A practical computational framework for $n = 1$ clinical trials

Thomas Yankeelov, Professor, Biomedical Engineering

Abstract: The goal of this project is 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.

Over the past decade we have pioneered physics- and biology-based, mathematical models designed to be initialized and calibrated with patient-specific imaging data acquired before and during therapy to make patient-specific predictions concerning outcomes. These models have matured to the point where they now offer accurate predictions of the spatio-temporal dynamics of tumor response. The focus of this application is to extend our formalism to simulate a range of interventions *via* patient specific digital twins, and then employ the methods of optimal control theory to identify personalized therapeutic regimens designed to dramatically outperform the standard-of-care treatment protocols. In this way, we are performing clinical trials on individual patients (i.e., $n = 1$ clinical trials) using the methods of computational science. This work will be carried out using the advanced imaging and genomic data from the MD Anderson Triple Negative Breast Cancer Moonshot program which provides a patient set of 170 individuals, allowing us to perform 170 individualized clinical trials. As this project represents a transformative approach for predicting and optimizing the outcomes of cancer treatment on an individual patient basis before therapy commences, it is well-aligned with the vision of the Moncrief Grand Challenge Awards.