Master internship @ Paris Brain Institute, France
Inria team – "Aramis lab"

[MALMO]
MATHEMATICAL APPROACHES TO MODELING METABOLIC PLASTICITY AND HETEROGENEITY IN MELANOMA

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Project background: Cutaneous melanoma has rapidly evolved to become one of the most fatal forms of cancers today, accounting for approximately 57,000 deaths worldwide as of 2020 (Arnold et al., JAMA Dermatol 2022). Management of late-stage, metastatic melanoma is challenging. Despite rigorous therapies, clinical prognosis remains poor with an average survival time of 8 months (Garbe et al., Oncologist 2011). The infiltration of resident host cells by the cancer can stimulate molecular, cellular, and physical changes within the host tissue, creating a tumor microenvironment that is conducive to the survival and proliferation of melanoma.

In this study, our primary assumption is that chemotherapeutic resistance stems from the altered metabolic states within the tumor microenvironment. To date, our focus has been on the creation of a 2D segmentation model and 3D vascular pipeline using artificial intelligence (AI) algorithms to capture and assess evolving metabolic states. Our preliminary focus has been on blood vessels (although these original works will be extended to other cellular biomarkers, such as adipose sites). Through explication of blood vessel network characteristics, such as vascular shape and size, we can start understanding various metabolic states, particularly in treated versus non-treated conditions. Through the MALMO project, we are taking steps towards predicting treatment efficacy.

Our current reconstruction pipeline was designed for Whole Slide Images (WSIs) of melanoma tumors from Patient-Derived Xenograft (PDX) mouse models. So far, our primary focus has been on two imaging modalities: Hematoxylin and Eosin (H&E)- and cluster of differentiation 31 (CD31)-stained digital pathology slides. This involves the original, mouse-grown tumor being sliced into multiple sections and stained with the aforementioned staining techniques to visualize different cellular biomarkers. While the current 2D and 3D pipeline has been applied to H&E and CD31 images, we have in our possession a third and more rarely available imaging modality: the Hyperion. Hyperion images use a metal-tagged antibody-directed imaging mass cytometry platform and have a fluorescence appearance. Multiple stains can be visualized simultaneously, making it the one-stop-shop of imaging

modalities. However, the production of a single Hyperion image is time consuming and costly, and thus due to these constraints, only patches (rather than whole tissue sections) are available for processing. The next frontier in the MALMO project will be to carry out similar 2D and 3D processing but tailored towards the scarcely available Hyperion data.

Aim of the project: The objective of this project is to develop an algorithm that will receive the current patches of Hyperion data available and, using interpolation techniques and other imaging modalities available in the project (e.g., H&E and CD31) as a template, create whole Hyperion-marked tissue sections (i.e., image synthesis). The newly created whole-slide Hyperion images will then be applied to our existing 2D processing and 3D reconstruction pipeline.

Originality and expected impact of the project: The synthesis of whole tissue sections from a handful of patches will (1) ease the burden on the pathologists to produce complete datasets, (2) lead to the creation of complete datasets in a cost-effective and timely manner via using image synthesis techniques, and (3) expedite our understanding of treatment efficacy through our analyses of all whole tissue sections available using both real-time and synthesized data.

Working plan:
Data: Cutaneous melanoma tumors were extracted from humans during biopsy, then implanted in mice for growth, extraction and evaluation (**Figure 1**). PDX samples underwent serial sectioning at every 12µm over a depth of 2mm. Tissues underwent staining with H&E (red/purple staining), CD31 (blue/brown staining), and Hyperion (fluorescent coloring).

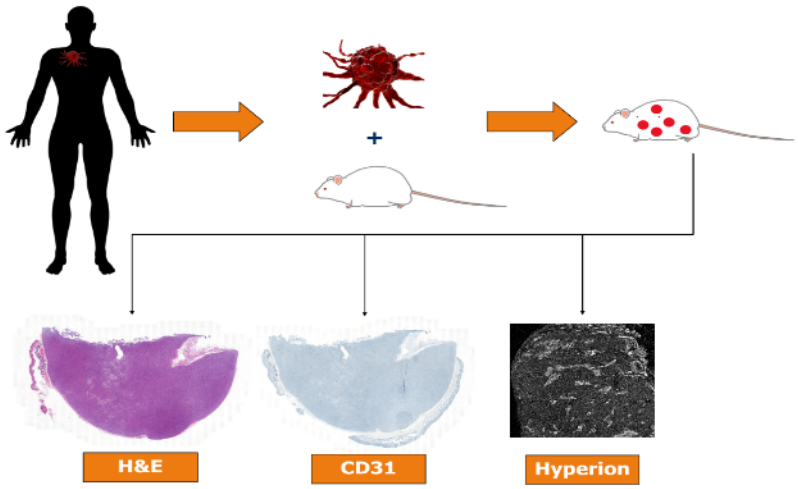

Figure 1

2D and 3D pipeline: The 3D vascular reconstruction pipeline includes the following steps: (A) images are exported and undergo several pre-processing techniques, including crop-centering, inpainting and cleaning of artefacts (i.e., removal of staining issues); (B) cleaned images undergo registration to ensure all images are aligned for the most accurate reconstruction; (C) given the size and resolution of WSIs, 2D information is extracted using patch-level segmentation to produce complete, segmented WSIs; and (D) all segmented WSIs undergo rendering and interpolation to produce a final 3D vascular model. The

objective of the 3D model is to then feed vascular-related information into the reaction diffusion model, designed to predict hypoxic states that could affect treatment efficacy.

Your steps in the project: The first part of your internship will consist of familiarizing yourself with the software currently used by pathologists, including QuPath and MCD Viewer. Your familiarity with these is essential to be able understand your data. Particularly given that WSIs are more challenging imaging modalities as compared to traditional medical images, such as MRIs. This is owing to their size and resolution, with a single digital pathology image being up too 100,000 pixels in length and 90,000 pixels in height. You will then proceed to assess currently available algorithms, the advantages, and challenges with these algorithms, as well as the gaps in these methods, particularly in their application to WSIs. Using this knowledge, you will create (with guidance from the supervision team), a new technique for synthesizing WSIs. You will justify the robustness of your method by comparing to it to current state-of-the-art methods using both quantitative and qualitative assessments.

Suited candidate profile: The candidate should have a solid background in Computer Science, with a special interest in machine and deep learning techniques, as well as mathematical modeling. Ideally, the candidate will be interested in applying their skills in the biomedical field. Important hands-on skills in computer science and data analysis are requested for this ambitious project. It is expected that the candidate is proficient in the use of the open-source programming language Python.

The candidate should have a strong interest in data analysis, numerical implementation and dealing with sparse and challenging datasets. The candidate must also possess good communication skills, particularly given that our team is multidisciplinary and consists of biologists, engineers, and theoreticians. The candidate must have very good skills in written and spoken English. We are seeking a motivated candidate, with a good track record, and an interest in working on high impact publications. Previous experience in working with medical data (incl. images) would also be valued. We encourage application from people with diverse backgrounds, including people with disability.

Project Partners:
Paris Brain Institute (ICM - Institut du Cerveau) - CNRS, Inserm, Sorbonne, AP-HP, INRIA team, Aramis : Located within the Pitié-Salpêtrière hospital, Paris, ICM is an international research center whose innovative concept and structure make it unique. The best scientists from all backgrounds and countries come together at the Institute to perform leading-edge research in this area. Daniel Racoceanu is Principal Investigator @ ICM and Professor at Sorbonne University, a multidisciplinary, research-intensive, world-class university. Located in the heart of Paris, with a regional presence, this university is committed to the success of its students and to meeting the scientific challenges of the 21st century. Thanks to its 55,300 students, 6,400 academic researchers and partner researchers, and 3,600 administrative and technical staff who make it a daily reality, Sorbonne University promotes diversity, creativity, innovation and openness to the world.

Laboratory of Pathogen Host Interactions (LPHI), Monpellier: LPHI is an innovative and high standard laboratory for basic research in biology. It hosts the Computational Systems Biology Team (CSBT), one of few of this kind in France, developing projects at the interface

between Biology, Physics and Mathematics. Team leader of CSBT, Ovidiu Radulescu is with University of Montpellier. Established in 1289, the University of Montpellier (UM) is the 6th largest university in France, with about 50,000 students including 7000 foreign students. One of the most innovative higher education institutions in the world, UM ranks very high in many international rankings : first in the world in the 2018 Shanghai ranking for Ecology, first most innovative French university in 2018 Reuter's ranking, 5th in France in 2018 Leiden's ranking for the quality of its scientific publications, 3rd French university in the 2019 "University Impact ranking" of Times Higher Education. These increasingly outstanding results reflect the dynamism triggered by the Montpellier University of Excellence I-SITE project since the prestigious certification was obtained in March 2017. Montpellier is a vibrant and sunny Southern France city. It benefits of the Mediterranean coast and proximity of the Cevennes mountain range, has a beautiful old city centre and great infrastructures.

The Institut de Recherche en Cancérologie de Montpellier (IRCM): IRCM is embedded in Montpellier Cancer Center. This research institute has raised its research to the highest international level in the field of fundamental and applied oncology. Research is carried out in close collaboration with the clinical departments of the Centre de Lutte Contre le Cancer de Montpellier (ICM: Institut du Cancer de Montpellier), and industrial partners. Jointly operated by Inserm, ICM and the University of Montpellier, the IRCM now brings together more than 200 people, researchers, clinicians, technicians and students, organized into 17 research teams supported by efficient core facilities and support services, including an innovative mass cytometry imaging platform that will be central to our project. In an extremely competitive and rapidly evolving field of research, the objectives of IRCM is to accelerate innovation and transfer new discoveries to the clinic.