RESEARCH CENTER
Saclay - Île-de-France

FIELD

Activity Report 2019

Section Application Domains

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AVIZ Project-Team

4. Application Domains

4.1. Natural Sciences

As part of a CORDI PhD project, we collaborate with researchers at CERN on interactive data visualization using augmented reality, with the goal to better understand this new visualization environment and to support the physicists in analysing their 3D particle collision data. As part of another CORDI PhD project, we collaborate with researchers at the German Center for Climate Computation (DKRZ), to better understand collaborative data exploration and interaction in immersive analytics contexts. Finally, as part of the Inria IPL "Naviscope," we collaborate with researchers at INRA (as well as other Inria teams) on interactive visualization tools for the exploration of plant embryo development.

4.2. Social Sciences

We collaborate with social science researchers from EHESS Paris on the visualization of dynamic networks; they use our systems (GeneaQuilts [56], Vistorian [64], PAOHVis [7]) and teach them to students and researchers. Our tools are used daily by ethnographers and historians to study the evolution of social relations over time. In the social sciences, many datasets are gathered by individual researchers to answer a specific question, and automated analytical methods cannot be applied to these small datasets. Furthermore, the studies are often focused on specific persons or organizations and not always on the modeling or prediction of the behavior of large populations. The tools we design to visualize complex multivariate dynamic networks are unique and suited to typical research questions shared by a large number of researchers. This line of research is supported by the DataIA "HistorIA" project, and by the "IVAN" European project. We also collaborate on the BART initiative, a joint project with IRT-SystemX on the analysis and visualization of blockchain data, in collaboration with economists from Université Paris-Sud.

4.3. Medicine

We collaborate with CMAP/Polytechnique on the analysis and visualization of CNAM Data "parcours de santé" to help referent doctors and epidemiologists make sense of French health data. In particular, we are working on a subset of the CNAM Data focused on urinary problems, and we have received a very positive feedback from doctors who can see what happens to the patients treated in France vs. what they thought happened through the literature. This project is starting but is already getting a lot of traction from our partners in medicine, epidemiology, and economy of health.

CEDAR Project-Team

4. Application Domains

4.1. Cloud Computing

Cloud computing services are strongly developing and more and more companies and institutions resort to running their computations in the cloud, in order to avoid the hassle of running their own infrastructure. Today's cloud service providers guarantee machine availabilities in their Service Level Agreement (SLA), without any guarantees on performance measures according to a specific cost budget. Running analytics on big data systems require the user not to only reserve the suitable cloud instances over which the big data system will be running, but also setting many system parameters like the degree of parallelism and granularity of scheduling. Chosing values for these parameters, and chosing cloud instances need to meet user objectives regarding latency, throughput and cost measures, which is a complex task if it's done manually by the user. Hence, we need need to transform cloud service models from availabily to user performance objective rises and leads to the problem of multi-objective optimization. Research carried out in the team within the ERC project "Big and Fast Data Analytics" aims to develop a novel optimization framework for providing guarantees on the performance while controlling the cost of data processing in the cloud.

4.2. Computational Journalism

Modern journalism increasingly relies on content management technologies in order to represent, store, and query source data and media objects themselves. Writing news articles increasingly requires consulting several sources, interpreting their findings in context, and crossing links between related sources of information. CEDARresearch results directly applicable to this area provide techniques and tools for rich Web content warehouse management. Within the ANR ContentCheck project, and also as part of our international collaboration with the AIST institute from Japan, we work on one hand, to lay down foundations for computational data journalism and fact checking, and also work to devise concrete algorithms and platforms to help journalists perform their work better and/or faster. This work is carried in collaboration with Le Monde's "Les Décodeurs".

On a related topic, heterogeneous data integration under a virtual graph abstract model is studied within the ICODA Inria project which has started in September 2017. There, we collaborate with Les Décodeurs as well as with Ouest France and Agence France Presse (AFP). The data and knowledge integration framework resulting from this work will support journalists' effort to organize and analyze their knowledge and exploit it in order to produce new content.

CELESTE Project-Team

4. Application Domains

4.1. Neglected tropical diseases

CELESTE collaborates with Anavaj Sakuntabhai and Philippe Dussart (Pasteur Institute) on predicting dengue severity using only low-dimensional clinical data obtained at hospital arrival. Further collaborations are underway in dengue fever and encephalitis with researchers at the Pasteur Institute, including with Jean-David Pommier.

4.2. Pharmacovigilance

In pharmacovigilance, the goal is to detect, as soon as possible, potential associations between certain drugs and adverse effects, which appeared after the authorized marketing of these drugs. Preceding works showed the importance of defining an adapted methodology to deal with the size of the individual data (around 250000 reports, 2000 drugs, 4000 adverse effects) and their sparsity. We will explore several aspects from software point of view to statistical strategies as sub-sampling.

4.3. Electricity load consumption: forecasting and control

CELESTE has a long-term collaboration with EDF R&D about electricity consumption. An important problem is to forecast consumption. We currently work on an approach involving back and forth disaggregation (of the total consumption into the consumptions of well-chosen groups/regions) and aggregation of local estimates. We also work on consumption control by price incentives sent to specific users (volunteers), seeing it as a bandit problem.

4.4. Reliability

Collected product lifetime data is often non-homogeneous, affected by production variability and differing real-world usage. Usually, this variability is not controlled or observed in any way, but needs to be taken into account for reliability analysis. Latent structure models are flexible models commonly used to model unobservable causes of variability.

CELESTE currently collaborates with PSA Group. To dimension its vehicles, the PSA Group uses a reliability design method called Strength-Stress, which takes into consideration both the statistical distribution of part strength and the statistical distribution of customer load (called Stress). In order to minimize the risk of in-service failure, the probability that a severe customer will encounter a weak part must be quantified. Severity quantification is not simple since vehicle use and driver behaviour can be severe for some types of materials and not for others. The aim of the study is then to define a new and richer notion of the severity from the PSA databases resulting either from tests or client usages. This will lead to a more robust and accurate parts dimensioning method.

4.5. Spectroscopic imaging analysis of ancient materials

Ancient materials, encountered in archaeology and paleontology are often complex, heterogeneous and poorly characterized before physico-chemical analysis. A popular technique is to gather as much physico-chemical information as possible, is spectro-microscopy or spectral imaging, where a full spectra, made of more than a thousand samples, is measured for each pixel. The produced data is tensorial with two or three spatial dimensions and one or more spectral dimensions, and requires the combination of an "image" approach with a "curve analysis" approach. Since 2010 CELESTE (previously SELECT) collaborates with Serge Cohen (IPANEMA) on clustering problems, taking spatial constraints into account.

4.6. Forecast of dwell time during train parking at stations

This is a Cifre PhD in collaboration with SNCF.

One of the factors in the punctuality of trains in dense areas (and management crisis in the event of an incident on a line) is the respect of both the travel time between two stations and the parking time in a station. These depend, among other things, on the train, its mission, the schedule, the instantaneous charge, and the configuration of the platform or station. Preliminary internal studies at SNCF have shown that the problem is complex. From a dataset concerning line E of the Transilien in Paris, we will address prediction (machine learning) and modeling (statistics): (1) construct a model of station-hours, station-hours-type of train, by example using co-clustering techniques; (2) study the correlations between the number of passengers (load), up and down flows, and parking times, and possibly other variables to be defined; (3) model the flows or loads (within the same station, or the same train) as a stochastic process; (4) develop a realistic digital simulator of passenger flows and test different scenarios of incidents and resolution, in order to propose effective solutions.

4.7. Fatigue aided-design

This is a Cifre PhD in collaboration with PSA.

The digitalization of design is at the heart of the processes of automotive manufacturers departments, to enable them to reduce costs and development time. This also applies to reliability studies of certain components of the chassis of a vehicle, and the will is to drastically reduce the number of physical tests to tend towards an almost entirely digital design having only one phase of validation. Deterministic models, although developed from detailed design drawings, can predict behaviors different from those observed on the structure during testing. These deviations can be due to the more or less faithful discretization of the geometry, the uncertainties on some parameters of the model (such as the properties of the materials, the boundary conditions), or the random loadings undergone by the structure (Beck and Katafygiotis, 1998). It is important to make available new methods in addition to the classical finite element (FE) deterministic modeling, to enable the exploitation of the accumulated data over the years for all the projects: computation results, measurements and test data.

One of the objectives of this project is to propose a probabilistic modeling of the behavior of a structure starting from a FE model, taking into account the non assignable fluctuations of the model, in order to define a probabilistic criterion of rupture and its margins of confidence. The following three steps are envisaged: (1) Define relevant prior information using business experience feedback (REX) and use a Bayesian estimation to calibrate the parameters. This REX is consequent and will require advanced statistical processing of machine learning, and in particular in clustering to identify similarities or similar patterns among several models. The estimation will use Bayesian non-iterative methods (Celeux and Pamphile, 2019), which are less expensive and less unstable than conventional methods. This will test their effectiveness in this context. (2) Select important parameters (physical or modeling). (3) Define a probabilistic criterion of coaxial fatigue taking into account both the random behavior of the structure and the material (Fouchereau et al., 2014) extending the existing deterministic criteria (Dang-Van, 1993).

COMETE Project-Team

4. Application Domains

4.1. Security and privacy

Participants: Catuscia Palamidessi, Konstantinos Chatzikokolakis, Ehab Elsalamouny, Ali Kassem, Anna Pazii, Marco Romanelli, Natasha Fernandes.

The aim of our research is the specification and verification of protocols used in mobile distributed systems, in particular security protocols. We are especially interested in protocols for *information hiding*.

Information hiding is a generic term which we use here to refer to the problem of preventing the disclosure of information which is supposed to be secret or confidential. The most prominent research areas which are concerned with this problem are those of *secure information flow* and of *privacy*.

Secure information flow refers to the problem of avoiding the so-called *propagation* of secret data due to their processing. It was initially considered as related to software, and the research focussed on type systems and other kind of static analysis to prevent dangerous operations, Nowadays the setting is more general, and a large part of the research effort is directed towards the investigation of probabilistic scenarios and treaths.

Privacy denotes the issue of preventing certain information to become publicly known. It may refer to the protection of *private data* (credit card number, personal info etc.), of the agent's identity (*anonymity*), of the link between information and user (*unlinkability*), of its activities (*unobservability*), and of its *mobility* (*untraceability)*.

The common denominator of this class of problems is that an adversary can try to infer the private information (*secrets*) from the information that he can access (*observables*). The solution is then to obfuscate the link between secrets and observables as much as possible, and often the use randomization, i.e. the introduction of *noise*, can help to achieve this purpose. The system can then be seen as a *noisy channel*, in the information-theoretic sense, between the secrets and the observables.

We intend to explore the rich set of concepts and techniques in the fields of information theory and hypothesis testing to establish the foundations of quantitive information flow and of privacy, and to develop heuristics and methods to improve mechanisms for the protection of secret information. Our approach will be based on the specification of protocols in the probabilistic asynchronous π-calculus, and the application of model-checking to compute the matrices associated to the corresponding channels.

COMMANDS Project-Team

4. Application Domains

4.1. Energy management for hybrid vehicles

In collaboraton with Ifpen and in the framework of A. Le Rhun's thesis, we have developped a methodology for the optimal energy management for hybrid vehicles, based on a statistical analysis of the traffic. See [12], [12], [7].

4.2. Biological cells culture

In collaboration with the Inbio team (Inst. Pasteur and Inria) we started to study the optimization of protein production based on cell culture.

DATASHAPE Project-Team (section vide)

DEDUCTEAM Project-Team

4. Application Domains

4.1. Interoperability

Our main impact applications, for instance to proofs of programs, or to air traffic control, are through our cooperation with other teams.

As a matter of fact, we view our work on interoperability and on the design of a formal proof encyclopedia as a service to the formal proof community.

DEFI Project-Team

4. Application Domains

4.1. Radar and GPR applications

Conventional radar imaging techniques (ISAR, GPR, etc.) use backscattering data to image targets. The commonly used inversion algorithms are mainly based on the use of weak scattering approximations such as the Born or Kirchhoff approximation leading to very simple linear models, but at the expense of ignoring multiple scattering and polarization effects. The success of such an approach is evident in the wide use of synthetic aperture radar techniques.

However, the use of backscattering data makes 3-D imaging a very challenging problem (it is not even well understood theoretically) and as pointed out by Brett Borden in the context of airborne radar: “In recent years it has become quite apparent that the problems associated with radar target identification efforts will not vanish with the development of more sensitive radar receivers or increased signal-to-noise levels. In addition it has (slowly) been realized that greater amounts of data - or even additional “kinds” of radar data, such as added polarization or greatly extended bandwidth - will all suffer from the same basic limitations affiliated with incorrect model assumptions. Moreover, in the face of these problems it is important to ask how (and if) the complications associated with radar based automatic target recognition can be surmounted.” This comment also applies to the more complex GPR problem.

Our research themes will incorporate the development, analysis and testing of several novel methods, such as sampling methods, level set methods or topological gradient methods, for ground penetrating radar application (imaging of urban infrastructures, landmines detection, underground waste deposits monitoring,) using multistatic data.

4.2. Biomedical imaging

Among emerging medical imaging techniques we are particularly interested in those using low to moderate frequency regimes. These include Microwave Tomography, Electrical Impedance Tomography and also the closely related Optical Tomography technique. They all have the advantage of being potentially safe and relatively cheap modalities and can also be used in complementarity with well established techniques such as X-ray computed tomography or Magnetic Resonance Imaging.

With these modalities tissues are differentiated and, consequentially can be imaged, based on differences in dielectric properties (some recent studies have proved that dielectric properties of biological tissues can be a strong indicator of the tissues functional and pathological conditions, for instance, tissue blood content, ischemia, infarction, hypoxia, malignancies, edema and others). The main challenge for these functionalities is to built a 3-D imaging algorithm capable of treating multi-static measurements to provide real-time images with highest (reasonably) expected resolutions and in a sufficiently robust way.

Another important biomedical application is brain imaging. We are for instance interested in the use of EEG and MEG techniques as complementary tools to MRI. They are applied for instance to localize epileptic centers or active zones (functional imaging). Here the problem is different and consists into performing passive imaging: the epileptic centers act as electrical sources and imaging is performed from measurements of induced currents. Incorporating the structure of the skull is primordial in improving the resolution of the imaging procedure. Doing this in a reasonably quick manner is still an active research area, and the use of asymptotic models would offer a promising solution to fix this issue.

4.3. Non destructive testing and parameter identification

One challenging problem in this vast area is the identification and imaging of defaults in anisotropic media. For instance this problem is of great importance in aeronautic constructions due to the growing use of composite materials. It also arises in applications linked with the evaluation of wood quality, like locating knots in timber in order to optimize timber-cutting in sawmills, or evaluating wood integrity before cutting trees. The anisotropy of the propagative media renders the analysis of diffracted waves more complex since one cannot only relies on the use of backscattered waves. Another difficulty comes from the fact that the micro-structure of the media is generally not well known a priori.

Our concern will be focused on the determination of qualitative information on the size of defaults and their physical properties rather than a complete imaging which for anisotropic media is in general impossible. For instance, in the case of homogeneous background, one can link the size of the inclusion and the index of refraction to the first eigenvalue of so-called interior transmission problem. These eigenvalues can be determined form the measured data and a rough localization of the default. Our goal is to extend this kind of idea to the cases where both the propagative media and the inclusion are anisotropic. The generalization to the case of cracks or screens has also to be investigated.

In the context of nuclear waste management many studies are conducted on the possibility of storing waste in a deep geological clay layer. To assess the reliability of such a storage without leakage it is necessary to have a precise knowledge of the porous media parameters (porosity, tortuosity, permeability, etc.). The large range of space and time scales involved in this process requires a high degree of precision as well as tight bounds on the uncertainties. Many physical experiments are conducted in situ which are designed for providing data for parameters identification. For example, the determination of the damaged zone (caused by excavation) around the repository area is of paramount importance since microcracks yield drastic changes in the permeability. Level set methods are a tool of choice for characterizing this damaged zone.

4.4. Diffusion MRI

In biological tissues, water is abundant and magnetic resonance imaging (MRI) exploits the magnetic property of the nucleus of the water proton. The imaging contrast (the variations in the grayscale in an image) in standard MRI can be from either proton density, T1 (spin-lattice) relaxation, or T2 (spin-spin) relaxation and the contrast in the image gives some information on the physiological properties of the biological tissue at different physical locations of the sample. The resolution of MRI is on the order of millimeters: the greyscale value shown in the imaging pixel represents the volume-averaged value taken over all the physical locations contained that pixel.

In diffusion MRI, the image contrast comes from a measure of the average distance the water molecules have moved (diffused) during a certain amount of time. The Pulsed Gradient Spin Echo (PGSE) sequence is a commonly used sequence of applied magnetic fields to encode the diffusion of water protons. The term 'pulsed' means that the magnetic fields are short in duration, an the term gradient means that the magnetic fields vary linearly in space along a particular direction. First, the water protons in tissue are labelled with nuclear spin at a precession frequency that varies as a function of the physical positions of the water molecules via the application of a pulsed (short in duration, lasting on the order of ten milliseconds) magnetic field. Because the precessing frequencies of the water molecules vary, the signal, which measures the aggregate phase of the water molecules, will be reduced due to phase cancellations. Some time (usually tens of milliseconds) after the first pulsed magnetic field, another pulsed magnetic field is applied to reverse the spins of the water molecules. The time between the applications of two pulsed magnetic fields is called the 'diffusion time'. If the water molecules have not moved during the diffusion time, the phase dispersion will be reversed, hence the signal loss will also be reversed, the signal is called refocused. However, if the molecules have moved during the diffusion time, the refocusing will be incomplete and the signal detected by the MRI scanner if weaker than if the water molecules have not moved. This lack of complete refocusing is called the signal attenuation and is the basis of the image contrast in DMRI. the pixels showning more signal attenuation is associated with further water displacement during the diffusion time, which may be linked to physiological factors, such as higher cell membrane permeability, larger cell sizes, higher extra-cellular volume fraction.

We model the nuclear magnetization of water protons in a sample due to diffusion-encoding magnetic fields by a multiple compartment Bloch-Torrey partial differential equation, which is a diffusive-type time-dependent PDE. The DMRI signal is the integral of the solution of the Bloch-Torrey PDE. In a homogeneous medium, the intrinsic diffusion coeffcient D will appear as the slope of the semi-log plot of the signal (in approporiate units). However, because during typical scanning times, 50-100ms, water molecules have had time to travel a diffusion distance which is long compared to the average size of the cells, the slope of the semi-log plot of the signal is in fact a measure of an 'effective' diffusion coefficient. In DMRI applications, this measured quantity is called the 'apparent diffusion coefficient' (ADC) and provides the most commonly used form the image contrast for DMRI. This ADC is closely related to the effective diffusion coefficient obtainable from mathematical homogenization theory.

4.5. Fluid flow applications

Specific actions are devoted to the problem of atmospheric reentry simulations. We focus on several aspects : i) on the development of innovative algorithms improving the prediction of hypersonic flows and including system uncertainties, ii) on the application of these methods to the atmospheric reentry of space vehicles for the control and the optimization of the trajectory, iii) on the debris reentry, which is of fundamental importance for NASA, CNES and ESA. Several works are already initiated with funding from CNES, Thales, and ASL. An ongoing activity concerns the design of the Thermal Protection System (TPS) that shields the spacecraft from aerothermal heating, generated by friction at the surface of the vehicle. The TPS is usually composed of different classes of materials, depending on the mission and the planned trajectory. One major issue is to model accurately the material response to ensure a safe design. High-fidelity material modeling for ablative materials has been developed by NASA, but a lot of work is still needed concerning the assessment of physical and modeling uncertainties during the design process. Our objective is to set up a predictive numerical tool to reliably estimate the response of ablative materials for different aerothermal conditions.

An important effort is dedicated to the simulation of fluids featuring complex thermodynamic behavior, in the context of two distinct projects: the VIPER project, funded by Aquitaine Region, and a project with CWI (Scientific Computing Group). Dense gases (DGs) are defined as single-phase vapors operating at temperatures and pressures conditions close to the saturation curve. The interest in studying complex dynamics of compressible dense gas flows comes from the potential technological advantages of using these fluids in energy conversion cycles, such as in Organic Rankine Cycles (ORCs) which used dense gases as energy converters for biomass fuels and low-grade heat from geothermal or industrial waste heat sources. Since these fluids feature large uncertainties in their estimated thermodynamic properties (critical properties, acentric factor, etc.), a meaningful numerical prediction of the performance must necessarily take into account these uncertainties. Other sources of uncertainties include, but are not limited to, the inlet boundary conditions which are often unknown in dense gases applications. Moreover, a robust optimization must also include the more generic uncertainty introduced by the machining tolerance in the construction of the turbine blades.

DISCO Project-Team

4. Application Domains

4.1. Analysis and Control of life sciences systems

The team is involved in life sciences applications. The two main lines are the analysis of bioreactors models (microorganisms; bacteria, microalgae, yeast, etc..) and the modeling of cell dynamics in Acute Myeloblastic Leukemias (AML) in collaboration with St Antoine Hospital in Paris. A recent subject is the modelling of epidemics for tropical diseases.

4.2. Energy Management

The team is interested in Energy management and considers control problems in energy networks.

EX-SITU Project-Team

4. Application Domains

4.1. Creative industries

We work closely with creative professionals in the arts and in design, including music composers, musicians, and sound engineers; painters and illustrators; dancers and choreographers; theater groups; game designers; graphic and industrial designers; and architects.

4.2. Scientific research

We work with creative professionals in the sciences and engineering, including neuroscientists and doctors; programmers and statisticians; chemists and astrophysicists; and researchers in fluid mechanics.

GAMMA Project-Team (section vide)

GRACE Project-Team

4. Application Domains

4.1. Application Domain: cybersecurity

Participants: Guénaël Renault, Benjamin Smith, François Morain, Alexis Challande, Simon Montoya, Maxime Anvari.

We are interesting in developing some interactions between cryptography and cybersecurity. In particular, we develop some researches in embedded security (side channels and fault attack), software security (finding vulnerability efficiently) and privacy (security of TOR).

4.2. Application Domain: blockchains

Participants: Daniel Augot, Sarah Bordage, Matthieu Rambaud, Lucas Benmouffok, Hanna-Mae Bisserier.

The huge interest shown by companies for blockchains and cryptocurrencies have attracted the attention of mainstream industries for new, advanced uses of cryptographic, beyond confidentiality, integrity and authentication. In particular, zero-knowledge proofs, computation with encrypted data, etc, are now revealing their potential in the blockchain context. Team Grace is investigating two topics in these areas: secure multiparty computation and so-called “STARKS”.

Secure multiparty computation enables several participants to compute a common function of data they each secretly own, without each participant revealing his data to the other participants. This area has seen great progress in recent years, and the cryptogaphic protocols are now mature enough for practical use. This topic is new to project-team Grace, and we will investigate it in the context of blockchains, through the lenses of use for private “smart contracts”. A PhD student has been hired since October, funded by IRT System-X.

Daniel Augot is involved in blockchains from the point of view of cryptography for better blockchains, mainly for improving privacy. A PhD student has been enrolled at IRT System-X, to study pratical use cases of Secure Multiparty Computaiton.

Also Daniel Augot, together with Julian Prat (economist, ENSAE), is leading a Polytechnique teaching and research “chair”, funded by CapGemini, for blockchains in the industry, B2B platforms, supply chains, etc.

4.3. Cloud storage

The team is concerned with several aspect of reliability and security of cloud storage, obtained mainly with tools from coding theory. On the privacy side, we build protocols for so-called Private Information Retrieval which enable a user to query a remote database for an entry, while not revealing his query. For instance, a user could query a service for stock quotes without revealing with company he is interested in. On the availability side, we study protocols for proofs of retrievability, which enable a user to get assurance that a huge file is still available on a remote server, with a low bandwith protocol which does not require to download the whole file. For instance, in a peer-to-peer distributed storage system, where nodes could be rewarded for storing data, they can be audited with proof of retrievability protocols to make sure they indeed hold the data.

We investigate these problems with algebraic coding theory, mainly codes with locality (locally decodable codes, locally recoverable codes, and so on).

An M2 intern, Maxime Roméas, Bordeaux university, studied the constructive cryptography model, "A study of the Constructive Cryptography model of Maurer et. al." 5 months, followed by a PhD grant from IP Paris/Ecole Polytechnique for a 3-year doctorate (Oct 2019-Sept 2022): "The Constructive Cryptography paradigm applied to Interactive Cryptographic Proofs".

The Constructive Cryptography framework redefines basic cryptographic primitives and protocols starting from discrete systems of three types (resources, converters, and distinguishers). This not only permits to construct them effectively, but also lighten and sharpen their security proofs. One strength of this model is its composability. The purpose of the PhD is to apply this model to rephrase existing interactive cryptographic proofs so as to assert their genuine security, as well as to design new proofs. The main concern here is security and privacy in Distributed Storage settings.

ILDA Project-Team

4. Application Domains

4.1. Mission-critical systems

Mission-critical contexts of use include emergency response & management, and critical infrastructure operations, such as public transportation systems, communications and power distribution networks, or the operations of large scientific instruments such as particle accelerators and astronomical observatories. Central to these contexts of work is the notion of situation awareness [25], i.e., how workers perceive and understand elements of the environment with respect to time and space, such as maps and geolocated data feeds from the field, and how they form mental models that help them predict future states of those elements. One of the main challenges is how to best assist subject-matter experts in constructing correct mental models and making informed decisions, often under time pressure. This can be achieved by providing them with, or helping them efficiently identify and correlate, relevant and timely information extracted from large amounts of raw data, taking into account the often cooperative nature of their work and the need for task coordination. With this application area, our goal is to investigate novel ways of interacting with computing systems that improve collaborative data analysis capabilities and decision support assistance in a mission-critical, often time-constrained, work context.

Relevant publications by team members this year: [13], [19], [12].

4.2. Exploratory analysis of scientific data

Many scientific disciplines are increasingly data-driven, including astronomy, molecular biology, particle physics, or neuroanatomy. While making the right decision under time pressure is often less of critical issue when analyzing scientific data, at least not on the same temporal scale as truly time-critical systems, scientists are still faced with large-to-huge amounts of data. No matter their origin (experiments, remote observations, large-scale simulations), these data are difficult to understand and analyze in depth because of their sheer size and complexity. Challenges include how to help scientists freely-yet-efficiently explore their data, keep a trace of the multiple data processing paths they considered to verify their hypotheses and make it easy to backtrack, and how to relate observations made on different parts of the data and insights gained at different moments during the exploration process. With this application area, our goal is to investigate how data-centric interactive systems can improve collaborative scientific data exploration, where users' goals are more open-ended, and where roles, collaboration and coordination patterns [48] differ from those observed in mission-critical contexts of work.

Relevant publications by team members last year: [16], [24], [14], [18].

LIFEWARE Project-Team

4. Application Domains

4.1. Preamble

Our collaborative work on biological applications is expected to serve as a basis for groundbreaking advances in cell functioning understanding, cell monitoring and control, and novel therapy design and optimization. Our collaborations with biologists are focused on **concrete biological questions**, and on the building of predictive models of biological systems to answer them. Furthermore, one important application of our research is the development of a **modeling software** for computational systems biology.

4.2. Modeling software for systems biology and synthetic biology

Since 2002, we develop an open-source software environment for modeling and analyzing biochemical reaction systems. This software, called the Biochemical Abstract Machine (BIOCHAM), is compatible with SBML for importing and exporting models from repositories such as BioModels. It can perform a variety of static analyses, specify behaviors in Boolean or quantitative temporal logics, search parameter values satisfying temporal constraints, and make various simulations. While the primary reason of this development effort is to be able to **implement our ideas and experiment them quickly on a large scale**, BIOCHAM is used by other groups either for building models, for comparing techniques, or for teaching (see statistics in software section). BIOCHAM-WEB is a web application which makes it possible to use BIOCHAM without any installation. We plan to continue developing BIOCHAM for these different purposes and improve the software quality.

4.3. Coupled models of the cell cycle and the circadian clock

Recent advances in cancer chronotherapy techniques support the evidence that there exist important links between the cell cycle and the circadian clock genes. One purpose for modeling these links is to better understand how to efficiently target malignant cells depending on the phase of the day and patient characterictics. These questions are at the heart of our collaboration with Franck Delaunay (CNRS Nice) and Francis Lévi (Univ. Warwick, GB, formerly INSERM Hopital Paul Brousse, Villejuif) and of our participation in the ANR HYCLOCK project and in the submitted EU H2020 C2SyM proposal, following the former EU EraNet Sysbio C5SYS and FP6 TEMPO projects. In the past, we developed a coupled model of the Cell Cycle, Circadian Clock, DNA Repair System, Irinotecan Metabolism and Exposure Control under Temporal Logic Constraints [0]. We now focus on the bidirectional coupling between the cell cycle and the circadian clock and expect to gain fundamental insights on this complex coupling from computational modeling and single-cell experiments.

4.4. Biosensor design and implementation in non-living protocells

In collaboration with Franck Molina (CNRS, Sys2Diag, Montpellier) and Jie-Hong Jiang (NTU, Taiwan) we ambition to apply our techniques to the design and implementation of high-level functions in non-living vesicles for medical applications, such as biosensors for medical diagnosis [0]. Our approach is based on purely protein computation and on our ability to compile controllers and programs in biochemical reactions. The realization will be prototyped using a microfluidic device at CNRS Sys2Diag which will allow us to precisely control the size of the vesicles and the concentrations of the injected proteins. It is worth noting that the choice of non-living chassis, in contrast to living cells in synthetic biology, is particularly appealing for security considerations and compliance to forthcoming EU regulation.

[0] Elisabetta De Maria, François Fages, Aurélien Rizk, Sylvain Soliman. Design, Optimization, and Predictions of a Coupled Model of the Cell Cycle, Circadian Clock, DNA Repair System, Irinotecan Metabolism and Exposure Control under Temporal Logic Constraints. Theoretical Computer Science, 412(21):2108 2127, 2011.

[0] Alexis Courbet, Patrick Amar, François Fages, Eric Renard, Franck Molina. Computer-aided biochemical programming of synthetic microreactors as diagnostic devices. Molecular Systems Biology, 14(4), 2018.

4.5. Functional characterization of the resistance of bacterial populations to antimicrobial treatments

Antibiotic resistance is becoming a problem of central importance at a global level. Two mechanisms are at the origin of non-susceptibility to antimicrobial treatments. The first one comes from adaptation of bacterial cells to antibacterial treatments, notably through the modification of efflux pumps or the expression of enzymes that degrade the antibiotics. Cells are individually resistant. The second one, typically found in resistances to β-lactams, a broad class of antibiotics, originates from the release in the environment of the antibiotic degrading enzymes by the dead cells. This leads to population effects by which cells become collectively resilient.

The functional characterization of these different effects is important for the best use of antibiotics (antibiotic stewardship). In collaboration with Lingchong You (Duke University) and with Philippe Glaser (Institut Pasteur), we develop experimental platforms, models, and optimal model calibration methods that gives precise estimations of individual resistance and collective resilience of bacterial populations to antibiotic treatments.

M3DISIM Project-Team (section vide)

MEXICO Project-Team

4. Application Domains

4.1. Telecommunications

Participants: Stefan Haar, Serge Haddad.

MExICo's research is motivated by problems of system management in several domains, such as:

- In the domain of service oriented computing, it is often necessary to insert some Web service into an existing orchestrated business process, e.g. to replace another component after failures. This requires to ensure, often actively, conformance to the interaction protocol. One therefore needs to synthesize adaptators for every component in order to steer its interaction with the surrounding processes.
- Still in the domain of telecommunications, the supervision of a network tends to move from out-of-band technology, with a fixed dedicated supervision infrastructure, to in-band supervision where the supervision process uses the supervised network itself. This new setting requires to revisit the existing supervision techniques using control and diagnosis tools.

Currently, we have no active cooperation on these subjects.

4.2. Biological Regulation Networks

Participants: Thomas Chatain, Matthias Fuegger, Stefan Haar, Serge Haddad, Juraj Kolcak, Hugues Mandon, Stefan Schwoon.

We have begun in 2014 to examine concurrency issues in systems biology, and are currently enlarging the scope of our research's applications in this direction. To see the context, note that in recent years, a considerable shift of biologists' interest can be observed, from the mapping of static genotypes to gene expression, i.e. the processes in which genetic information is used in producing functional products. These processes are far from being uniquely determined by the gene itself, or even jointly with static properties of the environment; rather, regulation occurs throughout the expression processes, with specific mechanisms increasing or decreasing the production of various products, and thus modulating the outcome. These regulations are central in understanding cell fate (how does the cell differenciate ? Do mutations occur ? etc), and progress there hinges on our capacity to analyse, predict, monitor and control complex and variegated processes. We have applied Petri net unfolding techniques for the efficient computation of attractors in a regulatory network; that is, to identify strongly connected reachability components that correspond to stable evolutions, e.g. of a cell that differentiates into a specific functionality (or mutation). This constitutes the starting point of a broader research with Petri net unfolding techniques in regulation. In fact, the use of ordinary Petri nets for capturing regulatory network (RN) dynamics overcomes the limitations of traditional RN models : those impose e.g. Monotonicity properties in the influence that one factor had upon another, i.e. always increasing or always decreasing, and were thus unable to cover all actual behaviours. Rather, we follow the more refined model of boolean networks of automata, where the local states of the different factors jointly detemine which state transitions are possible. For these connectors, ordinary PNs constitute a first approximation, improving greatly over the literature but leaving room for improvement in terms of introducing more refined logical connectors. Future work thus involves transcending this class of PN models. Via unfoldings, one has access – provided efficient techniques are available – to all behaviours of the model, rather than over-or under-approximations as previously. This opens the way to efficiently searching in particular for determinants of the cell fate : which attractors are reachable from a given stage, and what are the factors that decide in favor of one or the other attractor, etc. Our current research focusses cellular reprogramming on the one hand, and distributed algorithms in wild or synthetic biological systems on the other. The latter is a distributed algorithms' view on microbiological systems, both with the goal to model and analyze existing microbiological systems as distributed systems, and to design and implement distributed algorithms in synthesized microbiological systems. Envisioned major long-term goals are drug production and medical treatment via synthesized bacterial colonies. We are approaching our goal of a distributed algorithm's view of microbiological systems from several directions: (i) Timing plays a crucial role in microbiological systems. Similar to modern VLSI circuits, dominating loading effects and noise render classical delay models unfeasible. In previous work we showed limitations of current delay models and presented a class of new delay models, so called involution channels. In [26] we showed that involution channels are still in accordance with Newtonian physics, even in presence of noise. (ii) In [7] we analyzed metastability in circuits by a three-valued Kleene logic, presented a general technique to build circuits that can tolerate a certain degree of metastability at its inputs, and showed the presence of a computational hierarchy. Again, we expect metastability to play a crucial role in microbiological systems, as similar to modern VLSI circuits, loading effects are pronounced. (iii) We studied agreement problems in highly dynamic networks without stability guarantees [28], [27]. We expect such networks to occur in bacterial cultures where bacteria communicate by producing and sensing small signal molecules like AHL. Both works also have theoretically relevant implications: The work in [27] presents the first approximate agreement protocol in a multidimensional space with time complexity independent of the dimension, working also in presence of Byzantine faults. In [28] we proved a tight lower bound on convergence rates and time complexity of asymptotic and approximate agreement in dynamic and classical static fault models. (iv) We are currently working with Manish Kushwaha (INRA), and Thomas Nowak (LRI) on biological infection models for E. coli colonies and M13 phages.

4.3. Metabolic Networks

Participant: Philippe Dague.

Analysis of metabolic networks in presence of biological (thermodynamical, kinetic, gene regulatory) constraints has been studied achieving a complete mathematical characterization of the solutions space at steady state (generalization of the elementary flux modes) and investigating related computing methods.

4.4. Transportation Systems

Participants: Thomas Chatain, Stefan Haar, Serge Haddad, Stefan Schwoon.

- **Autonomous Vehicles.** The validation of safety properties is a crucial concern for the design of computer guided systems, in particular for automated transport systems. Our approach consists in analyzing the interactions of a randomized environment (roads, cross-sections, etc.) with a vehicle controller.
- **Multimodal Transport Networks.** We are interested in predicting and harnessing the propagation of perturbations across different transportation modes.

OPIS Project-Team

4. Application Domains

4.1. Sparse signal processing in chemistry

Participants: Marc Castella, Emilie Chouzenoux, Arthur Marmin, Jean-Christophe Pesquet (Collaboration: Laurent Duval, IFPEN, Rueil Malmaison)

Mass Spectrometry (MS) is a powerful tool used for robust, accurate, and sensitive detection and quantification of molecules of interest. Thanks to its sensibility and selectivity, MS is widely used in proteomics such anti-doping, metabolomics, medicine or structural biology. In particular, it has applications in clinical research, personalized medicine, diagnosis process and tumours profiling and pharmaceutical quality control. In an MS experiment, the raw signal arising from the molecule ionization in an ion beam is measured as a function of time via Fourier Transform-based measures such as Ion Cyclotron Resonance (FT-ICR) and Orbitrap. A spectral analysis step is then performed to improve the quality of data. The goal is then to determine from this observed pattern distribution the most probable chemical composition of the sample, through the determination of the monoisotopic mass, charge state and abundance of each present molecule. This amounts to solve a large scale signal estimation problem under specific sparsity constraints [35], [55]. Collaboration with Dr. L. Duval, Research Engineer at IFP Energies Nouvelles, France is on-going in this applicative context.

4.2. Image restoration for two-photon microscopy

Participants: Emilie Chouzenoux, Jean-Christophe Pesquet, Mathieu Chalvidal (Collaboration: Claire Lefort, XLIM, CNRS, Limoges)

Through an ongoing collaboration with physicists from XLIM laboratory (CNRS, Limoges, France), we propose advanced mathematical and computational solutions for multiphoton microscopy (MPM) 3D image restoration. This modality enjoys many benefits such as a decrease in phototoxicity and increase in penetration depth. However, blur and noise issues can be more severe than with standard confocal images. Our objective is to drastically improve the quality of the generated images and their resolution by improving the characterization of the PSF of the system [12] and compensating its effect. We consider the application of the improved MPM imaging tool to the microscopic analysis of muscle ultrastructure and composition, with the aim to help diagnosing muscle disorders including rare and orphan muscle pathologies.

4.3. Representation Learning for Biological Networks

Participants: Fragkiskos Malliaros, Abdulkadir Çelikkanat (Collaboration: Duong Nguyen, UC San Diego)

Networks (or graphs) are ubiquitous in the domain of biology, as many biological systems can naturally be mapped to graph structures. Characteristic examples include protein-protein interaction and gene regulatory networks. To this extend, machine learning on graphs is an important task with many practical applications in network biology. For example, in the case on protein-protein interaction networks, predicting the function of a protein is a key task that assigns biochemical roles to proteins. The main challenge here is to find appropriate representations of the graph structure, in order to be easily exploited by machine learning models. The traditional approach to the problem was relying on the extraction of “hand-crafted" discriminating features that encode information about the graph, based on user-defined heuristics. Nevertheless, this approach has demonstrated severe limitations, as the learning process heavily depends on the manually extracted features. To this end, feature (or representation) learning techniques can be used to automatically learn to encode the graph structure into low-dimensional feature vectors – which can later be used in learning tasks. Our goal here is to develop a systematic framework for large-scale representation learning on biological graphs. Our approach takes advantage of the clustering structure of these networks, to further enhance the ability of the learned features to capture intrinsic structural properties.

4.4. Breast tomosynthesis

Participants: Emilie Chouzenoux, Jean-Christophe Pesquet, Maissa Sghaier (collaboration G. Palma, GE Healthcare)
Breast cancer is the most frequently diagnosed cancer for women. Mammography is the most used imagery tool for detecting and diagnosing this type of cancer. Since it consists of a 2D projection method, this technique is sensitive to geometrical limitations such as the superimposition of tissues which may reduce the visibility of lesions or make even appear false structures which are interpreted by radiologists as suspicious signs. Digital breast tomosynthesis allows these limitations to be circumvented. This technique is grounded on the acquisition of a set of projections with a limited angle view. Then, a 3D estimation of the sensed object is performed from this set of projections, so reducing the overlap of structures and improving the visibility and detectability of lesions possibly present in the breast. The objective of our work is to develop a high quality reconstruction methodology where the full pipeline of data processing is modeled [50].

4.5. Inference of gene regulatory networks

Participants: Surabhi Jagtap, Fragkiskos Malliaros, Jean-Christophe Pesquet (collaboration A. Pirayre and L. Duval, IFPEN)
The discovery of novel gene regulatory processes improves the understanding of cell phenotypic responses to external stimuli for many biological applications, such as medicine, environment or biotechnologies. To this purpose, transcriptomic data are generated and analyzed from DNA microarrays or more recently RNAseq experiments. They consist in genetic expression level sequences obtained for all genes of a studied organism placed in dierent living conditions. From these data, gene regulation mechanisms can be recovered by revealing topological links encoded in graphs. In regulatory graphs, nodes correspond to genes. A link between two nodes is identified if a regulation relationship exists between the two corresponding genes. In our work, we propose to address this network inference problem with recently developed techniques pertaining to graph optimization. Given all the pairwise gene regulation information available, we propose to determine the presence of edges in the considered GRN by adopting an energy optimization formulation integrating additional constraints. Either biological (information about gene interactions) or structural (information about node connectivity) a priori are considered to restrict the space of possible solutions. Different priors lead to different properties of the global cost function, for which various optimization strategies, either discrete and continuous, can be applied.

4.6. Imaging biomarkers and characterization for chronic lung diseases

Participants: Guillaume Chassagnon, Maria Vakalopoulou (in collaboration with Marie-Pierre Revel and Nikos Paragios: AP-HP - Hopital Cochin Broca Hotel Dieu; Therapanacea)
Diagnosis and staging of chronic lung diseases is a major challenge for both patient care and approval of new treatments. Among imaging techniques, computed tomography (CT) is the gold standard for in vivo morphological assessment of lung parenchyma currently offering the highest spatial resolution in chronic lung diseases. Although CT is widely used its optimal use in clinical practice and as an endpoint in clinical trials remains controversial. Our goal is to develop quantitative imaging biomarkers that allow (i)severity assessment (based on the correlation to functional and clinical data) and (ii) monitoring the disease progression. In the current analysis we focus on scleroderma and cystic fibrosis as models for restrictive and obstructive lung disease, respectively. Two different approaches are investigated: disease assessment by deep convolutional neural networks and assessment of the regional lung elasticity through deformable registration. This work is in collaboration with the Department of Radiology, Cochin Hospital, Paris.

4.7. Imaging radiomics and genes to assess immunotherapy

Participants: Samy Ammari, Enzo Batistella, Emilie Chouzenoux, Théo Estienne, Marvin Lerousseau, Hugues Talbot, Roger Sun, Maria Vakalopoulou (in collaboration with Corinne Balleyguier, Caroline Caramella, Éric Deutsch, Nathalie Lassau, Institut de Cancérologie Gustave Roussy, Nikos Paragios, Therapanacea)

Because responses of cancer patients to immunotherapy can vary considerably, innovative predictors of response to treatment are urgently needed to improve patients outcomes.

We have aimed to develop and independently validate a radiomics-based biomarkers of tumour-infiltrating CD8 cells in patients included in phase 1 trials of anti-programmed cell death protein (PD)-1 or anti-programmed cell death ligand 1 (PD-L1) mono-therapy. We also aimed to evaluate the association between the biomarker, tumour immune phenotype and clinical outcomes of these patients.

Concurrently, we have evaluated various ways of estimating patient response to treatment based on well-established radiomics such as estimated tumour count and volumes. Among published metrics, we have select those that shown good predictive power and proposed a new one, which is particularly effective for patient with a poor response [63].

Furthermore, we have developed and validated a novel imaging-based decision-making algorithm for use by the clinician that helps differentiate pituitary metastasis from autoimmune hypophysitis in patients undergoing immune checkpoint blockade therapy [21].

These works are in collaboration with the Institut de Cance´rologie Gustave Roussy Paris.

4.8. Development of a heart ventricle vessel generation model for perfusion analysis

Participant: Hugues Talbot (collaboration with L. Najman ESIEE Paris, I. Vignon-Clementel, REO Team leader, Inria, Charles Taylor, Heartflow Inc.)
Cardio-vascular diseases are the leading cause of mortality in the world. Understanding these diseases is a current, challenging and essential research project. The leading cause of heart malfunction are stenoses causing ischemia in the coronary vessels. Current CT and MRI technology can assess coronary diseases but are typically invasive, requiring catheterization and relatively toxic contrast agents injection. In collaboration with the REO team headed by Irène Vignon-Clementel, and Heartflow, a US based company, we have in the past worked to use image-based exams only, limiting the use of contrast agents and in many cases eliminating catheterisation. Heartflow is current the market leader in non-invasive coronary exams.

Unfortunately, current imaging technology is unable to assess the full length of coronary vessels. CT is limited to a resolution of about 1mm, whereas coronary vessels can be much smaller, down to about 10 micrometers in diameter. Blood perfusion throughout the heart muscle can provide insight regarding coronary health in areas that CT or MRI cannot assess. Perfusion imaging with PET or a Gamma camera, the current gold standard, is an invasive technology requiring the use of radioactive tracers.

We have investigated patient-specific vessel generation models together with porous model simulations in order to propose a forward model of perfusion imaging, based on the known patient data, computer flow dynamic simulations as well as experimental data consistent with known vessel and heart muscle physiology. The objective of this work is to both provide a useful, complex forward model of perfusion image generation, and to solve the inverse problem of locating and assessing coronary diseases given a perfusion exam, even though the affected vessels may be too small to be imaged directly.

In 2019, we have produced a functional myocardial perfusion model consisting of the CT-derived segmented coronary vessels, a simulated vessel tree consisting of several thousands of terminal vessels, filling the myocardium in a patient-specific way, consistent with physiology data, physics-based and empirically-observed vessel growth rules, and a porous medium. We have produced a CFD code capable of simulating blood flow in all three coupled compartments, which allows us to simulate perfusion realistically.

PARIETAL Project-Team

4. Application Domains

4.1. Cognitive neuroscience

4.1.1. Macroscopic Functional cartography with functional Magnetic Resonance Imaging (fMRI)

The brain as a highly structured organ, with both functional specialization and a complex network organization. While most of the knowledge historically comes from lesion studies and animal electophysiological recordings, the development of non-invasive imaging modalities, such as fMRI, has made it possible to study routinely high-level cognition in humans since the early 90's. This has opened major questions on the interplay between mind and brain , such as: How is the function of cortical territories constrained by anatomy (connectivity) ? How to assess the specificity of brain regions ? How can one characterize reliably inter-subject differences ?

4.1.2. Analysis of brain Connectivity

Functional connectivity is defined as the interaction structure that underlies brain function. Since the beginning of fMRI, it has been observed that remote regions sustain high correlation in their spontaneous activity, i.e. in the absence of a driving task. This means that the signals observed during resting-state define a signature of the connectivity of brain regions. The main interest of resting-state fMRI is that it provides easy-to-acquire functional markers that have recently been proved to be very powerful for population studies.

4.1.3. Modeling of brain processes (MEG)

While fMRI has been very useful in defining the function of regions at the mm scale, Magneto-encephalography (MEG) provides the other piece of the puzzle, namely temporal dynamics of brain activity, at the ms scale. MEG is also non-invasive. It makes it possible to keep track of precise schedule of mental operations and their interactions. It also opens the way toward a study of the rhythmic activity of the brain. On the other hand, the localization of brain activity with MEG entails the solution of a hard inverse problem.

4.1.4. Current challenges in human neuroimaging (acquisition+analysis)

Human neuroimaging targets two major goals: *i)* the study of neural responses involved in sensory, motor or cognitive functions, in relation to models from cognitive psychology, i.e. the identification of neurophysiological and neuroanatomical correlates of cognition; *ii)* the identification of markers in brain structure and function of neurological or psychiatric diseases. Both goals have to deal with a tension between

- the search for higher spatial [0] resolution to increase **spatial specificity** of brain signals, and clarify the nature (function and structure) of brain regions. This motivates efforts for high-field imaging and more efficient acquisitions, such as compressed sensing schemes, as well as better source localization methods from M/EEG data.
- the importance of inferring brain features with **population-level** validity, hence, contaminated with high variability within observed cohorts, which blurs the information at the population level and ultimately limits the spatial resolution of these observations.

[0] and to some extent, temporal, but for the sake of simplicity we focus here on spatial aspects.

Importantly, the signal-to-noise ratio (SNR) of the data remains limited due to both resolution improvements [0] and between-subject variability. Altogether, these factors have led to realize that results of neuroimaging studies were **statistically weak**, i.e. plagued with low power and leading to unreliable inference [72], and particularly so due to the typically number of subjects included in brain imaging studies (20 to 30, this number tends to increase [73]): this is at the core of the *neuroimaging reproducibility crisis*. This crisis is deeply related to a second issue, namely that only few neuroimaging datasets are publicly available, making it impossible to re-assess a posteriori the information conveyed by the data. Fortunately, the situation improves, lead by projects such as NeuroVault or OpenfMRI. A framework for integrating such datasets is however still missing.

[0] The SNR of the acquired signal is proportional to the voxel size, hence an improvement by a factor of 2 in image resolution along each dimension is payed by a factor of 8 in terms of SNR.

PARSIFAL Project-Team

4. Application Domains

4.1. Automated Theorem Proving

The Parsifal team studies the structure of mathematical proofs, in ways that often makes them more amenable to automated theorem proving – automatically searching the space of proof candidates for a statement to find an actual proof – or a counter-example.

(Due to fundamental computability limits, fully-automatic proving is only possible for simple statements, but this field has been making a lot of progress in recent years, and is in particular interested with the idea of generating verifiable evidence for the proofs that are found, which fits squarely within the expertise of Parsial.)

4.2. Proof-assistants

The team work on the structure of proofs also suggests ways that they could be presented to a user, edited and maintained, in particular in "proof assistants", automated tool to assist the writing of mathematical proofs with automatic checking of their correctness.

4.3. Programming language design

Our work also gives insight on the structure and properties of programming languages. We can improve the design or implementation of programming languages, help programmers or language implementors reason about the correctness of the programs in a given language, or reason about the cost of execution of a program.

PETRUS Project-Team

4. Application Domains

4.1. Personal cloud, home care, IoT, sensing, surveys

As stated in the software section, the Petrus research strategy aims at materializing its scientific contributions in an advanced hardware/software platform with the expectation to produce a real societal impact. Hence, our software activity is structured around a common Secure Personal Cloud platform rather than several isolated demonstrators. This platform will serve as the foundation to develop a few emblematic applications. Several privacy-preserving applications can actually be targeted by a Personal Cloud platform, like: (i) smart disclosure applications allowing the individual to recover her personal data from external sources (e.g., bank, online shopping activity, insurance, etc.), integrate them and cross them to perform personal big data tasks (e.g., to improve her budget management) ; (ii) management of personal medical records for care coordination and well-being improvement; (iii) privacy-aware data management for the IoT (e.g., in sensors, quantified-self devices, smart meters); (iv) community-based sensing and community data sharing; (v) privacy-preserving studies (e.g., cohorts, public surveys, privacy-preserving data publishing). Such applications overlap with all the research axes described above but each of them also presents its own specificities. For instance, the smart disclosure applications will focus primarily on sharing models and enforcement, the IoT applications require to look with priority at the embedded data management and sustainability issues, while community-based sensing and privacy-preserving studies demand to study secure and efficient global query processing. Among these applications domains, one is already receiving a particular attention from our team. Indeed, we gained a strong expertise in the management and protection of healthcare data through our past DMSP (Dossier Medico-Social Partagé) experiment in the field. This expertise is being exploited to develop a dedicated healthcare and well-being personal cloud platform. We are currently deploying 10000 boxes equipped with PlugDB in the context of the DomYcile project. In this context, we are currently setting up an Inria Innovation Lab with the Hippocad company to industrialize this platform and deploy it at large scale (see Section the bilateral contract OwnCare II-Lab).

POEMS Project-Team (section vide)

RANDOPT Project-Team

4. Application Domains

4.1. Application Domains

Applications of black-box algorithms occur in various domains. Industry but also researchers in other academic domains have a great need to apply black-box algorithms on a daily basis. We do not target a specific application domain and are interested in possible black-box applications stemming from various origins. This is for us intrinsic to the nature of the methods we develop that are general purpose algorithms. Hence our strategy with respect to applications can be seen as opportunistic and our main selection criteria when approached by colleagues who want to develop a collaboration around an application is whether we judge the application interesting: that is the application brings new challenges and/or gives us the opportunity to work on topics we already intended to work on.

The concrete applications related to industrial collaborations we are currently dealing with are:

- With Thales for the theses of Konstantinos Varelas and Paul Dufossé (DGA-CIFRE theses) related to the design of radars (shape optimization of the wave form). Those theses investigate the development of large-scale variants of CMA-ES and constrained-handling for CMA-ES.
- With Storengy, a subsidiary of Engie specialized in gas storage for the thesis of Cheikh Touré. Different multiobjective applications are considered in this context but the primary motivation of Storengy is to get at their disposal a better multiobjective variant of CMA-ES which is the main objective of the developments within the thesis.
- With PSA in the context of the OpenLab and the thesis of Marie-Ange Dahito for the design of part of a car body.
- With Onera in the context of the thesis of Alann Cheral related to the optimization of the choice of hyperspectral bandwidth.

SPECFUN Project-Team

4. Application Domains

4.1. Computer Algebra in Mathematics

Our expertise in computer algebra and complexity-driven design of algebraic algorithms has applications in various domains, including:

- combinatorics, especially the study of combinatorial walks,
- theoretical computer science, like by the study of automatic sequences,
- number theory, by the analysis of the nature of so-called periods.

TAU Project-Team

4. Application Domains

4.1. Computational Social Sciences

Participants: Philippe Caillou, Isabelle Guyon, Michèle Sebag, Paola Tubaro
Collaboration: Jean-Pierre Nadal (EHESS); Marco Cuturi, Bruno Crépon (ENSAE); Thierry Weil (Mines); Jean-Luc Bazet (RITM)

Computational Social Sciences (CSS) studies social and economic phenomena, ranging from technological innovation to politics, from media to social networks, from human resources to education, from inequalities to health. It combines perspectives from different scientific disciplines, building upon the tradition of computer simulation and modeling of complex social systems [102] on the one hand, and data science on the other hand, fueled by the capacity to collect and analyze massive amounts of digital data.

The emerging field of CSS raises formidable challenges along three dimensions. Firstly, the definition of the research questions, the formulation of hypotheses and the validation of the results require a tight pluridisciplinary interaction and dialogue between researchers from different backgrounds. Secondly, the development of CSS is a touchstone for ethical AI. On the one hand, CSS gains ground in major, data-rich private companies; on the other hand, public researchers around the world are engaging in an effort to use it for the benefit of society as a whole [124]. The key technical difficulties related to data and model biases, and to self-fulfilling prophecies have been discussed in section 3.1 . Thirdly, CSS does not only regard scientists: it is essential that the civil society participate in the science of society [152].

TAO was involved in CSS for the last five years, and its activities have been strengthened thanks to P. Tubaro's and I. Guyon's expertises respectively in sociology and economics, and in causal modeling. Details are given in Section 7.3 .

4.2. Energy Management

Participants: Isabelle Guyon, Marc Schoenauer, Michèle Sebag
PhD: Victor Berger, Benjamin Donnot, Balthazar Donon, Herilalaina Rakotoarison
Collaboration: Antoine Marot, Patrick Panciatici (RTE), Vincent Renault (Artelys)

Energy Management has been an application domain of choice for TAO since the end 2000s, with main partners SME Artelys (METIS Ilab Inria; ADEME project POST; on-going ADEME project NEXT), RTE (See.4C European challenge; two CIFRE PhDs), and, since Oct. 2019, IFPEN. The goals concern i) optimal planning over several spatio-temporal scales, from investments on continental Europe/North Africa grid at the decade scale (POST), to daily planning of local or regional power networks (NEXT); ii) monitoring and control of the French grid enforcing the prevention of power breaks (RTE); iii) improvement of house-made numerical methods using data-intense learning in all aspects of IFPEN activities (as described in Section 3.2).
Optimal planning over long periods of time amounts to optimal sequential decision under high uncertainties, ranging from stochastic uncertainties (weather, market prices, demand prediction) handled based on massive data, to non-stochastic uncertainties (e.g., political decisions about the nuclear policy) handled through defining and selecting a tractable number of scenarios. Note that non-anticipativity constraints forbid the use of dynamic programming-related methods; this led to propose the *Direct Value Search* method [77] at the end of the POST project.

The daily maintainance of power grids requires the building of approximate predictive models on the top of any given network topology. Deep Networks are natural candidates for such modelling, considering the size of the French grid ($\sim$ 10000 nodes), but the representation of the topology is a challenge when, e.g. the RTE goal is to quickly ensure the "n-1" security constraint (the network should remain safe even if any of the 10000 nodes fails). Existing simulators are too slow to be used in real time, and the size of actual grids makes it intractable to train surrogate models for all possible (n-1) topologies (see Section 7.4 for more details).

Furthermore, predictive models of local grids are based on the estimated consumption of end-customers: Linky meters only provide coarse grain information due to privacy issues, and very few samples of fine-grained consumption are available (from volunteer customers). A first task is to transfer knowledge from small data to the whole domain of application. A second task is to directly predict the peaks of consumption based on the user cluster profiles and their representativity (see Section 7.4.2).

4.3. Data-driven Numerical Modeling

Participants: Alessandro Bucci, Guillaume Charpiat, Cécile Germain, Isabelle Guyon, Flora Jay, Marc Schoenauer, Michèle Sebag
PhD and Post-doc: Victor Estrade, Loris Felardos, Adrian Pol, Théophile Sanchez, Wenzhuo Liu
Collaboration: D. Rousseau (LAL), M. Pierini (CERN)

As said (section 3.2), in domains where both first principle-based models and equations, and empirical or simulated data are available, their combined usage can support more accurate modelling and prediction, and when appropriate, optimization, control and design. This section describes such applications, with the goal of improving the time-to-design chain through fast interactions between the simulation, optimization, control and design stages. The expected advances regard: i) the quality of the models or simulators (through data assimilation, e.g. coupling first principles and data, or repairing/extending closed-form models); ii) the exploitation of data derived from different distributions and/or related phenomenons; and, most interestingly, iii) the task of optimal design and the assessment of the resulting designs.

The proposed approaches are based on generative and adversarial modelling [121], [106], extending both the generator and the discriminator modules to take advantage of the domain knowledge.

A first challenge regards the design of the model space, and the architecture used to enforce the known domain properties (symmetries, invariance operators, temporal structures). When appropriate, data from different distributions (e.g. simulated vs real-world data) will be reconciled, for instance taking inspiration from real-valued non-volume preserving transformations [85] in order to preserve the natural interpretation.
Another challenge regards the validation of the models and solutions of the optimal design problems. The more flexible the models, the more intensive the validation must be, as reminded by Leon Bottou. Along this way, generative models will be used to support the design of "what if" scenarios, to enhance anomaly detection and monitoring via refined likelihood criteria.

In the application case of dynamical systems such as fluid mechanics, the goal of incorporating machine learning into classical simulators is to speed up the simulations. Many possible tracks are possible for this; for instance one can search to provide better initialization heuristics to solvers (which make sure that physical constraints are satisfied, and which are responsible of most of the computational complexity of simulations) at each time step; one can also aim at predicting directly the state at $t + 100$, for instance, or at learning a representation space where the dynamics are linear (Koopman - von Neumann). The topic is very active in the deep learning community. To guarantee the quality of the predictions, concepts such as Liapunov coefficients (which express the speed at which simulated trajectories diverge from the true ones) can provide a suitable theoretical framework.

TOCCATA Project-Team

4. Application Domains

4.1. Safety-Critical Software

The application domains we target involve safety-critical software, that is where a high-level guarantee of soundness of functional execution of the software is wanted. Currently our industrial collaborations or impact mainly belong to the domain of transportation: aerospace, aviation, railway, automotive.

Transfer to aeronautics: Airbus France Development of the control software of Airbus planes historically includes advanced usage of formal methods. A first aspect is the usage of the CompCert verified compiler for compiling C source code. Our work in cooperation with Gallium team for the safe compilation of floating-point arithmetic operations [2] is directly in application in this context. A second aspect is the usage of the Frama-C environment for static analysis to verify the C source code. In this context, both our tools Why3 and Alt-Ergo are indirectly used to verify C code.

Transfer to the community of Atelier B In the former ANR project BWare, we investigated the use of Why3 and Alt-Ergo as an alternative back-end for checking proof obligations generated by *Atelier B*, whose main applications are railroad-related https://www.atelierb.eu/en/. The transfer effort continues nowadays through the FUI project LCHIP.

ProofInUse joint lab: transfer to the community of Ada development Through the creation of the ProofInUse joint lab (https://www.adacore.com/proofinuse) in 2014, with AdaCore company (https://www.adacore.com/), we have a growing impact on the community of industrial development of safety-critical applications written in Ada. See the web page https://www.adacore.com/industries for a an overview of AdaCore's customer projects, in particular those involving the use of the SPARK Pro tool set. This impact involves both the use of Why3 for generating VCs on Ada source codes, and the use of Alt-Ergo for performing proofs of those VCs.

The impact of ProofInUse can also be measured in term of job creation: the first two ProofInUse engineers, D. Hauzar and C. Fumex, employed initially on Inria temporary positions, have now been hired on permanent positions in AdaCore company. It is also interesting to notice that this effort allowed AdaCore company to get new customers, in particular the domains of application of deductive formal verification went beyond the historical domain of aerospace: application in automotive (https://www.adacore.com/customers/toyota-itc-japan) cyber-security (https://www.adacore.com/customers/multi-level-security-workstation), health (artificial heart, https://www.adacore.com/customers/total-artificial-heart).

Extension of ProofInUse joint lab The current plans for continuation of the ProofInUse joint lab (https://why3.gitlabpages.inria.fr/proofinuse/) include extension at a larger perimeter than Ada applications. We started to collaborate with the TrustInSoft company (https://trust-in-soft.com/) for the verification of C and C++ codes, including the use of Why3 to design verified and reusable C libraries (ongoing CIFRE PhD thesis). We also started to collaborate with Mitsubishi Electric in Rennes (http://www.mitsubishielectric-rce.eu/xindex.php) for a specific usage of Why3 for verifying embedded devices (logic controllers).

Generally speaking, we believe that our increasing industrial impact is a representative success for our general goal of spreading deductive verification methods to a larger audience, and we are firmly engaged into continuing such kind of actions in the future.

TRIBE Project-Team (section vide)

TROPICAL Project-Team

4. Application Domains

4.1. Discrete event systems (manufacturing systems, networks)

One important class of applications of max-plus algebra comes from discrete event dynamical systems [56]. In particular, modelling timed systems subject to synchronization and concurrency phenomena leads to studying dynamical systems that are non-smooth, but which have remarkable structural properties (nonexpansiveness in certain metrics , monotonicity) or combinatorial properties. Algebraic methods allow one to obtain analytical expressions for performance measures (throughput, waiting time, etc). A recent application, to emergency call centers, can be found in [46].

4.2. Optimal control and games

Optimal control and game theory have numerous well established applications fields: mathematical economy and finance, stock optimization, optimization of networks, decision making, etc. In most of these applications, one needs either to derive analytical or qualitative properties of solutions, or design exact or approximation algorithms adapted to large scale problems.

4.3. Operations Research

We develop, or have developed, several aspects of operations research, including the application of stochastic control to optimal pricing, optimal measurement in networks [112]. Applications of tropical methods arise in particular from discrete optimization [62], [63], scheduling problems with and-or constraints [103], or product mix auctions [120].

4.4. Computing program and dynamical systems invariants

A number of programs and systems verification questions, in which safety considerations are involved, reduce to computing invariant subsets of dynamical systems. This approach appears in various guises in computer science, for instance in static analysis of program by abstract interpretation, along the lines of P. and R. Cousot [69], but also in control (eg, computing safety regions by solving Isaacs PDEs). These invariant sets are often sought in some tractable effective class: ellipsoids, polyhedra, parametric classes of polyhedra with a controlled complexity (the so called “templates” introduced by Sankaranarayanan, Sipma and Manna [113]), shadows of sets represented by linear matrix inequalities, disjunctive constraints represented by tropical polyhedra [48], etc. The computation of invariants boils down to solving large scale fixed point problems. The latter are of the same nature as the ones encountered in the theory of zero-sum games, and so, the techniques developed in the previous research directions (especially methods of monotonicity, nonexpansiveness, discretization of PDEs, etc) apply to the present setting, see e.g. [76], [81] for the application of policy iteration type algorithms, or for the application for fixed point problems over the space of quadratic forms [7]. The problem of computation of invariants is indeed a key issue needing the methods of several fields: convex and nonconvex programming, semidefinite programming and symbolic computation (to handle semialgebraic invariants), nonlinear fixed point theory, approximation theory, tropical methods (to handle disjunctions), and formal proof (to certify numerical invariants or inequalities).

XPOP Project-Team

4. Application Domains

4.1. Surface Enhanced Raman Spectroscopy

(joint project with HEGP, AP-HP, and Lip(Sys)2, Université Paris-Saclay)

The objective of this work is to evaluate the feasibility of an evolving technique, surface enhanced Raman spectroscopy (SERS) for the analysis of cytotoxic drug concentration. This technique using silver nanoparticles was applied for quantitative analysis of 5-fluorouracil, one of the most widely used molecules in oncology [8].

In view of the high spectral variability observed between the various repetitions of the experiment, and the observed nonlinear interaction between signal concentration and intensity, nonlinear regression methods that take these variabilities into account have been developed.

4.2. Management of severe trauma

(joint project with the Traumabase group, AP-HP)

Major trauma is defined as any injury that endangers the life or the functional integrity of a person. It has been shown that management of major trauma based on standardized and protocol based care improves prognosis of patients especially for the two main causes of death in major trauma i.e., hemorrhage and traumatic brain injury.

However, evidence shows that patient management even in mature trauma systems often exceeds acceptable time frames, and despite existing guidelines deviations from protocol-based care are often observed. These deviations lead to a high variability in care and are associated with bad outcome such as inadequate hemorrhage control or delayed transfusion. Two main factors explain these observations. First, decision-making in trauma care is particularly demanding, because it requires rapid and complex decisions under time pressure in a very dynamic and multi-player environment characterized by high levels of uncertainty and stress. Second, being a complex and multiplayer process, trauma care is affected by fragmentation. Fragmentation is often the result of loss or deformation of information.

This disruptive influence prevents providers to engage with each other and commit to the care process.In order to respond to this challenge, our program has set the ambitious goal to develop a trauma decision support tool, the TraumaMatrix. The program aims to provide an integrative decision support and information management solution to clinicians for the first 24 hours of major trauma management. This program is divided into three steps.

Based on a detailed and high quality trauma database, Step 1 consists in developing the mathematical tools and models to predict trauma specific outcomes and decisions. This step raises considerable scientific and methodological challenges.

Step 2 will use these methods to apply them to develop in close cooperation with trauma care experts the decision support tool and develop a user friendly and ergonomic interface to be used by clinicians.

Step 3 will further develop the tool and interface and test in real-time its impact on clinician decision making and patient outcome.

4.3. Precision medicine and pharmacogenomics

(joint project with Dassault Systèmes)

Pharmacogenomics involves using an individual's genome to determine whether or not a particular therapy, or dose of therapy, will be effective. Indeed, people's reaction to a given drug depends on their physiological state and environmental factors, but also to their individual genetic make-up.

Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. While some advances in precision medicine have been made, the practice is not currently in use for most diseases.

Currently, in the traditional population approach, inter-individual variability in the reaction to drugs is modeled using covariates such as weight, age, sex, ethnic origin, etc. Genetic polymorphisms susceptible to modify pharmacokinetic or pharmacodynamic parameters are much harder to include, especially as there are millions of possible polymorphisms (and thus covariates) per patient.

The challenge is to determine which genetic covariates are associated to some PKPD parameters and/or implicated in patient responses to a given drug.

Another problem encountered is the dependence of genes, as indeed, gene expression is a highly regulated process. In cases where the explanatory variables (genomic variants) are correlated, Lasso-type methods for model selection are thwarted.

There is therefore a clear need for new methods and algorithms for the estimation, validation and selection of mixed effects models adapted to the problems of genomic medicine.

A target application of this project concerns the lung cancer.

EGFR (Epidermal Growth Factor Receptor) is a cell surface protein that binds to epidermal growth factor. We know that deregulation of the downstream signaling pathway of EGFR is involved in the development of lung cancers and several gene mutations responsible for this deregulation are known.

Our objective is to identify the variants responsible for the disruption of this pathway using a modelling approach. The data that should be available for developing such model are ERK (Extracellular signal–regulated kinases) phosphorylation time series, obtained from different genetic profiles.

The model that we aim to develop will describe the relationship between the parameters of the pathway and the genomic covariates, i.e. the genetic profile. Variants related to the pathway include: variants that modify the affinity binding of ligands to receptors, variants that modify the total amount of protein, variants that affect the catalytic site,...

4.4. Oncology

(joint project with the Biochemistry lab of Ecole Polytechnique and Institut Curie)

In cancer, the most dreadful event is the formation of metastases that disseminate tumor cells throughout the organism. Cutaneous melanoma is a cancer, where the primary tumor can easily be removed by surgery. However, this cancer is of poor prognosis; because melanomas metastasize often and rapidly. Many melanomas arise from excessive exposure to mutagenic UV from the sun or sunbeds. As a consequence, the mutational burden of melanomas is generally high

RAC1 encodes a small GTPase that induces cell cycle progression and migration of melanoblasts during embryonic development. Patients with the recurrent P29S mutation of RAC1 have 3-fold increased odds at having regional lymph nodes invaded at the time of diagnosis. RAC1 is unlikely to be a good therapeutic target, since a potential inhibitor that would block its catalytic activity, would also lock it into the active GTP-bound state. This project thus investigates the possibility of targeting the signaling pathway downstream of RAC1.

XPOP is mainly involved in Task 1 of the project: *Identifying deregulations and mutations of the ARP2/3 pathway in melanoma patients*.

Association of over-expression or down-regulation of each marker with poor prognosis in terms of invasion of regional lymph nodes, metastases and survival, will be examined using classical univariate and multivariate analysis. We will then develop specific statistical models for survival analysis in order to associate prognosis factors to each composition of complexes. Indeed, one has to implement the further constraint that each subunit has to be contributed by one of several paralogous subunits. An original method previously developed by XPOP has already been successfully applied to WAVE complex data in breast cancer.

The developed models will be rendered user-friendly though a dedicated Rsoftware package.

This project can represent a significant step forward in precision medicine of the cutaneous melanoma.

4.5. Anesthesiology

(joint project with AP-HP Lariboisière and M3DISIM)

Two hundred million general anaesthesias are performed worldwide every year. Low blood pressure during anaesthesia is common and has been identified as a major factor in morbidity and mortality. These events require great reactivity in order to correct them as quickly as possible and impose constraints of reliability and reactivity to monitoring and treatment.

Recently, studies have demonstrated the usefulness of noradrelanine in preventing and treating intraoperative hypotension. The handling of this drug requires great vigilance with regard to the correct dosage. Currently, these drugs are administered manually by the healthcare staff in bolus and/or continuous infusion. This represents a heavy workload and suffers from a great deal of variability in order to find the right dosage for the desired effect on blood pressure.

The objective of this project is to automate the administration of noradrelanine with a closed-loop system that makes it possible to control the treatment in real time to an instantaneous blood pressure measurement.

4.6. Intracellular processes

(joint project with the InBio and IBIS inria teams and the MSC lab, UMR 7057)

Significant cell-to-cell heterogeneity is ubiquitously-observed in isogenic cell populations. Cells respond differently to a same stimulation. For example, accounting for such heterogeneity is essential to quantitatively understand why some bacteria survive antibiotic treatments, some cancer cells escape drug-induced suicide, stem cell do not differentiate, or some cells are not infected by pathogens.

The origins of the variability of biological processes and phenotypes are multifarious. Indeed, the observed heterogeneity of cell responses to a common stimulus can originate from differences in cell phenotypes (age, cell size, ribosome and transcription factor concentrations, etc), from spatio-temporal variations of the cell environments and from the intrinsic randomness of biochemical reactions. From systems and synthetic biology perspectives, understanding the exact contributions of these different sources of heterogeneity on the variability of cell responses is a central question.

The main ambition of this project is to propose a paradigm change in the quantitative modelling of cellular processes by shifting from mean-cell models to single-cell and population models. The main contribution of XPOP focuses on methodological developments for mixed-effects model identification in the context of growing cell populations [9].

- Mixed-effects models usually consider an homogeneous population of independent individuals. This assumption does not hold when the population of cells (i.e. the statistical individuals) consists of several generations of dividing cells. We then need to account for inheritance of single-cell parameters in this population. More precisely, the problem is to attribute the new state and parameter values to newborn cells given (the current estimated values for) the mother.
- The mixed-effects modelling framework corresponds to a strong assumption: differences between cells are static in time (ie, cell-specific parameters have fixed values). However, it is likely that for any given cell, ribosome levels slowly vary across time, since like any other protein, ribosomes are

produced in a stochastic manner. We will therefore extend our modelling framework so as to account for the possible random fluctuations of parameter values in individual cells. Extensions based on stochastic differential equations will be investigated.

- Identifiability is a fundamental prerequisite for model identification and is also closely connected to optimal experimental design. We will derive criteria for theoretical identifiability, in which different parameter values lead to non-identical probability distributions, and for structural identifiability, which concerns the algebraic properties of the structural model, i.e. the ODE system. We will then address the problem of practical identifiability, whereby the model may be theoretically identifiable but the design of the experiment may make parameter estimation difficult and imprecise. An interesting problem is whether accounting for lineage effects can help practical identifiability of the parameters of the individuals in presence of measurement and biological noise.

4.7. Population pharmacometrics

(joint project with Lixoft)

Pharmacometrics involves the analysis and interpretation of data produced in pre-clinical and clinical trials. Population pharmacokinetics studies the variability in drug exposure for clinically safe and effective doses by focusing on identification of patient characteristics which significantly affect or are highly correlated with this variability. Disease progress modeling uses mathematical models to describe, explain, investigate and predict the changes in disease status as a function of time. A disease progress model incorporates functions describing natural disease progression and drug action.

The model based drug development (MBDD) approach establishes quantitative targets for each development step and optimizes the design of each study to meet the target. Optimizing study design requires simulations, which in turn require models. In order to arrive at a meaningful design, mechanisms need to be understood and correctly represented in the mathematical model. Furthermore, the model has to be predictive for future studies. This requirement precludes all purely empirical modeling; instead, models have to be mechanistic.

In particular, physiologically based pharmacokinetic models attempt to mathematically transcribe anatomical, physiological, physical, and chemical descriptions of phenomena involved in the ADME (Absorption - Distribution - Metabolism - Elimination) processes. A system of ordinary differential equations for the quantity of substance in each compartment involves parameters representing blood flow, pulmonary ventilation rate, organ volume, etc.

The ability to describe variability in pharmacometrics model is essential. The nonlinear mixed-effects modeling approach does this by combining the structural model component (the ODE system) with a statistical model, describing the distribution of the parameters between subjects and within subjects, as well as quantifying the unexplained or residual variability within subjects.

The objective of XPOP is to develop new methods for models defined by a very large ODE system, a large number of parameters and a large number of covariates. Contributions of XPOP in this domain are mainly methodological and there is no privileged therapeutic application at this stage [7], [21], [14].

However, it is expected that these new methods will be implemented in software tools, including MONOLIX and Rpackages for practical use.

4.8. Mass spectrometry

(joint project with the Molecular Chemistry Laboratory, LCM, of Ecole Polytechnique)

One of the main recent developments in analytical chemistry is the rapid democratization of high-resolution mass spectrometers. These instruments produce extremely complex mass spectra, which can include several hundred thousand ions when analyzing complex samples. The analysis of complex matrices (biological, agri-food, cosmetic, pharmaceutical, environmental, etc.) is precisely one of the major analytical challenges of this new century. Academic and industrial researchers are particularly interested in trying to quickly and effectively establish the chemical consequences of an event on a complex matrix. This may include, for example, searching for pesticide degradation products and metabolites in fruits and vegetables, photoproducts of active ingredients in a cosmetic emulsion exposed to UV rays or chlorination products of biocides in hospital effluents. The main difficulty of this type of analysis is based on the high spatial and temporal variability of the samples, which is in addition to the experimental uncertainties inherent in any measurement and requires a large number of samples and analyses to be carried out and computerized data processing (up to 16 million per mass spectrum).

A collaboration between XPOP and the Molecular Chemistry Laboratory (LCM) of the Ecole Polytechnique began in 2018. Our objective is to develop new methods for the statistical analysis of mass spectrometry data.

These methods are implemented in the SPIX software.