Parallel Tempering for Generation of Virtual Patients and Virtual Populations in QSP Models

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Introduction

- Virtual patient (VP) and virtual population (VPop) development is a critical and challenging aspect of QSP modeling
- VPs differ from each other in sensitive parameter values relevant for clinical variability
- Each VP must meet data constraints, and the VPop must reproduce observed clinical distributions
- Parallel tempering [1] is a method for parameter estimation in which better global and local sampling efficiency allows for more complete sampling of complex, high-dimensional parameter spaces, avoiding getting stuck in local minima
- Here, we attempt to leverage a parallel tempering implementation (PTempEst) to calibrate a reference VP while simultaneously building a complete VPop

Objectives

- Investigate whether PTempEst can be used to create VPs and VPops in a QSP model
- Compare the efficiency of the PTempEst method with a brute-force sampling and filtering method

Methods

A published MAPK signaling model was extended to include mouse xenograft tumor growth.

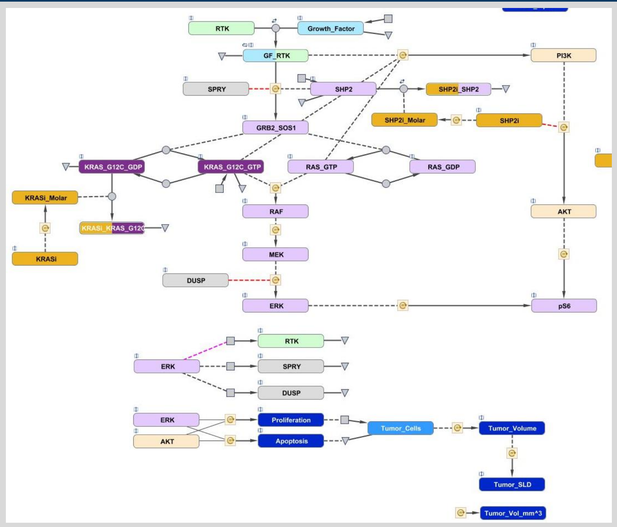

Figure 1. PhysioMap® of the expanded MAPK signaling model. PTempEst code and the QSP model were implemented in MATLAB® / SimBiology®.

- A module of tumor growth driven by ERK and AKT activity was added to a published model of MAPK signaling [2]
- Values for 14 parameters were estimated using PTempEst to fit published data [3] from KRASi and SHP2i treatment in mice

PTempEst was used to estimate parameter values for a best-fit VP and a VPop.

- Six MCMC chains were run in parallel using Metropolis-Hastings sampling, each at a different 'temperature'
  - Higher temperatures allow for greater step acceptance probability and exploration of parameter space
- Chains swap temperatures periodically to ensure both local and global search of parameter space
- Parameters are sampled from prior distributions
- Parameter set acceptance is weighted based on proximity to the target mean and normalized based on the width of the target standard deviation, creating an ensemble of solutions around the mean

A second VPop was created by random sampling.

- Parameters were randomly sampled using the same prior distributions as in the PTempEst approach
- VPs were simulated without treatment and with both pathway inhibitors (KRASi and SHP2i)
- VPs that did not pass the filtering criteria for each treatment were eliminated

Results

The PTempEst reference VP matches the average response.

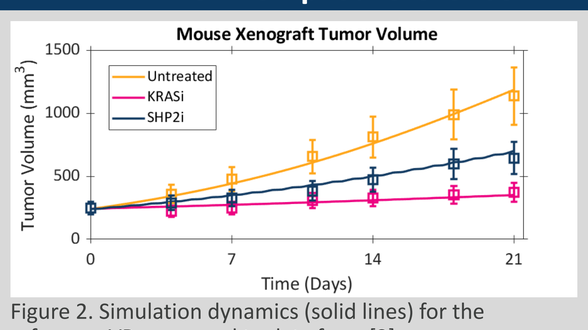

Figure 2. Simulation dynamics (solid lines) for the reference VP compared to data from [3].

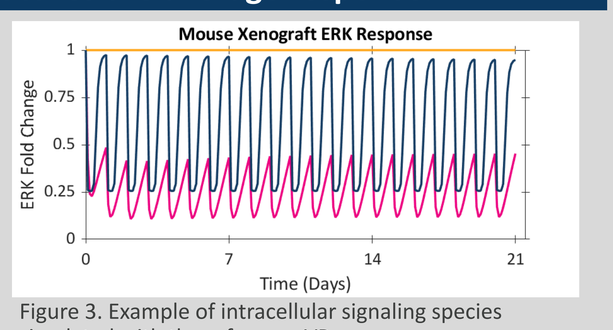

Figure 3. Example of intracellular signaling species simulated with the reference VP.

- The single best fit parameter set resulting from parallel tempering is used as the reference VP
- This VP matches the average tumor growth rate from untreated mice and the response to both KRASi and SHP2i treatment [3]
- Intracellular signaling responses can be examined to ensure they qualitatively agree with additional evidence, such as in vitro data

The PTempEst VPop captures variability across all treatment conditions.

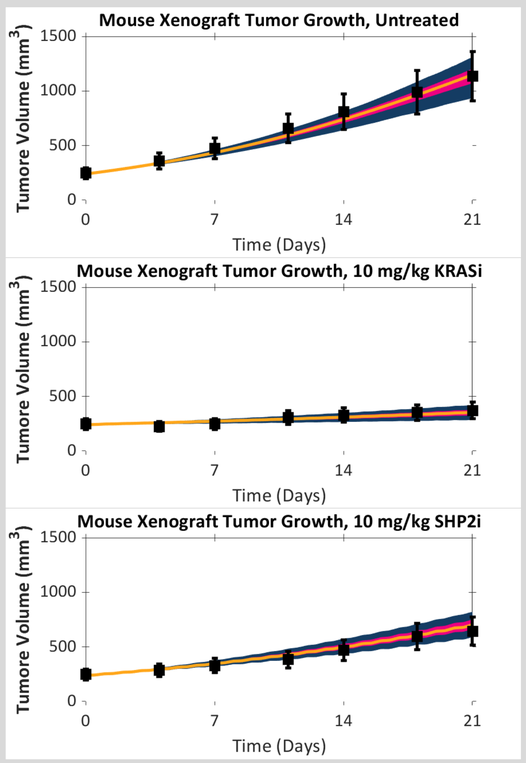

Figure 4. VPop responses to untreated growth (top), KRASi therapy (middle) and SHP2i therapy (bottom) compared to data [3].

- Identification of the best-fit parameter set also yielded and additional 6,402 unique parameter sets that fell within the error bars and can serve as the VPop
- Simulations of the full VPop match the variability in the data sets used for optimization
- By optimizing against three conditions simultaneously we obtain a robust and realistically-behaved population that can be further analyzed to identify drivers of treatment response to different therapies

Legend
Orange: Population Mean
Pink: 25-75% of Population
Blue: 5-95% of Population
Black: Experimental Data [3]

The random sampling method did not result in a VPop satisfying all conditions.

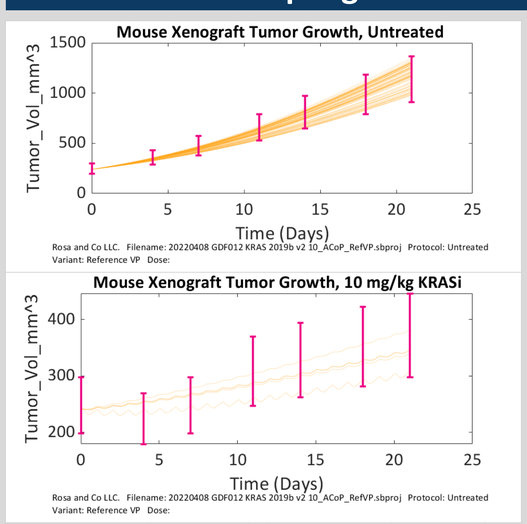

Figure 5. VPs that passed the Untreated (top) and the Untreated and KRASi (bottom) filtering criteria.

- 10,000 parameter sets were randomly sampled
- 68 VPs passed the untreated filtering criteria
- 5 VPs passed the untreated + KRASi filtering criteria
- 0 VPs passed the criteria for all three therapies
- Random sampling proved extremely inefficient at generating a VPop to match constraints for all three conditions

The PTempEst approach successfully generated a VPop that matches complex, dynamic constraints with significantly interrelated parameters.

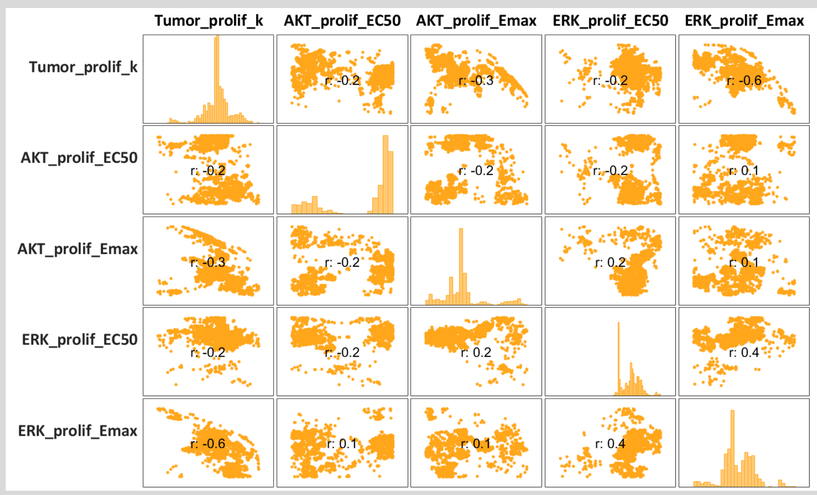

Figure 6. Correlation matrix showing relationships between select parameters. Each dot represents one VP in the PTempEst VPop.

- The marginal distribution of pairs of parameters estimated by PTempEst reflects the complex relationships between parameters that makes random sampling inefficient

Conclusions

- PTempEst facilitates simultaneous calibration of a best-fit reference VP and a VPop that matches target distributions
- This approach is particularly effective in complex scenarios, such as:
  - Multiple data constraints, such as dynamic time courses for several therapies
  - Highly correlated parameter values that make random sampling inefficient
- Using PTempEst greatly accelerates VPop development in QSP models

REFERENCES
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[2] Sayama H, et al. Virtual clinical trial simulations for a novel KRASG12C inhibitor (ASP2453) in non-small cell lung cancer. CPT Pharmacometrics Syst Pharmacol. (2021)
[3] Shi Z, et al. D-1553: A novel KRASG12C inhibitor with potent and selective cellular and in vivo antitumor activity. Cancer Sci. (2023)

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