3iA Côte d'Azur
Interdisciplinary Institute for Artificial Intelligence

Ph.D. research topic

- Title of the proposed topic: **Machine and Deep Learning models for predicting response to immunotherapy in oncology from a federated multicenter database.**
- Research axis of the 3IA: **Axe 2**
- **Supervisor (name, affiliation, email): Olivier HUMBERT**, University professor - Hospital practitioner, Antoine Lacassagne Cancer Center, Université Côte d'Azur, Nice, olivier.humbert@univ-cotedazur.fr
- Potential co-supervisor (name, affiliation):
- The laboratory and/or research group: TIRO-MATOs Lab, UMR 4320, Medical School of Nice.

Apply by sending an email directly to the supervisor.
The application will include:

- Letter of recommendation of the supervisor indicated above
- Curriculum vitæ.
- Motivation Letter.
- Academic transcripts of a master's degree(s) or equivalent.
- At least, one letter of recommendation.
- Internship report, if possible.

⇨ **All the requested documents must be gathered and concatenated in a single PDF file named in the following format: LAST NAME of the candidate_Last Name of the supervisor_2023.pdf**

- **Description of the topic:**

In patients with metastatic non-small cell lung cancer, predictive Biomarkers of response to immune checkpoints inhibitors (immunotherapy) are needed to identify patients who will benefit from immunotherapy alone. In these patients, the systematic combination with chemotherapy could be avoided, leading to therapeutic de-escalation.

Recent preliminary studies have demonstrated that ^{18}FDG PET/CT, a 3D whole-body 3D, provides strong predictive and prognostic biomarkers of tumor response to immunotherapy. These imaging biomarkers are extracted from metastatic tumor load, tumor microenvironment and patients' immune system. Beyond standard statistical analysis of a few identified imaging biomarkers, deep learning-based convolutional neural networks (CNNs) are becoming a key tool for identifying complex imaging

patterns to predict the response of a particular patient to a particular treatment. CNNs hold a great promise as automatic diagnostic and predictive tools based on feature extraction learned directly from medical PET/CT images.

The objective of this PhD will be to exploit a large database from the ongoing "FEDERATED PET" project (see box below). We will tackle two challenges for the definition of AI driven image-based biomarkers in medical imaging applications:

- Classification of response to immunotherapy based on the analysis of volumetric PET images. This task requires handling extremely high-dimensional data represented in volumetric whole-body images, developing attention mechanisms that can identify response features of very small sizes and heterogeneous shapes as compared to the image volume.

- Segmentation of tumor lesions on PET images. This task requires the definition of protocols for the segmentation of very small areas, thus resort to anomaly detection techniques, such as based on generative models of image appearances.

The training for these 2 tasks will be performed with both centralized and federated learning. Performances of the 2 approaches will be compared. Moreover, multimodal analysis models will be developed in order to identify optimal fusion techniques to maximize the predictive power of appearance and segmentation-based features. Finally, robust annotation methods will be developed for the segmentation task to be learned in a federated setting, based on an active learning paradigm to be optimized in the collaborative setup of federated learning.

The PhD student will work on 2 medical databases (non-small cell cancer patients treated with immunotherapy):
- A monocentric database (Antoine Lacassagne center), of about 300 patients with PET/CT + clinical data, including for some of them biological samples (metabolomic analysis).
- A multicenter database of about 1000 PET/CT exams from 8 hospitals, connected to each other by a federated infrastructure developed by INRIA (Fed-BioMed).

As this is an interdisciplinary "mathematics and medicine" project, co-supervision by a doctor-mathematician pair is planned (INRIA/EURECOM).

The FEDERATED-PET project aims to exploit the full potential of deep learning to maximise the predictive and prognostic information contained in PET/CT images and provide a new generation of Artificial Intelligence (AI) based immunotherapy biomarkers. Among the main issues for development of AI algorithms is the availability of large, curated and multicentric training medical data, stored in a single and centralized repository. To tackle this problem, the FEDERATED-PET project aims at establishing the first French Federated Learning (FL) initiative for the collaborative Deep Learning analysis of 3D PET/CT images and clinical data, leveraging on state-of-the-art FL platforms and a large hospital network. FL offers a unique opportunity to collaboratively learn a shared model across multiple hospitals, solving the crucial problem of medical data sharing and exchange. The project is funded by INCA, DGOS and INRIA for more than one million euros.