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Integration of Pathology, Radiology, and *in vitro* Data in Patient-Calibrated Cancer Simulations: Recent Advances and Future Outlook for Ductal Carcinoma In Situ (DCIS)

Ductal carcinoma in situ (DCIS), a significant precursor to invasive ductal carcinoma, is commonly detected as a subtle pattern of calcifications in mammograms. Such radiologic imaging is used to plan surgical resection of the tumor, but multiple surgeries are often required for complete excision. Pathologists use pre-surgical biopsies to stage the DCIS and help choose therapies. Some investigations are developing molecular profiling to help stratify patients and select therapeutic agents. For DCIS and more broadly in clinical oncology, there is currently no technique to quantitatively combine these diverse data sources to improve surgical and therapeutic planning; such planning generally also cannot incorporate novel *in vitro* measurements. Mechanistic, patient-calibrated computational models may provide a quantitative link between multiple patient data types, provides a platform for testing leading cancer biology hypotheses, and could help to extrapolate *in vitro* experimental findings to likely *in vivo* tumor behavior in individual patients.

We have recently developed a biologically-grounded agent-based model of tumor cells, where cell motion is determined by biomechanical forces, phenotype is controlled by microenvironment-dependent stochastic processes, and detailed phenotype sub-models describe cell volume changes, including the first model of cell calcification [1]. This work introduced the first patient-specific calibration to pathology data from a single time point (e.g., from a biopsy), and predicted DCIS growth rates and mammography-pathology size correlations; all predictions were quantitatively consistent with the clinical literature. We recently combined this work with a coarse-graining method to calibrate a continuum model of patient-specific DCIS surgical excision volumes; the predictions were reasonably successful in 14 of 17 test cases [2]. We are currently performing extensive, phenotype-specific *in vitro* time-course measurements of cell volume in breast cancer cell lines, allowing model refinements and more accurate simulation of emergent tumor behavior [3]. In an ongoing validation study, we are calibrating this refined model to predict patient-specific DCIS growth rates and mammography-pathology correlations in 5-10 patients, with validation against each patient's mammographic imaging [4]. All these pieces point to a day when mechanistic models are refined and constrained by *in vitro* measurements of relevant standardized or primary (patient-derived) cell lines, calibrated to patient pathology and other molecular profiling, and used to predict growth rates and estimate spatially-varying optimal surgical margins that surgeons can overlay on mammographic imaging. We close by discussing the wider outlook for patient-specific simulations beyond DCIS. We anticipate that such efforts will play an increasing role in driving experimental cell biology, testing and challenging current cancer biology orthodoxy, and ultimately improving clinical care.

References

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