Activity Report 2016

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. Members

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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 [41].

SIM (Structured Illumination Microscopy): high-resolution light microscopy using structured patterns and interference analysis [49].

TIRF (Total Internal Reflectance): 2D optical microscopy using evanescent waves and total reflectance [40].

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

Light microscopy, especially fluorescence microscopy, has taken a prominent role in life science research due to its ability to investigate the 3D interior of cells and organisms. It enables to visualize, in vitro and in vivo, particular biomolecules and proteins (gene expression) with high specificity through fluorescent labeling (GFP - Green Fluorescence Protein probes) both at the microscopic and nanoscopic scales. Nevertheless, the mechanisms of life are very complex and driven by multimolecular interactions: mitotic spindle, cell signaling complexes, intracellular transport, cell morphogenesis and motility... A dynamical quantitative and integrated description of molecular interactions and coordination within macromolecular complexes at different scales appears essential today for the global understanding of live mechanisms. A long-term research consists in inferring the relationships between the dynamics of macromolecules and their functions. This constitutes one of the challenges of modern biology. The proposed mathematical models and algorithms are mainly developed to identify molecular processes in fundamental biology but they have also a strong potential for applications in biotechnology and medicine: disease diagnosis, detection of genomic instabilities, deterioration of cell cycle, epigenetic mechanisms and cancer prevention.

2.3. Objectives in cell imaging

Facing the amount of information provided by high-throughput multidimensional microscopy, the SERPICO team investigates computational and statistical models to better elucidate the role of specific proteins inside their multiprotein complexes and to help to decipher the dynamic coordination and organization of molecular complexes at the single cell level. We investigate image processing methods, mathematical models, and algorithms to build an integrated imaging approach that bridges the resolution gaps between the molecule and the whole cell, in space and time [63]. We address the following topics:

- Image superresolution/image denoising required to preserve 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 and modelling of molecule trafficking at different spatial and temporal scales (e.g. biophysical model assimilation for dynamic representation in video-microscopy and prediction in biology.

We focus on the cellular and molecular mechanisms involved in membrane transport and trafficking at the scale of a single cell.

2.4. Main challenges in image processing for multimodal and multidimensional microscopy

In most cases, modern microscopy in biology is characterized by a large number of dimensions that fits 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 bio-molecular 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 a comparative analysis of 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 (i.e. image processing) which are limiting factors in front of the data, and to favor the organization and the interpretation of the information associated to this data corpus. It motivates and requires innovative mathematical tools and concepts: data fusion, image registration, superresolution, data mining, life dynamics modelling, ...

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 participate in several projects (PhD and post-doc supervision, contracts...) with biologists in the field of cell biology and microscopy. We have promoted and designed non-parametric methods since prior knowledge cannot be easily taken into account for extracting unattended but desired information from image data. We have proposed user-friendly algorithms for processing 3D or 4D data.

The scientific projects of the SERPICO team are complementary to the other on-going and planned projects of the UMR 144 CNRS-Institut Curie Unit. A subset of projects is 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. Our projects rely partially on the results and advances of these instrumental projects and a positive synergy is foreseen.

3. Research Program

3.1. Statistics and algorithms for computational microscopy

Many live-cell fluorescence imaging experiments are limited in time to prevent phototoxicity and photobleaching. The amount of light and time required to observe entire cell divisions can generate biological artifacts. In order to produce images compatible with the dynamic processes in living cells as seen in video-microscopy, we study the potential of denoising, superresolution, tracking, and motion analysis methods in the Bayesian and the robust statistics framework to extract information and to improve image resolution while preserving cell integrity.

In this area, we have already demonstrated that image denoising allows images to be taken more frequently or over a longer period of time [6]. The major advantage is to preserve cell integrity over time since spatio-temporal information can be restored using computational methods [9], [3], [10], [5]. This idea has been successfully applied to wide-field, spinning-disk confocal microscopy [2], TIRF [40], fast live imaging and 3D-PALM using the OMX system in collaboration with J. Sedat and M. Gustafsson at UCSF [6]. The corresponding ND-SAFIR denoiser software (see Section 6.7) has been licensed to a large set of laboratories over the world. New information restoration and image denoising methods are currently investigated to make SIM imaging compatible with the imaging of molecular dynamics in live cells. Unlike other optical sub-diffraction limited techniques (e.g. STED [51], PALM [41]) SIM has the strong advantage of versatility when considering the photo-physical properties of the fluorescent probes [49]. Such developments are also required to be compatible with "high-throughput microscopy" since several hundreds of cells are observed at the same time and the exposure times are typically reduced.

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

3.2.1. Motion analysis and tracking

The main challenge is to detect and track xFP tags with high precision in movies representing several Giga-Bytes of image data. The data are most often collected and processed automatically to generate information on partial or complete trajectories. Accordingly, we address both the methodological and computational issues involved in object detection and multiple objects tracking in order to better quantify motion in cell biology. Classical tracking methods have limitations as the number of objects and clutter increase. It is necessary to correctly associate measurements with tracked objects, i.e. to solve the difficult data association problem [57]. Data association even combined with sophisticated particle filtering techniques [60] or matching techniques [58] is problematic when tracking several hundreds of similar objects with variable velocities. Developing new optical flow and robust tracking methods and models in this area is then very stimulating since the problems we have to solve are really challenging and new for applied mathematics. In motion analysis, the goal is to formulate the problem of optical flow estimations in ways that take physical causes of brightness constancy violations into account [46], [50]. The interpretation of computed flow fields enables to provide spatio-temporal signatures of particular dynamic processes (e.g. Brownian and directed motion) and could help to complete the traffic modelling.

3.2.2. Event detection and motion classification

Protein complexes in living cells undergo multiple states of local concentration or dissociation, sometimes associated with diffusion processes. These events can be observed at the plasma membrane with TIRF microscopy. The difficulty arises when it becomes necessary to distinguish continuous motions due to trafficking from sudden events due to molecule concentrations or their dissociations. Typically, plasma membrane vesicle docking, membrane coat constitution or vesicle endocytosis are related to these issues.

Several approaches can be considered for the automatic detection of appearing and vanishing particles (or spots) in wide-field and TIRF microscopy images. Ideally this could be performed by tracking all the vesicles contained in the cell [60], [48]. Among the methods proposed to detect particles in microscopy images [61], [59], none is dedicated to the detection of a small number of particles appearing or disappearing suddenly between two time steps. Our way of handling small blob appearances/dis-appearances originates from the observation that two successive images are redundant and that occlusions correspond to blobs in one image which cannot be reconstructed from the other image [2] (see also [44]). Furthermore, recognizing dynamic protein behaviors in live cell fluorescence microscopy is of paramount importance to understand cell mechanisms. In our studies, it is challenging to classify intermingled dynamics of vesicular movements, docking/tethering, and ultimately, plasma membrane fusion of vesicles that leads to membrane diffusion or exocytosis of cargo proteins. Our aim is then to model, detect, estimate and classify subcellular dynamic events in TIRF microscopy image sequences. We investigate methods that exploits space-time information extracted from a couple of successive images to classify several types of motion (directed, diffusive (or Brownian) and confined motion) or compound motion.

3.3. From models to image data: simulation and modelling of membrane transport

Mathematical biology is a field in expansion, which has evolved into various branches and paradigms to address problems at various scales ranging from ecology to molecular structures. Nowadays, system biology [52], [63] aims at modelling systems as a whole in an integrative perspective instead of focusing on independent biophysical processes. One of the goals of these approaches is the cell in silico as investigated at Harvard Medical School (http://vcp.med.harvard.edu/) or the VCell of the University of Connecticut Health Center (http://www.nrcam.uchc.edu/). Previous simulation-based methods have been investigated to explain the spatial organization of microtubules [53] but the method is not integrative and a single scale is used to describe the visual patterns. In this line of work, we propose several contributions to combine imaging, traffic and membrane transport modelling in cell biology.

In this area, we focus on the analysis of transport intermediates (vesicles) that deliver cellular components to appropriate places within cells. We have already investigated the concept of Network Tomography (NT) [62] mainly developed for internet traffic estimation. The idea is to determine mean traffic intensities based on statistics accumulated over a period of time. The measurements are usually the number of vesicles detected at each destination region receiver. The NT concept has been investigated also for simulation [4] since it can be used to statistically mimic the contents of real traffic image sequences. In the future, we plan to incorporate more prior knowledge on dynamics to improve representation. An important challenge is to correlate stochastic, dynamical, one-dimensional *in silico* models studied at the nano-scale in biophysics, to 3D images acquired in vivo at the scale of few hundred nanometers.

4. Application Domains

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

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).

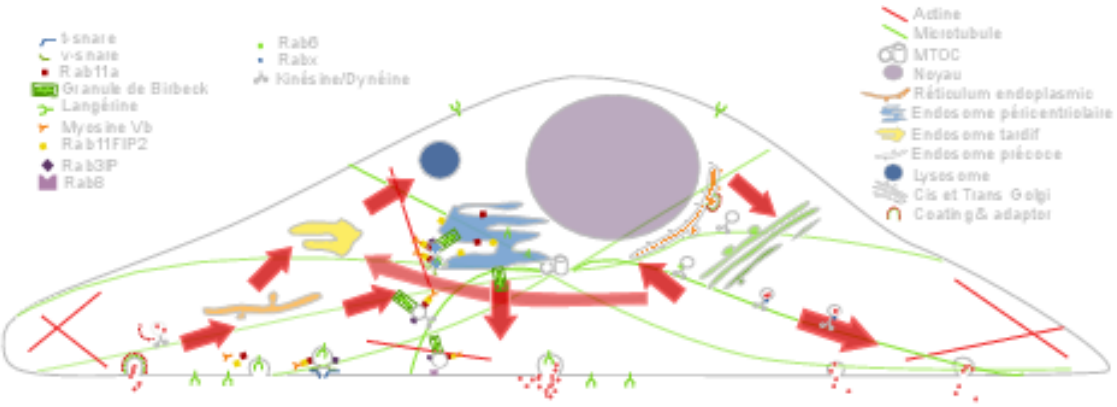

Figure 1. Cargo Langerin Trafficking controlled by Rab11A/Rab11FIP2/MyoVb platform.

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

5.1.1. New projects

The 4 year-ANR-DALLISH proposal (PRC / Challenge 7 / Topic 5), coordinated by the Serpico Team-Project, has been accepted in September 2016.

The CytoDI Associated Team, in collaboration with University of Texas, SouthWestern Medical Center, Dallas (TX, USA) started in January 2016.

6. New Software and Platforms

6.1. TMA-Lib

KEYWORD: Biomedical imaging
FUNCTIONAL DESCRIPTION: The TMA-LIB enables to jointly detect (adaptive wavelet transform), segment (parametric active contours) and restore (artifact correction and deconvolution) TMA (Tissue MicroArrays) images.

- **Participants**: Hoai Nam Nguyen, Charles Kervrann.
- **Partner:** INNOPSYS Company.
- **Contact:** Charles Kervrann.
- **Languages:** C/C++, Matlab.

6.2. QuantEv

KEYWORD: Biomedical imaging

FUNCTIONAL DESCRIPTION: The QUANTEV software is dedicated to the analysis of the spatial distribution of intracellular events represented by any static or dynamical descriptor (e.g. detected points, segmented regions, trajectories...), 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**: Thierry Pécot, Charles Kervrann, Jean Salamero.
- **Contact:** Thierry Pécot, Charles Kervrann.
- **On-line demo:** http://mobyle-serpico.rennes.inria.fr/cgi-bin/portal.py#forms::...
- **Languages:** C/C++ and JAVA (plug-in ICY: http://icy.bioimageanalysis.org).

6.3. C-CRAFT

KEYWORD: Biomedical imaging
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**: Thierry Pécot, Charles Kervrann, Patrick Bouthemy, Jean Salamero.
- **Contact:** Thierry Pécot, Charles Kervrann.
- **On-line demo:** http://mobyle-serpico.rennes.inria.fr/cgi-bin/portal.py#forms::C-CRAFT
- **Languages:** C/C++ and JAVA (plug-in ICY: http://icy.bioimageanalysis.org/plugin/C-CRAFT).
- **Reference:** [12]

6.4. ATLAS

KEYWORD: Biomedical imaging
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 dynamics. 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/ standard deviation 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**: Antoine Basset, Patrick Bouthemy, Thierry Pécot, Charles Kervrann.
- **Contact:** Thierry Pécot, Patrick Bouthemy, Charles Kervrann.
- **On-line demo:** http://mobyle-serpico.rennes.inria.fr/cgi-bin/portal.py#forms::ATLAS
- **Language:** C/C++.
- **Reference:** [1]

6.5. Hullkground

KEYWORDS: Bioinformatics - Biomedical imaging

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 shape-based scale-space method.

- **Participants:** Anatole Chessel, Jean Salamero, Charles Kervrann.
- **Contact:** Charles Kervrann.
- **APP deposit number:** IDDN.FR.001.400005.000.S.P.2009.000.21000
- **On-line demo:** http://mobyle-serpico.rennes.inria.fr/cgi-bin/portal.py#forms::Hullkground
- **Free distribution:** http://serpico.rennes.inria.fr/doku.php?id=software:hullkground:hullkground
- **Language:** JAVA (plug-in IMAGEJ: http://rsbweb.nih.gov/ij/).

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 photo-bleaching 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.

- **Participants:** Patrick Bouthemy, Jean-Marc Odobez, Fabien Spindler.
- **Contact:** Patrick Bouthemy, Fabien Spindler.
- **APP deposit number:** FR.001.520021.001.S.A.1998.000.21000 / release 1.3.11, January 2005)
- **Free academic software distribution:** http://www.irisa.fr/vista/Motion2D
- **On-line demo:** http://mobyle-serpico.rennes.inria.fr/cgi-bin/portal.py#forms::Motion2D
- **Languages:** C/C++ and JAVA (plug-in IMAGEJ: http://rsbweb.nih.gov/ij/).

6.7. ND-SAFIR

KEYWORDS: Biology - Health - Image analysis - Photonic imaging - Fluorescence microscopy - Biomedical imaging

SCIENTIFIC DESCRIPTION: The ND-SAFIR software removes additive Gaussian and non-Gaussian noise in still 2D or 3D images or in 2D or 3D image sequences (without any motion computation) [5]. The method is unsupervised and is based on a pointwise selection of small image patches of fixed size (a data-driven adapted way) in spatial or space-time neighbourhood of each pixel (or voxel). The main idea is to modify each pixel (or voxel) using the weighted sum of intensities within an adaptive 2D or 3D (or 2D or 3D + time) neighbourhood and to use image patches to take into account complex spatial interactions. The neighbourhood size is selected at each spatial or space-time position according to a bias-variance criterion. The algorithm requires no tuning of control parameters (already calibrated with statistical arguments) and no library of image patches. The method has been applied to real noisy images (old photographs, JPEG-coded images, videos, ...) and is exploited in different biomedical application domains (time-lapse fluorescence microscopy, video-microscopy, MRI imagery, X-ray imagery, ultrasound imagery, ...).

- **Participants:** Jérôme Boulanger, Charles Kervrann, Patrick Bouthemy, Jean Salamero.
- **Partners:** INRA, PiCT - CNRS - Institut Curie.
- **APP deposit number:** IDDN.FR.001.190033.002.S.A.2007.000.21000 / new release 3.0 in 2013)
- **Free academic software distribution:** Binaries of the software ND-SAFIR are freely and electronically distributed (http://serpico.rennes.inria.fr/doku.php?id=software:nd-safir:index).
- **On-line demo:** http://mobyle-serpico.rennes.inria.fr/cgi-bin/portal.py#forms::NDSafir
- **Languages:** C/C++, MATLAB and JAVA (plug-in IMAGEJ: http://rsbweb.nih.gov/ij/). The C/C++ software has been developed under Linux using the CImg library and has been tested over several platforms such as Linux/Unix, Windows XP and Mac OS.
- **Commercial licence agreements:** Innopsys, Roper Scientfic, Photmetrics, Nikon Europe BV (2016).
- **Reference:** [5]

6.8. F2D-SAFIR

KEYWORD: Biomedical imaging
FUNCTIONAL DESCRIPTION: The F2D -SAFIR software removes mixed Gaussian-Poisson noise in large 2D images, typically $10^3 \times 10^3$ 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 dedicated to microarrays image denoising, was licensed to the INNOPSYS company which develops scanners for disease diagnosis and multiple applications (gene expression, genotyping, aCGH, ChIP-chip, microRNA, ...).

- **Participant**: Charles Kervrann.
- **Partner:** INRA.
- **Contact:** Charles Kervrann.
- **APP deposit number:** IDDN.FR.001.190033.001.S.A.2007.000.21000
- **Language:** C/C++.

6.9. TubuleJ

KEYWORDS: Bioinformatics - Biomedical imaging

FUNCTIONAL DESCRIPTION: The TUBULEJ software written in java (plug-in ImageJ) is devoted to the analysis of microtubules and helical structures in 2D cryo electron microscope images. The software straightens curved microtubule images by estimating automatically point locations on the microtubule axis. The estimation of microtubule principal axis relies on microtubule cylindrical shape analyzed in the Fourier domain. A user-friendly interface enables to filter straight fiber images by selecting manually the layer lines of interest in the Fourier domain. This software can be used to generate a set of 2D projection views from a single microtubule projection view and a few parameters of this microtubule structure.

- **Participants:** Denis Chrétien, Charles Kervrann, Sophie Blestel.
- **Contact:** Denis Chrétien.
- **Partners:** University of Rennes 1, CNRS.
- **APP deposit number:** IDDN.FR.001.240023.000.S.P.2011.000.21000
- **On-line demo:** http://equipes.igdr.univ-rennes1.fr/en/tips/Software/TubuleJ/
- **Language:** JAVA (plug-in IMAGEJ: http://rsbweb.nih.gov/ij/).

6.10. Cryo-Seg

KEYWORDS: Bioinformatics - Biomedical imaging
FUNCTIONAL DESCRIPTION: The CRYO-SEG software has been developed to detect microtubule structures and helical structures in 2D cryo electron microscope images. Cryo electron tomography allows 3D observation of biological specimens in their hydrated state. Segmentation is formulated as Maximum A Posteriori estimation problem and exploits image patches to take into account spatial contexts (Markov Random Fields). Because of the contrast anisotropy in the specimen thickness direction, the whole tomogram is segmented section by section, with an automatic update of reference patches. This algorithm has been evaluated on synthetic data and on cryo electron tomograms of in vitro microtubules. On real data, this segmentation method extracts the most contrasted regions of microtubules, and 3D visualization is improved.

- **Participants:** Denis Chrétien, Charles Kervrann, Sophie Blestel.
- **Contact:** Denis Chrétien.
- **Partners:** University of Rennes 1, CNRS.
- **Languages:** C/C++ and JAVA (plug-in IMAGEJ: http://rsbweb.nih.gov/ij/).

6.11. Platforms

6.11.1. Mobyle@Serpico plateform and software distribution

The objective is to disseminate the distribution of SERPICO image processing software for biologists:

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 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[12], ATLAS[1], HOTSPOTDETECTION[56], HULLKGROUND[45], KLTRACKER[55], MOTION2D[54], MS-DETECT[47], ND-SAFIR[5], OPTICALFLOW and FLUX ESTIMATION [12]. 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).

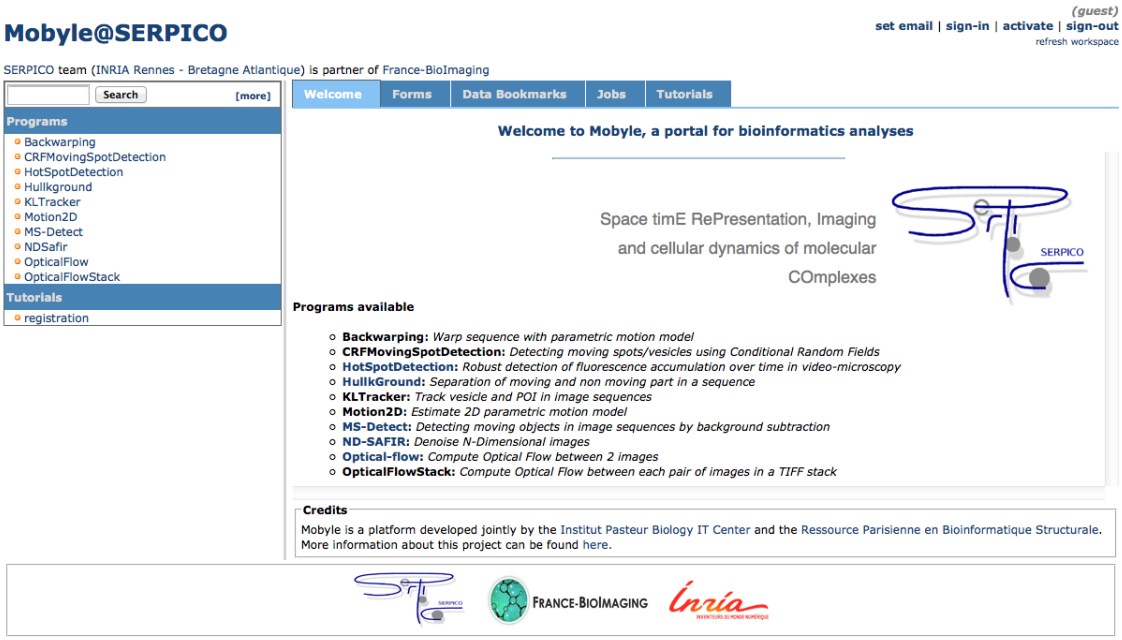

*Figure 2. Mobyle@*SERPICO *web portal.*

IMAGEJ **plug-ins**: 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 [5], HULLKGROUND [45], MOTION2D [54], HOTSPOTDETECTION [56], STLAS [1]. The C-CRAFT algorithm [12] has been developped for the image processing ICY platform (http://icy.bioimageanalysis.org/).

Institut Curie CID iManage database: The microscopy facility of Institut Curie has co-developped a commercial database system (CID iManage/Strand Avadis company). The database can be searched via meta-data and includes menu selections that enable to run remote processing from a cluster. We have integrated ND-SAFIR and HULLKGROUND in the interface environment to allow the database users to process their images easily, and store associated results and parameters used.

- **Participants:** Thierry Pécot, Charles Kervrann, Charles Deltel (Inria Rennes SED).
- **Contact:** Thierry Pécot, Charles Kervrann.

6.11.2. 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:** Thierry Pécot, Charles Kervrann, Charles Deltel (Inria Rennes SED).

7. New Results

7.1. Statistical aggregation methods for image denoising and estimation

Participants: Charles Kervrann, Frédéric Lavancier.

In the line of the Non-Local means [43] and ND-SAFIR [9], [10], [5] 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 that our algorithm improves significantly the classical NL-means, and is competitive when compared to the more sophisticated NL-means filters both in terms of PSNR values and visual quality.

Previously, we investigated statistical aggregation methods which optimally combine several estimators to produce a boosted solution [11]. In this range of work, we also introduced in [24] a general method to combine estimators in order to produce a better estimate. From a theoretical point of view, we proved that this method is optimal in some sense. It is illustrated on standard statistical problems in parametric and semi-parametric models where the averaging estimator outperforms the initial estimators in most cases. This method has been subsequently adapted in [39] to models in spatial statistics. As part of an on-going work, we are applying this method to improve patch-based image denoising algorithms.

References: [24] [39]

Collaborators: Qiyu Jin (School of Mathematical Science, Inner Mongolia University, China),
Ion Grama and Quansheng Liu (University of Bretagne-Sud, Vannes),
Paul Rochet (Laboratoire de Mathématiques Jean Leray (LMJL), University of Nantes).

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

Participants: Hoai Nam Nguyen, Giovanni Petrazzuoli, Aminata Diouf, Charles Kervrann.

In fluorescence microscopy, the image quality is limited by out-of-focus blur and high noise. Traditionally, image deconvolution is needed to estimate a good quality version of the observed image. The result of deconvolution depends heavily on the choice of the regularization term and the noise dependent fidelity term. The regularization functional should be designed to remove noise while preserving image discontinuities. Accordingly, we investigated new regularization terms to preserve fine details of underlying structures and we studied appropriate proximal algorithms. The deconvolution method has been especially dedicated to large 2D 20000×60000 images acquired with ISO scan imager (see Fig.3). The images are preliminary pre-processed to compensate non constant pixel displacement during acquisition/scanning (dejittering effect). The method has also been evaluated on 2D Vimentin filament images (UTSW, CytoDI Associated Team) to facilitate filament segmentation. The method is able to process a 512×512 image in 250 ms with a non optimized implementation.

Collaborators: Vincent Paveau and Cyril Cauchois (Innopys company),
Philippe Roudot (UTSW, Dallas, USA).

7.3. Quantifying the spatial distribution of intracellular events

Participants: Thierry Pécot, Charles Kervrann.

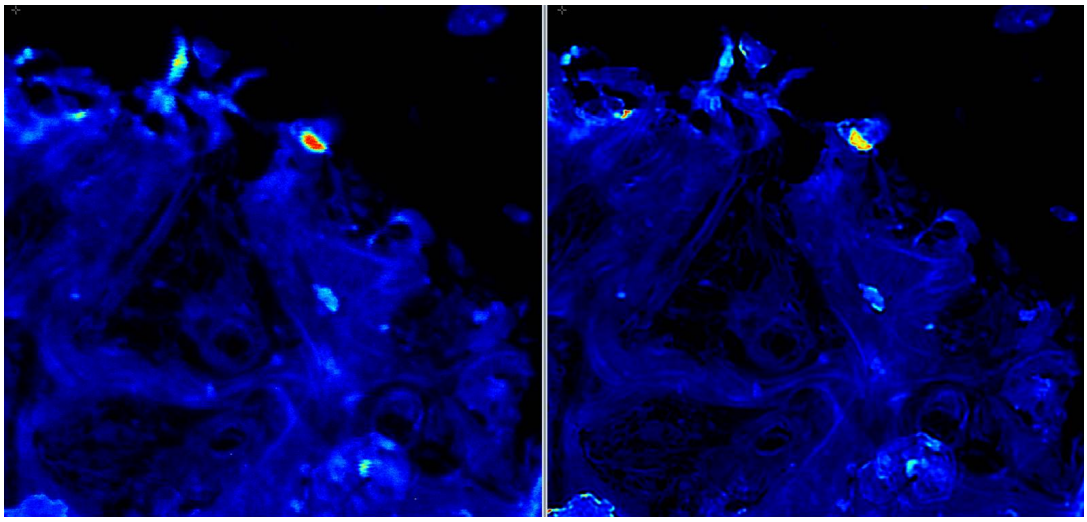

Figure 3. Illustration of image dejittering and deconvolution algorithms applied to a selected fluorescence region extracted from a large TMA image (by courtesy of Innopsys).

Automated processing of fluorescence microscopy data allows quantifying cell phenotypes in an objective and reproducible way. However, most computational methods are based on the complex combination of heterogeneous features such as statistical, geometrical, morphological and frequency properties, which makes difficult to draw definitive biological conclusions. Additionally, most experimental designs, especially at single cell level, pool together data coming from replicated experiments of a given condition, neglecting the biological variability between individual cells. To address these issues, we developed a generic and non-parametric framework (QuantEv) to study the spatio-temporal distribution of moving Rab6 membranes and the effect of actin disruption on Rab11 trafficking in coordination with cell shape. The main advantage of QuantEv is to process robustly and accurately homogeneous and heterogeneous populations. As demonstration, we compared the results obtained by QuantEv with those from kernel density maps, for Rab6 positive membranes on crossbow- and disk-shaped cells.

Collaborators: Jean Salamero, Jérôme Boulanger and Liu Zengzhen (UMR 144 CNRS-Institut Curie).

7.4. 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.

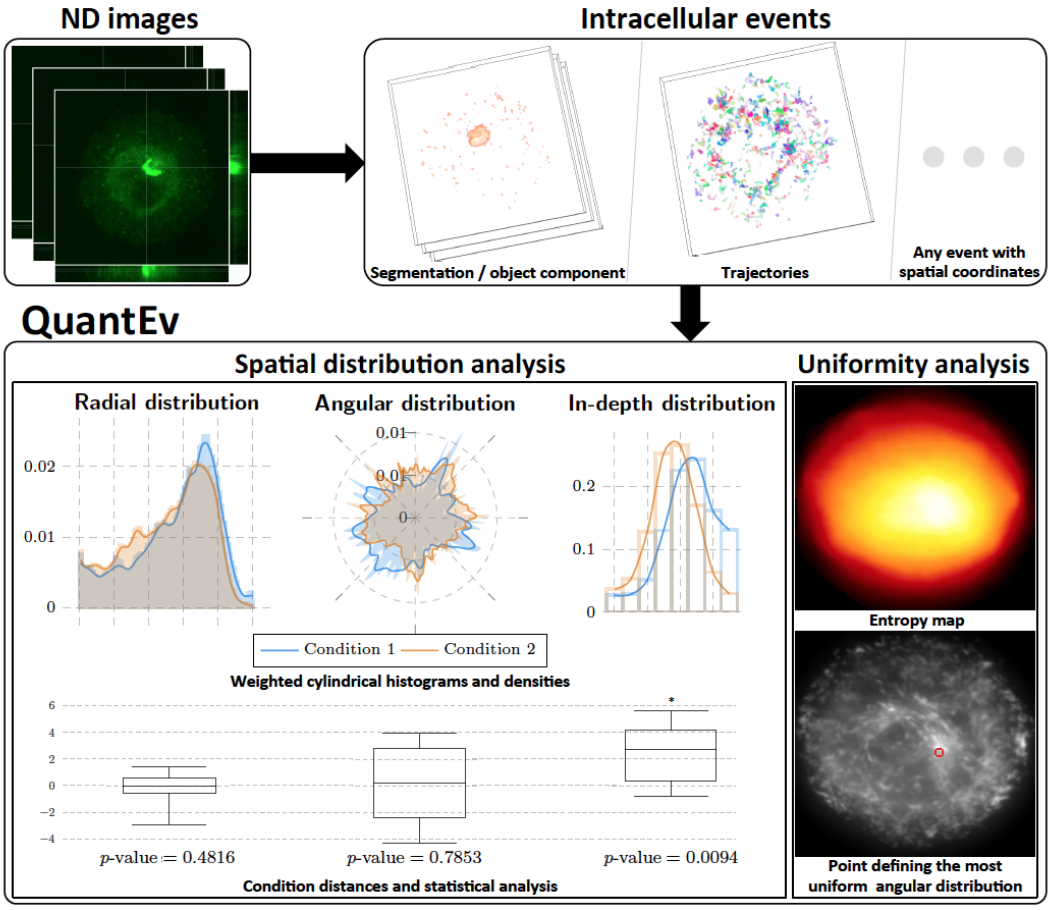

Figure 4. Overview of QuantEv approach.

This year, we have continued our study of correlation-based methods for local diffusion estimation in TIRFM images. Our original method was tested on both synthetic and real images showing an isolated diffusion event, and a robust algorithm was developed to cope with noisy data. Our first model was linear and had only two parameters to estimate. Diffusion coefficient estimation was accurate on synthetic images even with moderate to low signal-to-noise ratio, and within reasonable margins of error on real images with little noise. We have then extended our mathematical model by using a global approach subject to initial local diffusion conditions. Isolated diffusion events are well described, but this new model can also handle the case of noisy images with non-uniform background, and the case of two or more diffusion events in the region of interest. The extended model is non-linear but has few parameters to estimate. An iterative minimization method is used to fit the model parameters to the data points (see Fig. 5). Despite non-linearity, results are accurate on images with pure diffusion events and show robustness to background. The quality of parameters estimation is barely influenced by the length and size of the input TIRFM sequence, which is not the case with standard correlation methods. We have thus developed a correlation-based method that is able to estimate diffusion in a variety of cases in TIRFM images (Fig. 5).

Collaborators: Francois Waharte (UMR 144 CNRS-Institut Curie, PICT-IBiSA),
Perrine Paul-Gilloteaux (UMS 3556, IRS-UN, Nantes).

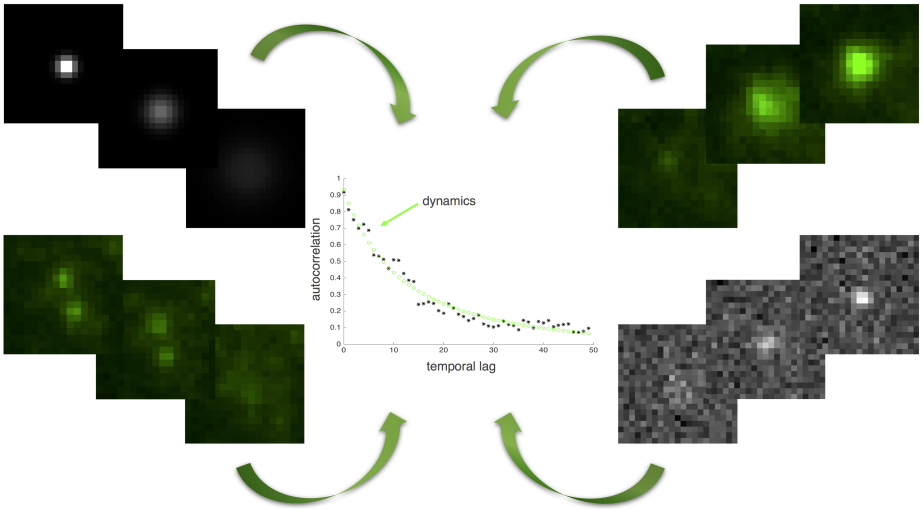

Figure 5. Local diffusion estimation in both synthetic (black and white spots) and real TIRF images (green spots, UMR 144 CNRS-Institut Curie, PICT-IBiSA). Only three frames of each sequence are shown. The computed autocorrelation values (in black) for different temporal lag values, and the fitting function for these values (in green) are given (plot in the middle) for the upper-right sequence.

7.5. Colocalization for live cell and super-resolution imaging

Participants: Frédéric Lavancier, Thierry Pécot, Charles Kervrann.

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. In statistics, this amounts to characterizing the joint spatial repartition and the spatial overlap between different fluorescent labels. Two distinct categories of colocalization approaches are considered to address this issue: intensity-based methods and object-based methods. The popular (intensity-based) Pearson's correlation method, which returns values between -1 and +1, is known to be sensitive to high intensity backgrounds and provides errors if the signal-to-noise ratio (SNR) is typically low. The object-based method, recommended in single molecule imaging, analyses the spatial distribution of the two sets of detected spots by using point process statistics.

Accordingly, we developed an original, fast, robust-to-noise and versatile approach that reconciles intensity-based and object-based methods for both conventional diffraction-limited microscopy and sub-resolved microscopy. The procedure is only controlled by a p-value and tests whether the Pearson correlation between two binary images is significantly positive. This amount 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, the method handles 2D and 3D images, variable SNRs and any kind of cell shapes. It is able to colocalize large regions with small dots, as it is the case in TIRF-PALM experiments and to detect negative colocalization. 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. Finally, the method provides maps to geocolocalize molecule interactions in specific image regions.

Collaborators: Jean Salamero and Liu Zengzhen (UMR 144 CNRS-Institut Curie).

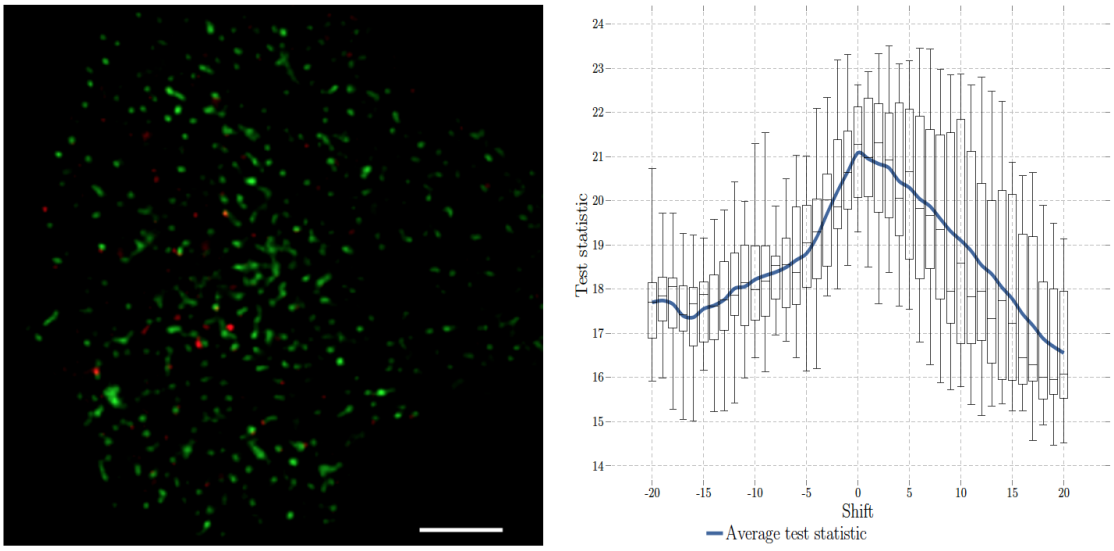

Figure 6. Illustration of statistical spatio-temporal colocalization. a) Average intensity projection of a 3D TIRF acquisition showing m-Cherry Langerin (red channel) and GFP Rab11A proteins (green channel) (courtesy of UMR 144 CNRS-Institut Curie); b) test statistic value with respect to the shift between frames.

7.6. 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. We assume that the motions of particles follow a certain class of random process: the diffusion processes. In 2015, we developed a statistical test to classify the intracellular motions into three groups : free diffusion (*i-e* Brownian motion), subdiffusion and superdiffusion. This method is an alternative to the commonly used Mean Square Displacement (MSD) analysis. This year, we have studied theoretical properties of our procedure. We have shown that it behaves well asymptotically, that is when we observe the particle trajectory for a very long time, for certain parametric models. The models on which we assess our procedure are representative of the three classes aforementioned and extensively used in the literature. Among them we can cite Brownian motion with drift, Ornstein-Uhlenbeck process and fractional Brownian motion. An illustration of the testing procedure is shown in Fig. 7.

We also extend our method to address two different questions. First, we are interested in testing a large number of trajectories. The first version of our test is a single test procedure. It is known that applying multiple times a test without care leads to a high number of false positives. Then, we modify our initial method to overcome this problem. Secondly, in the case in which we observe very long trajectories, it is likely that the particle motion changes over time. Therefore, we are currently adapting our initial procedure to detect change-point along a single trajectory.

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

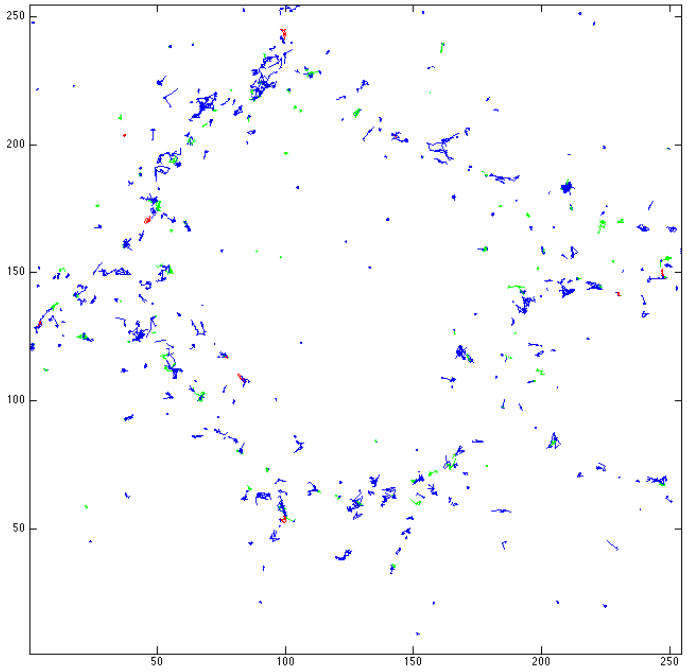

Figure 7. Labelling of the dynamics of trajectories in Single Particle Tracking PALM (Courtesy of Institut Interdisciplinaire de Neurosciences CNRS UMR 5297). The color code is green for subdiffusion, blue for Brownian motion and red for superdiffusion.

7.7. Inference for spatial Gibbs point processes

Participant: Frédéric Lavancier.

Gibbs point processes are popular and widely used models in spatial statistics to describe the repartition of points or geometrical structures in space. They initially arose from statistical physics where they are models for interacting particles. They are now used in as different domains as astronomy, biology, computer science, ecology, forestry, image analysis and materials science.

Assuming a parametric form of the Gibbs interaction, the natural method to estimate the parameters is likelihood inference. Since its first use in the 80's, this method is conjectured to be consistent and efficient. However the theoretical properties of maximum likelihood for Gibbs point processes remain largely unknown. In [17], we partly solved this 30 years old conjecture by proving the consistency of the likelihood procedure for a large class of Gibbs models. As important examples, we deduce the consistency of the maximum likelihood estimator for all parameters of the Strauss model, the hardcore Strauss model, the Lennard-Jones model and the area-interaction model, which are commonly used models in practice.

A practical issue of likelihood estimation yet is that this method depends on an intractable normalizing constant that has to be approximated by simulation. To avoid this problem, other methods of estimation have been introduced, including pseudo-likelihood estimation. The theoretical properties of the pseudo-likelihood method are fairly well known in the case of finite-range Gibbs interactions. However this setting rules out some major Gibbs model as the Lennard-Jones model. In [16], we extend the pseudo-likelihood procedure to infinite range Gibbs interactions and we prove its consistency and its asymptotic normality.

References: [16] [17]

Collaborators: David Dereudre (Laboratoire Paul Painlevé (UMR 8524), University of Lille 1),
Jean-François Coeurjolly (Laboratoire Jean Kutzmann, University of Grenoble).

7.8. Statistical aspects of Determinantal Point Processes

Participant: Frédéric Lavancier.

Determinantal point processes (DPPs) have been introduced in their general form by Macchi (1975) and have been extensively studied from a probabilistic point of view in the 2000's (one of the main reason being their central role in random matrix theory). In a previous work, we have demonstrated that DPPs provide useful models for the description of spatial point pattern datasets where nearby points repel each other.

In [15], we have addressed the question of how repulsive a stationary DPP can be, in order to assess the range of practical situations this promising class of models may model. We determine the most repulsive DPP (in some sense) and we introduce new parametric families of stationary DPPs that can cover a large range of DPPs, from the stationary Poisson process (the case of no interaction) to the most repulsive DPP. Some theoretical aspects of inference for stationary DPPs are tackled in [13] and [14]. In the former study we establish the Brillinger mixing property of stationary DPPs, a first important step toward asymptotic inference. In the latter contribution, we exploit this result to deduce the consistency and asymptotic properties of contrast estimators for stationary DPPs.

References: [13] [15] [14]

Collaborators: Christophe Ange Napoléon Biscio (LMJL, University of Nantes),
Jesper Möller (Department of Mathematical Sciences, Aalborg University, Denmark),
Ege Rubak (Department of Mathematical Sciences, Aalborg University, Denmark).

7.9. Modeling aggregation and regularity in spatial point pattern datasets

Participant: Frédéric Lavancier.

In the spatial point process literature, analysis of spatial point pattern datasets are often classified into three main cases: (i) Regularity (or inhibition or repulsiveness), modelled by Gibbs point processes, hard core processes like Matern hard core models, and determinantal point processes; (ii) Complete spatial randomness, modelled by Poisson point processes; (iii) Aggregation (or clustering), modelled by Poisson cluster processes and Cox processes. For applications the classification (i)-(iii) can be too simplistic, and there is a lack of useful spatial point process models with, loosely speaking, aggregation on the large scale and regularity on the small scale. For instance, we may be interested in such a model for the repartition of the centres of vesicles in a cell, that exhibit some spatial clustering at large scales while having a minimal distance between them.

In [23], we have considered a dependent thinning of a regular point process with the aim of obtaining aggregation on the large scale and regularity on the small scale in the resulting target point process of retained points. Various parametric models for the underlying processes are suggested and the properties of the target point process are studied. Simulation and inference procedures are discussed when a realization of the target point process is observed, depending on whether the thinned points are also observed or not.

Reference: [23]
Collaborator: Jesper Möller (Department of Mathematical Sciences, Aalborg University, Denmark).

7.10. Multi-scale spot segmentation with automatic selection of image scales

Participants: Bertha Mayela Toledo Acosta, Patrick Bouthemy.

Detecting spot-like objects of different sizes in images is required for many applications. A spot detection framework can be divided in three sub-steps : first, image preprocessing to smooth out noise; second, signal enhancement to highlight spots; third, spot detection by thresholding; the two first ones being often merged in a single operator. However, elements of interest do not all correspond to the same image scale, if the collection includes subgroups of different sizes or if perspective effects occur. Then, the need is not merely the selection of the optimal image scale, but of all the meaningful scales. We dealt with the problem of multi-scale spot detection while automatically selecting the meaningful scales. Our primary interest is to detect particles in microscopy images, but our method can be applied to other types of images as well. We defined an original criterion based on the a contrario approach and the LoG scale-space framework to automatically select the meaningful scales. We designed a coarse-to-fine multi-scale spot segmentation scheme involving a locally adaptive thresholding across scales, to come up with the final map of segmented spots. We carried out experimental results on simulated and real images of different types, and we demonstrated that our method outperforms other existing methods.

Reference: paper accepted, ICASSP'2017.
Collaborator: Antoine Basset (CNES, Toulouse).

7.11. Multi-modal registration for correlative light-electron microscopy

Participants: Bertha Mayela Toledo Acosta, Patrick Bouthemy, Charles Kervrann.

We pursue our work on correlative light-electron microscopy (CLEM), which combines the strengths of two different imaging modalities, light microscopy (LM) and electron microscopy (EM), to jointly study intracellular dynamics and ultrastructure of a biological sample. CLEM registration is an important and difficult problem given the significant differences between LM and EM images regarding resolution, field of view, image size and appearance. We designed an automated approach for retracing and registering CLEM images, by implementing a patch-based search using a common Laplacian of Gaussian (LoG) image representation of the LM and EM images. We have redefined the geometry of the patch, opting for a disk-shaped patch. The search (or retracing) step uses histogram-based methods as they are invariant to rotation, and it provides a pre-registration by producing the estimate of the translation component. Usually, there is a large disparity on the orientation of EM and LM images. To handle this problem, we have implemented a mutual information-based method to compute the rotation between the EM and LM patches and to refine the registration. We have also tackled the registration issue in both directions (LM to EM, and EM to LM), and compared our approach to a correlation-based method.

We have tested our approach on a larger set of real CLEM images (provided by Institut Curie) presenting a large diversity in content, image size, and appearance, further validating our method (see Fig. 8). We are currently exploring how our automated CLEM registration method could be exploited to guide EM acquisition within a coarse-to-fine framework.

Reference: [35]
Collaborators: Xavier Heiligenstein (UMR 144 CNRS-Institut Curie),
Grégoire Malandain (Inria, Morpheme EPC, Sophia-Antipolis).

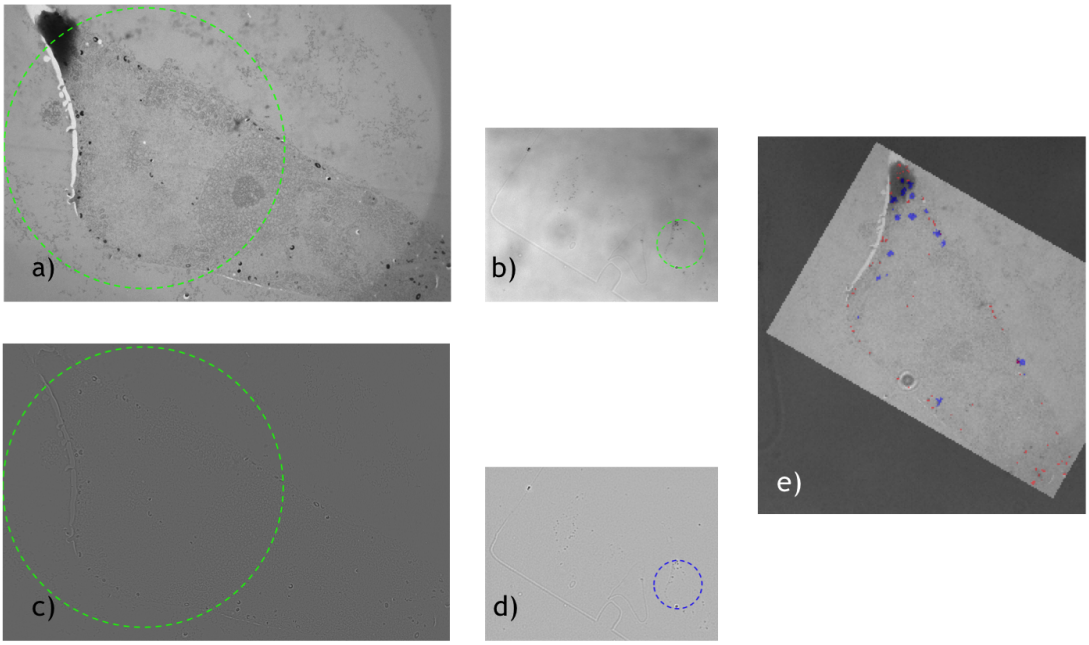

Figure 8. Figure 1. CLEM experiment (images from UMR 144 CNRS-Institut Curie, Xavier Heiligenstein): a) EM image with Region of Interest (ROI) framed in green; b) ground-truth location of the corresponding LM patch framed in green; c) ROI delineated in the Log-EM image, framed in green; d) selected patch (SP) in the LoG-LM image, framed in blue to be comaprd with the green disk in b); f) overlay (after registration).

7.12. Denoising and compensation of the missing wedge in cryo electron tomography

Participants: Emmanuel Moebel, Charles Kervrann.

In this study, we address two important issues in cryo electron tomography (CET) images: reduction of noise and restoration of information in the missing wedge (MW). The MW is responsible for several type 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. 9). 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.

Several aspects of the method have been studied in order to gain a deeper understanding of this strategy: different kinds of noise as well as several denoising algorithms (BM3D, NL-Bayes, NL-means, Total Variation...) have been evaluated. Furthermore, different kinds of transforms have been tested in order to apply the constraint (Fourier transform, Cosine transform, pseudo-polar Fourier transform). Also, a process has been set up in order to evaluate the performance of the proposed method on experimental data. Thus, convincing results on experimental data have been achieved (see Fig. 9) using the Fourier Shell Correlation (FSC) as an evaluation metric. In order to measure the quality of the recovered MW only, we also compute the FSC over the MW support ("constrained FSC").

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

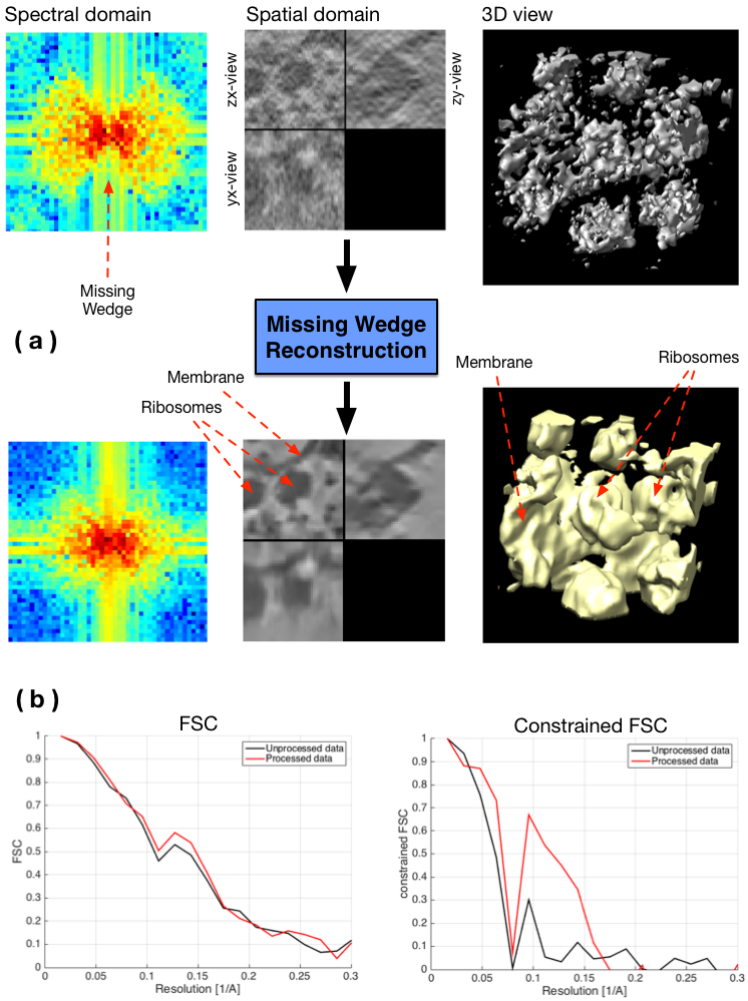

Figure 9. Experimental sub-tomogram containing ribosomes attached to a membrane. (a) Top row: original data in the spectral (left) and spatial (middle) domains and 3D view of the thresholded data (right). Bottom row: denoised data shown as above. (b) FSC and constrained FSC measures of the method input (in black) and output (in red). All measures are wrt the same reference.

7.13. Spatially-variant kernel for optical flow under low signal-to-noise ratios

Participant: Charles Kervrann.

Local and global approaches can be identified as the two main classes of optical flow estimation methods. This year, we have proposed a framework to combine the advantages of these two principles, namely robustness to noise of the local approach and discontinuity preservation of the global approach. The idea is to adapt spatially the local support of the local parametric constraint in the combined local-global model [42]. To this end, we jointly estimate the motion field and the parameters of the spatial support. We apply our approach to the case of Gaussian filtering, and we derive efficient minimization schemes for usual data terms. The estimation of a spatially varying standard deviation map prevents from the smoothing of motion discontinuities, while ensuring robustness to noise. We validated our method for a standard model and demonstrated how a baseline approach with pixel-wise data term can be improved when integrated in our framework. The method has been evaluated on the Middlebury benchmark with ground truth and on real fluorescence microscopy data for which noise is the main limitation for usual optical flow methods.

Collaborator: Denis Fortun (EPFL-BIG, Lausanne, Switzerland)
Noémie Debroux (Laboratory of Mathematics, INSA Rouen, Normandie University)

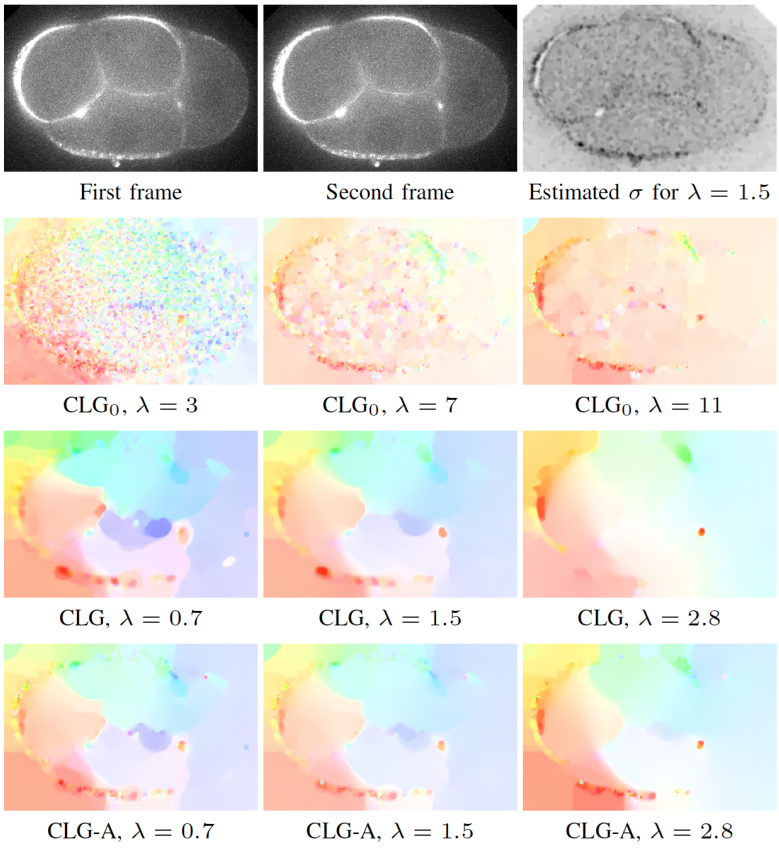

Figure 10. Visual results obtained with variants of CLG ("Combined Local-Global") methods for several values of regularization parameters λ: CLG-A (our adaptive CLG), CLG_0 (pointwise method) and CLG ([42]) on a image pair from a CElegans sequence.

7.14. Frame-based hierarchical motion decomposition and segmentation

Participants: Juan Manuel Perez Rua, Patrick Bouthemy.

A number of applications in video analysis rely on a per-frame motion segmentation of the scene as key preprocessing step. Moreover, different settings in video production require extracting segmentation masks of multiple moving objects and object parts in a hierarchical fashion. In order to tackle this problem, we propose to analyze and exploit the compositional structure of scene motion to provide a segmentation which is not purely driven by local image information. Specifically, we leveraged a hierarchical motion-based partition of the scene to capture a mid-level understanding of the dynamic video content. To recover the decomposition tree, we formulated the problem as a per-pixel label selection interleaved with motion models estimation. The labels represent the set of nodes from the initial proposal tree which are selected to explain globally the input correspondence field. We carried out experimental results showing the strengths of this approach in comparison to current video segmentation approaches. Indeed, they demonstrated the superior ability of our method to capture the main moving objects of the scene in the first layer of the tree, and to segment them in moving parts in deeper layers. As such, we believe our segmentation method is closer to the complex needs of video editing than current hierarchical segmentation approaches.

Reference: [34]
Collaborators: Tomas Crivelli and Patrick Pérez (Technicolor).

7.15. Trajectory-based discovery of motion hierarchies in video sequences

Participants: Juan Manuel Perez Rua, Patrick Bouthemy.

The dynamic content of physical scenes is largely compositional, that is, the movements of the objects and of their parts are hierarchically organized and relate through composition along this hierarchy. This structure also prevails in the apparent 2D motion that a video captures. Visual motion in the scene is roughly organized along a tree, with the dominant motion (typically induced by camera motion) at the root, and motion components adding up along the branches. Accessing this visual motion hierarchy is important to get a better understanding of dynamic scenes and is useful for video manipulation. We proposed to capture it through learned, tree-structured sparse coding of point trajectories. We found that dictionary learning and sparse coding provide appealing tools to disentangle this latent hierarchical structure. More precisely, we introduced a new tree-structured dictionary learning method that allows describing each track with a few basis functions, all but one being inherited from its parent in the structure. The sparse codes thus associated to the tracks capture the desired structure and lend themselves naturally to hierarchical clustering of the collection. We showed through experiments on motion capture data that our model is able to extract moving segments along with their organization. We also obtained competitive results on the task of segmenting objects in real video sequences from trajectories.

Reference: [33]
Collaborators: Tomas Crivelli and Patrick Pérez (Technicolor).

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: Hoai Nam Nguyen, Charles Kervrann.

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

A three-year contract has been established with Innopsys in 2013 to support Hoai Nam Nguyen's PhD thesis. The objective is to investigate and develop methods and algorithms dedicated to fluorescence images acquired by the scanners and devices designed by the company. In this project, we focus on i/ localization and segmentation fluorescence tissue microarrays (TMA) cores in very large 2D images; ii/ de-arraying of digital images and correction of grid deformation adapted to devices; iii/ correction of scanning artifacts to improve image reconstruction; iv/ deconvolution, denoising and superresolution of fluorescence TMA images corrupted by Poisson noise. The algorithms will be integrated into the plateforms and devices 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 on January 2015 for a CIFRE grant supporting Juan Manuel Perez Rua's PhD thesis. The purpose is to investigate new methods for extracting meaningful mid-level motion-related descriptors that may help for the semantic discovery of the scene. In 2015, we started with the occlusion detection problem. We have proposed a novel approach where occlusion in the next frame or not is formulated in terms of visual reconstruction. Our approach outperforms state-of-the-art occlusion detection methods on the challenging MPI Sintel dataset. In 2016, we have developed two hierarchical motion segmentation methods involving a compositional motion representation. The first one follows a frame-based labeling approach which amounts to the minimization of 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 three-year contract has been established with OBSYS in 2016. The objective is to investigate and develop methods and algorithms dedicated to the control of a microscope set-up and to the analysis of fluorescence images. Fast and robust algorithms will be especially developed to improve image reconstruction of 3D-TIRF microscope images. The algorithms will be integrated into the plateforms and devices designed by OBSYS.

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).

The Fourmentin-Guilbert Foundation 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 Fourmentin-Guilbert Foundation 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 and evaluate novel methods from the field of 3D shape retrieval for identifying, localizing and counting macromolecules (e.g., 70S ribosome) within a tomogram. This project is also supported by "Region Bretagne".

9. Partnerships and Cooperations

9.1. Regional Initiatives

ENSAI-CREST: Statistical methods and models for image registration, Vincent Briane PhD thesis 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).

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 A.G. Caranfil's PhD thesis).

9.2. National Initiatives

9.2.1. France-BioImaging project

Participants: Charles Kervrann, Patrick Bouthemy, Thierry Pécot, Emmanuel Moebel, Ancageorgiana Caranfil.

The goal of the project 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. We address the following 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 is co-head of the IPDM (Image Processing and Data Management) node of the FBI network composed of 6 nodes.
Funding: Investissement d'Avenir - Infrastructures Nationales en Biologie et Santé ANR (2011-2016).
Partners: CNRS, Institut Jacques Monod, Institut Pasteur, Institut Curie, ENS Ulm, Ecole Polytechnique, INRA, INSERM.

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, Patrick Bouthemy, Vincent Briane, Ancageorgiana Caranfil.

The Lattice Light Sheet Microscopy (LLS-M) represents at present 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 condition, imaging two molecular markers of the endocytosis pathway and using cutting-edge LLS-M can result into up to one Terabyte of data, at the spatial resolution of 100-200 nanometers in 3D. In such a situation, it is found the usual conventional image reconstruction algorithms and image analysis methods developed for 3D fluorescence microscopy are likely to fail to process a deluge of voxels generated by LLS-M instruments. The goal of the project is then to develop new paradigms and computational strategies for image reconstruction and 3D molecule tracking/motion estimation. Furthermore, establishing correspondences between the image-based measurements and features (e.g., motion vectors, trajectories), stochastic motion models and the underlying biological and biophysical information remains a challenging task.

The impact of the project will be three-fold. First, our new image processing paradigms and improved algorithms (allowing faster, more resolved and more accurate results) will have direct benefits in modern bioimaging. Second, the methods and algorithms will apply to decipher molecular mechanisms of protein transports, here focused on endocytosis/exocytosis. Finally, in a larger perspective, the quantitative description of protein transport will be a prerequisite for understanding the functioning of a cell in normal and pathological situations, as default in protein transport appeared over the years, as a major contributory factor to a number of diseases, including cancer, viral infection and neurodegenerative diseases.
Funding: ANR - Agence Nationale de la Recherche
Partners: Inria (SERPICO, BEAGLE, Fluminance), INRA MaIAGE Unit Jouy-en-Josas, Institut Curie (UMR CNRS 144 & U1143 Inserm UMR 3666) Paris

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.

9.4. International Initiatives

9.4.1. Informal International Partners

Collaboration with Max-Planck Institute, Martinsried (Germany), Dr. Julio Ortiz: 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 in progress with Frédéric Lavancier).

Collaboration with EPFL (M. Unser's Team, Switzerland). D. Fortun: optical flow computing (project in progress with Charles Kervrann).

9.4.2. 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

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 first meeting took place in Dallas in May 2016 as originally scheduled, to discuss and update current research direction and discuss scientific progress.

9.5. International Research Visitors

9.5.1. Visits to International Teams

Visit of 3 months of Juan Manuel Perez Rua in the Philip Torr's team (University of Oxford, UK).
Visit of 1 one week of Vincent Briane to the ESGI (European Study Group in Industry) in Dublin (Ireland, July 2016).

Visit of 1 one week of Vincent Briane to the University of Limerick (K. Burke's team) (Ireland, November 2016).

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific Events Organisation

10.1.1.1. Member of the Organizing Committees

Frédéric Lavancier and Charles Kervrann were head of the organizing committee of the international workshop "Spatial Statistics and Image Analysis in Biology" (SSIAB'16), Inria Rennes, May 2016.

Frédéric Lavancier was head of the workshop "Spatio-Temporal Models and Statistics", IRMAR University of Rennes 1, LMJL University of Nantes, ENSAI, University of Rennes 2, INRA Rennes, Inria Rennes, April 2016.

Patrick Bouthemy and Thierry Pécot were respectively main organizer and co-organizer of the BioImage Computing workshop in conjunction with ECCV'2016, Amsterdam, October 2016.

Patrick Bouthemy and Charles Kervrann were respectively main organizer and co-organizer of the mini-symposium "Image analysis advances in dynamic microscopy and live cell imaging" in SIAM Conference on Imaging Sciences, Albuquerque, New-Mexico, USA, May 2016.

Charles Kervrann was member of the organization committee of the Microscopy school MiFoBio'2016, Seignosse, October 2016.

10.1.2. Scientific Events Selection

10.1.2.1. Member of the Conference Program Committees

Charles Kervrann: member of the scientific committee of RFIA'2016 (Clermont-Ferrand), Associated Editor for the conference ISBI'2017, member of the scientific committee of the "Image the Cell 2017" conference (Rennes), member of the scientific committee "Journées d'Imagerie Optique Non-Conventionnelle" (JIONC'2016 and JIONC'2017).

Patrick Bouthemy: Associate Editor for the conference ISBI'2016 and ISBI'2017, Area Chair of ICIP'2016, member of the program committee of RFIA'2016.

Thierry Pécot: member of the program committee of BIOIMAGING'2016.

10.1.2.2. Reviewer

Charles Kervrann: reviewer for ICIP'2016, ICASSP'2016, ISBI'2016, ICASSP'2017, ICIP'2017.

Patrick Bouthemy: reviewer for ICIP'2016, ISBI'2016.

Thierry Pécot: reviewer for ISBI'2016, BIOIMAGING'2016.

10.1.3. Journal

10.1.3.1. Member of the Editorial Boards

Charles Kervrann is Guest Editor of the special issue entitled "Advanced Signal Processing in Microscopy and Cell Imaging" of the IEEE Selected Topics in Signal Processing Journal, February 2016.

Charles Kervrann is Associate Editor of the IEEE Signal Processing Letters journal (since January 2015).

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, IEEE Transactions on Computational Imaging, SIAM J. on Imaging Sciences, Methods, expert for the project evaluation in the framework of FONDECYT Science Council (Chile).

Patrick Bouthemy: IEEE Transactions on Image Processing, Mathematical Problems in Engineering, IEEE Signal Processing Letters, IEEE Robotics and Automation Letters, Applied Soft Computing Journal, Computational Intelligence and Neuroscience.

Frédéric Lavancier: Spatial Statistics, R Journal

Thierry Pécot: Bioinformatics, IEEE Transactions on Medical Imaging.

10.1.4. Invited Talks

Charles Kervrann:

Invited talk at the FBI seminar (Paris centre), Computational methods for diffusion, motion and molecular interaction estimation, Pont l'Eveque, February 2016.

Invited talk at the Forum Mathématique Diderot, Computational analysis of intracellular membrane dynamics: from live cell images to biophysical model, Paris, March 2016.

Seminar UTSW, Danuser's lab, Computational analysis of intracellular membrane dynamics: from live cell images to biophysical model, Dallas, TX, USA, May 2016.

Invited talk at SIAM Conference on Imaging Sciences, PEWA: Patch-based Exponentially Weighted Aggregation for image denoising, Albuquerque, New-Mexico, USA, May 2016.

Patrick Bouthemy

Invited talk at SIAM Conference on Imaging Sciences, A scale-adaptive method for retracing and registering in correlative light-electron microscopy, Albuquerque, New-Mexico, USA, May 2016.

Vincent Briane:

Invited talk at SSIAB'2016 workshop, An adaptive statistical test to detect non Brownian diffusion from particle trajectories, Inria Rennes, May 2016.

Thierry Pécot:

Invited talk at SSIAB'2016 workshop, A non-parametric procedure for co-localization studies in fluorescence microscopy, Inria Rennes, May 2016.

Talk and practical course at Microscopy school MiFoBio'2016, mage processing methods for the temporal analysis of moving particles, Seignosse, October 2016.

Seminar IGDR, QuantEv: Quantifying the spatial distribution of intracellular events, Rennes, November 2016.

Frédéric Lavancier:

Seminar of Statistics and Probability in Lille 1, Determinantal point process models and statistical inference, Lille, March 2016.

Seminar in Statistics of University Toulouse 1, A general procedure to combine estimators, Toulouse, June 2016.

Invited talk at "Journées MAS", Determinantal point process models and statistical inference, Grenoble, August 2016.

10.1.5. Scientific Expertise

Charles Kervrann:

Member of the IEEE BISP "Biomedical Image and Signal Processing" committee.

Member of executive board of the GdR MIV (2588 - Microscopie Fonctionnelle du Vivant) CNRS.

Member of the scientific committee of the Interdisciplinary MiFoBio School CNRS (http://www.mifobio.fr).

Patrick Bouthemy:

Member of the board of AFRIF (Association Française pour la Reconnaissance et l'Interprétation des Formes).

Member of the Research Committee of Telecom Bretagne.

Frédéric Lavancier:

Elected member of CNU section 26.

Expert for the project evaluation in the framework of FNRS (Fonds de la Recherche Scientifique), Belgium.

10.1.6. Research Administration

Charles Kervrann:

Member of the executive board of the project committee of the Inria Rennes - Bretagne Atlantique centre.

Member of the Scientific Council of the INRA Rennes Research Centre.

Co-head of the "BioImage Informatics" node (ANR France-BioImaging project, National Infrastructure en Biologie et Santé).

Patrick Bouthemy:

Head of Excellence Lab CominLabs since April 2014.

Deputy member of the board of directors and member of the Selection and Validation Committee of the Images & Réseaux competitivity cluster.

Deputy member of the board of directors of IRT (Technological Research Institute) b<>com.

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, 9 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

PhD in progress: Arnaud Poinas, Inference for inhomogeneous determinantal point processes, started in September 2016, supervised by Bernard Delyon and Frédéric Lavancier

PhD in progress: Hoai Nam Nguyen, Methods and algorithms for tissue microarrays image analysis, started in October 2013, supervised by Charles Kervrann and Vincent Paveau (Innopsys).

PhD in progress: Vincent Briane, Statistical methods and models for motion analysis in microscopy, started in October 2014, supervised by Charles Kervrann and Myriam Vimond (ENSAI-CREST).

PhD in progress: 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.

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

PhD in progress: Juan Manuel Perez Rua, Semantically meaningful motion descriptors for video understanding, started in January 2015, supervised by Patrick Bouthemy in collaboration with Tomas Crivelli and Patrick Pérez (Technicolor).

PhD in progress: 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.

PhD in progress: Sandeep Manandhar, Optical flow methods for 3D fluoresence imaging, started in October 2016, supervised by Patrick Bouthemy and Charles Kervrann.

10.2.3. Juries

Referee of PhD thesis: G. Michelin (University of Côte d'Azur, supervised by G. Malandain) [P. Bouthemy], L. Azzari (Tampere University of Technology, Finland, supervised by A. Foi) [C. Kervrann], H. Robjani (University of Strasbourg, supervised by C. Ronse) [C. Kervrann].

11. Bibliography

Major publications by the team in recent years

[1] A. BASSET, J. BOULANGER, J. SALAMERO, P. BOUTHEMY, C. KERVRANN. *Adaptive spot detection with optimal scale selection in fluorescence microscopy images*, in "IEEE Transactions on Image Processing", November 2015, vol. 24, n° 11, 16 p. [*DOI :* 10.1109/TIP.2015.2450996], https://hal.inria.fr/hal-01248290

[2] J. BOULANGER, A. GIDON, C. KERVRANN, J. SALAMERO. *A patch-based method for repetitive and transient event detection in fluorescence imaging*, in "PLoS ONE", Oct 2010, vol. 5, n° 10 [*DOI :* 10.1371/JOURNAL.PONE.0013190]

[3] J. BOULANGER, C. KERVRANN, P. BOUTHEMY. *Space-time adaptation for patch based image sequence restoration*, in "IEEE Transactions on Pattern Analysis and Machine Intelligence", 2007, vol. 29, n° 6, pp. 1096–1102

[4] J. BOULANGER, C. KERVRANN, P. BOUTHEMY. *A simulation and estimation framework for intracellular dynamics and trafficking in video-microscopy and fluorescence imagery*, in "Medical Image Analysis", 2009, vol. 13, pp. 132–142

[5] J. BOULANGER, C. KERVRANN, P. BOUTHEMY, P. ELBAU, J.-B. SIBARITA, J. SALAMERO. *Patch-based nonlocal functional for denoising fluorescence microscopy image sequences*, in "IEEE Transactions on Medical Imaging", Feb 2010, vol. 29, n° 2, pp. 442-453 [*DOI :* 10.1109/TMI.2009.2033991]

[6] P.M. CARLTON, J. BOULANGER, C. KERVRANN, J.-B. SIBARITA, J. SALAMERO, S. GORDON-MESSER, J. HABER, S. HAASE, L. SHAO, L. WINOTO, A. MATSUDA, P. KNER, S. USAWA, Y. STRUKOV, M. GUSTAFSSON, Z. KAM, D. AGARD, J.W. SEDAT. *Fast live simultaneous multiwavelength four-dimensional optical microscopy*, in "Proc Natl Acad Sci USA", Sep 2010, vol. 107, n° 37, pp. 16016-16022 [*DOI :* 10.1073/PNAS.1004037107]

[7] T. CRIVELLI, B. CERNUSCHI-FRIAS, P. BOUTHEMY, J.-F. YAO. *Motion Textures: Modeling, Classification, and Segmentation Using Mixed-State*, in "SIAM Journal on Imaging Sciences", December 2013, vol. 6, n° 4, pp. 2484-2520 [*DOI :* 10.1137/120872048], https://hal.inria.fr/hal-00931667

[8] A. GIDON, S. BARDIN, B. CINQUIN, J. BOULANGER, F. WAHARTE, L. HÉLIOT, H. DE LA SALLE, D. HANAU, C. KERVRANN, B. GOUD, J. SALAMERO. *A Rab11A/myosin Vb/Rab11-FIP2 complex frames two late recycling steps of langerin from the ERC to the plasma membrane*, in "Traffic", April 2012, vol. 13, n° 6, pp. 815-833 [*DOI :* 10.1111/J.1600-0854.2012.01354.X], https://hal.inria.fr/hal-00782005

[9] C. KERVRANN, J. BOULANGER. *Optimal spatial adaptation for patch-based image denoising*, in "IEEE Transactions on Image Processing", 2006, vol. 15, n° 10, pp. 2866–2878

[10] C. KERVRANN, J. BOULANGER. *Local adaptivity to variable smoothness for exemplar-based image denoising and representation*, in "International Journal of Computer Vision", August 2008, vol. 79, n° 1, pp. 45–69

[11] C. KERVRANN. *PEWA: Patch-based Exponentially Weighted Aggregation for image denoising*, in "NIPS - Neural Information Processing Systems", Montreal, Canada, Neural Information Processing Systems Foundation, December 2014, https://hal.inria.fr/hal-01103358

[12] T. PÉCOT, P. BOUTHEMY, J. BOULANGER, A. CHESSEL, S. BARDIN, J. SALAMERO, C. KERVRANN. *Background Fluorescence Estimation and Vesicle Segmentation in Live Cell Imaging with Conditional Random Fields*, in "IEEE Transactions on Image Processing", February 2015, vol. 24, n° 2, 14 p. [*DOI :* 10.1109/TIP.2014.2380178], https://hal.inria.fr/hal-01103126

Publications of the year

Articles in International Peer-Reviewed Journals

[13] C. A. N. BISCIO, F. LAVANCIER. *Brillinger mixing of determinantal point processes and statistical applications*, in "Electronic journal of statistics ", March 2016, vol. 10, n° 1, pp. 582-607, https://hal.archives-ouvertes.fr/hal-01179831

[14] C. A. N. BISCIO, F. LAVANCIER. *Contrast estimation for parametric stationary determinantal point processes*, in "Scandinavian Journal of Statistics", 2016, https://hal.archives-ouvertes.fr/hal-01215582

[15] C. A. N. BISCIO, F. LAVANCIER. *Quantifying repulsiveness of determinantal point processes*, in "Bernoulli", May 2016, vol. 22, n° 4, pp. 2001-2028, https://hal.archives-ouvertes.fr/hal-01003155

[16] J.-F. COEURJOLLY, F. LAVANCIER. *Parametric estimation of pairwise Gibbs point processes with infinite range interaction*, in "Bernoulli", January 2016, https://hal.archives-ouvertes.fr/hal-01092225

[17] D. DEREUDRE, F. LAVANCIER. *Consistency of likelihood estimation for Gibbs point processes*, in "The Annals of Statistics", 2016, https://hal.archives-ouvertes.fr/hal-01144877

[18] D. FORTUN, P. BOUTHEMY, C. KERVRANN. *A Variational Aggregation Framework for Patch-Based Optical Flow Estimation*, in "Journal of Mathematical Imaging and Vision", 2016, vol. 56, pp. 280 - 299 [*DOI :* 10.1007/s10851-016-0664-6], https://hal.archives-ouvertes.fr/hal-01408771

[19] D. FORTUN, P. BOUTHEMY, C. KERVRANN. *Aggregation of local parametric candidates with exemplar-based occlusion handling for optical flow*, in "Computer Vision and Image Understanding", January 2016, 17 p. [*DOI :* 10.1016/J.CVIU.2015.11.020], https://hal.inria.fr/hal-01001758

[20] M. JAIN, H. JÉGOU, P. BOUTHEMY. *Improved Motion Description for Action Classification* , in "Frontiers in information and communication technologies", January 2016 [*DOI :* 10.3389/FICT.2015.00028], https://hal.inria.fr/hal-01401833

[21] C. KERVRANN, S. T. ACTON, J.-C. OLIVO-MARIN, C. O. S. SORZANO, M. UNSER. *Introduction to the issue on Advanced Signal Processing in Microscopy and Cell Imaging*, in "IEEE Journal of Selected Topics in Signal Processing", 2016, vol. 10, n^{o} 1, pp. 3-5 [*DOI :* 10.1109/JSTSP.2015.2511299], https://hal.archives-ouvertes.fr/hal-01251394

[22] C. KERVRANN, C. O. S. SORZANO, S. T. ACTON, J.-C. OLIVO-MARIN, M. UNSER. *A Guided Tour of Selected Image Processing and Analysis Methods for Fluorescence and Electron Microscopy*, in "IEEE Selected Topics in Signal Processing", February 2016, vol. 10, n^{o} 2, pp. 6-30, https://hal.inria.fr/hal-01246375

[23] F. LAVANCIER, J. MØLLER. *Modelling aggregation on the large scale and regularity on the small scale in spatial point pattern datasets*, in "Scandinavian Journal of Statistics", 2016, vol. 43, n^{o} 2, pp. 587-609, https://hal.archives-ouvertes.fr/hal-01155646

[24] F. LAVANCIER, P. ROCHET. *A general procedure to combine estimators*, in "Computational Statistics and Data Analysis", 2016, vol. 94, pp. 175-192, https://hal.archives-ouvertes.fr/hal-00936024

[25] T. PÉCOT, C. KERVRANN, J. SALAMERO, J. BOULANGER. *Counting-based particle flux estimation for traffic analysis in live cell imaging*, in "IEEE Journal of Selected Topics in Signal Processing", February 2016, vol. 10, n^{o} 1, pp. 203-216, https://hal.inria.fr/hal-01417147

Invited Conferences

[26] V. BRIANE, M. VIMOND, C. KERVRANN. *An adaptive statistical test to detect non Brownian diffusion from particle trajectories*, in "Workshop SSIAB - Spatial Statistics and Image Analysis in Biology", Rennes, France, May 2016, https://hal.inria.fr/hal-01416812

[27] C. KERVRANN. *PEWA: Patch-Based Exponentially Weighted Aggregation for Image Denoising*, in "SIAM Imaging Science", Albuquerque, United States, SIAM, May 2016, https://hal.inria.fr/hal-01416847

[28] T. PÉCOT, F. LAVANCIER, C. KERVRANN. *A non-parametric procedure for co-localization studies in fluorescence microscopy*, in "Workshop SSIAB - Spatial Statistics and Image Analysis in Biology", Rennes, France, May 2016, https://hal.inria.fr/hal-01416844

[29] B. M. TOLEDO ACOSTA, P. BOUTHEMY, C. KERVRANN. *A scale-adaptive method for retracing and registering in correlative light-electron microscopy*, in "SIAM Imaging Science", Albuquerque, United States, SIAM, May 2016, https://hal.inria.fr/hal-01416850

International Conferences with Proceedings

[30] P. BOUTHEMY, B. M. TOLEDO ACOSTA, B. DELYON. *Robust selection of parametric motion models in image sequences*, in "2016 IEEE International Conference on Image Processing (ICIP)", Phoenix, United States, October 2016, pp. 3743 - 3747 [*DOI :* 10.1109/ICIP.2016.7533059], https://hal.inria.fr/hal-01400895

[31] V. BRIANE, M. VIMOND, C. KERVRANN. *An adaptive statistical test to detect non Brownian diffusion from particle trajectories*, in "ISBI 2016 - IEEE Symposium on Biomedical Imaging", Prague, Czech Republic, IEEE, April 2016, pp. 1-4, https://hal.inria.fr/hal-01416855

[32] J.-M. PÉREZ-RÚA, T. CRIVELLI, P. BOUTHEMY, P. PÉREZ. *Determining occlusions from space and time image reconstructions*, in "2016 IEEE Conference on Computer Vision and Pattern Recognition (CVPR)", Las Vegas, United States, June 2016, Peer-reviewed paper accepted for presentation at the IEEE Conference on Computer Vision and Pattern Recognition 2016, in Las Vegas, USA, https://hal.archives-ouvertes.fr/hal-01307703

[33] J.-M. PÉREZ-RÚA, T. CRIVELLI, P. PÉREZ, P. BOUTHEMY. *Discovering motion hierarchies via tree-structured coding of trajectories*, in "Proceedings of the British Machine Vision Conference 2016", York, United Kingdom, BMVA, September 2016, https://hal.archives-ouvertes.fr/hal-01358454

[34] J.-M. PÉREZ-RÚA, T. CRIVELLI, P. PÉREZ, P. BOUTHEMY. *Hierarchical Motion Decomposition for Dynamic Scene Parsing* , in "2016 IEEE International Conference on Image Processing (ICIP)", Phoenix, United States, IEEE, September 2016, Peer-reviewed paper accepted for presentation at the IEEE International Conference on Image Processing 2016, https://hal.archives-ouvertes.fr/hal-01314095

[35] B. M. TOLEDO ACOSTA, P. BOUTHEMY, C. KERVRANN. *A Common Image Representation And A Patch-Based Search For Correlative Light-Electron-Microscopy (Clem) Registration*, in "2016 IEEE 13th International Symposium on Biomedical Imaging (ISBI)", Prague, Czech Republic, April 2016, pp. 257- 260 [*DOI :* 10.1109/ISBI.2016.7493258], https://hal.inria.fr/hal-01400854

National Conferences with Proceedings

[36] A. BASSET, P. BOUTHEMY, J. BOULANGER, F. WAHARTE, J. SALAMERO, C. KERVRANN. *Modélisation et estimation de la diffusion de protéines à l'exocytose dans des séquences d'images de microscopie TIRF*, in "Reconnaissance des Formes et l'Intelligence Artificielle (RFIA'16)", Clermont-Ferrand, France, Association Française de Reconnaissance et d'Interprétation des Formes (AFRIF), Association Française d'Intelligence Artificielle (AFIA), June 2016, pp. 1-8, https://hal.inria.fr/hal-01416868

[37] V. BRIANE, C. KERVRANN, M. VIMOND. *Test statistique pour détecter les diffusions non browniennes*, in "48e Journées de Statistique", Montpellier, France, SFdS, May 2016, pp. 1-6, https://hal.inria.fr/hal-01416862

Conferences without Proceedings

[38] E. MOEBEL, C. KERVRANN. *Denoising and compensation of the missing wedge in cryo electron tomography*, in "16th European Microscopy Congress", Lyon, France, European Microscopy Society, August 2016, https://hal.inria.fr/hal-01416801

Other Publications

[39] F. LAVANCIER, P. ROCHET. *A tutorial on estimator averaging in Spatial Statistics models*, July 2016, working paper or preprint, https://hal.archives-ouvertes.fr/hal-01341125

References in notes

[40] D. AXELROD. *Total Internal Reflection Fluorescent Microscopy in cell biology*, in "Traffic", 2004, vol. 2, pp. 4658–4668

[41] E. BETZIG, G. PATTERSON, R. SOUGRAT, O. LINDWASSER, S. OLENYCH, J. BONIFACINO, M. DAVIDSON, J. LIPPINCOTT-SCHWARTZ, H. HESS. *Imaging intracelluar fluorescent proteins at nanometer resolution*, in "Science", 2006, vol. 313, pp. 1642–1645

[42] A. BRUHN, J. WEICKERT, C. SCHNÖRR. *Lucas/Kanade meets Horn/jaqaSchunck: combining local and global optic flow methods*, in "International Journal of Computer Vision", 2005, vol. 61, n^o 3, pp. 211–231

[43] A. BUADES, B. COLL, J.-M. MOREL. *A review of image denoising algorithms, with a new one*, in "SIAM J. Multiscale Modeling & Simulation", 2005, vol. 4, n^o 2, pp. 490–530

[44] A. CHESSEL, B. CINQUIN, S. BARDIN, J. BOULANGER, J. SALAMERO, C. KERVRANN. *A detection-based framework for the analysis of recycling in TIRF microscopy*, in "IEEE International Symposium on Biomedical Imaging: From Nano to Macro (ISBI 2010)", Pays-Bas Rotterdam, IEEE Signal Processing Society, Apr 2010, pp. 1281-1284 [*DOI :* 10.1109/ISBI.2010.5490230]

[45] A. CHESSEL, B. CINQUIN, S. BARDIN, J. SALAMERO, C. KERVRANN. *Computational geometry-based scale-space and modal image decomposition: application to light video-microscopy imaging*, in "Conf. on Scale Space and Variational Methods (SSVM'09)", Voss, Norway, June 2009, pp. 770–781

[46] T. CORPETTI, E. MÉMIN, P. PÉREZ. *Dense estimation fluid flows*, in "IEEE Trans. Pattern Analysis and Machine Intelligence", 2002, vol. 24, n^o 3, pp. 365–380

[47] T. CRIVELLI, P. BOUTHEMY, B. CERNUSCHI-FRIAS, J.-F. YAO. *Simultaneous motion detection and background reconstruction with a conditional mixed-state Markov random field*, in "International Journal of Computer Vision", 2011, vol. 94, n^o 3, pp. 295–316

[48] A. GENOVESIO, T. LIEDL, V. EMILIANI, W. PARAK, M. COPPEY-MOISAN, J.-C. OLIVO-MARIN. *Multiple particle tracking in 3D+t microscopy: method and application to the tracking of endocytosed quantum dots*, in "IEEE Trans. Image Processing", 2006, vol. 15, n^o 5, pp. 1062–1070

[49] M. GUSTAFSSON, L. SHAO, P.M. CARLTON, R. WANG, I. GOLUBOVSKAYA, W. CANDE, D. AGARD, J.W. SEDAT. *3D resolution doubling in wide-filed fluorescence microscopy by structured illumination*, in "Biophysical J.", 2008, vol. 94, pp. 4957–4970

[50] H. HAUSSECKER, D. FLEET. *Computing optical flow with physical models of brightness variation*, in "IEEE Trans. Pattern Analysis and Machine Intelligence", 2001, vol. 23, n^o 6, pp. 661–673

[51] T. KLAR, S. JAKOBS, M. DYBA, A. EGNER, S. HELL. *Fluorescence microscopy with diffraction resolution barrier broken by stimulated emission*, in "Proc. Natl. Acad. Sci. USA", 2000, vol. 97, pp. 8206–8210

[52] C. LAVELLE, H. BERRY, G. BESLON, F. GINELLI, J. GIAVITTO, Z. KAPOULA, A. LE BIVIC, N. PEYRIERAS, O. RADULESCU, A. SIX, V. THOMAS-VASLIN, P. BOURGINE. *From molecules to organisms: towards multiscale integrated model of biological systems*, in "Theoretical Biology Insights", 2008, vol. 1, pp. 13–22

[53] F. NÉDÉLEC. *Computer simulations reveal motor properties generating stable antiparallel microtubule interactions*, in "The Journal of Cell Biology", 2002, vol. 158, n° 6, pp. 1005–1015

[54] S. OZERE, P. BOUTHEMY, F. SPINDLER, P. PAUL-GILLOTEAUX, C. KERVRANN. *Robust parametric stabilization of moving cells with intensity correction in light microscopy image sequences*, in "10th International Symposium on Biomedical Imaging (ISBI)", IEEE, 2013, pp. 468–471

[55] M. PINOT, V. STEINER, B. DEHAPIOT, B.-K. YOO, F. CHESNEL, L. BLANCHOIN, C. KERVRANN, Z. GUEROUI. *Confinement induces actin flow in a meiotic cytoplasm*, in "Proceedings National Academy of Sciences USA", July 2012, vol. 109, n° 29, pp. 11705–11710 [*DOI :* 10.1073/PNAS.1121583109], http://hal.inria.fr/inserm-00717415

[56] T. PÉCOT, C. KERVRANN, S. BARDIN, B. GOUD, J. SALAMERO. *Patch-based Markov models for event detection in fluorescence bioimaging*, in "Int. Conf. on Medical Image Computing and Computer Assisted Intervention (MICCAI'08)", New York City, USA, September 2008, vol. 2, pp. 95–103

[57] P. PÉREZ, J. VERMAAK, A. BLAKE. *Data fusion for visual tracking with particles*, in "Proc. IEEE", 2004, vol. 92, n° 3, pp. 495–513

[58] I. SBALZARINI, P. KOUMOUTSAKOS. *Feature point tracking and trajectory analysis for video Imaging in cell biology*, in "J. Structural Biology", 2005, vol. 151, pp. 182–195

[59] I. SMAL, M. LOOG, W. NIESSEN, E. MEIJERING. *Quantitative comparison of spot detection methods in fluorescence microscopy*, in "IEEE Trans. Medical Imaging", 2010, vol. 29, n° 2, pp. 282–301

[60] I. SMAL, E. MEIJERING, K. DRAEGESTEIN, N. GALJART, I. GRIGORIEV, A. AKHMANOVA, M. VAN ROYEN, A. HOUTSMULLER, W. NIESSEN. *Multiple object tracking in molecular bioimaging by Rao-Blackwellized marginal particle filtering,*, in "Medical Image Analysis", 2008, vol. 12, n° 6, pp. 764–777

[61] D. THOMANN, D. RINES, P. SORGER, G. DANUSER. *Automatic fluorescent tag detection in 3D with super-resolution: application to the analysis of chromosome movement*, in "J. Microscopy", 2002, vol. 298, n° Part 1, pp. 49–64

[62] Y. VARDI. *Network tomography: estimating source-destination traffic intensities from link data*, in "J. American Statistical Association", 1996, vol. 91, pp. 365–377

[63] T. WALTER, D. SHATTUCK, R. BALDOCK, M. BASTIN, A. CARPENTER, S. DUCE, J. ELLENBERG, A. FRASER, N. HAMILTON, S. PIEPER, M. RAGAN, J. SCHNEIDER, P. TOMANCAK, J. HERICHE. *Visualization of image data from cells to organisms*, in "Nature Methods", 2010, vol. 7, n° 3 (Suppl), pp. S26–41