Combing AI methods and mesoscale numerical modeling for characterization of heterogeneity in melanoma

One 6 months internship (starting in the first quarter of 2021) is available at the **University of Montpellier. The internship is offered jointly with Sorbonne University (Paris) and with the Cancer Research Institute in Montpellier**. We are looking for master or engineering students with excellent skills in machine learning, mathematics (partial differential equations) and numerical analysis; proficiency in Python and Matlab is also required; knowledge in biology will be appreciated.

Context: Despite the recent development of new therapies, invasive melanoma represents a major health issue with a fatal outcome. 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. We have previously developed several mathematical models allowing to predict the development of heterogeneity in melanoma tumors[1]. These models, based on partial differential equations (PDE) in time, space and several cellular internal variables, 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. In this project, deep learning (discriminative) approaches will be reinforced by generative approaches issued from PDE mathematical models. This methodological combination (discriminative – generative) has been proven to be effective in most of the recent challenges in computational pathology.

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Problem(s): The project aims at solving three problems. i) identify and quantify specific patterns of melanoma cells (in our case, using deep learning) ii) develop a numerical model using the output of i) as initial data to predict development of heterogeneity in melanoma tumors at a metabolic level and iii) refine the numerical model using spatially-defined functional data obtained by a multiplexed biomarker tissue imaging technique (Hyperion).

Solution(s): Identification of specific patterns. As a training set, we will analyze a series of hematoxylin and eosin-stained melanoma tissue sections. The approach comprises segmentation and classification of several tissues (adipocytes, blood vessels, epithelium, tumour) using a supervised deep learning algorithm. Graph based mathematical morphology will be used to characterize the tissue heterogeneity in space and generate samples with similar characteristics in silico [2]. The final objective of our project is to determine blood vessel densities and predict intra-tumoral nutrient/oxygen gradients.

PDE mathematical model and Hyperion data. We will extend the partial differential equation based mathematical formalism introduced in [1] to cope with distribution of cells in metabolic dimensions. The mesoscale equations will be obtained using the Liouville equation with advection fluxes given by the ODE flow in the metabolic variables. Model order reduction techniques based on tropical scaling and singular perturbations [3] will be used to reduce the number of metabolic variable and render the model more tractable for numerical integration. Pseudo-spectral methods can also handle a large number of dimensions and will be tested in the context of our models.

Spatially-resolved multiplexed tissue imaging on the Hyperion system uniquely brings together the high-multiplex capabilities of mass cytometry with tissue imaging. The system uses metal-tagged antibodies that allow simultaneous interrogation of tens of protein markers in tissues and tumors at subcellular resolution while preserving the information in tissue architecture and cell morphology. The multiplexed spatial distributions obtained with Hyperion at the Cancer Research Institute in

Montpellier will be directly compared with the predictions of the numerical model, allowing the model validation and the parameter training. We expect to confirm preliminary modelling results obtained by our teams predicting metabolic zoning heterogeneity.

References

[1] Arran Hodgkinson, Laurent Le Cam, Dumitru Trucu, and Ovidiu Radulescu, Spatio-Genetic and Phenotypic Modelling Elucidates Resistance and Re-sensitisation to Treatment in Heterogeneous Melanoma, Journal of Theoretical Biology, 2019, 466:84-105.

[2] Bassem Ben Cheik, Nicolas Elie, Benoit Plancoulaine, Catherine Bor-Angelier, and Daniel Racoceanu. Spatial interaction analysis with graph based mathematical morphology for histopathology. 2017 IEEE 14th International Symposium on Biomedical Imaging (ISBI 2017).

[3] Radulescu O, Vakulenko S, Grigoriev D. Model Reduction of Biochemical Reactions Networks by Tropical Analysis Methods. Mathematical Modelling of Natural Phenomena (2015) 10: 124-138.

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To apply send a CV + motivation letter + names and email addresses of referees to Ovidiu Radulescu (ovidiu.radulescu@umontpellier.fr).