Activity Report 2015

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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Emmanuel Moebel [Inria, from Nov 2015, granted by Région Bretagne]
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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 [48].

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 [64]. 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 [5]. The major advantage is to preserve cell integrity over time since spatio-temporal information can be restored using computational methods [8], [2], [9], [4]. This idea has been successfully applied to wide-field, spinning-disk confocal microscopy [1], TIRF [40], fast live imaging and 3D-PALM using the OMX system in collaboration with J. Sedat and M. Gustafsson at UCSF [5]. The corresponding ND-SAFIR denoiser software (see Section 6.5) 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 [48]. 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 [58]. Data association even combined with sophisticated particle filtering techniques [61] or matching techniques [59] 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 [44], [49]. 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 [61], [46]. Among the methods proposed to detect particles in microscopy images [62], [60], 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 [1] (see also [42]). 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], [64] 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) [63] 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 [3] 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. Biological pilot models: Birbeck granule and Melanosome biogenesis

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).

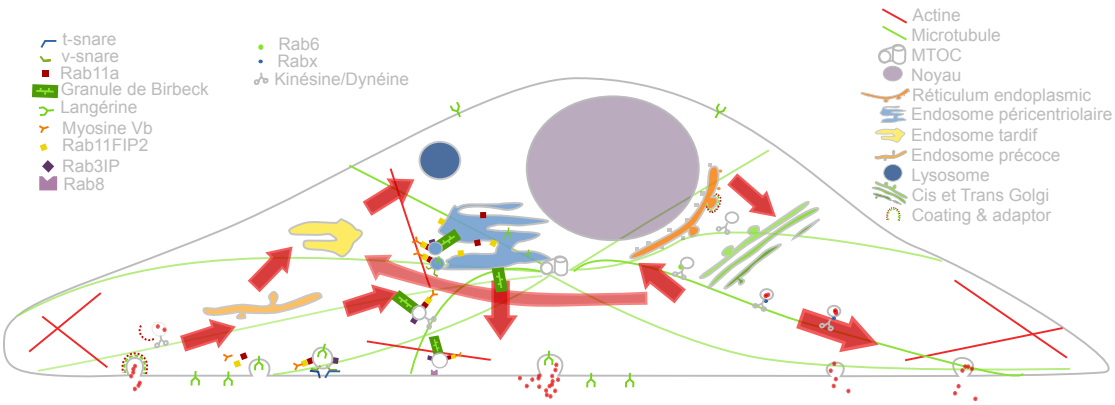

Figure 1. Cargo Langerin Trafficking controlled by Rab11A/Rab11FIP2/MyoVb platform.

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.

5. Highlights of the Year

5.1. Highlights of the Year

Publication of overview papers

Publication of two tutorial-style overview papers:

- D. Fortun, P. Bouthemy, C. Kervrann. Optic flow modeling and computation: a survey, Computer Vision and Image Understanding, 134:1-21, 2015.
- 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, IEEE Journal of Signal Topics in Signal Processing (Special issue on Advanced Signal Processing in Microscopy and Cell Imaging, Lead Guest Editor: C. Kervrann), 10(1):1-25, 2016.

6. New Software and Platforms

6.1. 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:** [26]

6.2. ATLAS

KEYWORD: Biomedical imaging
FUNCTIONAL DESCRIPTION: The ATLAS software enables to detect spots in 2D fluoresence 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:** [12]

6.3. 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 shapes-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/)

6.4. 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/)

6.5. 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) [4]. 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:** [4]

6.6. 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++

6.7. 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.

- **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/)

6.8. 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/)

6.9. Platforms

6.9.1. Mobyle@Serpico plateform and software distribution

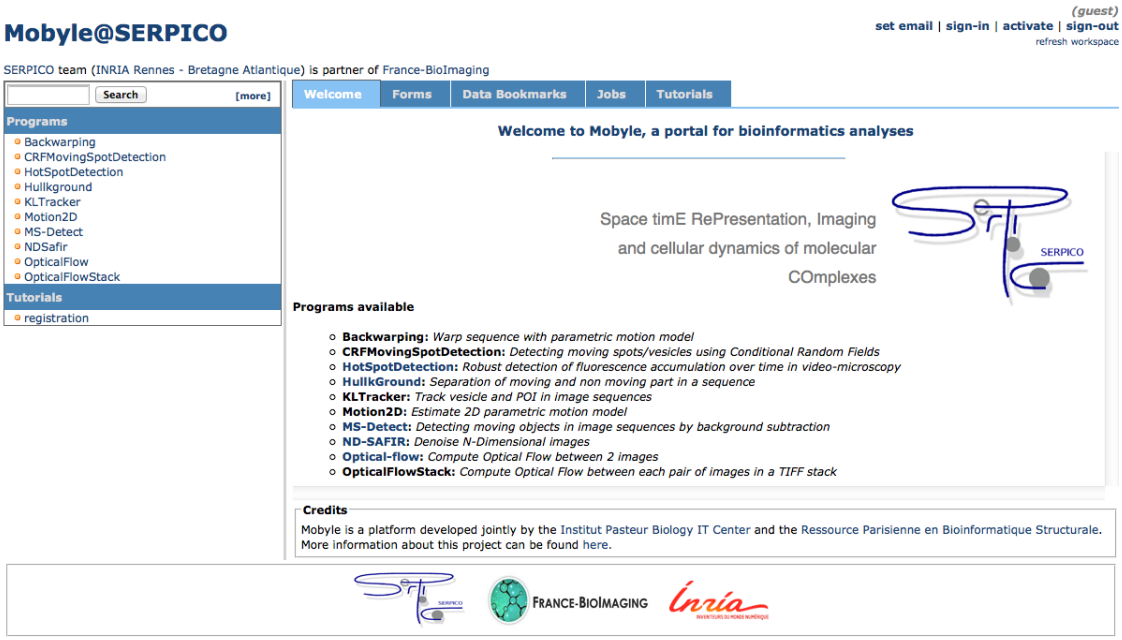

Figure 2. Mobyle@SERPICO web portal.

The objective is to disseminate the distribution of SERPICO image processing software for biologist users:
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: C-CRAFT[26], ATLAS[12], HOTSPOTDETECTION[57], HULLKGROUND[43], KLTRACKER[55], MOTION2D[54], MS-DETECT[45], ND-SAFIR[4], OPTICALFLOW and FLUX ESTIMATION [26]. The web interface makes our image processing methods available for biologist users at Mobyle@SERPICO (http://mobyle-serpico.rennes.inria.fr/cgi-bin/portal.py#welcome) without any installation or configuration on their own. The size of submitted images is limited to 200 MegaBytes per user and all the results are kept 15 days. The web portal and calculations run on a server with 2 CPU x 8 cores, 64 GigaBytes of RAM (500 MegaBytes for each user / Data is saved for 3 months).

IMAGEJ *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 [4], HULLKGROUND [43], MOTION2D [54], HOTSPOTDETECTION [57], STLAS [12]. The C-CRAFT algorithm [26] 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.

6.9.2. 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.

We have already proposed a general statistical aggregation method which combines image patches denoised with several commonly-used algorithms [10]. We showed that weakly denoised versions of the input image obtained with standard methods, can serve to compute an efficient patch-based aggregated estimator. In our approach, the Stein's Unbiased Risk Estimator (SURE) is used to evaluate each denoised candidate image patch and to compute the exponential weighted aggregation (EWA) estimator. This year, we adapted this framework (PEWA) to denoise images corrupted by mixed Gaussian-Poisson in 2D fluorescence image sequences.

In this range of work, we have 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. As part of an on-going work, we are applying this method to improve patch-based image denoising algorithms.

Reference: [24]

Collaborators: Paul Rochet (Laboratoire de Mathématiques Jean Leray (LMJL), University of Nantes).

7.2. Image deconvolution algorithms for tagged-RNA and gene localization in live yeast

Participant: 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. The regularization functional should be designed to remove noise while retaining the image structure. In this study, we investigated non quadratic regularization terms to preserve fine details of underlying structures and we studied appropriate optimization algorithms. The deconvolution method has been especially dedicated for 3D high-precision gene localization in cell nuclei [47]. For illustration, tagged gene (green marker) and tagged nucleoporins/nuclear periphery (red marker) are shown in Fig. 3. A noisy and blurred image can affect the nuclear membrane estimation and gene detection and, consequently, the computed related distances.

Collaborators: Giovanni Petrazzuoli (Inserm U944, CNRS UMR 9212, Hôpital Saint-Louis, Paris),
Catherine Dargemont (Inserm U944, CNRS UMR 9212, Hôpital Saint-Louis, Paris),
Jean Salamero (UMR 144 CNRS-Institut Curie, PICT-IBiSA).

7.3. Estimation of the reference point giving the most uniform angular distribution

Participants: Thierry Pécot, Patrick Bouthemy, Charles Kervrann.

Rab11 proteins are trafficking from the Endosomal Recycling Compartment (ERC) to locations in the cell membrane where they eventually fuse. In this study, we assume that the Rab11 positive membranes are uniformly distributed around the ERC at the cell membrane. To test this hypothesis, we estimate the angular distribution of Rab11 positive membranes from several image sequences acquired with a TIRF microscope at the cell membrane level by considering all the points located in the cell as a reference point. We then compute the entropy of angular distribution for each point and estimate the ERC location as the reference point that gives the maximum entropy for the angular distribution (see Fig. 4). These results are very close to the ERC locations manually annotated by experts.

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

7.4. Modeling and estimation of protein release and diffusion in TIRFM

Participants: Antoine Basset, Charles Kervrann, Patrick Bouthemy.

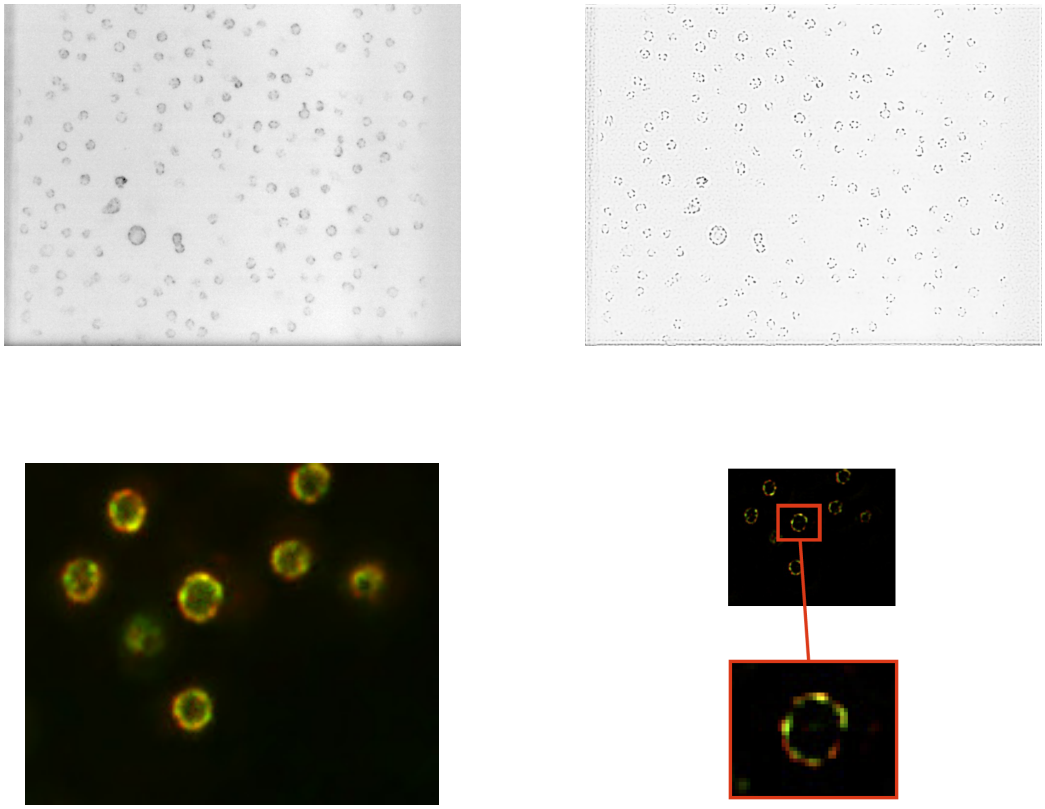

Figure 3. Deconvolution of 3D image depicting tagged gene and tagged nucleoporins/nuclear periphery. First row: deconvolution (right) of a tagged nucleoporin image (left). Second row: blurred image of tagged gene and nucleoporins (left) and zoom-in view of the deblurred image.

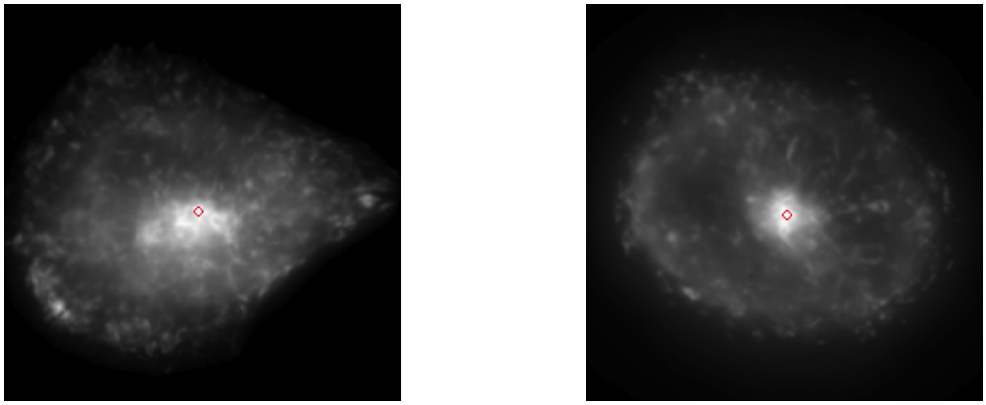

Figure 4. Estimation of reference points (red circles) for Rab11 traffic comparison, registration and quantification.

We have pursued our work on membrane dynamics, still following a local approach in space and time. We have proposed a new model to account for the full behavior of cargo transmembrane proteins during the vesicle fusion to the plasma membrane at the end of the exocytosis process (see Fig. 5). It combines release and diffusion steps. The former is represented by an exponential decay to account for a continuous release of the proteins from the vesicle to the plasma membrane. We can relax the usual point source assumption, and we name our model the "Small-extent Source with Exponential Decay release" (SSED). An iterative minimization method is used to estimate simultaneously both biophysical parameters, i.e., the release rate and the diffusion coefficient, for every active vesicle detected in the total internal reference fluorescence microscopy (TIRFM) image sequence. Quantitative evaluation has demonstrated the efficiency of the method, which has also allowed us to exhibit differences in the behaviors of Transferrin receptor (TfR) and Langerin proteins.

Collaborators: Jean Salamero (UMR 144 CNRS-Institut Curie, PICT-IBiSA),
Jérôme Boulanger (UMR 144 CNRS-Institut Curie).

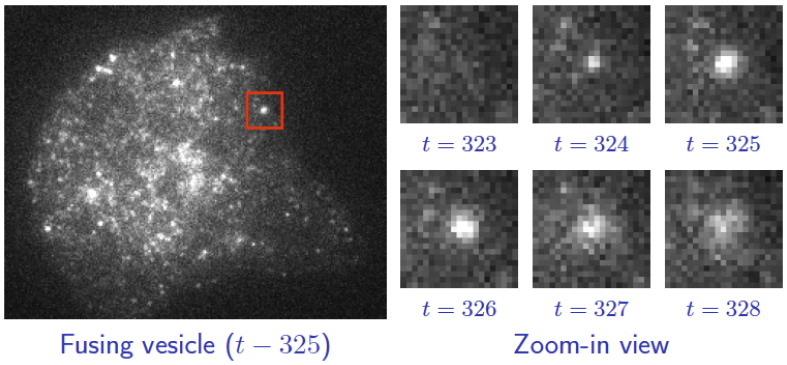

Figure 5. Left: Fusing vesicle (frame in red) in a TIRFM (UMR 144 CNRS-Institut Curie, PICT-IBiSA) sequence (frame 325, 50ms/frame). Right: Zoom-in view of the temporal evolution of the fusing vesicle.

7.5. Counting-based particle flux estimation for traffic analysis in live cell imaging

Participants: Thierry Pécot, Charles Kervrann.

In this study, we have proposed an original traffic analysis approach based on the counting of particles from frame to frame. Object tracking methods or optical flow methods are generally considered to analyze the dynamic contents of intracellular video-microscopy. The suggested method lies between these two well-known approaches. Instead of tracking each moving particle, we estimate fluxes of particles between predefined and adjacent regions. Our three-step counting-based approach is as follows:

- The cell is uniformly partitioned into fixed-size and fixed-shape regions.
- The moving particles are automatically detected using an appropriate algorithm.
- The fluxes are estimated with sparse constraints from an image pair at each time step from temporal variations of the number of particles in each region of the uniform tessellation. Except for some trivial cases, the flux estimation is actually an ill-posed problem and additional constraints are necessary to find the optimal solution.

The problem is formulated as the minimization of a global cost function and the approach allows us to process image sequences with a high number of particles and a high rate of particle appearances and disappearances. We studied the influence of object density, image partition scale, motion amplitude and particle appearances/disappearances in a large variety of simulations. The potential of the method has been demonstrated on real image sequences showing GFP-tagged Rab6 trafficking in confocal microscopy.

Reference: [26]

Collaborators: Jean Salamero (UMR 144 CNRS-Institut Curie, PICT-IBiSA), Jérôme Boulanger (UMR 144 CNRS-Institut Curie).

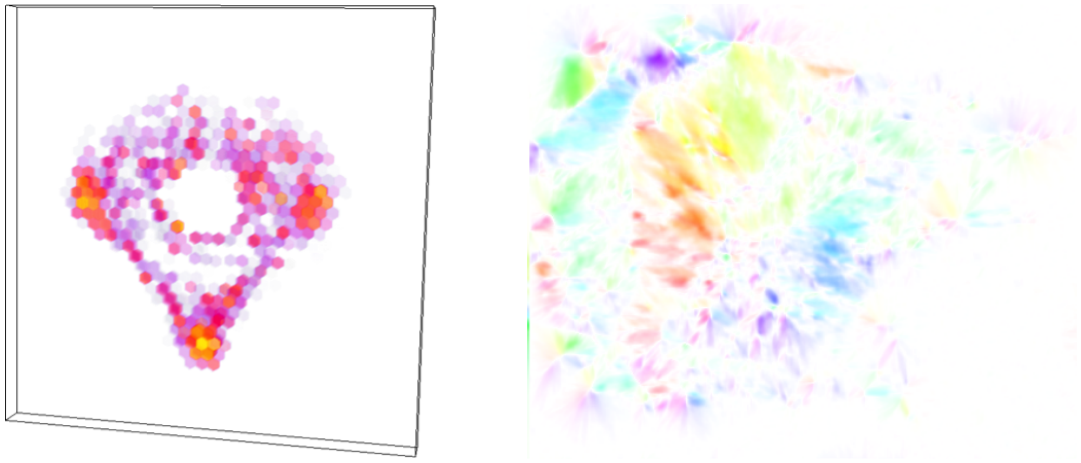

Figure 6. Left: Spatial distribution of GFP-tagged Rab6 vesicle numbers estimated when considering a regular 3D tesselation. Right: Estimation of directional/intensity flows of actin filaments for an image sequence acquired in TIRF microscopy (UMR 144 CNRS-Institut Curie, PICT-IBiSA).

7.6. Tracking of astral microtubules at the cell cortex

Participants: Frédéric Logé-Munerel, Thierry Pécot, Antoine Basset, Charles Kervrann.

In this study, we are currently interested in the influence of the mechanical properties of astral microtubules in the centering mechanisms of the mitotic spindle, giving it a robust positioning. In their previous studies, the CeDRE group (IGDR Rennes) identified two subpopulations of astral microtubules that either push or pull the cell cortex. To better understand these mechanisms, they acquired image sequences at the cortex level where astral microtubules extremities come to exert forces. In order to characterize the two subpopulations of astral microtubules during the mitosis in the unicellular embryos of C. Elegans life span, that is the period during which the microtubule is touching the cell cortex, has to be measured for every single microtubule. A short life span corresponds to a pulling force and a long life span corresponds to a pushing force. Detecting and tracking microtubules at the cell cortex has to be done to collect these measures. This year, F. Logé-Munerel (internship Master 1, supervisors: T. Pécot and C. Kervrann) improved the analysis workflow and calibrated the parameters of the algorithms to successfully track the microtubules. This workflow is composed of the ND-SAFIR denoising algorithm [4], the ATLAS detection algorithm [12] and the ASTRE tracking algorithm [56]. The experimental results are currently compared with results obtained by the CeDRE group using the U-track platform [50] (see Fig. 7).

Collaborators: Jacques Pécréaux and Hélène Bouvrais (CeDRE group, IGDR Rennes, CNRS UMR 6290).

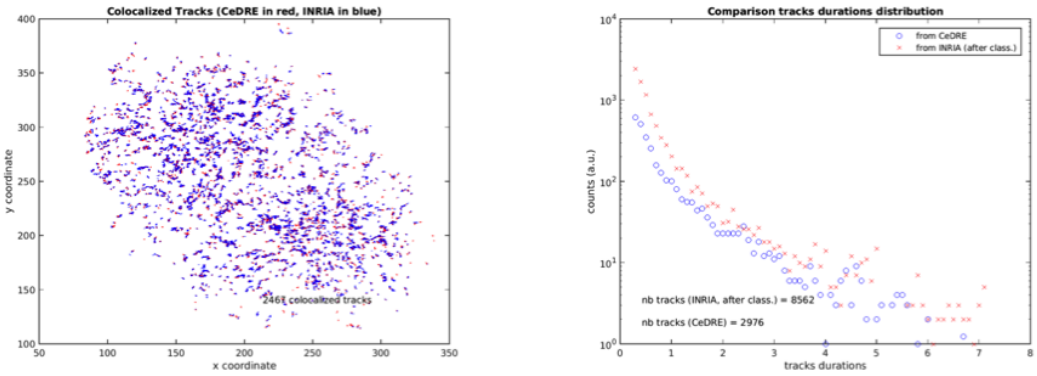

Figure 7.

Microtubule extremities detection and tracking in fluorescence microscopy (embryo of C. Elegans, IGDR - Institute of Genetics and Developmental biology of Rennes, CNRS UMR 6290).

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

Participants: Ancageorgiana Caranfil, Antoine Basset, 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 observation methods exist, including TIRFM (Total Internal Reflection Fluorescence Microscopy), that has 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 global model cannot be determined. The goal of this study was to build a correlation-like method to estimate local diffusion parameters in TIRFM images. Using a correlation approach similar to TICS (Temporal Image Correlation Spectroscopy) with an adapted local model, we have developed a novel correlation-based method to estimate the diffusion coefficient for every diffusion event in TIRFM images. We turned the non-linear model of the TICS method into a linear one, and made it rely on less parameters than the other estimation methods. Results are excellent for sequences with a good signal-to-noise ratio (see Fig. 8); however, time and space dependencies are introduced with the presence of moderate-to-strong image noise. Although only synthetic images have been used so far, studies of real-life TIRFM images are forthcoming, along with refinements to make the method robust to noise.

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

7.8. Co-localization between proteins : testing procedure and generative models

Participants: Frédéric Lavancier, Thierry Pécot, Charles Kervrann.

In the context of bioimaging, co-localization 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. An illustration of the co-localization of green (Langerin protein) and red (Rab11 GTPase protein) fluorescence is shown in Fig. 9 (the images were segmented by applying the ATLAS algorithm [12]). In our framework, the spatial repartition

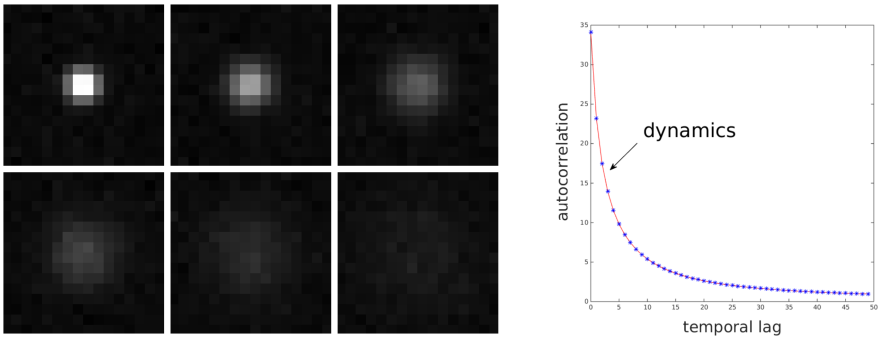

Figure 8. Left: first six instances of a TIRFM image sequence showing a diffusion event. Right: the correlation-based method is applied on the TIRFM sequence; both the computed values of the autocorrelation, for different values of the temporal lag, and the fitting function for these values are represented.

of proteins in the same cell is modeled by a union of random balls, possibly overlapping, and a Gibbs interaction is introduced to take into account the possible interaction between the two co-expressed proteins. A simulation algorithm is described and an inference procedure, based on the Takacs-Fiksel method, is proposed to estimate the interaction parameter. This estimation allows us to determine the presence of co-localization and to quantify the degree of interactions. On the other hand, this model can be used as a generator for synthesized images of co-localized proteins, in a view to assess testing procedures as the one explained below.

In an on-going project, we are developing a non-parametric testing procedure for co-localization. It is mainly based on the overlap area, corresponding to yellow spots as displayed in the right-hand side image of Fig. 9. Our first experiments on synthesized images showed that our procedure is more powerful than all existing methods to detect co-localization. Moreover this testing procedure turns out to be robust to different shapes and sizes of objects segmented by any competitive algorithm.

Reference: [36]

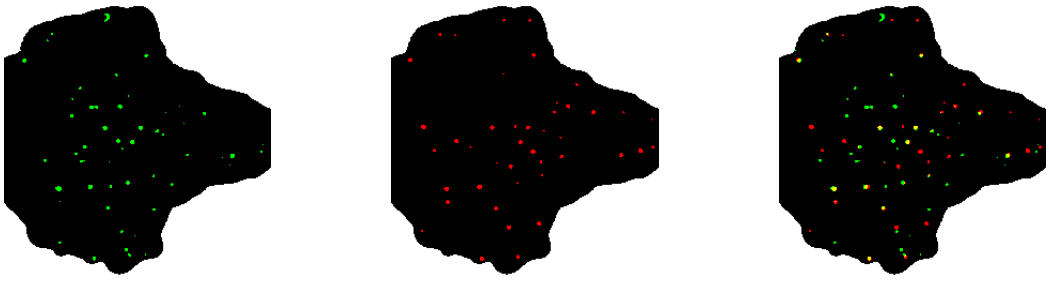

Figure 9. M10 cell showing Langerin proteins (left, in green) and Rab11 GTPase proteins (middle, in red). Right: superposition of the two previous images resulting in some possible yellow spots (co-expression of proteins within the same pixel).

7.9. 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. We have proposed a statistical method able to classify the motion of the observed trajectories into three groups: "confined", "directed" and "free diffusion" (namely Brownian motion). This method is an alternative to the commonly used Mean Square Displacement (MSD) analysis. We assessed our procedure on both simulations and real cases; an example of confined diffusion is the Ornstein-Uhlenbeck process while an example of directed diffusion is the Brownian motion with constant drift. The method is currently applied to investigate membrane trafficking (Rab11/Langerin (see Fig. 10) and Rab11/TfR protein sequences) using the following procedure:

1. Tracking of particles with any competitive algorithm.
2. Statistical test /classification applied on tracks longer than ten time points.
3. Estimation of diffusion parameters (e.g. drift, diffusion, ...).

Each trajectory is labelled with the most likely process and the parameters of the underlying process are estimated. Future work will concern the detection of change of motion dynamic over time. Some results of our test on the Langerin protein sequence are shown in Fig. 10.

Collaborator: Myriam Vimond (ENSAI Rennes).

7.10. 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 [39], we have 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 deduced 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 models as the Lennard-Jones model. In [15], we have extended the pseudo-likelihood procedure to infinite range Gibbs interactions and proved its consistency and its asymptotic normality.

References: [15], [39]

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

7.11. Statistical aspects of Determinantal Point Processes

Participant: Frédéric Lavancier.

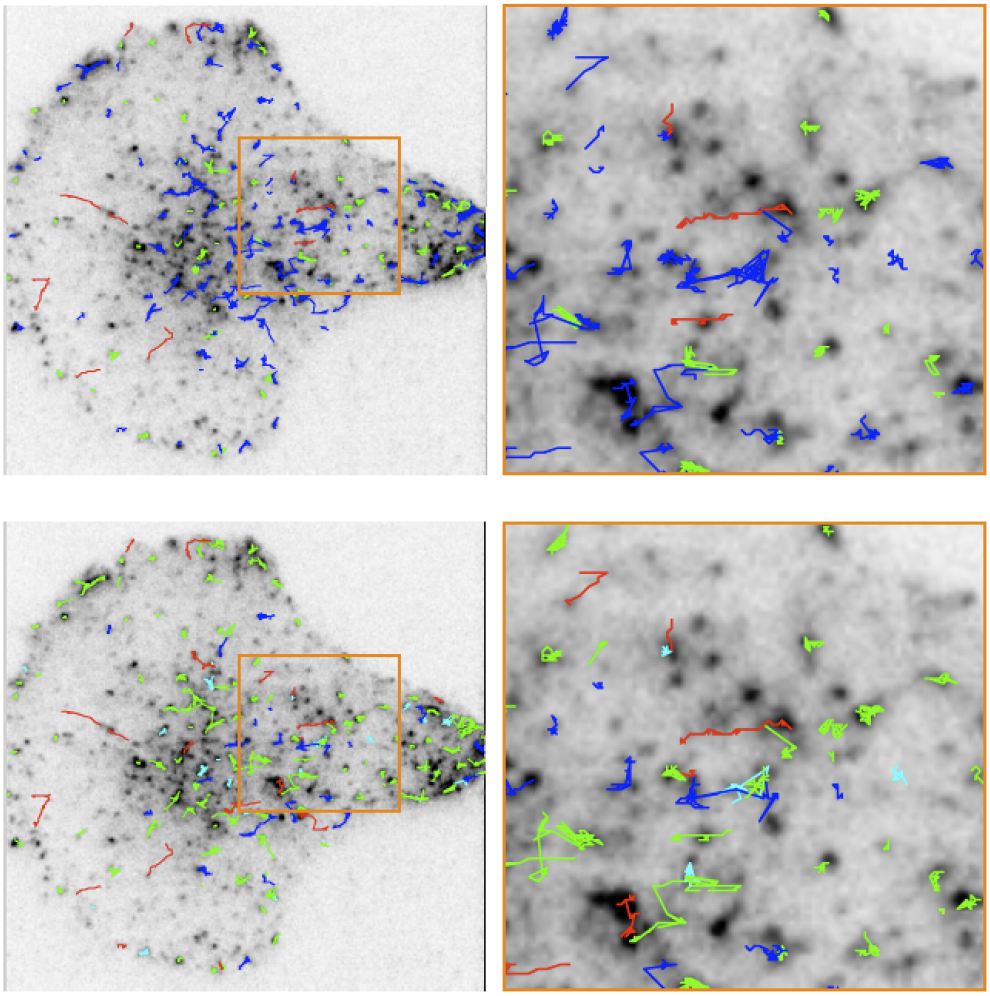

Figure 10. Labelling of the dynamics of trajectories on the Langerin protein sequence (Courtesy of UMR 144 CNRS-Institut Curie and PICT IBiSA). We display only the trajectories appearing on the first 100 frames. The color code is red for directed Brownian, green for Ornstein-Uhlenbeck, blue for Brownian, cyan for motionless. Top panel is labelled with our test, bottom panel with the MSD method.

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 [23], we have demonstrated that DPPs provide useful models for the description of spatial point pattern datasets where nearby points repel each other. We have exploited the appealing probabilistic properties of DPPs to develop parametric models, where the likelihood and moment expressions can be easily evaluated and realizations can be quickly simulated. We have discussed how statistical inference is conducted using the likelihood or moment properties of DPP models, and we provided freely available software for simulation and statistical inference.

In [13], 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 [37] and [38]. In the former study we have established the Brillinger mixing property of stationary DPPs, a first important step toward asymptotic inference. In the latter contribution, we have exploited this result to deduce the consistency and asymptotic properties of contrast estimators for stationary DPPs.

References: [23], [13], [37], [38]

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

7.12. Modelling 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 [22], 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 have been discussed when a realization of the target point process is observed, depending on whether the thinned points are also observed or not. Some typical simulations of the target processes are shown in Fig. 11.

Reference: [22]

Collaborator: Jesper Møller (Department of Mathematical Sciences, Aalborg University, Denmark).

7.13. Retracing and registration for Correlative light-electron microscopy (CLEM)

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

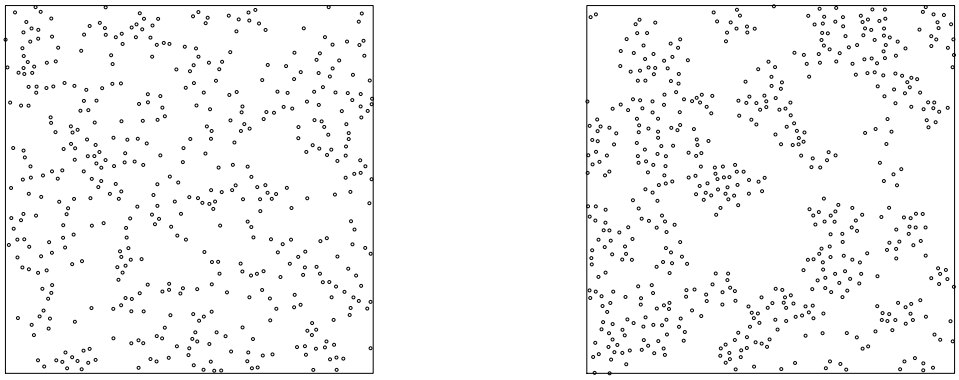

Figure 11. Examples of simulations with aggregation on the large scale and regularity on the small scale.

Correlative light-electron microscopy (CLEM) enables to relate cell dynamics visualized in light microscopy (LM) with cell structure provided by electron microscopy (EM) for a better understanding of cell mechanisms. Registration of LM and EM modalities is then a timely, important but difficult open problem, which still requires some manual assistance. LM and EM images are indeed of very different size, spatial resolution, field of view, and appearance. We have investigated an original automated approach for the retracing-and-registration stage of the overall CLEM workflow (see Fig. 12). Pairing between the LM region of interest (ROI) and the corresponding EM patch relies on a common representation for both images, based on the LoG (Laplacian of Gaussian) transform with an adaptive associated scale (or blurring). We exploit histograms of the LoG values or histograms supplied by the LDP (Local Directional Pattern) texture descriptor, with associated histogram distances, to solve the EM patch search issue. The search step supplies a pre-registration, which is refined by the estimation of an affine motion model to overlay the EM image onto the LM image around the ROI. Preliminary results on real CLEM images provided by UMR 144 CNRS-Institut Curie demonstrated the interest and efficiency of the proposed method.

Collaborators: Perrine Paul-Gilloteaux and Xavier Heiligenstein (UMR 144 CNRS-Institut Curie).

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

Participants: Emmanuel Moebel, Charles Kervrann.

In this study, we have addressed two important issues in cryo electron tomography (CET) images: the low signal-to-noise ratio and the presence of a missing wedge (MW) of information in the spectral domain. Indeed, according to the Fourier slice theorem, limited angle tomography results into an incomplete sampling of the Fourier domain. Therefore, the Fourier domain is separated into two regions: the known spectrum (KS) and the unknown spectrum, the latter having the shape of a missing wedge (see Fig. 13). The proposed method tackles both issues jointly, by iteratively applying a denoising algorithm in order to fill up the MW, and proceeds as follows:

1. Excitation step: Add noise into the MW.
2. Denoising step: Apply a patch-based denoising algorithm.
3. Repeat steps 1 and 2, by keeping KS constant through the iterations.

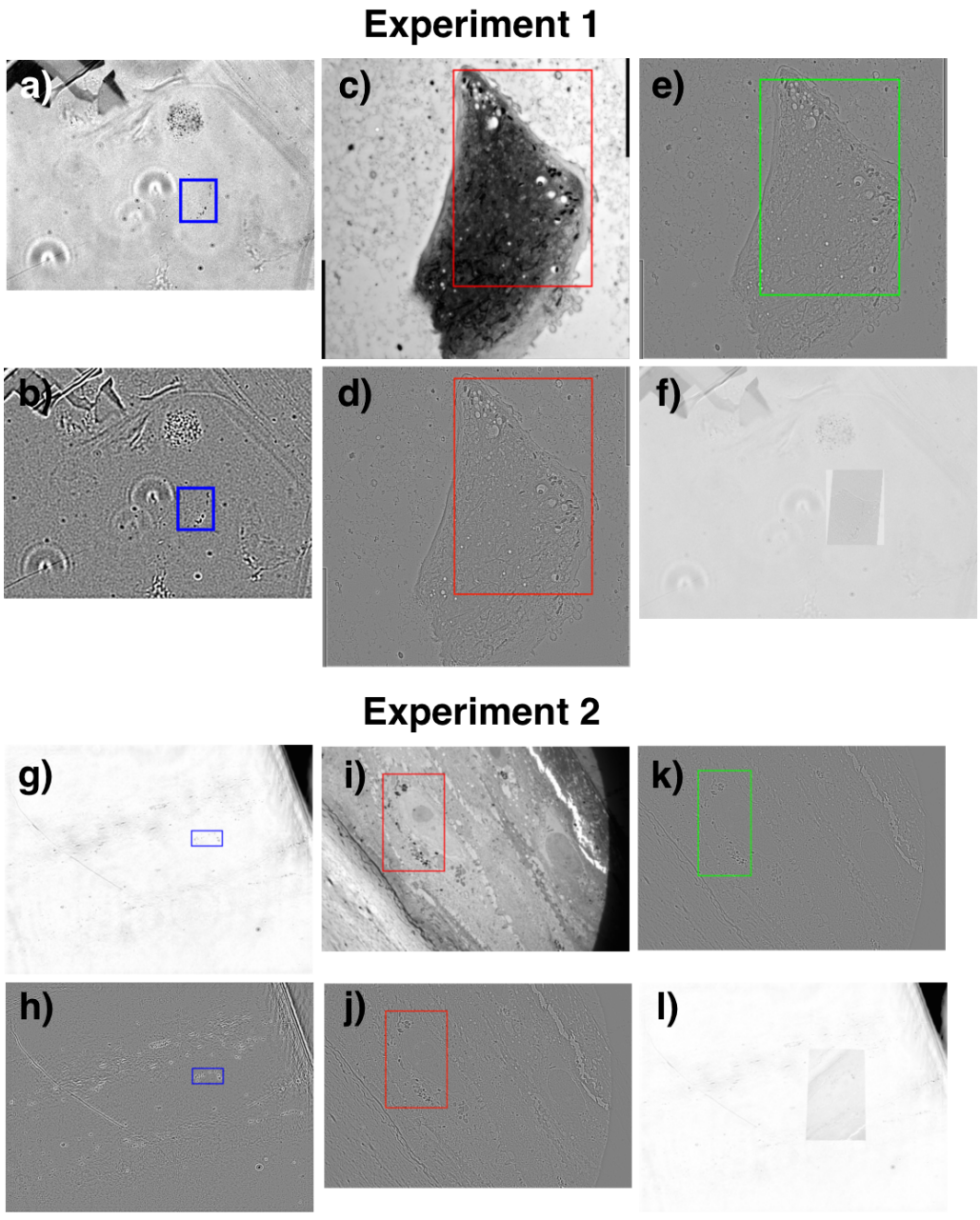

Figure 12. CLEM experiment #1: a) LM image with Region of Interest (ROI) framed in blue; b) same ROI delineated in the LoG-LM image; c) ground-truth location of the corresponding EM patch framed in red; d) the same but in the LoG-EM image; e) selected patch (SP) in the LoG-EM image in green; f) overlay (after registration) of the (decimated) EM image on the LM image around the ROI. CLEM experiment #2: g) LM-ROI in blue; h) LoG-LM-ROI; i) EM-GT in red; j) LoG-EM-GT; k) LoG-EM selected patch; l) Overlay of EM on LM around ROI.

The excitation step is used to randomly initialize the coefficients of the MW, whereas the denoising step acts as a spatial regularization. The employed denoising algorithm, which exploits the self-similarity of the image, filters out coefficient values which are dissimilar to KS, thereby keeping similar ones. By iterating these steps, we are able to diffuse the information contained in KS into the MW.

An application example on experimental data can be seen on Fig. 13, which shows the data in both spectral and spatial domain. The data contains a spherical gold particle, deformed by MW induced artifacts: elongation of the object, side- and ray-artifacts. From the residue image it can be seen that noise and MW artifacts have been reduced, while preserving the details of the image. Experiments are being performed to verify if particle detection and alignment are enhanced by using the method as a pre-processing step.

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

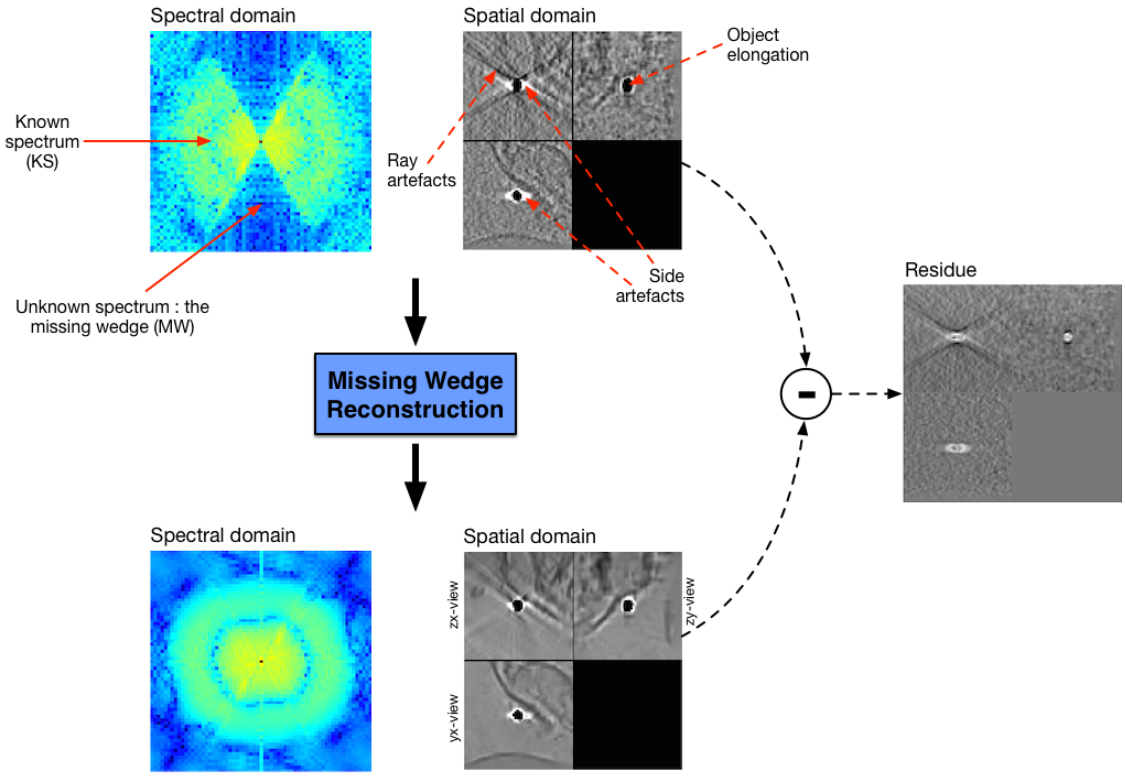

Figure 13. Experimental result of denoising and compensation of the missing wedge in cryo electron tomography.

7.15. Algorithms for row registration to improve quality of Tissue MicroArray (TMA) images

Participants: Hoai Nam Nguyen, Charles Kervrann.

Row jittering is a common problem arising in medical imaging devices such as CT (Computer Tomography) and MRI (Magnetic Resonance Imaging) scanners due to errors of synchronization during image acquisition process. On scanners designed and developed by Innopsys, the problem becomes more challenging mainly because the pixel displacement is non constant along each row (Fig. 14) and possibly sub-pixel (i.e. non integer translation). To overcome this drawback, we first proposed a window-based algorithm to approximate the translation at each pixel by selecting the value that best minimizes a matching criteria over a finite set of possible sub-pixel translations. We obtained satisfying results with this method on real data with fast computation time (see Fig. 14). Furthermore, this matching criteria has been considered as a data fidelity term and was combined to a regularization term to promote a smooth solution and correct small artifacts which were not removed with the window-based method. To minimize the energy functional, we have adopted the quadratic relaxation technique and proximal method. This algorithm is slower and is initalized by the window-based algorithm to produce very encouraging results and elimination of all undesirable artifacts (see Fig. 14).

Collaborators: Vincent Paveau and Cyril Cauchois (Innopys).

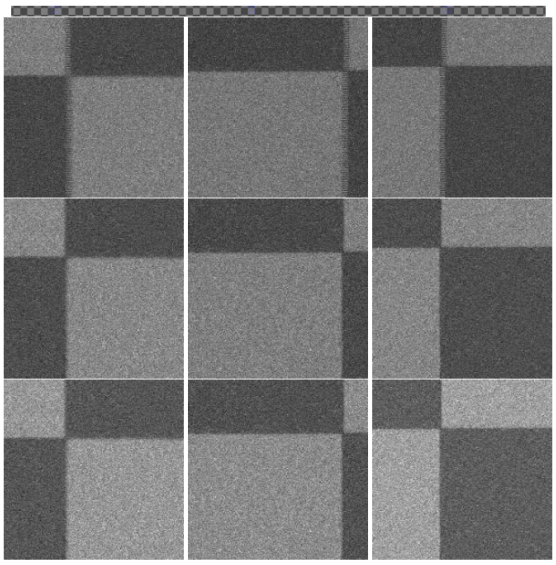

Figure 14. Illustration of the two-row registration algorithms. First row : full width input image (by courtesy of Innopsys). Second row : zooms on input image (blue boxes). Third row : corrected with window-based algorithm. Fourth row : corrected with variational method.

7.16. Robust motion model selection

Participants: Patrick Bouthemy, Bertha Mayela Toledo Acosta.

Parametric motion models are commonly used in image sequence analysis for different tasks. A robust estimation framework is usually required to reliably compute the motion model. However, choosing the most appropriate model in that estimation context is still an open issue. Indeed, penalizing the model complexity while maximizing the size of the inlier set may be contradictory. In this study, we proposed a robust motion model selection method which relies on the Fisher statistic. We also derived an interpretation of it as a robust C_P-Mallows criterion. The resulting criterion is straightforward to compute and explicitly involves the aforementioned trade-off between maximizing the size of the inlier set and minimizing the complexity

(i.e., the number of parameters) of the selected motion model. We have conducted a comparative experimental evaluation on synthetic and real image sequences demonstrating that our criterion outperforms the RBIC criterion.

Collaborator: Bernard Delyon (IRMAR Rennes).

7.17. Anomaly detection in crowded scenes

Participants: Juan Manuel Perez Rua, Antoine Basset, Patrick Bouthemy.

We have defined an original motion-based method to detect and localize abnormal events in videos of crowded scenes. The algorithm relies on so-called labeled affine flows, involving both affine motion types and affine velocity vectors, and on view-based crowd motion classes. At every pixel the crowd motion class is inferred from the affine motion model selected among a set of candidate models estimated over a collection of windows. Then, the image is subdivided in blocks where local crowd motion class histograms weighted by the affine motion vector magnitudes are computed. They are block-wise compared to histograms of normal behaviors with a combined distance. More specifically, we introduce the so-called local outlier factor (LOF) to detect anomalous blocks. LOF is a local flexible measure of the relative density of data points in a feature space, here the space of crowd motion class histograms. By thresholding the LOF value, we can detect an abnormal event in a given block at a given time. Comparative experiments on several real datasets demonstrated that our method is competitive with methods relying on far more elaborated models and exploiting both appearance and motion, while yielding superior performance over motion-based anomaly detection methods.

7.18. Occlusion detection in image sequences

Participants: Juan Manuel Perez Rua, Patrick Bouthemy.

The problem of localizing occlusions between consecutive frames of a video is important but rarely tackled on its own. In most works, it is tightly interleaved with the computation of accurate optical flows, which leads to a delicate chicken-and-egg problem. With this in mind, we proposed a novel approach to occlusion detection where visibility or not of a point in next frame is formulated in terms of visual reconstruction. The key issue is now to determine how well a pixel in the first image can be "reconstructed" from co-located colors in the next image. We first exploited this reasoning at the pixel level with a new detection criterion. Contrary to the ubiquitous displaced-frame-difference, the proposed alternative does not critically depend on a pre-computed, dense displacement field, while being shown to be more effective. We then leveraged this local modeling within an energy-minimization framework that delivers occlusion maps. An easy-to-obtain collection of parametric motion models is exploited within the energy to provide the required level of motion information. Our approach outperforms state-of-the-art detection methods on the challenging MPI Sintel dataset.

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).

A three-year contract has been established with Innopsis in 2013 to support Hoai Nam Nguyen's Ph-D 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 Innopsis.

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 Ph-D 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. Contrary to the ubiquitous displaced-frame-difference, the proposed alternative does not critically depend on a pre-computed, dense displacement field, while being shown to be more effective. We then leverage this local modeling within an energy-minimization framework that delivers occlusion maps. An easy-to-obtain collection of parametric motion models is exploited within the energy to provide the required level of motion information. Our approach outperforms state-of-the-art occlusion detection methods on the challenging MPI Sintel dataset.

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.

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.

9.3. European Initiatives

9.3.1. Collaborations with Major European Organizations

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. Inria International Partners

9.4.1.1. Informal International Partners

Collaboration with UT Southwestern Medical Center, Dallas (TX), Prof. Gaudenz Danuser: Object tracking in video-microscopy.

Collaboration with Max-Planck Institute, Martinsried (Germany), Dr. Julio Ortiz: Detection and segmentation of macromolecules in cryo-electron tomography.

Collaboration with Aalborg University (Denmark), Prof. Jesper Møller: Modeling aggregation on the large scale and regularity on the small scale in spatial point pattern datasets (visit of Frédéric Lavancier from 26-30 January 2015).

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific events organisation

10.1.1.1. Member of the organizing committees

Charles Kervrann was member of the organizing committee of the international "Quantitative BioImaging" (QBI'15) conference, Institut Pasteur, Paris, January 2015 (180 participants).

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

Frédéric Lavancier is 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.

10.1.2. Scientific events selection

10.1.2.1. Member of the conference program committees

Charles Kervrann: Associated Editor for the conference ISBI'2015, member of the program committee of JOBIM'15 (Clermont-Ferrand), member of the scientific committee "Journées d'Imagerie Optique Non-Conventionnelle" (JIONC'2015, JIONC'2016).

Patrick Bouthemy: Associate Editor for the conference ISBI'2016.

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

10.1.2.2. Reviewer

Charles Kervrann: reviewer for ICIP'2015, ICASSP'2015, SSVM'2015, EMMCPRV'2015, NIPS'15, ICASSP'2016, ISBI'2016.

Patrick Bouthemy: reviewer for ICIP'2015, ISBI'2015.

Frédéric Lavancier: reviewer for "Spatial Statistics: Emerging Patterns" 2015.

Thierry Pécot: reviewer for ISBI'2015, 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 (publication in 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 Image Processing, Journal Mathematical Imaging and Vision, Medical Image Analysis, Traitement du Signal.

Patrick Bouthemy: IEEE Transactions on Image Processing, Medical Image Analysis, Mathematical Problems in Engineering.

Frédéric Lavancier: Applications of Mathematics, Bernoulli, Computational Statistics and Data Analysis, Journal of the Royal Statistical Society Series B, R Journal, Médecine/Sciences, Metrika, Statistics.

Thierry Pécot: Bioinformatics.

10.1.4. Invited talks

Charles Kervrann:

Seminar Mine-Telecom & University of Paris Descartes, PEWA: Patch-based Exponentially Weighted Aggregation for image denoising, Paris, December 2015.

Seminar IBC LIRMM, Imagerie biologique à l'échelle cellulaire: enjeux et défis en traitement d'images, Montpellier, December 2015.

GdR Plasmonique Moléculaire et Spectrosocopies Exaltées (PMSE), Imagerie biologique à l'échelle cellulaire: analyse quantitative de la diffusion, Inria Rocquencourt, November 2015.

GdR Microscopie et Imagerie du Vivant (MIV), A statistical test to detect non Brownian diffusion adapting to the length of the observed trajectory (with V. Briane), ENS Lyon, Novembre 2015.

Seminar INSA Rouen, PEWA: Patch-based Exponentially Weighted Aggregation for image denoising, Rouen, November 2015.

Invited talk Researcher School "Biophysics: from Measurements to Models in Biology", Biological imaging: context and challenges in image processing, 2 hours, Les Houches, Octobre 2015.

Seminar Telecom-Physique Strasbourg, Imagerie biologique à l'échelle cellulaire: enjeux et défis en traitement d'images, Strasbourg, June 2015.

Invited talk PhD School I2S LIRMM, Imagerie biologique: enjeux et défis en traitement d'images, 3 hours, Montpellier, April 2015.

Invited talk "Quantitative BioImaging" (QBI'15) conference, Joint localization estimation and classification of membrane dynamics in TIRF microscopy image sequences (with J. Salamero), Paris, January 2015.

Thierry Pécot:

Invited talk "Cycle de vie des images en microscopie", Mobyle@SERPICO: Image processing methods on a Mobyle Web Portal (with C. Kervrann), Paris, December 2015.

GdR Microscopie et Imagerie du Vivant (MIV) (Mini-symposium on BioImage Informatics), Counting-based particle flux estimation for traffic analysis in live cell imaging (with C. Kervrann, J. Salamero and J. Boulanger) , Paris, November 2015.

Invited talk FBI Annual Meeting, Particle flux estimation for traffic analysis in live cell imaging (with C. Kervrann, J. Salamero and J. Boulanger), Paris, September 2015.

Contributed talk "Quantitative BioImaging" (QBI'15) conference, A quantitative approach for space-time membrane trafficking orientation (with J. Boulanger, P. Bouthemy, S. Bardin, J. Salamero and C. Kervrann, Paris, January 2015.

Invited talk European BioImage Analysis Symposium (EuBIAS'15), Mobyle@SERPICO: Image processing methods for the temporal analysis of moving particles on a Mobyle Web Portal (with C. Kervrann), Paris, January 2015.

Frédéric Lavancier:

Seminar of University of Paris 6, A general procedure to combine estimators, Paris, March 2015.

Seminar of University of Toulouse 3, Determinantal point process models and statistical inference, Toulouse, October 2015.

Seminar Institut Henri Poincaré (IHP), Determinantal point process models and statistical inference, Paris, October 2015.

Invited talk Journées STAR, A general procedure to combine estimators, Rennes, October 2015.

Seminar of University of Torino, Determinantal point process models and statistical inference, Turin, Italy, October 2015.

Contributed talk at "Spatial Statistics: Emerging Patterns" conference, Combining estimators in spatial statistics, Avignon, June 2015.

Invited talk at "Geometric Science of Information" (GSI'15), A two-color interacting random balls model for co-localization analysis of proteins (with C. Kervrann), Palaiseau, October 2015.

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 board of the GRETSI (Groupement de Recherche en Traitement du Signal et des Images).

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:

Master: From BioImage Processing to BioImage Informatics, 5 hours, coordinator of the module (30 hours), Master 2 Research IRIV, Telecom-Physique Strasbourg & 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, Hoai Nam Nguyen), 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.

Licence: Descriptive Statistics, 12 hours, Licence 3 Mathematics & Economy, University of Nantes.

10.2.2. Supervision

PhD: Christophe Biscio, Contribution to the modeling and the parametric estimation of determinantal point processes, University of Nantes, September 2015, supervised by Frédéric Lavancier.

PhD: Antoine Basset, Detection and characterization of dynamical events recognition in image sequences: application to membrane fusion in TIRF microscopy, University of Rennes 1, December 2015, supervised by Patrick Bouthemy and Charles Kervrann in collaboration with Jérôme Boulanger and Jean Salamero (UMR 144 CNRS-Institut Curie).

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).

10.2.3. Juries

Referee of Habilitation thesis: S. Jonic (University of Pierre and Marie Curie) [C. Kervrann].

Referee of PhD thesis: X. Wang (Ecole Centrale de Lyon, supervised by L. Chen) [P. Bouthemy].

Chair of PhD thesis juries: Y. Karpate (University of Rennes 1, supervised by C. Barillot) [P. Bouthemy], H. Mi (University of Rouen, supervised by S. Ruan) [P. Bouthemy].

11. Bibliography

Major publications by the team in recent years

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[3] 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

[4] 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^{o} 2, pp. 442-453 [*DOI :* 10.1109/TMI.2009.2033991]

[5] 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^{o} 37, pp. 16016-16022 [*DOI :* 10.1073/PNAS.1004037107]

[6] 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^{o} 4, pp. 2484-2520 [*DOI :* 10.1137/120872048], https://hal.inria.fr/hal-00931667

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

[9] 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^{o} 1, pp. 45–69

[10] 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

Publications of the year

Doctoral Dissertations and Habilitation Theses

[11] A. BASSET. *Detection and characterization with local statistical approaches of dynamical events in image sequences: Application to membrane fusion in TIRF microscopy*, Université Rennes 1, December 2015, https://hal.inria.fr/tel-01259185

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[12] 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^{o} 11, 16 p. [*DOI :* 10.1109/TIP.2015.2450996], https://hal.inria.fr/hal-01248290

[13] C. A. N. BISCIO, F. LAVANCIER. *Quantifying repulsiveness of determinantal point processes*, in "Bernoulli", 2016, https://hal.archives-ouvertes.fr/hal-01003155

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