Mathematical Modeling of Hemodynamic Responses to Burn Injury and Resuscitation

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1. Motivation and Background

❖ Background: Burn Injury and Resuscitation
- Thermal injury leads to hypovolemia and circulatory shock via remarkable fluid transfer from blood to tissue
- The goal of burn resuscitation protocol is to restore blood volume hemodynamic stability
- Burn resuscitation is often guided by the urinary output (UO)

❖ Motivation: Model-Based Development and Testing of Burn Resuscitation Protocols
- To aid the systematic development of burn resuscitation protocols
- To evaluate burn resuscitation protocols for effectiveness using in silico and hardware-in-loop testing

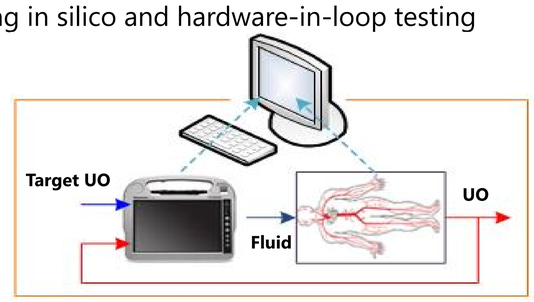


Fig. 1: In-silico testing of burn-resuscitation model

❖ To be useful, the model must predict blood volume and urine output responses to burn resuscitation under hemodynamic changes induced by burn injury **(Fig. 2).**

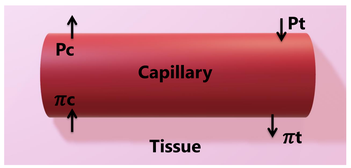
2. Volume Kinetics Model

❖ Comprised of three compartments containing water and protein **(Fig. 3)**:
1) Vascular compartment, 2) Burnt tissue and 3) Intact tissue

❖ The water balance between them and the homeostasis in each is maintained by:
1) Capillary filtration, 2) Lymphatic return and 3) Urinary output

❖ Main volume regulation principles:
1) Conservation of fluid and protein (**Fig. 3, Eq. 1, Eq. 2**)
2) Starling equation describes capillary filtration (**Fig. 4, Eq. 3**)

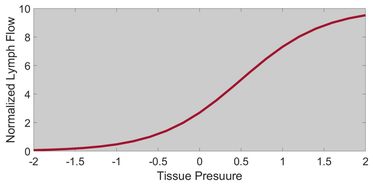
Fig. 4: Schematics of Starling forces. Pc and Pt represent the hydrostatic pressure in capillary and tissue, where πc and πt are colloid osmotic pressure which opposes filtration. Kf and σ are parameters to be identified.
hydrostatic pressure is a function of compartment's fluid volume, where colloid osmotic pressure is dependent on protein concentration.



$$J_{filtration} = K_f \times (P_C - P_t - \sigma \times (\pi_c - \pi_t)) \quad \textbf{(Eq. 3)}$$

❖ When fluid accumulates in the tissue, lymph return increases due to the increased pressure. At the same time, lymphatic valves open, facilitating lymph increase even more. A new model for lymph flow is constructed to allow for:
1) The resultant nonlinear pressure-lymph flow relationship
2) Lymph flow reaching maximum threshold when all valves open, resulting in a bounded increase

Fig. 5: Shows the nonlinear relationship between lymphatic flow and tissue pressure. Despite its linear counterpart, this model can predict behaviors such as the exponential increase in lymphatic return, its nearly zero value in extremely negative pressures, and fluid accumulation as a result of the upper bound exerted on the lymphatic flow.



Proposed Model: Overview

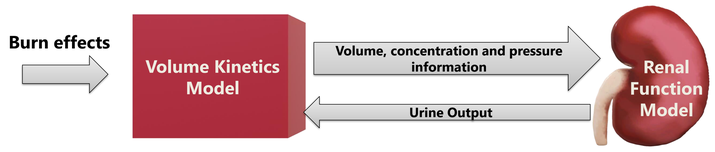


Fig. 2: The desired model includes a 1) **volume kinetic** model capable of predicting **blood and protein** flow assuming isotonic input and output, 2) a **renal function** model predicting **UO** as a function of volume kinetic states, 3) individualized **burn-induced changes** inflicted on volume kinetics model

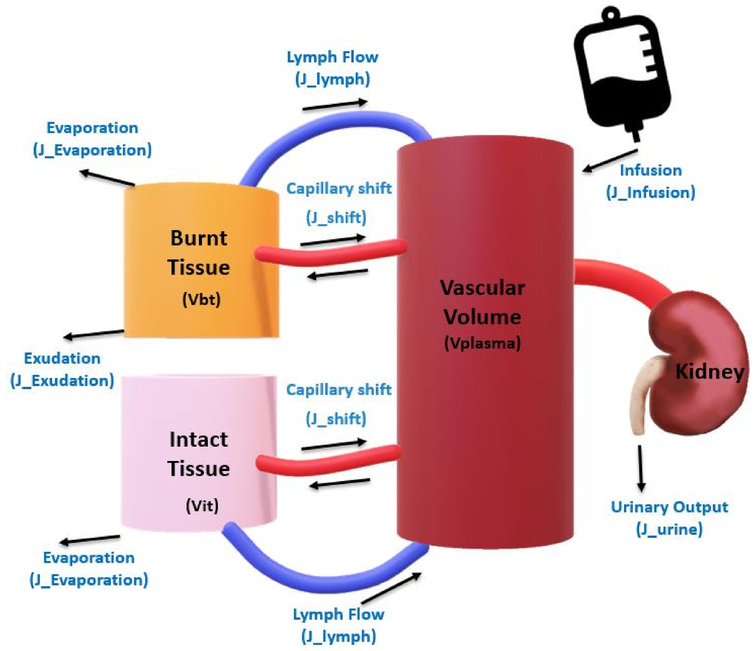


Fig. 3: Shows how different compartments interact. J represents the flow. The positive direction of J_shift is considered to be from plasma to the tissue and is estimated using the Starling equation. Protein flow directions are the same, described by the Coupled Starling Equation.

$$\frac{d(V_i)}{dt} = \sum \pm J_k \quad \textbf{(Eq. 1)}$$

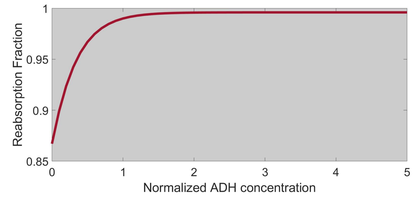
e.g. $$\frac{d(V_{plasma})}{dt} = \sum(-J_{shift} + J_{lymph}) + J_{Infusion} - J_{urine} \quad \textbf{(Eq. 2)}$$

3. Renal Function Model

❖ Based on the physiology of urine output we developed a model comprised of two parts:
1) Glomerular Filtration Rate (GFR) :
   - Modeled as a function of Starling forces in the glomeruli
   - Starling forces modeled as a function of the states of the vascular volume model
2) Water Reabsorption Fraction (RF)
   - Modeled as a dose-response function of anti-diuretic hormone (ADH) concentration
   - ADH secretion rate increase when plasma volume decreases. Considering the fact that its metabolism rate depends on its concentration in blood, ADH can be modeled as a closed loop feedback control system **(Eq. 4)**

$$\frac{d(ADH)}{dt} = -C_1 \times ADH - C_2 \times \Delta V_{plasma} \quad \textbf{(Eq. 4)}$$

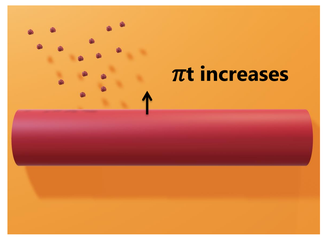
Fig. 6: Illustrates the dose-response relationship between RF, and ADH concentration in plasma. The relationship is steeper when ADH concentration decreases, consistent with the fact that diuresis is more effective than antidiuresis

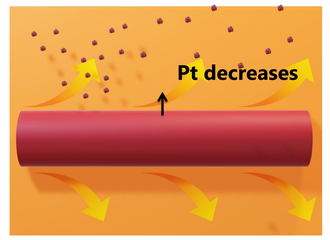


$$UO = GFR \times (1 - RF) \quad \textbf{(Eq. 5)}$$

4. Burn and Fluid Balance

❖ There are three abnormalities happening in burnt tissue, that we believe initiate the chain of events after thermal injury, leading to edema, hypovolemia, hypotension, etc.:

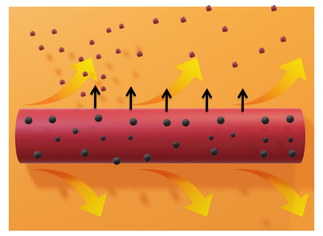




1) Protein denaturation:
- Leads to increased colloid osmotic pressure
- Pulls the water inward

2) Strong negative hydrostatic pressure:
- Affects tissue compliance
- Pulls the water into the tissue

3) Increased Starling Parameters
- Capillary permeability to protein and filtration surface area increase due to inflammation of the capillary wall
- Fluid and protein move from plasma to both burnt and intact tissue



5. Results

❖ The model has been identified and preliminarily evaluated using data recorded from nine sheep with 40% burn and treated with Lactated Ringer (LR) for the first 48 hours postburn

❖ Vascular volume (PV) and UO predictions, variables of interest, are fitted on experimental data (**Fig. 7**, **Table 1**)

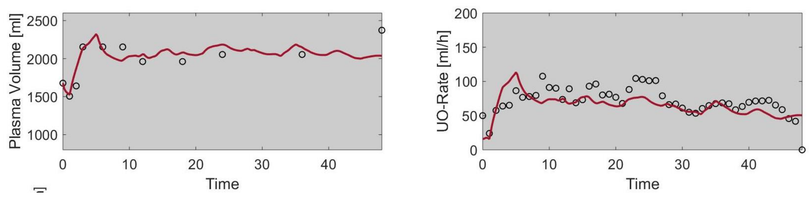


Fig. 7: Plasma volume (left plot) and UO rate (right plot) predictions (solid red line) are shown against experimental data (circles) for one subject. For 7 out of nine subjects the model is able to predict both plasma volume and UO trends with acceptable accuracy.

	Plasma Volume	Urinary Output
RMSE (ml)- Mean(SD)	160(43)	22.1(12)
NRMSE (%)-Mean(SD)	21(2)	17(5)

Table 1: The average of absolute and normalized mean squared error for the nine sheep

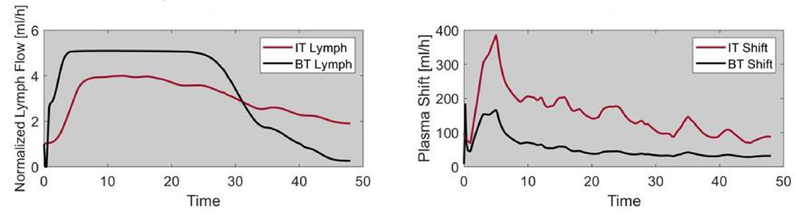


Fig. 8: Lymphatic flow and shift in both burnt and intact tissue for the course of 48 hours postburn. Predictions are consistent with literature

❖ Predictions for lymphatic flow and protein concentration follow the trend reported in experimental data

❖ Predictions for capillary shift, exudation and evaporation are in accordance with the behavior reported in literature

❖ All the identified parameters are within the physiologically meaningful range

Acknowledgment

This material is based upon work supported by the USAMRMC (Contract No. W81XWH-16-C-0179) and National Science Foundation (NSF) CAREER Award (Grant No. 1748762). Any opinions, findings and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the USAMRMC and NSF.