Improved Hemorrhage and Resuscitation Simulations Validated with Swine Data

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INTRODUCTON

- Hemorrhage is one of the leading causes of preventable death on the battlefield.
- Current validated hemorrhage models focus on the post-injury "golden hour".
- Models representing hemorrhage over prolonged care, including fluid resuscitation are needed.
- Pulse Physiology Engine[1] is an open source computational physiology engine composed of lumped parameter models that represent different systems and equipment (Figure 1).
- These models are coupled with differential equations that represent feedback mechanisms, and PK/PD models.
- In this work, we improve the models to represent tissue death and metabolic effects and validate the model outputs against swine data.

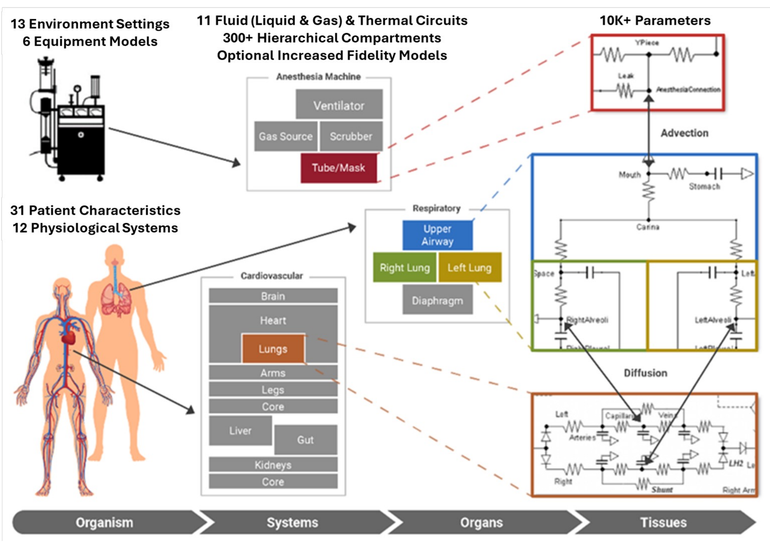

Figure 1: Pulse Physiology Engine

METHODS

Pulse Models

- The Pulse cardiovascular and respiratory circuits are modular and dynamic, enabling the addition of fluid paths for hemorrhage and fluid resuscitation (Figure 2) and the tuning of resistors to the pressure and flow needs of the system.
- A path is added to specific compartments (extremities, spleen, venous) to represent hemorrhage where either a flow rate (A) or a severity (B) can be specified.
- A resuscitation path (C) was added to the venous compartment to administer fluids with a substance and a flow rate specified.
- The baroreceptor model calculates the sympathetic and parasympathetic response of the nervous system and scales the heart rate, mean arterial pressure, venous compliance, and heart elastance.[2]
- The energy model calculates consumption and production of key metabolites, including oxygen, carbon dioxide, and lactate based on the needs of the system.[3]

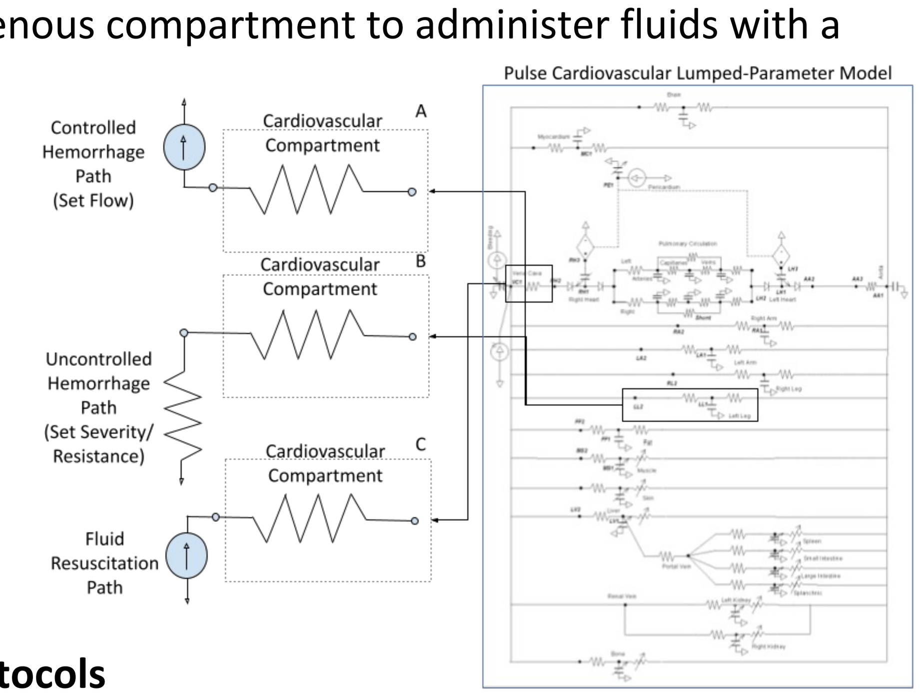

Figure 2: Modular and Dynamic Cardiovascular Circuit

Table 1: Hemorrhage Experimental Protocols

Source	Hemorrhage Protocol	Resuscitation Protocol		Species	Calibration Category
Guyton Et Al[4]	Hemorrhage til Death 100 mL/min	NA		Dog	Baroreceptor
Guyton Et Al[4]	Group 1 – 25% Loss Group 2 – 35% Loss Group 3 – 40% Loss Group 4 – 44% Loss Group 5 – 48% Loss Group 6 – 50% Loss	NA		Dog	Baroreceptor
Frankel Et Al[5] Constant 20	30 mL/kg – 20 min 0 mL/kg – 40 min	RL – 28 mL/min & Blood – 14 mL/min	- 60 min	Swine	Baroreceptor Metabolic
		0 mL/min	- 60 min		
Frankel Et Al[5] Physiologic 20	30 mL/kg – 7 min 20 mL/kg – 13 min	RL – 28 mL/min& Blood – 14 mL/min	- 60 min	Swine	Baroreceptor Metabolic
		0 mL/min	- 60 min		
Treml Et Al[6]	65% Loss – 20 min 0 mL/min – 120 min	NA		Swine	Baroreceptor Metabolic Pulmonary

Table 2: Calibration Parameters and Outputs

Behavior	Parameters	Outputs
Baroreceptor	Heart Rate Scaling Cardiovascular Resistance Scaling Venous Compliance Scaling Heart Elastance Scaling	Mean Arterial Pressure (MAP) Heart Rate (HR) Cardiac Output (CO)
Metabolic	Aerobic Lactate Production	Lactate Blood Concentration
Pulmonary	Pulmonary Shunt Resistance Pulmonary Capillary Resistance	Pulmonary Shunt Arterial Oxygen Partial Pressure (PaO_2) Arterial Carbon Dioxide Partial Pressure ($PaCO_2$)

Model Calibration

- Hemorrhage experiments conducted on dogs and swine were replicated in Pulse (Table 1).
- The experimental data was associated with 3 categories: baroreceptor, metabolic, and pulmonary.
- The parameters and outputs associated with each category are shown in Table 2.

Model Validation

- The experimental protocol on swine show in Figure 3 was simulated with the calibrated Pulse model and compared to data collected by the experimental team at JHU.

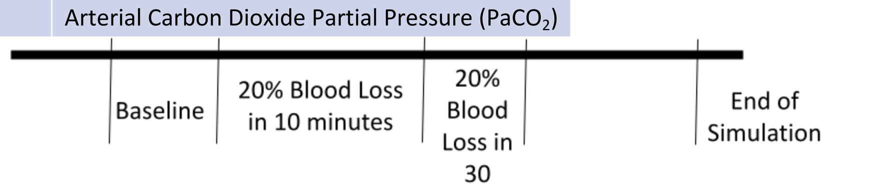

Figure 3: JHU Experimental Protocol

RESULTS

Model Calibration – Guyton Et Al (Figure 3)

- The normalized mean arterial pressure and the cardiac output (Figure 3) were calibrated to fit the Guyton Et Al data with good agreement in the compensatory (A), the rapid decompensation (B), the last-ditch (C), and the failure to survive (D) phases. The last-ditch effort is overly robust in the Pulse model.
- The six groups were likewise compared to the Pulse model results with reasonable agreement. Groups V and VI shown instability representative of a failure to survive.

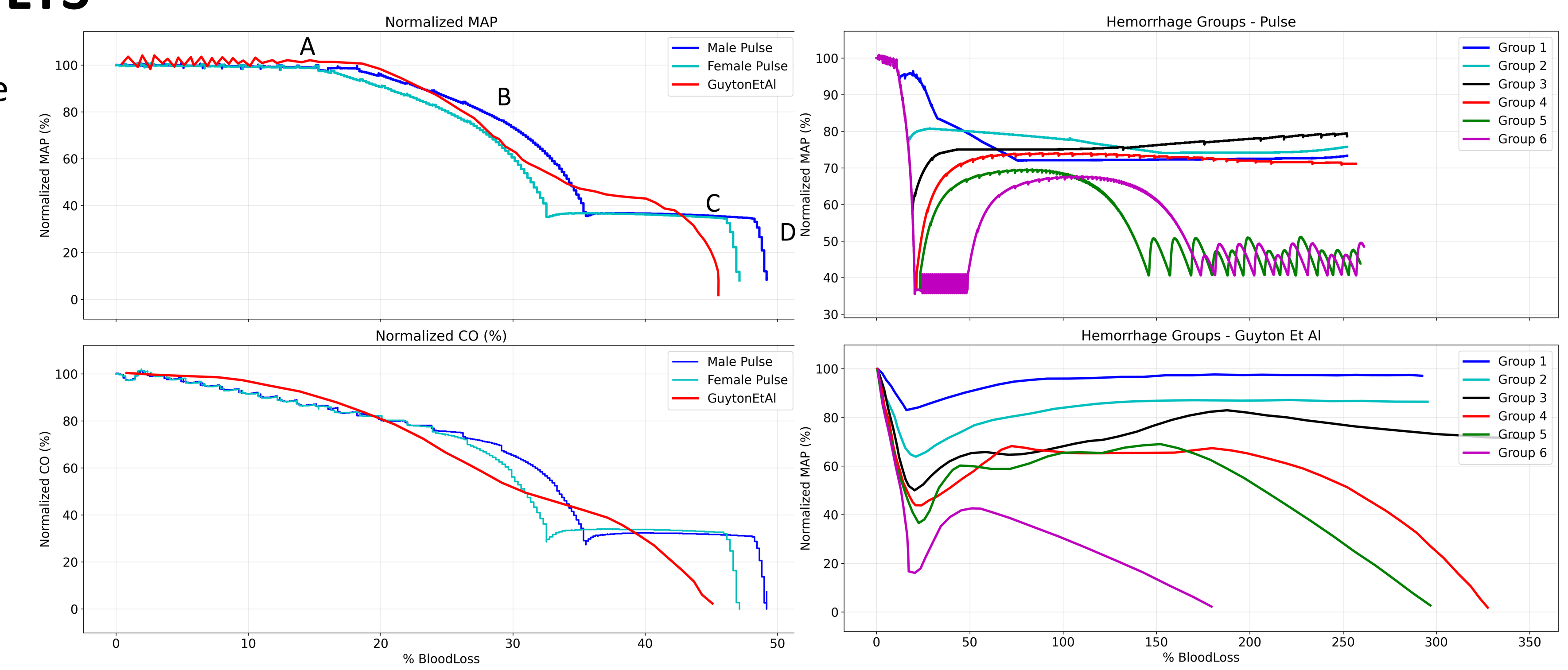

Figure 3: Calibration Results using Guyton Et Al.

Model Calibration – Frankel Et Al (Figure 4)

- The average mean arterial pressure of the swine at baseline was 70 mmHg, which is too low for a healthy human in Pulse to stabilize. The MAP was normalized for comparison.
- The difference in hemorrhage rate has a significant impact on recovery in the Pulse simulations. Pulse also shows the compensatory
- The blood pressure recovery is nearly identical for Pulse simulation and the Frankel et al Constant 20 protocol. While Pulse shows an early recovery prior to fluid resuscitation in the Physiologic 20 protocol.
- The heart rate drops significantly in the Pulse simulations during fluid resuscitation and will need to be further studied.

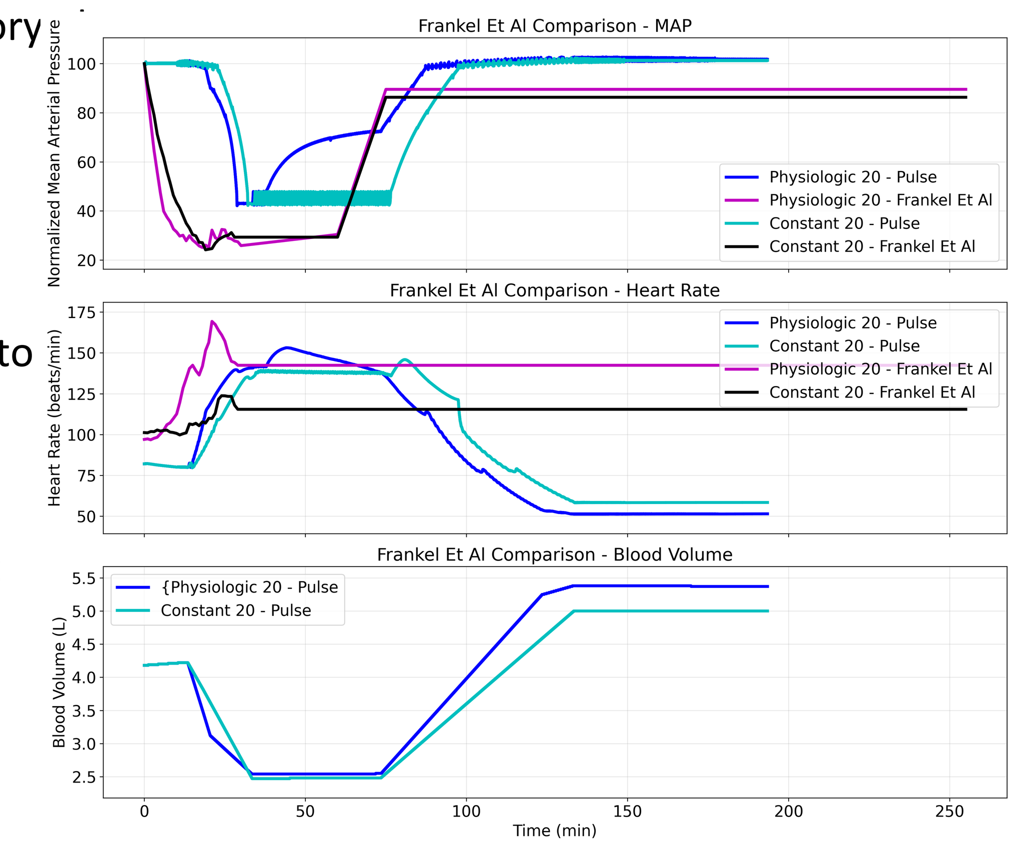

Figure 4: Frankel Et Al Calibration Results

Model Calibration – Treml Et Al (Table 4)

- The blood gas data calculated by Pulse was in direct contradiction to the Treml Et Al data.
- The pulmonary shunt response from Pulse agreed with Treml et al during hemorrhage but deviated post shock.
- The metabolic lactate response met expectations throughout the protocol.
- As with Frankel Et Al, the Pulse heart rate begins to drop in contradiction to the experimental data.

Table 4: Treml Et Al Calibration

Parameter	Baseline	Time 1 - Shock		Time 2 – Post Shock 60 min	
Heart Rate (beats/min) Treml Et Al Pulse	89 71	151 126	PASS	164 104	FAIL
Systemic Arterial Pressure (mmHg) Treml Et Al Pulse	105 115	47 58.8	PASS	50 77	PASS
Cardiac Output (L/min) Treml Et Al Pulse	5.1 5.08	2.6 2.4	PASS	2.0 2.9	FAIL
Lactate (g/dL) Treml Et Al Pulse	15 15.5	44 24.4	PASS	95 94.3	PASS
PaO_2(mmHg) Treml Et Al Pulse	74 87	80 70	FAIL	90 66	FAIL
$PaCO_2$(mmHg) Treml Et Al Pulse	37 40	32 46	FAIL	38 57	PASS
Shunt(%CO) Treml Et Al Pulse	3.9 4.07	1.3 3.06	PASS	0.7 3.85	FAIL

Model Validation

- As with other swine experiments, we do not see the compensatory phase in the JHU experimental data.
- The pressure drop in Pulse is therefore delayed compared to the swine data.
- The overall pressure drop is similar in both the swine data and the Pulse data.
- The heart rate increase is similar when accounting for the initial difference between the simulation and the experiment.

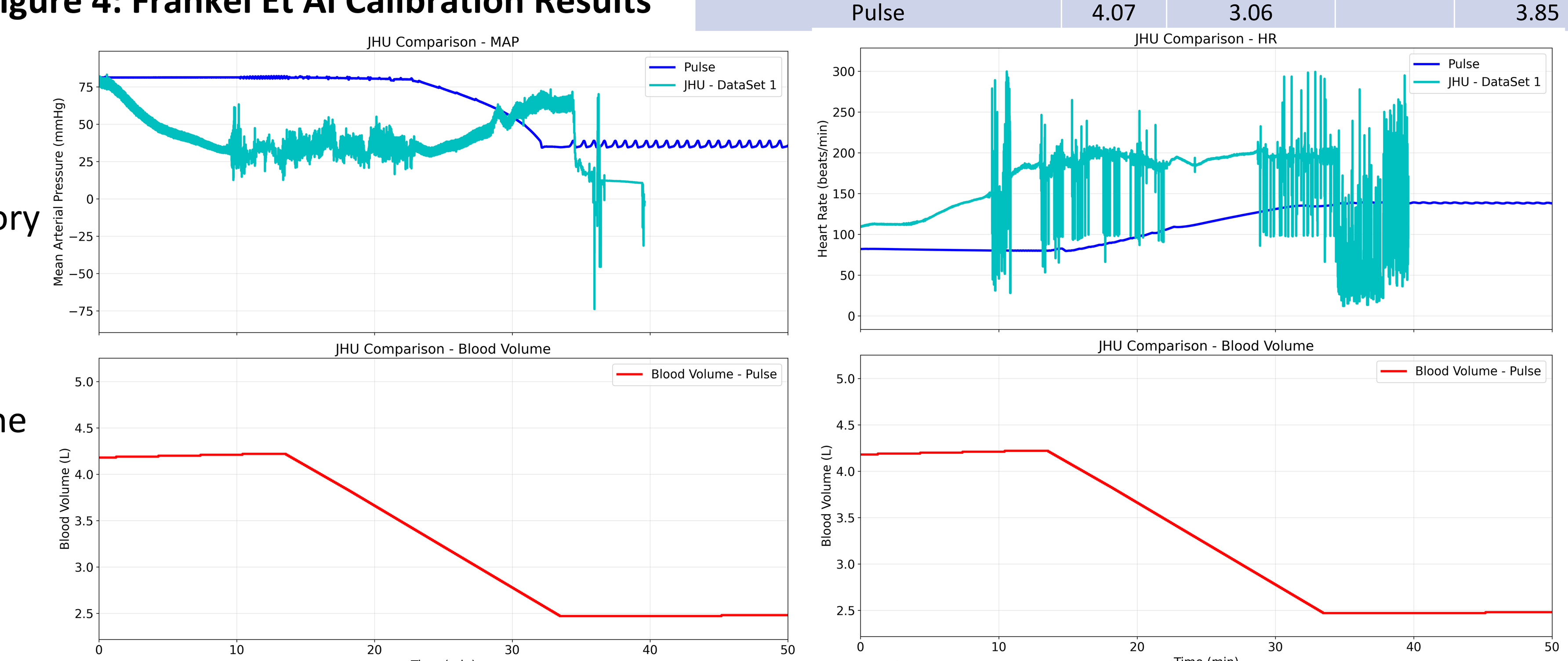

Figure 5: Validation Results

DISCUSSION

- The Pulse model was able to simulate outputs across a range of hemorrhage rates and volumes with and without fluid resuscitation.
- The compensatory phase is widely accepted in human physiology and supported by lower body negative pressure experiments in humans. However, it did not appear in the Frankel et al data.
- The lactate changes were represented accurately by Pulse; however, the blood gases showed contrary trends. It is unclear what physiologic mechanism is causing this response in the experimental data, so further research is required prior to model updates.
- Future work will focus heart rate decline in the Pulse simulations and the blood gas response.
- Further work will also be conducted to compare the simulations to experimental data collected at JHU and Vanderbilt as part of the GoldEvac program.

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