Even More Efficient Generation and Selection of Virtual Populations in Quantitative Systems Pharmacology Models

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Quantitative systems pharmacology (QSP) models mechanistically describe a biological system and the effect of drug treatment on system behavior [1]. Because these models rarely are identifiable from the available data, the uncertainty in physiological parameters may be sampled to create alternative parameterizations of the model, sometimes termed "virtual patients" (VPs). In order to reproduce the statistics of a clinical population, VPs are often weighted to form a virtual population that reflects the baseline characteristics of the clinical cohort [2].

Recently, we introduced a novel technique to efficiently generate VPs and, from this ensemble, demonstrated how to select a virtual population that matched the observed data without the need for weighting [3]. This new technique complements or improves upon previous methods both by eliminating the need for pre-defined parameter groupings [4] and by avoiding over-weighting of individual solutions [2].

While the first version of our algorithm has been tested successfully against several different QSP models [5], there remain several opportunities for improvement. The main focus of this project will be to improve the efficiency of initial VP generation. Currently, the algorithm requires the pre-computation of a large number of VPs so that an efficient selection process can take place to form the virtual population. In some cases, we have rejected over 1,000 VPs for each one that is accepted into the final virtual population. This inefficient generation process is acceptable as long as the generation of very large cohorts of VPs is not rate limiting.

However, in more complicated models [6] the generation of 100,000+ VPs is infeasible due to computational cost. Using published models of lipoprotein metabolism [7]-[9] as examples for testing, the IMSM Workshop project team will identify and implement algorithms that may allow us to dramatically reduce the computational inefficiency of the initial VP generation step. Possible initial starting points include modification of the cost-function, or importance sampling techniques, such as implementing a Markov Chain Monte Carlo method [10], [11] or similar.

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