CALIBRATING THE SIMBIOSYS TUMORSCOPE FOR THE FIGHT ON CANCER: A SCENARIO ANALYSIS ENGINE FOR DETERMINING OPTIMAL THERAPY CHOICE

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PI: Joseph R. Peterson[1]
Co-PIs: John A. Cole[1], Tyler M. Earnest[1], Michael J. Hallock[1]

[1]SimBioSys, Inc.

EXECUTIVE SUMMARY

Use of the most toxic drugs in a "scorched earth strategy" is common in the treatment of breast cancer, even though less toxic drugs have only single-digit lower rates of success. To address this issue, the TumorScope software was calibrated to accurately predict the response of breast cancer to the various drugs commonly used for treatment. Calibration resulted in high correlation between predicted and actual outcomes for nearly 200 patients spanning all types of breast cancer. More pertinent to treatment planning, TumorScope was able to improve the accuracy of identifying patient/drug combinations that will achieve pathological complete response (PCR) after treatment by two to three times that of the current state-of-the-art method. PCR is the strongest predictor of long-term survival for breast cancer patients and the desired outcome for all drug-based therapies. Physicians can thus use the computational analysis of different therapies produced by TumorScope to weigh likelihood of therapy success versus drug toxicity.

RESEARCH CHALLENGE

Despite significant advances in cancer treatment in both the number and efficacy of therapies, success rates of any individual therapy remain low. This is especially true in breast cancer where, while overall five-year survival rates tend to be greater than 70%, the efficacy rates of any individual therapy range from 20% to 40%. Critically missing is a way for physicians to distinguish which therapy will be most effective for each patient, or whether none of the available therapies will work. As a consequence, many patients are prescribed a therapy, often at high physical, mental, and monetary cost, that is either too extreme or completely ineffective.

Take, for example, the decision between prescribing an anthracycline-containing (ACT) or a docetaxel-containing (TC) chemotherapy. While ACT therapies, at a population level, have an approximately 3% higher efficacy, it comes at the risk of higher toxicity during treatment, an elevated risk of heart disease, and an approximately 1% likelihood of the patient developing leukemia. Yet, owing to the slightly higher efficacy rate, ACT therapies are much more commonly used, and physicians are faced with no way to argue for using the less toxic TC.

What is needed is a method of predicting the likelihood of success for different therapies that does not increase the number or cost of laboratory tests. SimBioSys set out to solve this problem by developing TumorScope, a personalized medicine approach that constructs realistic, 3D models of patients' tumors that, when coupled with novel simulation algorithms, can be used to perform scenario analysis (Fig. 1a).

METHODS & CODES

Simulations were performed using a proprietary simulation engine known as TumorScope. Data from nearly 200 breast cancer patients who underwent neoadjuvant (presurgery) chemotherapy [1–3] were used to construct initial conditions for the simulations. The data set represents patients of all common breast cancer types as well as drugs, including chemotherapy and immunotherapy. At several times throughout the course of therapy, clinical outcomes such as tumor volume, tumor longest dimension, and overall pathological response were used to assess the accuracy and applicability of a particular parameter set. Parameter sets were varied systematically for each drug to minimize the deviation between predicted results and clinically measured results.

RESULTS & IMPACT

Simulations included a 3D representation of the local environment with the various tissues found around the breast tumor (Fig. 1a). The TumorScope software simulated the interactions among the tissues along with their biology, the drug perfusion (Fig. 1b), and resulting response of the tumor to different drug regimens (Fig. 1c). Depending on the drug regimen—that is, the combination of drugs chosen and frequency of administration—a patient's tumor response might be drastically different. As demonstrated in Fig. 1c, a patient given the same combination of drugs every three weeks (*e.g.*, a "standard regimen"; Fig. 1c, left) or every two weeks (*e.g.*, a "dose-dense regimen"; Fig. 1c, right) can lead to either progression or regression of the tumor mass. Empowered with this information, the physician and patient may opt for the more toxic dose-dense regimen.

As with every predictive model, TumorScope had freely tunable parameters. To make accurate predictions, model parameters were systematically tuned to match predictions with clinical outcomes. The research team leveraged the large number of GPUs available on Blue Waters to perform thousands of simulations of the approximately 200 patients undergoing different treatments, with different parameters.

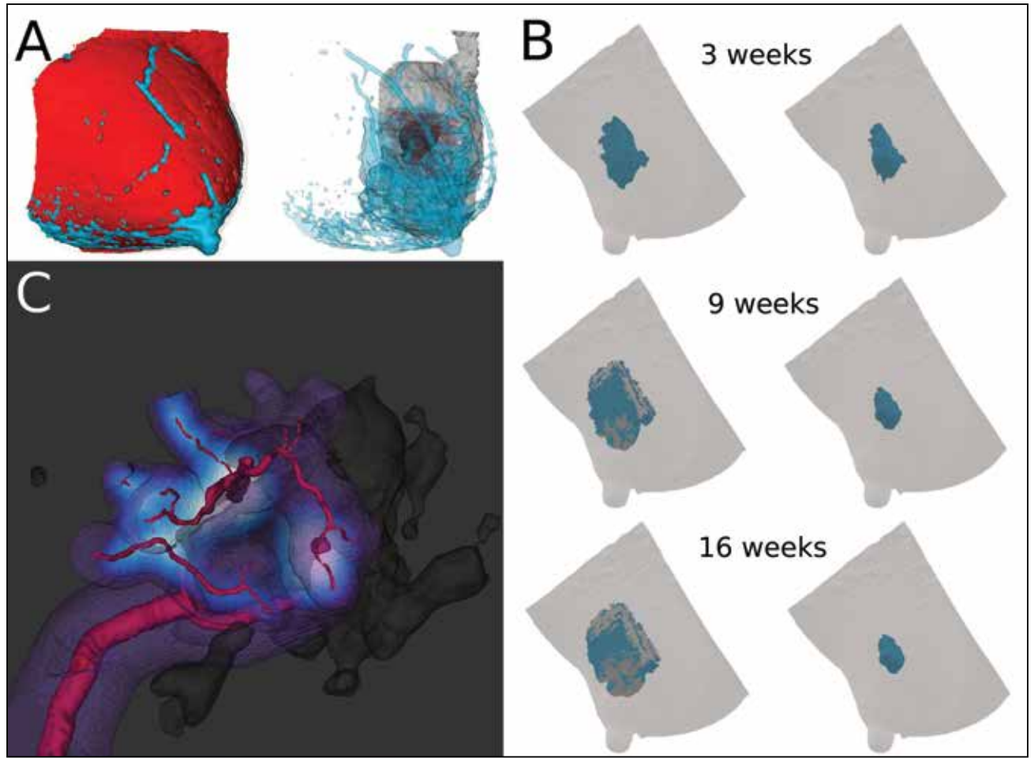

Figure 1: (A) Three-dimensional model of a patient's breast tumor including fat (red), fibroglandular tissues (blue), and tumor tissues (black). (B) Close-up of the patient's tumor in a realistic microenvironment including simulated drug perfusion (purple) out of the vascular network (red). (C) The same patient simulated with a dose-dense (right) and standard dose (left) chemotherapy regimen, demonstrating how choice of chemotherapy and regimen can lead to drastic differences in tumor regression (right) or progression (left) over the course of treatment. The tumor is shown in blue and the breast skin is outlined in transparent gray.

Calibration resulted in a high correlation between prediction and calibration data, indicating a good model fit. Pertinent to treatment planning, TumorScope improved the accuracy of identifying patient/drug combinations that achieve pathological complete response (PCR) by two to three times that of the current state-of-the-art method. Since PCR is the strongest predictor of long-term survival for breast cancer patients, physicians can use TumorScope to identify which therapies will achieve PCR (if any), and potentially deescalate therapy when less toxic drugs are predicted to give rise to the same extent of response as more toxic alternatives.

WHY BLUE WATERS

The Blue Waters system has been critical for the calibration of the TumorScope prediction engine. Calibration required simulating the response of hundreds of patients to various therapies while varying a number of parameters. Even with the fast time-to-solution of the predictive engine (one prediction per hour), a calibration process of this scale would have required months to years of computer time to complete. By leveraging the large number of GPUs available on Blue Waters, these calibration processes could be performed in just a few days. The computer allocation during the 2018–2019 year effectively allowed for the complete tuning of the TumorScope software for breast cancer.