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and Closed-Loop Trauma Resuscitation

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14. ABSTRACT Our long-term goal is to deliver automated closed-loop fluid and drug resuscitation systems for combat casualty and trauma care. We have prototyped and performed extensive animal studies of such systems for hemorrhagic shock and bum shock. However, animal studies alone may not be sufficient to demonstrate the safety of these systems. A key component to demonstrating the safety of these systems is to use mathematical models that describe the physiology of shock and its response to a full range of injuries and therapies. The focus of this grant is to establish such mathematical models.					
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1. INTRODUCTION:

Our long-term goal is to deliver automated closed-loop fluid and drug resuscitation systems for combat casualty and trauma care. We have prototyped and performed extensive animal studies of such systems for hemorrhagic shock and burn shock. However, animal studies alone may not be sufficient to demonstrate the safety of these systems across the wide range of patient and clinical conditions they may need to be used in during critical care. The focus of this grant is to establish mathematical models as the foundation for the development and evaluation of closed-loop trauma resuscitation algorithms and demonstrate the utility of these models in the development and optimization of closed-loop resuscitation algorithms. We will 1) Develop mathematical models of trauma-induced shock and resuscitation specifically for developing and evaluating closed-loop resuscitation control algorithms. We perform animal studies to provide the key data to develop models. 2) Perform quantitative evaluation of mathematical models of trauma-induced shock and resuscitation. 3) Establish utility of the mathematical models by comparing in silico versus animal testing of closed-loop resuscitation algorithms. Future autonomous closed-loop resuscitation systems well validated with extensive in silico safety and efficacy testing based on mathematical models will allow Medics, Forward Surgical Teams and Combat Support Hospitals to apply resuscitation therapies near equivalent to that of the trauma center standards.

2. KEYWORDS:

Provide a brief list of keywords (limit to 20 words).

Shock Treatment, Burns, Hemorrhage, Closed Loop, Fluids, Pressors, Hypotension

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Year 01: Development of Mathematical Models of Trauma-Induced Shock and Resuscitation Develop: 1) An extensive set of physiological data of responses to injuries and therapeutics using anesthetized swine animal experiments. 2) New mathematical models suited to the development and validation of closed-loop fluid resuscitation algorithms for hemorrhage and burns, and refractory shock.

Year 02: Quantitative Evaluation of Mathematical Models of Trauma-Induced Shock and Resuscitation Deliver: 1) Three mathematical models: Burn

model and hemorrhage models (completed) and the Refractory shock model and vasopressor resuscitation model (advanced). Validation data for the burn model was provided by a large cohort of patient data. Animal studies of hemorrhage were used for validation and extension of the hemorrhage model to heart rate control. 2) A new closed loop fluid resuscitation algorithm was developed for hemorrhage and in silico simulation testing was begun.

No Cost Extension Year 03: **Establish Utility of the Mathematical Models by Comparing In Silico and Animal Testing of Closed Loop Resuscitation Algorithms** The vasopressor treatment model of refractory shock will be completed. Quantitative assessments of the developed mathematical model of hemorrhage will be performed with co-experiments of fluid resuscitation of anesthetized hemorrhaged swine and in silico.

What was accomplished under these goals?

1. Major Activities

Animal studies. We continued to perform animal studies of hemorrhages and fluid therapy. We started studies of refractory shock (nitroprusside) and vasopressor-(phenylephrine).

Mathematical Models. Hemorrhage tuning and validation of the hemorrhage model and fluid resuscitation was performed with our new dataset. We have largely finished this model. We also developed a model of heart rate control.

Burns. We completed the burn model and used historic data of burn patients to validate the model.

Pressor Use. Studies of refractory shock and vasopressor-phenylephrine were performed in our lab and good progress on its mathematical modeling was accomplished.

2. Specific Objectives

To develop mathematical models of fluid therapy of hemorrhage and burn shock and vasopressor drug therapy.

3. Significant Results or Key Outcomes

We performed more animal experiments on hemorrhage and refractory shock and resuscitation with fluids and pressors, respectively. The hemorrhaged blood

pressure model was completed and enhanced with heart rate model, see 3b. A mathematical Burn Model is now completed and validated, see 3b. Progress is reported for the vasopressor model, 3c. The new hemorrhage closed loop model and treatment algorithm was developed, see 3d.

3.a. Animal Studies Physiological Dataset

Data Handling. We have physiological data from 15 swine studies of hemorrhage and resuscitation. Each animal had multiple scenarios of induced shock and treatment. Data was manually recorded every 5 into 10 minutes and converted to Excel. Shorter sampling times were often performed during and just after bolus fluid or start of pressor therapy. We collected high resolution hemodynamic data, 1,000 Hz, from the vital signs monitor to include ECG, arterial pressure, pulmonary arterial pressure, central venous pressure, and end tidal CO₂. A Doppler flow meter was used to capture rate of infusions and bleeding rate. Blood samples were taken for hematocrit determinations Cardiac output was measured by thermal dilution every 10-15 minutes. Total peripheral resistance is calculated by the modelers during their analysis.

Protocols in General. After surgery and stabilization, there was a one hour baseline period, then each protocol had four to seven periods of shock and resuscitation. Multiple protocols were then performed and in general varied between studies. The exact protocols were discussed and established before each experiment (video-teleconference call) with the modelers and the animal study group. The goal was to provide the modelers with shock and fluid-pressor challenges and their time points needed to develop and test the model. Typically, for hemorrhage we performed an initial shock period in which blood was removed until mean arterial pressure was equal to a predetermined set target, e.g. 40 mmHg, and held at that pressure by additional bleeding or stopped. Each protocol had and multiple fluid boluses equal to 200-mL to 500 mL per 80m Kg per 80 kg. Typically, additional hemorrhages were performed after or during resuscitation to mimic internal uncontrolled hemorrhage. This provided typical adult human sized boluses. We used 5% albumin for bolus fluids; 5% albumin has the volume expanding effects of plasma or whole blood. We studied rapid bolus and slow boluses. Typically for refractory shock,

Representative studies

Fluid/ Hemorrhage and CL study 66Y (44.8 kg), 1/21/2021

- Prior to experimentation, 66y was anesthetized using ketamine and buprenorphine, followed by continuous sedation with propofol.
- Baseline recordings were made for 30 minutes (MAP 118mmHg).
- Hemorrhage started at body wt. per minute (44.8 ml/min). MAP of 44mmhg achieved after 20 minutes of hemorrhage.

- Hemorrhage was stopped and slow resuscitation initiated, (25 ml albumin per minute) with a total of 150 ml bolus of albumin given. MAP of 93mmhg was achieved post bolus.
- We then resumed constant slow continuous hemorrhage (22.4ml/min) to simulate internal uncontrolled bleeding. And again administered slow resuscitation with a total bolus of 150 ml albumin. A MAP of only 46mmhg was recorded 30 minutes post continuous slow bleed and slow resuscitation. Total albumin bolus given over this first course of study 300ml.
- Continuous slow hemorrhage was stopped and halt the hemorrhaged blood was returned, and the animal stabilized for the closed loop experiment over 45 minutes.
- Baseline hemodynamic recordings taken, (MAP 110mmHg). Fast hemorrhage of 70ml/min to target MAP of 40mmHg started. Hemorrhage stopped after MAP 41mmHg reached 5 minutes post fast hemorrhage initiation.
- Closed loop system turned on and fluids (Albumin) given to animal using our closed loop system and an algorithm, previously described (1, 2). MAP of 77mmHg was reached after 30 minutes of closed loop system initiation. Animal remained stable for 1 hour.

Pressor Study 100y (70.2 kg). 4/13/2021

Prior to experimentation, the animal was anesthetized using ketamine and buprenorphine, followed by continuous sedation with propofol.

- We administered sodium nitroprusside (SNP) continuously at varying rates to induce hypotension (simulated vasoplegia/refractory shock), while boluses of phenylephrine (PHP) were administered to resuscitate to MAP mean arterial pressure. SNP infusions were adjusted to reduce MAP to a target of 40 mmHg to 50mmHg. Then SNP doses were adjusted every ten minutes in a randomized range from 0.3µg/kg/mL to 5µg/kg/mL over 1 hour to induce unstable blood pressure.
- A resident anesthesiologist manually administered boluses of PHP in 1-mL (100µg/mL) increments to achieve and maintain MAP of 90 mmHg. This high target blood pressure is representative of what would be needed to resuscitate a casualty with traumatic brain injury. A total of 10mL PHP was administered over the course of the 1-hr study. The injection times of PHP boluses were recorded using a commercial Hypotensive Decision Assist device.
- A second period of hypotension using the same doses and pattern of the SNP as above was performed, but this time the PHP was administered by closed loop PI controller that we previously developed and tested(3, 4).

3.a. References

1. Ying H, Sheppard LC. Real-time expert-system-based fuzzy control of mean arterial pressure in pigs with sodium nitroprusside infusion. *Med Prog Technol.* 1990;16:69-76.
2. Marques NR, Ford BJ, Khan MN, Kinsky M, Deyo DJ, Mileski WJ, et al. Automated closed-loop resuscitation of multiple hemorrhages: a comparison between fuzzy logic and decision table controllers in a sheep model. *Disaster and military medicine.* 2017;3:1.
3. Wassar T, Luspay T, Upendar KR, Moisi M, Voigt RB, Marques NR, et al. Automatic Control of Arterial Pressure for Hypotensive Patients using Phenylephrine. *International Journal of Modelling and Simulation.* 2014;34(4):187-98.
4. Marques NR, Whitehead WE, Kallu UR, Kinsky MP, Funston JS, Wassar T, et al. Physician-Directed Versus Computerized Closed-Loop Control of Blood Pressure Using Phenylephrine in a Swine Model. *Anesthesia and analgesia.* 2017;125(1):110-6.

In the July 2020-June 2021 performance period, we have made significant progress in developing mathematical models capable of replicating hemodynamic responses to hemorrhage, burn, and vasoplegia injuries as well as fluid resuscitation. We summarize our modeling progress to date here.

3.b. Hemorrhage Mathematical Model Pressure and Heart Rate Modeling

Goal: To derive a systems-level lumped-parameter mathematical model that can replicate hemodynamic responses to hemorrhage and fluid resuscitation.

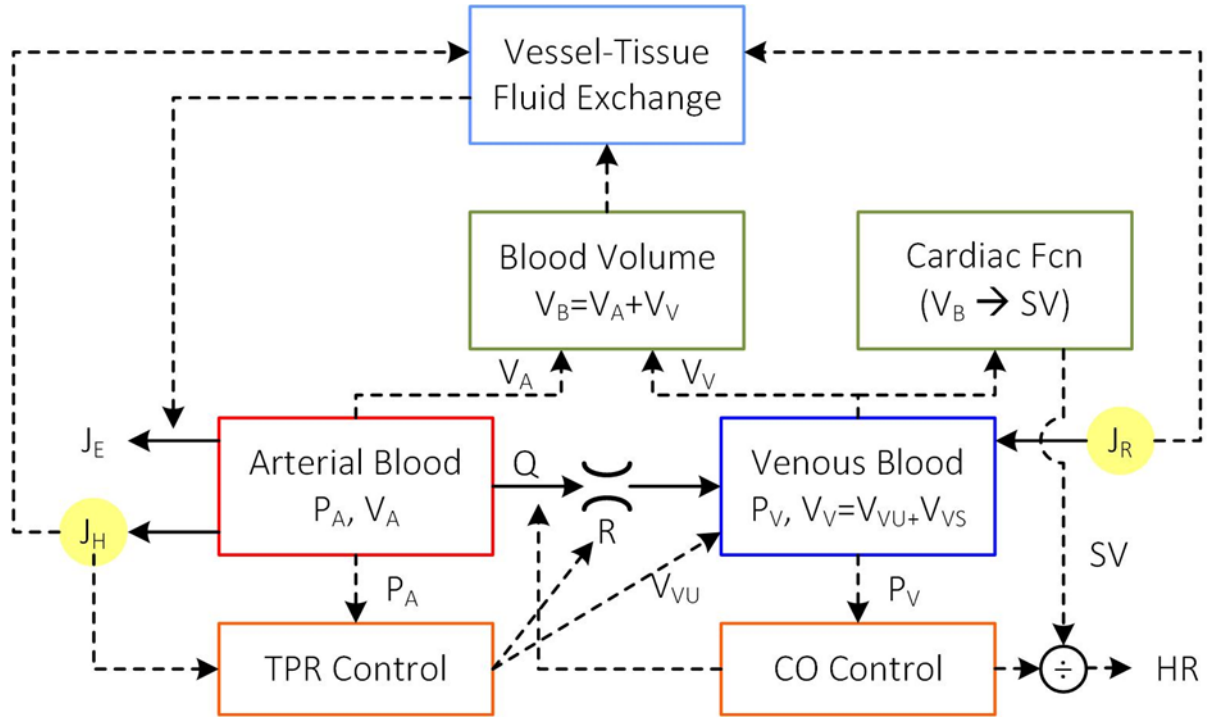


Fig. 1: A mathematical model to replicate volume kinetic and hemodynamic responses to hemorrhage injury and resuscitation. Solid lines and dashed lines represent the flow of physical quantity and information, respectively. It consists of blood volume kinetics in arterial and venous vessels, vessel-tissue fluid exchange, and autonomic nervous control of cardiac output (CO) and total peripheral resistance (TPR). P_A , P_V : arterial and venous blood pressures (BP). V_A , V_V : arterial and venous blood volumes (BV). V_{VU} and V_{VS} : unstressed and stressed venous BV. J_H and J_R are the inputs of the physiological model: the rates of hemorrhage and hemorrhage resuscitation. Q : CO. R : TPR. J_E : the rate of vessel-tissue fluid exchange.

Approach: Expanding our prior collaborative work, we developed a mathematical model to replicate blood volume (BV) kinetic and hemodynamic responses to hemorrhage and fluid resuscitation (Fig. 1). The mathematical model consists of arterial and venous BVs, stroke volume (SV) as a dynamic function proportional to unstressed venous BV (based on the assumption that arterial and unstressed venous volumes represent unstressed BV), autonomic nervous control of cardiac output (CO; based on preload or venous BP) and total peripheral resistance (TPR; based on afterload or arterial BP), and BP as a product of CO and TPR. In addition, it also includes hematocrit (HCT) dynamics due to (presumably) (i) delayed red blood cell (RBC) mixing in trauma and (ii) RBCs furnished from an unknown reservoir in the body. An additional component under ongoing development by FDA is a mathematical model of heart rate control. We examined the ability of the mathematical model to replicate the hemodynamic responses to hemorrhage and fluid resuscitation using the experimental

data collected from the animal study in this project, which involves (i) acute hemorrhage and (ii) slow continuous hemorrhage as well as fluid resuscitation.

Results: We conducted preliminary evaluation of the mathematical model by calibrating it to the experimental acute hemorrhage and resuscitation data collected from the animal study in this project (N=12). Table 1 summarizes the goodness of fit metrics achieved by the mathematical model. Fig. 2 presents a representative example of experimental vs model-replicated HCT, CO, BP, and SV responses.

Table 1: Goodness of fit metrics associated with the mathematical model of hemorrhage and fluid resuscitation.

Model	HCT Error [%]	CO Error [L/min]	BP Error [mmHg]	SV Error [ml]
	0.79±0.29	0.38±0.15	5.03±1.86	3.56±2.39

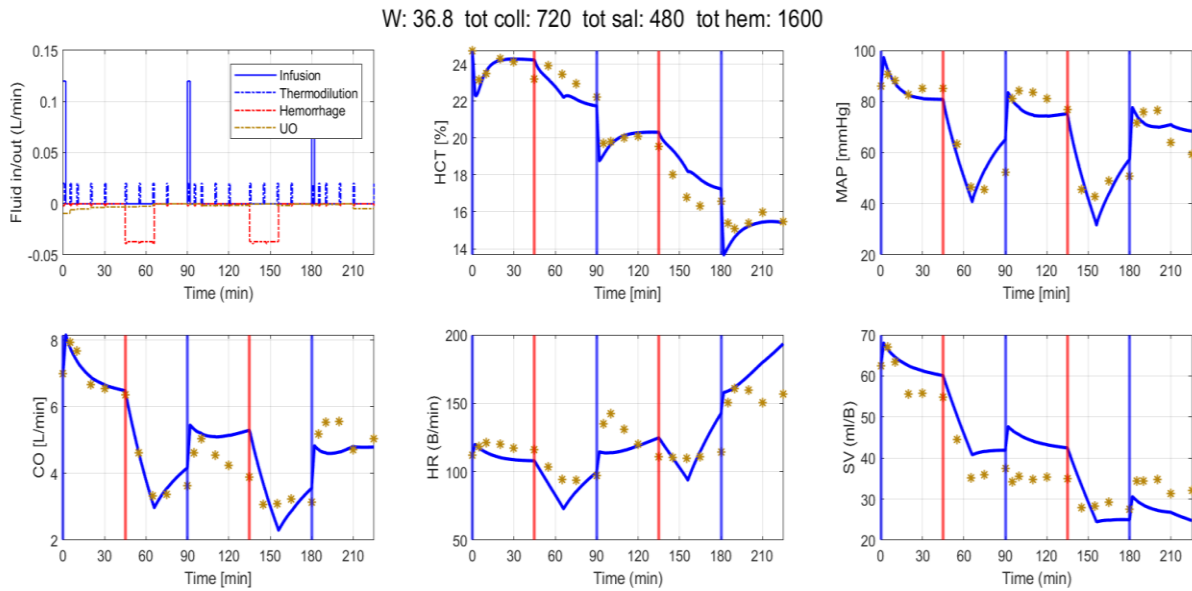


Fig. 2: A representative example of mathematical model's response to hemorrhage and colloid bolus administration. Gold stars: experimental data. Blue line: model prediction.

Our New Mathematical Modeling of Heart Rate Control

We developed and tested a mathematical model of heart rate response to hemorrhage and fluid resuscitation. The mathematical model is built upon the physiological responses observed during our past in-house animal experiments. As reported in prior

studies (e.g., [1]), a significant increase in heart rate is produced shortly after severe hemorrhage starts. The amount of initial increase in heart rate was proportionally associated with the amount of reduction in BV [2,3]. Heart rate was often suggested as an endpoint for directing fluid therapy [2]. Thus, some decline in heart rate due to fluid therapy may be expected.

We developed a mathematical model consisting of two major effects: (i) response to blood loss (HR_V), and (ii) response to fluid administration (HR_U):

$$\dot{HR}(t) = \dot{HR}_V(t) + \dot{HR}_U(t)$$

As for the heart rate response to blood loss, our observation of the experimental data revealed a consistent increase in heart rate over the 180 min experiment period, with a sudden initial rise during the blood loss followed by its alleviation when the bleeding stops:

$$\dot{HR}_V(t) = G_1 \dot{V}(t) + \mathbb{C}(t)$$

$\dot{V} > 0$ is the rate of hemorrhage and $G_1 > 0$ replicates the sudden rise in heart rate during bleeding. In addition, $\mathbb{C}$ represents the modulation of heart rate to replicate a consistent uptrend due to hemorrhage and is modeled by a proportional-integral controller:

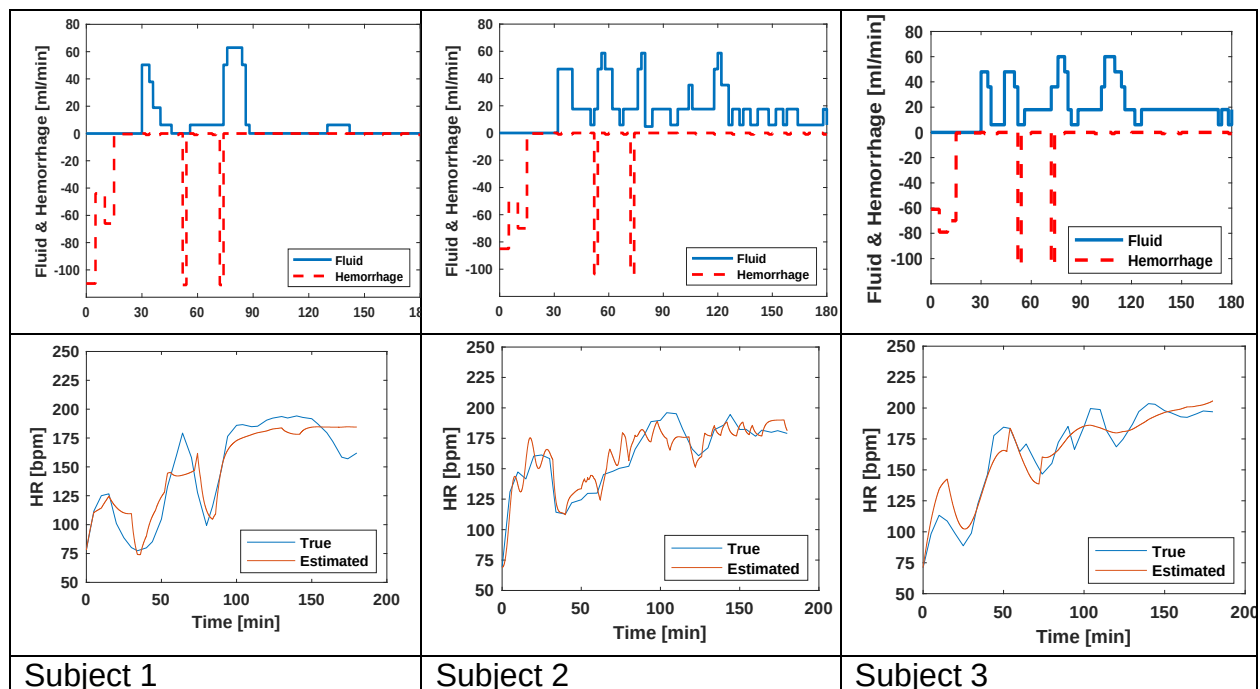
$$\mathbb{C}(t) = -K_P e(t) - K_I \int e(t) dt, \quad e(t) = HR(t) - \int G_2 \dot{V}(t)^{P_1} dt$$

which dictates the mathematical model to replicate the heart rate uptrend over time by reducing the error term $e(t)$. On the other hand, the effect of fluid infusion is modeled by a drop in heart rate during the infusion:

$$\dot{HR}_U(t) = G_3 \dot{U}(t)^{P_2}$$

where $\dot{U} > 0$ is the rate of fluid infusion, and $G_3 < 0$ to replicate the instantaneous drop in heart rate during fluid infusion.

While the mathematical model is preliminary and will be further refined and validated, it could estimate heart rate response to hemorrhage and fluid resuscitation in three subjects, as shown below. The adequate goodness of fit between the measured and model-predicted heart rate responses shows the effectiveness of the mathematical model in capturing the dynamics of heart rate response to hemorrhage and fluid resuscitation.



3.b. References

1. Secher NH, Bie P. Bradycardia during reversible haemorrhagic shock – a forgotten observation? *Clinical Physiology* 1985; 5: 315–323.
2. Secher NH, Van Lieshout JJ. Heart rate during haemorrhage: time for reappraisal. *J Physiol.* 2010;588(Pt 1):19. doi:10.1113/jphysiol.2009.184499
3. Gupta RK, Fahim M. Regulation of cardiovascular functions during acute blood loss. *Indian J Physiol Pharmacol.* 2005 Apr;49(2):213-9. PMID: 16170991.

Conclusion and Plan for Hemorrhage Model: We developed a systems-level lumped-parameter mathematical model of hemorrhage and fluid resuscitation. We showed the ability of the mathematical model to replicate hemodynamic responses to acute hemorrhage and resuscitation using the experimental data collected from the animal study in this project. We are evaluating the ability of the mathematical model to replicate hemodynamic responses to slow and continuous hemorrhage and resuscitation using the experimental data collected from the animal study in this project. In year 03, we plan to optimize the mathematical model based on these evaluations. Then, we will examine the efficacy of the mathematical model in replicating hemorrhage and fluid resuscitation in closed-loop controlled resuscitation setting.

3.c. Burn Mathematical Model

Burn Injury and Fluid Resuscitation Modeling

Goal: To derive a systems-level lumped-parameter mathematical model that can replicate hemodynamic responses to burn injury and fluid resuscitation.

Approach: Expanding our prior collaborative work, we developed a mathematical model to replicate blood volume (BV) kinetic and kidney function responses to burn injury and fluid resuscitation (Fig. 3). In brief, the mathematical model includes 3 main components: blood volume kinetics, kidney function, and pathophysiological perturbations triggered by burn injury.

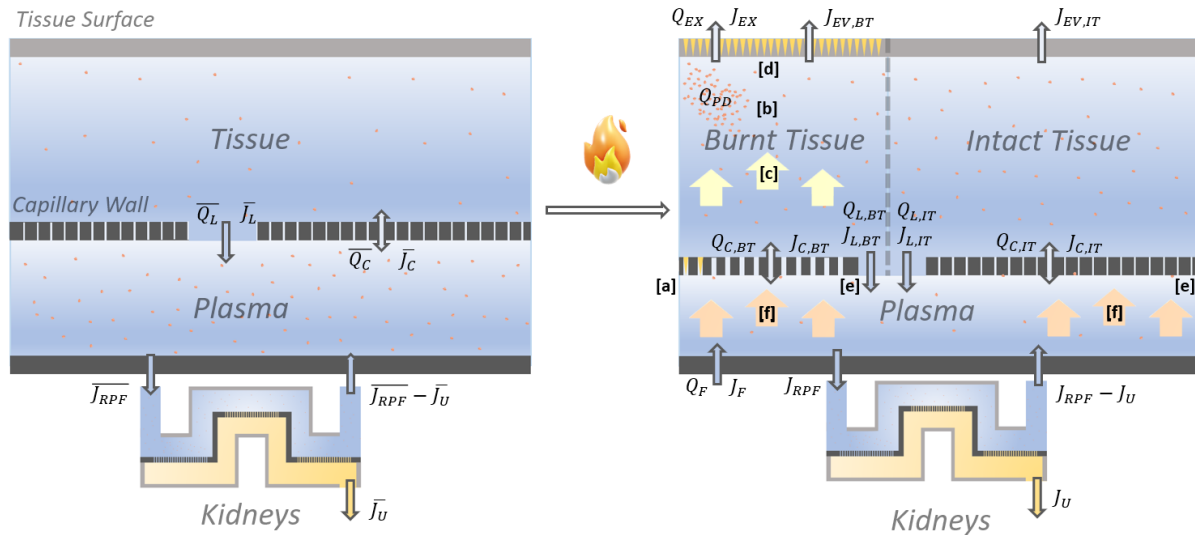


Fig. 3: Mathematical model capable of predicting volume kinetic and kidney function responses to burn injury and resuscitation. Upon the onset of burn injury from normal state (left), water and protein volumes in the intravascular compartment (“Plasma”) decrease, while tissue compartment is divided into intact and burnt tissue compartments associated with protein content higher than normal state (“Burnt Tissues” and “Intact Tissues”) (right). The model consists of (i) volume kinetics to replicate water volume and protein concentration in the intravascular and the tissue compartments, (ii) kidney function to replicate UO response to alterations in intravascular water and protein volumes (“Kidneys”), and (iii) burn-induced perturbations in volume kinetics and renal function as a cascade of biochemical, molecular, and mechanical events (denoted as “[a]” to “[f]”). J: water flow. Q: albumin flow. Subscripts: C (capillary filtration); L (lymph flow); F (fluid infusion); U (UO); RPF (renal plasma flow); EX (exudation); EV (evaporation); PD (protein denaturation); BT (burnt tissues); IT (intact tissues). [a]: Partial destruction of capillaries in burnt tissues.

[b]: Denaturation of protein in burnt tissues. [c] Transient negative hydrostatic pressure in burnt tissues. [d]: Increased dermal fluid loss. [e]: Time-varying changes in capillary filtration and albumin permeability. [f]: Vasodilation. $\bar{X}$ represents X in normal (pre-burn) state.

Using clinical datasets collected from 233 burn patients receiving burn resuscitation, we improved and validated a mathematical model developed in our prior work to enable its in-human application.

Results: Table 2 summarizes normalized mean absolute error (NMAE), correlation coefficient, urinary output (UO) range-based agreement pertaining to < 30 , $30 < < 50$, and > 50 ml/h, or < 0.5 , $0.5 < < 1$, and > 1 ml/kg-hr, and the Bland-Altman statistics (i.e., the limits of agreement), all associated with the optimized mathematical model. Fig. 4 presents examples of actual versus model-predicted UO responses associated with eight patients with various burn injury severity in the test dataset. The mathematical model based on the training dataset exhibited adequate predictive capability for UO response to burn injury and resuscitation in both training and test datasets (Table 2 and Fig. 4). In particular, the mathematical model worked equally well in both training and test datasets, both in terms of average statistics and robustness (e.g., NMAE was 15% with small IQR of 6%; Table 2). Further, it could capture the physiological differences in burn patients across diverse TBSA range, including those associated with comparable weight ((a) versus (e) and (c) versus (g) in Fig. 4) and those associated with distinct weight ((b) versus (f) and (d) versus (h) in Fig. 4). In addition, the mathematical model showed a high degree of UO range-based agreement ($> 90\%$ (when weight-normalized) and $> 78\%$ (when not weight-normalized) of model-predicted UO resided in the same range to actual UO; Table 2). Noting that existing burn resuscitation protocols determine the hourly resuscitation dose based on the range of UO, the results suggest that the mathematical model may serve as a valuable platform for non-clinical testing of burn resuscitation protocols and algorithms. In sum, we illustrated that the mathematical model developed in this project can replicate physiological responses in burn patients associated with wide demographic characteristics and injury severity.

Table 2: Normalized mean absolute error (NMAE: median (IQR)), correlation coefficient (r value), Bland-Altman statistics (bias $\pm 2 \times$ SD), and range-based agreement (median (IQR)) associated with urinary output (UO) prediction by the mathematical model.

	Training Dataset (N=120)	Test Dataset (N=113)
NMAE [%]	14.8 (6.0)	15.4 (6.0)
Correlation Coefficient (r Value)	0.67	0.82
Limits of Agreement [ml/hr]	-3 $\pm$ 57	+2 $\pm$ 45
UO Range-Based Agreement [%] (< 30 , $30 < < 50$, and > 50 ml/h)	78 (15)	83 (14)

UO Range-Based Agreement [%] (<0.5 , $0.5 < 1$, and >1 ml/kg·h)	90 (16)	92 (16)
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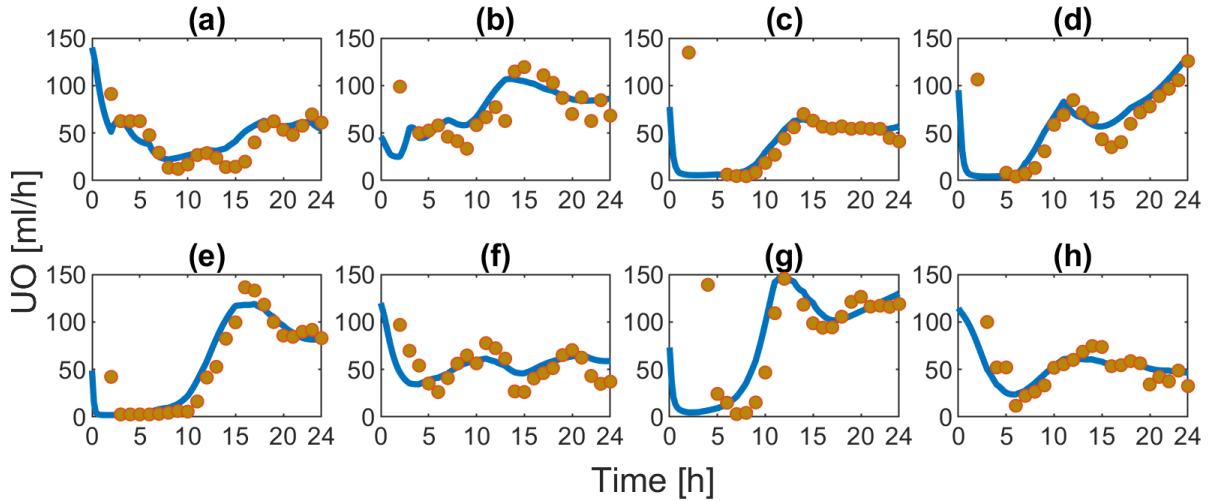


Fig. 4: Actual versus model-predicted urinary output (UO) responses of eight burn patients associated with various injury severity and weight. Circles: actual UO. Solid lines: model-predicted UO. (a) TBSA 27% with 80 kg weight. (b) TBSA 36% with 66 kg weight. (c) TBSA 46% with 90 kg weight. (d) TBSA 60% with 71 kg weight. (e) TBSA 24% with 81 kg weight. (f) TBSA 35% with 94 kg weight. (g) TBSA 50% with 89 kg weight. (h) TBSA 60% with 102 kg weight.

Conclusion and Plan: Our ongoing work on burn injury and resuscitation modeling is to enhance physiological transparency of a subset of component in the mathematical model with extensive validation. Once the enhancement task is completed, we will proceed and apply the enhanced mathematical model for generation of plausible virtual burn patients as well as for virtual assessment of burn resuscitation protocols and algorithms.

3.c. Vasoplegia and Pressor Resuscitation Modeling

Goal: To derive a systems-level lumped-parameter mathematical model that can replicate hemodynamic responses to vasoplegia and vasopressor resuscitation.

Approach: We conceived a mathematical model including blood volume (BV) kinetics and CV hemodynamics in Fig. 5, where P_A and P_V indicate arterial and venous blood

pressures; V_A , V_V , V_{VU} , and V_{VS} represent arterial BV, venous BV, unstressed venous BV, and stressed venous BV; J_{PHP} is the rates of phenylephrine (PHP; vasopressor of choice in this project) infusion; and Q and R are CO and TPR.

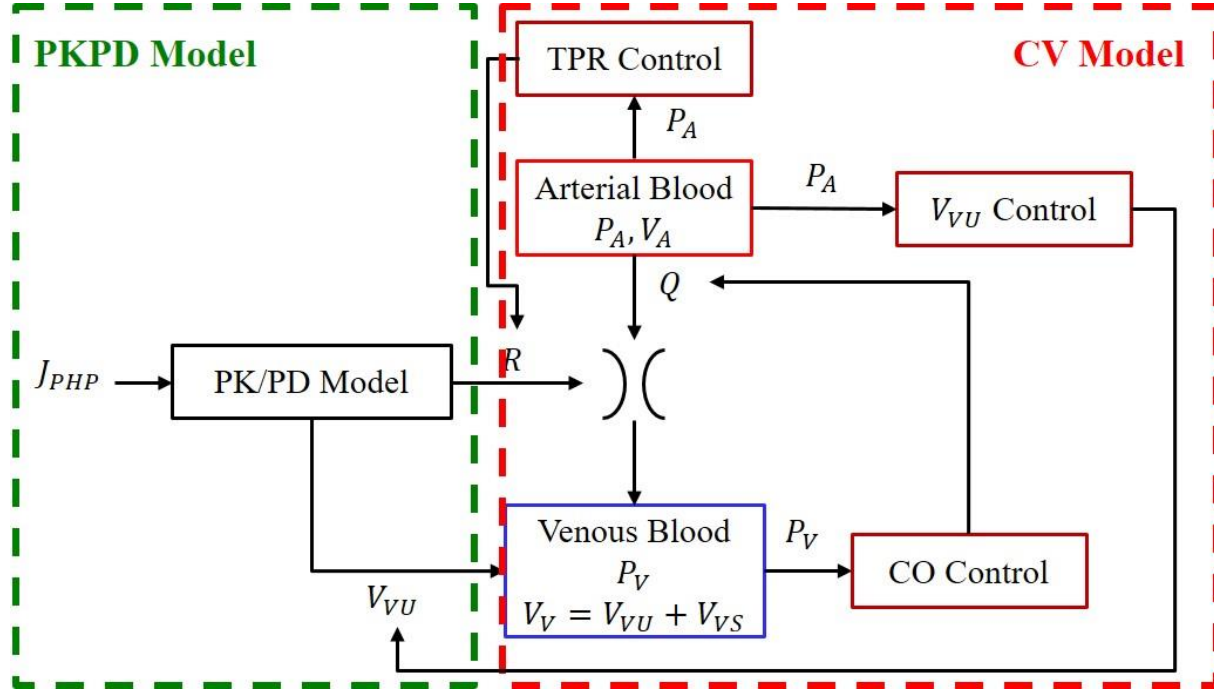


Fig. 5: Cardiovascular and pharmacological effects of Intravenous PHP infusion.

We used experimental data collected from the animal study in this project to evaluate the ability of the mathematical model to replicate CV responses to PHP resuscitation with and without simulated vasoplegia (by infusion of sodium nitroprusside (SNP) (N=10; 11 data segments without simulated vasoplegia and 4 data segments with simulated vasoplegia).

Results: Although we expect to make additional improvements, the mathematical model already shows promising results in replicating CO, TPR, and BP responses to the infusion of PHP both with and without simulated vasoplegia. Table 3 summarizes the goodness of fit metrics (in terms of normalized root-mean-squared error (NRMSE)) achieved by the mathematical model. Fig. 6 presents a representative example of experimental vs model-replicated CO, TPR, and BP responses.

Table 3: Goodness of fit metrics associated with the mathematical model of vasopressor resuscitation.

(a) RMSE

Simulated Vasoplegia	CO Error [L/min]	TPR Error [mmHg/(L/min)]	BP Error [mmHg]
No	0.12±0.09	1.67±0.97	1.90±0.80
Yes	0.10±0.08	1.01±0.57	2.55±1.12
All	0.11±0.08	1.49±0.93	2.07±0.94

(b) NRMSE

Simulated Vasoplegia	CO Error [%]	TPR Error [%]	BP Error [%]
No	4.19±2.54	4.16±2.38	1.72±0.96
Yes	2.97±1.92	3.53±1.52	2.81±1.55
All	3.57±2.31	3.99±2.20	2.01±1.24

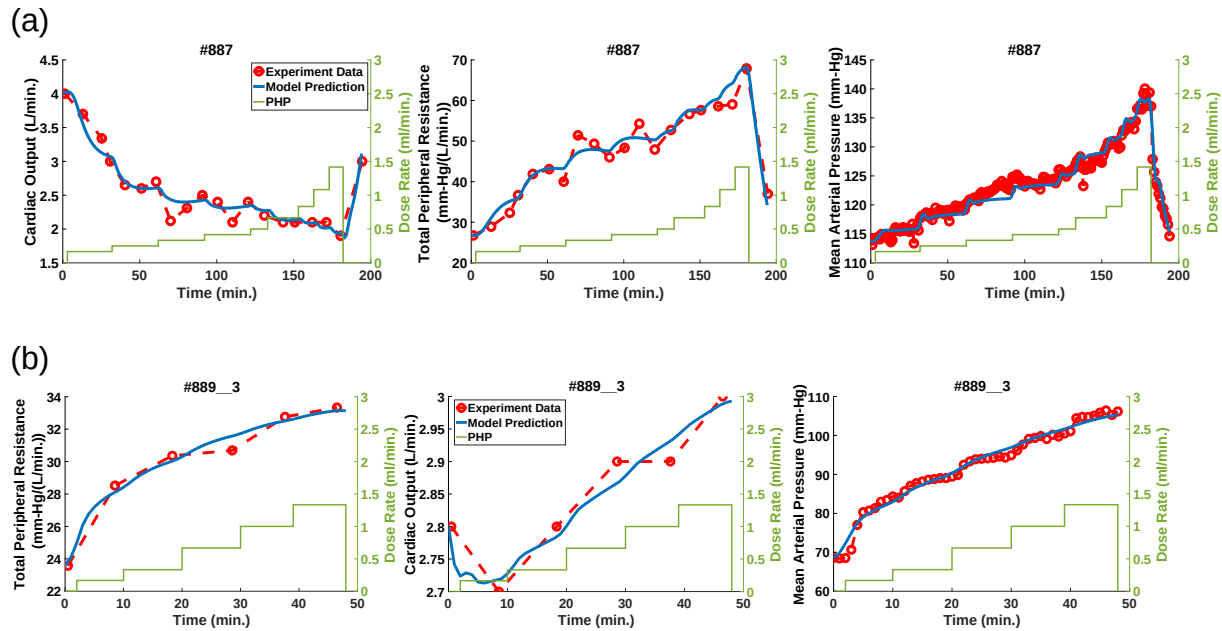


Fig. 6: A representative example of mathematical model's response to PHP infusion (a) with simulated vasoplegia and (b) without simulated vasoplegia. Red dashed lines and circles: experimental data. Blue solid line: model prediction.

Conclusion and Plan: We demonstrated the feasibility of deriving a mathematical model that can replicate hemodynamic responses to vasopressor resuscitation in vasoplegia. We are currently making a few improvements to the mathematical model before freezing it for blind external evaluation. Once we freeze the mathematical model, we will perform blind external evaluation of the mathematical model using fresh data not used during the mathematical model development phase.

3d. Physiological Model-Based Closed-Loop Control Design

Goal: To design and analyze a physiological model-based closed-loop control algorithm to be used in the animal study to collect experimental data for blind, external evaluation of the mathematical model of hemorrhage-fluid resuscitation developed in the project (Fig. 1).

Approach: We designed and analyzed a closed-loop hemorrhage resuscitation control algorithm capable of conducting colloid infusions to regulate a subject's mean arterial pressure (MAP). In this preliminary effort, we intended to develop a closed-loop control algorithm that meets a few practical considerations: (i) it should have a sufficiently simple structure for easy implementation; (ii) it should be able to accommodate multiple speeds of response characteristics and user-specified MAP set point; and (iii) it should exhibit favorable transient and steady-state performance. Details of the control design is given in **Appendix A**, which immediately follows this section.

Results: Our in silico simulation of the closed-loop control algorithm showed promise for its use in the animal study. Fig. 7 shows the results of testing the presented 2-DOF PI colloid resuscitation algorithm on a cohort of virtual subjects. Fig. 7(a) corresponds to a slow control speed setting, while Fig. 7(b) corresponds to a fast control speed setting. It is noted that the desired speed of response can be chosen by a user. The simulation results demonstrate that the control algorithm is capable of regulating MAP in the cohort of virtual subjects, and this regulation is achieved by performing colloid administration at practically feasible infusion rates. Hence, the results suggest that the closed-loop control algorithm may be useful in producing diverse hemodynamic responses in the animal study for extensive blind, external evaluation of the mathematical model of hemorrhage-fluid resuscitation.

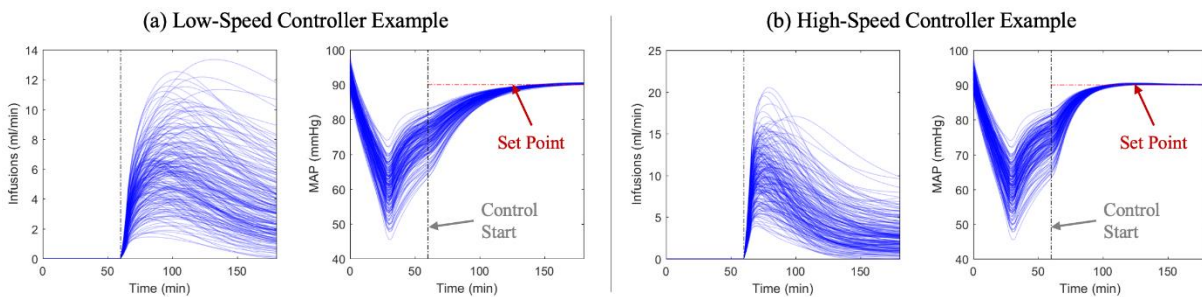


Fig. 7. In-silico testing results for the 2-DOF PI colloid resuscitation control algorithm.

Conclusion and Plan: We developed a simple closed-loop colloid resuscitation algorithm that can be readily used in the animal study to create diverse hemodynamic responses in the animals. We have collaborated with UTMB to embed the control algorithm in a tablet to be used in the animal study. We plan to resume the animal study and perform in vivo data collection from September 2021.

The Closed-Loop Control Algorithm Model and Analysis Details

Control Design and Tuning: We utilize a 2-DOF proportional-integral (PI) architecture, represented by the following equations:

$$G_r(s) = bK_p + \frac{K_I}{s}, \quad G_y(s) = K_p + \frac{K_I}{s} \quad (1)$$

where s is the Laplace operator, and K_p , K_I , and b are the controller parameters. To tune the parameters, we (i) formulated a reduced-order mathematical model of hemorrhage-fluid resuscitation (represented by the plant P in Fig. A1) based on the mathematical model of hemorrhage-fluid resuscitation developed in this project, and (ii) calculated the 2-DOF PI control parameters to achieve a desired speed of response (specified by a user) with minimal overshoot based on the reduced-order mathematical model.

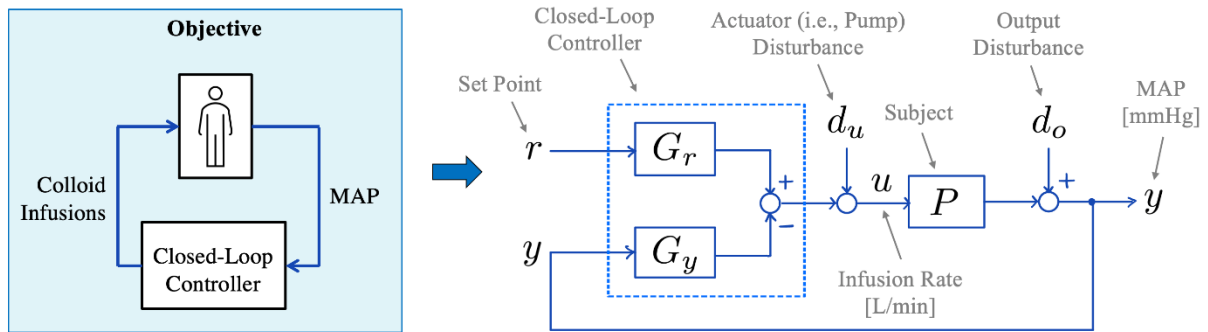


Fig. A1. Schematic view of the 2-DOF PI control loop, to be used for closed-loop colloid resuscitation.

Control Algorithm Analysis: Analysis of the control loop using the reduced-order mathematical model suggested adequate performance in regulating the set point and mitigating both actuator and output disturbances (Fig. A2). In addition, further analysis of the control loop showed that the designed controller is robustly stable with respect to the changes in the relationship between BV and BP.

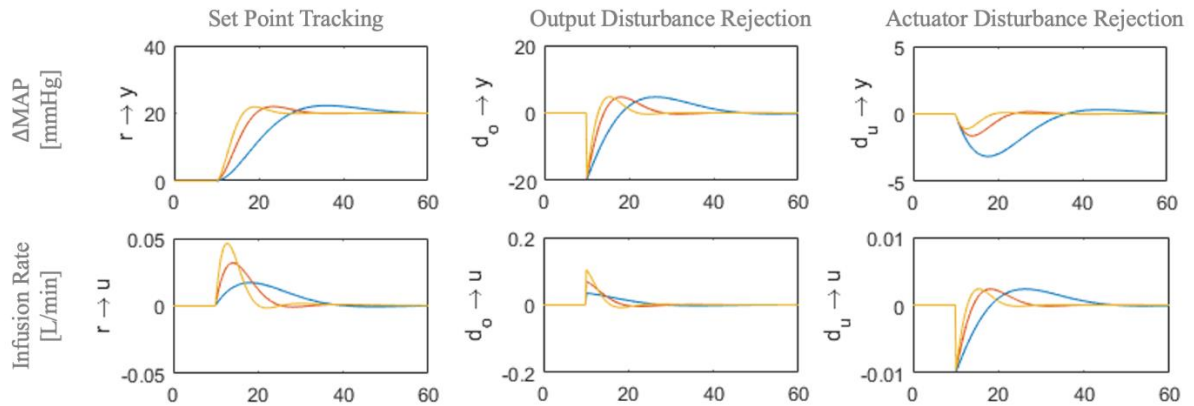


Fig. A2. Control loop analysis for the 2-DOF PI colloid resuscitation control algorithm.

In-Silico Testing: To perform a preliminary assessment of the efficacy of the closed-loop control algorithm, we tested it against a cohort of “virtual subjects”. These virtual

subjects are derived using a novel machine learning-based method developed by us, by (i) considering the mathematical model of hemorrhage-fluid resuscitation developed in this project and (ii) creating a cohort of virtual subjects with large variations in physiological responses by characterizing the mathematical model with realistically randomized model parameters. In the test, each virtual subject is first subjected to a large hemorrhage, and subsequently connected with the control algorithm to receive resuscitation with colloid infusion.

- **Stated goals not met.**

Our final goal of comparing the in silico model testing compared to swine has not yet been done and will be done in NCE Year 03

- **What opportunities for training and professional development has the project provided?**

Nothing to report

- **How were the results disseminated to communities of interest?**

Results of our research has been distributed in three manuscript, four Proceedings papers and two abstracts to the to the Research Community. See publications below.

- **What do you plan to do during the next reporting period to accomplish the goals?**

Plans for year 03

Hemorrhagic Shock and Fluid Resuscitation Model: Using our evaluations of the ability of the hemorrhage mathematical model to replicate hemodynamic responses to slow and continuous hemorrhage and resuscitation based on the experimental data collected from hemorrhage animal studies. In year 03, we plan to optimize the mathematical model based on these evaluations. Then, we will examine the efficacy of the mathematical model in replicating hemorrhage and fluid resuscitation in closed-loop controlled resuscitation setting.

Burn Injury and Fluid Resuscitation Model: Our ongoing work on burn injury and resuscitation modeling is to enhance physiological transparency of a subset of component in the mathematical model with extensive validation. Once the enhancement task is completed, we will proceed and apply the enhanced

mathematical model for generation of plausible virtual burn patients as well as for virtual assessment of burn resuscitation protocols and algorithms.

Refractory Shock and Pressor Treatment Model: We demonstrated the feasibility of deriving a mathematical model that can replicate hemodynamic responses to vasopressor resuscitation in vasoplegia. We will continue to make a few improvements to the mathematical model before freezing it for blind external evaluation. Once we freeze the mathematical model, we will perform blind external evaluation of the mathematical model using fresh data not used during the mathematical model development phase.

Physiological Model-Based Closed-Loop Control Design: We plan to use our newly designed closed loop software (model and algorithm) and system (small transport vital signs monitor, computer hub, and digital controlled IV pump). Quantitative assessments of the developed mathematical model of hemorrhage will be performed with co-experiments of fluid resuscitation of anesthetized hemorrhaged swine and in silico.

Mathematical Models as Regulatory Science Tools: Once mathematical model validation is completed, the performance of the mathematical model will be examined in a closed-loop setting through an in silico closed-loop control of fluid resuscitation under hemorrhage injury and vasopressor infusion under simulated vasoplegia. Results obtained from comparing characteristics of physiological closed-loop control (PCLC) response under the use of the mathematical model versus animal subjects will gauge the effectiveness of our validated mathematical model in PCLC assessment, including the predictive capability of in silico PCLC evaluations to predict experimental results. This may lead to new measures of PCLC performance and refined acceptability criteria for in silico evaluation of PCLC medical systems. The results will provide (i) a mathematical model and simulation methods for in silico evaluation of automated fluid resuscitation and vasopressor infusion systems that may serve as a regulatory science tool supported by robust validation evidence, (ii) a framework that can be followed by other mathematical model developers to generate evidence and establish the credibility of computational simulations for other types of PCLC devices (e.g., ventilators). The project team plans to make the data and mathematical model publicly available to help biomedical companies and researchers use the mathematical model/data for assessment of their medical devices and algorithms with similar intended use, or development and validation of their own mathematical models.

4. IMPACT

- **What was the impact on the development of the principal discipline(s) of the project?**

The mathematical models that we are developing may provide the medical community, industry, and the FDA the means to better assess the safety and efficacy of autonomous care systems. While these models contribute to the general physiological modelling literature, they are designed to provide specific tools for those developing closed loop resuscitation systems.

- **What was the impact on other disciplines?**

Nothing to report

- **What was the impact on technology transfer?**

Nothing to report

- **What was the impact on society beyond science and**

technology? Nothing to report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

There are no changes to our overall plan and objectives. However, having a Year 03 no cost extension will allow us to define our model better and do spend more time on the in silico and swine experiments comparison of hemorrhage and treatment. The need for a no cost extended year was based on delays in hiring, lost animal experiments due to the Covid Pandemic and early administrative delays receiving DOD approval of animal protocols,

- **Actual or anticipated problems or delays and actions or plans to resolve them**

We had delays in Year 01, due to ACURO approval delays, Covid lab shut down and delays in hiring. We caught up some in Year 02, but the Year 03 no cost extension will allow us to finish major objectives.

- **on expenditures.**

Because of the delays in hiring some personnel, a delay due to ACURA approval, and work stoppage due to Covid Pandemic our expenditures are behind, but will be used to support Year 03 efforts.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

None

- **Significant changes in use or care of human subjects**

Not applicable

- **Significant changes in use or care of vertebrate animals**

None

- **Significant changes in use of biohazards and/or select**

agents None used, nothing to report.

6. PRODUCTS:

Publications, conference papers, and presentations

For 2020 – 2021 We report three manuscripts, four Proceedings papers and two abstracts.

Manuscripts

1. R. Bighamian, J.O. Hahn, G.C. Kramer, C.G. Scully, "Accuracy Assessment Methods for Physiological Model Selection toward In Silico Evaluation of Closed-Loop Controlled Medical Devices," *PLOS One*, Vol. 16, No. 4, Article e0251001.
2. G. ArabiDarrehDor, A. Tivay, R. Bighamian, C. Meador, G.C. Kramer, J.O. Hahn, J. Salinas, "Mathematical Model of Volume Kinetics and Renal Function after Burn Injury and Resuscitation," *Burns*, Vol. 47, No. 2, pp. 371-386, March 2021.
3. G. ArabiDarrehDor, A. Tivay, C. Meador, G.C. Kramer, J.O. Hahn, J. Salinas, "Mathematical Modeling, In-Human Evaluation, and Analysis of Volume Kinetics and Kidney Function after Burn Injury and Resuscitation," *IEEE Transactions on Biomedical Engineering*, In Press 2021.

Proceeding Papers

4. A. Tivay, G.C. Kramer, J.O. Hahn, "Virtual Patient Generation using Physiological Models through a Compressed Latent Parameterization," *American Control Conference*, Virtual Meeting, pp. 1335-1340, July 1-3, 2020.
5. R. Bighamian, J.O. Hahn, G.C. Kramer, C.G. Scully, "Physiological Model Selection for in Silico Evaluation of Closed-Loop Controlled Medical Devices," *IEEE Engineering in Medicine and Biology Conference (Research Poster Paper)*, Virtual Meeting, October 31-November 4, 2021.
6. A. Tivay, G.C. Kramer, J.O. Hahn, "Inference-Based Subject Atypicality and Signal Quality Indicators for Physiological Data," *Medical Cyber-Physical Systems and Internet of Medical Things Workshop*, CPS Week, Virtual Meeting, May 18, 2021.
7. A. Tivay, J.O. Hahn, "Obtaining Robust Personalized and Generative Physiological Models through Collective Inference," *IEEE International Conference on Biomedical and Health Informatics*, Virtual Meeting, July 27-30, 2021.

Abstracts

8. G.A. DarrehDor, A. Tivay, C. Meador, G.C. Kramer, J.O. Hahn, J. Salinas, "A Human-Based Mathematical Model for in-Silico Evaluation of Burn Injury Resuscitation Algorithms: Validation and Analysis," *Military Health System Research Symposium*, Kissimmee, FL, August 23-26, 2021 (accepted, but cancelled, o be published online).
9. G.A. DarrehDor, A. Tivay, R. Bighamian, C. Meador, G.C. Kramer, J.O. Hahn, J. Salinas, "Development and Evaluation of a Mathematical Model of Volume Kinetics and Renal Function after Burn Injury and Resuscitation," *Military Health System Research Symposium*, Kissimmee, FL, August 17-20, 2020 (Cancelled, published online).
10. R. Bighamian, J.O. Hahn, G.C. Kramer, C.G. Scully, "Physiological Model Selection for In Silico Evaluation of Closed-Loop Medical Devices," *FDA Science Forum*, Virtual Meeting, May 26-27, 2021.

Website(s) or other Internet site(s)

None

Technologies

Nothing to Report

Inventions, patent applications, and/or licenses

Nothing to Report

Other Products

Four mathematical models produced: one for burn shock and fluid resuscitation, one for hemorrhagic hypovolemia and fluid therapy, one for phenylephrine treatment of experimentally vasoplegia and finally a model for a closed loop resuscitation system with closed loop treatment algorithms for hemorrhage.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

We have added one postdoctoral fellow to project, Dr. Catherine Sampson, see below.

Investigators Name: George Kramer, PhD
Project Role: PI, UTMB
12 months, from project start

Name: Jin-Oh Hahn, PhD
Project Role: Co-I, University of Maryland
12 months, from project start

Name: Michael Kinsky, MD
Project Role: Co-I, UTMB
No Change; 12 months, from project start

Name: Christopher Scully, PhD
Project Role: Co-I, Food & Drug Administration
Researcher ID 0001-8244-0832
12 months, from project start

Name: Ramin Bighamian
Project Role: Co-I, Food & Drug
12 months from project start

Contribution to Project: Blood volume model enhancement to be used for physiologic closed-loop control evaluation. Regulatory perspectives and performed working on planning the data collection methods and analyses for model evaluation. No change in months worked.

Name: Ali Tivay
Project Role: PhD Student, University of Maryland
Researcher ID 0002-2003-1109
Months worked on project: 12 months 2020-21

Contribution to Project: Parameter estimation and enhanced modeling of cardiovascular responses to hemorrhage and fluid resuscitation. No change in months worked.

Name: Ghazal Arabidarrehdor
Project Role: PhD Student, Univ. of Maryland
Months worked on project: 12 months 2020-21

Role on Project: Burn and blood volume model enhancement to be used for physiologic closed-loop control evaluation.

Name: Randy Salisbury
Project Role: Research Associate II, UTMB
Months worked on project: 10 months from year 2021

Contribution to Project: Animal surgery and experiments. Worked two less months this year.

Name: Catherine Sampson, PhD
Project Role Postdoctoral fellow
Project Role: Animal surgery, runs experiments, data collection and analysis
Months worked on project: 6 months year 20-2021

Name: Ali Shah Syed, MD
Project Role Research Scientist
Project Role: Animal surgery, runs experiments, data collection and analysis
Months worked on project: 12 months year 2020-2021

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

No change in support

Same key investigators as above and their Organizations at project start.
University of Maryland – Mathematical Modeling engineers
FDA – Regulatory and Clinical Perspective of Modeling
UTMB – Animal studies

8. SPECIAL REPORTING REQUIREMENTS

None

9. APPENDICES

Publications attached

Peer reviewed Manuscript.

R. Bighamian, J.O. Hahn, G.C. Kramer, C.G. Scully, "Accuracy Assessment Methods for Physiological Model Selection toward In Silico Evaluation of Closed-Loop Controlled Medical Devices," *PLOS One*, Vol. 16, No. 4, Article e0251001.

Mathematical Modeling of Hemodynamics in Trauma-Induced Shock for Closed-Loop Fluid and Drug Resuscitation

and Task Title: FORWARD - Autonomous and Unmanned Medical Capability

PI: GC Kramer

Org: UTMB, Univ. Maryland, FDA

Award Amount: \$1,294,591



Specific Aims:

- 1) Development of Mathematical Models of Trauma-Induced Shock and Resuscitation
- 2) Quantitative Evaluation of Mathematical Models of Trauma-Induced Shock and Resuscitation
- 3) Establish Utility of the Mathematical Models by Comparing In Silico and Animal Testing of Closed Loop Resuscitation Algorithms

Approach: Advance closed-loop algorithms for fluid and drug resuscitation for trauma care by developing, validating, and utilizing mathematical models. We perform closed loop treatments experiments in swine and compare to closed loop in silico experiments. Synergism and deleterious interplay of two closed-loop therapies, fluids and pressors will be examined.

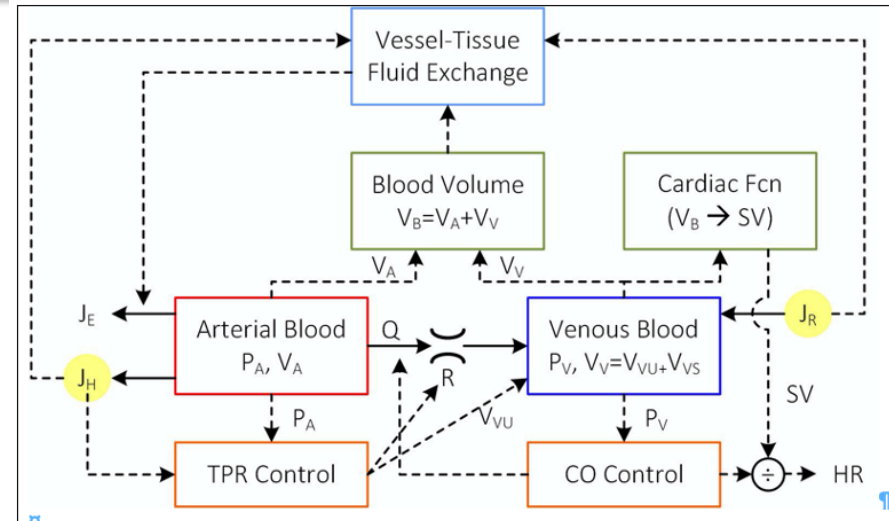


Fig. 1: A mathematical model to replicate volume kinetic and hemodynamic responses to hemorrhage injury and resuscitation.

Timeline and Cost

	Aims and Goals	Year 01	Year 02
Aim 1:	Swine Studies Data Generation, n= 32		
Aim 1:	Model Development		
Aim 2:	Swine Studies Data Generation, n= 32		
Aim 2:	Model Evaluation		
Aim 3:	In Silico, Closed Loop (CL) vs. Animal CL data		
Remaining work to be done in NCE Year 03.		Estimated Budget:	
		\$645,635	\$648,956

Goals/Milestones

Year 01 Goal – Perform animal studies of dose response (fluids & pressors) generating data for model development. Develop mathematical models for shock and treatment with fluids and drugs.

Year 02 Goals – Perform animal studies and complete all models with validation analyses. Develop closed loop model and treatment algorithm for fluid therapy of hemorrhage.

Year 03 Goals Use in silico testing and animal studies with identical protocols of injury for model and algorithm validation and evaluation of safety and efficacy.

Budget Expenditure to Date 7/1/21 per ledger \$798,510.06

Updated: July 2021

G. ArabiDarrehDor, A. Tivay, R. Bighamian, C. Meador, G.C. Kramer, J.O. Hahn, J. Salinas, "Mathematical Model of Volume Kinetics and Renal Function after Burn Injury and Resuscitation," *Burns*, Vol. 47, No. 2, pp. 371-386, March 2021.

Accuracy assessment methods for physiological model selection toward evaluation of closed-loop controlled medical devices

Ramin Bighamian , Jin-Oh Hahn, George Kramer, Christopher Scully

Published: April 30, 2021 • <https://doi.org/10.1371/journal.pone.0251001>

Abstract

Physiological closed-loop controlled (PCLC) medical devices are complex systems integrating one or more medical devices with a patient's physiology through closed-loop control algorithms; introducing many failure modes and parameters that impact performance. These control algorithms should be tested through safety and efficacy trials to compare their performance to the standard of care and determine whether there is sufficient evidence of safety for their use in real care setting. With this aim, credible mathematical models have been constructed and used throughout the development and evaluation phases of a PCLC medical device to support the engineering design and improve safety aspects. Uncertainties about the fidelity of these models and ambiguities about the choice of measures for modeling performance need to be addressed before a reliable PCLC evaluation can be achieved. This research develops tools for evaluating the accuracy of physiological models and establishes fundamental measures for predictive capability assessment across different physiological models. As a case study, we built a refined physiological model of blood volume (BV) response by expanding an original model we developed in our prior work. Using experimental data collected from 16 sheep undergoing hemorrhage and fluid resuscitation, first, we compared the calibration performance of the two candidate physiological models, i.e., original and refined, using root-mean-squared error (RMSE), Akaike information criterion (AIC), and a new multi-dimensional approach utilizing normalized features extracted from the fitting error. Compared to the original model, the refined model demonstrated a significant improvement in calibration performance in terms of RMSE (9%, $P = 0.03$) and multi-dimensional measure (48%, $P = 0.02$), while a comparable AIC between the two models verified that the enhanced calibration performance in the refined model is not due to data over-fitting. Second, we compared the physiological predictive capability of the two models under three different scenarios: prediction of subject-specific steady-state BV response, subject-specific transient BV response to hemorrhage perturbation, and leave-one-out inter-subject BV response. Results indicated enhanced accuracy and predictive capability for the refined physiological model with significantly larger proportion of measurements that were within the prediction envelope in the transient and leave-one-out prediction scenarios ($P < 0.02$). All together, this study helps to identify and merge new methods for credibility assessment and physiological model selection, leading to a more efficient process for PCLC medical device evaluation.

Citation: Bighamian R, Hahn J-O, Kramer G, Scully C (2021) Accuracy assessment methods for physiological model selection toward evaluation of closed-loop controlled medical devices. PLoS ONE 16(4): e0251001. <https://doi.org/10.1371/journal.pone.0251001>

Editor: Chi-Hua Chen, Fuzhou University, CHINA

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Data Availability: All relevant data are within the manuscript and its [Supporting information](#) files.

Funding: This work was supported in part by the U.S. Army (Grant No. W81XWH-19-1-0322) [JH & GK] and the U.S. Office of Naval Research (ONR) (Grant No. N00014-19-1-2402) [JH]. Sponsors did not play any role in the study design.

Competing interests: The authors have declared that no competing interests exist.

Introduction

Physiological closed-loop controlled (PCLC) medical devices pertain to a rapidly advancing technology that work based on feedback from physiological sensors to make their own decisions for patient treatment without human input. These devices and their algorithms have been studied across a range of different applications [1–7]. During the 2015 public workshop on PCLC challenges and opportunities held by the U.S. Food and Drug Administration (FDA), it was emphasized that compared to the standard of care, a well-designed PCLC medical device can benefit patients, physicians, and more broadly the quality of healthcare by ensuring the delivery of effective therapy with reduced side effects and length of hospital stay and lowering the level of workload in hospitals [8, 9]. These potential benefits have inspired researchers to introduce automation in the biomedical instruments ever since, to which the Transparency Market Research has predicted a compound annual growth rate of 8.8% for the global healthcare automation market over the forecast period of 2017–2025 [10].

The autonomous nature of PCLC medical devices, however, has made researchers approach with a certain degree of caution. The decision for dose adjustment and treatment delivery made by the technology instead of human clinicians introduces new sources of hazard and safety issues for patients, such as algorithm robustness, stability, and hardware-software integrability [9, 11, 12]. Furthermore, the automation brings complexity to the design and use of the biomedical devices as compared to their use in manual care [8, 9]. Due to these challenges, development of tools and verification methods for the safety properties of PCLC medical devices is essential before they can be used in practice.

To take advantage of the technology's promise against the given potential drawbacks inherent in the use of a PCLC medical device, appropriate hardware and software design as well as evaluation techniques must be ensured to demonstrate the performance and maximize safety precautions required before the device becomes available to patients. This can be obtained by a combination of data from nonclinical laboratory, animal, and clinical testing [13, 14]. Laboratory studies involve controlled environments that are different from those of standard care, while animal studies and clinical trials are expensive in time, effort and costs and have to comply with ethical requirements; thus, are often limited and prohibitive. For a specific intended use, running a small number of clinical studies does not guarantee that a device is safe everywhere, particularly for automated PCLC medical devices that may have performance affected by various patient responses and disturbance conditions that may not occur during a clinical study [15]. Due to these challenges, computational modeling has been proposed as an alternative approach to answer the critical questions related to the safety and effectiveness of a device [14]. Well-designed mathematical models can generate physiological variables corresponding to virtual patients and satisfy the need for creating inter- and intra-subject variability. They can be used to simulate wide spectrum of patient physiology and possibly their interaction with sensors and actuators, including those associated with the worst-case conditions that are less likely to happen in a limited number of clinical trials.

Uncertainties about the quality and fidelity of mathematical models and ambiguities about choice of measures for modeling performance need to be addressed before PCLC medical devices can be reliably evaluated. This can be done through validation processes to quantitatively establish the extent to which a mathematical model is an adequate representation of the real world [16]. Validation process in the field of medical device is an open-ended task and includes response assessment of mathematical models with respect to the real physiology. These models are often complex, with diverse structure and strong coupling between physiological compartments and mechanisms. Due to these complexities, conceptual questions immediately arise regarding proper ways to assess the adequacy of such mathematical models. In particular, the accuracy of the models may not be evaluated in a substantive way, except when inputs, boundary conditions, and model predictions are in very close vicinity of conditions in the calibration database [17]. Prior studies have mostly quantified the accuracy by comparing experimental data and responses computed by a mathematical model calibrated (fitted) to those data, assuming that the validation domain and its intended use fall within the experimental inputs and conditions used for model calibration (e.g., [18–20]). For a model to be used for PCLC medical device assessment, however, inputs and boundary conditions could be outside of the ones in calibration data. Thus, a mathematical model should be tested in terms of its predictive capability against physiological states and conditions for which it has not been calibrated, via numerical interpolation or extrapolation of the model to specific conditions defined by its intended use [21].

While mathematical models have been proposed in different physiological domains, there is no consensus about criteria for proper model selection toward evaluating PCLC medical devices. In particular, no guidance is available on proper number of parameters, goodness of fit, or predictive capability of a mathematical model for an effective PCLC medical device assessment. Furthermore, the mathematical model must not be judged based on the PCLC testing results since the PCLC medical device performance does not indicate the extent to which the mathematical model adequately represents physiological measurements—thus, assessment of a computational model should be performed in advance and independently from the PCLC medical device evaluation. Instead, a comparison can be made between different physiological models to choose the one with the best calibration performance while not overfitting the data due to a large number of parameters, and the best predictive capability during different treatment scenarios. Hence, it is essential to establish methods to assess both calibration performances and predictive capability across multiple candidate physiological models for PCLC medical device assessment.

To address the above mentioned challenge, this research develops tools for properly assessing accuracy of physiological models and establishes fundamental measures for evaluating predictive capability across different mathematical models. This research only engages in comparing the physiology-based first principles models—which as opposed to their black-box counterparts, are limited in their variety due to the use of physiological principles. Therefore, as a case study, we examine the adequacy of lumped-parameter mathematical models of patient physiology developed for evaluating PCLC fluid resuscitation devices. We build a refined physiological model of blood volume (BV) response by expanding an original model we developed in our prior research [19, 20]. We use the experimental data collected from sheep subjects undergoing hemorrhage and fluid resuscitation. First, we compare the calibration performance of two candidate physiological models, i.e., original and refined, using root-mean-squared error (RMSE), Akaike information criterion (AIC), and a new multi-dimensional approach that utilizes normalized features extracted from fitting error. Then, the accuracy and predictive capability of the two mathematical models are compared under three different scenarios, i.e., their use in 1) subject-specific prediction of steady-state response, 2) subject-specific interpolation of transient response to hemorrhage, and 3) prediction of the entire (transient and steady-state) response through a leave-one-out procedure. While this research proposes tools and methods for selecting the best between multiple candidate physiological models, it does not intend to provide recommendations on whether or not further refinement is needed for a mathematical model before it can be used for the PCLC medical device evaluation.

The remainder of this paper is organized as follows: section Materials and Methods presents two mathematical models of BV response to hemorrhage and fluid resuscitation that are compared in this research, describes the animal data used, and elaborates on the tools employed for model accuracy and predictive capability assessment. The comparison between the two candidates mathematical models is then made under three different scenarios, which is presented and discussed in Results and Discussion sections.

Materials and methods

In this section, we first present the two candidate physiological models and elaborate how the original model is expanded to develop the refined model. After describing the experimental data, we present the parameter identifiability analysis for each model, parameter estimation procedures, and the methods employed for model calibration assessment and evaluation of the model accuracy and predictive capability between the two candidate models.

Candidate physiological models of blood volume response

In this section, we briefly present the original model of BV response. Next, we show how this model is expanded to develop the refined model of BV response.

Model 1: The original BV model.

The details on this model can be found in our previous research [19, 20]. This mathematical model is built based on the physiological principle related to body fluid balance, indicating a gain (fluid infusion) or loss (hemorrhage and urinary output) perturbation in BV is distributed between the intravascular and interstitial fluid compartments to regulate the ratio between their volume changes [22] (see Fig 1). This distribution mechanism is modeled through a feedback controller that adjusts the rate of fluid shift between the two compartments to achieve a desired steady-state BV response (see Fig 1A and 1B). Since the inter-compartmental fluid shift behaves differently under the gain or loss situation due to the different compositions of the involved fluids, the model assumes distinct distribution ratios for infusion versus loss rate (see Fig 1C, left picture) [20]. For a given rate of infusion U and loss V at each time t , the desired steady-state change in BV, r_{BV} , is defined as:

(1)

where a_U and a_V denote the fluid distribution ratio between intravascular and interstitial compartments under gain and loss situations. This equation formulates the physiological principle associated with steady-state change in BV response. In the steady-state, the intravascular compartment gains $1/(1 + a_U)$ or loses $1/(1 + a_V)$ fraction of the total infusion or loss, respectively. In other words, in the steady-state, the remaining $a_U/(1 + a_U)$ or $a_V/(1 + a_V)$ fraction transfers to or is removed from the interstitial compartment.



Fig 1. Lumped parameter model of blood volume (BV) response to fluid infusion and hemorrhage.

(A): The model includes intravascular and interstitial (extravascular) fluid compartments with a bi-directional inter-compartmental fluid shift. The sign of e_{BV} , which is the discrepancy between the change in BV (ΔBV) and desired steady-state change in BV (r_{BV}), determines the direction of shift. As shown in the figure, a negative e_{BV} sets a shift of fluid toward interstitial compartment. (B): Fluid shift is modeled through a control-theoretic approach (see part A) and computed through the proportional-integral response to e_{BV} ; a larger e_{BV} leads to a larger amount of shift to achieve desired response. (C): r_{BV} is shown for the original and refined model. This is the main difference between the two models, in which r_{BV} in the refined model is affected by both the rate of infusion and loss and the current desired state of BV response for infusion and loss (right picture), while r_{BV} in the original model is only determined based on the rate of infusion and loss (left picture).

<https://doi.org/10.1371/journal.pone.0251001.g001>

The feedback controller replicating inter-compartmental shift attempts to minimize the difference between change in BV response (ΔBV) and r_{BV} , denoted by e_{BV} ($e_{BV} = r_{BV} - \Delta BV$; see Fig 1A). The shift is computed by a proportional-integral (PI) response to e_{BV} at each time, driving the BV response to its desired state (see Fig 1B):

(2)

where K_p and K_i denote the controller's proportional and integral gains. The direction of shift is determined by the sign of error, e.g., a negative e_{BV} sets a shift of fluid toward interstitial compartment (see Fig 1A).

By seeking the conservation of volume for the intravascular compartment, the rate of change in BV response can be obtained as follows:

(3)

Combining Eqs 1 to 3 leads us to the following equation for governing the BV response subject to fluid gain and loss:

(4)

Model 2: The refined BV model.

The fluid distribution ratios a_U and a_V in the original model are assumed to be constant over the entire range of BV no matter how much the intravascular volume has expanded or compressed during fluid perturbation. Based on the physiological principles, however, the distribution ratio parameters can vary over time depending on the state of intravascular volume expansion or compression [22]. For example, looking toward the steady-state response to a same amount of fluid infusion, intravascular

compartment can gain a larger fraction of fluid (smaller α_u) when the BV is at a lower range. However, when the BV is at a higher range, the shift of fluid toward interstitial volume becomes more pronounced (larger α_u) which avoids intravascular fluid overload. This motivate us to enhance the original model with a refined r_{BV} that is dynamically corrected over time as the state of BV response updates, even when no infusion or hemorrhage input is present (see the right picture in Fig 1C):

(5)

(6)

(7)

where $r_{BV,u}$ and A_u denote the desired steady-state change in BV and state parameter due to infusion, while $r_{BV,v}$ and A_v indicate the same parameters for the fluid loss. Using the revised model of r_{BV} , the refined model is obtained as below:

(8)

where $r_{BV,u}(t)$ and $r_{BV,v}(t)$ are shown in Eqs 6 and 7.

Experimental data

Details about experimental data can be found in our prior study [23]. In short, the BV data were collected from 11 conscious sheep undergoing hemorrhage and fluid infusion. All the animals received Lactated Ringer's solution (LR), a commonly used crystalloid fluid. In a separate study, 5 of the animals received Hextend (Hex), made from natural sources of starch. These 5 animals received LR and Hex in a randomized order, each 5 days apart from the last experiment.

Each study lasted for 180 min. After a baseline measurement, each study was started with a 25 ml/kg hemorrhage, lasted for 15 min. 15 min after the end of hemorrhage, fluid infusion was started and continued for 150 min, until the experiment ended. Rate of fluid administration was determined by a closed-loop controller described in a prior work [23]. Two additional 5 ml/kg hemorrhage was also applied 35 and 55 min after the end of first hemorrhage, each lasted for 5 min.

Baseline BV, $BV(0)$, was measured in each animal using indocyanine green dye (ICG) [24]. Hematocrit (Hct), the ratio between the red blood cell (RBC) volume and BV, was measured every 5 or 10 min throughout the experiment and used to compute the change in BV at each measurement point t_k :

(9)

(10)

(11)

where PV , H , and V_H are plasma volume, Hct, and amount of blood withdrawn for hemorrhage, respectively.

Model parameter estimation

The approach we take to learn the model parameters is the maximum-likelihood estimation (MLE), which finds the parameter values maximizing the likelihood of measured BV response to hemorrhage and fluid infusion. The original mathematical model includes 4 parameters to tune, i.e., $\{\alpha_u, \alpha_v, K_p, K_i\}$, while the refined model has two additional parameters, $\{A_u, A_v\}$. We first assess the identifiability of each model. Next, we define an optimization problem to determine the model parameters with the best fitting performance.

Structural identifiability analysis.

Original model. In this section, we convert the original model to the frequency domain for simple assessment of the model identifiability. By taking the Laplace transform of Eq 4, the following equation is obtained:

(12)

where s is the complex frequency variable with a unit of sec^{-1} [25]. Based on estimation theory [26], with a perturbation input that is rich in the frequency content and as a result by virtue of an informative data set Φ [27], the vector Θ becomes fully identifiable with a unique set of parameters. Simply put, K_p can be determined from the 1st element, K_i from the 2nd, α_u from the 4th and α_v from the 5th element of Θ . Although the model identifiability is obvious from Eq 12, the model parameters should be obtained through an optimization problem for the best calibration results.

Refined model. We take the Laplace transform of the refined model. First, using Eqs 5–7, the following frequency domain equation is obtained for $r_{BV,u}$ and $r_{BV,v}$:

(13)

(14)

By taking the Laplace transform of [Eq 8](#) and using [Eqs 13](#) and [14](#), the following equation is obtained in the frequency domain.

(15)

Similarly, when subject to a fluid perturbation input with rich frequency content and thus, an informative data set Φ , the vector Θ is fully identifiable [\[27\]](#). For instance, K_p , K_i , A_u , and A_v can be determined by simultaneously solving 1st to 4th elements, a_u from either 6th, 8th, or 10th, and a_v from either 7th, 9th, or 11th element. Again, for a better calibration performance, an optimization problem involving all the elements needs to be solved.

Practical identifiability analysis.

A variance-based global sensitivity analysis [\[28\]](#) was performed to identify the behavior of model parameters subject to the range of estimated parameters and individual profiles of hemorrhage and fluid infusion. Unlike local sensitivity analysis methods, this method varies all parameters simultaneously and each variable is adjusted through its entire range identified across all individual subjects receiving LR or Hex. Once the range of each model parameter is identified (see the next subsection Parameter Estimation), each parameter is simulated 1000 times via a uniform distribution. The first-order or main effect G of i^{th} parameter on the BV response under individual input profile is computed through a Monte Carlo simulation:

(16)

where V_i is the effect of i^{th} parameter on BV variation, leveraged over variation in other model parameters (refer to [\[29\]](#) for more details about calculating V_i). It is standardized by the total variance in BV response to provide a fractional contribution. Therefore, the first-order effects across all the parameters should add up to 1. For better assessment, the sensitivity indices were reported at 4 different time instants: 30 min, 80 min, 120 min, and 180 min. Similar to prior studies [\[30–33\]](#), at each time, first-order sensitivity indices less than 0.01 are regarded as insensitive parameters. We also consider those larger than 0.1 as highly sensitive and the ones between 0.01 and 0.1 as sensitive parameters. A parameter whose sensitivity index is less than 0.01 at all time instants is considered insignificant and might be removed with minimal degradation in the model performance.

Parameter estimation.

The models presented in the last section provide an approximation of BV response over time

(17)

where $k = 1, \dots, K$ is the time index for K successive discrete observations, $\hat{y}_k$ is the model reproduced BV response for a chosen Θ , and $\epsilon(t_k)$ is the error between the model output and BV observations over time. Assuming that $\epsilon(t_k)$ is distributed normally, independently, and identically with mean $E(\epsilon(t_k)) = 0$ and variance $V(\epsilon(t_k)) = \sigma^2$ for all t_k , the following equation is defined according to a normal distribution.

(18)

Therefore, the observations $\Delta BV(t)$ have a density function which are the same form as those of the ϵ . Thus, the likelihood function of Θ and σ^2 , based on the sample, is

(19)

The log-likelihood function L^* is obtained by taking the logarithm of [Eq 19](#).

(20)

To identify the model parameters, an optimization problem is defined

(21)

where $\gamma > 0$ is the L_2 penalty term, $\|\cdot\|_2$ denotes the L_2 norm operator and penalizes the L_2 norm of the model parameters to force them to be small with reduced estimation variance, thus to avoid over-fitting. Using ΔBV measured for a given subject, solution to the optimization problem [21](#) minimizes the negative log-likelihood and derive the set of optimal parameters, i.e., $\{a_u, a_v, K_p, K_i\}$ for the original and $\{a_u, a_v, K_p, K_i, A_u, A_v\}$ for the refined model, leading to a fully individualized model with minimum discrepancy between the true versus model-reproduced BV response.

We tuned the regularization parameter $\gamma > 0$ for each data-set using an inner-level validation procedure. We used three different penalty levels, $\gamma > 0 \in \{1, 3, 5\}$, identified the parameters for both models using the first 120 min of the data, and reproduced the remaining 60 min. For each model, the penalty with the least AIC value (see Eq 23) was selected and used in solving the optimization problem (Eq 21).

Model evaluation

We compared the original and refined models in terms of their calibration performance and predictive capability. For a comprehensive assessment, the models were examined through different tools and techniques explained below.

Model calibration assessment.

We used data from 16 animals (11 LR and 5 Hex) to identify 16 individualized models. For each subject, we utilized measured BV data and solved Eq 21 to identify the optimum set of parameters for each subject. The model reproduced BV response was then compared with its true counterpart and the following measures were reported:

Root-mean-squared error. RMSE is the square root of the second moment of the estimation error, which aggregates the estimation error for various times into a single value, computed by

(22)

Akaike information criterion. AIC is a model selection tool and deals with the trade-off between model's accuracy and complexity to prevent over-fitting. AIC seeks a model that has a good fit to the true data but with fewer parameters, and is defined as

(23)

where L^* is the log-likelihood function defined in Eq 20, and P is the number of model parameters, 4 in the original and 6 in the refined model.

Multi-dimensional measure. Mean-squared error is the sum of variance and square of the bias observed in an estimation. As a result, RMSE outputs a trade-off between variance and bias but not their segregated values [34]. A comprehensive fitting assessment, however, requires to examine the adequacy of multiple estimation features individually defined over time and the range of the data. For instance, an underfitting occurs when the model shows low variance but high bias, while overfitting leads to a fit with high variance and low bias [35]. Therefore, a joint measure of features cannot completely determine the extent to which a model captures the underlying structure of the data. Here, we developed a tool that considers multiple individual features of a model calibrated to each subject to examine the fitting performance between the two models. We defined four features, bias, standard error of residuals, trend of error over time, and trend of error over the BV range. We fitted both models to each individual subject using Eq 21 and collected the features for both original and refined models. We then normalized the features to have values between 0 and 1 across all the subjects. Next, we statistically compared the features in a 4-dimensional space in Cartesian coordinates. In addition, for each individual fit, we identified the Euclidean distance as a distance between the origin and the points corresponding to the normalized features

(24)

where U_d and f denote the Euclidean distance and features, respectively. We identified and compared the euclidean distance values across the original and refined models.

Predictive capability assessment.

Besides the calibration performance assessment described above, it is important to quantitatively examine the extent to which a mathematical model is an adequate representation of physiological measurements under conditions for which the model has not been calibrated, as the intended use inputs and boundary conditions can be different from those in the calibration data. In addition, a model fitted to a physiological variable may be judged as fit for purpose and may not adequately work against new data, even those obtained from the same subject, in the same environment, and for a similar intended application [36]. Therefore, accuracy assessment of a predicted response by an interpolation or extrapolation of the model to diverse inputs and boundary conditions is essential. To include a wide range of fluid perturbation conditions for predictive capability performance assessment, we examined the model response prediction under three different scenarios, shown in Fig 2. First, we assessed the adequacy of subject-specific predictions for the steady-state BV responses, during the last 30 min of each experiment, and through an extrapolation of the model response that was calibrated to a sub-sample of data occurred earlier (upper panel in Fig 2). We considered this as steady-state response prediction since no hemorrhage took place during this time and the amount of inputted fluid and BV variation were much less compared to those in earlier times. Second, we assessed the subject-specific predictions for a transient BV responses during 45-80 min, which includes the second and third hemorrhage events, through an interpolation of the model response calibrated to a sub-sample of the remaining data, i.e., those outside of 45-80 min time range (middle panel in Fig 2). Finally, we assessed the entire BV response prediction for each individual through a leave-one-out procedure, where the model parameters were selected based on their values identified from all other subjects (lower panel in Fig 2). These three scenarios are very distinct and replicate different input profiles—e.g., low and large fluid perturbation in the steady-state and transient prediction scenarios—and boundary conditions, where the leave-one-out procedure intends a new subject with different treatments and environmental uncertainty as compared to others. It is noted that the effects of sensor inaccuracy have not been explicitly considered in this study. BV response measurements are used for predictive performance evaluation, assuming that the effects of noise in measurements are included in the reported prediction interval in the Results section.



Fig 2.

Predictive capability assessment under three scenarios, (A): subject specific prediction of steady-state BV response (150⁺-180 min) via bootstrapping the rest of data (0-150 min), (B): subject specific prediction of transient BV response to second and third hemorrhage perturbations (45-80 min) via bootstrapping the rest of data (0-45⁻ and 80⁺-180 min), (C): Leave-one-out prediction of BV response in each subject using the normal distribution of parameters identified in other subjects (for more details please refer to text). The distribution of a_U in the original model and A_U in the refined model was identified based on LR or Hex, depending on whether the subject received LR or Hex, and not a combination of both LR and Hex due to their distinct dispersion. Green and purple colors show the data used for model calibration and prediction assessment, respectively.

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(A) Subject-specific prediction of steady-state BV response. The 95% confidence interval for model-predicted steady-state BV response was obtained through a sub-sampling procedure, known as bootstrapping. For each individual, we selected a 75% sub-sample of BV data collected in 0-150 min time range and fitted both models to the sub-sampled data. We used a 75% sub-sample to avoid the large parameter estimation uncertainty and keep the number of experimental data points at least 4 times as large as the number of model parameters. Next, the identified models were used to predict the steady-state BV responses occurred after 150 min till the end of experiment. We repeated this procedure for 100 times (it is noted that the bootstrapping results remained unchanged by doing this for more than 100 times). After collecting all predicted responses, we used the percentile method for constructing the 95% confidence interval, which included all the predictions between the 2.5th and 97.5th percentiles of the forecast at each prediction time.

After collecting the 95% confidence interval, we measured and compared predictive capability of the two mathematical models by evaluating their forecasts. In this work, we used the interval score developed in [37], that measures a confidence interval using a performance score. The score rewards a forecast for a narrower prediction envelope, while applies a penalty, the magnitude of which depends on a significance level α , when the measurement misses the confidence interval. For a prediction point t_k , if $\hat{y}_k$ and $\hat{y}_k^{\pm}$ are the lower and upper $(1 - \alpha) \times 100\%$ prediction envelope and $\Delta BV(t_k)$ is the true measurement, the interval score is defined as

(25)

In this study, the significance level α is considered to be 0.05. The identified scores were compared between the two models using statistical methods. We also compared the proportion of measurements that were within the prediction envelope, denoted as PM , for both original and refined models.

(B) Subject-specific prediction of transient BV response to perturbation. The 95% confidence interval for model predicted BV response to the second and third hemorrhage events was obtained through a sub-sampling procedure. For each individual, the BV response was predicted in the 45-80 min time span, using a model fitted through 75% sub-sample of the remaining BV data. This procedure was repeated for 100 times. The percentile method was used to construct the 95% confidence interval at each prediction point. The forecast interval performance at each prediction point was measured using the interval score defined in Eq 25. The identified scores as well as proportion of measurements within the prediction envelope were compared between the two models using statistical methods.

(C) Leave-one-out prediction of BV response. We predicted the BV response for each individual using both original and refined mathematical models and tuned parameters in other subjects. In each subject, a sample of size 1000 was generated for each parameter through a normal distribution identified from the tuned parameters in other subjects and within the lower and upper bound of these parameters. Except the a_U in the original model and A_U in the refined model, normal distribution of a parameter was identified from its values across other 15 subjects, while the lower and upper bound were minimum and maximum values across the range of the parameter in those 15 subjects. Normal distribution of a_U in the original or A_U in the refined model was determined solely based on the parameter values in LR or Hex subjects, depending on type of fluid given to the subject, and not their combination due to the distinct dispersion of the parameter between two groups (for more details please see Table 1 in the Results section). Since no clear correlation was seen between each pair of parameters (original model $r^2 = 0.11 \pm 0.14$, refined model $r^2 = 0.15 \pm 0.15$), all the parameters were allowed to freely change within their range, i.e., regardless of variation in other parameters, and based on their identified distribution. The leave-one-out BV response confidence intervals were predicted through 1000 simulations, the parameters of which were randomly selected from the normally distributed samples. The percentile method was used to construct the 95% confidence interval at each point. The performance of the model forecast at each time was measured through interval score and proportion of measurements within the prediction envelope and examined between the two models.



Table 1. Calibrated parameters for the original and refined models across LR and HEX data, along with the P -values (2-sample unequal t-test) reported between the identified parameters for each model.

Underline bold numbers indicates significant difference between the parameters for LR and HEX data. The calibrated parameters for each subject are provided in the Supporting information section.

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Results

In this section, we first present the identified parameters in both mathematical models and show how the identified parameters differ between LR and Hex. Next, the calibration performance is presented and compared between the two models. Finally, predictive capability assessments are shown and examined in both models.

Parameter estimation and identifiability analysis

Original and refined model parameters were identified by solving Eq 21 in each individual subject. Table 1 shows the averaged identified parameters grouped per model and fluid type. Statistical test performed for each parameter and across fluid types shows that the mean of only one parameter in each model is significantly different between LR and Hex: a_U in the original model ($P = 2 \times 10^{-6}$, 2-sample unequal t-test, LR: $N = 11$ and HEX: $N = 5$); and A_U in the refined model ($P = 0.04$, 2-sample unequal t-test, LR: $N = 11$ and Hex: $N = 5$). Given that the models have different dynamic characteristics and mechanisms in updating the reference blood volume, a comparison between the common parameters of the two models was not made.

Using the identified range of parameters, global sensitivity indices were computed using Eq 16 and a Monte Carlo simulation. The sensitivity indices were averaged across all 16 subjects and reported at 30 min, 80 min, 120 min, and 180 min.

(26)

(27)

It is clear that all parameters in both models remain significant as there is no parameter with a sensitivity index less than 0.01 at all time instants. At time 30 min, before the fluid infusion is initiated, a_U in the original model and A_U and a_U in the refined model are insensitive, while a_V in the original model and A_V and a_V in the refined model remain highly sensitive. At time instants greater than 30 min and when fluid has started to be given to subjects, a_U in the original model and A_U in the refined model become highly sensitive, and a_U in the refined model turn to be sensitive, all supporting the adequacy of the results. In addition, K_p and K_i , those in the refined model in particular, are mostly sensitive at 30 min, when the rate of fluid shift between intravascular and interstitial compartments is presumably maximal.

Model calibration assessment.

Table 2 compares the goodness-of-fit and calibration performance between the two models using three different methods: RMSE, AIC, and multi-dimensional measure. Averaged among all individuals, the results show that the RMSE is significantly lower in the refined model (see Table 2, $P = 0.03$, paired t-test, $N = 16$). In addition, the refined model shows comparable AIC to that of the original model, as among all 16 subjects, the frequency in which each model attained the minimum AIC is equal, i.e., each model is suggested as the better model in 8 subjects (see Table 2), indicating the better calibration performance is not due to over-fitting the BV data. Fig 3 shows the multi-dimensional measure in a 4-dimensional space, where the Euclidean distance for each point, i.e., each individual, can be obtained as the distance between the point from the origin. As it can be seen from the figure, the points in the refined model are scattered in closer vicinity of the origin as compared to the original model. This is also evidenced from Table 2, where among the multi-dimensional error features in the 4-D space, bias, standard error of residuals, and trend of error over the BV range are significantly smaller in the refined model ($P < 0.04$, paired t-test, $N = 16$), while a comparable trend of error over time is seen between the two models ($P = 0.08$, paired t-test, $N = 16$). In addition, the Euclidean distance is significantly smaller in the refined model ($P = 0.02$, paired t-test, $N = 16$). In summary, the results show that the calibration performance is significantly enhanced in the refined model.



Table 2. Model calibration assessment based on root-mean-squared error (RMSE), Akaike information criterion (AIC) and the frequency in which each model attained the minimum AIC (FR), and multi-dimensional measure.

Regarding the multi-dimensional measure, 4-D features, i.e., bias, standard error of residuals, trend of error over time, and trend of error over the BV range, as well as the Euclidean distance defined in Eq 24 are computed and compared between the two models. Results show that the refined model has significantly better performance in terms of RMSE and multi-dimensional measure. In addition, the models are comparable in terms of AIC, where among all 16 subjects, the frequency in which each model attained the minimum AIC is equal, i.e., 8. P-values are obtained using paired t-test. Underline bold numbers indicates significant difference between calibration performance of the two models.

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Fig 3. Multi-dimensional measure shown for 16 individuals in both original (left) and refined (right) mathematical models.

As compared to the original model, the points in the refined model are significantly closer to the origin in terms of bias, standard error of residuals, and trend of error over the BV range ($P < 0.04$, paired t-test, $N = 16$), while comparable trend of error over time is observed between the two models ($P = 0.08$, paired t-test, $N = 16$). Averaged Euclidean distance from each point is also significantly smaller in the refined model (see Table 2, $P = 0.02$, paired t-test, $N = 16$).

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Predictive capability assessment.

Fig 4 shows the predictive capability assessment for both models and under 3 different scenarios for a representative subject. In the first scenario, shown in the upper panel, the steady-state response (150–180 min) was predicted by fitting a 75% sub-sample of the remaining data. As it can be seen, the prediction envelope of the refined mathematical model (right column) is much closer to the measurements and includes two out of three measurements (i.e., the last two data points in the prediction region), while the prediction envelope of the original model (middle column) includes only one measurement (i.e., the last data point in the prediction region). In the second scenario, shown in the middle panel, the transient response to the second and third hemorrhage events was predicted by fitting a 75% sub-sample of data in 0–45 min and 80–180 min range. It can be seen from Fig 4 that the prediction envelope in the refined model is closer to the measurement, where it includes four out of nine measurements (i.e., the first four data points in the prediction region), as compared to one measurement in the original model (i.e., the fourth data point in the prediction region). In the third scenario, shown in the lower panel, the prediction envelope is obtained through a leave-one-out procedure. It is seen from the figure that the prediction envelope corresponding to the refined model includes one more measurement compared to the original model. The refined model, however, produces a slightly wider prediction envelope after 60 min, leading to slightly larger interval scores. Averaged across all individuals, Table 3 compares the predictive capability performance between the two models and under the three scenarios. The results indicate that the original and refined models similarly perform in the steady-state response prediction, whereas the means of interval score and proportion of measurements within the prediction envelope do not show a significant difference (interval score: $P = 0.3$, paired t-test, $N = 45$; proportion of measurements: $P = 0.8$, Chi-squared test, $N = 45$). The refined model shows significantly better performance in transient response prediction, whereas both the interval score and proportion of measurements within the prediction envelope are significantly better in the refined model (interval score: $P = 7 \times 10^{-4}$, paired t-test, $N = 127$; proportion of measurements: $P = 0.02$, Chi-squared test, $N = 127$). Finally, the interval score for the leave-one-out procedure was comparable in both models ($P = 0.8$, paired t-test, $N = 438$). However, significantly larger number of measurements were included in the refined model's prediction envelope ($P = 3 \times 10^{-3}$, Chi-squared test, $N = 438$).



Fig 4. Predictive capability assessment across the original (middle column) and refined (right column) mathematical models under three scenarios.

A) upper panel: predicting the steady-state response (150–180 min) by fitting a 75% sub-sample of BV measurement between 0–150 min, B) middle panel: predicting transient response (45–80 min) by fitting a 75% sub-sample of BV measurement between 0–45 and 80–180 min, C) lower panel: leave-one-out prediction of the inter-subject response using a normal distribution of identified parameters in other individuals.

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Table 3. Predictive capability assessment for different prediction scenarios in both original and refined models.

S and PM indicate the prediction interval score and proportion of measurements within the prediction envelope and are reported for prediction of steady-state BV response (150–180 min, i.e., $S_{150-180}$ and $PM_{150-180}$), prediction of transient response (45–80 min, i.e., S_{45-80} and PM_{45-80}), and leave-one-out prediction (i.e., $S_{Leave-One-Out}$ and $PM_{Leave-One-Out}$). P-values for the S and PM are obtained using paired t-test and Chi-squared test, respectively. Underline bold numbers indicates significant difference between the two models.

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Discussion

Toward the goal of establishing methods to compare models intended for use in PCLC medical device assessment and determine a mathematical model that better represents the physiological measurement, we proposed a pathway that can be potentially used as a guide for physiological model selection between candidate mathematical models. As a case study, we compared two physiological models for BV response to fluid perturbation: the original model that was developed in our prior work [19, 20], and a refined model that was built in this research, based on an expansion to the original model. This research focuses on first-principle physiological —as opposed to black-box— models aimed for PCLC medical device assessment. Our methods, therefore, should assess the models in terms of their physiological transparency and allow to compare the modeling performance in both calibration as well as predictive capability. We formulated a maximum likelihood estimation problem to separately identify the parameters for each model. We compared the calibration performance in terms of RMSE, AIC, and multi-dimensional measure. In addition, the predictive capability of the models were assessed under three different scenarios to investigate the adequacy of their predicted response under different input profiles and hemodynamic conditions. To compare the predictive capability, we used two measures: interval score (S) [37] and the proportion of measurements within the prediction envelope (PM). Based on the results, the refined mathematical model turned out to better represent the BV physiological data since it (1) significantly improved individualized model calibration performance to the experimental data, (2) did not increase the risk of overfitting despite its larger number of parameters compared to the original model, and (3) showed significantly enhanced predictive capability in subject-specific transient response prediction to hemorrhage, while at least comparable performance in steady-state and leave-one-out predictions. Taken together, the proposed mathematical approach can serve as a tool to select the best between multiple candidate physiological models for evaluation of PCLC medical devices.

A physiological model should be identifiable and transparent

A model to be used for performance evaluation of a PCLC medical device should be identifiable, that is, the model parameters can be uniquely estimated under the input and boundary conditions relevant to the intended use of a device. Based on Eqs 12 and 15, it was shown that similar to the original model, the refined mathematical model which involves more parameters is theoretically identifiable. In addition, the optimization problem in Eq 21 was solved using different initial conditions for the parameters, where the identified parameters remained unchanged, further supporting the identifiability of both models. Furthermore, based on Eqs 26 and 27, it was shown that all parameters in both models are significant, as their global sensitivity indices are not less than 0.01 at all the reported time instants.

Regarding the model transparency, both models are expected to be physiologically interpretable. In the original model, a_u denotes the steady-state distribution of fluid between intravascular and interstitial compartments under fluid administration. Unlike LR, Hex is made of high-molecular-weight hydroxyethyl starch 6% in isotonic saline, causing the body to keep the fluid longer in the intravascular space rather than leaving through its vascular endothelium [38]. Therefore, it is anticipated to have a smaller a_u for Hex compared to LR, as seen in Table 1 ($P = 2 \times 10^{-6}$). The original model dictates the reference BV (r_{BV}) to update only during fluid administration, as shown in Eq 1. However, r_{BV} can change continuously over time, even in the absence of fluid administration. Indeed, it is an individual's physiology that mostly determines the dynamics of change in BV response over time, so much as when no infusion is present. Motivated by this, the refined physiological model is built based on the concept that patient's physiology can continuously alter the target state of BV, due to the dynamics of change in the colloid osmotic concentration in plasma [22]. Table 1 indicates that, while a_u in the refined model is still slightly smaller under Hex administration ($P = 0.3$), it is the state parameter A_u and its dynamical impact on r_{BV} —through subject's physiology—that constructs the basis of difference in BV response to Hex and LR fluids ($P = 0.04$). Based on Eq 13, a smaller A_u leads to a larger low-frequency (DC) gain, amplifying the steady-state BV response under Hex administration. All together, A_u in the refined model represent a physiological mechanism modulating the target BV state under different fluid types.

Selected model offers enhanced model calibration

The refined mathematical model can serve as a better model in terms of the model calibration performance. While it is important for a model to adequately capture the dynamics of change in physiological data used to infer the model parameters, the model should not be overly complex to avoid over-fitting. In this work, we assess the adequacy of data calibration using RMSE, AIC to evaluate the trade-off between complexity and accuracy of each model, and a new multi-dimensional measure that compares the adequacy of 4 major estimation features individually defined over time and range of the data. First, the results reported in Table 2 show that, compared to the original model, the refined model has significantly smaller RMSE ($P = 0.03$). It is noted that the RMSE in both original and refined models have a large standard deviation, which is due to large calibration error seen in one of the animal subjects—subject number 14 shown in Fig 3. Second, the models are comparable in terms of AIC, where the frequency in which each model attained the minimum AIC is equal. This indicates that enhanced calibration performance in the refined model is not trivial and not obtained due to over-fitting the BV data. Instead, the calibration performance improvement is based on the physiological model refinement and inclusion of the dynamic behavior of BV response to fluid perturbation. Finally, the multi-dimensional measure in the refined model is significantly smaller than the original model ($P = 0.02$), as seen in Fig 3. The figure clearly depicts how error features in the refined model are scattered in closer vicinity of the origin, leading to a significantly smaller average Euclidean distance from the origin to each point. It is noted that based on the figure and results shown in Table 2, the refined model significantly improves the calibration performance in terms of three estimation error features; bias, standard error of residuals, and trend of error over the BV range ($P < 0.04$), while the trend of error over time is comparable between the two models ($P = 0.08$). All together, the results indicate the suitability of the refined model in fitting BV data.

Selected model offers enhanced predictive capability performance

The refined mathematical model performs better in terms of predictive capability against physiological states and under conditions to which the model has not been calibrated. This has been shown based on the predictive capability performance obtained under three different scenarios. The performance was measured via S score and proportion of measurements within the prediction envelope. As it is seen from Table 3, refined and original models showed comparable prediction performance in the steady-state BV response scenario, where S score as well as proportion of measurement that were within the prediction envelope were not significantly different ($P > 0.34$). Enhanced prediction performance of the refined model was the most evident in the transient BV response scenario, where the S score was significantly smaller ($P = 7 \times 10^{-4}$) and larger proportion of data points were within the generated prediction envelope ($P = 0.02$). While some of this discrepancy in prediction performance is due to different quality of calibration via training data (see results on calibration performance), a model with larger number of parameters can inherently explore a broader range of patient heterogeneity, named patient cohorts, thus, constructing a wider prediction envelope. As a result, the refined model has led to a broader prediction envelope to include a larger number of measurements, i.e., 15%, but not too wide to get a larger S score than the original model. Similarly, the refined model led to a significantly larger proportion of measurement within the prediction envelope for the leave-one-out scenario ($P = 3 \times 10^{-3}$). However, due to the same reason mentioned earlier, S score was identified to be similar between the two models ($P = 0.79$). Taken together, the refined model performed significantly better in the transient BV response and leave-one-out scenarios, while similar performance was seen for the steady-state response prediction. It is noted that the S scores identified in this study are obtained for a 0.05 significance level. A smaller significance level will benefit the refined model as its prediction envelopes contain a larger percentage of measurements. These evaluation results obtained by the use of experimental data suggest that for future evaluation of PCLC medical devices for fluid resuscitation, the refined model may lead to more realistic virtual patient cohorts for inputs and boundary conditions to which the model is not calibrated. Therefore, it may provide more credible results when testing PCLC medical device performance.

Study limitation

This research provide a comparison pathway to select a model between a set of candidate models. As a case study, we examined the proposed pathway for two physiological models of BV response to fluid perturbation, intended for fluid resuscitation PCLC medical devices. This study, however, needs to be extended to other physiological domains, e.g., respiratory treatment, that are outside of the scope of the models in this work, or when patients go under multiple interactive PCLC medical devices. In addition, we studied the models that correspond only to the physiological response, while the effects of sensor inaccuracy or input

disturbance has not been explicitly considered. Instead, data measured from the animal subjects that may have been contaminated by noise were used for model evaluation. Given that these factors play a major role in PCLC medical device performance assessment, some work is needed to determine the effects of inaccuracy of hardware on model performance assessment. Finally, the results of this research are based on only 16 subjects. This proposed pathway should be further examined when a smaller or larger number of subjects are used for model calibration, which could potentially emphasize the need for comparison methods between candidate models and lead to best practices for computational models based on the subject sample size.

Conclusion

This research developed tools for model selection and evaluation of first-principle physiological models for use in PCLC medical device assessment. As a case study, we used two physiological models of BV response to fluid perturbation; one developed in our prior work and another expanded from the original model in this research. The models were compared in three aspects of identifiability and interpretability, model calibration, and predictive capability performance. We showed that between the two candidate mathematical models, the refined model performed better, or at least comparable, in all three aspects and thus, it could offer more credibility toward PCLC medical device assessment. The developed pathway in this research can be extended to model selection in other physiological domains.

Supporting information

S1 File. Calibrated parameters for the original model.

<https://doi.org/10.1371/journal.pone.0251001.s001>
(PDF)

S2 File. Calibrated parameters for the refined model.

<https://doi.org/10.1371/journal.pone.0251001.s002>
(PDF)

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Mathematical Modeling, In-Human Evaluation and Analysis of Volume Kinetics and Kidney Function after Burn Injury and Resuscitation

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Abstract— Objective: Existing burn resuscitation protocols exhibit a large variability in treatment efficacy. Hence, they must be further optimized based on comprehensive knowledge of burn pathophysiology. A physics-based mathematical model that can replicate physiological responses in diverse burn patients can serve as an attractive basis to perform non-clinical testing of burn resuscitation protocols and to expand knowledge on burn pathophysiology. We intend to develop, optimize, validate, and analyze a mathematical model to replicate physiological responses in burn patients. **Methods:** Using clinical datasets collected from 233 burn patients receiving burn resuscitation, we developed and validated a mathematical model applicable to computer-aided in-human burn resuscitation trial and knowledge expansion. Using the validated mathematical model, we examined possible physiological mechanisms responsible for the cohort-dependent differences in burn pathophysiology between younger versus older patients, female versus male patients, and patients with versus without inhalational injury. **Results:** We demonstrated that the mathematical model can replicate physiological responses in burn patients associated with wide demographic characteristics and injury severity, and that an increased inflammatory response to injury may be a key contributing factor in increasing the mortality risk of older patients and patients with inhalation injury via an increase in the fluid retention. **Conclusion:** We developed and validated a physiologically plausible mathematical model of volume kinetic and kidney function after burn injury and resuscitation suited to in-human application. **Significance:** The mathematical model may provide an attractive platform to conduct non-clinical testing of burn resuscitation protocols and test new hypotheses on burn pathophysiology.

Index Terms—Burn injury and resuscitation, computer-aided clinical trial, digital twin, volume kinetics, kidney function.

I. INTRODUCTION

BURN is a leading cause of unintentional injury and death in the United States. According to a recent fact sheet from the American Burn Association, burn injury is the 8th leading

cause of death in adults >65 years old, 3rd in children 5-9 years old, and 5th in children 1-4 years old [1]. Each year, there are nearly 500,000 burn injury incidences only across the United States, among which 40,000 are hospitalized. Burn injury results in severe inflammatory responses that lead to increased leakage of intravascular water into the tissues, which, if not treated, engenders fatal consequences such as hypovolemic shock, ischemia, multiple organ failure, and generalized edema [2], [3]. The majority of burn patients treated in burn centers survive, but many of them suffer from complications [4], [5].

Currently, treatment of burn patients involves a resuscitation protocol in which the dose of the resuscitation fluid is titrated frequently to maintain the urinary output (UO) response in a burn patient to a therapeutic target range (e.g., 30-50 ml/hr or 0.5-1.0 ml/kg·h [6]) [7]. Yet, existing resuscitation protocols exhibit a large variability in treatment efficacy, due to many factors such as the inter-patient differences in response to burn injury and resuscitation as well as the incomplete knowledge of the pathophysiology underlying burn injury, which collectively complicates therapeutic decision-making. Hence, there is an ongoing effort to optimize burn resuscitation protocols [8]–[10]. However, due to the ongoing limitations, today's burn resuscitation often starts with an established burn resuscitation protocol but is subsequently titrated in an ad-hoc fashion to the physiological responses (including UO) in an individual patient to hopefully optimize the therapeutic efficacy. Unfortunately, current treatments tend to over-resuscitate the patients [11], which would exacerbate edema and expose the patients to an elevated risk of side effects, e.g., pulmonary edema, limb and abdominal compartment syndrome, necrosis, and death, due to the accumulation of resuscitation fluid (known as “fluid creep”) [12], [13]. Hence, burn resuscitation regimens must be optimized based on complete knowledge of burn pathophysiology in order to best maintain organ functions in burn patients while minimizing adverse complications.

Development and optimization of burn resuscitation

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protocols is challenging, because (i) burn injury is less common than other widespread injuries (i.e., protocol optimization is hampered by the small number of burn injury cases) and (ii) it is unethical to test a new treatment protocol with unproven efficacy and safety in critically ill burn patients. From this standpoint, a mathematical model that can replicate physiological responses to burn injury and resuscitation in diverse burn patients can serve as an attractive basis to (i) perform non-clinical testing of emerging burn resuscitation protocols as medical digital twin [14], [15] and (ii) expand knowledge on burn pathophysiology [16]. However, existing mathematical models are not yet ideal for such purposes for at least three reasons. First, some mathematical models cannot be applied to test many existing burn resuscitation protocols based on UO, simply because they were not developed to predict UO responses to burn injury and resuscitation [17]–[21]. Second, most existing mathematical models have not been extensively proven in humans. In fact, the ability of existing mathematical models to replicate UO and other physiological responses to burn injury and resuscitation was validated in a prohibitively small number of patients [22]–[27] or only at the group level [17]–[21]. Third, some mathematical models (especially those reported early) [22]–[27] do not reflect up-to-date knowledge of burn-related physiology and pathophysiology gained in recent experimental and clinical investigations, regarding in particular the burn-induced perturbations in volume kinetics, kidney function, lymphatic flow, and tissue pressure-volume relationships [2], [28]–[30]. Hence, closing these gaps may lead us to an enhanced mathematical model of burn injury and resuscitation ideally suited to the development and testing of emerging burn resuscitation protocols and algorithms as well as to the expansion of our knowledge of burn pathophysiology.

In this paper, we intend to develop, extensively validate, and analyze a mathematical model capable of replicating volume kinetic and kidney function responses to burn injury and resuscitation in burn patients. By leveraging clinical datasets collected from 233 real burn patients receiving resuscitation, we developed a mathematical model suited to computer-aided in-human burn resuscitation trial and knowledge expansion, by expanding our prior work and utilizing systematic parametric sensitivity analysis and regularization. We investigated the validity of the mathematical model by testing its physiological plausibility in a dedicated test dataset. Using the validated mathematical model, we examined possible mechanisms responsible for the cohort-dependent differences in burn pathophysiology by comparing the mathematical models fitted exclusively to younger versus older patients, female versus male patients, and patients with versus without inhalational injury. To the best of our knowledge, our mathematical model may be the first mathematical model extensively validated for use as digital twin of real burn patients.

This paper is organized as follows. Section II provides an overview of the mathematical model as well as the details of the clinical dataset and data analysis. Section III presents the results. Section IV is devoted to the discussion of major findings. Section V concludes the paper with future directions. Full details of mathematical equations and parameter values are

provided in the Supplementary Document (Appendix and Table AI).

II. MATERIALS AND METHODS

A. Mathematical Model

We continued to develop a mathematical model capable of predicting volume kinetic and kidney function responses to burn injury and resuscitation developed in our prior work [31]. The mathematical model consists of (i) volume kinetics to replicate water volume and protein concentration dynamics in the intravascular and the tissue compartments (“Volume Kinetics” in Fig. 1(a); see Appendix A provided in Supplementary Document), (ii) kidney functions to replicate UO response to changes in intravascular water and protein volumes (“Kidneys” in Fig. 1(a); see Appendix B provided in Supplementary Document), and (iii) transient perturbations in volume kinetics induced by burn as a chain of biochemical, molecular, and mechanical events (“Burn Perturbations to Volume Kinetics” in Fig. 1(b); see Appendix C provided in Supplementary Document). The volume kinetics was represented using a three-compartmental model with intravascular space (including arterial and venous vessels, shown as “Plasma” in Fig. 1), intact tissues, and burnt tissues as separate compartments. These compartments describe the volumes of water (V_P , V_{IT} , V_{BT} ; whose dynamics is governed by Eq. (4)) and protein therein (A_P , A_{IT} , A_{BT} ; whose dynamics is governed by Eq. (5)) as functions of time. It was assumed that albumin serves as the surrogate of all the protein contributing to capillary filtration and colloid oncotic balance [32]. As shown in Fig. 1, the change in these volumes are dictated by (i) inter-compartmental flows of the lymphatic drainage (water J_L and protein Q_L ; Eq. (8)–(9)) and capillary filtration (J_C and Q_C ; Eq. (6) and Eq. (10)); (ii) external inputs representing the gain via burn resuscitation (J_F and Q_F); and (iii) outputs representing the kidneys’ net filtration and reabsorption of renal plasma flow (i.e., UO J_U ; Eq. (15) and Eq. (26)), as well as burn-induced evaporation (J_{EV} ; Eq. (34)) and exudation (J_{EX} and Q_{EX} ; Eq. (35)). The kidney function was represented by a lumped-parameter model developed in our prior work [31], which includes a hybrid combination of first-principles and phenomenological elements that describe UO control governed by the kidneys, including the glomerular filtration rate (GFR; J_{GFR} in Fig. 1 and Eq. (16)–(18)) modulated by the Starling forces due to the change in the intravascular water and protein volumes (i.e., plasma volume), the reabsorption by the glomerulotubular balance ($J_{RR,GT}$ in Fig. 1 and Eq. (19)–(20)), and the reabsorption and sodium osmosis modulated by the antidiuretic hormone (ADH; $J_{RR,ADH}$ in Fig. 1 and Eq. (19)–(25)). The transient perturbations in volume kinetics and kidney function triggered by burn injury were represented by an array of time-varying phenomenological models acting on various parameters and variables in the mathematical model of volume kinetics to replicate local and systemic pathophysiological changes caused by burn injury, including (i) partial destruction of capillaries in burnt tissues (a in Fig. 1; Eq. (28)–(29)), (ii) denaturation of protein in burnt tissues (b in Fig.

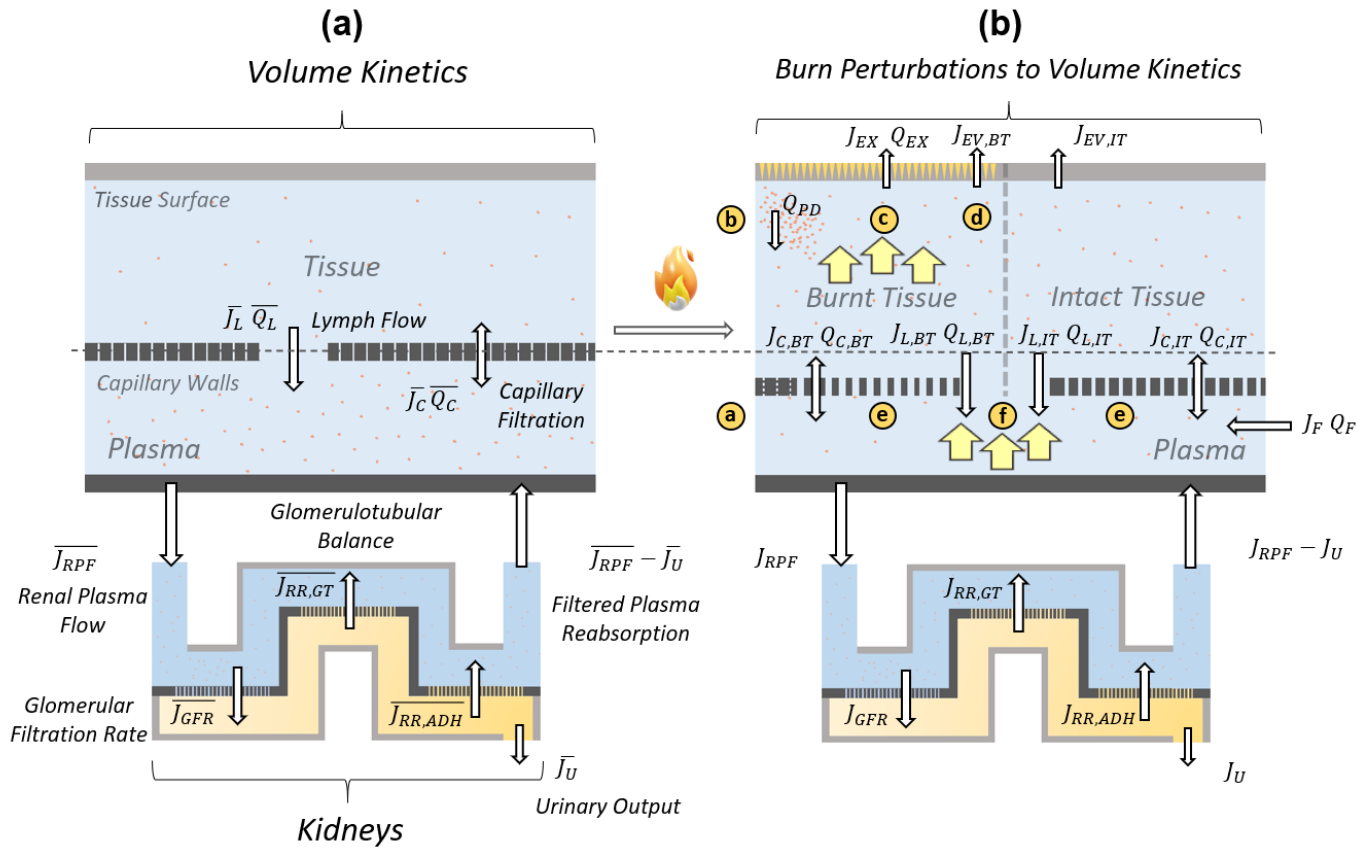


Fig. 1. Mathematical model capable of predicting volume kinetic and kidney function responses to burn injury and resuscitation. Fig. 1(a) shows normal state, where the water (blue background) and protein (pink dots) balance between the intravascular compartment (“Plasma”) and the tissue is preserved by the capillary filtration through the capillary pores (thin rectangles in the capillary wall) and lymph flow. The plasma is filtered by the renal plasma flow into the kidney by way of the renal regulatory mechanisms including the glomerulotubular balance and the Antidiuretic hormone. Upon the onset of burn injury, the water and protein volumes in the plasma decrease, while tissue compartment is divided into intact and burnt tissue compartments associated with water and protein content higher than normal state (“Burnt Tissue” and “Intact Tissue”) (Fig.1(b)). J : water flow. Q : albumin flow. Subscripts: C (capillary filtration); L (lymph flow); F (fluid infusion); U (UO); RPF (renal plasma flow); GFR (glomerular filtration rate); RR,GT (reabsorption rate by glomerulotubular balance); RR,ADH (reabsorption rate by Antidiuretic hormone); EX (exudation); EV (evaporation); PD (protein denaturation); BT (burnt tissues); IT (intact tissues). The yellow circles represent the perturbations that lead to the redistribution of water and protein. a: Partial destruction of capillaries in burnt tissues (shown as occluded capillary pores). b: Denaturation of protein in burnt tissues. c Transient negative hydrostatic pressure in burnt tissues, which draws water into the burnt tissues. d: Increased dermal fluid loss. e: Time-varying changes in capillary filtration and albumin permeability (shown as enlarged capillary pores). [f]: Vasodilation, which pushes water out of plasma. $\bar{X}$ represents X in normal (pre-burn) state.

1; Eq. (31)), (iii) transient negative hydrostatic pressure in burnt tissues (c in Fig. 1; Eq. (32)), (iv) increased dermal fluid loss (d in Fig. 1; Eq. (34)-(35)), (v) time-dependent changes in capillary filtration and albumin permeability (e in Fig. 1; Eq. (28)-(30)), and (vi) vasodilation (f in Fig. 1; Eq. (36)). The disruption of the kidney function was the consequence of the perturbations occurring in volume kinetics as governed by Eq. (16)-(26). The equations associated with the mathematical model is summarized in Appendix provided in Supplementary Document.

B. Clinical Dataset

The clinical dataset used in this paper was furnished from two sources. The first source included 207 burn patients admitted to a burn intensive care unit (ICU) in December 2007-June 2009 [33]. These patients were treated with the aid of a clinical decision support system capable of recommending the hour-by-hour dose of lactated ringer (LR) to maintain UO at a target range of 30-50 ml/hr [10]. The care providers had the authority to override the recommendation. The dataset included hourly UO and LR dose as well as demographics including age,

gender, and weight, total burn surface area (TBSA), the presence of inhalation injury, and the time of arrival. The second source included 53 burn patients. 29 patients were treated with the aid of the same clinical decision support system, while 24 patients were treated with the contemporary resuscitation protocols. The dataset included hourly UO and LR dose as well as demographics including age and weight, TBSA, and the time of arrival (gender and presence of inhalation injury were not known). Collectively, age, weight, and TBSA of the patients in the dataset were 47 ± 18 years, 87 ± 22 kg, and $40 \pm 18\%$, respectively. The overall mortality rate of the patients was 30%. In the first source, 77% of the patients were male and 11% of the patients were associated with inhalation injury.

We randomly split the clinical dataset into training dataset to enhance and optimize the mathematical model ($N=120$) and test dataset ($N=113$) to validate the optimized mathematical model after excluding 27 burn injury patients associated with prohibitively small number of UO measurements (≤ 10). The demographic and injury severity of the burn patients in the

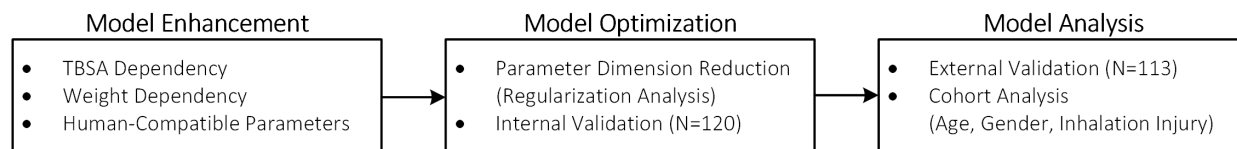


Fig. 2. Analysis procedure. (i) The mathematical model was enhanced to enable in-human application by incorporating TBSA and weight dependence and human-compatible parameter values. (ii) The enhanced mathematical model was optimized to enable its use with limited clinical measurements by model fitting analysis with regularization. The optimized model was internally validated using training dataset consisting of 120 burn patients. (iii) The mathematical model was externally validated using testing dataset consisting of 113 burn patients. The mathematical model was analyzed to garner insights on the pathophysiological differences depending on age, gender, and inhalation injury.

training and test datasets were comparable (age: 45 ± 19 years versus 49 ± 18 years; weight: 85 ± 18 kg versus 86 ± 22 kg; TBSA $41.5 \pm 17.6\%$ versus 38 ± 18). The average hourly UO measurements in the training and test datasets were 23 ± 2 samples and 20 ± 4 samples, respectively.

C. Analysis

We conducted the analysis of the clinical dataset to continue to develop, optimize and validate the mathematical model to enable its in-human application (Fig. 2). First, we continued to develop the mathematical model by (i) including TBSA and weight dependency as well as human-compatible parameters to make it globally applicable to burn injury patients associated with diverse demographic characteristics and injury severity (“Model Enhancement” in Fig. 2), and then (ii) optimizing the mathematical model, by systematically reducing the parameter dimension using the training dataset, to make it compatible with sparse clinical measurements (“Model Optimization” in Fig. 2). Second, we validated the optimized mathematical model using the test dataset in terms of its predictive capability and physiological plausibility (“Model Analysis” in Fig. 2). Third, we scrutinized the mathematical models determined specifically for various categorical patient cohorts to gain insights on meaningful pathophysiological characteristics in these categorical patient cohorts (“Model Analysis” in Fig. 2). Details regarding the continued development, optimization, and analysis of the mathematical model are given in II.C.1, II.C.2, and II.C.3 below and are summarized in Table II.

1) Mathematical Model Enhancement

The clinical dataset presents major challenges in estimating all the parameters in the mathematical model on an individual patient basis. First, the burn patients in the clinical dataset exhibit large variability in the demographic characteristics as well as in the severity of burn injury (TBSA ranging between 16% and 100%), both of which increase the inter-individual variability in physiological responses to burn injury and resuscitation. Second, the number of parameters in the mathematical model is excessively large relative to the available measurements (i.e., hourly resuscitation dose and UO are the only measurements available to characterize these burn patients). To address these challenges and seamlessly apply the mathematical model to real burn patients, we leveraged the training dataset to further develop the mathematical model by (i) extending it to accommodate the variability in weight, TBSA, and species as well as (ii) systematically reducing the number of parameters to be estimated using the clinical dataset.

First, we categorized the parameters in the mathematical model into subject-invariant and subject-specific parameters.

We categorized as subject-invariant parameters (i) those whose values appear consistent in multiple prior literatures (mostly associated with extensive properties and first principles components in the mathematical model, e.g., nominal water volume and albumin content in the intravascular and tissue compartments and the hydrostatic pressure in Bowman’s capsule) and (ii) those whose values must be selected to yield mechanistically relevant physiological responses (e.g., parameters associated with the tissue compliance model, which must be chosen to result in physically relevant tissue hydrostatic pressure for a range of tissue volumes). The values of these subject-invariant parameters were mostly determined based on the existing literature (see Table AI provided in Supplementary Document for specific literatures we leveraged to determine these values). We categorized as subject-specific parameters (i) those whose values can exhibit large variability across burn injury patients (e.g., parameters pertaining to burn-induced perturbations and nominal glomerular filtration coefficient), (ii) those whose values have rarely been reported in the literature (e.g., capillary elastance and nominal lymphatic drainage rate), and (iii) those whose values are inherently unknown (e.g., parameters associated with phenomenological elements in the mathematical model). After all, a total of 58 parameters were categorized into 34 subject-invariant (“I” in Table AI) and 24 subject-specific (“S” and “SS” Table AI) parameters.

Second, we improved the mathematical model to accommodate the variability in weight and injury severity in the clinical dataset as well as to increase its suitability to real burn patients. To incorporate the weight dependence into pertinent parameters, we employed a linear allometric relationship by making them linear functions of weight, so that they assume typical values reported in the literature in case of a reference man (70 kg). These parameters include extensive parameters such as the water and protein volumes in the intravascular ($\bar{V}_p$ and $\bar{A}_p$ in Table AI), intact tissue ($\bar{V}_{IT}$ and $\bar{A}_{IT}$ in Table AI), and burnt tissue ($\bar{V}_{BT}$ and $\bar{A}_{BT}$ in Table AI) compartments, capillary filtration rate ($\bar{J}_c$ in Table AI), and lymphatic drainage ($\bar{J}_L$ in Table AI) to list a few. One exception to the linear allometric relationship was the total body surface area (S_B in Table AI), which was made a function of weight through the Haycock formula (Eq. (34c)) and the weight-height relationship reported in the literature [34]. To incorporate the TBSA dependence into pertinent parameters, we (i) made the extensive parameters associated with the burnt tissue compartment functions of TBSA (ϵ_B in Table AI) and (ii) expanded the plausible ranges of subject-specific parameter values associated with burn-induced pathophysiological responses so that the estimated parameter values avoid saturation at the pre-specified upper and

lower bounds. These parameters include those representing the intensity of the inflammatory responses induced by burn injury such as the maximum increase in the capillary pore radius to albumin radius ratio (i.e. pore ratio) in the intact ($M_{\alpha_{IT}}$ in Table AI) and burnt ($M_{\alpha_{BT}}$ in Table AI) tissue capillary bed, the maximum drop in the burnt tissue hydrostatic pressure ($M_{P_{BT}}$ in Table AI), and the maximum increase in the capillary hydrostatic pressure (M_{P_C} in Table AI) to list a few. To make the mathematical model (which was initially developed based on the dataset collected from animals in our prior work [31]) more compatible with human burn patients, we refined the values of a number of parameters that are inherently different between animals and humans according to the literature (see Table AI for references). These parameters include nominal albumin concentration in the intravascular ($[\bar{A}_p]$ in Table AI), intact tissue ($[\bar{A}_{IT}]$ in Table AI), and burnt tissue ($[\bar{A}_{BT}]$ in Table AI) compartments, colloid oncotic pressure constant (C_o in Table AI), nominal capillary hydrostatic pressure ($\bar{P}_c$ in Table AI), and the total body surface area (S_B in Table AI).

2) Mathematical Model Optimization, Training, and Validation

Using the training dataset, we optimized the mathematical model for in-human use by reducing the number of the subject-specific parameters that must be estimated on an individual patient basis. As described above, we down-selected 24 subject-specific parameters in the mathematical model that must be estimated using the hourly UO and LR dose measurements. Noting that the information content in the hourly UO and LR dose measurements may not be sufficient to robustly estimate all these 24 parameters, we capitalized on the training dataset to split the subject-specific parameters into parameters sensitive versus insensitive to the LR dose-UO input-output relationship. Then, we estimated the sensitive subject-specific parameters on an individual patient basis while fixing the insensitive parameters (together with the 34 subject-invariant parameters) at their typical (i.e., group average) values. First, we determined the typical values of all the 24 subject-specific parameters by fitting the mathematical model to the LR dose-UO measurements pertaining to all the patients in the training dataset based on the pooled approach [35]. This task was accomplished by solving the following optimization problem using a multi-start gradient descent method (“globalssearch” in conjunction with “fmincon”) in MATLAB (MathWorks, Natick, MA):

$$\begin{aligned} \bar{\theta} &= \arg \min_{\theta} \bar{J}(\theta) \\ &= \arg \min_{\theta} \sum_{i=1}^N \sqrt{\left(\sum_{k=1}^{D_i} \frac{|u o_i^d(t_k) - u o_i(t_k, \theta)|}{U O_i} \right)^2}, \end{aligned} \quad (1)$$

where $\bar{\theta}$ is the vector of typical values of subject-specific parameters, θ is the vector of 24 subject-specific parameters (i.e., a vector containing the 24 subject-specific parameters in Table AI), N is the number of subjects, D_i is the number of UO measurements for the subject i during the treatment, $u o_i^d(t_k)$ is the value of UO associated with the subject i measured at time t_k , $u o_i(t_k, \theta)$ is the value of UO associated with the subject i at time t_k predicted by the mathematical model for a given θ , and

$U O_i$ is the normalization factor for UO associated with the subject i , which is defined as the range of $u o_i^d$ multiplied by D_i . Second, we classified the subject-specific parameters into sensitive and insensitive groups by quantifying and comparing the degree of inter-individual variability associated with all the subject-specific parameters. This task was accomplished by solving the following optimization problem for fitting with regularization [36] on an individual patient basis using a multi-start gradient descent method (“globalssearch” in conjunction with “fmincon”) in MATLAB (MathWorks, Natick, MA):

$$\begin{aligned} \theta_i &= \arg \min_{\theta} J_i(\theta) \\ &= \arg \min_{\theta} \sqrt{\left(\sum_{k=1}^{D_i} \frac{|u o_i^d(t_k) - u o_i(t_k, \theta)|}{U O_i} \right)^2} + \lambda_p \sum_{l=1}^{24} \left| \frac{\theta(l) - \bar{\theta}(l)}{\theta_l} \right|, \end{aligned} \quad (2)$$

where θ_i is the vector of 24 subject-specific parameters associated with the subject i , λ_p is the regularization weight, and θ_l is the normalization factor for the l -th element $\theta(l)$ of θ , which was defined so that all the elements in θ are homogeneously ranged approximately between 0 and 1. The regularization discourages the parameters from deviating from their respective typical values unless really needed to achieve superior goodness of fit. Hence, the subset of subject-specific parameters exhibiting deviations from the typical values in many subjects may be viewed as subject-specific parameters sensitive to the LR dose-UO input-output relationship. In this paper, we selected sensitive subject-specific parameters as those whose deviations exceeded a threshold value when averaged across all the 120 patients in the training dataset. Third, we ascertained the ability of the mathematical model (with the chosen sensitive subject-specific parameters) to faithfully replicate the UO responses to the LR dose in the training dataset, as well as its physiological plausibility. To this aim, we estimated the sensitive subject-specific parameters by solving the following optimization problem on an individual patient basis using a multi-start gradient descent method (“globalssearch” in conjunction with “fmincon”) in MATLAB (MathWorks, Natick, MA) while fixing the remaining (insensitive subject-specific and subject-invariant) parameters at the respective typical values:

$$\tilde{\theta}_i = \arg \min_{\tilde{\theta}} \tilde{J}_i(\tilde{\theta}) = \arg \min_{\tilde{\theta}} \sqrt{\left(\sum_{k=1}^{D_i} \frac{|u o_i^d(t_k) - y_i(t_k, \tilde{\theta})|}{U O_i} \right)^2} \quad (3)$$

where $\tilde{\theta}$ is the vector of sensitive subject-specific parameters selected by solving Eq. (2) (i.e., it is a subset of θ), and $\tilde{\theta}_i$ is $\tilde{\theta}$ estimated for the subject i . Then, we examined the faithfulness of the mathematical model in terms of (i) normalized mean absolute error (NMAE) [31], (ii) correlation coefficient, and (iii) UO range agreement, all between measured versus model-replicated UO on an individual patient basis, and (iv) Bland-Altman statistics between all measured versus model-replicated UO. We computed the UO range-based agreement by specifying UO ranges of interest and then for each range computing the percentage of actual UO in the range whose model-predicted UO also resides in the same range. In addition, we examined the physiological plausibility of the mathematical

model in terms of (i) both typical and subject-specific model parameter values (e.g., by comparing them with the values reported in the existing literature) as well as (ii) the plausibility of the volume kinetic and kidney function responses predicted by the mathematical model equipped with typical parameter values. We repeated the above procedure to optimize the mathematical model (i.e., Eq. (1)-(3)) so that it can yield minimal number of sensitive subject-specific parameters and adequate faithfulness and physiological plausibility.

Using the test dataset, we externally validated the faithfulness and physiological plausibility of the optimized mathematical model on an individual patient basis, in terms of the same metrics used above.

3) Mathematical Model Analysis

In addition to the optimization and validation of the mathematical model for in-human application (II.C.1-II.C.2), we also sought to garner in-depth insights and expand the knowledge on burn pathophysiology using the mathematical model. In particular, existing literature suggests that patients who are older [37], female [38]–[40], and associated with inhalation injury [37], [41], as well as those who are associated with severe burn injury [37] and/or receive delayed treatment [42] have a higher risk of mortality. The mathematical model already incorporates TBSA and arrival time post-burn, thereby allowing it to predict more severe responses to burn injury associated with large TBSA and delayed resuscitation treatments. However, it does not explicitly account for the effect of age, gender, and inhalation injury.

To investigate if the mathematical model can elucidate the age-, gender-, and inhalation injury-dependent differences in the burn physiological and pathophysiological mechanisms, we fitted the (optimized and validated) mathematical model separately to (i) younger versus older patients, (ii) female versus male patients, and (iii) patients with versus without inhalation injury. We used the patients in the training dataset ($N=120$), since they were associated with consistent treatment durations (i.e., 24 hours monitoring in most patients) compared to the test dataset. We excluded 16 patients since they did not have gender specification. We defined older patients as those with age above the median age of the 104 patients (45 years), and younger patients otherwise. Using these 104 patients in the training dataset, we built the group-average mathematical models associated with younger ($N=52$) versus older ($N=52$) patients, (ii) female ($N=22$) versus male ($N=82$) patients, and (iii) patients with ($N=11$) versus without ($N=93$) inhalation injury, all by solving a hybrid of the optimization problems in Eq. (1) and Eq. (3) (specifically, solving Eq. (1) only with respect to sensitive subject-specific parameters rather than all the sensitive parameters) based on the dataset associated with the specific patient groups. Then, we examined if the model parameter values for the two groups in each of the three categories (age, gender, and inhalation injury) exhibited meaningful contrasting differences that provide clinically important physiological insights.

III. RESULTS

The iterative optimization of the mathematical model using the training dataset resulted in a mathematical model with seven

sensitive subject-specific parameters in total, including the nominal capillary pore radius to albumin radius ratio ($\bar{\alpha}$), the maximum increase in the pore ratio in the intact (M_{aIT}) and the burnt (M_{aBT}) tissue capillary bed, the maximum increase in the capillary hydrostatic pressure (M_{PC}), the slow decay rate associated with the increase in the capillary hydrostatic pressure ($\lambda_{1,PC}$), the tubule-glomerular feedback sensitivity (K_{TGF}), and the nominal water reabsorption rate in the collecting ducts ($\bar{J}_{RR,ADH}$). Table I summarizes NMAE, correlation coefficient, UO range-based agreement pertaining to < 30 , $30 < 50$, and > 50 ml/h, or < 0.5 , $0.5 < 1$, and > 1 ml/kg-hr, and the Bland-Altman statistics (i.e., the limits of agreement), all associated with the optimized mathematical model. Fig. 3 presents examples of actual versus model-predicted UO responses associated with eight patients with various burn injury severity in the test dataset (details discussed in IV.A). Fig. 4 presents volume kinetic and kidney function responses to burn injury and burn resuscitation predicted by the group-average mathematical model in response to group-average burn resuscitation LR dose (details discussed in IV.A). Fig. 5 shows the weight-normalized PV, intravascular water gain (LR dose) and loss (capillary filtration in excess of lymphatic flow), and the burn resuscitation effectiveness (defined as the weight-normalized intravascular water gain rate (i.e., LR dose minus capillary filtration in excess of lymphatic flow) divided by the weight-normalized LR dose) throughout the 24-hour treatment period as predicted by the group-average mathematical model (details discussed in IV.B). Table II summarizes (i) demographics, (ii) statistical characteristics of fluid retention and UO relative to its treatment target range (30-50 ml/hr), and (iii) group-average model parameter values related to burn-induced inflammatory perturbations, all associated with the two patient groups in the three categories.

IV. DISCUSSION

Developing treatment strategies and expanding knowledge associated with burn injury present formidable challenges due to its complex pathophysiology, large inter-patient variability, and its less common incidence compared to other widespread injuries despite its devastating impact on the mortality and the quality of life. High-fidelity mathematical models capable of replicating volume kinetic and kidney function responses to burn injury and resuscitation has the potential to advance both treatment development and knowledge expansion aspects of burn resuscitation. Regardless, to the best of our knowledge, no mathematical model exists that has been developed and extensively validated using clinical datasets from real burn patients. In this paper, we present our continued development, extensive in-human validation, and analysis of a mathematical model for the study of burn injury and resuscitation, which is equipped with contemporary knowledge on the burn-related physiology and pathophysiology.

A. In-Human Credibility

The enhanced/optimized mathematical model based on the training dataset exhibited adequate predictive capability for UO

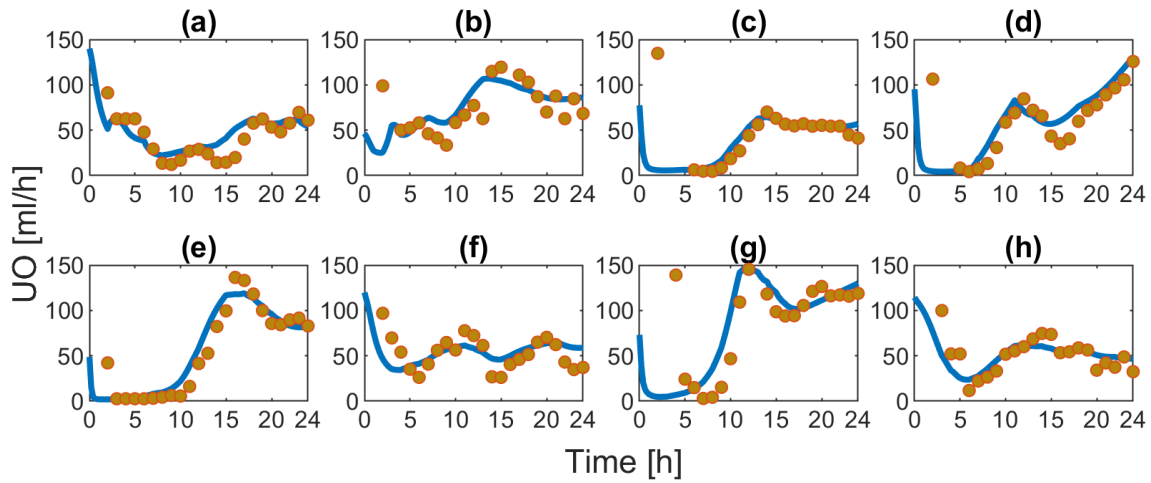


Fig. 3. Actual versus model-predicted urinary output (UO) responses of eight burn patients associated with various injury severity and weight. Circles: actual UO. Solid lines: model-predicted UO. (a) TBSA 27% with 80 kg weight. (b) TBSA 36% with 66 kg weight. (c) TBSA 46% with 90 kg weight. (d) TBSA 60% with 71 kg weight. (e) TBSA 24% with 81 kg weight. (f) TBSA 35% with 94 kg weight. (g) TBSA 50% with 89 kg weight. (h) TBSA 60% with 102 kg weight.

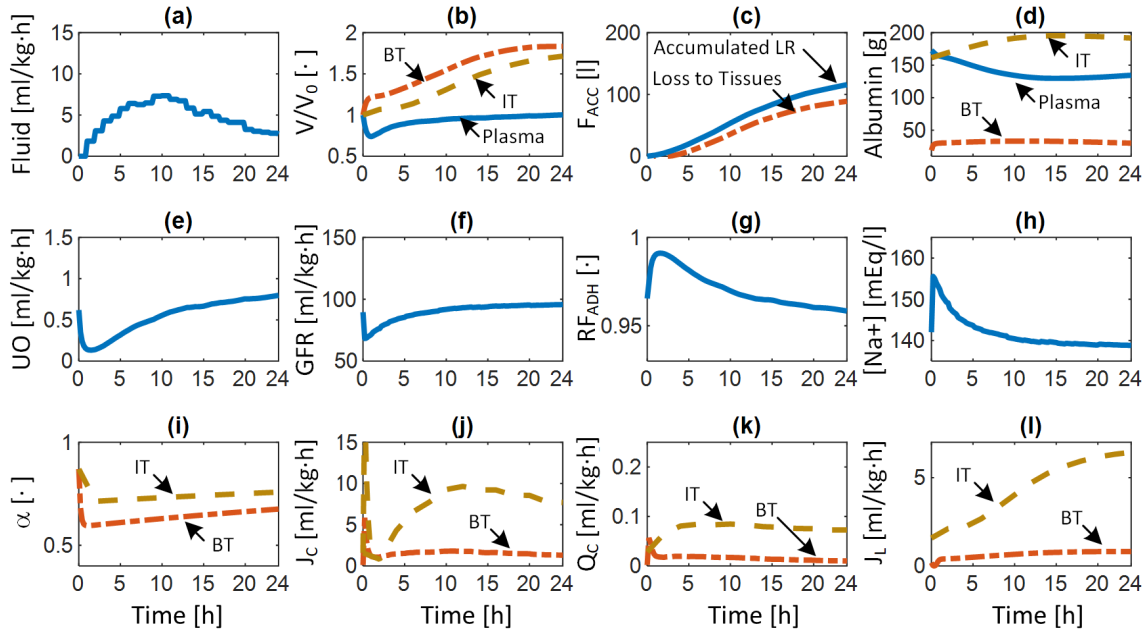


Fig. 4. Volume kinetic and kidney function responses to burn injury and burn resuscitation during initial 24 hours post-burn, predicted by the group-average mathematical model. V/V_0 : water volume relative to its initial value. F_{acc} : accumulated fluid. RF_{adh} : reabsorption fraction due to ADH (see Appendix B provided in Supplementary Document). α : capillary pore radius ratio (see Appendix C provided in Supplementary Document). J_c : capillary filtration. Q_c : albumin transport across the capillary wall. J_l : lymphatic flow. (b) and (d): Blue solid, brown dashed, and orange dash-dot lines correspond to plasma, intact tissues, and burnt tissues, respectively. (c): Blue solid and orange dash-dot lines are weight-normalized accumulated resuscitation LR volume and water loss to tissues (i.e., capillary filtration in excess of lymphatic flow), respectively. (i)-(l): Brown dashed and orange dash-dot lines correspond to intact and burnt tissues, respectively. IT: intact tissues. BT: burnt tissues.

response to burn injury and resuscitation in both training and test datasets (Table I and Fig. 3). In particular, the mathematical model worked equally well in both training and test datasets, both in terms of average statistics and robustness (e.g., NMAE was 15% with small IQR of 6%; Table I). Further, it could capture the physiological differences in burn patients across diverse TBSA range, including those associated with comparable weight ((a) versus (e) and (c) versus (g) in Fig. 3) and those associated with distinct weight ((b) versus (f) and (d) versus (h) in Fig. 3). In addition, the mathematical model showed a high degree of UO range-based agreement (>90% (when weight-normalized) and >78% (when not weight-

normalized) of model-predicted UO resided in the same range to actual UO; Table I). Noting that existing burn resuscitation protocols determine the hourly resuscitation dose based on the range of UO, the results suggest that the mathematical model may serve as a valuable platform for non-clinical testing of burn resuscitation protocols and algorithms.

In addition to UO, the mathematical model was able to predict the overall volume kinetic and kidney function responses to burn injury and resuscitation in a realistic way: the behaviors of the internal volume kinetic and kidney variables were consistent with the contemporary knowledge on burn pathophysiology as well as findings from recent studies (Fig. 4).

Table I. Normalized mean absolute error (NMAE: median (IQR)), correlation coefficient (r value), Bland-Altman statistics (bias $\pm$ 2 $\times$ SD), and range-based agreement (median (IQR)) associated with urinary output (UO) prediction by the mathematical model.

	Training Dataset (N=120)	Test Dataset (N=113)
NMAE [%]	14.8 (6.0)	15.4 (6.0)
Correlation Coefficient (r Value)	0.67	0.82
Limits of Agreement [ml/hr]	-3 $\pm$ 57	+2 $\pm$ 45
UO Range-Based Agreement [%]		
(< 30 , $30 < < 50$, and > 50 ml/h)	78 (15)	83 (14)
UO Range-Based Agreement [%]		
(< 0.5 , $0.5 < < 1$, and > 1 ml/kg-h)	90 (16)	92 (16)

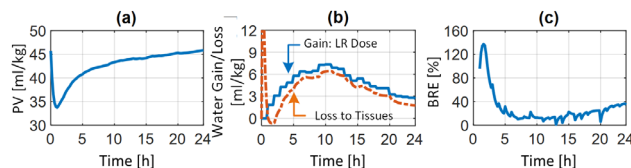


Fig. 5. Group-average prediction of (a) weight-normalized plasma volume (PV), (b) weight-normalized intravascular water gain (LR dose: blue solid) and loss (capillary filtration minus lymphatic flow: orange dashed) rates, and (c) burn resuscitation effectiveness (BRE).

Specifically, the group-average mathematical model predicted that (i) plasma volume and UO showed an anticipated trend of initial decline upon the onset of burn injury and subsequent recovery with the initiation of burn resuscitation and later with the return of resuscitation fluid leaked into the tissues back to the blood (Fig. 4(b), Fig. 4(c), and Fig. 4(e)) [43], [44]; (ii) burnt and intact tissue volumes increased up to nearly twice their initial values, peaking and starting to decay approximately at 24 hours post-burn (Fig. 4(b)) [45]–[47]; (iii) plasma albumin was transported into burnt and intact tissues due to the perturbations in albumin reflection and permeability-surface area coefficients (Fig. 4(d) and Fig. 4(k)) triggered by burn-induced increase in the capillary pore size that decreased the capillary pore radius ratio in both burnt and intact tissue (Fig. 4(i)) [48]; (iv) GFR increased just a few hours post-burn even before plasma volume (Fig. 4(f)) [49]; and (v) sodium concentration decreased after burn injury and resuscitation (Fig. 4(h)) [50].

Importantly, the mathematical model could predict UO as well as physiologically plausible volume kinetic and kidney function responses once physiologically acceptable values were assigned to its parameters. In fact, the majority of the parameters equipped with physiological implications assumed values comparable to typical values and/or those reported in the literature both on the individual and population-average basis (Table AI).

In sum, we demonstrated that the mathematical model can faithfully replicate the volume kinetic and kidney function responses in a wide range of burn patients, both in terms of the adequacy of the model-predicted responses and the plausibility of the model parameter values.

B. Insights on Burn Resuscitation Effectiveness

One strength of the mathematical model presented in this paper is its ability to replicate overall responses of a burn patient to injury and resuscitation, including those that cannot be clinically measured. Exploiting this advantage, we sought to garner insights on the effectiveness of burn resuscitation in a typical patient subject to burn injury. It is known that the

homeostasis in volume kinetics is severely disrupted after burn injury due to the activation of multiple inflammatory mediators, which in turn causes a large portion of the resuscitation fluid to leak out of the intravascular compartment via capillary filtration. Although this leakage is partially recovered by the increase in lymphatic flow, $>50\%$ of the resuscitation fluid can leak out of the intravascular compartment in the initial hours post-burn in extensive burn injury [51], [52]. In this regard, burn resuscitation effectiveness represents the portion of the resuscitation fluid actually used to expand plasma volume. Based on the investigation and interpretation of >50 physiological variables including those presented in Fig. 4 and Fig. 5, we could garner the following insights on the important physiological and pathophysiological mechanisms responsible for the effectiveness of burn resuscitation during the initial 24 hours post-burn. Initially, there is a large and fast fluid shift from the blood to the intact and burnt tissues immediately after burn injury for up to one hour, leading to a large decrease in the plasma volume (Fig. 4(j) and Fig. 5(a)). Our mathematical model suggests that major mechanisms responsible for this initial loss of plasma volume may be negative hydrostatic pressure, protein denaturation in burnt tissues, and systemic increase in the capillary hydrostatic pressure. After this initial phase, a decrease in the capillary filtration and the self-regulation of plasma volume occur for up to one hour. Our mathematical model suggests that major mechanisms responsible for this phase may be the reduction in the plasma volume and the resulting decrease in the capillary hydrostatic pressure, the recovery of hydrostatic pressure in the burnt tissues, and the increase in the lymphatic flow (Fig. 4(l)). The effectiveness of burn resuscitation during this phase is very high ($>100\%$), meaning that plasma volume is expanded based on almost all the resuscitation fluid as well as the fluid returning from the edematous (burnt and intact) tissues (Fig. 5(c)). Subsequently, burn resuscitation effectiveness is deteriorated quickly as the capillary filtration of water and protein increases again due to the opened capillary pores (Fig. 4(i)) and the increase in the plasma volume. Our mathematical model suggests that major mechanisms responsible for this phase may include the increase in the protein concentration in both burnt and intact tissues as well as the hypoproteinemia in the blood (Fig. 4(d)), which altogether increase the osmotic pressure gradient toward tissues and promote capillary filtration of both water and protein (thereby forming a vicious circle). Burn resuscitation effectiveness reaches its minimum level of 2%–15% at 10–15 hours after the initiation of treatment, which is in close agreement with the literature suggesting maximal edema formation in this period post-burn [45]. Finally, burn resuscitation effectiveness increases back to approximately 40% at 24 hours after the initiation of treatment. Our

Table II: Demographics, characteristics of fluid resuscitation, fluid retention, and urinary output (UO) relative to its treatment target range (30-50 ml/hr), and group-average model parameter values related to burn-induced inflammatory perturbations, all associated with the two patient groups in (a) age (younger versus older patients), (b) gender (female versus male patients), and (c) inhalation injury (patients with versus without inhalation injury) categories. Fluid retention is computed as the total resuscitation fluid (LR) volume minus the total UO during the 24 hours of treatment. Fluid resuscitation and fluid retention are shown in mean $\pm$ SD, while UO is shown in median (IQR). $M_{\alpha_{BT}}$, $M_{\alpha_{IT}}$, and M_{P_C} are group-average values of burn-induced inflammatory perturbation parameters in the mathematical model.

(a) Age		
	Younger (N=52)	Older (N=52)
Weight [kg]	86 (21)	84 (15)
Injury Severity (TBSA) [%]	44 (17)	38 (17)
Mortality Rate [%]	18	42
Fluid Resuscitation [ml/kg-%]	3.27 $\pm$ 1.18	4.20 $\pm$ 1.59
Fluid Retention [ml/kg-%]	2.78 $\pm$ 1.16	3.75 $\pm$ 1.6
30 ml/hr $\leq$ UO $\leq$ 50 ml/hr	26 (15)	23 (16)
UO<30 ml/hr	21 (14)	34 (20)
UO>50 ml/hr	53 (18)	42 (20)
$M_{\alpha_{BT}}$	0.23	0.54
$M_{\alpha_{IT}}$	0.19	0.19
M_{P_C}	0.05	1.70
(b) Gender		
	Female (N=22)	Male (N=82)
Weight [kg]	74 (17)	88 (17)
Injury Severity (TBSA) [%]	38 (13)	43 (19)
Mortality Rate [%]	37	27
Fluid Resuscitation [ml/kg-%]	4.0 $\pm$ 1.24	3.67 $\pm$ 1.52
Fluid Retention [ml/kg-%]	3.43 $\pm$ 1.2	3.2 $\pm$ 1.5
30 ml/hr $\leq$ UO $\leq$ 50 ml/hr	28 (14)	24 (16)
UO<30 ml/hr	32 (15)	26 (20)
UO>50 ml/hr	40 (16)	50 (20)
$M_{\alpha_{BT}}$	0.32	0.48
$M_{\alpha_{IT}}$	0.16	0.15
M_{P_C}	2.26	1.73
(c) Inhalation Injury		
	Injury (N=11)	No Injury (N=93)
Weight [kg]	77 (15)	86 (18)
Injury Severity (TBSA) [%]	46 (14)	41 (18)
Mortality Rate [%]	40	29
Fluid Resuscitation [ml/kg-%]	4.33 $\pm$ 1.19	3.66 $\pm$ 1.49
Fluid Retention [ml/kg-%]	3.9 $\pm$ 1.2	3.0 $\pm$ 1.5
30 ml/hr $\leq$ UO $\leq$ 50 ml/hr	24 (16)	24 (15)
UO<30 ml/hr	31 (23)	27 (18)
UO>50 ml/hr	44 (19)	48 (20)
$M_{\alpha_{BT}}$	0.52	0.31
$M_{\alpha_{IT}}$	0.19	0.18
M_{P_C}	1.47	0.13

mathematical model suggests that major mechanisms responsible for this recovery may include the recovery of lymphatic flow to return excessive water and protein to the blood as well as the gradual decrease in the capillary pore size, which altogether decreases the fluid extravasation rate.

C. Cohort-Dependent Differences in Burn Pathophysiology

The analysis of datasets associated with various categorical patient cohorts (with respect to age, gender, and inhalation injury) provided meaningful insights on the cohort-dependent differences in burn physiology and pathophysiology (Table II). To begin with, the mathematical model was able to replicate

UO response to burn injury and resuscitation associated with all the categorical patient cohorts (younger versus older, female versus male, and patients with and without inhalation injury).

First, between younger versus older patients, the latter had much higher mortality rate and higher portion of UO responses below the target therapeutic range than the former despite its smaller group-average TBSA and higher level of weight-normalized LR dose, which leads to higher fluid retention in the latter (Table II(a)). Comparing the mathematical models fitted to younger versus older burn patients, the latter was associated with higher inflammation factors (including the larger increase in capillary pore size in the burnt tissues ($M_{\alpha_{BT}}$) and the capillary hydrostatic pressure (M_{P_C})).

Second, between patients with versus without inhalation injury, the former likewise had >1.3 times higher mortality rate and higher portion of UO responses below the target therapeutic range than the latter (Table II(c)). Comparing the mathematical models fitted to burn patients with versus without inhalation injury, the former exhibited higher inflammation factors (including the larger increase in capillary pore size ($M_{\alpha_{IT}}$ and $M_{\alpha_{BT}}$) and capillary hydrostatic pressure (M_{P_C})) similarly to the older patient cohort. Existing literature shows the possible association between fluid retention and edema versus mortality and complication rates in burn patients [12]. In addition, both literature and our dataset indicate higher fluid retention and edema as well as higher mortality rates in older patients and patients with inhalation injury [53], [54]. From this standpoint, our mathematical model analysis predict that higher inflammation may be a key contributing factor in increasing the mortality risk of older patients and patients with inhalation injury via an increase in the fluid retention. Our prediction is in fact consistent with the contemporary knowledge in the literature identifying inflammation as an important mediator of increased fluid retention and edema with the increased mortality rate in older patients [55], [56] and patients with inhalation injury [57], [58], although other causes can play a role (e.g., degraded cardiovascular efficiency in elderly burn patients [59]). Although our mathematical model analysis reveals possible mechanisms responsible for higher mortality rate, the exact cause is yet to be clearly elucidated. Regardless, lower burn resuscitation effectiveness in older patients and patients with inhalation injury relative to younger patients and patients without inhalation injury remains true, and our mathematical model was able to replicate the age- and inhalation injury-dependent differences in burn resuscitation effectiveness. Hence, our mathematical model may serve as an effective basis to develop and validate burn resuscitation protocols and algorithms suited to these categorical patient cohorts.

Third, between female and male patients, neither the dataset nor the mathematical model showed any meaningful difference in terms of inflammation and fluid retention (Table II(b)). This contrasts against some literature identifying the female gender as a mediator of mortality risk associated with burn injury, as confirmed by our dataset (1.3 times the mortality rate in males). Hence, our mathematical model analysis suggests that higher mortality risk in female burn patients may be attributed to factors other than an increase in the inflammation and the corresponding increase in the fluid retention, especially those

not manifested in the initial 24 hours post-burn. In fact, a prior study performed on mice showed that the difference in the inflammatory responses in female and male subjects was not clear until 6 days post-burn [60]. The exact mechanisms responsible for the gender difference in burn-induced mortality risk are still unknown and must be unveiled.

V. CONCLUSIONS

The main outcome of this paper is a physiologically plausible mathematical model capable of replicating volume kinetic and kidney function responses to burn injury and resuscitation suited to in-human application. To the best of our knowledge, the mathematical model presented in this paper may be the first of its kind developed and extensively validated using large clinical datasets from real burn patients. We anticipate that the mathematical model may provide an attractive platform to conduct non-clinical testing of burn resuscitation protocols and test new hypotheses on burn pathophysiology. Future effort must be exerted to investigate the potential of the mathematical model as medical digital twin for disciplined development and rigorous stress testing of emerging burn resuscitation algorithms and as a cornerstone to expand our understanding of burns.

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