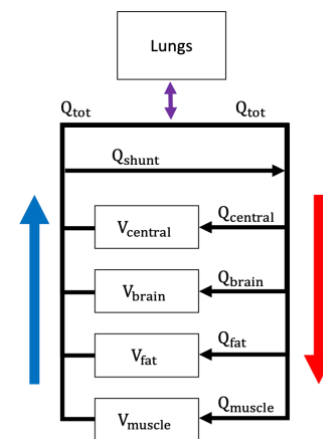
Finally, Qiu and Bai [41] developed a highly coupled model of hemodynamics and gas exchange. Their hemodynamic simulation is very high fidelity, containing 30 compartments for each of the arteries, veins, and peripheral microcirculation trees, along with a four-chamber heart model and a simple controller based on chemoreceptors and CO<sub>2</sub> concentration. An understanding of their work is highly insightful for the desired direction of the proposed modeling effort, particularly with regard to ventilation mechanics, control, and metabolic tissue consumption/production of O<sub>2</sub> and CO<sub>2</sub>. Their use case is to simulate the effects of hypoxia and the use of supplemental oxygen at altitude. As such, certain aspects of their model, such as the interaction of hemodynamics and gas transport, are excellent base references. At the same time, due to their intended use, they do not model any control related to hemodynamic flow regulation (the arterial baroreflex and cardiopulmonary reflex) or account for the effects of gravity or exercise on either circulation or pulmonary mechanics. Their circulatory model and control system is shown in Figure 4.



**Figure 4. Coupled circulatory and transport model.** Adapted from “Multiple modeling in the study of interaction of hemodynamics and gas exchange,” by A. Qiu and J. Bai, 2001, *Computers in Biology and Medicine*, 31, p. 61 [41].

*Sea mammal models*—Outside of human physiology, there has been extensive modeling of respiratory mechanics and physiology for the study of breath hold diving in sea mammals. Davis and Kanatous [70] developed a five-compartment model of a Weddell Seal *Leptonychotes weddellii*. They modeled regional rates of tissue oxygen consumption during aerobic dives by integrating cardiac output, convective oxygen transport, regional blood flow, and muscle oxymyoglobin desaturation using Fick’s principle. Davis et al. [71] later used the same model to study the dive response, in which heart rate slows, peripheral blood flow is reduced (peripheral tissue becomes anaerobic), and oxygenated blood is diverted to the heart and brain. Their work is relevant to human respiratory/metabolic physiology as the techniques developed in the modeling could be applied to the study of blood flow changes towards skeletal muscles and away from the splanchnic circulation during exercise [72].

Separately, Bostrom, Fahlman, and Jones [73] developed a model of ventilation mechanics for diving mammals based on an older model by Denison and Kooyman [74]. Their work examined tracheal collapse under pressure as a delay mechanism for preventing alveolar collapse. This model was later combined with a cardiovascular transport model developed by Fahlman et al. [75] based on the previously describe human model by Olszowka and Rahn [42]. Fahlman’s original model of the cardiovascular system (including gas transport) of the bottlenose dolphin *Tursiops truncatus* is shown in Figure 5.



**Figure 5. *Tursiops truncatus* gas exchange model.** Adapted from “Deep diving mammals: Dive behavior and circulatory adjustments contribute to bends avoidance,” by A. Fahlman et al., 2006, *Respiratory Physiology & Neurobiology*, 153, p. 68 [75].

In appearance it is very similar to the work of Davis and Kanatous [70], with the main functional difference being that Davis and Kanatous’ model only modeled oxygen transport whereas the Fahlman model also considers transport of N<sub>2</sub>. Fahlman’s model [75] was used to study bends avoidance via circulatory adjustment regulating tissue N<sub>2</sub> content. The combined simulation [76] more generally modeled gaseous exchange (O<sub>2</sub>, CO<sub>2</sub>, and N<sub>2</sub>) between the alveoli and

circulatory systems during breath hold diving. Fahlman et al. later used this model to compare two subspecies of *Tursiops truncatus* [77] and performed validation conducting experimental studies to investigate cross species applicability to *Delphinapterus leucas* (Belugas) [78]. Fahlman’s work is of interest for two reasons: first, it provides a very comprehensive three-gas diffusion model (methodology that could be applied in human physiology to study the risk of decompression sickness (DCS) in microgravity); second, the methodology for oxygen consumption modeling for various mammalian tissues under aerobic dive conditions could be used as a starting point for modeling muscle oxygen usage in humans performing aerobic exercise.

Finally, Wright and Davis [79] adapted the model previously developed by Davis and Kanatous [70] to study the effect of myoglobin (Mb) concentration on aerobic dive limits in *Leptonychotes weddellii*. This study is notable as the methodology for modeling skeletal muscle O<sub>2</sub> content could be applied to human models incorporating exercise in microgravity (where studies have shown a decrease in Mb content [80] and long duration shifts between type I and type II muscle fibers which contain different levels of Mb [81]).

### 3. MODEL DEVELOPMENT

#### Outline approach

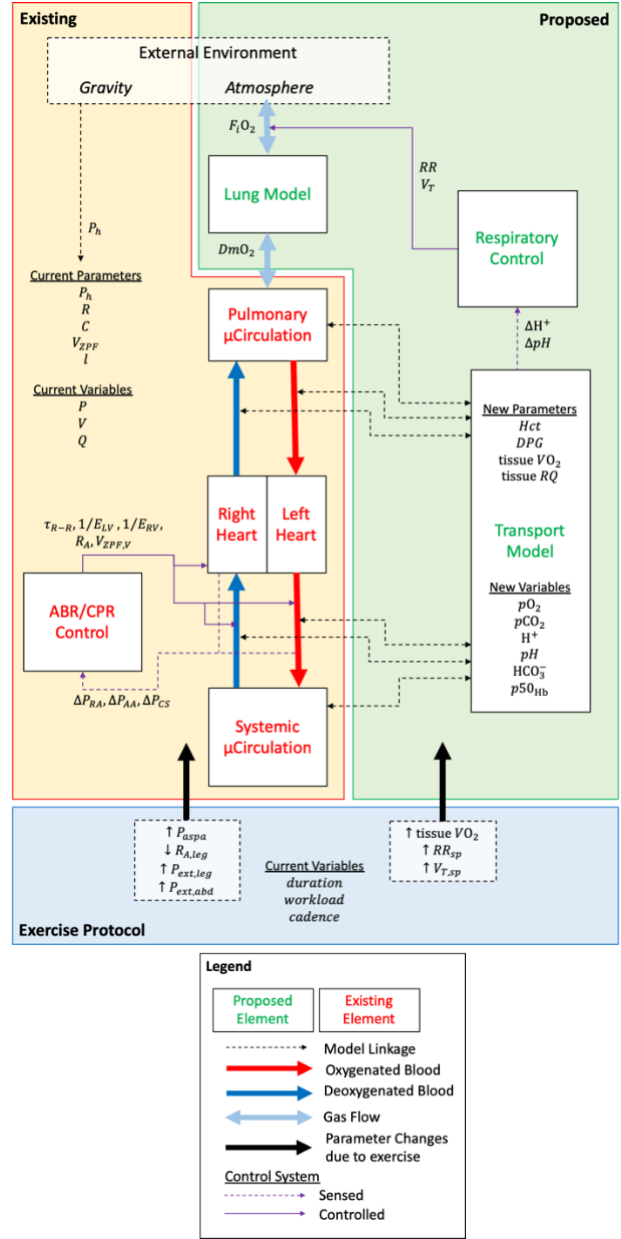
Our modeling approach entails a six-stage process, followed by two validation studies (described later). At the point of paper submission, only stages 1 and 2 have been accomplished, and the plan for the subsequent stages is described below. An architecture diagram showing both the existing modeled elements, along with the proposed future elements is shown in Figure 6.

#### Development stages

1. MATLAB to C conversion.
2. Development of lungs and pulmonary ventilation model.
3. Modeling diffusion from lungs into pulmonary microcirculation.
4. Development of two-gas transport model.
5. Development of respiratory control system model.
6. Development of exercise model.

#### Stage 1: MATLAB to C conversion

Heldt’s model was originally developed in C with a java front end, and it was later migrated to MATLAB and Simulink by Zamanian and Diaz-Artiles [18], [19]. This increased usability due to the visual nature of Simulink, but also had a significantly detrimental impact on model speed and performance. The first stage was to return the model to its original C implementation, incorporating the additions made by Zamanian and Diaz-Artiles. The java front end was completely removed for ease of implementation, but could be redeveloped and reintegrated as an additional final stage. The new elements of the model will all be implemented in C and integrated into the model.



**Figure 6. Proposed model architecture; existing model elements are shown in red, new elements in green.**

#### Stage 2: Development of lungs and pulmonary ventilation model

**Pulmonary ventilation**—The first element to be modeled is a representation of the lungs and pulmonary ventilation. Here we first model alveolar ventilation using the alveolar ventilation equation:

$$\dot{V}_A = RR \times (V_T - V_D) \quad (4)$$

where  $\dot{V}_A$  is alveolar ventilation, RR is respiration rate,  $V_T$  is tidal volume, and  $V_D$  is dead space. Here dead space is defined as a global parameter, whereas respiration rate and tidal volume are parameters controlled by the respiratory

control system with given set points,  $RR^{sp}$  and  $V_T^{sp}$  respectively.

By using the AGE with West and Cruickshank and Hischauer's adjustments for apneic mass-transfer oxygenation [26]–[28], we model the O<sub>2</sub> and CO<sub>2</sub> content of the alveoli as a function of inspired O<sub>2</sub>,  $F_{I_{O_2}}$ , and alveolar ventilation. This is a satisfactory model, but to add higher fidelity we must consider changes in alveolar ventilation based on posture and gravity.

Both West and Luks [27] and Prisk, Paiva, and West [22] detail the variation of ventilation across the height of the lung when upright. To model this variation, we follow an approach taken by Mogensen [82], [83], splitting the lung into  $n$  compartments, taken as equal volume slices with an associated thickness based on a first order approximation of the anatomical shape of the lung. With the average alveolar ventilation calculated in equation 4, we model the individual compartment ventilations to keep the same overall average ventilation. This is achieved by fitting our model to experimental studies given by West and Luks [27]. We use modifications for subject posture  $\alpha$  and gravity conditions  $g_h$  similar to the methodology described below for pulmonary circulation.

To link our pulmonary model with the baseline hemodynamic model, as a first order estimate on the timescales of the model, we assume that alveolar ventilation affects internal alveolar partial pressures in the lungs in essentially a continuous fashion (this means that there is no difference between inspiration and expiration, this could be adapted later to improve fidelity). Therefore the only link to the hemodynamic model aside from the direct gas exchange discussed below is the changing pressure in the intrathoracic cavity with the ventilation cycle, modeled as a piecewise waveform function dependent on RR and  $V_T$  with a shape given by Hall [39]. Having considered pulmonary ventilation, we must also consider perfusion in the pulmonary circulation in order to understand both sides of the AGE.

*Pulmonary circulation*—The lung model consists of  $n$  pneumatic compartments with varying alveolar ventilation,  $\dot{V}_A$ . Each of these pneumatic compartments transfers air to a pulmonary capillary compartment, represented by  $n$  resistors arranged in parallel. This series of parallel Starling resistors represents the different perfusion zones related to varying capillary pressure across the height of the lung.

To model this series of resistors, we modify a method proposed by Heldt [12]. By assuming an apex-to-base lung height  $H$ , with a distance above the left atrium of  $h$  (assuming 80% of the lung parenchyma sits above the level of the heart [84]), and  $n$  compartments as described above, the differential flow in an element  $dq(h)$  is then given by:

$$dq(h) = \begin{cases} 0 & \text{Zone I} \\ \frac{P_{pa} - \rho g_h h \sin \alpha - P_{alv}}{HR_p} dh & \text{Zone II} \\ \frac{P_{pa} - P_{pv}}{HR_p} dh & \text{Zone III} \end{cases} \quad (5)$$

where  $P_{pa}$ ,  $P_{pv}$ , and  $P_{alv}$  are the pulmonary artery, pulmonary vein, and alveolar pressures;  $\rho$  is the density of blood,  $\alpha$  is the angle of the subject with respect to the horizontal (i.e., 90° for standing), and  $R_p$  is the macroscopic pulmonary resistance assuming every capillary behaves like a Zone III Starling resistor.  $g_h$  is a parameter that defines the gravitational condition (either constant for a planetary gravity field or varying with  $h$  for centrifugation).

The zones are determined by:

$$\begin{aligned} h_2 < h < \frac{4H}{5} & \quad \text{Zone I} \\ h_1 < h < h_2 & \quad \text{Zone II} \\ -\frac{H}{5} < h < h_1 & \quad \text{Zone III} \end{aligned} \quad (6)$$

Where  $h_1$  and  $h_2$  are defined implicitly by:

$$\begin{aligned} \rho g_h h_1 \sin \alpha &= P_{pv} - P_{alv} \\ \rho g_h h_2 \sin \alpha &= P_{pa} - P_{alv} \end{aligned} \quad (7)$$

For each one of the  $n$  compartments, we perform a mathematical optimization subroutine that solves, at each time step, for the locations of  $h_1$  and  $h_2$  (the zone boundaries) considering the instantaneous pressures, gravity, and angle. Then, the subroutine integrates equation 5 in a piecewise fashion for each compartment. This gives the instantaneous flow in each compartment,  $q_n$ , from which we can calculate the instantaneous volume of each compartment,  $V_C$ , that will be used in stage 3 to determine gas exchange.

*Parameter estimation*—A number of additional global parameters have been used. Their initial values are shown below in Table 1 with references to where they are sourced from (detail not discussed here):

**Table 1. Initial parameter assignment for pulmonary ventilation.**

Parameter	Units	Value	Ref
$RR^{sp}$	breaths/min	16	[39] <sub>1</sub>
$V_T^{sp}$	ml	500	[39] <sub>2</sub>
$V_D$	ml	150	[39]
$P_{ext}$	mmHg	760	[85]
$F_{I_{O_2}}$	%	20.95	[85]

*1*Involuntary breathing, normal range 12 to 20. Used as a set point for respiratory control.

*2*Used as a set point for respiratory control – can increase up to vital capacity (around 4600 ml [39]).



### Stage 3: Modeling diffusion from lungs into pulmonary microcirculation

The diffusion of O<sub>2</sub> and CO<sub>2</sub> across the pulmonary membrane into the pulmonary circulation is modeled using the approach given by Wagner and West [30]. The rate of oxygen transfer in a single compartment is given by:

$$\frac{d[\text{O}_2]}{dt} = \frac{100}{V_C} \cdot D_{L\text{O}_2} \cdot (P_{A\text{O}_2} - P_{p\text{CO}_2}) \quad (8)$$

where [O<sub>2</sub>] is the amount of oxygen in 100 ml of blood, V<sub>C</sub> is the volume of the compartment, D<sub>L<sub>O<sub>2</sub></sub> is the instantaneous compartment oxygen diffusing capacity, and P<sub>A<sub>O<sub>2</sub></sub> and P<sub>p<sub>CO<sub>2</sub></sub> are the alveolar and pulmonary capillary partial oxygen pressures respectively. A nearly identical equation exists for CO<sub>2</sub>, just with the capillary and alveolar partial pressures reversed.</sub></sub></sub>

D<sub>L</sub> (both O<sub>2</sub> and CO<sub>2</sub>) can be found from the relationship between the alveolar-capillary membrane diffusing capacity D<sub>m</sub>, V<sub>C</sub>, and a rate of reaction θ given as:

$$\frac{1}{D_L} = \frac{1}{D_m} + \frac{1}{\theta \cdot V_C} \quad (9)$$

with θ dependent on a parameter  $k'_c$ , which was experimentally determined by Straub et al. [86], [87], and later modeled by Bretherick et al. [65] as a function of the blood O<sub>2</sub> saturation in the compartments, S<sub>O<sub>2</sub></sub>, the solubility of O<sub>2</sub> in water (a function of temperature), α<sub>O<sub>2</sub></sub>, and the molar concentration of hemoglobin in the blood, c<sub>Hb</sub>. c<sub>Hb</sub> is defined as a global parameter (see parameter assignment below), whereas S<sub>O<sub>2</sub></sub> is calculated from the concentration of O<sub>2</sub> and CO<sub>2</sub> in the compartment – see stage 4.

Given boundary conditions of the flow in each individual pulmonary microcirculation compartment, along with the pulmonary artery concentration of blood (see below), equation 8 can be integrated to give the pulmonary venous blood concentrations (both O<sub>2</sub> and CO<sub>2</sub>). We then use Fick's principle to update the alveolar partial pressures.

Note that here, if we vary the external gravity conditions, we are altering both alveolar ventilation, and pulmonary microcirculation perfusion, changing the balance of equation 8.

*Parameter estimation*—A number of additional global parameters have been used. Their initial values are shown in Table 2, with references to where they are sourced from (detail not discussed here):

**Table 2. Initial parameter assignment for pulmonary diffusion.**

Parameter	Units	Value	Standard Deviation	Ref
V <sub>C</sub>	l	0.0863	0.0175	[88] <sub>1</sub>
D <sub>m<sub>O<sub>2</sub></sub></sub>	mmol/min/kPa	22.7	4.16	[88] <sub>2</sub>
D <sub>m<sub>CO<sub>2</sub></sub></sub>	mmol/min/kPa	20D <sub>m<sub>O<sub>2</sub></sub></sub>	–	[39] <sub>3</sub>

D <sub>L<sub>CO<sub>2</sub></sub></sub>	mmol/min/kPa	D <sub>m<sub>CO<sub>2</sub></sub></sub>	–	[34] <sub>4</sub>
c <sub>Hb</sub>	M = mol/l	2.36E-3	1.32E-4	[89] <sub>5</sub>
T	K	310.19	0.36	[90] <sub>6</sub>

<sup>1</sup>This value is for the total set of capillaries (male subjects), divided by 5n to find the value per capillary compartment.

<sup>2</sup>The measured value is actually D<sub>m<sub>CO<sub>2</sub></sub></sub> and the equivalent value for O<sub>2</sub> is found from the ratios of the square roots of the molecular weights and solubilities [91], approximately 1.23 [92].

<sup>3</sup>The alveolar-capillary membrane diffusing capacity of CO<sub>2</sub> is set at 20 times that of O<sub>2</sub>.

<sup>4</sup>The instantaneous compartment diffusing capacity for CO<sub>2</sub> is set equal to the membrane diffusing capacity implying an infinitely fast rate of reaction for CO<sub>2</sub>.

<sup>5</sup>Caucasian males aged 30-39.

<sup>6</sup>Rectal temperature.

### Stage 4: Development of two-gas transport model

The transport model is developed by updating the existing hemodynamic model. At present, each lumped parameter element is described by a single code structure containing pressures, flows, volumes, and compliances, along with some of their derivatives and some additional system data. This structure is updated to contain two new variables, the concentration of O<sub>2</sub> and CO<sub>2</sub>, [O<sub>2</sub>] and [CO<sub>2</sub>].

With little loss of accuracy, we assume that all gaseous exchange is confined to the microcirculations where the fenestrated endothelial intima promotes diffusion i.e., exchange occurs in the pulmonary microcirculation (as described in stage 3), along with the upper body, renal, splanchnic, and lower body microcirculations. Due to the function and structure of the arteries and veins, with both thick smooth muscle media and collagen adventitia occluding gaseous transfer, little exchange happens in the majority of the compartments in the baseline model of the systemic circulation.

We set a number of additional global parameters including Hematocrit, *Hct*, erythrocytic 2,3-diphosphoglycerate (2,3-DPG) concentration, *DPG*, and base excess, *BE*, along with the new compartment variables [O<sub>2</sub>] and [CO<sub>2</sub>]. Saturation of O<sub>2</sub>, S<sub>O<sub>2</sub></sub>, is calculated for each compartment using a method modified from Bretherick et al. [65]. This saturation is used in both the pulmonary and systemic microcirculations to set diffusion rates of O<sub>2</sub> and CO<sub>2</sub>.

In brief, the pH of a compartment is set using simultaneous solutions to the Henderson-Hasselbalch Equation [93] and Zander's formulation of the van Slyke Equation [94]–[96]. With the pH, we use an iterative numerical process to determine the CO<sub>2</sub> tension, P<sub>CO<sub>2</sub></sub> (considering relative concentrations of CO<sub>2</sub> bound in Hb, in bicarbonate, and dissolved in the blood); the level of O<sub>2</sub> tension at which Hb is 50% saturated, P<sub>50</sub>; and the O<sub>2</sub> tension, P<sub>O<sub>2</sub></sub>. Finally, we calculate the O<sub>2</sub> saturation, using a formula given by Dash and Bassingthwaite [34]:

$$S_{O_2} = \frac{(P_{O_2}/P_{50})^{2.7}}{1+(P_{O_2}/P_{50})^{2.7}} \quad (9)$$

This saturation can be calculated for each compartment, though it remains constant throughout the microcirculations (i.e., one value for the arteries, one for the veins), only being changed in the pulmonary and systemic microcirculations, where it is used to set the diffusion rate.

*Oxygen uptake in the systemic microcirculation*—For the systemic microcirculation, there are four compartments (upper body, renal, splanchnic, and lower body). Here the values that influence gaseous exchange are the  $O_2$  saturation level calculated above, along with the tissue consumption in each compartment  $c$ ,  $\dot{V}O_{2c}$ , and respiratory quotient,  $RQ$  (a global parameter primarily dependent on diet).

The challenge here is setting the individual  $\dot{V}O_{2c}$  values at rest (exercise adaptation is covered in stage 6). As a first estimate we use the values in Table 3, modified from [97].

**Table 3. Percentages of total oxygen consumption in compartments at rest.**

Compartment	Percentage of Total $\dot{V}O_2$ [%]
Upper Body	35 <sub>1</sub>
Renal	7
Splanchnic	31 <sub>2</sub>
Lower Body	27

*1Initially includes both cerebral and coronary circulation; we recognize that we may have to adjust model or values to get a better representation of coronary circulation at exercise.*

*2Also includes cutaneous and other uptakes, as these are included as part of the Splanchnic compartment in Heldt's original model [12].*

*Parameter estimation*—A number of additional global parameters have been used. Their initial values are shown in Table 4, with references to where they are sourced from (detail not discussed here)

**Table 4. Initial parameter assignment for transport model.**

Parameter	Units	Value	Standard Deviation	Ref
<i>Hct</i>	–	0.465	0.032	[98] <sub>1</sub>
<i>BE</i>	mEq/l	0	±2	[99] <sub>2</sub>
<i>DPG</i>	M = mol/l	2.20E-3	1.83E-3 to 2.75E-3	[100] <sub>3</sub>
<i>RQ</i>	–	0.92	0.7 to 1.0	[101] <sub>4</sub>

*1Caucasian males aged 18-79.*

*2Initially set as zero, nominal range (±2SD) given.*

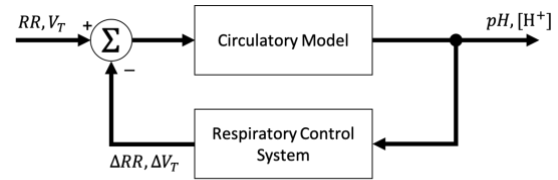
*3Range (±2SD) given, 14.5 (12.1-18.1)  $\mu\text{mol/g Hb}$ , male subjects.*

*4Primarily based on diet. Value selected is for astronauts on ISS, normal value is ~0.8 and clinical range (±2SD) given from [102].*

#### Stage 5: Development of respiratory control system

A control system will be added to the model in addition to Heldt's arterial baroreflex (ABR) and cardiopulmonary reflex (CPR) loops to simulate changes in pulmonary ventilation due to varying tissue oxygenation demand. At present, the form of this control system is yet to be determined, however it is envisaged that the complicated

interaction of the dorsal and ventral groups of the medulla, the pneumotaxic center of the upper pons, and the ion sensitive chemoreceptors will be combined into one or two feedback control systems varying respiration rate and tidal volume based on blood composition. A functional schematic of the proposed system is shown in Figure 7.



**Figure 7. Functional schematic of proposed respiratory control system, changes in blood pH and  $H^+$  concentration (due to hypercapnia) increase respiration rate and tidal volume above set points (which may vary with exercise as a central command driven response) to increase pulmonary exchange.**

#### Stage 6: Development of exercise model

The final modeling stage is to incorporate the effects of exercise. At present, the work of Diaz-Artiles [19] manually adapts physiological parameters in the system, including ABR set point, external pressures in legs and abdomen, and leg arterial resistance based on exercise duration, workload, and cadence.

We consider the same cycle ergometer exercise, but we intend to control model parameters more systematically to reflect the set of physiological changes that induce exercise by combining the appropriate mechanisms through: 1) rapid central command driven response mediating both vagal withdrawal at the onset of exercise and ABR, respiration rate, and ventilation depth set points with exercise intensity; 2) a global increase in sympathetic nervous activity; 3) local responses in the contracting skeletal muscle (i.e., the lower body compartment) reflecting the intensity dependent time course of mechano- and chemo- responses that lead to local hyperemia including muscle pump and functional sympatholysis; and 4) metabolic increases related to the local demand for  $O_2$  in contracting skeletal muscle. We use a number of sources, including the work of Rowell [103], Klabunde [104], and West and Luks [27] to model the interaction of the various mechanisms. Also we use experimental studies involving examination of exercising subjects with multiple catheterizations, such as Calbet et al. [105], to derive models of specific tissue demand that varies with exercise intensity.

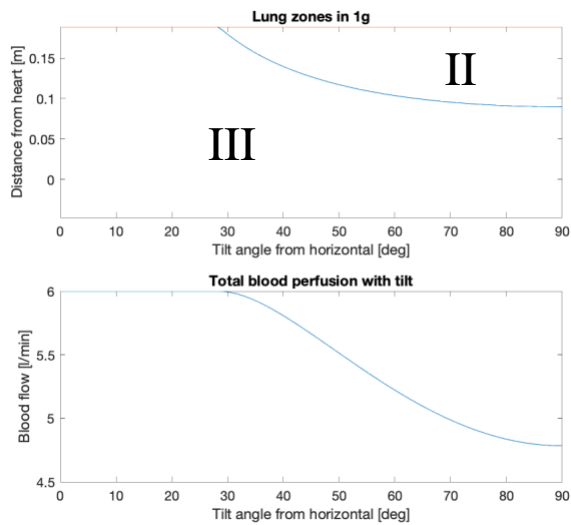
#### Validation

The final two stages of the approach will focus on validation of the developed model. Initially, the model will be fit to cycle exercise on a tilt table simulating hypo-gravity environments, for example the data compiled by Perez, Navarro Titchell, and Diaz-Artiles [24]. Additional experiments may be required. The model will then be extended to include the effects of short radius centrifugation

and will be validated with experimental data to be collected on the new short-radius centrifuge at Texas A&M University. The procedure for fitting and validating the model will closely follow the approaches taken by Heldt [12] and Diaz-Artiles [19].

#### 4. PRELIMINARY RESULTS

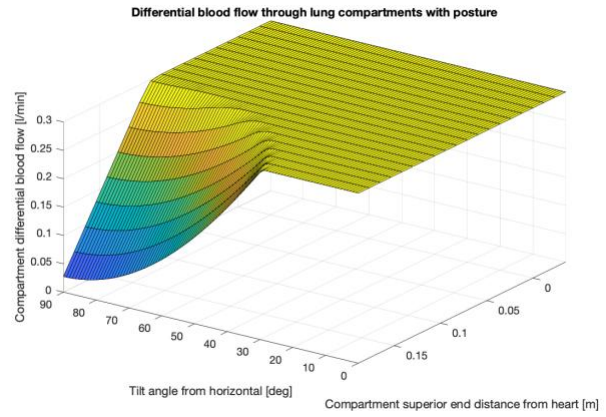
Due to the nature of modeling, it is impossible to generate preliminary systemic results until the entire model is completed. It is however possible to test individual stages of the model in a piecemeal way, even though it is hard to gain insight into the eventual system response. As one example, Figure 8 shows the pulmonary perfusion model in a subject at different orientations in 1g. Here the number of compartments,  $n$ , is taken to be infinite, giving a smooth response.



**Figure 8. Continuous ( $n = \infty$ ) pulmonary circulation model at 1g showing (top) lung zones with tilt angle from supine (0 deg) to upright (90 deg), and (bottom) total blood perfusion.**

The top plot shows the lung zones when the subject is supine (0 deg), to upright (90 deg) Note: in a healthy person there is normally no zone I. These results show that when supine, all of the flow is zone III (continuous flow), but as the subject moves to upright, the top part of the lung begins to exhibit zone II (intermittent) flow due to the gravitational effect. In the bottom plot, the total blood perfusion is shown, ranging from 6 l/min in supine position to just below 5 l/min in the upright position (as a quick check, these agree well with textbook resting values, even with no control [104]).

Finally, Figure 9 shows this same principle applied to a lung made of 20 compartments.



**Figure 9. Surface plot showing flow in each compartment of a 20 compartment pulmonary circulation model varying with tilt angle from supine to upright at 1g.**

In this case, when the subject is in a supine position (0 deg), there is an equal flow across all compartments (on the right of the plot), but when upright, compartments near the apex of the parenchyma (lower left corner) exhibit intermittent, zone II flow.

These simple examples demonstrate that our approach to model the pulmonary circulation model seems appropriate, and we expect it to function properly when integrated with other parts of the model.

#### 5. CONCLUSION

##### *Future work*

This paper outlines the working plan and proposed modifications to build a cardiopulmonary model that will incorporate an additional pulmonary function to our existing cardiovascular model. The baseline model is very well structured, allowing progressive addition of other functions representing each of the additional stages. Certain relationships, such as determining  $S_{O_2}$  from  $[O_2]$ , require mathematical non-linear optimization routines, which will either be drawn from existing open source libraries or hand coded using numerical recipes such as those given by Press et al. [106].

Validation will be performed by conducting (or using the data from existing) experimental studies and reproducing an identical procedure in the computational model. The model can then be tuned to the data using one or two parameters, for example Diaz-Artiles, Heldt, and Young [107] use mean arterial pressure (MAP) and total peripheral resistance (TPR) for this purpose. Once tuned to the experiment, the remainder of the model outcomes can be visualized to see if they fit within the variation of the experimental data. Once validated, the model can then be used to analyze hypothetical scenarios, conditions, and subjects.

Finally, we could run a sensitivity analysis using Latin Hypercube Sampling and Partial Rank Correlation

Coefficients [21] to determine which are the most important parameters of the new pulmonary function. Once fully integrated and validated, our pulmonary/metabolic system becomes a part of the baseline model that will be used for any future modeling studies planned e.g., see Whittle and Diaz-Artiles [108] for an outline plan for looking at cardiovascular changes on long duration spaceflight.

#### *Application outside of the space domain*

Development of a complete, lumped-parameter cardiopulmonary model has also marked utility outside of the space domain. Five additional prospective uses can be considered. First, in aviation, there is much research on the effects of altitude on pilot performance. Changing atmospheric parameters could give a dynamic model of the cardiovascular system in a hypobaric environment that would be of interest to both military and civilian studies of physiology in high altitude flight. Second, exercise physiology studies would benefit from a greater understanding of the interaction between the cardiovascular and pulmonary systems, particularly at the limits of aerobic performance. Third, there are medical pathologies related to reduced function of the cardiopulmonary system that could benefit from the development of the integrated model described herein, with minor modifications to model the effects of specific diseases. Fourth, diving medicine is greatly interested in the study of oxygen transport in the blood; thus, the model could provide additional insight into studies of breath hold diving, similar to the work already mentioned that has been done for sea mammals. Further extensions to the model by adding transport of N<sub>2</sub> could allow studies of decompression sickness (DCS) to be undertaken (note, this could also be applied in the space domain to consider risks of DCS during extravehicular activity, EVA [109]). Finally, this model could be used as a teaching resource, with for example a simple java front end accessible to students. ,

#### *Summary*

To conclude, this paper has outlined the need to study the pulmonary and metabolic transport system in microgravity, particularly with regard to the risk from reduced aerobic capacity ( $\dot{V}O_{2max}$ ) that is not currently effectively mitigated. By obtaining theoretical dose response curves for aerobic performance, which can be compared with new and existing experimental studies, it will be possible to better understand the effects of gravity on human physiology, especially in terms of acute responses but it could also be applied to chronic responses induced by hypovolemia and reduced hematocrit. Our proposed modeling effort will provide invaluable insight into the operational risks of hypogravity on aerobic performance for future exploration class missions as well as the development of integrated countermeasure protocols.

We have proposed that computational modeling is one effective way to study human physiology in altered-gravity environments. We specifically propose to extend an existing

model of the cardiovascular system by adding pulmonary function that is not currently being included. Whilst the current state of the model allows understanding of the cardiovascular system, these incremental additions extend its reach and allow additional compounding effects to also be considered.

We have performed an extensive literature review covering various physiological aspects of the systems we intent to model. We then discussed the proposed model extension in detail, outlining a six-stage process to incorporate pulmonary function, gas exchange, gas transport, respiratory control, and exercise adaptations, including the mathematics behind the physiology. Finally, we have discussed future model validation using experimental studies, and showed some preliminary results of our pulmonary circulation model.

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