IN PARTNERSHIP WITH:
CNRS

Université Nice - Sophia Antipolis

Activity Report 2017

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
- B1.1.3. - Cellular biology
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- B2.6. - Biological and medical imaging

1. Personnel

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Florence Besse [CNRS, Senior Researcher, HDR]

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Christelle Requena [Inria, until Jun 2017]
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External Collaborators

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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. New Software and Platforms

4.1. BioLib

KEYWORD: Biomedical imaging
FUNCTIONAL DESCRIPTION: Library of image analysis for biology: object detection, tracking

- Participants: Étienne Delclaux, Grégoire Malandain, Sylvain Prigent and Xavier Descombes
- Contact: Xavier Descombes

4.2. PIB

Biological imaging platform
FUNCTIONAL DESCRIPTION: This platform, based on the DTK meta-platform, aims at gathering the team software development, and at providing a visual development tool.

- Participants: Étienne Delclaux, Grégoire Malandain and Xavier Descombes
- Contact: Xavier Descombes

4.3. Stracking

KEYWORDS: Bioinformatics - Biology - Biomedical imaging

SCIENTIFIC DESCRIPTION: Head Tracking and Flagellum Tracing for Sperm Motility Analysis : Sperm quality assessment plays an essential role in human fertility and animal breeding. Manual analysis is time-consuming and subject to intra- and inter-observer variability. To automate the analysis process, as well as to offer a means of statistical analysis that may not be achieved by visual inspection, we present a computational framework that tracks the heads and traces the tails for analyzing sperm motility, one of the most important attributes in semen quality evaluation. Our framework consists of 3 modules: head detection, head tracking, and flagellum tracing. The head detection module detects the sperm heads from the image data, and the detected heads are the inputs to the head tracking module for obtaining the head trajectories. Finally, a flagellum tracing algorithm is proposed to obtain the flagellar beat patterns.
FUNCTIONAL DESCRIPTION: This software is developed within the ANR project MOTIMO. It allows to segment and track spermatozoons from confocal microscopy image sequences.

- Participants: Grégoire Malandain, Huei Fang Yang, Sylvain Prigent and Xavier Descombes
- Contact: Xavier Descombes

5. New Results

5.1. DIC (differential-interference-contrast) microscopy

Participants: Lola-Xiomara Bautista Rozo, Laure Blanc-Féraud.

This work is made in collaboration with Simone Rebegoldi, Marco Prato and Luca Zanni are in the Dipartimento di Scienze Fisiche, Informatiche e Matematiche, Universita di Modena e Reggio Emilia, Modena, Italy.

he DIC (differential-interference-contrast) microscopy states the problem of image phase reconstruction which is ill-posed (under-determinated) and non-convex optimization problem. We have worked on the phase reconstruction from color images by optimization of a non linear least-squares-like discrepancy term regularized with a total variation functional. We have considered two different penalties, the first one being the total variation (TV) functional which is suitable for piecewise constant images, while the second is the hypersurface (HS) potential, which is a smooth generalization of the TV able to reconstruct both sharp and smooth variations of the unknown phase. Since the latter choice leads to the minimization of a smooth functional, we developed a limited memory gradient method, in which suitable adaptive steplength parameters are chosen to improve the convergence rate of the algorithm. As concerns the TV–based model, we addressed the minimization problem by means of a recently proposed linesearch–based forward–backward method able to handle the nonsmoothness of the TV functional. Numerical tests show that in the case of smooth TV minimization funcitonal, the performance of the limited memory gradient method is much better than those of the conjugate gradient approaches proposed in the literature, in terms of number of function/gradient evaluations and, therefore, computational time. In the case of TV functional, despite the difficulties due to the presence of a nondifferentiable term, also the linesearch–based forward–backward method proposed in this case is able to provide reconstructed images with a computational cost comparable to that of the gradient methods, thus leaving to a potential user freedom to choose the desired regularizer without losing in efficiency.

This work has been done during the PhD thesis of Lola Bautista defended in June 2017 [1]. It has been published in the journal Inverse Problems in 2017 [4].

5.2. Towards a continuous relaxation of the $\ell_2 - \ell_0$ constrained 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 minimization problem is of interest in signal processing, with application to compressed sensing, source separation and super-resolution imaging.

This problem has previously been relaxed, among other methods, by using the convex ℓ_1 norm instead of the ℓ_0 norm, but depending on the specific problem the global minimizer may not be the same.

The goal of our work is to propose a continuous exact relaxation of the ℓ_2-ℓ_0 constrained problem. The initial problem is non-continuous and is therefore from an algorithmic point of view difficult to minimize. A continuous exact relaxation has the same global minimizers as the initial problem, and a local minimizer of the relaxation is a local minimizer of the initial problem, with possible less local minimizers than the initial problem. Solving the initial ℓ_2-ℓ_0 constrained problem is equivalent, in the sense of the global minimizers, to solving the continuous relaxed form. Furthermore, a continuous exact relaxation provides better properties for the objective function in terms of minimization, because of the continuity and the number of local minimizers.

Based on the recent works of Marcus Carlson [17] we propose a continuous exact relaxation of the ℓ_2-ℓ_0 constrained problem S_γ, with an algorithm to minimize the function.

In order to increase the quality of the optimization, we have to chose "the best" exact relaxation. Inspired by the work by Emmanuel Soubies [23] we have computed the convex hull of the initial problem for a special case. The penalty term obtain, f_{cr} may be a continuous relaxation with respect to the initial problem, with fewer local minimizers than the initial problem and the relaxation S_γ (see figure 1). This has to be proven.

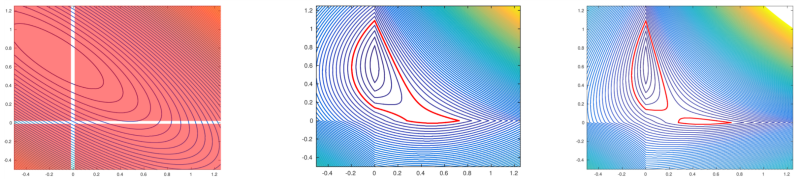

Figure 1. From the left to the right. The initial problem, the relaxation using f_{cr} and the relaxation using S_γ. The level lines of the relaxations are illustrated with a common level line marked in red.

The work will be presented at Mathematical Image Analysis 2018 conference in Berlin on the form of a poster.

5.3. Reconstruction of mosaic of microscopic images

Participants: Kévin 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. The cause of this has not be identified so far: this may be due to small geometric mis-alignement in the imaging device, or to the command of the micrometer table.

We thus investigate the stability of this residual offset with respect to time and to the image position within the mosaic.

5.4. Detection of cytoneme

Participants: Christelle Requena, Xavier Descombes.

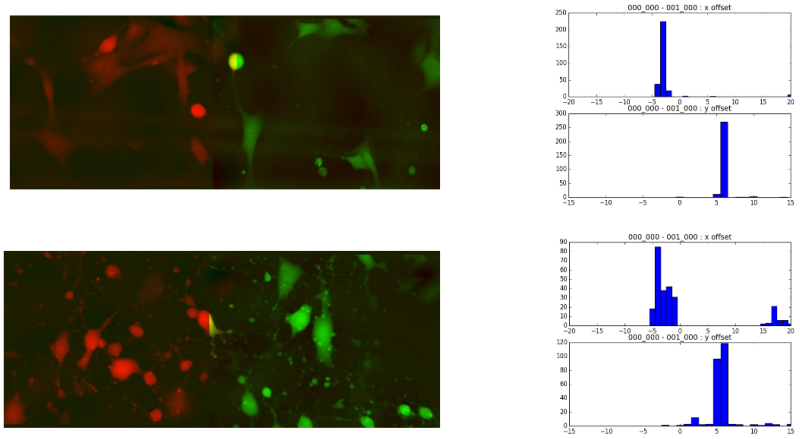

Figure 2. Example of mosaics reconstructed with two different datasets whose pairs of images were acquired at the same positions (0,0) in red and (1,0) in green. Histograms represent the offsets for all offsets overtime.

This work is made in collaboration with Pascal Thérond, Tamas Matusek and Caterina Novelli (iBV). It is supported by the ANR project HMOVE.

Cellular communication is one of the most important processes for understanding and controlling morphogenesis (the set of laws that determine the structure of tissues and organs during embryonic development) necessary for the development of an organism. This 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".

Due to the amount of information to be processed and the time required to study this information, it is essential to be able to provide image processing tools through which reliable, automatic and effective methods are proposed for these studies. In this work we have developped a pipeline for membrane extension and vesicles detection from in vivo data obtained by confocal microscopy. The vesicles are detected using a marked point process modeling. The cell extension detection embed the membrane detection using active contours and the filament detection using a tophat operator, the Frangi filter and Dijkstra algorithm. With this detection tool (exemplified in Figure 3), we have characterized a mutant population compared to a wild population of drosophila wings with respect to Hedgehog signalization. Interestingly we have shown that a significative difference appears in the cytonemes length but not in their number.

5.5. 3D+t segmentation of single growing axons

Participants: Nadège Guiglielmoni, Caroline Medioni, Florence Besse, Xavier Descombes, Grégoire Malandain.

Our work is motivated by the study of developmental axonal remodeling, a genetically-controlled process characterized by a degeneration step followed by a rapid regrowth of axons. Here, we focus our interest on the axonal regrowth phase, which can be studied during brain development, using the fruit fly, *Drosophila melanogaster*, as a model system.

During the regrowth, small dynamical branches can be observed: they emanate from long stable branches and have generally a short lifetime. Such small branches may contribute to rebuild the axon connectivity during the adult stage. A better knowledge of the mechanisms controlling the dynamic of these branches may contribute to a better understanding of neuronal morphogenesis. In this work, we are particularly interested in the quantification of this process, for which the extraction of both the main and second branches is required.

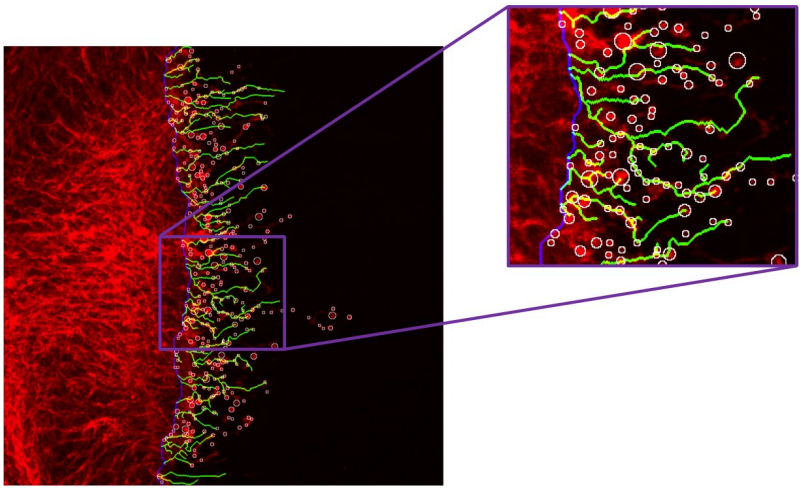

Figure 3. Cytoneme (green filaments) and Hedgehog vesicles detection (white circles).

Neuron tracing is still a challenge in neuroinformatics. Despite the huge progresses made during the last decades, this problem is still an open question. This is exacerbated with the development of new imaging techniques, that produce more and more images with improved quality and/or resolution. Among these, live-imaging techniques are more and more prominent. Indeed, acquisitions of 3D image sequences over long periods of time, in particular, have enabled neurobiologists to follow complex processes such as the development of neuronal populations. However, they produce time series of 3D volumes, for which there does not exist dedicated tracing approach.

Apart slight movements, the dynamic changes of axons are due to growing or retracting branches. Thus, we designed a topologically constrained tracking method that first ensures that the tree structure of the axon and its branches is preserved through the time sequence, and second enables a slight displacement of the axon (within an user-specified extend), while mimicing both the retraction and the growth of branches. Results are presented in figure 4.

5.6. Detection and characterization of mitochondrials networks

Participants: Kévin Giulietti, Xavier Descombes.

This work is made in collaboration with Frédéric Bost, Stephan Clavel, Aurélie Charazac, Celia Decondé le Butor (C3M).

We consider in this project a high content microscopy based screening focused on the effects of endocrine disruptors on prostatic cancer cells metabolism. Specifically, we developed our automatic computational tool to detect and classify mitochondrial network morphology from microscopy acquired images. The first step consists in binarizing the image and the binary pattern representing the mitochondrial network is classified in a second step. To binarize the mitochondrial network we consider the different level sets in the original image. A score is computed on each connected component of the level set pyramid depending on the contrast between the component and the neighboring background and on a shape criteria. We thus select the best scored component considering a compromise between the component contrast and a shape prior. We then run a k-mean clustering on the set defined by all the mitochondrial component extracted from the whole database. The different estimated classes are typical mitochondrial network element such as filaments or blobs. An image is then classified based on its signature defined by the number of mitochondrial element detected for each of the pre-defined classes (see Figure5). This classification scheme provides a discrimination framework based on

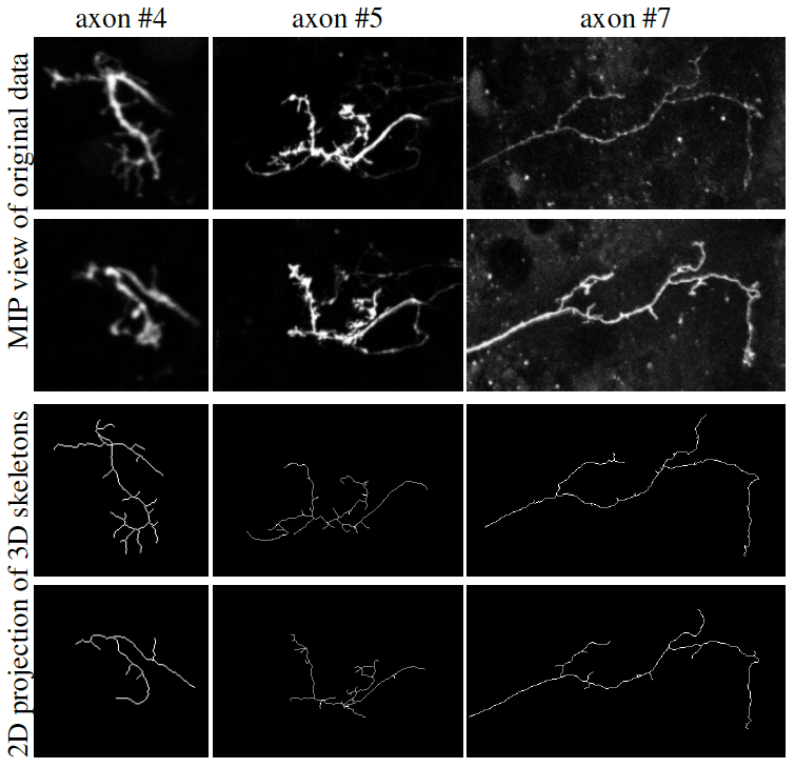

Figure 4. From top to bottom: MIP view of the first time point, MIP view of the last time point, 2D projection of the skeleton of the first time point, 2D projection of the skeleton of the last time point (series are made of 170 time points, with a 5 min time interval). Loops in skeleton projection views are projection artifacts.

geometrical and topological mitochondrial network properties than can differentiate for example filamentous and aggregate networks. This tool will be used for automatically specifying the effect of endocrine disruptors.

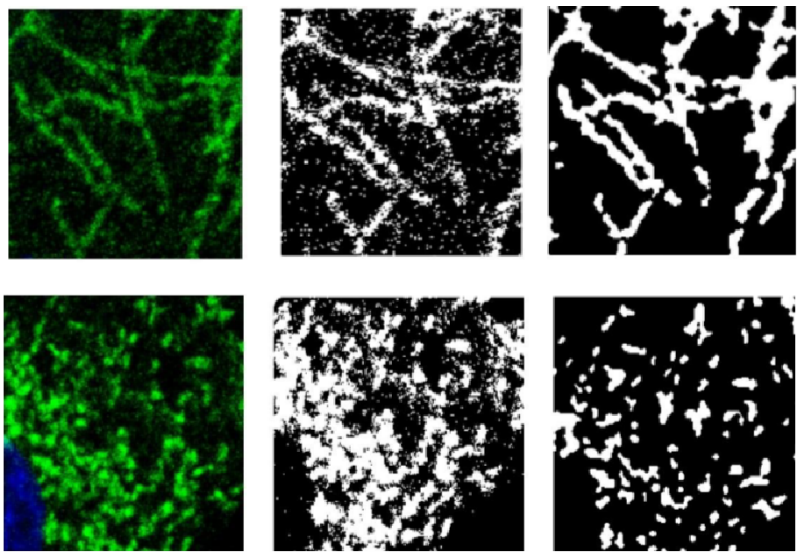

Figure 5. Detection of mitochondria filamentous/tubular (zoomed) network (top row), hyperfilamentous network (middle row) and aggregates network (bottom row). From left to right panels we have first input images (in green mitochondrial networks and in blue nuclei of the cells). Then binaries masks of mitochondrial networks using an automatic threshold. Then binaries masks resulting from our own developed method. Finally, classification of mitochondrial networks : in blue the filamentous/tubular forms, in green the hyperfilamentous form and in red the blobs forms.

5.7. Detection and classification of neuronal extensions on fluorescence microscopy images: application to the study of metabolic diseases such as obesity or anorexia

Participants: Sarah Laroui, Eric Debreuve, Xavier Descombes.

This work is made in collaboration with Céline Cansell and Carole Rovere (IPMC, Sophia Antipolis).

The goal of this project is to classify 3D images of neuronal cells (astrocytes and microglia) into mice fed normally and mice fed with a high-fat diet (see Fig. 6). The distinction can be made in two different areas of interest of the hypothalamus: Median Eminence (EM) and Arcuate Nucleus (ARC).

Astrocytes are perceived as networks. Our goal is to find out if there is a difference in the organization of these networks between the two areas of interest and between the two mouse models. Regarding inflammatory cells (microglias), we first segment each cell body and their extensions using a Frangi filter bank to enhance filamentous structures. This produces network pieces that must be joined to build one network per microglia. Thus, we connect filaments to soma and filaments to filaments using minimal paths (using an image-based, anisotropic metric) computed by dynamic programming. Finally, we extract geometrical and topological parameters such as the length and width of the extensions, the number of branches ... These parameters will be used for clustering microglia networks in order to identity the different populations.

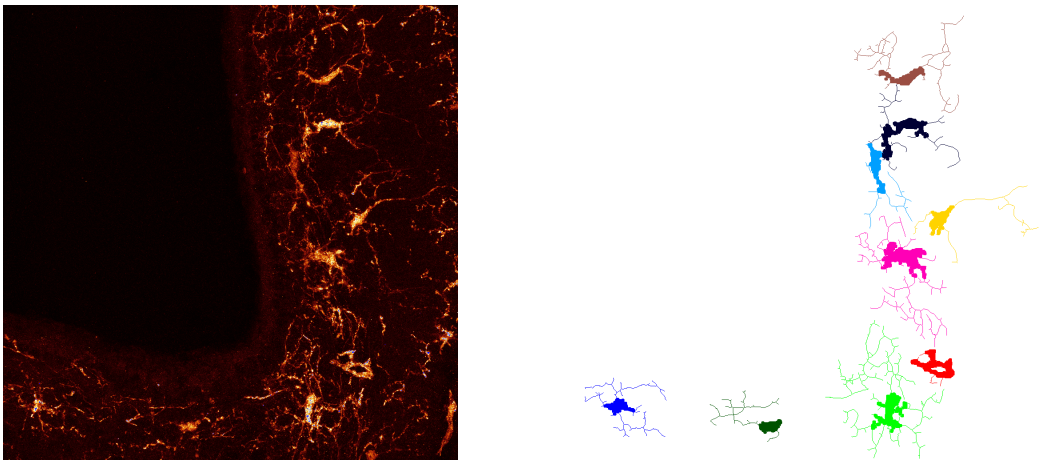

Figure 6. Maximum intensity projection (MIP) of the original image of microglias (left) and MIP of the network detection result (right).

5.8. Automatic recognition of fungi phenotype by extraction and classification of morphometric parameters

Participants: Sarah Laroui, Eric Debreuve, Xavier Descombes.

This work is made in collaboration with Aurelia Vernay (Bayer) as part of a contract with Bayer.

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 (see Fig. 7), which could be associated with the molecule Mode of Action.

In this context, we developed a robust image analysis and classification method relying on morphometric characteristics to automatically detect fungi observed using transmitted light microscopy, and classify them into predefined phenotypes. The detection task has been implemented in a classical way using a combination of mathematical morphology operations and active contours. The classification task has been solved in a supervised learning context.

Since a fungus can be described as tubular extensions connected to a spore (a roundish "root" cell), we proposed to describe such an object by its skeleton together with the distances from the skeleton to the fungus boundary. The skeleton was then converted into a valued graph. We selected a dozen topological and morphological features such as the number of nodes, the length of the longest branch, or the average and variance of the per-branch average skeleton-to-boundary distances.

These features were used in a supervised machine learning framework. Specifically, a cascade of two classifiers was proposed, the first one based on a decision tree to reject non relevant phenotypes (spores and mycelium), the second one to actually determine the phenotypes of the fungi. This second classifier was a Random Forest learned on the provided learning set composed of sample fungi from two phenotypes. Note that the classification accuracy can be computed either in a per-fungus way, or in a per-image way. Indeed, a given image corresponds to a unique chemical treatment so that all the fungi it contains exhibit the same phenotype (up to the natural biological variations), which can therefore be associated to the image itself. This per-image phenotype can be obtained by a majority vote among the individual fungus phenotypes. It represents the answer the biologists need. For the 2-phenotype problem we worked on, we obtained an image classification accuracy of around 90%, which is more than encouraging. In order to allow for a future, deeper analysis of the

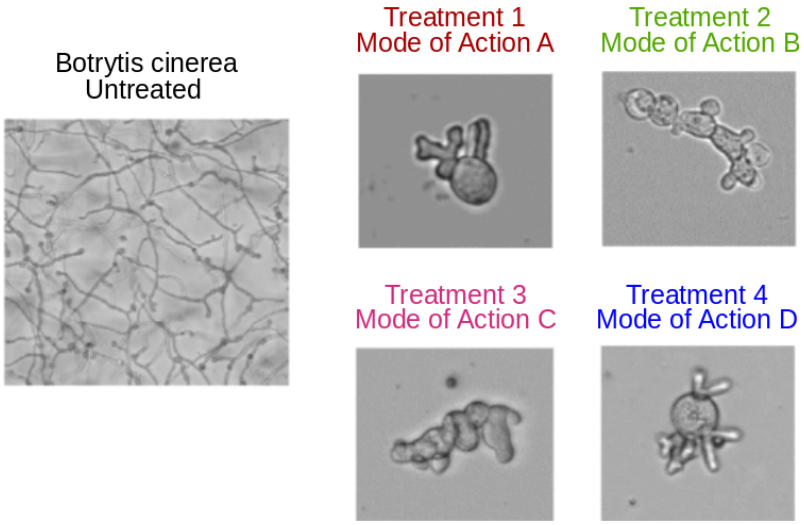

Figure 7. Characteristic phenotypic signatures for different chemical treatments (transmitted light microscopy, ImageXpress microscope, 10x lens).

features characterizing each phenotype, we also computed the influence of each feature on the classification accuracy.

5.9. Density and repartition of cytoplasmic RNP (RiboNucleoprotein Particles) granules containing the Imp protein

Participants: Eric Debreuve, Xavier Descombes.

As part of the ANR project RNAGRIMP [1] (section 7.2.1), 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...) (see Fig. 8).

A specific CellProfiler [2] pipeline has been developed for this, and CellProfiler Analyst [3] has been used to learn a decision tree for automatic nuclei (hence, cell) classification. The next step is to segment (i.e., extract automatically the region of) 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. We developed an active contour-based segmentation method relying on local image contrast with an initialization provided by a marked point process detection of ellipses [18] (see Fig. 8). Then, the detection of the particles can be performed inside the segmented cytoplasms (using a method called SPADE previously developed by the team).

5.10. Renal cell carcinoma classification from histopathological images

Participants: Mohammed Lamine Benomar, Nilgoon Zarei, Eric Debreuve, Xavier Descombes.

[1] Imp = IGF-II mRNA-binding protein; IGF = Insulin-like Growth Factor; mRNA = Messenger Ribonucleic Acid.
[2] http://cellprofiler.org
[3] http://cellprofiler.org/cp-analyst

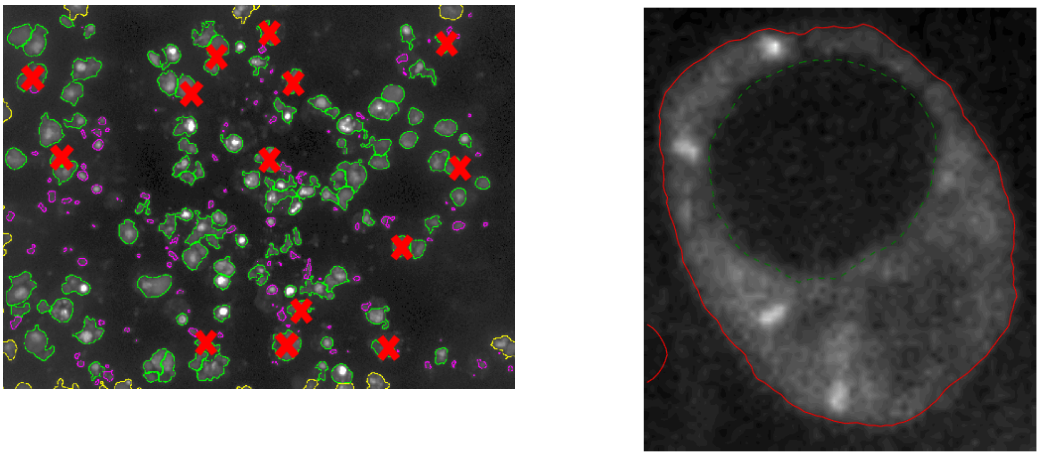

Figure 8. (left) Automatic classification of the detected nuclei into living (encircled in green) or dead (with a red cross). Objects encircled in yellow are cropped by the field of view, and objects encircled in purple are too small ; they are all discarded. (right) Active contour segmentation of the cytoplasm of a cell (previously classified as a living cell). Red contour: cytoplasm external boundary. Green, dashed contour: nucleus boundary (also cytoplasm internal boundary).

This work is made in collaboration with Damien Ambrosetti (MD, Pasteur Hospital, Nice).

The renal cell carcinoma is the most frequent type of kidney cancer (between 90% and 95% of all cases). Twelve classes of carcinoma can be distinguished, among which the clear cell carcinoma (CCRCC) and the papillary carcinoma (PRCC) are the two most common ones (75% and 10% of the cases, respectively). After the carcinoma has been diagnosed, the tumor is ablated and prepared for histological examination (fixation, staining, slicing, observation with a microscope) (see Fig. 9).

Along with genetic tests and protein reactions, the histological study allows to classify and grade the tumor in order to make a prognosis and monitor the patient treatment. Clinically speaking, digital histology is a recent domain (routinely, histological slices are studied by MDs directly on the microscope). The classical works on digital histology deal with the automatic analysis of cells (size, density ...). However, one crucial factor for carcinoma classification is the structure of the vascular network. Coarsely, CCRCC is characterized by a "fishnet" structure while the PRCC has a tree-like structure.

In this context, we proposed to extract the vascular network from a given histological slice, compute features of the underlying graph structure, and classify the tumor into CCRCC or PRCC based on these features [24]. Then, we started to focus on performing a higher-level analysis of the vascular graphs. It can be noted that cells that are close to the vascular network naturally tend to align with it. Thus there might be specific "cell-vascular network" arrangements for each type of carcinoma. Our plan is to look for repeated subgraph patterns using pattern matching methods on labeled graphs, where a pattern would be a combination of (i) topological features from the graph, (ii) nearby cell features, and (iii) measures characterizing the coherence between nearby cells and the network (cell-to-network distances, cell density along the network, degree of alignment with the network...). There are chances that each carcinoma type exhibits a set of patterns that appear with a high frequency, therefore being characteristic of the given type. Such patterns would then represent discriminant features for carcinoma classification.

5.11. Comprehensive comparison of multi-labeled images

Participants: Gaël Michelin, Grégoire Malandain.

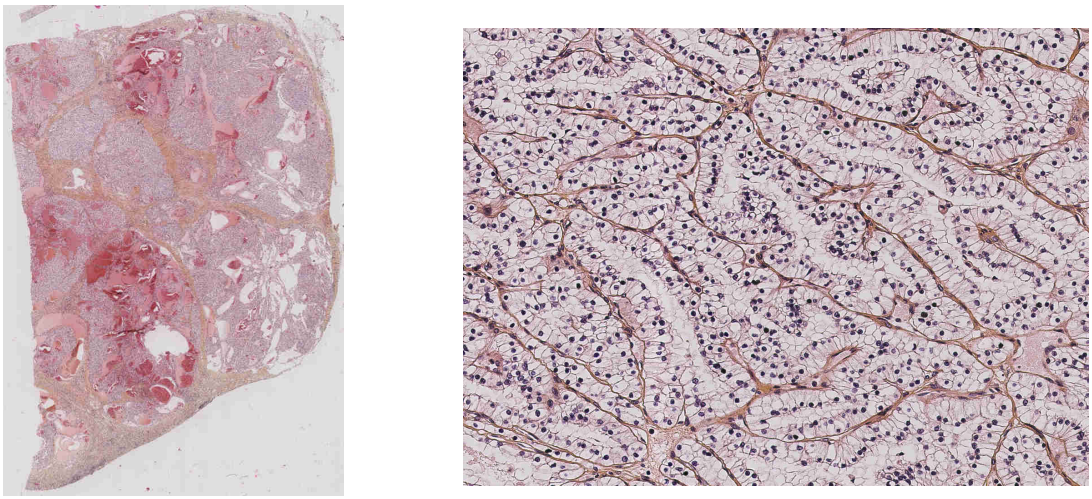

Figure 9. A histological slice through a kidney tumor: the whole slice (left) and a close-up (right) (the vascular network has a brownish color; the cell nuclei have a dark violet color).

The data used for this work are courtesy of Yassin Refahi (Sainsbury Laboratory, Cambridge university) and Ulla-Maj Fiuza (CRBM, CNRS, Montpellier 1 & 2 university).

In the context of developmental biology, 3D+t microscopy imaging allows to quantitatively study the morphogenesis at the cellular level, but requires automated segmentation methods to handle the huge quantities of data. To minimize the necessary and tedious user interaction to correct unavoidable errors (3D images may have up to thousands of cells), it is desirable to improve such segmentation methods. This, in turn, motivates the need for a comprehensive evaluation methodology that will allow to automatically compare the outputs of two segmentation methods, not only in terms of cell border accuracy, but also in terms of cell detection.

The aim of the present work is to propose such an original comprehensive segmentation comparison method that provides an objective way for multi-object segmentation comparison. This method enables to determine automatically a region-to-region correspondence map and provides asymmetric shape similarity indexes between two segmented images, with a robustness to potential region border variations. We illustrate the applicability of the proposed method with two examples in figure 10.

5.12. Grouped Local Automated Cell Extractor (GLACE)

Participants: Gaël Michelin, Grégoire Malandain.

This work is made in collaboration with Julien Laussu, Patrick Lemaire (CRBM, CNRS, Montpellier 1 & 2 university), Emmanuel Faure (IRIT, CNRS, Toulouse) and Christophe Godin (Inria Virtual Plants team, Montpellier).

In developmental biology, the embryogenesis study relies in particular on image-based studies. Today, fluorescent confocal microscopy is a means for *in vivo* imaging of developing organisms at cell level with a high spatio-temporal resolution. To handle such 3D+t image sequences, adapted computer-assisted methods are highly desirable in order to extract essential information from these data.

More specifically, for developing ascidian embryos, an existing framework called `ASTEC` [19] is used by biologists in order to extract the cell segmentation and lineage from some 3D+t sequences. However, remaining issues about segmentation accuracy motivated us to propose a new framework as an alternative to `ASTEC` for cell segmentation and tracking. The originality of the proposed Grouped Local Automated Cell

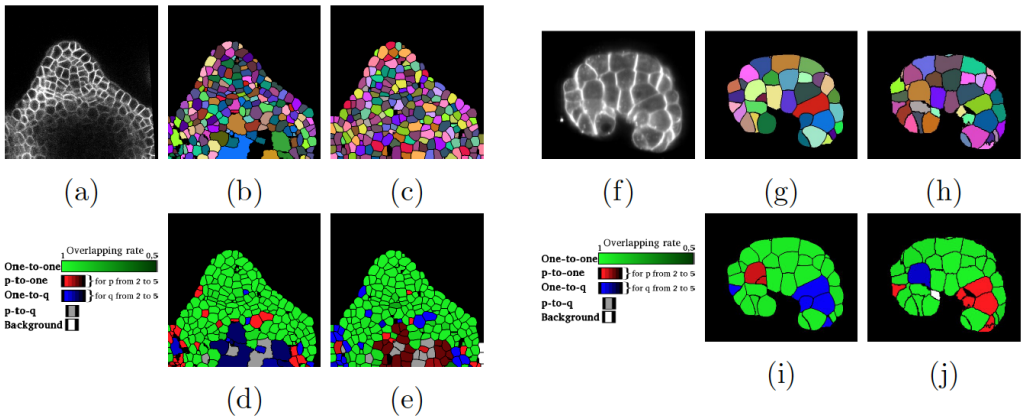

Figure 10. Cut-views of original 3D intensity images (a,f), the associated pairs of corresponding segmentations (b-c,g-h) and the results of regions association for each segmentation determined by the proposed method with the proposed method. (a-e) Floral meristem image. (f-j) Ascidian image.

Extractor (GLACE) framework is to segment the i–th image of a sequence by applying *locally* the original 3D cell segmentation framework of [21] for all the regions of interest defined by the segmented cells of the $i-1$–th image of the sequence. The union of all the local reconstructions provides the segmentation of the i–th image of the sequence (figure 11). The GLACE framework does not replace the ASTEC framework, however they provide complementary results for embryo image sequence reconstructions.

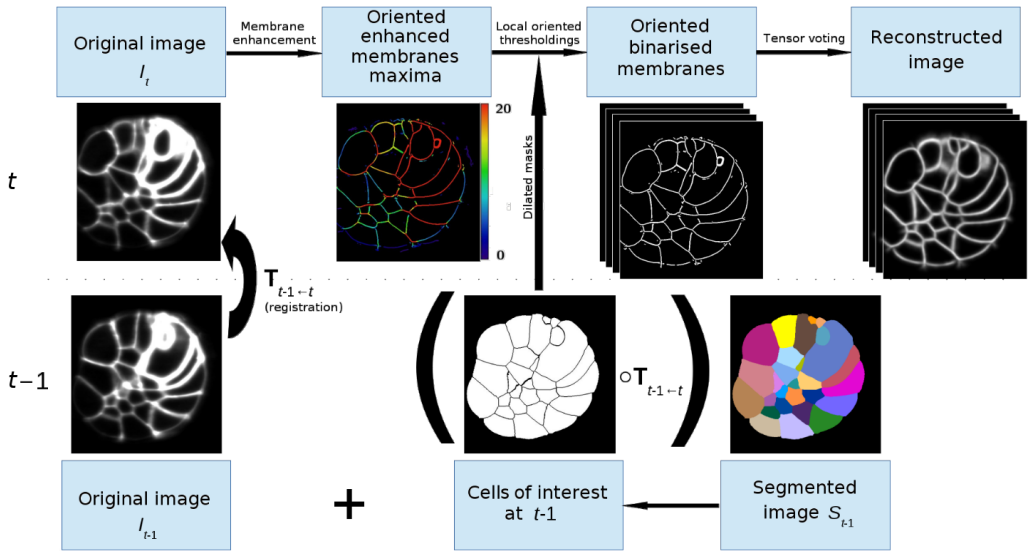

Figure 11. Pipeline for GLACE.

5.13. Ascidian embryo cell lineage registration in 3D+t image sequences

Participants: Gaël Michelin, Grégoire Malandain.

This work is made in collaboration with Julien Laussu, Patrick Lemaire (CRBM, CNRS, Montpellier 1 & 2 university) and Christophe Godin (Inria Virtual Plants team, Montpellier).

Until gastrulation, ascidian embryos have a very stereotyped and invariant development, so that it is possible to establish a cell-to-cell mapping between two developing embryos at a same developing stage. We proposed in a previous work a method for geometric registration that determines a linear (affine) transformation superimposing a test embryo into a reference one and that draws a cell-to-cell mapping up [20].

In the current work, we extend this framework for the determination of cell lineage mapping between two developing ascidian embryos by propagating an initial cell-to-cell mapping to the cell descendants since the cell correspondences are inherited for the ascidian embryo (figure 12 (top)). To do so, we use the information provided by the 3D+t sequences segmentation and lineage such as cell volume, life-span and relative position in the embryos. We experimented on real data the proposed cell lineage registration framework (figure 12 (bottom)).

5.14. Towards construction of digital atlases of plant tissues

Participants: Gaël Michelin, Grégoire Malandain.

This work is made in collaboration with Yassin Refahi (Sainsbury Laboratory, Cambridge university), Jonathan Legrand, Jan Traas (RDP, ENS Lyon, INRA, CNRS, Lyon) and Christophe Godin (Inria Virtual Plants team, Montpellier).

In developmental biology, the study of model organisms aims for the understanding of genetic mechanisms responsible of morphogenesis. Today, fluorescent confocal microscopy is a means for in vivo imaging of developing plants at cell level with a high spatio-temporal resolution.

We propose in this work some dedicated computational tools for the study of such 3D+t sequences. These methods offer the means to compare temporal sequences of flower development and to build 4D digital atlases of developing arabidposis floral meristems on which every individual can be projected (figure 13), opening the avenue to the statical analysis of populations.

5.15. 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 Asclepios team).

Percutaneous Coronary Intervention (PCI) is a minimally procedure which is used to treat coronary artery narrowing. During the guidewire navigation, the lesion is crossed and in some cases, the physician could benefit from a visual assessment of the coronary wall. The x-ray imaging interventional system used for per-operative guidance is not able to display this information mostly by lack of density resolution. On the contrary, Computed Tomography Angiography (CTA) is a modality which has the capability of capturing the characteristics of the vessel wall.

Fusing pre-operative CT angiography with per-operative angiographic and fluoroscopic images is thus considered by physicians as a potentially useful tool for improved guidance. To be adopted, this tool has required the development of tracking methods adapted to the deformations of the arteries caused by the cardiac motion. We have proposed a 3D/2D temporal tracking of one coronary vessel, based on a spline deformation, using pairings with a controlled 2D stretching or contraction along the paired curves and a preservation of the length of the 3D curve which corresponds to the anatomic propriety [8], [9]. Experiments were conducted on a database of 10 vessels from 5 distinct patients, with dedicated metrics assessing both the global registration and the local coherency of the position along the vessel. The proposed results demonstrate the efficiency of the proposed method, with an average standard deviation of 2 mm for the localization of landmarks (see Fig. 14).

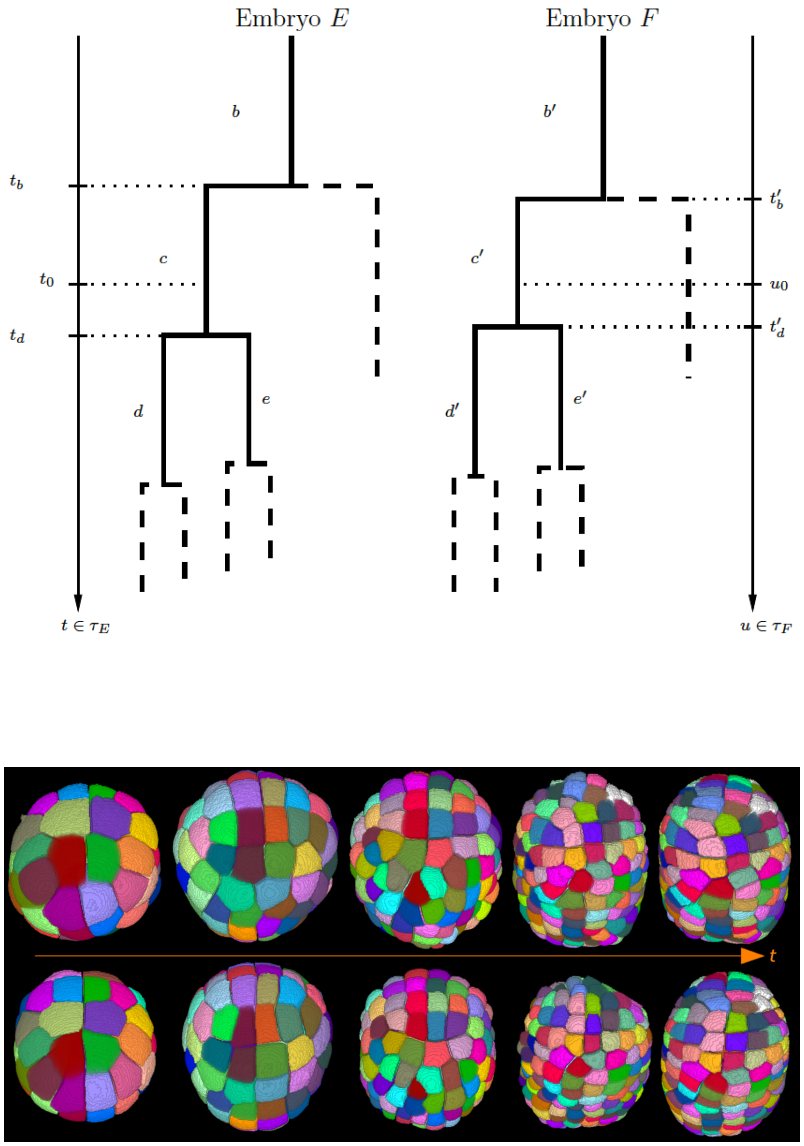

Figure 12. Ascidian embryo cell lineage registration. Top: sub-lineages from embryos E and F showing labels c and c' in correspondence with their birth (t_b) and death (t_d) (respectively t'_b and t'_d) time-points, mother cells (b and b') and daughters ((d, e) and (d', e')) along embryo lifespans τ_E and τ_F. Bottom: result of lineages registration between two developing embryos. Mapped cells appear with the same color. Cells in white are those for whom no corresponding cell was found in the other embryo. First column: cell-to-cell initial mapping.

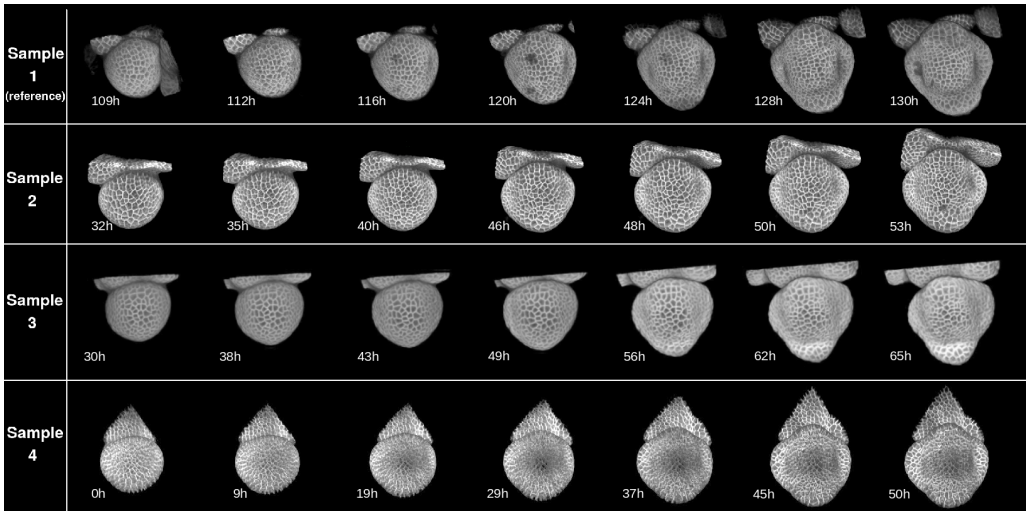

Figure 13. Visualization of the valid spatio-temporal sample alignments following the proposed registration method at different floral meristem developmental phases. One can observe the reliability of the registration method to identify developmental phases equivalences between the different samples.

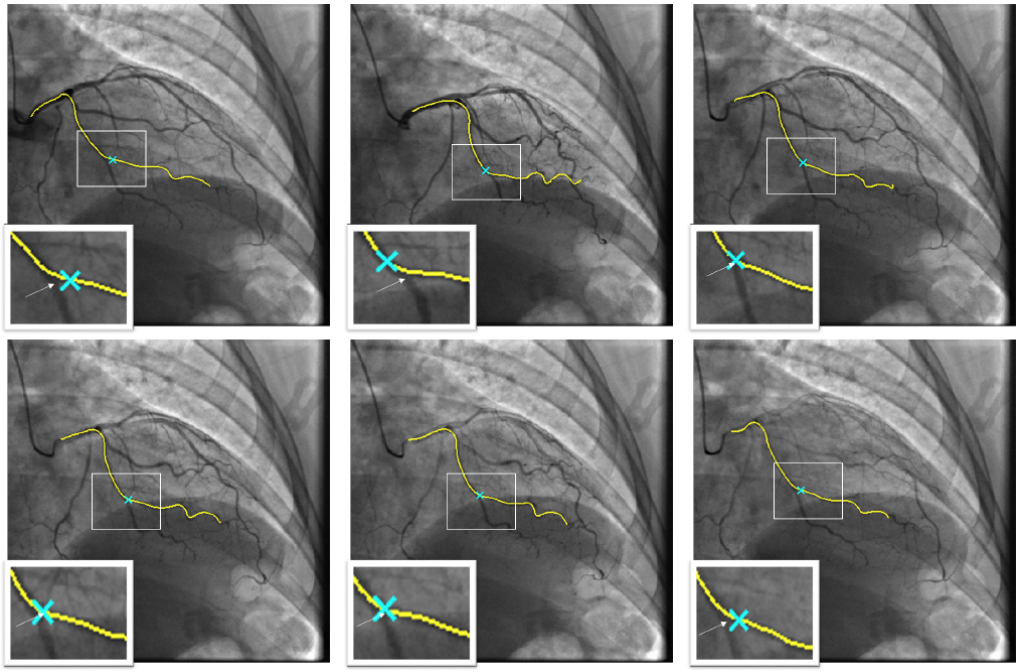

Figure 14. Visualization of the valid spatio-temporal sample alignments following the proposed registration method at different floral meristem developmental phases. One can observe the reliability of the registration method to identify developmental phases equivalences between the different samples.

5.16. Modelling axon growth from in vivo data

Participants: Agustina Razetti, Xavier Descombes, Caroline Medioni, Florence Besse.

Axons develop embedded in mechanically constrained environments. Thus, to fully understand this dynamical process, one must take into account collective mechanisms and mechanical interactions within the axonal populations. However, techniques to directly measure this from living brains are today lacking or heavy to implement. This interdisciplinary work intends to close the gap between classic in vitro experimental assumptions and real in vivo situations, where the final neuronal morphology is acquired through a dynamical and environmental-dependent process. We use as biological model Drosophila γ axon remodeling and analyze, for the first time to our knowledge, the mechanical situation of a whole population of γ neurons (650 individuals) growing together in a constraint space (i.e. medial lobe of the Mushroom Body).

We have designed a mathematical model of single axon growth based on Gaussian Markov Chains with two parameters, accounting for axon rigidity and attraction to the target field. We used this model to simulate the growing axons embedded in space constraint populations to test our hypothesis. We explored new branch formation mechanisms to mimic the growth of wild type γ axons population , as well as predict different mutant phenotypes. This approach allowed also to analyze dynamical aspects of the γ neuron collective growth process such as speed and density in function of space and time, which help to explain several characteristics of the γ neuron morphology and behavior during development. Among the obtained results, the proposed model is able to reproduce the intra-population morphological variability. Interestingly, applying the ESA distance between trees previously developed in the team [22] showed that real axons present shapes that showcase a compromise between collective elongation and morphological variability, essential for axonal connectivity (Figure 15). Finally, we explored other branch occurrence strategies –from uniformly random to occurrence upon mechanical interactions- to contrast and validate with previously developed hypothesis on the importance of branching for axonal elongation in vivo.

5.17. Jump point detection and parameter estimation from piecewise homogeneous Markov chains

Participants: Agustina Razetti, Xavier Descombes.

Piecewise homogeneous Markov chain processes can be applied to diverse phenomena of various nature, such as genetics, physics. Recent bibliography has focused on these systems, proposing different alternatives to detect the jump points and be able to separate between different phases of the signals. The Markov chain is usually defined by its transition matrix and the change points are modeled by a hidden Markov process. In this work, we focus on the Gaussian case with a Bernoulli distribution governing the change points. We have developped two different theoretical frameworks: one Bayesian with a Bernoulli prior, and the other one statistic-oriented, proposing a test of hypothesis based on ratio of likelihoods. For both cases we provide with robust algorithms to detect the jump points and reduce the error in the estimations of the parameters of the main model. We compare both methods and investigate their limits and advantages. We finally provided practical examples to showcase the power of the proposed approach (see Figure 16).

6. Bilateral Contracts and Grants with Industry

6.1. 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 6 months (from jan. 2017 to jun. 2017) companion contract for the Master intership of S. Laroui.

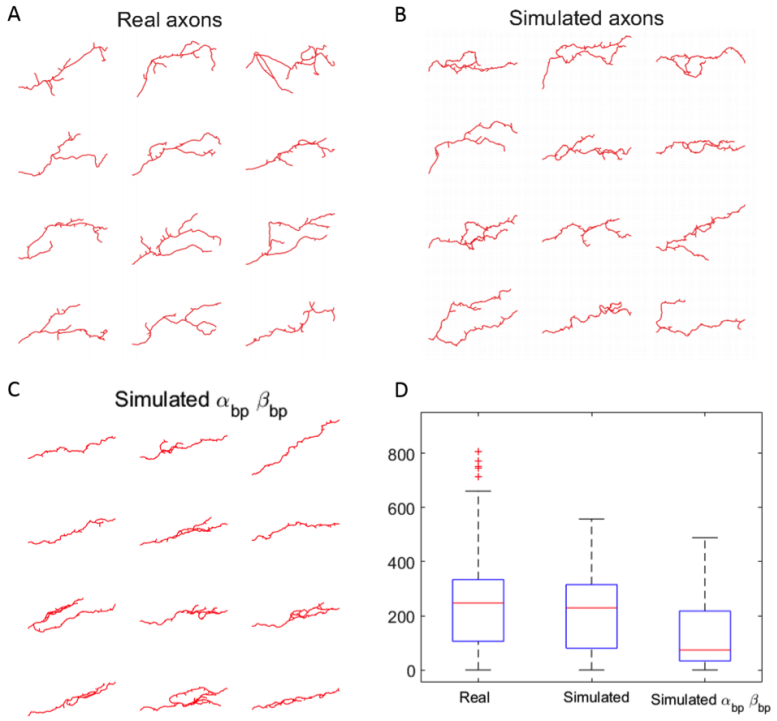

Figure 15. Impact of the parameter value on axonal morphologies. (A) Real wild type γ axons. (B) Axons simulated with parameters estimated from data. (C) Axons simulated with optimal parameters regarding collective elongation. (D) Intra-group variability measured with the ESA distance between all the axons in each group (A-C).

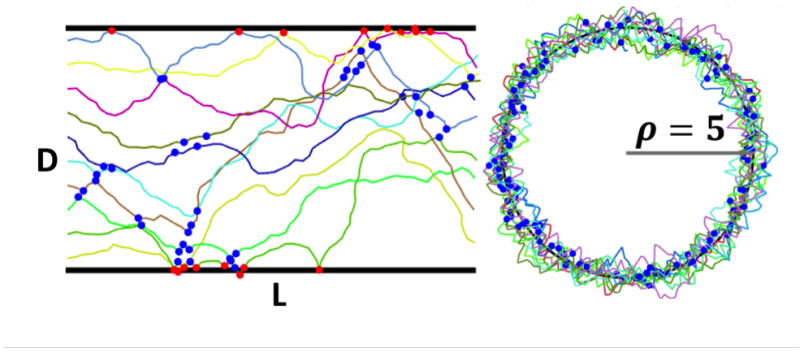

Figure 16. Two application examples. 10 particles of equal mass moving are shown at each case. When they collide another particle or the external limits, they follow elastic punctual collisions (shown by stars and circles). Left: particles inside a tube of diameter D and length L; right: particles moving around a circle of radius ρ.

7. Partnerships and Cooperations

7.1. Regional Initiatives

7.1.1. Labex Signalife

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

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

Florence Besse and Xavier Descombes participated in the selection committee for LabeX PhD program students.

7.1.2. Idex UCA Jedi

Four projects leading by team members were funded.

7.2. National Initiatives

7.2.1. ANR RNAGRIMP

Participants: Florence Besse [PI], Xavier Descombes, Eric Debreuve, Djampa Kozlowski.

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.

7.2.2. ANR HMOVE

Participants: Xavier Descombes, Eric Debreuve, Christelle Requena.

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.

7.2.3. 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.

7.2.4. ANR PhaseQuant

Participants: Grégoire Malandain, Eric Debreuve.

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.

7.2.5. Inria Large-scale initiative Morphogenetics

Participants: Grégoire Malandain, Xavier Descombes, Gaël Michelin.

This action gathers the expertise of three Inria research teams (Virtual Plants, Morpheme, and Evasion) and other groups (RDP (ENS-CNRS–INRA, Lyon), RFD (CEA-INRA-CNRS, Grenoble)) and aimed at understanding how shape and architecture in plants are controlled by genes during development. To do so, we will study the spatio-temporal relationship between genetic regulation and plant shape utilizing recently developed imaging techniques together with molecular genetics and computational modeling. Rather than concentrating on the molecular networks, the project will study plant development across scales. In this context we will focus on the Arabidopsis flower, currently one of the best-characterized plant systems.

7.2.6. 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).

7.3. International Initiatives

7.3.1. Participation in Other International Programs

ECOS-Nord France - Colombie 2015-2017: visit of the Pr Arturo Plata from the University Industrial of Santnder, Bucaramanga, Columbia, in June 2017.

7.4. International Research Visitors

7.4.1. Visits of International Scientists

7.4.1.1. Internships

Nilgoon Zarei:University of British Columbia, Vancouver, Canada, Jul 2017 - Dec 2017

A Novel approach for Renal Cell Carcinoma Classification Using Vascular, Morphological and Spatial Information

Mohammed Lamine Benomar: PhD, Université Abou Bekr Belkaid Tlemcen, Algérie, from October 2016 until April 2017.

Combinaison adaptative des informations texture et couleur pour la segmentation d'images médicales

Vanna Lisa Coli: PhD, University of Modena and Reggio Emilia, Bologna Italy., from January to April 2017.

TV regularization for the reconstruction of microwave tomographic imagery, with application to the detection of cerebrovascular accidents.

8. Dissemination

8.1. Promoting Scientific Activities

8.1.1. Scientific Events Selection

8.1.1.1. Member of the Conference Program Committees

Laure Blanc-Féraud was a Associated Editor for the Workshop NCMIP 2017 New Computational method in Inverse Problems and the Conference IEEE ISBI 2018.

Eric Debreuve was a member of the Program Committee of ACIVS 2017 (Advanced Concepts for Intelligent Vision Systems).

8.1.1.2. Reviewer

Laure Blanc-Féraud was a reviewer for the conferences ISBI, GRETSI, NCMIP.

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 reviewer for the conferences ISBI, ICIP, ICASSP, and GRETSI.

Grégoire Malandain was reviewer for the conferences EMBC, ISBI, MICCAI, and GRETSI.

8.1.2. Journal

8.1.2.1. Member of the Editorial Boards

Laure Blanc-Féraud was Associated Editor for the journals SIAM Imaging Sciences and the Revue Traitement du Signal.

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

8.1.2.2. Reviewer - Reviewing Activities

Laure Blanc-Féraud was a reviewer for the journals ...

Eric Debreuve was a reviewer for the journals ...

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

Grégoire Malandain was reviewer for the journals BMC Medical Imaging and International Journal of Computer Assisted Radiology and Surgery.

8.1.3. Invited Talks

Florence Besse was invited to DENA 2017 (Workshop on Expanding Networks Dynamics : Modeling, Analysis and Simulation of multi-scale spatial exploration under constraints), Nov 2017, Nice and to the Canceropole PACA annual meeting, June 2017, Saint-Raphaël.

Laure Blanc-Féraud was invited to the Workshop on Sparsity in Applied Mathematics and Statistics, Brussels Belgium, 1-2 June 2017.

8.1.4. Leadership within the Scientific Community

Florence Besse is a member of the scientific council of the IDEX JEDI Academy 2, and a member of the scientific council of the LabeX Signalife program.

Laure Blanc-Féraud is the directrice of the GdR 720 ISIS du CNRS: standard scientific animation (see website gdrisis.fr) and organization of the general meeting in november 2017 (100 participants over 3 days). She was also chair of the scientific council of Academy 1 of Idex UCA JEDI.

Xavier Descombes is member of the Scientific Committee of the competitivness pole Optitech, member of IEEE BISP (Biomedical Imaging Signal Processing) Technical Committee and member of the Scientific Committee of Labex SIGNALIFE.

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.

8.1.5. Scientific Expertise

Laure Blanc-Féraud was expert for the Italian Ministery of Research (MUIR) and for the FNRS (Belgium).

Eric Debreuve was an expert for a CIFRE PhD proposal.

Xavier Descombes is an expert for the DRRT (Paca, Ile de France, Bretagne) and for the ANR.

8.1.6. Research Administration

Laure Blanc-Féraud was member of the Academic Council of COMUE UCA and member of the scientific council of ITAV (Toulouse) and GdR MIV (Microscopie Fonctionnelle du Vivant).

Xavier Descombes is member of the "comité des projets" and the "comité de centre" of Inria CRISAM.

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

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

IUT: Agustina Razetti, principes des transmissions radio, 12h Eq. TD, IUT Nice Côte d'Azur, Université de Nice Sophia Antipolis, France.

IUT: Agustina Razetti, initiation Matlab, 6h Eq. TD, IUT Nice Côte d'Azur, Université de Nice Sophia Antipolis, France.

Licence: Arne Bechensteen, Outils pour la physique , 36h, L1, Polytech Nice Sophia , France.

Licence: Arne Bechensteen, Programmation impérative PeiP1 , 29.5h, L1, Polytech Nice Sophia, France.

Master: Gaël Michelin, Traitement Numérique des Images, 10h Eq. TD, Niveau M2, EPU, Université de Nice Sophia Antipolis, France.

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

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.

Licence: Caroline Medioni, Imagerie tissulaire, 15H, L3, Université Nice Côte d'Azur, France

Master: Caroline Medioni, Master "Sciences de la vie" jury , juin 2017

Master/Engineer: Eric Debreuve, Data Mining, 27.5h EqTD, Master 2/Engineer 5th year, UNS.

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.

8.2.2. Supervision

PhD: Lola Baustista, Reconstruction de phase pour la microscopie à Contraste Interférentiel Différentiel, Université Côte d'Azur, 30 june 2017.

PhD in progress: Agustina Razetti, Modelling and characterizing axon growth from in vivo data, 1st november 2014, Xavier Descombes (advisor), Florence Besse, Caroline Medioni (co-supervisors).

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

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.

8.2.3. Internships

Arne Henrik Bechensteen: INSA Toulouse, Towards a continuous relaxation of the ℓ_0 constrained problem. Supervisors: L. Blanc-Féraud, G. Aubert.

Kévin Giulietti: M2 SVS, Université Nice Sophia Antipolis, Détection et caractérisation de réseaux mitochondriaux à partir d'images de microscopie. Supervisor: X. Descombes.

Nadège Guiglielmoni: M2 AMIB, université Paris Sud, Reconstruction 3D d'axones uniques et multiples et analyse quantitative des branches sur des données temporelles dans le cerveau de la drosophile. Supervisors: C. Medioni, G. Malandain.

Christelle Requena: M2 SVS, Université Nice Sophia Antipolis, Détections d'extensions membranaires impliquées dans les communications cellaulaires à partir d'images de microscopie in vivo. Supervisor: X. Descombes.

Sarah Laroui: M2 SVS-BIM, UNS, Automatic recognition of fungi phenotype by extraction and classification of morphometric parameters. Supervisors: E. Debreuve, X. Descombes.

8.2.4. Juries

Laure Blanc-Féraud participated to the PhD thesis committees of Lola Bautista (MORPHEME) as supervisor and of Simon Labouesse (Institut fresnel) as reviewer, and to the HDR jury of Aurelia Fraisse (L2S, Gif sur Yvette) as reviewer and of El-Hadi Djermoune (CRAN, Nancy).

Florence Besse participated to the PhD thesis committee of A. Samacoits (Pierre et Marie Curie univ.).

Xavier Descombes participated as reviewer to the PhD thesis committee of Vincent Briane (Rennes univ.) and Zhilin Li (CMLA Cachan).

Grégoire Malandain participated as reviewer to the PhD thesis committee of Hoai-Nam Nguyen (Rennes univ.).

8.3. Popularization

Anca Grapa, Kévin Giulietti and Gaël Michelin participated as exhibitors to the "Fête de la science 2017" manifestation in Juan-les-Pins (palais des congrès). The objective was to initiate non-scientic audience to the research issues in Morpheme team, and more generally to numerical science.

Laure Blanc-Féraud gave a talk for the PhD students association of the doctoral school STIC of Université Côte d'Azur "Voir l'intérieur d'une cellule vivante : lunettes numériques au secours du microscope" , mai 2017.

9. Bibliography

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Articles in International Peer-Reviewed Journals

[2] D. PEURICHARD, F. DELEBECQUE, A. LORSIGNOL, C. BARREAU, J. ROUQUETTE, X. DESCOMBES, L. CASTEILLA, P. DEGOND. *Simple mechanical cues could explain adipose tissue morphology*, in "Journal of theoretical biology", September 2017, vol. 429, 21 p. , https://hal.inria.fr/hal-01576486

[3] Y. QUÉAU, R. MECCA, J.-D. DUROU, X. DESCOMBES. *Photometric Stereo with Only Two Images: A Theoretical Study and Numerical Resolution*, in "Image and Vision Computing", January 2017, n^{o} 57, pp. 175–191 [*DOI :* 10.1016/J.IMAVIS.2016.11.006], https://hal.archives-ouvertes.fr/hal-01334657

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