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Physiological Model Selection for in Silico Evaluation of Closed-Loop Controlled Medical Devices

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***Abstract*— Physiological closed-loop controlled (PCLC) medical devices are systems integrating medical devices with a patient's physiology through closed-loop control algorithms. Mathematical models are used throughout the development and evaluation of PCLC devices. Uncertainties about the fidelity of these models need to be addressed before achieving a reliable PCLC evaluation. To identify the best candidate model for in silico evaluation of PCLC devices, this research develops tools for assessing and comparing accuracy and predictive capability performance across multiple models.**

***Clinical Relevance*— This research develops tools to support the safety and effectiveness of PCLC medical devices, thus promoting public health.**

I. 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. Amid the high cost and ethical challenges in clinical trials, computational models have been used to assess the safety and effectiveness of PCLC devices. Uncertainties about the quality and fidelity of mathematical models and ambiguities about choice of measures for modeling performance need to be addressed before PCLC devices can be reliably evaluated. For instance, inputs to and boundary conditions of a model could be outside of the ones used 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 [1].

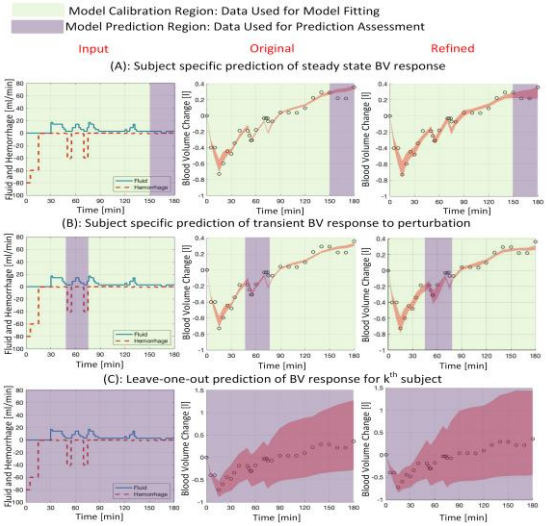

Figure 1. Predictive capability assessment in a representative subject under three scenarios; upper panel: prediction of steady state BV response, middle panel: prediction of transient BV response to blood loss, lower panel: prediction of leave-one-out inter-subject BV response.

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II. METHODS

A refined mathematical model of blood volume (BV) response was built by expanding an original one we previously developed [2]. We used the experimental data collected from 16 sheep undergoing fluid perturbation. First, the calibration performance of the two candidate models, i.e., original and refined, was compared using root-mean-square error (RMSE), Akaike information criterion (AIC), and a new multi-dimensional approach that examines four normalized features, i.e., bias, trend of error over BV range and time, and standard error of residuals, all extracted from the model fitting error. Second, predictive capability of the two models was compared 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.

III. RESULTS

The refined model demonstrated a significant calibration performance improvement in terms of RMSE (9%, $P = 0.03$) and multi-dimensional measure (48%, $P = 0.02$), while a comparable AIC between the two models suggested that its enhanced calibration performance is not due to data over-fitting. Results also indicated enhanced accuracy and predictive capability performance for the refined model with significantly larger proportion of measurements that were within the prediction envelope in the transient and leave-one-out prediction scenarios ($P < 0.02$). Figure 1 shows predictive capability assessment under the three scenarios in a representative subject.

IV. DISCUSSION & CONCLUSION

This study helps to identify new methods for credibility assessment and model selection for PCLC medical device evaluation.

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