Patient-calibrated modeling of ductal carcinoma in situ (DCIS): From microscopic measurements to macroscopic predictions of clinical progression

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Abstract:

Ductal carcinoma in situ (DCIS)—a type of breast cancer whose growth is confined to the duct lumen—is a significant precursor to invasive breast carcinoma. DCIS is commonly detected as a subtle pattern of calcifications in mammograms. These mammograms are also used to plan surgical resection of the tumor (lumpectomy), but multiple surgeries are often required to fully eliminate DCIS. This highlights deficiencies in the current use of mammography in planning surgery.

We have developed an agent-based cell model of DCIS, where cell motion is determined by the balance of biomechanical forces, and each cell's phenotype is determined by microenvironment-dependent stochastic processes. The model is rigorously calibrated to patient immunohistochemical (Ki-67, cleaved Caspase-3) and morphometric (viable rim thickness, duct radius, cell density) data, making possible patient-specific simulation and quantitative predictions of clinical DCIS progression.

After simulating 45 days of a solid-type DCIS with comedonecrosis, the model predicted:

(1) variation in the patient's Ki-67 data cannot be fully explained by oxygenation heterogeneity, pointing to additional signaling and/or genetic variations;

(2) necrotic cell lysis acts as a biomechanical stress relief, and is responsible for the linear DCIS growth observed in mammography;

(3) the rate of the DCIS tumor's advance varies with the duct radius;

(4) the tumor grows 7 to 10 mm per year—a finding that is consistent with mammographic data; and

(5) a tumor's mammographic size is linearly correlated with its (post-operative) pathologic size—in quantitative agreement with the clinical literature.

This work illustrates that physical conservation laws (as codified in a computational model) can provide new insight on the biophysical underpinnings of cancer. It also suggests that it will one day be possible to augment mammographic and other patient imaging modalities with rigorously-calibrated models that predict the (spatially-varying) optimal surgical margins based upon the patient's histopathologic data.

Keywords:

ductal carcinoma in situ (DCIS)
patient-specific model calibration
model-guided surgical planning