Even More Efficient Generation and Selection of Virtual Populations in Quantitative Systems Pharmacology Models
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Objectives: We evaluated approaches for exploring parametric uncertainty and response variability to improve the efficiency of simulation and exploration of QSP models. Our goal was to identify if one, or a combination of, global optimization algorithm(s) was optimal for building virtual populations (Vpops). We aimed to generate these Vpops without sacrificing “diversity” of virtual patients’ (VPs) pathophysiologies and phenotypes.

Methods: Using our previously published algorithm (1) we tested several established and one novel algorithm to improve the efficiency of VP/Vpop generation, including:
1. Simulated annealing (SA), original method
2. Nested Simulated Annealing (NSA), a novel method that transforms the cost function.
3. Metropolis-Hastings (MH)
4. Genetic Algorithm (GA)

We compared each method against several test criteria (e.g., computational cost to generate Vpop, VP yield per iteration, VP diversity) using a model of lipoprotein metabolism (2) as a use case.

Results: Each method improved the original algorithm along at least one criterion. For example, several methods required significantly fewer plausible patients (precursors to VPs, (1)) to create a reasonable Vpop (Fig. 1), but we found there may be tradeoffs in terms of diversity of the VPs.

Conclusions: Creating Vpops for exploring uncertainty and variability of QSP models remains a computational and scientific challenge. The methods described above may serve to guide the selection of an optimization scheme for achieving both goodness-of-fit to data and a diverse Vpop suitable for predicting response to novel therapies. However, the final choice of algorithm will be highly dependent on the particular model and goal(s) of the analysis.