

“Unmixing” Tissue Gene Expression Signatures from Tumor Biopsies

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Abstract

Emergent molecular measurement methods, such as DNA microarray, qRT-PCR, and many others, offer tremendous promise for the personalized treatment of cancer. These technologies measure the amount of specific proteins, RNA, DNA or other molecular targets from tumor specimens with the goal of “fingerprinting” individual cancers. Tumor specimens are heterogeneous; an individual specimen typically contains unknown amounts of multiple tissue types. Thus, the measured molecular concentrations result from an unknown mixture of tissue types, and must be normalized to account for the composition of the mixture.

For example, a breast tumor biopsy may contain normal, dysplastic and cancerous epithelial cells, as well as stromal components (fatty and connective tissue) and blood and lymphatic vessels. Our diagnostic interest focuses solely on the dysplastic and cancerous epithelial cells. The remaining tissue components serve to “contaminate” the signal of interest. The proportion of each of the tissue components changes as a function of patient characteristics (e.g., age), and varies spatially across the tumor region. Because each of the tissue components produces a different molecular signature, and the amount of each tissue type is specimen dependent, we must estimate the tissue composition of the specimen, and adjust the molecular signal for this composition.

Using the idea of a chemical mass balance, we consider the total measured concentrations to be a weighted sum of the individual tissue signatures, where weights are determined by the relative amounts of the different tissue types. We develop a compositional source apportionment model to estimate the relative amounts of tissue components in a tumor specimen. We then use these estimates to infer the tissue-specific concentrations of key molecular targets for sub-typing individual tumors. We anticipate these specific measurements will greatly improve our ability to discriminate between different classes of tumors, and allow more precise matching of each patient to the appropriate treatment.