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 specific R&D can be difficult to assess and validate. Many model characters, such as synergies, crosstalks, and dynamics, which make physiologic models useful for complex diseases and drug analysis problems, also make model validation difficult. Rosa routinely uses decision-focused physiologic modeling − PhysioPD™ modeling − to support decision-making in pharmaceutical R&D.

If physiologic models are to be used for robust decision making, then a process for model selection, validation and uncertainty assessment is required.

Methods
To evaluate model uncertainties and validate a model we use a multiphase approach which has a standard set of testing criteria largely defined before the model is built, with additional criteria added as needed. The testing process is iterative throughout the model-building process.

Firstly, we review the mathematical equations (differential and algebraic), pathway structure, scientific basis, and data used to build the model. Hypotheses and assumptions are rigorously documented within the model.

Secondly, we evaluate each pathway and/or module separately. Specifically, we compare its predictions to external data, which were deliberately not used to build the model. For instance, we build the model using literature data and test using client data.

Thirdly, the entire model is evaluated by comparing predicted output to data from a broad range of distinct experiments that challenge the model from different directions.

Finally, we use sensitivity analysis to establish biologically sound parameter ranges and to measure parameter accuracy to determine whether the accuracy is appropriate for how the model will be used: for exploration, trial design, or otherwise.

Large physiologic models provide significant insights for R&D, but can be difficult to assess and validate.

PhysioPD models range from simple to very complex. This medium-sized model contains 120 states and 180 parameters.

Model components were tested and validated, then integrated into the whole model.

The final iteration of the Decision Diagram defines the minimal model structure required to evaluate the Objective Function.

Inclusion of uncertainties and testing of glycogenolysis within the model.

The entire model was tested and shown to meet defined criteria.

Sensitivity analysis of the PhysioPD model was used to evaluate individual parameters and some covariates.

The size and flexibility of PhysioPD models allow the user to change its scope and to add or alter pathways and still be able to validate the model.

A decision focus makes it possible to validate large physiologic models.

The validation process is critical whether the model is used for exploration or for decision making. Such validation requires that the assumptions and hypotheses used to develop the model be explicit. The validation process produces scientific insights that can be translated to increase decision-maker understanding. Validation also results in insights that further the understanding of complex chronic diseases and novel drug targets.

Decision-focused validation and uncertainty analysis should be an integral part of how all physiologic models are developed and used.