

Title: Validation and Uncertainty Analysis of Physiologic Models

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Objectives: Mathematical modeling of human physiology is becoming a standard in drug development, and is a critical source of insights for medical research. Physiologic models focused on addressing specific R&D decisions provide value and offer significantly predictive power. When these models are utilized as part of a decision making process, some scientific uncertainties are addressed in the model. However, in building physiologic models, we need to address model uncertainties, both parametric and structural. Understanding the model uncertainties enables the user to better understand and manage the scientific uncertainties in the decision. Model validation reassures the user that the model will function appropriately if the model is used as an exploratory tool or if the model is used for trial design. Medium to large physiologic models can be difficult to validate, and it can be difficult to assess the model uncertainties. Many of the characteristics, such as cooperativity and the dynamics, which make physiologic models useful for complex disease and drug analysis problems, also make standard uncertainty analysis of the model difficult. Rosa routinely uses physiologic modeling to support decision-making in pharmaceutical R&D and has developed specific methodologies to validate models and analyze model uncertainties both parametric and structural.

Methods: To evaluate model uncertainties and validate a model we use a multi step approach which has a standard set of testing criteria defined before the model is built, with additional criteria added as needed. The testing process is iterative throughout the model building process. First, we review the mathematic equations and formulas, pathway structure in the model, scientific basis, and data used to build the model. Hypotheses and assumptions are documented within the model. Second, we evaluate each pathway and/or module separately and compare its predictions to external data which were not used to build the model. Then, the entire model is evaluated by comparing predicted output to comparator data from multiple comprehensive experiments. Finally, we employ sensitivity analysis to establish appropriate parameter ranges and to assure that the accuracy of the parameters is appropriate for the use of the model either as an exploratory tool or in trial design.

Results: We will show the validation and the testing results for a model and provide examples of how the validation procedures were integrated into the model development. We will provide case studies to explain how the validation process altered model development. Lastly, we will show how the validation process rendered the model reliable and how this impacted the decision making process.

Conclusions: Medium to large physiologic models can be validated and the model uncertainties evaluated, and the process is critical whether the model is used for exploration or for decision making. The validation process makes explicit the assumptions and hypotheses that were used to develop the model and contributes to decision clarity. The process of validating the model increases user understanding of model function, and this can provide insight directly relevant to decision-making especially in complex chronic diseases and for novel drug targets. Validation and uncertainty analysis should be incorporated into the development of all physiologic models.