3iA Côte d'Azur
Interdisciplinary Institute for Artificial Intelligence

Ph.D. research topic

- Title of the proposed topic: **Super-resolution in fluorescence microscopy images by generative learning methods**
- Research axis of the 3IA: : axis 3 AI for Computational Biology and Bio-inspired AI
- **Supervisor (name, affiliation, email):** Laure Blanc-Féraud, CNRS, blancf@i3s.unice.fr
- Potential co-supervisor (name, affiliation): Luca Calatroni, CNRS, calatroni@i3s.unice.fr, Sebastien Schaub, CNRS, sebastien.schaub@imev-mer.fr
- The laboratory and/or research group: Morpheme team (I3S, INRIA SAM, iBV)

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

- Curriculum vitæ.
- Motivation Letter.
- Academic transcripts of a master's degree(s) or equivalent.
- At least, one letter of recommendation.
- Internship report, if possible.
- Marks of the Master 1 and 2.

- **Description of the topic:**

Conventional optical microscopy techniques, as confocal microscopes, are widely used in biology for cellular and sub-cellular structures investigation in live cells. However, their spatial resolution is limited by the light diffraction phenomena, typically around 200nm in the transverse plane and 400nm in the optical axis. Over the recent years, several super-resolution techniques have been developed to bypass this limit and the Morpheme team has acquired a great expertise in this domain (see e.g. [1,2,4]).

The super-resolved image reconstruction problem is formalized in mathematical terms as an ill-posed inverse problem which is regularized by introducing a sparsity-promoting penalization. A more recent and increasingly popular class of methods producing out- standing results in many applied fields is based on the use of learning approaches. Among them, generative learning approaches as Generative Adversarial Networks (GANs) and Variational Auto Encoder (VAE) have the ability, upon training, of generating samples from the unknown distribution of given images. The context of interest for this PhD thesis project is the one of fluctuation-based super-resolution microscopy, where images are acquired from a sequence of short time exposure acquisitions. This approach is harmless for the biological sample and does not require specific microscope or fluorophore preparation. In this context, in our recent work [3] we proposed an approach based on the use of GANs to obtain a high-resolution image from noisy and blurred data. The strategy considered is based on the adversarial training of

the parameters of a physical simulator and of a discriminator network such that, at convergence, the distributions of the simulated and real images coincide.

- **Objective of the PhD thesis**

The purpose of this PhD thesis is to develop new methods combining data-driven and model-based approaches for the problem of super-resolution by molecule fluctuations. The fluctuation model in FluoGAN is so far approximated for simplicity purposes in the optimization procedure and will be extended in the thesis to a more precise one. VAE approach constitutes also a good alternative in this context and will be developed. Beyond the general approach, additional regularizing terms may have to be incorporated in the loss functions to promote fine structures (e.g. points or curves) in the super-resolved image as well as physically meaningful reconstruction. Furthermore, automatic parameter strategies will be investigated to limit the impact of algorithmic parameters on the final solution. Reconstruction properties of the generative models considered will be studied.
Methods and algorithms will be validated on data acquired on a calibrated fluorescent slide as well as on *Ostreopsis fibronectin*, a key element in the reproduction process of this toxic algae in view to explain their proliferation.

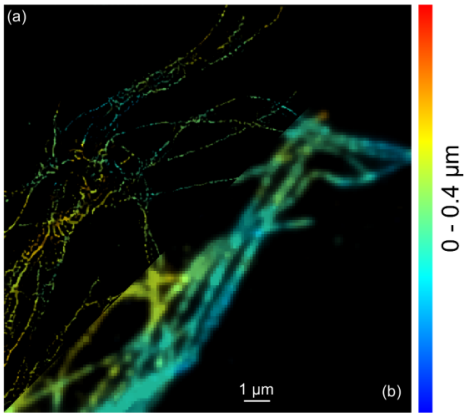

Figure 1 MA-TIRF super-resolution using the COL0RME approach (top left) in comparison with standard deconvolution approaches. Color quantifies depth [4].

[1] S. Gazagnes, E. Soubies, and L. Blanc-Féraud, "High density molecule localization for super-resolution microscopy using CEL0 based sparse approximation," in 2017 IEEE 14th International Symposium on Biomedical Imaging (ISBI 2017), pp. 28–31, 2017.
[2] V. Stergiopoulou, L. Calatroni, H. de Morais Goulart, S. Schaub, and L. Blanc-Féraud, "COL0RME: Super-resolution microscopy based on sparse blinking/fluctuating fluorophore localization and intensity estimation," Biological Imaging, vol. 2, 2022.
[3] M. Cachia, V. Stergiopoulou, L. Calatroni, S. Schaub, and L. Blanc-Féraud, "Fluorescence image deconvolution microscopy via generative adversarial learning (FluoGAN)," 2022. HAL preprint: https://hal.archives-ouvertes.fr/hal-03790156
*[4] V. Stergiopoulou, L. Calatroni, S. Schaub, and L. Blanc-Féraud, "*3D Image Super-Resolution by fluorophore fluctuations and MA-TIRF Microscopy reconstruction (3D-COL0RME)", *2022 IEEE 19th International Symposium on Biomedical Imaging (ISBI), 2022.*

- **Candidate profile:** Master student (M2 level) in signal/image processing, applied mathematics, data science and artificial intelligence with a strong background in mathematical image processing, inverse problems, learning, optimization, digital manipulation of images (in MATLAB, Python. . .) and use of libraries for deep learning (PyTorch/Tensorflow. . .), with a general interest in biology.