Physiological model selection for in silico evaluation of closed-loop medical devices

Ramin Bighamian[1], Jin-Oh Hahn[2], George Kramer[3], Christopher Scully[1]
[1]Office of Science and Engineering Laboratories, Center for Devices and Radiological Health, United States Food and Drug Administration, Silver Spring, MD, USA
[2]Department of Mechanical Engineering, University of Maryland, College Park, MD, USA [3]Department of Anesthesiology, The University of Texas Medical Branch, Galveston, TX, USA

Abstract

- Physiological closed-loop controlled (PCLC) medical devices are complex systems integrating one or more medical devices with a patient's physiology through closed-loop control algorithms. PCLC medical devices may introduce many failure modes and parameters that impact performance.
- These control algorithms should be tested through safety and efficacy trials to compare their performance to the standard of care.
- Mathematical models have been developed and used throughout the development and evaluation phases of a PCLC device. Uncertainties about the fidelity of these models need to be addressed before a reliable PCLC evaluation is achieved.
- To identify the best candidate model toward in silico evaluation of PCLC devices, this research develops tools for properly assessing model accuracy and establishes fundamental measures for evaluating predictive capability performance across multiple models.

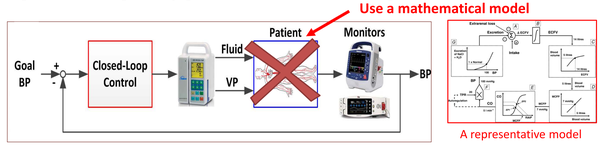


Figure 1. In silico evaluation of closed-loop algorithms

Introduction

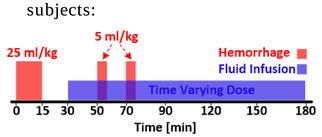
- Per IEC 60601-1-10 standard for requirements for the development of PCLCs, the responses of a PCLC shall be specified during normal use, including worst-case patient transfer element and conditions. Thus, mathematical models should be able to generate these worst-case conditions.
- Prior studies have mostly quantified the accuracy of models by comparing experimental data and responses computed by a mathematical model calibrated (fitted) to those data. For a model to be used for PCLC medical device assessment, however, inputs and boundary conditions could be outside of the ones 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.
- To address this, as a case study, this research examines the adequacy of two lumped-parameter mathematical models of patient physiology developed for evaluating PCLC fluid resuscitation devices:

  ❖Original model of blood volume (BV) response developed in our prior research "Front. Physiol. 2016; 7: 390".

  ❖Refined model of BV response built by expanding the original model.

Materials and Methods

- Model parameters in both original and refined BV models are identified by solving an optimization problem using data from 16 animal (sheep) subjects:



Type of Fluids	Lactated Ringer (LR) Hextend (Hex)
Number of Subjects	(LR) 11, (Hex) 5
Hemorrhages/ Infusion Time	15, 5, 5 min / 150 min
Hemorrhage Dose	25, 5, 5 ml/kg
Fluid Dose	Time Varying

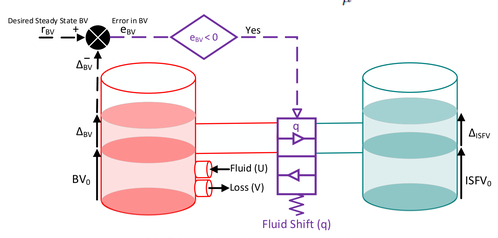
Figure 2. Experimental protocol and fluid type information

Eq. 1 $$\Delta BV(t_k) = \Delta\hat{B}V(t_k)|\Theta + \epsilon(t_k)$$

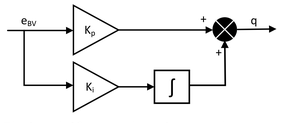
Eq. 2 $$N(\epsilon; 0, \sigma^2) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\{\frac{-1}{2\sigma^2}(\Delta BV(t_k) - \Delta\hat{B}V(t_k)|\Theta)^2\}$$

Eq. 3 $$L^*(\Theta, \sigma) = -\frac{K}{2}\ln(2\pi) - \frac{K}{2}\ln(\sigma^2)$$
$$-\frac{1}{2\sigma^2}(\Delta BV(t_k) - \Delta\hat{B}V(t_k)|\Theta)'(\Delta BV(t_k) - \Delta\hat{B}V(t_k)|\Theta)$$

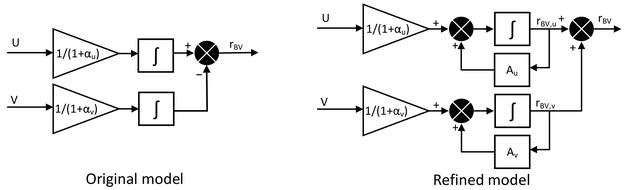
Eq. 4 $$\mu^{ML} = \{\Theta^*, \sigma^*\} = \arg\min_{\mu}(-L^*(\Theta, \sigma) + 2\gamma\|\Theta\|_2)$$



(A) Blood volume model structure



(B) Fluid shift mechanism sub-model



(C) Desired steady state blood volume sub-model

Figure 3. Lumped parameter original and refined models of blood volume response to fluid infusion and hemorrhage.

Results and Discussion

Both models are structurally and practically identifiable:

❖ It was shown that subject to a rich perturbation applied to the system, model parameters in both models are fully identifiable.

❖ A global sensitivity analysis (G) performed by simultaneously varying all parameters through their entire identified range indicated that all the parameters are significant and sensitive.

$$G_i^{Original} = \begin{array}{c} \\ \alpha_u \\ \alpha_v \\ K_p \\ K_i \end{array} \begin{array}{c} \begin{array}{cccc} T30 & T80 & T120 & T180 \end{array} \\ \begin{pmatrix} 0.004 & 0.491 & 0.698 & 0.795 \\ 0.830 & 0.442 & 0.270 & 0.177 \\ 0.014 & 0.021 & 0.014 & 0.015 \\ 0.153 & 0.046 & 0.018 & 0.012 \end{pmatrix} \end{array}$$

$$G_i^{Refined} = \begin{array}{c} \\ A_u \\ A_v \\ \alpha_u \\ \alpha_v \\ K_p \\ K_i \end{array} \begin{array}{c} \begin{array}{cccc} T30 & T80 & T120 & T180 \end{array} \\ \begin{pmatrix} 0.002 & 0.342 & 0.364 & 0.296 \\ 0.239 & 0.402 & 0.478 & 0.631 \\ 0.002 & 0.100 & 0.020 & 0.024 \\ 0.639 & 0.148 & 0.106 & 0.049 \\ 0.096 & 0.002 & 0.016 & 0.001 \\ 0.022 & 0.005 & 0.016 & 0.001 \end{pmatrix} \end{array}$$

Both models are transparent:

❖ Hex is made of larger molecules as compared with LR. Thus, the body keeps the fluid longer in the intravascular space. This phenomenon was indicated by smaller α_u in the original model and larger A_u in the refined model, both under HEX administration. See Table 1.

❖ The original model dictates the reference blood volume (r_{BV}) to update only during fluid perturbation. However, r_{BV} can change continuously over time based on an individual's physiology. This phenomenon was only seen in the refined model.

Table 1. Calibrated parameters for the original and refined models across Lactated Ringer's (LR) and Hextend (HEX) fluid administration

	A_u	A_v	α_u	α_v	K_p	K_i
Original Model (LR)	-	-	1.72±0.66	1.06±0.78	0.08±0.04	0.003±0.001
Original Model (HEX)	-	-	-0.18±0.31	0.91±0.46	0.13±0.08	0.007±0.004
P-value (Original)	-	-	**2e-6**	0.63	0.25	0.09
Refined Model (LR)	-0.16±0.23	-0.007±0.006	0.20±0.69	0.60±0.47	0.28±0.36	0.01±0.01
Refined Model (HEX)	-0.004±0.006	-0.006±0.005	0.06±0.27	0.64±0.30	0.19 ±0.14	0.01±0.003
P-value (Refined)	**0.04**	0.63	0.30	0.83	0.47	0.57

Refined model can serve as a better model in terms of calibration performance:

❖ The refined model had significantly smaller root-mean-square error (RMSE). See Table 2.

❖ The refined model had significantly better performance as of the multi-dimensional measures. See Table 2.

❖ Both models were similar in terms of Akaike information criterion (AIC). Thus, better fitting performance in the refined model was not trivial.

Table 2. Calibrated parameters for the original and refined models across Lactated Ringer's (LR) and Hextend (HEX) fluid administration

	RMSE	AIC (FR)	Multi-dimensional 4-D features & Euclidean distance
Original Model	60.4±73.2	-96.5±36.2 (8)	[0.24±0.29,0.24±0.23,0.14±0.24,0.22±0.29] & 0.46±0.49
Refined Model	55.4±68.1	-100±35.1 (8)	[0.11±0.16,0.20±0.19,0.06±0.07,0.14±0.17] & 0.31±0.27
P-value	**0.03**	0.06	**0.03±0.03** & **0.02**

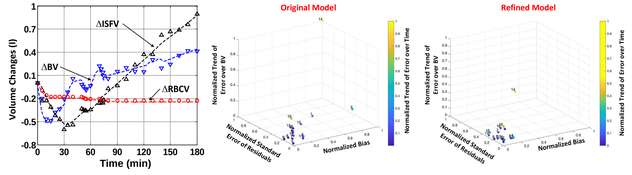


Figure 4. A representative fitting performance (left) and multi-dimensional measure shown for 16 individuals in both original (middle) and refined (right) mathematical models..

Refined model has better predictive capability performance:

❖ Refined and original models showed comparable prediction performance in the steady-state BV response scenario. See Table 3.

❖ Enhanced prediction performance of the refined model was the most evident in the transient BV response scenario. See Table 3.

❖ The refined model led to a significantly larger proportion of measurement within the prediction envelope for the leave-one-out scenario. See Table 3.

Table 3. Predictive capability assessment for different prediction scenarios. S: interval score which rewards a forecast for narrower prediction envelope and penalizes if prediction is outside of the envelope. PM: Proportion of measurements within the prediction interval

	$S_{150-180}$	$PM_{150-180}$	S_{45-80}	PM_{45-80}	$S_{Leave-One-Out}$	$PM_{Leave-One-Out}$
Original Model	2.4±3.6	24%	2.1±2.4	28%	1.0±1.6	88%
Refined Model	2.7±3.8	27%	1.7±2.4	43%	1.0±1.3	94%
P-value	0.34	0.81	**7e-4**	**0.02**	0.79	**3e-3**

Figure 5. A representative predictive capability assessment across the original and refined mathematical models under three scenarios.

Conclusion

As a case study, we used two physiological models of BV response to fluid perturbation; one developed in our prior work and another expanded from the original model in this research. The models were compared in three aspects of identifiability and interpretability, model calibration, and predictive capability performance. We showed that between the two candidate mathematical models, the refined model performed better, or at least comparable, in all three aspects and thus, it could offer more credibility toward PCLC medical device assessment.