Master Internship offer

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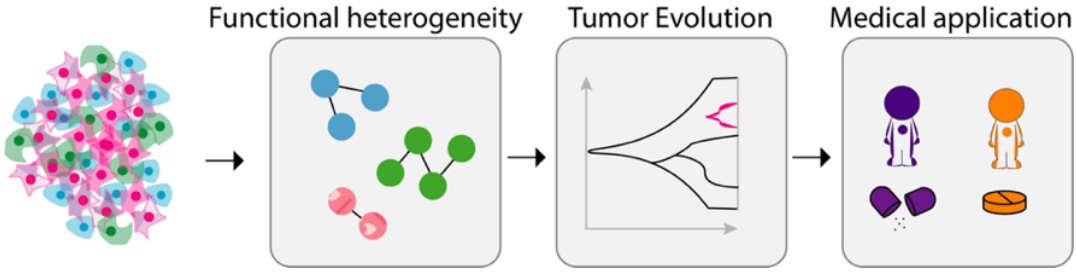
Computational approaches to study tumor heterogeneity and evolution of tumor cells populations

Current research on personalized oncology is expanding, in particular thanks to the reduction of sequencing costs allowing the generation of multi-omics profiles at the scale of individual tumors and individual cells. However, efforts to understand the extensive heterogeneity of tumors have heretofore been largely limited to cancer cells due to the lack of methods to study these cells together with their environment. Through a multidisciplinary approach, the goal of our group is to overcome this obstacle and expand our understanding of cancers as complex ecosystems, taking into account all cell states and functions present within a tumor.



Scientific Background:

Cancer cell populations exhibit genetic, epigenetic, transcriptional and phenotypical heterogeneity, between patients, as well as inside patient. Except for genetic variations, diversity in cancer cells strongly relies on macro and micro environmental cues, that triggers inheritable modifications which will influence tumor cells proliferation. [1]. Environmental cues can be separated in two main classes: extrinsic factors (such as patient history and drug treatment) and intrinsic factors, such as tumor micro-environment (TME) cellular composition. TME should be considered like a dynamic environmental variable, heterogeneous among and between patients, that has a major impact on tumor cells growth, division, resistance and metastasis [2]. From a methodological perspective, TME composition also strongly impacts the molecular profiling of the samples, as all cells presents in the TME (and not only tumor cells) will contribute to the recorded signal. Thus, heterogeneity and composition of the TME affect cancer cells behaviors, patient's stratification according to molecular properties, biomarkers detection and therefore personalized associated treatment, such as targeted therapies [3].

At the molecular level, tumor composition is difficult to assess and quantify, as it is hidden inside the bulk molecular profiles of the samples (averaged profile from millions of cells), with all cells present in the tumor (and not only cancer cells) contributing to the recorded signal. Deciphering tumor heterogeneity is methodologically highly challenging, but solving this issue will open new avenues towards a better understanding of the mechanisms by which tumors can evolve within an organism. In addition, it will offer leads to predict the patient response to treatment, notably in the context of personalized therapies.

2 Master internship subjects :

Subject 1: Inference of tumor functional heterogeneity

Computational inference of TME composition currently relies on deconvolution approaches that are impaired (i) by the lack of biological significance of estimated cell types and (ii) by the poor quality of biological reference cell types. A major reason for the failure of current theoretical inference of cellular heterogeneity is based on the fact that they do not consider the true biological behavior of a tumor ecosystem*: cells interact with each other, they have a dynamic behavior and their condition evolves with the tumor*. Instead of trying to infer heterogeneity at the cellular level, we focus on the functional modules structuring tumor heterogeneity.

The intern will combine multimodal information sources to leverage the identification of functional modules structuring tumor heterogeneity. To infer these functional modules, he/she will combine (i) the *a priori* knowledge of multilayer networks architecture in humans (experimental-based protein-protein interactions or inferred interaction pathways) and (ii) a personalized differential analysis at the molecular level, using a method we recently published that infers differential molecular profiles in each individual analyzed (PenDA [4]).

Subject 2: Development of joint deconvolution algorithms to quantify tumor heterogeneity from multiomic data.

Latest advances in deconvolution algorithms quantitatively inferring tumor composition rely on single-omic approaches (based on transcriptomes [5] or methylomes [6]). Multi-omics approaches (multiple measurements of all molecular events of different types from the same sample) are powerful means to address heterogeneity problems. For instance, combining gene expression and DNA methylation (DNAm, a non-heritable chemical modification of the DNA sequence that regulates gene expression) captures different properties of cellular states while reducing the impact of experimental and biological noise. Here we want to test how integration of complex multiomic datasets might improve the performances of deconvolution algorithms.

The intern will focus on the development of joint deconvolution algorithms. The deconvolution problem can be considered either as a mere dimension reduction problem -that will be the focus of the beginning of the internship-, or as an embedding problem where the subspace should feature components interpretable as cell types -that will be the focus of the end of the internship. Joint deconvolution methods will be evaluated with a ranking pipeline that is currently being developed in the team.

Required skills:

- Master degree in bioinformatics or data analysis (experience in sequencing data analysis and -omic data integration would be considered as an advantage)
- Good communication skills that allow productive interactions with an interdisciplinary team (including computer scientists, biologists and cancer pathologists)
- Programming skills (R, Python, bash), prior experience with relevant analytical software and related packages, knowledge of biostatistics would be appreciated
- Experience in artificial intelligence and machine learning would be appreciated
- Ability to communicate in both spoken and written English
- Autonomous and rigorous with a critical mind, ability to handle and analyze large and various data sets with biological and clinical information
- Prior experience with cancer is not mandatory

Location and supervision:

The candidate will be hosted in the Mathematics and Algorithms for Genomics (MAGe) team in the TIMC laboratory in Grenoble, made of researchers, engineers and students with skills in bioinformatics, genetics, statistics and physics. The intern will be supervised by Magali Richard, a CNRS researcher with an interdisciplinary expertise in experimental and computational genomics.

References:

[1] Lloyd et al (2016) *Cancer Research*. **76** : 3136; [2] Marusyk et al (2020*) Cancer cells*. **37** : 471; [3] Puleo et al (2018) *Gastroentreology*. **155**: 1999; [4] Richard et al (2020) *PLOS Computational Biology*. **16**: e1007869; [5] Avila Cobos et al (2020) *Nat. Commun*. **11**: 5650; [6] Scherer et al (2020) Nat. Protocol. **15**, 3240-3263