Validation and Uncertainty Analysis of Physiological Models

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Objectives: Mathematical modeling of human physiology is becoming standard practice in drug development, and it is a critical source of insights for medical research. Physiological models that address specific R&D decisions provide significant value and offer considerable predictive power. These models are ideal for addressing the key scientific and clinical uncertainties that are at the core of decisions. Such uncertainties typically fall into two distinct categories: parametric and structural. Parametric uncertainties refer to specific model parameters and play a critical role when the model is used to design clinical trials or other major experimental studies. In contrast, structural uncertainties refer to model structure – e.g., competing hypotheses – and play an essential role when the model is used for investigation, for example, to understand drug-disease mechanisms of action or sources of disease and drug-action variability across patients. Whether the model is used for trial design or as an investigational tool, proper model validation is critical because it reassures scientists that model results are reliable. For medium to large physiological models, validation can be difficult because it requires that model uncertainties be properly assessed. Many characteristics of the underlying physiology, such as cooperativity and dynamics, make the assessment of such uncertainties particularly challenging. Rosa routinely uses physiological modeling to support decision-making in pharmaceutical R&D and has developed specific methodologies to validate models and assess parametric and structural model uncertainties.

Methods: To assess model uncertainties and validate a model we use a multistep approach that applies a standard set of testing criteria defined before the model is built, with additional criteria added as required. The testing process is iterative throughout the model-building process. At first, the model's overall scientific basis, differential and algebraic equations, pathway structure, and supporting data are reviewed. Hypotheses and assumptions are documented within the model. Secondly, we evaluate each pathway and/or module separately and compare its predictions to external data that were not made available when the model was built. Then, the entire model is evaluated by comparing predicted output to comparator data from multiple comprehensive experiments. Finally, we apply sensitivity analysis to establish appropriate parameter ranges and to assure that the accuracy of the parameters is appropriate for using the model either as an investigational tool or for trial design.

Results: We will first show model validation and testing results and provide examples of how the validation procedures were integrated into the model development. Then, using case studies we will explain how the validation process altered model development. Lastly, we will show how the validation process yielded a reliable model and how this reliability affected the decision making process.

Conclusions: When used for decision-making, medium to large physiological models can be validated and their uncertainties reliably assessed. Validation and uncertainty assessment are critical whether the model is used for investigation or for trial design. The validation process makes explicit the assumptions and hypotheses that were used to develop the model, contributes to decision clarity, and increases user understanding of model function. Physiological model validation can generate decision-making insight, particularly regarding chronic, progressively degenerative diseases and/or novel drug targets. Validation and uncertainty assessment should become an integral component of any physiological model development endeavor.