IN PARTNERSHIP WITH:
CNRS

Université Nice - Sophia Antipolis

Activity Report 2018

Project-Team MORPHEME

Morphologie et Images

IN COLLABORATION WITH: Institut de Biologie de Valrose, Laboratoire informatique, signaux systèmes de Sophia Antipolis (I3S)

RESEARCH CENTER
Sophia Antipolis - Méditerranée

THEME
Computational Biology

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Project-Team MORPHEME

Creation of the Team: 2011 September 01, updated into Project-Team: 2013 July 01

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Other Research Topics and Application Domains:

B1.1. - Biology
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B2.6. - Biological and medical imaging

1. Team, Visitors, External Collaborators

Research Scientists

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Laure Blanc-Féraud [CNRS, Senior Researcher, HDR]
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Grégoire Malandain [Inria, Senior Researcher, HDR]
Caroline Medioni [CNRS, Researcher]
Florence Besse [CNRS, Senior Researcher, HDR]

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Emmanuelle Poulain [GEMS (cifre)]
Agustina Razetti [Univ de Nice - Sophia Antipolis, until Mar 2018]

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Sarah Laroui [Inria, from Apr 2018 until Jul 2018]
Gaël Michelin [Inria, until Apr 2018, granted by ANR DIG-EM project]

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Cedric Girard Riboulleau [Inria, until Jun 2018]
Guillaume Lavisse [Inria, until Jun 2018]
Raphael Pages [Inria, from Mar 2018 until Aug 2018]
Baptiste Pouthier [Inria, from Jun 2018 until Sep 2018]

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Fabienne de Graeve [Univ de Nice - Sophia Antipolis, Associate Professor, from May 2018 until Aug 2018]
Sébastien Schaub [CNRS, from Oct 2018]

2. Overall Objectives

2.1. Overall Objectives

Morpheme is a joint project between Inria, CNRS and the University of Nice-Sophia Antipolis, involving the Computer Science, Signals and Systems Laboratory (I3S) (UMR 6070) and the Institute for Biology of Valrose (iBV) (CNRS/INSERM).

The scientific objectives of MORPHEME are to characterize and model the development and the morphological properties of biological structures from the cell to the supra-cellular scale. Being at the interface between computational science and biology, we plan to understand the morphological changes that occur during development combining in vivo imaging, image processing and computational modeling.

The morphology and topology of mesoscopic structures, indeed, do have a key influence on the functional behavior of organs. Our goal is to characterize different populations or development conditions based on the shape of cellular and supra-cellular structures, including micro-vascular networks and dendrite/axon networks. Using microscopy or tomography images, we plan to extract quantitative parameters to characterize morphometry over time and in different samples. We will then statistically analyze shapes and complex structures to identify relevant markers and define classification tools. Finally, we will propose models explaining the temporal evolution of the observed samples. With this, we hope to better understand the development of normal tissues, but also characterize at the supra-cellular level different pathologies such as the Fragile X Syndrome, Alzheimer or diabetes.

3. Research Program

3.1. Research program

The recent advent of an increasing number of new microscopy techniques giving access to high throughput screenings and micro or nano-metric resolutions provides a means for quantitative imaging of biological structures and phenomena. To conduct quantitative biological studies based on these new data, it is necessary to develop non-standard specific tools. This requires using a multi-disciplinary approach. We need biologists to define experiment protocols and interpret the results, but also physicists to model the sensors, computer scientists to develop algorithms and mathematicians to model the resulting information. These different expertises are combined within the Morpheme team. This generates a fecund frame for exchanging expertise, knowledge, leading to an optimal framework for the different tasks (imaging, image analysis, classification, modeling). We thus aim at providing adapted and robust tools required to describe, explain and model fundamental phenomena underlying the morphogenesis of cellular and supra-cellular biological structures. Combining experimental manipulations, in vivo imaging, image processing and computational modeling, we plan to provide methods for the quantitative analysis of the morphological changes that occur during development. This is of key importance as the morphology and topology of mesoscopic structures govern organ and cell function. Alterations in the genetic programs underlying cellular morphogenesis have been linked to a range of pathologies.
Biological questions we will focus on include:

1. what are the parameters and the factors controlling the establishment of ramified structures? (Are they really organize to ensure maximal coverage? How are genetic and physical constraints limiting their morphology?),
2. how are newly generated cells incorporated into reorganizing tissues during development? (is the relative position of cells governed by the lineage they belong to?)

Our goal is to characterize different populations or development conditions based on the shape of cellular and supra-cellular structures, e.g. micro-vascular networks, dendrite/axon networks, tissues from 2D, 2D+t, 3D or 3D+t images (obtained with confocal microscopy, video-microscopy, photon-microscopy or micro-tomography). We plan to extract shapes or quantitative parameters to characterize the morphometric properties of different samples. On the one hand, we will propose numerical and biological models explaining the temporal evolution of the sample, and on the other hand, we will statistically analyze shapes and complex structures to identify relevant markers for classification purposes. This should contribute to a better understanding of the development of normal tissues but also to a characterization at the supra-cellular scale of different pathologies such as Alzheimer, cancer, diabetes, or the Fragile X Syndrome. In this multidisciplinary context, several challenges have to be faced. The expertise of biologists concerning sample generation, as well as optimization of experimental protocols and imaging conditions, is of course crucial. However, the imaging protocols optimized for a qualitative analysis may be sub-optimal for quantitative biology. Second, sample imaging is only a first step, as we need to extract quantitative information. Achieving quantitative imaging remains an open issue in biology, and requires close interactions between biologists, computer scientists and applied mathematicians. On the one hand, experimental and imaging protocols should integrate constraints from the downstream computer-assisted analysis, yielding to a trade-off between qualitative optimized and quantitative optimized protocols. On the other hand, computer analysis should integrate constraints specific to the biological problem, from acquisition to quantitative information extraction. There is therefore a need of specificity for embedding precise biological information for a given task. Besides, a level of generality is also desirable for addressing data from different teams acquired with different protocols and/or sensors. The mathematical modeling of the physics of the acquisition system will yield higher performance reconstruction/restoration algorithms in terms of accuracy. Therefore, physicists and computer scientists have to work together. Quantitative information extraction also has to deal with both the complexity of the structures of interest (e.g., very dense network, small structure detection in a volume, multiscale behavior, ...) and the unavoidable defects of in vivo imaging (artifacts, missing data, ...). Incorporating biological expertise in model-based segmentation methods provides the required specificity while robustness gained from a methodological analysis increases

the generality. Finally, beyond image processing, we aim at quantifying and then statistically analyzing shapes and complex structures (e.g., neuronal or vascular networks), static or in evolution, taking into account variability. In this context, learning methods will be developed for determining (dis)similarity measures between two samples or for determining directly a classification rule using discriminative models, generative models, or hybrid models. Besides, some metrics for comparing, classifying and characterizing objects under study are necessary. We will construct such metrics for biological structures such as neuronal or vascular networks. Attention will be paid to computational cost and scalability of the developed algorithms: biological experimentations generally yield huge data sets resulting from high throughput screenings. The research of Morpheme will be developed along the following axes:

- **Imaging:** this includes i) definition of the studied populations (experimental conditions) and preparation of samples, ii) definition of relevant quantitative characteristics and optimized acquisition protocol (staining, imaging, ...) for the specific biological question, and iii) reconstruction/restoration of native data to improve the image readability and interpretation.
- **Feature extraction:** this consists in detecting and delineating the biological structures of interest from images. Embedding biological properties in the algorithms and models is a key issue. Two main challenges are the variability, both in shape and scale, of biological structures and the huge size of data sets. Following features along time will allow to address morphogenesis and structure development.
- **Classification/Interpretation:** considering a database of images containing different populations, we can infer the parameters associated with a given model on each dataset from which the biological structure under study has been extracted. We plan to define classification schemes for characterizing the different populations based either on the model parameters, or on some specific metric between the extracted structures.
- **Modeling:** two aspects will be considered. This first one consists in modeling biological phenomena such as axon growing or network topology in different contexts. One main advantage of our team is the possibility to use the image information for calibrating and/or validating the biological models. Calibration induces parameter inference as a main challenge. The second aspect consists in using a prior based on biological properties for extracting relevant information from images. Here again, combining biology and computer science expertise is a key point.

4. Highlights of the Year

4.1. Highlights of the Year

4.1.1. Awards

Emmanuel Soubies won the Phd Prize of the GdR MIA (Mathématiques de l'Imagerie et de ses Applications)

5. New Software and Platforms

5.1. Obj.MPP

KEYWORDS: Object detection - Marked Point Process - Parametric model

FUNCTIONAL DESCRIPTION: Obj.MPP implements the detection of parametric objects using a Marked Point Process (MPP). A parametric object is an n-dimensional piece of signal defined by a finite set of parameters. Detecting an object in a signal amounts to finding a position at which the signal can be described well enough by a specific set of parameters (unknowns of the detection problem). The detection task amounts to finding all such objects. Typically, the signal is a 2-dimensional grayscale image and the parametric objects are bright disks on a dark background. In this case, each object is defined by a single parameter: the disk radius. Note however that the core function of Obj.MPP is not tied to a particular context (2-dimensional imaging is just an example).

- Author: Eric Debreuve
- Contact: Eric Debreuve
- Publications: Stochastic geometry for image analysis - Multiple objects detection in biological images using a marked point process framework - An efficient optimizer for simple point process models - Multiple Birth and Cut Algorithm for Multiple Object Detection
- URL: https://team.inria.fr/morpheme/obj-mpp-object-detection-using-a-marked-point-process/

5.2. ATOLS

Adaptative Threshold Operator based on Level Sets
KEYWORDS: Object detection - Level Set
FUNCTIONAL DESCRIPTION: Atols is a Python script allowing to detect features on images using a contrast scoring. Thus, it's possible to detect features at different levels of intensity unlike a simple threshold which would only keep features above its value.

- Authors: Kevin Giulietti and Guillaume Lavisse
- Contact: Xavier Descombes
- URL: https://team.inria.fr/morpheme/software/

5.3. Small particle detection

KEYWORDS: Image processing - Image segmentation - Object detection - Computational biology - Fluorescence microscopy - Biomedical imaging
FUNCTIONAL DESCRIPTION: An algorithm primarily design to detect objects whose sizes aren't larger a few pixels (particles) on fluorescence microscopy images.

It is an simplified version of marked point process.

- Contact: Nicolas Cedilnik
- Publications: SPADE: A Small Particle Detection Method Using A Dictionary Of Shapes Within The Marked Point Process Framework - SPADE: A Small Particle Detection Method Using A Dictionary Of Shapes Within The Marked Point Process Framework
- URL: https://gitlab.inria.fr/ncedilni/spade

6. New Results

6.1. Exact biconvex reformulation of the $\ell_2 - \ell_0$ minimization problem

Participants: Gilles Aubert, Arne Henrik Bechensteen, Laure Blanc-Féraud.

We focus on the problem of minimizing the least-squares loss function under the constraint that the reconstructed signal is at maximum k-sparse. This is called the ℓ_2-ℓ_0 constrained problem. The ℓ_0 pseudo-norm counts the number of non-zero elements in a vector. The minimization problem is of interest in signal processing, with a wide range of applications such as compressed sensing, source separation, and super-resolution imaging.

Based on the results of [20], we reformulate the ℓ_0 pseudo-norm exactly as a convex minimization problem by introducing an auxiliary variable. We then propose an exact biconvex reformulation of the $\ell_2 - \ell_0$ constrained and penalized problems. We give correspondence results between minimizer of the initial function and the reformulated ones. The reformulation is biconvex. This property is used to derive a minimization algorithm.

We apply the algorithm to the problem of Single-Molecule Localization Microscopy and compare the results with the well-known IHT algorithm [13]. Both visually and numerically the biconvex reformulations perform better. This work has been presented at the iTWIST 2018 workshop [5].

Furthermore, the algorithm has been compared to the IRL1-CEL0 [14] and Deep-STORM [15] (see figure 1). The IRL1-CEL0 minimizes an exact relaxation [19] of the $\ell_2 - \ell_0$ penalized form and Deep-STORM is an algorithm that uses deep-learning and convolutional network to localize the molecules. This work has been accepted to the ISBI 2019 conference.

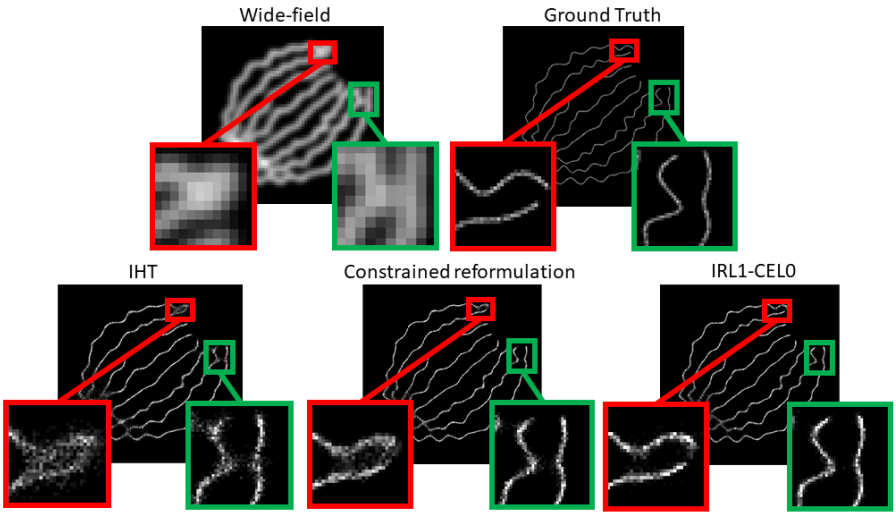

Figure 1. Reconstruction by the different algorithms. Data set from ISBI 2013 challenge [18].

6.2. Reconstruction of mosaic of microscopic images

Participants: Kevin Giulietti, Eric Debreuve, Grégoire Malandain.

This work takes place within the ANR PhaseQuant.

In microscopy imaging, a trade-off has to be made between a high resolution, that enables to see details, and the width of the field of view, that enables to see many objects. Such a trade-off is avoided by mosaicing, which consists in the acquisition of several images, say $N \times N$, with a small overlap between images. This way, an image with a N larger field of view can be reconstructed with the same resolution than a single microscopic image.

Such an imaging protocol is available on many microscopy software. Basically, displacements of the table on which lies the material to be imaged are programmed, and used to reconstruct the mosaic. However, it appears (at the overlapping areas) that a residual offset is still present. Analysis of acquisitions of both real and controlled experiments demonstrate that the table motions are not exactly reproducible (see figure 2), and that the cause of the offset is twofold: first a mis-alignement of the micrometer table axis with respect to the microscope axis, and second errors in the displacement computed by the micrometer table. Thanks to an

image-based calculation of the axis mis-alignement, it has been shown that the first type error can easily be corrected.

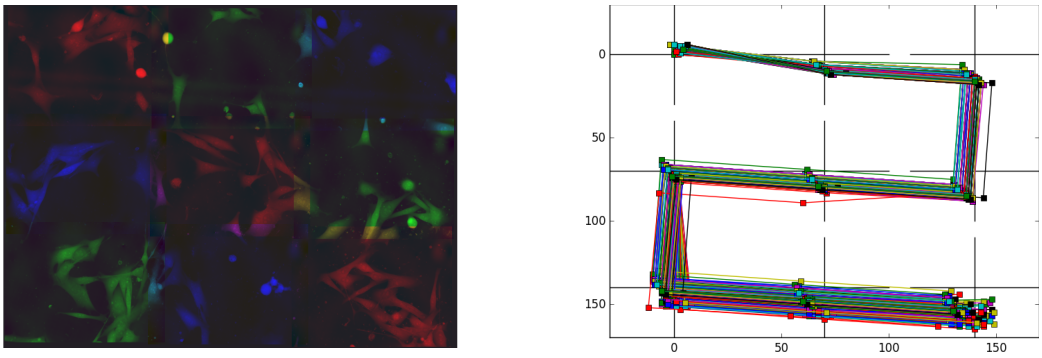

Figure 2. Example of a mosaic reconstructed for one acquisition timepoint. Estimation of the relative image position through time for the whole sequence (displacements with respect to the expected position have been magnified for visualization purpose).

6.3. Cytoplasm segmentation from cells confocal microscopy images

Participants: Somia Rahmoun, Fabienne de Graeve, Eric Debreuve, Xavier Descombes.

This work takes place within the ANR RNAGRIMP.

As part of the ANR project RNAGRIMP, two series of images have been acquired using fluorescence microscopy: one where the cell cytoplasm has been stained with GFP (Green Fluorescent Protein), the second where the nuclei have been stained with DAPI (4',6-diamidino-2-phenylindole). The first steps are detecting the nuclei on the DAPI images and learning a classification procedure into living cell or dead cell based on morphological and radiometric nuclei properties (average intensity, area, granularity, circularity ...).

A specific CellProfiler pipeline has been developed for this, and CellProfiler Analyst has been used to learn a decision tree for automatic nuclei (hence, cell) classification.

The next step is to segment the cell cytoplasms on the GFP images. Indeed, the target RNP-IMP granules appear in that compartment of the cell and are visible through their GFP response. This segmentation problem is particularly difficult due the heterogeneity of the cells intensity. This heterogeneity even appears within a given cell. Besides, cells sometimes form clusters in which there is no clear separation between adjacent cells. In this context, we have considered a two steps algorithm to segment the cytoplasm. The first step consists of the image segmentation in small areas called superpixels that represent adjacent pixels with similar intensity. We have evaluated and compared different strategies (based on iterative clustering, minimum spanning tree, persistent edge selection ...) to achieve such a segmentation. Finally, we have selected an automatic algorithm based on the watershed transform. We are currently developing an algorithm to merge superpixels into the final segmentation.

Meanwhile, we have developed a supervised software to manually merge the superpixels (see Fig. 3). This tool can also be used by biologist to correct any segmentation error.

6.4. Cytoneme detection and characterization

Participants: Eric Debreuve, Xavier Descombes.

This work is made in collaboration with Caterina Novelli, Tamas Matusek, Pascal Thérond (iBV).

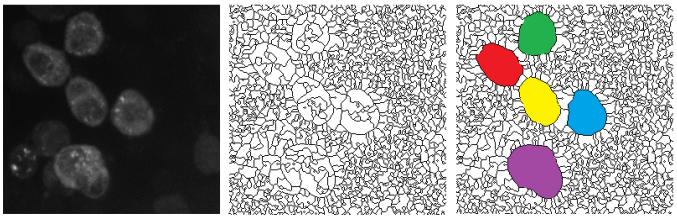

Figure 3. Superpixels merging: each color corresponds to a cell that is obtained by merging several superpixels.

This work is supported by the ANR project HMOVE. Cellular communication is one of the most important processes for controlling the morphogenesis of organs (i.e. the set of laws that determine the structure of tissues and organs during embryonic development). Understanding the communication both ways is an important issue in the field of developmental biology and it has recently been shown that the exchange of information between cells is controlled by long cellular extensions called "cytonemes". Last year, we had developed a pipeline for automatic cell membrane detection and cytoneme extraction from in vivo images obtained by confocal microscopy. When testing the proposed method on new images with varying acquisition conditions, we found it to be less reliable than expected. While retaining the same general philosophy (use of Frangi enhancement filter, skeletonization, and Dijkstra shortest path algorithm), we largely rethought the approach to make it more robust to acquisition conditions, more reliable in general, and faster (see Fig. 4). Some topological and geometrical features are then computed on the graph-based representation of the cytonemes in order to characterize in which respect wild-type and mutant conditions are different or similar. A journal paper is in preparation based on the analysis and interpretation of these results by our biologist colleagues.

6.5. Classification and Modeling of the Fibronectin Network in Extracellular Matrices

Participants: Anca-Ioana Grapa, Laure Blanc-Féraud, Xavier Descombes, Sébastien Schaub.

This work is done in collaboration with Ellen Van Obberghen-Schilling and Georgios Efthymiou (iBV).

We are interested in the numerical analysis and modeling of the Fibronectin (FN) network, a major extracellular matrix (ECM) molecule expressed in pathological states (fibrosis, cancer, etc). Our goal is to develop numerical quantitative biomarkers that describe the organization of the different FN networks from 2D confocal miscroscopy images (Figure 5).

In a previous work, we have derived a pipeline to classify a given tissue among the four FN variants (cell-derived matrices), based on a decomposition into discrete fast curvelet transform coefficients. We ensured the invariance to rotation of the coefficients and then fed them to a DAG-SVM multiclassifier, in order to prove their discriminative ability in the context of classification of the four FN variants. The results were published in [7].

The second step of our work consists in setting up the modeling of the FN networks starting from a graph-based representation, built on top of Gabor features (fiber scale, orientation, etc). More specifically, Gabor filters are used to enhance the fibrillar structures, followed by a morphological skeletonization of the maximum response of the Gabor filter set. We then derive the corresponding graph networks that generate relevant fiber geometry statistics (e.g fiber length, node degree, node density, etc).

Starting from the graph networks, we manage to reconnect the missing fibers in the skeleton, that are due to previous morphological operations. To do so, we use the Gabor maximum response as a guideline for reconnection, and connect the fibers within a predefined cone sector around the local fiber orientation. The

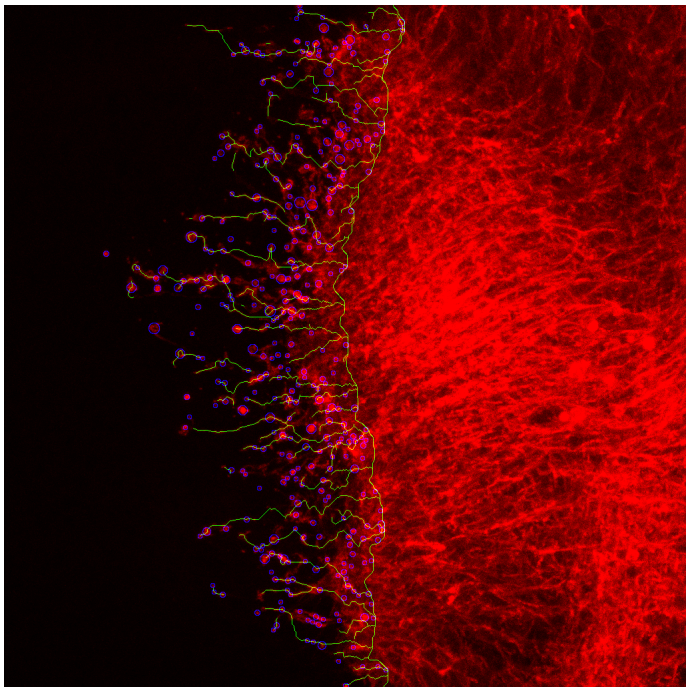

Figure 4. A result of membrane detection and cytoneme extraction.

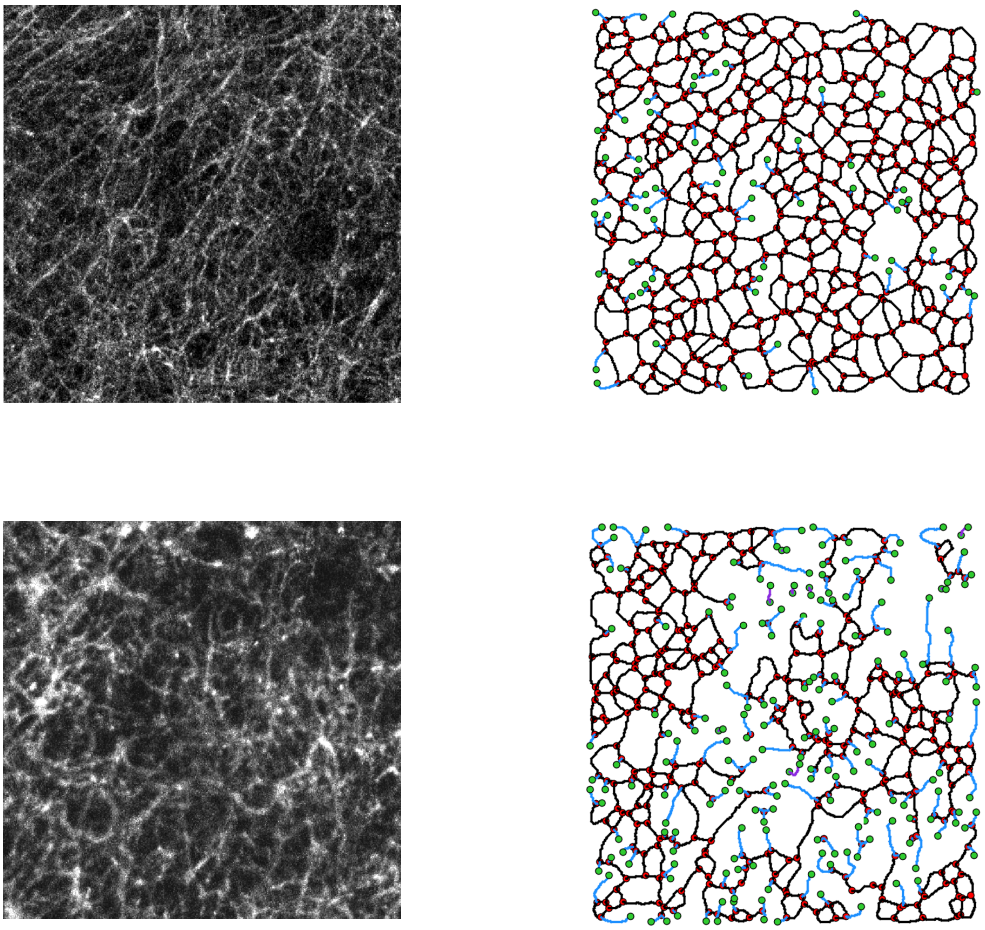

Figure 5. Different variants of FN and their associated graph networks. Top row: A+ fibronectin; bottom row: A-B- fibronectin. Left: confocal images; right: associated graphs.

graph parameters corresponding to the improved skeletonizations of the four FN variants, are then classified by a DAG-SVM. It is thus shown that graph features can discriminate among the FN variants.

The next step concerns the development of a metric between graph networks that takes into account their topology, to provide a meaningful distance between them. We currently investigate methods based on optimal transport, that are able to compare discrete probability distributions and respect the local geometry. The techniques that rely on graph structures to compute a geodesic distance (e.g. Gromov-Wasserstein) and/or barycenter of structured data (e.g. mesh structures) [16], serve as inspiration for our work. The distance is obtained following a minimization of the cost of transport of the mass from one distribution to the other. Despite the fact that they consider the intrinsic distance within each space (i.e graphs) in the cost formulation, these methods don't explicitly take into account the graph structure defined by the adjacency matrices. To counteract some of the shortcomings, we consider parallel graph-matching methods and redefine our problem in a many-to-many graph matching context, where the distance between the graphs is given by the optimal alignment of their structure determined by the mapping between the vertices [21].

Finally, we analyze the advantages and drawbacks of the two techniques both for small-size graphs as well as for FN graphs to derive an appropriate formulation of the distance among them, which will be useful to compare the FN fiber networks.

6.6. Detection of Brain Strokes Using Microwave Tomography

Participant: Laure Blanc-Féraud.

This work is done in collaboration with Vanna Lisa Coli and Juliette Leblond (EPI Factas, Inria Sophia), Pierre-Henri Tournier (Université Sorbonne, CNRS, LJLL, Inria, Paris) , Victorita Dolean (Université Côte d'Azur, CNRS, LJAD, Nice), Ibtissam El Kanfoud, Christian Pichot, Claire Migliaccio (Université Côte d'Azur, CNRS, LEAT, Sophia Antipolis).

Brain strokes are one of the leading causes of disability and mortality in adults in developed countries. The ischemic stroke (85% of total cases) and hemorrhagic stroke (15%) must be treated with opposite therapies, so that the determination of the stroke nature must be made quickly to apply the appropriate treatment. Recent works in biomedical imaging showed that strokes produce variations on brain tissues complex electric permittivity that can be detected by means of microwave tomography.

We present here some synthetic results obtained with an experimental microwave tomography-based portable system for the early detection and monitoring of brain strokes (Figure 6). The determination of electric permittivity requires the solution of a coupled direct-inverse problem, where massive parallel computation from domain decomposition method and regularization techniques for optimization methods are employed. Synthetic data are obtained with electromagnetic simulations and a noise model developed for the specific problem, which has been derived from measurements errors with the experimental imaging system.

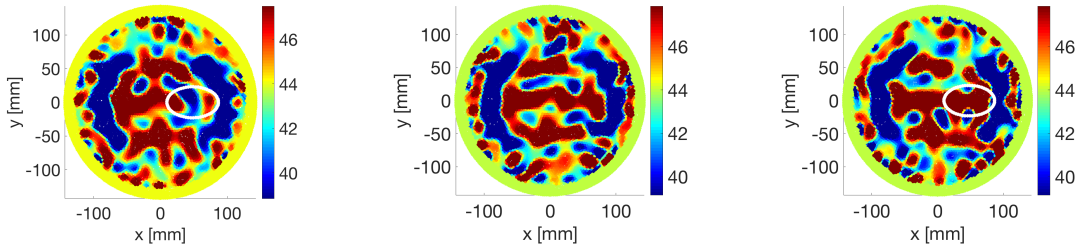

Figure 6. From left to right: brain with ischemic stroke, healthy brain and brain with hemorrhagic stroke (real part of permittivity ϵ_r).

6.7. Organoid growth tracking

Participants: Cédric Girard Riboulleau, Xavier Descombes.

This work is a collaboration with F.-R. Roustan, S. Torrino, S. Clavel and F. Bost from C3M. It was partially supported by the UCA Jedi Idex.

Organoid culture is a major challenge toward personalized medicine. It is now possible to partially reconstruct the structure of organs from a single biopsy. This new technology named organoid for sane cells or tumoroid for cancer cells allows the test of different molecules on cells withdrawn on a patient to retrieve the most efficient one for this patient. In this context, the main goal of this work is to develop a numerical scheme to automatically assess the effect of a given treatment on the organoid growth. We consider a time sequence of 2D confocal microscopy images of a population of organoids. We have considered different approaches to detect the organoids in the images. These approaches include edge detection using Canny filter, thresholding combined with mathematical morphology tools, texture analysis through Markov Random Fields, marked point processes. We have also modified several times the imaging protocol in order to simplify the object detection. To evaluate the growth of each organoid we have to match the objects detected in two consecutive frames. We have developed a matching algorithm based on a majority voting. We compute the vector between every pair of detected objects on both frames. Assuming that there is only a translation between the two frames we estimate it as the most represented vector. With this framework we have shown that the studied treatment has stopped the organoid growth (see figure 7).

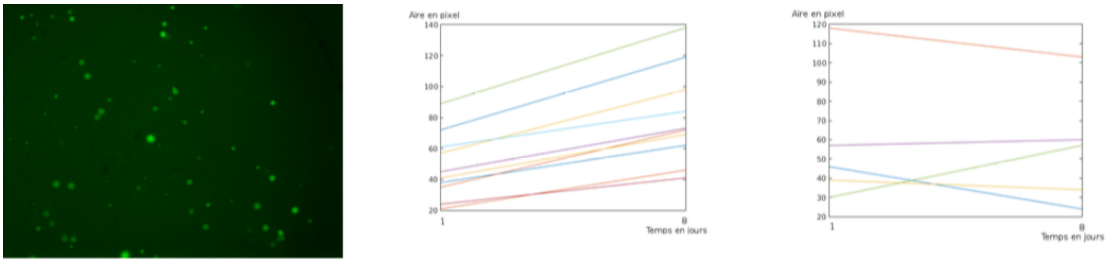

Figure 7. Image of organoids (left), Temporal evolution of some organoid size without treatment (middle) and with treatment (right).

6.8. Vesicles tracking

Participants: Raphael Pages, Xavier Descombes.

This work is a collaboration with P. Juan, M. Furthauer from iBV. It was partially supported by the UCA Jedi Idex.

We take advantage of the optical transparency of the zebrafish to study the formation, transport and function of extracellular vesicles in vivo. In the zebrafish Left/Right Organizer (LRO) a cilia-driven fluid flow promotes the directional transport of extracellular vesicles in the organ lumen. We have developed a software to analyze the vesicles trajectory. Assuming that the speed is slow enough, the detection is performed by considering the 2D+t time sequence of data as a 3D volume in which the vesicle trajectories are represented by tubular shapes. We first remove the background in each slice by subtracting a temporal mean computed on a sliding window. The trajectories are than enhanced by a Frangi filter followed by a top hat operator. Finally, the trajectories are obtained by a threshold and filtered to remove those corresponding to cilia movement. To compare different populations we then compute a mean shape of the LRO using an elastic shape metric. The trajectories detected on the different samples of a given population are then projected onto this common space. To have a dense representation of the vesicles speed inside the LRO we then extrapolate the detected trajectories on the whole population using a Markov random field regularization (see figure 8).

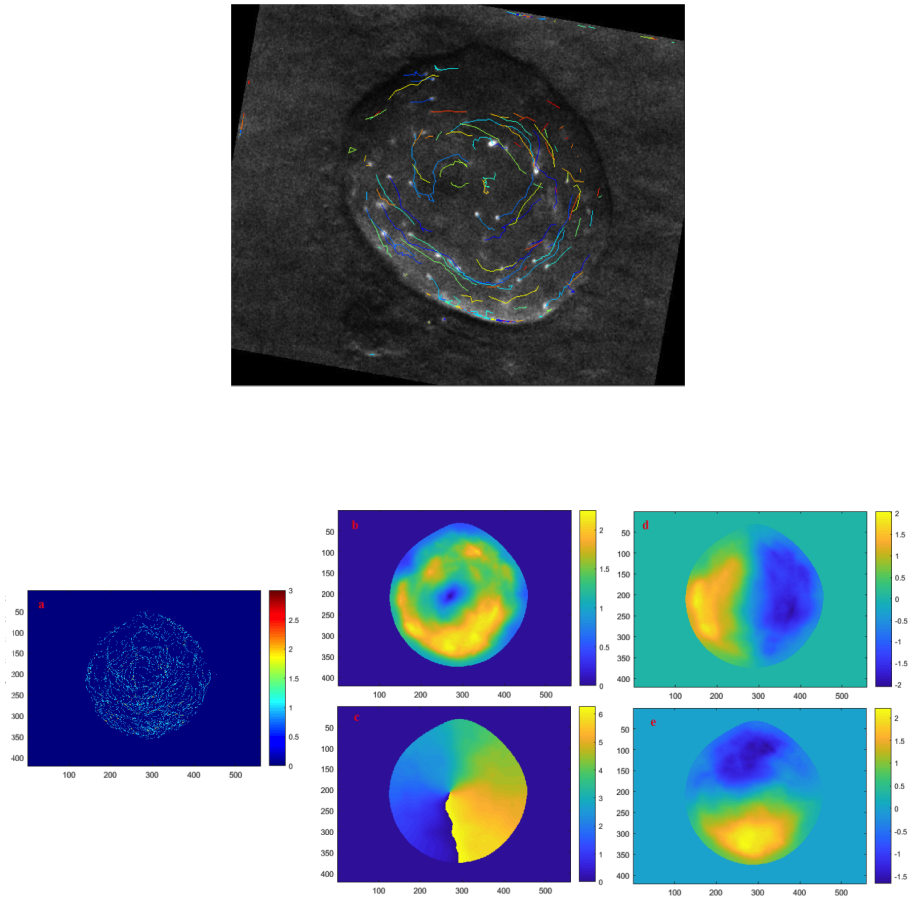

Figure 8. Trajectories detected on one LRO (top). Bottom: trajectories detected the whole population (right a), horizonal (b), vertical (c) radial (d) and angular (e) speeds.

6.9. Comparison of tracking strategies

Participants: Sarah Laroui, Grégoire Malandain, Gaël Michelin.

This work takes place within the ANR PhaseQuant.

In video-microscopy, subject-based studies require the tracking of every individual to both quantify its dynamics (speed, etc) and detect special events (mitosis). In high throughput experiments, manual annotation or correction of sequences is not feasible, and computed-based strategies are definitevely prefered. In such a context, where cells have already been segmented in video-microscopy images (by a third party method), this work aims to assess different tracking strategies in presence of unavoidable segmentation errors (missing cells, over- or under-segmentations).

Two main strategies have been under examination. In the first one, all pairing hypothesis (based on a proximity criteria) have been generated. Further stages of both selection of plausible pairings or rejection of non-plausible ones have been tested to end up with tracking results. In the second one, pairings are built progressively based on their plausibility (one cell can be paired forward to 0, 1 or 2 cells; one cell can be paired backward to 0 or 1 cell). In both strategies, jumps are allowed to take into account possible segmentation errors.

It appears that the first strategie is more likely to end up with undecidable unplausible situations, that can not occur, by construction, with the second one.

6.10. 3D Coronary vessel tracking in x-ray projections

Participants: Emmanuelle Poulain, Grégoire Malandain.

This work is made in collaboration with Régis Vaillant (GE-Healthcare, Buc, France) and Nicholas Ayache (Inria Epione team).

Percutaneous Coronary Intervention (PCI) is a minimally procedure which is used to treat coronary artery narrowing. The physician intervenes on the patient under the guidance of an x-ray imaging system. This system is not able to display a visual assessment of the coronary wall, contrary to the pre-operative Computed Tomography Angiography (CTA). To help physician to exploit this information during the course of the procedure, registering these two modalities would be useful. To this aim, we first proposed in a previous work a method of 3D coronary tracking of the main vessel in x-ray projections [17]. Although, we faced a segmentation problem when we wanted to move from the tracking of one vessel to the entire set. For this reason, we have worked this year on the vessel centerline extraction in x-ray projection images.

2D Angiographic images are often first enhanced, before centerline extraction, by dedicated filters, e.g. Hessian based filters. Such filters exhibit critical defects, one of them being the non-uniform response for vessels of different sizes. This fact largely compromised the next step of centerline extraction. This last step requires a threshold step which is usually not clearly explained in other established methods. We worked on a model-based study of two widely used Hessian-based filter. It demonstrates that the non-uniform response for vessels of different sizes is due to the projective effect, and further enables to propose an X-ray projection dedicated method for centerline extraction which overpass this behavior. It is complemented by a component-based hysteresis thresholding. Last, the huge variability of coronary image aspect, due to imaging parameters, makes the threshold choice quite complex. We have shown that the thresholds can be determined automatically taking into account the kilovoltage peak (kVp), one key technical parameter of the X-ray acquisition. These thresholds are determined without any a priori on the image content. This technique not only allows to obtain an almost optimal segmentation, but also performs well for non-injected frames. Results of our proposed method and methods from state of the art are presented in Fig. 9.

6.11. Mitochondrial network detection and classification

Participants: Guillaume Lavisse, Xavier Descombes.

This work is a collaboration with C. Badot and M. Chami from IPMC and A. Charezac, S. Clavel and F. Bost from C3M. It was partially supported by the UCA Jedi Idex.

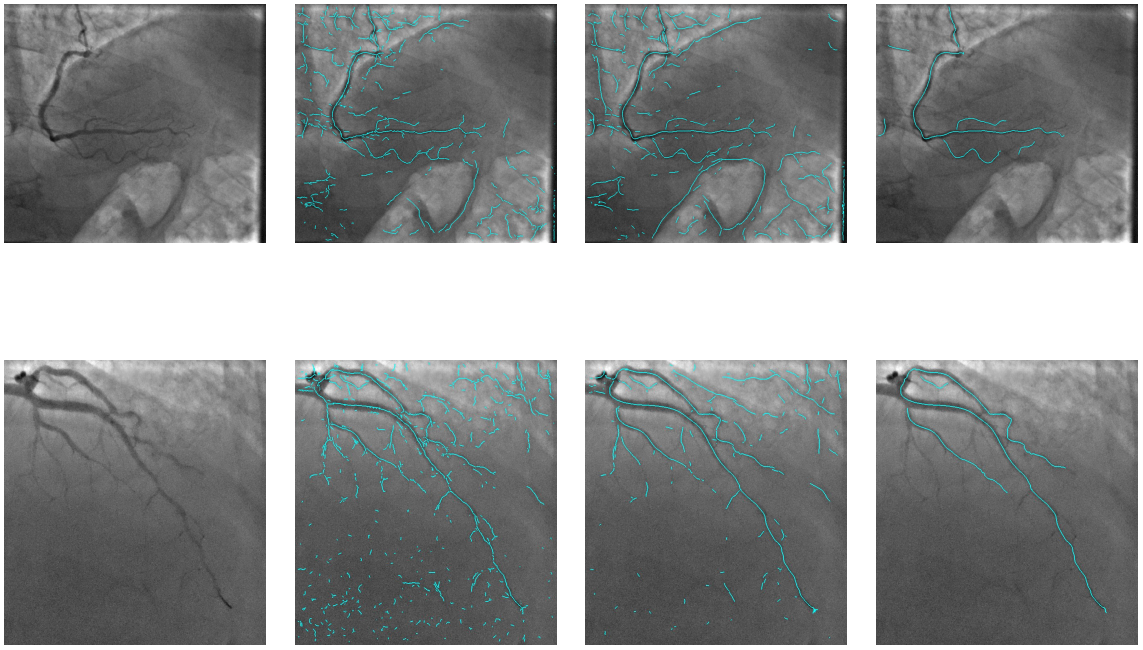

Figure 9. The obtained results of the different methods on a right coronary sample (first line), and left coronary sample (second line). From left to right: the original image, the result of Frangi (OPHT), the result of Krissian (OPHT), and the result of the proposed method (CCHT). The two first methods were tuned to obtain the same sensitivity than the third one.

Last year we had developed a framework to classify mitochondrial networks. In this framework, mitchondrial networks are first binarized using our algorithm ATOLS. Some geometrical features are then computed for each connected component providing a clustering at the object level in the feature space. A signature of a given image is then defined by the ratio of objects in the different classes. A second classification, performed by an SVM on this signature, provides a global class for the image. The different classes are defined as fragmented, tubular and filamentous. This year, we have validated this framework on two other databases, one consisting of cultured cells, the other being constituted of Alzheimer neuronal cells. The results were not satisfactory compared to those obtained on the first database last year. This is mainly due to the signal heterogeneity within an image. To compensate this heterogeneity we have applied a local normalization (see figure 10). We then have recovered classification performances comparable to those obtained by an expert. The next step consists in following in time the mitochondria of Alzheimer neuron. To this aim, we have developed a matching algorithm between two sets of mitochondria based on geometrical features and location of detected objects at two different instants.

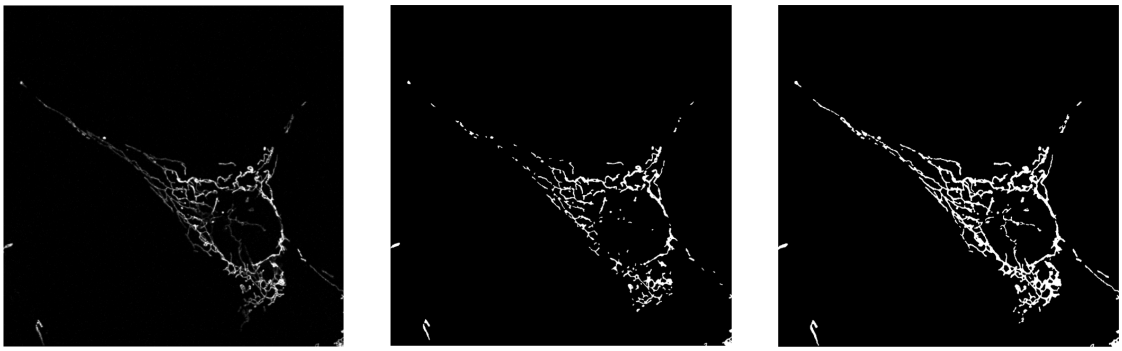

Figure 10. Image of Mitochondria (left), Binarization obtained without local normalization (middle) and with local normalization (right).

6.12. Botrytis cinerea phenotype recognition and classification: toward the establishment of links between phenotypes and antifungal molecules

Participants: Sarah Laroui, Eric Debreuve, Xavier Descombes.

This work is a collaboration with Aurelia Vernay (Bayer, Lyon, France).

Botrytis cinerea is a reference model of filamentous phytopathogen fungi. Some chemical treatments can lead to characteristic morphological changes, or phenotypic signatures, observable with transmitted light microscopy. These phenotypes could be associated with the treatment Mode of Action (figure 11). The goal of this work is the recognition of already known phenotypes but also the detection of new phenotypes. Because of the different dose-response effects, each given molecule is tested at ten concentrations.

In this context, we are developing a robust image analysis and classification framework relying on morphometric and topological characteristics to automatically recognize such phenotypes. Specifically, these characteristics are used in a supervised machine-learning framework to learn a Random Forest classifier.

After object detection, we calculate the skeleton of each object and we converted them into graphs, a more convenient data structure. Two types of parameters were extracted: those calculated globally on all the objects of an image like for example the number of objects and the skeleton length variance, and those computed on each object of an image like the number of nodes, the mean branch length and the object area.

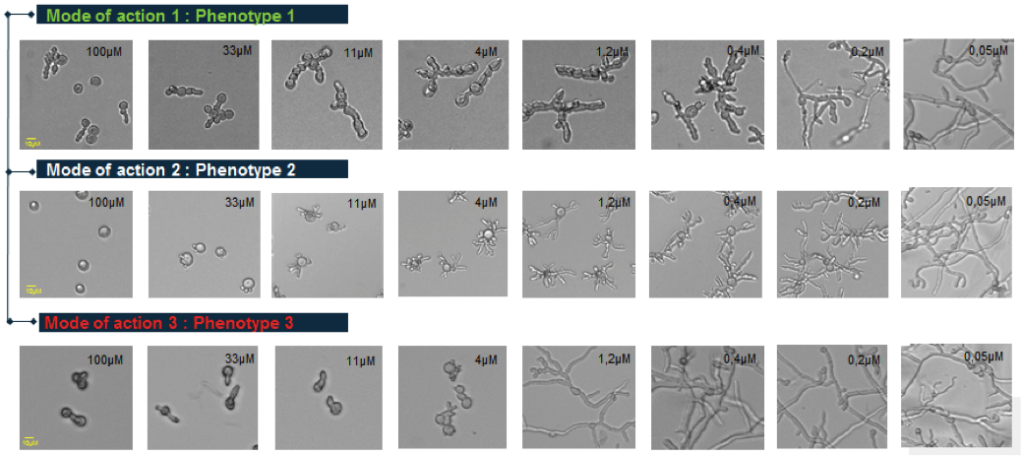

Figure 11. Each row depicts the observed phenotypic signatures associated with a given molecules. Columns correspond to different molecule concentrations.

6.13. Automatic zooplankton classification using hierarchical approaches

Participants: Eric Debreuve, Baptiste Pouthier.

This work is made in collaboration with Frédéric Precioso (I3S) and Jean-Olivier Irisson (Laboratoire d'Océanographie de Villefranche-sur-mer).

In marine ecology routine, zooplankton organisms are imaged using a single camera system. With the purpose of building an automatic classifier of plankton images, databases of annotated images are built. For each species, such databases contain a set of images of similar organisms, but seen under different point of views, i.e., having potentially very different appearances. Hence, learning an automatic classifier for zooplankton from such databases is difficult. In consequence, feeding the learning process with as much information as possible is essential. One piece of information we have access to is a taxonomic structure (hence hierarchical structure) of zooplankton species established by environmental biologists (see Fig. 12). Therefore, we have explored (and we continue to explore) different strategies to use such a hierarchy in the learning process, from the straightforward one consisting of learning a coarse-to-fine tree of independent convolutional neural networks (CNNs) to using neural network architectures explicitly accounting for hierarchical constraints.

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

General Electric Healthcare: a 36 months (from feb. 2016 to jan. 2019) companion contract for the Cifre thesis of E. Poulain.
Bayer, Lyon: a 36 months (from aug. 2018 to jul. 2021) companion contract for the Cifre thesis of S. Laroui.

8. Partnerships and Cooperations

8.1. Regional Initiatives

8.1.1. Labex Signalife

The MORPHEME team is member of the SIGNALIFE Laboratory of Excellence.

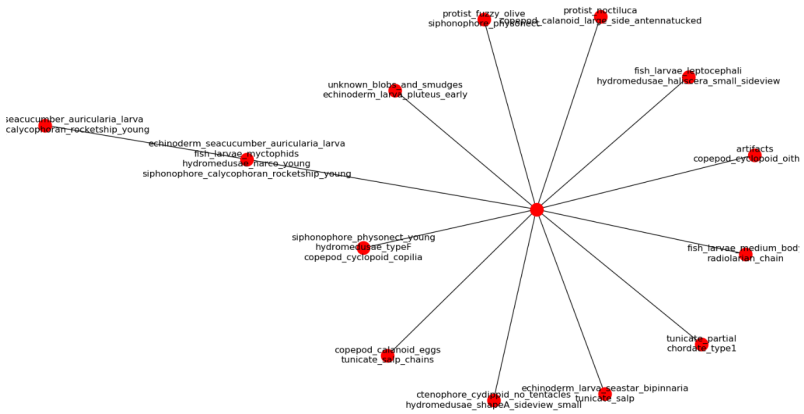

Figure 12. An Illustration of the zooplankton taxonomy.

Florence Besse and Xavier Descombes are members of the Scientific Committee.

8.1.2. Idex UCA Jedi

Florence Besse is a member of the scientific council of the IDEX JEDI Academy 2.

Laure Blanc-Féraud is chair of the scientific council of Academy 1 of Idex UCA JEDI.

A number of projects has been partially funded by the Idex.

- Artificial intelligence application to the identification of functional traits of zooplankton from high-resolution images (ARTIFACTZ) collaboration with Laval University, Québec / UCA Coll. with : F. Maps (ULaval), D. Laurandeau (ULaval),L. Guidi (LOV), S. Ayata (LOV), J.-O. Irisson (LOV) Participants : E. Debreuve
- Biological Image Super-resolution Enhanced with Tensor (Biset) supported by Académie 1 RISE Coll. with G. Favier (I3S), G. Sandoz (iBV) Participants : E. Debreuve, L. Blanc-Féraud, S. Schaub
- Quantitative analysis of exovesicle transport dynamics in the zebrafish Left/Right organizer. supported by Academy 2 "Complex Systems" Coll. with M. Furthauer (PI, iBV), T. Juan (iBV) Participants: R. Pages, X. Descombes
- Study of a complex biological system pf prostate organoid: applications in biomedical research. supported by Academy 2 "Complex Systems" Coll. with F. Bost (PI, C3M), S. Clavel (C3M), R.F. Roustan (C3M), S. Torrino (C3M). Participants: C. Girard-Riboulleau, X. Descombes
- Imaging analysis for mitochondrial network tracking and recgnition. supported by Academy 1 "Living Sciences" Coll. with M. Chami (IPMC), C. Badot (IPMC), F. Bost (C3M), S. Clavel (C3M), A. Charezac (C3M) Participants: G. Lavisse, X. Descombes.

8.1.3. 3AI Côte d'Azur

Laure Blanc-Féraud is a member of the scientific committee of the 3IA proposal of Nice.

8.2. National Initiatives

8.2.1. ANR RNAGRIMP

Participants: Florence Besse [PI], Fabienne de Graeve, Xavier Descombes, Eric Debreuve.

Here, we propose to study the molecular bases underlying the assembly and regulation of RNA granules, using the highly conserved IMP-containing granules as a paradigm. Specifically, we propose to perform an unbiased genome-wide RNAi screen on Drosophila cultured cells to identify mutant conditions in which the organization and/or distribution of IMP-containing granules is altered. To quantitatively and statistically analyze mutant conditions, and to define precise and coherent classes of mutants, we will combine high throughput microscopy with the development of a computational pipeline optimized for automatic analysis and classification of images. The function of positive hits isolated in the screen will then be validated in vivo in Drosophila neurons using fly genetics and imaging techniques, and characterized at the molecular and cellular levels using biochemical assays, in vitro phase transition experiments and live-imaging. Finally, the functional conservation of identified regulators will be tested in zebrafish embryos combining gene inactivation and live-imaging techniques. This integrative study will provide the first comprehensive analysis of the functional network that regulates the properties of the conserved IMP RNA granules. Our characterization of the identified regulators in vivo in neuronal cells will be of particular significance in the light of recent evidence linking the progression of several degenerative human diseases to the accumulation of non-functional RNA/protein aggregates.

This 4-years project started january, 2016 and is leaded by F. Besse (iBV, Nice). Participants are iBV, institut de biologie Paris Seine (IBPS, Paris), and Morpheme.

8.2.2. ANR HMOVE

Participants: Xavier Descombes, Eric Debreuve.

Among the signaling molecules involved in animal morphogenesis are the Hedgehog (Hh) family proteins which act at distance to direct cell fate decisions in invertebrate and vertebrate tissues. To study the underlying process we will develop accurate tracking algorithm to compare trajectories of different Hh pools transportation in live animals. This will allow us to analyze the contribution of the different carriers in the establishment of the Hh gradient. Moreover, we will develop new methods to modify the spatio-temporal and dynamical properties of the extra-cellular Hh gradient and separate the contribution of the apical versus basal Hh pools. We will complete this study with a genome-wide screen to identify genes and related cellular processes responsible for Hh release. The particular interest of this collaboration lies in the combination of development of tracking algorithm to analyze Hh distribution and trajectories with extremely powerful genetics, ease of in vivo manipulation and lack of genetic redundancy of Drosophila.

This 4-years project started january, 2016 and is leaded by P. Thérond (iBV, Nice). Participants are iBV and Morpheme.

8.2.3. ANR DIG-EM

Participants: Grégoire Malandain, Xavier Descombes, Gaël Michelin.

Morphogenesis controls the proper spatial organization of the various cell types. While the comparatively simple process of patterning and cell differentiation has received considerable attention, the genetic and evolutionary drivers of morphogenesis are much less understood. In particular, we very poorly understand why some morphogenetic processes evolve very rapidly, while others show remarkable evolutionary stability.

This research program aims at developing a high-throughput computational framework to analyze and formalize high-throughput 4D imaging data, in order to quantify and formally represent with cellular resolution the average development of an organism and its variations within and between species. In addition to its biological interest, a major output of the project will thus be the development of robust general computational methods for the analysis, visualization and representation of massive high-throughput light-sheet data sets.

This 4-years project started october the 1st, 2014 and is leaded by P. Lemaire (CRBM, Montpellier). Participants are the CRBM, and two Inria project-team, Morpheme and Virtual Plants.

8.2.4. ANR PhaseQuant

Participants: Grégoire Malandain, Eric Debreuve, Kevin Giulietti, Sarah Laroui.

The PhaseQuantHD project aims at developing a high-content imaging system using quadriwave lateral shearing interferometry as a quantitative phase imaging modality. Automated analysis methods will be developed and optimized for this modality. Finally an open biological study question will be treated with the system.

This 3-years project started october the 1st, 2014 and is leaded by B. Wattelier (Phasics, Palaiseau). Participants are Phasics, and three academic teams TIRO (UNS/CEA/CAL), Nice, Mediacoding (I3S, Sophia-Antipolis), and Morpheme.

8.2.5. Inria Large-scale initiative Naviscope

Participant: Grégoire Malandain.

This action gathers the expertise of seven Inria research teams (Aviz, Beagle, Hybrid, Morpheme, Parietal, Serpico and Mosaic) and other groups (MaIAGE, INRA, Jouy-en-Josas and UMR 144, Institut Curie Paris) and aimed at developing original and cutting-edge visualization and navigation methods to assist scientists, enabling semi-automatic analysis, manipulation, and investigation of temporal series of multi-valued volumetric images, with a strong focus on live cell imaging and microscopy application domains. More precisely, the three following challenges will be addressed:

- Novel machine learning methods able to detect the main regions of interest, and automatic quantification of sparse sets of molecular interactions and cell processes during navigation to save memory and computational resources.
- Novel visualization methods able to encode 3D motion/deformation vectors and dynamics features with color/texture-based and non-sub-resolved representations, abstractions, and discretization, as used to show 2D motion and deformation vectors and patterns.
- Effective machine learning-driven navigation and interaction techniques for complex functional 3D+Time data enabling the analysis of sparse sets of localized intra-cellular events and cell processes (migration, division, etc.).

8.2.6. Octopus Project

Participant: Eric Debreuve.

The Octopus project deals with automatic classification of images of zooplankton. It is conducted in collaboration with the Laboratoire d'Océanographie de Villefranche-sur-mer (LOV) et l'ENSTA Paris. The kickoff meeting took place in May 2015 and a 3-day *brainstorming* meeting on Deep Learning took place in December 2015. Participants are I3S (Frédéric Precioso and Mélanie Ducoffe), LOV (Marc Picheral and Jean-Olivier Irisson), and ENSTA Paris (Antoine Manzanera).

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific Events Selection

9.1.1.1. Member of the Conference Program Committees

Eric Debreuve was a member of the Program Committee of ACIVS 2018 (Advanced Concepts for Intelligent Vision Systems) and Reconnaissance des Formes, Image, Apprentissage (RFIAP).

9.1.1.2. Reviewer

Laure Blanc-Féraud was a reviewer for the conferences IEEE ICIP and ICASSP.

Eric Debreuve was a reviewer for the conferences IEEE International Symposium on Biomedical Imaging (ISBI) and IEEE International Conference on Image Processing (ICIP).

Xavier Descombes was a reviewer for ISBI18, ICASSP18 and ICIP18.

Grégoire Malandain was a reviewer for the conferences EMBS, ISBI and MICCAI.

9.1.2. Journal

9.1.2.1. Member of the Editorial Boards

Laure Blanc-Féraud was Associated Editor for the journals SIAM Imaging Sciences. She was also responsible of the editorial field "Image" of the SCIENCES new editorial project of ISTE/WILEY Group which concerns the publication of collections of multi-authored titles in the fields of pure and applied sciences, health and humanities.

Xavier Descombes is Associated Editor for the journal Digital Signal Processing.

9.1.2.2. Reviewer - Reviewing Activities

Laure Blanc-Féraud was a reviewer for the Journal of Optimization Theory and Applications.

Eric Debreuve was a reviewer for the journals Digital Signal Processing (Elsevier) and Pattern Recognition (Elsevier).

Xavier Descombes was reviewer for the journals IEEE TMI and Digital Signal Processing.

Grégoire Malandain was reviewer for the journal IEEE TMI.

9.1.3. Invited Talks

Florence Besse gave a talk ”Modeling Cell fate” at the Jacques Monod Conférence, November 2018.

Laure Blanc-Féraud was invited to the Workshop on Computational Methods for Inverse Problems in Imaging, Como Italy, 16-18 July 2018, and to the OSA Imaging and Applied Optics Congress, Orlando, USA, 25-28 June 2018.

Xavier Descombes was invited to give a talk at Tlemcen Univeristy during the Biomedical Doctoral School day. He was invited to give a talk at the SIAM conference on Imaging Science in Bologna. He was also a speaker during the C@UCA days in Fréjus and during Modelife days in Nice, workshops organized within the UCA Jedi Idex.

9.1.4. Leadership within the Scientific Community

Laure Blanc-Féraud is the directrice of the GdR 720 ISIS of CNRS (see website gdrisis.fr).

Xavier Descombes is member of IEEE BISP (Biomedical Imaging Signal Processing) Technical Committee.

Grégoire Malandain is member of the IEEE/EMB Technical Committee on Biomedical Imaging and Image Processing (BIIP). He is an member of the Scientific Committee of the MIA department of INRA.

9.1.5. Scientific Expertise

Laure Blanc-Féraud was president of the HCERES expert committee visit of the LTCI Lab (4-6 Dec.). She is a member of the ANR scientific evaluation committee ASTRID. She was part of the selection committee of section 61 of CNU for a professor position in Paris-Est University. She was expert for the CPER Numeric of Poitiers. She was member of the Commission d’admission CRCN of CNRS INS2I. Laure Blanc-Féraud was expert for the Italian Ministery of Research (MUIR) and for the FNRS (Belgium).

Xavier Descombes is an expert for the DRRT (Paca, Ile de France, Bretagne). He is member of the committee “Mathématiques et Sciences du Numérique pour la santé et la biologie” of ANR. He was in the HCERES committee to evaluate MAP5 laboratory.

9.1.6. Research Administration

Xavier Descombes is member of the "comité des projets" of Inria CRISAM. He is a member of the Comité Permanent des Ressources Humaines (CPRH), UNS, section 61.

Eric Debreuve is a member of the Comité Permanent des Ressources Humaines (CPRH), UNS, section 61.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Licence: Arne Bechensteen, Outils pour la physique, 42h, L1, Polytech Nice Sophia, France

Licence: Arne Bechensteen, Programmation impérative PeiP1, 12h, L1, Polytech Nice Sophia, France

Master: Arne Bechensteen, Traitement Numérique des Images, 10h, M2, Polytech Nice Sophia, France

Master: Florence Besse, genetic tools for the study of neuronal networks, 4h, Université Côte d'Azur, France.

Master: Florence Besse, RNA localization and neuronal morphology, 4h, Université Côte d'Azur, France.

Master: Laure Blanc-Féraud, management of the module Traitements numériques des images (24h), teaching 5h CM.

Master : Eric Debreuve, scientific image processing, 9h EqTD, master SVS, Université Côte d'Azur, France

Master/Engineer : Debreuve, data mining, 27h EqTD, M2/Engineer 5, Université Côte d'Azur, France

Master: Xavier Descombes, Traitement d'images, Analyse de données, Techniques avancées de traitement d'images, 10h Eq. TD, Niveau M2, ISAE, France.

Master: Xavier Descombes, Traitement d'images, master VIM, 12h Eq. TD, Niveau M2, Université Côte d'Azur, France.

Master: Xavier Descombes, Bio-imagerie, master IRIV, 6h Eq. TD, Niveau M2, Université de Strasbourg, France

Master: Xavier Descombes, Analyse d'images, master GBM, 9h Eq. TD, Niveau M2, Université Côte d'Azur, France.

Master: Xavier Descombes, Traitement d'images scientifiques, master SVS, 6h Eq. TD Niveau M2, Université Côte d'Azur.

Master : Anca Grapa, Traitement d'images, master GBM, 12h Eq. TD, Niveau M1, Université Côte d'Azur, France.

Master : Anca Grapa, Compression, Analysis and Visualization of Multimedia Content, master SSTIM (GMD), Niveau M2, 14h Eq. TD, PolyTech Nice Sophia, France.

9.2.2. Supervision

PhD in progress: Arne Bechensteen, TIRF-MA and super-resolution by sparse estimation method, 2 October 2017, Laure Blanc-Féraud, Gilles Aubert, Sébastien Schaub.

PhD in progress: Anca-Ioana Grapa, Characterization of the organization of the Extracellular Matrix (ECM) by Image Processing , 19 September 2016, Laure Blanc-Féraud, Xavier Descombes, E. van Obberghen, (iBV).

PhD in progress: Sarah Laroui, Classification and modelling of botrytis cinerea fungi growth from microscope images: toward the establishment of links between phenotypes and antifongic molecules, 1st August 2018, Eric Debreuve, Xavier Descombes

PhD in progress: Emmanuelle Poulain, Fluoroscopy/CTA dynamic registration, 1st february 2016, Grégoire Malandain.

9.2.3. Internships

Baptiste Pouthier, Hierarchical deep learning for zooplankton image classification, Polytech Nice-Sophia Antipolis, UNS/UCA - MAM4, Eric Debreuve (sup.).

Simon Bahadoran, Deep learning for PALM superresolution in fluorescence microscopy. Supervisors: Laure Blanc-Féraud, Eric Debreuve.

Cédric Girard Riboulleau, Morphological tracking of organoids for the prostate cancer, Master BIM, Université Côte D'Azur, Xavier Descombes (sup.).

Guillaume Lavisse, Detection, classification and characterization of mitochondrial networks: application to Alzheimer desease and cancer, Master BIM, Université Côte D'Azur, Xavier Descombes (sup.).

Raphael Pages, Quantitative analyse of vesicles transport within the Left/Right organizer in the zebrafish, Master MAPI3, Université Paul Sabatier Toulouse, Xavier Descombes (sup.).

9.2.4. Juries

Laure Blanc-Féraud participated to the PhD thesis committees of Clara Barbanson (Télécom ParisTech & ONERA) as member, Quentin Denoyelle (Ceremade, Dauphine University) as president, William Meiniel (Pasteur Institute) as president, and to the HDR jury of Nabil El Korso (Paris Nanterre university) as member.

Xavier Descombes participated to the PhD committes of Agustina Razetti (Morpheme) as supervisor, Tran Thi Nhu Hoa (IPAL, Singapore and Sorbonne University), Amine Benomar (Tlemcen University, Algeria) and Jessica Sodjo (Bordeaux University) as a reviewer and Jean-Dominique Favreau (Titane, Inria) as an examinator. He was reviewer in the HDR juries of Sylvain Faisan (Strasbourg University) and Adel Hafiane (Orléans University).

Grégoire Malandain participated as reviewer to the PhD thesis committee of Ketan Bacchuwar (Paris Est univ.), Marc Filippi (Grenoble Alpes univ.), Julie Robic (Paris Est univ.), as member to the PhD thesis committee of Bertha Mayela Toledo Acosta (Rennes I univ.), and as reviewer to the HDR thesis committee of Antoine Vacavant (Clermont Auvergne univ.).

9.3. Popularization

9.3.1. Interventions

The Morpheme team took part in "La fête de la Science" both at Inria and during the "Village de la Science" in Juan-Les-Pins. Sarah Laroui, Somia Rahnmoun and Arne Bechensteen were holding a stand in these events.

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] A. RAZETTI. *Modelling and characterizing axon growth from in vivo data*, Université Côte d'Azur, April 2018, https://tel.archives-ouvertes.fr/tel-01868324

Articles in International Peer-Reviewed Journals

[2] I. DAVID, P. L. KOHNKE, J. FEHRENBACH, A. R. LOPES SIMOES, E. DEBREUVE, X. DESCOMBES, F. PLOURABOUÉ, P. DEGOND, X. DRUART. *New objective measurements of semen wave motion are associated with fertility in sheep*, in "Reproduction, Fertility and Development", 2018, vol. 30, n^{o} 6, pp. 889-896 [*DOI :* 10.1071/RD17472], https://hal.archives-ouvertes.fr/hal-01808988

[3] K. McDole, L. Guignard, F. Amat, A. Berger, G. Malandain, L. Royer, S. Turaga, K. Branson, P. Keller. *In Toto Imaging and Reconstruction of Post-Implantation Mouse Development at the Single-Cell Level*, in "Cell", October 2018, vol. 175, n° 3, pp. 859 - 876.e33 [*DOI :* 10.1016/j.cell.2018.09.031], https://hal.inria.fr/hal-01900416

[4] A. Razetti, C. Medioni, G. Malandain, F. Besse, X. Descombes. *A stochastic framework to model axon interactions within growing neuronal populations*, in "PLoS Computational Biology", December 2018, vol. 14, n° 12, e1006627 p. , https://hal.inria.fr/hal-01953244

International Conferences with Proceedings

[5] A. Bechensteen, L. Blanc-Féraud, G. Aubert. *Single molecule localization by $\ell_2 - \ell_0$ constrained optimization*, in "iTWIST 2018", Marseille, France, November 2018, https://arxiv.org/abs/1812.05971 , https://hal.inria.fr/hal-01957427

[6] V. l. Coli, P.-H. Tournier, V. Dolean, I. El Kanfoud, C. Pichot, C. Migliaccio, L. Blanc-Féraud. *Detection of Brain Strokes Using Microwave Tomography*, in "International Symposium on Antennas and Propagation and USNC-URSI Radio Science Meeting", Boston, United States, IEEE, July 2018, https://hal.archives-ouvertes.fr/hal-01824526

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[8] B. M. Toledo Acosta, X. Heiligenstein, G. Malandain, P. Bouthemy. *Intensity-based matching and registration for 3D correlative microscopy with large discrepancies*, in "ISBI 2018 - IEEE 15th International Symposium on Biomedical Imaging", Washington, United States, IEEE, April 2018, pp. 493-496 [*DOI :* 10.1109/ISBI.2018.8363623], https://hal.inria.fr/hal-01930740

Conferences without Proceedings

[9] N. Cedilnik, E. Debreuve, F. De Graeve, F. Besse, X. Descombes. *SPADE: A Small Particle Detection Method Using A Dictionary Of Shapes Within The Marked Point Process Framework*, in "IEEE International Symposium on Biomedical Imaging (ISBI) 2018", Washington, DC, United States, April 2018, https://hal.inria.fr/hal-01867805

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