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Bridging scales: combining population statistics with tissue dynamics to link primary and metastatic disease

To provide a better understanding of the relationship between primary tumor growth rates and metastatic burden, we present a method that combines population-level incidence data and tissue level growth dynamics. At the population level, we utilize a Monte Carlo simulation model of clinical cancer stage progression that was fit to the NCI Surveillance, Epidemiology, and End Results (SEER) database. At the tissue level, we use a system of partial differential equations (PDEs) to develop a spatio-temporal model of tumor growth and invasion based on the angiogenic cascade. By coupling models from both scales, the population scale metastatic burden can be explained in terms of the primary tumor vascular response and circulating tumor cell (CTC) fraction.

The population model suggests that lung tumors grow faster and shed a significant number of cells into the circulation at small sizes, whereas breast tumors grow slower and do not significantly shed cells until becoming larger. The PDE model can recapitulate these results but reveals a more dynamical relationship between the primary tumor and the CTCs. Both the PDE model and the statistical model predict exponential growth for the metastatic burden, however, there is some disparity over the primary tumor dynamics. With adequate blood supply the primary grows exponentially, but this cannot be sustained when vasculature is limited. The latter case is better correlated with power law growth. By modifying parameters in the PDE model we can account for different primary tumor dynamics that subsequently lead to different growth dynamics of the CTCs.

The vascular response is the key, both driving growth and connecting the primary tumor to metastatic burden. Whilst we do not explicitly model the metastatic population, we are able to disengage the direct dependency of the metastatic burden on primary tumor growth by introducing the CTC population as an intermediary. These results also highlight the need for pathological attributes of both primary tumor and metastases to be incorporated in databases such as SEER.