2022-2023 Grand Challenge Award Final Report

Awardee: **Thomas Yankeelov, Professor**
Biomedical Engineering

Research Award Title: **A Practical Computational Framework
for $n = 1$ Clinical Trials**

Research Summary

The goal of this project was to develop advanced, but practical, mathematical methods for prospectively predicting and optimizing the response of the individual breast cancer patient to neoadjuvant therapy (NAT; i.e., treatment administered prior to surgery). Importantly, patients who achieve a complete response to NAT have increased recurrence-free survival; conversely, patients who have residual disease after NAT are at increased risk of early recurrence and death. If it could be definitively determined—early in the course of NAT—that a therapeutic regimen is unlikely to achieve a complete response, then the ineffective treatment could be replaced with an alternative strategy, potentially improving outcomes. Currently, the response of breast tumors to NAT is neither predicted nor optimized, it is merely assessed. With therapeutic options increasing, we simply must develop accurate and rapid methods for predicting response so that treatments can be customized on an individual patient basis. To attack this problem, we sought to construct the mathematical formalism to predict the eventual tumor response using only pretreatment patient data, and then construct digital twins capable of identifying patient-specific, therapeutic regimens hypothesized to dramatically outperform the standard-of-care regimen.

We developed a method to use multi-parametric MRI to integrate mechanism-based modeling and deep learning to predict the spatio-temporal response of breast cancer to NAT—and do so before treatment is initiated. Patients enrolled in the breast cancer Moonshot Program at MD Anderson received multi-parametric MRI exams before (V1) and during (V2, V3) NAT. For each patient, we calibrated a simplified version of our mechanism-based model to all imaging visits to determine model parameters describing the spatiotemporal changes in tumor cellularity in response to NAT. We then trained a convolutional neural network (CNN) over a cohort (n = 94) to predict the calibrated model parameters from the V1 MRI data. The predicted parameters were then used in the mechanism-based model to predict tumor cellularity at V2 and V3. Receiver operator characteristic analysis shows that the CNN-predicted tumor cellularity at V3 achieves an area under curve of 0.72 in the test cohort (n = 24) for differentiating between patients who do and do not respond to therapy. We are working to improve this result by adjusting our CNN to predict calibrated parameters in our more comprehensive mechanism-based model. To the best of our knowledge, this is the first time spatio-temporally resolved predictions of tumor response have been obtained using only the pre-treatment images.

Another critical barrier to improving response to NAT is the lack of rigorous ways to personally tailor therapeutic regimens. To address this problem, we developed a method to systematically investigate alternative therapeutic regimens on a patient-specific basis in a group of chemo-sensitive patients (n = 37; 19 pCR, 18 non-pCR) who received only NAC for the treatment of triple negative breast cancer. In particular, we quantified response when altering the schedules of Adriamycin/Cytoxan/Taxol (A/C/T) administration. Each patient's digital twin was used to predict response to 128 clinically reasonable schedules

of A/C/T administration; i.e., eight candidate A/C schedules in a combination with 16 candidate Taxol schedules (Table 1).

Table 1: Candidate Therapeutic Schedules.

Treatment	No. of Cycles	Duration of Therapy (days)
A/C	4	56, 60, 64, 68, 72, 76, 80, 84
Taxol	12	56, 60, 64, 68, 72, 76, 80, 84
Taxol	4	56, 60, 64, 68, 72, 76, 80, 84

The predicted response (pCR or non-pCR) from each alternative schedule is compared to the response the patient experienced from the treatment regimen they actually received. Without changing the total therapeutic dose, shortening the duration of either A/C or Taxol administration increases the treatment efficacy to different degrees in different patients. In particular, eight patients who had residual disease after their actual treatment were predicted to achieve pCR had they have received dense-dose Taxol administration (i.e., four cycles Taxol, two weeks per cycle), indicating a nearly 22% improvement of pCR rate in the cohort. Figure 1 summarizes the outcomes predicted by a subset of these combinations for one patient.

Figure 1: The surface plot shows what the final tumor burden (vertical axis) is predicted to be given a range of combinations of A/C and Taxol. Note that the black circle indicates the NAT regimen the patient actually received which led to a non-pCR outcome (i.e., residual disease). The blue circles indicate other standard-of-care (SOC) options that, in theory, would have led to a better outcome. This raises exciting hypotheses about how to treat future patients.
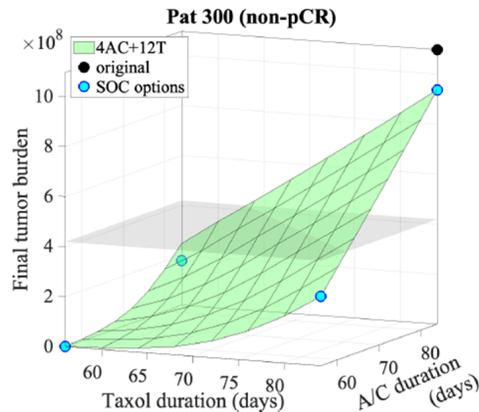
Preliminary results of the study demonstrate that the digital twin approach provides a unique opportunity for improving the response of triple negative breast cancer to NAT through patient-specific optimization of the therapeutic schedule. Ongoing efforts are focused on accounting for toxicity and investigating the effects of altering therapy types and doses in combination with the schedule strategies on the patient response. We believe this patient-specific approach to oncology will move the focus from the population "average" to the individual, resulting in a true paradigm shift to the current clinical care model. Importantly, the methods summarized above are applicable to any cancer for which NAT is indicated and the requisite data is available.

Publications

- Laubenbacher R, Adler F, A G, Castiglione F, Eubank S, Fonseca LL, Glazier J, Helikar T, Jett-Tilton M, Kirschner D, Macklin P, Mehrad B, Moore B, Pasour V, Shmulevich I, Smith A, Voigt I, Yankeelov TE, Ziemssen T. Forum on Precision Immunology: Immune Digital Twins. npj Systems Biology and Applications, 2024, accepted.

- Jarrett AM, Song PN, Reeves K, Lima EABF, Larimer B, Yankeelov TE, Sorace AG. Investigating tumor-host response dynamics in preclinical immunotherapy experiments using a stepwise mathematical modeling strategy. Mathematical Biosciences, 2023 Dec:366:109106.

- Yankeelov TE, Hormuth II DA, Lima EABF, Lorenzo G, Wu C, Okereke LC, Rauch GM, Venkatesan Am, Chung C. Designing clinical trials for patients who are not average. iScience, 2023;27:108589.

- Lorenzo G, Jarrett AM, Meyerd CT, Quaranta C, Tyson DR, Yankeelov TE. Identifying mechanisms driving the early response of triple negative breast cancer patients to neoadjuvant chemotherapy using a mechanistic model integrating in vitro and in vivo imaging data. Engineering with Computers, 2023, Jun 27;13(1):10387.

- Phillips CM, Lima EABF, Wu C, Jarrett AM, Zhou Z, Elshafeey N, Ma J, Rauch GM, Yankeelov TE. Assessing the identifiability of model selection frameworks for the prediction of patient outcomes in the clinical breast cancer setting. Journal of Computational Science, 2023, Volume 69, May 2023, 102006.

Presentations (most relevant to this award)

- "Integrating Quantitative MRI with Computational Modeling to Predict the Response of Breast Cancers to Neoadjuvant Therapy". 10th International Congress on Industrial and Applied Mathematics. 22 August 2023. Virtual talk. *Invited lecture.*

- "Quantitative Imaging to Enable Actionable, Patient-specific Digital Twins". NCI Cancer Imaging Program. 10 August 2023. Virtual talk. *Invited lecture.*

- "Predictive Oncology through Imaging-based Mathematical Modeling". Society of Nuclear Medicine & Molecular Imaging Annual Meeting. 27 June 2023. Chicago, Illinois, USA. *Invited lecture.*

- "Mathematical Modeling for Practical, Patient-specific Digital Twins". Colorado State University's Quantitative Cell & Molecular Biology Program. 12 June 2023. Ft. Collins, Colorado, USA. *Invited lecture.*

- "Integrating Imaging and Modeling to Enable Practical Digital Twins for Oncology". BioITWorld Conference & Expo. 16 May 2023. Boston MA, USA. Virtual Talk. *Invited lecture.*

- "Imaging-based Digital Twins for Oncology". The Web Conference 2023: AI in Health. 1 May 2023. Austin, Texas, USA. *Invited talk.*

- "AI and Big Data: Because Who Needs Science?". Annual Meeting of the European Society of Molecular Imaging. 16 March 2023. Salzburg, Austria. *Invited talk.*

- "Imaging-based Digital Twins for Breast Cancer". Annual Meeting of the European Society of Molecular Imaging. 16 March 2023. Salzburg, Austria. *Invited talk.*

- "Opportunities for Imaging and Modeling in Cancer Immunotherapy". Forum On Precision Immunology: Immune Digital Twins. 24 February 2023. Orlando, Florida, USA. *Invited talk.*

- "Towards Ddigital Twins in Oncology". National Academy of Sciences Workshop on Opportunities and Challenges for Digital Twins in Biomedical Sciences. 30 January 2023. Virtual talk. *Invited lecture.*

- "Towards n = 1 Clinical Trials for Oncology". Banff International Research Station Workshop on Computational Modelling of Cancer Biology and Treatments. 23 January 2023. *Invited "lightening talk".*

- "Towards MRI-based Digital Twins for Breast Cancer". ISMRM Workshop on Cancer Imaging. 4 November, 2022. Invited Keynote Lecture.

- "Predicting Patient-specific Putcomes via Imaging-based Mathematical Models". Oak Ridge National Laboratory Workshop on Cancer Targeted Therapies November 2, 2022. Virtual lecture. *Invited lecture.*

- "Towards Practical Digital Twins for Clinical Oncology", 2nd International Conference on Biological Engineering and Medical Science (ICBioMed 2022), November 7-13, 2022. Virtual lecture. *Invited lecture.*

Awards

- NIH contract via Leidos Biomedical Research, Inc. for developing digital twin software, IDIQ Subcontract 23X068, pending.