A Model of Anaerobic Tissue Perfusion During Trauma –Lactate Trajectory Curvature Can Determine Recovery

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Abstract

# Introduction

Hemorrhage, characterized by the loss of blood from the circulatory system, is a critical physiological event often encountered in trauma, surgery, and various pathological conditions. Its consequences extend far beyond mere blood loss, triggering a cascade of systemic responses that profoundly impact cardiovascular function, tissue perfusion, and metabolic homeostasis1–5. Concomitantly, hemorrhage-induced acid-base disturbances play a pivotal role in shaping the physiological response to blood loss, influencing cellular metabolism, oxygen delivery, and overall systemic equilibrium6–8. Understanding the intricate interplay between hemorrhage and acid-base disturbances is crucial for elucidating the mechanisms underlying physiological compensation and decompensation in response to blood loss. Moreover, accurate modeling of these phenomena holds significant clinical relevance, aiding in the prediction of patient outcomes, optimization of resuscitative strategies, and refinement of therapeutic interventions9–12.

Despite advancements in our understanding of hemorrhagic shock and acid-base disturbances, significant gaps persist in both clinical practice and modeling approaches. Firstly, current clinical guidelines for managing hemorrhagic shock often lack specificity regarding the optimal resuscitative strategies to mitigate associated acid-base imbalances13–15. While fluid resuscitation remains a cornerstone intervention, the choice of fluid type, volume, and timing remains contentious, particularly in the context of concurrent acid-base disturbances. Various recommended treatments may cause additional harm when administered16,17. For example, transfusion protocols have evolved over the past century to recommend permissive hypotension, and limited crystalloid administration18. Moreover, the individualized nature of patient responses to resuscitative efforts necessitates a more nuanced approach that integrates dynamic physiological parameters, such as tissue perfusion, oxygen delivery, and metabolic status.

Secondly, existing models often oversimplify the complex interplay between hemorrhage and acid-base disturbances, overlooking key determinants or feedback mechanisms, often focusing on one singular mechanism as opposed to integration and connection of multiple processes19. Many models predominantly focus on cardiovascular hemostasis, not stressing systems into circulatory shock20–22. This fails to capture the complex physiological nature of hemorrhagic shock and its impact on acid-base balance and peripheral systems. Consequently, there is a pressing need for integrative modeling approaches that account for the dynamic interactions between cardiovascular, respiratory, nervous, and metabolic systems during hemorrhage-induced acid-base perturbations. The aim of models of this type is facilitation of the development of more effective resuscitative strategies and analysis of synthetically generated data that may be tailored to individual patient profiles.

In this paper, we present an integrative modeling framework aimed at elucidating the complex interactions between hemorrhage and acid-base disturbances in physiology. Leveraging computational techniques and mathematical simulations, our approach offers a comprehensive examination of the dynamic physiological processes that unfold during hemorrhagic events, encompassing alterations in cardiovascular dynamics, fluid shifts, tissue oxygenation, and acid-base balance. Central to our modeling paradigm is the incorporation of established physiological principles, and principles of oxygen transport and consumption. By integrating these concepts within a cohesive computational framework, we aim to provide a nuanced understanding of the multifaceted responses elicited by hemorrhage and their impact on systemic acid-base equilibrium.

We use this model to generate synthetic data and analyze this data in the form of patient trajectories. These trajectories may inform recovery characteristics and are not able to be properly studied in experimental patient data due to the lag time involved in laboratory measurements of patient blood. We show that for worsening hemorrhage there is a distinct shape to the maximum curvature point in the patient trajectory. This curvature is studied over a diverse patient population, and we report statistics on its variance for this given population. We show that for these statistics, patient recovery can be defined by a curve fit to the maximum curvature for a given patient hemorrhage, creating a potentially useful clinical measurement tool, as lactate measurements, coupled to a more available measurement such as blood pressure, can be analyzed against this curve to determine patient state.

# Materials and Methods

We construct a model of the cardiopulmonary system coupled to oxygen diffusion, blood-gas binding and transport, anaerobic tissue perfusion, and nervous system autoregulation in the BioGears physiology engine23 as this platform provides coupling to various other systems in the body to determine global physiological patient response. In addition, BioGears has a robust application programming interface (API) that allows for programming diverse patient trauma scenarios and extraction of data broadly (heart rate) or at a more refined level (lactate concentration in the renal tubules). The BioGears physiology engine has been successfully used in modeling of sepsis24, burn25, hemorrhage26, and used as the patient physiology in many healthcare simulation studies27,28.

## Cardiopulmonary System – Circulation and Respiration

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| Figure 1 – Cardiovascular circuit structure for the BioGears circulatory system. Respiratory, cerebral, tissue, and renal circuits are omitted for brevity. Left and right ventricle drive the system through elastance changes. Pulmonary arteries oversee oxygen diffusion between the respiratory (gas) circuit into the cardiovascular (liquid) circuit. |

Following the work done in whole-body physiological models that include circulation29–32, we model the circulation by constructing an electrical circuit analog that characterizes the fluid dynamics. Flow rates and pressures are approximated by current and voltage and computed each time step. Using this approximation, we compute the state of the circulation leveraging Kirchhoff’s voltage and current laws at each node on the graph. We begin by denoting ground as our reference node the label nodes in the system and initialize certain node pressures as a function of experimental data33,34 or are optimized for desired patient dynamics. Once nodes are labeled and initialized we perform modified nodal analysis35 to populate a matrix that contains the system dynamics. For each node we use Kirchhoff’s current and voltage laws to solve for unknown quantities. If Voltage is defined across a resistor, we use Ohm’s law to define a relationship between current and voltage. Using this denotation, we construct the following matrix equation:

Here, the G matrix is the nodal admittance matrix (conductance matrix for resistors). B is a matrix representing the connection of voltage sources to nodes. C is the transpose of B. D is a diagonal matrix representing the internal resistances of voltage sources. Vn is the unknown voltages and Im denotes the unknown currents. Is and Vs denote the current and voltage sources in the system. For our implementation, we note that Is is zero. To handle the compliances in the system we approximate using backward euler step to compute the current for a given capacitor C:

Thus, for each capacitor connecting nodes i and j, we have:

Now defining , we can derive an update scheme for the G and Z matrices to be:

We note that along the diagonal, we sum the capacitance contribution in the G matrix. Once the matrix is constructed, we use LU factorization to solve the sparse system.

To drive the circulation, building on prior work36, we construct a driver function that relates elastance to cardiac cycle time:

Here Ev denotes the elacitance for a given ventrical with associated max and min values and f is a nonlinear relationship between current simulation time and period of contraction for a given cardiac cycle:

Here T is our cardiac cycle length and alpha and n denotes shape parameters that are fit to a pressure volume curve.

The gas transport equations for the respiratory circuit are identical to the cardiovascular system, with one exception, the driver. We derive our driver function to relate the respiratory muscle pressure (negative pressure) to the respiratory cycle time:

Here I, E, and T are the inspiratory, expiratory, and total respiration times, respectively. The value τ is a time constant for the expiration period and is estimated as E / 5. The total breathing cycle time T is obtained from the inverse of the respiration rate determined by the chemoreceptor model (omitted from this paper for brevity). I and E are calculated using the inspiratory: expiratory ratio from the previous time step, which is modified by irregular physiology like asthma and COPD. The chemoreceptor model also updates the driver amplitude, Pmax. The baseline value of Pmax for each virtual patient is determined during engine initialization by modifying the amplitude at the requested patient respiration rate until a stable tidal volume is obtained. These drivers are both manipulated by the nervous system depending on the state of the patient. For our massive hemorrhage model, we develop the baroreceptors to buffer the pressure drops occurring due to blood loss.

## Baroreceptor Response

The baroreceptor mechanism provides rapid negative feedback control of arterial pressure. A drop in arterial pressure is sensed by the baroreceptors and leads to an increase in sympathetic activity and vagal (parasympathetic) withdrawal. These changes operate with the goal of maintaining arterial pressure at its healthy resting level. We distinguish between aortic, carotid, and low-pressure (cardiopulmonary) receptors. Aortic and carotid receptors are both sensitive to changes in systolic arterial pressure, but their relative locations in the body affect this response. Aortic baroreceptors respond to the transmural pressure between the aorta and the intrapleural space. The carotid baroreceptors, located a distance above the heart, are affected by pressure head (except when an individual is lying down). Low-pressure receptors are located near the venous return to the heart and are therefore sensitive to the central venous pressure and pleural pressure. We us a stress-strain relationship to calculate the signal generated at the aortic and carotid baroreceptors37 and a first-order, low-pass filter to generate the low-pressure receptors signal38. Thus, we describe the strain exerted on aortic and carotid baroreceptors as:

Here εw is the wall strain, Pinput is the systolic pressure for the carotid baroreceptor and the difference between systolic and plural pressure for the aortic baroceptors, A is the maximum stressed to unstressed vessel cross-sectional area, qw is the steepness of response, and sw is the operating point of the baroreceptor response. The operating pressure is the systolic pressure after initialization of the patient. We note that the operating point may also be influenced by drugs, pain, or exercise although these adjustments were not considered for this manuscript.

We model adaptation39,39,40 by adjusting the operating point as a function of systolic arterial pressure:

Here the value of kadapt is chosen to generate an approximately 16-hour half-life for the baroreceptors to adapt to a step change in systolic pressure. We further model the baroreceptor response as a spring dashpot system where we represent the strain induced by a stress in the system to be:

Here the strain, is processed in the central nervous system. To model the low-pressure baroreceptor signal generation, we introduce a low-pass filter that samples the transmural pressure between the venous return (CVP) and the pleural space:

And connect this model to the firing rate:

Here fcp is the firing rate processed by the CNS. τcp and fcp,max are the time constant for the response and the maximum firing rate, while CVPbase and Ppleural,base represent the normal central venous and pleural pressures. Following similar work19,20,41,42, we then weight the signal produced in the afferent arm of the central nervous system to produce the final afferent signal. We omit model details of the peripheral chemoreceptors, and pulmonary stretch receptors as they are not relevant for the current study.

## Hypoperfusion Model

For a given tissue compartment, during circulation, the cells request a baseline level of oxygen to support ATP creation. During periods of hypoperfusion, the tissue reverts to anerobic activity, generating lactate. This generation perturbs the ph value of the blood, resulting in changes in the biding activity of red blood cells7,8,43. We generate a model based upon prior work, that couples the strong ion difference in the blood, ph, and (as circulated by the cardiovascular model) bound and unbound o2 bicarbonate and co2:

We solve this system for its root at each time step for each liquid compartment in the cardiovascular system to determine oxygen binding during a hemorrhage event. To further perturb the anerobic activity, we also scale lactate levels as a function of total blood volume in the patient:

L is lactate mass, and V denotes blood volume. Parameter values for this expression were chosen to validate well with experimental data (see results section). Due to the major role the kidneys play in filtering lactate from the blood and adjusting pH balance in the blood44, we introduce a relationship between mass transported into the renal tubules and blood pH:

Here M denotes the mass of lactate in the renal capillaries, and pH denotes the pH in the blood. Parameters were qualitatively measured to capture recovery time post bleed. This value scales the amount of lactate filtered by the kidney’s by moving mass into the tubules for clearance. At each time step we move lactate mass into the tubules:

## Calculating Curvature of Trajectories

We have now constructed a model of the hemodynamics of the patient, given stresses introduced by hypovolemia. We effectively connected the circulation to a regulatory model of the nervous system, able to buffer changes in arterial and venous pressures. Using this we may extract time series data from the simulation during a hemorrhage event. For a given trajectory that we will define as

Given as time series data where the x,y points consist of patient physiological data extracted from the physiology model. We assume x,y and only dependent upon t and may consist of things like: heart rate, respiration rate, lactate concentration in the blood, ect… For this trajectory, to extract maximum curvature value during trauma and subsequent recovery, we first smooth the data using a convolution for each array x,y over a discrete window:

Here 1 denotes a normalized ones vector over our window size, m, and x can be interchanged with any physiological variable we are extracting from the model. This operation effectively smoothest the data over the window size. This operation is critical as a curvature algorithm will converge to high frequency found on the trajectory path, not necessarily the global curvature maximum over the simulation. After smoothing we compute the curvature along the trajectory:

From this expression we can extract the maximum curvature over a given trajectory to determine the inflection point in which the patient begins their recover. We aim to analyze this point over the x,y domain to segment the plane into disease state.

# Results

## Physiology of Hemorrhage

We begin by configuring the patient with a series of increasingly severe hemorrhages and investigate the overall cardiovascular patient physiology as a function of this severity. In the constructed scenario, we initialize the hemorrhage, and then proceed to let them bleed for 10 minutes which we assume to approximate a standard emergency transit time. Once the patient has been successfully transferred to a healthcare institution, we begin a transfusion protocol, in line with hemorrhage severity10,14,18,45. After an addition 10 minutes of fluid resuscitation, we assume the patient has had their bleeding stopped via a surgical intervention and continue resuscitation until the shock index, here defined to be the ration between heart rate and systolic pressure, is below 146–48. We note qualitative validation of the behavior of our model through the generalized increase of heart rate and decreases in blood pressure pH and blood volume, Figure 2.

We note that the recovery phase in physiological response to hemorrhage is much longer, as the baroreceptors continue to remain diminished until blood volume and pressure recover fully during the scenario.

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| A graph of different colored lines  Description automatically generated with medium confidence |
| Figure 2 – Cardiovascular metrics reported for varying levels of initial hemorrhage. The extreme hemorrhage case, 230 mL/min, the patient “dies” before resuscitation can achieve hemodynamic stability. |

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# Discussions

# Conclusions

# Conflict of Interest

*The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest*.

# Author Contributions

The Author Contributions section is mandatory for all articles, including articles by sole authors. If an appropriate statement is not provided on submission, a standard one will be inserted during the production process. The Author Contributions statement must describe the contributions of individual authors referred to by their initials and, in doing so, all authors agree to be accountable for the content of the work. Please see [here](http://home.frontiersin.org/about/author-guidelines#AuthorandContributors) for full authorship criteria.

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