IN PARTNERSHIP WITH:
CNRS

Université Nice - Sophia Antipolis

Activity Report 2014

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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Laure Blanc-Féraud [CNRS, Senior Researcher, HdR]
Eric Debreuve [CNRS, Researcher, HdR]
Xavier Descombes [Team leader, Inria, Senior Researcher, HdR]
Grégoire Malandain [Inria, Senior Researcher, HdR]
Caroline Medioni [CNRS, Researcher, 20%]
Sébastien Schaub [CNRS, IR, 20%]

Engineer

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Sonia Chaibi [visitor in Jan-Feb 2014]
Gaël Michelin [Inria]
Alejandro Mottini [PhD defended Oct the 30th]
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Jane Desplanques [Inria, on maternity leave from Nov 2014]
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Others

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2. Overall Objectives

2.1. Overall Objectives

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

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

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

3. Research Program

3.1. Research Program

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

1. what are the parameters and the factors controlling the establishment of ramified structures? (Are they really organize to ensure maximal coverage? How are 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 Software and Platforms

4.1. New Software

4.1.1. Stracking

This software is developed within the ANR project MOTIMO. It allows to segment and track spermatozoons from confocal microscopy image sequences [12]. It has been transferred to IFMT, one of our partner of MOTIMO.

4.2. Platforms

4.2.1. Biological Image Platform (PIB)

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

5. New Results

5.1. Highlights of the Year

- Laure Blanc-Féraud was General Program chair of the conference IEEE ISBI 2014 in Beijing.

5.2. Sparse 3D reconstruction in fluorescence imaging

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

Sparse reconstruction Super-resolution microscopy techniques allow to overstep the diffraction limit of conventional optics. Theses techniques are very promising since they give access to the visualisation of finer structures which is of fundamental importance in biology. In this work we deal with Multiple-Angle Total Internal Reflection Microscopy (MA-TIRFM) which allows reconstructing 3D sub-cellular structures of a single layer of $\sim 300\ nm$ behind the glass coverslip with a high axial resolution. The 3D volume reconstruction from a set of 2D measurements is an ill-posed inverse problem and requires some regularization. Our aim in this work is to propose a new reconstruction method for sparse structures that is robust to Poisson noise and background fluorescence. The sparse property of the solution can be seen as a regularizer using the ℓ_0-norm. Let us denote $\mathrm{f} \in \mathrm{R}^N$ the unknown fluorophore density, then the problem states as

$$\widehat{\mathrm{f}} = \arg\min_{\mathrm{f}\in\mathrm{R}^N} \left(\mathrm{J}_d(\mathrm{f}) + \lambda\|\mathrm{f}\|_0\right) \tag{1}$$

where J_d is defined from the likelihood function of the observation given f, $\lambda > 0$ is a weight parameter and $\|\cdot\|_0$ denotes the ℓ_0-norm (which counts the number of nonzero components of f). In order to solve this combinatorial problem, we propose a new algorithm based on a smoothed ℓ_0-norm allowing minimizing the non-convex energy (1). Following [20], the idea is to approach the ℓ_0-norm by a suitable continuous function depending on a positive parameter and tending to the ℓ_0-norm when the parameter tends to zero. Then the algorithm solves a sequence of functionals which starts with a convex one (on a large convex set) and introduce progressively the non-convexity of the ℓ_0-norm (Graduated Non Convexity approach). Figure 1 shows the accuracy of the method on a simulated membrane.

Axial profile calibration In order to turn on real sample reconstructions we need to perform a calibration of the TIRF microscope. Its principle is based on an evanescent wave with an exponential theoretical decay. However this decay is generally not a pure exponential in practice and we need to have a good knowledge about it. Then based on a phantom specimen of known geometry (bead) we are working on a method to estimate experimentally/numerically this decay profile and calibrate all parameters of the system.

5.3. Penalty analysis for sparse solutions of underdeterminated linear systems of equations

Participants: Emmanuel Soubies, Laure Blanc-Féraud, Gilles Aubert.

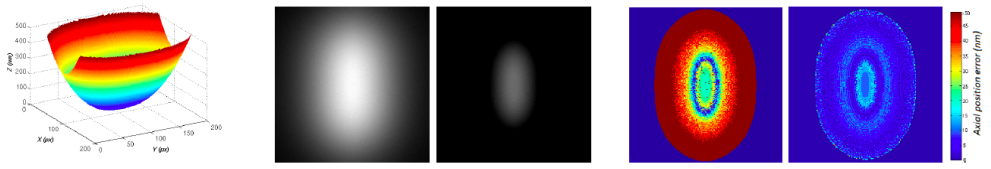

Figure 1. From left to right: Simulated membrane, Microscope acquisition (numerical simulations) with two different incident angles. The two images on the right represent position errors (nm) in the axial direction of the reconstructed membrane obtained with different algorithms: Richardson-Lucy algorithm without regularization (left) and our algorithm with $\lambda = 0.001$ *(right).*

In many applications such as compression to reduce data storage, compressed sensing to recover a signal from fewer measurements, source separation, image decomposition and many others, one aims to compute a sparse solution of an underdetermined linear systems of equations. Thus finding such sparse solutions is currently an active research topic. This problem can be formulated as a least squares problem regularized with the ℓ_0-norm. We consider the penalized form

$$\widehat{\mathrm{x}} = \arg\min_{\mathrm{x}\in \mathrm{R}^N} \left(\frac{1}{2}\|A\mathrm{x} - d\|^2 + \lambda \|\mathrm{x}\|_0 \right) \tag{2}$$

where $A \in \mathrm{R}^{M\times N}$, $d \in \mathrm{R}^M$ represents the data and $\lambda > 0$ is an hyperparameter characterizing the trade-off between data fidelity and sparsity.

It is well known that reaching a global solution of this $\ell_2 - \ell_0$ functional is a NP-hard combinatorial problem. Besides the non-convexity of this 'norm', its discontinuity at zero makes the minimization of the overall functional a hard task. In this work we focus on non-convex continuous penalties widely used to approximate the ℓ_0-norm which usually lead to better results than the classical ℓ_1 convex relaxation since they are more 'ℓ_0-like'. Based on some results in one dimension, we propose the Exact ℓ_0 penalty (El0). In one dimension and when the matrix A is orthogonal, replacing the ℓ_0-norm in (2) by this penalty gives the convex hull of the overall function. Then we have proved, for any matrix $A \in \mathrm{R}^{M\times N}$, that the global minimizers of the ℓ_2- El0 objective function are the same as for the $\ell_2 - \ell_0$ functional. We also demonstrate that all the local minimizers of this approximated functional are local minimizers for $\ell_2 - \ell_0$ while numerical experiments show that the reciprocal is in general false and that the objective function penalized with El0 admits less local minimizers than the $\ell_2 - \ell_0$ functional. Then, this work provides in some way an equivalence between the initial $\ell_2 - \ell_0$ problem and its approximation using the El0 penalty. One can address problem (2) by replacing the ℓ_0-norm with the El0 penalty which provides better properties for the objective function although the problem remains non-convex. Recently, some authors have proposed algorithms and proved their convergence to critical points of non-smooth non-convex functionals like ℓ_0-El0. Based on such algorithms, we propose a macro algorithm and prove its convergence to a (local) minimizer of the initial $\ell_2 - \ell_0$ functional.

5.4. Motion compensation in two-photon microscopy temporal series

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

Acquisitions of 3D image sequences over long period of time, in particular, have enabled neurobiologists to follow complex processes such as the development of neuronal populations or degenerative events occurring in pathological contexts, improving our understanding of the mechanisms involved in brain development and function. In most cases, live samples are moving/growing during long-term imaging. Therefore it is required to compensate for this global 3D motion before measuring the dynamics of the structure of interest. We have proposed a method to compute a coherent 3D motion over a whole temporal sequence of 3D volumes (Figure 2), which is able to capture subtle sub-voxelic displacements.

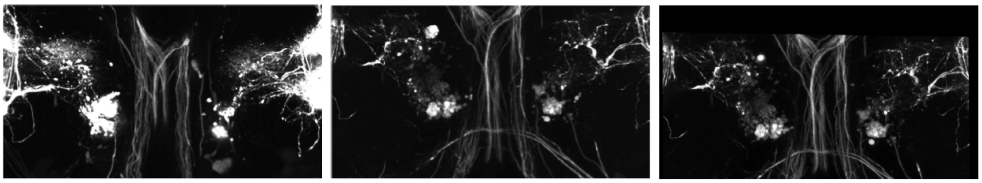

Figure 2. Left and middle: mip views of both the first and the last volumes of a temporal series. Right: mip view of the last volume after motion compensation.

5.5. Axon Growth Imaging and Modeling

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

The modeling part of this work has been made in collaboration with S. Komech, E. Pechersky and E. Zhizhina from IITP (Russian Academy of Science)

In Drosophila brain, at metamorphosis, Mushroom Body gamma neurons undergo axonal remodeling characterized by a pruning of larval branches followed by regrowth and branching/arborization of adult processes. Axonal regrowth at this stage is essential to consolidate the adult brain and its success is determined by the trajectories followed by the axons and their branches. These trajectories depend on both extracellular guidance signals, and on a complex internal molecular machinery capable to read these signals and act in consequence. F. Besse's team at the IBV Institute has identified genes involved in this regrowth and branching processes [19]. A better understanding of the role of these genes will help to unravel the molecular mechanisms behind these fundamental processes, and lead to a better understanding of the neuronal morphology in both healthy and pathological conditions.

During this PhD project, mathematical and computational tools will be developed to characterize and compare the axonal regrowth and branching dynamics. Different populations of regrowing gamma axons will be considered (i.e. wild type and presenting mutations in relevant genes). The study will be based on both static 3D confocal images of axonal trees, and two-photon in vivo 4D image sequences showing either a single GFP positive regrowing axon or the entire population of regrowing gamma axons marked with GFP. In a first part we have begun to collect data. This includes three parts: i) fly stock maintenance, crossing and selection; ii) sample preparation consisting in pupal brain dissection, medium preparation and sample final assembly; iii) imaging: using different microscopy techniques, eg.confocal/two-photon, microscopy and light sheet microscopy, and acquisition of 4D image sequences. Thanks to an imaging technique developed by C. Medioni in F. Besse's laboratory, we have been able to monitor axonal regrowth and branching at early steps in individual neurons, and to follow them for about 15 hours using the two-photon microscope. These movies will be used in the future to develop the mathematical modeling of axonal regrowth/branching process (see figure 3). Our early works concerning modeling have consisted in investigating some models based on continuous time random walks and characterizing the main axon branch through topological entropy [8] [22].

5.6. Markov Chain for Axon Growth Modeling

Participants: Alejandro Mottini, Xavier Descombes, Florence Besse.

In this work we have defined a 2D discrete stochastic model for the simulation of axonal biogenesis [8]. The model is defined by a third order Markov Chain. The model considers two main processes: the growth process that models the elongation and shape of the neurites and the bifurcation process that models the generation of branches. The growth process depends, among other variables, on the external attraction field generated by a chemoattractant molecule secreted by the target area.

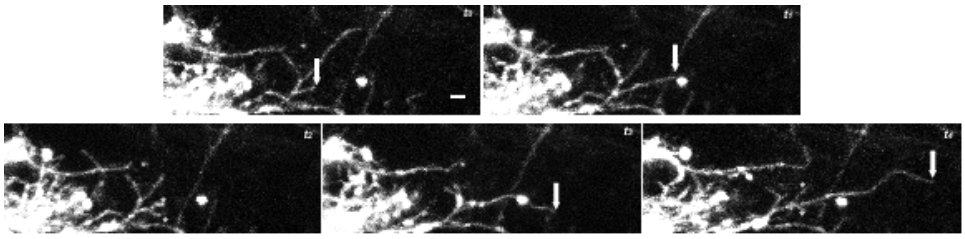

Figure 3. Images extracted from a movie recorded on a two-photon microscope (maximum intensity projection): single axon at the regrowing stage within Drosophila brain. Axons are marked with GFP. t0-t1: elongation step, t2: retraction and branching event, t3: elongation and t4: elongation and branching step. Arrows shows axonal tips and asterisks, the formation of branches. Scale bars for each image: 10μm.

For the validation, we have fluorescently labeled single neurons within intact adult Drosophila fly brains, and have acquired 3D fluorescent confocal microscopy images of their axonal trees. Both normal neurons and neurons in which the function of the imp (mutant type 1) or profilin (mutant type 2) genes was inactivated were imaged. imp encodes a conserved RNA binding protein controlling subcellular mRNA transport and local protein synthesis, and is essential for axonal remodeling. profilin encodes a regulator of the actin cytoskeleton involved in axonal pathfinding. Mutations in these two conserved genes have been linked to neurological pathologies.

Each image stack has a resolution of $0.093967 \times 0.093967 \times 0.814067 \mu m$ and two channels. The morphology of single axonal trees is visible in the first channel and was manually segmented by an experienced biologist. The morphology of the overall neuronal structure in which axons are developing is visible in the second channel. In total, 53 images (18 normal, 21 type 1 mutant and 14 type 2 mutant) were used. In order to study the attraction field of the populations, all stacks were registered against the first image of the normal population. This was performed using the second channel of each image.

We then have estimated the model parameters to generate two fields for each population, a scalar field that represents the axon flexibility and a vector field that represents the attraction field. Since we obtain some estimates on a sparse set of points in the x, y plane, we extrapolate the fields using a Gaussian Markov Random Field. By qualitatively analyzing the resulting images we have determined that there is no relevant difference on the attraction field between the three populations. We have observed that the field points towards the target area and that its norm is stronger at the starting point of the axons and weaker near the target area, which is consistent with biological expectations. The same procedure was used to analyze the difference on the scalar fields for each population (see Figure 4). In this case we can detect a significant difference between the populations.

5.7. Cells detection using segmentation competition

Participants: Emmanuelle Poulain, Emmanuel Soubies, Sylvain Prigent, Xavier Descombes.

Image segmentation has been widely investigated in particular in the context of bioimaging for cells detection. In some cases, the background is clearly identifiable so that a binary mask of the objects can be computed using simple techniques such as thresholding. Therefore, isolated objects are easily recognizable while splitting clusters of objects, which are connected components in the binary mask, remains a challenging task. In fluorescent microscopy devices used for live imaging – *e.g.* confocal, biphoton, Selective Plane Illumination Microscope (SPIM) – an additional difficulty comes from the multiple degradations of the acquired images such as strong noise, spatially varying blur and light attenuation which makes the segmentation a hard task even for selecting a suitable threshold for the background. Since many years, researchers have developed

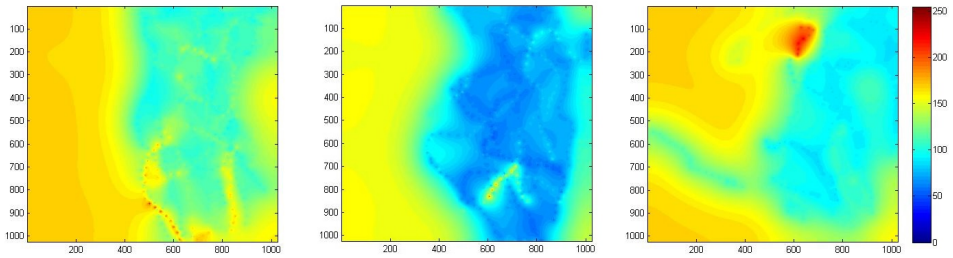

Figure 4. Markov Chain parameter scalar field for the normal (left), mutant type 1 (middle) and mutant type 2 (right) populations.

several methods to perform such segmentation. An efficient approach consists in generating seeds that define regions using geometric information through a distance, as in the markers controlled watershed algorithm [21], or image gradient for the active contour approach. These approaches give accurate results providing the seeds are well chosen that is still an open issue. Bayesian approaches, such as marked point process, avoid this bottleneck by selecting randomly generated shapes through the minimization of an energy function. However, they are restricted to low dimensional parametric shapes, such as disks or ellipses, due to computational issues. Tuning the parameters of the segmentation algorithms mentioned above in order to obtain accurate results on the whole image can also be extremely tricky whereas it is much easier to obtain accurate results on different parts of the image using different sets of parameters. To overcome these limits we propose to combine both approaches by generating shapes from state of the art segmentation algorithms using random seeds and/or different sets of parameters. These shapes define a dictionary of candidates from which a competition process, using the Multiple Birth and Cut algorithm, extracts the most relevant shapes. We have validated this selection approach on synthetic data and on a multicellular tumor spheroide slice by comparing the obtained results with two different state of the art segmentation methods to build the dictionary of shapes and compare the performance of our competition approach with the ImageJ particle analyser (see figure 5).

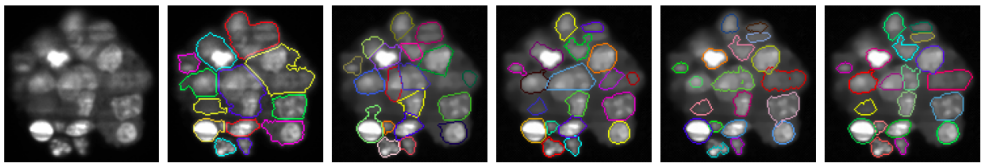

Figure 5. Spheroids of tumor cells stained with a fluorescent nuclear marker (top line left). Fiji Particle Analyzer result (top line right). Results of our approach with dictionary generated by RS-SKIZ with 800 repetitions and a threshold value fixed to 70 (middle line left) MTRS-SKIZ with 80 repetitions and 10 different thresholds (middle line right) MPRS-FM with 100 repetitions and 8 different values for the Fast Marching parameter used to stop the expansion (bottom line left), concatenation of MTRS-SKIZ and MPRS-FM dictionaries (bottom line right).

5.8. Graph cut and attractive interactions

Participants: Tarun Yellamraju, Emmanuel Soubies, Sylvain Prigent, Xavier Descombes.

Marked point processes have proved to be very efficient for segmenting a collection of objects from digital images. The multiple birth and death algorithm provides an optimization framework that allows reasonable time computation. This algorithm has to be embedded in a simluated annealing framework which involves parameters tuning (initial temperature and cooling scheme). This tedious task can be overcame considering a graph cut algorithm instead of the death step. The algorithm then consists in successively adding new random objects in the configuration and selecting the most relevant using the graph cut algorithm. In the graph construction a node is associated to each object. Unfortunately, the regularity condition imposed by the graph cut prevents to consider attractive interactions such as clustering or alignment constraints, which restricts the model to repulsive properties such as non overlap between objects. To overcome this restriction we have investigated new graph constructions by considering nodes defined by clusters of interacting objects. Different strategies have been compared to avoid being tracked in local minima defined by clusters while minimizing the number of required iterations. First results have been obtained on a seeds detection problem (see figure 6).

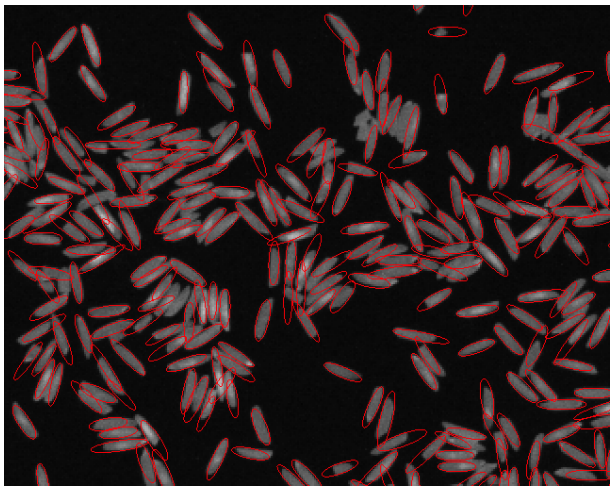

Figure 6. Rice seeds detection using a marked point processes and a birth and cut algorithm (Rice image has been given by Alpha MOS and LAAS-CNRS).

5.9. Cell-to-cell ascidian embryo registration

Participants: Gaël Michelin, Grégoire Malandain.

This work is made in collaboration with Léo Guignard and Christophe Godin (Virtual Plants) and Patrick Lemaire (CRBM), within the Morphogenetics Inria Project Lab.

Recent microscopy techniques allow imaging temporal 3D stacks of developing organs or embryos with a cellular level of resolution and with a sufficient acquisition frequency to accurately track cell lineages. Imaging multiple organs or embryos in different experimental conditions may help to decipher the impact of genetic backgrounds and environmental inputs on the developmental program. For this, we need to precisely compare distinct individuals and to compute population statistics. The first step of this procedure is to develop methods to register individuals.

From a previous work of cell segmentation from microscopy images [6], we propose an approach to extract the Left-Right symmetry plane of embryos at early stages (Figure 7). Then we use the symmetry information to both register these embryos at a similar developmental stage and obtain a cell-to-cell mapping. We assessed

the symmetry plane extraction on more than 100 images from 10 individuals between 32-cells and late-neurula development stage. The cell-to-cell registration was performed on 5 distinct individuals at 64-cells and 112-cells stage (Figure 8).

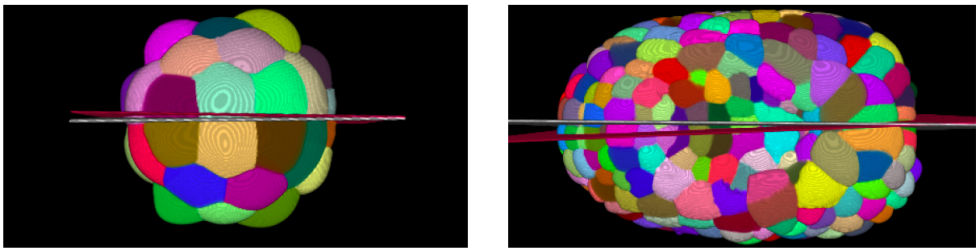

Figure 7. Left-Right symmetry plane initialization (red) and final estimation (white) on (left) a 32-cells stage embryo and (right) a neurula stage embryo.

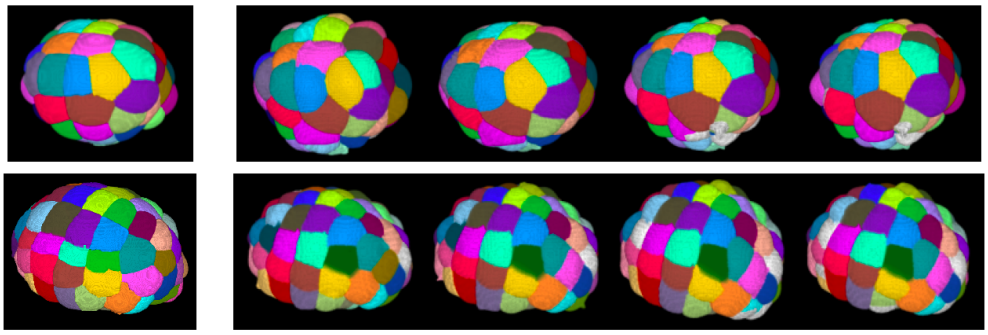

Figure 8. Cell-to-cell mapping between reference image (left) and test images (right) at 64-cells stage (first line) and at 112-cells stage (last line). The reference images are taken from the same individual, the test images are taken at different time-points of a second individual. On the test images, white cells are those that have not been matched to a reference cell.

5.10. Quantitative comparison of micro-vasculatures

Participants: Manon Linder, Grégoire Malandain.

This work is made in collaboration with Cécile Duplaa and Thierry Couffinhal (INSERM).

Angiogenesis is a key component of ontogenesis, but also of tumor development or in some pathology repair (i.e. ischemia). Deciphering the underlying mechanisms of vessel formation is of importance. We aimed at identifying and characterizing the genetic components that are involved in this development. This requires to compare the effect of each gene with respect to the others, hence appeals for quantitative comparisons. We developed a methodology that first transforms a vascular image into a tree and second quantitatively analyze 3D vascular trees (see Figure 9) We conduct real experiments with images of the renal arterial network of different mutant mice, through the development of quantitative measurements that allow for group study.

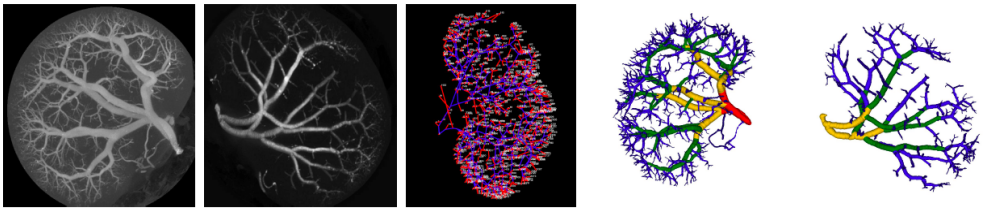

Figure 9. From left to right: two mip views of mouse kidneys acquired with a micro-CT (control and Fzd4 & Fzd6 KO mouse); a labeled tree built from an image; Diameter-defined Strahler classification of arterial trees.

5.11. Pre-clinical molecular dynamic image analysis: 99mTc- pertechnetate biodistribution model of murine stomach with micro-SPECT

Participants: Marine Breuilly, Grégoire Malandain.

This work is jointly conducted with Thierry Pourcher, Jacques Darcourt, Philippe Franken, Kaouthar Chatti, and Philippe Pognonec from the Transporter in Imagery and Oncologic Radiotherapy team (TIRO, CEA-CAL-UNSA).

This project investigates the potential retention of iodide in the stomach, for a better understanding of the iodide biodistribution in the body and more precisely of its potential antiseptic role. To that end, we study the uptake of the ^{99m}Tc-pertechnetate (an iodide analog) within the murine stomach observed thanks to a SPECT camera. Using the coupled SPECT and CT device dedicated to small animals, functional information targeted by a specific radiotracer (^{99m}Tc-pertechnetate) can be imaged dynamically.

The temporal evolution of the uptake is analysed thanks to a dedicated multi-compartment model. The addressed challenges consist in 1) estimating the time-activity curves for the different compartments, and 2) identifying the model parameters.

- ^{99m}-pertechnetate is an iodide analog regarding to the NIS gene. Thus iodide uptake kinetics can be studied through the study of ^{99m}Tc- pertechnetate biodistribution.
- Dynamic SPECT images exhibit a progressive accumulation of ^{99m}Tc-pertechnetate in the stomach wall and diffusion in the stomach cavity.
- The workflow that has been previously proposed in [18] was tested on a larger dataset of five subjects, yielding promising results: The computed model parameters are coherent, and the computed parameter values suggested that there is some iodide retention in the stomach wall.
- A comparison of the dedicated method for extraction of time activity curves with the ones extracted with Pixies software is on-going.
- A comparison of the dedicated method for solving the inverse problem of the compartmental analysis with methods developed by the Turku PET Centre is on-going.

5.12. Massal motility measures to automatically predict fertility scores

Participants: Ana Rita Lopes Simoes, Eric Debreuve.

This work has been done in the scope of the ANR project MOTIMO. We developed a method for automatic scoring of sperm samples in order to predict fertility for the farming industry. The method was applied to samples from rams and goats. A given sample is a video composed of a hundred frames (see Fig. 10).

We analyzed video samples acquired according to four modalities or protocols: drop, chamber, fluorescent beads with a 4x zoom, and fluorescent beads with 10x zoom. Two options have been considered. (1) An optical flow method has been applied to the videos in order to estimate the apparent motion of the seminal fluid (see Fig. 10). Some statistical features of interest (such as entropy) were extracted from the obtained motion fields in order to characterize the sperm massal motility. (2) The second option consisted of tracking the beads on the 4x or the 10x fluorescence videos (see Fig. 10). Some features of interest were also extracted from the resulting bead trajectories. Then using either of these feature sets (obtained with options (1) and (2)), a regression analysis (linear and kernel SVM) was conducted on a subset of the available videos (the learning set) so as to define a prediction function taking features as input and outputting a fertility score. The scores computed by this function were compared to scores assigned by experts. We used the coefficient of determination (commonly denoted by R^2) as a performance measure of the learned prediction function. The best results were obtained using tracking on the ram videos showing fluorescent beads with a 4x zoom ($R^2 = 0.9$). The results on the goat videos were not as satisfying ($R^2 \simeq 0.65$), but the partner providing the videos expressed some concerns about the quality of the acquisition campaign for these data.

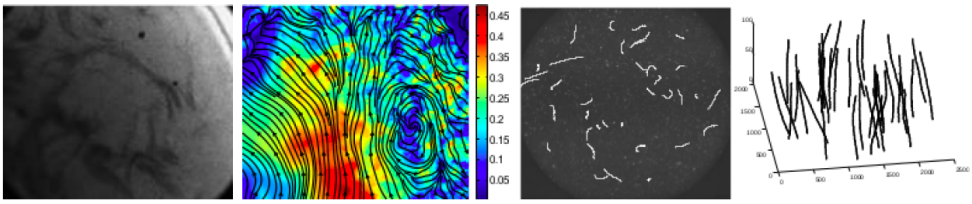

Figure 10. Predicting fertility based on massal motility measures. (Left) One frame of a video for the "drop" modality; (Middle) An example of computed optic flow; (Right: image+plot) An example of bead trajectories.

5.13. Sample selection for SVM learning on large data sets

Participants: Sonia Chaibi, Xavier Descombes, Eric Debreuve.

Support Vector Machines (SVM) represent a popular framework of supervised learning. However, it is not well adapted to large data sets since learning is performed by an optimization procedure involving the whole data set. Yet, in the end, only a small subset of the samples (the so-called support vectors) is retained for prediction. Of course, efficient algorithms exist. Still, it can be interesting to filter out as many samples as possible (the ones that will surely not be part of the support vectors) before initiating the learning procedure.

Sonia Chaibi, a PhD student from UBMA, Algeria, visited the team for a month to collaborate on this subject. The method relies on successive unsupervised sample clustering steps. After each clustering, the homogeneity of the clusters in terms of sample class assignment is used to decide which samples are unlikely to be close to the separation hyperplane (and hence unlikely to be selected as support vectors), and which samples are apparently close to this hyperplane. The former ones can be discarded, thus reducing greatly the number of samples to be processed by the SVM algorithm, while the latter ones are kept, preserving the precision of the separation hyperplane as much as possible.

5.14. Morphological Analysis and Feature Extraction of Neurons from Mouse Cortices Multiscale 3D Microscopic Images

Participants: Alexis Zubiolo, Xavier Descombes, Eric Debreuve.

This work is jointly conducted with Kawssar Harb and Michèle Studer (iBV).

We propose a framework to analyze the morphology of mouse neurons in the layer V of the cortex from 3D microscopic images. We are given 8 sets of images, each of which is composed of a 10x image showing the whole neurons, and a few (2 to 5) 40x images focusing on the somas. The framework consists in segmenting the neurons on both types of images to compute a set of specific morphological features, and in establishing the correspondence between the neurons to combine the features we obtained, in a fully automatic fashion. On the 10x images, we use a multiple birth and cut algorithm to segment the sections of the apical dendrites. Merging these intersections provides the localization of the first branching of the apical dendrite (see Fig. 11 (left)). On the 40x images, we compute an hysteresis threshold to obtain a first segmentation (somas and dendrites starts) and apply iterative morphological operators to reconstruct the full dendrites (see Fig. 11 (middle)). The correspondence map between the two types of images is done using a bipartite graph matching model that associates each neuron configuration of a 40x image – a constellation – to a subset of neurons in the 10 image – the galaxy – (see Fig. 11 (right)).

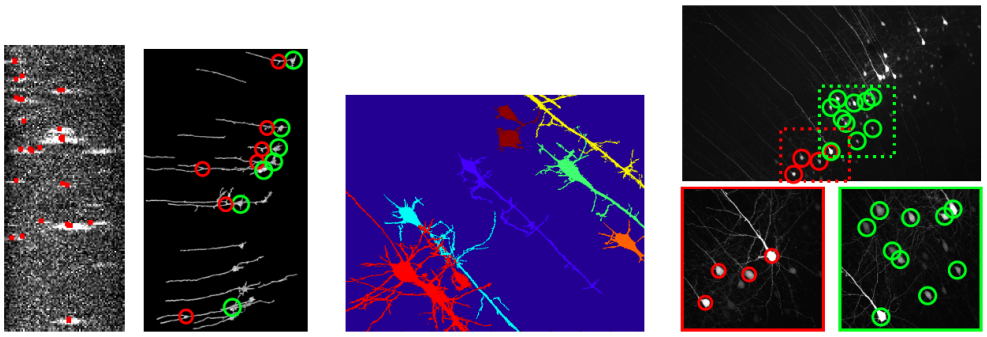

Figure 11. Left: neuron segmentation on the 10x image. Middle: full neuron reconstruction from the 40x image. Right: 10x-40x image maching.

5.15. Whole-Slide Image Analysis of Renal Cell Carcinoma

Participants: Ana Rita Lopes Simoes, Eric Debreuve, Alexis Zubiolo, Xavier Descombes.

This work is jointly conducted with Thierry Pourcher, and Philippe Pognonec (TIRO, CEA-CAL-UNSA), and Damien Ambrosetti (CHU, Nice).

We study histology images of kidney cancer that present different subpopulations of cells (tumor, healthy tissue, stroma, fat, blood, ...). The goal is to analyze the images to help determine the cancer type and stage. Given the resolution of the images ($0.25\mu m$) that leads to very large images (around 100k$\times$100k pixels), a multiscale approach has been considered. At a larger scale, we focus on the cellular architecture and the vascular networks. Regions of interest (ROIs) have been detected with a pixelwise clustering based on neighborhood features (see Fig. 12 (left)). At a smaller scale, we extract more precise information from the cells (nucleus and cytoplasm sizes, shapes and colors, ...). The nuclei of the cells have been segmented using an Hessian determinant-based method (see Fig. 12 (middle)) which enables us to establish statistics about their size. Information on the vascular arborization has been extracted with a Frangi vesselness followed by a cleaning and gap filling post-processing (see Fig. 12 (right)).

6. Partnerships and Cooperations

6.1. Regional Initiatives

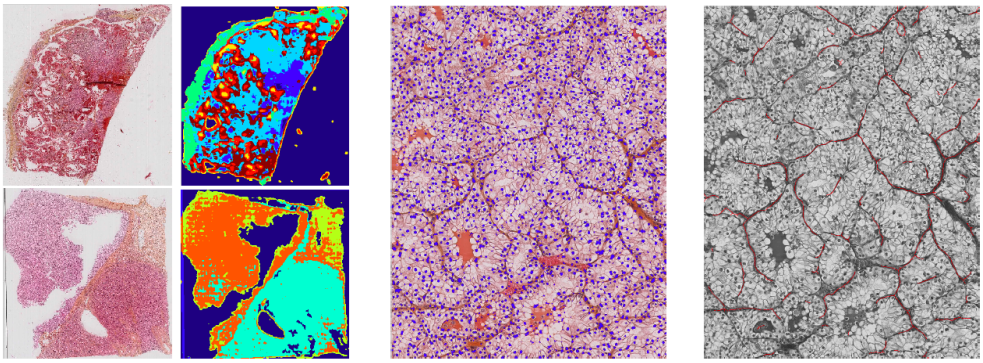

Figure 12. ROI detection (left), Nuclei segmentation in blue (middle) and Vascular arborization extraction in red (right)

- iBV, "Genetics of mouse brain development" (Michèle Studer 's group): morphological analysis of neurons within the layer V of mice cortex
- TIRO group (CEA, UNS, Lacassagne center): histopathology analysis
- TIRO group (CEA, UNS, Lacassagne center): dynamics of iodin in the stomachal wall

6.2. National Initiatives

6.2.1. LABEX SIGNALIFE

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

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

Florence Besse and Grégoire Malandain participated in the selection committee for LabeX PhD programme students.

6.2.2. 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)

6.2.3. 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.

6.2.4. ANR DIG-EM

Participants: Grégoire Malandain, Xavier Descombes.

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

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

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

6.2.5. ANR PhaseQuant

Participants: Grégoire Malandain, Eric Debreuve.

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

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

6.2.6. 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.

6.3. International Initiatives

6.3.1. Participation In other International Programs

We have obtained a CNRS/RAS project between IITP Moscow (S. Komech, E. Pechersky and E. Zhizhina) and Morpheme team (X. Descombes, A. Razetti).

6.4. International Research Visitors

6.4.1. Visits of International Scientists

Elena Zhizhina, Evgueny Pechersky and Serguei Komech from IITP Moscow (Russian Academy of Science) was invited one week in november.

Sonia Chaibi, PhD student at Badji Mokhtar-Annaba University (Algeria) has visited the Morpheme team during two months (january-february).

6.4.1.1. Internships

Tarun Yellamraju : IIT Bombay, Bachelor. Marked poiont process, graph cut and attractive interactions. Supervisors: X. Descombes.

6.4.2. Visits to International Teams

Xavier Descombes has visited the IITP in Moscow during one week in july within a CNRS/RAS program.

7. Dissemination

7.1. Promoting Scientific Activities

7.1.1. Scientific events organisation

7.1.1.1. general chair, scientific chair

Laure Blanc-Féraud was General Program chair of the conference IEEE ISBI 2014 in Beijing.

7.1.1.2. member of the organizing committee

Eric Debreuve was member of the organizing committees of ICIP 2014 (International Conference on Image Processing) as Area chair and of EUSIPCO 2015 (European Signal Processing Conference) as Area chair.

Xavier Descombes was member of organization board for the "OPTITECH Event 2015".

7.1.2. Scientific events selection

7.1.2.1. responsable of the conference program committee

Laure Blanc-Féraud was General Program chair of the conference IEEE ISBI 2014 in Beijing.

7.1.2.2. member of the conference program committee

Eric Debreuve was member of program committee of RFIA 2014 (congrès national sur la Reconnaissance des Formes et l'Intelligence Artificielle).

Xavier Descombes was associated editor for the conference ICIP 2014.

Laure Blanc-Féraud was associate editor of the workshop on New Computational Methods in Inverse Problems - NCMIP 2014 (NCMIP) in ENS Cachan.

Grégoire Malandain was an associate editor for the conference ISBI 2015.

7.1.2.3. reviewer

Eric Debreuve was reviewer for ISBI 2014 (International Symposium on Biological Imaging).

Xavier Descombes was reviewer for ISBI 2014, ICIP 2014 ,ICASSP 2014.

Laure Blanc-Féraud was reviewer the conferences ISBI 2014, ICIP 2014 ,ICASSP 2014.

7.1.3. Journal

7.1.3.1. member of the editorial board

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

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

7.1.3.2. reviewer

Eric Debreuve was reviewer for IEEE Transactions on Medical Imaging, Journal of Mathematical Imaging and Vision (Springer), Journal of Computational Physics (Elsevier), Pattern Recognition (Elsevier).

Xavier Descombes was reviewer for IEEE TMI, IEEE IP, ...

7.1.4. Scientific animation

Xavier Descombes is associated member of IEEE BISP (Biomedical Imaging Signal Processing), member of the Scientific Committee of the competitivness pole Optitech, expert for the MESR within the CIR program. He was in the jury of a MdC recruitment jury in Paris V and in the committee for Transverse master fellowship at Inria CRI-SAM.

Laure Blanc-Féraud is director of GdR 720 ISIS of CNRS. She is member of the IEEE BISP (Biomedical Imaging Signal Processing) Technical Committee, she is member of the scientific steering committee of ANR for Defi 7 on "société de l'information et de la communication), she was part of the group of the SNR (national research strategy) for defining the strategy of the MENESR concerning the défi 7, she was member of the scientific council of Institute INS2I of CNRS, invited member of the scientific council of Institute INSIS of CNRS (till september 2014), member of "bureau du comité des projets" Inria SAM (till july 2014). 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). She is part of the evaluation committee of ONERA DTIM department. She is expert member of the Italian Ministry for Education.

Grégoire 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. From september the 1st, he is the head of the committee "Comité de suivi doctoral" of the Inria CRI-SAM.

7.2. Teaching - Supervision - Juries

7.2.1. Teaching

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

DUT: Marine Breuilly, Télécommunications: Initiation à la mesure du signal, 64h Eq. TD, niveau DUT 1ère année, IUT de Nice Côte d'Azur , France

DUT: Marine Breuilly, Acquisition et codage de l'information, 6h Eq. TD, niveau DUT 1ère année, IUT de Nice Côte d'Azur , France

Master: Eric Debreuve, Inverse problems in image processing, 28.5h Eq. TD, master 2, Université de Nice Sophia Antipolis, France.

Master: Eric Debreuve, Basis of image processing, 13h Eq. TD, master 2, 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, Universitéde Nice Sophia Antipolis, France.

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

Master : Xavier Descombes, Support Vector Machines, 3h Eq. TD, Niveau M2, ENSHEEIT, France.

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

Master: Emmanuel Soubies, Imagerie Numérique, 6h Eq.TD, Master 2 ISAB, Université de Nice Sophia Antipolis, France.

Licence: Emmanuel Soubies, Images et Filtres, 54h Eq.TD, Niveau L3 , EPU, Université de Nice Sophia Antipolis, France.

Master: Caroline Medioni, Microscopie appliquée à la biologie, 20h Eq. TD, Niveau M2, Université de Nice Sophia Antipolis, France.

License: Caroline Medioni, Microscopy and Cell Biology courses, 20h, Niveau L3, Université de Nice Sophia Antipolis, France.

License: Alexis Zubiolo, Introduction to Computer Science, 18h Eq. TD, L1, Université de Nice Sophia Antipolis, France.

License: Alexis Zubiolo, Web Programming, 48h Eq. TD, L1, Université de Nice Sophia Antipolis, France.

7.2.2. Supervision

PhD: Alejandro Mottini, Axon Morphology Analysis: from Image Processing to Modelling, Nice Sophia Antipolis university, defended october the 30th, Xavier Descombes (advisor), Florence Besse (co-supervisor).

PhD in progress: Lola Baustista, Fluorescence confocal microscopy image restoration, 1st november 2013, Laure Blanc-Féraud.

PhD in progress: Gaël Michelin, Quantitative tools for morphogenesis study, 1st october 2013, Grégoire Malandain (advisor).

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

PhD in progress: Emmanuel Soubies, MA-TIRF reconstruction, 1st october 2013, Laure Blanc-Féraud and Sébastien Schaub.

PhD in progress, Alexis Zubiolo, Statistical Machine Learning for Automatic Cell Classification, 1st october 2012, Eric Debreuve (advisor).

7.2.3. Internships

Manon Linder: 4th year of Institut Supérieur des BioSciences, Quantitative comparison of micro-vasculatures, Supervisor: G. Malandain.

Emmanuelle Poulain: M1 Paris VI. Image segmentation using graph cut and MPP. Supervisor: X. Descombes.

7.2.4. Juries

Florence Besse participated as referee to the PhD thesis committee of Alejandro Mottini (Nice Sophia Antipolis university)

Laure Blanc-Féraud participated as chair to the PhD thesis committee of A. Drogoul (JAD of UNS), as reviewer of the HDR of Hervé Carfantan (Toulouse University) and PhD thesis of Makhlad Chahid (Bordeaux university).

Eric Debreuve participated as reviewer to the PhD thesis committee of A. Emilien (Bordeaux university)

Xavier Descombes was in the jury of A. Mottini PhD defense at University of Nice Sophia Antipolis. He was reviewer for two PhD dissertation in France (S. Rigaud at Rennes University and J. Gul Mohammed at Paris VI university) and for one PhD dissertation in England (D. Nam at Bristol University).

Grégoire Malandain participated as chair to the PhD thesis committee of J. Legrand (ENS Lyon), as reviewer to the PhD thesis of G. Brunel (Montpellier 2 univ.), and as reviewer to the HdR of F. Rousseau (Strasbourg univ.).

7.2.5. Participation to workshops, conferences, seminars, invitations

- Florence Besse made an oral presentation on "Imp promotes axonal remodeling by regulating profilin mRNA during brain development" during the EMBO workshop on neuronal remodeling (March 2014, Ein-Gedi, Israel).
- Caroline Medioni made an oral presentation on "mRNA transport and axonal remodeling" during the Neuronal network days (June 2014, Paris, Institut du Fer à Moulin)
- Caroline Medioni made an oral presentation on "Live imaging of mRNA transport and axonal remodeling using two photon microscopy" during the Journée CoRéBio in Marseille (November 2014, CIML, Luminy).
- Caroline Medioni and Grégoire Malandain organized a pratical on "Imaging axonal regrowth: from data acquisition to image treatment" during the microscopy school MIFOBIO (October 2014, Seignosse, France).
- Grégoire Malandain gave a lecture on "registration methods for multimodal imaging" during the microscopy school MIFOBIO (October 2014, Seignosse, France).
- Grégoire Malandain gave a lecture on "Towards population studies in embryogenesis: a cell-to-cell mapping method for ascidian embryos" at a Colloquium Centre Blaise Pascal-Laboratoires Joliot-Curie (november 2014, ENS, Lyon).

7.3. Popularization

Eric Debreuve was invited to give a presentation for the seminar series "Café-in", Inria CRI SA-M, November 2014.

8. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] A. MOTTINI. *Axon Morphology Analysis: from Image Processing to Modelling*, Universite de Nice Sophia-Antipolis (UNS), September 2014, https://hal.inria.fr/tel-01074620

Articles in International Peer-Reviewed Journals

[2] S. BEN HADJ, L. BLANC-FÉRAUD, G. AUBERT. *Space Variant Blind Image Restoration* *, in "SIAM Journal on Imaging Sciences", 2014, vol. 7, pp. 2196 - 2225 [*DOI :* 10.1137/130945776], https://hal.inria.fr/hal-01096491

[3] A. HABBAL, H. BARELLI, G. MALANDAIN. *Assessing the ability of the 2D Fisher-KPP equation to model cell-sheet wound closure*, in "Mathematical Biosciences", June 2014, vol. 252, 15 p. , https://hal.inria.fr/hal-00923588

[4] A. MOTTINI, X. DESCOMBES, F. BESSE. *From Curves to Trees: A Tree-like Shapes Distance Using the Elastic Shape Analysis Framework*, in "Neuroinformatics", November 2014, 12 p. [*DOI :* 10.1007/s12021-014-9255-0], https://hal.inria.fr/hal-01086777

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[5] L. GUIGNARD, C. GODIN, U.-M. FIUZA, L. HUFNAGEL, P. LEMAIRE, G. MALANDAIN. *Spatio-temporal registration of embryo images*, in "ISBI - International Symposium on Biomedical Imaging", Pekin, China, IEEE, April 2014, https://hal.inria.fr/hal-00919142

[6] G. MICHELIN, L. GUIGNARD, U.-M. FIUZA, G. MALANDAIN. *Embryo Cell Membranes Reconstruction by Tensor Voting*, in "ISBI - International Symposium on Biomedical Imaging", Beijing, China, IEEE, April 2014, https://hal.inria.fr/hal-00915000

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[14] G. MICHELIN, L. GUIGNARD, U.-M. FIUZA, P. LEMAIRE, C. GODIN, G. MALANDAIN. *Cell Pairings for Ascidian Embryo Registration*, in "ISBI - International Symposium on Biomedical Imaging", New York, United States, April 2015, https://hal.inria.fr/hal-01113166

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