Combined in vivo and in silico quantitative modeling of post-surgery metastatic development

Sébastien Benzekry, INRIA Bordeaux

Abstract:
For most of the cases, first line treatment of a solid cancer disease starts with ablation of the primary tumor. What then drives patients survival relies on the occurrence and growth of metastases and our ability to control these processes. In this context, it is of fundamental importance to develop clinically relevant animal models of metastases that mimic the disease natural history and integrate its fundamental steps: a) primary tumor growth, b) surgery and c) post-surgical metastatic development. To potentiate the data analysis from these models and assist theoretical thinking behind the empirical data, we developed a modeling methodology that has two main components: a general semi-mechanistic mathematical model based on general laws of the disease and a nonlinear mixed-effects part for statistical confrontation of the model to the data. We demonstrate here that the model was able to fit and predict pre- and post-surgical data from two clinically relevant animal models (an orthotopic xenograft breast model and a syngeneic orthotopic kidney model), both at the level of individual and population dynamics, and we derive minimally parameterized versions of the model that ensure optimal trade-off between identifiability and goodness-of-fit. The model is also able to fit clinical data of metastatic relapse probability stratified by primary tumor size in a cohort of 1647 patients diagnosed with breast cancer, with significant goodness-of-fit ($p=0.0157$). We further used our methodology to give theoretical insights on the quantitative impact of primary tumor size at surgery on survival. As a nontrivial finding from our analysis, we identify a highly nonlinear relationship between these two quantities, which suggests a size threshold for significant efficacy of surgery in delaying metastatic relapse and improving survival.