Activity Report 2017

Project-Team SERPICO

Space-timE RePresentation, Imaging and cellular dynamics of molecular COmplexes

RESEARCH CENTER
Rennes - Bretagne-Atlantique

THEME
Computational Biology

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Project-Team SERPICO

Creation of the Team: 2010 January 01, updated into Project-Team: 2013 July 01

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1. Personnel

Research Scientists

Charles Kervrann [Team leader, Inria, Senior Researcher, HDR]

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Sylvain Prima [Inria, Researcher, Visiting scientist]

Faculty Member
Frédéric Lavancier [Univ de Nantes, Associate Professor, until Aug 2017, HDR]

PhD Students
Vincent Briane [Inria, granted by Inria & ENSAI-CREST, until Nov 2017]
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Yunjiao Lu [INRA, INRA grant, from Oct 2017]
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Sandeep Manandhar [Inria, CORDI-S grant]
Emmanuel Moebel [Inria, granted by Fourmentin-Guilbert & Région Bretagne]
Juan Manuel Perez Rua [Technicolor, granted by CIFRE, until Jan 2018]
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Interns
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Thibaut Dubois [Inria, from Jun 2017 until Aug 2017]
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Léo Maczyta [Inria, from Mar 2017 until Jul 2017]

Administrative Assistant
Huguette Bechu [Inria]

2. Overall Objectives

2.1. Glossary

FLIM (Fluorescence Lifetime Microscopy Imaging): imaging of fluorescent molecule lifetimes.
PALM (Photo-Activated Localization Microscopy): high-resolution microscopy using stochastic photo-activation of fluorophores and adjustment of point spread functions [38].
SIM (Structured Illumination Microscopy): high-resolution light microscopy using structured patterns and interference analysis [42].
TIRF (Total Internal Reflectance): 2D optical microscopy using evanescent waves and total reflectance [37].
Cryo-EM (Cryo-Electron Tomography): 3D representation of sub-cellular and molecular objects of 5-20 nanometres, frozen at very low temperatures, from 2D projections using a transmission electron microscope.

2.2. Scientific context and motivations

During the past two decades, biological imaging has undergone a revolution in the development of new microscopy techniques that allow visualization of tissues, cells, proteins and macromolecular structures at all levels of resolution, physiological states, chemical composition and dynamics. Thanks to recent advances in optics, digital sensors and labeling probes (e.g., Colored Fluorescence Protein), one can now visualize subcellular components and organelles at the scale of several hundreds of nanometers to a few dozens nanometers. As a result, fluorescent microscopy and multimodal imaging (fluorophores at various wavelengths) have become the workhorse of modern biology. All the technological advances in microscopy have created new issues and challenges for researchers in quantitative image processing and analysis. Since the digital processing is now part of the imaging loop, image processing may even drive imaging. A brilliant example of this shift in paradigm is super-resolution localization microscopy (PALM, STED), which was awarded the 2014 Nobel Prize in Chemistry.

2.3. Challenges in biological image processing and quantitative microscopy

In most cases, modern microscopy in biology is characterized by a large number of dimensions that fit perfectly with the complexity of biological features: two or three spatial dimensions, at macro to nano-scales, and one temporal dimension, sometimes spectrally defined and often corresponding to one particular biomolecular species. Dynamic microscopy is also characterized by the nature of the observable objects (cells, organelles, single molecules, ...), by the large number of small size and mobile elements (chromosomes, vesicles, ...), by the complexity of the dynamic processes involving many entities or group of entities sometimes interacting, by particular phenomena of coalescence often linked to image resolution problems, finally by the association, dissociation, recomposition or constitution of those entities (such as membrane fusion and budding). Thus, the corpus of data to be considered for any analysis involving multiple image series acquisitions is massive (up to few GigaBytes per hour). Therefore, it becomes necessary to facilitate and rationalize the production of those multidimensional data, to improve post acquisition analysis, and to favor the organization and the interpretation of the information extracted from this data corpus. It motivates innovative methods and concepts for data fusion, image registration, super-resolution, data mining... More importantly, modern microscopy has led to recent breakthroughs, related to the potential interactions between molecules in the cell. A long-term research consists now in inferring the relationships between the dynamics of macromolecules and their functions. Research on computational biology and quantitative bioimaging lies at the core of the activities of Serpico team.

2.4. Objectives of Serpico in cell imaging

In order to tackle the aforementioned challenges, the Serpico team aims to develop innovative approaches and paradigms for image reconstruction, 3D molecule tracking and motion estimation, and biophysical parameter estimation to face the huge data volumes acquired with cutting-edge microscopy set-ups. To this end, applied mathematics, image processing and analysis have to be considered in association with biophysics and biology. To be successful, a sustained synergy between all these scientific domains is necessary. To improve state-of-the-art methods and solve important problems in computational bioimaging, the members of Serpico especially address the following topics:

- Image restoration/reconstruction motivated by preserving cell integrity (photo-toxicity versus exposure time) and image analysis in multidimensional microscopy;
- Motion analysis and computation of molecule trajectories in live-cell imaging to study molecular interactions in space and time;
- Computational simulation, modelling and estimation of molecule trafficking and interactions at different spatial and temporal scales.

The resulting mathematical models and algorithms will help biologists to decipher molecular processes in fundamental biology and will be exploited for health applications: disease diagnosis, detection of genomic instabilities, deterioration of cell cycle, cancer prevention.

We have successfully developed statistical and variational aggregation methods for image denoising and optical flow, and elaborated powerful methods for image colocalization, diffusion estimation, trajectory estimation-classification, and multimodal registration. An additional issue was the design and distribution of software tools for the biological image analysis and microscopy communities. Finally, the team has focused on the cellular and molecular mechanisms involved in molecule and protein transport and trafficking at the scale of a single cell. Our contributions are detailed in the next sections along three research axes.

2.5. Organization and collaborations

In collaboration with UMR 144 CNRS-Institut Curie (“Space Time imaging of Endomembranes and organelles Dynamics” team) and PICT-IBiSA (Cell and Tissue Imaging Facilities), the members of the Serpico team have participated in several projects (PhD and post-doc supervision, contracts...) in the field of cell biology and microscopy. We have promoted non-parametric methods since prior knowledge cannot be easily taken

into account for extracting unattended but desired information from image data. We have also proposed user-friendly algorithms for processing 2D and 3D image sequences. The projects of Serpico were in line with several studies led in the UMR 144 CNRS-Institut Curie Unit. A subset of studies was related to instrumentation in electronic and photonic microscopy (PICT-IBiSA platform) including computational aspects on the reconstruction and enhancement of images related to sub-diffraction light microscopy and multimodal approaches. Serpico projects relied partially on the advances of these instrumental projects and a positive synergy was established.

3. Research Program

3.1. Statistics and algorithms for computational microscopy

Fluorescence microscopy limitations are due to the optical aberrations, the resolution of the microscopy system, and the photon budget available for the biological specimen. Hence, new concepts have been defined to address challenging image restoration and molecule detection problems while preserving the integrity of samples. Accordingly, the main stream regarding denoising, deconvolution, registration and detection algorithms advocates appropriate signal processing framework to improve spatial resolution, while at the same time pushing the illumination to extreme low levels in order to limit photo-damages and phototoxicity [7], [6]. As a consequence, the question of adapting cutting-edge signal denoising and deconvolution, object detection, and image registration methods to 3D fluorescence microscopy imaging has retained the attention of several teams over the world.

In this area, the Serpico team has developed a strong expertise in key topics in computational imaging including image denoising and deconvolution, object detection and multimodal image registration. Several algorithms proposed by the team outperformed the state-of-the-art results, and some developments are compatible with "high-throughput microscopy" and the processing of several hundreds of cells. We especially promoted non local, non-parametric and patch-based methods to solve well-known inverse problems or more original reconstruction problems. A recent research direction consists in adapting the deep learning concept to solve challenging detection and reconstruction problems in microscopy. We have investigated convolution neural networks to detect small macromolecules in 3D noisy electron images with promising results. The next step consists in proposing smart paradigms and architectures to save memory and computations.

More generally, many inverse problems and image processing become intractable with modern 3D microscopy, because very large temporal series of volumes (200 to 1000 images per second for one 3D stack) are acquired for several hours. Novel strategies are needed for 3D image denoising, deconvolution and reconstruction since computation is extremely heavy. Accordingly, we will adapt the estimator aggregation approach developed for optical flow computation to meet the requirements of 3D image processing. We plan to investigate regularization-based aggregation energy over super-voxels to reduce complexity, combined to modern optimization algorithms. Finally, we will design parallelized algorithms that fast process 3D images, perform energy minimization in few seconds per image, and run on low-cost graphics processor boards (GPU).

3.2. From image data to motion descriptors: trajectory computation and dynamics analysis

Several particle tracking methods for intracellular analysis have been tailored to cope with different types of cellular and subcellular motion down to Brownian single molecule behavior. Many algorithms were carefully evaluated on the particle tracking challenge dataset published in the Nature Methods journal in 2014 [8]. Actually, there is no definitive solution to the particle tracking problem which remains application-dependent in most cases. The work of Serpico in particle motion analysis is significant in multiple ways, and inserts within a very active international context. One of the remaining key open issues is the tracking of objects with heterogeneous movements in crowded configurations. Moreover, particle tracking methods are not always adapted for motion analysis, especially when the density of moving features hampers the individual extraction

of objects of interest undergoing complex motion. Estimating flow fields can be more appropriate to capture the complex dynamics observed in biological sequences. The existing optical flow methods can be classified into two main categories: i/ local methods impose a parametric motion model (e.g. local translation) in a given neighborhood; ii/ global methods estimate the dense motion field by minimizing a global energy functional composed of a data term and a regularization term.

The Serpico team has developed a strong expertise in key topics, especially in object tracking for fluorescence microscopy, optical flow computation and high-level analysis of motion descriptors and trajectories. Several algorithms proposed by the team are very competitive when compared to the state-of-the-art results, and our new paradigms offer promising ways for molecule traffic quantification and analysis. Amongst the problems that we currently address, we can mention: computation of 3D optical flow for large-size images, combination of two frame-based differential methods and sparse sets of trajectories, detection and analysis of unexpected local motion patterns in global coherent collective motion. Development of efficient numerical schemes will be central in the future but visualization methods are also crucial for evaluation and quality assessment. Another direction of research consists in exploiting deep learning to 3D optical flow so as to develop efficient numerical schemes that naturally capture complex motion patterns. Investigation in machine learning and statistics will be actually conducted in the team in the two first research axes to address a large range of inverse problems in bioimaging. Deep learning is an appealing approach since expertise of biologists, via iterative annotation of training data, will be included in the design of image analysis schemes.

3.3. Biological and biophysical models and spatial statistics for quantitative bioimaging

A number of stochastic mathematical models were proposed to describe various intracellular trafficking, where molecules and proteins are transported to their destinations via free diffusion, subdiffusion and ballistic motion representing movements along the cytoskeleton networks assisted by molecular motors. Accordingly, the study of diffusion and stochastic dynamics has known a growing interest in bio-mathematics, biophysics and cell biology with the popularization of fluorescence dynamical microscopy and super-resolution imaging. In this area, the competing teams mainly studied MSD and fluorescence correlation spectroscopy methods.

In the recent period, the Serpico team achieved important results for diffusion-related dynamics involved in exocytosis mechanisms. Robustness to noise has been well investigated, but robustness to environmental effects has yet to be effectively achieved. Particular attention has been given to the estimation of particle motion regime changes, but the available results are still limited for analysing short tracks. The analysis of spatiotemporal molecular interactions from set of 3D computed trajectories or motion vector fields (e.g., co-alignment) must be investigated to fully quantify specific molecular machineries. We have already made efforts in that directions this year (e.g., for colocalization) but important experiments are required to make our preliminary algorithms reliable enough and well adapted to specific transport mechanisms.

Accordingly, we will study quantification methods to represent interactions between molecules and trafficking around three lines of research. First, we will focus on 3D space-time global and local object-based co-orientation and co-alignment methods, in the line of previous work on colocalization, to quantify interactions between molecular species. In addition, given N tracks associated to N molecular species, interaction descriptors, dynamics models and stochastic graphical models representing molecular machines will be studied in the statistical data assimilation framework. Second, we will analyse approaches to estimate molecular mobility, active transport and motion regime changes from computed trajectories in the Lagrangian and Eulerian settings. We will focus on the concept of super-resolution to provide spatially high-resolved maps of diffusion and active transport parameters based on stochastic biophysical models and sparse image representation. Third, we plan to extend the aggregation framework dedicated to optical flow to the problem of diffusion-transport estimation. Finally, we will investigate data assimilation methods to better combine algorithms, models, and experiments in an iterative and virtuous circle. The overview of ultrastructural organization will be achieved by additional 3D electron microscopy technologies.

4. Application Domains

4.1. Modeling and analysis of membrane transport and molecule trafficking at the single cell scale

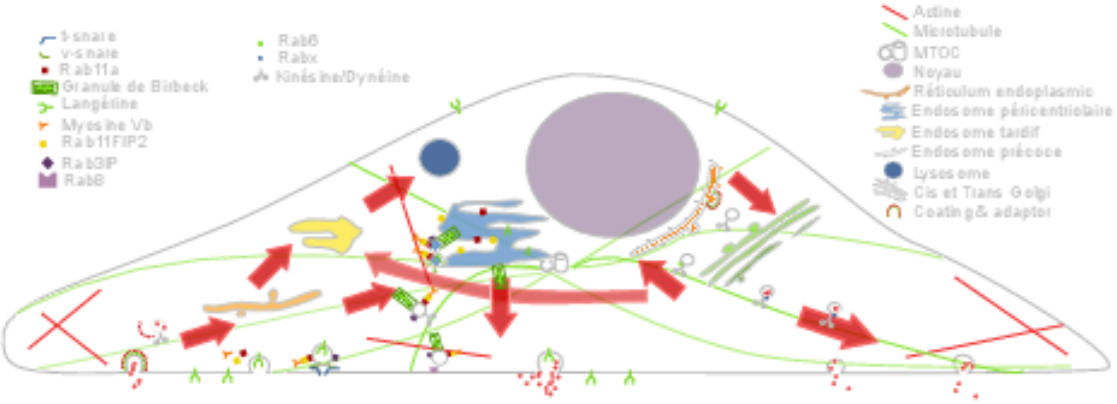

Figure 1. Cargo Langerin Trafficking controlled by Rab11A/Rab11FIP2/MyoVb platform.

In the past recent years, research carried at UMR 144 CNRS-Institut Curie ("Space Time imaging of Endomembranes and organelles Dynamics" team) contributed to a better understanding of the intracellular compartimentation of specialized model cells such as melanocytes and Langerhans cells, the components and structural events involved in the biogenesis of their specialized organelles: melanosomes and Birbeck granules, respectively. These studies have started to highlight: i/ multiple sorting and structural events involved in the biogenesis of these organelles; ii/ complexity of the endo-melanosomal network of these highly specialized cells; iii/ complex molecular architecture organizing and coordinating their dynamics; iv/ intracellular transport steps affected in genetic diseases, among which the Hermansky Pudlak syndrome (HPS) or involved in viral infection (HIV and Langerin in Langerhans cells).

In this context, the central aim of SERPICO is to understand how the different machineries of molecular components involved are interconnected and coordinated to generate such specialized structures. We need to address the following topics:

1. developing new bioimaging approaches to observe and statistically analyze such coordinated dynamics in live material;
2. correlating this statistically relevant spatiotemporal organization of protein networks with the biological architectures and at the ultrastructural level;
3. modeling intracellular transport of those reference biological complex systems and proposing new experimental plans in an iterative and virtuous circle;
4. managing and analyzing the workflow of image data obtained along different multidimensional microscopy modalities.

These studies are essential to unravel the complexity of the endomembrane system and how different machineries evolve together (e.g. see Fig. 1). They help to control cell organization and function at different scales through an integrative workflow of methodological and technological developments.

At long term, these studies will shed light on the cellular and molecular mechanisms underlying antigen presentation, viral infection or defense mechanisms, skin pigmentation, the pathogenesis of hereditary genetic disorders (lysosomal diseases, immune disorders) and on the mechanisms underlying cell transformation. Our methodological goal is also to link dynamics information obtained through diffraction limited light microscopy, eventually at a time regime compatible with live cell imaging. The overview of ultrastructural organization will be achieved by complementary electron microscopical methods. Image visualization and quantitative analysis are of course important and essential issues in this context.

4.2. Imaging and analysis of cytokskeleton dynamics during cell migration

The ability to migrate in space is among the most fundamental functions of eukaryotic cells and thus is one of the best-studied phenomena in biology. During embryonic development, cell movements result in a massive reorganization of the embryo, from a simple spherical ball of cells into a multi-layered organism; many of the cells at or near the surface of the embryo move to a new, more interior location. Moreover, inadequate or inappropriate migration of immune cells is also critically important for the delivery of protective immune responses to tissues and for wound healing. Finally, cell migration may facilitate the dissemination of tumor cells in blood and organs and eventually the formation of secondary tumors and metastases.

It has been established that the cytoskeleton, composed of actin filaments, microtubules and intermediate filaments (elongated structures with a diameter of a few dozens of nanometers), is essential for several cell mechanisms, including cell migration, cell division and molecule trafficking:

i/ the actin filaments promote cell protrusion, adhesion and retraction;

ii/ the microtubules are the support of molecule traffic and cell polarization;

iii/ the intermediate filaments are hypothesized to control microtubule organization.

Nevertheless, the mechanical and chemical states of migrating cells under various external conditions remain largely unknown. In the last decade, high-resolution microscopy methods led to the discovery of novel aspects of cell migration. Most approaches and models are limited to migration in 2D, justified by the flatness of the cell-motile mechanisms. However, the mechanical patterns that govern migration in 2D models are often not essential for efficient migration in 3D. Accordingly, recent very challenging 3D models of cells moving on flat surfaces have begun to emerge. The key challenge, however, is to understand how a 3D motile cell crawls through the 3D extracellular matrix.

The objective of SERPICO is to develop high-end signal processing and computer vision tools to unfold the dynamical coordination of microtubules, actin filaments and intermediate filaments in 3D, involved in cell migration, cell division and molecule trafficking.

5. Highlights of the Year

5.1. Highlights of the Year

The Serpico team will be the organizer of the 7th International Conference on “Quantitative BioImaging” (QBI) in January 2019 (300 attendees) in Rennes.

Juan Manual Perez Ru, Vincent Briane and Hoai-Nam Nguyeen defended their PhD thesis in December 2017.

6. New Software and Platforms

6.1. ATLAS

KEYWORDS: Image segmentation - Object detection - Photonic imaging - Image analysis - Fluorescence microscopy

FUNCTIONAL DESCRIPTION: The ATLAS software enables to detect spots in 2D fluorescence images. The spot size is automatically selected and the detection threshold adapts to the local image contrasts. ATLAS relies on the Laplacian of Gaussian (LoG) filter, which both reduces noise and enhances spots. A multiscale representation of the image is built to automatically select the optimal LoG variance. Local statistics of the LoG image are estimated in a Gaussian window, and the detection threshold is pointwise inferred from a probability of false alarm (PFA). The user only has to specify: i/ size of the Gaussian window, ii/ PFA value. The Gaussian window must be about the size of the background structures, increasing the PFA increases the number of detections.

- Participants: Patrick Bouthemy, Charles Kervrann, Jean Salamero, Jérôme Boulanger and Antoine Basset
- Partner: UMR 144 CNRS - Institut Curie
- Contact: Patrick Bouthemy
- Publication: Adaptive spot detection with optimal scale selection in fluorescence microscopy images
- URL: http://mobyle-serpico.rennes.inria.fr/cgi-bin/portal.py#forms::ATLAS

6.2. C-CRAFT

KEYWORDS: Fluorescence microscopy - Photonic imaging - Image analysis - Detection - 3D - Health - Biology - Segmentation
FUNCTIONAL DESCRIPTION: The C-CRAFT software enables to jointly segment small particles and estimate background in 2D or 3D fluorescence microscopy image sequences. The vesicle segmentation and background estimation problem is formulated as a global energy minimization problem in the Conditional Random Field framework. A patch-based image representation is used to detect spatial irregularity in the image. An iterative scheme based on graph-cut algorithm is proposed for energy minimization.

- Participants: Patrick Bouthemy, Jean Salamero, Charles Kervrann and Thierry Pécot
- Partner: UMR 144 CNRS - Institut Curie
- Contact: Charles Kervrann
- Publication: Background Fluorescence Estimation and Vesicle Segmentation in Live Cell Imaging with Conditional Random Fields
- URL: http://mobyle-serpico.rennes.inria.fr/cgi-bin/portal.py#forms::C-CRAFT

6.3. F2D-SAFIR

KEYWORDS: Biomedical imaging - Photonic imaging - Fluorescence microscopy - Image processing
FUNCTIONAL DESCRIPTION: The F2D-SAFIR software removes mixed Gaussian-Poisson noise in large 2D images, typically 10000 x 10000 pixels, in a few seconds. The method is unsupervised and is a simplified version of the method related to the ND-SAFIR software. The software is dedicated to microarrays image denoising for disease diagnosis and multiple applications (gene expression, genotyping, aCGH, ChIP-chip, microRNA, ...).

- Participant: Charles Kervrann
- Partner: INRA
- Contact: Charles Kervrann

6.4. GcoPS

KEYWORDS: Photonic imaging - Fluorescence microscopy - Image processing - Statistic analysis

FUNCTIONAL DESCRIPTION: The GCOPS (Geo-Co-Positioning System) software is dedicated to the co-localization of fluorescence image pairs for both conventional and super-resolution microscopy. The procedure is only controlled by a p-value and tests whether the Pearson correlation between two binary images is significantly positive. It amounts to quantifying the interaction strength by the area/volume of the intersection between the two binary images viewed as random distributions of geometrical objects. Under mild assumptions, it turns out that the appropriately normalized Pearson correlation follows a standard normal distribution under the null hypothesis if the number of image pixels is large. Unlike previous methods, GcoPS handles 2D and 3D images, variable SNRs and any kind of cell shapes. It is able to co-localize large regions with small dots, as it is the case in TIRF-PALM experiments and to detect negative co-localization. The typical processing time is two milliseconds per image pair in 2D and a few seconds in 3D, with no dependence on the number of objects per image. In addition, the method provides maps to geo-co-localize molecule interactions in specific image regions.

- Participants: Frédéric Lavancier, Thierry Pécot and Liu Zengzhen
- Partners: Université de Nantes - UMR 144 CNRS - Institut Curie
- Contact: Charles Kervrann
- Publication: A Fast Automatic Colocalization Method for 3D Live Cell and Super-Resolution Microscopy
- URL: http://icy.bioimageanalysis.org/plugin/GcoPS

6.5. Hullkground

KEYWORDS: Biomedical imaging - Photonic imaging - Fluorescence microscopy - Image processing
FUNCTIONAL DESCRIPTION: The HullkGround software decomposes a fluorescence microscopy image sequence into two dynamic components: i) an image sequence showing mobile objects, ii) an image sequence showing the slightly moving background. Each temporal signal of the sequence is processed individually and analyzed with computational geometry tools. The convex hull is estimated automatically for each pixel and subtracted to the original signal. The method is unsupervised, requires no parameter tuning and is a simplified version of the shapes-based scale-space method.

- Participants: Anatole Chessel, Charles Kervrann and Jean Salamero
- Partner: UMR 144 CNRS - Institut Curie
- Contact: Charles Kervrann
- URL: http://mobyle-serpico.rennes.inria.fr/cgi-bin/portal.py#forms::Hullkground

6.6. Motion2D

KEYWORDS: Image sequence - Motion model - 2D
FUNCTIONAL DESCRIPTION: The Motion2D software is a multi-platform object-oriented library to estimate 2D parametric motion models in an image sequence. It can handle several types of motion models, namely, constant (translation), affine, and quadratic models. Moreover, it includes the possibility of accounting for a global variation of illumination and more recently for temporal image intensity decay (e.g. due to photobleaching decay in fluorescence microscopy). The use of such motion models has been proved adequate and efficient for solving problems such as optic flow computation, motion segmentation, detection of independent moving objects, object tracking, or camera motion estimation, and in numerous application domains (video surveillance, visual servoing for robots, video coding, video indexing), including biological imaging (image stack registration, motion compensation in videomicroscopy). Motion2D is an extended and optimized implementation of the robust, multi-resolution and incremental estimation method (exploiting only the spatio-temporal derivatives of the image intensity function). Real-time processing is achievable for motion models involving up to six parameters. Motion2D can be applied to the entire image or to any pre-defined window or region in the image.

RELEASE FUNCTIONAL DESCRIPTION: Modifications and improvements in the PNG image file support. Support RAW and Mpeg2 video format as input (see CReader). The available video format which can be handled by the motion estimator are given by CReader::EReaderFormat. For the results, video sequences can be writen using the format specified by CWriter::EWriterFormat. Support Fedora 3 (g++ 3.4.2).

- Participants: Charles Kervrann, Fabien Spindler, Jean Marc Odobez, Patrick Bouthemy and Thierry Pécot
- Contact: Patrick Bouthemy
- URL: http://www.irisa.fr/vista/Motion2D/

6.7. ND-SAFIR

KEYWORDS: Fluorescence microscopy - Photonic imaging - Image analysis - Health - Biomedical imaging
SCIENTIFIC DESCRIPTION: ND-SAFIR is a software for denoising n-dimentionnal images especially dedicated to microscopy image sequence analysis. It is able to deal with 2D, 3D, 2D+time, 3D+time images have one or more color channel. It is adapted to Gaussian and Poisson-Gaussian noise which are usually encountered in photonic imaging. Several papers describe the detail of the method used in ndsafir to recover noise free images (see references).

- Participants: Charles Kervrann, Patrick Bouthemy, Jean Salamero and Jérôme Boulanger
- Partners: INRA - PiCT - UMR 144 CNRS - Institut Curie
- Contact: Charles Kervrann
- URL: http://serpico.rennes.inria.fr/doku.php?id=software:nd-safir:index

6.8. OWF

KEYWORDS: Image filter - Image processing - Statistics
FUNCTIONAL DESCRIPTION: The OWF software enables to denoise images corrupted by additive white Gaussian noise. In the line of work of the Non-Local means and ND-SAFIR algorithms, this adaptive estimator is based on the weighted average of observations taken in a neighborhood with weights depending on the similarity of local patches. The idea is to compute adaptive weights that best minimize an upper bound of the pointwise L2 risk. The spatially varying smoothing parameter is automatically adjusted to the image context. The proposed algorithm is fast and easy to control and is competitive when compared to the more sophisticated NL-means filters.

- Participants: Ion Grama, Quansheng Liu and Qiyu Jin
- Partner: University of Bretagne-Sud
- Contact: Charles Kervrann
- Publication: Non-local means and optimal weights for noise removal
- URL: http://serpico.rennes.inria.fr/doku.php?id=software:owf

6.9. QuantEv

KEYWORDS: Photonic imaging - Fluorescence microscopy - Biomedical imaging - Image analysis - Image sequence - Statistic analysis

FUNCTIONAL DESCRIPTION: The QUANTEV software analyzes the spatial distribution of intracellular events represented by any static or dynamical descriptor, provided that the descriptors are associated with spatial coordinates. QUANTEV first computes 3D histograms of descriptors in a cylindrical coordinate system with computational cell shape normalization, enabling comparisons between cells of different shape. Densities are obtained via adaptive kernel density estimation, and we use the Circular Earth Mover's Distance to measure the dissimilarity between densities associated to different experimental conditions. A statistical analysis on these distances reliably takes into account the biological variability over replicated experiments.

- Participants: Jean Salamero, Jérôme Boulanger and Liu Zengzhen
- Partner: UMR 144 CNRS - Institut Curie
- Contact: Charles Kervrann
- Publication: QuantEv: quantifying the spatial distribution of intracellular events
- URL: http://mobyle-serpico.rennes.inria.fr/cgi-bin/portal.py#forms::QuantEv-Densities

6.10. TMA-Lib

KEYWORDS: Photonic imaging - Fluorescence microscopy - Biomedical imaging - Image processing
FUNCTIONAL DESCRIPTION: The TMA-LIB enables to jointly detect suing adaptive wavelet transform, segment with parametric active contours and restore (i.e., artifact correction and deconvolution) TMA (Tissue MicroArrays) images.

- Participants: Cyril Cauchois, Vincent Paveau and Hoai Nam Nguyen
- Partner: Innopsys
- Contact: Charles Kervrann
- Publications: A variational method for dejittering large fluorescence line scanner images - Generalized Sparse Variation Regularization for Large Fluorescence Image Deconvolution - ATMAD : robust image analysis for Automatic Tissue MicroArray De-arraying

6.11. TOTH

KEYWORDS: Photonic imaging - Fluorescence microscopy - Biomedical imaging - Classification - Statistical categorisation techniques - Statistics - Image sequence - Visual tracking
FUNCTIONAL DESCRIPTION: The TOTH software classifies trajectories of biomolecules computed with tracking algorithms. Trajectories in living cells are generally modelled with three types of diffusion processes: (i) free diffusion, (ii) subdiffusion or (iii) superdiffusion. We used a test approach with the Brownian motion as the null hypothesis, and developed a non-parametric three-decision test whose alternatives are subdiffusion and superdiffusion. First, we built a single test procedure for testing a single trajectory. Second, we proposed a multiple test procedure for testing a collection of trajectories. These procedures control respectively the type I error and the false discovery rate. Our approach can be considered as an alternative to the Mean Square Displacement (MSD) method commonly used to address this issue. It gives more reliable results as confirmed by our Monte Carlo simulations and evaluations on real sequences of images depicting protein dynamics acquired with TIRF or SPT-PALM microscopy.

- Participants: Vincent Briane and Myriam Vimond
- Partner: ENSAI
- Contact: Charles Kervrann
- Publication: A Statistical Analysis of Particle Trajectories in Living Cells
- URL: http://serpico.rennes.inria.fr/doku.php?id=software:thot:index

6.12. Platforms

6.12.1. Mobyle@Serpico plateform and software distribution

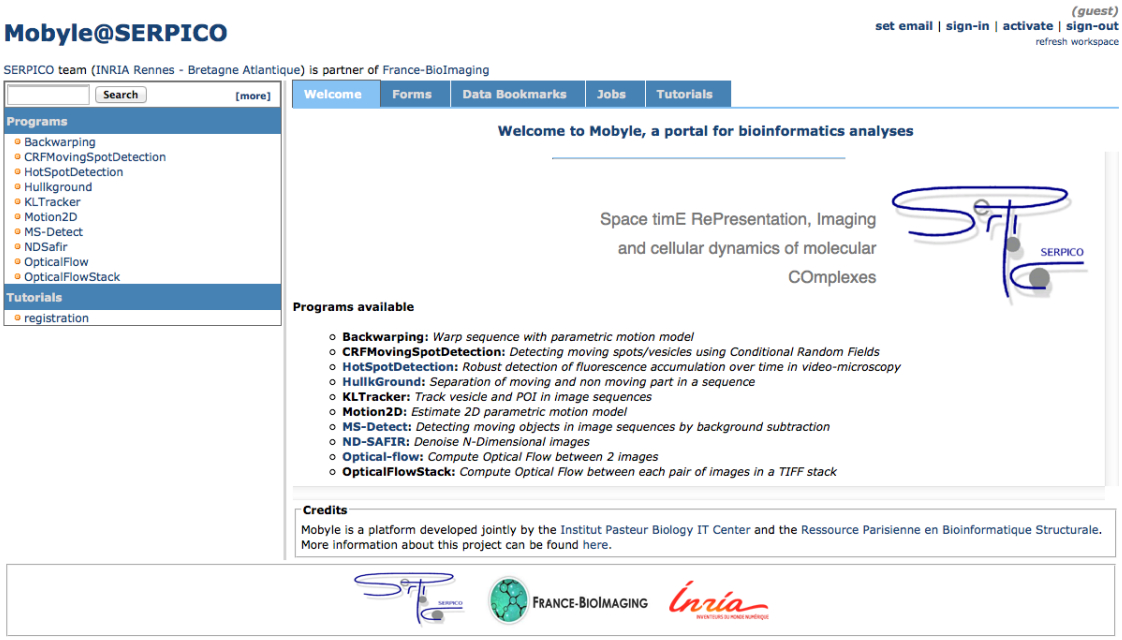

*Figure 2. Mobyle@*SERPICO *web portal.*

The objective is to disseminate the distribution of SERPICO image processing software in the community of cell biology and cell imaging.

Free binaries: software packages have been compiled for the main operating systems (Linux, MacOS, Windows) using CMake (see http://www.cmake.org/). They are freely available on the team website under a proprietary license (e.g. ND-SAFIR and HULLKGROUND are distributed this way at http://serpico.rennes.inria.fr/doku.php?id=software:index).

Mobyle@Serpico web portal: An on-line version (http://mobyle-serpico.rennes.inria.fr) of the image processing algorithms has been developped using the Mobyle framework (Institut Pasteur, see http://mobyle.pasteur.fr/). The main role of this web portal (see Fig. 2) is to demonstrate the performance of the programs developed by the team: QUANTEV, C-CRAFT[14], ATLAS[1], HULLKGROUND[40], KLTRACKER[44], MOTION2D[43], MS-DETECT[41], ND-SAFIR[6], OPTICALFLOW and FLUX ESTIMATION [14]. The web interface makes our image processing methods available for biologists at Mobyle@SERPICO (http://mobyle-serpico.rennes.inria.fr/cgi-bin/portal.py#welcome) without any installation or configuration on their own. The size of submitted images is limited to 200 MegaBytes per user and all the results are kept 15 days. The web portal and calculations run on a server with 2 CPU x 8 cores, 64 GigaBytes of RAM (500 MegaBytes for each user / Data is saved for 3 months).

ImageJ plugins: IMAGEJ (see http://rsb.info.nih.gov/ij/) is a widely used image visualization and analysis software for biologist users. We have developed IMAGEJ plug-in JAVA versions of the following software: ND-SAFIR [6], HULLKGROUND [40], MOTION2D [43], ATLAS [1]. The C-CRAFT algorithm [14] has been developped for the image processing ICY platform (http://icy.bioimageanalysis.org/).

- **Contact:** Charles Kervrann, Charles Deltel (Inria Rennes SED).
- **Partner:** UMR 144 CNRS-Institut Curie and France-BioImaging.

6.12.2. IGRIDA-Serpico cluster

The IGRIDA-Serpico cluster of 200 nodes is opened for end-users for large scale computing and data sets processing (200 TeraBytes).

- **Batch Scheduler:** OAR
- **File management:** Puppet / Git / Capistrano
- **OS:** Linux Debian 7
- **User connexion:** public ssh key
- **Contact:** Charles Kervrann, Charles Deltel (Inria Rennes SED).

7. New Results

7.1. Statistical methods for image denoising and reconstruction

Participants: Emmanuel Moebel, Charles Kervrann.

In the line of the Non-Local (NL) means [39] and ND-SAFIR [11], [12], [6] denoising algorithms, we have proposed a novel adaptive estimator based on the weighted average of observations taken in a neighborhood with weights depending on image data. The idea is to compute adaptive weights that best minimize an upper bound of the pointwise L_2 risk. In the framework of adaptive estimation, we show that the "oracle" weights depend on the unknown image and are optimal if we consider triangular kernels instead of the commonly-used Gaussian kernel. Furthermore, we propose a way to automatically choose the spatially varying smoothing parameter for adaptive denoising. Under conventional minimal regularity conditions, the obtained estimator converges at the usual optimal rate. The implementation of the proposed algorithm is also straightforward. The simulations show first that our algorithm improves significantly the classical NL-means. Second, the simulations demonstrate that it is competitive when compared to state-of-the-art denoisers both in terms of PSNR values and visual quality.

Meanwhile, we investigated statistical aggregation methods which optimally combine several estimators to produce a boosted solution [13]. This approach has been especially investigated to restore spectral information in the missing wedge (MW) in cryo-electron tomography (CET). The MW is known to be responsible for several types of imaging artifacts, and arises because of limited angle tomography: it is observable in the Fourier domain and is depicted by a region where Fourier coefficient values are unknown (see Fig. 3). The proposed stochastic method tackles the restoration problem by filling up the MW by iterating following steps: adding noise into the MW (step 1) and applying a denoising algorithm (step 2). The role of the first step is to propose candidates for the missing Fourier coefficients and the second step acts as a regularizer. A constraint is added in the spectral domain by imposing the known Fourier coefficients to be unchanged through iterations. Different denoising algorithms (BM3D, NL-Bayes, NL-means...) have been compared. Furthermore, different transforms have been tested in order to apply the constraint (Fourier transform, Cosine transform, pseudo-polar Fourier transform). Finally, we showed that this strategy can be embedded into a Monte-Carlo simulation framework and amounts to computing an aggregated estimator [13]. Convincing results have been achieved (see Fig. 3) using the Fourier Shell Correlation (FSC) as an evaluation metric.

References: [18]

Collaborators: Qiyu Jin (School of Mathematical Science, Inner Mongolia University, China),
Ion Grama and Quansheng Liu (University of Bretagne-Sud, Vannes),
Damien Larivière (Fondation Fourmentin-Guilbert),

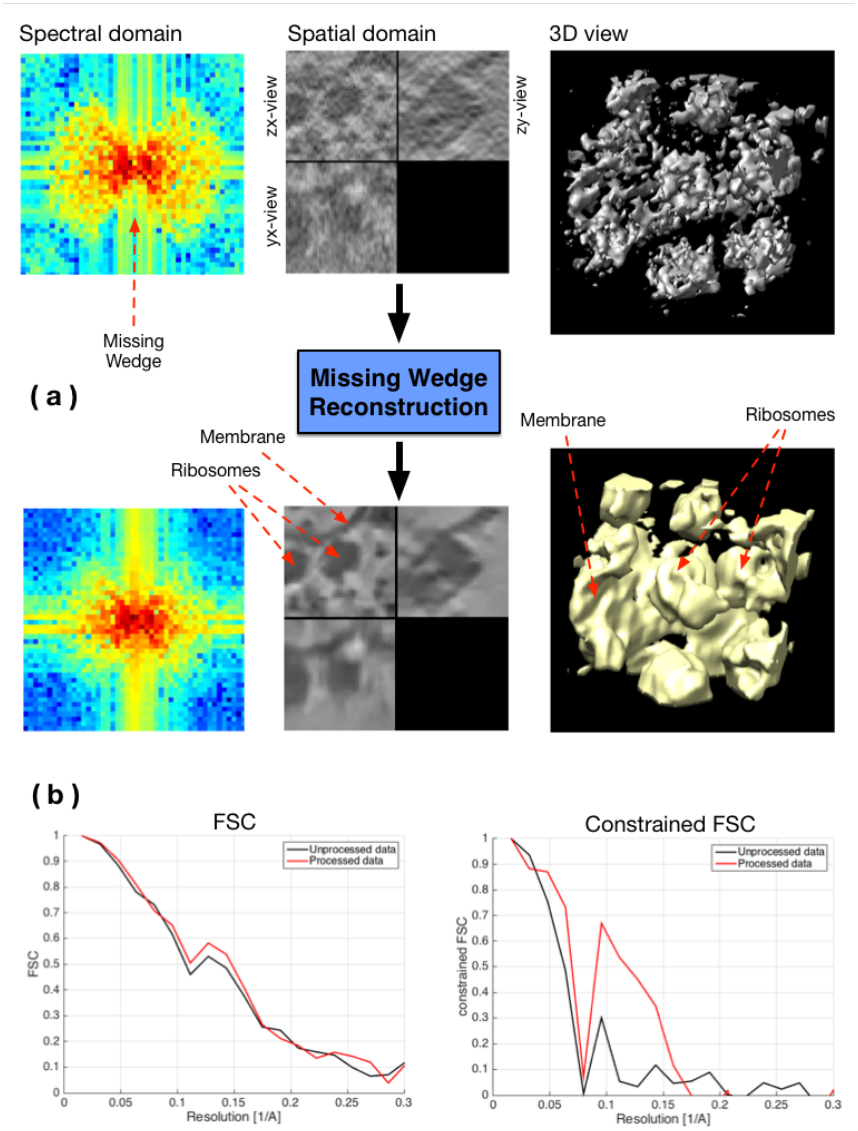

Figure 3. Experimental sub-tomogram containing ribosomes attached to a membrane. (a) Top row: original data in the spectral (left) and spatial (middle) domains and 3D view of the thresholded data (right). Bottom row: denoised data shown as above. (b) FSC and constrained FSC measures of the method input (in black) and output (in red). All measures are wrt the same reference.

Julio Ortiz (Max-Planck Institute, Martinsried, Germany).

7.2. Algorithms for dejittering and deconvolving fluorescence Tissue MicroArray (TMA) images

Participant: Charles Kervrann.

In the thesis of H.-N. Nguyen, we developed dedicated image processing methods to improve quality of Tissue Microarray (TMA) images acquired by fluorescence scanners. Images are first acquired pixel by pixel along each line, with a change of scan direction between two subsequent lines. Such scanning system often suffers from pixel mis-positioning (jitter) due to imperfect synchronization of mechanical and electronic components. To correct these scanning artifacts, we proposed a variational method based on the estimation of pixel displacements on subsequent lines. This method, inspired from optical flow methods, consists in estimating a dense displacement field by minimizing an energy function composed of a non-convex data fidelity term and a convex regularization term. We used half-quadratic splitting technique to decouple the original problem into two small sub-problems: one is convex and can be solved by standard optimization algorithm, the other is non-convex but can be solved by a complete search. We showed that our method is able to remove efficiently the rolling effect due to jitter, even in the case of huge images and large non-integer displacements.

Second, to improve the resolution of acquired fluorescence images, we introduced a method of image deconvolution by considering a family of convex regularizers. The considered regularizers are generalized from the concept of Sparse Variation which combines the L1 norm and Total Variation (TV) to favors the colocalization of high-intensity pixels and high-magnitude gradient. The experiments showed that the proposed regularization approach produces competitive deconvolution results on fluorescence images, compared to those obtained with other approaches such as TV or the Schatten norm of Hessian matrix. The final deconvolution algorithm has been dedicated to large 2D 20000×60000 images acquired with ISO scan imager (see Fig.4). The method is able to process a 512×512 image in 250 ms (Matlab) with a non optimized implementation.

References: [32], [34]

Collaborators: Vincent Paveau and Cyril Cauchois (Innopys company), Hoai-Nam Nguyen.

7.3. Correlation-based method for membrane diffusion estimation during exocytosis in TIRFM

Participants: Ancageorgiana Caranfil, Charles Kervrann.

The dynamics of the plasma membrane of the cell is not fully understood yet; one of the crucial aspects to clarify is the diffusion process during exocytosis. Several image acquisition modalities exist, including TIRFM (Total Internal Reflection Fluorescence Microscopy), that have successfully been used to determine the successive steps of exocytosis. However, computing characteristic values for plasma membrane dynamics is problematic, as the experimental conditions have a strong influence on the obtained data, and a general model of molecular interaction dynamics cannot be determined.

In the PhD thesis of A. Caranfil, we have developed a computational approach to adapt the popular temporal image correlation spectroscopy (TICS) method to the analysis of a single fusing vesicle. The biophysical diffusion model parameters (for TfR protein) are estimated by an Approximate Bayesian Computing procedure which supplies the conditional expectation and maximum a posteriori estimators from temporal correlation data. Unlike TICS, our approach is robust to noise, estimation window size, spot location and non-uniform background. It can serve in biological studies investigating diffusion processes involved in exocytosis mechanisms.

Collaborators: Francois Waharte (UMR 144 CNRS-Institut Curie, PICT-IBiSA).

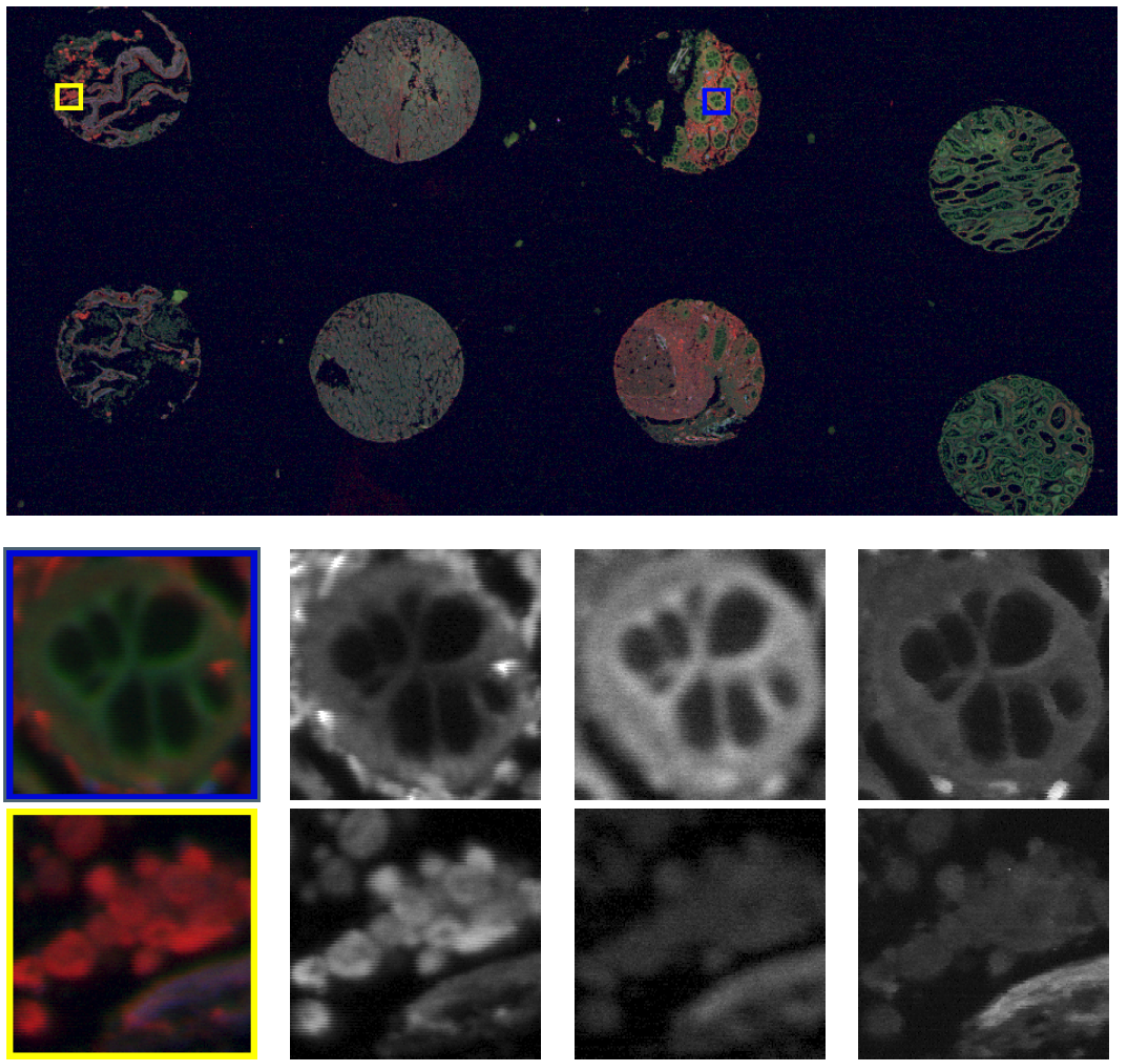

Figure 4. Three-color fluorescence image of eight tissue microarray cores. A region of interest of $4.7 \times 2.8mm^2$ *was scanned using the fluorescence scanner named InnoScan 1100AL equipped with three excitation wavelengths* ($488nm, 532nm$ *and* $635nm$) *at the spatial resolution* $0.5\mu m^2$*/ pixel, corresponding to an image of* 9544×4704 *pixels. Two areas which are bordered by two blue and yellow boxes are selected for visual comparison. First row: full size image. Second and third rows: zoom-in views of two selected areas; from left to right: 3 synchronized colors (red* ($488nm$)*, green* ($532nm$) *and blue* ($635nm$) *channels) displayed separately (courtesy of Innopsys).*

7.4. Classification of diffusion dynamics from particle trajectories

Participants: Vincent Briane, Charles Kervrann.

In this study, we are currently interested in describing the dynamics of particles inside live cell. Inference on the modes of mobility of molecules is central in cell biology since it reflects the interactions between the structures of the cell. In this work, we assume that the motions of particles follow a certain class of random process: the diffusion processes. Diffusions are stochastic processes with continuous paths and can model a large range of intracellular movements. Biophysicists distinguish three main types of diffusions, namely Brownian motion, superdiffusion and subdiffusion. These different diffusion processes correspond to distinct biological scenarios. A particle evolving freely inside the cytosol or along the plasma membrane is modelled by Brownian motion; the particle does not travel along any particular direction and can take a very long time to go to a precise area in the cell. Active intracellular transport can overcome this difficulty so that motion is faster in a given direction. In this case, particles are carried by molecular motors along microtubular filament networks and their motion is modelled with superdiffusion. Subdiffusion can be observed in two cases i/ when the particle is confined in a microdomain, ii/ when the particle is hindered by molecular crowding and encounters dynamic or fixed obstacles.

To address several issues in dynamics classification, we have developed a statistical test for classifying the observed trajectories into the three groups of diffusion of interest, namely Brownian motion, super-diffusion and subdiffusion. We have also designed an algorithm to detect the changes of dynamics along a single trajectory (see Fig. 5). We define the change points as the instants at which the particle switches from one diffusion type (Brownian motion, superdiffusion or subdiffusion) to another one. Finally, we have combined a clustering algorithm with our test procedure to identify micro domains, that is, zones where the particles are confined. Molecular interactions of great importance for the functioning of the cell take place in such areas.

Collaborators: Myriam Vimond (ENSAI Rennes),
Jean Salamero (UMR 144 CNRS-Institut Curie).

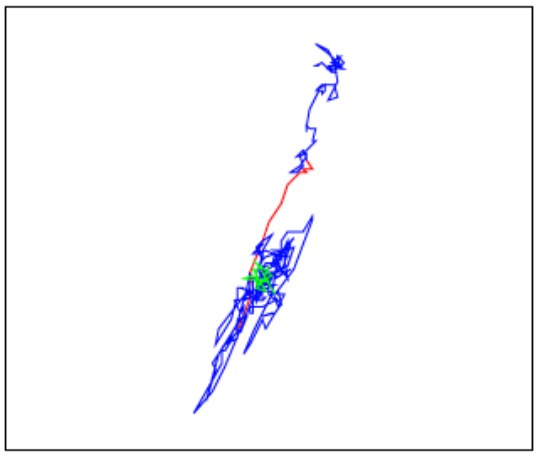

Figure 5. Change point detection on trajectories depicting neuronal mRNPs. The blue parts correspond to Brownian portions of the trajectory, red part to superdiffusive portions, green part to the subdiffusive portion.

7.5. Spatial statistics, point patterns, and colocalization in fluorescence imaging

Participants: Frédéric Lavancier, Charles Kervrann.

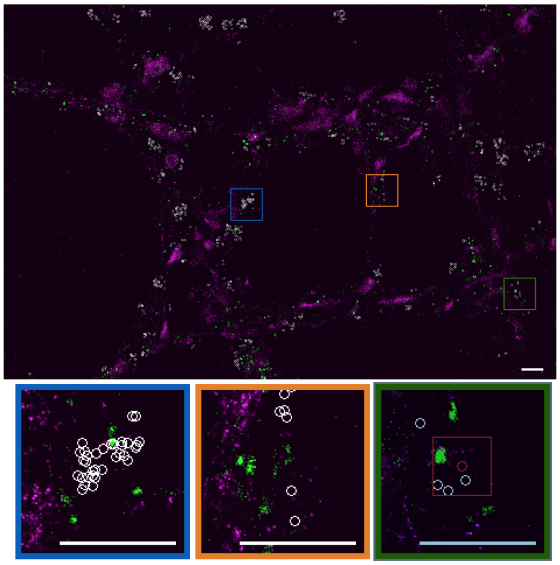

Figure 6. DSTORM acquisition of cells from hippocampi of mice expressing BDNF proteins (green channel) and vGlut (purple channel), with three zoomed-in regions (bottom). The colocalization regions identified by GcoPS are represented as white circles. The red rectangle represents the window used to find the colocalization hit shown as a red circle. The scale bars correspond to 1μm

In the context of bioimaging, colocalization refers to the detection of emissions from two or more fluorescent molecules within the same pixel of the image. This approach enables to quantify the protein-protein interactions inside the cell, just at the resolution limit of the microscope. It refers to the detection of emissions from two or more fluorescent molecules within the same pixel of the image. Colocalization is an open problem for which no satisfying solution has been found up to now. Accordingly, we proposed an objective, robust-to-noise colocalization method (GcoPS – Geo-coPositioning System)) which only requires the adjustment of a p-value that guarantees more reproducibility and more objective interpretation. It is based on the statistical analysis of the intersection (area/volume) between the two 2D or 3D binary segmented images. GcoPS handles 2D and 3D images, variable signal-to-noise ratios and any fluorescence image pair acquired with conventional or super-resolution microscopy (see Fig. 6). To our knowledge, no existing method offers the same robustness and precision level with such an easy control of the algorithm. In a recent study (internships 2017), we started to adapt this framework to analyze the spatiotemporal molecular interactions from set of 3D computed trajectories or motion vector fields (e.g., co-alignment), and then to fully quantify specific molecular machineries.

More generally, analysis of molecule and protein localization, of interactions and spatial distributions in living cells is helpful to understand functions in the cell and to compare spatialized phenotypes. This is also true with the emergence of single-molecule localization microscopy techniques (e.g., PALM), relying on the cumulative spatial localization of fluorescently tagged markers, and whose outputs are sets of spatial coordinates of single molecules. Accordingly, we were interested in the spatial distribution of single molecules that exhibit some randomness, regularity and spatial clustering (or aggregation) at large scales, while having a minimal distance between them. In that context, we theoretically studied several point processes able to represent the spatial organization of points. We focused on determinantal point processes (DDP), since they are able to describe spatial point patterns where nearby points repel or repulse each other. We also partly solved a 30 years old conjecture by proving the consistency of the likelihood procedure for a large class of Gibbs models (e.g., Strauss model, area-interaction model) which are commonly used models in practice. We extended the pseudo-

likelihood procedure to infinite range Gibbs interactions, and we proved its consistency and its asymptotic normality. All these models are now well understood and will be used in future works to analyse point patterns in cell imaging, generally described by Poisson point processes.

References: [30], [31], [35]

Collaborators: Jean Salamero and Liu Zengzhen (UMR 144 CNRS-Institut Curie),
David Dereudre (Laboratoire Paul Painlevé (UMR 8524), University of Lille 1),
Jean-François Coeurjolly (Laboratoire Jean Kutzmann, University of Grenoble).

7.6. Data assimilation and modeling of cell division mechanism

Participants: Ancageorgiana Caranfil, Charles Kervrann.

Nowadays, medical challenges demand a profound understanding of cellular mechanisms. Research in biology, biophysics and medical domain unravelled a significant part of the general processes occurring at the cellular level. It has enabled the understanding of much smaller scale processes, but our knowledge on these mechanisms is still limited as new, more complex issues need to be solved. In this context, we aim at understanding the role and interaction of the molecular key players at different scales, and their individual and collective impact on the global mechanism at the cell level. To this purpose, we have focused on the dynamics of the spindle during cell division mechanism. Our approach consists in creating a biophysical model for this mechanism, and uses data assimilation to adjust the model and optimally integrate the information from the observations. The overall spindle behaviour is led by the spindle poles behaviour. This year, we have proposed a new biophysical model for the posterior spindle pole functioning during metaphase and anaphase, that explains the oscillatory behaviour with a minimum number of parameters. Estimating the model parameters is ongoing, and will provide insights on molecular players role as well as guidance for future experiments to further investigate the dynamics of the spindle during cell division. First, we have focused on the temporal aspect. Spatial information on microtubules and molecular motors will be included in the model in the next part of this work.

Collaborators: Yann Le Cunff and Jacques Pécréaux (IGDR Institute of Genetics & Development of Rennes).

7.7. Quantifying the spatial distribution of intracellular events

Participant: Charles Kervrann.

Automated processing of fluorescence microscopy data allows to quantify cell phenotypes in an objective and reproducible way. However, most computational methods are based on the complex combination of heterogeneous features expressing geometrical, morphological and frequency properties, which makes difficult to draw definitive biological conclusions. Additionally, most experimental designs pool together data coming from replicated experiments of a given condition, neglecting the biological variability between individual cells. Hence, we developed a generic and nonparametric density framework (QuantEv) to discriminate spatiotemporal distributions (using circular Earth mover's distance) of moving proteins detected by any appropriate algorithm. The main advantage of QuantEv is to robustly process 2D and 3D data, and accurately analyse homogeneous and heterogeneous populations. As proof-of-principle, we first quantitatively characterized protein trafficking of Rab6 positive membranes between the Golgi apparatus and the plasma membrane. Next, we demonstrated that Rab11 positive membranes uniformly distribute around the Endosomal Recycling Compartment (ERC), regardless of the cell shape. Finally, we showed that actin organization is cell shape dependent, and evaluated its influence on the distribution of exocytosis/recycling vesicles. QuantEv is a flexible method which enables to quantify any intracellular trafficking in 3D flat or rounded, constrained or non-constrained, adherent or non-adherent cells.

References: [36]

Collaborators: Thierry Pécot (Hollings Cancer Center, Medical Univ. South Carolina, Charleston, USA),
Jean Salamero, Jérôme Boulanger and Liu Zengzhen (UMR 144 CNRS-Institut Curie).

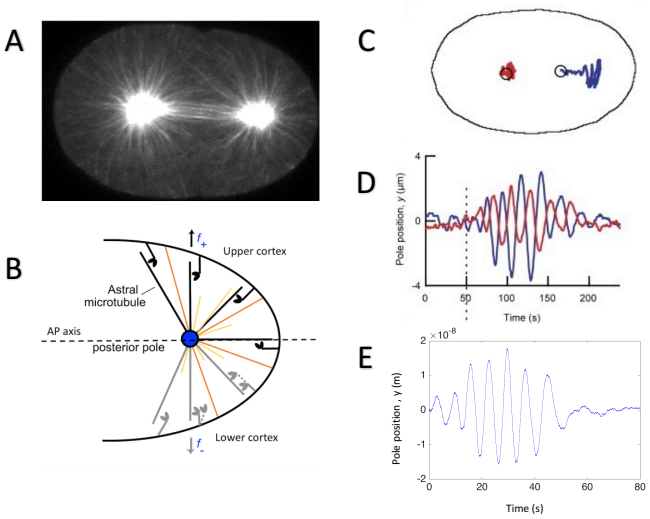

Figure 7. Illustration of the cell division mechanism observed in fluorescence microscopy (A). Sketch of one centrosome and connected to microtubules in the cell (B), experiments and tracking of the two centrosomes (C and D), and simulation of centrosome oscillations (E).

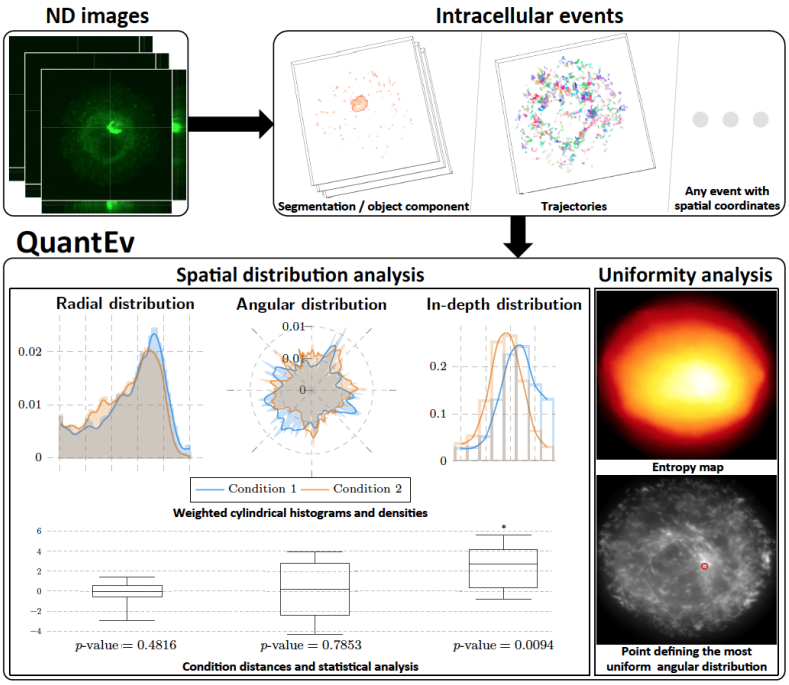

Figure 8. Overview of QuantEv approach.

7.8. 3D registration for correlative light-electron microscopy

Participants: Bertha Mayela Toledo Acosta, Patrick Bouthemy.

In recent years, correlative light and electron microscopy (CLEM) has become an attractive tool in the bio-imaging field. Biologists can collect complementary information from light microscopy (LM) and electron microscopy (EM), respectively on the dynamics and on the structure of the cell. An overlay of the LM and EM images is needed to combine information from the LM and EM sources. We are developing a 3D automated CLEM method to register EM and LM image stacks. Given the significant gap between the field of view, position and orientation of the EM and LM stacks, it is not possible to estimate directly the 3D registration. We first compute a 2D maximum intensity projection (MPI) of the LM stack along the Z-axis, and we match 2D EM regions of interest (ROI), extracted from different EM slices, into the 2D LM-MPI image. From the resulting location candidates, we estimate with a robust criterion the 2D XY-shift to pre-align the LM and EM stacks. Afterwards, a 3D affine transformation between 3D-LM-ROI and 3D-EM–ROI can be estimated using mutual information. We successfully tested this framework on two first 3D correlative microscopy datasets.

Collaborators: Xavier Heiligenstein (UMR 144 CNRS-Institut Curie),
Grégoire Malandain (Inria, Morpheme EPC, Sophia-Antipolis).

7.9. Fast optical flow methods for 3D fluorescence microscopy

Participants: Sandeep Manandhar, Patrick Bouthemy, Charles Kervrann.

Estimating motion of cells and of subcellular particles is crucial for deciphering cell mechanisms and understanding cell behaviors. Modern 3D light microscopy (LM) for cell biology enables to observe cell dynamics at a good resolution, in both space and time, motivating the development of 3D optical flow methods. However, the acquired 3D LM image sequences exhibit several specificities making 3D motion computation a difficult problem. We have defined an original and efficient two-stage estimation method for light microscopy image volumes. The method, developed in the frame of S. Manandhar PhD thesis, takes a pair of LM image volumes as input, segments the 2D slices of the source volume in super-pixels, and first estimates the 3D displacement vectors of the super-pixel centers. To this end, we have extended the well-known PatchMatch method to 3D volumes, where correspondences act between voxels. Both the propagation and the random search steps were adapted to 3D volumes. Then, a weighted interpolation has been designed to recover the dense 3D flow field for all the voxels, from the sparse 3D displacement field. The super-pixel segmentation is exploited to define the neighborhood for interpolation, and the interpolation weights take into account intensity edges and local motion differences to preserve flow discontinuities. The experimental results show good gain in execution speed, and accuracy evaluated in computer-generated 3D data with ground-truth. The results were promising on two real 3D LM image sequences supplied by USTW. The sequences depict blebbing in a MV3 cell (see Fig. 9). The cell membrane protrudes increasing the surface area of the cell. These protrusions, referred to as blebs, appear and disappear in interval of minutes, the bleb appearance corresponding to the stretching of a local region of the cell membrane. The total computation time was for the first sequence 163 seconds (resp. 101s for the second sequence), with 19 (resp. 49), 120 (resp. 44) and 24 (resp. 8) seconds for super-pixel generation, 3D patch matching, and interpolation respectively, on a computer with 2.8 GHz Intel i7 processor and 16 GB of RAM.

Collaborators: Philippe Roudot and Gaudenz Danuser (UTSW, Dallas, USA).

7.10. 3D Convolutional Neural Networks for macromolecule localization in cryo-electron tomograms of intact cells

Participants: Emmanuel Moebel, Charles Kervrann.

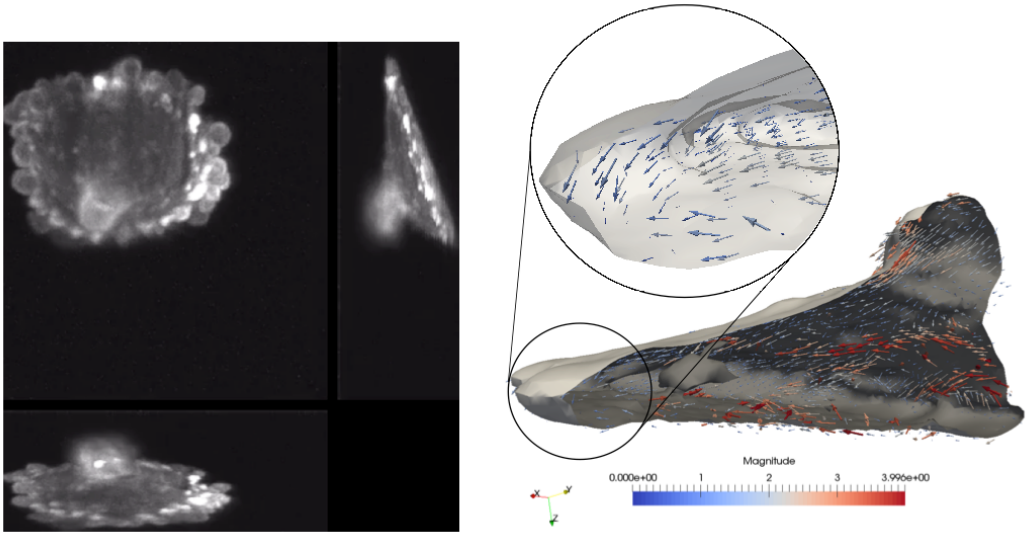

Figure 9. Illustration of 3D optical flow computation to analyze bleb deformation during cell migration in Bessel beam light sheet microscopy (input images by courtesy of Danuser lab, UTSW Dallas, USA).

In this study, we focus on macromolecule localization and classification in cryo-electron tomography (CET) images. Biologists are in need for efficient methods to localize macro-molecules (e.g. ribosomes) in frozen cell samples. The high amount of noise and imaging artifacts are the reasons why very few computational methods exist for this task. In fact, the most used method today is template matching (TM) whose resulting score map comprises a high amount of false positives. Therefore, it is necessary to apply post-processing techniques (ROI selection, classification) in order to refine the localization results. We propose an alternative localization method to TM, based on a convolutional neural network (CNN). The idea is to propose a robust and more straight-forward approach, allowing to bypass the conventional processing chain. By using python toolboxes optimized for GPU computing (elektronn, keras), we are able to reach computation time much lower than the current approach. Results on synthetic data demonstrate the superiority of our approach compared to TM. In addition, we applied our method on experimental data in order to localize sub-classes of ribosomes (membrane-bound and cytoplasmic ribosomes), a task difficult to achieve with TM alone. We are currently in the process of publishing these results. Future perspectives include localizing smaller macro-molecules, like proteasomes.

Collaborators: Damien Larivière (Fondation Fourmentin-Guilbert),
Julio Ortiz, Antonio Martinez (Max-Planck Institute, Martinsried, Germany).

7.11. Estimation of parametric motion models with deep neural networks

Participants: Juan Manuel Perez Rua, Patrick Bouthemy.

We have proposed an end-to-end learning architecture for estimating a parametric motion model for a moving scene. We handle motion outliers by using the supervised training trick that is used by stacked denoising auto-encoders. Here, we define motion outliers as regions of the image whose motion does not correspond with the estimated parametric motion model. In other words, we seek to find a parametrized dominant motion of the dynamic scene. We leverage stacked hourglass networks with a final hard-coded block corresponding to

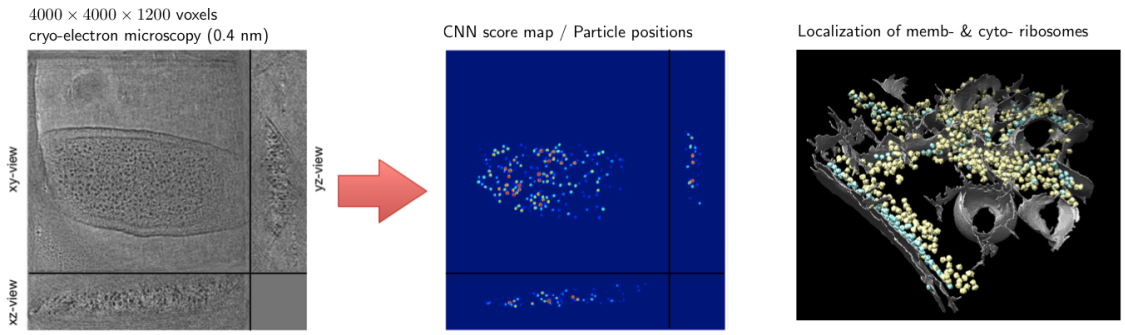

Figure 10. Illustration of 3D CNN to localize ribosomes isolated in the cytoplasm and close to the cell membrane in cryo-electron tomography (courtesy of Max-Planck Institute, Martinsried, Germany).

the global parametric motion model estimator. This block replaces the decoder part of a convolutional auto-encoder network, and it is end-to-end trainable since it involves linear operations only. Moreover, the hard-wired decoder allows the network to output the values of the parametric motion model given an input moving scene, even when the supervision acts on optical flow maps and not the motion model values. This means that our network is able to provide, as a by-product, a concise code that can be used as motion descriptor.

Collaborators: Tomas Crivelli and Patrick Pérez (Technicolor).

7.12. Motion saliency in video sequences

Participants: Léo Maczyta, Patrick Bouthemy.

Dynamic (or motion) saliency is a means to detect unexpected or rare dynamic behaviors in video sequences acquired by a stationary or a mobile imaging device. Finding salient dynamic information in each image of a sequence is indeed crucial in many situations. We aim to extract saliency only from motion information, and to exhibit salient motion in contrast to its space-time context with no prior on the nature of both. So far, we have investigated a simpler problem than saliency map estimation. We deal with the classification of each image of a sequence as dynamically salient or not, that is, containing salient motion or not. We have explored convolutional neural network (CNN). We have designed two different networks. The first one relies on two intensity images, the first input image and the second image warped with the parametric dominant motion estimated between the two input images. The second one takes as input the difference between the computed optical flow and parametric dominant flow.

Collaborators: Olivier Lemeur (EPC Sirocco, Inria Rennes - Bretagne Atlantique).

8. Bilateral Contracts and Grants with Industry

8.1. Bilateral Contracts with Industry

8.1.1. Contract with Innopsys: Tissue microarrays (TMA) image analysis

Participants: Charles Kervrann.

Collaborators: Vincent Paveau and Cyril Cauchois (Innopys company).

A three-year contract has been established with Innopsys in 2013 to support the PhD thesis of Hoai-Nam Nguyen. The objective was to investigate and develop methods and algorithms dedicated to fluorescence images acquired by scanners and devices designed by the company. In this project, we focused on localization and segmentation of fluorescence tissue microarrays (TMA) cores in very large 2D images, de-arraying of digital images and correction of grid deformation adapted to devices, correction of scanning artifacts to improve image reconstruction and deconvolution of fluorescence TMA images. The algorithms are currently embedded into software and hardware products designed by Innopsys.

8.1.2. Contract (CIFRE) with Technicolor: Semantically meaningful motion descriptors for video understanding

Participants: Juan Manuel Perez Rua, Patrick Bouthemy.

Collaborators: Tomas Crivelli and Patrick Pérez (Technicolor).

A three-year contract has been established with Technicolor in January 2015 for a CIFRE grant supporting the PhD thesis of Juan Manuel Pérez Rúa. The purpose was to investigate new methods for extracting meaningful mid-level motion-related descriptors that may help for the semantic discovery of the content. First, we addressed the occlusion detection problem and proposed a novel approach where occlusion is formulated in terms of visual reconstruction. Contrary to the usual approaches, the proposed alternative does not critically depend on a pre-computed, dense displacement field, while being shown to be more effective. Second, we developed two hierarchical motion segmentation methods involving a compositional motion representation. The first one follows a frame-based labeling approach which amounts to minimizing a global energy function. The second one is trajectory-based and relies on tree-structured learning and sparse coding.

8.1.3. Contract with OBSYS: microscope set-up control and inverse problems in microscopy

Participants: Giovanni Petrazzuoli, Charles Kervrann.

Collaborators: Charles Gudeudry (OBSYS).

A two-year contract was established with OBSYS in 2016 for hiring an expert-engineer (12 months). The objective is to investigate and develop software for the control of a microscope set-up and the analysis of fluorescence images. Fast and robust algorithms have been especially developed to improve image reconstruction of 3D-TIRF microscope images. The algorithms will be embedded into platforms and devices designed by OBSYS. Giovanni Petrazzuoli has been hired in August 2017 on a full-time R&D engineer position in OBSYS (CDI). The collaboration with Inria will be pursued in 2018.

8.2. Bilateral grants with industry

8.2.1. Fourmentin-Guilbert Foundation: Macromolecule detection in cryo-electron tomograms

Participants: Emmanuel Moebel, Charles Kervrann.

Collaborator: Damien Larivière (Fourmentin-Guilbert Foundation).

A three-year contract was established with Fondation Fourmentin-Guilbert to partly support the PhD thesis of Emmanuel Moebel. The Fondation Fourmentin-Guilbert strives for building a virtual E. coli bacteria. Information about the position of macromolecules within the cell is necessary to achieve such a 3D molecularly-detailed model. The Fondation Fourmentin-Guilbert supports cutting-edge *in-situ* cryo-electron tomography combined with image processing at the Max-Planck Institute of Biochemistry to map the spatial distribution of the ribosomes, and obtain structural information on the complexes they form *in-situ* with cofactors and other ribosomes. The objective of the project is to explore novel methods from the field of 3D shape retrieval for identifying and counting macromolecules within a tomogram. This project is also supported by Région Bretagne.

9. Partnerships and Cooperations

9.1. Regional Initiatives

ENSAI-CREST: Statistical methods and models for image registration, PhD thesis of Vincent Briane is co-funded by Inria and ENSAI-CREST and co-supervised by Myriam Vimond (ENSAI-CREST).

Région Bretagne: Identification, localization and enumeration of ribosomes within a tomogram by combining state-of-the-art denoising methods and object descriptor-based recognition (CATLAS, see Section 8.2.1) (PhD thesis of Emmnuel Moebel); motion saliency in video sequences (PhD thesis of Léo Maczyta).

BioGenOuest: Collaboration with S. Prigent (engineer) in charge of the organization of image processing services for Biogenouest bio-imaging facilities.

IGDR: Collaboration with J. Pecreaux, Y. Le Cunff (co-supervision of PhD thesis of A. Caranfil).

9.2. National Initiatives

9.2.1. France-BioImaging project

Participants: Charles Kervrann, Patrick Bouthemy.

The goal of the France-BioImaging project (http://france-bioimaging.org/) is to build a distributed coordinated French infrastructure for photonic and electronic cellular bioimaging, dedicated to innovation, training and technology transfer. High-computing capacities are needed to exhaustively analyse image flows. Serpico is co-head of the IPDM (Image Processing and Data Management) node of the FBI network composed of 6 nodes. In this context, we address the following scientific problems: i/ exhaustive analysis of bioimaging data sets; ii/ deciphering of key steps of biological mechanisms at organ, tissular, cellular and molecular levels through the systematic use of time-lapse 3D microscopy and image processing methods; iii/ storage and indexing of extracted and associated data and metadata through an intelligent data management system. Serpico recruited R&D engineers (2011-2016) to disseminate image processing software, to build the Mobyle@Serpico web portal and to manage the IGRIDA-Serpico cluster (200 nodes; batch scheduler: OAR; File management: Puppet/Git/Capistrano; OS: Linux Debian 7; User connexion: public ssh key) opened for end-users and dedicated to large scale computing and data sets processing (storage: 200 TeraBytes).

- **Coordinator:**CNRS (Jean Salamero, UMR 144 CNRS-Institut Curie).
- **Partners:**University of Paris-Diderot-Paris 7, Aix-Marseille University, University of Bordeaux, University of Montpellier, Institut Pasteur, Institut Curie, Inria, ENS Ulm, University of Paris Descartes, UPMC, Ecole Polytechnique, Inserm.
- **Funding:**Investissement d'Avenir Infrastructures Nationales en Biologie et Santé, ANR INBS-PIA 2011.
- **Total amount:**26 000 Keuros (Inria Serpico: 606 Keuros).

9.2.2. ANR DALLISH project (2016-2020): Data Assimilation and Lattice LIght SHeet imaging for endocytosis/exocytosis pathway modeling in the whole cell

Participants: Charles Kervrann, Vincent Briane, Ancageorgiana Caranfil, Antoine Salomon.

Cutting-edge LLS microscopy represents the novel generation of 3D fluorescence microscopes dedicated to single cell analysis, generating extraordinarily high resolved and sharp, but huge 3D images and videos. One single live cell experiment in one single biological condition can result into up to one terabyte of data.The goal of the project is to develop new paradigms and computational strategies for image reconstruction and 3D molecule tracking/motion estimation. Furthermore, establishing correspondences between image-based measurements and features, stochastic motion models, and underlying biological and biophysical information remains a challenging task. In a larger perspective, the quantitative description of image data corresponding to protein transport will be a prerequisite for understanding the functioning of a cell in normal and pathological situations including cancer, viral infection and neurodegenerative diseases.

- **Coordinator:**Inria (Charles Kervrann)
- **Partners:**Inria (Serpico, Beagle, Fluminance teams), INRA MaIAGE Unit Jouy-en-Josas, Institut Curie (UMR 144 CNRS & U1143 Inserm UMR 3666) Paris
- **Funding:**ANR (Agence Nationale de la Recherche) PRC (Collaborative Research Project)
- **Total amount:**440 Keuros (Inria Serpico: 170 Keuros).

9.3. European Initiatives

9.3.1. Major European Organizations with which the Team have followed Collaborations

ESFRI Euro-BioImaging initiative: SERPICO participates in the ESFRI Euro-BioImaging project, one of the four new biomedical science projects in the roadmap of the European Strategic Forum on Research Infrastructures (ESFRI). The mission of Euro-BioImaging is to provide access, service and training to state-of-the-art imaging technologies and foster the cooperation and networking at the national and European level including multidisciplinary scientists, industry, regional, national and European authorities. SERPICO also participates to the French counterpart, the so-called "France-BioImaging" (FBI) network which gathers several outstanding cellular imaging centers (microscopy, spectroscopy, probe engineering and signal processing) as described in Section 9.2.1.

- **Coordinator:** EMBL (Jan Ellenberg, Heideldberg, Germany)
- **Partners:** 15 european countries in 2017
- **Funding:** Member states of the European Union

9.4. International Initiatives

9.4.1. Informal International Partners

Collaboration with Max-Planck Institute, Martinsried (Germany), Dr. Julio Ortiz and Antonio Martinez: Detection and segmentation of macromolecules in cryo-electron tomography (project in progress with Emmanuel Moebel and Charles Kervrann).

Collaboration with Aalborg University (Denmark), Prof. Rasmus Waagepetersen: Estimating equations for inhomogeneous determinantal point processes (project with Frédéric Lavancier).

9.4.2. Inria Associate Teams Not Involved in an Inria International Labs

9.4.2.1. CytoDI Inria Associated-Team

Title: Quantitative Imaging of Cytoskeleton Dynamics in 3D

International Partner:

University of Texas, SouthWestern Medical Center, Dallas (United States) - Gaudenz Danuser

Start year: 2016

See also: http://serpico.rennes.inria.fr/doku.php?id=research:cytodi

Participants: Sandeep Manandhar, Patrick Bouthemy, Charles Kervrann.

The main scientific goal of the Associated-Team is the spatiotemporal characterization and comparison of cytoskeleton networks involved in cell migration and observed through live cell imaging in three dimensions (3D). Those networks include the cytoskeleton, i.e., microtubules (MT), intermediate filaments (IF), dynamically resolvable by Bessel Beam Light Sheet fluorescent microscopy. The goal will be achieved through the design of local and global descriptors of the spatial conformation and deformation of the cytoskeleton. Subsequently, general metrics to compare and classify the MT and IF networks will be investigated. This study will be carried out on oncogenically transformed lung cancer epithelial cells.

The second meeting of the AT CytoDI took place in Rennes in July 2017 (visit of P. Roudot and K. Dean), to discuss and update current research direction and discuss scientific progress. Several meetings were organized with students (S. Manandhar, V. Briane, E. Moebel, T. Dubois, Q. Delannoy) to synchronize development in optical flow, co-orientation and visualization. The Danuser team focused on presenting recent imaging and analysis capacities as well as the current solution in development for the systematic analysis, contextualization and interpretation of 3D dynamics for quantitative biology.

9.5. International Research Visitors

9.5.1. Visits to International Teams

Emmanuel Moebel attended a summer school (one week): Signal Processing Meets Deep Learning (Capri, Italy, 4-8 september 2017).
Sandeep Manandhar attended a summer school (one week): VISion Understanding and Machine intelligence (Porto, Portugal, 7-14 July 2017).

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific Events Organisation

10.1.1.1. Member of the Organizing Committees

- Charles Kervrann is head of the organizing committee of the "Quantitative BioImaging" (QBI'2019) conference (Rennes, January 2019).

- Patrick Bouthemy was co-organizer of the BioImage Computing (BIC) workshop in conjunction with ICCV'2017 (Venice, Italy).

10.1.2. Scientific Events Selection

10.1.2.1. Member of the Conference Program Committees

- Charles Kervrann: senior PC (Program Committee) of "BioImage Informatics 2017" conference, member of the scientific committee of the "Imaging the Cell 2017" conference (Rennes), member of the scientific committee of RFIAP'2018 (Marne-la-Vallée), Associated Editor for the ISBI'2018 conference, member of the scientific committee of the JIONC workshop (GdR Ondes, since 2014).

- Patrick Bouthemy: Associate Editor for the ISBI'2017 conference, member of the program committee of the IPTA'2017 conference.

10.1.2.2. Reviewer

- Charles Kervrann: reviewer for ICIP'2017, ICASSP'2017, ISBI'2017, and SSVM'2017, PBIC'2017.

10.1.3. Journal

10.1.3.1. Member of the Editorial Boards

- Charles Kervrann is Associate Editor of the IEEE Signal Processing Letters journal.

- Patrick Bouthemy is co-editor in chief of the open access journal Frontiers in ICT, specialty Computer Image Analysis.

10.1.3.2. Reviewer - Reviewing Activities

- Charles Kervrann: BMC Bioinformatics, Int. J. Computer Vision, SIAM J. on Imaging Sciences, Machine Vision and Applications.

10.1.4. Invited Talks

- Charles Kervrann: Invited talk at II SLAS "HCS – High Contents Screening" conference (Madrid, Spain), "Connecting The Dots – Intelligent Trackers" workshop (LAL-Orsay), and GdR ImaBio (with V. Briane, University of Montpellier; with E. Moebel, Inria Rennes); Invited seminars at IDIAP (Martigny, Switzerland).
- Patrick Bouthemy: Invited speaker at 5ème colloque de la Société Française des Microscopies (Bordeaux).
- Frédéric Lavancier: Invited talks at GdR ImaBio-FBI "BioImage Informatics" (Rennes).

10.1.5. Leadership within the Scientific Community

- Charles Kervrann is member of the IEEE BISP "Biomedical Image and Signal Processing" (https://signalprocessingsociety.org/get-involved/bio-imaging-and-signal-processing) committee (expert committee for ISBI, ICASSP and ICIP conferences). He is member of the executive board of the GdR MIV/ImaBio (2588 - Microscopie Fonctionnelle du Vivant) CNRS. He is member of the scientific committee of the Interdisciplinary MiFoBio School CNRS (http://gdr-miv.fr/mifobio2018/).
- Patrick Bouthemy is member of the board of AFRIF (Association Française pour la Reconnaissance et l'Interprétation des Formes).

10.1.6. Scientific Expertise

- Charles Kervrann was expert for the international project evaluation in the framework of Luxembourg NRF (National Research Fund – RESCOM program). He was expert for the national project evaluation in the framework of DIM ELICIT Institut Pasteur - Région Ile-de-France in 2017. He was member of the selection committee for a Professor position at the University of Bordeaux (Section CNU 26, Mathematics) in 2017.
- Patrick Bouthemy was member of the evaluation committee of the ANR-DGA MALIN Challenge, member of the HCERES visiting committee of the DI-ENS (Département d'Informatique - Ecole Nationale supérieure Paris) (November 2017). He is member of the Research Committee of IMT Atlantique. He was member of the committee for professor promotion at IMT Atlantique in 2017.

10.1.7. Research Administration

- Charles Kervrann is member of the executive board of the project committee of the Inria Rennes
- Bretagne Atlantique centre since 2010. He is Co-head of the "BioImage Informatics" node (ANR France-BioImaging project, National Infrastructure en Biologie et Santé) since 2011.
- Patrick Bouthemy has been head of Excellence Lab (Labex) CominLabs (http://www.cominlabs.ueb.eu) since April 2014. He is deputy member of the board of directors and member of the selection and validation committee of the Images & Réseaux competitivity cluster (http://images-et-reseaux.com/). He is deputy member of the board of directors of IRT (Technological Research Institute) b<>com (https://b-com.com/). He is the Inria representative in the steering committee of the DGA-Inria collaboration.
- Frédéric Lavancier is an elected member of CNU section 26.

10.2. Teaching - Supervision - Juries

10.2.1. Teaching

Charles Kervrann:

- Engineer Degree: Genomics and Informatics, 4.5 hours, Ecole Nationale Supérieure des Mines de Paris.
- Master: From Bioimage Processing to BioImage Informatics, 5 hours, coordinator of the module (30 hours), Master 2 Research IRIV, Telecom-Physique Strasbourg and University of Strasbourg.
- Master: Geometric Modeling for Shapes and Images, 6 hours, Master 2 Research SISEA, University of Rennes 1.
- Engineer Degree and Master 2 Statistics and Mathematics: Statistical Models and Image Analysis, 37 hours + 15 hours (TP, Emmanuel Moebel), 3rd year, Ecole Nationale de la Statistique et de l'Analyse de l'Information (ENSAI), Rennes.

Patrick Bouthemy:

- Master: Analysis of Image Sequences, 18 hours, Master 2 Research SISEA, ISTIC & University of Rennes 1.

- Master: Video Indexing, 3 hours, Master 2 Research Computer Science, ISTIC & University of Rennes 1.

- Engineer Degree and Master 2 Research IRIV: Motion Analysis, 12 hours, Telecom-Physique Strasbourg & University of Strasbourg.

Frédéric Lavancier:

- Master: Linear Models, 36 hours, Master 2 Mathematics & Engineering, option Statistics, University of Nantes.

- Master: Time Series, 36 hours, Master 2 Mathematics & Engineering, option Statistics, University of Nantes.

10.2.2. Supervision

- Arnaud Poinas, inference for inhomogeneous determinantal point processes, started in September 2016, supervised by Bernard Delyon and Frédéric Lavancier.

- Vincent Briane, statistical tests for particle trajectory analysis: application to intracellular imaging, started in October 2014, supervised by Charles Kervrann and Myriam Vimond (ENSAI-CREST).

- Bertha Mayela Toledo Acosta, methods and algorithms for 3D image registration and correlative microscopy, started in October 2014, supervised by Patrick Bouthemy and Charles Kervrann.

- Emmanuel Moebel, new strategies for the nonambiguous identification and enumeration of macromolecules in cryo-electron tomograms, started in November 2015, supervised by Charles Kervrann.

- Juan Manuel Perez Rua, hierarchical motion-based video analysis with applications to video post-production, started in January 2015, supervised by Patrick Bouthemy in collaboration with Tomas Crivelli and Patrick Pérez (Technicolor).

- Ancageorgiana Caranfil, data assimilation methods for cell division mechanisms and molecule trafficking analysis, started in December 2016, supervised by Charles Kervrann and Yann Le Cunff.

- Sandeep Manandhar, optical flow methods for 3D fluorescence imaging, started in October 2016, supervised by Patrick Bouthemy and Charles Kervrann.

- Yunjiao Lu, intracellular dynamics and super-resolution imaging: analysis of bacteria wall at the molecular scale, started in October 2017, supervised by Charles Kervrann and Rut Carballido-Lopez.

- Antoine Salomon, statistical aggregation for image analysis in fluorescence microscopy and super-resolution, started in November 2017, supervised by Charles Kervrann.

- Léo Maczyta, motion saliency in video sequences, started in October 2017, supervised by Patrick Bouthemy and Olivier Lemeur.

10.2.3. Juries

Referee of PhD thesis: F. Zhou (University of Oxford, supervised by J. Rittscher) [P. Bouthemy], R. Giraud (University of Bordeaux, supervised by N. Papadakis) [P. Bouthemy], C. Jiang (University of Bourgogne, supervised by C. Demonceaux) [P. Bouthemy], A. Samacoïts (Institut Pasteur - UPMC, supervised by C. Zimmer) [C. Kervrann].

President of PhD thesis jury: F. Deslandes (INRA, supervised by B. Laroche), I. Ahmet (University of Rennes 1, supervised by T. Furon).

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