IN PARTNERSHIP WITH:
CNRS

Université Nice - Sophia Antipolis

Activity Report 2012

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 and Bioinformatics

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Team MORPHEME

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

Creation of the Team: September 01, 2011 .

1. Members

Research Scientists

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Laure Blanc-Féraud [Senior Researcher CNRS, HdR]
Eric Debreuve [Junior Researcher CNRS, HdR]
Xavier Descombes [Team leader, Senior Researcher Inria, HdR]
Grégoire Malandain [Senior Researcher Inria, 80% in Morpheme, HdR]

Engineer

Sébastien Schaub [Engineer iBV, PhD, 20 % in Morpheme]

PhD Students

Saima Ben Hadj [Funding: ANR DIAMOND. She started her PhD in April 2010.]
Mikael Carlavan [Funded by the French Space Agency (CNES) in collaboration with Thales Alenia Space.]
Alejandro Mottini [Alejandro Mottini is PhD since october 2011 with an ED STIC grant.]
Sylvain Prigent [Funded by Galderma R&D. His started his PhD in November 2009. He is a post-doc funded by UNS since december 2012.]
Alexis Zubiolo [Funded by ED STIC. His started his PhD in October 2012, he was previously an M2 intern during six month.]

Post-Doctoral Fellows

Daniele Grazziani [Funding: FUI GYROVISION.]
Huei Fang Yang [Funded by ARC DADA from october 2011 to september 2012 and by ANR MOTIMMO since october 2012.]

Administrative Assistants

Christine Foggia [Inria, 40% in the project]
Micheline Hagneré [CNRS, Assistant of pole SIS at I3S]

Others

Anny Hank [Anny Hank was an M2 intern during six months]
Clarens Caraccio [Clarens Caraccio was an M1 intern during two months]

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) . It has been created in 2011 as “Equipe”.

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 "grade de chevalier dans l'Ordre National du Mérite".

3. Scientific Foundations

3.1. Scientific Foundations

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 imag- ing 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, $\cdots$) and the unavoidable defects of in vivo imaging (artifacts, missing data, $\cdots$). 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, $\cdots$) 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. Software

4.1. Software

4.1.1. Deposits

The software MAD V2.0 was deposited with the APP in November 2012. It deals with the melasma severity scoring from multi-spectral imaging.

4.1.2. Transfers

The software MAD V2.0 was transferred to Galderma R&D.

5. New Results

5.1. Imaging

5.1.1. ML estimation of wavelet regularization hyperparameters in inverse problems

Participant: Laure Blanc-Féraud.

This work was made in collaboration with Caroline Chaux from LATP (Marseille) and Roberto Cavicchioli and Luca Zanni from University of Modena (Italy).

Parameter estimation, Maximum likelihood estimation, Wavelet transforms, Deconvolution, Gradi- ent methods

We are interested in regularizing hyperparameter estimation by maximum likelihood in inverse problems with wavelet regularization. One parameter per subband is estimated by gradient ascent algorithm.We have to face with two main difficulties: i) sampling the a posteriori image distribution to compute the gradient of the objective function; ii) choosing a suited step-size to ensure good convergence properties of the gradient ascent algorithm. We first show that introducing an auxiliary variable makes the sampling feasible using classical Metropolis-Hastings algorithm and Gibbs sampler. Secondly, we propose an adaptive step-size selection and a line-search strategy to improve the gradient-based method. Good performances of the proposed approach are demonstrated on both synthetic and real data.

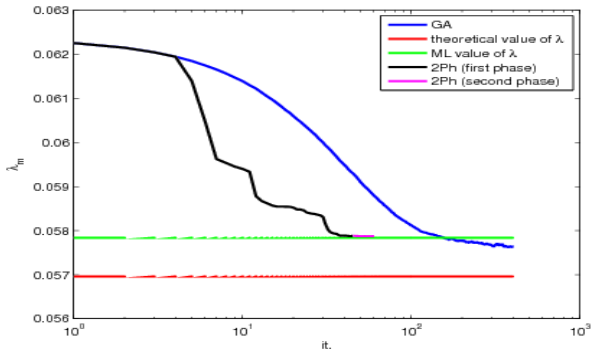


Figure 1. λ_m behavior over iterations of ascent algorithm for a sub band at first level of wavelet decomposition

5.1.2. Joint optimization of noisy image coding and denoising

Participants: Mikael Carlavan, Laure Blanc-Féraud.

this work was made in collaboration with Marc Antonini (I3S), Roberto Camarero and Christophe Latry (CNES) and Yves Bobichon (TAS).

coding, denoising, wavelet transform, global rate-distortion optimization

This work concerns the study of optimal noisy source coding/denoising. A global optimization of the problem is usually difficult to perform as the global fidelity criterion needs to be optimized in the same time over the sets of both coding and denoising parameters. Most of the bibliography in this domain is based on the fact that, for a specific criterion, the global optimization problem can be simply separated into two independent optimization problems: The noisy image should be first optimally denoised and this denoised image should then be optimally coded. In many applications however, the layout of the acquisition imaging chain is fixed and can not be changed, that is a denoising step can not be inserted before coding. For this reason, we are concerned here with the problem of global joint optimization in the case the denoising step is performed, as usual, after coding/decoding. In this configuration, we showed on a simple case how to express the global distortion as a function of the coding and denoising parameters. We presented an algorithm to minimize this distortion to get the optimal values of these parameters. Figure 2 shows results of this joint optimization algorithm, on the classical test image *Barbara*, in comparison to the usual disjoint optimization technique, which consists in selecting the coding and the denoising parameters such that the coding and the denoising errors are independently minimized. On the range of validity of the proposed model, we see that the joint optimized distortion slightly outperforms the disjoint optimized distortion (in the presented example, the PSNR of the reconstructed image increases of $0.4\ dB$ at 1.85 bits/pixels). The interesting point of the proposed method is that it allows to reach the same global error than the disjoint optimized technique but for a lower coding rate. For example, on this image, the joint optimization technique reaches at 1.42 bits/pixel the same distortion than the one obtained at 2.04 bits/pixels for the disjoint optimization technique. The benefit in terms of compression performances of the joint optimization appears then to be very significant.

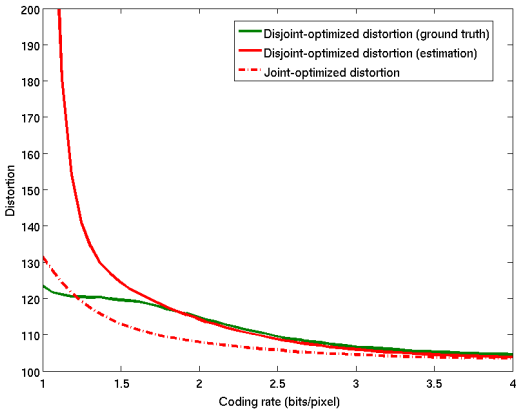


Figure 2. Comparison of the disjoint optimized distortion (ground truth and estimation) to the joint optimized distortion Barbara.

5.1.3. Blind deconvolution

Participants: Saima Ben Hadj, Laure Blanc-Féraud.

This research takes place within the ANR DIAMOND. This work was made in collaboration with Gilles Aubert, Laboratoire J. Dieudonné (CNRS,UNS).

One of our tasks within the ANR Diamond project is the blind restoration of images coming from Confocal laser scanning microscopy (CLSM). CLSM is a powerful technique for studying biological specimens in three dimensions by optical sectioning. Nevertheless, it suffers from some artifacts. First, CLSM images are affected by a depth-variant (DV) blur due to spherical aberrations induced by refractive index mismatch between the different media composing the system as well as the specimen. Second, CLSM images are corrupted with a

Poisson noise due to low illumination. Because of these intrinsic optical limitations, it is essential to remove both DV blur and noise from these images by digital processing.

In this context, we first study space-variant (SV) blur models and prove that a model where the SV point spread function (PSF) is approximated by a convex combination of a set of space-invariant (SI) PSFs is efficient and adequate to the inversion problem [30] [10]. Afterwards, we focus on the non-bind restoration problem and we fit a fast restoration method based on a domain decomposition technique [33] to our DV blur model [10], [9].

Recently, we focus on the blind case. In fact, in practice it is difficult to obtain the DV PSF in spite of the existence of theoretical PSF models [34], because these models are dependent on some unknown acquisition parameters (e.g. the refractive index (RI) of the specimen). Therefore a blind or semi-blind restoration algorithm is needed for this system. We propose two methods for this problem : In the first method, we define a criterion to be jointly minimized w.r.t to the image and the PSF set. In this method, the intensities of each SI PSF are estimated at every voxel. Although the big number of parameters to be estimated, the method allows more freedom on the shape of the PSF which could be more or less deformed according to spherical aberration level. We provide a theoretical proof of the existence of a minimizer of the considered problem [23]. Then, we perform the minimization by following an alternate minimization scheme, each elementary minimization is performed using the recently proposed scaled gradient projection (SGP) algorithm that has shown a fast convergence rate [29]. Results on simulated CLSM images and comparison with another alternate scheme based on a regularized version of the Richardson–Lucy algorithm [31] are shown in Fig. 3. In the second blind method, we use a Gaussian approximation of each of the SI PSFs. This presents the advantage of significantly reducing the number of parameters to be estimated but constraints the PSF shape. We prove on simulated data that the first method provides more accurate restoration result than the second one.

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

Figure 3. (Y, Z) sections of blind restoration results on a simulated CLSM image. (a) original image, (b) simulated observation, (c) restoration using our blind restoration method using SGP algorithm, (d) restoration using a regularized Richardson–Lucy algorithm embedded in an alternate scheme.

5.1.4. Morphogenesis of living organisms

Participant: Grégoire Malandain.

This research takes place within the Inria Large-scale initiative Morphogenetics.

This work was made in collaboration with Christophe Godin and Léo Guignard from Virtual Plants.

super-resolution, SPIM, morphogenesis

We extended a previous work [32] for the reconstruction of microscopic images. In particular, we extended the super-resolution image reconstruction (where several images, acquired from different viewpoints, are fused) to the lightsheet (or SPIM for Selective Plane Illumination Microscope) microscope modality. This modality offers a high acquisition speed, allowing imaging an organism frequently. As an exemple, Phallusia mammillata and Ciona intestinalis embryos can be imaged from 32 cells to around 1000 cells. The organism is captured from four different angles every 2 minutes during 2 hours (collaboration with CRBM Montpellier and EMBL Heidelberg).

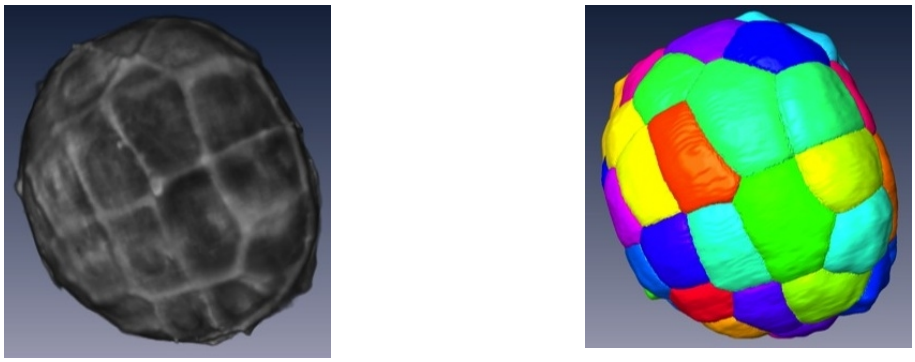


Figure 4. Left: 3D rendering of a reconstructed image of a Phallusia mammillata embryo; right: segmentation of cells.

5.2. Features Extraction

5.2.1. Axon extraction from fluorescent confocal microscopy images

Participants: Alejandro Mottini, Xavier Descombes, Florence Besse.

It it known that the analysis of axonal topologies allows biologists to study the causes of neurological diseases such as Fragile X Syndrome and Spinal Muscular Atrophy. In order to perform the morphological analysis of axons, it is first necessary to segment them. Therefore, the automatic extraction of axons is a key problem in the field of neuron axon analysis.

For this purpose, biologists label single neurons within intact adult Drosophila fly brains and acquire 3D fluorescent confocal microscopy images of their axonal trees. These images need to be segmented.

In our work presented in [16], we propose a new approach for the automatic extraction of axons from fluorescent confocal microscopy images which combines algorithms for filament enhancement, binarization, skeletonization and gap filling in a pipeline capable of extracting the axons containing a single labeled neuron. Unlike other segmentation methods found in the literature, the proposed is fully automatic and designed to work on 3D image stacks. This allows us to analyze large image databases.

The method performance was tested on 12 real 3D images and the results quantitatively evaluated by calculating the RMSE between the tracing done by an experienced biologist and the automatic tracing obtained by our method. The good results obtained in the validation show the potential use of this technique in helping biologists for extracting axonal trees from confocal microscope images (see figures 5 and 6).

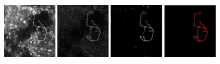


Figure 5. Results obtained on each step of the algorithm for one image stack (maximum intensity projections). From left to right: original image, filament enhancement, binarization and final result.

5.2.2. Dendrite spine detection from X-ray tomographic volumes

Participants: Anny Hank, Xavier Descombes, Grégoire Malandain.

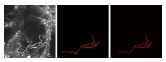


Figure 6. Comparison between original image (left), our result (middle) and ground truth (right) for two images (maximum intensity projections).

We have developped an automated algorithm for detecting dendritic spines from XRMT data. XRMT data allows imaging a large volume of tissue, and therefore a higher number of spines than laser scanning microscopy. We have shown that despite the lower image quality compared to microscopic data, we were able to extract dendritic spines. The main idea of the proposed approach is to define a mask for performing the spine detection without facing the false alarms problem as we introduce some information on spines localization. We therefore first extract the dendrites themselves and then compute the spine mask based on prior knowledge on their distance to dendrites. To extract dendrite we first compute the medial axis thanks to a multi-scale Hessian-based method. Then, we extract segments by a 3D Hough transform and reconstruct the dendrites using a conditional dilation. The spine mask is defined nerby the detected dendrites using anatomical parameters described in the literature. A point process defined on this mask provides the spine detection.

To exemplify the proposed approach, a subvolume ($220 \times 180 \times 100$) has been extracted from a XRMT volume that is given on figure 7. As expected, the spines appear as small objects, whose size is close to the image resolution, along the tubular structures representing dendrites. Using the localization information to detect spine is essential to prevent false alarms due to noise or to the deviation of dendrites from a cylinder model. Figure 7 shows the detected dendrite medial axis and the obtained spine detection. The obtained results are promising and correspond to a visual inspection of the data. Forthcoming validation study will allow to better assess the quality of the detection by providing a quantitative evaluation.

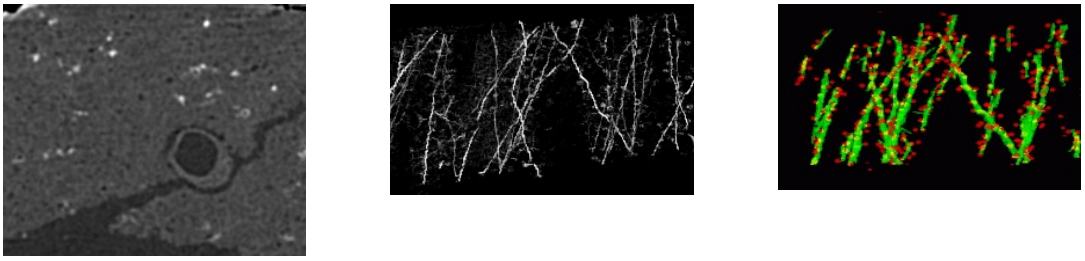


Figure 7. XMRT slice (left), dendrites medial axis (middle) and spine detection (in red) (right)

5.2.3. Cell detection

Participant: Xavier Descombes.

This work was done in collaboration with Emmanuel Soubies and Pierre Weiss from ITAV (Toulouse)

We have proposed some improvements of the Multiple Birth and Cut algorithm (MBC) in order to extract nuclei in 2D and 3D images. We have introduced a new contrast invariant energy that is robust to degradations encountered in fluorescence microscopy (e.g. local radiometry attenuations). Another contribution of this work is a fast algorithm to determine whether two ellipses (2D) or ellipsoids (3D) intersect. Finally, we propose a new heuristic that strongly improves the convergence rates. The algorithm alternates between two birth steps. The first one consists in generating objects uniformly at random and the second one consists in perturbing the

current configuration locally. Performance of this modified birth step is evaluated and examples on various image types show the wide applicability of the method in the field of bio-imaging.

Figure 8 left shows the segmentation result on a Drosophila embryo obtained using SPIM imaging. This is a rather easy case, since nuclei shapes vary little. The images are impaired by various defects: blur, stripes and attenuation. Despite this relatively poor image quality, the segmentation results are almost perfect. The computing time is 5 minutes using a C++ implementation. The image size is 700×350. Figure 8 right presents a more difficult case, where the image is highly deteriorated. Nuclei cannot be identified in the image center. Moreover, nuclei variability is important meaning that the state space size χ is large. Some nuclei are in mitosis (see e.g. top-left). In spite of these difficulties, the MBC algorithm provides acceptable results. They would allow to make statistics on the cell location and orientation, which is a major problem in biology. The computing times for this example is 30 minutes.

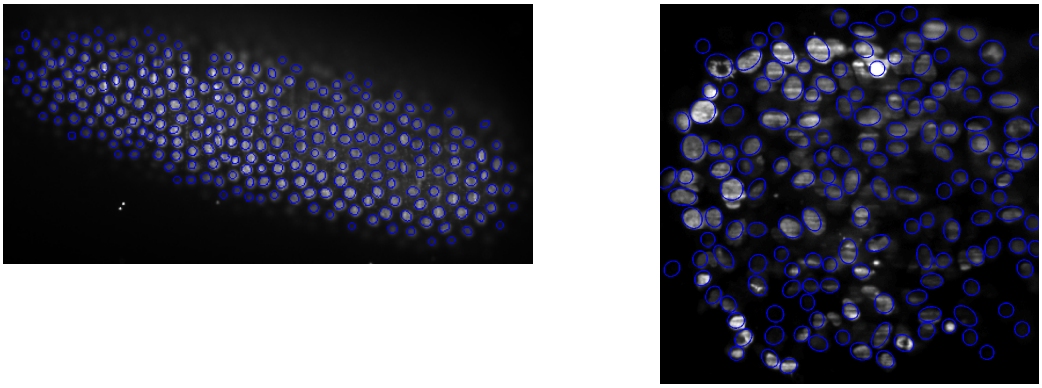


Figure 8. 2D segmentations of a nuclei of Drosophila embryo (left) and a multicellular tumor spheroid (right).

5.2.4. Spermatozoid tracking

Participants: Clarens Caraccio, Xavier Descombes.

In this work, we have proposed an algorithm for tracking spermatozoid in a sequence of confocal images. We first detect the spermatozoids by thresholding the result of a top hat operator. The thresold is automatically estimated using Otsu's method. We then analyse the different connected components to detect overlaps between adjacent spermatozoids. Temporal neighbors are selected based on the spatial consistency of the object sets between two consecutive time. A first result is given on figure 9.

5.3. Classification

5.3.1. Axon morphology comparison using elastic shape analysis

Participants: Alejandro Mottini, Xavier Descombes, Florence Besse.

It is known that neuronal morphology impacts network connectivity, thus providing information on its functioning. Moreover, it allows the characterization of pathological states. Therefore, the analysis of the morphological differences between normal and pathological structures is of paramount importance.

We present a new method for comparing reconstructions of axonal trees (obtained, for example, by applying our segmentation method on confocal microscopy images of normal and mutant axonal trees) which takes into account both topological and geometrical information and is based on the Elastic Shape Analysis Framework. The method computes the geodesic between two axons in a space of tree like shapes, and the distance between the two is defined as the length of the geodesic. Moreover, our method is capable of showing how one axon transforms into the other by taking intermediate points in the geodesic.

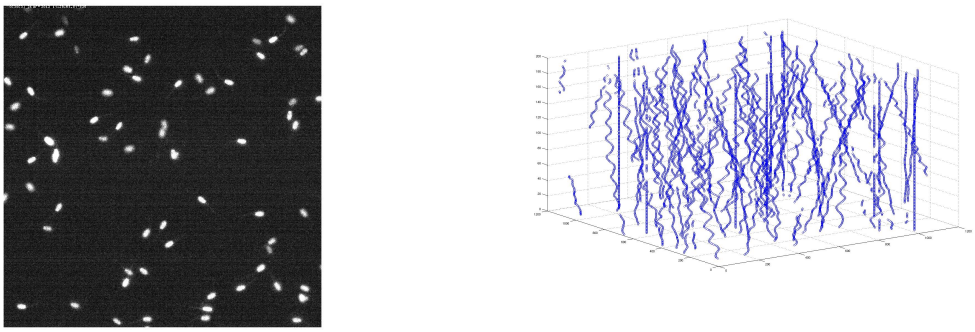


Figure 9. Original confocal image and estimated spermatozoid trajectories.

We consider two axonal trees T_1 and T_2, each consisting of an axon and several branches (and possibly sub branches). All are represented by 3D open curves in $\mathbb{R}^3$ (see Figure 10). We start by defining the matching function M such that $M : (0, 1, 2, ...n) \times (0, 1, ..., m)$, where n and m are the number of branches in T_1 and T_2 respectively. The matching function matches the branches of the two trees, for example, by assigning branch $i = 1$ of T_1 to branch $j = 3$ of T_2. We then define a branch function C which indicates, for a given time t_c, how many branches remain after $\beta(t_c)$ (see Figure 10). We only take into account branches which have a match in the other axonal tree. Finally, we define the distance between two axonal trees T_1, T_2 as:

$$D(T_1, T_2) = \min_M d((\beta_1(t), C1(t, M)), (\beta_2(t), C2(t, M))) + \sum_{(i,j)} \alpha_{i,j} M(i, j) D(T_1(i), T_2(j)) \qquad (1)$$

where β_k is the main curve (axon) of tree k, C_k its branch function, M the matching function, $\alpha_{i,j}$ a weight parameter and $D(T_1(i), T_2(j))$ the distance between the matched branches of the two trees. All distances between simple curves are calculated using the elastic shape analysis framework.

The method performance was tested on a group of 22 (11 normal and 11 mutant) 3D images, each containing one axonal tree manually segmented by an experienced biologist from a set of real confocal microscopy images. The mean and standard deviation of the inter and intra class distances between the neurons were calculated and results suggest that the proposed method is able to distinguish between the two populations (an average interpopulation to intrapopulation distance ratio of 1:21 and 1:28 were obtained). In addition, we computed the optimum transformations between axons. An example is shown in figure 11. This result was obtained by taking intermediate points along the geodesic between the two trees.

Figure 10. Axonal tree diagrams (a) and their corresponding C functions for a given M (b).

5.3.2. Vascular network segmentation from X-ray tomographic volumes

Participant: Xavier Descombes.

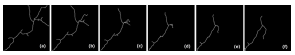


Figure 11. Optimum transformation between two axonal trees (transformation starts in (a) and finishes in (f), maximum intensity projections).

This work was made in collaboration with Franck Plouraboué and Abdelakim El Boustani from IMFT, Caroline Fonta from CerCo, Géraldine LeDuc from ESRF, Raphael Serduc from INSERM and Tim Weitkamp from Synchrotron Soleil.

Micro-tomography produces high resolution images of biological structures such as vascular networks. We have defined a new approach for segmenting vascular network into pathological and normal regions from considering their micro-vessel 3D structure only. We consider a partition of the volume obtained by a watershed algorithm based on the distance from the nearest vessel. Each territory, defined as Local Vascular Territory (*a Local Vascular Territory (LVT) is a connected region corresponding to the catchment bassin associated with a vascular element. It can be obtained through the watershed computation on the opposite distance map from the vessels and is not connected to the sample border.*), is characterized by its volume and the local vascular density. The volume and density maps are first regularized by minimizing the total variation, within a Markov Random Field framework, using a graph cut algorithm . Then, a new approach is proposed to segment the volume from the two previous restored images using an iterative algorithm based on hypothesis testing. We consider the variables density and volume for each LVT and the populations constituted by the different classes obtained by the segmentation at a given step. Classes which are not statistically significantly different are merged using a MANOVA. This blind segmentation provides different regions which have been interprated by expert as tumor, necrosis, tumor periphery and sane tissue 12.

5.3.3. Statistical analysis of skin pigmentation under treatment

Participants: Sylvain Prigent, Xavier Descombes.

This work was partially funded by a contract with Galderma R&D [http://www.galderma.com/RampD.aspx]. It was made in collaboration with J. Zerubia from Ayin team.

multispectral imaging, skin, hyperpigmentation, hypothesis tests, statistical inferences

One of the steps to evaluate the efficacy of a therapeutic solution is to test it on a clinical trial involving several populations of patients. Each population receives a studied treatment and a reference treatment for the disease. For facial hyper-pigmentation, a group of N_e patients receives the treatment on one cheek and a comparator on the other. The comparator can be a reference treatment or a placebo. To this end patients are selected to have the same hyper-pigmentation severity on the two cheeks. Then multi-spectral images are taken at different time t along the treatment period.
We propose a methodology to assess the efficacy a treatment by calculating three differential criteria: the darkness, the area and the homogeneity. The darkness measure the average intensity of the disease on a gray scaled image I obtained by a linear combination of the spectral bands of the original multi-spectral image. A differential darkness is then obtained by measuring the deviation between the initial measurement at time t_0, and the measurement at time t_k. The differential area criterion is calculated by analyzing the histogram of $I_{diff} = I_{t_0} - I_{t_k}$ a difference gray scale image between two measurements in a time series. The differential homogeneity criterion is obtaining with a multi-scale analysis of I_{diff} adapted from the Statistical Parametric Mapping (SPM) methodology. Indeed, statistical inferences allow to assign a probability of change to each region of I_{diff} above a set of thresholds. These probabilities are calculated with respect to the maximum intensity and the spatial extend of each region. An integration of the obtained statistical map denoted SM, allows to get a homogeneity criterion.

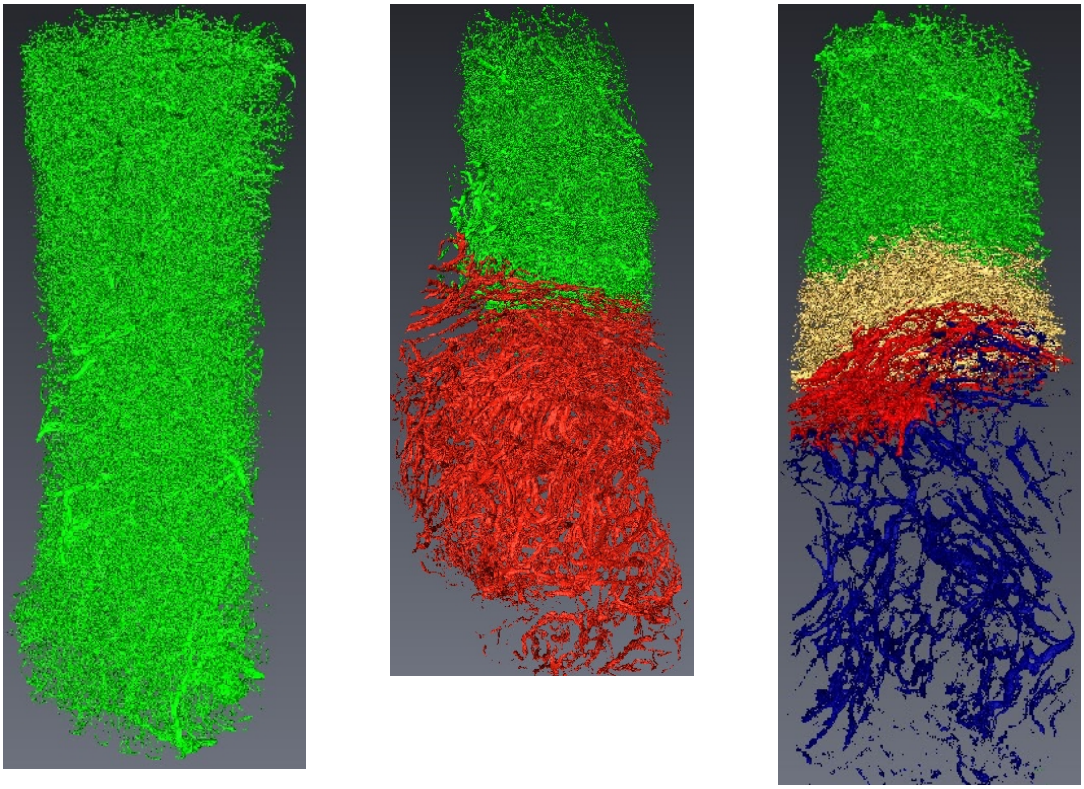
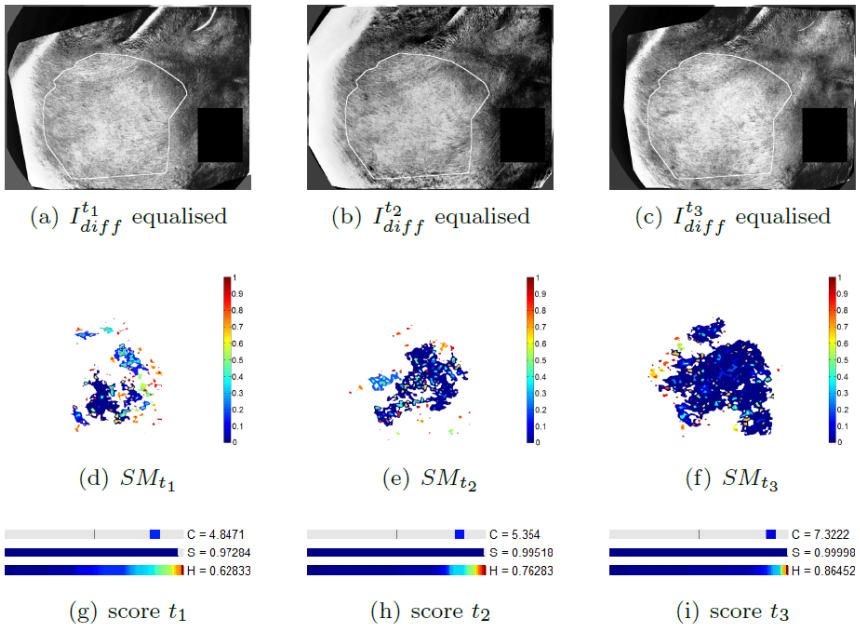


Figure 12. Examples of segmentation: tumor (red), necrosis (blue), tumor periphery (yellow) and sane (green)

The figure 13 illustrates the differential score calculated on a patient whose pathology decreases during the clinical trial. The proposed differential score have been tested in a full clinical study and provided results that agreed with the clinical analysis. This work have been patented and published in Inria research reports [25], [26].



(a) $I_{diff}^{t_1}$ equalised (b) $I_{diff}^{t_2}$ equalised (c) $I_{diff}^{t_3}$ equalised

(d) SM_{t_1} (e) SM_{t_2} (f) SM_{t_3}

(g) score t_1 (h) score t_2 (i) score t_3

Figure 13. I_{diff}, SM and differential score for the three measurements t_1, t_2, t_3 calculated for a patient whose disease decreases.

5.3.4. A Recursive Approach For Multiclass Support Vector Machine: Application to automatic classification of endomicroscopic videos

Participants: Alexis Zubiolo, Eric Debreuve.

This work is made in collaboration with Barbara André (Mauna Kea Technologies)

The problem of automatic image (or video, or object) classification is to find a function that maps an image to a class or category among a number of predefined classes. An image can be viewed as a vector of high-dimension. In practice, it is preferable to deal with a synthetic signature of lower dimension. Therefore, the two classical steps of image classification are: image signature extraction and signature-based image classification. The classification rule can be learned from a set of training sample images manually classified by experts. This is known as supervised statistical learning where *statistical* refers to the use of samples and *supervised* refers to the sample classes being provided. We are interested in the learning aspect of the multiclass [1] problem when using a binary classification approach as a building block. We chose the Support Vector Machine (SVM), a well-known binary classifier.

Among the proposed extensions of binary classification methods to multiclass (three classes or more), the one-versus-one and one-versus-all approaches are the most popular ones. Let us suppose that there are $p \geq 3$ classes. The idea of the one-versus-all strategy is to oppose to any of the classes the union of the remaining $p - 1$ classes. Then, p SVM classifiers are determined, each one scoring, say, positively for one of the classes.

[1] Traditionally in classification, *multiclass* means "three classes or more" while the two-class case is referred to as binary classification.

The one-versus-one strategy opposes the classes by pair for all possible pairs. Therefore, $\frac{p(p-1)}{2}$ SVMs are determined and classification is performed by a majority vote.

As an alternative to these aforementioned strategies (as well as to other, less popular ones), we developed a recursive learning strategy. A tree of SVMs is built, achieving three goals: a fair balance in the number of samples used in each binary SVM learnings, a logarithmic complexity for classification ($\log_2(p)$ compared to the linear or quadratic complexities of one-versus-all or one-versus-one, respectively), and a coherent, incremental classification procedure (as opposed to selecting the final class based on possibly competing partial decisions). During learning, at each node of the tree, a combinatorial search is performed to determine an optimal separation of the current classification problem into two sub-problems. The proposed method was applied to automatic classification of endomicroscopic videos.

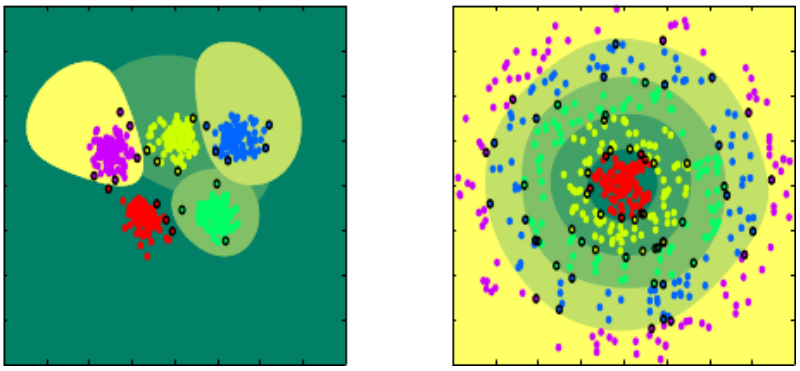


Figure 14. Illustration of the proposed recursive approach for multiclass Support Vector Machine. Colored dots: learning feature samples; Encircled dots: computed support vectors; Colored areas: computed class regions. Left: classical example; Right: concentric example.

5.4. Modeling

5.4.1. Tracking Growing Axons in Fluorescent Microscopy Images

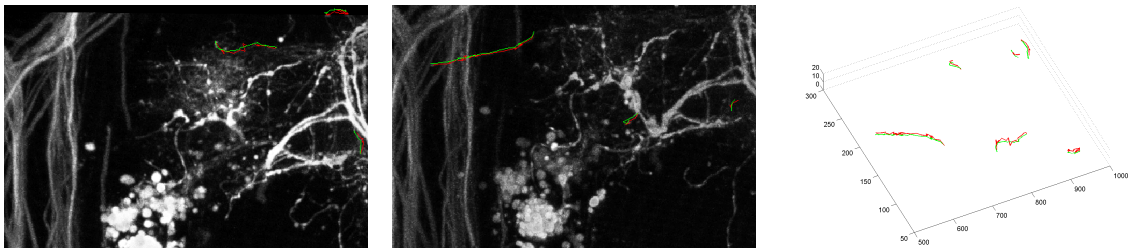
Participants: Huei Fang Yang, Florence Besse, Xavier Descombes.

This work has been done in collaboration with Caroline Medioni from iBV.

Analyzing how growing axons correctly reach their target neurons is essential for biologists to better understand the development of a nervous system. Analysis of the properties of axon growth requires detecting axonal tips and tracking their trajectories within complex and large data sets. When performed manually, the tracking task is arduous and time-consuming. To this end, we proposed a tracking method, based on the particle filtering technique, to follow the traces of axonal tips that appear as small bright spots in the $3D + t$ fluorescent two-photon microscopy images exhibiting low signal-to-noise ratios (SNR) and complex background. Our tracking method uses multiple dynamic models in the proposal distribution to predict the positions of the growing axons. Moreover, it incorporates object appearance, motion characteristics of the growing axons, and filament information in the computation of the observation model. The integration of these three sources results in improved accuracy of recovered trajectories. The experimental results obtained from the microscopy images, presented in Figure 15, showed that the proposed method can successfully estimate trajectories of growing axons, demonstrating its effectiveness even under the presence of noise and complex background.

5.4.2. Trajectory Simulation of Growing Axons:

Participants: Huei Fang Yang, Florence Besse, Xavier Descombes.



(a) (b) (c)

Figure 15. Visual comparison between the tracking results of the proposed method and the manually created ground truth in 2D and 3D. The red trajectories are produced by the proposed method, and the green are the ground truth manually created by the expert; both are overlaid on the MIPs (a) and (b) and visualized in 3D (c). The computer generated tracks are consistent with the ground truth in general, with minor differences between the estimated positions and the ground truth positions. The differences are caused by the noise and by the effect of complex background.

This work has been done in collaboration with Caroline Medioni from iBV.

It is established in biology that axons reach their target cells in the developing nervous system by the guidance of molecular gradients. To better understand how growing axons react to the molecular cues, either attractant or repellent, we simulated the trajectories of growing axons using a mathematical model that investigates the effect of molecular gradients on the axon's growth angle. Figure 16 shows the simulated trajectories of 50 growing axons. The initial position of axons is $(0, 0)$, and the red point on the right denotes the target cell that secretes the attractant cue.

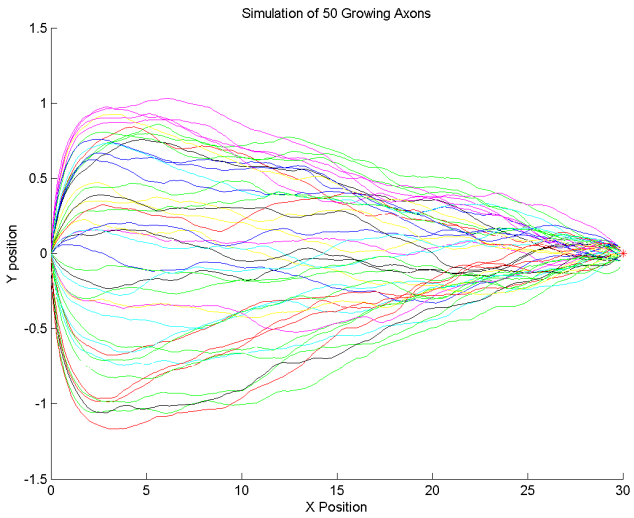


Figure 16. Simulated trajectories of 50 growing axons. The initial position of 50 axons is set to $(0, 0)$, and the red point on the right represents the target cell that secretes the attractant cue.

6. Bilateral Contracts and Grants with Industry

6.1. Bilateral Contracts with Industry

6.1.1. Galderma Sophia-Antipolis

Participants: Sylvain Prigent, Xavier Descombes.

Contribution of multi and hyperspectral imaging to skin pigmentation evaluation. Contract #4383.

In collaboration with Joisane Zerubia from Ayin team.

6.2. Bilateral Grants with Industry

6.2.1. CNES Toulouse and TAS Cannes

Participants: Mikael Carlavan, Laure Blanc-Féraud.

Optimization of the compression-restoration chain for satellite images.

7. Partnerships and Cooperations

7.1. National Initiatives

7.1.1. LABEX SIGNALIFE

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

7.1.2. ARC DADA

Participants: Xavier Descombes [PI], Florence Besse, Huei Fang Yang, Alejandro Mottini.

The DADA project (Description et Analyse Dynamique de la Croissance Axonale) is a common projet with the SERPICO team from Inria Bretagne (Charles Kervrann). The goal is to develop new computational techniques to track axons during their growth. We consider 4D data obtained on a bi-photons microscope. In a longer term, we expect to model the morphological develpement of axons in different populations to characterize some disorders such as the fragile-X symdrom. (DADA).

7.1.3. ANR DIAMOND

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

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).

(DIAMOND)

7.1.4. ANR MOTIMO

Participants: Laure Blanc-Féraud, Xavier Descombes, Eric Debreuve, Huei Fang Yang, Clarens Caraccio.

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

7.1.5. 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.

7.1.6. Inria Large-scale initiative Morphogenetics

Participants: Grégoire Malandain, Xavier Descombes.

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.

7.1.7. PEPII 1

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

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

7.1.8. PEPII 2

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

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

7.1.9. Informal collaboration

Participant: Eric Debreuve.

- Partners: Barbara André, Mauna Kea Technologies, Paris, France
- Subject: Automatic classification of endomicroscopic videos

7.2. International Research Visitors

7.2.1. Visits of International Scientists

- Roberto Cavicchioli, PhD student, University de Modena and Reggio Emilia. Visting period 01/04/2012 - 30/06/2012; MAEE Research grant.
- Alexandre Dufour, Pasteur Institute, Unité d'Analyse d'Images Quantitative CNRS URA 2582 "Interactions et dynamique cellulaires". 3 december 2012, seminar at I3S.
- Caroline Fonta, CerCo, Toulouse, 7 december 2012, seminar at iBV.
- Charles Deledalle, Ceremade, Paris Dauphine, 3 august 2012, seminar at I3S.

8. Dissemination

8.1. Scientific Animation

- Florence Besse was reviewer for UPMC, AFM, DFG (grant agencies).

- Laure Blanc-Féraud was reviewer for IEEE Trans on Signal processing, Inverse Problems, Signal Image and Video processing (Eurasip) and the conferences IEEE ISBI, IEEE ICIP, IEEE ICASSP. She is associate editor for "Revue Traitement du Signal". She was co-organisor of the workshop on New Computational Methods in Inverse Problems - NCMIP 2012 (NCMIP) and was associate editor for the conferences : RFIA 2012, Workshop MIA 2012, Workshop NCMIP 2012, International conference IEEE ISBI 2013. She is member of the IEEE BISP (Biomedical Imaging Signal Processing) Technical Committee, member of the evaluation committee of the ANR, program blanc SIMI3, member of the scientific council of Institute INS2I of CNRS, member of bureau du comité des projets Inria SAM and supplant member of CNECA (Comité National des Enseignants Chercheurs en Agriculture). She is director of GdR ISIS of CNRS
- Xavier Descombes was reviewer for the conference ISBI 2012 and the journals IEEE TMI, IEEE IP $\cdots$ He 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 and associate member of IEEE BISP (Biomedical Imaging Signal Processing) Technical Committee.
- Saima Ben Hadj was reviewer for Signal Image and Video Processing.
- Eric Debreuve was member of the Program Committee of Advanced Concepts for Intelligent Vision Systems (ACIVS) 2012 and member of the Technical Program Committee of European Signal Processing Conference (EUSIPCO) 2012. He was reviewer for *IEEE* Transactions on Image Processing, *Springer* Machine Vision and Applications, *Springer* Multimedia Tools and Applications, *Lavoisier* Revue Traitement du Signal.
- Grégoire Malandain was a member of the Local Organizing Committee of the International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI'12) in Nice. He was also a member of the review committee of International Conference on Pattern Recognition (ICPR'12) and the International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI'12). He is member of the Scientific Committee of the MIA department of INRA.

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

License : Alejandro Mottini, Informatique générale, 24 heures équivalent TD , niveau L1, UNS, France

License : Alejandro Mottini, Introduction au web, 16 heures équivalent TD , niveau L1, UNS, France

Master : Mikael Carlavan, Traitement Numérique des Images, 10 heures équivalent TD , niveau M2, UNS, France

Master : Alejandro Mottini, Outils Mathematiques pour l'Image, 2 heures équivalent TD , niveau M2, UNS, France

Master : Xavier Descombes, Analyse d'image, 12 heures équivalent TD , niveau M2, UNS EPU, France

Master : Xavier Descombes, Traitement d'images, 6,25 heures équivalent TD , niveau M2, ISAE, France

Master : Xavier Descombes, Reconnaissance de formes et analyse de données, 6,25 heures équivalent TD , niveau M2, ISAE, France

Master : Xavier Descombes, Techniques avancées en signal et image, 5 heures équivalent TD , niveau M2, ISAE, France

Master : Xavier Descombes, Imagerie numérique, 16 heures équivalent TD , niveau M2, UNS, France

Master : Laure Blanc-Féraud, Deconvolution and denoising for confocal microscopy, 18heqTD, niveau M2, université de Nice Sophia Antipolis, France.

Master : Laure Blanc-Féraud, Traitement numérique des images, 12eqTD, niveau M2, université de Nice Sophia Antipolis, France.

Master : Laure Blanc-Féraud, Imagerie numérique, 12eqTD, niveau M2, université de Nice Sophia Antipolis, France.

Master : Eric Debreuve, Introduction to Inverse Problems in Image Processing, 28.5 Eq. TD, Niveau M2, Université de Nice-Sophia Antipolis, France.

Master: Eric Debreuve, Basics of Image Processing, 17.5 Eq. TD, Niveau M2, Université de Nice-Sophia Antipolis, France.

Master: Alexis Zubiolo, Digital Image Processing, 10h Eq. TD, Université de Nice-Sophia Antipolis, France.

Licence: Alexis Zubiolo, Computer Science, Introduction to Computer Science, 19h Eq. TD, Université de Nice-Sophia Antipolis, France.

8.2.2. Supervision

HdR : Florence Besse, Régulation des ARNms et Morphogenèse axonale chez la drosophile, soutenue le 19 octobre 2012.

PhD : Sylvain Prigent, Apport de l'imagerie multi et hyperspectrale pour l'évaluation de la pigmentation de la peau, UNS, soutenue le 11 novembre 2012, Xavier Descombes (advisor), Josiane Zeruria, Inria CRI-SAM (co-advisor)

PhD in progress : Alejandro Mottini, Métriques de graphes pour la caractérisation des axones, depuis octobre 2011, Xavier Descombes (advisor), Florence Besse (co-supervisor).

PhD in progress : Mikale Carlavan, Optimization of the compression-restoration chain for satellite images, Laure Blanc-Féraud (advisor) M. Antonini, I3S (co-advisor).

PhD in progress, Saima Ben Hadj, Blind restoration of space variant 3D confocal microscopic images, Laure Blanc-Féraud (advisor).

PhD in progress, Roberto Cavicchioli, fast gradient method for hyperparameter estimation in wavelet regularization inverse problems in imaging, Laure Blanc-Féraud (co-advisor during 3 months).

PhD in progress, Alexis Zubiolo, Statistical Machine Learning for Automatic Cell Classification, Eric Debreuve (advisor).

8.2.3. Juries

HDR : Florence Besse, referee of a Habilitation committee at Univ. Paris 11

PhD : Florence Besse, referee of a PhD committee committee at UMPMC, Villefranche sur mer

PhD : Xavier Descombes, referee of the PhD thesis committee of Sylvain Prigent, UNS

PhD : Xavier Descombes, reviewer of the PhD thesis committee of Marcello Pereyra, ENSEEIHT

PhD : Xavier Descombes, reviewer of the PhD thesis committee of Pauline Julian, ENSEEIHT

PhD : Xavier Descombes, reviewer of the PhD thesis committee of Guillaume Zinck, Univ. Bordeaux 1

PhD : Laure Blanc-Féraud, referee of the PhD committee of Raphaël Soulard, XLIM.

HDR : Laure Blanc-Féraud, reviewer of the Habilitation of Thomas Rodet, University Paris Sud.

HDR : Laure Blanc-Féraud, reviewer of the Habilitation of Jérôme Gilles, ENS Cachan.

PhD : Grégoire Malandain, reviewer of the PhD thesis committee of V. Bismuth (Paris-Est University)

PhD : Grégoire Malandain, reviewer of the PhD thesis committee of P. Chassignet (École Polytechnique)

PhD : Grégoire Malandain, reviewer of the PhD thesis committee of C. Person (Lorraine University),

PhD : Grégoire Malandain, reviewer of the PhD thesis committee of G. Pizaine (Telecom ParisTech),

HDR : Grégoire Malandain, reviewer of the Habilitation committee of J. Debayle (Saint-Étienne University),

PhD : Grégoire Malandain, referee of the medicine thesis of M. Laffon (Nice University).

8.3. Popularization

Xavier Descombes has given a conference at lycée René Char (Avignon) within the program “Science au Lycée”

Xavier Descombes has given a seminar at “journée Traitement d’images” organized by Optitec at LSI Luminy (Marseille)

Xavier Descombes has given a seminar at "Matinale des Pôles" organized by the foundation of Sophia Antipolis

9. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] F. BESSE. *Régulation des ARNms et Morphogenèse axonale chez la drosophile*, Université de Nice Sophia-Antipolis, October 2012, HDR.

[2] S. PRIGENT. *Apport de l’imagerie multi et hyperspectrale pour l’évaluation de la pigmentation de la peau*, Université de Nice Sophia-Antipolis, November 2012, http://hal.inria.fr/tel-00764831.

Articles in International Peer-Reviewed Journals

[3] C. BENEDEK, X. DESCOMBES, J. ZERUBIA. *Building Development Monitoring in Multitemporal Remotely Sensed Image Pairs with Stochastic Birth-Death Dynamics*, in "IEEE Transactions on Pattern Analysis and Machine Intelligence", January 2012, vol. 34, n^{o} 1, p. 33-50 [*DOI :* 10.1109/TPAMI.2011.94], http://hal.inria.fr/hal-00730552.

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[9] S. BEN HADJ, L. BLANC-FÉRAUD. *Depth-variant image restoration in 3D fluorescence microscopy: two approaches under Gaussian and Poissonian noise conditions*, in "IEEE International Symposium on Biomedical Imaging (ISBI)", Barcelone, Spain, May 2012, http://hal.inria.fr/hal-00684983.

[10] S. BEN HADJ, L. BLANC-FÉRAUD. *Modeling and removing depth-variant blur from 3D fluorescence microscopy*, in "International Conference on Acoustics, Speech, and Signal Processing (ICASSP)", Kyoto, Japan, March 2012, http://hal.inria.fr/hal-00684975.

[11] L. BLANC-FÉRAUD. *ML estimation of hyperparameters in inverse problems with wavelet regularisation*, in "Workshop Optimization Techniques for Inverse Problems II", Modena, France, September 2012, http://hal.inria.fr/hal-00766745.

[12] M. BREUILLY, G. MALANDAIN, N. AYACHE, J. DARCOURT, T. POURCHER, P. FRANKEN. *Simulated breath-hold reconstruction in micro-SPECT: application to peritoneal metastases expressing NIS as reporter gene*, in "2012 SNM Annual Meeting", Miami Beach, United States, May 2012, http://hal.inria.fr/hal-00759962.

[13] M. CARLAVAN, L. BLANC-FÉRAUD, M. ANTONINI, C. THIEBAUT, C. LATRY, Y. BOBICHON. *A satellite imaging chain based on the Compressed Sensing technique*, in "On-Board Payload Data Compression Workshop", Barcelone, Spain, October 2012, http://hal.inria.fr/hal-00748523.

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[18] M. BREUILLY, G. MALANDAIN, J. DARCOURT, T. POURCHER, P. FRANKEN. *Prise en compte du mouvemenmt respiratoire du petit animal pour la reconstruction 3D temps synchronisé : application aux métastases*

péritonéales, in "50ème Colloque de Médecine Nucléaire de Langue Française", Montpellier, France, April 2012, http://hal.inria.fr/hal-00759954.

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[20] X. DESCOMBES. *Interacting Adaptive Filters for Multiple Objects Detection*, in "Mathematical Methods for Signal and Image Analysis and Representation", L. FLORACK, R. DUITS, G. JONGBLOED, M.-C. VAN LIESHOUT, L. DAVIES (editors), Computational Imaging and Vision, Springer, 2012, vol. 41, p. 221-239 [*DOI :* 10.1007/978-1-4471-2353-8_13], http://hal.inria.fr/hal-00669582.

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