State of Validation Evidence for Computational Models Used for Design and Evaluation of Physiological Closed-Loop Mechanical Ventilation Devices

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Background: Mathematical models of physiological systems have potential to contribute to the design and evaluation of innovative and emerging safety-critical closed-loop mechanical ventilation systems. By leveraging such non-clinical test methods, it is possible to perform rigorous stress testing of controllers in a wide range of simulated challenging clinical scenarios. One of the biggest hurdles facing model-based design and evaluation of closed-loop mechanical ventilation is model validation and absence of a validation framework. In the fields of computational sciences, validation of the computational model of the system including assessing the uncertainty of the model form, parameter identifiability/sensitivity analysis, and uncertainty quantification is a critical component to enabling confidence in the testing results that rely on the model [1].

Methods: A literature review was performed to characterize state of validation evidence for models used in design and evaluation of closed-loop mechanical ventilation devices. The search was conducted based on articles found in Web of Science using the following criteria: 1) keywords such as closed-loop control, mechanical ventilation, and computational mathematical model/simulation. 2) The span of search was from 1980 to 2017. 3) The results were narrowed mathematical modeling studies specifically focused on the design and/or evaluation of closed-loop mechanical ventilation devices. Overall, 16 articles were reviewed.

Results: There have been some foundational modeling efforts [2-5] which have been referenced by authors in subsequent studies towards the design and evaluation of closed-loop mechanical ventilation systems. Robust objective validation evidence, such as information on and rationale for model form, selection/ identification of parameters, parameter sensitivity analysis, and uncertainty quantification were scarce, fragmented and in some cases [5] could not be found. Additionally, quantitative assessment of model performance on independent data either has not been conducted [3,5] or has been conducted under test inputs different than those in ICU, such as exercise and for a narrow range of model outputs [2]. Such foundational studies, while lacking basic validation evidence for their model use as a tool for design and evaluation automated mechanical ventilators, often were utilized in other studies (either by the same authors [6-8,18] or by other investigators [9,10], which invites additional modifications to the model, such as simplification of model structure [9,11], simplifying assumptions on model parameters (i.e. keeping them constant) [11-13], and addition of sub-models [14]. Such modifications are often done with minimal consideration to basic validity and context of use of the original model and without justification that the previous validation results apply despite model modifications. This further complicates the validation of such models and hampers their utility for design and regulatory evaluation of automated mechanical ventilators. Recent data-driven modeling [15-17] are reported where models were directly developed from data to estimate parameters of underlying physiology. The models developed by [15, 16] were tuned using clinical data. However, a robust sensitivity analysis could not be found in [16] and for [15] the sensitivity analysis was not followed by a quantification of uncertainty in model parameters or inputs. The models were evaluated on calibration data but performance criteria were not established prior to the evaluation of the calibration procedure. Furthermore, it appears that the extent of validation stopped at the calibration level, and that the models were not evaluated on independent data to assess predictive capability of the model [15-17] before it was used in the context of design and/or evaluation of the controller.

Conclusion: Rigorous model validation has not been reported in the literature for design and evaluation of closed-loop mechanical ventilation. A framework for evaluation of such model to assist in evaluating the validity of the model with specific attention to concepts such as identifiability, parametric sensitivity, and uncertainty quantification [18] is needed.

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