Pathway-Driven Parameter Sampling Improves Quality and Efficiency of QSP Virtual Patient Generation

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Objectives: Virtual patients (VPs) are widely used in QSP modeling to explore the impact of variability and uncertainty on clinical response. In one method of VP creation, selected parameters are randomly sampled from a feasible range, protocols are simulated, and VPs are accepted or rejected based on constraints on model output behavior. While the random sampling method is functional, this approach does not account for biological relationships between model parameters. Chosen parameter values may be individually within their reported range, but be unrealistic in combination with other parameter values. Quantitative data for the correlations between parameters is generally not available. Therefore, VPs may satisfy all quantitative data constraints but still be biologically unrealistic. This work describes a methodology for conditional parameter sampling based on grouping parameters by biological pathway that results in more realistic correlations between biologically related parameters and enables more efficient generation of clinically relevant VPs with a range of variability in the most sensitive pathways.

Methods: A previously developed psoriasis QSP model was used to demonstrate the method. The first step in the new methodology is to group parameters by pathway or subsystem and to perform pathway level sensitivitiy analysis to identify the most sensitive *pathways* (not parameters) contributing to outcomes of interest, including the multi-factorial SPASI score. Sensitive parameters on sensitive pathways with known or suspected uncertainty or variability were chosen for VP creation. In addition, the likely relationship between the parameters was set based on biological reasoning. For example, production rate parameters for pro-inflammatory mediators are

assumed to be positively correlated. Parameter sampling ranges were set to achieve three "strength" levels (strong, moderate, or weak) for each pathway. Parameters that were positively correlated were drawn from the same segment of the parameter range. Strength levels for each pathway were systematically varied to create a cohort of VPs with a wide range of variability in the sensitive pathways. We compared VPs created by this new method to VPs created by random independent sampling over the entire parameter range for the same sensitive parameters, with no a priori relationships assumed between parameters.

Results: Both sets of VPs met all of the quantitative data constraints, but the pathway-driven method produced VPs that were more biologically plausible, i.e., satisfied additional qualitative constraints. In particular, the method avoided VPs with combinations of parameter values that are unlikely to occur. In addition, by avoiding parameter combinations that counteract each other, the pathway-driven approach was more efficient at creating VPs with greater variability at the pathway level.

Conclusions: The pathway-driven approach to VP generation is a method of generating biologically relevant VPs that is intuitive and straightforward to implement. The VPs created using this method are better suited for analysis of model pathway effects on outcomes and exploration of the impacts of biological variability and uncertainty.