A mathematical framework to optimize combination therapy for triple-negative breast cancer in obese mice

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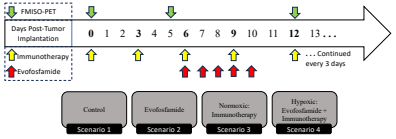
Motivation

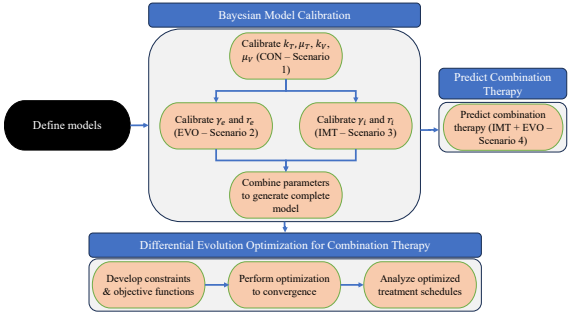
Obesity-associated triple-negative breast cancer (TNBC) presents a particularly challenging clinical scenario, as these tumors are both aggressive and deeply influenced by the hypoxic microenvironments that obesity promotes. At the same time, emerging evidence suggests that obesity can paradoxically enhance responses to certain immunotherapies, creating a complex and poorly understood therapeutic landscape in which standard, empirically chosen regimens may be far from optimal. Evofosfamide, a hypoxia-activated prodrug, is a promising candidate to exploit these microenvironmental features, yet there is little quantitative guidance on how to schedule and dose it in combination with immunotherapy for obese patients. Existing mathematical models of cancer therapy often focus on group-level behavior, rely on gradient-based optimization that can struggle with stiff or non-smooth systems, and rarely incorporate both longitudinal tumor burden and hypoxia-sensitive imaging data in obese TNBC models. This gap limits our ability to predict how individual tumors will respond to different treatment schedules and to systematically search for regimens that balance tumor control with toxicity. To address this, we propose a mouse-specific, heuristic modeling framework that couples mechanistic ODE models, Bayesian calibration to rich in vivo data, and gradient-free optimization to explore and improve combination evofosfamide–immunotherapy schedules in hypoxic, high-fat-diet TNBC models.

Research Goal

The goal of this project is to develop and calibrate a murine-specific mathematical model of tumor and vascular dynamics under evofosfamide and immunotherapy, and to integrate it with a differential-evolution optimization scheme that identifies combination therapy schedules minimizing final tumor volume, total tumor burden, or total drug dose.

Experimental Design





Model Design

$$\frac{dT}{dt} = \underbrace{k_T T}_{\text{exponential growth}} - \underbrace{\mu_T TV}_{\text{immune response}} - \sum_{j=1}^{N_j} \underbrace{\gamma_i \exp(-r_i(t-t_{ij}^*))H(t-t_{ij}^*)TV}_{\text{immunotherapy death rate increase}},$$

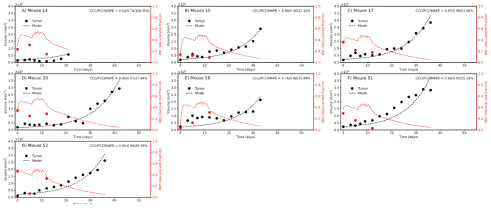
$$\frac{dV}{dt} = \underbrace{k_V(1-V)}_{\text{vessel growth}} - \underbrace{\mu_V TV}_{\text{vessel deterioration}} + \sum_{k=1}^{N_k} \underbrace{\gamma_e \exp(-r_e(t-t_{ek}^*))H(t-t_{ek}^*)(1-V)}_{\text{vascular normalization due to evofosfamide}}.$$

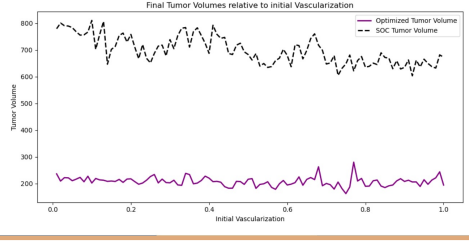
- T: Tumor volume
- V: Well-vascularized tumor fraction $\Rightarrow V = 1 -$ Hypoxic fraction

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Prediction and Optimizations





Conclusion & Future Steps

This work presents a heuristic, gradient-independent framework capable of modeling, predicting, and optimizing combination immunotherapy–evofosfamide treatment strategies for triple-negative breast cancer in obese, hypoxic murine models. By integrating longitudinal tumor volume and vascularization data into a calibrated nonlinear ODE system, the approach achieves high predictive accuracy across control, monotherapy, and combination-therapy settings (CCC up to 0.97 for calibration and 0.93 for combination-therapy prediction). Optimization via differential evolution further demonstrates that intelligently scheduled combination therapy can substantially reduce final tumor volume, total tumor burden, or overall drug exposure relative to standard-of-care protocols. Looking ahead, this framework establishes a foundation for generating *in silico* treatment strategies and developing digital twins for personalized oncology. Future efforts should extend this modeling approach to additional drug mechanisms, integrate richer biological measurements (e.g., spatial hypoxia maps, immune profiling), and validate optimized schedules in prospective *in vivo* studies. Broader translation to patient-specific modeling represents a promising next step toward clinically actionable, computationally guided combination therapy design.