IN PARTNERSHIP WITH:
CNRS

Université Nice - Sophia Antipolis

Activity Report 2016

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

Keywords:

Computer Science and Digital Science:

3.4. - Machine learning and statistics
3.4.1. - Supervised learning
3.4.2. - Unsupervised learning
3.4.4. - Optimization and learning
3.4.6. - Neural networks
3.4.7. - Kernel methods
3.4.8. - Deep learning
5.3. - Image processing and analysis
5.3.2. - Sparse modeling and image representation
5.3.4. - Registration
5.4.1. - Object recognition
5.4.3. - Content retrieval
5.4.4. - 3D and spatio-temporal reconstruction
5.4.5. - Object tracking and motion analysis
5.4.6. - Object localization
5.9. - Signal processing
5.9.3. - Reconstruction, enhancement
5.9.5. - Sparsity-aware processing
5.9.6. - Optimization tools
6.1. - Mathematical Modeling
6.1.1. - Continuous Modeling (PDE, ODE)
6.1.2. - Stochastic Modeling (SPDE, SDE)
6.3.1. - Inverse problems

Other Research Topics and Application Domains:

1.1. - Biology
1.1.3. - Cellular biology
1.1.4. - Developmental biology
2.6. - Biological and medical imaging

1. Members

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Caroline Medioni [CNRS, Researcher, 20%]

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Raphael Meunier [Inria, Intern, from Jun 2016 until Sep 2016]

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. SPADE: Small PArticle DEtection

FUNCTIONAL DESCRIPTION SPADE is an algorithm primarily designed to detect objects whose size is smaller than a few pixels (particles) on fluorescence microscopy images. It is a simplified version of a marked point process based on a shape dictionnary.

- Participants: N. Cedilnik, E. Debreuve, and X. Descombes
- Contact: Xavier Descombes

5. New Results

5.1. Multi-Angle TIRF reconstruction for studying the cell adhesion phenomenon

Participants: Emmanuel Soubies, Laure Blanc-Féraud, Sébastien Schaub.

This work is made in collaboration with Agata Radwanska and Ellen Van Obberghen-Schilling from Institut de Biologie Valrose (iBV) at Nice.

Understanding cell adhesion mechanism is of a major importance in biology for example in the context of tumoral angiogenesis [1]. However, this process occurs at the vicinity of the cell membrane within a layer of a few hundred nanometer making classical microscopy devices unable to image such biological structures due to their lack of resolution in the axial direction. An interesting alternative would be to use a multi-angle total internal reflection illumination together with numerical reconstruction algorithms in order to reach a nanoscale precision in the axial direction.

Following this idea, we made use of our previous work on MA-TIRF reconstruction to produce color-coded maps (see the example on Figure 1), with an axial resolution of 20 nm, of biological samples provided by Agata Radwanska and Ellen Van Obberghen-Schilling from the Institut de Biologie Valrose. The information obtained from the study of the reconstructed images have confirmed known behaviors of some proteins involved in the cell adhesion process allowing us, by this way, to complete the validation of our reconstruction method. Moreover, the 3D reconstructions have provided new information concerning the axial position of the observed biological proteins, information which was unavailable for previous studies conducted with other microscopy systems.

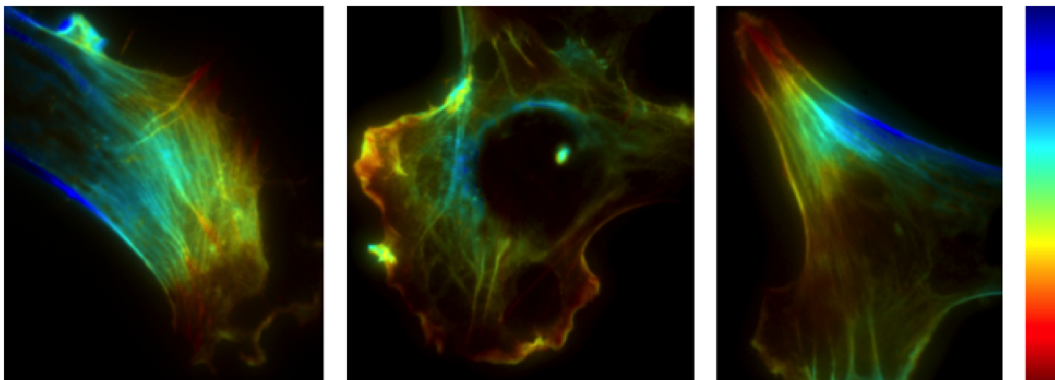

Figure 1. Example of color-coded representations for the reconstructed samples. The colors correspond to the depth (in the axial direction) of the biological structures (in the colorbar on the right: red = 0 nm and dark blue = 400 nm).

5.2. Exact continuous penalties for ℓ_2-ℓ_0 minimization: Application to Photo Activated Localization Microscopy (PALM)

Participants: Simon Gazagnes, Emmanuel Soubies, Laure Blanc-Féraud.

In conventional microscopy techniques, the spatial resolution of an image is limited by the diffraction phenomena. Recent methods like photo-activated localization microscopy (PALM) allow high-precision molecule localization by sequentially activating and imaging a small random set of fluorescent molecules in the sample. However, the quality of this super-resolved image is related to the density of emitters activated at each acquisition and the numerical method used to locate molecules.

Applications for these microscopy techniques are then mainly restricted by the number of acquisitions required to obtain the superresolved image. One way to overcome this limitation is to increase the density of emitters activated at each acquisition. Nevertheless, it will cause overlapping for a certain number of spots on the acquired image which makes the localization of the underlying molecules a harder task. Considering such

[1] Process of blood vessels creation from existing ones.

a high density setting, we have proposed to perform the molecules localization by solving a ℓ_0-penalized least squares criteria through the minimization of the Continuous Exact ℓ_0 (CEL0) relaxation that we have previously proposed. The method has provided interesting results, competing with state of the art methods, as shown on Figure 2. This work has been submitted for the conference ISBI 2017.

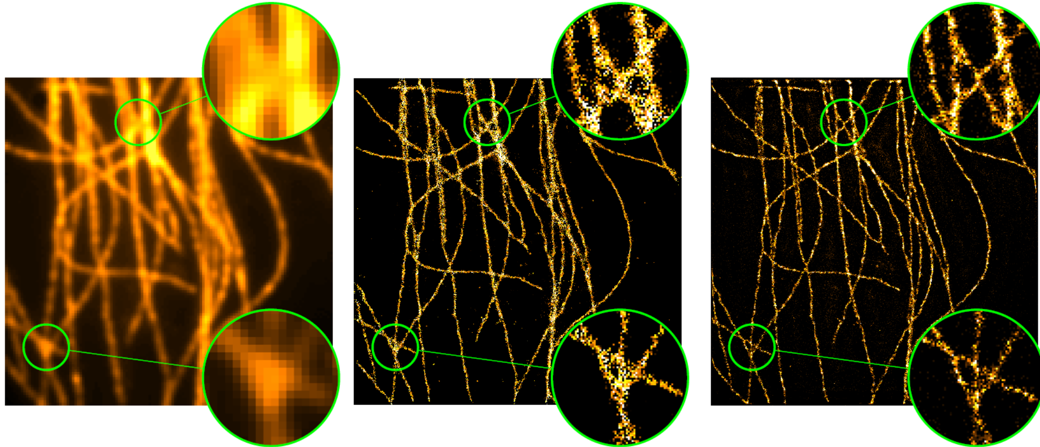

Figure 2. From left to right: Conventional Wide Field image, PALM with DAOSTORM (state of the art algorithm) reconstruction, PALM with the proposed reconstruction.

5.3. Exact continuous penalties for ℓ_2-ℓ_0 minimization: Application to Channel and Direction Of Arrival (DOA) estimation problems

Participants: Emmanuel Soubies, Laure Blanc-Féraud.

This work is made in collaboration with Adilson Chinatto, Cynthia Junqueira, João M. T. Romano (University of Campinas, Brazil) and Pascal Larzabal, Jean-Pierre Barbot (ENS Cachan, SATIE Lab).

In this work, we have proposed to extend the Continuous Exact ℓ_0 (CEL0) penalty, which we initially introduced for the real single measurement vector (SMV) case, to complex SMV and complex multiple measurement vector (MMV) situations involving structured sparsity. Such an extension is necessary to address sparse signal processing estimation problems like augmented resolution channel estimation and direction of arrival (DOA) estimation for which the mixture matrix do not verify restrict isometry property (RIP) and incoherence conditions. We thereby have derived a row-structured version of the CEL0 penalty and showed that the relations between minimizers of the resulting relaxation and those of the initial ℓ_0-penalised least squares criteria, that we previously showed in the real SMV case, are still valid for complex SMV and MMV situations using the proposed row-structured CEL0 penalty. Finally, we have employed state of the art nonsmooth nonconvex algorithms to minimize the proposed relaxation and we have compared the results obtained by our method with those provided by the well known iterative hard thresholding (IHT) algorithm as well as some classical algorithms for the studied problems. We have shown that minimizing the row-structured CEL0 relaxation provides better estimation results than IHT, which minimizes directly with the initial ℓ_0-penalized least-squares criteria, and than classical algorithms used for such problems where the mixture matrix is highly correlated. Moreover, the proposed method is able to reach the oracle RMSE in some cases. This work has been submitted to the IEEE Transaction on Signal Processing journal.

5.4. Phase estimation in Differential Interference Contrast (DIC) microscopy

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

We address the problem of estimating the phase from color images acquired with differential-interference-contrast microscopy. In particular, we consider the nonlinear and nonconvex optimization problem obtained by regularizing a least-squares-like discrepancy term with a total variation functional, possibly smoothed with the introduction of a positive constant. We deeply investigate the analytic properties of the resulting objective function, proving the existence of minimum points, and several optimization methods able to address the minimization problem. Besides revisiting the conjugate gradient method proposed in the literature for this problem and comparing it with standard conjugate gradient approaches, we introduce more recent effective optimization tools able to obtain both in the smooth and in the non smooth case accurate reconstructions with a reduced computational demand.

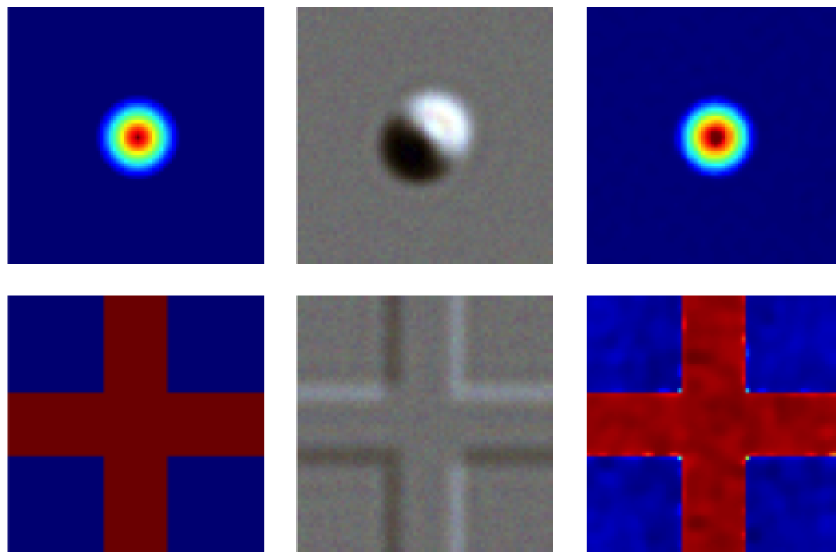

Figure 3. Data and results for the cone (top row) and cross (bottom row) objects. From left to right: true object, noisy DIC color image taken at shear angle $\frac{\pi}{4}$ rad *and corrupted with white Gaussian noise at SNR = 4.5 dB, and reconstructed phase with the LMSD method from observations at shear angles equal to* $-\pi/4$ rad *and* $\pi/4$ rad.

5.5. White Blood Cells Segmentation and Classification in Bone Marrow Images

Participants: Mohammed Lamine Benomar, Xavier Descombes.

This work is made in collaboration with Chikh Amine and Mourtada Benazzouz from GBM Lab. (Tlemcen University). Our experiments were performed on an image database acquired in the Hemobiology service of the Tlemcen Hospital (Algeria).

The differential count of white blood cells (WBC) for medical diagnosis requires a careful observation in peripheral blood and bone marrow microscopic images in order to detect abnormal or suspicious cells. However, this process (screening) is time consuming, requiring concentration, experience and competence of the expert. The diagnosis depends on the correct recognition of cells. For that, computer analysis image system is required to automate the process in order to help experts, reduce the time and increase the accuracy. The main important steps in such systems are segmentation and classification of white blood cells.

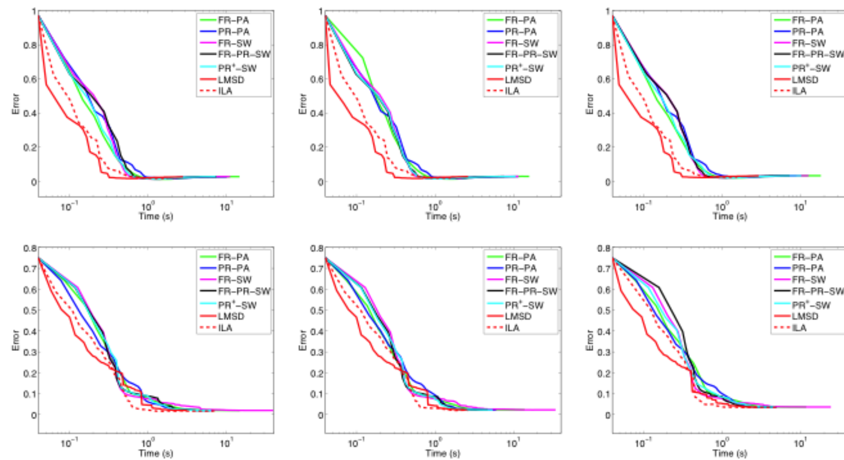

Figure 4. Error versus computational time plots for the cone (top row) and cross (bottom row) objects. From left to right: noise-free data, SNR = 9 dB and SNR = 4.5 dB.

The proposed approach to locate WBC in bone marrow microscopic smear could be divided into three main steps: pre-processing, segmentation and classification. The main concept of the segmentation and classification algorithm employed uses WBCs color, texture and morphological properties.

The first step is to reveal chromatic characteristics of the WBC by applying decorrelation stretch to multi-channel RGB image, simple color transformation and Otsu thresholding to suppress background and most of the red blood cells. In the segmentation step, two techniques have been used which are Marker Controlled Watershed followed by MLE (Maximum Likelihood Estimator) to differentiate between WBC, the grouped red blood cells and artifacts using shape, color and texture features. Then Otsu thresholding based on HSL color space to separate WBC nucleus and cytoplasm (see Figure 5). Finally, white blood cells were classified into two categories related to the type of Myeloma, this step is based on features extraction and then applying a classifier.

5.6. Classification of the extracellular matrix

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

This work is made in collaboration with Ellen Van Obberghen eand Georgios Efthymiou (iBV).

Cells of multicellular organisms interact continually with their local environment which is largely determined by the extracellular matrix (ECM). The biochemical, topological and physical properties (stiffness, elasticity) of the ECM regulate many physiological processes (embryonic development and tissue repair) and their dysregulation plays a key role in the evolution of inflammatory, fibrotic and tumoral diseases. Fibronectin (FN) is a major component of the ECM. The biologists at iBV have identified certain molecular mechanisms involved in the assembly of FN into fibrillar arrays (FN fibrillogenesis) on the cell surface. The resulting fibrillar networks display variable densities and organizations that convey specific biological signals to the cells that encounter them (see figure 6).

We have developed a classification scheme that consists in clustering features extracted from the images to define a texture dictionary. The extracellular matrix are then classified with respect to their signature on this dictionary. We have compared two sets of features that are SIFT histograms and the curvelet coefficients. The

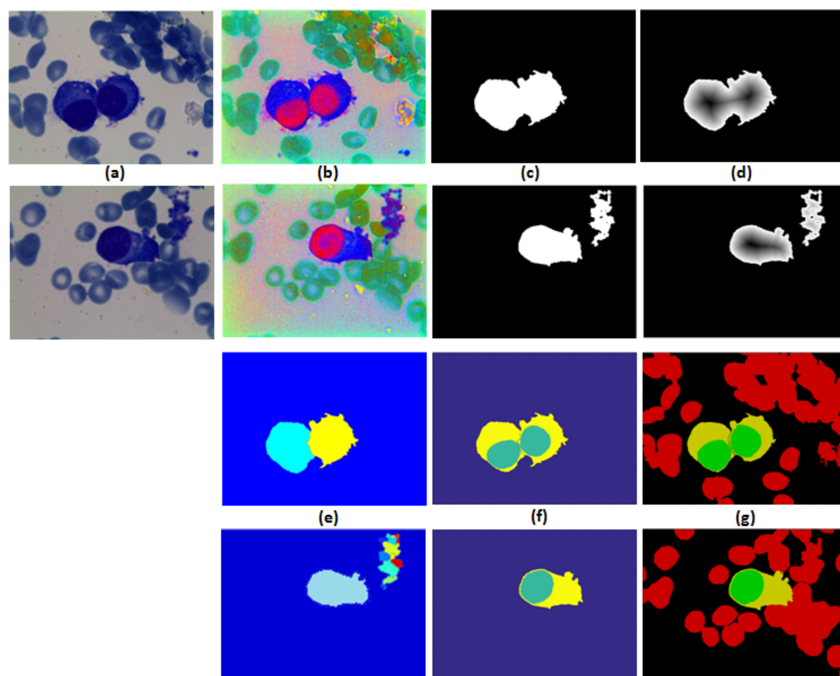

Figure 5. Image segmentation step: (a) Input image, (b) RGB Decorrelation stretch, (c) Binary mask, (d) Distance transform, (e) Watershed, (f) Segmented cell, (g) Ground truth.

SIFT approach appears to be more discriminant for classification purposes but the curvelet approach is better suited for modeling the texture. Next step will consists in modeling the extracellular matrix.

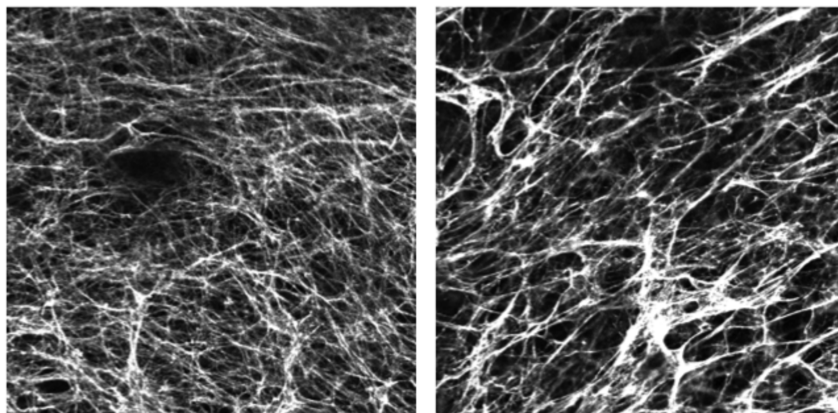

Figure 6. Two examples of extracellular matrices.

5.7. CNuclei/cytoplasm detection and classification in genome-wide RNAi screens

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

This work is made in collaboration with Fabienne De Graeve (iBV).

The work described hereafter is part of the RNAGRIMP ANR project which started in January 2016 and lasts 48 months (see Section 7.2.1). A pilot genome-wide RNAi (Ribonucleic Acid interference) screen on Drosophila cultured cells has been performed with different mutant conditions. The purpose is to study the density and repartition of cytoplasmic RNP (RiboNucleoprotein Particles) granules containing the IMP protein (IGF-II mRNA-binding protein where IGF stands for Insulin-like Growth Factor).

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). A first task that must be accomplished is to detect the nuclei on the DAPI images, and to learn a classification procedure into *living cell* or *dead cell* based on morphologic and radiometric nuclei properties. A CellProfiler [2] pipeline has been developed to automatically detect the nuclei and compute some properties on them. The detection was based on the following main steps: intensity re-scaling, Kapur-based thresholding, and small object discarding. For each detected nucleus, the computed properties were (non-exhaustive list) average intensity, area, granularity, circularity ...

Then, a learning set has been built where a significant number of nuclei were manually assigned their correct (*living* or *dead*) class by a biologist of the team. This learning set was fed to CellProfiler Analyst [3] in order to learn a decision tree for automatic nuclei (hence, cell) classification (see Fig 7, left).

Once the living cell nuclei have been identified on the DAPI images, the next step is to segment (*i.e.*, extract automatically the region of) their cytoplasm 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 are developing an active contour-based segmentation method relying on local image contrast. The current version still has to be robustified in order to be applicable batchwise (see Fig 7, right).

[2] http://cellprofiler.org
[3] http://cellprofiler.org/cp-analyst

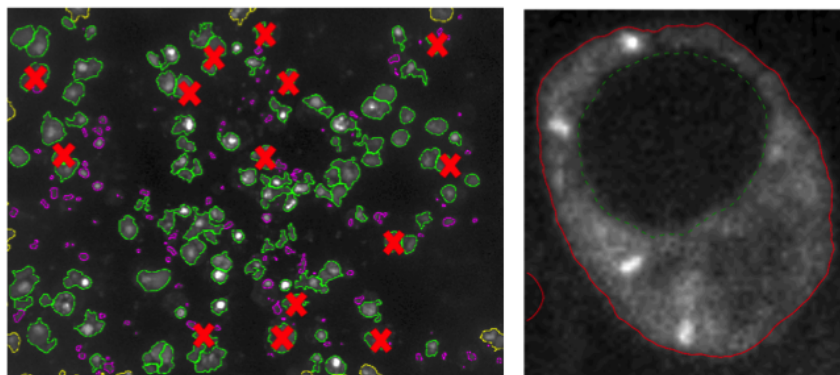

Figure 7. Left: automatic classification of the detected nuclei into living (encircled in green) or dead (with a red cross); objects encircled in yellow are cropped by the field of view, and objects encircled in purple are too small ; they are all discarded. Right: active contour segmentation of the cytoplasm of a cell (previously classified as a living cell); red contour: cytoplasm external boundary; green, dashed contour: nucleus boundary (also cytoplasm internal boundary).

5.8. Small Particle Detection

Participants: Nicolas Cedilnik, Xavier Descombes, Eric Debreuve, Florence Besse.

This work is made in collaboration with Fabienne De Graeve (iBV).

One task of the RNAGRIMP project is to detect RNA granules from fluorescent images. These granules have their size close to the image resolution, they typically represent very few pixels. At this scale, shape parametric models are only crude approximations of the object geometry and not adapted for a detection task. To overcome this difficulty we have defined a shape dictionary consisting of all the shapes included in a five by five tile and satisfying some properties of regularity and convexity. Then we are mimicking the marked point process framework by defining an energy function on the finite sets of shapes as the sum of a data term, applied on each object, and a non overlapping constraint between neighboring objects. The solution minimizing the energy is approximated by a greedy algorithm. We have compared different data terms and shown better performances than the traditional threshold approaches and the wavelet based approach as provided by the software Icy.

5.9. Inter-individual spatio-temporal registration strategies applied to 3D microscopy image sequences of Arabidopsis floral meristems

Participants: Gaël Michelin, Grégoire Malandain.

This work is made in collaboration with Yassin Refahi (Sainsbury Lab., University of Cambridge), Jan Traas (ENS Lyon) and Christophe Godin (Inria Virtual Plants team, Montpellier).

In developmental biology, the study of model organisms such as the plant *Arabidopsis thaliana* aims at understanding genetic mechanisms responsible of morphogenesis. Today, fluorescent confocal microscopy is a means for *in vivo* imaging of organs of interest such as Arabidopsis floral meristems at cell level with a high spatio-temporal resolution. To handle such 3D+t image sequences, adapted computer-assisted methods are highly desirable. Moreover, the inter-individual development variability quantification requires the ability to register spatio-temporal image sequences from a population of individuals.

In the related work, we propose a dedicated tool for the inter-individual spatio-temporal sequence-to-sequence registration applied to developing Arabidopsis flower meristems. We also discuss the different strategies that may be adopted by the user for the method application in order to assist the choice of parameters for the registration method such as:

- the image primitives to be registered;
- the initialization of the image-to-sequence registration optimization process;
- the initialization "propagation" strategy for sequence-to-sequence registration;
- the parameters selection for the optimization step.

Figure 8 shows the result of the temporal registration between three interpolated image sequences of developing Arabidopsis floral meristems. Figure 9 shows an example of spatial registration between two images from different floral meristems at the same developing stage.

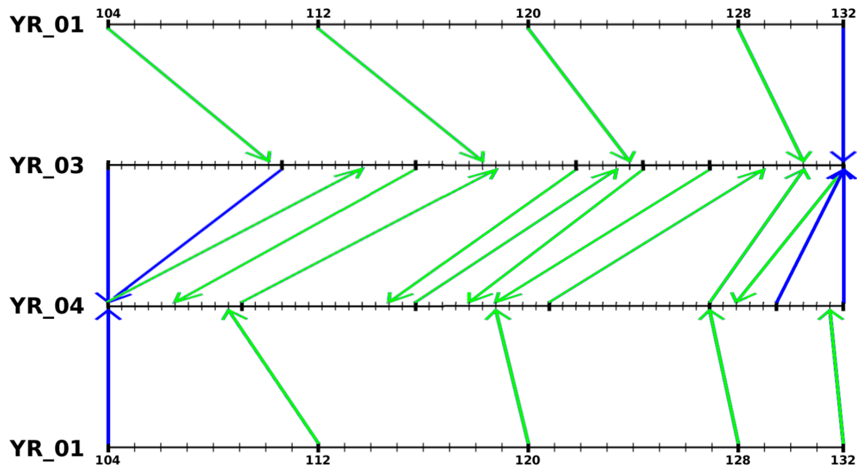

Figure 8. Inter-individual temporal registration result between three floral meristem 3D+t interpolated image sequences. Blue arrows correspond to border registrations.

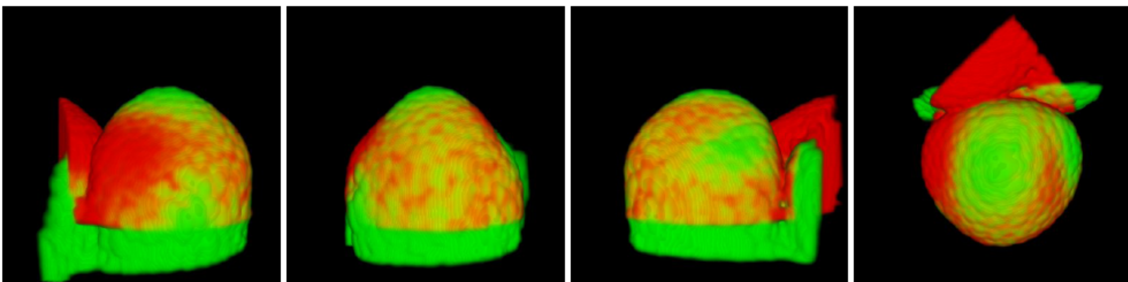

Figure 9. 3D views of the spatial registration of images from two flower meristems (in red and green) at the same developing stage.

5.10. Coherent temporal extrapolation of labeled images

Participants: Gaël Michelin, Grégoire Malandain.

In developmental imaging, 3D+t series of microscopic images allows to follow the organism development at the cell level and has become the standard way of imaging the development of living organs. Dedicated tools for cell segmentation in 3D images as well as cell lineage calculation from 3D+t sequences have been proposed to analyze these data. For some applications (such as section 5.9), it may be desirable to interpolate images at intermediary time-points. However, the known methods do not allow to locally handle the topological changes (ie cell. division).

In the present work, we propose an extrapolation method that coherently deformed the images to be interpolated so that to guarantee a topological continuity of borders (see figure 10).

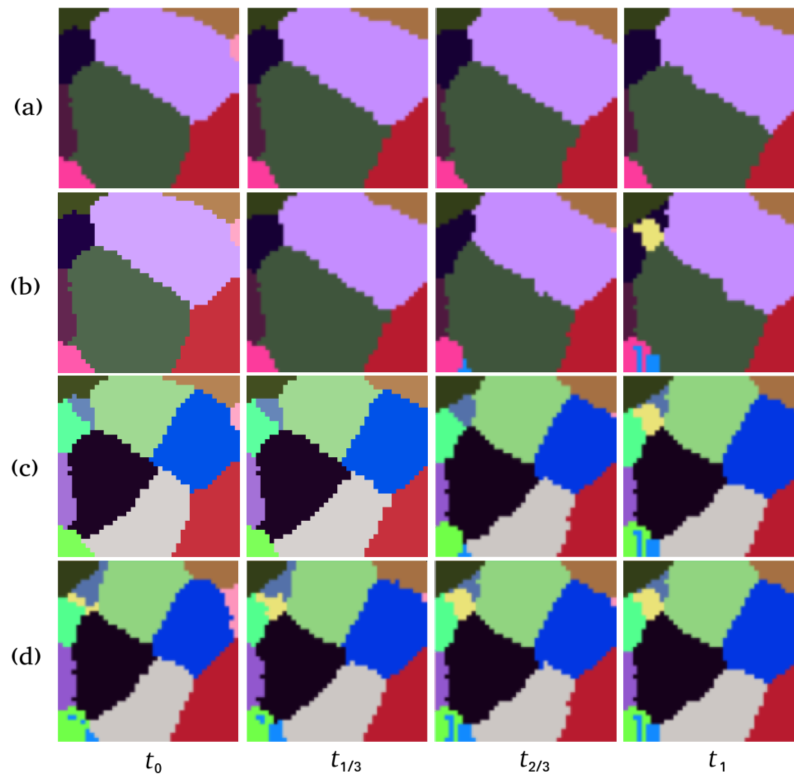

Figure 10. Images compounded of labeled regions at increasing time. (a) and (d) are the original sequences. One can see that the region borders of the corresponding groups of regions of these sequences do not superimpose perfectly. (b) and (c) are the images of transformed regions respectively from the sequences (a) and (d) so that the corresponding region borders superimpose perfectly with the constraint that the image of (a) at t_0 and the image of (d) at t_1 are not modified.

5.11. 3D/2D Coronary Arteries dynamic registration

Participants: Emmanuelle Poulain, Grégoire Malandain.

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

Integrating vessel information, extracted from pre-operative 3D CT angiography images, into a live fluoroscopic 2D sequence can greatly improve the guidance of percutaneous coronary interventions. We are developing a framework aiming at deformed a vessel 3D from the CT so that it moves along the cardiac cycle observed through the 2D angiographic sequence.

The vessel is approximated by a spline which will be deformed thanks to a gradient descent with a length constraint. The length preservation of the vessel allows us to provide a realistic movement, i.e any point will keep its curvilinear abscissa along the spline. This is exemplified by figure 11 where the vessel projection and a remarkable point is tracked at 3 different cardiac phases.

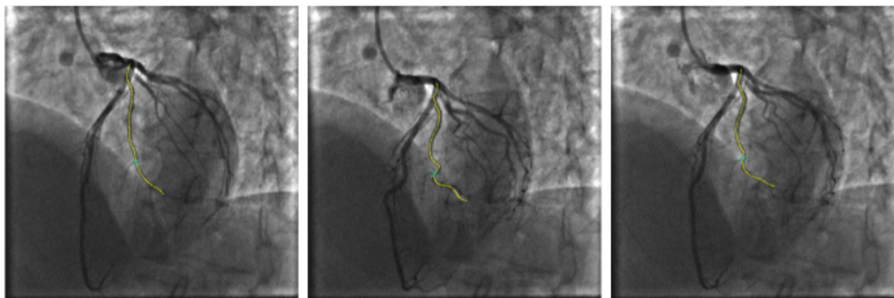

Figure 11. The 3 images show the projection of a 3D vessel in yellow and a remarkable point on the vessel (bifurcation) in blue at 3 different phases of the cardiac cycle.

5.12. Modelling axon growth from in vivo data

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

During the first part of this work, we focused at identifying the main morphological features that allow to describe and discriminate genetically different Drosophila Gamma neurons, as well as to automatically assess a quantification of the overall morphological distance between them [8]. The second part, developed this year, approaches the process of neuron growth and morphogenesis in pupal stage. Important advances have already been achieved in identifying the main factors involved in neuron development. The next step that has to be done is concerning how we approach the question.

In this work we intend to close the gap between classic in vitro experimental assumptions and real in vivo situations, where the final neuronal morphology is acquired through a dynamic and environmental-dependent process. In particular, the branch formation process - how or why branches are created - has been belittled or over-simplified by neuron development models. In our opinion, this represents a constraint in the general understanding of neuron development, hierarchy of the neuronal tree and adult functionality.

Our goal is to bring light to the mechanisms of branch formation during development in realistic conditions. We study the particular case of Drosophila Gamma neuron remodeling and analyze, for the first time to our knowledge, the mechanical situation of a whole population of Gamma neurons (650 individuals) growing together in a constraint space (i.e. medial lobe of the Mushroom Body). We hypothesize that one kind of branches are born when the growing tip encounters a mechanical obstacle (i.e. other neurons or the lobe limits), enhancing the probability that at least one neurite reaches the end of the lobe. We model the neurites growth by a Gaussian Markov chain, and the parameters of the model –which account for axon elasticity and guiding cues attractiveness- are estimated from data.

Our database is composed by different sets –wild type and mutations- of confocal images of a single neuron that we treated, segmented and normalized. We show that the proposed mechanistic branch generation process is plausible, and explore unsolved problems concerning the understanding of some particular Gamma neuron mutation phenotypes. This approach allows us also to analyze dynamic aspects of the Gamma neuron collective growth process such as speed and density in function of space and time, which help to explain several characteristics of the Gamma neuron morphology and behavior during development. Figure 12 shows examples of wild type as well as imp mutant neurons of our database and contrasts them with neurons from simulations that are morphologically close.

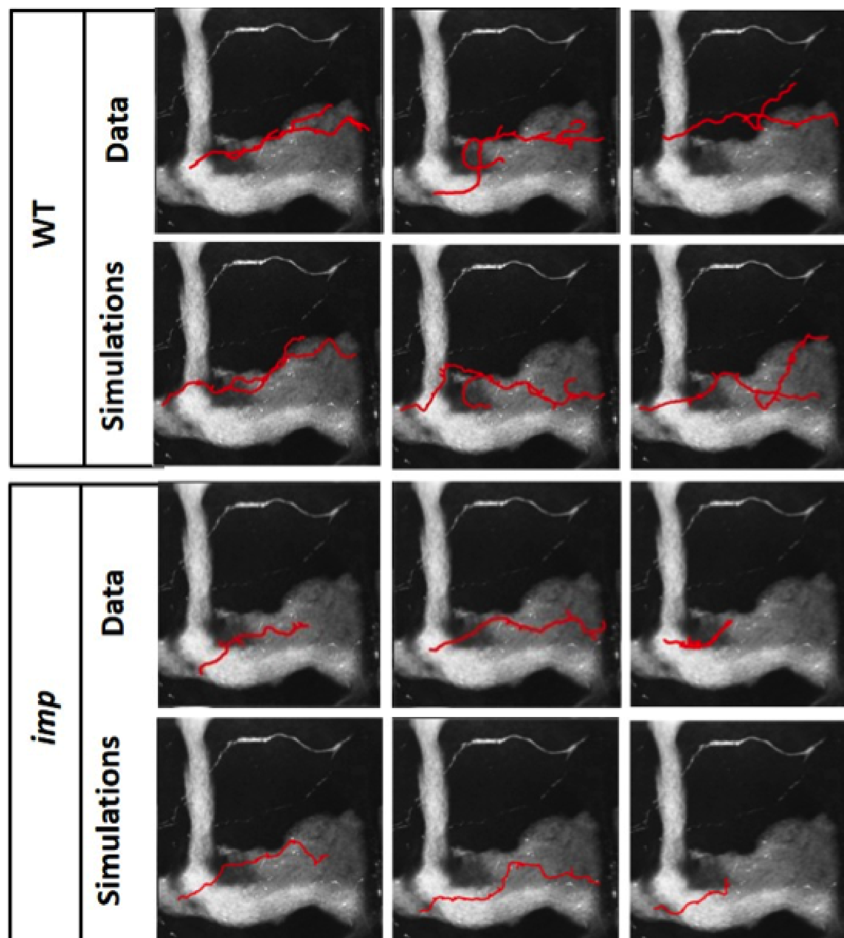

Figure 12. Wild type and imp mutant neurons from the database, contrasted to very similar neurons from our simulations.

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. In December, we signed a collaboration contract with Bayer, Lyon, to fund a Master 2 internship with some overhead on the topic of automatic cell classification. The intern will start working on the subject in January 2017.

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.

7.2. National Initiatives

7.2.1. ANR RNAGRIMP

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

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.

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. European Initiatives

7.3.1. Collaborations in European Programs, Except FP7 & H2020

- COST Action (The COST Program is supported by the EU Framework Program H2020). We are part of a consortium of teams which submitted in December a COST Action proposal on machine learning and intelligent systems for the marine and aquatic sciences.

7.4. International Research Visitors

7.4.1. Visits of International Scientists

7.4.1.1. Internships

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

Hibetallah Ouazaa, PhD, National Engineering School of Tunis, from May 2016 until Jun 2016

8. Dissemination

8.1. Promoting Scientific Activities

8.1.1. Scientific Events Organisation

8.1.1.1. Member of the Organizing Committees

Florence Besse was a co-organizer of the SIgnalife Maths-Bio workshop (Sophia, Nov 2016)

8.1.2. Scientific Events Selection

8.1.2.1. Member of the Conference Program Committees

Laure Blanc-Féraud was associate editor of the workshops: New Computational Methods in Inverse Problems - NCMIP 2016 (NCMIP) in ENS Cachan, and Optimization Techniques for Inverse Problems III, Modena Italy 1-21 September 2016

Eric Debreuve: Advanced Concepts for Intelligent Vision Systems (ACIVS) and Reconnaissance des Formes et l'Intelligence Artificielle (RFIA)

Grégoire Malandain was in charge of a special session "Approches RF et vision en imagerie biologique et médicale" at RFIA.

8.1.2.2. Reviewer

Laure Blanc-Féraud was a reviewer for the conference ICIP.

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

Xavier Descombes was reviewer for the conferences ISBI, ICASSP and ICIP.

Grégoire Malandain was reviewer for the conferences EMBC, ISBI, ICPR, MICCAI, and the Second Workshop on BioImage Computing at ECCV 2016.

8.1.3. Journal

8.1.3.1. Member of the Editorial Boards

Laure Blanc-Féraud is Associate Editor of SIAM Journal Imaging Sciences and Traitement du Signal Journal.

Xavier Descombes is associated editor of DSP (Digital Signal Processing).

8.1.3.2. Reviewer - Reviewing Activities

Laure Blanc-Féraud was reviewer for the Journal Signal Processing.

Eric Debreuve was reviewer for the journals IEEE Transactions on Medical Imaging, Signal Processing: Image Communication (Elsevier), and Digital Signal Processing (Elsevier).

Xavier Descombes was reviewer for the journals IEEE on IP, Pattern Recognition and DSP.

Grégoire Malandain was reviewer for the journals CVIU NeuroImage and MedIA.

8.1.4. Invited Talks

Laure Blanc-Féraud was invited to give a talk at the workshops: NCMIP'16 in Cachan in May, ATLAS Workshop organized by the GdR MaDICS in Grenoble in May, and Optimization Techniques for Inverses Problems III in Modena Italy in September.

Xavier Descombes was invited to give a talk at the workshop “Mathématiques et Biologie” organized within the labex Signalife programm.

8.1.5. Leadership within the Scientific Community

Florence Besse is a member of the scientific council (CAC) of the University Cote d'Azur (UCA), 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 director of GdR 720 ISIS of CNRS, a group for the animation of research at national french level on the thematics Signal Image and Vision. This group includes around 160 academic laboratories and twenty industrial partners totaling almost 3,000 members. She heads the scientific committee of academy 1 of UCA (COMUE université Côte d'Azur) and 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.

8.1.6. Scientific Expertise

Laure Blanc-Féraud is part of the scientific committee of the Institut des Technologies Avancées en sciences du Vivant" (ITAV, USR CNRS 3505). She headed the HCERES expert committee (18 members) of LabSTICC Lab in Brest and headed the recruitment panel "Comité de sélection" of a MCF at University Paris Descartes in section 26. Sha was member of the scientific committee of the "rencontres du numériques" of ANR. She is expert member of the MIUR: Italian Ministry for Education, University and Research (Italy) and expert for the Fund for Scientific Research - FNRS (Belgium). She was expert for an application at a director of research position in ONERA DTIM.

Xavier Descombes is an expert for the DRRT within the CIR (”Crédit Impot Recherche”) and JEI (”Jeunes Entreprise Innovantes”) programs.

8.1.7. Research Administration

Laure Blanc-Féraud was member of the steering committee of the "défi 7" of the ANR. She was member of the CNRS admission for chargé de recherche at INS2I of CNRS. She is member of the academic council of UCA (COMUE université Côte d'Azur).

Xavier Descombes is member of the "comité des projets" and the "comité de centre" of Inria CRI-SAM.

Grégoire Malandain is the head of the committee "Comité de suivi doctoral” of the Inria CRI-SAM.

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

Master: Florence Besse, Genetic control of neuronal branching, 2h, Université Côte d'Azur, France.

Master: Florence Besse, Dissection of neuronal circuits, 4h, Université Côte d'Azur, France.

Master: Florence Besse, Post-transcriptional regulation of neuronal development and maturation, 2h, Nancy, France.

Master : Laure Blanc-Féraud, Fluorescence image restoration, 18h Eq. TD, M2 Computational Biology , University Nice Sophia Antipolis, France.

Master : Laure Blanc-Féraud, Traitement numérique des images, 12h Eq. TD, M2 VIM , EPU University Nice Sophia Antipolis, France.

Master/Engineer: Eric Debreuve, Data Mining, 27.5h équivalent TD, M2/Engineer 5th year, Université Côte d'Azur, France

Master: Eric Debreuve, Introduction to Inverse Problems in Image Processing, 28.5h équivalent TD, International M2, 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: Gaël Michelin, Traitement Numérique des Images, 8h Eq. TD, Niveau M2, EPU, Université Côte d'Azur, France.

IUT : A. Razetti, initiation à la mesure du signal, 30h Eq. TD, IUT Nice Côte d'Azur, Université Côte d'Azur, France.

Licence : Emmanuel Soubies, Images et Filtres, 54h Eq.TD, Niveau L3 , EPU, Université Côte d'Azur, France.

8.2.2. Supervision

PhD: Emmanuel Soubies, Sur quelques problèmes de reconstruction en imagerie MA-TIRF et en optimisation parcimonieuse par relaxations continue exacte de critères pénalisés en norme ℓ_0, Université Côte d'Azur, 14 october 2016.

PhD: Gaël Michelin, Outils d'analyse d'images et recalage d'individus pour l'étude de la morphogénèse animale et végétale, 28 october 2016.

PhD in progress: Lola Baustista, DIC microscopy image reconstruction, 1st november 2013, Laure Blanc-Féraud.

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

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

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

Nicolas Cedilnik: M1 BIM, UNS, Small particle detection. Supervisors: X. Descombes.

Simon Gazagnes: M2 INSA Lyon. Sparse 3D reconstruction for TIRF-PALM Imaging. Supervisors: L. Blanc-Féraud, E. Soubies.

Djampa Kozlowski: M2 BIM, UNS, Nuclei detection and classification in genome-wide RNAi screens. Supervisors: X. Descombes, F. Besse, F. de Graeve (iBV).

Raphaël Meunier: M1 INSA Toulouse. Classification of the extracellular matrix. Supervisors: X. Descombes, L. Blanc-Féraud.

8.2.4. Juries

Laure Blanc-Féraud participated to the PhD thesis committee of Sébastien Combrexelles (IRIT Toulouse), as reviewer of the HDR of Gabriele Facciolo (ENS Cachan) and reviewer of the 2 PhD thesis: Fred NGole MBoula (CEA Saclay), Meriem Ben Abdallah (CRAN Nancy).

Xavier Descombes participated to the PhD thesis committee of A. Sarr (Univ. de Bretagne)

Grégoire Malandain participated as chair to the PhD thesis committee of D. Chen (Paris Dauphine univ.), G. Michelin (Côte d'Azur univ.) as reviewer to the PhD thesis committee of O. Merveille (Paris Est univ.), A. Sironi (EPFL), and as committee head to the PhD thesis committee of P. Samarakoon (Grenoble Alpes univ.).

8.3. Popularization

Xavier Descombes was invited to give a talk at "La fête de la science" in Juan Les Pins.

The Morpheme team has animated a stand during the "fête de la science" in Juan Les Pins.

9. Bibliography

Publications of the year

Articles in International Peer-Reviewed Journals

[1] X. DESCOMBES. *Multiple objects detection in biological images using a marked point process framework*, in "Methods", 2016 [*DOI :* 10.1016/J.YMETH.2016.09.009], https://hal.inria.fr/hal-01383165

[2] A. HALIMI, P. HONEINE, M. KHAROUF, C. RICHARD, J.-Y. TOURNERET. *Estimating the Intrinsic Dimension of Hyperspectral Images Using a Noise-Whitened Eigengap Approach*, in "IEEE Transactions on Geoscience and Remote Sensing", July 2016, vol. vol. 54, n^{o} n° 7, pp. 3811-3821 [*DOI :* 10.1109/TGRS.2016.2528298], https://hal.archives-ouvertes.fr/hal-01325467

[3] E. SOUBIES, L. BLANC-FÉRAUD, G. AUBERT. *ERRATUM: A Continuous Exact l0 penalty (CEL0) for least squares regularized problem*, in "SIAM J. on Imaging Science (SIIMS)", March 2016, vol. 9, n° 1, pp. 490–494. [*DOI :* 10.1137/15M1038384], https://hal.inria.fr/hal-01267679

Invited Conferences

[4] L. BLANC-FÉRAUD, E. SOUBIES, G. AUBERT. *Some results on sparse L2-L0 reconstruction: Continuous Exact L0 penalties*, in "NCMIP 2016 - New Computational Methods for Inverse Problem", Cachan, France, ENS Cachan, April 2016, https://hal.inria.fr/hal-01349670

[5] L. BLANC-FÉRAUD, E. SOUBIES, G. AUBERT. *Some results on sparse L2-L0 reconstruction: Continuous Exact L0 penalties*, in "Workshop ATLAS on mathematical and algorithmimcal approaches for high dimensional problems in data sciences", Grenoble, France, GdR MaDICS, May 2016, https://hal.archives-ouvertes.fr/hal-01358112

International Conferences with Proceedings

[6] L. BAUTISTA, S. REBEGOLDI, L. BLANC-FÉRAUD, M. PRATO, L. ZANNI, A. PLATA. *Phase Estimation in Differential-Interference-Contrast (DIC) Microscopy*, in "IEEE International Symposium on Biomedical Imaging (ISBI)", Prague, Czech Republic, April 2016, pp. 136-139, https://hal.inria.fr/hal-01255004

[7] G. MICHELIN, Y. REFAHI, R. WIGHTMAN, H. JÖNSSON, J. J. TRAAS, C. GODIN, G. MALANDAIN. *Spatio-temporal registration of 3D microscopy image sequences of Arabidopsis floral meristems*, in "ISBI - International Symposium on Biomedical Imaging", Prague, Czech Republic, April 2016 [*DOI :* 10.1109/ISBI.2015.7163872], https://hal.inria.fr/hal-01251151

[8] A. RAZETTI, X. DESCOMBES, C. MEDIONI, F. BESSE. *Statistical Characterization, Modelling and Classification of Morphological Changes in imp Mutant Drosophila Gamma Neurons*, in "BIOSTEC 2016 - The 9h International Joint Conference on Biomedical Engineering Systems and Technologies", Rome, Italy, February 2016, https://hal.inria.fr/hal-01290499

[9] E. SOUBIES, S. SCHAUB, A. RADWANSKA, E. VAN OBBERGHEN-SCHILLING, L. BLANC-FÉRAUD, G. AUBERT. *A Framework for Multi-angle Tirf Microscope Calibration*, in "ISBI - International Symposium on Biomedical Imaging", Prague, Czech Republic, IEEE, April 2016, 4 p. [*DOI :* 10.1109/ISBI.2016.7493355], https://hal.inria.fr/hal-01257736

[10] A. ZUBIOLO, E. DEBREUVE, D. AMBROSETTI, P. POGNONEC, X. DESCOMBES. *Is the Vascular Network Discriminant Enough to Classify Renal Cell Carcinoma?*, in "International Workshop on Content-based Multimedia Indexing (CBMI)", Bucarest, Romania, June 2016 [*DOI :* 10.1109/CBMI.2016.7500255], https://hal.archives-ouvertes.fr/hal-01344247

Conferences without Proceedings

[11] S. REBEGOLDI, L. BAUTISTA, L. BLANC-FÉRAUD, M. PRATO, L. ZANNI, A. PLATA. *Accelerated gradient-based methods for phase estimation in differential-interference-contrast microscopy*, in "SIMAI 2016: Società Italiana di Matematica Aplicata e Industriale", Milan, Italy, September 2016, https://hal.inria.fr/hal-01426330

[12] S. REBEGOLDI, L. BAUTISTA, M. PRATO, L. ZANNI, L. BLANC-FÉRAUD, A. PLATA. *An efficient gradient-based method for differential-interference-contrast microscopy*, in "NUMTA 2016: Numerical Computations: Theory and Algorithms", Calabria, Italy, June 2016, https://hal.inria.fr/hal-01426337

Other Publications

[13] Y. QUÉAU, R. MECCA, J.-D. DUROU, X. DESCOMBES. *Photometric Stereo with Only Two Images: A Theoretical Study and Numerical Resolution*, November 2016, working paper or preprint [*DOI :* 10.1016/J.IMAVIS.2016.11.006], https://hal.archives-ouvertes.fr/hal-01334657

[14] S. REBEGOLDI, L. BAUTISTA, L. BLANC-FÉRAUD, M. PRATO, L. ZANNI, A. PLATA. *Optimization methods for phase estimation in differential-interference-contrast (DIC) microscopy*, September 2016, Workshop on Optimization Techniques for Inverse Problems III, Poster, https://hal.inria.fr/hal-01426317

[15] E. SOUBIES, L. BLANC-FÉRAUD, G. AUBERT. *A unified view of exact continuous penalties for l2-l0 minimization*, February 2016, working paper or preprint, https://hal.inria.fr/hal-01267701