IN PARTNERSHIP WITH:
CNRS

Université Nice - Sophia Antipolis

Activity Report 2013

Project-Team MORPHEME

Morphologie et Images

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

RESEARCH CENTER
Sophia Antipolis - Méditerranée

THEME
Computational Biology

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Project-Team MORPHEME

Keywords: Computational Biology, Image Processing, Classification, Inverse Problem, Modeling

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

1. Members

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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.

2.2. Highlights of the Year

- Laure Blanc Féraud has obtained the "prix Montbonnot Inria" from the Academy of Science.

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 genetical 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 Results

4.1. 3D reconstruction in fluorescence imaging

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

This work was made in collaboration with Gilles Aubert, Laboratoire J.A. Dieudonné (CNRS,UNS).

We propose a new model for the reconstruction of biological structures using Multiple-Angle Total Internal Reflection Fluorescence Microscopy (MA-TIRFM). This recent microscopy technique allows the visualization of sub-cellular structures around the plasma membrane which is of fundamental importance in the comprehension of exchanges mechanisms of the cell. We present a 3D reconstruction method based on a shape prior information on the observed structures and robust to shot noise and background fluorescence. A novelty with respect to the state of the art is to propose a method allowing the recovery of multiple objects aligned along the axial axis.

TIRFM principle is based on the total internal reflection phenomenon of a light beam at the interface between two mediums of refractive indices n_i (incident) and n_t (transmitted) which produces an evanescent wave capable of exciting fluorophores that are near the coverslip surface. Excited fluorophores emit photons that are then collected by a CCD camera to produce a resulting 2D image (radial dimension). The 2D image formation is formulated as follows [29]:

$$S(x,y,\alpha) = I_0(\alpha) \int_0^\infty R(x,y,z) \exp\left(-\frac{z}{d(\alpha,\lambda)}\right) dz \tag{1}$$

where $S(x,y,\alpha)$ is the recorded image for the incident angle α, $R(x,y,z)$ denote the 3D unknown fluorophore density, $I_0(\alpha)$ is the intensity at the interface $d(\alpha,\lambda)$ is the penetration depth (theoretically known) and λ is the incident light wavelength. The problem is then to determine R in (1) from acquisitions S_α with different incident angles.

In order to solve this ill-posed inverse problem, we model the 3D unknown fluorophore density by a collection of parametrized objects defined on a state space $\mathcal{X} = P \times M$ by their location $\rho \in P$ and their marks (i.e geometric attributes $\omega \in M$). The optimization problem can be formulated as a minimization problem where both the number of objects in the model and their parameters have to be estimated. This difficult combinatorial optimization problem is tackled by using a Marked Point Process approach [36] which allows modelling interactions between the objects in order to regularize the inverse problem.

Figure 1 right shows the Root Mean Square Errors (RMSE) of each estimated parameter for different noise levels on simulated data. We obtain a hight accuracy reconstruction with an RMSE less than $10\ nm$ for the radial position (x,y) and the radius. A larger RMSE (between 80 and $125\ nm$, depending on the noise level) is found on the axial position vesicles estimation. As we can see on figure 1 left, the error on the axial position estimation is due to the deepest objects ($> 300\ nm$), objects close to the glass interface are well estimated. Figure 1 right shows also the robustness of the model with respect to shot noise and background fluorescence since the errors remain almost constant with the increasing noise level. The proposed method have also been tested on a real sample of beads of known diameters in order to quantify the quality of the reconstruction. The obtained results are promising for feature estimation of predefined shape structures [17].

4.2. Depth-variant blind restoration for confocal microscopy

Participants: Saima Ben Hadj, Laure Blanc-Féraud.

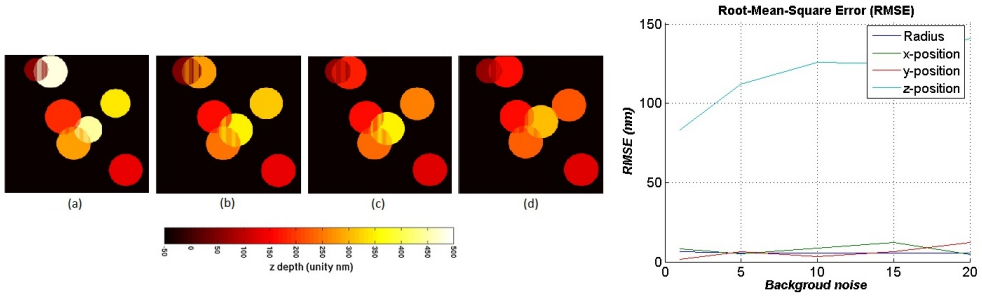


Figure 1. Left : Reconstructions for different noise levels (colors represent z positions of objects). (a) Simulated sample, (b) → (c) → (d) : Reconstruction for an increasing level of noise. Right : RMSE for different noise levels.

3D images of confocal microscopy basically suffer from two types of distortions: a depth-variant (DV) blur due to the variation of the refractive index between the different mediums composing the system and the imaged specimen, and a Poisson noise due to photon counting process at the sensor.

The Point Spread Function (PSF) is depth-variant and its knowledge is crucial for the restoration of these images. Nevertheless, the PSF is inaccessible in practice since it depends on the optical characteristics of the biological specimen and thus needs to be estimated for each different specimen.

In our previous work [5], [4], we developed a method for the joint estimation of the specimen function (the sharp and clean image) and the 3D DV PSF by minimizing a criterion arising from the maximum a posteriori approach. The DV PSF is approximated by a convex combination of a set of space-invariant PSFs taken at different depths.

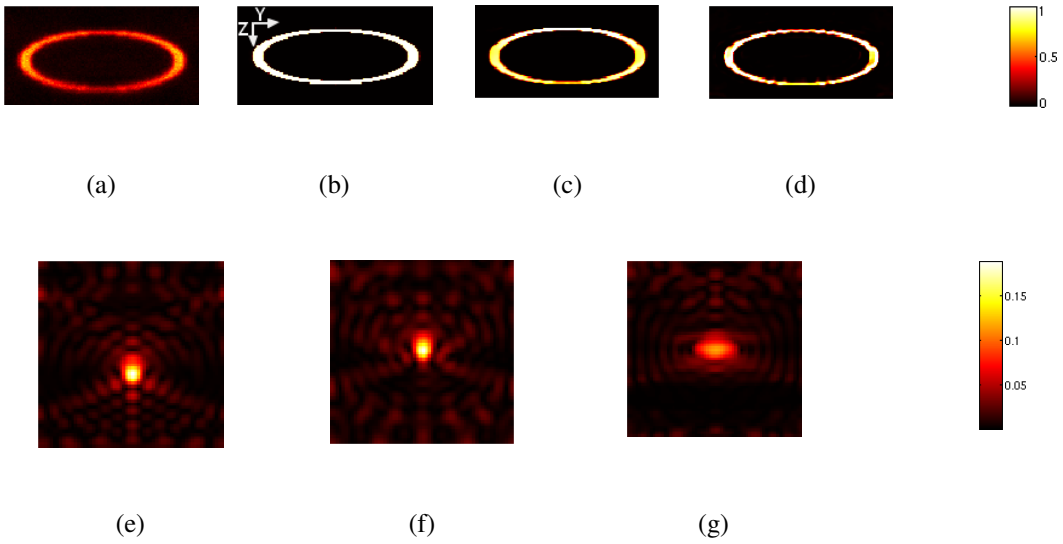
Recently, we proposed to consider additional constraints on the PSF coming from the optical system modeling [21], [6]. In fact, the confocal microscopy PSF is related to the magnitude of a complex function known as *complex valued-amplitude PSF* whose shape and support are given in the Fourier domain by the numerical aperture of the optical system [30], [35]. This latter is known as it is given by the system manufacturer. We incorporate this constraint in the joint PSF and image estimation algorithm [5] by using the Gerchberg-Saxton algorithm (GS) [31] since it allows to alternate constraints in the spatial and frequency domains. Numerical tests on a simulated image of a bead shell are encouraging (cf. figures 2 (a), (b), (c), and (d) presenting z-slices of the original image, simulated and reconstructed images). In particular, the added constraint allows to better estimate the PSF shape compared to the previous method [5] (cf. figures 2 (e), (f), and (g)).

4.3. Head Tracking and Flagellum Tracing for Sperm Motility Analysis

Participants: Huei Fang Yang, Xavier Descombes, Grégoire Malandain, Sylvain Prigent.

This work is supported in part by ANR MOTIMO project.

Sperm quality assessment plays an important role in human fertility and animal breeding. One of the most important attributes for evaluating semen quality is sperm motility, according to the World Health Organization (WHO) report. When performed manually, semen analysis based on sperm motility is labor-intensive and subject to intra- and inter-observer variability. Computer-assisted sperm analysis (CASA) systems, in contrast, provide rapid and objective semen fertility assessment. In addition, they also offer a means of statistical analysis that may not be achieved by visual assessment. Hence, automated sperm motility analysis systems are highly desirable.



(a) (b) (c) (d)

(e) (f) (g)

Figure 2. (Y, Z) slices of the simulated observation (a), true image (b) and PSF (e), estimated image (c) and PSF (f) with the additional PSF constraints, estimated image (d) and PSF (g) without the additional PSF constraints.

We present a computational framework designed to track the heads and trace the tails for quantitative analysis of sperm motility, which is illustrated in Figure 3. Our framework includes 3 modules: head detection, head registration, and flagellum tracing. These modules are performed sequentially to obtain the head trajectories and flagellar beat patterns. First, the head detection module detects the sperm heads in the first image of the image data using a Multiple Birth and Cut (MBC) algorithm. The detections are the inputs to the head registration module for obtaining the head trajectories and angles of head rotation. We use a block matching method to register the heads in the subsequent images with respect to the positions and angles of those detected in the first image. This is different from other tracking methods that consider only the head positions. Finally, we propose a flagellum tracing algorithm, based on a Markov chain Monte Carlo (MCMC) sampling method, to obtain the flagellar beat patterns.

We validate our framework using two microscopy image sequences of ram semen samples that were imaged at two different conditions, at which the sperms behave differently. The results show the effectiveness of our framework [19].

4.4. Tree-like Shapes Distance Using the Elastic Shape Analysis Framework

Participants: Alejandro Mottini, Xavier Descombes, Florence Besse.

The analysis and comparison of tree-like shapes is of great importance since many structures in nature can be described by them. In the field of biomedical imaging, trees have been used to describe structures such as neurons, blood vessels and lung airways. Since it is known that axon morphology provides information on their functioning and allows the characterization of pathological states, it is of paramount importance to develop methods to analyze their shape and to quantify differences in structures

We have developed a new method for comparing tree-like shapes that takes into account both topological and geometrical information [14], [15]. Our metric combines the Elastic Shape Analysis Framework originally designed for comparing shapes of 3D closed curves in Euclidean spaces with a matching process between branches. Moreover, the method is able to compute the mean shape of a population of trees.

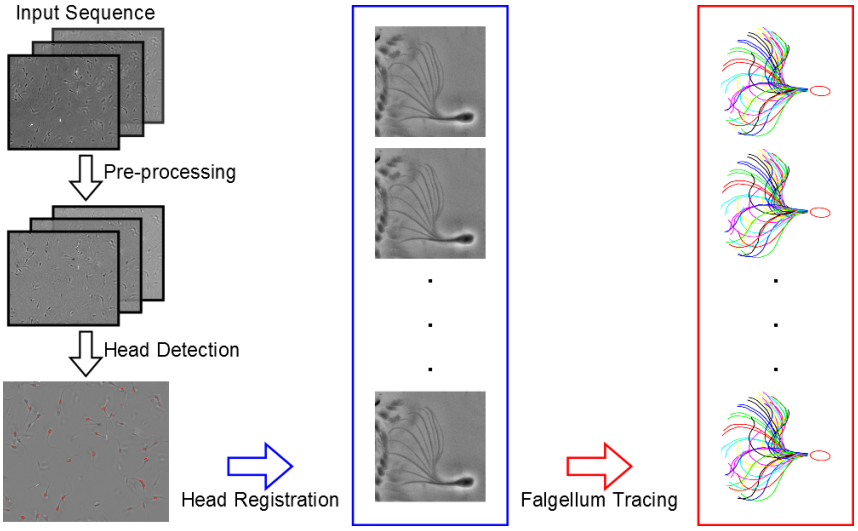


Figure 3. Overview of the proposed framework. The input to our framework is an image sequence. The pre-processing step is to remove the inhomogeneous background and noise. The three main modules in our framework are head detection, head registration, and flagellum tracing. These three modules perform sequentially to obtain the head trajectories and flagellar beat patterns for sperm motility analysis. Note that the output of the head registration module is image sequences for each individual sperms in which the heads are registered. Here, we show the minimum intensity projection (MinIP) of the image sequence.

As a first application, we used our method for the comparison of axon morphology. The performance was tested on a group of 61 (20 normal, 24 type one mutant and 17 type two mutant) 3D images, each containing one axonal tree. We have calculated inter and intra class distances between them and implemented a classification scheme. We have compared our results with the ones obtained by three other methods. Results showed that the proposed method better distinguishes between the two populations than the other methods.

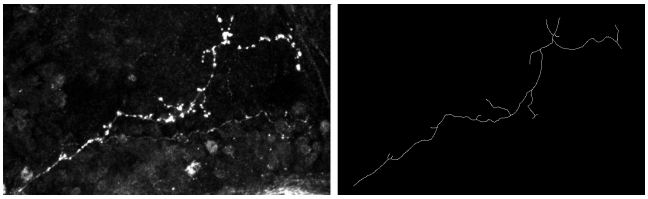


Figure 4. Original confocal microscopy image of an axonal tree (left) and its tracing (right) (maximum intensity projections).

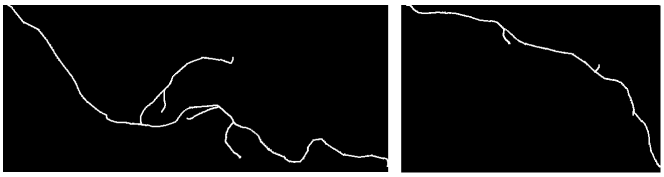


Figure 5. Mean normal (left) and mutant (right) axonal trees (2D projections).

4.5. 3D Modeling of developing organisms

Participants: Gaël Michelin, Grégoire Malandain, Léo Guignard [Virtual Plants], Christophe Godin [Virtual Plants].

This work is made in collaboration with Patrick Lemaire (CRBM).
Image-based studies of developing organs or embryos produce a huge quantity of data. To handle such high-throughput experimental protocols, automated computer-assisted methods are highly desirable. We aim at designing an efficient cell segmentation method from microscopic images. Similary to another work [32], the proposed approach is twofold: first, cell membranes are enhanced or extracted by the means of structure-based filters, and then perceptual grouping (i.e. tensor voting) allows to correct for segmentation gaps (see figure 6). We assessed different structure-based filters as well as different perceptual grouping strategies to identify the most efficient combination, in term of result quality and computational cost [13].

4.6. Spatio-temporal registration of embryo images

Participants: Grégoire Malandain, Léo Guignard [Virtual Plants], Christophe Godin [Virtual Plants].

This work is made in collaboration with Patrick Lemaire (CRBM).

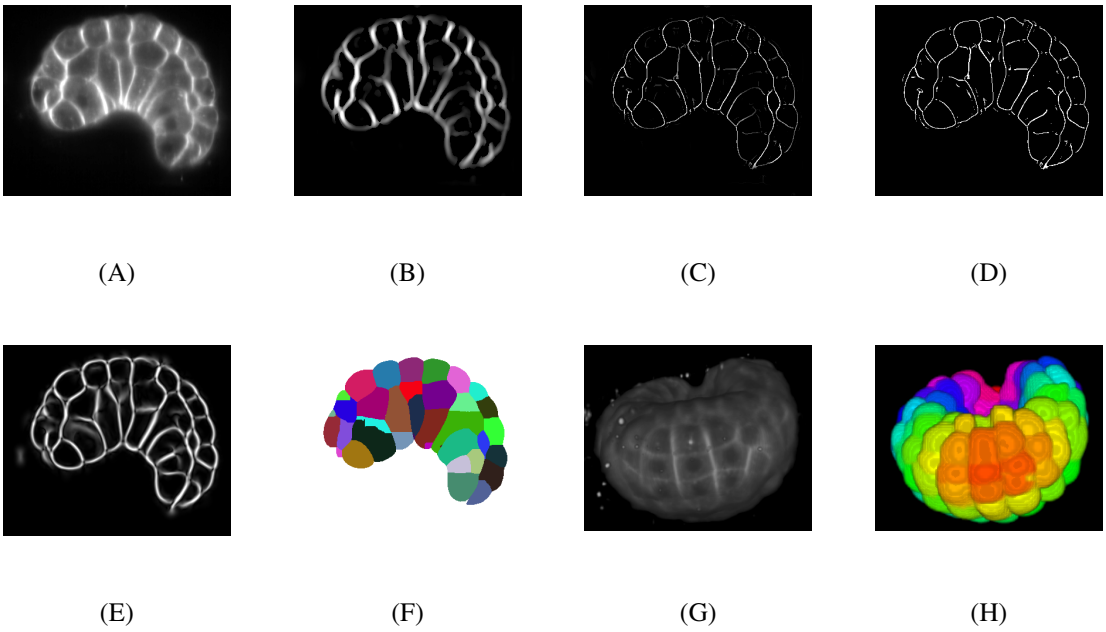


Figure 6. Illustrations of the different steps of the algorithm: (A) a 2D slice of original image, (B) the resulting surface detector response, (C) the directional extrema of the response image, (D) the deduced binarisation of the cell membranes, (E) the result of Tensor Voting applied to binarised image, (F) the cells segmentation computed from (E), (G) a 3D view of original image, (H) a 3D view of the cells segmentation.

Current imaging techniques can capture temporal sequences of 3D images with very high time resolution over several hours. Comparing sequences covering the same time period opens the way to the study of developmental variability. Stitching together sequences captured from different embryos may help producing a sequence covering the whole development of the animal of interest. For this, it is necessary to align two sequences in both time and space.

We developed a method to align two 3D+t time series, based on the detection and pairing of 3D+t landmarks. These landmarks, which correspond to periods of fast morphogenetic change, are deduced from the analysis of the non-linear transformations that allow to co-register pairs of consecutive 3D images in each sequence (see figure 7). [12].

4.7. Characterizing cell membrane properties

Participants: Sylvain Prigent, Xavier Descombes, Grégoire Malandain, Hélène Barelli [IPMC].

Some mammalian cells show striking differences in the acyl chain composition of their membrane phospholipids. In most cases, the majority of phospholipids bear one saturated and one monounsaturated acyl chains at positions 1 and 2 or the glycerol, respectively. However, some cells and notably neurons contain large amounts of phospholipids with a polyunsaturated fatty acyl chain, generally at position 2. The aim of this work is to compare the impact of the phospholipid polyunsaturation vs monounsaturation on the mechanical and functional properties of the plasma membrane.

For this task, we currently investigate how phospholipid insaturation affects the ability of specialized protein machineries involved in transport vesicle formation, by first detecting vesicles in 2D+t sequences of microscopic images of individual cells, and then tracking detected vesicles through the temporal sequences (see figure8) [23].

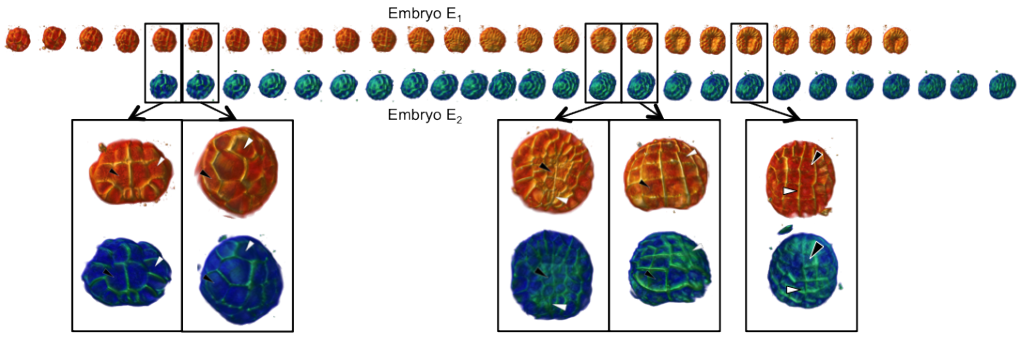


Figure 7. Spatio-temporal registration of two time-series of embryo. Enlarged renderings indicate the registered timepoints. Notice that the temporal registration is not linear since the interval length between two registered time is different from one embryo to the next.

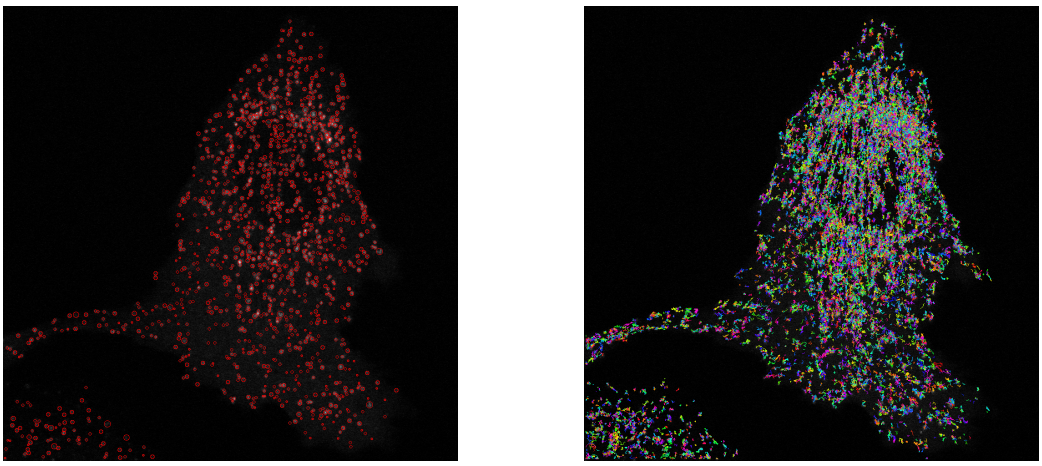


Figure 8. Left: detection of individual vesicles in one image of the sequence. Right: resulting paths of tracked vesicles through the 2D+t sequence.

4.8. Tracking growing axons in 3D+t fluorescent two-photon microscopy images

Participants: Sylvain Prigent, Xavier Descombes [contact], Florence Besse, Caroline Medioni.

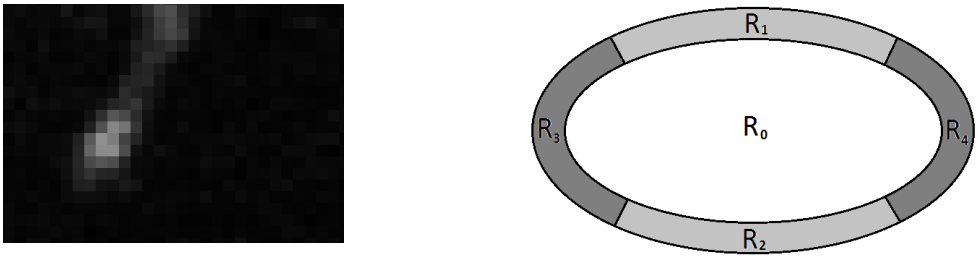
During the maturation of the nervous system, neuronal cells emit cellular extensions (dendrites, axons) allowing them to connect to other neurons, and thus, establish a network in which information is transmitted and/or stored. The formation of axonal extensions and directed migration of these extensions are two key processes controlling the morphology of neuronal cells, and then the number and nature of partners in a given network within a neuron. These two processes are controlled by both external factors to neuronal cell (guidance molecules, neurotrophic signals, ...) and internal factors (transcription factors, post-transcriptional regulators, regulators of the actin cytoskeleton or microtubules, ...). The goal of this work is to automatically extract axonal trajectories from images to then be able to model the processes controlling the morphology of neuronal cells.

The images we use are 3D+t images of growing drosophila brains obtained with a bi-photon confocal microscope. A single movie is about 200 3D frames that correspond to an acquisition every 5 minutes.

The developed method to extract axonal trajectories from 3D+t images is made of 3 main steps. The first step is to detect axonal tips on each 3D frame of the movie. This detection is performed using Marked Point Process. We designed a dedicated model based on an ellipse shape, a prior of no-overlapping between detected ellipses, and a data term calculated by:

$$d = \min(d_B(R_0, R_1), d_B(R_0, R_2), \max(d_B(R_0, R_3), d_B(R_0, R_4)))$$

where d_B denote the Bhattacharyya distance, R_0 the set of pixels inside the ellipse and R_1, R_2, R_3, R_4 four sets of pixels obtained by partitioning the ellipse contour into 4 regions around the ellipse vertex (see figure 9).

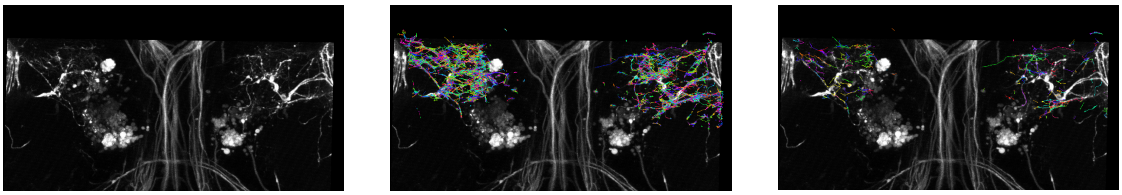


(a) (b)

Figure 9. (a) Zoom on an axon tip. (b) Proposed ellipse model to detect an axon tip.

The second step consists to track the axons along the time frames by linking the tips detections. We designed an association tracking algorithm that builds a graph by connecting spatially close detections in neighboring frames. Negative costs have been introduced to favor long tracks. Then we ran sequentially the shortest path algorithm on this graph to obtain axons trajectories (see figure 10 (b)).

As the axonal tips size is close to the image resolution, the proposed method as the drawback to give false alarms trajectories. We then added a last processing step that aim to analyze the trajectories and remove those that do not correspond to axonal trajectories. This filtering removes three types of trajectories: 1) the trajectories that follow static regions of the image, 2) the short trajectories (less than 5 frames) and 3) random walk trajectories. An example of final automatic tracking is shown in figure 10 (c).



(a) (b) (c)

Figure 10. (a) 2D projection of the last frame. (b) Obtained tracks using the association tracking method. (c) Obtained tracks after false alarms removing.

4.9. A Hierarchical, Graph-cut-based Approach for Extending a Binary Classifier to Multiclass – Illustration with Support Vector Machines

Participants: Alexis Zubiolo, Eric Debreuve, Grégoire Malandain.

The problem of automatic data classification is to build a procedure that maps a datum to a class, or category, among a number of predefined classes. The building of such a procedure is the learning step. Using this procedure to map data to classes is referred to as classification or prediction. The procedure is therefore a classification, or prediction, rule. A datum (text document, sound, image, video, 3-dimensional mesh...) is usually converted to a vector of real values, possibly living in a high-dimensional space, also called signature. Offline, supervised learning relies on a learning set and a learning algorithm. A learning set is a set of signatures that have been tagged with their respective class by an expert. The learning algorithm input is formed by this set together with some parameters, its output being a prediction rule. Some learning algorithm, or method, apply only to the 2-class case. Yet, adapting such a binary classifier to a multiclass context might be preferred to using intrinsically multiclass algorithms, for example if it has strong theoretical grounds and/or nice properties; if free, fast and reliable implementations are available...The most common multiclass extensions of a binary classifier are the one-versus-all (OVA) (or one-versus-rest) and one-versus-one (OVO) approaches. In any extension, several binary classifiers are first learned between pairs of groups of classes. Then, all or some of these classifiers are called when predicting the classes of new samples. When the number of classes increases, the number of classifiers involved in the learning and the prediction steps becomes computationally prohibitive. Hierarchical combinations of classifiers can limit the prediction complexity to a logarithmic law in the number of classes (at best). Combinatorial approaches can be found in the literature. Because of their high learning complexity, these approaches are often disregarded in favor of an approximation trading optimality for computational feasibility. In our work, the high combinatorial complexity is overcome by formulating the hierarchical splitting problems as optimal graph partitionings solved with a minimal cut algorithm. In fact, as this algorithm performs only few additions and comparisons, its impact on the whole procedure is not significant. A modified minimal cut algorithm is also proposed in order to encourage balanced hierarchical decompositions (see Fig. 11). The proposed method is illustrated with the Support Vector Machine (SVM) as the binary classifier. Experimentally, it is shown to perform similarly to well-known multiclass extensions while having a learning complexity only slightly higher than OVO and a prediction complexity ranging from logarithmic to linear. This work has been accepted to the International Conference on Computer Vision Theory and Application (VISAPP 2014) [20].

4.10. Classification of neurons to study Parkinson's disease

Participants: Alexis Zubiolo, Eric Debreuve, Xavier Descombes.

This work has been made in collaboration with Michèle Studer's team at iBV

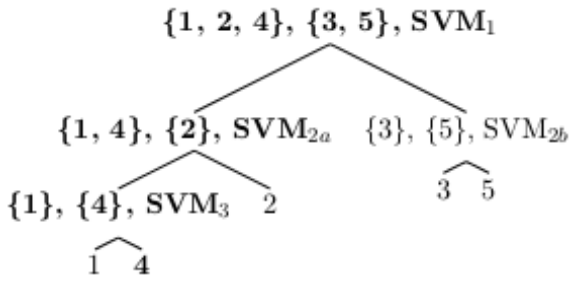
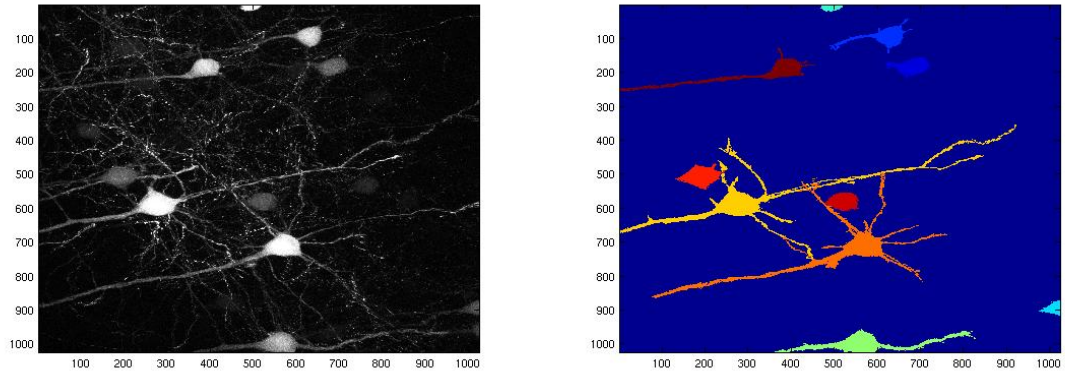


Figure 11. Type of tree that the proposed method builds during the learning stage (illustration with 5 classes). An example of classification of a new image signature is also illustrated by showing the visited nodes in boldface (read from root to leaf).

In this project, the goal is to perform unsupervised classification of rat neurons in order to study the Parkinson's disease. The Institut de Biologie Valrose (iBV) provided us with 3-D images of rat cortices obtained by confocal microscopy. The discriminant features between normal and pathological neurons include the number of dendrites, the length and diameter of the apical dendrite, the shape and size of the soma$\cdots$ For each neuron, these features have to be computed automatically from the images. The specificity of this problem is that, for each rat cortex, we are given several images:

- one low resolution (LR) image which shows an overall view of the cortex and allows to compute the features related to the apical dendrite;
- some high resolution (HR) images (typically between 4 and 6) which provide close-ups of the somas of the neurons and allow to compute the other features.

This work consists in (1) extracting the neurons from the images (see Fig. 12), (2) matching the corresponding neurons in the HR and the LR images, (3) computing the features for each neuron, and (4) classifying the neurons, for example using a kernel Support Vector Machine (SVM).



(a) (b)

Figure 12. Extraction of the neurons from the high-resolution image.

4.11. Curve and graph classification using a specific metric and kernel Support Vector Machines

Participants: Vladimir Gutov, Eric Debreuve, Xavier Descombes.

The analysis and comparison of trees are of great importance since many natural structures can be described using such models. In biology, lung airways, neurons, blood vessels$\cdots$ can be represented by trees (or, more generally, by graphs). Starting from a biological problem (automatically classifying neurons as wild or mutant), we studied the question of using Support Vector Machines (SVM) to classify continuous data such as curves, trees and graphs. Indeed, SVMs are designed for discrete data, looking for an optimal separation hyperplane or manifold in a discrete normed space. Manifolds are found when the original, linear SVM formulation is extended using the so-called kernel trick. The Gaussian kernel is the most popular one. By definition, the isotropic Gaussian kernel involves the two sample data to be compared through the distance between them. This opens the application of Gaussian-kernelized SVMs to any normed space. When dealing with (continuous) curves, the Fréchet distance can be used. We also tested a metric based on shape analysis [34]. Finally, a (meta-)distance between trees proved to be efficient in comparing axons [33] (see Fig. 13). The "meta" qualifier means that this distance builds upon a metric between curves and is valid for any such metric. It was tested using the shape-based metric [34]. We adapted an open-source SVM implementation to be able to use the three aforementioned metrics (two between curves, one between trees) and we validated the classification approach on synthetic data and on a small database of 20 wild-type neurons and 24 mutants provided by biologists.

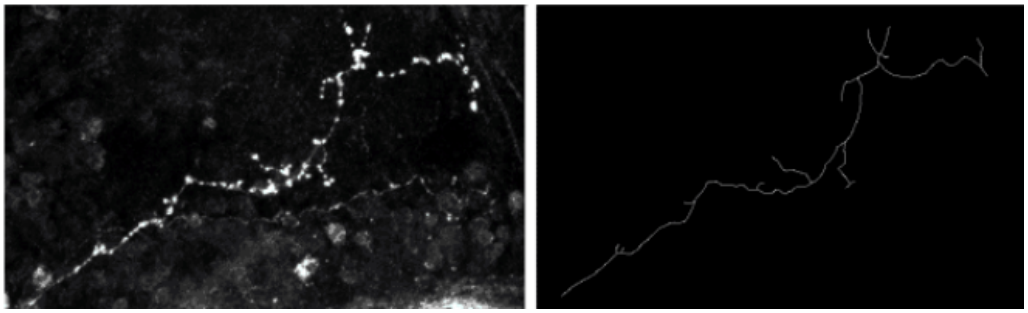


Figure 13. Left: Axonal tree imaged with a confocal microscope (maximum intensity projection of the 3-D acquisition). Right: Manual extraction of the axon.

4.12. Random forests for zooplankton classification

Participant: Eric Debreuve.

This work has been made in collaboration with Florent Baronian (Engineering student), Luc Deneire (I3S) and Marc Picheral (LOV)

An UVP embedded system (Underwater Vision Profiler) is a device mainly composed of a digital camera with a fixed focal distance, and a flash system designed to illuminate only the focal plane. The device is attached to a boat by a cable and it is let going deep to take pictures at various depths. The purpose of such acquisition campaigns is to analyze the population of zooplankton organisms in different oceanic regions (see Fig. 14). The fifth version of the UVP developed at the Laboratoire d'Océanographie de Villefranche (LOV) only stores the pictures. All the processing is done offline: zooplankton organisms are segmented, features are extracted and a classification into types of organisms is performed. With the upcoming sixth version, the goal is to make the device smaller, lighter, and autonomous (for some time) in order to be placed it in appliances designed to

drift or navigate autonomously for weeks or months. This imposes to perform all the image processing tasks aboard, which limits the available processing power. Our work is to propose a classification method taking into account the constraints given by the teams in charge of the hardware design. We implemented a Random forest-based classifier which combines both good performances and low computational requirements. Since the images contain a lot of spurious objects called aggregates, we proposed a two-stage approach: the first stage is either a binary classifier or model checker tailored to eliminate the aggregates, while the second stage actually classifies the zooplankton organisms. We tested a combination of a one-class SVM (model checker) and a Random forest, and a combination of two Random forests, the first one being restricted to a binary classifier. Results were encouraging.

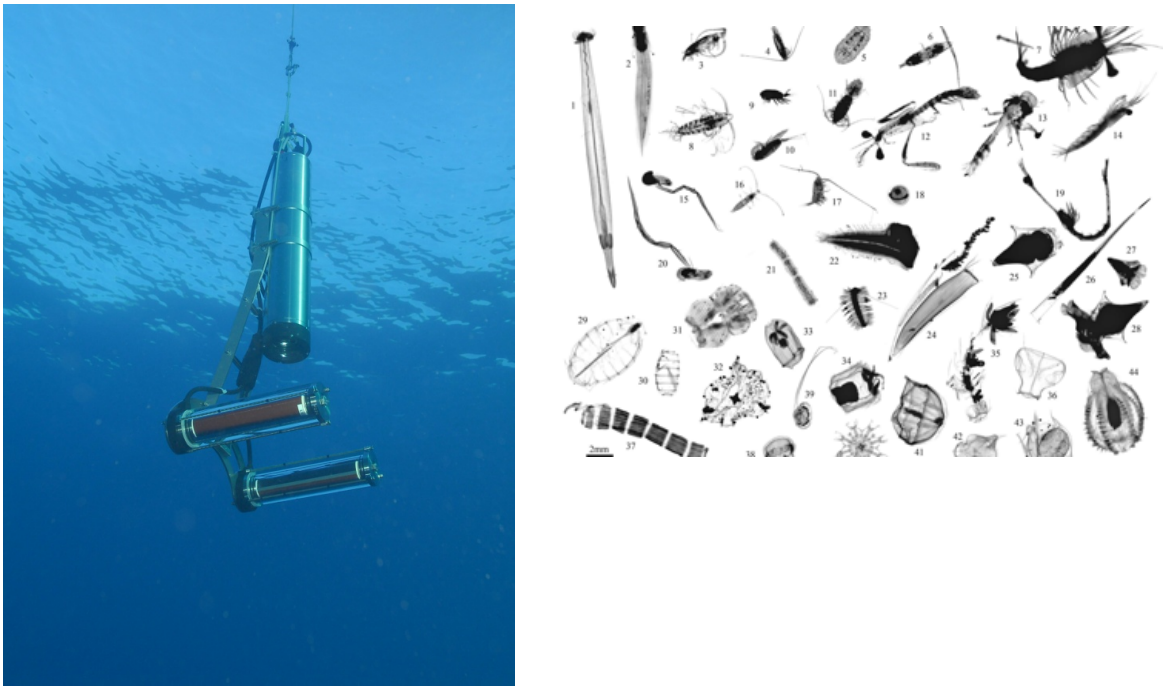


Figure 14. Left: Version 5 of the UVP embedded system (Underwater Vision Profiler) used to take pictures of the zooplankton at different depths. Right: Some organisms composing the zooplankton (Lars Stemmann, LOV). Images acquired by the UVP have a much worse resolution.

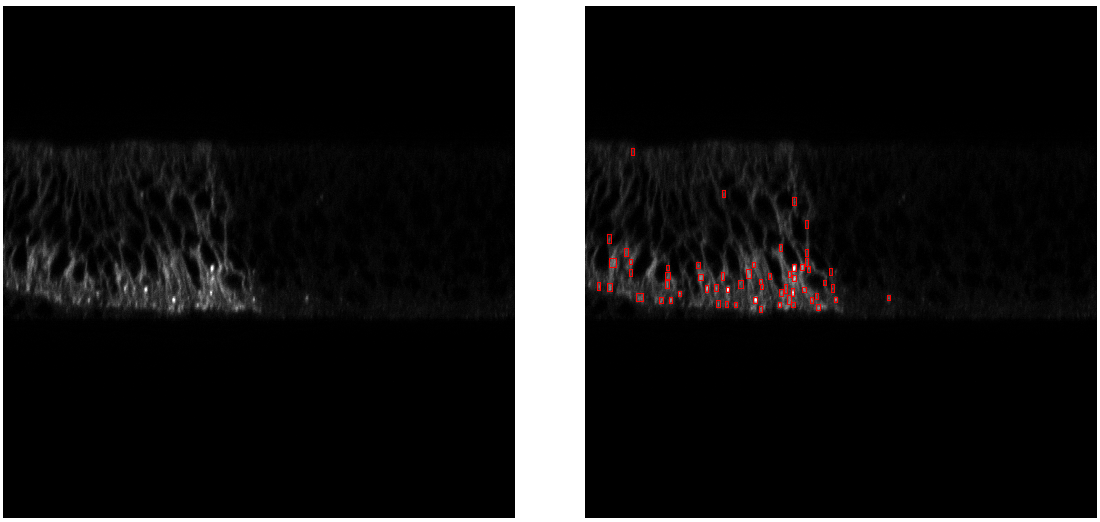
4.13. Detection of Hedgehog protein using confocal imaging

Participants: Sylvain Prigent, Xavier Descombes.

This work was made in collaboration with P. Therond's group at iBV

P. Therond's lab is focusing on the understanding of how the secreted Hedgehog (Hh) morphogen, a dually lipidated highly hydrophobic molecule bound to membranes, is secreted, released and transported from the place of production in Drosophila. High resolution microscopy developed to identify and visualize such processes was successfully applied to address this question, but dynamics of membrane transport is still poorly understood mainly due to the lack of a reliable model or the need of fixation.

To statistically quantify the position of a population of Hedgehog proteins inside a cell, we need an automatic image processing method that detect each individual Hedgehog proteins in a 3D confocal image. The 3D images are obtained either by scanning Z slices (see figure 15), or by scanning XY slices (see figure 16). For both types of images, we used Marked Point Process (MPP) to detect 2D objects independently on each frame since proteins appear only in one slice. Using the Z slices, we observed that proteins appear as vertical rectangles whose size is close to the image resolution. We then design an MPP model to search for a configuration of vertically oriented rectangles that do not overlap one to each other. To define a data term for a given rectangle in the image, we calculate the Bhattacharyya distance between the population of pixels inside the rectangle and the population of pixels in the border of the rectangle. For the XY slices, we defined an MPP model to search for circles that do not overlap one to each other, and the data term is calculated with the Bhattacharyya distance as for the rectangle model. Examples of obtained results are shown in figures 15 and 16.



(a) (b)

Figure 15. Example of proteins detection on a single z image slice (a) Original z slice. (b) Obtained proteins detection.

5. Bilateral Contracts and Grants with Industry

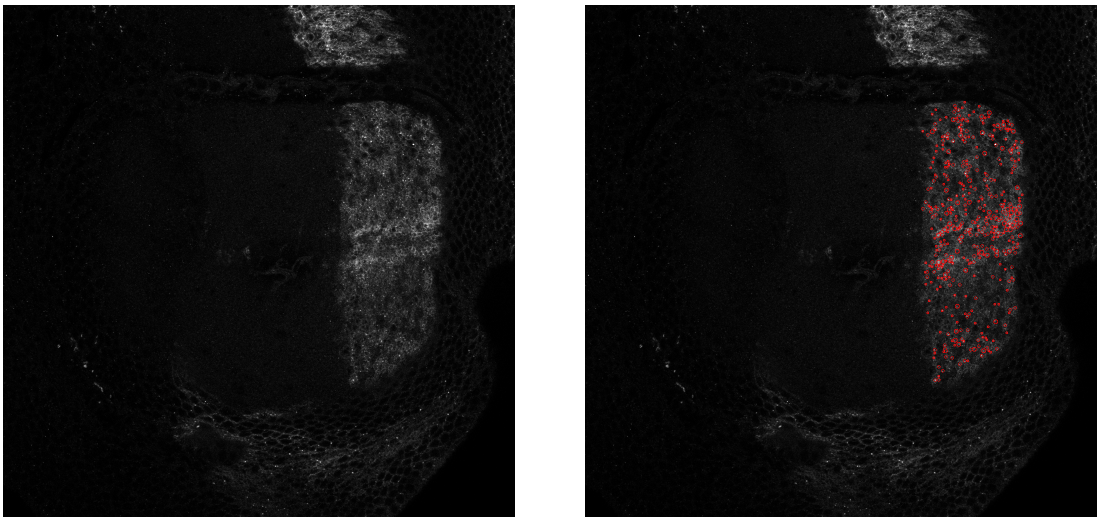
5.1. Bilateral Contracts with Industry

Participants: Grégoire Malandain, Thomas Benseghir [Asclepios].

The work of Thomas Benseghir, 3D/2D Coronary Registration for Interventional Cardiology Guidance, is supported by a CIFRE PhD fellowship from the General Electric Medical Helthcare company.

6. Partnerships and Cooperations

6.1. Regional Initiatives



(a) (b)

Figure 16. Example of proteins detection on a single xy image slice (a) Original xy slice. (b) Obtained proteins detection.

- We started a collaboration with the team TIRO (Transporteurs en Imagerie et Radiothérapie en Oncologie), CEA/UNS/Centre Antoine Lacassagne, Nice, concerning the detection of tumorous cells in kidney histopathology (see Fig. 17). Although the images have a very high resolution, the problem is extremely difficult due to the similarity between different type of cells.

  A coarse-to-fine approach seems perfectly adapted since the acquisitions are performed at several resolutions. Typically, six resolutions are available (see Table 1). However, contrarily to what is usually done, we do not plan to develop a unique approach, to apply it to the coarser resolution, and to use the corresponding result projected onto the following resolution as the initialization of the next step. Our idea is to think of which approach to take at each resolution level, and to gradually improve the detection confidence from "this broad area might contain tumorous cells" to "with high confidence, this small, finely delineated region is a tumorous cell". For example, we might start with histogram analysis or simple thresholding methods on the coarser resolution. Then, texture analysis could be performed in intermediate resolutions. Finally, fine radiometric and shape analyses could be done on the full resolution image to achieve object-level detection.
- We have a collaboration with the Laboratoire d'Océanographie de Villefranche (LOV), CNRS/Université Pierre et Marie Curie, concerning automatic classification of zooplankton organisms for an embedded system called UVP for Underwater Vision Profiler (see Section 4.12).
- We have a collaboration with IPMC (H. Barelli) on vesicules tracking for characterizing cell membrane properties (see Section 4.7).

6.2. National Initiatives

6.2.1. LABEX SIGNALIFE

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

6.2.2. ANR DIAMOND

Participants: Laure Blanc-Féraud [PI], Saima Ben Hadj.

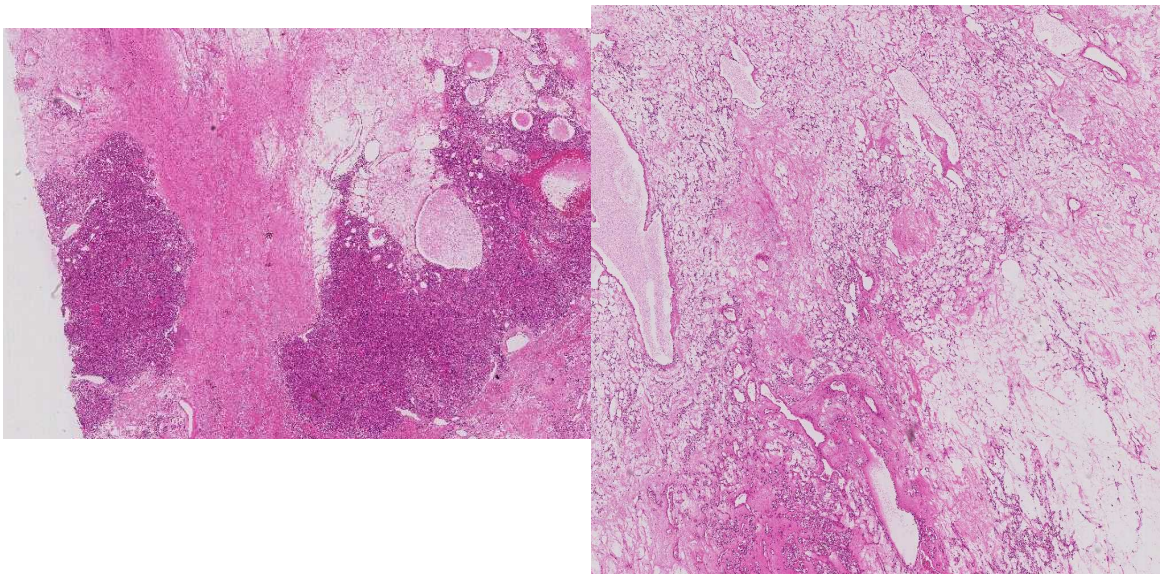


Figure 17. An example of image acquired for kidney histopathology. Left: low resolution; Right: intermediate resolution.

Table 1. Typical resolutions of the acquisitions in kidney histopathology.

	Full res.	Res. 1	Res. 2	Res. 3	Res. 4	Low res.
Width (rounded)	95 000	25 000	6000	1500	370	90
Height (rounded)	70 000	18 000	4500	1100	275	70
1-D downsampling factor	1	4	16	64	256	1024

In collaboration with the Pasteur Institute (Jean-Chritophe Olivo Marin) , the MIPS laboratory of Université de Haute Alsace (Alain Dieterlen, Bruno Colicchio) , the LIGM of Université Paris-Est (Jean-Christophe Pesquet, Caroline Chaux, Hugues Talbot), and INRA Sophia-Antipolis (Gilbert Engler). Details on the (website)

6.2.3. ANR MOTIMO

Participants: Laure Blanc-Féraud, Xavier Descombes, Eric Debreuve, Huei Fang Yang, Ana Rita Lopes Simoes.

In collaboration with Institut de Mathématiques de Toulouse, INRA, Institut de Mécanique des Fluides de Toulouse, Laboratoire J-A Dieudonné, et IMV Technologies (PME). Details on the (website)

6.2.4. ANR POXADRONO

Participants: Florence Besse [PI], Xavier Descombes, Laure Blanc-Féraud.

The young researcher ANR project POXADRONO is in collaboration with Caroline Medioni, Hélène Bruckert, Giovanni Marchetti, Charlène Perrois and Lucile Palin from iBV. It aims at studying ARN regulation in the control of growth and axonal guidance by using a combination of live-imaging, quantitative analysis of images, bio-informatic analysis and genetic screening.

6.2.5. 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 modelling. 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-characterised plant systems.

6.2.6. PEPII 1

Participants: Laure Blanc-Féraud, Xavier Descombes [PI], Alejandro Mottini.

This project aims at studying graphs in biological context (axons, vascular networks ...). In collaboration with Institut de Mécanique des Fluides de Toulouse, CerCo (Toulouse) .

6.2.7. PEPII 2

Participants: Laure Blanc-Féraud [PI], Xavier Descombes, Eric Debreuve.

In collaboration with Institut de Mathématiques de Toulouse, INRA, Institut de Mécanique des Fluides de Toulouse, Laboratoire J-A Dieudonné, et IMV Technologies (PME).

6.3. International Research Visitors

6.3.1. Visits of International Scientists

- Evgueny Pechersky from IITP Moscow (Russian Academy of Science) was invited one week in december.

6.3.1.1. Internships

- Vladimir Gutov : Master BioComp, UNS, Curves and Trees classification using SVM. Supervisors: E. Debreuve, X. Descombes.
- Gael Michelin : ENSEEIHT, Planar structures detection and tracking in biological images. Supervisor: Grégoire Malandain.
- Emmanuel Soubies : INSA Toulouse, Numerical methods for 3D biological structures reconstruction in fluorescent microscopy. Supervisors: L. Blanc-Féraud, Gilles Aubert.

- Nektaria Pappa : Master BioComp, UNS, Lobule detection from confocal microscopy images. Supervisor X. Descombes (with F. Plouraboué from IMFT)
- Anirudh Chakravarthi : Master BioComp, UNS, Dendrties dection from confocal microscopy images. Supervisor X. Descombes (with M. Studer from iBV).

6.3.2. Visits to International Teams

- Xavier has visited the Bristol University during one week in december. He was a Benjamin Maeker invited professor.

7. Dissemination

7.1. Scientific Animation

- Florence Besse was co-organiser of the first Labex Signalife meeting, grant reviewer for ANR and reviewer for PLoS ONE, WIRES Developmental Biology.
- Xavier Descombes was reviewer for the conference ISBI 2013 and the journals IEEE TMI, IEEE IP,... He is associated editor of DSP (Digital Signal Processing), expert for the DRRT Provence Alpes Côte d'AZur and DRRT Paris Ile de France. He is member of the Scientific Committee of the competitivness pole Optitech, associate member of IEEE BISP (Biomedical Imaging Signal Processing) Technical Committee and member of the Scientific Committee of Labex SIGNALIFE. Xavier Descombes was in the jury of an AAP Cancer call for project launched by INSERM. He was also in a MdC recruitment jury in Toulouse.

  Xavier Descombes was invited to give seminar or lectures in Strasbourg University, in the annual workshop on stochastic geometry organized in Grenoble, in the summer school in Cabreret, in a workshop in Toulouse orgnaized by the labex CIMI and at Institut Curie during the GdR workshop on computational biology.
- Eric Debreuve is member of the steering committee of Laboratoire I3S and coordinator of Pôle SIS (Signals, Images, Systems) of Laboratoire I3S (includes the management of a 25000-euro funding provided by the lab). He is member of the Board of the Association GRETSI (Groupement de Recherche en Traitement du Signal et des Images) and was reviewer for IEEE: Transactions on Medical Imaging; Springer: Multimedia Tools and Applications, Machine Vision and Applications; Elsevier: Pattern Recognition, Signal Processing; Revue Traitement du Signal. He was member of conference technical program committees (Advanced Concepts for Intelligent Vision Systems (ACIVS), Poznan, Poland and IEEE International Symposium on Biomedical Imaging (ISBI), Beijing, China.
- Laure Blanc-Féraud is Associate Editor of SIAM Journal Imaging Sciences and Traitement du Signal Journal. She is director of GdR ISIS of CNRS. She is Program chair of the conference IEEE ISBI 2014 in Beijing. She is member of the IEEE BISP (Biomedical Imaging Signal Processing) Technical Committee, she was vice chair of the evaluation committee of the ANR program blanc SIMI3 (till july 2013), she is member of the scientific steering committee of ANR (from september 2013), member of the scientific council of Institute INS2I of CNRS, invited member of the scientific council of Institute INSIS of CNRS , member of "bureau du comité des projets" Inria SAM and alternate member of CNECA (Comité National des Enseignants Chercheurs en Agriculture). She is part of the scientific committee of laboratory GreyC (UMR CNRS 6072) and of "'Institut des Technologies Avancées en sciences du Vivant" (ITAV, USR CNRS 3505).

  Laure Blanc-Féraud was reviewer for Inverse Problems journal and the conferences IEEE ISBI, IEEE ICIP, IEEE ICASSP. She was co-organisor of the workshop on New Computational Methods in Inverse Problems - NCMIP 2013 (NCMIP) in ENS Cachan and was associate editor for the conferences : IEEE ISBI'13, Workshop NCMIP 2013. She was in the scientific committees of the european workshop on Visual Information Processing (EUVIP 2013) and of the 11th International workshop on Adaptation and Learning in Control and Signal Processing (ALCOSP 2013).

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

  G. Malandain is a member of the editorial board of the journal International Journal on Computer Vision (Kluwer). He was an associate editor for the conference ISBI 2014, and serves as reviewer for the conferences DGCI 2013, ISBI 2103, MICCAI 2013 and ICCV 2013.
- Caroline Medioni gave an oral communication at Cold Spring Harbor meeting: Neurobiology of Drosophila in New York and at the "Journées régionales de la Cancéropole PACA".

7.2. Teaching - Supervision - Juries

7.2.1. Teaching

- Master : Emmanuel Soubies, Traitement Numérique des Images, 10h Eq. TD, Niveau M2, Université de Nice Sophia Antipolis, France.
- Master : Florence Besse, Contrôle génétique de la morphologie neuronale, 3h Eq. TD, Niveau M2, Université de Nice Sophia Antipolis, France.
- Master : Florence Besee, Réseaux neuronaux : de la structure à la fonction, 3h Eq. TD, Niveau M2, Université de Nice Sophia Antipolis, France.
- License : Alejandro Mottini, Introduction au Web, 24h Eq. TD, Niveau L1, Université de Nice Sophia Antipolis, France.
- License : Alejandro Mottini, Systèmes Informatiques, 20h Eq. TD, Niveau L1, Université de Nice Sophia Antipolis, France.
- Master : Alejandro Mottini, Outils Mathématiques pour l'Image, 8h Eq. TD, Niveau M2, Université de Nice Sophia Antipolis, France.
- Master : Alejandro Mottini, Traitement d'images, 8h Eq. TD, Niveau M2, Université de Nice Sophia Antipolis, France.
- Master : Xavier Descombes, Traitement d'images, Analyse de données, Techniques avancées de traitement d'images, 30h Eq. TD, Niveau M2, ISAE, France.
- Master : Xavier Descombes, Traitement d'images, master ISAB, 12h Eq. TD, Niveau M2, Université de Nice Sophia Antipolis, France.
- Master : Xavier Descombes, Traitement d'images, master VIM, 12h Eq. TD, Niveau M2, Université de Nice Sophia Antipolis, France.
- Master : Xavier Descombes, Bio-imagerie, master IRIV, 6h Eq. TD, Niveau M2, Université de Strasbourg, France.
- Master : Eric Debreuve, Introduction to inverse problems in image processing, 29 h Eq. TD, Master 2 in Computational Biology and Biomedicine/5th year Polytech'Nice-Sophia, Université Nice Sophia Antipolis.
- Master : Eric Debreuve, Basics of image processing, 13h Eq. TD, Master 2 "Génie Biomédical", Université Nice Sophia Antipolis.
- Licence : Alexis Zubiolo, Informatique Générale, 36 heures en équivalent TD, niveau L1, Département Informatique de l'Université de Nice Sophia Antipolis, France
- Licence : Alexis Zubiolo, Programmation Web (HTML & CSS), 12 heures en équivalent TD, niveau L1, Département Informatique de l'Université de Nice Sophia Antipolis, France
- Licence : Alexis Zubiolo, Algorithmique et Programmation Objet, 18 heures en équivalent TD, niveau L2, Département Informatique de l'Université de Nice Sophia Antipolis, France
- Master : Laure Blanc-Féraud, Fluorescence image restoration, 18h, M2 Computational Biology , University Nice Sophia Antipolis, France

- Master : Laure Blanc-Féraud, Image restoration, 12h, M2 ISAB, University Nice Sophia Antipolis, France
- Master : Laure Blanc-Féraud, Traitement numérique des images, 12h Eq. TD, M2 VIM , EPU University Nice Sophia Antipolis, France
- Licence : Caroline Medioni. microscopie optique pratiques et théoriques, 15h Eq. TD, L3, University Nice Sophia Antipolis, France

7.2.2. Supervision

- PhD in progress : Gaël Michelin, Quantitative tools for morphogenesis study, 1st october 2011, Grégoire Malandain (advisor).
- PhD in progress : Alejandro Mottini, Métriques de graphes pour la caractérisation des axones, 1st october 2011, Xavier Descombes (advisor), Florence Besse (co-supervisor).
- PhD in progress, Alexis Zubiolo, Statistical Machine Learning for Automatic Cell Classification, Eric Debreuve (advisor).
- PhD : Saima Ben Hadj, Blind restoration of space variant 3D confocal microscopic images, University Nice Sophia Antipolis, 17 April 2013, Laure Blanc-Féraud
- PhD : Mikael Carlavan, Optimization of the compression-restoration chain for satellite images, University Nice Sophia Antipolis, 10 June 2013, Laure Blanc-Féraud and Marc Antonini.
- PhD in progress : Emmanuel Soubies, MA-TIRF reconstruction, 1st october 2013, Laure Blanc-Féraud and Sébastien Schaub.
- PhD in progress : Lola Baustista, Fluorescence confocal microscopy image restoration, 1st november 2013, Laure Blanc-Féraud.

7.2.3. Juries

- Florence Besse was in one HDR jury at University of Montpellier and one PhD jury at UPMC Paris and Université Paris Sud.
- Eric Debreuve was examiner in the PhD jury of Thomas Peel, Université d'Aix-Marseille, Laboratoire d'Analyse, Topologie, Probabilités (LATP)/Laboratoire d'Informatique Fondamentale de Marseille (LIF). Title: "Algorithmes de poursuite stochastiques et inégalités de concentration empiriques pour l'apprentissage statistique", november 2013.
- PhD : Laure Blanc-Féraud, referee of the PhD committee of Moncef Hidane, University of Caen
- HDR : Laure Blanc-Féraud, referee of the HDR committee of David Mary, University Nice Sophia Antipolis
- PhD : Laure Blanc-Féraud was examiner for 1 HDR and 4 PhD.
- Grégoire Malandain participated as supervisor to the PhD thesis committee of Marine Breuilly (Nice-Sophia Antipolis University), as reviewer to the PhD thesis committee of C. Hughes (INSA Lyon), as chair to the PhD thesis committee of B. Xiang (Ecole Centrale Paris) and V. Delmon (INSA Lyon), as reviewer to the HDR thesis committee of C. Fetita (UPMC) and as referee to the HDR thesis committee of H. Talbot (Paris Est Univ.)

7.3. Popularization

- Xavier Descombes has given a conference in Nice within the program "Science au Lycée".
- Xavier Descombes has given a seminar in Marseille University in a workshop dedicated to multidisciplinarity.

8. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] S. BEN HADJ. , *Restauration d'images 3D de microscopie de fluorescence en présence d'aberrations optiques*, Université Nice Sophia Antipolis, April 2013, http://hal.inria.fr/tel-00847334

Articles in International Peer-Reviewed Journals

[2] M. BREUILLY, G. MALANDAIN, J. GUGLIELMI, R. MARSAULT, T. POURCHER, P. FRANKEN, J. DARCOURT. *Amplitude-based data selection for optimal retrospective reconstruction in micro-SPECT*, in "Physics in Medicine and Biology", April 2013, vol. 58, n^{o} 8, pp. 2657-2674 [*DOI :* 10.1088/0031-9155/58/8/2657], http://hal.inria.fr/hal-00799381

Invited Conferences

[3] A. HABBAL, H. BARELLI, G. MALANDAIN. *Modeling cell sheet wound closure*, in "Applied Mathematics, Modeling and Computational Science (AMMCS)", Waterloo, Ontario, Canada, Wilfrid Laurier University with AIMS and SIAM, 2013, http://hal.inria.fr/hal-00923626

International Conferences with Proceedings

[4] S. BEN HADJ, L. BLANC-FÉRAUD, G. AUBERT, G. ENGLER, E. MAALOUF, B. COLICCHIO, A. DIETERLEN. *Blind depth-variant blur removal in confocal microscopy*, in "ISBI - International Symposium on Biomedical Imaging", San Francisco, United States, IEEE, April 2013, http://hal.inria.fr/hal-00920191

[5] S. BEN HADJ, L. BLANC-FÉRAUD, G. AUBERT, E. GILBERT. *Blind restoration of confocal microscopy images in presence of a depth-variant blur and Poisson noise*, in "ICASSP - International Conference on Acoustics, Speech and Signal Processing", Vancouver, Canada, IEEE, May 2013, http://hal.inria.fr/hal-00920192

[6] S. BEN HADJ, L. BLANC-FÉRAUD, E. GILBERT. *Depth-variant blind restoration with pupil-phase constraints for 3D confocal microscopy*, in "3rd International Workshop on New Computational Methods for Inverse Problems", Paris, France, May 2013, http://hal.inria.fr/hal-00920193

[7] T. BENSEGHIR, G. MALANDAIN, R. VAILLANT. *Iterative Closest Curve: a Framework for Curvilinear Structure Registration Application to 2D/3D Coronary Arteries Registration*, in "MICCAI - Medical Image Computing and Computer Assisted Intervention", Nagoya, Japan, K. MORI, I. SAKUMA, Y. SATO, C. BARILLOT, N. NAVAB (editors), Lecture Notes in Computer Science, Springer, 2013, vol. 8149, pp. 179-186 [*DOI :* 10.1007/978-3-642-40811-3_23], http://hal.inria.fr/hal-00833196

[8] M. BREUILLY, G. MALANDAIN, N. AYACHE, J. GUGLIELMI, T. POURCHER, P. FRANKEN, J. DARCOURT. *Image-based motion detection in 4D images and application to respiratory motion suppression*, in "ISBI - International Symposium on Biomedical Imaging", San Francisco, United States, IEEE, April 2013, pp. 792-795, http://hal.inria.fr/hal-00799368

[9] R. CAVICCHIOLI, C. CHAUX, L. BLANC-FÉRAUD, L. ZANNI. *ML estimation of wavelet regularization hyperparameters in inverse problems*, in "ICASSP - International Conference on Acoustics, Speech, and Signal Processing", Vancouver, Canada, IEEE, May 2013, 5 p. , http://hal.inria.fr/hal-00825819

[10] X. DESCOMBES, G. MALANDAIN, C. FONTA, L. NEGYESSY, R. MOSKO. *Automatic dendrite spines detection from X-ray tomography volumes*, in "ISBI - International Symposium on Biomedical Imaging", San fancisco, United States, IEEE, 2013, http://hal.inria.fr/hal-00793573

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