Predictive Capability of a Mathematical Model of Heart Rate Response to Fluid Perturbation

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Background: Physiological closed-loop controlled (PCLC) medical devices control the state of patients by using physiological feedback in a closed-loop manner. These devices are complex systems with a large number of failure modes and parameters that affect performance. In addition, PCLC devices minimize human adjustment of parameters compared to current clinical care, and thus, assessing the performance of this type of device is essential. Validated mathematical models can be used to create virtual patient cohorts to study the performance of PCLC devices under different simulated physiological conditions. However, in silico assessment of PCLC devices raises its own challenges due to the lack of transparent and validated models available and methods for demonstrating their credibility. This research evaluates the predictive capability performance of a physiological mathematical model of heart rate (HR) response to hemorrhagic shock and fluid infusion for the potential role of testing automated fluid resuscitation systems. The initial version of the model was presented at the 2022 Annual STA meeting.

Method: We used our previously developed mathematical model of HR response to blood loss and fluid infusion, built based on a control-oriented modeling approach. The model is evaluated in terms of model predictive capability performance via a leave-one-out procedure (21 sheep subjects) and an independent dataset (6 sheep subjects) collected under a different experimental protocol. The data collection protocols were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Texas Medical Branch [1]. A novel compartment-based virtual cohort generation tool as well as one based on the uniform distribution of individual model parameters were used in each analysis.

Result: Analysis performed using the leave-one-out approach (i.e., 21 subjects) showed that, out of 16000 simulated subjects, the model was able to generate at least one simulated subject that was close to the real subject within an error margin of 9.6+/-3.2% normalized root mean square error (NRMSE). Furthermore, analysis on the independent data collected using a different experimental protocol revealed that, out of 18522 simulated subjects, the model was able to generate at least one simulated subject within an error margin of 11.1+/-1.2% NRMSE for each real subject. The generated envelope of simulated subjects showed that 95% of the testing datasets presented simulated HR patterns that were close to the real data and within a deviation of 50% from the observed data.

Conclusion: We evaluated our previously developed mathematical model of HR in terms of its predictive capability performance. It was shown that the model is able to replicate the normal- and worst-case conditions within the testing dataset. The results show that the model can be incorporated into our existing hemodynamic models to create a virtual cohort of patients for testing PCLC devices for hemorrhagic applications.

References:

[1] A. D. Rafie *et al.*, "Hypotensive resuscitation of multiple hemorrhages using crystalloid and colloids," *Shock*, vol. 22, 2004.

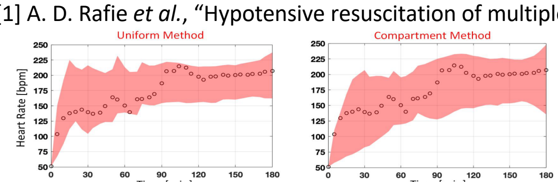

Figure 1: Predictive capability assessment for a fully virtual subject. The plots depict the envelopes of simulated virtual subjects using the independent dataset with the uniform method (left) and the compartment method (right) of cohort generation.