Deep learning-based morphometric unmixing of ex vivo multiplex 3D imaging data

Joint project

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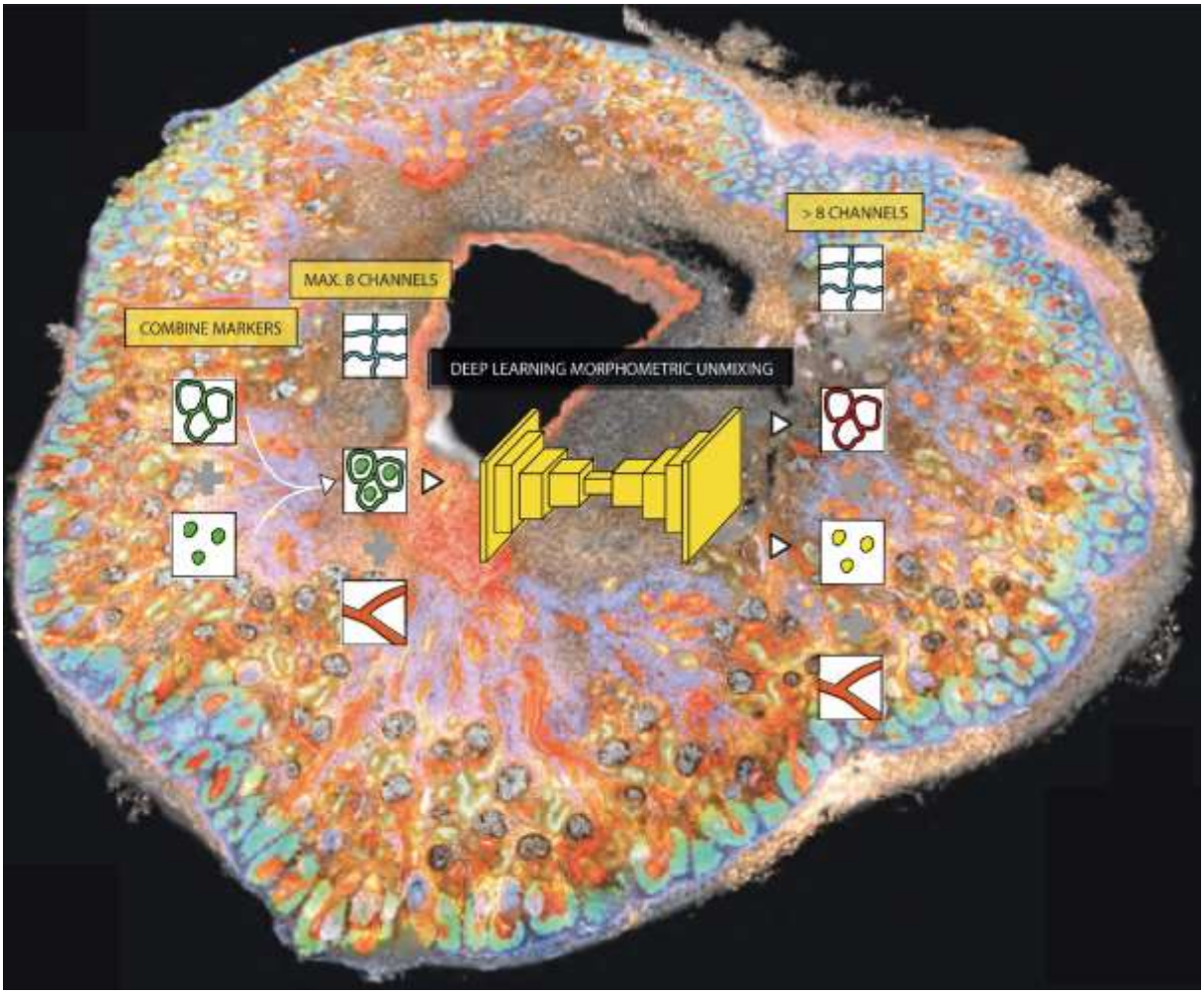

Background:

Single-cell resolution volumetric imaging permits the exploration of intact tissues (Rios et al, 2019, van Ineveld & Kleinnijenhuis, 2021), revealing the spatial and phenotypic relationships between diverse cell types that both organ development and cellular function depend on. One of the main limitations of volumetric imaging is the amount of markers that can be imaged simultaneous, a desired outcome to fully assess the composition of a tissue. To advance the potential of volumetric imaging, we have recently developed multispectral Large-scale Single-cell Resolution 3D (mLSR-3D) imaging for 'on-the-fly' linear unmixing single-scan acquisition of 8 spectrally-resolved fluorophores combined with SegmenTation Analysis by ParaLlelization of 3D Datasets (STAPL-3D), an automated pipeline for

(sub)cellular feature extraction and subsequent analysis of the millions of cells present within tissue (van Ineveld & Kleinnijenhuis, 2021). Applying this technique to human fetal kidney and Wilms tumor we were able to identified previously unreported tumor-specific populations, uniquely characterized by their spatial embedding or novel morphological attributes. To further unravel the highly complex spatial cellular organization within (cancer) tissue it is necessary to further expand the amount of cell types that can be resolved with our approach.

In this project we will apply deep learning (DL) in order to discriminate between different markers based on their subcellular distribution. Recent DL methods allow to transform auto-fluorescence images of an unlabeled tissue (or an aspecific staining) to a stained-version of the same sample (e.g. a pseudo-H&E staining; Rivenson et al., 2019). We aim to build on this methodology to unmix images with a unique spectral profile containing markers with distinct subcellular localization. Overall this approach with allow to increase the amount of markers that we are able to visualize in one same sample, thus better decomposing tissue complexity.

Aim: Development of a deep learning model to discriminate between of specific subcellular markers that share the same fluorescent properties.

Experimental approach For our aim we will apply a conditional adversarial networks for image-to-image translation. We will use a source dataset (two markers with distinct subcellular localization with the same spectral properties, stained with the same fluorophore) and a target dataset (each marker has specific spectral properties, stained with different fluorophores). These data will be used by the student to train a Consistent Adversarial Network for image to image translation between both sets. We will general several datasets consisting of combinations of markers with differing subcellular localization to assess for the wide application of our approach. This will allow us to identify distinct markers types in fixed tissue imaging, foregoing specific markers. This approach will be first applied to human kidney fetal tissues which is a highly organized structure that allows for assessment of the method and finally will be applied to Wilms tumor or other pediatric tumor material available, with the overarching purpose of getting insight into microenvironmental components that are influence tumor progression.

Methodology applied by the master student: The successful applicant will get the chance to work in the inspiring field of deep learning for medical image processing. He/she/they will learn to work with microscopy images acquired with methodology at the forefront of 3D (live) imaging and analyze them according to the latest insights in image processing. This not only includes the exciting prospect of getting to grips with increasingly essential machine learning methods (recently developed unpaired image to image translation), but also offers mastering the more general skills in 3D image analysis (e.g., image registration, artefact correction, segmentation). These skills are all in very high demand across a multitude of fields in (medical) imaging, in academia as well as industry. To be successful in this

challenging assignment, technical curiosity, persistance and (Python) coding skills are indispensable; massive motivation for helping us fight this dire disease even more so.

Literature of interest:

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