QSP-IO: A multiscale quantitative systems pharmacology model for immuno-oncology applications

Richard J. Sové[1], Hanwen Wang[1], Huilin Ma[1], and Aleksander S. Popel[1,2]

[1] Department of Biomedical Engineering, School of Medicine, Johns Hopkins University, Baltimore, MD, USA
[2] Department of Oncology and Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA

Introduction

- Immunotherapy has become one of the most exciting breakthroughs in cancer research
- Upon proper education and activation, the immune system has the capability to eradicate cancerous tumors[1]
- Immunotherapies modulate the activity of major immune cells towards enhanced recognition and killing of cancer cells through distinct mechanisms, the most successful ones being the immune checkpoint inhibitors (e.g. anti-PD1, anti-PD-L1 and anti-CTLA-4)[1]
- General response rates to immunotherapies are highly variable and only a small subset of patients would respond favorably even in biomarker-selected cohorts[2]
- **Objective:** to develop an integrative mechanistic understanding of cancer-immune cell interactions using state-of-the-art, multiscale models to help answer critical questions, with the ultimate goal to reduce clinical trial failures and improve treatment efficacies in patients
- The use of multiscale quantitative systems pharmacology (QSP) models has become widely used[4-6] and due to the rapid discovery of novel mechanisms and therapies in immuno-oncology, there is a need for rapid model development
- In this work, we present QSP-IO, a modularized QSP modeling platform based in MATLAB (MathWorks, Natick, MA) that allows efficient formulation of physiology-based immuno-oncology models and quantitative simulation of patient outcomes in response to different immunotherapy combinations
- QSP-IO can be downloaded at www.github.com/popellab/qspio

Methods

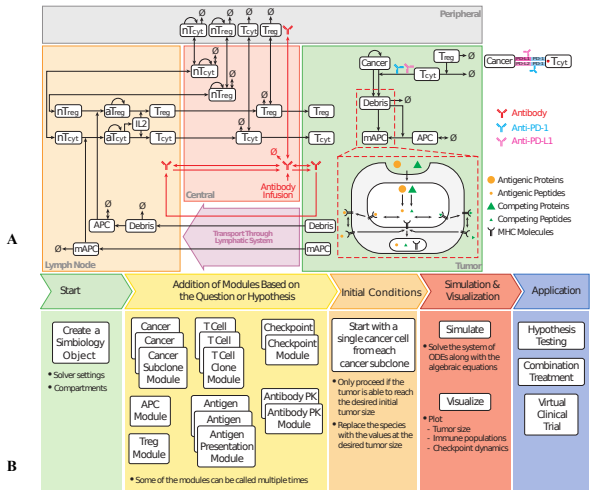

Figure 1. Overview of QSP-IO. A. Diagram of immuno-oncology QSP model interactions. Naïve and mature antigen presenting cells are represented by APC and mAPC, respectively, and naïve and proliferating T cells are represented by nT and aT, respectively. **B.** Workflow for creating a model in QSP-IO. The user starts by creating a SimBiology object using the QSP-IO's initialization function. Module can be added to include the necessary detail in the model based on the research questions. The initial conditions are then generated based on the model parameters using the novel initial conditions procedure. Finally, the simulations can be run using standard SimBiology functions and visualization can be preformed using MATLAB plot functions or using QSP-IO's plotting function.

Results

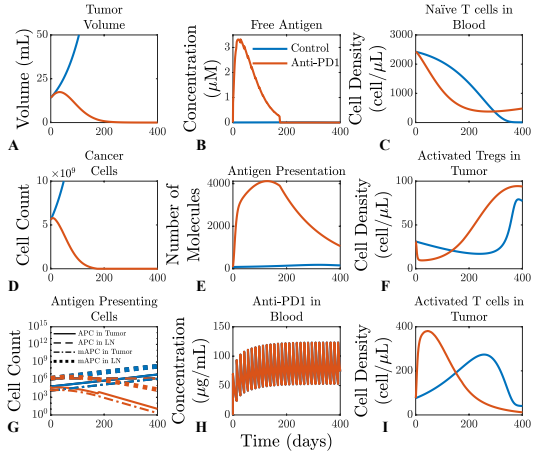

Figure 2. Simulation results as a function of time for control (blue) and anti-PD-1 treatment (red). A. Tumor volume **B.** Concentration of free antigen in the tumor. **C.** Naïve T cell density in the blood. **D.** Number of cancer cells. **E.** Number of antigen-MHC complex molecules per APC binding site. **F.** Activated Treg density in the blood. **G.** Number of antigen presenting cells. **H.** Concentration of nivolumab in the blood. **I.** Activated T cell density in the tumor.

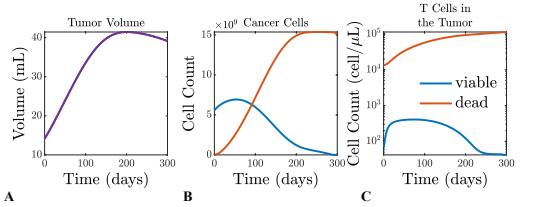

Figure 3. Simulated pseudo progression. A. Tumor volume as a function of time. **B.** Number of viable (blue) and dead (red) cancer cells as a function of time. **C.** Cell count for viable (blue) and exhausted (red) T cells as a function of time. The parameters from Example 1 were used with k_{clear} = 0.001 day^{-1} and k_{Tcell} = 8.7 day^{-1} to demonstrate the pseudo-progression phenomenon.

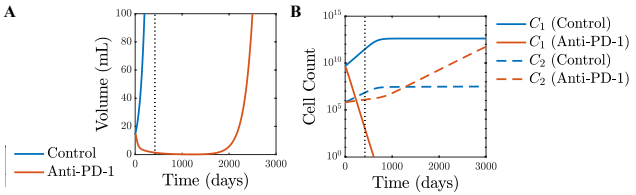

Figure 4. Simulated resistance. Simulation of a patient with two different cancer cell clones, C1 and C2: where C2 has a slower growth rate and lower rate of death from T cells. The simulation is run over approximately 8 years (3000 days), with treatment given for one year. **A.** Tumor volume as a function of time. **B.** Number of cancer cells as a function of time. The vertical dotted line indicates the end of the treatment.

Results

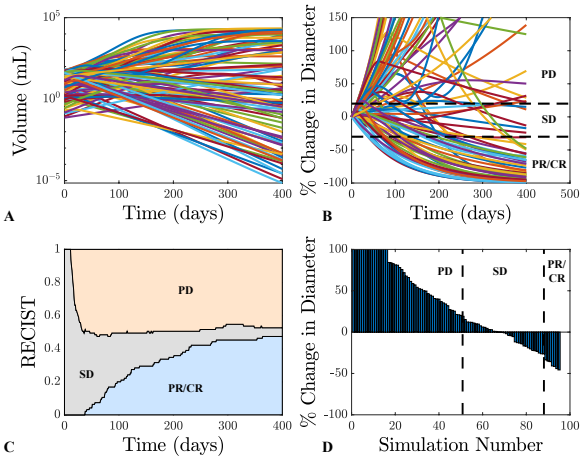

Figure 4. Latin Hypercube Sampling of parameter space. A. Tumor volume as a function of time for a Latin Hypercube Sampling (LHS) (n = 100) of a subset of the parameter space; five of the 100 parameterizations did not reach the initial tumor diameter. Ten parameters were varied over a physiological range; see Table 1. **B.** Percent change in tumor diameter as a function of time for the LHS. Dashed lines indicate the threshold for the Response Evaluation Criteria In Solid Tumors (RECIST); regions are labeled with PR/CR for partial/complete response, SD for stable disease and PD for progressive disease. **C.** RECIST values as a function of time for the LHS. **D.** Waterfall plot showing the percent change in diameter at 60 days following the start of treatment. Each bar represents a simulation, with height representing the percent change in tumor diameter.

Conclusion

- We present a readily reproducible modular model platform to conduct *in silico* virtual clinical trials on patient cohorts of interest
- Our platform allows us to make step-by-step modifications to our models based on insights on the effect of therapeutics on the immune system and resistance mechanism in tumor development from ongoing clinical trials
- This work serves as an important step towards the development of personalized medicine in immuno-oncology

References

[1] Popovic, Jaffee, and Zaidi, "Emerging strategies for combination checkpoint modulators in cancer immunotherapy" J. Clin. Invest., 2018.
[2] Haslam and Prasad, "Estimation of the percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor immunotherapy drugs" JAMA Netw, 2019.
[3] Wang *et al.*, "In silico simulation of a clinical trial with anti-CTLA-4 and anti-PD-L1 immunotherapies in metastatic breast cancer using a systems pharmacology model" R Soc Open Sci, 2019.
[4] Milberg *et al.*, "A QSP Model for Predicting Clinical Responses to Monotherapy, Combination and Sequential Therapy Following CTLA-4, PD-1, and PD-L1 Checkpoint Blockade" Sci Rep, 2019.
[5] Jafarnejad *et al.*, "A Computational Model of Neoadjuvant PD-1 Inhibition in Non-Small Cell Lung Cancer" AAPS J, 2019.
[6] Wang et al., "Conducting a Virtual Clinical Trial in HER2-Negative Breast Cancer Using a Quantitative Systems Pharmacology Model with an Epigenetic Modulator and Immune Checkpoint Inhibitors" Front Bioeng Biotechnol, 2020.

Supported by NIH grants U01CA212007 and R01CA138264