Combined genomic, phenotypic and spatial analysis of intra-tumor heterogeneity

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In the course of cancer progression, tumors become increasingly heterogeneous. This intra-tumor heterogeneity is displayed on multiple levels. The population of cells within a single tumor is in fact a collection of sub-populations (subclones) that carry different genomic alterations. Such type of heterogeneity is called *genomic heterogeneit*y and is quantified from mutations in the tumor DNA. On top of that, tumor heterogeneity is exhibited on a phenotypic level, since tumor cells are intermixed with many other cell types. Such *phenotypic heterogeneity* can be inferred from gene expression data, using methods that deconvolute the measured expression signal into signals coming from different cell types (for example, different types of immune cells). On top of that, phenotypic heterogeneity can be characterized by image segmentation algorithms that recognize different cell types or tissues in histopathological tumor images. The spatial organization of the tumor and its microenvironment can vary, depending on the location of the tumor cells and the surrounding stroma, immune and necrotic cells. We will refer to this type of heterogeneity as *spatial heterogeneity*. Spatial heterogeneity can be assessed either again from tumor imaging or from spatial transcriptomics.

Tumor heterogeneity is predictive of cancer patient outcomes. Increased genomic tumor heterogeneity is associated with poor survival and complicates cancer treatment, as different subclones may show different response to therapy. It is increasingly appreciated that tumor heterogeneity is in fact an outcome of the evolutionary interplay between the growing tumor and its environment. Due to recent emergence of efficient immunotherapies, current studies put most focus on investigating the tumor-immune system interactions. Analysis of spatial heterogeneity in the tumor microenvironment revealed its importance in cancer progression and led to identification of new biomarkers. Combining the analysis of different types of heterogeneity has the potential to bring our understanding of cancer to the next level. Development of tools for combined heterogeneity analysis is an open problem. Here, we aim to propose and implement new computational approaches to study combined tumor heterogeneity and apply them to lung, colorectal and prostate cancer data. We anticipate that this new, full perspective on tumor heterogeneity will lead to novel, prognostic and predictive cancer biomarkers and will eventually be used in personalized treatment of this disease.