IN PARTNERSHIP WITH:
CNRS

Université de Lorraine

Activity Report 2017

Project-Team BIGS

Biology, genetics and statistics

IN COLLABORATION WITH: Institut Elie Cartan de Lorraine (IECL)

RESEARCH CENTER
Nancy - Grand Est

THEME
Computational Biology

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Creation of the Team: 2009 January 01, updated into Project-Team: 2011 January 01

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1. Personnel

Research Scientists

Romain Azais [Inria, Researcher]
Bruno Scherrer [Inria, Researcher, HDR]

Faculty Members

Anne Gégout Petit [Team leader, Univ de Lorraine, Professor, HDR]
Thierry Bastogne [Univ de Lorraine, Associate Professor, HDR]
Sandie Ferrigno [Univ de Lorraine, Associate Professor]
Sophie Mezieres [Univ de Lorraine, Associate Professor]
Jean Marie Monnez [Univ de Lorraine, Professor, HDR]
Aurelie Muller-Gueudin [Univ de Lorraine, Associate Professor]
Samy Tindel [Univ de Lorraine, Professor, HDR]
Pierre Vallois [Univ de Lorraine, Professor, HDR]

Post-Doctoral Fellow

Florian Bouguet [Inria, until Aug 2017]

PhD Students

Lévy Batista [Univ de Lorraine, until Oct 2017]
Kévin Duarte [Centre hospitalier universitaire de Nancy]
Florine Greciet [Autre entreprise privée]
Pauline Guyot [Univ de Lorraine]
Clemence Karmann [Inria]
Nassim Sahki [Inria, from Nov 2017]

Interns

Amady Ba [Univ de la Méditerranée, from May 2017 until Jun 2017]
Halimatou Bachir Abdou [INRA, from Jul 2017 until Sep 2017]

Administrative Assistant

Celine Simon [Inria]

External Collaborator

Celine Lacaux [Univ d'Avignon et des pays du Vaucluse, HDR]

2. Overall Objectives

2.1. Overall Objectives

BIGS is a team common to Inria, CNRS and Université de Lorraine, via the Institut Élie Cartan, UMR 7502 CNRS-UL laboratory in mathematics, of which Inria is a strong partner. One member of BIGS, T. Bastogne, comes from the Centre de Recherche en Automatique de Nancy (CRAN), laboratory in the domain of Automatics with which BIGS has strong relations in the domain "Health-Biology-Signal". Our research is mainly focused on stochastic modeling and statistics for a methodological purpose but also aiming at a better understanding of biological systems. BIGS is composed of applied mathematicians whose research interests mainly concern probability and statistics. More precisely, our attention is directed on (1) stochastic modeling, (2) estimation and control for stochastic processes, (3) algorithms and estimation for graph data and (4) regression and machine learning. The main objective of BIGS is to exploit these skills in applied mathematics to provide a better understanding of some issues arising in life sciences, with a special focus on (1) tumor growth, (2) photodynamic therapy, (3) genomic data and micro-organisms population study, (4) epidemiology and e-health.

3. Research Program

3.1. Introduction

We give here the main lines of our research that belongs to the domains of probability and statistics. For a better understanding, we made the choice to structure them in four items. Although this choice was not arbitrary, the outlines between these items are sometimes fuzzy because each of them deals with modeling and inference and they are all interconnected.

3.2. Stochastic modeling

Our aim is to propose relevant stochastic frameworks for the modeling and the understanding of biological systems. The stochastic processes are particularly suitable for this purpose. Among them, Markov chains give a first framework for the modeling of population of cells [79], [56]. Piecewise deterministic processes are non diffusion processes also frequently used in the biological context [45], [55], [47]. Among Markov model, we also developed strong expertise about processes derived from Brownian motion and Stochastic Differential Equations [71], [54]. For instance, knowledge about Brownian or random walk excursions [78], [70] helps to analyse genetic sequences and to develop inference about it. However, nature provides us with many examples of systems such that the observed signal has a given Hölder regularity, which does not correspond to the one we might expect from a system driven by ordinary Brownian motion. This situation is commonly handled by noisy equations driven by Gaussian processes such as fractional Brownian motion of fractional fields. The basic aspects of these differential equations are now well understood, mainly thanks to the so-called *rough paths* tools [62], but also invoking the Russo-Vallois integration techniques [72]. The specific issue of Volterra equations driven by fractional Brownian motion, which is central for the subdiffusion within proteins problem, is addressed in [46]. Many generalizations (Gaussian or not) of this model have been recently proposed for some Gaussian locally self-similar fields, or for some non-Gaussian models [59], or for anisotropic models [42].

3.3. Estimation and control for stochastic processes

We develop inference about stochastic processes that we use for modeling. Control of stochastic processes is also a way to optimise administration (dose, frequency) of therapy.

There are many estimation techniques for diffusion processes or coefficients of fractional or multifractional Brownian motion according to a set of observations [58], [37], [44]. But, the inference problem for diffusions driven by a fractional Brownian motion has been in its infancy. Our team has a good expertise about inference of the jump rate and the kernel of Piecewise Deterministic Markov Processes (PDMP) [34], [35], [33], [36]. However, there are many directions to go further into. For instance, previous works made the assumption of a complete observation of jumps and mode, that is unrealistic in practice. We tackle the problem of inference of "Hidden PDMP". About pharmacokinetics modeling inference, we want to take into account for presence of timing noise and identification from longitudinal data. We have expertise on this subjects [38], and we also used mixed models to estimate tumor growth [39].

We consider the control of stochastic processes within the framework of Markov Decision Processes [69] and their generalization known as multi-player stochastic games, with a particular focus on infinite-horizon problems. In this context, we are interested in the complexity analysis of standard algorithms, as well as the proposition and analysis of numerical approximate schemes for large problems in the spirit of [41]. Regarding complexity, a central topic of research is the analysis of the Policy Iteration algorithm, which has made significant progress in the last years [81], [68], [53], [77], but is still not fully understood. For large problems, we have a long experience of sensitivity analysis of approximate dynamic programming algorithms for Markov Decision Processes [75], [74], [76], [61], [73], and we currently investigate whether/how similar ideas may be adapted to multi-player stochastic games.

3.4. Algorithms and estimation for graph data

A graph data structure consists of a set of nodes, together with a set of pairs of these nodes called edges. This type of data is frequently used in biology because they provide a mathematical representation of many concepts such as biological structures and networks of relationships in a population. Some attention has recently been focused in the group on modeling and inference for graph data.

Network inference is the process of making inference about the link between two variables taking into account the information about other variables. [80] gives a very good introduction and many references about network inference and mining. Many methods are available to infer and test edges in Gaussian Graphical models [80], [63], [50], [51]. However, when dealing with abundance data, because inflated zero data, we are far from gaussian assumption and we want to develop inference in this case.

Among graphs, trees play a special role because they offer a good model for many biological concepts, from RNA to phylogenetic trees through plant structures. Our research deals with several aspects of tree data. In particular, we work on statistical inference for this type of data under a given stochastic model. We also work on lossy compression of trees via linear directed acyclic graphs. These methods enable us to compute distances between tree data faster than from the original structures and with a high accuracy.

3.5. Regression and machine learning

Regression models or machine learning aim at inferring statistical links between a variable of interest and covariates. In biological study, it is always important to develop adapted learning methods both in the context of *standard* data and also for data of high dimension (with sometimes few observations) and very massive or online data.

Many methods are available to estimate conditional quantiles and test dependencies [67], [57]. Among them we have developed nonparametric estimation by local analysis via kernel methods [48], [49] and we want to study properties of this estimator in order to derive a measure of risk like confidence band and test. We study also many other regression models like survival analysis, spatio temporal models with covariates. Among the multiple regression models, we want to develop omnibus test that examine several assumptions together.

Concerning the analysis of high dimensional data, our view on the topic relies on the *French data analysis school*, specifically on Factorial Analysis tools. In this context, stochastic approximation is an essential tool [60], which allows one to approximate eigenvectors in a stepwise manner [66], [64], [65]. BIGS aims at performing accurate classification or clustering by taking advantage of the possibility of updating the information "online" using stochastic approximation algorithms [43]. We focus on several incremental procedures for regression and data analysis like linear and logistic regressions and PCA.

We also focus on the biological context of high-throughput bioassays in which several hundreds or thousands of biological signals are measured for a posterior analysis. We have to account for the inter-individual variability within the modeling procedure. We aim at developing a new solution based on an ARX (Auto Regressive model with eXternal inputs) model structure using the EM (Expectation-Maximisation) algorithm for the estimation of the model parameters.

4. Application Domains

4.1. Tumor growth-oncology

On this subject, we have new collaborations with clinicians and we want to propose branching processes to model appearance of mutations in tumor. The observed process is the "circulating DNA" (ctDNA). The final purpose is to use ctDNA as a early biomarker of the resistance to an immunotherapy treatment. It is the subject of gthe ITMO project. Another subject is the identification of dynamic network of expression We continue our work on low-grade gliomas. The ongoing collaboration with Montpellier CHU, and a new one with Montreal CRHUM should provide us more data. We initiate as well interactions with researchers from Montreal LIO to

extend the previous work. We still have much work to do in modeling to reach our goal of a decision-aid tool for personalised medicine. In the same context, there is a question of clustering analysis of a brain cartography obtained by sensorial simulations during awake surgery.

4.2. Genomic data and micro-organisms population study

Despite of his 'G' in the name of BIGS, Genetics is not central in the applications of the team. However, we want to contribute to a better understanding of the correlations between genes trough their expression data and of the genetic bases of drug response and disease. We have contributed to methods detecting proteomics and transcriptomics variables linked with the outcome of a treatme

4.3. Epidemiology and e-health

We have many works to do in our ongoing projects in the context of personalized medicine with "CHU Nancy". They deal with biomarkers research; prognostic value of quantitative variables and events and scoring, of adverse events. We also want to develop our expertise in rupture detection in a project with APHP for the detection of adverse events, earlier than the clinical signs and symptoms. The clinical relevance of predictive analytics is obvious for high-risk patients such as those with solid organ transplantation or severe chronic respiratory disease for instance. The main challenge is the rupture detection in multivariate and heterogeneous signals (for instance daily measures of electrocardiogram (during 30mn), body temperature, spirometry parameters, sleep duration, etc ... Other collaborations with clinicians concern foetopathology and we want to use our work on conditional distribution function to explain fetal and child growth. We have data from the "Service de foetopathologie et de placentologie" of the "Maternité Régionale Universitaire" (CHU Nancy).

4.4. Dynamics of telomeres

The telomeres are disposable buffers at the ends of chromosomes which are truncated during cell division; so that, over time, due to each cell division, the telomere ends become shorter. By this way, they are markers of aging. Trough a beginning collaboration with Pr A. Benetos, geriatrician at CHU Nancy, we recently data on the distribution of the length of telomeres from blood cells. With some members of Inria team TOSCA, we want to work in three connected directions: (1) refine methodology for the analysis of the available data; (2) propose a dynamical model for the lengths of telomeres and study its mathematical properties (long term behavior, quasi-stationarity, etc); and (3) use these properties to develop new statistical methods. A slot of postdoc position is already planned in the Lorraine Université d'Excellence, LUE project GEENAGE (managed by CHU Nancy).

5. New Software and Platforms

5.1. Angio-Analytics

KEYWORDS: Health - Cancer - Biomedical imaging
SCIENTIFIC DESCRIPTION: This tool allows the pharmacodynamic characterization of anti-vascular effects in anti-cancer treatments. It uses time series of in vivo images provided by intra-vital microscopy. Such in vivo images are obtained owing to skinfold chambers placed on mice skin. The automatized analysis is split up into two steps that were completely performed separately and manually before. The first steps corresponds to image processing to identify characteristics of the vascular network. The last step is the system identification of the pharmacodynamic response and the statistical analysis of the model parameters.
FUNCTIONAL DESCRIPTION: Angio-Analytics allows the pharmacodynamic characterization of anti-vascular effects in anti-cancer treatments.

- Participant: Thierry Bastogne
- Contact: Thierry Bastogne

5.2. In silico

In silico design of nanoparticles for the treatment of cancers by enhanced radiotherapy
KEYWORDS: Bioinformatics - Cancer - Drug development
FUNCTIONAL DESCRIPTION: To speed up the preclinical development of medical engineered nanomaterials, we have designed an integrated computing platform dedicated to the virtual screening of nanostructured materials activated by X-ray making it possible to select nano-objects presenting interesting medical properties faster. The main advantage of this in silico design approach is to virtually screen a lot of possible formulations and to rapidly select the most promising ones. The platform can currently handle the accelerated design of radiation therapy enhancing nanoparticles and medical imaging nano-sized contrast agents as well as the comparison between nano-objects and the optimization of existing materials.

- Participant: Thierry Bastogne
- Contact: Thierry Bastogne

5.3. SesIndexCreatoR

FUNCTIONAL DESCRIPTION: This package allows computing and visualizing socioeconomic indices and categories distributions from datasets of socioeconomic variables (These tools were developed as part of the EquitArea Project, a public health program).

- Participants: Benoît Lalloué, Jean-Marie Monnez, Nolwenn Le Meur and Severine Deguen
- Contact: Benoît Lalloué
- URL: http://www.equitarea.org/documents/packages_1.0-0/

6. New Results

6.1. Stochastic modelling

Participants: T. Bastogne, P. Vallois, S. Wantz-Mezieres, L. Batista, A. Gégout-Petit

Because of the observation of longitudinal data for each subject in medicine, we have to care about the random effect due to the subject and to choose adapted models like mixed effect models [39], [40]. We recently improved this methodology for the analysis of data collected in vivo for growth tumor for the biopharmaceutical company Transgene. The problem was to measure the differential effect of treatments (different molecules and doses) on the dynamics of the tumor taking into account the effect of censoring [10].

In the framework of the esca-illness of vines, we developed different spatial models and spatio-temporal models for different purposes: (1) study the distribution and the dynamics of esca vines in order to tackle the aggregation and the potential spread of the illness (2) propose a spatio-temporal model in order to capture the dynamics of cases and measure the effects of environmental covariates. For purpose (1), we propose different tests based on the join count statistics [6].

6.2. Estimation and control for Markov Processes

Participants: R. Azais, F. Bouguet, T. Bastogne

We have developed statistical inference techniques for estimating the jump rate of PDMPs (piecewise-deterministic Markov processes) [2] which is an essential step to build relevant application models. In [2], we state a new characterization of the jump rate when the transition kernel only charges a discrete subset of the state space and deduce from it a competitive nonparametric technique for estimating this feature of interest. Our methodologies have been illustrated on numerical examples and real data. We also investigated the probabilistic properties of the PDMPs [5] or more general Markov processes [31] that could be useful to study properties of estimators.

A bit more generally, we have made contributions to a variety of specific estimation problems. We considered the problem of estimation of integrals under Markov design, which has a large variety of applications, in particular in biology and climatology. In [24], we have developed and analyzed a technique for estimating the average value over space when sensors describe a Markovian trajectory; this method leads to rates that are better than the traditional "root n"-rate, where n is the sample size, and was applied to the evaluation of the average temperature of oceans.

Control of stochastic processes is also a way to optimise administration (dose, frequency) of therapy. In [8], we have presented the design and validation of a real time controller able to track a preset photobleaching trajectory by modulating the width of light impulses during the treatment sessions, which is useful in a Photodynamic therapy context. This innovative solution was validated by *in vivo* experiments that have shown a significantly improvement of reproducibility of the inter-individual photobleaching kinetics. This innovative controller is the first personalized solution able to adapt in realtime the dose of light to be applied in photodynamic therapy.

6.3. Algorithms and Estimation for graph data

Participants: R. Azais, F. Bouguet, T. Bastogne

Tree-structured data naturally appear in various fields, particularly in biology where plants and blood vessels may be described by trees. The paper [27] is devoted to the estimation of the relative scale of ordered trees that share the same layout. The theoretical study is achieved for the stochastic model of conditioned Galton-Watson trees. New estimators are introduced and their consistency is stated. A comparison is made with an existing approach of the literature. A simulation study shows the good behavior of our procedure on finite-sample sizes.

6.4. Regression and machine learning

Participants: A. Gégout-Petit, A. Muller-Gueudin, T. Bastogne, L. Batista, R. Azais, S. Ferrigno, K. Duarte, J.-M. Monnez

We consider the problem of sequential least square multidimensional linear regression using a stochastic approximation process. The choice of the stepsize may be crucial in this type of process. In order to avoid the risk of numerical explosion which can be encountered, we define three processes with a variable or a constant stepsize and establish their convergence. Finally these processes are compared to classic processes on 11 datasets, 6 with a continuous output and 5 with a binary output, for a fixed total number of observations used and then for a fixed processing time. It appears that the third-defined process with a very simple choice of the stepsize gives usually the best results [32].

We study many other regression models like survival analysis, spatio temporal models with covariates. Among the multiple regression models, we want to test, thanks to simulation methods, validity of their assumptions [25]. Tests of this kind are called omnibus test. An omnibus test is an overall test that examines several assumptions together, the most known omnibus test is the one for testing gaussianity (that examines both skewness and kurtosis).

In the purpose of selecting factors linked to the efficiency of a treatment in the context of high dimension (about 100.000 covariates), we have developed a new methodology to select and rank covariates associated to a variable of interest in a context of high-dimensional data under dependence but few observations. The methodology imbricates successively rough selection, clustering of variables, decorrelation of variables using Factor Latent Analysis, selection using aggregation of adapted methods and finally ranking through bootstrap replications. Simulations study shows the interest of the decorrelation inside the different clusters of covariates. The methodology was applied to select covariates among genomics, proteomics covariates linked to the success of a immunotherapy treatment for lung cancer [21], [19], [20].

We also focus on the biological context of high-throughput and high-content bioassays in which several hundreds or thousands of biological signals are measured for a posterior analysis. In this experimental context, each culture well is a biological system in which the output variable is the cell proliferation, the input variable can be an electrical or a light stimulus signal and the covariate may be the type of cells, type of medium or tested compounds. The ambition is to identify a batch of several thousands of wells in a single step with the same model structure. Mixed effects models are largely used in regression but up to now they have rarely been used in the field of dynamical system identification. Our approach aims at developing a new solution based on an ARX (Auto Regressive model with eXternal inputs) model structure using the EM (Expectation-Maximisation) algorithm for the estimation of the model parameter [13], [10].

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

7.1.1. Bilateral Contracts with Industry

7.1.1.1. Transgene 1. (2016-2017)

Participants: A. Gégout-Petit, A. Muller-Gueudin, Y. Shi
Transgene (Euronext: TNG), part of Institut Mérieux, is a publicly traded French biopharmaceutical company focused on discovering and developing targeted immunotherapies for the treatment of cancer and infectious diseases. B. Bastien, head of the biostatistics team appeals to BIGS to select covariates among genomics, proteomics expressions linked to the success of a treatment of the lung cancer. This subject was the purpose of the master thesis of Y. Shi and a paper on the subject is in preparation.

7.1.1.2. Transgene 2. (2016-2017)

Participants: T. Bastogne, L. Batista, P. Vallois
Transgene (Euronext: TNG), part of Institut Mérieux, is a publicly traded French biopharmaceutical company focused on discovering and developing targeted immunotherapies for the treatment of cancer and infectious diseases. B. Bastien, head of the biostatistics team appeals to BIGS to model data collected in vivo for growth tumor and to measure the effect of the treatment on the dynamics of the tumor.

7.1.1.3. SAFRAN Aircraft Engines (2016-2019)

Participants: R. Azaïs, A. Gégout-Petit, F. Greciet
SAFRAN Aircraft Engines designs and products Aircraft Engines. For the design of pieces, they have to understand mechanism of crack propagation under different conditions. It appeals to BIGS for modeling crack propagation with Piecewise Deterministic Markov Processes (PDMP). It is the subject of F. Greciet PhD, granted by ANRT. F. Greciet presented her work during a Fédération Charles Hermite Journey on November the 23th. She was laureat of "Mathématiques, oxygene du monde numérique" poster challenge [52].

7.1.1.4. CYBERNANO (2014-2017)

Participants: T. Bastogne, L. Batista, P. Guyot
Cybernano is a start-up founded in 2013 by one BIGS member: T. Bastogne. Cybernano develops computational services to analyze high-content data in cell biology for applications in oncology, cardiotoxicity and virology. After the end of his PhD (2017), L. Batista became chief technical officer of Cybernano. A EuroStars project proposal was submitted in Sep. 2017 in which Cybernano will be the leader and BIGS a scientific partner (Eurostars is a H2020 programme that supports research-performing small and medium enterprises).

8. Partnerships and Cooperations

8.1. National Initiatives

- *Popart (2016-2017)* In the framework of collaboration with A. Deveau of Inra Nancy, A. Gégout-Petit and A. Muller-Gueudin are included in the Inra "Microbial Ecosystems & Metaomics, Call 2016" Project "Popart"for "Regulation of the Poplar microbiome by its host: is the immune system involved ? ". The aim is to develop methodology for the inference of regulation network betwen micro-organisms around Poplar. The specificity of the data is the inflation of zeros that has to be taken into account.
- GDR 3475 Analyse Multifractale, Funding organism: CNRS, Leader: S. Jaffard (Université Paris-Est), Céline Lacaux
- GDR 3477 Géométrie stochastic, Funding organism: CNRS, Leader: P. Calka (Université Rouen), Céline Lacaux
- FHU CARTAGE (Fédération Hospitalo Universitaire Cardial and ARTerial AGEing ; leader : Pr Athanase BENETOS), Jean-Marie Monnez
- RHU Fight HF (Fighting Heart Failure ; leader : Pr Patrick ROSSIGNOL), located at the University Hospital of Nancy, Jean-Marie Monnez
- Project "Handle your heart", team responsible for the creation of a drug prescription support software for the treatment of heart failure, head: Jean-Marie Monnez
- "ITMO Physics, mathematics applied to Cancer" (2017-2019): "Modeling ctDNA dynamics for detecting targeted therapy", Funding organisms: ITMO Cancer, ITMO Technologies pour la santé de l'alliance nationale pour les sciences de la vie et de la santé (AVIESAN), INCa, Leader: N. Champagnat (Inria TOSCA), Participants: A. Gégout-Petit, A. Muller-Gueudin, P. Vallois
- Modular, multivalent and multiplexed tools for dual molecular imaging (2017-2020), Funding organism: ANR, Leader: B Kuhnast (CEA). Participant: T. Bastogne.

8.2. European Initiatives

8.2.1. Collaborations in European Programs, Except FP7 & H2020

- Photobrain project. AGuIX theranostic nanoparticles for vascular-targeted interstitial photodynamic therapy of brain tumors, project **EuroNanoMed II**, resp.: M. Barberi-Heyob, (2015-2017), participant: T. Bastogne.
- NanoBit Project. Nanoscintillator-Porphyrin Complexes for Bimodal RadioPhotoDynamic Therapy, project **EuroNanoMed II**, resp.: P. Juzenas, (2016-2018), participant: T. Bastogne.

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific Events Organisation

- BIGS team has organized a two-days workshop "Statistique pour les processus de Markov déterministes par morceaux" in Nancy, with about 40 participants, among which most members of the team. See http://pdmp2017.iecl.univ-lorraine.fr/

9.1.2. Scientific Events Selection

9.1.2.1. Chair of Conference Program Committees

- A. Gégout-Petit is chair of 2017 "Congrès Francophone International de l'Enseignement de la Statistique" (CFIES), Grenoble, September, 2017.

9.1.3. Journal

P. Vallois is in the editorial board of "Risk and Decision Analysis".

9.1.3.1. Reviewer - Reviewing Activities

All the BIGS members are regular reviewers for journals in probability, statistics and machine learning as: Bernoulli, Scandinavian Journal of statistics, Stochastics, Journal of Statistical Planning Inference, Journal of theoretical Biology, IEEE Trans. Biomedical Eng., Theoretical Biology and Medical Modelling, Royal Society of Chemistry, Signal Processing: Image Communication, Mathematical Biosciences, LIDA, Annals of Applied Probability, Annals of Operations Research and Journal of Machine Learning Research, as well as conferences such as ICML, World IFAC Congress, FOSBE, ALCOSP...

9.1.4. Leadership within the Scientific Community

- Anne Gégout-Petit is member of the board of the European Regional Council of the Bernoulli society
- Céline Lacaux is responsible of the *Statistic team*, Laboratory of Mathematic of Avignon (since September 2016)

9.1.5. Scientific Expertise

- T. Bastogne: scientific expert in Biostatistics and Signal Processing in Nanomedicine for CYBERnano (start-up).

9.1.6. Research Administration

- A. Gégout-Petit: elected member of the laboratory of mathematics "Institut Elie Cartan de Lorraine".
- Céline Lacaux is
  - member of the bord of the SMAI-MAS group,
  - elected member of the council of the Laboratory Mathematics of Avignon,
  - correspondant AMIES pour Avignon,
  - Member of the scientific committee of GDR 3477 Stochastic Geometry.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

R. Azaïs and B. Scherrer excepted, BIGS members have teaching obligations at "Université de Lorraine" and are teaching at least 192 hours each year. They teach probability and statistics at different level (Licence, Master, Engineering school). Many of them have pedagogical responsibilities.

9.2.2. Supervision

- PhD : Clémence Karmann, " Network inference for zero-inflated models", Grant : Inria-Cordis. Advisors: A. Gégout-Petit, A. Muller-Gueudin.
- PhD : Florine Gréciet, " Modèles markoviens déterministes par morceaux cachés pour la propagation de fissures", grant CIFRE SAFRAN AIRCRAFT ENGINES, Advisors : R. Azaïs, A. Gégout-Petit.
- PhD : Kévin Duarte, "Aide à la décision médicale et télémédecine dans le suivi de l'insuffisance cardiaque", Advisors : J.-M. Monnez and E. Albuisson.
- Post-doc: Florian Bouguet. Advisors: Romain Azaïs, Anne Gégout-Petit, Aurélie Muller-Gueudin.
- Post-doc: Benoît Henry (starting in Dec. 2016). Advisors: Romain Azaïs with Inria team Madynes.
- Master: all BIGS members regularly supervise project and internship of master IMOI students
- Engineering school: all BIGS members regularly supervise project of "Ecole des Mines ", ENSEM or EEIGM students

10. Bibliography

Publications of the year

Articles in International Peer-Reviewed Journals

[1] M. ABDALLAH, M. BLONSKI, S. WANTZ-MÉZIÈRES, Y. GAUDEAU, L. TAILLANDIER, J.-M. MOUREAUX. *On the relevance of two manual tumor volume estimation methods for diffuse low-grade gliomas*, in "Healthcare Technology Letters", 2018, forthcoming [*DOI :* 10.1049/HTL.2017.0013], https://hal.inria.fr/hal-01654158

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