Integrating experimental data and multiphysics modeling to describe nutrient-limited growth of HER2-positive breast cancer spheroids

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Multicellular tumor spheroids (MCTS) are increasingly used as *in vitro* models of breast cancer (BC) because they better recapitulate the 3D architecture, cell-cell interactions and microenvironment of solid tumors than conventional 2D cultures. However, their biological and structural complexity limits the quantitative analysis of tumor growth, nutrient transport, and necrosis development using experimental methods alone. In parallel, most available *in silico* tumor models rely on simplified assumptions and lack direct experimental validation, which limits their translational applicability.

In this work, an experimentally validated multiphysics computational model was developed to describe the growth and nutrient-limited behavior of HER2+ BC spheroids. The model was implemented in COMSOL Multiphysics® and integrates Gompertzian growth kinetics, deformable geometry, nutrient diffusion and time-dependent porosity. An expanding smooth mesh was used to represent spheroid growth and its influence on mass transport. Glucose and oxygen dynamics were described using coupled convection-diffusion-reaction equations, in which uptake rates were linked to the fraction of viable cells.

To validate the model, extensive experimental data were generated over 7 days of culture. Spheroid size, cell viability, and necrotic core formation were quantified by CLSM, while glucose consumption was analyzed by HPLC and spheroid porosity was determined from histological sections. Key model parameters related to growth and glucose uptake were estimated by nonlinear GRG optimization to minimize differences between experimental and simulated data.

The model accurately reproduced spheroid growth and glucose consumption, with mean absolute errors below 7% and 2%, respectively. Simulations showed the progressive development of steep nutrient gradients as spheroids enlarged. While oxygen concentrations remained above decaying levels, glucose in the spheroid core decreased below critical values after day 5, consistent with the experimentally observed expansion of the necrotic region. Comparison of simulated nutrient profiles with CLSM data allowed to identify a glucose threshold of approximately 0.08 mM as critical for necrosis in HER2+ BC spheroids.

Overall, this experimentally grounded multiphysics framework provided a realistic representation of HER2-overexpressing BC spheroid behavior under nutrient-limited conditions. By integrating growth, mechanics, porosity and metabolism, it may offer a valuable platform for studying tumor physiology and predicting drug efficacy in 3D tumor models, supporting more reliable preclinical and digital-twin approaches in BC research.

References

[1] C. Nieto, A. González-Garcinuño, E.M. Martín del Valle, 2026. Integrating simulation and experimental validation of nutrient-limited growth in breast cancer spheroids. Eur. J. Pharm. Sci., 216, 107370.