1/ Project supervisor:

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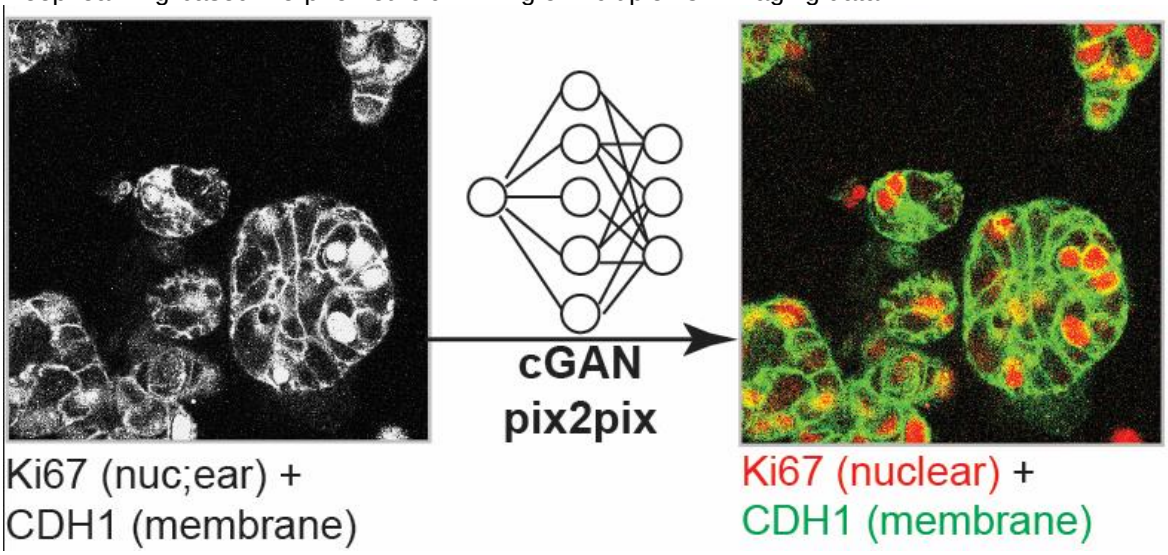
2/ Project title:

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



3/ Summary:

Single-cell resolution volumetric imaging is an uprising technique in the biomedical research as it permits to generate cellular maps of human healthy and tumoral tissues that can widen our knowledge of a disease (Rios et al, 2019, van Ineveld & Kleinnijenhuis, 2021). One of the main limitations of volumetric imaging is the amount of markers that can be imaged simultaneously, 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 identify 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 Attention-Guided Generative Adversial 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 organoid imaging data, for from live and fixed tissues.

4/ References:

- https://arxiv.org/pdf/1911.11897.pdf
- Ravian L. van Ineveld, Michiel Kleinnijenhuis, Maria Alieva, Sam de Blank, Mario Barrera Roman, Esmée J. van Vliet, Clara Martínez Mir, Hannah R. Johnson, Frank L. Bos, Raimond Heukers, Susana M. Chuva de Sousa Lopes, Jarno Drost, Johanna F. Dekkers, Ellen J. Wehrens, and Anne C. Rios. Revealing the spatio-phenotypic patterning of cells in healthy and tumor tissues with mLSR-3D and STAPL-3D. Nature Biotechnology, in press. 2021.Phillip Isola, Jun-Yan Zhu, Tinghui Zhou, Alexei A. Efros. Image-to-Image Translation with Conditional Adversarial Networks. CVPR, 2017
- Jan Tønnesen et al, Super-Resolution Imaging of the Extracellular Space in Living Brain Tissue, Cell, 2018.
- Yair Rivenson et al, Virtual histological staining of unlabelled tissue autofluorescence images via deep learning, Nature Biomedical Engeneering, 2019.

5/ Expected skills:

The successful applicant will get the chance of getting to grips with increasingly essential machine learning methods (deep-learning), but more general skills in 3D image analysis (e.g., image processing, resolution conversion, segmentation, tracking). He/she/they will learn to work with distinct types of data: video data and fixed multiplex imaging data. To be successful in this challenging assignment, technical curiosity, persistence and (Python/R) coding skills are indispensable; massive motivation for image analysis even more so.

6/ Bioinformatics human resources (for guiding the computational work):
Dr. Maria Alieva will be the daily the daily supervisor of the student for computational work. Two other computational members of Dr Alieva team guide and support the student. Additionally, the student will be integrated in the computational team of the Rios group and the Prinses Maxima Center (Netherlands), with whom we collaborate on this project and others. We have shared lab and computational meetings (in English), with two-three other computational scientists providing guidance and feedback on the project and a unique opportunity to get integrated into an international scientific environment.

7/ Computational infrastructure:

Most part of the project is expected to be carried on the personal laptop of the student, with remote connection to HPC, Google Colab Pro account (with more potent GPUs available) or 2-3 high-end workstations (shared resources of the team).

8/ Possibility of funding:

Although funding is not anticipated for this TFM, there is potential for further opportunities, such as pursuing a Ph.D. or securing a research assistant position in the group.