Evaluation of Parallel Tempering for Efficient Generation of Virtual Populations

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Introduction

- Virtual Patients (VPs) and Virtual Populations (VPops) are used to explore clinical variability and uncertainty in QSP modeling
- Existing methods for improved VPop generation include Simulated Annealing, Genetic Algorithms, and Metropolis Hastings [1]
- Parallel Tempering [2] is a well-established method for parameter estimation that enables more complete/comprehensive sampling of complex, high-dimensional parameter spaces
- Here, an implementation of Parallel Tempering for VPop generation is compared to Simulated Annealing and Metropolis Hastings for a published model

Objectives

- Adapt parallel tempering (PTempEst) algorithm for VPop generation
- Evaluate and compare performance of Parallel Tempering (PTempEst), Simulated Annealing (SA) and Metropolis-Hastings (MH) in terms of convergence and sampling quality
- Propose PTempEst as a viable alternative for accelerating VPop development by assessing its computational cost and goodness of fit relative to existing methods

Methods

A published MAPK signaling model was used for evaluation of the three VPop algorithms.

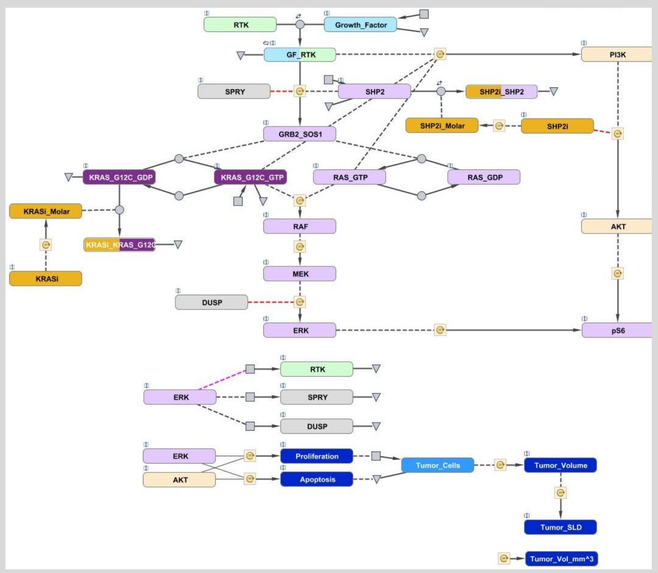

Figure 1. PhysioMap® of the MAPK signaling model. PTempEst code and the QSP model were implemented in MATLAB® / SimBiology®.

- A published MAPK model was adapted to describe mouse xenograft tumor growth [3]
- A set of 14 parameters known to impact tumor growth were selected for variation in the VPops
- Published mouse xenograft data for three treatment protocols (untreated, KRASi, and SHP2i) were used to calibrate the populations

A reference virtual patient was developed as the starting point for the virtual populations.

- A reference virtual patient was calibrated to match average tumor growth in the mouse xenograft data across treatments [4]

The Parallel Tempering algorithm was adapted for development of virtual populations.

- Parallel tempering was configured with 4 parallel MCMC chains at different temperatures
- Uniform prior distributions were assumed for parameter sampling
- Each chain was set to “swap” following 25 MCMC steps
- Each “swap” represents a unique virtual patient in the virtual population

Published Simulated Annealing and Metropolis-Hastings algorithms were modified for use with the MAPK signaling model.

- Implementations for Simulated Annealing and Metropolis-Hastings were previously published for use with a lipoprotein metabolism model [1]
- The cost function for the Simulated Annealing algorithm was configured to optimize within data bounds for the xenograft treatment protocols
- Similarly, the cost function in the Metropolis-Hastings algorithm was adapted to score based on the fit to a multivariate normal distribution of the three xenograft data outcomes

Results

All three algorithms showed a reasonable match to observable target data ranges.

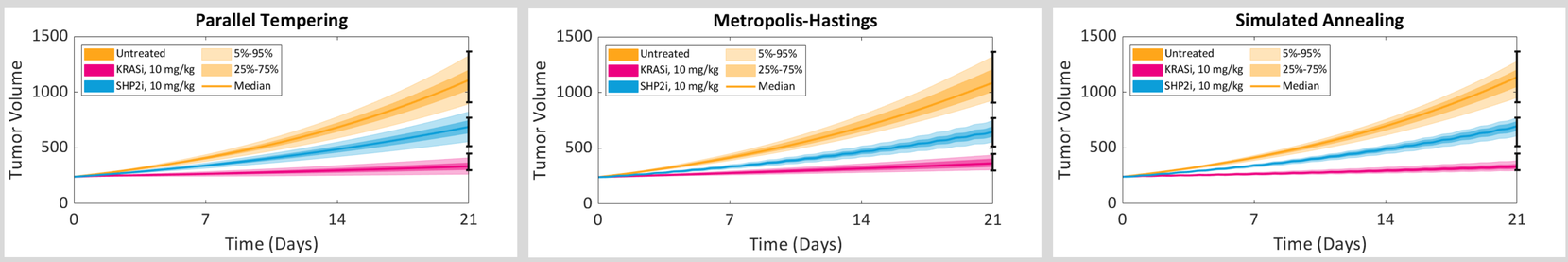

Figure 2. Virtual population simulations compared to xenograft data [3].

- Percentile ranges (25%-75%, 5%-95%, shaded) for the simulated outcomes were compared to data bounds (black) for each treatment protocol
- All three algorithms were able to cover target data ranges across therapies

All three algorithms showed comparable goodness of fit for observable outcomes.

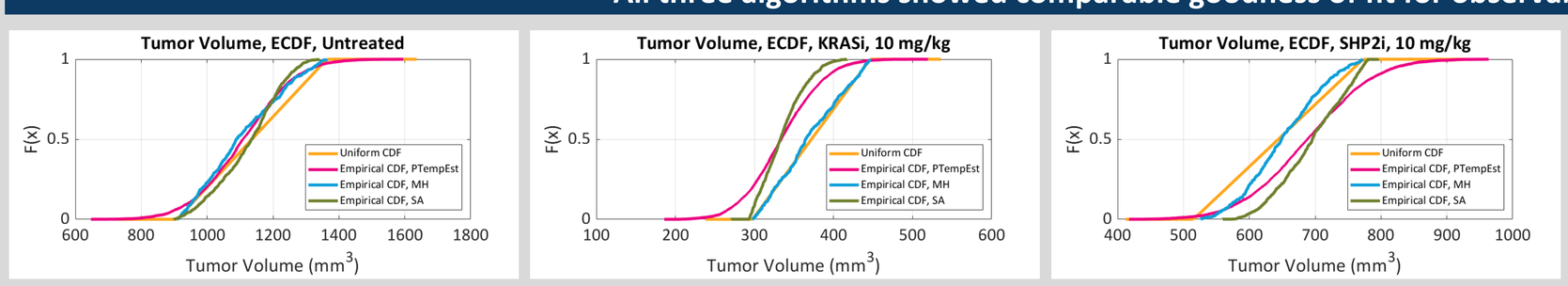

Figure 3. Empirical CDFs showing distribution comparisons across algorithms for the tumor volume readout.

- Empirical CDFs for tumor volume were compared to the uniform CDF for each treatment protocol to evaluate distributional goodness of fit
- Goodness of fit was comparable across approaches for the three therapy protocols tested

Parallel Tempering demonstrated significant time savings compared to the other algorithms.

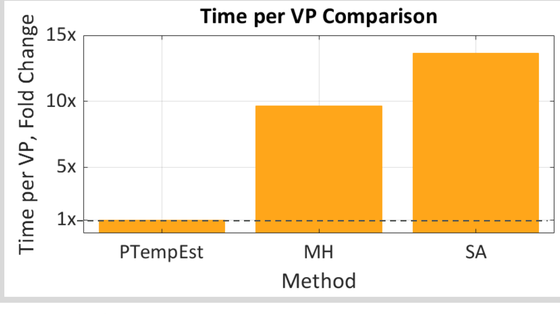

Figure 4. Time per VP relative to parallel tempering.

- Time per VP (total simulation time/total # plausible VPs) is compared relative to Parallel Tempering for each algorithm
- Parallel Tempering showed cost savings greater than 10x

Conclusions

- Parallel Tempering offers a competitive alternative to other established methods for virtual population generation
- Parallel Tempering significantly improves efficiency in virtual population generation while maintaining goodness of fit

REFERENCES
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