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INTRODUCING [MALMO]: MATHEMATICAL APPROACHES TO MODELLING METABOLIC PLASTICITY AND HETEROGENEITY IN MELANOMA

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Context

Historically, malignant melanoma skin cancer was once a rare occurrence. However, over the past few decades, particularly following the mid-1950s, melanoma has evolved to become one of the most fatal forms of cancers, accounting for approximately 50,000 deaths worldwide annually.^{1,2} To illustrate, the study by Geller *et al.*, which used the Connecticut Tumor Registry (the longest, population-based cancer registry in the United States) showed an increased incidence rate of 17-fold [1.9 to 33.5 per 100,000] in men, and nine-fold [2.6 to 25.3 per 100,000] in women between 1950 to 2007.²

Surgical intervention at early stages of the disease have increased survival rates. For patients with metastatic disease, surgical treatment alone is not curative and must be coupled with chemotherapy for an improved line of defense.³ However, even with the evolution of new and novel treatments, the management of metastatic melanoma is complex, with metastatic-affected patients having median overall survival time of ~8 months.⁴ Metastasis is a multi-step process, involving the local invasion of tumor-associated stroma, intravasation into blood and lymphatic vessels, survival in peripheral blood (i.e., circulating tumor cells), extravasation into distant organs, and colonization to form metastases.⁵

In these newly emerged metastatic sites, the cancer cells are presented with new metabolic challenges. Additionally, the tumor microenvironment is typically poorly vascularized, resulting in deprivation of nutrients and oxygen. These conditions lead to a metabolic rewiring, in which the cancer adapts to modified metabolic changes, ensuring its survival and proliferation even under such stressful conditions.⁶ While it has been established that metabolic alterations of cancer cells influence the efficacy of chemotherapeutic treatments, the underlying mechanisms of this process are not completely understood.

Our project aims at understanding how tumor heterogeneity contributes to melanoma progression, with a particular interest in metabolic heterogeneity of melanoma cells. We are interested in understanding the molecular mechanisms underlying the metabolic rewiring of melanoma cells and its role in the phenotypic

plasticity of these cancer cells - a major driver of resistance to cancer therapies. In this paper, we provide a succinct synopsis of our project and present preliminary findings.

Method

This study aims to combine mathematical modelling with state-of-the-art artificial intelligence (AI) algorithms – including machine learning (ML) and deep learning (DL) methods – to automate pathology grading systems, conduct quantitative image analysis (including feature extraction of relevant biomarkers), and develop a model to predict the development of heterogeneity in melanoma tumors.

Data

The Melanoma Patient-Derived Xenograft (PDX) model was utilized. This process involves the extraction of cutaneous melanoma tumor tissues from human patients following surgery or biopsy methods, followed by the implantation and growth of human-extracted samples in mice. The mice-harvested samples then underwent serial sectioning, with each slide having a thickness of 4 μ m. Slides were stained with hematoxylin and eosin (H&E) and cluster of differentiation 31 (CD31). Slides were digitized into whole slide images (WSIs). Further images were acquired using the Hyperion imaging system (Fluidigm), which uses a metal-tagged antibody-directed imaging mass cytometry platform.⁷

Mathematical modelling

Given the complexity of melanoma pathogenesis, the mathematical model of melanoma progression should include several biological scales, including molecular, cellular, and tissular. The models that are being created in this project are based on partial differential equations (PDE) in time, space and several cellular internal variables, and aim to integrate inter- and intra-cellular scale variables in a consistent mesoscale representation and cope with spatially resolved single cell data generated by cutting-edge multiplexed biomarker tissue imaging devices.

Image analysis and artificial intelligence

In this project, various AI methods will be used to quantify the tumor spatial heterogeneity at different scales (distribution of blood vessels, invasion fronts, cell clusters and distribution of metabolic markers) from H&E- and CD31-stained histological sections, as well as Hyperion images. Ultimately, these methods will feed the mathematical model with information (initial data and parameters) needed for predicting tumor evolution upon targeted therapy. A particular accent will be set on the explicability of the innovative AI approaches, allowing us to develop a creative framework.

Results

Figure 1 demonstrates some preliminary results for segmentation of blood vessels from H&E-stained WSIs using the AI-based model U-Net.⁸ When compared to the ground truth labels, we can see the AI is already showing promise in automated pathology grading.

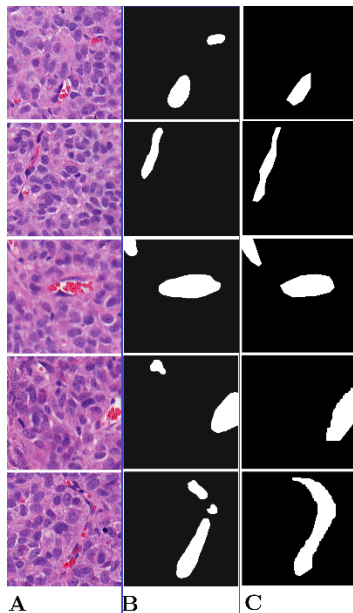


Figure 1: Segmentation of blood vessels from H&E-stained WSIs using AI. A. Original sections of H&E, B. Output from the U-Net model, and C. Ground-truth labels to compare the AI prediction.

Discussion

We propose a study in which mathematical modelling is coupled with AI-methods, aimed at understanding melanoma progression by quantifying pathological and structural features of H&E- and CD31-stained WSIs, as well as Hyperion imaging. Metabolic rewiring ensures melanoma cancer cells thrive even under the most stressful conditions. Understanding this rewiring and developing a prediction model based on AI and mathematics will assist in improving treatment efficacy. We have demonstrated some preliminary results illustrate the performance of our automated WSI grading method based on the U-Net architecture.

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