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Development and Validation of a Mathematical Model for Simulation of Hemorrhagic Shock and Fluid Resuscitation

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1. Motivation and Background

❖**Motivation**:

- Physiological closed-loop controlled medical devices offer an exciting opportunity to treat hemorrhage in low-resource settings.
- Such potential also increases the need for regulatory science tools suited to the time and cost-effective evaluation of these devices.

❖**Objectives**:

- To develop a framework for the evaluation of mathematical models intended for use in the computer-aided clinical trials of automated medical devices.
- To validate the mathematical model capable of replicating hemodynamic responses to hemorrhage and fluid resuscitation using the framework.

❖**Background**:

- We have developed a hybrid physics-based and phenomenological mathematical model capable of replicating acute hemodynamic responses to hemorrhage and resuscitation.
- We used in vivo data collected from 27 sheep and 12 pigs undergoing hemorrhagic shock and fluid resuscitation to train and validate the model using a novel validation framework.

Acknowledgment

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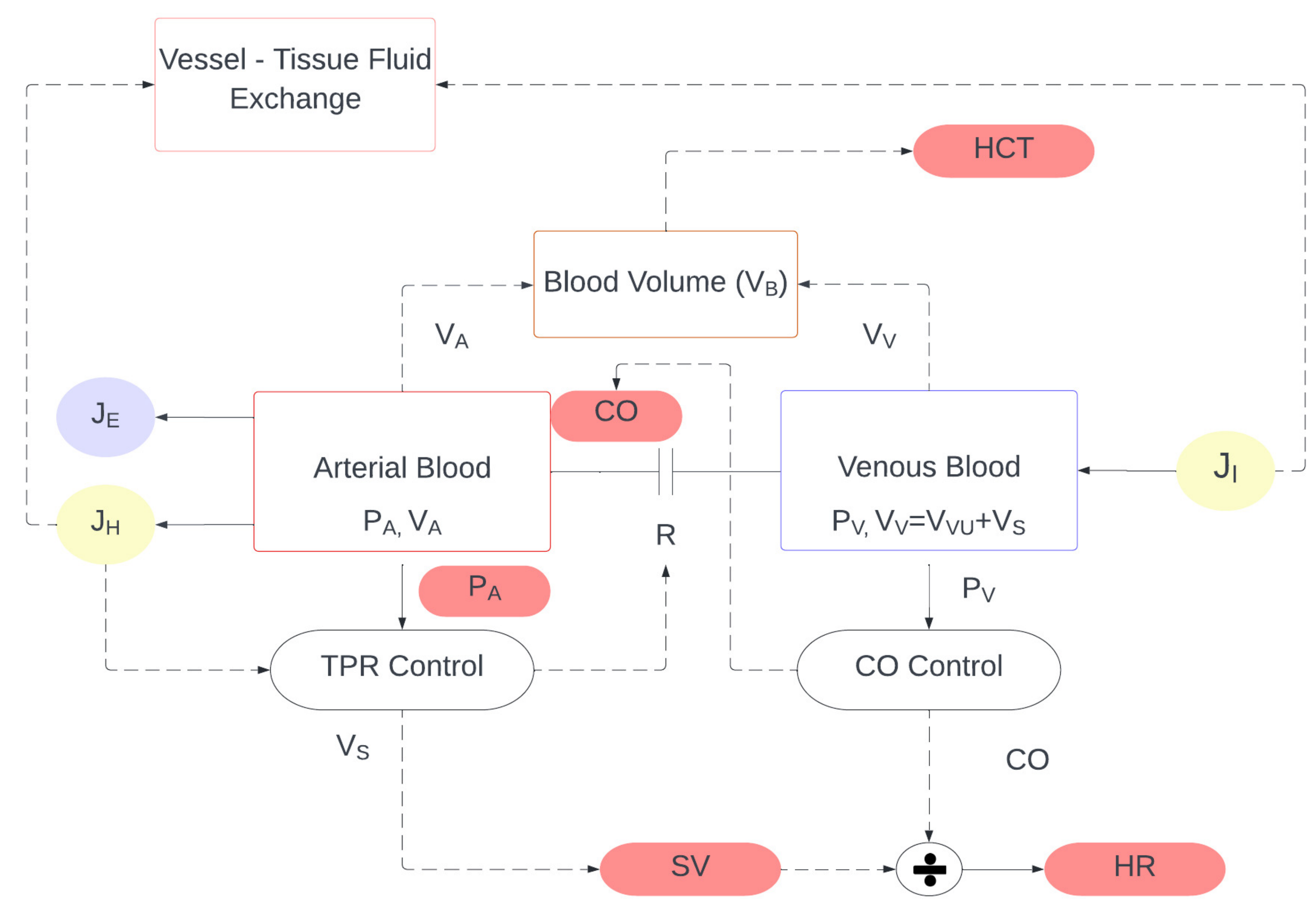
2. Methodology

❖**Mathematical Model**:



- The model takes hemorrhage rate (J_H) and fluid infusion rate (J_I) as inputs, and predicts hematocrit (HCT), cardiac output (CO), mean arterial blood pressure (P_A), stroke volume (SV), and heart rate (HR).

❖**Validation Framework**:

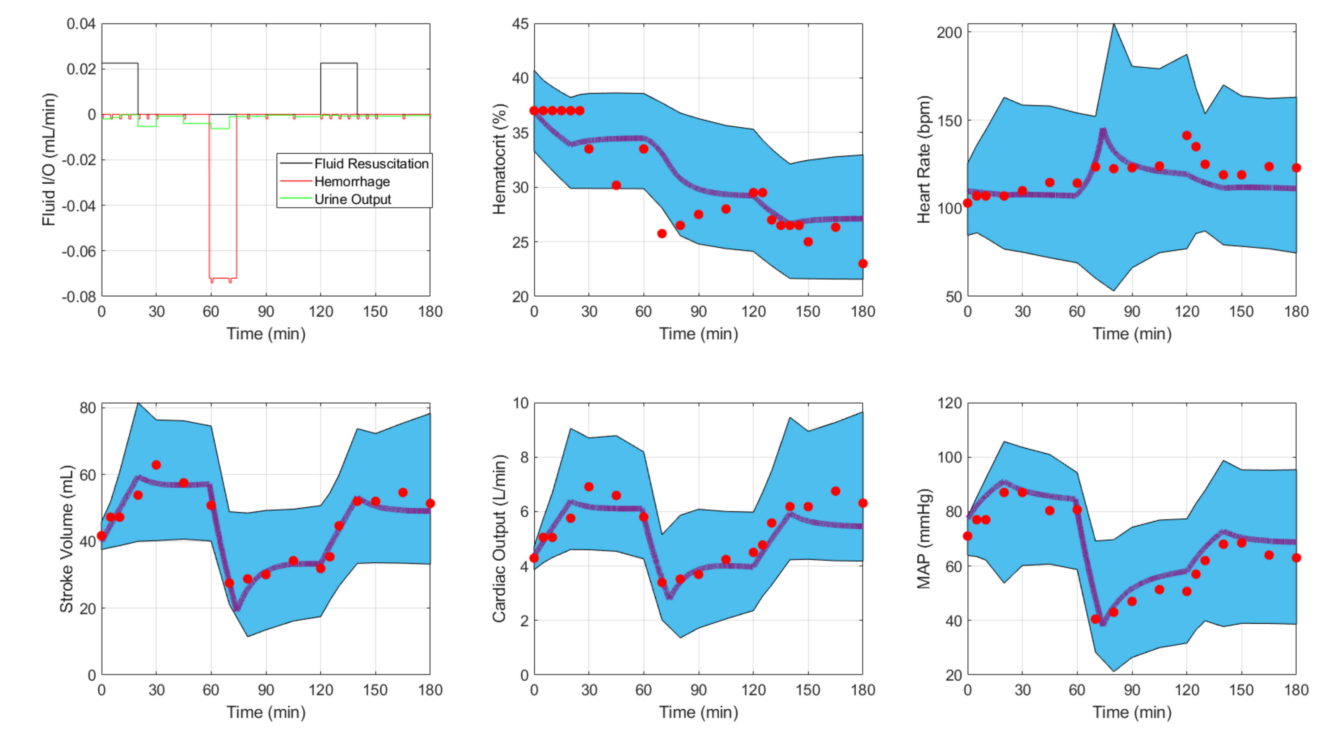
- First, we conducted a leave-one-subject-out (LOSO) analysis using a sheep dataset. Then, we conducted an external validation by training the model on the sheep dataset and validating it on the pig dataset.
- In each round of validation, we generated 50000 virtual patients (VPs) using a novel collective inference method that can learn both subject-level and cohort-level characteristics and used these VPs on the test subjects to qualitatively and quantitatively evaluate the model.
- We calculated two metrics representing the predictive capability performance of the mathematical model:

(i) Closest Root-Mean-Squared-Error (CRMSE) between experimental response of the test subject and the VP closest to the test subject

(ii) Normalized Interval Score (NIS), calculated from the bound formed by the relevant VPs (normalized RMSE =< 25%)

3. Results

- The following plot shows a representative example of the bound formed by the relevant VPs (in blue color), experimental data (in red circles), and the closest VP (as a purple line).



- The following table shows the average RMSE and NIS scores calculated from the LOSO analysis and external validation. NIS is lowest when the bound is smallest and all data points are inside the bound. We consider NIS<1 to be good and NIS<1.5 to be reasonable.

	HCT(%)	CO(lpm)	MAP(mmHg)	SV(L)	HR(bpm)
CRMSE (LOSO)	1±0.6	0.5±0.3	10±4	5±2	24±14
CRMSE (PIG)	2±1	0.5±0.3	8±4	4±3	12±6
NIS (LOSO)	0.7±0.6	1.4±1.1	1.1±0.8	1.2±0.9	1±0.7
NIS (PIG)	0.7±0.5	0.8±0.4	1.2±1.9	1.5±1.7	0.9±0.3

4. Conclusion

- The mathematical model developed in our work could replicate a broad range of hemodynamic responses to hemorrhagic shock and fluid resuscitation even on unseen experimental data.